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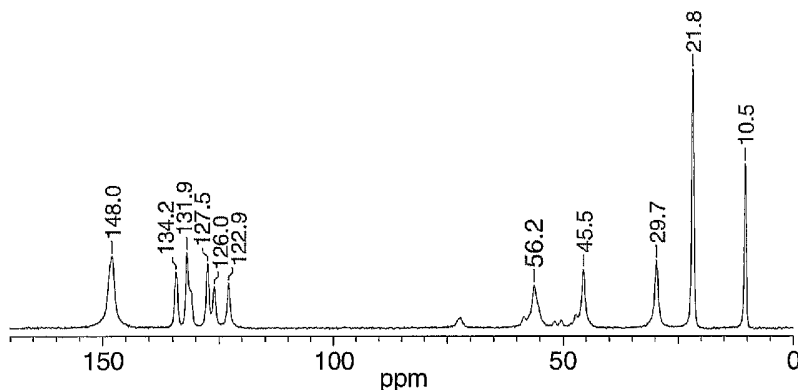
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(54) Title: POLYMORPHS OF 1-(2-METHYLPROPYL)-1H-IMIDAZO[4,5-C][1,5]NAPHTHYRIDIN-4-AMINE ETHANESULFONATE



(57) Abstract: The invention provides various crystalline forms of 1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine ethanesulfonate, pharmaceutical compositions, methods of making, and methods of use.

**POLYMORPHS OF
1-(2-METHYLPROPYL)-1*H*-IMIDAZO[4,5-*c*][1,5]NAPHTHYRIDIN-4-AMINE
ETHANESULFONATE**

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RELATED APPLICATIONS

The present invention claims priority to U. S. Provisional Application Serial No. 60/641129, filed on December 30, 2004, and U. S. Provisional Application Serial No. 60/708679, filed on August 16, 2005, both of which are incorporated herein by reference.

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BACKGROUND

The compound 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine has been found to be a useful immune response modifier (IRM) due to its ability to induce cytokine biosynthesis (U. S. Pat. No. 6,194,425). However, formulating and manufacturing pharmaceutical products can present many unforeseen challenges.

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SUMMARY OF THE INVENTION

It has now been found that the compound 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate can crystallize in more than one type of molecular packing with more than one type of internal crystal lattice. The respective resulting crystal structures can have, for example, different unit cells. This phenomenon of "identical chemical structure but different internal structure" is referred to as polymorphism, and the species having different molecular structures are referred to as polymorphs. As used herein, the term "polymorph" includes both true polymorphs, which have identical chemical structure, and pseudopolymorphs, which contain different hydration and/or solvent levels in the unit cell.

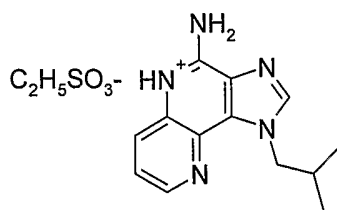
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Because of the existence of polymorphs, manufacturing may not be as reproducible as desired unless significant controls are in place. Furthermore, such polymorphs can have different properties, for example, different stabilities. Thus, there is a desire to identify polymorphic variants of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate in an effort to gain control over manufacturing and stability issues related to such compound.

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This invention thus provides, among other things, various crystalline forms of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate, the structure of which is as follows:



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Three forms (Forms A, C, and D) are monohydrates, and one form (Form B) contains a variable hydrate level. One form (Form E) is anhydrous.

In one aspect, the invention provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate in crystalline Form A.

Form A can be characterized in several different ways. Using X-ray powder diffraction, Form A is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern with peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, and 26.40 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta. Alternatively, using data obtained from X-ray powder diffraction, Form A is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having a unit cell with crystal interplanar spacings: about 13.76 Angstroms, about 9.60 Angstroms, and about 3.37 Angstroms. Alternatively, using solid state ^{13}C NMR, Form A is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having peaks at 144.8 parts per million (ppm), 124.7 ppm, and 55.9 ppm, wherein each of these values is ± 0.3 ppm.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) characterized by an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, 12.77 degrees two-theta, 15.87 degrees two-theta, 18.55 degrees two-theta, 19.15 degrees two-theta, 19.46 degrees two-theta, 22.10 degrees two-

theta, 24.14 degrees two-theta, 26.40 degrees two-theta, and 28.49 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) characterized by an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 7.72 degrees two-theta, 9.20 degrees two-theta, 11.63 degrees two-theta, 12.77 degrees two-theta, 15.39 degrees two-theta, 15.87 degrees two-theta, 16.32 degrees two-theta, 17.48 degrees two-theta, 18.55 degrees two-theta, 19.15 degrees two-theta, 19.46 degrees two-theta, 20.96 degrees two-theta, 22.10 degrees two-theta, 22.55 degrees two-theta, 23.00. 24.14 degrees two-theta, 24.97 degrees two-theta, 26.40 degrees two-theta, 27.36 degrees two-theta, 28.09 degrees two-theta, 28.49 degrees two-theta, 29.34 degrees two-theta, 30.87 degrees two-theta, 32.20 degrees two-theta, 33.68 degrees two-theta, and 34.21 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 1.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) characterized by a solid state ^{13}C NMR spectrum having peaks at 148.3 ppm, 144.8 ppm, 134.1 ppm, 132.0 ppm, 127.5 ppm, 124.7 ppm, 55.9 ppm, 45.8 ppm, 30.4 ppm, 21.3 ppm, and 9.8 ppm, wherein each of these values is ± 0.3 ppm.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) characterized by a solid state ^{13}C NMR spectrum substantially as depicted in Figure 2.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) characterized by at least one of the following; an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, 12.77 degrees two-theta, 15.87 degrees two-theta, 18.55 degrees two-theta, 19.15 degrees two-theta, 19.46 degrees two-theta, 22.10 degrees two-theta, 24.14 degrees two-theta, 26.40 degrees two-theta, and 28.49 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta; or a

solid state ^{13}C NMR spectrum having peaks at 148.3 ppm, 144.8 ppm, 134.1 ppm, 132.0 ppm, 127.5 ppm, 124.7 ppm, 55.9 ppm, 45.8 ppm, 30.4 ppm, 21.3 ppm, and 9.8 ppm, wherein each of these values is ± 0.3 ppm; and further characterized by at least one of the following: a weight loss of 4.4% to 5.4% over a temperature range of 45 °C to 85 °C as measured by thermogravimetric analysis; or an IR spectrum substantially as depicted in Figure 3.

Form B can be characterized in several different ways. Using X-ray powder diffraction, Form B is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate having an X-ray powder diffraction pattern with peaks at 6.11 degrees two-theta, 15.15 degrees two-theta, and 25.55 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta. Alternatively, using data obtained from X-ray powder diffraction, Form B is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate having a unit cell with crystal interplanar spacings: about 14.45 Angstroms, about 5.84 Angstroms, and about 3.48 Angstroms.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form B) characterized by an X-ray powder diffraction pattern having peaks at 6.11 degrees two-theta, 6.46 degrees two-theta, 12.13 degrees two-theta, 12.80 degrees two-theta, 15.15 degrees two-theta, 15.95 degrees two-theta, 18.62 degrees two-theta, 19.12 degrees two-theta, 19.52 degrees two-theta, 20.60 degrees two-theta, 21.14 degrees two-theta, 24.21 degrees two-theta, 25.55 degrees two-theta, 27.13 degrees two-theta, and 28.52 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form B) characterized by an X-ray powder diffraction pattern having peaks at 6.11 degrees two-theta, 6.46 degrees two-theta, 7.48 degrees two-theta, 8.76 degrees two-theta, 9.20 degrees two-theta, 10.64 degrees two-theta, 11.62 degrees two-theta, 12.13 degrees two-theta, 12.80 degrees two-theta, 14.77 degrees two-theta, 15.15 degrees two-theta, 15.95 degrees two-theta, 16.48 degrees two-theta, 17.47 degrees two-theta, 18.62 degrees two-theta, 19.12 degrees two-theta, 19.52 degrees two-theta, 19.88 degrees two-theta, 20.60 degrees two-theta, 21.14 degrees two-theta, 21.82 degrees two-theta, 22.24 degrees two-theta,

22.57 degrees two-theta, 22.81 degrees two-theta, 24.21 degrees two-theta, 25.55 degrees two-theta, 26.48 degrees two-theta, 27.13 degrees two-theta, 28.52 degrees two-theta, 29.94 degrees two-theta, 31.39 degrees two-theta, 32.19 degrees two-theta, 33.69 degrees two-theta, and 34.50 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form B) characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 4.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form B) characterized by an X-ray powder diffraction pattern having peaks at 6.11 degrees two-theta, 6.46 degrees two-theta, 12.13 degrees two-theta, 12.80 degrees two-theta, 15.15 degrees two-theta, 15.95 degrees two-theta, 18.62 degrees two-theta, 19.12 degrees two-theta, 19.52 degrees two-theta, 20.60 degrees two-theta, 21.14 degrees two-theta, 24.21 degrees two-theta, 25.55 degrees two-theta, 27.13 degrees two-theta, and 28.52 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta and an IR spectrum substantially as depicted in Figure 19.

Form C can be characterized in several different ways. Using X-ray powder diffraction, Form C is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern with peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, and 16.70 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta. Alternatively, using X-ray powder diffraction, Form C is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having a unit cell with crystal interplanar spacings: about 12.66 Angstroms, about 8.42 Angstroms, and about 5.30 Angstroms. Alternatively, using solid state ^{13}C NMR, Form C is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having peaks at 127.5 ppm, 126.0 ppm, and 122.9 ppm, wherein each of these values is ± 0.3 ppm.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form C) characterized by an X-ray powder diffraction pattern having peaks at 6.98 degrees two-

theta, 10.50 degrees two-theta, 10.70 degrees two-theta, 16.70 degrees two-theta, 18.11 degrees two-theta, 18.88 degrees two-theta, 21.11 degrees two-theta, 26.02 degrees two-theta, and 28.51 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

5 The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form C) characterized by an X-ray powder diffraction pattern having peaks at 6.98 degrees two-theta, 8.96 degrees two-theta, 10.50 degrees two-theta, 10.70 degrees two-theta, 11.60 degrees two-theta, 14.46 degrees two-theta, 16.70 degrees two-theta, 17.27 degrees two-theta, 18.11 degrees two-theta, 18.47 degrees two-theta, 18.88 degrees two-theta, 20.57 degrees two-theta, 21.11 degrees two-theta, 21.39 degrees two-theta, 22.52 degrees two-theta, 23.04 degrees two-theta, 23.35 degrees two-theta, 23.84 degrees two-theta, 24.35 degrees two-theta, 26.02 degrees two-theta, 27.33 degrees two-theta, 27.92 degrees two-theta, 28.51 degrees two-theta, 29.42 degrees two-theta, 30.19 degrees two-theta, 31.47 degrees two-theta, 31.80 degrees two-theta, 32.45 degrees two-theta, 33.02 degrees two-theta, and 33.73 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

20 The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form C) characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 7.

25 The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form C) characterized by a solid state ^{13}C NMR spectrum having peaks at 148.0 ppm, 134.2 ppm, 131.9 ppm, 131.0 ppm, 127.5 ppm, 126.0 ppm, 122.9 ppm, 56.2 ppm, 45.5 ppm, 29.7 ppm, 21.8 ppm, and 10.5 ppm, wherein each of these values is ± 0.3 ppm.

30 The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form C) characterized by a solid state ^{13}C NMR spectrum substantially as depicted in Figure 8.

 The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form C) characterized by at least one of the following: an X-ray powder diffraction pattern

having peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, 10.70 degrees two-theta, 16.70 degrees two-theta, 18.11 degrees two-theta, 18.88 degrees two-theta, 21.11 degrees two-theta, 26.02 degrees two-theta, and 28.51 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta; or a solid state ^{13}C NMR spectrum having peaks at
5 148.0 ppm, 134.2 ppm, 131.9 ppm, 131.0 ppm, 127.5 ppm, 126.0 ppm, 122.9 ppm, 56.2 ppm, 45.5 ppm, 29.7 ppm, 21.8 ppm, and 10.5 ppm, wherein each of these values is ± 0.3 ppm; and further characterized by at least one of the following: a weight loss of 4.3% to 5.3% over a temperature range of 70 °C to 100 °C as measured by thermogravimetric analysis; or an IR spectrum substantially as depicted in Figure 16.

10 Form D can be characterized in several different ways. Using X-ray powder diffraction, Form D is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern with peaks at 7.35 degrees two-theta, 8.68 degrees two-theta, and 12.61 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta. Alternatively,
15 using X-ray powder diffraction, Form D is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having a unit cell with crystal interplanar spacings: about 12.02 Angstroms, about 10.18 Angstroms, and about 7.02 Angstroms.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-
20 imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form D) characterized by an X-ray powder diffraction pattern having peaks at 6.33 degrees two-theta, 7.04 degrees two-theta, 7.35 degrees two-theta, 8.68 degrees two-theta, 12.61 degrees two-theta, 14.74 degrees two-theta, 15.82 degrees two-theta, 17.35 degrees two-theta, 19.80 degrees two-theta, 21.68 degrees two-theta, and 24.12 degrees two-theta,
25 wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form D) characterized by an X-ray powder diffraction pattern having peaks at 6.33 degrees two-theta, 7.04 degrees two-theta, 7.35 degrees two-theta, 8.68 degrees two-theta, 10.61
30 degrees two-theta, 11.68 degrees two-theta, 12.61 degrees two-theta, 14.74 degrees two-theta, 15.82 degrees two-theta, 17.35 degrees two-theta, 18.08 degrees two-theta, 18.93 degrees two-theta, 19.80 degrees two-theta, 21.20 degrees two-theta, 21.68 degrees two-

theta, 22.02 degrees two-theta, 22.81 degrees two-theta, 23.06 degrees two-theta, 24.12 degrees two-theta, 25.25 degrees two-theta, 26.23 degrees two-theta, 27.31 degrees two-theta, 27.64 degrees two-theta, 28.21 degrees two-theta, 29.51 degrees two-theta, 30.03 degrees two-theta, 31.02 degrees two-theta, 31.47 degrees two-theta, 32.30 degrees two-theta, and 34.39 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form D) characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 23.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form D) characterized by an X-ray powder diffraction pattern having peaks at 6.33 degrees two-theta, 7.04 degrees two-theta, 7.35 degrees two-theta, 8.68 degrees two-theta, 12.61 degrees two-theta, 14.74 degrees two-theta, 15.82 degrees two-theta, 17.35 degrees two-theta, 19.80 degrees two-theta, 21.68 degrees two-theta, and 24.12 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta; and further characterized by at least one of the following: a weight loss of 4.2% to 5.2% over a temperature range of 55 °C to 95 °C as measured by thermogravimetric analysis; or an IR spectrum substantially as depicted in Figure 20.

In one aspect, the invention also provides a mixture of two or more polymorphs of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5] naphthyridin-4-amine ethanesulfonate selected from crystalline Form A, crystalline Form B, crystalline Form C, and crystalline Form D.

In yet another aspect, the invention provides a pharmaceutical composition prepared by a method that includes combining a pharmaceutically acceptable carrier and a polymorph in crystalline Form A, crystalline Form B, crystalline Form C, or crystalline Form D, or a mixture thereof in an amount effective to provide a therapeutically effective amount of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

In another aspect, the invention provides a pharmaceutical composition that includes a polymorph in crystalline Form A, crystalline Form B, crystalline Form C, crystalline Form D, or a mixture thereof.

In certain aspects, the invention provides methods of inducing cytokine biosynthesis in an animal, treating a viral disease in an animal, and/or treating a neoplastic disease in an animal by administering a pharmaceutical composition prepared by a method that includes combining a pharmaceutically acceptable carrier and a polymorph in
5 crystalline Form A, crystalline Form B, crystalline Form C, or crystalline Form D, or a mixture thereof in an amount effective to provide a therapeutically effective amount of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate to the animal.

The invention also provides methods of inducing cytokine biosynthesis in an
10 animal, treating a viral disease in an animal, and/or treating a neoplastic disease in an animal by administering an effective amount of a polymorph in crystalline Form A, crystalline Form B, crystalline Form C, or crystalline Form D, or a mixture thereof, to the animal.

In one aspect, the invention provides a method for preparing a crystalline form of
15 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate. The method includes: combining the free base of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine with ethanesulfonic acid and a carrier to form a mixture, wherein the carrier includes an organic liquid and optionally water; heating the free base, ethanesulfonic acid, and/or carrier prior to combining them, and/or heating the mixture
20 thereof; and forming a precipitate in the mixture.

In a further aspect, the invention provides a method of obtaining crystalline Form C of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate from crystalline Form B. The method includes: combining Form B with a carrier that includes an organic liquid and optionally water to form a mixture; and agitating the
25 mixture for a time sufficient to provide at least a portion of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate in crystalline Form C.

In a further aspect, the invention provides a method of obtaining crystalline Form A of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate from crystalline Form B. The method includes exposing Form B to an atmosphere that
30 includes water vapor.

In a further aspect, the invention provides a method of obtaining crystalline Form B of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate

from crystalline Form A. The method includes removing at least a portion of the water from crystalline Form A.

In another aspect, the invention provides a method for preparing 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. The method includes:
5 providing 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in a carrier that includes a lower alcohol; combining the 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in the carrier with an ammonia- or ammonium-containing reagent to form a first mixture; combining an arylsulfonyl halide with the first mixture to form a
10 second mixture; allowing the components of the second mixture to react for a period of time sufficient to form 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine; and combining the second mixture with an aqueous base.

The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

As used herein, "a", "an", "the", "at least one", "at least a portion of" and "one or
15 more" are used interchangeably. Thus, for example, a composition that comprises an effective amount of "a" polymorph, for example, can be interpreted to mean that the composition includes "one or more" polymorph. Furthermore, a "composition" as used herein can consist of just one polymorph without any other components (e.g., pharmaceutically acceptable carrier).

20 The term "a therapeutically effective amount" or "effective amount" means an amount of the compound sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, antitumor activity, and/or antiviral activity. The exact amount of a polymorph used to prepare a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical
25 nature of the compound, the nature of the carrier, and the intended dosing regimen.

The term "solvate" refers to an amorphous or crystalline material (preferably, crystalline material) having one or more molecules of associated solvent (preferably, within the crystal lattice). The term "hydrate" refers to an amorphous or crystalline material (preferably crystalline material) having associated water molecules (preferably
30 within the crystal lattice). A monohydrate has approximately one molecule of water per molecule of the IRM. The water content refers to wt-% water as determined by the known Karl Fisher method.

As used herein, the term "polymorph" includes both true polymorphs, which have identical chemical structure, and pseudopolymorphs, which contain different hydration and/or solvent levels in the unit cell.

As used herein in connection with a measured quantity, the term "about" refers to that variation in the measured quantity as would be expected by the skilled artisan making the measurement and exercising a level of care commensurate with the objective of the measurement and the precision of the measuring equipment used.

As used herein in connection with a spectrum (e.g., NMR, IR) or an X-ray diffraction pattern shown in a figure, the term "substantially" refers to the fact that the peak positions can shift up to the errors provided and peak intensities can vary as would be expected by one of skill in the art, depending on sample preparation and experimental technique.

The term "salt" is used herein to refer to a salt in any of its pharmaceutically acceptable forms, including solvates, hydrates, polymorphs, and the like, as well as dissolved. It should be understood that the term "salt" includes any or all of such forms, whether explicitly stated or not. Thus "salt" is used to encompass amorphous salt, crystalline salt, crystalline salt hydrate, crystalline salt solvate, salt in solution, and combinations thereof.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a representative X-ray diffraction diagram of crystalline Form A of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Figure 2 is a representative solid state ¹³C NMR spectrum of crystalline Form A of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Figure 3 is a representative solid state IR spectrum of crystalline Form A of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Figure 4 is a representative X-ray diffraction diagram of crystalline Form B 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Figure 5 is a representative solid state ¹³C NMR spectrum of crystalline Form E of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

5 Figure 6 is a representative solid state IR spectrum of crystalline Form E of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Figure 7 is a representative X-ray diffraction diagram of crystalline Form C of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

10 Figure 8 is a representative solid state ¹³C NMR spectrum of crystalline Form C of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Figure 9 is a representative solid state IR spectrum of crystalline Form C of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

15 Figure 10 is a representative thermogram of crystalline Form A of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate, which shows an overlay of data obtained by DSC and TGA.

Figure 11 is a representative thermogram of crystalline Form B of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate, which shows an overlay of data obtained by DSC and TGA.

20 Figure 12 is a representative thermogram of crystalline Form C of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate, which shows an overlay of data obtained by DSC and TGA.

Figure 13 is a representative water sorption isotherm curve for crystalline Form A of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate.

25 Figure 14 is a representative water sorption isotherm curve for crystalline Form B of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Figure 15 is a representative water sorption isotherm curve for crystalline Form C of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate.

30 Figure 16 is a representative solid state IR spectrum of crystalline Form C of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Figure 17 is a representative thermogram of crystalline Form C of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate.

Figure 18 a representative X-ray diffraction diagram of crystalline Form E of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Figure 19 is a representative solid state IR spectrum of crystalline Form B of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Figure 20 is a representative solid state IR spectrum of crystalline Form D of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Figure 21 is a representative thermogram of crystalline Form D of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate.

Figure 22 a representative water sorption isotherm curve for crystalline Form D of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate.

Figure 23 representative X-ray diffraction diagram of crystalline Form D of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention provides five crystalline forms of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate, denominated Form A, B, C, D, and E. Forms A, C, and D are monohydrates, and Form B contains a variable hydrate level. Form E is anhydrous.

Various techniques can be used to characterize crystalline material, including, for example, X-ray powder diffraction (XRPD), solid state ¹³C nuclear magnetic resonance (NMR) spectroscopy, solid state infrared (IR) spectroscopy, thermal analysis (e.g., thermogravimetry (TGA), differential thermal analysis (DTA), and differential scanning calorimetry (DSC)), and the like. Typically, any polymorphs presented herein can be characterized to particular advantage using such techniques. For example, different polymorphs of the same compound typically exhibit diffraction patterns with unique sets of diffraction peaks that can be expressed in two-theta angles and unit cells with unique

interplanar spacings (Angstroms). Such techniques are well known to one of skill in the art. Data presented herein were obtained under the conditions described in the Examples Section.

A monohydrate of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate herein is preferably characterized by a water content of 4.0% to 6.3% as determined by Karl Fisher analysis. The amount of water in a crystalline Form of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate can also be characterized by thermogravimetric analysis (TGA). Crystalline Forms A, C, and D of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate are monohydrates and have been characterized by having a water content of 4.2% to 5.2%, and more typically 4.6% to 5.0%, as determined by TGA analysis. A hemihydrate of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate herein is preferably characterized by a water content of 2.0% to 3.2% as determined by Karl Fisher analysis. Crystalline Form B of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate has been experimentally determined to be hygroscopic.

Form A can be characterized in several different ways. Using X-ray powder diffraction, Form A is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern with peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, and 26.40 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta (and preferably, having peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, 12.77 degrees two-theta, 22.10 degrees two-theta, and 26.40 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta).

Alternatively, using data obtained from X-ray powder diffraction, Form A is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having a unit cell with crystal interplanar spacings: about 13.76 Angstroms, about 9.60 Angstroms, and about 3.37 Angstroms.

Alternatively, and preferably, the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) can be characterized, for example, by a unit cell with crystal interplanar spacings of: about 13.76 Angstroms, about 9.60 Angstroms, about 6.92 Angstroms, about 4.02 Angstroms, and about 3.37 Angstroms (and more preferably, about 13.76 Angstroms,

about 9.60 Angstroms, about 6.92 Angstroms, about 5.58 Angstroms, about 4.78 Angstroms, about 4.63 Angstroms, about 4.56 Angstroms, about 4.02 Angstroms, about 3.68 Angstroms, about 3.37 Angstroms, and about 3.13 Angstroms).

Alternatively, using solid state ^{13}C NMR, Form A is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having peaks at 144.8 ppm, 124.7 ppm, and 55.9 ppm, wherein each of these values is ± 0.3 ppm (preferably, having peaks at 144.8 ppm, 132.0 ppm, 124.7 ppm, or 55.9 ppm, or having peaks at 148.3 ppm, 144.8 ppm, 127.5 ppm, 124.7 ppm, and 55.9 ppm, wherein each of these values is ± 0.3 ppm). Using solid state ^{13}C NMR, Form A can also be characterized as the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having peaks at 144.8 ppm, 132.0 ppm, and 124.7 ppm, wherein each of these values is ± 0.3 ppm.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) characterized by an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, 12.77 degrees two-theta, 15.87 degrees two-theta, 18.55 degrees two-theta, 19.15 degrees two-theta, 19.46 degrees two-theta, 22.10 degrees two-theta, 24.14 degrees two-theta, 26.40 degrees two-theta, and 28.49 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta. Preferably, this polymorph is also characterized by a solid state ^{13}C NMR spectrum having peaks at 144.8 ppm, 124.7 ppm, and 55.9 ppm, wherein each of these values is ± 0.3 ppm.

The polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) can also be characterized, for example, by relative intensity peak strength levels for the above-identified peaks of high (6.41 degrees two-theta), medium (9.20 degrees two-theta), medium (12.77 degrees two-theta), medium low (15.87 degrees two-theta), medium low (18.55 degrees two-theta), medium low (19.15 degrees two-theta), medium low (19.46 degrees two-theta), medium low (22.10 degrees two-theta), medium low (24.14 degrees two-theta), medium (26.40 degrees two-theta), and medium low (28.49 degrees two-theta) wherein peak strengths categorize relative intensities according to the following scheme: High is 85.0-100.0%; Medium High is 70.0-84.9%; Medium is 20.0-69.9%; Medium Low is 5.0-19.9%; and Low is less than 5.0%.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) characterized by an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 7.72 degrees two-theta, 9.20 degrees two-theta, 11.63 degrees two-theta, 12.77
5 degrees two-theta, 15.39 degrees two-theta, 15.87 degrees two-theta, 16.32 degrees two-theta, 17.48 degrees two-theta, 18.55 degrees two-theta, 19.15 degrees two-theta, 19.46 degrees two-theta, 20.96 degrees two-theta, 22.10 degrees two-theta, 22.55 degrees two-theta, 23.00 degrees two-theta, 24.14 degrees two-theta, 24.97 degrees two-theta, 26.40 degrees two-theta, 27.36 degrees two-theta, 28.09 degrees two-theta, 28.49 degrees two-
10 theta, 29.34 degrees two-theta, 30.87 degrees two-theta, 32.20 degrees two-theta, 33.68 degrees two-theta, and 34.21 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form
15 A) characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 1.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) characterized by a solid state ^{13}C NMR spectrum having peaks at 148.3 ppm, 144.8
20 ppm, 134.1 ppm, 132.0 ppm, 127.5 ppm, 124.7 ppm, 55.9 ppm, 45.8 ppm, 30.4 ppm, 21.3 ppm, and 9.8 ppm, wherein each of these values is ± 0.3 ppm. Preferably, this polymorph is also characterized by an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, and 26.40 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

25 The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form A) characterized by a solid state ^{13}C NMR spectrum substantially as depicted in Figure 2.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form
30 A) characterized by at least one of the following: an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, 12.77 degrees two-theta, 15.87 degrees two-theta, 18.55 degrees two-theta, 19.15 degrees two-theta, 19.46 degrees

two-theta, 22.10 degrees two-theta, 24.14 degrees two-theta, 26.40 degrees two-theta, and 28.49 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta; or a solid state ^{13}C NMR spectrum having peaks at 148.3 ppm, 144.8 ppm, 134.1 ppm, 132.0 ppm, 127.5 ppm, 124.7 ppm, 55.9 ppm, 45.8 ppm, 30.4 ppm, 21.3 ppm, and 9.8 ppm, wherein each of these values is ± 0.3 ppm; and further characterized by at least one of the following: a weight loss of 4.4% to 5.4% over a temperature range of 45 °C to 85 °C as measured by thermogravimetric analysis; or an IR spectrum substantially as depicted in Figure 3.

Form B can be characterized in several different ways. Using X-ray powder diffraction, Form B is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate having an X-ray powder diffraction pattern with peaks at 6.11 degrees two-theta, 15.15 degrees two-theta, and 25.55 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta (preferably, having peaks at 6.11 degrees two-theta, 12.13 degrees two-theta, 15.15 degrees two-theta, 25.55 degrees two-theta, and 27.13 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta).

Alternatively, using data obtained from X-ray powder diffraction, Form B is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate having a unit cell with crystal interplanar spacings: about 14.45 Angstroms, about 5.84 Angstroms, and about 3.48 Angstroms.

Alternatively, Form B of the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate can be characterized, for example, by a unit cell with crystal interplanar spacings of: about 14.45 Angstroms, about 7.28 Angstroms, about 5.84 Angstroms, about 3.48 Angstroms, and about 3.28 Angstroms. More preferably, Form B of the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate can be characterized, for example, by a unit cell with crystal interplanar spacings of: about 14.45 Angstroms, about 13.67 Angstroms, about 7.28 Angstroms, about 6.90 Angstroms, about 5.84 Angstroms, about 5.55 Angstroms, about 4.76 Angstroms, about 4.64 Angstroms, about 4.54 Angstroms, about 4.31 Angstroms, about 4.20 Angstroms, about 3.67 Angstroms, about 3.48 Angstroms, about 3.28 Angstroms, and about 3.13 Angstroms.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form B) characterized by an X-ray powder diffraction pattern having peaks at 6.11 degrees two-theta, 6.46 degrees two-theta, 12.13 degrees two-theta, 12.80 degrees two-theta, 15.15 degrees two-theta, 15.95 degrees two-theta, 18.62 degrees two-theta, 19.12 degrees two-theta, 19.52 degrees two-theta, 20.60 degrees two-theta, 21.14 degrees two-theta, 24.21 degrees two-theta, 25.55 degrees two-theta, 27.13 degrees two-theta, and 28.52 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form B) can also be characterized, for example, by relative intensity peak strength levels for the above-identified peaks of high (6.11 degrees two-theta), high (6.46 degrees two-theta), medium (12.13 degrees two-theta), medium (12.80 degrees two-theta), medium (15.15 degrees two-theta), medium (15.95 degrees two-theta), medium low (18.62 degrees two-theta), medium (19.12 degrees two-theta), medium low (19.52 degrees two-theta), medium low (20.60 degrees two-theta), medium (21.14 degrees two-theta), medium (24.21 degrees two-theta), medium (25.55 degrees two-theta), medium (27.13 degrees two-theta), and medium low (28.52 degrees two-theta) wherein peak strengths categorize relative intensities according to the following scheme: High is 85.0-100.0%; Medium High is 70.0-84.9%; Medium is 20.0-69.9%; Medium Low is 5.0-19.9%; and Low is less than 5.0%.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form B) characterized by an X-ray powder diffraction pattern having peaks at 6.11 degrees two-theta, 6.46 degrees two-theta, 7.48 degrees two-theta, 8.76 degrees two-theta, 9.20 degrees two-theta, 10.64 degrees two-theta, 11.62 degrees two-theta, 12.13 degrees two-theta, 12.80 degrees two-theta, 14.77 degrees two-theta, 15.15 degrees two-theta, 15.95 degrees two-theta, 16.48 degrees two-theta, 17.47 degrees two-theta, 18.62 degrees two-theta, 19.12 degrees two-theta, 19.52 degrees two-theta, 19.88 degrees two-theta, 20.60 degrees two-theta, 21.14 degrees two-theta, 21.82 degrees two-theta, 22.24 degrees two-theta, 22.57 degrees two-theta, 22.81 degrees two-theta, 24.21 degrees two-theta, 25.55 degrees two-theta, 26.48 degrees two-theta, 27.13 degrees two-theta, 28.52 degrees two-theta, 29.94 degrees two-theta, 31.39 degrees two-theta, 32.19 degrees two-theta, 33.69 degrees

two-theta, and 34.50 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form B) characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 4.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form B) characterized by an X-ray powder diffraction pattern having peaks at 6.11 degrees two-theta, 6.46 degrees two-theta, 12.13 degrees two-theta, 12.80 degrees two-theta, 15.15 degrees two-theta, 15.95 degrees two-theta, 18.62 degrees two-theta, 19.12 degrees two-theta, 19.52 degrees two-theta, 20.60 degrees two-theta, 21.14 degrees two-theta, 24.21 degrees two-theta, 25.55 degrees two-theta, 27.13 degrees two-theta, and 28.52 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta; and by an IR spectrum substantially as depicted in Figure 19.

In another embodiment, crystalline Form B of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate is characterized by having an IR spectrum substantially as depicted in Figure 19.

Form C can be characterized in several different ways. Using X-ray powder diffraction, Form C is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern with peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, and 16.70 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta (preferably, having peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, 16.70 degrees two-theta, 18.11 degrees two-theta, and 26.02 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta).

Alternatively, using data obtained from X-ray powder diffraction, Form C is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having a unit cell with crystal interplanar spacings: about 12.66 Angstroms, about 8.42 Angstroms, and about 5.30 Angstroms.

Alternatively, and preferably, Form C of the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate can be characterized, for example, by a unit cell with crystal interplanar spacings of: about 12.66

Angstroms, about 8.42 Angstroms, about 5.30 Angstroms, about 4.89 Angstroms, and about 3.42 Angstroms. Alternatively, and more preferably, Form C of the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate can be characterized, for example, by a unit cell with crystal interplanar spacings of: about 12.66 Angstroms, about 8.42 Angstroms, about 8.26 Angstroms, about 5.30 Angstroms, about 4.89 Angstroms, about 4.70 Angstroms, about 4.21 Angstroms, about 3.42 Angstroms, and about 3.13 Angstroms.

Alternatively, using solid state ¹³C NMR, Form C is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having peaks at 127.5 ppm, 126.0 ppm, and 122.9 ppm, wherein each of these values is ± 0.3 ppm (preferably, having peaks at 131.9 ppm, 127.5 ppm, 126.0 ppm, 122.9 ppm, and 56.2 ppm, wherein each of these values is ± 0.3 ppm).

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form C) characterized by an X-ray powder diffraction pattern having peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, 10.70 degrees two-theta, 16.70 degrees two-theta, 18.11 degrees two-theta, 18.88 degrees two-theta, 21.11 degrees two-theta, 26.02 degrees two-theta, and 28.51 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta. Preferably, this polymorph is also characterized by a solid state ¹³C NMR spectrum having peaks at 127.5 ppm, 126.0 ppm, and 122.9 ppm, wherein each of these values is ± 0.3 ppm.

The polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form C) can also be characterized, for example, by relative intensity peak strength levels for the above-identified peaks of high (6.98 degrees two-theta), medium low (10.50 degrees two-theta), medium low (10.70 degrees two-theta), medium low (16.70 degrees two-theta), medium (18.11 degrees two-theta), medium (18.88 degrees two-theta), medium (21.11 degrees two-theta), medium low (26.02 degrees two-theta), and medium low (28.51 degrees two-theta), wherein peak strengths categorize relative intensities according to the following scheme: High is 85.0-100.0%; Medium High is 70.0-84.9%; Medium is 20.0-69.9%; Medium Low is 5.0-19.9%; and Low is less than 5.0%.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form C) characterized by an X-ray powder diffraction pattern having peaks at 6.98 degrees two-theta, 8.96 degrees two-theta, 10.50 degrees two-theta, 10.70 degrees two-theta, 11.60
5 degrees two-theta, 14.46 degrees two-theta, 16.70 degrees two-theta, 17.27 degrees two-theta, 18.11 degrees two-theta, 18.47 degrees two-theta, 18.88 degrees two-theta, 20.57 degrees two-theta, 21.11 degrees two-theta, 21.39 degrees two-theta, 22.52 degrees two-theta, 23.04 degrees two-theta, 23.35 degrees two-theta, 23.84 degrees two-theta, 24.35 degrees two-theta, 26.02 degrees two-theta, 27.33 degrees two-theta, 27.92 degrees two-
10 theta, 28.51 degrees two-theta, 29.42 degrees two-theta, 30.19 degrees two-theta, 31.47 degrees two-theta, 31.80 degrees two-theta, 32.45 degrees two-theta, 33.02 degrees two-theta, and 33.73 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form C) characterized by an X-ray powder diffraction pattern substantially as depicted in Figure
15 7.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form
20 C) characterized by a solid state ^{13}C NMR spectrum having peaks at 148.0 ppm, 134.2 ppm, 131.9 ppm, 131.0 ppm, 127.5 ppm, 126.0 ppm, 122.9 ppm, 56.2 ppm, 45.5 ppm, 29.7 ppm, 21.8 ppm, and 10.5 ppm, wherein each of these values is ± 0.3 ppm. Preferably, this polymorph is also characterized by an X-ray powder diffraction pattern having peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, and 16.70 degrees two-
25 theta, wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form C) characterized by a solid state ^{13}C NMR spectrum substantially as depicted in Figure 8.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form
30 C) characterized by at least one of the following; an X-ray powder diffraction pattern having peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, 10.70 degrees two-theta,

16.70 degrees two-theta, 18.11 degrees two-theta, 18.88 degrees two-theta, 21.11 degrees two-theta, 26.02 degrees two-theta, and 28.51 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta; or a solid state ^{13}C NMR spectrum having peaks at 148.0 ppm, 134.2 ppm, 131.9 ppm, 131.0 ppm, 127.5 ppm, 126.0 ppm, 122.9 ppm, 56.2 ppm, 45.5 ppm, 29.7 ppm, 21.8 ppm, and 10.5 ppm, wherein each of these values is ± 0.3 ppm; and further characterized by at least one of the following: a weight loss of 4.3% to 5.3% over a temperature range of 70 °C to 100 °C as measured by thermogravimetric analysis; or an IR spectrum substantially as depicted in Figure 16.

Form D can be characterized in several different ways. Using X-ray powder diffraction, Form D is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern with peaks at 7.35 degrees two-theta, 8.68 degrees two-theta, and 12.61 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta (preferably, having peaks at 6.33 degrees two-theta, 7.35 degrees two-theta, 8.68 degrees two-theta, 12.61 degrees two-theta, and 17.35 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta).

Alternatively, using data obtained from X-ray powder diffraction, Form D is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having a unit cell with crystal interplanar spacings: about 12.02 Angstroms, about 10.18 Angstroms, and about 7.02 Angstroms.

Alternatively, and preferably, Form D of the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate can be characterized, for example, by a unit cell with crystal interplanar spacings of: about 13.96 Angstroms, about 12.02 Angstroms, about 10.18 Angstroms, about 7.02 Angstroms, and about 5.11 Angstroms. Alternatively, and more preferably, Form D of the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate can be characterized, for example, by a unit cell with crystal interplanar spacings of: about 13.96 Angstroms, about 12.54 Angstroms, about 12.02 Angstroms, about 10.18 Angstroms, about 7.02 Angstroms, about 6.00 Angstroms, about 5.60 Angstroms, about 5.11 Angstroms, about 4.48 Angstroms, about 4.10 Angstroms, and about 3.69 Angstroms.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form D) characterized by an X-ray powder diffraction pattern having peaks at 6.33 degrees two-theta, 7.04 degrees two-theta, 7.35 degrees two-theta, 8.68 degrees two-theta, 12.61
5 degrees two-theta, 14.74 degrees two-theta, 15.82 degrees two-theta, 17.35 degrees two-theta, 19.80 degrees two-theta, 21.68 degrees two-theta, and 24.12 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form D) can also be characterized, for
10 example, by relative intensity peak strength levels for the above-identified peaks of high (6.33 degrees two-theta), medium low (7.04 degrees two-theta), medium low (7.35 degrees two-theta), medium (12.61 degrees two-theta), medium-low (14.74 degrees two-theta), medium-low (15.82 degrees two-theta), medium (17.35 degrees two-theta), medium-low (19.80 degrees two-theta), medium-low (21.68 degrees two-theta), and
15 medium-low (24.12 degrees two-theta), wherein peak strengths categorize relative intensities according to the following scheme: High is 85.0-100.0%; Medium High is 70.0-84.9%; Medium is 20.0-69.9%; Medium Low is 5.0-19.9%; and Low is less than 5.0%.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form
20 D) characterized by an X-ray powder diffraction pattern having peaks at 6.33 degrees two-theta, 7.04 degrees two-theta, 7.35 degrees two-theta, 8.68 degrees two-theta, 10.61 degrees two-theta, 11.68 degrees two-theta, 12.61 degrees two-theta, 14.74 degrees two-theta, 15.82 degrees two-theta, 17.35 degrees two-theta, 18.08 degrees two-theta, 18.93 degrees two-theta, 19.80 degrees two-theta, 21.20 degrees two-theta, 21.68 degrees two-theta, 22.02 degrees two-theta, 22.81 degrees two-theta, 23.06 degrees two-theta, 24.12
25 degrees two-theta, 25.25 degrees two-theta, 26.23 degrees two-theta, 27.31 degrees two-theta, 27.64 degrees two-theta, 28.21 degrees two-theta, 29.51 degrees two-theta, 30.03 degrees two-theta, 31.02 degrees two-theta, 31.47 degrees two-theta, 32.30 degrees two-theta, and 34.39 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
30

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form

D) characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 23.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (preferably, Form D) characterized by an X-ray powder diffraction pattern having peaks at 6.33 degrees two-theta, 7.04 degrees two-theta, 7.35 degrees two-theta, 8.68 degrees two-theta, 12.61 degrees two-theta, 14.74 degrees two-theta, 15.82 degrees two-theta, 17.35 degrees two-theta, 19.80 degrees two-theta, 21.68 degrees two-theta, and 24.12 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta; and further characterized by at least one of the following: a weight loss of 4.2% to 5.2% over a temperature range of 55 °C to 95 °C as measured by thermogravimetric analysis; or an IR spectrum substantially as depicted in Figure 20.

Form E can be characterized in several different ways. Using X-ray powder diffraction, Form E is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate having an X-ray powder diffraction pattern with peaks at 5.80 degrees two-theta, 16.80 degrees two-theta, and 17.52 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta (preferably, having peaks at 5.80 degrees two-theta, 11.59 degrees two-theta, 16.80 degrees two-theta, 17.52 degrees two-theta, and 20.68 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta).

Alternatively, using data obtained from X-ray powder diffraction, Form E is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate having a unit cell with crystal interplanar spacings: about 15.23 Angstroms, about 5.27 Angstroms, and about 5.06 Angstroms.

Alternatively, and preferably, Form E of the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate can be characterized, for example, by a unit cell with crystal interplanar spacings of: about 15.23 Angstroms, about 7.63 Angstroms, about 5.27 Angstroms, about 5.06 Angstroms, and about 4.29 Angstroms. Alternatively, and more preferably, Form E of the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate can be characterized, for example, by a unit cell with crystal interplanar spacings of: about 15.23 Angstroms, about

10.18 Angstroms, about 7.63 Angstroms, about 5.27 Angstroms, about 5.06 Angstroms, about 4.29 Angstroms, and about 4.23 Angstroms.

Alternatively, using solid state ^{13}C NMR, Form E is the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate having peaks at 148.4 ppm, 134.7 ppm, 126.7 ppm, and 123.3 ppm, wherein each of these values is $\pm$ 0.3 ppm (preferably, having peaks at 148.4 ppm, 134.7 ppm, 126.7 ppm, 123.3 ppm, 30.0 ppm, and 10.6 ppm, wherein each of these values is $\pm$ 0.3 ppm).

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form E) characterized by an X-ray powder diffraction pattern having peaks at 5.80 degrees two-theta, 8.68 degrees two-theta, 11.59 degrees two-theta, 16.80 degrees two-theta, 17.52 degrees two-theta, 20.68 degrees two-theta, and 21.00 degrees two-theta, wherein each of these values is $\pm$ 0.15 degree two-theta. Preferably, this polymorph is also characterized by a solid state ^{13}C NMR spectrum having peaks at 148.4 ppm, 134.7 ppm, 126.7 ppm, and 123.3 ppm, wherein each of these values is $\pm$ 0.3 ppm.

The polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form E) can also be characterized, for example, by relative intensity peak strength levels for the above-identified peaks of high (5.80 degrees two-theta), low (8.68 degrees two-theta), medium low (11.59 degrees two-theta), medium low (16.80 degrees two-theta), medium (17.52 degrees two-theta), medium low (20.68 degrees two-theta), and medium low (21.00 degrees two-theta), wherein peak strengths categorize relative intensities according to the following scheme: High is 85.0-100.0%; Medium High is 70.0-84.9%; Medium is 20.0-69.9%; Medium Low is 5.0-19.9%; and Low is less than 5.0%.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form E) characterized by an X-ray powder diffraction pattern having peaks at 5.80 degrees two-theta, 8.68 degrees two-theta, 11.59 degrees two-theta, 16.80 degrees two-theta, 17.52 degrees two-theta, 18.25 degrees two-theta, 20.04 degrees two-theta, 20.68 degrees two-theta, 21.00 degrees two-theta, 21.92 degrees two-theta, 22.92 degrees two-theta, 23.60 degrees two-theta, 24.16 degrees two-theta, 25.20 degrees two-theta, 26.80 degrees two-theta, 27.68 degrees two-theta, 28.21 degrees two-theta, 28.88 degrees two-theta, 29.16

degrees two-theta, 29.99 degrees two-theta, 30.67 degrees two-theta, 32.24 degrees two-theta, 32.99 degrees two-theta, 33.40 degrees two-theta, 33.90 degrees two-theta, and 34.34 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form E) characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 18.

The present invention provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form E) characterized by a solid state ^{13}C NMR spectrum having peaks at 148.4 ppm, 134.7 ppm, 131.1 ppm, 126.7 ppm, 123.3 ppm, 56.0 ppm, 46.0 ppm, 30.0 ppm, 21.9 ppm, and 10.6 ppm, wherein each of these values is ± 0.3 ppm. Preferably, this polymorph is also characterized by an X-ray powder diffraction pattern having peaks at 5.80 degrees two-theta, 16.80 degrees two-theta, and 17.52 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form E) characterized by a solid state ^{13}C NMR spectrum substantially as depicted in Figure 5.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form E) characterized by at least one of the following: an X-ray powder diffraction pattern having peaks at 5.80, 8.68, 11.59, 16.80, 17.52, 20.68, and 21.00, wherein each of these values is ± 0.15 degree two-theta; or a solid state ^{13}C NMR spectrum having peaks at 148.4 ppm, 134.7 ppm, 131.1 ppm, 126.7 ppm, 123.3 ppm, 56.0 ppm, 46.0 ppm, 30.0 ppm, 21.9 ppm, and 10.6 ppm, wherein each of these values is ± 0.3 ppm; and further characterized by an IR spectrum with peaks at 1682 cm^{-1} , 1213 cm^{-1} , 1149 cm^{-1} , and 1037 cm^{-1} , wherein each of these values is $\pm 2\text{ cm}^{-1}$.

The present invention also provides a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (preferably, Form E) characterized by an IR spectrum substantially as depicted in Figure 6.

The invention also provides methods of preparation of the various crystalline Forms of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine

ethanesulfonate. The method includes combining the free base of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine with ethanesulfonic acid and a carrier to form a mixture, wherein the carrier includes an organic liquid and optionally water; heating the free base, ethanesulfonic acid, and/or carrier prior to combining them, and/or heating the mixture thereof; and forming a precipitate in the mixture. In one embodiment, combining includes adding ethanesulfonic acid to the free base in the carrier.

In some embodiments, the carrier includes 1 volume percent (vol-% or % v/v) to 15 vol-% water in an organic liquid, although in some embodiments the carrier includes less than 1 vol-% water. In some embodiments, particularly when the method provides a crystalline monohydrate and more particularly when the method provides Crystalline Form C, the carrier includes at least 2 moles of water per mole of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine free base present.

In some embodiments, the organic liquid is a lower alcohol (i.e., a C₁₋₄ alcohol) such as isopropyl alcohol, methanol, ethanol, *sec*-butanol, or *n*-propanol, toluene, acetone, acetonitrile, methyl acetate, ethyl acetate, isopropyl acetate, isobutyl acetate, or tetrahydrofuran. In some embodiments, the organic liquid is ethyl acetate. If ethyl acetate is used, typically Crystalline Form C is formed.

In one embodiment, forming a precipitate includes cooling the mixture to form a precipitate, although other methods known to one of skill in the art can be used if desired. Preferably, cooling the mixture occurs at a rate of less than 2.0 °C per minute. Typically, this cooling rate results in the formation of Crystalline Form C. In another embodiment, cooling the mixture occurs at a rate greater than or equal to 2.0 °C per minute. Typically, this cooling rate results in the formation of Crystalline Form A.

In one embodiment, the method further includes: optionally adding an additional organic liquid to the mixture comprising the precipitate; separating at least a portion of the precipitate from at least a portion of the mixture; washing the precipitate; and at least partially drying the precipitate. In some embodiments, the additional organic liquid is an ether, preferably *tert*-butyl methyl ether. In some embodiments, the additional organic liquid is acetone, tetrahydrofuran, 1,2-dimethoxyethane, diethoxymethane, methyl acetate, ethyl acetate, isopropyl acetate, isobutyl acetate, heptanes, toluene, or xylenes. Typically, when the additional organic liquid is an ether, crystalline Form B or crystalline Form C is formed.

One skilled in the art will appreciate that there are many ways to separate the precipitate from the mixture, such as filtering, decanting, and centrifugation. In one embodiment, the precipitate is separated by filtration. After separation, the precipitate may optionally be washed with an organic liquid such as an ether, preferably, *tert*-butyl methyl ether, or lower alcohol, toluene, acetone, acetonitrile, methyl acetate, ethyl acetate, isopropyl acetate, isobutyl acetate, heptanes, xylenes, or tetrahydrofuran to remove impurities.

One skilled in the art will appreciate that there are many ways to at least partially dry the precipitate. This includes, for example, using elevated temperatures, desiccation, reduced pressure, using a dry (e.g., nitrogen) atmosphere, and the like. In one embodiment, at least partially drying the precipitate occurs at a temperature range of 25 °C to 60 °C. In another method, at least partially drying the precipitate occurs under at least a partial vacuum.

In yet another embodiment, a method is provided that produces crystalline Form C of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate from crystalline Form B. The method includes: combining Form B with a carrier comprising an organic liquid and optionally water to form a mixture; and agitating the mixture for a time sufficient to provide at least a portion of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate in crystalline Form C. In one embodiment, the mixture is agitated for at least 8 hours. One skilled in the art will appreciate that there are many means for agitating a mixture such as stirring, shaking, and sonicating.

In one embodiment, the carrier includes water, isopropyl alcohol, *tert*-butyl methyl ether, or combinations thereof. In one embodiment, the carrier includes at least 2 moles of water per mole of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine free base present. Preferably, the carrier includes 2% to 5% water, 5% to 10% isopropyl alcohol, and 85% to 93% *tert*-butyl methyl ether. In some embodiments, the carrier includes one or more organic liquids selected from a lower alcohol, *tert*-butyl methyl ether, acetone, tetrahydrofuran, 1,2-dimethoxyethane, diethoxymethane, methyl acetate, ethyl acetate, isopropyl acetate, isobutyl acetate, heptanes, toluene, and xylenes.

In another embodiment, at least a portion of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate is separated from at least a portion of the mixture. In yet another embodiment, the 1-(2-methylpropyl)-1*H*-imidazo[4,5-

c][1,5]naphthyridin-4-amine ethanesulfonate is washed and at least partially dried.

The present invention also provides a method of producing crystalline Form A of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate from crystalline Form B. The method includes exposing Form B to an atmosphere that includes
5 water vapor. In one embodiment, the atmosphere including water vapor has at least 30% relative humidity. One skilled in the art may appreciate that other atmospheric conditions may achieve the same result.

The present invention also provides a method of producing crystalline Form B of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate from
10 crystalline Form A. The method includes removing at least a portion of the water from crystalline Form A. In one embodiment, removing water from crystalline Form A includes exposing crystalline Form A to a desiccant. In another embodiment, removing water from crystalline Form A includes exposing Form A to at least a partial vacuum. In yet another embodiment, crystalline Form A is exposed to heat for a period of time and at
15 a temperature sufficient to convert at least a portion of crystalline Form A to crystalline Form B. In one embodiment, heating crystalline Form A is carried out at a temperature greater than or equal to 40 °C.

The present invention provides a method for preparing 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. The method includes providing 1-(2-
20 methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in a carrier that includes a lower alcohol; combining the 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in the carrier with an ammonia- or ammonium-containing reagent to form a first mixture; combining an arylsulfonyl halide with the first mixture to form a second mixture; allowing the components of the second mixture to react for a period of
25 time sufficient to form 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine; and combining the second mixture with an aqueous base.

In some embodiments of these methods, the ammonia- or ammonium-containing reagent includes ammonium hydroxide in water. In some embodiments of these methods, the arylsulfonyl halide is benzenesulfonyl chloride or *p*-toluenesulfonyl chloride. In some
30 embodiments of these methods, the aqueous base is aqueous sodium hydroxide, although other alkali metal hydroxides (e.g., potassium hydroxide) or other aqueous bases (e.g., sodium carbonate, potassium carbonate) can be used if desired.

In some embodiments of these methods, the ammonia- or ammonium- containing reagent is added prior to the arylsulfonyl halide. In some embodiments these methods can further include separating at least a portion of the resultant 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine from at least a portion of the second mixture, and, if desired, further include washing and at least partially drying the resultant 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

The present invention also provides a mixture of two or more polymorphs of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5] naphthyridin-4-amine ethanesulfonate Forms A, B, C, and D. The present invention further provides a pharmaceutical composition prepared by a method that includes combining a pharmaceutically acceptable carrier and a polymorph of any one of Forms A, B, C, and/or Form D in an amount effective to provide a therapeutically effective amount of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate. The carrier is "acceptable" in the sense of being compatible with the other ingredients of the formulation. In certain embodiments, a pharmaceutical composition is provided that includes a therapeutically effective amount of a polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate in any one of crystalline Forms A, B, C, or D.

Further, in certain embodiments, there is provided a method of inducing cytokine biosynthesis in an animal by administering an effective amount of a polymorph (or a pharmaceutical composition containing such polymorph or manufactured using such polymorph) described herein to the animal. In another embodiment, there is provided a method of treating a viral disease in an animal by administering a therapeutically effective amount of a polymorph (or a pharmaceutical composition containing such polymorph or manufactured using such polymorph) described herein to the animal. In another embodiment, there is provided a method of treating a neoplastic disease in an animal by administering a therapeutically effective amount of a polymorph (or a pharmaceutical composition containing such polymorph or manufactured using such polymorph) described herein to the animal.

Preparation of the Compounds

As used herein, the terms "alkyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups. Unless otherwise specified, these

groups contain from 1 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, and cyclohexyl.

Unless otherwise specified, "alkylene" is the divalent form of the "alkyl", defined above. The term "alkylenyl" is used when "alkylene" is substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

A "lower alcohol" is understood to be a straight chain or branched chain alcohol containing one to four carbon atoms. Examples include, methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol, *sec*-butanol, and *tert*-butanol.

The term "aryl" in reference to "arylsulfonyl halide" includes carbocyclic aromatic rings or ring systems that may be unsubstituted or substituted. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl. Examples of substituents that may be present on the aryl group include alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, cyano, aryl, aryloxy, and arylalkyleneoxy. In certain embodiments, "aryl" in reference to "arylsulfonyl halide" is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, cyano, aryl, aryloxy, and arylalkyleneoxy.

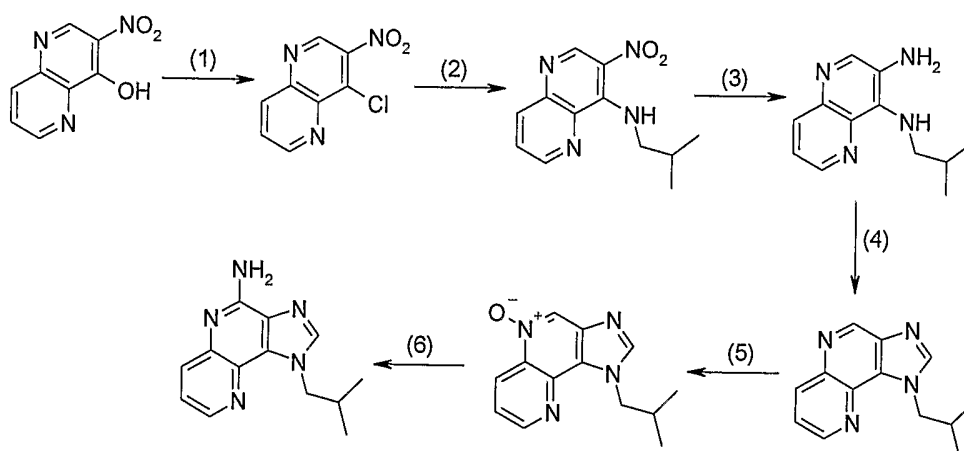
1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine can be prepared according to the route shown in Scheme I. Steps (1) through (6) of Reaction Scheme I can be carried out according to the methods described in U.S. Patent 6,194,425 (Gerster et al.) or modifications thereof as described immediately below and in the EXAMPLES below.

In step (6) of Scheme I, 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine is aminated to provide 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. Step (6) involves the activation of 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction can be carried out by

adding ammonium hydroxide to a solution of 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at room temperature, and the product can be isolated from the reaction mixture using conventional methods.

In one aspect of the invention the reaction in step (6) of Reaction Scheme I is carried out by combining ammonium hydroxide, ammonia, or another suitable aminating agent listed above with 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in a suitable medium such as a lower alcohol or a mixture containing a lower alcohol. The resulting mixture can then be combined with an arylsulfonyl halide to provide 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine in a mixture which is then combined with an aqueous base. The aqueous base is preferably an aqueous alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide. Alternatively, an aqueous solution of potassium carbonate or sodium carbonate may be used. The reaction can be conveniently carried out by adding ammonium hydroxide or an alcoholic ammonia solution to a solution of 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in methanol, ethanol, or isopropanol and then adding benzenesulfonyl chloride or *p*-toluenesulfonyl chloride. The reaction can be carried out at room temperature. Aqueous sodium hydroxide can then be added, and the product can be isolated using conventional techniques. Typically the product precipitates under the reaction conditions and can be separated from the reaction mixture by conventional methods.

Scheme I



Different crystalline forms of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate are typically prepared according to Scheme II. In steps (1) and (2) of Scheme II, a solution or suspension of the free base of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine is prepared by combining the free base with one or more organic liquids or a mixture of one or more organic liquids and water. The resulting solution or suspension may be heated to an elevated temperature, for example, the reflux temperature of the solvent, before combining it with ethanesulfonic acid in step (3). The solution or suspension may also be combined with ethanesulfonic acid at room temperature. Solutions of ethanesulfonic acid or the neat compound may be used. Several organic liquids may be used; these include, for example, a lower alcohol, toluene, acetone, acetonitrile, methyl acetate, ethyl acetate, isopropyl acetate, isobutyl acetate, and tetrahydrofuran (THF). Other examples of organic liquids that may be used include heptane, *tert*-butyl methyl ether, *N,N*-dimethylformamide (DMF), 1-methyl-2-pyrrolidinone (NMP), dichloromethane, and xylene. Mixtures including any two or more of these organic liquids may also be used. Useful mixtures of organic liquids include mixtures of heptane and *tert*-butyl methyl ether, isopropanol, 2-butanol, THF, dichloromethane, ethyl acetate, or toluene; mixtures of *tert*-butyl methyl ether and a lower alcohol, THF, dichloromethane, ethyl acetate, or toluene; mixtures of isopropanol and dichloromethane, ethyl acetate, or toluene; mixtures of 2-butanol and THF, dichloromethane, or toluene; mixtures of THF and dichloromethane, ethyl acetate, or toluene; dichloromethane and ethyl acetate; dichloromethane and toluene; and ethyl acetate and toluene. Water can optionally be combined with the organic liquid or organic liquid mixture. Useful amounts of water that may be combined with the organic liquid or organic liquid mixture include 1% to 15% v/v (volume percent). Preferably, the amount of water that is combined is 1% to 10% v/v. More preferably, the amount of water is 1% to 5% v/v, most preferably 1% to 3% v/v. Many commercially available organic solvents already contain up to 1% v/v water. The amount of water that can be combined with the organic liquid may also be measured in terms of equivalents (mole/mole) with respect to the amount of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine free base present. Preferably, the amount of water present is not less than 2 equivalents (mole/mole) with respect to the amount of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. More preferably, 2 to 10 moles of water are present for every mole of 1-(2-

methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. Most preferably, 2 to 5 moles of water are present for every mole of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. The choice of organic liquid mixture in these steps may determine the identity of the isolated polymorph regardless of how subsequent steps are carried out. For example, when a mixture of 2% v/v water in ethyl acetate is used in steps (1) through (3) of Scheme II, Form C is typically isolated at the end of the procedure. When isopropyl alcohol containing less than 1% v/v water is used as a solvent, usually Form B is isolated at the end of the procedure (see step 7a), but Form A or Form C may be isolated. When isopropyl alcohol containing at least 2 moles of water per mole of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine free base is used as a solvent, usually Form C is isolated. More particularly, when isopropyl alcohol containing 4 ± 0.5 moles of water per mole of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine free base is used as a solvent, usually Form C is isolated. In general, for most organic liquids or mixtures of organic liquids, Form C is usually isolated when the solvent used contains at least two moles of water per mole of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine free base. The heating of the solution or suspension prepared in step (3) may be carried out for a few minutes, more than 15 minutes, more than an hour, more than four hours, or more than 24 hours up to the limit of when the salt begins to decompose.

In steps (4a) and (4b) of Scheme II, the hot solution of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate is cooled to form a precipitate. The cooling in steps (4a) and (4b) may be carried out to room temperature or below room temperature in the range of -20 °C to 25 °C. Steps (4a) and (4b) differ in the rate of cooling that is used. In step (4b), a slow cooling rate is used. A slow rate may be less than 2 °C/minute; preferably it is less than 1 °C/minute. More preferably, a slow rate is less than 0.75 °C/minute. Most preferably, it may be in the range of 0.1 °C/minute to 0.5 °C/minute. In some cases it may be as low as 0.05 °C/minute. In step (4a), a fast cooling rate is used. A fast cooling rate may be characterized by a rate that is achieved when a small volume (less than 100 mL) of solution or suspension is allowed to cool while standing at room temperature. Preferably, a fast cooling rate is greater than 2 °C/minute; more preferably it is greater than 4 °C/minute. The cooling rate of a hot solution of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate may be a

determining factor in the identity of the isolated polymorph. For example, when a hot solution of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate in 2% v/v water/isopropyl alcohol is cooled at a fast rate, usually Form A is isolated. When this same solution is cooled at a slow rate, usually Form C is isolated. Different amounts of water, for example, 1% to 15% v/v may be used in combination with isopropyl alcohol to achieve the same results.

Other methods of forming a precipitate in steps (4a) and (4b) are possible as would be understood by one skilled in the art. These methods include, for example, introducing another organic liquid in which the salt is poorly soluble. For example, *tert*-butyl methyl ether can be combined with a solution of the salt in acetonitrile, 2-butanol, dichloromethane, or THF, wherein any of these solutions may contain at least two moles of water for every mole of salt. The salt solution may be added to *tert*-butyl methyl ether, or *tert*-butyl methyl ether can be added slowly or quickly to the salt solution. In some embodiments, *tert*-butyl methyl ether is added slowly to the salt solution to provide crystalline Form C.

In step (5a) or (5c) of Scheme II, the precipitated salt is separated from the suspension. Usually this is carried out by filtration, but other methods, such as decanting the liquid, are known to one skilled in the art. In step (5b) of Scheme II, an additional liquid is added to the salt suspension before the separation of step (6b) or (6c). The additional liquid may be used to help separate the solid by facilitating the removal of the suspension from the reaction flask. The additional liquid may be an ether, for example, *tert*-butyl methyl ether. The additional liquid may also be acetone, tetrahydrofuran, 1,2-dimethoxyethane, diethoxymethane, methyl acetate, ethyl acetate, isopropyl acetate, isobutyl acetate, heptanes, toluene, and xylenes. The identity of the additional liquid may have an effect on the crystalline form of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate that is isolated. In one example, when *tert*-butyl methyl ether was added in step (5b), 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate was isolated in crystalline Form B. In another example, when *tert*-butyl methyl ether was added in step (5b), Form C was obtained. The separation in steps (6b) and (6c) can be carried out as described for steps (5a) or (5c) above.

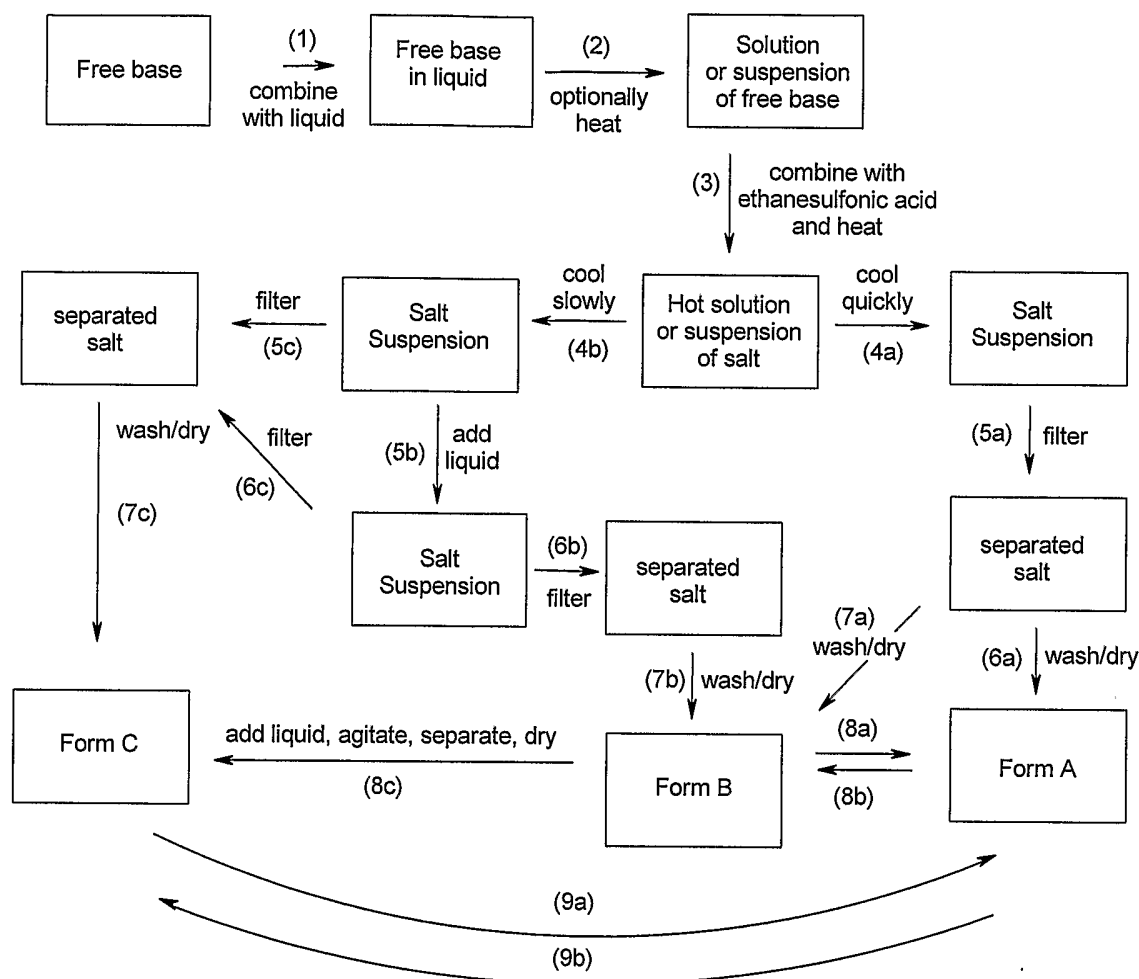
In step (6a), (7c), (7b) or (7a) the separated salt is washed and dried. Washing the salt is usually carried out using one or more organic liquids or a mixture of one or more organic liquids and water. The same liquids described in steps (1) and (2) or step (5b) may be used. If Form B, which is hygroscopic, is desired, washing with an anhydrous solvent may be preferred. Washing with a mixture of liquids that contain water may provide either Form A or Form C, which are monohydrates, depending on other process steps. Drying in step (6a), (7c), (7b) or (7a) may be carried out by heating, by placing the salt under vacuum, by using a flow of inert gas, or combinations thereof. During the drying step, heating in the range of 25 °C to 65 °C is preferred. When drying is carried out under partial vacuum, a vacuum in the range of 2×10^2 Pascals (Pa) to 1×10^5 Pa is preferred. The conditions of the drying step may have an effect on the identity of the crystalline form that is obtained; in some instances, mixtures of polymorphs may be obtained depending on the extent of drying. If drying is carried out by vacuum filtration under a stream of anhydrous nitrogen at a temperature of 35 °C to 45 °C, Form B may be obtained. If drying of Form A or Form C is carried out under vacuum at a temperature in the range of 55 °C to 85 °C, water may be removed from the crystal lattice, and some of Form B may result. For some embodiments, Form C may be dried under a vacuum in the range of 2×10^2 Pa to 1×10^5 Pa at a temperature in the range of 30 °C to 55 °C, more preferably, 35 °C to 55 °C. Form C may also be dried at a temperature in the range of 40 °C to 50 °C or at a temperature in the range of 30 °C to 40 °C. For some embodiments, Form A may be dried at room temperature by vacuum filtration under a stream of air.

Steps (8a), (8b), (8c), and (9a) of Scheme II describe the transformation of a particular crystalline form of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate into another crystalline form or into a mixture of crystalline forms. In step (8a) of Scheme II, Form B can be converted into Form A by exposure to greater than or equal to 30% relative humidity, preferably greater than 50% relative humidity. This step may be carried out in a variety of ways, including storing Form B over water in a sealed container. If no particular care is taken to keep Form B under anhydrous conditions and the crystals are stored at ambient conditions, often Form B is converted to mixtures of Form B and Form A. In step (8b) of Scheme II, Form A can be converted to Form B by heating Form A to a temperature of 75 °C to 85 °C under vacuum. Form A can also be converted to Form B or mixtures of Form A and Form B by storing Form A in the

presence of a desiccant. In step (8c) of Scheme II, Form C is obtained from Form B by adding a liquid or mixture of liquids to Form B, agitating the resulting mixture, separating the salt from the mixture, and drying the salt. The mixture of liquids may include one or more organic liquids and water. Suitable organic liquids include a lower alcohol, *tert*-butyl methyl ether, acetone, tetrahydrofuran, 1,2-dimethoxyethane, diethoxymethane, methyl acetate, ethyl acetate, isopropyl acetate, isobutyl acetate, heptanes, toluene, and xylenes. For some embodiments, the mixture of liquids includes water, isopropyl alcohol, and *tert*-butyl methyl ether. For certain of these embodiments, the mixture of liquids includes 2% to 5% water by volume, 5% to 10% isopropyl alcohol by volume, and 85% to 93% *tert*-butyl methyl ether by volume. For some embodiments, the mixture of liquids includes at least 2 moles of water per mole of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate present. Agitating the mixture may be carried out using a number of methods, such as stirring, shaking, and sonicating. Agitating should usually be carried out for a period of more than 4 hours, more than 8 hours, or more preferably, in the range of 24 hours to 36 hours. The crystalline Form C may be separated and dried using the methods described above. In this process, some of Form A may be formed as well. In step (9a) of Scheme II, Form C is converted to Form A. This conversion may be carried out by heating Form C at an elevated temperature, such as 85 °C to 95 °C, for a time period in the range of 35 to 45 hours. When this process is used, either Form A or a mixture of Form A and Form B may be obtained. Step (9a) may also be carried out to varying degrees by stirring a suspension of Form C in the presence of seed crystals of Form A and Form B in certain solvents at 28 °C for an extended time, such as a period of three weeks. Preferred solvents for this transformation include methanol, ethanol, isopropanol, 2-butanol, ethyl acetate, and acetonitrile, and mixtures of isopropanol and *tert*-butyl methyl ether, THF, or ethyl acetate; mixtures of 2-butanol and ethyl acetate; and mixtures of methanol and *tert*-butyl methyl ether. Preferably, the solvents or solvent mixtures contain no added water. Step (9a) may also be carried out by recrystallizing Form C in *tert*-butyl methyl ether in the absence of water.

In step (9b), Form A is at least partially converted to Form C. Step (9b) can be carried out by grinding Form A in an organic liquid such as methanol, isopropanol, NMP, *tert*-butyl methyl ether with or without a small amount of water. This procedure can also be used in step (8c) to convert Form B to Form C.

Scheme II

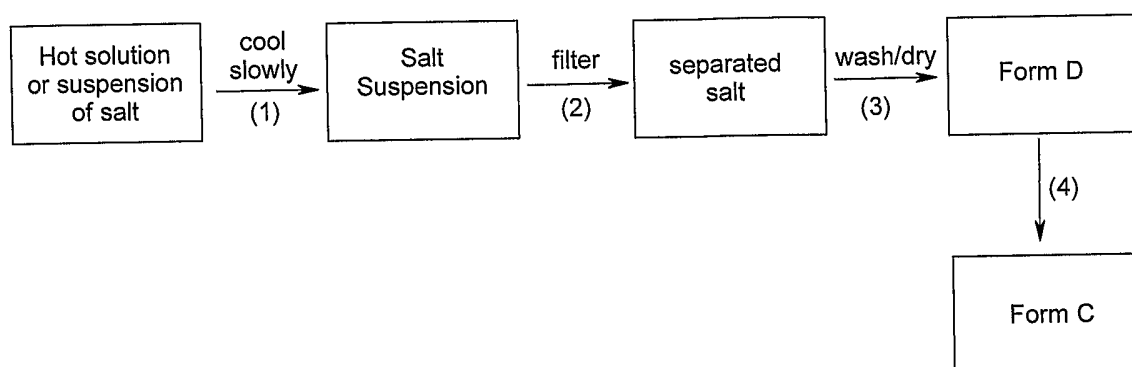


For some embodiments, crystalline forms of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate can be prepared according to Scheme III. The hot solution or suspension of salt in Scheme III can be prepared according to the methods described in steps (1) and (2) of Scheme II. The choice of organic liquid mixture used to prepare the hot solution or suspension of salt can influence the identity of the isolated polymorph. In certain embodiments, *tert*-butyl methyl ether containing at least two moles of water per mole of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate provides Form D when steps (1), (2), and (3) of Scheme III are carried out under the conditions described in steps (4b), (5c), and (7c) of Scheme II. In certain of these embodiments, the rate at which the hot solution or suspension of salt is

cooled in step (1) is 1 °C per minute. Other processes of preparing Form D are described in the EXAMPLES below.

In step (4) of Scheme III, Form D is at least partially converted to Form C. Step (4) can be carried out by exposing Form D to greater than 40% relative humidity. Step (4) can also be carried out by grinding Form D in a small amount of water and organic liquid such as methanol, isopropanol, NMP, and *tert*-butyl methyl ether.

Scheme III



Each of Form A, Form B, Form C, and Form D can be converted to Form E by heating. This conversion can take place when either Form A or Form B is heated to greater than 40 °C or when either Form C or Form D is heated to greater than 90 °C. Form E can also be prepared by drying Form B in a desiccator for a few days.

Other processes for preparing different crystalline forms of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate or for the interconversion of the different crystalline forms are described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate in combination with a pharmaceutically acceptable carrier. Certain pharmaceutical compositions may contain 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate in crystalline Form A, crystalline Form B, crystalline Form C, and/or crystalline Form D. Pharmaceutical compositions may also be manufactured using (and, as needed, testing and controlling for) crystalline Forms A, B, C,

D, and/or E, where the resulting composition may or may not include such Forms (e.g., the compound may be dissolved in the final product). Because it is relatively stable, Form C is one of the preferred crystalline forms for use in manufacturing of compositions containing 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate. Thus, one or more of the polymorph Forms are added as part of the composition manufacturing process, to one or more other ingredients included in the process.

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate can be administered as the single therapeutic agent in the treatment regimen, or it may be administered in combination with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate has been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate is useful as an immune response modifier that can modulate the immune response in a number of different ways, rendering it useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate generally include interferon- α (IFN- α) and/or tumor necrosis factor- α (TNF- α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate include IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a polymorph or pharmaceutical composition of the invention to the animal. The animal to which the polymorph or pharmaceutical composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the polymorph or

pharmaceutical composition may provide therapeutic treatment. Alternatively, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate may be administered to the animal prior to the animal acquiring the disease so that administration of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate may cause proliferation and differentiation of B-lymphocytes.

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN- γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5, and IL-13 may be inhibited upon administration of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the polymorph or pharmaceutical composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus

(e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV), a coronavirus (e.g., SARS), a papovavirus, (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases, such as, for example, diseases resulting from infection by bacteria of, for example, the genus *Escherichia*, *Enterobacter*, *Salmonella*, *Staphylococci*, *Shigella*, *Listeria*, *Aerobacter*, *Helicobacter*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Streptococcus*, *Chlamydia*, *Mycoplasma*, *Pneumococcus*, *Neisseria*, *Clostridium*, *Bacillus*, *Corynebacterium*, *Mycobacterium*, *Campylobacter*, *Vibrio*, *Serratia*, *Providencia*, *Chromobacterium*, *Brucella*, *Yersinia*, *Haemophilus*, or *Bordetella*;

(c) other infectious diseases, such as fungal diseases, such as, for example, candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases, such as, for example, malaria, pneumocystis carinii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, aenal cell leukemia, Kaposi's sarcoma, melanoma, renal cell carcinoma, leukemias, such as, for example, myelogenous leukemia, chronic lymphocytic leukemia, and multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, hairy cell leukemia, and other cancers; and

(e) T_H2-mediated, atopic, and autoimmune diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, Ommen's syndrome, discoid lupus, alopecia areata, inhibition of keloid formation and other types of scarring, and enhancing wound healing, including chronic wounds.

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate also may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens;

polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, and hepatitis C, influenza A and influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate may also be particularly helpful in individuals having compromised immune function. For example, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate. An animal may also be vaccinated by administering an effective of the polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate, or any of the embodiments described herein, or a combination thereof to the animal as a vaccine adjuvant.

An amount of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 nanograms per kilograms (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μ g/kg) to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of

treating a neoplastic disease in an animal comprising administering an effective amount of a polymorph or pharmaceutical composition of the invention to the animal.

An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. An amount of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg.

In certain embodiments, there is provided a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a polymorph or pharmaceutical composition described herein to the animal. In another embodiment, there is provided a method of treating a viral disease in an animal comprising administering a therapeutically effective amount of a polymorph or pharmaceutical composition described herein to the animal. In another embodiment, there is provided a method of treating a neoplastic disease in an animal comprising administering a therapeutically effective amount of a polymorph or pharmaceutical composition described herein to the animal. In another embodiment, there is provided a method of vaccinating an animal comprising administering an effective amount of a polymorph or pharmaceutical composition described herein to the animal as a vaccine adjuvant.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

Test Methods

Powder X-ray Diffraction Analysis

Some reflection geometry data were collected in the form of a ($\theta/2\theta$) survey scan by use of a Philips (PANalytical, Natick, MA) vertical diffractometer, copper K α radiation,

and proportional detector registry of the scattered radiation. The diffractometer is fitted with variable incident beam slits, fixed diffracted beam slits, and a graphite diffracted beam monochromator. The sample was milled in an agate mortar and applied as a dry powder to a zero background specimen holder composed of single crystal quartz. The survey scan was conducted from 3 to 55 degrees (2θ) using a 0.04-degree step size and 6-second dwell time. X-ray generator settings of 45 kV and 35 mA were employed. Analysis of resulting powder diffraction data was accomplished by use of Jade (version 6, Materials Data Inc., Livermore, CA) diffraction software suite. Some X-ray powder diffraction data were collected on a Bruker D8 Vertical Diffractometer in θ/θ configuration, copper K_α radiation, equipped with a variable divergence slit and a position sensitive high-speed detector (Vantec-1) using a step size of 0.034 or 0.051 degrees (2θ) and a dwell time of 0.5 or one second. The lightly ground samples were applied as dry powders to a zero background holder composed of single crystal quartz or silicon.

Solid State ^{13}C Nuclear Magnetic Resonance (NMR) Spectroscopy

Solid State ^{13}C NMR spectra were obtained on a Varian 400 MHz wide-bore INOVA spectrometer using a variable amplitude cross-polarization pulse sequence. The chemical shifts were referenced to tetramethylsilane using hexamethyl benzene as external standard. Due to the experimental conditions (magic angle alignment and lock signal drift), the chemical shifts may vary in the range of ± 0.3 ppm. For the spectrum shown in Figure 2, 14.6 K MAS was used, and the small peak at 2.4 ppm is spinning side band. For the spectrum shown in Figure 5, 14.5 K MAS was used, the small peak at 3.7 ppm is spinning side band, and the sharp peaks at 64.1 and 25.8 ppm are instrumental artifacts. For the spectrum shown in Figure 8, 7.6 K MAS was used, and the small peaks without peak labels in 75-45 ppm range are spinning side bands.

Thermal Analysis

Differential Scanning Calorimetric (DSC) analysis and Thermogravimetric Analysis (TGA) were performed using TA Instruments MDSC Q1000 (Figures 10 – 12) or a TA Instruments MDSC 2920 (Figures 17 and 21) and TGA 2950, respectively. The DSC instrument was calibrated using indium and tin standards. The temperature

calibration on the TGA instrument was performed using nickel and alumel standards. A heating rate of 10 °C/minute was applied for both analyses. Nitrogen purge at 50 mL/minute was applied for both DSC and TGA. For DSC (Figures 17 and 21), a hermetically sealed sample pan with a pinhole was used to reduce the measurement variability of the dehydration event.

Water Sorption Analysis

The automated analysis of water sorption was performed using a VTI Symmetrical Gravimetric Analyzer Model 100 (SGA-100) operated in Step-Isotherm mode. The sample was exposed to a cycle of relative humidity (RH) conditions at 25 °C. The relative humidity was cycled from 5% to 95% and back to 5% in increments of 5%, and the weight of the sample at each stage was recorded after equilibration (less than 0.01% weight change within 5 minutes). The percent weight change of the sample as a function of the relative humidity was plotted to yield the adsorption/desorption isotherm.

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectra were obtained on a Nicolet Magna-IR Spectrometer 750, using an ENDURANCE single-reflection attenuated total reflection (ATR) accessory. A neat sample was placed on the diamond sampling crystal, and the spectrum was collected from 4000 to 525 wavenumbers (cm^{-1}). ATR spectral correction software was utilized.

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

Example 1

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form C

Part A

Under an argon atmosphere, 1,5-naphthyridin-4-ol (1.6 kilograms (kg), 11 moles (mol)) was added in portions of 160 grams (g) with continuous stirring to fuming nitric

acid (16 liters (L)) while maintaining the reaction temperature at 45.5 °C or below. After the addition, the reaction was stirred for 23 minutes (min) at about 45 °C, heated to reflux over a period of 2.25 hours, heated at reflux (90 °C to 95 °C) for five hours, and allowed to cool to room temperature overnight. The reaction mixture was then cooled to 7.5 °C, and water (16 L) was slowly added while maintaining the reaction temperature below 25 °C. The resulting mixture was cooled to 9 °C, and ammonium hydroxide (20 L) was slowly added to adjust the mixture to pH 6.2 while maintaining the temperature below 15 °C. The resulting mixture was stirred for ten minutes and cooled to 2.8 °C. The resulting solid was isolated by filtration, washed with cold water (2 x 2.2 L, 4 °C), dried under vacuum at room temperature, and dried under vacuum at 75 °C for 47 hours to provide 1.778 kg of 3-nitro[1,5]naphthyridin-4-ol.

Part B

Under an argon atmosphere, a solution of 3-nitro[1,5]naphthyridin-4-ol (1.778 kg, 9.30 mol) in *N,N*-dimethylformamide (DMF) (16 L) was stirred for 45 minutes at 17 °C. Phosphorous oxychloride (2.095 kg, 13.7 mol) was added slowly while maintaining the temperature at about 20 °C, and then the reaction was stirred for 15.25 hours at 20 °C. With continuous stirring, the reaction mixture was then added over a period of 55 minutes to water (76 L) that had been cooled to 4.5 °C. During the addition, the temperature of the mixture was not allowed to exceed 10 °C, and the temperature was 9.5 °C at the end of the addition. The mixture resulting from the addition was stirred for 100 minutes while cooling from 9.5 °C to 2.5 °C. A solid formed and was isolated by filtration, washed with water (2 x 8 L), and dried with suction to provide 3.3 kg of 4-chloro-3-nitro[1,5]naphthyridine.

Part C

A solution of the material from Part B in dichloromethane (26 L) was heated to 31 °C, and sodium sulfate (2 kg) and magnesium sulfate (500 g) were added. The resulting mixture was stirred for one hour and then filtered. The filter cake was washed with dichloromethane (5 L), and the filtrate was transferred to another vessel with additional dichloromethane (8 L). Under an argon atmosphere and with continuous stirring, isobutylamine (2.5 L) was added to the filtrate while maintaining a reaction temperature of

17 °C to 24 °C. The reaction was stirred for 13.5 hours at a temperature of 17 °C to 24 °C and then concentrated to dryness under reduced pressure at 40 °C. The resulting solid was mixed with water (18 L), and the resulting mixture was stirred at 20 °C to 21 °C for three hours and then filtered. The isolated solid was washed with water (3 x 3 L), pulled dry
5 under vacuum, and further dried under vacuum for 16.5 hours at 75 °C to provide 1.98 kg of *N*⁴-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine. The product was split into five portions.

Part D

10 A Parr vessel was charged with toluene (3.86 L), 2-propanol (386 milliliters (mL)), *N*⁴-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine (386 g, 1.56 mol), and 5% platinum on carbon (77.2 g, 50% w/w (weight percent) in water). The vessel was sealed and purged three times with nitrogen while the reaction mixture was stirred. The reaction mixture was then placed under hydrogen pressure (2.1×10^5 pascals (Pa) to 4.1×10^5 Pa,
15 30 pounds per square inch (psi) to 60 psi) for 130 minutes while maintaining the temperature between 18 °C and 22 °C. This reaction was repeated four more times with reaction times ranging from 120 minutes to 215 minutes and reaction temperatures ranging from 19 °C to 24 °C. The five runs were combined, treated with magnesium sulfate (2 kg), allowed to stand for 90 minutes, and filtered through a layer of CELITE filter agent. The
20 filter cake was washed with 1:1 toluene/2-propanol (4 L) and then toluene (16 L), and the filtrate was concentrated under reduced pressure at approximately 40 °C to provide 1.59 kg of *N*⁴-(2-methylpropyl)[1,5]naphthyridin-3,4-diamine as an oil.

Parts A through D were repeated on the same scale to provide an additional 1.236 kg of *N*⁴-(2-methylpropyl)[1,5]naphthyridin-3,4-diamine as an oil.
25

Part E

Under an atmosphere of argon, diethoxymethyl acetate (2.24 L, 13.7 mol) was added to a solution of *N*⁴-(2-methylpropyl)[1,5]naphthyridin-3,4-diamine (2.826 kg, 13.07 mol) in toluene (32.5 L) with continuous stirring while maintaining the reaction
30 temperature at or below 30.3 °C. The reaction mixture was stirred for 40 minutes at a temperature of 30.1 °C to 30.3 °C, heated to reflux over a period of 45 minutes, heated at reflux (92.5 °C to 98.5 °C) for 185 minutes, and allowed to cool to room temperature

overnight. Saturated aqueous potassium carbonate (6 L) was added, and the resulting mixture was stirred for 32 minutes at a temperature of 29.3 °C to 30.3 °C and subsequently allowed to stand for 53 minutes. The organic fraction was separated and concentrated under reduced pressure at a temperature of 55 °C to 65 °C over a period of seven hours.

5 The resulting oil was triturated with heptane (3 L) at 20 °C to form a solid, which was isolated by filtration with agitation, washed with cold heptane (1.5 L at 5 °C) and allowed to air-dry to provide 2.593 kg of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine.

Part F

10 A solution of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (2.593 kg, 11.46 mol) in chloroform (2.8 L) was stirred for one hour at a temperature of 17.5 °C to 18 °C, and then 3-chloroperoxybenzoic acid (2.864 g of 70% pure material, 11.6 mol) was added in five portions approximately five minutes apart. During the addition, the temperature of the reaction increased from 16.4 °C to 26.1 °C. After the addition, the
15 reaction mixture was stirred for 20 hours, and the reaction temperature decreased from 26.1 °C to 17.5 °C. The reaction mixture was then stirred for thirty minutes with 1% w/w aqueous sodium carbonate (4 x 3.2 L, 30 minutes between washings). The organic fraction was concentrated under reduced pressure at 40 °C. The residue (4.6 kg) was triturated with diethyl ether (7.5 L) for 68 minutes, and the resulting solid was isolated by
20 filtration with agitation, washed with diethyl ether (4.5 L), and dried under suction to provide 3.304 kg of 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine.

Part G

25 Aqueous ammonium hydroxide (21 L of 28% by weight (w/w)) was added with continuous stirring to a solution of the material from Part F in dichloromethane (34 L) while maintaining the reaction temperature at or below 11.5 °C. With continuous stirring, *p*-toluenesulfonyl chloride (1.786 kg, 9.368 mol) was added in portions over a period of one hour while maintaining the reaction temperature at 16.4 °C to 25 °C. The reaction was stirred for 140 minutes and determined to be incomplete by high-performance liquid
30 chromatography analysis, additional *p*-toluenesulfonyl chloride (180 g, 0.94 mol) was added, and the reaction was stirred for one additional hour. Water (21 L) was added to the reaction mixture, and the resulting mixture was stirred for 30 minutes and allowed to stand

for 14.5 hours. The organic fraction was separated and concentrated under reduced pressure at 40 °C over a period of 8.25 hours. The residue (1.004 kg) was heated at reflux in acetonitrile (10.04 L) for 128 minutes. The suspension was allowed to cool to 20 °C, and the resulting solid was isolated by filtration, washed with cold acetonitrile (1.4 L at 4 °C), and air-dried to provide 360 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-
5 *c*][1,5]naphthyridin-4-amine. A solid was present in the reserved aqueous fraction, and the solid was isolated by filtration, washed with water (4 x 2000 mL), and dried under suction to provide 1.925 kg of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. The two solids were combined and heated at reflux in 90% w/w methanol/water (22.85 L) for 310 minutes, and the suspension was allowed to cool to 24.1 °C overnight. The resulting solid was isolated by filtration, washed with cold 90% w/w methanol/water (1.5 L at 5 °C), and dried in a vacuum oven at 75 °C and 1.0×10^5 Pa for five days to provide 1.368 kg of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a light yellow solid.

Part H

With stirring, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (300 g, 1.24 mol) followed by a rinse of 2% (v/v) water/isopropyl alcohol (100 mL) was added to a vessel containing 2% (v/v) water/isopropyl alcohol (2000 mL), and the
20 resulting mixture was heated to 81 °C. A solution of ethanesulfonic acid (151 g of 95%, 1.37 mol) in 2% (v/v) water/isopropyl alcohol (600 mL) was added slowly to the reaction mixture over a period of approximately 20 minutes. During the addition, the mixture became a clear solution, and the temperature was 81 °C to 82 °C. The addition funnel was rinsed with 2% v/v water/isopropyl alcohol (320 mL); the temperature dropped during the
25 addition but returned to reflux. The resulting solution was heated at reflux for 8 minutes and then cooled slowly to room temperature at a rate of 0.2 °C/minute (57 °C over 234 minutes). The resulting slurry was then further cooled at a rate of 0.2 °C/minute to a temperature of 0 °C to 5 °C (i.e., the slurry was cooled 21 °C over a period of 130 minutes). The solid was isolated by filtration using cold 2% (v/v) water/isopropyl alcohol (400 mL, 3.5 °C) to rinse and aid in the transfer. The solid was washed with cold 2% (v/v)
30 water/isopropyl alcohol (300 mL, 3.5 °C), dried at about 43 °C under 1.69×10^4 Pa to 1.70×10^4 Pa (169 mbar to 170 mbar) for 23 hours and 40 minutes to provide 455 g of 1-(2-

5 methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate. The material was processed in a Hamilton Beach 14-speed blender to provide a white "cotton-like" solid, mp 221.5 °C - 223.4 °C. Anal. Calcd. for $C_{13}H_{15}N_5 \cdot C_2H_6O_3S \cdot H_2O$: C, 48.77; H, 6.28; N, 18.96. Found: C, 48.70; H, 6.25; N, 18.96. This material was characterized by powder X-ray diffraction analysis, solid state ^{13}C NMR spectroscopy, water sorption analysis, thermogravimetric analysis, differential scanning calorimetry, and FTIR spectroscopy. The powder X-ray diffraction pattern is shown in Figure 7. The solid state ^{13}C NMR spectrum is shown in Figure 8. DSC/TGA overlays are shown in Figures 12 and 17, and the water sorption isotherm is shown in Figure 15. The FTIR spectrum is shown in Figure 16.

Example 2

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form C

15 Part A

Under an argon atmosphere, a solution of 3-nitro[1,5]naphthyridin-4-ol (0.800 kg, 4.19 mol) in DMF (8 L) was cooled to 19 °C. Phosphorous oxychloride (803.6 g, 5.24 mol) was added over a period of 70 minutes while maintaining the temperature at 19 °C to 20 °C. A precipitate formed, and the reaction was stirred overnight at room temperature. The reaction mixture was divided in two, and each half was then added with stirring to ice water (13 to 15 L) while maintaining the temperature below 15 °C. The resulting mixtures were stirred for 30 minutes, and the resulting solids were isolated by filtration, washed with cold water (2 L), and combined. The solid was then mixed with dichloromethane (about 9 L) and heated to 30 °C. The organic fraction was removed, and the rest of the mixture was filtered through a layer of CELITE filter agent. The filter cake was washed with dichloromethane (2 L). The filtrate was combined with the organic fraction, and the resulting solution was allowed to stand over sodium sulfate until it was used in Part B.

Part B

30 The mixture from Part A was filtered. Under a nitrogen atmosphere and with stirring, isobutylamine (766.2 g, 10.48 millimoles (mmol)) was added to the filtrate over a period of 95 minutes while maintaining a reaction temperature of 19 °C to 25 °C. The

reaction was stirred overnight at room temperature and then concentrated to dryness under reduced pressure. The resulting solid was stirred with deionized water (16 L) overnight at room temperature, isolated by filtration, and dried under vacuum for 26.5 hours at 62 °C to provide 0.92 kg of *N*⁴-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine as a yellow solid. The product was split into three portions.

Part C

A Parr vessel was charged with toluene (2.3 L), 2-propanol (230 mL), *N*⁴-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine (230 g, 0.924 mol), and 5% platinum on carbon (23.0 g). The vessel was sealed and purged three times with nitrogen while the reaction mixture was shaken. The reaction mixture was then placed under hydrogen pressure (3.4×10^5 Pa, 50 psi) overnight. Additional 5% platinum on carbon (7 g) was added, and the reaction was placed under hydrogen pressure (3.4×10^5 Pa, 50 psi) overnight. The reaction mixture was filtered through a layer of CELITE filter agent. The filter cake was washed with 10:1 toluene/2-propanol, and the filtrate was concentrated under reduced pressure to provide 201.7 g of *N*⁴-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine as a dark oil. The material was mixed with material from two other runs and used in Part D.

Part D

Under an atmosphere of nitrogen, pyridine hydrochloride (6.94 g, 56.5 mmol) was added to a solution of *N*⁴-(2-methylpropyl)[1,5]naphthyridin-3,4-diamine (642.0 g, 2.97 mol) in toluene (3.3 L), and the resulting mixture was stirred until a homogenous solution was achieved. The solution was heated to 90 °C, and triethyl orthoformate (484.6 g, 3.27 mol) was added. When the reaction temperature had reached 100 °C, the addition was stopped, and additional pyridine hydrochloride (6.94 g, 56.5 mmol) was added. The addition was resumed and carried out over a period of 65 minutes while maintaining a reaction temperature in the range of 93 °C to 105 °C and removing the volatiles formed during the reaction by distillation. The reaction was heated at about 90 °C for 25 minutes, allowed to cool to room temperature, and allowed to stir overnight. Additional pyridine hydrochloride (2 g) was then added and the reaction was heated to 112 °C until 2.4 L of distillate were collected. The reaction was then allowed to cool to room temperature,

diluted with toluene, stirred for two days, and washed with aqueous sodium carbonate (3 L of 5%). The organic fraction was separated and dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting dark oil was triturated with hexane (1.5 L) to form a solid, which was collected by filtration, washed with hexane (250 mL), and dried under vacuum at a temperature of 50 °C to 52 °C to provide 440.4 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as a tan solid. A portion of this material was mixed with material from another run and used in Part E.

Part E

A solution of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (554.3 g, 2.45 mol) in dichloromethane (5.54 L) was cooled to 6 °C, and 3-chloroperoxybenzoic acid (665 g of 70% pure material, 2.70 mmol) was added in portions (75 g each) every ten minutes while maintaining the reaction temperature at or below 20 °C to provide a solution of 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in dichloromethane.

Part F

Aqueous ammonium hydroxide (5 L of 28% w/w) was added with continuous stirring to the solution from Part E, and the mixture was cooled to a temperature of 8 °C to 10 °C. With continuous stirring, a solution of *p*-toluenesulfonyl chloride (506 g, 2.70 mol) in dichloromethane (2 L), which had been filtered through a 10- to 20-micron porous fritted filter, was added slowly over a period of 55 minutes while maintaining the reaction temperature at 14 °C to 16 °C. The reaction was stirred for about 48 hours; it warmed to 20 °C during this time. The reaction mixture was cooled to a temperature of 3.5 °C, and the resulting solid was isolated by filtration and washed sequentially with cold dichloromethane (500 mL) and water (2 L). The solid was stirred in an aqueous solution (3 L) of sodium carbonate (125 g) and sodium thiosulfate (35 g) for five hours, isolated by filtration, and washed with deionized water. The solids were stirred overnight in deionized water (2 L), isolated by filtration, washed with deionized water (200 mL), and dried under vacuum at 58 °C to 64 °C for 24 hours to provide 384.8 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine, which was mixed with material from another run to provide 721 g of product. The product was heated to reflux in 90% w/w methanol/water (3.605 L) over 30 minutes, heated at reflux for 150 minutes,

and allowed to cool slowly to 20 °C overnight. The resulting solid was isolated by filtration, washed with 90% w/w methanol/water (300 mL), and dried in a vacuum oven at 70 °C for 24 hours to provide 705.6 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as an off-white solid.

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Part G

A mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (100.0 g, 0.414 mol) and 2% (v/v) deionized water/isopropyl alcohol (700 mL) was heated to reflux with moderate stirring, and ethanesulfonic acid (95% purity, 52.8 g, 0.456 mol) was added over a period of ten minutes using an addition funnel. The funnel was rinsed with 2% (v/v) deionized water/isopropyl alcohol (300 mL), and the resulting solution was heated at reflux for 30 minutes. The solution was stirred and allowed to cool overnight at a rate of 0.5 °C/minute to a temperature of 28 °C. The resulting thick suspension was further cooled to 21 °C for 50 minutes, and the solid was collected by vacuum filtration, washed with 2% (v/v) deionized water/isopropyl alcohol (300 mL), and dried under vacuum for 21.5 hours at 46 °C to 47 °C to provide 142.0 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate as a white solid, mp 220.0-221.0 °C. Anal. Calcd. for C₁₃H₁₅N₅•C₂H₆O₃S•H₂O: C, 48.77; H, 6.28; N, 18.96. Found: C, 48.76; H, 6.53; N, 19.01. The material was analyzed by powder X-ray diffraction analysis and found to be consistent with Figure 7.

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Example 3

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form C

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine prepared in Example 1, Parts A through G was used as the starting material for this example. A mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (2.0 g, 8.3 mmol) and 2% (v/v) deionized water/isopropyl alcohol (20 mL) was heated to reflux with moderate stirring, and ethanesulfonic acid (1.0 g, 9.1 mmol) was added followed by a 2% (v/v) deionized water/isopropyl alcohol (6 mL) rinse, and the resulting solution was heated at reflux for 15 minutes. The solution was stirred and allowed to cool at a rate of 0.5 °C/minute for one hour, 0.33 °C/minute during the second hour, and 0.1 °C/minute during

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the third hour. Stirring was continued for another 22 hours, with the temperature leveling at 20 °C. The resulting solid was collected by vacuum filtration, washed with 2% (v/v) deionized water/isopropyl alcohol (15 mL), and dried under vacuum (1.6×10^3 Pa to 2.1×10^3 Pa) (12 mmHg to 16 mmHg) for 20 hours at 45 °C to 46 °C to provide 2.79 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate as a white solid. Anal. Calcd. for $C_{13}H_{15}N_5 \cdot C_2H_6O_3S \cdot H_2O$: C, 48.76; H, 6.30; N, 18.96. Found: C, 48.76; H, 6.43; N, 18.99. This material was characterized by powder X-ray diffraction analysis, DSC, TGA, and water sorption analysis. The powder X-ray diffraction pattern was found to be consistent with Figure 7. The DSC, TGA, and water sorption data were found to be consistent with that shown in Figures 12 and 15.

Example 4

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form C

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine prepared in Example 1, Parts A through G was used as the starting material for this example. A mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (2.0 g, 8.3 mmol) and 2% (v/v) deionized water/isopropyl alcohol (20 mL) was heated to reflux with moderate stirring, and ethanesulfonic acid (1.0 g, 9.1 mmol) was added followed by a 2% (v/v) deionized water/isopropyl alcohol (6 mL) rinse, and the resulting solution was heated at reflux for 15 minutes. The solution was stirred and allowed to cool at a rate of 0.25 °C/minute for two hours, 0.23 °C/minute during the third hour, and 0.13 °C/minute during the fourth hour. Stirring was continued for another 45 hours, with the temperature leveling at 24 °C. The resulting solid was collected by vacuum filtration, washed with 2% (v/v) deionized water/isopropyl alcohol (15 mL), and dried under vacuum (2.6×10^2 Pa to 2.1×10^3 Pa) (2 mmHg to 16 mmHg) for 20 hours at 46 °C to 47 °C to provide 2.74 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate as a white solid. This material was characterized by powder X-ray diffraction analysis, DSC, TGA, and water sorption analysis. The powder X-ray diffraction pattern was found to be consistent with Figure 7. The DSC, TGA, and water sorption data were found to be consistent with that shown in Figures 12 and 15.

Example 5

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine
ethanesulfonate monohydrate – Form C

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine prepared in
Example 1, Parts A through G was used as the starting material for this example. A
mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (2.0 g, 8.3
mmol) and 2% (v/v) deionized water/ethyl acetate (14 mL) was heated to reflux with
moderate stirring, and ethanesulfonic acid (1.0 g, 9.1 mmol) was added followed by a 2%
(v/v) deionized water/ethyl acetate (6 mL) rinse, and the resulting suspension was heated
at reflux for 15 minutes and allowed to cool overnight. The resulting solid was collected
by vacuum filtration, washed with 2% (v/v) deionized water/ethyl acetate (15 mL), and
dried under vacuum (2.6×10^2 Pa to 2.1×10^3 Pa) (2 mmHg to 16 mmHg) for 21 hours at
46 °C to 47 °C to provide 2.91 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-
c][1,5]naphthyridin-4-amine ethanesulfonate monohydrate as white needles. Anal. Calcd.
for $C_{13}H_{15}N_5 \cdot C_2H_6O_3S \cdot H_2O$: C, 48.76; H, 6.30; N, 18.96. Found: C, 48.48; H, 6.47; N,
18.93. This material was characterized by powder X-ray diffraction analysis, DSC, TGA,
and water sorption analysis. The powder X-ray diffraction pattern was found to be
consistent with Figure 7. The DSC, TGA, and water sorption data were found to be
consistent with that shown in Figures 12 and 15.

Example 6

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine
ethanesulfonate – Form B

Part A

Under a nitrogen atmosphere, a suspension of 3-nitro-1,5-naphthyridin-4-ol (12.00
kg, 67.78 mol) in DMF (49 L) was stirred for 30 minutes at a temperature of 20 °C to 24
°C. Phosphorous oxychloride (10.6 kg, 69.1 mol) was added slowly over a period of 53
minutes while maintaining the temperature at 20.6 °C to 25.6 °C. Additional DMF (5 L)
was used to rinse the addition vessel and added to the reaction. The reaction was stirred
for 19 hours and 17 minutes at a temperature of 20 °C to 24 °C and then added quickly,
over a period of four minutes, to purified water (275 L) that had been cooled to 8.4 °C.
During the addition, the temperature of the mixture did not exceed 18 °C. Additional

water (80 L) was used to rinse the original vessel and added quickly to the resulting mixture, which ranged in temperature from 16.6 °C to 17.2 °C during this addition. The mixture resulting from the additions was stirred for 30 minutes while cooling to a temperature of approximately 10 °C. A solid formed and was isolated by filtration and washed with cold water (6 x 33 L at 10 °C) to provide 20.55 kg of 4-chloro-3-nitro[1,5]naphthyridine, which contained some water and was used in Part B within 2.75 hours of filtration.

Part B

Isobutylamine (9.4 kg, 12.8 L, 130 mol) was added to a stirred suspension of the material from Part A (20.55 kg) in tetrahydrofuran (67 L) over a period of 77 minutes while maintaining a reaction temperature of 20 °C to 27 °C. The addition of isobutylamine was followed by a rinse with tetrahydrofuran (5 L). The reaction was stirred for 190 minutes at a temperature of 20 °C to 24 °C, and then water (288 L) was added over a period of about one hour while maintaining the reaction temperature at 21.4 °C to 23.8 °C. The resulting mixture was stirred at 20 °C to 24 °C for 75 minutes and then filtered. The isolated solid was washed with water (4 x 25 L) that had also been used to rinse the reaction vessel, pulled dry under vacuum, and further dried under vacuum for 60 hours at a temperature of 45 °C to 55 °C to provide 13.7 kg of *N*⁴-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine.

Part C

A hydrogenation vessel was charged with *N*⁴-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine (13.7 kg, 55.6 mol) and 3% platinum on carbon (0.79 kg, 34.61% w/w in water), purged with nitrogen, charged with toluene (670.0 kg) and 2-propanol (37.0 kg), and purged with nitrogen. The vessel was sealed and purged three times with hydrogen. The reaction mixture was then placed under hydrogen pressure (1.2 x 10⁵ Pa, 17 psi) for 170 minutes while stirring and maintaining the temperature between 18 °C and 22 °C. The reaction mixture was filtered through a filter pad. The filter cake was washed with toluene (87 kg), and the filtrate was concentrated under reduced pressure at approximately 25 °C to provide a solution of *N*⁴-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine in toluene (approximately 15 mL/g).

Part D

The solution from Part C (196 L) was cooled to a temperature of -5°C to 0°C under an atmosphere of nitrogen, and *p*-toluenesulfonic acid (0.520 kg, 2.73 mol) was added. The reaction was purged with nitrogen and heated to a temperature of 88°C to 92°C over a period of 87 minutes. Triethyl orthoformate (9.4 kg, 63 mol) was slowly added with stirring over a period of 64 minutes; during the addition, the reaction temperature was increased from 89.4°C to 94°C . The addition vessel was rinsed with toluene (5 L) which, in turn, was also added to the reaction. The reaction mixture was stirred and heated at reflux (98°C to 100°C) for 195 minutes; the ethanol distillate was collected. The reaction was purged three times with nitrogen, cooled to a temperature of 0°C to 5°C over a period of three hours, purged three times with nitrogen, and heated to a temperature of 20°C to 24°C . The reaction mixture was washed sequentially with aqueous sodium carbonate (41 L of 1% w/w) for one hour and water (41 L) for one hour, while allowing the layers to separate for one hour after each washing. The organic fraction was then concentrated under reduced pressure at a temperature of 21.6°C , cooled to a temperature of 0°C to 5°C , and purged with nitrogen to provide 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as a solution in toluene (approximately 7.3 mL/g).

Part E

The solution from Part D (102 L) was heated to a temperature of 45°C to 50°C and purged with nitrogen. Under a nitrogen atmosphere, peracetic acid (12.1 kg of 40 weight percent (wt. % or w/w)) was added over a period of 137 minutes while maintaining the reaction temperature at 45.6°C to 50°C and purging the system with nitrogen every 30 minutes. The addition vessel was rinsed with toluene (5 L) which, in turn, was also added to the reaction. The reaction was stirred for 247 minutes at a temperature of 47.5°C to 49.7°C while purging the system with nitrogen every thirty minutes, and then cooled to a temperature of 0°C to 5°C . The reaction was purged with nitrogen and heated to a temperature of 43°C to 47°C . While maintaining this temperature, aqueous sodium metabisulfite (51 L of 4% w/w) was added over a period of 28 minutes, and aqueous sodium hydroxide (50 L of 10.5% w/w) was added over a period of 28 minutes. Water (7 L) was added, and the reaction temperature was adjusted to 48°C to 52°C and stirred for

30 minutes. The resulting mixture was cooled to a temperature of 3 °C to 7 °C over a period of about four hours and then was maintained at this temperature for 249 minutes. A solid was present and was isolated by filtration, washed with cold water (3 x 25 L at 3 °C to 7 °C), dried by suction, and further dried under vacuum at 25 °C to 35 °C for about 137 hours to provide 10.8 kg of 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as a yellow solid.

Part F

Under a nitrogen atmosphere, aqueous ammonium hydroxide (11.5 kg of 28% w/w) was quickly added with continuous stirring to a suspension of 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (10.8 kg, 44.6 mol) in methanol (77 L) while maintaining the reaction temperature at 20.6 °C to 21.4 °C. Methanol (10 L) was used to rinse the addition vessel and also added to the reaction. The reaction was stirred for 29 minutes. With continuous stirring, benzenesulfonyl chloride (8.2 kg, 46 mol) was added over a period of 50 minutes while maintaining the reaction temperature at 20 °C to 29.6 °C. Methanol (10 L) was used to rinse the addition vessel and also added to the reaction. The reaction was stirred for 66 minutes at 20.4 °C to 22.5 °C and purged three times with nitrogen. The reaction was determined to be incomplete by high-performance liquid chromatography analysis. Additional benzenesulfonyl chloride (0.8 kg, 4.5 mol) was added over a period of 12 minutes while maintaining the reaction temperature at 22.9 °C to 23.7 °C. An additional methanol (5 L) was added, and the reaction then stirred for 67 minutes at a temperature of 21.6 °C to 24.1 °C. Aqueous sodium hydroxide (32 L of 10% w/w) was added to the reaction mixture over a period of 30 minutes while maintaining the reaction temperature between 22 °C and 23 °C. Water (10 L), used to rinse the addition vessel, was added to the reaction mixture. The resulting mixture was cooled to 12 °C over a period of 39 minutes and stirred for two hours at a temperature in the range of 10.6 °C and 12.0 °C. A precipitate was present and was isolated by filtration and washed with cold (8 °C to 12 °C) 59:41 methanol/water v/v (2 x 11 L), with each wash allowed to soak into the filter cake for 10 minutes. The filter cake was washed with cold (8 °C to 12 °C) water (4 x 25 L), with each wash allowed to soak into the filter cake for 10 minutes, and dried under vacuum at a temperature of 45 °C to 55 °C for 24 hours to provide 8.25 kg of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a light yellow solid. A

portion of the solid (2.75 kg) was mixed with 2-butanol (371 L), and the resulting mixture was heated to reflux with stirring over a period of 93 minutes, heated at 99 °C for 20 minutes, cooled to a temperature of 60 °C to 65 °C over a period of 45 minutes, and filtered into another warm vessel. The solution was then cooled to a temperature of 20 °C to 25 °C with stirring, concentrated under reduced pressure at a temperature of 21.4 °C to a minimum volume required for stirring, and purged with nitrogen. A second portion of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a light yellow solid (2.75 kg) and a second volume of 2-butanol (371 L) were added, and the refluxing, filtering, and concentration processes were repeated. A third portion of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a light yellow solid (2.60 kg) and a third volume of 2-butanol (371 L) were added, and the refluxing and filtering processes were repeated. The solution was cooled to 20 °C, and additional 2-butanol (20 L) was added. The refluxing, filtering, and concentration processes were repeated. The resulting mixture (198 L total) was heated to reflux with stirring over a period of 70 minutes, heated at 97 °C for 20 minutes, cooled at a rate of 0.5 °C per minute to a temperature of 68 °C to 72 °C, cooled to a temperature of 3 °C to 5 °C over a period of 154 minutes, stirred at a temperature of 4.3 °C to 5 °C for two hours, and filtered with no agitation. The filter cake was washed with cold (3 °C to 5 °C) 2-butanol (50 L) that had been used to wash the crystallization vessel and blown dry without agitation for one hour under a nitrogen flow. The solid was dried on the filter with no agitation at a temperature of 46 °C to 50 °C under vacuum (900 mbar to 980 mbar, 9.0×10^4 Pa to 9.8×10^4 Pa) with small nitrogen sweep for twelve hours to provide 6.50 kg of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

Part G

Under a nitrogen atmosphere, isopropyl alcohol (88 L) was added to 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (3.45 kg, 14.3 mol), and the mixture was stirred and heated to 81 °C. Aqueous ethanesulfonic acid (2.5 kg of 70% w/w, 16 mol) was added over a period of 15 minutes, and the addition vessel was rinsed with isopropyl alcohol (10 L). The mixture was heated at reflux for 30 minutes, cooled to a temperature of 60 °C to 65 °C, and filtered through a 5-micron filter into another warm vessel. Heated isopropyl alcohol (temperature of 60 °C to 65 °C) was used to rinse the

first vessel and added to the solution. The filtrate was heated at reflux (81 °C) for 37 minutes and then cooled to a temperature of 45 °C to 55 °C over the course of 85 minutes (approximately 0.4 °C/min). The reaction was further cooled to a temperature of 23 °C - 27 °C over 130 minutes (approximately 0.15 °C/min to 0.25 °C/min) and then stirred at a temperature of 23 °C to 27 °C for 100 minutes before the addition of *tert*-butyl methyl ether (MTBE) (123 mL) over a period of 92 minutes. The resulting mixture was stirred at a temperature of 24 °C to 25 °C for 63 minutes, cooled to 4 °C over 115 minutes (approximately 0.18 °C/min), and stirred at a temperature of 4 °C to 5 °C for 125 minutes. The slurry was transferred over a period of 11 minutes to a nitrogen-purged filter in 2 portions, using nitrogen pressure to assist filtration. MTBE (88 L) was added to the crystallization vessel, cooled to a temperature of 1 °C to 5 °C and then transferred to the filter to wash the product cake. No agitation was used during the filtration. The solid was dried on the filter with no agitation at a temperature of 35 °C to 45 °C under vacuum (900 mbar to 980 mbar, 9.0×10^4 Pa to 9.8×10^4 Pa) with small nitrogen sweep for six hours to provide 3.8 kg of Form B as a solid. This material was characterized by DSC, TGA, and water sorption analysis. The overlay of the DSC and TGA data is shown in Figure 11, and the water sorption isotherm is shown in Figure 14. A sample of the material was dried in a desiccator for a few days, and, as a result, Form E was formed. The solid state ^{13}C NMR spectrum of Form E is shown in Figure 5, and the FTIR spectrum of Form E is shown in Figure 6.

Example 7

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form C

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate, Form B, prepared in Example 6, was slurried in a water (400 mL)/isopropyl alcohol (1 L)/MTBE (15 L) mixture for 24 to 36 hours. The slurry was filtered and washed with MTBE. The product was dried at 40 °C under vacuum (980 mbar, 9.8×10^4 Pa) to provide 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate Form C as a white solid. This material was characterized by powder X-ray

diffraction analysis and FTIR spectroscopy. The powder X-ray diffraction pattern was found to be consistent with Figure 7. The FTIR spectrum is shown in Figure 9.

Example 8

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate – Form B

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine prepared in Example 1, Parts A through G was used as the starting material for this example. A solution of ethanesulfonic acid (0.33 mL of a 0.167 g/mL solution in isopropyl alcohol, 0.50 mmol) was added to a mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (100 mg, 0.4 mmol) and isopropyl alcohol (0.7 mL), and the mixture was heated with stirring until it became homogeneous. The solution was allowed to cool, and a precipitate formed. The precipitate was isolated by filtration, washed with cold isopropyl alcohol, and dried under vacuum at 43 °C to provide 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate as a white powder. This sample was characterized by powder X-ray diffraction analysis, DSC, TGA, and water sorption analysis. The powder X-ray diffraction pattern is shown in Figure 4. The DSC and TGA data were consistent with those shown in Figure 11, and the water sorption isotherm was consistent with Figure 14.

Example 9

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form A with a trace of Form B

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine prepared in Example 1, Parts A through G was used as the starting material for this example. A mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (2.4890 g, 10.315 mmol) and isopropyl alcohol (57.5 mL) was heated to reflux with moderate stirring, and a solution of ethanesulfonic acid (1.2502 g, 11.352 mmol) in isopropyl alcohol (30 mL) was added slowly. The resulting solution was heated at reflux for one hour and allowed to cool to room temperature over a period of 15 to 20 minutes. The reaction flask was then cooled in an ice water bath for 20 to 25 minutes. The resulting solid was collected by vacuum filtration, washed with ice cold isopropyl alcohol (2 x 10

mL), and dried under vacuum (1.0×10^5 Pa) (30 inches Hg) for 22.25 hours at 43 °C to provide 2.6885 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate. This material was analyzed by powder X-ray diffraction analysis, and the pattern was found to be consistent with Figure 1.

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Example 10

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form A

10 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate, Form B, (304 mg, prepared in Example 6) was placed in a clean crystallization dish, placed in a bell jar containing water, and stored for 36 hours at room temperature to provide Form A. This material was characterized by powder X-ray diffraction analysis, and the pattern was found to be consistent with Figure 1.

15

Example 11

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form A

Part A

20 To DMF (500 mL) at 4 °C, was slowly added phosphorous oxychloride (615 g, 4.01 mol). The resulting pale orange viscous solution was added via cannula into a flask charged with 3-nitro[1,5]naphthyridin-4-ol (590 g, 3.09 mol) in DMF (5.5 L). The reaction was stirred vigorously and maintained at room temperature overnight. The reaction was quenched with cold water (4 L) and stirred for one hour. A tan precipitate formed, and the mixture was extracted with dichloromethane (6 x 500 mL). The
25 combined dichloromethane fractions were washed with brine (500 mL) to provide a solution of 4-chloro-3-nitro[1,5]naphthyridine in dichloromethane, which was used in Part B.

Part B

30 Isobutylamine (565 g, 7.72 mol, 4 equivalents) was slowly added to the solution from Part A. The reaction was quenched by the addition of water (1 L), and the resulting mixture was stirred for 15 minutes and then filtered to provide 45 g of a bright yellow

solid. The filtrate layers were separated, and the organic fraction was concentrated under reduced pressure to provide a yellow solid. The solids were combined and stirred vigorously with water (3 L) for one hour. The yellow solid was then collected by vacuum filtration and dried overnight in a vacuum oven to give 542 g of *N*⁴-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine.

Part C

*N*⁴-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine (542 g) was dissolved in toluene (5 L) and 2-propanol (500 mL) and hydrogenated according to a modification of the method of Part C of Example 2. Initially 50 g of 5% platinum on carbon were added to the reaction, and after hydrogenation was carried out overnight, an additional 25 g were added to reaction mixture. After the reaction mixture was filtered through a layer of CELITE filter agent, the filter cake was washed with toluene until the filtrate was colorless. The filtrate was concentrated to dryness to yield 435 g of *N*⁴-(2-methylpropyl)[1,5]naphthyridin-3,4-diamine as a dark syrup.

Part D

Diethoxymethyl acetate (1.0 equivalent) was added with stirring to a solution of *N*⁴-(2-methylpropyl)[1,5]naphthyridin-3,4-diamine (434 g, 2.01 mol) in toluene (5 L), and the reaction mixture was heated at reflux until the reaction was complete as determined by high-performance liquid chromatography (HPLC) analysis. The reaction mixture was cooled to room temperature and washed with saturated aqueous potassium carbonate (1 L). The organic layer was separated and concentrated to a dark orange syrup, which crystallized upon standing for approximately one hour. The solid was collected by vacuum filtration, rinsed with heptane (250 mL), and air-dried to provide 365 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine, which was used without purification.

Part E

3-Chloroperoxybenzoic acid (549 g of 50% purity, 1.59 mol) was slowly added over a period of 30 minutes to a stirred solution of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (360 g, 1.6 mol) in chloroform (4 L) at room temperature. The reaction was maintained at room temperature overnight and then washed with aqueous

sodium carbonate (4 x 500 mL of a 1% solution). The chloroform layer was concentrated under reduced pressure to a gold syrup, which was triturated with diethyl ether (1 L) for one hour to form a solid. The solid was isolated by filtration to provide 490 g of 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as an off-white solid.

5

Part F

The material from Part E (489 g, 1.22 mol) was dissolved in dichloromethane (5 L) and concentrated ammonium hydroxide (3 L), and the reaction was stirred at room temperature. *p*-Toluenesulfonyl chloride (257 g, 1.34 mol) was added as a solid in portions over one hour; the reaction temperature was 16 °C to 37 °C. After the reaction was stirred for two hours, some starting material remained. Additional *p*-toluenesulfonyl chloride (25 g) was added, and stirring was continued for an additional hour. Water (3 L) was added, and the layers were allowed to separate. The reaction mixture separated into three fractions: aqueous, emulsion and dichloromethane. The dichloromethane layer was removed from flask and concentrated under reduced pressure to a gold syrup. The syrup was heated in acetonitrile (10 mL/g), and upon cooling, an off-white solid precipitated (70 g). The emulsion layer was filtered, and an off-white solid was collected. The solid was washed with water (500 mL) and air-dried (185 g). The solids were combined to yield 255 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. A portion of the product (152 g) was heated at reflux in 10% (v/v) water in methanol (1500 mL) for four hours with vigorous stirring. The reaction mixture was allowed to cool to room temperature, and the resulting white solid was collected by filtration and dried in vacuum oven to provide 132 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

25

Part G

Ethanesulfonic acid (1 equivalent) was added to a mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (3.0 g, 12 mmol) and isopropyl alcohol (40 mL), and the mixture was heated until it became homogeneous. The solution was allowed to cool, and a precipitate formed. The precipitate was isolated by filtration, washed with isopropyl alcohol, and air-dried on the filter funnel to provide 3.4 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate as a white powder. Anal. Calcd. for C₁₃H₁₅N₃•C₂H₆O₃S•H₂O: C, 48.77; H, 6.28; N, 18.96. Found:

30

C, 48.77; H, 6.11; N, 18.77. This sample was characterized by powder X-ray diffraction analysis, TGA, and DSC. The powder X-ray diffraction pattern is shown in Figure 1. The overlay of the TGA and DSC data is shown in Figure 10. A sample of this material was heated to 150 °C to provide Form E. The x-ray diffraction pattern of Form E is shown in Figure 18.

Example 12

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Mixture of Form C and Form B

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (Form C, prepared in Example 1, 1.0 g) was stirred in 2% (v/v) deionized water/isopropyl alcohol (10 mL) and then heated with a mantle at reflux for 15 minutes. The heat was turned off for ten minutes, and then the heating mantle was removed. The solution was allowed to cool to room temperature and further cooled to approximately 0 °C. The resulting solid was collected by vacuum filtration, washed with a small amount of cold 2% (v/v) deionized water/isopropyl alcohol, and dried under vacuum for 24 hours at a temperature of 45 °C to 46 °C to provide 0.90 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate. Anal. Calcd. for $C_{13}H_{15}N_5 \cdot C_2H_6O_3S \cdot H_2O$: C, 48.76; H, 6.30; N, 18.96. Found: C, 48.90; H, 6.18; N, 19.08. This material was characterized by powder X-ray diffraction analysis.

Example 13

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Mixture of Form C and Form B

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine prepared in Example 1, Parts A through G was used as the starting material for this example. A mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (1.0 g, 4.1 mmol) and 2% (v/v) deionized water/isopropyl alcohol (7 mL) was heated to reflux with stirring, and ethanesulfonic acid (0.5 g, 4.5 mmol) was added followed by a 2% (v/v) deionized water/isopropyl alcohol (3 mL) rinse. The resulting solution was heated at reflux for 15 minutes and allowed to cool as described in Example 12 and further cooled to approximately 0 °C. The resulting solid was collected by vacuum filtration, washed

twice with a small amount of cold 2% (v/v) deionized water/isopropyl alcohol, and dried under vacuum for 24 hours at a temperature of 45 °C to 46 °C to provide 1.41 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate. Anal. Calcd. for C₁₃H₁₅N₅•C₂H₆O₃S•H₂O: C, 48.76; H, 6.30; N, 18.96. Found: C, 49.10; H, 6.09; N, 18.97. This material was characterized by powder X-ray diffraction analysis and solid state ¹³C NMR spectroscopy.

Example 14

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form A with a trace of Form B

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate (Form C, prepared in Example 7, 3.18 g) was placed in a clean cell culture dish and heated at 90 °C for about 40 hours to provide Form A with a trace of Form B. This material was analyzed by powder X-ray diffraction analysis, solid state ¹³C NMR spectroscopy, FTIR spectroscopy, and water sorption analysis. The powder X-ray diffraction pattern was found to be consistent with Figure 1, and the ¹³C NMR spectrum, FTIR spectrum, and water sorption isotherm are shown in Figures 2, 3, and 13 respectively.

CYTOKINE INDUCTION IN HUMAN CELLS

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate has been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609," *Journal of Leukocyte Biology*, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4×10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μ M.

Incubation

The solution of test compound is added at 60 μ M to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μ M). The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37 °C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4 °C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at -30 °C to -70 °C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

5 Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

10 CYTOKINE INDUCTION INTRAVAGINALLY

In the examples of the gel formulations below the serum and intravaginal cytokine data were obtained using the following general test method.

15 Rats were acclimated to collars (Lomir Biomedical, Malone, NY) around the neck on two consecutive days prior to actual dosing. Rats were collared to prevent ingestion of the drug. Animals were then dosed intravaginally with 50 μ L of gel. Rats received one intravaginal dose with samples collected at various times following dosing. Blood was collected by cardiac puncture. Blood was allowed to clot briefly at room temperature and serum was separated from the clot via centrifugation. The serum was stored at -20°C until it was analyzed for cytokine concentrations.

20 Following blood collection, the rats were euthanized and their vaginal tract, including the cervix, was then removed and the tissue was weighed, placed in a sealed 1.8 mL cryovial and flash frozen in liquid nitrogen. The frozen vaginal tissue sample was then suspended in 1.0 mL of RPMI medium (Celox, St. Paul, MN) containing 10% fetal bovine serum (Atlas, Fort Collins, CO), 2 mM L-glutamine, penicillin/streptomycin and 2-mercaptoethanol (RPMI complete) combined with a protease inhibitor cocktail set III (Calbiochem, San Diego, CA). The tissue was homogenized using a Tissue Tearor (Biospec Products, Bartlesville, OK) for approximately one minute. The tissue suspension was then centrifuged at 2000 rpm for 10 minutes under refrigeration to pellet the debris, and the supernatant collected and stored at -20°C until analyzed for cytokine concentrations.

ELISA kits for rat tumor necrosis factor-alpha (TNF) were purchased from BD PharMingen (San Diego, CA) and the rat monocyte chemoattractant protein-1 (MCP-1) ELISA kits were purchased from BioSource Intl. (Camarillo, CA). Both kits were performed according to manufacturer's specifications. Results for both TNF and MCP-1 are expressed in pg/mL and are normalized per 200 mg of tissue. The sensitivity of the TNF ELISA, based on the lowest value used to form the standard curve, is 63 pg/mL and for the MCP-1 ELISA it is 12 pg/mL.

VISCOSITY TEST METHOD

In the Examples below the viscosity is determined at 20 ± 0.5 °C using a Haake RS series rheometer equipped with a 35 mm 2° cone using a controlled rate step test between 1 and 80 s^{-1} with an interpolation at 16 s^{-1} for viscosity versus shear rate. The values reported in the Examples are the values at 16 s^{-1} .

Examples 16-18

The gels shown in Table 1 below were prepared using the following method.

Step 1: The parabens were dissolved in propylene glycol. 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate was then dissolved in the solution.

Step 2: Edetate disodium was dissolved in water. Carbomer 974P was dispersed in the solution.

Step 3: The solution from Step 1 was added to the dispersion from Step 2 while mixing. 20% Tromethamine solution was added to the mixture to adjust the pH.

Table 1			
Ingredient	Gels (% w/w)		
	Ex 16	Ex 17	Ex 18
Drug (ethanesulfonate monohydrate)	0.0153	0.0469	0.153
Carbomer 974P	1.50	1.50	1.70
Propylene glycol	15.00	15.00	15.00
Methylparaben	0.15	0.15	0.15
Propylparaben	0.03	0.03	0.03
Edetate disodium	0.05	0.05	0.05
20% Tromethamine solution	0.54	0.85	1.25
Purified water	82.7147	82.5231	81.667
pH	3.8	4.0	4.0
Viscosity (cps)	6000	7000	7000

Examples 19–26

The gels of Examples 19, 20, and 22 were prepared using the general method of Examples 16–18. The gels of Examples 21, 23, 24, 25, and 26 were prepared using the following method.

Step 1: The parabens were dissolved in propylene glycol (approximately 66 wt-% of the total amount used to achieve the final wt-% in the gel). 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate was then dissolved in the solution.

Step 2: Edetate disodium was dissolved in water. The remainder of the propylene glycol was added. Carbomer 974P was added and mixing was continued until the carbomer was completely hydrated.

Step 3: The solution from Step 1 was added to the dispersion from Step 2 while mixing. After mixing was complete the pH was measured.

Table 2								
Ingredient	Gels (% w/w)							
	Ex 19	Ex 20	Ex 21	Ex 22	Ex 23	Ex 24	Ex 25	Ex 26
Drug (ethanesulfonate monohydrate)	0.153	0.153	0.153	0.459	0.459	0.765	1.531	4.593
Carbomer 974P	2.10	2.10	2.10	2.00	2.10	2.10	2.50	2.30
Propylene glycol	15.00	30.00	60.00	30.00	60.00	60.00	60.00	60.00
Methylparaben	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Propylparaben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Edetate disodium	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Tromethamine	0.27	0.27	0.00	0.35	0.00	0.00	0.00	0.00
Purified water	82.25	67.25	37.52	66.96	37.21	36.91	35.74	32.88
pH	4.0	4.2	3.8	4.3	3.6	3.2	2.9	2.5

The gels of Examples 19-26 were found to induce cytokines following a single dose using the test method described above with the following exceptions: the tissue samples were centrifuged at 3000 rpm for 10 minutes, all samples were subject to a dilution factor of 1:2 for TNF and 1:4 for MCP-1, and the sensitivity of the TNF ELISA, based on the lowest value used to form the standard curve, was 31 pg/mL. In addition, the gels of Examples 23, 25, and 26 were found to induce cytokines following a single dose using the test method described above.

Examples 27-31

The gels shown in Table 3 below were prepared using the following method.
 Step 1: The parabens were dissolved in propylene glycol (approximately 66 wt-% of the total amount used to achieve the final wt-% in the gel). 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate was then dissolved in the solution.

Step 2: Edetate disodium was dissolved in water. The remainder of the propylene glycol was added. Carbomer 974P and xanthan gum, if used, were added sequentially and mixing was continued until the thickener(s) was completely hydrated.

Step 3: The solution from Step 1 was added to the dispersion from Step 2 while mixing.

5 After mixing was complete the pH was measured.

Table 3					
Ingredient	Gels (% w/w)				
	Ex 27	Ex 28	Ex 29	Ex 30	Ex 31
Drug (ethanesulfonate monohydrate)	1.531	1.531	1.531	1.531	1.531
Carbomer 974P	1.25	1.50	1.50	2.00	2.50
Xanthan gum	1.75	1.50	1.50	1.00	0.00
Propylene glycol	50.00	50.00	60.00	60.00	60.00
Methylparaben	0.15	0.15	0.15	0.15	0.15
Propylparaben	0.03	0.03	0.03	0.03	0.03
Edetate disodium	0.05	0.05	0.05	0.05	0.05
Purified water	45.24	45.24	35.24	35.24	35.74
pH	3.0	2.8	3.2	3.1	2.9

10 The gels of Examples 27-31 were found to induce cytokines following a single dose using the test method described above.

Examples 32-35

15 The gels of Examples 32-34 were prepared using the general method of Examples 27-31. The gel of Example 35 was prepared using the general method of Examples 16-18 except that the tromethamine was omitted.

Table 4				
Ingredient	Gels (% w/w)			
	Ex 32	Ex 33	Ex 34	Ex 35
Drug (ethanesulfonate monohydrate)	1.531	1.531	1.531	1.531
Carbomer 974P	2.00	1.00	2.00	2.50
Xanthan gum	1.00	2.00	1.00	0.00
Propylene glycol	50.00	50.00	60.00	60.00
Methylparaben	0.15	0.15	0.15	0.15
Propylparaben	0.03	0.03	0.03	0.03
Edetate disodium	0.05	0.05	0.05	0.05
20% Tromethamine solution	1.44	1.00	0.59	0.00
Purified water	43.80	44.24	34.65	35.74
pH	3.4	3.5	3.4	3.1
Viscosity (cps)	11000	7550	ND	ND

ND = not determined

The gels of Examples 32-35 were used to induce cytokines following a single dose using the test method described above.

5

Examples 36-40

The gels of Examples 36-40 were prepared using the general method of Examples 16-18 except that both the carbomer and xanthan gum were added in Step 2.

Table 5					
Ingredient	Gels (% w/w)				
	Ex 36	Ex 37	Ex 38	Ex 39	Ex 40
Drug (ethanesulfonate monohydrate)	0.15	0.45	0.75	1.50	4.50
Carbomer 974P	2.20	2.33	2.50	2.00	1.75
Xanthan gum	1.10	1.17	1.25	1.00	0.88
Propylene glycol	15.00	30.00	30.00	40.00	60.00
Methylparaben	0.15	0.15	0.15	0.15	0.15
Propylparaben	0.03	0.03	0.03	0.03	0.03
Edetate disodium	0.05	0.05	0.05	0.05	0.05
20% Tromethamine solution	0.50	1.25	0.67	1.70	2.00
Purified water	80.82	64.57	64.60	53.57	30.64
pH	4.0	4.0	3.5	3.5	3.0
Viscosity	8900	11000	8600	12000	17000

Example 41

The gel shown in Table 6 below was prepared using the following method.

Step 1: Edetate disodium was dissolved in water (approximately 99 % of the total amount used to achieve the final wt% in the gel).

Step 2: The parabens were dissolved in propylene glycol. 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate was then dissolved in the solution.

Step 3: Carbomer 974P and xanthan gum were added sequentially to the solution from Step 1 while mixing and mixing was continued until the thickeners were completely hydrated.

Step 4: The solution from step 2 was added to the dispersion from step 3 while mixing.

Step 5: Tromethamine was dissolved in water (20% by weight tromethamine) and the solution was added to the gel from step 4 while mixing. Mixing was continued until the gel was uniform. After mixing was complete the pH was measured.

Table 6	
Ingredient	Example 41 Gel (% w/w)
Drug (ethanesulfonate monohydrate)	0.15
Carbomer 974P	2.20
Xanthan gum	1.10
Propylene glycol	15.00
Methylparaben	0.15
Propylparaben	0.03
Edetate disodium	0.05
Tromethamine	0.20
Purified water	81.12
pH	3.8
Viscosity (cps)	10700

Example 42

The gel shown in Table 7 below was prepared using the following method.

5 Step 1: The parabens were dissolved in propylene glycol. 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate was then dissolved in the solution.

Step 2: Edetate disodium was dissolved in water (approximately half of the total amount used to achieve the final wt% in the gel).

10 Step 3: Carbomer 974P, xanthan gum, the solution from step 2, and water (approximately half of the total amount used to achieve the final wt% in the gel) were added sequentially to the solution from Step 1 while mixing and mixing was continued until the thickeners were completely hydrated.

Step 4: Tromethamine was dissolved in water (20% by weight tromethamine) and the
15 solution was added to the gel from step 3 while mixing. Mixing was continued until the gel was uniform. After mixing was complete the pH was measured.

Table 7	
Ingredient	Example 42 Gel (% w/w)
Drug (ethanesulfonate monohydrate)	1.50
Carbomer 974P	2.00
Xanthan gum	1.00
Propylene glycol	40.00
Methylparaben	0.15
Propylparaben	0.03
Edetate disodium	0.05
Tromethamine	0.40
Purified water	54.87
pH	3.6
Viscosity (cps)	7800

Example 43

The gel shown in Table 8 below was prepared using the following method.

Step 1: The parabens were dissolved in propylene glycol. 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate was added in 3 separate portions while mixing. Mixing was continued until the drug was completely dissolved.

Step 2: Edetate disodium was dissolved in water (approximately a third of the total amount used to achieve the final wt% in the gel).

Step 3: Carbomer 974P, xanthan gum, the solution from step 2, and water (approximately two thirds of the total amount used to achieve the final wt% in the gel) were added sequentially to the solution from Step 1 while mixing and mixing was continued until the thickeners were completely hydrated.

Step 4: Tromethamine was dissolved in water (20% by weight tromethamine) and the solution was added to the gel from step 3 while mixing. Mixing was continued until the gel was uniform. After mixing was complete the pH was measured.

Table 8	
Ingredient	Example 43 Gel (% w/w)
Drug (ethanesulfonate monohydrate)	4.50
Carbomer 974P	1.75
Xanthan gum	0.88
Propylene glycol	50.00
Methylparaben	0.15
Propylparaben	0.03
Edetate disodium	0.05
Tromethamine	0.65
Purified water	41.99
pH	3.0
Viscosity (cps)	7100

Other useful formulations are disclosed in copending US application 60/698416.

5

Example 44

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine
ethanesulfonate monohydrate – Form C

Part A

Under a nitrogen atmosphere, a suspension of 3-nitro-1,5-naphthyridin-4-ol (1.00
10 kg, 5.23 mol) in DMF (4.5 L) was cooled in an ice bath. Phosphorous oxychloride (882.5
g, 5.75 mol) was added slowly over a period of one hour while maintaining the
temperature at 16 °C to 20 °C. After the addition was complete, the reaction was stirred
for three hours at a temperature of 20 °C to 24 °C and then added quickly to two portions
of demineralized water (12.5 L each) at 20 °C to 24 °C. During the addition, the
15 temperature of the mixtures was allowed to reach 29.5 °C to 30.5 °C. The resulting
mixtures were cooled to a temperature of approximately 10 °C over a period of 60
minutes. A solid formed in each mixture and was isolated by filtration, and each solid was
washed with demineralized water (2 x 2 L and 1 x 1 L) until the pH of the filtrate equaled
the pH of demineralized water. The tan solid product, 4-chloro-3-nitro[1,5]naphthyridine,
20 contained water and was used in Part B within one hour.

Part B

Isobutylamine (784 g, 10.7 mol) was added to a suspension of the material from Part A in tetrahydrofuran (6 L) over a period of 45 minutes while maintaining a reaction temperature of 17 °C to 27 °C. When the addition was 75% complete, yellow needles
5 formed in the solution. After the addition was complete, the reaction was stirred for 30 minutes at a temperature of 21.5 °C to 22.5 °C and then added with stirring to two portions of demineralized water (12 L each). The resulting mixtures were stirred for 30 minutes. The solid formed in each mixture was isolated by filtration, and each solid was washed with demineralized water (2 x 2 L) until the pH of the filtrate equaled the pH of
10 demineralized water. The solids were then dried overnight on the filter funnels to provide 1.225 kg of *N*⁴-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine as a yellow solid, which was combined with material from another run.

Part C

15 A hydrogenation vessel was charged with a suspension of *N*⁴-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine (0.300 kg, 1.22 mol) in toluene (5 L), and magnesium sulfate (50 g) was added followed by 5% platinum on carbon (15 g) wet with toluene (500 mL). The reaction mixture was placed under hydrogen pressure (3.4 x 10⁵ Pa, 50 psi) on a Parr shaker at room temperature for 20 hours and then filtered through a layer of CELITE
20 filter agent. The filter cake was washed with toluene (500 mL), and the filtrate was concentrated under reduced pressure to a volume of 4.5 L to provide a solution of *N*⁴-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine in toluene.

Part D

25 The solution from Part C was combined with *p*-toluenesulfonic acid monohydrate (11.4 g, 59.9 mmol). The reaction was heated to a temperature of 90 °C, and triethyl orthoformate (0.178 kg, 1.2 mol) was added over a period of 60 minutes. After the addition was complete, the reaction mixture was heated at 100 °C for two hours, and the ethanol distillate (350 mL) was collected. The reaction mixture was cooled to room
30 temperature, stirred overnight, and then treated with aqueous sodium carbonate (1 L of 1% w/w) and stored to provide 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in

toluene and aqueous sodium carbonate. The material was combined with material from two additional runs on the same scale.

Part E.

5 The aqueous layer from the material from Part D was separated, and the toluene solution was washed with deionized water (2.7 L). The toluene layer was separated and concentrated under reduced pressure to a volume of 7 L. The toluene solution was then heated to 50 °C, and peracetic acid (841 mL of 32% w/w in dilute acetic acid) was added over a period of two hours while maintaining the reaction temperature at 45 °C to 55 °C.
10 After the addition was complete, the reaction was heated at 50 °C overnight and then stirred at 40 °C to 50 °C while sodium metabisulfite (137 g in 3.33 L of deionized water) was added over a period of ten minutes. Aqueous sodium hydroxide (0.576 L of 50% w/w in 3.564 L water) was added over a period of 30 minutes. The resulting mixture was stirred for 30 minutes at approximately 50 °C and then cooled to a temperature of
15 approximately 10 °C for one hour. A yellow precipitate was present and was isolated by filtration, washed with deionized water (5 L), dried by suction overnight, and further dried in a vacuum oven at 40 °C to 50 °C for about 24 hours to provide 0.693 kg of 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine as a light yellow solid.

20 Part F

Concentrated aqueous ammonium hydroxide (660 mL) was added to a suspension of 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (0.520 kg, 1.93 mol) in methanol (4.7 L), and the reaction temperature was adjusted to 20 °C. Benzenesulfonyl chloride (0.716 kg, 4.05 mol) was added slowly over a period of 75 minutes while
25 maintaining the reaction temperature below 26 °C with external cooling. After the addition was complete, the reaction was stirred for two hours at approximately 25 °C. Sodium hydroxide (154 g in 2 L of deionized water) was then added to the reaction mixture while maintaining the reaction temperature at approximately 25 °C with external cooling. The resulting mixture was cooled to a temperature less than 10 °C for two hours.
30 A precipitate formed and was isolated by filtration and washed sequentially with 3:2 methanol/deionized water (2 x 500 mL) and deionized water (7.5 L) until the pH of the filtrate was neutral. The filter cake was dried overnight on the filter funnel to provide

0.426 kg of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a light yellow crystalline solid.

Part G

5 A suspension of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (0.300 kg, 1.24 mol) in isopropyl alcohol (10 L) was heated slowly, and water (23 mL, 1.28 mol) was added. Aqueous ethanesulfonic acid (214 g of 70% w/w, 1.36 mol ethanesulfonic acid, 3.6 mol water) was added over a period of ten minutes at 60 °C, and all the solids dissolved. After the addition was complete, the reaction was allowed to heat
10 to 82 °C. The reaction was cooled from 80 °C to 50 °C over a period of three hours (0.17 °C/min) and then allowed to cool to room temperature overnight with slow stirring. White crystals were present. MTBE (10 L) was added, and the mixture was cooled to approximately 5 °C and maintained for two hours. The crystals were collected by filtration, washed with MTBE (10 L), dried overnight on the filter funnel, and further dried
15 in a vacuum oven at 35 °C for three days to provide 372 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate as white needles. This material was characterized by powder X-ray diffraction analysis, TGA, and FTIR spectroscopy, and the data were found to be consistent with those shown in Figures 7, 12, and 9, respectively.

20

Example 45

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate – Form B

Part A

25 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (32.0 g, 0.133 mol, prepared in Example 1 Parts A through G, and 218 g, 0.903 mol, prepared in Example 6 Parts A through F) was combined with isopropyl alcohol (8.325 L). Deionized water (20.6 mL, 1.14 mol) and aqueous ethanesulfonic acid (179.6 g of 70% w/w, 1.14 mol ethanesulfonic acid, 3.0 mol water) were added, and the mixture was heated to reflux
30 and allowed to cool to room temperature slowly overnight with slow stirring. Cold MTBE (8.325 L at -10 °C) was added, and the mixture was stirred for two hours in an ice bath. Solid 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate

was present and was collected by filtration, washed with MTBE (8 L), dried on the filter for four hours, and further dried in a vacuum oven at 35 °C for three days. The filtrate was concentrated under reduced pressure to provide a second crop of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate, which was isolated by
5 filtration. This process was repeated several times, and the second crops were combined and used in Part B.

Part B

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate
10 from Part A (433 g, 1.17 mol) was mixed with deionized water (84.4 g, 4.69 mmol) and isopropyl alcohol (10 L). The mixture was heated to reflux and allowed to cool to room temperature slowly overnight with slow mixing. Cold MTBE (10 L at -10 °C) was added, and the mixture was stirred for two hours in an ice bath. Solid 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate was present and was collected
15 by filtration, washed with MTBE (10 L), dried on the filter for four hours, and further dried in a vacuum oven at 35 °C overnight. The filtrate was concentrated under reduced pressure to provide an additional crop of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate. The process was repeated.

20 Part C

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate (100.0 g, 0.271 mol), recovered from the filtrate from Part B, was mixed with deionized water (1 L) and activated carbon (10 g). The mixture was heated to 95 °C and filtered hot through a layer of CELITE filter agent. The filter cake was washed with hot deionized
25 water (500 mL). The filtrate was cool quickly to 20 °C using an ice bath. Aqueous sodium hydroxide (approximately 30 g of 50% w/w) was added to adjust to a pH greater than 12. The mixture was cooled to 20 °C. A solid was present and was isolated by filtration and dried overnight to provide 32 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. The process was repeated with 387 g of 1-(2-methylpropyl)-
30 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate to provide 121 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

Part D

A mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (50.0 g, 0.207 mol) and isopropyl alcohol (1.5 L) was heated to 60 °C, and aqueous ethanesulfonic acid (35.0 g of 70% w/w, 0.228 mol ethanesulfonic acid, 0.58 mol water) was added. After the addition was complete, the reaction was allowed to heat to 82 °C over a period of 40 minutes. The reaction was maintained at 82 °C for two hours, and 500 mL of isopropyl alcohol was removed by distillation during this time. The heat was removed, and the reaction was allowed to cool without external control to room temperature. After two hours, the reaction temperature was 32 °C, and it was further cooled to 20 °C. A solid was present and was collected by filtration and washed with isopropyl alcohol. Half of the solid was dried in a vacuum oven for 20 hours at 80 °C to provide 27 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate. The material was characterized by powder X-ray diffraction analysis, and the data were found to be consistent with Figure 4. The material was also characterized by FTIR spectroscopy, and the spectrum is shown in Figure 19.

Example 46

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form A

The other half of the solid collected in Part D of Example 45 was air-dried on the filter funnel overnight to provide 29 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate. The material was characterized by powder X-ray diffraction analysis, FTIR spectroscopy, TGA, and DSC and the data were found to be consistent with Figures 1, 3, and 10 respectively.

Example 47

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form D

A mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine, prepared as described in Example 6, (10.0 g, 41.4 mmol) and MTBE (280 mL) was heated to 55 ± 2 °C, and aqueous ethanesulfonic acid (7.2 g of 69.8% w/w, 46 mmol ethanesulfonic acid, 120 mmol water) was added over a period of five minutes followed

by a rinse of additional MTBE (20 mL). The resulting suspension was heated at reflux (55 ± 2 °C) for 105 minutes and then cooled to 5 ± 2 °C at a rate of 1 °C/minute. A solid was present; it was collected by filtration at 5 ± 2 °C, washed with cold (5 °C) MTBE (100 mL and then 50 mL), and dried for 21 hours under vacuum (1.0×10^4 Pa, 100 mbar) at 42 °C to provide 14.1 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate. The material was characterized by powder X-ray diffraction analysis, FTIR spectroscopy, DSC, TGA, and water sorption analysis. The FTIR spectrum is shown in Figure 20. The overlay of the DSC and TGA data is shown in Figure 21, and the water sorption isotherm is shown in Figure 22. The x-ray powder diffraction pattern was found to be consistent with Figure 23.

Example 48

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form D

Part A

Crude 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine, prepared as described in Example 6, Parts A through F, (67.0 g, 0.278 mol) was heated at reflux in *n*-butanol (1340 mL). When the product was dissolved, activated Charcoal (6.7 g) was added, and heating at 116 °C - 118 °C was maintained for 15 minutes. The mixture was then hot-filtered (approximately 112 °C) through CELITE filter agent, and the filter cake was washed with *n*-butanol (200 mL). The filtrate was concentrated to a volume of approximately 800 mL. The resulting yellow solution was then cooled to 3 °C at a rate of 0.5° C/minute and stirred at this temperature overnight. The product crystallized upon cooling. The solid was collected by filtration, washed with cold *n*-butanol (2 x 65 mL), and dried under vacuum at 45 °C to provide 60.9 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

Part B

A mixture of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (20.0 g, 82.9 mmol) and MTBE (560 mL) was heated to 55 ± 2 °C, and aqueous ethanesulfonic acid (14.4 g of 69.8% w/w, 91.3 mmol ethanesulfonic acid, 242 mmol water) was added over a period of five minutes followed by a rinse of additional MTBE

(40 mL). The resulting suspension was heated at reflux (55 ± 2 °C) for 55 minutes and then cooled to 5 ± 2 °C at a rate of approximately 1 °C/minute. A solid was present; it was collected by filtration at 5 ± 2 °C, washed with cold (5 °C) MTBE (200 mL and then 100 mL), and dried for 20.5 hours under vacuum (1.0×10^4 Pa, 100 mbar) at 42 °C to provide 14.1 g of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate. The material was characterized by powder X-ray diffraction analysis, and the pattern was found to be consistent with Figure 23.

Example 49

Preparation of 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate – Form D

A suspension of Form C of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate, prepared in Example 7, (508.6 mg, 1.37 mmol), in *N,N*-dimethylformamide (2 mL, containing a maximum of 50 ppm water) was placed in a reaction tube and stirred for one hour on a Pierce React-Therm III Heating/Stirring Module (model 18935) at 28 °C. Crystals of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate Form A, prepared in Example 10, (2.9 mg, 0.0078 mmol), and Form B, prepared in Example 6, (2.8 mg, 0.0076 mmol) were added, and the resulting slurry was stirred at 28 °C for three weeks. The solids were collected by vacuum filtration on 0.2 micron WHATMAN ashless filter paper and air-dried to provide 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate. The material was characterized by powder X-ray diffraction analysis, and the pattern is shown in Figure 23.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and

embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate in crystalline Form A.
- 5 2. The polymorph of claim 1 having an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, and 26.40 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
- 10 3. The polymorph of claim 2 having an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, 12.77 degrees two-theta, 22.10 degrees two-theta, and 26.40 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
- 15 4. The polymorph of claim 1 having a unit cell with the following crystal interplanar spacings: about 13.76 Angstroms, about 9.60 Angstroms, and about 3.37 Angstroms.
- 20 5. The polymorph of claim 1 having a solid state ^{13}C NMR spectrum having peaks at 144.8 ppm, 124.7 ppm, and 55.9 ppm, wherein each of these values is ± 0.3 ppm.
- 25 6. The polymorph of claim 5 having a solid state ^{13}C NMR spectrum having peaks at 144.8 ppm, 132.0 ppm, 124.7 ppm, and 55.9 ppm, wherein each of these values is ± 0.3 ppm.
- 30 7. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, 12.77 degrees two-theta, 15.87 degrees two-theta, 18.55 degrees two-theta, 19.15 degrees two-theta, 19.46 degrees two-theta, 22.10 degrees two-theta, 24.14 degrees two-theta, 26.40 degrees two-theta, and 28.49 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

8. The polymorph of claim 7 having a solid state ^{13}C NMR spectrum having peaks at 144.8 ppm, 124.7 ppm, and 55.9 ppm, wherein each of these values is ± 0.3 ppm.
- 5 9. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 7.72 degrees two-theta, 9.20 degrees two-theta, 11.63 degrees two-theta, 12.77 degrees two-theta, 15.39 degrees two-theta, 15.87 degrees two-theta, 16.32 degrees two-theta, 17.48 degrees two-theta, 18.55 degrees two-theta, 19.15 degrees two-theta, 19.46 degrees two-theta, 20.96 degrees two-theta, 22.10 degrees two-theta, 22.55 degrees two-theta, 23.00 degrees two-theta, 24.14 degrees two-theta, 24.97 degrees two-theta, 26.40 degrees two-theta, 27.36 degrees two-theta, 28.09 degrees two-theta, 28.49 degrees two-theta, 29.34 degrees two-theta, 30.87 degrees two-theta, 32.20 degrees two-theta, 33.68 degrees two-theta, and 34.21 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
- 10 10. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern substantially as depicted in Figure 1.
- 20 11. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having a solid state ^{13}C NMR spectrum having peaks at 148.3 ppm, 144.8 ppm, 134.1 ppm, 132.0 ppm, 127.5 ppm, 124.7 ppm, 55.9 ppm, 45.8 ppm, 30.4 ppm, 21.3 ppm, and 9.8 ppm, wherein each of these values is ± 0.3 ppm.
- 25 12. The polymorph of claim 11 having an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, and 26.40 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
- 30

13. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having a solid state ^{13}C NMR spectrum substantially as depicted in Figure 2.
- 5 14. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate characterized by at least one of the following;
- an X-ray powder diffraction pattern having peaks at 6.41 degrees two-theta, 9.20 degrees two-theta, 12.77 degrees two-theta, 15.87 degrees two-theta, 18.55 degrees two-theta, 19.15 degrees two-theta, 19.46 degrees two-theta, 22.10 degrees two-theta, 24.14 degrees two-theta, 26.40 degrees two-theta, and 28.49 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta; or
- 10 a solid state ^{13}C NMR spectrum having peaks at 148.3 ppm, 144.8 ppm, 134.1 ppm, 132.0 ppm, 127.5 ppm, 124.7 ppm, 55.9 ppm, 45.8 ppm, 30.4 ppm, 21.3 ppm, and 9.8 ppm, wherein each of these values is ± 0.3 ppm;
- 15 and further characterized by at least one of the following:
- a weight loss of 4.4% to 5.4% over a temperature range of 45 °C to 85 °C as measured by thermogravimetric analysis; or
- an IR spectrum substantially as depicted in Figure 3.
- 20 15. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate in crystalline Form B.
16. The polymorph of claim 15 having an X-ray powder diffraction pattern having peaks at 6.11 degrees two-theta, 15.15 degrees two-theta, and 25.55 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
- 25
17. The polymorph of claim 16 having an X-ray powder diffraction pattern having peaks at 6.11 degrees two-theta, 12.13 degrees two-theta, 15.15 degrees two-theta, 25.55 degrees two-theta, and 27.13 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
- 30

18. The polymorph of claim 15 having a unit cell with the following crystal interplanar spacings: about 14.45 Angstroms, about 5.84 Angstroms, and about 3.48 Angstroms.
- 5 19. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate having an X-ray powder diffraction pattern having peaks at 6.11 degrees two-theta, 6.46 degrees two-theta, 12.13 degrees two-theta, 12.80 degrees two-theta, 15.15 degrees two-theta, 15.95 degrees two-theta, 18.62 degrees two-theta, 19.12 degrees two-theta, 19.52 degrees two-theta, 20.60 degrees two-theta, 21.14 degrees two-theta, 24.21 degrees two-theta, 25.55 degrees two-theta, 27.13 degrees two-theta, and 28.52 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
- 10
20. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate having an X-ray powder diffraction pattern having peaks at 6.11 degrees two-theta, 6.46 degrees two-theta, 7.48 degrees two-theta, 8.76 degrees two-theta, 9.20 degrees two-theta, 10.64 degrees two-theta, 11.62 degrees two-theta, 12.13 degrees two-theta, 12.80 degrees two-theta, 14.77 degrees two-theta, 15.15 degrees two-theta, 15.95 degrees two-theta, 16.48 degrees two-theta, 17.47 degrees two-theta, 18.62 degrees two-theta, 19.12 degrees two-theta, 19.52 degrees two-theta, 19.88 degrees two-theta, 20.60 degrees two-theta, 21.14 degrees two-theta, 21.82 degrees two-theta, 22.24 degrees two-theta, 22.57 degrees two-theta, 22.81 degrees two-theta, 24.21 degrees two-theta, 25.55 degrees two-theta, 26.48 degrees two-theta, 27.13 degrees two-theta, 28.52 degrees two-theta, 29.94 degrees two-theta, 31.39 degrees two-theta, 32.19 degrees two-theta, 33.69 degrees two-theta, and 34.50 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
- 15
- 20
- 25
- 30 21. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate having an X-ray powder diffraction pattern substantially as depicted in Figure 4.

22. A polymorph of 1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine ethanesulfonate characterized by:
- an X-ray powder diffraction pattern having peaks at 6.11 degrees two-theta, 6.46 degrees two-theta, 12.13 degrees two-theta, 12.80 degrees two-theta, 15.15
5 degrees two-theta, 15.95 degrees two-theta, 18.62 degrees two-theta, 19.12 degrees two-theta, 19.52 degrees two-theta, 20.60 degrees two-theta, 21.14 degrees two-theta, 24.21 degrees two-theta, 25.55 degrees two-theta, 27.13 degrees two-theta, and 28.52 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta; and
- 10 an IR spectrum substantially as depicted in Figure 19.
23. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-c][1,5]naphthyridin-4-amine ethanesulfonate monohydrate in crystalline Form C.
- 15 24. The polymorph of claim 23 having an X-ray powder diffraction pattern having peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, and 16.70 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
- 20 25. The polymorph of claim 24 having an X-ray powder diffraction pattern having peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, 16.70 degrees two-theta, 18.11 degrees two-theta, and 26.02 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
- 25 26. The polymorph of claim 23 having a unit cell with the following crystal interplanar spacings: about 12.66 Angstroms, about 8.42 Angstroms, and about 5.30 Angstroms.
- 30 27. The polymorph of claim 23 having a solid state ^{13}C NMR spectrum having peaks at 127.5 ppm, 126.0 ppm, and 122.9 ppm, wherein each of these values is ± 0.3 ppm.

28. The polymorph of claim 27 having a solid state ^{13}C NMR spectrum having peaks at 131.9 ppm, 127.5 ppm, 126.0 ppm, 122.9 ppm, and 56.2 ppm, wherein each of these values is ± 0.3 ppm.
- 5 29. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern having peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, 10.70 degrees two-theta, 16.70 degrees two-theta, 18.11 degrees two-theta, 18.88 degrees two-theta, 21.11 degrees two-theta, 26.02 degrees two-theta, and 28.51 degrees two-theta, wherein
10 each of these values is ± 0.15 degree two-theta.
30. The polymorph of claim 29 having a solid state ^{13}C NMR spectrum having peaks at 127.5 ppm, 126.0 ppm, and 122.9 ppm, wherein each of these values is ± 0.3 ppm.
- 15 31. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern having peaks at 6.98 degrees two-theta, 8.96 degrees two-theta, 10.50 degrees two-theta, 10.70 degrees two-theta, 11.60 degrees two-theta, 14.46 degrees two-theta, 16.70
20 degrees two-theta, 17.27 degrees two-theta, 18.11 degrees two-theta, 18.47 degrees two-theta, 18.88 degrees two-theta, 20.57 degrees two-theta, 21.11 degrees two-theta, 21.39 degrees two-theta, 22.52 degrees two-theta, 23.04 degrees two-theta, 23.35 degrees two-theta, 23.84 degrees two-theta, 24.35 degrees two-theta, 26.02 degrees two-theta, 27.33 degrees two-theta, 27.92 degrees two-theta, 28.51 degrees
25 two-theta, 29.42 degrees two-theta, 30.19 degrees two-theta, 31.47 degrees two-theta, 31.80 degrees two-theta, 32.45 degrees two-theta, 33.02 degrees two-theta, and 33.73 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
- 30 32. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern

substantially as depicted in Figure 7.

33. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having a solid state ¹³C NMR spectrum having peaks
5 at 148.0 ppm, 134.2 ppm, 131.9 ppm, 131.0 ppm, 127.5 ppm, 126.0 ppm, 122.9 ppm, 56.2 ppm, 45.5 ppm, 29.7 ppm, 21.8 ppm, and 10.5 ppm, wherein each of these values is ± 0.3 ppm.
34. The polymorph of claim 33 having an X-ray powder diffraction pattern having
10 peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, and 16.70 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
35. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having a solid state ¹³C NMR spectrum substantially
15 as depicted in Figure 8.
36. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate characterized by at least one of the following;
20 an X-ray powder diffraction pattern having peaks at 6.98 degrees two-theta, 10.50 degrees two-theta, 10.70 degrees two-theta, 16.70 degrees two-theta, 18.11 degrees two-theta, 18.88 degrees two-theta, 21.11 degrees two-theta, 26.02 degrees two-theta, and 28.51 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta; or
a solid state ¹³C NMR spectrum having peaks at 148.0 ppm, 134.2 ppm,
25 131.9 ppm, 131.0 ppm, 127.5 ppm, 126.0 ppm, 122.9 ppm, 56.2 ppm, 45.5 ppm, 29.7 ppm, 21.8 ppm, and 10.5 ppm, wherein each of these values is ± 0.3 ppm;
and further characterized by at least one of the following:
a weight loss of 4.3% to 5.3% over a temperature range of 70 °C to 100 °C
as measured by thermogravimetric analysis; or
30 an IR spectrum substantially as depicted in Figure 16.

37. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate in crystalline Form D.
38. The polymorph of claim 37 having an X-ray powder diffraction pattern having peaks at 7.35 degrees two-theta, 8.68 degrees two-theta, and 12.61 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
39. The polymorph of claim 33 having an X-ray powder diffraction pattern having peaks at 6.33 degrees two-theta, 7.35 degrees two-theta, 8.68 degrees two-theta, 12.61 degrees two-theta, and 17.35 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
40. The polymorph of claim 37 having a unit cell with the following crystal interplanar spacings: about 12.02 Angstroms, about 10.18 Angstroms, and about 7.02 Angstroms.
41. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern having peaks at 6.33 degrees two-theta, 7.04 degrees two-theta, 7.35 degrees two-theta, 8.68 degrees two-theta, 12.61 degrees two-theta, 14.74 degrees two-theta, 15.82 degrees two-theta, 17.35 degrees two-theta, 19.80 degrees two-theta, 21.68 degrees two-theta, and 24.12 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.
42. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern having peaks at 6.33 degrees two-theta, 7.04 degrees two-theta, 7.35 degrees two-theta, 8.68 degrees two-theta, 10.61 degrees two-theta, 11.68 degrees two-theta, 12.61 degrees two-theta, 14.74 degrees two-theta, 15.82 degrees two-theta, 17.35 degrees two-theta, 18.08 degrees two-theta, 18.93 degrees two-theta, 19.80 degrees two-theta, 21.20 degrees two-theta, 21.68 degrees two-theta, 22.02 degrees two-theta, 22.81 degrees two-theta, 23.06 degrees two-theta, 24.12 degrees two-theta, 25.25

degrees two-theta, 26.23 degrees two-theta, 27.31 degrees two-theta, 27.64 degrees two-theta, 28.21 degrees two-theta, 29.51 degrees two-theta, 30.03 degrees two-theta, 31.02 degrees two-theta, 31.47 degrees two-theta, 32.30 degrees two-theta, and 34.39 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta.

43. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate having an X-ray powder diffraction pattern substantially as depicted in Figure 23.

44. A polymorph of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate monohydrate characterized by:

an X-ray powder diffraction pattern having peaks at 6.33 degrees two-theta, 7.04 degrees two-theta, 7.35 degrees two-theta, 8.68 degrees two-theta, 12.61 degrees two-theta, 14.74 degrees two-theta, 15.82 degrees two-theta, 17.35 degrees two-theta, 19.80 degrees two-theta, 21.68 degrees two-theta, and 24.12 degrees two-theta, wherein each of these values is ± 0.15 degree two-theta;

and further characterized by at least one of the following:

a weight loss of 4.2% to 5.2% over a temperature range of 55 °C to 95 °C as measured by thermogravimetric analysis; or

an IR spectrum substantially as depicted in Figure 20.

45. A mixture of two or more polymorphs of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5] naphthyridin-4-amine ethanesulfonate as described in claims 1 through 44.

46. A pharmaceutical composition prepared by a method comprising combining a pharmaceutically acceptable carrier and a polymorph of any one of claims 1 through 44 or a mixture of claim 45 in an amount effective to provide a therapeutically effective amount of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.

47. A pharmaceutical composition comprising a therapeutically effective amount of a polymorph of any one of claims 1 through 44 or a mixture of claim 45.
- 5 48. A method of treating a neoplastic disease in an animal comprising administering a pharmaceutical composition of claim 46 or claim 47.
49. A method of treating a viral disease in an animal comprising administering a pharmaceutical composition of claim 46 or claim 47.
- 10 50. A method of inducing cytokine biosynthesis in an animal comprising administering a pharmaceutical composition of claim 46 or claim 47.
51. A method for preparing a crystalline form of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate, the method comprising:
- 15 combining the free base of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine with ethanesulfonic acid and a carrier to form a mixture, wherein the carrier comprises an organic liquid and optionally water;
- heating the free base, ethanesulfonic acid, and/or carrier prior to combining them, and/or heating the mixture thereof; and
- 20 forming a precipitate in the mixture.
52. The method of claim 51 wherein forming a precipitate comprises cooling the mixture to form a precipitate.
- 25 53. The method of claim 52 wherein cooling occurs at a rate less than 2.0 °C per minute.
54. The method of claim 53 wherein the carrier comprises at least 2 moles of water per mole of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine free base present.
- 30

55. The method of claim 52 or 53 wherein the crystalline form of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate is Form C.
56. The method of claim 52 wherein cooling occurs at a rate greater than or equal to 2.0 °C per minute.
57. The method of claim 56 wherein the carrier comprises 1 vol-% to 15 vol-% water in an organic liquid.
58. The method of claim 56 or claim 57 wherein the crystalline form of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate is Form A.
59. The method of claim 51 wherein the carrier comprises at least 2 moles of water per mole of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine free base present.
60. The method of claim 59 wherein the crystalline form of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate is either Form A or Form C.
61. The method of any one of claims 51, 54, 57, and 59 wherein the organic liquid is a C₁₋₄ alcohol.
62. The method of claim 51 wherein the carrier comprises less than 1 vol-% water.
63. The method of claim 59 wherein the organic liquid is ethyl acetate.
64. The method of claim 63 wherein the crystalline form of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate is Form C.

65. The method of claim 51 wherein combining comprises adding ethanesulfonic acid to the free base in the carrier.
66. The method of claim 51 further comprising:
5 optionally adding an additional organic liquid to the mixture comprising the precipitate;
separating at least a portion of the precipitate from at least a portion of the mixture;
washing the precipitate; and
10 at least partially drying the precipitate.
67. The method of claim 66 wherein the additional organic liquid is an ether.
68. The method of claim 67 wherein the additional organic liquid is *tert*-butyl methyl
15 ether.
69. The method of claim 68 wherein 1-(2-methylpropyl)-1*H*-imidazo[4,5-
c][1,5]naphthyridin-4-amine ethanesulfonate is prepared in crystalline Form B or
crystalline Form C.
20
70. The method of claim 66 wherein at least partially drying the precipitate occurs at a temperature range of 25 °C to 60 °C.
71. The method of claim 70 wherein at least partially drying the precipitate occurs
25 under at least a partial vacuum.
72. A method of obtaining crystalline Form C of 1-(2-methylpropyl)-1*H*-imidazo[4,5-
c][1,5]naphthyridin-4-amine ethanesulfonate from crystalline Form B, the method comprising:
30 combining Form B with a carrier comprising an organic liquid and
optionally water to form a mixture; and
agitating the mixture for a time sufficient to provide at least a portion of 1-

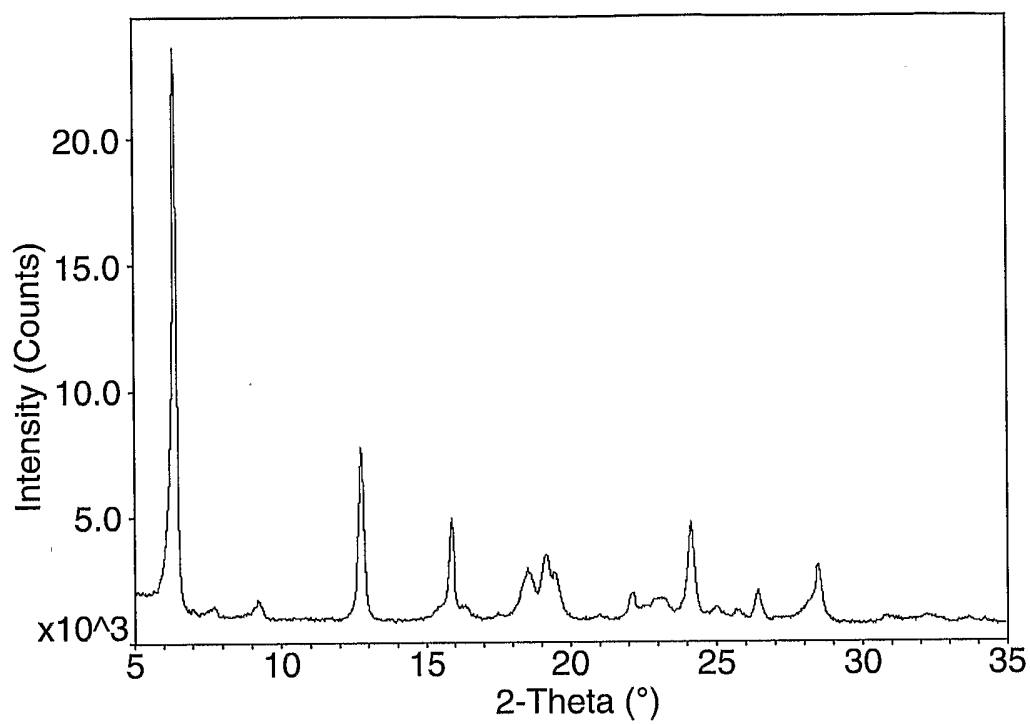
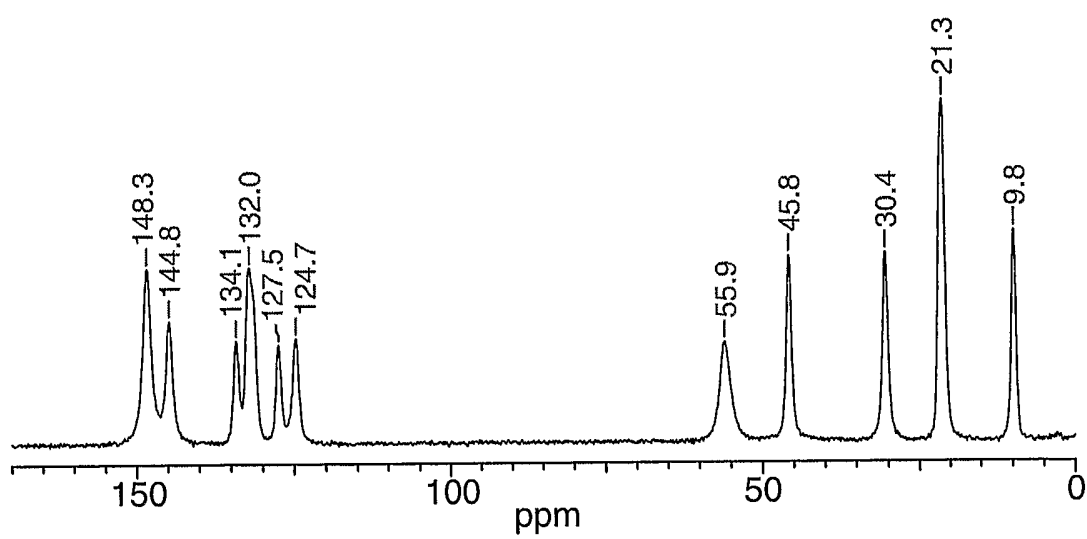
(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate in crystalline Form C.

- 5 73. The method of claim 72 wherein the carrier comprises water, isopropyl alcohol, or *tert*-butyl methyl ether.
74. The method of claim 73 wherein the carrier contains 2% to 5% water, 5% to 10% isopropyl alcohol, and 85% to 93% *tert*-butyl methyl ether.
- 10 75. The method of claim 72 wherein the mixture is agitated for at least 8 hours.
76. The method of claim 72 further comprising separating at least a portion of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate from at least a portion of the mixture.
- 15 77. The method of claim 76 further comprising washing and at least partially drying 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate.
- 20 78. A method of obtaining crystalline Form A of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate from crystalline Form B, the method comprising exposing Form B to an atmosphere comprising water vapor.
79. The method of claim 78 wherein the atmosphere comprising water vapor has at least 30% relative humidity.
- 25 80. A method of forming crystalline Form B of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate from crystalline Form A, the method comprising removing at least a portion of the water from crystalline Form A.
- 30 81. The method of claim 80 wherein removing water from crystalline Form A comprises exposing crystalline Form A to a desiccant.

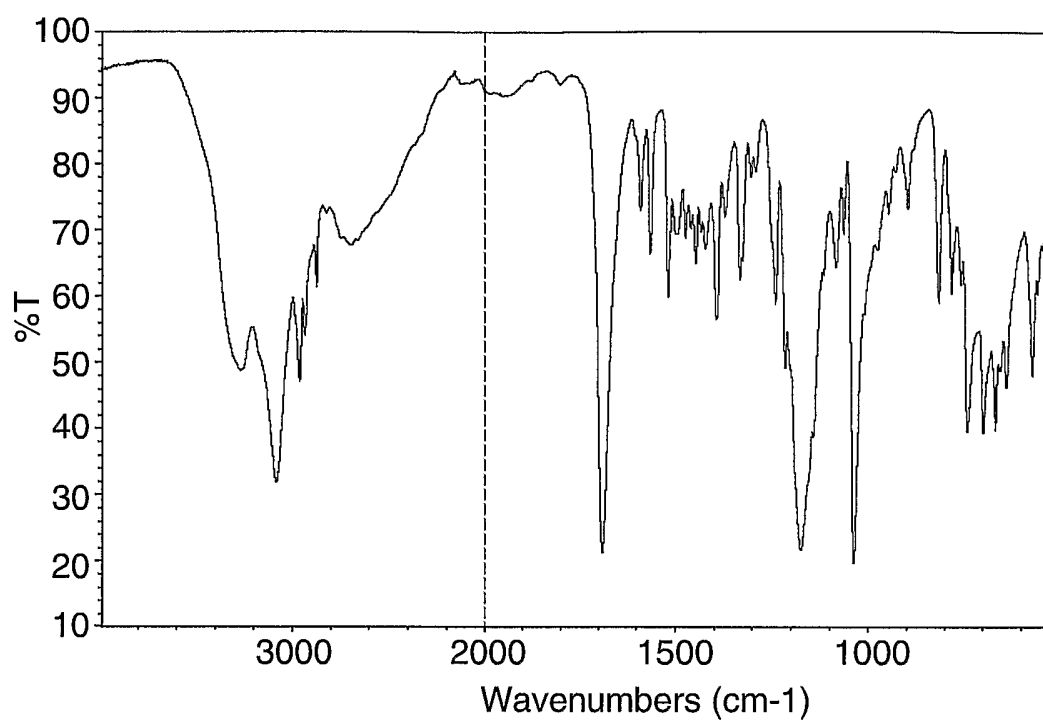
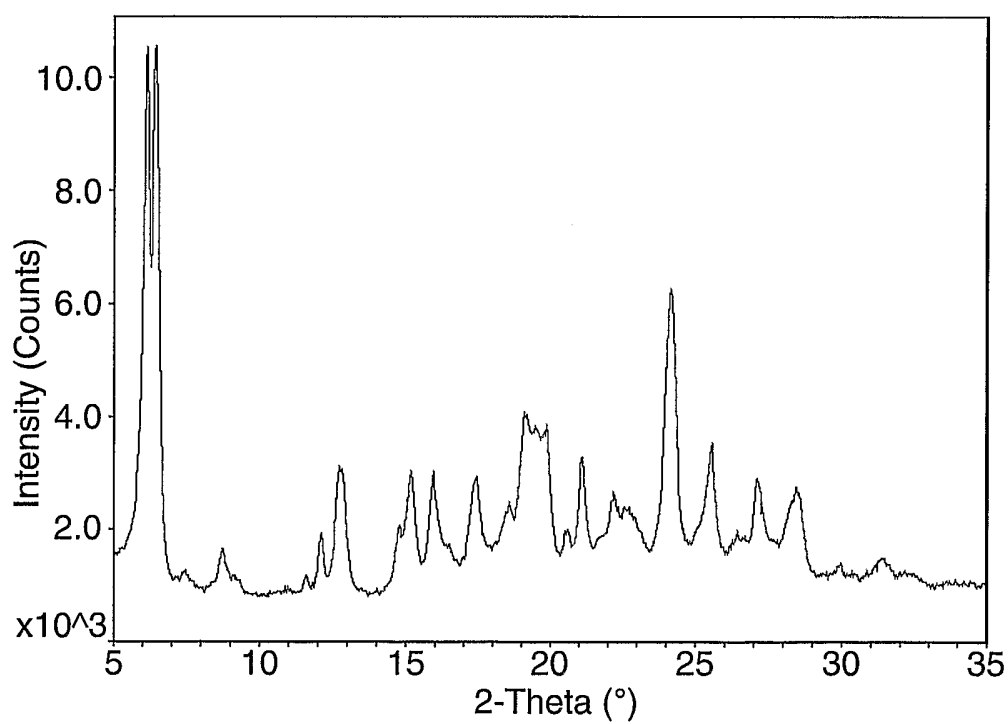
82. The method of claim 80 wherein removing water from Form A comprises exposing Form A to at least a partial vacuum.
83. The method of claim 81 or claim 82 further comprising heating crystalline Form A for a period of time and temperature sufficient to convert at least a portion of crystalline Form A to crystalline Form B.
84. The method of claim 83 wherein heating crystalline Form A is carried out at a temperature greater than or equal to 40 °C.
85. A method for preparing 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine, the method comprising:
- providing 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in a carrier comprising a lower alcohol;
 - combining the 1-(2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridine in the carrier with an ammonia- or ammonium-containing reagent to form a first mixture;
 - combining an arylsulfonyl halide with the first mixture to form a second mixture;
 - allowing the components of the second mixture to react for a period of time sufficient to form 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine; and
 - combining the second mixture with an aqueous base.
86. The method of claim 85 wherein the ammonia- or ammonium- containing reagent comprises ammonium hydroxide in water.
87. The method of claim 85 wherein the arylsulfonyl halide is benzenesulfonyl chloride or *p*-toluenesulfonyl chloride.

88. The method of claim 85 wherein the ammonia- or ammonium- containing reagent is added prior to the arylsulfonyl halide.
89. The method of claim 85 wherein the aqueous base comprises aqueous sodium hydroxide.
90. The method of claim 85 further comprising separating at least a portion of resultant 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine from at least a portion of the second mixture.
91. The method of claim 90 further comprising washing and at least partially drying the resultant 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.
92. A process for making a pharmaceutical composition containing 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate comprising the step of adding crystalline 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine ethanesulfonate in polymorph Form A, B, C, D, or E as part of a composition manufacturing process.
93. The process of claim 92, wherein Form C of the polymorph is used.
94. The process of claim 92 or 93, wherein the polymorph Form A, B, C, D, or E is tested and controlled for.

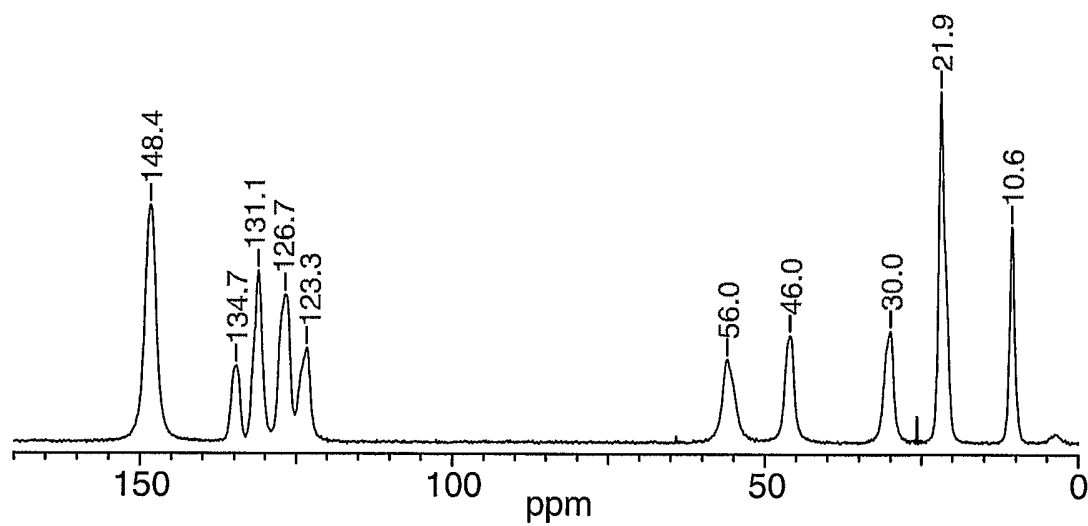
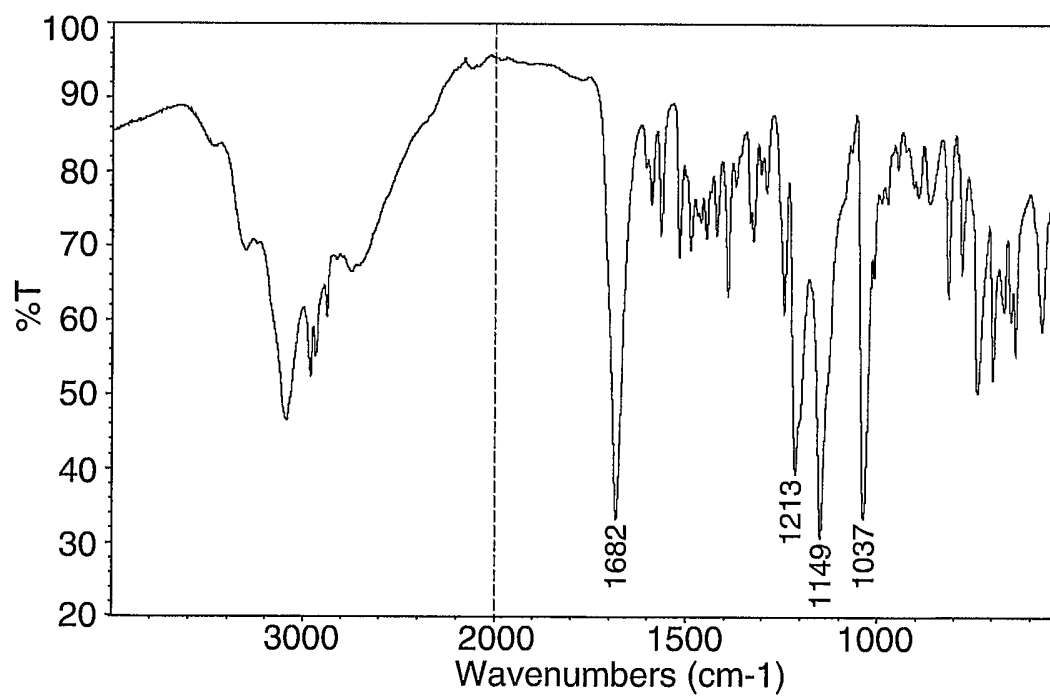
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*Fig. 1**Fig. 2*

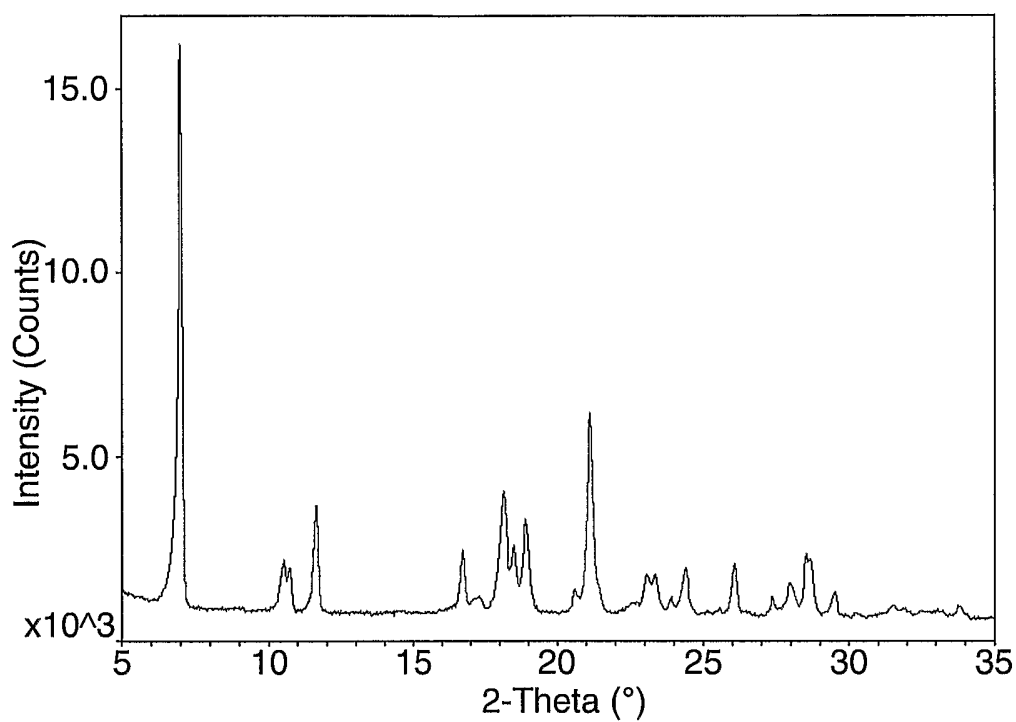
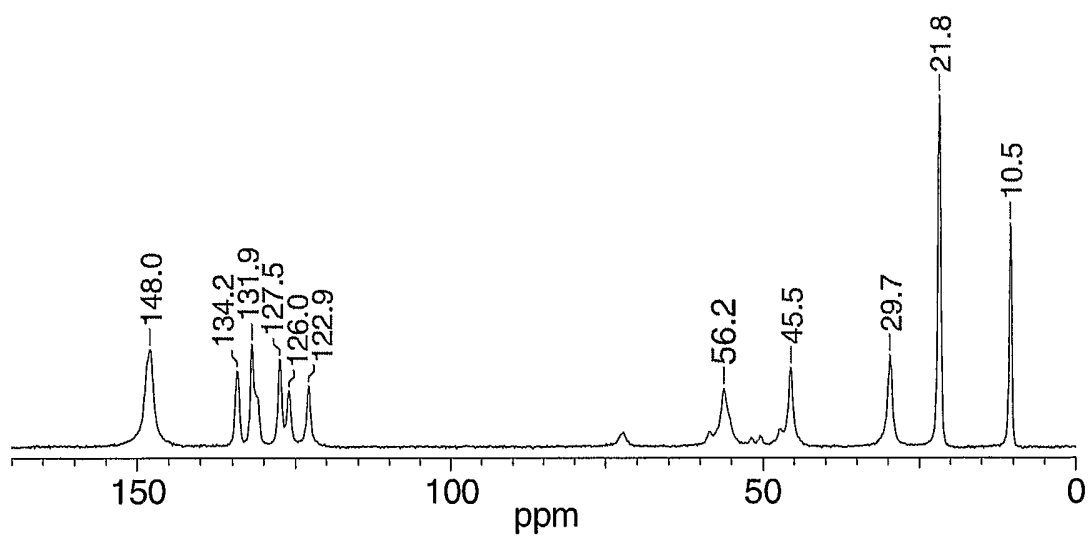
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*Fig. 3**Fig. 4*

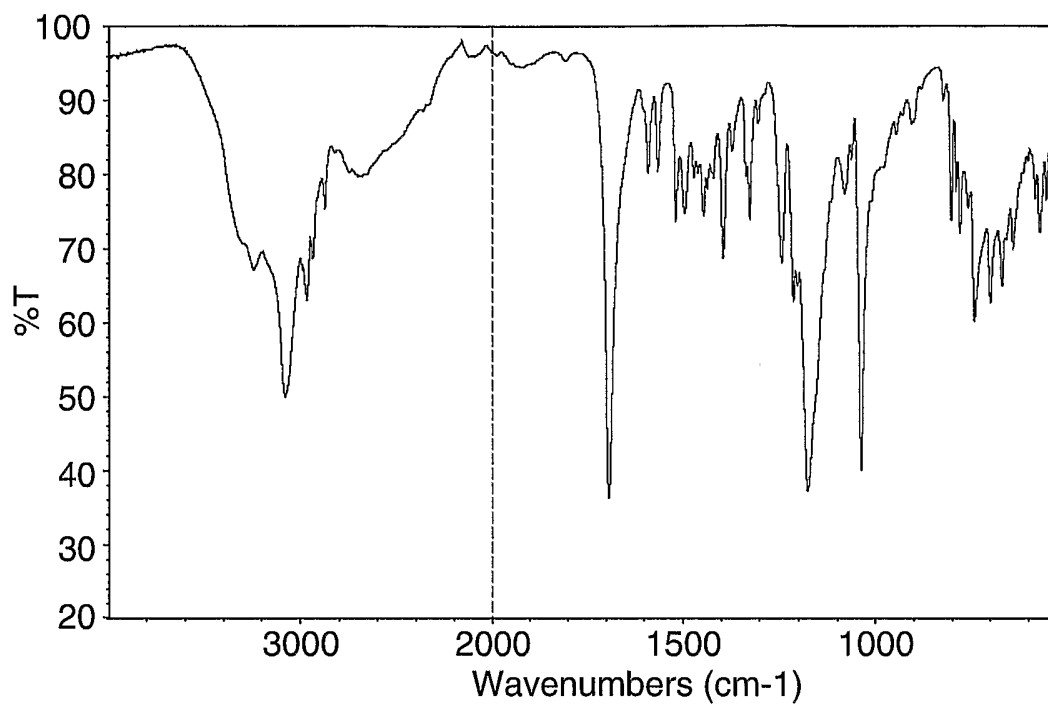
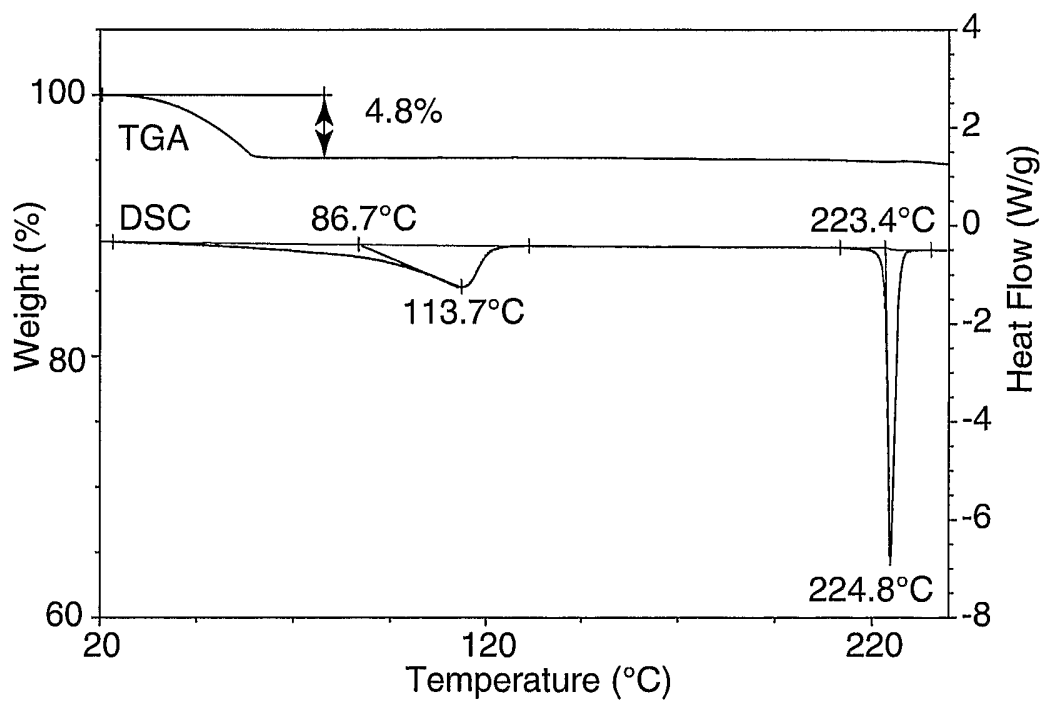
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*Fig. 5**Fig. 6*

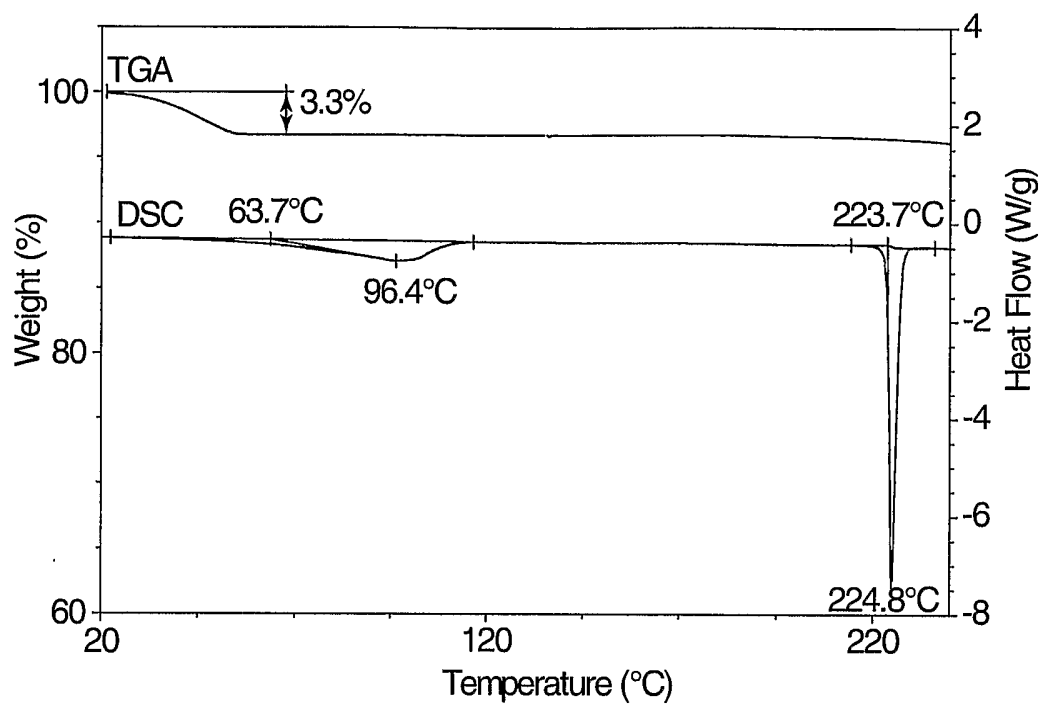
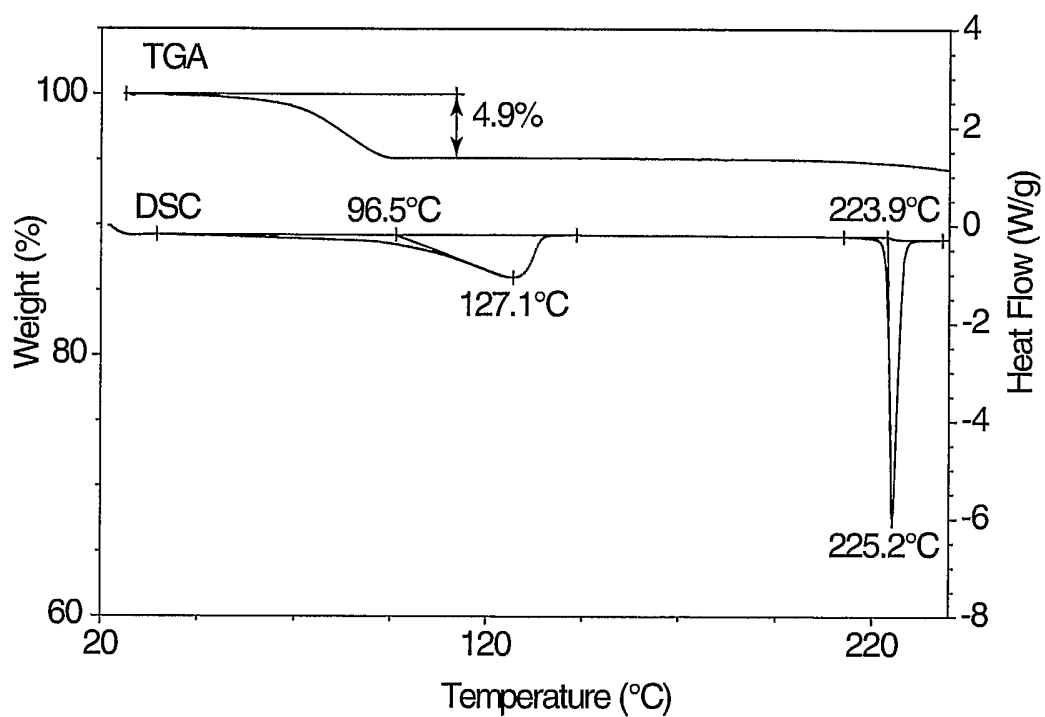
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*Fig. 7**Fig. 8*

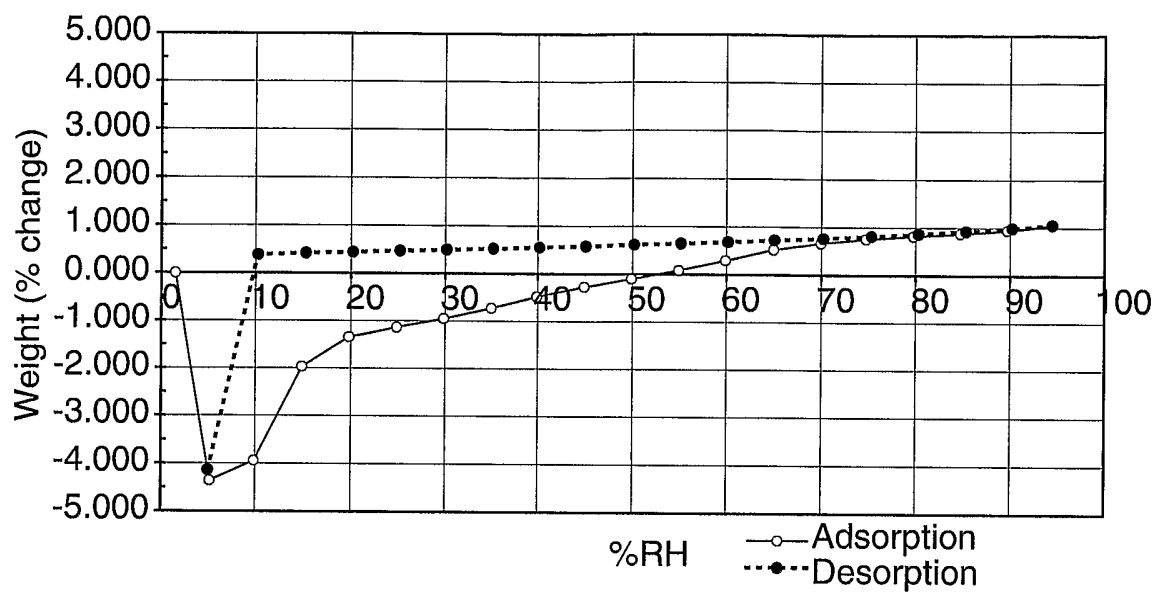
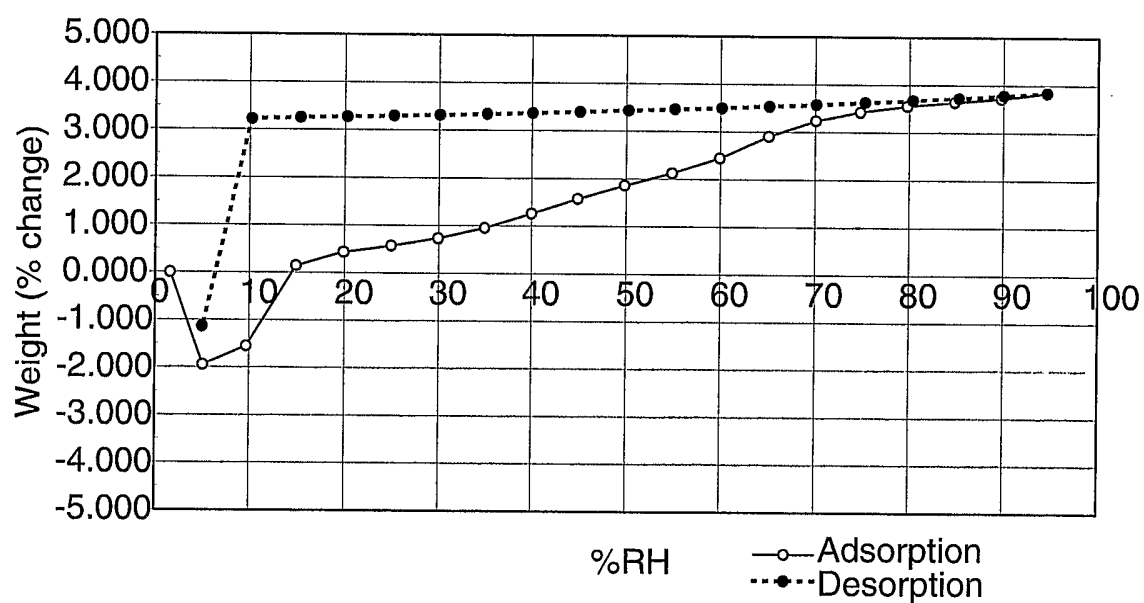
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*Fig. 9**Fig. 10*

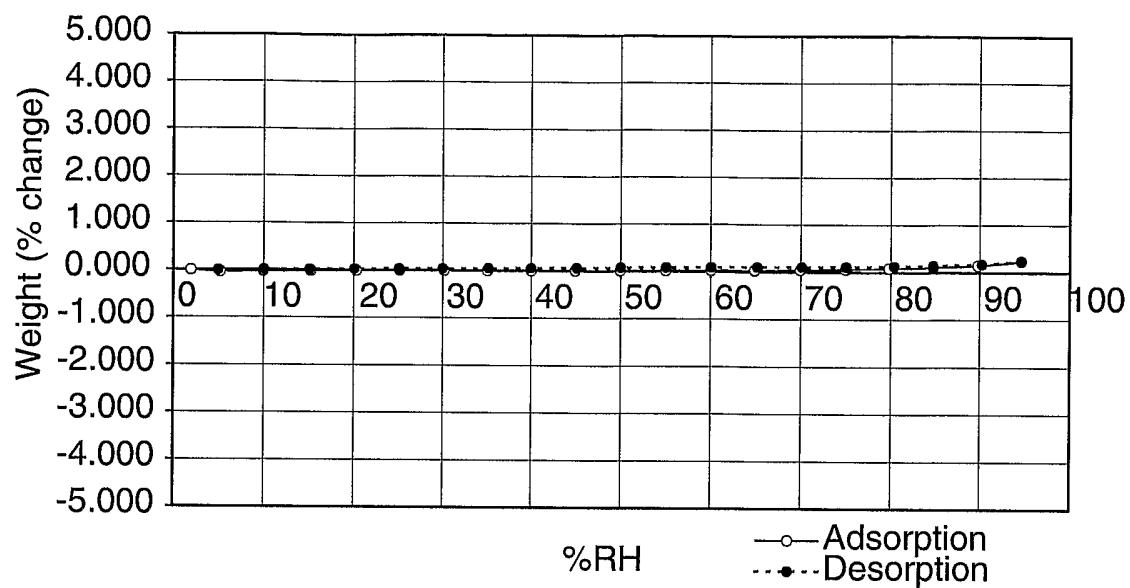
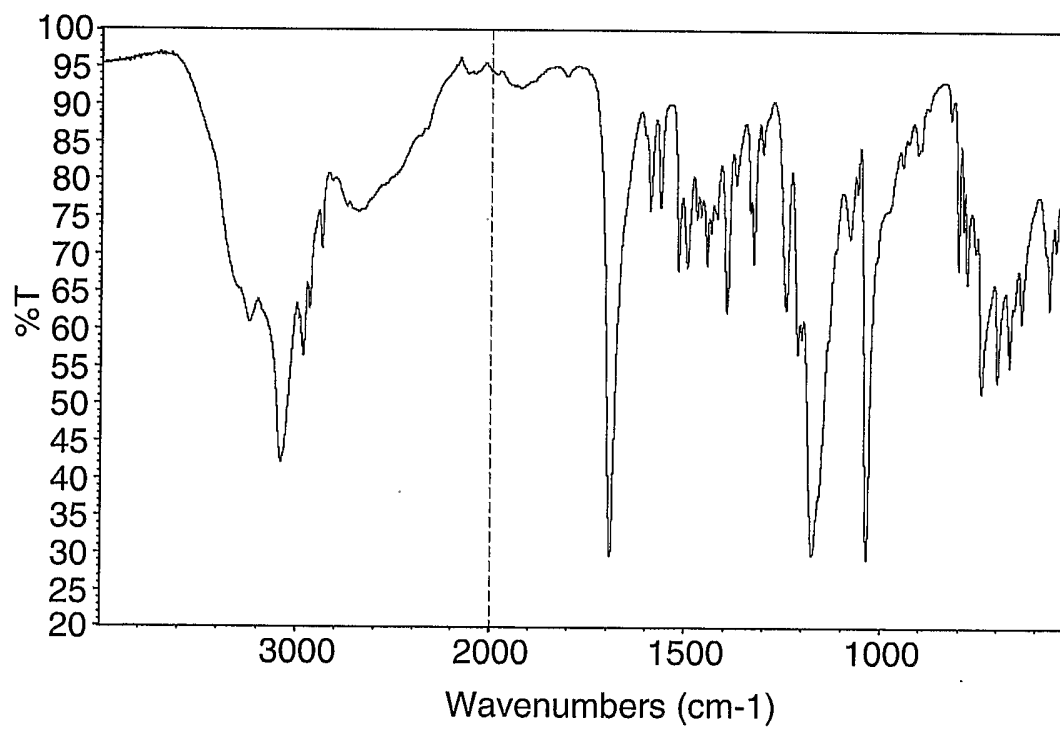
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*Fig. 11**Fig. 12*

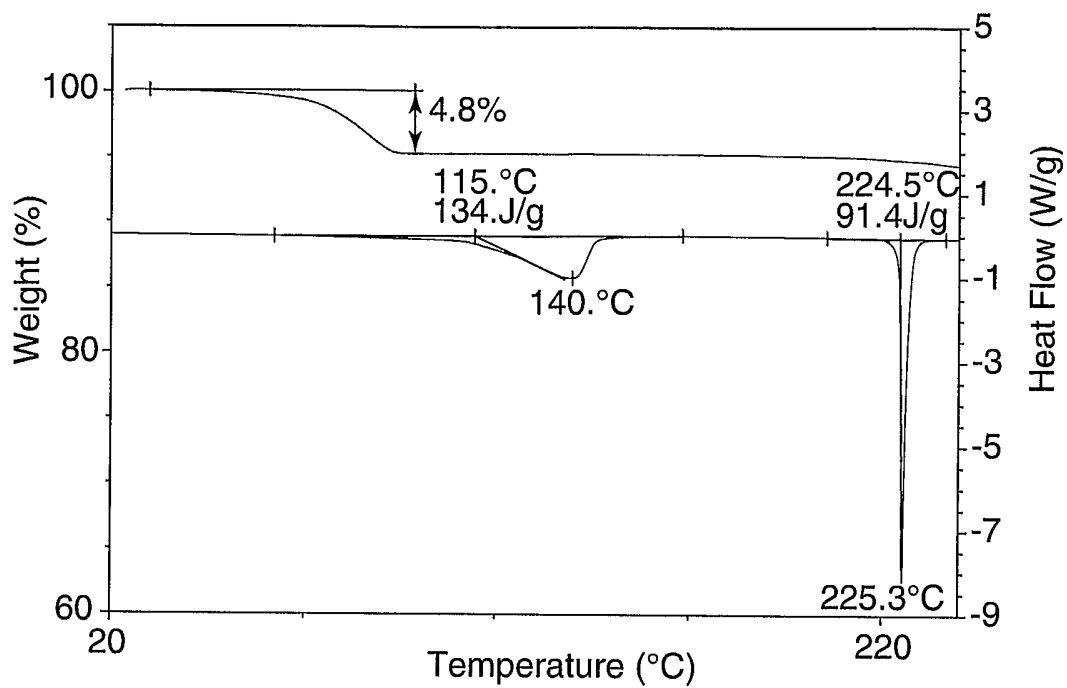
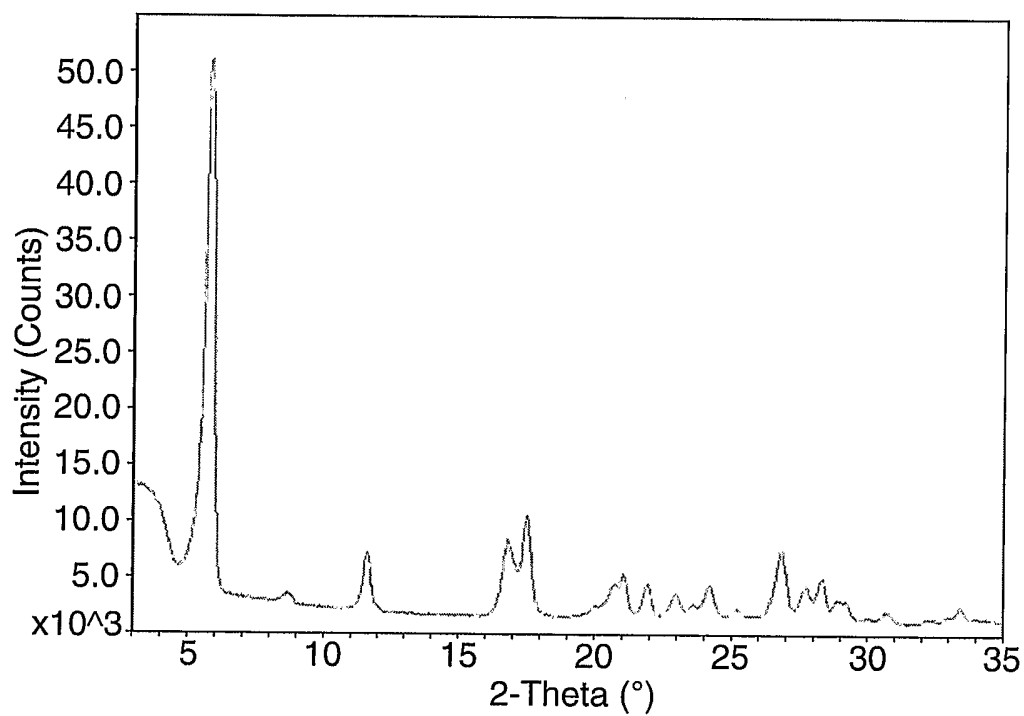
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*Fig. 13**Fig. 14*

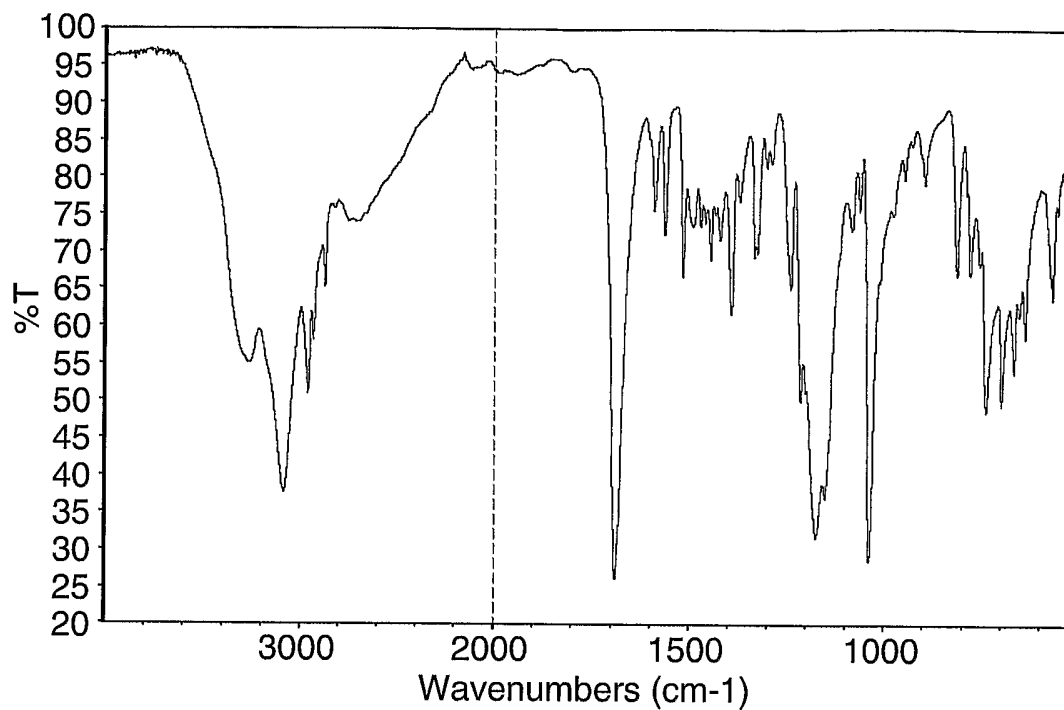
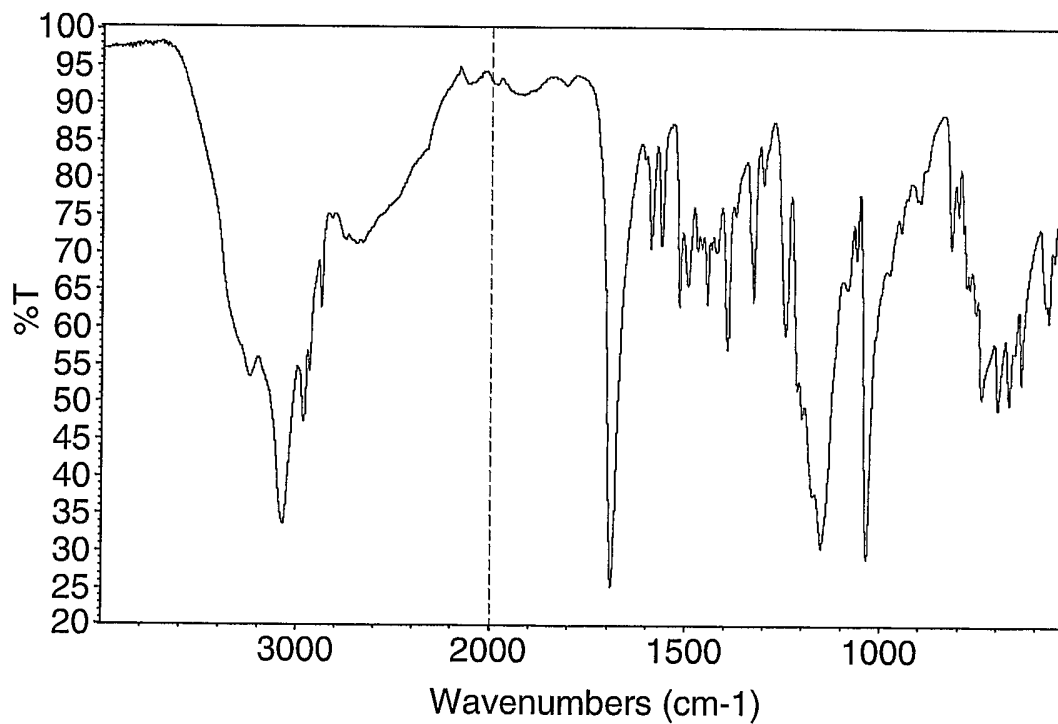
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*Fig. 15**Fig. 16*

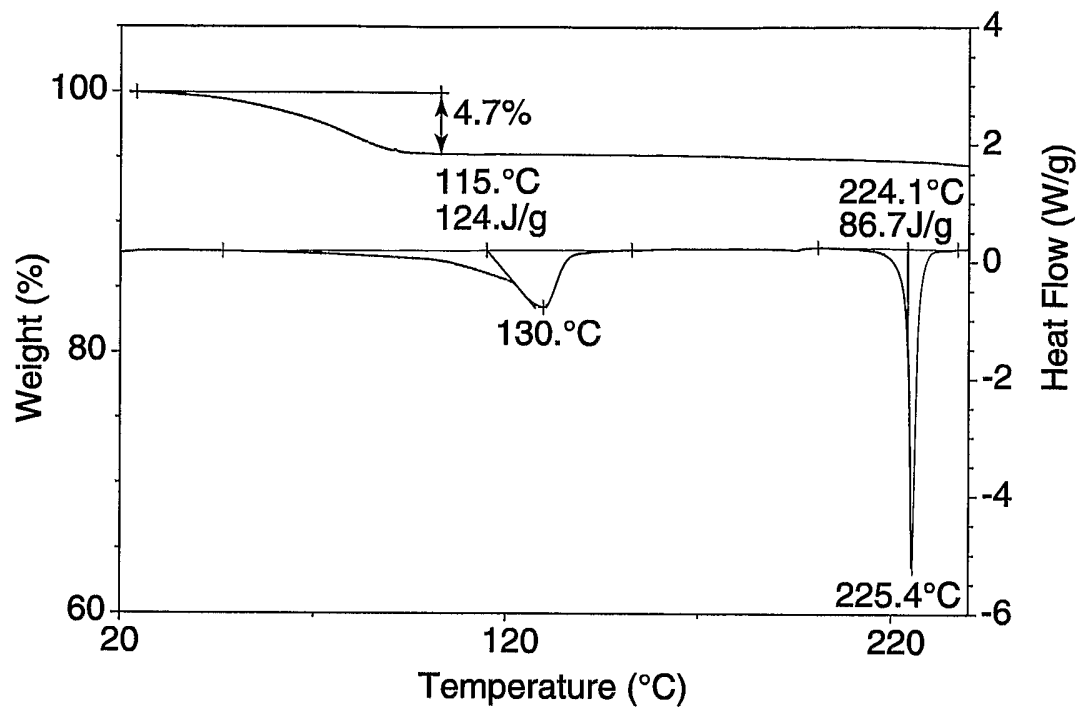
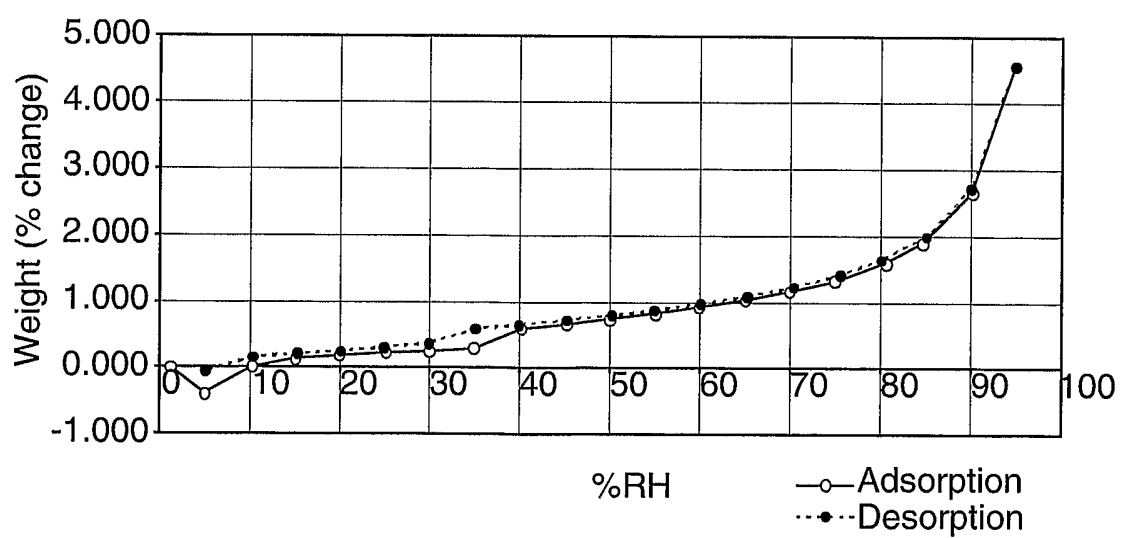
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*Fig. 17**Fig. 18*

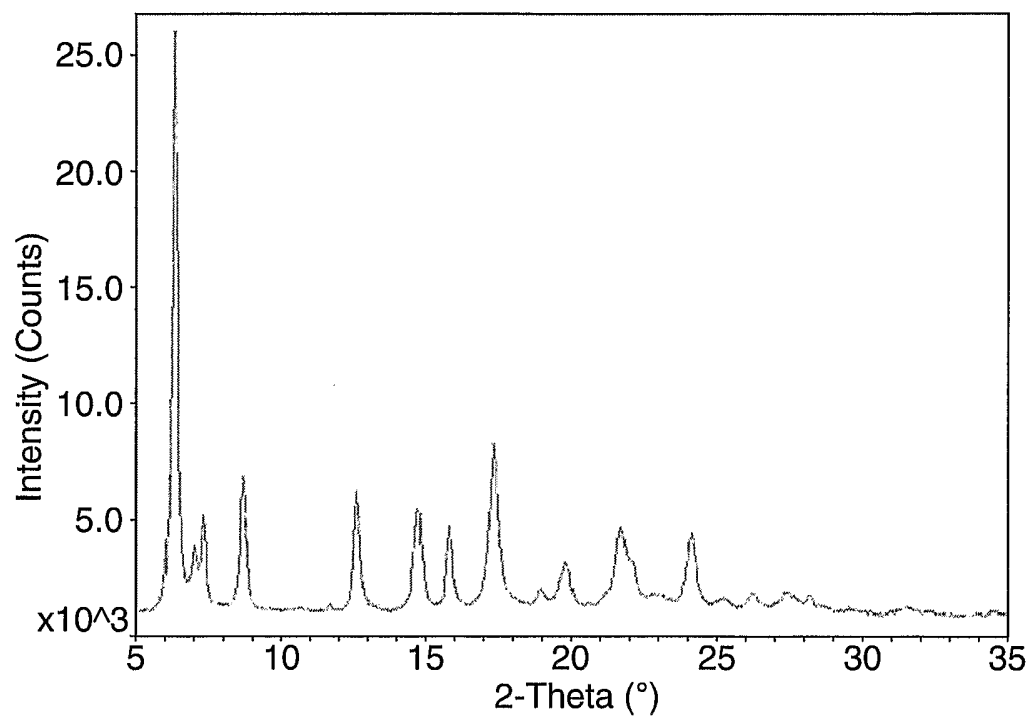
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*Fig. 19**Fig. 20*

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*Fig. 21**Fig. 22*

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*Fig. 23*