

CLAIMS

WHAT IS CLAIMED IS:

1. A crystalline salt or co-crystal of 2',6-difluoro-5'-[3-(1-hydroxy-1-methylethyl)-imidazo[1,2-b][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile with phosphoric acid, wherein the crystalline salt or co-crystal has at least one of the following properties:
 - (a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in FIG. 19, when measured using the parameters described in Table 1;
 - (b) an XRPD pattern substantially the same as shown in FIG. 1, when measured using the parameters described in Table 1;
 - (c) an XRPD pattern having characteristic peak locations of at least three values selected from the group consisting of: about 6.4, 7.5, 10.2, 12.7, 13.3, 14.5, 16.0, 17.1, 17.4, 17.9, 18.5, 19.1, 19.7, 20.3, 20.9, 21.5, 22.6, 23.7, 26.2, 26.7, 26.9, 27.5, 28.4, 30.2, and 32.1 ± 0.2 degrees, 2-theta, when measured using the parameters described in Table 1;
 - (d) an XRPD pattern having characteristic peak locations of at least three values selected from the group consisting of: about 6.4, 7.5, 12.7, 13.3, 17.1, 17.4, 18.5, 19.1, 19.7, 26.7, 30.2, and 32.1 ± 0.2 degrees, 2-Theta, when measured using the parameters described in Table 1;
 - (e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in FIG. 2A;
 - (f) a DSC thermogram with an endothermic peak at about 205°C;
 - (g) stable for at least a week at about 40° C; and
 - (h) stable for at least a week at about 25° C.
2. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal provides an XRPD pattern substantially the same as shown in FIG. 19, when measured using the parameters described in Table 1.
3. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal provides an XRPD pattern substantially the same as shown in FIG. 1, when measured using the parameters described in Table 1.
4. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal provides an XRPD pattern having characteristic peak locations of at least three values selected from the group consisting of: about 6.4, 7.5, 10.2, 12.7, 13.3, 14.5, 16.0, 17.1, 17.4, 17.9, 18.5, 19.1, 19.7, 20.3, 20.9, 21.5, 22.6, 23.7, 26.2, 26.7, 26.9, 27.5, 28.4, 30.2,

- and 32.1 ± 0.2 degrees, 2-theta, when measured using the parameters described in Table 1.
5. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal provides an XRPD pattern having characteristic peak locations of at least six values selected from the group consisting of: about 6.4, 7.5, 10.2, 12.7, 13.3, 14.5, 16.0, 17.1, 17.4, 17.9, 18.5, 19.1, 19.7, 20.3, 20.9, 21.5, 22.6, 23.7, 26.2, 26.7, 26.9, 27.5, 28.4, 30.2, and 32.1 ± 0.2 degrees, 2-theta, when measured using the parameters described in Table 1.
 6. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal provides an XRPD pattern having characteristic peak locations of at least three values selected from the group consisting of: about 6.4, 7.5, 12.7, 13.3, 17.1, 17.4, 18.5, 19.1, 19.7, 26.7, 30.2, and 32.1 ± 0.2 degrees, 2-Theta, when measured using the parameters described in Table 1.
 7. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal provides a DSC thermogram substantially the same as shown in FIG. 2A.
 8. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal provides a DSC thermogram with an endothermic peak at about 205°C.
 9. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal is stable for at least a month at about 40° C.
 10. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal is stable for at least a month at about 25° C.
 11. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal provides substantially the same XRPD pattern post-storage at 40° C and 75% RH for at least a week.
 12. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal provides substantially the same XRPD pattern post-storage at 40° C and 75% RH for at least two weeks.
 13. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal is a salt.
 14. The crystalline salt or co-crystal of claim 1, wherein the crystalline salt or co-crystal is a co-crystal.
 15. A crystalline polymorph of 2',6-difluoro-5'-[3-(1-hydroxy-1-methylethyl)-imidazo[1,2-b][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile, of Form C, providing an X-ray Powder Diffraction (XRPD) pattern having characteristic peak locations of at least three values selected from the group consisting of about: 5.4, 10.8, 12.3, 12.6, 13.5, 14.8, 15.9, 16.3,

- 16.4, 17.3, 17.8, 19.3, 20.4, 21.5, 21.7, 22.7, 23.4, 24.4, 24.7, 25.0, 26.1, 26.6, 27.0, 27.2, 27.5, 28.4, 28.7, 29.0, 29.6, 30.2, and 32.3 ± 0.2 -degrees, 2-theta, when measured using the parameters described in Table 1.
16. The crystalline polymorph of claim 15, wherein the crystalline polymorph exhibits an XRPD pattern having characteristic peak locations of at least three values selected from the group consisting of about: 5.4, 10.8, 12.3, 12.6, 13.5, 14.8, 16.2, 17.3, 19.3, 20.4, 21.7, 22.7, 23.4, 24.4, 25.0, 27.2, 29.6, and 32.2 ± 0.2 degrees, 2-theta, when measured using the parameters described in Table 1.
17. The crystalline polymorph of claim 15 or 16, wherein the crystalline polymorph provides an XRPD pattern substantially the same as an XRPD pattern labelled as Form C in FIG. 12.
18. The crystalline polymorph of any one of claims 15 to 17, wherein the crystalline polymorph has a differential scanning calorimetry (DSC) thermogram comprising an endothermic peak at about 210 °C.
19. The crystalline polymorph of any one of claims 15 to 18, wherein the crystalline polymorph has a DSC thermogram substantially the same as shown in FIG. 13.
20. A crystalline polymorph of 2',6-difluoro-5'-[3-(1-hydroxy-1-methylethyl)-imidazo[1,2-b][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile, of Form B, providing an X-ray Powder Diffraction (XRPD) Pattern having characteristic peak locations of at least three values selected from the group consisting of about: 7.4, 7.7, 10.0, 13.2, 17.2, 20.4, and 29.9 ± 0.2 degrees, 2-theta, when measured using the parameters described in Table 1.
21. The crystalline polymorph of claim 20, providing an XRPD pattern substantially the same as shown in Figure 11.
22. The crystalline polymorph of claim 20 or 21, wherein the crystalline polymorph is an ethanol solvate.
23. A crystalline salt or co-crystal of 2',6-difluoro-5'-[3-(1-hydroxy-1-methylethyl)-imidazo[1,2-b][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile with toluenesulfonic acid providing an X-ray Powder Diffraction (XRPD) pattern having characteristic peak locations of at least three values selected from the group consisting of about: 7.0, 12.4, 12.6, 13.0, 14.1, 15.4, 15.7, 16.3, 17.5, 18.3, 19.0, 21.0, 22.3, 23.0, and 24.9 ± 0.2 degrees, 2-theta, when measured using the parameters described in Table 1.
24. The crystalline salt or co-crystal of claim 23, providing an XRPD pattern substantially the same as shown in Figure 17.
25. The crystalline salt or co-crystal of claim 23 or 24, wherein the crystalline salt or co-crystal is a hydrate or solvate.

26. The crystalline salt or co-crystal of any one of claims 23 to 25, wherein the crystalline salt or co-crystal provides a differential scanning calorimetry (DSC) thermogram comprising an endothermic peak at about 170°C.
27. The crystalline salt or co-crystal of any one of claims 23 to 26, wherein the crystalline salt or co-crystal provides a DSC thermogram substantially the same as shown in Figure 18.
28. A therapeutic or prophylactic composition comprising a compound according to any one of claims 1-27.
29. A method of treating a condition or a disorder in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound according to any of claims 1-27 or a composition according to claim 28 to said subject.
30. The method of claim 29, wherein the condition or disorder is associated with $\alpha 2/\alpha 3$ GABAA receptor.
31. The method of claim 29, wherein the condition or disorder is selected from: pain, anxiety, epilepsies, muscle spasms, pruritus, itch, cognitive impairment, alcohol dependence, drug addition, schizophrenia, depression, autism, panic disorder, and generalized anxiety disorder.
32. The method of claim 31, wherein the condition or disorder is pain.
33. The method of claim 32, wherein the pain is Fibromyalgia, Inflammatory pain, Neuropathic pain, Peripheral Diabetic Neuropathy, Chemotherapy induced pain, HIV associated Neuropathy, Post-herpetic neuralgia, Musculoskeletal pain, Rheumatoid arthritis, Osteoarthritis, Post-operative pain, Burn pain, Sunburn pain, or Phantom limb pain.
34. The method of claim 31, wherein the condition or disorder is itch.
35. The method of claim 34, wherein the itch is Chronic Itch, Neurogenic itch, Uremic Pruritus, Neurodermatitis, Notalgia Paresthetica, Atopic Dermatitis, Prurigo Nodularis, Psoriasis, Psychogenic itch or Aquagenic Itch.
36. The method of claim 31, wherein the condition or disorder is epilepsy.
37. The method of claim 36, wherein the epilepsy is Focal epilepsy, Generalized epilepsy, Dravet Syndrome, Childhood absence epilepsy (CEA), Juvenile absence epilepsy, Juvenile myoclonic epilepsy (JME), West Syndrome, Lennox-Gastaut syndrome (LGS), Sunflower Syndrome, Staticus epilepticus, Nerve agent induced seizures, Tremors from alcohol withdrawal, Traumatic Brain Injury, Tuberous Sclerosis Complex, Doose Syndrome, Rasmussen's Syndrome, Early myoclonic encephalopathy, Malignant migrating partial seizures of infancy, Epilepsy with continuous spike and waves during

slow wave sleep, Landau-Kleffner syndrome, Benign epilepsy with centrotemporal spikes, Benign familial neonatal infantile seizures, Cortical dysplasia focal epilepsy syndrome, Generalized epilepsy with febrile seizure plus (GEFS+), Myoclonic atonic epilepsy, Malignant migrating partial seizures of infancy, Ohtahara syndrome (a.k.a. early infantile epileptic encephalopathy), or Partial epilepsy and febrile seizures plus.

38. The method of claim 31, wherein the condition or disorder is autism.
39. The method of claim 38, wherein the autism is an autism resulting from SCN2a mutation, fragile X syndrome, or autism related to ion-channel dysfunction.
40. A method for preparing a crystalline salt or co-crystal of 2',6-difluoro-5'-[3-(1-hydroxy-1-methylethyl)-imidazo[1,2-b][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile with phosphoric acid, the method comprising
 crystallizing 2',6-difluoro-5'-[3-(1-hydroxy-1-methylethyl)-imidazo[1,2-b][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile phosphate from a solution comprising one or more of: ethyl acetate, methyl ethyl ketone, 2-methyl butanone, dimethyl sulfoxide, dimethylformamide, dimethyl acetamide, acetone, water, tetrahydrofuran (THF), 2-methyl-THF, isopropyl acetate (IPAC), acetonitrile, and dichloromethane,
 wherein the crystalline salt or co-crystal provides an X-ray Powder Diffraction (XRPD) pattern having characteristic peak locations of at least three values selected from the group consisting of: about 6.4, 7.5, 10.2, 12.7, 13.3, 14.5, 16.0, 17.1, 17.4, 17.9, 18.5, 19.1, 19.7, 20.3, 20.9, 21.5, 22.6, 23.7, 26.2, 26.7, 26.9, 27.5, 28.4, 30.2, and 32.1 ± 0.2 degrees, 2-theta, when measured using the parameters described in Table 1.
41. The method of claim 40, wherein the crystalline salt or co-crystal provides an XRPD pattern having characteristic peak locations of at least three values selected from the group consisting of: about 6.4, 7.5, 12.7, 13.3, 17.1, 17.4, 18.5, 19.1, 19.7, 26.7, 30.2, and 32.1 ± 0.2 degrees, 2-Theta, when measured using the parameters described in Table 1.
42. The method of claim 40 or 41, wherein the crystalline salt or co-crystal provides an XRPD pattern substantially the same as shown in FIG. 19, when measured using the parameters described in Table 1.