

GABAA POSITIVE ALLOSTERIC MODULATOR COMPOUNDS, METHODS OF MAKING, AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/659,226, filed April 18, 2018, which is hereby incorporated by reference in its entirety.

SUMMARY

[0001a] In one aspect, the present disclosure refers to 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.

[0001b] In another aspect, the present disclosure refers to 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.

[0001c] In yet another aspect, the present disclosure refers to 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.

[0001d] In a further aspect, the present disclosure refers to 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.

[0001e] In another aspect, the present disclosure refers to a therapeutic or prophylactic composition comprising a crystalline salt or co-crystal according to any one of claims 1-14 and 23-27 or a crystalline polymorph according to any one of claims 15-22.

[0001f] In yet another aspect, the present disclosure refers to a use of a crystalline salt or co-crystal according to any one of claims 1-14 and 23-27 or a crystalline polymorph according to any one of claims 15-22 or a composition according to claim 28, in the manufacture of a medicament for treating a condition or a disorder in a subject in need thereof.

[0001g] In a further aspect, the present disclosure refers to a crystalline salt or co-crystal according to any one of claims 1-14 and 23-27 or a crystalline polymorph according to any one of claims 15-22 or a composition according to claim 28, for use in therapy.

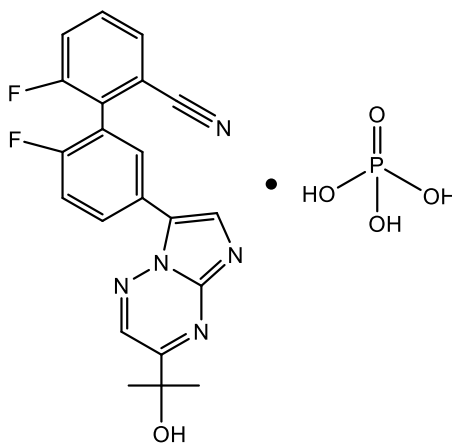
[0001h] In another aspect, the present disclosure refers to a method for preparing a crystalline salt or co-crystal of 2',6-difluoro-5'-[3-(1-hydroxy-1-methylethyl)-imidazo[1,2-b][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile with phosphoric acid, the method comprising

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, 2θ , when measured using the parameters described in Table 1.

[0002] The present disclosure generally pertains to salts and polymorphs of 2',6-difluoro-5'-[3-(1-hydroxy-1-methylethyl)-imidazo[1,2-b][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile (designated herein as TPA023B), including but not limited to stable polymorphs of the salt of TPA023B with phosphoric acid:



MW: $489.37 \text{ g}\cdot\text{mol}^{-1}$

MF: $\text{C}_{21}\text{H}_{15}\text{F}_2\text{N}_5\text{O} \cdot \text{H}_3\text{PO}_4$

[0003] Polymorphs of the free base compound are also described. These polymorphs are suitable for use as the active pharmaceutical ingredient of products intended for therapeutic use in either humans or animals, and also as chemical intermediates in the synthesis of active pharmaceutical ingredients.

[0004] In one example, disclosed herein is 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, 2θ , 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 $32.1 \pm$

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. In some examples, 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. In some examples, 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. In some examples, 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. In some examples, 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. In some examples, 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. In some examples, the crystalline salt or co-crystal provides a DSC thermogram substantially the same as shown in FIG. 2A. In some examples, the crystalline salt or co-crystal provides a DSC thermogram with an endothermic peak at about 205°C. In some examples, the crystalline salt or co-crystal is stable for at least a month at about 40° C. In some examples, the crystalline salt or co-crystal is stable for at least a month at about 25° C. In some examples, 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. In some examples, 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. In some examples, the crystalline salt or co-crystal is a salt. In some examples, the crystalline salt or co-crystal is a co-crystal.

[0005] In another example, disclosed herein is 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. In some examples, 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. In some examples, the crystalline polymorph provides an XRPD pattern substantially the same as an XRPD pattern labelled as Form C in FIG. 12. In some examples, the crystalline polymorph has a differential scanning calorimetry (DSC) thermogram comprising an endothermic peak at about 210 °C. In some examples, the crystalline polymorph has a DSC thermogram substantially the same as shown in FIG. 13. 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. In some examples, the crystalline polymorph provides an XRPD pattern substantially the same as shown in Figure 11. In some examples, the crystalline polymorph is an ethanol solvate.

[0006] In yet another example, disclosed herein is 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. In some examples, the crystalline salt or co-crystal provides an XRPD pattern substantially the same as shown in Figure 17. In some examples, the crystalline salt or co-crystal is a hydrate or solvate. In some examples, the crystalline salt or co-crystal provides a differential scanning calorimetry (DSC) thermogram comprising an endothermic peak at about 170°C. In some examples, the crystalline salt or co-crystal provides a DSC thermogram substantially the same as shown in Figure 18.

[0007] In one example, disclosed herein is a therapeutic or prophylactic composition comprising a described compound.

[0008] In another example, disclosed herein is 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 or a composition described herein to said subject. In some examples, the condition or disorder is associated with $\alpha 2/\alpha 3$ GABAA receptor. In some examples, 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. In some examples, the condition or disorder is pain. In some examples, 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. In some examples, the condition or disorder is itch. In some examples, the itch is Chronic Itch, Neurogenic itch, Uremic Pruritus, Neurodermatitis, Atopic Dermatitis, Prurigo Nodularis, Notalgia Parasthetica, Psoriasis, Psychogenic itch or Aquagenic Itch. In some examples, the condition or disorder is epilepsy. In some examples, 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. In some examples, the condition or disorder is autism. In some examples, the autism is an autism resulting from SCN2a mutation, fragile X syndrome, or autism related to ion-channel dysfunction.

[0009] In one example, disclosed herein is 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. In some examples, 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. In some examples, 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.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0010] Figure 1 illustrates an XRPD pattern for TPA023B phosphate Form A
- [0011] Figures 2A-2C illustrate a DSC/TGA thermogram for TPA023B phosphate Form A (Figure 2A); an NMR spectrum of TPA023B phosphate Form A (Figure 2B); and an additional DSC/TGA thermogram for TPA023B phosphate Form A (Figure 2C)
- [0012] Figure 3 illustrates an XRPD pattern for TPA023B Phosphate Pattern B
- [0013] Figure 4 illustrates an DSC/TGA thermogram for TPA023B phosphate Pattern B
- [0014] Figure 5 illustrates an XRPD pattern for TPA023B free base Form C
- [0015] Figure 6 illustrates a DSC/TGA thermogram for TPA023B free base Form C
- [0016] Figure 7 illustrates an XRPD pattern for TPA023B phosphate mixture comprising TPA023B Phosphate Form A
- [0017] Figure 8 illustrates a DSC/TGA thermogram for TPA023B phosphate mixture comprising TPA023B Phosphate Form A
- [0018] Figure 9 illustrates an XRPD pattern for TPA023B freebase Form A
- [0019] Figures 10A and 10B illustrate a DSC/TGA thermogram for TPA023B freebase Form A (Figure 10A); and an NMR spectrum of TPA023B freebase Form A (Figure 10B)
- [0020] Figure 11 illustrates an XRPD pattern for TPA023B freebase Form B
- [0021] Figure 12 illustrates an XRPD pattern for TPA023B freebase Form C
- [0022] Figure 13 illustrates a DSC thermogram for TPA023B freebase Form C
- [0023] Figure 14 illustrates an XRPD pattern for TPA023B freebase mixture comprising free base Form A
- [0024] Figure 15 illustrates an XRPD pattern for TPA023B chloride Pattern A
- [0025] Figure 16 illustrates a DSC/TGA thermogram for TPA023B chloride Pattern A
- [0026] Figures 17A and 18B illustrate an XRPD pattern for TPA023B tosylate Form A

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 crystalline salt or co-crystal according to any one of claims 1-14 and 23-27 or a crystalline polymorph according to any one of claims 15-22.
29. Use of a crystalline salt or co-crystal according to any one of claims 1-14 and 23-27 or a crystalline polymorph according to any one of claims 15-22 or a composition according to claim 28, in the manufacture of a medicament for treating a condition or a disorder in a subject in need thereof.
30. The use of claim 29, wherein the condition or disorder is associated with $\alpha 2/\alpha 3$ GABAA receptor.
31. The use 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 use of claim 31, wherein the condition or disorder is pain.
33. The use 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 use of claim 31, wherein the condition or disorder is itch.
35. The use 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 use of claim 31, wherein the condition or disorder is epilepsy.
37. The use 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 use of claim 31, wherein the condition or disorder is autism.
 39. The use 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 crystalline salt or co-crystal according to any one of claims 1-14 and 23-27 or a crystalline polymorph according to any one of claims 15-22 or a composition according to claim 28, for use in therapy.
 41. 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.
 42. The method of claim 41, 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.
 43. The method of claim 41 or 42, 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.