# CRYSTALLINE AND SALT FORMS OF PPAR AGONIST COMPOUNDS

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/404,474, filed on October 5, 2016. The entire teachings of the aforementioned application are incorporated herein by reference.

## FIELD OF THE INVENTION

This disclosure relates to solid forms of compounds capable of activating PPARδ for use in drug substance and drug product development, and related compositions and methods.

## BACKGROUND OF THE INVENTION

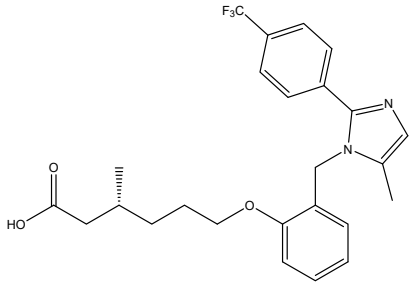
Peroxisome proliferator-activated receptor delta (PPARδ) is a nuclear receptor that is capable of regulating mitochondria biosynthesis. As shown in PCT/2014/033088, incorporated herein by reference, modulating the activity of PPARδ is useful for the treatment of diseases, developmental delays, and symptoms related to mitochondrial dysfunction, such as Alpers Disease, MERRF-Myoclonic epilepsy and ragged-red fiber disease, Pearson Syndrome, and the like. Modulation PPARδ activity is effective in the treatment of other conditions, such as muscular diseases, demyelinating diseases, vascular diseases, and metabolic diseases. Indeed, PPARδ is an important biological target for compounds used to help treat and prevent mitochondrial diseases, muscle-related diseases and disorders, and other related conditions.

Compound A of Formula (I) and Compound B of Formula (II) are PPARδ agonists. There is a need for salt forms of these compounds that are crystalline and otherwise have physical properties that are amenable to large scale manufacture. There is also a need for pharmaceutical formulations in which these drug candidates are stable and are effectively delivered to the patient.

## SUMMARY

Provided herein, *inter alia*, are salts of Compound A and Compound B and compositions comprising such compounds that are useful for increasing PPARδ activity.

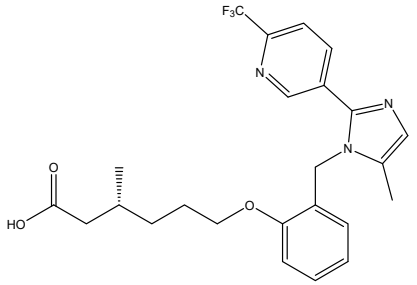
In one aspect of the present disclosure, there is provided a compound of Formula (I):



Formula (I),

in the form of a hemisulfate salt.

In another aspect of the present disclosure, there is provided a compound of Formula (II):



Formula (II),

in the form of a meglumine salt or a hydrate of the meglumine salt.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

In another aspect of the present disclosure, there is provided a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition disclosed herein for use in therapy.

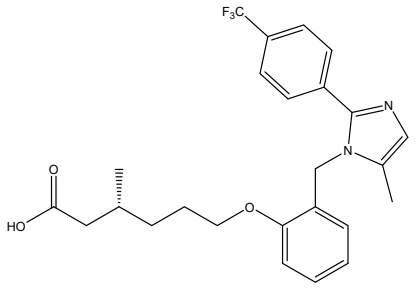
In a further aspect of the present disclosure, there is provided a use of a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition disclosed herein in the manufacture of a medicament for the treatment of a PPARδ related disease or condition in a subject, wherein the medicament is to be administered to the subject in need thereof, wherein the PPARδ related disease is a muscle structure disorder, a neuronal activation disorder, a muscle fatigue disorder, a muscle mass

disorder, a mitochondrial disease, a beta oxidation disease, a metabolic disease, a cancer, a vascular disease, an ocular vascular disease, a muscular eye disease, or a renal disease.

In another aspect of the present disclosure, there is provided a use of a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient, in the manufacture of a medicament for the treatment of a PPARδ related disease or condition in a subject, wherein the PPARδ related disease or condition is Duchenne Muscular Dystrophy.

In a further aspect of the present disclosure, there is provided a use of a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient, in the manufacture of a medicament for the treatment of a PPARδ related disease or condition in a subject, wherein the PPARδ related disease or condition is acute kidney injury.

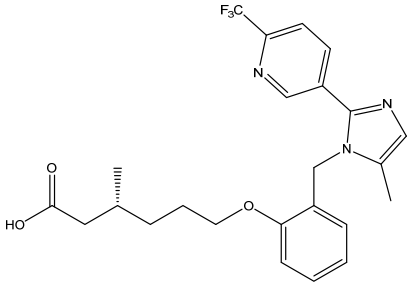
In one example, provided herein is Compound A of the Formula (I):



(I)

in the form of a hemisulfate salt. In one example, the hemisulfate salt of Compound A is crystalline. Thus, in one example, the crystalline the hemisulfate salt of Compound A is characterized by an X-ray powder diffraction pattern substantially in accordance with FIG. 1 or FIG. 2.

In another example, provided herein is Compound B of the Formula (II):



(II)

in the form of a meglumine salt or a hydrated form of the meglumine salt.

Pharmaceutical compositions of the salts of Compound A and Compound B also are disclosed herein. Particular examples comprise a pharmaceutically acceptable carrier or excipient and one or more of the disclosed compounds. The pharmaceutical compositions of the present disclosure can be used in therapy, *e.g.*, for treating a PPARδ-related disease or condition in a subject.

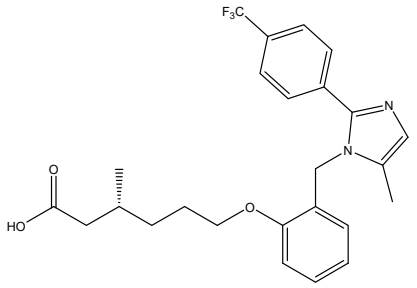
Another examplecomprises treating a PPARδ-related disease or condition in a subject by administering to the subject a therapeutically effective amount of one or both of the disclosed compounds, or a pharmaceutical composition comprising the compound(s).

Also provided herein is the use of one or more of the disclosed compounds, or a pharmaceutical composition comprising one or both of the disclosed compounds, for the preparation of a medicament for the treatment of a PPARδ-related disease or condition.

CLAIMS

What is claimed is:

1. A compound of Formula (I):




Formula (I),

in the form of a hemisulfate salt.

2. The compound of claim 1 in crystalline form.

3. The compound of claim 2 characterized by an X-ray powder diffraction pattern substantially in accordance with FIG. 1 or FIG. 2, wherein the X-ray powder diffraction pattern is collected using Cu K alpha (1.5406 Angstrom) radiation.

4. The compound of claim 2 characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles 7.3±0.2°, 14.7±0.2°, 19.1±0.2°, and 22.3±0.2°, wherein the X-ray powder diffraction pattern is collected using Cu K alpha (1.5406 Angstrom) radiation.

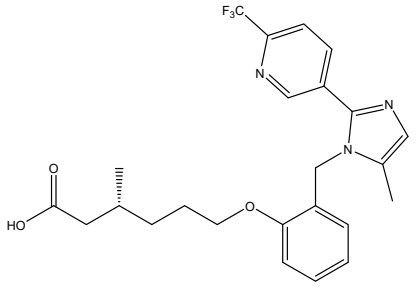
5. The compound of claim 4 characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at one or more of angles 8.3±0.2°, 15.8±0.2°, 16.5±0.2°, 19.7±0.2°, or 25.8±0.2°, wherein the X-ray powder diffraction pattern is collected using Cu K alpha (1.5406 Angstrom) radiation.

6. The compound of claim 2 characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles 6.7±0.2°, 13.5±0.2°, 17.4±0.2°, and 18.1±0.2°, wherein the X-ray powder diffraction pattern is collected using Cu K alpha (1.5406 Angstrom) radiation.

7. The compound of claim 6 further characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at one or more of angles 14.5±0.2°, 16.1±0.2°, 22.4±0.2°, 23.2 ±0.2°, or 23.4 ±0.2°, wherein the X-ray powder diffraction pattern is collected using Cu K alpha (1.5406 Angstrom) radiation.

8. The compound of any one of claims 2–7, wherein greater than 90% of the compound is in crystalline form.

9. A compound of Formula (II):



Formula (II),

in the form of a meglumine salt or a hydrate of the meglumine salt.

10. The compound of claim 9, wherein the compound is in the form of a monohydrate.

11. The compound of claim 9, wherein the compound is unhydrated.

12. A pharmaceutical composition comprising a compound of any one of claims 1–11 and a pharmaceutically acceptable excipient.

13. A therapeutically effective amount of a compound of any one of claims 1–11, or a pharmaceutical composition of claim 12 for use in therapy.

14. Use of a therapeutically effective amount of a compound of any one of claims 1–11, or a pharmaceutical composition of claim 12 in the manufacture of a medicament for the treatment of a PPARδ related disease or condition in a subject, wherein the medicament is to be administered to the subject in need thereof, wherein the PPARδ related disease is a muscle structure disorder, a neuronal activation disorder, a muscle fatigue disorder, a muscle mass disorder, a mitochondrial disease, a beta oxidation disease, a metabolic disease, a cancer, a vascular disease, an ocular vascular disease, a muscular eye disease, or a renal disease.

15. The use of claim 14, wherein:

the muscle structure disorder is selected from Bethlem myopathy, central core disease, congenital fiber type disproportion, distal muscular dystrophy (MD), Duchenne & Becker MD, Emery-Dreifuss MD, facioscapulohumeral MD, hyaline body myopathy, limb-girdle MD, a muscle sodium channel disorders, myotonic chondrodystrophy, myotonic dystrophy, myotubular myopathy, nemaline body disease, oculopharyngeal MD, or stress urinary incontinence;

the neuronal activation disorder is selected from amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease, Guillain-Barre syndrome, Lambert-Eaton syndrome, multiple sclerosis,

myasthenia gravis, nerve lesion, peripheral neuropathy, spinal muscular atrophy, tardy ulnar nerve palsy, or toxic myoneural disorder;

the muscle fatigue disorder is selected from chronic fatigue syndrome, glycogen storage disease, fibromyalgia, Friedreich's ataxia, intermittent claudication, lipid storage myopathy, MELAS, mucopolysaccharidosis, Pompe disease, or thyrotoxic myopathy; the muscle mass disorder is cachexia, cartilage degeneration, cerebral palsy, compartment syndrome, critical illness myopathy, inclusion body myositis, muscular atrophy (disuse), sarcopenia, steroid myopathy, or systemic lupus erythematosus;

the mitochondrial disease is selected from Alpers's Disease, CPEO-Chronic progressive external ophthalmoplegia, Kearns-Sayra Syndrome (KSS), Leber Hereditary Optic Neuropathy (LHON), MELAS-Mitochondrial myopathy, encephalomyopathy, lactic acidosis, and stroke-like episodes, MERRF-Myoclonic epilepsy and ragged-red fiber disease, NARP-neurogenic muscle weakness, ataxia, and retinitis pigmentosa, or Pearson Syndrome;

the beta oxidation disease is selected from carnitine palmitoyltransferase ( CPT ) II deficiency, very long-chain acyl-CoA dehydrogenase (LCHAD or VLCAD) deficiency, trifunctional enzyme deficiency, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, short-chain acyl-CoA dehydrogenase (SCAD) deficiency or riboflavin-responsive disorders of β-oxidation (RR -MADD);

the metabolic disease is selected from hyperlipidemia, dyslipidemia, hyperchlolesterolemia, hypertriglyceridemia, HDL hypocholesterolemia, LDL hypercholesterolemia, VLDL hyperproteinemia, dyslipoproteinemia, apolipoprotein A-I hypoproteinemia, atherosclerosis, disease of arterial sclerosis, disease of cardiovascular systems, cerebrovascular disease, peripheral circulatory disease, metabolic syndrome, syndrome X, obesity, diabetes (type I or II), hyperglycemia, insulin resistance, impaired glucose tolerance, hyperinsulinism, diabetic complication, cardiac insufficiency, cardiac infarction, cardiomyopathy, hypertension, Non-alcoholic fatty liver disease (NAFLD), Nonalcoholic steatohepatitis (NASH), thrombus, Alzheimer disease, neurodegenerative disease, demyelinating disease, adrenoleukodystrophy, dermatitis, psoriasis, acne, trichosis, inflammation, arthritis, asthma, hypersensitive intestine syndrome, ulcerative colitis, Crohn's disease, or pancreatitis;

the cancer is a cancer of the colon, large intestine, skin, breast, prostate, ovary, or lung;

the vascular disease is selected from peripheral vascular insufficiency, peripheral vascular disease, intermittent claudication, peripheral vascular disease (PVD), peripheral

artery disease (PAD), peripheral artery occlusive disease (PAOD), or peripheral obliterative arteriopathy;

the ocular vascular disease is selected from age-related macular degeneration (AMD), stargardt disease, hypertensive retinopathy, diabetic retinopathy, retinopathy, macular degeneration, retinal haemorrhage, or glaucoma;

the muscular eye disease is selected from strabismus, progressive external ophthalmoplegia, esotropia, exotropia, a disorder of refraction and accommodation, hypermetropia, myopia, astigmatism, anisometropia, presbyopia, a disorders of accommodation, or internal ophthalmoplegia; and

the renal disease is selected from glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, acute nephritis, recurrent hematuria, persistent hematuria, chronic nephritis, rapidly progressive nephritis, acute kidney injury, chronic renal failure, diabetic nephropathy, or Bartter's syndrome.

16. Use of a therapeutically effective amount of a compound of any one of claims 1–8, or a pharmaceutical composition comprising a compound of any one of claims 1–8 and a pharmaceutically acceptable excipient, in the manufacture of a medicament for the treatment of a PPARδ related disease or condition in a subject, wherein the PPARδ related disease or condition is Duchenne Muscular Dystrophy.

17. Use of a therapeutically effective amount of a compound of any one of claims 9–11, or a pharmaceutical composition comprising a compound of any one of claims 9-11 and a pharmaceutically acceptable excipient, in the manufacture of a medicament for the treatment of a PPARδ related disease or condition in a subject, wherein the PPARδ related disease or condition is acute kidney injury.