CRYSTALLINE FORMS OF A MAGL INHIBITOR

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/423,126, filed on November 16, 2016, which is herein incorporated by reference in its entirety.

BACKGROUND

[0002] Monoacylglycerol lipase (MAGL) is an enzyme responsible for hydrolyzing endocannabinoids such as 2-AG (2-arachidonoylglycerol), an arachidonate based lipid, in the nervous system. The serine hydrolase α-β-hydrolase domain 6 (ABHD6) is another lipid mediator.

SUMMARY OF THE INVENTION

[0003] Described herein is the MAGL inhibitor 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, including pharmaceutically acceptable solvates (including hydrates), polymorphs, and amorphous phases, and methods of uses thereof. Also described are pharmaceutically acceptable salts of the MAGL inhibitor 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, including pharmaceutically acceptable solvates (including hydrates), polymorphs, and amorphous phases, and methods of uses thereof. 1,1,1,3,3,3-Hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, as well as the pharmaceutically acceptable salts thereof, are used in the manufacture of medicaments for the treatment of diseases or conditions that are associated with MAGL activity.

[0004] Also described herein are methods for preparing crystalline forms of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate. Further described are pharmaceutical compositions that include the crystalline forms and methods of using the MAGL inhibitor in the treatment of diseases or conditions (including diseases or conditions wherein irreversible inhibition of MAGL provides therapeutic benefit to a mammal having the disease or condition).

[0005] In one embodiment is a crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt, including solvate thereof.

[0006] In another embodiment, the crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a free base.

hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein. In some embodiments the pain is neuropathic pain. In some embodiments, the pain is inflammatory pain.

[0035] In another aspect, provided herein is a method of treating epilepsy/seizure disorder, multiple sclerosis, neuromyelitis optica (NMO), Tourette syndrome, Alzheimer disease, or abdominal pain associated with irritable bowel syndrome in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein. In some embodiments is a method of treating epilepsy/seizure disorder, multiple sclerosis, neuromyelitis optica (NMO), Tourette syndrome, Alzheimer disease, or abdominal pain associated with irritable bowel syndrome in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical composition of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein.

[0036] In another aspect, provided herein is a method of treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclussive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein. In some embodiments is a method of treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclussive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical

composition of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein.

[0037] In another aspect, provided herein is a method of treating dystonia in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein. In some embodiments is a method of treating dystonia in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical composition of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein.

[0038] In another aspect, provided herein is a pharmaceutically acceptable salt of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), wherein the pharmaceutically acceptable salt is a mono-hydrochloride salt, bis-hydrochloride salt, fumarate salt, besylate salt, or mesylate salt. In some embodiments, the

CLAIMS

We Claim:

1. A crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate , wherein the crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt is Form 2 having an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.6° 2-Theta, 14.3° 2-Theta, 15.6° 2-Theta, 19.0° 2-Theta, 19.8° 2-Theta, and 20.7° 2-Theta.
2. A crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, wherein the crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate fumarate salt has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 13.6° 2-Theta, 14.1° 2-Theta, 14.3° 2-Theta, 20.0° 2-Theta, and 21.9° 2-Theta.
3. A pharmaceutical composition comprising the crystalline form of any one of claims 1-2, or a pharmaceutically acceptable salt, or solvate thereof, and at least one inactive ingredient selected from pharmaceutically acceptable carriers, diluents, and excipients.
4. The pharmaceutical composition of claim 3 for use in therapy.