

(S)-3-((6-FLUOROPYRIDIN-3-YL)METHYL)-1-(5-(PYRIDIN-4-YL)-4H-1,2,4-
TRIAZOL-3-YL)PIPERIDIN-2-ONE BENZENESULFONATE

FIELD OF THE INVENTION

[0001] The present invention is directed to (S)-3-((6-fluoropyridin-3-yl)methyl)-1-(5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)piperidin-2-one benzenesulfonate, crystalline forms of the compound, to pharmaceutical compositions comprising the compound, and methods of using the compound to treat and prevent pathological conditions involving axonal degeneration.

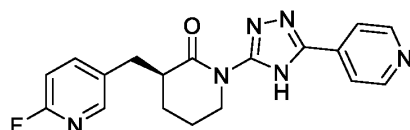
BACKGROUND OF THE INVENTION

[0002] Axonal degeneration is a major feature of pathological conditions such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), diabetic peripheral neuropathy, chemotherapy-induced peripheral neuropathy, inherited neuropathy, traumatic brain injury, and glaucoma. These conditions affect millions of patients and present a significant financial burden worldwide.

[0003] Sterile Alpha and Toll/Interleukin receptor-1 (TIR) motif-containing 1 (SARM1) has been identified as the central executioner in the injury-induced axon death pathway known as Wallerian degeneration (O'Neill, L.A. & Bowie, A.G., *Nat. Rev. Immunol.*, 2007, 7, 353-364; Osterloh, J.M., et al., *Science*, 2012, 337, 481-484; Gerdts, J., et al., *J. Neurosci.* 33, 2013, 13569-13580). Mechanistic studies have revealed that activation of SARM1 via axonal injury or forced dimerization of SARM1-TIR domains promotes rapid depletion of nicotinamide adenine dinucleotide (NAD⁺), resulting in axonal degradation (Gerdts, J., et al., *Science*, 2015, 348, 453-457). Genetic knockout of SARM1 allows for preservation of axons for fourteen or more days after nerve transection (Osterloh, J.M., et al., *Science*, 2012, 337, 481-484; Gerdts, J., et al. *J. Neurosci.*, 2013, 33, 13569-13580) and improves functional outcomes in mice after traumatic brain injury (Henninger, N. et al., *Brain* 139, 2016, 1094-1105). In addition to the role of SARM1 in direct axonal injury, SARM1 is also required for axonal degeneration observed in conditions such as chemotherapy-induced peripheral neuropathy. Loss of SARM1 blocks chemotherapy-induced peripheral neuropathy,

inhibiting both axonal degeneration and heightened pain sensitivity that develops after chemotherapeutic vincristine treatment (Geisler et al, *Brain*, 2016, 139, 3092-3108).

[0004] WO 2022/046606 A1 discloses certain inhibitors of SARM1, including (S)-3-((6-fluoropyridin-3-yl)methyl)-1-(5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)piperidin-2-one free base (Compound I-23-a as described therein):



Compound I-23-a

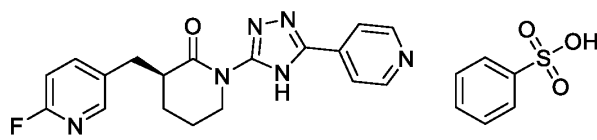
SUMMARY OF THE INVENTION

[0005] Early form and stability work on Compound I-23-a as obtained through the synthetic methods disclosed in WO 2022/046606 A1 revealed that the material is subject to the formation of several polymorphs and solvates, including a monohydrate form which is readily generated by subjecting the anhydrous form to standard room humidity conditions. Furthermore, it was later determined that a number of salt forms of the compound present with the same issues as the free base and additional unfavorable properties, such as poor crystallinity and dissociation in water. For these reasons it was concluded that neither the free base nor the specific salt forms would be suitable for further development into a commercial active pharmaceutical ingredient (API).

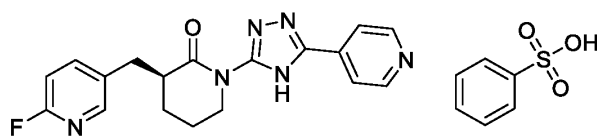
[0006] Among all the salts tested, (S)-3-((6-fluoropyridin-3-yl)methyl)-1-(5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)piperidin-2-one benzenesulfonate was initially obtained as a mixture of two forms as detected by X-ray powder diffraction (XRPD). Further synthetic and characterization work allowed the isolation of a single form of the benzenesulfonate salt, which was surprisingly found to be highly crystalline, high melting, non-hygroscopic and stable under a variety of conditions.

DETAILED DESCRIPTION OF THE INVENTION

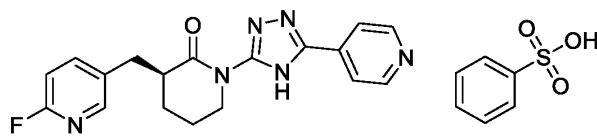
[0007] Accordingly, the present invention provides a compound of the formula:



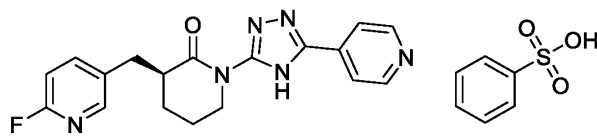
or a hydrate or solvate thereof. In a further embodiment the compound is:



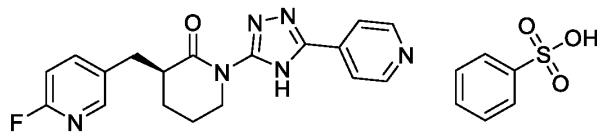
In another embodiment, the present invention provides a compound of the formula:



which is crystalline. In another embodiment, the present invention provides a compound of the formula:

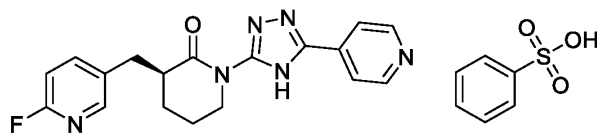


which is crystalline, and which is characterized by an X-ray powder diffraction pattern using CuK α radiation comprising a peak at diffraction angle 2θ of 16.6° , and one or more peaks at 5.7° , 21.7° or 22.9° ($\pm 0.2^\circ$ respectively). In a further embodiment, the present invention provides a compound of the formula:



which is crystalline, and which is characterized by a solid state ^{13}C NMR spectrum comprising peaks at the following ppm: 175.5, 173.5, 163.6, 161.2, 153.8, 148.7, 147.4,

145.6, 144.3, 143.4, 141.2, 139.7, 134.6, 133.0, 130.5, 127.9, 121.5, 109.5, 108.3, 48.246, 45.9, 43.7, 42.8, 33.2, 32.3, 25.0, 20.0 (± 0.2 ppm). In another embodiment, the present invention provides a compound of the formula:



which is crystalline, and which is characterized by:

- an X-ray powder diffraction pattern using CuK α radiation comprising a peak at diffraction angle 2θ of 16.6° , and one or more peaks at 5.7° , 21.7° or 22.9° ($\pm 0.2^\circ$ respectively), and
- a solid state ^{13}C NMR spectrum comprising peaks at the following ppm: 175.5, 173.5, 163.6, 161.2, 153.8, 148.7, 147.4, 145.6, 144.3, 143.4, 141.2, 139.7, 134.6, 133.0, 130.5, 127.9, 121.5, 109.5, 108.3, 48.2, 45.9, 43.7, 42.8, 33.2, 32.3, 25.0, 20.0 (± 0.2 ppm).

[0008] The present invention also provides a pharmaceutical composition comprising a compound according to any of the above embodiments, with one or more pharmaceutically acceptable carriers, diluents or excipients.

[0009] The present invention further provides a method of inhibiting SARM1 in a patient comprising administering to a patient in need of such treatment an effective amount of a compound according to any of the above embodiments. The present invention further provides a method of treating or preventing a disease associated with SARM1 activation in a patient comprising administering to a patient in need of such treatment an effective amount of a compound according to any of the above embodiments. The present invention further provides a method of treating or preventing a disease associated with axonal degeneration in a patient comprising administering to a patient in need of such treatment an effective amount of a compound according to any of the above embodiments. The present invention further provides a method of treating or preventing a disease selected from amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), diabetic neuropathy and chemotherapy-induced peripheral neuropathy (CIPN) in a

patient comprising administering to a patient in need of such treatment an effective amount of a compound according to any of the above embodiments.

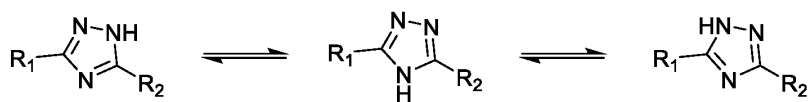
[0010] The present invention also provides a compound according to any one of the above embodiments for use in therapy. The present invention also provides a compound according to any one of the above embodiments for use in the treatment or prevention of a disease associated with SARM1 activation. The present invention also provides a compound according to any one of the above embodiments for use in the treatment or prevention of a disease associated with axonal degeneration. The present invention also provides a compound according to any one of the above embodiments for use in the treatment of a disease selected from amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), diabetic neuropathy and chemotherapy-induced peripheral neuropathy (CIPN).

[0011] The present invention provides the use of a compound according to any of the above embodiments for the manufacture of a medicament for in the treatment or prevention of a disease associated with SARM1 activation. The present invention provides the use of a compound according to any of the above embodiments for the manufacture of a medicament for in the treatment or prevention of a disease associated with axonal degeneration. The present invention provides the use of a compound according to any of the above embodiments for the manufacture of a medicament for in the treatment or prevention of a disease selected from amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), diabetic neuropathy and chemotherapy-induced peripheral neuropathy (CIPN).

[0012] As used herein, the term “patient” refers to a human. As used herein, the term “preventing” refers to preventing the occurrence of a disease or averting resulting complications after its onset. As used herein, the term “treating” includes slowing, stopping, or reversing the progression or severity of an existing symptom or disorder. As used herein, the term “effective amount” refers to the amount or dose of compound of the invention which, upon single or multiple dose administration to the patient, provides the desired effect in the patient under diagnosis or treatment. As used herein, the term “SARM1” refers to sterile alpha and TIR motif containing 1.

[0013] The compounds of the present invention are preferably formulated as pharmaceutical compositions administered by any route which makes the compound bioavailable, including oral, intravenous, subcutaneous, and transdermal. Most preferably, such compositions are for oral administration. Such pharmaceutical compositions and processes for preparing the same are well known in the art (See, *e.g.*, Remington: The Science and Practice of Pharmacy, A. Adejare, Editor, 23rd Edition, Elsevier Academic Press, 2020).

[0014] The compounds of the present invention contain a 5- and 3- substituted 1,2,4-triazole moiety. It is well-appreciated in the art that this moiety can exist in three tautomeric forms:



It will be further appreciated that the depiction of the compounds of the present invention in one specific tautomeric form does not exclude the possibility of the compounds existing in any of the three tautomeric forms shown above.

[0015] Certain abbreviations are defined in Table 1 below.

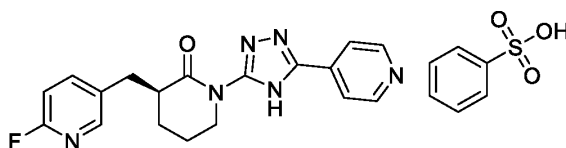
Table 1 – Abbreviations

Symbol	Definition
°C	Degree centigrade
2θ	Angle between incident and reflected X-ray beams
CuKα	X-ray energy equivalent to 8.04 kiloelectronvolt (keV)
ee	Enantiomeric excess
EtOAc	Ethyl acetate
g	Grams
HCl	Hydrochloric acid

kHz	Kilohertz
M	Molar
MHz	Megahertz
mL	Milliliter
mmol	Millimole
Mp	Melting point
ms	Millisecond
NMR	Nuclear magnetic resonance
SSNMR	Solid state nuclear magnetic resonance
ppm	Part per million
vRH XRPD	Variable relative humidity x-ray powder diffraction
XRPD	X-ray powder diffraction

EXAMPLES

[0016] Example 1: (S)-3-((6-fluoropyridin-3-yl)methyl)-1-(5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)piperidin-2-one benzenesulfonate



[0017] Benzenesulfonic acid (417 g, 1.74 mmol) was dissolved in dimethyl sulfoxide (800 mL) with stirring at 10 to 30 °C for 0.5 hours. 870 g of (S)-3-((6-fluoropyridin-3-yl)methyl)-1-(5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)piperidin-2-one was dissolved in dimethyl sulfoxide (2400 mL) and the reactor adjusted to 10 to 30 °C. The benzenesulfonic acid solution was added dropwise to the (S)-3-((6-fluoropyridin-3-yl)methyl)-1-(5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)piperidin-2-one solution and the

temperature adjusted to between 45 and 55 °C. The mixture was stirred for 2 hours, and the resulting suspension filtered. Dimethyl sulfoxide (800 mL) followed by isopropyl alcohol (2400 mL) were added to the filtrate. Seeds (8 g) of Form I were added, and the mixture stirred for 2 hours at 45 to 55 °C. Isopropyl alcohol (17600 mL) was added dropwise for over 10 hours followed by an additional 2 hours of stirring at 45 to 55 °C. The mixture was cooled to 5 °C over the course of 5 hours and stirred for an additional 3 hours at 5 °C. The resulting suspension was filtered, and the wet cake washed with isopropyl alcohol (3200 mL), and dried for 40 hours at 50 °C, to give (S)-3-((6-fluoropyridin-3-yl)methyl)-1-(5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)piperidin-2-one; benzenesulfonic acid (1018 g, 97.18% purity and 97.4% ee). Mp: 234°C. X-Ray Powder diffraction (XRPD) of Example 1

XRPD method

The XRPD patterns of crystalline solids are obtained on a Bruker D8 Endeavor X-ray powder diffractometer, equipped with a CuK α (1.5418Å) source and a Lynxeye™ detector, operating at 40 kV and 40 mA. The sample is scanned between 4 and 42 2 θ °, with a step size of 0.009 2 θ ° and a scan rate of 0.5 seconds/step, and using 0.3° primary slit opening, and 3.9° PSD opening. The dry powder of Example 1 is packed on a quartz sample holder and a smooth surface is obtained using a glass slide. The crystal form diffraction patterns are collected at ambient temperature and relative humidity. Crystal peak positions are determined in MDI-Jade after whole pattern shifting based on an internal NIST 675 standard with peaks at 8.853 and 26.774 2 θ °. It is well known in the crystallographic art that, for any given crystal form, the relative intensities of the diffraction peaks may vary due to preferred orientation resulting from factors such as crystal morphology and habit. Where the effects of preferred orientation are present, peak intensities are altered, but the characteristic peak positions of the polymorph are unchanged. See, *e.g.* The United States Pharmacopeia #23, National Formulary #18, pages 1843-1844, 1995. Furthermore, it is also well known in the crystallography art that for any given crystal form the angular peak positions may vary slightly. For example, peak positions can shift due to a variation in the temperature at which a sample is analyzed, sample displacement, or the presence or absence of an internal standard. In the present case, a peak position variability of ± 0.2 2 θ ° is presumed to take into account

these potential variations without hindering the unequivocal identification of the indicated crystal form. Confirmation of a crystal form may be made based on any unique combination of distinguishing peaks.

A prepared sample of Example 1 is characterized by an XRPD pattern using $\text{CuK}\alpha$ radiation as comprising diffraction angles (2θ) as described in Table 2 below, and in particular comprising a peak at diffraction angle 2θ of 16.6° and one or more peaks at 5.7° , 21.7° or 22.9° , with a tolerance for the diffraction angles of 0.2° .

Table 2 - XRPD peaks for Example 1 arranged by relative intensity.

Peak	Angle (2θ) $\pm 0.2^\circ$	Relative Intensity
1	16.6°	100.0%
2	5.7°	99.2%
3	21.7°	31.4%
4	22.9°	28.1%
5	23.7°	25.6%
6	25.6°	17.0%
7	25.9°	16.0%
8	18.6°	14.3%
9	11.3°	13.5%
10	12.2°	13.0%
11	16.2°	11.9%
12	22.6°	11.9%
13	26.1°	11.6%
14	15.2°	11.2%
15	17.3°	10.9%

[0018] Solid state NMR (SSNMR) of Example 1

SSNMR method

The SSNMR spectrum was acquired on an Agilent DD2-400 spectrometer (Larmor frequencies: ^{13}C = 100.547 MHz, ^1H = 399.811 MHz). The sample of Example 1 was packed into a 4 mm pencil type silicon nitride rotor and rotated at 12 kHz at the magic angle. The spectrum was acquired at ambient temperature with phase modulated (SPINAL-64) high power ^1H decoupling during the acquisition time, a ramped amplitude cross polarization contact time of 5 ms, a 30 ms acquisition time, a 10 s delay between scans, a spectral width of 45 kHz with 2678 data points, and 1600 co-added scans. the free induction decay (FID) was processed using Agilent VnmrJ 3.2A software with 65536 points and an exponential line broadening factor of 10 Hz to improve the signal-to-noise ratio. The first three data points of the FID were back predicted using the VNMR linear prediction algorithm to produce a flat baseline. the chemical shifts of the spectral peaks were externally referenced to the carbonyl carbon resonance of glycine at 176.5 ppm.

A prepared sample of Example 1 is characterized by the SSNMR peaks presented in Table 3 below.

Table 3 – ^{13}C SSNMR data for Example 1.

Index	PPM	Height
1	175.5	31.5
2	173.5	34.7
3	163.6	23.0
4	161.2	36.5
5	153.8	108.1
6	148.7	36.2
7	147.4	71.1
8	145.6	77.8
9	144.3	66.8

10	143.4	40.6
11	141.2	34.9
12	139.7	67.3
13	134.6	18.8
14	133.0	135.3
15	130.5	74.0
16	127.9	78.4
17	121.5	66.8
18	109.5	32.2
19	108.3	31.3
20	48.2	40.5
21	45.9	35.9
22	43.7	50.5
23	42.8	43.7
24	33.2	43.2
25	32.3	41.7
26	25.0	72.8
27	20.0	86.2

[0019] Variable humidity XRPD (vRH XRPD) testing of Example 1

A sample of Example 1 was started at 5% RH, then stepped in 10% increments up to a high of 90% RH then back down in the same fashion. No crystalline form changes in the vRH XRPD of Example 1 were observed under these conditions.

[0020] Solid state stability testing of Example 1

Samples of Example 1 were exposed to the conditions described in Table 4 below for 14 days. Example 1 was chemically and physically stable under all the tested conditions, with only a minor increase in total residual substance (TRS) percentage of 0.56% up exposure to 70°C/ 75% RH for 14 days.

Table 4 – Solid state stability testing

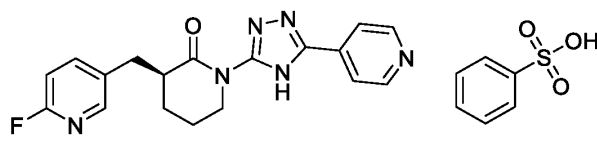
Condition	TRS increase (%)
Light	None
40°C	None
40°C/ 75% RH	None
50°C/ 30% RH	None
50°C/ 50% RH	None
70°C	None
70°C/ 75% RH	0.56

The experimental data gathered on the solid form (S)-3-((6-fluoropyridin-3-yl)methyl)-1-(5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)piperidin-2-one benzenesulfonate (Example 1) described herein evidence that it is highly crystalline, high melting, non-hygroscopic and stable under a variety of conditions.

CLAIMS

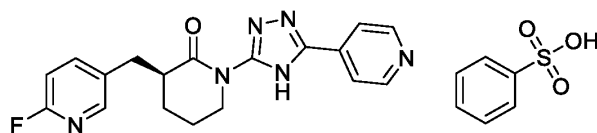
What is claimed is:

1. A compound of the formula:



or a hydrate or solvate thereof.

2. The compound according to claim 1, which is:



3. The compound according to claim 1 or 2, which is crystalline.
4. The compound according to any one of claims 1 to 3, which is crystalline, and which is characterized by an X-ray powder diffraction pattern using CuK α radiation comprising a peak at diffraction angle 2θ of 16.6° , and one or more peaks at 5.7° , 21.7° or 22.9° ($\pm 0.2^\circ$ respectively).
5. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4 with one or more pharmaceutically acceptable carriers, diluents, or excipients.
6. A method of inhibiting SARM1 in a patient comprising administering to a patient in need of such treatment an effective amount of a compound according to any one of claims 1 to 4, or the pharmaceutical composition according to claim 5.
7. A method of treating or preventing a disease associated with SARM1 activation in a patient comprising administering to a patient in need of such treatment an effective amount of a compound according to any one of claims 1 to 4, or the pharmaceutical composition according to claim 5.
8. A method of treating or preventing a disease associated with axonal degeneration in a patient comprising administering to a patient in need of such treatment an

effective amount of a compound according to any one of claims 1 to 4, or the pharmaceutical composition according to claim 5.

9. A method of treating or preventing a disease selected from amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), diabetic neuropathy and chemotherapy-induced peripheral neuropathy (CIPN) in a patient comprising administering to a patient in need of such treatment an effective amount of a compound according to any one of claims 1 to 4, or the pharmaceutical composition according to claim 5.
10. A compound according to any one of claims 1 to 4 for use in therapy.
11. A compound according to any one of claims 1 to 4 for use in the treatment or prevention of a disease associated with SARM1 activation.
12. A compound according to any one of claims 1 to 4 for use in the treatment or prevention of a disease associated with axonal degeneration.
13. A compound according to any one of claims 1 to 4 for use in the treatment of a disease selected from amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), diabetic neuropathy and chemotherapy-induced peripheral neuropathy (CIPN).