

PHARMACEUTICALLY ACCEPTABLE SALTS OF 3-(2,3-DIFLUOROPHENOXY)AZETIDINE
AND USES THEREOF

Technical field

5 The present disclosure concerns pharmaceutically acceptable salts of the compound 3-(2,3-difluorophenoxy)azetidine, a method for manufacturing thereof and uses thereof. More specifically, the present disclosure concerns a succinic acid salt and a tartaric acid salt of 3-(2,3-difluorophenoxy)azetidine.

10 **Background**

The cerebral cortex encompasses several major regions of the brain that are involved in higher functions such as thought, feelings, memory and planning. Monoamines, such as dopamine, norepinephrine and serotonin, are important as neurotransmitters for mammalian cortical function. The ascending serotonergic and noradrenergic pathways
15 innervate virtually all regions of the brain, including the cerebral cortex. The dopaminergic neurons of the CNS have more distinct projections, including the meso-cortical pathway primarily innervating the frontal cortex in addition to a number of specific subcortical pathways. Primary or secondary dysfunctions in the activity of the monoamine pathways innervating the cerebral cortex lead to aberrations of the activity
20 at cortical dopamine, norepinephrine and serotonin receptors and subsequently to manifestations of psychiatric and neurological symptoms.

The monoamines of the cortex modulate several aspects of cortical functions controlling affect, anxiety, motivation, cognition, attention, arousal and wakefulness. Thus, the catecholamines, dopamine and norepinephrine exert strong influence on the frontal
25 cortical areas, the integrity of which is essential for the so-called executive cognitive functions related to e.g., attention, planning of actions and impulse control. Norepinephrine is a major part in the circuitry regulating anxiety and fear and is thus believed to be dysregulated in anxiety disorders such as panic disorders, generalized
30 anxiety disorder (GAD) and specific phobias. Concerning mood and affective functions, the usefulness of compounds facilitating particularly norepinephrine and serotonin neurotransmission in the treatment of depression and anxiety has strongly contributed to the widely accepted concept that these neurotransmitters are both involved in the regulation of affective functions.

35 Prog Neuro-Psychopharm & Bio Psych, 2013, 45, 54-63 discloses that compounds specifically affecting the transmission of monoamines, more precisely norepinephrine, dopamine and serotonin, are successfully used to alleviate the affective, cognitive, or

attentional symptoms in patients suffering from e.g., depression, anxiety and attention deficit hyperactivity disorder (ADHD). In addition, Biol Psych, 2011, 69(12); 89-99 discloses that all current pharmacological treatments for ADHD facilitate catecholamine transmission. Furthermore, Front Cell Neurosci, 2015, 9; 1-23 discloses that
5 modulation of monoaminergic transmission has been suggested as a promising principle for the treatment of autism spectrum disorders.

Neurosci & Biobehav Rev, 2013, 37; 1363-79 discloses that in Alzheimer's disease, progressive degeneration of ascending monoamine systems has been linked to
10 cognitive as well as non-cognitive symptoms, and pharmacological interventions leading to enhanced monoamine transmission have been suggested as a strategy both for symptomatic and disease-modifying treatments of Alzheimer's disease.

Furthermore, the monoamine systems in the cortex are known to be directly or
15 indirectly involved in the core symptoms of schizophrenia. It has been proposed that this disorder emerges as various pathological etiologies converge upon cortical synaptic processes leading to dysregulation of the cortical micro-circuitry, which is clinically manifested as the symptoms of schizophrenia (Harrison et al., Mol Psych, 2005, 10; 40-68). This cortical micro-circuitry is regulated by several neurotransmitters,
20 including glutamate, GABA, and dopamine. It has further been proposed that pharmacological enhancement of cortical dopamine transmission could restore the function of this microcircuitry, providing a useful strategy for improved treatment of schizophrenia (Abi-Dargham et al., Eur Psych, 2005, 20; 15-27).

25 WO 2010/022055 discloses certain 3-phenoxy-azetidine derivatives as synthetic intermediates in the synthesis of inhibitors of voltage-gated sodium channels. The compound 3-(2,3-difluorophenoxy)azetidine in non-salt form is one of the synthetic intermediates.

30 The database SciFinder discloses the compound 3-(2,3-difluorophenoxy)azetidine in non-salt form as a chemical that is commercially available.

WO 2018/091687 discloses 3-phenoxy-azetidine derivatives, useful for modulating levels of monoamines, such as dopamine, norepinephrine and serotonin, in cerebral
35 cortical areas of the mammalian brain, and more specifically for the treatment of central nervous system disorders. It is disclosed that the compound of Formula I may be an isotope labelled analog of or a pharmaceutically acceptable salt of 3-(2,3-difluorophenoxy)azetidine. Example 1A discloses 3-(2,3-difluorophenoxy)azetidine

hydrochloric acid salt. Example 1B discloses 3-(2,3-difluorophenoxy)azetidine fumaric acid salt.

The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge

The further investigation and development of 3-(2,3-difluorophenoxy)azetidine has revealed a need for a form of 3-(2,3-difluorophenoxy)azetidine exhibiting satisfactory pharmaceutical properties as well as satisfactory handling and drug properties, in particular on an industrial scale. Furthermore, there is a need for a form of 3-(2,3-difluorophenoxy)azetidine with a high chemical stability such as a high chemical stability in solution.

Brief description of the drawings

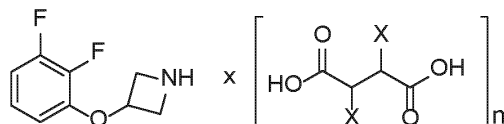
Figure 1 shows an XRP diffractogram of the salt of Formula IIIa11.

Figure 2 shows an XRP diffractogram of the salt of Formula IIIb2.

Summary

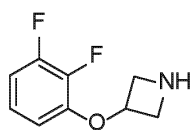
It is an object of the present disclosure to provide a form of 3-(2,3-difluorophenoxy)azetidine that exhibits satisfactory pharmaceutical properties as well as handling and drug properties, in particular on an industrial scale. It is also an object of the present disclosure to provide a form of 3-(2,3-difluorophenoxy)azetidine allowing for manufacturing in high purity on an industrial scale. Furthermore, it is an object of the present disclosure to provide a form of 3-(2,3-difluorophenoxy)azetidine with a high chemical stability such as a high chemical stability in solution. Further, it is an object of the present disclosure to provide aspects and/or advantages not provided by hitherto known technique.

The present disclosure provides a salt of Formula III:

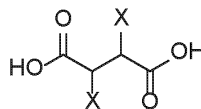


Formula III

said salt being a combination of a compound of Formula I and an acid of Formula II:



Formula I



Formula II

in a ratio of 1:n,

wherein

- 5 X is OH or H; and
n is 0.5 or 1.

The present disclosure also provides a pharmaceutical composition comprising a salt of Formula III as described herein in admixture with a pharmaceutically acceptable
10 excipient, carrier and/or diluent.

Further, the present disclosure provides a salt of Formula III, or a pharmaceutical composition as described herein, for use as a medicament.

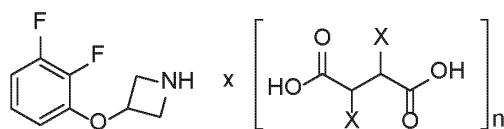
- 15 The present disclosure also provides a salt of Formula III, or a pharmaceutical composition as described herein, for use in the treatment and/or prevention of a disease, disorder and/or condition selected from the group consisting of dementia, cognitive impairment, autism spectrum disorder, affective disorder, schizophrenia, anxiety disorder, attention deficit hyperactivity disorder (ADHD), movement disorder,
20 postural instability and pathological apathy.

The present disclosure also provides the use of a salt of Formula III, or a pharmaceutical composition as described herein, for the manufacture of a medicament in the treatment and/or prevention of a disease, disorder and/or condition selected
25 from the group consisting of dementia, cognitive impairment, autism spectrum disorder, affective disorder, schizophrenia, anxiety disorder, attention deficit hyperactivity disorder (ADHD), movement disorder, postural instability and pathological apathy.

- 30 The present disclosure also provides a method for the treatment and/or prevention of a disease, disorder and/or condition selected from the group consisting of dementia, cognitive impairment, autism spectrum disorder, affective disorder, schizophrenia, anxiety disorder, attention deficit hyperactivity disorder (ADHD), movement disorder, postural instability and pathological apathy, said method comprising administering to
35 a mammal, such as a human or an animal, in need thereof, an effective amount, such as a therapeutically effective amount, of a salt of Formula III, or a pharmaceutical composition as described herein.

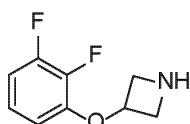
Description

The present disclosure provides a salt of Formula III:

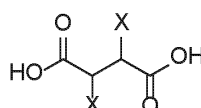


Formula III

- 5 said salt being a combination of a compound of Formula I and an acid of Formula II:



Formula I



Formula II

in a ratio of 1:n,

- 10 wherein

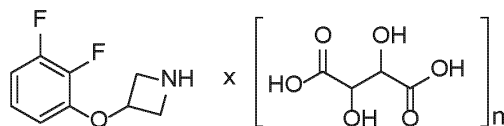
X is OH or H; and

n is 0.5 or 1.

Further, values of X and n will now follow. It will be appreciated that such values may

- 15 be used with any of the definitions, examples and/or claims described herein.

For instance, when X is OH and n is 0.5 or 1 there is provided a salt of Formula IIIa being a combination of the compound of Formula I and tartaric acid:



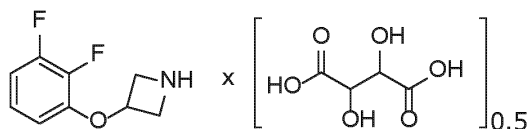
Formula IIIa

- 20

The tartaric acid described herein may be L-(+)-tartaric acid and/or D-(-)-tartaric acid. The tartaric acid may be provided as a racemic mixture. Alternatively, the tartaric acid of the salt of Formula IIIa may be L-(+)-tartaric acid.

- 25 The value for n may be 0.5. Alternatively, the value for n may be 1.

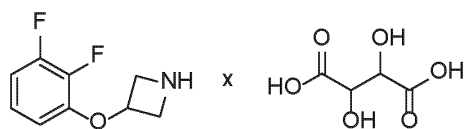
When n is 0.5 for the salt of Formula IIIa there is provided a salt of Formula IIIa1:



Formula IIIa1

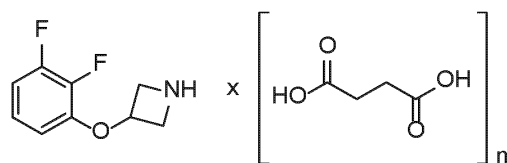
In an example, the tartaric acid of the salt of Formula IIIa may be L-(+)-tartaric acid and n may be 0.5. This salt may be denominated a salt of Formula IIIa11.

- 5 When n is 1 for the salt of Formula IIIa there is provided a salt of Formula IIIa2:



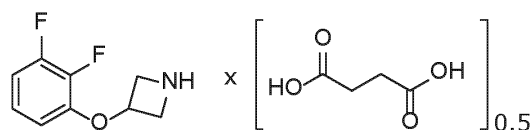
Formula IIIa2

- Further, X may be H and n may be 0.5 or 1 thereby providing a salt of Formula IIIb
10 being a combination of the compound of Formula I and succinic acid:



Formula IIIb

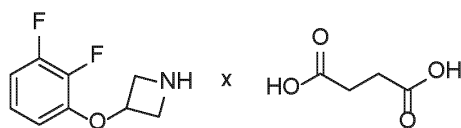
When n is 0.5 for the salt of Formula IIIb there is provided a salt of Formula IIIb1:



15

Formula IIIb1

Further, when n is 1 for the salt of Formula IIIb there is provided a salt of
Formula IIIb2:



20

Formula IIIb2

The salt of Formula III as described herein is pharmaceutically acceptable and has
unexpectedly been found to be crystalline and non-hygroscopic. Further, it has been
25 found to have a high melting point, high chemical purity and an acceptable, i.e.
satisfactory, water solubility. The high melting point is a benefit in , for instance, tablet
making. The satisfactory water solubility makes it suitable for any administration to a
patient such as a human, such as oral administration.

Thus, there is provided a salt of Formula III as described herein characterised by being crystalline. The crystallinity may be determined by XRPD or any other appropriate method. The crystallinity of the salt of Formula III, which makes it well-defined
5 with respect to, for instance, melting point and/or XRPD, is a benefit in e.g. making tablets. It is also believed to enhance storage stability. The crystallinity of the salt of Formula III may be about 80% or more such as about 85% or more, about 90% or more, about 95% or more, about 99% or more, or about 100% as measured by XRPD or any other appropriate method. In particular, the crystallinity of the salt of Formula
10 III may be 95% or 99% or more.

The salt of Formula IIIa, such as a salt of Formula IIIa11, may be characterized by an XRP diffractogram as shown in Figure 1. Additionally or alternatively, the salt of Formula IIIa may be characterized by an XRP diffractogram comprising a peak at
15 about 27.4 degrees 2θ and one or more peaks selected from the following: about 17.8, about 19.5, about 19.9, about 21.6 degrees 2θ .

The salt of Formula IIIb, such as a salt of Formula IIIb2, may be characterized by an XRP diffractogram as shown in Figure 2. Additionally or alternatively, the salt of
20 Formula IIIb may be characterized by an XRP diffractogram comprising a peak at about 12.5 degrees 2θ and one or more peaks selected from the following: about 13.3, about 16.5, about 19.3, about 22.4, about 23.3, about 24.1, about 24.9, about 25.9, about 26.9 degrees 2θ .

25 The fact that the salt of Formula III is not hygroscopic is advantageous since it allows for storage without or substantially without being affected by surrounding humidity. Of course, this is important and useful upon storing the salt in the context of e.g. industrial production of a pharmaceutical. It has been found that the salt of Formula III changes its weight by $\pm 0.2\%$ by weight or less at any humidity such as any relative
30 humidity as described herein. Thus, the salt of Formula III is not hygroscopic or substantially not hygroscopic. In an example, the salt of Formula III changes its weight by $\pm 0.2\%$ or less at a relative humidity of about 80%. The relative humidity may be measured at room temperature, i.e. a temperature from about 20 °C to about 25 °C such as about 22 °C.

35

In this document, the relative humidity intends the ratio of the partial pressure of water vapour in air to the equilibrium pressure of water at a given temperature and at atmospheric pressure.

The salt of Formula III has been found to have a high melting point. This is a benefit since it allows for e.g. tablet making. For example, the melting point may be within the range of from about 135 °C to about 190 °C. Additionally, the salt of Formula III
5 has been found to have a satisfactory water solubility. For instance, the water solubility may be within the range of from about 15 mg/mL to about 75 mg/mL. The water solubility may be determined as described in this document.

Thus, there is provided a salt of Formula III as described herein having a melting point
10 within the range of from about 135 °C to about 190 °C and/or a water solubility within the range of from about 15 mg/mL to about 75 mg/mL. For instance, the salt of Formula IIIa such as the salt of Formula IIIa11 may have a melting point of about 181.5 °C and/or a water solubility from about 53 mg/mL to about 106 mg/mL. In a further example, the salt of Formula IIIb such as the salt of Formula IIIb2 may have a
15 melting point of about 150.2 °C and/or a water solubility from about 20 mg/mL to about 40 mg/mL. The water solubility may be determined as described in this document.

Furthermore, the salt of Formula III has been found to have a high chemical stability
20 in solution. This is a benefit when the salt is processed such as, for instance, when the salt is purified by e.g. recrystallization, manufactured and/or formulated by e.g. a spray-drying technique. In particular, the salt of Formula III has been found to be chemically stable in methanol solution at room temperature (i.e. a temperature from about 20 °C to about 25 °C such as about 22 °C), at a temperature of about 37 °C
25 and/or at a temperature of about 50 °C for about 48 hours or more such as for about 168 hours or more.

The present disclosure also provides a pharmaceutical composition comprising a salt of Formula III as described herein in admixture with a pharmaceutically acceptable
30 excipient, carrier and/or diluent.

The pharmaceutical composition described herein may be an oral pharmaceutical composition. For example, the oral pharmaceutical composition may be provided as a liquid preparation such as a syrup, suspension or solution. Alternatively, the oral
35 pharmaceutical composition may be provided as a solid such as a tablet, capsule, pill or lozenge. In particular, the oral pharmaceutical formulation may be a capsule or a tablet such as a caplet.

Further, there is provided a salt of Formula III, or a pharmaceutical composition as described herein, for use as a medicament.

5 The present disclosure also provides a salt of Formula III, or a pharmaceutical composition as described herein, for use in the treatment and/or prevention of a disease, disorder and/or condition selected from the group consisting of dementia, cognitive impairment, autism spectrum disorder, affective disorder, schizophrenia, anxiety disorder, attention deficit hyperactivity disorder (ADHD), movement disorder, postural instability and pathological apathy. For instance, the disease, disorder and/or
10 condition may be selected from the group consisting of dementia, cognitive impairment, schizophrenia and pathological apathy. In a further example, the disease, disorder and/or condition may comprise or consist of pathological apathy. The cognitive impairment may be age-related cognitive impairment or cognitive impairment associated with neurodegenerative disorder(s) and/or disease(s). The
15 postural instability may comprise or consist of fall(s). The pathological apathy may comprise or consist of apathy as defined according to an apathy measurement scale known in the art such as Apathy Evaluation Scale, Apathy Motivation Index, Dimensional Apathy Scale, Lille Apathy Rating Scale. Further, the pathological apathy may be associated with a neurodegenerative disease or disorder such as dementia,
20 Alzheimer's disease or Parkinson's disease. In particular, the pathological apathy may be associated with Parkinson's disease. The aforementioned disease, disorder and/or condition may occur in association with a neurological or psychiatric disorder such as schizophrenia, depression, dementia, and/or a neurodegenerative disorder. In a further example, the aforementioned disease, disorder and/or condition may occur
25 in association with a neurodegenerative disease or disorder such as Parkinson's disease, Alzheimer's disease, vascular dementia, Huntington's disease, or dementia associated with stroke. In still a further example, the aforementioned disease, disorder and/or condition may occur in association with Parkinson's disease or Alzheimer's disease.

30

Further, there is provided a salt of Formula III, or a pharmaceutical composition as described herein, for the manufacture of a medicament for use in the treatment and/or prevention of a disease, disorder and/or condition selected from the group consisting of dementia, cognitive impairment, autism spectrum disorder(s), affective disorder,
35 schizophrenia, anxiety disorder, attention deficit hyperactivity disorder (ADHD), movement disorder, postural instability and apathy. For instance, the disease, disorder and/or condition may be selected from the group consisting of dementia, cognitive impairment, schizophrenia and pathological apathy. In a further example, the disease,

disorder and/or condition may comprise or consist of pathological apathy. The cognitive impairment may be age-related cognitive impairment or cognitive impairment associated with neurodegenerative disorder(s) and/or disease(s). The postural instability may comprise or consist of fall(s). The pathological apathy may

5 comprise or consist of apathy as defined according to an apathy measurement scale known in the art such as Apathy Evaluation Scale, Apathy Motivation Index, Dimensional Apathy Scale, Lille Apathy Rating Scale. Further, the pathological apathy may be associated with a neurodegenerative disease or disorder such as dementia, Alzheimer's disease or Parkinson's disease. In particular, the pathological apathy

10 may be associated with Parkinson's disease. The aforementioned disease, disorder and/or condition may occur in association with a neurological or psychiatric disorder such as schizophrenia, depression, dementia, and/or a neurodegenerative disorder. In a further example, the aforementioned disease, disorder and/or condition may occur in association with a neurodegenerative disease or disorder such as Parkinson's

15 disease, Alzheimer's disease, vascular dementia, Huntington's disease, or dementia associated with stroke. In still a further example, the aforementioned disease, disorder and/or condition may occur in association with Parkinson's disease or Alzheimer's disease.

20 The present disclosure also provides a method for the treatment and/or prevention of a disease, disorder and/or condition selected from the group consisting of dementia, cognitive impairment, autism spectrum disorder, affective disorder, schizophrenia, anxiety disorder, attention deficit hyperactivity disorder (ADHD), movement disorder, postural instability and pathological apathy, said method comprising administering to

25 a mammal, such as a human or an animal, in need thereof, an effective amount such as a therapeutically effective amount of a salt of Formula III, or a pharmaceutical composition as described herein. For instance, the disease, disorder and/or condition may be selected from the group consisting of dementia, cognitive impairment, schizophrenia and pathological apathy. In a further example, the disease, disorder

30 and/or condition may comprise or consist of pathological apathy. The cognitive impairment may be age-related cognitive impairment or cognitive impairment associated with neurodegenerative disorder(s) and/or disease(s). The postural instability may comprise or consist of fall(s). The pathological apathy may comprise or consist of apathy as defined according to an apathy measurement scale known in

35 the art such as Apathy Evaluation Scale, Apathy Motivation Index, Dimensional Apathy Scale, Lille Apathy Rating Scale. Further, the pathological apathy may be associated with a neurodegenerative disease or disorder such as dementia, Alzheimer's disease or Parkinson's disease. In particular, the pathological apathy may be associated with

Parkinson's disease. The aforementioned disease, disorder and/or condition may occur in association with a neurological or psychiatric disorder such as schizophrenia, depression, dementia, and/or a neurodegenerative disorder. In a further example, the aforementioned disease, disorder and/or condition may occur in association with a neurodegenerative disease or disorder such as Parkinson's disease, Alzheimer's disease, vascular dementia, Huntington's disease, or dementia associated with stroke. In still a further example, the aforementioned disease, disorder and/or condition may occur in association with Parkinson's disease or Alzheimer's disease.

As used herein, the term prevention includes references to the prophylaxis and/or preventing of the disease, disorder and/or condition. In particular, the term may refer to achieving a reduction in the likelihood of the patient (or healthy subject) developing the condition (for example, at least a 10% reduction, such as at least a 20%, 30% or 40% reduction, e.g. at least a 50% reduction).

Further, as used herein the term therapeutically effective amount refers to an amount of a compound that confers a therapeutic effect on the treated patient. The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of and/or feels an effect).

The salt of Formula III may be prepared by combining a compound of Formula I as described herein with an acid of Formula II as described herein. Further, the compound of Formula I may be prepared as described in WO 2018/091687 and/or using methods known in the art.

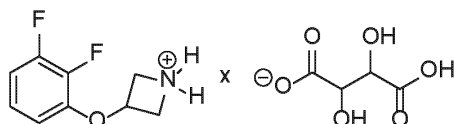
Accordingly, the present disclosure also provides a method for preparing a salt of Formula III as described herein said method comprising the steps of:

- providing a compound of Formula I as described herein and an acid of Formula II as described herein in a ratio of 1:n such as a ratio of 1:0.5 or 1:1;
- combining said compound of Formula I with said acid of Formula II in a solvent such as THF or ethanol or a mixture of ethanol and water to form a solution; and
- allowing the salt of Formula III to precipitate; and
- isolating said precipitate comprising or consisting of the salt of Formula III.

Salts

In this document, the chemical structure of the salt of Formula III comprising a combination of the compound of Formula I and the acid of Formula II has been drawn as a complex wherein the acidic proton(s) of the acid is attached to said acid. However,

the skilled person understands that the acidic proton(s) of the acid of Formula II may be attached to the nitrogen atom of the compound of Formula I and/or shared between the nitrogen atom of the compound of Formula I and the acid of Formula II, and this is also intended to be encompassed by the salt described herein. For instance, the salt of Formula IIIa2 being a 1:1 combination of the compound of Formula I and tartaric acid may also be represented as:



Labelled Compounds

10 Compounds of the present disclosure may be used in their labelled or unlabelled form. In the context of this present disclosure the labelled compound has one or more atoms replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. The labelling will allow easy quantitative detection of said compound.

15

In an example, there is provided a salt of Formula III as described herein wherein one or more of the hydrogen atoms of the compound of Formula I is/are replaced with deuterium.

20 Labelled compounds of the present disclosure may be useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods, and for in vivo receptor imaging. Labelled compounds of the present disclosure may contain at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this present disclosure the radionuclide may be selected from isotopes
25 of hydrogen, carbon, nitrogen, fluorine and oxygen, such as ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{18}O , ^{17}O , ^{19}F and ^{18}F . It is known that substitution with heavier isotopes, such as substitution of one or more hydrogen atoms with deuterium (^2H) might provide pharmacological advantages in some instances, such as increased metabolic stability.

30

The physical method for detecting a labelled compound of the present disclosure may be selected from Position Emission Tomography (PET), Single Photon Imaging Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), or combinations thereof.

Combinations

It will be appreciated that the salt(s) of the present disclosure may be combined with a further pharmaceutical drug for use in the treatment and/or prevention of CNS disorder(s) and/or disease(s). The further pharmaceutical drug may be L-DOPA, a
5 Selective Serotonin Reuptake Inhibitor, an antidepressant such as bupropion (i.e. (RS)-2-(*tert*-Butylamino)-1-(3-chlorophenyl)propan-1-one; CAS number 34911-55-2), a CNS stimulant such as methylphenidate (i.e. methyl phenyl(piperidin-2-yl)acetate; CAS number 20748-11-2) and/or an antipsychotic. Thus, there is provided
10 kit of parts comprising: (i) a salt of the present disclosure such as a salt of Formula II I as described herein, (ii) a pharmaceutical drug selected from the group consisting of L-DOPA, a Selective Serotonin Reuptake Inhibitor, an antidepressant such as bupropion (i.e. (RS)-2-(*tert*-Butylamino)-1-(3-chlorophenyl)propan-1-one; CAS number 34911-55-2), a CNS stimulant such as methylphenidate (i.e. methyl phenyl(piperidin-2-yl)acetate; CAS number 20748-11-2) and an antipsychotic, and (iii) optionally instructions
15 for separate, simultaneous or sequential administration of (i) and (ii).

The invention will be further described by reference to the following examples, which are not intended to limit the scope of the invention.

20

Examples

In this document the naming of the compounds was made using ChemDraw Ultra, version 12.0.2. 1076. If the chemical name and the chemical structure are inconsistent the chemical structure should be considered to be the correct structure.

25

Abbreviations

AAC	Accelerated Aging Conditions
ACN	acetonitrile
ADHD	attention deficit hyperactivity disorder
30 aq.	aqueous
CNS	central nervous system
CAT	Computed Axial X-ray Tomography
DCM	dichloromethane
DMSO	dimethylsulphoxide
35 DSC	Differential Scanning Calorimetry
DVS	Dynamic Vapor Sorption
EtOH	ethanol
Fig.	Figure

	g	gram(s)
	GABA	gamma-aminobutyric acid
	GAD	generalized anxiety disorder
	h	hour(s)
5	HOAc	Acetic acid
	kg	kilogram(s)
	L	liter(s)
	LC	low crystalline or liquid chromatography
	LC MS	Liquid Chromatography Mass Spectroscopy
10	mg	milligram(s)
	min.	minute(s)
	mL	milliliter(s)
	MRI	Magnetic Resonance Imaging
	MRS	Magnetic Resonance Spectroscopy
15	MTBE	methyl <i>tert</i> -butyl ether
	NMR	Nuclear Magnetic Resonance
	RH	relative humidity
	PET	Position Emission Tomography
	RT	room temperature
20	SPECT	Single Photon Imaging Computed Tomography
	TGMS	Thermogravimetric Analysis coupled with Mass Spectroscopy
	THF	tetrahydrofuran
	w/w	weight by weight
	XRP	X-Ray Powder
25	XRPD	X-Ray Powder Diffraction
	HR-XRPD	High Resolution X-Ray Powder Diffraction
	HT-XRPD	High Throughput X-Ray Powder Diffraction

General

- 30 Reagents and solvents were used as purchased without purification.
NMR analysis were performed on an NMR instrument operating at 500 MHz unless otherwise stated. The solvent peak was used as internal standard.

XRPD data were collected using HT-XRPD and/or HR-XRPD.

35

HT-XRPD:

HT-XRPD patterns were obtained using a high-throughput XRPD set-up. The plates were mounted on a Bruker General Area Detector Diffraction System (GADDS) equipped with a VÅNTEC-500 gas area detector corrected for intensity and geometric variations. The calibration of the measurement accuracy (peaks position) was performed using NIST SRM1976 standard (Corundum).

Data collection was carried out at room temperature using monochromatic Cu K α radiation in the 2θ region between 1.5° and 41.5° , which is the most distinctive part of the XRPD pattern. The diffraction pattern of each well was collected in two 2θ ranges ($1.5^\circ \leq 2\theta \leq 21.5^\circ$ for the first frame, and $19.5^\circ \leq 2\theta \leq 41.5^\circ$ for the second) with an exposure time of 90s for each frame. No background subtraction or curve smoothing was applied to the XRPD patterns.

HR-XRPD:

The HR-XRPD data were collected on D8 Advance diffractometer using Cu K α 1 radiation ($1.54056 \text{ \AA}$) with germanium monochromator at RT. Diffraction data were collected in the 2θ range $2.15 - 41.5^\circ$. Detector scan on solid state LynxEye detector was performed using 0.016° per step with 15 sec/step scan speed. The samples were measured in 8 mm long glass capillaries with 0.3 mm outer diameter.

Hygroscopicity test

The hygroscopicity was measured using Dynamic Vapor Sorption (DVS9 collected on a DVS Adventure system from Surface Measurement Systems (London, UK). The sample size was approximately 10 mg of solid material. A full sorption and desorption isotherm was recorded by varying the relative humidity from 40-95-0-40 % in steps of 10% with 1 h equilibration time at a constant temperature of 25°C . Afterwards, the sample was measured by HT-XRPD.

According to the percentage water uptake at $25^\circ\text{C}/80\% \text{ RH}$ during the first sorption cycle of sorption isotherm the materials were classified as in Table 1 below.

Table 1

Classification	% Water uptake at $25^\circ\text{C}/80\% \text{ RH}$ (w/w)
Non-hygroscopic	0 - 0.2
Slightly hygroscopic	0.2 - 2.0
Moderately hygroscopic	2.0 - 15.0
Very hygroscopic	>15.0

Water solubility test

The water solubility was assessed by adding aliquots of water at room temperature to 4-8 mg of the salt. The water solubility was found to be acceptable if it was equal to or above that of 3-(2,3-difluorophenoxy)azetidine, i.e. equal to or above 5 mg/mL.

Differential Scanning Calorimetry (DSC) analysis

The melting point was determined using DSC analysis performed as follows. Thermal events were obtained from DSC thermograms, recorded with a heat flux DSC3+ STARE system(Mettler-Toledo GmbH, Switzerland). The DSC3+ was calibrated for temperature and enthalpy with a small piece of indium (m.p. = 156.6°C; δH_f = 28.45 J/g) and zinc (m.p. = 419.6°C; δH_f = 107.5 J/g). Samples (circa 2 mg) were sealed in standard 40 μ L aluminum pans, pin-holed and heated in the DSC from 25 °C to 300 °C, at a heating rate of 10 °C/min. Dry N₂ gas, at a flow rate of 50 mL/min was used to purge the DSC equipment during measurement.

Test for chemical stability in solution

The chemical stability in solution was assessed for two different salts of 3-(2,3-difluorophenoxy)azetidine according to the present invention as well as for one salt of 3-(2,3-difluorophenoxy)azetidine according to the prior art. The tests were performed in methanol solution at two different temperatures (37°C and 50°C) for a period up to one week. The analyses of the samples were performed by liquid chromatography (LC) coupled to mass spectrometry (MS). The levels of 3-(2,3-difluorophenoxy)azetidine and possible degradation products were measured by LC-MS/UV detection, LC/MSD iQ Singlequad (Agilent). The HPLC module included a binary pump system, vacuum degasser, thermostatted autosampler and thermostatted column compartment. Column; Poroshell 120 EC C18 (2.7*100 mm, 4.6 μ m)

Mobile phase A: 0.03% HOAc in Milli-Q water

Mobile phase B: 0.03% HOAc in acetonitrile

Flow rate: 1.0 ml/min

Elution gradient:

Time (min)	0	0.5	5.5	8.5	9.5
Solvent A (%)	95	95	5	5	95
Solvent B (%)	5	5	95	95	5

Mass spectrometric parameters:

Polarity: Positive/Negative mode, ESI+/-

Desolvation temperature: 325°C

Capillary voltage: 3.5 kV

Mass range (m/z): 100-1000 m/z

Injection volume: 2.0 µL

UV: (190-400 nm) 250 nm

5 **Synthesis of acid addition salts of the compound of Formula II, i.e. 3-(2,3-difluorophenoxy)azetidine**

10 The compound 3-(2,3-difluorophenoxy)azetidine, i.e. the compound of Formula I described herein, was combined with a number of different acids using Method A or Method B described below.

Method A:

15 Aliquots of a 1 M aqueous solution of the acid or the neat solid acid was added to a saturated solution of the compound of Formula I in either THF or acetonitrile. Subsequently, the mixture was subjected to a temperature profile of one heating cycle to 50 °C followed by cooling to 5 °C for four hours and final aging at 5 °C for approximately 72 hours.

Method B:

20 A suspension of the compound of Formula II and the acid was prepared in ethanol. Subsequently, the mixture was subjected to a temperature profile of 3 heating-cooling cycles between 5 – 50 °C and final aging at 25 °C for 72 hours.

25 After the procedures described for Method A and Method B, respectively, the resulting solid was separated by centrifugation, dried and analyzed by High Throughput XRPD (HT-XRPD). If no solid precipitated, the solvent of the solution was evaporated at ambient conditions overnight and subsequently at 50 °C under vacuum overnight. Subsequently, the solid was exposed to accelerated aging conditions (AAC), i.e. exposed to a temperature of 40 °C and a relative humidity (RH) of 75% for 48 hours.

30 The solid having been subjected to AAC was then re-analyzed by XRPD to assess its physical stability. If no, substantially no or a very minor change had taken place the solid was considered to be stable. The solid was also subjected to ocular inspection to observe any change such as discoloration. The salt was considered not to be stable if its XRPD spectrum differed significantly from the one taken before the AAC treatment

35 and/or if ocular inspection revealed a change in colour or the like. Novel XRPD patterns different from XRPD patterns of 3-(2,3-difluorophenoxy)azetidine and the acid were considered a potential hit of a crystalline salt. The potential crystalline salt was named with the abbreviation for the salt followed by a number as shown in Table 1.

The base/acid ratio of the obtained salt forms was determined by ^1H NMR spectroscopy with a relaxation time of at least 10 seconds or by elemental analysis.

- 5 The results are shown in Table 2. Different solvents were tried for the crystallization. For example, for the preparation of the hydrochloric acid salts the solvents ethanol, tetrahydrofuran and acetonitrile were each tried separately. In the column "Chemical stability", most of the salt forms were found to be chemically stable upon exposure to Accelerated Aging Conditions if indicated so by XRPD and ocular inspection as described
- 10 above.

Table 2

Acid (Abbreviation of acid)	Salt form	Solvent	Ratio of the added acid to the compound of Formula I	Chemical stability
Hydrochloric acid (HCl)	HCl2	EtOH, THF, ACN	1.1:1	Yes
Sulphuric acid (SUL)	SUL1	EtOH, THF, ACN	1.1:1	No
	SUL2	EtOH	0.5:1	No
	SUL3	EtOH, ACN	0.5:1	No
	SUL4	THF	0.5:1	No
<i>p</i> -Toluene sulfonic acid (TOS)	TOS1	EtOH, THF	1.1:1	No
		ACN	1.1:1	Yes
L-Tartaric acid (TAR)	TAR1	THF, ACN	1.1:1	Yes
	TAR2	THF	1.1:1	Yes
		EtOH	0.5:1	Yes
	TAR3 LC	ACN	0.5:1	No
	TAR4	EtOH, THF, ACN	1.1:1	Yes
		ACN	0.5:1	Yes
	TAR5 LC	EtOH	1.1:1	No
L-Malic acid (MAL)	MAL1	ACN	1.1:1	Yes
	MAL2 (oily)	ACN	1.1:1	No
		EtOH	0.5:1	No

	MAL3(oily)	EtOH,ACN,THF	0.5:1	No
	MAL4	ACN	0.5:1	No
Benzoic acid (BEN)	BEN1	EtOH, THF	1.1:1	No
	BEN1	ACN	1.1:1	No
Succinic acid (SUC)	SUC1	THF	0.5:1	Yes
	SUC1	EtOH	1.1:1	Yes
	SUC1+SUC2	EtOH,THF	1.1:1	Yes
	SUC1+ traces of SUC2	ACN	0.5:1	Yes
Ethane-1,2- disulfonic acid (EDY)	EDY1	EtOH,THF,ACN	1.1:1	No
	EDY1	EtOH,THF,ACN	0.5:1	No
Acetic acid	ACA1 (gel)	ACN	1:1	No
	ACA2 (gel)	EtOH	1:1	No
Methanesulfonic acid (MES)	MES1	EtOH,THF,ACN	1:1	No
Adipic acid (ADI)	ADI1	EtOH,THF,ACN	1:1	No
	ADI1	EtOH,THF,ACN	0.5:1	No
Glutaric acid (GLT)	GLTI1 (gel)	EtOH,THF,ACN	1:1	No
	GLTI1 (gel)	EtOH,THF,ACN	0.5:1	No
Malonic acid (MAO)	MAO1	EtOH,THF,ACN	1:1	Yes (wet)
	MAO1	EtOH,THF,ACN	0.5:1	Yes (wet)
	MAO2+ MAO1	EtOH,ACN	1:1	No
	MAO2+ MAO1	EtOH,ACN	0.5:1	No
	MAO3	THF	0.5:1	No

The salt forms in Table 1 which were chemically stable in the AAC test or converted into a chemically stable form after exposure to the AAC test were investigated further as follows.

Hydrochloric acid salts

The hygroscopicity of the HCl salt form indicated in Table 2 was evaluated by DVS analysis and found to be about 6% at 80% RH, i.e. this HCL salt form was moderately hygroscopic.

5

Thus, the above-mentioned hydrochloric acid salt form was found to be hygroscopic. Further, the water solubility was found to be above 180 mg/mL.

Fumaric acid salt

- 10 The hygroscopicity of the fumarate salt form according to Example 1B in WO 2018/091687 was investigated and found to be 0.3% at 80% RH, i.e. the fumaric acid salt was slightly hygroscopic. Further, the water solubility of the fumarate salt was found to be about 16 mg/mL.

15 p-Toluene sulfonic acid salt

The hygroscopicity of the TOS1 salt form was found to be 3% at 80% RH, i.e. the TOS1 salt form was moderately hygroscopic. Thus, the TOS1 salt form was found to be hygroscopic. Further, the qualitative water solubility was found to be about 10 mg/mL.

20 L-Tartaric acid salt

The TAR1 salt form was the most common salt form for the tartaric acid salt. Thermal analysis of the TAR1 salt form showed that it was a sesqui-hydrate containing 1.5 equivalents of water which dehydrated between 30 °C and 100 °C. The thermal behaviour was characterized by a broad endotherm corresponding to the water loss.

- 25 No other thermal events were detected after dehydration indicating that the crystal structure collapses after the water loss. It was concluded that the TAR1 salt form is not suitable for development due to the risk for dehydration and possible amorphization.

- 30 The TAR3 and TAR5 salt forms became deliquescent upon exposure to AAC.

- The TAR2 salt form appeared to be an anhydrous hemi-L-tartrate salt. The melting point of the TAR2 salt form was 181.5 °C. DVS analysis showed that TAR2 has a water uptake below 0.2% at 80% RH. The aqueous solubility was in the range of 53-106 mg/mL. A very small amount of the TAR2 salt form converted to the TAR4 salt form upon exposure to AAC.
- 35

It was concluded that the TAR2 salt form is non-hygroscopic. Further, it was concluded that the TAR2 salt form has a satisfactory water solubility. Moreover, the high melting point of 181.5 °C for the TAR2 salt form makes it suitable for manufacturing of a pharmaceutical composition such as a tablet.

5

¹H NMR analysis of the TAR2 salt showed that the salt was a combination of the compound of Formula I and L-tartaric acid taken in a ratio of 1:0.5.

10 XRPD analysis is provided the diffractogram in Figure 1. The main characteristic peaks, with positions and relative intensities, have been extracted from the diffractogram in Figure 1 and is given in the table below.

Table summarizing the peaks from Figure 1

Angle 2θ [°]	d-value [Å]	Relative intensity [%]
6.99	12.64	21
12.86	6.88	13
14.00	6.32	30
15.07	5.87	15
16.72	5.30	22
17.80	4.98	43
19.49	4.55	41
19.93	4.45	38
20.75	4.28	34
21.60	4.11	46
22.70	3.91	19
23.68	3.75	28
24.12	3.69	32
26.40	3.37	9
27.43	3.25	100
28.16	3.17	18
29.22	3.05	16
29.69	3.01	11
30.27	2.95	9
32.57	2.75	8

Succinic acid salt

The hygroscopicity of the SUC1 salt form was found to be less than 0.2% at 80% RH. Thus, the SUC1 salt form was found to be non-hygroscopic. Further, the qualitative water solubility was found to be from 20 to 40 mg/mL. As indicated by TGMS and ¹HNMR the SUC1 salt form is an anhydrous mono-succinate salt with a melting temperature of 150.2 °C as determined by Differential Scanning calorimetry(DSC). SUC1 salt containing minor amounts of the SUC2 salt form were formed when EtOH/THF or ACN were used as solvents.

It was concluded that the succinic acid salt, such as the SUC1 salt, is non-hygroscopic. Further, it was concluded that the succinic acid salt, such as the SUC1 salt form described herein, has a satisfactory water solubility. Moreover, the high melting point of 150.2 °C for the SUC1 salt form makes it suitable for manufacturing of a pharmaceutical composition such as a tablet. Further, the fact that only two polymorphic forms were identified and the ease of forming only the SUC1 salt form was found to be a benefit in relation to manufacturing and control of drug properties.

¹H NMR analysis of the SUC1 salt showed that the salt was a combination of the compound of Formula I and succinic acid taken in a ratio of 1:1.

XRPD analysis provided the diffractogram in Figure 2. The main characteristic peaks, with positions and relative intensities, have been extracted from the diffractogram in Figure 2 and is given in the table below.

Table summarizing the peaks from Figure 2

Angle 2θ [°]	d-value [Å]	Relative intensity [%]
11.60	7.62	32
12.46	7.10	100
13.32	6.64	43
16.46	5.38	90
17.09	5.19	23
18.35	4.83	19
19.34	4.59	64
20.24	4.38	25
21.98	4.04	34

22.43	3.96	49
23.31	3.81	49
24.15	3.68	58
24.86	3.58	70
25.88	3.44	69
26.87	3.32	87
28.40	3.14	21
28.92	3.09	16
29.98	2.98	25
30.63	2.92	20
32.17	2.78	16

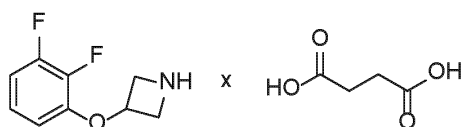
Malonate salt

MAO1 was found to be the most relevant crystal form based on crystallinity and physical stability. MAO2 converted to MAO1 while MAO3 became deliquescent upon exposure to AAC.

¹H NMR analysis showed salt formation with a free base (i.e. the compound of Formula I): malonic acid stoichiometry of 1:1. Thermal analysis indicated that MAO1 is an anhydrous phase which starts decomposing at 120 °C and melts/decomposes at 154.6 °C. The aqueous solubility was found to be between 40-80 mg/mL. The DVS analysis showed that MAO1 is moderately hygroscopic with a water uptake of 3.4% at 80% RH. Thus, the malonic acid salt is hygroscopic.

Example 1

3-(2,3-difluorophenoxy)azetidine succinic acid salt



A) 3-(2,3-difluorophenoxy)azetidine

To a 50-L reactor DMSO (20 L) was charged, followed by *tert*-butyl 3-[(4-methylphenyl)sulfonyl]oxy}-1-azetidinecarboxylate (3.03 kg, 9.2 mol), 2,3-difluorophenol (1.32 kg, 10.2 mol) and potassium carbonate (2.30 kg, 16.6 mol). The reaction mixture was heated to an internal temperature of 70 °C for 16 hours.

Additional amount of potassium carbonate (230 g, 1.66 mol) was added and stirring was continued at 70-75 °C for 6 hours. The temperature was increased to 80 °C and the mixture was stirred for additional 16 hours. The mixture was diluted with MTBE (15 L) and then water (15 L) was added. The two layers were separated and the organic layer was washed with an aqueous 10% Na₂CO₃ solution (5 L), 10% NaCl (3 × 5 L) and with water (5 L). The solution was charged to a 50-L reactor and then an aqueous HCl solution (37%, 5.65 kg, 57 mol) was added. The reaction mixture was stirred at an internal temperature of 22 °C for 16 hours and then water (15 L) was added. Most of the MTBE was evaporated and then the aqueous layer was extracted with a new portion of MTBE (15 L). The two layers were separated and the organic phase was discarded. The aqueous solution was cooled to 10 °C and then pH adjusted with NaOH aq. solution (50%, 3.95 kg) until a pH of 14 was obtained, keeping the internal temperature below 35 °C during the addition. The solution was extracted twice with DCM (25 L and 13 L). The combined organic layers were washed with water (13 L) and then concentrated under reduced pressure until the volume left was approximately 13 L. THF (13 L) was added, and distillation was continued until the volume left was approximately 11 L. Water (25 L) was added, and the solution was concentrated under reduced pressure until the volume left was approximately 23 L. The formed slurry was stirred at 20 °C for 1 hour and then cooled to 10 - 15 °C for 17 hours. The precipitate was isolated by filtration and the filter cake was washed with water (2 × 2.5 L) and then dried on the filter by pulling air through it at room temperature for 70 hours. There was obtained 1.51 kg (92%) of the title compound as a solid. LC MS m/z 186 [M+H]⁺. LC purity: 99.8 %-area.

B) 3-(2,3-difluorophenoxy)azetidine succinic acid salt

To a 50-L reactor EtOH (15 L) was charged, followed by succinic acid (954 g, 8.08 mol). The slurry was stirred at internal temperature of 32 °C for almost 2 h until full dissolution of acid was achieved. The solution was discharged from the reactor and stored at room for one day. The reactor was rinsed with EtOH and then charged with EtOH (15 L) and water (3 L). 3-(2,3-difluorophenoxy)azetidine (1.5 kg, 8.10 mol) was added and the mixture was stirred at internal temperature of 55 °C for 1 h until full dissolution of the amine was achieved. The solution was cooled to room temperature and discharged from the reactor. The reactor was rinsed with EtOH and then the amine solution as well as the succinic acid solution was charged back to the reactor through a filter. The mixture was heated to an internal temperature of 75 °C for 51 minutes. After the mixture gradually was cooled to an internal temperature of 5 °C (5 degrees per 20 min), the formed slurry was stirred at 5 °C for 15 h. The product was isolated by filtration and the filter cake was washed twice with EtOH (2 × 1.5 L) and then dried on the filter by pulling air through it at room temperature for almost three days. There

was obtained 1.73 kg (71%) of the succinic acid salt of 3-(2,3-difluorophenoxy)azetidine as a white solid. LC MS m/z 186 [M+H]⁺. LC purity: 99.8 %-area. ¹H NMR (300 MHz, DMSO-d₆): δ 2.33 (s, 4H), 3.84 (m, 2H), 4.14 (m, 2H), 5.12 (m, 1H), 6.78 (m, 1H), 7.1-7.2 (m, 2H), 10.18 (b, 3H). 3H), 1.8-2.0 (m, 5H), 1.73 (m, 4H), 1.65 (m, 2H), 1.55 (m, 3H), 1.15 (m, 1H), 0.89 (t, 3H). The NMR spectrum showed a ratio of 1:1 between the above-identified azetidine derivative and succinic acid. Thus, in this example the succinic acid salt of 3-(2,3-difluorophenoxy)-azetidine is provided as a combination of 3-(2,3-difluorophenoxy)azetidine and succinic acid taken in a ratio of 1:1.

10

Example 2

3-(2,3-difluorophenoxy)azetidine hemi L-(+)-tartaric acid salt

To a 1-L round bottom flask a mixture of EtOH and water (19:1, 600 mL) was charged, followed by 3-(2,3-difluorophenoxy)azetidine (75.3 g, 0.40 mol). Thereafter, L-(+)-tartaric acid (33.6 g, 0.22 mol) dissolved in a mixture of EtOH and water (19:1, 150 mL) was added. The slurry was stirred at an internal temperature of 76 °C for 40 min until almost all solid was dissolved. Water (55 mL) was then added portion wise until a clear solution was achieved. After stirring at 76 °C for 5 min the mixture was cooled to room temperature. The obtained white slurry was stirred at 0-5 °C for 2 h. The precipitate was isolated by filtration and the filter cake was washed twice with a mixture of EtOH and water (19:1, 2 x 75 mL). The product was dried on the filter by pulling air through it at room temperature for 16 hours and then in vacuo at 40°C for 24 h. There was obtained 84.4 g (80%) of the title compound as a white solid. m/z 186 [M+H]⁺. LC purity: 100 %-area. ¹H NMR (400 MHz, D₂O): δ 4.28 (m, 3H), 4.55 (m, 2H), 5.21 (m, 1H), 6.65 (m, 1H), 6.93 (m, 1H), 7.06 (m, 1H). The NMR spectrum showed a ratio of 2:1 between the above identified azetidine derivative and L-tartaric acid. Thus, in this example the L-tartaric acid salt of 3-(2,3-difluorophenoxy)-azetidine is provided as a combination of 3-(2,3-difluorophenoxy)-azetidine and L-tartaric acid taken in a ratio of 1:0.5.

30

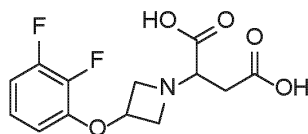
Comparative Example: 3-(2,3-difluorophenoxy)azetidine fumaric acid salt



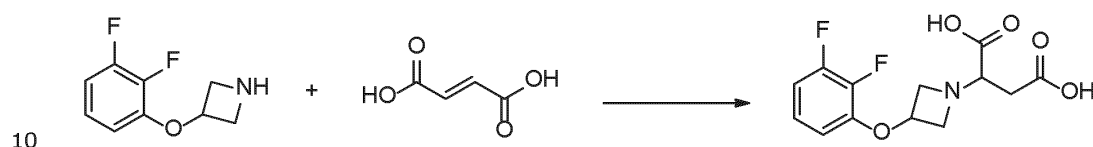
In this comparative example 3-(2,3-difluorophenoxy)azetidine fumaric acid salt from Example 1B in WO 2018/091687 was re-evaluated. After re-examining the LC MS chromatogram of the fumarate salt of 3-(2,3-difluorophenoxy)azetidine in Example 1B

of WO 2018/091687, it was observed that the product was contaminated with 2-4% of an impurity having an m/z of 300 in negative mode and an m/z of 302 in positive mode. It was concluded that said impurity is an adduct of the amine and fumaric acid, of which chemical structure is depicted below.

5



It is believed that the formation of this impurity is due to a Michael-addition reaction between 3-(2,3-difluorophenoxy)azetidine and fumaric acid according to the reaction scheme depicted below.



10

Even though the content of the Michael-adduct impurity was seemingly low (2-4%), it is likely to cause problems during upscaling of the reaction, such as upscaling to industrial production, where additional steps such as a step for removing impurities negatively impact the overall performance and viability of the upscaling. Further, this side reaction leading to the Michael-adduct impurity is likely to take place to a larger extent when the reaction is run on a big scale such as an industrial scale where process conditions typically involve e.g. longer reaction times which would favour the formation of the Michael-adduct impurity.

20

Example 3

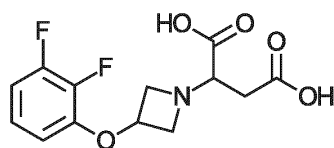
Chemical stability in methanol solution at 37°C and 50°C

Three different salts of 3-(2,3-difluorophenoxy)azetidine were investigated in the chemical stability test: 1) succinic acid salt according to Example 1, 2) hemi L-(+)-tartaric acid salt according to Example 2, and 3) fumaric acid salt according to Example 1B in WO 2018/091687 (prior art compound). 2.0 mg of each test compound was weighed into each vial, one for each temperature. The vials were diluted with 1 mL methanol. At each timepoint, the samples were diluted with Milli-Q water, i.e. ultrapure water, to a final concentration of approximately 600-700 μM in relation to 3-(2,3-difluorophenoxy)azetidine (Formula I). The timepoints were one, two, three, four, 24, 48 hours and one week.

30

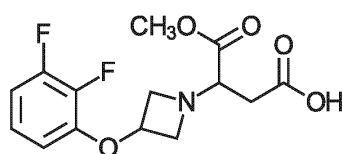
Possible degradation products being formed were detected and characterized by LC MS. Thus, the chemical structure of the major degradation product in the solution of

the fumaric acid salt of 3-(2,3-difluorophenoxy)azetidine was determined to be the Michael adduct according to Formula A as shown below.

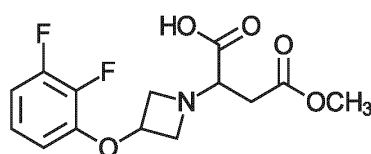


Formula A

- 5 The chemical structures for the second and third highest degradation products in the same methanol solution were determined to be the two regio isomers of a mono methyl ester of the Michael adduct according to Formula B and Formula C. However, it was not possible to determine which one of the two regio isomers that corresponded to which one of the two peaks in the chromatogram.



Formula B



Formula C

10 The retention time for 3-(2,3-difluorophenoxy)azetidine (Formula I) was 3.7-3.8 min. whereas the retention time for degradation product according to Formula A was 4.0-4.1 min. Retention times for the two degradation products according to Formula B and Formula C were 4.2-4.3 min and 4.4-4.5 min, respectively. The LC Area % of the three different degradation products increased over time and for instance, the LC Area % after one week at 50°C were the following: Formula A, 60.2%, Formula B (or Formula C), 11.6% and Formula C (or Formula B), 3.5%.

20

The results from the stability study of the methanol solution of the succinic acid salt of 3-(2,3-difluorophenoxy)azetidine at 37°C and 50°C are shown in Table 3. The detected compound which elutes at 3.7-3.8 min is the non-salt form of 3-(2,3-difluorophenoxy)azetidine and that compound is named Formula I in the table. The corresponding results from the methanol solution of the hemi L-(+)-tartaric acid salt and the fumaric acid salt of 3-(2,3-difluorophenoxy)azetidine are shown in Table 4 and Table 5, respectively.

25

Table 3. Chemical stability in methanol solution for succinic acid salt of 3-(2,3-difluorophenoxy)azetidine at 37°C and 50°C, respectively

Time (h)	Area % of Formula I at 37°C	Area % of Formula I at 50°C
0	100	100
1	100	100
2	100	100
3	100	100
4	100	100
24	100	100
48	100	100
168	100	100

5 Table 4. Chemical stability in methanol solution for hemi L-(+)-tartaric acid salt of 3-(2,3-difluorophenoxy)azetidine at 37°C and 50°C, respectively

Time (h)	Area % of Formula I at 37°C	Area % of Formula I at 50°C
0	100	100
1	100	100
2	100	100
3	100	100
4	100	100
24	100	100
48	100	100
168	100	100

Table 5. Chemical stability in methanol solution for fumaric acid salt of 3-(2,3-difluorophenoxy)azetidine at 37°C and 50°C, respectively

Time (h)	Area % of Formula I at 37°C	Area % of Formula I at 50°C
0	97.2	97.2
1	96.3	90.3
2	92.4	85.3
3	90.4	81.4
4	89.5	76.5
24	71.3	56.3
48	66.9	52.4
168	48.4	23.6

As shown in Table 5, the fumaric acid salt of 3-(2,3- difluorophenoxy)azetidine (prior art compound according to Example 1B in WO 2018/091687) degrades significantly in methanol solution at 37°C. The degradation is even more significant at 50°C when almost half the amount of the drug has degraded after two days. In contrast, and as shown in Table 3 and Table 4, neither the corresponding succinic acid salt, nor the corresponding hemi L-(+)-tartaric acid salt degrades at any of the tested temperatures in methanol solution. Thus, the two salts of the invention have a very high stability in solution even when being in methanol solution at 50°C for one week.

10 Remarks

As shown hereinabove, both the succinic acid salt and the hemi L-(+)-tartaric acid salt of the compound of Formula I are non-hygroscopic, have a high melting point, good water solubility and are stable in solution which allows for e.g. handling and/or storage without or substantially without degradation. Thus, both salts have properties making them suitable for use as a pharmaceutical or for processing into a pharmaceutical composition.

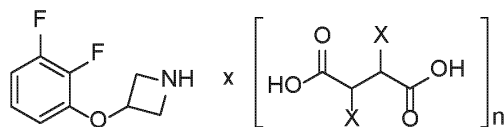
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2. Biol Psych, 2011, 69(12); 89-99.
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5. Mol Psych, 2005, 1 O; 40-68.
6. Eur Psych, 2005, 20; 15-27.
7. WO 2010/022055
- 10 8. WO 2018/091687

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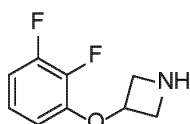
Claims

1. A salt of Formula III:

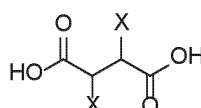


Formula III

- 5 said salt being a combination of a compound of Formula I and an acid of Formula II:



Formula I



Formula II

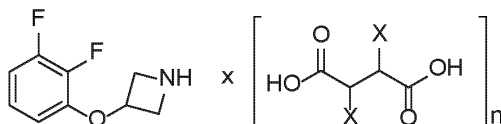
in a ratio of 1:n,

10 wherein

X is OH or H; and

n is 0.5 or 1.

- 15 2. The salt of Formula III according to claim 1, wherein X is OH thereby providing a salt of Formula IIIa being a combination of the compound of Formula I and tartaric acid:



Formula IIIa

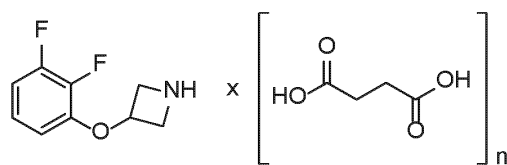
- 20 3. The salt of Formula IIIa according to claim 2, wherein the tartaric acid is L-(+)-tartaric acid.

4. The salt of Formula IIIa according to claim 2, wherein the tartaric acid is D-(-)-tartaric acid.

25

5. The salt of Formula IIIa according to claim 2, wherein the tartaric acid is L-(+)-tartaric acid and D-(-)-tartaric acid.

- 30 6. The salt of Formula III according to claim 1, wherein X is H thereby forming a salt of Formula IIIb being a combination of the compound of Formula I and succinic acid:



Formula IIIb

7. The salt of Formula III according to any one of the preceding claims, wherein n is 0.5.
8. The salt of Formula III according to any one of claims 1-6, wherein n is 1.
9. The salt according to any one of the preceding claims, characterised by being crystalline.
10. The salt of Formula III according to any one of claims 1-5, 7 or 9, characterized by an XRP diffractogram comprising a peak at 27.4 degrees 2θ and one or more peaks selected from the following: 17.8, 19.5, 19.9, 21.6 degrees 2θ.
11. The salt of Formula III according to any one of claims 1-5, 7 or 9, characterized by an XRP diffractogram as shown in Figure 1.
12. The salt of Formula III according to any one of claims 1, 6, 8 or 9, characterized by an XRP diffractogram comprising a peak at 12.5 degrees 2θ and one or more peaks selected from the following: 13.3, 16.5, 19.3, 22.4, 23.3, 24.1, 24.9, 25.9, 26.9 degrees 2θ.
13. The salt of Formula III according to any one of claims 1, 6, 8 or 9, characterized by an XRP diffractogram as shown in Figure 2.
14. The salt of Formula III according to any one of the preceding claims, wherein one or more of the hydrogen atoms of the compound of Formula I is/are replaced with deuterium.
15. The salt of Formula III according to any one of the preceding claims, wherein said salt changes its weight by about ± 0.2% by weight or less at any humidity, such as any relative humidity such as a relative humidity of 80% measured at a temperature from 20 °C to 25 °C.
16. The salt of Formula III according to any one of claims 1-5 or 7-11, which has a water solubility from 53 mg/mL to 106 mg/mL and/ or a melting point of 181.5 °C.

17. The salt of Formula III according to any one of claims 1, 6-9, 12 or 13, which has a water solubility from 20 mg/mL to 40 mg/mL and/ or a melting point of 150.2 °C.
- 5 18. The salt of Formula III according to any one of the preceding claims, wherein said salt is chemically stable in methanol solution at room temperature, at a temperature of 37 °C and/or at a temperature of 50 °C for 48 hours or more such as for 168 hours or more.
- 10 19. A pharmaceutical composition comprising the salt of Formula III according to any one of the preceding claims in admixture with a pharmaceutically acceptable excipient, carrier and/or diluent.
- 15 20. The salt of Formula III as defined in any one of claims 1-18, or the pharmaceutical composition according to claim 19 for use as a medicament.
- 20 21. The salt of Formula III as defined in any one of claims 1-18, or the pharmaceutical composition according to claim 19 for use in the treatment and/or prevention of a disease, disorder and/or condition selected from the group consisting of dementia, cognitive impairment, autism spectrum disorder, affective disorder, schizophrenia, anxiety disorder, attention deficit hyperactivity disorder (ADHD), movement disorder, postural instability and
- 25 pathological apathy.
22. The salt of Formula III for use according to claim 21, or the pharmaceutical composition for use according to claim 21 wherein the disease, disorder and/or condition is pathological apathy.
- 30 23. The salt of Formula III for use according to claim 22, the pharmaceutical composition for use according to claim 22 wherein the pathological apathy is as defined in an apathy measurement scale.
- 35 24. The salt of Formula III for use according to claim 23, or the pharmaceutical composition for use according to claim 23 wherein the apathy measurement scale is one or more of the following: Apathy Evaluation Scale, Apathy Motivation Index, Dimensional Apathy Scale, Lille Apathy Rating Scale.
- 40

25. The salt of Formula III for use according to any one of claims 21-24, or
the pharmaceutical composition for use according to any one of claims 21-24
wherein the pathological apathy is associated with a neurodegenerative disease
such as dementia, Alzheimer's disease or Parkinson's disease.
- 5 26. The salt of Formula III for use according to claim 25, or
the pharmaceutical composition for use according to claim 25
wherein the neurodegenerative disease is Parkinson's disease.
- 10 27. Use of a salt of Formula III as defined in any one of claims 1-18 or a
pharmaceutical composition according to claim 19
for the manufacture of a medicament for the treatment and/or prevention of a
disease, disorder and/or condition selected from the group consisting of
dementia, cognitive impairment, autism spectrum disorder, affective disorder,
15 schizophrenia, anxiety disorder, attention deficit hyperactivity disorder (ADHD),
movement disorder, postural instability and pathological apathy.
28. The use according to claim 27, wherein the disease, disorder and/or condition is
pathological apathy.
- 20 29. The use according to claim 28, wherein the pathological apathy is as defined in an
apathy measurement scale.
30. The use according to claim 29, wherein the apathy measurement scale is one or
25 more of the following: Apathy Evaluation Scale, Apathy Motivation Index,
Dimensional Apathy Scale, Lille Apathy Rating Scale.
31. The use according to any one of claims 27-30, wherein the pathological apathy is
associated with a neurodegenerative disease such as dementia, Alzheimer's
30 disease or Parkinson's disease.
32. The use according to claim 31, wherein the neurodegenerative disease is
Parkinson's disease.
- 35 33. A method for the treatment and/or prevention of a disease, disorder and/or
condition selected from the group consisting of dementia, cognitive impairment,
autism spectrum disorder, affective disorder, schizophrenia, anxiety disorder,
attention deficit hyperactivity disorder (ADHD), movement disorder, postural
instability and pathological apathy, said method comprising administering to a
40 mammal, such as a human or an animal, in need thereof, an effective amount,

such as a therapeutically effective amount, of a salt of Formula III as defined in any one of claims 1-18 or a pharmaceutical composition as defined in claim 19.

34. The method according to claim 33, wherein the disease, disorder and/or condition
5 is pathological apathy.

35. The method according to claim 34, wherein the pathological apathy is as defined in an apathy measurement scale.

10 36. The method according to claim 35, wherein the apathy measurement scale is one or more of the following: Apathy Evaluation Scale, Apathy Motivation Index, Dimensional Apathy Scale, Lille Apathy Rating Scale.

37. The method according to any one of claims 33-36, wherein the pathological
15 apathy is associated with a neurodegenerative disease such as dementia, Alzheimer's disease or Parkinson's disease.

38. The method according to claim 36, wherein the neurodegenerative disease is Parkinson's disease.

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