

COMPOUNDS FOR TREATMENT OF A HYPERKINETIC MOVEMENT DISORDER

FIELD OF THE INVENTION

The invention relates to racemic and diastereoisomerically enriched 1-[[2-(methoxymethyl)-
5 6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R*,2R*)-2-(trifluoromethyl)-
cyclopropyl]-2H-pyrrol-5-one compounds, processes for preparing them, pharmaceutical
compositions containing them and their use as pharmaceuticals for treatment of a
hyperkinetic movement disorder in a mammal.

BACKGROUND OF THE INVENTION

10 Hyperkinetic movement disorders (HMDs) also referred to as dyskinesias are characterized
by abnormal, often repetitive, involuntary movements overlapped to normal motor activity. Its
5 major types are Tremors, Chorea, Dystonia, Myoclonus and Tics. Specific disorders are
Huntington's disease chorea, tardive dyskinesia, Tourette Syndrome (and possible related
hyperkinetic disorders like chorea in general, ballism, dystonia). Tics are the most common
15 hyperkinetic disorder in children. Dystonia, stereotypies, choreoathetosis, tremors, and
myoclonus also occur but are less common. Many hyperkinetic movement disorders
manifest with multiple types of movements, which may include a combination of the various
hyperkinesias.

HMDs can be itself a disease entity or a sign of another underlying neurologic condition.
20 They can result from genetic abnormalities and neurodegenerative diseases; structural
lesions; infection; drugs and toxins; or psychogenic causes. Psychiatric illnesses and
corresponding long-term neuroleptic medications have been associated with HMD (i.e.
tardive dyskinesia). Similarly, antiparkinsonian drug therapy can be responsible for the
development of chorea and dystonia after several years of treatment (i.e. L-Dopa-induced
25 dyskinesia. However, in many cases they have no clear cause and are thus identified as
idiopathic.

Tremor, especially essential tremor (ET), is the most frequent type of HMD seen in clinical
practice. An estimated 10-20 million individuals in the United States live with ET.
Huntington's Disease is the most frequent cause of chorea with a worldwide prevalence of 5-
30 14/100,000 people. Anywhere from 2-50 children/million develop early-onset dystonia and
30-7,000 adults/million develop late-onset dystonia. Adult-onset focal dystonia is by far the
most frequent form of isolated dystonia. Focal dystonia is approximately tenfold more

common than generalized dystonia. Cervical dystonia is the most frequently documented focal dystonia. Tardive dyskinesia represents a group of delayed-onset persistent iatrogenic movement disorders which is consecutive to exposure to dopamine receptor-blocking agents (DRBA -“neuroleptics”). The overall prevalence rates of tardive dyskinesia are close to 30% for patients treated with DRBA. The prevalence in general population is about 180/100,000.

Basal ganglia (BG) are a complex network of nuclei in the forebrain which play critical roles in motor control (facilitation of smooth voluntary movements). BG consist in a group of subcortical nuclei: globus pallidus, caudate nucleus, putamen, substantia nigra and subthalamic nucleus and, any damage/disorganization may lead to motor and cognitive disabilities. Movements are regulated by two distinct pathways that process signals through the basal ganglia: the direct and the indirect pathway, with dopamine facilitating the motor loop in these two pathways. These pathways have opposite effects on thalamus. Stimulation of the direct pathway induces excitation of thalamic neurons (which in turn make excitatory connections onto cortical neurons). Stimulation of the indirect pathway induces inhibition of thalamic neurons (rendering them unable to excite motor cortex neurons). The normal functioning of the basal ganglia involves a balance between the activity of these two pathways. One hypothesis is that the “direct pathway selectively facilitates certain motor (or cognitive) programs in the cerebral cortex that are adaptive for the present task, whereas the “indirect pathway” simultaneously inhibits the execution of competing motor programs.

Basal ganglia dysfunction may result in a wide range of neurological conditions which involved control and movement disorders and cognitive deficits: Tourette syndrome, obsessive compulsive disorder, addiction, Parkinson’s disease, Huntington’s disease, dystonia, hemiballismus.

More specifically for HMDS, tremors are associated with brainstem, cerebellum or thalamic lesion. Chorea and ballism have been linked to lesions in the subthalamic nucleus. Dystonia is primarily associated with dysfunction of the putamen or globus pallidus. Tics can also involve inflammation or degeneration of the basal ganglia in rare cases. Tardive dyskinesia has been traditionally attributed to hypersensitivity and upregulation of dopamine D2 receptors in the motor striatum due to chronic dopamine receptor blockade. Among all HMDS, there appears to be decreased neural firing rates in the inhibitory output nuclei of the basal ganglia leading to a subsequent disinhibition of the thalamocortical activity, leading to cortical overstimulation which in turn gives rise to uncontrolled/involuntary movements.

Currently there are only a few medications that have been shown to afford at most a modest, mostly transient benefit to the patients suffering from HMDs. Oral medications (e.g. anti-epileptics, anticholinergics, dopamine depletors, beta blockers, GABA agonists) primarily act via inhibitory pathways in attempt to suppress abnormal movement except for dopa-responsive dystonia which improves with use of dopaminergics such as levodopa. Certain focal or multifocal movement disorders can be targeted with botulinum toxin injections to reduce activity in antagonist muscles with some success. More severe or generalized HMDs may require neuromodulation with intrathecal baclofen or deep brain stimulation (DBS). For some, relaxation therapies (e.g. yoga, biofeedback) and avoidance of aggravating stimuli (e.g. caffeine, stressors) will also decrease the frequency and severity of tremor, tics and dystonia.

Reversible vesicular monoamine transporter-2 (VMAT-2) inhibitors, which block a transporter that packages monoamines (e.g. dopamine, noradrenalin, serotonin and histamine) into presynaptic vesicles for release into the synaptic cleft, have been tested for the treatment of tardive dyskinesia. This transporter is widely distributed into the brain with some regional specificity which corresponds to monoaminergic brain regions.

Tetrabenazine was the first VMAT-2 inhibitors approved. Then, deutetrabenazine and valbenazine were consecutively developed and, they exhibit an improved pharmacokinetic and pharmacodynamic profile than tetrabenazine. These two recent molecules are FDA approved for both tardive dyskinesia and Huntington's disease chorea.

Medications that block or lessen dopamine are also used for the management of tics in Tourette syndrome, with Aripiprazole, Haloperidol and Pimozide as the only pharmacological treatments approved by FDA.

Trihexyphenidyl can be used to treat tremor and dystonia but is poorly tolerated. Pramipexole, beta-blockers, anti-epileptics and benzodiazepines have been used to treat tremors and myoclonus with mixed success. Botulinum toxin injections are useful for focal and multifocal dystonia. Generalized dystonia may benefit from intrathecal baclofen therapy. DBS has shown benefit for multiple HMDs especially essential tremor, tremor due to Parkinson's disease and primary generalized dystonia.

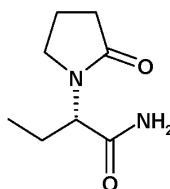
Drug addiction is a chronic and relapsing psychiatric disorder, characterized by compulsive seeking and taking of the drug despite the negative consequences, craving, and feeling of a

negative state when the drug is withdrawn. Several phases are present in addiction: phases of active and excessive consumption of the drug, phases of more controlled use, phases of abstinence and episode of relapse. These different stages in the process are associated with various behavioral and neurobiological mechanisms: (1) binge & intoxication, (2)
5 withdrawal/negative affect and (3) preoccupation/anticipation.

The dopaminergic system and basal ganglia are highly involved in the drug addiction process. Dopamine is a neurotransmitter which plays an important role in addiction by contributing to pleasurable sensations, reinforcing behaviors and triggering craving. The limbic sector of the basal ganglia (i.e. nucleus accumbens, ventral pallidum and ventral
10 tegmental are) are highly suggested to play a central role in reward learning and addiction process. Several highly addictive drugs, including cocaine, amphetamine, nicotine, opioids are thought to work by increasing the efficacy of the dopamine signaling in the mesocortical pathway. "Drug sensitization" is developing when repeated exposure to drug use causes hypersensitivity to drugs and other stimuli associated with them. This hypersensitivity in turn
15 causes an increased craving for drugs, triggering an exaggerated interest for these ones.

The "incentive-sensitization theory" dissociates the neural circuitry supporting "drug-liking" and "drug wanting". Incentive salience or "wanting", a form of motivation, is generated by large and robust neural system that includes mesolimbic dopamine. This theory assumes that drug addiction is the excessive amplification of the psychological "wanting", specifically
20 triggered by cues, without any specific amplification of "liking". This process would result from the long-lasting changes in dopamine-related motivation systems of susceptible individuals, called neural sensitization (Berridge & Robinson, Am Psychol. 71(8) (2016)).

Levetiracetam or (S)-(-)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide, is a laevorotatory compound, disclosed in the European patent No. EP-162036 as being a protective agent for
25 the treatment and the prevention of hypoxic and ischemic type aggressions of the central nervous system. Levetiracetam has the following structure:



Levetiracetam has been approved and is marketed as Keppra[®], in many countries including the European Union and the United States for the treatment of various forms of epilepsy, a therapeutic indication for which it has been demonstrated that its dextrorotatory enantiomer (R)-(+)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide completely lacks activity (Gower *et al.*, Eur. J. Pharmacol. 222, 193-203 (1992)).

Levetiracetam has also be considered as a potential alternative therapy for Tourette syndrome (Martinez-Granero *et al.* Neuropsychiatric Dis and Treat. 6, 309-316 (2010)). One randomized placebo-controlled double-blind study (Awaad *et al.* J Pediatr Neurol. 7, 257-263 (2009)), including 24 children aged 6-18 years old with TS and associated diagnoses of epilepsy or headache, received Levetiracetam (Lev) (500 to 1250 mg/day) or placebo in a randomized sequence over 8 weeks. Over twelve patients how received Lev, nine of them showed improvement in tics, two were lost to follow-up, and one patient with comorbidities (ADHD and OCD) discontinued Lev because of aggressiveness.

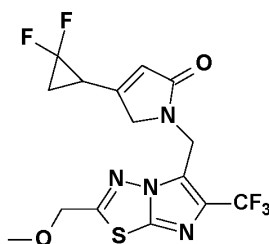
The efficacy and safety of levetiracetam was also evaluated in tardive dyskinesia in a double-blind, placebo-controlled, randomized study (Woods *et al.* J Clin Psychiatry 69:4, 546-554 (2008)). In this study, a total of fifty antipsychotic-treated patients were assigned at random to receive levetiracetam 500 to 3000 mg/day or placebo for twelve weeks. Mixed regression models revealed that Abnormal Involuntary Movement Scale (AIMS) total score declined 43.5% from baseline in the lev group compared to 18.7% for placebo (p=0.022).

The effect of a single dose of 1,000 mg of levetiracetam on essential tremor was investigated in 24 patients in a double-blind, placebo-controlled trial. There was a significant reduction of hand tremor for at least 2 hours as measured by accelerometry and functional tests. However, levetiracetam was never developed and approved for the treatment of tremor, tardive dyskinesia or tics in Tourette syndrome. Levetiracetam belongs to a chemical group of molecules referred to as racetams.

Further racetam-type drugs include piracetam, oxiracetam, aniracetam, pramiracetam and phenylpiracetam, which have been used in humans and some of which are available as dietary supplements. As add-on therapy, Piracetam appears to benefit individuals with myoclonus epilepsy and tardive dyskinesia.

Imidazothiadiazole pyrrolidone compounds are disclosed in WO 2011/047860.

In WO 2019/215062 pyrrole-5-one compounds are disclosed for the treatment of epilepsy; Compounds 17-A and 17-B bearing a gem-difluorocyclopropyl moiety are specifically exemplified:



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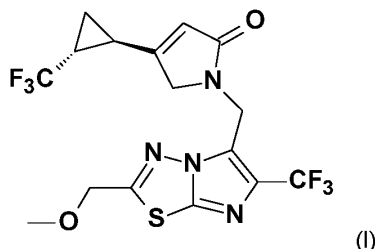
SUMMARY OF THE INVENTION

The present invention relates to compounds, compositions and methods for the treatment of a hyperkinetic movement disorder in a mammal.

Further aspects of the invention will become apparent from the detailed specification.

DETAILED DESCRIPTION OF THE INVENTION

- 10 A first aspect of the present invention is a compound of formula (I) in racemic form or in an enriched diastereomeric purity



as well as its pharmaceutically acceptable salts and metabolites.

- 15 A specific embodiment is 1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one, in one embodiment in a diastereomeric excess of at least 90% (d.e), preferably at least 94% (d.e), more preferably at least, and most preferably at least 98% (d.e).

Another specific embodiment is 1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1S,2S)-2-(trifluoro-methyl)cyclopropyl]-2H-pyrrol-5-one (enantiomer 2), in one embodiment in a diastereomeric excess of at least 90% (d.e), preferably at least 94% (d.e), more preferably at least, and most preferably at least 98% (d.e).

- 5 Compounds (I) are intended to include a racemic form, or one or more enantiomeric, diastereomeric, or geometric isomers, or a mixture thereof. Additionally, any formula given herein is intended to refer also to a hydrate, solvate, or polymorph of such a compound, or a mixture thereof.

- Compounds (I) are also intended to represent unlabeled forms as well as isotopically labeled
10 forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P ,
15 ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , and ^{125}I , respectively. Such isotopically labelled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or ^{11}C labeled
20 compound may be particularly preferred for PET or SPECT studies. PET and SPECT studies may be performed as described, for example, by Brooks, D.J., "Positron Emission Tomography and Single-Photon Emission Computed Tomography in Central Nervous System Drug Development," NeuroRx 2005, 2(2), 226-236, and references cited therein. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain
25 therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled
30 reagent.

The invention also includes pharmaceutically acceptable salts of the compounds represented by formula (I), preferably of those described herein and pharmaceutical compositions comprising such salts, and methods of using such salts.

- A "pharmaceutically acceptable salt" is intended to mean a salt of a free acid of a compound represented herein that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. See, generally, S.M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977, 66, 1-19. Preferred pharmaceutically acceptable salts are those that
- 5 are pharmacologically effective and suitable for contact with the tissues of subjects without undue toxicity, irritation, or allergic response. A compound described herein may possess a sufficiently acidic group, a sufficiently basic group, both types of functional groups, or more than one of each type, and accordingly react with a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.
- 10 Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates,
- 15 butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, methylsulfonates, propylsulfonates, besylates, xylenesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, and mandelates. Lists of other suitable
- 20 pharmaceutically acceptable salts are found in Remington's Pharmaceutical Sciences, 17th Edition, Mack Publishing Company, Easton, Pa., 1985.

- A pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the
- 25 like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, lauric acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an α -hydroxy acid, such as mandelic acid, citric acid, or tartaric acid,
- 30 an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid, naphthoic acid, or cinnamic acid, a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, or ethanesulfonic acid, or any compatible mixture of acids such as those given as examples herein, and any other acid

and mixture thereof that are regarded as equivalents or acceptable substitutes in light of the ordinary level of skill in this technology.

The invention also relates to pharmaceutically acceptable prodrugs of the compounds of formula (I), and treatment methods employing such pharmaceutically acceptable prodrugs.

- 5 The term "prodrug" means a precursor of a designated compound that, following administration to a subject, yields the compound in vivo via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to the compound of formula (I)). A "pharmaceutically acceptable prodrug" is a prodrug that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to the subject. Illustrative procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The present invention also relates to pharmaceutically active metabolites of compounds of formula (I), and uses of such metabolites in the methods of the invention. A

- 15 "pharmaceutically active metabolite" means a pharmacologically active product of metabolism in the body of a compound of formula (I) or salt thereof. Prodrugs and active metabolites of a compound may be determined using routine techniques known or available in the art. See, e.g., Bertolini et al., J. Med. Chem. 1997, 40, 2011-2016; Shan et al., J. Pharm. Sci. 1997, 86 (7), 765-767; Bagshawe, Drug Dev. Res. 1995, 34, 220-230; Bodor, Adv. Drug Res. 1984, 13, 255-331; Bundgaard, Design of Prodrugs (Elsevier Press, 1985); and Larsen, Design and Application of Prodrugs, Drug Design and Development (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

- 1-[[2-(hydroxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]-thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one is a metabolite of compounds of formula (I), in one embodiment in a diastereomeric excess of at least 90% (d.e), preferably at least 94% (d.e), more preferably at least, and most preferably at least 98% (d.e).

Compounds of this invention are useful as a medicament.

Specifically, compounds of this invention they may be used as a medicament in the treatment of a hyperkinetic movement disorder. Specific hyperkinetic movement disorders are : Huntington's disease, Tourette syndrome or neuroleptics-induced tardive dyskinesia. Other preferred indications include drug addiction (e.g. due to amphetamine,

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methamphetamine, cocaine, nicotine, opioid, alcohol, MDMA and the like) and drug use disorders; involving all the different stages associated with the disease (i.e. drug consumption, craving and relapse).

5 The methods of the invention comprise administration to a mammal (preferably a human) suffering from above mentioned conditions or disorders, of a compound according to the invention in an amount sufficient to alleviate or prevent the disorder or condition.

Pharmaceutical compositions comprising compounds according to the invention can, for example, be administered orally, parenterally, i.e., intravenously, intramuscularly or subcutaneously, intrathecally, transdermally (patch), by inhalation or intranasally.

10 For oral administration, the compounds of the invention may be provided in a solid form, such as a tablet or capsule, or as a solution, emulsion, or suspension. To prepare the oral compositions, the compounds of the invention may be formulated to yield a dosage of, e.g., from about 0.01 to about 50 mg/kg daily, or from about 0.05 to about 20 mg/kg daily, or from about 0.1 to about 10 mg/kg daily. Additional dosages include from about 0.1 mg to 1 g
15 daily, from about 1 mg to about 10 mg daily, from about 10 mg to about 50 mg daily, from about 50 mg to about 250 mg daily, or from about 250 mg to 1 g daily. Oral tablets may include the active ingredient(s) mixed with compatible pharmaceutically acceptable excipients such as diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert
20 fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are exemplary disintegrating agents. Binding agents may include starch and gelatin.
25 The lubricating agent, if present, may be magnesium stearate, stearic acid, or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract or may be coated with an enteric coating.

Capsules for oral administration include hard and soft gelatin capsules. To prepare hard
30 gelatin capsules, active ingredient(s) may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the active ingredient with water, an oil such

as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

Liquids for oral administration may be in the form of suspensions, solutions, emulsions, or syrups, or may be lyophilized or presented as a dry product for reconstitution with water or
5 other suitable vehicle before use. Such liquid compositions may optionally contain:
pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for
10 example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

The terms "treatment of conditions associated with enhancement or improvement of a hyperkinetic movement disorder or "to counteract a hyperkinetic movement disorder" or
"treatment of a hyperkinetic movement disorder " or "improving a hyperkinetic movement
15 disorder".

The compounds according to the present invention may be used for the manufacture of a pharmaceutical composition for the treatment of a hyperkinetic movement disorder as well as drug addiction and drug use disorders. Such compositions typically contain the active pharmaceutical ingredient and a pharmaceutically acceptable excipient.

20 The invention also contemplates compositions which can release the active substance in a controlled manner. Pharmaceutical compositions which can be used for parenteral administration are in conventional form such as aqueous or oily solutions or suspensions generally contained in ampoules, disposable syringes, glass or plastics vials or infusion containers.

25 In addition to the active ingredient, these solutions or suspensions can optionally also contain a sterile diluent such as water for injection, a physiological saline solution, oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents, antibacterial agents such as benzyl alcohol, antioxidants such as ascorbic acid or sodium bisulphite, chelating agents such as ethylene diaminetetraacetic acid, buffers such as acetates, citrates
30 or phosphates and agents for adjusting the osmolarity, such as sodium chloride or dextrose.

Also comprised by the present invention are pharmaceutical compositions containing the compound of the present invention in the form of a pharmaceutically acceptable co-crystal.

Such pharmaceutical compositions may furthermore contain known or marketed therapeutic agents used in the treatment of a hyperkinetic movement disorder or drug addiction/drug use disorders.

Examples of such therapeutic agents that may be used in pharmaceuticals compositions may be but not limited to quetiapine fumarate, aripiprazole, risperidone/paliperidone, olanzapine, cariprazine HCl, lurasidone HCl, ziprasidone HCl, haloperidol/droperidol, clozapine, quetiapine fumarate extended release, but also iloperidone, flunarizine and cinnarizine, loxapine, asenapine, pimozide, molindone, lithium, chlorpromazine, triflupromazine, thioridazine, mesoridazine, trifluoperazine, prochlorperazine, perphenazine, fluphenazine, perazine, metoclopramide, tiapride, sulpiride, clebopride, remoxipride, veralipride, amisulpride, levosulpiride, duloxetine, citalopram, olanzapine, chlorprothixene, thiothixene, amoxapine; all compounds that could potentially cause tardive dyskinesia.

Unexpectedly, the compound according to the present invention induces significant dopamine reduction in the striatum (main structure from the Basal Ganglia) without affecting other monoamines levels (i.e. serotonin and norepinephrine) in the rest of the brain like the cortex and prefrontal cortex. It is believed that reduction of dopamine, in any assay aiming at measuring dopamine levels in the striatum, is predictive and suitable for identifying any potential effect addressing HMD or psychostimulants used disorder. Inhibition of the hyperdopaminergic function is considered to be related with antihyperkinetic movement effect and, with the treatment of addiction to psychostimulants and to psychostimulant used disorders (Koch et al. Pharm & Therapeutics, 212 (2020); Alvers et al. Psychopharmacology, 224 (2012)).

EXAMPLES

The following examples illustrate how the compounds covered by formula (I) may be synthesized. They are provided for illustrative purposes only and are not intended, nor should they be construed, as limiting the invention in any manner. Those skilled in the art will appreciate that routine variations and modifications of the following examples can be made without exceeding the spirit or scope of the invention.

The following Examples illustrates the preparation of compound of formula (I) according to the present invention.

EXAMPLES**Abbreviations/recurrent reagents**

ACN: Acetonitrile

DCM: Dichloromethane

5 DMSO: Dimethylsulfoxide

h: Hour

HPLC: High Pressure Liquid Chromatography

IPAC: Isopropyl acetate

LCMS: Liquid Chromatography Mass Spectrometry

10 MeOH: Methanol

min.: minutes

MTBE: methyl *tert*-butylether

NMR: Nuclear magnetic resonance

Rac: racemic

15 RuPhos: 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl

RT: room temperature

SFC: Supercritical Fluid Chromatography

TLC: Thin Layer Chromatography

IUPAC names have been determined using Biovia Draw 20.1.

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Analytical methods

All reactions involving air or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere using dried solvents and glassware. Commercial solvents and reagents were generally used without further purification, including anhydrous solvents when appropriate (generally Sure-Seal™ products from Aldrich Chemical Company or AcroSeal™ from ACROS Organics). In general reactions were followed by thin layer chromatography, HPLC or mass spectrometry analyses.

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Mass spectrometric measurements in LCMS mode are performed using different methods and instrument as follows:

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- Acid LCMS Method 1:

A QDA Waters simple quadrupole mass spectrometer is used for LCMS analysis. This spectrometer is equipped with an ESI source and an UPLC Acquity with diode array detector

(200 to 400 nm). Data is acquired in a full MS scan from m/z 70 to 800 in positive/negative modes with an acidic elution. The reverse phase separation is carried out at 45 °C on a Waters Acquity UPLC HSS T3 1.8 μ m (2.1x50 mm) column for acidic elution. Gradient elution is done with H₂O/ACN/TFA (95/5/0.05%) (solvent A) and ACN (solvent B).

5

Time (min)	A (%)	B (%)	Flow (mL/min)
0	99	1	0.8
0.15	99	1	0.8
1.60	5	95	0.8
1.65	5	95	0.8
2	5	95	0.8
2.05	99	1	0.8
2.75	99	1	0.8

Products were generally dried under vacuum before final analyses and submission to biological testing.

NMR spectra were recorded on a BRUKER AVANCEIII 400 MHz-Ultrashield NMR

10 Spectrometer fitted with a Windows 7 Professional workstation running Topspin 3.2 software and a 5 mm Double Resonance Broadband Probe (PABBI ¹H/¹⁹F-BB Z-GRD Z82021/0075) or a 1 mm Triple Resonance Probe (PATXI ¹H/ D-¹³C/¹⁵N Z-GRD Z868301/004).

Chemical shifts are referenced to signals deriving from residual protons of the deuterated solvents (DMSO-*d*₆, MeOH-*d*₄ or CDCl₃). Chemical shifts are given in parts per million (ppm)

15 and coupling constants (J) in Hertz (Hz). Spin multiplicities are given as broad (br), singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m).

The absolute configuration of compounds was determined using VCD spectroscopy: IR and VCD spectra were recorded on a BioTools ChiralIR-2X MIR FT-VCD spectrometer equipped with dual photoelastic modulators (dualPEM). Samples of 5 mg were dissolved in 150 μ L CDCl₃ and transferred to a BaF₂ liquid IR cell with a path length of 0.075 mm before IR/VCD data was collected between 1,000-2,000 cm⁻¹ for up to 16 hours. Theoretical IR/VCD spectra were generated at the B3PW91/cc-pVTZ level of theory using the Maestro (Schrodinger, Inc.) and Gaussian09 (Gaussian Inc.) software packages. A visual comparison

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of the experimental and theoretical datasets was made using Excel (Microsoft) and CompareVOA (BioTools Inc.).

All final products were analysed by LCMS in both basic and acid modes, as follows:

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- Basic LCMS Method 1:

A QDA Waters simple quadrupole mass spectrometer is used for LCMS analysis. This spectrometer is equipped with an ESI source and an UPLC Acquity Classic with diode array detector (210 to 400 nm). Data is acquired in a full MS scan from m/z 70 to 800 in positive/negative modes with a basic elution. The reverse phase separation is carried out at 45 °C on a Waters Acquity UPLC BEH C18 1.7 µm (2.1x100 mm) column for basic elution. Gradient elution is done with H₂O/ACN/ammonium formate (95/5/63 mg/L) + 100 µL/L NH₄OH (solvent A) and ACN/H₂O/ammonium formate (95/5/63 mg/L) + 100 µL/L NH₄OH (solvent B). Injection volume: 1 µL. Full flow in MS.

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Time (min) (mL/min)	A (%)	B (%)	Flow
0	99	1	0.4
0.8	99	1	0.4
5.30	0	100	0.4
5.35	0	100	0.5
7.30	0	100	0.5
7.35	99	1	0.4
9	90	1	0.4

- Acid LCMS Method 2:

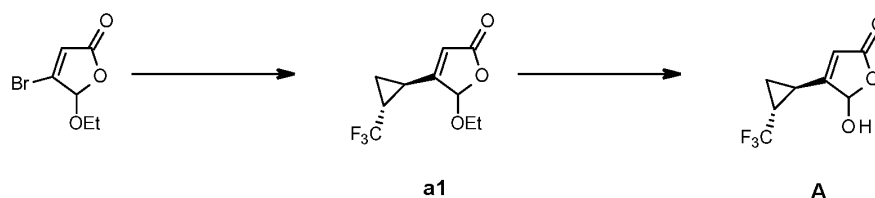
A QDA Waters simple quadrupole mass spectrometer is used for LCMS analysis. This spectrometer is equipped with an ESI source and an UPLC Acquity Hclass with diode array detector (210 to 400 nm). Data are acquired in a full MS scan from m/z 70 to 800 in positive/negative modes with an acidic elution. The reverse phase separation is carried out

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at 45 °C on a Waters Acquity UPLC HSS T3 1.8 µm (2.1x100 mm) column for acidic elution. Gradient elution is done with H₂O/ACN/TFA (95/5/0.05%) (solvent A) and ACN (solvent B).

Time (min) (mL/min)	A (%)	B (%)	Flow
0	99	1	0.4
0.8	99	1	0.4
5.3	5	95	0.4
5.35	5	95	0.5
7.3	5	95	0.5
7.35	99	1	0.4
9	99	1	0.4

5 **1. Preparation of intermediate A** – rac-2-hydroxy-3-[(1R*,2R*)-2-(trifluoromethyl)-
cyclopropyl]-2H-furan-5-one



10 **1.1. Synthesis of rac-2-ethoxy-3-[(1R*,2R*)-2-(trifluoromethyl)cyclopropyl]-2H-furan-5-one **a1****

To a solution of 4-bromo-5-ethoxy-2(5H)-furanone (CAS: 32978-38-4, 31.38 g, 147.04 mmol) and rac-6-methyl-2-[(1R*,2R*)-2-(trifluoromethyl)cyclopropyl]-1,3,6,2-dioxazaborocane-4,8-dione (CAS: 1309955-07-4, 44.9 g, 161.3 mmol) in toluene (750 mL) were added RuPhos (15.48 g, 32.52 mmol) and palladium(II) acetate (3.88 g, 16.43 mmol) keeping the external temperature of the vessel at 95°C. Then, potassium carbonate (81.06 g, 590 mmol) dissolved in water (150 mL) was added at once and the reaction mixture was stirred while maintaining the internal temperature of the reaction at 85°C. After 2 h, the reaction mixture was cooled down to 15°C and the reaction mixture was quenched with 650 mL of water. The

mixture was stirred at RT for 0.5 h, filtered through a pad of celite, and the aqueous phase was extracted twice with 300mL of toluene. The combined organic layers were dried over MgSO₄, filtered and the solvent was removed under vacuum to afford a dark brown oil subsequently purified by flash chromatography (Biotage Isolera Four, 330 g Interchim silica gel column in a gradient of Heptane/DCM). The purest fraction was collected and the solvent was evaporated until dryness to afford rac-2-ethoxy-3-[(1R*,2R*)-2-(trifluoromethyl)cyclopropyl]-2H-furan-5-one **a1** (27.3 g, 75% yield) as a yellow oil.

¹H NMR: (400 MHz, CDCl₃) δ 5.85 (d, 1H), 5.74 (d, 1H), 3.93 (mult., 1H), 3.75 (mult., 1H), 2.20 - 2.06 (m, 1H), 2.00 - 1.89 (m, 1H), 1.53 - 1.33 (m, 2H), 1.32 - 1.21 (m, 3H).

LC/MS acid: [M+H]⁺ = 237

1.2. Synthesis of rac-2-hydroxy-3-[(1R*,2R*)-2-(trifluoromethyl)cyclopropyl]-2H-furan-5-one **A**

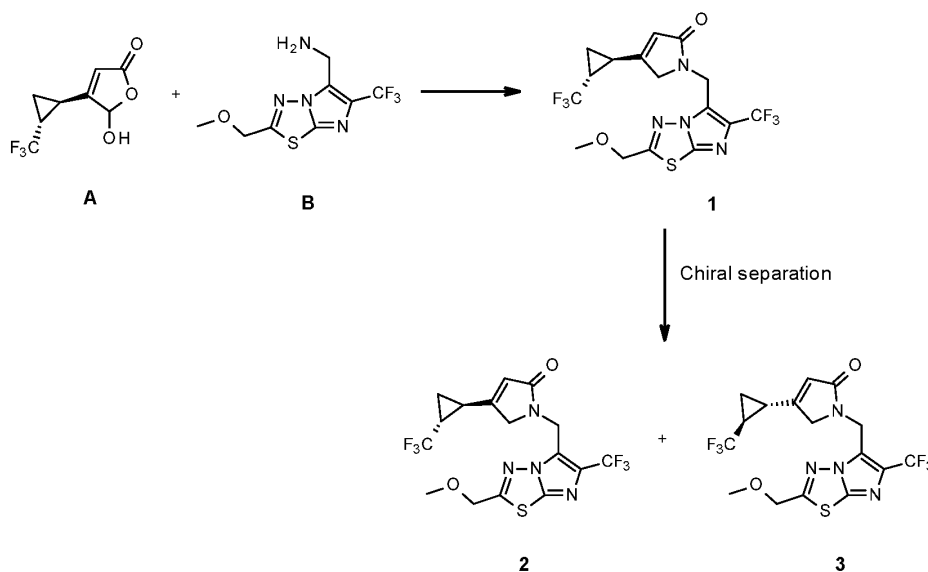
Tetrafluoroboric acid (48 wt.% in water, 220 mL) was added at RT to a stirred solution of rac-2-ethoxy-3-[(1R*,2R*)-2-(trifluoromethyl)cyclopropyl]-2H-furan-5-one **a1** (27.3 g, 109.9 mmol) in ACN (110 mL) and the resulting mixture was stirred at room temperature for 72 h. To the reaction mixture was again added tetrafluoroboric acid (48 wt.% in water, 25 mL) and the reaction mixture was stirred overnight. The reaction mixture was diluted with 500 mL of DCM and 500 mL of water were added. The mixture was quenched portion wise and carefully (at RT) with 150 g of sodium carbonate (over a period of 4 h). At the end of the addition, the pH of the aqueous phase was at 7.5. The organic and the aqueous phases were separated, and the aqueous phase was extracted again twice with 500 mL of DCM. The combined organic phases were dried over MgSO₄, filtered and the solvent was removed under limited vacuum (bath at 40°C – 500 mbar max). 2-hydroxy-3-[(1R*,2R*)-2-(trifluoromethyl)cyclo-propyl]-2H-furan-5-one **A** was obtained as an oil (product in solution of ACN and DCM) (72.8 g, qNMR purity: 30.6%) and was used as such in the next step.

¹H NMR: (400 MHz, CDCl₃) δ 5.99 (mult., 1H), 5.85 (d, J = 17.5 Hz, 1H), 4.97 (dd, J = 14.3, 7.6 Hz, 1H), 2.22 - 2.11 (m, 1H), 1.54 - 1.37 (m, 1H), 1.33 - 1.24 (m, 1H). Hydroxy proton not visible.

LC/MS acid: [M+H]⁺ = 209

2. Preparation of compounds 2 and 3 - 1-[[2-(methoxymethyl)-6-(trifluoromethyl)-imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one **2** and 1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1S,2S)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one **3**

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A mixture of rac-2-hydroxy-3-[(1R*,2R*)-2-(trifluoromethyl)cyclopropyl]-2H-furan-5-one **A** (72.84 g, 107.2 mmol) and [2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methanamine **B** (29.5 g, 109 mmol) (CAS: 1403586-73-1, afforded according to the method set out in WO 2019/215062) in MeOH (200 mL) was stirred at RT overnight. The mixture was cooled down to 0°C, sodium borohydride (12.1 g, 321.4 mmol) was added portion wise and the mixture was stirred for 3 h at RT. Acetic acid (19 mL, 331 mmol) was added dropwise and the mixture was stirred for 16 h at RT. The reaction mixture was poured in 250 mL of water and the aqueous layer was extracted twice with 250 mL of DCM. The combined organic layers were dried over MgSO₄, filtered, and concentrated to dryness to afford a light-yellow solid which was purified by flash chromatography (Biotage Isolera Four, 330 g Interchim silica gel column in a gradient of DCM/MeOH). The purest fraction was collected and the solvent was evaporated to afford rac-1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R*,2R*)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one **1** (31.6 g, 66% yield).

¹H NMR: (400 MHz, CDCl₃) δ 5.83 (s, 1H), 5.03 (s, 2H), 4.75 (s, 2H), 3.79 (s, 2H), 3.52 (s, 3H), 2.02 (dt, J = 10.0, 5.3 Hz, 1H), 1.79 (dq, J = 11.1, 6.0 Hz, 1H), 1.40 (dt, J = 10.1, 5.8 Hz, 1H), 1.09 (dt, J = 10.8, 6.0 Hz, 1H).

LC/MS acid: [M+H]⁺ = 441

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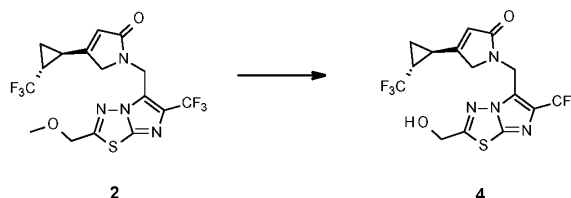
rac-1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-
[(1R*,2R*)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one **1** (86.4 g) was separated by
preparative SFC (Pic Solution Prep 600 - ChiralPak IH 76.5x260mm 20μm - CO₂ + IPA 15%
- 700 mL/min., RT) to give 1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]-
thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one **2**
(Enantiomer 1, first eluted, 40.9 g, 45.6% yield) and 1-[[2-(methoxymethyl)-6-(trifluoro-
methyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1S,2S)-2-(trifluoromethyl)cyclopropyl]-
2H-pyrrol-5-one **3** (Enantiomer 2, second eluted, 18.2g).

1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-
[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one **2** (40.89 g, 87.76 mmol) was
dissolved in MTBE (120 mL) at RT. Heptane (42 mL) was added dropwise. The mixture was
then stirred at 20°C for 2h, cooled down to 10°C over a period of 2 h and the mixture was
stirred overnight at 10°C. The solid was filtered and washed twice with the mother liquor
phase, washed finally with 50 mL of fresh heptane and the solid was dried for 72 h in an
oven at 35°C to afford 1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-
b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one **2**
as a white crystalline solid (32.8 g, 85% yield).

1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-
[(1S,2S)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one **3** (18.2 g, 34.65 mmol) was
dissolved in a mixture of IPAC (50 mL) and heptane (120 mL) at 45°C. The mixture was
cooled down to 10°C over a period of 10 h, then the mixture was stirred overnight at 10°C.
The suspension was cooled down to 0°C, then heptane (200 mL) was added dropwise. The
solid was filtered and washed once with heptane (40 mL). The solid was dried for 16 h, at
35°C, in a vacuum oven to afford 1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-
b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1S,2S)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one **3**
(14.7 g, 95% yield).

Analytical Chiral HPLC (Chiralpak IB, 1.5 mL/min., 30°C, heptane 70% - IPA 30% - DEA
0.1%, 215 bar): **2**: 4.65 min, **3**: 4.17 min

Preparation of compound 4 - 1-[[2-(hydroxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]-thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one



- 5 Boron tribromide (1 M solution in dichloromethane, 22.7 mL) is added at room temperature to a solution of 1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one **2** (2 g, 4.54 mmol) in dichloromethane (22.7 mL). The reaction mixture is stirred for 45 minutes at room temperature. Methanol is added slowly and carefully until the precipitate that was formed in
- 10 the reaction mixture disappeared completely. Solvents are evaporated under reduce pressure, water is added to the residue and the aqueous phase is extracted three times with ethyl acetate. Combined organic layers are dried over MgSO_4 , filtered and evaporated under reduce pressure to afford pure 1-[[2-(hydroxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one as
- 15 a white solid (1.91g, 98.6% yield).

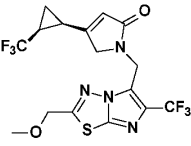
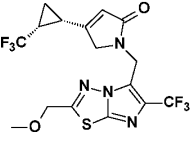
^1H NMR: (400 MHz, $\text{DMSO}-d_6$) δ 6.52 (s, 1H), 5.98 (s, 1H), 4.94-4.81 (m, 4H), 3.88 (s, 2H), 2.41-2.33 (m, 1H), 2.23 (dt, $J=10.3, 5.4$ Hz, 1H), 1.35-1.13 (m, 2H)

LC/MS acid: $[\text{M}+\text{H}]^+ = 427$

- 20 Table (I) indicates the IUPAC name (generated Biovia Draw 20.1) of the compound, the ion peak observed in mass spectroscopy and the ^1H NMR description.

Table I: Example Compounds.

n°	Compound NAME	Structure	MS (MH ⁺)	¹ H NMR (400 MHz)
2	1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)-cyclopropyl]-2H-pyrrol-5-one (enantiomer 1)		441	(CDCl ₃) δ 5.82 (s, 1H), 5.03 (s, 2H), 4.75 (s, 2H), 3.78 (d, J = 1.4 Hz, 2H), 3.52 (s, 3H), 2.02 (dt, J = 9.9, 5.1 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.40 (dt, J = 9.3, 5.7 Hz, 1H), 1.13 – 1.03 (m, 1H)
3	1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1S,2S)-2-(trifluoromethyl)-cyclopropyl]-2H-pyrrol-5-one (enantiomer 2)		441	(CDCl ₃) δ 5.82 (s, 1H), 5.03 (s, 2H), 4.75 (s, 2H), 3.78 (d, J = 1.4 Hz, 2H), 3.52 (s, 3H), 2.02 (dt, J = 9.9, 5.1 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.40 (dt, J = 9.3, 5.7 Hz, 1H), 1.13 – 1.03 (m, 1H)
4	1-[[2-(hydroxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)-cyclopropyl]-2H-pyrrol-5-one		427	(DMSO- <i>d</i> ₆) δ 6.52 (s, 1H), 5.98 (s, 1H), 4.94-4.81 (m, 4H), 3.88 (s, 2H), 2.41-2.33 (m, 1H), 2.23 (dt, J=10.3, 5.4 Hz, 1H), 1.35-1.13 (m, 2H)

n°	Compound NAME	Structure	MS (MH ⁺)	¹ H NMR (400 MHz)
5	1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R,2S)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one		441	(DMSO- <i>d</i> ₆) δ 5.94 (d, J = 1.7 Hz, 1H), 5.00 – 4.86 (m, 2H), 4.82 (s, 2H), 4.06 (dd, J = 19.5, 1.6 Hz, 1H), 3.82 (dd, J = 19.3, 1.6 Hz, 1H), 3.43 (s, 3H), 2.20 (qd, J = 8.5, 6.2 Hz, 1H), 2.11 (q, J = 8.4 Hz, 1H), 1.38 (q, J = 6.2 Hz, 1H), 1.29 (td, J = 9.1, 4.6 Hz, 1H)
6	1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1S,2R)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one		441	(DMSO- <i>d</i> ₆) δ 5.94 (s, 1H), 5.01 – 4.86 (m, 2H), 4.82 (s, 2H), 4.06 (d, J = 19.4 Hz, 1H), 3.82 (d, J = 19.4 Hz, 1H), 3.43 (s, 3H), 2.24 – 2.15 (m, 1H), 2.11 (q, J = 8.4 Hz, 1H), 1.38 (q, J = 6.2 Hz, 1H), 1.33 – 1.23 (m, 1H).

Cytochrome P450 inhibition and time-dependent inhibition

To assess the inhibitory potential of cytochrome P450 isoforms, the test compound (6 concentrations ranging from 0.1 - 25 μM) or vehicle was pre-incubated with human liver microsomes (HLM) under three different experimental conditions; for 0 minutes (to assess reversible inhibition), and for 30 minutes in the presence and absence of NADPH (to assess time-dependent inhibition), before incubation with a probe substrate: phenacetin (CYP1A2), diclofenac (CYP2C9), S-Mephenytoin (2C19), Dextromethorphan (CYP2D6), Midazolam and Testosterone (CYP3A4).

Reagents & Materials

0.1M Phosphate Buffer pH 7.4 at 37°C.

Pooled HLM (provided by a reputable commercial supplier, and stored at 80°C prior to use) prepared in above buffer at 400x incubation protein concentration.

- 5 NADPH –100 mM solution prepared in buffer immediately prior to pre-incubation and stored on ice until use ; incubation concentration is 1 or 2mM, for – or + NADPH pre-incubation samples, respectively.

Assay performed with a Tecan automation system, using 37°C and a shaking speed of 700 rpm.

10 Compound Preparation

Test compound (1 µL) and human liver microsomes (395 µL) were either pre-incubated for 30 minutes in the absence and presence of NADPH (4 µL of buffer or NADPH, respectively) or undergo a 0 min pre-incubation (4 µL of buffer). Then probe substrate (1 µL) and NADPH (4 µL) were added to all conditions (in a total incubation volume of 405 µL) and incubated for 15 5 or 15 (2C19 only) minutes, with formation of metabolites monitored. Time dependent inhibitors, were included as a positive control.

CYP	Probe / Metabolite	[HLM] mg/ml	Positive Control Inhibitor (highest concentration)
1A2	Phenacetin (18 µM) / acetaminophen	0.1	Furafylline (25 µM)
2C9	Diclofenac (7 µM) / 4-hydroxydiclofenac	0.5	Tienilic acid (10 µM)
2C19	S-Mephenytoin (50 µM) /	0.5	Fluoxetine (100 µM)
2D6	Dextromethorphan (2 µM) / dextrorphan	0.1	Paroxetine (1 µM)
3A4	Midazolam (2.5 µM) / 1-hydroxymidazolam	0.1	Verapamil (25 µM)
3A4	Testosterone (50 µM) /	0.1	Verapamil (25 µM)

Sample Analysis

- 20 An aliquot of 50 µL for each condition was transferred to a 96-well plate, and reactions were terminated by addition of ice-cold methanol (100 µL) containing a cocktail of deuterated internal standards. The termination plates were centrifuged at 2500 rpm for 30 minutes at 4 °C and supernatant (40 µL) was transferred to fresh 96-well plates. Formic acid in deionised water (60 µL) (final concentration 0.1 %) was added prior to analysis by LC-MS/MS using a generic method.

25 Data Analysis

A decrease in the formation of the metabolite compared to vehicle control is used to calculate an IC_{50} value (test compound concentration which produces 50 % inhibition) for each experimental condition, via a Simple Inhibitory model Winnonlin model 103), as follows:

$$E = E_{\max} (1 - C / (C + [EC_{50}]))$$

- 5 Where E is effect and C is the test compound concentration.

The EC_{50} value is dependent only on the inhibition effect of the test compound we refer to as IC_{50} . Three IC_{50} values were determined; with 0 minutes pre-incubation (for reversible inhibition), and 30 minutes in presence and absence of NADPH (to assess time-dependent inhibition). The fold shift in IC_{50} is calculated using the following equation:

- 10 Fold Shift = $(IC_{50} \text{ from 30 minute pre-incubation without NADPH}) / (IC_{50} \text{ from 30 minute pre-incubation with NADPH})$

Compounds from the invention display IC_{50} values on all CYP P450 isoforms $>25 \mu M$ (without NADPH) and $>20 \mu M$ (with NADPH) showing very low CYP inhibitory activity.

15

Monoamines quantification in brain tissues

All experiments were performed according to the guidelines of the European Directive 2010/63/EU and Belgian legislation and, were approved by the ethical committee for animal experimentation of UCB Biopharma SRL.

- 20 Male Sprague Dawley rats (Janvier, France) were housed in groups of 2 rats per cage and could habituate to the new environment for at least one week before experimentation. Animals were housed in a temperature (20-21°C) and humidity regulated (~40%) environment, with a 12:12 light/dark cycle (light on at 06:00 AM). All animals had free access to standard pellet food and water. The weight of the rats was ~300g at the time of drug testing. Additional enrichment was provided (red cylinders). Animal health was monitored daily by the animal care staff and by the experimenters on the day of experimentation.
- 25 Rats were injected (5mL/kg) intraperitoneally (ip) with Compound 2 at a dose of 0 (n=12), 0.1 (n=8), 0.3 (n=8) and 1 (n=8) mg/kg and were placed back in their home cage. The compound was administered as a suspension formulated in a vehicle solution containing 1% (w/v) methylcellulose (400 cps), 0.1% (w/v) Silicone antifoam 1510 US and 0.1% (w/v)
- 30 Tween80 in water. Rats were sacrificed 45 min post-administration; blood was collected from the heart and brains were rapidly removed. Plasma was obtained through centrifugation at

3000g for 15 min at 4°C. Striatum, cortex and prefrontal cortex (PFC) were carefully dissected (on ice). All samples were stored at -80°C until analysis.

To evaluate the effect of Compound 2 on monoamine levels in distinct brain regions, Dopamine (DA), Norepinephrine (NE) and serotonin (5-HT) levels were measured in various
5 brain areas. Compound exposure was measured in plasma.

To measure the levels of DA, NE and 5-HT, tissue samples were homogenized in 1/20 (v/v) EDTA 0.3 mM/HClO₄ 0.05N and centrifuged at 150000 rpm at 4°C for 15 minutes. 10 µL of the supernatant were injected in an HPLC. The HPLC System used was a Thermo Scientific
10 Vanquish UHPLC (Ultra high performance (pressure) liquid chromatography) system coupled to a Thermo Scientific Q Exactive Plus high-resolution mass spectrometer. The software used was Thermo Scientific Xcalibur. The autosampler temperature was set to 15°C. The analytical UPLC columns was a Waters Acquity HSS T3, 1.8 µm, 100x2.1mm ID operated at 40°C. Flow rate was 0.4 ml/min. Analyses were performed in a gradient mode
15 with a run cycle time of 12 min.

Mobile phase A was Ammonium Formate 10 mM in water & mobile phase B 100% Acetonitrile. Volume injected was 10 µl on column.

For statistical analysis, a one-way ANOVA was used to assess the effect of different doses of Compound 2 (0, 0.1, 0.3 and 1mg/kg) on monoamines levels in various brain regions,
20 followed by subsequent Tukey post-hoc tests aiming to compare differences between the four means. Variance homogeneity (Levene's test for equal variances) and normality were checked before every set of data analysis. No transformation was required.

The results shows that Compound 2 selectively decreases dopamine levels in the striatum
25 without significantly affecting other monoamines (NE or 5-HT) in this brain region.

Unexpectedly, compound 2 doesn't modulate either DA, NE and 5-HT in different brain regions than the striatum like the cortex and prefrontal cortex.

This observation is supported by the following statistical analysis:

- DA levels in the striatum: one-way ANOVA shows a significant dose effect [$F(3,32)=4.97$,
30 $p<0.01$]. Post-hoc analysis reveals a significant difference between the 1mg/kg dose and the vehicle group ($p<0.01$).
- 5-HT levels in the striatum: one-way ANOVA doesn't show any significant effect of the dose [$F(3,32)=2.65$, $p>0.05$].

- DA levels in the PFC: one-way ANOVA doesn't show any significant effect of the dose [F(3,32)=0.77, $p>0.05$].
- 5-HT level in the PFC: one-way ANOVA doesn't show any significant effect of the dose [F(3,32)=0.63, $p>0.05$].

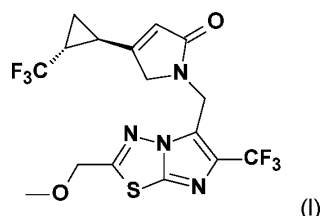
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Figure1 shows that Compound 2 administration results in significant dopamine reduction specifically in the striatum and not in other brain area like the prefrontal cortex. This effect is also specific for dopamine and does not concern serotonin and norepinephrine. We can then conclude that compound 2 whilst fully brain penetrant has a specific effect on dopamine regulation in the basal ganglia.

10

CLAIMS

1. A compound of formula (I) in racemic form or in an enriched diastereomeric purity



as well as its pharmaceutically acceptable salt as well as its primary metabolite.

2. A compound according to claim 1, which is 1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one.
3. A compound according to claim 1, which is 1-[[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1S,2S)-2-(trifluoromethyl)cyclopropyl]-2H-pyrrol-5-one.
4. A compound according to any of claims 1 to 3, which is the primary metabolite of compound (I) 1-[[2-(hydroxymethyl)-6-(trifluoromethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl]-3-[(1R,2R)-2-(trifluoromethyl)-cyclopropyl]-2H-pyrrol-5-one.
5. A compound according to any of claims 2 to 4, which is in a diastereomeric excess of at least 90% (d.e).
6. A compound according to any of the preceding claims for use as a medicament.
7. A compound according to any of the claims 1 to 5, for use as a medicament in the treatment of a hyperkinetic movement disorder.
8. A compound according to claim 7, wherein the hyperkinetic movement disorder is selected from Huntington's disease, Tourette syndrome or neuroleptics-induced tardive dyskinesia or drug addiction/substance use disorders.
9. A pharmaceutical composition containing a compound according to any of claims 1 to 5, as well as a suitable pharmaceutically acceptable excipient.