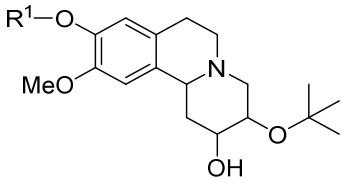
The present disclosure fulfills these, such as, improved *in vitro* VMAT2 potency or improved pharmacokinetics, or both, and other needs, as evident in reference to the following disclosure.

SUMMARY

One example of the present disclosure encompasses, *inter alia*, a compound of Formula (**Ia**):



(**Ia**) ,

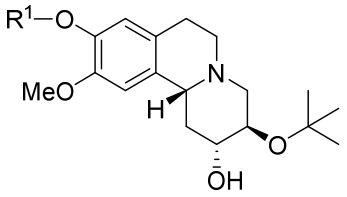
or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is selected from: C_3-C_7-cycloalkyl-C_1-C_4-alkylene, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_1-C_4-alkyl-O-C_2-C_4-alkylene, C_3-C_7-cycloalkyl-O-C_2-C_4-alkylene, 3-7-membered-heterocyclyl, 3-7-membered-heterocyclyl-C_1-C_4-alkylene, C_4-C_8-bicycloalkyl-C_1-C_4-alkylene, C_4-C_7-cycloalkenyl, 5-11-membered-spiro-heterocyclyl, C_5-C_{11}-spiro-cycloalkyl, cubanyl-C_1-C_4-alkylene, and 4-8-membered-heterobicyclyl-C_1-C_4-alkylene;

wherein each R^1 group is optionally substituted with one or more substituents selected from: cyano-C_1-C_4-alkylene, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, C_1-C_4-alkylsulfonyl, C_3-C_6-cycloalkyl, hydroxyl, C_1-C_4-alkoxy, and C_2-C_4-dialkylamino.

In one aspect, the present disclosure refers to a compound of Formula (**Ie**):



(**Ie**) ,

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from: methyl, methyl-d_3, 2,2-difluoropropyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, cyclopropyl, (1-fluorocyclopropyl)methyl, 2-hydroxypropyl, ethyl, ethyl-d_5, isopropyl, 2-methoxyethyl, (cyclopropyl)methyl, (cyclopropyl)methyl-d_2, 3-fluoropropyl, 2-fluoroethyl, 2-((2-cyanopropan-2-yl)oxy)ethyl, 1,1,1-trifluoropropan-2-yl, 2,2-difluoroethyl, oxetan-3-yl, oxetan-3-ylmethyl, (oxetan-2-yl)methyl,

3,3,3-trifluoro-2-hydroxypropyl, 4,4,4-trifluorobutyl, 3-methoxypropyl, (3,3-difluorocyclobutyl)methyl, (1-(difluoromethyl)cyclopropyl)methyl, 5,5,5-trifluoropentyl, (3-fluorobicyclo[1.1.1]pentan-1-yl)methyl, fluoromethyl, (2,2-difluorocyclopropyl)methyl, 2-(trifluoromethoxy)ethyl, 3-fluorocyclobutyl, (2-fluorocyclopropyl)methyl, and 2-fluoropropyl.

Also provided herein are pharmaceutical products selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising a compound, as described herein, or a pharmaceutically acceptable salt thereof. In one aspect, the present disclosure refers to a pharmaceutical product selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising the compound as described herein, or a pharmaceutically acceptable salt thereof.

Also provided herein are pharmaceutical products selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising a compound, as described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In one aspect, the present disclosure refers to a pharmaceutical product selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising the compound as described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Also provided herein are pharmaceutical compositions comprising a compound, as described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In one aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Also provided herein are methods for preparing a pharmaceutical composition comprising the step of admixing a compound, as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In one aspect, the present disclosure refers to a method for preparing a pharmaceutical composition comprising: the step of admixing a compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Also provided herein are methods of treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder in a subject in need thereof, comprising administering to the subject a compound,

selected from the group consisting of: tardive dyskinesia, Tourette's syndrome, Huntington's disease, tics, chorea associated with Huntington's disease, ataxia, chorea, dystonia, hemifacial spasm, myoclonus, restless leg syndrome, and tremors.

Also provided herein are methods of treating a hyperkinetic movement disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the hyperkinetic movement disorder is tardive dyskinesia.

Also provided herein are methods of treating a hyperkinetic movement disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the hyperkinetic movement disorder is Huntington's disease.

Also provided herein are methods of treating a hyperkinetic movement disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the hyperkinetic movement disorder is chorea associated with Huntington's disease.

Also provided herein are methods of treating a neurological or psychiatric disease or disorder in a subject in need thereof, comprising administering to the subject a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; wherein the neurological or psychiatric disease or disorder is selected from schizophrenia and schizoaffective disorder. In some examples, the neurological or psychiatric disease or disorder is schizophrenia. In some examples, the neurological or psychiatric disease or disorder is schizoaffective disorder. In some examples, the neurological or psychiatric disease or disorder is obsessive-compulsive disorder. In some examples, the neurological or psychiatric disease or disorder is treatment-refractory obsessive-compulsive disorder. In some examples, the neurological or psychiatric disease or disorder is autism spectrum disorder. In some examples, the method comprises using the compound, salt, product, or composition in adjunctive therapy.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a vesicular

monoamine transporter-2 (VMAT2) disease or disorder selected from: an ataxias or spinal muscular atrophy; a chorea; a congenital malformation, deformation, or abnormality; a dementia; an oral cavity, salivary gland, or jaw disease; a dyskinesia; a dystonia; an endocrine, nutritional, or metabolic disease; an epilepsy; a habit or impulse disorder; a Huntington's disease or related disorder; a mood or psychotic disorder; a neurotic, stress-related, and somatoform disorder; a degenerative disease of the basal ganglia; an extrapyramidal and movement disorder; a neurological or psychiatric disease or disorder; a nervous system or motor function disorder; a Parkinson's/parkinsonism disorder; a pediatric-onset behavioral and emotional disorder; a pervasive developmental disorder; and a substance abuse or dependence disorder. In one aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder selected from: an ataxias or spinal muscular atrophy; a chorea; a congenital malformation, deformation, or abnormality; a dementia; an oral cavity, salivary gland, or jaw disease; a dyskinesia; a dystonia; an endocrine, nutritional, or metabolic disease; an epilepsy; a habit or impulse disorder; a Huntington's disease or related disorder; a mood or psychotic disorder; a neurotic, stress-related, and somatoform disorder; a degenerative disease of the basal ganglia; an extrapyramidal and movement disorder; a neurological or psychiatric disease or disorder; a nervous system or motor function disorder; a Parkinson's/parkinsonism disorder; a pediatric-onset behavioral and emotional disorder; a pervasive developmental disorder; and a substance abuse or dependence disorder.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder. In one aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder selected from the group consisting of: hyperkinetic movement disorder, schizophrenia, schizoaffective disorder, a mood disorder, treatment-refractory obsessive-compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder, Rett syndrome, and chorea-acanthocytosis. In one aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder selected from the group consisting of: hyperkinetic movement disorder, schizophrenia, schizoaffective disorder, a mood disorder, treatment-refractory obsessive-compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder, Rett syndrome, and chorea-acanthocytosis.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a hyperkinetic movement disorder. In one aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a hyperkinetic movement disorder.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a hyperkinetic movement disorder; wherein the hyperkinetic movement disorder is selected from the group consisting of: tardive dyskinesia, Tourette's syndrome, Huntington's disease, tics, chorea associated with Huntington's disease, ataxia, chorea, dystonia, hemifacial spasm, myoclonus, restless leg syndrome, and tremors. In one aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a hyperkinetic movement disorder; wherein the hyperkinetic movement disorder is selected from the group consisting of: tardive dyskinesia, Tourette's syndrome, Huntington's disease, tics, chorea associated with Huntington's disease, ataxia, chorea, dystonia, hemifacial spasm, myoclonus, restless leg syndrome, and tremors.Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating tardive dyskinesia. In one aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating tardive dyskinesia.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical

composition as described herein; in the manufacture of a medicament for treating Huntington's disease. In one aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating Huntington's disease.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating chorea associated with Huntington's disease. In one aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating chorea associated with Huntington's disease.

Also provided herein are uses of a compound, as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; in the manufacture of a medicament for treating a neurological or psychiatric disease or disorder, wherein the neurological or psychiatric disease or disorder is selected from schizophrenia and schizoaffective disorder. In some examples, the neurological or psychiatric disease or disorder is schizophrenia. In some examples, the neurological or psychiatric disease or disorder is schizoaffective disorder. In some examples, the neurological or psychiatric disease or disorder is obsessive-compulsive disorder. In some examples, the neurological or psychiatric disease or disorder is treatment-refractory obsessive-compulsive disorder. In some examples, the neurological or psychiatric disease or disorder is autism spectrum disorder. In some examples, treatment comprises using the compound, salt, product, or composition in adjunctive therapy.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy. In one aspect, the present disclosure refers to a compound as described herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical product as described herein; or a pharmaceutical composition as described herein; for use in therapy.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a vesicular monoamine transporter-2 (VMAT2) disease or disorder selected from: an ataxias or spinal muscular atrophy; a chorea; a congenital malformation, deformation, or abnormality; a dementia; an oral cavity, salivary gland, or jaw disease; a dyskinesia; a dystonia; an endocrine, nutritional, or metabolic disease; an epilepsy; a habit or impulse disorder; a Huntington’s disease or related disorder; a mood or psychotic disorder; a neurotic, stress-related, and somatoform disorder; a degenerative disease of the basal ganglia; an extrapyramidal and movement disorder; a neurological or psychiatric disease or disorder; a nervous system or motor function disorder; a Parkinson’s/parkinsonism disorder; a pediatric-onset behavioral and emotional disorder; a pervasive developmental disorder; and a substance abuse or dependence disorder.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a neurological or psychiatric disease or disorder.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a neurological or psychiatric disease or disorder selected

from the group consisting of: hyperkinetic movement disorder, schizophrenia, schizoaffective disorder, a mood disorder, treatment-refractory obsessive-compulsive disorder, neurological dysfunction associated with Lesch-Nyhan syndrome, agitation associated with Alzheimer's disease, Fragile X syndrome or Fragile X-associated tremor-ataxia syndrome, autism spectrum disorder, Rett syndrome, and chorea-acanthocytosis.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a hyperkinetic movement disorder.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a hyperkinetic movement disorder; wherein the hyperkinetic movement disorder is selected from the group consisting of: tardive dyskinesia, Tourette's syndrome, Huntington's disease, tics, chorea associated with Huntington's disease, ataxia, chorea, dystonia, hemifacial spasm, myoclonus, restless leg syndrome, and tremors.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating tardive dyskinesia.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating Huntington's disease.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating chorea associated with Huntington's disease.

Also provided herein are compounds, as described herein, or a pharmaceutically acceptable salt thereof, for use in a method for treating a neurological or psychiatric disease or disorder, wherein the neurological or psychiatric disease or disorder is selected from schizophrenia and schizoaffective disorder. In some examples, the neurological or psychiatric disease or disorder is schizophrenia. In some examples, the neurological or psychiatric disease or disorder is schizoaffective disorder. In some examples, the neurological or psychiatric disease or disorder is obsessive-compulsive disorder. In some examples, the neurological or psychiatric disease or disorder is treatment-refractory obsessive-compulsive disorder. In some examples, the neurological or psychiatric disease or disorder is autism spectrum disorder. In some examples, the method for treating comprises using the compound, salt, product, or composition in adjunctive therapy.

These and other aspects of the disclosure disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A shows a general synthetic scheme for the preparation of certain compounds of Formula (**Ia**) and intermediates related thereto, wherein R^1 is methyl. In this representative example, R^1 is methyl and is introduced in **Compound 2-3**.

FIG. 1B shows a general synthetic scheme for the preparation of certain compounds of Formula (**Ia**) and an intermediate related thereto, wherein R^1 is methyl. In this representative example,