

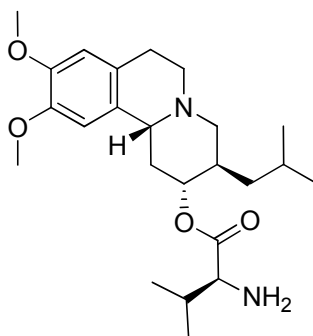
fluctuating response, the need for frequent intake do to TBZ rapid metabolism, and side effects. Side effects associated with TBZ include sedation, depression, akathisia, and parkinsonism.

[0005] TBZ, which contains two chiral centers and is a racemic mix of two stereoisomers, is rapidly and extensively metabolized in vivo to its reduced form, 3-isobutyl-9, 10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ol, also known as dihydrotetrabenazine (DHTBZ). DHTBZ is thought to exist as four individual isomers: ($\pm$) alpha-DHTBZ and ($\pm$) beta-DHTBZ. The 2R, 3R, 11bR or (+) alpha-DHTBZ is believed to be the absolute configuration of the active metabolite. (Kilbourn *et al.*, *Chirality*, 1997, 9, 59-62). Tetrabenazine has orphan drug status in US and is approved in certain European countries. Its use is also allowed for therapy of chorea in patients with Huntington's disease. However, tetrabenazine is rapidly metabolized and must frequently be administered throughout the day. (Muller, *Expert Opin. Investig. Drugs*, 2015, 24, 737-742). Therefore, there is an unmet need in the art to develop effective therapeutics for treatment of hyperkinetic movement disorders, including tardive dyskinesia.

[0006] Valbenazine, (*S*)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester, the purified prodrug of the (+)- α -isomer of dihydrotetrabenazine, recently showed a distinctive improvement in the treatment of hyperkinetic movement disorders, including tardive dyskinesia symptoms, with improved pharmacokinetic and tolerability profiles.

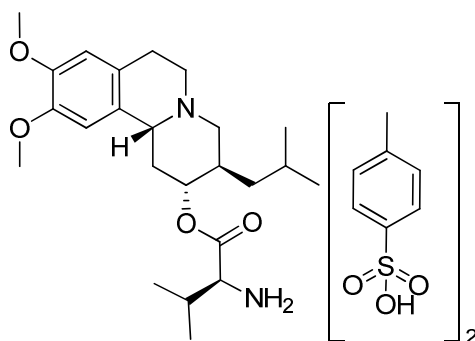
SUMMARY

[0007] Provided herein are pharmaceutically acceptable salts of (*S*)-2-amino-3-methyl-butyric acid (2R,3R,11bR)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl ester of Formula:



or an isotopic variant thereof; or solvate thereof.

[0008] Provided herein is a crystalline form of (*S*)-(*2R,3R,11bR*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate) of Formula I:



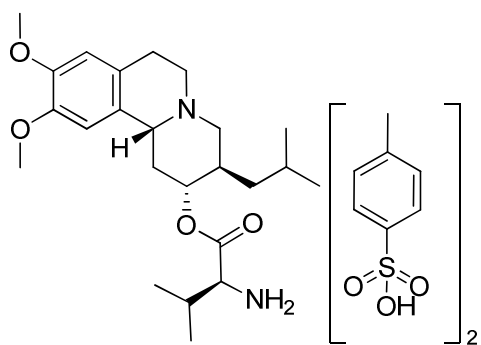
(I)

or an isotopic variant thereof; or solvate thereof.

[0009] Also provided herein are Forms I, II, III, IV, V, and VI of (*S*)-(*2R,3R,11bR*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate) (Formula I) or an isotopic variant thereof or solvate thereof.

[0009a] In one aspect, the present disclosure refers to a crystal form of the compound of Formula I:

3a

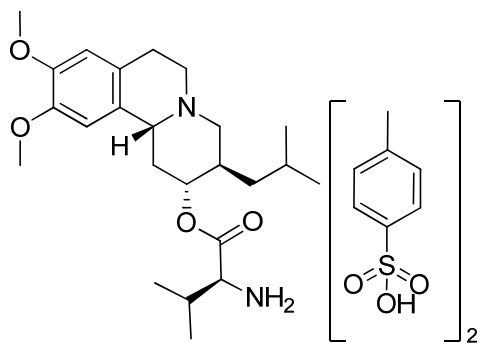


having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of:

a) 6.3, 17.9, and $19.7^{\circ} \pm 0.2^{\circ}$; or of:

b) 6.3, 18.3, and $19.8^{\circ} \pm 0.2^{\circ}$.

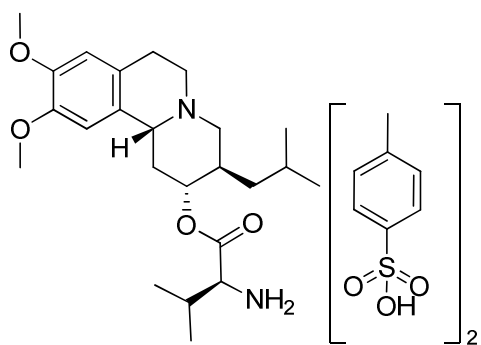
[0009b] In one aspect, the present disclosure refers to a crystal form of the compound of Formula I:



having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 5.7, 15.3, and $22.5^{\circ} \pm 0.2^{\circ}$.

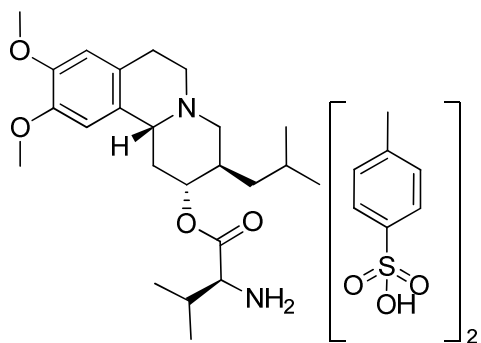
[0009c] In one aspect, the present disclosure refers to a crystal form of the compound of Formula I:

3b



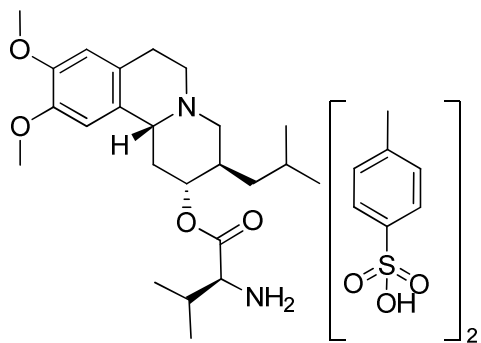
having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 6.2, 10.4, and $20.2^{\circ} \pm 0.2^{\circ}$.

[0009d] In one aspect, the present disclosure refers to a crystal form of the compound of Formula I:



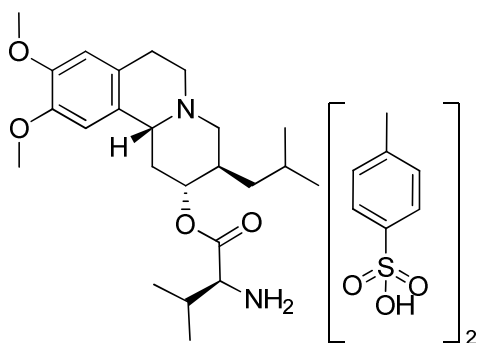
having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 6.7, 7.9, and $23.7^{\circ} \pm 0.2^{\circ}$.

[0009e] In one aspect, the present disclosure refers to a crystal form of the compound of Formula I:



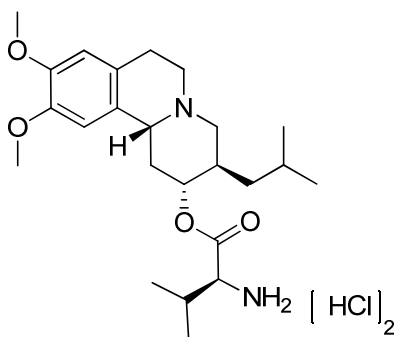
having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 6.8, 5.4, and $8.0^{\circ} \pm 0.2^{\circ}$.

[0009f] In one aspect, the present disclosure refers to amorphous:



having an X-Ray diffraction pattern substantially as shown in FIG. 19.

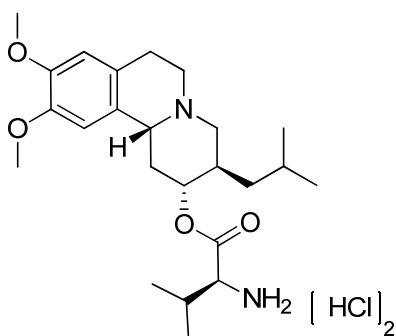
[0009g] In one aspect, the present disclosure refers to a crystal form of the compound of Formula II:



having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 7.2, 9.2, and $18.0^{\circ} \pm 0.2^{\circ}$.

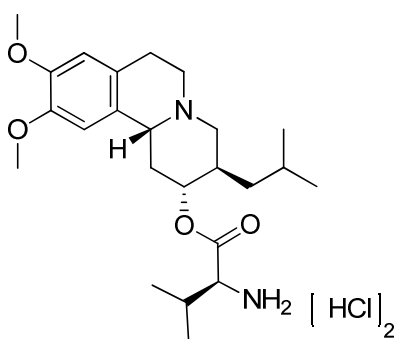
[0009h] In one aspect, the present disclosure refers to a crystal form of the compound of Formula II:

3d



having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 4.8, 13.3, and $24.9^{\circ} \pm 0.2^{\circ}$.

[0009i] In one aspect, the present disclosure refers to amorphous:



having an X-Ray diffraction pattern substantially as shown in FIG. 26.

[0010] Provided herein is a process for preparing a crystalline form of (*S*)-(2*R*,3*R*,11*bR*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate) (Formula I) or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof comprising dissolving (*S*)-

(2*R*,3*R*,11*bR*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate) (Formula I) in a solvent at a first temperature.

[0011] Provided herein is a pharmaceutical composition comprising a crystalline form of (*S*)-(2*R*,3*R*,11*bR*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate) (Formula I) or an isotopic variant thereof; or solvate thereof. In one aspect, the present disclosure refers to a pharmaceutical composition comprising the crystal form as disclosed herein and a pharmaceutically acceptable carrier.

[0012] Provided herein is a method for the treatment, prevention, or amelioration of one or more symptoms of hyperkinetic disorder, comprising administering to a subject a pharmaceutically acceptable salt of (*S*)-2-amino-3-methyl-butyrac acid (2*R*,3*R*,11*bR*)-3-isobutyl-9,10-dimethoxy-1,3,4,6,7,11*b*-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-yl or an isotopic variant thereof; or solvate thereof.

[0013] Provided herein is a method for the treatment, prevention, or amelioration of one or more symptoms of hyperkinetic disorder, comprising administering to a subject a crystalline form of (*S*)-(2*R*,3*R*,11*bR*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate) (Formula I) or an isotopic variant thereof; or solvate thereof.

[0013a] In one aspect, the present disclosure refers to use of the crystal form as disclosed herein in the manufacture of a medicament for ameliorating one or more symptoms of a hyperkinetic disorder.

[0013b] In one aspect, the present disclosure refers to use of the crystal form as disclosed herein in the manufacture of a medicament for inhibiting vesicular monoamine transporter isoform 2 in a subject.

BRIEF DESCRIPTION OF THE FIGURES

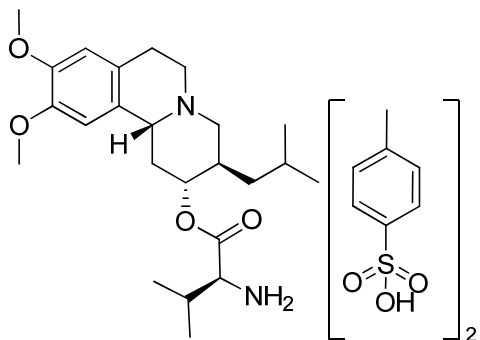
[0014] FIG. 1 depicts an exemplary X-ray powder (XRP) diffractogram of a sample of (*S*)-(2*R*,3*R*,11*bR*)-3-isobutyl-9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro-1*H*-pyrido[2,1-*a*]isoquinolin-2-yl 2-amino-3-methylbutanoate di(4-methylbenzenesulfonate) (Formula I) in crystalline Form I.

[0015] FIG. 2 depicts exemplary Thermogravimetric Analysis (TGA) thermogram (dotted line) and Differential Scanning Calorimetry (DSC) diffractogram (solid line) of a sample of Formula I in crystalline Form I.

[0016] FIG. 3 depicts an exemplary Gravimetric Vapor Sorption (GVS) of a sample of Formula I in crystalline Form I.

What is claimed is:

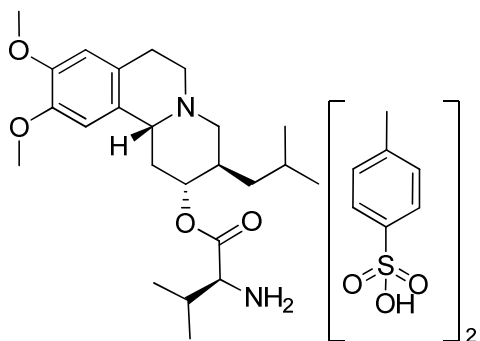
1. A crystal form of the compound of Formula I:



having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of:

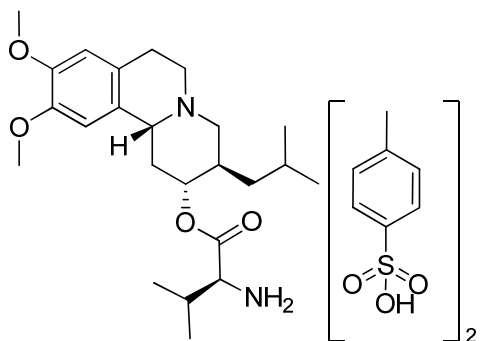
- a) 6.3, 17.9, and $19.7^\circ \pm 0.2^\circ$; or of:
- b) 6.3, 18.3, and $19.8^\circ \pm 0.2^\circ$.

2. A crystal form of the compound of Formula I:



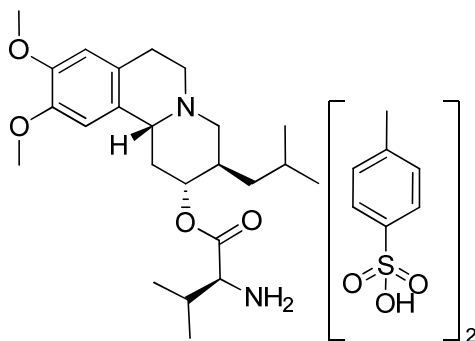
having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 5.7, 15.3, and $22.5^\circ \pm 0.2^\circ$.

3. A crystal form of the compound of Formula I:



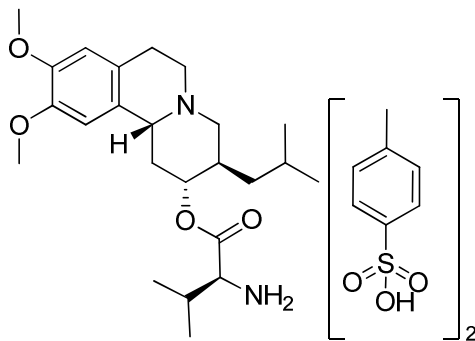
having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 6.2, 10.4, and $20.2^{\circ} \pm 0.2^{\circ}$.

4. A crystal form of the compound of Formula I:



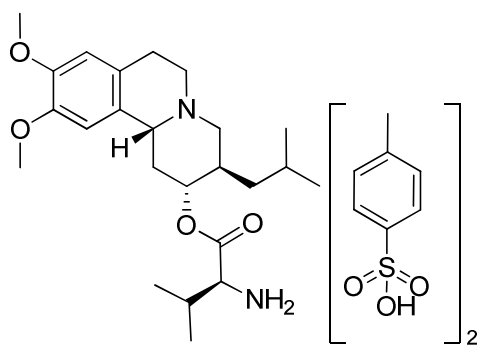
having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 6.7, 7.9, and $23.7^{\circ} \pm 0.2^{\circ}$.

5. A crystal form of the compound of Formula I:



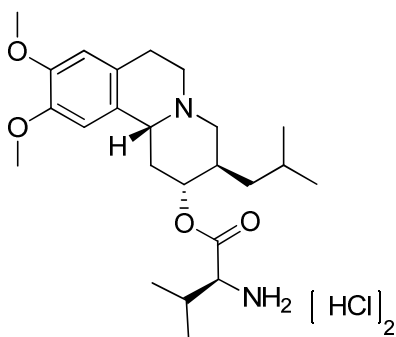
having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 6.8, 5.4, and $8.0^{\circ} \pm 0.2^{\circ}$.

6. Amorphous:



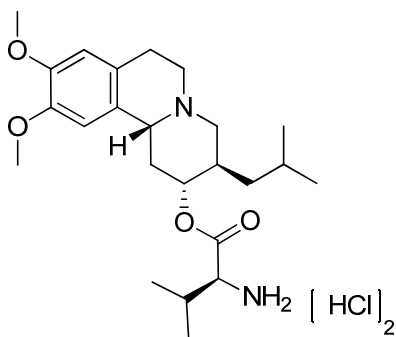
having an X-Ray diffraction pattern substantially as shown in FIG. 19.

7. A crystal form of the compound of Formula II:



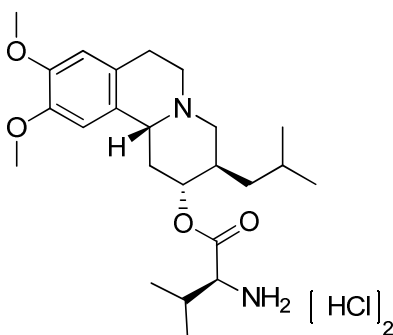
having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 7.2, 9.2, and 18.0°±0.2°.

8. A crystal form of the compound of Formula II:



having an XRPD pattern comprising X-Ray diffraction peaks at two-theta angles of 4.8, 13.3, and 24.9°±0.2°.

9. Amorphous:



having an X-Ray diffraction pattern substantially as shown in FIG. 26.

10. A pharmaceutical composition comprising the crystal form of claim 1 and a pharmaceutically acceptable carrier.
11. The pharmaceutical composition of claim 10, wherein the composition is formulated for oral administration.
12. The pharmaceutical composition of claim 10, wherein the composition is formulated as a single dosage form.
13. Use of the crystal form of claim 1 in the manufacture of a medicament for ameliorating one or more symptoms of a hyperkinetic disorder.
14. The use according to claim 13, wherein the hyperkinetic disorder is Huntington's disease, tardive dyskinesia, Tourette's syndrome, dystonia, hemiballismus, chorea, or tics.
15. The use according to claim 14, wherein the hyperkinetic disorder is tardive dyskinesia.
16. The use according to claim 14, wherein the hyperkinetic disorder is Tourette's syndrome.
17. Use of the crystal form of claim 1 in the manufacture of a medicament for inhibiting vesicular monoamine transporter isoform 2 in a subject.