



US012384783B2

(12) **United States Patent**
Wennogle et al.

(10) **Patent No.:** **US 12,384,783 B2**

(45) **Date of Patent:** **Aug. 12, 2025**

(54) **SALTS AND CRYSTALS**

(71) Applicant: **INTRA-CELLULAR THERAPIES, INC.**, New York, NY (US)

(72) Inventors: **Lawrence P. Wennogle**, Hillsborough, NJ (US); **Peng Li**, New Milford, NJ (US); **Edwin Aret**, Almere (NL)

(73) Assignee: **INTRA-CELLULAR THERAPIES, INC.**, Bedminster, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 309 days.

(21) Appl. No.: **17/815,843**

(22) Filed: **Jul. 28, 2022**

(65) **Prior Publication Data**

US 2022/0363682 A1 Nov. 17, 2022

Related U.S. Application Data

(62) Division of application No. 16/649,515, filed as application No. PCT/US2018/052922 on Sep. 26, 2018, now Pat. No. 11,440,911.

(60) Provisional application No. 62/563,341, filed on Sep. 26, 2017.

(51) **Int. Cl.**
C07D 471/16 (2006.01)

(52) **U.S. Cl.**
CPC **C07D 471/16** (2013.01); **C07B 2200/13** (2013.01)

(58) **Field of Classification Search**
CPC **C07D 471/16**
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,162,318 A 7/1979 Silvestrini
5,114,976 A 5/1992 Norden
5,151,419 A 9/1992 Perenyi et al.
6,548,493 B1 4/2003 Robichaud et al.
6,552,017 B1 4/2003 Robichaud et al.
6,699,852 B2 3/2004 Robichaud et al.
6,713,471 B1 3/2004 Robichaud et al.
6,759,554 B2 7/2004 Buchwald et al.
6,849,619 B2 2/2005 Robichaud et al.
7,071,186 B2 7/2006 Robichaud et al.
7,081,455 B2 7/2006 Robichaud et al.
7,109,339 B2 9/2006 Lee et al.
7,183,282 B2 2/2007 Robichaud et al.
RE39,679 E 6/2007 Robichaud et al.
RE39,680 E 6/2007 Robichaud et al.
7,238,690 B2 7/2007 Robichaud et al.
7,462,641 B2 12/2008 Igo et al.
7,799,785 B2 9/2010 Cid-Nunez et al.
7,998,971 B2 8/2011 Barlow et al.
8,309,722 B2 11/2012 Tomesch et al.
8,598,119 B2 12/2013 Mates et al.
8,648,077 B2 2/2014 Tomesch et al.
8,779,139 B2 7/2014 Tomesch et al.
8,791,138 B2 7/2014 Seeman et al.

8,993,572 B2 3/2015 Mates et al.
9,168,258 B2 10/2015 Mates et al.
9,199,995 B2 12/2015 Tomesch et al.
9,315,504 B2 4/2016 Tomesch et al.
9,371,324 B2 6/2016 Mates et al.
9,428,506 B2 8/2016 Mates et al.
9,586,960 B2 3/2017 Tomesch et al.
9,616,061 B2 4/2017 Mates et al.
9,708,322 B2 7/2017 Peng et al.
9,745,300 B2 8/2017 Mates et al.
9,751,883 B2 9/2017 Tomesch et al.
9,956,227 B2 5/2018 Vanover et al.
10,072,010 B2 9/2018 Li et al.
10,077,267 B2 9/2018 Mates et al.
10,117,867 B2 11/2018 Mates et al.
10,221,176 B2 3/2019 Tomesch et al.
10,245,260 B2 4/2019 Yao et al.
10,322,134 B2 6/2019 Vanover et al.
10,464,938 B2 11/2019 Tomesch et al.
10,472,359 B2 11/2019 Li et al.
10,597,394 B2 3/2020 Mates et al.
10,597,395 B2 3/2020 Tomesch et al.
10,654,854 B2 5/2020 Li et al.
10,682,354 B2 6/2020 Wennogle
10,688,097 B2 6/2020 Yao et al.
10,695,345 B2 6/2020 Li et al.
10,702,522 B2 7/2020 Mates et al.
10,716,786 B2 7/2020 Li et al.
10,799,500 B2 10/2020 Yao et al.
10,844,061 B2 11/2020 Li et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CN 109867674 A 6/2019
WO WO 2009/017836 A1 2/2009

(Continued)

OTHER PUBLICATIONS

Longo et al., "The Novel Antipsychotic Lumateperone (ITI-007) in the Treatment of Schizophrenia: A Systematic Review," *Brain Sci.* Nov. 26, 2023;13(12):1641. (Year: 2023).*

Suppes et al., "Adjunctive lumateperone (ITI-007) in the treatment of bipolar depression: Results from a randomized placebo-controlled clinical trial," *Bipolar Disorders*, 2023;25:478-488. (Year: 2023).*

Vanover et al., "Dopamine D2 receptor occupancy of lumateperone (ITI-007): a Positron Emission Tomography Study in patients with schizophrenia," *Neuropsychopharmacology* Jun. 11, 2018. (Year: 2018).*

(Continued)

Primary Examiner — Jared Barsky

(74) *Attorney, Agent, or Firm* — Hoxie & Associates LLC

(57) **ABSTRACT**

The disclosure provides new, stable, pharmaceutically acceptable hydrochloride salt forms of 1-(4-fluoro-phenyl)-4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-butan-1-one, together with methods of making and using them, and pharmaceutical compositions comprising them.

8 Claims, 4 Drawing Sheets

(56)

References Cited

U.S. PATENT DOCUMENTS

10,899,762	B2	1/2021	Mates et al.
10,906,906	B2	2/2021	Li et al.
10,960,009	B2	3/2021	Vanover et al.
10,960,010	B2	3/2021	Vanover et al.
10,961,245	B2	3/2021	Li et al.
11,014,925	B2	5/2021	Li et al.
11,026,951	B2	6/2021	Vanover et al.
11,052,083	B2	7/2021	Li et al.
11,053,245	B2	7/2021	Mates et al.
11,066,407	B2	7/2021	Tomesch et al.
11,096,944	B2	8/2021	Yao et al.
11,124,514	B2	9/2021	Mates et al.
RE48,825	E	11/2021	Tomesch et al.
RE48,839	E	12/2021	Mates et al.
11,311,536	B2	4/2022	Li et al.
11,331,316	B2	5/2022	Li et al.
11,332,469	B2	5/2022	Mittelman et al.
11,376,249	B2	7/2022	Li et al.
11,407,751	B2	8/2022	Tomesch et al.
11,427,587	B2	8/2022	Li et al.
11,440,911	B2	9/2022	Wennogle et al.
11,453,670	B2	9/2022	Li et al.
11,560,382	B2	1/2023	Mates et al.
11,680,065	B2	6/2023	Li et al.
11,723,909	B2	8/2023	Yao et al.
11,806,347	B2	11/2023	Li et al.
11,806,348	B2	11/2023	Li et al.
11,957,791	B2	4/2024	Li et al.
11,958,852	B2	4/2024	Mates et al.
11,980,617	B2	5/2024	Snyder et al.
12,070,459	B2	8/2024	Li et al.
12,090,155	B2	9/2024	Mates et al.
12,144,808	B2	11/2024	Li et al.
2010/0204470	A1	8/2010	Wieser et al.
2015/0072964	A1	3/2015	Mates et al.
2015/0079172	A1	3/2015	Mates et al.
2015/0080404	A1	3/2015	Mates et al.
2018/0271862	A1	9/2018	Li et al.
2019/0112309	A1	4/2019	Li et al.
2019/0112310	A1	4/2019	Li et al.
2019/0211015	A1	7/2019	Mittelman et al.
2019/0231780	A1	8/2019	Yao et al.
2020/0102309	A1	4/2020	Li et al.
2020/0148683	A1	5/2020	Peddy et al.
2020/0157100	A1	5/2020	Li
2020/0392135	A1	12/2020	Wennogle et al.
2020/0407362	A1	12/2020	Mates et al.
2021/0002280	A1	1/2021	Mates et al.
2021/0008065	A1	1/2021	Li et al.
2021/0009592	A1	1/2021	Li et al.
2021/0315891	A1	10/2021	Li et al.
2022/0024924	A1	1/2022	Janton et al.
2022/0041600	A1	2/2022	Li
2022/0056031	A1	2/2022	Li et al.
2022/0362241	A1	11/2022	Davis et al.
2023/0271962	A1	8/2023	Li et al.
2023/0339951	A1	10/2023	Li et al.
2023/0346787	A1	11/2023	Yao et al.
2023/0355616	A1	11/2023	Mates et al.
2023/0372336	A1	11/2023	Dutheil et al.
2024/0000781	A1	1/2024	Li
2024/0115565	A1	4/2024	Li
2024/0279228	A1	8/2024	Li
2024/0307386	A1	9/2024	Snyder et al.

FOREIGN PATENT DOCUMENTS

WO	WO 2018/106916	A1	6/2018
WO	WO 2019/102240	A1	5/2019
WO	WO 2020/182978	A1	9/2020
WO	WO 2022/199708	A1	9/2022

OTHER PUBLICATIONS

Intra-Cellular Therapies Announces Successful Outcome of a Phase II Clinical Trial With ITI-007 in Patients With Sleep Maintenance

Insomnia | Intra-Cellular Therapies Inc. (date accessed Jan. 14, 2025), press release dated Jan. 13, 2009 for treating insomnia with Iti-007. (Year: 2025).*

Poster Presentations Monday Jul. 23, 2018, Vanover et al., "ITI-007 (Lumateperone) for the treatment of Agitation in Patients with Dementia, Including Alzheimer's Disease," *Alzheimer's & Dementia* vol. 14, Issue 7S Part 12. (Year: 2018).*

Peterson, et al., "Expanding the Scope of Crystal Form Evaluation in Pharmaceutical Science", *J Pharm Pharmaceut Sci.*, 9(3), pp. 317-326, (2006).

"Clinical Trial Evaluating ITI-007 (Lumateperone) as a Monotherapy for the Treatment of Bipolar," ClinicalTrials.gov (Identifier: NCT02600494), 5 pages, (2015).

Aiken, C., "An Overview of Atypical Antipsychotics for Bipolar Depression," published on Jan. 3, 2020 at <https://www.psychiatristimes.com/view/overview-atypical-antipsychotics-bipolar-depression>, 11 pages.

Barman, R. et al., "Newer Antipsychotics: Brexpiprazole, Cariprazine, and Lumateperone: A Pledge or Another Unkept Promise?," *World J. Psychiatr.*, vol. 11, No. 12, pp. 1228-1238, (2021).

Bavin, M., "Polymorphism in Process Development," *Chemistry & Industry*, pp. 527-529, (1989).

Berge, S. et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, vol. 66, No. 1, pp. 1-19, (1977).

Bharate, S., "Recent Developments in Pharmaceutical Salts: FDA Approvals From 2015 to 2019," *Drug Discovery Today*, vol. 26, No. 2, pp. 384-398, (2021).

Brittain, H. et al., "Chapter 5: Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," *Polymorphism in Pharmaceutical Solids*, 25 pages, (1999).

Calabrese, J. et al., "Efficacy and Safety of Lumateperone for Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder: A Phase 3 Randomized Placebo-Controlled Trial," *American Journal of Psychiatry*, vol. 178, No. 12, pp. 1098-1106, (2021), published online Sep. 23, 2021, DOI: <https://doi.org/10.1176/appi.aip.2021.20091339>.

Correll, C. et al., "Efficacy and Safety of Lumateperone for Treatment of Schizophrenia A Randomized Clinical Trial," *JAMA Psychiatry*, vol. 77, No. 4, pp. 349-358, (2020).

Davis, R. et al., "ITI-007: A Novel Treatment for Behavioral Disturbances Associated with Dementia and Related Disorders," *Clinical Trials in Alzheimer's Disease (CTAD) Congress 2014* (2014) (poster presentation).

Davis, R. et al., "Rationale for the Development of Low Doses of ITI-007 for the Treatment of Behavioral Disturbances Associated with Dementia," *The Journal of Prevention of Alzheimer's Disease*, 2(4):302 (2015) (*Clinical Trials in Alzheimer's Disease (CTAD) Congress, Symposium Summary OC51*).

Davis, R. et al., "Lumateperone (ITI-007), A Novel Drug in Development for the Treatment of Agitation in Patients with Dementia, including Alzheimer's Disease: Rationale and Clinical Design," *The Journal of Prevention of Alzheimer's Disease*, 4(4):372 (2017) (*Clinical Trials in Alzheimer's Disease (CTAD) Congress, Symposium Summary P93*).

Edinoff, A. et al., "Lumateperone for the Treatment of Schizophrenia," *Psychopharmacology Bulletin*, vol. 50, No. 4, pp. 32-59, (2020).

Grant, D., "Polymorphism in Pharmaceutical Solids", Chapter 1, pp. 1-10 (1999).

Harvey, P. et al., "Lumateperone Improves Negative Symptoms Related to Emotional Experience (Avolition) in Patient with Schizophrenia," Abstract presented at the American Society of Clinical Psychopharmacology (ASCP) Annual Meeting: May 29-Jun. 1, 2018: Miami, FL.

Hlavinka, E., "Schizophrenia Tx Eases Depression in Bipolar Disorder: Lumateperone Offers Greater Rate of Response, Remission versus Placebo," *Medpage Today*, 7 pages, (2020); <https://www.medpagetoday.com/meetingcoverage/psychcongress/88584>.

Kendrick, T., "The Newer, 'Atypical' Antipsychotic Drugs—Their Development and Current Therapeutic Use," *British J. General Practice*, vol. 49, pp. 745-749, (1999).

(56)

References Cited

OTHER PUBLICATIONS

- Khorana, N. et al., "Gamma-Carbolines: Binding at 5-HT_{5A} Serotonin Receptors," *Bioorganic & Medicinal Chemistry*, vol. 11, D. 717-722, p. 718, Table 1, (2003).
- Kumar, B. et al., "Lumateperone: A New Treatment Approach for Neuropsychiatric Disorders," *Drugs of Today*, vol. 54, No. 12, pp. 713-719, (2018).
- Paulekuhn, G. et al., "Trends in Active Pharmaceutical Ingredient Salt Selection based on Analysis of the Orange Book Database," *J Med Chem.*, vol. 50, pp. 6665-6672, (2007).
- Press Release, "Intra-Cellular Therapies Announces Additional Results From Phase I/II Clinical Trial for ITI-007 in Healthy Geriatric Subjects and Patients With Dementia," Intra-Cellular Therapies, Press Release Date: Nov. 21, 2014.
- Press Release, "Intra-Cellular Therapies Announces Top-Line Results from the Second Phase 3 Trial of ITI-007 in Patients with Schizophrenia (Study '302)," Intra-Cellular Therapies, Press Release Date: Sep. 28, 2016, 8 pages, available at: <https://globenewswire.com/news-release/2016/09/28/875435/0/en/Intra-Cellular-Therapies-Announces-Top-Line-Results-from-the-Second-Phase-3-Trial-of-ITI-007-in-Patients-with-Schizophrenia-Study-302.html>.
- Press Release, "Intra-Cellular Therapies Reports Positive Final Results of a Phase II Clinical Trial With ITI-007 in Patients with Sleep Maintenance Insomnia," Intra-Cellular Therapies, Press Release Date: Mar. 10, 2009, 3 pages, available at: <https://ir.intracellulartherapies.com/static-files/375e1667-6457-4cd9-95dc-616ca3b5d02b>.
- Press Release, "Intra-Cellular Therapies Announces Positive Top-Line Results from a Phase 3 Trial of Lumateperone in Patient with Bipolar Depression," Intra-Cellular Therapies, Press Release Date: Jul. 8, 2019.
- Press Release, "Intra-Cellular Therapies Presents Data on Symptom Improvement by Lumateperone on Negative Symptoms, Depression, and Social Function in Patients with Schizophrenia at the American Society of Clinical Psychopharmacology (ASCP) Annual Meeting," Intra-Cellular Therapies, Press Release Date: May 31, 2018, (<https://ir.intracellulartherapies.com/newsreleases/>).
- Saal, C. et al., "Pharmaceutical Salts: A Summary on Doses of Salt Formers from the Orange Book," *European Journal of Pharmaceutical Sciences*, vol. 49, pp. 614-623, (2013).
- Satlin, A. et al., "ITI-007 (Lumateperone) for the Treatment of Agitation in Patients with Dementia, including Alzheimer's Disease," *Alzheimer's & Dementia*, vol. 14, No. 7, pp. 678-679, (2018), (Alzheimer's Assoc. International Conference 2018, summary of Poster P2-032).
- Satlin, A. et al., "ITI-007 (Lumateperone) for the Treatment of Agitation in Patients with Dementia, including Alzheimer's Disease," Poster P2-032, Alzheimer's Assoc. International Conference 2018, (2018).
- Serajuddin, A., "Salt formation to improve drug solubility," *Advanced Drug Delivery Reviews*, vol. 59, pp. 603-616, (2007).
- Stahl & Wermouth (Eds.), "Handbook of Pharmaceutical Salts Properties, Selection, and Use," Wiley-VCH, pp. 167-168, 170-173, 216-217 (2002).
- Stahl & Wermouth (Eds.), "Handbook of Pharmaceutical Salts Properties, Selection, and Use," Wiley-VCH, pp. 258-261 (2002).
- Vanover, K. et al., "Dopamine D2 receptor occupancy of lumateperone (ITI-007): a Positron Emission Tomography Study in patients with schizophrenia," *Neuropsychopharmacology*, vol. 44, pp. 598-605, (2019).
- Vanover, K. et al., "ITI-007: A Novel Therapy for the Treatment of Schizophrenia and Related Psychoses," *International Clinical Psychopharmacology*, vol. 26, e56, 1 page, (2011).
- Vanover, K. et al., "A Novel Approach to Address an Unmet Need in the Treatment of Schizophrenia and Depression: Lumateperone, an Innovative Modulator of Dopamine, Serotonin, and Glutamate," Abstract presented at the American Society of Clinical Psychopharmacology (ASCP) Annual Meeting, May 29-Jun. 1, 2018; Miami, FL.
- Vanover, K. et al., "Lumateperone (ITI-007): A Novel Investigational Agent with Broad Therapeutic Potential Across Multiple Neuropsychiatric Disorders," *European Neuropsychopharmacology*, vol. 27, pp. S660-S661 (2017) (Summary of ECNP Poster p. 1.g.038).
- Vanover, K. et al., Abstracts of the 13th International Congress on Schizophrenia (ICOSR) (Apr. 2-6, 2011), *Schizophrenia Bull.*, vol. 37, Suppl. 1., p. 325, (2011).
- Vyas, P. et al., "An Evaluation of Lumateperone Tosylate for the Treatment of Schizophrenia," *Expert Opinion on Pharmacotherapy*, vol. 21, No. 2, pp. 139-145, (2020); <https://doi.org/10.1080/14656566.2019.1695778>.
- Wennogle, L. et al., "Activation of NMDA and AMPA Receptors by Lumateperone (ITI-007): Implications for Antidepressant Activity," Abstract presented at the 2017 Collegium Internationale Neuro-Psychopharmacologicum (CINP) Thematic Meeting: Treatment Resistant Depression; Jul. 20-22, 2017; Prague.
- Balbach, et al. "Pharmaceutical evaluation of early development candidates 'the 100 mg-approach'," *International Journal of Pharmaceutics*, vol. 275, pp. 1-12 (2004).
- Bastin, "Salt Selection and Optimized Procedures for Pharmaceutical New Chemical Entities," *Organic Process and Research Development*, vol. 4, No. 5, pp. 427-435 (2000).
- Byrn, "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations," vol. 12, No. 7, pp. 945-954 (1995).
- Caira M.R., "Crystalline Polymorphism of Organic Compounds," *Design of Organic Solids, Topics in Current Chemistry*, 198:163-208 (1998).
- Davis, et al. "ITI-007 demonstrates brain occupancy at serotonin 5-HT_{2A} and dopamine D2 receptors and serotonin transporters using positron emission tomography in healthy volunteers," *Psychopharmacology*, Published Online Apr. 7, 2015, 10 pages.
- Davis, et al., "ITI-007 in the treatment of schizophrenia: from novel pharmacology to clinical outcomes," *Expert Review of Neurotherapeutics*, vol. 16, No. 6, pp. 601-614 (2016).
- Gadade, et al., "Pharmaceutical Cocrystals: Regulatory and Strategic Aspects, Design and Development," *Adv Phann Bull*, vol. 6, No. 4, pp. 479-494, (2016).
- Grant, "Polymorphism in Pharmaceutical Solids", Chapter 1, pp. 1-10 (1999).
- Guillory, "Polymorphism in Pharmaceutical Solids", Chapter 5, pp. 183-226 (1999).
- Haynes, "Occurrence of Pharmaceutically Acceptable Anions and Cations in the Cambridge Database," *Journal of Pharmaceutical Sciences*, vol. 94, No. 10, pp. 2111-2120 (2005).
- International Search Report for International Application No. PCT/US2018/052922, mailed Nov. 26, 2018, 3 pages.
- Jain, et al., "Polymorphism in Pharmacy", *Indian Drugs*, vol. 23, No. 6, pp. 315-316 (1986).
- Lee, et al., "Novel, Highly Potent, Selective 5-HT_{2A}/D2 Receptor Antagonists as Potential Atypical Antipsychotics," *Bioorg. Med. Chem. Lett.*, vol. 13, pp. 767-770, (2003).
- Li, et al., "Discovery of a Tetracyclic Quinoxaline Derivative as a Potent and Orally Active Multifunctional Drug Candidate for the Treatment of Neuropsychiatric and Neurological Disorders," vol. 57, pp. 2670-2682 (2014).
- Li, et al., "Dopamine Targeting Drugs for the Treatment of Schizophrenia: Past, Present and Future," *Current Topics in Medicinal Chemistry*, vol. 16, pp. 3385-3403 (2016).
- Marek, et al., "Synergistic Action of 5-HT_{2A} Antagonists and Selective Serotonin Reuptake Inhibitors in Neuropsychiatric Disorders," *Neuropsychopharmacology*, vol. 28, pp. 402-412 (2003).
- Nagai, et al., "Synthesis of 2, 3, 4, 4a, 5, 9b-hexahydro-1H-pyrido [4,3-b] indole derivatives and their central nervous system activities," *Journal of Medicinal Chemistry*, vol. 22, No. 6, pp. 677-683, (1979).
- Newman, et al., "Solid-State Analysis of the Active Pharmaceutical Ingredient in Drug Products," *Drug Discovery Today*, vol. 8, No. 9, pp. 898-903 (2003).
- Savjani et al., "Drug Solubility: Importance and Enhancement Techniques," *International Scholarly Research Network Pharmaceutics* (2012), vol. 2012, pp. 1-10.
- Singhal, et al., "Drug polymorphism and dosage form design: a practical perspective", *Advanced Drug Delivery Reviews*, vol. 56, pp. 335-347 (2004).

(56)

References Cited

OTHER PUBLICATIONS

Snyder, et al., "Functional Profile of a Novel Modulator of Serotonin, Dopamine, and Glutamate Neurotransmission," *Psychopharmacology*, vol. 232, pp. 605-621 (2015).

Vippagunta, et al., "Crystalline Solids," *Advanced Drug Delivery Reviews*, vol. 48, 24 pages, (2001).

Bastin, R. et al., "Salt Selection and Optimized Procedures for Pharmaceutical New Chemical Entities," *Organic Process and Research Development*, vol. 4, No. 5, pp. 427-435, (2000).

Dutheil, S., et al. "Lumateperone Normalizes Pathological Levels of Acute Inflammation through Important Pathways Known to Be Involved in Mood Regulation," *The Journal of Neuroscience*, vol. 43, No. 5, pp. 863-877, (2023).

Gramigna, J., "Lumateperone Safe, Effective for Depressive Symptoms Among Patients with Bipolar Disorders," *American Society of Clinical Psychopharmacology Annual Meeting*, Jun. 2, 2020, 3 pages.

Lee, T. et al., "Novel, Highly Potent, Selective 5-HT_{2A}/D₂ Receptor Antagonists as Potential Atypical Antipsychotics," *Bioorganic & Medicinal Chemistry Letters*, vol. 13, pp. 767-770, (2003).

Liebermann, J. et al., "ITI-007 for the Treatment of Schizophrenia: A 4-Week Randomized, Double-Blind, Controlled Trial," *Biological Psychiatry*, vol. 79, pp. 952-961, (2016).

Snyder, G. et al., "Chapter 11: A review of the pharmacology and clinical profile of lumateperone for the treatment of schizophrenia," *Advances in Pharmacology*, vol. 90, pp. 253-276, 31 pages, (2021).

Suppes, T. et al., "Adjunctive lumateperone (ITI-007) in the treatment of bipolar depression: Results from a randomized placebo-controlled clinical trial," *Bipolar Disorders*, vol. 25, pp. 478-488, 11 pages, (2023).

* cited by examiner

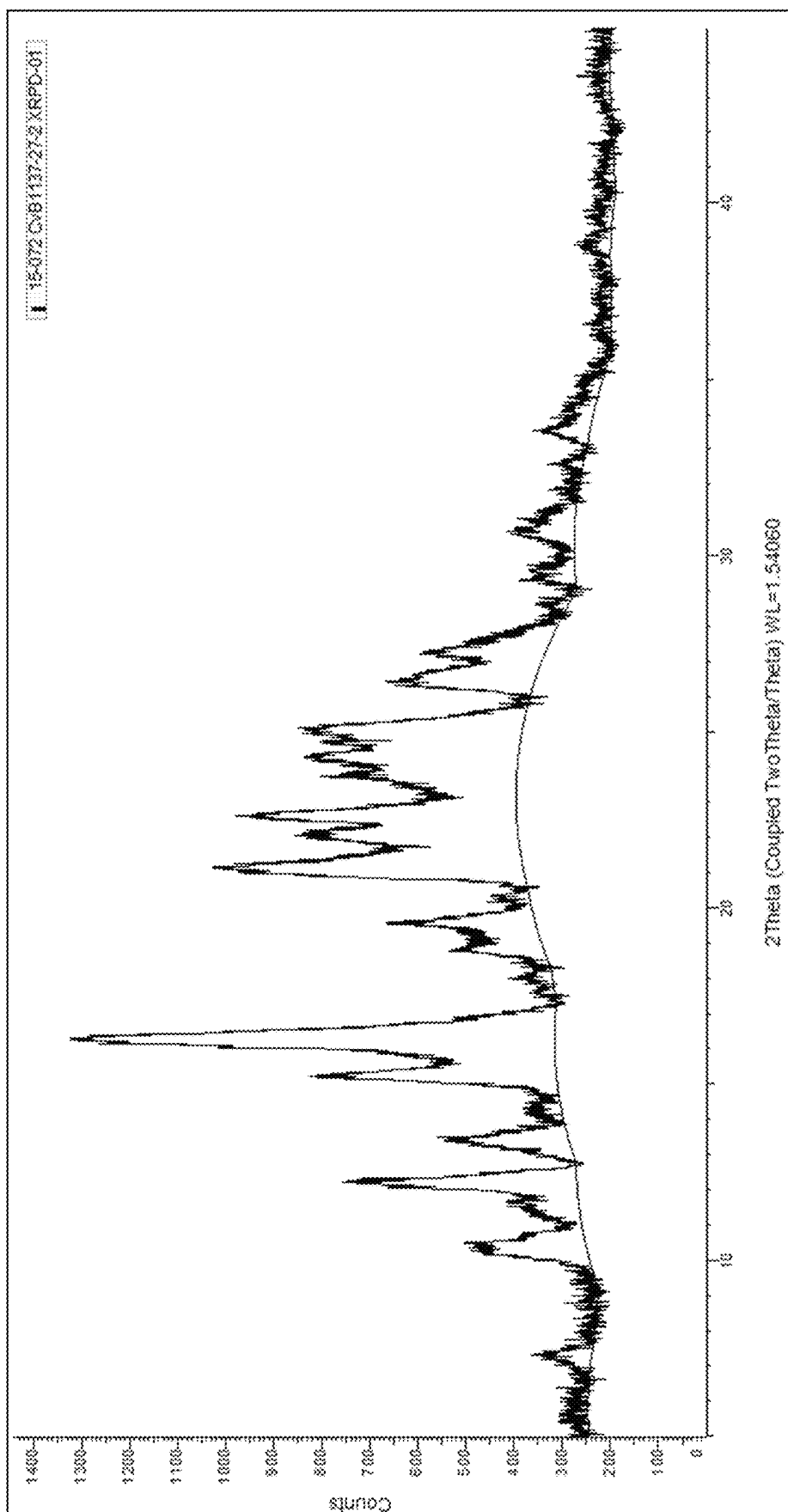


FIG. 1

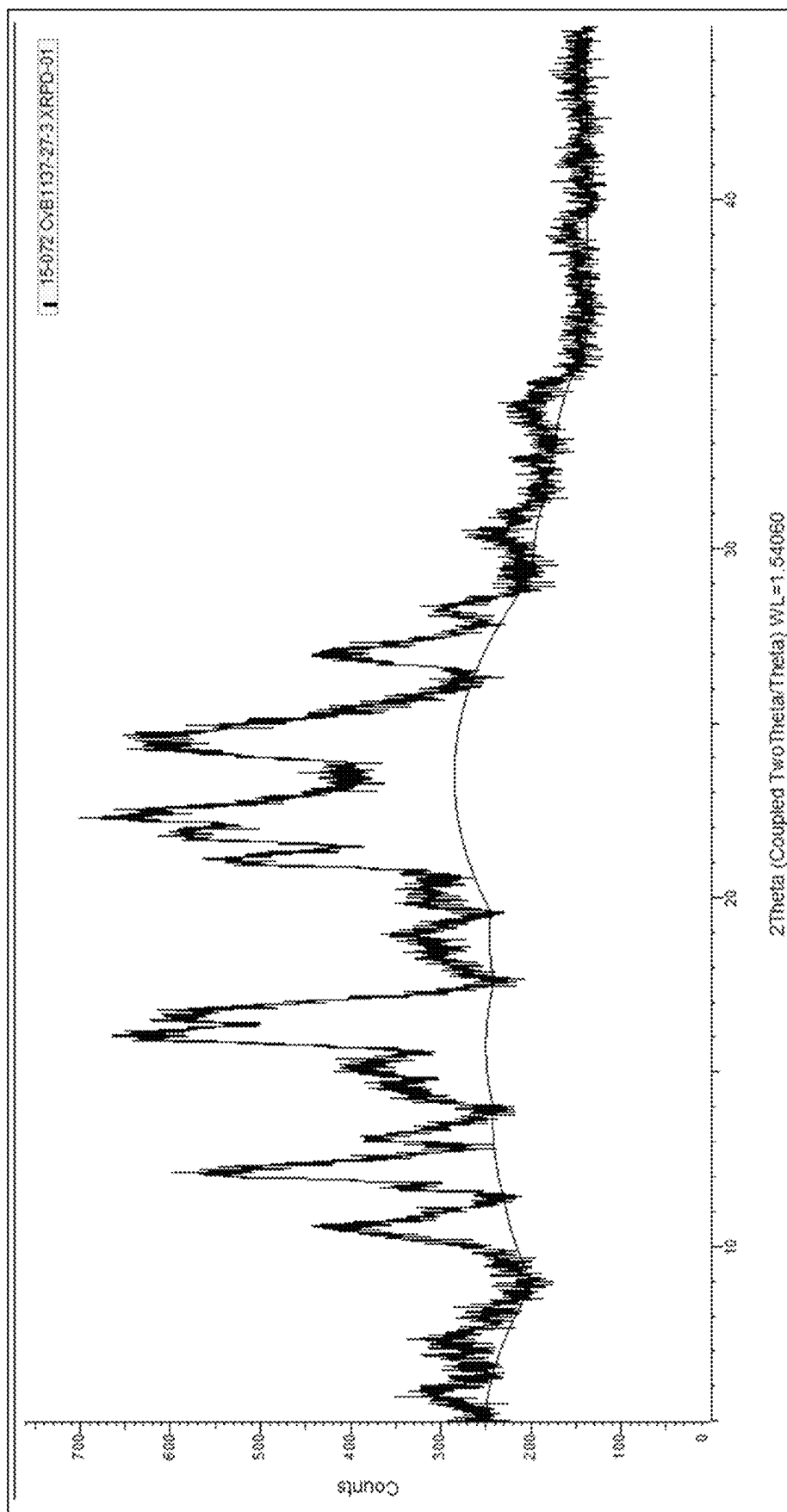


FIG. 2

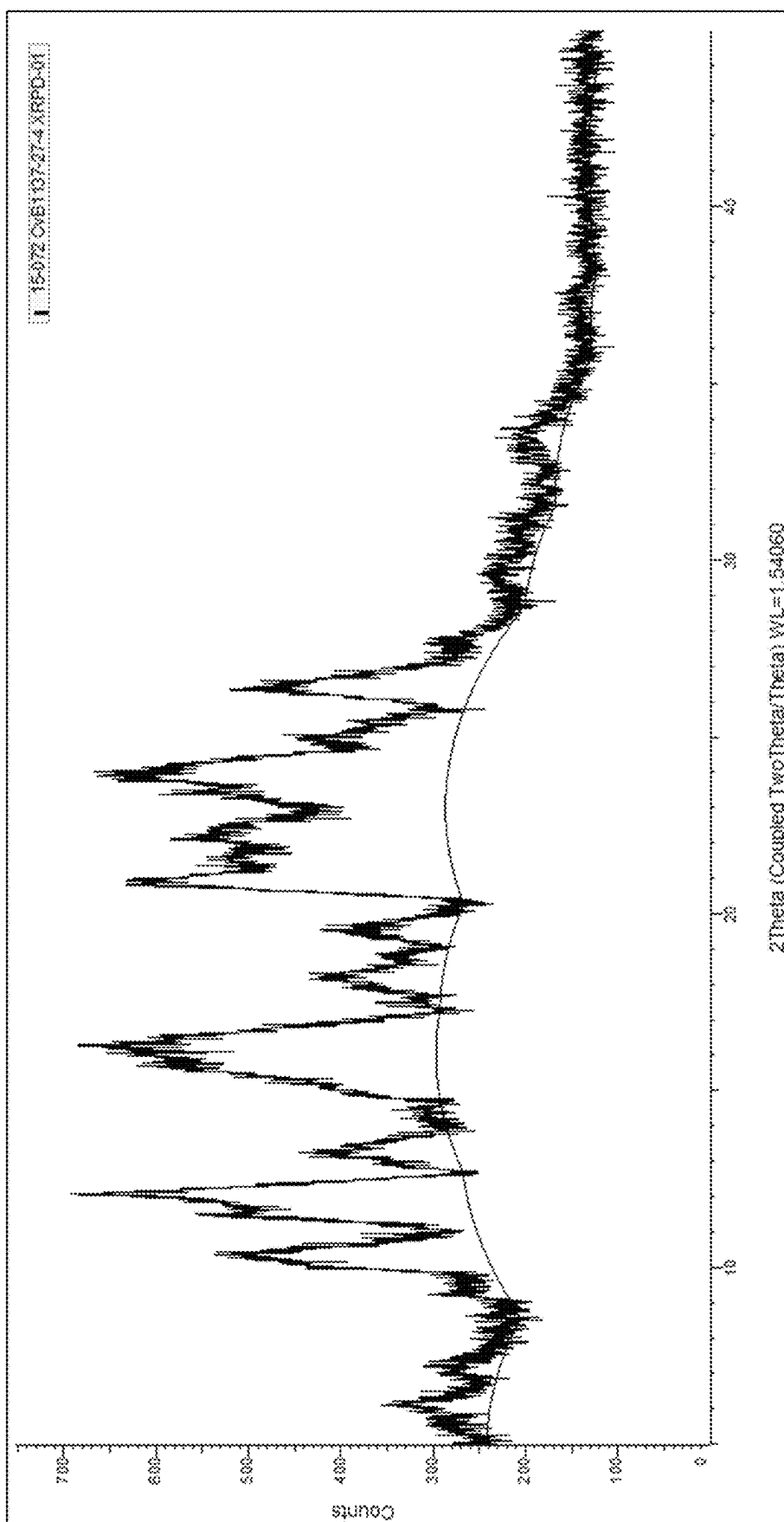


FIG. 3

15-071d1 competitive slurry 5kC XRPD-01
15-072d1 competitive slurry RT XRPD-01

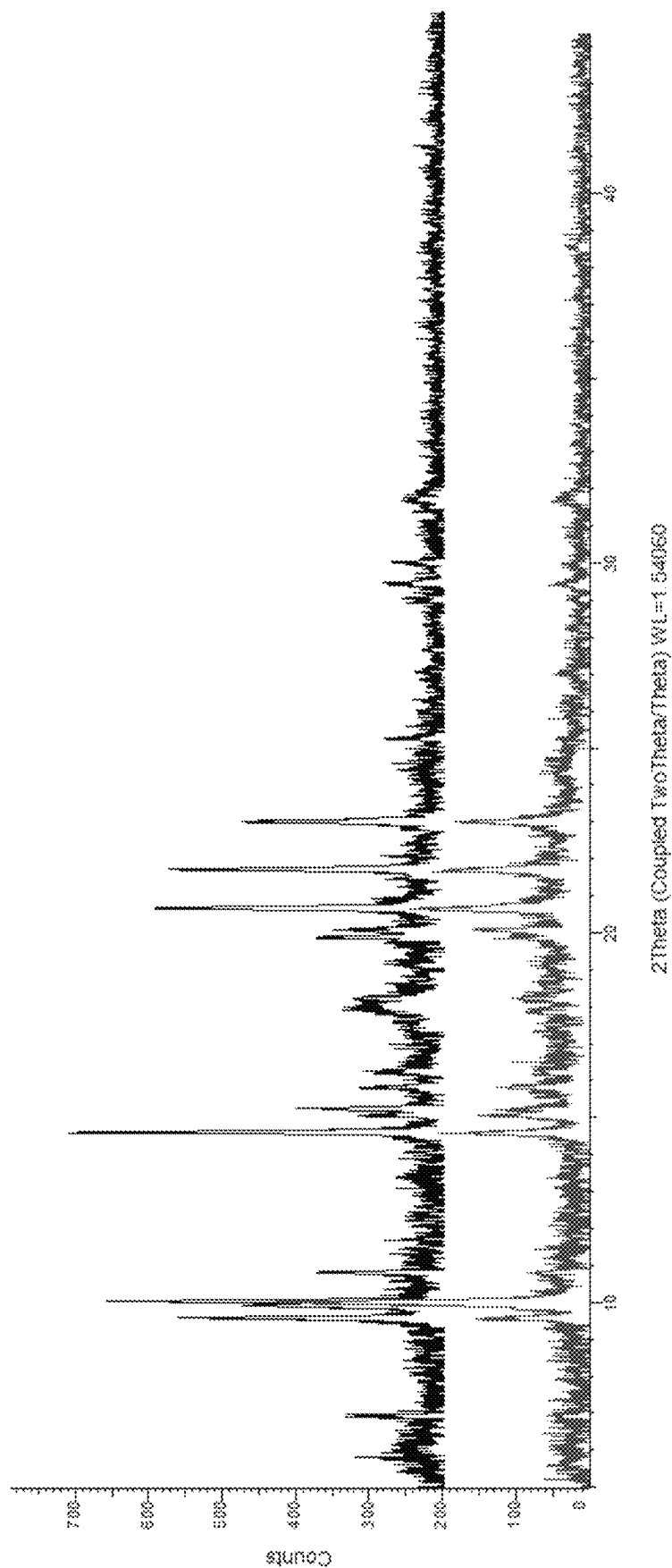


FIG. 4

1

SALTS AND CRYSTALS

CROSS-REFERENCE TO RELATED APPLICATIONS

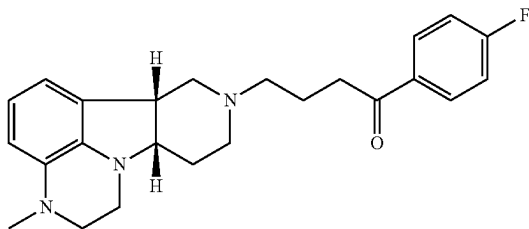
This application is a divisional application of U.S. non-provisional application Ser. No. 16/649,515, filed on Mar. 20, 2020, which is a national stage application under 35 U.S.C. § 371 of International Application No. PCT/US2018/052922, filed on Sep. 26, 2018, which claims priority to and the benefit of U.S. Provisional Application No. 62/563,341, filed on Sep. 26, 2017, the contents of which are hereby incorporated by reference in its entirety.

FIELD

This disclosure relates to certain novel salts and crystal forms of a substituted heterocycle fused gamma-carboline, the manufacture thereof, pharmaceutical compositions thereof, and use thereof, e.g., in the treatment of diseases or abnormal conditions involving or mediated by the 5-HT_{2A} receptor, serotonin transporter (SERT), and/or dopamine D₁/D₂ receptor signaling pathways.

BACKGROUND

1-(4-fluoro-phenyl)-4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-butan-1-one (sometimes referred to as 4-((6bR, 10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone, and also known as Lumateperone or as ITI-007), has the following structure:



ITI-007 is a potent 5-HT_{2A} receptor ligand (K_i=0.5 nM) with strong affinity for dopamine (DA) D₂ receptors (K_i=32 nM) and the serotonin transporter (SERT) (K_i=62 nM) but negligible binding to receptors (e.g., H₁ histaminergic, 5-HT_{2C}, and muscarinic) associated with cognitive and metabolic side effects of antipsychotic drugs. ITI-007 is currently in clinical trials, i.e., for treatment of schizophrenia. While ITI-007 is a promising drug, its production and formulation present challenges. In free base form, ITI-007 is an oily, sticky solid, with poor aqueous solubility. Making salts of the compound has proven to be unusually difficult. A hydrochloride salt form of ITI-007 was disclosed in U.S. Pat. No. 7,183,282, but this particular salt form was hygroscopic and showed poor stability. It was obtained by precipitation from diethyl ether. A toluenesulfonic acid addition salt (tosylate) of ITI-007 was finally identified and described in WO 2009/114181, and its equivalent US 2011/112105, the contents of each of which are hereby incorporated by reference in their entireties.

There is a need for alternative stable and pharmaceutically acceptable salts and polymorphs of ITI-007.

2

SUMMARY

In an effort to find new salts and polymorphs of ITI-007, an extensive salt screen was undertaken. ITI-007 does not readily form salts with other common, pharmaceutically acceptable acids, despite the good solubility of the free base in a variety of organic solvents. Eventually, a toluenesulfonic acid addition salt (tosylate) was prepared, as described in WO 2009/114181 and US 2011/112105, but no other stable salts were found. Finally, a major salt screen was carried out, wherein the free base compound was studied in different solvent systems and under different conditions, and then systematically screened using a selection of over 100 acids under different conditions and with different solvent, co-solvent and anti-solvent systems, to identify possible salt forms. Following extensive screening and experimentation, three new hydrochloride polymorphs were discovered. These hydrochloride salt forms are crystalline and stable.

The disclosure thus provides new hydrochloride salt forms of ITI-007, which are especially advantageous for use in the preparation of galenic formulations, together with methods of making and using the same.

Further areas of applicability of the present invention will become apparent from the detailed description provided hereinafter. It should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are intended for purposes of illustration only and are not intended to limit the scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will become more fully understood from the detailed description and the accompanying drawings, wherein:

FIG. 1 depicts an X-ray powder diffraction pattern for an ITI-007 hydrochloride salt crystal (Polymorph 1).

FIG. 2 depicts an X-ray powder diffraction pattern for an ITI-007 hydrochloride salt crystal (Polymorph 2).

FIG. 3 depicts an X-ray powder diffraction pattern for an ITI-007 hydrochloride salt crystal (Polymorph 3).

FIG. 4 depicts an X-ray powder diffraction patterns obtained from ITI-007 hydrochloride salt competitive slurry experiments in 1-butanol (top: 50° C.; bottom: RT).

DETAILED DESCRIPTION

The following description of the preferred embodiment(s) is merely exemplary in nature and is in no way intended to limit the invention, its application, or uses.

As used throughout, ranges are used as shorthand for describing each and every value that is within the range. Any value within the range can be selected as the terminus of the range. In addition, all references cited herein are hereby incorporated by referenced in their entireties. In the event of a conflict in a definition in the present disclosure and that of a cited reference, the present disclosure controls.

Unless otherwise specified, all percentages and amounts expressed herein and elsewhere in the specification should be understood to refer to percentages by weight. The amounts given are based on the active weight of the material.

In a first embodiment, the invention provides 1-(4-fluorophenyl)-4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-

3

8-yl)-butan-1-one (ITI-007) in stable hydrochloride salt form (Salt 1). The invention therefore provides the following:

- 1.1. Salt 1 in solid form.
- 1.2. Salt 1 or 1.1 in crystalline form, e.g., dry crystalline form.
- 1.3. Salt 1.2 in a homogeneous crystal form, free or substantially free of other forms, e.g., free or substantially free, e.g., less than 10 wt. %, preferably less than about 5 wt. %, more preferably less than about 2 wt. %, still preferably less than about 1 wt. %, still preferably less than about 0.1%, most preferably less than about 0.01 wt. %, of amorphous forms.
- 1.4. Any foregoing form of Salt 1 in crystalline form, when crystallized from a mixture of hydrochloric acid and ITI-007, e.g. in an organic solvent, e.g., comprising toluene, ethyl acetate, cyclopropylmethyl ether (CPME), acetonitrile, 1-butanol, or mixtures thereof; e.g., wherein the hydrochloric acid and ITI-007 are in a molar ratio of about 1:1 or about 1:2.
- 1.5. Any foregoing form of Salt 1 which is a solvate, e.g., an ethyl acetate solvate, or a toluene solvate, or a CPME solvate, or a 1-butanol solvate.
- 1.6. Any foregoing form of Salt 1 which is not a solvate.
- 1.7. Any foregoing form of Salt 1 which is a hydrate.
- 1.8. Any foregoing form of Salt 1 which is not a hydrate.
- 1.9. Any foregoing form of Salt 1 formed by combining free ITI-007 free base and hydrochloric acid in a molar ratio from 1:1 to 1:2, e.g., a 1:1 molar ratio or a 1:2 molar ratio.
- 1.10. Any foregoing form of Salt 1, wherein the salt is formed from a slurry experiment in ethyl acetate to yield Polymorph 1, e.g., using a 1:1 molar ratio of ITI-007 free base to hydrochloride acid in CPME
- 1.11. Salt 1.10, wherein a DSC analysis shows two endothermic events, at 117° C. and 228° C., e.g. wherein a DSC/TGA analysis shows the first endothermic event at $T_{onset}=110^{\circ}\text{C.}$, $T_{peak}=117^{\circ}\text{C.}$ and $\Delta E=-15\text{ J/g.}$ and the second event at $T_{onset}=218^{\circ}\text{C.}$, $T_{peak}=228^{\circ}\text{C.}$ and $\Delta E=-39\text{ J/g.}$
- 1.12. Salt 1.10 or 1.11, in the form of a crystal having an X-ray powder diffraction pattern corresponding to the d-spacing and/or angle (2-theta) values of the following table, for example at least five, or at least six, or at least seven, or at least eight of said values, e.g., taking into account potential variations due to sample purity and instrument variation, for example 2 θ shifts due to variation in X-ray wavelength, e.g., wherein the X-ray powder diffraction pattern is generated using an X-ray diffractometer with a copper anode and a nickel filter, e.g., comprising at least those peaks having a relative intensity of at least 0.4, e.g., at least 0.5, e.g., at least 0.6, e.g., comprising peaks 1, 2, 6, 7, 8, and 9:

XRPD (Cu anode, Ni filter) for Hydrochloride Salt Crystal Polymorph 1			
#	Angle	d Value	Rel. Intensity
1	7.28967	12.11707	0.086731
2	10.2809	8.59734	0.200258
3	10.442	8.465061	0.200747
4	12.21318	7.241127	0.433615
5	13.42102	6.592047	0.224916
6	15.23882	5.809543	0.438444
7	16.28812	5.437572	1
8	16.80838	5.27042	0.215476
9	18.82491	4.710149	0.181319
10	19.56592	4.533406	0.249163
11	21.14059	4.199153	0.652782

4

-continued

XRPD (Cu anode, Ni filter) for Hydrochloride Salt Crystal Polymorph 1			
#	Angle	d Value	Rel. Intensity
12	22.06027	4.026127	0.400921
13	22.07126	4.024148	0.42148
14	22.62619	3.926692	0.559073
15	23.78436	3.738039	0.298317
16	24.30932	3.658491	0.445871
17	25.02641	3.555265	0.440086
18	26.3953	3.373907	0.26406
19	26.44407	3.367795	0.277233
20	26.5014	3.360641	0.252958
21	27.23728	3.271492	0.230046
22	29.35735	3.039883	0.073715
23	33.52987	2.670518	0.091379

- 1.13. Any form of Salt 1.10-1.12, in the form of a crystal having an X-ray powder diffraction pattern corresponding to FIG. 1, e.g., taking into account potential variations due to sample purity and instrument variation, for example 2 θ shifts due to variation in X-ray wavelength, e.g., an X-ray powder diffraction pattern corresponding to FIG. 1 generated using an X-ray diffractometer with a copper anode and a nickel filter.
- 1.14. Any form of Salt 1.10-1.13, in the form of a crystal having an X-ray powder diffraction pattern having at least 5, or at least 6, or at least 7, or at least 8, peaks having angle (2-theta) values selected from the group consisting of about 7.29, 10.28, 10.44, 12.21, 13.42, 15.24, 16.29, 16.81, 18.82, 19.57, 21.14, 22.06, 22.07, 22.63, 23.78, 24.31, 25.03, 26.40, 26.44, 26.50, 27.24, 29.36, and 33.53, taking into account potential variations due to sample purity and instrument variation, wherein the X-ray powder diffraction pattern is generated using an X-ray diffractometer with a copper anode and a nickel filter.
- 1.15. Any form of Salt 1.10-1.14, in the form of a crystal having an X-ray powder diffraction pattern having at least 5, or at least 6, or at least 7, or at least 8, peaks having d-spacing values selected from the group consisting of about 12.12, 8.60, 8.47, 7.24, 6.59, 5.81, 5.44, 5.27, 4.71, 4.53, 4.20, 4.03, 4.02, 3.93, 3.74, 3.66, 3.56, 3.37, 3.37, 3.36, 3.27, 3.04, and 2.67, taking into account potential variations due to sample purity and instrument variation, wherein the X-ray powder diffraction pattern is generated using an X-ray diffractometer with a copper anode and a nickel filter.
- 1.16. Any form of Salt 1.10-1.15, in the form of a crystal having an X-ray powder diffraction pattern having at least 5, or at least 6, or at least 7, or at least 8, peaks having angle (2-theta) values and/or d-spacing values as provided in 1.14 and 1.15.
- 1.17. Any form of Salt 1.10-1.16, in the form of a crystal having an X-ray powder diffraction powder having relative angle (2-theta) values as provided in the table of embodiment 1.12, wherein the values are shifted by up to ± 0.2 degrees, e.g., wherein the values are substantially uniformly shifted by up to ± 0.2 degrees.
- 1.18. Any form of Salt 1 or 1.1-1.9, wherein the salt is formed from a slurry experiment in toluene to yield Polymorph 2, e.g., using a 1:1 molar ratio of ITI-007 free base to hydrochloride acid in CPME.
- 1.19. Salt 1.18, wherein a DSC analysis shows two endothermic events, at 121° C. and 228° C., e.g. wherein a DSC/TGA analysis shows a first endothermic event at $T_{onset}=108^{\circ}\text{C.}$, $T_{peak}=121^{\circ}\text{C.}$ and $\Delta E=-23\text{ J/g.}$ and the second event at $T_{onset}=215^{\circ}\text{C.}$, $T_{peak}=228^{\circ}\text{C.}$ and $\Delta E=-57\text{ J/g.}$

5

1.20. Salt 1.18 or 1.19, in the form of a crystal having an X-ray powder diffraction pattern corresponding to the d-spacing and/or angle (2-theta) values of the following table, for example at least five, or at least six, or at least seven, or at least eight of said values, e.g., taking into account potential variations due to sample purity and instrument variation, for example 2 θ shifts due to variation in X-ray wavelength, e.g., wherein the X-ray powder diffraction pattern is generated using an X-ray diffractometer with a copper anode and a nickel filter, e.g., comprising at least those peaks having a relative intensity of at least 0.4, e.g., at least 0.5, e.g., at least 0.6, e.g., comprising peaks 1, 2, 6, 7, 8, and 9:

XRPD (Cu anode, Ni filter) for Hydrochloride Salt Crystal Polymorph 2			
#	Angle	d Value	Rel. Intensity
1	10.51587	8.405758	0.510923
2	11.72088	7.54414	0.189459
3	12.09875	7.309357	0.796857
4	13.11974	6.74274	0.311634
5	14.24802	6.21123	0.24302
6	16.03021	5.524469	0.999989
7	16.56551	5.347139	0.83136
8	16.6931	5.306556	0.7834
9	18.93689	4.682549	0.251913
10	19.84092	4.471187	0.162883
11	21.09046	4.209022	0.703611
12	20.84009	4.25902	0.269821
13	21.77743	4.077775	0.750891
14	22.29105	3.984963	1
15	22.46965	3.953692	0.838087
16	24.20198	3.674474	0.667304
17	24.61919	3.61314	0.846243
18	26.8244	3.320902	0.36495
19	28.28183	3.152993	0.182531

1.21. Any form of Salt 1.18-1.20, in the form of a crystal having an X-ray powder diffraction pattern corresponding to FIG. 2, e.g., taking into account potential variations due to sample purity and instrument variation, for example 2 θ shifts due to variation in X-ray wavelength, e.g., an X-ray powder diffraction pattern corresponding to FIG. 2 generated using an X-ray diffractometer with a copper anode and a nickel filter.

1.22. Any form of Salt 1.18-1.21, in the form of a crystal having an X-ray powder diffraction pattern having at least 5, or at least 6, or at least 7, or at least 8, peaks having angle (2-theta) values selected from the group consisting of about 10.52, 11.72, 12.10, 13.12, 14.25, 16.03, 16.57, 16.69, 18.94, 19.84, 21.09, 20.84, 21.78, 22.29, 22.47, 23.20, 24.62, 26.82, and 28.28, taking into account potential variations due to sample purity and instrument variation, wherein the X-ray powder diffraction pattern is generated using an X-ray diffractometer with a copper anode and a nickel filter.

1.23. Any form of Salt 1.18-1.22, in the form of a crystal having an X-ray powder diffraction pattern having at least 5, or at least 6, or at least 7, or at least 8, peaks having d-spacing values selected from the group consisting of about 8.41, 7.54, 7.31, 6.74, 6.21, 5.52, 5.35, 5.31, 4.68, 4.47, 4.21, 4.26, 4.08, 3.98, 3.95, 3.67, 3.61, 3.32, and 3.15, taking into account potential variations due to sample purity and instrument variation, wherein the X-ray powder diffraction pattern is generated using an X-ray diffractometer with a copper anode and a nickel filter.

1.24. Any form of Salt 1.18-1.23, in the form of a crystal having an X-ray powder diffraction pattern having at least

6

5, or at least 6, or at least 7, or at least 8, peaks having angle (2-theta) values and/or d-spacing values as provided in 1.22 and 1.23.

1.25. Any form of Salt 1.18-1.24, in the form of a crystal having an X-ray powder diffraction powder having relative angle (2-theta) values as provided in the table of embodiment 1.20, wherein the values are shifted by up to ± 0.2 degrees, e.g., wherein the values are substantially uniformly shifted by up to ± 0.2 degrees.

1.26. Any form of Salt 1 or 1.1-1.9, wherein the salt is formed from a slurry experiment in CPME to yield Polymorph 3, e.g., using a 1:1 molar ratio of ITI-007 free base to hydrochloride acid in CPME.

1.27. Salt 1.26, wherein a DSC analysis shows two endothermic events, at 122° C. and 209° C., e.g. wherein a DSC/TGA analysis shows a first endothermic event at $T_{onset}=97^{\circ}$ C., $T_{peak}=122^{\circ}$ C. and $\Delta E=-38$ J/g, and the second event at $T_{onset}=192^{\circ}$ C., $T_{peak}=209^{\circ}$ C. and $\Delta E=-13$ J/g.

1.28. Salt 1.26 or 1.27, in the form of a crystal having an X-ray powder diffraction pattern corresponding to the d-spacing and/or angle (2-theta) values of the following table, for example at least five, or at least six, or at least seven, or at least eight of said values, e.g., taking into account potential variations due to sample purity and instrument variation, for example 2 θ shifts due to variation in X-ray wavelength, e.g., wherein the X-ray powder diffraction pattern is generated using an X-ray diffractometer with a copper anode and a nickel filter, e.g., comprising at least those peaks having a relative intensity of at least 0.4, e.g., at least 0.5, e.g., at least 0.6, e.g., comprising peaks 1, 2, 6, 7, 8, and 9:

XRPD (Cu anode, Ni filter) for Hydrochloride Salt Crystal Polymorph 3			
#	Angle	d Value	Rel. Intensity
1	6.113585	14.44517	0.204101
2	10.09204	8.757802	0.489434
3	10.35476	8.536179	0.605859
4	11.54239	7.660397	0.585963
5	12.08467	7.317844	1
6	12.93047	6.841012	0.161332
7	13.23207	6.685754	0.254659
8	15.77195	5.614344	0.712069
9	18.19631	4.871422	0.250223
10	19.51964	4.544048	0.326853
11	20.92257	4.242415	0.744994
12	23.86984	3.724845	0.732022
13	24.96878	3.563339	0.326213
14	26.39552	3.373879	0.575626

1.29. Any form of Salt 1.26-1.28, in the form of a crystal having an X-ray powder diffraction pattern corresponding to FIG. 3, e.g., taking into account potential variations due to sample purity and instrument variation, for example 2 θ shifts due to variation in X-ray wavelength, e.g., an X-ray powder diffraction pattern corresponding to FIG. 3 generated using an X-ray diffractometer with a copper anode and a nickel filter.

1.30. Any form of Salt 1.26-1.29, in the form of a crystal having an X-ray powder diffraction pattern having at least 5, or at least 6, or at least 7, or at least 8, peaks having angle (2-theta) values selected from the group consisting of about 6.11, 10.09, 10.35, 11.54, 12.08, 12.93, 13.23, 15.77, 18.20, 19.52, 20.92, 23.87, 24.97, and 26.40, taking into account potential variations due to sample purity and instrument variation, wherein the X-ray pow-

der diffraction pattern is generated using an X-ray diffractometer with a copper anode and a nickel filter.

1.31. Any form of Salt 1.26-1.30, in the form of a crystal having an X-ray powder diffraction pattern having at least 5, or at least 6, or at least 7, or at least 8, peaks having d-spacing values selected from the group consisting of about 14.45, 8.76, 8.54, 7.66, 7.32, 6.84, 6.69, 5.61, 4.87, 4.54, 4.24, 3.73, 3.56, and 3.37, taking into account potential variations due to sample purity and instrument variation, wherein the X-ray powder diffraction pattern is generated using an X-ray diffractometer with a copper anode and a nickel filter.

1.32. Any form of Salt 1.26-1.31, in the form of a crystal having an X-ray powder diffraction pattern having at least 5, or at least 6, or at least 7, or at least 8, peaks having angle (2-theta) values and/or d-spacing values as provided in 1.30 and 1.31.

1.33. Any form of Salt 1.26-1.32, in the form of a crystal having an X-ray powder diffraction powder having relative angle (2-theta) values as provided in the table of embodiment 1.28, wherein the values are shifted by up to ± 0.2 degrees, e.g., wherein the values are substantially uniformly shifted by up to ± 0.2 degrees.

1.34. Any foregoing form of Salt 1 wherein the ITI-007 is deuterated, e.g., wherein the deuterium:protium ratio at one or more specified positions in the molecule is significantly higher, e.g., at least $2\times$, for example at least $10\times$ higher, than the natural isotope ratios or the isotope ratios at other positions in the molecule; for example, any foregoing form of Salt 1 wherein the $-\text{CH}_2-$ adjacent to the methylated nitrogen moiety and/or adjacent to the carbonyl moiety of ITI-007 is deuterated, e.g., is in the form of $-\text{CHD}-$ or $-\text{CD}_2-$ at levels which are significantly higher than the natural deuterium:protium isotope ratio or the deuterium:protium isotope ratio at other positions in the molecule, and/or wherein the methyl group is deuterated, e.g., is CD_3- , e.g., at levels which are significantly higher than the natural deuterium:protium isotope ratio or the deuterium:protium isotope ratio at other positions in the molecule, e.g., as described in WO 2015/154025, the contents of which are incorporated herein by reference.

1.35. Any foregoing form of Salt 1 exhibiting any combination of characteristics as described in 1.1-1.34.

In another embodiment, the invention provides a process (Process 1) for the production of Salt 1, comprising

(a) reacting 1-(4-fluoro-phenyl)-4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-butan-1-one (ITI-007) free base with hydrochloric acid, e.g., together with an organic solvent (e.g., comprising toluene, ethyl acetate, CPME, acetonitrile, 1-butanol, or mixtures thereof), for example, wherein the hydrochloric acid and ITI-007 are in a molar ratio of from 1:1 to 1:2, or about 1:1, or about 1:2; and

(b) recovering the hydrochloride salt thus formed, e.g., recovering a salt according to any of Salt 1, et seq. above.

In an embodiment of Process 1, the hydrochloric acid is provided as a gas (hydrogen chloride), or as an aqueous solution, or as a solution in an organic solvent, e.g., selected from methanol, ethanol, isopropanol, cyclopropylmethyl ether (CPME), diethyl ether, 1,4-dioxane, or any mixture thereof.

In another embodiment of Process 1, the reaction step (a) comprises dissolving or suspending the ITI-007 free base in an organic solvent, e.g., selected from toluene, ethyl acetate, CPME, acetonitrile, 1-butanol, or mixtures thereof, and adding thereto the hydrochloric acid. In another embodiment

of Process 1, the reaction step (a) comprises combining the ITI-007 free base with the hydrochloric acid and adding thereto an organic solvent, e.g., selected from toluene, ethyl acetate, CPME, acetonitrile, 1-butanol, or mixtures thereof.

In some embodiments of Process 1, the process step (a) is carried out as a batch process, and in other embodiments the process step (a) is carried out as a continuous (flow) process.

In another embodiment, the invention provides a method of purifying 1-(4-fluoro-phenyl)-4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8-yl)-butan-1-one (ITI-007) in free or salt form, comprising reacting a crude solution of ITI-007 with hydrochloric acid, and recovering the hydrochloride salt thus formed, e.g., in accordance with Process 1, and optionally converting the hydrochloride salt back to ITI-007 free base or to another salt form.

In another embodiment, the invention provides the use of hydrochloric acid in a method of isolating and/or purifying ITI-007.

As used herein, "hydrochloric acid" refers pure (gaseous) hydrogen chloride, hydrochloric acid in water (aqueous hydrochloric acid), or hydrochloric acid in an organic solvent (i.e., hydrogen chloride in an organic solvent), wherein the organic solvent may be selected from any suitable organic solvent capable of dissolving hydrogen chloride, such as, methanol, ethanol, isopropanol, cyclopropylmethyl ether (CPME), diethyl ether, 1,4-dioxane, or any mixture thereof.

In another embodiment, the invention provides a pharmaceutical composition comprising Salt 1, e.g., any of Salt 1.1-1.35, as active ingredient, in combination or association with a pharmaceutically acceptable diluent or carrier.

In another embodiment, the invention provides pharmaceutical composition comprising Salt 1, e.g., any of Salt 1.1-1.35, as active ingredient, in combination or association with a pharmaceutically acceptable diluent or carrier, wherein the Salt 1 is predominantly, or is entirely or substantially entirely, in dry crystalline form.

In a particular embodiment, the invention provides a pharmaceutical composition comprising Salt 1, e.g., any of Salt 1.1-1.35, as active ingredient, in combination or association with a pharmaceutically acceptable diluent or carrier, in the form of an injectable depot form, to provide extended release of ITI-007.

In another embodiment, the invention provides Salt 1, e.g., any of Salt 1.1-1.35, or a pharmaceutical composition comprising Salt 1, e.g., any of Salt 1.1-1.35, for use in treating a disease or abnormal condition involving or mediated by the 5-HT_{2A} receptor, serotonin transporter (SERT), and/or dopamine D_1/D_2 receptor signaling pathways, e.g., a disorder selected from obesity, anorexia, bulimia, depression, anxiety, psychosis, schizophrenia, migraine, obsessive-compulsive disorder, sexual disorders, depression, schizophrenia, migraine, attention deficit disorder, attention deficit hyperactivity disorder, obsessive-compulsive disorder, sleep disorders, conditions associated with cephalic pain, social phobias, or dementia.

In another embodiment, the invention provides a method for the prophylaxis or treatment of a human suffering from a disease or abnormal condition involving or mediated by the 5-HT_{2A} receptor, serotonin transporter (SERT), and/or dopamine D_1/D_2 receptor signaling pathways, e.g., a disorder selected from obesity, anorexia, bulimia, depression, anxiety, psychosis, schizophrenia, migraine, obsessive-compulsive disorder, sexual disorders, depression, schizophrenia, migraine, attention deficit disorder, attention deficit hyperactivity disorder, obsessive-compulsive disorder, sleep

disorders, conditions associated with cephalic pain, social phobias, or dementia, comprising administering to a patient in need thereof a therapeutically effective amount of any of Salt 1, et seq.

EXAMPLES

The following equipment and methods are used to isolate and characterize the exemplified salt forms:

X-ray powder diffraction (XRPD): The X-ray powder diffraction studies are performed using a Bruker AXS D2 PHASER in Bragg-Brentano configuration, equipment #1549/#2353. The equipment uses a Cu anode at 30 kV, 10 mA; sample stage standard rotating; monochromatization by a β -filter (0.5% Ni). Slits: fixed divergence slits 1.0 mm ($\approx 0.61^\circ$), primary axial Soller slit 2.5° , secondary axial Soller slit 2.5° . Detector: Linear detector LYNXEYE with receiving slit 5° detector opening. The standard sample holder (0.1 mm cavity in (510) silicon wafer) has a minimal contribution to the background signal. Measurement conditions: scan range $5\text{--}45^\circ 2\theta$, sample rotation 5 rpm, 0.5 s/step, $0.010^\circ/\text{step}$, 3.0 mm detector slit; and all measuring conditions are logged in the instrument control file. As system suitability, corundum sample A26-B26-S (NIST standard) is measured daily. The software used for data collection is Diffrac.Commander v2.0.26. Data analysis is done using Diffrac.Eva v1.4. No background correction or smoothing is applied to the patterns.

Simultaneous thermogravimetry (TGA) and differential scanning calorimetry (DSC) or TGA/DSC analysis: The TGA/DSC studies are performed using a Mettler Toledo TGA/DSC1 Stare System, equipment #1547, auto-sampler equipped, using pin-holed Al-crucibles of 40 μl . Measurement conditions: 5 min 30.0°C ., $30.0\text{--}350.0^\circ\text{C}$. with $10^\circ\text{C}/\text{min}$., N₂ flow of 40 ml/min. The software used for instrument control and data analysis is STARe v12.10.

Differential scanning calorimetry (DSC): The DSC studies are performed using a Mettler Toledo DSC1 STARe System, equipment #1564. The samples are made using Al crucibles (40 μl ; pierced). Typically 1-8 mg of sample is loaded onto a pre-weighed Al crucible and is kept at 30°C . for 5 minutes, after which it is heated at $10^\circ\text{C}/\text{min}$ from 30°C . to 350°C . and kept at 350°C . for 1 minute. A nitrogen purge of 40 ml/min is maintained over the sample. As system suitability check Indium and Zinc are used as references. The software used for data collection and evaluation is STARe Software v12.10 build 5937. No corrections are applied to the thermogram.

Polarized light microscopy (PLM): The microscopy studies are performed using an AxioVert 35M, equipped with an AxioCamERc 5s, equipment #1612. The microscope is equipped with four lenses: Zeiss A-Plan $5\times/0.12$, Zeiss A-Plan $10\times/0.25$, LD A-Plan $20\times/0.30$ and Achros TIGMAT $32\times/0.40$. Data collection and evaluation is performed using Carl Zeiss Zen AxioVision Blue Edition Lite 2011 v1.0.0.0 software. A small amount of sample is loaded on an object glass and carefully spread until a thin layer is obtained.

Dynamic Vapour Sorption (DVS): The Dynamic Vapour Sorption studies are performed using a Surface Measurement Systems Ltd. DVS-1 No Video, equipment #2126. The sample is loaded into a balance pan, typically 20-30 mg, and equilibrated at 0% RH. After the material was dried, the RH is increased with 10% per step for 1 hour per increment, ending at 95% RH. After completion of the sorption cycle, the sample was dried using the same method. The software

used for data collection is DVS-1 No Video. Data analysis is performed using DVS Standard Analysis Suite v6.3.0 (Standard).

Particle size distribution (PSD): The particle size distribution studies are performed using a Malvern Instruments Mastersizer, equipment #1712. The Mastersizer uses a 300 RF lens range of $0.05\text{--}900\text{ }\mu\text{m}$. Polydisperse is used as analysis model. Measurement conditions: before each sample measurement a background measurement is performed, the background scan time is 12 seconds (12000 snaps). Each sample is dispersed in Multipar G, refractive index of 1.42. The obscuration range on sample dispersion is between 10%-30%. Each sample is measured 6 times at $t=0$ and $t=30$ minutes and the measurement scan time is 10 seconds (10000 snaps). The targeted stirring speed of the sample dispersion unit is 2000 ± 10 rpm. Data collection and evaluation is performed using Mastersizer S Version 2.19 software.

Capillary Melting Point: The capillary melting point is determined on a Büchi Melting Point B-545, equipment #000011, conform USP guidelines.

X-ray fluorescence (XRF): The X-ray fluorescence studies are performed using a Bruker AXS S2 RANGER, equipment #2006. Using an end-window X-ray tube with Palladium anode and an ultra-thin Beryllium window ($75\text{ }\mu\text{m}$) for superior light element analysis. As detector the Xflash V5 detector with Cr, Ti, Al, Ta collimator (energy resolution $<129\text{ eV FWHM}$ at $100\text{ }000\text{ cps MnK}\alpha$) is used. The S2 Ranger is equipped with an autosampler with integrated 28 position X-Y automatic sample changer with exchangeable tray, which allows maximum sample diameter of 40 mm. Samples are mounted in steel rings of 51.5 mm diameter for automatic operation. Measurement conditions: disposable liquid cups (35 mm inner diameter, 40 mm outer diameter) with polypropylene foil $5\text{ }\mu\text{m}$. As system suitability check a copper disk is measured daily and a glass disk, containing several elements, is measured weekly. The software used for data collection is S2 Ranger Control Software V4.1.0. Data analysis is performed using SPECTRA EDX V2.4.3 evaluation software. No background correction or smoothing is applied to the patterns.

Fourier transform infrared spectroscopy (FT-IR): The FT-IR studies are performed using a Thermo Scientific Nicolet iS50, equipment #2357. An attenuated total reflectance (ATR) technique was used with a beam splitter of KBr. Experiment setup of the collected sample is used number of scans 16 with a resolution of 4 from 400 cm^{-1} to 4000 cm^{-1} . The software OMNIC version 9.2 is used for data collection and evaluation.

Thermogravimetric analysis (TGA) with infrared spectroscopy (TGA-IR): In TGA-IR, the off-gassing materials are directed through a transfer line to a gas cell, where the infrared light interacts with the gases. The temperature ramp and first derivative weight loss information from the TGA is shown as a Gram-Schmidt (GS) profile; the GS profile essentially shows the total change in the IR signal relative to the initial state. In most cases, the GS and the derivative weight loss will be similar in shape, although the intensity of the two can differ. For this experiment are two devices coupled to each other. The TGA studies are performed using a Mettler Toledo TGA/DSC1 STARe System with a 34-position auto sampler, equipment #1547. The samples are made using Al crucibles (100 μl ; pierced). Typically 20-50 mg of sample is loaded into a pre-weighed Al crucible and is kept at 30°C . for 5 minutes after which it is heated at $10^\circ\text{C}/\text{min}$ from 30°C . to 350°C . A nitrogen purge of 40 ml/min is maintained over the sample. The TGA-IR module of the

11

Nicolet iS50 is coupled to the TGA/DSC1. The IR studies were performed using a Thermo Scientific Nicolet iS50, equipment #2357. Experiment setup of the collected series, the profile Gram-Schmidt is used number of scans 10 with a resolution of 4. The software OMNIC version 9.2 is used for data collection and evaluation.

High performance liquid chromatography (HPLC): The high performance liquid chromatography analyses are performed on LC-31, equipped with an Agilent 1100 series G1322A degasser equipment #1894, an Agilent 1100 series G1311A quaternary pump equipment #1895, an Agilent 1100 series G1313A ALS equipment #1896, an Agilent 1100 series G1318A column equipment #1897 and an Agilent 1100 series G1314A VWD equipment #1898/LC-34, equipped with an Agilent 1200 series G1379B degasser equipment #2254, an Agilent 1100 series G1311A quaternary pump equipment #2255, Agilent 1100 series G1367A WPALS equipment #1656, an Agilent 1100 series G1316A column equipment #2257 and an Agilent 1100 series G1315B DAD equipment #2258. Data is collected and evaluated using Agilent ChemStation for LC systems Rev. B.04.02[96]. Solutions are prepared as follows: Mobile phase A: Add 800 ml of MilliQ water to a 1 L volumetric flask. Add 1 ml of TFA and homogenize. Fill up to the mark with MilliQ; Mobile phase B: Add 800 ml of Acetonitrile to a 1 L volumetric flask. Add 1 ml of TFA and homogenize. Fill up to the mark with Acetonitrile; Diluent: 50/50 MeOH/ACN.

Example 1: Salt Crystal Screen

Solubility of ITI-007 free base in various solvents is evaluated, and based on the results of the solubility range, suitable solvents are selected for the salt screen. The salt screen is divided into seven separate screens, using 90 different counterions, six different solvents, and including four different crystallization methods (slurry crystallization, cooling crystallization, evaporation and precipitation). The counterions are selected based upon availability and potential suitability to form pharmaceutically acceptable acid addition salts. They include the class I, II and III acids identified in Stahl P. H., Wermuch C. G. (editors), Handbook of Pharmaceutical Salts, IUPAC (2008). A total of 624 counterion/solvent/ratio variations are tested, and each of these is studied using each of the four crystallization methods. Of the 624 combinations tested, only nine combinations produce candidate crystalline salts: six hydrochloric acid conditions, and one condition each for oxalic acid, cyclamic acid and 4-aminosalicylic acid.

For the hydrochloric acid screens, both hydrochloric acid in CPME and hydrochloric acid in isopropanol are used. The molar ratio of free base to acid is 1:1 or 1:2. The reaction solvents screened include acetonitrile, methanol, isopropanol, ethyl acetate, toluene and CPME.

Candidate crystalline salts are observed for the following HCl conditions: (1) HCl/CPME in CPME solvent at a 1:1 molar ratio (slurry crystallization); (2) HCl/CPME in CPME solvent at a 1:2 molar ratio (slurry crystallization); (3) HCl/CPME in toluene solvent at a 1:2 molar ratio (slurry crystallization); (4) HCl/CPME in ethyl acetate solvent at a 1:2 molar ratio (slurry crystallization); (5) HCl/CPME in toluene solvent at a 1:1 molar ratio (cooling crystallization); and (6) HCl/isopropanol in ethyl acetate solvent at a 1:2 molar ratio (precipitation crystallization). The candidate crystalline salts are each obtained as powders, varying in color from yellow to grey. FT-IR analysis confirms these candidates to be salts, each showing approximately 70%

12

similarity with the free base and showing HCl present. XRPD analysis confirms that each of these candidates are crystalline. LC-MS analysis confirms that there is no decomposition of the free base structure.

To confirm the formation of new hydrochloride salt crystals, scale-up experiments are conducted as follows.

Example 2: Hydrochloride Crystal Salt Polymorph

1

Approximately one gram of ITI-007 free base is added to ethyl acetate solvent at a concentration of 100 mg/mL. Hydrochloric acid in CPME solution is added to provide a 1:1 molar ratio of ITI-007 free base to HCl. The mixture is slurried at 50° C. overnight. The mixture is allowed to cool down to room temperature and is filtered and dried to give a yellow/brown solid. XRPD analysis shows the hydrochloride to be a crystalline solid. The XRPD pattern is shown in FIG. 1; the peaks are identified in tabular form in table 1:

TABLE 1

XRPD peak list hydrochloride salt polymorph 1			
#	Angle	d Value	Rel. Intensity
1	7.28967	12.11707	0.086731
2	10.2809	8.59734	0.200258
3	10.442	8.465061	0.200747
4	12.21318	7.241127	0.433615
5	13.42102	6.592047	0.224916
6	15.23882	5.809543	0.438444
7	16.28812	5.437572	1
8	16.80838	5.27042	0.215476
9	18.82491	4.710149	0.181319
10	19.56592	4.533406	0.249163
11	21.14059	4.199153	0.652782
12	22.06027	4.026127	0.400921
13	22.07126	4.024148	0.42148
14	22.62619	3.926692	0.559073
15	23.78436	3.738039	0.298317
16	24.30932	3.658491	0.445871
17	25.02641	3.555265	0.440086
18	26.3953	3.373907	0.26406
19	26.44407	3.367795	0.277233
20	26.5014	3.360641	0.252958
21	27.23728	3.271492	0.230046
22	29.35735	3.039883	0.073715
23	33.52987	2.670518	0.091379

The hydrochloride salt is also analyzed by DSC/TGA, DVS, HPLC, ¹H-NMR and FT-IR. DSC/TGA analysis shows two endothermic events, the first endothermic event at T_{onset}=110° C., T_{peak}=117° C. and ΔE=-15 J/g, and the second event at T_{onset}=218° C., T_{peak}=228° C. and ΔE=-39 J/g. Both endothermic events are linked to a mass loss, of 4% and 13%, respectively. TGR-IR analysis shows these mass losses to be primarily ethyl acetate and water, indicating that an ethyl acetate solvate has formed. Analysis of the HPLC data shows a purity of 94% purity for this solvate. FT-IR analysis confirms the chemical structure. Dynamic vapor sorption (DVS) analysis shows some stepwise sorption; the total mass uptake at 95 RH % is 5%. This salt is thus moderately hygroscopic.

13
TABLE 2

Analytical results scale-up synthesis of the hydrochloride salt Polymorph 1					
Solvent	Appearance	DVS Hygro- scopicity (%)	DSC (T _{peak} ° C.)	DVS: Mass loss (%)	HPLC purity (area %)
Ethyl acetate	Yellow/brown solid	5	117 228	4 13	94

Example 3: Hydrochloride Crystal Salt Polymorph 2

Approximately one gram of ITI-007 free base is added to toluene solvent at a concentration of 100 mg/mL. Hydrochloric acid in CPME solution is added to provide a 1:1 molar ratio of ITI-007 free base to HCl. The mixture is slurried at 50° C. overnight. The mixture is allowed to cool down to room temperature and is filtered and dried to give a yellow/brown solid. XRPD analysis shows the hydrochloride to be a crystalline solid. The XRPD pattern is shown in FIG. 2; the peaks are identified in tabular form in table 3:

TABLE 3

XRPD peak list hydrochloride salt polymorph 2			
#	Angle	d Value	Rel. Intensity
1	10.51587	8.405758	0.510923
2	11.72088	7.54414	0.189459
3	12.09875	7.309357	0.796857
4	13.11974	6.74274	0.311634
5	14.24802	6.21123	0.24302
6	16.03021	5.524469	0.999989
7	16.56551	5.347139	0.83136
8	16.6931	5.306556	0.7834
9	18.93689	4.682549	0.251913
10	19.84092	4.471187	0.162883
11	21.09046	4.209022	0.703611
12	20.84009	4.25902	0.269821
13	21.77743	4.077775	0.750891
14	22.29105	3.984963	1
15	22.46965	3.953692	0.838087
16	24.20198	3.674474	0.667304
17	24.61919	3.61314	0.846243
18	26.8244	3.320902	0.36495
19	28.28183	3.152993	0.182531

The hydrochloride salt is analyzed by DVS, DSC/TGA and HPLC, and the results are summarized in table 4. DSC/TGA analysis shows two endothermic events, the first at T_{onset}=108° C., T_{peak}=121° C. and ΔE=-23 J/g, and the second at T_{onset}=215° C., T_{peak}=228° C. and ΔE=-57 J/g. Both endothermic events are linked to a mass loss, of 4% and 13%, respectively. TGR-IR analysis shows these mass losses to be primarily toluene and water, indicating that a toluene solvate has formed. Analysis of the HPLC data shows a purity of 90% purity for this solvate. FT-IR analysis confirms the chemical structure. Dynamic vapor sorption (DVS) analysis shows some stepwise sorption; the total mass uptake at 95 RH % is 12%. This salt is thus moderately hygroscopic.

14
TABLE 4

Analytical results scale-up synthesis of the hydrochloride salt polymorph 2					
Solvent	Appearance	DVS Hygroscopicity (%)	DSC (T _{peak} ° C.)	Mass loss (%)	HPLC purity (area %)
Toluene	Yellow/brown solid	12	121 228	4 13	90

Example 4: Hydrochloride Crystal Salt Polymorph 3

Approximately one gram of ITI-007 free base is added to CPME solvent at a concentration of 100 mg/mL. Hydrochloric acid in CPME solution is added to provide a 1:1 molar ratio of ITI-007 free base to HCl. The mixture is slurried at 50° C. overnight. The mixture is allowed to cool down to room temperature and is filtered and dried to give an off-white powdery solid. XRPD analysis shows the hydrochloride to be a crystalline solid. The XRPD pattern is shown in FIG. 3; the peaks are identified in tabular form in table 5:

TABLE 5

XRPD peak list of the cyclamate salt			
#	Angle	d Value	Rel. Intensity
1	6.113585	14.44517	0.204101
2	10.09204	8.757802	0.489434
3	10.35476	8.536179	0.605859
4	11.54239	7.660397	0.585963
5	12.08467	7.317844	1
6	12.93047	6.841012	0.161332
7	13.23207	6.685754	0.254659
8	15.77195	5.614344	0.712069
9	18.19631	4.871422	0.250223
10	19.51964	4.544048	0.326853
11	20.92257	4.242415	0.744994
12	23.86984	3.724845	0.732022
13	24.96878	3.563339	0.326213
14	26.39552	3.373879	0.575626

The hydrochloride salt is analyzed by DVS, DSC/TGA and HPLC. The results are summarized in table 6. DSC/TGA analysis shows two endothermic events, the first at T_{onset}=97° C., T_{peak}=122° C. and ΔE=-38 J/g, and the second event at T_{onset}=192° C., T_{peak}=209° C. and ΔE=-13 J/g. Both endothermic events are linked to a mass loss, of 7% and 13%, respectively. TGR-IR analysis shows these mass losses to be primarily CPME and water, indicating that a CPME solvate has formed. Analysis of the HPLC data shows a purity of 80% purity for this solvate. FT-IR analysis confirms the chemical structure. Dynamic vapor sorption (DVS) analysis shows some stepwise sorption; the total mass uptake at 95 RH % is 10%. This salt is thus moderately hygroscopic.

TABLE 6

Analytical results scale-up synthesis of the hydrochloride salt Polymorph 3.					
Solvent	Appearance	DVS Hygro- scopicity (%)	DSC (T _{peak} ° C.)	Mass loss (%)	HPLC purity (area %)
CPME	Off-White powder	10	122 209	7 13	80

Example 5: Competitive Stability Test of
Hydrochloride Crystal Salt Polymorphs

To determine the most stable of the three hydrochloride crystal salt polymorphs, a competitive slurry in 1-butanol is performed. Equal masses of the three polymorphs obtained according to Examples 2-4 above are mixed and slurried at room temperature and at 50° C. for 24 hours. XRPD analysis is then performed. Both slurry conditions result in a new crystalline pattern, suggesting the formation of a new solvate form. The XRPD spectra are shown in FIG. 4 (top: 50° C.; bottom: RT). DSC/TGA analysis shows two endothermic events, the first at $T_{onset}=142^{\circ}\text{C.}$, $T_{peak}=150^{\circ}\text{C.}$ and $\Delta E=-14\text{ J/g.}$ and the second event at $T_{onset}=203^{\circ}\text{C.}$, $T_{peak}=216^{\circ}\text{C.}$ and $\Delta E=-17\text{ J/g.}$ The TGA profiles shows three mass losses. The first two of 6% and 8% correspond, respectively, to the two endothermic events. TGR-IR analysis shows the first two of these mass losses to be primarily 1-butanol and water, indicating that a 1-butanol solvate has formed. The third mass loss occurs above 240° C. and likely corresponds to decomposition.

The invention claimed is:

1. A method for the treatment of a human suffering from a disease or abnormal condition involving or mediated by the 5-HT_{2A} receptor, serotonin transporter (SERT), and/or dopamine D₁/D₂ receptor signaling pathways comprising administering to said human an effective amount of hydrochloride salt of 1-(4-fluoro-phenyl)-4-((6bR, 10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido [3',4': 4,5]pyrrolo [1,2,3-de]quinoxalin-8-yl)-butan-1-one, wherein the salt is in crystalline form and wherein the crystalline form is selected from the group consisting of:

- (a) polymorph 1 having an X-ray diffraction pattern having at least five angle (2-theta) values selected from the group consisting of 7.29, 10.28, 10.44, 12.21, 13.42, 15.24, 16.29, 16.81, 18.82, 19.57, 21.14, 22.06, 22.07, 22.63, 23.78, 24.31, 25.03, 26.40, 26.44, 26.50, 27.24, 29.36, and 33.53, and/or at least five d-spacing values selected from the group consisting of 12.12, 8.60, 8.47, 7.24, 6.59, 5.81, 5.44, 5.27, 4.71, 4.53, 4.20, 4.03, 4.02, 3.93, 3.74, 3.66, 3.56, 3.37, 3.37, 3.36, 3.27, 3.04, and 2.67;
- (b) polymorph 2 having an X-ray diffraction pattern having at least five angle (2-theta) values selected from the group consisting of 10.52, 11.72, 12.10, 13.12, 14.25, 16.03, 16.57, 16.69, 18.94, 19.84, 21.09, 20.84, 21.78, 22.29, 22.47, 23.20, 24.62, 26.82, and 28.28, and/or d-spacing values selected from the group consisting of 8.41, 7.54, 7.31, 6.74, 6.21, 5.52, 5.35, 5.31, 4.68, 4.47, 4.21, 4.26, 4.08, 3.98, 3.95, 3.67, 3.61, 3.32, and 3.15; and
- (c) polymorph 3 having an X-ray diffraction pattern having at least five angle (2-theta) values selected from the group consisting of 6.11, 10.09, 10.35, 11.54, 12.08,

12.93, 13.23, 15.77, 18.20, 19.52, 20.92, 23.87, 24.97, and 26.40, and/or d-spacing values selected from the group consisting of 14.45, 8.76, 8.54, 7.66, 7.32, 6.84, 6.69, 5.61, 4.87, 4.54, 4.24, 3.73, 3.56, and 3.37;

and wherein the disease or condition is selected from depression, anxiety, psychosis, schizophrenia, social phobias, and dementia.

2. The method according to claim 1, wherein the patient is administered a pharmaceutical composition comprising the hydrochloride salt of 1-(4-fluoro-phenyl)-4-((6bR, 10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H,7H-pyrido [3',4': 4,5]pyrrolo [1,2,3-de]quinoxalin-8-yl)-butan-1-one, in combination or association with a pharmaceutically acceptable diluent or carrier.

3. The method according to claim 1, wherein the disease or condition is selected from depression, anxiety, psychosis, and schizophrenia.

4. The method according to claim 3, wherein the disease or condition is selected from depression, anxiety, and schizophrenia.

5. The method according to claim 4, wherein the disease or condition is schizophrenia.

6. The method according to claim 1, wherein the crystalline form of the hydrochloride salt is the salt characterized as polymorph 1 having an X-ray diffraction pattern having at least five angle (2-theta) values selected from the group consisting of 7.29, 10.28, 10.44, 12.21, 13.42, 15.24, 16.29, 16.81, 18.82, 19.57, 21.14, 22.06, 22.07, 22.63, 23.78, 24.31, 25.03, 26.40, 26.44, 26.50, 27.24, 29.36, and 33.53, and/or at least five d-spacing values selected from the group consisting of 12.12, 8.60, 8.47, 7.24, 6.59, 5.81, 5.44, 5.27, 4.71, 4.53, 4.20, 4.03, 4.02, 3.93, 3.74, 3.66, 3.56, 3.37, 3.37, 3.36, 3.27, 3.04, and 2.67.

7. The method according to claim 1, wherein the crystalline form of the hydrochloride salt is the salt characterized as polymorph 2 having an X-ray diffraction pattern having at least five angle (2-theta) values selected from the group consisting of 10.52, 11.72, 12.10, 13.12, 14.25, 16.03, 16.57, 16.69, 18.94, 19.84, 21.09, 20.84, 21.78, 22.29, 22.47, 23.20, 24.62, 26.82, and 28.28, and/or d-spacing values selected from the group consisting of 8.41, 7.54, 7.31, 6.74, 6.21, 5.52, 5.35, 5.31, 4.68, 4.47, 4.21, 4.26, 4.08, 3.98, 3.95, 3.67, 3.61, 3.32, and 3.15.

8. The method according to claim 1, wherein the crystalline form of the hydrochloride salt is the salt characterized as polymorph 3 having an X-ray diffraction pattern having at least five angle (2-theta) values selected from the group consisting of 6.11, 10.09, 10.35, 11.54, 12.08, 12.93, 13.23, 15.77, 18.20, 19.52, 20.92, 23.87, 24.97, and 26.40, and/or d-spacing values selected from the group consisting of 14.45, 8.76, 8.54, 7.66, 7.32, 6.84, 6.69, 5.61, 4.87, 4.54, 4.24, 3.73, 3.56, and 3.37.

* * * * *