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NEW SYNTHESIS OF LUMATEPERONE TOSYLATE

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Abstract – A new and practical synthesis of lumateperone tosylate is developed. The intermediate, ethyl (4a*S*,9b*R*)-6-bromo-1,3,4,4a,5,9b-hexahydro-2*H*-pyrido-[4,3-*b*]indole-2-carboxylate (**12**), is prepared on kilograms scale in 31% overall yield and >99% ee. (6b*R*,10a*S*)-3-Methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline hydrochloride (**16-HCl**) is obtained through reductamination reaction, palladium catalyzed cyclization and ester hydrolysis in 60% yield over 3 steps and >98% purity. Lumateperone tosylate is produced on 20 g scale in 65% yield over 2 steps and >99% purity (HPLC). Purification methods of the intermediates and the final product involved in the route are developed.

Lumateperone tosylate (**1**, Scheme 1, Caplyta^{TM}), developed by Intra-Cellular Therapies, Inc., was approved by the U.S. Food and Drug Administration (FDA) in Dec. 2019, for the treatment of schizophrenia in adults.[1] The efficacy of lumateperone could be mediated through a combination of antagonist activity at central serotonin 5-HT_{2A} receptors and postsynaptic antagonist activity at central dopamine D_2 receptors.[2]

With regard to the synthesis of lumateperone (**2**), a couple of routes had been reported, as shown in Scheme 1. As early as 2000, lumateperone (**2**) was prepared as the racemic form.[3] 3,4-Dihydroquinoxalin-2(1*H*)-one (**3**) was used as the starting material, the nitrosation product **4** was condensed with ethyl 4-oxopiperidine-1-carboxylate (**5**) to give the 1*H*-pyrrolo[1,2,3-*de*]quinoxalin-2(3*H*)-one **6** in 35% yield over 2 steps, which was hydrogenated by $NaBH_3CN$ in TFA to give the 5,6-dihydro-1*H*-pyrrolo[1,2,3-*de*]quinoxalin-2(3*H*)-one **7** in 89% yield.

Scheme 1. Reagents and conditions: (a) AcOH, $NaNO_2$, 0−5 °C, 71%; (b) Zn, AcOH, HCl, 10−100 °C, 50%; (c) $NaBH_3CN$, TFA, rt, 89%; (d) HCl, EtOH, reflux, 6 h, 76%; (e) TFA, Et_3SiH, rt, 19 h, 83%; (f) $ClCO_2Et$, TEA, THF, rt, 1 h, 84%; (g) $Pd_2(dba)_3$, *t*-BuONa, BINAP, toluene, 105 °C, 93%; (h) ethyl bromoacetate, Na_2CO_3, KI, acetone, reflux, 16 h, 73%; (i) MeI, K_2CO_3, acetone, 109 °C (pressure bottle), 6 h, 99%; (j) BH_3-THF, THF, reflux, 3 h, 99%; (k) KOH, *n*-BuOH, 120 °C, 3 h, 99%; (l) TEA, dioxane, toluene, reflux, 23% (chiral HPLC separation); (m) *p*-toluenesulfonic acid, *i*-PrOAc, 53%; (n) *S*-(+)-mandelic acid, 33%; (o) $ClCO_2Et$, TEA, THF, rt, 1 h, 95%; (p) *N*-methylchloroacetamide, DIPEA, dioxane, reflux, 18 h; (q) K_2CO_3, CuI, *N*,*N'*-dimethylethylenediamine, dioxane, reflux, 14 h, 70%; (r) BH_3-THF, THF, reflux, 3 h, 89%; (s) HCl, H_2O, reflux, 15 h, 88%; (t) KI, DIPEA, dioxane, 95 °C, 17 h, 93%.

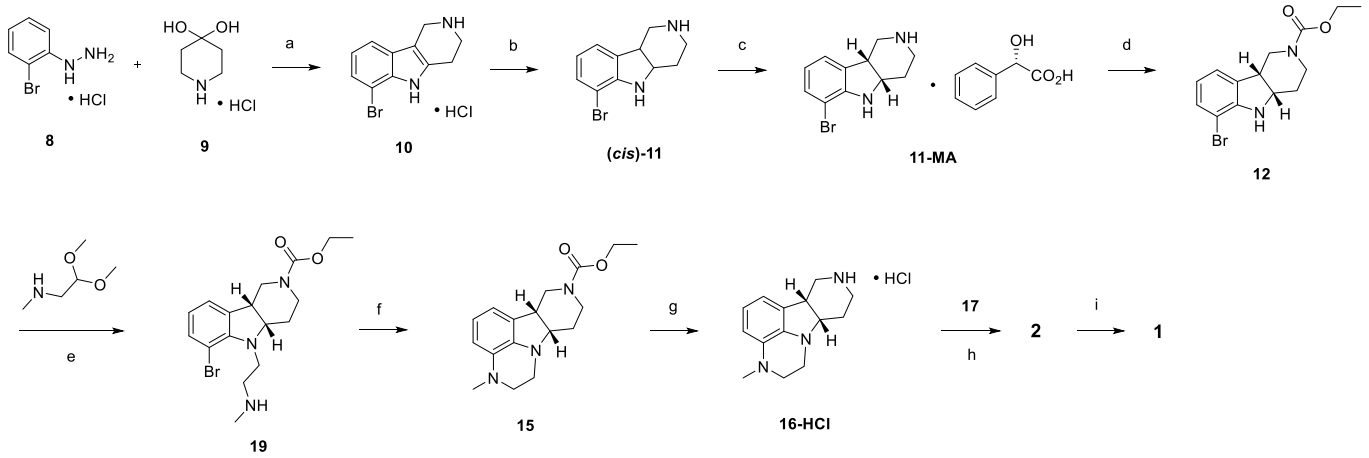
Compound **7** can also be prepared from an improved method.[4] 2-Bromophenylhydrazine hydrochloride (**8**) and 4,4-piperidinediol hydrochloride (**9**) were condensed, then hydrogenated by Et_3SiH in TFA to give 6-bromo-hexahydro-1*H*-pyrido[4,3-*b*]indole (***cis*)-11** in 63% overall yield, which was subsequently substituted by diphenylmethanimine and ethyl bromoacetate successively to give **7** in 68% yield over 2 steps. The key intermediate 3-methyl-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline (***cis*)-16** was obtained from **7** through methylation, carbonyl reduction, ester hydrolysis successively in 97% overall yield. Lumateperone (**2**) was obtained by coupling (***cis*)-16** with 3-chloro-4'-fluorobutyrophenone (**17**), and separated by chiral pre-HPLC in 23% yield on a 480 mg scale. The final **1** was obtained by salted with *p*-toluenesulfonic acid in 53% yield, which was unsuited for scale-up preparation.

The optically pure intermediate (4a*S*,9b*R*)-6-bromo-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (**11**) can be obtained from (***cis*)-11** though resolution by *S*-(+)-mandelic acid in 33% yield and >99% ee.[5] Compound **14** was then prepared from **12** and *N*-methylchloroacetamide through a "One-Pot" process in 70% yield. Lumateperone (**2**) was obtained through the several similar reaction processes in medium to high yield, in a 300 g scale.

Based on our own experimental results, we found that compound **14** was very unstable, which decomposed when dried in drying box at 40 °C or in solvents (CH_2Cl_2, or EtOAc) at room temperature over 2 h, for some reasons we were not sure. Compound **15** was prepared from **14** with BH_3-THF (3.8 eq mol), which would lead to security risks especially during the work-up operation. Moreover, compound **16** was difficult to purify since it was a viscous oil at room temperature, so the hydrochloride form of **16** should be a better choice for the scale-up process.

In order to develop an efficient and practical method for preparing of lumateperone tosylate (**1**), a new synthetic route was developed successfully, as shown in Scheme 2. 6-Bromo-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole hydrochloride (**10**) was prepared from compounds **8** and **9** based on the reported method in 91% yield.[4] The next hydrogenation was carried out in methanesulfonic acid and triethylsilane to give compound (***cis*)-11** in 89% yield on a kilogram scale, which was resoluted with *S*-(+)-mandelic acid in methanol to give (4a*S*,9b*R*)-6-bromo-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (*S*)-mandelate (**11-MA**) in 41% isolated yield and >99% ee. Compound **11-MA** was reacted with ethyl chloroformate in THF at room temperature to give the ethyl 2*H*-pyrido[4,3-*b*]indole-2-carboxylate **12** in 94% isolated yield and >99% purity, which was reacted with (2,2-dimethoxyethyl)methylamine in TFA and triethylsilane through a reductamination reaction to give the ethyl (4a*S*,9b*R*)-6-bromo-5-(2-(methylamino)ethyl)-1,3,4,4a,5,9b-hexahydro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (**19**) in good yield.[6,7] Ethyl 1*H*-pyrido-[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline-8(7*H*)-carboxylate **15** was obtained in 71% yield and 98% purity from **19** through a coupling reaction catalyzed by $Pd(OAc)_2$ and

(2-dimethylamino-1,1'-biphenyl-2-yl)-dicyclohexylphosphine (DavePhos).[8,9] Heated **15** with concentrated hydrochloric acid for 18 h gave the hydrochloride **16-HCl** after purifying by crystallization from *i*-PrOH in 85% yield and 98% purity.[10] Treatment of **16-HCl** directly with 3-chloro-4'-fluorobutyrophenone (**17**) under basic condition afforded lumateperone (**2**) in 91% yield, which was salted with *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) in EtOAc to give **1** in 71% isolated yield and >99% purity.



Scheme 2. Reagents and conditions: (a) HCl, H_2O, EtOH, 65−75 °C, 8 h, 91%; (b) $MeSO_3H$, Et_3SiH, 30−40 °C, 4 h, 89%; (c) *S*-(+)-mandelic acid, MeOH, 41%; (d) $ClCO_2Et$, Na_2CO_3, THF, 20−30 °C, 2 h, 94%; (e) TFA, Et_3SiH, CH_2Cl_2, 30−35 °C, 20 h; (f) Cs_2CO_3, $Pd(OAc)_2$, DavePhos, toluene, 90−100 °C, 16 h, 71% (steps e and f); (g) HCl, H_2O, reflux, 18 h, 85%; (h) KI, DIPEA, dioxane, 100 °C, 12 h, 91%; (i) *p*-TsOH·H_2O, EtOAc, 71%.

In conclusion, an improved and practical synthesis of lumateperone tosylate (**1**) was developed. The intermediate, ethyl (4a*S*,9b*R*)-6-bromo-1,3,4,4a,5,9b-hexahydro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (**12**), was prepared on kilograms scale in 31% overall yield and >99% ee. (6b*R*,10a*S*)-3-Methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline hydrochloride (**16-HCl**) was obtained through reductamination reaction, palladium catalyzed cyclization and ester hydrolysis in 60% yield over 3 steps and >98% purity. Compound **1** was produced on 20 g scale in 65% yield over 2 steps and >99% purity (HPLC). Purification methods of the intermediates and the final product involved in the route are developed.

EXPERIMENTAL

All commercially available chemicals and solvents were used as received without any further purification. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker UltraShield 400 Plus spectrometer using TMS as an internal standard. Mass spectra were obtained from a Finnigan MAT-95/711 spectrometer. Melting

points were measured on a Shenguang WRS-1B melting point apparatus and uncorrected. The HPLC data were acquired using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump. The purity of the compounds was based on the areas of HPLC UV.

6-Bromo-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole hydrochloride (10). In a 50 L reactor, a suspension of 2-bromophenylhydrazine hydrochloride (**8**, 5.0 kg, 22.4 mol), 4,4-piperidinediol hydrochloride (**9**, 3.6 kg, 23.4 mol), and conc. hydrochloric acid (3.2 kg, 30 mol) in EtOH (20 kg) was stirred and heated to 65−75 °C for 8 h to give a light brown suspension. The reaction mixture was cooled to room temperature, the resulting solid was collected by suction filtration, washed with EtOH (1 L × 2), and dried at 50 °C for 12 h to give **10** (5.8 kg, 91%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.3 (s, 1H), 9.61 (s, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 4.28 (s, 2H), 3.45 (t, J = 6.2 Hz, 2H), 3.05 (t, J = 6.2 Hz, 2H). ESI-MS (*m/z*) 251 $[M+H]^+$.

HPLC Conditions: Column: Agilent InertSustain C18 (250 mm × 4.6 mm × 5 μm); Detection: 210 nm, 244 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 35 min; Mobile phase A: water; Mobile phase B: MeOH/formic acid=100/0.1; Gradient program: Mobile phase A/Mobile phase B = 10/90: t_R = 11.18 min, purity: 97.49% (210 nm), 97.76% (244 nm).

6-Bromo-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (*cis*-11). Compound **10** (5.0 kg, 17.4 mol) was charged into a 50 L reactor. $MeSO_3H$ (20 kg) was added and stirred slowly to the reactor at the ambient temperature over 1 h, and the resulted acid gases were absorbed by aqueous NaOH solution. Et_3SiH (8.1 kg, 70 mol) was added slowly to the reaction mixture at 30−40 °C over 3 h. The reaction solution was stirred at 30−40 °C for another 1 h. The lower layer of the solution was separated and added slowly to cooled 40% aqueous NaOH solution (20 kg) in a 50 L reactor over 3 h, keeping the reaction temperature below 40 °C. The resulting solid was collected by suction filtration, washed with EtOH (1 L × 2), and dried at 50 °C for 12 h to give ***cis*-11** (3.9 kg, 89%) as an off-white solid. mp 109.6−114.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.15 (dd, J = 8.0, 1.6 Hz, 1H), 7.12 (d, J = 8.0 Hz, 0.5H), 7.07 (d, J = 7.2 Hz, 1H), 6.99 (dd, J = 7.2, 1.6 Hz, 0.5H), 6.51−6.56 (m, 1.5H), 5.67 (d, J = 1.6 Hz, 1H), 5.54 (d, J = 1.6 Hz, 0.5H), 3.80−3.82 (m, 1H), 3.74−3.76 (m, 0.5H), 3.17−3.22 (m, 1.5H), 3.01−3.07 (m, 1H), 2.78−2.84 (m, 2H), 2.49−2.57 (m, 2H), 1.85−1.88 (m, 1H), 1.75−1.81 (m, 2H). ESI-MS (*m/z*) 253 $[M+H]^+$.

HPLC Conditions: Column: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 210 nm, 244 nm; Flow rate: 0.8 mL/min; Temperature: 40 °C; Injection volume: 1 μL; Solvent: MeOH;

Concentration: 0.2 mg/mL; Running time: 40 min; mobile phase A: water; mobile phase B: MeOH/triethylamine = 100:0.1; elution gradient: Mobile phase A/mobile phase B = 10/90: t_R = 9.59 min, purity: 99.02% (210 nm), 98.24% (244 nm).

Chiral HPLC Conditions: Column: Daicel CHIRALPAK IC; Detection: 210 nm, 230 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection volume: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 25 min; Mobile phase A: *n*-hexane; mobile phase B: *i*-PrOH; elution gradient: mobile phase A/mobile phase B = 90/10: t_R = 6.77 min (52.93%), t_R = 7.58 min (46.96%) (210 nm); t_R = 6.77 min (65.40%), t_R = 7.58 min (34.38%) (230 nm).

(4a*S*,9b*R*)-6-Bromo-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (*S*)-mandelate (11-MA). MeOH (10 kg) and ***cis*-11** (3 kg, 11.8 mol) was charged into a 50 L reactor, stirred and heated to 40−50 °C. A solution of *S*-(+)-mandelic acid (1.8 kg, 11.8 mol) in MeOH (5 kg) was added to the reaction suspension over 1 h at 50−60 °C to give a clear solution. The solution was cooled to 30−40 °C and hold for 3−4 h, then cooled to 10−20 °C and hold for 1−2 h. The resulting solid was collected by suction filtration, washed with cooled MeOH (1 L × 2), and dried at 50 °C for 12 h to give **11-MA** (1.96 kg, 41%) as an off-white solid. mp 215.6−218.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37−7.35 (m, 2H), 7.26−7.15 (m, 4H), 7.10 (d, J = 7.6 Hz, 1H), 6.57 (t, J = 7.6 Hz, 1H), 5.81 (s, 1H), 4.58 (s, 1H), 3.79 (brs, 1H), 3.31−3.25 (m, 1H), 3.18−3.14 (m, 1H), 3.01−2.89 (m, 2H), 2.58 (t, J = 10.4 Hz, 1H), 1.93−1.84 (m, 2H). ESI-MS (*m/z*) 255 $[M+H]^+$, 287 $[M+Na]^+$.

Chiral HPLC Conditions: Column: Daicel CHIRALPAK IC; Detection: 210 nm, 230 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection volume: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 25 min; Mobile phase A: *n*-hexane; Mobile phase B: *i*-PrOH; elution gradient: Mobile phase A/Mobile phase B = 90/10: t_R = 6.77 min, 99.28% (210 nm), 99.18% (230 nm). (*S*-mandelic acid: t_R = 4.1 min).

Ethyl (4a*S*,9b*R*)-6-bromo-1,3,4,4a,5,9b-hexahydro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (12). A suspension of **11-MA** (1.8 kg, 4.44 mol) and Na_2CO_3 (540 g, 5.0 mol) in THF (8 kg) was stirred at 15−20 °C for 20 min. Ethyl chloroformate (490 g, 4.5 mol) was added dropwise at 20−30 °C over 2 h. The white suspension was stirred for another 30 min. The reaction mixture was concentrated under reduced pressure to give a white solid. The solid was mixed with water (8 kg) and stirred at 20−30 °C for 2 h. The resulting solid was collected by suction filtration, and was mixed with MeOH (1.5 kg) and stirred at 20−30 °C for 30 min. The resulting solid was collected by suction filtration, washed with MeOH

(300 mL × 2), and dried at 50 °C for 12 h to give **12** (1.36 kg, 94%) as a white solid. mp 144.8−147.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.14 (d, J = 7.6 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.50 (t, J = 7.6 Hz, 1H), 5.70 (s, 1H), 4.20−3.70 (m, 3H), 3.60 (brs, 1H), 3.50−3.20 (m, 4H), 1.90−1.75 (m, 1H), 1.65 (brs, 1H), 1.16 (t, J = 8.0 Hz, 3H). ESI-MS (*m/z*) 327 $[M+H]^+$.

HPLC Conditions: Column: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 210 nm; Flow rate: 0.8 mL/min; Temperature: 40 °C; Injection volume: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Running time: 40 min; mobile phase A: water; mobile phase B: MeOH/triethylamine = 100:0.1; elution gradient: Mobile phase A/mobile phase B = 10/90: t_R = 21.24 min, purity: 99.61%.

Chiral HPLC Conditions: Column: Daicel CHIRALPAK IC; Detection: 210 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection volume: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 50 min; Mobile phase A: *n*-hexane; mobile phase B: *i*-PrOH; elution gradient: mobile phase A/mobile phase B = 90/10: t_R = 18.66 min, purity: 99.60%.

Ethyl (4a*S*,9b*R*)-6-bromo-5-(2-(methylamino)ethyl)-1,3,4,4a,5,9b-hexahydro-2*H*-pyrido[4,3-*b*]-indole-2-carboxylate (19). A solution of **12** (32.5 g, 0.1 mol), triethylsilane (46.5 g, 0.4 mol) and TFA (125 g, 1.1 mol) in CH_2Cl_2 (200 mL) was stirred at 25−30 °C. (2,2-Dimethoxyethyl)methylamine (47.6 g, 0.4 mol) was added to the reaction solution over 2 h and stirred at 30−35 °C for another 16 h. The solvents were removed under reduced pressure to give a light-tan oil. CH_2Cl_2 (350 mL) and water (200 mL) were added to the residue. The solution was stirred at room temperature for 10 min, the organic layer was separated and washed with sat. aq. $NaHCO_3$ (200 mL × 1) and brine (200 mL × 1) respectively, and dried by anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give crude **19** (39 g) as a brown oil, purity 93.18% (HPLC), which was used directly at the next step. The analysis sample was purified by column chromatography as a light-yellow viscous oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21(d, J = 8.0 Hz, 1H), 7.09 (d, J = 7.1 Hz, 1H), 6.64 (t, J = 7.6 Hz, 1H), 4.67 (t, J = 5.2 Hz, 1H), 4.00–3.92 (m, 3H), 3.91–3.83 (m, 2H), 3.59 (brs, 4H), 3.25–3.16 (m, 2H), 3.06 (d, J = 5.3 Hz, 2H), 2.62 (s, 3H), 2.56 (s, 3H), 2.01–1.92 (m, 1H), 1.70 (s, 1H), 1.12 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.03, 135.17, 133.25, 123.85, 121.23, 118.91, 115.95, 62.00, 60.94, 54.61, 49.35, 47.19, 44.18, 42.19, 33.47, 33.14, 14.87. ESI-MS (*m/z*) 382 $[M+H]^+$. *Anal.* Calcd for $C_{17}H_{24}BrN_3O_2$: C, 53.41; H, 6.33; N, 10.99. Found: C, 54.03; H, 6.29; N, 11.10.

HPLC Conditions: Column: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 244 nm; Flow rate: 0.8 mL/min; Temperature: 40 °C; Injection volume: 1 μL; Solvent: MeOH; Concentration: 0.2

mg/mL; Running time: 40 min; mobile phase A: water; mobile phase B: MeOH/triethylamine = 100:0.1; elution gradient: Mobile phase A/mobile phase B = 10/90: t_R = 12.448 min, purity: 93.18%.

Ethyl (6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]-quinoxaline-8(7*H*)-carboxylate (15). A suspension of crude **19** (39 g, 0.093 mol), Cs_2CO_3 (48.8 g, 0.15 mol) and $Pd(OAc)_2$ (1.1 g, 0.005 mol), DavePhos (1.9 g, 0.005 mol) in toluene (400 mL) was stirred at 90−100 °C for 16 h under N_2 atmosphere to give a brown solution. After cooled to room temperature, the reaction mixture was filtered through a celite pad and the filtrate was washed with water (200 mL × 1), 1 N HCl (200 mL × 1) and brine (200 mL × 1) respectively. The solvent was removed under reduced pressure to give light-yellow solid. EtOH (100 mL) and active charcoal (3 g) was added to the residue and heated to 50−60 °C for 15 min. The mixture was filtered in hot, the filtrate was concentrated under reduced pressure to give crude **15** (21.3 g, 71%) as a light-yellow oil, purity 96.05% (HPLC), which was used directly at the next step. The analysis sample was purified by column chromatography as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (t, J = 7.6 Hz, 1H), 6.67 (d, J = 7.2 Hz, 1H), 6.49 (d, J = 7.6 Hz, 1H), 3.78−4.24 (m, 4H), 3.54−3.64 (m, 1H), 3.22−3.38 (m, 3H), 3.02−23.22 (m, 2H), 2.72−2.94 (m, 5H), 1.79−1.95 (m, 2H), 1.28 (t, J = 7.0 Hz, 3H). ESI-MS (*m/z*) 302 $[M+H]^+$.

HPLC Conditions: Column: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 244 nm; Flow rate: 0.8 mL/min; Temperature: 40 °C; Injection volume: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Running time: 35 min; mobile phase A: water; mobile phase B: MeOH/triethylamine = 100:0.1; elution gradient: Mobile phase A/mobile phase B = 10/90: t_R = 11.907 min, purity: 96.05%.

(6b*R*,10a*S*)-3-Methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline hydrochloride (16-HCl). A suspension of crude **15** (21 g, 0.067 mol) and conc. hydrochloric acid (150 mL) was stirred and heated to 90−100 °C for 18 h to give a clear solution. Water was removed under reduced pressure to give a light-yellow solid. The solid which was mixed with *i*-PrOH (70 mL), stirred and heated to reflux for 1 h to give a light-brown suspension, and cooled to room temperature. The resulting solid was collected by suction filtration, washed with *i*-PrOH (10 mL × 2), and dried at 50 °C for 6 h to give **16-HCl** (15.1 g, 85%) as a light-purple solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 1H), 9.32 (s, 1H), 6.82 (s, 3H), 3.70–3.35 (m, 6H), 3.20 (brs, 1H), 2.96 (brs, 4H), 2.62–2.54 (m, 1H), 2.18 (s, 3H). ESI-MS (*m/z*) 230 $[M+H]^+$.

HPLC Conditions: Column: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 215 nm; Flow rate: 0.8 mL/min; Temperature: 40 °C; Injection volume: 1 μL; Solvent: MeOH; Concentration: 0.2

mg/mL; Running time: 45 min; mobile phase A: water; mobile phase B: MeOH/triethylamine = 100:0.1; elution gradient: Mobile phase A/mobile phase B = 10/90: t_R = 5.993 min, purity: 98.88%.

Lumateperone (2). A suspension of **16-HCl** (15.0 g, 0.056 mol), 3-chloro-4'-fluorobutyrophenone (**17**, 13.5 g, 0.067 mol), KI (11.3 g, 0.067 mol) and DIPEA (18.4 g, 0.14 mol) in dioxane (150 mL) was stirred and heated to 100 °C for 12 h. The white suspension was cooled to 40−50 °C and filtered through celite pad. The filtrate was concentrated under reduced pressure to give a brown oil. The oil was dissolved into 2 N HCl (150 mL) and washed with EtOAc (70 mL × 2). The water layer was cooled to 5−10 °C, treated dropwise with 40% NaOH (30 mL) to pH~13. The water solution was washed with EtOAc (80 mL × 2). The combined organic layer was washed with water (80 mL × 1) and brine (80 mL × 1) respectively, concentrated under reduced pressure to give **2** (20.1 g, 91%) as a light-brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 6.48 (d, J = 7.2 Hz, 1H), 6.38 (d, J = 8.0 Hz, 1H), 6.30 (d, J = 8.0 Hz, 1H), 3.35−3.50 (m, 2H), 3.15−3.45 (m, 3H), 3.18−2.90 (m, 3H), 2.65−2.69 (m, 1H), 2.71 (s, 3H), 2.52−2.63 (m, 2H), 2.27−2.22 (m, 2H), 2.20−2.00 (m, 1H), 1.60−1.80 (m, 4H), 1.65−1.55 (m, 1H).

HPLC Conditions: Column: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 210 nm, 244 nm; Flow rate: 0.8 mL/min; Temperature: 40 °C; Injection volume: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Running time: 40 min; mobile phase A: water; mobile phase B: MeOH /triethylamine = 100:0.1; elution gradient: Mobile phase A/mobile phase B = 10/90: t_R = 22.59 min, purity: 98.09% (210 nm); 98.29% (244 nm).

Lumateperone tosylate (1). A solution of *p*-TsOH·H_2O (9.4 g, 0.05 mol) in EtOAc (70 mL) was added slowly to the solution of **2** (20.0 g, 0.049 mol) in EtOAc (50 mL) at 10−20 °C, and stirred at 5−10 °C for another 1 h. The resulting solid was collected by suction filtration, washed with EtOAc (10 mL × 2), and dried at 50 °C for 6 h to give **1** (19.6 g, 71%) as a gray solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08−8.02 (m, 1H), 7.50 (d, J = 7.8 Hz, 4H), 7.36 (t, J = 7.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 4H), 6.75−6.65 (m, 2H), 3.65−3.35 (m, 5H), 3.21−3.02 (m, 5H), 3.08−2.92 (m, 3H), 2.81 (s, 1H), 2.29 (s, 6H), 2.27−1.94 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.67, 166.79, 164.29, 145.62, 138.47, 133.58, 133.55, 131.36 (J = 9.5 Hz), 128.25, 128.66, 125.96, 121.11, 116.20 (J = 22.1 Hz), 62.56, 56.05, 52.74, 50.72, 48.13, 43.36, 38.88, 38.82, 35.35, 35.27, 21.99, 21.25, 18.46. ESI-MS (*m/z*) 394 $[M+H]^+$.

HPLC Conditions: Column: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 210 nm, 244 nm; Flow rate: 0.8 mL/min; Temperature: 40 °C; Injection volume: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Running time: 40 min; mobile phase A: water; mobile phase B: MeOH

/triethylamine = 100:0.1; elution gradient: Mobile phase A/mobile phase B = 10/90: t_R = 22.59 min, purity: 99.26% (210 nm); 99.31% (244 nm). *p*-TsOH (t_R = 5.227 min).

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