Crystal structure and X-ray powder diffraction data for Lumateperone tosylate

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X-ray powder diffraction data, unit-cell parameters, and space group for the Lumateperone tosylate, $C_{24}H_{29}FN_3O{\cdot}C_7H_7O_3S$, are reported [$a = 15.5848(10)$ Å, $b = 6.0700(4)$ Å, $c = 31.3201(14)$ Å, $\beta = 96.544(5)°$, $V = 2943.58$ Å^3, $Z = 4$, and space group $C2$]. In each case, all measured lines were indexed and were consistent with the corresponding space group. The single-crystal data of Lumateperone tosylate is also reported, respectively [$a = 15.626(3)$ Å, $b = 6.0806(10)$ Å, $c = 31.415(5)$ Å, $\beta = 96.609(7)°$, $V = 2965.1(8)$ Å^3, $Z = 4$, and space group $C2$]. The experimental powder diffraction pattern has been well matched with the simulated pattern derived from the single-crystal data with preferred orientation in the [002] direction (orientation coefficient = 0.75).

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Keywords: X-ray powder diffraction data, Lumateperone tosylate, solid-state form, preferred orientation

I. INTRODUCTION

Lumateperone (Lumateperone tosylate, ITI-007, 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)-1-(4-fluoro-phenyl)-butan-1-one 4-methylbenzenesulfonate) is a novel, orally available agent for the treatment of schizophrenia and other neuropsychiatric and neurological disorders (Blair, 2020; Mazza et al., 2020; Maini et al., 2021; Pahwa et al., 2021). Due to its ability to modulate serotonin, dopamine, and glutamate neurotransmission, Lumateperone can be considered a multi-target-directed ligand and a multifunctional modulator of the serotoninergic system with possible precognitive, antipsychotic, antidepressant, and anxiolytic properties, implicated in serious mental illness (Kumar et al., 2018; Frampton, 2020; Greenwood et al., 2021; Maini et al., 2021; Syed and Brasic, 2021; Cao et al., 2022; Titulaer et al., 2022). Thus, in December 2019, the U.S. Food and Drug Administration (FDA) approved Lumateperone for the treatment of patients with schizophrenia. The chemical structure of Lumateperone is shown in Figure 1 and its salts, such as Lumateperone tosylate (Wennogle and Tomesch, 2008), ditosylate (Janton et al., 2016), oxalate, 4-aminosalicylate, cyclamate (Wennogle et al., 2016), chlorhydrate (Li and Wennogle, 2017), besylate (Janton et al., 2018), mono/di-naphthalenesulfonate (Lengauer et al., 2019), and isonicotinamide and nicotinamide (Wennogle et al., 2016) were reported, but their crystal structures have not been reported yet. The current clinically available Lumateperone product ITI-007 is Lumateperone tosylate.

We have not found this compound in the CSD database (Groom et al., 2016) or in the PDF4+ database (Gates-Rector and Blanton, 2019). Therefore, we have decided to characterize this compound by X-ray powder diffraction (XRD) technique and X-ray single-crystal diffraction techniques. In our study, we present powder data for Lumateperone tosylate.

II. EXPERIMENTAL

A. Sample preparations

The sample was supplied by Zhejiang Ausun Pharmaceutical Co., LTD (purity >99.9%) and used without further purification. Dissolving Lumateperone tosylate

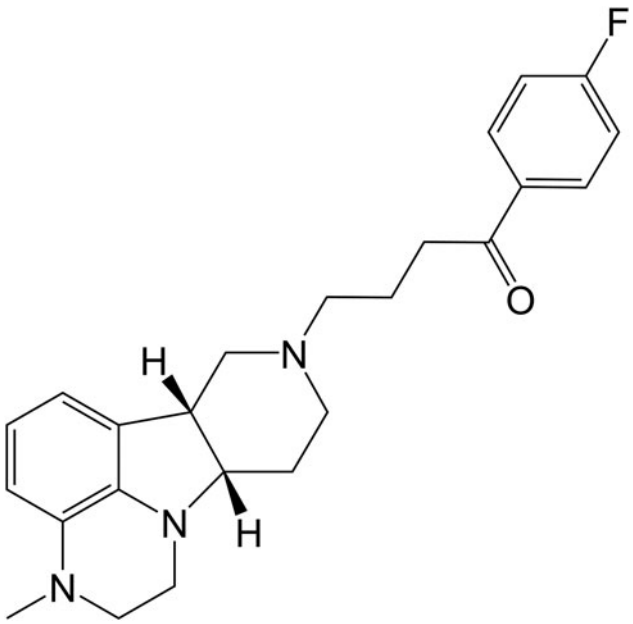

Figure 1. Chemical structure of Lumateperone.

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TABLE I. X-ray powder diffraction data of Lumateperone tosylate

$2\theta_{obs}$ (°)	d_{obs} (Å)	$(I/I_o)_{obs}$	h	k	l	$2\theta_{cal}$ (°)	d_{cal} (Å)	$\Delta 2\theta$ (°)
2.836	31.1273	34.0	0	0	1	2.837	31.1161	−0.001
5.677	15.5547	100.0	0	0	2	5.676	15.5580	0.001
8.514	10.3765	13.5	0	0	3	8.518	10.3720	−0.004
11.364	7.7801	9.4	0	0	4	11.366	7.7790	−0.002
12.090	7.3149	18.2	2	0	1	12.082	7.3197	0.008
12.163	7.2707	17.3	−2	0	2	12.166	7.2692	−0.003
13.332	6.6358	10.8	2	0	2	13.332	6.6359	0.000
13.459	6.5735	1.4	−2	0	3	13.459	6.5735	0.000
14.220	6.2234	1.1	0	0	5	14.220	6.2232	0.000
15.030	5.8896	1.7	2	0	3	15.028	5.8906	0.002
15.186	5.8296	1.5	−2	0	4	15.186	5.8295	0.000
15.663	5.6531	4.3	1	1	0	15.668	5.6513	−0.005
15.808	5.6015	13.9	−1	1	1	15.809	5.6014	−0.001
16.037	5.5221	17.8	1	1	1	16.043	5.5201	−0.006
16.445	5.3859	11.9	−1	1	2	16.451	5.3840	−0.006
16.895	5.2435	12.0	1	1	2	16.899	5.2422	−0.004
17.043	5.1984	46.9	2	0	4	17.041	5.1991	0.002
17.219	5.1457	4.1	−2	0	5	17.221	5.1451	−0.002
17.533	5.0540	7.4	−1	1	3	17.542	5.0515	−0.009
18.167	4.8791	18.1	1	1	3	18.172	4.8780	−0.005
19.005	4.6658	16.1	−1	1	4	19.007	4.6653	−0.002
19.275	4.6012	2.6	2	0	5	19.275	4.6011	0.000
19.786	4.4835	9.8	1	1	4	19.782	4.4843	0.004
19.956	4.4457	18.3	0	0	7	19.958	4.4452	−0.002
20.768	4.2735	3.7	−1	1	5	20.771	4.2731	−0.003
21.659	4.0998	8.4	1	1	5	21.660	4.0997	−0.001
21.873	4.0601	1.9	−2	0	7	21.875	4.0598	−0.002
22.592	3.9325	18.2	3	1	0	22.595	3.9319	−0.003
22.819	3.8939	11.9	−3	1	2	22.823	3.8932	−0.004
23.024	3.8597	8.3	3	1	1	23.026	3.8595	−0.002
23.473	3.7869	10.6	−3	1	3	23.471	3.7872	0.002
23.743	3.7444	7.4	1	1	6	23.745	3.7442	−0.002
24.313	3.6579	18.0	4	0	2	24.300	3.6599	0.013
24.940	3.5673	0.6	−1	1	7	24.945	3.5667	−0.005
25.664	3.4683	2.7	−4	0	5	25.660	3.4689	0.004
25.707	3.4626	2.9	−3	1	5	25.708	3.4626	−0.001
25.995	3.4250	5.7	1	1	7	25.992	3.4253	0.003
26.246	3.3927	0.6	3	1	4	26.247	3.3926	−0.001
26.998	3.3000	1.3	−2	0	9	26.998	3.3000	0.000
27.265	3.2683	3.6	−1	1	8	27.266	3.2681	−0.001
28.366	3.1438	1.0	1	1	8	28.369	3.1435	−0.003
28.949	3.0818	1.1	−3	1	7	28.958	3.0808	−0.009
29.448	3.0307	0.8	2	0	9	29.447	3.0309	0.001
29.540	3.0215	0.7	0	2	1	29.548	3.0207	−0.008
29.702	3.0054	2.4	−1	1	9	29.702	3.0054	0.000
29.970	2.9791	0.9	0	2	2	29.972	2.9789	−0.002
30.325	2.9450	0.5	4	0	6	30.322	2.9453	0.003
30.869	2.8943	1.2	−3	1	8	30.877	2.8936	−0.008
31.628	2.8266	1.9	3	1	7	31.636	2.8259	−0.008
31.916	2.8018	0.6	−2	2	2	31.928	2.8007	−0.012
32.266	2.7721	0.5	−5	1	1	32.262	2.7725	0.004
32.349	2.7652	0.8	−5	1	2	32.355	2.7647	−0.006
32.409	2.7603	0.2	−2	0	11	32.409	2.7603	0.000
32.676	2.7383	0.4	−4	0	9	32.677	2.7382	−0.001
32.958	2.7155	0.5	−3	1	9	32.953	2.7159	0.005
33.534	2.6702	1.4	5	1	2	33.538	2.6699	−0.004
34.192	2.6203	0.9	0	2	6	34.204	2.6194	−0.012
34.272	2.6144	1.0	−2	2	5	34.275	2.6141	−0.003
34.558	2.5933	1.2	0	0	12	34.563	2.5930	−0.005
34.846	2.5726	2.6	−4	0	10	34.847	2.5726	−0.001
35.161	2.5502	1.1	−3	1	10	35.163	2.5501	−0.002
35.341	2.5377	0.7	−6	0	4	35.348	2.5372	−0.007
35.596	2.5201	0.4	5	1	4	35.590	2.5205	0.006
35.809	2.5056	0.1	0	2	7	35.795	2.5065	0.014
36.057	2.4889	0.1	1	1	11	36.064	2.4885	−0.007
36.116	2.4850	0.5	−6	0	5	36.100	2.4861	0.016

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TABLE I. Continued

$2\theta_{obs}$ (°)	d_{obs} (Å)	$(I/I_o)_{obs}$	h	k	l	$2\theta_{cal}$ (°)	d_{cal} (Å)	$\Delta 2\theta$ (°)
36.815	2.4394	0.4	2	2	6	36.821	2.4390	−0.006
36.934	2.4318	0.8	5	1	5	36.931	2.4320	0.003
37.534	2.3943	1.0	−4	2	1	37.535	2.3943	−0.001
38.375	2.3438	0.2	3	1	10	38.387	2.3430	−0.012
38.495	2.3367	0.2	4	2	2	38.503	2.3362	−0.008
39.267	2.2925	0.1	4	2	3	39.268	2.2925	−0.001
39.516	2.2786	0.8	−4	0	12	39.534	2.2777	−0.018
40.254	2.2386	0.5	−1	1	13	40.270	2.2377	−0.016
40.852	2.2072	0.8	3	1	11	40.851	2.2072	0.001
41.539	2.1722	0.7	1	1	13	41.548	2.1718	−0.009
41.620	2.1682	0.5	−4	2	7	41.615	2.1685	0.005
42.424	2.1289	0.8	6	0	7	42.425	2.1289	−0.001
43.078	2.0981	0.9	−1	1	14	43.074	2.0983	0.004
43.410	2.0829	0.8	3	1	12	43.403	2.0832	0.007
43.841	2.0634	0.4	−2	0	15	43.841	2.0634	0.000
44.334	2.0415	0.4	−2	2	11	44.323	2.0420	0.011
44.557	2.0319	0.3	7	1	2	44.564	2.0316	−0.007
45.470	1.9931	0.1	−5	1	12	45.475	1.9930	−0.005
46.033	1.9701	1.1	3	1	13	46.036	1.9700	−0.003
46.837	1.9381	0.1	−2	0	16	46.812	1.9391	0.025
47.263	1.9216	0.1	1	1	15	47.262	1.9217	0.001
47.709	1.9047	0.6	−3	1	15	47.722	1.9042	−0.013
48.372	1.8802	0.1	−1	3	6	48.362	1.8805	0.010
48.783	1.8653	0.2	−2	2	13	48.790	1.8650	−0.007

(1.0 g) in the methanol (5 mL) at 50−60°C and slow cooling of the solutions yielded needle crystals of Lumateperone tosylate. Then, the crystals were dried, smashed, and front-loaded into a zero background plate and limited force was used to make the sample surface flat.

B. Powder diffraction data collection

XRD data were collected at room temperature on Bruker D8 Discover diffractometer with parafocusing Bragg–Brentano geometry and one-dimensional LynxEye XE-T detector using a *Cu Kα* radiation ($\lambda = 1.5418$ Å), and operated at 42 kV and 100 mA. The scan 2θ range was from 2° to 50° with a step size of 0.02° and a counting time of 2.0 s/step. In order to reduce the influence of preference orientation, rotating modes with a speed rate of 20 r/min were used. The software package MDI-Jade version 9.4 (Materials Data Inc., USA) (MDI, 2009) was used to smooth the data, fit the background, and eliminate the Kα2 component and the top of the smoothed peaks were used to determine the peak positions and intensities of the diffraction peaks (Table I). The *d*-spacing was calculated using Cu $K\alpha_1$ radiation ($\lambda = 1.5406$ Å).

C. Single-crystal diffraction data collection

X-ray single-crystal diffraction data were collected at room temperature with a Bruker D8 Venture diffractometer with *Ga Kα* radiation ($\lambda = 1.34139$ Å) for cell determination and subsequent data collection. Data reduction was performed by APEX4 software and multi-scan absorption correction was applied. Using Olex2 (Dolomanov et al., 2009), the crystal structure was solved by ShelXT (Sheldrick, 2015a) and refined with full-matrix least-squares methods with anisotropic thermal parameters for all non-hydrogen atoms on F^2 using SHELXL (Sheldrick, 2015b). Diamond (Brandenburg and Putz, 2005) was used to prepare the figures and packing diagrams.

III. RESULTS AND DISCUSSION

Indexing of the experimental XRD patterns and unit-cell refinements was done using MDI-Jade. In the process of refinement, only zero-offset parameter (−0.00102°) was added and refined. The cell refinement results showed that Lumateperone tosylate is monoclinic with space group *C*2 and unit-cell parameters: $a = 15.5848(10)$ Å, $b = 6.0700(4)$ Å,

TABLE II. Crystal and experimental data Lumateperone tosylate

System	Lumateperone tosylate
Chemical formula	$C_{24}H_{29}FN_3O{\cdot}C_7H_7O_3S$
Formula weight	565.69
Space group	*C*2
Temperature (K)	293
Crystal size (mm)	0.185 × 0.065 × 0.043
Unit-cell parameters (Å, °)	$a = 15.626(3)$
	$b = 6.0806(10)$
	$c = 31.415(5)$
	$\beta = 96.609(7)$
Vol (Å^3)	2965.1(8)
Z	4
D_{cal} (g cm^{-3})	1.267
μ (mm^{-1})	0.878
$F(000)$	1200
θ range for data collection (°)	2.464–60.149
Index ranges	$-20 \le h \le 20$, $-7 \le k \le 7$, $-40 \le l \le 39$
Reflection collected/ Independent	35 599/6543 ($R_{int} = 0.1488$)
Data/restraints/parameters	6543/1/363
Goodness-of-fit (S)b on F^2	0.952
Final R indexes [$I \ge 2\sigma(I)$]	$R_1 = 0.0814$, $wR_2 = 0.2366$
Residual density max/min / (e.Å^{-3})	0.257/−0.538

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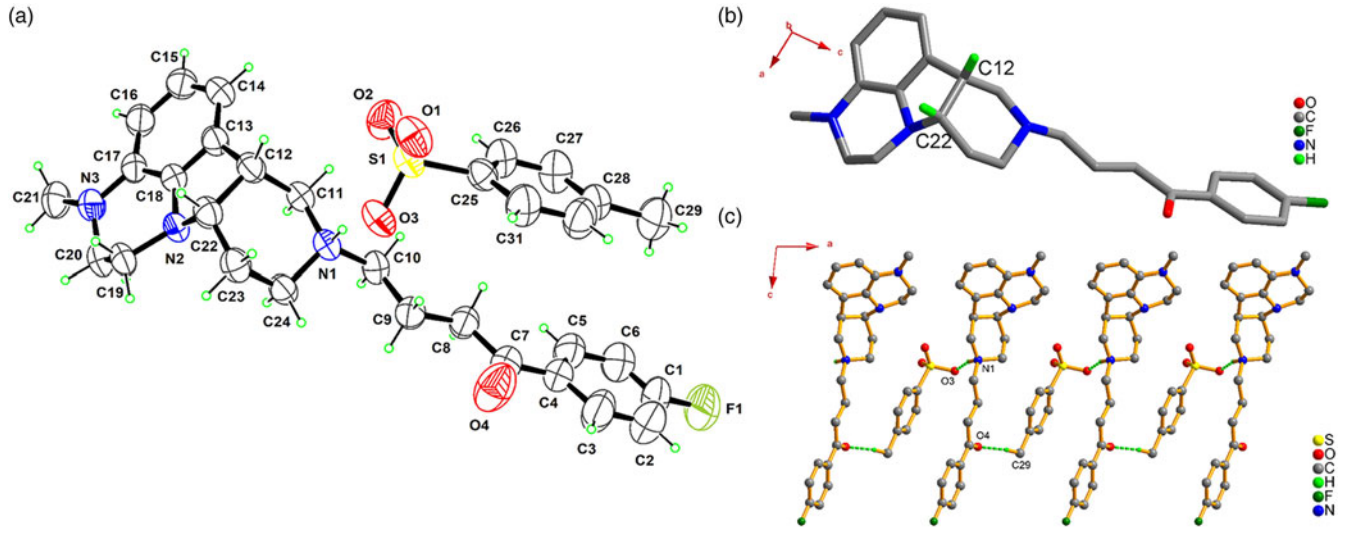

Figure 2. (a) Asymmetric unit of Lumateperone tosylate shown in thermal ellipsoid model with 30% probability. (b) Molecular configuration diagram of Lumateperone. (c) 1D hydrogen bonding chains of Lumateperone tosylate viewed along the *b* axis.

$c = 31.3201(14)$ Å, $\beta = 96.544(5)°$, unit-cell volume $V = 2943.58$ Å^3, $Z = 4$. The figure of merit is $F_{30} = 422.3(30)$ (Smith and Snyder, 1979). The values of $2\theta_{obs}$, d_{obs}, I_{obs}, h, k, l, $2\theta_{cal}$, d_{cal}, and $\Delta 2\theta$ are listed in Table I.

Based on the single-crystal data, the structures of Lumateperone tosylate were solved and refined. The detailed crystallographic information is summarized in Table II and the asymmetric units with the corresponding atom labeling scheme are illustrated in Figure 2(a). In the crystal structure, the expected proton transfer was found between Lumateperone and toluene sulfonic acid, forming Lumateperone cation protonated at the N atom of the hydro-pyridine group. Hydrogen bonds N1–H1···O3 linked Lumateperone cations and tosylate anions. In Figure 2(b), two chiral C atoms (C12, C22) of Lumateperone molecules existed "*R*" and "*S*" configurations, respectively. The hydrogen bonds (N1–H1···O3 and C29–H29C···O4) between Lumateperone cations and tosylate anions linked Lumateperone molecules into an infinite straight chain along the *a* direction in Figure 2(c). Hydrogen bond interactions were listed in Supplementary Table SII.

Despite the use of careful grinding and sample rotation during measurement, an evidently preferred orientation was observed in the experimental XRD pattern due to the needle-like crystal morphology of Lumateperone tosylate. An orientation coefficient of 0.75 at the [002] direction (refined by WPF refinement in Jade) was added to the simulated pattern derived from the single-crystal data. The comparison of the experimental powder diffraction pattern and the simulated pattern is shown in Figure 3. Results showed that both single-crystal and powder diffraction methods can get similar structure data and the deviations of the unit-cell parameters and unit-cell volume were between 0.03% and 0.36%.

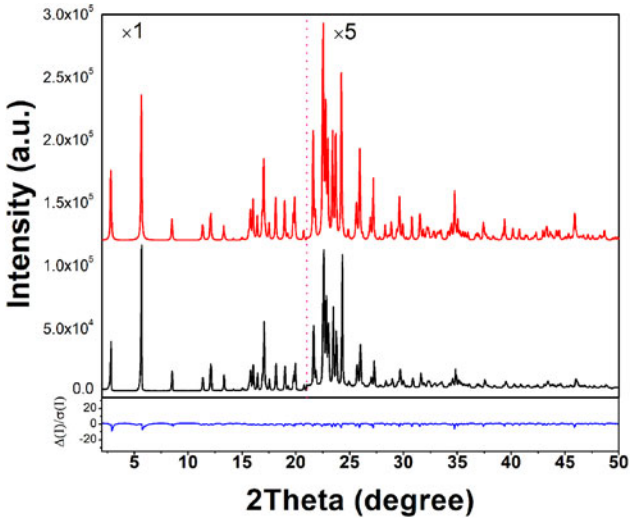

Figure 3. X-ray powder diffraction pattern (black line) and the simulated pattern (red line) of the crystal structure with preferred orientation in the [002] direction (orientation coefficient = 0.75) (red line) of Lumateperone tosylate. The blue curve is the normalized error plot. The vertical scale has been multiplied by a factor 5× for $2\theta > 21°$.

IV. DEPOSITED DATA

CIF and/or RAW data files were deposited with ICDD. You may request this data from ICDD at pdj@icdd.com.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S0885715623000337.

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