X-ray powder diffraction data for ESP15228, $C_{19}H_{34}O_5$, a bempedoic acid metabolite

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X-ray powder diffraction data, including unit cell parameters and space group assignment, for the ESP15228 species of $C_{19}H_{34}O_5$ formula, are here reported [$a = 6.0434(6)$, $b = 12.2543(6)$, $c = 14.0285(8)$ Å, $\alpha = 86.584(3)$, $\beta = 85.707(10)$, $\gamma = 78.801(5)°$, $V = 1015.2(1)$ Å^3, $Z = 2$, $\rho_{calc} = 1.152$ g cm^{-3}, and space group P-1]. All measured lines were indexed and no detectable impurities were observed.

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Key words: ESP15228, bempedoic acid, X-ray powder diffraction, indexing

I. INTRODUCTION

The chemical species of $C_{19}H_{34}O_5$ formula (IUPAC name: 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid, sketched in Figure 1) and originally labeled ESP15228 (CAS No. 413624-71-2) is an intermediate compound in the synthesis of bempedoic acid (BA) (Pathy, 2019). BA is a first-in-class medication for the treatment of hypercholesterolemia approved by the US FDA (Food and Drug Administration, 2020) and EMA (European Medical Agency, 2020), and widely marketed with the tradenames of Nexletol, Nexlizet, and Nustendi, among others. ESP15228 is also a known metabolite of the pristine BA drug and was proved to be pharmacologically active.

The analytical characterization of ESP15228 in the solid state requires the identification of crystalline form(s) by conventional X-ray powder diffraction (XRPD) techniques, well beyond phase identification by pattern matching. To this goal, pure batches of ESP15228 were prepared and their XRPD was interpreted by cell determination and peak indexing. Accordingly, in this communication, we provide the detailed list of diffraction peaks, lattice parameters, and space group symmetry, useful for crystal phase recognition and the simultaneous detection of impurity peaks.

II. EXPERIMENTAL

A. Sample preparation

The sample was prepared in Chemessentia's lab, using the following synthetic approach. The corresponding diethyl ester, prepared according to PCT application WO 2020/ 257573 (Copp et al., 2020), was hydrolyzed by means of aqueous NaOH in ethanol solution. The derived diacid was then crystallized as tiny creamy irregular plates from MTBE/heptane, as per PCT application WO 2004/ 067489 (Dasseux and Oniciu, 2004). The same crystal form (XRPD evidence) is obtained if crystallization is carried out using an iPrOAc/heptane mixture.

The sample was characterized also by DSC, melting point 82°C (onset); FT-IR peaks, cm^{-1}: 2929, 2904, 2866, 1709, 1690, 1471, 1409, 1191, 947, 881, 783, 765; ^{1}H-NMR (DMSO-d_6): 1.18 (m, 8H), 1.42 (m, 8H), 2.37 (t, J = 7.3 Hz, 4H), 1.07 (s, 12H).

B. Diffraction data collection and reduction

Powders of ESP15228 were gently ground in an agate mortar and packed in a 0.2 mm deep sample holder (a silicon zero-background plate). XRPD data collection was performed at 294 K using a D8 Advance diffractometer (Bruker AXS, Karlsruhe, Germany) equipped with a Lynxeye detector and Ni-filtered Cu-Kα radiation ($\lambda_{CuK\alpha1} = 1.5406$ Å, $\lambda_{CuK\alpha2} = 1.5444$ Å). The diffraction data were collected in the 3–40° 2θ angular range, sampling at step size $\Delta 2\theta = 0.02°$, and a counting time of 3 s step^{-1}. HV generator settings, 40 kV, 40 mA; goniometer radius, 250 mm; fixed divergence slit, 0.2 mm; 2.5° Soller slits (2×).

Cell determination (indexing) was attempted using the first 25 observable low-angle peaks, with accurate positions determined by profile fitting methods and the Fundamental Parameters Approach (Cheary and Coelho, 1992). These

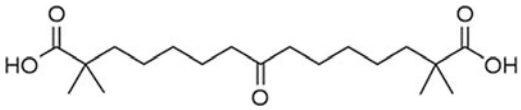

Figure 1. Molecular diagram of ESP15228.

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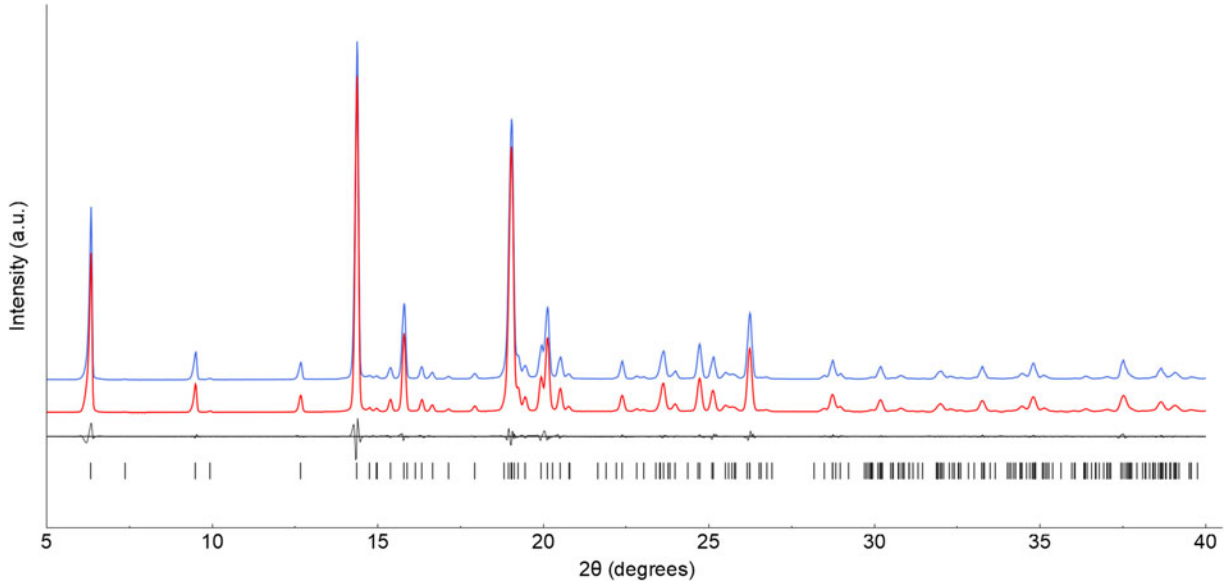

Figure 2. X-ray powder diffraction pattern of ESP15228, collected with Cu-Kα at 294 K (blue line) and the Le Bail simulated pattern (red line), vertically offset for better comparison. Difference plot and peak markers are shown in gray in the bottom section.

values were fed into the Single Value Decomposition routine (Coelho, 2003) of TOPAS-R, which provided initial triclinic cell parameters: $a = 6.05$, $b = 14.03$, $c = 19.48$ Å, $\alpha = 131.3$, $\beta = 67.7$, $\gamma = 85.7°$, $V = 1015.7$ Å^3, GOF(25) = 36.6. All measured lines in the raw data were indexed. Cell reduction to $a = 6.05$, $b = 12.25$, $c = 14.03$ Å, $\alpha = 86.6$, $\beta = 85.7$, $\gamma = 78.8°$, was performed with the aid of Wlepage program (Laugier and Bochu, 2003).

TABLE I. Indexed X-ray powder diffraction data for ESP15228 (d-values calculated by $\lambda_{CuK\alpha1} = 1.5406$ Å).

$2\theta_{obs}$ (°)	d_{obs} (Å)	I_{obs}	h	k	l	$2\theta_{cal}$ (°)	d_{cal} (Å)	$\Delta 2\theta$(°)
6.330	13.952	45	0	0	1	6.323	13.979	0.007
7.357	12.007	1	0	1	0	7.361	12.008	−0.005
9.491	9.311	8	0	1	1	9.488	9.322	0.004
9.926	8.904	1	0	−1	1	9.927	8.910	−0.001
12.665	6.984	5	0	0	2	12.665	6.989	0.000
14.366	6.160	100	0	1	2	14.369	6.164	−0.002
14.750	6.001	1	0	2	0	14.754	6.004	−0.003
14.955	5.919	1	0	−1	2	14.954	5.924	0.001
15.374	5.759	4	1	1	0	15.386	5.759	−0.012
15.788	5.609	24	0	2	1	15.795	5.610	−0.007
16.321	5.427	4	0	−2	1	16.331	5.428	−0.010
16.635	5.325	2	1	0	−1	16.650	5.324	−0.015
17.132	5.171	1	1	1	−1	17.144	5.172	−0.012
17.924	4.945	2	1	−1	0	17.937	4.945	−0.013
18.971	4.674	42	1	0	2	19.018	4.666	−0.047
19.048	4.655	61	0	0	3	19.046	4.660	0.002
19.243	4.609	7	1	−1	−1	19.249	4.611	−0.006
19.449	4.560	5	1	2	1	19.458	4.562	−0.009
19.940	4.449	11	0	−2	2	19.930	4.455	0.010
20.117	4.410	25	0	1	3	20.124	4.412	−0.007
20.505	4.328	8	1	2	−1	20.516	4.329	−0.011
20.765	4.274	2	0	−1	3	20.760	4.279	0.004
22.368	3.971	6	1	−1	−2	22.387	3.971	−0.019
22.820	3.894	1	0	3	1	22.828	3.896	−0.008
23.019	3.864	1	1	−2	0	23.032	3.861	−0.013
23.603	3.766	10	0	2	3	23.628	3.765	−0.025
23.975	3.709	3	1	−2	−1	23.988	3.710	−0.013
24.705	3.601	12	0	−2	3	24.714	3.602	−0.009
25.053	3.552	1	1	0	−3	25.085	3.550	−0.032
25.140	3.539	8	0	3	2	25.127	3.544	0.013
25.499	3.490	2	0	0	4	25.488	3.495	0.011
25.728	3.460	1	1	3	−1	25.697	3.467	0.031
26.223	3.396	26	0	1	4	26.231	3.397	−0.008

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At this stage, the whole-profile fitting method, using Le Bail technique (Le Bail, 2005), was employed to fit the 5–40° 2θ range, using a 5th order Chebyshev polynomial as a background trace, a 1/cosθ-dependent Lorentzian broadening (average crystal size = 940 nm) and an additional tanθ-dependent Gaussian broadening accounting for microstrain ($\langle\epsilon^2\rangle^{1/2}$ = 0.24). A minor correction for a systematic peak shift, possibly due to sample transparency effects, was also introduced. Final profile agreement factors, for the observed and calculated traces drawn in Figure 2: $R_p = 0.051$ and $R_{wp} = 0.071$.

III. RESULTS AND DISCUSSION

The Le Bail refinement confirmed that ESP15228 is triclinic with space group P-1 and unit cell parameters a = 6.0434(6), b = 12.2543(6), c = 14.0285(8) Å, α = 86.584(3), β = 85.707(10), γ = 78.801(5)°, unit cell volume V = 1015.2 (1) Å^3. As per Hofmann's rules (Hofmann, 2002), the expected molecular volume is 483.2 Å^3, indicating $Z = 2$ and a 1.152 g cm^{-3} calculated density (for a molecular mass of 342.47 dalton). The values of $2\theta_{obs}$, d_{obs}, I_{obs}, h, k, l, $2\theta_{cal}$, d_{cal}, $\Delta 2\theta$ are listed in Table I. Extraction of peak positions and intensities for reflections falling above $2\theta = 27°$ proved difficult, due to their low(er) intensity, peak widths, and severe overlap. Indeed, while the assignment of *hkl* triplets to these peaks is possible, it is not an unambiguous procedure and, for the scope of automatic search-matching procedures, of little use. Indeed, the >30 clearly indexed lines provided in Table I, jointly with the unit cell parameters listed above, are considered more than sufficient.

Worthy of note, though isostructural to ESP15228, bempenoic acid is not isomorphous with the title compound. Deposited in the CSD database with code IQUXIE (Copp et al., 2020), the crystal structure of the latter species is monoclinic, $P2_1/c$, with V = 2075.4 Å^3 and $Z = 4$. This leads to a molecular volume of *ca.* 519 Å^3, slightly larger (as expected) than the 508 Å^3 value found for ESP15228. The *ca.* 11 Å^3 difference nicely corresponds to 2 × 5.08 Å^3 estimate for the atomic volume of two hydrogen atoms. Noteworthy, the very distinct crystal structures of bempenoic acid and ESP15228 enable their easy fingerprinting, and the detection of one form, as a contaminant, within the other (predominant) crystal phase.

Work can be anticipated in the direction of solving and refining, from powder diffraction data, the unknown structure of ESP15228, which so far resisted solution, due to the molecular flexibility (6 center-of-mass and molecular rotations + 14 torsional angles, neglecting CH_3 rotations, using the *Z*-matrix formalism).

DATA AVAILABILITY

The ESP15228_diffraction_pattern.xy file (ASCII format) has been deposited with ICDD. You may request these data from ICDD at pdj@icdd.com.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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