Crystal structure of vismodegib, C_{19}H_{14}Cl_2N_2O_3S

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(Received 24 July 2022; accepted 20 September 2022)

The crystal structure of vismodegib has been solved and refined using synchrotron X-ray powder diffraction data, and optimized using density functional theory techniques. Vismodegib crystallizes in space group P21/a (#14) with a = 16.92070(20), b = 10.20235(4), c = 12.16161(10) Å, β = 108.6802(3)°, V = 1988.873(9) Å³, and Z = 4. The crystal structure consists of corrugated layers of molecules parallel to the bc-plane. There is only one classical hydrogen bond in the structure, between the amide nitrogen atom and the N atom of the pyridine ring. Pairs of these hydrogen bonds link the molecules into dimers, with a graph set R2,2(14) > a > a. The powder pattern has been submitted to ICDD for inclusion in the Powder Diffraction File™ (PDF®).

Key words: vismodegib, Erivedge, crystal structure, Rietveld refinement, density functional theory

I. INTRODUCTION

Vismodegib (sold under the brand name Erivedge) is used to treat unresectable or metastatic basal cell carcinoma. It belongs to a class of medicines referred to as hedgehog pathway inhibitors due to its ability to block the action of a protein that signals cancer cells to multiply (MedLine, 2022). The systematic name (CAS Registry Number 879085-55-9) is 2-chloro-N-(4-chloro-3-pyridin-2-ylphenyl)-4-methylsulfonylbenzamide. A two-dimensional molecular diagram is shown in Figure 1.

Vismodegib was a commercial reagent, purchased from TargetMol (Lot #120202), and was used as-received. The white powder was packed into a 1.5 mm diameter Kapton capillary, and rotated during the measurement at ∼50 Hz. The powder pattern was measured at 295 K at beamline 11-BM of the Advanced Photon Source at Argonne National Laboratory using a wavelength of 0.458968(2) Å from 0.5 to 50° 2θ with a step size of 0.001° and a counting time of 0.1 s per step. The high-resolution powder diffraction data were collected using twelve silicon crystal analyzers that allow for high angular resolution, high precision, and accurate peak positions. A mixture of silicon (NIST SRM 640c) and alumina (NIST SRM 676a; Cline et al., 2011) standard (ratio Al_2O_3:Si = 2:1 by weight) was used to calibrate the instrument and refine the monochromatic wavelength used in the experiment.
The pattern was indexed using N-TREOR (Altomare et al., 2013) on a primitive monoclinic unit cell with $a = 16.8934$, $b = 10.1866$, $c = 12.1444$ Å, $\beta = 106.68^\circ$, $V = 1979.79$ Å$^3$, and $Z = 4$. A reduced cell search in the Cambridge Structural Database (Groom et al., 2016) yielded 18 hits, but no structures of vismodegib derivatives. The suggested space group was $P2_1/\alpha$, which was confirmed by successful solution and refinement of the structure. The structure was solved by direct methods using EXPO2014 (Altomare et al., 2013). Some atom types had to be reassigned manually, and the hydrogen atoms were added using Materials Studio (Dassault, 2021).

Rietveld refinement was carried out using GSAS-II (Toby and Von Dreele, 2013). Only the 2.0–25.0° portion of the pattern was included in the refinement ($d_{\text{min}} = 0.886$ Å). All non-H bond distances and angles (plus the plane of the fused ring system) were subjected to restraints, based on a Mercury/Mogul Geometry Check (Bruno et al., 2004; Sykes et al., 2011). The Mogul average and standard deviation for each quantity were used as the restraint parameters. The restraints contributed 2.1% to the final $\chi^2$. The hydrogen atoms were included in calculated positions, which were recalculated during the refinement using Materials Studio (Dassault, 2021). The $U_{iso}$ of the heavy atoms were grouped by chemical

Figure 2. The Rietveld plot for the refinement of vismodegib. The blue crosses represent the observed data points, and the green line is the calculated pattern. The cyan curve is the normalized error plot. The red curve indicates the background. The vertical scale has been multiplied by a factor of 20x for $2\theta > 13.0^\circ$. The row of blue tick marks indicates the calculated reflection positions.

Figure 3. Comparison of the synchrotron pattern of vismodegib (black) to that reported by Parthasaradhi Reddy et al. (2014; green) for the prior art Form I, which we identified as the stable Form B. The patent pattern, measured using Cu $K\alpha$ radiation, was digitized using UN-SCAN-IT (Silk Scientific, 2013), and converted to the synchrotron wavelength of 0.458968 Å using JADE Pro (MDI, 2022). Image generated using JADE Pro (MDI, 2022).
similarity. The two Cl atoms were refined anisotropically. The $U_{iso}$ for the H atoms were fixed at $1.3 \times U_{iso}$ of the heavy atoms to which they are attached. The peak profiles were described using the generalized microstrain model. The background was modeled using a 3-term shifted Chebyshev polynomial, and a peak at $6.65^\circ 2\theta$ was used to model the scattering from the Kapton capillary and any amorphous component.

The final refinement of 122 variables using 28,045 observations and 71 restraints yielded the residuals $R_{wp} = 0.1300$ and $\text{GOF} = 3.27$. The largest peak (2.20 Å from C15) and hole (1.94 Å from C19) in the difference Fourier map were $0.50(12)$ and $-0.53(12)$ eÅ$^{-3}$, respectively. The largest errors in the difference plot (Figure 2) are in the shapes of many of the strong low-angle peaks, and suggest that the sample may have suffered beam damage during the measurement.

The crystal structure was optimized using VASP (Kresse and Furthmüller, 1996) (fixed experimental unit cell) through the MedeA graphical interface (Materials Design, 2016). The calculation was carried out on 16 2.4 GHz processors (each with 4 GB RAM) of a 64-processor HP Proliant DL580 Generation 7 Linux cluster at North Central College. The calculation used the GGA-PBE functional, a plane wave cutoff energy of 400.0 eV, and a $k$-point spacing of 0.5 Å$^{-1}$ leading to a $2 \times 2 \times 2$ mesh, and took $\sim 64.7$ h. A single-point density functional calculation (fixed experimental cell) and population analysis were carried out using CRYSTAL17 (Dovesi et al., 2018). The basis sets for the H, C, N, and O atoms in the calculation were those of Gatti et al. (1994), and those for S and Cl were those of Peintinger et al. (2013). The calculations were run on a 3.5 GHz PC using 8 $k$-points and the B3LYP functional, and took $\sim 2.6$ h.

III. RESULTS AND DISCUSSION

The synchrotron powder pattern of this study matches the pattern for Form I reported by Parthasaradhi Reddy et al. (2014) well enough to conclude that they represent the same material (Figure 3), corresponding to the thermodynamically
stable Form B of vismodegib. The root-mean-square (rms) Cartesian displacement between the non-H atoms in the Rietveld-refined and DFT-optimized structures is only 0.055 Å (Figure 4), and the maximum difference is 0.118 Å. The excellent agreement is strong evidence that the structure is correct (van de Streek and Neumann, 2014). This discussion concentrates on the DFT-optimized structure. The asymmetric unit (with atom numbering) is illustrated in Figure 5. The best view of the crystal structure is down the b-axis (Figure 6). The crystal structure consists of corrugated layers of molecules parallel to the bc-plane.

All of the bond distances and bond angles fall within the normal ranges indicated by a Mercury/Mogul Geometry check (Macrae et al., 2020). The torsion angles involving rotation about the C20–C22 bond are flagged as unusual. These represent the orientation of the pyridine ring with respect to one of the chlorinated phenyl rings, and indicate that the overall conformation of the molecule in the solid state is unusual.

Quantum chemical geometry optimization of the vismodegib molecule (DFT/B3LYP/6-31G*/water) using Spartan ‘18 (Wavefunction, 2020) indicated that the observed conformation is 5.8 kcal mol⁻¹ higher in energy than the local minimum, which has more-normal torsion angles about the C20–C22 bond and a different orientation of the methylsulfone group. A conformational analysis (MMFF force field) indicates that the minimum-energy conformation is 1.9 kcal mol⁻¹ lower in energy, with further differences in the C20–C22 rotation and the different orientation of the methylsulfone group. Intermolecular interactions seem to be important in determining the solid-state conformation.

Analysis of the contributions to the total crystal energy of the structure using the Forcite module of Materials Studio (Dassault, 2021) suggests that the intramolecular deformation energy is dominated by angle distortion terms. The intermolecular energy is dominated by electrostatic attractions, which in this force field analysis include hydrogen bonds. The hydrogen bonds are better analyzed using the results of the DFT calculation.

There is only one classical hydrogen bond in the structure (Table I), N7–H31⋯N8. This is between the amide nitrogen atom and the N atom of the pyridine ring. Pairs of these hydrogen bonds link the molecules into dimers, with a graph set (Etter, 1990; Bernstein et al., 1995; Shields et al., 2000) R2,2(14)>a > a (Figure 7). Five C–H⋯O and two C–H⋯Cl hydrogen bonds also contribute to the lattice energy.

The volume enclosed by the Hirshfeld surface of vismodegib (Figure 8; Hirshfeld, 1977; Turner et al., 2017) is 478.87 Å³, 96.31% of 1/4 the unit cell volume. The packing density is thus fairly dense. The only significant-close contacts (red in Figure 8) involve the hydrogen bonds. The volume/non-hydrogen atom is larger than normal at 18.4 Å³, reflecting the presence of the two Cl atoms.

The Bravais–Friedel–Donnay–Harker (Bravais, 1866; Friedel, 1907; Donnay and Harker, 1937) morphology suggests that we might expect blocky morphology for vismodegib, with {001} as principal faces. A second-order spherical harmonic

<table>
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<th>H-Bond</th>
<th>D-H (Å)</th>
<th>H⋯A (Å)</th>
<th>D⋯A (Å)</th>
<th>D-H⋯A (°)</th>
<th>Overlap (e)</th>
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<tr>
<td>N7–H31⋯N8</td>
<td>1.054</td>
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<td>3.941</td>
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<td>0.013</td>
</tr>
</tbody>
</table>

Figure 6. The crystal structure of vismodegib, viewed down the b-axis. Image generated using Diamond (Crystal Impact, 2022).
preferred orientation model was included in the refinement. The texture index was 1.018(0), indicating that preferred orientation was not significant for this rotated capillary specimen. The powder pattern of vismodegib from this synchrotron data set has been submitted to ICDD for inclusion in the Powder Diffraction File.

IV. DEPOSITED DATA

The Crystallographic Information Framework (CIF) files containing the results of the Rietveld refinement (including the raw data) and the DFT geometry optimization were deposited with the ICDD. The data can be requested at pdj@icdd.com.

ACKNOWLEDGEMENTS

The use of the Advanced Photon Source at Argonne National Laboratory was supported by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract No. DE-AC02-06CH11357. This work was partially supported by the International Centre for
Diffraction Data. We thank Lynn Ribaud and Saul Lapidus for their assistance in the data collection.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.


