

Crystal structure of imepitoin, C₁₃H₁₄ClN₃O₂James A. Kaduk ^{1,2,a)} Amy M. Gindhart ³ Stacy Gates-Rector ³ and Thomas N. Blanton ³¹Illinois Institute of Technology, 3101 S. Dearborn St., Chicago, IL 60616, USA²North Central College, 131 S. Loomis St., Naperville, IL 60540, USA³ICDD, 12 Campus Blvd., Newtown Square, PA 19073-3273, USA

(Received 25 June 2022; accepted 25 August 2022)

The crystal structure of imepitoin has been solved and refined using synchrotron X-ray powder diffraction data, and optimized using density functional techniques. Imepitoin crystallizes in space group *Pbca* (#61) with $a = 12.35541(2)$, $b = 28.43308(8)$, $c = 7.340917(7)$ Å, $V = 2578.882(7)$ Å³, and $Z = 8$. The roughly planar molecules stack along the *c*-axis. There are no traditional hydrogen bonds in the structure, but several intramolecular and intermolecular C–H...O, C–H...N, and C–H...Cl hydrogen bonds contribute to the crystal energy. The powder pattern has been submitted to ICDD for inclusion in the Powder Diffraction File™ (PDF®). © The Author(s), 2022. Published by Cambridge University Press on behalf of International Centre for Diffraction Data. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited. [doi:10.1017/S0885715622000392]

Key words: imepitoin, Pexion, powder diffraction, Rietveld refinement, density functional theory

I. INTRODUCTION

Imepitoin (sold under the brand name Pexion®) is an anti-convulsant which is used in veterinary medicine to treat epilepsy and noise aversion in dogs. It is a centrally acting antiepileptic drug, which acts as a low affinity partial agonist of the benzodiazepine receptor. Imepitoin was originally developed for treatment of epilepsy in humans but was abandoned for human use when efficacy was found to be reduced in smokers. The systematic name (CAS Registry Number 188116-07-6) is 3-(4-chlorophenyl)-5-morpholin-4-yl-4H-imidazol-2-one. A two-dimensional molecular diagram is shown in Figure 1.

Imepitoin is the subject of US Patent 9,469,611 (Rundfeldt *et al.*, 2016; Boehringer Ingelheim), but no X-ray powder diffraction data are provided. We are unaware of any published powder data for imepitoin.

This work was carried out as part of a project (Kaduk *et al.*, 2014) to determine the crystal structures of large-volume commercial pharmaceuticals, and include high-quality powder diffraction data for them in the Powder Diffraction File (Gates-Rector and Blanton, 2019).

II. EXPERIMENTAL

Imepitoin was a commercial reagent, purchased from TargetMol (Batch #119530), 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 (Antao *et al.*, 2008; Lee *et al.*, 2008; Wang *et al.*, 2008) of the Advanced Photon Source at Argonne National Laboratory using a wavelength of 0.458208(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 silicon (NIST SRM 640c) and alumina (SRM 676a) standard (ratio Al₂O₃: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 JADE Pro 8.1 (MDI, 2021) and N-TREOR (Altomare *et al.*, 2013) on a high-quality primitive orthorhombic unit cell with $a = 12.35862$, $b = 28.44084$, $c = 7.34228$ Å, $V = 2580.74$ Å³, and $Z = 8$. The suggested space group was *Pbca*, which was confirmed by successful solution and refinement of the structure. A reduced cell search in the Cambridge Structural Database (Groom *et al.*, 2016)

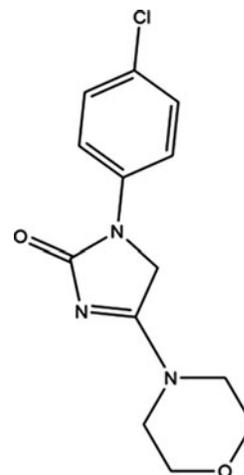


Figure 1. The 2D molecular structure of imepitoin.

^{a)} Author to whom correspondence should be addressed. Electronic mail: kaduk@polycrystallography.com

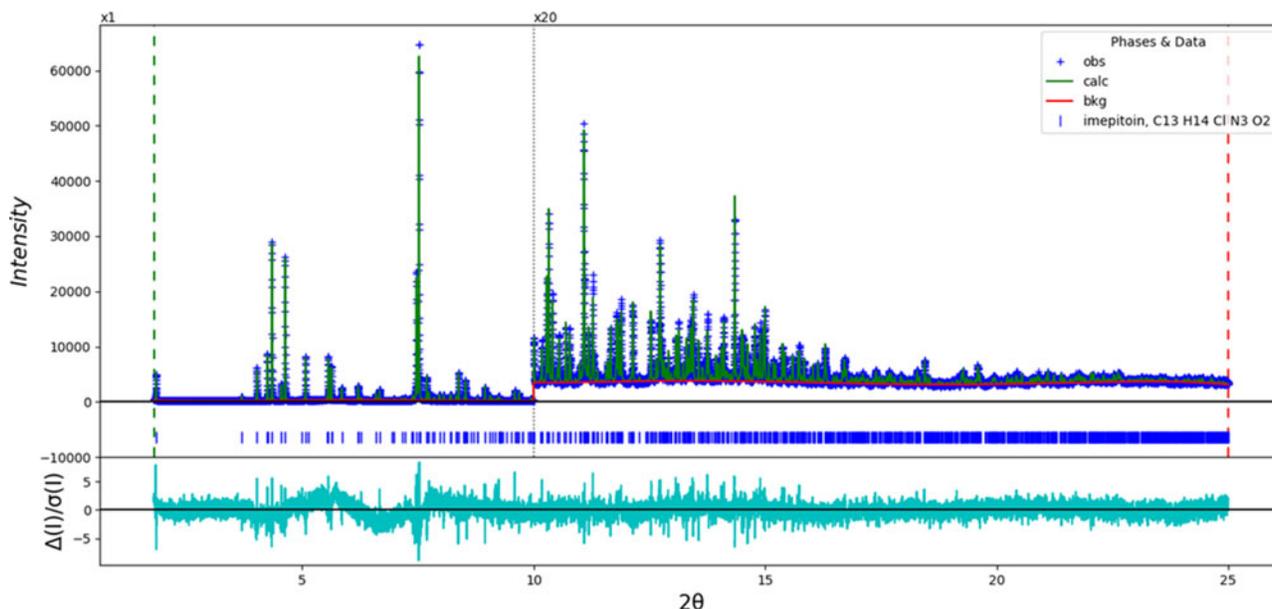


Figure 2. The Rietveld plot for the refinement of imepitoin. The blue crosses represent the observed data points, and the green line is the calculated pattern. The cyan curve is the normalized error plot. The vertical scale has been multiplied by a factor of $20\times$ for $2\theta > 10.0^\circ$.

combined with C, H, Cl, N, and O only, yielded five hits, but no structures of imepitoin derivatives.

The structure was solved by direct methods as implemented in EXPO2014 (Altomare *et al.*, 2013), using the COVMAP option on all trials. Some atom types had to be reassigned manually. The hydrogen atoms were added in positions calculated using Materials Studio (Dassault, 2021); the positions were re-calculated during the refinement.

Rietveld refinement was carried out using GSAS-II (Toby and Von Dreele, 2013). Only the $1.8\text{--}25.0^\circ$ portion of the pattern was included in the refinement ($d_{\min} = 1.058 \text{ \AA}$). All non-H bond distances and angles 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 3.3% to the final χ^2 . The hydrogen atoms were included in calculated positions, which were recalculated during the refinement using Materials Studio (Dassault, 2021). The U_{iso} were grouped by chemical similarity. The U_{iso} for the H atoms were fixed at $1.3\times$ the 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 6-term shifted Chebyshev polynomial, plus a peak at $5.76^\circ 2\theta$ to model the scattering from the Kapton capillary and any amorphous component.

The final refinement of 82 variables using 23 237 observations and 50 restraints yielded the residuals $R_{\text{wp}} = 0.0704$ and $\text{GOF} = 1.34$. The largest peak (0.11 \AA from C11) and hole (1.92 \AA from C14) in the difference Fourier map were $0.33(6)$ and $-0.27(6) e\text{\AA}^{-3}$, respectively. The largest errors in the difference plot (Figure 2) are in the shapes of some of the strong low-angle peaks.

The structure of imepitoin 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 \AA^{-1} leading to a $2 \times 1 \times 2$ mesh, and took $\sim 28 \text{ h}$. 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 that for Cl was that 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 $\sim 2.2 \text{ h}$.

III. RESULTS AND DISCUSSION

The root-mean-square (rms) Cartesian displacement between the Rietveld-refined and DFT-optimized structures of imepitoin is 0.025 \AA (Figure 3). The excellent agreement provides 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 4. The best view of the crystal structure is down the c -axis (Figure 5). The roughly planar molecules stack along the c -axis.

All of the bond distances and angles fall within the normal ranges indicated by a Mercury/Mogul Geometry check

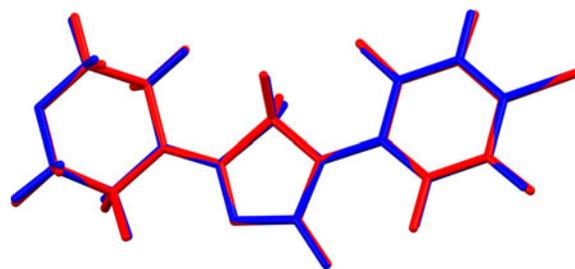


Figure 3. Comparison of the Rietveld-refined (red) and VASP-optimized (blue) structures of imepitoin. The rms Cartesian displacement is 0.025 \AA . Image generated using Mercury (Macrae *et al.*, 2020).

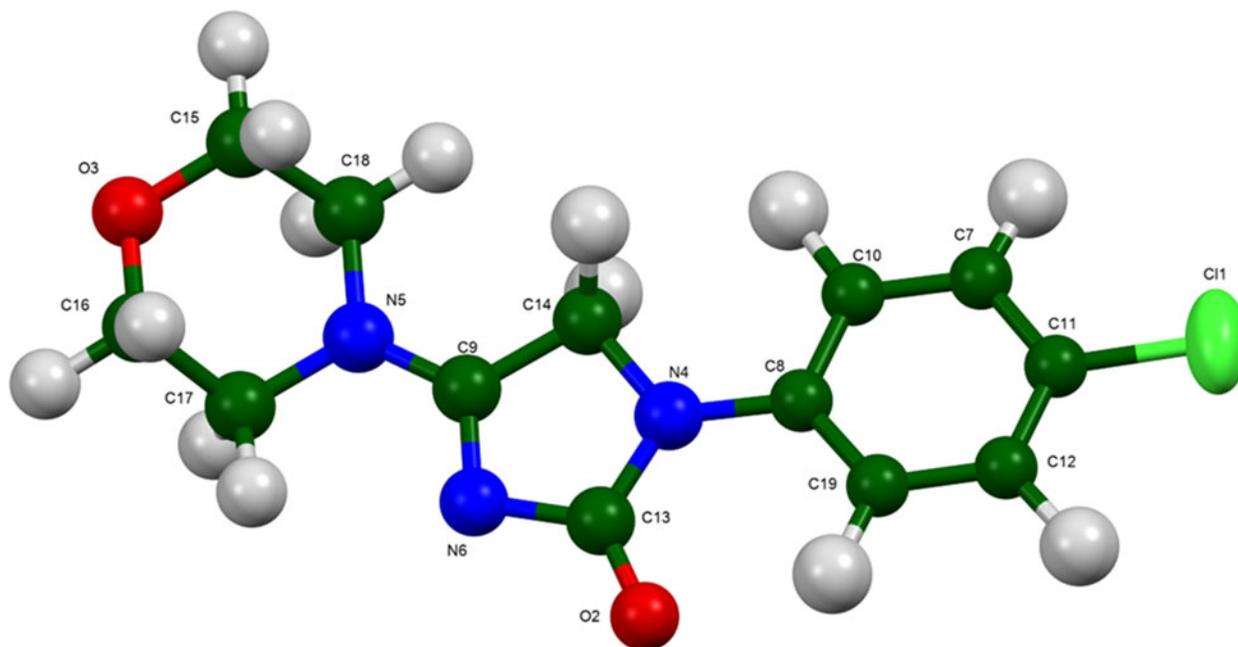


Figure 4. The asymmetric unit of imepitoin, with the atom numbering. The atoms are represented by 50% probability spheroids/ellipsoids. Image generated using Mercury (Macrae *et al.*, 2020).

(Macrae *et al.*, 2020). Quantum chemical geometry optimization of the imepitoin molecule (DFT/B3LYP/6-31G*/water) using Spartan '18 (Wavefunction, 2020) indicated that the observed conformation is within $1.2 \text{ kcal mol}^{-1}$ of the global minimum-energy 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 deformation terms. The

intermolecular energy is dominated by electrostatic attractions, which in this force field analysis also include hydrogen bonds. The hydrogen bonds are better analyzed using the results of the DFT calculation. There are no traditional hydrogen bonds in the structure (Table I), but several intramolecular and intermolecular C–H...O, C–H...N, and C–H...Cl hydrogen bonds contribute to the crystal energy.

The volume enclosed by the Hirshfeld surface of the imepitoin molecule (Figure 6; Hirshfeld, 1977; Turner *et al.*,

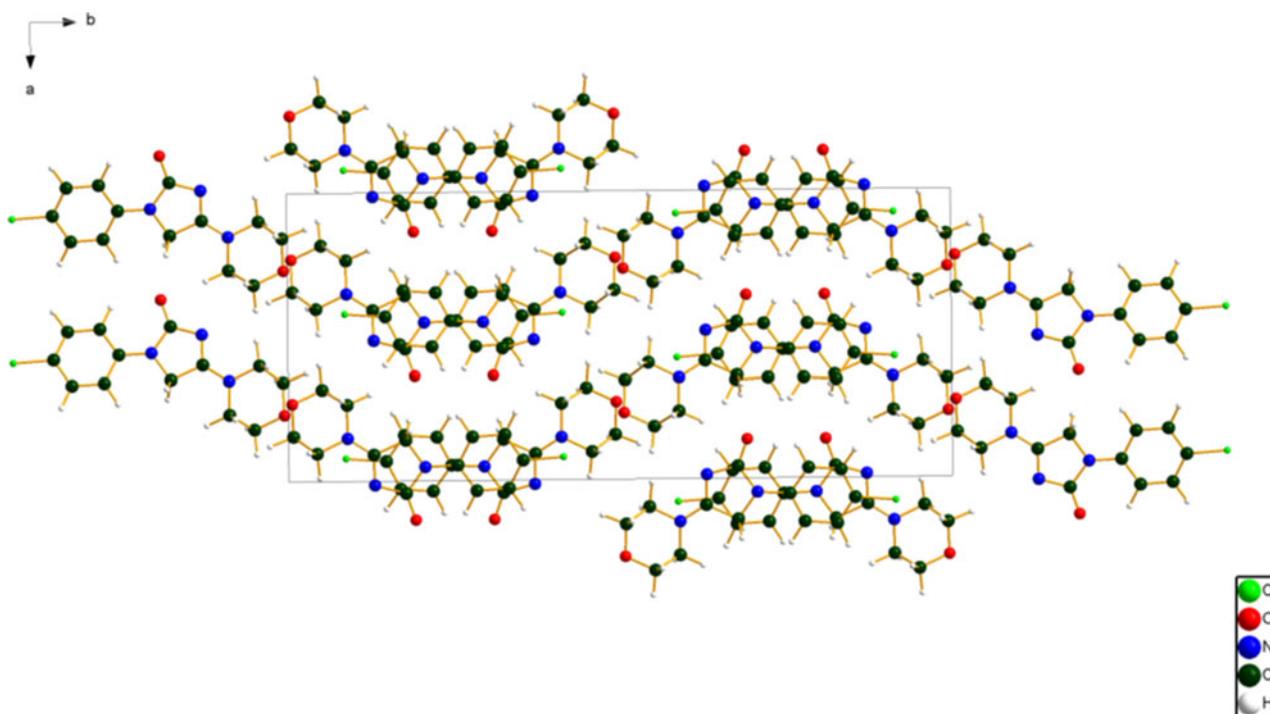


Figure 5. The crystal structure of imepitoin, viewed down the *c*-axis. Image generated using Diamond (Crystal Impact, 2022).

TABLE I. Hydrogen bonds (CRYSTAL17) in imepitoin

| H-Bond | D-H (Å) | H...A (Å) | D...A (Å) | D-H...A (°) | Overlap (e) |
|---------------|---------|--------------------|-----------|-------------|-------------|
| C14–H23...O2 | 1.102 | 2.128 | 3.200 | 163.3 | 0.028 |
| C19–H33...O2 | 1.087 | 2.177 ^a | 2.895 | 121.3 | 0.020 |
| C7–H20...O2 | 1.090 | 2.471 | 3.234 | 125.9 | 0.016 |
| C18–H32...O2 | 1.097 | 2.664 | 3.685 | 154.6 | 0.012 |
| C16–H28...O3 | 1.105 | 2.574 | 3.482 | 138.8 | 0.012 |
| C17–H29...N6 | 1.096 | 2.380 ^a | 2.857 | 104.4 | 0.010 |
| C15–H26...C11 | 1.097 | 3.059 | 3.995 | 143.5 | 0.012 |

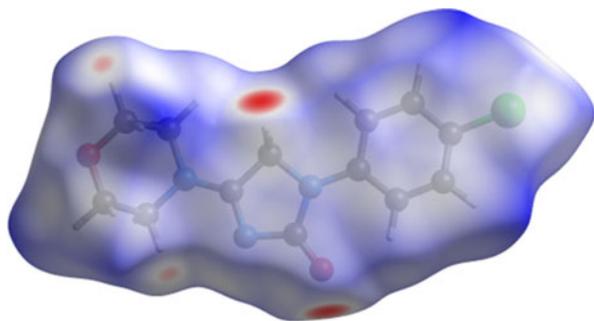
^aIntramolecular.

Figure 6. The Hirshfeld surface of imepitoin. Intermolecular contacts longer than the sums of the van der Waals radii are colored blue, and contacts shorter than the sums of the radii are colored red. Contacts equal to the sums of radii are white.

2017) is 315.98 \AA^3 , 98.02% of 1/8 the unit cell volume. The packing density is thus fairly typical. The only significant-close contacts (red in Figure 6) involve the hydrogen bonds. The volume/non-hydrogen atom is 17.0 \AA^3 .

The Bravais–Friedel–Donnay–Harker (Bravais, 1866; Friedel, 1907; Donnay and Harker, 1937) morphology suggests that we might expect platy morphology for imepitoin, with {010} as the major faces. A second-order spherical harmonic model was included in the refinement. The texture index was 1.002(0), indicating that preferred orientation was slight in this rotated capillary specimen. The powder pattern of imepitoin from this synchrotron dataset 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 conflict of interest to declare.

- Altomare, A., Cuocci, C., Giacovazzo, C., Moliterni, A., Rizzi, R., Corriero, N., and Falcicchio, A. (2013). “EXPO2013: a kit of tools for phasing crystal structures from powder data,” *J. Appl. Crystallogr.* **46**, 1231–1235.
- Antao, S. M., Hassan, I., Wang, J., Lee, P. L., and Toby, B. H. (2008). “State-of-the-art high-resolution powder X-ray diffraction (HRPXRD) illustrated with Rietveld refinement of quartz, sodalite, tremolite, and meionite,” *Can. Mineral.* **46**, 1501–1509.
- Bravais, A. (1866). *Etudes Cristallographiques* (Gauthier Villars, Paris).
- Bruno, I. J., Cole, J. C., Kessler, M., Luo, J., Motherwell, W. D. S., Purkis, L. H., Smith, B. R., Taylor, R., Cooper, R. I., Harris, S. E., and Orpen, A. G. (2004). “Retrieval of crystallographically-derived molecular geometry information,” *J. Chem. Inf. Sci.* **44**, 2133–2144.
- Crystal Impact - Dr. H. Putz & Dr. K. Brandenburg (2022). Diamond - Crystal and Molecular Structure Visualization. Kreuzherrenstr. 102, 53227 Bonn, Germany. Available at: <https://www.crystalimpact.de/diamond>.
- Dassault Systèmes (2021). *Materials Studio 2021* (BIOVIA, San Diego, CA).
- Donnay, J. D. H. and Harker, D. (1937). “A new law of crystal morphology extending the law of Bravais,” *Am. Mineral.* **22**, 446–447.
- Dovesi, R., Erba, A., Orlando, R., Zicovich-Wilson, C. M., Civalleri, B., Maschio, L., Rerat, M., Casassa, S., Baima, J., Salustro, S., and Kirtman, B. (2018). “Quantum-mechanical condensed matter simulations with CRYSTAL,” *WIREs Comput. Mol. Sci.* **8**, e1360.
- Friedel, G. (1907). “Etudes sur la loi de Bravais,” *Bull. Soc. Fr. Mineral.* **30**, 326–455.
- Gates-Rector, S. and Blanton, T. (2019). “The Powder Diffraction File: a quality materials characterization database,” *Powd. Diffr.* **39**(4), 352–360.
- Gatti, C., Saunders, V. R., and Roetti, C. (1994). “Crystal-field effects on the topological properties of the electron-density in molecular crystals - the case of urea,” *J. Chem. Phys.* **101**, 10686–10696.
- Groom, C. R., Bruno, I. J., Lightfoot, M. P., and Ward, S. C. (2016). “The Cambridge Structural Database,” *Acta Crystallogr. Sect. B: Struct. Sci., Cryst. Eng. Mater.* **72**, 171–179.
- Hirshfeld, F. L. (1977). “Bonded-atom fragments for describing molecular charge densities,” *Theor. Chem. Acta* **44**, 129–138.
- Kaduk, J. A., Crowder, C. E., Zhong, K., Fawcett, T. G., and Suchomel, M. R. (2014). “Crystal structure of atomoxetine hydrochloride (Strattera), $C_{17}H_{22}NOCl$,” *Powd. Diffr.* **29**(3), 269–273.
- Kresse, G. and Furthmüller, J. (1996). “Efficiency of ab-initio total energy calculations for metals and semiconductors using a plane-wave basis set,” *Comput. Mater. Sci.* **6**, 15–50.
- Lee, P. L., Shu, D., Ramanathan, M., Preissner, C., Wang, J., Beno, M. A., Von Dreele, R. B., Ribaud, L., Kurtz, C., Antao, S. M., Jiao, X., and Toby, B. H. (2008). “A twelve-analyzer detector system for high-resolution powder diffraction,” *J. Synchrotron Radiat.* **15**(5), 427–432.
- Macrae, C. F., Sovago, I., Cottrell, S. J., Galek, P. T. A., McCabe, P., Pidcock, E., Platings, M., Shields, G. P., Stevens, J. S., Towler, M., and Wood, P. A. (2020). “Mercury 4.0: from visualization to design and prediction,” *J. Appl. Crystallogr.* **53**, 226–235.
- Materials Design (2016). Medea 2.20.4 (Materials Design Inc., Angel Fire, NM).
- MDI (2021). *JADE Pro Version 8.1 (Computer Software)* (Materials Data, Livermore, CA, USA).
- Peintinger, M. F., Vilela Oliveira, D., and Bredow, T. (2013). “Consistent Gaussian basis sets of triple-zeta valence with polarization quality for solid-state calculations,” *J. Comput. Chem.* **34**, 451–459.
- Rundfeldt, C., Dost, R., Loscher, W., Tipold, A., Unverferth, K., and Lankau, H.-J. (2016). “Use of dihydroimidazolones for the treatment of dogs,” United States Patent 9,469,611 B2.

- Sykes, R. A., McCabe, P., Allen, F. H., Battle, G. M., Bruno, I. J., and Wood, P. A. (2011). "New software for statistical analysis of Cambridge Structural Database data," *J. Appl. Crystallogr.* **44**, 882–886.
- Toby, B. H. and Von Dreele, R. B. (2013). "GSAS II: the genesis of a modern open source all purpose crystallography software package," *J. Appl. Crystallogr.* **46**, 544–549.
- Turner, M. J., McKinnon, J. J., Wolff, S. K., Grimwood, D. J., Spackman, P. R., Jayatilaka, D., and Spackman, M. A. (2017). *CrystalExplorer17* (University of Western Australia). Available at: <http://hirshfeldsurface.net>.
- van de Streek, J. and Neumann, M. A. (2014). "Validation of molecular crystal structures from powder diffraction data with dispersion-corrected density functional theory (DFT-D)," *Acta Crystallogr. Sect. B: Struct. Sci., Cryst. Eng. Mater.* **70**(6), 1020–1032.
- Wang, J., Toby, B. H., Lee, P. L., Ribaud, L., Antao, S. M., Kurtz, C., Ramanathan, M., Von Dreele, R. B., and Beno, M. A. (2008). "A dedicated powder diffraction beamline at the advanced photon source: commissioning and early operational results," *Rev. Sci. Instrum.* **79**, 085105.
- Wavefunction, Inc. (2020). Spartan '18 Version 1.4.5, Wavefunction Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92612.