DATA REPORT

Powder X-ray diffraction of daclatasvir dihydrochloride Form N-2 (Daklinza®), $C_{40}H_{52}N_8O_6Cl_2$

Ryan L. Hodge,[1] James A. Kaduk ®,[1,a)] Amy M. Gindhart,[2] and Thomas N. Blanton ®[2]

[1]North Central College, 131 S. Loomis St., Naperville, Illinois 60540, USA
[2]ICDD, 12 Campus Blvd., Newtown Square, Pennsylvania 19073-3273, USA

The crystal structure of daclatasvir dihydrochloride Form N-2 (Daklinza®) has been refined using synchrotron X-ray powder diffraction data and optimized using density functional theory techniques. Daclatasvir dihydrochloride, Form N-2, crystallizes in space group $P1$ (#1) with $a = 7.54808$ (15), $b = 9.5566$ (5), $c = 16.2641$ (11) Å, $\alpha = 74.0642$ (24), $\beta = 84.0026$ (13), $\gamma = 70.6322$ (5)°, $V = 1064.150$ (11) Å^3, and $Z = 1$. The hydrogen bonds were identified and quantified. Strong N–H⋯Cl hydrogen bonds link the cations and anions in chains along the a-axis. The powder pattern has been submitted to ICDD® for inclusion in the Powder Diffraction File™ (PDF®). © *The Author(s), 2021. Published by Cambridge University Press on behalf of International Centre for Diffraction Data.*
[doi:10.1017/S0885715621000397]

Key words: daclatasvir dihydrochloride, Daklinza, Rietveld refinement, density functional theory

I.

Daclatasvir, under the trade name Daklinza, is used in combination with other drugs to treat hepatitis C. No daclatasvir crystal structures are reported in the Cambridge Structural Database (Groom *et al.*, 2016) as of the completion of the current study. A search of the primary literature yielded International Patent Application WO 2009/020828 A1 (Kim *et al.*, 2009; Bristol-Myers Squibb), which reports the crystal structure of daclatasvir dihydrochloride Form N-2, determined using single-crystal X-ray measurements. A powder diffraction pattern for daclatasvir dihydrochloride Form N-2 is provided in WO 2009/020828 A1 (Figure 1); however, the *d*-spacings of only 11 diffraction peaks without intensity data are reported supporting the need for a complete powder diffraction data set that can be used as a reference for phase identification. Two additional daclatasvir dihydrochloride forms, Forms L1 and Form L2, are reported in International Patent Application WO 2018/007984 A1 (Sanpuhi *et al.*, 2018; Lupin). The reported Forms L1 and L2 powder X-ray diffraction peak data do not match the data for Form N-2.

In this work, the sample was ordered from TargetMol (Batch #115989) and analyzed as-received. The diffraction data for this study were collected on beamline 11-BM at the Advanced Photon Source, Argonne National Laboratory. The room temperature (295 K) crystal structure was refined (Figure 2) using synchrotron powder diffraction data ($\lambda = 0.458119$ (2) Å) and optimized using density functional theory techniques. The structure was refined using GSAS-II (Toby and Von Dreele, 2013) with $d_{min} = 1.058$ Å. Commercial daclatasvir dihydrochloride (CAS #1009119-65-6) crystallizes in space group $P1$ (#1) with $a = 7.54808$ (15), $b = 9.5566$ (5), $c = 16.2641$ (11) Å, $\alpha = 74.0642$ (24), $\beta = 84.0026$ (13), $\gamma = 70.6322$ (5)°, $V = 1064.150$ (11) Å^3, and $Z = 1$. All bond distances and angles were restrained using the results of a Mercury Mogul Geometry Check ((Bruno *et al.*, 2004; Sykes *et al.*, 2011; Figure 3). The DFT optimization was carried out, along with a Mulliken population analysis, using CRYSTAL14 (Dovesi *et al.*, 2014); the B3LYP functional and 8 k-points were used. The basis sets for the H, C, N, and O atoms were those of Gatti *et al.* (1994), and the basis set for Cl was that of Peintinger *et al.* (2013).

As expected, all four protonated nitrogen atoms of the imidazole rings form strong hydrogen bonds to the chloride anions (Table I). These N–H⋯Cl hydrogen bonds link the molecules along the a-axis. Several C–H groups act as donors in C–H⋯Cl bonds to the chloride anions. Both inter- and intramolecular N–H⋯O hydrogen bonds are present. The energies of the N–H⋯O hydrogen bonds were calculated using the correlation of Wheatley and Kaduk (2019). Several inter- and intramolecular C–H⋯O hydrogen bonds also contribute to the lattice energy.

The X-ray powder diffraction pattern and structure data from this study have been submitted to ICDD for inclusion in the Powder Diffraction File (Gates-Rector and Blanton, 2019).

II. DEPOSITED DATA

CIF files were deposited with ICDD. You may request this data from info@icdd.com.

a)Author to whom correspondence should be addressed. Electronic mail: kaduk@polycrystallography.com
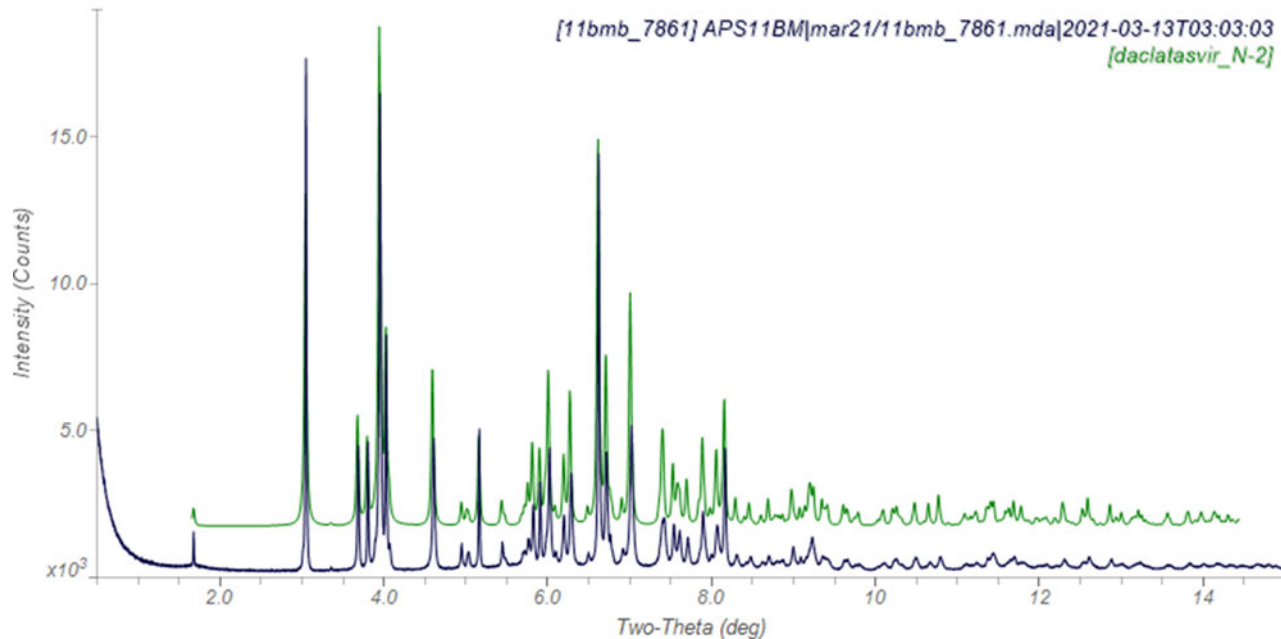
Figure 1. Comparison of the synchrotron powder diffraction pattern from this study of daclatasvir dihydrochloride Form N-2 (black) to the powder diffraction pattern of Form N-2 (green) calculated from the structure of Kim *et al.* (2009).
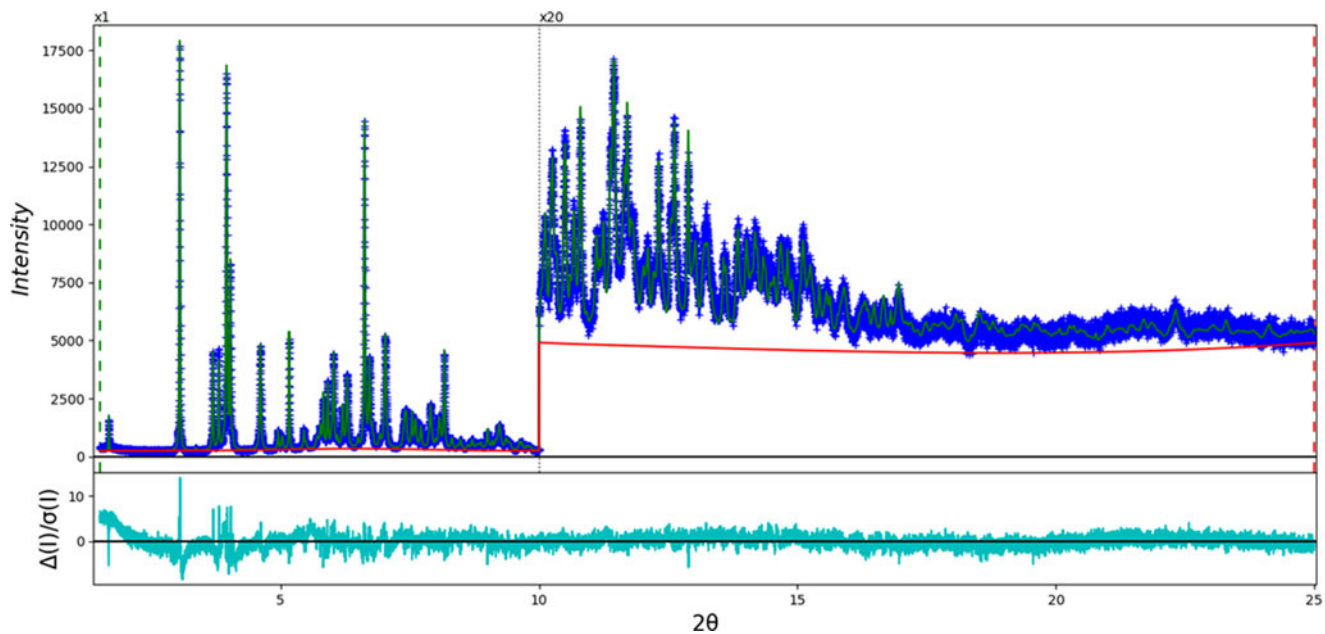

Figure 2. The Rietveld plot for daclatasvir dihydrochloride Form N-2. The blue crosses represent the observed data points, and the green line is the calculated pattern. The cyan curve is the normalized error plot. The vertical scale has been multiplied by a factor of 20× for $2\theta > 10.0°$.
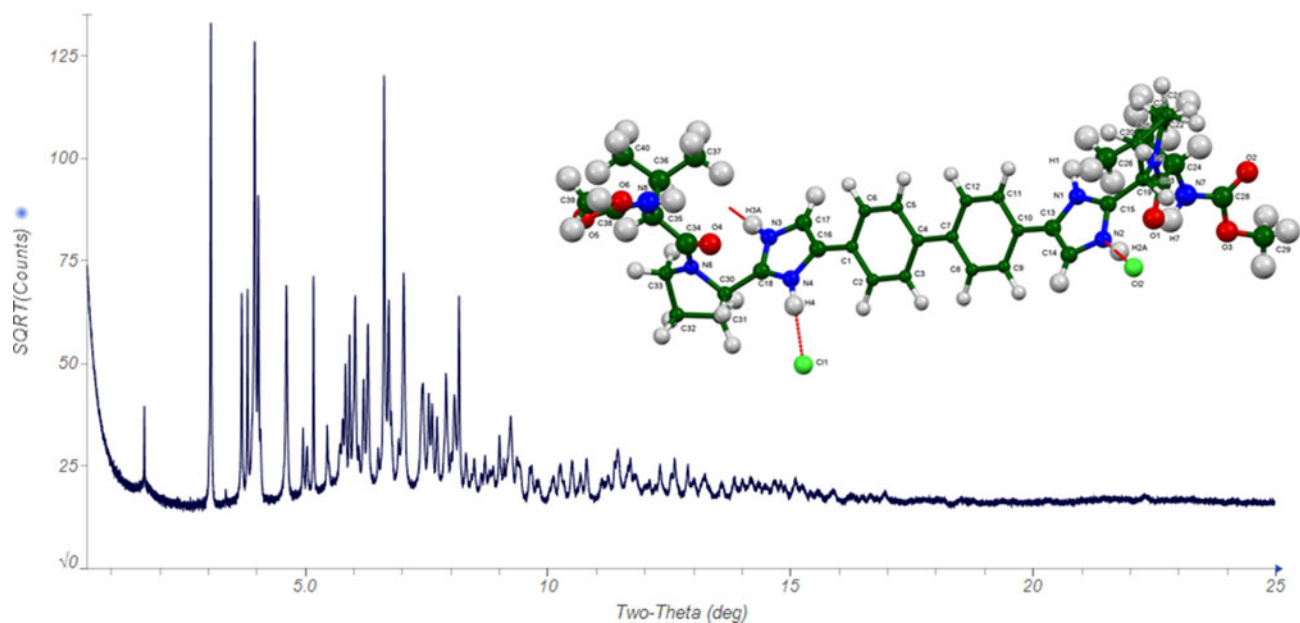
Figure 3. The powder diffraction pattern of daclatasvir dihydrochloride Form N-2 from this study (note that the vertical scale is the square root of the observed intensity) and the refined molecular structure (inset). The atoms are represented by 50% probability spheroids.

TABLE I. Hydrogen bonds (CRYSTAL14) in daclatasvir dihydrochloride, Form N-2

H-bond	D–A (Å)	H···A (Å)	D···A (Å)	D–H···A (°)	Overlap (e)	E (kcal mol^{-1})
N3–H3A···Cl1	1.048	2.025	3.053	166.2	0.113	
N2–H2A···Cl2	1.044	2.036	3.030	158.3	0.102	
N1–H1···Cl2	1.042	2.067	3.075	162.1	0.096	
N4–H4···Cl1	1.042	2.069	3.057	157.3	0.093	
C11–H11···Cl2	1.087	2.695	3.715	156.2	0.034	
C2–H2···Cl1	1.087	2.845	3.817	148.9	0.028	
C8–H8···Cl2	1.083	2.644	3.591	145.7	0.027	
C5–H5···Cl1	1.084	2.688	3.651	147.7	0.027	
C3–H3···Cl2	1.085	2.812	3.838	157.7	0.026	
C33–H33A···Cl1	1.095	2.723	3.663	143.6	0.025	
C12–H12···Cl1	1.085	3.089	4.064	149.9	0.016	
C20–H20A···Cl2	1.094	3.082	3.890	131.1	0.012	
C36–H36···Cl1	1.096	3.160	4.073	141.2	0.010	
N8–H8A···O4	1.017	2.213[a]	2.627	102.4	0.025	3.6
N7–H7···O1	1.015	2.263[a]	2.627	99.3	0.024	3.6
N8–H8A···O3	1.017	2.321	3.298	160.6	0.022	3.4
N7–H7···O6	1.015	2.281	3.209	151.4	0.022	3.4
C21–H21B···O5	1.093	2.514	3.409	138.3	0.016	
C24–H24···O2	1.094	2.408[a]	2.870	103.6	0.015	
C35–H35···O5	1.093	2.423[a]	2.879	103.3	0.015	
C27–H27C···O1	1.094	2.600	3.665	164.2	0.014	
C32–H32B···O2	1.093	2.594	3.468	136.4	0.013	
C19–H19···O5	1.096	2.511	3.351	132.6	0.012	
C39–H39B···O1	1.088	2.538	3.387	134.1	0.012	
C30–H30···O2	1.094	2.581	3.377	128.9	0.011	
C29–H29B···O4	1.087	2.428	3.200	126.8	0.011	

[a]Intramolecular.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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.

Dovesi, R., Orlando, R., Erba, A., Zicovich-Wilson, C. M., Civalleri, B., Casassa, S., Maschio, L., Ferrabone, M., De La Pierre, M., D-Arco, P., Noël, Y., Causà, M., and Kirtman, B. (**2014**). "CRYSTAL14: a program for the ab initio investigation of crystalline solids," Int. J. Quantum Chem. **114**, 1287–1317.

Gates-Rector, S. and Blanton, T. N. (**2019**). "The powder diffraction file: a quality materials characterization database," Powder Diff. **34**(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.

Kim, S., Gao, Q., and Yang, F. (**2009**) "Crystalline form of methyl ((1S)-1-(((2S)-2-(4'(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl)carbamate dihydrochloride salt," International Patent Application WO 2009/020828 A1.

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.

Sanpuhi, P., Shfvdavkar, R. B., Singh, G. P., Ray, P. C., Singh, G. P., Sadaphal, V. A., Rajput, L. D., and Lande, H. M. (**2018**). "Crystalline forms of daclatasvir dihydrochloride," International Patent Application WO 2018/007984 A1.

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.

Wheatley, A. M. and Kaduk, J. A. (**2019**). "Crystal structures of ammonium citrates," Powder Diffr. **34**, 35–43.