# Powder X-ray diffraction of acalabrutinib dihydrate Form III, $C_{26}H_{23}N_7O_2(H_2O)_2$

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The crystal structure of acalabrutinib dihydrate Form III has been refined using synchrotron X-ray powder diffraction data, and optimized using density functional techniques. Acalabrutinib dihydrate Form III crystallizes in space group $P2_1$ (#4) with $a = 8.38117(5)$, $b = 21.16085(14)$, $c = 14.12494(16)$ Å, $\beta = 94.5343(6)°$, $V = 2497.256(20)$ Å$^3$, and $Z = 4$ ($Z' = 2$) at 295 K. The crystal structure consists of herringbone layers parallel to the *ac*-plane. Hydrogen bonds between the acalabrutinib and water molecules generate a three-dimensional framework. Each water molecule acts as a donor in two hydrogen bonds and as an acceptor in at least one hydrogen bond. Amino groups and pyridine N atoms link the acalabrutinib molecules into dimers. The powder pattern has been submitted to ICDD for inclusion in the Powder Diffraction File™ (PDF®).
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Acalabrutinib (sold under the brand name Calquence) is used to treat various types of non-Hodgkin lymphoma like chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Acalabrutinib is a kinase inhibitor used for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior cancer therapy. The systematic name (CAS Registry Number 1420477-60-6) is 4-[8-amino-3-[(2*S*)-1-but-2-ynoylpyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl]-*N*-pyridin-2-ylbenzamide. The crystal structures of Forms I (anhydrous) and III (dihydrate, CAS Registry Number 2648852-74-6) of acalabrutinib, as well as powder data for several other forms and derivatives, are reported in US Patent 9,796,721 B2 (Blatter et al., 2017; Acerta Pharma B.V.). 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).

The synchrotron X-ray powder diffraction pattern (Figure 1) of a commercial reagent (purchased from TargetMol, lot #119209) was measured at 11-BM at APS (Antao et al., 2008; Lee et al., 2008; Wang et al., 2008) using a wavelength of 0.459744(2) Å. The pattern was indexed using JADE Pro (MDI, 2023). The unit cell matched that reported for the single-crystal structure of Form III dihydrate by Blatter et al. (2017), which is not in the Cambridge Structural Database. Only the major component of a disordered portion of the molecule was included in the model. The structure was refined (Figure 2) using GSAS-II (Toby and Von Dreele, 2013), and optimized using VASP (Kresse and Furthmüller, 1996). A single-point density functional calculation (fixed experimental cell) and population analysis was carried out using CRYSTAL23 (Erba et al., 2023).

The crystal structure (Figure 3) consists of herringbone layers parallel to the *ac*-plane, or alternatively as slightly wavy layers parallel to the *bc*-plane. Hydrogen bonds between the acalabrutinib and water molecules generate a three-dimensional framework. Each water molecule acts as a donor in two hydrogen bonds (Table I) and as an acceptor in at least one hydrogen bond. The amino groups N19 and N54 of the two independent molecules, with the pyridine N atoms N15 and N50, link the acalabrutinib molecules into dimers. The amino groups N25 and N60 form hydrogen bonds to water molecules. The energies of the O–H···O hydrogen bonds were calculated using the correlation of Rammohan and Kaduk (2018), and the energies of the N–H···O hydrogen bonds were calculated using the correlation of Wheatley and Kaduk (2019). A variety of C–H···O and C–H···N hydrogen bonds also contribute to the lattice energy.

## I. DEPOSITED DATA

The powder pattern of acalabrutinib dihydrate Form III from this synchrotron data set has been submitted to ICDD for inclusion in the Powder Diffraction File. The Crystallographic Information Framework (CIF) files

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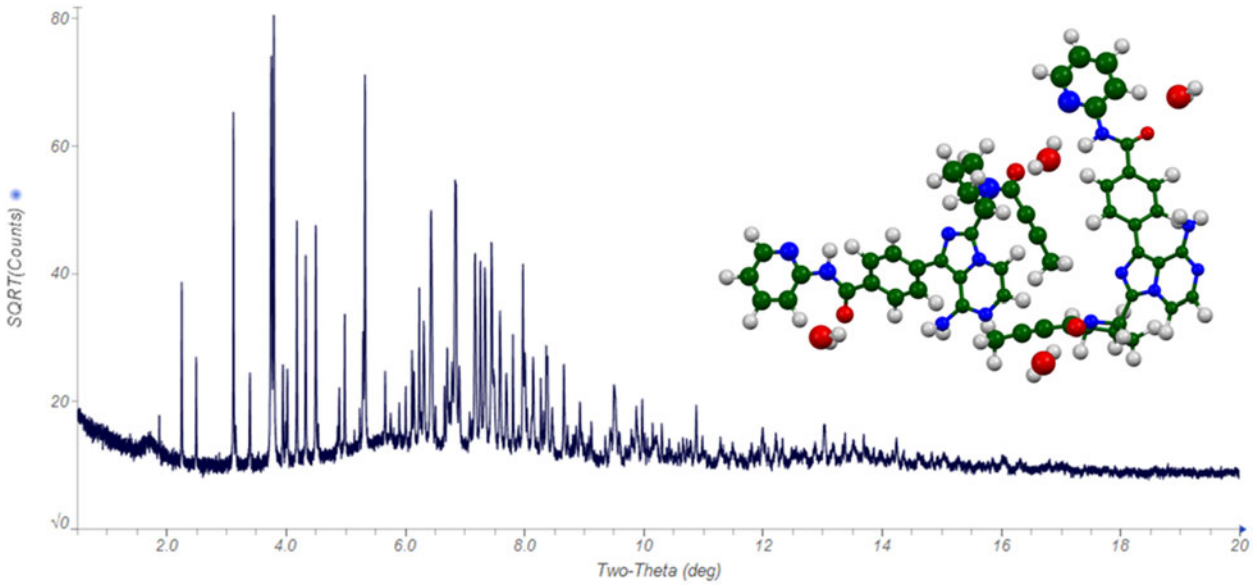


Figure 1. The synchrotron X-ray powder diffraction pattern of acalabrutinib dihydrate Form III. The *y*-axis is the square root of the intensity. The inset shows a ball-and-stick drawing of the asymmetric unit of acalabrutinib dihydrate. Image generated using JADE Pro (MDI, 2023) and Mercury (Macrae et al., 2020).

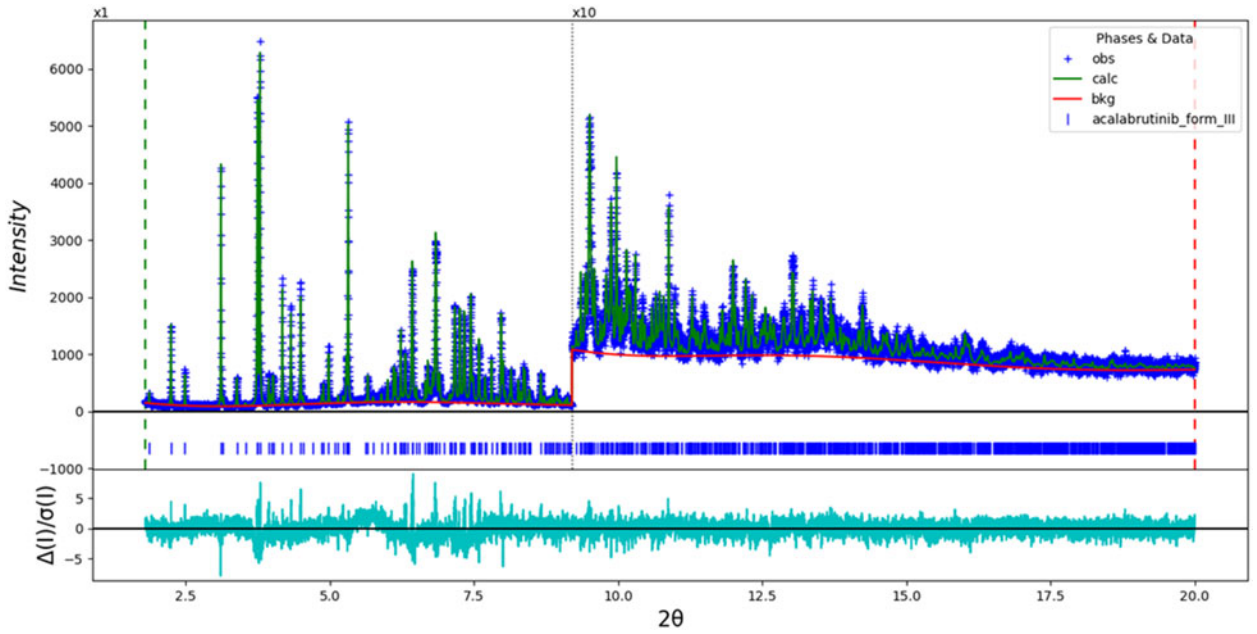


Figure 2. The Rietveld plot for the refinement of acalabrutinib dihydrate Form III. The blue crosses represent the observed data points, and the green line is the calculated pattern. The cyan curve is the normalized error plot, and the red line is the background curve. The vertical scale has been multiplied by a factor of 10× for $2\theta > 9.2°$.



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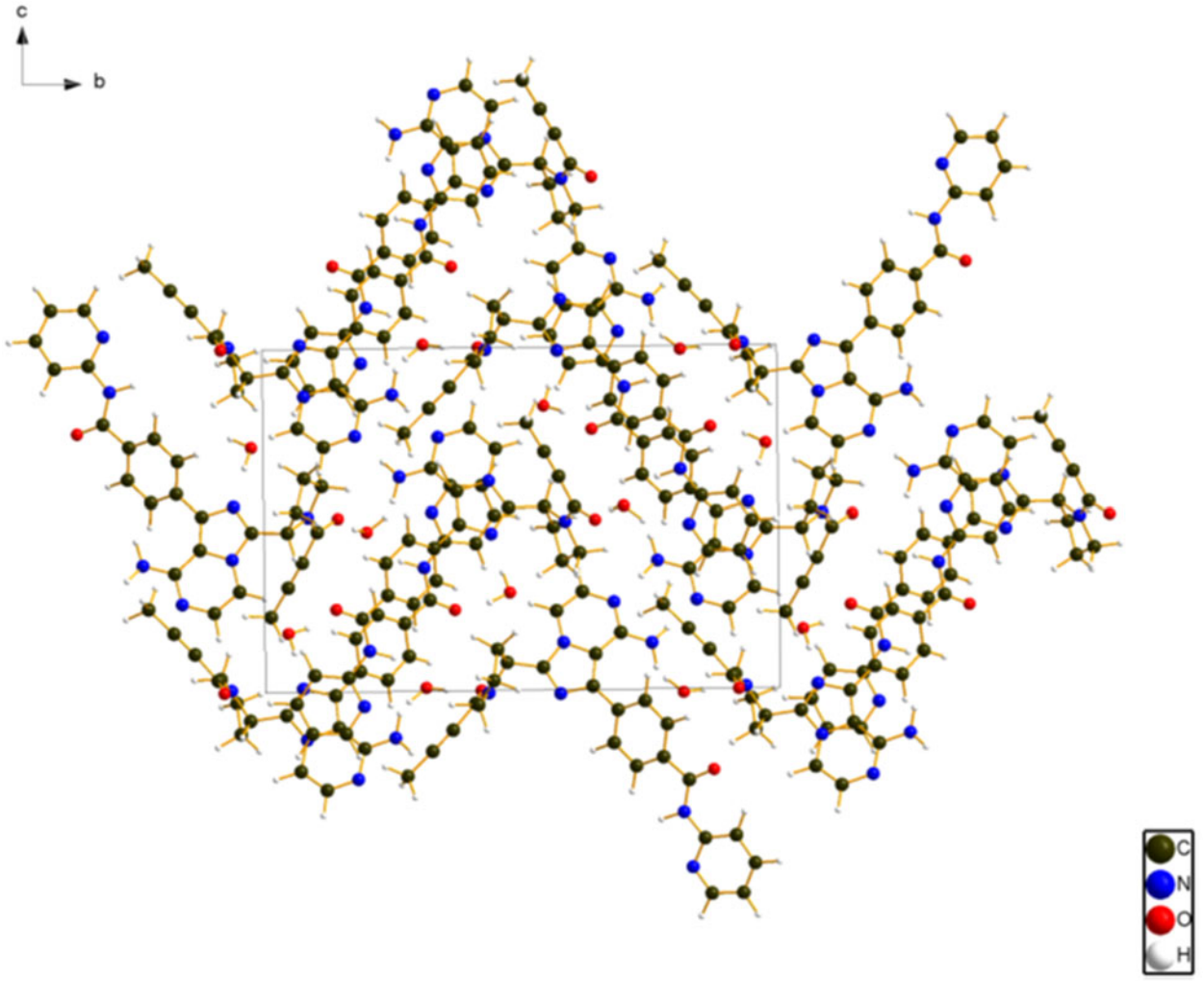


Figure 3. The crystal structure of acalabrutinib dihydrate Form III, viewed down the *a*-axis. Image generated using Diamond (Crystal Impact, 2023).

TABLE I. Hydrogen bonds (CRYSTAL23) in acalabrutinib dihydrate Form III.

| H-Bond | D-H (Å) | H···A (Å) | D···A (Å) | D-H···A (°) | Overlap (*e*) | E (kcal mol$^{-1}$) |
|---|---|---|---|---|---|---|
| O74–H128···N11 | 0.996 | 1.862 | 2.857 | 177.4 | 0.054 | |
| O74–H127···O70 | 0.975 | 2.611 | 3.437 | 142.7 | 0.010 | 5.5 |
| C29–H93···O74 | 1.092 | 2.331 | 3.361 | 156.5 | 0.026 | |
| O73–H126···N46 | 0.989 | 1.953 | 2.938 | 173.5 | 0.048 | |
| O73–H125···O35 | 0.983 | 1.979 | 2.932 | 162.5 | 0.037 | 10.5 |
| C17–H86···O73 | 1.084 | 2.444 | 3.247 | 129.8 | 0.018 | |
| C1–H75···O73 | 1.102 | 2.276 | 3.352 | 164.7 | 0.036 | |
| O72–H124···N27 | 0.994 | 1.922 | 2.808 | 147.0 | 0.055 | |
| O72–H123···O69 | 0.993 | 1.809 | 2.800 | 175.5 | 0.055 | 12.8 |
| N54–H111···O72 | 1.017 | 2.560 | 3.191 | 119.9 | 0.015 | |
| C42–H104···O72 | 1.096 | 2.547 | 3.540 | 150.0 | 0.013 | |
| N25–H91···O72 | 1.037 | 1.885 | 2.848 | 152.9 | 0.076 | 6.4 |
| C22–H90···O72 | 1.091 | 2.620 | 3.524 | 139.7 | 0.012 | |
| O71–H122···N62 | 0.992 | 1.941 | 2.819 | 146.1 | 0.053 | |
| O71–H121···O34 | 0.993 | 1.744 | 2.732 | 172.7 | 0.058 | 13.2 |
| N60–H114···O71 | 1.038 | 1.850 | 2.819 | 153.8 | 0.073 | 6.2 |
| C57–H113···O71 | 1.091 | 2.472 | 3.439 | 147.1 | 0.020 | |
| C8–H83···O71 | 1.101 | 2.433 | 3.508 | 165.0 | 0.026 | |
| N54–H110···N15 | 1.041 | 1.943 | 2.983 | 177.1 | 0.070 | |
| N19–H87···N50 | 1.043 | 1.908 | 2.949 | 175.8 | 0.076 | |
| N19–H88···O34 | 1.016 | 2.410 | 3.068 | 121.7 | 0.014 | |

*Continued*



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TABLE I. Continued

| H-Bond | D-H (Å) | H···A (Å) | D···A (Å) | D-H···A (°) | Overlap (*e*) | E (kcal mol$^{-1}$) |
|---|---|---|---|---|---|---|
| C67–H119···O70 | 1.089 | 2.399[a] | 2.775 | 98.4 | 0.015 | |
| C66–H118···O70 | 1.085 | 2.172[a] | 2.854 | 118.5 | 0.013 | |
| C51–H108···O34 | 1.090 | 2.284 | 3.279 | 150.8 | 0.021 | |
| C44–H107···O70 | 1.100 | 2.354 | 3.221 | 134.4 | 0.013 | |
| C36–H100···N19 | 1.100 | 2.553 | 3.609 | 160.6 | 0.010 | |
| C36–H99···C63 | 1.100 | 2.537 | 3.561 | 154.4 | 0.010 | |
| C32–H96···O35 | 1.091 | 2.511[a] | 2.834 | 95.6 | 0.011 | |
| C31–H93···O35 | 1.086 | 2.351[a] | 2.937 | 112.1 | 0.011 | |
| C30–H94···O69 | 1.090 | 2.313 | 3.326 | 153.8 | 0.022 | |
| C9–H84···O35 | 1.099 | 2.691 | 3.730 | 157.4 | 0.013 | |

[a]Intramolecular.

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.

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## CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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