Electronic Supplementary Material (ESI) for CrystEngComm.

SUPPORTING INFORMATION FOR:

An Unprecedented Case of Dodecamorphism: The Twelfth Polymorph of Aripiprazole Formed by Seeding with Its Active Metabolite

Tarek A. Zeidan,[a,] Jacob T. Trotta,[a] Pranoti A. Tilak,[a] Mark A. Oliveira,[a] Renato A. Chiarella,[a] Bruce M. Foxman,[b] Örn Almarsson,[a,c] and Magali B. Hickey[a]*

[a] Alkermes, Inc., 852 Winter Street, Waltham, MA 02451-1420.

[b] Department of Chemistry, Brandeis University, 415 South Street, MS 015, Waltham MA 02454.

[c] Current address: Moderna Inc., 200 Technology Square, Cambridge, MA 02139, USA.

* To whom correspondence should be addressed. Email: tarek.zeidan@alkermes.com

Phone: +1 781 609 6538. Fax: +1 781 609 5855.

Microscopy. Crystal morphology was determined with an Olympus BX51 Reflected Polarized Light Microscope.

Thermal Analysis. Differential scanning calorimetry (DSC) curves were acquired using a TA Instruments Q1000. Typically, 1 – 2 mg of sample was weighed into an aluminum pan, sealed with a pinhole lid, and heated at 10 °C/min from room temperature (RT) to 200 °C. Thermal gravimetric analysis (TGA) was performed on a TA Instruments TGA Q500 or Q5000. Samples of 10 – 30 mg were heated at 10 °C/min from RT to 250 °C. The data were processed using Universal Analysis 2000 Version 4.3A.

Powder X-ray Diffraction (PXRD). PXRD was performed on a Rigaku DMAX Rapid diffractometer equipped with a CCD (charged coupled device) camera (Rigaku/MSC, Woodlands, TX) with an attached capillary goniometer with φ rotation and ω oscillation and a collimated Cu Kα radiation (1.54178 Å) operating at 46 kV / 40 mA. Data were processed using DIFFRAC.EVA V3.0.

Single Crystal X-ray Diffraction (SCXRD) of Aripiprazole Form IX (CCDC reference number 1422248). A suitable single crystal identified by microscopy was mounted on a Nylon loop using very small amount of Paratone oil and placed in a cooled nitrogen gas stream at 173 K on an APEX II CCD fine focus sealed tube diffractometer with graphite-monochromated Mo Kα (0.71073 Å) radiation. All diffractometer manipulations, including data collection, integration, scaling, and absorption corrections were carried out using the Bruker Apex2 software.[1] Data were measured using a series of combinations of phi and omega scans with 10 s frame exposures and 0.5° frame widths.

The final refinement of this structure was carried out at Brandeis University. The structure was refined (full-matrix-least squares) using the Oxford University *Crystals for*

Windows program.[2] All non-hydrogen atoms were refined using anisotropic displacement parameters. After location of H atoms on electron-density difference maps, the H atoms attached to ordered atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C---H in the range 0.93--0.98 Å and U_{iso} (H) in the range 1.2-1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints.[3] Inspection of the ADPs for atoms C(26) and C(27) strongly indicated disorder; accordingly, these were split and refined, using ADPs for the C(270)/C(271) pair and isotropic displacement parameters for the C(260)/C(261) pair. (The interatomic separation between atoms C270 and C271 is 0.77 Å, and the separation between atoms C260 and C261 is 0.46 Å. As one might expect, with data collection carried out to a resolution of 0.83 Å, atoms C260 and C261 could not be modeled satisfactorily by using ADP's (interpenetrated displacement ellipsoids result!). Thus C260 and C261 were modeled by using isotropic displacement parameters.) The occupancies of the two ring orientations [C(260)/C(270) and C(261)/C(271)] were constrained to sum to 1.0. Populations of the two components are equal within experimental error [0.500(11)]. The final least-squares refinement converged to $R_1 = 0.0345$ ($I > 2\sigma(I)$, 3118 data) and $wR_2 = 0.0824$ (F^2, 3931 data, 280 parameters).

1. Apex2, Version 2 User Manual, M86-E01078, Bruker Analytical X-ray Systems, Madison, WI, June 2006.

2. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Cryst.* **2003**, *36*, 1487; Prout, C.K;. Pearce, L.J. CAMERON, Chemical Crystallography Laboratory, Oxford, UK, 1996.

3. Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Cryst.* **2010**, *43*, 1100–1107.

A NOTE ON DISORDERED RING CONFORMATIONS. Cremer-Pople ring puckering analysis, as carried out using the program *PLATON,* reveals the following information:

a) For the six-membered ring involving atoms C261 and C271, Q = 0.390(6) Å, Q_2 = 0.305(4) Å, Q_3 = 0.243(4) Å, θ = 51.5º and φ_2 = 191.3(7)º .

b) For the six-membered ring involving atoms C260 and C270, Q = 0.416(6) Å, Q_2 = 0.322(4) Å, Q_3 = -0.263(4) Å, θ = 129.3º and φ_2 = 32.3(7)º [If we compare the two rings after a transformation to place each in the same absolute configuration, the values for θ and φ_2 become 50.7(6)º and = 212.3(7)º. Both rings have nearly half-chair configurations, and the puckering parameters are quite similar.

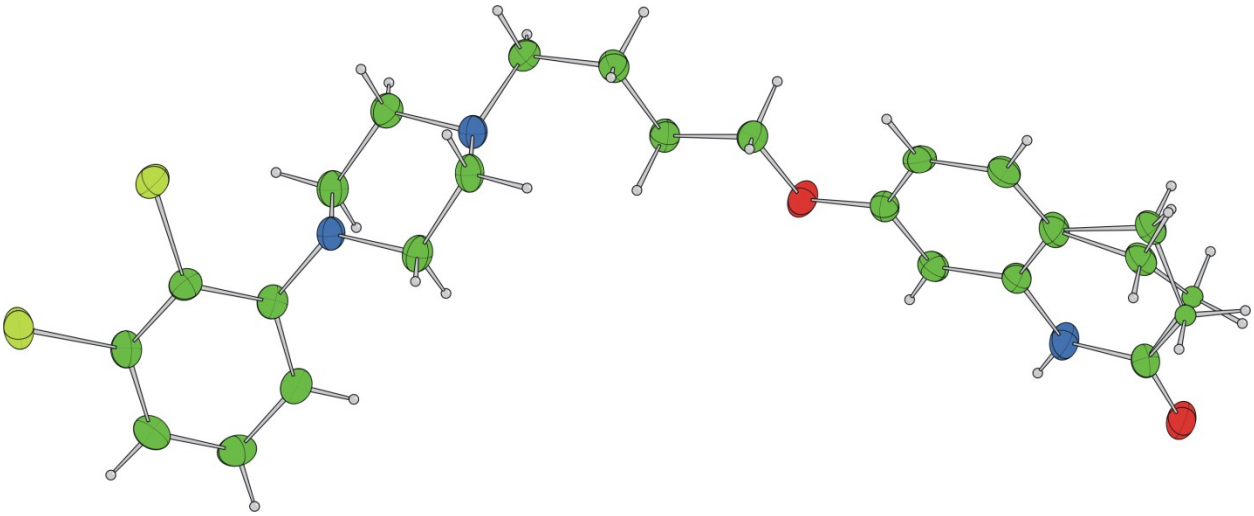

Fig. S 1. Molecular structure of APZ Form IX, showing 50% displacement ellipsoids for atoms refined by using anisotropic displacement parameters.

APZ Form IX:

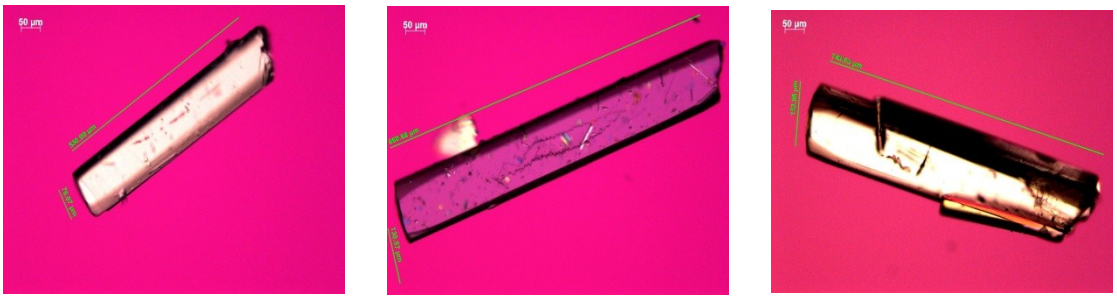

Fig. S 2. Microscope images of APZ Form IX single crystals used in HPLC purity analysis.

Determining the purity of APZ form IX by HPLC. Single crystals (Fig. S 2) of APZ form IX were dissolved individually in a 9:1 THF/water diluent and run on HPLC with a method capable of separating APZ and dAPZ. Table S 1 summarizes the HPLC method developed to separate dAPZ and APZ with retention times 1.9 and 2.2 min, respectively, (Fig. S 3). Fig. S 4 shows an example of HPLC chromatogram of a single crystal of APZ form IX with >99.9% purity and no detectable dAPZ (>0.01%). The method can detect up to 0.01% dAPZ per area.

HPLC analysis was performed using a Waters Alliance 2695 equipped with a Photodiode Array detector. Data were analyzed using Empower software.

Table S 1. HPLC Method

Mobile A	100mM sodium perchlorate, 20mM Phosphate Buffer, 20% MeCN	
Mobile B	100mM sodium perchlorate, 90% MeCN	
Diluent	90% THF, 10% water	
Column	Zorbax SB-C8 Rapid Resolution 3.5 µm, 4.6 x 75 mm ID	
Injection Volume	10 µL	
Column Temp	30 °C	
Wavelength	280 nm	
Flow rate	1.5 mL/min	
Gradient:		
Time	% Mobile A	% Mobile B
0.01	65	35
1.00	65	35
2.00	25	75
7.00	25	75

7.50	65	35
10.00	65	35

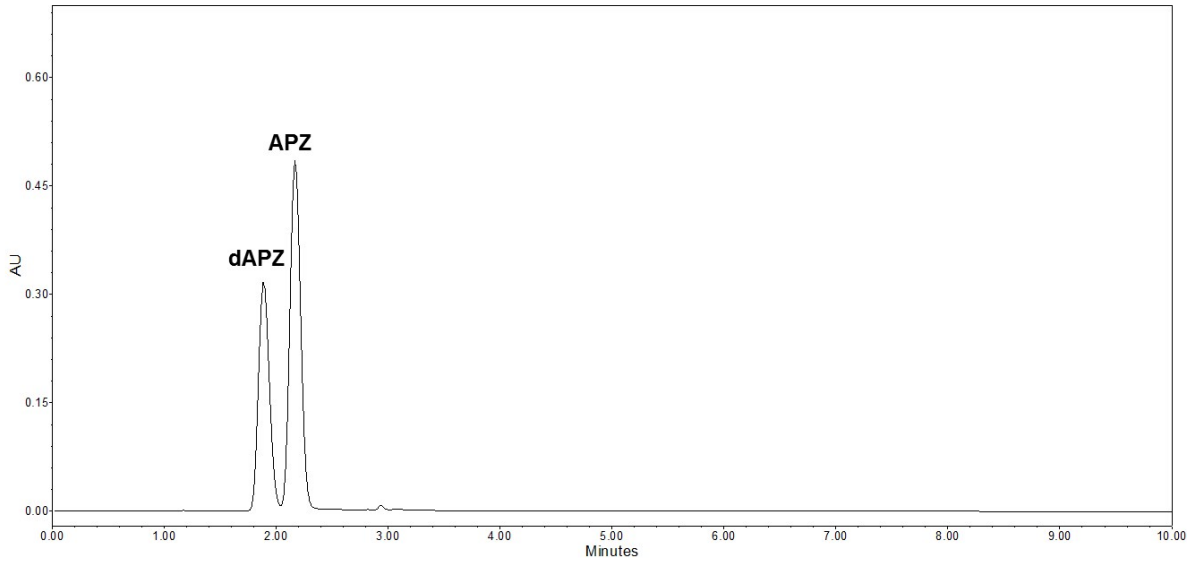

Fig. S 3. HPLC chromatogram of a solution of APZ and dAPZ mixture showing the two peaks resolved.

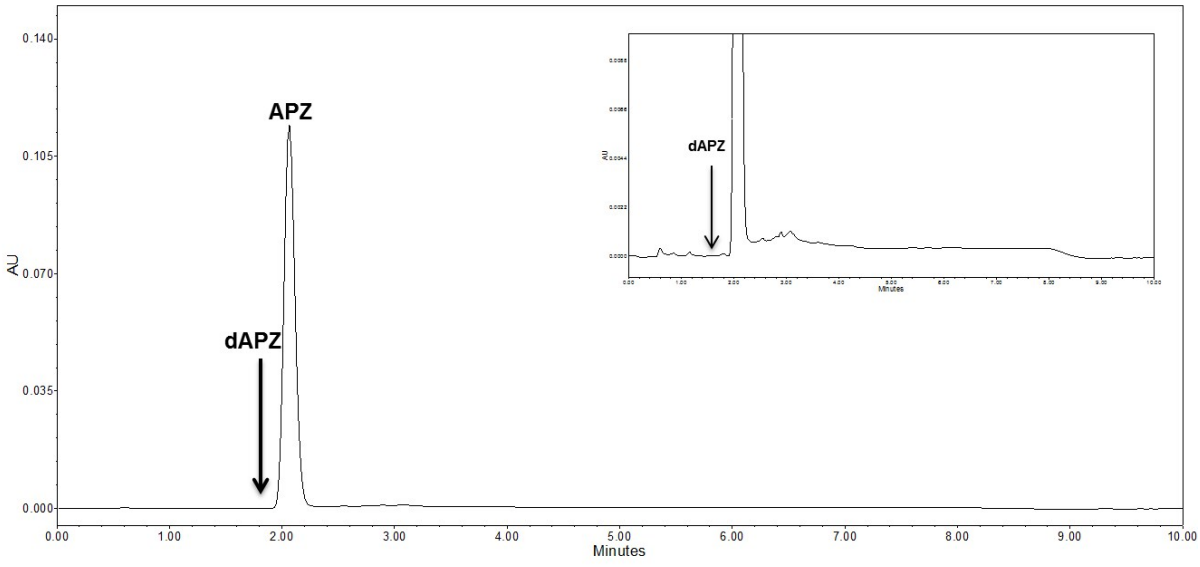

Fig. S 4. HPLC chromatogram of a single crystal of APZ from IX showing the absence of dAPZ. The inset provides a zoomed view of the y-axis.

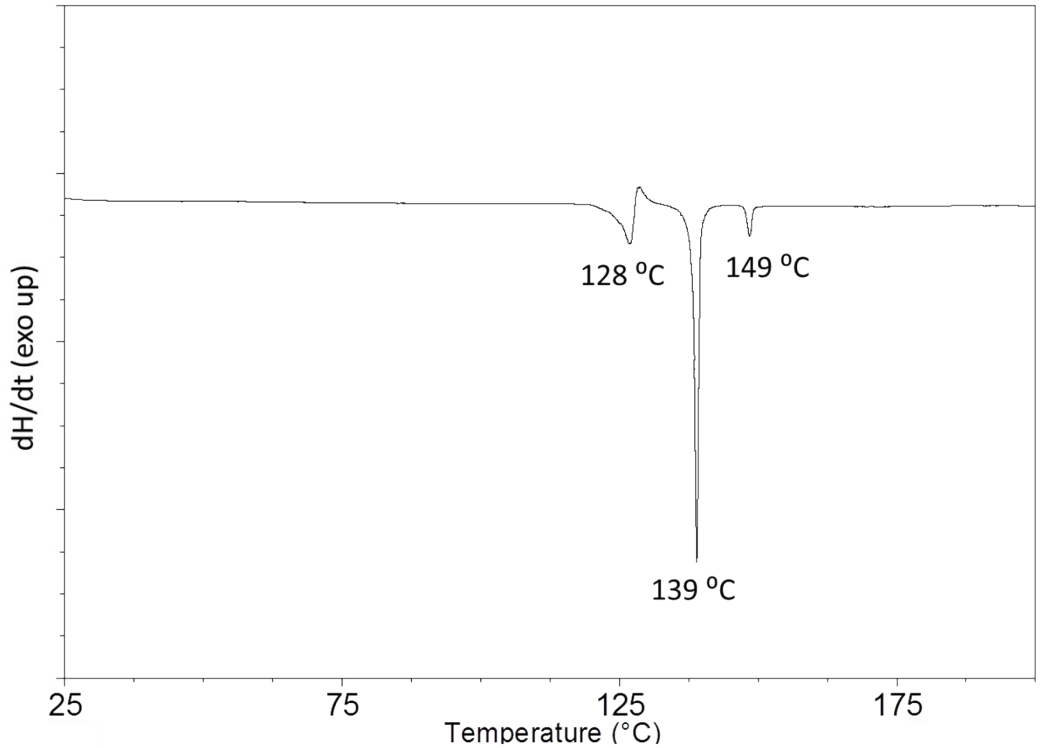

Fig. S 5. DSC curve of APZ Form IX (10 °C/min heating rate). Form IX melts at ca. 128 °C with concomitant recrystallization to a mixture of APZ form III and I which melts at 139 and 149 °C, respectively. Endo = down.

Table S 2. Complete Crystallographic data for APZ Form IX, and dAPZ Form V compared to APZ Forms I, II, III, IV, X, VI, VII and VIII

From	APZ Form IX	dAPZ Form V[4]	APZ Form I[5]	APZ Form II[5]	APZ Form III[5]	APZ Form IV[5]	APZ Form X°[5]	APZ Form VI[6]	APZ Form VII[7]	APZ Form VIII[8]
CSD REF Code		QIFJAS02	MELFIT01	MELFIT02	MELFIT03	MELFIT04	MELFIT05	MELFIT06	MELFIT07	MELFIT09
Chemical formula	$C_{23}H_{27}Cl_2N_3O_2$	$C_{23}H_{25}Cl_2N_3O_2$	$C_{24.5}H_{30.5}Cl_2N_3O_{2.5}$	$C_{23}H_{27}Cl_2N_3O_2$	$C_{23}H_{27}Cl_2N_3O_2$	$C_{23}H_{27}Cl_2N_3O_2$	$C_{23}H_{27}Cl_2N_3O_2$	$C_{23}H_{27}Cl_2N_3O_2$	$C_{23}H_{27}Cl_2N_3O_2$	$C_{23}H_{27}Cl_2N_3O_2$
Formula weight	448.38	446.36	448.38	448.38	448.38	448.38	448.38	448.38	448.38	448.38
Temperature (K)	173(2)	173(2)	293.(2)	293.(2)	293.(2)	293.(2)	293.(2)	293.(2)	90	226
Crystal system	Monoclinic	Monoclinic	monoclinic	orthorhombic	triclinic	triclinic	monoclinic	Triclinic	triclinic	Orthorhombic
Space group	$P2_1/n$	$P2_1/n$	$P2_1$	$Pna2_1$	P-1	P-1	$P2_1$	P-1	P-1	$Pna2_1$
Morphology	Plate	Plate	Plate	Needle	Plate	Thin plate	Plate			
a (Å)	16.6133(10)	16.3186(3)	8.6789(17)	23.519(5)	10.220(2)	8.5180(5)	8.8669(18)	12.2626(7)	7.0266(15)	23.610(4)
b (Å)	6.9533(4)	7.05320(10)	7.5683(15)	12.657(3)	12.208(2)	9.0350(7)	7.7623(16)	13.7872(8)	9.977(2)	12.457(2)
c (Å)	19.4632(11	19.1212(3)	17.381(4)	7.7560(16)	18.837(4)	30.417(2)	16.485(3)	14.7405(9)	15.945(3)	7.7044(13)
α (°)	90	90	90.00	90.00	82.28(3)	88.072(6)	90.00	101.396(1)	81.773(4)	90.00
β (°)	106.9900(10)	105.8940(10)	94.50(3)	90.00	82.52(3)	86.550(6)	93.25(3)	108.921(1)	78.728(4)	90.00
γ (°)	90	90	90.00	90.00	82.88(3)	73.874(6)	90.00	98.847(1)	85.888(4)	90.00
V (Å^3)	2150.2(2)	2116.68(6)	1138.14	2308.81	2295.5	2244.3(6)	1132.8	2246.3(1)	1083.8(7)	2265.9
Z	4	4	2	4	4	4	2	4	2	4
d_{calc} (Mg/m^3)	1.385	1.401	1.308	1.290	1.297	1.327	1.315	1.326	1.374	1.314
R-Factor (%)	3.45	3.23	5.67	10.03	8	5.67	4.45	4.63	2.86	4.17

[4] Zeidan, T. A.; Trotta, J. T.; Chiarella, R. A.; Oliveira, M. A.; Hickey, M. B.; Almarsson, Ö.**;** Remenar J. F. *Cryst. Growth Des.* **2013,** *13*, 2036.
[5] Braun, D. E.; Gelbrich, Y.; Kahlenberg, V.; Tessadri, R.; Wieser, J.; Griesser, U. J. *J. Pharm. Sci.* **2009**, *98*, 2010.
[6] Nanubolu, J. B.; Sridhar, B.; Ravikumar, K.; Cherukuvada, S. *CrystEngComm* **2013**, *15*, 4677.
[7] Delaney, S. P.; Pan, D.; Yin, S. X.; Smith, T. M.; Korter, T. M. *Cryst. Growth Des.* **2013**, *13*, 2943.
[8] Delaney, S. P.; Smith, T. M.; Pan, D.; Yin, S. X.; Korter, T. M. *Cryst. Growth Des.* **2014**, *14*, 5004.

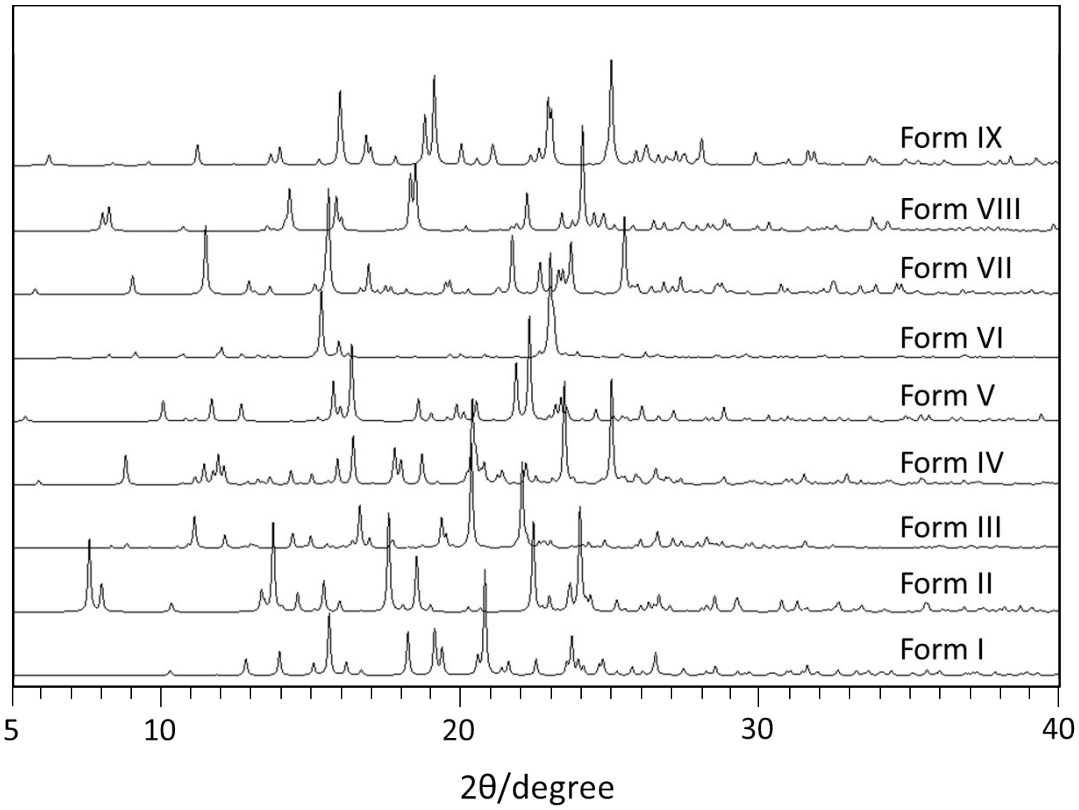

Fig. S 6. Overlay of the calculated PXRD patterns of APZ polymorphs.

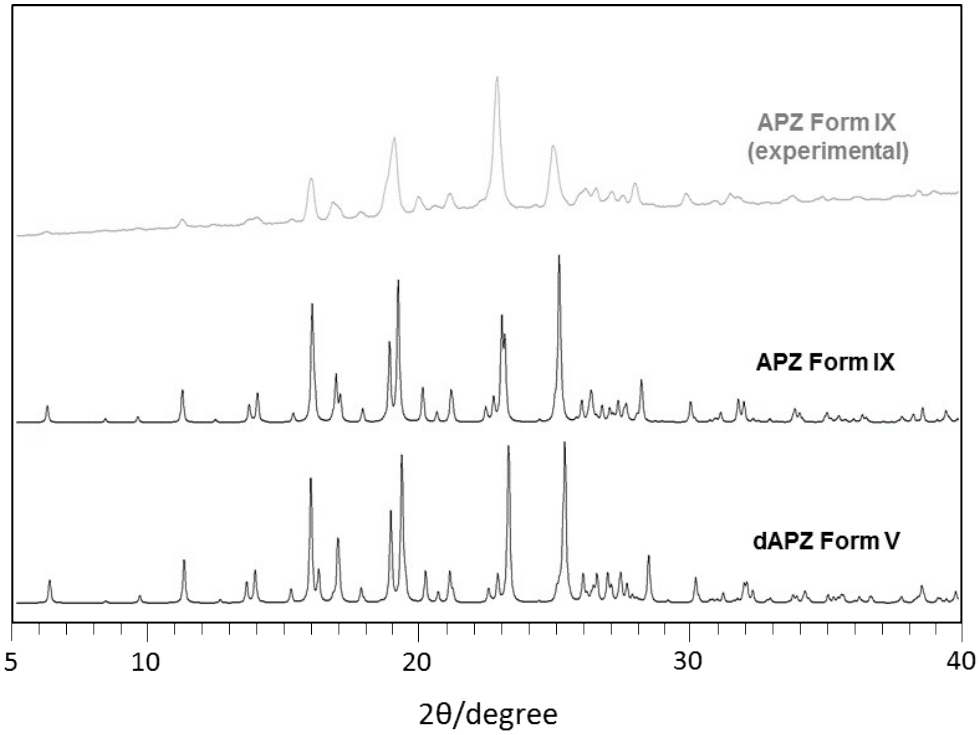

Fig. S 7. Overlays of the calculated and experimental powder X-ray diffraction patterns from APZ form IX (black) and dAPZ form V (grey).

Table S 3. Torsion Angles (°) characterizing similarity in the conformation of APZ Forms IX and dAPZ Form V

Crystal Form	**APZ Form IX**	**dAPZ Form V**
C5-N4-C7-C12	156.75	156.92
C6-N1-C13-C14	53.21	53.27
N1-C13-C14-C15	55.31	55.39
C13-C14-C15-C16	177.95	176.22
C14-C15-C16-O17	177.46	178.07
C15-C16-O17-C18	179.42	178.47
C16-O17-C18-C19	179.39	177.99

Table S 4. Geometrical Parameters for Intermolecular Interactions[a] in APZ Form IX and dAPZ Form V.

Form	Interaction	D (X-H)	*d* Å	D Å	θ°
APZ Form IX	N(24)-H•••O(28)	0.86	2.03	2.86	161
	N(24)-H•••C(25)	0.86	2.82	3.62	155
	C(9)-Cl•••O(28)	1.73	3.18	4.93	171
	C(26)-H•••C(10)	0.95	2.66	3.47	143
	C(27)-H•••C(8)-Cl	0.97	2.84	3.52	128
	C(27)-H•••C(16)-H	0.97	2.32	2.95	122
dAPZ Form V	N(24)-H•••O(28)	0.88	1.97	2.79	155
	N(24)-H•••C(25)	0.88	2.77	3.56	152
	C(9)-Cl•••O(28)	1.74	3.15	4.88	170
	C(10)-H•••C(25)	0.95	2.88	3.52	126

[a] Cut-off: sum of van der Waals radii

APZ 1-Propanol Hemi-solvate:

Preperation: 50 mg of aripiprazole were dissolved in 1 mL of 1-propanol. The hot solution was left to cool down to ambient tempearture. The crystallized solid were filtered and characterized.

Single Crystal X-ray Diffraction (SCXRD) of APZ 1-Propanol Hemi-solvate (CCDC reference number 1422249). A suitable single crystal identified by microscopy was mounted on a Nylon loop using very small amount of Paratone oil and placed in a cooled nitrogen gas stream at 173 K on an APEX II CCD fine focus sealed tube diffractometer with graphite-monochromated Mo Kα (0.71073 Å) radiation. All diffractometer manipulations, including data collection, integration, scaling, and absorption corrections were carried out using the Bruker Apex2 software.[1] Data were measured using a series of combinations of phi and omega scans with 10 s frame exposures and 0.5° frame widths.

The final refinement of this structure was carried out at Brandeis University. The structure was refined (full-matrix-least squares) using the Oxford University *Crystals for Windows* program.[2] All non-hydrogen atoms were refined using anisotropic displacement parameters. After location of H atoms on electron-density difference maps, the H atoms attached to ordered atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C---H in the range 0.93--0.98 Å and U_{iso} (H) in the range 1.2-1.5 times U_{eq} of the parent atom), after which the positions of non-acidic H atoms were refined with riding constraints.[3] H atoms attached to O and N were refined by using isotropic displacement parameters, including distance, angle and vibration restraints. The final least-squares refinement converged to $R_1 = 0.0451$ ($I > 2\sigma(I)$, 3620 data) and $wR_2 = 0.0977$ (F^2, 4304 data, 295 parameters). The 1-propanol solvate crystallizes on a crystallographic 1-bar position, and thus fixed occupancies of 0.5 were assigned to each C, H and O atom. In Figure S-7, only one of the disordered molecules is shown. Details

of the refinement, as well as responses to disorder-related CIF alerts, are available in the deposited CIF file.

1. Apex2, Version 2 User Manual, M86-E01078, Bruker Analytical X-ray Systems, Madison, WI, June 2006.

2. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Cryst.* **2003**, *36*, 1487; Prout, C.K;. Pearce, L.J. CAMERON, Chemical Crystallography Laboratory, Oxford, UK, 1996.

3. Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Cryst.* **2010**, *43*, 1100–1107.

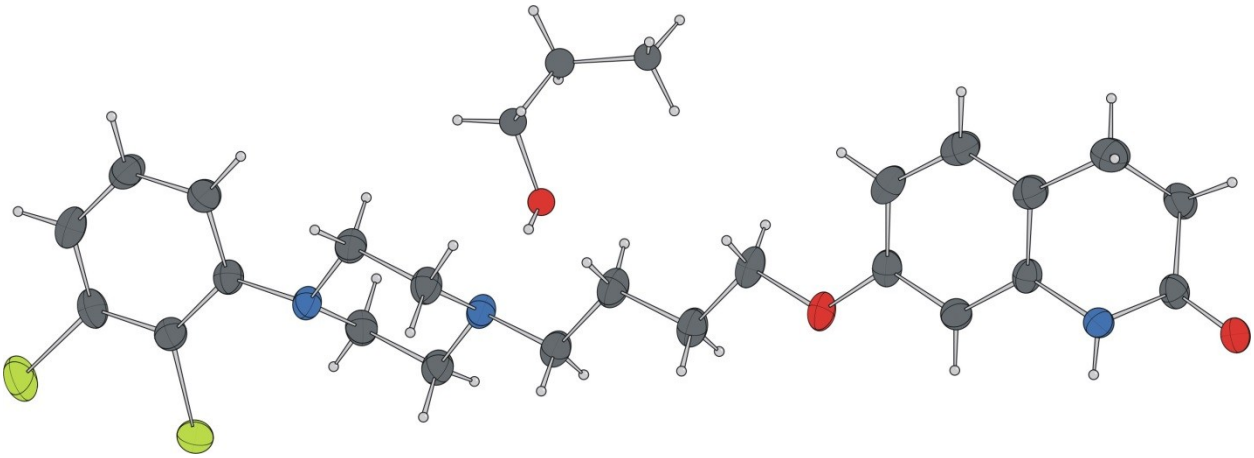

Figure S 7. Asymmetric unit of APZ 1-propanol hemi-solvate. Only one of two disordered orientations of the disordered solvate molecule is shown.

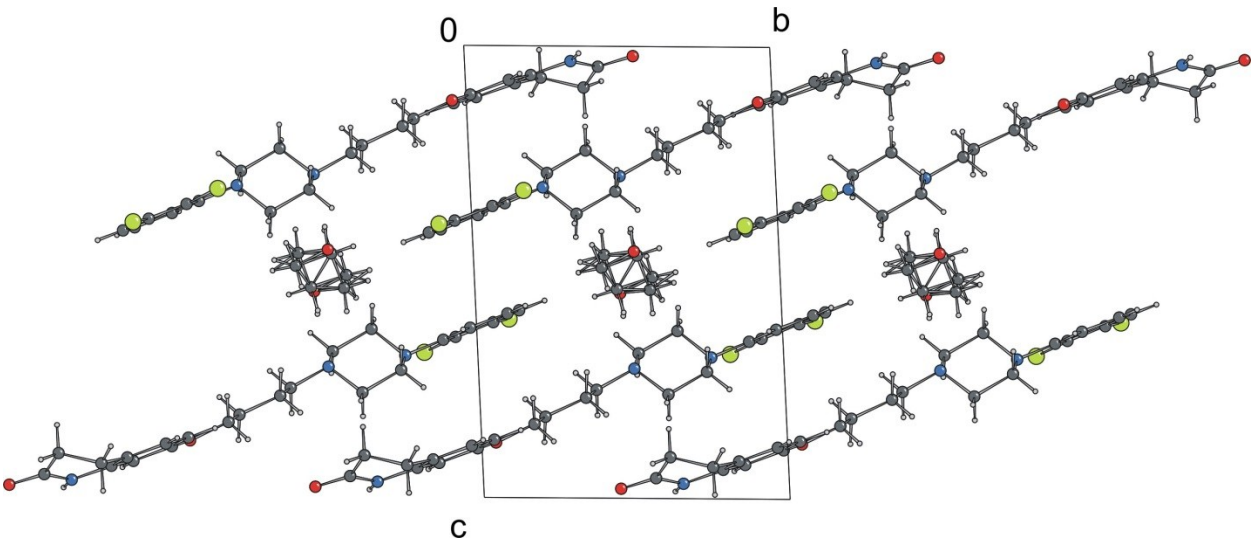

Figure S 8. Crystal packing of APZ 1-propanol hemi-solvate along the crystallographic *a*-axis. The disorder of the solvate molecule is shown in this Figure.

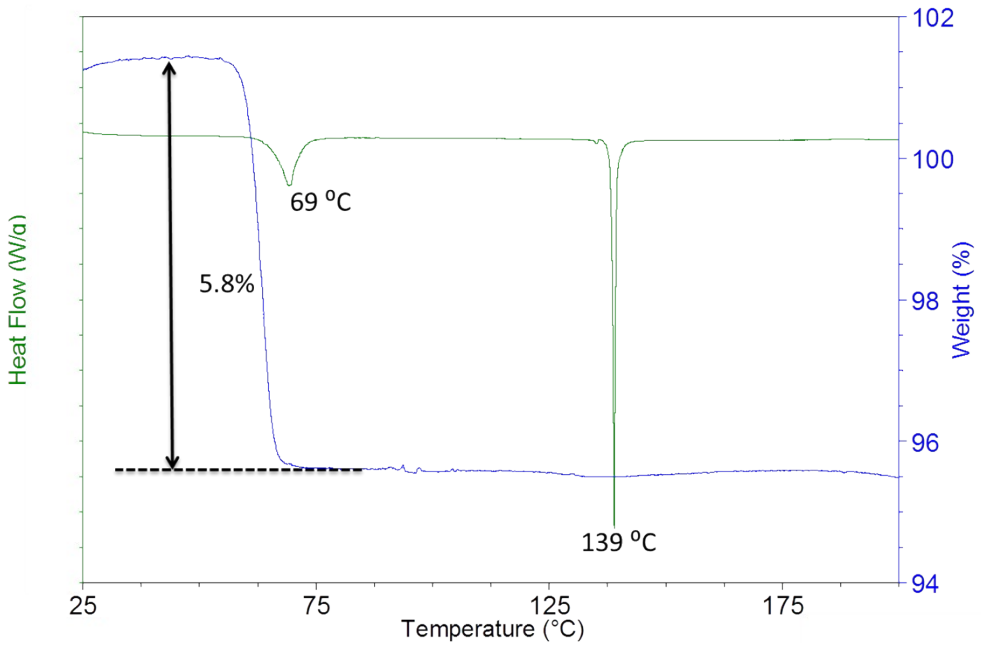

Fig. S 10. DSC and TGA curves of APZ 1-propanol hemi-solvate (10 °C/min heating rate). Desolvation occurs at 66-69 °C (theoretical weight % of solvent = 6.2%) and yields form III which melts at 139 °C.

Table S 5. Complete Crystallographic data for APZ 1-propanol hemi-solvate

From	APZ 1-propanol hemi-solvate
Chemical formula	$C_{24.5}H_{30.5}Cl_2N_3O_{2.5}$
Formula weight	477.92
Temperature (K)	173(2)
Crystal system	Triclinic
Space group	*P*-1
morphology	Plate
a (Å)	7.7282(6)
b (Å)	10.7005(8)
c (Å)	15.4954(12)
α (°)	83.8630(10)
β (°)	78.1910(10)
γ (°)	73.5760(10)
V (Å^3)	1201.46(16)
Z	2
d_{calc} (Mg/m^3)	1.321
R-Factor (%), I > 2σ(I)	4.51 (3620 data)

APZ Propylene Glycol Hemi-solvate:

Preperation: 100 mg of aripiprazole were dissolved in 2 mL of propylene glycol. The hot solution was left to cool down to ambient tempearture. The crystallized solid were filtered and characterized.

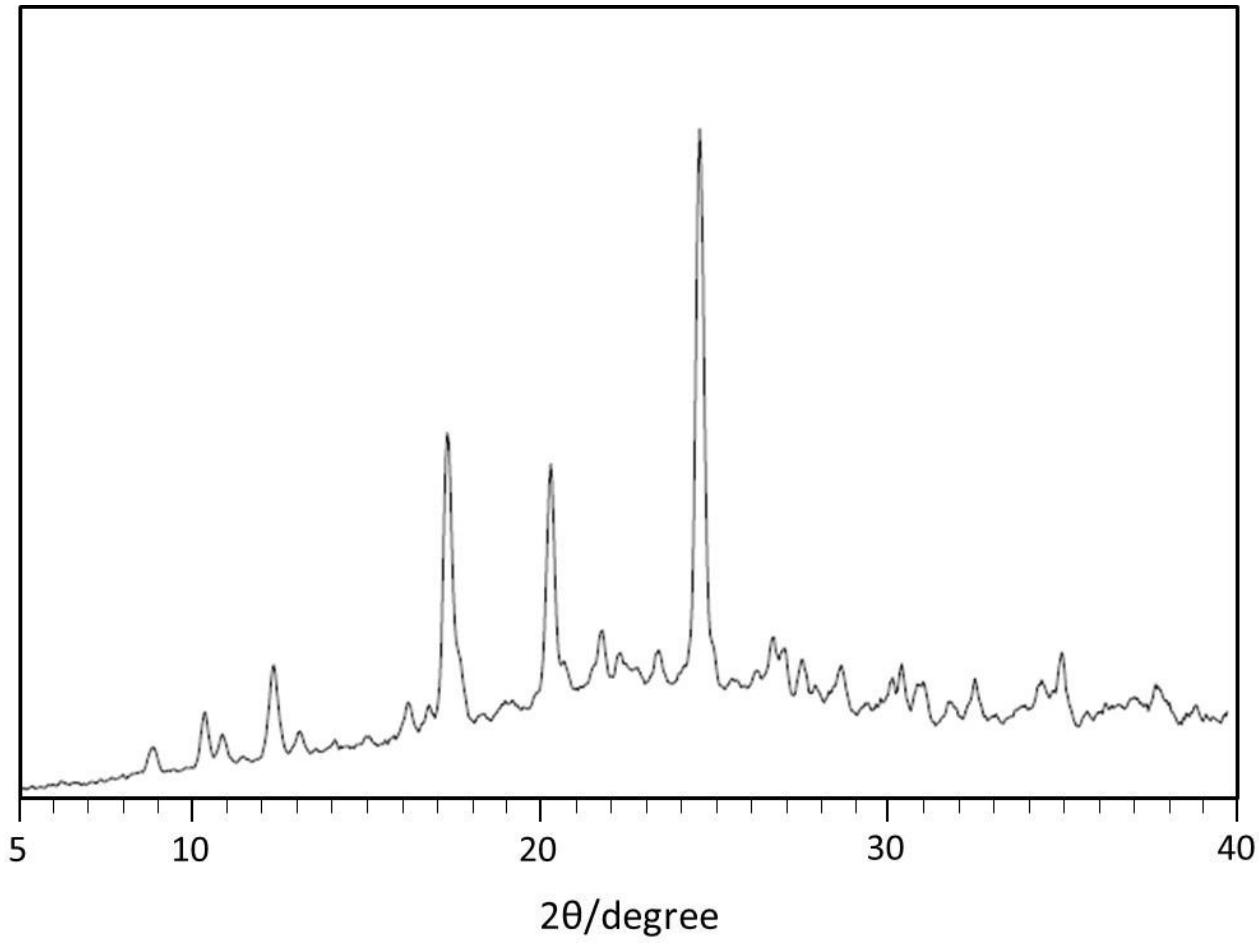

Fig. S 11. PXRD patterns of all APZ propylene glycol hemi-solvate. The pattern is identical to Form VI in reference: US Patent 7,504,504 issued 17 March 2009 (see Figure S 11). The form was referenced as Form VI in Brittain, H. G. *Profiles of Drug Substances, Excipients, Relat. Metodol* **2012**, *37*, 1.

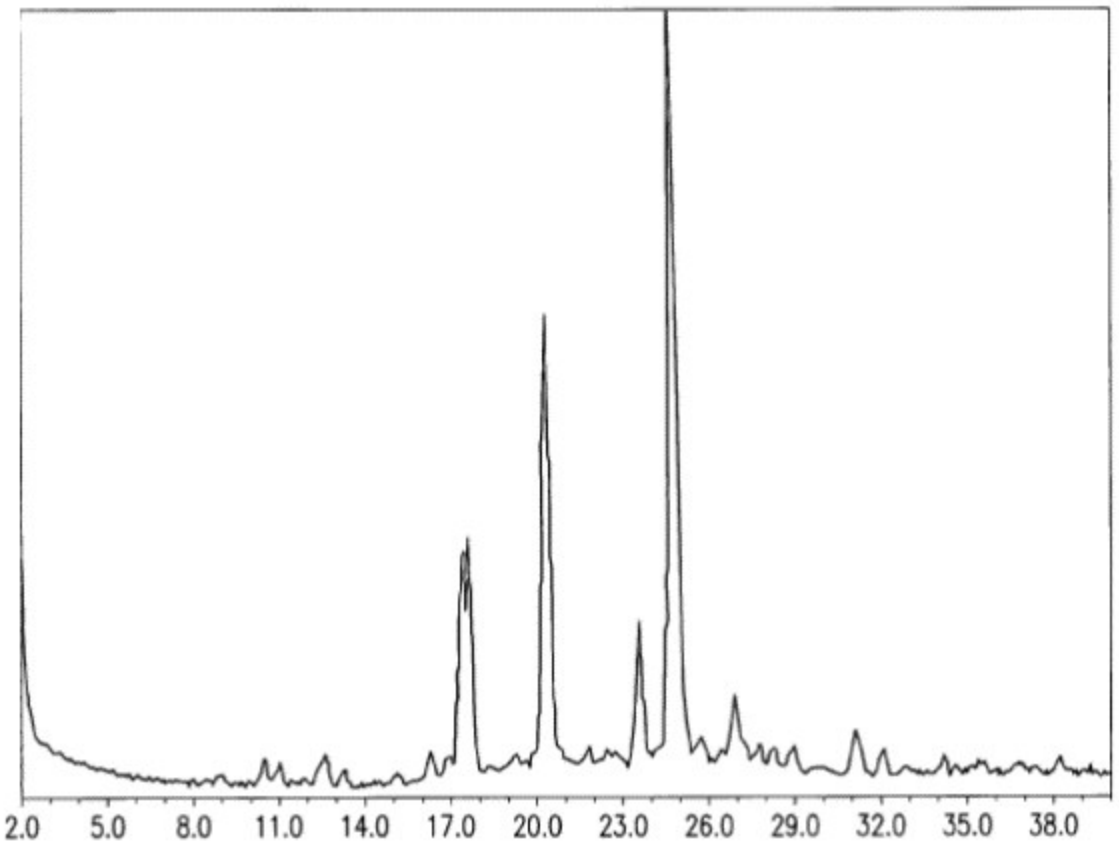

Fig. S 12. PXRD patterns of Form VI from reproduced from reference: (US Patent 7,504,504 issued 17 March 2009). This form was referenced in Brittain, H. G. *Profiles of Drug Substances, Excipients, Relat. Metodol* **2012**, *37*, 1.

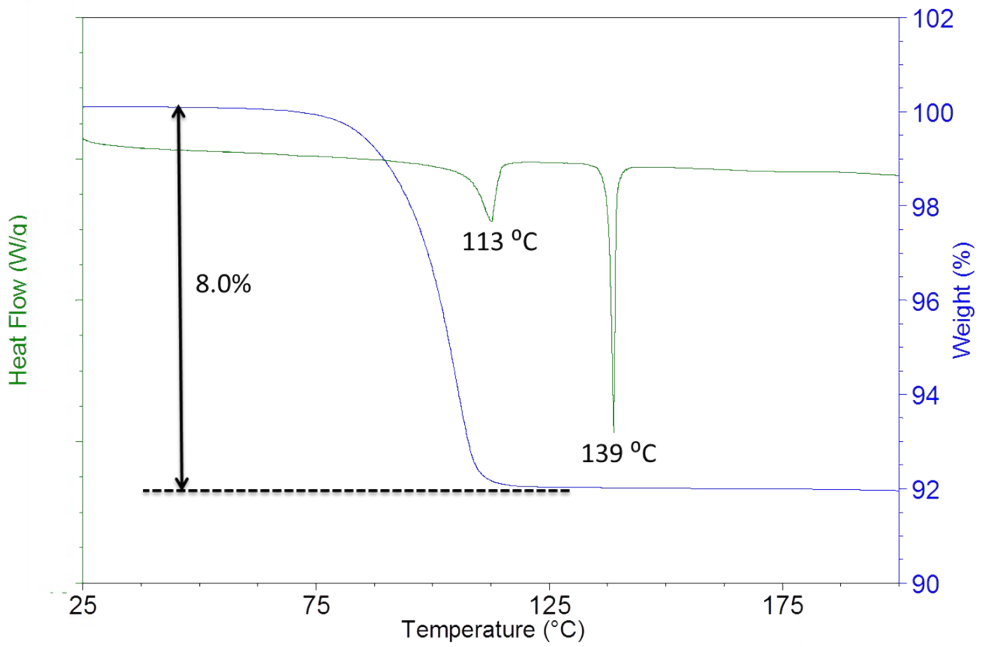

Fig. S 13. DSC and TGA curves of APZ propylene glycol hemi-solvate (10 °C/min heating rate). Desolvation occurs at 100-117 °C (theoretical weight % of solvent = 7.8%) and yields form III which melts at 139 °C.