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**Supporting information for article:**

**Understanding the formation of apremilast cocrystals**

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**S1. Experimental data****Table S1** Experimental details for crystallographic measurements of APR form B and APR:RES, APR:PIC, APR:IMI and APR:HQU cocrystals.

APR FORM B cocrystal	
Crystal data	
Chemical formula	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>7</sub> S
M <sub>r</sub>	460.49
Crystal system, space group	Monoclinic, P2 <sub>1</sub>
Temperature (K)	293
a, b, c (Å)	8.71353 (13), 29.4960 (6), 17.6717 (2)
b (°)	97.9370 (14)
V (Å <sup>3</sup> )	4498.36 (12)
Z	8
Radiation type	Cu Kα
m (mm <sup>-1</sup> )	1.68
Crystal size (mm)	0.31 × 0.06 × 0.02
Data collection	
Diffractometer	SuperNova, Dual, Cu at zero, TitanS2
Absorption correction	Multi-scan <i>CrysAlis PRO</i> , Agilent Technologies, Version 1.171.37.35h (release 09-02-2015 CrysAlis171 .NET) (compiled Feb 9 2015, 16:26:32) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T <sub>min</sub> , T <sub>max</sub>	0.817, 1.000
No. of measured, independent and observed [I > 2s(I)] reflections	43359, 17606, 14660
R <sub>int</sub>	0.038
(sin q/l) <sub>max</sub> (Å <sup>-1</sup> )	0.628
Refinement	
R[F <sup>2</sup> > 2s(F <sup>2</sup> )], wR(F <sup>2</sup> ), S	0.045, 0.119, 1.03
No. of reflections	17606
No. of parameters	1169

No. of restraints	1
H-atom treatment	H-atom parameters constrained
D $\rho_{\max}$ , D $\rho_{\min}$ (e Å <sup>-3</sup> )	0.17, -0.30
Absolute structure	Flack x determined using 5723 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.004 (8)
APR:RES cocrystal	
Crystal data	
Chemical formula	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>7</sub> S·0.5(C <sub>6</sub> H <sub>6</sub> O <sub>2</sub> )·0.5(H <sub>2</sub> O)
M <sub>r</sub>	524.55
Crystal system, space group	Tetragonal, P4 <sub>1</sub> 2 <sub>1</sub> 2
Temperature (K)	100
a, c (Å)	12.89179 (7), 29.5087 (3)
V (Å <sup>3</sup> )	4904.29 (7)
Z	8
Radiation type	Cu Ka
m (mm <sup>-1</sup> )	1.66
Crystal size (mm)	0.48 × 0.30 × 0.16
Data collection	
Diffractometer	SuperNova, Dual, Cu at zero, TitanS2
Absorption correction	Multi-scan CrysAlis PRO, Agilent Technologies, Version 1.171.37.35h (release 09-02-2015 CrysAlis171 .NET) (compiled Feb 9 2015, 16:26:32) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T <sub>min</sub> , T <sub>max</sub>	0.250, 1.000
No. of measured, independent and observed [I > 2s(I)] reflections	38451, 5001, 4965
R <sub>int</sub>	0.048
(sin q/l) <sub>max</sub> (Å <sup>-1</sup> )	0.626
Refinement	
R[F <sup>2</sup> > 2s(F <sup>2</sup> )], wR(F <sup>2</sup> ), S	0.047, 0.132, 1.08
No. of reflections	5001

No. of parameters	360
No. of restraints	96
H-atom treatment	H-atom parameters constrained
D $\rho_{\max}$ , D $\rho_{\min}$ (e Å <sup>-3</sup> )	0.90, -0.63
Absolute structure	Flack x determined using 1998 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.001 (6)
APR:PIC cocrystal	
Crystal data	
Chemical formula	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>7</sub> S·0.5(C <sub>6</sub> H <sub>6</sub> N <sub>2</sub> O)
M <sub>r</sub>	521.55
Crystal system, space group	Tetragonal, P4 <sub>1</sub> 2 <sub>1</sub> 2
Temperature (K)	100
a, c (Å)	12.81222 (8), 29.7274 (3)
V (Å <sup>3</sup> )	4879.84 (7)
Z	8
Radiation type	Cu Ka
m (mm <sup>-1</sup> )	1.65
Crystal size (mm)	0.41 × 0.28 × 0.25
Data collection	
Diffractometer	SuperNova, Dual, Cu at zero, TitanS2
Absorption correction	Multi-scan CrysAlis PRO, Agilent Technologies, Version 1.171.37.35h (release 09-02-2015 CrysAlis171 .NET) (compiled Feb 9 2015, 16:26:32) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T <sub>min</sub> , T <sub>max</sub>	0.746, 1.000
No. of measured, independent and observed [I > 2s(I)] reflections	38165, 4980, 4953
R <sub>int</sub>	0.021
(sin q/l) <sub>max</sub> (Å <sup>-1</sup> )	0.627
Refinement	
R[F <sup>2</sup> > 2s(F <sup>2</sup> )], wR(F <sup>2</sup> ), S	0.058, 0.160, 1.07

No. of reflections	4980
No. of parameters	363
No. of restraints	115
H-atom treatment	H-atom parameters constrained
D $\rho_{\max}$ , D $\rho_{\min}$ (e Å <sup>-3</sup> )	1.06, -0.63
Absolute structure	Flack x determined using 2008 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.002 (4)
APR:IMI cocrystal	
Crystal data	
Chemical formula	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>7</sub> S·0.5(C <sub>3</sub> H <sub>6</sub> N <sub>2</sub> O)
M <sub>r</sub>	501.52
Crystal system, space group	Tetragonal, P4 <sub>1</sub> 2 <sub>1</sub> 2
Temperature (K)	100
a, c (Å)	12.85808 (14), 29.5715 (4)
V (Å <sup>3</sup> )	4889.07 (13)
Z	8
Radiation type	Cu Ka
m (mm <sup>-1</sup> )	1.62
Crystal size (mm)	0.47 × 0.24 × 0.12
Data collection	
Diffractometer	SuperNova, Dual, Cu at zero, TitanS2
Absorption correction	Multi-scan CrysAlis PRO, Agilent Technologies, Version 1.171.37.35h (release 09-02-2015 CrysAlis171 .NET) (compiled Feb 9 2015, 16:26:32) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T <sub>min</sub> , T <sub>max</sub>	0.576, 1.000
No. of measured, independent and observed [I > 2s(I)] reflections	38007, 5005, 4888
R <sub>int</sub>	0.040
(sin q/l) <sub>max</sub> (Å <sup>-1</sup> )	0.627
Refinement	
R[F <sup>2</sup> > 2s(F <sup>2</sup> )]	0.063, 0.179, 1.05

$wR(F^2), S$	
No. of reflections	5005
No. of parameters	335
No. of restraints	66
H-atom treatment	H-atom parameters constrained
$D\rho_{\max}, D\rho_{\min}$ (e Å <sup>-3</sup> )	1.98, -0.96
Absolute structure	Flack x determined using 1984 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.006 (6)
APR:HQU cocrystal	
Crystal data	
Chemical formula	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>7</sub> S·0.5(C <sub>6</sub> H <sub>8</sub> O <sub>3</sub> )
$M_r$	524.55
Crystal system, space group	Tetragonal, P4 <sub>1</sub> 2 <sub>1</sub> 2
Temperature (K)	100
$a, c$ (Å)	12.88747 (7), 29.5246 (3)
$V$ (Å <sup>3</sup> )	4903.65 (7)
Z	8
Radiation type	Cu $K\alpha$
m (mm <sup>-1</sup> )	1.66
Crystal size (mm)	0.26 × 0.16 × 0.12
Data collection	
Diffractometer	SuperNova, Dual, Cu at zero, TitanS2
Absorption correction	Multi-scan <i>CrysAlis PRO</i> , Agilent Technologies, Version 1.171.37.35h (release 09-02-2015 CrysAlis171 .NET) (compiled Feb 9 2015, 16:26:32) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
$T_{\min}, T_{\max}$	0.603, 1.000
No. of measured, independent and observed [ $I > 2s(I)$ ] reflections	38399, 5046, 5005
$R_{\text{int}}$	0.027
(sin q/l) <sub>max</sub> (Å <sup>-1</sup> )	0.628
Refinement	

$R[F^2 > 2s(F^2)]$ , $wR(F^2), S$	0.060, 0.172, 1.06
No. of reflections	5046
No. of parameters	359
No. of restraints	114
H-atom treatment	H-atom parameters constrained
$D\rho_{\max}, D\rho_{\min}$ (e Å <sup>-3</sup> )	1.23, -0.97
Absolute structure	Flack x determined using 2039 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.003 (4)

In APR:IMI cocrystal relatively high residual density has been observed. This is the result of two effects: (i) a very strong hydrogen bond of imidazole nitrogen with water, which in consequence leads to a weak hydrogen contact of water with ethoxyl oxygen of APR, not listed in the checkcif contacts; (ii) relatively small imidazole ring could be modeled in more than two orientation but this interpretation did not result in better refinement statistics, so we decided to use similar disorder model as for all investigated cocrystals, which in turn left the observed residual density.

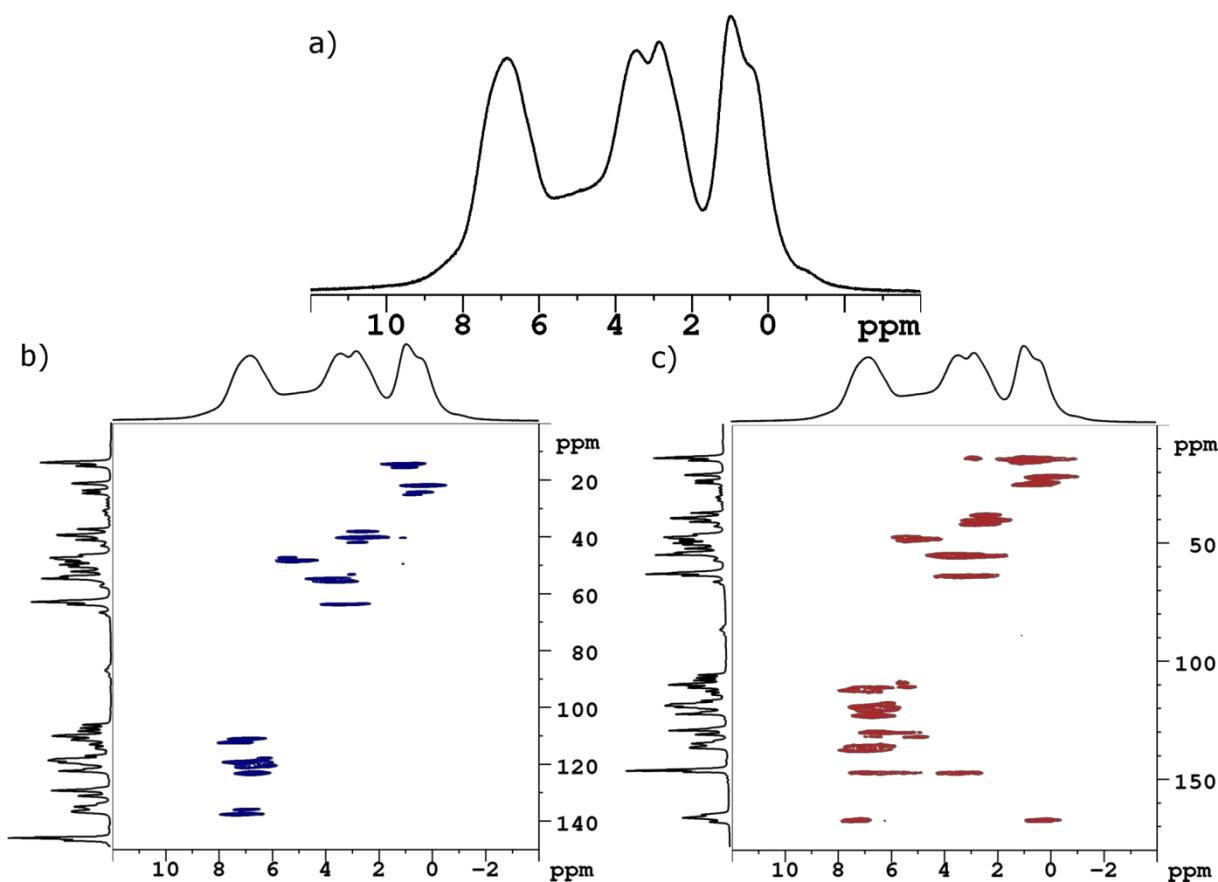
**Table S2** <sup>1</sup>H and <sup>13</sup>C Signal assignment for APR form B.

atom	molecule A		molecule B		molecule C		molecule D	
1	135.7		135.7		136.3		134.6	
2	120.1	6.5	120.7	6.9	123.1	6.7	120.1	6.5
3	137.4	7.1	137.4	7.1	137.4	7.1	135.7	6.9
4	119.0	6.8	119.4	6.6	119.4	6.6	119.4	6.6
5	130.0		129.2		130.0		130.0	
6	169.2		167.2		167.2		167.2	
7	167.2		169.2		169.2		167.2	
8	113.7		114.8		113.7		115.2	
9	167.2		166.0		166.0		166.0	
10	21.6	0.3	24.1	0.5	21.6	0.3	25.1	0.8
11	47.9	5.0	48.3	5.3	46.8	5.4	47.9	5.0
12	52.8	4.8; 3.0	50.4	4.6; 3.6	49.4	4.6; 3.0	51.2	4.7; 3.0
13	39.8	2.4	40.1	2.8	37.8	2.6	41.6	2.8
14	131.9		130.0		130.0		131.9	
15	109.0	5.7	107.9	5.9	106.8	5.6	110.6	5.6
16	147.7		146.8		146.8		147.7	

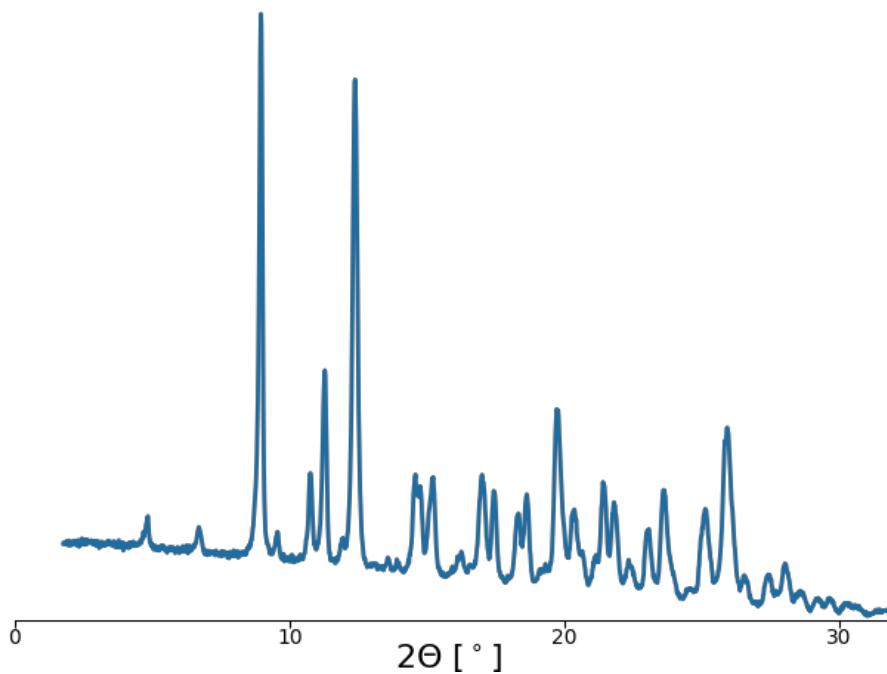
17	146.8		147.7		146.8		146.8	
18	112.1	7.4	110.7	6.9	110.7	6.9	111.9	7.4
19	117.7	6.3	123.1	6.7	122.4	6.7	119.0	6.8
20	64.5	3.7	63.6	2.9	63.2	3.7	63.6	3.7
21	15.5	1.0	14.0	1.0	14.3	1.0	14.3	1.0
22	54.5	3.5	54.7	3.8	55.4	3.5	55.4	3.8
NH		7.2		7.2		7.2		7.3

**Table S3** Calculated <sup>1</sup>H and <sup>13</sup>C chemical shieldings for APR form B.

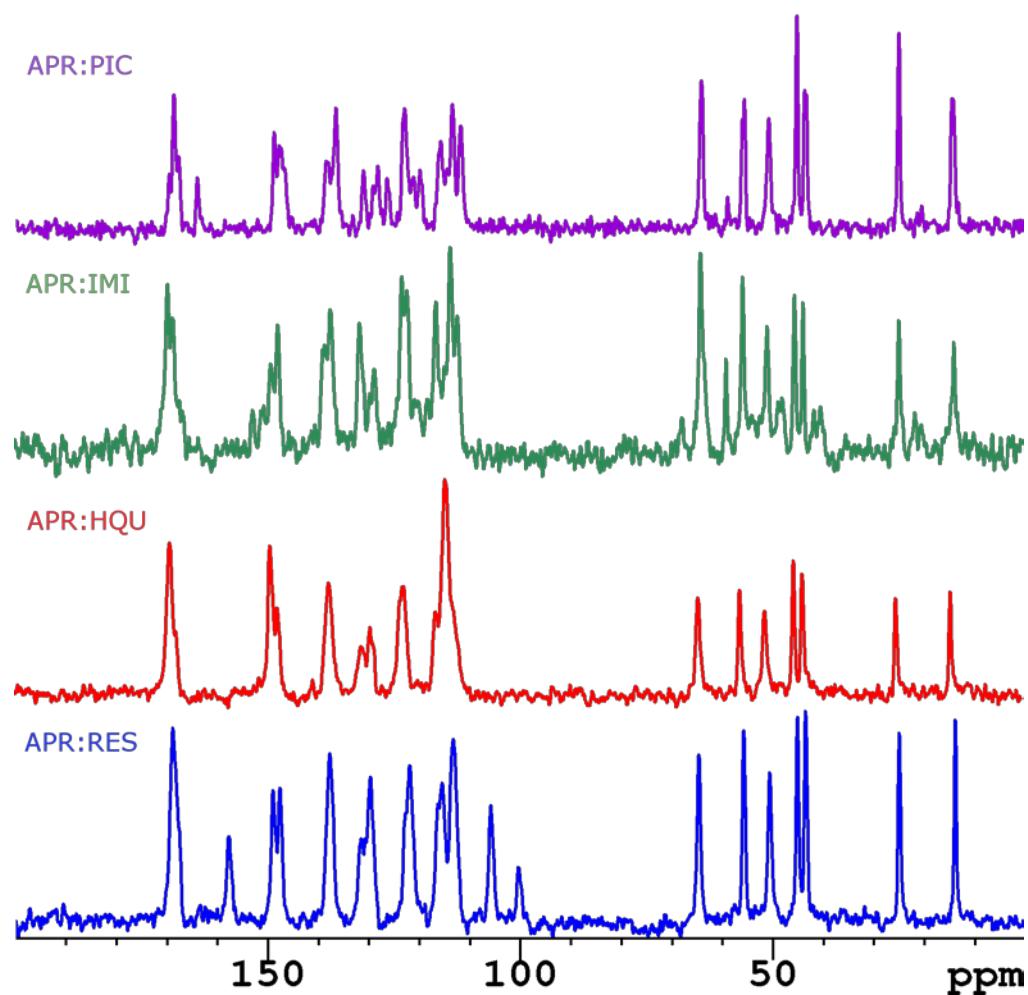
atom	molecule A		molecule B		molecule C		molecule D	
1	33,6		33,5		32,8		34,9	
2	48,2	23,4	47,3	22,5	45,1	22,8	48,1	22,9
3	29,8	22,8	29,6	22,6	29,4	22,5	32,0	23,1
4	50,6	23,3	49,9	23,0	49,9	22,7	49,1	23,2
5	39,8		40,9		40,1		40,3	
6	-2,0		0,8		0,1		-0,7	
7	-1,0		-2,9		-2,7		-1,2	
8	58,0		56,7		57,6		55,9	
9	1,0		1,6		1,1		1,2	
10	152,7	29,6	149,0	29,5	152,5	29,7	147,4	29,1
11	121,5	24,5	120,9	24,3	122,8	24,0	121,7	24,6
12	115,0	25,0; 26,8	118,4	25,4; 25,5	118,9	25,6; 26,3	116,7	25,0; 26,0
13	130,3	27,6	130,3	27,0	132,0	27,1	128,8	26,8
14	37,4		39,6		39,4		38,0	
15	61,8	24,1	62,8	23,9	64,1	23,9	60,2	24,4
16	19,9		20,8		21,1		20,5	
17	21,4		20,3		21,1		20,9	
18	57,7	22,1	59,5	22,8	59,4	23,2	58,8	22,3
19	50,7	22,9	47,0	23,2	47,0	22,7	50,6	23,0
20	103,8	26,0	104,6	26,5	104,8	26,4	104,7	26,3
21	157,7	28,7	159,9	29,1	159,6	28,7	159,3	28,8
22	115,4	25,6	115,0	26,1	114,4	25,9	114,5	26,0
NH		21,9		21,7		21,8		21,6



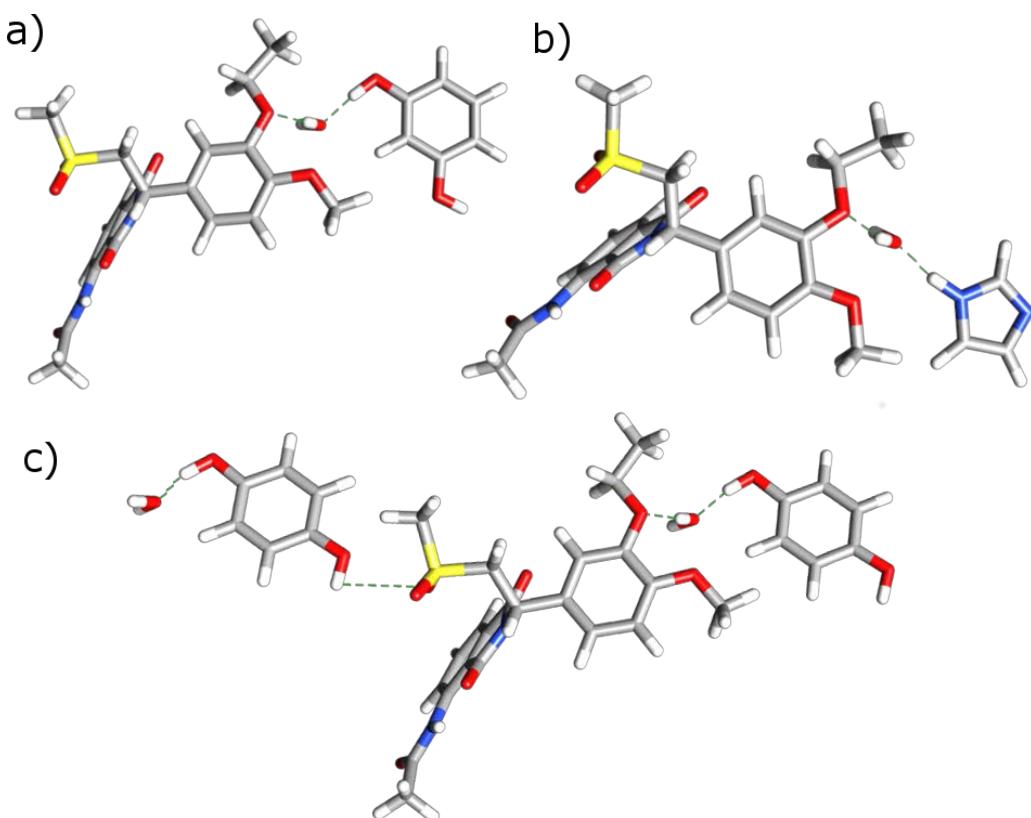
**Figure S1**  $^1\text{H}$  and  $\text{inv-}^1\text{H}-^{13}\text{C}$  HETCOR solid-state NMR spectra registered under 60 kHz rotation for APR form B: a)  $^1\text{H}$  spectrum, b) HETCOR with short contact time (100  $\mu\text{s}$ ), c) HETCOR with long contact time (2 ms).



**Figure S2** Powder X-Ray diffraction pattern for form B



**Figure S3**  $^{13}\text{C}$  NMR spectra for the studied cocrystals.

**Data for calculation of energy contributions to the cocrystals formation (Gaussian calculations)**

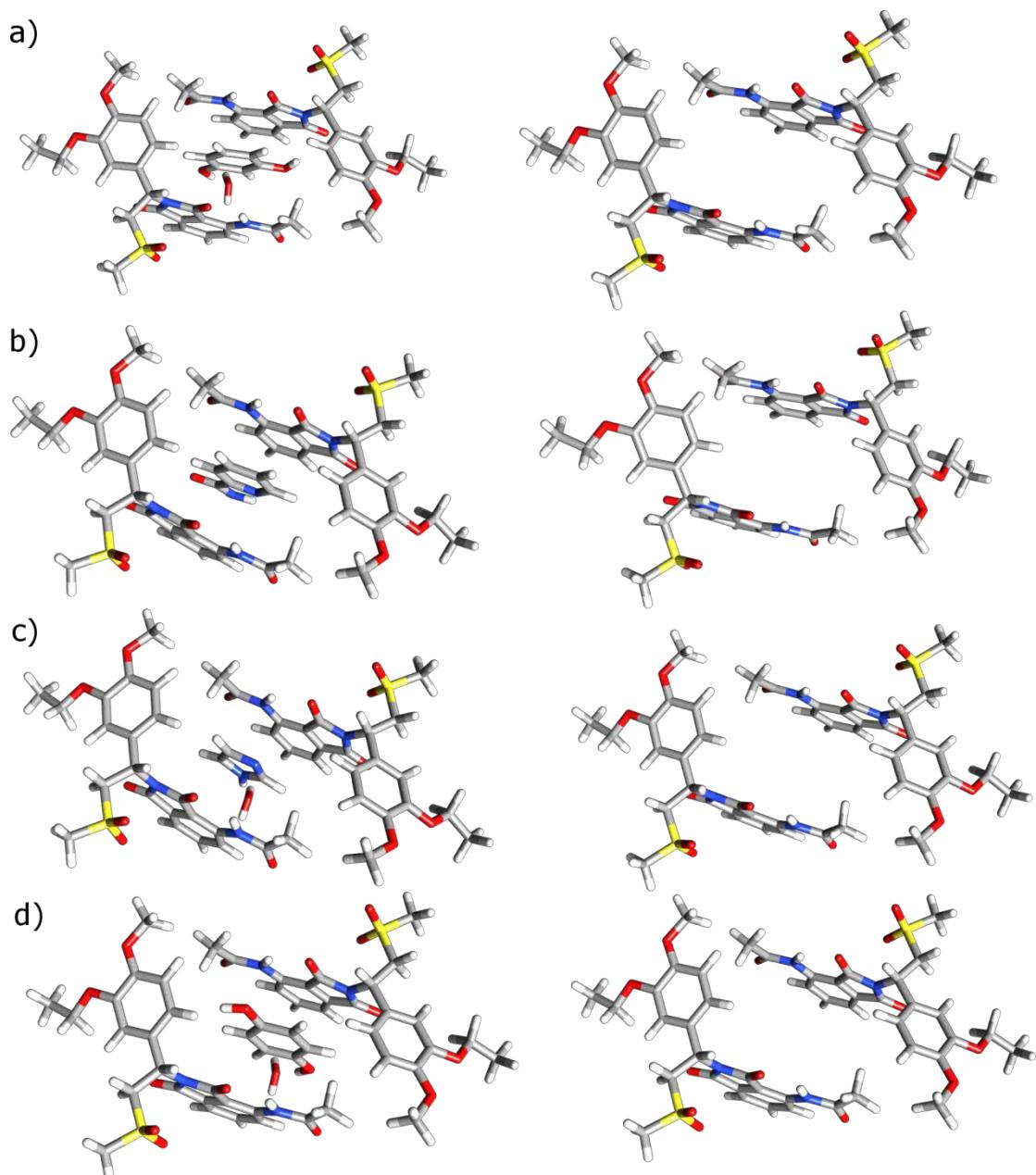
**Figure S4** Clusters for the calculations of contribution of hydrogen bonds between APR and a coformer to the intermolecular energy of cocrystals: a) APR:HQU, b) APR:IMI, c) APR:RES.

**Table S4** Data for the calculations of contribution of hydrogen bonds between APR and a coformer to the intermolecular energy of the studied cocrystals.

	E <sub>CLUSTER</sub> [Hartree]	E <sub>APR</sub> [Hartree]	E <sub>COFORMER</sub> [Hartree]	E <sub>CLUSTER</sub> – (E <sub>APR</sub> + nE <sub>COFORMER</sub> ) [Hartree]	E <sub>CLUSTER</sub> – (E <sub>APR</sub> + nE <sub>COFORMER</sub> ) [kJ/mol]	Final per asymmetric unit [kJ/mol]	E <sup>HB_APRA</sup>
APR:HQU	-2806.15	-1887.57	-459.275	-0.02951	-77.4674	-39	
APR:IMI	-2190.34	-1887.57	-302.748	-0.02089	-54.8486	-27	
APR:RES	-2346.87	-1887.57	-459.28	-0.02151	-56.4792	-28	

**Table S5** Data for the calculations of contribution of hydrogen bonds ‘inside’ a coformer to the intermolecular energy of the studied cocrystals.

	$E_{COF+H_2O}$ [Hartree]	$E_{COFORMER}$ [Hartree]	$E_{H_2O}$ [Hartree]	$E_{COF+H_2O} - (E_{H_2O} + E_{COFORMER})$ [Hartree]	$E_{COF+H_2O} - (E_{H_2O} + E_{COFORMER})$ [kJ/mol]	Final per unit [kJ/mol]	$E^{HB\_coformer}$
APR:HQU	-459.275	-382.8123	-76.4468	-0.0158164	-41.526	-21	
APR:IMI	-302.7482	-226.2863	-76.4472	-0.014673	-38.524	-19	
APR:RES	-459.2805	-382.8156	-76.447	-0.017832	-46.818	-23	



**Figure S5** Clusters for the calculations of contribution of aromatic – aromatic interactions between APR and a coformer to the intermolecular energy of cocrystals and corresponding ‘empty’ pockets formed by APR molecules: a) APR:RES, b) APR:PIC, c) APR:IMI, d) APR:HQU.

**Table S6** Data for the calculations of contribution of aromatic – aromatic interactions between APR and a coformer to the intermolecular energy of cocrystals and corresponding ‘empty’ pockets formed by APR molecules. In each case two possible positions of a coformer was regarded (referred to as a and b).

	E in [Hartree]			E in [kJ/mol]			$E^{Ar-Ar}$ per asymmetric unit
	$E_{2APR+COF+H2O}$	$E_{APR\_EMPTY}$	$E_{COF+H2O}$	$E_{2APR+COF+H2O}$	$E_{2APR+COF+H2O} - (E_{APR\_EMPTY} + E_{COF+H2O})$	Final	
				$- (E_{APR\_EMPTY} + E_{COF+H2O})$	$(E_{APR\_EMPTY} + E_{COF+H2O})$	asymmetric unit	
APR:RESa	-4234.475	-3775.15	-459.280	-0.04733	-124.3	-62	
APR:RESb	-4234.475	-3775.15	-459.281	-0.04739	-124.4	-62	
APR:PICa	-4192.317	-3775.15	-417.133	-0.03748	-98.4	-49	
APR:PICb	-4192.316	-3775.14	-417.133	-0.03727	-97.8	-49	
APR:IMIa	-4077.931	-3775.15	-302.748	-0.03649	-95.8	-48	
APR:IMIb	-4077.93	-3775.15	-302.748	-0.03642	-95.6	-48	
APR:HQUa	-4234.464	-3775.14	-459.275	-0.04435	-116.5	-58	
APR:HQUb	-4234.464	-3775.14	-459.275	-0.04438	-116.5	-58	

#### Data for calculation of energy contributions to the cocrystals formation (CASTEP calculations)

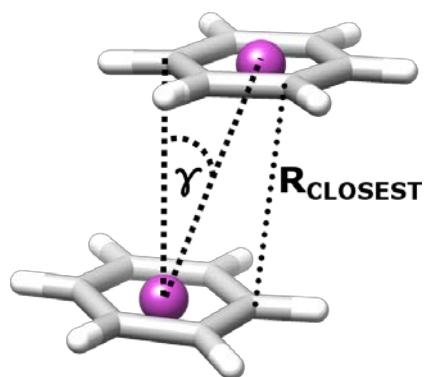
**Table S7** Data for calculations of stabilization energies of the cocrystals (in eV). In each case two possible positions of a coformer was regarded (referred to as a and b).

	$E_{COCR}$	$E_{APR\_B}$	$E_{COF}$	$E_{H2O}$	$E_{APR\_B} + 0.5E_{COF} + 0.5E_{H2O}$	$E_{COCR} - (E_{APR\_B} + 0.5E_{COF} + 0.5E_{H2O})$
APR:RESa	-8988.0134	-7790.53	-1922.38	-472.65	-8988.0462	0.032762
APR:RESb	-8988.0139	-7790.53	-1922.38	-472.65	-8988.0462	0.032324
APR:PICa	-8808.5782	-7790.53	-2036.23		-8808.6432	0.065036
APR:PICb	-8808.5808	-7790.53	-2036.23		-8808.6432	0.062349
APR:IMIa	-8572.1329	-7790.53	-1090.90	-472.65	-8572.306	0.173079
APR:IMIb	-8572.1312	-7790.53	-1090.90	-472.65	-8572.306	0.174804
APR:HQUa	-8987.8373	-7790.53	-1922.32	-472.65	-8988.0142	0.17687
APR:HQUb	-8987.8388	-7790.53	-1922.32	-472.65	-8988.0142	0.175408

### Intermolecular interactions found in form B of APR and in APR cocrystals

**Table S8** Intermolecular hydrogen bond lengths (in Å, expressed as O···O/N distances) and geometry parameters for aromatic – aromatic interactions ( $R_{CLOSEST}$  distance in Å and  $\gamma$  angle in °, calculated as shown in Figure S6). For form B of APR letters A, B, C and D denote 4 unique molecules in an asymmetric part of a unit cell.

Hydrogen bonds			
crystal	interacting atoms	distance	
APR:RES	H <sub>2</sub> O···OH-Ar (RES)	2.65	
	H <sub>2</sub> O···OMe-Ar (APR)	3.01	
APR:IMI	H <sub>2</sub> O···N (IMI)	2.05	
	H <sub>2</sub> O···OMe (APR)	3.96	
APR:HQU	H <sub>2</sub> O···OH-Ar (HQU)	1.93	
	H <sub>2</sub> O···OEt-Ar (APR)	3.19	
	(HQU)Ar-HO···O <sub>2</sub> S-CH <sub>3</sub> (APR)	2.11	
Aromatic – aromatic interactions			
crystal	interacting rings	R <sub>CLOSEST</sub>	$\gamma$ angle
APR form B	Ar(OMe)(OEt) ··· Ar(OMe)(OEt) (A:B)	3.79	63.3
	Ar(OMe)(OEt) ··· Ar(OMe)(OEt) (C:D)	3.83	69.6
	Isoindol ··· Isoindol (A:B)	3.46	60.5
	Isoindol ··· Isoindol (C:D)	3.47	59.9
APR:RES	Isoindol (APR) ··· Phenyl (RES)	3.35	54.4
	Isoindol (APR) ··· Ar(OMe)(OEt) (APR)	3.67	33.5
APR:PIC	Isoindol (APR) ··· Pyridine (PIC)	3.37	57.3
	Isoindol (APR) ··· Ar(OMe)(OEt) (APR)	3.64	35.3
APR:IMI	Isoindol (APR) ··· Imidazole (IMI)	3.37	53.6
	Isoindol (APR) ··· Ar(OMe)(OEt) (APR)	3.65	34.3
APR:HQU	Isoindol (APR) ··· Phenyl (HQU)	3.42	61.3
	Isoindol (APR) ··· Ar(OMe)(OEt) (APR)	3.68	33.7



**Figure S6** Geometric parameters for aromatic – aromatic interactions given in Table S7. Purple balls mark centroids of the interacting aromatic ring.