Supplementary Information

Molecular Packing of Pharmaceuticals Analyzed with Paramagnetic Relaxation Enhancement and Ultrafast Magic Angle Spinning NMR

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Powder X-ray Diffraction

Powder XRD was conducted on a PANalytical X'Pert Pro X-ray diffractometer (PANalytical, USA) with a Cu Kα (λ = 0.15418 nm) radiation source, using a step size of 0.0334° and an integration time of 3 s at room temperature.

Table S1. ^{13}C and ^{1}H chemical shifts of posaconazaole in crystalline (left) and solution (right) state.

	Solid-state NMR			Solution NMR[2]	
^{13}C No.	^{13}C CS (ppm)[1]	^{1}H CS (ppm)*	^{13}C No.	^{13}C CS (ppm)	^{1}H CS (ppm)
2	67.2	3.85	2	69	3.66
3	38.4	2.96	3	38.9	2.61
4	45.4	3.15	4	37.5	2.3
5	82.3	-	5	84.3	-
6	66.5	3.95	6	70.7	3.9
8	151.4	-	8	153	-
9	115.0	6.95	9	115.1	6.78
10	116.9	7.54	10	118.5	6.93
11	145.3	-	11	145.8	-
12	116.9	7.54	12	118.5	6.93
13	115.0	6.95	13	115.1	6.78
14	128.5	-	14	125.4	-
15	158.8	-	15	159	-
16	105.4	7.73	16	104.5	6.85
17	163.2	-	17	162.8	-
18	110.0	7.19	18	111.3	6.82
19	128.2	8.23	19	128.6	7.38
20	56.3	5.05/5.85	20	56	4.58
23	149.7	8.78	23	151	7.79
25	146.4	8.98	25	144.6	8.11
27	49.3	3.46	27	50.6	3.25
28	48.2	3.46	28	49.2	3.36
30	48.2	3.46	30	49.2	3.36
31	49.3	3.46	31	50.6	3.25
34	149.7	-	34	150.7	-
35	116.9	7.54	35	116.6	7.03
36	122.0	9.5	38	123.6	7.43
37	127.9	-	37	125.5	-
38	121.1	8.78	36	123.6	7.43
39	116.9	7.54	39	116.6	7.03
41	153.9	-	41	153.1	-
44	135.1	11.07	44	134.6	7.67
46	65.1	4.73	47	68.9	4.06
47	69.2	4.73	46	63.5	4.02
49	22.2	1.65	49	23.5	1.94
50	9.2	0.34	50	10.7	0.94
51	22.2	2.24	51	21	1.22

* ^{1}H chemical shifts are tentatively assigned.

Table S2. Full [19]F-^{1}H and [1]H-^{1}H inter-nuclear contacts identified in [1]H-detected 2Ds and corresponding distance data derived from X-ray diffraction.[3] Note that a range of [19]F-^{1}H and [1]H-^{1}H proximities are reported here since multiple protons might exist and connect to same carbon atom.

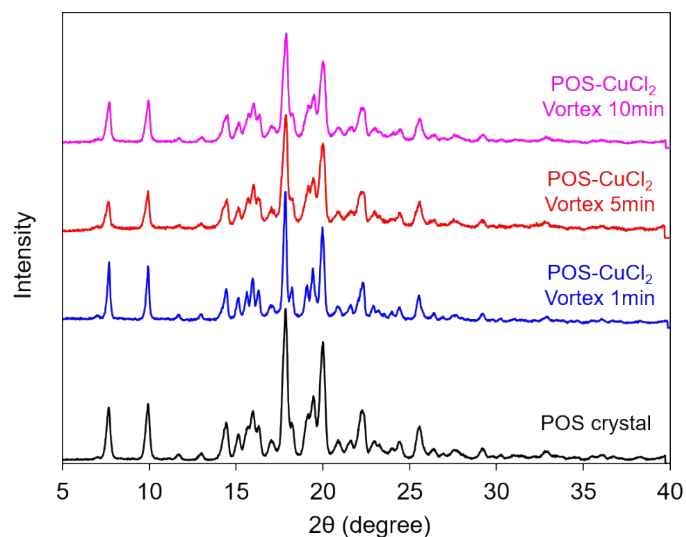| 2D experiments	Spin contacts	Intramolecular	Intermolecular	Inter-nuclear distance from X-ray (Å) [3]
[1]H-^{19}F HETCOR 50 μs contact time $\nu_R = 60$ kHz	[1]H-[19]F	F2-H16		2.53
	[1]H-[19]F	F1-H16		2.55
	[1]H-[19]F	F1-H18		2.53
	[1]H-[19]F		F1-H23	2.43
	[1]H-[19]F		F1-H49/51	3.73-5.29
[1]H-^{19}F HETCOR 1 ms contact time $\nu_R = 60$ kHz	[1]H-[19]F	F2-H18		5.02
	[1]H-[19]F		F1-H46/47	3.45/5.80
	[1]H-[19]F		F1-H50	5.76-6.48
	[1]H-[19]F		F2-H23	5.53
	[1]H-[19]F		F2-H49/51	3.73-5.37
	[1]H-[19]F		F2-H46/47	5.62-5.92
	[1]H-[19]F		F2-H50	4.76-6.02
[1]H-^{1}H RFDR $\nu_R = 60$ kHz	[1]H-[1]H	H50-H49/51		2.32-5.91
	[1]H-[1]H	H50-H46/47		2.53-4.71
	[1]H-[1]H	H49/51-H46/47		2.29-3.51
	[1]H-[1]H	H44-H46/47		4.63-5.00
	[1]H-[1]H	H44-H38		2.31
	[1]H-[1]H		H44-H25	3.74
[1]H-^{1}H RFDR $\nu_R = 110$ kHz	[1]H-[1]H		H50-H3/4	2.40-5.79
	[1]H-[1]H		H50-H2	4.36-6.48
	[1]H-[1]H		H50-H6	4.50-6.41
	[1]H-[1]H	H50-H44		4.18-5.58
	[1]H-[1]H	H49-H51		2.27-4.15
	[1]H-[1]H		H51-H20	4.08-6.25
	[1]H-[1]H		H51-H16	2.78-4.31
	[1]H-[1]H		H51-H25	4.54-5.23
	[1]H-[1]H	H3-H2/H6		2.28-2.83
	[1]H-[1]H	H4-H2/H6		2.46-3.90
	[1]H-[1]H	H3/4-H25		4.52-5.38
	[1]H-[1]H		H3/4-H38	4.8-6.62
	[1]H-[1]H		H3/4-H36	5.35-6.97
	[1]H-[1]H		H6-H36	3.25-3.96
	[1]H-[1]H		H46/47-H20	3.74-6.40
	[1]H-[1]H		H46/47-H16	4.00-5.45
	[1]H-[1]H	H46/47-H38		6.31-6.36
	[1]H-[1]H		H46/47-H25	2.85-4.81
	[1]H-[1]H	H20-H23/25		2.61-4.95
	[1]H-[1]H		H20-H38	6.03-7.18
	[1]H-[1]H	H16-H23/H25		6.64-7.48

Figure S1. PXRD patterns of crystalline POSA without (black) and with (colored) Cu(II) doping on particles surface at different vortex times.
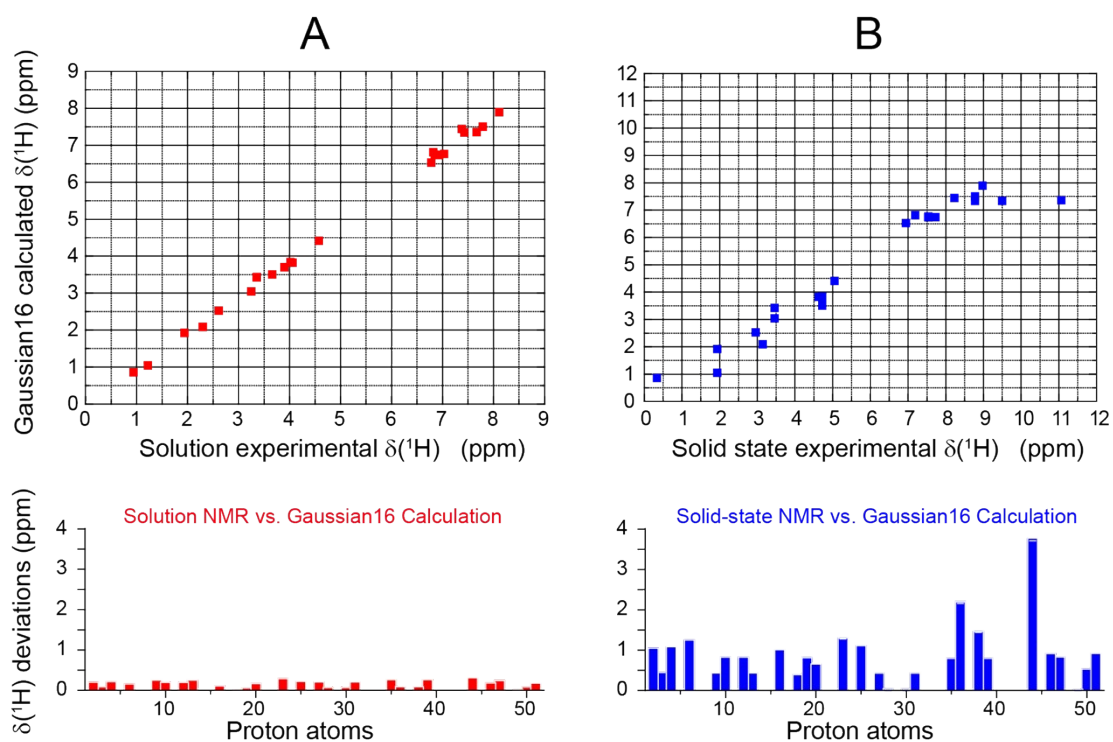

Figure S2. Comparison of ^{1}H chemical shifts in POSA calculated using Gaussian16 with experimental values in solution (A) and solid-state (B).
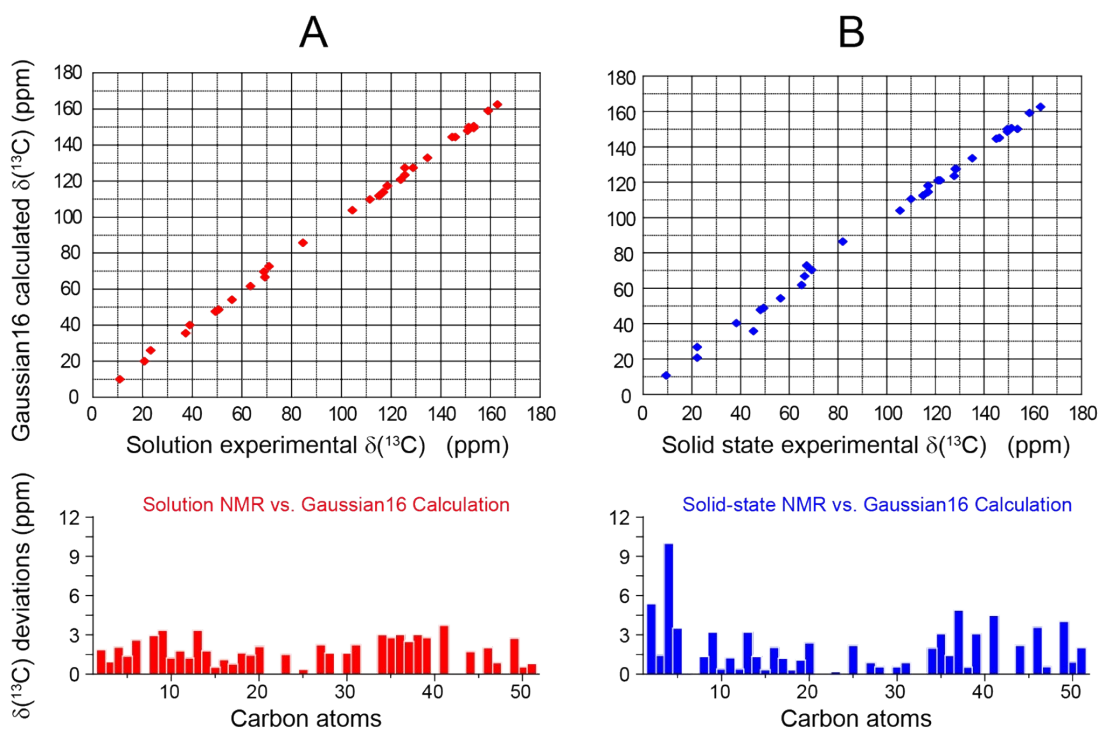
Figure S3. Comparison of ^{13}C chemical shifts in POSA calculated using Gaussian16 with experimental values in solution (A) and solid-state (B).
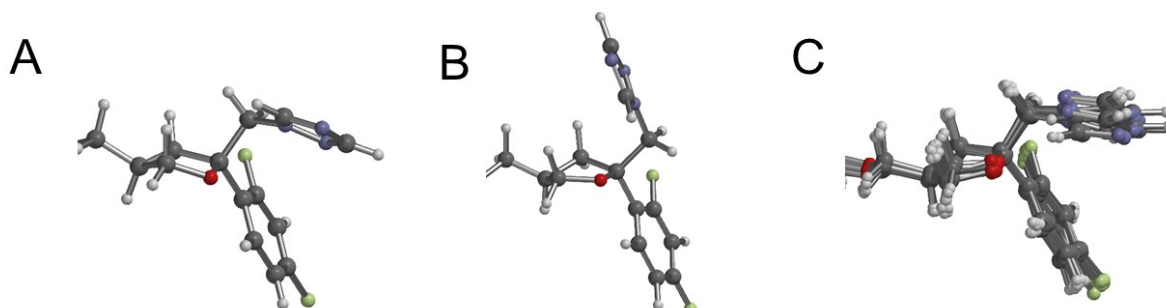

Figure S4. Conformational comparison of the difluorophenyl end of POSA in solid state (A), lowest energy conformation in solution (B) and eight high-energy solution conformations (DE = 3.0- 5.0 kcal/mol) with similar ring orientation to that in the solid state.

Reference

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