Electronic Supplementary Material (ESI) for CrystEngComm

Sixth polymorph of Aripiprazole - an antipsychotic drug.

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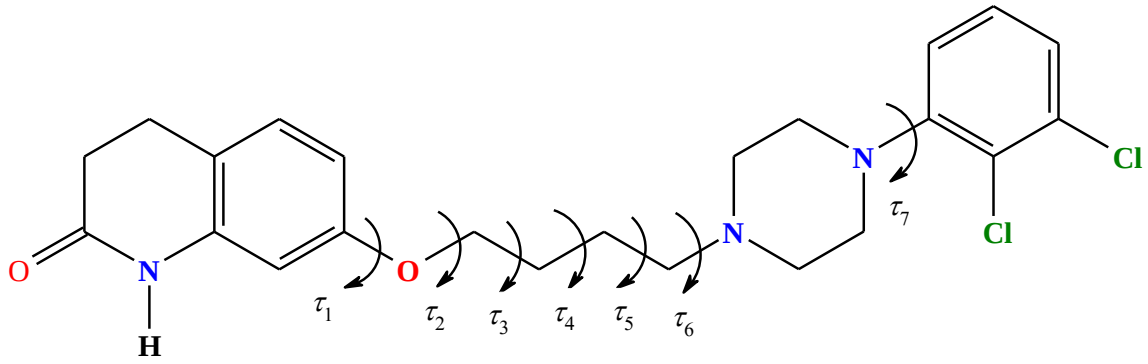
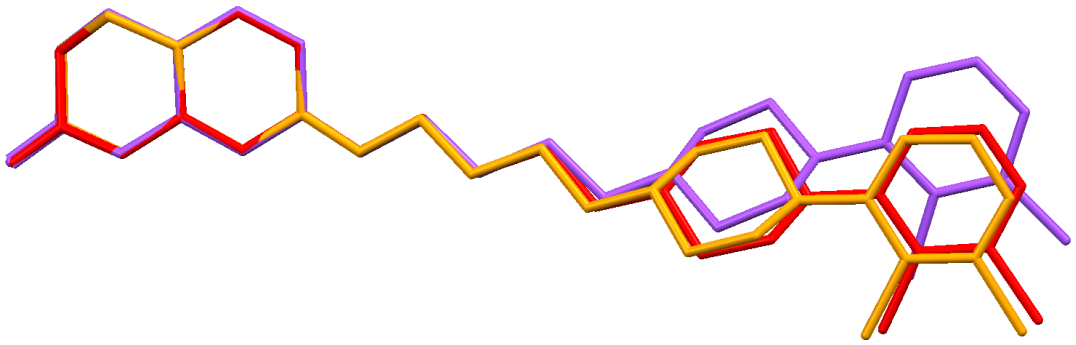


(a)



(b)

Figure S1. (a) The molecular structure of aripiprazole showing seven freely rotatable bonds. (b) An overlay of aripiprazole conformations from new polymorph (molecule A-red, molecule B-orange) and geometry optimized conformation (purple). There are only minor torsion angle differences; accordingly, their conformer energies are very close.

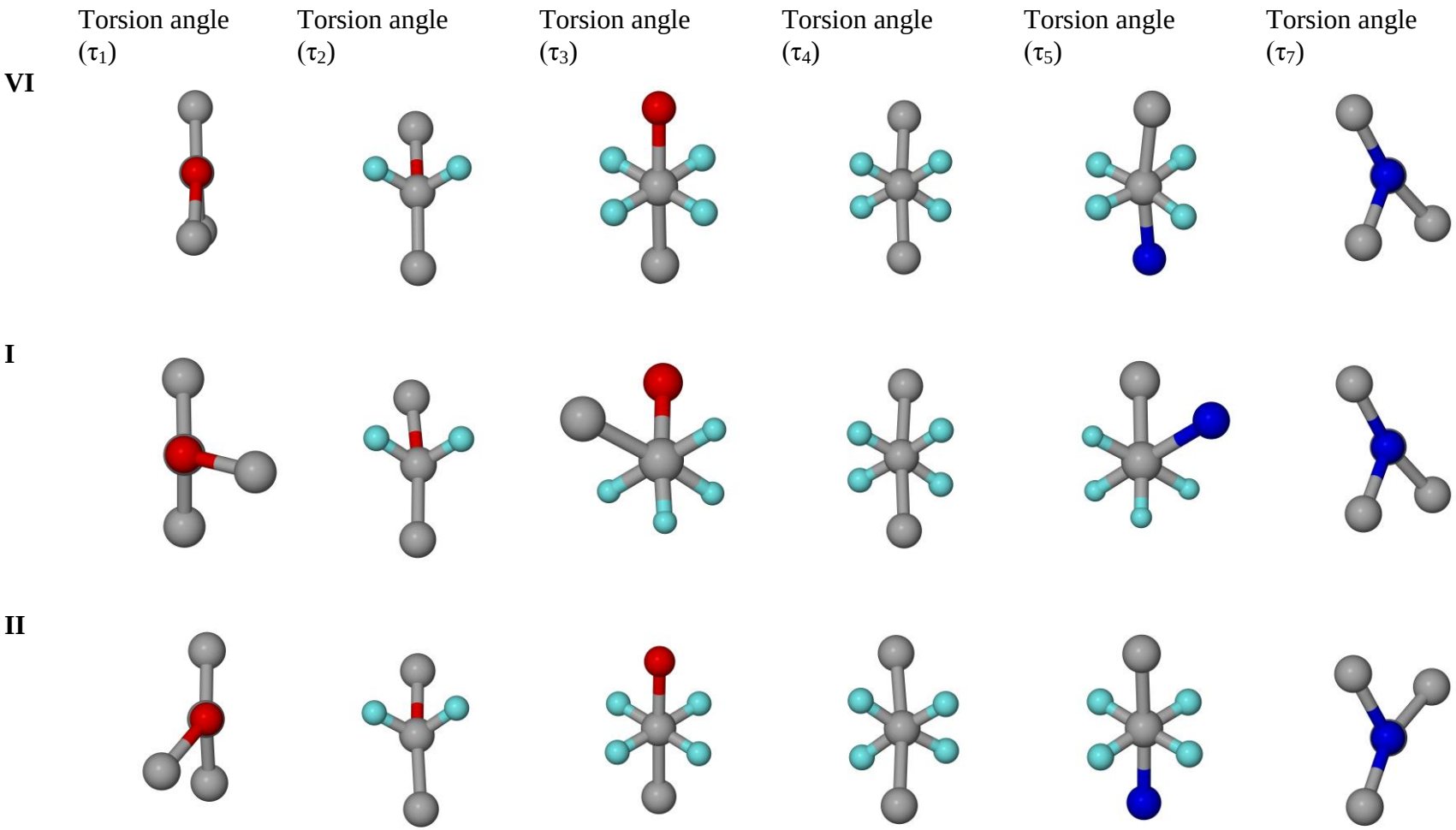
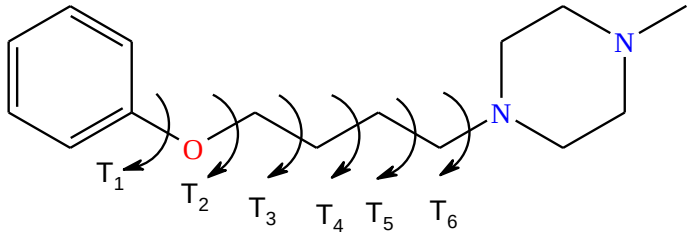


Figure S2: Newman projections of various torsion angles in polymorph VI, I and II.

In order to achieve faster computations, aripiprazole molecule was slightly modified for scanning remaining 4 torsion angles - τ_2, τ_4, τ_5, τ_6. The energy profile is largely unaffected when remote groups on the molecule is removed.[3d] This has also been verified by scanning two torsion angles (τ_1 and τ_3) for aripiprazole and modified aripiprazole. Their energy profiles are found to be identical. Scanning τ_1 indicated a highest energy maximum in both the aripiprazole and truncated aripiprazole at 90˚ and the energy value is also nearly identical (3.0 kcalmol^{-1} for the former and 2.9 kcalmol,$^{-1}$ for the latter). Similarly, scanning τ_3 for both these compounds indicated an identical energy profile.



Trucated aripiprazole

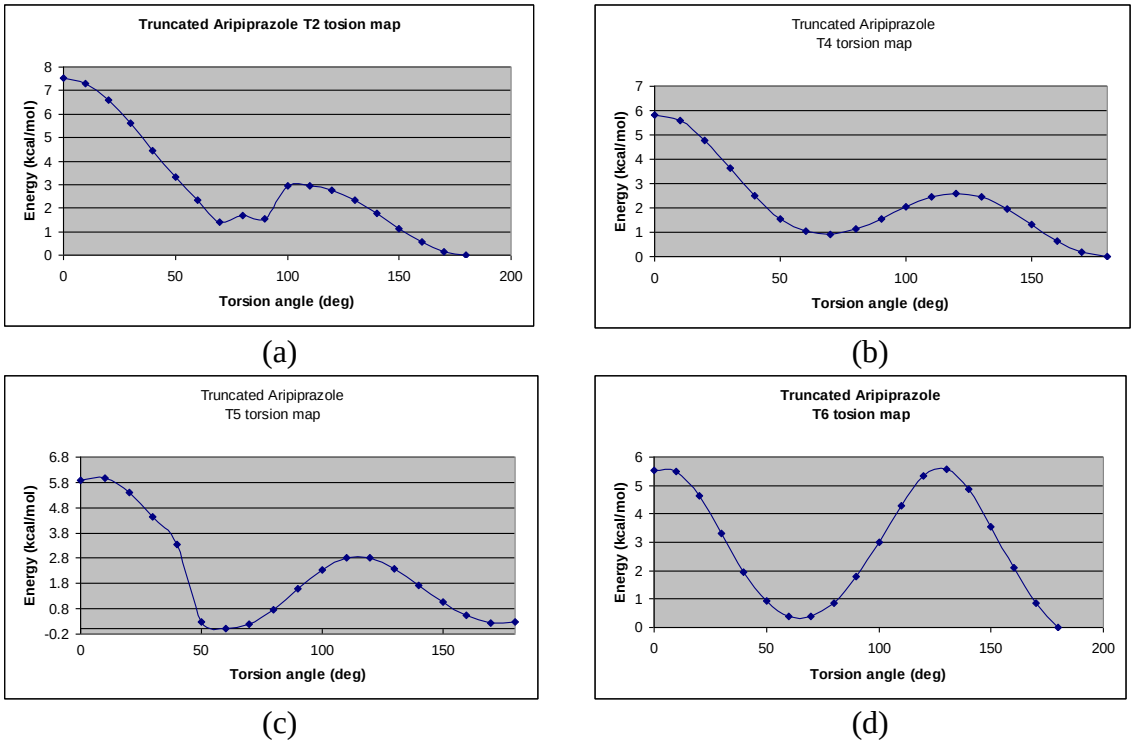


Figure S3: The relative change in the energy is plotted as a function of three torsion angles of aripiprazole. Scanning τ_2 (a), τ_4 (b), τ_5 (c) and τ_6 (d) indicated two high energy maxima at 0˚ and 120˚, and two low-energy minima at 60˚ and 180˚. These energy-torsion maps indicated the presence of several low-energy molecular conformations in the molecule.

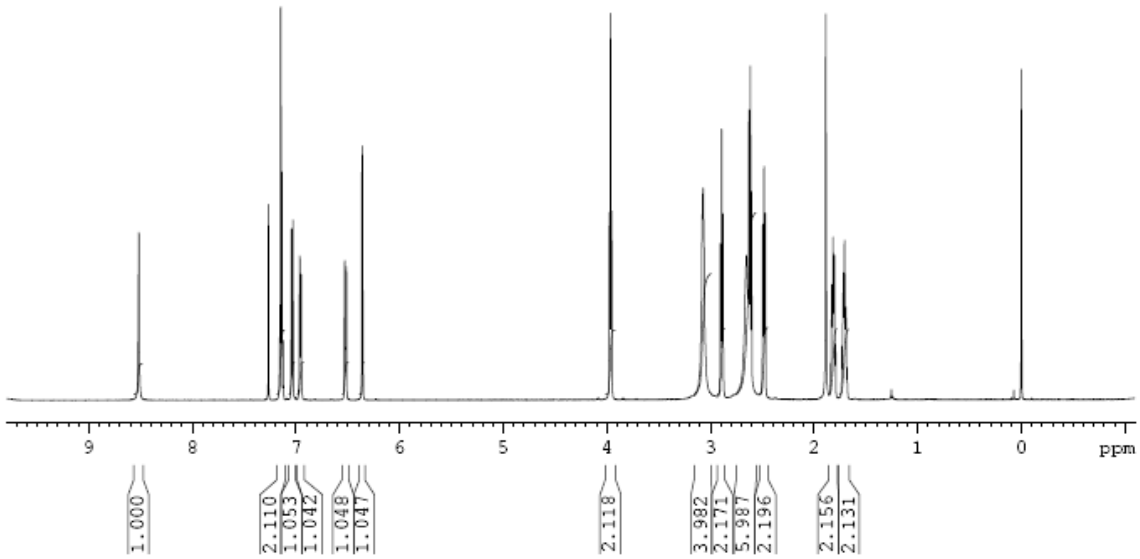


Figure S4a: ^{1}H NMR spectrum of Aripiprazole ($CDCl_3$, 298 K, 600 MHz): 8.52 (s,1H), 7.14-7.15 (m,2H), 7.04 (d,1H,J=8.30 Hz), 6.96 (dd,1H,J=7.10,2.52Hz), 6.52 (dd,1H,J=8.30,2.30 Hz), 6.36 (d,1H,J=2.30 Hz), 3.96 (t,2H,J=6.25 Hz), 3.07 (m,4H), 2.89 (t,2H,J=7.50 Hz), 2.65 (m,4H), 2.62 (t,2H,J=7.50 Hz), 2.48 (t,2H,J=7.55 Hz), 1.82 (m,2H), 1.71 (m,2H).

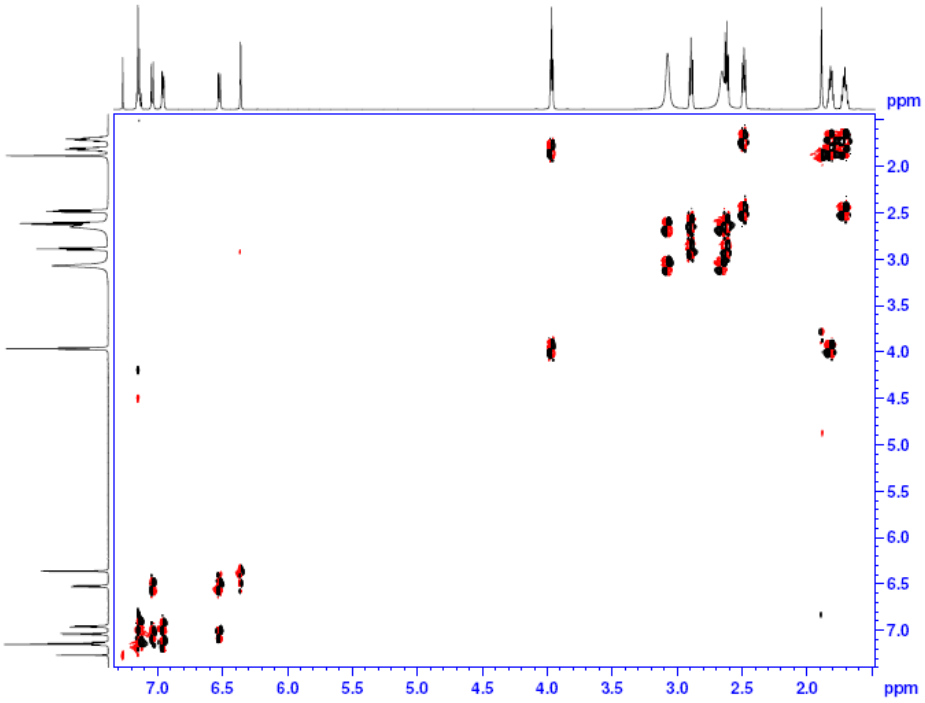


Figure S4b: COSY spectrum of Aripiprazole (600 MHz, $CDCl_3$, 298 K)

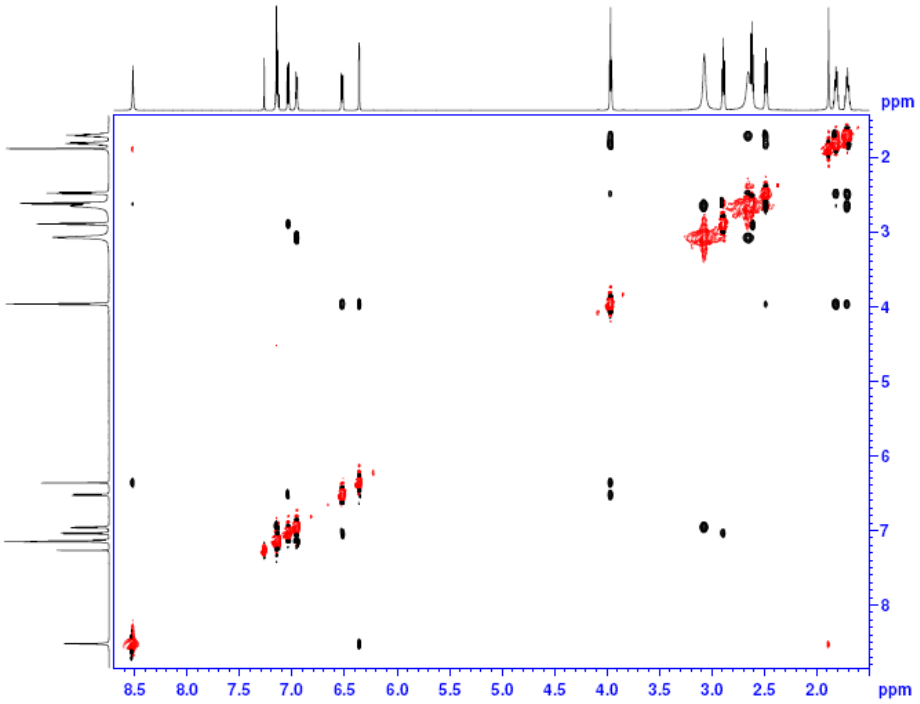


Figure S4c: NOESY spectrum of Aripiprazole (600 MHz, $CDCl_3$, 298 K)

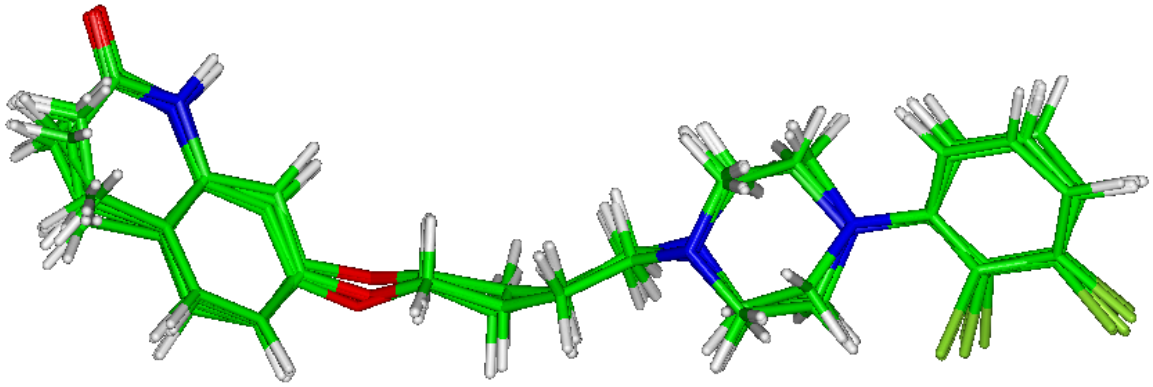


Figure S4d: Superimposition of the energy minimized structures of Aripiprazole in $CDCl_3$ obtained from MD studies

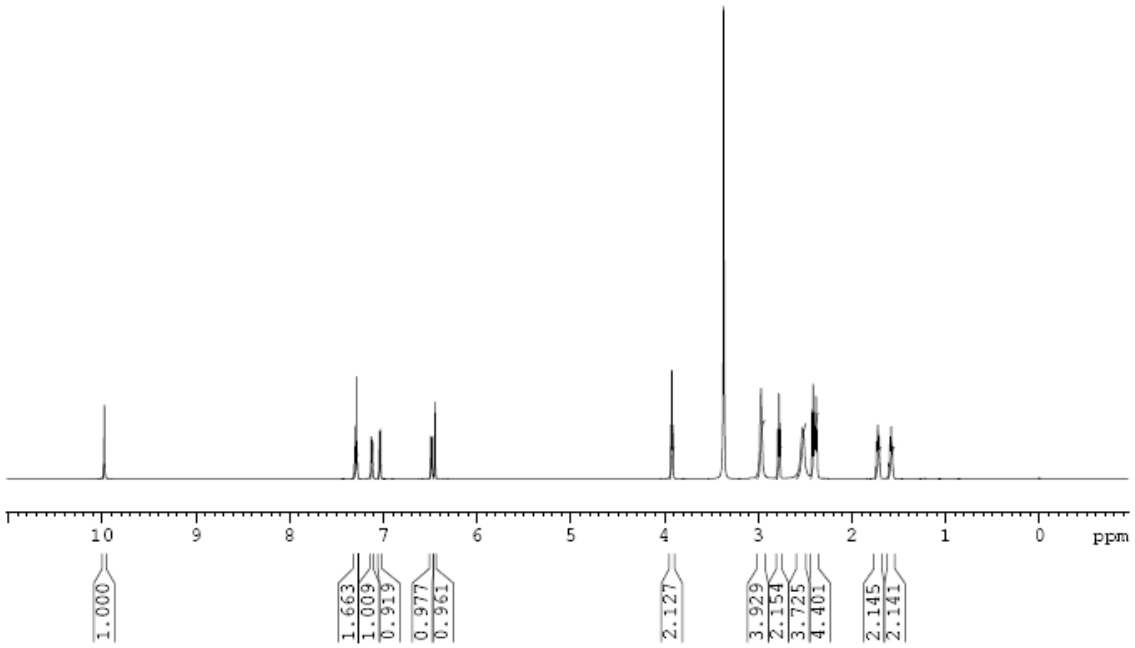


Figure S5a: ^{1}H-NMR spectral data of Aripiprazole (DMSO-d_6, 298 K, 600 MHz): 9.98 (s,1H), 7.28-7.30 (m,2H), 7.12 (dd,1H,J=7.10,2.35 Hz), 7.04 (d,1H,J=8.30 Hz), 6.48 (dd,1H,J=8.30,2.35 Hz), 6.45 (d,1H,J=2.35 Hz), 3.96 (t,2H,J=6.45 Hz), 2.97 (m,4H), 2.78 (t,2H,J=7.45 Hz), 2.52 (m,4H), 2.41 (t,2H,J=7.45 Hz), 2.38 (t,2H,J=7.15 Hz), 1.72 (m,2H), 1.58 (m,2H).

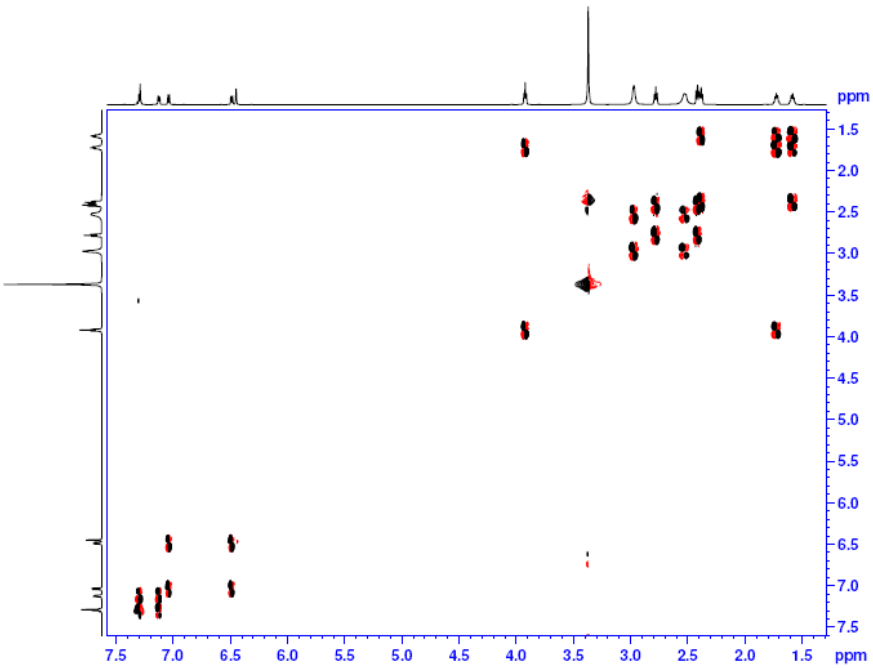


Figure S5b: COSY spectrum of Aripiprazole (600 MHz, DMSO-d_6, 298 K).

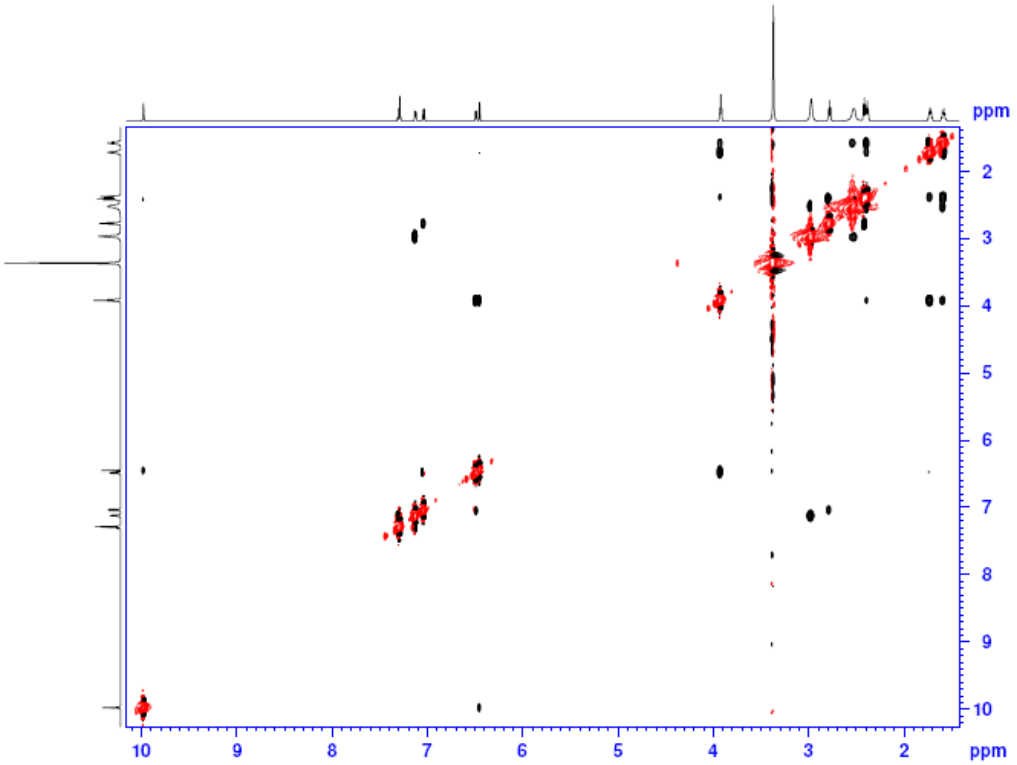


Figure S5c: NOESY spectrum of Aripiprazole (600 MHz, DMSO-d_6, 298 K).

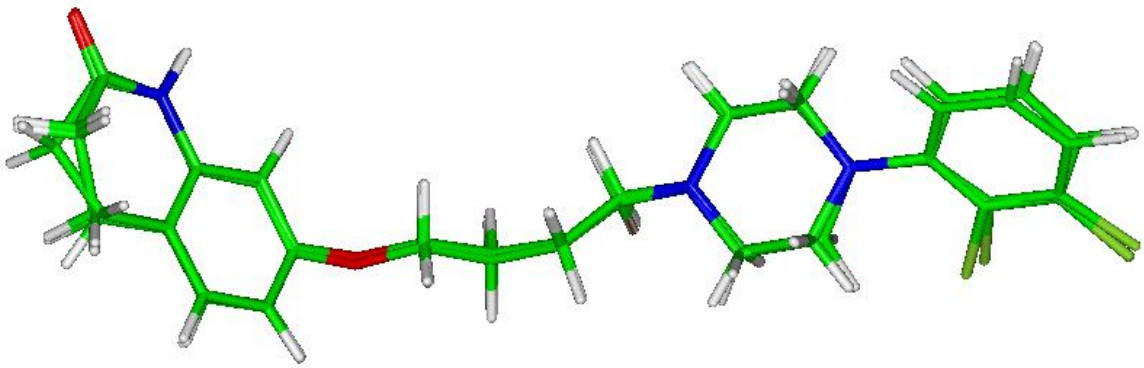


Figure S5d: Superimposition of the energy minimized structures of Aripiprazole in DMSO-d_6 obtained from MD studies.

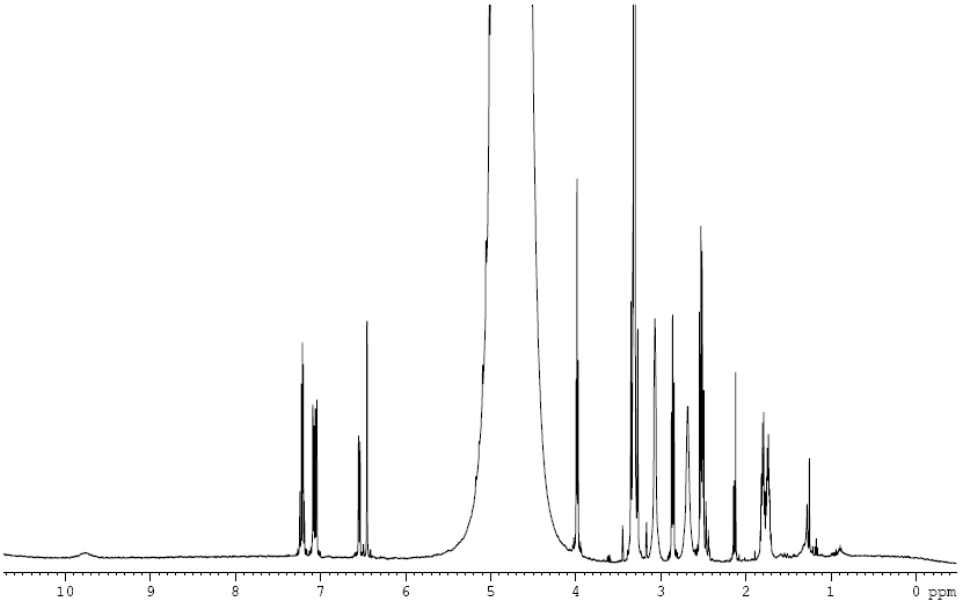


Figure S6: ^{1}H NMR spectrum of Aripiprazole (CD_3OH, 298 K, 500 MHz): 9.80 (bs,1H), 7.18-7.24 (m,2H), 7.02-7.09 (m,2H), 6.54 (dd,1H,J=8.25,2.45 Hz), 6.44 (d,1H,J=2.49 Hz), 3.97 (t,2H,J=6.15 Hz), 3.06 (m,4H), 2.85 (t,2H,J=7.35 Hz), 2.67 (m,4H), 2.47-2.54 (m,4H), 1.79 (m,2H), 1.73 (m,2H).

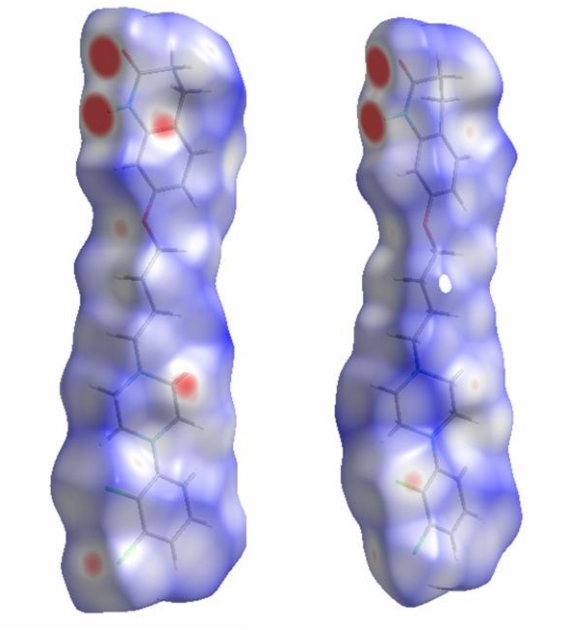


Figure S7: Hirshfeld surface plots mapped with d_{norm} property are shown for two symmetry independent molecules in form VI. The d_{norm} property displays surface with red-white-blue color scheme, where, red spots highlight shorter intermolecular contacts, white areas indicate contacts with the *van der Waals* radii separation, and blue region represents contacts above the *van der Walls* radii. The d_{norm} range used for generating the surface plots is -0.6 to 1.5. The differences between the two symmetry independent molecules are visually apparent in the number of red spots and the variations in the intensity of other colors.

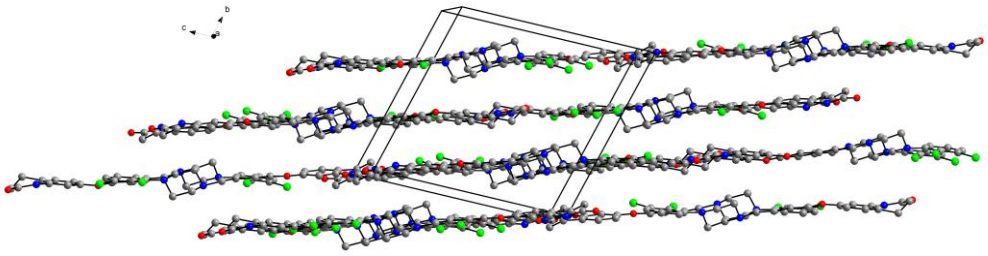


Figure S8: The two dimensional layer of molecules are stacked in the third dimension to complete the crystal packing.

Table S1. Torsion angle variations in 9 conformers of 6 polymorphs and their comparison with the values of geometry minimised conformer.

Polymorph	τ_1	τ_2	τ_3	τ_4	τ_5	τ_6	τ_7
Form I	76.38	-173.71	63.05	174.70	-60.18	167.27	70.96
Form II	44.1	176.24	178.92	173.28	- 177.96	-159.39	68.83
Form III_A[a]	178.92	179.66	177.48	161.79	174.20	159.87	75.37
Form III_B[a]	175.79	166.07	178.95	175.92	172.92	168.12	73.12
Form IV_A[a]	175.69	176.7	179.63	176.52	169.41	167.47	70.39
Form IV_B[a]	178.36	175.33	175.24	178.25	179.60	173.10	69.26
Form V	173.10	178.82	174.41	169.62	170.60	156.07	68.23
Form VI_A[a]	176.29	178.54	178.63	175.90	168.86	169.13	-62.64
Form VI_B[a]	171.94	-170.61	-178.49	178.19	171.05	170.79	-67.77
Geometry minimised	179.67	179.87	178.29	175.53	171.68	164.84	-72.88

[a] Molecules A and B represent symmetry independent molecules in polymorphs III, IV and VI.

Table S2. The percentage contribution of various intermolecular contacts to the Hirshfeld surface.

Polymorph	Stronger contacts / %		Weaker contacts / %			
	O…H	N…H	CL…H	C…H	H…H	Others[b]
Form I	10.1	1.8	18.0	18.8	49.4	1.9
Form II	9.2	2.1	17.4	15.7	50.9	3.9
Form III_A[a]	13.2	2.4	17.1	18.2	46.2	2.6
Form III_B[a]	9.4	1.5	20.0	16.9	48.5	3.5
Form IV_A[a]	11.7	3.7	14.6	15.5	49.2	4.9
Form IV_B[a]	8.5	2.9	20.0	15.0	48.4	4.8
Form V	10.8	2.3	17.5	17.9	48.1	3.2
Form VI_A[a]	9.8	3.0	17.5	17.2	48.1	4.2
Form VI_B[a]	12.1	3.4	16.0	15.1	48.5	4.8

[a]Molecules A and B represent symmetry independent molecules in the asymmetric unit of forms III, IV and VI. [b]Other interactions include Cl…O, Cl…N, Cl…Cl, Cl…C, C…O and C…C.

Table S3. Crystallisation conditions for obtaining various polymorphs of Aripiprazole.

Polymorph	Space group	Crystallisation technique and Solvent used
Form I	Non-centrosymmetric $P2_1$	Melt crystallisation at 130 ˚C Or Heating form III to 140 ˚C.[a]
Form II	Non-centrosymmetric $Pna2_1$	Crystallisation from Acetonitrile at 70˚C. Or stirring a suspension of APPZ in 1-butanol or acetonitrile for 1h between 65-75˚C.[a]
Form III	Centrosymmetric $P\bar{1}$	Crystallisation from various solvents like 1-butanol, ethyl acetate, xylene, n-hexane.[a] Crystallisation from 1,4-dioxane.[b] Crystallised fom Ethyl acetate and hexane combinations.[c]
Form IV	Centrosymmetric $P\bar{1}$	Crystallisation from tolune, dioxane, 2-propanol and acetonitrile.[a]
Form V	Non-centrosymmetric $P2_1$	Crystallisation from acetone, 1-propanol, 2-propanol, acetonitrile, 1-butanol.[a]
Form VI	Centrosymmetric $P\bar{1}$	Crystallisation from Ethyl acetate and hexane combination.

[a]Reference 9 in the main article
[b]Reference 8 in the main article
[c]The present article.

CSD analysis: The Cambridge Structural Database version 5.3, November 2011 release with February 2012 update[10] was searched for total number of amides. Only structures with 3D coordinates, organic, no errors, no disorder, no ions, no powder and no polymeric were the search criteria. All chiral structures are excluded using the algorithm provided by Eppel et.al.[20a] A total of 12,612 achiral amide moelcules were left. To extract only achiral moelcules in the non-centrosymmetric space groups,[20b] the following space groups are used as query filters. These are $P2_1$, $P2_12_12_1$, $P1$, $Pna2_1$, $Pca2_1$, Pc, Fdd_2, $P4_12_12$, $Cmc2_1$, $R3$, $P3_12_1$, C_2, $P2_12_12$, $C2_12_12$, $P4_32_12$, $R3c$, $P4_1$, $P3_1$, $P6_3$, Iba_2, $P6_1$, Cm, $P3_22_1$, $R3_2$, $I4_1cd$, $I4$, $P2$, $P6_3mc$, $P3_1c$, $P6_122$, $P222_1$, $P2_13$, $P3_2$, $P4_3$, $P6_5$, $R3m$, Pnn_2, $P3$, $I4_1$, $I222$, $P22_12$, $Pba2$, $Ama2$. The search resulted 2012 molecules belonging to the required criteria. They were subdivided into *cis* and *trans* amides using torsion angle constraints in the query.