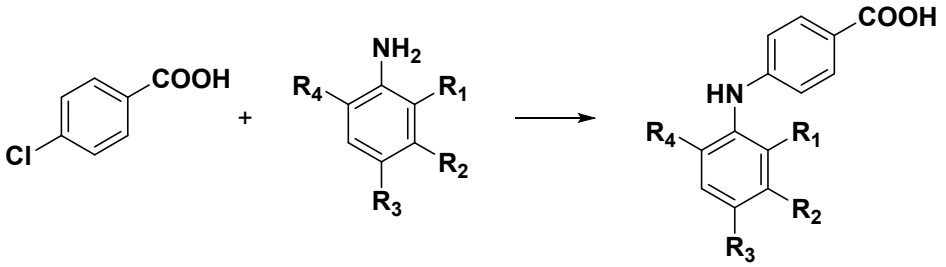
Electronic Supplementary Material (ESI) for RSC Advances.

Solvatomorphism and First-time Observation of Acid-Acid Catemer in 4-Phenylamino-benzoic Acids

Synthesis



1: $R_1 = R_2 = R_3 = R_4 = H$
2: $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$
3: $R_2 = CH_3$, $R_1 = R_3 = R_4 = H$
4: $R_3 = CH_3$, $R_1 = R_2 = R_4 = H$
5: $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$
6: $R_2 = R_3 = CH_3$, $R_1 = R_4 = H$
7: $R_1 = R_4 = CH_3$, $R_2 = R_3 = H$
8: $R_1 = R_2 = R_3 = R_4 = CH_3$

General procedure for the synthesis:

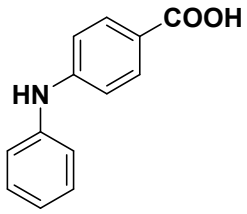
To a solution of 4-phenylamino-benzoic acids (1.50 g, 9.58 mmol), amine (14.37 mmol) in DMF (8.00 mL) were added Cs_2CO_3 (4.68 g, 14.37 mmol), BINAP (0.60 g, 0.96 mmol) and $Pd(OAc)_2$ (0.22 g, 0.96 mmol). The reaction mixture was stirred at 120 ℃ for 24 hours. DMF was removed *in vacuo*. Then 90 mL water was added, and the mixture was stirred for several minutes. After removing the unwanted solids by filtration, concentrated HCl (12 mol/L) was added dropwise to acidify the solution to pH = 2. Crude product precipitated as gray and black solid, and it was recovered by filtration. It was dried overnight in an oven at 60 ℃, and then purified by silica gel chromatography (eluent: PE/EA/AA = 200/1/1→150/1/0.75→100/1/0.5).

Characterization:

NMR spectra were recorded in DMSO-d_6 on an Agilent 400/54 Premium Shielded Spectrometer (Agilent, USA). The HRMS was measured using a Agilent 7800 (Agilent, USA) liquid chromatography-mass spectrometer (LC-MS). IR spectra were

recorded on a PerkinElmer FT-IR spectrometer (PerkinElmer, USA) with samples dispersed in KBr pellets.

4-Phenylamino-benzoic acid (1)



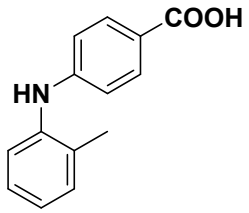
The product was obtained as white solid (0.88 g, 43%).

^{1}H NMR (400 MHz, DMSO-d_6) *δppm* 12.32 (s, 1H), 8.72 (s, 1H), 7.81 – 7.76 (m, 2H), 7.35 – 7.28 (m, 2H), 7.20 – 7.15 (m, 2H), 7.07 – 7.02 (m, 2H), 6.97 (tt, J = 7.2, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) *δppm* 167.2, 148.0, 141.5, 131.1, 129.3, 121.6, 120.6, 119.1, 114.0.

1-I: IR (KBr, cm^{-1}) 3408 (s), 1670 (s), 1596 (s), 1519 (s), 1500 (s), 1426 (s), 1312 (s), 1176 (s), 753 (s), 694 (s); mp: 160.5 ºC.

1-S: IR (KBr, cm^{-1}) 3418 (s), 1654 (s), 1588 (s), 1526 (s), 1406.08 (s), 1348 (s), 1315 (m), 1274 (s), 1177 (s), 1122 (m), 840 (s), 774 (s), 694 (s), 660 (m), 536 (m); mp: 158.1 ºC.

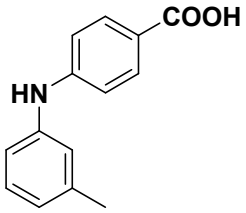
4-o-Tolylamino-benzoic acid (2)



The product was obtained as white solid (0.63 g, 29%).

^{1}H NMR (400 MHz, DMSO-d_6) *δppm* 12.19 (s, 1H), 8.11 (s, 1H), 7.76 – 7.70 (m, 2H), 7.29 – 7.16 (m, 3H), 7.06 (td, J = 7.2, 1.8 Hz, 1H), 6.79 – 6.73 (m, 2H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) *δppm* 167.7, 150.5, 139.8, 132.6, 131.6, 131.5, 127.14, 124.7, 124.0, 119.8, 113.6, 18.3; IR (KBr, cm^{-1}) 3401 (s), 3226 (m), 2925 (w), 1679 (s), 1644 (s), 1574 (s), 1492 (m), 1375 (s), 1339 (s), 1170 (s), 1108 (s), 946 (w), 843 (m), 774 (s); HRMS m/z (M + H^{+}) 228.1019; mp: 163.9 ºC.

4-m-Tolylamino-benzoic acid (3)



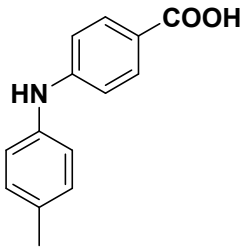
The product was obtained as light yellow solid (1.14 g, 52%).

^{1}H NMR (400 MHz, DMSO-d_6) δppm 12.28 (s, 1H), 8.64 (s, 1H), 7.83 – 7.71 (m, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.98 (d, J = 7.8 Hz, 2H), 6.79 (d, J = 7.4 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δppm 167.1, 148.3, 141.4, 138.5, 131.1, 129.1, 122.5, 120.2, 119.8, 116.3, 114.0, 21.1.

3-I: IR (KBr, cm^{-1}) 3419 (s), 2958 (w), 1655 (s), 1588 (s), 1408 (s), 1349 (s), 1276 (s), 1179 (s), 1123 (s), 946 (w), 841 (s), 785 (s), 775 (s), 695 (s); mp: 149.0 ºC.

3-S: IR (KBr, cm^{-1}) 3418 (s), 1654 (s), 1588 (s), 1526 (s), 1406 (s), 1348 (s), 1315 (m), 1274 (m), 1177 (s), 1161 (m), 1122 (m), 840 (s), 774 (s), 694 (s), 660 (s), 536 (s); mp: 149.6 ºC.

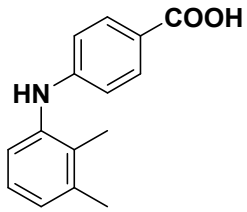
4-p-Tolylamino-benzoic acid (4)



The product was obtained as white solid (0.55 g, 25%).

^{1}H NMR (400 MHz, DMSO-d_6) δppm 12.24 (s, 1H), 8.58 (s, 1H), 7.78 – 7.72 (m, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.00 – 6.95 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δppm 167.1, 148.7, 138.7, 131.1, 130.9, 129.7, 119.9, 119.7, 113.4, 20.3; IR (KBr, cm^{-1}) 3411 (s), 3022 (w), 2913 (w), 1670 (s), 1599 (s), 1516 (s), 1429 (s), 1304 (s), 1177 (s), 1122 (w), 946 (w), 831 (s), 811 (s); mp: 187.6 ºC.

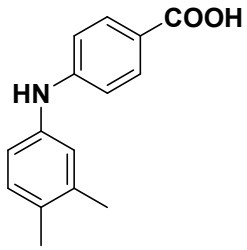
4-(2,3-Dimethyl-phenylamino)-benzoic acid (5)



The product was obtained as brown solid (0.78 g, 34 %).

^{1}H NMR (400 MHz, DMSO-d_6) *δppm* 12.18 (s, 1H), 8.18 (s, 1H), 7.73 – 7.68 (m, 2H), 7.12 – 6.98 (m, 3H), 6.69 – 6.64 (m, 2H), 2.27 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (125 MHz , DMSO-d_6) *δppm* 167.8, 151.2, 139.5, 138.3, 132.1, 131.6, 126.7, 126.4, 122.8, 119.3, 113.2, 20.7, 14.4; IR (KBr, cm^{-1}) 3384 (s), 3056 (w), 2982 (w), 1660 (s), 1608 (s), 1577 (s), 1522 (m), 1471 (m), 1416 (s), 1372 (w), 1320 (s), 1292 (s), 1181 (s), 960 (w), 842 (w), 775 (m), 653 (w), 553 (w); HRMS m/z (M + H^{+}) 242.1178; mp: 192.3 ºC.

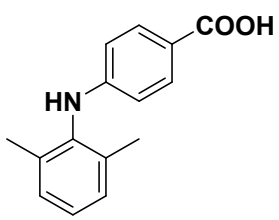
4-(3,4-Dimethyl-phenylamino)-benzoic acid (6)



The product was obtained as brown solid (0.88 g, 38%).

^{1}H NMR (400 MHz, DMSO-d_6) *δppm* 12.17 (s, 1H), 8.17 (s, 1H), 7.74 – 7.68 (m, 2H), 7.12 – 6.98 (m, 3H), 6.69 – 6.63 (m, 2H), 2.27 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) *δppm* 167.7, 149.4, 139.4, 137.5, 131.6, 130.6, 130.4, 121.8, 120.0, 117.9, 113.8, 20.0, 19.1; IR (KBr, cm^{-1}) 3410 (s), 2977 (m), 1665 (s), 1598 (s), 1506 (s), 1426 (s), 1319 (s), 1293 (s), 1173 (s), 948 (s), 846 (s), 769 (s), 696 (s), 653 (s), 545 (s); HRMS m/z (M + H^{+}) 242.1177; mp: 186.6 ºC.

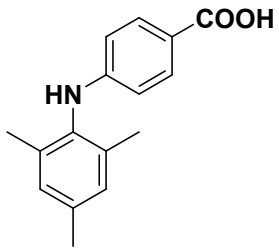
4-(2,6-Dimethyl-phenylamino)-benzoic acid (7)



The product was obtained as brown solid (0.70 g, 30%).

^{1}H NMR (400 MHz, DMSO-d_6) δppm 12.09 (s, 1H), 8.03 (s, 1H), 7.72 – 7.65 (m, 2H), 7.18 – 7.08 (m, 3H), 6.40 (d, J = 8.3 Hz, 2H), 2.13 (s, 7H); ^{13}C NMR (125 MHz , DMSO-d_6) δppm 167.8, 151.5, 137.7, 136.5, 131.8, 128.9, 126.7, 118.6, 111.8, 18.4; IR (KBr, cm^{-1}) 3404 (s), 3058 (w), 2985 (w), 1666 (s), 1606 (s), 1523 (m), 1486 (m), 1418 (s), 1338 (s), 1291 (s), 1175 (s), 940 (m), 843 (s), 775 (s), 645 (s), 546 (s), 497 (s); HRMS m/z (M + H^{+}) 242.1177; mp: 217.7 ºC.

4-(mesitylamino)-benzoic acid (8)



The product was obtained as white solid (0.79 g, 32%).

^{1}H NMR (400 MHz, DMSO-d_6) δppm 12.19 (s, 1H), 8.11 (s, 1H), 7.76 – 7.70 (m, 2H), 7.29 – 7.16 (m, 3H), 7.06 (td, J = 7.2, 1.8 Hz, 1H), 6.79 – 6.73 (m, 2H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δppm 167.9, 151.8, 136.3, 136.2, 135.7, 135.0, 131.8, 129.5, 118.4, 111.6, 21.0, 18.3, 18.2; HRMS m/z (M + H^{+}) 256.1334.

8-I: IR (KBr, cm^{-1}) 3378 (s), 1672 (s), 1599 (s), 1576 (s), 1484 (s), 1417 (s), 1337 (s), 1313 (s), 1290 (s), 1171 (s), 842 (m), 774 (s), 646 (w), 550 (m); mp: 226 .9 ºC.

8-S: IR (KBr, cm^{-1}) 3457 (w), 3377 (s), 2980 (w), 2543 (w), 1672 (s), 1600 (s), 1521 (s), 1484 (s), 1417 (s), 1337 (s), 1313 (s), 1290 (s), 1222 (m), 1171 (s), 1111 (w), 1035 (w), 957 (m), 842 (w), 774 (s), 699 (m), 646 (m), 568 (w), 550 (w); mp: 221 .1 ºC.

Note: the melting points were measured with DSC, and the onset temperatures were recorded.

Crystallization

Example: MeOH was added dropwise to 30 mg compound **1** until it was just dissolved, then the solution was filtered into a 5 mL vial and placed in a fume hood. The solvent was evaporated slowly until crystals were obtained.

Table S1. Solvents Used for Crystallization and Crystal Form(s) Obtained

solvent	method	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
MeOH	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
Acetone	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
$CHCl_3$	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
EA	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
DCM	slow evaporation	**1-I**	**2-I**	**3-II**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
EtOH	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
CH_3CN	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
Ether	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
IPA	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
DMSO	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
THF	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
AA	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
DMF	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
PhH	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
PhMe	slow evaporation	**1-I**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-I**
Py	slow evaporation	**1-S**	**2-I**	**3-I**	**4-I**	**5-I**	**6-I**	**7-I**	**8-S**

(MeOH: methanol; $CHCl_3$: chloroform; EA: ethyl acetate; DCM: dichloromethane; EtOH: ethanol; CH_3CN: acetonitrile; IPA: 2-propanol; DMSO: dimethylsulfoxide; THF: tetrahydrofuran; AA: acetic acid; DMF: dimethyl formamide; PhH: benzene; PhMe: methylbenzene; Py: pyridine.)

IR

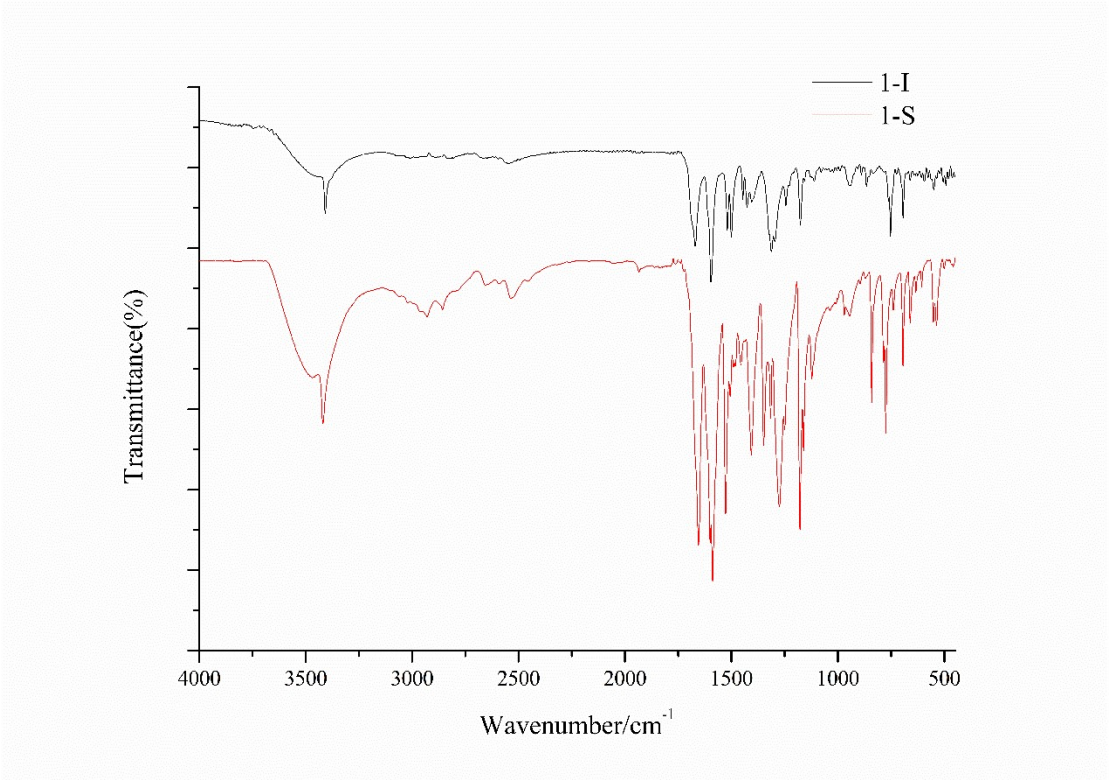


Figure S1. IR spectra of the two crystal forms of compound **1**.

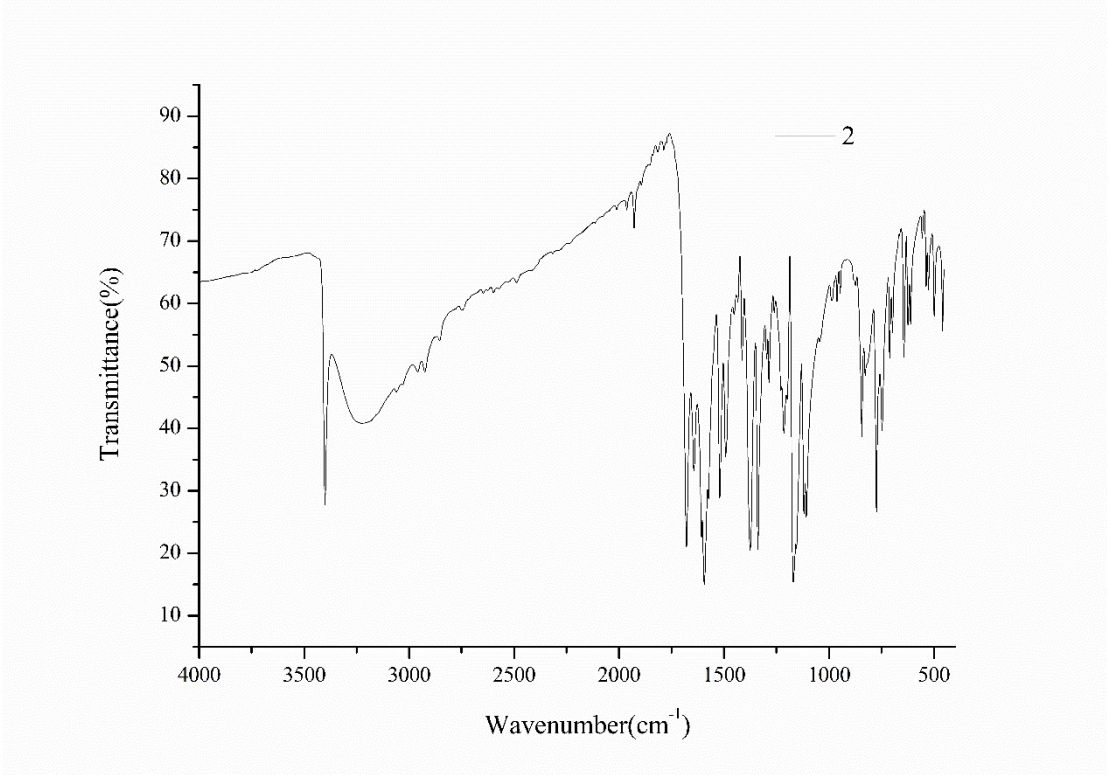


Figure S2. IR spectrum of compound **2**.

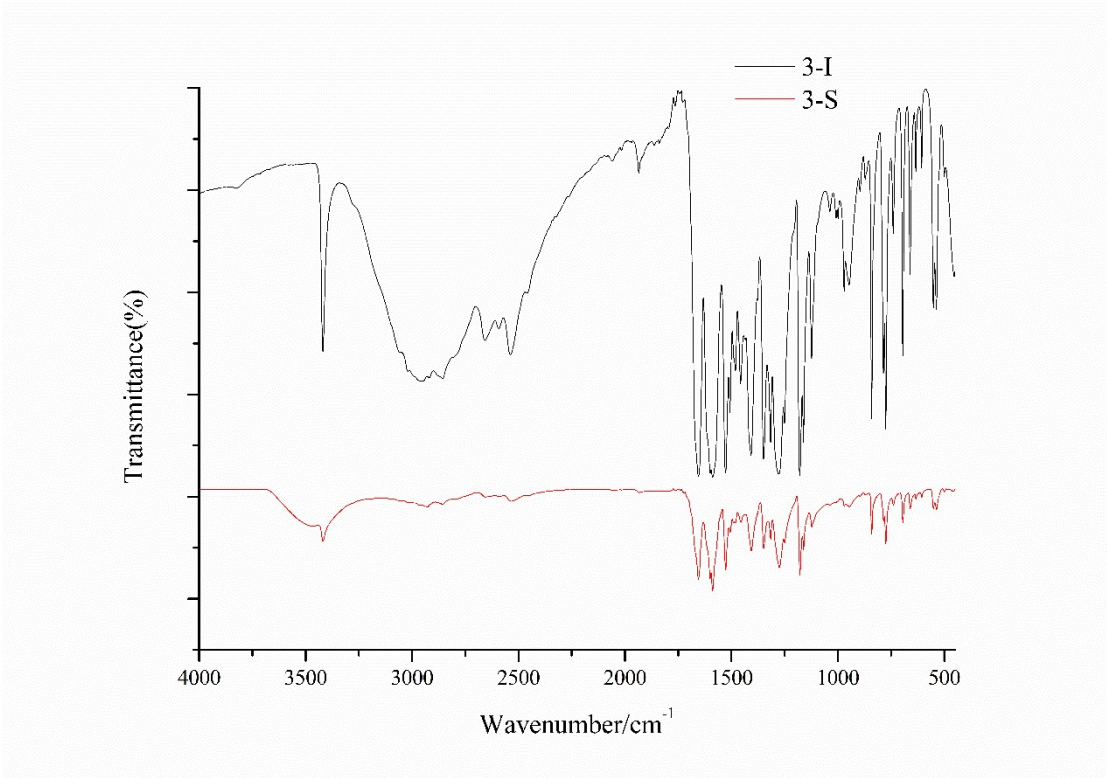


Figure S3. IR spectra of the two crystal forms of compound **3**.

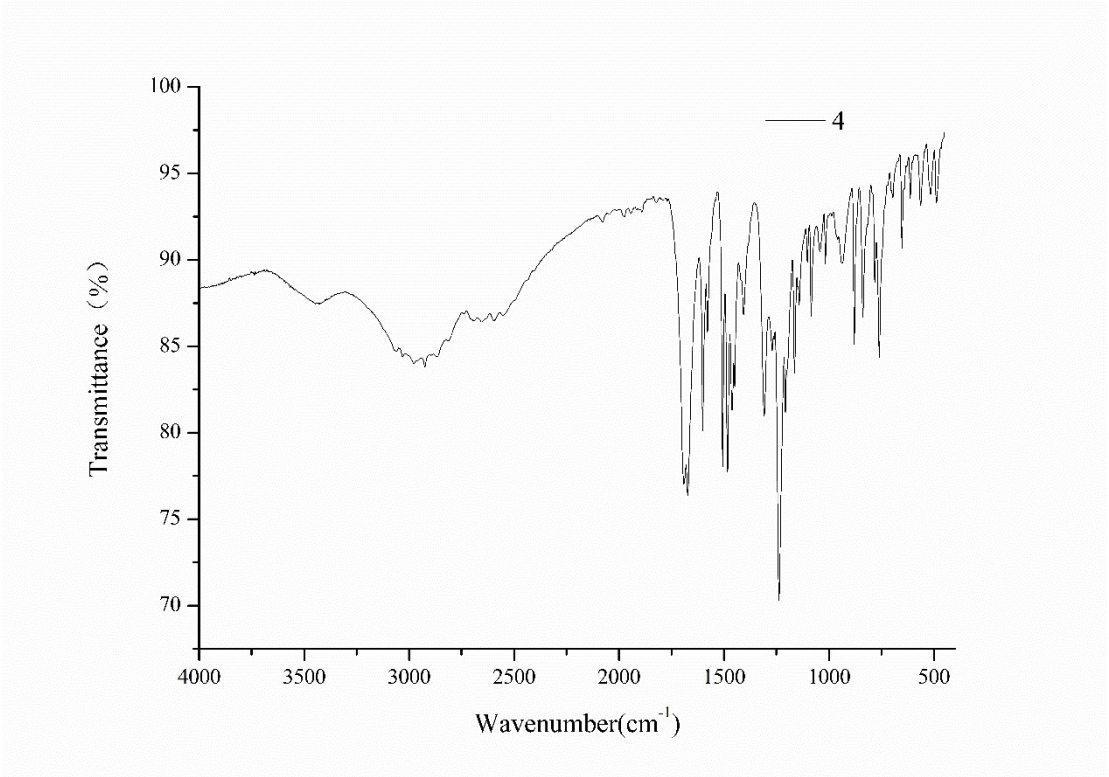


Figure S4. IR spectrum of compound **4**.

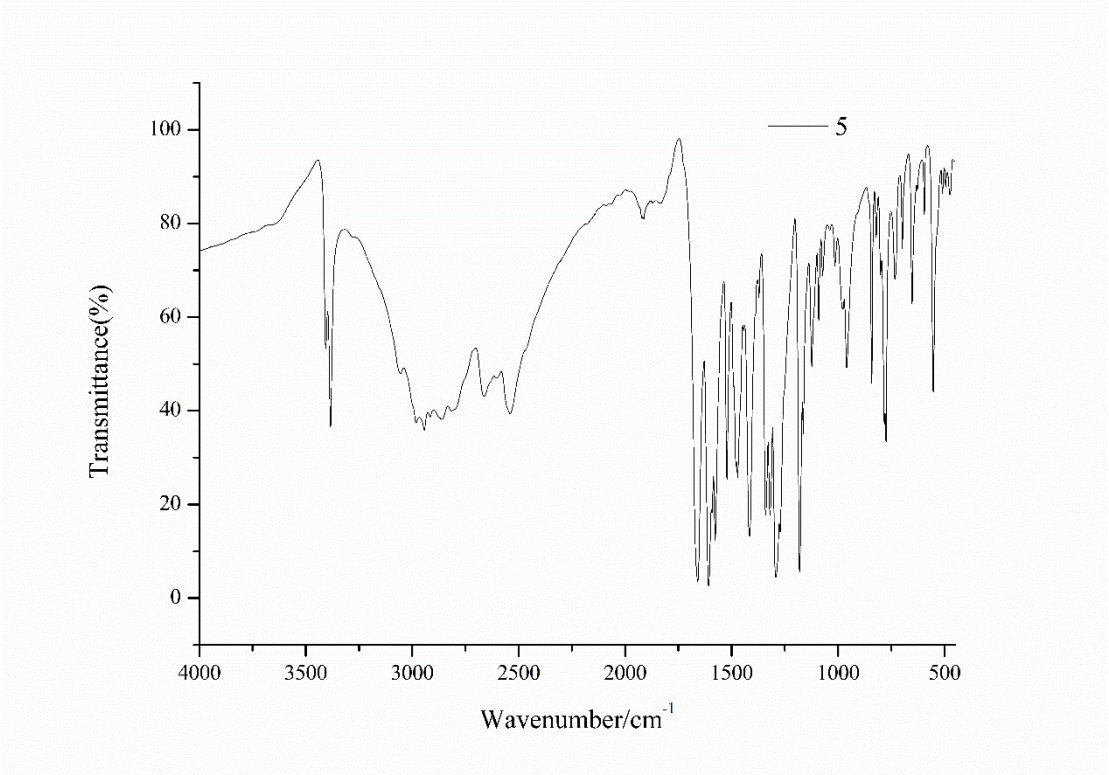


Figure S5. IR spectrum of compound **5**.

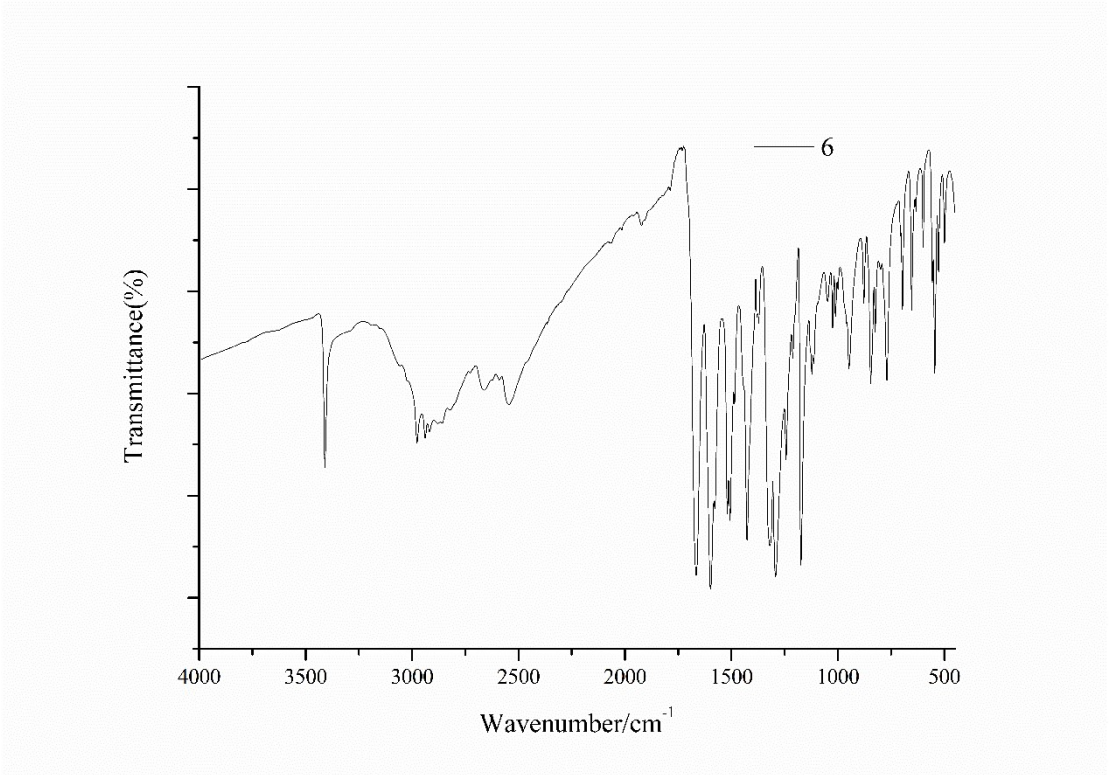


Figure S6. IR spectrum of compound **6**.

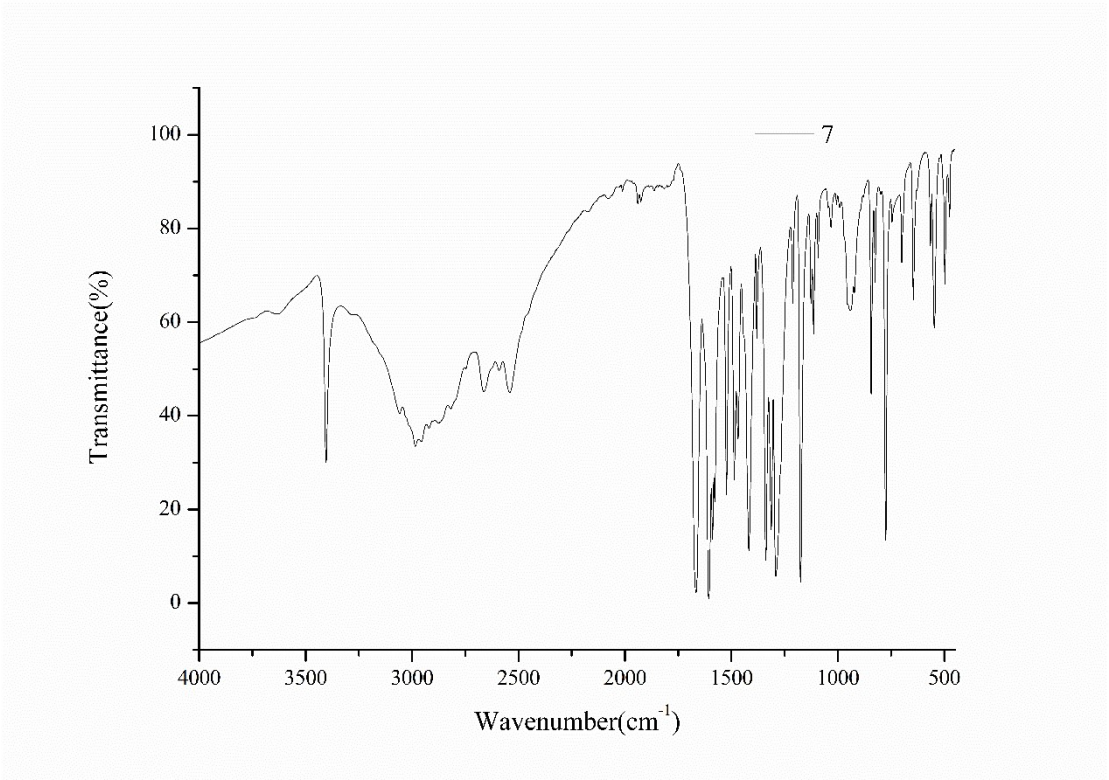


Figure S7. IR spectrum of compound **7**.

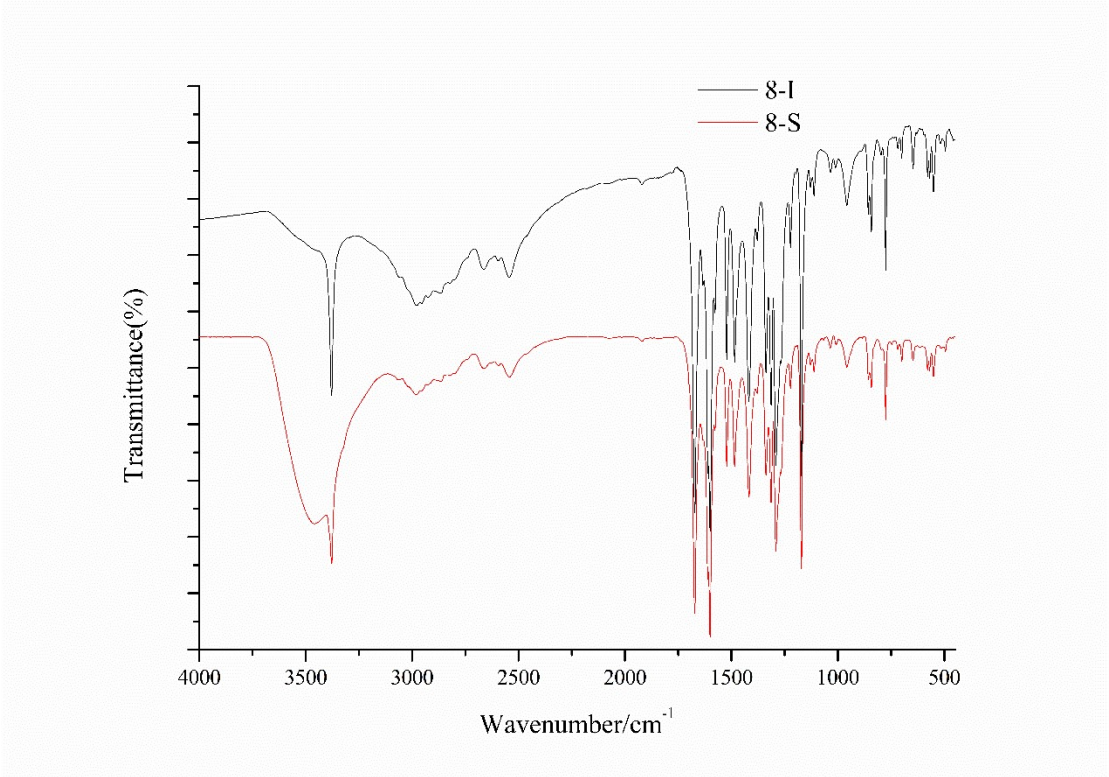


Figure S8. IR spectra of the two crystal forms of compound **8**.

PXRD

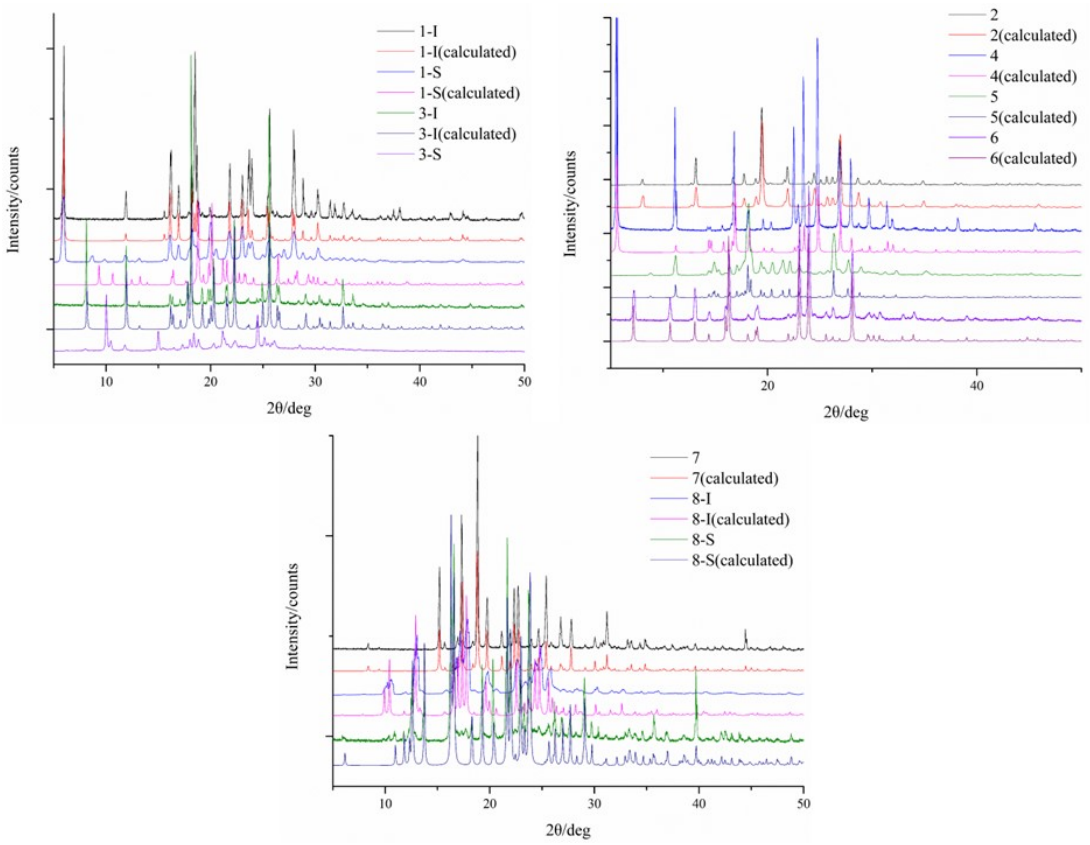


Figure S9. PXRD patterns of the crystal form(s) of compounds **1-8**.

Computational Results

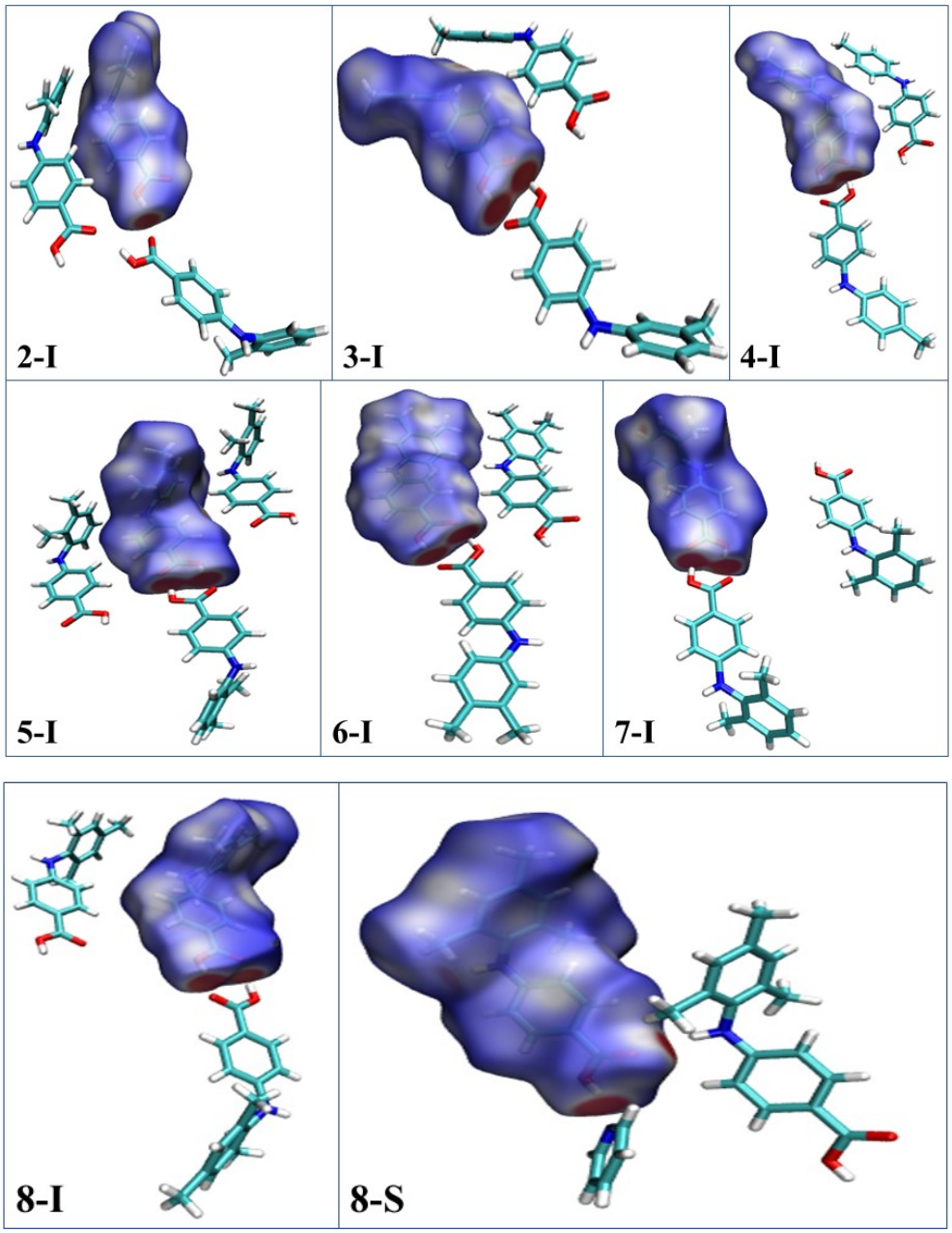


Figure S10. Hirshfeld surface analysis of the crystal(s) of compounds **2**-**8**.

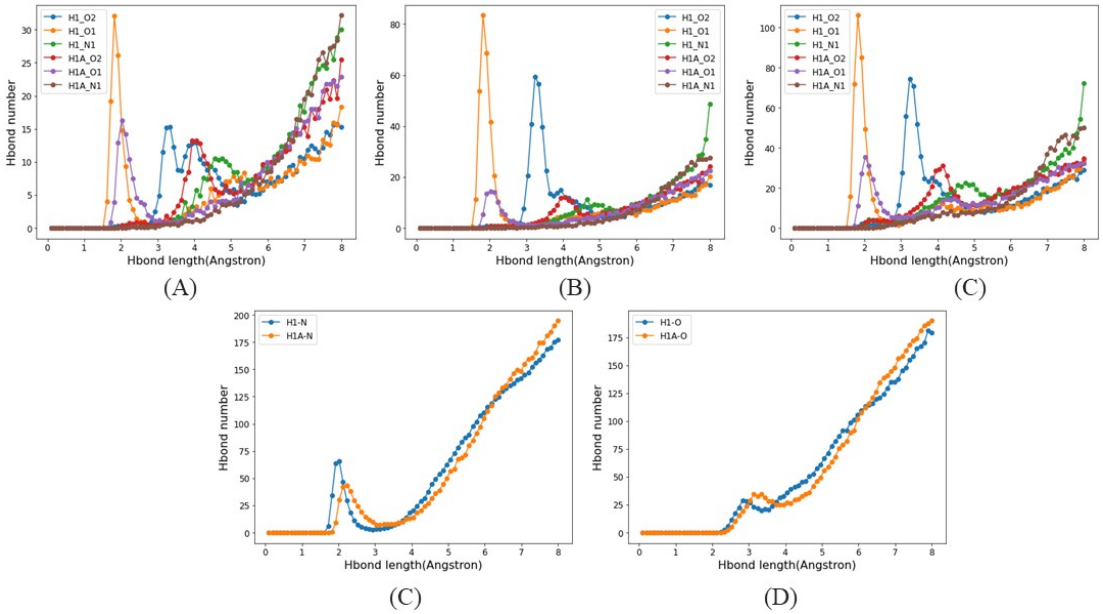


Figure S11. Hydrogen bond types and lengths between molecules in solutions of molecule **2**. A-C), Hydrogen bonds in API dimers in PID, THF and BEN; D-E), Hydrogen bonds in dimers of API and solvent in PID and THF.

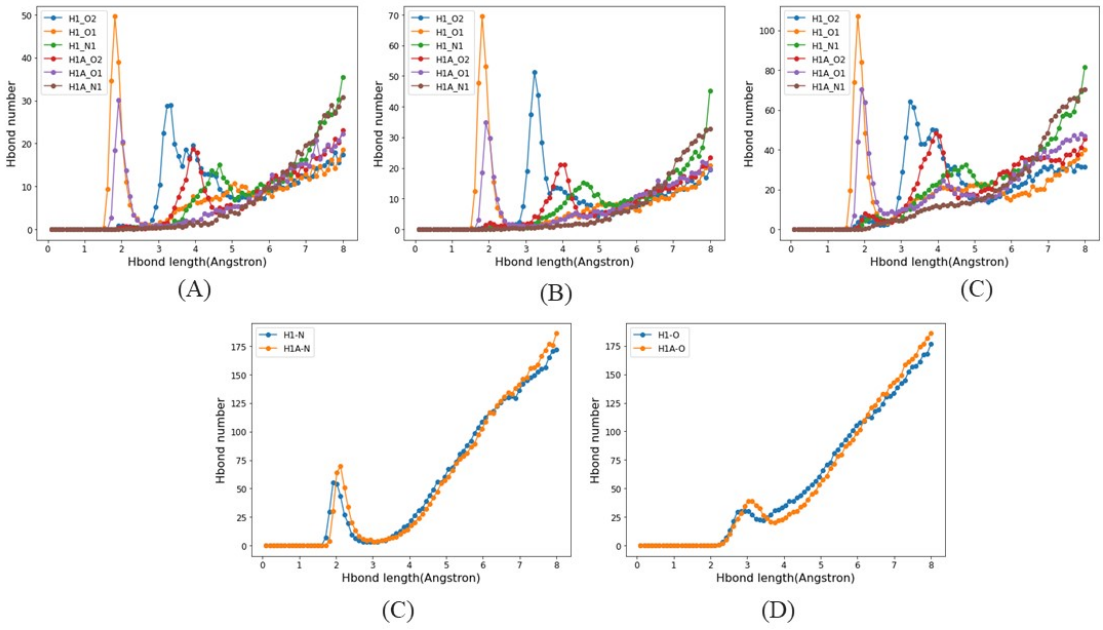


Figure S12. Hydrogen bond types and lengths between molecules in solutions of molecule **4**. A-C), Hydrogen bonds in API dimers in PID, THF and BEN; D-E), Hydrogen bonds in dimers of API and solvent in PID and THF.

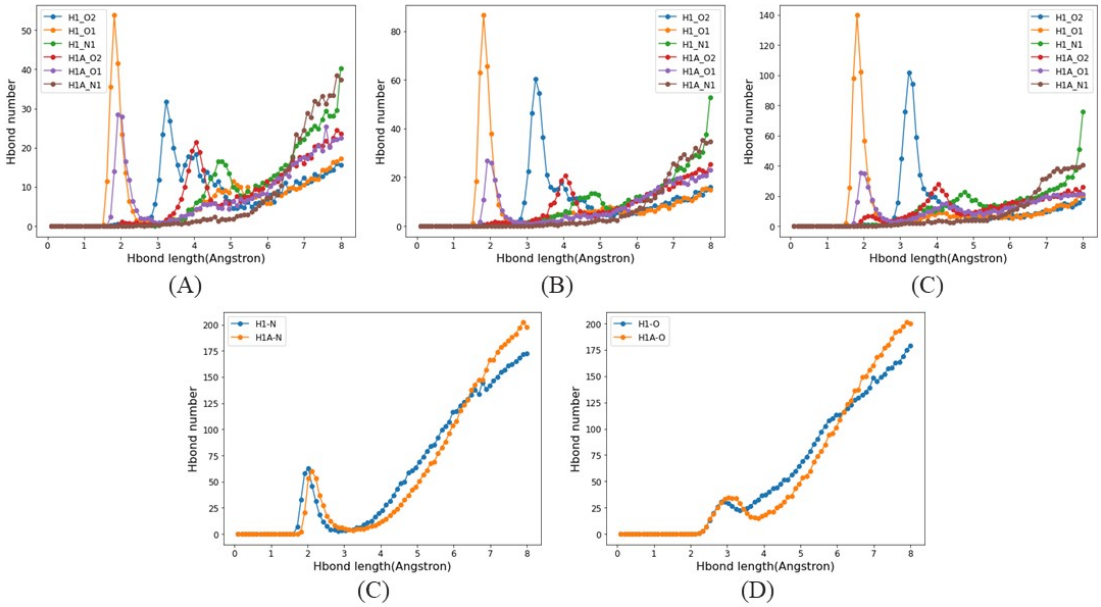


Figure S13. Hydrogen bond types and lengths between molecules in solutions of molecule **8**. A-C), Hydrogen bonds in API dimers in PID, THF and BEN; D-E), Hydrogen bonds in dimers of API and solvent in PID and THF.