Electronic Supplementary Material (ESI) for CrystEngComm.

Supplementary data for

Cocrystal formation by anti-solvent slurry

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Experimental section

Materials and general methods

CBZ was purchased from Shanghai Shengde Pharmaceutical Technology Co., Ltd. Malonic acid, succinic acid, glutaric acid, adipic acid, DL-malic acid, benzoic acid, cinnamic acid, salicylic acid, acetylsalicylic acid, vanillic acid, 2, 6-pyridinedicarboxylic acid, benzamide, isonicotinamide, nicotinamide, saccharin and 4, 4'-bipyridine were purchased from Aladdin Reagent Inc. L(+)-tartaric acid, L-malic acid, 1-hydroxy-2-naphthoic acid, 4-hydroxybenzoic acid, 2, 4-dihydroxybenzoic acid, 2, 5-dihydroxybenzoic acid, 2, 6-dihydroxybenzoic acid, 4-hydroxybenzamide and naringenin were purchased from Energy Chemical. All other chemicals and solvents were commercially available and used as received. Powder X-ray Diffraction (PXRD) analysis was performed on a Rigaku MiniFlex 600 X-ray diffractometer equipped with a D/teX Ultra one-dimensional detector, using Cu Kα radiation (λ = 1.541862 Å) generated at 40 kV and 15 mA. Each sample was placed on a silicon disk and measured over an angular range of 3−40 ° (2θ) with a step size of 0.0142° (2θ) and a dwell time of 0.1 s. Thermogravimetric (TG) analysis was performed using a Netzsch TG 209F3 instrument under nitrogen atmosphere. Each sample was placed on an alumina crucible and heated from 40 °C to 500 °C at a heating rate of 10 °C/min. Differential scanning calorimetry (DSC) was recorded on a Netzsch DSC 200 F3 instrument with nitrogen atmosphere. Each sample was placed on an aluminum sample pan and heated from 40 °C to the decomposition temperature of the sample at a heating rate of 10 °C/min. ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were acquired on a Bruker 400 MHz spectrometer using dimethyl sulfoxide-d6 as solvent and TMS (0 ppm) as internal standard.

General procedure of each anti-solvent slurry experiment

A stoichiometric ratio mixture of CBZ and co-former (with the total mass of 20 mg) was added to 1 mL anti-solvent (*n*-heptane) with addition of 10-100 μL (MeOH/MeCN/EtOAc/ACE). The resulting suspension was stirred under 600 rpm for 24-48 hours and was then filtered. The obtained solid was dried under air and was examined by PXRD.

Anti-solvent slurry experiment 1: CBZ-malonic acid cocrystal (2:1)

A stoichiometric mixture of CBZ (16.4 mg, 0.070 mmol) and malonic acid (3.6 mg, 0.035 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature. A stoichiometric mixture of CBZ (0.82 mg, 0.0035 mmol) and malonic acid (0.18 mg, 0.0017 mmol) was added to 0.5 mL heptane with addition of 1 µL MeOH and left to stir for 30 min at room temperature. A stoichiometric mixture of CBZ (82.0 g, 0.35 mol) and malonic acid (18.0 g, 0.17 mol) was added to 500 mL heptane with addition of 50 µL MeOH and left to stir for 30 min at room temperature.

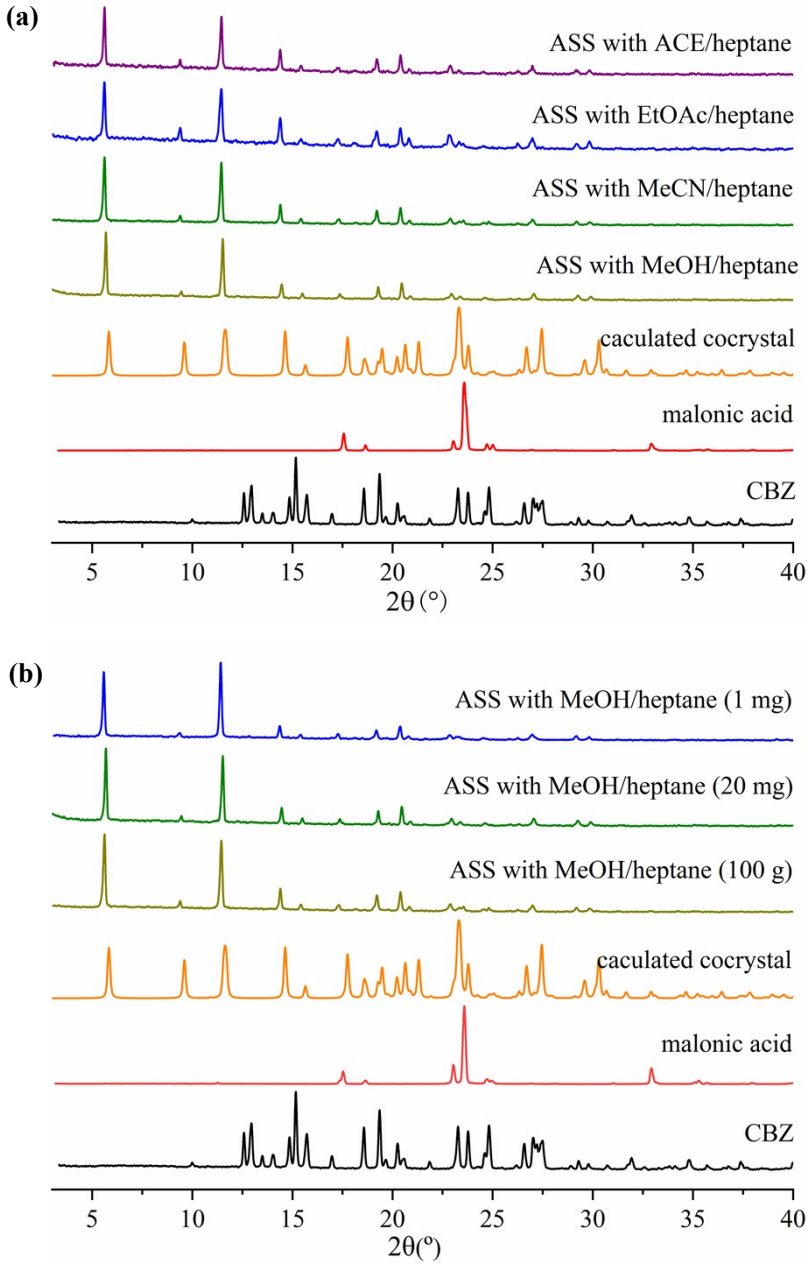


Fig. S1 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments (a) with different solvents and (b) on varying scales of CBZ/malonic acid system.

Anti-solvent slurry experiment 2: CBZ-succinic acid cocrystal (2:1)

A stoichiometric mixture of CBZ (16.0 mg, 0.068 mmol) and succinic acid (4.0 mg, 0.034 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

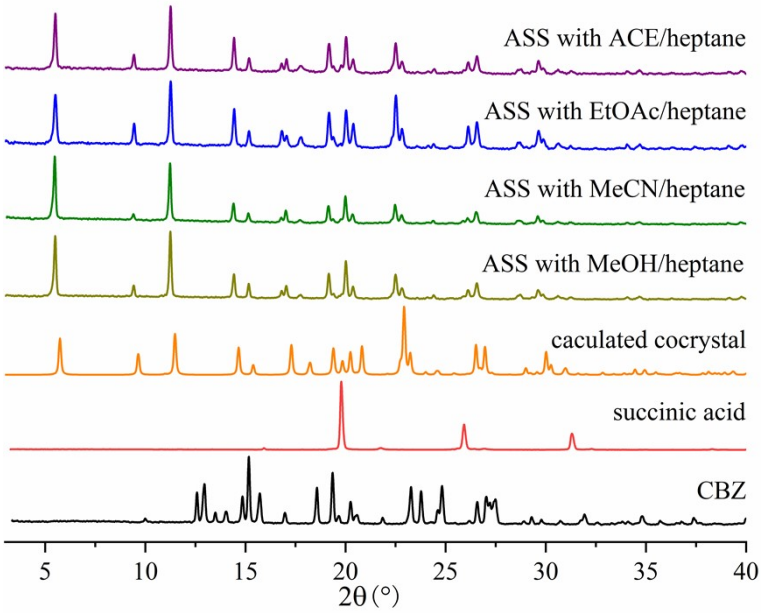


Fig. S2 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/succinic acid system.

Anti-solvent slurry experiment 3: CBZ-glutaric acid cocrystal (1:1)

An equimolar mixture of CBZ (12.8 mg, 0.055 mmol) and glutaric acid (7.2 mg, 0.055 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

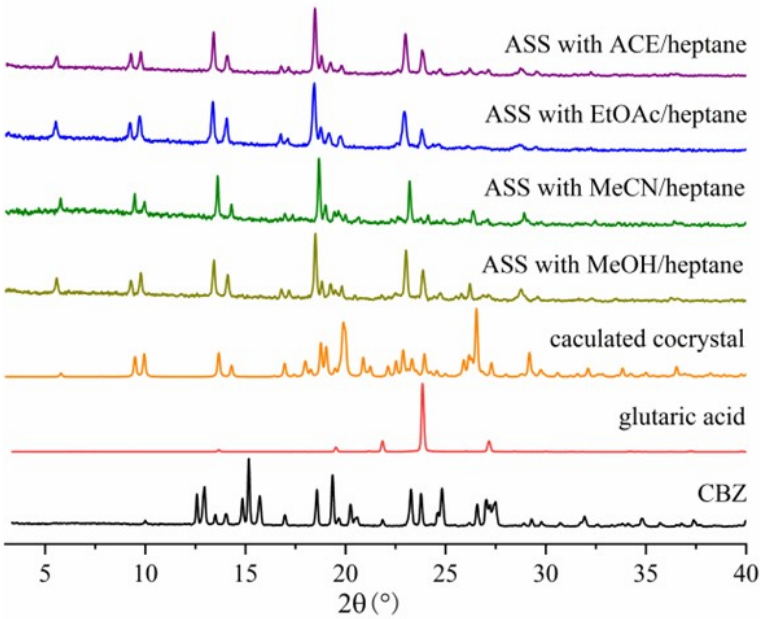


Fig. S3 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/glutaric acid system.

Anti-solvent slurry experiment 4: CBZ-adipic acid cocrystal (2:1)

A stoichiometric mixture of CBZ (15.3 mg, 0.065 mmol) and adipic acid (4.7 mg, 0.032 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

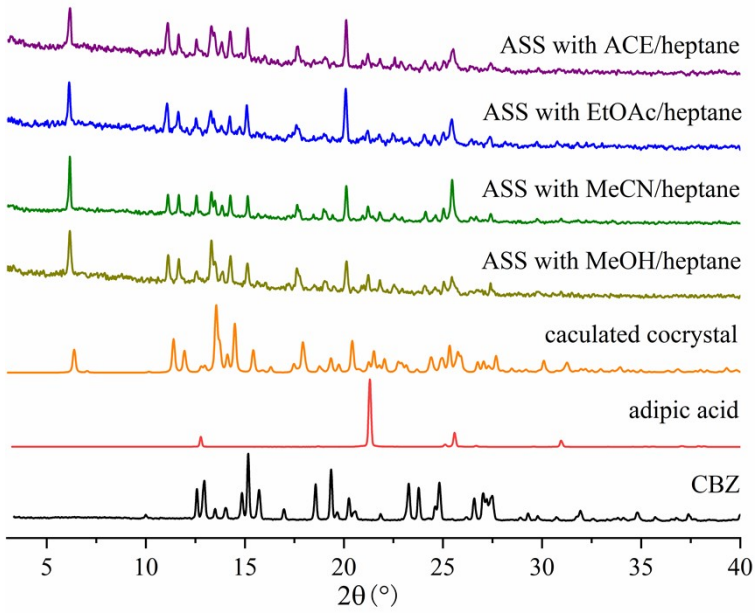


Fig. S4 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/adipic acid system.

Anti-solvent slurry experiment 5: CBZ-L(+)-tartaric acid cocrystal (1:1)

An equimolar mixture of CBZ (12.2 mg, 0.052 mmol) and L(+)-tartaric acid (7.8 mg, 0.052 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 48 hours at room temperature.

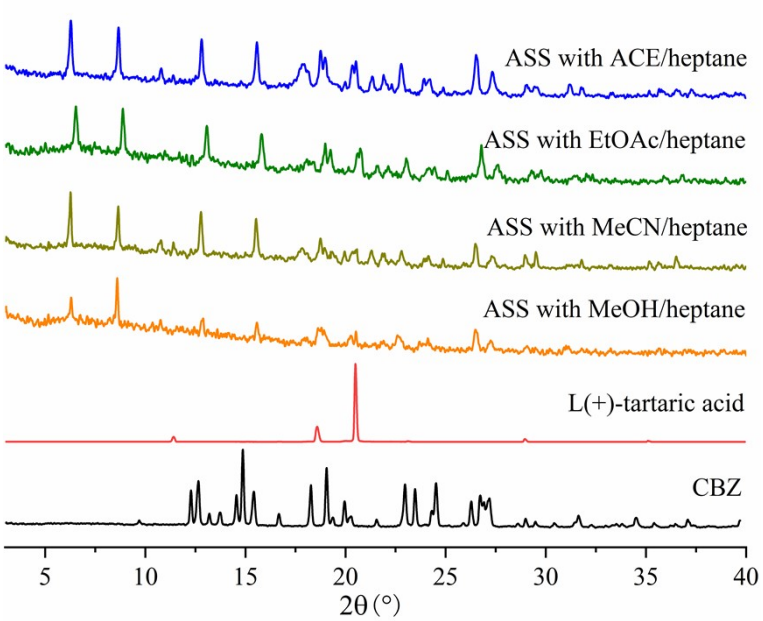


Fig. S5 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/L(+)-tartaric acid system.

Anti-solvent slurry experiment 6: CBZ-L-malic acid cocrystal (1:1)

An equimolar mixture of CBZ (12.8 mg, 0.054 mmol) and L-malic acid (7.2 mg, 0.054 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 48 hours at room temperature.

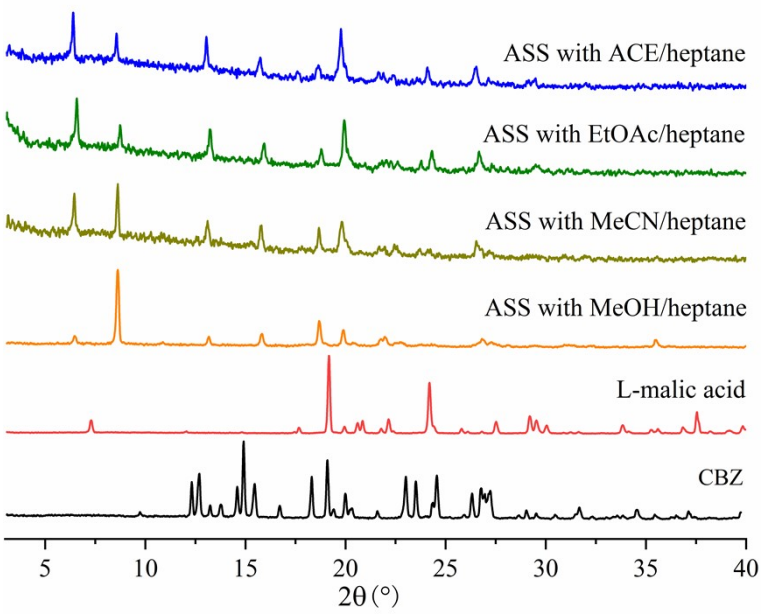
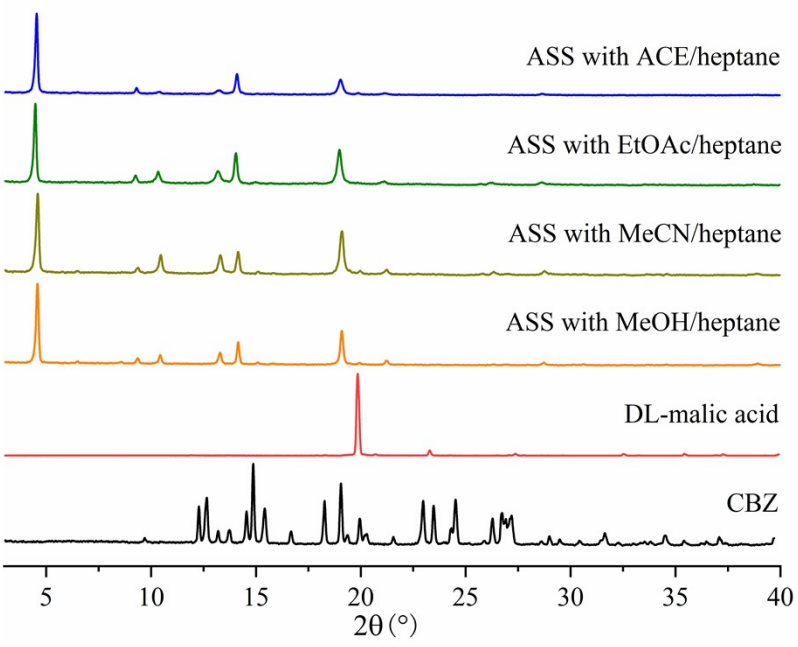


Fig. S6 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/L-malic acid system.

Anti-solvent slurry experiment 7: CBZ-DL-malic acid cocrystal (1:1)

An equimolar mixture of CBZ (12.8 mg, 0.054 mmol) and DL-malic acid (7.2 mg, 0.054 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

(a)



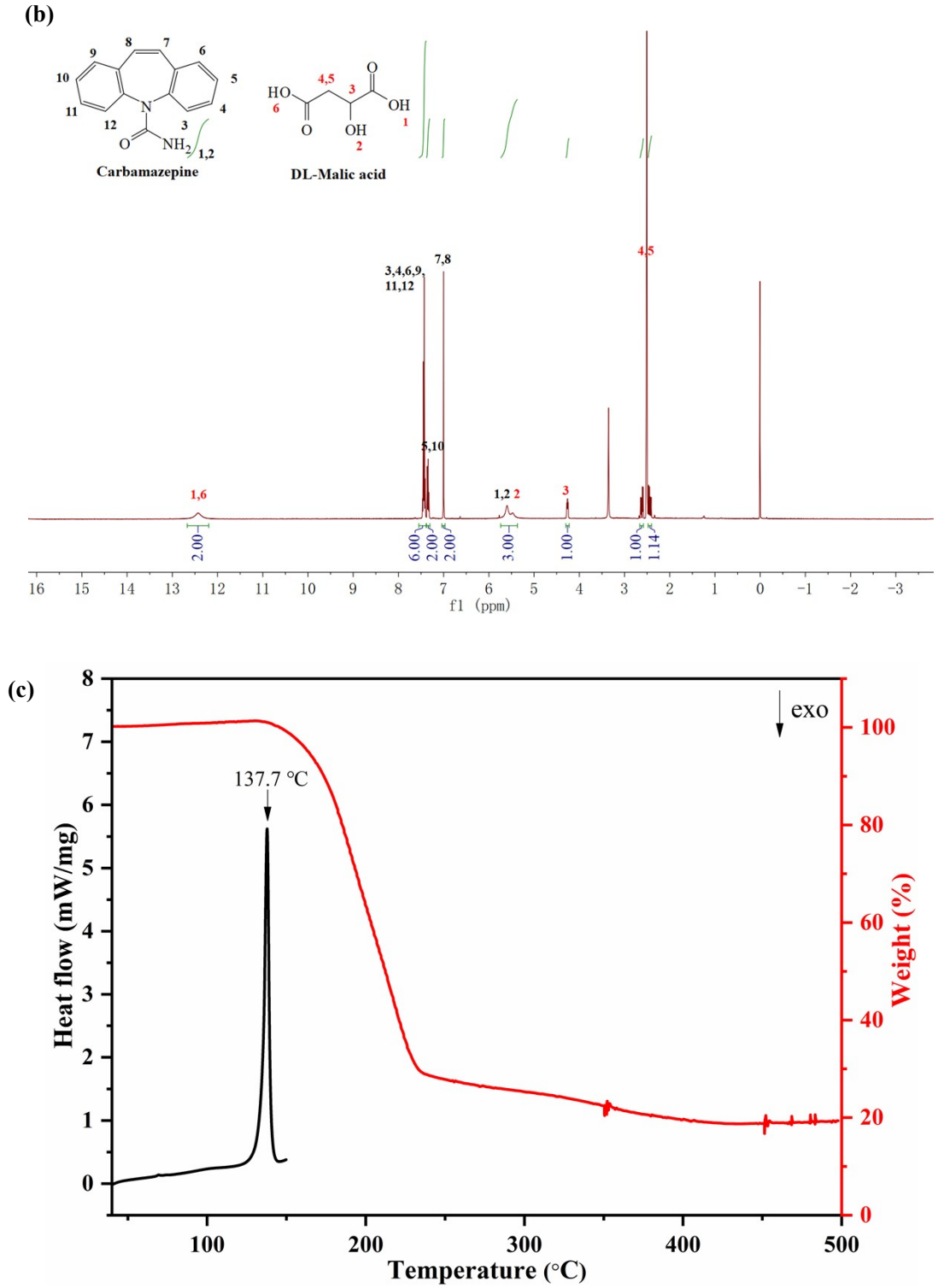


Fig. S7 (a) PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/DL-malic acid system. (b) ^{1}H NMR spectrum and (c) TG-DSC curve of CBZ-DL-malic acid cocrystal.

Anti-solvent slurry experiment 8: CBZ-benzoic acid cocrystal (1:1)

An equimolar mixture of CBZ (13.2 mg, 0.056 mmol) and benzoic acid (6.8 mg, 0.056 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

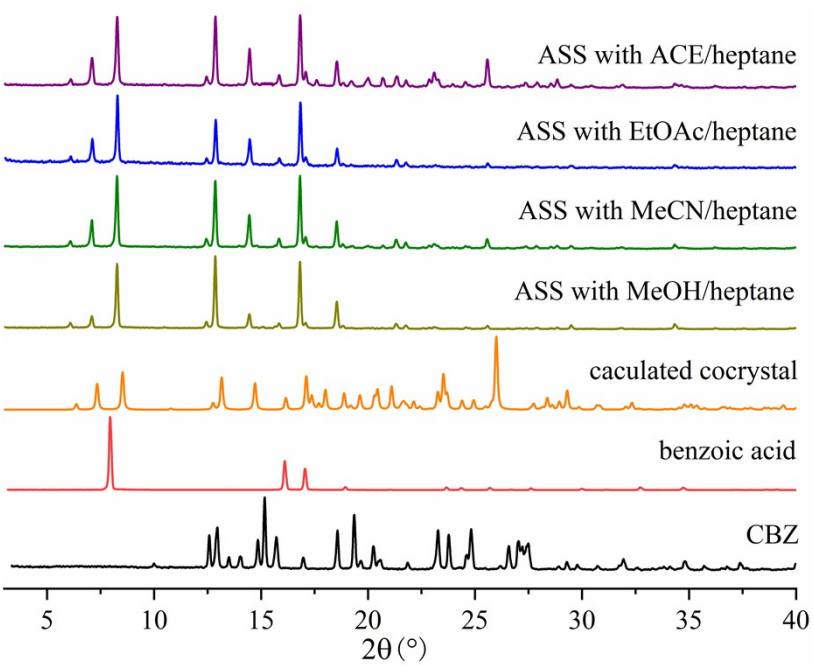


Fig. S8 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/benzoic acid system.

Anti-solvent slurry experiment 9: CBZ-cinnamic acid (1:1)

An equimolar mixture of CBZ (12.3 mg, 0.052 mmol) and cinnamic acid (7.7 mg, 0.052 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

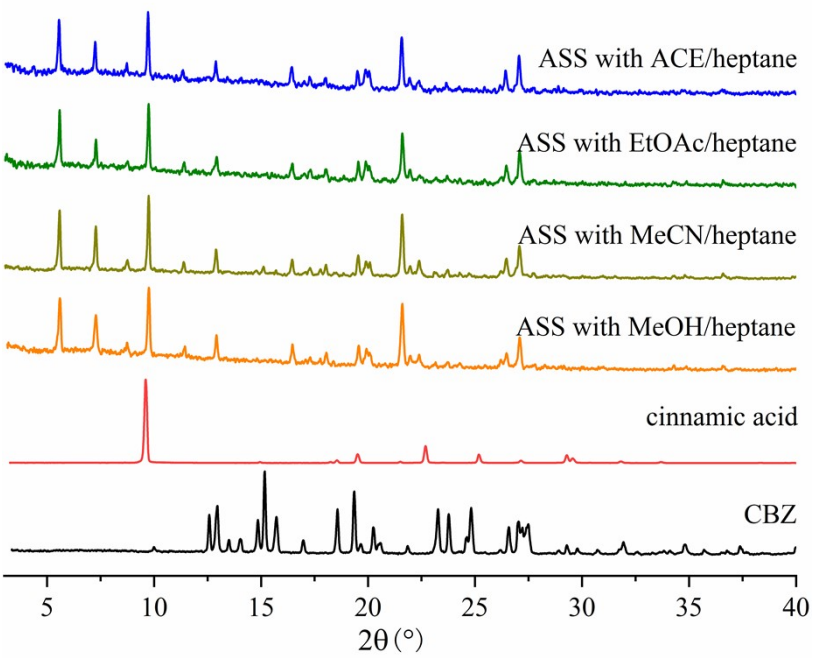


Fig. S9 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/cinnamic acid system.

Anti-solvent slurry experiment 10: CBZ-salicylic acid cocrystal (1:1)

An equimolar mixture of CBZ (12.6 mg, 0.053 mmol) and salicylic acid (7.4 mg, 0.054 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

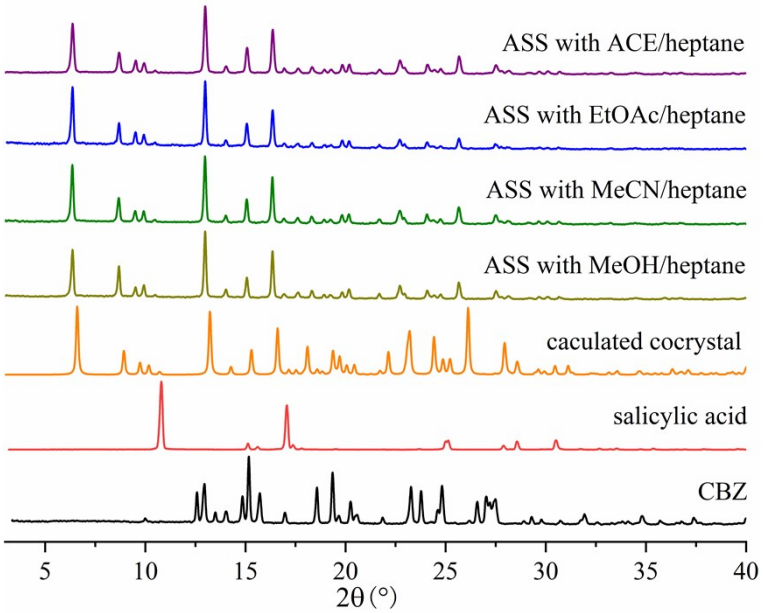


Fig. S10 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/salicylic acid system.

Anti-solvent slurry experiment 11: CBZ-acetylsalicylic acid cocrystal (1:1)

An equimolar mixture of CBZ (11.3 mg, 0.048 mmol) and acetylsalicylic acid (8.7 mg, 0.048 mmol) was added to 1 mL heptane with addition of 40 µL MeOH/40 µL MeCN/100 µL EtOAc/40 µL ACE and left to stir for 24 hours at room temperature.

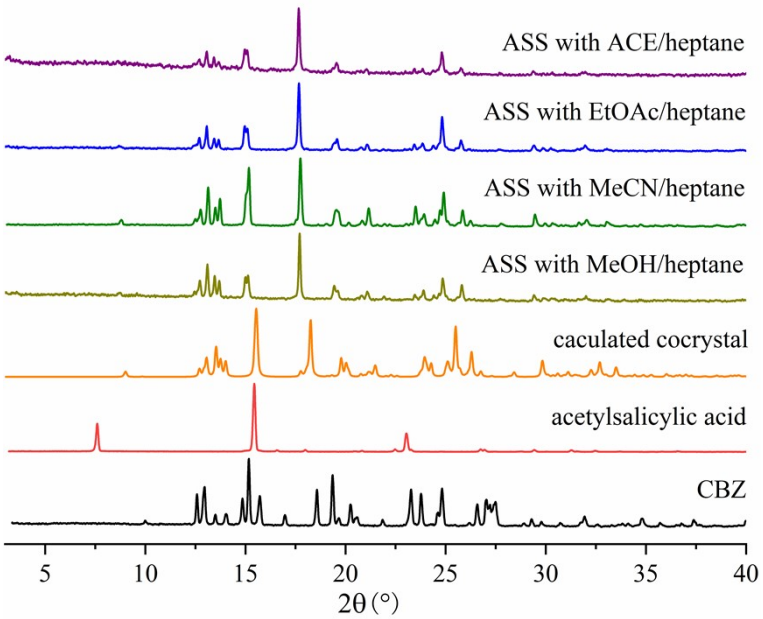


Fig. S11 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/acetylsalicylic acid system.

Anti-solvent slurry experiment 12: CBZ-1-hydroxy-2-naphthoic acid cocrystal (1:1)

An equimolar mixture of CBZ (11.1 mg, 0.047 mmol) and 1-hydroxy-2-naphthoic acid (8.9 mg, 0.047 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

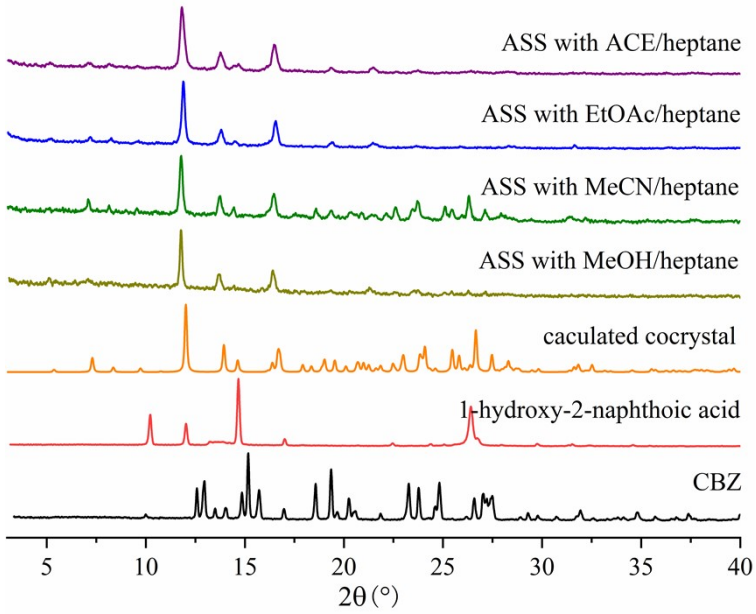


Fig. S12 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/1-hydroxy-2-naphthoic acid system.

Anti-solvent slurry experiment 13: CBZ-4-hydroxybenzoic acid cocrystal (1:1)

An equimolar mixture of CBZ (12.6 mg, 0.053 mmol) and 4-hydroxybenzoic acid (7.4 mg, 0.053 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

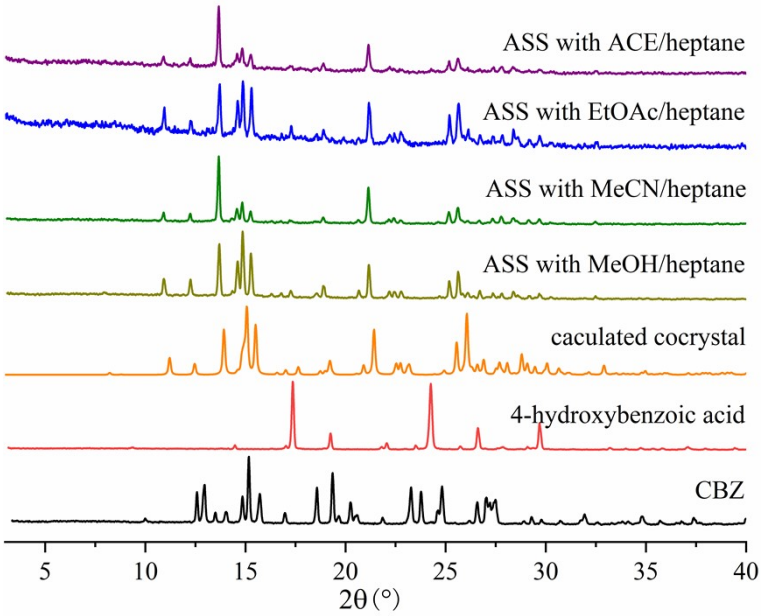


Fig. S13 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/4-hydroxybenzoic acid system.

Anti-solvent slurry experiment 14: CBZ-vanillic acid cocrystal hydrate (1:1:1)
An equimolar mixture of CBZ (11.7 mg, 0.050 mmol) and vanillic acid (8.3 mg, 0.049 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/40 µL MeCN/100 µL EtOAc/100 µL ACE and left to stir for 24 hours at room temperature.

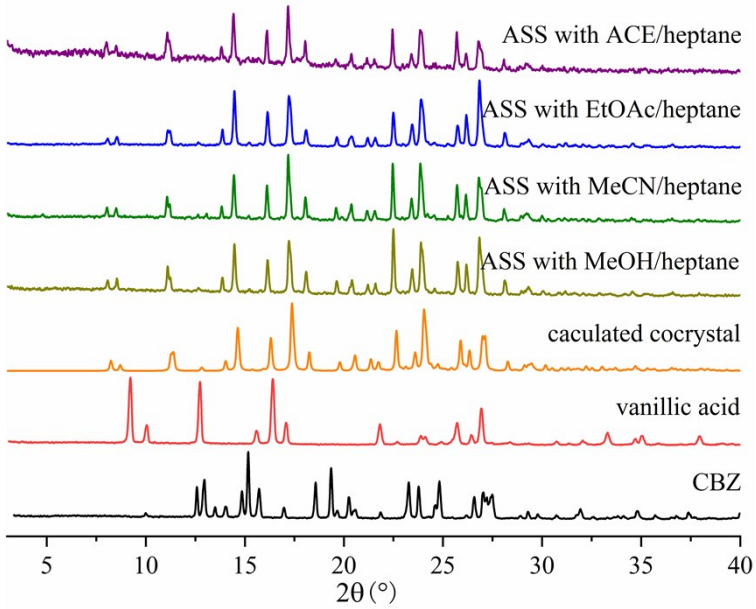


Fig. S14 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/vanillic acid system.

Anti-solvent slurry experiment 15: CBZ-2, 4-dihydroxybenzoic acid cocrystal (1:1)
An equimolar mixture of CBZ (12.1 mg, 0.051 mmol) and 2, 4-dihydroxybenzoic acid (7.9 mg, 0.051 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

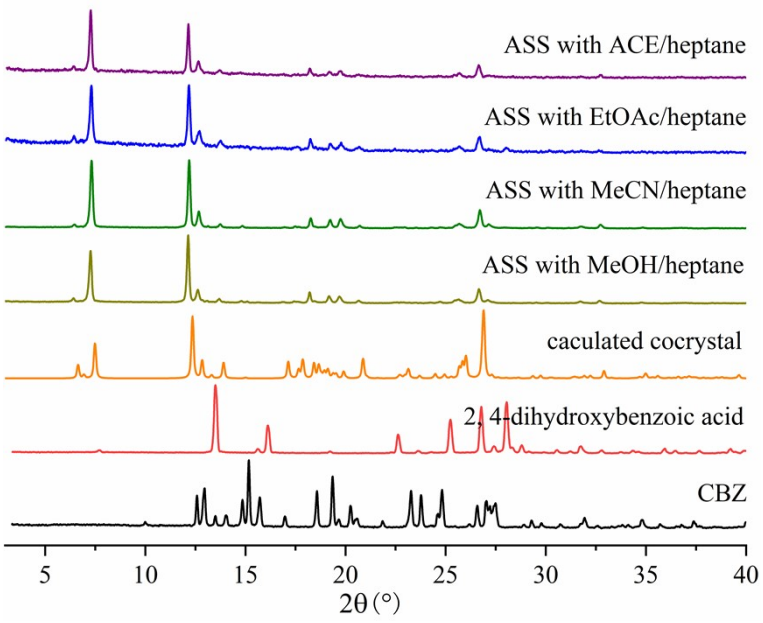


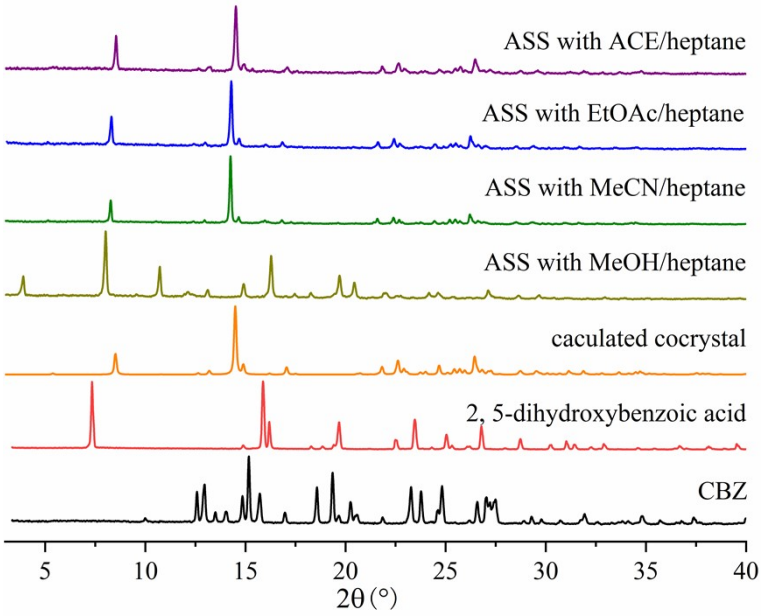
Fig. S15 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/2, 4-

dihydroxybenzoic acid system.

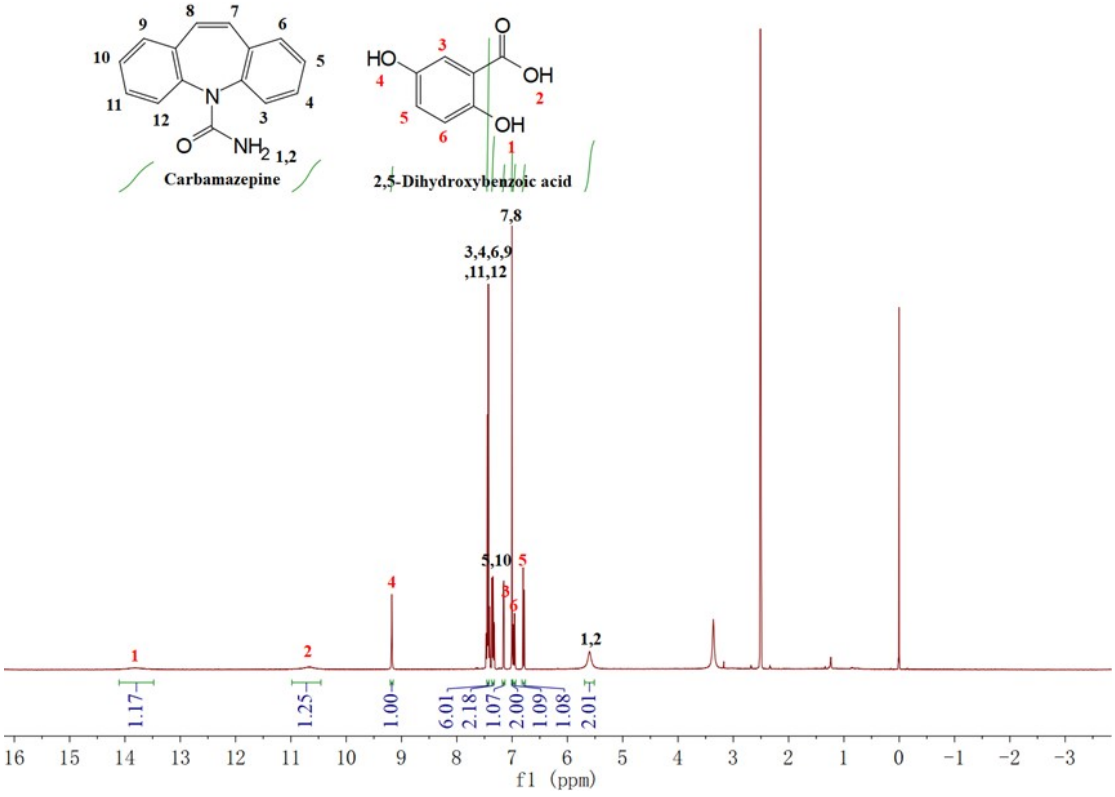
Anti-solvent slurry experiment 16: CBZ-2, 5-dihydroxybenzoic acid cocrystal (1:1)

An equimolar mixture of CBZ (12.1 mg, 0.051 mmol) and 2, 5-dihydroxybenzoic acid (7.9 mg, 0.051 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

(a)



(b)



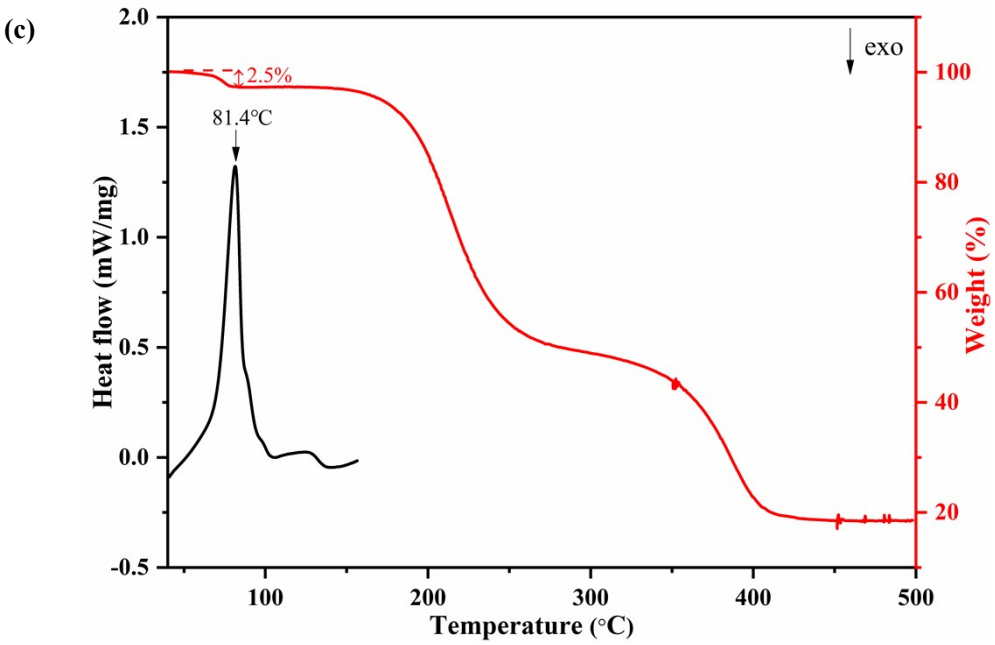


Fig. S16 (a) PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/2, 5-dihydroxybenzoic acid system. (b) ^{1}H NMR spectrum and (c) TG-DSC curve of the newly obtained hemihydrate of CBZ-2, 5-dihydroxybenzoic acid cocrystal during ASS with MeOH.

Anti-solvent slurry experiment 17: CBZ-2, 6-dihydroxybenzoic acid cocrystal (1:1)

An equimolar mixture of CBZ (12.1 mg, 0.051 mmol) and 2, 6-dihydroxybenzoic acid (7.9 mg, 0.051 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

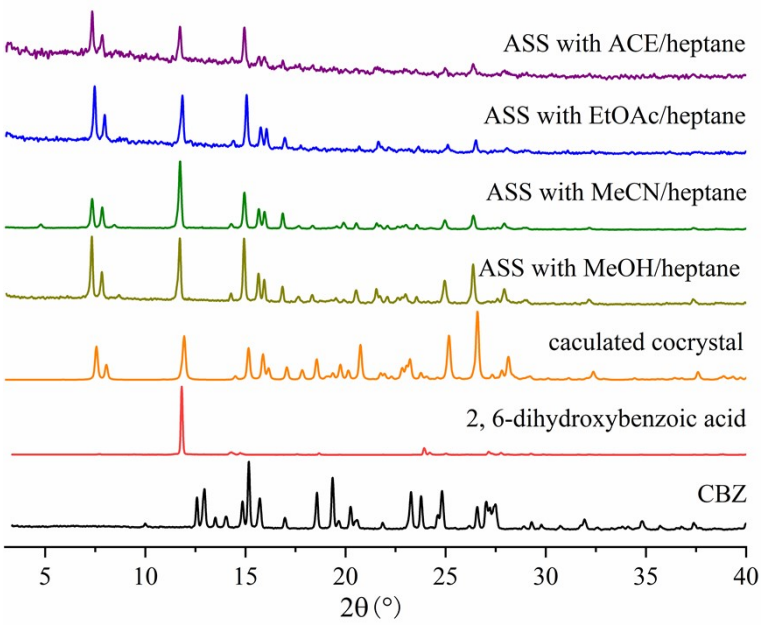


Fig. S17 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/2, 6-dihydroxybenzoic acid system.

Anti-solvent slurry experiment 18: CBZ-2, 6-pyridinedicarboxylic acid cocrystal (1:1)

An equimolar mixture of CBZ (11.7 mg, 0.050 mmol) and 2, 6-pyridinedicarboxylic acid (8.3 mg, 0.050 mmol) was added to 1 mL heptane with addition of 20 μL MeOH/40 μL MeCN/40 μL EtOAc/10 μL ACE and left to stir for 48 hours at room temperature.

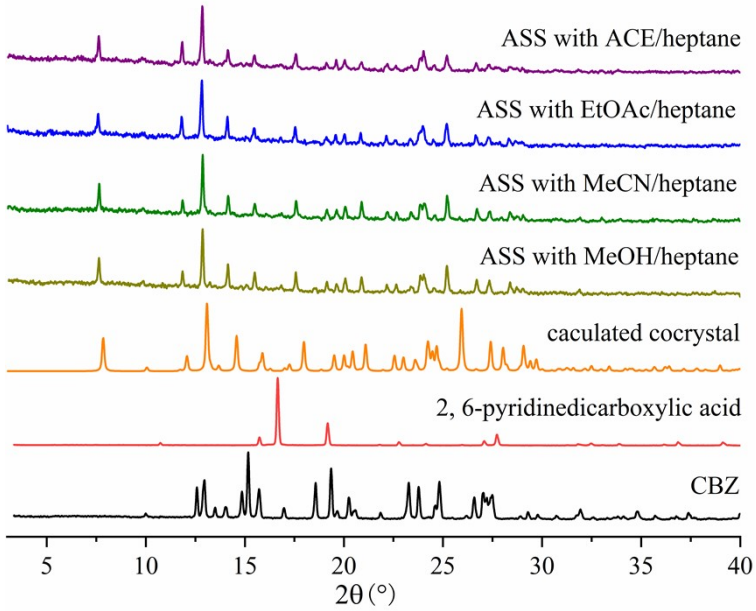


Fig. S18 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/2, 6-pyridinedicarboxylic acid system.

Anti-solvent slurry experiment 19: CBZ-benzamide cocrystal (1:1)

An equimolar mixture of CBZ (13.2 mg, 0.056 mmol) and benzamide (6.8 mg, 0.056 mmol) was added to 1 mL heptane with addition of 10 μL MeOH/10 μL MeCN/10 μL EtOAc/10 μL ACE and left to stir for 24 hours at room temperature.

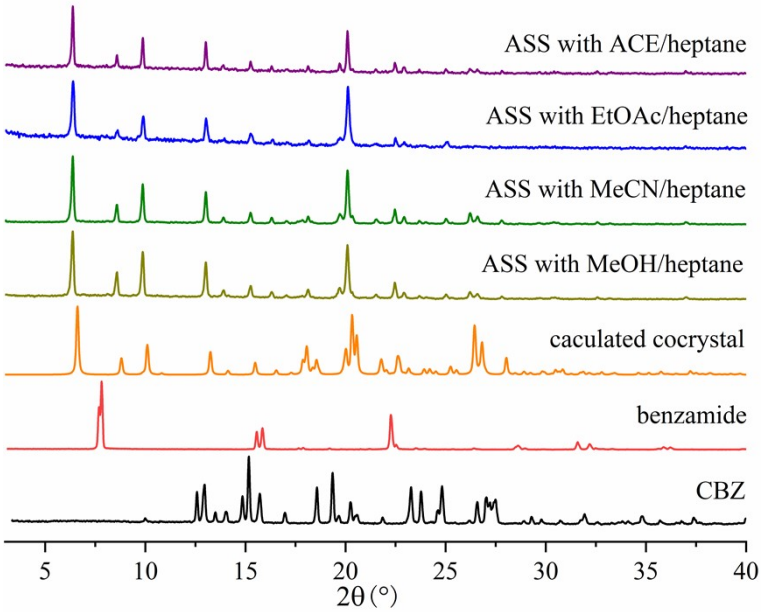


Fig. S19 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of

CBZ/benzamide system.

Anti-solvent slurry experiment 20: CBZ-isonicotinamide cocrystal (1:1)

An equimolar mixture of CBZ (13.2 mg, 0.056 mmol) and isonicotinamide (6.8 mg, 0.056 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

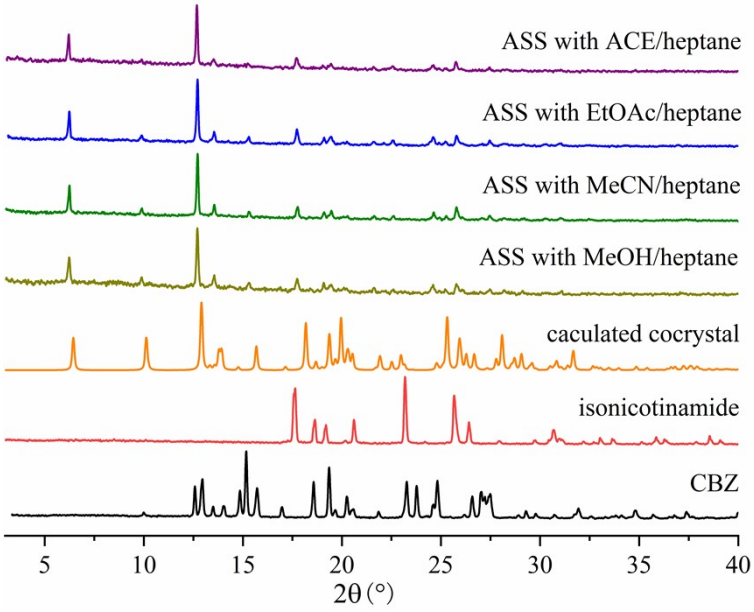


Fig. S20 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/ isonicotinamide system.

Anti-solvent slurry experiment 21: CBZ-nicotinamide cocrystal (1:1)

An equimolar mixture of CBZ (13.2 mg, 0.056 mmol) and nicotinamide (6.8 mg, 0.056 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

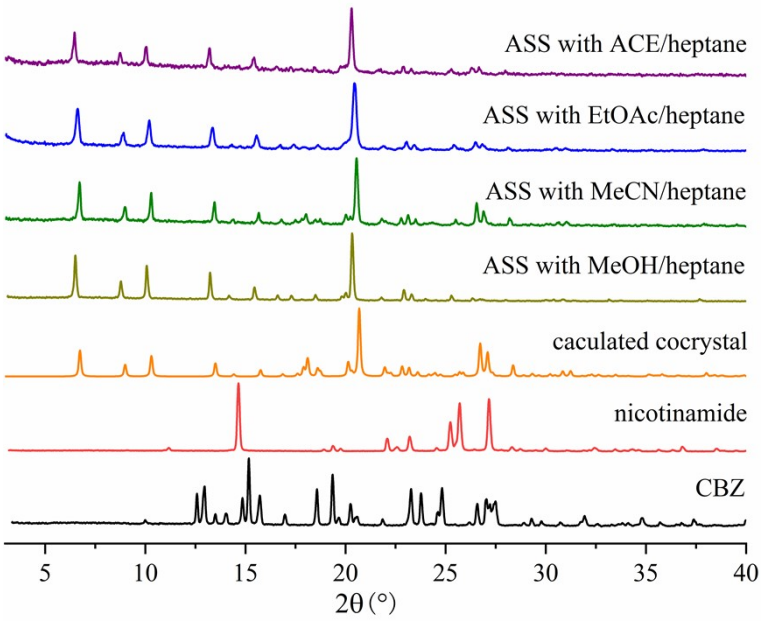


Fig. S21 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/

nicotinamide system.

Anti-solvent slurry experiment 22: CBZ-4-hydroxybenzamide cocrystal (1:1)

An equimolar mixture of CBZ (12.7 mg, 0.054 mmol) and 4-hydroxybenzamide (7.4 mg, 0.054 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

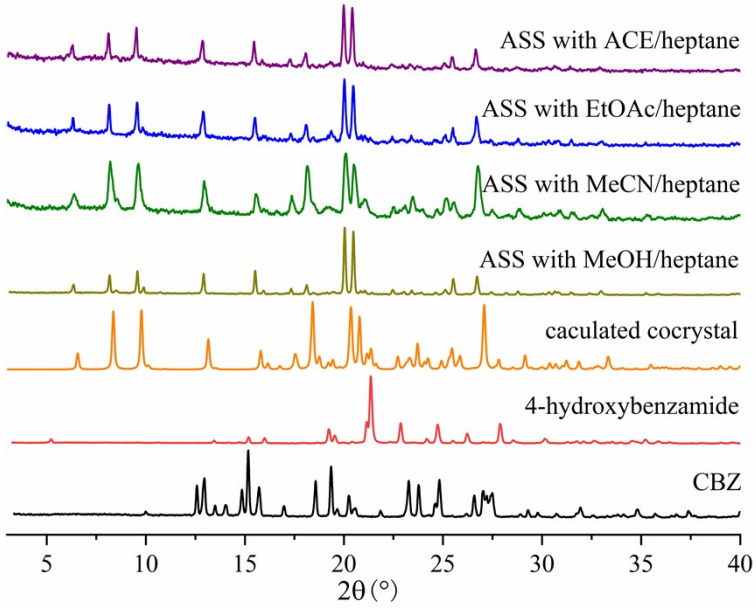


Fig. S22 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/4-hydroxybenzamide system.

Anti-solvent slurry experiment 23: CBZ-saccharin (1:1)

An equimolar mixture of CBZ (11.3 mg, 0.048 mmol) and saccharin (8.7 mg, 0.048 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

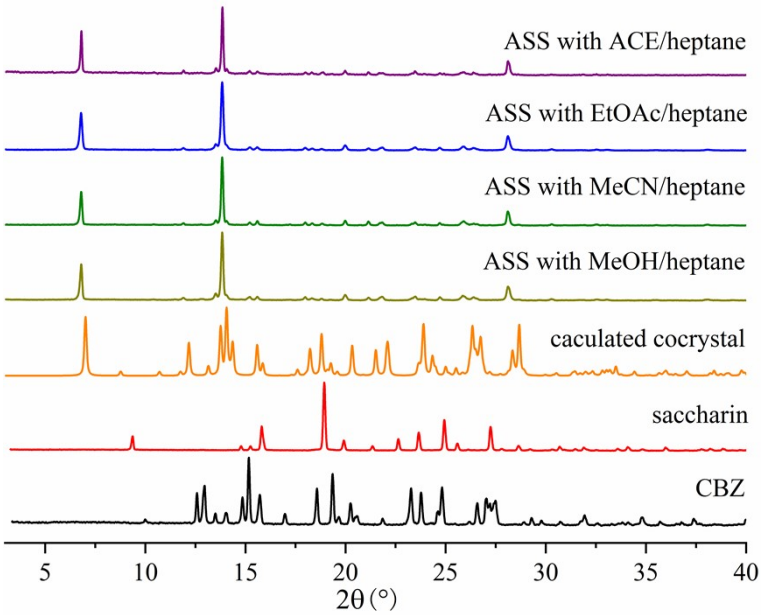


Fig. S23 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/saccharin system.

Anti-solvent slurry experiment 24: CBZ-4, 4'-bipyridine cocrystal (2:1)
A stoichiometric mixture of CBZ (15.0 mg, 0.063 mmol) and 4, 4'-bipyridine (5.0 mg, 0.032 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/10 µL MeCN/10 µL EtOAc/10 µL ACE and left to stir for 24 hours at room temperature.

Slurry experiment: CBZ-4, 4'-bipyridine cocrystal (2:1)
A stoichiometric mixture of CBZ (636.0 mg, 2.69 mmol) and 4, 4'-bipyridine (210.2 mg, 1.35 mmol) was added to 1 mL ACE and left to stir for 24 hours at room temperature.

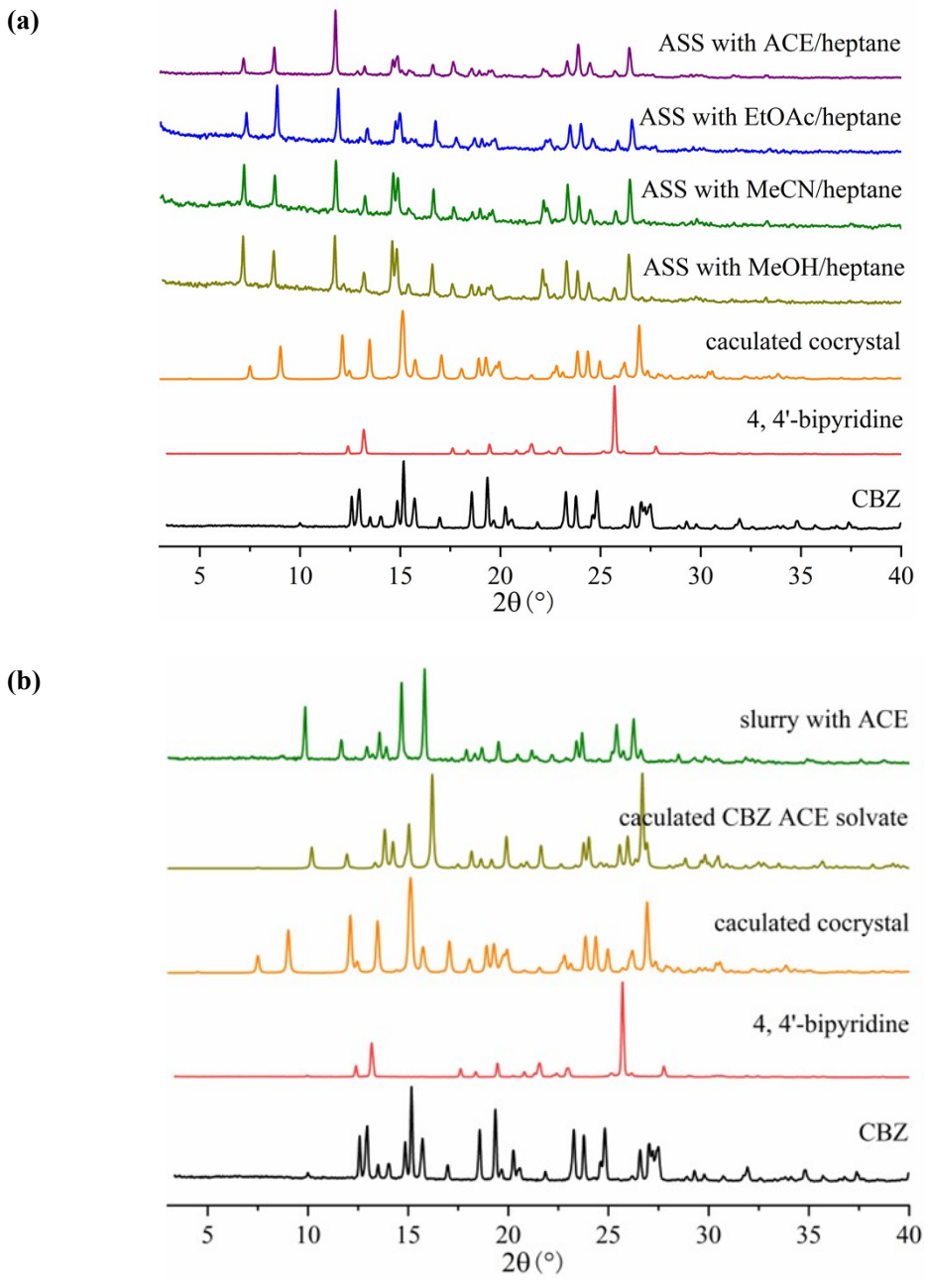


Fig. S24 PXRD patterns of the outcome of (a) anti-solvent slurry (ASS) experiments and (b) slurry

experiments of CBZ/4, 4'-bipyridine system.

Anti-solvent slurry experiment 25: CBZ-naringenin cocrystal (1:1)

An equimolar mixture of CBZ (9.3 mg, 0.039 mmol) and naringenin (10.7 mg, 0.039 mmol) was added to 1 mL heptane with addition of 10 µL MeOH/40 µL MeCN/100 µL EtOAc/100 µL ACE and left to stir for 48 hours at room temperature.

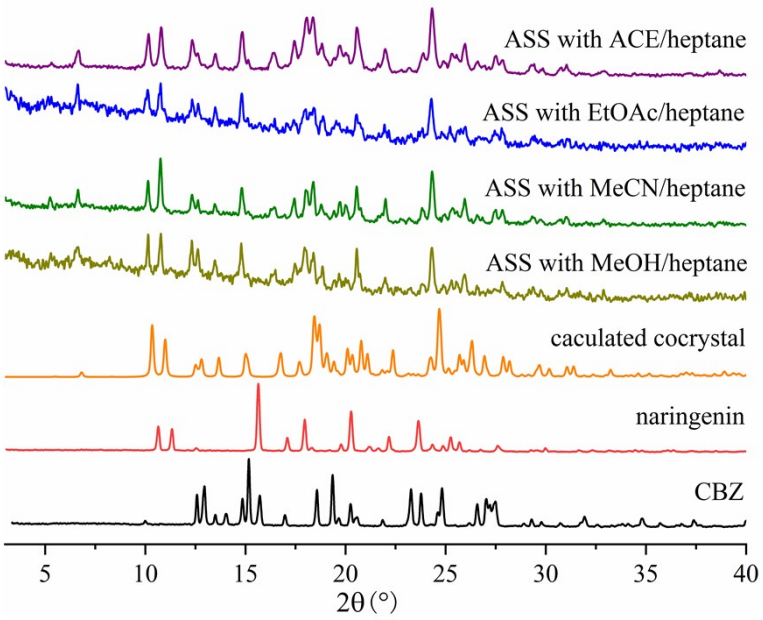


Fig. S25 PXRD patterns of the outcome of anti-solvent slurry (ASS) experiments of CBZ/naringenin system.