# Supporting Information

## New Solid Forms of Tetrahydrocurcumin with Improved Solubility

*Fanyu Tian,[ab] Mengyuan Xia,[bc] Hao Wang,[ab] Bingrui Zhang,[bc] Zhenfeng Ding,[bc] Xiaoyi Rong,[b] Bingqing Zhu,[*b] and Xuefeng Mei[*abc]*

[a] School of Chinese Materia Medica, Nanjing University of Chinese Medicine, 138 Xianlin Avenue, Nanjing 210023, China.

[b] Pharmaceutical Analytical & Solid-State Chemistry Research Center, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China.

[c] University of Chinese Academy of Sciences, No. 19A Yuquan Road, Beijing 100049, China.

**[*]Corresponding authors**

E-mail addresses: zhubingq@simm.ac.cn (B.Q. Zhu), xuefengmei@simm.ac.cn (X.F. Mei).

**Table S1** The coformers of curcumin cocrystals.

| NO. | Coformer | NO. | Coformer |
|---|---|---|---|
| 1 | Resorcinol[1] | 18 | Trimesic acid[2] |
| 2 | Pyrogallol[1] | 19 | Hydroxyquinol[2, 3] |
| 3 | Phloroglucinol[4] | 20 | Ascorbic acid[5] |
| 4 | Praziquantel[6] | 21 | Cinnamic acid[7] |
| 5 | 4,4′-bipyridine-N,N′-dioxide[8] | 22 | Resveratrol[9] |
| 6 | Nicotinamide[10] | 23 | 2-aminobenzimidazole[11] |
| 7 | Piperazine[10] | 24 | L-lysine[11] |
| 8 | Isonicotinamide[10] | 25 | Dextrose[12] |
| 9 | Methyl paraben[13] | 26 | L-proline[14] |
| 10 | Piperidine[10] | 27 | 4,4′-bipyridine[15] |
| 11 | Naproxen sodium[10] | 28 | N-acetylcysteine [16] |
| 12 | Ibuprofen sodium[10] | 29 | Tryptamine[17] |
| 13 | L-carnitine[18] | 30 | Piperine[14] |
| 14 | Saccharin[19] | 31 | Taconic acid[19] |
| 15 | Maleic acid[19] | 32 | Benzoic acid[19] |
| 16 | Catechol[20] | 33 | Hydroquinone[20] |
| 17 | Quercetin[21] | 34 | Isoniazid[22] |

**Table S2.** Coformers selected in cocrystal screening experiment for THC. Bold text indicates successful multicomponent crystal forms formation.

| NO. | Coformer | NO. | Coformer |
|---|---|---|---|
| 1 | **L-Proline** | 14 | Nicotinamide |
| 2 | **D-Proline** | 15 | Isonicotinamide |
| 3 | **DL-Proline** | 16 | Succinic acid |
| 4 | **Betaine** | 17 | Adipic acid |
| 5 | **4,4'-Bipyridine** | 18 | L-tartaric acid |
| 6 | L-Hydroxyproline | 19 | Citric acid monohydrate |
| 7 | Sarcosine | 20 | L-malic acid |
| 8 | Fat-soluble vitamin | 21 | L-ascorbic acid |
| 9 | Theophylline | 22 | L-glutamic acid |
| 10 | Theobromine | 23 | D-malic acid |
| 11 | Isoniazid | 24 | Benzoic acid |
| 12 | Vitamin B2 | 25 | Sorbic acid |
| 13 | Caffeine | 26 | Salicylic acid |

**Table S3.** List of H-bond lengths and angles for THC cocrystals

| Form | interaction | D-H/Å | H…A/ Å | D…A/ Å | ∠D-H…A/ deg | symmetry code |
|---|---|---|---|---|---|---|
| **THC-L-PRO** | O1–H1···O2 | 0.91 | 1.67 | 2.508(4) | 152 | |
| | N1-H1C…O7 | 0.91 | 2.20 | 3.017(4) | 150 | x,y,1+z |
| | N1-H1C…O8 | 0.91 | 2.26 | 3.022(4) | 140 | x,y,1+z |
| | N1-H1D…O3 | 0.91 | 2.28 | 3.086(4) | 147 | -1/2+x,3/2-y,1-z |
| | O4-H4…O7 | 0.84 | 1.95 | 2.707(4) | 149 | 1/2+x,3/2-y,1-z |
| | O6-H6…O8 | 0.84 | 1.96 | 2.687(4) | 144 | 1/2+x,3/2-y,1-z |
| **THC-D-PRO** | O2–H2···O1 | 0.84 | 1.75 | 2.501(5) | 148 | |
| | N1-H1C…O7 | 0.91 | 2.37 | 3.094(6) | 137 | x,y,-1+z |
| | N1-H1C…O8 | 0.91 | 2.11 | 2.951(6) | 154 | x,y,-1+z |
| | N1-H1D…O5 | 0.91 | 2.23 | 3.031(6) | 147 | 1/2-x,1/2+y,1-z |
| | O4-H4…O7 | 0.84 | 1.94 | 2.668(5) | 144 | 1/2-x,1/2+y,1-z |
| | O6-H6…O8 | 0.84 | 1.97 | 2.703(5) | 145 | 1/2-x,-1/2+y,1-z |
| **THC-DL-PRO** | O2–H2···O1 | 0.84 | 1.75 | 2.502(4) | 148 | |
| | N2-H2C…O8 | 0.91 | 2.07 | 2.921(7) | 154 | x,-1+y,z |
| | N2-H2D…O5 | 0.91 | 2.31 | 3.105(6) | 146 | x,y,-1+z |
| | O4-H4…O7 | 0.84 | 1.95 | 2.692(4) | 146 | x,y,z |
| | O6-H6…O8 | 0.84 | 1.95 | 2.707(4) | 149 | x,y,1+z |
| **THC-BPY** | O1–H1···O2 | 0.84 | 1.74 | 2.48(2) | 145 | |
| | O4-H4…N1 | 0.85 | 2.03 | 2.81(4) | 154 | 1+x,1+y,z |
| | O6-H6…N1 | 0.84 | 2.10 | 2.74(4) | 133 | -x,1+y,1-z |
| **THC-BTN** | O1–H1···O2 | 0.84 | 1.75 | 2.498(5) | 148 | |
| | O4-H4…O7 | 0.84 | 1.97 | 2.735(4) | 151 | 1-x,2-y,1-z |
| | O6-H6…O8 | 0.84 | 1.78 | 2.612(5) | 173 | -x,-1/2+y,3/2-z |

**Table S4** The melting enthalpy ($\Delta H_m$ ) of THC and its cocrystals.

| Form | $\Delta H_m$ (kJ/mol) | |
|---|---|---|
| | THC | cocrystal |
| THC-L-PRO | | 64.3±4.5 |
| THC-D-PRO | | 66.7±1.8 |
| THC-DL-PRO | 43.6±1.2 | 66.8±5.4 |
| THC-BPY | | 59.2±0.8 |
| THC-BTN | | 56.2±5.6 |

**Table S5.**THC concentration of solutions at 30 min and 120 min for the powder dissolution experiment of THC-L-PRO cocrystal.

| Time | Form | Concentration (μg/mL) | | |
|---|---|---|---|---|
| | | pH 2.0 | pH 4.5 | pH 6.8 |
| 30 min | THC | 47.7 | 40.2 | 42.3 |
| | THC-L-PRO | 138.7 | 79.2 | 78.0 |
| | THC-L-PRO VS THC | 2.9 | 2.0 | 1.8 |
| 120 min | THC | 55.0 | 57.2 | 42.9 |
| | THC-L-PRO | 139.3 | 90.7 | 68.8 |
| | THC-L-PRO VS THC | 2.5 | 1.6 | 1.6 |

**Table S6.**THC concentration of solutions at 30 min and 120 min for the powder dissolution experiment of polymorphs.

| Time | Form | Concentration (μg/mL) | | |
|---|---|---|---|---|
| | | pH 2.0 | pH 4.5 | pH 6.8 |
| 30 min | Form Ⅰ | 47.7 | 40.2 | 42.3 |
| | Form Ⅱ | 107.4 | 83.8 | 68.8 |
| | Form Ⅱ VS Form Ⅰ | 2.3 | 2.1 | 1.6 |
| 120 min | Form Ⅰ | 55.0 | 57.2 | 42.9 |
| | Form Ⅱ | 66.8 | 64.5 | 54.3 |
| | Form Ⅱ VS Form Ⅰ | 1.2 | 1.1 | 1.3 |

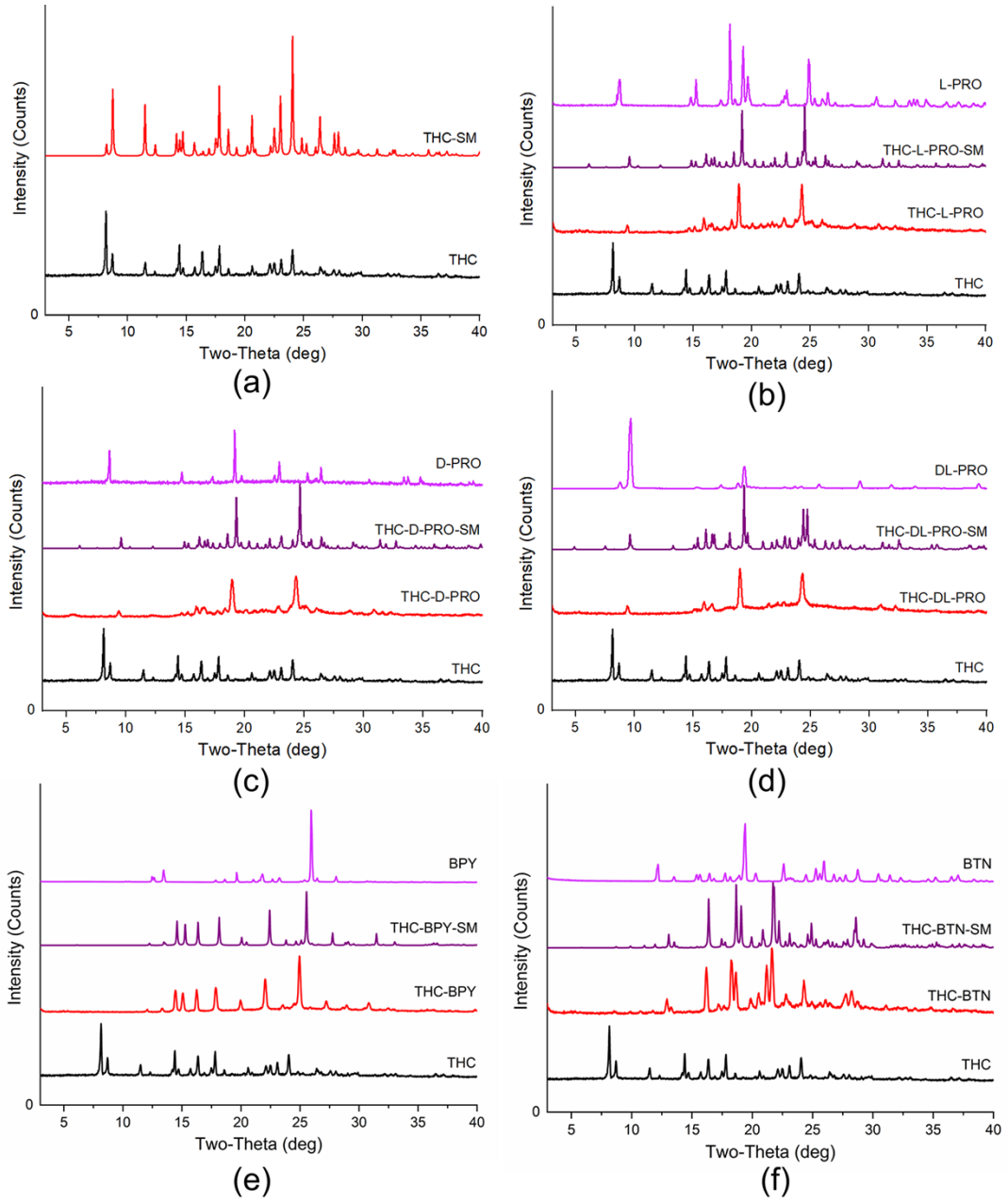


**Fig. S1.** Comparison between experimental and simulated PXPD of THC and THC cocrystals: (a) THC, (b) THC-L-PRO, (c) THC-D-PRO, (d) THC-DL-PRO, (e) THC-BPY, and (f) THC-BTN.

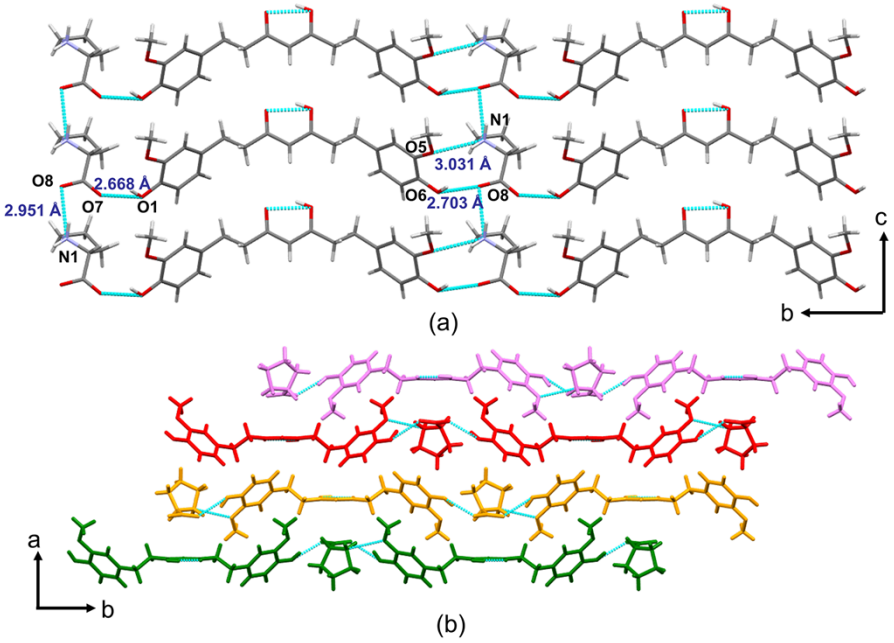


**Fig. S2.** Crystal structure of THC-D-PRO: (a) Hydrogen bonding mapping and 2D layer parallel to the *b*O*c* plane, and (b) 2D layer parallel to the *a*O*b* plane.

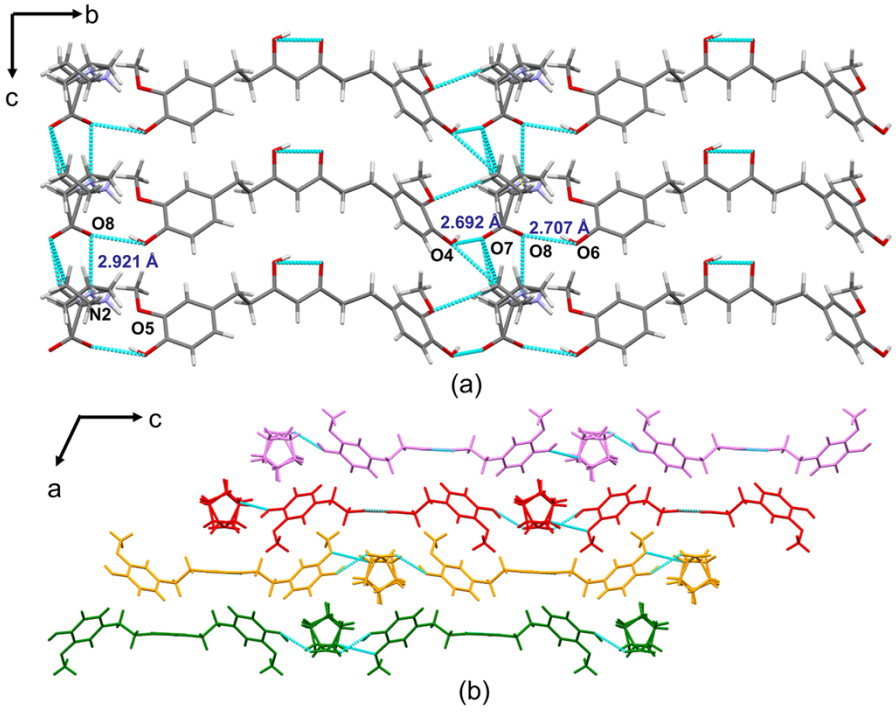


**Fig. S3.** Crystal structure of THC-DL-PRO: (a) Hydrogen bonding mapping and 2D layer parallel to the *b*O*c* plane, and (b) 2D layer parallel to the *a*O*c* plane.

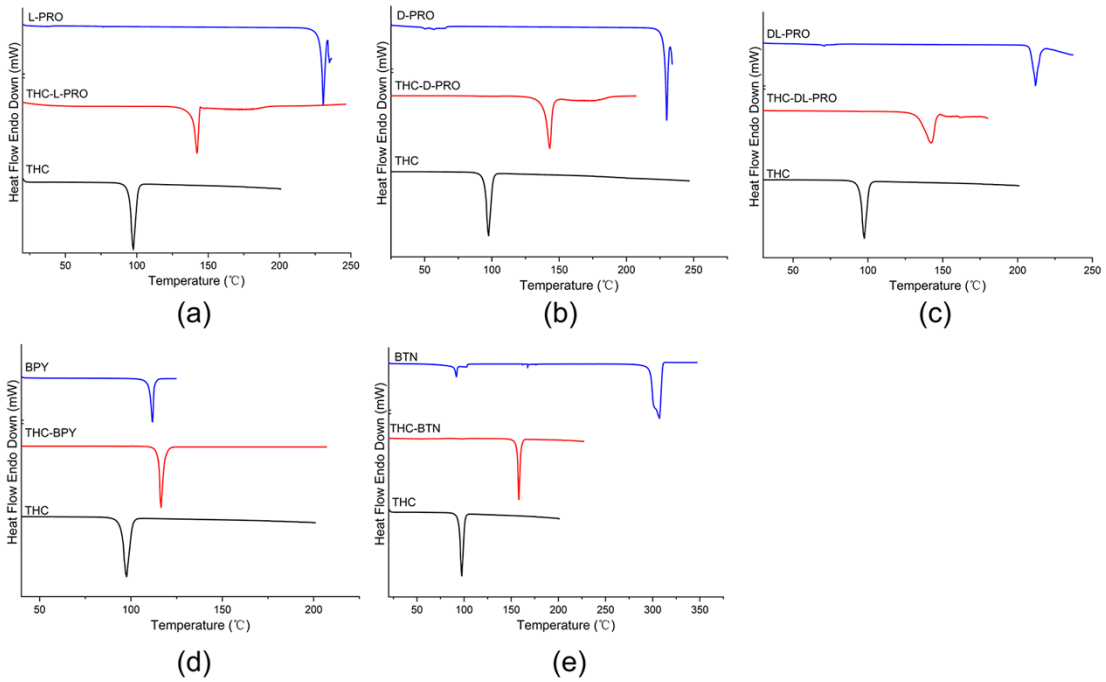


**Fig. S4.** Comparison of DSC diagrams among THC, coformers and corresponding cocrystals: (a) THC-L-PRO, (b) THC-D-PRO, (c) THC-DL-PRO, (d) THC-BPY, (e) THC-BTN.

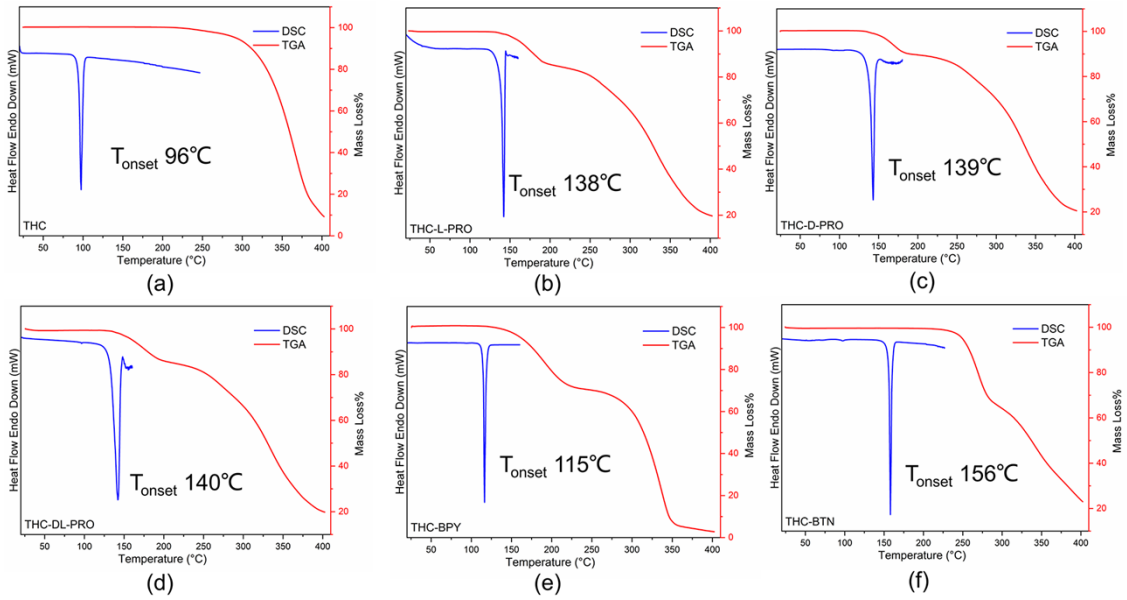


**Fig. S5** TGA-DSC profiles of (a) THC, (b) THC-L-PRO, (c) THC-D-PRO, (d) THC-DL-PRO, (e) THC-BPY and (f) THC-BTN.

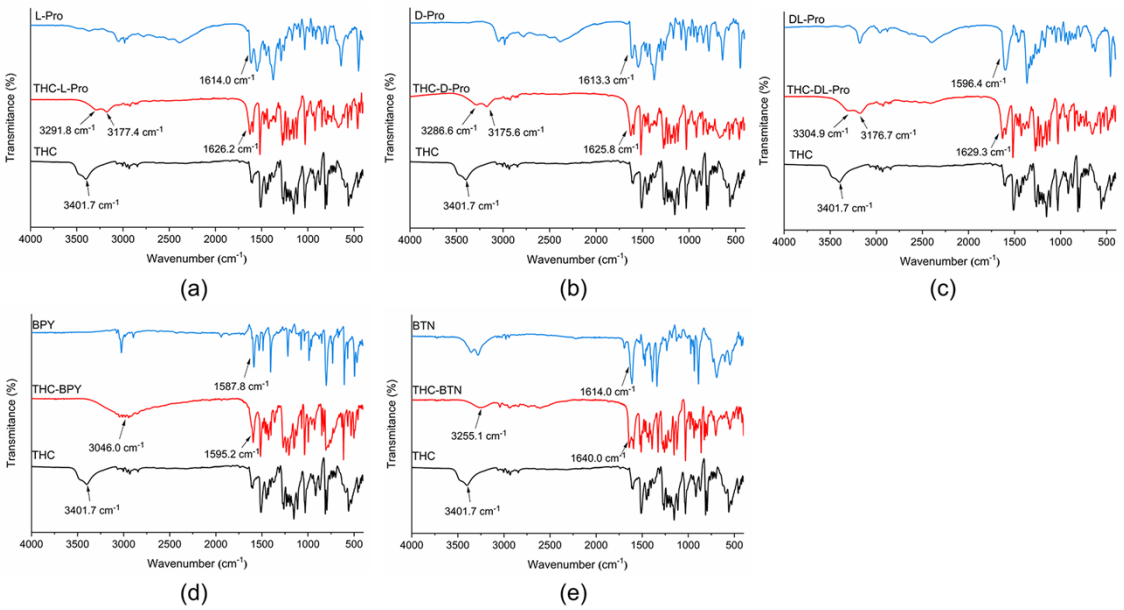


**Fig. S6.** Comparison of FT-IR profiles among THC, coformers and corresponding cocrystals: (a) THC-L-PRO, (b) THC-D-PRO, (c) THC-DL-PRO, (d) THC-BPY, (e) THC-BTN.

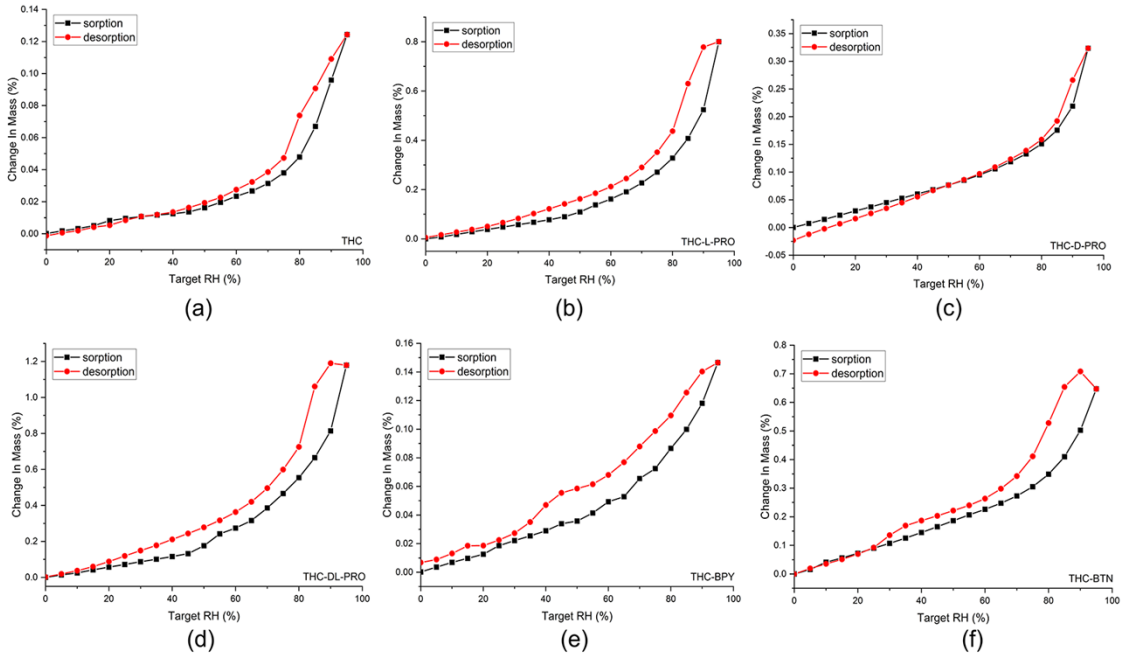


**Fig. S7.** DVS profiles of THC and THC cocrystals: (a) THC, (b) THC-L-PRO, (c) THC-D-PRO, and (d) THC-DL-PRO, (e) THC-BPY, (f) THC-BTN.

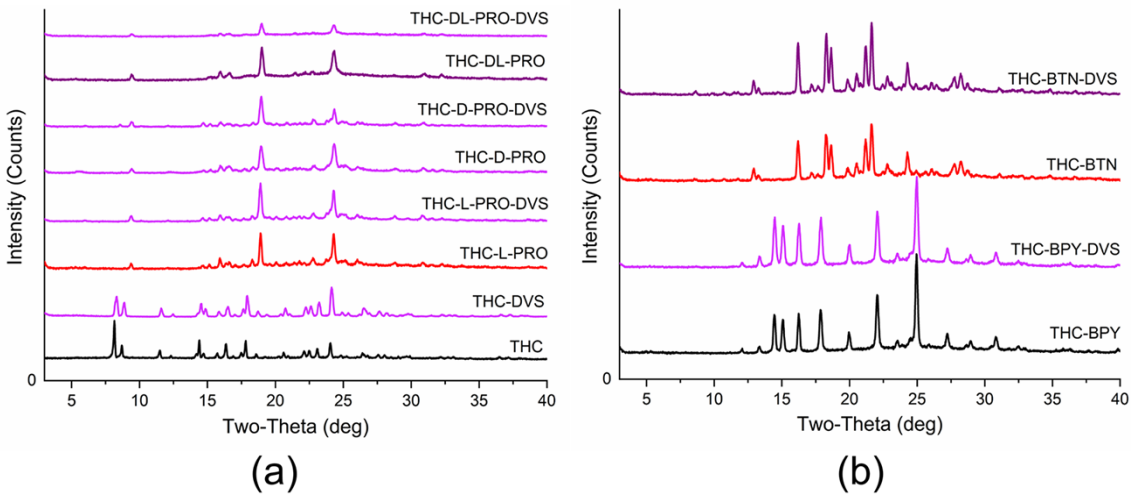


**Fig. S8.** PXRD patterns of THC and THC cocrystals after DVS experiments.

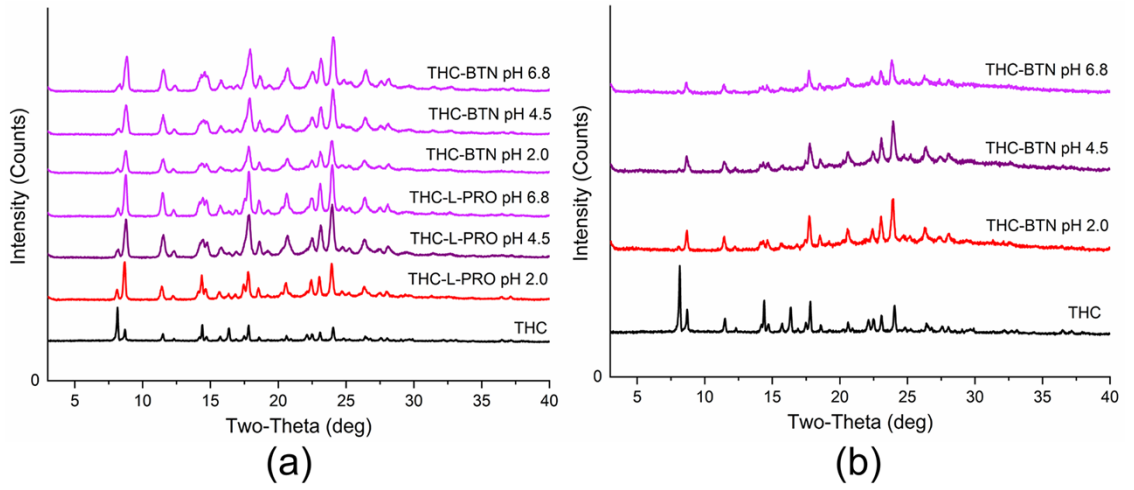


**Fig. S9.** PXRD patterns of (a) the undissolved solids after equilibrium solubility experiment and (b) the precipitates of THC-BTN from the dissolution experiments.

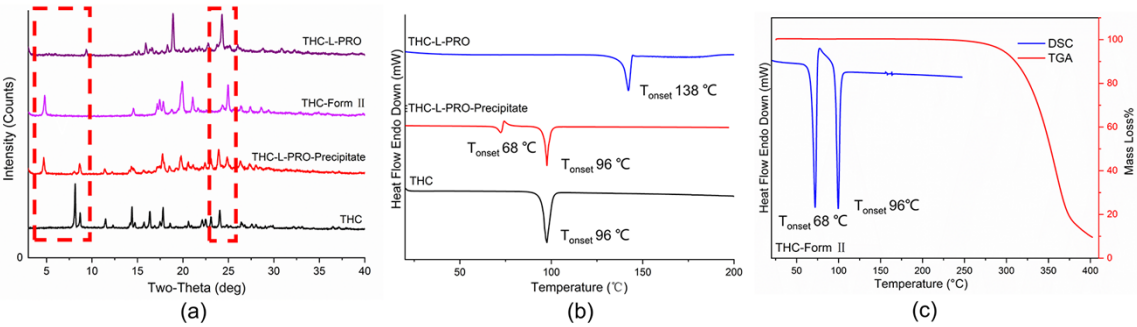


**Fig. S10.** (a) PXRD patterns of THC, the precipitate of THC-L-PRO from the dissolution experiment, THC-Form II and THC-L-PRO, (b) Comparison of DSC diagrams among THC, the precipitate of THC-L-PRO from the dissolution experiment and THC-L-PRO and (c) TGA-DSC profile of THC-Form II.

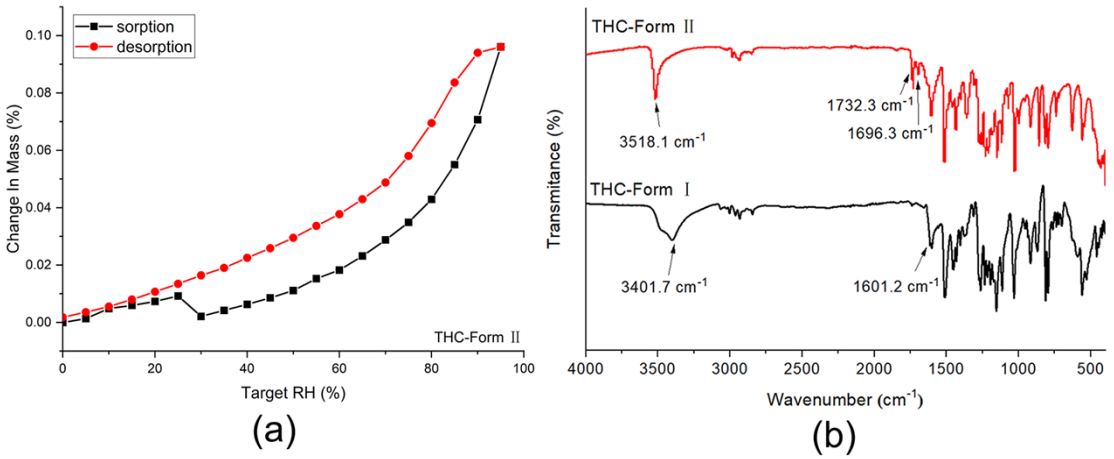


**Fig. S11.** (a) DVS profiles of THC-Form II and (b) Comparison of FT-IR profiles of THC-Form I and II.

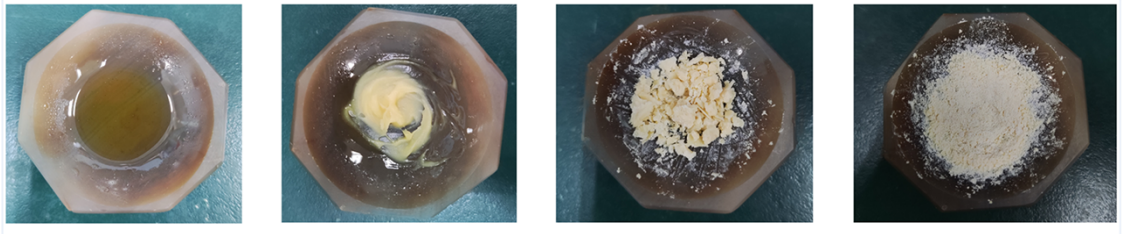

**Fig. S12.** Preparation process of THC-FORM II: The THC was melted by heating to 120°C and stirred continuously at room temperature until a solid sample was completely produced, which was then pulverized with a pestle.

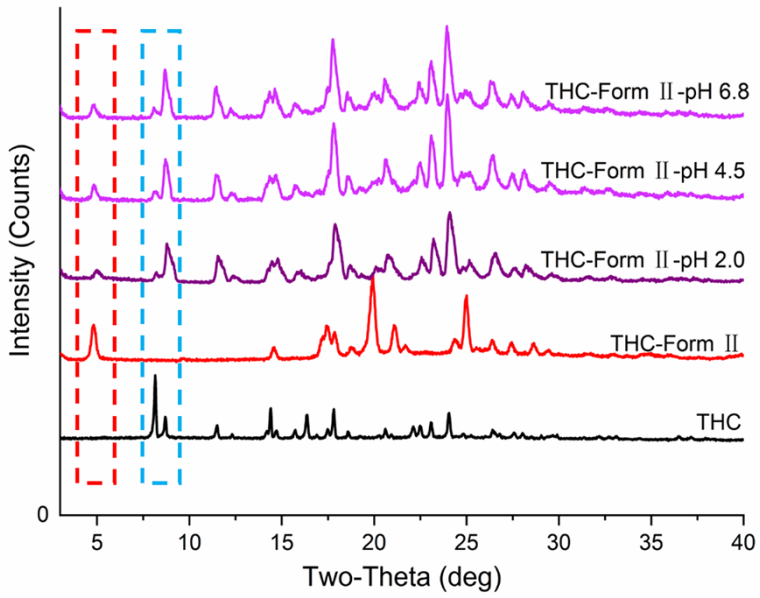


**Fig. S13.** PXRD results of the undissolved solids of THC-Form II after dissolution experiment.

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