Supporting Information

Solid-state characterization of 17β-estradiol co-crystals presenting improved dissolution and bioavailability

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Table S1. CSD statistics of possible supramolecular synthons in E2 with phenolic hydroxyl group [a]

Synthon	Both groups containing hits	Synthon hits with %
I (OH + N_{arom})	1771	906 (51.2%)
II (OH + amide)	3266	1280 (39.2%)
III (OH + acid)	1136	210 (18.5%)
IV (OH + 1°/2°/3° amine)	941/2095/2516	164/94/188 (8.0%)

[a] Survey constrains: intermolecular shorter than sum of VdW radii + 0.0, no disordered, no errors, no ions, and only organics.

Table S2. Results of the screening experiments for the formation of co-crystals with E2 in MeOH, ethyl acetate (EA), and tetrahydrofuran (THF).

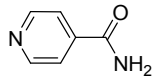
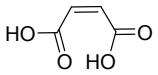
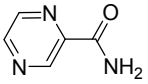
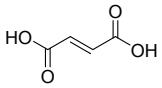
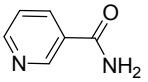
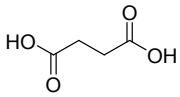
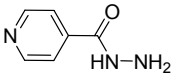
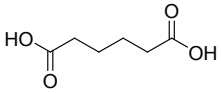
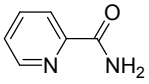
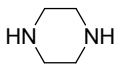
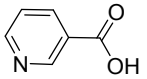
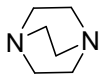
CCF	MeOH	EA	THF	CCF	MeOH	EA	THF
 isonicotinamide	✓	✓	**X**	 maleic acid	**X**	**X**	**X**
 pyrazinamide	**X**	**X**	**X**	 fumaric acid	**X**	**X**	**X**
 nicotinamide	**X**	**X**	**X**	 succinic acid	**X**	**X**	**X**
 isoniazide	**X**	**X**	**X**	 adipic acid	**X**	**X**	**X**
 picolinamide	**X**	**X**	**X**	 piperazine	✓	✓	✓
 nictinic acid	**X**	**X**	**X**	 allophanamide	**X**	**X**	**X**

Table S3. Hydrogen bonding distances and angles for E2 co-crystals

H bond	d(D-H)/Å	d(H···A)/Å	d(D···A) /Å	<DHA/°
co-crystal 1				
O1-H1···N1	0.877	1.894	2.764	171.50
O1'-H1'A···N3	0.820	1.948	2.767	176.18
O2'-H2'A···O5	0.851	2.021	2.852	164.84
O2-H2···O6	0.820	2.047	2.811	154.98
N4-H4B···O2'	0.863	2.058	2.908	167.75
N4-H4A···O1	0.900	2.121	3.004	166.53
N2-H2A···O2	0.923	1.990	2.884	162.40
N2-H2B···O1'	0.922	2.376	3.177	145.11
co-crystal 2				
O1-H1···N1	0.820	1.910	2.721	170.06
O3-H3···O1S	0.820	2.037	2.844	167.59
O2-H2C···N2	0.820	1.901	2.712	169.54
O4-H4A···O2S	0.820	2.140	2.860	146.51
O1S-H2S···O4	0.813	2.042	2.796	154.07
N1-H6S···O1S	0.880	2.245	3.096	163.00
N2-H5S···O2S	0.851	2.326	3.163	168.02
O1S-H1S···O2	0.794	2.110	2.897	171.27
O2S-H4S···O1	0.797	2.290	3.044	157.90
O2S-H3S···O3	0.806	2.031	2.836	177.46

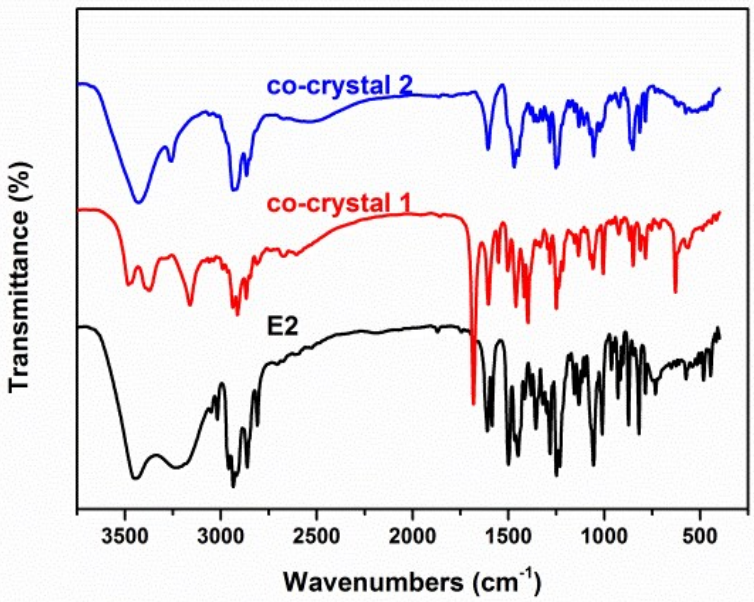
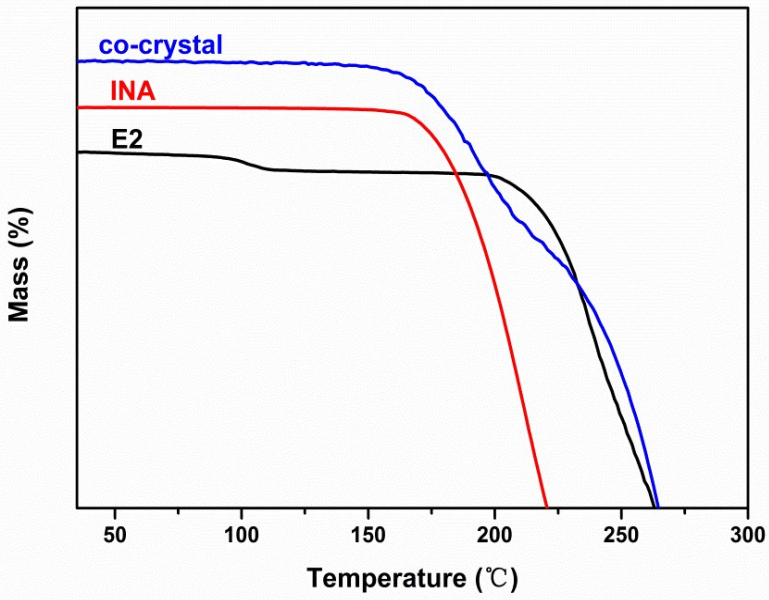
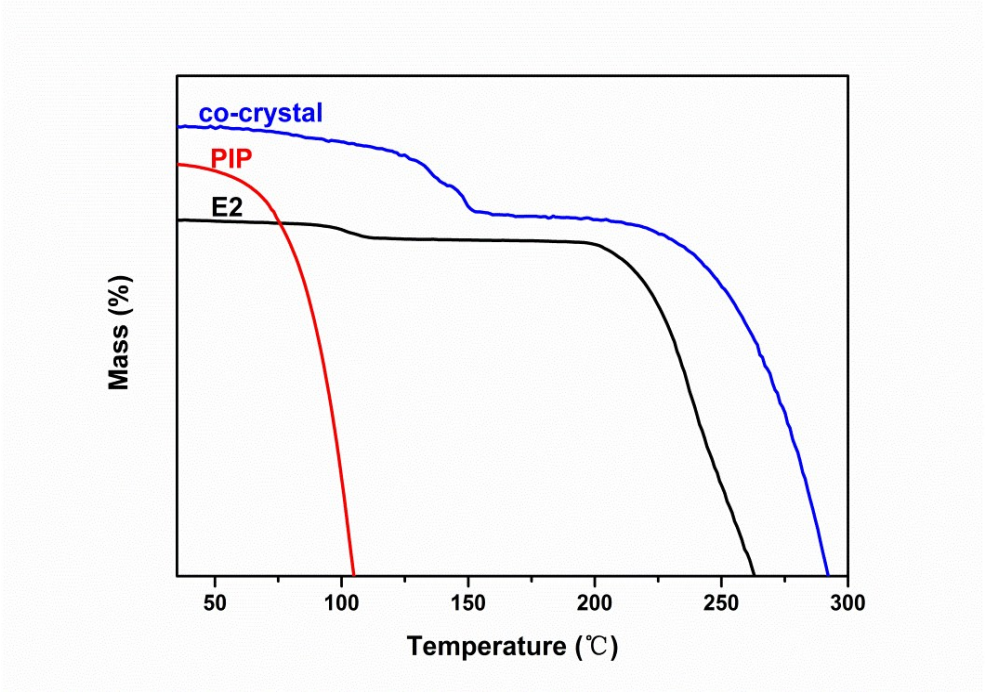


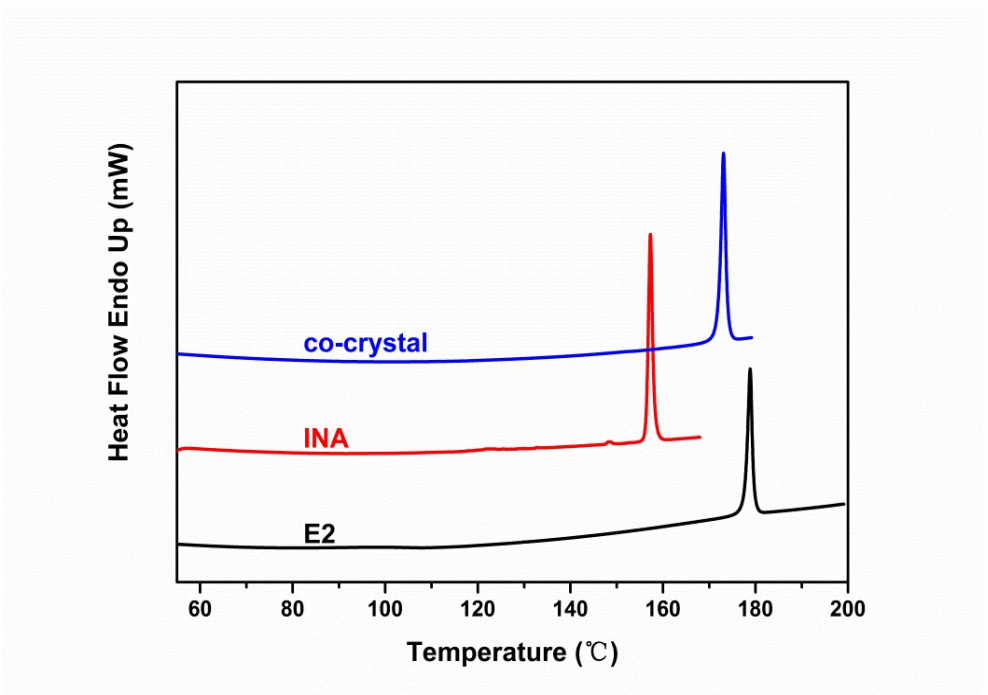
Figure S1. FT-IR spectroscopy of E2 co-crystals



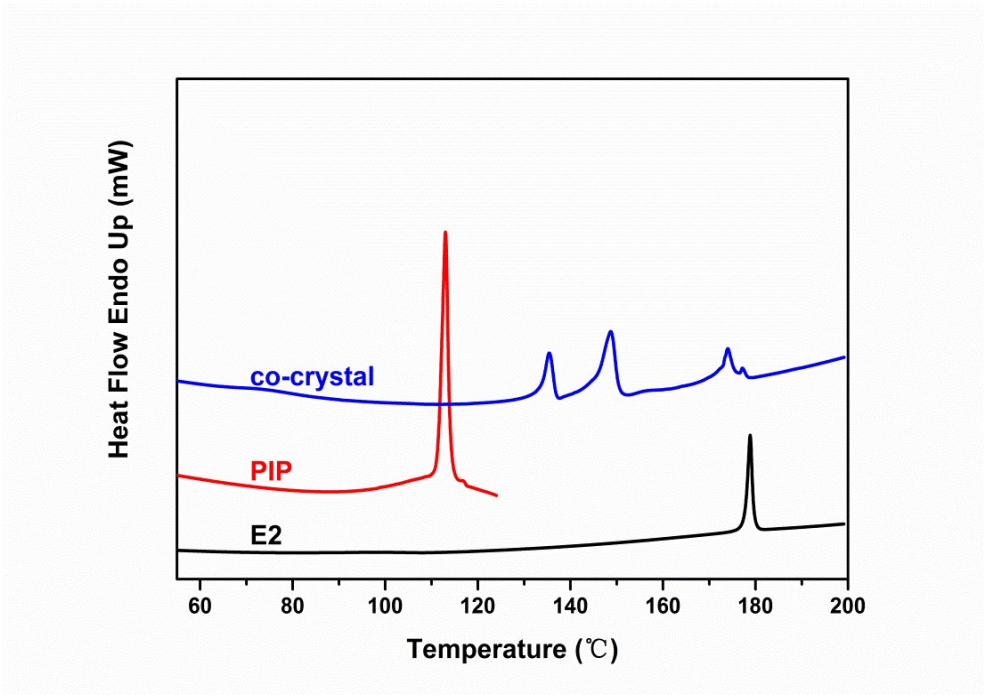
(a)


co-crystal
PIP
E2
Mass (%)
50
100
150
200
250
300
Temperature (℃)

(b)


co-crystal
INA
E2
Heat Flow Endo Up (mW)
60
80
100
120
140
160
180
200
Temperature (℃)

(c)



(d)

Figure S2. TGA and DSC thermograms of E2, co-former and its co-crystals (a) TGA of co-crystal **1**, (b) TGA of co-crystal **2**, (c) DSC of co-crystal **1** and (d) DSC of co-crystal **2**

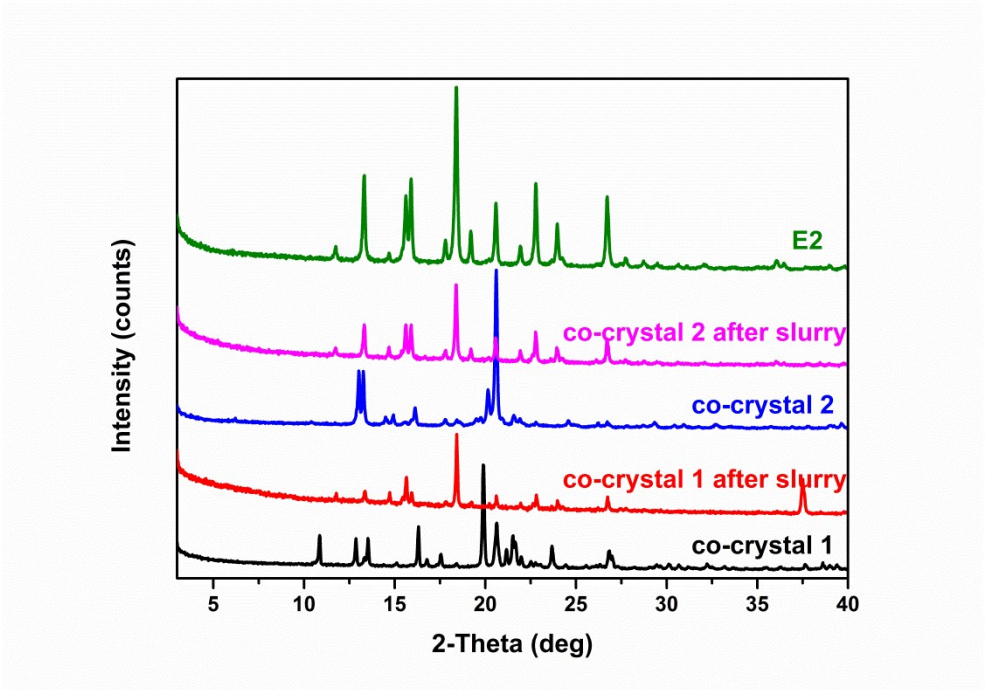


Figure S3. PXRD patterns of co-crystals **1** and **2** after slurry

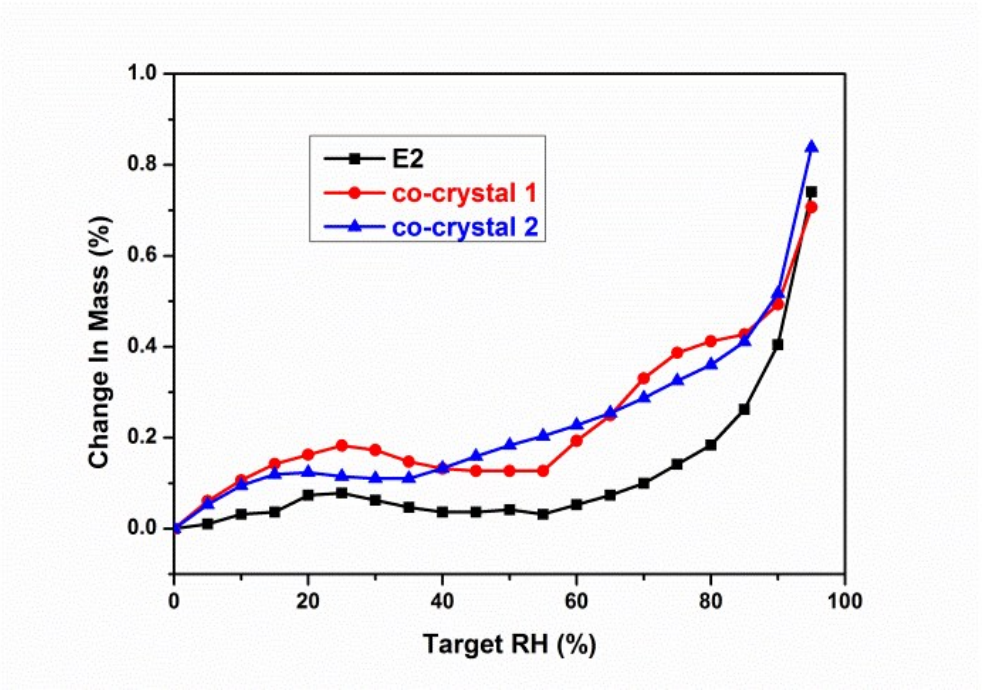


Figure S4. DVS profiles of E2 co-crystals