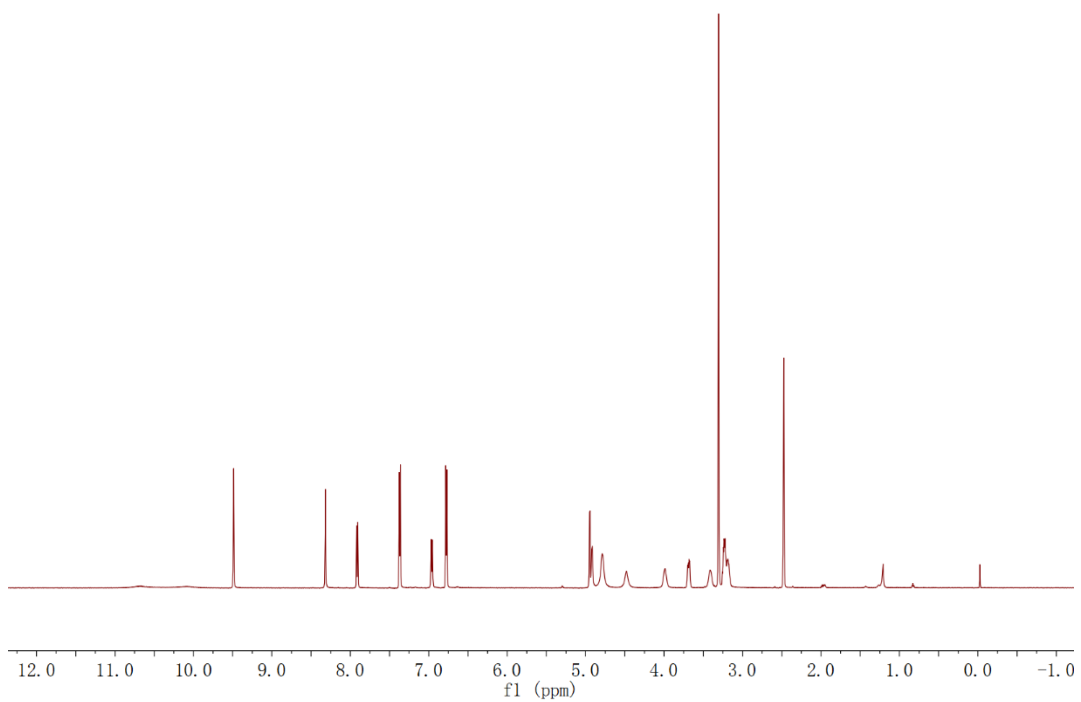


Enhancing the Physiochemical Properties of Puerarin via L-Proline Co-crystallization: Synthesis, Characterization, and Dissolution Studies of Two Phases of Pharmaceutical Co-crystals

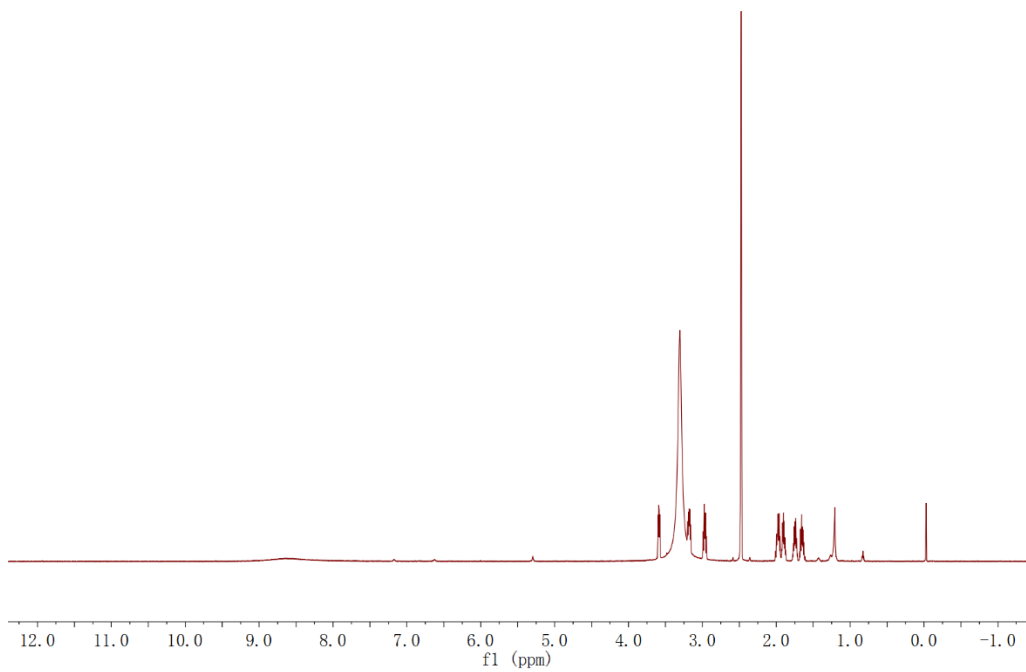
Muhammad Inam, Lu Liu, Jian-Wei Wang, Ka-Xi Yu, Chi-Uyen Phan, Jie Shen, Wen-Hua Zhang,
Guping Tang and Xiurong Hu*

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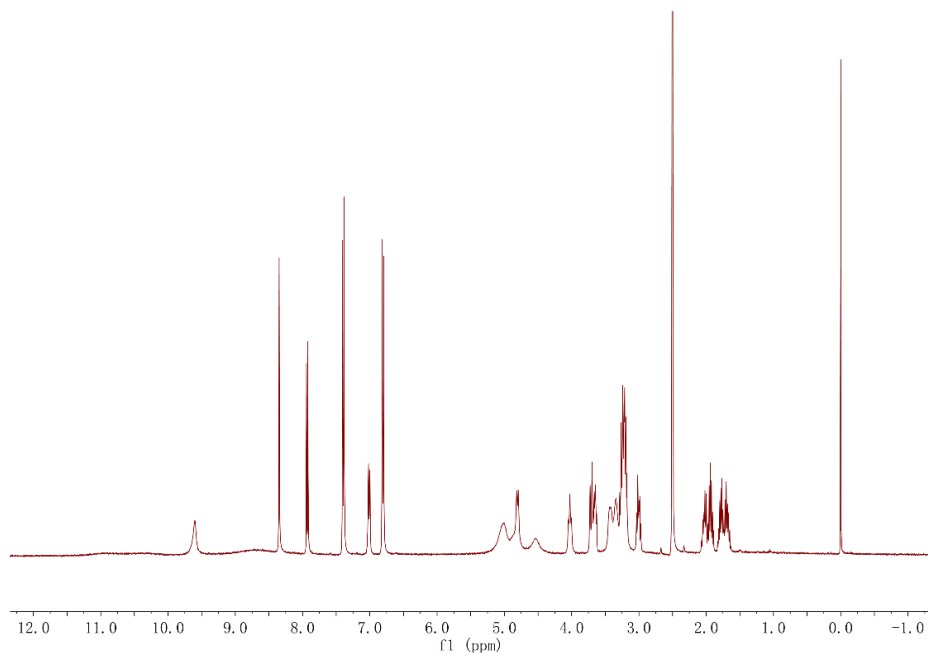
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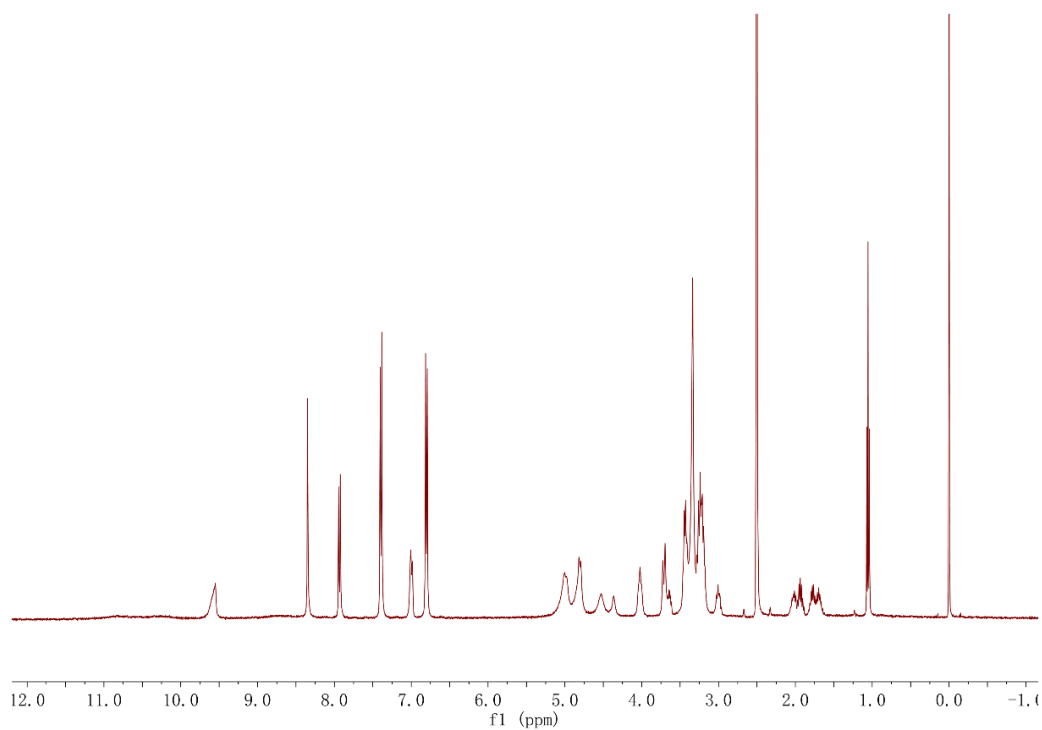
(a)



(b)

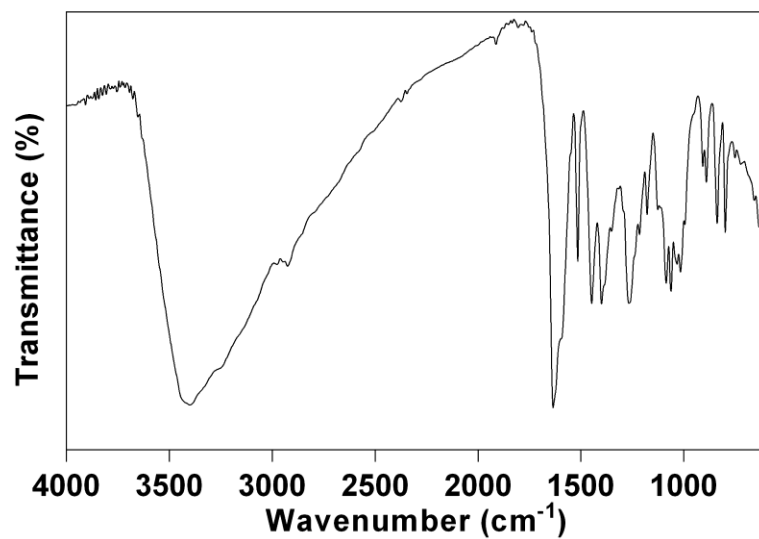


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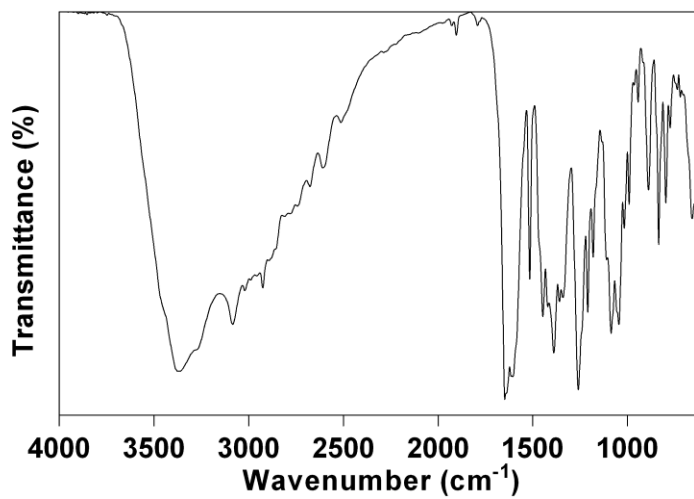


(d)

Figure S1 The ¹H NMR spectra of free PUE (a), PRO (b), I (c), and II (d).

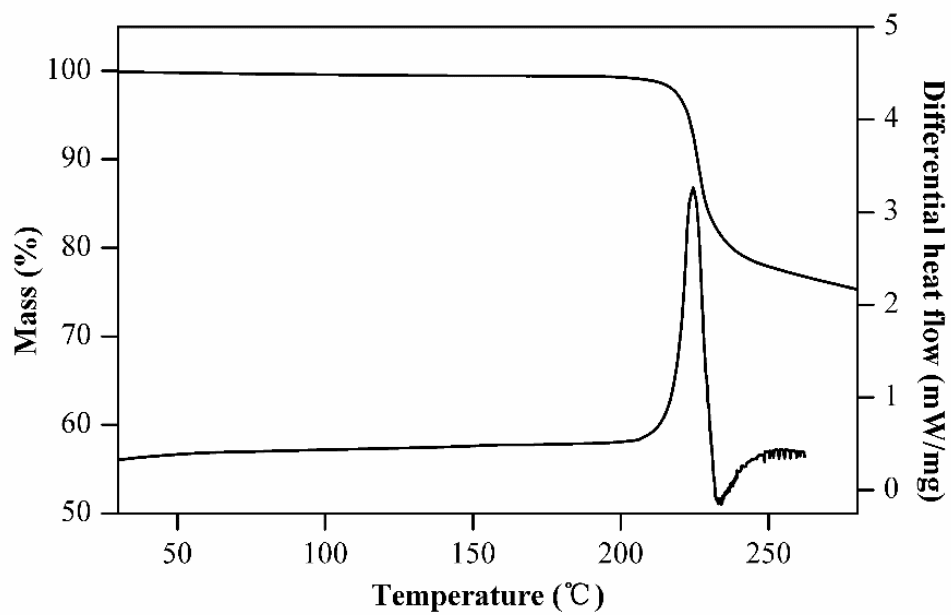


(a)

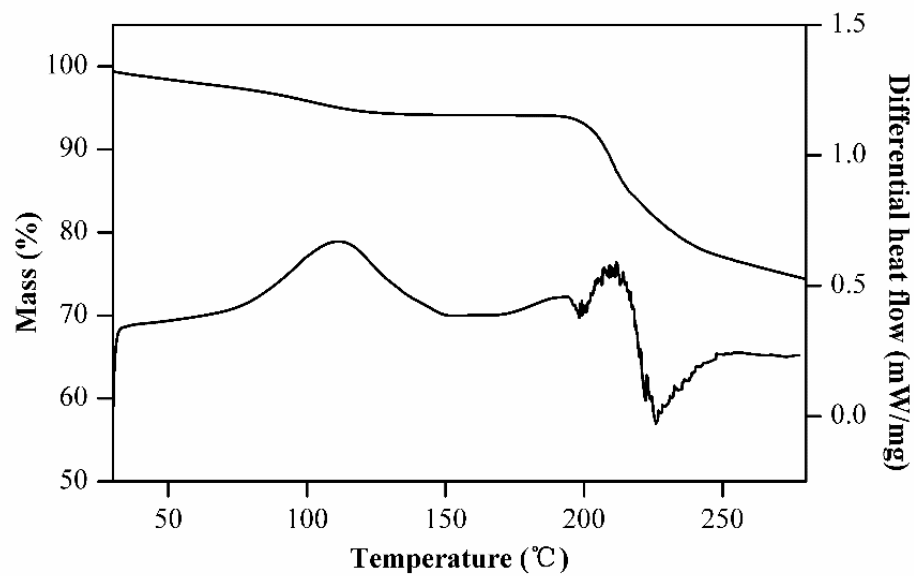


(b)

Figure S2 The FT-IR spectra of I (a) and II (b).



(a)



(b)

Figure S3 The TGA-DSC diagrams of I (a) and II (b).

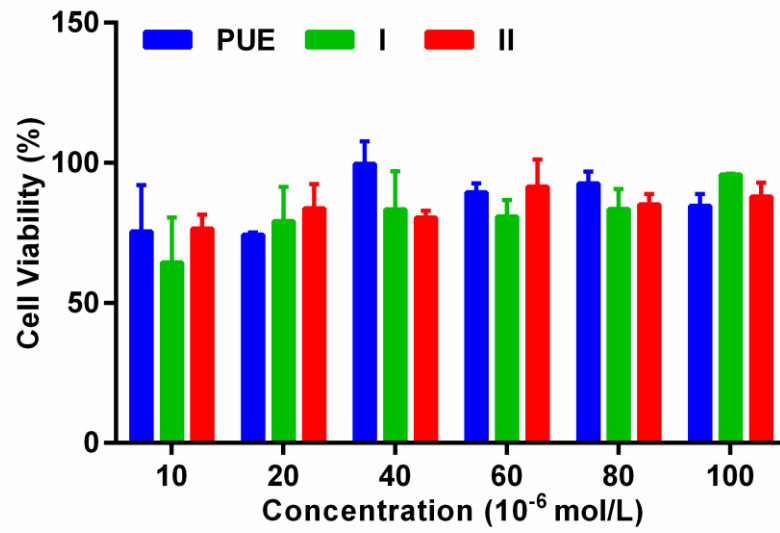


Figure S4. The cell viability data of PUE, I, and II against colon cancer CT-26 cell lines upon culturing 48 h.

Table S1 Hydrogen-bonding tables (Å and °) for I and II.

D-H...A	d(D-H)	d(H...A)	d(D...A)	∠(DHA)
[PUE][PRO] (I)				
O(7)-H(7)...O(8)#1	0.84	1.96	2.785(2)	168.3
O(9)-H(9)...O(6)#2	0.84	2.11	2.851(2)	146.3
O(9)-H(9)...O(1)#3	0.84	2.53	2.999(2)	116.5
O(8)-H(8)...O(10)	0.84	1.97	2.785(2)	164.0
O(6)-H(6)...O(3)#4	0.84	1.88	2.683(2)	160.1
O(4)-H(4)...O(5)	0.84	1.92	2.627(2)	141.8
O(1)-H(1)...O(11)#5	0.84	1.86	2.681(2)	164.5
N(1)-H(1B)...O(7)#6	0.91	2.10	2.886(2)	144.0
N(1)-H(1A)...O(10)#6	0.91	1.92	2.754(2)	151.8
N(1)-H(1B)...O(11)	0.91	2.19	2.661(2)	111.6
Symmetry codes: #1 $-x, y - 1/2, -z + 2$; #2 $x, y + 1, z$; #3 $-x + 1, y + 1/2, -z + 1$; #4 $-x, y - 1/2, -z + 1$; #5 $x, y, z - 1$; #6 $-x + 1, y + 1/2, -z + 2$.				
[PUE]₂[PRO]·EtOH·(H₂O)₂ (II)				
O(1B)-H(1O1)...O(13)#1	0.83	2.09	2.819(3)	145.9
O(1A)-H(1A)...O(5B)#2	0.82	2.28	3.092(3)	172.6
O(1A)-H(1A)...O(6B)#2	0.82	2.41	2.862(3)	116.1
O(4A)-H(4A)...O(5A)	0.82	1.93	2.632(2)	143.7
O(4B)-H(1O4)...O(5B)	0.83	2.45	3.086(2)	133.7
O(6B)-H(6B)...O(8A)#3	0.82	1.94	2.756(3)	175.6
O(7B)-H(7B)...O(13)#4	0.82	1.95	2.770(2)	174.5
O(7A)-H(7A)...O(7B)#5	0.82	1.95	2.747(2)	165.1
O(8A)-H(8A)...O(10)	0.82	1.87	2.677(3)	165.9
O(8B)-H(8B)...O(10)#4	0.82	1.92	2.727(3)	167.8
O(14)-H(1W)...O(6B)#6	0.83	2.25	2.938(3)	140.4
O(14)-H(1W)...O(7A)#2	0.83	2.26	2.848(3)	128.5
O(14)-H(2W)...O(1A)#7	0.83	2.47	3.155(4)	139.9
N(1)-H(1C)...O(14)	0.89	1.91	2.786(3)	169.4
N(1)-H(1D)...O(11)	0.89	2.13	2.604(3)	112.5
N(1)-H(1D)...O(12)	0.89	2.05	2.841(4)	148.3
Symmetry codes: #1 $x - 1, y + 1, z$; #2 $x, y - 1, z$; #3 $x, y, z + 1$; #4 $x - 1, y, z + 1$; #5 $x + 1, y, z - 1$; #6 $x, y - 1, z - 1$; #7 $x, y, z - 1$.				

Table S2 A list of the solubility (mg/mL) of PUE, I, and II.

Dissolution Medium	PUE		I		II	
	Average	SD (%)	Average	SD (%)	Average	SD (%)
Distilled Water	2.528	1.621	5.858	0.478	5.865	0.374
gastrointestinal tract at pH 1.2	1.513	1.247	3.972	0.249	3.470	1.674
phosphate buffer at pH 6.8	2.487	1.247	4.430	0.245	4.832	0.283

Table S3 Time-dependent dissolution rate (mg/mL) of PUE, I, and II in different medium.

Time (min)	PUE		I		II	
	Average	SD (%)	Average	SD (%)	Average	SD (%)
	Water					
5	0.062	0.000	0.220	0.094	0.131	0.094
10	0.109	0.094	0.343	0.125	0.210	0.082
15	0.190	0.125	0.452	0.047	0.281	0.170
20	0.250	0.327	0.533	0.294	0.457	0.125
25	0.294	0.386	0.591	0.205	0.567	0.047
30	0.506	0.047	0.674	0.189	0.701	0.125
40	0.611	0.216	0.767	0.163	1.450	0.082
50	0.692	0.356	0.945	0.327	2.110	0.082
60	0.821	0.170	1.045	0.368	2.490	0.000
80	0.896	0.082	1.373	0.330	2.840	0.000
100	0.935	0.125	1.503	0.283	3.203	0.424
120	1.031	0.170	1.645	0.400	3.410	0.818
	pH 1.2					
5	0.008	0.025	0.013	0.170	0.171	0.526
10	0.019	0.017	0.035	0.125	0.240	0.047
15	0.023	0.021	0.122	0.170	0.337	0.017
20	0.030	0.065	0.192	0.125	0.417	0.094
25	0.035	0.019	0.249	0.170	0.479	0.009
30	0.043	0.248	0.356	0.125	0.534	0.330
40	0.163	0.429	0.588	0.170	1.005	0.000
50	0.354	0.005	0.711	0.170	1.342	0.330
60	0.394	0.640	0.958	0.082	1.489	0.170
80	0.435	0.682	1.159	0.294	1.683	0.309
100	0.568	0.680	1.383	0.163	1.923	0.094
120	0.685	0.896	1.603	0.294	2.005	0.063
	pH 6.8					
5	0.078	0.000	0.207	0.047	0.121	0.170
10	0.110	0.205	0.291	0.082	0.212	0.125
15	0.168	0.125	0.384	0.094	0.352	0.170
20	0.244	0.125	0.493	0.125	0.446	0.189
25	0.274	0.094	0.570	0.082	0.537	0.082
30	0.347	0.082	0.664	0.141	0.861	0.047
40	0.415	0.082	0.786	0.170	1.059	0.047
50	0.444	0.082	0.850	0.047	1.503	0.471
60	0.504	0.094	0.918	0.205	2.210	0.047
80	0.560	0.000	1.183	0.170	2.723	0.250
100	0.641	0.082	1.265	0.082	3.138	0.589
120	0.785	0.050	1.303	0.170	3.370	0.245