Supporting Information

A Simple and Effective Purification of a SGLT-2 Inhibitor Cocrystal Rongliflozin L-Pyroglutamic acid: Coformer-induced Purification (CoIP)

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General remarks

PXRD were monitored on Empyrean Powder X-ray diffractometer. NMR spectras were recorded on a Bruker advance III HD 600 spectrometer in CDCl3 at 599 MHz (^{1}H NMR), 151 MHz (^{13}C NMR). High-resolution mass spectral analysis (HRMS) data were measured on Agilent 1260/6545 Q-TOF. IR date were measured on Nicolet IS10.

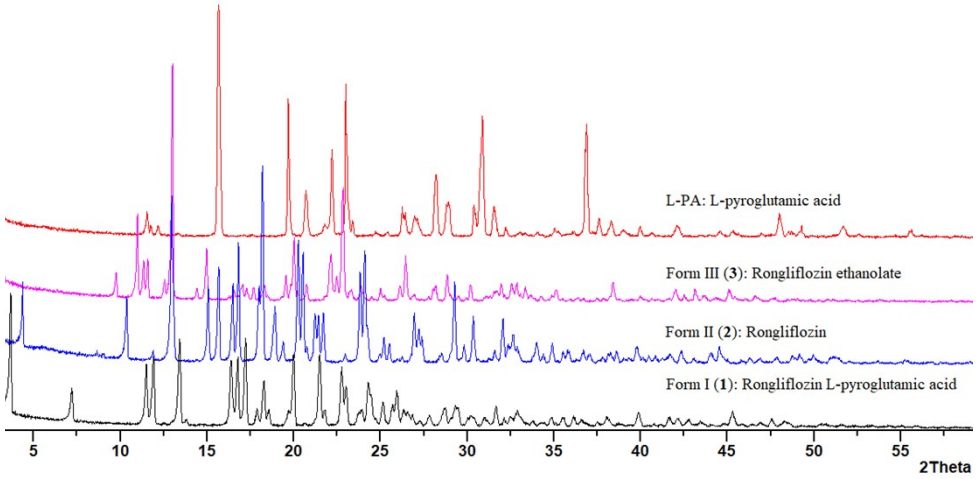
Synthetize of 3

(1R,2S,3S,4R,5S)-5-(4-chloro-3-(4-ethoxybenzyl) phenyl)-1-((R)-1-hydroxyethyl)-6,8-dioxabicyclo [3.2.1] octane-2,3,4-triol form II (**2)** (5 g, 11.1 mmol) was dissolved in ethanol (25 mL). The mixture was heated to 80 ^{o}C to form a clear solution then cooled to room temperature and stirred for 1 h. (1R,2S,3S,4R,5S)-5-(4-chloro-3-(4-ethoxybenzyl) phenyl)-1-((R)-1-hydroxyethyl)-6,8-dioxabicyclo [3.2.1] octane-2,3,4-triol ethanolate form III (**3**) was collected by filtration and dried in vacuum for 2 h at 60^{o}C in 98% (5.5 g). ^{1}H NMR (599 MHz, Chloroform-d) δ 7.35 (s, 1H), 7.26 (d, J = 6.0 Hz, 1H), 7.21 (d, J = 6.0 Hz, 1H), 7.02 (d, J = 6.0 Hz, 2H), 6.73 (d, J = 6.0 Hz, 2H), 5.11 (s, 1H), 4.83 (s, 1H), 4.12 (d, J = 6.0 Hz, 1H), 3.98 – 3.95 (m, 3H), 3.91 (q, J = 6.0 Hz, 3H), 3.88-3.85 (m, 1H), 3.76-3.72 (m, 2H), 3.69-3.64 (m, 3H), 3.27 (d, J = 6.0 Hz, 1H), 2.32 (s, 1H), 1.55 (s, 1H), 1.33 (t, J = 6.0 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.15 (d, J = 6.0 Hz, 3H).^{13}C NMR (151 MHz, Chloroform-d) δ 157.47, 139.04, 135.56, 135.07, 131.28, 129.82, 129.48, 129.11, 125.81, 114.59, 108.35, 84.68, 77.62, 76.65, 74.36, 69.65, 67.10, 63.51, 58.57, 38.59, 18.48, 17.65, 14.97. HRMS: (ESI) Calcd for $C_{23}H_{27}ClO_7$ $[M+NH_4]^+$: 468.1784; Found: 468.1793. IR (KBr, cm^{-1}): 3372, 3258, 3046, 3033, 2978, 2937,2914, 2899, 1617, 1583, 1513, 1471, 1456, 1432, 1393, 1241, 1177, 1101, 1051, 829, 811, 799.

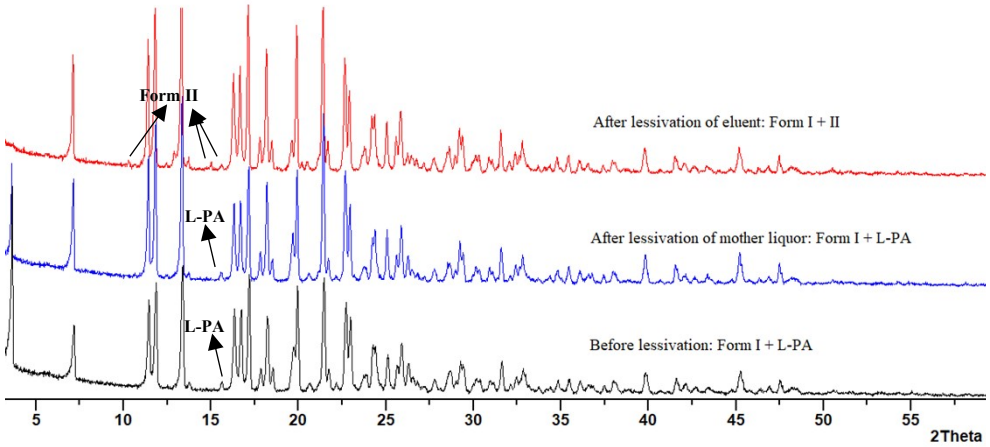
Kilogram scale Process of 1

A mixture of (1R,2S,3S,4R,5S)-5-(4-chloro-3-(4-ethoxybenzyl) phenyl)-1-((R)-1-hydroxyethyl)-6,8-dioxabicyclo [3.2.1] octane-2,3,4-triol ethanolate form III (**3**) (23.45 kg, 47.3 mol), L-pyroglutamic acid (24.31 kg, 4.0 equiv.), EtOH (35.9 L) and H_2O (70 L) was added into a 300 L reactor at room temperature. The slurry was heated to 65 °C and stirred until it is clear. The clear solution was cooled to 35±5 °C typically. Seed crystal form I (**1**) (0.70 kg, 3% g/g) was added when the solution was cooled to 34 °C and maintained for 1.5 h. Gradually, the slurry was cool to 30 °C and 25 °C in 3 hours, and finally stirred at 25 °C for 24 h. The slurry was collected on a centrifuge filter. The filter cake was washed with a mixed solution of EtOH (31.3 L)/H_2O (62.7 L) with L-pyroglutamic acid (1.64 kg, 7% g/g) pre-cooled to -15°C. The wet cake was dried under vacuum at 45 °C for 8 h. Pure cocrystal form I (**1**) was obtained as a white solid (24.91 kg, yield 91%). MP (DSC onset) = 96.91 ℃. ^{1}H NMR (599 MHz, DMSO-d_6) δ 12.77 (br, 1H), 7.91 (s, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 12.0 Hz, 1H), 7.31 (dd, J = 12.0, 2.0 Hz, 1H), 7.10 (d, J = 2.0 Hz , 2H), 6.83 (d, J = 2.0 Hz, 2H), 5.29 (s, 1H), 5.00 (s, 1H), 4.91 (d, J = 6.7 Hz, 1H), 4.63 (d, J = 6.1 Hz, 1H), 4.06 (dd, J = 12.0, 6.0 Hz, 1H), 3.99– 3.95 (m, 5H), 3.84 (p, J = 6.0 Hz, 1H), 3.77 (d, J = 12.0 Hz, 1H), 3.55 (d, J = 6.0 Hz, 1H), 3.44 (t, J = 12.0 Hz, 2H), 3.38 (s, 4H), 2.35-2.29 (m, 1H), 2.18-2.08 (m, 2), 1.99-1.94 (m, 1H), 1.29 (t, J = 12.0 Hz, 3H), 1.17 (d, J = 6.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 177.06, 174.48, 156.96, 138.17, 137.69, 131.16, 129.64, 129.42, 128.46, 126.29, 114.35, 107.60, 85.76, 77.32, 76.21, 72.95, 66.28, 65.00, 62.93, 54.79, 37.73, 29.10, 24.64, 17.90, 14.72. HRMS: (ESI) Calcd for $C_{23}H_{27}ClO_7$ $[M+NH_4]^+$: 468.1784, $C_5H_7NO_3$ $[M+H]^+$:130.0499; Found: 468.1774, 130.0490 respectively. IR (KBr, cm^{-1}): 3257, 2986, 2927, 1750, 1648, 1513, 1476, 1371, 1264, 1239, 1223, 1206, 1088, 1061, 821.

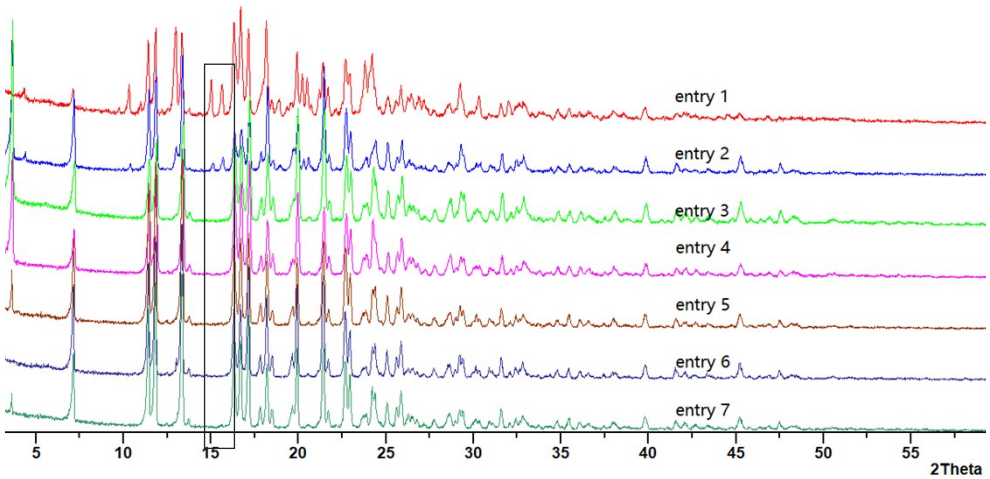
S1-PXRDs of Form I (**1**), II (**2**), III (**3**) and L-pyroglutamic acid (L-PA).



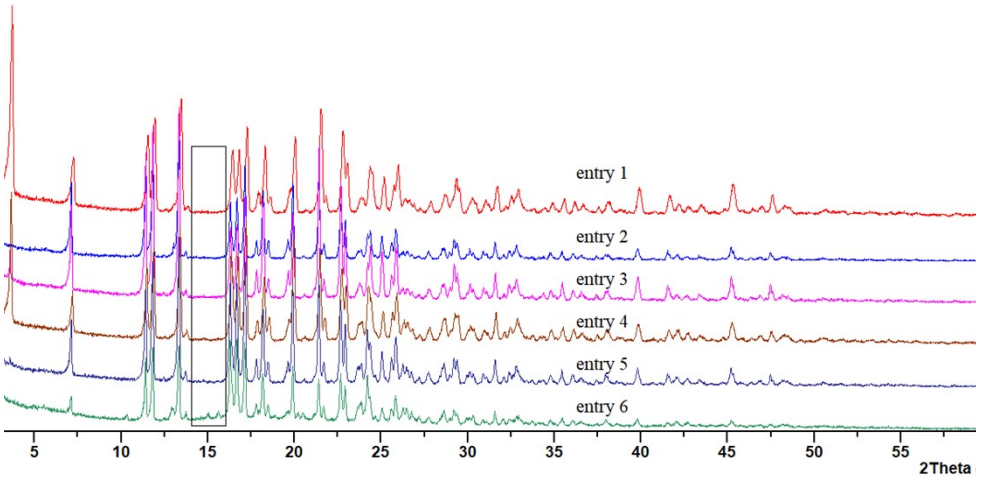
S2-Process-control experiment to monitoring the transformation in process



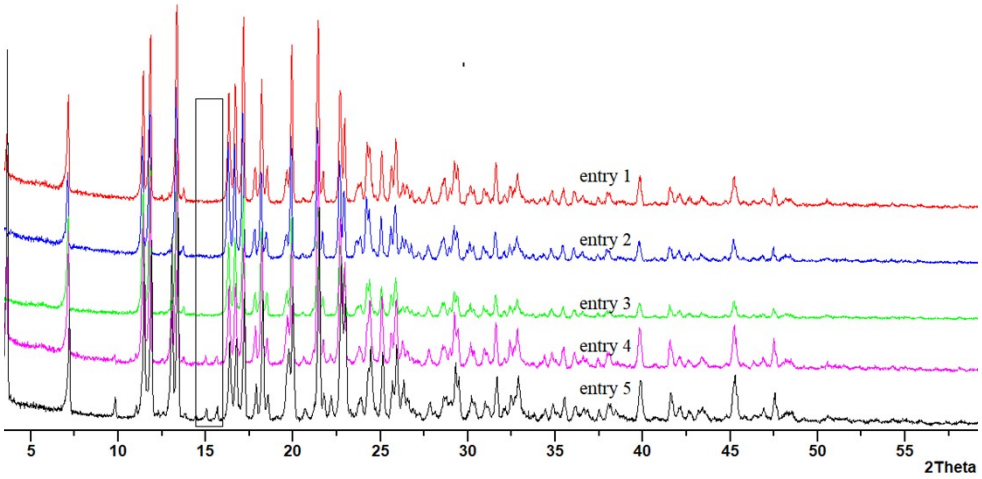
S3-PXRDs for Table **1**



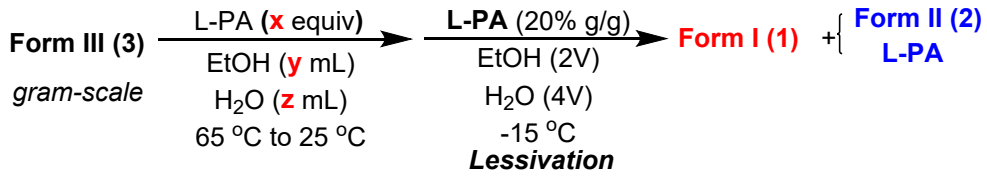
S4-PXRDs for Table **2**



S5-PXRDs for Table **3**

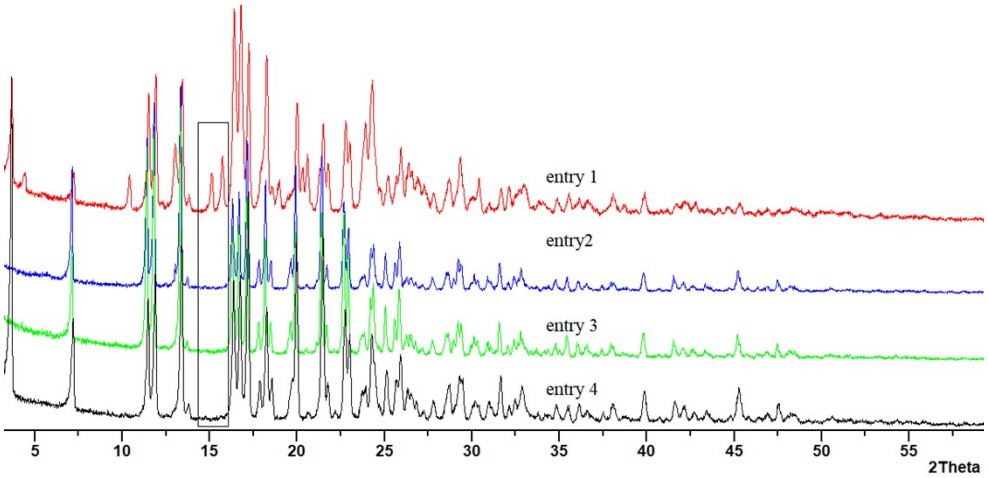


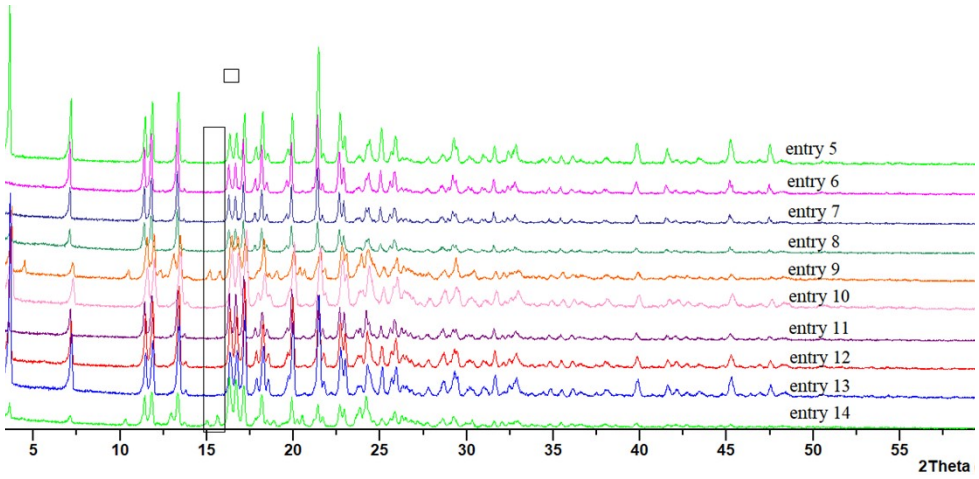
S6-Screening about other parameters and PXRDs



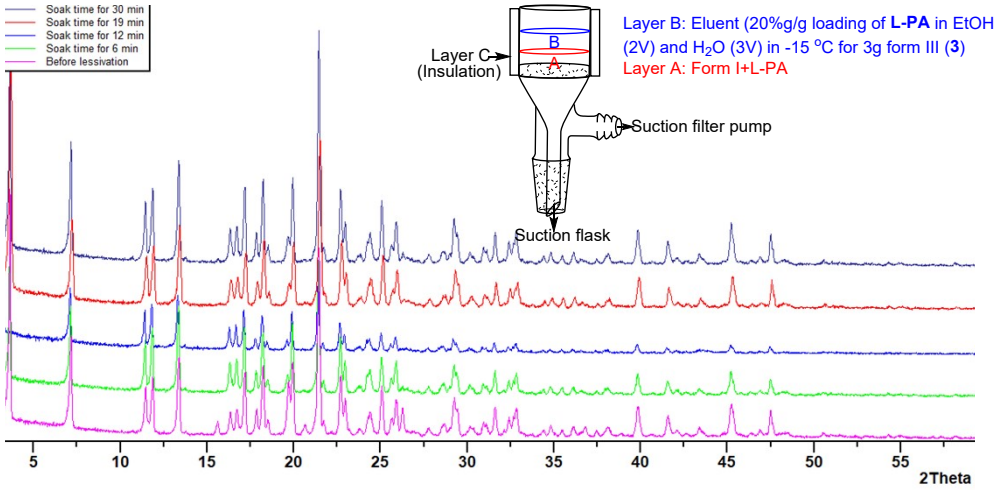
Entry	**3**	x	y:z	y/mL	z/mL	Yield of **1**	PXRD
1	3g	3.0	1:2	4.5	9.0	77%	Form I + II
2	3g	4.0	1:2	4.5	9.0	86%	Form I
3	3g	4.5	1:2	4.5	9.0	89%	Form I
4	3g	5.5	1:2	4.5	9.0	78%	Form I
5	3g	4.0	1:2	3.5	7.0	89%	Form I
6	3g	4.0	1:2	4.0	8.0	92%	Form I
7	3g	4.0	1:2	5.0	10.0	91%	Form I
8	3g	4.0	1:2	5.5	11	91%	Form I
9	3g	4.0	0:1	0	13.5	90%	Form I + II
10	3g	4.0	1:10	1.2	12.3	81%	Form I
11	3g	4.0	1:5	2.2	11.3	83%	Form I
12	3g	4.0	1:3	3.3	10.2	87%	Form I
13	3g	4.0	1:1.5	5.4	8.1	69%	Form I
14	3g	4.0	1:1	6.8	6.8	32%	Form I + II

Crystal seeds: 3%g/g of **3**; V: mL/g

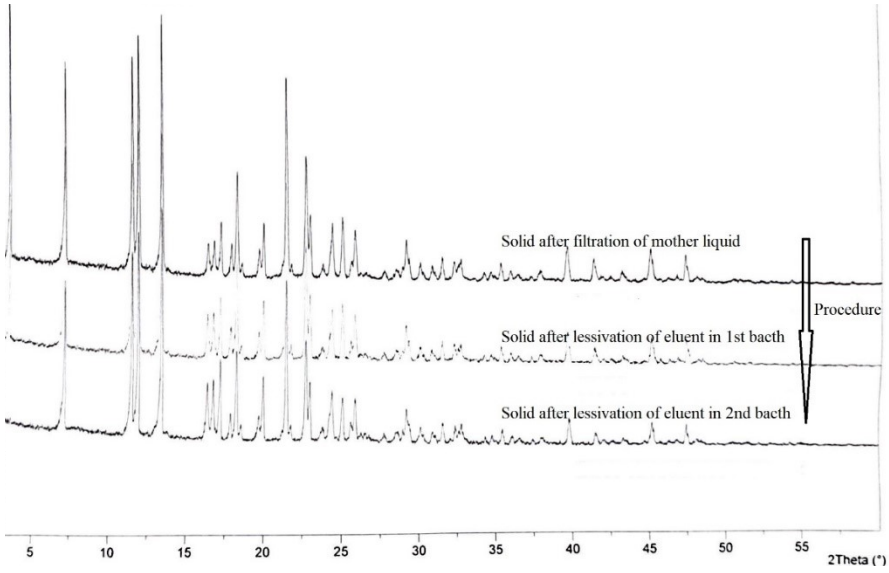




S7-The effect of soak time on purification.

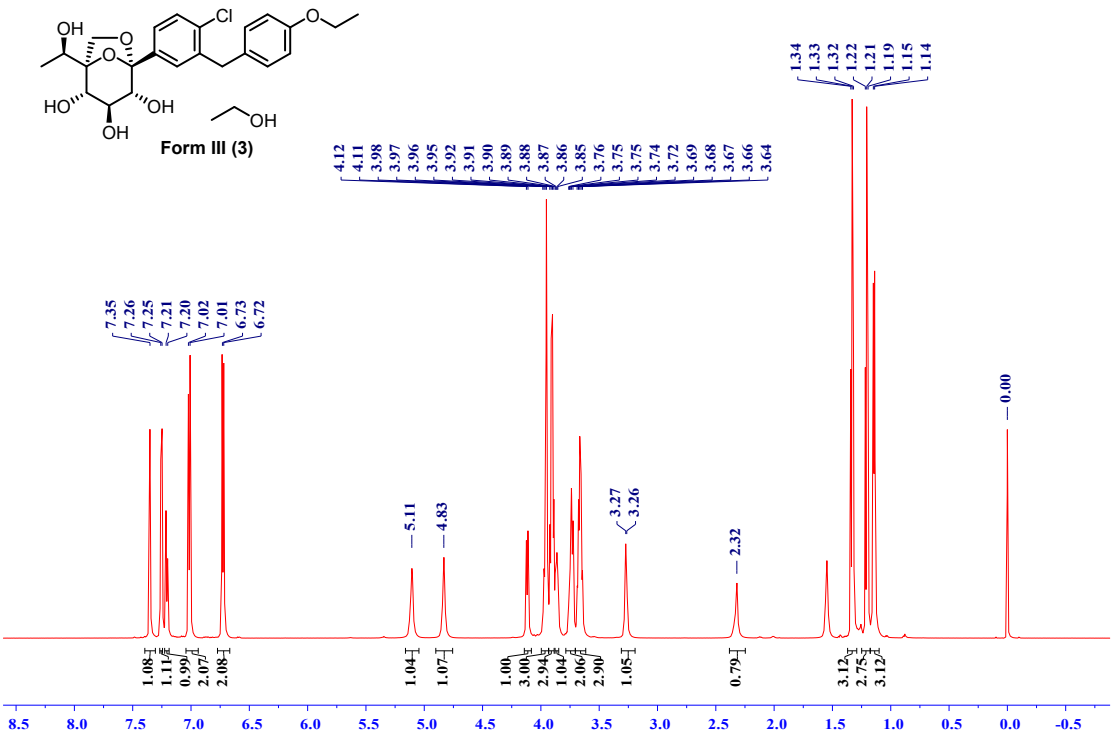


S8-PXRDs in different stages of form I using a centrifuge

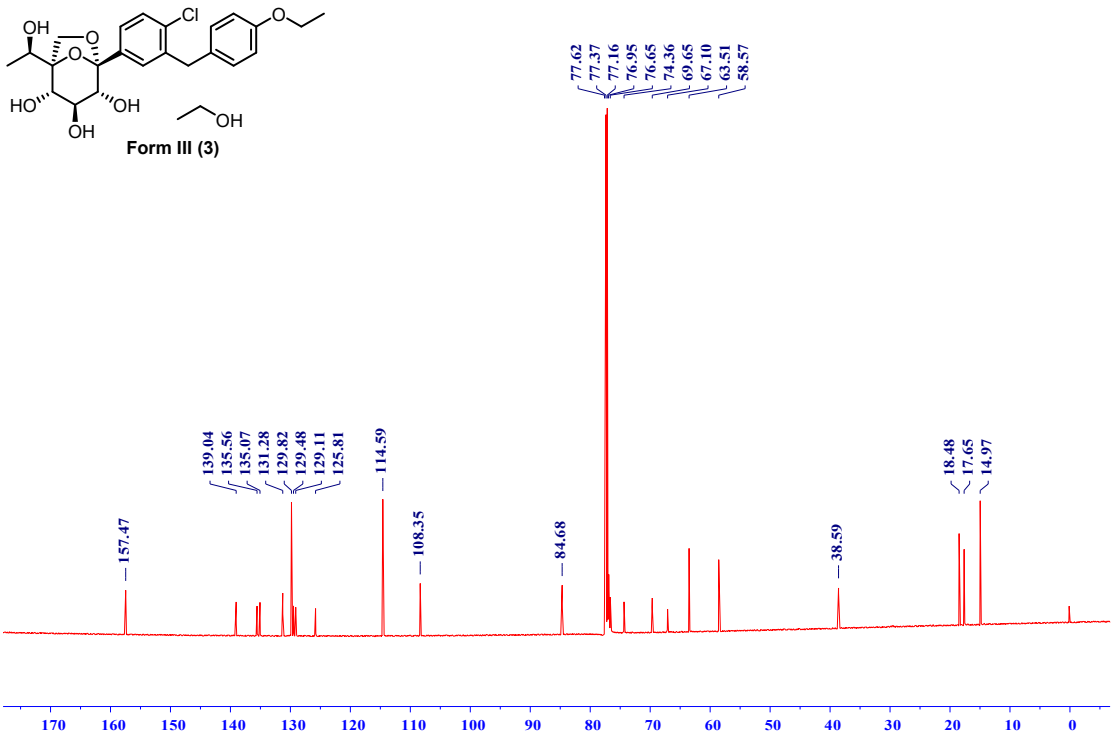


Spectrum of 3 and 1

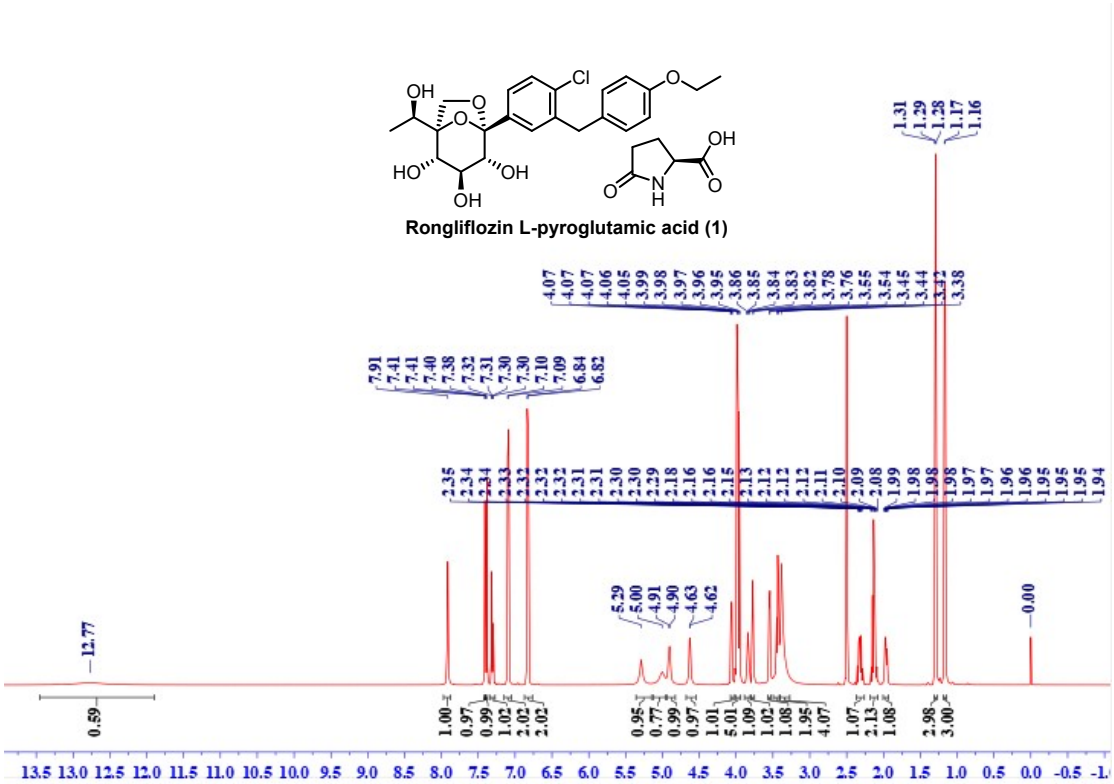
^{1}H NMR Spectrum of **3** (599 MHz, $CDCl_3$)



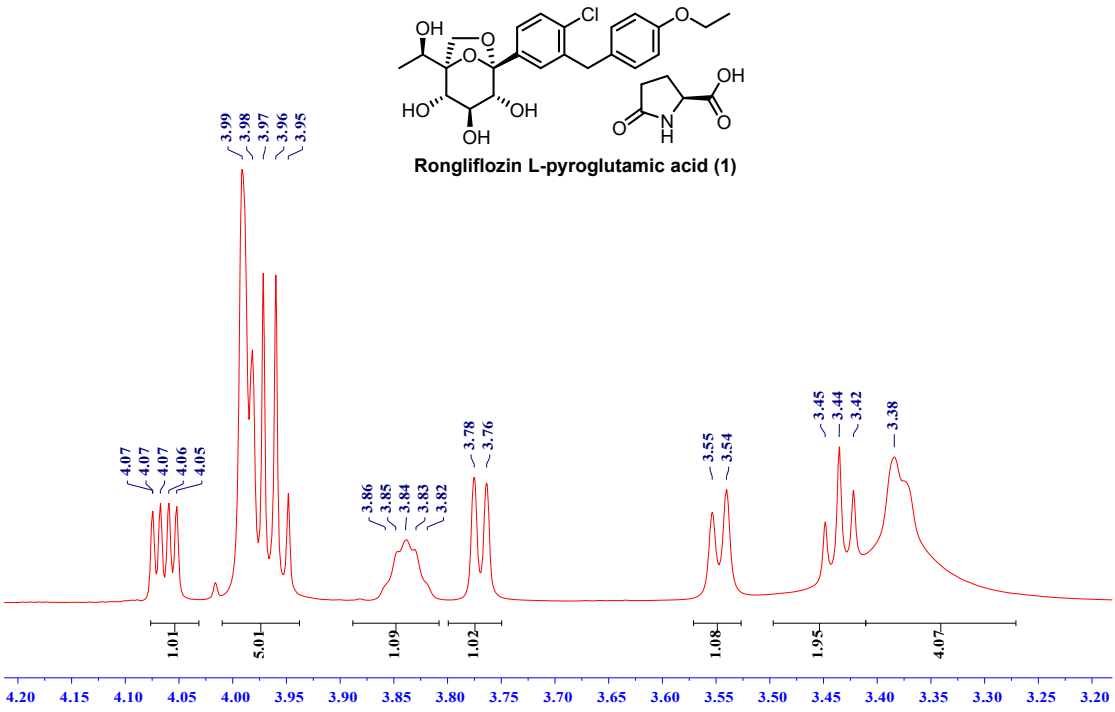
^{13}C NMR Spectrum of **4** (151 MHz, $CDCl_3$)

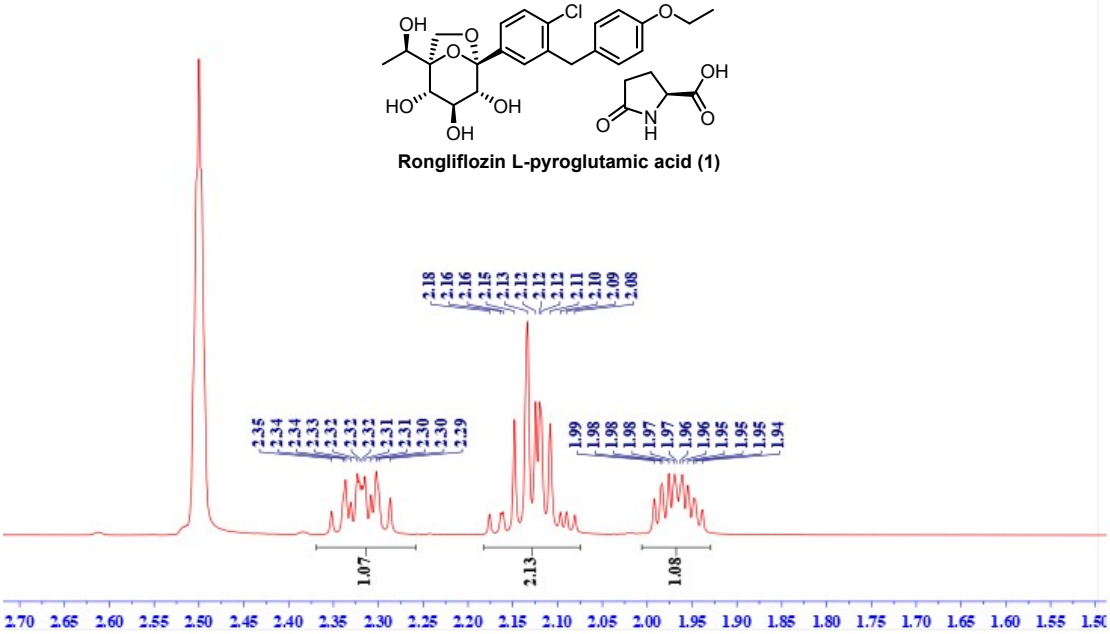


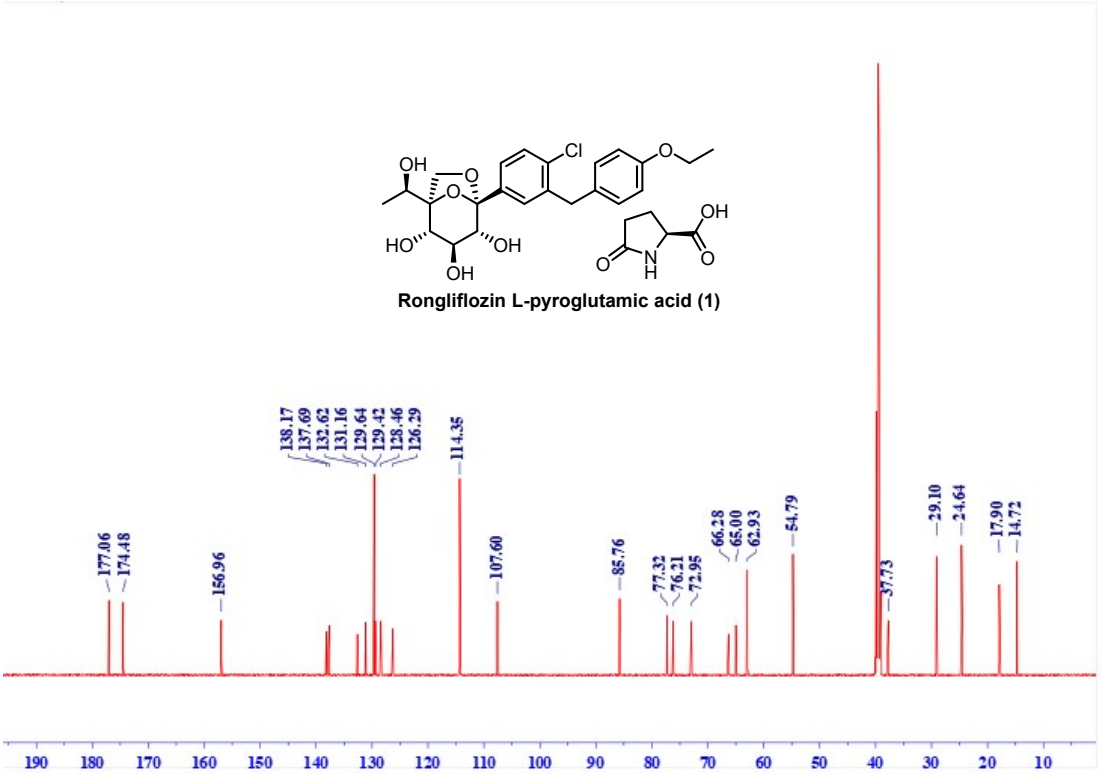
^{1}H NMR Spectrum of **1** (599 MHz, $CDCl_3$)



^{13}C NMR Spectrum of **1** (151 MHz, $CDCl_3$)




Rongliflozin L-pyroglutamic acid (1)
2.18 2.16 2.16 2.15 2.13 2.12 2.12 2.12 2.11 2.10 2.09 2.08
2.35 2.34 2.34 2.33 2.32 2.32 2.32 2.31 2.31 2.30 2.30 2.29
1.99 1.98 1.98 1.98 1.97 1.97 1.96 1.96 1.95 1.95 1.95 1.94
1.07
2.13
1.08
2.70 2.65 2.60 2.55 2.50 2.45 2.40 2.35 2.30 2.25 2.20 2.15 2.10 2.05 2.00 1.95 1.90 1.85 1.80 1.75 1.70 1.65 1.60 1.55


Rongliflozin L-pyroglutamic acid (1)
138.17
137.69
132.62
131.16
129.64
129.42
128.46
126.29
114.35
177.06
174.48
156.96
107.60
85.76
77.32
76.21
72.95
66.28
65.00
62.93
54.79
37.73
29.10
24.64
17.90
14.72
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10