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Electronic Supplementary Information (ESI)†

Novel Crystal Forms of Entresto: A Supramolecular Complex of Trisodium Sacubitril Valsartan Hemi-pentahydrate

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Contents

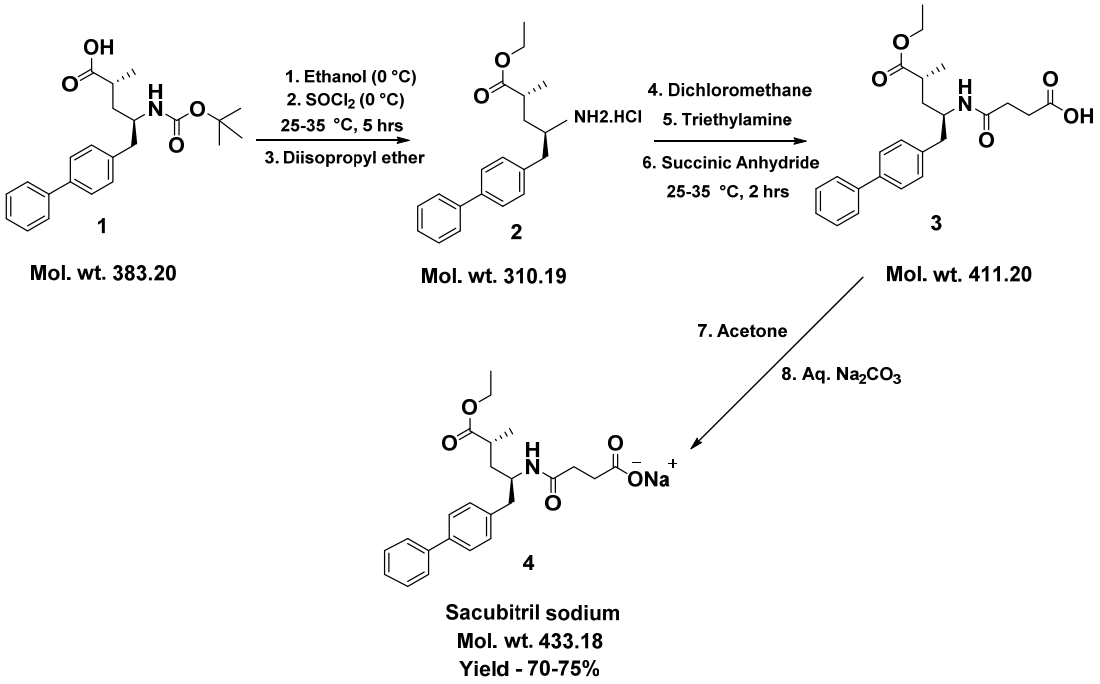
Experimental Section

Materials and Methods:

Valsartan and Sacubitril intermediate were procured from commercial sources. Both intermediates used for the synthesis of Entresto, i.e., valsartan disodium and sacubitril sodium, were synthesized using the literature procedure (ref. 34, 35 in the original paper). Synthesis of Entresto crystal forms was carried out by treating sacubitril sodium with valsartan disodium in different solvent media.

Preparation of the Sacubitril Sodium from the Intermediate

Sacubitril sodium (4) was prepared from the commercially available intermediate (1) in three easy steps.



Scheme S1. Synthesis scheme for the preparation of sacubitril sodium (**4**) from the intermediate 1.

Step-1: Preparation of Ethyl (2R, 4S)-5-([1, 1'-biphenyl]-4-yl)-4-amino-2-methylpentanoate hydrochloride (**2**)

Compound 1 (10 g, 26.09603 mmol) was taken in 30 mL ethanol at room temperature and cooled to 0-5 °C. About 2 mL (27.57 mmol) thionyl chloride was added to the mixture and stirred for 5 hours at 25-35 °C. After completing the reaction, the reaction mixture was concentrated at 50-55 °C under reduced pressure using a rotary evaporator. Approximately 130 mL di-isopropyl ether was added to the solid residue and stirred at 25-35 °C for about 1 hour to obtain the solid white product. The product was filtered and washed with di-isopropyl ether to get the wet cake which was dried at 50-55 °C under vacuum for 4 hours to obtain the required compound 2 (9.34 g, ~92% yield) (Figure S3, SI for ^{1}H NMR of compound **2**).

Step-2: Preparation of 4-(((2S,4R)-1-([1,1'-biphenyl]-4-yi)-5-ethoxy-4-methyl-5-oxopentan-2-yl)amino)-4-oxobutanoic acid (**3**)

Compound 2 (9 g, 29.014 mmol) was dissolved in 45 mL dichloromethane (DCM), to which 8.6 mL (TEA, 60.468 mmol) was added and the reaction mixture was stirred for 10 min. Succinic anhydride (3.88 g, 38.773 mmol) was added to the above mixture and stirred for 2 h at 25-35 °C. The reaction mixture was then cooled to 5-10 °C using an ice bath. 1 N hydrochloric acid (10 mL) was added to the above reaction mixture to adjust its pH (1.5-2.5) and stirred continuously for 15 min. The separated aqueous layer was extracted with 27 mL methylene dichloride. The combined organic layer was washed with water to adjust the pH 5-6. The separated methylene dichloride layer was concentrated to dryness under reduced pressure using a rotary evaporator at 40 °C. The sticky residue was degassed for 2 hours under vacuum at 40 °C to obtain **3** (8.13 g, ~ 90%). (Figure S4, SI for ^{1}H NMR of compound **3**).

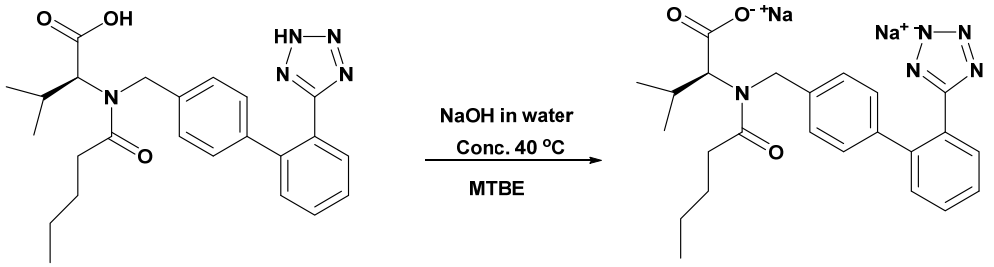
Step-3: Synthesis of Sacubitril Sodium (**4**)

Compound **3** (8 g, 19.455 mmol) was taken in 56 mL acetone to which 20% aqueous sodium carbonate (5.12 mL, 9.661 mmol) was added and stirred for 2 hours at room temperature (25-35 °C). The reaction mixture was concentrated to dryness under reduced pressure using a rotary evaporator at 40 °C and degassed for 1 hour at 40 °C. Isopropyl acetate (96 mL) was added to the residue and stirred overnight at 25-35 °C. The white solid obtained was filtered and washed with isopropyl acetate. The product was dried at 50-55 °C under vacuum for 4 hours to obtain sacubitril sodium (**4**) (5.75 g, ~72%). The compound was characterized using ^{1}H NMR, PXRD, DSC, techniques (Figures S5-S7, SI).

Sacubitril: ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 1.12 (d, J = 7.13 Hz, 3 H); 1.19 (t, J = 7.13 Hz, 3 H); 1.46 (s, 1 H); 1.89 (s, 1 H) 2.39 (s, 4 H); 2.55 (s, 1 H); 2.76 (dd, J = 6.75, 4.25 Hz, 2 H); 4.07 (dtd, J = 10.65, 7.12, 7.12, 3.50 Hz, 3 H); 7.24-7.33 (m, 3 H); 7.40 (t, J = 7.63 Hz, 2 H); 7.49-7.62 (m, 4 H).

Preparation of the Valsartan Disodium (5)

To a solution of valsartan (2 g, 4.59 mmol) in acetone (10 mL), the solution of sodium hydroxide (0.37 g, 9.17 mmol) in water (1.6 mL) was added and stirred continuously for 5 hours at room temperature. The reaction mixture was then concentrated to dryness under reduced pressure over a rotary evaporator at 40 °C and the solid residue obtained was degassed for 1 hour on a rotary evaporator. The solid residue was then taken in methyl tert-butyl ether (MTBE) (10 mL) and continuously stirred for 2 hours at room temperature. The white solid product obtained was filtered and washed with methyl tert-butyl ether (MTBE). The solid product was dried at 40 °C under vacuum for about 4 hours to obtain valsartan disodium (**5**) (1.85 g, ~92%). The compound was characterized using 1H NMR, PXRD and DSC techniques (Figures S8-S10, SI).



Scheme S2. Synthesis scheme for the preparation of valsartan disodium (**5**) from valsartan.

The same procedure was repeated several times to synthesize about 500 g of valsartan disodium. All the batches were characterized using PXRD, melting point and DSC techniques.

Valsartan disodium: ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 0.76 (d, *J* = 6.75 Hz, 1 H); 0.79 - 0.85 (m, 4 H); 0.92 (t, *J* = 7.38 Hz, 1 H); 0.95-1.00 (m, 3 H); 1.17-1.28 (m, 2 H); 1.31-1.40 (m, 1 H); 1.44-1.55 (m, 1 H); 1.63 (td, *J* = 7.32, 5.00 Hz, 1 H); 2.13-2.37 (m, 2 H); 4.52-4.61 (m, 1 H); 4.63 (d, *J* =17.64 Hz, 1 H); 4.73 (d, *J* = 17.51 Hz, 1 H); 6.99 (d, *J* = 8.25 Hz, 1 H); 7.08 (d, *J* =8.25 Hz, 1 H); 7.11-7.25 (m, 2 H); 7.47-7.56 (m, 2 H); 7.59-7.70 (m, 2 H).

Synthesis of Entresto:

Synthesis of Entresto has been attempted by carrying out the reactions of sacubitril sodium (4) and valsartan disodium (5) in different solvents and conditions. The utilization of different solvents/conditions for the reaction of sacubitril sodium (4) and valsartan disodium (5) resulted in the generation of a total of five novel crystalline forms of Entresto. These novel crystal forms have been labeled as Form-I, Form-II, Form-III, Form-IV and Form-V. All the novel crystal forms were characterized using suitable solid state characterization methods that include ^{1}H NMR, PXRD, DSC and IR.

Synthesis of Form-I

To the solution of Valsartan disodium (4.79 g, 10.00 mmol) in acetone (140 mL) and water (4 mL) the sacubitril sodium (4.35 g, 10.00 mmol) was added, stirred and sonicated at room temperature for about 10 minutes. The reaction mixture was then heated to reflux temperature ~80 ºC with continuous stirring for an hour. After cooling, the reaction mixture was concentrated under reduced pressure at 40 ºC using a rotary evaporator to obtain a solid gummy residue. The sticky solid product was taken in 30 mL acetone and again concentrated under reduced pressure at the rotary evaporator to get a crude sticky product which was degassed for an hour. The gummy solid was again taken in acetone (100 mL) and stirred for 6 hours at room temperature until free solid residue was precipitated. The product was then filtered and washed with acetone. The wet cake was dried under a vacuum oven for 6 h at 40 ºC to obtain 6.52 g of the product (71.5%).

Form I: ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 0.64 (d, *J* = 6.63 Hz, 2 H); 0.82 (d, *J* = 7.13 Hz, 2 H); 0.96 (dt, *J* =15.16, 7.05 Hz, 5 H); 1.12 (d, *J* =7.00 Hz, 3 H); 1.17-1.26 (m, 1 H); 1.34-1.48 (m, 3 H); 1.57-1.69 (m, 1 H); 1.86-1.99 (m, 3 H); 1.99-2.19 (m, 2 H); 2.32-2.49 (m, 7 H); 2.49-2.69 (m, 1 H); 2.73 (dd, *J* =13.63, 7.63 Hz, 1 H); 2.89 (dd, *J* =13.63, 5.63 Hz, 1 H); 3.33-3.39

(m, 12 H); 3.90 (d, *J* =10.63 Hz, 1 H); 4.08-4.19 (m, 1 H); 4.50-4.59 (m, 1 H); 7.00-7.21 (m, 4 H); 7.25-7.32 (m, 3 H); 7.36-7.40 (m, 3 H); 7.40-7.49 (m, 3 H); 7.49-7.61 (m, 4 H). (Figure S11, SI)

Synthesis of Form-II

The solution of Valsartan disodium (4.79 g, 10.00 mmol) and sacubitril sodium (4.33 g, 10.00 mmol) in ethanol (50 mL) was prepared and stirred at room temperature (30-35 ºC) for about 4 h. The reaction mixture was then concentrated under reduced pressure (550 mbar) at 40 ºC using a rotary evaporator to obtain a solid gummy residue which was further degassed for 1 h. The sticky solid product was then taken in 50 mL cyclohexane and stirred again at room temperature until the free solid residue was precipitated (1-2 h). The product was then filtered and washed with cyclohexane. The wet cake was dried under a vacuum oven for 6 h at 40 °C to obtain 6.02 g (65.5%).

Form II: ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.66 (d, *J* =6.63 Hz, 2 H); 0.78-0.86 (m, 2 H); 0.90-1.03 (m, 5 H); 1.13 (d, *J* =7.13 Hz, 3 H); 1.17-1.28 (m, 1 H); 1.34-1.57 (m, 3 H); 1.57-1.70 (m, 1 H); 1.84-1.97 (m, 3 H); 2.05-2.23 (m, 1 H); 2.26 (dd, *J* = 8.76, 6.38 Hz, 1 H); 2.35-2.48 (m, 5 H); 2.48-2.69 (m, 1 H); 2.72-2.83 (m, 2 H); 3.92 (d, *J* =10.63 Hz, 1 H); 4.02-4.16 (m, 1 H); 4.56 (d, *J* = 16.13 Hz, 1 H); 4.74-4.82 (m, 1 H); 7.00-7.21 (m, 4 H); 7.26-7.33 (m, 4 H); 7.36-7.45 (m, 4 H); 7.45-7.51 (m, 2 H); 7.51-7.56 (m, 2 H); 7.56-7.62 (m, 2 H). (Figure S12, SI)

Synthesis of Form-III

The solution of Valsartan disodium (4.79 g, 10.00 mmol) and sacubitril sodium (4.33 g, 10.00 mmol) in acetonitrile (50 mL) was prepared and stirred at room temperature (30-35 ºC) for about 4-5 h. The reaction mixture was then concentrated under reduced pressure at 40 ºC using a rotary evaporator to obtain a solid gummy residue which was further degassed for 1 h. The sticky solid product was then taken in 50 mL cyclohexane and stirred again at room temperature until the free solid residue was precipitated (1-2 h). The product was then filtered and washed with cyclohexane. The wet cake was dried under a vacuum oven for 4 h at 40 °C to obtain 6.12 g (~66%).

Form III: ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.64 (d, *J* =6.63 Hz,2 H); 0.76-0.85 (m, 2 H); 0.90-1.0 (m, 5 H); 1.10 (d, *J* = 7.00 Hz, 3 H); 1.16-1.24 (m, 1 H); 1.32-1.57(m, 3H); 1.56-1.68 (m, 1 H); 1.85-1.94 (m, 3 H); 2.00-2.18 (m, 1 H); 2.20-2.29 (m, 1 H); 2.32 (s, 1 H); 2.33-2.46 (m, 5 H); 2.47-2.68 (m, 1 H); 2.72 (dd, *J* =13.57, 7.57 Hz, 1 H); 2.85 (dd, *J* =13.57, 5.82 Hz, 1 H); 3.88 (d, *J* = 10.51 Hz, 1 H); 4.07-4.17 (m, 1 H); 4.48-4.56 (m, 1 H); 4.80 (m,1 H); 6.97-7.18 (m, 4 H); 7.23-7.31 (m, 4 H); 7.34-7.42 (m, 4 H); 7.42-7.47 (m, 2 H); 7.47-7.52 (m, 2 H); 7.52-7.61 (m, 2 H). (Figure S13, SI)

Synthesis of Form-IV

The solution of valsartan disodium (4.79 g, 10.00 mmol) and sacubitril sodium (4.33 g, 10.00 mmol) in chloroform (50 mL) was prepared and stirred at room temperature (30-35 ºC) for about 4-5 h. The reaction mixture was then concentrated under reduced pressure at 40 ºC using a rotary evaporator to obtain a solid gummy residue which was further degassed for 1 h. The sticky solid

product was then taken in 50 mL cyclohexane and stirred again at room temperature until the free solid residue was precipitated (1-2 h). The product was then filtered and washed with cyclohexane. The wet cake was dried under a vacuum oven for 4 h at 40 °C to obtain 6.25 g (~67%).

Form IV: ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.68 (d, *J* =6.38 Hz, 2 H); 0.79-0.87 (m, 3 H); 0.91-1.02 (m, 5 H); 1.14 (d, *J* = 7.13 Hz, 4 H); 1.18-1.27 (m, 5 H); 1.34-1.54 (m, 3 H); 1.58-1.69 (m, 1 H); 1.82-1.99 (m, 2 H); 2.35-2.46 (m, 5 H); 2.51-2.60 (m, 2 H); 2.77 (dd, *J* =6.75, 4.13 Hz, 3 H); 3.91 (d, *J* = 10.51 Hz, 1 H); 3.99-4.20 (m, 4 H); 4.88 (d, *J* = 2.13 Hz, 10 H); 6.98-7.19 (m, 4 H); 7.24-7.35 (m, 3H); 7.36-7.45 (m, 4 H); 7.46-7.52 (m, 2 H); 7.53 (d, *J* = 8.25 Hz, 2 H); 7.57-7.62 (m, 2 H). (Figure S14, SI)

Synthesis of Form-V

The solution of Valsartan disodium (4.79 g, 10.00 mmol) and sacubitril sodium (4.33 g, 10.00 mmol) in methanol (50 mL) was prepared and stirred at room temperature (30-35 ºC) for about 4-5 h. The reaction mixture was then concentrated under reduced pressure at 40 ºC using a rotary evaporator to obtain a solid gummy residue which was further degassed for 1 h. The sticky solid product was then taken in 50 mL cyclohexane and stirred again at room temperature until the free solid residue was precipitated (1-2 h). The product was then filtered and washed with cyclohexane. The wet cake was dried under a vacuum oven for 4 h at 40 °C to obtain 6.57 g (~72%). The same procedure was also repeated in THF to yield crystalline Form-V.

Form-V was also synthesized using a hot melt extruder. The extruder was initially maintained at 145 ºC (the melting point of Entresto). Dry valsartan disodium (4.79 g, 10.00 mmol) and sacubitril sodium (4.33 g, 10.00 mmol) were mechanically grounded for about 10 minutes at 145 ºC to yield 6.84 g (75 %).

Form V: ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 0.72 (d, *J* = 6.38 Hz, 2 H); 0.79-0.87 (m, 3 H); 0.90-1.02 (m, 5 H); 1.02-1.11 (m, 1 H); 1.13 (d, *J* = 7.00 Hz, 3 H); 1.20 (t, *J* = 7.13 Hz, 3 H); 1.23-1.31 (m, 1 H); 1.34-1.52 (m, 4 H); 1.53-1.60 (m, 1 H); 1.63 (br. s., 1 H); 1.85-1.97 (m, 7 H); 2.18 (br. s., 1 H); 2.26-2.48 (m, 6 H); 2.50-2.69 (m, 3 H); 2.70-2.86 (m, 3 H); 3.90 (d, *J* = 10.26 Hz, 1 H); 4.01-4.17 (m, 3 H); 4.59 (d, *J* = 15.51 Hz, 1 H); 4.75 (br. s., 1 H); 6.96-7.19 (m, 4H); 7.22-7.35 (m, 4 H); 7.36-7.46 (m, 4 H); 7.46-7.50 (m, 2 H); 7.50-7.55 (br. d., 2 H); 7.55-7.61 (m, 2 H). (Figure S15, SI)

The synthesis of different crystal forms of Entresto reproducibly at a higher scale was established using different solvents as listed in the Table S1. Proton NMR confirmed the product chemical purity in each batch.

Table S1. Solvent used in the synthesis of crystal forms of Entresto.

Sr. No.	Solvent used for the synthesis	Crystal form obtained
1	acetone	Form-I
2	ethanol	Form-II
3	acetonitrile, dichloromethane, ethyl acetate	Form-III
4	chloroform	Form-IV
5	methanol, THF, hot melt extruder	Form-V

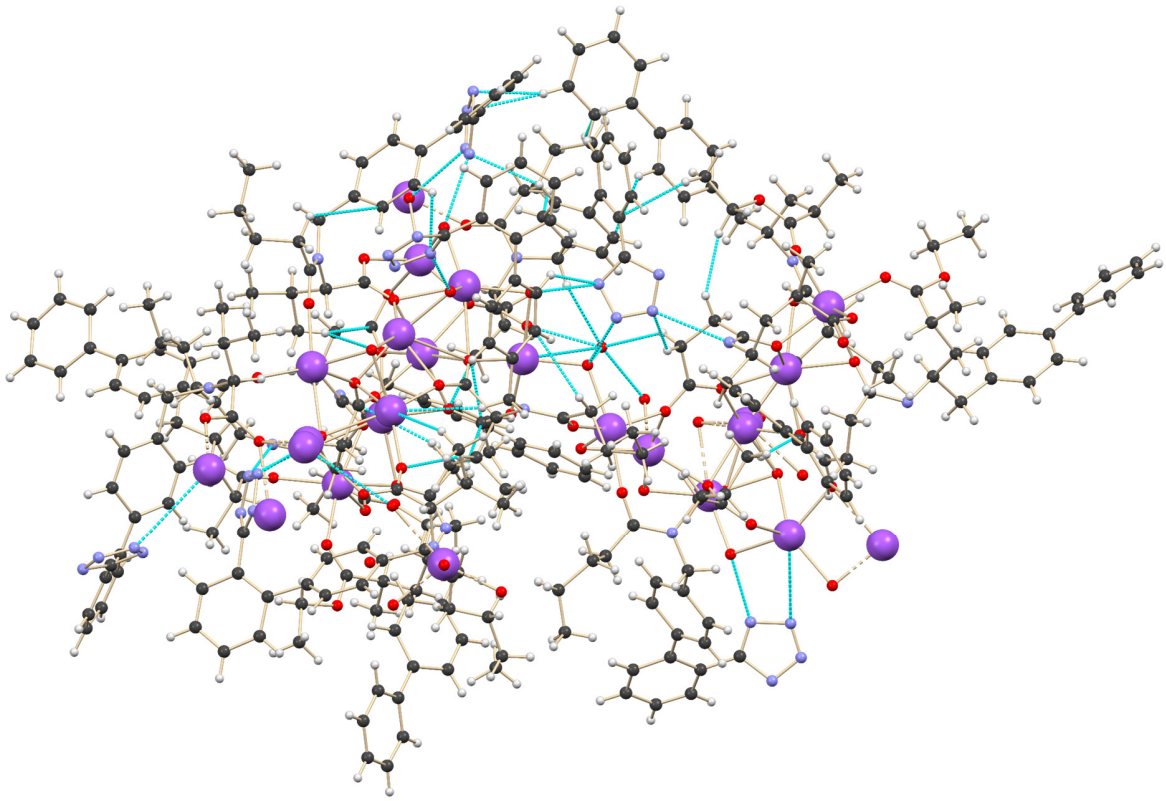


Figure S1. The ball and stick view of the crystal structure of Entresto. The atomic coordinates of the structure have been retrieved from the Cambridge Structural Database having reference no, REFCODE: NAQLAU. The dashed line (cyan) indicates hydrogen bonding and short contacts between sacubitril, valsartan and water molecules.

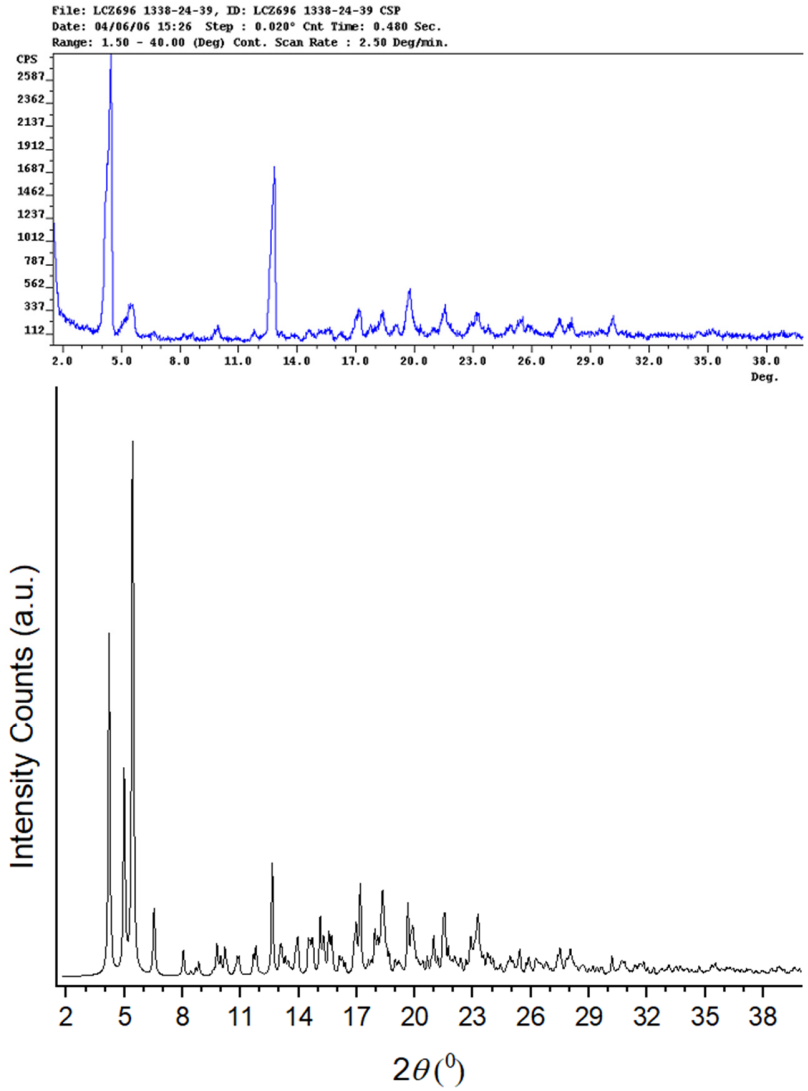


Figure S2. The overlay of PXRD profiles of Entresto, experimental PXRD data (top) and simulated PXRD data from single crystal XRD data (bottom). The single crystal diffraction data was retrieved from the Cambridge Structural Database (Refcode: NAQLAU) and the experimental PXRD pattern was taken from the supporting information file of the publication, *Tet. Lett.* 2012, *53*, 275–276.

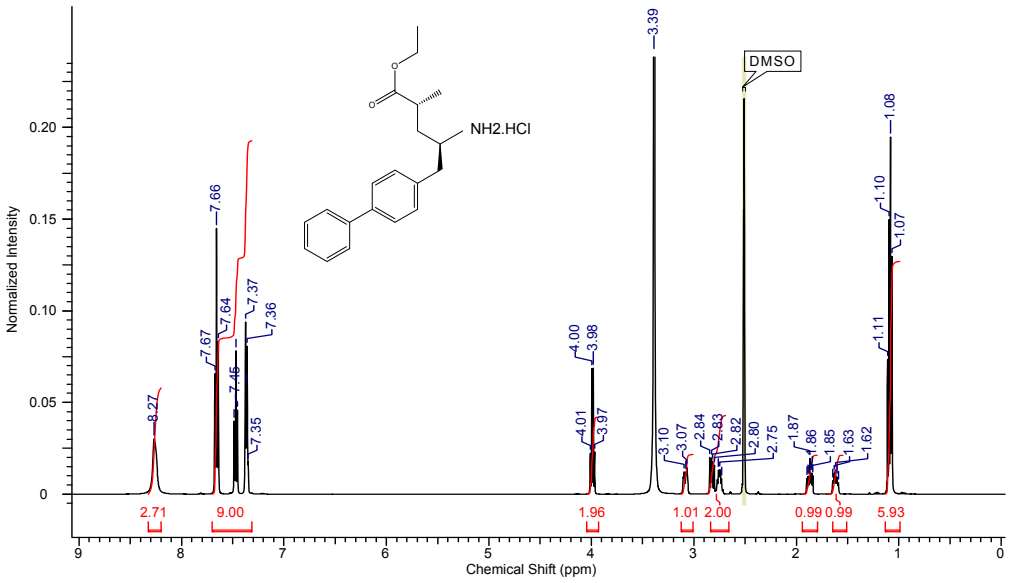


Figure S3. ^{1}H NMR spectrum of compound **2** in DMSO.

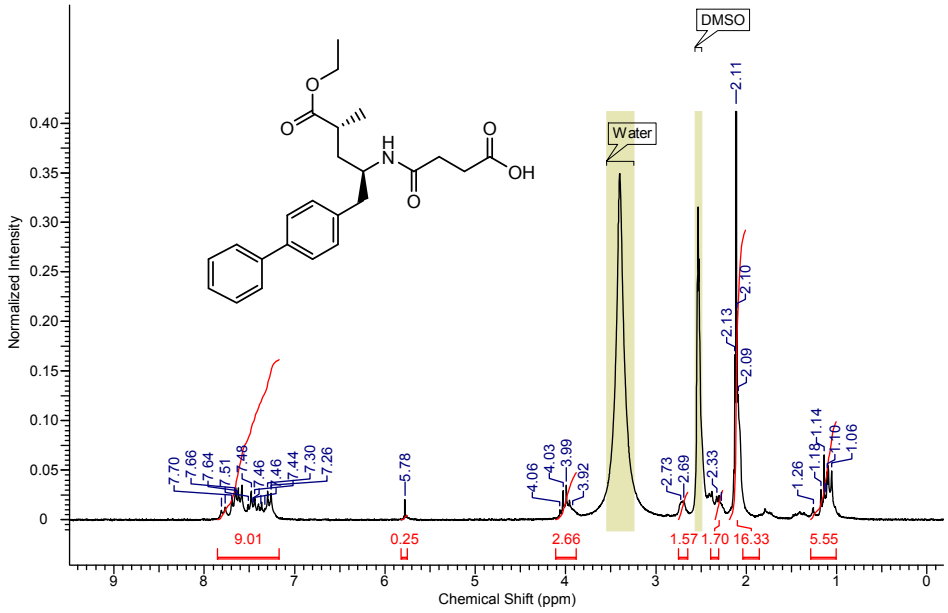


Figure S4. ^{1}H NMR spectrum of compound **3** in DMSO.

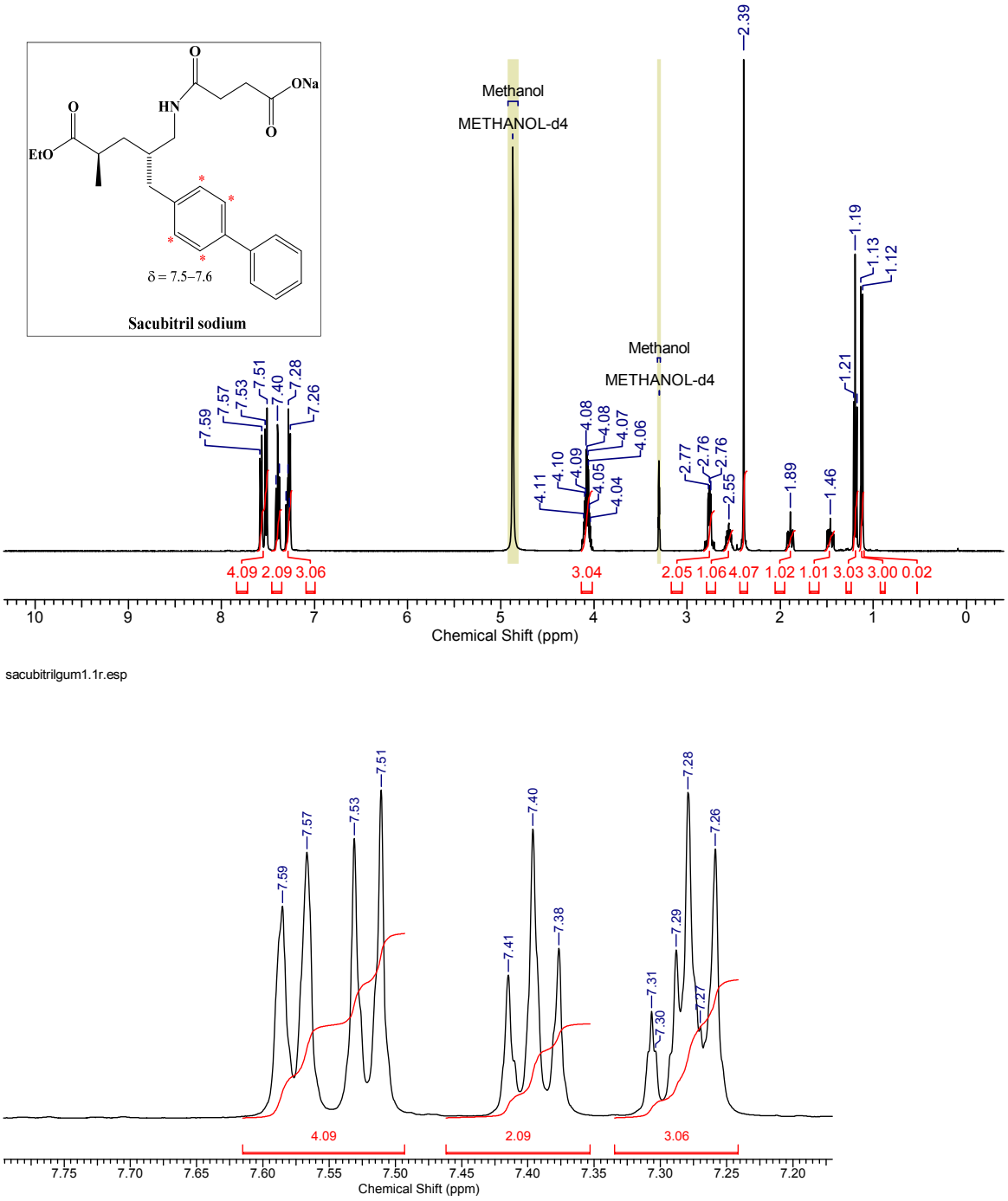


Figure S5. ^{1}H NMR spectrum of sacubitril sodium **4** in methanol d4.

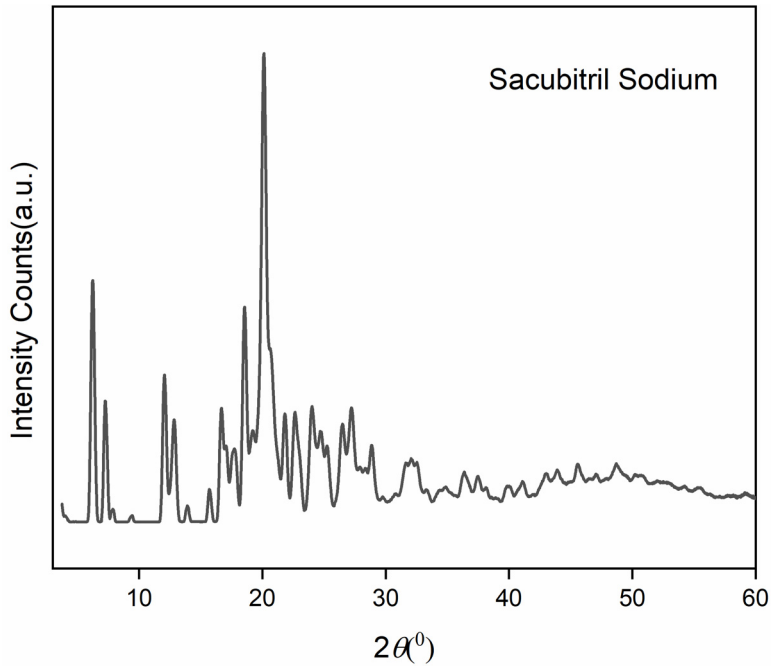


Figure S6. Powder X-ray diffraction profile of sacubitril sodium.

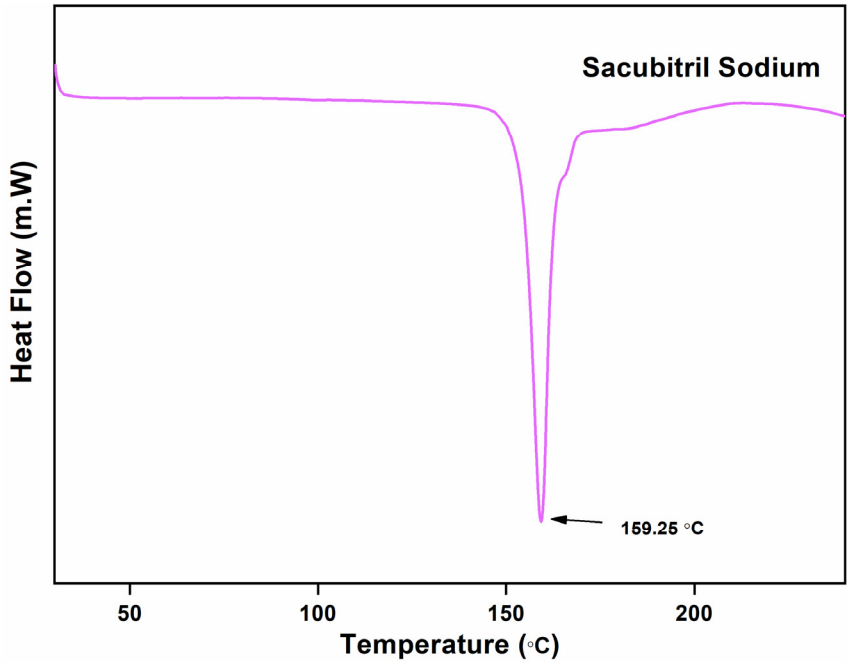


Figure S7. DSC thermogram of sacubitril sodium.

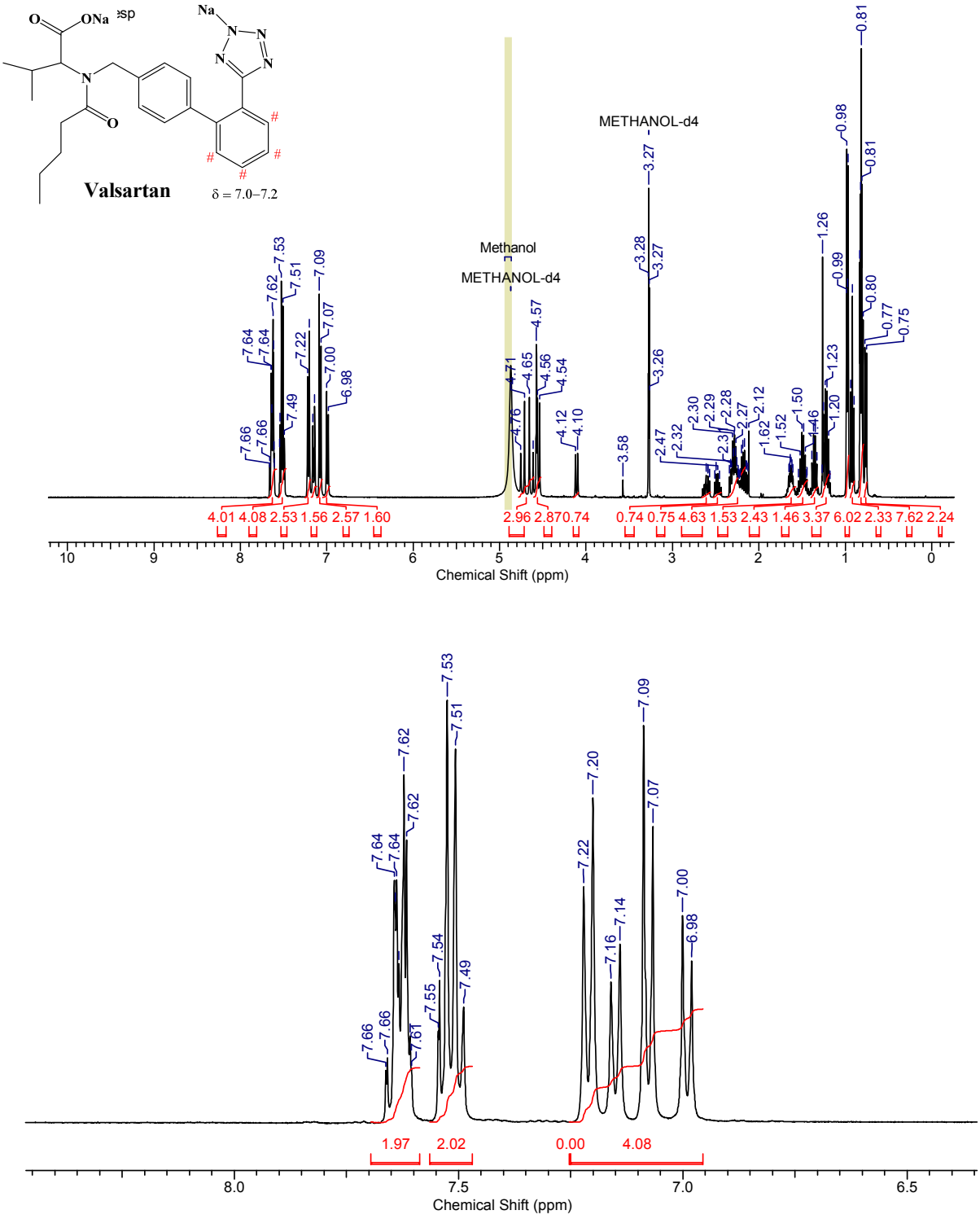


Figure S8. ^{1}H NMR spectrum of valsartan disodium **5** in methanol d4.

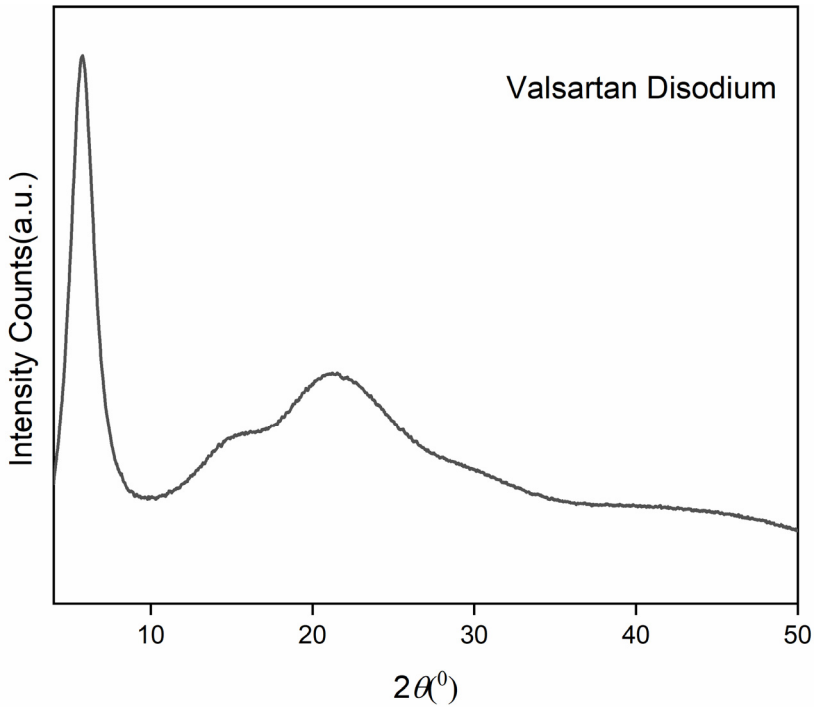


Figure S9. Powder X-ray diffraction profile of valsartan disodium.

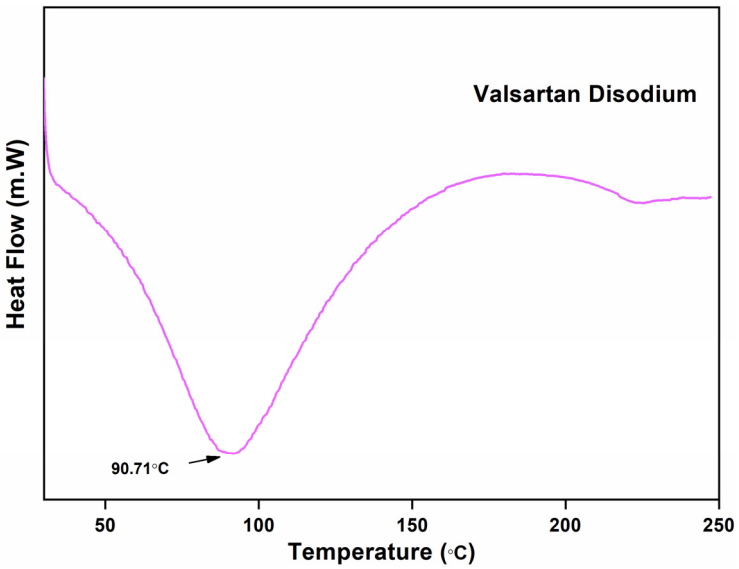


Figure S10. DSC thermogram of valsartan disodium.

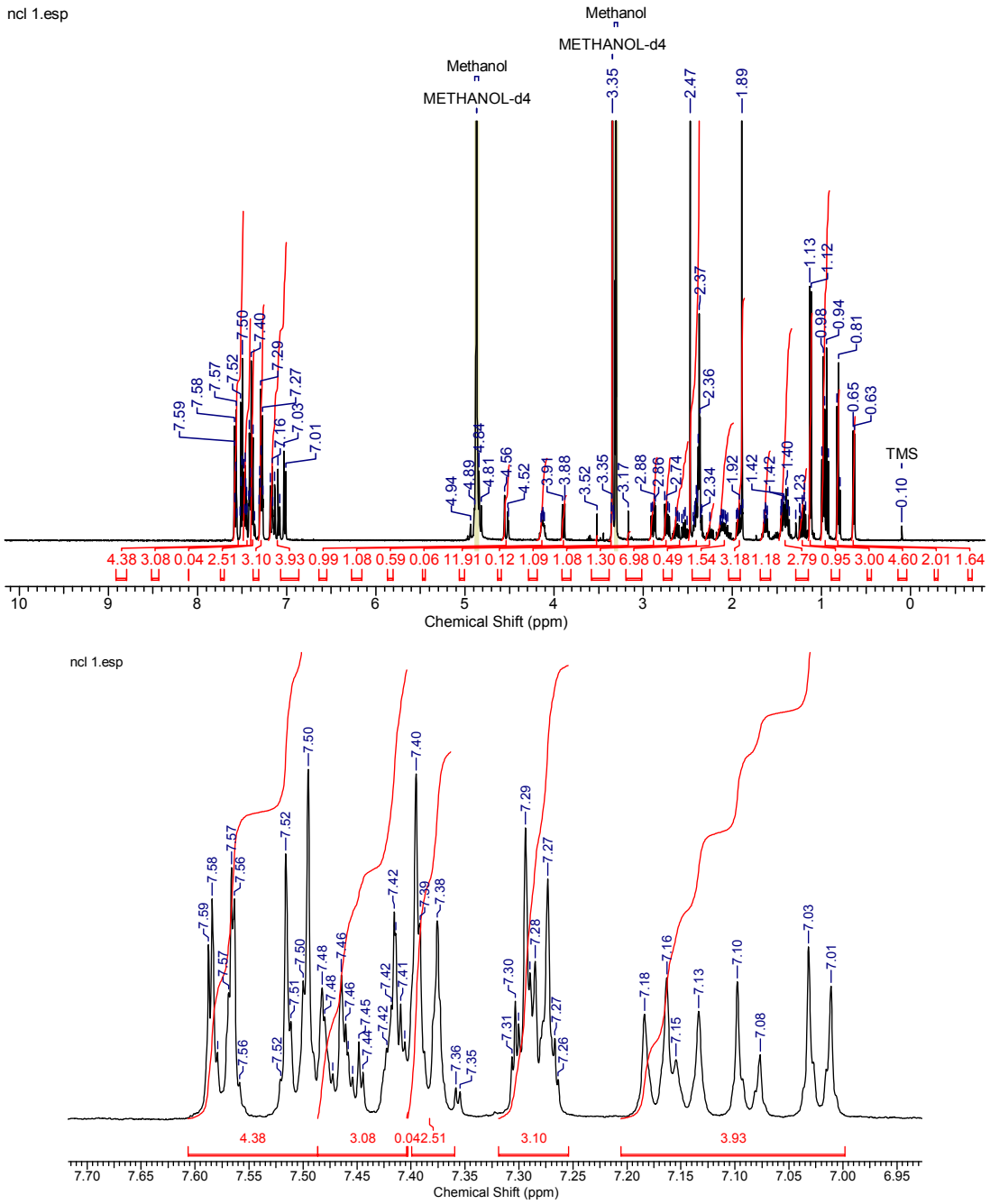


Figure S11. [1]H NMR spectrum of Form-I of Entresto in methanol d4.

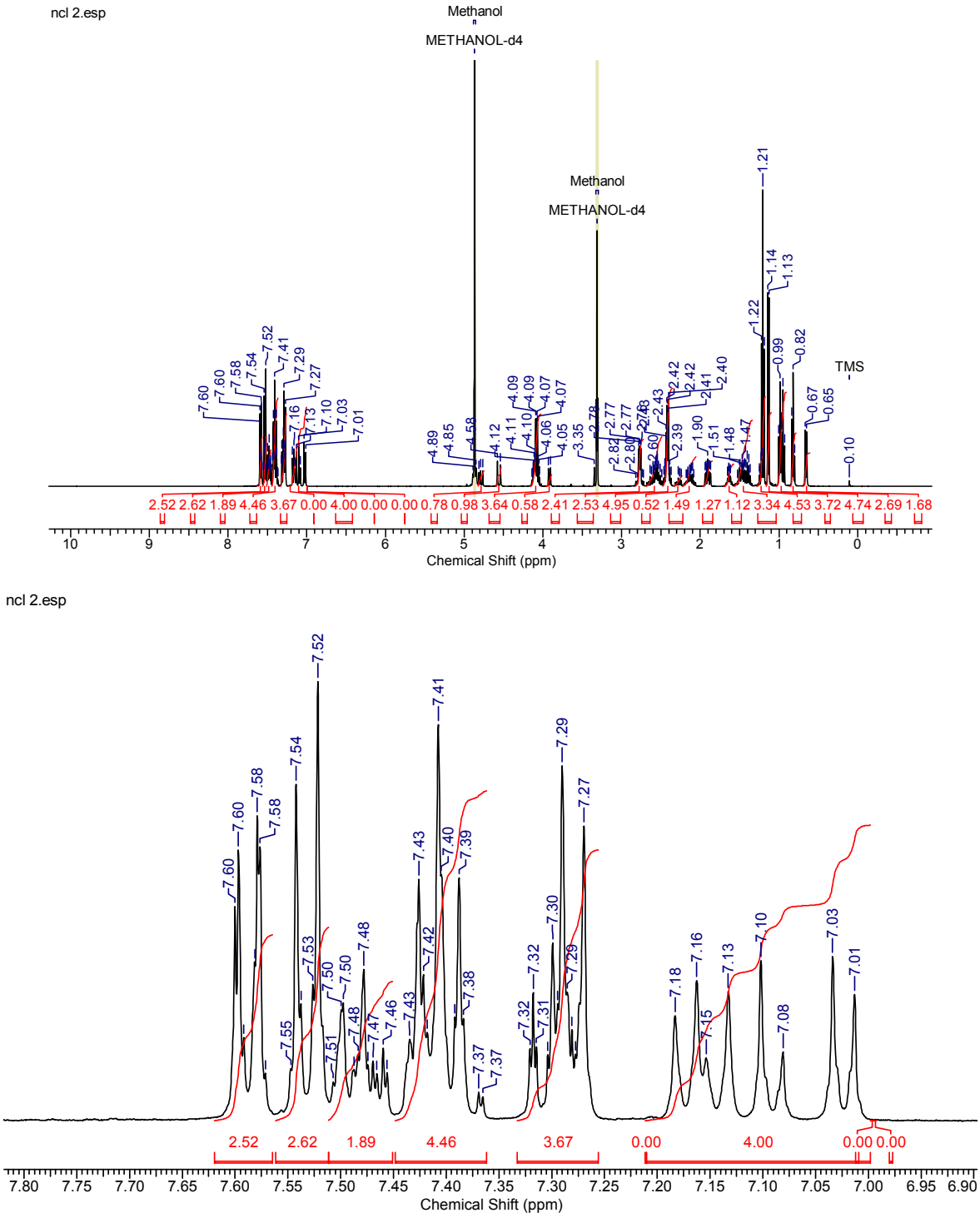


Figure S12. [1]H NMR spectrum of Form-II of Entresto in methanol d4.

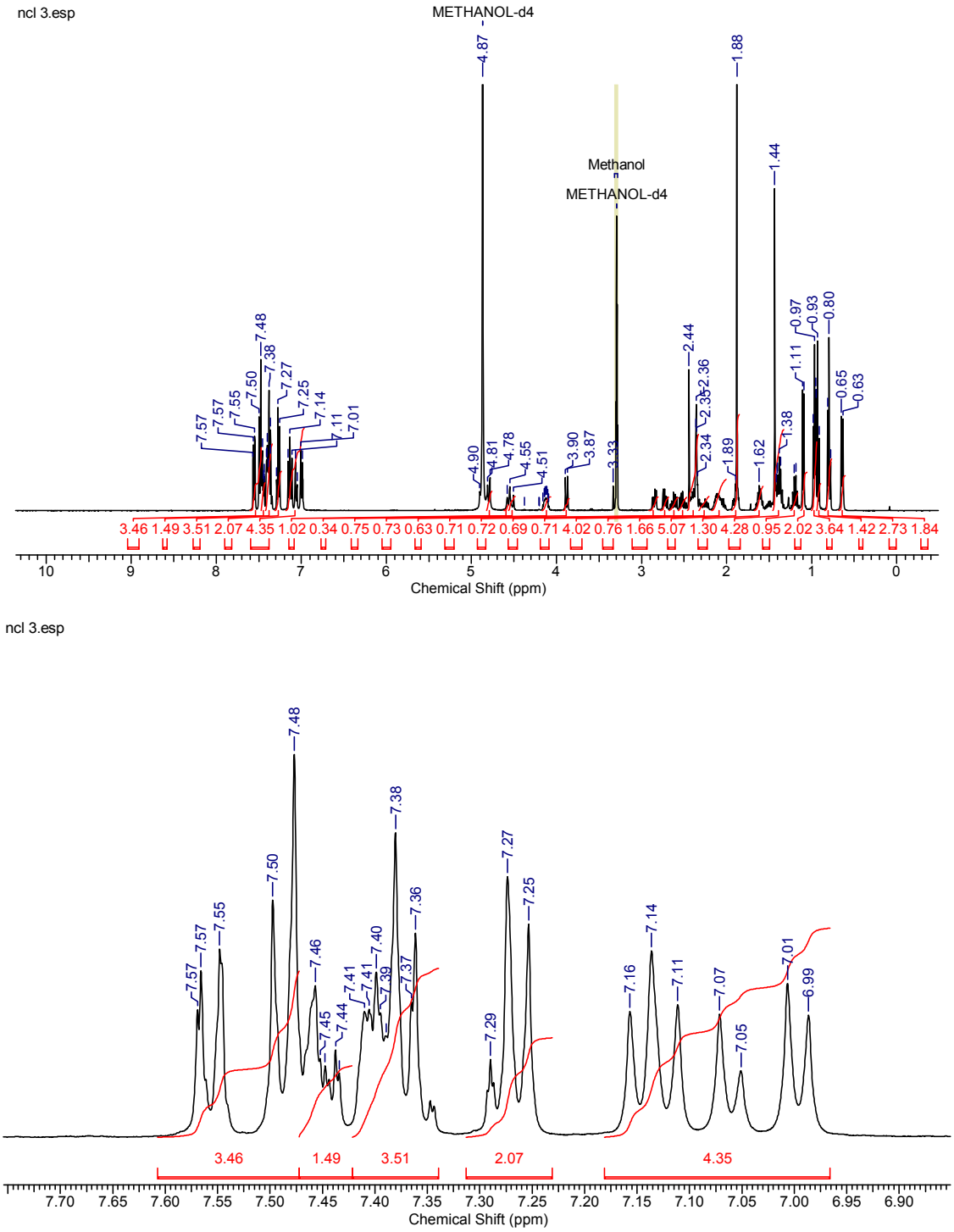


Figure S13. ^{1}H NMR spectrum of Form-III of Entresto in methanol d4.

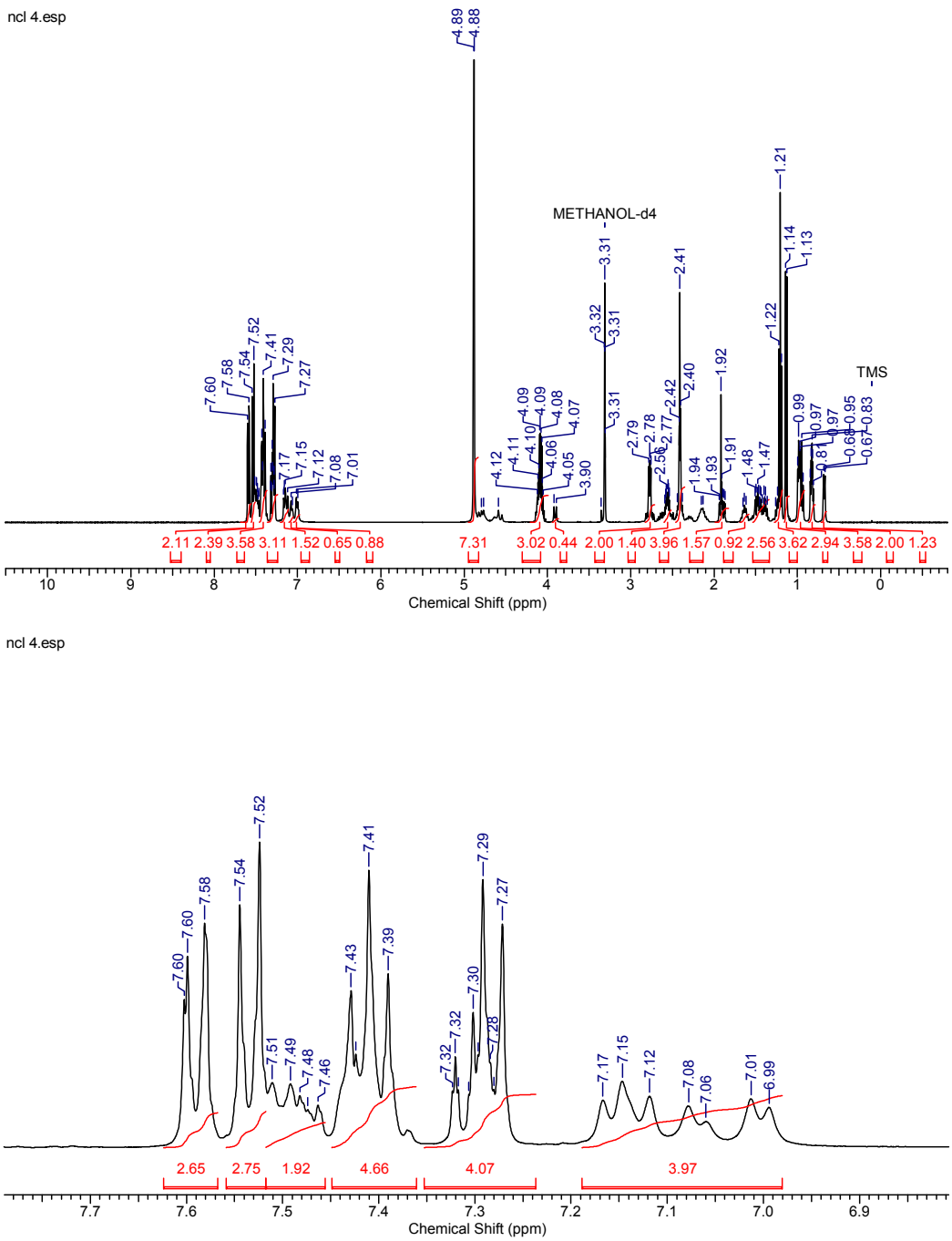


Figure S14. [1]H NMR spectrum of Form-IV of Entresto in methanol d4.

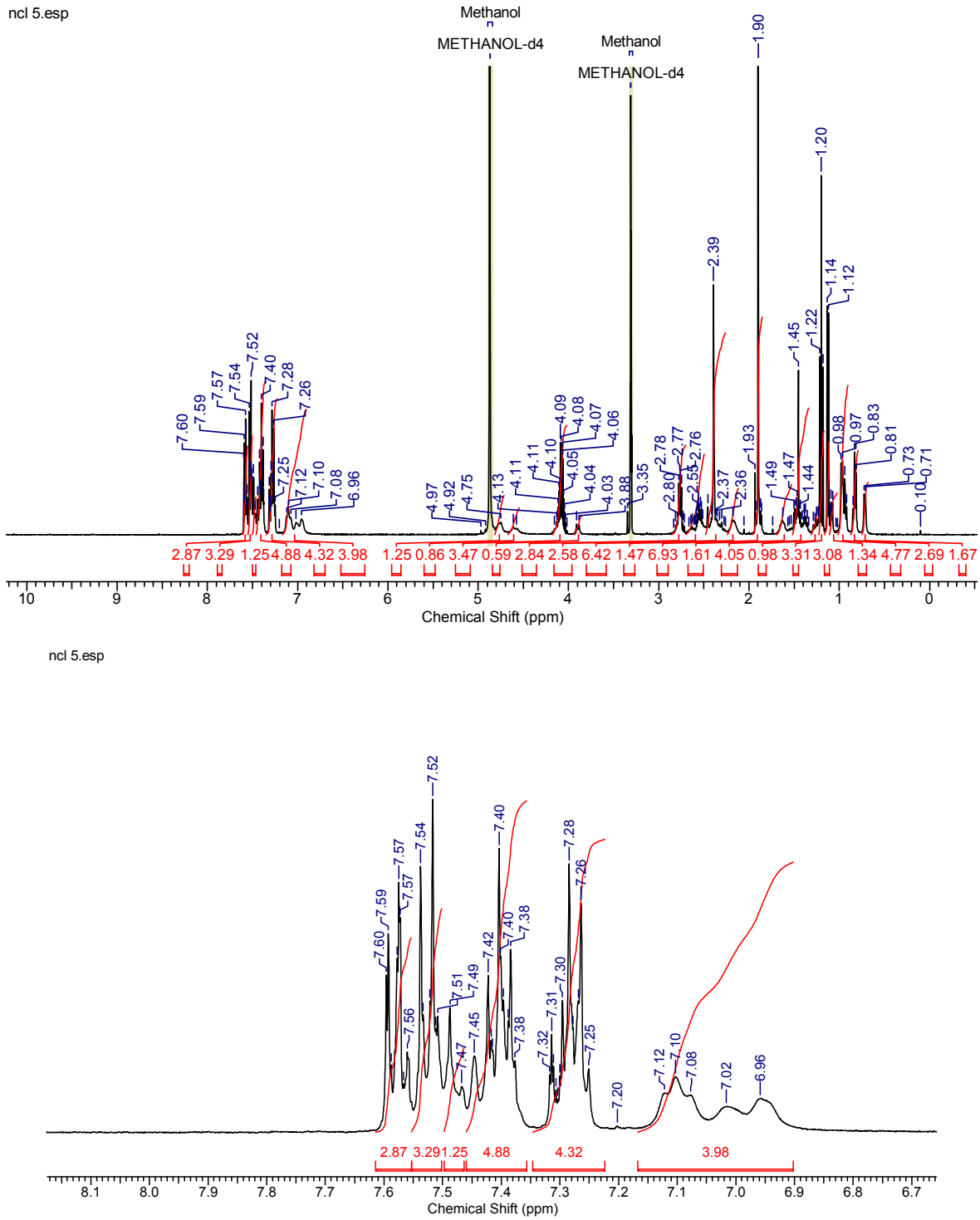


Figure S15. ^{1}H NMR spectrum of Form-V of Entresto in methanol d4.

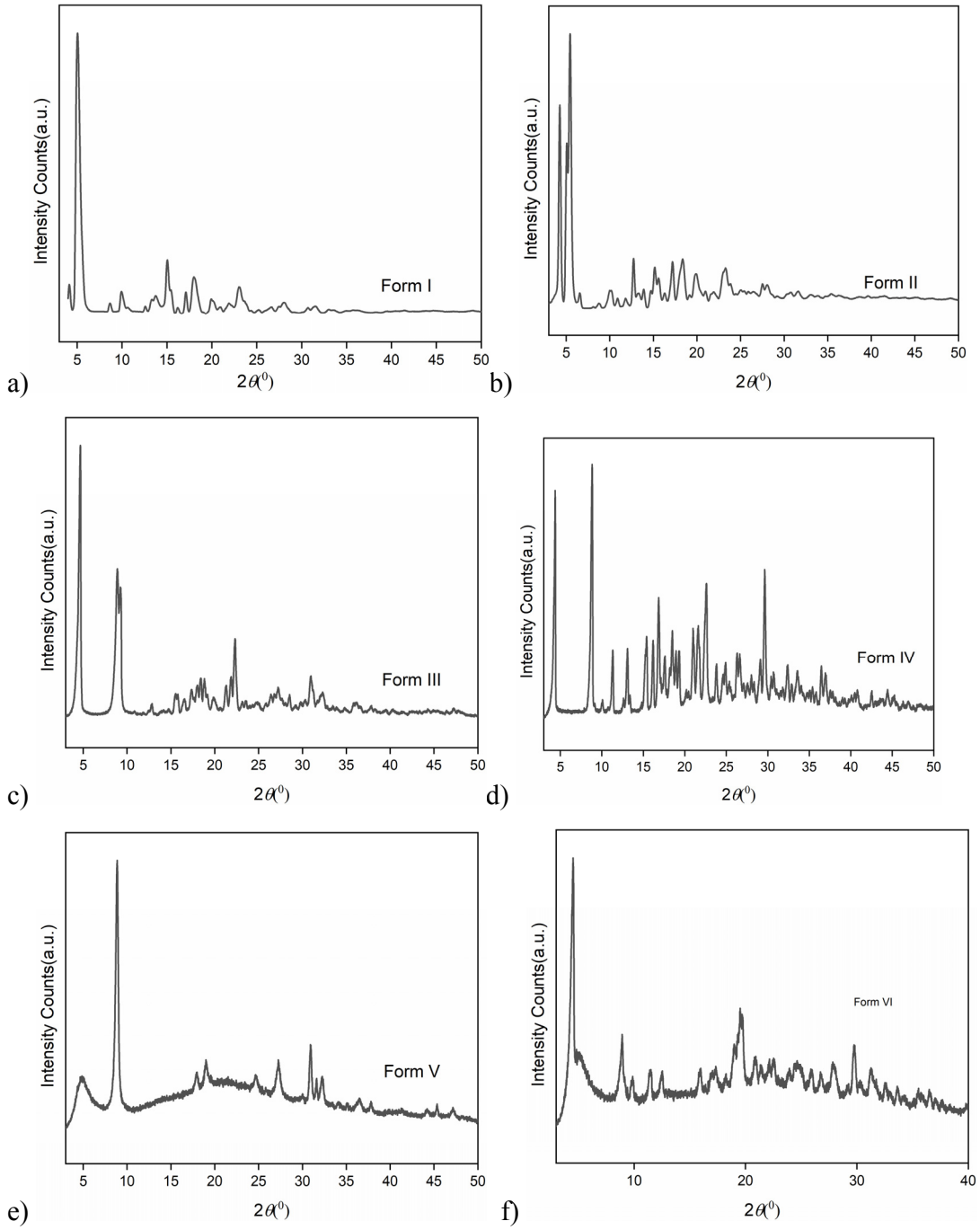


Figure S16. Powder X-ray diffraction pattern of different crystal forms (six) of Entresto.

Table S2. The characteristics powder diffraction peaks are described in terms of 2θ values for Form-I to Form-VI of Entresto crystalline forms with a standard deviation of ±0.01°.

	2θ peaks in degrees (°)					
Peak number	Form-I	Form-II	Form-III	Form-IV	Form-V	Form-VI
1	4.44	4.31	4.66	4.38	4.62	4.53
2	5.23	5.12	8.88	8.83	7.42	8.93
3	8.78	5.43	9.25	10.08	8.83	9.87
4	10.63	6.49	12.85	11.33	17.76	11.51
5	12.84	8.93	15.53	13.11	19.11	12.54
6	13.29	10.22	17.35	15.39	24.64	15.12
7	13.81	10.93	18.05	16.16	27.18	15.98
8	15.25	11.84	18.39	16.84	30.97	17.33
9	16.18	12.67	18.82	17.62	31.66	18.25
10	17.27	13.32	19.82	18.49	32.29	19.53
11	18.15	13.72	21.30	18.94		20.92
12	20.81	14.67	21.84	19.30		21.33
13	21.02	15.22	22.31	20.99		22.15
14	22.04	15.61	23.56	21.57		22.53
15	23.07	16.36	28.53	22.61		23.27
16	23.59	17.21	30.95	23.84		23.95
17	25.23	18.44	32.30	24.91		24.64
18	26.51	19.25		26.31		25.86
19	27.54	19.93		26.63		26.72
20	28.60	21.05		29.09		27.84
21	30.83	21.91		29.63		29.74

22	31.51	23.31		30.69		30.28
23		23.92		31.79		31.26
24		30.72		32.40		32.51
25		31.66		33.55		33.62
26				36.45		
27				36.94		

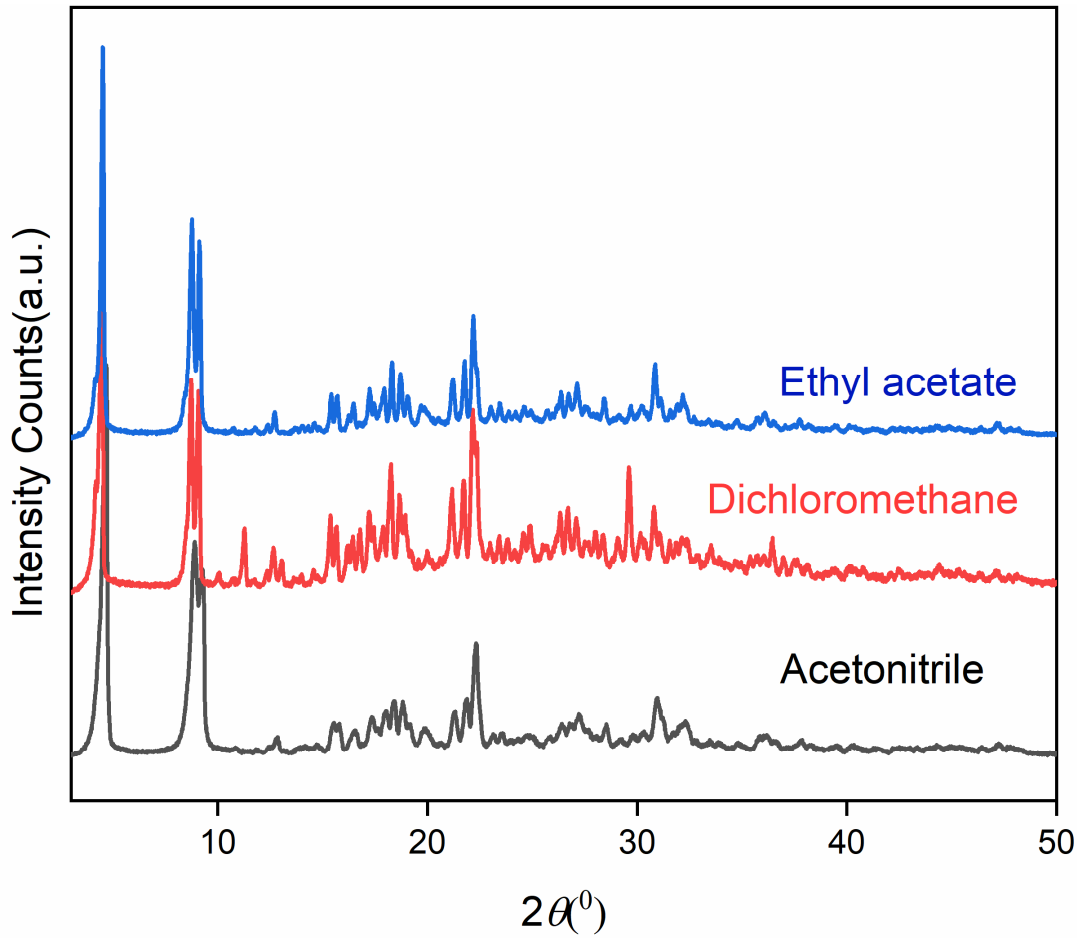


Figure S17. Powder X-ray diffraction pattern of crystal Form-III of Entresto obtained from different solvents show similarity. Entresto synthesized using chloroform solvent (Form-IV) showed a different PXRD pattern.

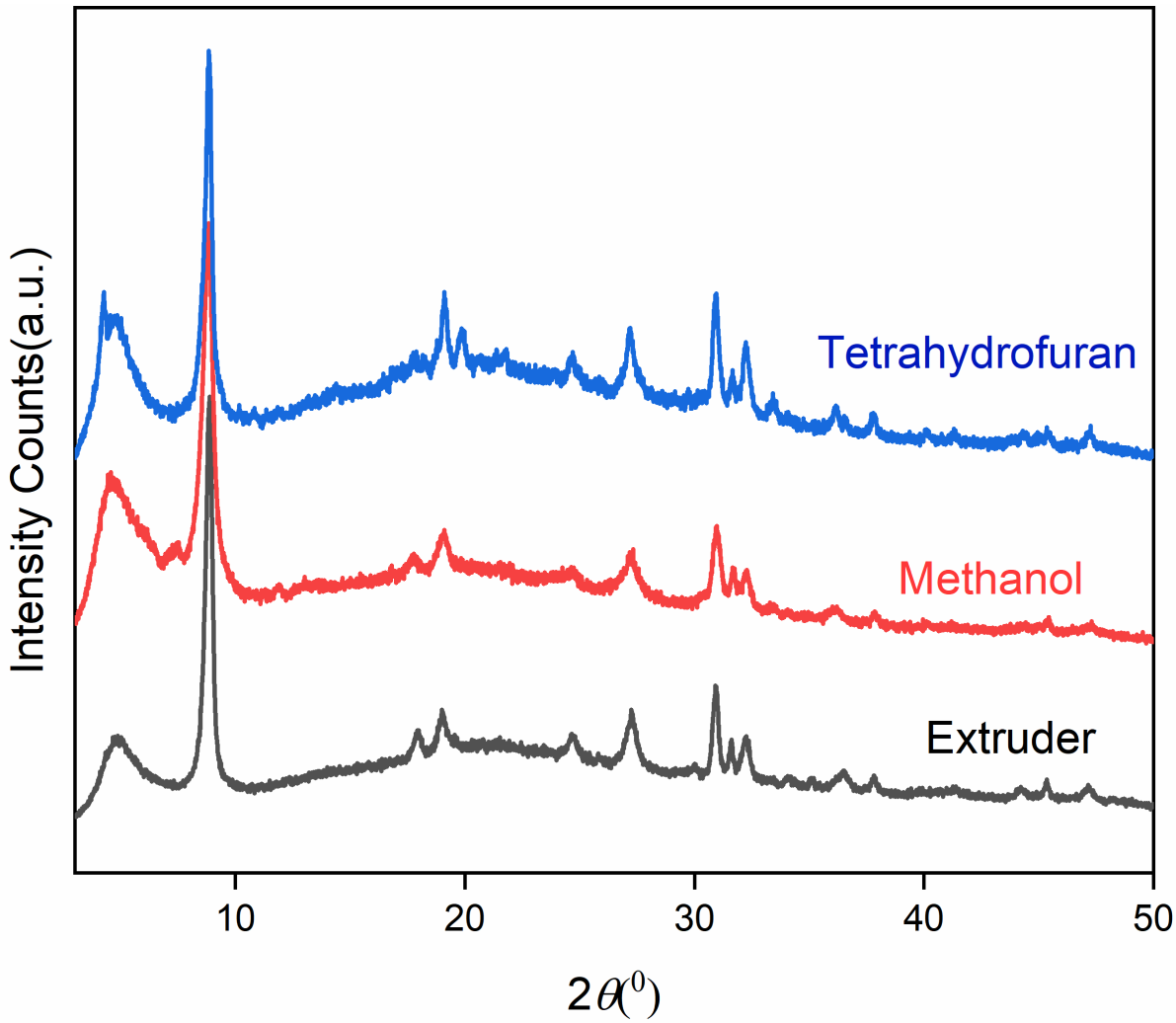


Figure S18. PXRD patterns of novel Form-V of Entresto synthesized using different processes.

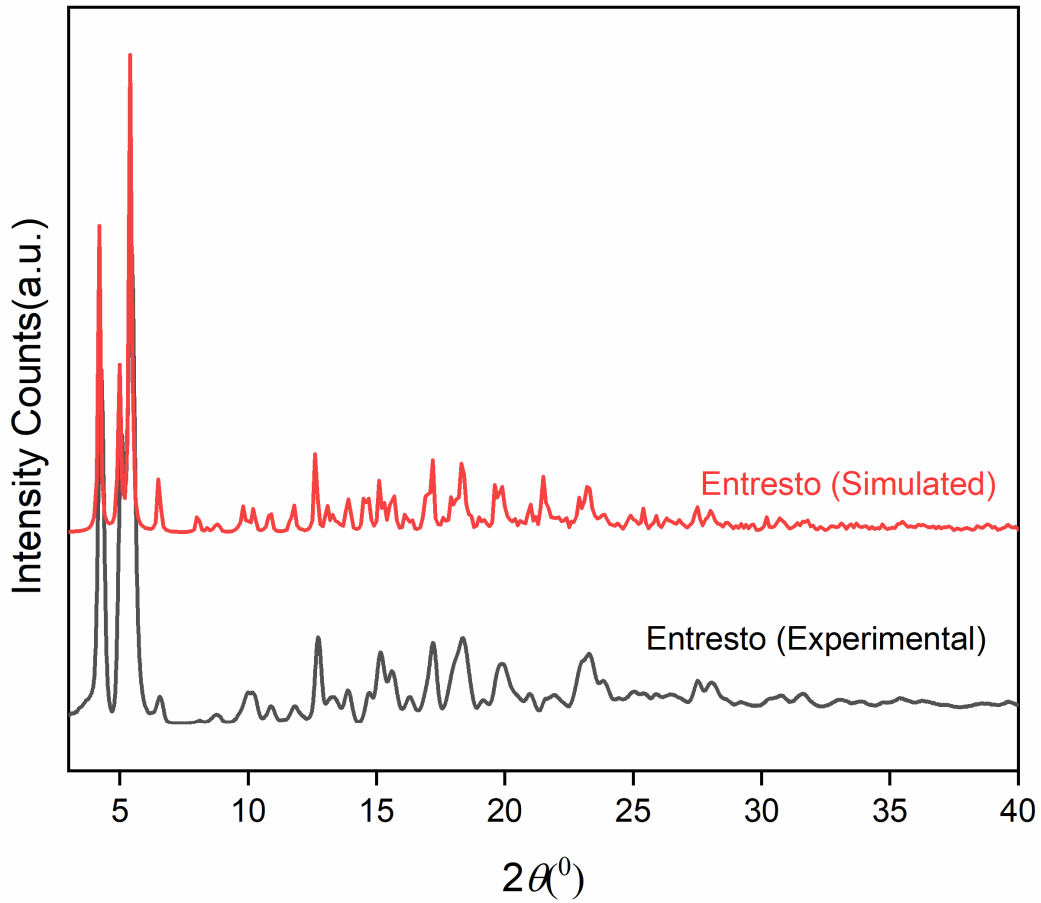


Figure S19. The powder X-ray diffraction profile of Form-II and simulated PXRD pattern from the single crystal XRD data of Entresto extracted from CSD).

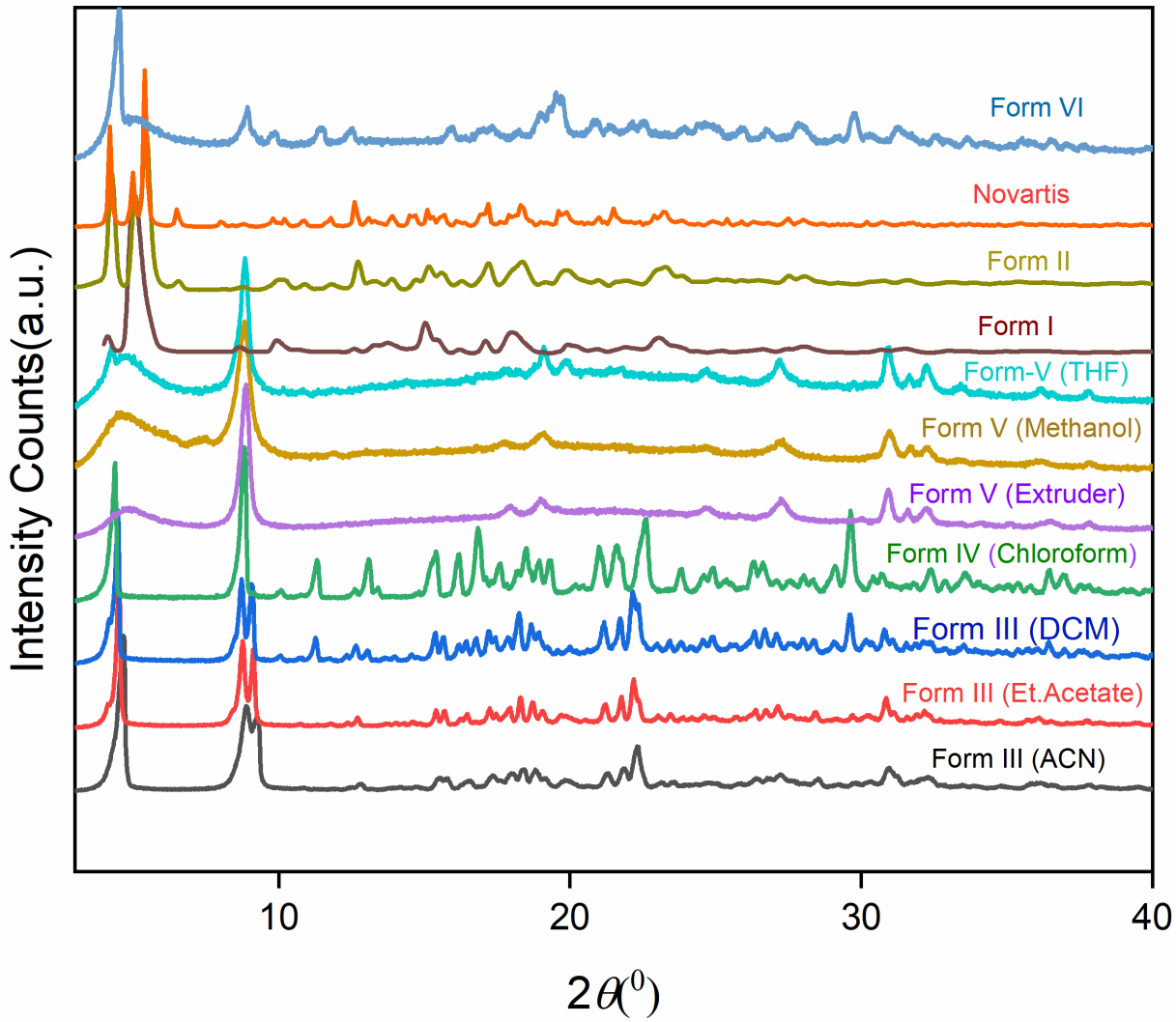


Figure S20. Overlay of the PXRD line pattern of all the solid phases of Entresto identified in this study shows the different crystal forms. The PXRD profile of Form-II (green) matches with the innovator (Novartis) product of Entresto (red), thereby indicating their similar crystal structure. The other crystal forms [Form-I, (blue), Form-III (magenta, yellow, dark blue), Form-IV (red), Form-V (green, blue)] of Entresto are different crystal forms by PXRD and supporting analysis.

We note that due to line broadening and partially overlapping peaks, there is possibility of more than one phase in certain samples, e.g., Form-III (DCM) could have some of Form-IV in it, Form-VI with broad peaks appears to have some amorphous Form-V, and Form-V (THF) shows some Form-VI, etc. A complete characterization of the related crystal structures will clarify the phase purity and molecular composition. including their water content.

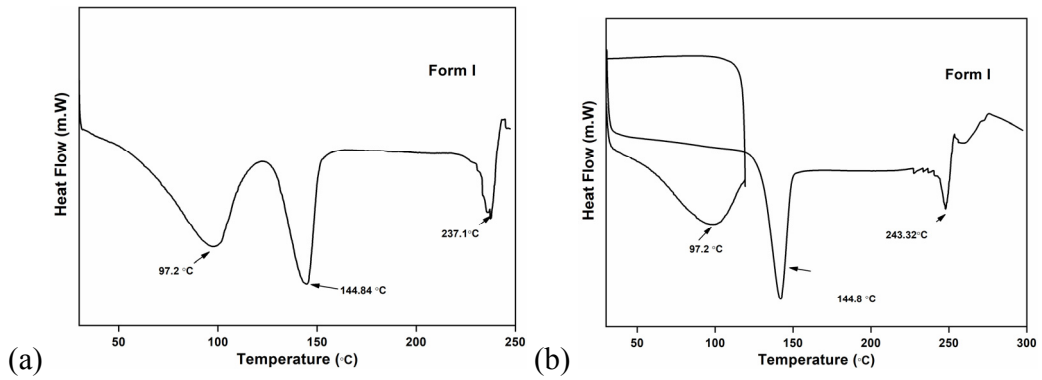


Figure S21. DSC Profiles of Form-I, (a) heating till 300 °C and (b) heating-cooling-heating cycle.

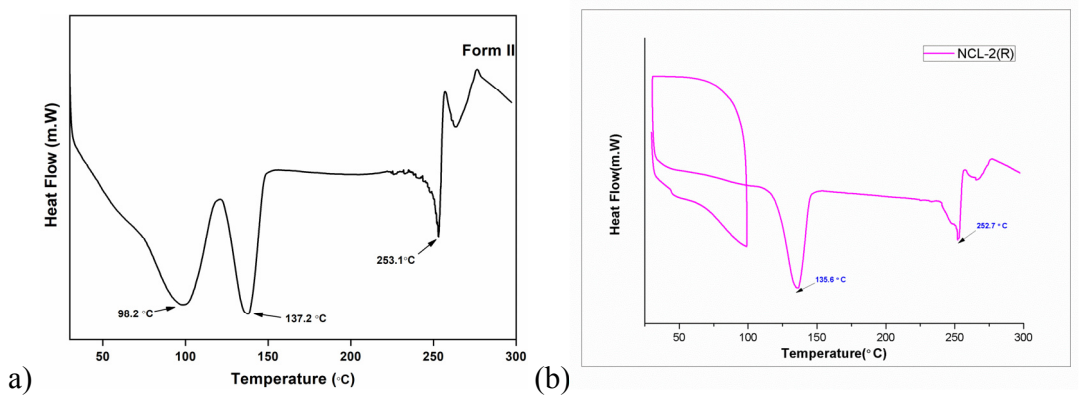


Figure S22. The DSC profile of Form-II of Entresto (a) heating till 300 °C and (b) heating-cooling-heating cycle.

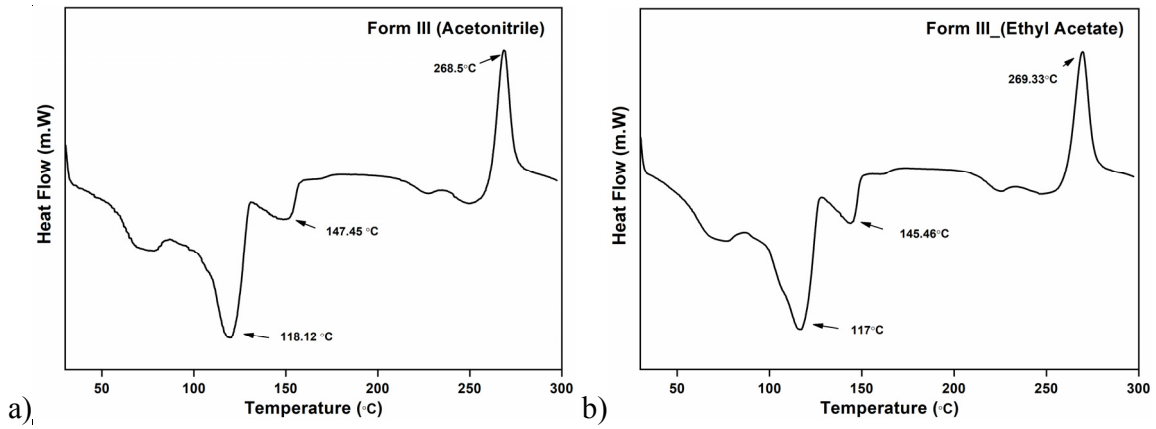


Figure S23. DSC profiles of Form-III of Entresto synthesized from (a) acetonitrile and (b) ethyl acetate.

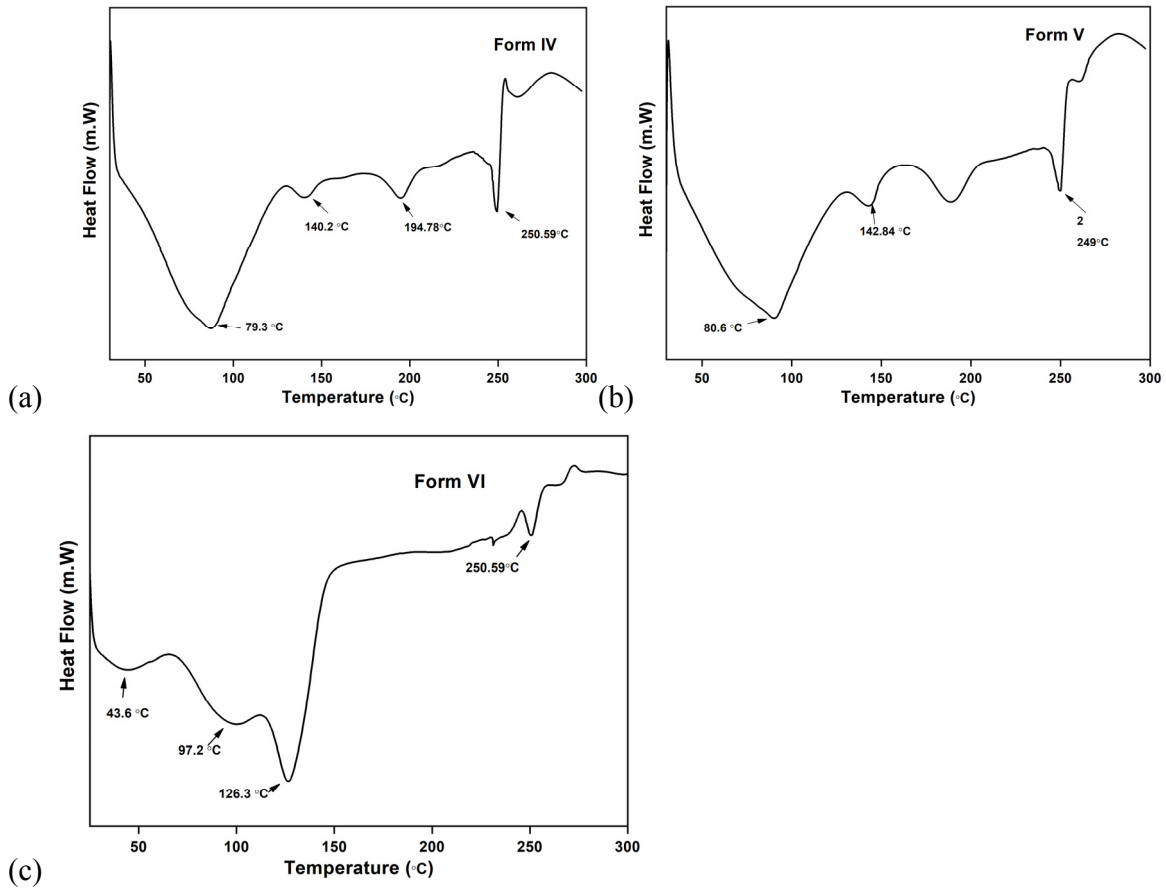


Figure S24. DSC profiles of (a) Form-IV, (b) Form-V and (c) Form-VI of Entresto.

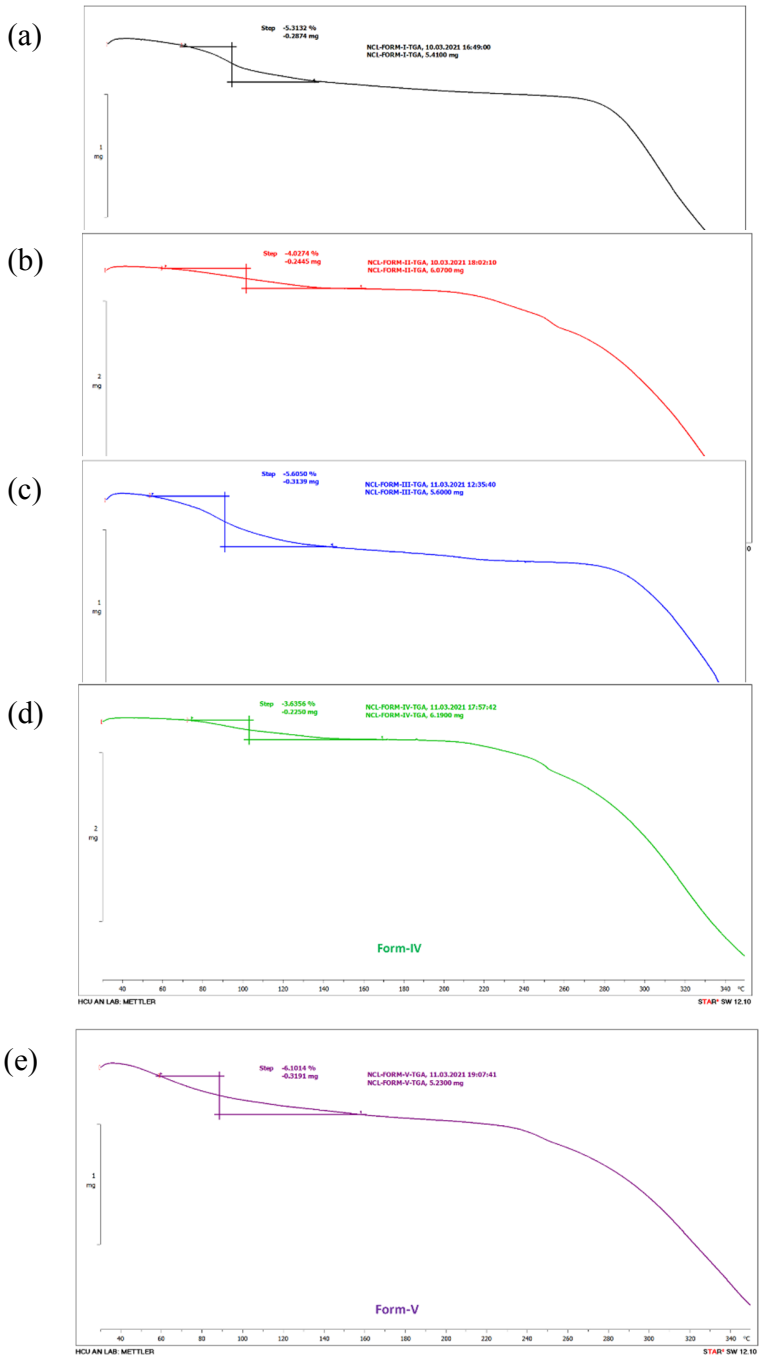


Figure S25. TGA profiles of crystal forms of Entresto, (a) Form-I, (b) Form-II, (c) Form -III, (d) Form-IV and (e) Form-V.

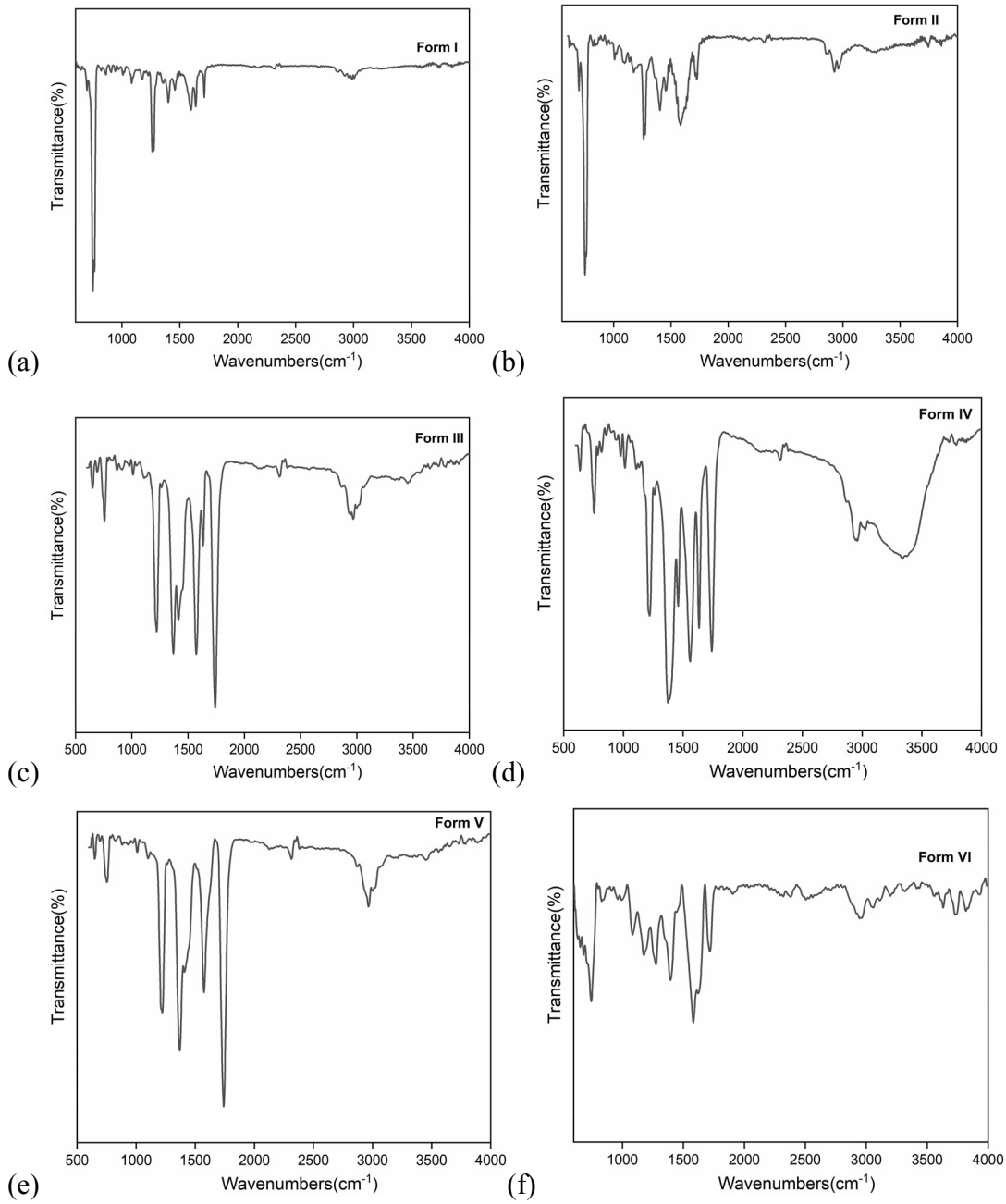


Figure S26. Infra-red spectrum of (a) Form-I, (b) Form-II, (c) Form-III, (d) Form-IV, (e) Form-V and (f) Form-VI.

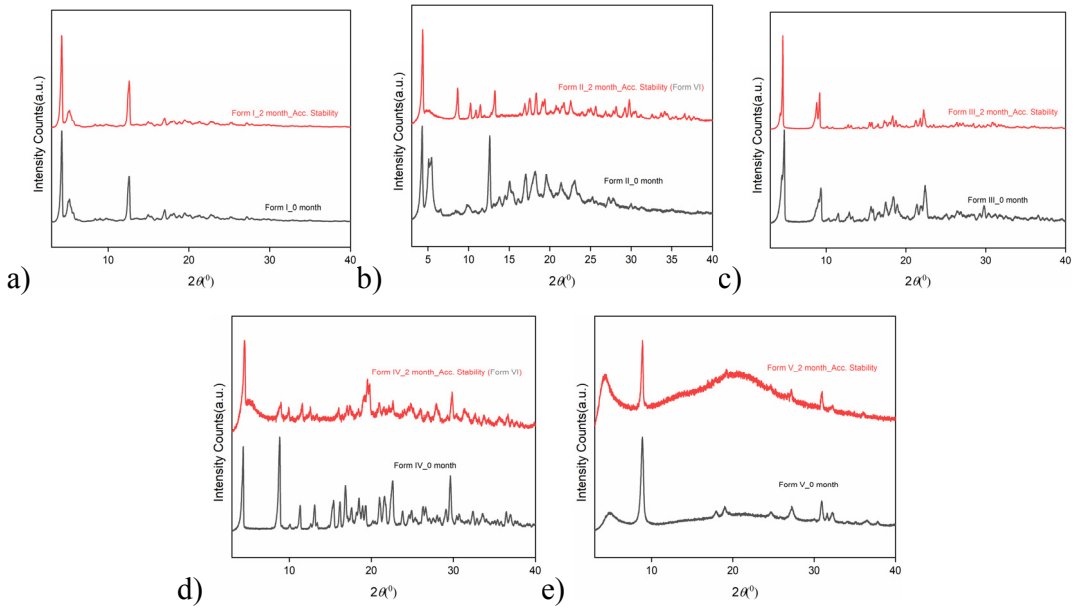


Figure S27. The PXRD profiles for (a) Form-I, (b) Form-II, (c) Form-III, (d) Form-IV, (e) Form-V recorded during stability studies, accelerated conditions.