SUPPORTING INFORMATION

A FACILE SYNTHESIS OF THALIDOMIDE

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1.1. Investigation for the effect of reaction parameters on the yield of N-phthaloyl-DL-glutamic acid (IV)

1.1.1. Effect of reaction solvent on the yield of N-phthaloyl-DL-glutamic acid (IV)

Experiment: A mixture of anhydride phthalic **(II)** (7.4 g, 0.05 mole), L-glutamic acid (7.35 g, 0.05 mole), 10mg 4-dimethylamino-pyridine and solvents (6 mL) as pyridine, DMF, acetonitrile, in round–bottom flask was heated for 1.5 hrs with stirring. The reaction mass was cooled to 75^{o}C and ice-cold water (45 mL) was added with stirring, the reaction mixture was adjusted to pH 1.2 with 6N HCl and stirring at 10-15^{o}C for 2 h. The white solid was separated, filtered, and washed with cool water (3 x 10 mL). (Results see **Table S1**)

Table S1. *Effect of reaction solvent types on the yield of N-phthaloyl-DL-glutamic acid (IV)*

No.	Solvent type	Temperature (^{0}C)	N-phthaloyl-DL-glutamic acid (IV)		
			Weight (g)	Melting point (^{0}C)	Yield (%)
1	**Pyridine**	**115**	11,04	**191-193**	**79.73**
2	DMF	153	9,67	191-192	69.87
3	Acetonitrile	81	9,03	192-193	65.23

Conclusion: The optimal solvent was pyridine (see No.1 in **table S1**)

1.1.2. Effect of reaction Temperature on the yield of IV

Experiment: The reaction preparation of **IV** was performed the same operation as *2.1.1,* but used solvent was pyridine, at different temperature on 80-82, 100-102 and 115^{0}C. (Results see **Table S2**)

Table S2. *Effect of reaction Temperature on the yield of* ***IV***

No.	Temperature (°C)	N-phthaloyl-DL-glutamic acid (IV)		
		Weight (g)	**Melting point (^{0}C)**	**Yield (%)**
1	**115**	11,08	**191-193**	**80.03**
2	100 – 102	10,59	191-192	76.49
3	80 - 82	9,91	191-192	71.52

Conclusion: The reaction temperature gives the best yield of **IV** was 115°C (see No.1 in **Table S2**)

1.1.3. Effect of water c of IV on the yield of IV

Experiment: The reaction preparation of **IV** was performed the same operation as *2.1.1,* solvent was pyridine but water used in separation of **IV** with different volume from 45 to 75 mL per 0.05 mole anhydride phthalic (Results see **Table S3)**

Table S3. *Effect of reaction water volume used in separation on the yield of* ***IV***

No.	Water volume (mL)	N-phthaloyl-DL-glutamic acid (IV)		
		Weight (g)	**Melting point (^{0}C)**	**Yield (%)**
1	45	11,09	192-193	80.15
2	**60**	11,38	**191-193**	**82.21**
3	75	11,02	191-192	79.59

Conclusion: The optimal water volume was 60 mL (see No.2 in **Table S3**)

1.1.4. Effect of molar ratio between anhydride phthalic and L-glutamic acid on the yield of IV

*Experiment***:** The reaction preparation of **IV** was performed the same operation as *2.1.1,* solvent was pyridine, water used in separation of **IV** was 60 mL per 0.05 mole anhydride

phthalic but molar ratio of anhydride phthalic and L-glutamic acid was 1:0,9; 1:1; 0,9:1, respectively. (Results see **Table S4)**

Table S4. *Effect of molar ratio between anhydride phthalic and L-glutamic acid on the yield of N-phthaloyl-DL-glutamic acid (**IV**)*

No.	Molar ratio of anhydride phthalic and L-glutamic acid	N-phthaloyl-DL-glutamic acid (IV)		
		Weight (g)	Melting point (^{0}C)	Yield (%)
1	1 : 0.9	11,15	192-193	80.54
2	**1 : 1**	11,47	**191-193**	**82.85**
3	0.9 : 1	11,04	191-192	79.74

Conclusion: The result found that using molar ratio of anhydride phthalic : L-glutamic acid was 1:1 got the highest yield (see No.2 in **Table S4**)

1.1.5. Effect of solvent volume on the yield of IV

Experiment: The reaction preparation of **IV** was performed the same operation as *2.1.1,* solvent was pyridine, water used in separation of **IV** was 60 mL per 0.05 mole anhydride phthalic, volume of pyridine as solvent was surveyed from 3 to 7 mL. (Results see **Table S5)**

Table S5. *Effect of pyridine volume on the yield of N-phthaloyl-DL-glutamic acid (**IV**)*

No.	Pyridine volume (ml)	N-phthaloyl-DL-glutamic acid (IV)		
		Weight (g)	Melting point (^{0}C)	Yield (%)
1	3	11,17	191-193	80.67
2	4	11,47	192-193	82.79
3	**5**	11,79	**191-193**	**85.12**
4	6	11,53	191-192	83.27
5	7	11,34	192-193	81.84

Conclusion: The optimal Pyridine volume got the highest yield was 5 mL per 0.05 mole anhydride phthalic (see No.3 in **Table S5**)

⇨ **Results.** The combination of reaction parameters found that the highest yield of N-phthaloyl-DL-glutamic acid (**IV**) were followed: Molar ratio of (Anhydride phthalic : L-glutamic acid) = (1 : 1); Solvent: pyridine (5ml); 4-DMAP = 10mg ; Temperature = 115ºC; Reaction time =1.5 hrs; Water volume (60 mL).

1.2. Experimental section

Synthesis of N-phthaloyl-DL-glutamic acid (IV). A solution of phthalic anhydride **II** (149.5 g, 1.0 mole), *L*-glutamic (147.4 g, 1.0 mole) and pyridine (375 mL) in a round–bottom flask was heated to 115ºC for 1.5 hrs with stirring. After the reaction was finished (1.5 hrs), the reaction temperature was reduced to 75ºC and ice-cold water (1000 mL) was added with stirring, the mixture was acidified using 6N HCl until pH = 1.2 and stirring at 10-15ºC for 2 hrs. The white solid was separated, filtered, washed with cool water (3 x 30 mL) and vacuum dried to afford *N*-phthaloyl-*DL*-glutamic acid (**IV**) (237.7g, 85.78%), mp: 191-193ºC; R_f = 0.42 (benzene : dioxane : formic acid = 75 : 20 : 5);

IR (KBr) υ_{max} (cm^{-1}): 3476 (O-H); 3065 - 2914 (C-H); 1715 (C=O, C1 and C3); 1611 (C=O, C13 and C14).

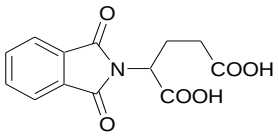
MS: m/z 276 $[M-H]^+$.

^{1}**H-NMR** (DMSO) δ (ppm): 12.65 (s, 2H, COOH); 7.88-7.90 (m, 4H: C5-H, C6-H, C7-H, C8-H); 4.79- 4.82 (m, 1H, C10-H); 2.25 – 2.51 (m, 4H, C11-H2 and C11-H2).

^{13}**C-NMR** (DMSO) δ (ppm): 173.7 (C13); 170.3 (C14); 167.4 (C1, C3); 134.8 (C6 and C7); 131.3 (C4 and C9); 123.4 (C5 and C8); 51.1 (C10); 30.4 (C12); 23.7 (C11).

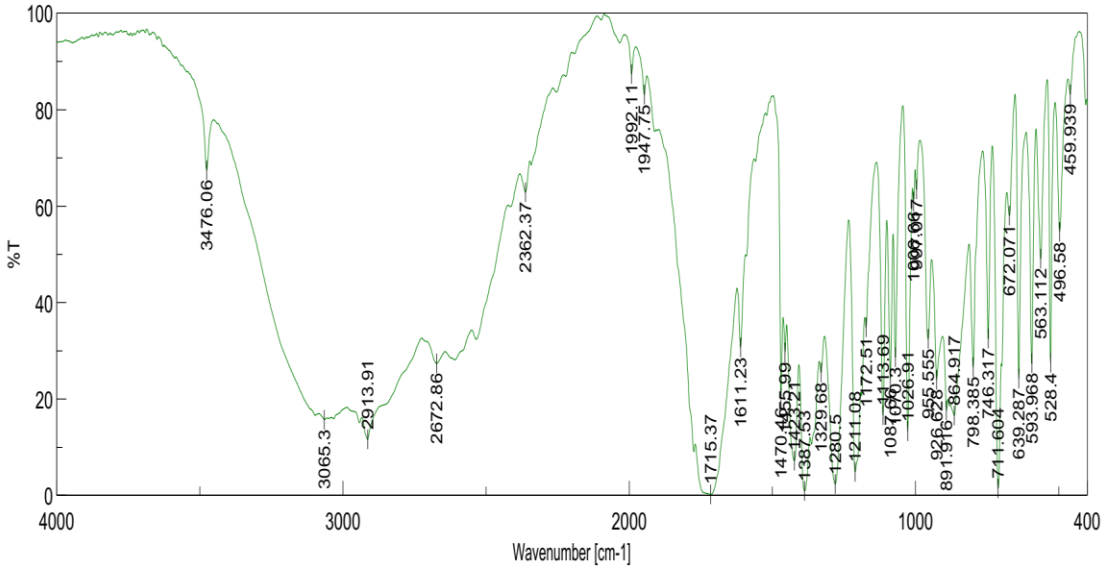
1.3. Analytical data (IR, MS, NMR) of N-phthaloyl-DL-glutamic acid (IV)

IR spectrum of N-phthaloyl-DL-glutamic acid (IV)



IV

IR (KBr) υ_{max} (cm-1): 3476 (O-H); 3065 - 2914 (C-H); 1715 (C=O, C1 and C3); 1611 (C=O, C13 and C14).



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Company HOC VIEN QUAN Y

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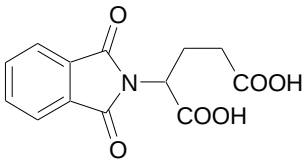
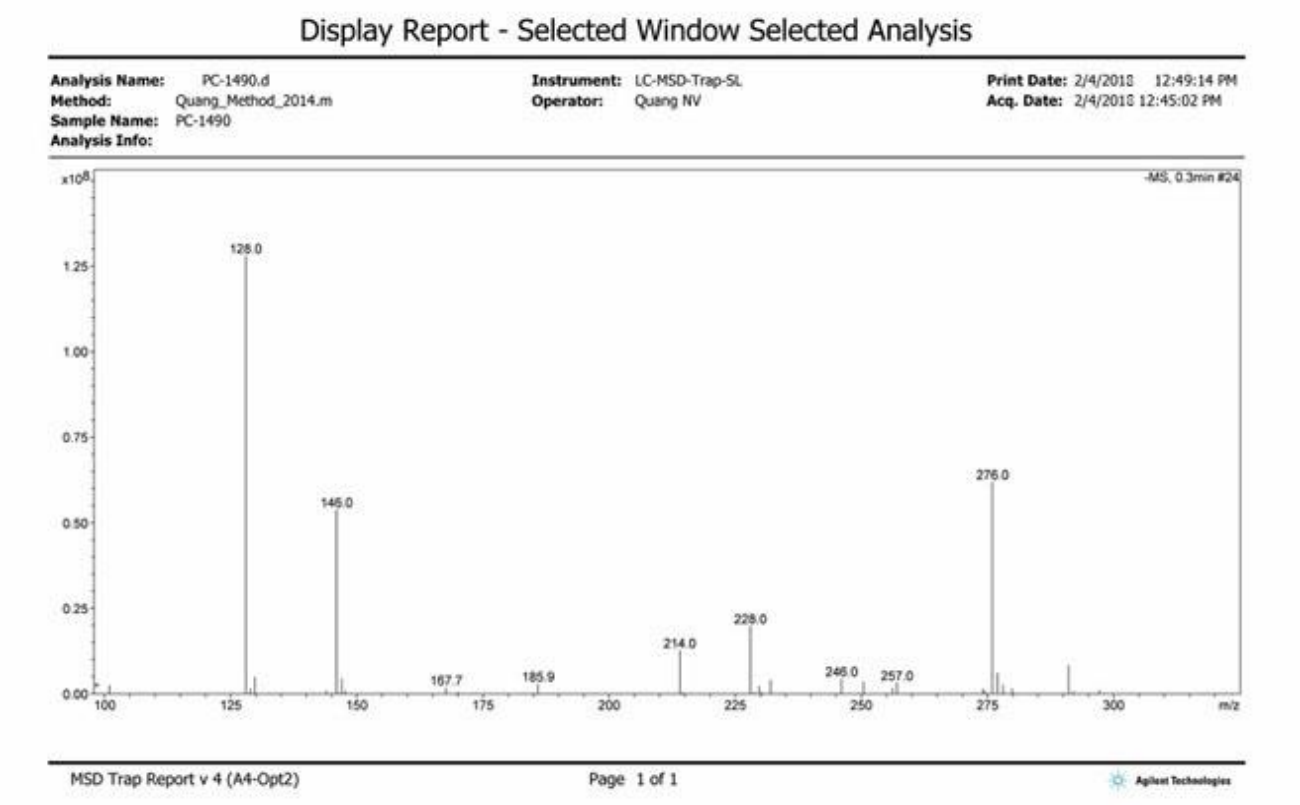
MS spectrum of N-phthaloyl-DL-glutamic acid (IV)

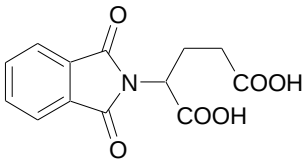


IV

MS: m/z 276 $[M-H]^+$.

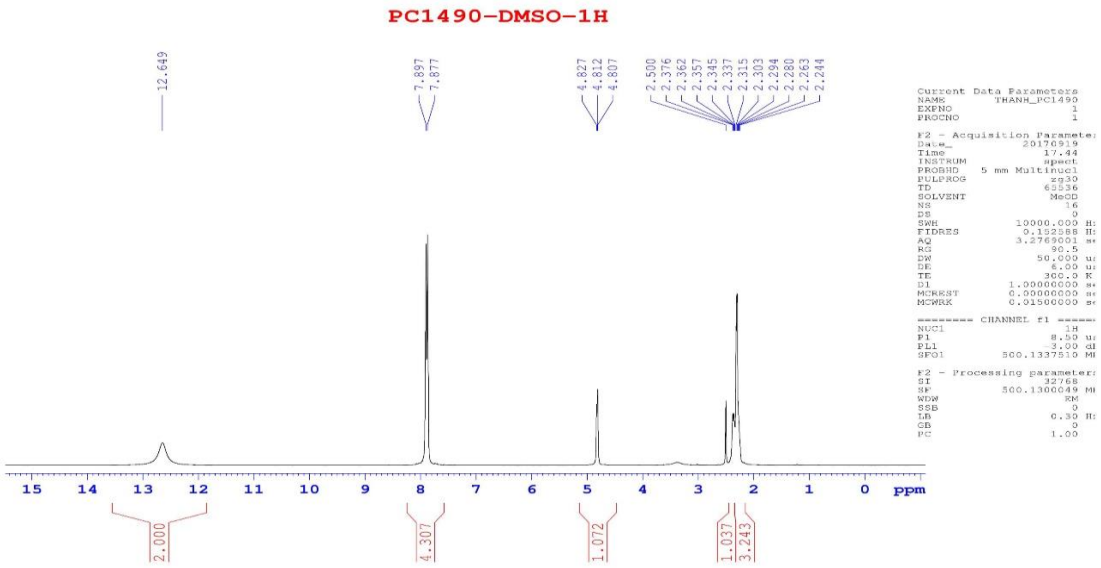


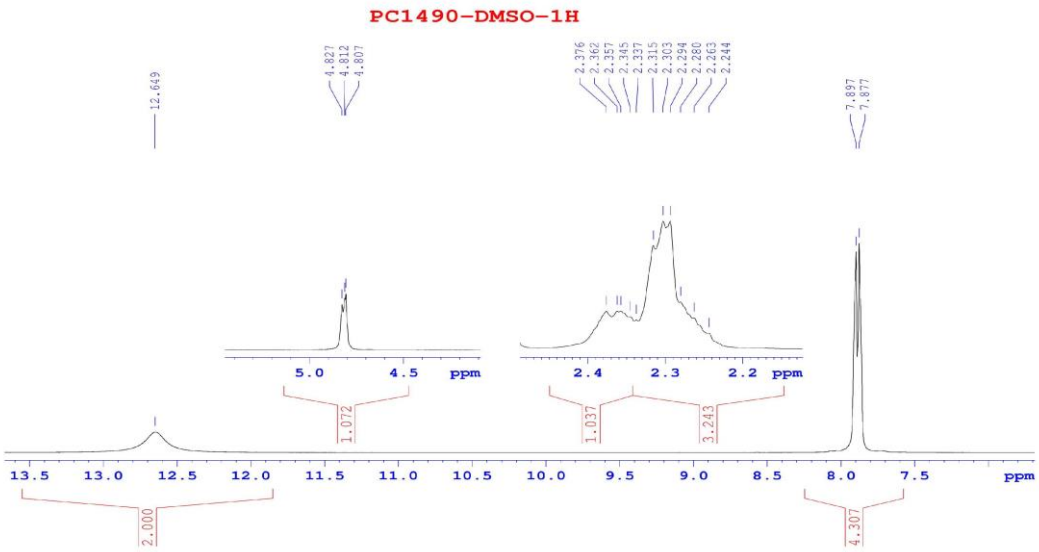
[1]H-NMR spectrum of N-phthaloyl-DL-glutamic acid (IV) in DMSO



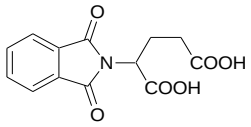
IV

[1]H-NMR (DMSO) δ (ppm): 12.65 (s, 2H, COOH); 7.88-7.90 (m, 4H: C5-H, C6-H, C7-H, C8-H); 4.79- 4.82 (m, 1H, C10-H); 2.25 – 2.51 (m, 4H, C11-H2 and C11-H2).



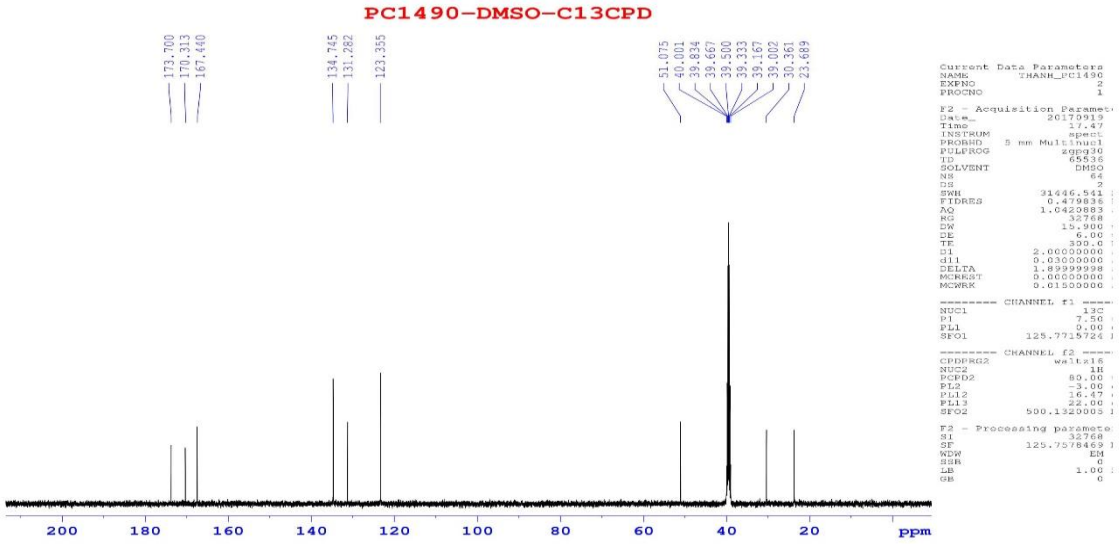


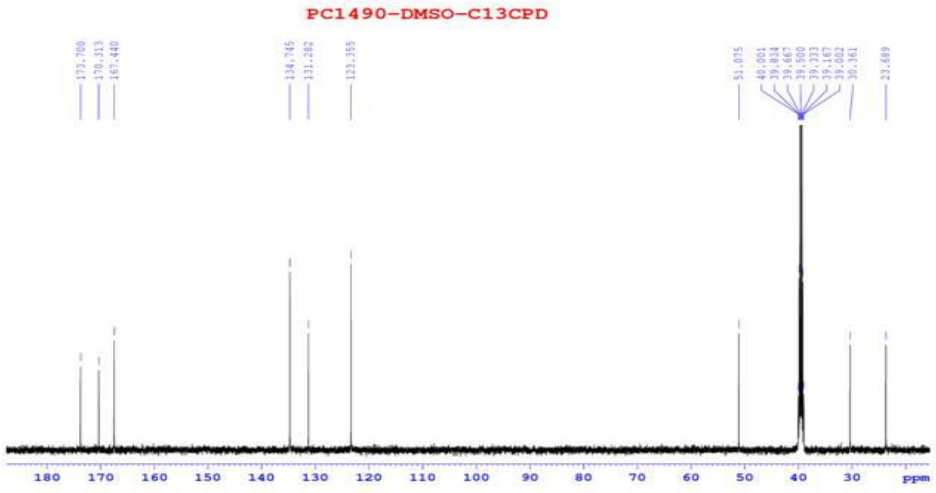
^{13}C-NMR spectrum of N-phthaloyl-DL-glutamic acid (IV) in DMSO



IV

^{13}C-NMR (DMSO) δ (ppm): 173.7 (C13); 170.3 (C14); 167.4 (C1, C3); 134.8 (C6 and C7); 131.3 (C4 and C9); 123.4 (C5 and C8); 51.1 (C10); 30.4 (C12); 23.7 (C11).





2. GENERAL PROCEDURE FOR THE SYNTHESIS OF THALIDOMIDE

2.1. Effect of reaction parameters on the synthesis of Thalidomide (I)

2.1.1. Effect of ammonia donor source on the yield of Thalidomide

Experiment: A mixture of *N*-phthaloyl-*DL*-glutamic acid (**IV**) (5.54 g, 0.02 mole), ammonia donor source (urea, thiourea, ammonium acetate, ammonium chloride, ammonium carbonate) (0.05 mole) and diphenyl ether (7 mL) was added. The reaction mass was heated for 45 min with stirring. The reaction mass was cooled to 100^{o}C and toluene (15 mL) was added, stirring for 20 min, the reaction was cooled to 5-10^{o}C for 1h. The reaction mixture was filtered, and washed with cool water (3 x 10 mL) received solid product. To this product, methanol (15 mL) was added, stirring and heating to reflux for 20 min. distilling out solvent ½ volume, cooling to 10-15^{o}C for 2 h, filtering to give crude product. (Results see **Table S6)**

Table S6. *Effect of ammonia donor source on the yield of Thalidomide* ***(I)***

No.	Ammonia donor source	Thalidomide		
		Weight (g)	**Melting point (^{0}C)**	**Yield (%)**
1	urea	3.16	269-271	61.23
2	Thiourea	3.70	269-270	71.65
3	Ammonium acetate	3.03	269-271	58.61
4	Ammonium chloride	1.51	270-271	29.31
5	Ammonium carbonate	-	-	-

Conclusion: The result found that using urea, thiourea, ammonium acetate, ammonium chloride as ammonium donor source got the product as compound **I** (see **Table S6**)

2.1.2. Effect of reaction Solvent on the yield of Thalidomide (1)

Experiment: The reaction preparation of **I** was performed the same operation as *3.1.1,* except ammonia donor source was ammonium acetate, but solvent used in reaction was different as dimethyl formamide (DMF), dimethyl acetamide (DMA), diphenyl ether (Ph_2O), respectively. (Results see **Table S7)**

Table S7. *Effect of reaction Solvent on the yield of Thalidomide*

No.	Solvent	Temperature (°C)	Thalidomide		
			Weight (g)	Melting point (^{0}C)	Yield (%)
1	DMF	153	1.97	269-270	38.19
2	DMA	165	2.03	269-270	39.23
3	**Ph_2O**	**180**	**3.22**	**269-271**	**62.45**

Conclusion: The optimal solvent was diphenyl ether (see No.3 in **Table S7**)

2.1.3. Effect of reaction temperature on the yield of Thalidomide

Experiment: The reaction preparation of I was performed the same operation as *3.1.1,* except ammonia donor source was ammonium acetate and the reaction was executed on different temperature was 160°C, 165°C, 170°C, 175°C, 180°C and 185°C. (Results see **Table S8)**

Table S8. *Effect of reaction temperature on the yield of Thalidomide*

No.	Temperature (°C)	Thalidomide		
		Weight (g)	Melting point (^{0}C)	Yield (%)
1	160	2.93	269-270	56.72
2	165	3.01	269-271	58.33
3	**170**	**3.13**	**269-271**	**62.45**
4	**175**	**3.24**	**269-271**	**62.81**
5	**180**	**3.25**	**270-271**	**62.98**
6	185	3.22	269-270	62.39

Conclusion: The reaction temperature gives the best yield of **I** was 170-175°C (between 170 and 180°C) (see No 3 and No 4 in **Table S8)**

2.1.4. Effect of molar ratio between thiourea and compound IV on the yield of Thalidomide (I)

Experiment: The reaction preparation of I was performed the same operation as *3.1.3,* the optimal temperature was 170-175°C, molar ratio of ammonium acetate and compound **IV** was 2:1; 2.5:1; 3:1; 3.5:1; 4:1 and 5:1 respectively. (Results see **Table S9)**

Table S9. *Effect of molar ratio between ammonium acetate and compound **IV** on the yield of **1***

No.	Molar ratio of CH_3COONH_4: compound IV	Thalidomide (1)		
		Weight (g)	Melting point (^{0}C)	Yield (%)
1	2.0 : 1	3.21	269-270	58.54
2	2.5 : 1	3.24	269-270	62.87
3	3.0 : 1	3.26	269-271	63.17
4	**3.5 : 1**	**3.31**	**270-271**	**64.22**
5	4.0 : 1	3.29	269-270	63.78
6	5.0:1	3.25	270-271	62.97

Conclusion: The result found that using molar ratio of ammonium acetate: compound **IV** was 3.5:1 got the highest yield (see No.4 in **Table S9**)

2.1.5. Effect of reaction Solvent volume on the yield of Thalidomide

Experiment: The reaction preparation of **I** was performed the same operation as *3.1.4,* except ammonia donor source was ammonium acetate, the optimal temperature was 170-175°C, molar ratio of ammonium acetate and compound **IV** was 3.5:1, volume of diphenyl ether surveyed from 3 mL to 7 mL. (Results see **Table S10)**

Table S10. *Effect of reaction Solvent volume on the yield of Thalidomide*

No.	Ph_2O volume (ml)	Thalidomide		
		Weight (g)	Melting point (^{0}C)	Yield (%)
1	3	3.19	269-271	61.75
2	4	3.31	269-270	64.17
3	**5**	**3.37**	**269-271**	**65.23**
4	6	3.33	270-271	64.97
5	7	3.32	269-270	64.43

Conclusion: The optimal diphenyl ether volume got the highest yield was 5 mL per 0.02 mole compound IV (see No.3 in **Table S10**)

⇨ **Results.** The optimal parameters of reaction for the highest yield of Thalidomide were followed: Compound **IV** (0.02 mole); Ammonium acetate (as ammonia donor source); Molar ratio of (ammonium acetate: compound **IV**) = (3.5 : 1); Ph_2O (5mL); Temperature = 170-175^{o}C; Reaction time = 45 min.

2.2. Experimental section

Synthesis of thalidomide (I). In a round-bottom flask, the mixture of *N*-phthaloyl-*DL*-glutamic acid (**IV**) (233 g, 0.8 mole), ammonium acetate (256 g, 2.8 mole) and diphenyl ether (200 ml) was added. The mixture temperature was raised to 170-175^{o}C and maintained for 45 min with stirring. The reaction temperature was reduced to 90^{o}C and ice-cold water (600 mL) was added. After stirred for 20 min, the mixture was maintained at 5-10^{o}C for 1 hrs, separated, filtered, and cleaned with cool water (3 x 40 mL) received a solid product. To this product, methanol (300 mL) was added, stirring and heating to reflux for 20 min, distilling out solvent ½ volume, cooling to 10-15^{o}C for 2 hrs, filtering to give a crude product. This process was repeated two times in 150 mL methanol to give raw thalidomide. Recrystallization of raw thalidomide from DMF-ethanol. The obtained

product was cleaned with cool ethanol and vacuum dried (60ºC, <1mmHg) to afford thalidomide (135.46 g, 65.57%), mp: 269-271ºC.

IR (KBr) υ_{max} (cm^{-1}): 3205 (N-H); 3098 (CH) and 2924 (CH_2); 1776 (C=O, C1 and C3); 1697 (C=O, C13 and C14).

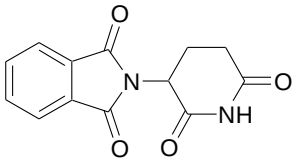
MS: m/z 257 $[M-H]^+$.

^{1}H-NMR (500 MHZ, DMSO) δ (ppm): 11.12 (s, 1H, NH); 7.88-7.94 (m, 4H, C5-H, C6-H, C7-H, C8-H); 5.14-5.20 (1H, C10-H, J=13.0 Hz and J = 5.5 Hz); 2.86-2.94 (m, 1H, C12-Ha); 2.05-2.10 (m, 2H, C11-H2); 2.05-2.10 (m, 1H, C12-Hb).

^{13}C-NMR (125 MHz, DMSO) δ (ppm): 171.7 (C13); 169.8 (C14); 167.1 (C1 and C3); 134.9 (C6 and C7); 131.2 (C4 and C9); 123.4 (C5 and C8); 49.0 (C10); 30.9 (C12); 22.0 (C11).

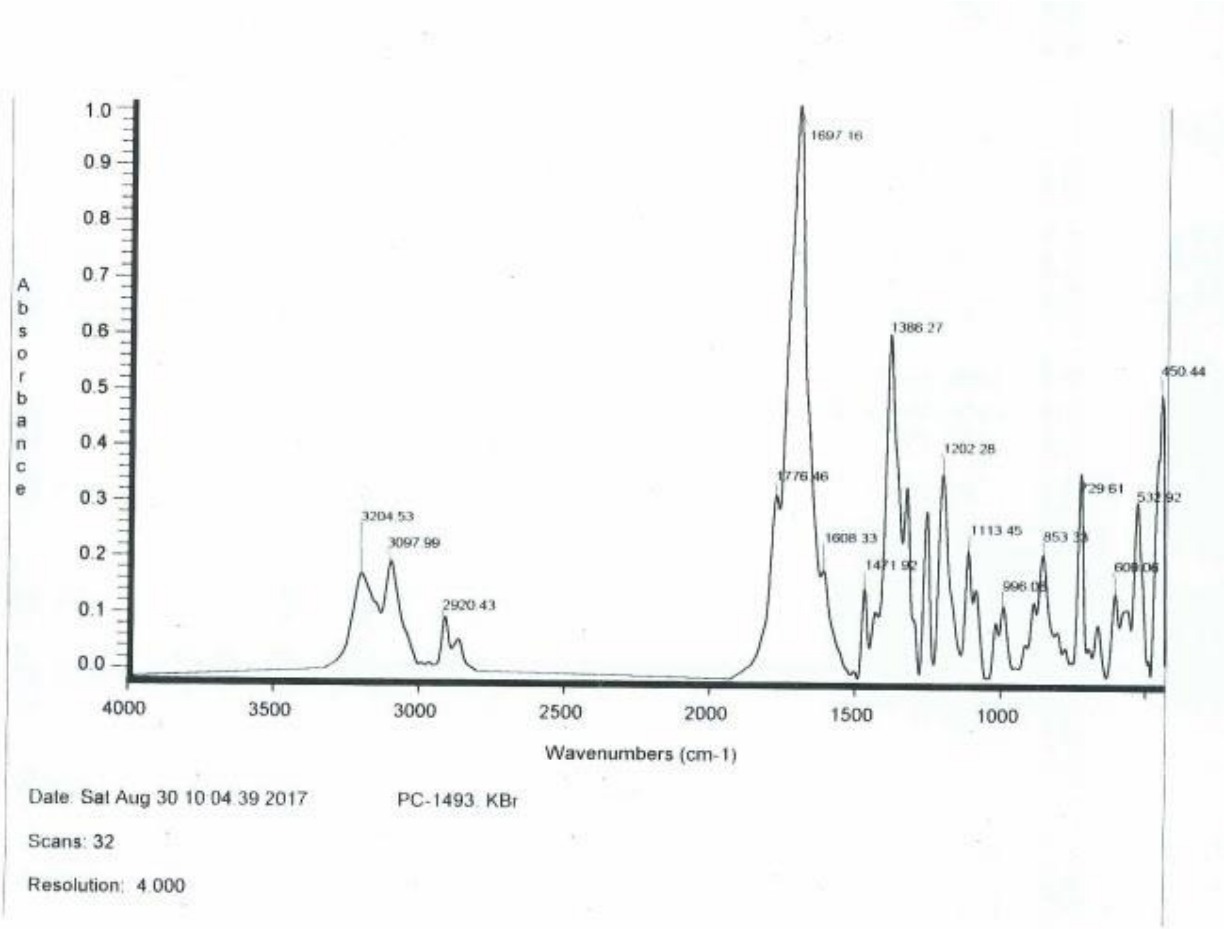
2.3. Analytical data (IR, MS, NMR) of Thalidomide

IR spectrum of Thalidomide

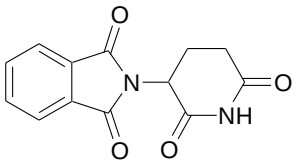


I

IR (KBr) υ_{max} (cm^{-1}): 3205 (N-H); 3098 (CH) and 2924 (CH_2); 1776 (C=O, C1 and C3); 1697 (C=O, C13 and C14).



MS spectrum of Thalidomide



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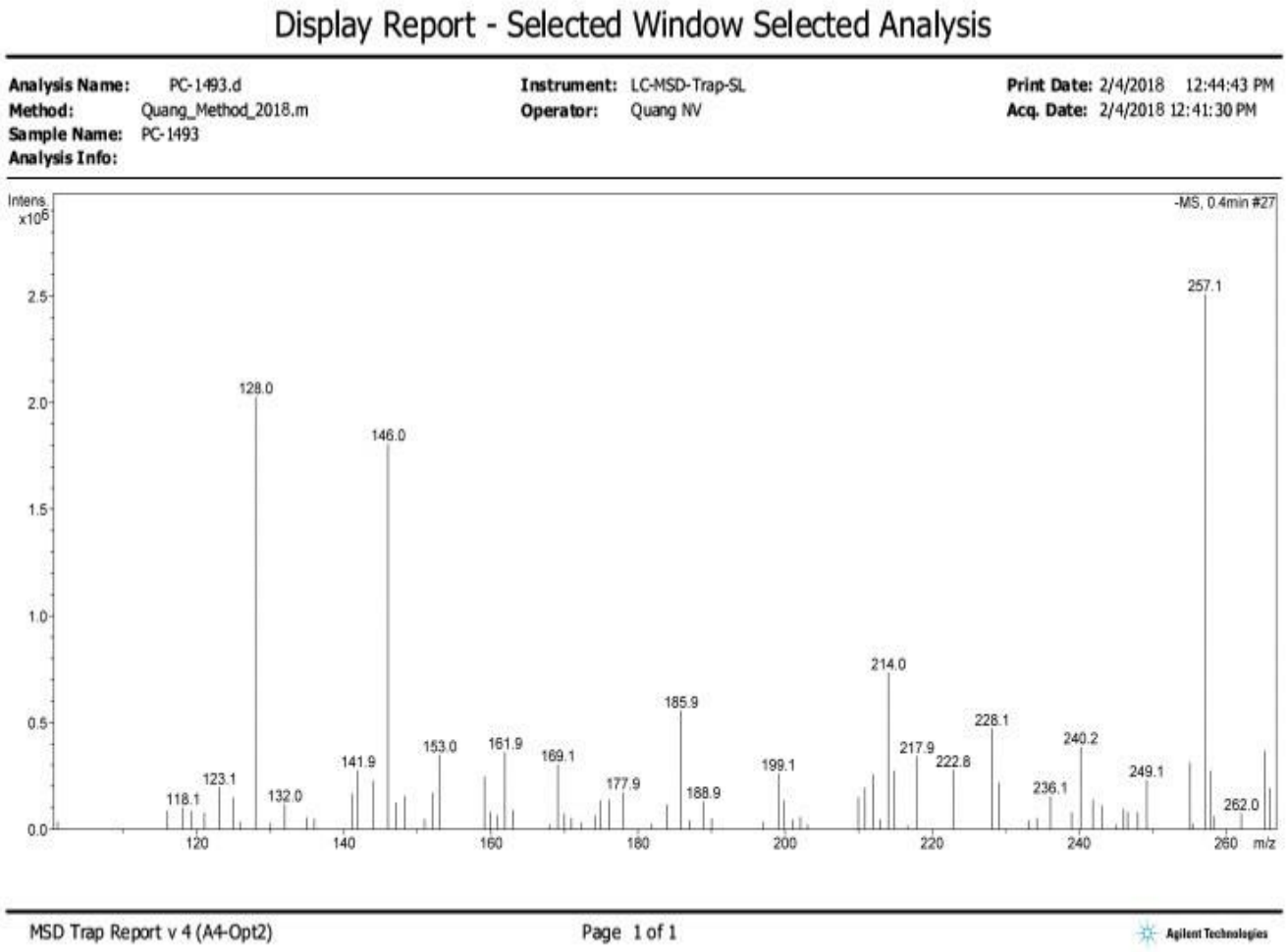
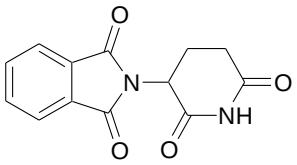
MS: m/z 257 $[M-H]^+$

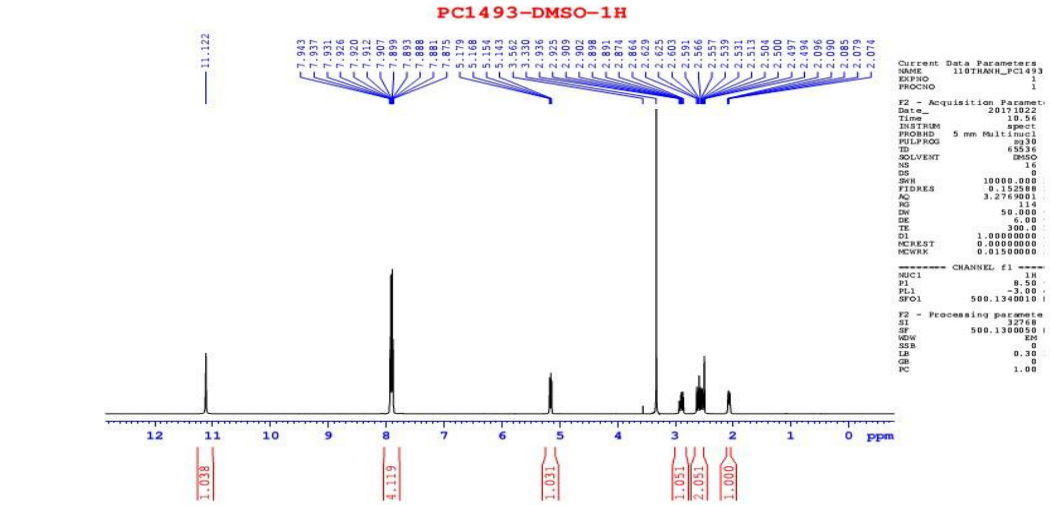


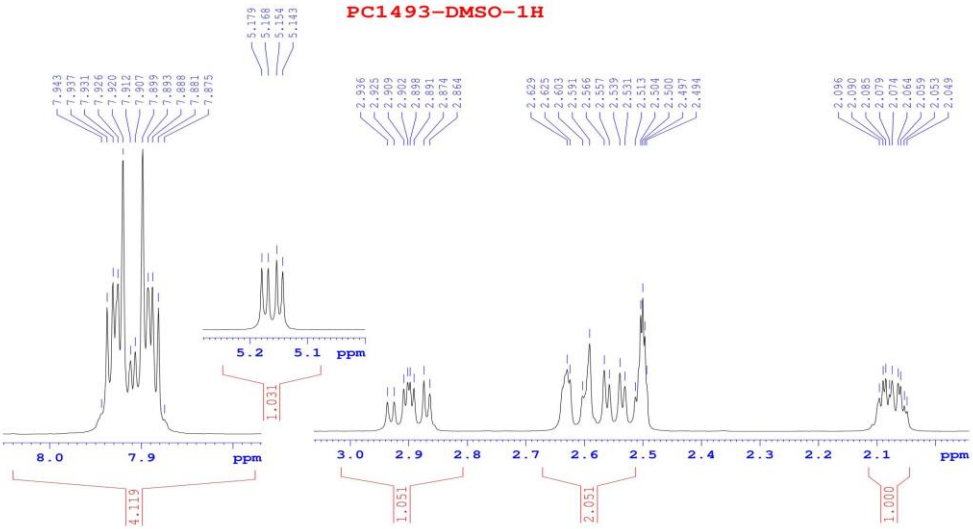
[1]H-NMR spectrum of Thalidomide



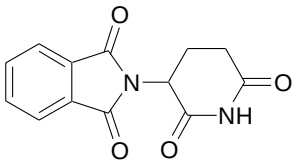
I

[1]H-NMR (500 MHz, DMSO) δ (ppm): 11.12 (s, 1H, NH); 7.88-7.94 (m, 4H, C5-H, C6-H, C7-H, C8-H); 5.14-5.20 (1H, C10-H, J=13.0 Hz and J = 5.5 Hz); 2.86-2.94 (m, 1H, C12-Ha); 2.05-2.10 (m, 2H, C11-H_2); 2.05-2.10 (m, 1H, C12-Hb).





^{13}C-NMR spectrum of Thalidomide



I

^{13}C-NMR (125 MHz, DMSO) δ (ppm): 171.7 (C13); 169.8 (C14); 167.1 (C1 and C3); 134.8 (C6 and C7); 131.2 (C4 and C9); 124.0 (C5 and C8); 49.0 (C10); 30.9 (C12); 22.0 (C11).