SUPPORTING INFORMATION

AN IMPROVED SYNTHESIS OF AMANTADINE HYDROCHLORIDE

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1. GENERAL PROCEDURE FOR THE SYNTHESIS OF *N*- (1-ADAMANTYL) ACETAMIDE

1.1. Effect of reaction parameters on the yield of *N*-(1-adamantyl) acetamide (4)

Table S1. Effect of reaction temperature on the yield of *N*-(1-adamantyl) acetamide (**4**)

No.	Temperature (°C)	Weight (g)	Yield (%)
1	35	1.68	43.37
2	45	2.31	59.64
3	55	2.57	66.35
5	**65**	**2.86**	**73.84**
6	75	2.37	61.19
7	85	1.99	51.38

Other reaction parameters. Time = 3.5 h; Molar ratio of (sulfuric acid: acetonitrile: adamantane) = (18: 5: 1).

Table S2. Effect of reaction time on the yield of *N*-(1-adamantyl) acetamide (**4**)

No.	Reaction time (h)	Weight (g)	Yield (%)
1	1.5	2.25	58.09
2	2.0	2.54	65.57
3	**2.5**	**2.99**	**77.19**
4	3.5	2.86	73.84
5	4.5	2.74	70.74

Other reaction parameters. Temperature = 65°C; Molar ratio of (sulfuric acid: acetonitrile: adamantane) = (18: 5: 1).

Table S3. Effect of molar ratio between CH_3CN and adamantane (**2**) on the yield of *N*-(1-adamantyl) acetamide (**4**)

No.	Molar ratio of CH_3CN : adamantane	Weight (g)	Yield (%)
1	2 : 1	2.18	56.28
2	3 : 1	2.67	68.93
3	**4 : 1**	**3.06**	**79.00**
4	5 : 1	2.99	77.19
5	6 : 1	2.88	74.35

Other reaction parameters. Time = 2.5 hours; Temperature = 65°C, Molar ratio of (sulfuric acid: adamantane) = (18: 1).

Table S4. Effect of molar ratio between sulfuric acid and adamantane (**2**) on the yield of *N*-(1-adamantyl) acetamide (**4**)

No.	Molar ratio of H_2SO_4 : adamantane	Weight (g)	Yield (%)
1	8 : 1	2.42	62.48
2	10 : 1	2.72	70.22
3	12 :1 :	2.96	76.42
4	**14 : 1**	**3.11**	**80.29**
5	16 : 1	3.07	79.26
6	18 : 1	3.06	79.00

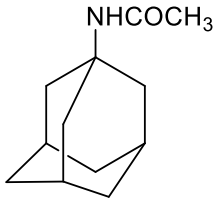
Other reaction parameters. Time = 2.5 h; Temperature = 65°C, Molar ratio of (acetonitrile: adamantane) = (4: 1).

⇨ **Results.** The combination of reaction parameters that gives the highest yield of *N*-(1-adamantyl) acetamide (**4**): Temperature = 60-65°C; Time = 2.5 h; Molar ratio of (sulfuric acid: acetonitrile: adamantane) = (14: 4: 1).

1.2. Experimental section

N-(1-adamantyl)acetamide (**4**)**.** To a mixture of 99.5% acetonitrile (400 mL, 7.66 mol) and 98% adamantane **2** (277g, 2.0 mol) was added dropwise 98% sulfuric acid (1.56 L, 28.4 mol) with stirring at 25-30ºC for 2 h. The reaction mixture was stirred at 60-65ºC for an additional 2.5 h. At the end of the reaction, ice water (5.00 L) was added to the reaction mixture and stirred for 1.0 h at 0-5ºC. The resulting mixture was then extracted with dichloromethane (8.00 L); the separated organic layer was washed with cold water (0-5ºC) and dried over Na_2SO_4. The solvent was removed under vacuum to yield **4** as a white solid**.** Yield: 314 g (82%). Purity (GC): 99.20%, t_R 15.90 min; mp 147-149ºC. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 5.45 (s, 1H), 2.06 (s, 3H), 2.00 (s, 6H), 1.91 (s, 3H), 1.67 (s, 6H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 169.32, 51.78, 41.58, 36.35, 29.41, 24.59. IR (KBr): cm^{-1} 3277.04 (N-H); 2900.03-2849.76 (C-H); 1643.57 (C=O). MS: m/z = 194.0 $[M+1]^+$, 151.9 $[M-COCH_3+1]^+$, 135.0 $[M-NHCOCH_3]^+$.

IR spectrum of *N*-(1-adamantyl)acetamide (4)



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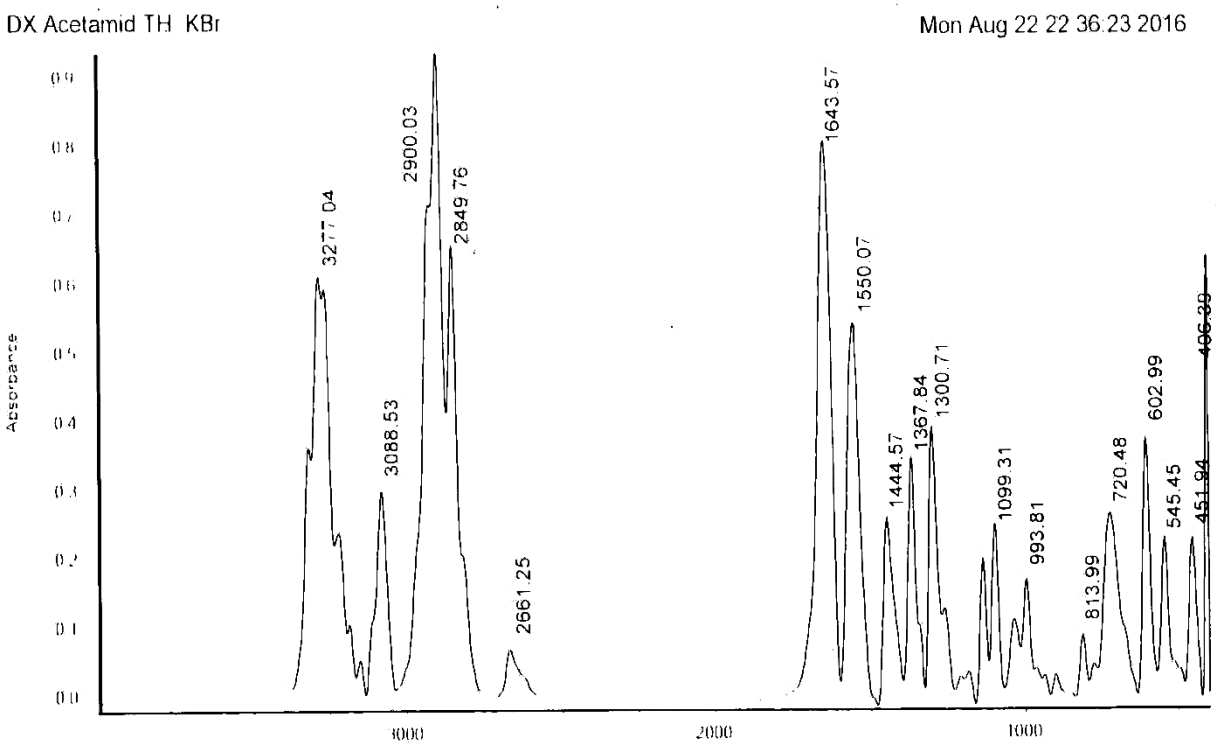
IR (KBr): cm-[1] 3277.04 (N-H); 2900.03-2849.76 (C-H); 1643.57 (C=O).



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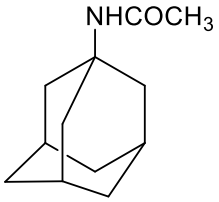

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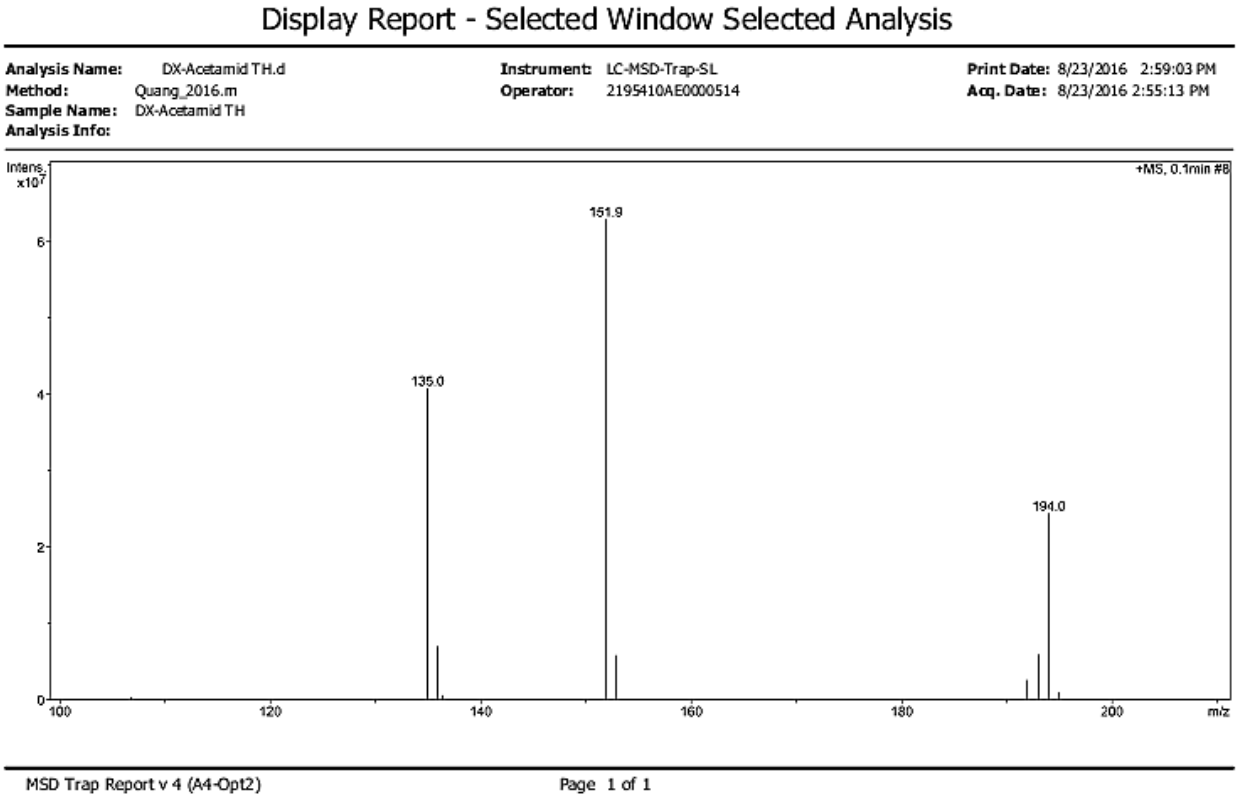
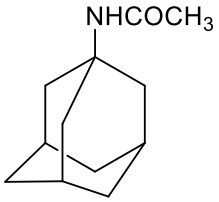
MS: m/z = 194.0 [M+1]+, 151.9 [M-$COCH_3$+1]+, 135.0 [M-$NHCOCH_3$]+.

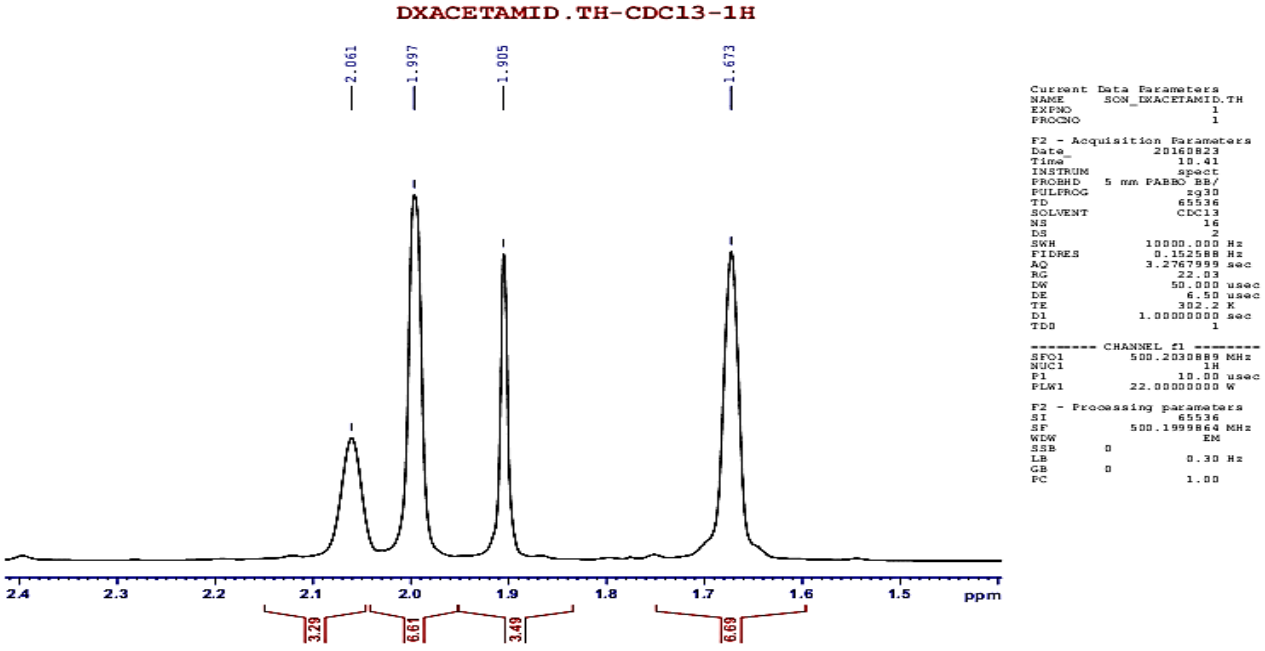


^{1}H-NMR spectrum of *N*-(1-adamantyl)acetamide (4) in $CDCl_3$

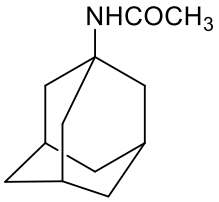


4

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 5.45 (s, 1H), 2.06 (s, 3H), 2.00 (s, 6H), 1.91 (s, 3H), 1.67 (s, 6H).



^{13}C-NMR spectrum of *N*-(1-adamantyl)acetamide (4) in $CDCl_3$



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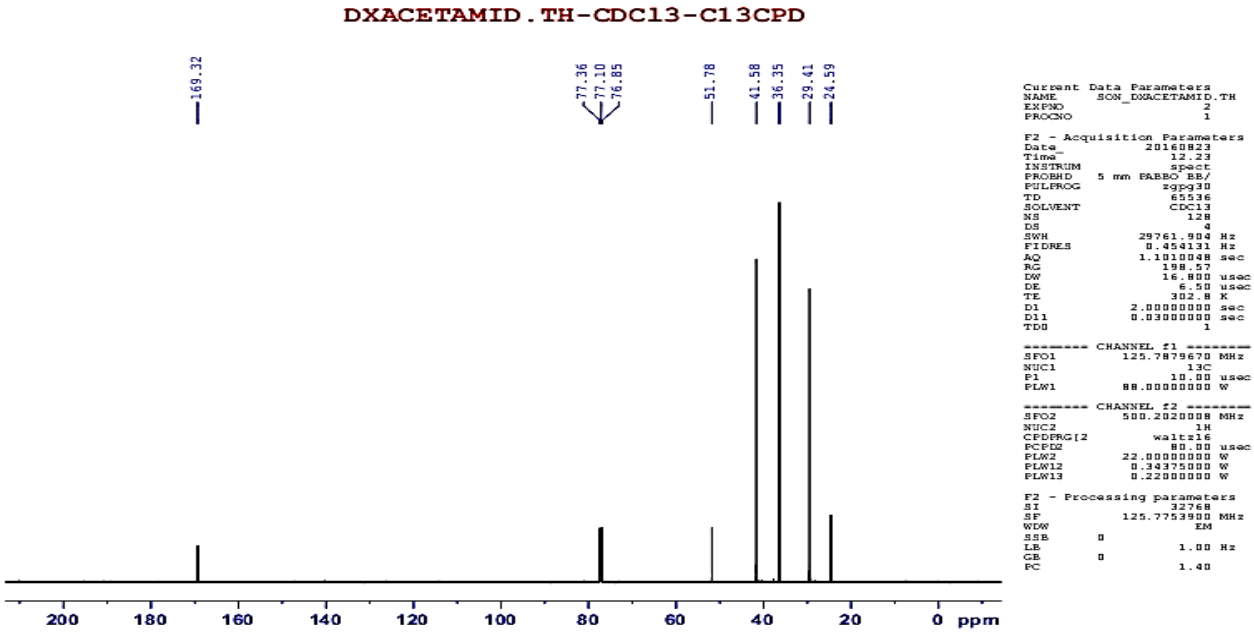
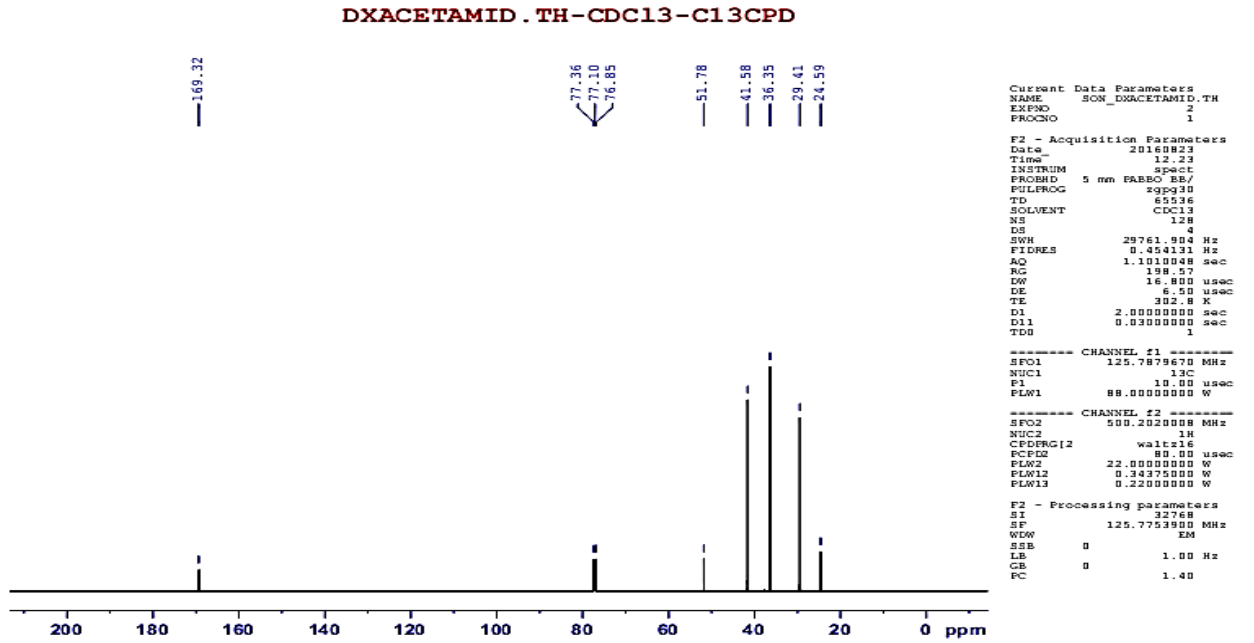
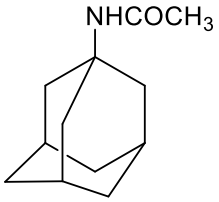
^{13}C-NMR ($CDCl_3$, 125 MHz): δ 169.32, 51.78, 41.58, 36.35, 29.41, 24.59.





GC data of the synthesized *N*-(1-adamantyl)acetamide (4)



4

GC conditions: FID Detector, temperature of 250ºC

Column: (5%-Phenyl)-methylpolysiloxane, length of 30 m, diameter of 0.32 mm, film layer of 0.25 μm.

Column temperature of 115ºC; Oven temperature of 250ºC

Injection volume: 1 μl.

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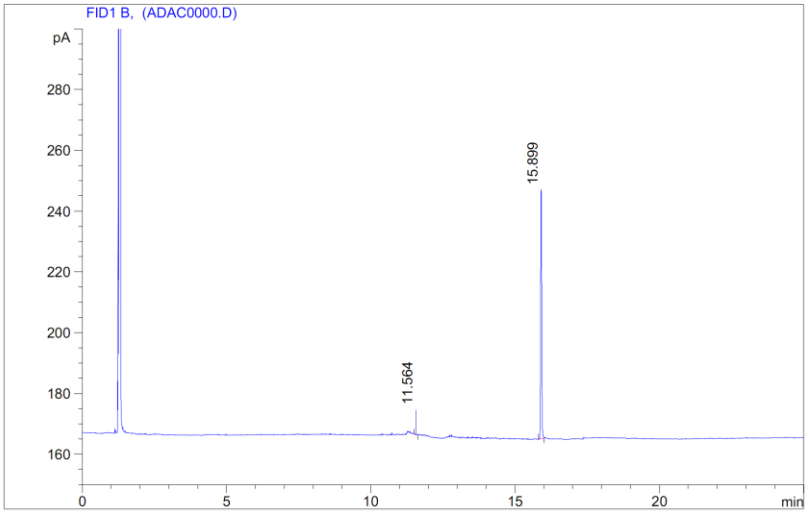


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Instrument 1     Wed, 2. Aug. 2017     10:21:24 am          Page 1 of 1
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Figure S1. GC chromatogram of the synthesized *N*-(1-adamantyl)acetamide (4)

2. GENERAL PROCEDURE FOR THE SYNTHESIS OF AMANTADINE HYDROCHLORIDE

2.1. Effect of reaction parameters on the synthesis of amantadine.HCl (1)

Table S5. Effect of temperature on the yield of amantadine.HCl (**1**)

No.	Temperature (°C)	Reaction time* (h)	Weight (g)	Yield (%)
1	188	3,5	0.84	55.62
2	150	4,5	1.00	66.22
3	140	7	1.03	68.20
4	130	6	1.12	74.16
5	**125**	**8**	**1.15**	**76.15**
6	120	10	1.14	75.49
7	110	15	1.03	68.20

Other reaction parameters. Molar ratio of reactants (KOH: PG: H_2O: *N*-(1-adamantyl)acetamide (**4**)) = (5: 8: 3.7: 1).

* Time for reaction to finish determined by TLC.

Table S6. Effect of reaction time on the yield of amantadine.HCl

No.	Reaction time (h)	Weight (g)	Yield (%)
1	6	1.02	67.54
3	7	1.08	71.51
4	8	1.15	76.15
5	**8.5**	**1.18**	**78.13**
6	9	1.15	76.15

Other reaction parameters. Temperature = 125°C; Molar ratio of reactants (KOH: PG: H_2O: *N*-(1-adamantyl)acetamide (**4**)) = (5 : 8 : 3.7 : 1).

Table S7. Effect of molar ratio of KOH to *N*-(1-adamantyl) acetamide (**4**) on the yield of amantadine .HCl

No.	Molar ratio of KOH: Compound 4	Weight (g)	Yield (%)
1	3.5 : 1	0.61	40.39
2	4.5 : 1	1.05	69.53
3	5.0 : 1	1.18	78.13
4	**5.5 : 1**	**1.21**	**80.12**
5	6.0 : 1	1.22	80.78

Other reaction parameters. Temperature = 125°C; Time = 8.5 h; Molar ratio of reactants (PG: H_2O: *N*-(1-adamantyl)acetamide (**4**)) = (8: 3.7: 1).

Table S8. Effect of mole ratio of PG to *N*-(1-adamantyl) acetamide (**4**) on the yields of amantadine. HCl

No.	Molar ratio of PG: Compound 4	Weight (g)	Yield (%)
1	5 : 1	0.99	65.55
2	6 : 1	1.19	78.80
3	**7 : 1**	**1.23**	**81.44**
4	8 : 1	1.21	80.12
5	9 : 1	1.18	78.13

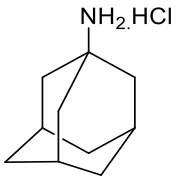
Other reaction parameters. Temperature = 125°C, Time = 8.5 h, Molar ratio of (KOH: H_2O: *N*-(1-adamantyl)acetamide) = (5.5 : 3.7 : 1).

⇨ **Results.** The combination of reaction parameters that gives the highest yield of amantadine. HCl: Temperature = 125°C; Time = 8.5 h; Molar ratio of (KOH: PG: H_2O: *N*-(1-adamantyl)acetamide molar ratio (**4**)) = (5.5: 7: 3.7: 1).

2.2. Experimental section

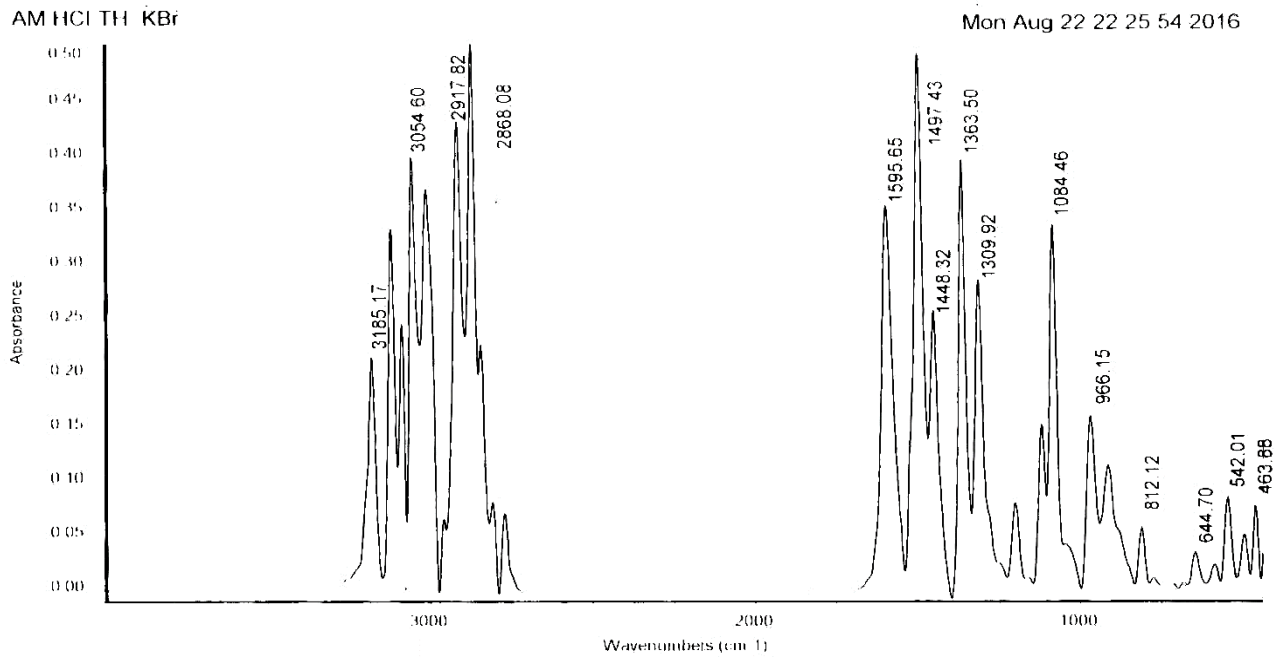
Amantadine hydrochloride (**1**)**.** A mixture of 82% potassium hydroxide (600 g, 8.74 mol), water (100 mL) and propylene glycol (750 mL) was stirred at room temperature for 1 h, to which was added **4** (290 g, 1.5 mol). The mixture was maintained at 125ºC-130ºC for 8.5 h, then cooled to room temperature and followed by the addition of ice-cold water (2.00 L). The reaction mixture was extracted with dichloromethane (3 x 2.00 L). The separated organic layer was concentrated by three-fold. To the concentrate was added 5N aq. HCl (1.40 L), stirred at 55-60ºC for 1 h, and then cooled to room temperature. The resulting aqueous layer was evaporated under vacuum to give a white solid, to which was added acetone (200 mL), stirred at 50ºC for 1 h, and then at 0-5ºC for additional 1 h. The obtained colorless precipitate was filtered off and dried under vacuum to give **1.** Yield: 232 g (82%). R_f = 0.5 ($CHCl_3$/MeOH/25% aqueous NH_3= 6:1:1). Purity (GC): 99.22%, t_R 10.10 min; mp 360ºC. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.28 (br, s, 3H), 2.15 (s, 3H), 2.04 (s, 6H); 1.69 (s, 6H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 52.95, 40.56, 35.38, 28.97. IR (KBr): cm^{-1} 3331.73-3185.17 (N-H); 3054.60-2917.82 (C-H); 1363.50 (C-N). MS: m/z = 151.9 $[M+1]^+$, 135.0 $[M-NH_2-1]^+$.

IR spectrum of amantadine hydrochloride (1)

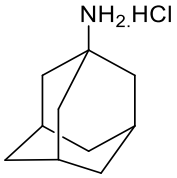


1 (Amantadine.HCl)

IR (KBr): cm^{-1} 3331.73-3185.17 (N-H); 3054.60-2917.82 (C-H); 1363.50 (C-N)

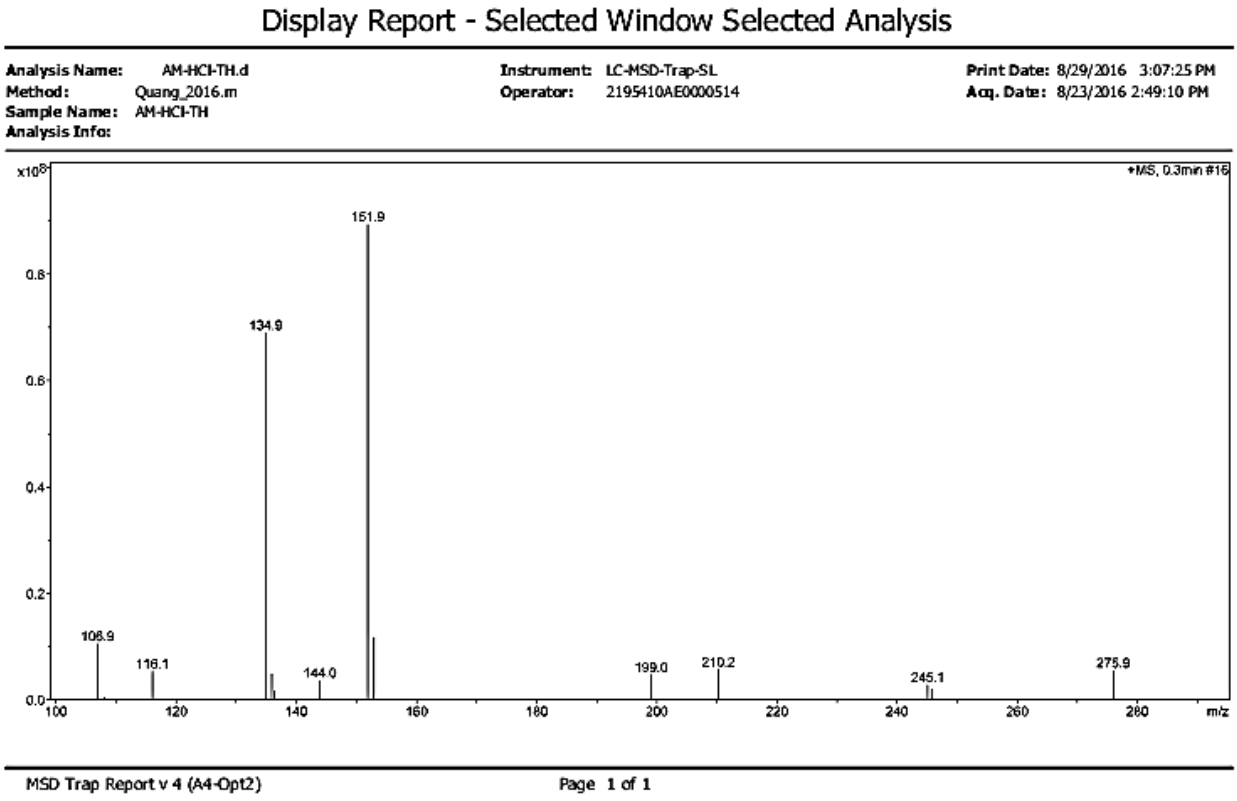


MS spectrum of amantadine hydrochloride (1)

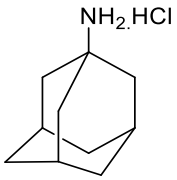


1 (Amantadine.HCl)

MS: m/z = 151.9 $[M+1]^+$, 135.0 $[M-NH_2-1]^+$.

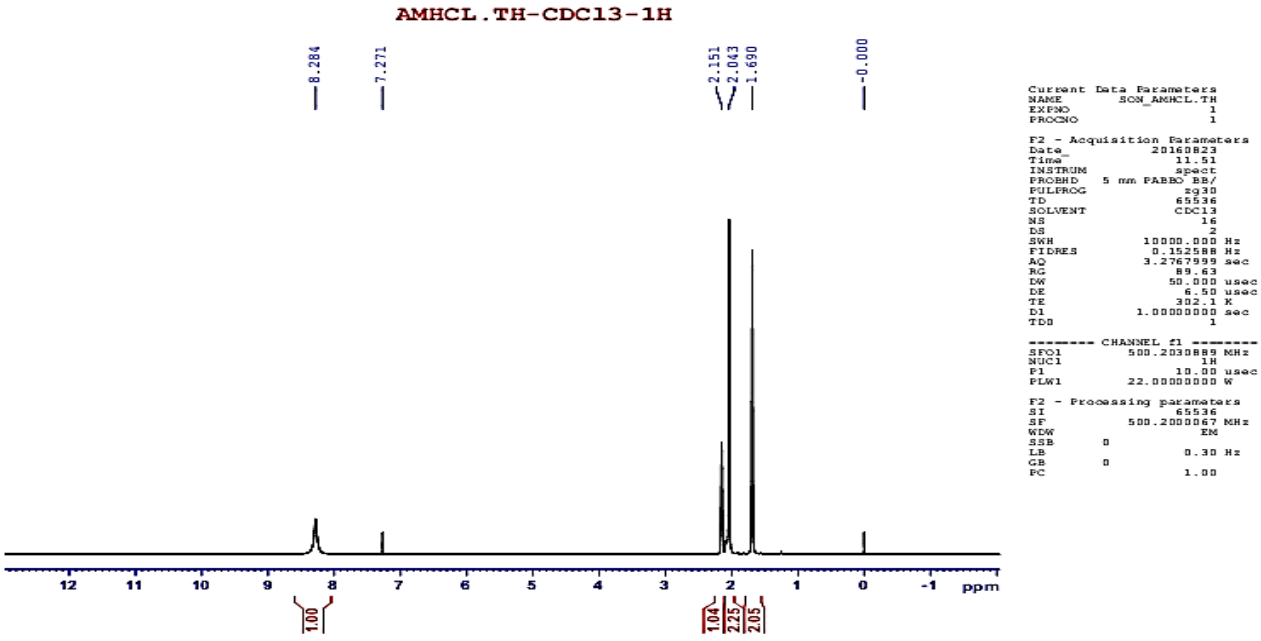


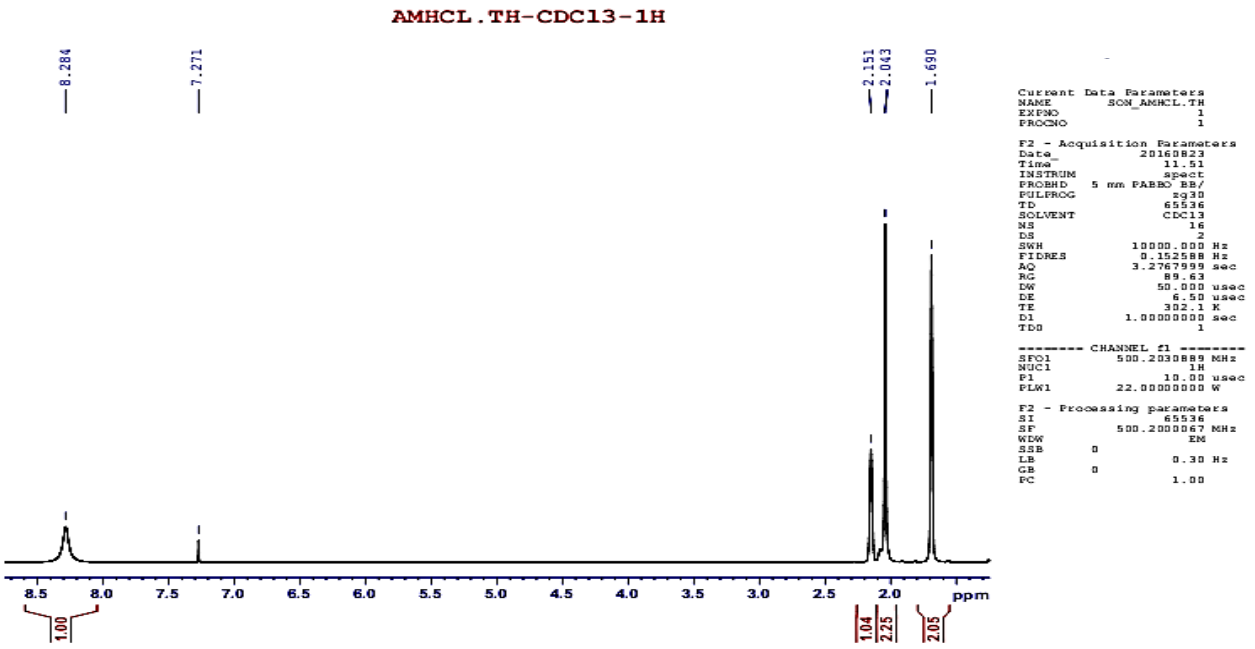
^{1}H-NMR spectrum of amantadine hydrochloride (1) in $CDCl_3$



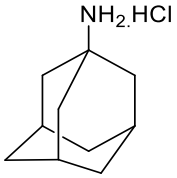
1 (Amantadine.HCl)

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.28 (br, s, 3H), 2.15 (s, 3H), 2.04 (s, 6H); 1.69 (s, 6H).



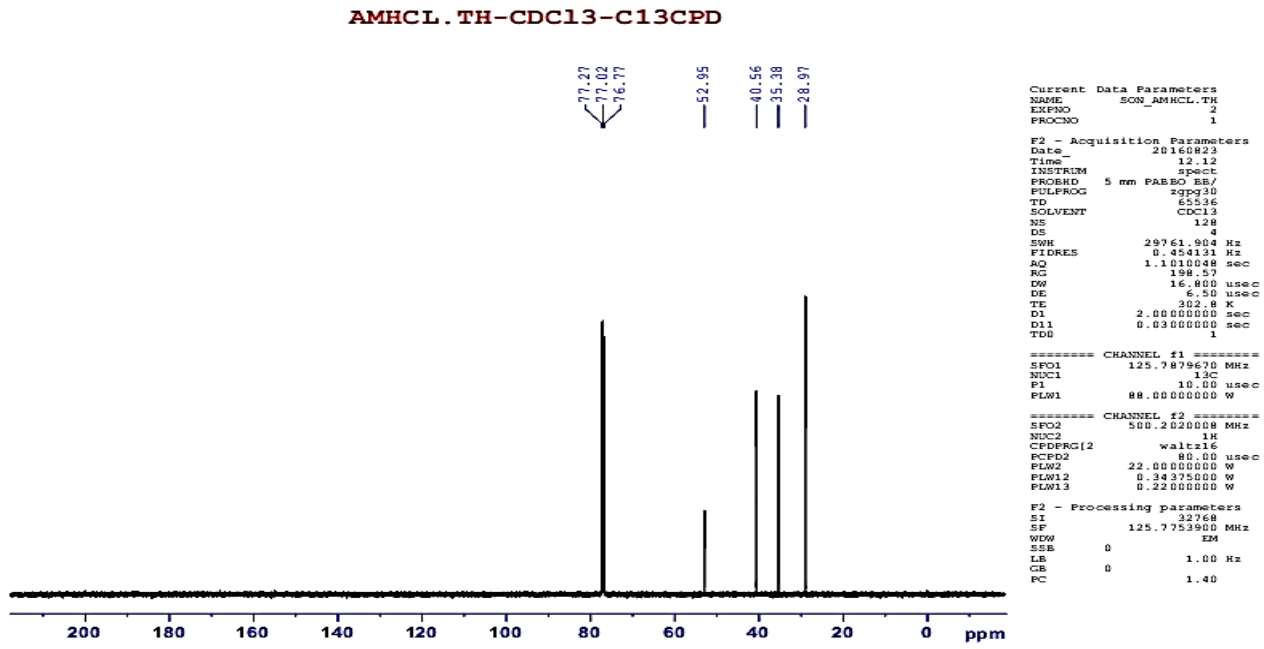


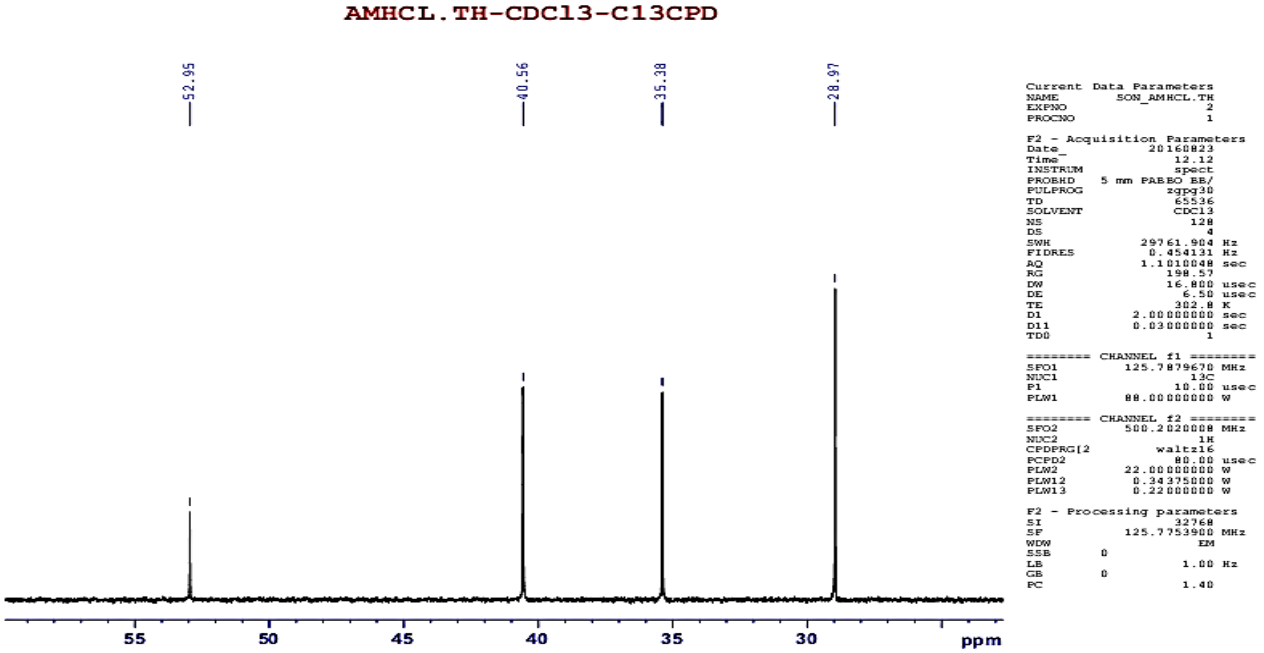
^{13}C-NMR spectrum of amantadine hydrochloride (1) in $CDCl_3$



1 (Amantadine.HCl)

^{13}C-NMR ($CDCl_3$, 125 MHz): δ 52.95, 40.56, 35.38, 28.97.





TLC of standard amantadine HCl (A), synthesized amantadine HCl (B), and a mixture of these two reagents (C)

Method: Silicagel Aluminium Art 5562 DC – Alurolle Kieselgel 60 F254 (Merck).

Solvent system: chloroform: methanol (9:1).

Visualization Reagents: Dragendorf reagent.

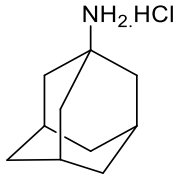
Samples for TLC: Synthesized amantadine. HCl, reference amantadine. HCl, and a mixture of these two reagents. The chemicals were dissolved in dichloromethane (0.1g/1ml).

Triple small spots of each solution were applied to a TLC plate. The plate was dried shortly in a vacuum chamber at room temperature. Development and visualization of TLC were performed following above conditions.

Results: Three red spots on TLC plate have the same R_f value, indicating that they could be the same compound.

Figure S2. TLC of amantadine HCl. (A) standard amantadine HCl, (B) synthesized amantadine HCl, (C) a mixture of the two reagents.

GC data of the synthesized amantadine hydrochloride (1)



1 (Amantadine.HCl)

GC condition: FID Detector, temperature of 250ºC

Column: (5%-Phenyl)-methylpolysiloxane, length of 30 m, diameter of 0.32 mm, film layer of 0.25 µm.

Column temperature of 115ºC; Oven temperature of 250ºC

Injection volume: 1 µl.

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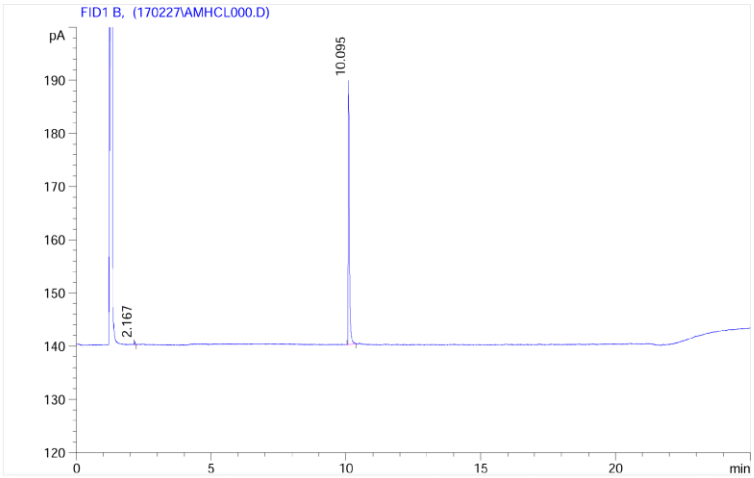


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|----|---------|-------|-------|-----------|--------|---------------|
|   1|    2.167|BP     |  0.030|     1.143|   0.779|               |
|   2|   10.095|MM T   |  0.049|   145.679|  99.221|               |
--------------------------------------------------------------------

================================================================================
                          *** End of Report ***
```

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Figure S3. GC chromatogram of the synthesized amantadine hydrochloride (1)