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Synthesis and characterization of process related impurities of an anti-convulsant drug-Lacosamide

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ABSTRACT

*The synthesis of **9** contaminants formed during the preparation of lacosamide **6** bulk drug was described. The unknown impurities were identified as (R)-tert-butyl 1-(benzylamino)-3-hydroxy-1-oxopropan-2-ylcarbamate **7**, 1,3-dibenzylurea **8**, isobutyl benzylcarbamate **9**, N-benzylacetamide **10**, (R)-isopropyl 1-(benzylamino)-3-methoxy-1-oxopropan-2-ylcarbamate **11**, (R)-2-amino-N-benzyl-3-hydroxy propanamide **12**, (R)-2-acetamido-N-benzyl-3-hydroxypropanamide **13**, (R)-2-acetamido-3-(benzylamino)-3-oxopropyl acetate **14** 2-acetamido-N-benzylacrylamide **15.** The structures of these compounds were established on the basis of spectral data (IR, 1H-NMR and MS).*

Keywords: Lacosamide, impurities, bulk drug, synthesis, contaminants.

INTRODUCTION

Lacosamide [1-2] **6**, chemically known as (R)-2-Acetamide N-benzyl-3-methoxypropanamide, having analgesic and anticonvulsant property, was approved under the trademark Vimpat by the U. S. Food and Drug Administration, for the adjunctive treatment of partial onset seizures[3].

Several methods were reported in literature for the preparation of Lacosamide [4-10]. However, no literature was reported regarding the related compounds synthesis. The preparation and characterization data of these related substances has been necessary for the preparation of reference compounds for the quality assurance of bulk drugs and drug formulations.

MATERIALS AND METHODS

Experimental: All melting points were determined with Polmon melting point apparatus. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 300 spectrometer. Chemical shifts were reported in ppm downfield from TMS as internal standard. Mass spectra were measured on Perkin Elmer PE SCIEX-API 2000 mass spectrometer. Elemental analyses were performed using a Heraeus CHN-O-Rapid instrument. Analytical HPLC were run with Zorbax Eclipsse XDB, C_{18}, 250 x 4.6 mm column at 210nm. "RT" denotes room temperature.

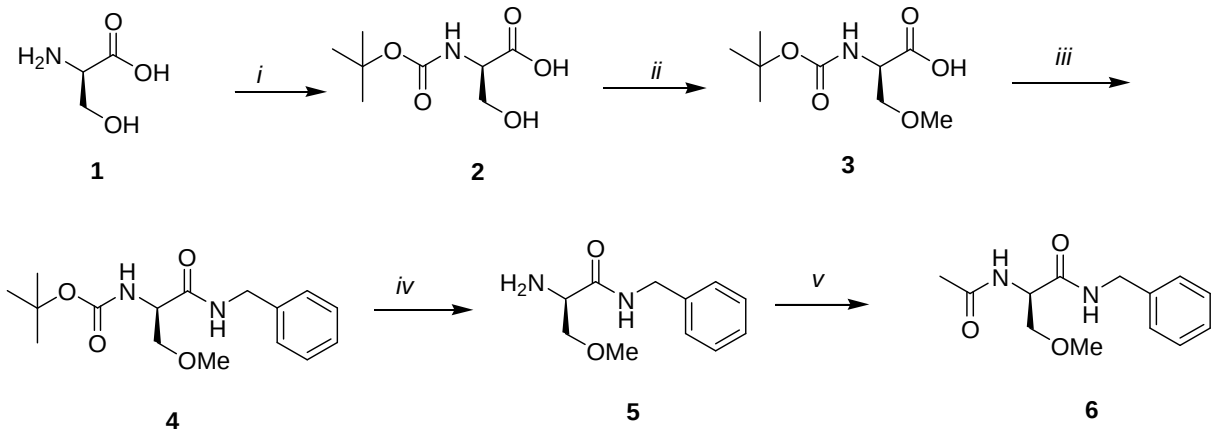
(R)-2-(Tert-butoxycarbonylamino)-3-hydroxypropanoic acid (2). Boc anhydride (114.3 g, 523.8 mmol) was added to the suspension of D-Serine (50 g, 476.2 mmol), N-methyl morpholine (72.2 g, 714.3 mmol) in water (200 mL) and 1,4-dioxane (200 mL). The reaction mass stirred at 25-30°C for 2 h, then concentrated by vacuum distillation to get **2** (95 g, 92%) as an light yellow viscous oil; purity 97% (by HPLC); IR (KBr, cm^{-1}) 3400, 2980, 1720, 1160; ^{1}H-NMR (300 MHz, DMSO) δ 1.38 (s, 9H), 3.63 (d, 2H, *J*=4.5 Hz), 3.94-4.00 (m, 1H), 6.70 (s, 1H, *J*=8.1 Hz); ^{13}C-NMR (300 MHz, DMSO) δ 28.3, 56.3, 61.6, 78.3, 155.5, 172.5; MS (ESI, *m/z*): 228 $[M+Na]^+$. Anal. Calcd. For $C_8H_{15}NO_5$ (205.21): C, 46.82; H, 7.37; N, 6.83; O, 38.98. Found: C, 46.78; H, 7.35; N, 6.91; O, 38.96.

(R)-2-(Tert-butoxycarbonylamino)-3-methoxypropanoic acid (3). Suspended the compound **2** (95 g, 463.4 mmol) in toluene (500 mL) and added simultaneously Dimethyl sulphate (240 g, 1904 mmol) and NaOH solution (50%w/w, 104.7 g, 2619 mmol) at 0-10°C. The reaction mass stirred at 5-10°C for 2 h. The reaction mass was diluted with water, separated toluene, adjust the pH to 3.5- 4.0 with 2N HCl, dissolved NaCl (75 g), extracted the product with methylene chloride to get **3** (100 g, 98.5%) as an colorless oil; purity 96% (by HPLC); IR (KBr, cm^{-1}) 2933, 2858, 1720, 1460, 773; ^{1}H-NMR (300 MHz, DMSO) δ 1.45 (s, 9H), 3.36 (s, 3H), 3.62 (dd, 1H, *J*=3.3, 9.6 Hz) 3.83 (dd, 1H, *J*=4.2, 7.8 Hz), 4.41 (d, 1H, *J*=3.6), 5.48 (d, 1H, *J*=7.8), 8.95 (s, 1H); ^{13}C-NMR (300 MHz, DMSO) δ 28.3, 55.0, 58.4, 71.6, 78.4, 155.5, 172.2; MS (ESI, *m/z*): 242 $[M+Na]^+$. Anal. Calcd. For $C_9H_{17}NO_5$ (219.23): C, 49.31; H, 7.82; N, 6.39; O, 36.48. Found: C, 49.33; H, 7.80; N, 6.37; O, 36.50.

(R)-Tert-butyl 1-(benzylamino)-3-methoxy-1-oxopropan-2-ylcarbamate (4). Isobutylchloroformate (64.8 g, 476.2 mmol) and N-methylmorpholine (57.7 g, 571.4 mmol) was added to compound **3** (100 g, 456.6 mmol) in methylene chloride at -8 to -13°C. The reaction mass was stirred at -8 to -10°C for 30 min, added benzylamine (50.9 g, 476.2 mmol) to reaction and was stirred for 1 h at 25-30°C. The methylene chloride solution was washed with water (300 mL), 1N HCl (300 mL), 6 % sodium bicarbonate solution (300 mL), water (300 mL) followed by concentration. Cyclohexane (500 mL) was added to residue, filtered the product and washed with cyclohexane (50 mL), dried at 40-45°C to yield **4** (110 g, 78 %) as a off white solid; purity 99.7% (by HPLC), mp 62-65°C; IR (KBr, cm^{-1}) 3325, 2951, 1681, 1649, 1531, 1170, 918, 748; ^{1}H-NMR (300 MHz, DMSO) δ 1.39 (s, 9H), 3.24 (s, 3H), 3.48 (d, 2H, *J*=5.7 Hz), 4.17 (d, 1H, *J*=6.9 Hz), 4.28 (s, 2H), 6.86 (d, 1H, *J*=8.1 Hz), 7.23-7.32 (m, 5H), 8.41 (t, 1H, *J*=5.7 Hz); ^{13}C-NMR (300 MHz, DMSO) δ 28.3, 42.1, 54.5, 58.3, 72.1, 78.4, 126.8, 127.1, 128.3, 139.4, 155.4, 170.2; MS (ESI, *m/z*): 309 $[M+H]^+$. Anal. Calcd. For $C_{16}H_{24}N_2O_4$ (308.37): C, 62.32; H, 7.84; N, 9.08; O, 20.75. Found: C, 62.37; H, 7.82; N, 9.10; O, 20.71.

(R)-2-Amino-N-benzyl-3-methoxypropanamide (5).
Hydrochloric acid (35%, 169.3 ml, 1623 mmol) was added to the solution of compound **4** (100 g, 325 mmol) in methylene chloride (500 mL) at 25-30°C. The reaction mass was stirred for 2 h. Then diluted with water, separated the layers. The aqueous layer pH was adjusted to 10.5 to 11.5 with 30% NaOH solution (260 ml, 1948 mmol), extracted the product with methylene chloride (500 mL), concentrated to get compound **5** (65 g, 96.2%) as an colorless oil; purity 99.2% (by HPLC); IR (KBr, cm^{-1}) 3300, 1650, 1150, 788; ^{1}H-NMR (300 MHz, DMSO) δ 1.88 (s, 2H) 3.25 (s, 3H), 3.33-3.45 (m, 3H), 4.28 (dd, 2H, *J*=3.6, 6.0 Hz), 7.20-7.34 (m, 5H), 8.37 (t, 1H, *J*=5.4 Hz); ^{13}C-NMR (300 MHz, DMSO) δ 42.0, 54.8, 58.3, 75.3, 126.8, 127.2, 128.3, 139.6, 173.1; MS (ESI, *m/z*): 209.0 $[M+H]^+$. Anal. Calcd. For $C_{11}H_{16}N_2O_2$ (208.26): C, 63.44; H, 7.74; N, 13.45; O, 15.37. Found: C, 63.48; H, 7.71; N, 13.48; O, 15.33.

(R)-2-Acetamido-N-benzyl-3-methoxypropanamide (6).
Acetic anhydride (36.5 g, 357.2 mmol) was added to the compound **5** (65 g, 312.5 mmol) at 10-15°C, stirred for 2 h, washed the reaction mass with water, 6% sodium bicarbonate solution, water followed by concentration. The obtained crude was diluted with ethyl acetate (300 mL) and cooled to 5-10°C for 3 h, filtered the product and dried, to yield 6 (60 g, 77 %) as a white solid; purity 99.9% (by HPLC), mp 142-144°C; IR (KBr, cm^{-1}) 3288, 3062, 2877, 1638, 1560, 1138, 796, 640; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.37 (s, 3H), 3.44 (dd, 1H, *J*=7.2, 9.0 Hz), 3.76 (dd, 1H, *J*=4.2, 9.3 Hz), 4.44 (t, 2H, 5.1), 4.58-4.64 (m, 1H), 6.63 (d, 1H, *J*=6.0 Hz), 7.0 (s, 1H), 7.24-7.35 (m, 5H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 23.0, 43.4, 52.4, 58.9, 71.7, 127.3, 127.3, 128.6, 137.8, 169.9, 170.3; MS (ESI, *m/z*): 251.0 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{18}N_2O_3$ (250.29): C, 62.38; H, 7.25; N, 11.19; O, 19.18. Found: C, 62.32; H, 7.28; N, 11.15; O, 19.25.

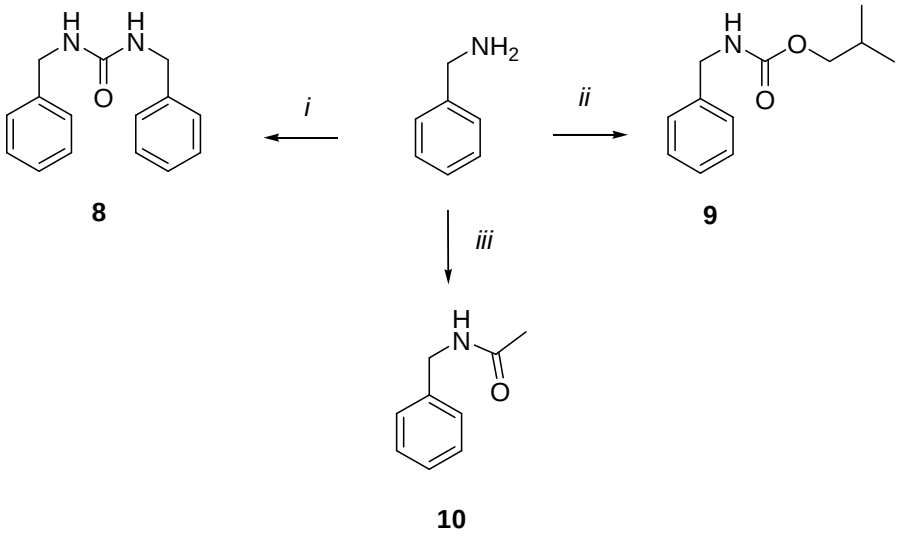


Scheme 1. *i.* Boc anhydride, TEA, H_2O; *ii.* NaOH, toluene, DMS, 5-10°C. *iii*. isobutyl chloroformate, N-methylmorpholine, benzylamine, -8 to -13°C. *iv.* HCl, RT. *v*. acetic anhydride

1,3-Dibenzylurea (**8).**
Triphosgene (24 g, 80.9 mmol) was added to the mixture of benzyl amine (20.0 g, 186.9 mmol), sodium bicarbonate (30 g, 357.1 mmol), toluene (200 mL) and water (100 mL) at 25-30°C. Stir for 1 h, separated the toluene layer, concentrated and isolated with acetone (100 mL), dried to get **8** (18 g, 80%) as an off white solid; purity 98.5% (by HPLC), mp 150-155 °C; IR (KBr, cm^{-1}) 3321, 3028, 2874, 1618, 1573, 1249, 1064; ^{1}H-NMR (300 MHz, DMSO) δ 4.24 (d, 4H, *J*=6.0 Hz), 6.46 (t, 2H, *J*=6.0 Hz), 7.26 (m, 10H); ^{13}C-NMR (300 MHz, DMSO) δ 43.1, 126.7, 127.1, 128.3, 141.0, 158.2; MS (ESI, *m/z*): 241 $[M+H]^+$. Anal. Calcd. For $C_{15}H_{16}N_2O$ (240.30): C, 74.97; H, 6.71; N, 11.66; O, 6.66. Found: C, 74.92; H, 6.69; N, 11.70; O, 6.69.

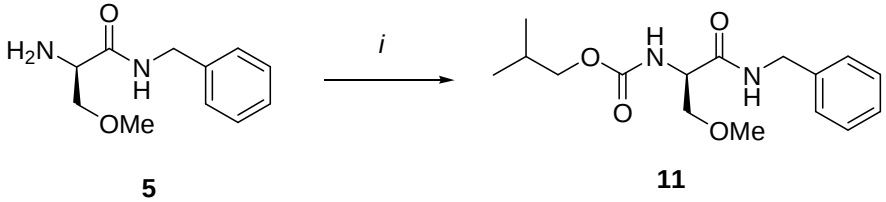
Isobutyl benzylcarbamate (9).
Isobutylchloroformate (12.76 g, 93.45 mmol) was added to the solution of benzylamine (10 g, 93.45 mmol) and N methylmorpholine (14.15 g, 140.2 mmol) in methylene chloride (150 mL) at 5-10°C. Raised the temperature to RT for 2 h. wash organic layer with water (80 mL), concentrated isolated the compound with hexane (80 mL), dried to get **9** (14 g, 72.3%) as a off white crystals; purity 99% (by HPLC), mp 37-39°C; IR (KBr, cm^{-1}) 3300, 2900, 2350, 1730; ^{1}H-NMR (300 MHz, DMSO) δ 0.88 (d, 6H, *J*=6.6 Hz), 1.87 (m, 1H), 3.76 (d, 2H, *J*=6.6 Hz), 4.20 (d, 2H, *J*=6.0 Hz), 7.30 (m, 5H), 7.66 (t, 1H, *J*=5.7 Hz); ^{13}C-NMR (300 MHz, DMSO) δ 19.0, 27.8, 43.8, 69.9, 126.8, 127.1, 128.3, 140.0, 156.8; MS (ESI, *m/z*): 208 $[M+H]^+$. Anal. Calcd. For $C_{12}H_{17}NO_2$ (207.27): C, 69.54; H, 8.27; N, 6.76; O, 15.43. Found: C, 69.51; H, 8.24; N, 6.78; O, 15.47.

N-Benzyl acetamide (10).
Acetic anhydride (10.5 g, 102.9 mmol) was added to the solution of benzylamine (10 g, 93.45 mmol) and N-methylmorpholine (11.3 g, 111.8 mmol) in methylene chloride (150 mL) at 5-10°C. Raise the temperature to RT, maintain for 2 h. wash organic layer with water (80 mL), concentrated isolated the compound with hexane (80 mL), dried to get **10** (12 g, 86%) as a off white powder; purity 99% (by HPLC), mp 58-60°C; IR (KBr, cm^{-1}) 3294, 1643, 1550, 1280, 748; ^{1}H-NMR (300 MHz, DMSO) δ 1.87 (s, 3H), 2.45 (s, 3H), 4.24 (d, 2H), 7.20-7.34 (m, 5H), 8.32 (s, 1H); ^{13}C-NMR (75 MHz, DMSO) δ 22.7, 42.3, 126.9, 127.4, 128.4, 139.8, 169.3; MS (ESI, *m/z*): 150.0 $[M+H]^+$. Anal. Calcd. For $C_9H_{11}NO$ (149.2): C, 72.46; H, 7.43; N, 9.39; O, 10.72. Found: C, 72.43; H, 7.45; N, 9.34; O, 10.78.



Scheme 2. *i.* Triphosgene, DCM. *ii*. Isobutylchloroformate, N-Methylmorpholine, DCM. *iii.* Acetic anhydride, DCM

(R)-Isopropyl 1-(benzylamino)-3-methoxy-1-oxopropan-2-ylcarbamate (**11).**
Isobutylchloroformate (6.56 g, 48 mmol) was added to the mixture of (R)-2-amino-N-benzyl-3-methoxypropanamide **5** (10 g, 48 mmol) and pyridine (5.7 g, 72 mmol) in methylene chloride (100 mL) at 5-10°C. After addition raise the temperature to RT, maintain for 2 h, wash the organic layer with water (80 mL), concentrated and isolated with hexane (80 mL), dried to get **11** (11 g, 77.8%) as a white powder; purity 98% (by HPLC), mp 105-108°C; IR (KBr, cm^{-1}) 3298, 3074, 2955, 1685, 1647, 1550, 1049, 694; ^{1}H-NMR (300 MHz, DMSO) δ 0.87 (d, 6H, *J*=6.3 Hz), 1.77-1.90 (m, 1H), 3.24 (s, 3H), 3.50 (d, 2H, *J*=6.0 Hz), 3.73 (d, 2H, *J*=6.6 Hz), 4.21 (m, 1H), 4.33 (d, 2H, *J*=6.3 Hz), 7.22-7.33 (m, 5H), 8.45 (t, 1H, *J*=5.4 Hz); ^{13}C-NMR (300 MHz, DMSO) δ 19.0, 27.7, 42.2, 54.7, 58.2, 70.1, 72.1, 126.8, 127.1, 128.3, 139.4, 156.3, 169.9; MS (ESI, *m/z*): 309 $[M+H]^+$. Anal. Calcd. For $C_{16}H_{24}N_2O_4$ (308.37): C, 62.32; H, 7.84; N, 9.08; O, 20.75. Found: C, 62.28; H, 7.86; N, 9.05; O, 20.81.



Scheme 3. *i.* isobutylchloroformate, pyridine, MDC

(R)-Tert-butyl 1-(benzylamino)-3-hydroxy-1-oxopropan-2-ylcarbamate (**7**).
Benzylamine (13.0 g, 121.9 mmol) was added to the mixture of compound **2** (25.0 g, 121.9 mmol), DCC (30.2 g, 146.4 mmol) and HOBt (1.86 g, 12.2 mmol) in methylene chloride (150 mL) at RT and maintained for 15 h, filter the salts and washed the organic layer with water (50 mL), concentrated and isolated with hexane (100 mL) and dried to get **7** (25 g, 69.7%) as a light yellow solid; purity 98.5% (by HPLC), mp 83-85 °C; IR (KBr, cm^{-1}) 3300, 1650, 1550; ^{1}H-NMR (300 MHz, DMSO) δ 1.39 (s, 9H), 3.57 (d, 2H, *J*=5.1 Hz), 3.96 (dd, 1H, *J*=5.4, 13.2), 4.26 (d, 2H, *J*=6.6 Hz), 4.84 (s, 1H), 6.64 (d, 1H, *J*=8.1 Hz), 7.19-7.31 (m, 5H), 8.28 (t, 1H, *J*=5.7 Hz); ^{13}C-NMR (300 MHz, DMSO) δ 28.1, 41.9, 56.9, 61.8, 78.1, 126.5, 126.9, 128.1, 139.3, 155.1, 170.4; MS (ESI, *m/z*): 295.0 $[M+H]^+$. Anal. Calcd. For $C_{15}H_{22}N_2O_4$ (294.35): C, 61.21; H, 7.53; N, 9.52; O, 21.74. Found: C, 61.23; H, 7.51; N, 9.58; O, 21.68.

(R)-2-Amino-N-benzyl-3-hydroxypropanamide hydrochloride (**12)**
Hydrochloric acid (17.7 mL, 169.9 mmol) was added to the solution of (R)-tert-butyl 1-(benzylamino)-3-hydroxy-1-oxopropan-2-ylcarbamate 7 (10 g, 33.97 mmol) in methylene chloride (100 mL) at RT. Maintain for 2 h. filtered the solid, dried to get **12** (5 g, 75.9%) as a light yellow solid; purity 98% (by HPLC); mp 76-78°C; IR (KBr, cm^{-1}) 3300, 2950, 2300, 1630, 1560, 1462, 1250, 1000; ^{1}H-NMR (300 MHz, DMSO) δ 3.73-3.87 (m, 3H), 4.34 (d, 2H, *J*=6.0 Hz), 5.51 (t, 1H), 7.22-7.36 (m, 5H), 8.21 (s, 3H), 8.96 (s, 1H); ^{13}C-NMR (300 MHz, DMSO) δ 42.2, 54.3,

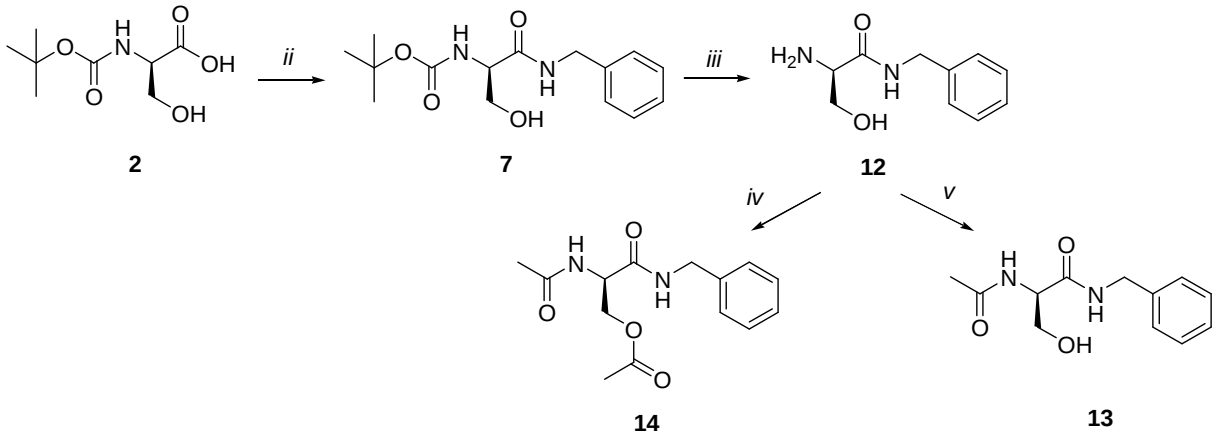
60.2, 126.8, 127.1, 128.2, 138.5, 166.7; MS (ESI, *m/z*): 195.0 $[M+H]^+$. Anal. Calcd. For $C_{10}H_{14}N_2O_2$ (194.23): C, 61.84; H, 7.27; N, 14.42; O, 16.47; Found: C, 61.80; H, 7.25; N, 14.46; O, 16.49.

(R)-2-Acetamido-N-benzyl-3-hydroxypropanamide (**13)**

Acetic anhydride (5.25 g, 51.54 mmol) was added to the solution of (R)-2-amino-N-benzyl-3-hydroxypropanamide **12** (10 g, 51.54 mmol) in methylene chloride (100 mL) at 10-15°C. maintain for 1 h at RT, filtered, dried to get **13** (9.5 g, 78.5%) as a off white powder; purity 98.5% (by HPLC); mp 134-136°C; IR (KBr, cm^{-1}) 3321, 3194, 2357, 1643, 1554, 1300, 1053, 732; ^{1}H-NMR (300 MHz, DMSO) δ 1.88 (s, 3H), 3.60 (t, 2H, *J*=5.4 Hz), 4.29 (t, 1H, *J*=2.7 Hz), 4.33 (d, 2H, *J*=5.7 Hz), 4.92 (t, 1H, *J*=5.4 Hz), 7.19-7.33 (m, 5H), 7.95 (d, 1H, *J*=7.8 Hz), 8.38 (t, 1H, *J*=6.0 Hz); ^{13}C-NMR (300 MHz, DMSO) δ 22.8, 42.2, 55.5, 61.9, 126.8, 127.1, 128.3, 139.5, 169.6, 170.4; MS (ESI, *m/z*): 237 $[M+H]^+$. Anal. Calcd. For $C_{12}H_{16}N_2O_3$ (236.27): C, 61.00; H, 6.82; N, 11.86; O, 20.32. Found: C, 61.04; H, 6.82; N, 11.88; O, 20.26.

(R)-2-Acetamido-3-(benzylamino)-3-oxopropyl acetate (14)

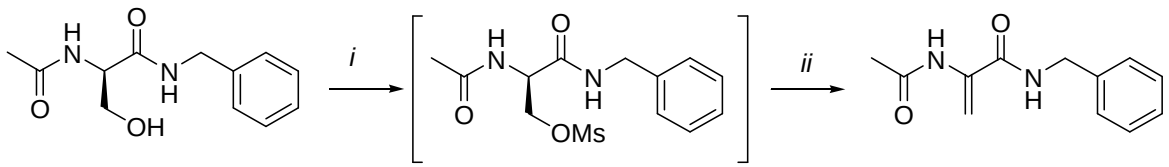
Acetic anhydride (11.57 g, 113.4 mmol) was added to the solution of **(**R)-2-amino-N-benzyl-3-hydroxypropanamide **12** (10 g, 51.54 mmol), K_2CO_3 (17.8 g, 128.9 mmol) in methylene chloride (200 mL) at 10-15°C. Maintain for 1 h at RT, wash organic layer with water (100 mL), concentrated, isolated with hexane (70 mL), dried to get **13** (9 g, 63%) as a off white powder; purity 99% (by HPLC); mp 134-138°C; IR (KBr, cm^{-1}) 3290, 1743, 1635, 1539, 1246, 1215, 1045, 698; ^{1}H-NMR (300 MHz, DMSO) δ 1.88 (s, 3H), 1.97 (s, 3H), 4.23 (dd, 2H, *J*=6.0 Hz, 23.7 Hz), 4.34 (dd, 2H, *J*=6 Hz, 17.1 Hz), 4.58 (m, 1H), 7.29 (m, 5H), 8.20 (d, 1H, *J*=8.1 Hz), 8.58 (t, 1H, *J*=6.0 Hz); ^{13}C-NMR (300 MHz, DMSO) δ 20.8, 22.7, 42.3, 51.8, 63.8, 126.9, 127.2, 128.4, 139.4, 169.1, 169.8, 170.2; MS (ESI, *m/z*): 279 $[M+H]^+$. Anal. Calcd. For $C_{17}H_{17}N_3O$ (278.13): C, 60.42; H, 6.52; N, 10.06; O, 23.0. Found: C, 60.38; H, 6.55; N, 10.12; O, 22.95.



Scheme 4. *i.* Boc anhydride, TEA, H_2O; *ii.* DCC, HOBt, benzylamine, RT. *iii*. HCl, RT. *iv.* acetic anhydride, K_2CO_3, DCM. *v*. acetic anhydride, DCM

2-Acetamido-N-benzylacrylamide (15)

Methane sulfonyl chloride (6 g, 52.4 mmol) was added to the mixture of compound 13 (10 g, 42.37 mmol) and N,N-Diisopropylethylamine (11 g, 85.3 mmol) in methylene chloride (100 mL) at 0 to -5°C in 30 min, stir for 30 min, wash organic layer with water (50 mL), concentrated, isolated with methanol (25 mL) at 0-5°C. Suspend the wet solid in methanol (50 mL) and add sodium methoxide (2 g, 37 mmol) at 20-25°C, stir for 30 min, add water (50 mL) and extract the product with ethyl acetate (100 mL), concentrated, purified with column chromatography (hexane: ethyl acetate) to get compound 15 (4 g, 43%) as an off white solid; purity 97% (by HPLC); mp 104-107°C; IR (KBr, cm^{-1}) 3300, 1630, 1550, 1470, 730; ^{1}H-NMR (300 MHz, DMSO) δ 2.00 (s, 3H), 4.35 (d, 2H, *J*=6.0 Hz), 5.43 (s, 1H), 6.02 (s, 1H), 7.20-7.34 (m, 5H), 8.83 (t, 1H, *J*=5.7 Hz), 9.08 (s, 1H); ^{13}C-NMR (300 MHz, DMSO) δ 23.7, 42.4, 102.9, 126.7, 127.1, 128.1, 136.1, 139.2, 164.0, 169.1; MS (ESI, *m/z*): 217 $[M-H]^+$. Anal. Calcd. For $C_{12}H_{14}N_2O_2$ (218.25): C, 66.04; H, 6.47; N, 12.84; O, 14.66. Found: C, 66.00; H, 6.46; N, 12.81; O, 14.73.



13 **15**

Scheme 5. *i*. Methanesulfonylchloride, DIPEA, DCM. *ii*. NaOMe, Methanol

RESULTS AND DISCUSSION

Lacosamide **6** was prepared from D-Serine by the known method [7] (Scheme 1). Its preparation from D-Serine, involves the steps of protection, methylation, benzylation, deprotection and acetylation.

It was observed during the benzylation, some of the batches of **4** were contaminated with impurities **7-10** in the range 0.1% to 0.5%. In the final acetylation step, we observed that some of the batches of Lacosamide **6** were contaminated with impurities **11-15** in the range from 0.1% to 0.5%. These all impurities were synthesized after identification by detection of mass by LC-MS and confirmed by HPLC. Therefore it is necessary to synthesize these impurities in pure form for the analytical method validation of Lacosamide **6** bulk drug [11-12]. Then, a comprehensive study has been carried out to prepare these contaminants.

During the preparation of **4**, the side reactions of benzyl amine and isobutyl chloroformate resulted 1,3-dibenzylurea **8** and benzylcarbamate **9**. 1,3-Dibenzylurea **8** is prepared by the reaction of triphosgene with benzylamine. Benzyl amine reacts with isobutyl chloroformate in the presence of base resulted benzylcarbamate **9**. The traces of benzyl amine was carry forwarded to final acetylation step which reacts with acetic anhydride to give N-benzylacetamide **10** (Scheme 2).

(R)-Isopropyl 1-(benzylamino)-3-methoxy-1-oxopropan-2-ylcarbamate **11** was one of the impurity found in **4**. It was prepared by reacting (R)-2-amino-N-benzyl-3-methoxypropanamide **5** with isobutylchloroformate (Scheme 3).
It was observed that during benzylation, the unreacted **2** was reacted with benzylamine leading to the formation of the (R)-tert-butyl 1-(benzylamino)-3-hydroxy-1-oxopropan-2-ylcarbamate **7**. It was prepared by the reaction of Boc serine **2** with benzylamine via DCC coupling method [13]. Compound **7** was deprotected [14-17] with HCl forms (R)-2-amino-N-benzyl-3-hydroxypropanamide **12** and it was react with acetic anhydride forms (R)-2-acetamido-N-benzyl-3-hydroxypropanamide **13,** (R)-2-acetamido-3-(benzylamino)-3-oxopropyl acetate **14** (Scheme 4).

During degradation studies, 2-acetamido-N-benzylacrylamide **15** as a degrading impurity was observed. It was prepared by the mesylation of des methyl lacosamide **13** with methane sulphonyl chloride followed by treatment with sodium methoxide (Scheme 5).

CONCLUSION

In summary, we report a method for the preparation of Lacosamide impurities in quite good yield and purity. Also, the spectral data (IR, 1H-NMR and MS) of these compounds was described.

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