Electronic supplementary informations

Synthesis and Biological Evaluation of Memantine Nitrates as Potential Treatment for Neurodegenerative Diseases

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METHODS

Chemistry

All chemicals and solvents were analytical grade and were used without further purification. Melting points were determined with a melting point apparatus (MPA100, OptiMelt) and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature on a 300 MHz spectrometer (AV-300, Bruker). The chemical shifts values were expressed in ppm relative to tetramethylsilane as an internal standard. Electrospray ionization mass spectra (ESI-MS) were obtained in the positive ion detection mode on a Agilent 1260 hybird SFC/MS. High resolution mass spectrometry (HRMS) was performed onperformed by the

AB SCIEX, Triple TOF 5600$^+$. Column chromatography was carried out using ordinary silica gel (Qingdao Haiyang Chemical Co., Ltd, 200-300 mesh). Elemental analysis was performed at the experimental center of Jinan University, Guangzhou, China, and the results were within ± 0.5% of the theoretical values.

1-Bromo-3-methyladamantane (4). Compound **4** was synthesized according to a published method.[1] Colorless oil, 87% yield.

1-Bromo-3-ethyladamantane (5). Compound **5** was synthesized according to a published method.[1] Colorless oil, 85% yield.

1-Bromo-3-propyladamantane (6). Compound **6** was synthesized according to a published method.[1] Colorless oil, 91% yield.

1-Acetamido-3-methyladamantane (7). Compound **7** was synthesized according to a published method.[2] White solid, 90% yield.

1-Acetamido-3-ethyladamantane (8). Compound **8** was synthesized according to a published method.[2] White solid, 83% yield.

1-Acetamido-3-propyladamantane (9). Compound **9** was synthesized according to a published method.[2] White solid, 78.2% yield.

1-Acetamido-3-methyl-5-hydroxyladamantane (10). To a mixture of concentrated HNO_3 (1 mL) and concentrated H_2SO_4 (9.4 mL) at 0 ^oC was added compound **7** (1.24 g, 6 mmol) in small batches. The mixture was stirred for 2 h in an ice bath and then the reaction was allowed to continue for another 30 h. The mixture was poured into 10 g of ice-water and stirred for 30 min. Sodium hydroxide (18 g, 450 mmol) was added into the solution in batches, followed by addition of ethyl acetate (100 mL). The mixture was stirred for 1 h and was filtered. The resulting residue was washed with ethyl acetate (20 mL × 5). The combined organics was washed with water and brine. The organics were dried over anhydrous Na_2SO_4. Removal of solvent in vacuo afforded a crude product. The crude product was purified by

recrystallization in ethyl acetate to afford compound **10** as a white solid (762 mg, 57% yield), mp 169.2-170.8 °C. ESI-MS: *m/z* 224.2 $[M + H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 3H, CH_3), 1.18-1.30 (d, *J* = 12 Hz, 4H), 1.38-1.49 (dd, *J* = 30 Hz, 21 Hz, 2H), 1.48-1.59 (dd, *J* = 21 Hz, 9Hz, 2H), 1.65-1.72 (m, 4H), 1.73 (s, 3H, $COCH_3$), 2.1 (m, 1H, CH), 4.46 (s, 1H, OH), 7.37 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.2, 30.2, 30.5, 33.7, 39.6, 42.5, 43.9, 47.3, 48.7, 51.7, 68.3, 169.0. Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92%; H, 9.48%; N, 6.27%. Found: C, 69.92%; H, 9.73%; N, 6.14%.

1-Acetamido-3-ethyl-5-hydroxyladamantane (11). Compound **11** was prepared using a similar method to that as described for synthesis of compound **10**. White solid, 55% yield. mp 108.5-109.9 °C. ESI-MS: *m/z* 238.2 $[M + H]^+$, ^1H NMR (300 MHz, DMSO-d_6) δ 0.73-0.87 (t, *J* = 7.5 Hz, 3H, CH_3), 1.12-1.19 (q, *J* = 7.5 Hz, 2H, CH_2), 1.20-1.28 (dd, *J* = 21 Hz, 9 Hz, 4H), 1.39-1.51 (q, *J* = 12 Hz, 2H), 1.47-1.57 (dd, *J* = 21 Hz, 9Hz, 2H), 1.72-1.78 (m, 7H, CH_2, $COCH_3$), 2.12-2.15 (m, 1H, CH), 4.46 (s, 1H, OH), 7.38 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.7, 24.2, 30.3, 36.3, 36.4, 44.3, 44.9, 49.1, 54.0, 68.3, 169.0. Calcd for $C_{14}H_{23}NO_2 \cdot 0.5H_2O$: C, 68.26%; H, 9.82%; N 5.69%. Found: C, 67.98%; H, 9.88%; N, 5.55%.

1-Acetamido-3-hydroxyl-5-propyl adamantane (12). Compound **12** was prepared using a similar method to that as described for synthesis of compound **10**. 60% yield. ESI-MS: *m/z* 251.4 $[M + H]^+$.

1-*tert*-Butylcarbamate-3-methyl-5-hydroxyadamantane (13). To compound **10** (1.1 g, 5 mmol) in diethylene glycol (20 mL) was added NaOH (2.5 g, 62.5 mmol). The mixture was stirred at 175 °C for 15 h. The mixture was cooled to room temperature and 50 mL of ice-water was added. The mixture was extracted with ethyl acetate (30 mL × 4). The combined organic solution was washed with 20 mL of water and brine in turn, and then dried over anhydrous Na_2SO_4. Removal of solvent in vacuo gave a crude product. To the crude in flask was added THF (20 mL), TEA (750 mg, 7.5 mmol), di-*tert*-butyl dicarbonate (1.64 g, 7.5

mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP). The reaction mixture was stirred at room temperature for 5 h. Isovolumetric of saturated NH_4Cl solution was added into the mixture. THF was removed in vacuo and the residue was extracted with ethyl acetate (20 mL× 4). The combined organic solution was washed with water and brine, and then dried over anhydrous Na_2SO_4. Solvent was removed in vacuo. The resulting residue was purified by column chromatography (petroleum ether: ethyl acetate = 3:1) to afford compound **13** as a white solid (819 mg, 58% yield), mp 129.5-130.4 ^oC. ESI-MS: *m/z* 282.3 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.82 (s, 3H, CH_3), 1.17-1.27 (m, 4H), 1.36 (s, 9H, $C(CH_3)_3$), 1.40-1.43 (m, 2H), 1.48 (s, 2H), 1.63-1.66 (d, J = 15 Hz, 4H) , 2.10 (s, 1H, CH), 4.04 (s, 1H, OH), 8.39 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.8, 30.2, 30.5, 33.7, 42.6, 43.9, 47.2, 48.9, 51.7, 53.1, 68.4, 77.3, 154.4. Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29%; H, 9.67%; N, 4.98%. Found: C, 68.41%; H, 9.51%; N, 4.58%.

1-*tert*-Butylcarbamate-3-ethyl-5-hydroxyadamantane (14). Compound **14** was prepared using a similar method to that as described for synthesis of compound **13**. White solid, 56% yield, mp 125.4-125.9 ^oC. ESI-MS: *m/z* 295.4 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, J = 7.5 Hz, 3H, CH_3), 1.11-1.18 (q, J = 7.5 Hz, 2H, CH_2), 1.18-1.22 (d, J =12 Hz, 4H), 1.36 (s, 9H, $C(CH_3)_3$), 1.42-1.46 (m, 4H), 1.64-67 (d, J = 12 Hz, 4H), 2.12 (m, 1H, CH), 4.43 (s, 1H, OH), 6.45 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.7, 28.8, 30.3, 35.3, 36.4, 39.9, 44.3, 45.1, 49.0, 49.3, 53.1, 68.4, 154.4. Anal. Calcd for $C_{17}H_{29}NO_3$: C, 69.12%; H, 9.89%; N 4.74%. Found: C, 69.33%; H, 9.56%; N, 4.76%.

1-*tert*-Butylcarbamate-3-propyl-5-hydroxyadamantane (15). Compound **15** was prepared using a similar method to that as described for synthesis of compound **13**. White solid, 53% yield. ^1H NMR (300 MHz, DMSO-d_6) δ 0.82-0.87 (t, J = 7.5 Hz, 3H, CH_3), 1.05-1.10 (m, 2H), 1.14-1.24 (m, 6H), 1.36 (s , 9H, $C(CH_3)_3$), 1.42-1.44 (m, 2H), 1.48 (s, 2H), 1.60-1.71 (dd, J = 21 Hz, 9 Hz, 4H), 2.11 (s, 1H, CH), 4.44 (s, 1H, OH), 6.44 (s, 1H, NH). ^{13}C NMR

(75 MHz, DMSO-d_6) δ 15.4, 16.1, 28.8, 30.4, 36.5, 40.4, 44.2, 45.5, 45.8, 49.2, 49.6, 53.0, 68.4, 77.5, 154.4. HRMS-ESI: Calcd for $C_{18}H_{31}NO_3$: 310.2377 $[M + H]^+$; found, 310.2375.

1-*tert*-Butylcarbamate-3-methyl-5-nitrateadamantane (16). To compound **13** (1.41 g, 5 mmol) in 30 mL anhydrous CH_2Cl_2 at 0 ^oC was added acetyl nitrate (fuming HNO_3 2 mL, acetic anhydrous 3 mL). The reaction mixture was stirred at 0 ^oC until the reaction was completed monitored by TLC detection. The solution was pour into 30 mL of ice-water and extracted with ethyl acetate (20 mL × 3). The combined organic solution was washed with aqueous sodium bicarbonate solution (1 N, 50 mL), water and brine, and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo. The resulting residue was purified by column chromatography (petroleum ether: ethyl acetate = 10:1) to afford compound **19** as colorless oil (1.1 g, 67.5% yield). ESI-MS: *m/z* 327.2 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 3 H, CH_3), 1.28-1.35 (m, 2H), 1.37 (s, 9H, $C(CH_3)_3$), 1.49-1.53 (d, J = 12 Hz, 1H), 1.63-1.71 (d, J = 12 Hz, 2H), 1.79-1.83 (d, J = 12 Hz, 1H), 1.89-1.99 (m, 2H), 2.20 (s, 2H), 2.28-2.32 (m, 1H, CH), 6.75 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.7, 29.6, 30.5, 34.4, 37.8, 41.7, 42.5, 45.1, 53.1, 91.8, 154.5.

1-*tert*-Butylcarbamate-3-ethyl-5-nitrateadamantane (17). Compound **17** was prepared using a similar method to that as described for synthesis of compound **16**. Colorless oil, 71% yield. ESI-MS: *m/z* 340 $[M]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.76-0.81 (t, J = 7.5 Hz, 3H, CH_3), 1.19-1.27 (q, J = 7.5 Hz, 2H, CH_2), 1.32 (m, 2H), 1.37 (s, 9H, $C(CH_3)_3$), 1.47-1.51 (d, J = 12 Hz,1H), 1.58-1.77(dd, J = 33 Hz, 12 Hz, 2H), 1.73 (s, 2H), 1.80-1.84 (d, J = 12 Hz, 1H), 1.91-2.01 (m, 2H), 2.19-2.26 (m, 2H), 2.31-2.33 (m, 1H), 6.73 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.4, 28.7, 30.3, 34.9, 37.2, 38.2, 39.8, 42.8, 44.6, 53.3, 92.1, 154.5. Anal. Calcd for $C_{17}H_{28}N_2O_5$: C, 59.98%; H, 8.29%; N, 8.23%. Found: C, 59.98%; H, 8.25%; N, 8.22%.

1-*tert*-Butylcarbamate-3-propyl-5-nitrateadamantane (18). Compound **18** was prepared

using a similar method to that as described for synthesis of compound **16**. Colorless oil, 78.7% yield. ESI-MS: *m/z* 377.2 $[M + Na]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.81-0.92 (m, 3H), 1.11-1.45 (m, 15H), 1.52 (dd, *J* = 16.9, 9.8 Hz, 1H), 1.60-1.87 (m, 5H), 1.95 (t, *J* = 12.3 Hz, 2H), 2.21 (s, 2H), 2.31 (s, 1H), 6.72 (s, 1H). ^{13}C NMR (75 MHz, DMSO) δ 15.2, 16.0, 28.7, 30.3, 37.2, 38.2, 42.9, 43.3, 45.2, 53.3, 71.6, 92.0, 143.5. HRMS-ESI: Calcd for $C_{18}H_{30}N_2O_5$: 355.2227 $[M + H]^+$; found 355.2229.

1-Amino-3-methyl-5-nitrateadamantane hydrochloride (MN-01). To compound **16** (650 mg, 2 mmol) in ether (1 mL) was added 5 mL of HCl saturated ethyl acetate. The mixture was stirred at room temperature and the reaction was monitored by TLC detection until compound **16** was completely converted. The mixture was filtered and the resulting solid was washed with ether to afford compound **MN-01** as a white solid (340 mg, 65.1% yield). ESI-MS: *m/z* 226.2 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.96 (s, 3H, CH_3), 1.30-1.45 (dd, *J* = 33 Hz, 12 Hz, 2H), 1.53-1.63 (dd, *J* = 18 Hz, 6 Hz,2H), 1.68-1.83 (m, 4H), 1.91-2.01 (m, 2H), 2.18-2.27 (dd, *J* = 18 Hz, 6 Hz, 2H), 2.37-2.44 (m, 1H, CH), 8.45 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.1, 30.1, 34.5, 37.3, 38.1, 41.0, 41.6, 44.5, 45.6, 53.9, 90.3. Anal. Calcd for $C_{11}H_{19}N_2O_3Cl{\cdot}0.2\ H_2O$: C, 49.61%; H, 7.34%; N, 10.52%. Found: C, 49.31%; H, 7.16%; N, 10.41%.

1-Amino-3-ethyl-5-nitrateadamantane hydrochloride (MN-02). Compound **MN-02** was prepared using a similar method to that as described for synthesis of compound **MN-01**. White solid, 60% yield. ESI-MS: *m/*z 241 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.77-0.82 (t, *J* = 7.5 Hz, 3H, CH_3), 1.25-1.32 (q, *J* = 7.5 Hz, 2H, CH_2), 1.29-1.44 (dd, *J* = 33 Hz, 12 Hz, 2H), 1.53-1.62 (m, 2H), 1.70-1.83 (m, 4H), 1.94-2.03 (m, 2H), 2.20-2.30 (dd, *J* = 18 Hz, 6 Hz, 2H), 2.43 (m, 1H, CH), 8.52 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.5, 30.0, 34.4, 37.4, 37.6, 38.4, 41.9, 42.3, 43.2, 54.0, 90.5. Anal. Calcd for $C_{12}H_{21}N_2O_3Cl{\cdot}0.3\ H_2O$: C, 51.08%; H, 7.72%; N, 9.93%. Found: C, 50.99%; H, 7.68%; N,

9.92%.

1-Amino-3-propyl-5-nitrateadamantane hydrochloride (MN-03). Compound **MN-03** was prepared using a similar method to that as described for synthesis of compound **MN-01**. White solid, 56.9% yield. ESI-MS: *m/*z 255.1 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, J = 5 Hz, 3H, CH_3), 1.21 (s, 4H), 1.37 (dd, J = 45 Hz, 15 Hz, 2H), 1.52-1.65 (m, 2H), 1.70-1.82 (q, J = 12 Hz, 2H), 1.93-2.01 (m, 2H), 2.20-2,29 (dd, J = 18 Hz, 6 Hz, 2H), 2.41 (m, 1H, CH), 8.56 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.1, 16.0, 30.0, 37.3, 38.4, 38.9, 41.8, 42.7, 43.6, 44.6, 53.9, 90.4. Anal. Calcd for $C_{13}H_{23}N_2O_3Cl{\cdot}0.2\ H_2O$: C, 53.04%; H, 8.01%; N, 9.52%. Found: C, 53.12%; H, 8.03%; N, 9.60%.

3-Methyl-1-adamantanol (19). To compound **1 (**4.5 g, 30 mmol) in a round bottom flask was added Br_2 (20 mL). The mixture was refluxed at 60 ^{o}C for 4 h and then cooled to room temperature. Sodium oxalate (24 g, 180 mmol) and water (40 mL) were added sequentially. The mixture was refluxed at 75 ^{o}C for 1.5 h. The mixture was poured into ice-water and Na_2SO_3 was added to remove the redundant Br_2. The mixture was filtered by vacuum filtration. The resulting solid was washed with water and dried to afford compound **19** without further purification (4.48 g, 90%). mp 129.6-130.2 ^{o}C. ESI-MS: *m/*z 166 $[M]^+$. The ^{1}H NMR and ^{13}C NMR of compounds 1**9** were accordance with those reported in literature.[3] Compound **19** was used directly in the next step without further purification.

3-Ethyl-1-adamantanol (20). Compound **20** was prepared using a similar method to that as described for synthesis of compound **19**. White solid, 85% yield, mp 65.5-66.1 ^{o}C, ESI-MS: *m/*z 180 $[M]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, 3H, J = 7.5 Hz, CH_3), 1.08-1.15 (q, 2H, J=7.5 Hz, CH_2), 1.28 (m, 6H), 1.46-1.56 (m, 6H), 2.05-2.09 (m, 2H, 2 × CH), 4.31 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.5, 30.6, 35.8, 36.0, 40.9, 45.3, 49.9, 67.3, 118.2.

3-Propyl-1-adamantanol (21). Compound **21** was prepared using a similar method to that as

described for synthesis of compound **19**. White solid, 83% yield, mp 67.7-69.3 °C. ^{1}H NMR (300 MHz, DMSO) δ 0.84 (t, *J* = 7.1 Hz, 3H), 0.97-1.12 (m, 2H), 1.11-1.37 (m, 8H), 1.38-1.63 (m, 6H), 2.06 (s, 2H), 4.31 (s, 1H). ^{13}C NMR (75 MHz, DMSO) δ 15.4, 15.9, 30.6, 35.9, 36.0, 41.4, 45.3, 46.5, 50.5, 67.3.

3-Methyl-1-adamantanecarboxylic acid (22). Concentrated H_2SO_4 (20 mL) was pre-cooled to 0-10 °C. Compound **19** (5 g, 30 mmol) dissolved in formic acid (7.6 mL, 200 mmol) was added into concentrated H_2SO_4 dropwise. The mixture was poured into 100 mL of ice-water after stirred for 4 h in an ice bath. The precipitate was filtered by vacuum filtration and washed with water. The solid was dissolved in aqueous NaOH solution and filtered. The aqueous layers were acidified with HCl solution to pH 2. The mixture was vacuum filtered and the resulting solid was washed with water and then dried to afford compound **22** as a white solid without further purification (4.9 g, 85% yield). mp 99.5-101.0 °C. ESI-MS: *m/z* 193.2 ([M-H]$^{-}$). The ^{1}H NMR and ^{13}C NMR data were in accordance with those reported in literature.[4]

3-Ethyl-1-adamantanecarboxylic acid (23). Compound **23** was synthesized using a similar method to that as described for synthesis of compound **22**. White solid, 77% yield, mp 104.5-105.3 °C. ESI-MS: *m/z* 207 [M - H]$^{-}$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.76 (t, *J* = 7.5 Hz, 3H, CH_3), 1.11 (q, *J* = 7.5 Hz, 2H, CH_2), 1.31-1.44 (m, 4H), 1.47 (s, 2H), 1.51-1.64 (m, 2H), 1.66-1.81(m, 4H), 2.01 (m, 2H), 11.99 (s, 1H, COOH).

3-Propyl-1-adamantanecarboxylic acid (24). Compound **24** was synthesized using a similar method to that as described for synthesis of compound **22**. White solid, 85.5% yield, mp 121.2-123.4 °C. ESI-MS: *m/z* 245.1 [M + Na]$^{+}$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82-0.87 (t, *J* = 7.5 Hz, 3H, CH_3), 1.02-1.07 (m, 2H), 1.13-1.29 (m, 2H, CH_2), 1.35-1.44 (m, 4H), 1.44 (s, 2H), 1.52-1.62 (m, 2H), 1.65-1.76 (dd, *J* = 18 Hz, 9 Hz, 4H), 2.00 (s, 2H, 2×CH), 11.99 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4, 15.7, 28.4, 32.6, 36.1, 38.6, 40.8, 41.4,

43.8, 46.7, 178.9.

3-Acetamido-5-methyladamantane-1-carboxylic acid (25). To a flask equipped with a condenser was added compound **22** (5 g, 26 mmol) and concentrated HNO_3 (3.9 mL). Concentrated H_2SO_4 (19 mL) was added in the suspension cooled at an ice bath dropwise. After the addition of concentrated H_2SO_4, acetonitrile (1.7 mL, 31 mmol) was added and the temperature was kept below 10 ^oC. The mixture was stirred for 1 h and was then poured into 100 mL of ice-water. The mixture was stirred overnight and vacuum filtered. The resulting solid was washed with water and dried to afford compound **25** as a white solid (4.53 g, 70% yield), mp >250 ^oC. ESI-MS: *m/z* 252.4 $[M + H]^+$. The ^1H NMR and ^{13}C NMR data were in accordance with those reported in literature.[4]

3-Acetamido-5-ethyl-1-adamantanecarboxylic acid (26). Compound **26** was prepared using a similar to that as described for synthesis of compound **25**. White solid, 73% yield, mp >250 ^oC. ESI-MS: *m/z* 266 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.74-0.79 (t, J = 7.5 Hz, 3H, CH_3), 1.12-1.19 (q, J = 7.5 Hz, 2H, CH_2), 1.26-1.35 (m, 2H), 1.36-1.47 (m, 2H), 1.52-1.70 (m, 4H), 1.74 (s, 3H, $COCH_3$), 1.73-1.85 (q, J = 12 Hz, 2H), 1.88-1.98(m, 2H,), 2.13 (m, 1H, CH), 7.43 (s, 1H, NH), 9.65 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.4, 24.2, 29.2, 34.4, 35.6, 42.3, 42.4, 44.9, 52.1, 169.2, 178.2.

3-Acetamido-5-propyl-1-adamantanecarboxylic acid (27). Compound **27** was prepared using a similar to that as described for synthesis of compound **25**. White solid, 82.8 % yield, mp 193.0-195.5 ^oC. ESI-MS: *m/z* 280.1 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.82-0.87 (t, J = 7.5 Hz, 3H, CH_3), 1.06-1.11 (m, 2H, CH_2), 1.15-1.26 (m, 2H), 1.28-1.37 (m, 2H, CH_2), 1.44 (s, 2H, CH_2), 1.51-1.64 (m, 4H), 1.74 (s, 3H, $COCH_3$), 1.73-1.85 (dd, J = 33 Hz, 12 Hz, 2H), 1.88-1.97 (m, 2H), 2.12 (s, 1H, CH), 7.42 (s, 1H, NH), 12.11 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4, 15.9, 24.2, 29.3, 34.5, 37.9, 42.3, 43.1, 45.4, 46.0, 52.1, 169.2, 178.2.

1-Acetamido-3-methyl-5-hydroxymethyladamantane (28). To compound **25** (2.5 g, 10 mmol) in THF at 0 °C was added TEA (2.1 mL, 15 mmol) and ethyl chloroformate (1.4 mL, 15 mmol). The mixture was stirred at room temperature for 4 h. The mixture was vacuum filtered and the residue was washed with THF. To the filtrate was added $NaBH_4$ (760 mg, 20 mmol). Water (2 mL) was added dropwise over 1 h and then another 50 mL of water was added. The organic solvent was removed in vacuo and the aqueous solution was extracted with ethyl acetate (30 mL × 4). The extraction was washed with HCl (0.5 N), water and brine and then dried over Na_2SO_4. Solvent was removed in vacuo. The resulting residue was purified by column chromatography (petroleum ether: ethyl acetate = 1:1) to afford compound **28** as a white solid (1.55 g, 65.2% yield), mp 143.7-144.3 °C. ESI-MS: *m/z* 238.4 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.81 (s, 3H, CH_3), 1.09 (s, 2H), 1.22-1.34 (q, J = 12 Hz, 4H), 1.52-1.62 (m, 4H), 1.73 (s, 3H, $COCH_3$), 1.75 (s, 2H), 2.07 (m, 1H), 3.02 (d, J = 6 Hz, 2H, CH_2O), 4.36 (t, J = 6 Hz, 1H, OH), 7.31 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.2, 29.6, 30.8, 31.9, 37.4, 37.9, 40.5, 42.7, 43.3, 45.6, 48.0, 52.5, 71.4, 169.1. Anal. Calcd for $C_{14}H_{23}NO_2$: C 70.85%, H 9.71%, N 5.90%. Found: C, 71.17%; H, 9.71%; N, 5.90%.

1-Acetamido-3-ethyl-5-hydroxymethyladamantane (29). Compound **29** was synthesized using a similar method to that as described for synthesis of compound **28**. White solid, 60% yield, mp 149.8-150.5 °C. ESI-MS: m/z 252.2 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, J = 7.5 Hz, 3H, CH_3), 1.08-1.17 (m, 4H, CH_2), 1.24-1.34 (q, J = 12 Hz, 4H), 1.55-1.59 (m, 4H), 1.73 (s, 3H, $COCH_3$), 1.77 (s, 2H), 2.09 (m, 1H, CH), 3.01-3.03 (d, J = 6 Hz, 2H, CH_2O), 4.36-4.40 (t, J = 6 Hz, 1H, OH), 7.33 (s, 1 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.6, 24.2, 29.4, 34.5, 35.9, 37.2, 38.2, 40.8, 40.9, 43.0, 45.6, 52.5, 71.5, 169.0. Anal. Calcd for $C_{15}H_{25}NO_2 \cdot 0.1\ H_2O$: C, 71.16%; H, 10.03%; N, 5.53%. Found: C, 70.90%; H, 9.90%; N, 5.80%.

1-Acetamido-3-propyl-5-hydroxymethyladamantane (30). Compound **30** was synthesized

using a similar method to that as described for synthesis of compound **28**. White solid, 74% yield, mp 160-162 ^{o}C. ESI-MS: *m/z* 266.2 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82-0.87 (t, J = 7.5 Hz, 3H, CH_3), 1.04-1.09 (m, 4H), 1.18-1.34 (m, 6H), 1.53-1.62 (m, 4H), 1.73 (s, 3H, $COCH_3$), 1.76 (m, *2*H), 2.08 (m, 1H, CH), 3.01-3.03 (d, J = 6 Hz, 2H, CH_2O), 4.35-4.39 (t, J = 6 Hz, 1H, OH), 7.32 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4, 16.0, 24.2, 29.5, 34.6, 38.2, 41.3, 43.0, 43.6, 46.1, 46.4, 52.5, 71.5, 169.0. HRMS-ESI: Calcd for $C_{16}H_{27}NO_2$: 266.2115 $[M + H]^+$; found 266.2119.

1-*tert*-Butylcarbamate-3-methyl-5-hydroxymethyladamantane (31). Compound **31** was synthesized using a similar method to that as described for synthesis of compound **13** from compound **10**. Colorless oil, 64% yield. ESI-MS: *m/z* 296.6 $[M + H]^+$. The ^{1}H NMR was in accordance with those reported in literature.[5]

1-*tert*-Butylcarbamate-3-ethyl-5-hydroxymethyladamantane (32). Compound **32** was synthesized using a similar method to that as described for synthesis of compound **13** from compound **10**. White solid, 68% yield, mp 125.4-125.9 ^{o}C. ESI-MS: *m/z* 310.3 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.73-0.78 (t, J = 7.5 Hz, 3H, CH_3), 1.06 (s, 2H), 1.09-1.17 (q, J = 9 Hz, 2H, CH_2), 1.20-1.26 (m, 4H), 1.36 (s, 9H, $C(CH_3)_3$), 1.42-1.57 (m, 4H), 1.62-1.74 (q, J = 12 Hz, 2H), 2.08 (m, 1H), 3.01-3.03 (d, J = 6 Hz, 2H, CH_2O), 4.37-4.40 (t, J = 6 Hz, 1H, OH), 6.36 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.6, 28.8, 29.4, 34.5, 35.8, 37.9, 38.2, 41.2, 43.0, 45.8, 51.6, 71.5, 77.5, 154.4. Anal. Calcd for $C_{18}H_{31}NO_3$: C, 69.86%; H, 10.10%; N, 4.53%. Found: C, 70.24%; H, 9.70%; N, 4.39%.

1-*tert*-Butylcarbamate-3-hydroxymethyl-5-propyladamantane (33). Compound **33** was synthesized using a similar method to that as described for synthesis of compound **13** from compound **10**. Colorless oil, 70.8% yield. ESI-MS: m/z 346.2 $[M + Na]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82-0.87 (t, J = 7.5 Hz, 3H, CH_3), 1.03-1.09 (m, 4H), 1.25-1.28 (m, 6H), 1.36 (s, 9H, $C(CH_3)_3$), 1.44-1.57 (m, 4H), 1.62-1.74 (q, J = 12 Hz, 2H), 2.05-2.08 (m, 1H, CH),

3.00-3.02 (d, J = 6 Hz, 2H, CH_2O), 4.35-4.37 (t, J = 6 Hz, 1H, OH), 6.35 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4, 16.0, 28.8, 29.5, 34.6, 37.3, 38.2, 41.1, 41.3, 43.5, 46.2, 46.4, 51.5, 71.5, 77.5, 154.4. HRMS-ESI: Calcd for $C_{19}H_{33}NO_3$: 324.2533 $[M + H]^+$; found 324.2536.

1-*tert*-Butylcarbamate-3-methyl-5-nitratemethyladamantane (34). Compound **34** was prepared using a similar method to that as described for synthesis of compound **16** from compound **13**. Colorless oil, 62.9% yield. ESI-MS: *m/z* 340.2 $[M]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 3H, CH_3), 1.15-1.24 (m, 2H), 1.30 (s, 2H), 1.36 (s, 9H, $C(CH_3)_3$), 1.43-1.47 (d, J = 12 Hz, 1H), 1.59-1.66 (m, 4H), 1.74-1.77 (d, J = 12 Hz, 1H), 2.06-2.14 (m, 1H, CH), 4.22 (s, 2H, CH_2O), 6.51 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.8, 29.2, 30.5, 31.8, 35.9, 37.2, 42.8, 44.7, 51.1, 82.6, 161.8. Anal. Calcd for $C_{18}H_{30}N_2O_3$: C, 59.98%; H, 8.29%; N 8.23%. Found: C, 60.13%; H, 8.12%; N, 8.25%.

1-*tert*-Butylcarbamate-3-ethyl-5-nitratemethyladamantane (35). Compound **35** was prepared using a similar method to that as described for synthesis of compound **16** from compound **13**. Colorless oil, 73.4% yield. ESI-MS: *m/z* 377.2 $[M + Na]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, J = 7.5 Hz, 3H, CH_3), 1.11-1.18 (m, 4H), 1.29 (m, 2 H), 1.36 (s, 9H, $C(CH_3)_3$), 1.41 (m, 2H), 1.42-1.86 (d, J = 12 Hz, 1H), 1.56-1.67 (m, 4H), 1.75-1.79 (d, J = 12 Hz, 1H), 2.12 (m, 1H), 4.23 (s, 2H, CH_2O), 6.50 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.5, 28.8, 28.0, 34.4, 35.5, 35.7, 37.5, 40.1, 40.7, 42.3, 45.3, 51.1, 77.7, 81.7, 154.4. Anal. Calcd for $C_{18}H_{30}N_2O_3$: C, 61.00%; H, 8.53%; N, 7.90%. Found: C, 61.02%; H, 8.44%; N, 7.92%.

1-*tert*-Butylcarbamate-3-nitratemethyl-5-propyladamantane (36). Compound **36** was prepared using a similar method to that as described for synthesis of compound **16** from compound **13**. Colorless oil, 74.1 % yield. ESI-MS: *m/z* 391.2 $[M + Na]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.82-0.87 (t, J = 7.5 Hz, 3H, CH_3), 1.05-1.10 (m, 2H), 1.18-1.23 (m, 4H),

1.31-1.39 (m, 4H), 1.36 (s, 9H, $C(CH_3)_3$), 1.44-1.48 (d, J = 12 Hz, 1 H), 1.58-1.71 (m, 4H), 1.75-1.79 (d, J = 12 Hz, 1H), 2.11-2.20 (m, 1H, CH), 4.20-4.25 (m, 2H, CH_2O), 6.50 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.3, 15.9, 28.7, 29.1, 34.5, 35.7, 37.5, 40.7, 42.2, 42.8, 45.7, 46.0, 51.0, 77.6, 81.7, 154.4. HRMS-ESI: Calcd for $C_{19}H_{32}N_2O_5$: 369.2384 [M + H]$^+$; found 369.2387.

1-Amino-3-methyl-5-nitratemathyladamantane hydrochloride (MN-04). Compound **MN-04** was synthesized using a similar method to that as described for synthesis of compound **MN-01** from compound **16**. White solid, 70.7% yield. ESI-MS: *m/z* 341.0 [M + H]$^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 0.88 (s, 3H, CH_3), 1.20-1.30 (dd, J = 12 Hz, 4 Hz, 2H), 1.34 (s, 2H), 1.42-1.43 (d, J = 2 Hz, 2H), 1.48-1.50 (d, J = 4 Hz, 2H), 1.54-1.64 (dd, J = 12 Hz, 4 Hz, 2H), 1.68-1.69 (d, J = 2 Hz, 2H), 2.18-2.24(m, 1H, CH), 4.29 (s, 2H, CH_2), 8.11 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.8, 29.9, 30.9, 31.9, 35.9, 36.5, 43.9, 46.5, 52.1, 80.8. Anal. Calcd for $C_{12}H_{21}N_2O_3Cl{\cdot}0.1\ H_2O$: C, 51.74%; H, 7.67%; N, 10.06%. Found: C, 51.44%; H, 7.46%; N, 9.98%.

1-Amino-3-ethyl-5-nitratemethyladamantane hydrochloride (MN-05). Compound **MN-05** was synthesized using a similar method to that as described for synthesis of compound **MN-01** from compound **16**. White solid, 65.5% yield. ESI-MS: *m/z* 255.1 [M + H]$^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.75-0.80 (t, J = 7.5 Hz, 3H, CH_3), 1.16-1.24 (q, J = 7.5 Hz, 2H, CH_2), 1.24-1.25 (m, 2H), 1.30-1.39 (m, 2H), 1.43 (s, 2H), 1.45-1.57 (dd, J = 12 Hz, 6 Hz, 2H), 1.57-1.63 (dd, J = 12 Hz, 6 Hz, 2H), 1.71 (s, 2H), 2.23 (m, 1H, CH), 4.30 (s, 2H, CH_2O), 8.21 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.4, 28.6, 34.5, 35.0, 36.8, 40.3, 41.6, 43.9, 52.3, 80.9. Anal. Calcd for $C_{13}H_{23}N_2O_3Cl{\cdot}0.3\ H_2O$: C, 52.72%; H, 8.03%; N, 9.46%. Found: C, 52.72%; H, 7.92%; N, 9.51%.

1-Amino-3-nitratemathyl-5-propyladamantane hydrochloride (MN-06). Compound **MN-06** was synthesized using a similar method to that as described for synthesis of compound

MN-01 from compound **16**. White solid, 78.7% yield, mp 209-211 °C. ESI-MS: m/z 269.1 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.84-0.88 (t, J = 6 Hz, 3H, CH_2), 1.14-1.20 (m, 4H), 1.24-1.26 (d, J = 6 Hz, 2H), 1.34 (s, 2H), 1.43 (s, 2H), 1.50-1.52 (d, J = 6 Hz, 2H), 1.61-1.63 (d, J = 6 Hz, 2H), 1.71 (s, 2H), 2.21 (s, 1H, CH), 4.28 (s, 2H, CH_2O), 8.31 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.2, 15.8, 28.6, 34.6, 35.7, 36.7, 41.2, 42.1, 44.3, 45.4, 52.3, 80.9. Anal. Calcd for $C_{14}H_{25}N_2O_3Cl \cdot 0.2\ H_2O$: C, 54.52%; H, 8.30%; N, 9.08%. Found: C, 54.62%; H, 8.78%; N, 9.01%.

Ethyl 3-(3-methyladamantane-1-yl)-propionate (37). To compound **4** (4.58 g, 20.0 mmol) in anhydrous toluene (45 mL) was added azodiisobutyronitrile (AIBN, 300 mg, 2 mmol), n-Bu_3SnH (7.0 g, 24 mmol) and ethyl acrylate (3 g, 30 mmol). The reaction mixture was refluxed for 2 h under N_2 atmosphere. The mixture was cooled to room temperature and was then poured into ammonia water (0.2 M, 105 mL). The mixture was extracted with ethyl acetate (30 mL × 4). The combined organic solution was washed with water and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo. The resulting residue was purified by column chromatography (petroleum ether:ethyl acetate = 20:1) to afford compound **37** as colorless oil (1.8 g, 36.0% yield). ESI-MS: m/z 251.1 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.77 (s, 3H, CH_3), 1.12 (s, 2H), 1.15-1.19 (t, J = 6 Hz, 3H, CH_3), 1.27-1.40 (m, 10H), 1.52 (s, 2H), 1.95 (m, 2H, 2 × CH), 2.18-2.23 (d, J = 15 Hz, 1H, CHHCOO), 2.19-2.22 (m, 1H, CHHCOO), 4.00-4.07 (q, J = 7.1 Hz, 2H, CH_2OCO). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.5, 28.1, 29.0, 30.5, 31.3, 32.8, 36.2, 38.7, 41.1, 44.0, 49.0, 60.1, 173.9. HRMS-ESI: Calcd for $C_{16}H_{26}O_2$: 251.2006 $[M + H]^+$; found 251.2009.

Ethyl 3-(3-ethyladamantane-1-yl)-propionate (38). Compound **38** was synthesized using a similar method to that as described for synthesis of compound **37**. Colorless oil, 62.8% yield. ESI-MS: *m/z* 287.0 $[M + Na]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.72-0.77 (t, J = 7.5 Hz, 3H, CH_3), 1.03-1.13 (q, J = 7.5 Hz, 2H, CH_2), 1.14 (m, 2H), 1.15-1.19 (t, J = 6 Hz, 3H, CH_3),

1.28-1.40 (m, 10 H), 1.53 (s, 2H), 1.97(m, 2H, 2 × CH), 2.18-2.24 (t, J = 8.1 Hz, 2H, CH_2COO), 4.00-4.07 (q, J = 6 Hz, 2H, CH_2OCO). HRMS-ESI: Calcd for $C_{11}H_{28}O_2$: 265.2162 $[M + H]^+$; found, 265.2154.

Ethyl 3-(3-propyladamantane-1-yl)-propionate (39). Compound **39** was synthesized using a similar method to that as described for synthesis of compound **37**. Colorless oil, 69.1% yield. ESI-MS: *m/z* 279.2 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, J = 7.2 Hz, 3H, CH_3), 0.95-1.06 (m, 2H, CH_2), 1.09-1.25 (m, 7H), 1.27-1.44 (m, 10H), 1.53 (s, 2H), 1.96 (s, 2H, 2 × CH), 2.11-2.29 (m, 2H, CH_2COO), 4.03 (q, J = 7.1 Hz, 2H, CH_2OCO). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.5, 15.4, 15.7, 28.1, 28.9, 32.7, 33.0, 36.6, 38.8, 41.5, 41.9, 47.0, 60.2, 174.0. HRMS-ESI: Calcd for $C_{18}H_{30}O_2$: 279.2319 $[M + H]^+$; found, 279.2321.

Ethyl 3-(3-ethyladamantane-1-yl)-isobutyrate (40). Compound **40** was synthesized using a similar method to that as described for synthesis of compound **37**, just instead the ethyl acrylate with ethyl methacrylate. Colorless oil, 43.2% yield. ESI-MS: *m/z* 279.1 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.71-0.76 (t, J = 7.5 Hz, 3H, CH_3), 1.03-1.09 (m, 8H), 1.15-1.25 (t, J = 7.5 Hz, 3H, CH_3), 1.25-1.42 (m, 8H), 1.52 (s, 2H), 1.58-1.66 (dd, J = 15 Hz, 6 Hz, 1H), 1.96 (s, 2H, 2 × CH), 2.41-2.48 (m, 1H, CH), 4.04 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.3, 14.5, 20.7, 28.8, 32.8, 33.3, 34.2, 36.5, 41.2, 41.3, 41.8, 42.0, 46.6, 48.3, 60.1, 177.3. HRMS-ESI: Calcd for $C_{18}H_{30}O_2$: 279.2319 $[M + H]^+$; found, 279.2324.

3-(3-Methyladamantane-1-yl)-propionic acid (41). To compound **37** (1.4 g, 6 mmol) in a solution of methanol (30 mL) and water (3 mL) was added KOH (3.4 g, 60 mmol). The reaction mixture was stirred for 12 h at room temperature. The solvent was removed in vacuo. The residue was diluted with water (50 mL) and washed with ethyl acetate (20 mL × 3). The aqueous phase was cooled to 0 °C and was acidified to pH 1 with 10% aqueous HCl. The mixture was extracted with ethyl acetate (50 mL × 4). The combined organic solution was washed with brine, water and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo

to afford compound **41** as a white solid without further purification (0.9 g, 72.6 % yield), mp 72.7-73.9 ^{o}C. ESI-MS: *m/z* 245.1 $[M + Na]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77 (s, 3H, CH_3), 1.12 (s, 2H), 1.29-1.40 (m, 10H), 1.52 (m, 2H), 1.95-1.97 (m, 2H, 2 × CH), 2.18-2.23 (d, *J* = 15 Hz, 1H, CHHCOO), 2.19-2.22 (m, 1H, CHHCOO), 11.96 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.1, 29.0, 30.5, 31.4, 32.8, 36.2, 38.8, 41.2, 44.0, 49.0, 175.6.

3-(3-Ethyladamantane-1-yl)-propionic acid (42). Compound **42** was synthesized using a similar method to that as described for synthesis of compound **41**. White solid, 87% yield,. ESI-MS: *m/z* 237.1 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, *J* = 7.5 Hz, 3H, CH_3), 1.04-1.10 (q, *J* = 7.5 Hz, 2H, CH_2), 1.10 (m, 2H), 1.28-1.40 (m, 10H), 1.54 (s, 2H), 1.97(s, 2H, 2 × CH), 2.12-2.16 (m, 2H, CH_2COO), 11.8 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.4, 28.1, 28.9, 32.6, 32.9, 36.4, 36.6, 38.9, 41.4, 41.6, 46.5, 175.6.

3-(3-Propyladamantane-1-yl)-propionic acid (43). Compound **43** was synthesized using a similar method to that as described for ynthesis of compound **41**. White solid, 89.7% yield, mp 63.3-65.2 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, *J* = 7.2 Hz, 3H, CH_3), 0.95-1.07 (m, 2H), 1.12 (s, 2H), 1.15-1.46 (m, 12H), 1.53 (s, 2H), 1.98 (m, 2H, 2 × CH), 2.05-2.23 (m, 2H, CH_2COO), 11.96 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4, 15.7, 28.1, 28.9, 32.6, 33.0, 36.6, 38.9, 41.6, 41.9, 47.0, 175.6. HRMS-ESI: Calcd for $C_{16}H_{26}O_2$: 251.2006 $[M + H]^+$; found, 251.2008.

3-(3-Ethyl-admantane-1-yl)-isobutyric acid (44). Compound **44** was synthesized using a similar method to that as described for synthesis of compound **41**. Colorless oil, 93.5% yield. ESI-MS: *m/z* 251.2 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.72-0.77 (t, *J* = 7.5 Hz, 3H, CH_3), 0.94 -1.00 (dd, *J* = 12 Hz, 3 Hz, 1H), 1.03-1.08 (m, 5H), 1.06-1.16 (dd, *J* = 18 Hz, 6 Hz, 2 H), 1.26-1.44 (m, 8H), 1.52 (s, 2H), 1.60-1.68 (dd, *J* = 15 Hz, 6 Hz, 1H), 1.95 (m, 2H, 2 × CH), 2.35-2.41 (m, 1H, CH), 11.99 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.3, 20.9, 28.8, 32.9, 34.4, 36.4, 36.6, 41.3, 41.4, 41.9, 46.8, 48.2, 179.1. HRMS-ESI: Calcd for

$C_{16}H_{26}O_2$: 251.2006 $[M + H]^+$; found, 251.2005.

3-(3-Acetamide-5-methyl-adamantane-1-yl)-propanic acid (45). Compound **45** was synthesized using a similar method to that as described for synthesis of compound **25** from compound **22**. Colorless oil, 45% yield. ESI-MS: m/z 280.2 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 3H, CH_3), 1.08 (s, 2H), 1.17-1.28 (m, 4H), 1.33-1.39 (t, J = 9 Hz, 2H), 1.50-1.56 (m, 4H), 1.73 (s, 5H, CH_2, $COCH_3$), 2.06 (m, 1H, CH), 2.10-2.15 (t, J = 9 Hz, 2H, CH_2COO), 7.34 (s, 1H, NH), 11.88 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.2, 28.3, 29.7, 30.6, 32.1, 34.5, 38.1, 43.0, 45.0, 47.7, 48.1, 52.5, 169.1, 175.5. HRMS-ESI: Calcd for $C_{16}H_{25}NO_3$: 280.1907 $[M + H]^+$; found 280.1906.

3-(3-Acetamide-5-ethyl-adamantane-1-yl)-propanic acid (46). Compound **46** was synthesized using a similar method to that as described for synthesis of compound **25** from compound **22**. Colorless oil, 80.6% yield. ESI-MS: m/z 293.38 $[M]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, J = 7.5 Hz, 3H, CH_3), 1.07-1.14 (m,6H), 1.21-1.43 (m, 6H), 1.49-1.61 (m, 4H), 1.73 (s, 3H, $COCH_3$), 1.76 (s, 2H, CH_2), 2.08 (m, 1H,CH), 2.11-2.26 (m, 2H, CH_2), 7.37 (s, 1H, NH), 11.66 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.5, 24.3, 28.0, 28.3, 29.6, 34.4, 34.7, 35.7, 38.2, 45.2, 45.4, 45.6, 52.5, 168.3, 175.5. Anal. Calcd for $C_{17}H_{27}NO_3 \cdot 0.1\ H_2O$: C, 69.17%; H, 9.29%; N, 4.74%. Found: C, 69.18%; H, 9.14%; N, 4.92%.

3-(3-Acetamide-5-propyl-adamantane-1-yl)-propanic acid (47). Compound **47** was synthesized using a similar method to that as described for synthesis of compound **25** from compound **22**. Colorless oil, 65% yield. ESI-MS: *m/z* 308.2 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, J = 7.0 Hz, 3H, CH_3) 0.95-1.14 (m, 4H), 1.28 (m, 8H), 1.46-1.65 (m, 4H), 1.74 (m, 5H), 2.11 (m, 3H), 7.34 (s, 1H, NH), 11.66 (s, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4, 15.9, 24.2, 28.3, 29.6, 34.3, 34.7, 38.2, 41.0, 45.4, 45.8, 46.1, 46.3, 52.5, 169.1, 175.5. HRMS-ESI: Calcd for $C_{18}H_{29}NO_3$: 308.2220 $[M + H]^+$; found 308.2221.

3-(3-Acetamide-5-ethyl-adamantane-1-yl)-isobutyric acid (48). Compound **48** was synthesized using a similar method to that as described for synthesis of compound **25** from compound **22**. Colorless oil, 80.0% yield. ESI-MS: *m/z* 308.1 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.72-0.77 (t, *J* = 7.5 Hz, 3H, CH_3), 0.84-0.86 (d, *J* = 7.5 Hz, 4H), 1.03-1.17 (m, 5H), 1.20-1.37 (m, 4H), 1.49-1.63 (m, 5H), 1.73 (s, 3H, $COCH_3$), 1.76 (s, 2H), 2.07 (s, 1H), 3.01-3.19 (dd, *J* = 42 Hz, 9Hz, 2H), 4.42 (s, 1H, OH), 7.34 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.4, 20.6, 24.2, 29.6, 30.5, 34.6, 35.2, 35.8, 41.6, 41.7, 45.2, 46.1, 46.2, 47.4, 52.6, 68.1, 169.1. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32%; H, 9.51%; N, 4.5%. Found: C, 70.16%; H, 9.35%; N, 4.35%.

1-Acetamide-3-methyl-5-hydroxypropyladamantane (49). Compound **49** was synthesized using a similar method to that as described for synthesis of compound **28** from compound **25**. Colorless oil, 60.2% yield. ^1H NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 3H, CH_3), 0.98-1.14 (m, 4H), 1.15-1.43 (m, 6H), 1.46-1.64 (m, 4H),1.73 (s, 3H, $COCH_3$), 1.75 (s, 2H), 2.01-2.12 (m, 1H, CH), 3.30-3.34 (m, *J* = 6 Hz, 2H, CH_2O), 4.36 (t, *J* = 6 Hz, 1H, OH), 7.32 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.2, 26.4, 29.8, 30.7, 32.1, 34.6, 39.8, 43.5, 45.5, 47.8, 48.7, 52.6, 62.1, 169.5. HRMS-ESI: Calcd for $C_{16}H_{27}NO_2$: 266.2115 $[M + H]^+$; found 266.2113.

1-Acetamide-3-ethyl-5-hydroxypropyladamantane (50). Compound **50** was synthesized using a similar method to that as described for synthesis of compound **28** from compound **25**. Colorless semisolid, 63.8% yield. ESI-MS: *m/z* 280.1 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, *J* = 7.5 Hz, 3H, CH_3), 1.06 (s, 2H), 1.09-1.16 (q, *J* = 7.5 Hz, 2H, CH_2), 1.21-1.32 (dd, *J* = 21 Hz, 9 Hz, 4H), 1.36-1.42 (m, 2H, CH_2), 1.51-1.61 (m, 4H), 1.73 (s, 3H, $COCH_3$), 1.76 (s, 2H, CH_2), 2.08 (m, 1H, CH), 2.21-2.26 (m, 2H, CH_2), 3.58 (s, 3H, CH_2O, OH), 7.35 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.5, 24.2, 28.0, 29.6, 34.3, 34.6, 35.7, 38.2, 45.2, 45.3, 45.5, 51.8, 52.5, 169.1. Anal. Calcd for $C_{17}H_{29}NO_2$: C, 73.07%; H,

10.46%; N, 5.01%. Found: C, 73.25%; H, 10.53%; N, 4.61%.

1-Acetamide-3-hydroxypropyl-5-propyladamantane (51). Compound **51** was synthesized using a similar method to that as described for synthesis of compound **28** from compound **25**. Colorless semisolid, 87.2% yield. ESI-MS: *m/z* 294.2 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, *J* = 7.0 Hz, 3H, CH_3), 0.98-1.14 (m, 6H), 1.16-1.45 (m, 8H), 1.45-1.66 (m, 4H), 1.74 (m, 5H), 2.03 (m, 1H, CH), 3.27-3.36 (m, 2H, CH_2O), 4.36 (t, *J* = 5.2 Hz, 1H, OH), 7.33 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4, 15.9, 24.2, 26.4, 29.7, 34.4, 34.8, 40.6, 41.1, 45.8, 46.3, 46.7, 52.6, 62.1, 169.1. HRMS-ESI: Calcd for $C_{18}H_{31}NO_2$: 294.2428 $[M + H]^+$; found, 294.2434.

1-Acetamide-3-ethyl-5-hydroxy-isobutyladamantane (52). Compound **52** was synthesized using a similar method to that as described for synthesis of compound **28** from compound **25**. Colorless oil, 71.5% yield. ESI-MS: *m/z* 294.2 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.72-0.77 (t, *J* = 7.5 Hz, 3H, CH_3), 0.84-0.86 (d, *J* = 7.5 Hz, 4H), 1.03-1.17 (m, 5H), 1.20-1.37 (m, 4H), 1.49-1.63 (m, 5H), 1.73 (s, 3H, $COCH_3$), 1.76 (s, 2H), 2.07 (s, 1H, CH), 3.01-3.19 (dd, *J* = 42 Hz, 9Hz, 2H), 4.42 (s, 1H, OH), 7.34 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.4, 20.6, 24.2, 29.6, 30.5, 34.6, 35.2, 35.8, 41.6, 41.7, 45.2, 46.1, 46.2, 47.4, 52.6, 68.1, 169.1. Anal. Calcd for $C_{18}H_{31}NO_2$: C, 73.67%; H, 10.65%; N, 4.77%. Found: C, 73.35%; H, 10.53%; N, 4.61%.

1-*tert*-Butylcarbamate-3-methyl-5-hydroxypropyladamantane (53). Compound **53** was synthesized using a similar method to that as described for synthesis of compound **13** from compound **10**. Colorless oil, 82% yield. ESI-MS: *m/z* 346.2 $[M + Na]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 3H, CH_3), 0.95-1.13 (m, 4H), 1.15-1.35 (m, 6H), 1.36 (s, 9H, $C(CH_3)_3$), 1.49 (d, *J* = 3 Hz, 4H),1.67 (s, 2H, CH_2), 2.05 (s, 1H, CH), 3.26-3.48 (m, 2H, CH_2O), 4.35 (t, *J* = 5.2 Hz, 1H, OH), 6.37 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.4, 28.8, 29.8, 30.8, 32.2, 34.6, 39.8, 40.8, 43.2, 45.6, 48.0, 48.7, 51.6, 62.1, 77.4, 154.3. HRMS-ESI: Calcd

for $C_{19}H_{33}NO_3$: 324.2533 $[M + H]^+$; found, 324.2534.

1-*tert*-Butylcarbamate-3-ethyl-5-hydroxypropyladamantane (54). Compound **54** was synthesized using a similar method to that as described for synthesis of compound **13** from compound **10**. Colorless oil, 63% yield. ESI-MS: *m/z* 338.4 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, J = 7.5 Hz, 3H, CH_3), 1.05-1.16 (m, 6H), 1.20-1.36 (m, 4H), 1.33-1.40 (m, 11H), 1.48-1.50 (d, J = 6 Hz, 4H), 2.06-2.08 (m, 1H), 3.31-3.37 (q, J = 6 Hz, 2H, CH_2O), 4.33-4.36 (t, J = 6 Hz, 1H, OH), 6.36 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.6, 26.4, 28.8, 29.7, 34.4, 34.7, 35.8, 37.7, 41.1, 46.1, 51.7, 62.1, 77.6, 155.6. Anal. Calcd for $C_{20}H_{35}NO_3$: C, 71.18%; H, 10.45%; N, 4.15%. Found: C, 71.15%; H, 10.11%; N, 4.00%.

1-*tert*-Butylcarbamate-3-hydroxypropyl-5-propyladamantane (55). Compound **55** was synthesized using a similar method to that as described for synthesis of compound **13** from compound **10**. Colorless oil, 78% yield. ESI-MS: *m/z* 352.3 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, J = 7.0 Hz, 3H, CH_3), 0.95-1.13 (m, 6H), 1.13-1.42 (m, 17H), 1.53 (m, 4H), 1.68 (s, 2H), 2.03 (m, 1H, CH), 3.29-3.34 (m, 2H, , CH_2O), 4.35 (t, J = 5.2 Hz, 1H, OH), 6.34 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4, 15.9, 26.4, 28.8, 29.7, 34.4, 34.8, 41.1, 46.0, 46.4, 46.7, 51.6, 62.1, 77.5, 154.2. HRMS-ESI: Calcd for $C_{21}H_{37}NO_3$: 352.2846 $[M + H]^+$; found, 352.2849.

1-*tert*-Butylcarbamate-3-ethyl-5-hydroxy-isobutyladamantine (56). Compound **56** was synthesized using a similar method to that as described for synthesis of compound **13** from compound **10**. Colorless oil, 56.5% yield. ESI-MS: *m/z* 374.2 $[M + Na]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, J = 7.9 Hz, 3H, CH_3), 0.80-0.82 (d, J = 6.0 Hz, 1H), 0.84-0.86 (d, J = 6.0 Hz, 3H, CH_3), 1.01-1.06 (m, 2H), 1.11-1.13 (m, 2H), 1.16-1.31 (td, J = 24 Hz, 6 Hz, 4H), 1.37 (s, 9H,$C(CH_3)_3$), 1,44-1.56 (m, 5H), 1.68 (s, 2H), 2.07 (m, 1H, CH), 2.98-3.06 (m, 2H), 3.15-3.22 (m, 1H), 4.40-4.44 (t, J = 6 Hz, 1H, OH), 6.34 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.6, 20.5, 28.8, 29.7, 30.6, 34.7, 35.6, 35.8, 40.4, 41.5, 41.7, 45.4, 46.6,

47.4, 51.6, 68.1, 77.4, 154.4. HRMS-ESI: Calcd for $C_{21}H_{37}NO_3$: 352.2846 $[M + H]^+$; found 352.2852.

1-*tert*-Butylcarbamate-3-methyl-5-nitratepropyladamantane (57). Compound **57** was synthesized using a similar method to that as described for synthesis of compound **16** from compound **13**. Colorless oil, 84.2% yield. ESI-MS: m/z 392.2 $[M + Na]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (s, 3H, CH_3), 1.08 (s, 2H), 1.11-1.19 (m, 2H), 1.22-1.26 (m, 4H), 1.32-1.43 (m, 9H), 1.44-1.54 (m, 4H), 1.54-1.65 (m, 2H), 1.65-1.73 (m, 2H), 2.07 (s, 1H), 4.48 (t, J = 6.6 Hz, 2H, CH_2O), 6.36 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.4, 28.8, 29.8, 30.7, 32.1, 34.6, 38.9, 40.0, 40.4, 43.1, 45.3, 47.9, 48.3, 51.6, 75.0, 77.5, 154.4. HRMS-ESI: Calcd for $C_{19}H_{32}N_2O_5$: 369.2384 $[M + H]^+$; found 369.2386.

1-*tert*-Butylcarbamate-3-ethyl-5-nitratepropyladamantane (58). Compound **58** was synthesized using a similar method to that as described for synthesis of compound **16** from compound **13**. Colorless oil, 53.4% yield. ESI-MS: *m/z* 405.2 $[M + Na]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, J = 7.5 Hz, 3H, CH_3), 1.01-1.09 (m, 2H), 1.11-1.18 (m, 4H), 1.23-1.33 (m, 4H), 1.36 (s, 1H), 1.47-1.51 (m, 2H), 1.55-1.65 (m, 2H), 1.68 (s, 2H), 2.08 (m, 1H, CH), 4.46-4.50 (t, J = 6 Hz, 2H, CH_2O), 6.40 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.1, 20.5, 28.5, 29.7, 34.6, 34.9, 35.6, 39.0, 40.2, 41.1, 45.7, 52.0, 74.0, 139.4. HRMS-ESI: Calcd for $C_{20}H_{34}N_2O_5$: 383.2540 $[M + H]^+$; found, 383.2542.

1-*tert*-Butylcarbamate-3-nitratepropyl-5-propyladamantane (59). Compound **59** was synthesized using a similar method to that as described for synthesis of compound **16** from compound **13**. Colorless oil, 77.6% yield. ESI-MS: *m/z* 419.2 $[M + Na]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (q, J = 7.4 Hz, 3H, CH_3), 1.00-1.11 (m, 4H), 1.11-1.33 (m, 8H), 1.34 (s, 9H, $C(CH_3)_3$), 1.51 (s, 4H), 1.60 (m, 2H), 1.69 (s, 2H), 2.03 (m, 1H, CH), 4.48 (t, J = 6.6 Hz, 2H, CH_2O), 6.36 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4, 15.9, 20.4, 28.8, 29.6, 34.4, 34.8, 39.0, 40.8, 41.0, 45.6, 45.9, 46.3, 51.5, 75.0, 77.5, 154.3. HRMS-ESI: Calcd for

$C_{21}H_{36}N_2O_5$: 397.2697 $[M + H]^+$; found, 397.2713.

1-*tert*-Butylcarbamate-3-ethyl-5-nitrate-isobutyladamantane (60). Compound **60** was synthesized using a similar method to that as described for synthesis of compound **16** from compound **13**. Colorless oil, 42.8 % yield. ESI-MS: *m/z* 419.2 $[M + Na]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, J = 7.5 Hz, 3H, CH_3), 0.93-1.01 (m, 4H), 1.07-1.15 (m, 4H), 1.18-1.20 (m, 2H), 1.24-1.30 (m, 4H), 1.36 (s, 9H, $C(CH_3)_3$), 1.44-1.52 (m, 4H), 1.65-1.69 (m, 2H), 1.91-2.01 (m, 1H, CH), 2.08 (m, 1H, CH), 4.20-4.36 (qd, J = 30 Hz, 6 Hz, 2H, CH_2O), 6.37 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.5, 20.1, 25.9, 28.7, 29.6, 34.7, 35.2, 35.7, 41.0, 41.2, 45.4, 46.1, 46.8, 51.5, 77.5, 79.4, 154.3. HRMS-ESI: Calcd for $C_{21}H_{36}N_2O_5$: 397.2697 $[M + H]^+$; found, 397.2698.

1-Amino-3-methyl-5-nitratepropyladamantane hydrochloride (MN-07). Compound **MN-07** was synthesized using a similar method to that as described for synthesis of compound **MN-01** from compound **16**. White solid, 66.0% yield. ESI-MS: *m/z* 269.1 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (s, 3H, CH_3), 1.06-1.23 (m, 4H), 1.26-1.35 (m, 4H), 1.41-1.47 (dd, J = 18 Hz, 6 Hz, 4H), 1.55-1.63 (m, 2H), 1.65-1.69 (m, 2H), 2.15-2.17 (m, 1H, CH), 4.49 (t, J = 6.5 Hz, 2H, CH_2O), 8.22 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.3, 26.3, 29.3, 30.1, 32.2, 34.7, 38.4, 39.2, 42.1, 44.1, 46.6, 47.4, 52.8, 74.8. HRMS-ESI: Calcd for $C_{14}H_{24}N_2O_3$: 269.1860 $[M + H]^+$; found, 269.1861.

1-Amino-3-ethyl-5-nitratepropyladamantane hydrochloride (MN-08). Compound **MN-08** was synthesized using a similar method to that as described for synthesis of compound **MN-01** from compound **16**. White solid, 39.4% yield. ESI-MS: *m/z* 283.1 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.74-0.79 (t, J = 7.5 Hz, 3H, CH_3), 1.05-1.23 (m, 6H), 1.25-1.35 (m, 4H), 1.39-1.52 (m, 4H), 1.56-1.63 (m, 2H), 1.67 (m, 2H), 2.18 (m, 1H), 4.47-4.51 (t, J = 6 Hz, 2H, CH_2O), 8.18 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.5, 20.3, 29.1, 34.6, 34.9, 35.2, 38.5, 39.6, 41.1, 44.1, 44.5, 45.0, 52.9, 74.8. Anal. Calcd for $C_{15}H_{27}N_2O_3Cl$: C,

56.51%; H, 8.54%; N 8.79%. Found: C, 56.53%; H, 8.23%; N, 8.55%.

1-Amino-3-nitratepropyl-5-propyladamantane hydrochloride (MN-09). Compound **MN-09** was synthesized using a similar method to that as described for synthesis of compound **MN-01** from compound **16**. White solid, 63.6% yield. ESI-MS: *m/z* 297.2([M + H]$^+$). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.85 (t, J = 6.7 Hz, 3H, CH_3), 1.18 (m, 12H), 1.40-1.82 (m, 8H), 2.16 (s, 1H, CH), 4.49 (t, J = 6.4 Hz, 2H, CH_2O), 8.26 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.3, 15.9, 20.3, 29.2, 34.6, 34.9, 38.5, 39.5, 40.1, 40.7, 44.4, 44.6, 45.5, 45.6, 52.8, 74.8. Anal. Calcd for $C_{16}H_{29}ClN_2O_3$·0.1 H_2O: C, 57.42%; H, 8.79%; N, 8.37%. Found: C, 57.15%; H, 8.89%; N, 8.36%.

1-Amino-3-ethyl-5-nitrate-isobutyladamantane trifluoroacetate (MN-11). Compound **MN-11** was synthesized using a similar method to that as described for synthesis of compound **MN-01** from compound **16** (71.2% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77 (t, J = 7.4 Hz, 3H, CH_3), 0.96 (d, J = 6.7 Hz, 3H, CH_3), 0.99-1.10 (m, 2H), 1.10-1.22 (m, 3H), 1.23-1.41 (m, 5H), 1.41-1.56 (m, 4H), 1.67 (s, 2H), 1.95 (d, J = 3.9 Hz, 1H, CH), 2.18 (s, 1H, CH), 4.30 (m, 2H, CH_2O), 8.13 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.4, 20.0, 25.9, 29.2, 34.8, 35.3, 39.8, 40.1, 44.4, 45.2, 45.3, 45.4, 46.3, 52.5, 79.2, 117.6, 158.7. HRMS-ESI: Calcd for $C_{16}H_{28}N_2O_3$: 297.2173 [M + H]$^+$; found, 297.2180.

1-(2-Oxopropyl)-3-ethyladamantane (61). Compound **61** was synthesized according to published method.[6] Colorless oil, 71.3% yield. The ^{1}H NMR and ^{13}C NMR data were in accordance with those reported in literature.[6]

1-(2-hydroxypropyl)-3-ethyladamantane (62). To compound **61** (1.4 g, 6.4 mmol) in ethanol (20 mL) was added $NaBH_4$ (0.73 g, 19 mmol). The mixture was stirred at room temperature for 4 h. Water (10 mL) was added to the mixture and the organic solvent was removed in vacuo. The aqueous solution was extracted with ethyl acetate (30 mL × 4). The combined organics was washed with HCl (0.5 N), water and brine and then dried over

Na_2SO_4. Solvent was removed in vacuo. The resulting residue was purified by column chromatography (petroleum ether: ethyl acetate = 2:1) to afford compound **62** as colorless oil (1.2 g, 84.9% yield). The ^1H NMR and ^{13}C NMR data were in accordance with those reported in literature.[6]

1-(2-Acetoxylpropyl)-3-ethyladamantane (63). Compound **62** (1.0 g, 4.5 mmol) was dissolved in 10 mL of acetic anhydride and a catalytic amount of $HClO_4$ was added. The mixture was stirred at room temperature for 3 h. The mixture was poured in 30 mL of ice-water and was then extracted with ethyl acetate (30 mL × 4). The combined organic solution was washed with 40 mL of saturated $NaHCO_3$ solution and brine. The organics were dried over anhydrous Na_2SO_4. Solvent was removed in vacuo. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 18:1) to afford compound **63** as colorless oil (750 mg, 63% yield). ESI-MS: *m/z* 287.2 $[M + Na]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.72-0.77 (t, J = 7.5 Hz, 3H, CH_3), 1.03-1.14 (m, 7H), 1.30-1.36 (m, 4H), 1.39-1.48 (m, 4H), 1.53 (m, 2H), 1.59-1.79 (m, 2H), 1.95 (s, 5H), 2.08 (m, 1H, CH), 3.93-4.00 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.3, 21.7, 24.9, 28.8, 32.8, 36.4, 36.5, 41.2, 41.4, 42.1, 42.2, 49.9, 67.0, 170.2.

1-Acetamide-3-(2-hydroxypropyl)-5-ethyladamantane (64). To compound **63** (780 mg, 3 mmol) in concentrated HNO_3 (0.75 mL) cooled on an ice bath was added concentrated H_2SO_4 (4.4 mL) dropwise. The mixture was stirred for 1 h. Acetonitrile (1.8 mL) was added dropwise to the mixture. The mixture was stirred for 1 h on an ice bath. The mixture was poured into 10 mL of ice-water, followed by extraction with ethyl acetate (20 mL × 4). The combined organics were washed with saturated brine and dried over Na_2SO_4. Solvent was removed in vacuo. The resulting residue was purified by column chromatography (petroleum ether: ethyl acetate = 1:1) to afford compound **64** as colorless oil (650 mg 68.7% yield). ESI-MS: *m/z* 322.2 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.72-0.77 (t, J = 7.5 Hz, 3H,

CH_3), 1.07-1.19 (m, 7H), 1.19-1.37 (m, 6H), 1.46-1.54 (m, 4H), 1.73 (m, 5H), 1.95 (s, 3H), 2.05 (m, 1H, CH), 4.89-4.99 (m, 1H), 7.34 (s, 1H).

1-*tert*-Butylcarbamate-3-ethyl-5-(2-hydroxypropyl) adamantane (65). Compound **65** was prepared using a similar method to that as described for synthesis of compound **13** from compound **10**. Colorless oil, 59% yield. ESI-MS: *m/z* 338.5 $[M + Na]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (t, J = 7.5 Hz, 3H, CH_3), 1.02-1.04 (m, 7H), 1.09-1.11 (m, 4H), 1.15-1.23 (m, 4H), 1. 36 (s, 11H), 1.41-1.46 (m, 2H), 1.58-1.66 (m, 4H), 2.05 (m, 1H, CH), 3.75-3.79 (m, 1H), 4.13 (d, J = 7.5 Hz, 1H, OH), 6.31 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.6, 21.2, 21.5, 26.8, 28.8, 29.7, 34.6, 34.7, 40.2, 41.5, 46.4, 47.9, 51.6, 53.2, 62.7, 77.3, 154.3, 172.5.

1-tert-Butylcarbamate-3-ethyl-5-(2-nitratepropyl) adamantane (66). Compound **65** was prepared using a similar method to that as described for synthesis of compound **16** from compound **13**. Colorless oil, 55 yield. ESI-MS: *m/z* 383.4 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.72-0.77 (t, J = 7.5 Hz, 3H, CH_3), 1.08-1.16 (m, 4H), 1.25 (2, 2H), 1.30-1.32 (d, J = 7.5 Hz, 5H), 1.35 (s, 13H), 1.9 (m, 2H), 1.57 (m, 2H), 2.08 (m, 1H, CH), 5.23 (s, 1H), 6.41 (s, 1H).

1-Amino-3-ethyl-5-(2-nitatepropyl) adamantane hydrochloride (MN-10). Compound **MN-10** was prepared using a similar method to that as described for synthesis of compound **MN-01** from compound **16**. White solid, 65% yield. ESI-MS: *m/z* 282.2 $[M + Na]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.73-0.78 (t, J = 7.5 Hz, 3H, CH_3), 1.09-1.16 (m, 4H), 1.29-1.32 (m, 7H), 1.36 (m, 2H), 1.41-1.48 (m, 4H), 1.65 (s, 3H), 2.16-2.19 (m, 1H), 5.27 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 7.4, 20.7, 29.1, 34.0, 34.8, 35.2, 44.0, 44.1, 44.6, 44.7, 45.1, 46.3, 52.5, 79.2.

1,3-Dibromoadamantane (68). To a mixture of adamantine **67** (6.8 g, 50 mmol) and Fe powder (0.6 g) in a three-neck flask was added bromine (30 mL) dropwise. The mixture

stirred for 2 h on an ice bath. The reaction mixture was poured into 200 mL of aqueous Na_2SO_3 solution to discharge the bromine color. The mixture was extracted with ethyl acetate (40 mL × 4) and the combined organics were washed with saturated $NaHCO_3$ solution and brine. The organics were dried over Na_2SO_4. Removal of solvent in vacuo gave a crude product. The crude product was recrystallized in methanol to afford compound **68** as a white solid (11.6 g, 78.9% yield), mp 107.5-108.5 ^oC. The ^1H NMR and ^{13}C NMR were in accordance with those reported in literature.[7]

1,3-Adamantanediol (69). To a mixture of acetone and water (70 mL, 1:1) was added compound **68** (5.88 g, 20 mmol) and the mixture was refluxed for 3 h. The mixture was filtered and the filtrate was lay to stand for overnight. The mixture was filtered. The resulting solid was washed with water and was then dried to afford compound **69** as a white solid (2.3 g, 68.5% yield), mp>250 ^oC, ESI-MS: *m/z* 169.2 $[M + H]^+$. The ^1H NMR and ^{13}C NMR data were in accordance with those reported in literature.[8]

1,3-Adamantanedicarboxylic acid (70). To compound **69** (8.4 g, 50 mmol) in concentrated H_2SO_4 (56 mL) cooled on an ice bath was added formic acid (5 mL) dropwise. The mixture was stirred on an ice bath for 2 h and then at room temperature for another 10 h. The mixture was pour into 200 mL of ice-water and stirred vigorously. After filtered, the resulting solid was washed with water. The solid was dissolved in aqueous NaOH solution and filtered. The residue was washed with water. The combined aqueous solution was acidified to the pH 2 with diluted hydrochloric acid. The mixture was filtered and the resulting solid was washed with water. The solid was dried to to afford compound **70** as a white solid (8.9 g, 79.5% yield), mp>250 ^oC. ESI-MS: *m/z* 223.2 $[M - H]^-$. The ^1H NMR and ^{13}C NMR data were in accordance with those reported in literature.[9]

1,3-Dihydroxymethyl adamantane (72). To **c**ompounds **70** (3.23 g, 10 mmol) in THF (50 mL) on an ice bath was added TEA (4 mL, 30 mmol) and ethyl chloroformate (2.9 mL, 30

mmol) sequentially. The mixture was stirred at room temperature for 4 h. The mixture was filtered and the solid was washed with THF. $NaBH_4$ (2.3 g, 60 mmol) was added into the filtrate. Water (3 mL) was added dropwise over 1 h and then 50 mL water was added to quench the reaction. The organic solvent was removed in vacuo and the aqueous layer was extracted with ethyl acetate (40 mL × 3). The combined organics were washed with hydrochloric acid (0.5 N), water and brine. The organics were dried over Na_2SO_4. Removal of solvent in vacuo gave a solid, which was washed with CH_2Cl_2 to afford compound **72** as a white solid (1.22 g, 62.1% yield), mp 174.9-175.3 ^oC. ESI-MS: *m/z* 274.2 $[M + 2K]^{2+}$. The ^1H NMR and ^{13}C NMR data were in accordance with those reported in literature.[10]

1,3-Dihydroxyethyl adamantane (73). Compound **73** was prepared using a similar method to that as described for synthesis of compound **72**. White solid, 63.8% yield, mp 118.6-119.4 ^oC. ESI-MS: *m/z* 309.3 $[M + H]^+$. The ^1H NMR and ^{13}C NMR data were in accordance with those reported in literature.[11]

1,3-Diacetoxylmethyl adamantane (74). Compound **74** was synthesized using a similar method to that as described for synthesis of compound **63**. Colorless oil, 90% yield. ESI-MS: *m/z* 298.3 $[M + H_2O]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.28 (s, 2H), 1.36-1.52 (dd, J = 18 Hz, 6 Hz, 8H), 1.59 (m, 2H), 2.02 (s, 8H, 2×CH, 2×$COCH_3$), 3.66 (s, 4H, 2 × CH_2O). ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.1, 27.8, 33.6, 36.2, 38.5, 40.7, 73.1, 170.9. HRMS-ESI: Calcd for $C_{16}H_{24}O_4$: 281.1747 $[M + H]^+$; found, 281.1750.

1,3-Diacetoxylethyl adamantane (75). Compound **75** was synthesized using a similar method to that as described for synthesis of compound **63**. Colorless oil, 92.9% yield. ESI-MS: *m/z* 309.3 $[M + H_2O]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.25 (s, 2H), 1.35-1.47 (m, 12H), 1.55 (s, 2H), 1.98 (s, 8H, 2 × CH, 2 × $OCOCH_3$), 4.04 (t, J = 6 Hz, 4H, 2 × CH_2O). ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.3, 28.7, 32.4, 36.3, 41.5, 42.1, 47.2, 60.5, 170.8. HRMS-ESI: Calcd for $C_{18}H_{28}O_4$: 309.2060 $[M + H]^+$; found, 309.2062.

1-Acetamide-3,5-diacetoxylmethyl adamantane (76). Compound **76** was synthesized using a similar method to that as described for synthesis of compound **64**. White solid, 62% yield, mp 142.4-143.5 ^{o}C. ESI-MS: *m/z* 360.3 $[M + Na]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.18-1.28 (dd, *J* = 18 Hz, 6 Hz, 2H), 1.32-1.43 (q, *J* = 12 Hz, 4H), 1.67 (s, 4H), 1.74 (s, 3H, $COCH_3$), 1.81 (s, 2H), 2.02 (s, 6H, 2 × $OCOCH_3$), 2.15 (m, 1H, CH), 3.70 (s, 4H, 2 × CH_2O), 7.45 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.1, 24.1, 28.7, 35.4, 37.7, 42.4, 51.7, 72.4, 169.2, 170.9. Anal. Calcd for $C_{18}H_{27}NO_5$: C 64.07%, H 8.07%, N 4.15%. Found: C, 64.09%; H, 7.75%; N, 4.11%.

1-Acetamide-3,5-diacetoxylethyl adamantane (77). Compound **77** was synthesized using a similar method to that as described for synthesis of compound **64**. Colorless oil, 57.9% yield. ESI-MS: *m/z* 366.3 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21 (s, 2H), 1.32-1.36 (m, 4H), 1.40-1.45 (t, *J* = 7.5 Hz, 4H), 1.63 (s, 4H), 1.74 (s, 3H, $COCH_3$), 1.76 (s, 2H), 2.02 (s, 6H, 2 × $OCOCH_3$), 2.07 (m, 1H, CH), 3.70 (t, *J* = 7.5 Hz, 4H, 2 × CH_2O), 7.38 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.3, 24.2, 29.5, 34.0, 40.6, 41.4, 45.5, 46.2, 52.2, 60.5, 169.1, 170.8. Anal. Calcd for $C_{20}H_{31}NO_5$: C, 65.73%; H, 8.85%; N, 3.83%. Found: C, 65.44%; H, 8.46%; N, 3.87%.

1-*tert*-Butylcarbamate-3,5-dihydroxymethyl adamantane (78). Compound **78** was synthesized using a similar method to that as described for synthesis of compound **13**. Colorless oil, 53% yield. ESI-MS: *m/z* 312.3 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (m, 2H), 1.21-1.34 (q, *J* = 12 Hz, 4H), 1.36 (s, 9H, $C(CH_3)_3$), 1.46-1.59 (q, *J* = 12 Hz, 4H), 1.67-1.68 (m, 2H), 2.07-2.11 (m, 1H, CH), 3.01-3.03 (d, *J* = 6 Hz, 4H, 2 × CH_2O), 4.35-4.39 (t, *J* = 6 Hz, 2H, 2 × OH), 6.39 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.8, 29.2, 37.1, 38.4, 40.6, 41.3, 43.2, 51.4, 71.5, 77.4, 154.3. Anal. Calcd for $C_{17}H_{29}NO_4$: C, 65.57%; H, 9.39%; N, 4.50%. Found: C, 65.76%; H, 9.50%; N, 4.36%.

1-*tert*-Butylcarbamate-3,5-dihydroxyethyl adamantane (79). Compound **79** was synthesized using a similar method to that as described for synthesis of compound **13**. White solid, 57% yield, mp 104.0-105.3 ^{o}C. ESI-MS: *m/z* 340.4 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10-1.20 (dd, *J* = 18 Hz, 6 Hz, 2H), 1.25-1.30 (m, 8H), 1.36 (s, 9H, $C(CH_3)_3$), 1.49-1.57 (m, 4H), 1.67 (d, *J* = 3.0 Hz, 2H), 2.03 (m, 1H, CH), 3.39-3.46 (dd, *J* = 13.5 Hz, 6.0 Hz, 2H, 2 × CHHO), 3.42-3.43 (d, *J* = 6.0 Hz, 2H, 2 × CHHO), 4.22 (t, *J* = 6.0 Hz, 2H, 2 × OH), 6.36 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.8, 29.6, 34.2, 41.2, 46.2, 46.4, 47.1, 51.4, 56.8, 60.2, 77.5, 154.3. Anal. Calcd for $C_{19}H_{33}NO_4$: C, 67.22%; H, 9.80%; N, 4.23%. Found: C, 67.28%; H, 9.80%; N, 4.20%.

1-*tert*-Butylcarbamete-3,5-dinitratemethyl adamantane (80). Compound **80** was synthesized using a similar method to that as described for synthesis of compound **16**. Colorless oil, 75% yield. ESI-MS: *m/z* 419.3 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.37 (s, 9H, $C(CH_3)_3$), 1.38-1.43 (m, 6H), 1.58-1.62 (d, *J* = 12 Hz, 2H), 1.72 (s, 2H), 1.77-1.81 (d, *J* = 12 Hz, 2H), 2.17 (m, 1H, CH), 4.25 (s, 4H, 2 × CH_2O), 6.67 (s, 1 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.4, 28.7, 35.3, 37.2, 39.2, 41.9, 50.5, 81.2, 154.7. Anal. Calcd for $C_{17}H_{27}N_3O_8$: C, 50.87%; H, 6.78%; N, 10.47%. Found: C, 51.18%; H, 6.58%; N, 10.43%.

1-*tert*-Butylcarbamete-3,5-dinitratethyl adamantane (81). Compound **81** was synthesized using a similar method to that as described for synthesis of compound **16**. Colorless oil, 72.3% yield. ESI-MS: *m/z* 452.1 $[M + Na]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.17-1.29 (q, *J* = 12 Hz, 2H), 1.36 (s, 13H), 1.49-1.53 (t, *J* = 6 Hz, 4H), 1.52-1.66 (dd, *J* = 33 Hz, 12 Hz, 4H), 1.68 (m, 2H), 2.09 (m, 1H, CH), 4.53-4.58 (t, *J* = 7.5 Hz, 4H, 2 × CH_2O), 6.46 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.7, 29.4, 34.0, 38.9, 45.4, 45.6, 51.3, 70.8, 77.6, 100.0, 154.3. Anal. Calcd for $C_{19}H_{31}N_3O_8$: C, 53.14%; H, 7.28%; N, 9.78%. Found: C, 52.95%; H, 7.26%; N, 9.72%.

1-Amino-3,5-dinitratemethyl adamantane hydrochloride (MN-12). Compound **MN-12**

was synthesized using a similar method to that as described for synthesis of compound **MN-01**. White solid, 65% yield. ESI-MS: *m/z* 255.1 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.38-1.54 (d, *J* = 18 Hz, 6H), 1.60-1.77 (d, *J* = 24 Hz, 6H), 2.27 (m, 1H, CH), 4.32 (s, 4H, 2×CH_2O), 8.27 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.0, 35.3, 36.4, 40.9, 51.7, 80.5. Anal. Calcd for $C_{12}H_{20}N_3O_6Cl$: C, 42.67%; H, 5.97%; N, 12.44%. Found: C, 42.48%; H, 6.08%; N, 12.64%.

1-Amino-3,5-dinitratethyl adamantane hydrochloride (MN-13). Compound **MN-13** was synthesized using a similar method to that as described for synthesis of compound **MN-01**. White solid, 58% yield. ESI-MS: *m/z* 255.1 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.22-1.36 (dd, *J* = 30 Hz, 12 Hz, 2H), 1.34-1.44 (m, 4H), 1.50-1.59 (m, 8H), 1.70 (s, 2H), 2.19 (m, 1H, CH), 4.55-4.59 (t, *J* = 6.0 Hz, 4H, 2×CH_2O), 8.29 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.0, 34.1, 38.5, 39.4, 44.2, 44.7, 52.5, 70.5. Anal. Calcd for $C_{14}H_{24}N_3O_6Cl$: C, 45.97%; H, 6.61%; N, 11.49%. Found: C, 45.61%; H, 6.48%; N, 11.31%.

1,3-Di-(2-oxopropyl) adamantane (82). To $AlBr_3$ (1.23 g, 4.6 mmol) in anhydrous CH_2Cl_2 (20 mL) on an ice bath was added compound **68** (600 mg, 2 mmol). The mixture was stirred for 10 min. Isopropenyl acetate (800 mg, 8 mmol) was added into the mixture and reaction was allowed to continue for 2 h. The mixture was poured into 50 mL of ice water, followed by extraction with ethyl acetate (30 mL × 4). The combined organic solution was washed with 50 mL of saturated brine and dried over Na_2SO_4. Solvent was removed in cacuo. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 7:1) to afford compound **82** as colorless oil (280 mg, 55.0 % yield). ESI-MS: *m/z* 266.2 $[M + H_2O]^+$. The ^1H NMR and ^{13}C NMR were in accordance with those reported in literature.[6]

1,3-Di-(2-hydroxypropyl) adamantane (83). To compound **82** (250 mg, 1 mmol) in ethanol (10 mL) was added $NaBH_4$ (114 mg, 3 mmol). The mixture was stirred at room temperature for 4 h. To the mixture was added water (10 mL) and the organic solvent was removed in

vacuo. The aqueous solution was extracted with ethyl acetate (30 mL × 4). The combined organic solution was washed with hydrochloric acid HCl (0.5 N), water and brine, and dried over Na_2SO_4. Solvent was removed in vacuo and the resulting residue was purified by column chromatography (petroleum ether: ethyl acetate = 6:1) to afford compound **83** as a white solid (150 mg, 60% yield), mp 69.1-71.9 ^oC. ESI-MS: *m/z* 270.2 $[M + H_2O]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.01-1.05 (m, 8H), 1.17-1.37 (m, 6H), 1.43 (s, 4H), 1.49-1.53 (d, *J* = 9 Hz, 4H), 1.92 (m, 2H, 2 × CH), 3.69-3.91 (m, 2H, 2 × CHO), 4.08-4.10 (d, *J* = 6 Hz, 2H, 2 × OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.9, 29.0, 29.1, 33.0, 36.7, 42.5, 42.6, 42.8, 48.7, 53.9, 62.6. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14%; H, 11.18%. Found: C, 76.24%; H, 11.01%.

1,3-Di-(2-acetoxylpropyl) adamantane (84). Compound **84** was prepared using a similar method to that as described for synthesis of compound **63**. White solid, 80% yield, mp 94.6-96.4 ^oC. ESI-MS: *m/z* 337.2 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.11-1.13 (d, *J* = 6.0 Hz, 6H, $2CH_3$), 1.15-1.25 (m, 4H), 1.30-1.42 (q, *J* = 9.0 Hz, 8H), 1.44-1.46 (d, *J* = 6.0 Hz, 2H), 1.49-1.51 (d, *J* = 6.0 Hz, 2H), 1.95 (s, 8H, 2 × $COCH_3$, 2 × CH), 4.93 (d, *J* = 5.9 Hz, 2H, 2 × CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.7, 22.5, 28.7, 32.7, 36.2, 41.8, 41.9, 47.7, 47.9, 67.0, 170.3. Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39%; H, 9.59%. Found: C, 71.42%; H, 9.52%.

1-Acetamide-3,5-di-(2-acetoxylpropyl) adamantane (85). Compound **85** was prepared using a similar method to that as described for synthesis of compound **64**. Colorless oil, 85.6% yield. ESI-MS: *m/z* 411.3 $[M + H_2O]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.11-1.13 (d, *J* = 6 Hz, 8H, 2 × CH_3), 1.23-1.35 (dd, *J* = 36 Hz, 12 Hz, 6H), 1.44-1.66 (m, 6H), 1.71-1.73 (m, 5H),1.96 (s, 6H, 2 × $OCOCH_3$), 2.01-2.13 (m, 1H, CH), 4.66-5.43 (t, *J* = 6 Hz, 2H, 2 × CH), 7.33 (s, 1H, NH). ^{13}C NMR (75 MHz, CD_3CN) δ 20.8, 21.5, 23.2, 29.6, 34.1, 40.5, 40.6, 40.7, 45.4, 46.6, 48.9, 52.6, 62.2, 169.8, 170.5. HRMS-ESI: Calcd for $C_{22}H_{35}NO_5$: 394.2588 $[M + H]^+$; found, 394.2601.

1-*tert*-Butylcarbamate-3,5-di-(2-hydroxypropyl) adamantane (86). Compound **86** was prepared using a similar method to that as described for synthesis of compound **13**. Colorless oil, 62.0% yield. ESI-MS: *m/z* 390.2 $[M + Na]^+$. ^1H NMR (300 MHz, MeOD-d_3) δ 1.15-1.17 (d, J = 6 Hz, 6H, 2 × CH_3), 1.21-1.27 (dd, J = 18 Hz, 3 Hz, 4H), 1.33-1.40 (m, 4H), 1.43-1.56 (m, 13H), 1.58 (m, 12H), 1.62-1.76 (dd, J = 42 Hz, 12 Hz, 2H), 1.69 (s, 2H), 1.81 (m, 2H), 2.08-2.20 (m, 1H, CH), 3.85-4.08 (m, 2H, 2×CH). ^{13}C NMR (75 MHz, CD_3CN-d_3) δ 25.5, 27.7, 29.8, 34.4, 40.4, 41.0, 46.2, 47.2, 51.7, 52.5, 63.2, 77.8, 171.6. HRMS-ESI: Calcd for $C_{21}H_{37}NO_4$: 368.2795 $[M + H]^+$; found, 368.2807.

1-*tert*-Butylcarbamate-3,5-di-(2-nitratepropyl) adamantine (87). Compound **87** was prepared using a similar method to that as described for synthesis of compound **16**. Colorless oil, 57.3% yield. ESI-MS: *m/z* 475.2 $[M+H_2O]^+$. ^1H NMR (300 MHz, C_6D_6) δ 0.72-1.04 (m, 14H), 1.12-1.68 (m, 17H), 1.76 (s, 1H, CH), 4.16 (s, 1H, NH), 4.91 (s, 2H, 2 × CH). ^{13}C NMR (75 MHz, C_6D_6) δ 20.2, 28.2, 29.3, 33.8, 39.7, 40.0, 40.2, 45.3, 46.2, 46.7, 51.0, 77.4, 78.2, 153.7.

1-Amino-3,5-di-(2-nitratepropyl) adamantane hydrochloride (MN-15). Compound **MN-15** was prepared using a similar method to that as described for synthesis of compound **MN-01**. White solid, 37% yield, mp 151.8-160.8 °C. ^1H NMR (300 MHz, C_6D_6) δ 1.17-1.28 (m, 2H), 1.31-1.33 (d, J = 6.0 Hz, 6H, 2 × CH_3), 1.35-1.44 (m, 4H), 1.43-1.49 (dd, J = 18 Hz, 3 Hz, 4H), 1.48-1.53 (m, 4H), 1.66 (s, 2H), 2.18 (m, 1H, CH), 5.22 (s, 2H, 2 × CH), 8.17 (s, 3H, NH_2HCl). ^{13}C NMR (300 MHz, DMSO-d_6) δ 20.7, 28.9, 34.2, 44.2, 46.2, 52.4, 79.1. HRMS-ESI: Calcd for $C_{16}H_{27}N_3O_6$: 358.1973 $[M + H]^+$; found, 358.1977.

Diethyl 3,3'-(adamantane-1,3-diyl) dipropionate (88). To compound **68** (588 mg, 2 mmol) in anhydrous toluene (6 mL) was added AIBN (33 mg, 0.2 mmol), n-Bu_3SnH (960 mg, 3.3 mmol) and ethyl acrylate (600 mg, 6 mmol) sequentially. The mixture was refluxed for 2 h under N_2 atmosphere. After cooled to room temperature, the mixture was poured into 20 mL

of ammonia water (0.2 M). The mixture was extracted with ethyl acetate (20 mL × 4). The combined organic solution was washed with water and dried over Na_2SO_4. Removal of solvent in vacuo gave a residue, which was purified by column chromatography (petroleum ether: ethyl acetate = 20:1) to afford compound **98** as colorless oil (313 mg, 46.6% yield). ESI-MS: *m/z* 337.4 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.11 (s, 2H), 1.15-1.19 (t, *J* = 6 Hz, 6H, 2 × CH_3), 1.28-1.39 (m, 12H), 1.53 (s, 2H), 1.97 (s, 2H, 2 × CH), 2.19-2.24 (m, 4H, 2 × CH_2COO), 4.03 (q, *J* = 6 Hz, 4H, 2 × CH_2OCO). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.5, 28.0, 28.8, 32.6, 36.4, 41.3, 46.3, 60.2, 174.0. HRMS-ESI: Calcd for $C_{20}H_{32}O_4$: 337.2373 $[M + H]^+$; found, 337.2371.

Diethyl 3,3'-(adamantane-1,3-diyl) diisobutyrate (89). Compound **89** was prepared using similar to than as described for synthesis of compound **88**. Colorless oil, 43.1% yield. ESI-MS: *m/z* 365.4 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.97-0.98 (d, *J* = 3 Hz, 4H), 1.02-1.07 (m, 8H), 1.15-1.22 (td, *J* = 9 Hz, 3 Hz, 6H, 2 × CH_3), 1.22-1.40 (dd, *J* = 42 Hz, 12 Hz, 4H), 1.32 (s, 4H), 1.50 (s, 2H), 1.57-1.65 (dd, *J* = 15 Hz, 6 Hz, 2H), 1.93 (s, 2H, 2 × CH), 2.42-2.47 (m, 2H, 2 × CHCOO), 3.98-4.11 (m, 4H, 2 × CH_2OCO). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.4, 20.6, 28.7, 33.3, 34.1, 36.3, 41.5, 41.6, 46.8, 47.0, 48.2, 60.1, 177.2. HRMS-ESI: Calcd for $C_{22}H_{36}O_4$: 365.2686 $[M + H]^+$; found, 365.2684.

Diethyl 3,3'-(5-acetamidoadamantane-1,3-diyl) dipropionate (90). Compound **90** was synthesized using a similar method to that as described for synthesis of compound **64** from compound **63**. Colorless oil, 57.9% yield. ESI-MS: *m/z* 394.2 $[M + H]^+$. ^1H NMR (DMSO-d_6) δ 1.07 (s, 2H), 1.15-1.19 (t, *J* = 6 Hz, 6H, 2 × CH_3),1.21-1.32 (dd, *J* = 21 Hz, 9 Hz, 4H), 1.35-1.41 (t, *J* = 9.0 Hz, 4H, 2 × CH_2), 1.56 (s, 4H), 1.73 (s, 3H, $COCH_3$), 1.75 (d, *J* = 3 Hz, 2H), 2.07 (s, 1H, CH), 2.21 (t, *J* = 9. 0 Hz, 4H, 2 × CH_2COO), 4.00-4.07 (q, *J* = 6.0 Hz, 4H, 2 × CH_2OCO), 7.35 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.5, 24.2, 28.2, 29.5, 34.3,

38.1, 45.2, 45.4, 52.4, 60.2, 169.1, 173.9. Anal. Calcd for $C_{22}H_{35}NO_5$: C, 67.15%; H, 8.96%; N, 3.56%. Found: C, 67.35%; H, 9.20%; N, 3.37%.

Diethyl 3,3'-(5-acetamidoadamantane-1,3-diyl) diisobutyrate (91). Compound **91** was synthesized using a similar method to that as described for synthesis of compound **64** from compound **63**. Colorless oil, 59.2% yield. ESI-MS: *m/z* 422.2 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.94-1.08 (m, 10H), 1.15-1.20 (m, 7H), 1.15-1.20 (td, *J* = 6 Hz, 3 Hz, 7H), 1.24 (s, 2H), 1.24-1.8 (d, J = 12 Hz, 1H), 1.46-1.68 (m, 6H), 1.72 (s, 5H), 2.04 (m, 1H, CH), 2.34-2.48 (m, 2H, 2 × CHCOO), 3.95-4.13 (m, 4H, 2×CH_2OCO), 7.32 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.4, 20.6, 24.2, 29.4, 34.3, 34.9, 47.5, 52.3, 60.3, 169.1, 177.2. HRMS-ESI: Calcd for $C_{22}H_{36}O_4$: 422.2901 $[M + H]^+$; found, 422.2911.

1-Acetamide-3,5-dihydroxypropyl adamantane (92). To a flask was added compound **90** (980 mg, 2.5 mmol), $NaBH_4$ (450 mg, 12 mmol), $AlCl_3$ (1.33 g, 10 mmol) and dry THF (20 mL). The mixture was refluxed for 3 h under N_2 atmosphere and then cooled to room temperature. The mixture was poured into 50 mL of ice-water and extracted with ethyl acetate (20 mL × 4). The combined organic solution was washed with water and brine. Removal of solvent gave a residue, which was purified by column chromatography (ethyl acetate: methanol= 10:1) to afford compound **92** as a white solid (410 mg, 53.1% yield), mp 147.8-149.7 °C. ESI-MS: *m/z* 310.1 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.05-1.09 (m, 6H), 1.22-1.39 (m, 8H), 1.51-1.60 (dd, *J* = 18 Hz, 6 Hz, 4H), 1.73 (s, 3H, $COCH_3$), 1.76 (s, 2H), 2.07 (m, 1H, CH), 3.30-3.36 (dd, *J* = 12 Hz, 6.0 Hz, 4H, 2 × CH_2O), 4.39 (t, *J* = 6.0 Hz, 2H, 2 × OH), 7.36 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.2, 26.4, 29.7, 34.4, 39.9, 40.6, 41.1, 45.8, 46.7, 52.6, 62.1, 169.1. Anal. Calcd for $C_{18}H_{31}NO_3$: C, 69.86%; H, 10.10%; N, 4.53%. Found: C, 69.77%; H, 10.04%; N, 4.37%.

1-Acetamide-3,5-dihydroxyisobutyl adamantane (93). Compound **93** was synthesized using a similar method to that as described for synthesis of compound **92**. Colorless oil, 55.6%

yield. ESI-MS: *m/z* 338.1 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.76-0.83 (dd, *J* = 15 Hz, 6 Hz, 2H), 0.84-0.87 (d, *J* = 9 Hz, 6H), 1.08-1.18 (m, 4H), 1.22-1.36 (m, 4H), 1.52-1.63 (m, 6H), 1.73 (s, 3H, $COCH_3$), 1,76 (s, 2H), 2.06 (m, 1H, CH), 2.97-3.06 (m, 2H, 2 × CHHO), 3.15-3.24 (m, 2H, 2 × CHHO), 4.42 (t, *J* = 5.0 Hz, 2H, 2 × OH), 7.33 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.6, 24.2, 29.6, 30.6, 35.2, 45.5, 46.1, 47.4, 52.5, 68.1, 169.1. Anal. Calcd for $C_{20}H_{35}NO_3$: C, 71.18%; H, 10.45%; N, 4.15%. Found: C, 70.88%; H, 10.13%; N, 4.47%.

1-*tert*-Butylcarbamate-3,5-dihydroxypropyl adamantane (94). Compound **94** was synthesized using a similar method to that as described for synthesis of compound **13**. White solid, 55.9% yield, mp 118.7-119.8 °C. ESI-MS: *m/z* 368.5 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.04-1.11 (m, 6H), 1.20-1.28 (m, 4H), 1.31-1.36 (m, 13H), 1.50 (s, 4H), 1.68 (s, 2H), 2.07 (m, 1H, CH), 3.36 (m, 4H, 2 × CH_2O), 4.34-4.37 (t, *J* = 6 Hz, 2H, 2 × OH), 6.36 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.4, 26.4, 28.8, 29.7, 34.5, 41.1, 46.0, 46.7, 51.5, 51.7, 62.1, 75.0, 154.4. Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63%; H, 10.15%; N, 3.81%. Found: C, 69.03%; H, 9.99%; N, 3.81%.

1-*tert*-Butylcarbamate-3,5-dihydroxyisobutyl adamantane (95). Compound **95** was synthesized using a similar method to that as described for synthesis of compound **13**. Colorless oil, 58.3% yield. ESI-MS: *m/z* 396.5 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.75-0.82 (dd, *J* = 15 Hz, 6 Hz, 2H), 0.84-0.86 (d, *J* = 6 Hz, 6H), 1.11-1.17 (m, 4H), 1.28 (m, 4H), 1.36 (s, 9H, $C(CH_3)_3$), 1.51 (s, 4H), 1.56 (m, 2H), 1.68 (s, 2H), 2.05 (m, 1H, CH), 3.02 (m, 2H, 2 × CHHO), 3.18 (m, 2H, 2 × CHHO), 4.42 (t, J = 6 Hz, 2H), 6.37 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.5, 28.8, 29.7, 30.6, 35.2, 41.5, 46.4, 47.4, 51.6, 68.1, 154.3. Anal. Calcd for $C_{23}H_{41}NO_4 \cdot 0.3\ H_2O$: C, 68.89%; H, 10.46%; N, 3.49%. Found: C, 68.93%; H, 10.36%; N, 3.79%.

1-*tert*-Butylcarbamate-3,5-dinitratepropyl adamantane (96). Compound **96** was

synthesized using a similar method to that as described for synthesis of compound **16**. Colorless oil, 72.3% yield. ESI-MS: *m/z* 452.1 $[M + Na]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.09 (s, 2H), 1.13-1.19 (m, 4H), 1.23-1.33 (m, 4H), 1.36 (s, 9H, $C(CH_3)_3$), 1.48-1.56 (m, 4H), 1.58-1.66 (m, 4H), 1.69 (s, 2H), 2.08 (m, 1H, CH), 4.46-4.50 (t, *J* = 6 Hz, 4H, 2 × CH_2O), 6.41 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.3, 28.8, 29.6, 34.4, 39.0, 40.6, 45.5, 45.8, 51.5, 75.0, 75.5, 154.3. Anal. Calcd for $C_{21}H_{35}NO_3$: C, 55.13%; H, 7.71%; N, 9.18%. Found: C, 55.44%; H, 7.26%; N, 9.50%.

1-*tert*-Butylcarbamate-3,5-dinitrateisobutyl adamantane (97). Compound **97** was synthesized using a similar method to that as described for synthesis of compound **16**. Colorless oil, 72.3% yield. ESI-MS: *m/z* 508.1 $[M+Na]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.93-0.96 (d, *J* = 9 Hz, 2×CH_3), 0.95-1.01 (dd, *J* = 15 Hz, 6 Hz, 2H), 1.13 (m, 2H), 1.18-1.20 (d, *J* = 6 Hz,1H), 1.22-1.24 (d, *J* = 6 Hz, 1H), 1.30 (s, 4H), 1.36 (s, 9H, $C(CH_3)_3$), 1.48-1.56 (m, 4H), 1.70 (m, 2H), 1.93-1.99 (m, 2H), 2.07 (m, 1H), 4.21-4.36 (m, 4H, 2 × CH_2O), 6.41(s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.1, 25.9, 28.7, 29.5, 31.6, 35.1, 45.9, 46.8, 51.4, 79.4, 152.1. HRMS-ESI: Calcd for $C_{22}H_{36}O_4$: 486.2810 $[M + H]^+$; found, 486.2813.

1-Amino-3,5-dinitratepropyl adamantane hydrochloride (MN-14). Compound **MN-14** was prepared using a similar method to that as described for synthesis of compound **MN-01**. White solid, 54.5% yield. ESI-MS: *m/z* 358.1 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.07-1.23 (m, 6H), 1.27-1.35 (m, 4H), 1.43-1.53 (m, 4H), 1.56-1.65 (m, 4H), 1.69 (s, 2H), 2.18 (m, 1H), 4.47-4.52 (t, *J* = 6.0 Hz, 4H, 2 × CH_2O), 8.23 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.3, 29.1, 34.6, 38.4, 44.4, 45.0, 52.7, 74.8. Anal. Calcd for $C_{16}H_{28}N_3O_6 \cdot 0.5\ H_2O$: C, 47.70%,; H, 7.26%; N, 10.43%. Found: C, 47.33%; H, 7.04%; N, 10.20%.

1-Amino-3,5-dinitratepisobutyl adamantane hydrochloride (MN-16). Compound **MN-16** was prepared using a similar method to that as described for synthesis of compound **MN-01**.

White solid, 33.5% yield. ESI-MS: *m/z* 386.1 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95-0.97 (d, J = 6 Hz, 6H, 2 × CH_3), 1.00-1.07 (dd, J = 15 Hz, 6 Hz, 2H, 2 × CH), 1.10-1.41 (m, 8H), 1.45-1.54 (m, 4H), 1.67 (s, 2H), 1.94 (m, 2H), 2.18 (m, 1H, CH), 4.23-4.36 (ddd, J = 21 Hz, 12 Hz, 9 Hz, 4H, 2 × CH_2O), 8.17 (s, 3H, NH_2HCl). ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.0, 25.9. 29.1, 35.3, 39.3, 44.8, 45.4, 46.2, 52.6, 79.2. Anal. Calcd for $C_{18}H_{32}N_3O_6Cl$: C, 51.24%; H, 7.64%; N, 9.96%. Found: C, 50.93%; H, 7.45%; N, 9.61%.

Biological evaluation

Protective effect on cultured cerebellar granule neurons

Cerebellar granule neurons were prepared and cultured according to a method published previously with minor modifications.[12] Briefly, after removal of meninges from the whole brain, cerebella was rapidly dissected and cut into small cubes. The matrixes were digested at 37 °C for 30 min in 1.5 mg/mL papain solution. After added HBSS buffer, tissue was sedimented by centrifugation, the supernatant was carefully removed, and the cerebellar tissue was resuspended in HBSS buffer. The tissue was mechanically dissociated using a long-stem Pasteur pipette and the cell suspension was centrifuged at 900 g for 5 min. After removed the supernatant, the cell pellet was resuspended in basal modified Eagle's (BME) medium containing 10% fetal bovine serum, 25 mM KCl, 2 mM glutamine, and penicillin (100 units/mL)/streptomycin (100 μg/mL). Neurons were seeded in 96 well plates (100 μL/well) at a concentration of 1.0-1.5 × 10^6 cells/mL. Cytosine arabinoside (10 μM) was added to the culture medium 24 h later to limit the growth of non-neuronal cells. Eight days after seeding, neurons were treated with new memantine nitrates or the positive control drug memantine for 2 h at indicated concentrations. The untreated control neurons were treated with a same volume of culture medium. The neurons except the control group were then exposed to 200 μM of glutamate for another 24 h in the presence of compounds. At the end

of exposure, the medium was removed and cells were incubated with 100 μL/well of PBS buffer containing 1 mg/mL of 3-(4,5)-dimethylthiahiazo(-z-y1)-3,5-di-phenytetrazoliumromide (MTT) for 4 h. MTT was then removed and DMSO 100 μL /well was added. Absorbance was read at 570 nm, and the results were expressed as the percentage of viable cells relative to the control group.

Vasodilation effects on aortic rings

The vasodilation assay was performed according to methods previously reported with minor modifications.[13,14] Briefly, male Sprague-Dawley rats (250-300 g) were anesthetized using 10% chloral hydrate. The thoracic cavity was opened immediately to isolate the thoracic aorta. After cleaning of the superficial adherent connective tissues, the aorta was cut into ring segments, 3-4 mm length. In some aortic rings, the endothelium was removed mechanically by gently rolling the lumen of the vessel on a thin wire wrapped with cotton. The aortic rings were placed between two stainless-steel stirrups and connected to an isometric force transducer (MLT0201, AD Instrument, AUS) to measure tension in the vessels. Aortic rings were then mounted in the standard organ chamber containing Krebs-Henseleit (KH) buffer with the following composition in mM: 118 NaCl, 4.7 KCl, 1.2 KH_2PO_4, 11 glucose, 1.2 $MgSO_4$, 25 $NaHCO_3$ and 2.4 $CaCl_2$. The solution was kept at pH 7.4 gassed with 5% CO_2/95% O_2 at 37 ^oC. Aortic rings were equilibrated for at least 60 min with the bath fluid changed every 15-20 min to achieve a resting tension of 1.2 g. Aortic rings were pre-contracted with 60 mM KCl to achieve consistent contraction. After washed with KH buffer, all vessels were returned to a resting tension of 1.2 g. Endothelium integrity was assessed qualitatively by the degree of relaxation induced by acetylcholine (3 μM) in the presence of contractile tone induced by phenylephrine (1 μM). For studies of endothelium-intact vessels, the rings were discarded if relaxation with acetylcholine did not reach 80% or greater. For studies of

endothelium-denuded vessels, the rings were discarded if there was 10% degree of relaxation or greater. Aortic rings with or without endothelium were pre-contracted with phenylephrine 1.0 μM. After the rings reached a stable contraction, memantine nitrates (10-140 μM) and the positive control isosorbide dinitrate (ISDN, 1-30 μM) were added cumulatively to the organ chamber. Additions were made as soon as a steady response was obtained with the preceding concentration. Cumulative concentration response curves for memantine nitrates and ISDN were constructed.

Protective effects on cultured cortical neurons

Cortical neurons were prepared and cultured as previously reported.[15] Neurons were seeded in 96-well plates (100 μL/well) at a density of 4-5 × 10^5 cells/mL and cultured in fresh neurobasal medium containing B27 supplements and GlutaMax at 37 ^oC in a humidified incubator with 5% CO_2/95% air atmosphere. Cytosine arabinoside (10 μM) was added to the culture medium 24 h later to limit the growth of non-neuronal cells. The culture medium was half changed to fresh medium every 3 days. After 11 days of culture *in vitro*, neurons were treated with **MN-05** or memantine at indicated concentrations for 2 h. The untreated control neurons were treated with a same volume of the culture medium. The neurons except the control group were then exposed to 200 μM of glutamate for another 24 h without removal of compounds. The cell viability was measured by MTT assay as aforementioned.

FDA and PI double-staining

After 11 days of culture, cortical neurons were treated with **MN-05** at concentrations of 5, 15 and 45 μM or memantine at a concentration of 5 μM for 2 h, followed by exposure to 200 μM of glutamate for another 24 h in the presence of compounds. The supernatant was removed and neurons were washed with HBSS for three times. The cortical neurons were

stained with FDA (10 μg/mL) and PI (5 μg/mL) for 15-20 min in darkness. Fluorescence images were taken by inverted fluorescence microscope (Olympas). Cell viability was measured as the percentage of green-positive viable cell versus red-positive dead cells.

Effect on intracellular calcium

The effect of **MN-05** on the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) was determined using laser scanning confocal microscope (Olympus IX70).[16] After 11 days of culture, cortical neurons were loaded with fluo-3/AM (5 μM) and 0.03% of Pluronic F-127 for 30 min at 37 ^oC in darkness, and then incubated with HBSS buffer for 30 min at room temperature. After incubation, cortical neurons were treated with **MN-05** or memantine for 5 min. The medium was changed to normal HBSS buffer before recording the images. Fluorescence images were taken using MetaFlour software (Universal Imaging Corp.) under 20× objective lens, with excitation at 506 nm and long-pass band emission filter at 526 nm. Baseline fluorescence was recorded for 20 s, after which glutamate (200 μM) was added and imaging continued for a further 280 s. From each experiment, 10 cells were chosen for analysis. Background fluorescence was automatically subtracted from all measurements. Fluorescence intensity was analyzed over time using MetaFlour software.

Effects on intracellular ROS and RNS

The effects of **MN-05** on the productions of ROS and RNS were conducted on cultured cortical neurons. Briefly, after 11 days of culture, cortical neurons were pretreated with **MN-05** or memantine at indicated concentrations for 2 h, followed by exposure to 200 μM of glutamate for another 12 h without removal of compounds. Fluorescence dyes H_2DCF-DA (5 μM), HPF (10 μM), DHE (5 μM), DAF-FM (5 μM) and DHR123 (10 μM) was added and incubated for 30 min to detect intracellular ROS, •OH, O_2•$^-$, NO and $ONOO^-$, respectively.

The fluorescence intensities were recorded on a BioTek microplate reader. After the measurement of fluorescence intensities, cell viability was measured by MTT assay. The extent of inhibition on ROS and RNS production was reflected by the mean fluorescence intensities. The mean fluorescence intensities were calculated by the formula: mean fluorescence intensities (%) = detected fluorescence intensities/cell viability × 100.

Effect on mitochondrial membrane potential

The effect of **MN-05** on mitochondrial membrane potential was tested using a previously reported method.[17] JC-1 was used as a molecular probe to measure mitochondrial membrane potential (Δψm). Cortical neurons were seeded on 96-well plates (100 μL/well) at a density of 4-5 × 10^5 cells/mL. After 11 days culture, cortical neurons were treated with **MN-05** or memantine at indicated concentrations for 2 h, followed by exposure to 200 μM of glutamate for 12 h in the presence of compounds. Cells were washed with JC-1 buffer and stained with 2 μM JC-1 for 20 min. Removed the supernatant and washed cells with JC-1 buffer for three times, and then added 100 μL of HBSS solution to each well. Fluorescence intensity was measured on a microplate reader at 488 nm excitation and 529 nm/590 nm dual emissions. The mitochondrial accumulation of JC-1 was dependent on Δψm and reflected by a shift in 529 nm and 590 nm emissions. Mitochondrial membrane depolarization was indicated by a decrease in the ratio of 590 nm to 529 nm emissions.

Statistical analysis

Data were analyzed using GraphPad Prism V5.0 (GraphPad Software, Inc., San Diego, CA, USA) and expressed as the means ± SD. One-way analysis of variance (ANOVA) followed by Tukey-Kramer post hoc tests were used to evaluate statistical differences among different treatment groups for studies *in vitro* and two-tail analysis followed by Student's t-test was

used for study *in vivo*. The value of statistical significance was set at $P< 0.05$.

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