Solid-Phase Synthesis of Anandamide Analogues

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Supporting Information

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium-benzophenone. The ion-exchange resin used in product purification, Dowex 50WX2-200, was washed with distilled water, MeOH, and CH_2Cl_2 prior to use. The filtration/workup cartridges were prepared by placing ~1 cm^3 of Florisil and ~2 cm^3 of the resin in a 5-mL plastic syringe equipped with a polyethylene frit. All of the glassware used in the solid-phase synthesis was silanized by treating with sigmacote. Flash chromatography was carried out using Merck silica gel 60 (230-400 mesh). Preparative TLC was carried out using Merck 60 F_{254} plates (0.5 or 1.0 mm) with ethyl acetate/hexanes or methanol/methylene chloride mixtures as eluants.
FT-IR spectra were recorded using a Thermo Nicolet AVATA 360 spectrometer equipped with a golden gate single reflection diamond ATR accessory. NMR spectra were recorded using either a Bruker DRX-500 or 600 spectrometer and calibrated using residual undeuterated solvent as an internal reference. High-resolution mass spectra (HRMS) were recorded at The Scripps Research Institute using MALDI-FTMS techniques. LC-MS spectra were obtained on a HP-1100, using a flow rate of 0.75 mL/min in a gradient of 25-99% acetonitrile in water (0.5% formic acid) in 8-12 min.

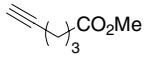
Final products were fully characterized (^{1}H-, ^{13}C-NMR and MS), except for a few compounds that did not yield sufficient material for reliable ^{13}C-NMR data. For compound 4i also the resolution of the ^{1}H-NMR spectrum was insufficient for publication, however, a clean mass spectrum was obtained. Intermediates were characterized by ^{1}H-NMR, and ^{13}C-NMR *or* MS.

General method for resin washing and drying: the resin was washed with DMF (3x), H_2O/DMF (1:1) (3x), methanol (3x), methylene chloride (3x) and the washing cycle was repeated three times. The resin was dried *in vacuo* overnight.

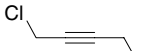
Off-beads analysis: about 50 mg resin was treated by 50% TFA in methylene chloride, shaken for 30 min, followed by filtration and washed with methylene chloride (3x); the solvent was removed and the residue was taken up in CH_2Cl_2 and concentrated (2x) and dried *in vacuo*. The sample was weighed and analyzed by NMR.

General method for the Cu-mediated coupling reactions in solid phase:

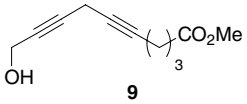
The terminal alkyne and propargyl bromide or chloride, CuI, NaI, K_2CO_3 were mixed in DMF and the mixture was shaken for 3 days. The reaction was monitored either by IR or by off-beads NMR analysis. The yield and purity were determined by off-beads analysis.



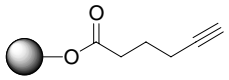
7 Ester **7**: A stirred solution of 5-hexynoic acid (5 g, 44.6 mmol), p-TSA (monohydrate) (58 mg, 0.3 mmol) in MeOH (8 mL) and CH_2Cl_2 (17 mL) was refluxed for 24 h. The mixture was quenched with saturated $NaHCO_3$ and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo* after filtration. 4.2 g (33.4 mmol) of **7** was obtained (75 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.70 (s, 3H), 2.50 (t, *J*=7.2 Hz, 2H), 2.30 (dt, *J*=7.2, 2.8 Hz, 2H), 2.0 (t, *J*=2.8 Hz, 1H), 1.88 (quint, *J*=7.2 Hz, 2H).



8 Alcohol **8**: To a solution of but-2-yn-1,4-diol (86.0 g, 1 mol) and pyridine (89.0 mL, 1.1 mol) in benzene (100 mL) was added thionyl chloride (80.2 mL, 1.1 mol) dropwise over a period of 6 h, while the temperature was maintained between 10 ^{o}C to 20 ^{o}C. The reaction mixture was then stirred overnight at room temperature. The mixture was poured into ice water (250 mL) and the benzene layer was separated. The aqueous phase was extracted with ether (4 x 100 mL) and the combined organic layers were washed with saturated $NaHCO_3$, followed by water and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification of the residue oil by distillation (55 ^{o}C/0.7 mm Hg) provided 52.3 g of **8** as colorless oil in 50 % yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.33 (dt, *J*=6.3, 1.9 Hz, 2H), 4.18 (t, *J*=1.9 Hz, 2H).

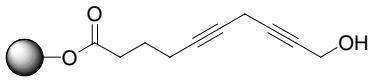


9 Diyne **9**: A mixture of K_2CO_3 (4.64 g, 33.6 mmol), CuI (12.80 g, 33.6 mmol), NaI (5.04 g, 33.6 mmol), ester **7** (4.23 g, 33.6 mmol) and alcohol **8** (3.53 g, 33.6 mmol) in DMF (68 mL) was stirred overnight at 25 ^{o}C. The mixture was diluted with EtOAc (100 mL) and plugged through a pad of celite. It was washed with saturated NH_4Cl (4 x 20 mL) and followed by brine. The solution was dried over $MgSO_4$ and the solvent was removed *in vacuo* after filtration. The residue was purified by flash chromatography on silica gel (EtOAc/Hex: 2/3) to give 6.06 g (93 %) of **9** as yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.27 (dt, *J*=6.0, 2.2 Hz, 2H), 3.70 (s, 3H), 3.20 (quint, *J*=2.2 Hz, 2H), 2.48 (t, *J*=7.4 Hz, 2H), 2.27 (tt, *J*=6.7, 2.2 Hz, 2H), 1.87 (quint, *J*=6.7 Hz, 2H).

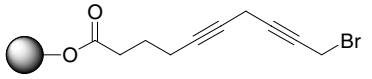


6 Polymer supported 5-hexynoic acid (**6**): A solution of 5-hexynoic acid (0.434 mL, 3.93 mmol) in 15 mL of DMF was treated with DIC (0.616 mL, 3.93 mmol) and stirred for 15 min at rt. Wang resin (1.36 g, 0.96 mmol/g, 1.31 mmol) was then added followed by DMAP (48.0 mg, 0.39 mmol) and NMM (0.45 mL, 3.93 mmol). The suspension was stirred overnight at rt under Ar. The resin was washed by the general washing method and dried. 66.5 mg of the dry resin was cleaved with 50 % TFA in

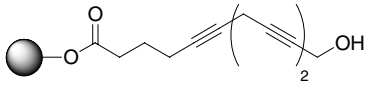
CH_2Cl_2 according to the general method to give 10 mg of acid with a loading value of 1.34 mmol/g (theoretical loading of the resin 0.877 mmol/g, quantitative).



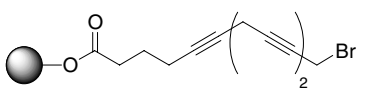
10a: To a mixture of CuI (45.7 mg, 0.24 mmol), NaI (36.0 mg, 0.24 mmol) and K_2CO_3 (33.1 mg, 0.24 mmol) in DMF (0.6 mL) was added resin **6** (59.9 mg, 1.34 mmol/g, 0.08 mmol) followed by alcohol **8** (84.3 mg, 0.8 mmol) under Ar. The suspension was shaken for 3 days at rt. The resin was filtered and washed according to the general method. 21.2 mg of the resin was cleaved by the TFA method to give 4.6 mg solid with a loading value of 1.22 mmol/g (theoretical: 1.25 mmol/g, yield 97 %, 92 % purity from ^{1}H NMR). For the corresponding acid obtained from the resin by TFA, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.27 (t, *J*=2.2 Hz, 2H), 3.17 (quint., *J*=2.3 Hz, 2H), 2.49 (t, *J*=7.2 Hz, 2H), 2.27 (m, 2H), 1.84 (quint., *J*=7.1 Hz, 2H), 1.25 (-OH). ^{13}C NMR (500 MHz, $CDCl_3$): δ 178.33, 80.65, 79.59, 78.37, 74.66, 51.20, 32.70, 23.35, 18.13, 9.82.



10b: Resin **10a** (116.1 mg, 0.146 mmol) was swollen in DCM (1.7 mL) for 15 min, and then cooled to –40 ^{o}C under Ar. CBr_4 (96.0 mg, 0.28 mmol) was added to the suspension followed by a solution of Ph_3P (77.0 mg, 0.28 mmol) in DCM (0.5 mL). The suspension was stirred mildly at –20 ^{o}C for 1 h. The suspension was diluted with DCM (2 mL), filtered and washed with DCM (5 x 15 mL). The resin was dried *in vacuo* overnight. Off-bead analysis: 34.6 mg of resin gave 6.5 mg of solid:loading value 0.78 mmol/g (theoretical: 1.1 mmol/g, yield 71 %), purity 88 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.92 (t, *J*=2.4 Hz, 2H), 3.22 (quint, *J*=2.3 Hz, 2H), 2.50 (t, *J*=7.4 Hz, 2H), 2.28 (m, 2H), 1.84 (quint., *J*=7.2 Hz, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 178.41, 81.75, 79.79, 75.38, 74.05, 69.29, 32.56, 23.44, 18.03, 14.78, 10.05.



11a: To a mixture of CuI (371.3 mg, 1.95 mmol), NaI (292.6 mg, 1.95 mmol) and K_2CO_3 (269.1 mg, 1.95 mmol) in DMF (3 mL) was added resin **10a** (304.6 mg, 0.78 mmol/g, 0.24 mmol) followed by propargyl alcohol (142.0 μL, 2.43 mmol) at rt under Ar. The vial was capped firmly and shaken for 3 days. After filtration and washing by the general method, the resin was dried *in vacuo*. Off-bead analysis: 34.9 mg resin gave 5.1 mg of solid compound:loading value 0.70 mmol/g (theoretical: 0.81 mmol/g, yield 86 %), purity 85 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.27 (t, *J*=2.1 Hz, 2H), 3.20 (t, *J*=2.3 Hz 2H), 3.13 (t, *J*=2.3 Hz, 2H), 2.50 (t, *J*=7.5 Hz, 2H), 2.27 (m, 2H), 1.83 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 178.03, 80.09, 79.39, 78.64, 75.27, 74.92, 73.83, 51.21, 32.48, 29.68, 23.43, 18.02, 9.86.



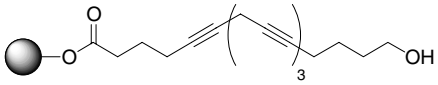
11b: resin **11a** was treated by the same method used to prepare **10b**: **11a** (92.2mg, 0.70 mmol/g, 0.064 mmol), CBr_4 (31.6 mg, 0.095 mmol) and Ph_3P (25.0 mg, 0.095 mmol) in DCM (1.5 mL). Off-bead analysis: 40.0 mg of the resin gave 7.3 mg of solid compound: loading value 0.65 mmol/g (theoretical: 0.66 mmol/g, yield 98 %), purity 83 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ3.91 (t, *J*=2.3 Hz, 2H), 3.23 (t,

J=2.3 Hz, 2H), 3.13 (t, *J*=2.4 Hz, 2H), 2.49 (t, *J*=7.4 Hz, 2H), 2.26 (m, 2H), 1.82 (quint, *J*=7.2 Hz, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 178.82, 81.67, 79.85, 77.69, 75.89, 75.18, 73.78, 69.73, 32.98, 23.92, 18.48, 18.15, 10.54.

Compounds **5**: prepared from resin **11b** by the same condition as used to prepare **11a**: resin **11b** (1 eq), and alkyne (10 eq) were added to the mixture of CuI (8 eq), NaI (8 eq), and K_2CO_3 (8 eq) in DMF (9 mL/ g resin) and shaken for 3 days. After filtration and washing by the general method, the resin was dried *in vacuo*.

5a **5a**: off-bead analysis: 22.5 mg of the resin gave 2.7 mg of compound:, loading value 0.44 mmol/g (theoretical: 0.65 mmol/g, yield 68%), purity 70%. For the corresponding acid obtained from the resin by TFA, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.75 (t, *J*=6.2 Hz, 2H), 3.14 (m, 6H), 2.49 (m, 2H), 2.45 (m, 2H), 2.26 (m, 2H), 1.82 (quint, *J*=7.1 0Hz, 2H).

5b **5b**: off-bead analysis: 21.2 mg of the resin gave 4.1 mg of compound:, loading value 0.65 mmol/g (theoretical: 0.62 mmol/g, quantitative), purity: 71%. For the corresponding acid obtained from the resin by TFA, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.14 (m, 6H), 2.49 (t, *J*=7.4 3Hz, 2H), 2.26 (m, 2H), 2.15 (m, 2H), 1.82 (quint, *J*=7.2 15Hz, 2H), 1.49 (m, 2H), 1.32 (m, 4H), 0.89 (t, *J*=6.8 0Hz, 3H).



5c **5c**: off-bead analysis: 27.7 mg of the resin gave 3.8 mg of compound: loading value 0.46 mmol/g (theoretical: 0.59 mmol/g, yield 78%), purity 60%. For the corresponding acid obtained from the resin by TFA, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.38 (t, *J*=6.5 Hz, 2H), 3.14 (m, 6H), 2.49 (m, 2H), 2.26 (m, 4H), 1.83 (m, 4H), 1.50 (m, 2H).

5d **5d**: off-bead analysis: 11.9 mg of resin gave 2.9 mg of compound: loading value 0.78 mmol/g (theoretical: 0.61 mmol/g, quantitative, purity 65%. For the corresponding acid obtained from the resin by TFA, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.13 (m, 6H), 2.49 (m, 2H), 2.26 (m, 2H), 2.15 (m, 2H), 1.82 (quint. *J*=7.4 Hz, 2H), 1.48 (m, 2H), 1.25 (m, 7H), 0.89 (t, *J*=6.8 Hz, 3H).

5e **5e**: off-bead analysis: 12.9 mg of resin gave 4.6 mg of compound:, loading value 1.25 mmol/g (theoretical: 0.62 mmol/g, quantitative, purity

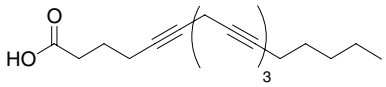
33%. For the corresponding acid obtained from the resin by TFA, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.28 (m, 2H), 3.13 (m, 6H), 2.52 (m, 3H), 2.28 (m, 2H), 1.85 (m, 2H), 1.25 (s, 1H), 0.88 (t, *J*=7.0 0Hz, 3H).

12

12: resin 5 was cleaved either by A) 50% TFA in DCM, 30 min, rt as general method or B) Me_3Al (3eq)/amine (5eq), 0°C/10 min then overnight/rt; the mixture was quenched with water and stirred for 10 min, then filtered through a filtration/workup cartridge to provide the crude product.

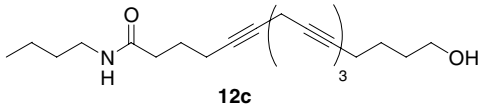
12a

12a: 144.0 mg resin **5a** was cleaved by 50% TFA in DCM, 1h, rt. 24.8 mg of brown solid was obtained which was subjected to chromatography (silica gel, Et_2O/Hex: 1/1) and two compounds were obtained: **12a** (11.4 mg, 45%) and **13a** (12 mg, 45%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.70 (t, *J*=6.2Hz, 2H), 3.15 (dd, *J*=2.4 Hz, 12.5 Hz, 6H), 2.50 (t, *J*=7.4 Hz, 2H), 2.25 (t, *J*=6.9 Hz, 2H), 1.83 (quint, *J*=7.1 Hz, 2H). HRMS (MALDI-FTMS) calcd. for $C_{17}H_{18}O_3$ $[M+Na]^+$ 293.1148, found 293.1145.



12b

12b: resin **5b** (155.0 mg, 0.09 mmol) was cleaved by method A as described above to give the crude product, which was purified by chromatography (silica gel, Et2O/Hex: 1/1) to provide pure product **12b** as a white solid (21.3 mg, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.15 (m, 6H), 2.45 (t, *J*=7.4 Hz, 2H), 2.26 (m, 2H), 2.15 (m, 2H), 1.82 (quint *J*=7.1 Hz, 2H), 1.49 (quint, *J*=7.2 Hz, 2H), 1.32 (m, 4H), 0.89 (t, *J*=7.9 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 178.68, 80.96, 79.27, 75.24, 74.92, 74.88, 74.29, 74.03, 73.57, 32.58, 31.06, 29.68, 28.39, 23.48, 22.19, 18.66, 18.06, 13.97, 9.82, 9.75, 9.72.

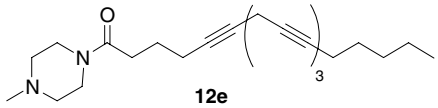


12c

12c: resin **5c** (106.2 mg, 0.049 mmol) was cleaved by method B to give product **12c** (18 mg, 96%), purity 57%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.56 (t, *J*=6.3 Hz, 2H), 3.24 (m, 2H), 3.12 (m, 6H), 2.28 (m, 2H), 1.83 (m, 4H), 1.48 (m, 4H), 1.35 (m, 6H), 0.95 (t, *J*=7.5 Hz, 3H). LC/MS (ESI) $[M+H]^+$ 354.2, $[M+Na]^+$ 376.2.

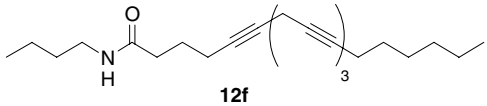
12d

12d: resin **5b** (43.3mg, 0.028 mmol) was cleaved by LDA (15 eq) and ethanolamine (20 eq) at 10 °C and 18h at rt to give **12d** (6.8 mg, 74%), purity 55%. LC/MS (ESI) $[M+H]^+$ 340.2, $[M+Na]^+$ 362.2.



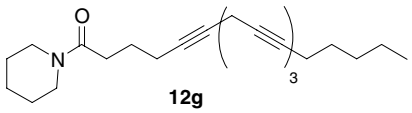
12e

12e: resin **5b** (105.0 mg, 0.068 mmol) was cleaved by method B to give **12e** (17.0 mg, 66%), purity 66%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.49 (m, 4H), 3.14 (m, 6H), 2.84 (m, 6H), 2.47 (m, 4H), 2.15 (m, 2H), 1.85 (m, 2H), 1.56 (m, 6H) 0.89 (t, *J*=7.0 Hz, 3H). LC/MS (ESI) $[M+H]^+$ 379.2, $[M+Na]^+$ 401.2.



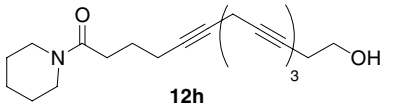
12f

12f: resin **5d** (153 mg, 0.16 mmol) was cleaved by method B to give **12f** (32.8 mg, 88%), purity 40%. LC/MS (ESI) $[M+H]^+$ 366.2, $[M+Na]^+$ 388.2.



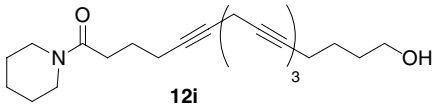
12g

12g: resin **5b** (114.7 mg, 0.068 mmol) was treated by method B to give **12g** (19.4 mg, 79%) with purity 75%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.55 (t, *J*=5.5 Hz, 2H), 3.43 (t, *J*=5.5 Hz, 2H), 3.14 (m, 6H), 2.43 (t, *J*=7.4 Hz, 2H) 2.25 (t, *J*=6.9 Hz, 2H), 2.14 (t, *J*=7.2 Hz, 2H), 1.83 (m, 2H), 1.58 (m, 4H) 1.54 (m, 6H), 1.32 (m, 2H), 0.90 (t, *J*=7.00 Hz, 3H). LC/MS (ESI) $[M+H]^+$ 364.2, $[M+Na]^+$ 386.2



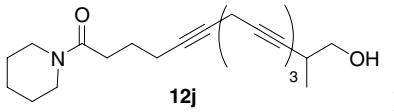
12h

12h: resin **5a** (71.2 mg, 0.031 mmol) was treated by method B to give **12h** (6.8 mg, 65%), purity 83%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.70 (t, *J*=6.3 Hz, 2H), 3.54 (t, *J*=5.5 Hz, 2H), 3.41 (m, 2H), 3.13 (m, 6H), 2.43 (m, 2H), 2.24 (m, 2H), 1.87 (m, 2H), 1.62 (m, 2H), 1.54 (m, 4H), 1.24 (m, 2H). LC/MS (ESI) $[M+H]^+$ 338.2, $[M+Na]^+$ 360.1.



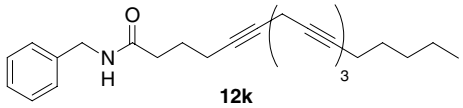
12i

12i: resin **5c** (97.2 mg, 0.0447 mmol) was treated by method B to give **12i** (6.1 mg, 37%), purity 86%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.67 (t, *J*=6.3 0Hz, 2H), 3.54 (t, *J*=5.4 0Hz, 2H), 3.42 (m, 2H), 3.13 (m, 6H), 2.43 (m, 2H), 2.28 (m, 2H), 1.84 (m, 4H), 1.6-1.54 (m, 10H). LC/MS (ESI) $[M+H]^+$ 366.2, $[M+Na]^+$ 388.1.



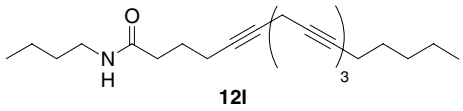
12j

12j: resin **5e** (137 mg, 0.17 mmol) was treated by method B to give **12j** (23.1 mg, 40%), purity 20%. LC/MS (ESI) $[M+H]^+$ 352.1, $[M+H-H_2O]^+$ 334.1.



12k

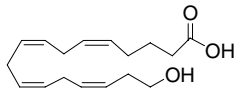
12k: resin **5b** (82.9 mg, 0.069 mmol) was treated by method B to give **12k** (15.1 mg, 57%) with purity 54%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (m, 2H), 7.32 (m, 3H), 6.99 (s, 1H), 4.45 (m, 2H), 3.11(m, 6H), 2.35 (t, *J*=7.70Hz, 2H), 2.24 (m, 4H), 2.14 (m, 2H), 1.85 (m, 2H), 1.47 (m, 2H), 1.32 (m, 2H), 089 (t, *J*=7.02Hz, 3H). LC/MS (ESI) $[M+H]^+$ 386.1.



12l

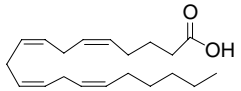
12l: resin **5b** (97.3 mg, 0.082 mmol) was treated by method B to provide **12l** (15.2 mg, 53%) with purity 70%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.24 (m, 2H), 3.13 (m, 6H), 2.27 (m, 2H), 2.21 (m, 2H), 2.13 (m, 2H), 1.82 (m, 2H), 1.74 (m, 2H), 1.32 (m, 4H), 0.89-0.91 (m, 6H). LC/MS (ESI) $[M+H]^+$ 352.2, $[M+Na]^+$ 374.2.

Compounds **4a-l** were prepared from **12a-l** by P-2 Ni catalytic hydrogenation ($Ni(OAc)_2 \cdot 4H_2O$ 2.24 eq; $NaBH_4$ 2.24 eq, 1M in absolute EtOH; ethylene diamine 2.24 eq; H_2 balloon; 3-4 h; rt) and the products were purified by PTLC.



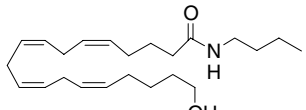
4a 40%

4a: by the general method, the reduction of 12a gave 4a in 40% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.3-5.5 (m, 8H), 3.70 (t, *J*=6.5 45Hz, 2H), 2.85 (m, 6H), 2.40 (m, 5H), 2.15 (m, 2H), 2.05 (m, 2H), 1.70 (t, *J*=7.3 Hz, 3H), 0.80 (m, 3H). HRMS (MALDI-FTMS) calcd. for $C_{17}H_{26}O_3$ $[M+Na]^+$ 301.1774, found: 301.1766.



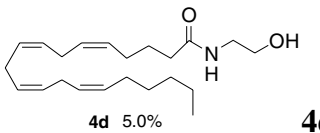
4b 34%

4b: yield 34%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.40 (m, 8H), 2.80 (m, 6H), 2.40 (m, 2H), 2.15 (m, 2H), 2.05 (m, 2H), 1.70 (m, 2H), 1.30 (m, 2H), 0.85 (m, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 130.51, 129.04, 128.74, 128.56, 127.85, 127.52, 63.07, 32.79, 31.51, 29.70, 27.20, 26.43, 25.60, 24.50, 22.57, 14.07. MS (ESI) $[M-H]^-$ 303.



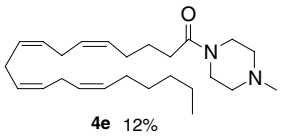
4c 30%

4c: yield 30%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.40 (m, 8H), 3.65 (t, *J*=6.6 Hz, 2H), 3.25 (q, *J*=6.5 Hz, 2H), 2.80 (m, 6H), 2.10 (m, 4H), 1.70 (m, 4H), 1.60 (m, 4H), 1.50 (m, 2H), 1.40 (m, 2H), 0.90 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 172.78, 129.91, 129.15, 129.08, 128.78, 128.71, 128.38, 128.15, 128.00, 68.13, 62.78, 39.21, 36.15, 32.36, 31.72, 30.94, 26.96, 26.67, 25.72, 25.65, 25.56, 20.06, 13.75. LC/MS (ESI) $[M+H]^+$ 362, $[M+Na]^+$ 384.



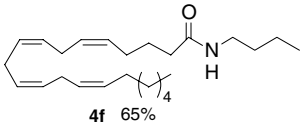
4d 5.0%

4d: yield 5.0%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.40 (m, 8H), 3.75 (t, *J*=4.7 Hz, 2H), 3.45 (q, *J*=5.2 Hz, 2H), 2.85 (m, 6H), 2.35 (t, *J*=7.5 Hz, 2H), 2.25 (q, *J*=6.5 Hz, 2H), 2.10 (q, *J*=6.4 Hz, 2H), 1.30 (m, 8H), 0.85 (t, *J*=6.5 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 174.18, 130.55, 129.04, 128.86, 128.56, 128.26, 128.15, 127.85, 127.51, 62.75, 42.49, 35.92, 31.52, 29.71, 29.33, 27.23, 26.62, 25.65, 25.43, 22.59, 14.09. HRMS (MALDI-FTMS) calcd. for $C_{22}H_{37}NO_2$ $[M+Na]^+$ 370.2716, 370.2720.



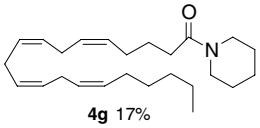
4e 12%

4e: yield 12%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.40 (m, 8H), 4.20 (m, 3H), 3.60 (m, 4H), 3.45 (m, 4H), 2.80 (m, 6H), 2.40 (m, 4H), 2.30 (m, 2H), 1.60 (m, 2H), 1.40 (m, 4H), 0.90 (m, 3H). HRMS (MALDI-FTMS) calcd. for $C_{25}H_{42}N_2O$ $[M+Na]^+$ 409.3189, found 409.3171. LC/MS (ESI) $[M+H]^+$ 387.3, $[M+Na]^+$ 409.3.



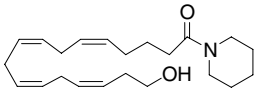
4f 65%

4f: yield 65%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.40 (m, 8H), 3.13 (m, 2H), 2.90 (m, 6H), 2.80 (m, 2H), 2.27 (m, 2H), 2.20 (m, 2H), 1.70(m, 2H), 1.50 (m, 4H), 1.30 (m, 8H), 0.92 (t, *J*=7.2 Hz, 3H) 0.88 (m, 3H). LC/MS (ESI) $[M+H]^+$ 374.3, $[M+Na]^+$ 396.3. HRMS (MALDI-FTMS) calcd. for $C_{25}H_{43}NO$ $[M+Na]^+$ 396.3237, found 396.3235.



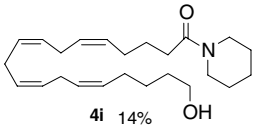
4g 17%

4g: yield 17%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.4 (m, 8H), 3.55 (t, *J*=5.4 Hz, 2H), 3.35 (t, 5.3 Hz, 2H), 2.89 (m, 6H), 2.30 (m, 2H), 2.00-2.15 (m, 4H), 1.60 (m, 6H), 1.20-1.30 (m, 8H), 0.90 (t, *J*=6.7 Hz, 3H). HRMS (MALDI-FTMS) calcd. for $C_{25}H_{41}NO$ $[M+H]^+$ 372.3261, found 372.3265. LC/MS (ESI) $[M+H]^+$ 372.3, $[M+Na]^+$ 394.3.



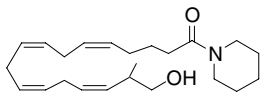
4h 18%

4h: yield 18%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.38 (m, 8H), 3.75 (t, *J*=6.5 Hz, 2H), 3.55 (t, *J*=5.5 Hz, 2H), 3.35 (m, 2H), 3.35 (m, 6H), 2.35 (m, 2H), 2.20 (m, 2H), 2.00 (m, 2H), 1.60 (m, 6H), 1.40 (m, 2H). HRMS (MALDI-FTMS) calcd. for $C_{22}H_{35}NO_2$ $[M+Na]^+$ 368.256, found 368.2555. LC/MS $[M+H]^+$ 346.2, $[M+Na]^+$ 368.2.



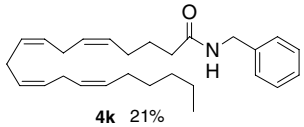
4i 14%

4i: yield 14%. LC/MS $[M+H]^+$ 374.2, $[M+Na]^+$ 396.3.



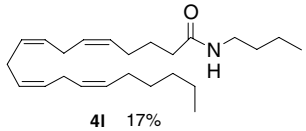
4j 5.9%

4j: yield 5.9%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.40 (m, 8H), 3.55 (br, 2H), 3.40 (br, 2H), 3.20 (m, 2H), 2.84 (m, 6H), 2.33 (m, 3H), 2.15 (m, 2H), 1.50-1.70 (m, 6H), 1.30 (m, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 199.54, 130.96, 129.43, 128.87, 128.70, 128.36, 68.14, 38.69, 30.33, 29.69, 28.91, 24.59, 23.72, 22.98, 14.05, 10.95. HRMS (MALDI-FTMS) calcd. for $C_{23}H_{37}NO_2$ $[M+Na]^+$ 382.2716, found 382.2723.



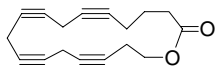
4k 21%

4k: yield 21%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20-7.40 (m, 5H), 5.35 (m, 8H), 4.45 (d, *J*=5.6 Hz, 2H), 2.79 (m, 6H), 2.22 (m, 2H), 2.00 (m, 4H), 1.75 (m, 4H), 1.30 (m, 4H), 0.90 (t, *J*=6.0 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 172.60, 138.28, 130.51, 129.06, 128.78, 128.72, 128.56, 128.20, 128.13, 127.85, 127.53, 127.49, 43.62, 36.07, 31.49, 29.69, 29.29, 27.19, 27.07, 26.66, 25.61, 25.49, 22.56, 14.07. HRMS (MALDI-FTMS) calcd. for $C_{27}H_{39}NO$ $[M+Na]^+$ 416.2924, found 416.2927. ESI $[M+Na]^+$ 416, $[M+Cl]^-$ 428. LC/MS $[M+H]^+$ 394.2, $[M+Na]^+$ 416.2.



4l 17%

4l: yield 17%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.34 (m, 8H), 3.25 (q, *J*=6.7 Hz, 2H), 2.70-2.90 (m, 6H), 2.20 (m, 6H), 1.80 (m, 2H), 1.70 (m, 2H), 1.50 (m, 4H), 1.30 (m, 4H), 0.90 (m, 6H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 187.10, 128.93, 128.79, 128.18, 127.85, 127.62, 127.27, 125.27, 124.29, 66.96, 39.24, 36.21, 31.75, 27.23, 25.65, 24.76, 22.59, 22.24, 20.09, 14.09, 13.77. HRMS (MALDI-FTMS) calcd. for $C_{24}H_{41}NO$ $[M+H]^+$ 360.3261, found 360.3256. LC/MS $[M+H]^+$ 360.3, $[M+Na]^+$ 382.3.



13a

13a: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.42 (t, *J*=6.9 Hz, 2H), 3.14 (m, 6H), 2.64 (tt, *J*=6.9 Hz, 2.26Hz, 2H), 2.49 (t, *J*=7.4 Hz, 2H), 2.27 (tt, *J*=6.9 Hz, 2.3 Hz, 2H), 1.83 (quint, *J*=7.1 Hz, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 177.86, 79.31, 76.34, 75.02, 74.88, 74.58, 74.52, 74.29, 74.10, 65.53, 32.44, 29.69, 23.49, 18.88, 18.05, 9.75. LC/MS ESI $[M+H]^+$ 251.3