Supporting information Appendix

Opioid mu agonist/mGluR$_5$ antagonist bivalent ligands produce potent antinociception in mice with inflammatory pain

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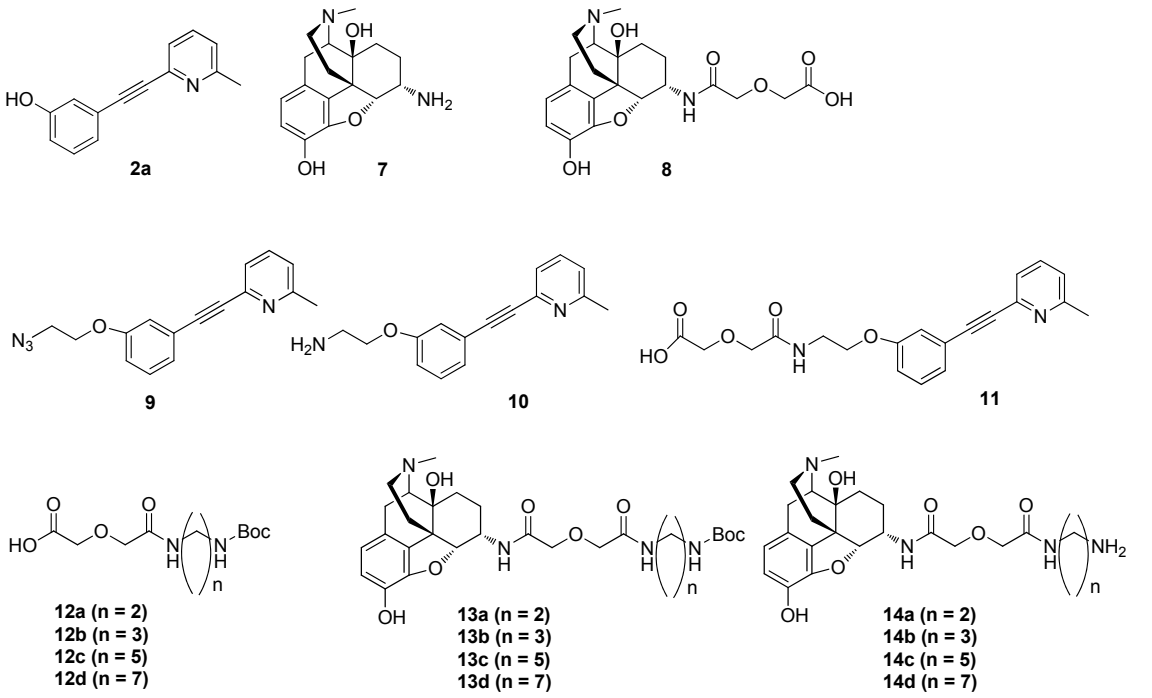
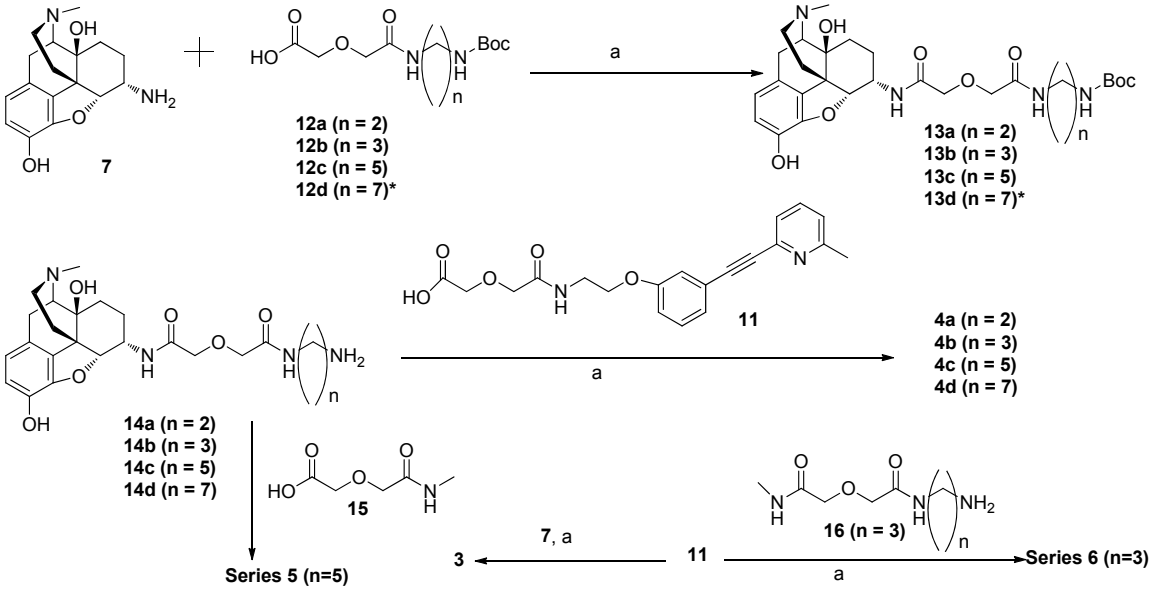
Appendix Contents:



SI Figure 1. Intermediates required for the synthesis of **3**, **4a-4d**, **5**, and **6**.



a) HOBt/DCC, DMF, 50 °C ; *) Cbz protected amine was used!

SI Figure 2. Synthetic scheme for bivalent ligands **3, 4a-4d** and monovalent ligands **5-6.**

EXPERIMENTAL SECTION

Chemistry

General. Oxymorphone was obtained from Mallinckrodt & Co. All other chemicals and solvents were purchased from Aldrich or Fisher without further purification. ^{1}H and ^{13}C NMR spectroscopy were obtained on 300 MHz on an Oxford Varian VXR 300 MHz NMR Spectrometer. Mass spectroscopy was obtained on Bruker BioTOF II mass spectrometry. Purities of bivalent ligands (**3**), (**4a-d**), and the monovalent ligands (**5-6**) were over 98% based on analysis on HPLC column (Phenomenex Luna SB-C18 (2) 5u 4.6×250mm) which was eluted with MeOH/Buffer (60:40) at a flow rate of 1 ml/min.

2-((3-methoxyphenyl)ethynyl)-6-methylpyridine, M-MPEP (2): To a solution of hydroxy-MPEP(1) (**2a**) in Hünig base in MeOH: MeCN (1:9, 5 mL) was added TMS diazomethane(2) (2M solution in Et_2O) dropwise. The reaction was allowed to stir for 1 hr. Removal of solvents in vacuum provided crude product. ^{1}HNMR analysis indicated the formation of desired product **2**.

***N*-((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)-2-(2-((2-(3-((6-methylpyridin-2-yl)ethynyl)phenoxy)ethyl)amino)-2-oxoethoxy)acetamide (3**): To acid **11** (0.146 g, 0.396 mmol) was added HOBt (0.059 g, 0.436 mmol), DCC (0.99 g, 0.476 mmol) and DMF (4 ml, 0.1M) followed by addition of α-oxymorphamine (**7**) (0.120 g, 0.396 mmol). After 24 h. TLC analysis indicated completion of reaction. The reaction mixture was filtered to remove urea followed by DMF removal in vacuum to crude product which was further purified on SiO_2 column chromatography using EtOAc (100%), and then the mixture (CH_2Cl_2/MeOH/NH_4OH, 95/4/1, v/v/v) as solvent to give 0.185 g (76%) of **3** as light yellow semi-solid. ^{1}H NMR (400 MHz, CD_3OD) 7.72 (t, 7.6Hz, 1H), 7.39 (d, 8Hz, 1H), 7.26-7.31 (m, 2H), 7.14-7.16 (m, 2H), 6.98-7.01 (m, 1H), 6.64 (d, 8.4Hz, 1H), 6.52 (d, 8.4Hz, 1H), 4.48-4.53 (m, 2H), 4.07-4.14 (m, 6H (one m and two singlet's), 3.62-3.73 (m, 2H), 3.12 (br d, 18.4Hz, 1H), 2.79 (d, 6.4Hz, 1H), 2.53-2.80 (m, 1H), 2.52 (s, 3H), 2.42 (d, 7.2Hz, 1H), 2.53 (s, 3H), 2.25 (d, 8.0Hz, 2H), 1.64-1.72 (m, 1H), 1.37-1.55 (m, 3H), 0.97-1.08 (m, 1H). ^{13}C NMR (100 MHz) 171.93, 170.74, 159.99, 159.91, 146.98, 143.01, 139.34, 138.65, 131.87, 130.83, 126.62, 125.76, 125.58, 124.41, 124.22, 120.28, 118.48, 118.47, 117.14, 90.30, 90.20, 89.00, 71.55, 71.16, 67.46, 65.78, 47.55, 47.15, 45.83, 43.37, 39.63, 34.46, 30.31, 23.90, 22.99, 21.58. MS(ESI)-TOF observed 653.3360 $(M+1)^+$, 675.3173 $(M+Na^+)$, required exact mass 652.2897.

***N*-((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)-2-((14-(3-((6-methylpyridin-2-yl)ethynyl)phenoxy)-2,7,11-trioxo-9-oxa-3,6,12-triazatetradecyl)oxy)acetamide) (4a)**: To the mixture of acid **11** (freshly prepared!, 0.142 g, 0.385 mmol, 1.1 eq), HOBt (0.069g, 0.510 mmol, 2.0 eq), DCC (0.105 g, 0.510 mmol, 2.0 eq) at 0 ^{o}C was added DMF (2 mL) and stirred for 15 min. A light yellow precipitated solution resulted. To this solution of amine **14a** (0.162.5 g, 0.351 mmol, 1.0 eq) in a solvent mixture of Hünig base/DMF (3 mL, 1/5, v/v) was added. The ice-water bath was removed and the reaction was allowed to stir at rt for 17 h. MS (ESI) of crude reaction mixture indicated the formation of the desired product. The solvent was removed in vacuum and further purification was performed over silica gel column chromatography using the mixture (CH_2Cl_2/MeOH/NH_4OH, 97/2.5/0.5, 95/4/1 to 89/10/1, v/v/v). The final product **4a** was isolated as amorphous light yellow solid (0.170 g, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, 8Hz, 2H), 7.14 (d, 8.0Hz, 1H), 7.10-7.04 (m, 3H), 7.03 (t, 8.0Hz, 2H), 7.02 (br s, 1H), 6.98-7.01 (m, 1H), 6.90 (d,d, 8Hz, 3.6Hz, 1H), 6.73 (d, 8Hz, 1H), 6.52 (d, 8Hz, 1H), 450-4.55 (m, 2H), 4.05-4.09 (m, 8H), 4.01 (d, 4Hz, 1H), 3.69-3.72 (m, 2H), 3.38-3.41 (p, 6.4Hz, 2H), 3.27-0.99 (unidentified peaks). ^{13}C NMR (100 MHz) δ 170.62, 169.99, 169.25, 168.09, 158.85, 158.23, 145.51, 142.19, 138.08, 136.71, 130.78, 129.57, 125.35, 124.86, 124.55, 123.25, 122.92, 119.33, 117.51, 115.92, 89,21, 88.73, 88.57, 76.86, 70.88, 70.71, 70.58, 70.36, 69.60, 66.33, 64.51, 53.50, 46.37, 45.83, 44.74, 43.05, 40.07, 39.07, 38.62, 33.31, 29.63, 29.11, 25.07, 24.35, 22.54, 22.07, 21.05. MS(ESI)-TOF observed 811.3301 $(M+1)^{+}$, required for $C_{43}H_{50}N_6O_{10}$ 810.3588.

***N*-((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)-2-((1-(3-((6-methylpyridin-2-yl)ethynyl)phenoxy)-4,8,14-trioxo-6-oxa-3,9,13-triazapentadecan-15-yl)oxy)acetamide (4b)**: To the mixture of acid **11** (freshly prepared!, 0.118 g, 0.321 mmol, 1.3 eq), HOBt (0.067g, 0.593 mmol, 2.0 eq), and DCC (0.102 g, 0.593 mmol, 2.0 eq) at 0^{o}C, DMF (2 mL) was added and stirred for 15 min. A light yellow precipitated solution resulted. To this solution, a solution of amine **14b** (0.126 g, 0.246 mmol, 1.0 eq) dissolved in the mixture of Hünig base/DMF (3 mL, 1/5, v/v) was added. The ice-water bath was removed and the reaction was allowed to stir at rt for 17 h. MS (ESI) of crude reaction mixture indicated the formation of the desired product. Then, the solvent was removed in vacuum and further purification was performed over silica gel column chromatography using the solvent mixture (CH_2Cl_2/MeOH/NH_4OH, 97/2.5/0.5, 95/4/1 to 89/10/1, v/v/v). The final product **4b** was isolated as amorphous light yellow solid

(0.067 g, 33% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (t, 5.6Hz, 1H), 7.82-7.88 (m, 2H), 7.61 (t, 7.6Hz, 1H), 7.36 (d, 7.6Hz, 1H), 7.20-7.28 (m, 2H), 7.13 (d,d, 8Hz, 4Hz, 2H), 7.03 (br s, 1H), 6.86 (dd, 8Hz, 2Hz, 1H), 6.70 (d, 8Hz, 1H), 6.51 (d, 8.0HZ, 1H), 4.51-4.58 (m, 2H), 4.00-4.08 (m, 8H), 3.64-3.67 (m, 2H), 3.30-3.42 (m, 4H), 3.08 (d, 19.2Hz, 1H), 2.78 (d, 6.4Hz, 1H), 2.50-2.58 (m, 4H), 2.34 (s, 3H), 2.15-2.41 (m, 6H), 1.69-1.70 (m, 3H), 1,49-1.56 (m, 2H), 1.33-1.39 (m, 1H), 1.25 (m, 1H), 0.98 (m, 1H). ^{13}C NMR (100 MHz) δ 169.97, 168.94, 168.91, 167.95, 158.71, 158.14, 145.14, 142.01, 137.95, 136.79, 130.71, 129.50, 125.29, 124.63, 124.50, 123.09, 122.94, 119.21, 117.55, 115.41, 70.97, 70.74, 70.45, 70.40, 69.51, 66.32, 64.45, 46.27, 45.63, 44.71, 42.95, 38.36, 35.55, 34.89, 33.14, 29.54, 28.99, 28.95, 28.87, 24.15, 21.98, 20.99. MS(ESI)-TOF observed 825.1723 (M+1), 847.1372 ($M+Na^+$), required for $C_{44}H_{52}N_6O_{10}$ 824.3745.

***N*-((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)-2-((1-(3-((6-methylpyridin-2-yl)ethynyl)phenoxy)-4,8,16-trioxo-6-oxa-3,9,15-triazaheptadecan-17-yl)oxy)acetamide (4c)**: To the mixture of acid **11** (freshly prepared!, 0.142 g, 0.385 mmol, 1.11 eq), HBTU (0.265 g, 0.695 mmol, 2.0 eq) and HOBt solution (1.40 mL of 0.5M HOBt solution in DMF, 0.695 mmol, 2.0 eq) was added at room temperature and stirred for 0.5 h. A light yellow solution with no precipitate resulted. To this solution, a solution of amine **14c** (0.200 g, 0.348 mmol, 1.0 eq) dissolved in the solvent mixture of Hünig base/DMF (3 mL, 1/5, v/v) was added. The reaction was allowed to stir at rt for 20 h. Then, the solvent was removed in vacuum and further purification was performed over silica gel column chromatography using the solvent mixture (CH_2Cl_2/MeOH/NH_4OH, 95/4/1 to 92/7.5/0.5, v/v/v). The final product **4c** was isolated as amorphous off white solid (0.251 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (t, 8Hz, 2H), 7.36 (d, 8.0Hz, 1H), 7.22-7.27 (m, 3H), 7.15 (t, 8.0Hz, 2H), 7.06 (br s, 1H), 6.98-7.01 (m, 1H), 6.90 (dd, 8Hz, 3.6Hz, 1H), 6.73 (d, 8Hz, 1H), 6.52 (d, 8Hz, 1H), 450-4.55 (m, 2H), 4.05-4.09 (m, 8H), 4.01 (d, 4Hz, 1H), 3.69-3.72 (m, 2H), 3.38-3.41 (p, 6.4Hz, 2H), 3.27-3.32 (m, 4H), 3.10 (d, 19Hz, 1H), 2.85 (dd, 13.2Hz, 7.2Hz, 2H), 2.76 (d, 6.4Hz, 1H), 2.57 (s, 3H), 2.16-2.41 (m, 3H), 2.33 (s, 3H), 1.70-1.80 (m, 1H), 1.50-1.62 (m, 6H), 1.29-1.36 (m, 3H), 0.99-1.20 (m, 1H). ^{13}C NMR (100 MHz) δ 169.36, 169.22, 169.01, 168.49, 158.63, 158.03, 145.59, 142.04, 138.05, 136.52, 130.50, 129.39, 125.15, 124.63, 124.36, 123.04, 122.71, 119.12, 117.73, 117.23, 115.72, 89.16, 88.48, 88.39, 71.15, 70.98, 70.67, 69.42, 66.11, 64.35, 51.88, 46.16, 45.62, 44.53, 42.88, 41.02, 38.90, 38.38, 38.26, 33.15, 29.04, 28.49, 28.24, 24.18, 23.46, 21.83, 20.96, 14.20. MS(ESI)-TOF observed 853.3502 (M+1), 875.3254 ($M+Na^+$), required for $C_{46}H_{56}N_6O_{10}$ 852.4058.

***N*-((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)-2-((1-(3-((6-methylpyridin-2-yl)ethynyl)phenoxy)-4,8,18-trioxo-6-oxa-3,9,17-triazanonadecan-19-yl)oxy)acetamide (4d)**: A solution of carboxylic acid **11** (158 mg, 0.42 mmol, 1eq), DCC (97.3 mg, 0.47 mmol, 1.1 eq), and HOBt (64 mg, 0.47 mmol, 1.1 eq) in DMF (4 mL) was stirred at rt. for 20 min. To this mixture, the amine **14d** (217 mg, 0.40 mmol, ~1 eq) was added in one portion, and the reaction mixture was stirred under N_2 at 50 ^oC for 24 h. The DCU precipitate was collected via vacuum filtration and the filtrate was added to ethyl ether (100 mL) to facilitate precipitation of the crude product. The crude product was isolated by vacuum filtration and purified further via flash chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH, 85/14.5/0.5, v/v/v).

Yield: 40 mg, 11%. ^{1}H-NMR (CD_2Cl_2): 7.62 (t, 8Hz, 2H), 7.36 (d, 8.0Hz, 1H), 7.22-7.27 (m, 3H), 7.15 (t, 8.0Hz, 2H), 7.06 (br s, 1H), 6.98-7.01 (m, 1H), 6.90 (dd, 8Hz, 3.6Hz, 1H), 6.73 (d, 8Hz, 1H), 6.52 (d, 8Hz, 1H), 450-4.55 (m, 2H), 4.05-4.09 (m, 8H), 4.01 (d, 4Hz, 1H), 3.69-3.72 (m, 2H), 3.38-3.41 (p, 6.4Hz, 2H), 3.27-0.99 (unidentified peaks). ^{13}C-NMR (CD_2Cl_2): 169.4, 169.0, 168.6, 168.5, 158.9, 158.4, 145.9, 142.1, 138.3, 136.5, 130.6, 129.6, 124.7, 124.3, 123.2, 122.8, 119.2, 118.02, 117.3, 115.8, 89.4, 88.6, 88.2, 71.5, 71.3, 71.1, 71.05, 70.9, 69.7, 68.5, 66.6, 65.6, 64.7, 52.8, 51.9, 46.2, 45.6, 44.3, 42, 39.1, 38.7, 38.4, 34.5, 31.5, 22.6, 22.6, 15.04, 13.8. MS(ESI)-TOF observed: 881.4440 $(M+H)^+$, required for $C_{48}H_{60}N_6O_{10}$ 880.4449.

***N*^{1}-(5-(2-(2-(((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)amino)-2-oxoethoxy)acetamido)pentyl)-N^5-methylglutaramide (5):** A solution of carboxylic acid **15** (0.053 g , 0.363 mmol, 1.1 eq), HOBt(0.049 g, 0.363 mmol, 1.1 eq), DCC(0.075 g, 0.363 mmol, 1.1 eq) in DMF (0.5 mL) was stirred for 30 min. Amine **14c** (0.165 g, 0.330 mmol, 1.0 eq) was added in one portion, and the reaction mixture was stirred under N_2 at rt for 72 h. The DCU precipitate was collected by vacuum filtration and the filtrate was added to ethyl ether (100 mL) to facilitative precipitation of the crude product. The product was collected by vacuum filtration and washed successively with diethyl ether (50 mL) and n-hexanes (50 mL). Further purification by flash chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH, 95/4/1, v/v/v) gave a yield of 0.083 g (40.3%); mp. 77ºC (softens), 89 ºC (melts). ^{1}H NMR (400 MHz, DMSO-d6) δ 8.94(br, s, 1H), 8.07-7.99(m, 3H), 7.55(d, 8.4Hz, 1H), 6.58(d, 8.4Hz, 1H), 6.48(d, 8.1Hz, 1H), 4.81(br, s, 2H), 4.47(d, 3.9Hz, 1H), 4.83-4.31(m, 1H), 3.98(s, 2H), 3.96(d, 3.0Hz, 2H), 3.12-3.01(m, 5H), 2.77-2.72(d, 1H), 2.64(d, 4.5Hz, 3H), 2.55(d, 1H), 2.40-2.37(m, 1H), 2.29(s, 3H), 2.19-2.09(m, 2H), 1.64-1.52(m, 1H),

1.47-1.23(m, 9H), 1.00-0.86(m, 1H); HR-FAB MS m/z 632.3294$(M+1)^+$, required for $C_{31}H_{45}N_5O_9$ 631.3217.

***N*-methyl-2-(1-(3-((6-methylpyridin-2-yl)ethynyl)phenoxy)-4,8,14-trioxo-6-oxa-3,9,13-triazapentadecan-15-yloxy)acetamide (6)**: To the mixture of acid **11** (freshly prepared!, 0.225 g, 0.610 mmol, 1.10 eq), a mixture of HBTU (0.421 g, 1.11 mmol, 2.0 eq) and HOBt solution (2.22 mL of 0.5M HOBt solution in DMF, 1.11 mmol, 2.0 eq) was added at rt and stirred for 20 min. To this resulting precipitated solution, a solution of amine **16** (0.133 g, 0.555 mmol, 1.0 eq) dissolved in a solvent mixture of Hunig base/ DMF(6 mL, 1/11, v/v) was added. This transparent light brown solution was allowed to stir at rt for 17 h. The solvent was removed in vacuum and further purification of the crude product over silica gel column chromatography using the solvent mixture (CH_2Cl_2/MeOH/NH_4OH, 92/7.5/0.5, v/v/v) gave 0.185 g (60%) the final product **6**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-6.96(m, 8H), 4.06(m, 2H), 4.01(s, 2H), 3.96(s, 2H), 3.92(s, 2H), 3.89(s, 2H), 3.60-3.2(m, 6H), 2.67(d, 4.8Hz, 3H), 2.49(s, 3H), 1.33(m, 2H). ^{13}C NMR (100 MHz) δ 169.57, 169.35, 169.16, 169.07, 168.99, 158.75, 158.16. 142.04, 136.86, 129.63, 124.65, 124.53, 123.12, 117.45, 116.08, 115.96, 88.77, 88.34, 70.36, 66.25, 55.0, 42.99, 38.29, 25.52, 24.25, 18.39, 16.97, 12.45. MS(ESI)-TOF observed 554.3867 (M+1), 576.3735 ($M+Na^+$), required for $C_{28}H_{35}N_5O_7$ 553.2536.

(5α,6α)-6-Amino-4,5-Epoxy-3,14-dihydroxy-17-methylmorphinan[α-Oxymorphamine] (7): The benzyl-protected α-oxymorphamine was dissolved in methanol (150 mL) and transferred to a Parr bottle (250 mL) containing a suspension of Pearlman's catalyst (20% $Pd(OH)_2$/C) (2.0 g, 25% by wt of substrate) in methanol (20 mL). The reaction was carried out at 70 PSI (H_2 gas) on the Par apparatus for 38h, at which time TLC (D/M/A, 89/10/1, v/v/v) showed the complete disappearance of starting material. The reaction mixture was filtered over Celite and the solvent was removed in vacuum to give a crude product. Purification by flash chromatography (silica gel, starting with CH_2Cl_2/MeOH/NH_4OH 94.5/5/0.5, v/v/v and switching to CH_2Cl_2/MeOH/NH_4OH, 89/10/1, v/v/v, midway through) gave 7.52 g (70.5 % yield over the last three steps) of amine; R_f = 0.1 (silica gel, D/M/A. 89/10/1. v/v/v). ^{1}H NMR (400 MHz, D_2O-d_2) δ 6.77(d, 8.4 Hz, 1H), 6.83(d, 8.4 Hz, 1H), 4.81(d, 3.9 Hz, 1H), 3.81(t, 4.2 Hz, 1Hz), 3.77(d, 3.9 Hz, 1H), 3.59(d, 6.9 Hz, 1H), 3.20-2.79 various un resolved peaks, 2.42(m, 1H), 1.03(m, 1H). HR-FAB MS/$C_{17}H_{22}N_2O_3$ $[M+H]^+$, calcd. 302.16304, found 302.1683.

2-(2-(((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)amino)-2-oxoethoxy)acetic acid (8): Diglycol anhydride (0.96 g, 8.267 mmol, 1.0 eq) was added (as a solid) in one portion to a stirred solution of α-oxymorphamine (**7**) (2.50 g, 8.267 mmol, 1.0 eq) in THF (110 mL). The flask was sealed with a septum and was stirred at rt for 18 h. The product was then collected by filtration and washed with THF to afford 3.00 g(86.7%) of the acid; mp>260 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, 8.1 Hz, 1H0, 6.56(d, 7.8 Hz, 2H), 6.50(d, 7.8 Hz, 2H), 4.45(d, 4.2 Hz, 1H), 4.37-4.28(m, 1H), 3.92(d, 1.5 Hz, 2H), 3.90(d, 1.8 Hz, 2H), 3.15(s, 1H), 2.79-2.72(m, 1H), 2.49-2.39(m, 5H), 2.33-2.23(m, 2H), 1.65-1.60(m, 1H), 1.48(d, 10.8 Hz, 1H), 1.34-1.27(m, 2H), 0.89-0.80(m, 1H).

2-((3-(2-azidoethoxy)phenyl)ethynyl)-6-methylpyridine (**9**): Added 5.5 mL of dry MeCN to a mixture of 3-hydroxy-MPEP (**2a**) (0.333 g, 1.59 mmol) and K_2CO_3 (1.1 g, 7.955 mmol) and allowed to react at room temperature for 40 min. To the light yellow slurry was added 2-azidoethyl 4-methylbenzenesulfonate(3) (0.576 g, 2.387 mmol) solution in MeCN (3 mL). The reaction was allowed to stirr at room temperature for 5 min. and then heated to 70 ^{o}C until TLC analysis indicated consumption of starting material (~5h). The reaction was allowed to cool to room temperature and concentrated in vacuum. The slurry obtained was added water and extracted with EtOAc (4 X 25 mL), dried over anhydrous $MgSO_4$, concentrated in vacuum to provide crude product which was further purified by column chromatography using EtOAc: Hex (1:5) to provide 0.414 g (93%) of **9** brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.22-7.30 (m, 2H), 7.15-7.16 (m, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.94-6.97 (m, 1H), 4.16 (t, J = 4.0 Hz, 2H), 3.61 (t, J = 4.0 Hz, 2H), 2.59 (s, 3H).

2-(3-((6-methylpyridin-2-yl)ethynyl)phenoxy)ethanamine (10): To a solution of azide **9** (0.147 g, 0.528 mmol) in 2.5 mL THF was added PPh_3 (0.208 g, 0.792 mmol) and 0.5 mL of water. Evolution of gas resulted and the reaction mixture was allowed to stir at room temperature over night. The reaction mixture was concentrated in vacuum, re-dissolved in EtOAc and passed through short SiO_2 column (length = 15 cm., diameter = 2.5 cm) while first washing with EtOAc to remove by-products and then with (CH_2Cl_2/ MeOH/NH_4OH, 89/10/1, v/v/v). The fractions containing the desired product are dried over anhydrous MgSO4, concentrated in vacuum to provide 0.110 g (86%) of **10** as light yellow oil.

^{1}H NMR (400 MHz, CD_3OD) 7.65 (t, 7.6Hz, 1H), 7.37 (d, 7.6, 1H), 7.27 (t, 8.4Hz, 1H), 7.14-7.21 (m, 3H), 6.98-7.00 (m, 1H), 3.99 (t, 5.2Hz, 2H), 2.99 (t, 5.3Hz, 2H), 2.49 (s, 3H). ^{13}C NMR (100

MHz) 160.19, 160.05, 143.14, 138.64, 130.84, 125.73, 125.55, 124.41, 124.33, 118.50, 117.20, 90.16, 89.01, 70.44, 41.75, 23.91.

2-(2-(2-(3-((6-methylpyridin-2-yl)ethynyl)phenoxy)ethylamino)-2-oxoethoxy)acetic acid (11): To a mixture of amine **10** (0.362 g, 1435 mmol) and commercially available diglycolic anhydride (0.172, 1.435 mmol) was added in THF (15 ml, 0.1 M). After 2 h. the TLC analysis indicated completion of reaction. Removal of solvent under reduced pressure, followed by purification of crude product on silica gel chromatography (THF/ MeOH, 1/4, v/v) provided 0.5 g (95%) of acid **11** as yellow fluffy solid. ^{1}H NMR (400 MHz, CD_3OD) 7.75 (t, 8Hz, 1H), 7.34 (d, 7.6Hz, 1H), 7.18-7.24 (m, 2H), 7.07-7.09 (m, 2H), 6.92-6.95 (m, 1H), 4.09 (s, 2H), 4.02 (t, 5.6Hz, 2H), 3.99 (s, 2H), 3.57 (t, 5.6Hz, 2H), 2.44 (s, 3H).

2,2-dimethyl-4,9-dioxo-3,11-dioxa-5,8-diazatridecan-13-oic acid (12a): To a colorless/ transparent solution of glycolic anhydride (0.44 g, 3.67 mmol, 1.0 eq) in THF (6 mL) at -50^{o}C was added *tert*-butyl (2-aminoethyl)carbamate (4) (0.581 ml, 0.588 g, 3.67 mmol, 1.0 eq) dropwise. The cold bath was removed and the reaction was allowed to stir at rt for 20 h. The solvent was removed to provide **12a** as a white solid (0.985 g, 97% yield).

MS(ESI)-TOF (negative) observed 275.1636 (M-1), required exact mass 276.1321.

2,2-dimethyl-4,12-dioxo-3,14-dioxa-5,11-diazahexadecan-16-oic acid (12c): To a colorless/ transparent solution of glycolic anhydride (0.3 g, 3.26 mmol, 1.0 eq) in THF (6 mL) at -50^{o}C, tert-butyl (5-aminopentyl)carbamate (0.7 ml, 0.66 g, 3.26 mmol, 1.0 eq) was added dropwise. The cold bath was removed and the reaction was allowed to stir at rt for 21 h. The solvent was removed in vacuum to provide **12c** as light yellow oil (1.038 g, quant. yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (t, 5.6Hz, 1H), 6.73 (t, 5.6Hz, 1H), 4.07 (s, 2H), 3.93 (s, 2H), 3.06 (dd, 13.2Hz, 6.8Hz, 2H), 2.87 (dd,13.0Hz, 6.8Hz, 2H), 1.35 (s, 9H), 1,14-1.23 (m, 2H). ^{13}C NMR (100 MHz) δ 171.49, 168.58, 155.59, 77.32, 70.19, 67.90, 38.10, 29.16, 28.82, 28.28, 23.67. MS(ESI)-TOF (negative) observed 317.2211 (M-1), required for $C_{10}H_{22}N_2O_2$ 318.1791.

3,13-dioxo-1-phenyl-2,15-dioxa-4,12-diazaheptadecan-17-oic acid (12d): Mono-Cbz protected heptadiamine 1,7 (2.59 g, 0.98 mmol) and glycolic anhydride (1.14 g, 0.98 mmol) were mixed in 200 mL anhydrous THF, and stirred overnight at room temperature. Next day, the precipitate that formed was filtered, and filtrate dried in vacuum.Yield: 70%. ^{1}H-NMR(d_6-DMSO)= 7.8 (m, 1H), 7.3-7.2(m, 5H), 7.1(m, 1H), 4.9(s, 2H), 4.0(s, 2H), 3.9 (s, 2H), 3.0-2.9(m, 4H), 1.4-1.2(m, 10H).

***tert*-butyl(2-(2-(2-(((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)amino)-2-oxoethoxy)acetamido)ethyl)carbamate (13a)**: To a solution of acid **12a** (0.550 g, 1.984 mmol, 1.5 eq) in DMF (1 ml) and CH_2Cl_2 (12 mL) was added EEDQ (0.496 g, 1.984 mmol, 1.5 eq) and stirred for 15 min. To this solution α-oxymorphamine (**7**) (0.4 g, 1.323 mmol, 1.0 eq) in CH_2Cl_2 (3 mL) was added. After 4 h., TLC analysis indicated completion of the reaction. The solvent was removed in vacuum and the crude product was purified over silica gel column chromatography using CH_2Cl_2 (100%), and then the mixture (CH_2Cl_2/MeOH/NH_4OH, 95/4/1, v/v/v). The final product **13a** was isolated as light brown amorphous solid (0.684 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (br d, 8.0Hz, 1H), 7.27 (br s, 1H), 6.63 (d, 8.0Hz, 1H), 6.46 (d, 8.0Hz, 1H), 5.55 (br s, 1H), 4.41-4.46 (m, 2H), 3.96-4.03 (m, 4H), 3.20-3.35 (m, 4H), 3.04 (br d,19.0Hz, 1H), 2.70 (d, 6.0Hz, 1H), 2.48-2.53 (dd, 12Hz, 6.4Hz, 1H), 2.26 (s, 3H), 2.14-2.34 (m, 3H), 1.63-1.72 (m, 1H), 1.46-1.56 (m, 2H), 1.34 (s, 9H), 0.85-0.96 (m, 1H). ^{13}C NMR (100 MHz) δ 169.61, 168.07, 157.53, 145.54, 138.16, 130.79, 125.37, 119.30, 117.49, 89.26, 79.95, 76.89, 71.03, 70.78, 69.57,64.57, 46.41, 45.66, 44.77, 43.08, 39.86, 39.69, 33.24, 29.15, 28.30, 22.03, 21.31.

MS(ESI)-TOF observed 583.2337 (M+Na), required for $C_{28}H_{40}N_4O_8$ 560.2846.

***tert*-butyl(3-(2-(2-(((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)amino)-2-oxoethoxy)acetamido)propyl)carbamate (13b)**:[♣] To a 25 mL flame dried round bottom flask, glycolic anhydride (0.069 g, 0.594 mmol, 1.1 eq) and THF (1 mL) was added followed by addition of tert-butyl (3-aminopropyl)carbamate (0.107g, 0.594 mol, 1.1 eq) and stirred at rt for 1.75 h. until TLC indicated completion of the reaction. To this mixture a solution of α-oxymorphamine (**7**) (0.173 g, 0.574 mmol, 1.0 eq) in minimum amount of DMF (0.4 mL) and EEDQ (0.213 g, 0.861 mmol, 1.5 eq) was added. The light brown solution was stirred at rt for 17 h. until TLC indicated completion of the reaction. After that the solvent was removed in vacuum to provide crude product which was purified over silica gel column chromatography using EtOAc (100%), and then the mixture (CH_2Cl_2/MeOH/NH_4OH, 95/5/1 to 90/10/1, v/v/v). The final product **13b** was isolated as amorphous off-white solid (0.195 g, 59% yield).

[♣] Acid **12b** was generated instantly and without isolation utilized.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (t, 6.0Hz, 1H), 7.55 (d, 5.6Hz, 1H), 7.37 (s, 1H), 6.7 (d, 8.0Hz, 1H), 6.52 (d, 8.8Hz, 1H), 5.57 (br s, 1H), 4.52-4.57 (m, 2H), 4.02-4.07 (m, 4H), 3.35-3.37 (m, 2H), 3.10-3.14 (m, 3H), 2.77 (d, 6.4Hz, 1H), 2.56 (dd, 18.4Hz, 6.4Hz, 1H), 2.19-2.42 (m, 3H), 2.34 (s, 3H), 1.70-1.76 (m 3H), 1.53-1.59 (m, 2H), 1.42 (s, 9H), 1.41 (m, 1H), 0.99-1.10 (m, 1H). ^{13}C NMR (100 MHz) δ169.32, 168.21, 156.38, 145.61, 138.14, 130.37, 124.80, 118.90, 117.73, 88.91, 78.84, 71.07, 70.90, 69.38, 64.27, 46.10, 45.60, 44.49, 42.79, 37.16, 35.94, 33.03, 29.37, 28.83, 28.30, 21.74, 20.83. MS(ESI)-TOF observed 575.3625 (M+1), 597.3467 ($M+Na^+$), required for $C_{29}H_{42}N_4O_8$ 574.3003.

***tert*-butyl(5-(2-(2-(((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)amino)-2-oxoethoxy)acetamido)pentyl)carbamate (13c)**: To a solution of acid **12c** (0.630 g, 1.984 mmol, 1.5 eq) in CH_2Cl_2 (6 mL) was added EEDQ (0.496 g, 1.984 mmol, 1.5 eq) and stirred for 10 min. followed by addition of a solution of α-oxymorphamine (**7**) (0.4 g, 1.323 mmol, 1.0 eq) in THF (3 mL). After 4.5 h., TLC analysis indicated completion of the reaction. Then, the solvent was removed in vacuum and the crude product was purified over silica gel column chromatography using CH_2Cl_2 (100%), and then the solvent mixture (CH_2Cl_2/MeOH/NH_4OH, 95/4/1, v/v/v). The final product **13c** was isolated as light brown amorphous solid (0.705 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.35 (br d, 7.6Hz, 1H), 7.25 (s, 1H), 6.76 (d, 8Hz, 1H), 6.67 (t, 6Hz, 1H), 6.54 (d, 8.0Hz, 1H), 4.72 (br s, 1H), 4.58 (br s, 2H), 4.02-4.13 (m, 4H), 3.30-3.37 (m, 2H), 3.10-3.14 (m, 3H), 2.78, (d, 7.0Hz, 1H), 2.57 (dd, 18Hz, 8Hz, 1H), 2.20-2.41 (m, 3H), 2.34 (s, 3H), 1.58-1.80 (m, 1H), 1.37-1.60 (m, 9H), 1.45 (s, 9H), 1.24-1.27 (m, 1H), 0.94-1.05 (m, 1H). ^{13}C NMR (100 MHz) δ 169.11, 168.27, 156.29, 149.44, 138.07, 130.59, 125.16, 119.08, 117.59, 89.26, 79.10, 71.22, 71.07, 69.47, 64.39, 60.21, 46.25, 45.59, 44.60, 42.94, 39.85, 39.06, 33.18, 29.37, 29.02, 28.51, 28.26, 23.53, 21.88, 21.02, 20.86.

***N*-(2-aminoethyl)-2-(2-(((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)amino)-2-oxoethoxy)acetamide (14a)**: To a cold (0 ^{o}C) solution of protected amine **13a** (0.684 g, 1.220 mmol, 1.0 eq) in 15 mL of CH_2Cl_2 was added dropwise trifluoroacetic acid (2.225 g, 1.50 mL, 19.52 mmol, 16.0 eq). The reaction was allowed to warm to rt and stirred for 2.5 h. at which point TLC indicated completion of reaction. The solvent was removed in vacuum. The resulting light yellow oil was re-dissolved in CH_2Cl_2 (15 mL) and cooled to 0 ^{o}C. To this oil excess HCl-ether solution (2.44 mL, 2M solution, 4.88 mmol, 4.0 eq) was added dropwise to give a

precipitated solution which was stirred for 0.5 hour. The reaction was concentrated in vacuum to provide a white solid which upon triturating with ether (under N_2) provided off-white solid. This solid was treated with CH_2Cl_2 (4 mL) followed by ether (15 mL) and the precipitate **14a** was filtered. The process was repeated twice and the resulting solid was filtered off to give **14a** as white solid (0.651 g, 100% yield). ^{1}H-NMR (DMSO-d_6): δ 9.1 (s(br), 1H), 8.5 (s, 1H), 6.5 (AB, J_{AB}=7.9 Hz, 2H), 5.7 (s, 1H), 5.0 (s, 1H), 4.7 (s, H), 4.35 (s(br), 2H), 4.0-1.0 (m, unresolved peaks). MS (ESI)-TOF observed 461.2322 $(M+1)^+$, required for $C_{23}H_{32}N_4O_6$ 460.2322 .

***N*-(3-aminopropyl)-2-(2-(((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)amino)-2-oxoethoxy)acetamide (14b)**: To a cold (0 ^{o}C) solution of protected amine **13b** (0.195 g, 0.339 mmol, 1.0 eq) in 4 mL of CH_2Cl_2, trifluroacetic acid (0.465 g, 0.420 mL, 4.071 mmol, 16.0 eq) was added dropwise. The reaction was allowed to warm to rt and stirred for 6 h. at which point TLC indicated completion of the reaction. The solvent was removed in vacuum. The resulting light yellow oil was re-dissolved in CH_2Cl_2 (3 mL) and cooled to 0^{o}C. To this oil, excess of HCl-ether solution (2 mL, 2M solution) was added dropwise to give a precipitated solution which was stirred for 10 h. Thereafter, the reaction was concentrated in vacuum to provide an off-white solid which upon triturating twice with ether followed by filtration provided **14b** as off-white solid (0.173 g, quant. yield). ^{1}H NMR (400 MHz, CD_3OD) δ 6.69 (d, 8.0Hz, 1H), 6.59 (d, 8.0Hz, 1H), 4.61-4.62 (m, 1H), 4.49-4.53 (m, 1H), 4.02 (s, 2H), 4.01 (s, 2H), 3.60 (d, 5.6Hz, 1H), 3.23-3.43 (m, 4H), 3.04 (dd, 20Hz, 6Hz, 1H), 2.92 (t, 7.2Hz, 2H), 2.86 (s, 3H), 2.51-2.56 (m, 1H), 1.75-1.86 (m, 3H), 1.56-1.63 (m, 2H), 1.43-1.48 (m, 1H), 1.01-1.11 (m, 1H). ^{13}C NMR (100 MHz) δ 172.53, 171.15, 147.11, 140.26, 129.88, 123.44, 121.01, 119.65, 89.06, 71.46, 71.10, 68.07, 63.70, 53.68, 47.82, 46.67, 42.12, 38.31, 36.70, 31.57, 30.20, 28.54, 25.11, 20.90, 9.42. MS(ESI)-TOF observed 475.2891 (M+1), 497.2708 $(M+Na^+)$, required for $C_{24}H_{34}N_4O_6$ 474.2478.

***N*-(5-aminopentyl)-2-(2-(((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)amino)-2-oxoethoxy)acetamide (14c)**: To a cold (0 ^{o}C) solution of protected amine **13c** (0.705 g, 1.170 mmol, 1.0 eq) in 15 mL of CH_2Cl_2, trifluoroacetic acid (2.96 g, 2.00 mL, 25.96 mmol, 22.0 eq) was added dropwise. The reaction was allowed to warm to rt and stirred for 2 h. at which point TLC indicated completion of the reaction. Then, the solvent was removed in vacuum. The

resulting light yellow oil **14c** was re-dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C. To this oil, excess of HCl-ether solution (2 mL, 2M solution) was added dropwise to give a precipitated solution which was stirred for 4 h. The reaction mixture was concentrated in vacuum to provide an white solid which upon triturating twice with ether (overnight under N_2) followed by filtration provided **14c** as amorphous white solid (0.622 g, 92% yield).

MS(ESI)-TOF observed 503.3018 (M+1), required for $C_{26}H_{38}N_4O_6$ 502.2791.

***N*-(7-aminoheptyl)-2-(2-(((4aS,7S,7aR,12bS)-4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-yl)amino)-2-oxoethoxy)acetamide (14d):** Acid **12d** (780 mg, 2 mmol, 1 eq), α-oxymorphamine (**3**) (614 mg, 2 mmol, 1 eq), and EEDQ (520 mg, 2.1 mmol) were mixed in 10 mL methylene chloride and stirred overnight. The next day, solvent was evaporated. Afterwards, the material was hydrogenated in methanol mediated by Pd/C(10%) (cat.) and 1,4-cyclohexadiene.

Yield: 852 mg (76.7%).

Methylaminocarbonylmethoxy-acetic acid (15)

To diglycolic anhydride (5.0 g, 43.08 mmol, 1 eq) a 2M THF solution of methylamine (25 mL, 43 mmol) was added in two portions. After 18 h the reaction mixture was concentrated in vacuum to afford crude **15** as oil (5). After removal of solvent under high vacuum (24 h) the product crystallized to give 6.34 g of 15; 57 ºC; ^{1}H NMR(DMSO-d_6) δ 12.76(s(br), 1H), 7.78(s(br), 1H), 4.08(s, 2H), 3.93(s, 2H), 2.61(d, 4.8Hz, 3H); ^{13}C NMR(DMSO-d_6) δ 172.2, 170.0, 71.0, 69.5, 25.8, 25.0

***tert*-butyl 3-(2-(2-(methylamino)-2-oxoethoxy)acetamido)propylcarbamate (16a)**: To a solution of acid **15** (0.38 g, 2.58 mmol, 1.5 eq) dissolved in CH_2Cl_2/ THF (8 mL, 1/1, v/v), EEDQ (0.64 g, 2.58 mmol, 1.5 eq) dissolved in DMF (0.2 mL) was added and stirred for 10 min. To this transparent solution, a solution of N-Boc-diaminopropane (0.3 g, 1.72 mmol, 1.0 eq) dissolved in THF (2 mL) was added. After 5.5 h., TLC analysis indicated completion of the reaction. The solvent was removed in vacuum and the crude product was purified over silica gel column chromatography using the solvent mixture (CH_2Cl_2/MeOH/NH_4OH, 95/4/1, v/v/v). The final product **16a** was isolated as light yellow amorphous solid (0.337 g, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (br s, 1H), 7.30 (br s, 1H), 5.61 (br s, 1H), 3.79 (s, 2H), 3.76 (s, 2H), 3.06-3.07 (m, 2H), 2.92-2.94 (m, 2H), 2.55 (d, 4.4Hz, 3H), 1.36 (m, 2H), 1.17 (s, 9H). ^{13}C NMR (100 MHz) δ 168.79, 168.07, 156.62, 78.51, 69.95, 35.98, 34.08, 29.12, 27.78, 25.13.

N-(3-aminopropyl)-2-(2-(methylamino)-2-oxoethoxy)acetamide hydrochloride (16): To a cold (0 ^{o}C) solution of protected amine **16a** (0.337 g, 1.11 mmol, 1.0 eq) in 6 mL of CH_2Cl_2, trifluoroacetic acid (2.03 g, 1.37 mL, 1.77 mmol, 16.0 eq) was added dropwise. The reaction was allowed to warm to rt and stirred for 2 h. at which point TLC indicated completion of the reaction. The solvent was removed in vacuum. The resulting light brown oil was re-dissolved in DCM (10 mL) and cooled to 0 ^{o}C. To this oil, ac excess of HCl-ether solution (0.666 mL of 2M solution, 13.32 mmol. 1.2 eq) was added dropwise which was stirred for 15 h. Then, the reaction was concentrated in vacuum to provide an oily product which upon triturating twice with ether followed by filtration in vacuum provided **16** as off-white semi solid (0.266 g, quant. yield).

1. Gasparini F, *et al.* (2002) [3H]-M-MPEP, a Potent, Subtype-Selective Radioligand for the Metabotropic Glutamate Receptor Subtype 5. *Bioorg. Med. Chem. Lett.* 12(3):407-409.