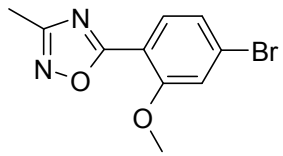
Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting information

Detailed experimental procedures for representative compounds: **11, 25,** and **42A** and supporting analytical data for compounds **3-44**. Description of HEK and PCN Aβ-assays. *In vivo* experimental details.

General

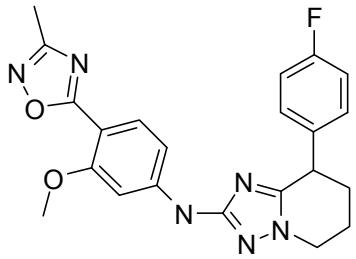
Commercially available anhydrous solvents were routinely used for reactions. Commercially available reagents were used as received. ^{1}H NMR spectra: 500MHz Bruker ultrashield spectrometer,400 MHz Varian Unity+ 400 NMR, or a Bruker Av400 NMR , δ in ppm rel. to the residual solvent signal as internal reference ($CDCl_3$ 7.27, DMSO-d_6 2.50, MeOD-d_4 3.31). MS: Waters LC-MS system where the ZQ was equipped with a combined APPI/APCI ion source alternatively a ZQ single quadrupole mass spectrometer equipped with an electrospray ion source (ESI).



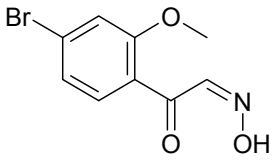
5-(4-Bromo-2-methoxyphenyl)-3-methyl-1,2,4-oxadiazole

4-Bromo-2-methoxybenzoic acid (1.7 g, 7.36 mmol) in dry DCM (30 mL) was treated with thionyl chloride (3.2 mL, 44.2 mmol) at rt under N_2 atmosphere. The mixture was refluxed for 2 hours. The volatiles were removed *in vacuo* and the residual solid was dissolved in dry toluene (30 mL) and treated with *N*-hydroxyacetimidamide (1.64 g, 22.1 mmol) and potassium carbonate (4.07 g, 29.4 mmol). The resulted mixture was refluxed overnight. The cold mixture was diluted with water and ethyl acetate. The phases were separated and the aqueous layer was washed with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated affording the product as white solid (1.36 g, 68 %): ^{1}H NMR (400 MHz, MeOH) δ ppm 7.87 (d, *J*=8.34 Hz, 1 H), 7.41 (d, *J*=1.77 Hz, 1

H), 7.27 (dd, *J*=8.59, 1.77 Hz, 1 H), 3.95 (s, 3 H), 2.40 (s, 3 H); MS (ESI) *m/z* 269, 271 $[M+H]^+$.



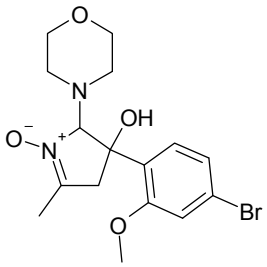
8-(4-Fluorophenyl)-N-(3-methoxy-4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (11). 8-(4-Fluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (80 mg, 0.34 mmol), 5-(4-bromo-2-methoxyphenyl)-3-methyl-1,2,4-oxadiazole (93 mg, 0.34 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride (28.3 mg, 0.03 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (19.9 mg, 0.03 mmol) and sodium tert-pentoxide (56.9 mg, 0.52 mmol) were mixed in dry toluene (3 mL). The mixture was heated to 110 °C under N_2 atmosphere for 2 hours. The mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and concentrated onto silica. The product was purified by silica column chromatography using DCM:[DCM:MeOH:NH_3=90:10:1] =100:0 to 70:30 gradient, 12 g column, 220 nm detection. The product was obtained as foamy solid (56 mg, 38 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.94 (d, *J*=8.59 Hz, 1 H), 7.48 (d, *J*=2.02 Hz, 1 H), 7.19 - 7.12 (m, 2 H), 7.08 - 7.01 (m, 2 H), 6.95 (s, 1 H), 6.86 (dd, *J*=8.59, 2.02 Hz, 1 H), 4.27 - 4.16 (m, 3 H), 3.98 (s, 3 H), 2.47 (s, 3 H), 2.36 (dd, *J*=7.45, 4.93 Hz, 1 H), 2.22 (dd, *J*=4.80, 2.53 Hz, 1 H), 2.18 - 2.07 (m, 1 H), 2.07 - 1.95 (m, 1 H); MS (ESI) *m/z* 421 $[M+H]^+$.



(2*Z*)-1-(4-Bromo-2-methoxyphenyl)-2-(*N*-hydroxyimino)ethan-1-one

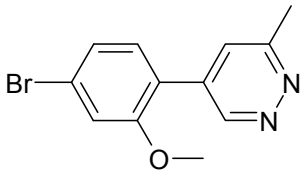
Sodium (138 mg, 6.0 mmol) was added to ethanol (12 mL) at room temperature. The mixture was stirred for 30 minutes. Isoamyl nitrite (0.81 mL, 6.0 mmol) and 1-(4-bromo-2-methoxyphenyl)ethan-1-one (1.15 g, 5.0 mmol) were added. The mixture was stirred at room

temperature for 3 days. The solvent was removed under reduced pressure. The residue was dissolved in 1 M hydrochloric acid (12 mL) and then extracted with DCM (x2). The organic phases were combined and dried over $MgSO_4$, concentrated under reduced pressure to afford a mixture of starting material and (2*Z*)-1-(4-bromo-2-methoxyphenyl)-2-(*N*-hydroxyimino)ethan-1-one (1:1). The crude mixture was used directly for the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.10 (s, 1 H), 7.47 (d, *J*=8.2 Hz, 1 H), 7.17 – 7.11 (m, 2 H), 3.88 (s, 3 H); MS (ESI) *m/z* 258 $[M+H]^+$.



3-(4-Bromo-2-methoxyphenyl)-3-hydroxy-5-methyl-2-(morpholin-4-yl)-3,4-dihydro-2*H*-pyrrol-1-ium-1-olate

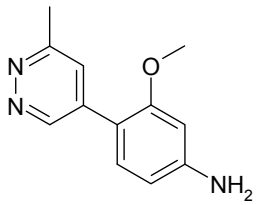
A mixture of (2*Z*)-1-(4-bromo-2-methoxyphenyl)-2-(*N*-hydroxyimino)ethan-1-one, morpholine (0.24 mL, 2.75 mmol) and acetone (10 mL) were stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the residue was triturated in MTBE to afford the title compound as a solid (360 mg, 19% for two steps): MS (ESI) *m/z* 385 $[M+H]^+$.



5-(4-Bromo-2-methoxyphenyl)-3-methylpyridazine

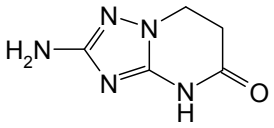
Hydrazine hydrate (4.8 mL, 99.0 mmol) was added to a solution of 3-(4-bromo-2-methoxyphenyl)-3-hydroxy-5-methyl-2-(morpholin-4-yl)-3,4-dihydro-2*H*-pyrrol-1-ium-1-olate (crude, 9.5 g, 24.7 mmol) in a mixture of water (115 mL) and acetic acid (4.4 mL) at room temperature. The reaction mixture was heated to 100 °C for 20 minutes and then cooled to room temperature. The resulting precipitate was collected by filtration and dried under high vacuum to afford 3.5 g of a yellow solid. The filtrate was concentrated and the residue was reacted again with hydrazine hydrate (4.8 mL, 99.0 mmol) in a mixture of water (115 mL) and acetic acid (4.4 mL). When the reaction was completed, water (200 mL) was added, and the reaction was stirred for 20 minutes. The formed black oil was separated and taken up in 10%

HCl solution. The aqueous phase was basified with 25% aqueous NaOH solution, extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with 20% to 70% ethyl acetate in heptane to afford the desired product (1.3 g, total 3.5 g + 1.3 g = 4.8 g, 70%) as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm, 9.21 (d, J = 2.1 Hz, 1 H), 7.68 (d, J = 2.4 Hz, 1 H), 7.45 (d, J = 8.2 Hz, 1 H), 7.41 (d, J = 1.8 Hz, 1 H), 7.32 (dd, J = 7.9, 1.8 Hz, 1 H), 3.86 (s, 3 H), 2.65 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 159.5, 157.3, 149.2, 135.2, 131.9, 126.0, 124.1, 124.0, 122.8, 115.3, 56.3, 21.8; MS (ESI) *m/z* 279, 281 $[M+H]^+$.



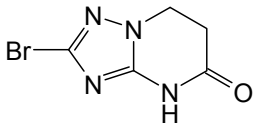
3-Methoxy-4-(6-methylpyridazin-4-yl)aniline

5-(4-Bromo-2-methoxyphenyl)-3-methylpyridazine (1.72 g, 6.20 mmol), $Pd_2(dba)_3$ (57 mg, 0.062 mmol), BINAP (116 mg, 0.19 mmol), sodium tert-butoxide (833 mg, 8.68 mmol), benzophenone imine (1.25 mL, 7.44 mmol) and toluene (30 mL) were added to a sealed tube. The flask was purged with N_2 three times. The reaction was stirred at 80 ^{o}C overnight and then cooled down, filtered through a pad of celite and the filter was washed with MTBE. The filtrate was concentrated. The residue was dissolved in methanol (60 mL). Sodium acetate (1.22 g, 14.90 mmol) and ammonium chloride (776 mg, 11.2 mmol) were added. The mixture was stirred at room temperature for 1 hour. Sodium carbonate (1.23 g, 11.60 mmol) was added and the mixture was stirred at room temperature for 10 minutes and then concentrated under reduced pressure. The residue was taken up in DCM. The organic phase was washed with water, brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with 0% to 1% methanol in ethyl acetate to afford the title compound (1.24 g ,93%) as a solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.23 (d, J = 2.1 Hz, 1 H), 7.45 (d, J = 2.1 Hz, 1 H), 7.20 (d, J = 8.2 Hz, 1 H), 6.38 (dd, J = 8.2, 2.1 Hz, 1 H), 6.31 (d, J = 2.1 Hz, 1 H), 3.95 (br s, 2 H), 3.82 (s, 3 H), 2.71 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 159.4, 158.5, 149.9, 149.8, 137.3, 131.4, 125.4, 113.7, 107.8, 98.3, 55.5, 22.5; MS (ESI) *m/z* 216 $[M+H]^+$.



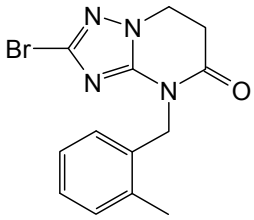
2-Amino-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one

A mixture of 1H-1,2,4-triazole-3,5-diamine (25 g, 252 mmol) and methyl acrylate (22.7 mL, 252 mmol) in pyridine (320 mL) was refluxed for 5 days. The mixture was cooled down to room temperature and the resulting precipitate was collected by filtration, washed with diethyl ether and dried *in vacuo*. The product was obtained as beige solid (26.4 g, 68 %): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.08 (s, 1 H), 5.23 (s, 2 H), 3.92 (t, *J*=7.33 Hz, 2 H), 2.78 (t, *J*=7.33 Hz, 2 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 167.76, 162.12, 148.45, 40.46, 30.39; MS (ESI) *m/z* 154 $[M+H]^+$.



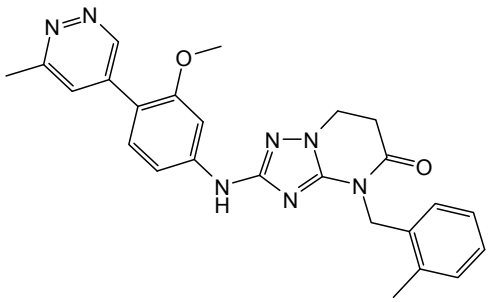
2-Bromo-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one

Isoamyl nitrite (3.50 mL, 26.12 mmol) and copper(II) bromide (5.83 g, 26.12 mmol) were added to 2-amino-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (4.00 g, 26.12 mmol) in anhydrous acetonitrile (200 mL). The reaction mixture was heated at 70 °C for 1.5 hours then cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between aqueous ammonium chloride (sat.) and ethyl acetate. The organic layer was washed with brine (x2), dried (Na_2SO4), filtered and concentrated under reduced pressure to give the title compound (2.07 g, 37 %). Since more of the product remained in water phase, it was further extracted with ethyl acetate (x4). Sodium chloride was added to the water phase then extracted again with ethyl acetate (x5). The water phase was concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate (x3), the combined organic layers were passed through a phase separator and concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate (x1), the organic layer was passed through a phase separator and concentrated under reduced pressure to give more 2-bromo-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (0.696 g, 12.3 %): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.56 (s, 1 H), 4.22 (t, *J*=7.25 Hz, 2 H), 2.87 (t, *J*=7.25 Hz, 2 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 167.43, 150.74, 136.89, 41.55, 30.03; MS (ESI) *m/z* 216, 218 $[M+H]^+$.



2-Bromo-4-(2-methylbenzyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one

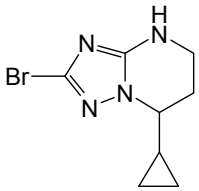
Sodium hydride (60 % in mineral oil) (0.224 g, 5.61 mmol) was added to a mixture of 2-bromo-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (1.13 g, 5.21 mmol) and anhydrous DMF (20 mL) at 0 °C under argon. The resulting mixture was stirred at 0°C for 30 min, then was 1-(bromomethyl)-2-methylbenzene (0.964 g, 5.21 mmol) added drop wise. The resulting mixture was stirred at room temperature for 1.5 hours during which a precipitate was formed. The mixture was poured onto ice-water, and the resulted solid was isolated by filtration then washed with cold water. The solid was dried under vacuum to give the product (1.615 g, 97 % yield) as solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.21 - 7.13 (m, 2 H), 7.13 - 7.07 (m, 1 H), 7.07 - 7.01 (m, 1 H), 4.91 (s, 2 H), 4.36 (t, *J*=7.25 Hz, 2 H), 3.13 (t, *J*=7.41 Hz, 2 H), 2.34 (s, 3 H); MS (ESI) *m/z* 321 $[M+H]^+$.



2-(3-Methoxy-4-(6-methylpyridazin-4-yl)phenylamino)-4-(2-methylbenzyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (25)

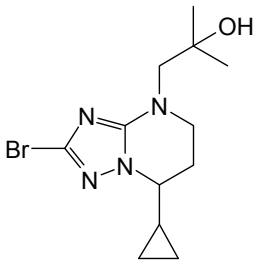
A 5 mL microwave vial was charged with 3-methoxy-4-(6-methylpyridazin-4-yl)aniline (75 mg, 0.35 mmol), 2-bromo-4-(2-methylbenzyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (135 mg, 0.42 mmol). DMA (1 mL) was added and the mixture was heated to get a clear solution which was diluted with dioxane (2 mL). Palladium acetate (11.8 mg, 0.05 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthenes (41 mg, 0.07 mmol) and cesium carbonate (171 mg, 0.53 mmol) were added. The mixture was heated at 125°C under N_2 atmosphere over night. The solvents were removed *in vacuo*. The crude product was purified by silica gel column chromatography using DCM : [DCM:MeOH=90:10] = 100:0 to 50:50

gradient. The resulted solid (approx 140 mg) was submitted for further purification by prep HPLC. (Waters Acquity, column: Acquity C18; 2.1 * 50mm; 1.7µm; mobilephase: 15-99.5% MeOH / 0.1% NH_3 buffer; flowrate: 0.65 mL/min). The title compound was obtained as solid (28 mg, 17%): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.59 (s, 1 H), 9.21 (d, *J*=2.02 Hz, 1 H), 7.63 (d, *J*=2.02 Hz, 1 H), 7.37 - 7.43 (m, 2 H), 7.03 - 7.23 (m, 5 H), 4.97 (s, 2 H), 4.30 (t, *J*=7.33 Hz, 2 H), 3.73 (s, 3 H), 3.17 (t, *J*=7.33 Hz, 2 H), 2.61 (s, 3 H), 2.35 (s, 3 H); MS (ESI) *m/z* 456 $[M+H]^+$.



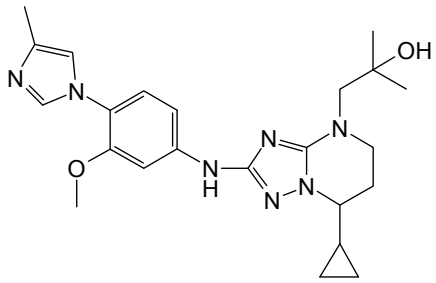
2-Bromo-7-cyclopropyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine

Lithium aluminum hydride (0.696 mL, 16.69 mmol) in dry degassed THF (20 mL) was added to 2-bromo-7-cyclopropyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (1.5 g, 5.83 mmol) in dry degassed THF (30 mL) at 0 °C under nitrogen. The resulting mixture was refluxed overnight. Then it was cooled to 0 °C. Saturated aqueous sodium sulfate solution (ca. 50 mL) was added drop wise until complete decomposition of $LiAlH_4$. Then the mixture was filtered and the filter cake was washed with ethyl acetate (3×40 mL) and water (3×20 mL). NaCl was added to the filtrate. The separated aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was dried *in vacuo* afforded the title compound as brown solid (1.29 g, 91 %): ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.88 (br. s., 1 H), 3.60 - 3.38 (m, 3 H), 2.24 - 2.05 (m, 2 H), 1.11 - 0.99 (m, 1 H), 0.80 - 0.66 (m, 2 H), 0.58 (tt, *J*=8.63, 5.40 Hz, 1 H), 0.36 - 0.23 (m, 1 H); MS (ESI) *m/z* 243, 245 $[M+H]^+$.



1-(2-Bromo-7-cyclopropyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-4(5H)-yl)-2-methylpropan-2-ol

2-Bromo-7-cyclopropyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (250 mg, 1.03 mmol), cesium carbonate (503 mg, 1.54 mmol) and isobutylene oxide (0.459 mL, 5.14 mmol) in dry DMF (3 mL) were heated to 150 °C in a microwave reactor for 2 hours. The mixture was cooled to room temperature and diluted with water and brine. The mixture was extracted with ethyl acetate (2x). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The title compound was obtained as a dry film (260 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.64 - 3.59 (m, 1 H), 3.50 - 3.43 (m, 2 H), 3.42 (d, *J*=1.01 Hz, 2 H), 2.23 (dd, *J*=5.43, 4.17 Hz, 1 H), 2.16 - 2.08 (m, 1 H), 1.29 - 1.25 (m, 6 H), 1.24 (s, 1 H), 1.05 (d, *J*=8.59 Hz, 1 H), 0.76 (d, *J*=6.06 Hz, 1 H), 0.73 - 0.66 (m, 1 H), 0.57 (s, 1 H), 0.37 - 0.24 (m, 1 H); MS (ESI) *m/z* 317, 315 $[M+H]^+$.



1-(7-Cyclopropyl-2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenylamino)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-4(5H)-yl)-2-methylpropan-2-ol (42A)

3-Methoxy-4-(4-methyl-1H-imidazol-1-yl)aniline (335 mg, 1.65 mmol), 1-(2-bromo-7-cyclopropyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-4(5H)-yl)-2-methylpropan-2-ol (520 mg, 1.65 mmol), palladium(II) acetate (56 mg, 0.25 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (191 mg, 0.33 mmol) and cesium carbonate (806 mg, 2.47 mmol) in dry degassed dioxane (10 mL) were heated at 125°C under nitrogen for 2 hours. The mixture was cooled to room temperature and filtered through a short pad of celite. The filter cake was washed with ethyl acetate (30 mL). The filtrate was concentrated onto silica gel. Chromatographic purification using DCM : [DCM:MeOH=9:1] = 100:0 to 50:50 gradient afforded the product as dry film. This material was subjected to chiral separation /SFC Berger Multigram II, column: LuxC2; 20*250 mm; 5µm; mobile phase: 25%MeOH+0.1%DEA; 75% CO_2; flow: 50ml/min; injections: 20 injections, 6.6mg in 0.2 ml MeOH/ providing Isomer 1, **42A** (84 mg, 11% yield) and isomer 2 **42B** (86 mg, 11% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.66 - 7.60 (m, 2 H), 7.10 (d, *J*=8.51 Hz, 1 H), 6.85 (s, 1 H), 6.70 (dd, *J*=8.35, 2.05 Hz, 1 H), 6.43 (s, 1 H), 3.87 (s, 3 H), 3.62 - 3.55 (m, 1 H), 3.44 - 3.33 (m, 4 H), 2.34 - 2.25 (m, 4 H), 2.21 - 2.13 (m, 1 H), 1.27 (d, *J*=3.78 Hz, 6 H), 1.11 - 1.04 (m, 1 H), 0.81 - 0.68 (m, 2 H),

0.59 (dd, *J*=9.30, 4.26 Hz, 1 H), 0.35 (dd, *J*=9.62, 5.20 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 155.6, 153.4, 142.0, 136.7, 125.8, 117.2, 107.9, 100.4, 71.7, 62.5, 58.5, 55.6, 46.6, 28.1, 27.6, 27.4, 15.7, 13.3, 4.7, 1.8; MS (ESI) *m/z* 438 $[M+H]^+$.

Synthesis of compounds 3-44

Compounds **3-15** were prepared using the method described for compound **11**.

Compounds **16-34** were prepared using the method described for compound **25**.

Compounds **35-44** were prepared using the method described for compound **42A**.

For **(19B)**, separation of enatiomers were performed using SFC Berger Multigram II, column: LuxC4; 20*250 mm; 5µm; mobile phase: 45%MeOH+0.1%DEA; 55% CO_2; flow: 50ml/min. The late eluting fraction was collected as **19B**. The enatiomers were analysed using column: Phenomenex Lux C4; 4.6*250 mm; 5µm ; mobile phase: 45% MeOH+0.1% DEA / 55% CO_2, column temperature 35°C, flow rate: 3 mL/min. t_R11.1 min.

Table S1. Summary of experimental data for compounds **3-44**

Cmpd No	**1H NMR (500 MHz, solvent) δ ppm**	**13C NMR (126 MHz, solvent) δ ppm**	**MS APCI+ (M+H)+ *(m/z)***
3	($CDCl_3$, 400MHz) 1.98 - 2.15 (m, 2 H) 2.20 (d, 1 H) 2.26 - 2.40 (m, 4 H) 3.80 (s, 3 H) 4.20 (m, 3 H) 6.66 (s, 1 H) 6.83 (s, 1 H) 6.88 (dd, 1 H) 7.10 (d, 1 H) 7.17 (d, 2 H) 7.32 (s, 1 H) 7.33 - 7.39 (m, 3 H) 7.58 (s, 1 H)	ND	401 (ESI)
4	($CDCl_3$) 1.98 - 2.07 (m, 1 H) 2.14 (m, 1 H) 2.22 - 2.30 (m, 1 H) 2.33 - 2.41 (m, 1 H) 4.19 - 4.31 (m, 3 H) 6.99 (dd, 1 H) 7.03 - 7.08 (m, 3 H) 7.13 - 7.18 (m, 2 H) 7.69 (d, 1 H) 8.22 (d, 1 H)	ND	351
5	($CDCl_3$) 1.98 (m, 1 H) 2.09 (m, 1 H) 2.20 (m, 1 H) 2.33 (m, 1 H) 3.69 (s, 2 H) 4.19 (m, 3 H) 6.65 (s, 1 H) 7.04 (t, 2 H) 7.14 (dd, 2 H) 7.23 (m, 2 H) 7.42 (m, 2 H)	ND	348
6	($CDCl_3$) 1.89 - 2.14 (m, 3 H), 2.16 - 2.26 (m, 1 H), 2.90 - 2.98 (m, 6 H), 4.13 (dd, 2 H), 4.24 (dd, 1 H), 7.05 - 7.19 (m, 2 H), 7.23 - 7.37 (m, 4 H), 7.49 (d, 2 H), 9.43 (s, 1 H)	ND	380 (ESI)
7	($CDCl_3$) 1.93 - 2.02 (m, 1 H) 2.03 - 2.13 (m, 1 H) 2.14 - 2.24 (m, 1 H) 2.28 - 2.36 (m, 1 H) 2.96 (d, 6 H) 3.66 (s, 2 H) 4.14 - 4.24 (m, 3 H)	ND	394

	6.58 (s, 1 H) 7.00 - 7.06 (m, 2 H) 7.11 - 7.20 (m, 4 H) 7.36 (d, 2 H)		
8	(METHANOL-d_4) 1.96 - 2.04 (m, 1 H) 2.05 - 2.13 (m, 1 H) 2.13 - 2.21 (m, 1 H) 2.30 - 2.37 (m, 1 H) 3.15 (s, 3 H) 4.15 - 4.23 (m, 2 H) 4.28 (t, 1 H) 4.43 (s, 2 H) 7.07 (t, 2 H) 7.18 - 7.23 (m, 2 H) 7.43 (dd, 1 H) 7.59 (d, 1 H) 7.80 (s, 1 H)	ND	378
9	(DMSO-d_6) 2.02 (m, 3 H) 2.20 (m, 1 H) 3.04 (s, 3 H) 4.13 (dd, 2 H) 4.23 (dd, 1 H) 7.05 (m, 1 H) 7.13 (m, 4 H) 7.29 (m, 2 H) 9.18 (s, 1 H)	ND	378
10	(DMSO-d_6) 1.89 - 1.99 (m, 1 H), 1.99 - 2.11 (m, 2 H), 2.13 (s, 3 H), 2.22 (dtd, 1 H), 3.83 (s, 3 H), 4.12 - 4.18 (m, 2 H), 4.27 (dd, 1 H), 7.03 (s, 1 H), 7.11 - 7.19 (m, 2 H), 7.23 - 7.30 (m, 2 H), 7.45 (d, 1 H), 7.62 - 7.69 (m, 2 H), 9.68 (s, 1 H)	(DMSO-d_6) 13.6, 20.9 , 29.8, 46.3, 53.3, 101.1, 112.4, 115.0 (d), 116.8, 130.1 (d), 136.0, 136.6, 136.8, 138.2, 150.9, 153.0, 155.0, 157.7, 161.1 (d)	420
11	(($CDCl_3$), 400MHz) 1.95 - 2.07 (m, 1 H) 2.07 - 2.18 (m, 1 H) 2.22 (dd, 1 H) 2.36 (dd, 1 H) 2.47 (s, 3 H) 3.98 (s, 3 H) 4.16 - 4.27 (m, 3 H) 6.86 (dd, 1 H) 6.95 (s, 1 H) 7.01 - 7.08 (m, 2 H) 7.12 - 7.19 (m, 2 H) 7.48 (d, 1 H) 7.94 (d, 1 H).	ND	421 (ESI)
12	(($CDCl_3$), 400MHz) 1.93 - 2.05 (m, 1 H) 2.05 - 2.14 (m, 1 H) 2.15 - 2.26 (m, 1 H) 2.33 (dd, 1 H) 3.40 (s, 3 H) 3.43 (br. s., 3 H) 4.15 - 4.26 (m, 3 H) 6.62 (s, 1 H) 6.82 - 6.88 (m, 1 H) 6.94 (dd, 1 H) 7.01 - 7.08 (m, 2 H) 7.12 - 7.19 (m, 2 H) 7.36 (d, 1 H).	ND	393 (ESI)
13[a]	ND	ND	t_R=0.57 min 373
14A	(DMSO-d_6) 1.96 (d, 1 H) 2.02 - 2.14 (m, 2 H) 2.17 - 2.25 (m, 1 H) 2.30 (s, 3 H) 3.74 (s, 3 H) 4.10 - 4.18 (m, 2 H) 4.25 (dd, 1 H) 7.12 - 7.18 (m, 3 H) 7.28 - 7.32 (m, 2 H) 7.35 (d, 1 H) 7.44 (d, 1 H) 8.57 (s, 1 H) 9.46 (s, 1 H)	ND	420 (ESI)
14B	(DMSO-d_6) 1.97 (d, 1 H) 2.01 - 2.14 (m, 2 H) 2.18 - 2.25 (m, 1 H) 2.31 (s, 3 H) 3.74 (s, 3 H) 4.15 (dd, 2 H) 4.25 (dd, 1 H) 7.12 - 7.18 (m, 3 H) 7.30 (dd, 2 H) 7.35 (d, 1 H) 7.44 (d, 1 H) 8.57 (s, 1 H) 9.46 (s, 1 H)	ND	420 (ESI)

15	(DMSO-d_6, 400MHz) 1.89 - 2.16 (m, 3 H) 2.17 - 2.27 (m, 1 H) 2.61 (s, 3 H) 3.76 (s, 3 H) 4.15 (t, 2 H) 4.25 (dd, 1 H) 7.11 - 7.23 (m, 3 H) 7.26 - 7.34 (m, 2 H) 7.37 - 7.45 (m, 2 H) 7.63 (d, 1 H) 9.22 (d 1 H) 9.53 (s, 1 H)	ND	429 (ESI)
16[a]	ND	ND	t_R=0.58 416
17	(DMSO-d_6) 2.13 (s, 3 H) 3.10 (t, 2 H) 3.71 (s, 3 H) 4.23 (t, 2 H) 5.00 (s, 2 H) 6.98 (s, 1 H) 7.15 (m, 2 H) 7.26 (m, 1 H) 7.33 (m, 4 H) 7.41 (d, 1 H) 7.60 (d, 1 H) 9.46 (s, 1 H)	(DMSO-d_6) 13.5, 30.5, 40. 7, 45.1, 55.4, 100.1, 107.7, 117.0, 118.0, 125.9, 127.0, 127.1, 128.4, 136.1, 136.7, 136.8, 142.2, 149.5, 152.6, 157.8, 166.3	430
18B	(DMSO-d_6) 1.25 (d, 3 H), 2.13 (s, 3 H), 3.23 - 3.32 (m, 1 H), 3.71 (s, 3 H), 3.95 (t, 1 H), 4.36 (dd, 1 H), 5.01 (m, 2 H), 6.98 (s, 1 H), 7.13 (m, 1 H), 7.17 (d, 1 H), 7.23 - 7.28 (m, 1 H), 7.30 - 7.35 (m, 4 H), 7.43 (d, 1 H), 7.60 (d, 1 H), 9.47 (s, 1 H)	(DMSO-d_6) 13.3, 13.6, 35.0, 45.5, 46.7, 55.5, 100.1, 107.7, 117.1, 118.0, 125.9, 127.0, 127.2, 128.4, 136.2, 136.7, 136.9, 142.2, 149.5, 152.6, 157.7, 169.3	444
19A	(($CDCl_3$)) 1.56 (d, 3 H) 2.38 (s, 3 H) 2.79 (dd, 1 H) 3.12 (dd, 1 H) 3.84 (s, 3 H) 4.42 (d, 1 H) 5.10 (d, 2 H) 6.66 (s, 1 H) 6.89 (s, 1 H) 6.92 (dd, 1 H) 7.16 (d, 1 H) 7.29 - 7.35 (m, 3 H) 7.43 - 7.48 (m, 3 H) 7.81 - 7.94 (m, 1 H)	ND	444 (ESI)
19B	(($CDCl_3$)) 1.56 (d, 3 H) 2.35 (s, 3 H) 2.79 (dd, 1 H) 3.12 (dd, 1 H) 3.84 (s, 3 H) 4.36 - 4.47 (m, 1 H) 5.10 (d, 2 H) 6.63 (s, 1 H) 6.88 (s, 1 H) 6.91 (dd, 1 H) 7.15 (d, 1 H) 7.28 - 7.36 (m, 3 H) 7.42 - 7.49 (m, 3 H) 7.74 - 7.79 (m, 1 H)	ND	444 (ESI)
20	(DMSO-d_6) 1.46 (s, 6H) 2.13 (s, 3H) 3.08 (s, 2H) 3.73 (s, 3H) 5.01 (s, 2H) 6.99 (s, 1H) 7.05 (s, 1H) 7.17 (m, 3H) 7.38 (m, 2H), 7.59 (m, 2H)	(DMSO-d_6) 13.6, 26.0, 44.0, 4.8, 54.9, 55.4, 100.144, 107.8, 115.2, 115.4, 117.1, 118.0, 125.8, 129.4 (d), 133.0 (d), 136.2, 136.9, 142.2, 148.1, 152.6, 157.6, 160.5, 162.4, 166.1	476
21	(DMSO-d_6) 1.02 (m, 2 H) 1.34 (m, 2 H) 2.12 (s, 3 H) 3.20 (s, 2 H) 3.72 (s, 3 H) 5.02 (s, 2 H) 6.99 (m, 2 H) 7.17 (m, 3 H) 7.40 (dd, 2 H) 7.50 (d, 1 H) 7.60 (s, 1 H) 9.53 (s, 1 H)	(DMSO-d_6) d 10.3, 13.6, 35.1, 37.8, 44.8, 55.3, 100.1, 107.8, 115.2, 115.4, 117.0, 118.0, 125.8, 129.2, 129.3, 132.8, 132.8, 136.2, 136.8, 142.0,	474

		149.9, 152.6, 157.3, 160.5, 162.4, 165.7	
22B	(DMSO-d_6) 1.50 (d, 3 H), 2.13 (s, 3 H), 3.01 (dd, 1 H), 3.18 (dd, 1 H), 3.71 (s, 3 H), 4.47 - 4.58 (m, 1 H), 5.00 (d, 1 H), 5.07 (d, 1 H), 6.98 (s, 1 H), 7.06 (dd, 1 H), 7.12 - 7.21 (m, 3 H), 7.29 (td, , 1 H), 7.52 (d, 1 H), 7.60 (s, 1 H), 9.49 (s, 1 H)	(DMSO-d_6) 13.6, 18.9, 38.0, 48.0, 55.3, 100.1, 107.7, 114.8 (dd), 115.5 (dd), 116.8 (dd), 117.1, 118.0, 125.7 (dd), 125.8, 136.2, 136.9, 142.2, 148.7, 152.6, 155.8 (dd), 159.3 (dd), 157.6, 166.4	480
23B	(DMSO-d_6) 0.34 - 0.43 (m, 1 H) 0.49 - 0.60 (m, 2 H) 0.62 - 0.71 (m, 1 H) 1.13 - 1.22 (m, 1 H) 2.13 (s, 3 H) 3.02 - 3.11 (m, 1 H) 3.33 (s, 1 H) 3.74 (s, 3 H) 3.80 - 3.90 (m, 1 H) 4.98 - 5.11 (m, 2 H) 6.98 (s, 2 H) 7.14 (s, 3 H) 7.24 - 7.33 (m, 1 H) 7.60 (d, 1 H) 7.63 - 7.70 (m, 1 H) 9.52 (s, 1 H)	ND	506
24B	(DMSO-d_6) 1.43 (d, 3 H), 2.13 (s, 3 H), 2.40 - 2.48 (m, 2 H), 2.54 - 2.71 (m, 3 H), 2.83 (dd, 1 H), 3.08 (dd, 1 H), 3.76 (s, 3 H), 3.93 (dd, 1 H), 4.00 (dd, 1 H), 4.38 - 4.46 (m, 1 H), 6.99 (s, 1 H), 7.10 (dd, 1 H), 7.17 (d, 1 H), 7.56 (d, 1 H), 7.61 (d, 1 H), 9.53 (s, 1 H)	ND	458
25	(DMSO-d_6) 2.35 (s, 3H) 2.60 (s, 3H) 3.18 (t, 2H) 3.72 (s, 3H) 4.30 (t, 2H) 4.96 (s, 2H) 7.15 (m, 5H) 7.39 (m, 2H) 7.63 (d, 1H) 9.21 (d, 1H) 9.58 (s, 1H)	ND	456 (ESI)
26[a]	ND	ND	t_R=0.69 min m/z=444
27[a]	ND	ND	t_R=0.64 min m/z=442
28[a]	ND	ND	t_R=0.67 min m/z=456
29[a]	ND	ND	t_R=0.67 min m/z=456
30	(DMSO-d_6) 2.34 (s, 3H) 2.62 (s, 3H) 3.16 (t, 2H) 3.69 (s, 3H) 4.28 (t, 2H) 7.12 (m, 5H) 7.27 (d, 2H) 7.36 (d, 1H) 8.75 (s, 2H) 9.46 (s, 1H)	ND	456 (ESI)
31	(DMSO-d_6) 2.30 (s, 3 H) 3.10 (s, 2 H) 3.74 (s, 3 H) 4.24 (s, 2 H) 5.01 (s, 2 H) 7.12 - 7.18 (m, 1 H) 7.23 - 7.29 (m, 1 H) 7.30 - 7.39 (m, 5 H) 7.43 - 7.48 (m, 1 H) 8.58 (s, 1 H) 9.54 (s, 1 H).	ND	431 (ESI)
32[a]	ND	ND	t_R=0.65 min m/z=465

33[a]	ND	ND	t_R=0.66 min m/z=499
34[a]	ND	ND	t_R=0.66 min m/z=446
35	(DMSO-d_6) 2.08 (m, 2 H), 2.13 (s, 3 H), 3.19 (m, 2 H), 3.72 (s, 3 H), 3.90 (t, 2 H), 4.57 (s, 2 H), 7.00 (br. s., 1 H), 7.11 - 7.18 (m, 2 H), 7.28 (m, 1 H), 7.32 - 7.39 (m, 4 H), 7.45 (d, 1 H), 7.65 (br. s., 1 H), 9.17 (s, 1 H)	(DMSO-d_6) 13.5, 21.4, 43.3, 43.9, 52.6, 55.4, 99.9, 107.5, 117.3, 117.4, 125.8, 127.3, 127.7, 128.5, 135.9 136.8, 137.6, 142.9, 152.6, 152.9, 156.5	416
36	(DMSO-d_6) 2.04 - 2.11 (m, 2 H), 2.12 (s, 3 H), 3.70 (s, 3 H), 3.88 - 4.05 (m, 2 H), 4.46 (d, 1 H), 4.81 (d, 1 H), 4.86 (t, 1 H), 6.33 (s, 1 H), 6.96 (s, 1 H), 7.10 - 7.17 (m, 2 H), 7.26 (sxt, 1 H), 7.34 (d, 4 H), 7.42 (d, 1 H), 7.58 (d, 1 H), 9.16 (s, 1 H)	ND	432
37[b]	ND	ND	432
38[c]	ND	ND	446
39	($CDCl_3$) 0.08 (q, 2 H) 0.42 - 0.51 (m, 2 H) 0.63 - 0.74 (m, 1 H) 1.54 (q, 2 H) 2.19 (quin, 2 H) 2.30 (s, 3 H) 3.27 - 3.37 (m, 2 H) 3.44 - 3.54 (m, 2 H) 3.84 (s, 3 H) 3.98 (t, 2 H) 6.66 (s, 1 H) 6.84 (s, 1 H) 6.88 (dd, 1 H) 7.10 (d, 1 H) 7.39 (d, 1 H) 7.61 (s, 1 H)	($CDCl_3$) 4.3, 8.5, 13.6, 21.9, 32.5, 43.7, 44.9, 50.1, 55.7, 100.4, 107.9, 117.1, 118.9, 126.0, 137.0, 137.1, 142.1, 153.2, 153.4, 156.8	294
40B	($CDCl_3$) 1.26 (s, 6 H) 1.53 (d, 3 H) 1.88 - 2.00 (m, 1 H) 2.23 - 2.34 (m, 4 H) 3.27 - 3.50 (m, 4 H) 3.85 (s, 3 H) 4.16 - 4.25 (m, 1 H) 6.44 (s, 1 H) 6.81 (dd, 1 H) 6.85 (s, 1 H) 7.10 (d, 1 H) 7.43 (d, 1 H) 7.61 (s, 1 H)	($CDCl_3$) 13.6, 20.5, 27.4, 27.6, 29.7, 46.7, 49.74, 55.6, 62.5, 71.7, 100.5, 107.9, 117.1, 119.1, 126.0, 137.0, 137.2, 141.8, 153.4, 153.5, 155.6	412
41B	($CDCl_3$) 1.25 (s, 6 H) 1.51 (d, 3 H) 1.80 (t, 2 H) 1.86 - 1.97 (m, 1 H) 2.30 (s, 4 H) 3.24 - 3.38 (m, 2 H) 3.58 (td, 2 H) 3.84 (s, 3 H) 4.18 (d, 1 H) 6.62 (s, 1 H) 6.82 - 6.85 (m, 1 H) 6.86 (d, 1 H) 7.09 (d, 1 H) 7.45 (d, 1 H) 7.60 (d, 1 H)	($CDCl_3$) 13.6, 20.6, 29.6, 29.9, 29.9, 40.1, 43.05, 43.1, 46.2, 49.6, 55.6, 69.6, 100.4, 107.8, 117.1, 118.9, 126.0, 137.1, 137.2, 141.9, 152.9, 153.4, 156.3	426
42A	($CDCl_3$) 0.30 - 0.39 (m, 1 H) 0.59 (t, 1 H) 0.67 - 0.82 (m, 2 H) 1.02 - 1.13 (m, 1 H) 1.27 (d, 6 H) 2.12 - 2.21 (m, 1 H) 2.30 (dd, 1 H) 2.33 (s, 3 H) 3.32 - 3.43 (m, 4 H) 3.54 - 3.62 (m, 1 H) 3.88 (s, 3 H) 4.80 - 5.28 (m, 1 H) 6.45 (s, 1 H) 6.70 (dd, 1 H) 6.86 (s, 1 H) 7.10 (d, 1 H) 7.63 (d, 1 H) 7.68 (br. s., 1 H)	($CDCl_3$) 1.8, 4.7, 13.3, 15.7, 27.4, 27.6, 28.1, 46.6, 55.6, 58.5, 62.5, 71.7, 100.4, 107.9, 117.2, 125.8, 136.7, 142.0, 153.4, 155.6	438

42B	($CDCl_3$) 0.30 - 0.40 (m, 1 H) 0.53 - 0.65 (m, 1 H) 0.67 - 0.82 (m, 2 H) 1.00 - 1.13 (m, 1 H) 1.27 (d, 6 H) 2.12 - 2.21 (m, 1 H) 2.25 - 2.31 (m, 1 H) 2.32 (s, 3 H) 3.33 - 3.44 (m, 4 H) 3.54 - 3.63 (m, 1 H) 3.87 (s, 3 H) 4.70 - 5.26 (m, 1 H) 6.44 (s, 1 H) 6.70 (dd, 1 H) 6.85 (s, 1 H) 7.10 (d, 1 H) 7.62 (d, 1 H) 7.65 (s, 1 H)	($CDCl_3$) 1.8, 4.7, 13.5, 15.7, 27.4, 27.6, 28.1, 46.6, 55.6, 58.5, 62.5, 71.7, 100.4, 107.9, 117.1, 125.9, 136.9, 141.9, 153.4, 153.4, 155.6	438
43B	($CDCl_3$) 0.34 (dd, 1 H) 0.58 (s, 1 H) 0.66 - 0.81 (m, 2 H) 1.05 (d, 1 H) 1.26 (d, 6 H) 1.81 (td, 2 H) 2.11 - 2.20 (m, 1 H) 2.26 (s, 1 H) 2.33 (s, 3 H) 3.25 - 3.32 (m, 1 H) 3.33 - 3.39 (m, 1 H) 3.40 - 3.48 (m, 1 H) 3.60 (t, 2 H) 3.87 (s, 3 H) 6.53 (s, 1 H) 6.74 (dd, 1 H) 6.86 (s, 1 H) 7.10 (d, 1 H) 7.67 (d, 1 H) 7.69 (br. s., 1 H)	($CDCl_3$) 1.7, 4.8, 13.3, 15.8, 27.9, 29.9, 40.2, 42.9, 46.2, 55.6, 58.5, 69.6, 100.3, 107.8, 117.2, 125.8, 136.7, 142.2, 152.8, 153.4, 156.2	452
44A	(DMSO-d6) d ppm 1.15 (s, 6 H), 2.08 - 2.17 (m, 4 H), 2.44 (td, 1 H), 3.25 - 3.32 (m, 2 H), 3.34 - 3.47 (m, 3 H), 3.58 (s, 3 H), 4.10 (q, 3 H), 4.64 (s, 1 H), 5.33 (t, 1 H), 6.93 (s, 1 H), 6.96 - 7.01 (m, 1 H), 7.06 (d, 1 H), 7.17 (d, 2 H), 7.29 (t, 1 H), 7.37 (t, 2 H), 7.41 - 7.46 (m, 1 H), 7.55 (s, 1 H), 9.15 (s, 1 H)	(DMSO-d6) δ 13.6, 27.4, 27.7, 30.0, 43.6, 55.2, 56.5, 60.0, 71.0, 99.9, 107.5, 117.1, 117.4, 125.7, 126.3, 127.3, 128.4, 136.1, 136.8, 141.7, 142.9, 152.5, 154.2, 156.4	474

a) UPLC-MS (Waters Quattro Premier XE), column: Acquity UPLC BEH C18 1.7µm 2.1x30 mm (Waters), Mobile phase: A: 2% acetonitrile in 10 mM ammonium acetate B: 80% acetonitrile in 10 mM ammonium acetate, Gradient: 2% B for 0.2 min, 2-100% B in 0.3 min, held at 100% B for 0.2 min and returned to initial condition in one step. Solvent delay 0.4 min, time between injections 1.5 min. Flow rate 0.6 ml/min

b) UPLC-HRMS: UPLC-HRMS (Waters LCT Premiere), column: Acquity UPLC BEH C18 1.7µm 2.1x30 mm (Waters), Mobile phase: A: 2% acetonitrile in 10mM Formic Acid and 1 mM ammonium acetate B: 80% acetonitrile in 10mM Formic Acid and 1 mM ammonium acetate, Gradient: 5-90% B for 8 min.

c) UPLC-MS: UPLC-MS (Micromass TQD), column: Acquity UPLC HSS T3 1.8 µm, 2.1·50 mm Waters).

Aβ-generation in HEK.APPswe-cells.

Compounds were diluted in 100% DMSO and stored at 20°C prior to use. Human Embryonic Kidney (HEK) cell line stably expressing APP with the Swedish mutation (APPswe) was cultured using Dulbecco´s Modified Eagles medium (DMEM) supplied with 4500g/l glucose, Na-pyruvate and GlutaMAX, 10% Foetal bovine serum, 100 U/ml penicillin-streptomycin (PEST), 1x non-essential amino acids (NEAA), 10 µM Hepes, 100 µg/ml Zeocine. Cryo-preserved cells (frozen and stored at -140°C in 90% cell media and 10% DMSO) were thawed, washed and plated in 384-well poly-d-lysine coated cell culture plates at about 10000-15000 cells/well, in 25 µL cell media. Next the cells were incubated for 15-24h at 37°C and 5% CO_2, after which cell medium was changed. Fresh medium containing test compound diluted x200 from prepared compound plate was added to the cells before further incubation for 4-6 hours at 37°C and 5% CO_2. After incubation with test compound the

amount of Aβ peptides, including Aβ42, Aβ40, Aβ39, Aβ38 and Aβ37, secreted to cell medium was analyzed using the electrochemiluminescence assay technology from Meso Scale Discovery Technology, in combination with specific antibodies raised against the different Aβ peptides. Standard curves, created with synthetic peptides were used to calculate the amount of different peptides secreted to the cell media. Potential cytotoxic effects of the compounds were assayed by measuring the ATP content (ViaLight) from cell lysate.

Aβ-generation in mousePCNs

Compounds were diluted in 100% DMSO and stored at 20°C prior to use. Primary cortical neuronal cells (PCN) were isolated from 16-day mouse embryos and cultured in Ham´s F12 media containing 10% Foetal bovine serum, 10mM Hepes, 2mM L-glutamine and 100U/ml Penicillin-Streptomycin. 150000-250000 cells/well, in 200µL cell media were seeded onto 96-well poly-D-Lysine coated plates. After incubation at 37°C, 5% CO_2 for five days, the media was exchanged for fresh medium containing test compound diluted x100, before further incubation for 16-20 hours at 37°C and 5% CO_2. After incubation with test compound the amount of Aβ42 peptides secreted to cell medium was analyzed using the solid phase sandwich Enzyme-Linked-Immuno-Sorbent Assay (ELISA)-kit from Invitrogen for detection of mouse βAmyloid 1-42. Potential cytotoxic effects of the compounds were assayed by measuring the ATP content (ViaLight) from cell lysate.

In vivo

Formulation of compound **19B** for PK studies: 5% dimethylamine (DMA) and 20% hydroxypropyl-β-cyclodextrine (HPbCD) (100 mg/ml), Formulation of compound **42A** for PK studies: 5% DMA in 0.1 M gluconic acid. In all cases fasted, C57bl/6 female mice were used, 3 animals/administration/compound. All animal experiments were performed in C57BL/6 mice (Harlan Laboratories) in accordance with relevant guidelines and regulations provided by the Swedish Board of Agriculture. The ethical permission was provided by the Stockholm Södra Animal Research Ethical Board. Aβ42 levels were analyzed by use of a commercial validated ELISA (Biosource).