Supplementary Material

The Identification and Preclinical Evaluation of the Bicyclic Pyrimidine γ-Secretase Modulator BMS-932481.

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General: Solvents for reactions were purchased from Aldrich in Sure-Seal bottles. Chromatograhy mobile phase solvents were HPLC grade, purchased from J. T. Baker. ^{1}H and ^{13}C NMR spectra were obtained on 400 MHz and 500 MHz Bruker NMR instruments. Compound purities for Compounds **1-4** were >99%, and intermediates **6-17** were >97% as determined by orthoginal HPLC determinations. High resolution mass spectrometry (HRMS) analyses were performed on a Fourier Transform Orbitrap mass spectrometer (QExactive+, Thermo Fisher Scientific, San Jose, CA) in positive or negative ionization electrospray mode operating at 100,000 resolution (full width at half height maximum, FWHM). The instrument was daily calibrated according to manufacturer's specifications resulting in mass accuracy of or better than 5 ppm. The operating software Xcalibur was used to calculate theoretical mass-to-charge values and to process the obtained data. The data is consistent with molecular formula(s), delta < 5 ppm, calculations based on 1H, 12C, 14N, 16O, 19F, and 35Cl.

N^2-(3-methoxy-4-(1*H*-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-6-phenyl-1,3,5-triazine-2,4-diamine (1).

To a mixture of 2,4-dichloro-6-phenyl-1,3,5-triazine (100. mg, 0.442 mmol) and 3-methoxy-4-(1*H*-1,2,4-triazol-1-yl)aniline (84 mg, 0.44 mmol) in DMF (4.4 mL) was added Hunig's base (155 µl, 0.885 mmol). The resulting mixture was stirred at rt for 1 h. The mixture became dark orange. To the mixture was then added methyl amine (2.0 M in THF) (221 µl, 0.442 mmol). The resulting mixture was stirred at rt 4 h. An additional 1 eq. of $MeNH_2$ was then added to the mixture which continued to stir at rt an additional 30 min. An additional 1 eq. of $MeNH_2$ was added and the resulting mixture was stirred at rt for 1 h. The mixture was then diluted with EtOAc, washed with water (2x), brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by silica gel chromatography (0 to 100% EtOAc/hexane gradient, followed by a hold at 100% EtOAc) gave N^2-(3-methoxy-4-(1*H*-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-6-phenyl-1,3,5-triazine-2,4-diamine (114 mg, 0.303 mmol, 68.6 % yield). ^{1}H NMR (500 MHz, DMSO-*d*6) δ ppm 9.93 (s, 0.67H), 9.79 (s, 0.33H), 8.86 (s, 1H), 8.41 (d, *J*=7.0 Hz, 0.66H), 8.34 (d, *J*=6.9 Hz, 1.34H), 8.23 (s, 0.67H), 8.16 (s, 1H), 8.07 (s, 0.33H), 7.76 (s, 0.67H), 7.63-7.37 (m, 5.3H), 3.91 (s, 3H), 2.99 (d, *J*=4.6 Hz, 1H), 2.94 (d, *J*=4.5 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 170.1, 166.8, 164.9, 151.6, 145.5, 142.0, 137.1, 132.0, 128.8, 128.4, 128.3, 125.6, 120.3, 112.0, 104.4, 56.3, 27.8. HRMS (ESI/FTMS) m/z: $[M - H]^-$ Calcd for $C_{19}H_{17}N_8O$ 373.1531; Found 373.1532.

6-benzyl-N^2-(3-methoxy-4-(4-methyl-1*H*-imidazol-1-yl)phenyl)-N^4-methyl-1,3,5-triazine-2,4-diamine (2).

In a flame-dried, 250 mL 3-necked flask fitted with a stopper and a reflux condenser was added benzyl bromide (11.2 g, 65.5 mmol) in ether (100 mL). Magnesium turnings (1.58 g, 65.0 mmol) were added, and the flask was blanketed with nitrogen. The reaction was initiated by warming the flask with a heat gun, after which time the mixture continued to reflux without added heat until most of the magnesium had been consumed. Into a separate flame-dried 500 mL 3-necked flask fitted with a thermometer and a dropping funnel was added trichlorotriazine (10.0 g, 54.2 mmol) in benzene (100 mL), and the solution cooled to 0 °C. The grignard solution was transferred into the addition funnel, and added dropwise. After the addition was complete, the reaction mixture was stirred for an additional 3 h at 0 °C, then warmed to room temperature overnight. The reaction was quenched with ammonium chloride solution, and the mixture was extracted 3 times into ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated in vacuo to afford a yellow solid. Recrystalization from hot hexane afforded 2-benzyl-4,6-dichloro-1,3,5-triazine (7.00 g, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.43-7.26 (m, 5H), 4.20 (s, 2H). A portion of this compound (1.20 g, 5.00 mmol) was taken up in trifluoroethanol (11 mL) and acetic acid (11 mL), and cooled to 0 °C. A solution of 3-methoxy-4-(4-methyl-1*H*-imidazol-1-yl)aniline (1.02 g, 5.02 mmol) in trifluoroethanol (11 mL) was then added dropwise, and the mixture was allowed to warm from 0 °C to rt overnight. The solvents were removed in vacuo, and the residue was triturated with ethyl acetate. The solid was filtered off, and the mother liquer was concentrated in vacuo. The resulting residue was taken up in CH_2Cl_2, and washed with $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Silica gel chromatography (10 to 100% EtOAc/hexane) afforded 4-benzyl-6-chloro-*N*-(3-methoxy-4-(4-methyl-1*H*-imidazol-1-yl)phenyl)-1,3,5-triazin-2-amine (1.86 g, 92% yield). LC–MS $(M+H)^+$ = 407.1. ^{1}H NMR (500 MHz, DMSO-*d*6, 60 °C) δ ppm 10.70 (s, 1H), 7.68 (s, 1H), 7.64 (br s, 1H), 7.39-7.21 (m, 7H), 7.06 (s, 1H), 4.05 (s, 2H), 3.75 (br s, 3H), 2.16 (s, 3H). A portion of this compound (125 mg, 0.308 mmol) was taken up in dioxane (2 mL) and THF (2 mL).

Triethylamine (0.2 mL) was then added, followed by a 2 M solution of methylamine in THF (0.17 mL, 0.34 mmol). After stirring at rt overnight, the solvents were removed in vacuo, and the residue taken up in EtOAc. The organic phase was washed with sodium bicarbonate solution, dried, filtered and concentrated. Purification by HPLC afforded 6-benzyl-N^2-(3-methoxy-4-(4-methyl-1*H*-imidazol-1-yl)phenyl)-N^4-methyl-1,3,5-triazine-2,4-diamine (compound **2**, 47 mg, 0.12 mmol, 38% yield). HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}N_7O$ 402.2037; Found 402.2030. ^{1}H NMR (500 MHz, DMSO-*d*6, 100 ^{o}C) δ ppm 9.31 (s, 1H), 7.91 (s, 1H), 7.62 (m, 1H), 7.38-7.27 (m, 5H), 7.26-7.09 (m, 3H), 7.00 (br s, 1H), 3.81 (br s, 2H), 3.78 (br s, 3H), 2.92-2.86 (br d, 3H), 2.18 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 176.4, 166.5, 164.6, 152.5, 141.0, 138.4, 137.3, 136.8, 129.5, 128.8, 126.8, 125.8, 120.5, 117.4, 111.8, 104.4, 56.1, 45.1, 27.8, 14.1.

(*S*)-N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (3).

A solution of 2-chloro-*N*-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (833 mg, 3.21 mmol) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (717.9 mg, 3.21 µmol) in THF (5.6 mL) and acetic acid (5.6 mL) was heated at 85 °C in a 350 mL high-pressure vessel overnight. The mixture was cooled to room temperature, and the solvents were removed in vacuo. The residue was dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate solution. The organic phase was separated and the aqueous phase was extracted with dichloromethane two more times. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel to give N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, which was contaminated with 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline. The material was triturated with methanol, cooled in the freezer, and filtered. The residue was washed with cold methanol and dried to give pure N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (673 mg, 47%) as light brown solid. LC–MS $(M+H)^+$ = 446.9. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.99 (d, *J*=1.8 Hz, 1H), 7.48 (s,

1H), 7.27 - 7.33 (m, 2H), 7.16 - 7.24 (m, 3H), 6.96 - 7.07 (m, 3H), 6.71 (dd, *J*=8.4, 1.7 Hz, 1H), 4.50 (br s, 1H), 4.20 (s, 1H), 3.48 (s, 3H), 3.11 (d, *J*=4.9 Hz, 3H), 2.59 - 2.79 (m, 3H), 2.01 - 2.13 (m, 1H). The racemic material was purified using chiral supercritical fluid chromatography (SFC) to afford 28.4 mg of peak A [(*S*), desired] and 27.4 mg of peak B [(*R*), undesired], Chiralpak OJ-H (30 x 250 mm, 5 μM), 40 % methanol (0.1% diethylamine) in CO_2, 35 °C, flow rate 70 mL/min for 16 min, absorbance 268 nm, 1mL of 15 mg/mL solution in methanol per injection (multiple stacked injections), t_R (peak A) = 5.0 min, t_R (peak B) 12.3 min. Compound purity = 99.9%. ^{1}H NMR (500 MHz, DMSO-*d*6) δ ppm 9.20 (s, 1H), 8.17 (d, *J*=2.2 Hz, 1H), 7.73 (d, *J*=1.6 Hz, 1H), 7.41 (d, *J*=1.6 Hz, 1H), 7.29 (t, *J*=7.4 Hz, 2H), 7.17 - 7.22 (m, 3H), 7.13 - 7.17 (m, 1H), 7.08 - 7.13 (m, 1H), 6.95 (q, *J*=4.5 Hz, 1H), 4.13 (t, *J*=8.2 Hz, 1H), 3.57 (br. s., 3H), 2.96 (d, *J*=4.7 Hz, 3H), 2.72 - 2.82 (m, 1H), 2.51 - 2.67 (m, 2H), 1.86 - 2.00 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 170.6, 159.4, 159.2, 151.8, 144.0, 142.8, 136.4, 127.8, 127.7, 126.8, 125.6, 125.0, 116.7, 116.4, 109.1, 107.7, 101.3, 54.9, 51.0, 32.3, 27.0, 25.2. $[\alpha]_D$ -74.3 (c 5.68, $CHCl_3$). Anal. Calcd for $C_{24}H_{23}N_6OCl \bullet 0.75H_2O$: C, 62.60; H, 5.36; N, 18.25. Found: C, 62.92; H, 5.28; N, 18.26. Karl Fischer water Calcd for 0.75 eq 2.93%, Found: 3.19%. HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{24}H_{24}N_6OCl$ 447.1695; Found 447.1700.

(*S*)-7-(4-fluorophenyl)-*N*^{2}-(3-methoxy-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl)-*N*^{4}-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (4).

To a solution of 2-chloro-7-(4-fluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (141 mg, 0.508 mmol) and 3-methoxy-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)aniline (208 mg, 1.02 mmol) in *N*-methyl-2-pyrrolidinone (4.1 mL) was added H_2SO_4 (43.4 μL, 0.813 mmol). The solution was heated to 100 °C. When the reaction was complete, water and $NaHCO_3$ were added. The material was extracted into CH_2Cl_2 three times, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was applied to silica gel and eluted with an EtOAc/Hexane gradient, which yielded 7-(4-fluorophenyl)-*N*^{2}-(3-methoxy-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl)-*N*^{4}-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (250. mg, 66% yield). LC/MS $(M+H)^+$ = 446.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ

ppm 9.43 (br. s., 1H), 8.47 (s, 1H), 7.77 (br. s., 1H), 7.54 (d, *J*=8.85 Hz, 1H), 7.14 - 7.20 (m, 2H), 6.99 (t, *J*=8.55 Hz, 2H), 4.88 (br. s., 1H), 4.24 - 4.31 (m, 1H), 3.71 (s, 3H), 3.15 (d, *J*=4.90 Hz, 3H), 2.73 - 2.82 (m, 1H), 2.63 - 2.72 (m, 2H), 2.46 (s, 3H), 2.06 - 2.16 (m, 1H). The racemic material was separated by SFC chiral chromatography to obtain homochiral material. SFC Method: Chiralpak OJ-H (30 x 150 mm), 30 % methanol (0.1% diethylamine) in CO_2, 100 bar, flow rate 50 mL/min for 12 min, absorbance 268 nm, injection 2.0 mL of 10 mg/mL solution in methanol, t_R (peak A, desired) = 4.7 min, t_R (peak B, undesired) 9.6 min. LC/MS $(M+H)^+$ = 446.2. LC R_t 13.03 min (Waters Sunfire 4.6X150 mm 10 to 100% B in A over 15 min, 1.5 mL/min. (A is 90:10:0.1 water:MeOH:TFA; B is 90:10:0.1 MeOH:water:TFA)). Compound purity 99.8%. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.21 (s, 1H), 8.58 (s, 1H), 8.18 (d, *J* = 2.14 Hz, 1H), 7.31 (d, J=8.85 Hz, 1H), 7.22 (dd, *J*=8.39, 5.65 Hz, 2H), 7.08 - 7.18 (m, 3H), 6.94 (d, *J* = 4.58 Hz, 1H), 4.16 (t, *J* = 8.09 Hz, 1H), 3.63 (s, 3H), 2.98 (d, *J* = 4.58 Hz, 3H), 2.72 - 2.85 (m, 1H), 2.53 - 2.67 (m, 2H), 2.31 (s, 3H), 1.85 - 1.97 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 170.9, 161.8 (d, *J* = 242 Hz), 159.9, 159.7, 159.3, 151.5, 145.2, 143.1, 140.6 (d, *J* = 2.73 Hz), 130.0 (d, *J* = 7.27 Hz, 2C), 124.8, 118.1, 115.1 (d, *J* = 20.9 Hz, 2C), 109.7, 108.2, 101.7, 55.4, 50.6, 32.8, 27.5, 25.6, 13.7. $[\alpha]_D$ -68.6 (c 3.69, $CHCl_3$). RMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{24}H_{25}N_7OF$ 446.2099; Found 446.2103. Anal. Calcd for $C_{24}H_{25}N_7OF$: C, 64.56; H, 5.64; N, 21.96. Found: C, 64.52; H, 5.36; N, 22.05.

2-Phenylcyclopentanone (6). Step 1. To a solution of 3.0 M solution of phenylmagnesium bromide in ether (49.7 mL, 149 mmol) was added THF (300 mL). This solution was cooled to 0 °C, and then cyclopentanone (13.2 mL, 149 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 30 min, then at reflux for 2 h. Ice (20 g) was added, followed by the addition of 6 N HCl until the precipitate dissolved. The product was extracted with ether three times, and the combined etherial layers were washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel to give cyclopentenylbenzene (21.5 g, 149 mmol, 100 % yield) as a colorless oil. LC/MS

$(M+H)^+$ = 145.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.48 (d, *J*=7.3 Hz, 2H), 7.35 (t, *J*=7.8 Hz, 2H), 7.22 - 7.27 (m, 1H), 6.22 (t, *J*=2.1 Hz, 1H), 2.70 - 2.80 (m, 2H), 2.52 - 2.64 (m, 2H), 2.01 - 2.12 (m, 2H). Step 2. A mixture of 30% hydrogen peroxide (23 mL, 150 mmol) and 85% formic acid (100 mL, 2.6 mol) was heated at 40 °C for 15 min. The mixture was carefully added to cyclopentenylbenzene (21.49 g, 149 mmol), whereupon an exotherm was noted. The resulting two-phase system was vigorously stirred at room temperature for 4 h, over which time the reaction mixture became homogenous. The reaction mixture was carefully quenched with saturated aqueous solution of sodium bicarbonate, and the product was extracted with ether. The combined etherial layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 2-phenylcyclopentanone (20.0 g, 125 mmol, 84 % yield) as a brown oil. HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{11}H_{13}O$ 161.0961; Found 161.0959. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.38 (t, *J*=7.3 Hz, 1H), 7.30 - 7.35 (m, 2H), 7.19 (d, *J*=7.3 Hz, 2H), 3.28 - 3.37 (m, 1H), 2.71 (dt, *J*=4.6, 2.7 Hz, 1H), 2.58 - 2.63 (m, 1H), 2.43 - 2.55 (m, 1H), 2.29 (ddd, *J*=19.0, 10.5, 9.0 Hz, 1H), 2.07 - 2.21 (m, 1H), 1.88 - 1.99 (m, 1H).

7-Phenyl-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (7). A solution of 2-phenylcyclopentanone (20.0 g, 125 mmol) and *N*-(chlorocarbonyl)isocyanate (23.7 g, 225 mmol) was stirred at 58 °C for 1 h, then at 130 °C for 45 min. The resulting tar was dissolved in ethyl acetate and neutralized with saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and filtered. The residue was purified by column chromatography on silica gel to give 7-phenyl-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (3.751 g, 16.36 mmol, 13 % yield) as brownish solid. HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{13}H_{12}O_3N$ 230.0812; Found 230.0813. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.34 (br s, 1H), 7.35 (t, *J*=7.3 Hz, 2H), 7.27 - 7.32 (m, 1H), 7.18 (d, *J*=7.3 Hz, 2H), 4.20 (t, *J*=7.6 Hz, 1H), 2.82 - 2.91 (m, 1H), 2.61 - 2.79 (m, 2H), 2.11 - 2.21 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 169.6, 160.1, 148.5, 139.4, 129.1, 127.8, 127.5, 112.8, 49.5, 30.5, 24.2.

2,4-Dichloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (8). Step 1. A solution of 7-phenyl-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4-(3*H*,5*H*)-dione (3.751 g, 16.36 mmol) in concentrated ammonia in water (80 mL, 16 mmol) was heated in a 350-

mL high-pressure flask for 5 h. After cooling to room temperature, the flask was carefully opened, and the solvent was removed in vacuo to give 7-phenyl-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4-(3*H*,5*H*)-dione (3.73 g, 16.3 mmol, 100% yield) as a brown solid. LC/MS $(M+H)^+$ = 229.1. ^{1}H NMR (500 MHz, dimethylsulfoxide-*d6*) δ ppm 7.34 (t, *J*=7.5 Hz, 2H), 7.26 (t, *J*=7.3 Hz, 1H), 7.18 (d, *J*=7.3 Hz, 2H), 5.39 (br s, 1H), 4.14 (d, *J*=7.3 Hz, 1H), 2.43 - 2.68 (m, 2H), 1.80 - 1.88 (m, 2H). Step 2. A solution of 7-phenyl-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4-(3*H*,5*H*)-dione (1.24 g, 5.44 mmol) in phosphoryl trichloride (14.9 mL, 163 mmol) was heated in microwave at 110 °C for 1 h. The mixture was poured onto ice, and once the ice melted, the product was extracted into dichloromethane three times. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuo, and the residue was quickly purified by column chromatography on silica gel to give 2,4-dichloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (3.132 g, 72%) as a light brown solid. HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2Cl_2$ 265.0294; Found 265.0295. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.31 - 7.37 (m, 2H), 7.27 (d, *J*=7.0 Hz, 1H), 7.15 (d, *J*=7.9 Hz, 2H), 4.44 (t, *J*=8.2 Hz, 1H), 3.09 - 3.18 (m, 1H), 2.97 - 3.06 (m, 1H), 2.73 (ddd, *J*=9.0, 4.7, 4.6 Hz, 1H), 2.26 (ddd, *J*=8.5, 7.0, 6.7 Hz, 1H).

2-Chloro-*N*-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (9). To a solution of 2,4-dichloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (395 mg, 1.49 mmol) in THF (3.7 mL) was added 2 M $MeNH_2$ in THF (3.7 mL, 7.5 mmol). The reaction mixture was allowed to stir at rt. When the reaction was complete, the solvent was removed and the residue was applied to silica gel. The desired compound was eluted with EtOAc/Hex to afford the desired 2-chloro-*N*-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (80.8 mg, 0.220 mmol, 69% yield). HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}N_3Cl$ 260.0949; Found 260.0949. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.07 (m, 3H), 6.96 (t, *J*=8.7 Hz, 2H), 4.72 (br s, 1H), 4.23 (t, *J*=7.2 Hz, 1H), 3.09 (d, *J*=4.9 Hz, 3H), 2.67 - 2.77 (m, 1H), 2.58 - 2.67 (m, 2H), 2.01 - 2.11 (m, 1H).

4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (11). Step 1. A mixture of 4-chloro-1*H*-imidazole (5.0 g, 49 mmol), 1-chloro-2-methoxy-4-nitrobenzene (9.15 g, 48.8 mmol), and potassium hydroxide flakes (2.74 g, 48.8 mmol) in anhydrous DMSO (50 mL) was

heated at 80 ºC for 20 h. The reaction mixture was allowed to cool to rt and was poured into 800 mL of water with vigorous stirring. The resulting yellow-orange precipitate was collected by vacuum filtration using a coarse sintered glass funnel. The crude wet solid was transferred to a 1 L Erlenmeyer flask. Absolute ethanol (250 mL) was added to the flask and the resulting suspension was heated until all of the solids dissolved. The clear solution was cooled to rt and the desired product slowly crystallized. After 2 h, the crystalline solid was collected by vacuum filtration and rinsed with 100 mL of fresh ethanol. The solid was dried under high vacuum to afford 4-chloro-1-(2-methoxy-4-nitrophenyl)-1*H*-imidazole (5.2 g, 42 % yield) as an off-white crystalline solid. LC/MS $(M+H)^+$ = 254.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.94 - 8.01 (m, 2H), 7.76 (d, *J*=1.53 Hz, 1H), 7.45 (d, *J*=8.55 Hz, 1H), 7.21 (d, *J*=1.53 Hz, 1H), 4.02 (s, 3H).
Step 2. Iron powder–325 mesh (4.6 g, 82 mmol) was added to a 500 mL round bottom flask charged with a mixture of 4-chloro-1-(2-methoxy-4-nitrophenyl)-1*H*-imidazole (5.2 g, 21 mmol), absolute ethanol (100 mL), and glacial acetic acid (50 mL). A water-cooled reflux condenser was attached to the flask and the heterogeneous mixture was heated to 100 ºC with vigorous stirring for 30 min. The reaction mixture was allowed to cool to rt and was added to a chilled and stirred solution of 3 M NaOH (290 mL). The resulting mixture was poured into a separatory funnel and extracted with EtOAc (3 x 250 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (4.57 g, 97 % yield) as a solid. HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{10}H_{11}N_3OCl$ 224.0585; Found 224.0584. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.47 (d, *J*=1.22 Hz, 1H), 7.00 (d, *J*=8.24 Hz, 1H), 6.99 (d, *J*=1.53 Hz, 1H), 6.32 (d, *J*=2.44 Hz, 1H), 6.29 (dd, *J*=8.24, 2.44 Hz, 1H), 3.88 (br. s., 2H), 3.78 (s, 3H).

Diethyl 2-(4-fluorophenyl)hexanedioate (13). To a solution of ethyl 2-(4-fluorophenyl)acetate (247 g, 1.36 mol) in DMF (1.36 L), ethyl 4-bromobutanoate (793 g, 4.07 mol) and cesium carbonate (1.33 kg, 4.07 mol) were added with stirring to create a slurry. The reaction mixture was placed in an oil bath at 70 °C and stirred for 72 h. The reaction was cooled to rt and diluted into a mixture of ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted twice more with ethyl

acetate. The organic layers were combined, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. DMF was removed by concentration under vacuum using a vacuum pump and an external temperature of 70 °C. A yellow oil was obtained. Silica gel chromatography (5% EtOAc/hexane) afforded diethyl 2-(4-fluorophenyl)hexanedioate (150 g, 510 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.00 (m, 2H), 4.13 (m, 4H), 3.48 (t, J = 9.6 Hz, 1H), 2.49 (t, J = 6.8 Hz, 2H), 2.17 (m, 2H), 1.61 (m, 2H), 1.24 (m, 6H). HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{16}H_{22}O_4F$ 297.1497; Found 297.1491.

Ethyl 3-(4-fluorophenyl)-2-oxocyclopentane-1-carboxylate (14).
Diethyl 2-(4-fluorophenyl)hexanedioate (37.0 g, 125 mmol) was dissolved in THF (300 mL), and cooled to ~5 deg. (ice/water bath). A 1 M solution of NaHMDS in THF (137 mL, 137 mmol) was added. The reaction mixture was stirred for 1 hr at 5 ^{o}C, and then warmed toroom temperature over 2 h. The reaction mixture was then cooled to ~0 ^{o}C, diluted with ethyl acetate (250 mL), and quenched with 1 N HCl until the mixture was at neutral pH. The organic layer was isolated, dried over $MgSO_4$, filtered and concentrated, yielding ethyl 3-(4-fluorophenyl)-2-oxocyclopentanecarboxylate (29.5 g, 118 mmol, 94% yield) as a mixture of diasteriomers. LC/MS $(M+Na)^+$ = 273.1. ^{1}H NMR (500 MHz, CDCl3) δ: 7.08 – 7.18 (m, 2H), 6.93 – 7.04 (m, 2H), 4.13 – 4.28 (m, 2H), 3.21–3.49 (2 multiplets, 2H), 1.90–2.60 (2 multiplets, 4H), 1.21 – 1.32 (2 app t, 3H). HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{14}H_{16}O_3F$ 251.1078; Found 251.1072.

2,4-Dichloro-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (15).
Step 1: To a melt of urea (30. g, 500 mmol) (bath temp 150 °C) was added ethyl 3-(4-fluorophenyl)-2-oxocyclopentanecarboxylate (23 g, 92 mmol) dropwise. The mixture was stirred overnight, open to the atmosphere to allow water and ethanol to escape from the reaction mixture. The mixture was then cooled to rt, and 125 mL MeOH was added. The mixture was stirred and heated with a heat gun until all the material was dissolved/suspended. Stirred for 30 min at rt, then for 30 min at 0 °C. The solids were collected on a Buchner funnel. The filter cake was carefully washed with a few mL of water, then a few mL of cold EtOAc to remove some color. The resulting solid was

placed in the vaccuum oven at 60 °C for 30 min. The crude mass containg urea was stirred in ~200 mL water for 20 min. The solids were again filtered on a Buchner funnel and dried in the vaccuum oven to obtain 7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diol (8.0 g, 33 mmol, 35% yield). Step 2: To a mixture of 7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diol (8.02 g, 32.6 mmol) and *N*,*N*-diethylaniline (5.70 ml, 35.8 mmol) was added phosphoryl trichloride (45.5 ml, 489 mmol). After heating at 103 °C for 4h, the mixture was cooled, and the volatiles were removed in vacuo. Ice was added to the residue, and upon melting the mixture was extracted three times with ether. The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. A quick EtOAc/Hexane gradient on silica gel afforded 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (7.10 g, 25.1 mmol, 77% yield), as an oil which solidified upon standing. LC/MS $(M+H)^+$ = 283.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.09 - 7.15 (m, 2H), 7.03 (t, *J*=8.5 Hz, 2H), 4.42 (t, *J*=8.4 Hz, 1H), 3.10 (dd, *J*=9.2, 4.6 Hz, 1H), 3.01 (d, *J*=8.2 Hz, 1H), 2.73 (d, *J*=8.9 Hz, 1H), 2.15 - 2.27 (m, 1H). HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{13}H_{10}N_2Cl_2F$ 283.0200; Found 283.0201.

2-Chloro-7-(4-fluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (16).

To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (500 mg, 1.8 mmol) in THF (5 mL) was added methylamine as a 2 M solution in THF (4.4 mL, 8.8 mmol). After 1.5 h, solvents were removed in vacuo. The material was loaded onto a 40 g silica cartridge and eluted with a 5% to 100% EtOAc/hexane gradient over 600 mL to afford 2-chloro-7-(4-fluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (401 mg, 1.4 mmol, 82 % yield). LC/MS $(M+H)^+$ = 278.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.05 - 7.10 (m, 2H), 6.93 – 6.99 (m, 2H), 4.63 - 4.72 (app br d, 1H), 4.21 - 4.26 (m, 1H), 3.09 (d, *J*=4.9 Hz, 3H), 2.59 - 2.77 (m, 3H), 2.02 - 2.10 (m, 1H). HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}N_3ClF$ 278.0855; Found 278.0853.

3-Methoxy-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)aniline (17).

Step 1: To a mixture of 3-methyl-1*H*-1,2,4-triazole (5.0 g, 60 mmol) and 1-chloro-2-methoxy-4-nitrobenzene (11.3 g, 60.2 mmol) in anhydrous DMSO (50 mL) was added KOH flakes (3.4 g, 48 mmol), and the mixture was heated at 80 ºC for 6 h. The reaction mixture was allowed to cool to rt and was poured into 800 mL of water with vigorous stirring. The aqueous mixture was extracted with EtOAc (3 x 200 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified using silica gel chromatography (0-2% MeOH/chloroform, linear gradient) to afford 1-(2-methoxy-4-nitrophenyl)-3-methyl-1*H*-1,2,4-triazole (3.7 g, 26 % yield). LC/MS $(M+H)^+$ = 235.2. Step 2: Palladium on carbon (10%, 1.2 g) was added under an atmosphere of nitrogen to a chilled (ice-water bath) solution of 1-(2-methoxy-4-nitrophenyl)-3-methyl-1*H*-1,2,4-triazole (3.7 g, 12.7 mmol) dissolved in methanol (250 mL). The flask was repeatedly evacuated and flushed with hydrogen gas (double balloon). The resulting mixture was allowed to warm to rt and left to stir for 18 h under the hydrogen atmosphere. The suspension was then purged with nitrogen gas, and the crude reaction mixture was filtered through a short diatomaceous earth plug. The reaction vessel and plug was washed with methanol. The filtrate was concentrated in vacuo to afford a residue which was dried on high vacuum overnight to afford 3-methoxy-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)aniline (2.44 g, 94 % yield) as a reddish solid. LC/MS $(M+H)^+$ 205.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.35 (s, 1H) 7.36 (d, *J*=8.55 Hz, 1H) 6.29 - 6.34 (m, 2H) 3.80 (s, 3H) 2.46 (s, 3H). HRMS (ESI/FTMS) m/z: $[M + H]^+$ Calcd for $C_{10}H_{13}N_4O$ 205.1084; Found 205.1082.

Biological assays:

Assays are described in reference 8: Toyn, J. H.; Thompson, L. A.; Lentz, K. A.; Meredith, J. E.; Burton, C. R.; Sankaranararyanan, S.; Guss, V.; Hall, T.; Iben, L. G.; Krause, C. M.; Krause, R.; Lin, X.-A.; Pierdomenico, M.; Polson, C.; Robertson, A. S.; Denton, R.; Grace, J. E.; Morrison, J.; Raybon, J.; Zhuo, X.; Snow, K.; Padmanabha, R.; Agler, M.; Esposito, K.; Harden, D.; Prack, M.; Varma, S.; Wong, V.; Zhu, Y.; Zvyaga, T.; Gerritz, S.; Marcin, L. R.; Higgins, M. A.; Shi, J.; Wei, C.; Cantone, J. L.; Drexler, D. M.; Macor, J. E.; Olson, R. E.; Ahlijanian, M. K.; Albright, C. F. Identification and preclinical pharmacology of the γ-secretase modulator BMS-869780. *Int. J. Alz. Dis.* **2014**:431858.

Animal care use statement:

All experimental procedures with animals followed National Institutes of Health guidelines and were authorized by and in compliance with policies of the Bristol-Myers Squibb Animal Use and Care Committee.