Supporting Information

Development of the kinase inactive PD173955 Analogs for Reducing production of Aβ Peptides.

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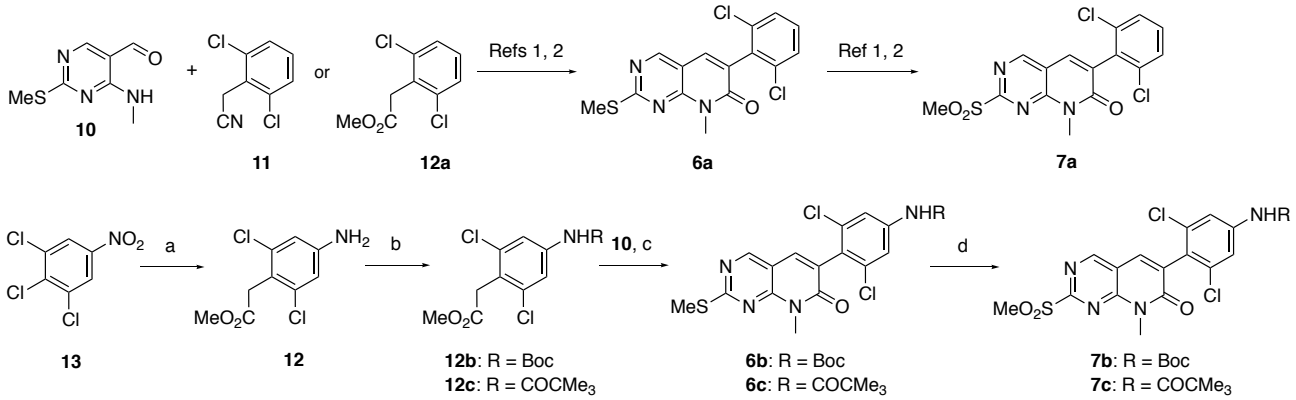
Chemical Methods. All commercial chemicals and solvents were reagent grade and used without further purification. Air-sensitive reactions were performed under Argon atmosphere. Microwave reactions were performed on Biotage Initiator. Column chromatography was performed using Biotage Isolera instrument and Silica gel SNAP columns. Analytical thin layer chromatography was performed on Merck 250 μM silica gel F_{254} plates, and preparative thin layer chromatography on Merck 1000 μM silica gel F_{254} plates obtained from EMD Millipore corporation. The identity of each product was determined using mass spectrometry (MS: Thermo Scientific LTQ XL; LC: Thermo Scientific Dionex Ultimate 3000) and NMR (Bruker 400 or 600 MHz instrument) using $CDCl_3$ as solvents unless otherwise mentioned. Chemical shifts are reported in δ values in ppm downfield from TMS as the internal standard. ^1H data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), integration.

1. Synthesis of key intermediates 7a-c. Compound **7a** was prepared by reacting aldehyde **10** with acetonitrile derivative **11**, as described elsewhere, followed by m-CPBA oxidation of the resulting product **6a** (Scheme S-1, upper).[1] Alternatively, compound **6a** was also prepared by reacting aldehyde **10** with ester **12a**, as described by Zhang, *et al*.[2] except that the reaction was performed in DMA. Compounds **7b** and **7c** were prepared starting with 3,4,5-trichloronitrobenzene, **13**, and converting the latter to **12b** and **12c** in 4 steps *via* a common amine intermediate **12** (Scheme S-1, lower). Subsequently, compounds **12b** and **12c** reacted with aldehyde **13**, as described for the synthesis of **6a**,[2] and the resulting products **6b** and **6c** were treated with m-CPBA to give **7b** and **7c**.



Scheme S-1. Synthesis of intermediates **7a-c**. Key: a) (i) K_2CO_3, $MeO_2CCH_2CO_2Me$, DMF, 100 ˚C, 16h, (ii) LiCl, aq DMSO, 105 ˚C, 16h, (iii) Raney Ni, 10% NH_2NH_2 in iPrOH, 0 ˚C – RT, 1.5 h. b) For **12b**: Boc_2O, toluene, 100 ˚C, 16 h, and for **12c**: $(Me_3CO)_3O$, CH_2Cl_2, DIEA, RT, 2 h. c) Cs_2CO_3, DMF or DMA, 100 ˚C, 18-36 h. d) m-CPBA, CH_2Cl_2, RT, 2 h.

1.1. Intermediates 12b and 12c.

i) Compound 12.[3] K_2CO_3 (4.2 g, 30 mmol) was added to a solution of **13** (2.26 g, 10 mmol) and dimethylmalonate (1.71 ml, 15 mmol) in dry DMF (20 ml), and the mixture was stirred at 100 ˚C overnight and then worked-up using diethyl ether/water/brine. Organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude product, 2-(2,6-dichloro-4-nitrophenyl)malonic acid dimethyl ester, was dried under vacuum and taken to next step without further purification.

LiCl (660 mg, 15.3 mmol) was added to a solution of the above-described product, substituted malonic acid diester, in DMSO-water (10:1, 22 ml) and the mixture was heated at 105 ˚C overnight. Reaction mixture was cooled and worked-up using water-EtOAc affording the decarboxylated product, methyl 2-(2,6-dichloro-4-nitrophenyl)acetate (1.27 g, 48%, 2 steps), after purification using Biotage. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (s, 2H), 4.08 (s, 2H), 3.73 (s, 3H).

A suspension of Raney Ni (0.25 ml) was added to a solution of the above-described product, methyl 2-(2,6-dichloro-4-nitrophenyl)acetate, (264 mg, 1 mmol) in iPrOH (5 ml) and hydrazine-monohydrate (0.5 ml) at 0 ˚C room temperature, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with EtOAc, filtered over Celite®, and the filtrate was washed using brine. EtOAc layer was dried over anhyd. $MgSO_4$, and concentrated under reduced pressure to afford amine **12** (200 mg, 84%) after purification using Biotage (Silica gel; Hexanes-EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) of **12**: δ 6.62 (s, 2H), 3.86 (s, 2H), 3.77 (br s, 2H), 3.69 (s, 3H).

ii) Compound 12b. Boc_2O (440 mg, 2 mmol) was added to amine **12** (200 mg, 0.85 mmol) in toluene (5 ml) and the mixture was stirred at 100 ˚C overnight. The reaction mixture was concentrated under pressure and the residue was purified using Biotage (Silica gel; Hexanes-EtOAc, 4:1) affording **12b**. ^{1}H NMR (600 MHz, $CDCl_3$) of **12b**: δ 8.04 (s, 1H), 6.97 (s, 2H), 3.92 (s, 2H), 3.70 (s, 3H), 1.51 (s, 9H).

iii) Compound 12c. Pivaloyl chloride (0.14 ml, 1.17 mmol) was added to a solution of amine **12** (120 mg, 0.51 mmol) and DIEA (0.4 ml, 2.35 mmol) in CH_2Cl_2 (5 ml) at ice-water temperature. After the mixture was stirred overnight at RT, it was worked-up using CH_2Cl_2/water. Organic layers were washed with aq $NaHCO_3$, dried over anhyd. $MgSO_4$, concentrated, and purified using Biotage (Silica gel; Hexanes-EtOAc, 4:1) to afford pure **16c** (110 mg, 68%).^{1}H NMR (400 MHz, $CDCl_3$) of **12c**: δ 7.58 (s, 2H), 7.32 (s, 2H), 3.94 (s, 2H), 3.69 (s, 3H), 1.28 (s, 9H).

1.2. Intermediates 6b and 6c.

Compound 6b. A mixture of **10** (94 mg, 0.5 mmol), **12b** (167 mg, 0.52 mmol) and Cs_2CO_3 (327 mg, 1 mmol) in dry DMF (3 ml) was heated at 100 ˚C for 3 h using microwave. Reaction mixture was filtered and the residue was washed with hot DMF, and filtrates were combined and concentrated under reduced pressure. Resulting residues were chromatographed using Biotage (Silica gel, Hexanes-EtOAc, 3:2) affording pure **12b** (90 mg, 38 %). ^{1}H NMR (600 MHz, $CDCl_3$) of **12b**: δ 8.68 (s, 1H), 7.59 (s, 1H), 7.47 (s, 2H), 7.07 (s, 1H), 3.85 (s, 3H), 2.68 (s, 3H), 1.50 (s, 9H). MS: *m/z* 467.06 $[M+H]^+$, Calcd. for $C_{20}H_{21}Cl_2N_4O_3S$; Found: 467.0.

Compound **6c** (76 mg, 29%) was prepared similarly using **10** (120 mg, 0.54 mmol), **12c** (177 mg, 0.57 mmol), and Cs_2CO_3 (360 mg, 1.1 mmol) in dry DMF (3 ml). ^{1}H NMR (600 MHz, $CDCl_3$) of **6c**: δ 8.65 (s, 1H), 7.69 (s, 1H), 7.65 (s, 2H), 7.56 (s, 1H), 3.83 (s, 3H), 2.65 (s, 3H), 1.28 (s, 9H). MS: *m/z* 451.07 $[M+H]^+$, Calcd. for $C_{20}H_{21}Cl_2N_4O_2S$; Found: 451.12.

1.3. Intermediates 7b and 7c. m-CPBA (75% by wt., 132 mg, 0.76 mmol) was added to a solution of compound **6b** (90 mg, 0.19 mmol) in CH_2Cl_2 (5 ml) at room temperature and the mixture was stirred for 2 hours affording crude sulfone product **7b** (90 mg, 95%) after work-up using CH_2Cl_2 and aq. $NaHCO_3$ solution. ^{1}H NMR (600 MHz, $CDCl_3$) of **7b:** δ 9.02 (s, 1H), 7.76 (s, 1H), 7.53 (s, 2H), 6.80 (s, 1H), 3.92 (s, 3H), 3.45 (s, 3H), 1.54 (s, 9H). MS: *m/z* 521.05 $[M+Na]^+$, Calcd. for $C_{20}H_{20}Cl_2N_4O_5SNa$; Found: 521.1.

Compound **6c** (74 mg, 0.17 mmol) were oxidized similarly using m-CPBA (84 mg, 0.36 mmol) in CH_2Cl_2 (2.5 ml) to afford **7c** (70 mg, 84 %). ^{1}H NMR (600 MHz, $CDCl_3$) of **7c:** δ 8.99 (s, 1H), 7.73 (s, 1H), 7.69 (s, 2H), 7.60 (s, 1H), 3.87 (s, 3H), 3.42 (s, 3H), 1.29 (s, 9H). MS: *m/z* 483.06 $[M+H]^+$, Calcd. for $C_{20}H_{21}Cl_2N_4O_4S$; Found: 483.11.

2. Synthesis and characterization of PD-173955 analogs. All analogs were prepared using key intermediates **7a**-**c** and **9**, and general methods A or B, as described below. All compounds were analyzed using LCMS (See: Table S-1). NMR of representative compounds are described below.

Method A (Representative example: compound **3m**). A mixture of intermediate **7a** (22 mg, 0.06 mmol), N-methyl-piperidinyl-piperazine (18 mg, 0.1 mmol) and DIEA (0.1 ml, 0.6 mmol) in THF-DMF (4:1, 1 ml) was heated at 80 ˚C using microwave for 1 h. Solvents were removed, and the residue was purified by PTLC (Silica gel; CH_2Cl_2-MeOH, 9:1) affording **3m** (20 mg, 69%).

Method B Representative example: compound **5n**). $Pd(PPh_3)_4$ (mg, 12 mg, 0.01 mmol) was added to a degassed mixture of intermediate **9** (67 mg, 0.2 mmol) and (4-((*tert*-butoxycarbonyl)amino)-phenyl)boronic acid (60 mg, 0.25 mmol) in DMF:Aq (2 M) K_2CO_3 (6:1, 1.4 ml) and heated at 120 ˚C using microwave for 0.5 h. Reaction mixture was worked-up using EtOAc/water, and purified using PTLC (Silica gel; Hexanes-EtOAc) to afford **5n** (65 mg, 72%).

2.1 Compounds 3a-p, 4a-m, and 5a-f. Prepared by heating **7a**, **7b**, or **7c** with various piperazine and amine derivatives and DIEA in THF-DMF using Method A.

3a (DV2-103): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.47 (s, 1H), 7.42 (1H, s), 7.40 (s, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 3.98 (t, *J* = 4.9 Hz, 4H), 3.73 (s, 3H), 2.99 (t, *J* = 4.9 Hz, 4H), 2.11 (br s, 1H). MS: *m/z* 390.09 $[M+H]^+$, Calcd. for $C_{18}H_{18}Cl_2N_5O$, Found: 390.19.

3l: ^{1}H NMR (400 MHz, CD_3OD): δ 8.78 (s, 1H), 7.79 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 8.36 Hz, 1H), 5.18 (br s, 1H), 3.75 (s, 3H), 3.68-3.58 (m, 8H), 3.35-3.31 (m, 2H), 3.16 (t, *J* = 12.2 Hz, 2H), 2.51 (d, *J* = 12.2 Hz, 2H), 2.14-2.11 (m, 3H). MS: *m/z* 473.15 $[M+H]^+$, Calcd. for $C_{23}H_{27}Cl_2N_6O$, Found: 473.1.

3m. ^{1}H NMR (400 MHz, $CDCl_3$) of 3m: δ 8.49 (s, 1H), 7.45 (s, 1H), 7.39 (d, *J* = 7.88 Hz, 2H), 7.23 (d, *J* = 7.80 Hz, 2H), 3.98 (br s, 4H), 3.72 (s, 3H), 2.96 (d, *J* = 10.24 Hz, 2H), 2.66 (br s, 4H), 2.34-2.30 (m, 1H), 2.31 (s, 3H), 2.02 (t, *J* = 10.68 Hz, 2H), 1.84 (d, *J* = 11.5 Hz, 2H), 1.72-1.66 (m, 2H). MS: *m/z* 487.17 $[M+H]^+$, Calcd. for $C_{24}H_{29}Cl_2N_4O$; Found: 486.9.

4k-Boc: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.45 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 8.0 Hz, 1H), 5.0 (d, *J* = 12.0 Hz, 1H), 4.37 (t, *J* = 7.0 Hz, 2H), 4.16 (br s, 2H), 3.73 (s, 3H), 2.92 (t, *J* = 12.3 Hz, 2H), 2.66 (br s, 2H), 2.51 (t, *J* = 6.2 Hz, 2H), 2.29 (m, 2H), 1.84 (d, *J* = 12.2 Hz, 2H), 1.70 (d, *J* = 12.2 Hz, 2H), 1.47 (s, 9H). MS: *m/z* 594.12 $[M+Na]^+$, Calcd. for $C_{29}H_{35}Cl_2N_5O_3Na$, Found: 494.3.

4k: ^{1}H NMR (400 MHz, CD_3OD): δ 8.72 (s, 1H), 7.76 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 1H), 3.77-3.66 (m, 2H), 3.72 (s, 3H), 3.59 (t, *J* = 5.0 Hz, 1H), 3.44 (d, *J* = 12.2 Hz, 2H), 3.12 (t, *J* = 11.7 Hz, 2H), 2.98 (t, *J* = 11.7 Hz, 2H), 2.03 (d, *J* = 10.9 Hz, 2H), 1.95 (d, *J* = 12.8 Hz, 2H), 1.62-1.52 (m, 4H), 1.40-1.29 (m, 2H). MS: *m/z* 472.16 $[M+H]^+$, Calcd. for $C_{24}H_{28}Cl_2N_5O$; Found: 472.1.

5a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.46 (s 2H), 7.44 (s, 1H), 3.98 (br s, 4H), 3.70 (s, 3H), 2.51 (t, *J* = 4.5 Hz, 4H), 2.39 (s, 1H), 2.35 (s, 3H), 1.50 (s, 9H). MS: *m/z* 519.16 $[M+H]^+$, Calcd. for $C_{24}H_{29}Cl_2N_6O_3$; Found: 519.2.

5b. ^{1}H NMR (400 MHz, $CDCl_3$) of 5b: δ 8.52 (s, 1H), 8.24 (br s, 2H), 7.48 (d, *J* = 5.40 Hz, 3H), 6.74 (br s, 2H), 4.11 (s, 4H), 3.72 (s, 3H), 3.38 (s, 1H), 3.54 (s, 4H), 1.48 (s, 9H). MS: *m/z* 582.17 $[M+H]^+$, Calcd. for $C_{28}H_{30}Cl_2N_7O_3$; Found: 582.1.

5c. ^{1}H NMR (400 MHz, $CDCl_3$) of 5c: δ 8.46 (s, 1H), 7.44 (d, *J* = 15.8 Hz, 2H), 3.94 (s, 4H), 3.67 (s, 3H), 2.97 (d, *J* = 10.3 Hz, 2H), 2.88 (s, 4H+3H), 2.63 (s, 4H), 2.29 (s, 4H), 2.08 (br s, 2H), 1.84 (d, *J* = 11.4 Hz, 2H), 1.66 (br d, *J* = 11.96 Hz, 2H), 1.48 (s, 9H). MS: *m/z* 602.23 $[M+H]^+$. Calcd. for $C_{29}H_{38}Cl_2N_7O_3$; Found: 602.1.

5d: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.87 (s, 1H), 7.65 (s, 2H), 7.44 (s, 1H), 4.04 (s, 4H), 3.75 (s, 3H), 2.53 (s, 4H), 2.38 (s, 3H), 1.28 (s, 9H). MS: *m/z* 503.17 $[M+H]^+$, Calcd. for $C_{24}H_{29}Cl_2N_6O_2$; Found: 503.2.

5f. ^{1}H NMR (400 MHz, $CDCl_3$) 5f: δ 8.45 (s, 1H), 7.64 (s, 2H), 7.41 (s, 3H), 3.92 (s, 4H), 3.65 (s, 3H), 3.50 (s, 4H), 3.21 (d, *J* = 11.32 Hz, 2H), 2.60 (br s, 4H), 2.54 (s, 3H), 2.51 (m, 1H), 1.93 (s, 4H), 1.23 (s, 9H). MS: *m/z* 586.26 $[M+H]^+$, Calcd. for $C_{29}H_{38}Cl_2N_7O_2$; Found: 582.1.

2.2. Compounds 5g-n. Prepared by $Pd(PPh_3)_4$-catalyzed Suzuki coupling of intermediate **9** with appropriate arylboronic acid and Aq. Cs_2CO_3 in 1,4-dioxane in a microwave vial using Method B.

5n: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.01 (s, 2H), 7.68-7.56 (m, 2H+1H), 7.42-7.33 (m, 2H), 6.72 (s, 1H), 3.99 (s, 4H), 3.72 (s, 3H), 2.54 (s, 4H), 2.35 (s, 3H), 1.53 (s, 9H). MS: *m/z* 451.24 $[M+H]^+$, calcd. for $C_{24}H_{31}N_6O_3$; found: 451.1.

3. Physicochemical data and ADME properties

3.1. Table S-1. Mass spectral data of additional PD173955 analogs

Entry	Product ID	Chem. Formula	Calcd. Mass	Obsvd. Mass $(M+H)^+$
1	**3b**	$C_{19}H_{19}Cl_2N_5O$	403.10	404.1092
2	**3c**	$C_{25}H_{23}C_{l2}N_5O$	479.13	480.1440
3	**3d**	$C_{20}H_{21}Cl_2N_5O_2$	433.11	434.1280
4	**3e**	$C_{21}H_{18}Cl_2N_6OS$	472.06	473.0826
5	**3f**	$C_{23}H_{21}Cl_2N_7O_2$	497.11	498.1191
6	**3g**	$C_{24}H_{20}Cl_3N_5O$	499.07	500.0834
7	**3h**	$C_{25}H_{20}Cl_2F_3N_5O$	533.10	534.1103
8	**3i**	$C_{23}H_{20}Cl_2N_6O$	466.11	467.1243
9	**3j**	$C_{23}H_{20}Cl_2N_6O$	466.11	467.1218
10	**3k**	$C_{23}H_{19}Cl_3N_6O$	500.07	501.0783
11	**3n**	$C_{25}H_{22}Cl_2N_6O_3$	524.11	525.1236
12	**3o**	$C_{24}H_{19}Cl_3N_6O_2$	528.06	529.009
13	**3p**	$C_{26}H_{23}Cl_2N_7O_2$	535.13	536.1416
14	**4a**	$C_{16}H_{14}Cl_2N_4O$	348.05	349.0634
15	**4b**	$C_{18}H_{18}Cl_2N_4O$	376.09	377.0923
16	**4c**	$C_{18}H_{16}Cl_2N_4O_2$	390.07	391.0803
17	**4d**	$C_{19}H_{18}Cl_2N_4O$	388.09	387.5721
18	**4e**	$C_{18}H_{19}Cl_2N_5O$	391.10	392.1029
19	**4f**	$C_{25}H_{22}Cl_2N_4O$	464.12	465.1264
20	**4g**	$C_{19}H_{18}Cl_2N_4O_2$	404.08	405.0963
21	**4h**	$C_{21}H_{23}Cl_2N_5O$	431.13	432.1408
22	**4i**	$C_{20}H_{17}Cl_2F_3N_4O$	456.07	457.0870
23	**4j**	$C_{20}H_{20}Cl_2N_4O_2$	418.10	419.1127
24	**4l**	$C_{24}H_{22}Cl_2N_6O$	480.12	481.1005
25	**4m**	$C_{24}H_{27}Cl_2N_5O$	471.16	472.1758
26	**5e**	$C_{28}H_{35}Cl_2N_7O_2$	571.22	572.30

27	**5g**	$C_{19}H_{21}N_5O$	335.17	336.1894
28	**5h**	$C_{21}H_{25}N_5O$	363.21	364.2152
29	**5i**	$C_{19}H_{20}ClN_5O$	369.14	370.1509
30	**5j**	$C_{19}H_{20}ClN_5O$	369.14	370.1475
31	**5k**	$C_{19}H_{20}ClN_5O$	369.14	370.1497
32	**5l**	$C_{19}H_{19}Cl_2N_5O$	403.10	404.1105
33	**5m**	$C_{19}H_{19}Cl_2N_5O$	403.10	404.1122

3.2. Table S-2. Calculated Physicochemical and ADME properties of active **3a** analogs[a]

Compd No	Mol Wt g/mol	tPSA Å^2	MLogP	GI absorption	BBB permeant	P-gp substrate	Synthetic accessibility
2	444.35	85.11	4.98	High	No	No	3.07
3a	390.27	63.05	3.19	High	Yes	No	2.88
3c	480.39	54.26	4.46	High	Yes	Yes	3.33
3l	473.40	66.29	3.47	High	Yes	Yes	3.85
3m	487.42	57.50	3.67	High	Yes	No	3.97
4m	472.41	54.26	4.47	High	Yes	Yes	3.88
5b	582.48	105.48	3.59	High	No	Yes	3.97
5c	602.56	95.83	3.73	High	No	Yes	4.74
5d	503.42	83.36	3.49	High	No	No	3.54
5f	586.56	86.60	3.69	High	No	Yes	4.58
5l	404.29	54.26	3.42	High	Yes	No	2.94

[a] Physicochemical data and ADME properties of 3a analogs were calculated using SwissADME (http://www.swissadme.ch/index.php) web tool.[4]

4. Screening and evaluation of PD173955 analogs.

Cell lines, antibodies, and reagents and kits for evaluation of compounds. N2a695 cells used to screen and evaluate **3a** analogs were available in house, and were cultured in 1:1 OptiMem Reduced Serum Media (Life Technologies): Dulbecco's Modified Eagle Medium ([+] 4.5 g/L D-glucose; [+] L-

Glutamine; [-] Sodium pyruvate (Life Technologies) supplemented with 5% fetal bovine serum, 0.4% Penstrep and 0.4% Geneticin and incubated at 37 °C in 5% CO_2. 96-Well ELISA plate for human Aβ40 peptide and V-Plex Plus MSD plate for Aβ Peptide Panel 1 (6E10) Kit (Catalog number K15200G) were obtained from Thermo Fischer and Meso Scale Discovery.

4.1. Aβ activity assay. Typically, 6-well tissue culture plates (Corning) were seeded with N2a695 cells at $4.0x10^5$ – $4.5x10^5$ N2a695 cells/mL, 2 mL/well for overnight incubation. Upon overnight incubation at 37 ˚C under 5% CO_2 atmosphere, media were exchanged with fresh media containing 10 μM solution of compounds (prepared from 10 mM solution in DMSO), and cells (>95% confluent) were further incubated for 5 hrs. Appropriate dilution of compounds was performed in DMSO before adding to media for lower concentrations. After cells were incubated with compounds for 5 h at 37 °C in 5% CO_2, culture media were collected. To measure soluble Aβ concentrations in culture media, these were transferred to strips of 96-well plate for human Aβ40 peptide (and Aβ42 peptide or to 96-well V-Plex Plus MSD (Mesoscale Discovery) plate for Aβ Peptide Panel 1 (6E10) Kit (Catalog number K15200G)) and processed as per manufacturer instructions. Signals for Aβ were measured using Perkin Elmer Envision and SQ120 MSD ELISA reader.

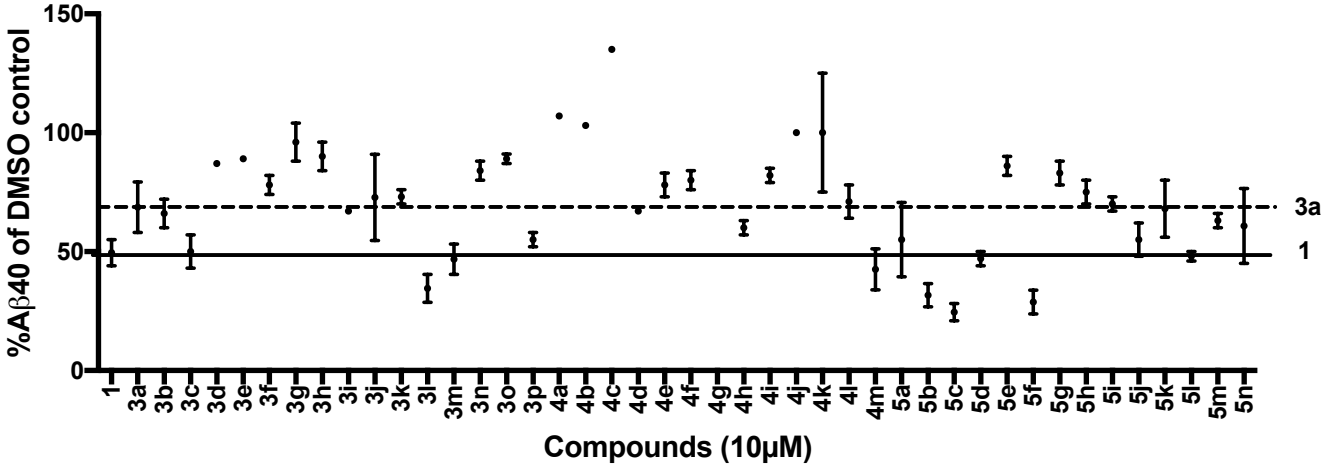


Figure S-1. Screening of PD173955 analogs **3a**-**p**, **4a**-**m**, and **5a**-**n** using N2a695 cells. Shown are average of 2 (in some case 1) independent assays in duplicates. Compound **4g** produced Aβ greater than 150% of DMSO control and is out of scale. We identified nine compounds, **3c**, **3l**-**m**, **4m**, **5b**-**d**, **5f**, and **5l** showing reduction of Aβ equal or greater than **1** for further evaluation.

4.2. *In vitro* kinase activity assay. The assay was performed by Luceome Biotechnolgies, LLC, using the general methods, as described.[5]

4.3. MTT assay. A 96-well plate was seeded with N2a695 cells (100,000 cells/ml, 200 µl) and kept in incubator stabilized at 37 ˚C and 5% CO_2 atmosphere. Media of the cells were exchanged with new media (100 µl) containing compounds (10 µM or appropriate concentration) or DMSO and Media alone (for controls) 24 hours later, and the plate was placed back in the incubator for another 5 or 24 h, as needed. MTT reagent (1:10 dilution using Media, 100 µl) was added to each well. Three hours later, solubilization buffer (100 µl) was added to each well and kept at 37 ˚C overnight to solubilize the formazan crystals, before the plate was cooled to room temperature and the absorbance was measured at 560 nm and 650 nm wavelength. The data were processed as described in product manual.

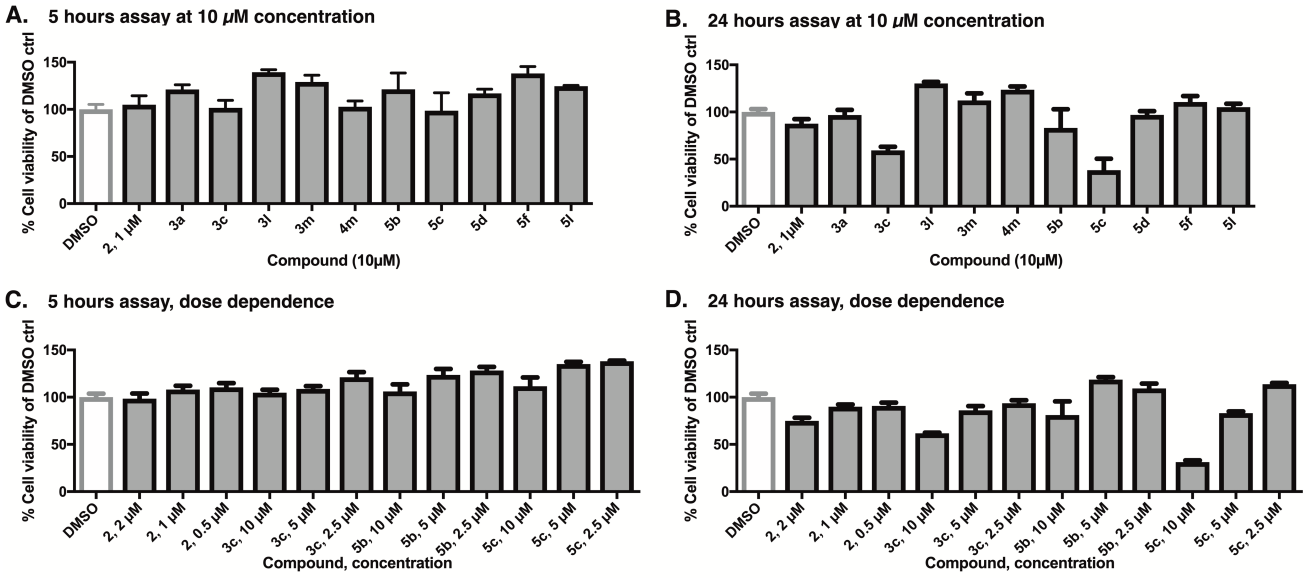


Figure S-2. Cellular toxicity of potent PD173955 analogs. Shown are cell viability of **2** and 9 potent analogs of **2** at 1 and 10 µM concentrations, respectively, in A and B, and dose dependence of 3 potentially toxic compounds in C and D, in 5- and 24-hours assays. Assays were performed in triplicates, and cell viability was determined as % of DMSO control.

4.4. APP metabolism study using supernatants from N2a cell transfected with APP-FL and C-99. N2a cells were transfected with full length APP (APP-FL) or with C-99. After 48 hours, media were exchanged with fresh media containing compound **3a** and analogs. Following 5 hours of incubation, cell supernatants were collected, and analyzed using MSD-ELISA to determine Aβ40 and Aβ42.

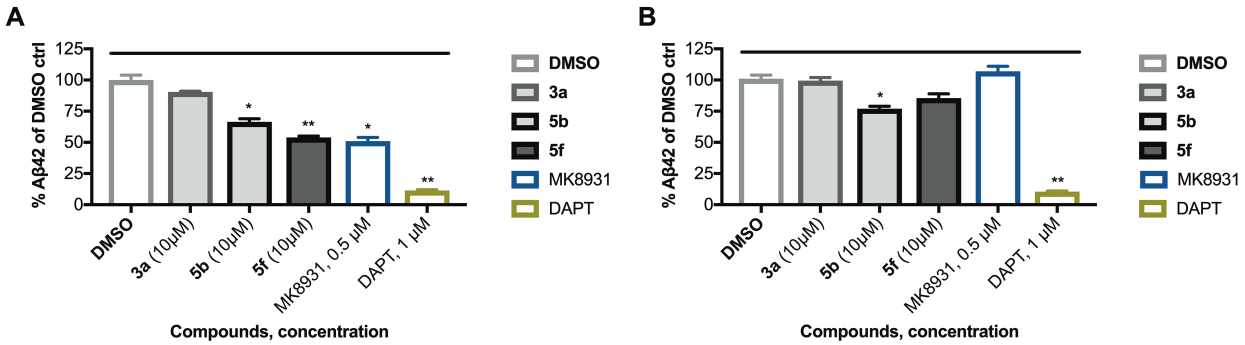


Figure S-3. Effects of **3a** analogs on production of Aβ42 peptide in N2a cells transfected with human (A) APP-FL or (B) APP-C99, measured by ELISA. DAPT is used as a positive control, and MK8931 is used as positive control in C and a negative control in D. All experiments were performed in duplicates, and results shown here are the representative of 2 independent experiments.

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