Aryl piperazinyl ureas as inhibitors of fatty acid amide hydrolase (FAAH) in rat, dog and primate.

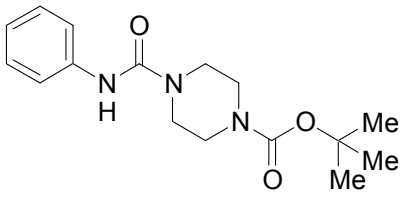
John M. Keith,[*] Rich Apodaca, Mark Tichenor, Wei Xiao, William Jones, Joan Pierce, Mark Seierstad, James Palmer, Michael Webb, Mark Karbarz, Brian Scott, Sandy Wilson, Lin Luo, Michelle Wennerholm, Leon Chang, Sean Brown, Michele Rizzolio, Raymond Rynberg, Sandra Chaplan and J. Guy Breitenbucher.

Table of Contents

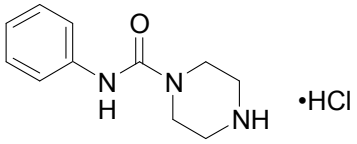
Purity of Final Products

Compound	Purity	Compound	Purity
1	>98%	**14**	>98%
3	>98%	**15**	>98%
4	>98%	**16**	>98%
5	>98%	**17**	>98%
6	>98%	**18**	>98%
7	>98%	**19**	>98%
8	>98%	**20**	>98%
9	>98%	**22**	>98%
10	98%	**23**	>98%
11	>98%	**24**	>98%
12	>98%	**25**	>98%
13	>98%	**26**	>98%

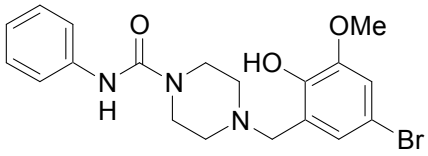
Preparation of Intermediates and Final Compounds



Intermediate A. To a 250 mL round-bottomed flask were added 5.027 g (27.0 mmol) Boc-piperazine, a stirbar and 100 mL dry DCM. The flask was purged with nitrogen and then charged, dropwise over 5 minutes, with 3.10 mL (28.4 mmol) phenyl isocyanate. The resultant mixture was stirred for 4 h at rt and then diluted with 300 mL DCM before washing with 1 M HCl (x1) and sat. $NaHCO_3$ (x1). The DCM layer was dried over $MgSO_4$, filtered and evaporated to dryness to give a white solid. The white solid was taken up in 125 mL hot EtOAc and the solution allowed to stand undisturbed overnight, during which time large white puff-ball crystals formed. The solid was isolated by vacuum filtration (5.67 g) and washed first with a small amount of EtOAc followed by hexanes. The hexane rinse triggered additional crystalization in the filtrate and that solid too was isolated by vacuum filtration (1.96 g) for a combined yield of 93%. MS (ESI): mass calcd. for $C_{16}H_{23}N_3O_3$, 305.17; m/z found, 328.1 $[M+Na]^+$. ^1H NMR (600 MHz, d_6-DMSO) δ 8.54 (s, 1H), 7.44 (dd, J = 1.2, 7.0 Hz, 2H), 7.24-7.21 (m, 2H), 6.95-6.92 (m, 1H), 3.43-3.41 (m, 4H), 3.36-3.34 (m, 4H), 1.42 (s, 9H).



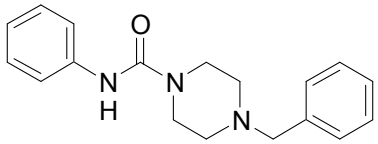
(2) To a 500 mL round-bottomed flask were added a stirbar, 5.03 g (16.5 mmol) substrate, 175 mL dry DCM and 13 mL 4.0 N HCl in dioxane. Within an hour a white precipitate had begun to form. The mixture was stirred for 18 h at rt under a nitrogen atmosphere and then analyzed by HPLC. The reaction mixture still had a considerable amount of starting material present so an additional 12 mL of 4 N HCl in dioxane was added and the mixture stirred further for 24 h, after which time the reaction was complete. The white precipitate was isolated by vacuum filtration and the solid washed with DCM. The solid was then dried further under high vacuum. Yield: 3.836 g (96%). MS (ESI): mass calcd. for $C_{11}H_{15}N_3O$, 205.12; m/z found, 206.1 $[M+Na]^+$. ^1H NMR (500 MHz, d_6-DMSO) δ 9.13 (br s, 1H), 8.76 (s, 1H), 7.46-7.44 (m, 2H), 7.23-7.22 (m, 2H), 6.97-6.94 (m, 1H), 3.67 (t, J = 5.0 Hz, 4H), 3.12 (t, J = 5.0 Hz, 4H).



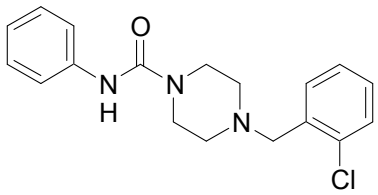
(1) To a 20 mL vial were added 31.5 mg (0.13 mmol) piperazine urea substrate, 137.9 mg (0.33 mmol) MP-$BH(OAc)_3$, 46.8 mg (0.20 mmol) 5-bromo-2-hydroxy-3-methoxybenzaldehyde, 2.0 mL THF and 0.20 mL (1.2 mmol) DIPEA. The vial was purged with nitrogen, capped and mixed on a shaker table for 24 h at rt. The reaction mixture was filtered and concentrated to dryness. The residue was purified by HPLC (Shimadzu with a 50 mm x 250 mm XBridge C_{18} column eluting with 25-100% ACN/water with 0.05% TFA @ 80 mL/min).

The fractions containing pure product were diluted with DCM and washed with sat. $NaHCO_3$. The organic layer was concentrated to dryness to give 25.0 mg (46%) of the pure product as the free base. MS (ESI): mass calcd. for $C_{19}H_{22}BrN_3O_3$, 419.08; m/z found, 420.0 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.33-7.31 (m, 2H), 7.27-7.26 (m, 2H), 7.05-7.02 (m, 1H), 6.94 (d, *J* = 1.8 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.54 (s, 1H), 3.86 (s, 3H), 3.69 (s, 2H), 3.53 (br s, 4H), 2.57 (br t, *J* = 4.2 Hz, 4H).

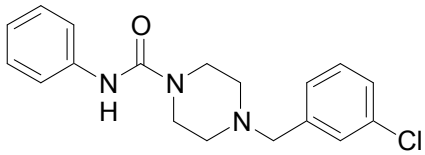
Compounds (**3**)-(**21**), except (**17**), were prepared using methods analogous to those used to synthesize compound (**1**).



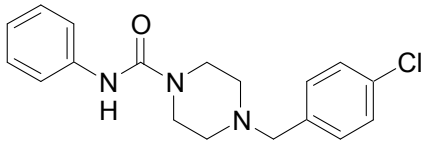
(**3**) Yield: 90%: MS (ESI^+): calcd for $C_{18}H_{21}N_3O$ m/z 295.17, found 296.2 $(M+H)^+$. ^1H NMR ($CDCl_3$): 7.34-7.28 (m, 5H), 7.27-7.22 (m, 4H), 7.02-6.97 (m, 1H), 6.54 (s, 1H), 3.52 (s, 2H), 3.48-3.45 (m, 4H), 2.45-2.43 (m, 4H).



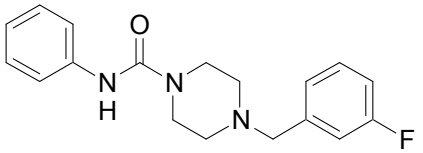
(**4**) Yield: 54%: MS (ESI): mass calcd. for $C_{18}H_{20}ClN_3O$, 329.13; m/z found, 330.1 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.37-7.33 (m, 3H), 7.27-7.24 (m, 3H), 7.22-7.19 (m, 1H), 7.02 (apparent tt, *J* = 1.2, 7.8 Hz, 1H), 6.50 (s, 1H), 3.64 (s, 2H), 3.49 (t, *J* = 4.8 Hz, 4H), 2.53 (t, *J* = 4.8 Hz, 4H).



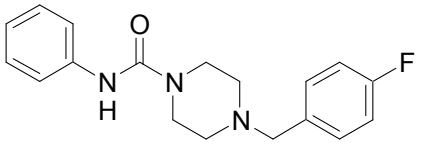
(**5**) Yield: 59%: MS (ESI): mass calcd. for $C_{18}H_{20}ClN_3O$, 329.13; m/z found, 330.1 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.34-7.32 (m, 3H), 7.26-7.24 (m, 4H), 7.21-7.18 (m, 1H), 7.01 (apparent tt, *J* = 1.2, 7.2 Hz, 1H), 6.53 (s, 1H), 3.49 (s, 2H), 3.48 (t, *J* = 5.4 Hz, 4H), 2.43 (t, *J* = 5.4 Hz, 4H).



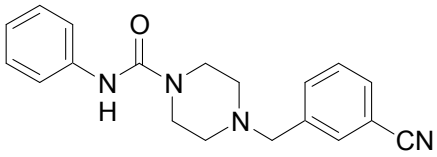
(**6**) Yield: 58%: MS (ESI): mass calcd. for $C_{18}H_{20}ClN_3O$, 329.13; m/z found, 330.1 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.34-7.32 (m, 2H), 7.31-7.29 (m, 2H), 7.27-7.24 (m, 4H), 7.02 (apparent tt, *J* = 1.2, 7.2 Hz, 1H), 6.48 (s, 1H), 3.48 (s, 2H), 3.47 (t, *J* = 5.4 Hz, 4H), 2.43 (t, *J* = 5.4 Hz, 4H).



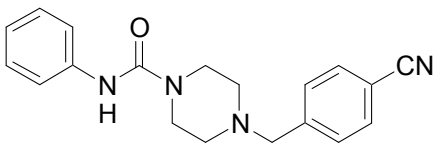
(**7**) Yield: 49%: MS (ESI): mass calcd. for $C_{18}H_{20}FN_3O$, 313.16; m/z found, 314.1 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.34-7.33 (m, 2H), 7.29-7.25 (m, 3H), 7.09-7.07 (m, 2H), 7.04-7.01 (m, 1H), 6.96 (apparent dt, *J* = 1.8, 8.4 Hz, 1H), 6.45 (s, 1H), 3.52 (s, 2H), 3.49 (t, *J* = 4.8 Hz, 4H), 2.46 (t, *J* = 4.8 Hz, 4H).



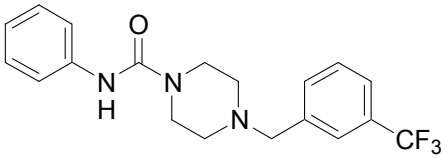
(**8**) Yield: 66%: MS (ESI): mass calcd. for $C_{18}H_{20}FN_3O$, 313.16; m/z found, 314.1 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 1.2, 9.0 Hz, 2H), 7.29-7.25 (m, 4H), 7.03-7.00 (m, 3H), 6.47 (s, 1H), 3.484 (s, 2H), 3.476 (t, *J* = 4.8 Hz, 4H), 2.44 (t, *J* = 4.8 Hz, 4H).



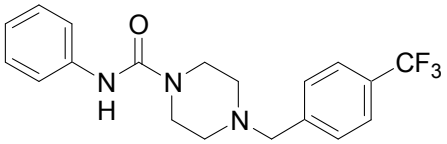
(**9**) Yield: 41%: MS (ESI): mass calcd. for $C_{19}H_{20}N_4O$, 320.16; m/z found, 321.1 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.57-7.56 (m, 2H), 7.44 (apparent t, *J* = 7.8 Hz, 1H), 7.35-7.33 (m, 2H), 7.28-7.26 (m, 2H), 7.03 (apparent tt, *J* = 1.2, 7.2 Hz, 1H), 6.48 (s, 1H), 3.55 (s, 2H), 3.50 (t, *J* = 5.4 Hz, 4H), 2.46 (t, *J* = 5.4 Hz, 4H).



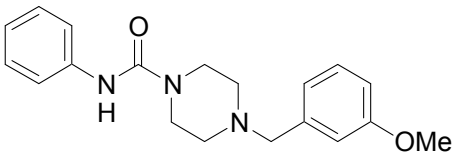
(**10**) Yield: 43%: MS (ESI): mass calcd. for $C_{19}H_{20}N_4O$, 320.16; m/z found, 321.1 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.63-7.62 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.35-7.33 (m, 2H), 7.28-7.26 (m, 2H), 7.03 (apparent tt, *J* = 1.2, 7.2 Hz, 1H), 6.45 (s, 1H), 3.58 (s, 2H), 3.50 (t, *J* = 5.4 Hz, 4H), 2.47 (t, *J* = 5.4 Hz, 4H).



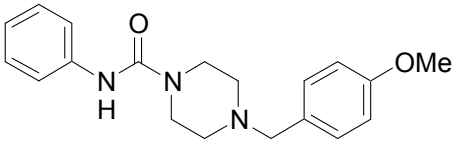
(**11**) Yield: 51%: MS (ESI): mass calcd. for $C_{19}H_{20}F_3N_3O$, 363.16; m/z found, 364.1 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.53 (apparent t, *J* = 7.2 Hz, 2H), 7.45 (apparent t, *J* = 7.2 Hz, 1H), 7.34-7.32 (m, 2H), 7.27-7.25 (m, 2H), 7.02 (apparent tt, *J* = 1.2, 7.2 Hz, 1H), 6.46 (s, 1H), 3.57 (s, 2H), 3.50 (t, *J* = 5.4 Hz, 4H), 2.46 (t, *J* = 5.4 Hz, 4H).



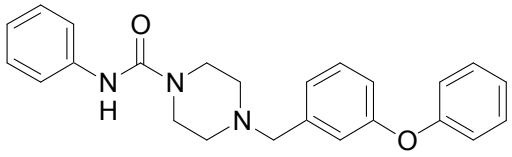
(**12**) Yield: 42%: MS (ESI): mass calcd. for $C_{19}H_{20}F_3N_3O$, 363.16; m/z found, 364.1 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.8 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.35-7.33 (m, 2H), 7.28-7.26 (m, 2H), 7.03 (apparent tt, *J* = 1.2, 7.2 Hz, 1H), 6.41 (s, 1H), 3.58 (s, 2H), 3.50 (t, *J* = 5.4 Hz, 4H), 2.47 (t, *J* = 5.4 Hz, 4H).



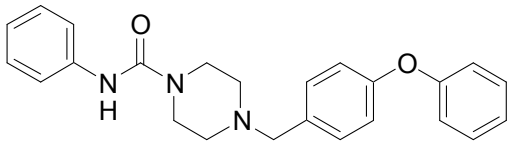
(**13**) Yield: 66%: MS (ESI): mass calcd. for $C_{19}H_{23}N_3O_2$, 325.18; m/z found, 326.1 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.34-7.32 (m, 2H), 7.27-7.23 (m, 3H), 7.02 (apparent tt, *J* = 1.2, 7.2 Hz, 1H), 6.91-6.90 (m, 2H), 6.82-6.80 (m, 1H), 6.45 (s, 1H), 3.1 (s, 3H), 3.50 (s, 2H), 3.48 (t, *J* = 5.4 Hz, 4H), 2.46 (t, *J* = 5.4 Hz, 4H).



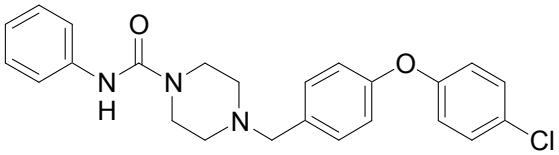
(**14**) Yield: 54%: MS (ESI): mass calcd. for $C_{19}H_{23}N_3O_2$, 325.18; m/z found, 326.2 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 1.2, 8.4 Hz, 2H), 7.27-7.22 (m, 4H), 7.03-7.00 (m, 1H), 6.87-6.86 (m, 2H), 6.45 (s, 1H), 3.80 (s, 2H), 3.473 (t, *J* = 5.4 Hz, 4H), 3.466 (s, 2H), 2.44 (t, *J* = 5.4 Hz, 4H).



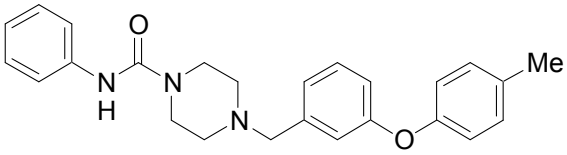
(**15**) Yield: 23%: MS (ESI): mass calcd. for $C_{24}H_{25}N_3O_2$, 387.20; m/z found, 388.2 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.36-7.32 (m, 4H), 7.30-7.26 (m, 3H), 7.12-7.09 (m, 1H), 7.07-7.05 (d, *J* = 7.8 Hz, 1H), 7.04-6.99 (m, 4H), 6.91 (dd, *J* = 1.8, 7.8 Hz, 1H), 6.34 (s, 1H), 3.52 (s, 2H), 3.49 (t, *J* = 5.4 Hz, 4H), 2.48 (t, *J* = 5.4 Hz, 4H).



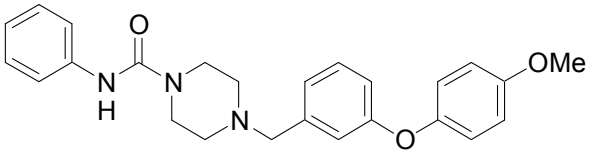
(**16**) Yield: 24%: MS (ESI): mass calcd. for $C_{24}H_{25}N_3O_2$, 387.20; m/z found, 388.2 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.35-7.32 (m, 4H), 7.29-7.26 (m, 4H), 7.10 (apparent tt, *J* = 1.2, 7.2 Hz, 1H), 7.04-7.00 (m, 3H), 6.98-6.96 (m, 2H), 6.38 (s, 1H), 3.51 (s, 2H), 3.50 (t, *J* = 5.4 Hz, 4H), 2.48 (t, *J* = 5.4 Hz, 4H).



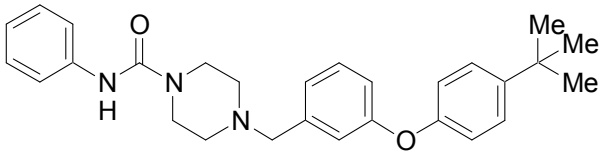
(**18**) Yield: 47%: MS (ESI): mass calcd. for $C_{24}H_{24}ClN_3O_2$, 421.16; m/z found, 422.1 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.35-7.33 (m, 2H), 7.29-7.25 (m, 6H), 7.02 (apparent tt, *J* = 1,2 7.2 Hz, 1H), 6.97-6.93 (m, 4H), 6.43 (s, 1H), 3.505 (s, 2H), 3.495 (t, *J* = 5.4 Hz, 4H), 2.47 (t, *J* = 5.4 Hz, 4H).



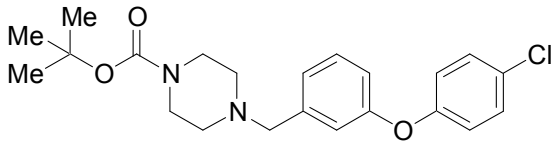
(**19**) Yield: 62%: MS (ESI): mass calcd. for $C_{25}H_{27}N_3O_2$, 401.21; m/z found, 402.2 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.8 Hz, 2H), 7.27-7.24 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.04-6.99 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.87 (dd, *J* = 1.8, 7.8 Hz, 1H), 6.44 (s, 1H), 3.49 (s, 2H), 3.47 (t, *J* = 5.4 Hz, 4H), 2.45 (t, *J* = 5.4 Hz, 4H), 2.34 (s, 3H).



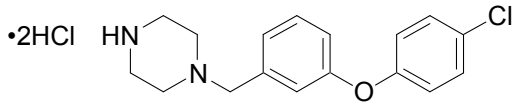
(**20**) Yield: 21%: MS (ESI): mass calcd. for $C_{25}H_{27}N_3O_3$, 417.21; m/z found, 418.2 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.35-7.33 (m, 2H), 7.29-7.23 (m, 3H), 7.04-6.95 (m, 5H), 6.91-6.87 (m, 2H), 6.84-6.82 (m, 1H), 6.35 (s, 1H), 3.81 (s, 3H), 3.50 (s, 2H), 3.48 (t, *J* = 5.4 Hz, 4H), 2.47 (t, *J* = 5.4 Hz, 4H).



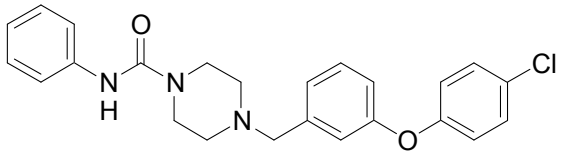
(**21**) Yield: 27%: MS (ESI): mass calcd. for $C_{28}H_{33}N_3O_2$, 443.26; m/z found, 444.2 $[M+H]^+$. ^1H NMR (600 MHz, $CDCl_3$) δ 7.36-7.32 (m, 4H), 7.28-7.24 (m, 3H), 7.05-7.00 (m, 3H), 6.95-6.92 (m, 2H), 6.89-6.88 (m, 1H), 3.50 (s, 2H), 3.47 (t, *J* = 5.4 Hz, 4H), 2.45 (t, *J* = 5.4 Hz, 4H), 1.32 (s, 9H).



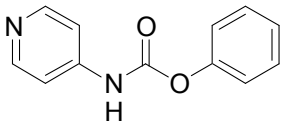
Intermediate B. To a dry 1-L round-bottomed flask were added a stirbar, 10.08 g (54.2 mmol) 1-Boc-piperazine, 18.82 g (80.9 mmol) 3-(4-chlorophenoxy)benzaldehyde and 500 mL dry DCM. The mixture was stirred until homogeneous and then treated with 35.32 g (0.167 mol) $NaBH(OAc)_3$. The mixture was stirred for 23 h under nitrogen at rt before diluting with DCM and washing with 1 N NaOH (x2) and sat. $NaHCO_3$ (x1), drying over $MgSO_4$, filtering and evaporating to dryness to afford the crude product. Chromatographic purification (330 g Isco column eluting with 0-5% 2 N NH_3 in MeOH/DCM) yielded 15.37 g (70%) of the desired product as a viscous oil that crystallized upon standing. MS (ESI): mass calcd. for $C_{22}H_{27}ClN_2O_3$, 402.17; m/z found, 403.2 $[M+H]^+$. ^1H NMR (500 MHz, d_6-DMSO) δ 7.46-7.41 (m, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 7.05-7.00 (m, 2H), 6.97 (s, 1H), 6.94-6.89 (m, 1H), 3.47 (s, 2H), 3.31-3.25 (br m, 4H), 2.31-2.26 (br m, 4H), 1.38 (9H, s).



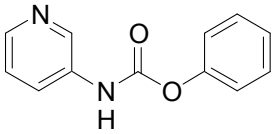
Intermediate C To a dry 1-L round-bottomed flask were added a stirbar, 15.37 g (**Intermediate B**, 38 mmol), 400 mL dry DCM and 48 mL 4.0 N HCl in 1,4-dioxane. The resultant mixture was stirred for 22.5 h and then filtered. The filtered solid was washed with DCM and then dried under high vacuum to give 7.11 g (50%) of the desired product as the bis HCl salt. MS (ESI): mass calcd. for $C_7H_{19}ClN_2O$, 302.12; m/z found, 303.1 $[M+H]^+$. ^1H NMR (500 MHz, d_4-methanol) δ 7.50 (t, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.27-7.24 (m, 1H), 7.15-7.11 (m, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 4.40 (s, 2H), 3.66–3.42 (br m, 8H).



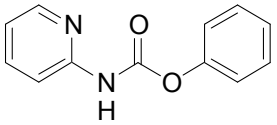
(**17**) To a 20 mL vial were added a stirbar, 52.3 mg (0.14 mmol) **Intermediate C**, 2.0 mL DCM, 0.10 mL (0.58 mmol) DIPEA and 16 µL (0.15 mmol) phenyl isocyanate. The resultant mixture was stirred for 23 h and then concentrated to dryness. The residue was subjected to HPLC purification (Shimadzu with XBridge C_{18} 250 mm x 50 mm column, eluting with 20-100% ACN/water with 0.05% TFA at 80 mL/min). The HPLC fractions containing product were combined, diluted with DCM and washed with sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness to give the product (45.3 mg, 77%) as a white solid. MS (ESI): mass calcd. for $C_{24}H_{24}ClN_3O_2$, 421.16; m/z found, 422.2 $[M+H]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.32 (m, 2H), 7.30-7.24 (m, 5H), 7.07 (d, *J* = 9.0 Hz, 1H), 7.03-6.99 (m, 2H), 6.95-6.92 (m, 2H), 6.89-6.88 (m, 1H), 6.50 (s, 1H), 3.50 (s, 2H), 3.47 (t, *J* = 5.0 Hz, 4H), 2.44 (t, *J* = 5.0 Hz, 4H).



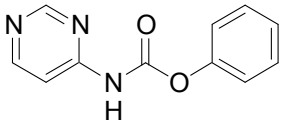
Intermediate D. To a solution consisting of pyridin-4-yl amine (9.62 g, 102 mmol) and 5:1 CH_3CN:H_2O (50 mL) at rt was added phenyl chloroformate (5.33 g, 34.1 mmol) dropwise. The reaction mixture was stirred for 0.5 h at rt, then diluted with EtOAc (300 mL) and extracted with saturated aqueous $NaHCO_3$ (300 mL), H_2O (300 mL), and saturated aqueous NaCl (200 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resulting solid was precipitated from EtoAc/Hexanes and dried under vacuum to provide the title compound as a white solid (1.702 g, 23%). MS (ESI^+): calcd for $C_{12}H_{10}N_2O_2$ m/z 214.07, found 215.1 $(M+H)^+$. ^1H NMR (d_6-acetone): 8.49-8.41 (m, 2H), 7.60-7.52 (m, 2H), 7.48-7.38 (m, 2H), 7.31-7.20 (m, 3H).



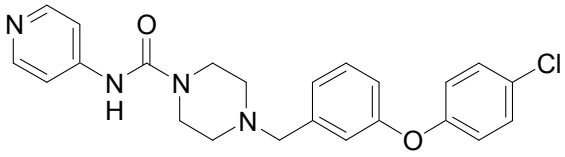
Intermediate E. To a solution consisting of pyridin-3-yl amine (9.49 g, 101 mmol) and pyridine (8.77 g, 111 mmol) in CH_3CN (80 mL) at 0 °C was added phenyl chloroformate (15.8 g, 101 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with H_2O (200 mL) and the resulting precipitate was filtered and dried under vacuum to provide the title compound as a tan solid (17.34 g, 80%). MS (ESI^+): calcd for $C_{12}H_{10}N_2O_2$ m/z 214.07, found 215.3 $(M+H)^+$. ^1H NMR (500 MHz, DMSO): 10.46 (s, 1H), 8.69 (d, *J* = 2.4 Hz, 1H), 8.27 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.47-7.41 (m, 2H), 7.37 (dd, *J* = 8.4, 4.7 Hz, 1H), 7.31-7.22 (m, 3H).



Intermediate F. To a solution consisting of pyridin-2-yl amine (1.32 g, 14.1 mmol), pyridine (1.23 mL, 15.3 mmol) and CH_3CN (15 mL) at rt was added phenyl chloroformate (2.00 g, 12.8 mmol) dropwise. The reaction mixture was stirred for 0.5 h at rt, then diluted with EtOAc (300 mL) and extracted with saturated aqueous $NaHCO_3$ (300 mL), H_2O (300 mL), then saturated aqueous NaCl (200 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resulting solid was precipitated from EtoAc/Hexanes and dried under vacuum to provide the title compound as a white solid (2.21 g, 81%). MS (ESI^+): calcd for $C_{12}H_{10}N_2O_2$ m/z 214.07, found 215.1 $(M+H)^+$. ^1H NMR (d_6-acetone): 9.47 (br s, 1H), 8.35-8.28 (m, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.84-7.76 (m, 1H), 7.49-7.39 (m, 2H), 7.30-7.21 (m, 3H), 7.10 (ddd, *J* = 7.3, 4.9, 1.0 Hz, 1H).

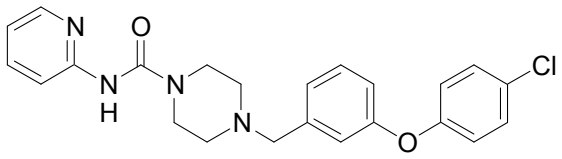


Intermediate G. To a 250 mL round-bottomed flask were added a stirbar, 4.25 g (44.7 mmol) 4-aminopyrimidine, 45 mL dry THF and 1.90 mL (15 mmol) phenyl chloroformate. The resultant heterogeneous mixture was stirred at rt for 31 h before pouring the reaction mixture into 600 mL of d.i. water. The aqueous suspension was stirred for 30 minutes and then filtered. The solid was air dried on the filter paper and then dried further under high vacuum to give 2.92 g (90%) of the desired product. MS (ESI^+): calcd for $C_{11}H_9N_3O_2$ m/z 215.07, found 216.1 $(M+H)^+$.

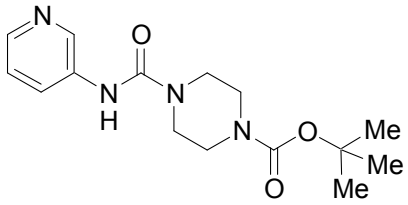


(**22**) To a solution consisting of 1-[3-(4-chloro-phenoxy)-benzyl]-piperazine hydrochloride (200 mg, 0.532 mmol), DIPEA (137 mg, 1.07 mmol) and DCE (3.0 mL) was added **Intermediate D** (114 mg, 0.532 mmol). The reaction mixture was stirred at room temperature for 16 h before removing the solvent under reduced pressure and purifying the residue chromatographicly (DCM/MeOH/NH_3) to give the title compound (252.5 mg, 73%). MS (ESI^+): calcd for $C_{23}H_{23}ClN_4O_2$ m/z 422.15, found 423.1 $(M+H)^+$. ^1H NMR (d_6-DMSO): 10.38 (s, 1H), 8.60 (d, *J* = 7.2 Hz, 2H), 7.90 (d, *J* = 7.3 Hz, 2H), 7.56-7.43 (m, 3H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.23-7.18 (m, 1H), 7.16 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.10 (d, *J* = 8.9 Hz, 2H), 4.45-4.08 (m, 2H), 4.35 (s, 2H), 3.57-2.92 (br m, 6H).

Compound (**23**) was prepared in an analogous manner to (**22**).

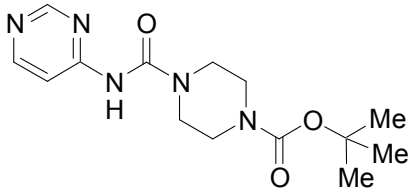


(**23**) Yield: 47%; MS (ESI$^+$): calcd for $C_{23}H_{23}ClN_4O_2$ m/z 422.15, found 423.2 $(M+H)^+$. ^{1}H NMR (d_6-DMSO): 11.22 (s, 1H), 8.99 (s, 1H), 8.63 (s, 1H), 8.37 (d, *J* = 5.4 Hz, 1H), 7.68 (d, *J* = 5.4 Hz, 1H), 7.55-7.38 (m, 4H), 7.33 (s, 1H), 7.18-7.06 (m, 3H), 4.35 (s, 2H), 4.21 (d, *J* = 13.6 Hz, 2H), 3.46-3.29 (m, 4H), 3.11-2.88 (m, 2H).

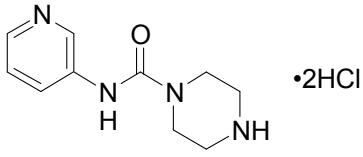


Intermediate H. To a 250 mL round-bottomed flask were added a stirbar, 11.0 g (51 mmol) **Intermediate E** and 100 mL dry DMSO. The mixture was stirred until homogeneous and then treated with 10 g (54 mmol) 1-Boc piperazine. The resulting mixture was stirred for 24 h at rt and then placed in an ice bath and immediately treated with 200 mL DI water thus causing a precipitate to form. The solid was isolated by vacuum filtration and then washed thoroughly with water. The solid was allowed to air dry on the filter paper (continous flow of air) and then dried further under high vacuum to give 15.9 g (102% of theoretical) of product. ^{1}H NMR (400 MHz, $CDCl_3$): 8.41 (d, *J* = 2.4 Hz, 1H), 8.26 (dd, *J* = 1.2, 4.8 Hz, 1H), 7.95 (ddd, *J* = 1.6, 2.4, 8.4 Hz, 1H), 7.22-7.20 (m, 1H), 6.65 (s, 1H), 3.49 (s, 8H), 1.46 (s, 9H).

Intermediate I was made using methods analogous to those used to prepare **Intermediate H**.

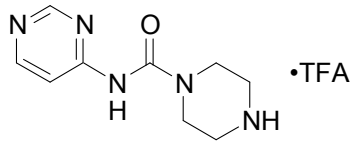


Intermediate I. Yield: 34%; MS (ESI$^+$): calcd for $C_{14}H_{21}N_5O_3$ m/z 307.16, found 308.2 $(M+H)^+$; ^{1}H NMR (600 MHz, d_4-MeOH): 8.72 (s, 1H), 8.46 (d, *J* = 6.0 Hz, 1H), 7.87 (dd, *J* = 1.2, 6.0 Hz, 1H), 3.56-3.55 (m, 4H), 3.49 (br s, 4H), 1.48 (s, 9H).



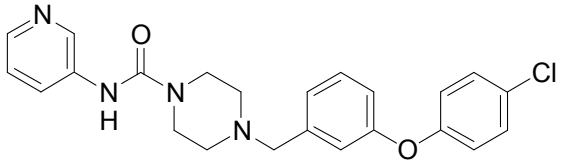
Intermediate J. To a 1-L round-bottomed flask were added a stirbar, 15.5 g **Intermediate H** (mmol) and 410 mL MeOH. The mixture was stirred until homogeneous and then treated with

152 mL 2 M $HCl_{(aq.)}$. The resultant mixture was stirred for 16 h at rt and then treated with 800 mL Et_2O to precipitate the product. The solid was isolated via vacuum filtration and then washed thoroughly with Et_2O. The solid was allowed to air dry on the filter paper (continous flow of air) and then dried further under high vacuum to give 10.6 g (75%) of product. ^{1}H NMR (400 MHz, d_4-MeOH): 9.24-9.23 (m, 1H), 8.60-8.57 (m, 1H), 8.48-8.46 (m, 1H), 7.99 (dd, *J* = 2.0, 8.8 Hz, 1H), 3.89 (t, *J* = 5.4 Hz, 4H), 3.34-3.30 (m, 4H).

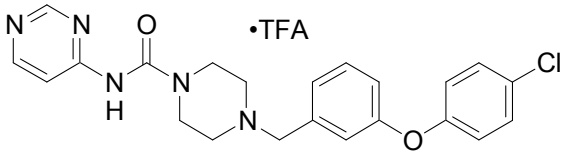


To a 100 mL round-bottomed flask were added a stirbar, 933.7 mg **Intermediate I**, 30 mL dry DCM and 2.50 mL (32 mmol) TFA. The resultant mixture was stirred for 20 h and then concentrated to dryness and dried under high vacuum to give 1.04 g (107% of theoretical) of the product as a viscous oil. MS (ESI^+): calcd for $C_9H_{131}N_5O$ m/z 207.11, found 208.2 $(M+H)^+$; ^{1}H NMR (600 MHz, d_4-MeOH): 9.04 (s, 1H), 8.65 (d, *J* = 6.6 Hz, 1H), 8.17 (dd, *J* = 0.6, 7.2 Hz, 1H), 3.86 (t, *J* = 5.4 Hz, 4H), 3.32 (t, *J* = 5.4 Hz, 4H).

Compounds (**24**) and (**25**) were prepared using methods analogous to those used to prepare (**1**).

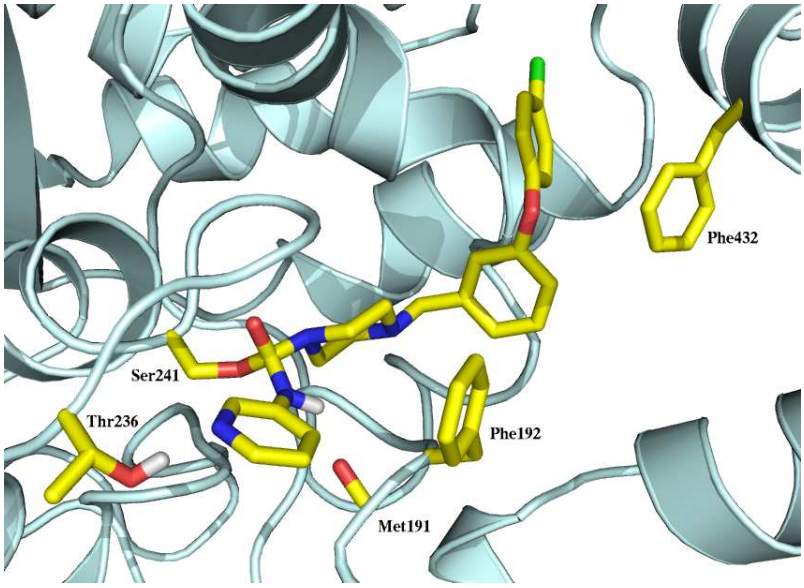


(**24**, **JNJ-40355003**) Yield: 82%; MS (ESI^+): calcd for $C_{23}H_{23}ClN_4O_2$ m/z 422.15, found 423.3 $(M+H)^+$. ^{1}H NMR (d_6-DMSO): 11.56 (br s, 1H), 10.29 (s, 1H), 9.11 (d, *J* = 2.3 Hz, 1H), 8.63-8.58 (m, 1H), 8.48 (d, *J* = 5.3 Hz, 1H), 7.90 (dd, *J* = 8.6, 5.5 Hz, 1H), 7.52-7.41 (m, 4H), 7.36-7.33 (m, 1H), 7.14-7.07 (m, 3H), 4.52-4.20 (br m, 2H), 4.35 (s, 2H), 3.55-3.22 (br m, 4H), 3.15-3.92 (br m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 156.30, 155.6, 154.7, 142.6, 141.3, 140.4, 137.1, 129.9, 129.8, 127.1, 126.3, 124.3, 123.1, 120.1, 118.9, 117.4, 61.3, 52.3, 43.7.

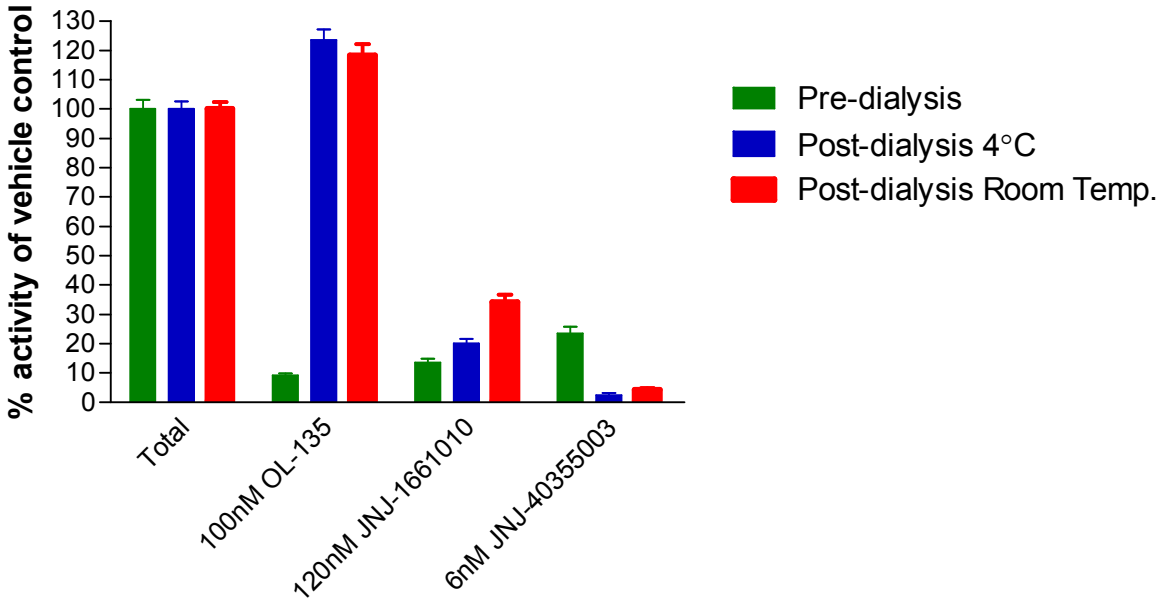


(**25**) Yield: 36%; MS (ESI^+): calcd for $C_{23}H_{22}ClN_5O_2$ m/z 423.15, found 424.2 $(M+H)^+$. ^{1}H NMR (d_4-MeOH): 8.99 (br s, 1H), 8.63 (br s, 1H), 8.11 (d, *J* = 7.2 Hz, 1H), 7.49 (apparent t, *J* = 7.8 Hz, 1H), 7.39-7.39 (m, 2H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.20 (apparent t, *J* = 1.8 Hz, 1H), 7.14-7.12 (m, 1H), 7.04-7.02 (m, 2H), 4.47-3.11 (br hump, 4 H), 4.38 (s, 2H), 3.36 (br s, 4H).

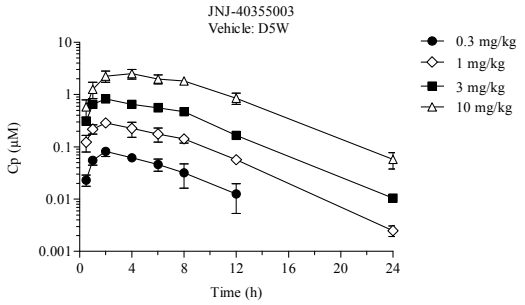
Supplemental Figure 1. JNJ-40355003 modeled in the humanized rFAAH active site



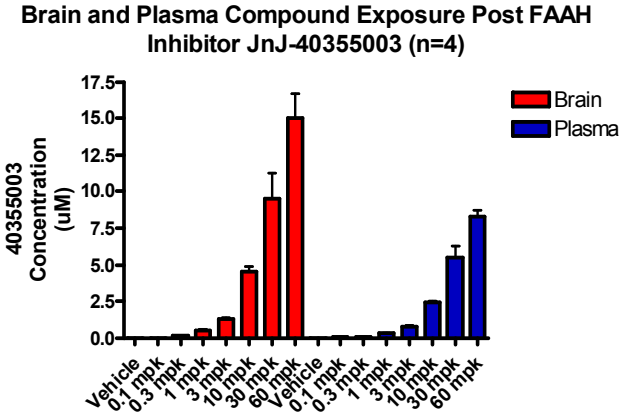
Supplemental Figure 2. Dialyzability of JNJ-40355003: Percentage FAAH activity following overnight dialysis at 4 °C or room temperature.



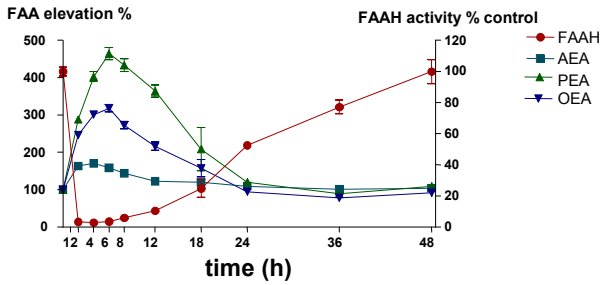
Supplementary Figure 3. JNJ-40355003 oral pk curves at 0.3, 1, 3 and 10 mg/kg (n = 4)



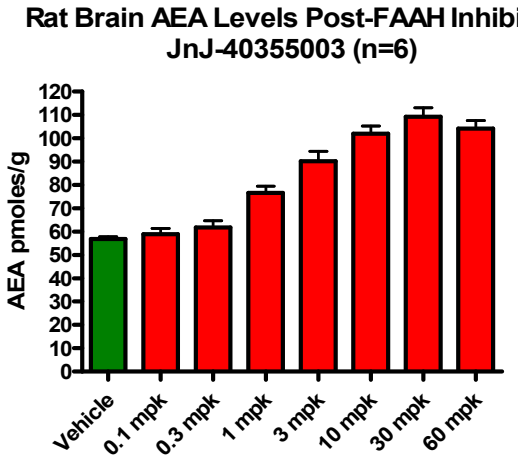
Supplementary Figure 4. $C_{t=4\ h}$ dose response with JNJ-40355003 (n = 4)

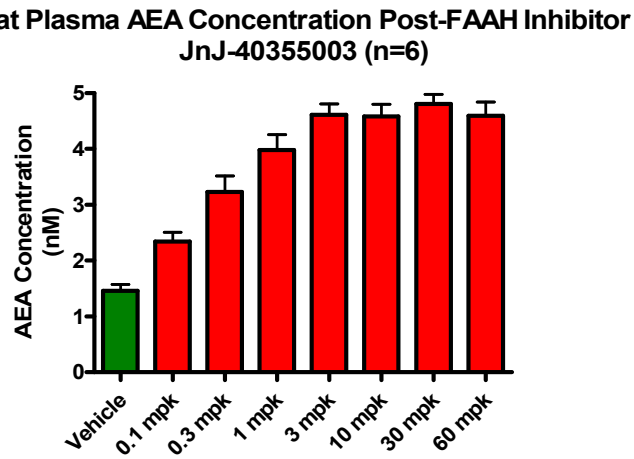


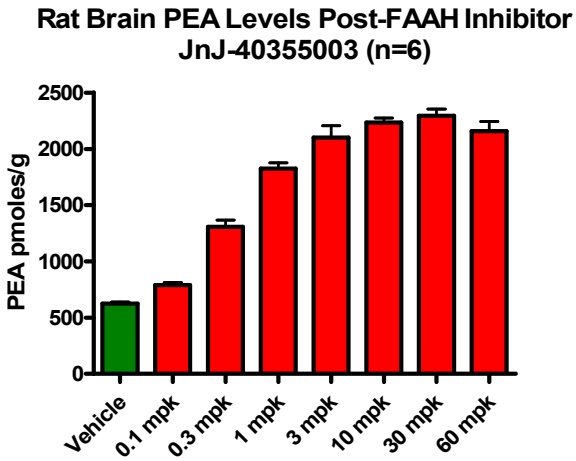
Supplementary Figure 5. FAAH inhibition and FAA levels in rat brain homogenates time course for JNJ-40355003 (3 mg/kg p.o., n = 4);

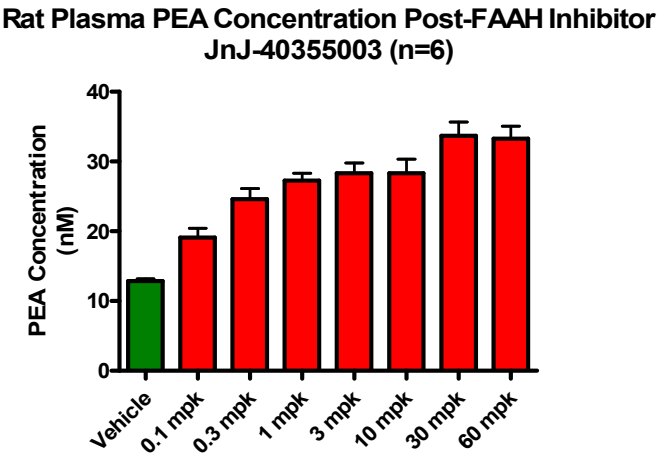


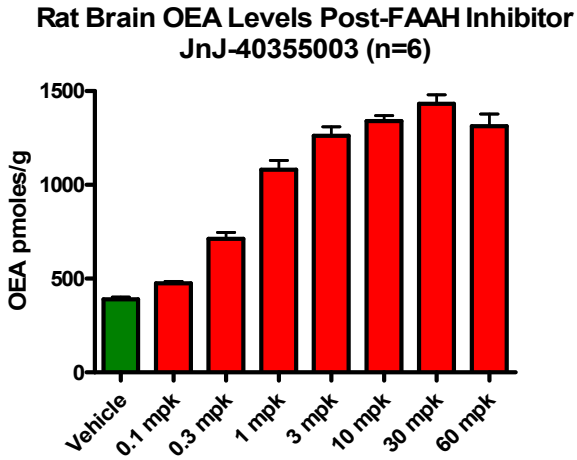
Supplementary Figure 6. Brain and plasma FAA elevation dose response in rat at t = 4 h for JNJ-40355003.

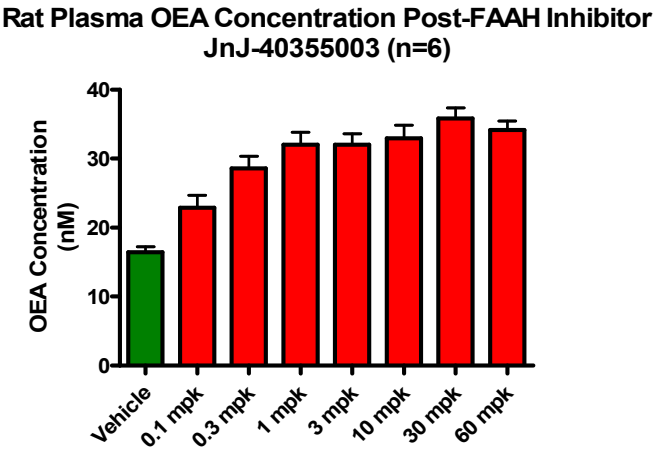




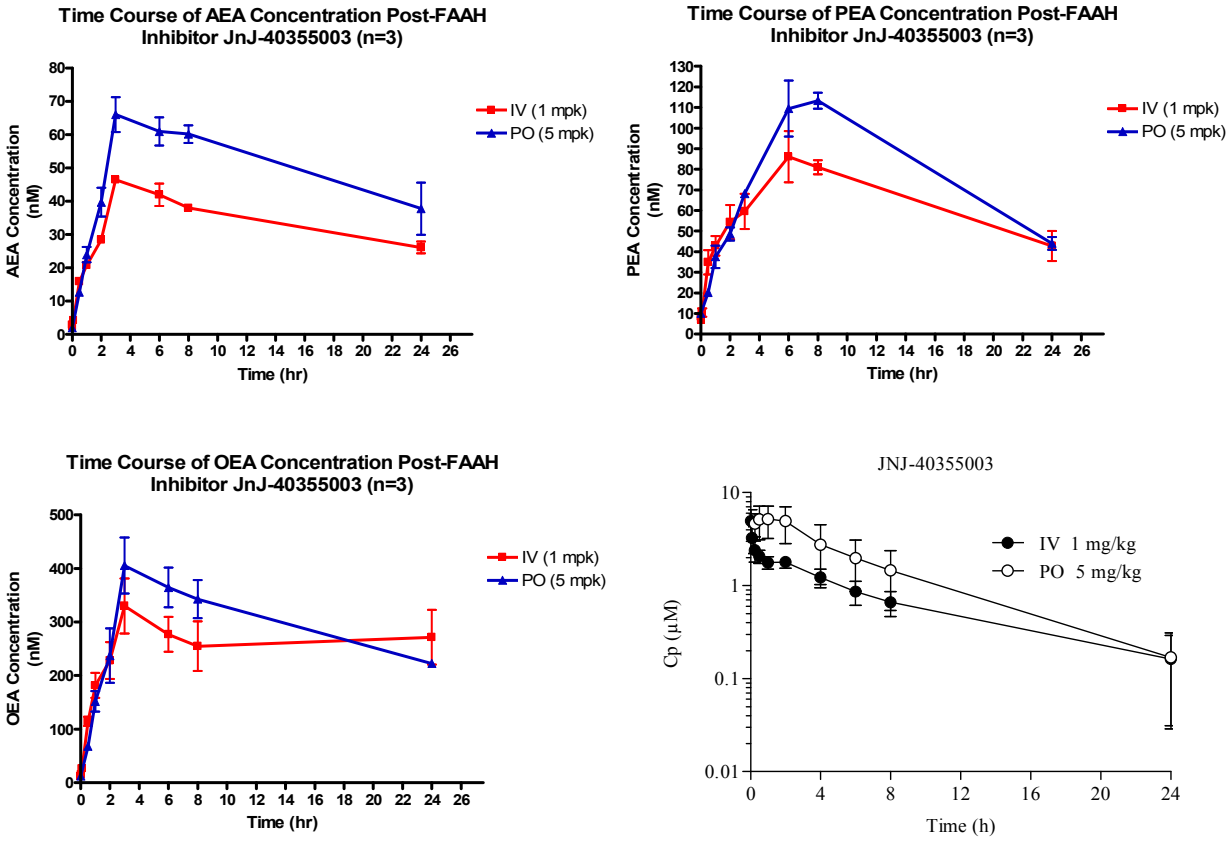








Supplementary Figure 7. Plasma FAA elevation time course and pk curves in beagle dogs (n = 3) for JNJ-40355003.



Supplementary Figure 8. Plasma FAA elevation time course and pk curves in cynomolgous monkeys (n = 3) for JNJ-40355003.