Supporting Information

Rational Design of Fatty Acid Amide Hydrolase Inhibitors that Act by Covalently Bonding to Two Active Site Residues

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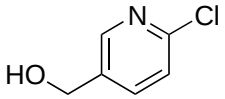
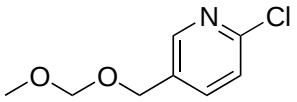
(6-Chloropyridin-3-yl)methanol (S1)



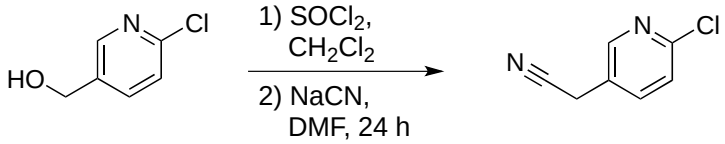
Methyl 6-chloronicotinate (1.00 g, 5.83 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. $LiAlH_4$ (220.96 mg, 5.83 mmol) was added portionwise. The mixture was allowed to slowly warm to room temperature and after 2 h the reaction was quenched with the addition of 5% HOAc in EtOH (1 mL). The solution was diluted with EtOAc, washed with 1 M HCl, saturated aqueous NaCl, and dried over Na_2SO_4. Evaporation yielded the crude alcohol that was purified by flash chromatography (SiO_2, 50% EtOAc–hexanes) to yield the alcohol (736 mg, 88%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66 (s, 1H), 8.07 (d, 1H, *J* = 7.4 Hz), 7.34 (d, 1H, *J* = 7.5 Hz), 4.61 (s, 2H), 3.65 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.6, 147.4, 137.4, 135.2, 123.7, 60.9.

2-Chloro-5-((methoxymethoxy)methyl)pyridine (S2)



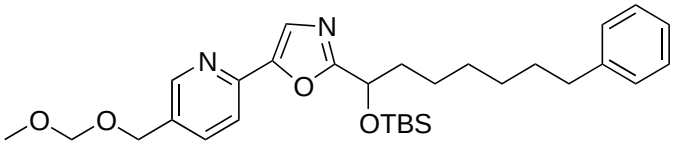
(6-Chloropyridin-3-yl)methanol (**S1**, 500 mg, 3.48 mmol) and *N*,*N*-diisopropyl ethylamine (0.75 mL, 4.18 mmol) were dissolved in anhydrous THF (10 mL) and the mixture was cooled to 0 °C. Chloromethylmethyl ether (0.3 mL, 4.18 mmol) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 6 h. The mixture was diluted with EtOAc, washed with saturated aqueous NaCl and dried over Na_2SO_4. Evaporation in vacuo yielded the crude product that was purified by flash chromatography (SiO_2, 40% EtOAc–hexanes) to yield **S2** (437 mg, 67%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.66 (s, 1H), 8.07 (d, 1H, *J* = 7.4 Hz), 7.34 (d, 1H, *J* = 7.5 Hz), 4.50 (s, 2H), 4.48 (s, 2H), 3.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.4, 149.5, 137.4, 131.2, 123.7, 97.2, 71.2, 55.6.

2-(6-Chloropyridin-3-yl)acetonitrile (S3)



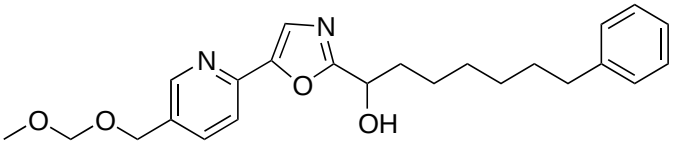
(6-Chloropyridin-3-yl)methanol (**S1**, 100 mg, 0.700 mmol) was first converted to the chloride by addition of thionyl chloride (0.2 mL, 0.840 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was allowed to stir for 2 h and the solvent was evacuated under N_2. The resulting crude chloride was redisolved in DMF (2 mL) to which sodium cyanide (103 mg, 2.10 mmol) was added. The mixture was allowed to stir under Ar for 24 h at which time the mixture was diluted with EtOAc, washed with saturated aqueous NaCl and dried over Na_2SO_4. Evaporation in vacuo yielded the crude product that was purified by flash chromatography (SiO_2, 60% EtOAc–hexanes) to yield **S3** (47 mg, 45% over 2 steps) as a light yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53 (s, 1H), 7.86 (d, 1H, *J* = 7.4 Hz), 7.21 (d, 1H, *J* = 7.5 Hz), 4.38 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.4, 149.5, 138.4, 131.2, 123.5, 117.2, 20.7.

2-(1-((*tert*-Butyldimethylsilyl)oxy)-7-phenylheptyl)-5-(5-((methoxylmethoxy)methyl)-pyridin-2-yl)oxazole (8)



5-Tributylstannyl oxazole **5** (200 mg, 0.302 mmol), $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) and 2-chloro-5-((methoxymethoxy)methyl)pyridine (**S2**, 68 mg, 0.362 mmol) were dissolved in anhydrous 1,4-dioxane (3 mL) and the mixture was warmed at reflux for 16 h under Ar. The mixture was diluted with EtOAc, washed with saturated aqueous NaCl, and dried over Na_2SO_4. Flash chromatography (SiO_2, 15% EtOAc–hexanes) afforded **8** (93 mg, 59%; typically 42–60%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.52 (s, 1H), 8.07 (d, 1H, *J* = 7.4 Hz), 7.86 (d, 1H, *J* = 7.5 Hz), 7.40–7.38 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (s, 1H), 4.93 (s, 2H), 4.50 (s, 2H), 3.98 (t, 1H, *J* = 6.5 Hz), 3.30 (s, 3H), 2.65 (t, 2H, *J* = 6.5 Hz), 1.68–1.66 (m, 4H), 1.44–1.42 (m, 6H), 1.02 (s, 9H), 0.32 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.3, 155.0, 148.4, 143.1, 137.5, 129.8, 128.6, 128.0 (2C), 125.1, 123.9, 122.5, 97.2, 78.4, 71.2, 55.6, 39.7, 35.7, 32.8, 31.8, 30.9, 29.2 (2C), 25.4 (4C), -5.2, -5.3; HRMS-ESI-TOF *m/z* 524.7670 ($[M+H]^+$, $C_{30}H_{44}N_2O_4Si$ requires 524.7669).

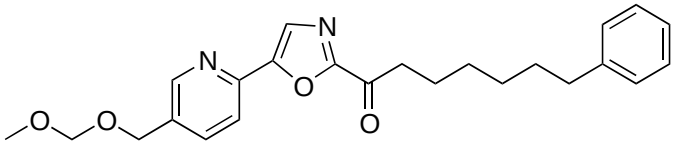
1-(5-(5-((Methoxymethoxy)methyl)pyridin-2-yl)-7-phenylheptan-1-ol (9)



2-(1-((*tert*-Butyldimethylsilyl)oxy)-7-phenylheptyl)-5-(5-((methoxylmethoxy)methyl)pyrinedin-2-yl)oxazole (**8**, 90 mg, 0.172 mmol) was dissolved in THF (1.5 mL), treated with Bu_4NF (1 M in THF, 0.2 mL, 0.206 mmol) and the solution was stirred at room temperature for 2 h under Ar. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 60% EtOAc–hexanes) yielded **9** (61 mg, 87%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.52 (s, 1H), 8.07 (d, 1H, *J* = 7.4

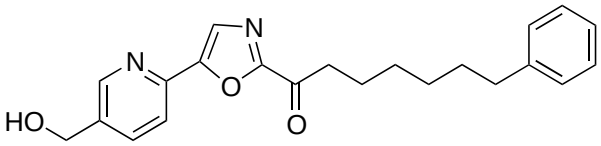
Hz), 7.86 (d, 1H, *J* = 7.5 Hz), 7.40–7.38 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (s, 1H), 4.93 (s, 2H), 4.50 (s, 2H), 3.98 (t, 1H, *J* = 6.5 Hz), 3.30 (s, 3H), 2.65 (t, 2H, *J* = 6.5 Hz), 1.68–1.66 (m, 4H), 1.44–1.42 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 160.3, 155.0, 150.0, 148.4, 143.1, 137.5, 129.8, 128.6 (2C), 128.0 (2C), 125.1, 123.9, 122.5, 97.2, 75.4, 71.2, 55.6, 38.7, 35.7, 32.8, 31.2, 29.8 (2C); HRMS-ESI-TOF *m/z* 410.5058 ($[M+H]^+$, $C_{24}H_{30}N_2O_4$ requires 410.5060).

1-(5-(5-((Methoxymethoxy)methyl)pyridin-2-yl)-7-phenylheptan-1-one (10)



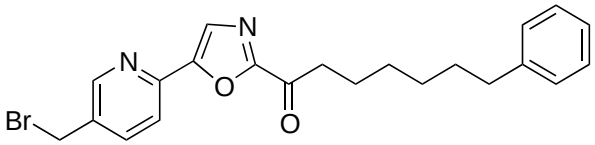
1-(5-(5-((Methoxymethoxy)methyl)pyridin-2-yl)-7-phenylheptan-1-ol (**9**, 50 mg, 0.123 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and Dess–Martin periodinane (62 mg, 0.146 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction mixture was reduced by half volume and adsorbed directly onto SiO_2. Flash chromatography (SiO_2, 20% EtOAc–hexanes) yielded **10** (44 mg, 88%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.52 (s, 1H), 8.07 (d, 1H, *J* = 7.4 Hz), 7.86 (d, 1H, *J* = 7.5 Hz), 7.40–7.38 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (s, 1H), 4.93 (s, 2H), 4.50 (s, 2H), 3.30 (s, 3H), 2.81 (t, 2H, *J* = 6.3 Hz), 2.65 (t, 2H, *J* = 6.5 Hz), 1.68–1.66 (m, 4H), 1.44–1.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 197.5, 160.3, 155.0, 150.0, 148.4, 143.1, 137.5, 129.8, 128.6 (2C), 128.0 (2C), 125.1, 123.9, 122.5, 97.2, 71.2, 55.6, 38.7, 35.7, 32.8, 31.2, 29.8 (2C); HRMS-ESI-TOF *m/z* 408.4902 ($[M+H]^+$, $C_{24}H_{28}N_2O_4$ requires 408.4901).

1-(5-(5-(Hydroxymethyl)pyridin-2-yl)oxazol-2-yl)-7-phenylheptan-1-one (11)



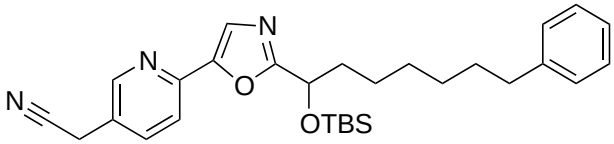
1-(5-(5-((Methoxymethoxy)methyl)pyridin-2-yl)-7-phenylheptan-1-one (**10**, 40 mg, 0.098 mmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C. A solution of 4 N HCl in 1,4-dioxane (0.2 mL, 0.12 mmol) was added. The mixture was stirred at room temperature for 2 h before the solvent was removed under N_2 to afford the crude alcohol which was then diluted with EtOAc, washed with saturated aqueous NaCl and dried over Na_2SO_4. This solvent was removed under reduced pressure and the mixture was subsequently purified by flash chromatography (SiO_2, 75% EtOAc–hexanes) to yield **11** (20 mg, 56%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.52 (s, 1H), 8.07 (d, 1H, *J* = 7.4 Hz), 7.86 (d, 1H, *J* = 7.5 Hz), 7.40–7.38 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (s, 1H), 4.61 (s, 2H), 2.81 (t, 2H, *J* = 6.3 Hz), 2.65 (t, 2H, *J* = 6.5 Hz), 1.68–1.66 (m, 4H), 1.44–1.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 197.5, 160.3, 155.0, 150.0, 148.4, 143.1, 137.5, 129.8, 128.6 (2C), 128.0 (2C), 125.1, 123.9, 122.5, 64.7, 38.7, 35.7, 32.8, 31.2, 29.8 (2C); HRMS-ESI-TOF *m/z* 364.4377 ($[M+H]^+$, $C_{22}H_{24}N_2O_3$ requires 364.4376).

1-(5-(5-(Bromomethyl)pyridin-2-yl)-7-phenylheptan-1-one (3)



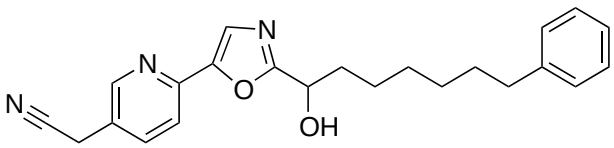
1-(5-(5-(Hydroxymethyl)pyridin-2-yl)oxazol-2-yl)-7-phenylheptan-1-one (**11**, 20 mg, 0.055 mmol) and CBr_4 (20 mg, 0.06 mmol) were dissolved in CH_2Cl_2 (1 mL). The mixture was cooled to 0 °C and triphenylphosphine (16 mg, 0.06 mmol) was added in small portions. The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was diluted with EtOAc, washed with saturated aqueous NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure and flash chromatography (SiO_2, 30% EtOAc–hexanes) yielded **3** (10 mg, 45%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.39 (s, 1H), 7.94 (d, 1H, *J* = 7.4 Hz), 7.62 (d, 1H, *J* = 7.5 Hz), 7.40–7.38 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (s, 1H), 4.56 (s, 2H), 2.81 (t, 2H, *J* = 6.3 Hz), 2.65 (t, 2H, *J* = 6.5 Hz), 1.68–1.66 (m, 4H), 1.44–1.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 198.4, 160.3, 155.0, 150.0, 148.4, 143.1, 137.5, 129.8, 128.6 (2C), 128.0 (2C), 125.1, 123.9, 122.5, 38.7, 35.7, 33.3, 32.8, 31.2, 29.8 (2C); HRMS-ESI-TOF *m/z* 427.3346 ($[M+H]^+$, $C_{22}H_{23}BrN_2O_2$ requires 427.3342).

2-(6-(2-(1-((*tert*-Butyldimethylsilyl)oxy)-7-phenylheptyl)oxazol-5-yl)pyridin-3-yl)acetonitrile (6)



5-Tributylstannyl oxazole **5** (100 mg, 0.150 mmol), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol), and 2-(6-chloropyridin-3-yl)acetonitrile (**S3**, 27 mg, 0.180 mmol) were dissolved in anhydrous 1,4-dioxane (2 mL) and the mixture was warmed at reflux for 16 h under Ar. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 30% EtOAc–hexanes) yielded **6** (50 mg, 67%) as a tan oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.39 (s, 1H), 7.94 (d, 1H, *J* = 7.4 Hz), 7.62 (d, 1H, *J* = 7.5 Hz), 7.40–7.38 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (s, 1H), 4.50 (t, 1H, *J* = 6.3 Hz), 4.33 (s, 2H), 2.65 (t, 2H, *J* = 6.5 Hz), 1.68–1.66 (m, 4H), 1.44–1.42 (m, 6H), 0.98 (s, 9H), 0.24 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.3, 155.0, 150.0, 148.4, 143.1, 137.5, 129.8, 128.6 (2C), 128.0 (2C), 125.1, 123.9, 122.5, 75.3, 38.7, 35.7, 32.8, 31.2, 30.9, 29.8 (2C), 25.9 (3C), 20.9, -5.2, -5.3, -5.4; HRMS-ESI-TOF *m/z* 489.7238 ($[M+H]^+$, $C_{29}H_{39}N_3O_2Si$ requires 489.7244).

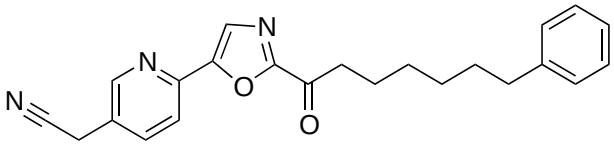
2-(6-(2-(1-Hydroxy-7-phenylheptyl)oxazol-5-yl)pyridin-3-yl)acetonitrile (7)



2-(6-(2-(1-((*tert*-Butyldimethylsilyl)oxy)-7-phenylheptyl)oxazol-5-yl)pyridin-3-yl)acetonitrile (**6**, 60 mg, 0.122 mmol) was dissolved in THF (1.2 mL), treated with Bu_4NF (1 M in THF, 0.15 mL, 0.15 mmol) and the solution was stirred at room temperature for 2 h under Ar. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4 and the solvent was removed under

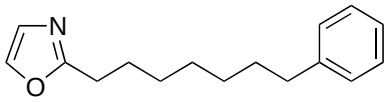
reduced pressure. Flash chromatography (SiO_2, 60% EtOAc–hexanes) yielded **7** (41 mg, 90%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.39 (s, 1H), 7.94 (d, 1H, *J* = 7.4 Hz), 7.62 (d, 1H, *J* = 7.5 Hz), 7.40–7.38 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (s, 1H), 4.50 (t, 1H, *J* = 6.3 Hz), 4.33 (s, 2H), 2.65 (t, 2H, *J* = 6.5 Hz), 1.68–1.66 (m, 4H), 1.44–1.42 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.3, 155.0, 150.0, 148.4, 143.1, 137.5, 129.8, 128.6 (2C), 128.0 (2C), 125.1, 123.9, 122.5, 75.3, 38.7, 35.7, 32.8, 31.2, 29.8 (2C), 20.9; HRMS-ESI-TOF *m/z* 375.4632 ($[M + H]^+$, $C_{23}H_{25}N_3O_5$ requires 375.4635).

2-(6-(2-(7-Phenylheptanol)oxazol-5-yl)pyridin-3-yl)acetonitrile (4)



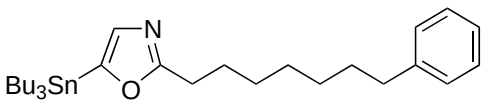
2-(6-(2-(1-Hydroxy-7-phenylheptyl)oxazol-5-yl)pyridin-3-yl)acetonitrile (**7**, 30 mg, 0.080 mmol) was dissolved in CH_2Cl_2 (1 mL) and Dess–Martin periodinane (40 mg, 0.096 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction mixture was reduced to half volume and directly loaded onto silica gel and purified by flash chromatography (SiO_2, 30% EtOAc–hexanes) to yield **4** (17 mg, 85%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.39 (s, 1H), 7.94 (d, 1H, *J* = 7.4 Hz), 7.62 (d, 1H, *J* = 7.5 Hz), 7.40–7.38 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (s, 1H), 4.33 (s, 2H), 2.81 (t, 2H, *J* = 6.3 Hz), 2.65 (t, 2H, *J* = 6.5 Hz), 1.68–1.66 (m, 4H), 1.44–1.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 197.4, 167.3, 155.0, 150.0, 148.4, 143.1, 137.5, 129.8, 128.6 (2C), 128.0 (2C), 125.1, 123.9, 122.5, 38.7, 35.7, 32.8, 31.2, 29.8 (2C), 20.9; HRMS-ESI-TOF *m/z* 373.4472 ($[M+H]^+$, $C_{23}H_{25}N_3O_2$ requires 373.4476).

2-(7-Phenylheptyl)oxazole (S5)



A solution of oxazole (50 mg, 0.725 mmol) in THF (2 mL) was treated with BH_3•THF (1 M in THF, 800 μL, 0.797 mmol). The reaction mixture was stirred at room temperature for 1 h before it was treated with *n*-BuLi (2.5 M, 320 μL, 0.797 mmol) at -78 °C for 40 min, followed by a solution of $Ph(CH_2)_7OTf$ (330 mg, 1.087 mmol) in THF (1 mL). The reaction mixture was stirred at 0 °C for 2 h, then room temperature overnight before it was quenched with H_2O and extracted with EtOAc. The organic layer was evaporated under reduced pressure and flash chromatography yielded **S5** (80 mg, 46%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (s, 1H), 7.36–7.33 (m, 2H), 7.26–7.23 (m, 3H), 7.09 (s, 1H), 3.00 (t, 2H, *J* = 7.5 Hz), 2.69 (t, 2H, *J* = 7.5 Hz), 1.75–1.69 (m, 4H), 1.51–1.47 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.7, 142.6, 139.7, 137.6, 128.5 (2C), 128.1 (2C), 127.0, 125.9, 35.7, 32.4, 31.2, 29.6, 29.4 (2C), 28.1; HRMS-ESI-TOF *m/z* 243.3345 ($[M+H]^+$, $C_{16}H_{21}NO$ requires 243.3340).

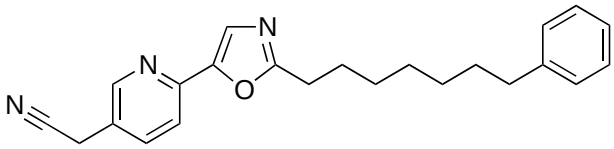
2-(7-Phenylheptyl)-5-(tributylstannyl)oxazole (S6)



2-(7-Phenylheptyl)oxazole (**S5**, 50 mg, 0.206 mmol) was dissolved in freshly distilled anhydrous THF (2 mL) and cooled to -78 °C before the solution was treated with 2.37 M *n*-BuLi (97 μL, 0.227 mmol)

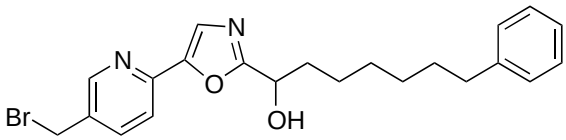
dropwise. The reaction mixture was stirred for 40 min at -78 C, treated with $SnBu_3Cl$ (0.15 mL, 0.06 mmol) and stirred for 5 min. The solution was warmed to room temperature and diluted with EtOAc, washed with saturated aqueous NaCl, and dried over Na_2SO_4. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 10% EtOAc–hexanes) yielded **S6** (77 mg, 70%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (s, 1H), 7.36–7.33 (m, 2H), 7.26–7.23 (m, 3H), 7.09 (s, 1H), 3.00 (t, 2H, *J* = 7.5 Hz), 2.69 (t, 2H, *J* = 7.5 Hz), 1.75–1.69 (m, 4H), 1.51–1.47 (m, 6H), 0.99 (s, 16H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.7, 142.6, 139.7, 137.6, 128.5 (2C), 128.1 (2C), 127.0, 125.9, 35.7, 32.4, 31.2, 29.6, 29.4 (2C), 27.2 (6C), 28.1, 15.6 (3C), 13.8 (3C); HRMS-ESI-TOF *m/z* 532.3882 ($[M+H]^+$, $C_{28}H_{47}NOSn$ requires 532.3889).

2-(6-(2-(7-Phenylheptyl)oxazol-5-yl)pyridin-3-yl)acetonitrile (13)



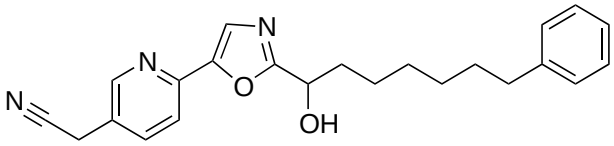
2-(7-Phenylheptyl)-5-(tributylstannyl)oxazole (**S6**, 30 mg, 0.056 mmol), $Pd(PPh_3)_4$ (7 mg, 0.005 mmol), and 2-(6-chloropyridin-3-yl)acetonitrile (**S3**, 11 mg, 0.067 mmol) were dissolved in anhydrous 1,4-dioxane (1.5 mL) and the mixture was warmed at reflux for 16 h under Ar. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 30% EtOAc–hexanes) yielded **13** (10 mg, 54%) as a tan solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.39 (s, 1H), 7.94 (d, 1H, *J* = 7.4 Hz), 7.63 (d, 1H, *J* = 7.5 Hz), 7.36–7.33 (m, 2H), 7.26–7.23 (m, 3H), 2.62 (t, 2H, *J* = 7.3 Hz), 2.55 (t, 2H, *J* = 7.5 Hz), 1.75–1.69 (m, 4H), 1.51–1.47 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.1, 156.8, 152.7, 149.0, 145.1, 142.2, 136.0, 133.8, 127.9, 127.8, 126.4, 125.2, 119.6, 65.9, 55.9, 38.6, 35.4, 32.7, 30.9, 28.6, 23.5; HRMS-ESI-TOF *m/z* 359.4640 ($[M+H]^+$, $C_{23}H_{25}N_3O$ requires 359.4641).

1-(5-(5-(Bromomethyl)pyridin-2-yl)oxazol-2-yl)-7-phenylheptan-1-ol (12)



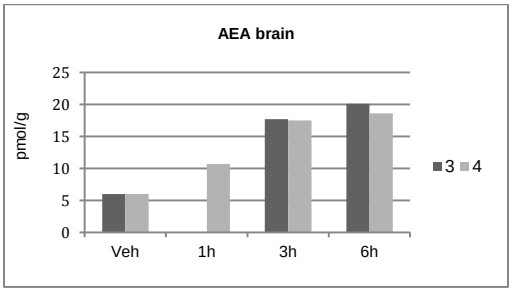
A sample of **3** (12 mg, 0.028 mmol) was dissolved in a 2:1 mixture of MeOH–THF (0.6 mL) and cooled to 0 °C. $NaBH_4$ (1.2 mg, 0.031mmol) was added to the cooled solution and the mixture was allowed to slowly warm to room temperature. After 1 h, the reaction was quenched with the addition of 5% AcOH in EtOH (1 mL) and the mixture was stirred for 30 min. The solution was diluted with EtOAc, washed with water and saturated aqueous NaCl, and dried over Na_2SO_4. Evaporation yielded the crude alcohol that was purified by preparative thin layer chromatography (SiO_2, 60% EtOAc–hexanes) to afford **12** (8.2 mg, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.39 (s, 1H), 7.94 (d, 1H, *J* = 7.4 Hz), 7.62 (d, 1H, *J* = 7.5 Hz), 7.40–7.38 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (s, 1H), 4.56 (s, 2H), 4.46 (t, 1H, *J* = 6.3 Hz), 2.65 (t, 2H, *J* = 6.5 Hz), 1.68–1.66 (m, 4H), 1.44–1.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 160.3, 155.0, 150.0, 148.4, 143.1, 137.5, 129.8, 128.6 (2C), 128.0 (2C), 125.1, 123.9, 122.5, 75.6, 38.7, 35.7, 33.3, 32.8, 31.2, 29.8 (2C); HRMS-ESI-TOF *m/z* 429.3507 ($[M+H]^+$, $C_{22}H_{25}BrN_2O_2$ requires 429.3501).

2-(6-(2-(1-Hydroxy-7-phenylheptyl)oxazol-5-yl)pyridin-3-yl)acetonitrile (7)



A sample of **4** (18 mg, 0.048 mmol) was dissolved in a 2:1 mixture of MeOH–THF (0.8 mL) and cooled to 0 °C. $NaBH_4$ (2 mg, 0.053 mmol) was added to the cooled solution and the mixture was allowed to slowly warm to room temperature. After 1 h, the reaction was quenched with the addition of 5% AcOH in EtOH (1 mL) and the mixture was stirred for 30 min. The solution was diluted with EtOAc, washed with water and saturated aqueous NaCl, and dried over Na_2SO_4. Evaporation yielded the crude alcohol that was purified by preparative thin layer chromatography (60% EtOAc–hexanes) to afford **7** (15 mg, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.39 (s, 1H), 7.94 (d, 1H, *J* = 7.4 Hz), 7.62 (d, 1H, *J* = 7.5 Hz), 7.40–7.38 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (s, 1H), 4.50 (t, 1H, *J* = 6.3 Hz), 4.33 (s, 2H), 2.65 (t, 2H, *J* = 6.5 Hz), 1.68–1.66 (m, 4H), 1.44–1.42 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.3, 155.0, 150.0, 148.4, 143.1, 137.5, 129.8, 128.6 (2C), 128.0 (2C), 125.1, 123.9, 122.5, 75.3, 38.7, 35.7, 32.8, 31.2, 29.8 (2C), 20.9; HRMS-ESI-TOF *m/z* 375.4633 ($[M + H]^+$, $C_{23}H_{25}N_3O_5$ requires 375.4635).

PD Studies of 3 and comparison with 4



AEA brain, pmol/g (fold increase)

	3	**4**
1 h	n.d.	10.7 (1.8)
3 h	17.7 (3.0)	17.5 (2.9)
6 h	20.1 (3.4)	18.6 (3.1)
Vehicle	6.0	6.0

Figure S1. Brain AEA levels 1-6 h post administration of **3**, i.p. at 30 mg/kg, and comparison with the effects of **4** reported in Figure 9.

ABPP screen of 3 and 4

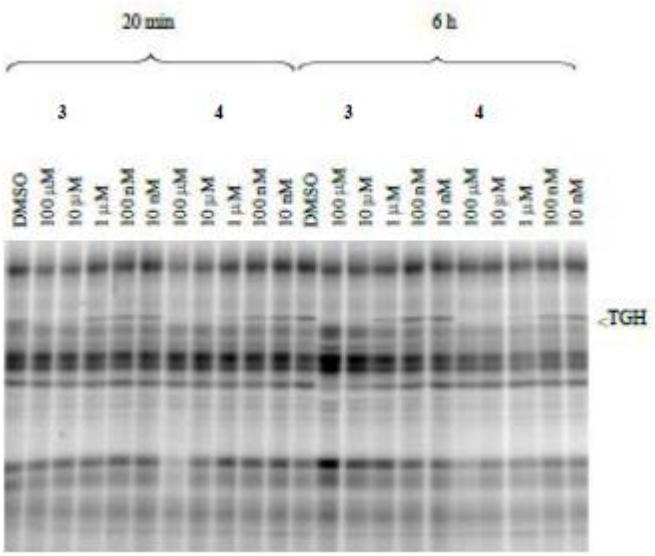
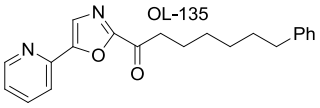


Figure S2. ABPP screen of **3** and **4** in mouse heart membrane proteome (1 mg/mL) with FP-rhodamine (100 nM). Inhibitor preincubation with the proteome was conducted at both 20 min and 6 h.



PK is linear (iv, 3 h post injection Cp)

Dose	Cp	Cp ratio	Dose ratio
2 mg/kg	0.016 µM		
6 mg/kg	0.063 µM	3.5	3
20 mg/kg	0.149 µM	11.3	10
30 mg/kg	0.254 µM	15.6	15
100 mg/kg	0.928 µM	56.8	50

Rat	Cl	Vz	Vss	$T_{1/2}$	Cmax	Cmax	AUCINF	AUClast	Tmax	%F
IV (2 mg/kg) (n = 3)	8.5 L/h/kg	34.9 L/kg	10.1 L/kg	2.8 h	5.4 µM	1808 µg/L	235 h*µg/L	219 h*µg/L		
IV (20 mg/kg) (n = 2)	7.2 L/h/kg	37.7 L/kg	9.5 L/kg	3.6 h	66.3 µM	22158 µg/L	2784 h*µg/L	2714 h*µg/L		
oral (10 mg/kg) (n = 3)					0.16 µM	53 µg/L	216 h*µg/L	127 h*µg/L	0.5 h	18%

from IV @20 mg/kg: plasma:brain conc equal (0.5-6 h).

Figure S3. PK data on compound **2**.