SUPPORTING INFORMATION

Structurally Designed *Trans*-2-phenylcyclopropylamine Derivatives Potently Inhibit Histone Demethylase LSD1/KDM1

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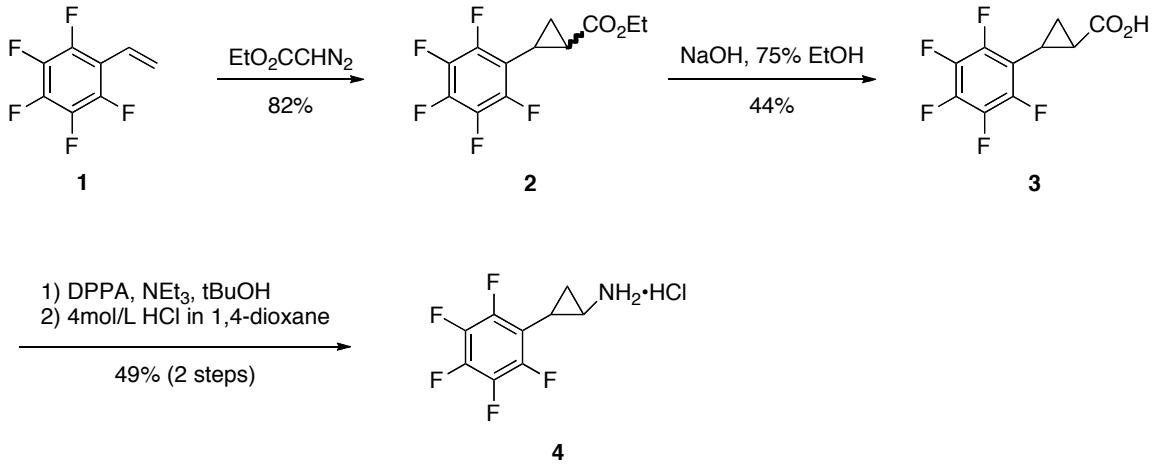
Experimental procedures

General procedure for the synthesis of 2-PFPA

All reagents and solvents were of the highest commercial quality and were used without purification. Thin layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F254, 0.25mm). ^{1}H-NMR spectra were recorded on a JEOL GSX-400 spectrometer at 400 MHz. ^{13}C-NMR spectra were recorded on either a JEOL JNM-LA 500 or a Bruker AVANCE 600 spectrometer at 125 or 150 MHz, respectively. Chemical shifts are expressed as parts per million (ppm), using solvent as an internal standard. Data are reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz). Infrared (IR) spectra were recorded on a JASCO FT/IR-680 Fourier-transform infrared spectrophotometer. Fast atom bombardment mass spectra (FAB-MS) and EI mass spectra, as well as high-resolution mass spectral (HRMS) data, were measured with a JEOL JMS-SX102A mass spectrometer. Column chromatography was performed on BW-200 or BW-300 resin (Fuji Silysia Chemical, Ltd.).

Synthetic scheme of *trans*-2-pentafluorophenylcyclopropylamine hydrochloride (2-PFPA)



Synthesis of ethyl 2-pentafluorophenylcyclopropanecarboxylate 2

The title compound was synthesized according to the reported procedure[1] with a slight modification. 2,3,4,5,6-Pentafluorostyrene **1** (5.0 g, 25.8 mmol) was added dropwise over 30 min to a stirred solution of freshly prepared ethyl diazoacetate (3.53 g, 30.7 mmol). The mixture was gradually warmed to 80˚C and stirred for 24 hours. The mixture was then cooled to room temperature and stirred for 22 hours. The crude product was purified by silica gel column chromatography eluted with EtOAc/n-hexane (1:20, v/v) to give colorless oil (5.93 g, Y. 82%), which was a mixture of stereoisomers. The analytical data obtained were identical to the reported values.[1] ^{1}H NMR (400 MHz, CDC1$_3$): δ (ppm) 4.21 (q, *J* = 7.2 Hz, 2H), 2.48-2.43 (m, 1H), 2.19-2.14 (m, 1H), 1.65-1.58 (m, 1H), 1.55-1.49 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); IR (neat) 2987, 1731, 1523, 1503, 1188, 997 cm^{-1}; HRMS-EI *m/z*: calcd for $C_{12}H_9F_5O_2$: 280.0523, found: 280.0531[M]$^+$.

Synthesis of *trans*-2-pentafluorophenylcyclopropanecarboxylic acid 3

The title compound was synthesized using the protocol for *trans*-2-phenylcyclopropanecarboxylic acid.[2,3] To the solution of 114 mg of NaOH (2.86 mmol) dissolved in 75% aqueous EtOH (5 mL) was added 1.00 g of the *cis-trans*-ester mixture **2** (3.57 mmol). The solution was refluxed for 7 h, and then cooled and diluted with H_2O (20 mL), and the unreacted ester was

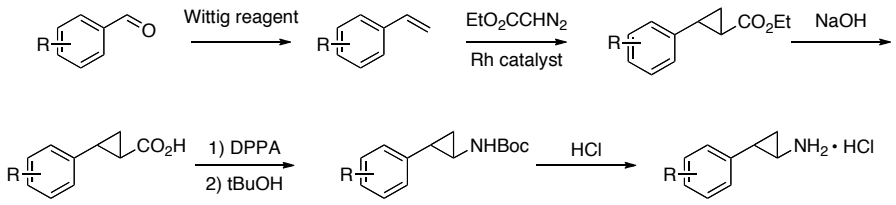
extracted with ether (20 mL x 2). The aqueous phase was acidified with conc. HCl to pH = 1, and a colorless solid appeared. The solid was collected and recrystallized to give the pure *trans*-acid as colorless plates (397 mg, Y. 44%). Mp 135-136 ˚C (lit: 133-134 ˚C)[1]; ^{1}H-NMR (400 MHz, $CDC1_3$): δ (ppm) 2.55-2.50 (m, 1H), 2.19-2.15 (m, 1H), 1.72-1.69 (m, 1H), 1.64-1.59 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 178.8, 146.0 (m), 140.2 (m), 137.6 (m), 112.7 (m), 20.8, 15.8, 15.3; IR (KBr) 3464, 1690, 1498, 996 cm^{-1}; HRMS-EI *m/z*: calcd for $C_{10}H_5F_5O_2$: 252.0210, found: 252.0213 $[M]^+$.

Synthesis of *trans*-2-pentafluorophenylcyclopropylamine hydrochloride 4 (2-PFPA)

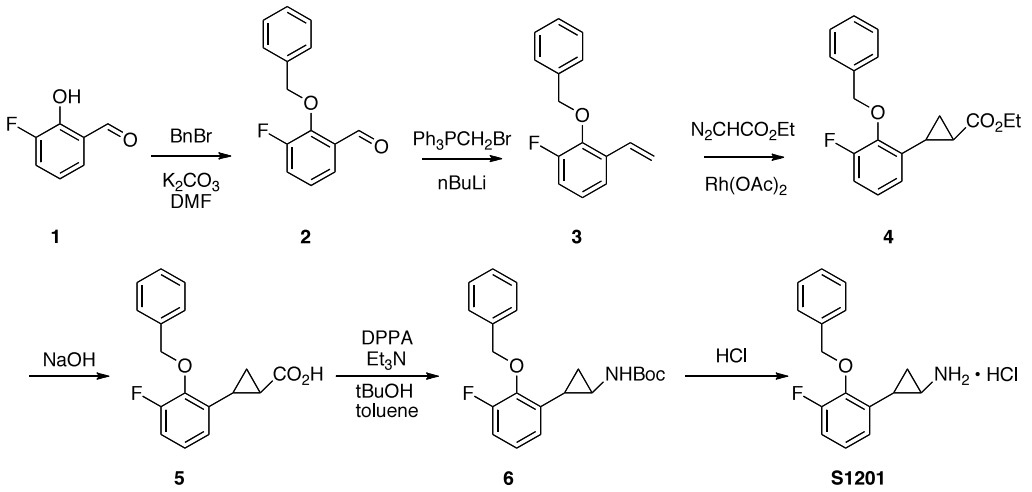
Trans-2-pentafluorophenylcyclopropanecarboxylic acid **3** (797 mg, 3.16 mmol), anhydrous NEt_3 (480 mg, 4.74 mmol), and diphenylphosphoryl azide (DPPA) (1.04 g, 3.79 mmol) were dissolved in anhydrous *t*BuOH (40 mL). To the reaction mixture, the activated molecular sieve 4A (500 mg) was added, and the mixture was refluxed for 56 h under Ar. The molecular sieve 4A was removed by filtration, and the resulting mixture was concentrated *in vacuo*. The residue was diluted with EtOAc (80 mL) and washed with 5% citric acid (80 mL), H_2O (80 mL), saturated $NaHCO_3$ (80 mL), and brine (80 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography eluted with EtOAc/n-hexane (1:9, v/v). The carbamate was obtained as a white solid. To the carbamate, 4 mol/L HCl in 1,4-dioxane (6.7 mL) was added, and the solution was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to produce a white solid. Recrystallization from MeOH/Et_2O yielded colorless needles (399 mg, Y. 49%). Mp 198-201˚C (decomp.); ^{1}H-NMR (400 MHz, CD_3OD): δ (ppm) 3.16-3.12 (m, 1H), 2.37-2.32 (m, 1H), 1.58-1.54 (m, 1H), 1.51-1.46 (m, 1H); ^{13}C-NMR (125 MHz, CD_3OD): δ (ppm) 147.6 (m), 141.7 (m), 138.9 (m), 113.2 (m), 30.0, 12.3, 11.9; IR (KBr) 2997, 2887, 1527, 1500, 1005 cm^{-1}; HRMS-EI *m/z*: calcd for $C_9H_6F_5N_1$: 223.0420, found: 223.0419 $[M]^+$; anal. calcd for $C_9H_7Cl_1F_5N_1$: C, 41.64; H, 2.72; N, 5.40, found: C, 41.58; H, 2.94; N, 5.43.

General procedure for the synthesis of other 2-PCPA derivatives

Other 2-PCPA derivatives were obtained by custom synthesis by ChemGenesis Inc. (Tokyo, Japan). These compounds were synthesized according to the following general scheme.



Synthesis of *trans*-2-(2-benzyloxy-3-fluorophenyl)cyclopropanamine hydrochloride (S1201)



Benzyl bromide (1.43 mL, 12.0 mmol) and K_2CO_3 (1.66 g, 12.0 mmol) were added to a solution of 3-fluorosalicyl aldehyde (**1**) (1.12 g, 8.0 mmol) in DMF (20 mL). After the mixture was stirred for 20 hours at room temperature, H_2O (30 mL) and AcOEt (60 mL) were added to the mixture. The separated aqueous phase was extracted with AcOEt (2 x 30 mL). The combined organic phases were washed with H_2O (3 x 30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 30 g) with hexane-AcOEt (95:5 to 85:15, v/v) as the eluant to afford **2** (1.82 g, 99%) as colorless oil.

Under Ar, *n*-BuLi (in hexane, 7.3 mL, 12.0 mmol) was added dropwise to a cold solution of methyltriphenylphosphonium bromide (4.5 g, 12.6 mmol) in dry THF (59 mL) at 0˚C over 10 min. After the mixture was stirred for 10 min at the same temperature, the solution of **2** (1.8 g, 7.8 mmol) in dry THF (14 mL) was added to the mixture at 0˚C. After stirring for 3 hours at the same temperature, the reaction mixture was quenched with H_2O (50 mL). The mixture was extracted with AcOEt (3 x 100 mL). The combined extracts were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 100g) with hexane-AcOEt (98:2, v/v) as an eluant to afford **3** (648 mg, 36%) as colorless oil.

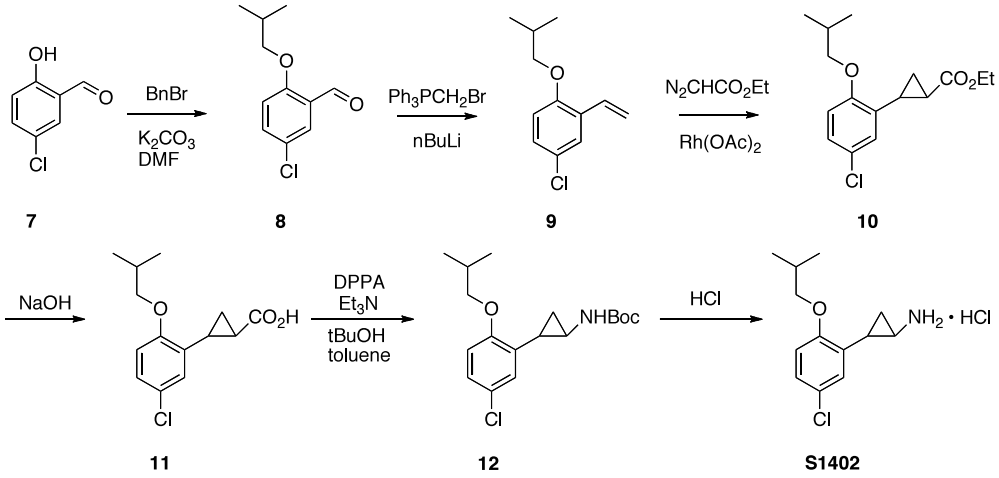
Under Ar, a solution of ethyl diazoacetate (1.34 g, 11.7 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise to a solution of **3** (900 mg, 3.9 mmol) and rhodium(II) acetate dimer (34 mg, 0.08 mmol) in dry CH_2Cl_2 (20 mL) over 3 hours while observing N_2 evolution. The mixture was stirred for 12 additional hours, and was concentrated. The crude product was purified by silica gel column chromatography (SiO_2 30 g) with hexane-AcOEt (99:1 to 90:10, v/v) as an eluant to afford **4** (918 mg, 75%) as a *cis*/*trans* mixture.

Then, 2 mol/L sodium hydroxide (3.0 mL) was added to the solution of **4** (910 mg, 2.9 mmol) in EtOH (10 mL). The mixture was stirred for 18 hours at room temperature, and diluted with 3 mol/L HCl (3.0 mL) and water (10 mL) at 0˚C. The mixture was extracted with AcOEt (2 x 40 mL). The combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 30g) with hexane-AcOEt (90:10, v/v) as an eluant to afford **5** (649 mg, 78%) as a *cis*/*trans* mixture.

Triethylamine (1.8 mL, 13 mmol) and diphenylphosphoryl azide (2.8 mL, 13 mmol) were added to a solution of **5** (2.5 g, 8.7 mmol) in dry toluene (50 mL) at room temperature. After the reaction mixture was refluxed for 1.5 hours, *t*-BuOH (50 mL) was added and refluxing was continued for 5 additional hours. After the reaction mixture was allowed to cool to room temperature, it was diluted with AcOEt (200 mL). The mixture was washed with 5% citric acid (40 mL), H_2O (40 mL), *sat*. $NaHCO_3$ (40 mL), H_2O (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was

purified by silica gel column chromatography (SiO_2 100g) with hexane-AcOEt (95:5 to 75:25, v/v) as an eluant to afford **6** (2.26 g) as a *cis*/*trans* mixture. The *cis*/*trans* mixture was triturated with hexane and dried *in vacuo* to give **6** (1.73 g, 56%) as the *trans* isomer. Finally, 4 N HCl/1,4-dioxane (5.0 mL) was added to the solution of **6** (500 mg, 1.4 mmol) in 1,4-dioxane (5.0 mL) and stirred for 3 hours. The mixture was concentrated. The crude product was triturated with Et_2O (5.0 mL) and dried *in vacuo* to give **S1201** (400 mg, 97%) as a colorless powder. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.71 (2H, br s), 7.54 (2H, m), 7.34-7.43 (3H, m), 7.14 (1H, m), 7.05 (1H, m), 6.74 (1H, d, *J* = 7.8 Hz), 5.14 (1H, B of ABq, *J* = 10.9 Hz), 5.01 (1H, A of ABq, *J* = 10.9 Hz), 2.88 (1H, m), 2.72 (1H, ddd, *J* = 3.8, 6.4, 10.1 Hz), 1.44 (m, 1H), 1.14 (1H, dt, *J* = 6.4, 7.5 Hz); ^{13}C-NMR (125 MHz, CD_3OD): δ (ppm) 157.0 (d, J = 245 Hz), 146.2 (d, J = 11 Hz), 138.3, 135.0, 129.7, 129.6, 129.5, 125.4, 121.8, 116.2 (d, J = 20 Hz), 76.9, 31.7, 17.4, 14.2; MS (FAB): *m*/*z* 258 $[M+H]^+$; HRMS-FAB *m*/*z*: calcd for $C_{16}H_{17}FNO$: 258.1294, found: 258.1298 $[M+H]^+$.

Synthesis of *trans*-2-(5-chloro-2-isobutoxyphenyl)cyclopropanamine hydrochloride (S1402)



1-Bromomethyl-2-propane (3.2 mL, 30 mmol) and K_2CO_3 (4.15 g, 30 mmol) were added to a solution of 5-chlorosalicylaldehyde (**7**) (3.13 g, 20 mmol) in DMF (50 mL). After the mixture was stirred for 24 hours at 60°C, H_2O (200 mL) and Et_2O (200 mL) were added to the mixture. The separated aqueous phase was extracted with Et_2O (2 x 200 mL). The combined organic phases were washed with H_2O (2 x 200 mL) and brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 100 g) with hexane-AcOEt (100:0 to 90:10, v/v) as the eluant to afford **8** (4.2 g, quant) as colorless oil.

Under Ar, *n*-BuLi (in hexane, 8.2 mL, 13.4 mmol) was added dropwise to a cold solution of methyltriphenylphosphonium bromide (4.93 g, 13.8 mmol) in dry THF (60 mL) at 0°C over 10 min. After the mixture was stirred for 10 min at the same temperature, the solution of **8** (1.96 g, 9.2 mmol) in dry THF (10 mL) was added to the mixture at 0°C. After stirring for 2 hours at the same temperature, the reaction mixture was quenched with H_2O (50 mL). The mixture was extracted with AcOEt (3 x 100 mL). The combined extracts were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 100 g) with hexane-AcOEt (99:1, v/v) as an eluant to afford **9** (2.63 g, quant) as colorless oil.

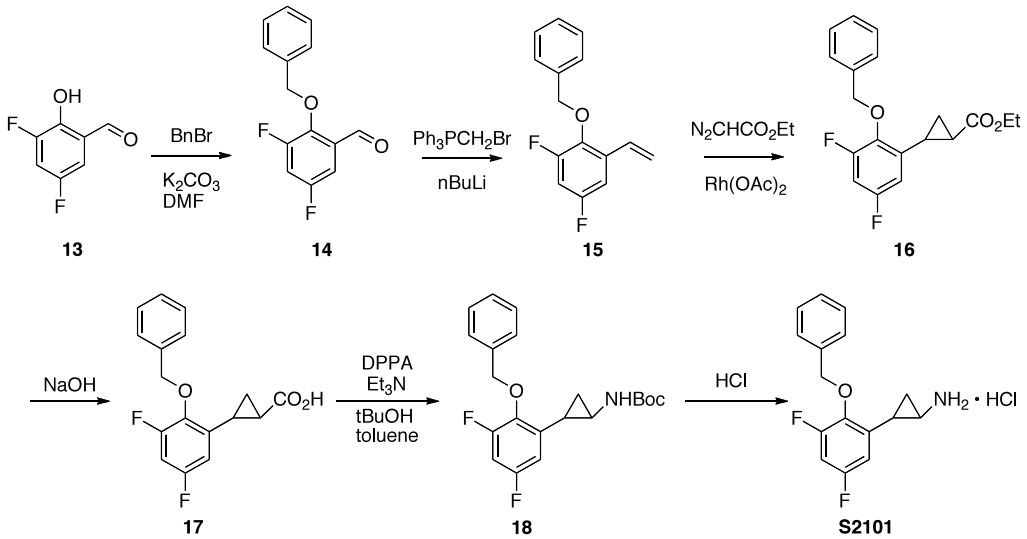
Under Ar, a solution of ethyl diazoacetate (3.6 g, 27 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise to a solution of **9** (2.6 g, as 9.2 mmol) and rhodium(II) acetate dimer (80 mg, 0.18 mmol) in dry CH_2Cl_2 (30 mL) over 6 hours while observing N_2 evolution. The mixture was stirred for 15 additional hours, and was concentrated. The crude product was purified by silica

gel column chromatography (SiO_2 95 g) with hexane-AcOEt (96:4, v/v) as an eluant to afford **10** (903 mg, 33%) as a *cis*/*trans* mixture.

Then, 2 mol/L sodium hydroxide (3 mL) was added to the solution of **10** (900 mg, 3.03 mmol) in EtOH (10 mL). The mixture was stirred for 20 hours at room temperature, and diluted with 3 mol/L HCl (5 mL) and water (10 mL) at 0˚C. The mixture was extracted with AcOEt (2 x 40 mL). The combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 30 g) with hexane-AcOEt (100:0 to 55:45, v/v) as an eluant to afford **11** (740 mg, 91%) as a *trans* isomer.

Triethylamine (0.6 mL, 4.32 mmol) and diphenylphosphoryl azide (0.92 mL, 4.32 mmol) were added to a solution of **11** (740 mg, 2.88 mmol) in dry toluene (8 mL) at room temperature. After the reaction mixture was refluxed for 1 hour, *t*-BuOH (5 mL) was added and refluxing was continued for 6 additional hours. After the reaction mixture was allowed to cool to room temperature, it was diluted with AcOEt (50 mL). The mixture was washed with 5% citric acid (10 mL), H_2O (10 mL), *sat*. $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 30 g) with hexane-AcOEt (100:0 to 85:15, v/v), triturated with hexane and dried *in vacuo* to give **12** (262 mg, 27%). Finally, 4 N HCl/1,4-dioxane (2 mL) was added to **12** (130 mg, 0.38 mmol) and stirred for 20 hours. The residue was diluted with CH_2Cl_2 (10 mL) and H_2O (5 mL) and then basified with 2 mol/L NaOH (0.2 mL). The separated aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 10 g) with CH_2Cl_2-MeOH (99:1 to 90:10, v/v) as an eluant to afford **S1402** as the free base. Then, 4 N HCl in 1,4-dioxane was added to the free **S1402**, which was concentrated to give **S1402** (57 mg, 54%) as the HCl salt. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.51 (br s, 3H), 7.21 (m, 1H), 6.98 (m, 2H), 3.80 (m, 2H), 2.97 (m, 1H), 2.60 (m, 1H), 2.06 (m, 1H), 1.37 (m, 1H), 1.16 (m, 1H), 1.02 (dd, 6H, J = 6.6 and 2.3 Hz); ^{13}C-NMR (125 MHz, CD_3OD): δ (ppm) 157.7, 129.8, 128.6, 127.0, 126.4, 113.9, 76.1, 31.2, 29.6, 19.7, 19.6, 17.7, 13.3; MS (EI): *m*/*z* 239, 241 $[M]^+$; HRMS-EI *m*/*z*: calcd for $C_{13}H_{18}ClNO$: 239.1077, 241.1047, found: 239.1083, 241.1050 $[M]^+$.

Synthesis of *trans*-2-(2-benzyloxy-3,5-difluorophenyl)cyclopropylamine hydrochloride (S2101)



Benzyl bromide (2.38 mL, 20.0 mmol) and K_2CO_3 (2.76 g, 20.0 mmol) were added to a solution of 3,5-difluorosalicylaldehyde (**13**) (2.37 g, 15.0 mmol) in DMF (30 mL). After the mixture was stirred for 18 hours at room temperature, H_2O (60 mL) and AcOEt (50 mL) were added to the mixture. The separated aqueous phase was extracted with AcOEt (2 x 50 mL). The combined organic phases were washed with H_2O (2 x 30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 100 g) with hexane-AcOEt (98:2 to 92:8, v/v) as the eluant to afford **14** (3.76 g, 77%) as colorless oil.

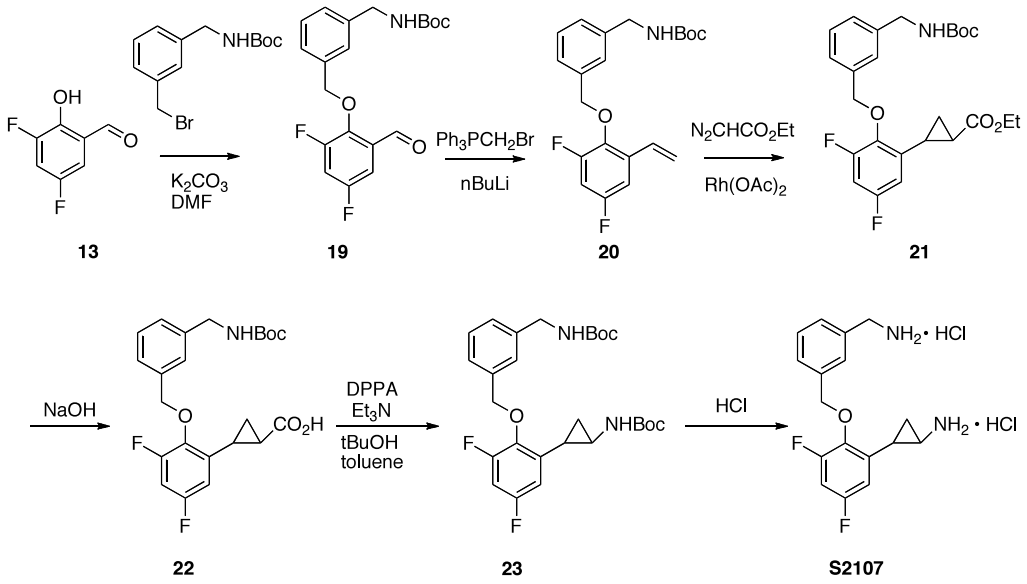
Under Ar, *n*-BuLi (in hexane, 5.3 mL, 8.70 mmol) was added dropwise to a cold solution of methyltriphenylphosphonium bromide (3.20 g, 8.90 mmol) in dry THF (40 mL) at 0˚C over 10 min. After the mixture was stirred for 10 min at the same temperature, the solution of **14** (1.48 g, 5.98 mmol) in dry THF (10 mL) was added to the mixture at 0˚C. After stirring for 1 hour at the same temperature, the reaction mixture was quenched with H_2O (50 mL). The mixture was extracted with AcOEt (3 x 100 mL). The combined extracts were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 100 g) with hexane-AcOEt (99:1 to 90:10, v/v) as an eluant to afford **15** (1.39 g, 71%) as colorless oil.

Under Ar, a solution of ethyl diazoacetate (2.27 g, 16.9 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise to a solution of **15** (1.39 g, 4.27 mmol) and rhodium(II) acetate dimer (49 mg, 0.11 mmol) in dry CH_2Cl_2 (20 mL) over 4 hours while observing N_2 evolution. The mixture was stirred for 18 additional hours, and was concentrated. The crude product was purified by silica gel column chromatography (SiO_2 50 g) with hexane-AcOEt (100:0 to 95:5 v/v) as an eluant to afford **16** (1.73 mg, 98%) as a *cis*/*trans* mixture.

Then, 2 mol/L sodium hydroxide (7.5 mL) was added to the solution of **16** (1.67 mg, 5.0 mmol) in EtOH (15 mL). The mixture was stirred for 18 hours at room temperature, and diluted with 3 mol/L HCl (7.5 mL) and water (30 mL) at 0˚C. The mixture was extracted with AcOEt (3 x 50 mL). The combined organic phases were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 30 g) with hexane-AcOEt (80:20 to 20:80, v/v) as an eluant to afford **17** (1.20 g, 80%) as a *cis*/*trans* mixture.

Triethylamine (0.83 mL, 5.98 mmol) and diphenylphosphoryl azide (1.29 mL, 5.98 mmol) were added to a solution of **17** (1.20 g, 3.99 mmol) in dry toluene (25 mL) at room temperature. After the reaction mixture was refluxed for 1 hour, *t*-BuOH (20 mL) was added and refluxing was continued for 5 additional hours. After the reaction mixture was allowed to cool to room temperature, it was diluted with AcOEt (100 mL). The mixture was washed with 5% citric acid (20 mL), H_2O (20 mL), *sat*. $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 50 g) with hexane-AcOEt (98:2 to 80:20, v/v) as an eluant to afford **18** as a *cis*/*trans* mixture. The *cis*/*trans* mixture was triturated with CH_2Cl_2-hexane (1:9, v/v) and dried *in vacuo* to give **18** (391 mg, 26%) as the *trans* isomer. Finally, 4 N HCl/1,4-dioxane (2 mL) was added to the solution of **18** (150 mg, 0.40 mmol) in 1,4-dioxane (2 mL) and stirred for 18 hours. The mixture was concentrated. The crude product was triturated with Et_2O (5 mL) and dried *in vacuo* to give **S2101** (102 mg, 80%) as a colorless powder. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.63 (br s, 3H), 7.52 (m, 2H), 7.42 (m, 3H), 7.20 (m, 1H), 6.71 (m, 1H), 5.10 (A of ABq, 1H, J = 10.9 Hz), 4.97 (B of ABq, 1H, J = 10.9 Hz), 2.95 (m, 1H), 2.71 (m, 1H), 1.45 (m, 1H), 1.22 (m, 1H); ^{13}C-NMR (125 MHz, CD_3OD): δ (ppm) 159.7 (dd, J = 242, 12 Hz), 157.0 (dd, J = 247, 13 Hz), 142.7 (d, J = 11 Hz), 138.0, 136.6, 129.8, 129.6, 129.6, 108.5 (d, J = 24 Hz), 104.2 (dd, J = 27, 24 Hz), 77.2, 31.9, 17.5, 14.5; MS (EI): *m*/*z* 275 $[M]^+$; HRMS-EI *m*/*z*: calcd for $C_{16}H_{15}F_2NO$: 275.1122, found: 275.1131 $[M]^+$.

Synthesis of *trans*-2-(2-(3-(aminomethyl)benzyloxy)-3,5-difluorophenyl)cyclopropylamine hydrochloride (S2107)



3-Boc-aminomethyl benzyl bromide (3.03 g, 10.1 mmol) and K_2CO_3 (1.24 g, 9.0 mmol) were added to a solution of 3,5-difluorosalicylaldehyde (**13**) (1.42 g, 9.0 mmol) in DMF (20 mL). After the mixture was stirred for 20 hours at room temperature, H_2O (100 mL) and Et_2O (100 mL) were added to the mixture. The separated organic phase was washed with H_2O (2 x 25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 100 g) with hexane-AcOEt (92:8 to 75:25, v/v) as the eluant to afford **19** (1.48 g, 44%) as colorless oil.

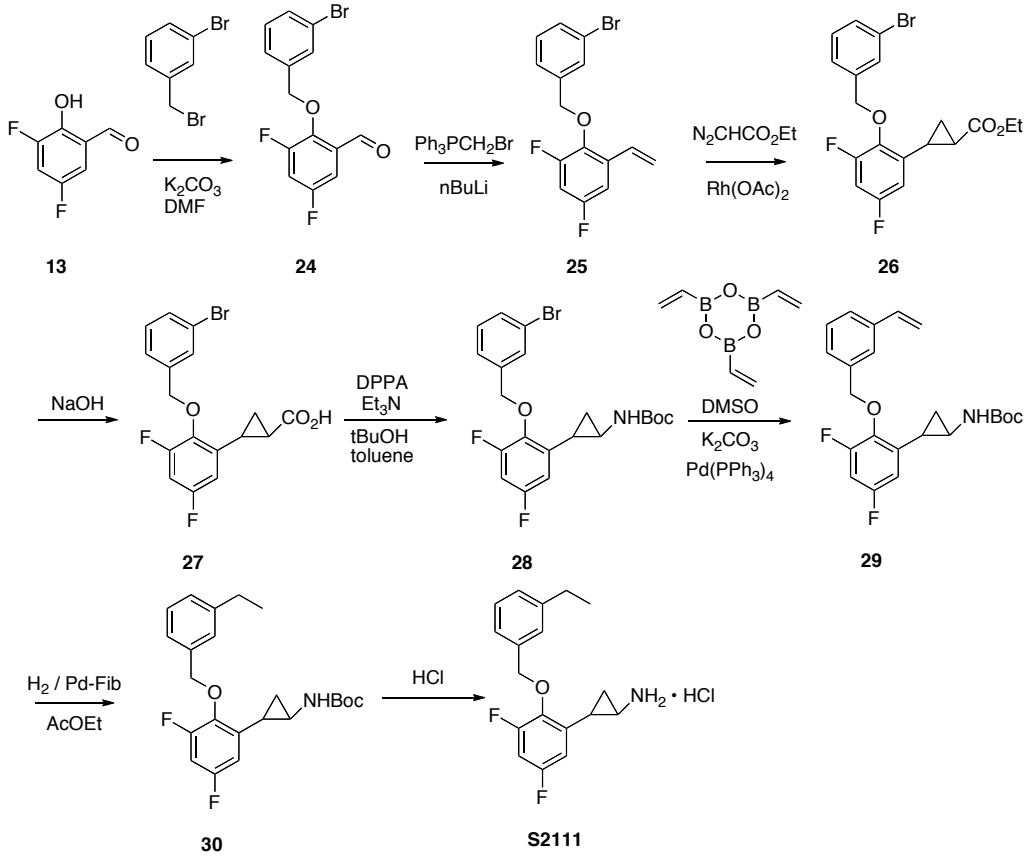
Under Ar, *n*-BuLi (in hexane, 3.6 mL, 5.9 mmol) was added dropwise to a cold solution of methyltriphenylphosphonium bromide (2.14 g, 5.98 mmol) in dry THF (30 mL) at 0°C over 10 min. After the mixture was stirred for 10 min at the same temperature, the solution of **19** (1.45 g, 3.84 mmol) in dry THF (10 mL) was added to the mixture at 0°C. After stirring for 2 hours at the same temperature, the reaction mixture was quenched with H_2O (25 mL). The mixture was extracted with AcOEt (3 x 50 mL). The combined extracts were washed with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 50 g) with hexane-AcOEt (95:5 to 80:20, v/v) as an eluant to afford **20** (1.14 g, 79%).

Under Ar, a solution of ethyl diazoacetate (1.18 g, 10.3 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise to a solution of **20** (1.1 g, 2.93 mmol) and rhodium(II) acetate dimer (27 mg, 0.06 mmol) in dry CH_2Cl_2 (20 mL) over 5 hours while observing N_2 evolution. The mixture was stirred for xx additional hours, and was concentrated. The crude product was purified by silica gel column chromatography (SiO_2 100 g) with hexane-AcOEt (85:15, v/v) as an eluant to afford **21** (480 mg, 35%) as a *cis*/*trans* mixture.

Then, 2 mol/L sodium hydroxide (2 mL) was added to the solution of **21** (480 mg, 1.04 mmol) in EtOH (10 mL). The mixture was stirred for 24 hours at room temperature, and diluted with 5% citric acid (5 mL) at 0°C. The mixture was extracted with AcOEt (2 x 50 mL). The combined organic phases were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 30 g) with hexane-AcOEt (90:10 to 30:70, v/v) as an eluant to afford **22** (178 mg, 39%) as a *cis*/*trans* mixture.

Triethylamine (0.082 mL, 0.59 mmol) and diphenylphosphoryl azide (0.127 mL, 0.59 mmol) were added to a solution of **22** (170 mg, 0.39 mmol) in dry toluene (5 mL) at room temperature. After the reaction mixture was refluxed for 1.5 hours, *t*-BuOH (5 mL) was added and refluxing was continued for 4 additional hours. After the reaction mixture was allowed to cool to room temperature, it was diluted with AcOEt (100 mL). The mixture was washed with 5% citric acid (20 mL), H_2O (20 mL), *sat*. $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 30 g) with hexane-AcOEt (95:5 to 60:40, v/v) as an eluant to afford **23** (119 mg, 60%). Finally, 4 N HCl/1,4-dioxane (2 mL) was added to the solution of **23** (50 mg, 0.099 mmol) in 1,4-dioxane (2 mL) and stirred for 20 hours. The mixture was concentrated to produce **S2107** (34 mg, 93%) as a colorless powder. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.77 (br s, 2H), 8.48 (Br s, 2H), 7.81 (s, 1H), 7.47 (m, 3H), 7.22 (m, 1H), 6.71 (m, 1H), 5.09 (A of ABq, 1H, J = 10.8 Hz), 4.97 (B of ABq, 1H, J = 10.8 Hz), 4.10 (br s, 2H), 2.97 (br m, 1H), 2.85 (br m, 1H), 1.55 (m, 1H), 1.22 (m, 1H); ^{13}C-NMR (150 MHz, CD_3OD): δ (ppm) 159.9 (dd, J = 242, 12 Hz), 157.0 (dd, J = 247, 13 Hz), 142.7 (d, J = 12 Hz), 139.2, 136.8, 134.9, 130.4, 130.3, 130.2, 130.1, 108.5 (d, J = 24 Hz), 104.3 (dd, J = 27, 24 Hz), 76.7, 44.2, 32.0, 17.3, 14.5; MS (FAB): *m/z* 305 $[M+H]^+$; HRMS-FAB *m/z*: calcd for $C_{17}H_{19}F_2N_2O$: 305.1466, found: 305.1472 $[M+H]^+$.

Synthesis of *trans*-2-(2-(3-ethylbenzyloxy)-3,5-difluorophenyl)cyclopropylamine hydrochloride (S2111)



3-Bromo benzyl bromide (5.0 g, 20.0 mmol) and K_2CO_3 (2.76 g, 20.0 mmol) were added to a solution of 3,5-difluorosalicylaldehyde (**13**) (2.37 g, 15.0 mmol) in DMF (30 mL). After the mixture was stirred for 18 hours at room temperature, H_2O (60 mL) and AcOEt (50 mL) were added to the mixture. The separated aqueous phase was extracted with

AcOEt (2 x 50 mL). The combined organic phases were washed with H_2O (2 x 30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was triturated with hexane (15 mL) to afford **24** (4.15 g, 85%) as a colorless powder.

Under Ar, *n*-BuLi (in hexane, 3.6 mL, 5.9 mmol) was added dropwise to a cold solution of methyltriphenylphosphonium bromide (2.14 g, 6 mmol) in dry THF (30 mL) at 0˚C over 10 min. After the mixture was stirred for 10 min at the same temperature, the solution of **24** (1.30 g, 4.0 mmol) in dry THF (10 mL) was added to the mixture at 0˚C. After stirring for 2 hours at the same temperature, the reaction mixture was quenched with H_2O (25 mL). The mixture was extracted with AcOEt (3 x 50 mL). The combined extracts were washed with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 50 g) with hexane-AcOEt (96:4 to 90:10, v/v) as an eluant to afford **25** (1.18 g, 91%).

Under Ar, a solution of ethyl diazoacetate (1.4 g, 10.5 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise to a solution of **25** (1.18 mg, 3.63 mmol) and rhodium(II) acetate dimer (32 mg, 0.07 mmol) in dry CH_2Cl_2 (25 mL) over 5 hours while observing N_2 evolution. The mixture was stirred for 18 additional hours, and was concentrated. The crude product was purified by silica gel column chromatography (SiO_2 30 g) with hexane-AcOEt (98:2 to 90:10, v/v) as an eluant to afford **26** (1.58 g, quant.) as a *cis*/*trans* mixture. The mixture was used for the next reaction without further purification.

Then, 2 mol/L sodium hydroxide (5 mL) was added to the solution of **26** (1.58 g, as 3.63 mmol) in EtOH (15 mL). The mixture was stirred for 24 hours at room temperature, and diluted with water (20 mL) and 3 mol/L HCl (4 mL) at 0˚C. The mixture was extracted with AcOEt (2 x 100 mL). The combined organic phases were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 100 g) with hexane-AcOEt (90:10 to 30:70, v/v) as an eluant to afford **27** (1.22 g, 88%) as a *cis*/*trans* mixture.

Triethylamine (0.65 mL, 4.65 mmol) and diphenylphosphoryl azide (1.0 mL, 4.65 mmol) were added to a solution of **27** (1.20 g, 3.1 mmol) in dry toluene (18 mL) at room temperature. After the reaction mixture was refluxed for 1.5 hours, *t*-BuOH (15 mL) was added and refluxing was continued for 10 additional hours. After the reaction mixture was allowed to cool to room temperature, it was diluted with AcOEt (100 mL). The mixture was washed with 5% citric acid (20 mL), H_2O (20 mL), *sat*. $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 50 g) with hexane-AcOEt (95:5 to 85:15, v/v) as an eluant to afford **28** (563 mg) as a *cis*/*trans* mixture. Under Ar, trivinylboroxine-pyridine complex (120 mg, 0.50 mmol), K_2CO_3 (410 mg, 3.0 mmol) and tetrakistriphenylphosphine palladium (30 mg, 0.02 mmol) were added to a solution of **28** (450 mg, 1.0 mol) in DMSO (3.0 mL). The mixture was heated at 90˚C for 20 hours. After the reaction mixture was allowed to cool to room temperature, H_2O (25 mL) was added. The mixture was extracted with AcOEt (2 x 100 mL). The combined organic phases were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (SiO_2 30 g) with hexane-AcOEt (95:5 to 80:20, v/v) as an eluant to afford **29** (126 mg) as a *cis*/*trans* mixture.

The compound **29** was subjected to hydrogenolysis under H_2 with Pd/Fib (50 mg) for 20 hours. After filtration to remove the catalyst, the filtrate was concentrated. The resultant compound **30** was used for the next reaction without further purification. Finally, 4 N HCl/1,4-dioxane (2 mL) was added to the solution of **30** in 1,4-dioxane (1 mL) and stirred for 19 hours. The mixture was concentrated. The residue was diluted with CH_2Cl_2 (5 mL) and then basified with 2 mol/L NaOH (1 mL). The mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered,

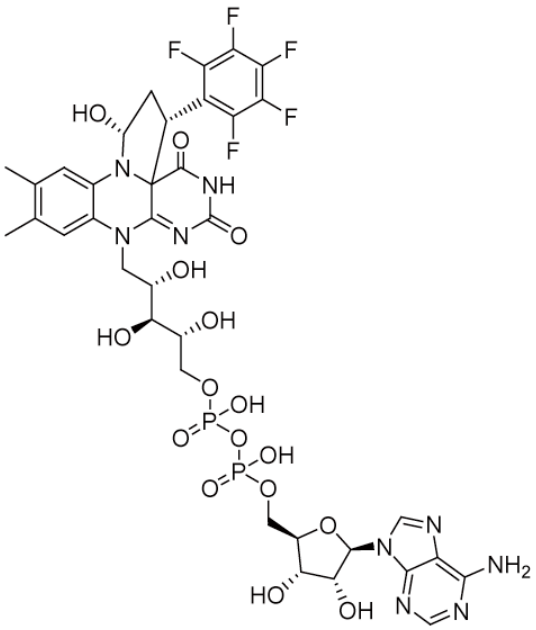
and concentrated. The crude product was purified by PTLC (CH_2Cl_2:MeOH=9:1). Then, 4 N HCl in 1,4-dioxane was added to the free **S2111**, which was concentrated to give **S2111** (53 mg, 16% 3 steps) as the HCl salt. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.60 (br m, 3H), 7.32-7.17 (m, 5H), 6.71 (m, 1H), 5.06 (A of ABq, 1H, *J* = 10.8 Hz), 4.94 (B of ABq, 1H, *J* = 10.8 Hz), 2.96 (m, 1H), 2.67 (m, 1H), 2.63 (q, 2H, *J* = 7.6 Hz), 1.44 (m, 1H), 1.23 (m, 1H), 1.18 (t, 3H, *J* = 7.6 Hz); ^{13}C-NMR (150 MHz, CD_3OD): δ (ppm) 159.7 (dd, J = 241, 12 Hz), 157.0 (dd, J = 247, 13 Hz), 145.9, 142.7 (d, J = 12 Hz), 138.0, 136.7, 129.6, 129.2, 129.1, 127.1, 108.4 (d, J = 27 Hz), 104.2 (dd, J = 27, 24 Hz), 77.3, 31.9, 29.8, 17.6, 16.2, 14.6; MS (EI): *m/z* 303 $[M]^+$, HRMS-EI *m/z*: calcd for $C_{18}H_{19}F_2NO$: 303.1435, found: 303.1434 $[M]^+$.

References

1. White, W. L., and R. Filler, R. (1971) *J. Chem. Soc. C* 2063–2068.
2. Walborsky, H. M., and Plonsker, L. (1961) *J. Am. Chem. Soc. 83*, 2138–2144.
3. Kaiser, C., Weinstock, J., and Olmstead, M. P. (1970) *Org. Syn. 50*, 94–97.

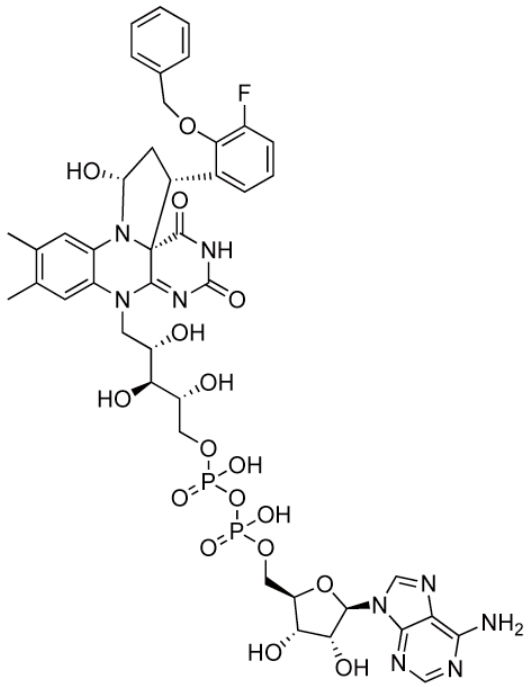
Figure S1: Chemical structures of the 2-PCPA derivatives. 2-PFPA-FAD reacted adduct (A), and S1201-FAD reacted adduct (B). The IUPAC names are listed below.

A



[(2R,3S,4R,5R)-5-(6-AMINO-9H-PURIN-9-YL)-3,4-DIHYDROXYTETRAHYDROFURAN-2-YL]METHYL (2R,3S,4S)-5-[(1R,3R,3AS)-1-HYDROXY-10,11-DIMETHYL-4,6-DIOXO-3-PENTAFLUOROPHENYL-2,3,5,6-TETRAHYDRO-1H-BENZO[G] PYRROLO [2,1-E]PTERIDIN-8(4H)-YL]-2,3,4-TRIHYDROXYPENTYL DIHYDROGEN DIPHOSPHATE

B



[(2R,3S,4R,5R)-5-(6-AMINO-9H-PURIN-9-YL)-3,4-DIHYDROXYTETRAHYDROFURAN-2-YL]METHYL (2R,3S,4S)-5-[(1R,3R,3AS)-1-HYDROXY-10,11-DIMETHYL-4,6-DIOXO-3-(3-FLUORO-2-PHENOXYPHENYL)-2,3,5,6-TETRAHYDRO-1H-BENZO[G] PYRROLO[2,1-E]PTERIDIN-8(4H)-YL]-2,3,4-TRIHYDROXYPENTYL DIHYDROGEN DIPHOSPHATE

Figure S2: Time-course inhibition analyses of MAO-A (A-D) and MAO-B (E-H). The compounds used are: (A, E) 2-PCPA; (B, F) 2-PFPA; (C, G) S1201; and (D, H) S2101.

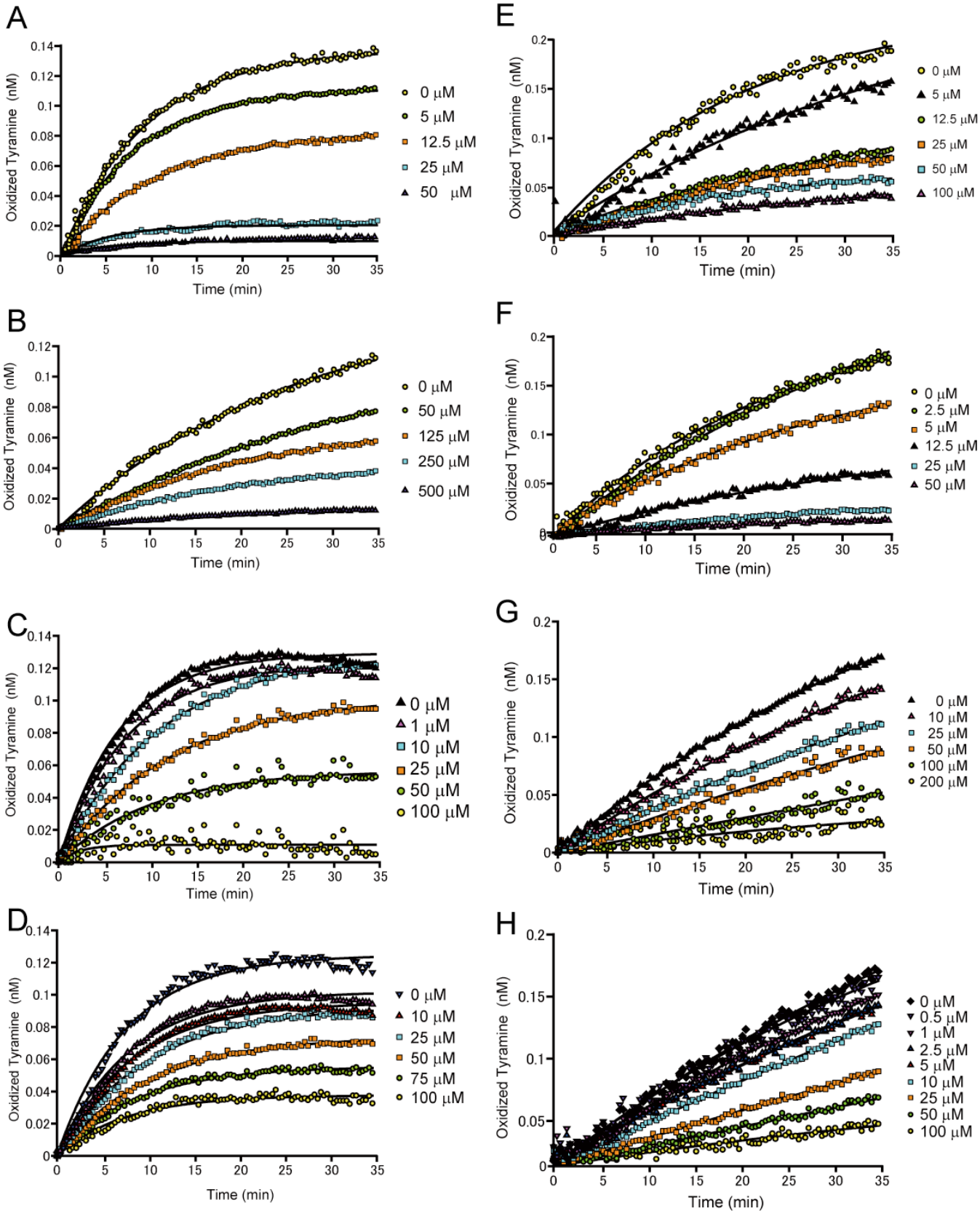


Figure S3: The modification of the *para* position in 2-PCPA is redundant (A). The structure of 2-PCPA—LSD1, in which the adduct is colored orange and the hypothetical *para*-modification is magenta. The surfaces of LSD1 are colored cyan. Note that the *para* modified phenyl moiety (magenta) has no surrounding LSD1 residues for interactions. Structure superimpositions of 2-PCPA—LSD1, 2-PFPA—LSD1 and S1201—LSD1 (B). The 2-PCPA—LSD1 adduct is colored orange, the 2-PFPA—LSD1 adduct is colored blue, and the S1201—LSD1 FAD is colored pink. The residues surrounding 2-PCPA—LSD1 are colored cyan, those surrounding 2-PFPA—LSD1 are colored green, and those surrounding S1201—LSD1 are colored light pink. Note that the LSD1 residues shift outward the most in 2-PCPA—LSD1, whereas in S1201—LSD1, the hydrophobic residues move closer to the extra phenyl ring, forming hydrophobic interactions.

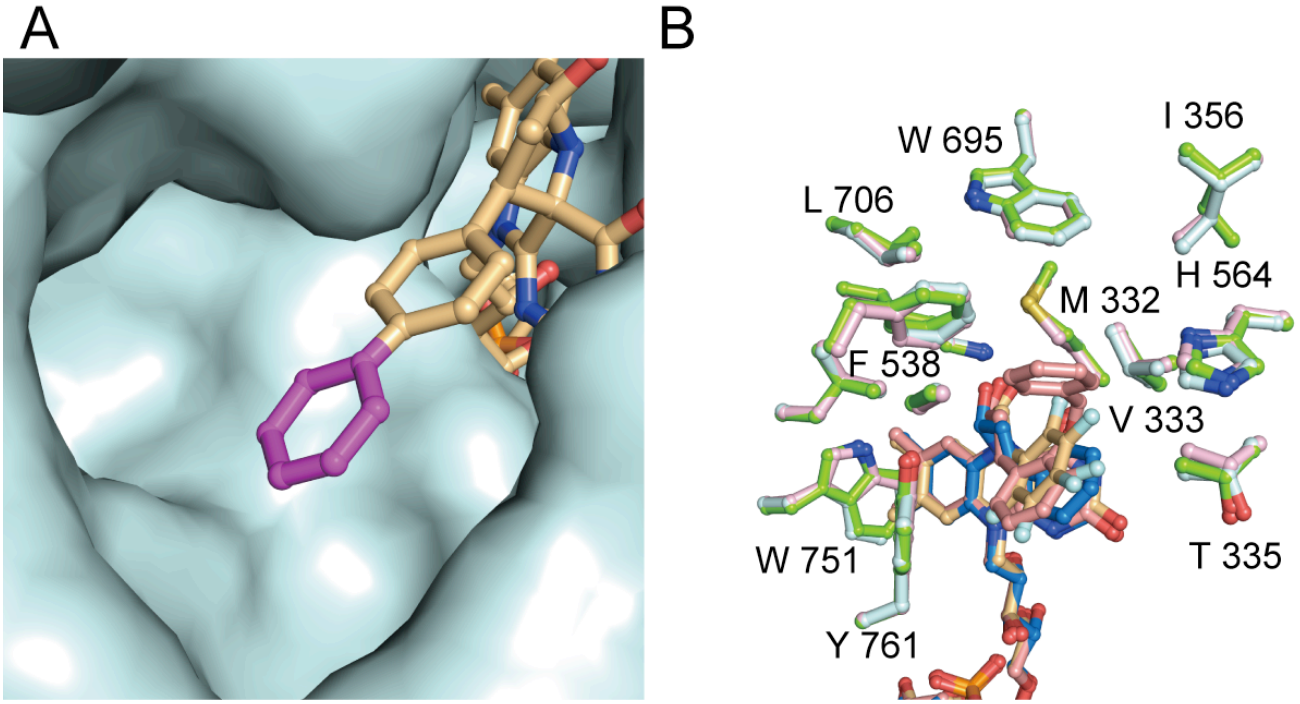


Table S1: Data collection and refinement statistics

	LSD1–2-PFPA	LSD1–S1201
Data collection		
Space group	*P*6(1)22	*P*6(1)22
Cell dimensions		
a, *b*, *c* (Å)	183.84, 183.84, 109.15	183.70, 183.70, 109.25
α, β, γ (°)	90, 90, 120	90, 90, 120
Resolution (Å)	50.0 - 3.20 (3.34 - 3.20)*	50.0 - 3.10 (3.29 - 3.10)*
R_{sym} or R_{merge}	22.6 (61.2)	16.6 (55.8)
I / σI	9.77 (2.11)	19.38 (5.13)
Completeness (%)	99.0 (99.1)	100 (99.9)
Redundancy	8.7 (3.1)	18.8 (18.5)
Refinement		
Resolution (Å)	47.73 - 3.20	47.71 - 3.10
No. reflections	18,396	20,212
R_{work} / R_{free}	23.1 / 27.2	24.6 / 30.3
No. atoms	5,101	5,203
Protein	5,033	5,131
Ligand/ion	68	72
Water	0	0
B-factors		
Protein	59.04	53.88
Ligand/ion	50.47	42.49
Water		
R.m.s. deviations		
Bond lengths (Å)	0.003	0.023
Bond angles (°)	0.9	2.7

*Values in parentheses are for highest-resolution shell.