# Supporting Information

## Further Advances in Optimizing (2-Phenylcyclopropyl)methylamines as Novel Serotonin 2C Agonists: Effects on Hyperlocomotion, Prepulse Inhibition, and Cognition Models

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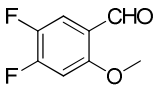
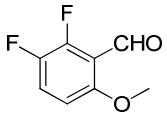
## 1. Synthetic procedures for compounds 16a–g, 18a–g, 19a–g, and characterization data of all chemical intermediates.

**General.** All chemicals and solvents were purchased from Sigma-Aldrich or Fisher Scientific, and were used as obtained without further purification. Microwave reactions were run in a Biotage Initiator microwave reactor. Synthetic intermediates were purified by CombiFlash flash chromatography on 230−400 mesh silica gel. $^{1}$H and $^{13}$C NMR spectra were recorded on Bruker DPX-400 or AVANCE-400 spectrometers; at 400 MHz and 100 MHz respectively. NMR chemical shifts were reported in $\delta$ (ppm) using residual solvent peaks as standard ($CDCl_3$–7.26 (H), 77.23 (C); $CD_3OD$–3.31 (H), 49.15 (C)).



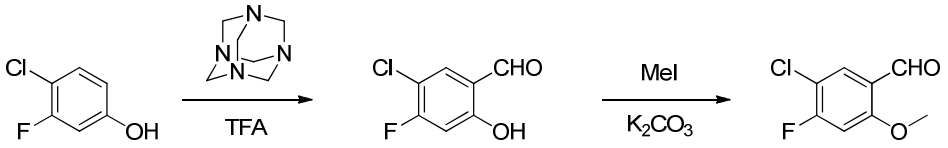

**11a**

**4,5-Difluoro-2-methoxybenzaldehyde (11a).** This starting material was purchased from Sigma-Aldrich.



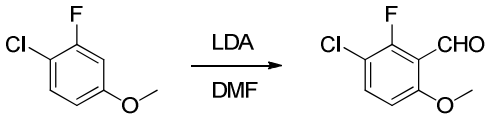

**11b**

**2,3-Difluoro-6-methoxybenzaldehyde (11b).** This starting material was purchased from Sigma-Aldrich.



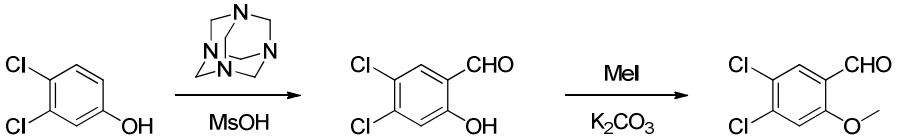

**11c**

**5-Chloro-4-fluoro-2-methoxybenzaldehyde (11c).** To a solution of 4-chloro-3-fluorophenol (14.8 g, 100 mmol) in trifluoroacetic acid (TFA) (100 mL) cooled to 0 °C was added hexamethylenetetramine (16.8 g, 120 mmol) in small portions while the temperature was kept below 20 °C. The mixture was then refluxed overnight before being cooled to room temperature, and conc. $H_2SO_4$ (4.0 mL) was added followed by water (100 mL). The mixture was extracted with DCM, the combined extracts were washed with water and brine, dried over $Na_2SO_4$, concentrated and purified by flash chromatography (0−20% EtOAc in hexanes) to give a light yellow solid (5.7 g). This solid was dissolved in anhydrous DMF (50 mL), $K_2CO_3$ (8.3 g, 60 mmol) and MeI (8.5 g, 60 mmol) were added, and the mixture was stirred at room temperature for 3 h. Water was then added the mixture was extracted with EtOAc, and the combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated and purified by flash chromatography (0−30% EtOAc in hexanes) to give the title compound as a white solid (5.1 g, 27% for 2 steps). $^{1}$H NMR ($CDCl_3$) $\delta$ 10.32 (s, 1H), 7.88 (d, $J$ = 8.4 Hz, 1H), 6.80 (d, $J$ = 10.4 Hz, 1H), 3.93 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 187.2, 162.6 (d, $J_{CF}$ = 256.4 Hz), 161.9 (d, $J_{CF}$ = 9.7 Hz), 130.5 (d, $J_{CF}$ = 2.6 Hz), 122.2 (d, $J_{CF}$ = 3.1 Hz), 113.8 (d, $J_{CF}$ = 18.4 Hz), 101.3 (d, $J_{CF}$ = 25.2 Hz), 56.5.



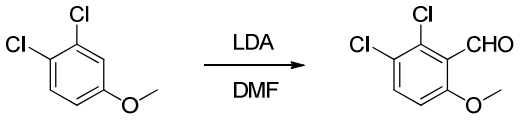

**11d**

**3-Chloro-2-fluoro-6-methoxybenzaldehyde (11d).** To a solution of $^{i}Pr_2NH$ (8.6 mL, 60 mmol) in anhydrous THF (50 mL) cooled to −78 °C was added slowly *n*-BuLi (2.5 M in cyclohexane, 24 mL, 60 mmol), and the solution was stirred for 30 min before a solution of 1-chloro-2-fluoro-4-methoxybenzene (8.03 g, 50 mmol) in anhydrous THF (50 mL) was added slowly while keeping the internal temperature below −70 °C. The mixture was stirred for 20 min before anhydrous DMF (10 mL) was added and the flask was slowly warmed to room temperature. Water was added and the mixture was extracted with EtOAc. The combined extracts were washed with brine, dried over $Na_2SO_4$ and concentrated. The crude material was purified by flash chromatography (0–20% EtOAc in hexanes) to give a yellow solid (8.9 g, 94%). $^1$H NMR ($CDCl_3$) $\delta$ 10.40 (s, 1H), 7.54 (dd, $J$ = 9.2, 8.0 Hz, 1H), 6.76 (dd, $J$ = 9.1, 1.2 Hz, 1H), 3.95 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 186.5, 160.7 (d, $J_{CF}$ = 4.6 Hz), 158.0 (d, $J_{CF}$ = 262.8 Hz), 135.9 (d, $J_{CF}$ = 2.5 Hz), 114.9 (d, $J_{CF}$ = 8.9 Hz), 113.6 (d, $J_{CF}$ = 17.7 Hz), 108.1 (d, $J_{CF}$ = 4.2 Hz), 56.6.




**11e**

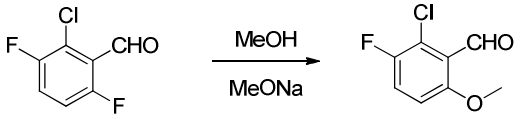
**4,5-Dichloro-2-methoxybenzaldehyde (11e).** To a solution of 3,4-dichlorophenol (20.0 g, 123 mmol) in methane sulfonic acid (120 mL) was added hexamethylenetetramine (18.8 g, 134 mmol) in small portions. The mixture was slowly heated to 105 °C and kept at 105 °C for 15 min before being cooled to room temperature and poured into ice-water (500 g). The mixture was extracted with EtOAc after the ice melted, and the extracts were combined, washed with brine, dried over $Na_2SO_4$, and concentrated to give a yellow solid (18.2 g). This solid was dissolved in DMF (100 mL), $K_2CO_3$ (26.2 g, 190 mmol) and MeI (27.0 g, 190 mmol) were added and the mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with EtOAc. The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated and purified by flash chromatography (0–30% EtOAc in hexanes) to give the title compound as a white solid (5.6 g, 22%). $^1$H NMR ($CDCl_3$) $\delta$ 10.34 (s, 1H), 7.87 (s, 1H), 7.10 (s, 1H), 3.94 (s, 3H).




**11f**

**2,3-Dichloro-6-methoxybenzaldehyde (11f).** To a solution of 3,4-dichloroanisole (12.5 g, 70.6 mmol) in anhydrous THF (100 mL) cooled to −78 °C was added dropwise *n*-BuLi (2.5 M in cyclohexane, 31 mL, 77.7 mmol), and the mixture was stirred at the same temperature for 0.5 h. Anhydrous DMF (6.0 mL, 77.7 mmol) was added, and the mixture was stirred for 15 min before being warmed to room temperature. Water was added and the mixture was extracted with EtOAc, and the combined extracts were washed with brine, dried over $Na_2SO_4$ and concentrated The

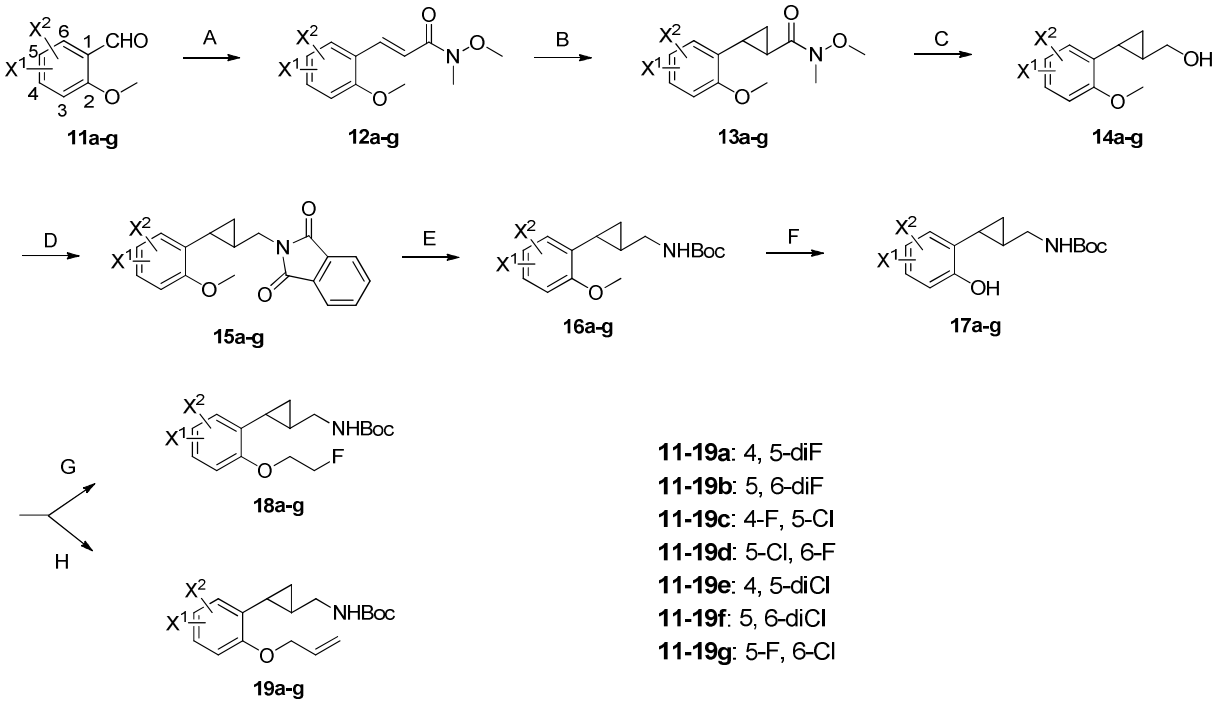
crude material was recrystallized from EtOAc/hexanes to give a light yellow solid (7.5 g, 52%). $^1$H NMR ($CDCl_3$) $\delta$ 10.42 (s, 1H), 7.54 (d, $J$ = 8.8 Hz, 1H), 6.87 (d, $J$ = 9.2 Hz, 1H), 3.90 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 188.7, 160.4, 134.9, 134.1, 126.2, 124.0, 111.4, 56.6.




**11g**

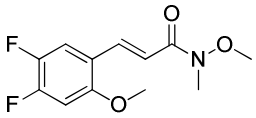
**2-Chloro-3-fluoro-6-methoxybenzaldehyde (11g).** 2-Chloro-3,6-difluorobenzaldehyde (5.0 g, 28 mmol) was dissolved in a mixture of anhydrous THF (20 mL) and methanol (50 mL) and heated to 60 °C. $NaOCH_3$ (25% wt% in methanol, 8.0 mL) was added, and the mixture was heated at 60 °C overnight. The mixture was then cooled to room temperature and concentrated. The residue was purified by flash chromatography (0–30% EtOAc in hexanes) to give a white solid (3.8 g, 72%). $^1$H NMR ($CDCl_3$) $\delta$ 10.47 (s, 1H), 7.29 (t, $J$ = 8.8 Hz, 1H), 6.88 (dd, $J$ = 9.2, 3.6 Hz, 1H), 3.91 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 188.6, 158.2, 152.9 (d, $J_{CF}$ = 241.0 Hz), 123.1, 123.0 (d, $J_{CF}$ = 19.1 Hz), 121.2 (d, $J_{CF}$ = 23.3 Hz), 110.9 (d, $J_{CF}$ = 6.9 Hz), 56.8.

**General scheme for the synthesis of compounds 16a–g, 18a–g, and 19a–g:**



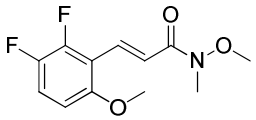

**11-19a**: 4, 5-diF
**11-19b**: 5, 6-diF
**11-19c**: 4-F, 5-Cl
**11-19d**: 5-Cl, 6-F
**11-19e**: 4, 5-diCl
**11-19f**: 5, 6-diCl
**11-19g**: 5-F, 6-Cl

**General Method A.** To a solution of benzaldehydes **11a**–**g** (1.0 eq) in anhydrous dichloromethane (0.1–0.2 mol/L) was added *N*-methoxy-*N*-methyl(triphenylphosphoranylidene)acetamide (1.2–1.5 eq), and the solution was stirred at room temperature overnight. The solution was then concentrated, and the residue was purified by flash chromatography to give intermediates **12a**–**g**.



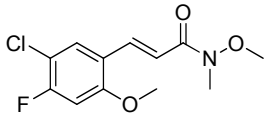
**12a**

**(*E*)-3-(4,5-Difluoro-2-methoxyphenyl)-*N*-methoxy-*N*-methylacrylamide (12a).** $^{1}$H NMR ($CDCl_3$) $\delta$ 7.91 (d, $J$ = 16.0 Hz, 1H), 7.36 (dd, $J$ = 11.2, 9.2 Hz, 1H), 6.97 (d, $J$ = 16.0 Hz, 1H), 6.72 (dd, $J$ = 12.0, 6.8 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.30 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.1, 154.9 (d, $J_{CF}$ = 7.4 Hz), 151.5 (dd, $J_{CF}$ = 250.3, 13.9 Hz), 144.7 (dd, $J_{CF}$ = 239.4, 13.1 Hz), 136.7, 120.7 (d, $J_{CF}$ = 9.0 Hz), 117.1 (d, $J_{CF}$ = 2.0 Hz), 116.2 (dd, $J_{CF}$ = 18.6, 1.7 Hz), 101.4 (d, $J_{CF}$ = 21.0 Hz), 62.0, 56.4, 32.7.



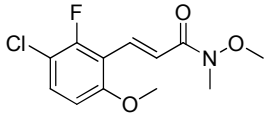
**12b**

**(*E*)-3-(2,3-Difluoro-6-methoxyphenyl)-*N*-methoxy-*N*-methylacrylamide (12b).** $^{1}$H NMR ($CDCl_3$) $\delta$ 7.89 (d, $J$ = 16.4 Hz, 1H), 7.33 (d, $J$ = 16.4 Hz, 1H), 7.09 (q, $J$ = 8.8 Hz, 1H), 6.61–6.57 (m, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.31 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.5, 155.0 (d, $J_{CF}$ = 5.3 Hz), 150.1 (dd, $J_{CF}$ = 252.0, 14.1 Hz), 146.5 (dd, $J_{CF}$ = 239.0, 13.5 Hz), 131.3 (d, $J_{CF}$ = 2.7 Hz), 121.6 (d, $J_{CF}$ = 11.0 Hz), 117.1 (dd, $J_{CF}$ = 20.5, 2.1 Hz), 115.0 (d, $J_{CF}$ = 10.2 Hz), 105.9 (d, $J_{CF}$ = 6.2, 3.8 Hz), 62.1, 56.5, 32.8.



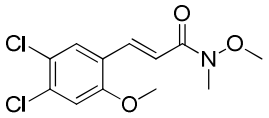
**12c**

**(*E*)-3-(5-Chloro-4-fluoro-2-methoxyphenyl)-*N*-methoxy-*N*-methylacrylamide (12c).** $^{1}$H NMR ($CDCl_3$) $\delta$ 7.90 (d, $J$ = 16.0 Hz, 1H), 7.57 (d, $J$ = 8.4 Hz, 1H), 7.00 (d, $J$ = 16.0 Hz, 1H), 6.72 (d, $J$ = 10.8 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.32 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.1, 159.4 (d, $J_{CF}$ = 258.8 Hz), 158.1, 136.5, 129.6, 121.9 (d, $J_{CF}$ = 3.6 Hz), 117.2, 112.5 (d, $J_{CF}$ = 18.4 Hz), 100.8 (d, $J_{CF}$ = 25.0 Hz), 62.0, 56.3, 32.7.



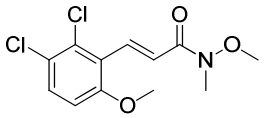
**12d**

**(*E*)-3-(3-Chloro-2-fluoro-6-methoxyphenyl)-*N*-methoxy-*N*-methylacrylamide (12d).** $^{1}$H NMR ($CDCl_3$) $\delta$ 7.90 (d, $J$ = 16.0 Hz, 1H), 7.35–7.28 (m, 2H), 6.66 (d, $J$ = 8.8 Hz), 3.88 (s, 3H), 3.75 (s, 3H), 3.31 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.5, 158.1 (d, $J_{CF}$ = 6.2 Hz), 157.4 (d, $J_{CF}$ = 252.3 Hz), 131.2, 130.7, 121.5 (d, $J_{CF}$ = 11.5 Hz), 114.6 (d, $J_{CF}$ = 13.3 Hz), 113.5 (d, $J_{CF}$ = 19.1 Hz), 107.3 (d, $J_{CF}$ = 3.5 Hz), 62.1, 56.4, 32.8.



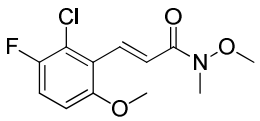
**12e**

**(*E*)-3-(4,5-Dichloro-2-methoxyphenyl)-*N*-methoxy-*N*-methylacrylamide (12e).** $^{1}$H NMR ($CDCl_3$) $\delta$ 7.90 (d, $J$ = 16.0 Hz, 1H), 7.60 (s, 1H), 7.04 (d, $J$ = 16.0 Hz, 1H), 6.98 (s, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.30 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.9, 157.1, 136.4, 134.1, 129.3, 124.8, 124.2, 118.0, 113.6, 62.1, 56.3, 32.7.



**12f**

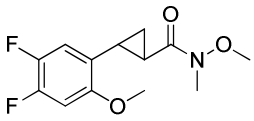
**(*E*)-3-(2,3-Dichloro-6-methoxyphenyl)-*N*-methoxy-*N*-methylacrylamide (12f).** $^{1}$H NMR ($CDCl_3$) $\delta$ 7.92 (d, $J$ = 16.0 Hz, 1H), 7.35 (d, $J$ = 8.8 Hz, 1H), 7.33 (d, $J$ = 16.0 Hz, 1H), 6.79 (d, $J$ = 8.8 Hz, 1H), 3.87 (s, 3H), 3.74 (s, 3H), 3.30 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.4, 158.0, 135.6, 134.0, 130.3, 125.6, 124.9, 123.3, 110.5, 62.1, 56.3, 32.8.



**12g**

**(*E*)-3-(2-Chloro-3-fluoro-6-methoxyphenyl)-*N*-methoxy-*N*-methylacrylamide (12g).** $^{1}$H NMR ($CDCl_3$) $\delta$ 7.93 (d, $J$ = 16.0 Hz, 1H), 7.42 (d, $J$ = 16.4 Hz, 1H), 7.08 (t, $J$ = 8.8 Hz, 1H), 6.78 (dd, $J$ = 9.2, 4.4 Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 3.31 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.4, 155.5 (d, $J_{CF}$ = 2.1 Hz), 153.1 (d, $J_{CF}$ = 238.9 Hz), 134.6 (d, $J_{CF}$ = 3.2 Hz), 124.2, 123.1, 122.8 (d, $J_{CF}$ = 18.6 Hz), 116.1 (d, $J_{CF}$ = 23.1 Hz), 109.9 (d, $J_{CF}$ = 7.5 Hz), 62.0, 56.4, 32.7.

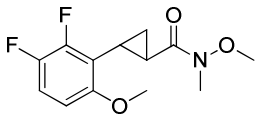
**General Method B.** Trimethylsulfoxonium iodide (1.5–2.0 eq) was suspended in anhydrous DMSO (~2 mmol/mL), and sodium hydride (1.5–2.0 eq) was added in small portions. The mixture was stirred at room temperature for 0.5 to 1 hour to afford a clear solution. A solution of acrylamides **12a**−**g** (1.0 eq) in anhydrous DMSO (2 mmol/mL) was then slowly added and the solution was stirred at room temperature overnight. Work-up with water and EtOAc and purification by flash chromatography afforded **13a**−**g** in high yields.



**13a**

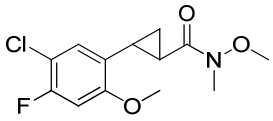
**2-(4,5-Difluoro-2-methoxyphenyl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (13a).** Colorless oil. $^{1}$H NMR ($CDCl_3$) $\delta$ 6.74 (dd, $J$ = 11.2, 9.2 Hz, 1H), 6.65 (dd, $J$ = 12.0, 6.8 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.24 (s, 3H), 2.66–2.60 (m, 1H), 2.29–2.25 (m, 1H), 1.60–1.55 (m, 1H), 1.23–1.18 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.2, 154.6 (d, $J_{CF}$ = 5.3 Hz), 148.9 (dd, $J_{CF}$ =

244.6, 13.3 Hz), 144.4 (dd, $J_{CF}$ = 238.0, 12.5 Hz), 125.5, 114.7 (d, $J_{CF}$ = 17.9, 1.6 Hz), 100.7 (d, $J_{CF}$ = 20.7 Hz), 61.8, 56.3, 32.8, 20.4, 20.3, 15.2.



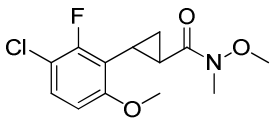
13b

**2-(2,3-Difluoro-6-methoxyphenyl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (13b).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.93 (q, $J$ = 9.6 Hz, 1H), 6.61 – 6.57 (m, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.24 (s, 3H), 2.67–2.64 (m, 1H), 2.51–2.45 (m, 1H), 1.56–1.47 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.9, 155.2 (dd, $J_{CF}$ = 6.1, 2.2 Hz), 150.1 (dd, $J_{CF}$ = 245.1, 14.0 Hz), 145.6 (dd, $J_{CF}$ = 238.5, 13.8 Hz), 118.4 (d, $J_{CF}$ = 10.9 Hz), 114.1 (dd, $J_{CF}$ = 17.7, 1.8 Hz), 105.4 (dd, $J_{CF}$ = 6.4, 3.5 Hz), 61.8, 56.3, 32.8, 18.3, 16.8, 15.2.



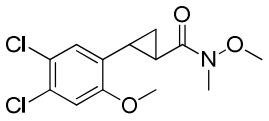
13c

**2-(5-Chloro-4-fluoro-2-methoxyphenyl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (13c).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 6.92 (d, $J$ = 8.0 Hz, 1H), 6.65 (d, $J$ = 10.8 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.24 (s, 3H), 2.63–2.58 (m, 1H), 2.29–2.24 (m, 1H), 1.59–1.54 (m, 1H), 1.27–1.21 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.2, 158.1 (d, $J_{CF}$ = 8.6 Hz), 157.2 (d, $J_{CF}$ = 245.1 Hz), 127.5, 126.4 (d, $J_{CF}$ = 3.3 Hz), 111.4 (d, $J_{CF}$ = 17.9 Hz), 100.1 (d, $J_{CF}$ = 24.8 Hz), 61.7, 56.1, 32.8, 20.3, 20.2, 14.9.



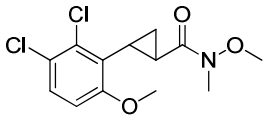
13d

**2-(3-Chloro-2-fluoro-6-methoxyphenyl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (13d).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.15 (t, $J$ = 8.8 Hz, 1H), 6.56 (dd, $J$ = 8.8, 1.6 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.23 (s, 3H), 2.64–2.61 (m, 1H), 2.48–2.43 (m, 1H), 1.55–1.45 (m, 2H).



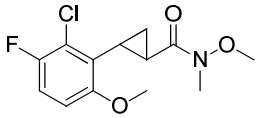
13e

**2-(4,5-Dichloro-2-methoxyphenyl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (13e).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 6.96 (s, 1H), 6.89 (s, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.24 (s, 3H), 2.65–2.57 (m, 1H), 2.31–2.28 (m, 1H), 1.61–1.57 (m, 1H), 1.29–1.24 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.1, 157.5, 130.5, 130.0, 127.5, 123.7, 112.6, 61.8, 56.1, 32.8, 20.5, 20.2, 15.1.



13f

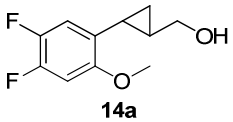
**2-(2,3-Dichloro-6-methoxyphenyl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (13f).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.29 (d, $J$ = 8.8 Hz, 1H), 6.72 (d, $J$ = 8.8 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.27 (s, 3H), 2.45–2.41 (m, 2H), 1.64–1.60 (m, 1H), 1.48–1.43 (m, 1H).



13g

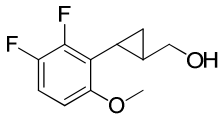
**2-(2-Chloro-3-fluoro-6-methoxyphenyl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (13g).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 6.98 (t, $J$ = 8.8 Hz, 1H), 6.69 (dd, $J$ = 9.2, 4.0 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.27 (s, 3H), 2.48–2.41 (m, 2H), 1.61–1.57 (m, 1H), 1.53–1.47 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.1, 155.5 (d, $J_{CF}$ = 2.1 Hz), 153.0 (d, $J_{CF}$ = 239.1 Hz), 128.1, 123.9 (d, $J_{CF}$ = 18.1 Hz), 114.1 (d, $J_{CF}$ = 22.7 Hz), 110.0 (d, $J_{CF}$ = 7.6 Hz), 61.7, 56.4, 32.8, 20.3, 19.6, 16.9.

**General Method C.** A solution of **13a**−**g** (1.0 eq) in anhydrous THF (0.1−0.2 mmol/mL) was cooled to −78 °C under argon. To this solution was added slowly DIBAL-H (1.0 M solution in THF, 2.0 eq) and the solution was stirred at −78 °C for 2−3 h. Saturated aqueous solution of Rochelle's salt was added to quench the reaction and the mixture was warmed to room temperature, stirred for 1 h and filtered. The solid was washed with EtOAc and the filtrate was extracted with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated to give the aldehydes as a colorless oil. This oil was dissolved in methanol (0.1−0.2 mmol/mL), $NaBH_4$ (1.5 eq) was added slowly and the mixture was stirred at room temperature for 30 min. The reaction was neutralized with 1N HCl and concentrated. The residue was dissolved in DCM and washed with water and brine, dried over sodium sulfate and concentrated. The crude material was purified by flash chromatography to give compounds **14a**−**g**.



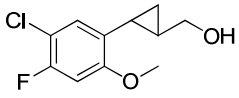
14a

**[2-(4,5-Difluoro-2-methoxyphenyl)cyclopropyl]methanol (14a).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.73 (dd, $J$ = 11.2, 9.2 Hz, 1H), 6.65 (dd, $J$ = 12.0, 6.8 Hz, 1H), 3.85–3.78 (m, 4H), 3.30 (dd, $J$ = 10.8, 8.4 Hz, 1H), 2.17 (br, 1H), 1.86–1.80 (m, 1H), 1.19–1.14 (m, 1H), 0.99–0.94 (m, 1H), 0.89–0.84 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 154.4 (d, $J_{CF}$ = 9.3 Hz), 148.7 (dd, $J_{CF}$ = 243.8, 13.6 Hz), 144.5 (dd, $J_{CF}$ = 238.2, 12.5 Hz), 126.6, 115.2 (d, $J_{CF}$ = 18.8 Hz), 100.5 (d, $J_{CF}$ = 21.1 Hz), 67.0, 56.4, 24.5, 16.1, 11.0.



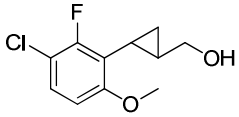

14b

**[2-(2,3-Difluoro-6-methoxyphenyl)cyclopropyl]methanol (14b).** Colorless oil. $^{1}$H NMR ($CDCl_3$) $\delta$ 6.93 (q, $J$ = 9.2 Hz, 1H), 6.52–6.48 (m, 1H), 3.87–3.81 (m, 4H), 3.32 (dd, $J$ = 10.8, 8.4 Hz, 1H), 2.29 (br, 1H), 1.63–1.59 (m, 1H), 1.46–1.42 (m, 1H), 1.28–1.24 (m, 1H), 0.94–0.91 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 155.1 (dd, $J_{CF}$ = 6.1, 2.2 Hz), 150.0 (dd, $J_{CF}$ = 244.7, 13.8 Hz), 145.8 (dd, $J_{CF}$ = 238.9, 14.0 Hz), 119.3 (d, $J_{CF}$ = 11.5 Hz), 113.7 (d, $J_{CF}$ = 18.2 Hz), 105.1 (dd, $J_{CF}$ = 6.6, 3.6 Hz), 67.3, 56.3, 22.7, 12.1, 11.1.



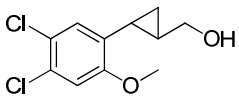

14c

**[2-(5-Chloro-4-fluoro-2-methoxyphenyl)cyclopropyl]methanol (14c).** Colorless oil. $^{1}$H NMR ($CDCl_3$) $\delta$ 6.93 (d, $J$ = 8.4 Hz, 1H), 6.66 (d, $J$ = 10.8 Hz, 1H), 3.86–3.82 (m, 4H), 3.31 (dd, $J$ = 11.2, 8.4 Hz, 1H), 1.88 (br, 1H), 1.84–1.79 (m, 1H), 1.20–1.16 (m, 1H), 1.03–0.98 (m, 1H), 0.90–0.85 (m, 1H).



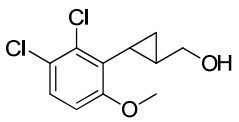

14d

**[2-(3-Chloro-2-fluoro-6-methoxyphenyl)cyclopropyl]methanol (14d).** Colorless oil. $^{1}$H NMR ($CDCl_3$) $\delta$ 7.18 (t, $J$ = 8.8 Hz, 1H), 6.58 (dd, $J$ = 8.8, 1.6 Hz, 1H), 3.90–3.84 (m, 4H), 3.31 (dd, $J$ = 10.8, 8.8 Hz, 1H), 1.94 (br, 1H), 1.63–1.58 (m, 1H), 1.44–1.39 (m, 1H), 1.28–1.23 (m, 1H), 0.96–0.90 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.5 (d, $J_{CF}$ = 6.9 Hz), 157.3 (d, $J_{CF}$ = 244.4 Hz), 127.7 (d, $J_{CF}$ = 1.4 Hz), 118.9 (d, $J_{CF}$ = 14.8 Hz), 113.5 (d, $J_{CF}$ = 19.5 Hz), 106.7 (d, $J_{CF}$ = 3.4 Hz), 67.3, 61.7, 56.2, 22.7 (d, $J_{CF}$ = 2.9 Hz), 12.2 (d, $J_{CF}$ = 2.7 Hz), 11.2 (d, $J_{CF}$ = 5.4 Hz).



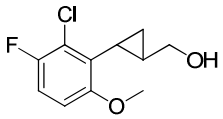

14e

**[2-(4,5-Dichloro-2-methoxyphenyl)cyclopropyl]methanol (14e).** Colorless oil. $^{1}$H NMR ($CDCl_3$) $\delta$ 6.96 (s, 1H), 6.89 (s, 1H), 3.86 (s, 3H), 3.83 (dd, $J$ = 11.2, 6.0 Hz, 1H), 3.31 (dd, $J$ = 11.2, 8.4 Hz, 1H), 1.93 (br, 1H), 1.87–1.82 (m, 1H), 1.25–1.20 (m, 1H), 1.05–1.00 (m, 1H), 0.92–0.87 (m, 1H).




14f

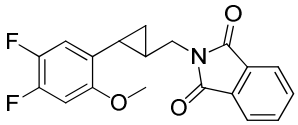
**[2-(2,3-Dichloro-6-methoxyphenyl)cyclopropyl]methanol (14f).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.29 (d, $J$ = 8.8 Hz, 1H), 6.72 (d, $J$ = 8.8 Hz, 1H), 3.87–3.82 (m, 4H), 3.46 (dd, $J$ = 10.8, 8.0 Hz, 1H), 2.10 (br, 1H), 1.61–1.55 (m, 1H), 1.44–1.39 (m, 1H), 1.10–1.01 (m, 2H).



**14g**

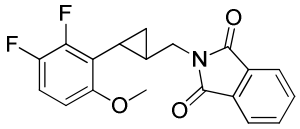
**[2-(2-Chloro-3-fluoro-6-methoxyphenyl)cyclopropyl]methanol (14g).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.98 (t, $J$ = 8.8 Hz, 1H), 6.70 (dd, $J$ = 9.2, 4.0 Hz, 1H), 3.87 (dd, $J$ = 10.8, 6.0 Hz, 1H), 3.43 (dd, $J$ = 10.8, 8.4 Hz, 1H), 1.96 (br, 1H), 1.60–1.56 (m, 1H), 1.44–1.42 (m, 1H), 1.15–1.10 (m, 1H), 1.05–1.01 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 155.5 (d, $J_{CF}$ = 2.1 Hz), 153.0 (d, $J_{CF}$ = 239.1 Hz), 129.0, 123.8 (d, $J_{CF}$ = 17.9 Hz), 113.8 (d, $J_{CF}$ = 22.7 Hz), 109.4 (d, $J_{CF}$ = 7.7 Hz), 67.1, 56.2, 23.4, 15.7, 12.8.

**General Method D.** To a solution of **14a**–**g** (1.0 eq), triphenylphosphine (1.5 eq) and phthalimide (1.5 eq) in anhydrous THF (0.1–0.2 mmol/mL for **14a**–**g**) cooled to 0 °C was slowly added diethyl azodicarboxylate (1.5 eq). The mixture was stirred at room temperature overnight. Concentration and flash chromatography provided compounds **15a**–**g** in good yields.



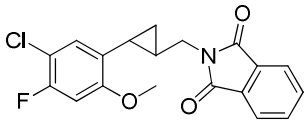
**15a**

**2-[[2-(4,5-Difluoro-2-methoxyphenyl)cyclopropyl]methyl]isoindoline-1,3-dione (15a).** Light yellow solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.88–7.83 (m, 2H), 7.74–7.71 (m, 2H), 6.65 (dd, $J$ = 11.2, 9.2 Hz, 1H), 6.52 (dd, $J$ = 12.0, 6.8 Hz, 1H), 3.78 (dd, $J$ = 14.0, 6.8 Hz, 1H), 3.63 (dd, $J$ = 10.8, 8.0 Hz, 1H), 3.47 (s, 3H), 2.10–2.14 (m, 1H), 1.39–1.35 (m, 1H), 1.02–0.92 (m, 2H).



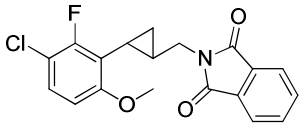
**15b**

**2-[[2-(2,3-Difluoro-6-methoxyphenyl)cyclopropyl]methyl]isoindoline-1,3-dione (15b).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.86–7.83 (m, 2H), 7.74–7.69 (m, 2H), 6.83 (q, $J$ = 9.2 Hz, 1H), 6.38–6.35 (m, 1H), 3.84 (dd, $J$ = 14.0, 6.8 Hz, 1H), 3.58 (dd, $J$ = 14.0, 8.4 Hz, 1H), 3.50 (s, 3H), 1.88–1.83 (m, 1H), 1.66–1.62 (m, 1H), 1.18–1.13 (m, 1H), 1.05–0.99 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.6 (2C), 155.2 (dd, $J_{CF}$ = 5.8, 1.8 Hz), 150.1 (dd, $J_{CF}$ = 244.5, 13.7 Hz), 145.5 (dd, $J_{CF}$ = 238.2, 14.0 Hz), 134.0 (2C), 132.4 (2C), 123.3 (2C), 119.1 (d, $J_{CF}$ = 11.3 Hz), 113.6 (d, $J_{CF}$ = 16.6 Hz), 105.0 (dd, $J_{CF}$ = 6.4, 3.5 Hz), 56.0, 42.4, 18.9, 12.8, 12.3.



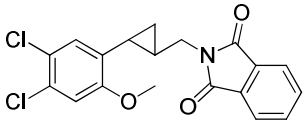

15c

**2-[[2-(5-Chloro-4-fluoro-2-methoxyphenyl)cyclopropyl]methyl]isoindoline-1,3-dione (15c).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.89–7.86 (m, 2H), 7.75–7.72 (m, 2H), 6.84 (d, $J$ = 8.4 Hz, 1H), 6.52 (d, $J$ = 11.2 Hz, 1H), 3.79 (dd, $J$ = 14.0, 6.8 Hz, 1H), 3.63 (dd, $J$ = 14.0, 8.0 Hz, 1H), 3.49 (s, 3H), 2.08–2.03 (m, 1H), 1.40–1.35 (m, 1H), 1.02–0.93 (m, 2H).



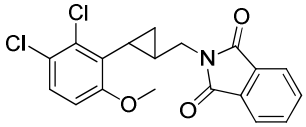

15d

**2-[[2-(3-Chloro-2-fluoro-6-methoxyphenyl)cyclopropyl]methyl]isoindoline-1,3-dione (15d).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.88–7.85 (m, 2H), 7.75–7.71 (m, 2H), 7.09 (t, $J$ = 8.8 Hz, 1H), 6.45 (d, $J$ = 8.8 Hz, 1H), 3.84 (dd, $J$ = 14.0, 6.0 Hz, 1H), 3.60 (dd, $J$ = 14.0, 8.4 Hz, 1H), 3.53 (s, 3H), 1.88–1.83 (m, 1H), 1.67–1.61 (m, 1H), 1.16–1.12 (m, 1H), 1.05–1.00 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.6 (2C), 158.6 (d, $J_{CF}$ = 6.8 Hz), 157.5 (d, $J_{CF}$ = 245.4 Hz), 134.1 (2C), 132.5 (2C), 127.6 (d, $J_{CF}$ = 1.4 Hz), 123.4 (2C), 118.8 (d, $J_{CF}$ = 14.7 Hz), 113.1 (d, $J_{CF}$ = 19.4 Hz), 106.7 (d, $J_{CF}$ = 3.4 Hz), 56.0, 42.3, 19.0, 13.0, 12.5.



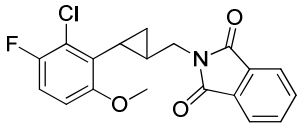

15e

**2-[[2-(4,5-Dichloro-2-methoxyphenyl)cyclopropyl]methyl]isoindoline-1,3-dione (15e).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.89–7.85 (m, 2H), 7.78–7.73 (m, 2H), 6.87 (s, 1H), 6.78 (s, 1H), 3.78 (dd, $J$ = 14.0, 6.8 Hz, 1H), 3.63 (dd, $J$ = 14.0, 8.0 Hz, 1H), 3.52 (s, 3H), 2.11–2.06 (m, 1H), 1.43–1.39 (m, 1H), 1.05–0.96 (m, 2H).




15f

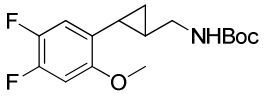
**2-[[2-(2,3-Dichloro-6-methoxyphenyl)cyclopropyl]methyl]isoindoline-1,3-dione (15f).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.90–7.85 (m, 2H), 7.75–7.71 (m, 2H), 7.22 (d, $J$ = 9.2 Hz, 1H), 6.60 (d, $J$ = 9.2 Hz, 1H), 3.89 (dd, $J$ = 14.0, 6.0 Hz, 1H), 3.67 (dd, $J$ = 14.0, 8.4 Hz, 1H), 3.55 (s, 3H), 1.84–1.81 (m, 1H), 1.65–1.60 (m, 1H), 1.17–1.13 (m, 1H), 0.97–0.93 (m, 1H).




15g

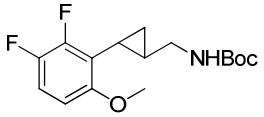
**2-[[2-(2-Chloro-3-fluoro-6-methoxyphenyl)cyclopropyl]methyl]isoindoline-1,3-dione (15g).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.89–7.85 (m, 2H), 7.75–7.71 (m, 2H), 6.91 (t, $J$ = 8.8 Hz, 1H), 6.58 (dd, $J$ = 9.0, 4.0 Hz, 1H), 3.89 (dd, $J$ = 14.0, 6.4 Hz, 1H), 3.66 (dd, $J$ = 14.0, 8.4 Hz), 3.54 (s, 3H), 1.86–1.80 (m, 1H), 1.67–1.64 (m, 1H), 1.16–1.10 (m, 1H), 1.04–0.98 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.7 (2C), 155.7, 153.0 (d, $J_{CF}$ = 238.8 Hz), 134.1 (2C), 132.5 (2C), 129.1, 124.1 (d, $J_{CF}$ = 17.8 Hz), 123.4 (2C), 113.7 (d, $J_{CF}$ = 22.7 Hz), 109.5 (d, $J_{CF}$ = 7.5 Hz), 56.1, 42.3, 20.0, 16.8, 14.0.

**General Method E.** To a solution of compounds **15a**−**g** (1.0 eq) in ethanol (~0.1 mol/L) was added hydrazine hydrate (3.0 eq), and the mixture was stirred at reflux for 3 h during which time a white solid formed. The mixture was then cooled to room temperature and concentrated. The residue was dissolved in 1N NaOH aqueous solution and extracted with dichloromethane. The combined extracts were washed with brine and dried over sodium sulfate. To this solution were added triethylamine (2.0 eq) and $Boc_2O$ (1.2 eq), and the mixture was stirred at room temperature for 30 min. The solution was then concentrated and the residue was purified by flash chromatography to provide **16a**−**g**.



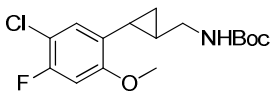
**16a**

***tert*-Butyl [[2-(4,5-Difluoro-2-methoxyphenyl)cyclopropyl]methyl]carbamate (16a).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 6.74 (dd, $J$ = 11.2, 9.2 Hz, 1H), 6.65 (dd, $J$ = 12.0, 6.8 Hz, 1H), 5.23 (br, 1H), 3.86 (s, 3H), 3.56–3.52 (m, 1H), 2.73–2.68 (m, 1H), 1.75–1.72 (m, 1H), 1.46 (s, 9H), 1.01–0.95 (m, 2H), 0.85–0.82 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.0, 154.5 (dd, $J_{CF}$ = 7.1, 2.0 Hz), 148.7 (dd, $J_{CF}$ = 243.9, 13.6 Hz), 144.4 (dd, $J_{CF}$ = 238.1, 12.4 Hz), 126.5 (d, $J_{CF}$ = 8.6 Hz), 115.5 (d, $J_{CF}$ = 18.7 Hz), 100.3 (d, $J_{CF}$ = 21.0 Hz), 79.2, 56.1, 45.2, 28.6 (3C), 21.5, 16.5, 11.3.



**16b**

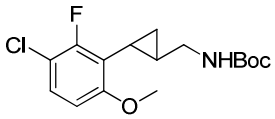
***tert*-Butyl [[2-(2,3-Difluoro-6-methoxyphenyl)cyclopropyl]methyl]carbamate (16b).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 6.93 (q, $J$ = 9.2 Hz, 1H), 6.52–6.48 (m, 1H), 5.28 (br, 1H), 3.85 (s, 3H), 3.59–3.54 (m, 1H), 2.74–2.68 (m, 1H), 1.53–1.50 (m, 1H), 1.45 (s, 9H), 1.23–1.18 (m, 2H), 0.91–0.86 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.0, 155.2 (d, $J_{CF}$ = 5.8 Hz), 150.2 (dd, $J_{CF}$ = 244.9, 13.8 Hz), 145.8 (dd, $J_{CF}$ = 224.7, 14.0 Hz), 119.2 (d, $J_{CF}$ = 11.4 Hz), 113.9 (d, $J_{CF}$ = 18.2 Hz), 104.9 (dd, $J_{CF}$ = 6.5, 3.5 Hz), 79.1, 56.0, 45.5, 28.6 (3C), 19.7, 12.4, 11.6.



**16c**

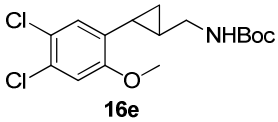
***tert*-Butyl [[2-(5-Chloro-4-fluoro-2-methoxyphenyl)cyclopropyl]methyl]carbamate (16c).** Light yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.91 (d, $J$ = 8.4 Hz, 1H), 6.64 (d, $J$ = 10.8 Hz, 1H), 5.19 (br, 1H), 3.87 (s, 3H), 3.54–3.50 (m, 1H), 2.74–2.69 (m, 1H), 1.74–1.69 (m, 1H), 1.45 (s, 9H), 1.01–

0.95 (m, 2H), 0.83–0.80 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.0 (d, $J_{CF}$ = 8.2 Hz), 157.0 (d, $J_{CF}$ = 244.7 Hz), 155.9, 128.2, 127.3 (d, $J_{CF}$ = 3.4 Hz), 111.3 (d, $J_{CF}$ = 17.6 Hz), 99.8 (d, $J_{CF}$ = 25.0 Hz), 79.1, 55.9, 45.1, 28.6 (3C), 21.1, 16.4, 11.1.



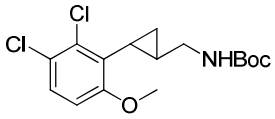

**16d**

***tert*-Butyl [[2-(3-Chloro-2-fluoro-6-methoxyphenyl)cyclopropyl]methyl]carbamate (16d).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.18 (t, $J$ = 8.8 Hz, 1H), 6.58 (dd, $J$ = 8.8, 1.6 Hz, 1H), 5.30 (br, 1H), 3.87 (s, 3H), 3.58–3.54 (m, 1H), 2.76–2.68 (m, 1H), 1.53–1.44 (m, 10H), 1.24–1.17 (m, 2H), 0.92–0.87 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.6 (d, $J_{CF}$ = 6.8 Hz), 157.5 (d, $J_{CF}$ = 245.4 Hz), 156.0, 127.8 (d, $J_{CF}$ = 3.4 Hz), 118.9 (d, $J_{CF}$ = 14.7 Hz), 113.4 (d, $J_{CF}$ = 19.5 Hz), 106.6 (d, $J_{CF}$ = 3.4 Hz), 79.1, 56.1, 45.5, 28.6 (3C), 19.8, 12.5, 11.8.



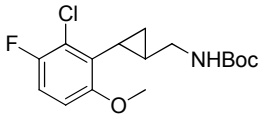

**16e**

***tert*-Butyl [[2-(4,5-Dichloro-2-methoxyphenyl)cyclopropyl]methyl]carbamate (16e).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 6.95 (s, 1H), 6.88 (s, 1H), 5.16 (br, 1H), 3.86 (s, 3H), 3.54–3.49 (m, 1H), 2.77–2.71 (m, 1H), 1.78–1.73 (m, 1H), 1.46 (s, 9H), 1.02–0.97 (m, 2H), 0.87–0.84 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.4, 155.9, 131.0, 130.1, 128.2, 123.7, 112.3, 79.1, 56.0, 45.0, 28.6 (3C), 21.6, 16.5, 11.5.




**16f**

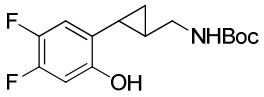
***tert*-Butyl [[2-(2,3-Dichloro-6-methoxyphenyl)cyclopropyl]methyl]carbamate (16f).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.28 (d, $J$ = 9.2 Hz, 1H), 6.71 (d, $J$ = 8.8 Hz, 1H), 5.20 (br, 1H), 3.85 (s, 3H), 3.52–3.47 (dd, $J$ = 12.0, 8.8 Hz, 1H), 2.90 (dd, $J$ = 12.0, 9.2 Hz, 1H), 1.55–1.45 (m, 10H), 1.27–1.21 (m, 1H), 1.02–0.95 (m, 2H).




**16g**

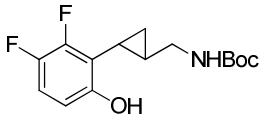
***tert*-Butyl [[2-(2-Chloro-3-fluoro-6-methoxyphenyl)cyclopropyl]methyl]carbamate (16g).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 6.98 (t, $J$ = 8.8 Hz, 1H), 6.69 (dd, $J$ = 9.0, 4.0 Hz, 1H), 5.22 (br, 1H), 3.85 (s, 3H), 3.53–3.48 (m, 1H), 2.91–2.85 (m, 1H), 1.53–1.49 (m, 1H), 1.47 (s, 3H), 1.27–1.24 (m, 1H), 1.06–0.97 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.1, 155.7, 153.2 (d, $J_{CF}$ = 239.0 Hz), 129.2, 124.2 (d, $J_{CF}$ = 17.8 Hz), 113.9 (d, $J_{CF}$ = 22.8 Hz), 109.3 (d, $J_{CF}$ = 7.5 Hz), 79.2, 56.2, 45.5, 28.7 (3C), 20.7, 16.3, 13.4.

**General Method F.** Compounds **16a**−**g** (1.0 eq) were dissolved in anhydrous DCM (0.1–0.2 mmol/mL) and the solution was cooled to −78 °C under argon. A solution of $BBr_3$ in DCM (3.0 eq) was added and the mixture was stirred at the same temperature for 2−3 h. Methanol was added cautiously to quench the reaction and the mixture was warmed to room temperature. The mixture was then concentrated. More methanol was added, and the solution was concentrated again. The residue was taken up in anhydrous DCM (0.1–0.2 mmol/mL) and cooled with ice bath. Triethylamine (10 eq) was added slowly to give a clear solution. $Boc_2O$ (1.2 eq) was added, and the mixture was stirred at room temperature for 30 min. The solution was concentrated, and the residue was purified by flash chromatography to give compounds **17a**−**g**.



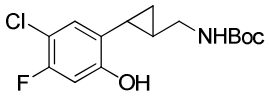
**17a**

***tert*-Butyl [[2-(4,5-Difluoro-2-hydroxyphenyl)cyclopropyl]methyl]carbamate (17a).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (br, 1H), 6.72–6.64 (m, 2H), 5.04 (br, 1H), 3.51–3.46 (m, 1H), 2.89–2.81 (m, 1H), 1.89–1.83 (m, 1H), 1.47 (s, 9H), 1.05–0.99 (m, 1H), 0.86–0.82 (m, 1H), 0.73–0.68 (m, 1H); $^{13}$C NMR ($CD_3OD$) $\delta$ 158.7, 153.5 (d, $J_{CF}$ = 7.2 Hz), 149.5 (dd, $J_{CF}$ = 241.4, 13.5 Hz), 145.0 (dd, $J_{CF}$ = 234.4, 12.5 Hz), 126.7, 115.5 (d, $J_{CF}$ = 18.5 Hz), 104.5 (d, $J_{CF}$ = 19.6 Hz), 80.2, 45.6, 28.9 (3C), 22.5, 17.2, 12.4.



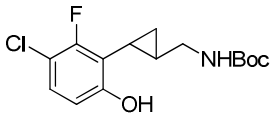
**17b**

***tert*-Butyl [[2-(2,3-Difluoro-6-hydroxyphenyl)cyclopropyl]methyl]carbamate (17b).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.00 (br, 1H), 6.88 (dd, $J$ = 18.8, 9.2 Hz, 1H), 6.58–6.54 (m, 1H), 5.04 (br, 1H), 3.60–3.55 (m, 1H), 2.92–2.88 (m, 1H), 1.62–1.58 (m, 1H), 1.47 (s, 9H), 1.18–1.14 (m, 2H), 0.92–0.88 (m, 1H); $^{13}$C NMR ($CD_3OD$) $\delta$ 158.7, 154.5 (d, $J_{CF}$ = 7.8 Hz), 151.4 (dd, $J_{CF}$ = 242.2, 13.8 Hz), 145.9 (dd, $J_{CF}$ = 235.0, 14.0 Hz), 119.0 (d, $J_{CF}$ = 11.5 Hz), 114.8 (d, $J_{CF}$ = 18.0 Hz), 110.5, 80.2, 45.8, 28.9 (3C), 20.7, 13.4, 12.1.



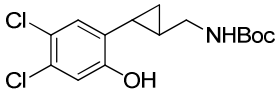
**17c**

***tert*-Butyl [[2-(5-Chloro-4-fluoro-2-hydroxyphenyl)cyclopropyl]methyl]carbamate (17c).** Light yellow solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.84 (br, 1H), 6.89 (d, $J$ = 8.0 Hz, 1H), 6.68 (d, $J$ = 10.4 Hz, 1H), 5.10 (br, 1H), 3.49–3.45 (m, 1H), 2.89–2.86 (m, 1H), 1.85–1.82 (m, 1H), 1.47 (s, 9H), 1.07–1.02 (m, 1H), 0.86–0.82 (m, 1H), 0.74–0.70 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.5, 157.4 (d, $J_{CF}$ = 243.0 Hz), 156.7 (d, $J_{CF}$ = 10.0 Hz), 128.6, 124.1, 110.5 (d, $J_{CF}$ = 16.7 Hz), 104.6 (d, $J_{CF}$ = 23.6 Hz), 81.0, 44.4, 28.6 (3C), 22.0, 18.1, 7.6.



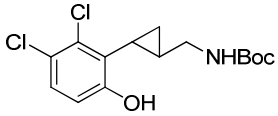

**17d**

***tert*-Butyl [[2-(3-Chloro-2-fluoro-6-hydroxyphenyl)cyclopropyl]methyl]carbamate (17d).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.39 (br, 1H), 7.07 (t, $J$ = 8.8 Hz, 1H), 6.62 (d, $J$ = 8.8 Hz), 5.12 (br, 1H), 3.89–3.54 (m, 1H), 2.93–2.88 (m, 1H), 1.62–1.56 (m, 1H), 1.47 (s, 9H), 1.15–1.12 (m, 2H), 0.92–0.86 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.8, 157.6 (d, $J_{CF}$ = 245.7 Hz), 156.5 (d, $J_{CF}$ = 5.5 Hz), 128.4, 116.4 (d, $J_{CF}$ = 14.6 Hz), 111.9, 111.8 (d, $J_{CF}$ = 19.1 Hz), 80.6, 44.3, 28.6 (3C), 20.0, 112.4, 10.7.



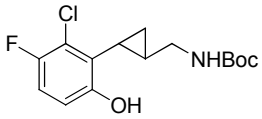

**17e**

***tert*-Butyl [[2-(4,5-Dichloro-2-hydroxyphenyl)cyclopropyl]methyl]carbamate (17e).** Light yellow solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.22 (s, 1H), 6.99 (s, 1H), 4.93 (br, 1H), 3.37–3.34 (m, 1H), 2.97–2.94 (m, 1H), 1.72–1.67 (m, 1H), 1.43 (s, 9H), 1.27–1.20 (m, 1H), 0.94–0.89 (m, 1H); $^{13}$C NMR ($CD_3OD$) $\delta$ 158.7, 156.9, 131.5, 130.2, 128.8, 123.1, 117.2, 80.2, 45.5, 28.9 (3C), 22.7, 17.2, 12.6.




**17f**

***tert*-Butyl [[2-(2,3-Dichloro-6-hydroxyphenyl)cyclopropyl]methyl]carbamate (17f).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 7.47 (br, 1H), 7.16 (d, $J$ = 8.8 Hz, 1H), 6.75 (d, $J$ = 8.8 Hz, 1H), 5.23 (br, 1H), 3.52–3.48 (m, 1H), 3.06–3.02 (m, 1H), 1.58–1.55 (m, 1H), 1.46 (s, 9H), 1.29–1.26 (m, 1H), 1.03–0.93 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.4, 155.9, 134.6, 128.8, 126.6, 123.9, 115.3, 80.4, 44.3, 28.6 (3C), 21.2, 16.5, 13.5.

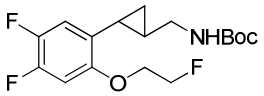



**17g**

***tert*-Butyl [[2-(2-Chloro-3-fluoro-6-hydroxyphenyl)cyclopropyl]methyl]carbamate (17g).** White solid. $^1$H NMR ($CDCl_3$) $\delta$ 6.91 (t, $J$ = 8.4 Hz, 1H), 6.73 (dd, $J$ = 8.8, 4.4 Hz, 1H), 5.12 (br, 1H), 3.53 (dd, $J$ = 14.0, 4.8 Hz, 1H), 3.02 (dd, $J$ = 14.0, 7.6 Hz, 1H), 1.61–1.55 (m, 1H), 1.46 (s, 9H), 1.25–1.20 (m, 1H), 1.03–0.96 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.4, 153.0 (d, $J_{CF}$ = 2.2 Hz), 152.7 (d, $J_{CF}$ = 237.8 Hz), 125.8, 123.1 (d, $J_{CF}$ = 18.4 Hz), 114.9 (d, $J_{CF}$ = 22.8 Hz), 114.4, 80.4, 44.3, 28.6 (3C), 20.8, 15.7, 12.9.

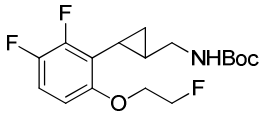
**General Method G.** A solution of compounds **17a**−**g** (1.0 eq), 2-fluoroethanol (2.0 eq) and triphenylphosphine (2.0 eq) in anhydrous THF (0.2−0.5 mmol/mL **17a**−**g**) was cooled to 0 °C. To this solution was slowly added diethyl azodicarboxylate (2.0 eq), and the solution was then

heated in a microwave reactor at 60 ºC for 45−60 min. The mixture was concentrated, and the residue was purified by flash chromatography to give compounds **18a**−**g**.



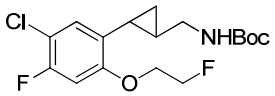

**18a**

***tert*-Butyl [[2-[4,5-Difluoro-2-(2-fluoroethoxy)phenyl]cyclopropyl]methyl]carbamate (18a).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.73 (dd, $J$ = 11.2, 8.8 Hz, 1H), 6.67 (dd, $J$ = 12.0, 6.4 Hz, 1H), 4.99 (br, 1H), 4.91–4.74 (m, 2H), 4.27–4.17 (m, 2H), 3.52–3.47 (m, 1H), 2.84–2.79 (m, 1H), 1.88–1.83 (m, 1H), 1.46 (s, 9H), 1.06–1.03 (m, 1H), 0.97–0.93 (m, 1H), 0.86–0.82 (m, 1H).



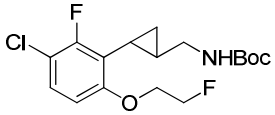

**18b**

***tert*-Butyl [[2-[2,3-Difluoro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methyl]carbamate (18b).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.89 (q, $J$ = 9.2 Hz, 1H), 6.50–6.47 (m, 1H), 5.03 (br, 1H), 4.84–4.82 (m, 1H), 4.72–4.70 (m, 1H), 4.23–4.13 (m, 2H), 3.43–3.39 (m, 1H), 2.91–2.84 (m, 1H), 1.62–1.57 (m, 1H), 1.43 (s, 9H), 1.37–1.31 (m, 1H), 1.19–1.13 (m, 1H), 0.88–0.83 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.0, 154.1 (dd, $J_{CF}$ = 5.7, 2.3 Hz), 150.3 (dd, $J_{CF}$ = 245.2, 13.7 Hz), 146.1 (dd, $J_{CF}$ = 239.7, 14.0 Hz), 120.3 (d, $J_{CF}$ = 11.3 Hz), 113.8 (dd, $J_{CF}$ = 18.3, 1.6 Hz), 106.7 (dd, $J_{CF}$ = 6.4, 3.6 Hz), 81.7 (d, $J_{CF}$ = 170.1 Hz), 79.1, 68.5 (d, $J_{CF}$ = 20.2 Hz), 45.3, 28.5 (3C), 19.7, 12.4, 11.7.



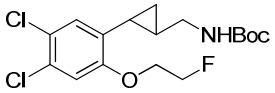

**18c**

***tert*-Butyl [[2-[5-Chloro-4-fluoro-2-(2-fluoroethoxy)phenyl]cyclopropyl]methyl]carbamate (18c).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.93 (d, $J$ = 8.4 Hz, 1H), 6.65 (d, $J$ = 10.8 Hz, 1H), 4.98 (br, 1H), 4.93–4.88 (m, 2H), 4.28–4.19 (m, 2H), 3.52–3.48 (m, 1H), 2.82–2.79 (m, 1H), 1.82–1.79 (m, 1H), 1.45 (s, 9H), 1.05–0.95 (m, 2H), 0.85–0.80 (m, 1H).



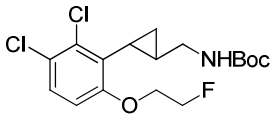

**18d**

***tert*-Butyl [[2-[3-Chloro-2-fluoro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methyl]carbamate (18d).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.14 (t, $J$ = 8.4 Hz, 1H), 6.53 (dd, $J$ = 8.8, 1.2 Hz, 1H), 5.01 (br, 1H), 4.84–4.82 (m, 1H), 4.72–4.70 (m, 1H), 4.25–4.15 (m, 2H), 3.43–3.39 (m, 1H), 2.92–2.85 (m, 1H), 1.60–1.55 (m, 1H), 1.43 (s, 9H), 1.35–1.29 (m, 1H), 1.15–1.10 (m, 1H), 0.87–0.83 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.6 (d, $J_{CF}$ = 245.7 Hz), 157.4 (d, $J_{CF}$ = 6.6 Hz), 156.0, 127.6, 119.6 (d, $J_{CF}$ = 14.7 Hz), 113.9 (d, $J_{CF}$ = 19.5 Hz), 107.9, 81.6 (d, $J_{CF}$ = 170.3 Hz), 79.1, 68.3 (d, $J_{CF}$ = 20.2 Hz), 45.3, 28.5 (3C), 19.7, 12.4, 11.8.



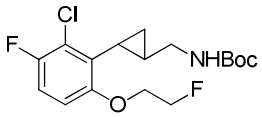

18e

***tert*-Butyl [[2-[4,5-Dichloro-2-(2-fluoroethoxy)phenyl]cyclopropyl]methyl]carbamate (18e).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.97 (s, 1H), 6.90 (s, 1H), 4.99 (br, 1H), 4.93–4.76 (m, 2H), 4.31–4.20 (m, 2H), 3.53–3.49 (m, 1H), 2.84–2.78 (m, 1H), 1.87–1.83 (m, 1H), 1.45 (s, 9H), 1.08–0.98 (m, 2H), 0.88–0.83 (m, 1H).




18f

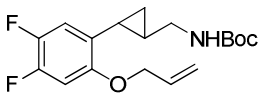
***tert*-Butyl [[2-[2,3-Dichloro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methyl]carbamate (18f).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.8 Hz, 1H), 6.67 (d, $J$ = 8.8 Hz, 1H), 4.99 (br, 1H), 4.86–4.84 (m, 1H), 4.74–4.72 (m, 1H), 4.23–4.14 (m, 2H), 3.33–3.29 (m, 1H), 3.14–3.07 (m, 1H), 1.58–1.53 (m, 1H), 1.44 (s, 9H), 1.39–1.33 (m, 1H), 0.98–0.92 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.1, 156.0, 135.7, 130.2, 128.3, 125.6, 111.2, 81.6 (d, $J_{CF}$ = 170.3 Hz), 79.1, 68.2 (d, $J_{CF}$ = 20.1 Hz), 45.1, 28.6 (3C), 21.2, 17.2, 14.0.




18g

***tert*-Butyl [[2-[2-Chloro-3-fluoro-6-(2-fluoroethoxy)phenyl]cyclopropyl]methyl]carbamate (18g).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.94 (t, $J$ = 8.8 Hz, 1H), 6.69–6.65 (m, 1H), 5.00 (br, 1H), 4.86–4.84 (m, 1H), 4.74–4.72 (m, 1H), 4.22–4.14 (m, 2H), 3.37–3.32 (m, 1H), 3.13–3.06 (m, 1H), 1.59–1.56 (m, 1H), 1.45 (s, 9H), 1.43–1.37 (m, 1H), 1.01–0.95 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.1, 154.4 (d, $J_{CF}$ = 2.2 Hz), 153.5 (d, $J_{CF}$ = 239.8 Hz), 130.0, 124.5 (d, $J_{CF}$ = 17.7 Hz), 113.9 (d, $J_{CF}$ = 22.8 Hz), 110.9, 81.8 (d, $J_{CF}$ = 170.2 Hz), 79.2, 68.5 (d, $J_{CF}$ = 20.0 Hz), 45.2, 28.6 (3C), 20.7, 16.3, 13.5.

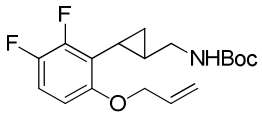
**General Method H.** To a solution of compounds **17a**−**g** (1.0 eq) in anhydrous DMF (0.2–0.5 mmol/mL) were added $Cs_2CO_3$ (2.0 eq) and allyl bromide (2.0 eq), and the mixture was heated in a microwave reactor at 80 ºC for 30−60min. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated. The crude product was purified by flash chromatography to give compounds **19a**−**g**.




19a

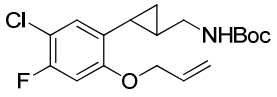
***tert*-Butyl [[2-[2-(Allyloxy)-4,5-difluorophenyl]cyclopropyl]methyl]carbamate (19a).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.72 (dd, $J$ = 11.2, 10.2 Hz, 1H), 6.65 (dd, $J$ = 12.0, 6.8 Hz,

1H), 6.16–6.06 (m, 1H), 5.42 (dd, $J$ = 17.2, 1.2 Hz, 1H), 5.34 (dd, $J$ = 10.8, 1.2 Hz, 1H), 5.03 (br, 1H), 4.61–4.51 (m, 2H), 3.53–3.49 (m, 1H), 2.81–2.75 (m, 1H), 1.85–1.80 (m, 1H), 1.46 (s, 9H), 1.01–0.93 (m, 2H), 0.85–0.80 (m, 1H).



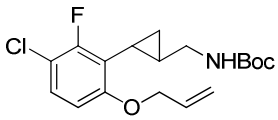

**19b**

***tert*-Butyl [[2-[6-(Allyloxy)-2,3-difluorophenyl]cyclopropyl]methyl]carbamate (19b).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.72 (q, $J$ = 9.2 Hz, 1H), 6.50–6.47 (m, 1H), 6.11–6.02 (m, 1H), 5.39 (dd, $J$ = 17.2, 1.2 Hz, 1H), 5.30 (d, $J$ = 10.4 Hz, 1H), 5.10 (br, 1H), 5.54 (d, $J$ = 4.4 Hz, 2H), 3.51–3.47 (m, 1H), 2.83–2.78 (m, 1H), 1.59–1.54 (m, 1H), 1.44 (s, 9H), 1.31–1.28 (m, 2H), 0.88–0.85 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.0, 154.2 (dd, $J_{CF}$ = 5.7, 2.0 Hz), 150.2 (dd, $J_{CF}$ = 244.9, 13.7 Hz), 145.7 (dd, $J_{CF}$ = 239.1, 14.0 Hz), 132.9, 119.7 (d, $J_{CF}$ = 11.2 Hz), 119.6, 113.7 (dd, $J_{CF}$ = 18.2, 1.6 Hz), 106.6 (dd, $J_{CF}$ = 6.4, 3.6 Hz), 79.1, 70.0, 45.5, 28.6 (3C), 19.6, 12.6, 11.7.



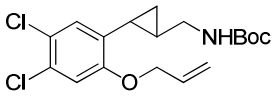

**19c**

***tert*-Butyl [[2-[2-(Allyloxy)-5-chloro-4-fluorophenyl]cyclopropyl]methyl]carbamate (19c).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.88 (d, $J$ = 8.4 Hz, 1H), 6.62 (d, $J$ = 10.8 Hz, 1H), 6.13–6.06 (m, 1H), 5.41 (d, $J$ = 17.2 Hz, 1H), 5.32 (d, $J$ = 10.8 Hz, 1H), 5.08 (br, 1H), 4.59–4.52 (m, 2H), 3.47 (dd, $J$ = 13.2, 8.0 Hz, 1H), 2.76 (dd, $J$ = 13.2, 8.0 Hz, 1H), 1.79–1.74 (m, 1H), 1.43 (s, 9H), 1.01–0.94 (m, 2H), 0.82–0.78 (m, 1H).




**19d**

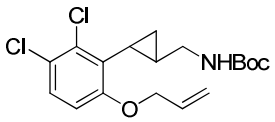
***tert*-Butyl [[2-[6-(Allyloxy)-3-chloro-2-fluorophenyl]cyclopropyl]methyl]carbamate (19d).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.08 (t, $J$ = 8.4 Hz, 1H), 6.52 (dd, $J$ = 8.8, 1.2 Hz, 1H), 6.08–6.02 (m, 1H), 5.37 (dd, $J$ = 17.2, 1.6 Hz, 1H), 5.29 (dd, $J$ = 10.8, 1.6 Hz, 1H), 5.10 (br, 1H), 4.53 (d, $J$ = 5.2 Hz, 2H), 3.48–3.44 (m, 1H), 2.81–2.77 (m, 1H), 1.55–1.51 (m, 1H), 1.42 (s, 9H), 1.27–1.22 (m, 1H), 1.14–1.11 (m, 1H), 0.86–0.83 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.5 (d, $J_{CF}$ = 245.5 Hz), 157.4 (d, $J_{CF}$ = 6.6 Hz), 155.9, 132.6, 127.5, 119.1 (d, $J_{CF}$ = 14.5 Hz), 118.7, 113.3 (d, $J_{CF}$ = 19.4 Hz), 107.9, 79.0, 69.8, 45.4, 28.5 (3C), 19.6, 12.6, 11.7.




**19e**

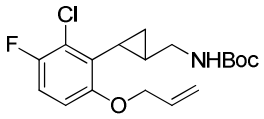
***tert*-Butyl [[2-[2-(Allyloxy)-4,5-dichlorophenyl]cyclopropyl]methyl]carbamate (19e).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.96 (s, 1H), 6.90 (s, 1H), 6.16–6.09 (m, 1H), 5.44 (d, $J$ = 17.2

Hz, 1H), 5.36 (d, $J$ = 10.4 Hz, 1H), 5.02 (br, 1H), 4.64–4.56 (m, 2H), 3.52–3.49 (m, 1H), 2.83–2.76 (m, 1H), 1.86–1.80 (m, 1H), 1.46 (s, 9H), 1.08–0.98 (m, 2H), 0.88–0.83 (m, 1H).




**19f**

***tert*-Butyl [[2-[6-(allyloxy)-2,3-dichlorophenyl]cyclopropyl]methyl]carbamate (19f).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.22 (d, $J$ = 8.8 Hz, 1H), 6.68 (d, $J$ = 8.8 Hz, 1H), 6.12–6.03 (m, 1H), 5.40 (d, $J$ = 17.2 Hz, 1H), 5.32 (dd, $J$ = 10.4 Hz, 1H), 5.06 (br, 1H), 4.53 (d, $J$ = 5.2 Hz, 2H), 3.42–3.39 (m, 1H), 3.02–2.98 (m, 1H), 1.55–1.53 (m, 1H), 1.45 (s, 9H), 1.33–1.28 (m, 1H), 0.98–0.94 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.2, 156.0, 135.5, 132.7, 129.8, 128.3, 125.1, 119.0, 111.4, 79.1, 69.9, 45.4, 28.6 (3C), 21.0, 17.3, 14.0.




**19g**

***tert*-Butyl [[2-[6-(Allyloxy)-2-chloro-3-fluorophenyl]cyclopropyl]methyl]carbamate (19g).** Colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.94 (t, $J$ = 8.8 Hz, 1H), 6.68 (dd, $J$ = 9.2, 4.4 Hz, 1H), 6.14–6.04 (m, 1H), 5.41 (dd, $J$ = 17.2, 1.2 Hz, 1H), 5.33 (dd, $J$ = 10.4, 1.2 Hz, 1H), 5.07 (br, 1H), 4.54 (d, $J$ = 5.6 Hz, 2H), 3.45–3.41 (m, 1H), 3.02–2.98 (m, 1H), 1.59–1.54 (m, 1H), 1.46 (s, 9H), 1.37–1.31 (m, 1H), 1.06–0.96 (m, 2H).

**2. Off-target screening data of compound (+)-22a.**

**Table S1.** Percent displacement of the radioligand by compound (+)-**22a** at 10 μM.[a]

| Family | Target | Inhibition at 10 μM (%) |
|---|---|---|
| **Serotonin Receptors** | 5-$HT_{1A}$ | 55.5 |
| | 5-$HT_{1B}$ | 19.6 |
| | 5-$HT_{1D}$ | 31.6 |
| | 5-$HT_{1E}$ | -9.6 |
| | 5-$HT_{2A}$ | 69.5 |
| | 5-$HT_{2B}$ | 96.5 |
| | 5-$HT_{2C}$ | 97.2 |
| | 5-$HT_3$ | 37.9 |
| | 5-$HT_{5A}$ | 24.7 |
| | 5-$HT_6$ | 92.7 |
| | 5-$HT_7$ | 61.4 |
| **Dopamine Receptors** | $D_1$ | 28.6 |
| | $D_2$ | 60.7 |
| | $D_3$ | 88.7 |

| | | |
|---|---|---|
| | $D_4$ | 72.7 |
| | $D_5$ | 19.3 |
| **Adrenergic Receptors** | $\alpha_{1A}$ | 46.2 |
| | $\alpha_{1B}$ | 18.9 |
| | $\alpha_{1D}$ | 23.4 |
| | $\alpha_{2A}$ | 85.3 |
| | $\alpha_{2B}$ | 63.3 |
| | $\alpha_{2C}$ | 89 |
| | $\beta_1$ | 32.3 |
| | $\beta_2$ | 72.1 |
| | $\beta_3$ | 3.6 |
| **Monoamine Transporters** | SERT | 67.1 |
| | DAT | 27.7 |
| | NET | -0.2 |
| **Benzodiazepine (BZP) Receptor** | Rat brain binding site | 45.4 |
| | Peripheral-type | -3.1 |
| **GABA Receptor** | $GABA_A$ | 24.8 |
| **Histamine Receptors** | $H_1$ | 32.2 |
| | $H_2$ | 55.2 |
| | $H_3$ | 15.4 |
| | $H_4$ | -5.7 |
| **Opioid receptors** | δ | 40.7 |
| | κ | 18.2 |
| | μ | 3.1 |
| **Muscarinic Acetylcholine Receptor** | $M_1$ | 18.5 |
| | $M_2$ | 16.5 |
| | $M_3$ | 36.6 |
| | $M_4$ | 41.5 |
| | $M_5$ | 59.9 |
| **Sigma Receptors** | $\sigma_1$ | 47.2 |
| | $\sigma_2$ | 50.3 |

[a] Binding profile of compound (+)-**22a** was tested by the National Institute of Mental Health's Psychoactive Drug Screening Program (NIMH PDSP), Contract # HHSN-271-2013-00017-C. The NIMH PDSP is directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda MD, USA. Each value represents the average of at least two experiments ($n \geq 2$). For experimental details please refer to the PDSP web site http://pdspdb.unc.edu/pdspWeb/.