

Supporting Information

Optimization of 2-Phenylcyclopropylmethylamines as Selective Serotonin 2C Agonists and Their Evaluation as Potential Antipsychotic Agents

Jianjun Cheng,[†] Patrick M. Giguère,[‡] Oluseye K. Onajole,[†] Wei Lv,[†] Arsen Gaisin,[†] Hendra Gunosewoyo,[†] Claire M. Schmerberg,[§] Vladimir M. Pogorelov,[§] Ramona M. Rodriguez,[§] Giulio Vistoli,[‡] William C. Wetsel,[⊥] Bryan L. Roth,[‡] and Alan P. Kozikowski^{*,†}

[†]Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, Chicago, IL 60612, United States

[‡]National Institute of Mental Health Psychoactive Drug Screening Program, Department of Pharmacology and Division of Chemical Biology and Medicinal Chemistry, University of North Carolina Chapel Hill Medical School, Chapel Hill, NC 27599, United States

[§]Department of Psychiatry and Behavioral Sciences, Mouse Behavioral and Neuroendocrine Analysis Core Facility, Duke University Medical Center, Durham, NC 27710, United States

[‡]Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, Via Mangiagalli 25, 20133 Milano, Italy

[⊥]Departments of Psychiatry and Behavioral Sciences, Cell Biology, and Neurobiology, Mouse Behavioral and Neuroendocrine Analysis Core Facility, Duke University Medical Center, Durham, NC 27710, United States

^{*}Corresponding Author. Phone: +1 312 996-7577. E-mail: kozikowa@uic.edu.

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
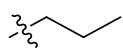
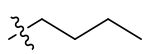

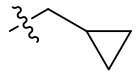
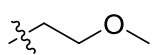
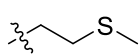
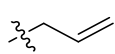
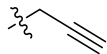
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1. Synthetic Procedures and Compounds Characterization Data

General. All chemicals and solvents were purchased from Sigma-Aldrich or Fisher Scientific, and used as obtained without further purification. Microwave reactions were run in Biotage Initiator microwave synthesizer. Synthetic intermediates were purified by CombiFlash flash chromatography on 230 – 400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-400 or AVANCE-400 spectrometer, at 400 MHz and 100 MHz respectively. NMR chemical shifts were reported in δ (ppm) using residual solvent peaks as standard (CDCl_3 – 7.26 ppm; CD_3OD – 3.31 ppm; DMSO-d_6 – 2.50 ppm). Mass spectra were measured in the ESI mode at an ionization potential of 70 eV with an LC-MS MSD (Hewlett-Packard). Purity of all final compounds (greater than 95%) was determined by analytical HPLC (ACE 3AQ C_{18} column (150 \times 4.6 mm, particle size 3 μM), 0.05% TFA in H_2O /0.05% TFA in MeOH gradient eluting system). Optical rotation values were recorded on Autopol IV automatic polarimeter.

General Method A: Preparation of *N*-Boc-amines 12a-12n and 15a-15d. Intermediate **11** and **14** was treated with the Williamson ether synthesis or Mitsunobu reaction conditions as described in Scheme 1 and Scheme 2. The reactions was monitored with TLC and the work-up was done with ethyl acetate and water. Crude product was purified with flash chromatography.

Table S1. Reaction conditions for the preparation of intermediates **12a-12n**.

Intermediate	R ¹	Condition	Yield
12a		EtI, K_2CO_3 (2.0 eq), DMF, microwave 110 $^\circ\text{C}$, 30 min	73%
12b		1-iodopropane (1.2 eq), Cs_2CO_3 (1.5 eq) in DMF, microwave 115 $^\circ\text{C}$, 45 min	80%
12c		2-iodobutane (6.0 eq), K_2CO_3 (6.0 eq) DMF (0.5 mL), microwave 100 $^\circ\text{C}$, 1 h	87%
12d		2-iodopropane (4.0 eq), K_2CO_3 (4.0 eq) DMF (0.5 mL), microwave 100 $^\circ\text{C}$, 1 h	79%
12e		(bromomethyl)cyclopropane (4.4 eq), K_2CO_3 (2 eq), DMF, microwave 110 $^\circ\text{C}$, 2.5 h	57%
12f		2-bromoethyl methyl ether (6.0 eq), K_2CO_3 (6.0 eq) DMF (0.5 mL), microwave 100 $^\circ\text{C}$, 1 h	81%
12g		2-Chloroethyl methyl sulfide (2.0 eq), K_2CO_3 (2.0 eq), DMF, microwave 90 $^\circ\text{C}$, 2 h	63%
12h		allyl bromide (6.0 eq), K_2CO_3 (6.0 eq), DMF (0.5 mL), microwave 60 $^\circ\text{C}$, 1.5 h, 88%	88%
12i		propargyl bromide (6.0 eq), K_2CO_3 (6.0 eq) DMF	88%

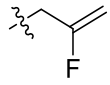
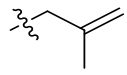
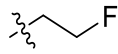
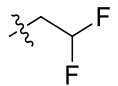
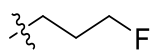
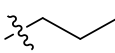
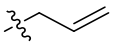
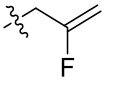
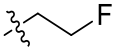
		(0.5 mL), microwave 60 °C, 1.5 h	
12j		3-chloro-2-fluoropropene (1.3 eq), Cs ₂ CO ₃ (1.2 eq) in DMF, microwave 115 °C, 45 min	97%
12k		3-bromo-2-methylpropene (4.8 eq), K ₂ CO ₃ (2.2 eq), DMF, microwave 110 °C, 2 h	68%
12l		2-fluoroethanol (2.5 eq), Ph ₃ P (2.5 eq), diethyl azodicarboxylate (2.5 eq), THF, microwave 60 °C, 45 min	81%
12m		1,1-difluoro-2-iodoethane (1.2 eq), Cs ₂ CO ₃ (1.5 eq) in DMF, microwave 115 °C, 45 min	65%
12n		3-fluoro-1-propanol (2.0 eq), <i>n</i> -Bu ₃ P (2.0 eq), 1,1'-(azodicarbonyl)-dipiperidine, THF, microwave 60 °C, 1 h	81%

Table S2. Reaction conditions for the preparation of intermediates **15a-15d**.

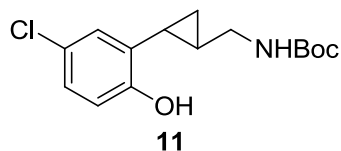
Intermediate	R ¹	Condition	Yield
15a		1-iodopropane (2.0 eq), Cs ₂ CO ₃ (1.5 eq) in DMF, microwave 100 °C, 45 min	83%
15b		allyl bromide (6.0 eq), K ₂ CO ₃ (6.0 eq) DMF (0.5 mL), microwave 60 °C, 1.5 h	78%
15c		3-chloro-2-fluoropropene (1.3 eq), Cs ₂ CO ₃ (1.2 eq) in DMF, microwave 115 °C, 45 min	98%
15d		2-fluoroethanol (2.5 eq), Ph ₃ P (2.5 eq), diethyl azodicarboxylate (2.5 eq), THF, microwave 60 °C, 45 min	98%

General Method B: Chiral Separation of *N*-Boc-amines **12a-12n and **15a-15d**.** The racemic intermediates were separated by chiral HPLC. Analytical conditions: RegisCell chiral column (25 cm × 4.6 mm, 10 μM), 1.5% – 15% EtOH in *n*-hexane as the fluent phase; preparative conditions: RegisPack chiral column (25 cm × 21.1 mm, 10 μM), 3% - 7.5% EtOH in *n*-hexane as the eluting system (isocratic eluent, stacked injections, flow rate = 18 mL/min, λ = 254 and 280 nm). (+)-**12a-12n** and (+)-**15a-15d** were isolated as the first-eluting peaks, with (-)-**12a-12n** and (-)-**15a-15d** as the second-eluting peaks, both after evaporation appeared as colorless oil or white solids. Optical purity of both enantiomers were determined on analysis HPLC after the

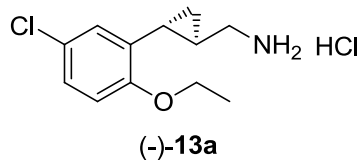
separation, and a second separation was done when necessary to guarantee > 90% *ee* optical purity.

General Method C: Deprotection of *N*-Boc-Amines to Afford HCl Salts (13a, 13b, 13e-13g, 13i-13n and 16a-16d). *N*-Boc-Amines was dissolved in 2M HCl (g) in diethyl ether (10 mL/mmol substrate) and stirred at room temperature for 24-48 h. The white solids formed were collected by filtration, washed with diethyl ether and dried over vacuum to give the HCl salts as white solids.

General Method D: Deprotection of *N*-Boc-Amines to Afford TFA Salts (13c, 13d and 13h). To a solution of the *N*-Boc protected precursor (1 mmol) in CH₂Cl₂ (10 mL) was added TFA (1 mL) at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated, and the residue was dissolved in water and methanol (ratio 4:1). The solution was filtered, and then purified by Shidmadzu preparative LC using the following conditions: ACE 5AQ Column (150 x 21.2 mm, particle size 5 μM); Method: 8-100% 0.05% TFA in MeOH/0.05% TFA in H₂O, 30 min; Flow rate = 17 mL/min with monitoring at 254 and 280 nm wavelengths. After the solvent was evaporated, the residue was dissolved in distilled water (2 - 3 mL) and lyophilized to obtain the TFA salt.

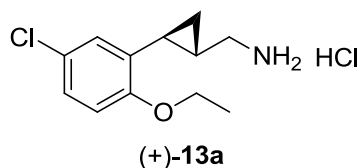


tert-Butyl ((2-(5-Chloro-2-hydroxyphenyl)cyclopropyl)methyl)carbamate (11). This compound was prepared according to the method described previously for *tert*-butyl ((2-(5-chloro-2-hydroxyphenyl)cyclopropyl)methyl) carbamate.¹ ¹H NMR (400 MHz, CDCl₃) δ 7.05 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.94 (d, *J* = 1.6 Hz, 1H), 6.81 (d, *J* = 8.4 Hz), 5.04 (br, 1H), 3.54 – 3.48 (m, 1H), 2.92 – 2.85 (m, 1H), 1.91 – 1.88 (m, 1H), 1.49 (s, 9H), 1.13 – 1.06 (m, 1H), 0.92 – 0.88 (m, 1H), 0.78 – 0.71 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 158.2, 155.4, 128.7, 127.5, 127.1, 124.4, 117.0, 80.8, 44.5, 28.6, 22.1, 18.3, 7.9.

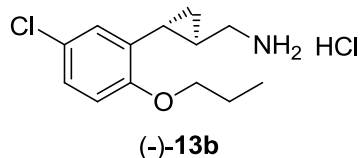


(-)-((1R, 2R)-2-(5-Chloro-2-ethoxyphenyl)cyclopropyl)methanamine Hydrochloride ((-)-13a). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.4%; ¹H NMR (400 MHz, CD₃OD) δ 7.13 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 4.13-4.06 (m, 2H), 3.06 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.99 (dd, *J* = 13.2, 5.6 Hz, 1H), 2.15 – 2.11 (m, 1H), 1.45 (t, *J* = 7.2 Hz, 3H), 1.35 – 1.32 (m, 1H), 1.13 – 1.08 (m, 1H), 1.06 – 1.02 (m, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 157.9, 132.7, 128.1, 127.5, 126.5, 113.8, 65.4, 45.1, 19.4, 18.2, 15.3, 13.6; HRMS calculated for C₁₂H₁₇ClNO ([M+H]⁺): 226.0999, found: 227.1001; [α]_D²⁰ -47.2 (*c* 0.5, MeOH).

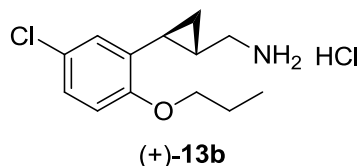
¹ Chen, G.; Cho, S. J.; Huang, X. P.; Jensen, N. H.; Svennebring, A.; Sassano, M. F.; Roth, B. L.; Kozikowski, A. P., Rational Drug Design Leading to the Identification of a Potent 5-HT(2C) Agonist Lacking 5-HT(2B) Activity. *ACS Med. Chem. Lett.* **2011**, 2 (12), 929-932.



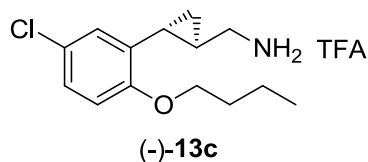
(+)-((1*S*, 2*S*)-2-(5-Chloro-2-ethoxyphenyl)cyclopropyl)methanamine Hydrochloride ((+)-13a). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.3%; ^1H NMR (400 MHz, CD_3OD) δ 7.14 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.95 (d, $J = 2.8$ Hz, 1H), 6.90 (d, $J = 8.8$ Hz, 1H), 4.13 – 4.06 (m, 2H), 3.06 (dd, $J = 12.8, 7.2$ Hz, 1H), 2.98 (dd, $J = 12.8, 8.0$ Hz, 1H), 2.15 – 2.11 (m, 1H), 1.45 (t, $J = 6.8$ Hz, 3H), 1.35 – 1.31 (m, 1H), 1.13 – 1.08 (m, 1H), 1.06 – 1.02 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.9, 132.7, 128.1, 127.5, 126.5, 113.8, 65.4, 45.1, 19.4, 18.2, 15.3, 13.6; HRMS calculated for $\text{C}_{12}\text{H}_{17}\text{ClNO}$ ($[\text{M}+\text{H}]^+$): 226.0999, found: 227.1003; $[\alpha]_{\text{D}}^{20} +39.4$ (c 0.5, MeOH).



(-)-((1*R*, 2*R*)-2-(5-Chloro-2-propoxyphenyl)cyclopropyl)methanamine Hydrochloride ((-)-13b). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.1%; ^1H NMR (CD_3OD , 360 MHz) δ 7.11 (dd, $J = 8.7, 2.6$ Hz, 1H), 6.94 (d, $J = 2.6$ Hz, 1H), 6.87 (d, $J = 8.7$ Hz, 1H), 3.96 (m, 1H), 3.12 (dd, $J = 13.1, 6.8$ Hz, 1H), 2.89 (dd, $J = 13.1, 8.2$ Hz, 1H), 2.14 – 2.09 (m, 1H), 1.89 – 1.82 (m, 2H), 1.37 – 1.32 (m, 1H), 1.10 – 1.01 (m, 5H); ^{13}C NMR (CD_3OD , 100 MHz) δ 156.7, 131.5, 126.8, 126.1, 125.2, 112.5, 70.1, 43.8, 22.5, 18.0, 17.0, 12.5, 9.8; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{19}\text{ClNO}$ ($[\text{M}+\text{H}]^+$): 240.1155, found: 240.1163; $[\alpha]_{\text{D}}^{20} -46.9$ (c 0.3, CD_3OD).

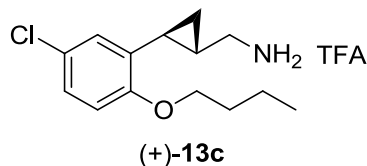


(+)-((1*S*, 2*S*)-2-(5-Chloro-2-propoxyphenyl)cyclopropyl)methanamine Hydrochloride ((+)-13b). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.3%; ^1H NMR (CD_3OD , 400 MHz) δ 7.13 (dd, $J = 8.7, 2.6$ Hz, 1H), 6.95 (d, $J = 2.6$ Hz, 1H), 6.89 (d, $J = 8.7$ Hz, 1H), 3.98 (m, 1H), 3.14 (dd, $J = 13.1, 6.8$ Hz, 1H), 2.91 (dd, $J = 13.1, 8.2$ Hz, 1H), 2.15 – 2.11 (m, 1H), 1.87 – 1.83 (m, 2H), 1.38 – 1.34 (m, 1H), 1.11 – 1.02 (m, 5H); HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{19}\text{ClNO}$ ($[\text{M}+\text{H}]^+$): 240.1155, found: 240.1220; $[\alpha]_{\text{D}}^{20} +43.4$ (c 0.2, CD_3OD).

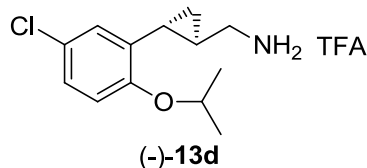


(-)-((1*R*, 2*R*)-2-(2-Butoxy-5-chlorophenyl)cyclopropyl)methanamine Trifluoroacetate ((-)-13c). This compound was prepared obtained with intermediate **11** employing General Method A,

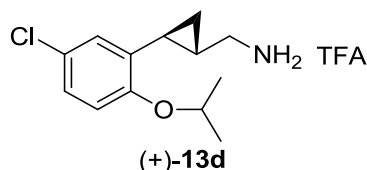
B and D. HPLC purity: 99.8% (10.8 min); ^1H NMR (CD_3OD , 400 MHz) δ 7.14 (dd, J = 2.4, 8.8 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 4.01 (m, 2H), 3.13 (dd, J = 13.2, 7.2 Hz, 1H), 2.90 (dd, J = 13.2, 7.2 Hz, 1H), 2.12 (m, 1H), 1.81 (m, 2H), 1.56 (m, 2H), 1.35 (m, 1H), 1.09 – 0.99 (m, 5H); ^{13}C NMR (CD_3OD , 100 MHz) δ 158.0, 132.7, 128.1, 127.4, 126.5, 113.8, 69.5, 45.1, 32.6, 20.5, 19.3, 18.3, 14.3, 13.7; HRMS (ESI) calculated for $\text{C}_{14}\text{H}_{21}\text{ClNO}$ ($[\text{M}+\text{H}]^+$): 254.1312, found: 254.1306; $[\alpha]_{\text{D}}^{20}$ -30.4 (c 0.12, CH_3OH).



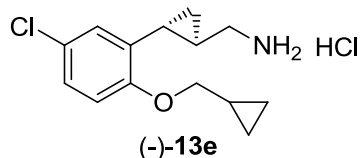
(+)-((1S, 1S)-2-(2-Butoxy-5-chlorophenyl)cyclopropyl)methanamine Trifluoroacetate ((+)-13c). This compound was obtained with intermediate **11** employing General Method A, B and D. HPLC purity: 99.8% (11.0 min); ^1H NMR (CD_3OD , 400 MHz) δ 7.14 (dd, J = 8.8, 2.4 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 4.01 (m, 2H), 3.13 (dd, J = 12.8, 6.8 Hz, 1H), 2.90 (dd, J = 12.8, 8.4 Hz, 1H), 2.12 (m, 1H), 1.81 (m, 2H), 1.54 (m, 2H), 1.33 (m, 1H), 1.08 – 0.99 (m, 5H); ^{13}C NMR (CD_3OD , 100 MHz) δ 158.0, 132.7, 128.1, 127.4, 126.5, 113.8, 69.5, 45.1, 32.6, 20.5, 19.3, 18.3, 14.3, 13.7; HRMS (ESI) calculated for $\text{C}_{14}\text{H}_{21}\text{ClNO}$ ($[\text{M}+\text{H}]^+$): 254.1312, found: 254.1317; $[\alpha]_{\text{D}}^{20}$ +32.0 (c 0.14, CH_3OH).



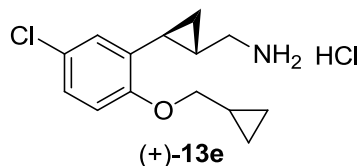
(-)-((1R, 2R)-2-(5-Chloro-2-isopropoxyphenyl)cyclopropyl)methanamine Trifluoroacetate ((-)-13d). This compound was obtained with intermediate **11** employing General Method A, B and D. HPLC purity: 99.6 % (9.4 min); ^1H NMR (CD_3OD , 400 MHz) δ 7.13 (dd, J = 8.8, 2.4 Hz, 1H), 6.93 (m, 2H), 4.63 (m, 1H), 3.14 (dd, J = 13.2, 6.8 Hz, 1H), 2.89 (dd, J = 12.8, 8.4 Hz, 1H), 2.10 (m, 1H), 1.38 – 1.33 (m, 7H), 1.08 – 1.01 (m, 2H); ^{13}C NMR (CD_3OD , 100 MHz) δ 156.7, 133.7, 128.0, 127.5, 126.5, 115.8, 72.1, 45.1, 22.6, 22.4, 19.5, 18.4, 13.8; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{19}\text{ClNO}$ ($[\text{M}+\text{H}]^+$): 240.1155, found: 240.1155; $[\alpha]_{\text{D}}^{20}$ -45.9 (c 0.17, CH_3OH).



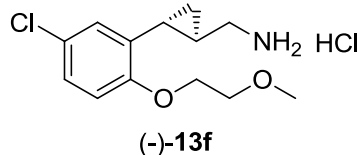
(+)-((1S, 2S)-2-(5-Chloro-2-isopropoxyphenyl)cyclopropyl)methanamine Trifluoroacetate ((+)-13d). This compound was obtained with intermediate **11** employing General Method A, B and D. HPLC purity: 98.5% (9.9 min); ^1H NMR (CD_3OD , 400 MHz) δ 7.12 (dd, J = 8.8, 2.4 Hz, 1H), 6.93 – 6.90 (m, 2H), 4.65 – 4.59 (m, 1H), 3.15 (dd, J = 13.2, 6.4 Hz, 1H), 2.89 (dd, J = 13.2, 8.0 Hz, 1H), 2.13 – 2.08 (m, 1H), 1.37 – 1.33 (m, 7H), 1.09 – 1.00 (m, 2H); ^{13}C NMR (CD_3OD , 100 MHz) δ 156.7, 133.7, 128.0, 127.5, 126.5, 115.8, 72.1, 45.1, 22.6, 22.4, 19.5, 18.4, 13.8; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{19}\text{ClNO}$ ($[\text{M}+\text{H}]^+$): 240.1155, found: 240.1156; $[\alpha]_{\text{D}}^{20}$ +44.7 (c 0.17, CH_3OH).



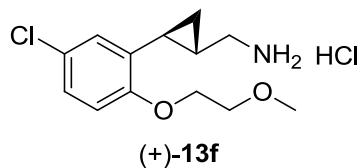
(-)-((1R, 2R)-2-(5-Chloro-2-(cyclopropylmethoxy)phenyl)cyclopropyl)methanamine Hydrochloride ((-)-13e). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 98.9%; ^1H NMR (CD_3OD , 400 MHz) δ 7.02 (dd, $J = 2.6, 8.7$ Hz, 1H), 6.84 (d, $J = 2.6$ Hz, 1H), 6.75 (d, $J = 8.7$ Hz, 1H), 3.79 (m, 1H), 3.71 (m, 1H), 2.91 (d, $J = 7.5$ Hz, 2H), 2.02 (m, 1H), 1.18 (m, 1H), 1.03 (m, 1H), 0.91 (m, 1H), 0.53 (m, 2H), 0.28 (m, 2H); ^{13}C NMR (CD_3OD , 100 MHz) δ 156.0, 130.6, 126.2, 125.7, 124.5, 112.0, 72.7, 43.2, 17.6, 16.3, 11.2, 9.3, 2.00, 1.6; HRMS (ESI) calculated for $\text{C}_{14}\text{H}_{19}\text{ClNO}$ ($[\text{M}+\text{H}]^+$): 252.1155, found: 252.1162; $[\alpha]_{\text{D}}^{20}$ -65.6 (c 0.1, CD_3OD).



(+)-((1S, 2S)-2-(5-Chloro-2-(cyclopropylmethoxy)phenyl)cyclopropyl)methanamine Hydrochloride ((+)-13e). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.2%; ^1H NMR (CD_3OD , 400 MHz) δ 7.15 (dd, $J = 2.6, 8.7$ Hz, 1H), 6.98 (d, $J = 2.6$ Hz, 1H), 6.88 (d, $J = 8.7$ Hz, 1H), 3.93 (m, 1H), 3.84 (m, 1H), 3.04 (d, $J = 7.5$ Hz, 2H), 2.13 (m, 1H), 1.31 (m, 1H), 1.16 (m, 1H), 1.05 (m, 1H), 0.66 (m, 2H), 0.41 (m, 2H); HRMS (ESI) calculated for $\text{C}_{14}\text{H}_{19}\text{ClNO}$ ($[\text{M}+\text{H}]^+$): 252.1155, found: 252.1165; $[\alpha]_{\text{D}}^{20}$ +62.7 (c 0.1, CD_3OD).

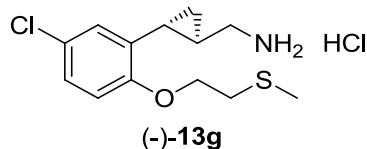


(-)-((1R, 2R)-2-(5-Chloro-2-(2-methoxyethoxy)phenyl)cyclopropyl)methanamine Hydrochloride ((-)-13f). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.2% (8.4 min); ^1H NMR (CD_3OD , 400 MHz) δ 7.26 (dd, $J = 2.6, 8.8$ Hz, 1H), 7.06 (d, $J = 2.5$ Hz, 1H), 7.01 (d, $J = 8.8$ Hz, 1H), 4.27 – 4.22 (m, 2H), 3.91 – 3.85 (m, 2H), 3.46 (s, 3H), 3.23 (dd, $J = 6.8, 13.1$ Hz, 1H), 2.98 (dd, $J = 8.2, 13.0$ Hz, 1H), 2.13 (m, 1H), 1.30 (m, 1H), 1.20 (m, 1H), 1.06 (m, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ 156.0, 132.1, 127.3, 126.6, 126.0, 114.1, 70.9, 68.1, 58.4, 44.0, 18.7, 16.6, 12.2; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{19}\text{ClNO}_2$ ($[\text{M}+\text{H}]^+$): 256.1104, found: 256.1095; $[\alpha]_{\text{D}}^{20}$ -18.2 (c 0.23, CD_3OD).



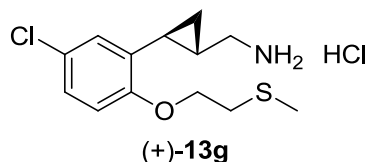
(+)-((1S, 2S)-[2-(5-Chloro-2-(2-methoxyethoxy)phenyl)cyclopropyl]methanamine

Hydrochloride ((+)-13f). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.6% (8.3 min); ^1H NMR (CD_3OD , 400 MHz) δ 7.25 (dd, $J = 2.6, 8.7$ Hz, 1H), 7.04 (d, $J = 2.4$ Hz, 1H), 6.99 (d, $J = 8.8$ Hz, 1H), 4.24 – 4.20 (m, 2H), 3.90 – 3.84 (m, 2H), 3.46 (s, 3H), 3.21 (dd, $J = 13.1, 6.8$ Hz, 1H), 2.98 (dd, $J = 13.0, 8.1$ Hz, 1H), 2.12 (m, 1H), 1.28 (m, 1H), 1.18 (m, 1H), 1.06 (m, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ 156.0, 132.1, 127.3, 126.6, 126.0, 114.1, 70.9, 68.1, 58.4, 44.0, 18.7, 16.6, 12.2; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{19}\text{ClNO}_2$ ($[\text{M}+\text{H}]^+$): 256.1104, found: 256.1101; $[\alpha]_{\text{D}}^{20} +11.7$ (c 0.35, CD_3OD).



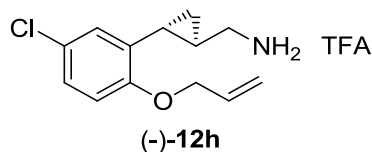
(-)-((1R, 2R)-2-(5-Chloro-2-(2-(methylthio)ethoxy)phenyl)cyclopropyl)methanamine

Hydrochloride ((-)-13g). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.4%; ^1H NMR (400 MHz, CD_3OD) δ 7.16 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.97 (d, $J = 2.4$ Hz, 1H), 6.94 (d, $J = 8.8$ Hz, 1H), 4.25 – 4.20 (m, 2H), 3.14 (dd, $J = 12.8, 7.2$ Hz, 2H), 2.98 – 2.92 (m, 3H), 2.20 (s, 3H), 2.17 – 2.11 (m, 1H), 1.33 – 1.28 (m, 1H), 1.18 – 1.12 (m, 1H), 1.07 – 1.02 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.6, 132.9, 128.2, 127.6, 127.0, 114.2, 68.9, 45.2, 34.4, 19.7, 18.3, 16.0, 13.3; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{19}\text{ClNOS}$ ($[\text{M}+\text{H}]^+$): 272.0876, found: 272.0874; $[\alpha]_{\text{D}}^{20} -41.6$ (c 0.4, MeOH).



(+)-((1S, 2S)-2-(5-Chloro-2-(2-(methylthio)ethoxy)phenyl)cyclopropyl)methanamine

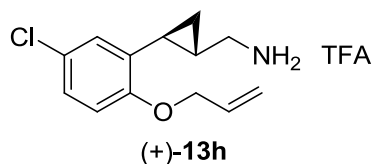
Hydrochloride ((+)-13g). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.5%; ^1H NMR (400 MHz, CD_3OD) δ 7.16 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.96 (d, $J = 2.8$ Hz, 1H), 6.94 (d, $J = 8.8$ Hz, 1H), 4.25 – 4.20 (m, 2H), 3.14 (dd, $J = 12.8, 7.2$ Hz, 2H), 2.98 – 2.92 (m, 3H), 2.20 (s, 3H), 2.17 – 2.11 (m, 1H), 1.33 – 1.27 (m, 1H), 1.18 – 1.12 (m, 1H), 1.07 – 1.03 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.6, 132.9, 128.2, 127.6, 127.0, 114.2, 68.9, 45.2, 34.4, 19.7, 18.3, 16.0, 13.3; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{19}\text{ClNOS}$ ($[\text{M}+\text{H}]^+$): 272.0876, found: 272.0870; $[\alpha]_{\text{D}}^{20} +44.9$ (c 0.4, MeOH).



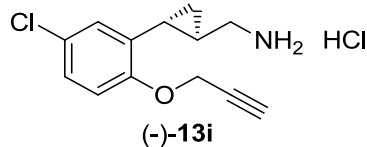
(-)-((1R, 2R)-[2-(2-(Allyloxy)-5-chlorophenyl)cyclopropyl]methanamine Trifluoroacetate ((-)-13h).

This compound was obtained with intermediate **11** employing General Method A, B and D as a colorless oil. HPLC purity: 99.8 % (9.6 min); ^1H NMR (CD_3OD , 400 MHz) δ 7.16 (dd, $J = 2.0, 8.8$ Hz, 1H), 6.97 (s, 1H), 6.94 (d, $J = 8.8$ Hz, 1H), 6.12 (m, 1H), 5.47 (d, $J = 17.2$ Hz, 1H), 5.33 (d, $J = 10.8$ Hz, 1H), 4.62 (d, $J = 5.2$ Hz, 2H), 3.03 (m, 2H), 2.15 (m, 1H), 1.32 (m, 1H), 1.12 – 1.02 (m, 2H); ^{13}C NMR (CD_3OD , 100 MHz) δ 157.5, 134.8, 132.8, 128.1, 127.6, 126.8, 118.4, 114.3, 70.6, 45.1, 19.4, 18.3, 13.5; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{ClNO}$ ($[\text{M}+\text{H}]^+$):

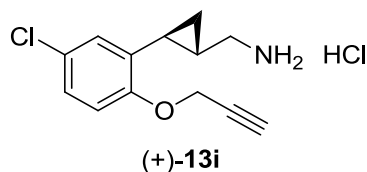
238.0999, found: 238.0994; $[\alpha]_D^{20}$ -54.2 (*c* 0.27, CH₃OH).



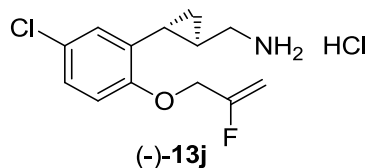
(+)-((1*S*, 2*S*)-2-(2-(Allyloxy)-5-chlorophenyl)cyclopropyl)methanamine Trifluoroacetate ((+)-13h**).** This compound was obtained with intermediate **11** employing General Method A, B and D as a colorless oil. HPLC purity: 99.6 % (9.7 min); ¹H NMR (CD₃OD, 400 MHz) δ 7.15 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.97 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.12 (m, 1H), 5.47 (d, *J* = 17.2 Hz, 1H), 5.33 (d, *J* = 10.4 Hz, 1H), 4.62 (d, *J* = 4.8 Hz, 2H), 3.03 (m, 2H), 2.15 (m, 1H), 1.33 (m, 1H), 1.14 – 1.01 (m, 2H); ¹³C NMR (CD₃OD, 100 MHz) δ 157.5, 134.8, 132.8, 128.1, 127.6, 126.8, 118.4, 114.3, 70.6, 45.1, 19.4, 18.3, 13.5; HRMS (ESI) calcd for C₁₃H₁₇ClNO ([M+H]⁺): 238.0999, found: 238.0999; $[\alpha]_D^{20}$ -54.2 (*c* 0.27, CH₃OH).



(-)-((1*R*, 2*R*)-2-(5-Chloro-2-(prop-2-yn-1-yloxy)phenyl)cyclopropyl)methanamine Hydrochloride ((-)-13i**).** This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.3 % (7.7 min); ¹H NMR (CD₃OD, 400 MHz) δ 7.16 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.03 – 6.99 (m, 2H), 4.82 (s, 2H), 3.09 – 3.05 (m, 2H), 2.99 (dd, *J* = 12.8, 8.0 Hz, 1H), 2.13 – 2.08 (m, 1H), 1.30 – 1.27 (m, 1H), 1.15 – 1.13 (m, 1H), 1.05 – 1.02 (m, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ 156.7, 133.1, 128.2, 128.0, 127.5, 114.6, 79.6, 77.6, 57.5, 45.1, 19.6, 18.1, 13.3; HRMS (ESI) calcd for C₁₃H₁₅NOCl ([M+H]⁺): 236.0842, found: 236.0842; $[\alpha]_D^{20}$ -32.7 (*c* 0.16, CH₃OH).

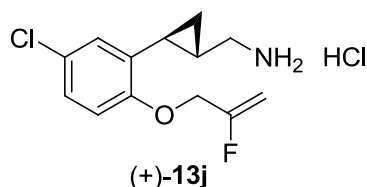


(+)-((1*S*, 2*S*)-2-(5-Chloro-2-(prop-2-yn-1-yloxy)phenyl)cyclopropyl)methanamine Hydrochloride ((+)-13i**).** This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 97.9 % (8.0 min); ¹H NMR (CD₃OD, 400 MHz) δ 7.16 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.03 – 6.99 (m, 2H), 4.81 (s, 2H), 3.09 – 3.04 (m, 2H), 2.99 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.13 – 2.08 (m, 1H), 1.31 – 1.27 (m, 1H), 1.16 – 1.12 (m, 1H), 1.06 – 1.02 (m, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ 156.7, 133.1, 128.2, 128.0, 127.5, 114.6, 79.6, 77.6, 57.5, 45.1, 19.6, 18.1, 13.3; HRMS (ESI) calcd for C₁₃H₁₅NOCl ([M+H]⁺): 236.0842, found: 236.0840; $[\alpha]_D^{20}$ +47.3 (*c* 0.22, CH₃OH).



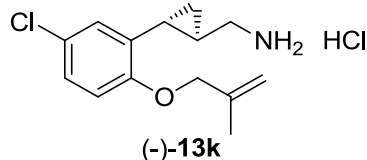
(-)-((1*R*, 2*R*)-2-(5-Chloro-2-((2-fluoroallyl)oxy)phenyl)cyclopropyl)methanamine

Hydrochloride ((-)-13j). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.3%; ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.06 (br, 3H), 7.20 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 2.8 Hz, 1H), 4.96 (dd, *J* = 10.4, 3.2 Hz, 1H), 4.88 (dd, *J* = 23.2, 3.2 Hz, 1H), 4.72 (d, *J* = 14.0 Hz, 2H), 2.92 – 2.81 (m, 2H), 2.08 – 2.04 (m, 1H), 1.43 – 1.38 (m, 1H), 1.02 – 0.93 (m, 2H); HRMS (ESI) calculated for C₁₃H₁₆ClFNO ([M+H]⁺): 256.0904, found: 256.0914; [α]_D²⁰ -40.7 (*c* 0.15, CD₃OD).



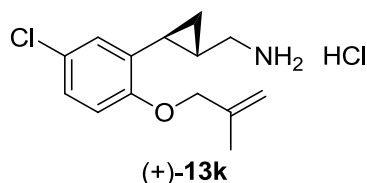
(+)-((1*S*, 2*S*)-2-(5-Chloro-2-((2-fluoroallyl)oxy)phenyl)cyclopropyl)methanamine

Hydrochloride ((+)-13j). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.4%; ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.06 (br, 3H), 7.20 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 2.8 Hz, 1H), 4.96 (dd, *J* = 10.4, 3.2 Hz, 1H), 4.88 (dd, *J* = 23.2, 3.2 Hz, 1H), 4.72 (d, *J* = 14.0 Hz, 2H), 2.92 – 2.81 (m, 2H), 2.08 – 2.04 (m, 1H), 1.43 – 1.38 (m, 1H), 1.02 – 0.93 (m, 2H); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 160.7 (d, *J*_{CF} = 255.7 Hz), 155.1, 132.4, 126.5, 126.2, 125.1, 114.1, 94.8 (d, *J*_{CF} = 15.4 Hz), 65.7 (d, *J*_{CF} = 32.3 Hz), 42.6, 17.8, 16.6, 13.4; HRMS (ESI) calculated for C₁₃H₁₆ClFNO ([M+H]⁺): 256.0904, found: 256.0906; [α]_D²⁰ +43.0 (*c* 0.2, CD₃OD).



(-)-((1*R*, 2*R*)-2-(5-Chloro-2-((2-methylallyl)oxy)phenyl)cyclopropyl)methanamine

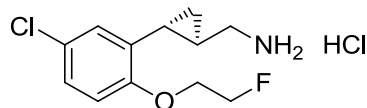
Hydrochloride ((-)-13k). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.1%; ¹H NMR (CD₃OD, 360 MHz) δ : 7.11 (dd, *J* = 2.6, 8.7 Hz, 1H), 6.94 (d, *J* = 2.6 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 1H), 5.08 (s, 1H), 4.98 (s, 1H), 4.49 (s, 2H), 3.08 (dd, *J* = 13.0, 8.2 Hz, 1H), 2.28 (dd, *J* = 13.0, 6.8 Hz, 1H), 2.16 – 2.12 (m, 1H), 1.83 (s, 3H), 1.70 (d, *J* = 3.4 Hz, 1H), 1.36 – 1.33 (m, 1H), 1.09 – 1.02 (m, 1H); HRMS (ESI) calculated for C₁₄H₁₉ClNO ([M+H]⁺): 252.1155, found: 252.1162; [α]_D²⁰ -45.2 (*c* 0.21, CD₃OD).



(+)-((1*S*, 2*S*)-2-(5-Chloro-2-((2-methylallyl)oxy)phenyl)cyclopropyl)methanamine

Hydrochloride ((+)-13k). This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 98.2%; ¹H NMR (CD₃OD, 360 MHz) δ 7.09 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.96 (d, *J* = 2.6 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 5.07 (s, 1H), 4.97 (s,

1H), 4.48 (s, 2H), 3.07 (dd, $J = 13.0, 8.2$ Hz, 1H), 2.87 (dd, $J = 13.0, 6.8$ Hz, 1H), 2.16 – 2.11 (m, 1H), 1.82 (s, 3H), 1.68 (d, $J = 3.4$ Hz, 1H), 1.36 – 1.32 (m, 1H), 1.08 – 1.00 (m, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ 156.3, 141.3, 131.6, 127.0, 126.8, 126.5, 126.1, 125.5, 113.1, 113.0, 112.0, 77.2, 72.0, 43.8, 28.7, 28.6, 18.5, 18.0, 17.3, 17.1, 12.4, 12.2; HRMS (ESI) calculated for $\text{C}_{14}\text{H}_{19}\text{ClNO}$ ($[\text{M}+\text{H}]^+$): 252.1155, found: 252.1167; $[\alpha]_{\text{D}}^{20} +43.6$ (c 0.3, CD_3OD).



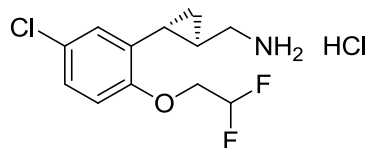
(-)-13l

(-)-((1R, 2R)-2-(5-Chloro-2-(2-fluoroethoxy)phenyl)cyclopropyl)methanamine Hydrochloride ((-)-13l).

This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 98.1%; ^1H NMR (400 MHz, D_2O) δ 7.10 (dd, $J = 9.7, 2.6$ Hz, 1H), 6.91 (d, $J = 2.4$ Hz, 1H), 6.84 (d, $J = 9.7$ Hz), 4.84 – 4.81 (m, 1H), 4.68 – 4.66 (m, 1H), 4.26 – 4.15 (m, 2H), 3.04 (dd, $J = 14.5, 7.8$ Hz, 1H), 2.92 (dd, $J = 14.4, 5.3$ Hz, 1H), 2.01 – 1.98 (m, 1H), 1.18 – 1.15 (m, 1H), 1.09 – 1.04 (m, 1H), 0.96 – 0.91 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 155.8, 132.0, 127.3, 126.8, 126.2, 114.1, 83.3 (d, $J_{\text{CF}} = 180.8$ Hz), 68.6 (d, $J_{\text{CF}} = 19.8$ Hz), 43.9, 18.7, 16.6, 12.2; HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{16}\text{ClFNO}$ ($[\text{M}+\text{H}]^+$): 244.0904, found: 244.0907; $[\alpha]_{\text{D}}^{20} -32.5$ (c 0.1, MeOH).

(+)-((1S, 2S)-2-(5-Chloro-2-(2-fluoroethoxy)phenyl)cyclopropyl)methanamine Hydrochloride ((+)-13l).

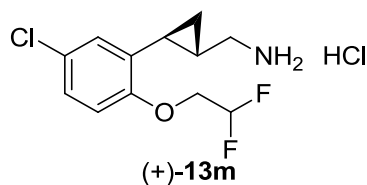
This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 97.6%; ^1H NMR (400 MHz, CD_3OD) δ 7.18 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.01 (d, $J = 2.4$ Hz, 1H), 6.95 (d, $J = 8.8$ Hz), 4.80 – 4.74 (m, 2H), 4.34 – 4.27 (m, 2H), 3.05 – 3.00 (m, 2H), 2.15 – 2.11 (m, 1H), 1.27 – 1.17 (m, 2H), 1.06 – 1.02 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 155.8, 132.0, 127.3, 126.8, 126.2, 114.1, 83.2 (d, $J_{\text{CF}} = 180.8$ Hz), 68.6 (d, $J_{\text{CF}} = 19.7$ Hz), 43.9, 18.7, 16.5, 12.1; HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{16}\text{ClFNO}$ ($[\text{M}+\text{H}]^+$): 244.0904, found: 244.0908; $[\alpha]_{\text{D}}^{20} +37.8$ (c 0.5, MeOH).



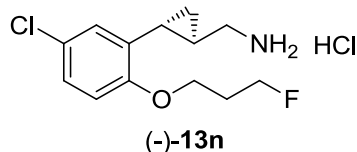
(-)-13m

(-)-((1R, 2R)-2-(5-Chloro-2-(2,2-difluoroethoxy)phenyl)cyclopropyl)methanamine Hydrochloride ((-)-13m).

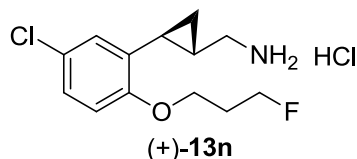
This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 98.9%; ^1H NMR (CD_3OD , 360 MHz) δ 7.15 (dd, $J = 8.7, 2.6$ Hz, 1H), 6.98 (d, $J = 2.6$ Hz, 1H), 6.93 (d, $J = 8.7$ Hz, 1H), 6.24 (tt, $J = 54.8, 3.6$ Hz, 1H), 4.27 (dt, $J = 14.2, 3.6$ Hz, 2H), 3.09 (dd, $J = 13.1, 6.9$ Hz, 1H), 2.90 (dd, $J = 13.1, 6.9$ Hz, 1H), 2.12 – 2.09 (m, 1H), 1.32 – 1.28 (m, 1H), 1.13 – 1.09 (m, 1H), 1.05 – 1.01 (m, 1H); ^{13}C NMR (CD_3OD , 90 MHz) δ 155.8, 131.9, 127.1, 126.7, 126.6, 114.3 (t, $J_{\text{CF}} = 238.0$ Hz), 113.2, 67.7 (t, $J_{\text{CF}} = 27.3$ Hz), 43.7, 18.3, 16.9, 12.1; HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{15}\text{ClF}_2\text{NO}$ ($[\text{M}+\text{H}]^+$): 262.0810, found: 262.0830; $[\alpha]_{\text{D}}^{20} -34.2$ (c 0.2, CD_3OD).



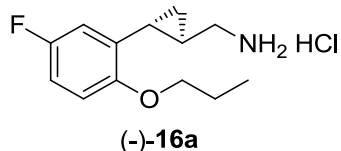
(+)-((1*S*, 2*S*)-2-(5-Chloro-2-(2, 2-difluoroethoxy)phenyl)cyclopropyl)methanamine Hydrochloride ((+)-13m**).** This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.2%; ¹H NMR (CD₃OD, 400 MHz) δ 7.18 (dd, J = 2.6, 8.7 Hz, 1H), 7.02 (d, J = 2.6 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 6.27 (tt, J = 54.8, 3.6 Hz, 1H), 4.30 (dt, J = 14.2, 3.6 Hz, 2H), 3.12 (dd, J = 13.1, 6.9 Hz, 1H), 2.93 (dd, J = 13.1, 6.9 Hz, 1H), 2.17 – 2.11 (m, 1H), 1.34 – 1.32 (m, 1H), 1.18 – 1.13 (m, 1H), 1.08 – 1.03 (m, 1H); HRMS (ESI) calculated for C₁₂H₁₅ClF₂NO ([M+H]⁺): 262.0810, found: 262.0816; [α]_D²⁰ +32.0 (c 0.25, CD₃OD).



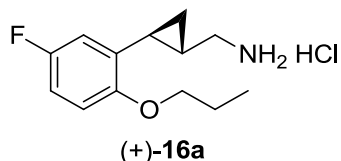
(-)-((1*R*, 2*R*)-2-(5-Chloro-2-(3-fluoropropoxy)phenyl)cyclopropyl)methanamine Hydrochloride ((-)-13n**).** This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.2%; ¹H NMR (400 MHz, D₂O) δ 7.25 (dd, J = 8.8, 2.4 Hz, 1H), 7.04 – 7.01 (m, 2H), 4.78 – 4.76 (m, 1H), 4.69 (t, J = 5.6 Hz, 1H), 4.27 – 4.21 (m, 2H), 3.17 (dd, J = 13.2, 7.2 Hz, 1H), 3.03 (dd, J = 13.2, 8.0 Hz, 1H), 2.30 – 2.15 (m, 3H), 1.42 – 1.38 (m, 1H), 1.14 – 1.05 (m, 2H); ¹³C NMR (100 MHz, D₂O) δ 155.5, 131.8, 126.9, 125.9, 125.6, 114.0, 82.3 (J_{CF} = 157.8 Hz), 65.6 (J_{CF} = 4.6 Hz), 43.6, 29.5 (d, J_{CF} = 19.2 Hz), 18.1, 16.2, 12.5; HRMS (ESI) calculated for C₁₃H₁₈ClFNO ([M+H]⁺): 258.1061, found: 258.1056; [α]_D²⁰ -51.4 (c 0.15, MeOH).



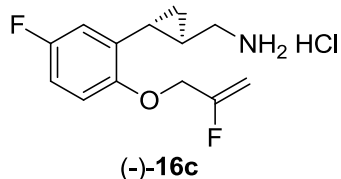
(+)-((1*S*, 2*S*)-2-(5-Chloro-2-(3-fluoropropoxy)phenyl)cyclopropyl)methanamine Hydrochloride ((+)-13n**).** This compound was obtained with intermediate **11** employing General Method A, B and C as a white solid. HPLC purity: 99.4%; ¹H NMR (400 MHz, CD₃OD) δ 7.15 (dd, J = 9.7, 2.9 Hz, 1H), 6.96 (d, J = 2.8 Hz, 1H), 6.90 (d, J = 9.8 Hz), 4.78 – 4.76 (m, 1H), 4.64 (t, J = 6.4 Hz, 1H), 4.18 – 4.11 (m, 2H), 3.15 (dd, J = 13.2, 7.2 Hz, 1H), 2.98 (dd, J = 13.2, 8.0 Hz, 1H), 2.26 – 2.04 (m, 3H), 1.36 – 1.31 (m, 1H), 1.08 – 1.01 (m, 2H); ¹³C NMR (D₂O, 100 MHz) δ 155.9, 132.0, 127.2, 126.2, 125.9, 114.2, 82.7 (J_{CF} = 175.4 Hz), 65.8 (d, J_{CF} = 5.5 Hz), 43.9, 29.9 (d, J_{CF} = 21.7 Hz), 18.4, 16.6, 12.8; HRMS (ESI) calculated for C₁₃H₁₈ClFNO ([M+H]⁺): 258.1061, found: 258.1064; [α]_D²⁰ +44.2 (c 0.15, MeOH).



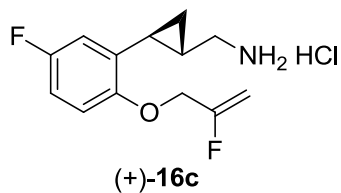
(-)-((1R, 2R)-2-(5-Fluoro-2-propoxyphenyl)cyclopropyl)methanamine Hydrochloride ((-)-16a). This compound was obtained with intermediate **14** employing General Method A, B and C as a white solid. HPLC purity: 99.5% (11.2 min); ^1H NMR (400 MHz, CD_3OD) δ 6.92 – 6.83 (m, 2H), 6.71 (dd, $J = 9.6, 2.8$ Hz, 1H), 4.02 – 3.92 (m, 2H), 3.13 (dd, $J = 13.2, 6.8$ Hz, 1H), 2.90 (dd, $J = 13.2, 8.0$ Hz, 1H), 2.20 – 2.15 (m, 1H), 1.90 – 1.81 (m, 2H), 1.37 – 1.32 (m, 1H), 1.11 – 1.01 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.6 (d, $J_{\text{CF}} = 235.0$ Hz), 155.4, 132.8 (d, $J_{\text{CF}} = 7.3$ Hz), 114.0 (d, $J_{\text{CF}} = 24.0$ Hz), 113.9 (d, $J_{\text{CF}} = 22.6$ Hz), 113.6 (d, $J_{\text{CF}} = 8.3$ Hz), 71.7, 45.1, 23.9, 19.6, 18.3, 13.9, 11.1; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{19}\text{FNO}$ ($[\text{M}+\text{H}]^+$): 224.1451, found: 224.1428; $[\alpha]_{\text{D}}^{20} -19.2$ (c 0.3, MeOH).



(+)-((1S, 2S)-2-(5-Fluoro-2-propoxyphenyl)cyclopropyl)methanamine Hydrochloride ((+)-16a). This compound was obtained with intermediate **14** employing General Method A, B and C as a white solid. HPLC purity: 99.4% (11.3 min); ^1H NMR (400 MHz, CD_3OD) δ 6.92 – 6.84 (m, 2H), 6.72 (dd, $J = 9.6, 2.8$ Hz, 1H), 4.02 – 3.93 (m, 2H), 3.14 (dd, $J = 13.2, 6.8$ Hz, 1H), 2.91 (dd, $J = 13.2, 8.0$ Hz, 1H), 2.21 – 2.15 (m, 1H), 1.91 – 1.81 (m, 2H), 1.38 – 1.33 (m, 1H), 1.12 – 1.02 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.6 (d, $J_{\text{CF}} = 235.2$ Hz), 155.4, 132.8 (d, $J_{\text{CF}} = 6.8$ Hz), 114.0 (d, $J_{\text{CF}} = 24.0$ Hz), 113.9 (d, $J_{\text{CF}} = 23.2$ Hz), 113.8 (d, $J_{\text{CF}} = 8.3$ Hz), 71.7, 45.1, 23.9, 19.6, 18.4, 13.9, 11.1; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{19}\text{FNO}$ ($[\text{M}+\text{H}]^+$): 224.1451, found: 224.1428; $[\alpha]_{\text{D}}^{20} +22.5$ (c 0.5, MeOH).



(-)-((1R, 2R)-2-(5-Fluoro-2-((2-fluoroallyl)oxy)phenyl)cyclopropyl)methanamine Hydrochloride ((-)-16c). This compound was obtained with intermediate **14** employing General Method A, B and C as a white solid. HPLC purity: 99.4% (9.6 min); ^1H NMR (400 MHz, CD_3OD) δ 6.98 (dd, $J = 8.8, 4.4$ Hz, 1H), 6.90 (dt, $J = 8.0, 2.8$ Hz, 1H), 6.76 (dd, $J = 9.2, 2.8$ Hz, 1H), 4.88 (dd, $J = 14.0, 3.2$ Hz, 1H), 4.80 (dd, $J = 41.6, 2.8$ Hz, 1H), 4.66 (d, $J = 14.0$ Hz, 2H), 3.11 (dd, $J = 13.2, 7.2$ Hz, 1H), 2.95 (dd, $J = 13.2, 8.0$ Hz, 1H), 2.21 – 2.15 (m, 1H), 1.37 – 1.32 (m, 1H), 1.15 – 1.05 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.0 (d, $J_{\text{CF}} = 256.2$ Hz), 159.2 (d, $J_{\text{CF}} = 236.7$ Hz), 154.5, 133.5 (d, $J_{\text{CF}} = 7.4$ Hz), 114.8 (d, $J_{\text{CF}} = 8.4$ Hz), 114.3, 114.2 (d, $J_{\text{CF}} = 48.3$ Hz), 94.8 (d, $J_{\text{CF}} = 16.7$ Hz), 67.8 (d, $J_{\text{CF}} = 32.4$ Hz), 45.0, 19.8, 18.2, 13.7; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{NO}$ ($[\text{M}+\text{H}]^+$): 240.1200, found: 240.1178; $[\alpha]_{\text{D}}^{20} -14.3$ (c 0.75, MeOH).



(+)-((1S, 2S)-2-(5-Fluoro-2-((2-fluoroallyl)oxy)phenyl)cyclopropyl)methanamine

Hydrochloride ((+)-16c). This compound was obtained with intermediate **14** employing General Method A, B and C as a white solid. HPLC purity: 99.3% (9.6 min); ^1H NMR (400 MHz, CD_3OD) δ 6.98 (dd, $J = 8.8, 4.4$ Hz, 1H), 6.90 (dt, $J = 8.0, 2.8$ Hz, 1H), 6.76 (dd, $J = 9.2, 2.8$ Hz, 1H), 4.88 (dd, $J = 14.0, 3.2$ Hz, 1H), 4.80 (dd, $J = 41.6, 2.8$ Hz, 1H), 4.66 (d, $J = 14.0$ Hz, 2H), 3.11 (dd, $J = 13.2, 6.8$ Hz, 1H), 2.95 (dd, $J = 13.2, 8.0$ Hz, 1H), 2.21 – 2.16 (m, 1H), 1.37 – 1.33 (m, 1H), 1.16 – 1.05 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.0 (d, $J_{\text{CF}} = 256.2$ Hz), 159.2 (d, $J_{\text{CF}} = 236.6$ Hz), 154.5, 133.5 (d, $J_{\text{CF}} = 7.5$ Hz), 114.9 (d, $J_{\text{CF}} = 8.6$ Hz), 114.3, 114.2 (d, $J_{\text{CF}} = 45.5$ Hz), 94.8 (d, $J_{\text{CF}} = 16.7$ Hz), 67.8 (d, $J_{\text{CF}} = 32.3$ Hz), 45.0, 19.8, 18.3, 13.7; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{NO}$ ($[\text{M}+\text{H}]^+$): 240.1200, found: 240.1176; $[\alpha]_{\text{D}}^{20} +16.0$ (c 0.3, MeOH).

2. Pharmacological profiling for compounds (+)-16b and (+)-16d.

Primary binding experiments were performed at 10 μ M for the two compounds and the percentage displacement of the radioligand was measured. Targets showing > 50 % inhibition of binding were selected for full concentration-response competitive binding experiments and binding constant sat equilibrium (K_i) were determined.

Table S3. Binding assays, K_i (nM) or % inhibition at 10 μ M ^a

Taget	Family	(+)-16b	(+)-16d
GPCRs			
5-HT_{1A}	serotonergic	376	30%
5-HT_{1B}	serotonergic	19.5%	10.2%
5-HT_{1D}	serotonergic	35.2%	12.3%
5-HT_{1E}	serotonergic	5.5%	0.9%
5-HT_{2A}	serotonergic	2253	7279
5-HT_{2B}	serotonergic	46	51
5-HT_{2C}	serotonergic	37	33
5-HT_{5a}	serotonergic	14.6%	9.9%
5-HT₆	serotonergic	738	1455
5-HT₇	serotonergic	309	1345
α_{1A}	adrenergic	50%	30.5%
α_{1B}	adrenergic	10.1%	0.4%
α_{1D}	adrenergic	26.1%	11.5%
α_{2A}	adrenergic	385	322
α_{2B}	adrenergic	804	1744
α_{2C}	adrenergic	784	2589
β₁	adrenergic	28.6%	20.4%
β₂	adrenergic	10.1%	3.6%

β_3	adrenergic	5.8%	1.3%
D₁	dopaminergic	35.4%	21%
D₂	dopaminergic	42.4%	23.8%
D₃	dopaminergic	811	1712
D₄	dopaminergic	9.6%	3.9%
D₅	dopaminergic	26.6%	6.9%
DOR	opioidergic	1.3%	6.1%
H₁	histaminergic	28.5%	31.6%
H₂	histaminergic	31.6%	19.9%
H₃	histaminergic	12.1%	3.5%
H₄	histaminergic	8.6%	5.6%
KOR	opioidergic	28.6%	>10000
M₁	muscarinergic	5.7%	9.2%
M₂	muscarinergic	6.2%	3.1%
M₃	muscarinergic	>10000	15.9%
M₄	muscarinergic	5.4%	3%
M₅	muscarinergic	42.2%	16.2%
MOR	opioidergic	18.3%	16.3%
Ion channels			
GABA_A	gabaminergic	18.7%	11.1%
5-HT₃	serotonergic	25.4%	11.3%
PBR	Peripheral benzodiazepine receptor (GABA _A)	3.5%	1.8%
BZP	Rat brain	9.6%	17.7%

	benzodiazepine receptor (GABA _A)	
Others receptors		
Sigma ₁	15.5%	25.3%
Sigma ₂	40.9%	38%
Transporter		
DAT	15.7%	3%
NET	35.6%	15.2%
SERT	<i>1370</i>	40.6%

^a K_i determinations and binding profiles were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2013-00017-C (NIMH PDSP). 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. For experimental details please refer to the PDSP web site <http://pdspdb.unc.edu/pdspWeb/>.

Data represent mean % inhibition (N = 4 determinations) for compounds tested at the indicated targets. K_i (nM) values were obtained from non-linear regression analysis of radioligand competition binding isotherms for targets at which significant inhibition (> 50%) was observed in the primary assay.

3. Molecular Modeling

The 5-HT_{2C} primary sequence was retrieved from UniProt (P28335, 5-HT_{2C}_HUMAN), and two 5-HT_{2C} homology models were generated. The first model (5-HT_{2C_inact}) was obtained by using the β_2 -AR as the template in its inactive state (PDB: 2RH1), while the second model (5-HT_{2C_act}) was generated by combining two templates, namely the resolved structure of 5-HT_{2B} in complex with ergotamine (PDB: 4IB4) and the β_2 -AR in its fully active state (PDB: 3SN6). This choice is due to the fact that ergotamine shows functional selectivity for 5-HT_{2B} and thus the resolved structure does not represent a fully active state. By combining the two templates, the generated active model should benefit from the high homology in the orthosteric site between 5-HT_{2B} and 5-HT_{2C}, while conserving features responsible for the fully activation as taken from β_2 -AR. In detail, the homology models were built by using Modeller9.12 using the default parameters and generating 20 models for each run.² Among the generated models, the best structures were selected according to the scores computed by Modeller9.12 (i.e. DOPE and GA341) as well as to the percentage of residues falling in the allowed regions of the Ramachandran Plot. The satisfactory structural quality of the two selected models was then assessed by (a) the agreement with the predicted secondary structure from the sequence alignment, as obtained using ClustalX (data not reported); (b) the lack of not predicted gaps; (c) the remarkable percentage of residues falling in the allowed regions of the Ramachandran Plot (88.9 % and 88.2 % for 5-HT_{2C_inact} and 5-HT_{2C_act}, respectively) and of the chi-space (96.7 % and 96.2%, for 5-HT_{2C_inact} and 5-HT_{2C_act}, respectively).

The so obtained structures were then completed by adding hydrogen atoms and to remain compatible with physiological pH, Asp, Glu, Lys and Arg residues were considered in their ionized form while His and Cys were maintained neutral by default. The completed models were carefully checked to avoid unphysical occurrences such as cis peptide bonds, wrong configurations, improper bond lengths, non-planar aromatic rings or colliding side-chains. Finally, the structures were optimized by a minimization made up by two phases: a first minimization without constraints until RMS = 0.1 kcal mol⁻¹ Å⁻¹ and then a second minimization with backbone fixed until RMS = 0.01 kcal mol⁻¹ Å⁻¹ to preserve their folding.

Docking simulations were carried out using PLANTS, which finds plausible ligand poses through ant colony optimization algorithms (ACO).³ For all docking simulations, PLANTS was used with default settings and without geometric constraints. The search was focused on a 10.0 Å radius sphere around Asp134 thus completely encompassing the binding cavity. For each ligand, speed 1 was used and 10 poses were generated and scored using the ChemPlp function. The so obtained best complexes were finally minimized by keeping all atoms fixed apart from those included within a 10.0 Å radius sphere around the bound ligand.

² Marti-Renom, M. A.; Stuart, A.; Fiser, A.; Sánchez, R.; Melo, F. Sali, A. Comparative protein structure modeling of genes and genomes. *Annu. Rev. Biophys. Biomol. Struct.* **2000**, *29*, 291-325.

³ Korb, O.; Stützle, T.; Exner, T. E. Empirical Scoring Functions for Advanced Protein-Ligand Docking with PLANTS. *J. Chem. Inf. Model.* **2009**, *49*, 84-96.