Supporting Information

Discovery of *N*-Substituted (2-Phenylcyclopropyl)methylamines as Functionally Selective Serotonin 2C Receptor Agonists for Potential Use as Antipsychotic Medications

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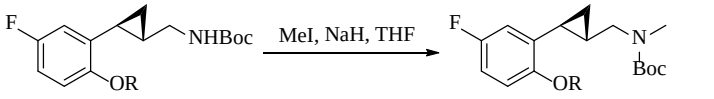
1. Synthetic procedures for compounds 14a-c, 24b, 34e, and 35e, and characterization data of all intermediates.

General. All chemicals and solvents were purchased from Sigma-Aldrich or Fisher Scientific and were used as obtained without further purification. Synthetic intermediates were purified on 230−400 mesh silica gel using a Teledyne CombiFlash R_f flash chromatograph. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-400 or AVANCE-400 spectrometer at 400 or 100 MHz, respectively. NMR chemical shifts are reported in δ (ppm) using residual solvent peaks as standards ($CDCl_3$, 7.26 (H), 77.16 (C); CD_3OD, 3.31 (H), 49.00 (C)). Mass spectra were measured using an LCMS-IT-TOF (Shimadzu) mass spectrometer in ESI mode.

Preparation of *N*-Boc-Amines 14a-c.



(-)-13a
(-)-13b
(-)-13c

14a R = Me
14b R = allyl
14c R = 2-fluoroethyl

***tert*-Butyl [[(1*S*, 2*S*)-2-(5-Fluoro-2-methoxyphenyl)cyclopropyl]methyl](methyl)**

Carbamate (14a). To a solution of (-)-**13a** (> 90% ee, Cheng, J. *et al.*, *J. Med. Chem.* **2016**, *59*, 578-591, Supporting Information) (170 mg, 0.55 mmol) in THF (12 mL) was added NaH (60% dispersion in mineral oil, 56 mg, 1.38 mmol). The mixture was stirred at room temperature for 30 min, and then methyl iodide (160 mg, 1.10 mmol) was added. The reaction mixture was stirred overnight at room temperature, quenched with water, and extracted with EtOAc. The organic phase was washed with brine,

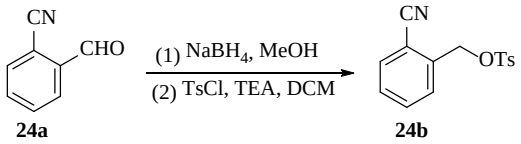
dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by flash chromatography to give the title compound (160 mg, 95% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.82 (td, J = 8.5, 2.9 Hz, 1H), 6.76 (dd, J = 8.9, 4.7 Hz, 1H), 6.54 (dd, J = 9.6, 3.0 Hz, 1H), 3.84 (s, 3H), 3.47 – 3.33 (m, 1H), 3.27 – 3.09 (m, 1H), 2.95 (s, 3H), 2.18 – 2.07 (m, 1H), 1.49 (s, 9H), 1.26 – 1.15 (m, 1H), 0.96 – 0.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.4 (d, J = 237.5 Hz), 155.9 (s), 154.42 (s), 133.0 (s), 112.3 (d, J = 23.6 Hz), 112.2 (d, J = 21.9 Hz),111.1 (d, J = 6.2 Hz), 56.1 (s), 34.4 (s), 31.4 (s), 27.6 (s, 3C), 21.2 (s), 16.2 (s), 13.0 (s); HRMS (ESI) calculated for $C_{17}H_{25}FNO_3$ ($[M+H]^+$), 310.1813; found, 310.1802.

***tert*-Butyl *N*-[[(1*S*, 2*S*)-2-[2-(Allyloxy)-5-fluorophenyl]cyclopropyl]methyl]-*N*-methylcarbamate (14b).** Prepared from (-)-**13b** (> 90% ee) by the same procedure as described for **14a**: ^{1}H NMR ($CDCl_3$) δ 6.81 – 6.68 (m, 2H), 6.50 (dd, J = 9.3, 3.0 Hz, 1H), 6.09 – 6.00 (m, 1H), 5.39 (dd, J = 17.2, 1.4 Hz, 1H), 5.26 (dd, J = 10.5, 1.4 Hz, 1H), 4.53 (d, J = 3.7 Hz, 2H), 3.47 – 3.28 (m, 1H), 3.19 (dd, J = 14.3, 6.8 Hz, 1H), 2.92 (s, 3H), 2.19 – 2.06 (m, 1H), 1.45 (s, 9H), 1.27 – 1.14 (m, 1H), 0.90 (t, J = 6.9 Hz, 2H); HRMS (ESI) calculated for $C_{19}H_{27}FNO_3$ ($[M+H]^+$), 336.1969; found, 336.1954.

***tert*-Butyl *N*-[(1*S*, 2*S*)-2-[2-[5-Fluoro-2-(2-fluoroethoxy)phenyl]cyclopropyl]methyl]-*N*-methylcarbamate (14c).** Prepared from (-)-**13c** (> 90% ee) by the same procedure as described for **14a**. ^{1}H NMR ($CDCl_3$) δ 6.85 – 6.74 (m, 2H), 6.54 (dd, J = 9.6, 2.7 Hz, 1H), 4.86 – 4.80 (m, 1H), 4.74 – 4.68 (m, 1H), 4.29 – 4.22 (m, 1H), 4.21 – 4.15 (m, 1H), 3.47 –

3.32 (m, 1H), 3.23 (dd, J = 14.2, 6.4 Hz, 1H), 2.95 (s, 3H), 2.20 – 2.09 (m, 1H), 1.48 (s, 9H), 1.27 – 1.19 (m, 1H), 0.96 – 0.90 (m, 2H); HRMS (ESI) calculated for $C_{18}H_{26}F_2NO_3$ ($[M+H]^+$), 342.1875; found, 342.1856.

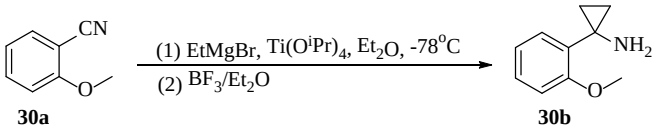
Preparation of 2-Cyanobenzyl 4-Methylbenzenesulfonate (24b)



24a **24b**

$NaBH_4$ (0.17 g, 4.5 mmol) was added slowly to a solution of 2-formylbenzonitrile (0.40 g, 3.0 mmol) in MeOH (10 mL). The mixture was stirred at room temperature for 30 min and then concentrated. The residue was dissolved in DCM, and the solution was washed with water and brine, dried over sodium sulfate, and concentrated to give the product, 2-(hydroxymethyl)benzonitrile, as a colorless oil. This oil was dissolved in DCM, and triethylamine (0.8 mL, 6.0 mmol) and *p*-toluenesulfonyl chloride (0.63 g, 3.3 mmol) were added. The reaction mixture was stirred at room temperature for 5 h, and then diluted with H_2O (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by flash chromatography to give the title compound (0.74 g, 86% yield): ^{1}H NMR ($CDCl_3$) δ 7.98, 7.31 (AA'XX' multiplet, $J_{AX} + J_{AX'}$ = 8.4 Hz, 4H), 7.92 (d, J = 7.6 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.54 – 7.47 (m, 2H), 5.59 (s, 2H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.5 (s), 144.8 (s), 143.5 (s), 138.7 (s), 134.7 (s), 129.5 (s), 129.4 (s, 2C), 128.8 (s), 127.6 (s, 2C), 125.7 (s), 121.6 (s), 76.4 (s), 21.7 (s); HRMS (ESI) calculated for $C_{15}H_{14}NO_3S$ ($[M+H]^+$), 288.0689; found, 288.0648.

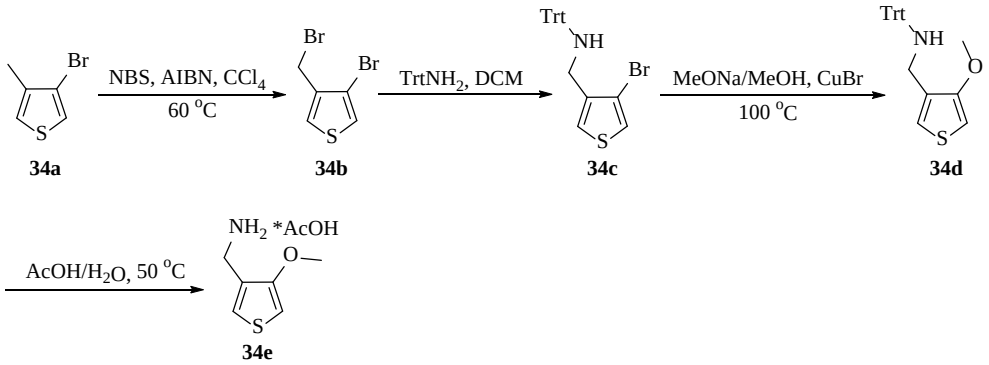
Preparation of 1-(2-Methoxyphenyl)cyclopropanamine (30b)



30a **30b**

Ethylmagnesium bromide (6.0 mmol, 3 M in ether) was added at -78 °C to a solution of 2-methoxybenzonitrile (3.0 mmol) and Ti(O*i*-Pr)$_4$ (1.0 mL, 3.3 mmol) in Et$_2$O (15 mL). The yellow solution was stirred for 10 min, then warmed to rt (1 h). BF$_3$·Et$_2$O (0.75 mL, 6 mmol) was added. The reaction mixture was stirred for 1 h, quenched with 1 N HCl (ca. 10 mL), and diluted with ether (ca. 15 mL). 2N NaOH was added to adjust the pH to 9 – 10, the phases were separated, and the aqueous phase was extracted with ether. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude product was purified by flash chromatography to give the title compound (250 mg, 53% yield) as a colorless oil: ^{1}H NMR (CDCl$_3$) δ 7.35 – 7.30 (m, 2H), 6.90 – 6.85 (m, 2H), 3.90 (s, 3H), 2.14 (br s, 2H), 0.95 – 0.80 (m, 4H); HRMS (ESI) calculated for C$_{10}$H$_{14}$NO ([M+H]$^+$), 164.1070; found, 164.1048.

Preparation of (4-Methoxythiophene-3-yl)methanamine Acetate (34e)



34a **34b** **34c** **34d** **34e**

3-Bromo-4-(bromomethyl)thiophene (34b). A mixture of 3-bromo-4-methylthiophene **34a** (1.08 g, 6.0 mmol), *N*-bromosuccinimide (1.10 g, 6.0 mmol), 2,2'-azobis(isobutyronitrile) (0.1 g), and carbon tetrachloride (30 mL) was

stirred at 60 ^{o}C for 5 hours. The resulting suspension was cooled to room temperature. The precipitate was filtered off and washed with a small volume of DCM. The filtrate was concentrated to give crude 3-bromo-4-bromomethylthiophene as a solid in quantitative yield, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 7.41 (d, J = 3.4 Hz, 1H), 7.31 (d, J = 3.4 Hz, 1H), 4.50 (s, 2H).

***N*-[(4-Bromothiophene-3-yl)methyl]-1,1,1-triphenylmethanamine (34c)**. To a solution of **34b** (510 mg, 2.0 mmol) in DCM (5 mL) was added tritylamine (1.04 g, 4.0 mmol), and the resulting solution was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue purified by column chromatography to give the protected amine (740 mg, 85% yield): ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 7.6 Hz, 6H), 7.46 (d, J = 3.2 Hz, 1H), 7.34 (t, J = 7.6 Hz, 6H), 7.27 – 7.23 (m, 4H), 3.30 (s, 2H), 2.04 (s, 1H); HRMS (ESI) calculated for $C_{24}H_{21}BrNS$ ($[M+H]^{+}$), 434.0573; found, 434.0552.

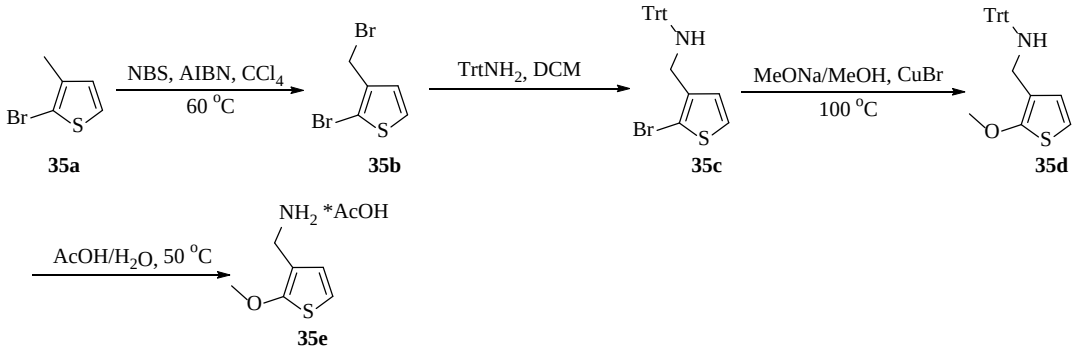
***N*-[(4-Methoxythiophene-3-yl)methyl]-1,1,1-triphenylmethanamine (34d)**. Under an Ar atmosphere, CuBr (30 mg) was added to a mixture of **34c** (100 mg, 0.23 mmol) and sodium methoxide solution (28 wt% in methanol, 5 mL). The reaction mixture was stirred at 100 ^{o}C for 24 h in a sealed tube. After cooling, saturated aqueous NH_4Cl solution was added. The resulting clear solution was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash chromatography to give the title compound (65 mg, 73% yield): ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 7.6 Hz, 6H), 7.32 (t, J = 7.6 Hz, 6H), 7.26 – 7.21 (m, 4H), 6.21 (d, J = 3.2 Hz, 1H), 3.76 (s, 3H), 3.23 (s, 2H), 2.10 (s, 1H); HRMS (ESI)

calculated for $C_{25}H_{24}NOS$ ($[M+H]^+$), 386.1573; found, 386.1543.

(4-Methoxythiophene-3-yl)methanamine Acetate (34e)

The solution of **34d** (60 mg, 0.15 mmol) in acetic acid (3 mL) and H_2O (0.5 mL) was stirred at 50 ^oC for 3 h and concentrated to give white solid. The solid was filtered off, washed with hexane, and dried *in vacuo* to give the acetic acid salt (30 mg, 100% yield): ^1H NMR ($CDCl_3$) δ 8.22 (br s, 3H), 7.23 (d, J = 3.2 Hz, 1H), 6.26 (d, J = 3.2 Hz, 1H), 3.91 (s, 2H), 3.85 (s, 3H), 1.91 (s, 3H); HRMS (ESI) calculated for $C_6H_{10}NOS$ ($[M+H]^+$), 144.0478; found, 144.0460.

Preparation of (2-Methoxythiophene-3-yl)methanamine Acetate (35e)



2-Bromo-3-(bromomethyl)thiophene (35b)

Prepared from 2-bromo-3-methylthiophene **35a** by the same procedure as described for **34b**: ^1H NMR ($CDCl_3$) δ 7.28 (d, J = 5.7 Hz, 1H), 7.03 (d, J = 5.7 Hz, 1H), 4.48 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 137.2 (s), 128.5 (s), 126.6 (s), 113.3 (s), 25.9 (s).

***N*-[(2-Bromothiophene-3-yl)methyl]-1,1,1-triphenylmethanamine (35c)**. Prepared from 2-bromo-3-(bromomethyl)thiophene **35b** by the same procedure as described for **34c** (180 mg, 90% yield): ^1H NMR ($CDCl_3$) δ 7.65 – 7.53 (m, 6H), 7.33 (t, J = 7.6 Hz, 6H), 7.29 – 7.19 (m, 4H), 7.13 (d, J = 5.6 Hz, 1H), 3.27 (s, 2H), 1.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 145.8 (s, 3C), 140.5 (s), 128.8 (s, 6C), 128.5 (s), 128.1 (s, 6C), 126.6

(s, 3C), 125.8 (s), 109.9 (s), 71.2 (s), 42.5 (s); HRMS (ESI) calculated for $C_{24}H_{21}BrNS$ ($[M+H]^+$), 434.0573; found, 434.0545.

***N*-[(2-Methoxythiophene-3-yl)methyl]-1,1,1-triphenylmethanamine (35d)**. Prepared from **35c** by the same procedure as described for **34d** (100 mg, 63% yield): ^{1}H NMR ($CDCl_3$) δ 7.56 (m, 6H), 7.32 – 7.27 (m, 6H), 7.23 – 7.19 (m, 3H), 6.88 (d, *J* = 5.8 Hz, 1H), 6.60 (d, *J* = 5.8 Hz, 1H), 3.81 (s, 3H), 3.20 (s, 2H); HRMS (ESI) calculated for $C_{25}H_{24}NOS$ ($[M+H]^+$), 386.1573; found, 386.1548.

(2-Methoxythiophene-3-yl)methanamine Acetate (35e). Prepared from **35d** by the same procedure as described for **34e** (55 mg, 100% yield): ^{1}H NMR ($CDCl_3$) δ 6.81 (d, *J* = 5.8 Hz, 1H), 6.58 (d, *J* = 5.8 Hz, 1H), 5.12 (br s, 3H), 3.93 (s, 3H), 3.78 (s, 2H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 175.9 (s), 161.2 (s), 125.4 (s), 117.5 (s), 110.3 (s), 61.0 (s), 35.2 (s), 21.6 (s); HRMS (ESI) calculated for $C_6H_{10}NOS$ ($[M+H]^+$), 144.0478; found, 144.0454.

2. Chiral separation methods for compounds 19-21, 26, 27, and 32.

The racemic free bases of **19-21**, **26**, **27**, and **32** were separated by preparative HPLC using a RegisPack chiral column (25 cm × 21.1 mm, 10 μm particle size) and 0.05% diethylamine (DEA) in 2-propanol/0.05% DEA in *n*-hexane as the eluent (flow rate = 18 mL/min, λ = 254 and 280 nm; isocratic eluent, stacked injections). The first and second peaks (Table S1) were collected and concentrated, and both were re-subjected to the same HPLC conditions to provide both enantiomers of **19-21**, **26**, **27**, and **32** with optical purities > 90% *ee* (determined by analytical HPLC using a RegisPack (25 cm × 4.6 mm, 10 μm) or ChromegaChiral CCJ (25 cm × 4.6 mm, 10 μm) chiral

column and 2-propanol (0.05% DEA)/ *n*-hexane (0.05% DEA) as the eluent. Specific rotations were recorded on a Rudolph Research Autopol IV automatic polarimeter. Both enantiomers of **19-21**, **26**, **27**, and **32** were converted into their HCl salts using 2 M HCl in ether.

Table S1. Chiral Separation of the Free Bases of **19-21**, **26**, **27**, and **32**.

Compounds (free base)	Enantiomers	Methods (2-propanol/ *n*-hexane[a], *v/v*)
19	(–); first peak	40/60
	(+); second peak	
20	(–); first peak	40/60
	(+); second peak	
21	(–); first peak	35/65
	(+); second peak	
26	(–); first peak	20/80
	(+); second peak	
27	(–); first peak	20/80
	(+); second peak	
32	(–); first peak	25/75
	(+); second peak	

[a] 0.05% diethylamine was added as modifier.

3. Binding assays for compounds (+)-15a and (+)-19.

For compound (+)-**19**，primary binding experiments were performed at 10 μM, 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 constants at equilibrium (K_i) were determined. For compound (+)-**15a**，binding affinities at 5-HT_{2C}, 5-HT_{2B}, and 5-HT_{2A} receptors were determined by competition binding.

Table S2. Binding assays for compound (+)-**19**.[a]

Family	Target	K_i (nM) or % inhibition at 10 μM
Serotonin Receptors	5-HT_{1A}	**1636**
	5- HT_{1B}	**4934**
	5- HT_{1D}	29.2%
	5- HT_{1E}	**5470**
	5- HT_{2A}	**3784**
	5- HT_{2B}	**411**
	5- HT_{2C}	**78**
	5- HT_3	32.0%
	5-HT_{5A}	**5855**
	5-HT_6	**1718**
	5-HT_7	**602**
Dopamine Receptors	D_1	**881**
	D_2	**4217**
	D_3	15.3%
	D_4	**1189**
	D_5	-1.5%
Adrenergic Receptors	α_1A	**446**
	α_1B	45.1%
	α_1D	**220**
	β_1	6.2%
	β_2	22.2%
	β_3	5.6%
Monoamine Transporters	SERT	**593**
	DAT	**3390**
	NET	**> 10000**
Benzodiazepine (BZP) Receptor	Rat brain binding site	-7.9%
	Peripheral-type	30.3%
GABA Receptor	$GABA_A$	14.8%
NMDA Receptor	NMDA	6.0%
Histamine Receptors	H_1	**308**
	H_2	**520**
	H_3	27.8%
	H_4	-1.0%
Opioid receptors	δ	31.6%
	κ	39.7%
	μ	49.7%
Muscarinic Acetylcholine Receptor	M_1	**> 10000**
	M_2	29.0%
	M_3	33.4%
	M_4	-20.9%
	M_5	42.3%

[a]Binding profiles and K_i determinations were 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. Each value represents the average of at least two experiments (n ⩾ 2). For experimental details please referto the PDSP web site http://pdspdb.unc.edu/pdspWeb/.

Table S3. Affinities of compound **(+)-15a** at 5-HT_{2C}, 5-HT_{2B}, and 5-HT_{2A} receptors.[a]

Target	K_i (nM)
5-HT_{2A} ([^{3}H]ketanserin)	**360.0**
5-HT_{2B} ([^{3}H]LSD)	**28.0**
5-HT_{2C} ([^{3}H]mesulergine)	**81.0**

[a]Affinity data were provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, using hot ligands [^{3}H]ketanserin for 5-HT_{2A}, [^{3}H]LSD for 5-HT_{2B}, and [^{3}H]mesulergine for 5-HT_{2C}. Each value represents the average of at least two experiments (n ≥ 2). For experimental details please refer to the PDSP web site http://pdspdb.unc.edu/pdspWeb/.