Synthesis and Structure Activity Relationship of Tetrahydroisoquinoline-based Potentiators of GluN2C and GluN2D Containing N-Methyl-D-Aspartate Receptors

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Table S1: Off-target actions of compound **83** at Serotonin and Adrenergic Receptors

Receptor	Radioligand binding in 5	n

	μM 83 (% control)	
Serotonin receptor 5-HT1A	87	4
Serotonin receptor 5-HT1B	76	4
Serotonin receptor 5-HT1D	101	4
Serotonin receptor 5-HT1E	86	4
Serotonin receptor 5-HT2A	106	4
Serotonin receptor 5-HT2B	64	4
Serotonin receptor 5-HT2C	100	4
Serotonin receptor 5-HT3	99	4
Serotonin receptor 5-HT5A	101	4
Serotonin receptor 5-HT6	118	4
Serotonin receptor 5-HT7	80	4
Adrenergic receptor α1A	117	4
Adrenergic receptor α1B	77	4
Adrenergic receptor α1D	95	4
Adrenergic receptor α2A	90	4
Adrenergic receptor α2B	85	4
Adrenergic receptor α2C	81	4
Adrenergic receptor β2	102	4
Adrenergic receptor β3	101	4

Receptor binding profiles of compound **83** was generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2008-025C(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. Radioligand binding to each receptor was measured in the presence of 5 μM compound **83** for all targets. For experimental details please refer to the PDSP web site http://pdsp.med.unc.edu/.

Table S2: Off-target actions of compound **83** at benzodiazepine site, dopamine, opioid, histamine, muscarinic, sigma, and peripheral benzodiazepine receptors, and norepenephrine, dopamine, and serotonin transporters

Receptor	Radioligand binding in 5 μM 83 (% control)	n
Benzodiazepine site in Rat Brain	113	4
Dopamine receptor D1	79	4
Dopamine receptor D2	79	4
Dopamine receptor D3	94	4
Dopamine receptor D4	84	4
Dopamine receptor D5	91	4
Opioid receptor (δ)	110	4
Opioid receptor (κ)	26	4
Opioid receptor (μ)	130	4
Histamine receptor H1	79	4
Histamine receptor H2	117	4
Histamine receptor H3	89	4
Muscarinic receptor M1	107	4
Muscarinic receptor M2	86	4
Muscarinic receptor M3	107	4
Muscarinic receptor M4	94	4
Muscarinic receptor M5	110	4
Sigma receptor 1	83	4
Sigma receptor 2	102	4
Peripheral Benzodiazepine Receptor	77	4
Noreepinephrine transporter	111	4
Dopamine transporter	85	4
Serotonin transporter	94	4

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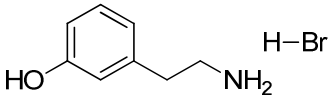
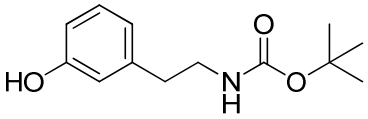
Chemistry Experimentals. Compounds not described were purchased from a commercial vendor. All purchased compounds were greater than 90% pure, as determined by the suppliers, by HPLC or NMR.

All reagents for synthesis were obtained from commercial suppliers and used without further purification. Reaction progress was monitored by thin layer chromatography (TLC) on precoated aluminum plates (silica gel 60 F254, 0.25 mm). Proton and carbon NMR spectra were recorded on an INOVA-400 (400 MHz) or VNMRS 400 (400 MHz). The spectra obtained were referenced to the residual solvent peak. Mass spectra were performed by the Emory University Mass Spectroscopy Center on either a VG 70-S Nier Johnson or JEOL instrument. Elemental analyses were performed by Atlantic Microlab Inc. Purity was established using HPLC unless indicated by combustion analysis. C, H, N agreed with proposed structures ±0.4% of theoretical values unless indicated. Optical activity was measured at 20^{o}C with a Perkin-Elmer model 341 polarimeter. Flash chromatography was performed on a Teldyne ISCO CombiFlash Companion System with prepackaged Teledyne RediSep or Silicycle normal phase columns with silica gel.

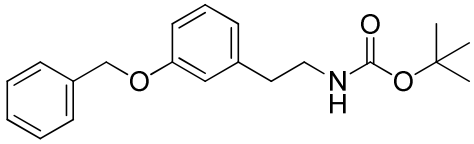


3-(2-aminoethyl)phenol hydrobromide (9). 3-methoxyphenethylamine (**8**, 1.0 g, 6.6 mmol) was dissolved in acetic acid (10 mL) and concentrated HBr (30 equiv, 11 mL) and heated to reflux. The solution was stirred at reflux for 4 hours and then cooled to room temperature. The volatiles were removed *in vacuo* using ethanol as an azeotrope to afford the title compound as a pale orange solid (1.4 g, 100%). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.13 (t, J = 7.8 Hz, 1H), 6.73-6.66 (m, 3H), 3.14 (t, J = 7.6 Hz, 2H), 2.87 (t, J = 7.6 Hz, 2H), ^{13}C NMR (100 MHz, CD_3OD) δ: 157.8, 138.1, 129.8, 119.6, 115.4, 114.0, 40.8, 33.3. HRMS calcd. for $C_8H_{12}NO$, 138.09134 $[M + H]^+$; found, 138.09124 $[M + H]^+$.

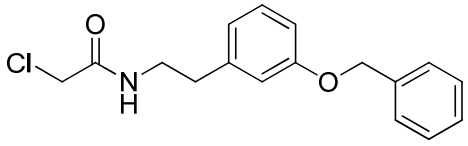


***tert*-butyl 3-hydroxyphenethylcarbamate (10).** Compound **9** (1.4 g, 6.6 mmol) was dissolved in DMF (2 mL) and dioxane (20 mL). Triethylamine (0.67 g, 6.6 mmol, 1.0 equiv) was added dropwise and the resulting mixture was stirred for 15 minutes. Di-*tert*-butyl dicarbonate (1.4 g, 6.6 mmol, 1.0 equiv) was added to the suspension and the reaction was stirred at room temperature for 18 hours. The volatiles were

removed *in vacuo* and the resulting residue was washed with water and extracted with EtOAc (3x). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. The crude oil was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.32 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16 (t, J = 7.8 Hz, 1H), 6.74-6.69 (m, 3H), 6.43 (s, 1H, broad), 4.65 (s, 1H, broad), 3.38 (q, J = 6.8 Hz, 2H), 2.74 (t, J = 6.8 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.5, 140.6, 129.9, 120.8, 116.0, 113.8, 41.8, 36.3, 28.6. HRMS calcd. for $C_{13}H_{20}NO_3$ 238.14377 [M + H]; found 238.14385 [M + H].

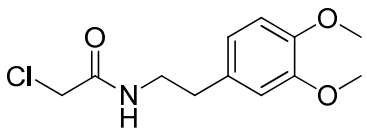


***tert*-butyl 3-(benzyloxy)phenethylcarbamate (11).** Compound **10** (3.0 g, 12.6 mmol) was dissolved in dry MeCN (50 mL). Cesium carbonate (4.1 g, 12.6 mmol, 1.0 equiv) was added to the solution and the resulting mixture was allowed to stir for 30 minutes. Benzyl bromide (3.5 g, 20.2 mmol, 1.6 equiv) was added and the reaction was allowed to stir for 24 hours. When TLC indicated complete conversion, water was added and the aqueous phase was extracted with EtOAc (2x). The organics were combined and washed with brine (3x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a light orange oil (3.1 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45-7.32 (m, 5H), 7.34-7.20 (m, 1H), 6.86-6.79 (m, 3H), 5.05 (s, 2H), 4.68 (s, 1H, broad), 3.37 (q, J = 6.6 Hz, 2H), 2.77 (t, 2H, J = 6.6 Hz), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 156.1, 140.9, 137.2, 129.8, 128.8, 128.2, 127.8, 121.7, 115.7,112.9, 79.4, 70.1, 41.9, 36.5, 28.7. HRMS calcd. for $C_{20}H_{25}NO_3Na$, 350.17267 [M + Na]; found 350.17267 [M + Na].

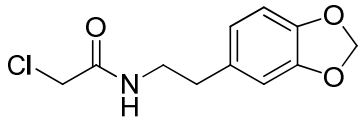


***N*-(3-(benzyloxy)phenethyl)-2-chloroacetamide (19).** Compound **11** (3.1 g, 9.5 mmol) was dissolved in diethyl ether (30 mL) and concentrated HCl (13 mL) and was allowed to stir at room temperature. After 2 hours, a white precipitate was present and TLC indicated complete consumption of starting material. The precipitate was filtered, washed with diethyl ether and carried on without purification. HRMS calcd. for $C_{15}H_{18}NO$, 228.13829 [M + H]; found 228.13807 [M + H]. Compound **12** (2.5 g, 9.5 mmol)was dissolved in DCM (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). After 30 minutes of stirring at room temperature, chloroacetyl chloride (1.4 g, 12.3 mmol, 1.3 equiv) was added to the biphasic mixture. After 2 hours, TLC indicated complete conversion. The organic layer was removed and the aqueous phase extracted with DCM (2x). The organics were combined, washed with brine (2x), dried over MgSO4, filtered and concentrated *in vacuo*. The resulting solid was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (2.09, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44-7.32 (m, 5H), 7.25-7.21 (m, 1H), 6.87-6.79 (m, 3H), 6.65 (s, 1H, broad), 5.05 (s, 2H), 4.00 (s, 2H), 3.54 (q, J = 7.0 Hz, 2H), 2.81 (t, J = 7.0 Hz, 2H). ^{13}C

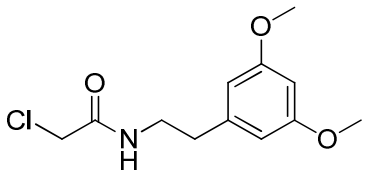
NMR (100 MHz, $CDCl_3$) δ: 166.1, 159.3, 140.2, 137.2, 130.0, 128.8, 128.2, 127.7, 121.6, 115.6, 113.2, 70.2, 42.9, 41.1, 35.7. HRMS calcd. for $C_{17}H_{19}NO_2Cl$, 304.10988 [M + H]; found 304.10954 [M + H].



2-chloro-*N*-(3,4-dimethoxyphenethyl)acetamide (20). Compound **20** was prepared according to Procedure II using 3,4-dimethoxyphenethylamine (**13**, 2.0 g, 11 mmol, 1.0 equiv) and chloroacetyl chloride (1.5 g, 13 mmol, 1.2 equiv) in DCM (40 mL). The crude solid was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.0 g, 70%). TLC (EtOAc:hexanes, 1:1 v/v): R_f = 0.43; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.84 (s, 1H, broad), 6.67 (d, *J*= 20 Hz, 1H), 6.59 (m, 2H), 3.84 (s, 2H), 3.70 (s, 3H), 3.68(s, 3H), 3.37 (q, *J*= 6.4 Hz, 2H), 2.63 (t, *J*= 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.1, 149.0, 147.8, 131.2, 120.8, 112.3, 111.5, 55.9, 55.9, 42.8. 41.3, 35.1. HRMS calcd. for $C_{12}H_{17}NO_3Cl$, 258.08915 $[M + H]^+$; found, 258.08945 $[M + H]^+$.

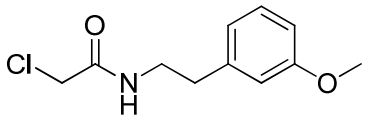


N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-2-chloroacetamide (21). 2-(1,3-benzodioxol-5-yl)ethanamine hydrochloride (**14**, 0.6 g, 3.0 mmol, 1.0 equiv) was dissolved in a mixture of DCM (20 mL) and saturated sodium bicarbonate solution (20 mL). The biphasic reaction mixture was cooled to 0 ^{o}C and chloroacetyl chloride (0.4 g, 3.6 mmol, 1.2 equiv) was added dropwise with stirring. Once the addition was complete, the reaction was warmed to room temperature and stirred for an additional 2 hours. After TLC indicated complete conversion, the organics were separated and the aqueous phase was extracted with DCM (2x). The combined organics were washed with 1M HCl and brine, dried over MgSO4, filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes) to afford the title compound as a white solid (0.54 g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.81 (s, 1H, broad), 6.69 (d, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 2 Hz, 1H), 6.58 (dd, J_1 = 1.6 Hz, J_2 = 8 Hz, 1H), 5.86 (s, 2H), 3.94 (s, 2H), 3.44 (q, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.2, 148.0, 146.5, 132.3, 121.8, 109.2, 108.6, 101.2, 42.9, 41.4, 35.3. HRMS calcd. For $C_{11}H_{13}NO_3Cl$, 242.05785 $[M + H]^+$; found 242.05823 $[M + H]^+$.

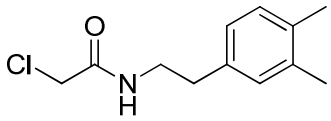


2-chloro-N-(3,5-dimethoxyphenethyl)acetamide (22). Compound **22** was prepared according to Procedure II using 3,5-dimethoxyphenethylamine (**15**, 3.0 g, 16.6 mmol, 1.0 equiv) and chloroacetyl chloride (2.2 g, 19.8 mmol, 1.2 equiv) in DCM (40 mL). The crude product was purified by silica gel

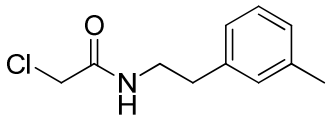
chromatography (0-70% EtOAc/hexanes) to afford the title compound as a white solid (2.9 g, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.79 (s, 1H, broad), 6.32 (s, 3H), 3.98 (s, 2H), 3.73 (s, 6H), 3.50 (q, J = 6.8 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.3, 161.2, 140.9, 106.8, 98.8, 55.5, 55.4, 42.8, 41.0, 35.9. HRMS calcd. for $C_{12}H_{17}NO_3Cl$, 258.08915 $[M + H]^+$; found, 258.08882 $[M + H]^+$.



2-chloro-N-(3-methoxyphenethyl)acetamide (23). Compound **23** was prepared according to Procedure II using 3-methoxyphenethylamine (**8**, 2.0 g, 13 mmol) and chloroacetyl chloride (1.5 g, 13 mmol, 1.0 equiv) in DCM (40 mL). The crude material was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.2 g, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22 (t, J = 7.6 Hz, 1H), 6.79-6.73 (m, 4H), 3.99 (s, 3H), 3.78 (s, 2H), 3.54 (q, J = 6.4 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 160.1, 140.2, 129.9. 121.2, 114.6, 112.3, 55.4, 42.9, 41.1, 35.7. HRMS calcd. for $C_{11}H_{15}NO_2Cl$, 228.07858 $[M + H]^+$; found 228.07848 $[M + H]^+$.

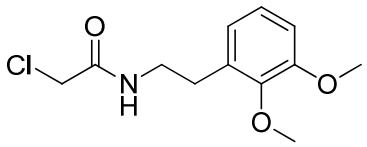


2-chloro-N-(3,4-dimethylphenethyl)acetamide (24). Compound **24** was prepared according to Procedure II using 3,4-dimethylphenethylamine (**16**, 2.0 g, 13.4 mmol, 1.0 equiv) and chloroacetyl chloride (4.5 g, 40 mmol, 3.0 equiv) in DCM (40 mL). The crude material was purified by silica gel chromatography (ISCO, Silicycle 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (2.5 g, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.07 (d, J = 7.4 Hz, 1H), 6.98 (s, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.89 (s, 1H, broad), 3.97 (s, 2H), 3.51 (q, J = 6.6 Hz, 2H), 2.78 (t, J = 6.6 Hz, 2H), 2.25 (s, 3H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.3, 137.1, 136.0, 135.0, 130.4, 130.3, 130.2, 126.3, 126.2, 42.9, 41.1, 35.2, 20.0, 19.6. HRMS calcd. for $C_{12}H_{17}NOCl$, 226.09932 $[M + H]^+$; found, 226.09932 $[M + H]^+$.

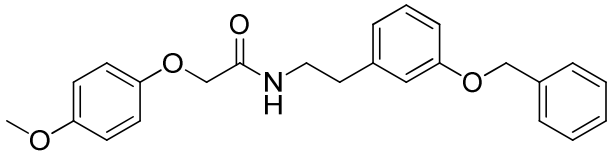


2-chloro-N-(3-methylphenethyl)acetamide (25). Compound **25** was prepared according to Procedure II using 3-methylphenethylamine (**17**, 2.0 g, 14.85 mmol, 1.0 equiv) and chloroacetyl chloride (2.0 g, 17.8 mmol, 1.2 equiv) in DCM (40 mL). The crude material was purified by silica gel chromatography (ISCO, RediSep 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an orange oil (2.3 g, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.19 (t, J = 7.6 Hz, 1H), 7.04-6.97 (m, 3H), 6.78 (s, 1H, broad), 3.97 (s, 2H), 3.51 (q, J= 7.2 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz)

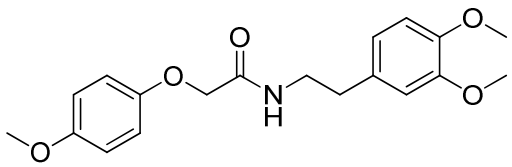
δ: 166.2, 138.6, 129.8, 128.8, 127.6, 126.0, 42.9, 41.3, 35.6, 21.6. HRMS calcd. for $C_{11}H_{15}NOCl$, 212.08367 $[M + H]^+$; found, 212.08299 $[M + H]^+$.



2-chloro-*N*-(2,3-dimethoxyphenethyl)acetamide (26). Compound **26** was prepared according to Procedure II using 2,3-dimethoxyphenethylamine (**18**, 2.0 g, 11.0 mmol, 1.0 equiv) and chloroacetyl chloride (1.5 g, 13.2 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 25g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.88 g, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.97 (t, J = 7.6 Hz, 1H), 6.95 (s, 1H, broad), 6.80 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 6.74 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 3.96 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.49 (q, J = 6.8 Hz, 2H), 2.84 (t, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.3, 153.0, 147.3, 132.6, 124.5, 122.6, 111.5, 60.9, 56.0, 42.8, 41.1, 29.9. HRMS calcd. for $C_{12}H_{17}NO_3Cl$, 258.08915 $[M + H]^+$; found, 258.08903 $[M + H]^+$.

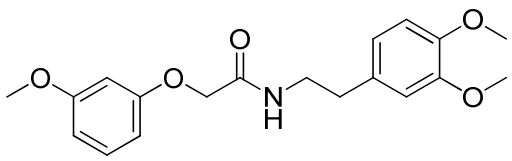


***N*-(3-(benzyloxy)phenethyl)-2-(4-methoxyphenoxy)acetamide (27).** Compound **27** was prepared according to Procedure C using **19** (2.1 g, 6.9 mmol, 1.0 equiv) and *p*-methoxyphenol (1.03 g, 8.3 mmol, 1.2 equiv) in MeCN (40 mL). The crude solid was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.1 g, 78%). TLC (EtOAc:hexanes, 1:2 v/v): R_f = 0.41; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43-7.31 (m, 5H), 7.21 (t, J = 7.8 Hz, 1H), 6.87-6.76 (m, 7H), 6.70 (m, 1H, broad), 5.02 (s, 2H), 4.40 (s, 2H), 3.73 (s, 3H), 3.59 (q, J = 6.8 Hz, 2H), 2.81 (t, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 159.3, 154.9, 151.6, 140.5, 137.2, 130.0, 128.8, 128.2, 127.8, 121.6, 115.9, 115.6, 115.0, 113.1, 70.1, 68.4, 55.9, 55.9, 40.2, 35.9. HRMS calcd. for $C_{24}H_{26}NO_4$, 392.18564 $[M + H]^+$; found, 392.18551 $[M + H]^+$.

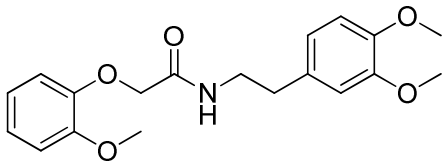


***N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (28).** Compound **28** was prepared according to Procedure III using **20** (2.2 g, 8.7 mmol, 1.2 equiv.) and *p*-methoxyphenol (0.90 g, 7.3 mmol) in MeCN (30 mL). The crude solid was purified by silica gel chromatography (ISCO, Silicycle 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.0 g, 80%). TLC (EtOAc:hexanes, 1:2 v/v): R_f = 0.34; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.68-6.84 (m, 8H), 4.42 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.58 (q, J= 6.4 Hz, 2H), 2.79 (t, J=7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.5, 154.9, 151.5, 149.2, 147.9, 131.2, 120.9, 115.8, 115.0, 112.0, 111.5, 68.4,

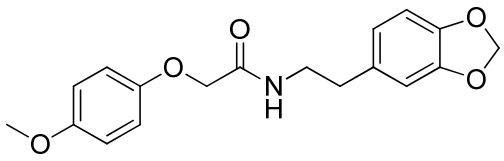
56.1, 56.0, 55.9, 40.4, 35.5. HRMS calcd. for $C_{19}H_{24}NO_3$, 346.16490 $[M + H]^+$; found, 346.16515 $[M + H]^+$.



N-(3,4-dimethoxyphenethyl)-2-(3-methoxyphenoxy)acetamide (29). Compound **29** was prepared according to Procedure III using 3-methoxyphenol (0.6 g, 0.52 mL, 4.8 mmol, 1.0 equiv) and **20** (1.5 g, 5.8 mmol, 1.2 equiv) in dry MeCN (40 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.5 g, 90% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.19 (t, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.70-6.66 (m, 3H), 6.57 (dd, J_1 = 1.4 Hz, J_2 = 8.4 Hz, 1H), 6.45-6.40 (m, 2H), 4.45 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.77 (s, 3H), 3.57 (q, J = 7.2 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.2, 161.2, 158.5, 149.2, 147.9, 131.2, 130.5, 120.9, 112.0, 111.5, 107.8, 106.7, 101.5, 67.6, 56.1, 56.0, 55.5, 40.4, 35.5. HRMS calcd. for $C_{19}H_{24}NO_5$, 346.16490 $[M + H]^+$; found, 346.16497 $[M + H]^+$.

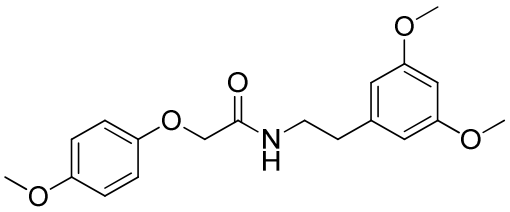


***N*-(3,4-dimethoxyphenethyl)-2-(2-methoxyphenoxy)acetamide (30).** Compound **30** was prepared according to Procedure III using **20** (1.5 g, 5.8 mmol, 1.2 equiv) and 2-methoxyphenol (0.6 g, 0.52 mL, 4.8 mmol, 1.0 equiv) in dry MeCN (40 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.1 g, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.06 (s, 1H, broad), 6.95 (m, 1H), 6.86-6.77 (m, 3H), 6.73-6.70 (m, 1H), 6.66-6.63 (m, 2H), 4.46 (s, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.53 (q, J = 7.2 Hz, 2H), 2.74 (t, J = 7.2 Hz, 2H). ^{13}C ($CDCl_3$, 100 MHz) δ: 168.7, 149.7, 149.1, 147.8, 147.3, 131.4, 123.2, 121.2, 120.8, 115.4, 112.1, 112.0, 111.5, 69.7, 56.0, 55.9, 55.8, 40.5, 35.5. HRMS calcd. for $C_{19}H_{24}NO_5$, 346.16490 $[M + H]^+$; found, 346.16484 $[M + H]^+$.

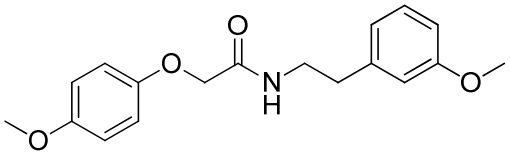


***N*-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-2-(4-methoxyphenoxy)acetamide (31).** Compound **31** was prepared according to Procedure III using **21** (0.5 g, 2.2 mmol, 1.0 equiv) and 4-methoxyphenol (0.3 g, 2.5 mmol, 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.56 g, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.84 (d, J = 9.2 Hz, 2H), 6.78 (d, J = 9.2 Hz, 2H), 6.73-6.57 (m, 3H), 5.93 (s, 2H), 4.41 (s, 2H), 3.77 (s, 3H), 3.54 (q, J = 6.8 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100

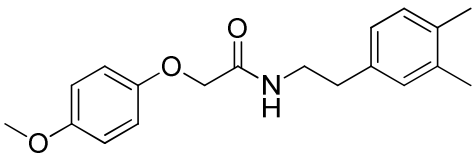
MHz) δ: 168.6, 154.9, 151.5, 148.1, 146.5, 132.5, 132.5, 121.9, 115.8, 115.0, 109.3, 108.6, 101.1, 68.3, 55.9, 40.4, 35.6. HRMS calcd. For $C_{18}H_{20}NO_5$, 330.13360 $[M + H]^+$; found 330.13387 $[M + H]^+$.



***N*-(3,5-dimethoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (32).** Compound **32** was prepared according to Procedure III using **22** (1.0 g, 3.9 mmol, 1.0 equiv) and 4-methoxyphenol (0.53, 4.3 mmol, 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.9 g, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.80-6.72 (m, 5H), 6.31 (s, 3H), 4.37 (s, 2H), 3.72 (s, 3H), 3.72 (s, 6H), 3.55 (q, J = 6.4 Hz, 2H), 2.75 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 161.2, 154.9, 151.6, 141.1, 115.8, 115.0, 106.9, 98.8, 68.4, 55.5, 40.1, 40.1, 36.1. HRMS calcd. for $C_{19}H_{24}NO_5$, 346.16490 $[M + H]^+$; found, 346.16497 $[M + H]^+$.

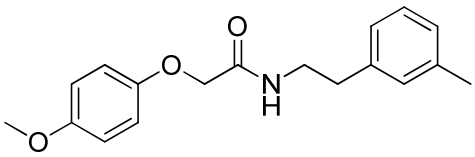


***N*-(3-methoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (33).** Compound **33** was prepared according to Procedure III using **23** (2.2 g, 10 mmol, 1.0 equiv) and 4-methoxyphenol (1.4 g, 12 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.5 g, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22 (t, J = 7.8 Hz, 1H), 6.84 (d, J = 9.2 Hz, 2H), 6.81-6.77 (m, 3H), 6.75-6.75 (m, 2H), 6.68 (s, 1H, broad), 4.42 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.61 (q, J = 6.8 Hz, 2H), 2.83 (t, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 160.1, 154.9, 151.5, 140.4, 129.9, 121.3, 115.8, 115.0, 114.5, 112.2, 55.9, 55.4, 55.3, 40.2, 35.9. HRMS calcd. For $C_{18}H_{22}NO_4$, 316.15433 $[M + H]^+$; found 316.15410 $[M + H]^+$.

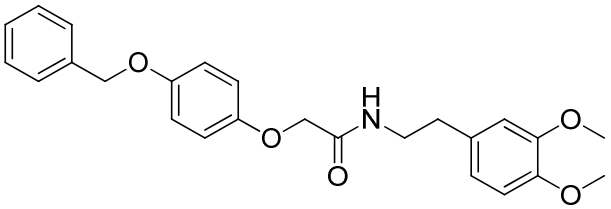


N-(3,4-dimethylphenethyl)-2-(4-methoxyphenoxy)acetamide (34). Compound **34** was prepared according to Procedure III using **24** (2.5 g, 11.1 mmol, 1.0 equiv) and 4-methoxyphenol (1.65 g, 13.3 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 40g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.7g, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.07 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 6.71 (s, 1H, broad), 4.43 (s, 2H), 3.78 (s, 3H), 3.58 (q, J = 6.8 Hz, 2H), 2.79 (t, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.9, 151.6, 137.1, 136.2, 135.0,

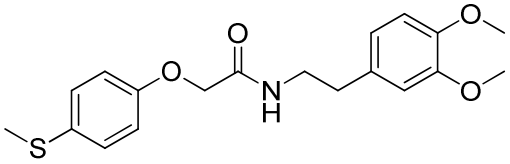
130.3, 126.3, 115.8, 115.0, 68.4, 55.9, 55.8, 40.5, 35.4, 19.9, 19.6. HRMS calcd. For $C_{19}H_{23}NO_3$, 314.17507 $[M + H]^+$; found 314.17489 $[M + H]^+$.



2-(4-methoxyphenoxy)-N-(3-methylphenethyl)acetamide (35). Compound **35** was prepared according to Procedure III using **25** (2.3 g, 10.9 mmol, 1.0 equiv) and 4-methoxyphenol (1.63 g, 13.1 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a pale orange solid (2.5 g, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.19 (t, J = 7.2 Hz, 1H), 7.07-6.96 (m, 3H), 6.85 (d, J = 9.0 Hz, 2H), 6.79 (d, J = 9.0 Hz, 2H), 6.71 (s, 1H, broad), 4.43 (s, 2H), 3.78 (s, 3H), 3.60 (q, J = 6.6 Hz, 2H), 2.82 (t, J = 6.6 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.9, 151.6, 138.7, 138.5, 129.8, 128.8, 127.6, 126.0, 115.8, 115.0, 68.4, 55.9, 40.3, 35.8, 21.6. HRMS calculated for $C_{18}H_{22}NO_3$, 300.15942 $[M + H]^+$, found 300.15920 $[M + H]^+$.

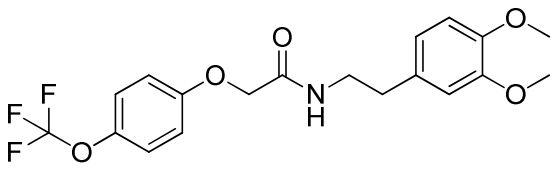


2-(4-(benzyloxy)phenoxy)-N-(3,4-dimethoxyphenethyl)acetamide (36). Compound **36** was prepared according to Procedure III using **20** (0.9 g, 3.5 mmol, 1.0 equiv) and 4-(benzyloxy)phenol (0.84, 4.2 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 24g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.1 g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44-7.30 (m, 5H), 6.92-6.90 (d, J = 9.2 Hz, 2H), 6.80-6.77 (m, 3H), 6.72-6.70 (m, 3H), 5.02 (s, 2H), 4.42 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.59 (q, J = 6.6 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.1, 151.7, 149.2, 147.9, 137.2, 131.2, 128.8, 128.2, 127.7, 120.9, 116.2, 115.8, 112.0, 111.5, 70.8, 68.3, 56.1, 56.0, 40.4, 35.5. HRMS calcd. For $C_{25}H_{27}NO_5$, 422.19620 $[M + H]^+$; found 422.19572 $[M + H]^+$.

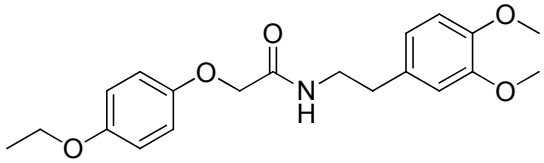


***N*-(3,4-dimethoxyphenethyl)-2-(4-(methylthio)phenoxy)acetamide (37).** Compound **37** was prepared according to Procedure III using **20** (1.2 g, 4.7 mmol) and 4-(methylmercapto)phenol (0.78 g, 5.6 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes) to afford the title compound as an off-white solid (1.2 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (d, J = 8.8 Hz, 2H), 6.77-6.74 (m, 3H),6.69-6.67 (m, 2H), 6.61 (s, 1H, broad), 4.42 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.56 (q, J = 6.4 Hz, 2H), 2.77 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.2, 155.6, 149.2, 147.9, 131.1, 129.7, 120.9, 115.5, 111.9, 111.5, 67.7,

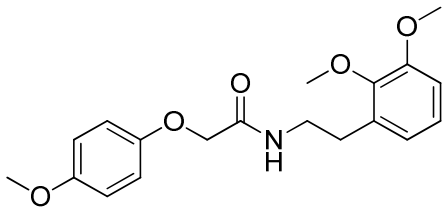
56.1, 56.0, 40.4, 35.5, 17.6. HRMS calcd. for $C_{19}H_{23}NO_4S$, 362.14206 $[M + H]^+$; found 362.14183 $[M + H]^+$.



***N*-(3,4-dimethoxyphenethyl)-2-(4-(trifluoromethoxy)phenoxy)acetamide (38).** Compound **38** was prepared according to Procedure C using **20** (1.0 g, 4.4 mmol, 1.2 equiv) and 4-trifluoromethoxyphenol (0.6 g, 3.4 mmol, 1.0 equiv) in dry MeCN (40 mL). The crude solid was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.0 g, 74% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.14 (d, J = 8.8 Hz, 2H), 6.83-6.58 (m, 6H), 4.43 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.58 (q, J = 7.2 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.8, 155.8, 149.2, 147.9, 131.1, 122.9, 120.9, 115.7, 112.0, 111.4, 67.9, 56.1, 56.0, 40.4, 35.4. HRMS calcd. for $C_{19}H_{21}O_5NF_3$, 400.13663 $[M + H]^+$; found, 400.13633 $[M + H]^+$.

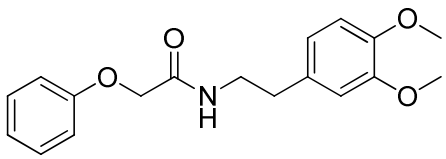


***N*-(3,4-dimethoxyphenethyl)-2-(4-ethoxyphenoxy)acetamide (39).** Compound **39** was prepared according to Procedure III using **20** (1.0 g, 3.9 mmol) and 4-ethoxyphenol (0.6 g, 4.7 mmol, 1.2 equiv) in dry MeCN (20 mL). The crude solid was purified by silica gel chromatography (ISCO, Silicycle 25 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.1 g, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.80-6.65 (m, 7H), 6.64 (s, 1H, broad), 4.38 (s, 2H), 3.94 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.54 (q, J = 6.8 Hz, 2H), 4.38 (s, 2H), 3.94 (q, J = 7.2 Hz, 2H), 2.76 (t, J = 7.2 Hz, 2H), 1.36 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.3, 151.5, 149.3, 148.0, 131.3, 120.9, 115.8, 115.7, 112.1, 111.6, 68.4, 64.2, 56.1, 56.0, 40.4, 35.5, 15.1. HRMS calcd. for $C_{20}H_{26}O_5N$, 360.18055 $[M + H]^+$; found, 360.18092 $[M + H]^+$.

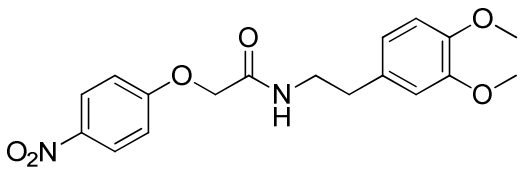


***N*-(2,3-dimethoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (40).** Compound **40** was prepared according to Procedure III using **26** (1.9 g, 7.3 mmol) and 4-methoxyphenol (1.1 g, 8.8 mmol, 1.2 equiv) in dry MeCN (40 mL). The crude residue was purified by silica gel chromatography (ISCO, Silicycle 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an off-clear oil (2.1 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.98 (m, 2H), 6.83 (m, 5H), 6.73 (m, 1H), 4.40 (s, 2H), 3.86 (s, 3H), 3.84

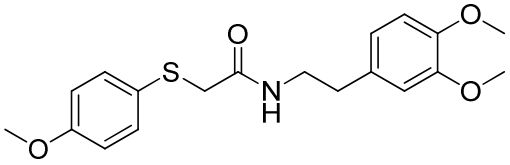
(s, 3H), 3.77 (s, 3H), 3.57 (q, J = 6.8 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.7, 154.8, 153.0, 151.7, 147.4, 132.7, 124.3, 122.4, 115.8, 115.0, 111.3, 68.3, 60.9, 55.9, 55.8, 40.1, 30.1. HRMS calcd. for $C_{19}H_{24}O_5N$, 346.16490 $[M + H]^+$; found, 346.16452 $[M + H]^+$.



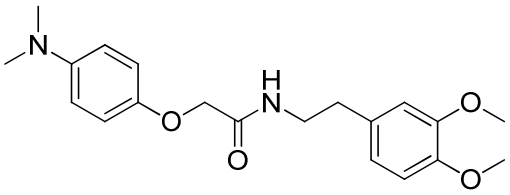
N-(3,4-dimethoxyphenethyl)-2-phenoxyacetamide (41). Compound **41** was prepared according to Procedure B using 3,4-dimethoxyphenethylamine (**13**, 1.0 g, 0.92 mL, 5.5 mmol, 1.0 equiv) and phenoxyacetyl chloride (1.2 g, 1.0 mL, 7.2 mmmol, 1.3 equiv). The crude solid was purified by silica gel chromatography (ISCO, Redisep 20-80% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.2 g, 69% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.24 (m, 2H), 7.00 (m, 1H), 6.83 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 7.6 Hz, 1H), 6.68-6.65 (m, 2H), 6.63 (s, 1H, broad), 4.46 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.56 (q, J = 6.4 Hz, 2H), 2.77 (t, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.3, 157.4, 149.3, 147.9, 131.2, 130.0, 122.3, 120.9, 114.8, 112.0, 111.5, 67.6, 56.1, 56.0, 40.4, 35.5.



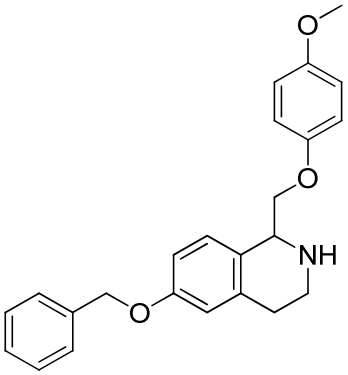
***N*-(3,4-dimethoxyphenethyl)-2-(4-nitrophenoxy)acetamide (42).** To a solution of *p*-nitrophenol (1.5 g, 10.8 mmol, 1.2 equiv) in dry DMF (27 mL) was added CsF (5.5 g, 36.0 mmol, 4.0 equiv) and the reaction mixture was allowed to stir for 2 hours. A solution of **20** (2.3 g, 9.0 mmol, 1.0 equiv) dissolved in dry DMF (10 mL) was added and the resulting reaction mixture stirred for 96 hours at 50 °C under an argon atmosphere. After TLC indicated complete conversion, water was added and the reaction mixture was extracted into DCM (3x). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 80 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a yellow solid (2.5 g, 76 %). TLC (EtOAc/hexanes, 1:1, v/v) R_f: 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.09-7.07 (m, 2H), 6.85-6.83 (m, 4H), 6.82-6.78 (m, 2H), 7.65 (s, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.59 (q, J_1 = 7.0 Hz, 2H), 2.79 (t, J = 7.0 Hz, 2H).^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 158.5, 154.9, 151.4 ,130.7, 129.9, 115.8, 115.0, 114.3, 68.3, 55.9, 55.5, 40.5, 34.9. HRMS calcd. for $C_{18}H_{20}N_2O_6$, 361.13941 $[M + H]^+$; found 361.13950 $[M + H]^+$.



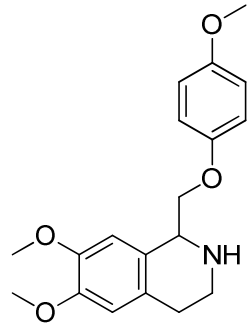
***N*-(3,4-dimethoxyphenethyl)-2-((4-methoxyphenyl)thio)acetamide (43).** Compound **43** was prepared according to Procedure III using **20** (2.0 g, 7.8 mmol) and 4-methoxybenzenethiol (1.3 g, 9.3 mmol, 1.2 equiv) in dry MeCN (40 mL). The crude residue was purified by silica gel chromatography (ISCO, Silicycle 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a yellow solid (2.2 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.13 (d, J = 9.2 Hz, 2H), 6.87 (s, 1H, broad), 6.80-6.76 (m, 3H), 6.69-6.65 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.50 (q, J = 7.2 Hz, 2H), 3.49 (s, 2H), 2.73 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.3, 159.4, 149.2, 147.9, 131.9, 131.2,125.0, 115.1, 115.0, 111.9, 111.8, 56.1, 55.6, 55.5, 41.1, 39.7, 35.2. HRMS calcd. for $C_{19}H_{24}O_4NS$, 362.14206 $[M + H]^+$; found, 362.14165 $[M + H]^+$.



***N*-(3,4-dimethoxyphenethyl)-2-(4-(dimethylamino)phenoxy)acetamide (44).** Compound **42** (2.5 g, 6.9 mmol) was dissolved in EtOH (15 ml) and subjected to hydrogenolysis conditions with 10% palladium on activated carbon (0.25 g) under a hydrogen atmosphere (1 atm) for 14 hours. The reaction mixture was filtered over celite and the filtrate was concentrated *in vacuo* to afford the aniline as a white solid (2.9 g, 97%). TLC (MeOH:DCM, 1:10, v/v) R_f: 0.71; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.76-6.75 (d, J = 16 Hz, 1H), 6.68-6.62 (m, 5H), 6.60-6.57 (m, 2H), 4.36 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.57-3.53 (q, J = 6.8 Hz, 2H), 3.48 (s, 2H), 2.77-2.74 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.9, 150.5, 149.2, 147.9, 141.5, 131.3, 120.9, 116.5, 116.0, 112.1, 111.6, 68.5, 56.1, 56.0, 40.4, 35.5. HRMS calcd. for $C_{18}H_{22}N_2O_4$, 331.16523 $[M + H]^+$; found 331.16467 $[M + H]^+$. The aniline (1.6 g, 4.9 mmol, 1.0 equiv) and paraformaldehyde (1.5 g, 48.9 mmol, 10.0 equiv) were dissolved in AcOH (32.6 ml). Sodium cyanoborohydride (1.5 g, 24.5 mmol, 5.0 equiv) was added to this solution and the reaction stirred for 18 hours. Upon completion, the reaction was made basic (pH 13) with 1N NaOH, and extracted into DCM. The organic layer was washed with water and brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 20 g column, 0-20% MeOH/DCM gradient) to afford the title compound as a white solid (1.56 g, 89%). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.76; ^{1}H NMR ($CDCl_3$, 400 MHz): 6.78-6.74 (m, 3H), 6.70-6.66 (m, 4H), 4.39 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.57 (m,2H), 2.86 (s, 6H), 2.79-2.75 (t, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.9, 149.5, 149.2, 147.9, 146.8, 131.3, 120.9, 115.8, 114.6, 112.0, 111.5, 68.5, 56.1, 56.0, 41.7, 40.4, 35.5. HRMS calcd. for $C_{20}H_{26}N_2O_4$, 359.19653 $[M + H]^+$; found 359.19603 $[M + H]^+$.

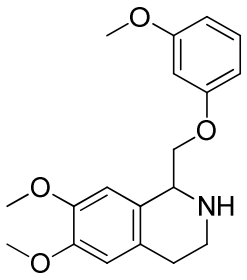


6-(benzyloxy)-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (63). Compound **45** was prepared according to Procedure IVusing **27** (2.1 g, 5.4 mmol). The mixture was filtered to afford a tan solid (2.0 g). The crude material was carried on without further purification. HRMS calcd. for $C_{24}H_{24}NO_3$, 374.17507 $[M + H]^+$; found, 374.17515 $[M + H]^+$. Compound **63** was prepared via Procedure VI using dihydroisoquinoline **45** (2.0 g, 5.4 mmol). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-10% MeOH/DCM gradient) to afford the title compound as an off-white foam (1.4 g, 70% over two steps). TLC (MeOH/DCM, 10:90 v/v): R_f= 0.56; ^{1}H NMR ($CDCl_3$, 400 MHz) δ:7.41-7.28 (m, 5H), 7.07-6.71 (m, 7H), 4.99 (s, 2H), 4.66 (m, 1H), 4.44-4.29 (m, 1H), 3.85-3.51 (m, 5H), 3.28-2.96 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.6, 154.7, 152.1, 136.8, 134.4, 128.9, 128.3, 127.7, 127.6, 120.9, 115.6, 115.7, 115.0, 114.7, 70.2, 69.2, 55.9, 54.2, 39.8, 26.1. HRMS calcd. for $C_{24}H_{26}NO_3$, 379.19072 $[M + H]^+$; found, 379.19171 $[M + H]^+$.

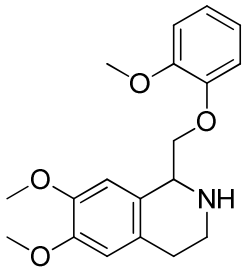


6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (64). Compound **46** was prepared according to Procedure IVIV using **28** (1.2 g, 3.5 mmol). The mixture was filtered to yield an off-white solid (1.1 g). The crude material was carried on without further purification. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.40 (s, 1H), 7.15 (d, *J*= 8.8 Hz, 2H), 7.12 (s, 1H), 6.90 (d, *J*=9.2 Hz), 5.60 (s, 2H), 3.97 (s, 3H), 3.93 (m, 2H), 3.91 (s, 3H), 3.75 (s, 3H), 3.15 (t, *J*=8.4 Hz, 2H) ^{13}C NMR (CD_3OD, 100 MHz) δ: 172.9, 157.7, 155.7, 151.0, 149.2, 134.5, 116.8, 115.0, 114.9, 111.4, 110.7, 66.7, 56.4, 55.4, 49.0, 41.3, 25.1. HRMS (m/z): $[M]^+$ calcd. for $C_{19}H_{22}NO_4$, 328.15433; found, 328.15416. Compound **64** was prepared via Procedure VI using dihydroisoquinoline **46** (1.8 g, 5.5 mmol). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-20% MeOH/DCM gradient) to afford the title compound as an off-white solid (1.2 g, 64% over two steps). TLC (MeOH/DCM, 5:95 v/v): R_f = 0.21; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.88 (d, *J*=9.2 Hz, 2H), 6.81 (d, *J*=9.2 Hz, 2H), 6.67 (s, 1H), 6.61 (s, 1H), 4.35 (t, *J*= 6 Hz, 1H), 4.13 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 3.22(m,

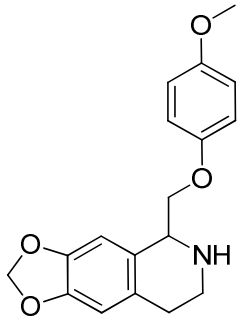
1H), 3.03 (m, 1H), 2.78 (q, *J*=5.2 Hz, 2H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.2, 153.1, 148.1, 147.4, 128.2, 126.5, 115.8, 114.8, 112.1, 109.7, 71.5, 56.2, 56.0, 55.9, 54.9, 39.9, 29.3. HRMS calcd. for $C_{19}H_{24}NO_4$, 330.16999 $[M + H]^+$; found, 330.16968 $[M + H]^+$.



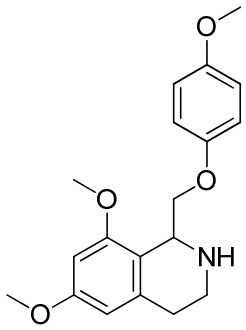
6,7-dimethoxy-1-((3-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (65). Compound **47** was prepared according to Procedure IV using **29** (1.5 g, 4.3 mmol, 1.0 equiv). The crude solid was filtered and dried to afford **47** as an off-white solid (1.4 g, 98% crude). The crude material was carried on without purification. Compound **65** was prepared via Procedure VI using **47** (1.4 g, 4.0 mmol, 1.0 equiv). The crude solid was purified by silica gel chromatography (ISCO, Redisep 12 g column, gradient 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.42 g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (m, 1H), 6.68 (s, 1H), 6.62 (s, 1H), 6.53 (m, 3H), 4.35 (t, *J*= 6.4 Hz, 1H), 4.13 (d, *J* = 6 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 3.20 (m, 1H), 3.02 (m, 1H), 2.76 (m, 2H). ^{13}C NMR (100 MHz, CDCl3) δ: 160.9, 160.1, 147.9, 147.2, 130.0, 128.2, 126.4, 111.9, 109.5, 106.7, 106.6, 101.1, 70.7, 56.0, 55.8, 44.3, 54.7, 39.7, 29.2. HRMS calcd. for $C_{19}H_{24}O_4N$, 330.16999 $[M + H]^+$; found, 330.17022 $[M + H]^+$.



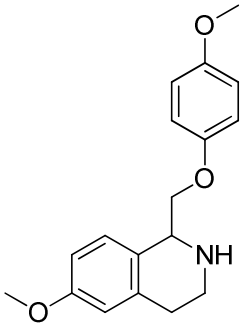
6,7-dimethoxy-1-((2-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (66). Compound **48** was prepared according to Procedure IV using **30** (1.1 g, 3.2 mmol, 1.0 equiv). The crude solid was filtered to afford an off-white solid (1.0 g). The crude material was carried on without purification. NMR (400 MHz, CD_3OD) δ: 7.33 (s, 1H), 7.24-7.22 (m, 1H), 7.13-7.06 (m, 3H), 6.97-6.92 (m, 1H), 5.61 (s, 2H), 3.97-3.3.86 (m, 11H), 3.20-3.15 (m, 2H). Compound **66** was prepared according to Procedure VI from **48** (1.0 g, 3.1 mmol, 1.0 equiv). The crude solid was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.5 g, 63%) . ^{1}H NMR (400 MHz, CDCl3) δ: 6.84 (m, 4H), 6.67 (s, 1H), 6.53 (s, 1H), 4.44 (t, *J*= 6 Hz), 4.22 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 3.27 (m, 1H), 3.09 (m, 1H), 2.80 (q, *J*= 5.6 Hz). ^{13}C (100 MHz, CDCl3) δ: 149.9, 148.3, 148.1, 147.6, 127.2, 124.8, 122.3, 121.2, 115.1, 112.1, 111.9, 109.8, 71.9, 56.1, 16.0, 55.9, 54.3, 39.7, 28.0. HRMS calcd. for $C_{19}H_{24}O_4N$, 330.16999 $[M + H]^+$; found, 330.17022 $[M + H]^+$.



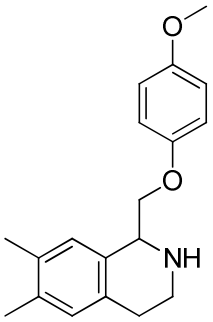
5-((4-methoxyphenoxy)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (67). Compound **49** was prepared according to Procedure IV using **31** (0.56 g, 1.7 mmol). The crude material was filtered off as an off-white solid (0.5 g). The crude solid was carried on without purification. Compound **67** was prepared according to Procedure VI with **49** (0.5 g, 1.6 mmol, 1.0 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.10, 20% over 2 steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.97 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 6.58 (s, 2H), 5.94 (d, J = 4 Hz, 2H), 4.55 (s, 4.53, 1H), 4.43-4.31 (m, 2H), 3.74 (s, 3H), 3.72 (s, 1H, broad), 3.56-3.47 (m, 1H), 3.27 (m, 1H), 3.11-3.07 (m, 1H), 2.98-2.96 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ:154.76, 152.0, 147.9, 147.2, 126.6, 121.4, 116.5, 144.8, 109.2, 106.0, 101.6, 69.2, 55.9, 55.8, 54.2, 39.7, 25.9. HRMS calcd. for $C_{18}H_{19}O_4N$, 314.13868 $[M + H]^+$; found, 314.13848 $[M + H]^+$.



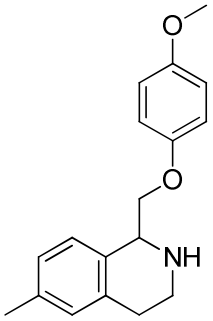
6,8-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (68). Compound **50** was prepared according to Procedure IV using **32** (0.9 g, 2.6 mmol). The crude solid was filtered and carried on without further purification. HRMS calcd. for $C_{19}H_{22}NO_5$ $[M + H]^+$, 328.15433; found, 328.15450 $[M + H]^+$. Compound **68** was prepared according to Procedure VI using **50** (0.84 g, 1.0 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.35 g, 41%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.96 (d, J = 9.4 Hz, 2H), 6.77 (d, J = 9.4 Hz, 2H), 6.32 (d, J = 2 Hz, 1H), 6.27 (d, J = 2 Hz, 1H), 4.93 (dd, J_1 = 2.8 Hz, J_2 = 6.2 Hz, 1H), 4.55 (dd, J_1 = 3.2 Hz, J_2 = 10.4 Hz, 1H), 4.15 (dd, J_1 = 8.4 Hz, J_2 = 10.6 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.80-3.73 (m, 1H), 3.74 (s, 3H), 3.48 (m, 2H), 3.30 (m, 1H), 2.98-2.91 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ:160.7, 157.5, 154.6, 152.2, 135.2, 116.6, 114.7, 109.4, 104.7, 97.6, 55.6, 50.5. HRMS calcd. for $C_{19}H_{24}O_4N$, 330.16999 $[M + H]^+$; found, 330.17026 $[M + H]^+$.



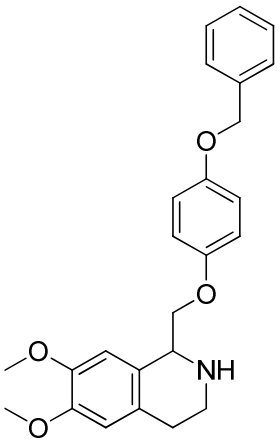
6-methoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (69). Compound **51** was synthesized according to Procedure IV from **33** (2.5 g, 8.0 mmol). The crude solid was filtered and characterized by HRMS and carried forward without further purification or characterization. HRMS calcd. for $[M + H]^+$ $C_{18}H_{20}NO_3$, 298.14377; found 298.14405 $[M + H]^+$. Compound **69** was prepared according to Procedure VI using **51** (3.11 g, 10.5 mmol). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (1.9 g, 61% over 2 steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.11 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 9.2 Hz, 2H), 6.84 (d, J = 9.2 Hz, 2H), 6.75 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 4.38 (dd, J_1 = 3.6 Hz, J_2 = 9.2 Hz, 1H), 4.16-4.05 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.26-3.21 (m, 1H), 3.10-3.08 (m, 1H), 2.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.4, 154.2, 153.1, 137.5, 127.7, 126.8, 115.8, 114.9, 114.2, 112.5, 71.4, 56.0, 55.9, 55.5, 54.9, 54.7, 39.8, 30.2. HRMS calcd. for $C_{18}H_{22}O_3N$, 300.15942 $[M + H]^+$; found, 300.15937 $[M + H]^+$.



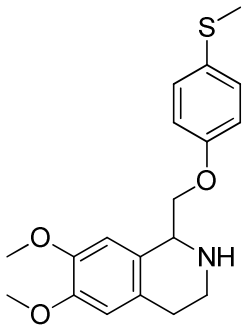
1-((4-methoxyphenoxy)methyl)-6,7-dimethyl-1,2,3,4-tetrahydroisoquinoline (70). Compound **52** was synthesized according to Procedure IV from **34** (2.7 g, 8.6 mmol). The crude material was filtered off as an off-white solid and used without further purification. Compound **70** was prepared according to Procedure VI from crude **52** (2.54 g, 8.6 mmol). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) and afforded the title compound as a white solid (0.5 g, 20% over two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.98 (d, J = 9.0 Hz, 2H), 6.91 (s, 1H), 6.88 (s, 1H), 6.79 (d, J = 9.0 Hz, 2H), 4.59 (dd, J_1 = 3.2 Hz, J_2 = 7.6 Hz, 1H), 4.41 (dd, J_1 = 4 Hz, J_2 = 10 Hz, 1H), 4.31 (dd, J_1 = 7.6 Hz, J_2 = 10 Hz, 1H), 3.75 (s, 3H), 3.49 (m, 1H), 3.22 (m, 1H), 3.05 (m, 1H), 2.94 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ:154.6, 152.3, 136.8, 135.5, 130.6, 127.2, 126.7, 116.4, 114.8, 69.5, 55.9, 55.8, 54.4, 40.0, 26.0, 19.7, 19.6. HRMS calcd. for $C_{19}H_{23}NO_2$, 298.18016 $[M + H]^+$; found, 298.17992 $[M + H]^+$.



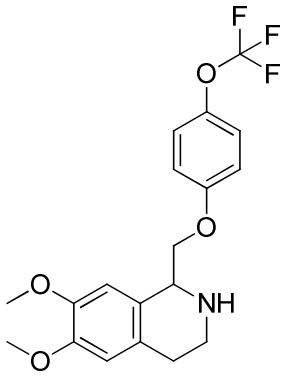
1-((4-methoxyphenoxy)methyl)-6-methyl-1,2,3,4-tetrahydroisoquinoline (71). Compound **53** was synthesized according to Procedure IV from **36** (2.5 g, 8.4 mmol). The crude material was filtered off as an off-white solid, dried and used without further purification. Compound **71** was prepared according to Procedure VI from crude **53** (1.4 g, 5.0 mmol). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) and afforded the title compound as a tan solid. (0.55 g, 23% over two steps). ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.25-7.18 (m, 1H), 7.12-7.05 (m, 3H), 6.97-6.91 (m, 2H), 6.87-6.84 (m, 2H), 4.54-4.18 (m, 2H), 3.72 (s, 3H), 3.62-3.38 (m, 3H), 3.13-2.96 (m, 2H), 2.31 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz) δ: 154.9, 152.2, 138.6, 136.5, 132.2, 128.7, 126.2, 115.8, 115.5, 114.6, 68.5, 54.9, 39.3, 32.0, 25.3, 19.9. HRMS calcd. for $C_{18}H_{22}NO_2$, 284.16451 $[M + H]^+$; found, 284.16463 $[M + H]^+$.



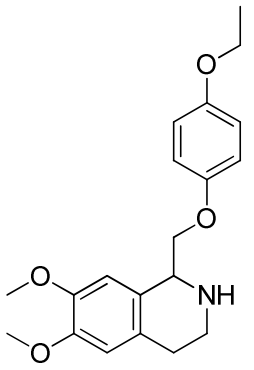
1-((4-(benzyloxy)phenoxy)methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (72). Compound **54** was synthesized according to Procedure IV using **36** (1.1 g, 2.6 mmol). The crude material was filtered off as an off-white solid and used without further purification. Compound **72** was prepared according to Procedure VI from **54** (1.0 g, 2.48 mmol). The crude material was purified by silica gel chromatography (ISCO, Redisep 12g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.18 g, 18% over two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42-7.29 (m, 5H), 7.00 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 6.61 (s, 2H), 4.99 (s, 2H), 4.64-4.61 (m, 1H), 4.46-4.35 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.53-3.47 (m, 1H), 3.28-3.22 (m, 1H), 3.13-3.07 (m, 1H), 3.03-2.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.9, 152.3, 149.3, 148.4, 137.3, 128.8, 128.2, 127.7, 125.3, 120.4, 116.5, 116.0, 108.9, 70.8, 56.4, 56.2, 54.2, 39.8, 25.6. HRMS calcd. for $C_{25}H_{28}NO_4$, 406.20129 $[M + H]^+$; found, 406.20148 $[M + H]^+$.



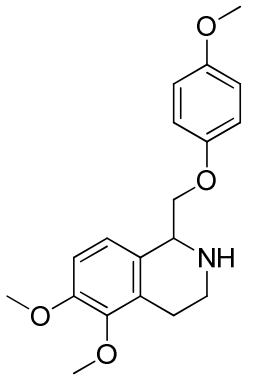
6,7-dimethoxy-1-((4-(methylthio)phenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (73). Compound **55** was synthesized according to Procedure IV using **37** (1.2 g, 3.3 mmol). The crude material was filtered off as an off-white solid and used without further purification. Compound **73** was prepared according to Procedure VI using **55** (1.4 g, 4.1 mmol). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as an off-white solid (0.6 g, 43% over two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.16-7.16 (m, 2H), 6.91-6.76 (m, 2H), 6.59-6.48 (m, 2H), 4.78-4.55 (m, 1H), 4.35 (m, 1H), 4.16-3.90 (m, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.47-3.37 (m, 1H), 3.25-3.22 (m, 1H), 3.04-2.65 (m, 2H), 2.38 (s, 3H). HRMS calcd. for $C_{19}H_{24}NO_3S$, 346.14714 $[M + H]^+$; found, 346.14693 $[M + H]^+$.



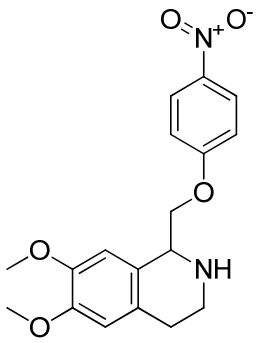
6,7-dimethoxy-1-((4-(trifluoromethoxy)phenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (74). Compound **56** was synthesized according to Procedure IV using **38** (1.0 g, 2.4 mmol). The crude material was filtered off as a white solid and used without further purification. ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.44 (s, 1H), 7.31 (m, 4H), 7.14 (s, 1H), 5.72 (s, 2H), 3.98 (s, 3H), 3.93-3.89 (m, 5H), 3.19-3.15 (m, 2H). Compound **74** was prepared according to Procedure VI using **38** (0.92 g, 2.4 mmol). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as an off-white solid (0.33 g, 36% over two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.11 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 6.63 (s, 1H), 6.60 (s, 1H), 4.65 (m, 1H), 4.50-4.42 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.49-3.38 (m, 2H), 3.28-3.18 (m, 1H), 3.11-3.04 (m, 1H), 2.98-2.90 (m, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 156.4, 149.3, 148.3, 143.6, 125.4, 122.7, 120.4, 116.2, 111.8, 108.9, 69.0, 56.3, 56.1, 53.8, 39.7, 25.4.



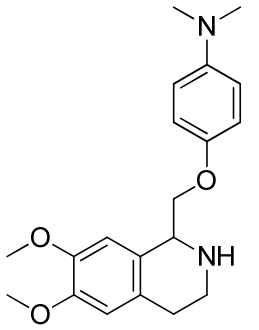
1-((4-ethoxyphenoxy)methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (75). Compound **57** was prepared according to Procedure IV using **39** (1.14 g, 3.2 mmol). The crude yellow solid was filtered and used without further purifications. HRMS calcd. for $C_{20}H_{24}NO_4$, 342.16999 $[M + H]^+$; found 342.17034 $[M + H]^+$. Compound **75** was prepared according to Procedure VI using **57** (1.1 g, 3.2 mmol). The crude material was purified by silica gel chromatography (ISCO, Silicycle 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.27 g, 25%). ^{1}H NMR (CD_3OD, 400 MHz) δ: 6.97 (d, J = 8.8 Hz), 6.77 (d, J = 9.2 Hz, 2H), 6.60 (s, 1H), 6.59 (s, 1H), 4.62 (m, 1H), 4.46-4.34 (m, 2H), 3.93 (q, J = 7.2 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.80-3.74 (m, 1H), 3.54 (m, 1H), 3.34-3.26 (m, 1H), 3.16-2.98 (m, 2H), 1.37 (t, J = 7.2, 3H). HRMS calcd. for $C_{20}H_{26}NO_4$, 344.18564 $[M + H]^+$; found, 344.18599 $[M + H]^+$.



5,6-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (76). Compound **58** was prepared according to Procedure IV using **40** (2.1 g, 6.2 mmol). The crude material was filtered as an off-white solid and used without further purification. HRMS calcd. for $C_{19}H_{22}NO_4$, 328.14533 $[M + H]^+$; found 328.15381 $[M + H]^+$. Compound **76** was prepared according to Procedure VI using **58** (2.0 g, 6.2 mmol). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as an off-white solid (0.45 g, 22% over two steps). ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.11 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 9.6 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.86 (m, 1H), 4.51 (dd, J = 4.0 Hz, J = 10.4 Hz, 1H), 4.24 (dd, J = 9.2 Hz, J = 10.8 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.73 (s, 3H), 3.64-3.59 (m, 1H), 3.42-3.37 (m, 1H), 3.08 (t, J = 6.4 Hz, 2H). ^{13}C NMR (CD_3OD, 100 MHz) δ: 155.1, 152.5, 152.0, 146.5, 126.4, 120.9, 115.8, 114.6, 111.8, 95.8, 65.2, 56.3, 55.4, 48.7, 42.0, 25.3. HRMS calcd. for $C_{19}H_{24}NO_4$, 330.16999 $[M + H]^+$; found, 330.16955 $[M + H]^+$.

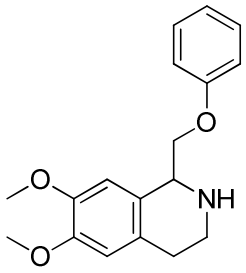


6,7-dimethoxy-1-((4-nitrophenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (77). Compound **59** was prepared according to Procedure IV using **42** (2.5 g, 6.8 mmol, 1.0 equiv). The crude solid was filtered to afford a yellow solid (3.0 g). The crude material was carried on without further purification. HRMS calcd. for $C_{18}H_{18}N_2O_5$, 343.12885 $[M + H]^+$; found 343.12898 $[M + H]^+$. Compound **77** was prepared via Procedure VI using **59** (3.0 g, 8.8 mmol, 1.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-20% MeOH/DCM gradient) to afford the title compound as a yellow solid (2.1 g, 70%). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.66; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.21-8.18 (m, 2H), 7.01-6.98 (m, 2H), 6.67 (s, 1H), 6.64 (s, 1H), 4.42 (m, 1H), 4.23 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.09 (m, 1H), 3.07 (m, 3H), 2.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 163.9, 148.3, 147.5, 141.8, 128.5, 126.2, 125.7, 114.7, 112.3, 109.6, 76.8, 71.8, 56.3, 56.1, 54.6, 39.9, 29.3. HRMS calcd. for $C_{18}H_{20}N_2O_5$, 345.14450 $[M + H]^+$; found 345.14450 $[M + H]^+$.

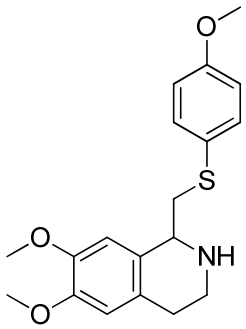


4-((6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methoxy)-*N*,*N*-dimethylaniline (78). Compound **60** was prepared according to Procedure IV using **44** (2.0 g, 4.4 mmol, 1.0 equiv). The crude solid was filtered to afford a brown solid (2.1 g). The crude material was carried on without further purification. HRMS calcd. for $C_{20}H_{24}N_2O_3$, 341.18597 $[M + H]^+$; found 341.18555 $[M + H]^+$. Compound **78** was prepared according to Procedure VI using **60** (2.7 g, 7.9 mmol, 1.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-20% MeOH/DCM gradient) to afford the title compound as a white solid (0.73 g, 27%) TLC (MeOH/DCM, 1:10, v/v) R_f: 0.69; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.88-6.86 (m, 2H), 6.73-6.71 (m, 2H), 6.66 (s, 1H), 6.60 (s, 1H), 4.33-4.30 (t, J = 6.0 Hz, 1H), 4.09-4.08 (d, J = 6 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.22-3.17 (m, 1H), 3.04-2.98 (m, 1H), 2.82 (s, 6H), 2.79-2.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 151.2, 148.0, 147.4, 146.3, 128.2, 126.7,

115.8, 114.9, 112.1, 109.7, 71.5, 56.2, 56.0, 55.0, 41.9, 39.8, 29.4. HRMS calcd. for $C_{20}H_{26}N_2O_3$, 343.20162 $[M + H]^+$; found 343.20124 $[M + H]^+$.

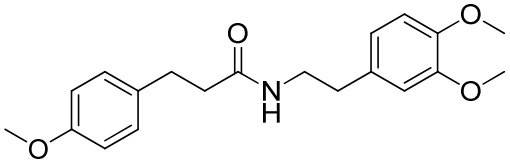


6,7-dimethoxy-1-(phenoxymethyl)-1,2,3,4-tetrahydroisoquinoline (79). Compound **61** was prepared according to Procedure IV using **41** (1.2 g, 3.5 mmol). The crude off-white solid (1.1 g) was carried on without further purification. HRMS (m/z): $[M]^+$ calcd. for $C_{18}H_{19}O_3N$ 298.14377; found 298.14369. Compound **79** was prepared via Procedure VI using **61** (1.1 g, 4.0 mmol). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0%-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.6 g, 54%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.26 (m, 2H), 6.97-6.94 (m, 3H), 6.68 (s, 1H), 6.61 (s, 1H), 4.37 (t, *J*= 5.6 Hz, 1H), 4.17 (d, *J* = 6.4 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.26-3.19 (m, 1H), 3.06-3.00 (m, 1H), 2.80-2.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.9, 148.2, 147.5, 129.7, 128.1, 126.4, 121.3,114.8, 112.1, 109.7, 70.7, 56.2, 56.1, 54.8, 39.9, 29.1.

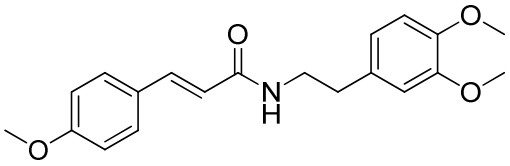


6,7-dimethoxy-1-(((4-methoxyphenyl)thio)methyl)-1,2,3,4-tetrahydroisoquinoline (80). Compound **62** was prepared according to Procedure IV using **43** (2.2 g, 6.1 mmol). The crude solid was filtered and carried on without further purification. HRMS calcd. for $C_{19}H_{22}NO_3S$, 344.13149 $[M + H]^+$; found 344.13095 $[M + H]^+$. Compund **80** was prepared according to Procedure VI using dihydroisoquinoline **62** (2.1 g, 6.1 mmol). The crude material was purified by silica gel chromatography (ISCO, Silicycle 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white amorphous solid (0.95 g, 45% over two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45 (d, *J* = 9.2 Hz, 2H), 6.80 (d, *J* = 9.2 Hz, 2H), 6.53 (s, 1H), 6.47 (s, 1H), 4.34 (t, *J* = 6.0 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.53-3.41 (m,

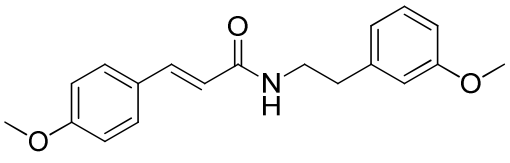
2H), 3.35-3.22 (m, 2H), 2.94 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.3, 148.6, 147.7, 134.3, 132.2, 125.8, 125.4, 114.9, 111.5, 109.9, 56.1, 55.6, 55.5, 53.2, 41.6, 26.4. HRMS calcd. for $C_{19}H_{23}NO_3S$, 346.14714 $[M + H]^+$; found, 346.14755 $[M + H]^+$.



***N*-(3,4-dimethoxyphenethyl)-3-(4-methoxyphenyl)propanamide (142).** Compound **142** was prepared according to Procedure C using 3,4-dimethoxyphenethylamine (**13**, 2.0 g, 11 mmol, 1.0 equiv) and 4-methoxyphenylpropionic acid (2.4 g, 13 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.5 g, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.05 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 9.0 Hz, 2H), 6.73 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 2 Hz, 1H), 6.58 (dd, J_1 = 2 Hz, J_2 = 8.2 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.41 (q, J = 7.2 Hz, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.4, 158.2, 149.2, 147.8, 133.1, 131.6, 129.5, 120.8, 114.1, 112.0, 111.9, 111.5, 56.1, 56.0, 55.5, 55.4, 40.9, 39.0, 35.5, 31.0. HRMS calcd. for $C_{20}H_{25}NO_4$, 344.18564 $[M + H]^+$; found, 344.18531 $[M + H]^+$.

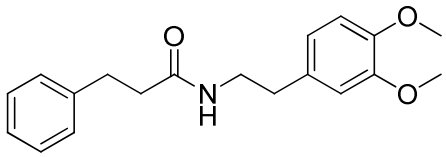


(*E*)-*N*-(3,4-dimethoxyphenethyl)-3-(4-methoxyphenyl)acrylamide (143). Compound **143** was prepared according to Procedure C using 3,4-dimethoxyphenethylamine (**13**, 1.0 g, 5.6 mmol, 1.0 equiv) and 4-methoxycinnamic acid (1.2 g, 6.0 mmol, 1.1 equiv). The crude yellow residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.8 g, 42%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (d, J = 15.6 Hz, 1H), 7.36 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.76-6.68 (m, 3H), 6.23 (d, J = 15.6 Hz, 1H), 6.09 (t, J = 5.6 Hz, 1H), 3.80 (s, 3H), 3.79 (d, 3H), 3.75 (s, 3H), 3.57 (q, J = 6.4 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H).^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.6, 161.0,149.1, 147.8, 140.6, 131.7, 129.5, 127.7, 120.9, 118.6, 114.4, 112.1, 111.5, 56.1, 56.0, 55.6, 55.5, 41.2, 35.5. HRMS calcd. for $C_{20}H_{23}NO_4$, 342.16999 $[M + H]^+$; found, 342.16957 $[M + H]^+$.

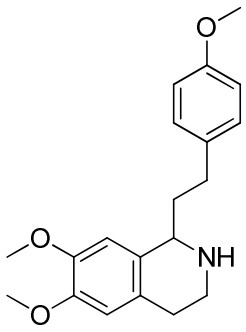


(*E*)-*N*-(3-methoxyphenethyl)-3-(4-methoxyphenyl)acrylamide (144). Compound **144** was prepared according to Procedure C using 3-methoxyphenethylamine (**8**, 3.0 g, 20 mmol, 1.0 equiv) and 4-

methoxycinnamic acid (3.5 g, 20 mmol, 1.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (4.1 g, 66%) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (d, *J* = 16 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.82-6.74 (m, 3H), 6.20 (d, *J* = 15.2 Hz, 1H), 5.78 (t, *J* = 5.4 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.62 (q, *J* = 6.8 Hz, 2H), 2.84 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.5, 161.1, 160.0, 1408, 129.9, 139.6, 127.7, 121.3, 118.5, 114.4, 112.1, 55.6, 55.5, 55.4, 55.3, 40.9. 36.0. HRMS calcd. for $C_{19}H_{21}NO_3$, 312.15942 $[M + H]^+$; found, 312.15894 $[M + H]^+$.

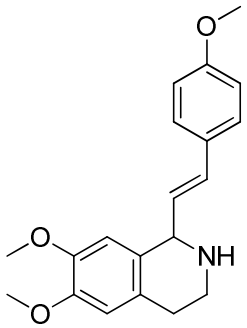


***N*-(3,4-dimethoxyphenethyl)-3-phenylpropanamide (145).** Compound **145** was prepared according to Procedure II using 3,4-dimethoxyphenethylamine (**13**, 1.0 g, 5.5 mmol) and phenylpropionic acid chloride (1.2 g, 7.2 mmol, 1.2 equiv). The crude white solid was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-50% EtOAc/hexanes) to afford the title compound as a white solid (1.7 g, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.17 (m, 5H), 6.77 (d, *J*= 7.6 Hz, 1H), 6.64 (m, 2H), 5.33 (s, 1H, broad), 3.86 (s, 3H), 3.85 (s, 3H), 3.46 (q, *J* = 6.2 Hz, 2H), 2.95 (t, *J* = 6 Hz, 2H), 2.69 (t, *J* = 6 Hz, 2H), 2.42 (t, *J* = 7.2 Hz, 2H). HRMS calcd. for $C_{19}H_{24}NO_3$, 314.17507 $[M + H]^+$; found, 314.17516 $[M + H]^+$.

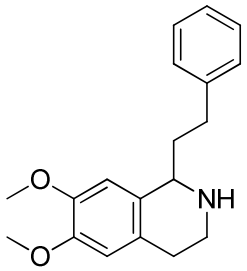


6,7-dimethoxy-1-(4-methoxyphenethyl)-1,2,3,4-tetrahydroisoquinoline (150). Compound **146** was prepared according to Procedure IV using **142** (2.5 g, 7.3 mmol, 1.0 equiv). The crude solid was filtered and carried on without further purification. HRMS calcd. for $C_{20}H_{23}NO_3$, 326.17507 $[M + H]^+$; found, 326.17475 $[M + H]^+$. Compound **150** was prepared via Procedure VI using **146** (3.0 g, 8.3 mmol, 1.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (1.9 g, 70% over two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.18 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.75 (s, 1H), 6.43 (s, 1H), 4.56-4.49 (m, 1H), 4.37 (s, 1H, broad), 3.80 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.63-3.51 (m, 1H), 3.23-

3.08 (m, 1H), 2.92-2.78 (m, 2H), 2.45-2.21 (m, 2H), 2.04-1.83 (m, 2H). HRMS calcd. for $C_{20}H_{26}NO_3$, 328.19072 $[M + H]^+$; found, 328.19057 $[M + H]^+$.

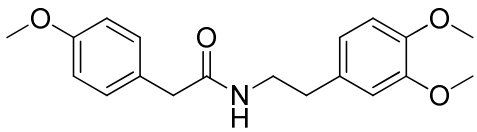


(*E*)-6,7-dimethoxy-1-(4-methoxystyryl)-1,2,3,4-tetrahydroisoquinoline (151). Compound **147** was prepared according to Procedure IV using **143** (0.8 g, 2.3 mmol, 1.0 equiv). The crude orange solid was filtered and carried on without further purification. ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.84-7.79 (m, 3H), 7.52 (s, 1H), 7.42 (d, *J* = 16 Hz, 1H), 7.12 (s, 1H), 7.04 (d, *J* = 9.2 Hz, 2H), 3.98 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 3.82 (t, *J* = 7.2 Hz, 2H), 3.12 (t, *J* = 7.6 Hz, 2H). HRMS calcd. for $C_{20}H_{21}NO_3$, 324.15942 $[M + H]^+$; found, 324.15928 $[M + H]^+$. Compound **151** was prepared via Procedure VI using **147** (0.76 g, 2.4 mmol, 1.0 equiv). The crude residue was subjected to flash column chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a yellow solid (0.44 g, 58% over two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36 (dd, J_1 = 2.2 Hz, J_2 = 8.8 Hz, 2H), 6.80 (dd, *J1* = 2.2 Hz, *J2* = 8.8 Hz, 2H), 6.59-6.55 (m, 2H), 6.44-6.37 (m, 2H), 4.97 (d, *J* = 6.8 Hz, 1H), 3.84-3.73 (m, 10H), 3.41 (m, 1H), 3.20 (m, 1H), 2.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 160.2, 149.1, 148.2, 138.0, 128.7, 128.3, 124.4, 122.4, 122.3, 114.3, 111.4, 110.3, 57.0, 56.2, 55.5, 55.4, 39.0, 25.2.). HRMS calcd. for $C_{20}H_{24}NO_3$, 326.17507 $[M + H]^+$; found, 326.17493 $[M + H]^+$.

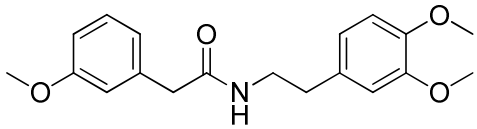


6,7-dimethoxy-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (153). Compound **149** was prepared according to Procedure V using **145 (**1.1 g, 3.5 mmol, 1.0 equiv). The crude white solid (0.65 g, 63% crude) was taken on without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.29-7.15 (m, 5H), 6.93 (s, 1H), 6.67 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.64 (t, *J* = 7.2 Hz, 2H), 2.97 (m, 2H), 2.59 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 150.9, 147.7, 142.3, 131.7, 128.7, 126.2, 122.2, 110.5, 108.7, 56.4, 56.1, 47.2, 38.1, 33.4, 26.1. Compound **153** was prepared via Procedure VI using **149** (0.94 g, 3.0 mmol). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.7 g, 73% over two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.28-7.14 (m, 5H), 6.56 (s, 1H), 6.54 (s, 1H), 3.98-3.86 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.26-3.16 (m, 1H), 2.91-3.01 (m, 1H), 2.86-2.58 (m, 4H), 1.97-2.16 (m, 3H). ^{13}C NMR

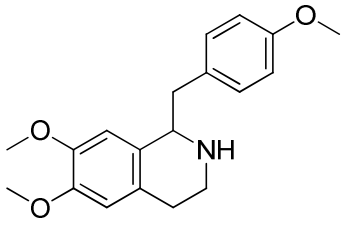
($CDCl_3$, 100 MHz) δ: 147.5, 147.4, 142.6, 131.5, 128.7, 127.5, 126.1, 112.0, 109.3, 56.2, 56.0, 55.3, 53.7, 41.3, 38.5, 32.7, 29.7. HRMS calcd. for $C_{19}H_{24}NO_2$, 298.18016 $[M + H]^+$; found, 298.18005 $[M + H]^+$.



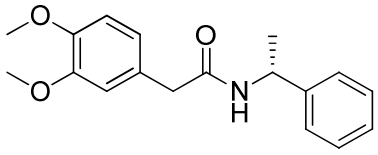
***N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenyl)acetamide (165)**. To a solution of 2-(4-methoxyphenyl)acetic acid (**163**, 3.5 g, 21 mmol) dissolved in DCM (20 ml), thionyl chloride (4.5 ml, 63 mmol) was added. The mixture was stirred for approximately 15 minutes then was immediately concentrated *in vacuo*. The resulting liquid was added to a cooled solution of 3,4-dimethoxyphenethylamine (**13**, 1.5 ml, 8.6 mmol) and triethylamine (3.6 ml, 26 mmol) in DCM (36 mL). The reaction was allowed to warm to room temperature and stirred for 3 hours. The reaction was quenched with 1M HCl and extracted with DCM (2x). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Silicycle 80 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.2 g, 26%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.09-7.05 (m, 2H), 6.85-6.81 (m, 2H), 6.73-6.71 (d, J = 7.9 Hz, 2H), 6.61-6.60 (d, J = 1.8 Hz, 1H), 6.56-6.53 (m, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.46 (s, 2H), 3.44-3.41 (t, J_1 = 6.4 Hz, 2H), 2.69-2.65 (t, J = 6.4 Hz 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 35.3, 41.0, 43.3, 55.5, 56.1, 111.4, 112.0, 114.6, 120.8, 126.8, 126.9, 130.8, 131.3, 147.8, 149.2, 159.0, 171.8. HRMS calcd. for $C_{19}H_{23}NO_4$, 330.16999 $[M + H]^+$; found 330.17031 $[M + H]^+$.



N-(3,4-dimethoxyphenethyl)-2-(3-methoxyphenyl)acetamide (166). To a solution of 2-(3-methoxyphenyl)acetic acid (**164**, 3.5 g, 21 mmol) dissolved in DCM (20 ml), thionyl chloride (4.5 ml, 63.2 mmol) was added. The mixture was stirred for approximately 15 minutes and was immediately concentrated *in vacuo*. The resulting liquid was added to a cooled solution of 3,4-dimethoxyphenethylamine (**13**, 1.5 ml, 8.6 mmol) and triethylamine (3.6 ml, 26 mmol) in DCM (36.3 mL). The reaction was allowed to warm to room temperature and stirred for 3 hours. The reaction was quenched with 1M HCl and extracted with DCM (2x). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 80 g column, 10-80% EtOAc/hexanes gradient) to afford a white solid (2.4 g, 84 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.23-7.19 (t,J = 8.2 Hz, 1H), 6.82-6.79 (m, 1H), 6.75 - 6.70 (m, 3H), 6.59 (dJ = 2 Hz, 1H), 6.54-6.52 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.48 (s, 2H), 3.45 - 3.40 (t, J = 6.7 Hz, 2H), 2.68-2.65 (t, J = 6.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.9, 160.2, 149.2, 147.7, 136.4, 131.3, 130.2, 121.8, 120.8, 115.1, 113.1, 111.9, 111.4, 56.1, 55.9, 55.3, 44.1, 40.1, 35.2. HRMS calcd. for $C_{19}H_{23}O_4N_1$, 330.17024 $[M + H]^+$; found 330.16999 $[M + H]^+$.

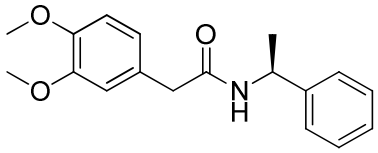


6,7-dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (169). Compound **167** was prepared according to Procedure IV using **165** (1.2 g, 3.7 mmol, 2.0 equiv). The crude solid was filtered to afford a green solid (0.88 g). The crude material was carried on without further purification. HRMS calcd. for $C_{19}H_{21}NO_3$, 312.15942 $[M + H]^+$; found 312.15977 $[M + H]^+$. Compound **169** was prepared via Procedure VI using **167** (0.88 g, 2.8 mmol, 2.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-20% MeOH/DCM gradient) to afford the title compound as a brown solid (1.2 g, 26 %); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.14-7.12 (d, J = 8.8 Hz, 2H), 6.85-6.83 (d, J = 8.5 Hz, 2H), 6.58 (s, 1H), 6.06 (s, 1H), 4.66-4.63 (m 1H), 3.85 (s, 3 H), 3.78 (s, 3H), 3.57 (s, 3H), 3.37-3.35 (m, 2H), 3.17-3.12 (m, 2H), 2.98-2.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.0, 148.7, 147.3, 131.4, 138.2, 123.9, 123.6, 114.3, 111.4, 110.1, 56.0, 55.7, 55.5, 40.4, 38.8, 25.5. HRMS calcd. for $C_{19}H_{23}NO_3N$, 314.17507 $[M + H]^+$; found 314.17543 $[M + H]^+$.

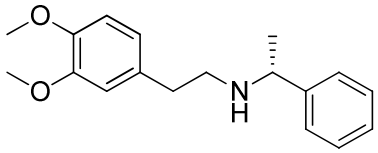


(R)-2-(3,4-dimethoxyphenyl)-N-(1-phenylethyl)acetamide (178-*R*).

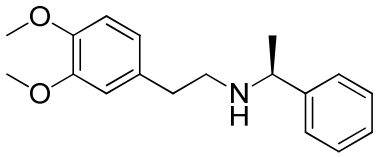
(*R*)-1-phenylethanamine (**177-*R*,** 1.1 g, 1.2 mL, 9.3 mmol) was dissolved in dry DCM (20 mL). A 5% aqueous solution of NaOH (30 mL) was added and the biphasic mixture was allowed to stir for 15 minutes. 3,4-dimethoxyacetyl chloride (**176**, 2.0, 1.6 mL, 37.5 mmol, 4.2 equiv) was added dropwise. The reaction was allowed to stir for 1 hour until TLC indicated complete conversion. The water was quenched by addition of water and extracted with DCM (2x). The combined organics were washed with brine, dried over MgSO4, filtered and concentrated in vacuo to give a light brown solid. The crude material was purified by silica gel chromatography (ISCO, Redisep 40 g column, 30-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.5 g, 90%). $[\alpha]^{20} = -12.1$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24-7.21 (m, 5H), 6.79-6.72 (m, 3H), 6.04 (s, 1H, broad), 5.10 (quin, J = 7.2 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.41 (s, 2H), 1.35 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 149.3, 148.4, 143.5, 128.8, 127.7, 127.4, 126.2, 121.7, 112.4, 111.6, 56.1, 56.0, 48.8, 43.5, 22.0. HRMS calc'd for $C_{18}H_{22}NO_3$, 300.15942 $[M+H]^+$, found 300.15942 $[M+H]^+$.



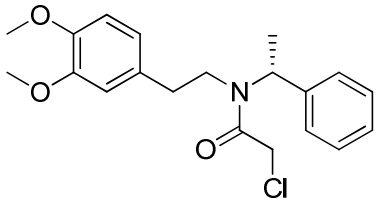
(*S*)-2-(3,4-dimethoxyphenyl)-N-(1-phenylethyl)acetamide (178-*S*). Compound **178-*S*** was synthesized as above for the *R*-enantiomer using (*S*)-1-phenylethanamine (**177-*S***, 1.1 g, 1.2 mL, 9.3 mmol) and 3,4-dimethoxyacetyl chloride (**176**, 2.0, 1.6 mL, 37.5 mmol, 4.2 equiv). The title compound was obtained as a white solid (2.0 g, 72%). $[\alpha]^{20} = +12.2$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25-7.14 (m, 5H), 6.78-6.71 (m, 3H), 6.04 (s, 1H, broad), 5.06 (quin, J = 7.2 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.43 (s, 2H), 1.34 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.4, 149.3, 148.6, 143.5, 129.0, 127.4, 127.4, 126.2, 121.7, 112.4, 111.3, 56.1, 56.2, 48.6, 43.5, 21.8. HRMS m/z calc'd for $C_{18}H_{22}NO_3$, 300.15942 $[M+H]^+$, found 300.15951 $[M+H]^+$.



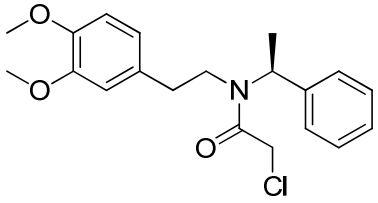
(*R*)-N-(3,4-dimethoxyphenethyl)-1-phenylethanamine (179-*R*). Compound **179-*R*** (3.6 g, 12 mmol) was dissolved in dry THF (50 mL). Boron trifluoride etherate (0.7 g, 0.6 mL, 4.8 mmol, 0.4 equiv) was added to the reaction and it was heated to reflux. Borane methyl sulfide complex (1.0 M in THF, 30.1 mL, 2.5 equiv) was added to the refluxing solution and the reaction was stirred at reflux for 2 hours. After cooling to room temperature, the reaction was cooled in an ice bath to 0 ^{o}C and 4.5 M HCl (40 mL) was added carefully. The resulting solution was allowed to stir at 0 ^{o}C for an additional 1 hour. The solution was allowed to warm to room temperature and stirred at room temperature for 1 hour. The volatiles were removed *in vacuo* and the resulting mixture was cooled to 0 ^{o}C and basified to pH 13 with solid KOH. Water and DCM were added to solubilize any salts that formed. The mixture was then extracted with DCM (4x) and combined organics were dried over $MgSO_4$. The title compound was afforded as a clear oil (3.1 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.27-7.17 (m, 5H), 6.72 (d, J=8.4 Hz, 1H), 6.65 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.72 (q, J=6.4 Hz, 1H), 2.63-2.73 (m, 4H), 1.29 (d, 3H, J= 6.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.1, 147.6, 145.6, 132.7, 128.6, 127.1, 126.7, 120.8, 112.0, 111.4, 58.4, 56.1, 56.0, 49.1, 36.0, 24.4. HRMS calc'd for $C_{18}H_{24}NO_2$, 286.18016 $[M + H]^+$, found 286.18019, $[M + H]^+$.



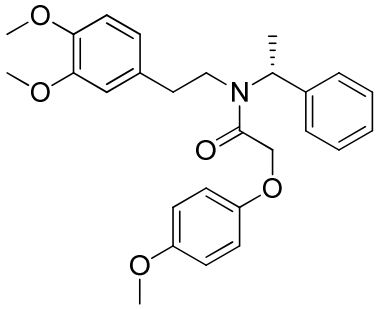
(S)-N-(3,4-dimethoxyphenethyl)-1-phenylethanamine (179-*S*). Compound **179-*S*** was synthesized as above with **180-*S*** (2.1 g, 7.0 mmol) to afford the title compound as a clear oil (1.9 g, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.19 (m, 5H), 6.76 (d, *J*=8.4 Hz, 1H), 6.71-6.65 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.74 (q, *J*=6.4 Hz, 1H), 2.74-2.65 (m, 4H), 1.30 (d, *J*= 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.0, 147.6, 145.8, 132.8, 128.6, 127.1, 126.7, 120.8, 112.0, 111.4, 58.4, 56.1, 56.0, 49.1, 36.1, 24.5. HRMS calc'd for $C_{18}H_{24}NO_2$, 286.18016 $[M + H]^+$, found 286.18015, $[M + H]^+$.



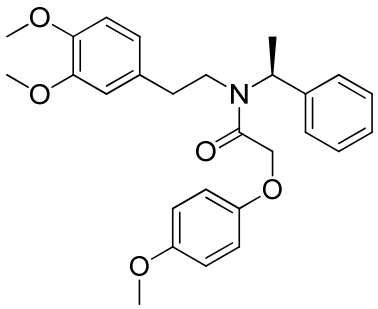
(*R*)-2-chloro-N-(3,4-dimethoxyphenethyl)-*N*-(1-phenylethyl)acetamide (180-*R*). Compound **179-*R*** (3.1 g, 10.9 mmol) was dissolved in dry DCM (40 ml). Triethylamine (3.3 g, 4.5 mL, 33 mmol, 3.0 equiv) was added and the reaction was cooled to 0 °C in an ice bath. 2-chloroacetyl chloride (1.5 g, 1.0 mL, 13 mmol, 1.2 equiv) was added dropwise and the reaction was allowed to warm to room temperature. After 1 hour, TLC indicated the reaction was complete. Water and 1M HCl were added to quench followed by extraction into DCM (2x). The combined organics were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the final product as an off-white solid (3.1 g, 78%, mixture of rotamers). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38-7.29 (m, 5H), 6.73-6.68 (m, 1H), 6.51-6.45 (m, 2H), 1H [5.94, 5.15 (m, m)], 2H [4.21, 4.97 (m, m)], 3.79 (s, 6H), 3.30-3.17 (m, 2H), 2.77-2.48 (m, 1H), 2.37-2.24 (m, 1H), 1.64-1.60 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ:167.0, 166.6, 149.3, 149.0, 148.1, 147.6, 140.2, 139.7, 132.1, 130.6, 129.0, 128.9, 128.3, 128.1, 127.3, 120.8, 120.7, 112.2, 111.8, 111.6, 56.2, 56.1, 56.0, 52.7, 50.0, 46.3, 46.2, 42.0, 41.8, 37.0, 34.3, 18.4, 16.8. HRMS calc'd for $C_{20}H_{25}NO_3Cl$, 362.15175 $[M + H]^+$, found 362.15131, $[M + H]^+$.



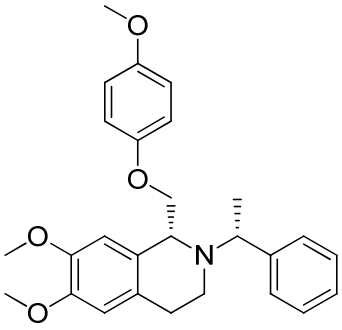
(*S*)-2-chloro-N-(3,4-dimethoxyphenethyl)-N-(1-phenylethyl)acetamide (180-*S*). Compound **180-*S*** was synthesized as above using **179-*S*** (1.9 g, 6.6 mmol). The title compound was obtained as an off-white solid (1.8 g, 76%, mixture of rotamers). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42-7.34 (m, 5H), 6.76-6.71 (m, 1H), 6.54-6.36 (m, 2H), 1H [5.99, 5.18 (m, m)], 2H [4.26, 4.00 (m, m)], 3.82 (s, 6H), 3.32-3.19 (m, 2H), 2.80-2.51 (m, 1H), 2.40-2.25 (m, 1H), 1.64-1.60 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.6, 149.0, 147.7, 140.2, 139.7, 132.1, 129.0, 128.8, 128.3, 127.3, 120.8, 120.6, 112.2, 111.8, 111.6, 111.3, 56.2, 56.1, 56.0, 52.6, 46.3, 46.2, 42.0, 41.8, 36.9, 34.3, 18.4, 16.8, 14.4. HRMS calc'd for $C_{20}H_{25}NO_3Cl$, 362.15175 $[M + H]^+$, found 362.15172, $[M + H]^+$.



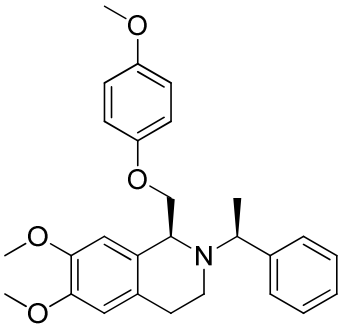
(*R*)-*N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenoxy)-*N*-(1-phenylethyl)acetamide (181-*R*). 4-methoxyphenol (0.25 g, 2.0 mmol, 1.2 equiv) was dissolved in dry MeCN (10 mL). To this solution was added cesium carbonate (2.2 g, 6.6 mmol, 4.0 equiv) and the reaction mixture was allowed to stir at room temperature for 1 hour. **180-*R*** (0.6 g, 1.7 mmol, 1.0 equiv) was dissolved in MeCN (10 mL) and then added to the reaction. The resulting mixture was allowed to stir at room temperature for 16 hours. After LCMS indicated complete consumption of starting material, the reaction was quenched by addition of saturated aqueous NH_4Cl solution and extracted into EtOAc (3x). The combined organics were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the final product as a pale yellow oil (0.6 g, 76%, mixture of rotamers). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37-7.21 (m, 5H), 6.93-6.81 (m, 4H), 6.70-6.65 (m, 1H), 6.49-6.33 (m, 2H), 1H [5.95, 5.30 (m, m)], 4.77-4.57 (m, 2H), 3.78-3.72 (m, 9H), 3.28-3.17 (m, 2H), 2.74-2.49 (m, 1H), 2.37-2.19 (m, 1H), 1.58 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.7, 168.5, 154.6, 153.3, 152.3, 150.9, 149.0, 148.0, 147.6, 140.4, 139.9, 132.2, 131.0, 128.9, 128.3, 128.1, 127.5, 120.8, 116.3, 115.9, 115.8, 115.0, 114.9, 112.2, 111.9, 111.6, 111.3, 69.0, 56.1, 56.0, 55.2, 52.7, 46.0, 36.8, 34.5, 18.2, 16.9, 14.4.



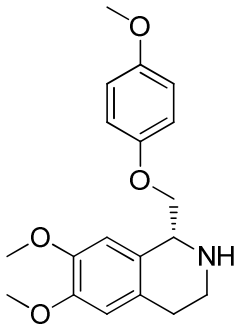
(*S*)-*N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenoxy)-*N*-(1-phenylethyl)acetamide (181-*S*). Compound **181-*S*** was synthesized as above with **180-*S*** (1.8 g, 5.1 mmol, 1.0 equiv), 4-methoxyphenol (0.76 g, 6.1 mmol, 1.2 equiv), and cesium carbonate (6.6 g, 20.3 mmol, 4.0 equiv). The title compound was obtained as a pale yellow oil (1.7 g, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34-7.26 (m, 5H), 6.91-6.78 (m, 4H), 6.70-6.64 (m, 1H), 6.49-6.32 (m, 2H), 1H [5.95, 5.28 (m, m)], 4.77-4.57 (m, 2H), 3.75-3.69 (m, 9H), 3.29-3.13 (m, 2H), 2.75-2.53 (m, 1H), 2.35-2.22 (m, 1H), 1.58 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.5, 168.2, 154.6, 152.4, 149.2, 149.0, 148.0, 140.5, 140.1, 132.3, 131.0, 128.9, 128.8, 128.3, 127.5, 120.8, 120.7, 115.9, 115.7, 114.9, 112.2, 111.9, 111.6, 111.3, 69.0, 68.6, 56.1, 56.0, 55.8, 55.1, 45.9, 36.8, 34.5, 18.2, 16.9.



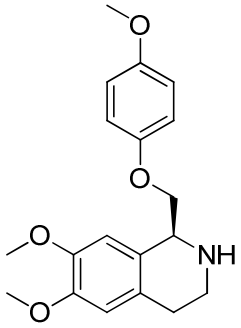
(*R*)-6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-2-((*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (182-*R*,*R*). The amide **181-*R*** (0.57g, 1.3 mmol, 1.0 equiv) was dissolved in dry toluene (20 mL). Phosphorous oxychloride (0.58 g, 0.36 mL, 3.58 mmol, 3.0 equiv) was added to this solution and the reaction was heated to reflux. After 4 hours, LCMS (C_8 column, 75-95% MeOH/water with 0.1% formic acid) indicated complete conversion of the starting material. The reaction was removed from heat and allowed to cool to room temperature. The volatiles were removed *in vacuo*. The resulting residue was dissolved in dry MeOH (15 mL) and cooled in a dry ice/acetone bath to -78 ^{o}C. Sodium borohydride (0.14 g, 3.8 mmol, 3.0 equiv) was added in portions of 50 mg at a time every 30 minutes. After the addition was complete, the reaction was allowed to stir at -78 ^{o}C for an additional 1 hour. Once the starting material was consumed as monitored by LCMS, the reaction was quenched by addition of 10% aqueous HCl solution at -78 ^{o}C. The MeOH was removed via rotary evaporation and the resulting mixture was cooled in an ice bath to 0 ^{o}C. The reaction mixture was basified to pH 13 with solid KOH. Water was added and the aqueous mixture was extracted with DCM (3x). The combined organics were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the final product as a white amorphous solid (0.15 g, 27%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40 (d, *J*= 7.6 Hz, 2H), 7.30 (m, 2H), 7.23-7.21 (m, 1H), 6.76-6.69 (m, 4H), 6.61-6.60 (m, 2H), 4.25-4.20 (m, 1H), 4.04 (t, *J* = 6.4 Hz, 1H), 3.92-3.86 (m, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 3.29-3.13 (m, 2H), 2.94-2.83 (m, 1H), 2.41-2.48 (m, 1H), 1.44 (d, *J*= 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.8, 153.2, 147.9, 147.3, 146.4, 128.5, 127.8, 127.7, 127.2, 115.4, 114.7, 111.8, 111.5, 72.2, 59.5, 57.8, 56.0 (2), 55.8, 40.9, 24.3, 21.2. HRMS calc'd for $C_{27}H_{32}NO_4$, 434.23259 $[M + H]^+$, found 434.23219, $[M + H]^+$.



(*S*)-6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-2-((*S*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (182-*S*,*S*). The compound **182-*S*,*S*** was synthesized according to the above procedure starting with **181-*S*** (1.3 g, 2.9 mmol). The resulting crude residue from the cyclization was subjected to sodium borohydride (0.34 g, 9.0 mmol, 3.0 equiv). Upon purification, the title compound was obtained as a white amorphous solid (0.6 g, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (d, *J*=7.2 Hz, 2H), 7.34 (t, *J*= 8.0 Hz, 2H), 7.26 (d, *J* = 7.2 Hz, 1H), 6.78 (d, *J*= 9.2 Hz, 2H), 6.74 (d, *J*=9.2 Hz, 2H), 6.65 (s, 1H), 6.64 (s, 1H), 4.27 (q, *J*= 6.8 Hz, 1H), 4.08 (t, *J* = 6.8 Hz, 1H), 3.93 (m, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.25 (m, 2H), 2.92 (m, 1H), 2.49 (m, 1H), 1.46 (d, *J*= 8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) δ: 153.9, 153.3, 148.0, 147.3, 146.4, 128.6, 127.9, 127.8, 127.2, 127.2, 115.5, 114.8, 111.9, 111.5, 72.3, 59.6, 57.9, 56.1, 56.1, 55.9, 40.9, 24.3, 21.7. HRMS calc'd for $C_{27}H_{32}NO_4$, 434.23259 $[M + H]^+$, found 434.23285, $[M + H]^+$.



(*R*)-6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (63-*R*). Compound **182-*R*,*R*** (0.15 g, 0.35 mmol) was dissolved in 200 proof EtOH (10 mL). Palladium on carbon (10%, 0.07 g, 0.07 mmol, 0.2 equiv) was added. The reaction vessel was purged (2x) with argon and vacuum. The flask was fitted with a septum and hydrogen balloon and was allowed to stir at room temperature for 24 hours. The reaction mixture was then filtered over a pad of celite and washed with MeOH and EtOAc. The solution was concentrated *in vacuo* and the resulting off-white amorphous solid was taken onto the next step without further purification (0.05 g, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.91-6.69 (m, 4H), 6.64 (s, 1H), 6.61 (s, 1H), 6.24 (s, 1H, broad), 4.49 (m, 1H), 4.29-4.17 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.79-3.71 (m, 3H), 3.38-3.10 (m, 2H), 2.94-2.81 (m, 2H). ^{13}C NMR (100 MHz, CDCl3) δ: 154.5, 152.6, 148.5, 147.8, 126.9, 123.9, 116.0, 114.8, 111.9, 109.3, 70.5, 56.3, 56.1, 55.8, 39.8, 27.7. HRMS calc'd for $C_{19}H_{24}NO_4$, 330.16999 $[M + H]^+$, found 330.17039, $[M + H]^+$.



(S)-6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (63-*S*). Compound **63-*S*** was synthesized as above with **182-*S*,*S*** (0.6 g, 1.4 mmol). The crude material was carried on without purification (0.4 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.98 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.60 (s, 1H), 6.59 (s, 1H), 4.45 (m, 1H), 4.25-4.13 (m, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.76-3.72 (m, 3H), 3.40-3.12 (m, 2H), 2.91-2.79 (m, 2H). ^{13}C NMR (100 MHz, CDCl3) δ: 154.8, 152.0, 149.2, 148.4, 125.1, 120.2, 116.6, 114.8, 111.8, 108.9, 69.2, 56.3, 56.1, 55.9, 39.8, 27.3. HRMS calc'd for $C_{19}H_{24}NO_4$, 330.16999 $[M + H]^+$, found 330.17021, $[M + H]^+$.