The Structure Activity Relationship of a Tetrahydroisoquinoline Class of *N*-Methyl-D-Aspartate Receptor Modulators that Potentiates GluN2B-Containing *N*-Methyl-D-Aspartate Receptors

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Table S1. **Potentiation of GluN2A**

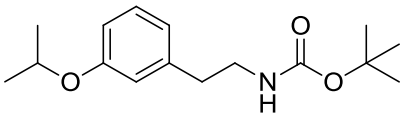
#	**GluN1/GluN2A $I_{30\mu M}$ / $I_{control}$ (mean ± SEM, %)**
88	123 ± 7.5
93	122 ± 5.3
105	154 ± 12
106	131 ± 9.4
114	140 ± 5.1
127	133 ± 3.5
128	147 ± 4.3
136	153 ± 3.4
139	122 ± 12
140	121 ± 3.3
***R*-(+)-2**	99 ± 6.7
***S*-(-)-2**	111 ± 1.6
***R*-(+)-138**	107 ± 2.3
***S*-(-)-138**	109 ± 2.1
***R*-(+)-97**	96 ± 2.3
***S*-(-)-97**	98 ± 2.6
***R*-(+)-142**	99 ± 2.7
***S*-(-)-142**	112 ± 2.3

The ratio of the current response to 100 μM glutamate and 30 μM glycine with test compound to the response to glutamate and glycine alone is shown for oocytes expressing GluN1/GluN2A. For some experiments, oocytes were injected with BAPTA to reduce amplitude dependent instability of the current response (see *Methods*). Data are from 4-12 oocytes from 1-3 frogs.

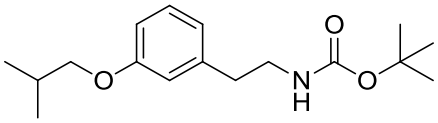
Table S2. Crystal data and structure refinement for *S*-(-)-138

Formula	$C_{27}H_{28}ClNO_3S$
$D_{calc.}$/ g cm^{-3}	1.298
μ/mm^{-1}	2.390
Formula Weight	482.01
Colour	colourless
Shape	plate
Max Size/mm	0.76
Mid Size/mm	0.48
Min Size/mm	0.15
T/K	173(2)
Crystal System	monoclinic
Flack Parameter	0.05(4)
Hooft Parameter	0.027(12)
Space Group	$P2_1$
a/Å	5.7587(3)
b/Å	16.3557(8)
c/Å	13.1050(6)
α/°	90
β/°	91.808(3)
γ/°	90
V/Å^3	1233.71(10)
Z	2
Z'	1
Θ_{min}/°	2.702
Θ_{max}/°	68.050

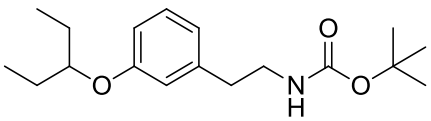
Measured Refl.	9144
Independent Refl.	4191
$I > 2\sigma(I)$	3383
R_{int}	0.0635
Parameters	302
Restraints	195
Largest Peak	0.932
Deepest Hole	-0.566
GooF	1.314
wR_2 (all data)	0.3083
wR_2	0.2798
R_1 (all data)	0.1243
R_1	0.1020



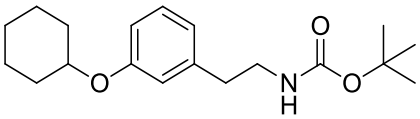
***tert*-butyl 3-isopropoxyphenethylcarbamate (4):** Compound **4** was prepared via procedure I using compound **3** (2.6 g, 11 mmol), potassium carbonate (5.0 g, 36 mmol) and 2-iodopropane (1.4 ml, 9.1 mmol) in dry DMF (28mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 80 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a clear oil (1.8 g, 72 %) TLC (MeOH:DCM, 1:10, v/v) R_f = 0.86; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.17 (t, *J* = 8.0 Hz, 1H), 6.75-6.70 (m, 3H), 4.55-4.51 (m, 1H), 3.36-3.35 (m, 2H), 2.73 (t, *J* = 7.2, 2H), 1.41 (s, 9H), 1.32 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.3, 156.1, 140.9, 129.8, 121.2, 116.6, 113.9, 79.4, 69.9, 41.9, 36.4, 28.6, 22.3; HRMS calcd. for $C_{16}H_{25}O_3N_1{}^{23}Na_1$, 280.19072 $[M + H]^+$; 280.19035 found, $[M + H]^+$.



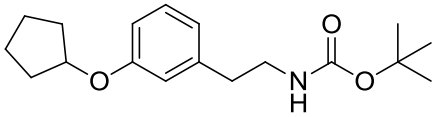
***tert*-butyl 3-isobutoxyphenethylcarbamate (5)**: Compound **5** was prepared via procedure I using compound **3** (3.5 g, 15 mmol), potassium carbonate (8.2 g, 59 mmol) and 1-iodo-2-methylpropane (2.6 ml, 22 mmol) in dry DMF (44 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 80 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a clear oil (1.5 g, 35 %) TLC (EtOAc/hexanes, 1:3, v/v) R_f = 0.58; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.19 (t, *J* = 8.0 Hz, 1H), 6.76-6.72 (m, 3H), 4.53 (bs, 1H), 3.69 (d, *J* = 6.4 Hz, 2H), 3.38-3.33 (m, 2H), 2.76-2.73 (m, 2H), 2.09-2.02 (m, 1H), 1.41 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 6H); HRMS calcd. for $C_{12}H_{20}ON$, 194.15394 $[M + H]^+$; 194.15390 found, $[M + H]^+$.



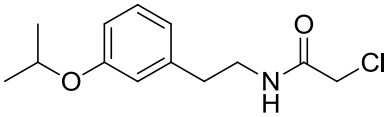
***tert*-butyl 3-(pentan-3-yloxy)phenethylcarbamate (6)**: Compound **6** was prepared via procedure II using compound **3** (3.0 g, 13 mmol), triphenylphosphine (3.3 g, 13mmol), triethylamine (1.8 ml, 13 mmol), 3-pentanol (1.6 ml, 15 mmol), and (*Z*)-diisopropyl diazene-1,2-dicarboxylate (2.1 ml, 13 mmol) in dry THF (13 ml). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a clear oil (1.3 g, 34 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.86; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17 (t, *J* = 8.0 Hz, 1H), 6.75-6.72 (m, 3H), 4.55 (bs, 1H), 4.12-4.06 (m, 1H), 3.38-3.33 (m, 2H), 2.73 (t, *J* = 6.8 Hz, 2H), 1.69-1.62 (m, 4H), 1.42 (s, 9H), 0.93 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.1, 156.1, 129.7, 121.1, 116.8, 113.9, 80.3, 79.3, 41.8, 36.4, 28.6, 22.3, 9.83; HRMS calcd. for $C_{13}H_{22}ON$, 208.16959 $[M + H]^+$; 208.16956 found, $[M + H]^+$.



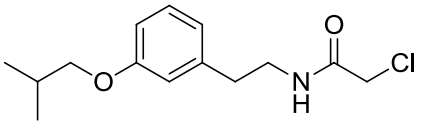
***tert*-butyl 3-(cyclohexyloxy)phenethylcarbamate (7)**: Compound **7** was prepared via procedure II using compound **3** (2.0 g, 8.4 mmol), triphenylphosphine (2.2 g, 8.4 mmol), triethylamine (1.2 ml, 8.4 mmol), cyclohexanol (0.88 ml, 8.4 mmol) and (*Z*)-diisopropyl diazene-1,2-dicarboxylate (1.4 ml, 8.4 mmol) in dry THF (8.4 ml). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.63 g, 23%). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.92; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17 (t, 1H, *J* = 15.6 Hz), 6.78-6.71 (m, 3H), 4.52 (bs, 1H), 4.24-4.18 (m, 1H), 3.36-3.35 (m, 2H), 2.75-2.72 (m, 2H), 1.98-1.94 (m, 2H), 1.82-1.78 (m, 2H) 1.54-1.26 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.1, 156.1, 140.7, 129.7, 121.1, 116.8, 114.0, 75.4, 63.3, 41.9, 36.4, 32.0, 28.6, 25.8, 24.0; HRMS calcd. for $C_{14}H_{22}ON$, 220.16959 $[M + H]^+$; 220.16960 found, $[M + H]^+$.



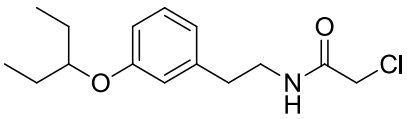
***tert*-butyl 3-(cyclopentyloxy)phenethylcarbamate (8):** Compound **8** was prepared via procedure I using compound **3** (1.2 g, 5.1 mmol), cesium carbonate (6.9 g, 21.2 mmol) and iodocyclopentane (0.83 ml, 4.3 mmol) in dry DMF (13 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 80 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.61 g, 47 %) TLC (MeOH:DCM, 1:10, v/v) R_f = 0.83; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.17 (t, *J* = 8.0 Hz, t), 6.73-6.69 (m, 3H), 4.75-4.71 (m, 1H), 4.53 (s, 1H), 3.78-3.33 (m, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 1.92-1.74 (m, 6H), 1.73-1.56 (m, 2H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.5, 156.1, 140.7, 129.7, 120.9, 116.3, 113.5, 79.2, 41.8, 36.4, 33.1, 28.6, 24.2; HRMS calcd. for $C_{18}H_{27}O_3N^{23}Na$, 382.18832 $[M + H]^+$; 382.18798 found, $[M + H]^+$.



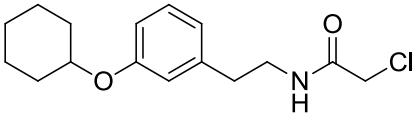
2-chloro-*N*-(3-isopropoxyphenethyl)acetamide (14): Compound **9** was prepared via procedure III using Compound **4** (2.9 g, 11 mmol). The compound was carried forward without further purification. HRMS calcd. for $C_{11}H_{18}O_1N_1$, 180.13829 $[M + H]^+$; 180.13808 found, $[M + H]^+$. Compound **14** was prepared via procedure IV amine **9** (2.2 g, 10 mmol), triethylamine (2.8 ml, 20 mmol) and 2-chloroacetyl chloride (0.97 ml, 12 mmol) in dry DCM (43 mL) and saturated $NaHCO_3$ (10. mL). The crude product was purified by silica gel chromatography (10-90 EtOAc/hexanes) to afford the title compound as a white oil (1.8 g, 71 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.58; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.20 (t, *J* = 7.6 Hz, 1H), 6.77-6.71 (m, 3H), 6.61 (bs, 1H), 4.56-4.49 (m, 1H), 4.00 (s, 2H), 3.54 (q, *J* = 7.2 Hz, *J* = 12.8 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 1.32 (s, 3H), 1.30 (s, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 166.1, 158.4, 140.1, 129.9, 121.1, 116.7, 114.2, 69.9, 42.9, 41.1, 35.7, 22.3; HRMS calcd. for $C_{13}H_{19}O_2N_1{}^{35}Cl_1$, 256.10988 $[M + H]^+$; 256.10950 found, $[M + H]^+$.



2-chloro-*N*-(3-isobutoxyphenethyl)acetamide (15): Compound **10** was prepared via procedure III using compound **5** (1.7 g, 5.8 mmol). The compound was carried forward without further purification. HRMS calcd. for $C_{12}H_{20}ON$, 194.15394 $[M + H]^+$; 194.15384 found, $[M + H]^+$. Compound **15** was prepared via procedure IV using amine **10** (1.3 g, 5.5 mmol), triethylamine (1.5 ml, 11 mmol) and 2-chloroacetyl chloride (0.52 ml, 6.6 mmol) in DCM (20 mL) and saturated $NaHCO_3$ (10. mL). The crude product was purified by silica gel chromatography (10-90% EtOAc/hexanes) to afford the title compound as a white oil (0.91 g, 62 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 074; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.24-7.19 (m, 2H), 6.78-6.73 (m, 3H), 6.60 (bs, 1H), 4.01 (s, 2H), 3.69 (d, *J* = 8.0 Hz, 2H), 3.55 (q, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 6.8 Hz, 2H), 2.09-2.03 (m, 1H), 1.00 (d, *J* = 6.0 Hz, 6H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 165.9, 159.8, 140.0, 129.9, 121.0, 115.2, 112.9, 74.5, 42.9, 41.1, 35.7, 28.5, 19.5; HRMS calcd. for $C_{14}H_{21}O_2N_1{}^{35}Cl_1$, 270.12553 $[M + H]^+$; 270.12551 found, $[M + H]^+$.

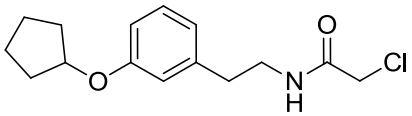


2-chloro-*N*-(3-(pentan-3-yloxy)phenethyl)acetamide (16): Compound **11** was prepared via procedure III using compound **6** (1.3 g, 4.3 mmol). The compound was carried forward without further purification. HRMS calcd. for $C_{13}H_{22}ON$, 208.16959 $[M + H]^+$; 208.16952 found, $[M + H]^+$. Compound **16** was prepared via procedure III using by amine **11** (1.1 g, 4.6 mmol), triethylamine (1.3 ml, 8.1 mmol) and 2-chloroacetyl chloride (0.44 ml, 5.5 mmol) in DCM (18 mL) and saturated $NaHCO_3$ (10. mL). The crude product was purified by silica gel chromatography (10-90 % EtOAc/hexanes) to afford the title compound as a white oil (0.74 g, 58 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.71; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.20 (t, *J* = 15.6 Hz, 1H), 6.77-6.72 (m, 3H), 6.62 (bs, 1H), 4.13-4.07 (m, 1H), 4.02 (s, 2H), 3.55 (q, *J* = 7.2 Hz, 2H), 2.79 (t, *J* = 6.8 Hz, 2H), 1.69-1.62 (m, 4H), 0.93 (t, *J* = 7.6 Hz, 6H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 116.0, 159.3, 140.1, 129.9, 120.9, 116.7, 114.2, 80.3, 42.9, 41.0, 35.7, 26.2, 9.8; HRMS calcd. for $C_{15}H_{23}O_2N^{35}Cl$, 284.14118 $[M + H]^+$; 284.14120 found, $[M + H]^+$.

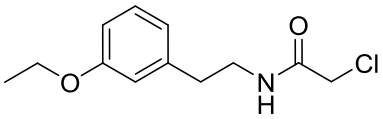


2-chloro-*N*-(3-(cyclohexyloxy)phenethyl)acetamide (17): Compound **12** was prepared via procedure III using compound **7** (1.1 g, 3.5 mmol). The compound was carried forward without further purification. HRMS calcd. for $C_{14}H_{22}ON$, 220.16960 $[M + H]^+$; 220.16955 found, $[M + H]^+$. Compound **17** was prepared via Procedure IV using amine **12** (0.86 g, 8.4 mmol), triethylamine (0.94 ml, 6.8 mmol) and 2-chloroacetyl chloride (0.33 ml, 4.1 mmol) in DCM (13 mL) and saturated $NaHCO_3$ (10. mL). The crude product was purified by silica gel chromatography (10-90% EtOAc/hexanes) to afford the title compound as a white solid (0.70 g, 70 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.50; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.19 (t, *J* = 7.6 Hz, 1H), 6.78-6.73 (m, 3H), 6.60 (bs, 1H), 4.25-4.19 (m, 1H), 4.00 (s, 2H), 3.54 (q, *J* = 7.2 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 1.98-1.94 (m, 2H), 1.80-1.77 (m, 2H), 1.58-1.45 (m, 3H), 1.39-1.26 (m,

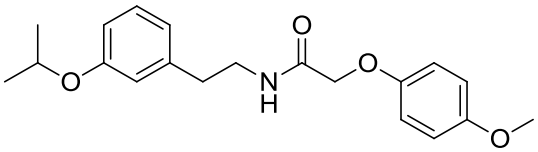
3H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 165.9, 158.3, 140.0, 129.9, 121.1, 116.7, 114.3, 75.6, 42.9, 41.1, 35.7, 32.1, 25.8, 24.0; HRMS calcd. for $C_{16}H_{23}O_2N^{35}Cl$, 296.14418 $[M + H]^+$; 296.14129 found, $[M + H]^+$.



2-chloro-*N*-(3-(cyclopentyloxy)phenethyl)acetamide (18): Compound **13** was prepared via procedure III using compound **8** (1.3 g, 4.5 mmol). The compound was carried forward without further purification. HRMS calcd. for $C_{13}H_{20}ON$, 206.15449 $[M + H]^+$; 206.15376 found, $[M + H]^+$. Compound **18** was prepared via procedure IV using amine **13** (1.0 g, 4.1 mmol), triethylamine (1.2 mL, 8.3 mmol) and 2-chloroacetyl chloride (0.40 ml, 5.0 mmol) in DCM (15 mL) and saturated $NaHCO_3$ (10. mL). The crude product was purified by silica gel chromatography (10-90 % EtOAc/hexanes) to afford the title compound as a white oil (0.61 g, 52 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.48; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.19 (t, *J* = 7.6 Hz, 1H), 6.75-6.73 (m, 2H), 6.70-6.69 (m, 1H), 6.59 (bs, 1H), 4.76-4.72 (m, 1H), 4.01 (s, 2H), 3.55 (q, *J* = 7.6 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 1.91-1.73 (m, 6H), 1.65-1.55 (m, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 166.0, 158.6, 139.9, 129.8, 120.8, 116.3, 113.8, 79.3, 42.9, 41.1, 35.7, 33.1, 24.2; HRMS calcd. for $C_{15}H_{20}O_2N^{35}Cl^{23}Na$, 304.10748 $[M + H]^+$; 304.10734 found, $[M + H]^+$.

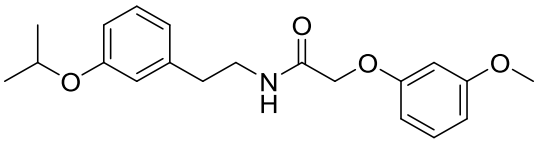


2-chloro-*N*-(3-ethoxyphenethyl)acetamide (19): Compound **19** was prepared via procedure IV using commercially available 2-(3-ethoxyphenyl)ethanamine (3.0 g, 18 mol), triethylamine (5.1, 33 mol), and 2-chloroacetyl chloride (1.7 ml, 22 mmol) in DCM (69 mL). The crude product was purified by silica gel chromatography (10-90 EtOAc/hexanes) to afford the title compound as a white solid (3.1 g, 71 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.48; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.26-7.22 (m, 1H), 6.80-6.75 (m, 3H), 6.63 (bs, 1H), 4.07-4.00 (m, 4H), 3.57 (q, *J* = 6.4 Hz, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 1.44-1.41 (m, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 159.2, 139.8, 129.7, 120.9, 114.9, 112.6, 63.3, 42.6, 40.8, 35.5, 14.8; HRMS calcd. for $C_{12}H_{17}O_2N^{35}Cl^{23}$, 242.09423 $[M + H]^+$; 242.09395 found, $[M + H]^+$.

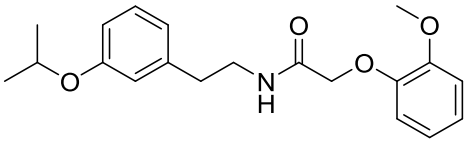


***N*-(3-isopropoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (20):** Compound **20** was prepared via procedure V using 4-methoxyphenol (1.1 g, 8.6 mmol) and Cs_2CO_3 (12 g, 36 mmol) in dry ACN (22 ml) and amide **14** (1.8 g, 7.2 mmol) in dry ACN (10. mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white oil (2.0 g, 82 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.30; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.19-7.15 (m, 1H), 6.82-6.66 (m, 7H), 4.54-4.49 (m, 1H), 4.39 (s, 2H), 3.75 (s, 3H), 3.59-3.53 (m,

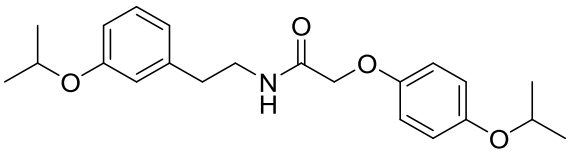
2H), 2.79 (t, *J*=6.8 Hz, 2H), 1.32-1.29 (m, 6H); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 168.6, 158.4, 154.9, 151.5, 140.3, 129.9, 121.1, 116.6, 115.9, 115.0, 113.9, 69.9, 68.4, 55.9, 40.2, 35.9, 22.3; HRMS calcd. for $C_{20}H_{25}O_4N_1$, 344.18564 $[M + H]^+$; 344.18515 found, $[M + H]^+$.



***N*-(3-isopropoxyphenethyl)-2-(3-methoxyphenoxy)acetamide (21):** Compound **21** was prepared via procedure V using 3-methoxyphenol (0.76 g, 6.1 mmol) and Cs_2CO_3 (6.6 g, 20. mmol) in dry ACN (15 mL) and amide **14** (1.3 g, 5.1 mmol) dry ACN (10 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a yellow oil (1.5 g, 84 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.68; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.20-7.15 (m, 2H), 6.75-6.69 (m, 3H), 6.62 (bs, 1H), 6.57-6.54 (m, 1H), 6.45-6.39 (m, 2H), 4.53-4.49 (m, 1H), 4.43 (s, 2H), 3.77 (s, 3H), 3.60-3.54 (m, 2H), 2.81-2.77 (t, *J* = 7.2 Hz, 2H) 1.31 (s, 3H), 1.29 (s, 3H);^{13}CNMR ($CDCl_3$, 100 MHz) δ: 168.2, 161.2, 158.5, 158.3, 140.3, 130.5, 129.9, 121.1, 116.6, 114.0, 107.8, 106.8, 101.5, 69.9, 67.5, 55.6, 40.3, 35.9, 22.3; HRMS calcd. for $C_{20}H_{25}O_4N_1$, 344.18564 $[M + H]^+$; 344.18527 found, $[M + H]^+$.

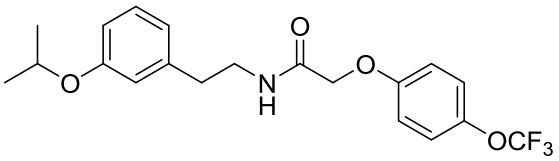


***N*-(3-isopropoxyphenethyl)-2-(2-methoxyphenoxy)acetamide (22):** Compound **22** was prepared via procedure V using 2-methoxyphenol (0.68 ml, 6.1 mmol) and Cs_2CO_3 (8.3 g, 25 mmol) in dry ACN (15mL) and amide **14** (1.3 g, 5.1 mmol) dry ACN (10 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a yellow solid (1.4 g, 82%). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.65; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 7.17-7.13 (t, *J* = 8.0 Hz, 1H), 7.03 (bs, 1H), 7.01-6.79 (m, 1H), 6.90-6.83 (m, 3H), 6.74-6.69 (m, 3H), 4.51-4.48 (m, 3H), 3.78 (s, 3H), 3.60-3.55 (q, *J* = 6.8 Hz, *J* = 13.2 Hz, 2H), 2.80-2.77 (t, *J* = 7.2 Hz, 2H), 1.30 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.8, 158.3, 149.8, 147.3, 140.5, 129.8, 123.3, 121.3, 121.1, 116.5, 115.7, 113.9, 112.2, 69.8, 69.8, 55.9, 40.3, 35.9, 22.3; HRMS calcd. for $C_{20}H_{25}O_4N_1$, 344.18564 $[M + H]^+$; 344.18551 found, $[M + H]^+$.

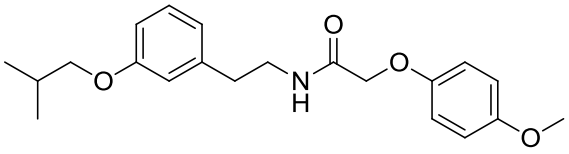


***N*-(3-isopropoxyphenethyl)-2-(4-isopropoxyphenoxy)acetamide (23):** Compound **23** was prepared via procedure V using 4-isopropoxyphenol (1.3 ml, 8.2 mmol) and Cs_2CO_3 (8.9 g, 27 mmol) in dry ACN (21 mL) and amide **14** (1.8 g, 6.8 mmol) dry ACN (10 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a yellow solid (1.8 g, 70%). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.65; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 7.20 (t, J = 7.5 Hz, 1H), 6.85-6.69 (m, 8H), 4.58-4.40 (m, 4H), 3.59 (q, J = 6.9 Hz, 2H), 2.81 (t, *J* = 6.9 Hz, 2H), 1.34-1.31 (12H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.4, 158.1, 152.8, 151.3, 140.2, 129.7,

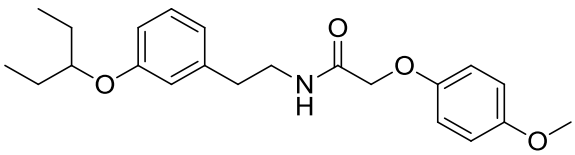
120.9, 117.4, 116.4, 115.6, 113.8, 70.7, 69.7, 68.1, 39.9, 35.7, 22.1; HRMS calcd. for $C_{22}H_{29}O_4N_1Na$, 394.19888 $[M + H]^+$; 394.19901 found, $[M + H]^+$.



N-(3-isopropoxyphenethyl)-2-(4-(trifluoromethoxy)phenoxy)acetamide (**24**): Compound **24** was prepared via procedure V using 4-(trifluoromethoxy)phenol (1.1 g, 6.1 mmol) and Cs_2CO_3 (6.6 g, 21 mmol) in dry ACN (15.3 ml) and amide **14** (1.3 g, 5.1 mmol) in dry ACN (10 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.6 g, 78%). TLC (EtOAc:hexanes, 1:1, v/v) Rf = 0.65; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.21-7.13 (m, 3H), 6.87-6.69 (m, 5H), 6.60 (bs, 1H), 4.54 (q, J = 6.0 Hz, 1H), 4.45 (s, 2H), 3.60 (q, J = 6.0 Hz, 2H), 2.81 (t, J = 6.0 Hz, 2H), 1.30-1.26 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.52, 158.13, 155.54, 145.15, 140.01, 129.70, 122.72, 120.83, 116.45, 115.52, 113.62, 109.98, 69.66, 67.67, 39.94, 35.61, 22.03. HRMS calcd. for $C_{20}H_{23}O_4N_1F_3$, 398.15737 $[M + H]^+$; 398.15768 found, $[M + H]^+$.

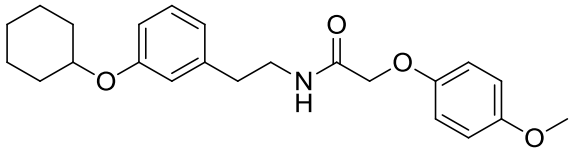


***N*-(3-isobutoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (25):** Compound **25** was prepared via procedure V using 4-methoxyphenol (0.50 g, 4.0 mmol) and Cs_2CO_3 (4.4 g, 14 mmol) in dry ACN (5.1 ml) and amide **15** (0.91 g, 3.4 mmol) in dry ACN (5.1 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.1 g, 92%). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.69; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.18 (t, *J* = 7.6 Hz, 1H), 6.82-6.71 (m, 7H), 6.66 (bs, 1H), 4.39 (s, 2H), 3.75 (s, 3H), 3.67 (d, *J* = 6.8 Hz, 2H), 3.57 (q, *J* = 6.4 Hz, 2H), 2.79 (t, *J* = 6.8 Hz, 2H), 2.08-2.01 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 159.7, 154.9, 151.5, 140.3, 129.9, 121.1, 115.8, 115.2, 115.0, 112.8, 74.5, 68.3, 55.9, 40.2, 35.9, 28.5, 19.5; HRMS calcd. for $C_{21}H_{28}O_4N_1$, 358.20129 $[M + H]^+$; 358.20125 found, $[M + H]^+$.

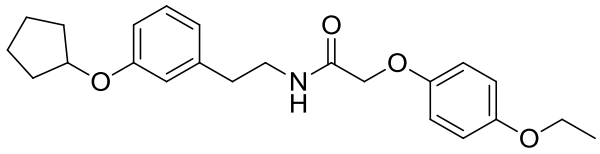


2-(4-methoxyphenoxy)-*N*-(3-(pentan-3-yloxy)phenethyl)acetamide (26): Compound **26** was prepared via procedure V using 4-methoxyphenol (0.39 g, 3.2 mmol) and Cs_2CO_3 (2.6 g, 7.9 mmol) in dry ACN (4.0 ml) and amide **16** (0.74 g, 2.6 mmol) in dry ACN (4.0 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title

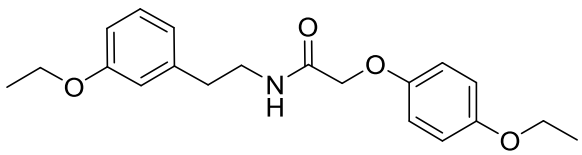
compound as a white solid (0.61 g, 63 %). TLC (EtOAc:hexanes, 1:1, v/v) Rf = 0.57; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17 (t, *J* = 8.0 Hz, 1H), 6,83-6.69 (m, 7H), 6.67 (bs, 1H), 4.10-4.07 (m, 1H), 3.76 (s, 1H), 3.58 (q, *J* = 6,4 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 1.68-1.61 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 159.2, 154.9, 151.5, 140.4, 129.9, 120.9, 116.7, 115.8, 115.0, 114.0, 80.2, 68.3, 55.9, 40.2, 35.9, 26.2, 9.8; HRMS calcd. for $C_{22}H_{30}O_4N$, 372.21694 $[M + H]^+$; 372.21711 found, $[M + H]^+$.



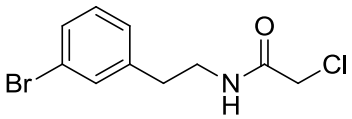
***N*-(3-(cyclohexyloxy)phenethyl)-2-(4-methoxyphenoxy)acetamide (27)**: Compound **27** was prepared via procedure V using 4-methoxyphenol (0.35 g, 2.8 mmol) and Cs_2CO_3 (3.1 g, 9.5 mmol) in dry ACN (7.1 ml) and amide **17** (0.70 g, 2.3 mmol) in dry ACN (7.1 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.52 g, 58 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.58; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17 (t, *J* = 8.0 Hz, 1H), 6.83-6.69 (m, 7H), 6.66 (bs, 1H), 4.39 (s, 1H), 4.24-4.18 (m, 1H), 3.76 (s, 3H), 3.58 (q, *J* = 6.8 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 1.97-1.94 (m, 2H), 1.78-1.76 (m, 2H), 1.57-1.24 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 158.3, 154.8, 151.5, 140.3, 129.8, 121.1, 116.8, 115.8, 115.0, 114.1, 75.5, 68.3, 55.9, 40.2, 35.9, 32.0, 25.8, 24.0; HRMS calcd. for $C_{23}H_{40}O_4N$, 384.21694 $[M + H]^+$; 384.21715 found, $[M + H]^+$.



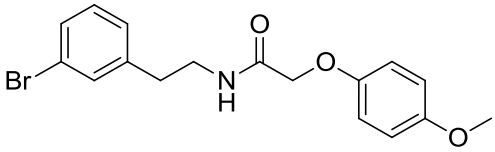
***N*-(3-(cyclopentyloxy)phenethyl)-2-(4-ethoxyphenoxy)acetamide (28)**: Compound **28** was prepared via Procedure V using 4-ethoxyphenol (0.73 g, 5.3 mmol) and Cs_2CO_3 (5.7 g, 14 mmol) in dry ACN (6.6 ml) and amide **18** (1.2 g, 4.4 mmol) in dry ACN (6.6 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.4 g, 86%). TLC (EtOAc:hexanes, 1:1, v/v) Rf = 0.81; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.19-7.15 (m, 1H), 6.82-6.69 (m, 7H), 6.65 (bs, 1H), 4.73-4.71 (m, 1H), 4.39 (s, 3H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.58 (q, *J* = 6.4 Hz, 2H), 2.79 (t, *J* = 6.8 Hz, 2H), 1.92-1.72 (m, 6H), 1.96-1.56 (m, 2H), 1.38 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 158.6, 154.2, 151.4, 140.3, 129.8, 120.9, 116.2, 115.8, 115.7, 113.7, 79.2, 68.3, 64.1, 40.2, 35.9, 33.1, 24.3, 15.1; HRMS calcd. for $C_{23}H_{30}O_4N$, 384.21694 $[M + H]^+$; 384.21704 found, $[M + H]^+$.



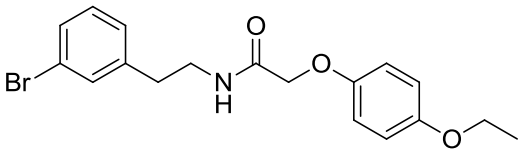
***N*-(3-ethoxyphenethyl)-2-(4-ethoxyphenoxy)acetamide (29):** Compound **29** was prepared via procedure V using 4-ethoxyphenol (2.1 g, 15 mmol) and Cs_2CO_3 (12 g, 38 mmol) in dry ACN (19 ml) and amide **19** (3.1 g, 12 mmol) in dry ACN (19 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 80 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.7 g, 62 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.27; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.21 (t, J = 10 Hz, 1H), 6.85-6.74 (m, 7H), 6,69 (bs, 1H), 4.41 (s, 2H), 4.04-3.95 (m, 4H), 3.63-3.55 (m, 2H), 2.82 (t, J = 8.4 Hz), 1.44-1.38 (m 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.4, 159.2, 154.0, 151.3, 140.1, 129.7, 120.9, 115.6, 115.5, 114.9, 112.5, 68.1, 63.9, 63.3, 39.9, 35.7, 14.8; HRMS calcd. for $C_{20}H_{26}O_4N$, 344.18563 $[M + H]^+$; 344.18564 found, $[M + H]^+$



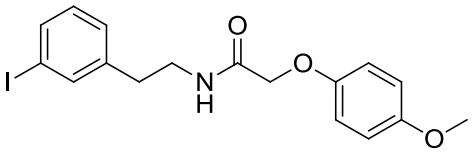
***N*-(3-bromophenethyl)-2-chloroacetamide (31)**: Compound **31** was prepared via procedure IV using 2-(3-bromophenyl)ethanamine (2.8 g, 20. mmol), triethylamine (5.6 mL, 40. mmol) and 2-chloroacetyl chloride (1.9 ml, 24 mmol). The crude product was purified by silica gel chromatography (10-90 % EtOAc/hexanes) to afford the title compound as a yellow solid (3.6 g, 65 %). TLC (EtOAc:hexanes, 1:1, v/v) Rf = 0.46; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.38-7.35 (m, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.13-7.11 (m, 1H), 6.59 (bs, 1H), 4.02 (s, 2H), 3.53 (q, *J* = 6.8 Hz, 2H), 2.81 (t, *J* = 6.8 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 166.1, 140.8, 132.0, 130.5, 130.1, 127.6, 122.9, 42.8, 40.9, 35.4; HRMS calcd. for $C_{10}H_{12}ON^{35}Cl^{79}Br$, 275.97853 $[M + H]^+$; 275.97861 found, $[M + H]^+$.



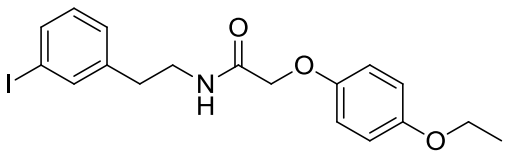
***N*-(3-bromophenethyl)-2-(4-methoxyphenoxy)acetamide (32)**: Compound **32** was prepared via procedure V using 4-methoxyphenol (1.9 g, 16 mmol) and Cs_2CO_3 (17 g, 52 mmol) in dry ACN (39 ml) and amide **31** (3.6 g, 13 mmol) in dry ACN (15 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80 % EtOAc/hexanes gradient) to afford the title compound as a white solid (3.9 g, 83 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.45; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36-7.33 (m, 2H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.08-7.06 (m, 1H), 6.83-6.76 (m, 4H), 6.63 (bs, 1H), 4.4 (s, 2H), 3.76 (s, 3H), 3.56 (q, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 1.68.7, 154.9, 151.5, 132.0, 130.4, 129.9, 127.6, 122.9, 115.8, 115.0, 68.3, 55.9, 40.1, 35.6; HRMS calcd. for $C_{17}H_{19}O_3N^{79}Br$, 364.05428 $[M + H]^+$; 364.05494 found, $[M + H]^+$.



***N*-(3-bromophenethyl)-2-(4-ethoxyphenoxy)acetamide (33)**: Compound **33** was prepared via procedure V using 4-ethoxyphenol (1.8 g, 13 mmol) in and Cs_2CO_3 (14 g, 43 mmol) dry ACN (33 ml) and amide **31** (3.0 g, 11 mmol) in dry ACN (10 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80 % EtOAc/hexanes gradient) to afford the title compound as a white solid (3.8 g, 92 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.47; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35-7.33 (m, 2H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.08-7.06 (m, 1H), 6.83-6.75 (m, 4H), 6.63 (bs, 1H), 4.39 (s, 2H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.57 (q, *J* = 6.4 Hz, 2H), 2.80 (t, *J* = 6.8, 2H), 1.38 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.7, 154.3, 151.4, 141.1, 132.0, 130.4, 129.9, 127.6, 122.9, 115.9, 115.7, 68.3, 64.2, 40.1, 35.6, 15.1; HRMS calcd. for $C_{18}H_{21}O_3N^{79}Br$, 378.06993 $[M + H]^+$; 378.07060 found, $[M + H]^+$.

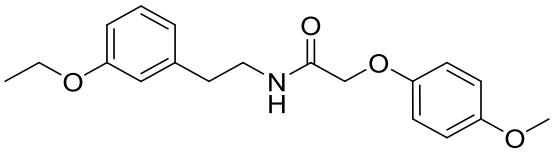


***N*-(3-iodophenethyl)-2-(4-methoxyphenoxy)acetamide (34)**: Compound **34** was prepared via procedure VI using amide **32** (2.0 g, 5.5 mmol), copper(I) iodide (0.052 g, 0.28 mmol), sodium iodide (1.2 g, 8.2 mmol), and *N*1,*N*2-dimethylethane-1,2-diamine (0.062 ml, 0.55 mmol) in dry dioxane (5.5 ml). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-90 % EtOAc/hexanes gradient) to afford the title compound as a white solid (1.8 g, 80 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.48; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.56-7.55 (m, 1H), 7.12-7.10 (m, 1H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.84-6.77 (m, 4H), 6.62 (bs, 1H), 4.41 (s, 2H), 3.76 (s, 3H), 3.58 (q, *J* = 6.8 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.7, 154.9, 151.5, 141.2, 137.9, 135.9, 130.6, 128.3, 115.9, 115.0, 94.9, 68.3, 55.9, 40.1, 35.5; HRMS calcd. for $C_{17}H_{19}O_3N^{127}I$, 412.04042 $[M + H]^+$; 412.04049 found, $[M + H]^+$.

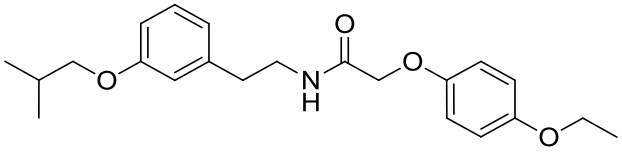


2-(4-ethoxyphenoxy)-*N*-(3-iodophenethyl)acetamide (35): Compound **35** was prepared via procedure VI using amide **33** (2.2 g, 5.8 mmol), copper(I) iodide (0.056 g, 0.29 mmol), sodium iodide (1.3 g, 8.8 mmol), *N1*,*N2*-dimethylethane-1,2-diamine (0.066 ml, 0.59 mmol) in dry dioxane (5.8 ml). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-90 % EtOAc/hexanes gradient) to afford the title compound as a white solid (1.7 g, 69 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.27; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.58-7.56 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.04-7.00 (m, 1H), 6.85-6.77 (m, 4H), 6.65 (bs, 1H), 4.42 (s, 2H), 4.01 (q, *J* = 7.2 Hz, 2H), 3.57 (q, *J* = 7.2 Hz, 2H), 2.79 (t, *J* = 6.8 Hz, 2H),

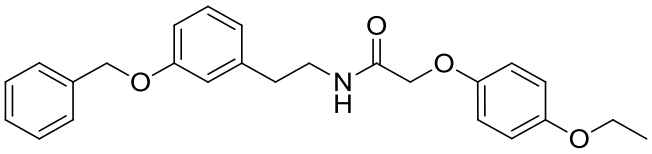
1.40 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.7, 154.3, 151.3, 141.2, 137.9, 135.9, 130.6, 128.3, 115.8, 115.7, 94.9, 68.3, 64.2, 40.0, 35.5, 15.1; HRMS calcd. for $C_{18}H_{21}O_3N^{127}I$, 426.05067 $[M + H]^+$; 426.050613 found, $[M + H]^+$.



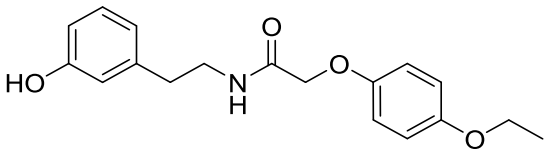
***N*-(3-ethoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (36)**: Compound **36** was prepared via procedure VII using amide **34** (2.0 g, 4.8 mmol), copper(I) iodide (0.093 g, 0.48 mmol), 1,10-phenanthroline (0.18 g, 0.97 mmol), and cesium carbonate (3.2 g, 9.7 mmol) in ethanol (2.4 ml, 41 mmol). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-90 % EtOAc/hexanes gradient) to afford the title compound as a yellow oil (0.67 g, 42 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 1.1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.23-7.19 (m, 1H), 6.86-6.74 (m, 7H), 6.69 (bs, 1H), 4.42 (s, 2H), 4.00 (q, *J* = 6.8 Hz, 2H), 3.78 (s, 3H), 3.6 (q, *J* = 6.4 Hz, 2H), 2.82 (t, *J* = 6.8 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 159.4, 154.9, 151.5, 140.3, 129.9, 121.2, 115.8, 115.2, 115.0, 112.7, 68.3, 63.5, 55.9, 40.2, 35.9, 15.1; HRMS calcd. for $C_{19}H_{24}O_4N$, 330.16998 $[M + H]^+$; 330.16922 found, $[M + H]^+$.



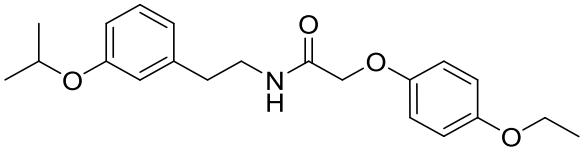
2-(4-ethoxyphenoxy)-*N*-(3-isobutoxyphenethyl)acetamide (37): Compound **37** was prepared via procedure VII using amide **35** (1.7 g, 4.0 mmol), copper(I) iodide (0.15 g, 0.81 mmol), 1,10-phenanthroline (0.15 g, 0.81 mmol), and cesium carbonate (2.6 g, 8.1 mmol) in 2-methylpropan-1-ol (4.0 ml, 44 mmol). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-90 % EtOAc/hexanes gradient) to afford the title compound as a white solid (0.54 g, 36 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.63; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20 (t, *J* = 8.0 Hz, 1H), 6.84-6.73 (m, 7H), 6.68 (bs, 1H), 4.42 (s, 2H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.70 (d, *J* = 6.8 Hz, 2H), 3.60 (q, *J* = 6.4 Hz, 2H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.10-2.04 (m, 1H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 159.7, 154.2, 151.4, 140.3, 129.8, 121.1, 115.8, 115.7, 115.2, 112.8, 74.5, 68.3, 64.2, 40.2, 35.9, 28.5, 19.5, 15.2; HRMS calcd. for $C_{23}H_{30}O_4N$, 372.21694 $[M + H]^+$; 372.21685 found, $[M + H]^+$.



***N*-(3-(benzyloxy)phenethyl)-2-(4-ethoxyphenoxy)acetamide (38)**: Compound **38** was prepared via procedure VII using amide **35** (2.5 g, 5.9 mmol), copper(I) iodide (0.11 g, 0.59 mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (0.28 g, 1.2 mmol), and cesium carbonate (3.8 g, 12 mmol) in phenylmethanol (7.4 ml, 55 mmol). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-90 % EtOAc/hexanes gradient) to afford the title compound as a white solid (1.8 g, 76 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.50; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44-7.33 (m, 5H), 7.22 (t, *J* = 7.6 Hz, 1H), 6.88-6.76 (m, 7H), 6.67 (s, 1H), 5.04 (s, 2H), 4.42 (s, 2H), 3.96 (q, *J* = 7.2 Hz, 2H), 3.60 (q, *J* = 6.4 Hz, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.7, 159.3, 154.3, 151.5, 140.5, 137.1, 129.9, 128.8, 128.2, 127.7, 121.6, 115.8, 115.7, 115.6, 113.1, 70.1, 68.3, 64.1, 40.1, 35.9, 15.1; HRMS calcd. for $C_{25}H_{28}O_4N$, 406.20128 $[M + H]^+$; 406.20141 found, $[M + H]^+$.

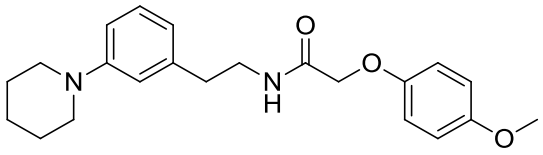


2-(4-ethoxypehnoxy)-*N*-(3-hydroxyphenethyl)acetamide (39): Compound **39** was prepared by dissolving amide **38** (1.3 g, 3.2 mmol) in MeOH (25 ml) and THF (10 ml) and adding dihydroxypalladium (0.26 g, 0.37 mmol). The reaction was hydrogenated at room temperature overnight using a balloon. After stirring overnight the reaction was filtered through a pad of celite washing with MeOH and EtOAc and the organic layer was concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-90 % EtOAc/hexanes gradient) to afford the title compound as a white solid (0.94 g, 91 %). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.44; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.16 (t, J = 8.0 Hz, 1H), 6.86-6.78 (m, 4H), 6.77-6.72 (m, 3H), 6.66-6.65 (m, 1H), 6.03 (bs, 1H), 4.43 (s, 2H), 3.98 (q, *J* = 7.2 Hz, 2H), 3.60 (q, *J* = 6.4 Hz, 2H), 2.80 (t, *J* = 6.8 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.1, 156.5, 151.4, 140.4, 130.1, 121.0, 115.8, 115.7, 113.9, 68.2, 64.2, 40.2, 35.8, 15.1; HRMS calcd. for $C_{18}H_{22}O_4N$, 316.15433 $[M + H]^+$; 316.15497 found, $[M + H]^+$.

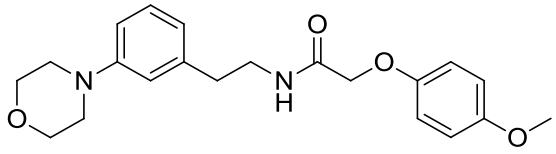


2-(4-ethoxyphenoxy)-*N*-(3-isopropoxyphenethyl)acetamide (40): To a solution of amide **39** (0.94 g, 2.9 mmol) in dry ACN (8.0 mL) and dry DMF (5.0 mL) was added cesium carbonate (2.9 g, 8.9 mmol). The reaction was allowed to stir for 2 hours before 2-iodopropane (0.36 mL, 3.6 mmol) was added and the reaction was heated to 60^{o}C and allowed to stir for 22 hours. The reaction was quenched with saturated aqueous ammonium chloride and extracted into EtOAc. The organic layer was washed with water (3x) and

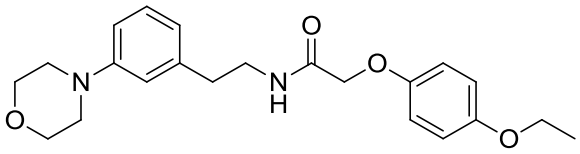
brine (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a yellow oil (0.93 g, 88%). TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.67; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20-7.15 (m, 1H), 6.83-6.70 (m, 7H), 6.65 (bs, 1H), 4.54-4.48 (m, 1H), 4.39 (s, 2H), 3.96 (q, *J* = 7.2 Hz, *J* = 14.0 Hz, 2H), 3.59-3.53 (m, 2H), 2.81-2.77 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$,100 MHz) δ: 168.6, 158.4, 154.3, 151.4, 140.4, 129.9, 121.1, 116.6, 115.8, 115.6, 113.9, 69.8, 68.3, 64.2, 40.2, 35.9, 22.3, 15.1; HRMS calcd. for $C_{21}H_{27}O_4N_1$, 358.20129 $[M + H]^+$; 358.20121 found, $[M + H]^+$.



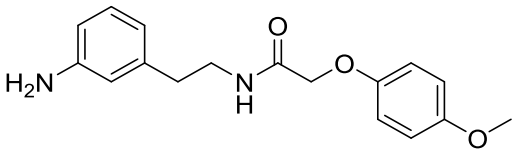
2-(4-methoxyphenoxy)-*N*-(3-(piperidin-1-yl)phenethyl)acetamide (41): Compound **41** was prepared via procedure VIII using amide **34** (2.0 g, 4.9 mmol), copper(I) iodide (0.19 g, 0.97 mmol), potassium carbonate (1.3 g, 9.7 mmol), L-proline (0.11 g, 0.97 mmol), and piperidine (0.72 ml, 7.3 mmol) in dry DMSO (15 ml). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-15 % MeOH:DCM gradient) to afford the title compound as a brown solid (1.5 g, 87 %) TLC (MeOH:DCM, 1:10, v/v) R_f = 0.84; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.15 (t, *J* = 7.6 Hz, 1H), 6.82-6.75 (m, 6H), 6.61-6.60 (m, 1H), 4.39 (s, 2H), 3.75 (s, 3H), 3.57 (q, *J* = 6.0 Hz, 2H), 3.10 (t, *J* = 5.6 Hz, 4H), 2.77 (t, *J* = 6.8 Hz, 2H), 1.69-1.64 (m, 4H), 1.56-1.51 (m, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.8, 152.8, 151.5, 139.5, 129.5, 119.8, 117.1, 115.9, 115.0, 114.9, 68.3, 55.9, 50.8, 40.3, 36.2, 26.0, 24.5; HRMS calcd. for $C_{26}H_{29}N_2O_3$, 469.21727 $[M + H]^+$; found 469.21723 $[M + H]^+$.



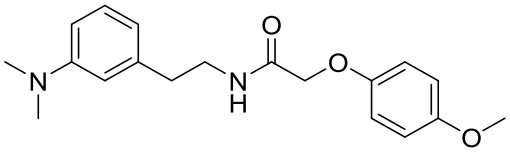
2-(4-methoxyphenoxy)-*N*-(3-morpholinophenethyl)acetamide (42): Compound **42** was prepared via procedure VIII using amide **34** (0.20 g, 0.49 mmol), copper(I) iodide (0.020 g, 0.097 mmol), potassium carbonate (0.13 g, 0.97 mmol), L-proline (0.011 g, 0.097 mmol), and morpholine (0.063 ml, 0.73 mmol) in dry DMSO (1.5 ml). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-15 % MeOH:DCM gradient) to afford the title compound as a red oil (0.18 g, 67 %) TLC (MeOH:DCM, 1:10, v/v) R_f = 0.60; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.19 (t, *J* = 8.0 Hz, 1H), 6.83-6.75 (m, 1H), 6.74-6.72 (m, 1H), 6.68-6.66 (m, 2H), 4.39 (s, 2H), 3.81 (t, *J* = 9.6 Hz, 4H), 3.75 (s, 3H), 3.57 (q, *J* = 6.4 Hz, 2H), 3.12 (t, *J* = 5.2 Hz, 4H), 2.79 (t, *J* = 7.2 Hz, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.9, 151.8, 139.8, 129.7, 120.7, 116.3, 115.8, 115.0, 114.1, 68.4, 67.1, 55.9, 49.5, 40.3, 36.2; HRMS calcd. for $C_{21}H_{27}N_2O_4$, 371.19653 $[M + H]^+$; found 371.19655 $[M + H]^+$.



2-(4-ethoxyphenoxy)-*N*-(3-morpholinophenethyl)acetamide (43): Compound **43** was prepared via procedure VIII using amide **35** (2.0 g, 4.7 mmol), copper(I) iodide (0.18 g, 0.94 mmol), potassium carbonate (1.3 g, 9.4 mmol), L-proline (0.11 g, 0.94 mmol), morpholine (0.61 ml, 7.1 mmol) in dry DMSO (14 ml). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-15 % MeOH:DCM gradient) to afford the title compound as a brown oil (0.77 g, 43 %) TLC (MeOH:DCM, 1:10, v/v) R_f = 0.90; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.22 (t, *J* = 8.0 Hz, 1H), 6.84-6.76 (m, 5H), 6.71-6.60 (m, 2H), 4.41 (s, 2H), 4.97 (q, *J* = 7.2 Hz, 2H), 3.84 (t, *J* = 4.8 Hz, 4H), 3.60 (q, *J* = 6.4 Hz, 2H), 3.14 (t, *J* = 5.2 Hz, 4H), 2.81 (t, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.3, 151.9, 151.5, 139.9, 129.7, 120.6, 116.3, 115.9, 115.7, 114.1, 68.4, 67.1, 64.2, 49.5, 40.3, 36.2, 15.1; HRMS calcd. for $C_{22}H_{29}N_2O_4$, 385.21218 $[M + H]^+$; found 385.21238 $[M + H]^+$.

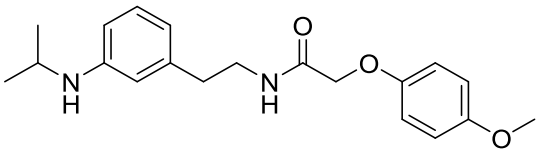


***N*-(3-aminophenethyl)-2-(4-methoxyphenoxy)acetamide (44):** A 10 mL sealed vial was charged with Cu(I) oxide (0.23 g, 1.6 mmol) and amide **35** (3.3 g, 7.9 mmol). The vial was sealed, evacuated, and purged with argon. Concentrated ammonium hydoxide (5.2 ml, 9.7 mmol) was added followed by NMP (5.2 ml) and the vial was submerged in an oil bath heated to 85 °C. After stirring for 48 hours, the reaction was allowed to cool to room temperature, quenched with water, and extracted into EtOAc. The organic layer was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-18 % MeOH:DCM gradient) to afford the title compound as a clear oil (1.7 g, 72 %) TLC (MeOH:DCM, 1:10, v/v) Rf = 0.90; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.09 (t, *J* = 7.8 Hz, 1H), 6.87-6.79 (m, 4H), 6.69 (bs, 1H), 6.55 (d, *J* = 7.8 Hz, 2H), 6.48 (s, 1H), 4.43 (s, 2H), 3.78 (s, 3H), 3.69 (bs, 2H), 3.58 (q, *J* = 6.6 Hz, 2H), 2.74 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ: 168.6, 154.9, 151.6, 146.9, 140.0, 129.8, 119.1, 115.9, 115.6, 115.0, 113.6, 68.4, 55.9, 40.2, 35.9; HRMS calcd. for $C_{17}H_{20}O_3N_2$, 301.15467 $[M + H]^+$; 301.15441 found, $[M + H]^+$.

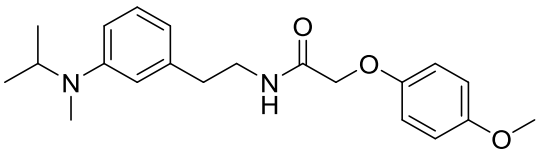


***N*-(3-(dimethylamino)phenethyl)-2-(4-methoxyphenoxy)acetamide (45):** Compound **45** was prepared via procedure IX using amide **44** (1.4 g, 4.7 mmol), paraformaldehyde (1.4 g, 47 mmol), and sodium cyanoborohydride (1.5 g, 24 mmol) in AcOH (15 mL). After stirring for 20 hours the TLC indicated completed conversion. The crude residue was purified by silica gel chromatography (ISCO, Redisep 20 g

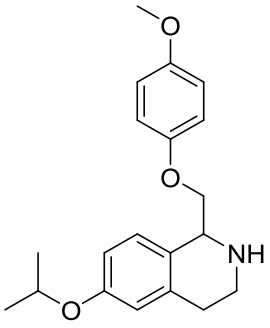
column, 0-20% MeOH/DCM gradient) to afford the title compound as a yellow oil (0.88 g, 57 %). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.76; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18-7.13 (t, *J* = 7.6 Hz, 1H), 6.83-6.75 (m, 4H), 6.68 (s, 1H), 6.62-6.59 (dd, *J* = 2.0 Hz, *J* = 8.0 Hz, 1H), 6.53-6.50 (m, 2H), 4.40 (s, 2H), 3.76 (s, 3H), 3.61-3.56 (q, *J* = 6.8 Hz, *J* = 12.8 Hz, 2H), 2.91 (s, 6H), 2.80-2.77 (t, *J* = 7.2 Hz, *J* = 14.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.9, 151.6, 151.1, 129.7, 129.6, 117.1, 115.9, 115.0, 113.1, 111.1, 68.4, 55.9, 40.9, 40.3, 36.3; HRMS calcd. for $C_{19}H_{25}O_3N_2$, 329.18597 $[M + H]^+$; found 329.18659 $[M + H]^+$.



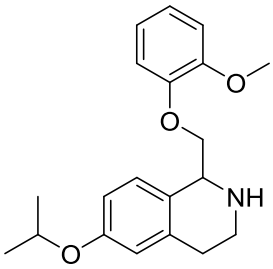
***N*-(3-(isopropylamino)phenethyl)-2-(4-methoxyphenoxy)acetamide (46):** To a solution of amide **44** (1.7 g, 5.7 mmol) in dry ACN (11 ml), propan-2-one (1.3 ml, 17 mmol) was added followed by sodium cyanoborohydride (1.1 g, 17 mmol). AcOH (11 ml) was added over a period of 10 minutes and the reaction was allowed to stir for 2 hours. AcOH (11 ml) was added again and after stirring for 10 additional minutes, the reaction was brought to 0^{o}C using an ice bath. The reaction was made basic using concentrated NH_4OH, extracted into EtOAc, washed with water and brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-90 % EtOAc:hexanes gradient) to afford the title compound as a clear oil (0.74 g, 32 %) TLC (EtOAc:hexanes, 1:1, v/v) R_f = 0.71; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.12-7.09 (m, 1H), 6.85-6.75 (m, 6H), 6.49-6.47 (m, 2H), 6.40 (s, 1H), 4.41 (s, 2H), 3.78 (s, 3H), 3.64-3.57 (m, 3H), 2.75 (t, *J* = 6.8 Hz, 2H), 1.20 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$,100 MHz) δ: 168.9, 154.9, 151.5, 147.9, 139.9, 129.9, 117.6, 116.2, 115.1, 113.9, 111.7, 68.3, 55.9, 44.5, 40.3, 35.9, 23.2; HRMS calcd. for $C_{20}H_{27}O_3N_2$, 343.20162 $[M + H]^+$; 343.20120 found, $[M + H]^+$.



***N*-(3-(isopropyl(methyl)amino)phenethyl)-2-(4-methoxyphenoxy)acetamide (47):** Compound **47** was prepared via procedure IX using amide **46** (0.79 g, 2.3 mmol), paraformaldehyde (0.69 g, 23 mmol), and sodium cyanoborohydride (0.73 g, 12 mmol) in AcOH (15 mL). After stirring for 4 hours the TLC indicated complete conversion. The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-20 % MeOH:DCM gradient) to afford the title compound as a clear oil (0.58 g, 70%) TLC (MeOH:DCM, 1:10, v/v) R_f = 0.65; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.14 (t, *J* = 8.0 Hz, 1H), 6.84-6.73 (m, 6H), 6.67-6.65 (m, 1H), 6.60 (s, 1H), 4.40 (s, 2H), 3.76 (s, 3H), 5.58 (q, *J* = 6.8 Hz, 3H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.70 (s, 3H), 1.13 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$,100 MHz) δ: 168.6, 154.9, 151.7, 150.7, 139.7, 129.7, 116.9, 115.9, 115.0, 113.7, 111.7, 68.4, 55.9, 49.1, 40.4, 36.4, 30.1, 23.2, 19.6; HRMS calcd. for $C_{21}H_{28}O_3N_2$, 357.21727 $[M + H]^+$; 357.21763 found, $[M + H]^+$.

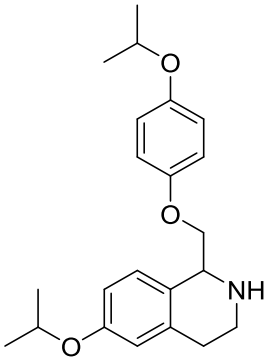


6-isopropoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (67): Dihydroisoquinoline **48** was prepared via procedure XI using amide **20** (2.0 g, 5.8 mmol) and phosphorus trichloride (1.6 mL, 18 mmol) in dry toluene (32 mL). The crude solid (4.5 g) was carried on without further purification. HRMS calcd. for $C_{20}H_{23}O_3N_1$, 326.17507 $[M + H]^+$; found 326.17461 $[M + H]^+$. Tetrahydroisoquinoline **67** was prepared via procedure XII using dihydroisoquinoline **48** (4.5 g, 14 mmol) and sodium borohydride (1.9 g, 50. mmol) in dry MeOH (70 mL). 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 green solid (0.52 g, 12 % over 2 steps). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.59; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.02-6.99 (d, *J* = 8.8 Hz, 1H), 6.98-6.94 (m, 2H), 6.77-6.71 (m, 3H), 6.62-6.61 (d, *J* = 2.4 Hz, 1H), 4.62-4.59 (q, *J* = 4.0 Hz, *J* = 6.8 Hz, 1H), 4.52-4.46 (m, 1H), 4.43-4.39 (m, 1H), 4.36-4.32 (m, 1H), 3.72 (s, 3H), 3.53 (m 1H), 3.24-3.13 (m, 2H), 2.99-2.93 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 157.8, 154.7, 152.1, 134.3, 127.5, 120.2, 116.6, 115.9, 115.4, 114.8, 70.2, 69.2, 55.9, 54.2, 39.8, 26.1, 22.3, 22.2; HRMS calcd. for $C_{20}H_{25}O_3N_1$, 328.19072 $[M + H]^+$; found 328.19109 $[M + H]^+$.

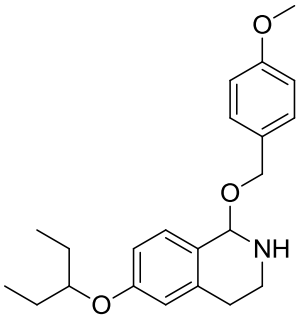


6-isopropoxy-1-((2-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (68): Dihydroisoquinoline **49** was prepared via procedure X using amide **22** (1.4 g, 4.2 mmol) and phosphorus trichloride (1.9 mL, 13 mmol) in dry toluene (24 mL). The crude solid (1.5 g) was carried on without further purification. HRMS calcd. for $C_{20}H_{23}O_3N_1$, 326.17507 $[M + H]^+$; found 326.17524 $[M + H]^+$. Tetrahydroisoquinoline **68** was prepared via procedure XII using dihydroisoquinoline **49** (1.5 g, 4.7 mmol) and sodium borohydride (0.50 g, 14 mmol) in dry MeOH (23 mL). 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 green solid (1.5 g, 36 % over 2 steps). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.55; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.05-7.02 (m, 2H), 6.69-6.93 (m, 1H), 6.84-6.81 (m, 1H), 6.72-6.69 (q, *J* = 2.4 Hz, *J* = 8.8 Hz, 1H), 6.62-6.61 (d, *J* = 1.6 Hz, 1H), 4.77-4.73 (m, 1H), 4.50-4.39 (m, 2H), 3.78 (s, 3H), 3.69-3.66 (m, 1H), 3.45-3.43 (m, 1H), 3.14-3.10 (m, 2H), 1.29 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 147.8, 147.4, 134.2, 127.9, 123.8,

121.6, 120.1, 117.8, 115.9, 115.4, 112.7, 71.4, 70.2, 56.3, 53.9, 39.6, 26.1, 22.2; HRMS calcd. for $C_{20}H_{25}O_3N_1$, 328.19072 $[M + H]^+$; found 328.19032 $[M + H]^+$.

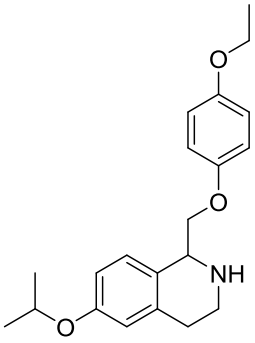


6-isopropoxy-1-((4-isopropoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (70):
Dihydroisoquinoline **51** was prepared via procedure XI using amide **23** (1.5 g, 4.1 mmol) and phosphorus trichloride (1.2 mL, 12 mmol) in dry toluene (21 mL). The crude solid (1.4 g) was carried on without further purification. HRMS calcd. for $C_{22}H_{28}O_3N_1$, 354.20637 $[M + H]^+$; found 354.20665 $[M + H]^+$. Tetrahydroisoquinoline **70** was prepared via procedure XII using dihydroisoquinoline **51** (1.4 g, 3.8 mmol) and sodium borohydride (0.38 g, 12 mmol) in dry MeOH (13 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 20 g column, 0-15% MeOH/DCM gradient) to afford the title compound as an off-white solid (0.24 g, 18 % over 2 steps). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.81; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.62 (bs, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.95-6.89 (m, 2H), 6.82-6.77 (m, 2H), 6.74-6.71 (dd, J = 2.4 Hz, J = 8.4 Hz, 1H), 6.64-6.63 (m, 1H), 4.55-4.47 (m, 2H), 4.44-4.36 (m, 1H), 4.33-4.20 (m, 2H), 3.44-3.36 (m, 1H), 3.19-3.10 (m, 1H), 3.00-2.88 (m, 2H), 1.32-1.27 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 157.1, 152.4, 152.3, 135.3, 127.3, 122.6, 117.3, 115.9, 115.8, 114.6, 70.7, 69.8, 54.2, 39.5, 27.5, 22.1, 22.0; HRMS calcd. for $C_{22}H_{30}O_3N_1$, 356.22202 $[M + H]^+$; found 356.22255 $[M + H]^+$.

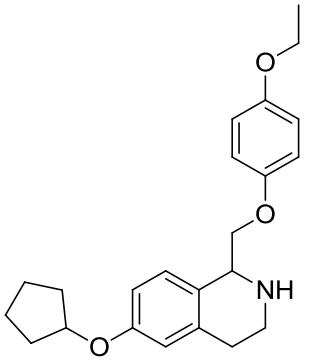


1-((4-methoxybenzyl)oxy)-6-(pentan-3-yloxy)-1,2,3,4-tetrahydroisoquinoline (73): Dihydroisoquinoline **54** was prepared via procedure X using amide **26** (0.61 g, 1.6 mmol) and phosphorus trichloride (1.0 mL, 5.0 mmol) in dry toluene (9.0 mL). The crude solid was carried on without further purification. HRMS calcd. for $C_{22}H_{28}O_3N$, 354.20637 $[M + H]^+$; found 354.20640 $[M + H]^+$. Tetrahydroisoquinoline **73** was prepared via procedure XII using **54** (0.35 g, 1.0 mmol) and sodium borohydride (0.11 g, 3.0 mmol) in dry

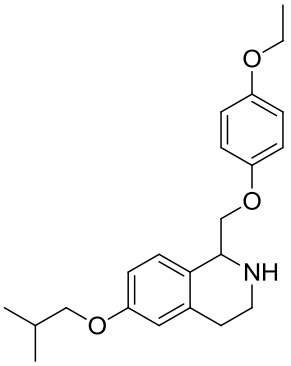
MeOH (5.0 mL). The crude residue was subjected to flash column chromatography (ISCO, Redisep 24 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a yellow foam (0.15 g, 43 % over 2 steps)**.** ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.98-6.95 (m, 1H), 6.89-6.86 (m, 1H), 6.82-6.69 (m, 3.5H), 6.65-6.62 (m, 0.5H), 6.58-6.56 (m, 1H), 4.84 (m, 0.5H), 4.56-4.54 (m, 0.5H), 4.33-4.19 (m, 1H), 4.14-3.90 (m, 2H), 3.70 (s, 3H), 3.54-3.48 (m, 0.5H), 3.19-3.09 (m, 1H), 2.99-2.83 (m, 1.5H)1.67-1.60 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.3, 154.5, 152.4, 134.9, 127.7, 116.3, 115.9, 115.6, 115.0, 114.7, 80.3, 69.9, 55.9, 53.6, 39.4, 26.2, 9.8; HRMS calcd. for $C_{22}H_{30}NO_3$, 356.22202 $[M + H]^+$; found, 356.22192 $[M + H]^+$.



1-((4-ethoxyphenoxy)methyl)-6-isopropoxy-1,2,3,4-tetrahydroisoquinoline (76): Dihydroisoquinoline **57** was prepared via procedure XI using amide **40** (1.6 g, 4.4 mmol) and phosphorous trichloride (1.2 mL, 13 mmol) in dry toluene (24 mL). The crude residue (4.9 g) was carried on without further purification. HRMS calcd. for $C_{21}H_{25}O_3N_1$, 340.19072 $[M + H]^+$; found 340.19116 $[M + H]^+$. Tetrahydroisoquinoline **76** was prepared via procedure XII using dihydroisoquinoline **57** (4.9 g, 14 mmol) and sodium borohydride (1.6 g, 43 mmol) in dry MeOH (71 mL). 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 yellow solid (0.70 g, 14 % over 2 steps). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.58; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.01-6.99 (d, *J* = 8.4 Hz, 1H), 6.94-6.89 (m, 2H), 6.77-6.70 (m, 3H), 6.60-6.59 (d, *J* = 2.4 Hz, 1H), 4.59-5.58 (m, 1H), 4.51-4.45 (m, 1H), 4.43-4.38 (m, 1H), 4.34-4.29 (m, 1H), 3.94-3.87 (q, *J* = 6.8 Hz, *J* = 13.6 Hz, 2H), 3.51-3.47 (m, 1H), 3.24-3.09 (m, 2H), 2.97-2.92 (m, 1H), 1.37-1.33 (t, *J* = 6.8 Hz, 3H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 157.7, 154.0, 152.1, 134.4, 127.5, 120.6, 116.6, 115.9, 115.5, 113.3, 70.1, 69.4, 64.1, 54.0, 39.8, 26.2, 22.3, 22.2, 15.1; HRMS calcd. for $C_{21}H_{27}O_3N_1$, 342.20637 $[M + H]^+$; found 342.20595 $[M + H]^+$.

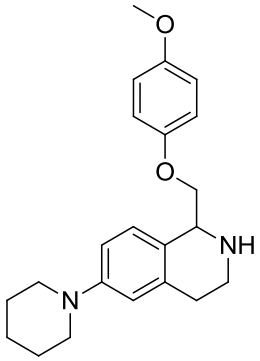


6-(cyclopentyloxy)-1-((4-ethoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (78): Dihydroisoquinoline **59** was prepared via procedure XI using amide **28** (1.4 g, 3.8 mmol) and phosphorous trichloride (2.3 mL, 11 mmol) in dry toluene (21 mL). The crude residue (1.1 g) was carried on without further purification. HRMS calcd. for $C_{23}H_{30}O_3N_1$, 368.22202 $[M + H]^+$; found 368.22225 $[M + H]^+$. Tetrahydroisoquinoline **78** was prepared via procedure XII using dihydroisoquinoline **59** (1.1 g, 3.0 mmol) and sodium borohydride (0.34 g, 8.9 mmol) in dry MeOH (15 mL). 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 an off-white solid (0.55 g, 51 %). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.83; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.02-6.94 (m, 3H), 6.78-6.71 (m, 3H), 6.62-6.61 (m, 1H), 4.72-4.68 (m, 1H), 4.61-4.59 (m, 1H), 4.42-4.31 (m, 2H), 3.94 (q, *J* = 6.8 Hz, 2H), 3.53-3.43 (m, 1H), 3.26-3.11 (m, 2H), 3.01-2.97 (m, 1H), 1.92-1.72 (m, 6H), 1.65-1.56 (m, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 157.9, 154.0, 152.0, 134.3, 127.3, 120.1, 116.4, 115.6, 115.4, 115.2, 79.5, 69.2, 64.1, 54.3, 39.8, 34.6, 33.0, 26.4, 24.2, 15.1; HRMS calcd. for $C_{23}H_{30}O_3N$, 368.22202 $[M + H]^+$; found 368.22227 $[M + H]^+$.

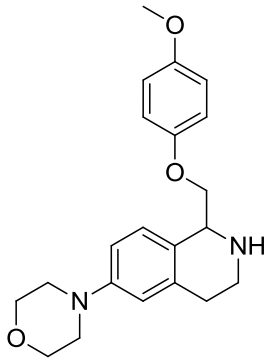


1-((4-ethoxyphenoxy)methyl)-6-isobutoxy-1,2,3,4-tetrahydroisoquinoline (79): Dihydroisoquinoline **60** was prepared via procedure X using amide **37** (0.54 g, 1.5 mmol) and phosphorous trichloride (0.90 mL, 4.4 mmol) in dry toluene (7.3 mL). The crude residue (0.68 g) was carried on without further purification. HRMS calcd. for $C_{22}H_{28}O_3N$, 354.20637 $[M + H]^+$; found 354.206654 $[M + H]^+$. Tetrahydroisoquinoline **79** was prepared via procedure XII using dihydroisoquinoline **60** (0.68 g, 1.9 mmol) and sodium borohydride (0.22 g, 5.8 mmol) in dry MeOH (9.7 mL). 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 green foam (0.35 g, 52 % over 2 steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.04-7.03 (m, 1H), 6.96-6.89 (m, 1H), 6.79-

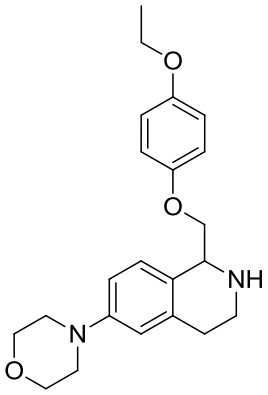
6.74 (m, 4H), 6.66-6.63 (m, 1H), 4.54-5.53 (m, 1H), 4.34-4.08 (m, 2H), 3.97-3.88 (m, 2H), 3.68 (d, *J* = 6.8 Hz, 2H), 3.49-3.39 (m, 1H), 3.28-3.26 (m, 1H), 3.21-2.91 (m, 2H), 2.10-2.02 (m, 1H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.4). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.8, 153.8, 152.3, 134.8, 127.6, 121.8, 116.3, 115.6, 115.4, 114.4, 114.0, 74.6, 69.8, 64.1, 53.7, 39.6, 28.5, 28.4, 26.5, 19.4, 15.1. HRMS calcd. for $C_{22}H_{30}O_3N$, 356.22202 $[M + H]^+$; found 356.22235 $[M + H]^+$.



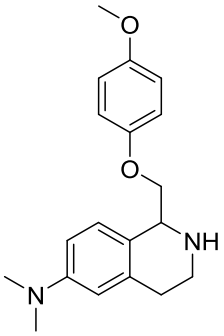
1-((4-methoxyphenoxy)methyl)-6-(piperidin-1-yl)-1,2,3,4-tetrahydroisoquinoline (80):
Dihydroisoquinoline **61** was prepared via procedure X using amide **41** (0.16 g, 0.45 mmol) and phosphorous trichloride (0.28 mL, 1.4 mmol) in dry toluene (2.2 mL). The crude residue (0.23 g) was carried on without further purification. HRMS calcd. for $C_{22}H_{27}O_2N_2$, 351.20670 $[M + H]^+$; found 351.20660 $[M + H]^+$. Tetrahydroisoquinoline **80** was prepared via procedure XII using dihydroisoquinoline **61** (0.23 g, 1.9 mmol) and sodium borohydride (0.073 g, 1.9 mmol) in dry MeOH (3.3 mL). 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 green foam (0.097 g, 43 % over 2 steps). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.43 ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.04 (d, *J* = 8.4 Hz, 1H), 6.89-6.75 (m, 5H), 6.68-6.67 (m, 1H), 4.35-4.32 (dd, *J* = 2.8 Hz, *J* = 9.2 Hz, 1H), 4.14-4.11 (m, 1H), 4.07-4.02 (m, 1H), 3.72 (s, 3H), 3.23-3.18 (m, 1H), 3.10 (t, *J* = 5.6 Hz, 4H), 3.06-2.99 (m, 1H), 2.81-2.79 (m, 2H), 1.71-1.65 (m, 4H), 1.58-1.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.2, 152.9, 151.2, 136.0, 127.2, 123.9, 116.8, 115.9, 115.0, 114.8, 71.0, 55.92, 54.6, 50.7, 40.1, 29.5, 26.0, 24.5; HRMS calcd. for $C_{22}H_{29}O_2N_2$, 353.22235 $[M + H]^+$; found 353.22243 $[M + H]^+$.



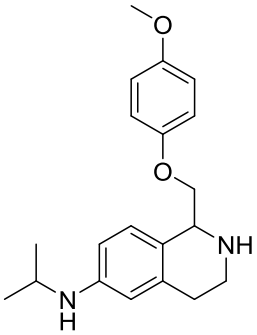
4-(1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)morpholine (81):
Dihydroisoquinoline **62** was prepared via procedure X using amide **42** (1.5 g, 3.9 mmol) and phosphorous trichloride (2.4 mL, 12 mmol) in dry toluene (19 mL). The crude residue (1.6 g) was carried on without further purification. HRMS calcd. for $C_{21}H_{25}O_3N_2$, 353.18597 $[M + H]^+$; found 353.18608 $[M + H]^+$.
Tetrahydroisoquinoline **81** was prepared via procedure XII using dihydroisoquinoline **62** (1.6 g, 4.6 mmol) and sodium borohydride (0.52 g, 14 mmol) in dry MeOH (23 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-20% MeOH/DCM gradient) to afford the title compound as a brown foam (0.47 g, 29 % over 2 steps). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.64; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.07 (d, *J* = 8.4 Hz, 1H), 6.87-6.79 (m, 4H), 6.76-6.74 (m, 1H), 6.71-6.65 (m, 1H), 4.36-4.33 (m, 1H), 4.14-4.03 (m, 2H), 3.85-3.83 (m, 4H), 3.76 (m, 3H), 3.25-3.19 (m, 1H), 3.13-3.11 (m, 4H), 3.05-2.99 (m, 1H), 2.83-2.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.2, 154.1, 150.1, 136.9, 127.4, 126.2, 116.2, 115.7, 114.8, 114.1, 71.4, 67.2, 55.9, 54.7, 49.5, 40.0, 30.3; HRMS calcd. for $C_{21}H_{30}O_2N_3$, 355.20162 $[M + H]^+$; found 355.20169 $[M + H]^+$.



4-(1-((4-ethoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)morpholine (82):
Dihydroisoquinoline **63** was prepared via procedure X using amide **43** (0.77 g, 2.0 mmol) and phosphorous trichloride (1.2 mL, 6.0 mmol) in dry toluene (10. mL). The crude residue (0.78 g) was carried on without further purification. HRMS calcd. for $C_{22}H_{27}O_2N_2$, 367.20162 $[M + H]^+$; found 367.20183 $[M + H]^+$.
Tetrahydroisoquinoline **82** was prepared via procedure XII using dihydroisoquinoline **63** (0.78 g, 2.1 mmol) and sodium borohydride (0.24 g, 6.4 mmol) in dry MeOH (11 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-20% MeOH/DCM gradient) to afford the title compound as a brown foam (0.41 g, 52 % over 2 steps). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.47; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.10 (d, *J* = 8.4 Hz, 1 H), 6.88-6.82 (m, 4H), 6.79-6.76 (dd, *J* = 2.4 Hz, *J* = 8.8 Hz, 1H), 6.69-6.68 (m, 1H), 4.37-4.34 (dd, *J* = 3.2 Hz, *J* = 8.8 Hz, 1H), 4.15-4.12 (m, 1H), 4.08-4.04 (m, 1H), 4.98 (q, *J* = 7.2 Hz, 2H), 3.87 (t, *J* = 4.4 Hz, 4H), 3.26-3.19 (m, 1H), 3.15 (t, *J* = 5.2 Hz, 4H), 3.06-3.00 (m, 1H), 2.84-2.82 (m, 2H), 1.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.5, 153.1, 137.1, 127.4, 126.5, 116.2, 115.7, 115.6, 114.0, 71.5, 67.2, 64.2, 54.8, 49.5, 40.0, 30.4, 15.2; HRMS calcd. for $C_{22}H_{29}O_2N_3$, 369.21727 $[M + H]^+$; found 369.21725 $[M + H]^+$.

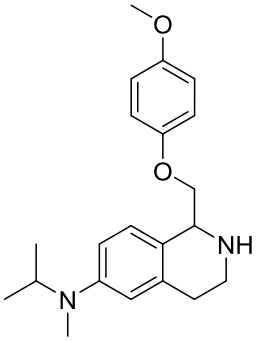


1-((4-methoxyphenoxy)methyl)-*N*,*N*-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-amine (83):
Dihydroisoquinoline **64** was prepared via procedure X using amide **45** (0.78 g, 2.4 mmol) and phosphoris trichloride (0.67 mL, 7.2 mmol) in dry toluene (13 mL). The crude solid (1.4 g) was carried on without further purification. HRMS calcd. for $C_{19}H_{23}O_2N_2$, 311.17540 $[M + H]^+$; found 311.17594 $[M + H]^+$. Tetrahydroisoquinoline **83** was prepared via procedure XII using dihydroisoquinoline **64** (1.4 g, 4.4 mmol) in dry MeOH (22 mL). 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 yellow solid (0.53 g, 39 % over 2 steps) TLC (MeOH/DCM, 1:10, v/v) R_f: 0.44; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.05-7.03 (d, *J* = 8.4 Hz, 1H), 6.88-6.79 (m, 4H), 6.61-6.58 (dd, *J* = 2.8 Hz, *J* = 4.8 Hz, 1H), 6.48-6.47 (d, *J* = 2.4 Hz, 1H), 4.35-4.32 (dd, *J* = 2.8 Hz, *J* = 9.2 Hz, 1H), 4.13-4.10 (dd, *J* = 3.2 Hz, *J* = 9.2 Hz, 1H), 4.06-4.02 (m, 1H), 3.75 (s, 3H), 3.23-3.18 (m, 1H), 3.04-2.98 (m, 1H), 2.91 (s, 6H), 2.83-2.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.1, 153.2, 149.7, 136.6, 127.3, 115.7, 114.8, 113.1, 111.3, 71.4, 55.9, 54.7, 40.8, 40.0, 30.1; HRMS calcd. for $C_{19}H_{25}O_2N_2$, 313.19105 $[M + H]^+$; found 313.19164 $[M + H]^+$.

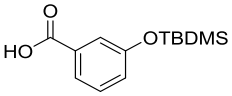


***N*-isopropyl-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinolin-6-amine (84):**
Dihydroisoquinoline **65** was prepared via procedure X using amide **46** (0.60 g, 1.8 mmol) and phosphorous trichloride (0.72 mL, 3.5 mmol) in dry toluene (8.7 mL). The crude residue (1.0 g) was carried on without further purification. HRMS calcd. for $C_{20}H_{25}O_2N_2$, 325.19105
$[M + H]^+$; found 325.19081 $[M + H]^+$. Tetrahydroisoquinoline **84** was prepared via procedure XII using dihydroisoquinoline **65** (1.0 g, 3.1 mmol) and sodium borohydride (0.23 g, 6.3 mmol) in dry MeOH (16 mL). 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 yellow solid (0.039 g, 3.8 % over 2 steps). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.64; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.98-6.96 (d, J = 8.4 Hz, 1H), 6.91-6.79 (m, 4H), 6.46-6.43 (dd, *J* = 2.4 Hz, J = 8.8 Hz, 1H), 6.36-6.36 (m, 1H), 4.38-4.35 (m, 1H), 4.17-4.13 (m,

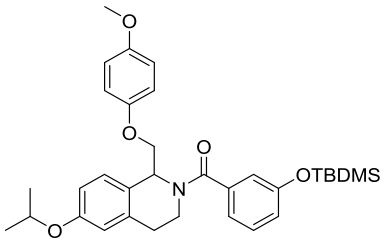
1H), 4.10-4.06 (m, 1H), 3.77 (s, 3H), 3.66-3.58 (m, 1H), 3.28-3.21 (m, 1H), 3.07-3.02 (m, 1H), 2.83-2.80 (m, 2H), 1.20 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.2, 153.1, 146.5, 136.7, 127.5, 122.2, 115.8, 114.8, 113.3, 111.9, 71.3, 55.9, 54.6, 44.4, 39.9, 29.7, 23.3; HRMS calcd. for $C_{20}H_{27}O_2N_2$, 327.20670 $[M + H]^+$; found 327.20623 $[M + H]^+$.



***N*-isopropyl-1-((4-methoxyphenoxy)methyl)-N-methyl-1,2,3,4-tetrahydroisoquinolin-6-amine (85):** Dihydroisoquinoline **66** was prepared via procedure X using amide **47** (0.58 g, 1.6 mmol) and phosphorous trichloride (0.75 mL, 4.9 mmol) in dry toluene (8.2 mL). The crude residue (0.92 g) was carried on without further purification. HRMS calcd. for $C_{21}H_{26}O_2N_2$, 339.20670 $[M + H]^+$; found 339.20656 $[M + H]^+$. Tetrahydroisoquinoline **85** was prepared via procedure XII using dihydroisoquinoline **66** (0.53 g, 1.6 mmol) and sodium borohydride (0.19 g, 4.9 mmol) in dry MeOH (8.2 mL). 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 yellow solid (0.27 g, 48 % over 2 steps). TLC (MeOH/DCM, 1:10, v/v) R_f: 0.49; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.06 (d, J = 8.4 Hz, 1H), 6.92-6.83 (m, 4H), 6.68-6.66 (m, 1H), 6.60-6.55 (m, 1H), 4.38-4.35 (m, 1H), 4.17-4.04 (m, 3H), 3.78 (s, 3H), 3.27-3.21 (m, 1H), 3.07-3.21 (m, 1H), 2.85-2.78 (m, 2H), 2.73 (s, 3H), 1.23-1.17 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.1, 153.3, 149.1, 136.8, 127.3, 122.5, 115.7, 114.8, 113.6, 111.6, 71.7, 55.9, 54.7, 49.0, 40.2, 30.6, 30.0, 19.6; HRMS calcd. for $C_{21}H_{28}O_2N_2$, 341.22235 $[M + H]^+$; found 341.22213 $[M + H]^+$.

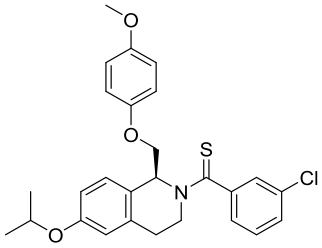


3-(tert-butyldimethylsilyloxy)benzoic acid (129): 3-hydroxybenzoic acid (1.0 g, 7.2 mmol), tert-butylchlorodimethylsilane (4.4 g, 29 mmol), and 1H-imidazole (2.9 g, 43 mmol) were dissolved in dry DMF (36 ml). The reaction was allowed to stir at room temperature overnight. The reaction was quenched with DI water and extracted into hexane, washed with water (3x) and brine (3x), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. THF (3.9 ml), AcOH (12 ml), and aater (3.9 ml) were added sequentially to the resulting white solid (2.0 g) and the reaction was stirred at room temperature for 2 hours. The reaction was quenched with water and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 10 – 80% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.65 g, 95%). TLC (EtOAc: hexanes, 1:1, v/v) Rf = 0.83; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.71-7.69 (m, 1H), 7.53-7.54 (m, 1H), 7.34-7.30 (t, J = 8.4 Hz, 1H), 7.09-7.06 (m, 1H), 0.98 (s, 9H), 0.21 (s, 6H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 172.2, 156.0, 130.8, 129.8, 126.0, 123.4, 121.7, 25.9, 18.4, -4.2; HRMS calcd. for $C_{13}H_{21}O_3Si$, 353.12545 $[M + H]^+$; found 353.12532 $[M + H]^+$.

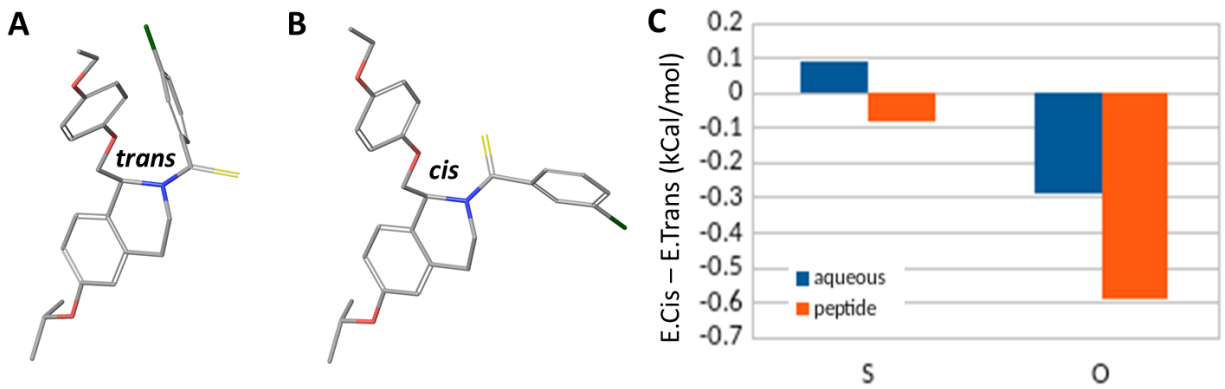


(3-(tert-butyldimethylsilyloxy)phenyl)(6-isopropoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (130): Tetrahydroisoquinoline **130** was prepared via procedure XIV using benzoic acid 130 (0.21 g, 0.84 mmol), N^1-((ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine (0.14 g, 0.92 mmol), N,N-dimethylpyridin-4-amine (0.11 g, 0.92 mmol), and tetrahydroisoquinoline **67** (.25 g, 0.76 mmol). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 10 – 80% EtOAc/hexanes gradient) to afford the title compound as a white foam (0.43 g, 59 % mixture of two amide rotamers) TLC (EtOAc: hexanes, 1:1, v/v) Rf = 0.74; ^{1}HNMR ($CDCl_3$, 400 MHz) δ: 7.29-7.19 (m, 2H), 7.07-6.94 (m, 1H), 6.88-6.66 (m, 8H), 5.97-5.94 (t, *J* = 4.8 Hz, 0.5H), 5.18-5.15 (dd, *J* = 4.0 Hz, *J* = 9.2 Hz, 0.5H), 4.86-4.81 (dd, *J* = 5.2 Hz, *J* = 12.8 Hz, 0.5H), 5.54-4.48 (m, 1H), 4.36-4.29 (m, 1H), 4.11-4.06 (m, 0.5 H), 3.93-3.89 (t, *J* = 4.8 Hz, 0.5H), 3.80-3.56 (m, 1H), 3.74 (s, 3H), 3.26-3.09 (m, 1H), 2.91-2.67 (m, 1.5H), 1.33-1.31 (d, 6H), 0.97-0.92 (m, 9H), 0.18 (s, 6H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 171.6, 170.9, 157.4, 156.9, 155.9, 155.7, 154.3, 154.2, 153.2, 152.8, 138.1, 137.9, 136.6, 135.7, 130.0, 129.7, 128.8, 25.5, 124.6, 121.5, 121.3, 120.6, 119.7, 119.6, 118.4, 116.2, 115.9, 115.8, 115.7, 114.8, 114.6, 114.3, 71.4, 70.1, 57.1, 55.9, 51.7, 42.8, 35.5, 30.0, 28.6, 25.9, 22.3, 18.3, -4.2; HRMS calcd. for $C_{33}H_{44}O_5N_1Si$, 562.29833$[M + H]^+$; found 562.29760 $[M + H]^+$.

Crystal structure data and experimental



Single crystals of $C_{27}H_{28}ClNO_3S$ (***S*-(-)-138**) were recrystallized from a mixture of DCM and hexane by slow evaporation. A suitable crystal (0.764×0.484×0.154 mm^3) was selected and mounted on a loop paratone oil on a Apex II Cu diffractometer. The crystal was kept at 173(2) K during data collection. Using Olex2[64], the structure was solved with the Superflip[65] structure solution program, using the Charge Flipping solution method. The model was refined with the ShelXL[66] refinement package using Least Squares minimization. Crystal data: M = 482.01, monoclinic, $P2_1$ (No. 4, a = 5.7587 Å, b = 16.3557 Å, c = 13.105 Å, β = 91.808°, α = γ = 90°,V = 1233.71(10) Å3, T = 173(2) K, Z = 2, μ (Mo Kα) = 2.390, 9144 reflections measured, 4191 unique (Rint = 0.0635) which were used in all calculations. The final wR2 was 0.3083 (all data) and R1 was 0.1020 (I > 2(I)). Crystals grown and data collected and analyzed by John Bacsa, PhD at the Emory X-crystallography core facility. Crystallographic data is summarized in Supplemental **Table S2**.



Supplemental Figure S1: *Trans* (A) and *cis* (B) conformations of S-(-)-**138** as calculated using Terachem at the B3LYP/6-311G(2p,2d) level with the polarizable continuum model with a dielectric of 78.30. (C) Energy differences calculated between *cis* and *trans* conformations for the thioamide (S) and amide (O) with both a dielectric of 78.30 (aqueous) and 7.00 (peptide).