Supporting Information

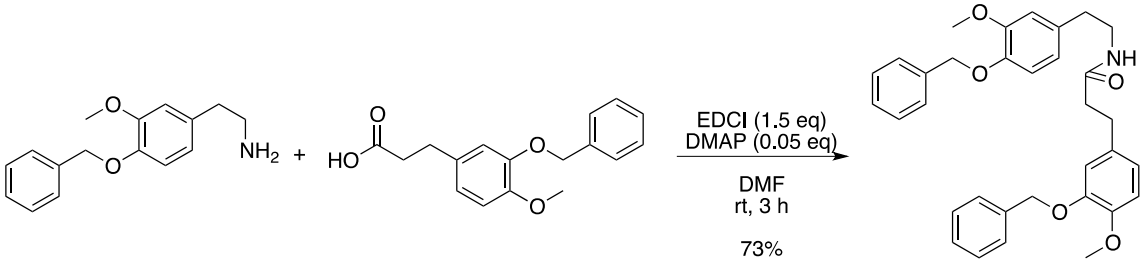
Synthetic procedure for isoquinoline 2 and the spectrum data of synthetic metofoline and Ro-04-2359.

General Information

Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. All reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. Anhydrous THF and MeCN were purchased from Kanto Chemical Co. Inc. Anhydrous DMF was purchased from Wako Pure Chemical Industries. Anhydrous MeOH was dried and distilled according to the standard protocols. Flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40–50 μm) using the indicated eluent. Analytical TLC was performed on Merck 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel. IR spectra were measured on a JASCO FT/IR-4100 spectorometer. NMR spectra were recorded on a JNM-AL400 spectrometer and a JEOL ECA600 spectrometer with tetramethylsilane (0 ppm) and chloroform (7.26 ppm) as an internal standard. Chemical shifts were expressed in δ (ppm) values, and coupling constants were expressed in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Mass spectra were recorded on a Brucker micrOTOF II (ESI).

Synthetic Procedure for Isoquinoline 2

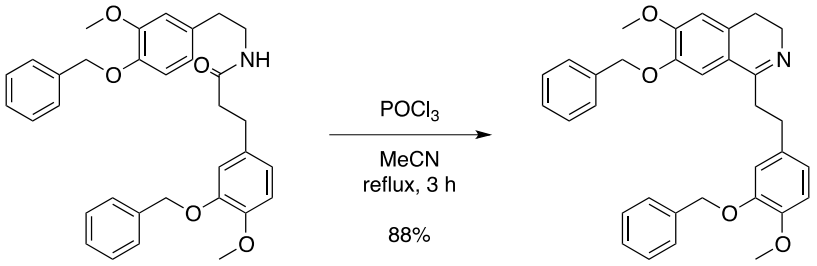
***N*-(4-(Benzyloxy)-3-methoxyphenethyl)-3-(3-(benzyloxy)-4-methoxyphenyl)propanamide**



To a stirred solution of 2-(4-(benzyloxy)-3-methoxyphenyl)ethanamine (1.0 g, 3.9 mmol) and 3-(3-(benzyloxy)-4-methoxyphenyl)propanoic acid (1.1 g, 3.9 mmol) in DMF (19 mL) were

added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (1.1 g, 5.9 mmol) and *N,N*-dimethyl-4-aminopyridine (DMAP) (24 mg, 0.20 mmol) at room temperature. The reaction mixture was stirred for 3 h. The reaction was quenched with water and the resulting mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by recrystalization from CH_2Cl_2 and hexanes to afford *N*-(4-(benzyloxy)-3-methoxyphenethyl)-3-(3-(benzyloxy)-4-methoxyphenyl)propanamide (1.5 g, 2.8 mmol, 73%) as a white solid; IR (neat, cm^{-1}) 3286, 2932, 1647, 1513, 1453, 1260, 1221, 1137, 1023, 772, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.42 (4H, m), 7.37–7.33 (4H, m), 7.30–7.23 (2H, m), 6.79 (2H, d, *J* = 8.4 Hz), 6.74 (1H, d, *J* = 2.0 Hz), 6.71 (1H, dd, *J* = 8.4, 2.0 Hz), 6.68 (1H, d, *J* = 2.0 Hz), 6.55 (1H, dd, *J* = 8.4, 2.0 Hz), 5.21 (1H, t, *J* = 7.2 Hz), 5.12 (4H, s), 3.85 (6H, s), 3.41 (2H, td, *J* = 7.2, 6.8 Hz), 2.83 (2H, t, *J* = 7.6 Hz), 2.65 (2H, t, *J* = 6.8 Hz), 2.33 (2H, t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 149.8, 148.3, 148.1, 146.9, 137.2, 137.1, 133.4, 132.0, 128.5, 127.8, 127.3, 127.3 121.0, 120.6, 114.7, 114.4, 112.5, 112.1, 71.1, 56.1, 40.5, 38.7, 35.2, 31.2; HRMS (ESI) calcd. for $C_{33}H_{36}NO_5$ $[M+H]^+$, 526.2588; found 526.2564.

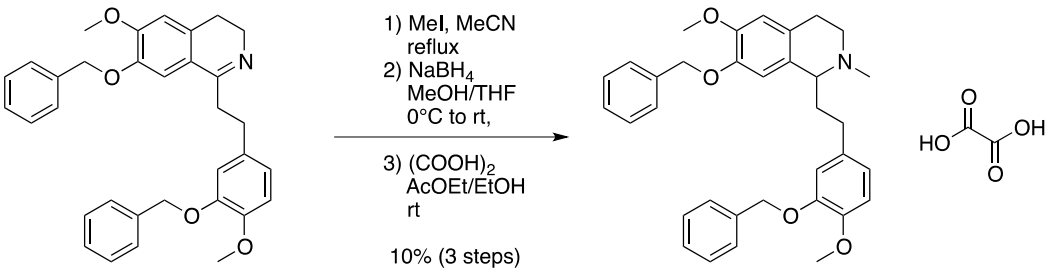
7-(Benzyloxy)-1-(3-(benzyloxy)-4-methoxyphenethyl)-6-methoxy-3,4-dihydroisoquinoline



To a stirred solution of *N*-(4-(benzyloxy)-3-methoxyphenethyl)-3-(3-(benzyloxy)-4-me thoxy-phenyl)propanamide (200 mg, 0.380 mmol) in MeCN (1.3 mL) was added $POCl_3$ (106 µL, 1.14 mmol) at room temperature. The reaction mixture was heated to reflux and stirred for 3 h. The reaction was quenched with 1 M HCl and the mixture was basified with 25% ammonium hydroxide solution. The resulting mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (MeOH/ CH_2Cl_2 = 1/30 to 1/10, gradually) to afford 7-(benzyloxy)-1-(3-(benzyloxy)-4-methoxyphenethyl)-6-

methoxy-3,4-dihydroisoquinoline (169 mg, 0.333 mmol, 88%) as a flesh colored solid; IR (neat, cm^{-1}) 2932, 2834, 1604, 1514, 1454, 1265, 1142, 1024, 747, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (4H, d, *J* = 7.2 Hz), 7.36–7.31 (4H, m), 7.27 (2H, t, *J* = 7.2 Hz), 6.97 (1H, s), 6.90 (1H, d, *J* = 8.4 Hz), 6.75–6.68 (3H, m), 5.10 (4H, s), 3.92 (3H, s), 3.86 (3H, s), 3.61 (2H, t, *J* = 7.2 Hz), 2.85–2.72 (4H, m), 2.58 (2H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 151.7, 148.1, 146.5, 137.3, 137.0, 134.5, 132.3, 128.5, 127.8, 127.3, 121.9, 120.9, 114.9, 112.4, 112.1, 110.8, 71.8, 71.1, 56.2, 56.0, 46.9, 37.7, 32.7, 25.9; HRMS (ESI) calcd. for $C_{33}H_{34}NO_4$ $[M+H]^+$, 508.2482; found 508.2461.

7-(Benzyloxy)-1-(3-(benzyloxy)-4-methoxyphenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline oxalate



To a stirred solution of 7-(benzyloxy)-1-(3-(benzyloxy)-4-methoxyphenethyl)-6-metho xy-3,4-dihydroisoquinoline (500 mg, 0.985 mmol) in MeCN (4.9 mL) was added MeI (336 µL, 5.39 mmol) at room temperature. The reaction mixture was heated to reflux and stirred for 2 h. After cooling to reaction temperature, additional MeI (1.0 mL, 16.0 mmol) and MeCN (2 mL) were added to the reaction mixture. The resulting mixture was heated to 60 °C and stirred for 28 h. The reaction mixture was concentrated under reduced pressure. The crude residue was subject to the next reaction without further purification.

To a stirred solution of the crude iminium compound in a mixture of MeOH (3.8 mL) and THF (3.8 mL) was added $NaBH_4$ (278 mg, 7.35 mmol) at room temperature. The reaction mixture was stirred for 17 h. The reaction was quenched with 1 M HCl and the resulting mixture was washed with Et_2O. The aqueous layer was basified with 25% ammonium hydroxide and the reaction mixture was extracted with CH_2Cl_2. The organic extract was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (MeOH/ CH_2Cl_2 = 1/30 to 1/10, gradually) to afford 7-(benzyloxy)-1-(3-(benzyloxy)-4-methoxyphenethyl)-6-

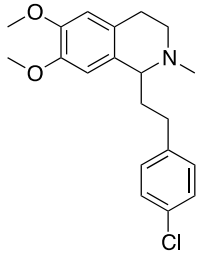
methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline.

To the isoquinoline in a mixture of EtOAc (970 μL) and EtOH (148 μL) was added oxalic acid (30 mg, 0.333 mmol). The resulting mixture was concentrated under reduced pressure. The precipitate was washed with Et_2O and recrystallized from *i*-PrOH to afford isoquinoline **2** (60 mg, 0.98 mmol, 10% over 3 steps) as a white solid; IR (neat, cm^{-1}) 3030, 2931, 2856, 1732, 1611, 1516, 1261, 1024, 751, 698; ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 7.2 Hz), 7.39 (2H, d, *J* = 7.2 Hz), 7.36–7.31 (4H, m), 7.27 (1H, t, *J* = 7.2 Hz), 7.22 (1H, t, *J* = 7.8 Hz), 6.79 (1H, d, *J* = 7.8 Hz), 6.68 (1H, s), 6.67 (1H, s), 6.60 (1H, d, *J* = 7.8 Hz), 6.42 (1H, s), 5.14 (1H, d, *J* = 13.2 Hz), 5.12 (2H, s), 5.06 (1H, d, *J* = 13.2 Hz), 4.04 (1H, br s), 3.89 (3H, s), 3.84 (3H, s), 3.59 (1H, br s), 3.39 (1H, br s), 3.09–3.00 (1H, m), 2.98 (1H, dd, *J* = 15.6, 5.4 Hz), 2.72 (3H, s), 2.56–2.49 (1H, m), 2.47–2.39 (1H, m), 2.39–2.30 (1H, m), 1.84–1.78 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 150.0, 148.4, 148.2, 147.0, 137.2, 136.5, 132.4, 128.7, 128.5, 128.1, 127.7, 127.4, 127.2, 112.6, 121.7, 121.1, 114.7, 113.6, 112.2, 111.9, 71.2, 71.0, 62.9, 56.1, 56.1, 44.8, 39.5, 31.6, 25.4, 21.8; HRMS (ESI) calcd. for $C_{34}H_{38}NO_4$ $[M\text{-}C_2O_4H]^+$, 524.2795; found 524.2772.

<u>The spectrum data of synthetic Metofoline and Ro-04-2359</u>

Metofoline;

1-(4-Chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

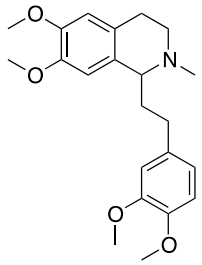


Metofoline was synthesized from 2-(3,4-dimethoxyphenyl)ethanamine and 3-(4-chlorophenyl)propanoic acid according to the procedure for isoquinoline **2**; A pale yellow solid IR (neat, cm^{-1}) 2925, 2841, 2783, 1607, 1519, 1261, 1108, 820; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, d, *J* = 8.0 Hz), 7.10 (2H, d, *J* = 8.0 Hz), 6.57 (1H, s), 6.52 (1H, s), 3.85 (3H, s), 3.82 (3H, s), 3.40 (1H, t, *J* = 4.8 Hz), 3.19–3.06 (1H, m), 2.80–2.67 (4H, m), 2.61–2.45 (1H, m), 2.74 (3H, s), 2.16–1.99 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 147.3, 141.4, 131.2, 129.8, 129.6, 128.3, 126.9, 111.4, 110.1, 62.6, 56.0, 55.8, 48.2, 42.7, 36.8, 30.8, 25.5; HRMS (ESI) calcd. for $C_{20}H_{25}ClNO_2$ $[M+H]^+$, 346.1568; found 346.1556. The spectrum data of this comopound were

identical with those reported in the literature.[1]

Ro-04-2359;

1-(3,4-Dimethoxyphenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline



Ro-04-2359 was synthesized from 2-(3,4-dimethoxyphenyl)ethanamine and 3-(3,4-dimethoxyphenyl)propanoic acid according to the procedure for isoquinoline **2**; A white solid IR (neat, cm^{-1}) 2918, 2841, 2767, 1588, 1514, 1463, 1256, 1029, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (1H, d, *J* = 7.6 Hz), 6.72 (1H, dd, *J* = 7.6, 2.0 Hz), 6.17 (1H, s), 6.57 (1H, s), 6.53 (1H, s), 3.86 (3H, s), 3.85 (3H, s), 3.84 (3H, s), 3.83 (3H, s), 3.42 (1H, t, *J* = 6.0 Hz), 3.17–3.12 (1H, m), 2.80–2.65 (4H, m), 2.56–2.50 (1H, m), 2.48 (3H, s), 2.07–2.01 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 147.3, 147.2, 147.0, 135.6, 129.9, 126.8, 120.1, 112.0, 111.3, 111.3, 110.2, 62.6, 55.9, 55.7, 48.1, 42.7, 37.0, 31.1, 25.4; HRMS (ESI) calcd. for $C_{22}H_{30}NO_4$ $[M+H]^+$, 372.2169; found 372.2153. The spectrum data of this comopound were identical with those reported in the literature.[2]

References

(1) Graulich, A.; Scuvee-Moreau, J.; Alleva, L.; Lamy, C.; Waroux, O.; Seutin, V.; Liegeois, J. F. Synthesis and radioligand binding studies of methoxylated 1,2,3,4-tetrahydroisoquinolinium derivatives as ligands of the apamin-sensitive Ca2+-activated K+ channels. *J. Med. Chem.* **2006**, *49*, 7208-7214.

(2) Barham, J. P.; John, M. P.; Murphy, J. A. One-pot functionalisation of N-substituted tetrahydroisoquinolines by photooxidation and tunable organometallic trapping of iminium intermediates. *Beilstein J. Org. Chem.* **2014**, *10*, 2981-2988.