Electronic Supplementary Information

Discovery of 7-hydroxyaporphines as conformational restricted ligands for beta-1 and beta-2 adrenergic receptors†

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1. General Experimental Conditions

All reactions involving air-sensitive reagents were carried out in oven-dried glassware equipped with a magnetic stir bar and fitted with rubber septa under argon unless otherwise stated. All commercially available chemicals and reagent grade solvents were used directly without further purification unless otherwise specified. All reactions were monitored by thin-layer chromatography (TLC) on Baker-flex® silica gel plates (IB2-F) using UV-light (254 and 365 nm) detection or visualizing agents (ninhydrin or phosphomolybdic acid stain). Flash column chromatography was conducted on silica gel (230–400 mesh) using Teledyne Isco CombiFlash® Rf. Melting points were measured using a Thomas Hoover Uni-Melt capillary melting point apparatus and are uncorrected. NMR spectra were recorded at room temperature using a JEOL ECA-500 (1H NMR at 500 MHz and 13C NMR at 125 MHz) or a JEOL ECX-400P (1H NMR at 400 MHz and 13C NMR at 100 MHz) with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given in parts per million (ppm) with reference to solvent signals [1H-NMR: CDCl₃ (7.26 ppm), CD₃OD (3.31 ppm), DMSO-d₆ (2.50 ppm); 13C-NMR: CDCl₃ (77.0 ppm), CD₃OD (49.15 ppm), DMSO-d₆ (39.51 ppm)]. Signal patterns are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (J) are given in Hz. High resolution mass spectra (HRMS) were performed by the University of Texas Mass Spectrometry facility using a quadrupole time-of-flight (Q-TOF) mass spectrometer with electrospray ionization (ESI). The spectra were reported as m/z (relative intensity) for the molecular ion [M]. Optical rotations were measured on ATAGO's polarimeter (POLAX-2L). Specific rotation [α]D values are given in units of 10⁻¹ deg cm² g⁻¹.
2. Functional Assays

The functional assays were conducted by Eurofins Panlab Discovery Service. Compound 2 was tested for both agonist and antagonist activities of the adrenergic receptor subtypes β₁ and β₂ using conditions described in Table S1. For functional antagonism, the β₁-adrenergic receptor was first agonized with isoproterenol to release cAMP. The agonism, detected by cAMP accumulation, was subsequently blocked through the treatment with either compound 2 (IC₅₀ = 0.017 ± 0.014 μM) or the positive control, atenolol (IC₅₀ = 0.40 ± 0.003 μM) as shown in Figure S1. Following a similar protocol, 2 and the positive control, ICI-118,551, inhibited the procaterol-induced cAMP increase at the β₂-adrenergic receptor with IC₅₀ values of 0.0069 ± 0.0027 μM and 0.00067 ± 0.00012 μM, respectively (Figure S2). In the absence of β₁ or β₂ agonists, compound 2 had no effect.

Table S1. Methods for β₁ and β₂-adrenergic receptor functional assays

<table>
<thead>
<tr>
<th>Target</th>
<th>Adrenergic β₁, adenylyl cyclase</th>
<th>Adrenergic β₂, adenylyl cyclase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitation method</td>
<td>HTRF quantitation of cAMP accumulation</td>
<td>HTRF quantitation of cAMP accumulation</td>
</tr>
<tr>
<td>Vehicle</td>
<td>0.40% DMSO</td>
<td>0.40% DMSO</td>
</tr>
<tr>
<td>Incubation time/temperature</td>
<td>15 minutes @ 37°C</td>
<td>20 minutes @ 37°C</td>
</tr>
<tr>
<td>Incubation buffer</td>
<td>HBSS, 5 mM HEPES, 0.1% BSA, 100 μM</td>
<td>HBSS, 5 mM HEPES, 0.1% BSA, 100 μM</td>
</tr>
<tr>
<td></td>
<td>IBMX, pH 7.4</td>
<td>IBMX, pH 7.4</td>
</tr>
</tbody>
</table>

Figure S1. Dose-response curves of 2 and atenolol (positive control) for inhibition of isoproterenol-induced cAMP increase in a β₁-adrenergic receptor functional assay.
Figure S2. Dose-response curves of 2 and ICI-118,551 (positive control) for inhibition of isoproterenol-induced cAMP increase in a β2-adrenergic receptor functional assay.
3. Synthetic Procedures

Methyl (R)-2-(2-chlorophenyl)-2-hydroxyacetate (9) To a solution of (R)-(−)-2-chloromandelic acid (7) (7.38 g, 39.5 mmol) in CH₃OH (15 mL) was added SOCl₂ (3.2 mL, 44 mmol) at 0 °C under argon. After being stirred at room temperature for 16 h, the reaction mixture was poured into saturated aqueous NaHCO₃ (100 mL). The mixture was then evaporated in vacuo to remove CH₃OH. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to afford 9 (7.9 g, 99%) as a colorless oil; H NMR (CDCl₃, 500 MHz) 7.40−7.39 (2 H, m), 7.29−7.27 (2 H, m), 5.57 (1 H, s), 3.78 (3 H, s); C NMR (CDCl₃, 125 MHz) 173.7, 135.9, 133.5, 130.0, 129.8, 128.8, 127.2, 70.3, 53.2; HRMS (ESI/Q-TOF) m/z [M + Na]⁺ calculated for C₉H₉ClO₃Na 223.0132; found 223.0132. The crude product was used directly in the next step.

Methyl (R)-2-(((4-(tert-butyldimethylsilyl)oxy)-3-methoxyphenethyl)carbamoyl)oxy)-2-(2-chlorophenyl)acetate (11) To a solution of triphosgene (630 mg, 2.1 mmol) in anhydrous toluene (5 mL) was added a solution of 8 (850 mg, 3.0 mmol) in anhydrous toluene (5 mL) under argon. The mixture was stirred at room temperature for 30 min and heated to 100 °C for another 1 h. The resulting mixture was then allowed to cool to room temperature and slowly added into a suspension of 9 (400 mg, 2.0 mmol) and triethylamine (340 μL, 2.4 mmol) in anhydrous CH₂Cl₂ (5 mL) under argon. After being stirred at room temperature for 16 h, the reaction was quenched by the addition of saturated aqueous NH₄Cl, evaporated in vacuo to remove excess toluene and CH₂Cl₂, and then partitioned between H₂O and EtOAc. Following neutralization with saturated aqueous NaHCO₃, the organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 5:95 to 7:93 to 10:90) to afford 11 (560 mg, 55%) as a colorless oil; [α]²⁴D −67 (c 1.5, CHCl₃); H NMR (CDCl₃, 500 MHz) 7.43−7.40 (2 H, m), 7.33−7.27 (2 H, m), 6.76 (1 H, d, J = 8.0 Hz), 6.67 (1 H, d, J = 2.0 Hz), 6.62 (1 H, dd, J = 8.0, 2.0 Hz), 4.98 (1H,
br, NH), 3.77 (3 H, s), 3.75 (3 H, s), 3.46–3.42 (2 H, m), 2.75 (2 H, t, $J = 7.0$ Hz), 0.99 (9 H, s), 0.14 (6 H, s); $^{13}$C NMR (CDCl$_3$, 125 MHz) 169.6, 155.0, 150.9, 143.6, 134.1, 132.5, 131.8, 130.4, 129.9, 129.4, 127.1, 120.9, 120.8, 112.6, 71.2, 55.4, 52.7, 42.5, 35.5, 25.7 (3 ×), 18.4, −4.7 (2 ×); HRMS (ESI/Q-TOF) $m/z$ [M + Na]$^+$ calculated for C$_{25}$H$_{34}$ClNO$_6$SiNa 530.1736; found 530.1740.

To a solution of 11 (308 mg, 0.61 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL) was added dropwise a solution of DIBAL-H (25% in toluene, 800 μL, 1.2 mmol) at −78 °C under argon, and the mixture was stirred at −78 °C for 1 h. Then, CH$_3$OH (500 μL) was added, and the reaction was stirred at −20 °C for 10 min. Following the addition of BF$_3$·OEt$_2$ (740 μL, 6 mmol), the resulting mixture was stirred at room temperature for another 1 h. This reaction mixture was quenched with H$_2$O (5 mL), evaporated in vacuo to remove excess CH$_3$OH, and then partitioned between H$_2$O and EtOAc. After neutralization with saturated aqueous NaHCO$_3$, the organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. To the crude mixture in anhydrous CH$_2$Cl$_2$ (5 mL) was added TBAF (1.0 M in THF, 470 μL, 4.7 mmol) under argon. After being stirred at room temperature for 10 min, the reaction was evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to afford 12 (132 mg, 64%) as a mixture of diastereomers ($dr$ 67:33 for the anti/syn isomers). Anti-isomer 12-anti could be obtained after several recrystallizations with EtOAc and hexane.

$(1R,10bR)$-1-(2-Chlorophenyl)-9-hydroxy-8-methoxy-5,6-dihydro-1H-oxazolo[4,3-a]isoquinolin-3(10bH)-one (12-anti) White prisms; mp 87–89 °C; [$\alpha$]$^2$$_D$ = −60 (c 2.4, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) 7.55 (1 H, dd, $J = 7.0$, 2.5 Hz), 7.47–7.46 (1 H, m), 7.40–7.34 (2 H, m), 6.89 (1 H, s), 6.61 (1 H, s), 5.73 (1 H, d, $J = 4.5$ Hz), 5.66 (1 H, s, PhOH), 4.82 (1 H, d, $J = 4.5$ Hz), 4.11 (1 H, ddd, $J = 13.0$, 6.0, 1.5 Hz), 3.88 (3 H, s), 3.20 (1 H, td, $J = 13.0$, 4.0 Hz), 3.10 (1 H, td, $J = 16.0$, 6.0 Hz), 2.61 (1 H, dd, $J = 16.0$, 4.0 Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz) 157.6, 146.2, 144.7, 135.7, 132.3, 130.2, 128.1, 127.5, 126.3, 125.5, 111.2, 110.9, 79.4, 61.4, 55.9, 39.4, 26.8; HRMS (ESI/Q-TOF) $m/z$ [M + H]$^+$ calculated for C$_{19}$H$_{17}$ClNO$_4$ 346.0841;
found 346.0840.

To 12 (dr 67:33) (39 mg, 0.11 mmol), Cs₂CO₃ (111 mg, 0.34 mmol) and XPhos precatalyst (8 mg, 0.011 mmol) was added anhydrous DMA (500 μL) under argon. The reaction was stirred at room temperature for 5 min and then put into a preheated oil bath (110 °C) for another 40 min. After being quenched by the addition of 1 N HCl(aq), the aqueous layer was extracted with EtOAc (2 × 30 mL). Following neutralization with saturated aqueous NaHCO₃, the combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 25:75 to 30:70 to 35:65 to 50:50) to afford 13-anti (24 mg, 70%) and 13-syn (8 mg, 24%) in a combined yield of 94%.

(3¹R,12bR)-8-Hydroxy-7-methoxy-3¹,4,5,12b-tetrahydro-2H-dibenzo[de,g]oxazolo[5,4,3-ij]quinolin-2-one (13-anti) White prisms; mp 218–219 ℃; [α]²⁵D −103 (c 0.97, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) 8.39 (1 H, d, J = 8.0 Hz), 7.47 (1 H, d, J = 7.5 Hz), 7.43 (1 H, t, J = 8.0 Hz), 7.35 (1 H, t, J = 7.5 Hz), 6.68 (1 H, s), 6.34 (1 H, s, PhOH), 4.79 (1 H, d, J = 13.0 Hz), 4.17 (1 H, d, J = 13.0 Hz), 4.01–3.97 (1 H, m), 3.94 (3 H, s), 3.47–3.42 (1 H, m), 3.04–2.97 (1 H, m), 2.94–2.90 (1 H, m); ¹³C NMR (CDCl₃, 125 MHz) 157.8, 147.3, 142.7, 133.5, 130.4, 129.6, 127.8, 127.7, 121.9, 121.3, 120.1, 116.0, 109.5, 81.6, 56.5, 56.2, 37.8, 26.7; HRMS (ESI/Q-TOF) m/z [M + H]+ calculated for C₁₈H₁₆NO₄ 310.1074; found 310.1079.

(3¹S,12bR)-8-Hydroxy-7-methoxy-3¹,4,5,12b-tetrahydro-2H-dibenzo[de,g]oxazolo[5,4,3-ij]quinolin-2-one (13-syn) White prisms; mp 237–239 ℃; [α]²⁴D −80 (c 0.5, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) 8.78 (1 H, d, J = 8.0 Hz), 7.54–7.50 (2 H, m), 7.35 (1 H, td, J = 7.5, 1.0 Hz), 6.76 (1 H, s), 6.45 (1 H, s, PhOH), 5.56 (1 H, d, J = 7.0 Hz), 4.70 (1 H, d, J = 7.0 Hz), 3.95 (3 H, s), 3.67 (1 H, dd, J = 11.0, 7.5 Hz), 3.52 (1 H, td, J = 11.0, 6.5 Hz), 2.92–2.80 (2 H, m); ¹³C NMR (CDCl₃, 125 MHz) 160.4, 146.9, 142.6, 132.1 (2 ×), 130.7, 129.1, 127.7, 126.9, 126.5, 123.6, 115.8, 110.1, 73.2, 56.5, 52.6, 40.4, 27.1; HRMS (ESI/Q-TOF) m/z [M + Na]+ calculated for C₁₈H₁₅NO₄Na 332.0893; found 332.0895.
(3'S,12bR)-7,8-Dimethoxy-3',4,5,12b-tetrahydro-2H-dibenzo[de,g]oxazolo[5,4,3-ij]quinolin-2-one (S1) To a solution of 13-syn (64 mg, 0.20 mmol) and Cs₂CO₃ (82 mg, 0.25 mmol) in anhydrous DMF (1 mL) was added CH₃I (16 μL, 0.25 mmol) under argon, and the mixture was stirred at room temperature for 16 h. After being quenched with H₂O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/CH₂Cl₂, 0:100 to 2:98) to afford S1 (62 mg, 93%) as a white solid; mp 236−237 °C; [α]²⁴D −78 (c 1.4, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) 8.77 (1 H, d, J = 8.0 Hz), 7.53−7.49 (2 H, m), 7.38−7.35 (1 H, m), 6.80 (1 H, s), 5.51 (1 H, d, J = 7.5 Hz), 4.67 (1 H, d, J = 7.5 Hz), 3.91 (3 H, s), 3.72 (3 H, s), 3.69−3.65 (1 H, m), 3.58−3.52 (1 H, m), 2.93−2.81 (2 H, m); ¹³C NMR (CDCl₃, 125 MHz) 160.4, 153.7, 146.0, 132.2, 131.9, 131.5, 131.1, 128.7, 128.2, 127.3, 123.4, 123.0, 112.1, 73.1, 60.2, 56.0, 52.5, 40.4, 27.3; HRMS (ESI/Q-TOF) m/z [M + Na]⁺ calculated for C₁₉H₁₇NO₄Na 346.1050; found 346.1056.

(6aS,7R)-1,2-Dimethoxy-5,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-7-ol (1) To a solution of S1 (17 mg, 0.053 mmol) in THF (3 mL) was added a solution of lithium aluminum hydride (LAH) (1.0 M in THF, 260 μL) at 0 °C under argon, and the mixture was stirred at room temperature for 1 h. After being quenched with saturated aqueous sodium potassium tartrate (5 mL) for 30 min, the aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). Following neutralization with saturated aqueous NaHCO₃, the combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH₃OH/CH₂Cl₂, 5:95 to 10:90) to afford 1 (13 mg, 83%) as a pale yellow solid; mp 81−82 °C; [α]²²D −145 (c 1.1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) 8.50 (1 H, d, J = 7.0 Hz), 7.43 (1 H, td, J = 7.0, 1.5 Hz), 7.38 (1 H, dd, J = 7.5, 1.0 Hz), 7.29 (1 H, dd, J = 7.5, 1.5 Hz), 6.66 (1 H, s), 4.54 (1 H, d, J = 2.5 Hz), 3.97 (1 H, s), 3.89 (3 H, s), 3.69 (3 H, s), 3.42 (1 H, dd, J = 12.0, 5.0 Hz), 3.13 (1 H, td, J = 12.0, 4.0 Hz), 2.99 (1 H, td, J = 16.0, 5.0 Hz), 2.70 (1 H, dd, J = 16.0, 4.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) 152.4, 145.2, 136.3, 131.3, 129.4, 129.0, 128.9, 127.8, 125.6, 123.4, 112.1, 71.1, 60.2, 57.1, 55.8, 42.8, 29.0; HRMS (ESI/Q-TOF) m/z [M + H]⁺ calculated for C₁₈H₂₀NO₃ 298.1438; found 298.1439.
(3R,12bR)-7,8-Dimethoxy-3',4,5,12b-tetrahydro-2H-dibenzo[de,g]oxazolo[5,4,3-ij]quinolin-2-one (S2) To a solution of 13-anti (18 mg, 0.058 mmol) and Cs$_2$CO$_3$ (23 mg, 0.07 mmol) in anhydrous DMF (0.5 mL) was added CH$_3$I (5 μL, 0.07 mmol) under argon, and the mixture was stirred at room temperature for 2 h. After being quenched with H$_2$O (5 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford S2 (14 mg, 75%) as a white solid; mp 196–197 °C; [α]$^{23}_D$ −70 (c 1.0, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) 8.40 (1 H, dd, $J = 7.0$, 1.5 Hz), 7.48 (1 H, d, $J = 7.0$ Hz), 7.44–7.37 (2 H, m), 6.76 (1 H, s), 4.82 (1 H, d, $J = 13.5$ Hz), 4.16 (1 H, d, $J = 13.5$ Hz), 4.03–3.98 (1 H, m), 3.91 (3 H, s), 3.75 (3 H, s), 3.50–3.44 (1 H, m), 3.07–2.94 (2 H, m); $^{13}$C NMR (CDCl$_3$, 125 MHz) 157.7, 153.7, 146.5, 134.0, 130.2, 129.6, 128.2, 128.1, 125.0, 123.7, 121.7, 121.3, 111.6, 81.5, 60.4, 56.2, 56.1, 37.7, 27.0; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calculated for C$_{19}$H$_{18}$NO$_4$ 324.1230; found 324.1235.

(6aR,7R)-1,2-Dimethoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-7-ol (2) To a solution of S2 (10 mg, 0.031 mmol) in THF (2 mL) was added 2 N NaOH$_{aq}$ (1 mL), and the mixture was stirred at 70 °C for 2 days. After being quenched with H$_2$O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH$_3$OH/CH$_2$Cl$_2$, 5:95 to 10:90) to afford 2 (7.6 mg, 82%) as a pale yellow solid; mp 89–91 °C; [α]$^{24}_D$ +78 (c 0.58, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) 8.37–8.35 (1 H, m), 7.73–7.72 (1 H, m), 7.38–7.33 (2 H, m), 6.65 (1 H, s), 4.55 (1 H, d, $J = 11.5$ Hz), 3.88 (3 H, s), 3.67 (1 H, d, $J = 11.5$ Hz), 3.64 (3 H, s), 3.40–3.37 (1 H, m), 3.10–3.03 (1 H, m), 2.98 (1 H, td, $J = 11.5$, 3.5 Hz), 2.73 (1 H, d, $J = 16.0$ Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz) 152.5, 145.1, 139.0, 130.2, 129.4, 128.1, 127.8, 127.4, 125.9, 124.3, 123.1, 111.8, 72.0, 60.3, 59.0, 55.9, 42.0, 28.9; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calculated for C$_{18}$H$_{20}$NO$_3$ 298.1438; found 298.1440.
rel-(31S,12bS)-7,8-Dimethoxy-31-methyl-31,4,5,12b-tetrahydro-2H-dibenzo[de, g]oxazolo[5,4,3-ij]quinoxalin-2-one (S3) To a solution of 14 (22 mg, 0.068 mmol) and Cs₂CO₃ (26 mg, 0.08 mmol) in anhydrous DMF (1 mL) was added CH₃I (5 μL, 0.08 mmol) under argon, and the mixture was stirred at room temperature for 16 h. After being quenched with H₂O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford S3 (20.7 mg, 90%) as a pale yellow foam; ¹H NMR (CDCl₃, 500 MHz) 8.37 (1 H, d, J = 8.5 Hz), 7.44–7.37 (3 H, m), 6.74 (1 H, s), 5.07 (1 H, s), 3.92–3.87 (4 H, m), 3.73 (3 H, s), 3.61 (1 H, dt, J = 12.5, 7.5 Hz), 3.02–2.99 (2 H, m), 0.95 (3 H, s); ¹³C NMR (CDCl₃, 125 MHz) 157.2, 153.4, 146.7, 132.6, 130.7, 129.3, 128.2, 128.1, 127.9, 124.6, 123.2, 121.9, 111.7, 84.3, 60.4, 56.3, 56.1, 36.2, 26.6, 16.6; HRMS (ESI/Q-TOF) m/z [M + H]⁺ calculated for C₂₀H₂₀NO₄ 338.1387; found 338.1390.

rel-(6aS,7S)-1,2-Dimethoxy-6a-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de, g]quinoxalin-7-ol (3) To a solution of S3 (22 mg, 0.065 mmol) in THF (1 mL) was added saturated KOH(aq) (1 mL), and the mixture was stirred at 75 °C for 3 days. After being quenched with H₂O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography on silica gel (CH₃OH/CH₂Cl₂, 5:95 to 10:90) to afford 3 (12 mg, 59%) as a white solid; mp > 250 °C (decomposed); ¹H NMR (CD₃OD, 400 MHz) 8.36–8.33 (1 H, m), 7.64–7.62 (1 H, m), 7.45–7.38 (2 H, m), 6.90 (1 H, s), 4.90 (1 H, s), 3.90 (3 H, s), 3.65 (3 H, s), 3.58–3.50 (2 H, m), 3.28–3.20 (1 H, m), 3.13–3.07 (1 H, m), 1.17 (3 H, s); ¹³C NMR (CD₃OD, 100 MHz) 155.3, 147.5, 138.9, 131.1, 129.6 (2 ×), 129.1, 127.4, 126.4, 125.6, 125.3, 113.5, 74.0, 60.9, 60.7, 56.6, 38.0, 26.0, 15.9; HRMS (ESI/Q-TOF) m/z [M + H]⁺ calculated for C₁₉H₂₂NO₃ 312.1594; found 312.1597.
(1R,10bR)-1-(2-Chlorophenyl)-8,9-dimethoxy-5,6-dihydro-1H-oxazolo[4,3-a]isoquinolin-3(10bH)-one (15) To a solution of 12-anti (35 mg, 0.10 mmol) and Cs$_2$CO$_3$ (39 mg, 0.12 mmol) in anhydrous DMF (1 mL) was added CH$_3$I (8 μL, 0.12 mmol) under argon, and the mixture was stirred at room temperature for 16 h. After being quenched with H$_2$O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford 15 (32 mg, 89%) as a white solid; mp 209–210 °C; [α]$_{D}^{24}$ −138 (c 1.3, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) 7.59 (1 H, dd, $J = 7.5, 1.5$ Hz), 7.47 (1 H, dd, $J = 7.5, 1.5$ Hz), 7.43–7.35 (2 H, m), 6.79 (1 H, s), 6.62 (1 H, s), 5.78 (1 H, d, $J = 5.0$ Hz), 4.83 (1 H, d, $J = 5.0$ Hz), 4.15 (1 H, dd, $J = 12.5, 5.5$ Hz), 3.87 (3 H, s), 3.82 (3 H, s), 3.31 (1 H, td, $J = 12.5, 4.0$ Hz), 3.10 (1 H, td, $J = 16.0, 5.5$ Hz), 2.60 (1 H, dd, $J = 16.0, 4.0$ Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz) 157.5, 148.5, 148.1, 136.1, 131.9, 130.3, 130.1, 128.2, 127.8, 126.0, 125.4, 111.8, 107.9, 79.2, 62.0, 55.9, 55.9, 39.3, 26.7; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calculated for C$_{19}$H$_{19}$ClNO$_4$ 360.0997; found 360.0997.

(R)-(2-Chlorophenyl)((R)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methanol (4) To a solution of 15 (19 mg, 0.05 mmol) in THF (3 mL) was added saturated KOH$_{(aq)}$ (1 mL), and the mixture was stirred at 75 °C for 1 day. After being quenched with H$_2$O (10 mL), the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH$_3$OH/CH$_2$Cl$_2$, 0:100 to 4:96) to afford 4 (12 mg, 72%) as a white foam; [α]$_{D}^{22}$ +8 (c 0.58, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz) 7.64 (1 H, d, $J = 6.4$ Hz), 7.37–7.32 (2 H, m), 7.25–7.22 (1 H, m), 6.58 (1 H, s), 6.43 (1 H, s), 5.32 (1 H, d, $J = 4.0$ Hz), 4.16 (1 H, d, $J = 4.0$ Hz), 3.85 (3 H, s), 3.66 (3 H, s), 3.27–3.22 (1 H, m), 3.04–2.98 (1 H, m), 2.89–2.82 (1 H, m), 2.68–2.63 (1 H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz) 147.7, 147.1, 139.8, 132.9, 129.4, 128.6, 128.2, 127.9, 127.0, 126.3, 111.3, 109.4, 71.9, 59.3, 55.8, 55.5, 40.2, 29.1; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calculated for C$_{18}$H$_{21}$ClNO$_3$ 334.1204; found 334.1207.
(R)-Methyl 2-(3,4-dimethoxyphenethylcarbamoyloxy)-2-phenylacetate (19) To a solution of triphosgene (252 mg, 0.85 mmol) in anhydrous toluene (3 mL) was added a solution of 3,4-dimethoxyphenethylamine (17) (170 μL, 1.0 mmol) in anhydrous toluene (3 mL) under argon. The mixture was stirred at room temperature for 30 min and heated to 100 °C for another 1 h. The resulting mixture was then allowed to cool to room temperature and slowly added into a suspension of 16 (166 mg, 1.0 mmol) and triethylamine (170 μL, 1.2 mmol) in anhydrous CH₂Cl₂ (5 mL) under argon. After being stirred at room temperature for 16 h, the reaction was quenched by the addition of saturated aqueous NH₄Cl, evaporated in vacuo to remove excess toluene and CH₂Cl₂, and then partitioned between H₂O and EtOAc. Following neutralization with saturated aqueous NaHCO₃, the organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75 to 30:70) to afford 19 (161 mg, 43%) as a colorless oil; [α]²²D −67 (c 1.8, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) 7.44−7.36 (5 H, m), 6.79 (1 H, d, J = 8.0 Hz), 6.74−6.72 (2 H, m), 5.92 (1 H, br, NH), 5.06 (1 H, s), 3.85 (6 H, s), 3.72 (3 H, s), 3.45−3.42 (2 H, m), 2.78−2.75 (2 H, m); ¹³C NMR (CDCl₃, 125 MHz) 170.0, 155.2, 148.9, 147.6, 134.1, 130.9, 129.1, 128.7 (2 ×), 127.6 (2 ×), 120.6, 111.8, 111.2, 74.5, 55.8, 55.8, 52.5, 42.4, 35.4; HRMS (ESI/Q-TOF) m/z [M + Na]⁺ calculated for C₂₀H₂₃NO₆Na 396.1418; found 396.1413.

(1R,10bR)-8,9-Dimethoxy-1-phenyl-5,6-dihydro-1H-oxazolo[4,3-a]isoquinolin-3(10bH)-one (20) To a solution of 19 (130 mg, 0.35 mmol) in anhydrous toluene (10 mL) was added dropwise a solution of DIBAL-H (25% in toluene, 470 μL, 0.7 mmol) at −78 °C under argon, and the mixture was stirred at −78 °C for 1 h. Then, CH₃OH (280 μL) was added, and the reaction was
stirred at −20 °C for 10 min. Following the addition of BF$_3$·OEt$_2$ (430 µL, 3.5 mmol), the resulting mixture was stirred at room temperature for another 1 h. This reaction mixture was quenched with H$_2$O (5 mL), evaporated in vacuo to remove excess CH$_3$OH, and then partitioned between H$_2$O and EtOAc. After neutralization with saturated aqueous NaHCO$_3$, the organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford 20 (60 mg, 52%) as a white solid; mp 175−176 °C; [α]$^2_{D}$ −126 (c 3.5, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz) 7.52−7.42 (5 H, m), 6.63 (1 H, s), 6.30 (1 H, s), 5.13 (1 H, d, $J$ = 7.5 Hz), 4.85 (1 H, d, $J$ = 7.5 Hz), 4.17 (1 H, dd, $J$ = 13.0, 5.5 Hz), 3.85 (3 H, s), 3.69 (3 H, s), 3.15 (1 H, td, $J$ = 13.0, 3.0 Hz), 3.01 (1 H, td, $J$ = 16.0, 5.5 Hz), 2.65 (1 H, dd, $J$ = 13.0, 3.0 Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz) 156.6, 148.3, 148.0, 137.7, 129.4, 129.0 (2 ×), 127.0 (2 ×), 125.7, 125.0, 111.9, 107.3, 83.9, 61.5, 55.8, 55.7, 38.5, 27.6; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calculated for C$_{19}$H$_{20}$NO$_4$ 326.1387; found 326.1393.

(R)-(R)-6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)(phenyl)methanol (5) To a solution of 20 (30 mg, 0.09 mmol) in THF (2 mL) was added saturated KOH$_{aq}$ (1 mL), and the mixture was stirred at 75 °C for 1 day. After being quenched with H$_2$O (10 mL), the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH$_3$OH/CH$_2$Cl$_2$, 5:95 to 10:90) to afford 5 (12 mg, 43%) as a pale yellow solid; mp 142−144 °C; [α]$^2_{D}$ +30 (c 0.83, CHCl$_3$); $^1$H NMR (CD$_3$OD, 500 MHz) 7.38−7.28 (5 H, m), 6.68 (1 H, s), 5.58 (1 H, s), 4.80 (1 H, d, $J$ = 8.0 Hz), 4.04 (1 H, d, $J$ = 8.0 Hz), 3.76 (3 H, s), 3.46−3.38 (1 H, m), 3.24 (3 H, s), 3.12−3.10 (1 H, m), 2.96−2.91 (1 H, m), 2.84−2.81 (1 H, m); $^{13}$C NMR (CD$_3$OD, 125 MHz) 149.6, 147.6, 143.6, 129.6 (2 ×), 129.2 (3 ×), 128.1, 125.6, 113.1, 112.8, 75.5, 62.3, 56.4, 55.8, 39.0, 28.5; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calculated for C$_{18}$H$_{22}$NO$_3$ 300.1594; found 300.1594.
(R)-N-(3,4-Dimethoxyphenethyl)-2-hydroxy-2-phenylacetamide (21) To a solution of methyl (R)-(−)-mandelate (16) (332 mg, 2.0 mmol) in THF (3 mL) and H₂O (3 mL) was added LiOH·H₂O (672 mg, 16.0 mmol), and the mixture was stirred at room temperature for 4 h. After being quenched with H₂O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to afford the mandelic acid as the crude product. To a solution of this crude product, 3,4-dimethoxyphenethylamine (17) (370 μL, 2.2 mmol) and HOBt hydrate (337 mg, 2.2 mmol) in anhydrous DMF (4 mL) was added EDC (422 mg, 2.2 mmol) under argon. The resulting mixture was stirred at room temperature for 16 h and then quenched by the addition of 1 N HCl (aq). The aqueous layer was extracted with EtOAc (2 × 20 mL). Following neutralization with saturated aqueous NaHCO₃, the combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 40:60) to afford 21 (433 mg, 69%) as a pale yellow oil; [α]²²D −39 (c 1.9, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) 7.33−7.29 (5 H, m), 6.73 (1 H, d, J = 8.4 Hz), 6.62 (1 H, d, J = 2.0 Hz), 6.56 (1 H, dd, J = 8.4, 2.0 Hz), 6.25 (1 H, br, NH), 4.94 (1 H, s), 3.84 (3 H, s), 3.80 (4 H, s, OCH₃ and OH), 3.51−3.44 (2 H, m), 2.72−2.67 (2 H, m); ¹³C NMR (CDCl₃, 100 MHz) 172.3, 148.7, 147.4, 139.4, 130.8, 128.4 (2 ×), 128.2, 126.5 (2 ×), 120.5, 111.6, 111.1, 73.8, 55.7, 55.6, 40.3, 34.9; HRMS (ESI/Q-TOF) m/z [M + Na]⁺ calculated for C₁₈H₂₁NO₄Na 338.1363; found 338.1360.

(R)-2-(3,4-Dimethoxyphenethylamino)-1-phenylethanol (6) To a solution of 21 (180 mg, 0.57 mmol) in THF (5 mL) was added NaBH₄ (45 mg, 1.2 mmol) at 0 °C under argon. Following the addition of BF₃·OEt₂ (300 μL, 2.4 mmol) dropwise at 0 °C under argon, the resulting mixture was stirred at 55 °C for 3 h. After completion of the reaction, the mixture was cooled to 0 °C, treated with H₂O (5 mL) and 6 N HCl (aq) (5 mL), and then heated at 55 °C for another 1 h. The
reaction mixture was cooled to room temperature, treated with 10% NaOH\(_{\text{aq}}\) to adjust the pH value to 10–12, and evaporated in vacuo to remove excess THF. After being partitioned between H\(_2\)O and CH\(_2\)Cl\(_2\), the organic layer was washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by column chromatography on silica gel (CH\(_3\)OH/CH\(_2\)Cl\(_2\), 5:95 to 10:90) to afford 6 (158 mg, 92%) as a white solid; \textbf{mp} 87–88 °C; [\(\alpha\)]\(_{22}^D\) = −38 (c 3.9, CHCl\(_3\)); \textbf{\(^1\)H NMR} (CDCl\(_3\), 500 MHz) 7.37–7.26 (5 H, m), 6.79 (1 H, d, \(J = 8.0\) Hz), 6.74–6.71 (2 H, m), 4.78 (1 H, dd, \(J = 9.0, 3.5\) Hz), 3.87 (3 H, s), 3.86 (3 H, s), 3.17 (1 H, br), 3.00–2.89 (3 H, m), 2.82–2.75 (3 H, m); \textbf{\(^{13}\)C NMR} (CDCl\(_3\), 125 MHz) 148.9, 147.5, 142.1, 131.7, 128.4 \((2 \times)\), 127.6, 125.8 \((2 \times)\), 120.6, 111.8, 111.2, 71.3, 56.7, 55.9, 55.8, 50.6, 35.5; \textbf{HRMS} (ESI/Q-TOF) \(m/z\) [M + H]\(^+\) calculated for C\(_{18}\)H\(_{24}\)NO\(_3\) 302.1751; found 302.1747.
4. Copies of the $^1$H and $^{13}$C NMR spectra

$^1$H NMR (CDCl$_3$, 500 MHz) spectra of 9

$^{13}$C NMR (CDCl$_3$, 125 MHz) spectra of 9
$^{1}H$ NMR (CDCl$_3$, 500 MHz) spectrum of 11

$^{13}$C NMR (CDCl$_3$, 125 MHz) spectrum of 11
$^1$H NMR (CDCl$_3$, 500 MHz) spectrum of 12-anti

$^{13}$C NMR (CDCl$_3$, 125 MHz) spectrum of 12-anti
$^{1}H\text{ NMR (CDCl}_3, 500\text{ MHz) spectrum of 13-anti}$

$^{13}C\text{ NMR (CDCl}_3, 125\text{ MHz) spectrum of 13-anti}$
$^1$H NMR (CDCl$_3$, 500 MHz) spectrum of 13-syn

$^{13}$C NMR (CDCl$_3$, 125 MHz) spectrum of 13-syn
\( ^1\text{H NMR (CDCl}_3, 500 \text{ MHz)} \) spectrum of S1

\( ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz)} \) spectrum of S1
$^1$H NMR (CDCl$_3$, 500 MHz) spectrum of 1

$^{13}$C NMR (CDCl$_3$, 125 MHz) spectrum of 1
$^{1}H$ NMR (CDCl$_3$, 500 MHz) spectrum of S2

$^{13}C$ NMR (CDCl$_3$, 125 MHz) spectrum of S2
$^1$H NMR (CDCl$_3$, 500 MHz) spectrum of 2

$^{13}$C NMR (CDCl$_3$, 125 MHz) spectrum of 2
$^1$H NMR (CDCl$_3$, 500 MHz) spectrum of S3

$^{13}$C NMR (CDCl$_3$, 125 MHz) spectrum of S3
$^1$H NMR (CD$_3$OD, 400 MHz) spectrum of 3

$^{13}$C (CD$_3$OD, 100 MHz) NMR spectrum of 3
$^1$H NMR (CDCl$_3$, 500 MHz) spectraum of 15

$^{13}$C NMR (CDCl$_3$, 125 MHz) spectrum of 15
$^1$H NMR (CDCl$_3$, 400 MHz) spectrum of 4

$^{13}$C NMR (CDCl$_3$, 100 MHz) spectrum of 4
$^1$H NMR (CDCl$_3$, 500 MHz) spectrum of 19

$^{13}$C NMR (CDCl$_3$, 125 MHz) spectrum of 19
$^1$H NMR (CDCl$_3$, 500 MHz) spectrum of 20

$^{13}$C NMR (CDCl$_3$, 125 MHz) spectrum of 20
$^1$H NMR (CD$_3$OD, 500 MHz) spectrum of 5

$^{13}$C NMR (CD$_3$OD, 125 MHz) spectrum of 5
$^1$H NMR (CDCl$_3$, 400 MHz) spectrum of 21

$^{13}$C NMR (CDCl$_3$, 100 MHz) spectrum of 21
$^1$H NMR (CDCl$_3$, 500 MHz) spectrum of 6

$^{13}$CNMR (CDCl$_3$, 125 MHz) spectrum of 6

S33