Supporting information

Synthesis and evaluation of nuciferine and roemerine enantiomers as 5-HT₂ and α₁ receptor antagonists

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General information
Column chromatography and analytical thin-layer chromatography (TLC) were performed using silica gel 60 (230–400 mesh) and pre-coated aluminum silica gel sheets (Kieselgel 60 F-254) from Merck (Darmstadt, Germany), respectively. Melting points were determined on a Mel-Temp II melting point instrument. ¹H and ¹³C NMR spectra were obtained using a Jeol ECA 400 (400 MHz) spectrometer at room temperature with TMS as the internal standard. Chemical shifts are reported in parts per million relative to CDCl₃ or TMS. Data for ¹H NMR are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, q = quartet, m = multiplet), coupling constants and integration. ¹³C NMR spectra were recorded with complete proton decoupling. MS analysis was performed on an Agilent 6500 series accurate mass Q-TOF. Optical rotations were recorded on a Jasco P-1020 polarimeter (Tokyo, Japan) at 589 nm. Enantiomeric purity was determined by chiral HPLC analysis on a Chiralcel OD-H column (150 x 4.6 mm, 5 µm, Daicel, Osaka, Japan), eluting with acetonitrile/isopropanol (gradient from 100% acetonitrile
to 90% acetonitrile over 5 min) at a flow rate of 0.6 mL min\(^{-1}\). The sample injection volume was 20 \(\mu\)L. The detection wavelength was set at 270 nm and the total analysis time was 10 min. Chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) or Merck (Darmstadt, Germany) and were of analytical grade.

**Experimental procedures and spectral data**

2-(2-Bromophenyl)-N-(3,4-dimethoxyphenethyl)acetamide (6a)\(^1\)

2-bromophenylacetic acid (0.215 g, 1 mmol) and oxalyl chloride (2.0 M solution in dichloromethane, 0.6 mL, 1.2 mmol) in dry dichloromethane (0.25 M) were stirred at room temperature in a flask attached to a bubbler. To this solution was added one drop of N,N-dimethylformamide and the solution was stirred for 2 h (or until the effervescence ceased). The solution was concentrated and then added dropwise to a solution of 2-(3,4-dimethoxyphenyl)ethanamine (0.181 g, 1 mmol) and triethylamine (0.28 mL, 2 mmol) in dry dichloromethane (5.0 mL) at 0°C. The reaction mixture was stirred at room temperature overnight and then quenched with brine and extracted with dichloromethane. The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc) to give the product as a pale yellow solid (0.340 g, 90 % yield); mp 130–131 °C (CH\(_2\)Cl\(_2\)), lit 127–129 °C (CHCl\(_3\)).

N-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-2-(2-bromophenyl)acetamide (6b)\(^2\)

This compound was prepared from 2-(benzo[d][1,3]dioxol-5-yl)ethanamine according to the procedure described for compound 6a to give the product as a pale yellow solid (0.271 g, 75 % yield); mp 130–132 °C (CH\(_2\)Cl\(_2\)), lit 129.1–131.8 °C (CHCl\(_3\)).

(S)-1-(2-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9a)\(^1\)

To a solution of amide 6a (0.378 g, 1 mmol) in dichloromethane (5.0 mL) in a round-bottomed flask equipped with a magnetic stirrer and a condenser was added phosphorus oxychloride (0.37 mL, 4 mmol) and the resulting mixture was refluxed for 8 h. The reaction mixture was then cooled to 0 °C and neutralised with saturated sodium carbonate solution. The resulting mixture was extracted with Et\(_2\)O to afford imine 7a. This compound was used immediately without further purification. A solution of dimeric dichloro(p-cymene)ruthenium(II) (18 mg, 0.03 mmol), 1,2-(R,R)-N-tosyl-1,2-diphenylethlenediamine 12 (23 mg, 0.062 mmol), and NEt\(_3\) (7 \(\mu\)L, 0.05 mmol) in DMF (1.0 mL) was stirred under
nitrogen for 1 h at 80 °C. The warm solution was added to the imine 7a in DMF (2.0 mL) and the mixture was cooled to 0 °C. A formic acid-triethylamine azeotropic mixture (5:2, 0.5 mL) was then added dropwise and the reaction mixture was stirred for 2 h at room temperature. Saturated potassium carbonate solution was added to the reaction mixture, which was then diluted with water and extracted with ethyl acetate. The combined organic phases were dried (Na₂SO₄) and evaporated under reduced pressure. The brown residue was purified by column chromatography on silica gel (EtOAc/NEt₃, 100:1 or CH₂Cl₂/MeOH, 10:1) to give the product as a yellow oil (0.326 g, 90 % yield).

(S)-5-(2-Bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (9b)²
This compound was prepared from amide 6b according to the procedure described for compound 9a to give the product as a pale yellow oil (0.277 g, 80 % yield).

(S)-Methyl 1-(2-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (10a)²
Methyl chloroformate (0.15 mL, 2 mmol) was added slowly to a solution of tetrahydroisoquinoline 9a (0.362, 1 mmol), diisopropylethylamine (0.33 mL, 2 mmol) and 1 mg of 4-(dimethylamino)pyridine in CH₂Cl₂ (5.0 mL) and the resulting mixture was stirred overnight at room temperature. The reaction mixture was then quenched by adding saturated ammonium chloride solution and extracted with CH₂Cl₂. The combined organic phases were purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to give the product as a brown solid (0.344 g, 82 % yield); mp 172–173 °C (CH₂Cl₂); lit 173–175 °C (CHCl₃).

(S)-Methyl 5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate (10b)
This compound was prepared from tetrahydroisoquinoline 9b according to the procedure described for compound 10a to give the product as a brown solid (0.364 g, 90 % yield); mp 185–187 °C (CH₂Cl₂). NMR analysis revealed the presence of two rotamers present in a 2.3:1 ratio. ¹H NMR (600 MHz, CDCl₃): δ = 2.58 (m, 1H), 2.65–3.39 (m, 4H), 3.09 (s, 3H), 4.18 (m, 1H), 5.26 (dd, J = 10.5, 3.6 Hz, 1H), 5.81 (d, J = 4 Hz, 2H), 6.49 (s, 1H), 6.66 (s, 1H), 6.95–7.02 (m, 3H), 7.46 (d, J = 7.6 Hz, 1H); minor rotamer: 2.55 (m, 1H), 2.65–3.39 (m, 4H), 3.49 (s, 3H), 3.81 (m, 1H), 5.33 (dd, J = 8.4, 5.6 Hz, 1H), 5.78 (d, J = 9.5 Hz, 2H), 6.42 (s, 1H), 6.66 (s, 1H), 7.07–7.12 (m, 3H), 7.42 (d, J = 8.0 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃):
δ = 28.6, 37.1, 42.8, 54.1, 100.9, 106.8, 108.6, 125.1, 127.3, 127.4, 128.2, 129.6, 131.6, 132.4, 137.7, 146.2, 146.5, 155.8; minor rotamer: 28.6, 38.7, 42.0, 52.6, 55.0, 100.8, 107.3, 108.3, 125.4, 127.1, 127.5, 128.2, 131.5, 132.6, 137.6, 145.9, 146.5, 155.8; HRMS: [M+Na]+ calcd for C_{19}H_{18}BrNaO_{4}: 426.0317 (100%), 428.0296 (97.3%), found: 426.0330, 428.0313.

(S)-Methyl 1,2-dimethoxy-6a,7-dihydro-4H-dibenzo[de,g]quinoline-6(5H)-carboxylate (12a)^2

Pd(OAc)$_2$ (11 mg, 0.05 mmol), KOAc (0.196 g, 2 mmol), DavePhos 11 (38 mg, 0.1 mmol) and tetrahydroisoquinoline 10a (0.42g, 1 mmol) were placed in a round-bottomed flask with a magnetic stirrer bar. The flask was purged for 5 min with nitrogen. DMA was then added (2.0 mL) and the resulting mixture was heated to 130 °C overnight. The reaction mixture was then concentrated and purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to give the product as a grey white solid (0.237 g, 70 % yield); mp 176–177 °C (CHCl$_3$), lit 176–177 °C (CHCl$_3$).

(S)-Methyl 7a,8-dihydro-5H-[1,3]dioxolo[4′,5′:4,5]benzo[1,2,3-de]benzo[g]quinoline-7(6H)-carboxylate (12b)^3

This compound was prepared from tetrahydroisoquinoline 10b according to the procedure described for compound 12a to give the product as a white solid (0.21 g, 65 % yield); mp 150–152 °C (CHCl$_3$), lit 152–153 °C (CHCl$_3$).

(S)-nuciferine (3a)^4

LiAlH$_4$ (2.0 M in THF, 0.6 mL, 1.2 mmol) was added to a stirred solution of tetrahydroisoquinoline 12a (0.339 g, 1 mmol) in dry THF (5 mL) at 0 °C under nitrogen and the resulting mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was slowly hydrolysed with water and extracted with diethyl ether, dried, filtered, evaporated and then purified by chromatography on silica gel (acetone or CH$_2$Cl$_2$/MeOH, 10:1) to give the product as a white solid (0.265 g, 90 % yield); mp 169–170 °C (CHCl$_3$), lit 165–167 °C (MeOH); $[\alpha]^{23}_D +149.5$ (c 2, CH$_2$Cl$_2$), lit $[\alpha]^{21}_D +165$ (c 0.26, EtOH); $^1$H NMR (CDCl$_3$, 400 MHz) δ = 2.57 (s, 3H), 2.66–2.72 (m, 2H), 3.06–3.11 (m, 2H), 3.13–3.20 (m, 2H), 3.65 (s, 3H), 3.88 (s, 3H), 6.63 (s, 1 H), 7.21–7.30 (m, 3H), 8.35 (d, J = 8.0, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ = 29.2, 35.1, 43.9, 53.3, 55.9, 60.2, 62.4, 111.3,
126.9, 127.0, 127.3, 127.9, 128.0, 128.3, 128.7, 132.2, 136.5, 145.2, 152.0; HRMS: [M+H]+
calcd for C_{19}H_{22}NO_{2}: 296.1651, found: 296.1655.

(S)-roemerine (3b)\textsuperscript{5,6}

This compound was prepared from tetrahydroisoquinoline 12b according to the procedure described for compound 3a to give the product as a white solid (0.251 g, 90% yield); mp 100–102 °C (CH₂Cl₂), lit\textsuperscript{5} 102–103 °C (Et₂O/pet ether); [α]\textsuperscript{23}D +44.0 (c 0.2, CH₂Cl₂), lit\textsuperscript{6} [α]\textsuperscript{20}D +69 (c 0.17, CHCl₃); \textsuperscript{1}H NMR (CDCl₃ + MeOH-d₄, 400 MHz) δ = 2.53 (s, 3H), 2.71–2.57 (m, 4H), 3.22–3.02 (m, 3H), 5.86 (d, J = 1.2, 1H), 6.01 (d, J = 1.2, 1H), 6.49 (s, 1H), 7.26–7.16 (m, 3H), 7.99 (d, J = 7.6, 1H); \textsuperscript{13}C NMR (CDCl₃ + MeOH-d₄, 100 MHz) δ = 27.0, 32.5, 42.2, 54.0, 63.6, 102.8, 108.4, 117.3, 121.5, 124.9, 128.2, 129.0, 129.4, 129.5, 131.1, 132.7, 145.1, 150.0; HRMS: [M+H]+, calcd for C_{18}H_{18}NO 280.1338, found: 280.1330.

References for supporting information

$^1$H and $^{13}$C NMR spectra of (S)-nuciferine (3a)
$^1$H and $^{13}$C NMR spectra of (S)-roemerine (3b)
HPLC chromatograms of (a) synthesised (±)-nuciferine, (b) synthesised (S)-nuciferine 99.9% ee and (c) commercial (R)-nuciferine 99.3% ee
HPLC chromatograms of (a) synthesised (±)-roemerine, (b) synthesised (S)-roemerine 96.3% ee and (c) commercial (R)-roemerine 99.8% ee