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Synthesis of methoxetamine, its metabolites and deuterium labelled analog as analytical standards and their HPLC and chiral capillary electrophoresis separation.

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Supplementary data

Experimental

Synthesis of 1-(3-methoxyphenyl)cyclohexan-1-ol (5)

A solution of 3-bromoanisole (4 g, 21 mmol) in dry THF (5 ml) was added dropwise to the mixture of Mg (0.6 g, 25 mmol) and I_2 (cat.) in dry THF (10 ml) under argon atmosphere at room temperature over 30 minutes. The reaction mixture was heated under reflux for 1 hour, then cooled to 0 °C. A solution of cyclohexanone (2.26 g, 23 mmol) in dry THF (5 ml) was added and stirred for 12 hours at room temperature. The reaction mixture was quenched by saturated NH_4Cl (aq., 10 ml) and extracted with Et_2O (3 x 100 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Crude product was further purified by flash chromatography (EtOAc/Hexane, 1:10). 1-(3-Methoxyphenyl)cyclohexan-1-ol (3.44 g, yield 78%) was isolated as a colorless liquid.

The analytical data corresponds with the literature[33]

^{1}H NMR (401 MHz, Chloroform-*d*) δ (ppm) 7.29 – 7.23 (m, 1H), 7.09 (dd, J = 2.5, 1.7 Hz, 1H), 7.07 (ddd, J = 7.7, 1.7, 1.0 Hz, 1H), 6.78 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 3.82 (s, 3H), 1.89 – 1.54 (m, 10H), 1.38 – 1.19 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 159.7, 151.5, 129.3, 117.1, 111.9, 110.9, 73.3, 55.4, 38.9, 25.6, 22.3.

Synthesis of 1-(Cyclohex-1-enyl)-3-methoxy-benzene (6)

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p-Toluenesulfonic acid (160 mg, 0.8 mmol) was added to the solution of compound **5** (3.47 g, 17 mmol) in benzene (15 ml). The reaction mixture was heated under reflux for 2 hours. Water formed in this reaction was removed by azeotropic distillation using Dean-Stark trap. The reaction mixture was cooled, washed with saturated $NaHCO_3$ (aq., 15 ml) and washed with water (15 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was done by flash chromatography (EtOAc/Hexane, 1:10). 1-Cyclohex-1-enyl-3-methoxybenzene (2.85 g, yield 90%) was obtained as a colorless liquid.

The analytical data corresponds with the literature[34]

^{1}H NMR (401 MHz, Chloroform-*d*) δ (ppm) 7.23 (t, J = 8.0 Hz, 1H), 6.99 (ddd, J = 7.7, 1.7, 1.0 Hz, 1H), 6.93 (dd, J = 2.5, 1.7 Hz, 1H), 6.78 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.13 (td, J = 4.0, 1.9 Hz, 1H), 3.82 (s, 3H), 2.40 (m, 2H), 2.22 (m, 2H), 1.87 – 1.73 (m, 2H), 1.71 – 1.63 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 159.7, 144.5, 136.6, 129.2, 125.2, 117.7, 112.0, 111.0, 55.3, 27.6, 26.0, 23.2, 22.3.

Synthesis of 1-(3-methoxyphenyl)- 1,2-epoxycyclohexane (7)

m-Chloroperbenzoic acid (4.61 g, 27 mmol) was added in one portion into a mixture of DCM (45 ml) and 5% aqueous $NaHCO_3$ (30 ml) solution. Compound **6** (2.8 g, 14.9 mmol) was added to the mixture at 0 °C, then the reaction mixture was stirred for 5 minutes, subsequently heated to RT and stirred for another 14 hours. The reaction mixture was extracted with DCM (3x 50 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was done by flash chromatography (EtOAc/Hexane, 1:10). 1-(3-Methoxyphenyl)-1,2-epoxycyclohexane (2.19 g, yield 72%) was obtained as a colorless liquid.

The analytical data corresponds with the literature[35]

^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.29 – 7.20 (m, 1H), 6.97 (ddd, J = 7.7, 1.6, 1.0 Hz, 1H), 6.93 (dd, J = 2.6, 1.6 Hz, 1H), 6.80 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 3.81 (s, 3H), 3.09 – 3.03 (m, 1H), 2.27 (ddd, J = 14.9, 8.5, 5.4 Hz, 1H), 2.15 – 2.07 (m, 1H), 2.02 – 1.96 (m, 2H), 1.66 – 1.51 (m, 2H), 1.51 – 1.40 (m, 1H), 1.39 – 1.24 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.8, 144.4, 129.4, 117.9, 112.9, 110.9, 62.1, 60.4, 55.4, 29.0, 24.8, 20.3, 19.9.

Synthesis of 2-bromo-2-(3-methoxyphenyl)cyclohexan-1-one (8)

Compound **7** (0.52 g, 2.5 mmol) was added to a mixture of chloroform (10 ml) and HBr (7 ml) at 20 °C and the reaction mixture was stirred for 30 minutes. The organic layer was separated and aqueous layer was extracted with chloroform (2 x 10 ml). The organic phases were combined and washed with 5 ml of saturated $NaHCO_3$ (aq), organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The product was dissolved in acetone (5 ml) and Jones Reagent was added slowly at 0°C. The oxidation was monitored by observing the colour change from orange to green. The reaction mixture was concentrated under reduced pressure, diluted with distilled water (10 ml) and extracted with DCM (3 x 10 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was done by flash chromatography (EtOAc/Hexane, 1:10). 2-Bromo-2-(3-methoxyphenyl)cyclohexan-1-one (0.46 g, yield 64%) was obtained as a yellowish liquid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (ddd, *J* = 8.2, 7.8, 0.5 Hz, 1H), 6.99 (ddd, *J* = 7.8, 1.9, 0.9 Hz, 1H), 6.96 (ddd, *J* = 2.4, 1.9, 0.4 Hz, 1H), 6.85 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 3.81 (s, 3H), 3.07 – 2.98 (m, 1H), 2.96 – 2.86 (m, 1H), 2.65 – 2.55 (m, 1H), 2.54 – 2.44 (m, 1H), 2.01 – 1.78 (m, 4H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 202.8, 159.9, 140.8, 129.9, 119.7, 113.8, 113.8, 72.7, 55.5, 42.8, 39.0, 27.4, 23.6. IR (ATR, cm^{-1}): ν_{max} = 3416, 1717, 1252. HRMS-APCI: m/z calculated for $C_{13}H_{16}Br_1O_2$ $[M+H]^+$ 283.0328, found: 283.0328.

Synthesis of 2-azido-2-(3-methoxyphenyl)cyclohexan-1-one (9)

NaN_3 (0.175 g, 2.7 mmol) was added in one portion into the solution of compound **8** (0.2 g, 0.7 mmol) in DMSO (10 ml). The mixture was stirred for 15 hours at RT. The reaction mixture was diluted with water (10 ml) and extracted with Et_2O (3x 25 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was done by flash chromatography (EtOAc/Hexane, 1:10). 2-Azido-2-(3-methoxyphenyl)cyclohexan-1-one (0.13 g, yield 76%) was obtained as a colorless liquid.

^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.37 (t, *J* = 8.0 Hz, 1H), 6.93 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.85 – 6.81 (m, 1H), 3.82 (s, 3H), 2.76 (dd, *J* = 14.3, 3.4 Hz, 1H), 2.61 – 2.47 (m, 1H), 2.40 (td, *J* = 13.4, 13.0, 6.1 Hz, 1H), 2.06 – 1.88 (m, 2H), 1.88 – 1.78 (m, 1H), 1.78 – 1.56 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.9, 160.5, 136.9, 130.6, 119.1, 114.2, 113.0, 74.5, 55.5, 40.1, 36.6, 27.5, 22.2. IR (ATR, cm^{-1}): ν_{max} =

3260, 1720, 1050. HRMS-ESI: m/z calculated for $C_{13}H_{15}N_3O_2$+Na $[M+Na]^+$ 268.1057, found 268.1057.

Synthesis of 2-amino-2-(3-methoxyphenyl)cyclohexan-1-one hydrochloride (10)

Compound **9** (0.1 g, 0.4 mmol) was dissolved in MeOH (7 ml) and Pd/C (10 mg, 10% Pd on charcoal) was added. The reaction mixture was stirred for 4 hours in an autoclave at RT under hydrogen (2 bar) atmosphere. The reaction mixture was vacuum filtered through celite, concentrated under reduced pressure and treated with a solution of HCl in Et_2O (2 ml). The solvent was evaporated and 2-amino-2-(3-methoxyphenyl)cyclohexan-1-one hydrochloride (99 mg, yield 95%) was obtained as a yellowish solid.

^{1}H NMR (401 MHz, Chloroform-*d*) δ 8.85 (s, 3H), 7.31 – 7.24 (m, 1H), 6.98 – 6.92 (m, 2H), 6.88 (dd, *J* = 7.8, 2.0 Hz, 1H), 3.78 (s, 3H), 3.13 (d, *J* = 14.2 Hz, 1H), 2.56 – 2.42 (m, 1H), 2.33 (qd, *J* = 16.1, 14.5, 4.9 Hz, 2H), 2.06 – 1.89 (m, 1H), 1.89 – 1.60 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 204.9, 160.4, 134.3, 130.5, 119.7, 116.7, 112.2, 67.7, 55.8, 38.9, 34.5, 27.3, 21.8. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.53 – 7.43 (m, 1H), 7.10 (ddd, *J* = 8.4, 2.5, 0.8 Hz, 1H), 7.03 (ddd, *J* = 7.8, 1.9, 0.8 Hz, 1H), 6.96 (t, *J* = 2.2 Hz, 1H), 3.85 (s, 3H), 3.12 (dq, *J* = 14.0, 2.9 Hz, 1H), 2.58 – 2.40 (m, 2H), 2.18 – 1.68 (m, 5H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 207.0, 162.3, 135.5, 132.3, 120.3, 116.4, 114.4, 68.2, 56.0, 39.9, 35.8, 28.6, 22.8. IR (ATR, cm^{-1}): ν_{max} = 3430, 1723. HRMS-ESI: m/z calculated for $C_{13}H_{18}N_1O_2$ $[M+H]^+$ 220.1332, found 220.1331. Melting point: 185 – 187 °C (Et_2O).

Synthesis of 2-amino-2-(3-methoxyphenyl)cyclohexan-1-ol (11)

$NaBH_4$ (26 mg, 0.68 mmol) was added slowly in portions to the solution of compound **10** (50 mg, 0.2 mmol) in MeOH (2 ml) at 0 °C. After 5 minutes the reaction mixture was heated to RT and stirred for 2 hours. The organic solvent was evaporated and the residue was dissolved in MeOH (5 ml) and evaporated repeatedly to remove organoborate impurities. The residue was dissolved in HCl (5 ml, 15% aq.) and washed with DCM (10 ml). The aqueous layer was separated, alkalized by treatment with saturated aqueous NaOH (5 ml) solution and extracted with Et_2O (3 x 10 ml). The organic layer was dried over $MgSO_4$, filtered and treated with a solution of HCl in Et_2O (2 ml). The solvent was evaporated and compound

2-amino-2-(3-methoxyphenyl)cyclohexan-1-ol hydrochloride was obtained as yellowish solid (33 mg, yield 65%).

^{1}H NMR (401 MHz, Methanol-d_4) δ 7.54 (s, 1H), 7.46 – 7.31 (m, 2H), 6.97 (d, J = 8.0 Hz, 1H), 4.07 (dd, J = 9.6, 3.7 Hz, 1H), 3.82 (s, 3H), 2.75 – 2.53 (m, 1H), 2.00 – 1.64 (m, 5H), 1.60 – 1.36 (m, 2H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 161.3, 139.3, 130.8, 121.6, 116.1, 115.0, 75.7, 62.2, 55.8, 34.2, 32.0, 24.3, 22.7. IR (ATR, cm^{-1}): ν_{max} = 3364, 1098, 1040. HRMS-ESI: m/z calculated for $C_{13}H_{20}N_1O_2$ $[M+H]^+$ 222.1489, found 222.1487. Melting point: 213 – 215 °C (Et_2O).

Synthesis of 2-amino-2-(3-hydroxyphenyl)cyclohexan-1-one hydrobromide (12)

Compound **10** (200 mg, 0.78 mmol) was dissolved in HBr (46% aq., 3 ml) and the reaction mixture was heated under reflux for 3 hours. The HBr was evaporated and further purification was done by flash chromatography on C18 silica (MeOH/ H_2O + 0.1% CH_3COOH, 1:10). Compound 2-amino-2-(3-hydroxyphenyl)cyclohexan-1-one hydrobromide was obtained as colorless solid (213 mg, yield 95%).

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.37 (ddd, J = 8.2, 7.7, 0.5 Hz, 1H), 6.92 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H), 6.88 (ddd, J = 7.8, 2.0, 0.9 Hz, 1H), 6.86 – 6.84 (m, 1H), 3.06 (dq, J = 13.8, 3.0 Hz, 1H), 2.55 – 2.45 (m, 2H), 2.15 – 1.68 (m, 5H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 207.1, 160.1, 135.5, 132.3, 118.9, 118.2, 115.1, 68.1, 39.9, 35.8, 28.6, 22.8. IR (ATR, cm^{-1}): ν_{max} = 3189, 3000, 1718, 1041. HRMS-ESI: m/z calculated for $C_{12}H_{15}N_1O_2$ $[M+H]^+$ 206.1176, found 206.1177. Melting point: 225 – 227 °C decomposition (Et_2O).

Synthesis of 3-(1-amino-2-hydroxycyclohexyl)phenol hydrochloride (13)

$NaBH_4$ (55 mg, 1.4 mmol) was added slowly in portions to the solution of compound **12** (100 mg, 0.41 mmol) in MeOH (3 ml) at 0 °C. After 5 minutes the reaction mixture was heated to RT and stirred for 2 hours. The organic solvent was evaporated and the residue was dissolved in MeOH (5 ml) and evaporated repeatedly to remove organoborate impurities. The residue was treated with a solution of HCl in Et_2O (2 ml) and the solvent was evaporated. Further purification was done by flash chromatography on C18 silica (MeOH/ H_2O + 0.1% CH_3COOH, 1:10). Compound 3-(1-amino-2-hydroxycyclohexyl)phenol hydrochloride was obtained as a yellowish solid (91 mg, yield 90%).

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.39 (t, J = 2.1 Hz, 1H), 7.31 (ddd, J = 8.0, 1.9, 1.2 Hz, 1H), 7.26 (t, J = 7.9 Hz, 1H), 6.82 (ddd, J = 7.8, 2.4, 1.2 Hz, 1H), 4.06 (dd, J = 9.6, 3.7 Hz, 1H), 2.61 (ddd, J = 13.4, 6.2, 3.3 Hz, 1H), 1.96 – 1.60 (m, 5H), 1.60 – 1.40 (m, 2H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 158.8, 139.4, 130.8, 120.3, 116.9, 116.6, 75.6, 62.1, 34.1, 31.9, 24.2, 22.7. IR (ATR, cm^{-1}): ν_{max} = 3218, 3000 HRMS-ESI: m/z calculated for $C_{12}H_{18}N_1O_2$ $[M+H]^+$ 208.1332, found 208.1332.

Synthesis of 2-amino-2-(3-(methoxy-d_3)phenyl)cyclohexan-1-on hydrochloride (14)

Compound **12** (230 mg, 0.8 mmol) was dissolved in MeOH (6 ml) and TEA (243 mg, 2.4 mmol) was added dropwise at room temperature. Ditertbutyldicarbonate (1.75 g, 8 mmol) was added to the reaction mixture in few portion within 48 hours. The reaction mixture was concentrated under reduced pressure, dissolved in Et_2O (30 ml) and washed with 1M aqueous HCl (10 ml). The organic layer was separated, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude colorless oil was dissolved in dry acetonitrile (6 ml) and dried K_2CO_3 (553 mg, 4 mmol) was added in one portion. CD_3I (145 mg, 1.0 mmol) was added dropwise to the reaction mixture under argon atmosphere. The reaction mixture was stirred 3 hours at 60 °C and then concentrated under reduced pressure. The residue was diluted with water (15 ml) and extracted with Et_2O (3 x 15 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in DCM (5 ml) with CF_3COOH (0.2 ml). The reaction mixture was stirred 3 hours at RT, then was treated with conc. HCl (5 ml) and extracted with water (3 x 10 ml). The aqueous layer was separated, alkalized by treatment with saturated aqueous NaOH (10 ml) and extracted with Et_2O (3 x 15 ml). The organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure and subsequently treated with a solution of HCl in Et_2O (2 ml). The solvent was evaporated and compound 2-amino-2-(3-methoxy-d3)phenyl)cyclohexan-1-one hydrochloride was obtained as a yellowish solid (47 mg, yield 22%).

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.49 (t, J = 8.0 Hz, 1H), 7.09 (ddd, J = 8.3, 2.5, 0.7 Hz, 1H), 7.03 (ddd, J = 7.8, 1.9, 0.8 Hz, 1H), 6.96 (t, J = 2.2 Hz, 1H), 3.13 (dq, J = 14.1, 2.8 Hz, 1H), 2.58 – 2.41 (m, 2H), 2.17 – 2.01 (m, 2H), 2.00 – 1.67 (m, 3H). ^{13}C NMR (101 MHz; Methanol-d_4) δ 207.0, 162.2, 135.5, 132.3, 120.3, 116.4, 114.3, 68.2, 55.2 (hept, J = 21.8 Hz), 39.9, 35.7, 28.6, 22.8. IR (ATR, cm^{-1}): ν_{max} = 3366, 1720, 1105. HRMS-ESI: m/z calculated for $C_{13}H_{16}N_1O_2D_3$ $[M+H]^+$ 223.1520; found 223.1523.

Synthesis of cyclopentyl(3-(methoxyphenyl)ketone (16)

A solution of cyclopentylbromide (0.6 g, 4 mmol) in dry THF (5 ml) was added dropwise to the mixture of Mg (98 mg, 4.1 mmol) and I_2 (cat.) in dry THF (10 ml) under argon atmosphere at RT. The reaction mixture was heated under reflux for 1 hour and then cooled to 0 °C. 3-methoxybenzonitrile (0.5 g, 3.8 mmol) in dry THF (5 ml) was added dropwise at 0 °C and the reaction mixture was stirred for 72 hours at room temperature. The reaction mixture was treated with saturated NH_4Cl (aq, 10 ml), diluted with water (50 ml) and extracted with Et_2O (3 x 60 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Further purification was done by flash chromatography (EtOAc/Hexane, 1:10). Compound cyclopentyl(3-methoxyphenyl)methanone was isolated as a colorless liquid (253 mg, yield 33%).

^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 2.0 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.6 Hz, 1H), 3.85 (s, 3H), 3.69 (p, *J* = 7.9 Hz, 1H), 1.98 – 1.83 (m, 4H), 1.79 – 1.57 (m, 4H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 202.7, 159.9, 138.5, 129.6, 121.2, 119.2, 112.9, 55.5, 46.6, 30.2, 26.4. IR (ATR, cm^{-1}): ν_{max} = 1678, 1038. HRMS-ESI: m/z calculated for $C_{13}H_{16}O_2$ $[M+H]^+$ 205.1223, found 205.1222.

Synthesis of 1-bromocyclopentyl(3-methoxyphenyl)ketone (17)

Compound **16** (1 g, 4.9 mmol) was dissolved in CCl_4 (5 ml) and Br_2 (480 mg, 6 mmol) in CCl_4 (5 ml) was added dropwise at 0 °C. The reaction mixture was stirred at RT for 30 minutes. The reaction mixture was treated with saturated $NaHCO_3$ (aq., 15 ml) and extracted with DCM (3 x 30 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield (1-bromocyclopentyl)(3-methoxyphenyl)methanone as a colorless liquid (973 mg, yield 80%).

^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.77 (ddd, J = 7.8, 1.6, 0.9 Hz, 1H), 7.65 (dd, J = 2.6, 1.6 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.09 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 3.86 (s, 3H), 2.58 – 2.35 (m, 4H), 2.15 – 1.97 (m, 2H), 1.87 – 1.73 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.3, 159.5, 136.2, 129.2, 122.9, 119.2, 115.0, 71.3, 55.6, 41.2, 23.6. IR (ATR, cm^{-1}): ν_{max} = 3327, 1672, 1267. HRMS-APCI: m/z calculated for $C_{13}H_{16}Br_1O_2$ $[M+H]^+$ 285.0308, found 285.0310.

Synthesis of 1-((ethylimino)(3-methoxyphenyl)methyl)cyclopentan-1-ol (18)

The mixture of compound **17** (0.9 g, 3.2 mmol) and $EtNH_2$ (5 ml) was stirred at 0 °C for 2 hours. The ethylamine was evaporated, Et_2O was added to the residue and solids were filtered off. The filtrate was evaporated and compound 1-((ethylimino)(3-methoxyphenyl)methyl)cyclopentan-1-ol was obtained as a yellowish liquid (694 mg, yield 88%).

^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.31 (dd, J = 8.4, 7.4 Hz, 1H), 6.93 – 6.87 (m, 1H), 6.64 – 6.59 (m, 1H), 6.58 – 6.55 (m, 1H), 3.81 (s, 3H), 3.18 – 3.08 (m, 2H), 1.97 – 1.70 (m, 4H), 1.70 – 1.42 (m, 4H), 1.18 – 1.07 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 174.1, 159.6, 136.7, 129.6, 119.9, 113.6, 113.3, 83.6, 55.4, 46.7, 38.4, 24.1, 16.2.

Synthesis of methoxetamine (3)

The synthesis of methoxetamine hydrochloride was carried out according to Hays *et al*. (2012) instructions and Stevens and Parke (1966) patent.[22,36] The compound **18** (600 mg, 2.4 mmol) was dissolved in decalin (2 ml) and stirred 15 hours at 190 °C in a microwave reactor. The reaction mixture was cooled to RT, diluted with DCM (20 ml) and extracted with 15% HCl (3 x 15 ml). The aqueous layer was separated, then it was made alkaline with saturated aqueous NaOH (30 ml) and extracted with Et_2O (3 x 40 ml). The organic layer was dried over $MgSO_4$, filtered, treated with a solution of HCl in Et_2O (2 ml) and the solvent was evaporated. Further purification was done by recrystallization from isopropyl alcohol. Methoxetamine hydrochloride was isolated as a yellowish solid and confirmed by NMR analysis (130 mg, 19% yield).[22,36]
^{1}H NMR (400 MHz, Methanol-d_4) δ 7.51 (ddd, J = 8.3, 7.7, 0.4 Hz, 1H), 7.13 (ddd, J = 8.3, 2.5, 0.8 Hz, 1H), 7.03 (ddd, J = 7.8, 1.9, 0.8 Hz, 1H), 6.97 (dd, J = 2.4, 1.9 Hz, 1H), 3.85 (s, 3H), 3.27 – 3.19 (m, 1H), 2.84 (dq, J = 12.2, 7.3 Hz, 1H), 2.55 – 2.41 (m, 3H), 2.15 – 1.94 (m, 3H), 1.89 – 1.68 (m, 2H), 1.22 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 207.0, 162.4, 132.8, 132.4, 121.4, 116.7, 115.4, 73.2, 56.0, 40.2, 38.5, 33.6, 28.6, 22.9, 11.6. IR (ATR, cm^{-1}): ν_{max} = 2715, 1725, 1122. HRMS-ESI: m/z calculated for $C_{15}H_{22}N_1O_2$ $[M+H]^+$ 248.1645, found 248.1647. Melting point: 248 – 249 °C (isopropanol).

Synthesis of 2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-ol hydrochloride (19)

$NaBH_4$ (23 mg, 0.61 mmol) was added slowly in portions to the solution of compound **3** (50 mg, 0.18 mmol) in MeOH (2 ml) at 0°C and the mixture was stirred for 2 hours at RT. The

organic solvent was evaporated and the residue was dissolved in MeOH (5 ml) and evaporated repeatedly to remove organoborate impurities. The residue was treated with a solution of HCl in Et_2O (2 ml) and the solvent was evaporated. Further purification was done by flash chromatography on C18 silica (MeOH/ H_2O + 0.1% CH_3COOH, 1:10). Compound 2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-ol hydrochloride was isolated as a yellowish solid (48 mg, yield 96%).

^{1}H NMR (401 MHz, Methanol-d4) δ 7.66 (t, J = 2.1 Hz, 1H), 7.45 (ddd, J = 8.0, 1.8, 1.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.00 (ddd, J = 8.1, 2.5, 0.9 Hz, 1H), 4.18 (dd, J = 10.7, 3.6 Hz, 1H), 3.83 (s, 3H), 2.94 (dq, J = 12.2, 7.2 Hz, 1H), 2.84 – 2.63 (m, 2H), 1.94 – 1.37 (m, 7H), 1.22 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d4) δ 161.4, 136.3, 130.9, 122.9, 117.3, 115.4, 76.5, 68.0, 55.8, 38.8, 32.7, 32.4, 25.0, 23.2, 11.9. IR (ATR, cm^{-1}): ν_{max} = 3308, 1093, 1044. HRMS-ESI: m/z calculated for $C_{15}H_{24}N_1O_2$ $[M+H]^+$ 250.1802, found 250.1802. Melting point: 235 – 238 °C (Et_2O).

Synthesis of 2-(ethylamino)-2-(3-hydroxyphenyl)cyclohexan-1-one hydrobromide (20)

Compound **3** (200 mg, 0.7 mmol) was dissolved in HBr (46% aq., 3 ml) and the reaction mixture was heated under reflux for 3 hours. The HBr was evaporated and further purification was done by flash chromatography on C18 silica (MeOH/ H_2O + 0.1% CH_3COOH, 1:10). Compound 2-(ethylamino)-2-(3-hydroxyphenyl)cyclohexan-1-one hydrobromide was isolated as a colorless solid (199 mg, yield 90%).

^{1}H NMR (400 MHz, Methanol-*d4*) δ 7.39 (t, J = 8.0 Hz, 1H), 6.95 (ddd, J = 8.2, 2.4, 0.8 Hz, 1H), 6.91 (ddd, J = 7.8, 1.9, 0.9 Hz, 1H), 6.88 (t, J = 2.1 Hz, 1H), 3.20 (dq, J = 14.2, 2.7 Hz, 1H), 2.83 (dq, J = 12.1, 7.3 Hz, 1H), 2.59 – 2.40 (m, 3H), 2.13 – 1.88 (m, 3H), 1.87 – 1.68 (m, 2H), 1.22 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-*d4*) δ 207.2, 160.1, 133.0, 132.2, 120.0, 118.5, 116.1, 73.1, 40.3, 38.6, 33.8, 28.5, 22.9, 11.8. IR (ATR, cm^{-1}): ν_{max} = 3186, 1727, 1705. HRMS-ESI: m/z calculated for $C_{14}H_{20}N_1O_2$ $[M+H]^+$ 234.1489, found 234.1490. Melting point: 188 – 190 °C (Et_2O).

Synthesis of 3-(1-(ethylamino)-2-hydroxycyclohexyl)phenol hydrochloride (21)

$NaBH_4$ (49 mg, 1.3 mmol) was added slowly in portions to the solution of compound **20** (100 mg, 0.37 mmol) in MeOH (2 ml) at 0 °C and the mixture was stirred for 2 hours at RT. The organic solvent was evaporated and the residue was dissolved in MeOH (5 ml) and evaporated repeatedly to remove organoborate impurities. The residue was treated with a solution of HCl in Et_2O (2 ml) and the solvent was evaporated. Further purification was done

by flash chromatography on C18 silica (MeOH/ H_2O + 0.1% CH_3COOH, 1:10). Compound 3-(1-(ethylamino)-2-hydroxycyclohexyl)phenol hydrochloride was isolated as a yellowish solid (73 mg, yield 72%).

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.48 (t, J = 2.1 Hz, 1H), 7.37 (ddd, J = 8.0, 1.9, 1.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 6.85 (ddd, J = 8.0, 2.4, 0.9 Hz, 1H), 4.14 (dd, J = 10.8, 3.6 Hz, 1H), 2.93 (dq, J = 12.2, 7.2 Hz, 1H), 2.82 – 2.60 (m, 2H), 1.94 – 1.81 (m, 1H), 1.81 – 1.58 (m, 4H), 1.58 – 1.36 (m, 2H), 1.21 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 159.0, 136.3, 130.9, 121.6, 118.2, 117.1, 76.5, 67.9, 38.8, 32.6, 32.4, 25.0, 23.2, 11.9. IR (ATR, cm^{-1}): ν_{max} = 3425, 3274. HRMS-ESI: m/z calculated for $C_{14}H_{22}N_1O_2$ $[M+H]^+$ 236.1645, found 236.1646. Melting point: 247 – 250 °C decomposition (Et_2O).

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