Synthesis and characterization in rodent brain of the subtype selective NR2B NMDA receptor ligand $[^{11}\text{C}]\text{Ro} 04\text{-}5595$ as a potential radiotracer for positron emission tomography

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General Information
Reactants, reagents and solvents used herein were procured from Sigma-Aldrich (Sigma-Aldrich AS, Norway) in analytical quality unless specified otherwise. Nuclear magnetic resonance spectra were recorded on a Bruker AVII 400 NMR instrument (Bruker ASX Nordic AB). Chemical shifts (δ) for proton (400 MHz) and 13C (100 MHz) resonances are reported in parts per million (ppm), relative to residual solvent signal (1H NMR CHCl3 δ = 7.226 ppm, 13C NMR CDCl3 δ = 77.06 ppm). Mass spectrometry was conducted on a maXis II ETD from Bruker Daltonics time of flight instrument with a flight tube of 3m using electron spray ionization in positive mode. Calculated exact mass is reported for the positively charged ion. The samples were prepared in a solution from methanol or acetonitrile in 1 mg/ml concentration. TLC was conducted on Silica gel 60 F254 coated aluminum TLC plates (Supelco, USA). Optical rotation was measured on a polarimeter (Perkin Elmer model 341) at 489 nM and 20 °C using a 10 cm long tube with 1 ml capacity. Values are averaged from at least 3 measurements using the same sample.

In vivo studies
Animals, Small animal PET Acquisition and Small animal PET Data analysis
The animal experiments were carried out in compliance with the Law on Animal Experiments of the Netherlands. The protocol was approved by the Institutional Animal Welfare Body of the Radboud University, Nijmegen (DEC 2014-208). Male outbred Sprague-Dawley (Hsd:Sprague Dawley® SD®) rats were obtained from Harlan (The Netherlands). The animals were housed in IVC bluelines cages maintained at a 12h light-dark cycle and were fed with standard laboratory chow and water ad libitum. After arrival from commercial supplier, rats were allowed to acclimatize for at least seven days. Prior to PET scanning, all rats were anesthetized with isoflurane/ medical air (induction: 5% isoflurane, maintenance: ≤ 2%) and kept on electronic heating pad during the entire study period. A cannula was placed in a tail vein for tracer injection. The brain was in the field of view. Before the emission scan, a transmission scan of 600s using a 57Co point source was performed. The emission scan for 90 min was started just before the tracer injection. PET data acquired was reconstructed in 24 time frames using a 3D ordered subsets expectation maximization (OSEM) algorithm. Datasets were totally corrected for random coincidences, scatter, attenuation and radiation decay.

Time activity curves (TACs) were determined using Inveon research workplace (Siemens medical solutions, Knoxville, TN). The summed PET time frames from each animal were manually co-registered to an MRI template of a rat brain with predefined volumes of interest (VOIs). The VOIs were transferred from the MRI template to the PET data, and tissue TACs were extracted.

In vivo metabolite analysis
The presence of radiometabolites in the tissue to be imaged could jeopardize the accurate quantification of a PET measurement. Therefore, we measured whether radiometabolites crossed the blood brain barrier and are confounding with our parent compound in the brain. For this analysis, rats were anesthetized and euthanized at 15 min (n = 2) post tracer injection. Terminal blood sample was collected and rat brains were dissected, homogenized and samples (plasma and brain) were analyzed for the presence of radioactive metabolites by RP-HPLC.
Table S1: Observed counts for metabolite analysis.

| Tissue                     | Bq/ml |
|----------------------------|-------|
| Blood                      | 27    |
| Plasma                     | 34    |
| Blood pellet               | 68    |
| Brain pellet               | 122   |
| Brain pellet supernatant   | 38    |

**Preparation of samples from in vivo experiment**

The collected blood was centrifuged at 6000 rpm for 4 min to acquire plasma. Plasma samples were then used for metabolite analysis after protein was removed by adding 1 volume of acetonitrile followed by centrifugation (5 min at 13,000 rpm). Furthermore, rat brains were dissected and cut into small pieces. One volume of acetonitrile was added, and tissue was homogenized for 2 min. The collected homogenate was centrifuged at 13,000 rpm for 5 min to remove cell debris and proteins. Plasma and brain samples of the supernatant were collected, filtered through a 0.45 µm Durapore (PVDF) filter and analyzed for the presence of radiolabeled metabolites by radio-HPLC. Supernatant samples (100 µL) were injected onto Xterra RP C18 2.1×150 mm, 5µm analytical column and eluted with 0.1 % Phosphoric acid in water (45%) and acetonitrile (55%) mixture at a column temperature of 30 °C and flow rate of 0.3 mL/min. For this method a wavelength of 218 nm was used for UV detection. The eluted fractions were collected in a separate counting vials from 0-3 min and 3-5 min and measured with an automated well-counter (Wallac Wizard 1480 automatic gamma counter).

**Wiping/Autoradiography**

**General autoradiography**

Brain tissues were cut using a Cryo Star NX-70 Cryostat (Thermo Fischer Scientific). LSC was done using a HIDEX 300 SL (HIDEX) and autoradiographic screen were read using a CR35 Bio Plus image plate scanner (Durr Medical).

**Equipment and chemicals:**

Microscope slides (VWR), Eppendorf’s (Costar), Pipettes and pipette tips (Thermoscientific), Storage Phosphor Screen BAS-IP TR 2015 E tritium screen and exposure cassette for unmounted screens (GE healthcare Life Sciences). Radio-ligand $[^3]$Hifenprodil (Perkin Elmer, 1.87 GBq/µmol), $[^3]$HRo 04-5595 (Tritec, 1.04 GBq/µmol), threo ifenprodil hemitartrate (Tocris Biosciences), GBR 12909 dihydrochloride (Tocris Biosciences), LSC cocktail (Perkin Elmer). Autoradiography data was evaluated AIDA imaging analyser software version 5.1 from Raytest. Curve fittings were made in GraphPad Prism 6 (GraphPad Software).

**Brain preparations (rat)**

Male Sprague-Dawley aged rats (> 400 g) were euthanised by decapitation and brains were removed, excised, fresh frozen in isopentane/liquid nitrogen and stored at -80 °C. On the day prior cutting, sections were taken out and a single vertical cut was made to separate the two hemispheres. The tissue was kept at -20 °C overnight. The following day, the tissues were immersed in fixing
glue and frozen once again. Sagittal and transversal sections (20 µl thick) containing areas of interest (cortex, thalamus and hippocampus) were cut at -20 °C using a cryo-microtome. The sections were placed on microscope slides and kept at -80 °C until use. Samples holding glue only were used as controls.

**Brain preparations (mouse)**
The wild type mice brains were prepared analogous to the rat brains but cut in coronal sections of 20 µm thickness.

**Experimental information wiping experiments:**
The method used was adapted from Carter et al. A circle was drawn around the tissue sections using a pap pen and samples were pre-incubated in 50 mM of Tris-HCl buffer (pH 7.4) for 15 minutes at r.t. (~22 °C). The buffer solution was poured off and the samples incubated in [3H]ifenprodil (27 nM of 1.87 GBq/µmol) in presence of tested compound (1 µM) and GBR 12909 (30 µM) for 2 hours. The solution was poured off and the sections washed at 0 degrees in Tris-HCl buffer for 3*5 minutes. A wetted filter paper was used to scrape the tissues of the slides and dissolved in a liquid scintillation cocktail (10 ml). The scintillation for each sample was recorded for 15 minutes. A blank sample was subtracted from the count-rate. Experiments were performed in triplicate. Experiments using compounds holding a nitro substituent was found to quench the light in the liquid scintillation counter and were excluded from the experiment. One nitro compound was used in the autoradiographic experiment.

**Autoradiography using [3H] ifenprodil**
Adult male Male Sprague-Dawley rat brain sections were thawed for 15 minutes at room temperature (~22 °C). A circle was drawn around the tissues using a pap pen and samples were pre-incubated in 50 mM Tris-HCl buffer (pH 7.4) for 15 minutes at r.t. The buffer solution was poured off and the samples incubated in [3H]ifenprodil (27 nM), 3 µM trifluoroperazine and 30 µM GBR-12909 and 1 µM and 10 µM of tested compound for 90 minutes. The sections were washed in buffer and deionised water (5+5+5 minutes, +10 seconds) at 0 degrees. The sections were thoroughly dried under a stream of air and subsequently positioned in a cassette and exposed for 4-5 weeks using a tritium screen. Experiments were performed in duplicate.

**Autoradiography using [3H] Ro 04-5595**
Adult male wild type mice coronal brain sections or adult male Male Sprague-Dawley rat transversal brain sections were thawed at 15 minutes at room temperature (~22 °C). The samples were pre-incubated in 50 mM Tris-HCl buffer (pH 7.4) for 15 minutes at r.t. The buffer solution was poured off and the samples incubated in [3H] Ro 04-5595 in varying concentrations up to 1.04 GBq/µmol for 90 minutes. The sections were washed in buffer and deionised water (5+5+5 minutes +10 seconds) at 0 degrees. The sections were thoroughly air dried and subsequently positioned in a cassette and exposed for 4-5 weeks using a tritium screen. Experiments were performed in triplicate.
Figure S1A: Baseline AR using $[^3]$H ifenprodil (27 nM), 3μM trifluoroperazine and 30μM GBR 12909.

Figure S1B: Baseline AR using $[^3]$H ifenprodil (27 nM), 3μM trifluoroperazine, 30μM GBR 12909 and 1 μM Ro 04-5595. Note displacement in hippocampus with no displacement in cerebellum.

Autoradiography using $[^3]$H ifenprodil and varying concentrations of Ro 04-5595

Table S2: specifically bound $[^3]$H ifenprodil in presence of increasing concentration of Ro 04-5595 determined via wiping, values are average values from triplicate wiping experiment, outliers are eliminated based on physical appearance of brain after incubation.

| log [Ro 04-5595] | % specifically bound |
|------------------|----------------------|
| -10,0            | 99,8                 |
| -9,5             | 100,0                |
| -9,0             | 96,1                 |
Figure S2A: Two site curve fit using Graphpad prism using values from Table S2.

IC₅₀ using graphpad = 39±4 nM

Cheng-Prusoff equation using $K_i = 20$ nM for ifenprodil⁵ which is in agreement with preliminary concentration dependent experiments by us varying the molar activity of ifenprodil give $K_i 17±2$ nM for Ro 04-5595 which is in agreement with $K_i = 20±3$ nM as reported by Mutel et al.⁶

Table S3: Specifically bound [³H]ifenprodil in hippocampus in presence of increasing concentration of Ro 04-5595 determined via autoradiography, values are average values from triplicate wiping experiment, outliers are eliminated based on brain tissue damage after incubation.

| log conc. (M) | % specifically bound | standard deviation | n=  |
|--------------|----------------------|-------------------|-----|
| -11          | 100                  | 3                 | 2   |
| -10          | 91                   | 5                 | 3   |
| -9           | 110                  | 0                 | 1   |
| -8           | 65                   | 2                 | 2   |
| -7           | 64                   | 14                | 3   |
| -6           | 31                   | 4                 | 3   |
| -5           | 0                    | 7                 | 3   |
Figure S2B: Two site curve fit using Graphpad prism using values from Table S3.

IC\textsubscript{50} = 5±10 nM

K\textsubscript{i} = 2±4 nM

**Autoradiography using [\textsuperscript{3}H]1 and varying concentrations of 1\textsuperscript{S} and 1\textsuperscript{R}**

Procedure as described above. Increasing concentrations of 1\textsuperscript{S} or 1\textsuperscript{R} were used to dilute the radioligands molar activity to create a concentration dependent saturation experiment. Experiments were performed in duplicate and 5 outliers removed from the data set based on physical appearance of sections (two values from data set using 1\textsuperscript{S} and three from data set using 1\textsuperscript{R} among both at 126 nM due to countrate was comparable to the control with no molar activity dilution. I assume a mistake was made and the radioligand not added). An Eadie Hofstedt plot was created using the specific binding in Bq/pixel converted to fmol bound 1 / mg tissue plotted vs fmol 1 / mg tissue * nM 1. I only include the values in the slope and the estimated B\textsubscript{max} should be seen as a good estimate of 500-1000 fmol/mg tissue.

Figure S3A: Eadie hofstedt plot used for estimating B\textsubscript{max} in cortex (0.5-1 nmol/ml) in rat which is comparable to previous estimates in rat brain (1.6 pmol/mg protein).\textsuperscript{3}
Figure S3B: Autoradiographs showing binding of $[^3]H$ I in sagittal rat brain sections. Note the displaced radioligand binding from cortex.

Figure S4. Co-injection of 1 (1 mg/ml; 416 g rat) (9.1 MBq) in a total volume of 0.83 ml.
Table S4: Displacement (%) of $[^3]$HIfenprodil in hippocampus and cerebellum at varying concentration.

| Compound | **Hippocampus** | | | **Cerebellum** | | |
|---|---|---|---|---|---|---|
| | 1 µM | 10 µM | | 1 µM | 10 µM | |
| 1 | 23±2% | 33±2% | no disp. | no disp. |
| 4a | 26±1% | 30±0% | 10±10% | 7±4% |
| 4c | 21±5% | 26±3% | 14±4% | 12±1% |
| 4g | 21±1% | N.D. | 15±2% | N.D. |
| 5a | 12±2% | 6±2% | 2±0% | 4±7% |
| 5e | 15±0% | 32±0% | 17±13% | 24±3% |
| 5h | 23±1% | 3±13% | 8±13% | no disp. |
| 6b | 25±2% | N.D. | 11±0% | N.D. |
| 6e | 19±2% | 22% | 5±5% | no disp. |
| 6-methoxy-2-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinolin-7-ol | 22±4% | 31±6% | 21±0% | 15±0% |
| 1-(4-iodophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline | 21±5% | 31±1% | 16±2% | 8±1% |

**HPLC purity**

NR2B Ligands were dissolved in DMSO (1 mg/ml) and injected (10 µl) into a Luna C18(2) column using a flow-rate of 1 ml/min and an isocratic mobile phase of aqueous TFA (3 mM) in AcN and 230 nm as detection wavelength.

**$^{11}$C-methylation**

$^{11}$C-Methylation of 1-(4-chlorophenethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol (0.4 mg, 1.3 µmol) was methylated using $^{11}$CH$_3$I using captive solvent radiosynthesis in DMF (50 µl) at 40 ºC via heating at 40 ºC for one minute. HPLC purification yielded 13±3% decay corrected yield (12-43 MBq/nmol in > 99% RCP).

**General imine formation**

To amine (1 eq) in EtOH was added aldehyde (1 eq) and evaporated to dryness under reduced pressure at 35 degrees. The crude was further dried via addition of a few millilitres of PhMe followed by evaporation to dryness under reduced pressure. Full conversion was observed using $^1$H-NMR.

**General hydrogenation**

To Raney Nickel in MeOH (5 ml) was added a magnetic stirrer bar and vigorously stirred for a few minutes. The solvent was poured off. The washing step was repeated two additional times. “Starting compound” dissolved in MeOH:AcOH; 4:1 (40 ml/mmol) was added and H$_2$ fitted. The reaction was left over night. Complete consumption was indicated via TLC analysis (staining with ceric ammonium molybdate stain). The catalyst was filtered off and solvents removed under reduced pressure. The reaction mixture was either basified with aqueous ammonia (for veratrole derivatives) or pH adjusted to 8-9 with sat. NaHCO$_3$ (for guaiacol derivatives) and extracted with EtOAc. The combined organic phases were washed with brine and dried over sodium sulphate.
The solvent was removed under reduced pressure and the crude purified via flash column chromatography affording the target compounds.

**General reductive amination**

To secondary amine dissolved in dichloroethane (10 ml/mmol; dimethyl) (30ml / mmol; desmethyl) and 37% formaldehyde in MeOH (10 eq). Full consumption of starting material was indicated by TLC analysis after 1 hour. Sodium triacetoxy borohydride (1.5 eq) was added and the reaction mixture was left to stir over night. The reaction mixture was either basified with aqueous ammonia (veratrols) or pH adjusted to 8-9 with sat. NaHCO₃ (guaiacols) and extracted with EtOAc. The combined organic phases were washed with brine and dried over sodium sulphate. The crude was purified using flash column chromatography (MeOH in DCM) affording the target compounds.

**General sandmeyer CuCl**

At 0 °C was aniline dissolved in 1.6 M aqueous HCl (6 ml/mmol) was added 1M aqueous sodium nitrite (1.2 eq for veratrols and 1.0 eq for guaiacols). The pale yellow reaction mixture was stirred for 30 minutes. 0.5 M CuCl in 37% aqueous HCl (1.5 eq) was added dropwise and the reaction mixture left to stir for 30 minutes. The reaction mixture was allowed to reach room temperature and kept until the reaction mixture was pale blue. The reaction mixture was basified (28% aqueous NH3 for veratrols and sat. NaHCO3 for guaiacols (pH 8-9)) and extracted with EtOAc. The combined organic phases were dried over sodium sulphate and evaporated to dryness under reduced pressure.

**General sandmeyer type reaction KI**

To aniline in acetonitrile (7 ml/mmol) was added p-toluenesulfonic acid monohydrate (4 eq.) and cooled to 10 °C. Drop wise was added an aqueous solution 4 ml/mmol of 1 M NaNO₂ and 1.25 M KI. The reaction was brought to room temperature and stirred for one hour. The reaction mixture was quenched using 1 M Na₂S₂O₃, diluted with EtOAc and basified using aqueous ammonia. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over sodium sulphate and the solvents removed under reduced pressure.

**General BBr₃ Demethylation**

To veratrole in dry DCM (0.5 ml / 10 mg) on ice was added 5 equivalents of 1 M BBr₃ in DCM and left to thaw and stir over night. The reaction mixture was cooled on ice, quenched with water and left to stir for 30 minutes. pH was adjusted to 8-9 by addition of sat. NaHCO₃ and the aqueous phase were extracted with EtOAc. The combined organic phases were washed with brine and dried over sodium sulphate. Solvents were removed under reduced pressure.
6,7-dimethoxy-2-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (6a) *Synthesised in accordance to general hydrogenation.* Purification via flash column chromatography using 7% MeOH in DCM yielded the target compound as yellow solids in 90% (63 mg, 0.20 mmol). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.30 – 7.23 (m, 2H), 7.22 – 7.14 (m, 3H), 6.58 (s, 1H), 6.55 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.44 (t, $J$ = 5.4 Hz, 1H), 3.21 – 3.12 (m, 1H), 2.81 – 2.68 (m, 4H), 2.62 – 2.53 (m, 1H), 2.49 (s, 3H), 2.12 – 2.03 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 147.4, 147.4, 143.0, 129.8, 128.6, 128.4, 126.8, 125.7, 111.4, 110.2, 62.9, 56.1, 55.9, 48.4, 42.8, 37.0, 31.7, 25.6. **HR-ESIMS:** $m/z$ 312.1959 [M+H]$^+$ (C$_{20}$H$_{26}$NO$_2$$^+$, calculated 312.1958). >95% HPLC UV purity 230 nm.

4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl)aniline (6e). *Synthesised in accordance to general hydrogenation.* Purification via flash column chromatography using 5% MeOH in DCM yielded the target compound as yellow oil in 70% that later solidified (497 mg, 1.52 mmol). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 6.98 (d, $J$ = 8.3 Hz, 2H), 6.61 (d, $J$ = 8.3 Hz, 2H), 6.57 (s, 1H), 6.54 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.53 (broad s, 2H), 3.42 (t, $J$ = 5.5 Hz, 1H), 3.21 – 3.11 (m, 1H), 2.83 – 2.58 (m, 4H), 2.53 – 2.43 (m, 1H), 2.47 (s, 3H), 2.10 – 1.93 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 147.4, 147.3, 144.2, 132.9, 130.0, 129.3, 126.6, 115.4, 111.4, 110.3, 62.8, 56.1, 55.9, 48.1, 42.7, 37.2, 30.9, 25.4. **HR-ESIMS:** $m/z$ 327.2070 [M+H]$^+$ (C$_{20}$H$_{27}$N$_2$O$_2$$^+$, calculated 327.2067). >95% HPLC UV purity 230 nm.
1-(4-aminophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (6f).
*Synthesised in accordance to general hydrogenation.* Purification via flash column chromatography using 8-15% MeOH in DCM yielded the target compound (70 mg, 0.22 mmol) in 41% as pale yellow solids. $^1$H NMR (400 MHz, Methanol-$d_4$) δ 7.29 – 7.21 (m, 2H), 6.76 – 6.72 (m, 2H), 6.71 (s, 1H), 6.63 (s, 1H), 6.59 (d, $J = 15.8$ Hz, 1H), 5.88 (dd, $J = 15.6, 8.9$ Hz, 1H), 3.89 (s, 1H), 3.86 (s, 3H), 3.18 (dt, $J = 10.4, 4.4$ Hz, 1H), 3.05 (ddd, $J = 16.1, 10.2, 5.6$ Hz, 1H), 2.80 (dt, $J = 15.8, 4.2$ Hz, 1H), 2.67 (td, $J = 10.9, 4.4$ Hz, 1H), 2.50 (s, 3H). $^{13}$C NMR (101 MHz, MeOD) δ 149.0, 148.1, 145.7, 136.2, 129.6, 128.6, 127.9, 126.1, 125.9, 116.4, 115.5, 112.6, 70.0, 56.4, 52.6, 44.0, 29.0. HR-ESIMS: m/z 313.1910 [M+H]$^+$ (C$_{19}$H$_{23}$N$_2$O$_2$$,^+$, calculated 313.1911). >95% HPLC UV purity 230 nm.

1-(4-fluorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (6c).
*Synthesised in accordance to general hydrogenation.* Purification via flash column chromatography using 4% MeOH in DCM yielded the target compound (151 mg, 0.458 mmol) in 82% as off white solids. $^1$H NMR (400 MHz, Chloroform-$d$) δ 7.16 – 7.09 (m, 2H), 6.99 – 6.90 (m, 2H), 6.57 (s, 1H), 6.54 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.40 (t, $J = 5.4$ Hz, 1H), 3.17 – 3.09 (m, 1H), 2.82 – 2.64 (m, 4H), 2.58 – 2.48 (m, 1H), 2.47 (s, 3H), 2.06 – 1.99 (m, 2H). $^{19}$F NMR (377 MHz, Chloroform-$d$) δ -118.2. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.3 (d, $^1$J$_{CF} = 243$ Hz), 147.5, 147.5, 138.7 (d, $^4$J$_{CF} = 3$ Hz), 129.9, 129.8 (d, $^3$J$_{CF} = 8$ Hz), 127.1, 115.1 (d, $^2$J$_{CF} = 21$ Hz), 111.5, 110.2, 62.8, 56.2, 56.0, 48.4, 42.9, 37.2, 30.9, 25.7. HR-ESIMS: m/z 330.1868 [M+H]$^+$ (C$_{20}$H$_{25}$FNO$_2$$,^+$, calculated 330.1864). >95% HPLC UV purity 230 nm.

6,7-dimethoxy-2-methyl-1-(4-(trifluoromethyl)phenethyl)-1,2,3,4-tetrahydroisoquinoline (6d).
*Synthesised in accordance to general hydrogenation.* Purification via flash column chromatography using 4% MeOH in DCM yielded the target compound (87 mg, 0.23 mmol) as pale green-yellow solids. $^1$H NMR (400 MHz, Chloroform-$d$) δ 7.51 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 6.58 (s, 1H), 6.53 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.43 (t, $J = 5.4$ Hz, 1H), 3.25 – 3.07 (m, 1H), 2.84 – 2.67 (m, 4H), 2.66 – 2.55 (m, 1H), 2.48 (s, 3H), 2.13 – 1.98 (m, 2H). $^{19}$F NMR (377 MHz, Chloroform-$d$) δ -62.3. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 148.0, 147.4, 140.4 (q,
$^{4}J_{CF} = 1$ Hz), 134.7, 131.8, 129.6 (q, $^{2}J_{CF} = 32$ Hz), 127.8, 126.7, 125.7 (q, $^{3}J_{CF} = 4$ Hz), 124.3 (q, $^{1}J_{CF} = 272$ Hz), 111.6, 111.0, 68.4, 56.2, 56.0, 51.3, 44.3, 28.9. HR-ESIMS: m/z 380.1832 [M+H]$^{+}$ (C$_{21}$H$_{25}$F$_{3}$NO$_{2}$, calculated 380.1832) >95% HPLC UV purity 230 nm.

1-(4-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (6b). Synthesised in accordance to general hydrogenation. Purification via flash column chromatography using 3% MeOH in DCM yielded the target compound (142 mg, 0.41 mmol) in 74% as yellow solids. $^{1}$H NMR (400 MHz, Chloroform-d) $\delta$ 7.24 – 7.20 (m, 2H), 7.12 – 7.07 (m, 2H), 6.57 (s, 1H), 6.53 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.40 (t, $J = 5.4$ Hz, 1H), 3.18 – 3.08 (m, 1H), 2.82 – 2.63 (m, 4H), 2.57 – 2.48 (m, 1H), 2.46 (s, 3H), 2.07 – 1.96 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_{3}$) $\delta$ 147.5, 147.4, 141.5, 131.3, 129.9, 129.8, 128.4, 127.0, 111.5, 110.1, 62.7, 56.2, 55.9, 48.3, 42.8, 36.9, 31.0, 25.6. HR-ESIMS: m/z 346.1568 [M+H]$^{+}$ (C$_{20}$H$_{25}$ClNO$_{2}$, calculated 346.1568). Analytical information was in agreement with Richter et. al.$^{4}$ Undetectable on UV, only trace absorption at 256 and 230 nm.

6-methoxy-1-phenethyl-1,2,3,4-tetrahydroisoquinolin-7-ol and 1-(4-chlorophenethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol. Synthesised in accordance to general hydrogenation. Purification via flash column chromatography yielded a mix of (proto and chloro analogue) in (18 mg) as yellow solids. The crude was further purified via HPLC (HS F5 column; 25 mm x 10 mm) 5 ml/min using 70% MeCN and 30% H$_{2}$O containing 0.1% TFA. The crude was loaded from mobile phase injecting 3.0 ml at 1 mg/ml per injection. Bulk solvents were removed under reduced pressure and pH adjusted to 8–9 using saturated NaHCO$_{3}$ and the aqueous phase extracted with EtOAc. The combined organic phases were dried over sodium sulphate and solvents were removed under reduced pressure obtaining 6-methoxy-1-phenethyl-1,2,3,4-tetrahydroisoquinolin-7-ol (4 mg, 14 µmol) in 16% as pale yellow solids (eluting at 8:50-11:40 minutes). $^{1}$H NMR (400 MHz, MeOH-d$_{4}$) $\delta$ 7.37 – 7.24 (m, 4H), 7.24 – 7.15 (m, 1H), 6.67 (s, 1H), 6.63 (s, 1H), 3.96 (dt, $J = 9.9, 4.9$ Hz, 1H), 3.28 (dt, $J = 12.3, 5.5$ Hz, 1H), 2.99 (ddd, $J = 12.5, 7.8$,
5.1 Hz, 1H), 2.90 – 2.68 (m, 4H), 2.20 – 2.00 (m, 2H). \(^{13}\)C NMR (101 MHz, MeOD) \(\delta\) 147.9, 146.0, 143.2, 131.0, 129.4, 129.5, 127.0, 126.6, 113.8, 113.0, 56.4, 56.0, 41.8, 38.9, 33.1, 29.1. **HR-ESIMS:** \(m/z\) 284.1646 [M+H]\(^+\) (C\(_{18}\)H\(_{22}\)NO\(_2\)\(^+\), calculated 284.1645) >95\% HPLC UV purity at 230 nm and 1-(4-chlorophenethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol (12 mg, 38 \(\mu\)mol) in 43\% as pale yellow solids obtained (eluting at 13.00-18.10 minutes). \(^1\)H NMR (400 MHz, MeOH-\(d_4\)) \(\delta\) 7.32 – 7.21 (m, 4H), 6.66 (s, 1H), 6.60 (s, 1H), 4.00 – 3.93 (m, 1H), 3.82 (s, 3H), 3.31 – 3.23 (m, 1H), 3.04 – 2.94 (m, 1H), 2.89 – 2.64 (m, 4H), 2.18 – 1.96 (m, 2H). \(^{13}\)C NMR (101 MHz, MeOD) \(\delta\) 147.9, 146.0, 142.1, 132.7, 131.0, 130.6, 129.5, 126.5, 113.8, 113.0, 56.4, 55.9, 41.8, 38.8, 32.4, 29.0. **HR-ESIMS:** \(m/z\) 318.1256 [M+H]\(^+\) (C\(_{18}\)H\(_{21}\)ClNO\(_2\)\(^+\), calculated 318.1255). (E)-1-(4-aminostyryl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (5i). *Synthesised in accordance to general hydrogenation.* Purification via flash column chromatography using 8-15\% MeOH in DCM yielded the target compound (66 mg, 0.21 mmol) in 57\% as yellow solids. \(^1\)H NMR (400 MHz, Methanol-\(d_4\)) \(\delta\) 7.23 – 7.18 (m, 2H), 6.71 – 6.62 (m, 3H), 6.58 (s, 1H), 6.53 (s, \(J = 15.8\) Hz, 2H), 5.83 (dd, \(J = 15.7, 9.0\) Hz, 1H), 3.84 (d, \(J = 8.9\) Hz, 1H), 3.81 (s, 3H), 3.13 (dt, \(J = 11.0\) Hz, 1H), 3.00 (ddd, \(J = 15.8, 9.9, 5.4\) Hz, 1H), 2.75 (dt, \(J = 16.4, 4.2\) Hz, 1H), 2.63 (td, \(J = 10.7, 4.4\) Hz, 1H), 2.45 (s, 3H). \(^{13}\)C NMR (101 MHz, MeOD) \(\delta\) 149.0, 148.2, 145.7, 136.4, 129.4, 128.6, 127.7, 125.8, 125.7, 116.3, 115.4, 112.5, 70.0, 56.4, 52.5, 44.0, 28.9. **HR-ESIMS:** \(m/z\) 311.1754 [M+H]\(^+\) (C\(_{19}\)H\(_{23}\)N\(_2\)O\(_2\)\(^+\), calculated 311.1754). >95\% HPLC UV purity 230 nm.

(E)-4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)vinyl)aniline (5h). To Raney nickel (adsorbed to magnetic stirrer bar and washed with MeOH (3*5 ml) was added (E)-6,7-dimethoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline (105 mg, 0.296 mmol) in MeOH (10 ml) under an atmosphere of argon. A balloon with H\(_2\) was fitted and the reaction closely monitored via TLC analysis. After full consumption of starting material was observed, the
solids were filtered off and washed with MeOH (2*5 ml). The solvent was removed under reduced pressure and purified using flash column chromatography (5% MeOH in DCM) yielding the target compound as pale yellow fluffy solids in 86% (83 mg, 0.256 mmol). $^1$H NMR (400 MHz, Chloroform-d) δ 7.17 (d, $J = 8.4$ Hz, 2H), 6.61 – 6.49 (m, 4H), 6.44 (d, $J = 15.7$ Hz, 1H), 5.86 (dd, $J = 15.7$, 8.8 Hz, 1H), 3.78 (s, 3H), 3.72 (d, $J = 8.8$ Hz, 1H), 3.67 (s, 3H), 3.57 (dd, $J = 32.5$, 20.6 Hz, 2H), 3.05 – 2.90 (m, 2H), 2.65 (dt, $J = 16.0$, 3.6 Hz, 1H), 2.54 – 2.46 (m, 1H), 2.39 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 147.8, 147.3, 146.2, 133.5, 128.8, 127.8, 127.6, 126.4, 115.2, 111.3, 111.1, 68.9, 56.1, 56.0, 51.5, 44.2, 28.9. HR-ESIMS: m/z 325.1913 [M+H]$^+$ (C$_{20}$H$_{25}$N$_2$O$_2$$,+$, calculated 325.1911). >95% HPLC UV purity 230 nm.

(E)-6,7-dimethoxy-2-methyl-1-(4-(trifluoromethyl)styryl)-1,2,3,4-tetrahydroisoquinoline
(5e). Synthesised in accordance to general reductive amination. Purification via flash column chromatography using 3% MeOH in DCM yielded the target compound as pale yellow solids in 88% (191 mg, 0.506 mmol). $^1$H NMR (400 MHz, Chloroform-d) δ 7.58 (d, $J = 8.3$ Hz, 2H), 7.51 (d, $J = 8.3$ Hz, 2H), 6.65 (d, $J = 15.9$ Hz, 1H), 6.63 (s, 1H), 6.57 (s, 1H), 6.26 (dd, $J = 15.9$, 8.7 Hz, 1H), 3.88 (s, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.09 (ddd, $J = 10.9$, 5.4, 3.6 Hz, 1H), 3.06 – 2.96 (m, 1H), 2.74 (dt, $J = 16.1$, 3.8 Hz, 1H), 2.59 (ddd, $J = 10.9$, 9.4, 4.2 Hz, 1H), 2.47 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 148.0, 147.4, 134.7, 131.8, 129.6 (q, $^2$J$_{CF} = 33$ Hz), 128.4, 127.8, 126.7, 125.7 (q, $^2$J$_{CF} = 3$ Hz), 124.3 (q, $^1$J$_{CF} = 272$ Hz), 111.6, 111.0, 68.4, 56.2, 56.0, 51.3, 44.3, 28.9. HR-ESIMS: m/z 378.1674 [M+H]$^+$ (C$_{21}$H$_{23}$F$_3$NO$_2$$,+$, calculated 378.1675). >95% HPLC UV purity 230 nm.

(E)-1-(4-chlorostyryl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline
(5b). Synthesised in accordance to general reductive amination. Purification via flash column chromatography using 4% MeOH in DCM yielded the target compound in 55% as yellow solids (275 mg, 0.80 mmol). $^1$H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.22 (m, 4H), 6.62 (s, 1H), 6.58 (s, 1H), 6.57 (d, $J = 15.8$ Hz, 1H), 6.12 (dd, $J = 15.8$, 8.8 Hz, 1H), 3.86 (s, 3H), 3.83 (d, $J = 8.8$ Hz), 3.75 (s, 3H), 3.14 – 2.94 (m, 2H), 2.72 (dt, $J = 16.1$, 3.8 Hz, 1H), 2.58 (ddd, $J = 10.7$, 9.4, 4.1 Hz, 1H), 2.46 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 147.9, 147.3, 135.4, 133.4, 133.4, 132.5, 132.0,
HR-ESIMS: m/z 344.1411 [M+H]⁺ (C₂₀H₂₃ClNO₂⁺, calculated 344.1412). >95% HPLC UV purity 230 nm.

(E)-6,7-dimethoxy-2-methyl-1-styryl-1,2,3,4-tetrahydroisoquinoline (5a). Synthesised in accordance to general reductive amination. Analytical data was in agreement to Parraga et. al. 95% HPLC UV purity 230 nm.

(E)-6,7-dimethoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline (5c).

Synthesised in accordance to general reductive amination. Purification via flash column chromatography using 3% MeOH in DCM yielded the target compound in 86% as pale yellow solids (408 mg, 1.15 mmol). ¹H NMR (400 MHz, Chloroform-d) δ 8.22 – 8.13 (m, 2H), 7.58 – 7.48 (m, 2H), 6.68 (d, J = 15.8 Hz, 1H), 6.63 (s, 1H), 6.54 (s, 1H), 6.35 (dd, J = 15.8, 8.7 Hz, 1H), 3.94 – 3.88 (d, J = 8.7 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.08 (ddd, J = 11.2, 5.3, 4.0 Hz, 1H), 3.03 – 2.94 (m, 1H), 2.74 (dt, J = 16.0, 4.1 Hz, 1H), 2.60 (ddd, J = 11.2, 9.5, 4.2 Hz, 1H), 2.47 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 148.1, 147.4, 147.1, 143.3, 137.0, 131.0, 127.3, 127.0, 126.8, 124.2, 111.6, 110.9, 68.2, 56.2, 56.0, 51.0, 44.3, 28.8. HR-ESIMS: m/z 355.1654 [M+H]⁺ (C₂₀H₂₃N₂O₃⁺, calculated 355.1652) >95% HPLC UV purity 230 nm

(E)-1-(4-fluorostyryl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (5d). Synthesised in accordance to general reductive amination. Purification via flash column chromatography using 5.5% MeOH in DCM yielded the target compound in 91% as pale yellow...
solids (171 mg, 0.52 mmol). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.43 – 7.34 (m, 2H), 7.05 – 6.96 (m, 2H), 6.62 (s, 1H), 6.59 (s, 1H), 6.58 (d, \(J = 15.8\) Hz, 1H), 6.06 (dd, \(J = 15.8, 8.8\) Hz, 1H), 3.86 (s, 3H), 3.82 (d, \(J = 8.8\) Hz, 1H), 3.75 (s, 3H), 3.13 – 3.04 (m, 1H), 3.04 – 2.96 (m, 1H), 2.72 (dt, \(J = 16.0, 3.7\) Hz, 1H), 2.58 (dd, \(J = 10.6, 9.5, 4.2\) Hz, 1H). \(^{13}\)C NMR (101 MHz, CDCl$_3$) \(\delta\) 162.5 (d, \(^{1}J_{CF} = 247\) Hz), 147.9, 147.3, 133.1 (d, \(^{4}J_{CF} = 3\) Hz), 132.1, 131.5 (d, \(^{5}J_{CF} = 2\) Hz), 128.3, 128.1 (d, \(^{3}J_{CF} = 8\) Hz), 126.6, 115.6 (d, \(^{2}J_{CF} = 22\) Hz), 111.5, 111.0, 68.6, 56.1, 56.0, 51.4, 44.3, 28.9, \(^{19}\)F NMR (377 MHz, Chloroform-\(d\)) \(\delta\) -114.5. HR-ESIMS: \(m/z\) 328.1708 \([M+H]^+\) (>95% HPLC UV purity 230 nm).

![Diagram of compound](image)

\((E)-6\text{-methoxy-2-methyl-1-(4-nitrostyryl)}-1,2,3,4\text{-tetrahydroisoquinolin-7-ol (5f). Synthesised in accordance to general reductive amination. Purification via flash column chromatography using 8% MeOH in DCM yielded the target compound as sticky yellow oil in 88% (191 mg, 0.506 mmol). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.21 – 8.13 (m, 2H), 7.58 – 7.45 (m, 2H), 6.66 (d, \(J = 15.8\) Hz, 1H), 6.64 (s, 1H), 6.61 (s, 1H), 6.31 (d, \(J = 15.9, 8.7\) Hz, 1H), 5.56 (broad s, 1H), 3.86 (s, 3H), 3.85 (d, \(J = 8.7\) Hz, 1H), 3.82 (d, \(J = 9.0\) Hz, 1H), 2.72 (dt, \(J = 16.1, 3.7\) Hz, 1H), 2.61 – 2.54 (m, 1H), 2.45 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl$_3$) \(\delta\) 147.0, 145.6, 143.8, 143.3, 136.9, 131.1, 128.1, 127.1, 126.0, 124.2, 113.6, 110.8, 68.3, 56.1, 51.5, 44.4, 29.0. HR-ESIMS: \(m/z\) 341.1496 \([M+H]^+\) (C$_{19}$H$_{21}$N$_{2}$O$_{4}$, calculated 341.1496). >95% HPLC UV purity 230 nm.)

![Diagram of compound](image)

\((E)-1-(4\text{-chlorostyryl)}-6\text{-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (5g). Synthesised in accordance to general reductive amination. Purification via flash column chromatography using 4% MeOH in DCM for flash column chromatography yielded sticky yellow oil in 48% (5 mg, 0.015 mmol). \(^1\)H NMR (400 MHz, MeOH-\(d_4\)) \(\delta\) 7.57 – 7.44 (m, 2H), 7.42 – 7.33 (m, 2H), 6.74 (s, 1H), 6.72 (d, \(J = 16.2\) Hz, 1H), 6.60 (s, 1H), 6.16 (dd, \(J = 15.8, 9.0\) Hz, 1H), 3.94 (d, \(J = 9.0\) Hz, 1H), 3.86 (s, 3H), 3.17 (ddd, \(J = 11.5, 5.4, 3.9\) Hz, 1H), 3.04 (ddd, \(J = 15.6, 9.9, 5.4\) Hz, 1H), 2.81 (dt, \(J = 16.3, 4.2\) Hz, 1H), 2.66 (ddd, \(J = 11.6, 9.9, 4.5\) Hz, 1H), 2.49 (s, 3H). \(^{13}\)C NMR (101 MHz, MeOD) \(\delta\) 148.2, 145.8, 136.7, 134.4, 134.3, 131.9, 129.8, 129.0, 129.0, 126.1,
115.3, 112.7, 69.5, 56.4, 52.4, 44.1, 29.1. HR-ESIMS: m/z 330.1255 [M+H]+ (C_{19}H_{21}ClNO_{2}^+, calculated 330.1255). >95% HPLC UV purity 230 nm.

6-methoxy-2-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinolin-7-ol. Synthesised in accordance to general reductive amination. Purification using 5% MeOH in DCM for flash column chromatography yielded a yellow oil in 87% (9 mg, 0.030 mmol). \(^1\)H NMR (400 MHz, MeOH-\(d_4\)) \(\delta\) 7.32 – 7.26 (m, 2H), 7.24 – 7.14 (m, 3H), 6.69 (s, 1H), 6.62 (s, 1H), 3.86 (s, 3H), 3.51 (t, \(J = 5.4\) Hz, 1H), 3.26 – 3.16 (m, 1H), 2.90 – 270 (m, 4H), 2.60 (ddd, \(J = 13.6, 10.6, 5.3\) Hz, 1H), 2.51 (s, 3H), 2.18 – 1.99 (m, 2H). \(^{13}\)C NMR (101 MHz, MeOD) \(\delta\) 146.4, 144.4, 142.2, 128.9, 127.9, 127.9, 125.3, 124.5, 113.2, 111.3, 62.6, 54.9, 47.7, 41.2, 36.0, 31.5, 24.7. HR-ESIMS: m/z 298.1804 [M+H]+ (C_{19}H_{21}N_{2}O_{4}^+, calculated 298.1802).

1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (1). Synthesised in accordance to general sandmeyer CuCl. Purification via flash column chromatography using 8% MeOH in DCM yielded the target compound in 38% (12 mg, 0.036) mmol as yellow solids. \(^1\)H NMR (400 MHz, Chloroform-\(d_2\)) \(\delta\) 7.24 – 7.19 (m, 2H), 7.13 – 7.07 (m, 2H), 6.64 (s, 1H), 6.55 (s, 1H), 5.29 (broad s, 1H), 3.86 (s, 3H), 3.37 (t, \(J = 5.4\) Hz, 1H), 3.17 – 3.07 (m, 1H), 2.80 – 2.61 (m, 4H), 2.55 – 2.47 (m, 1H), 2.45 (s, 3H), 2.01 (td, \(J = 8.2, 7.8, 5.3\) Hz, 2H). \(^{13}\)C NMR (101 MHz, CDCl_{3}) \(\delta\) 145.1, 144.0, 141.5, 131.4, 130.5, 130.0, 128.5, 126.3, 112.8, 110.8, 62.7, 56.0, 48.7, 42.9, 36.7, 30.8, 26.0. HR-ESIMS: m/z 332.1412 [M+H]+ (C_{19}H_{23}ClNO_{2}^+, calculated 332.1412).
1-(4-iodophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. Synthesised in accordance to general sandmeyer KI. Purification via flash column chromatography using 2% MeOH in DCM yielded the target compound as light brown solids in 46% (112 mg, 0.256 mmol). 1H NMR (400 MHz, Chloroform-d) δ 7.57 (t, J = 8.3 Hz, 2H), 6.93 (d, J = 8.3 Hz, 2H), 6.57 (s, 1H), 6.52 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.40 (t, J = 5.4 Hz, 1H), 3.18 – 3.07 (m, 1H), 2.81 – 2.63 (m, 4H), 2.54 – 2.48 (m, 1H), 2.46 (s, 3H), 2.02 (td, J = 8.3, 5.5 Hz, 2H).

13C NMR (101 MHz, CDCl3) δ 147.5, 147.5, 142.8, 137.4, 130.8, 129.8, 127.0, 111.5, 110.2, 90.6, 62.8, 56.0, 48.4, 42.9, 36.9, 31.1, 25.7.

HR-ESIMS: m/z 438.0928 [M+H]+ (C20H25INO2+, calculated 438.0925).

(E)-1-(4-iodostyryl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. Synthesised in accordance to general sandmeyer KI. Purification via flash column chromatography using 2% MeOH in DCM yielded the target compound as light brown solids in 62% as brown oil (40 mg, 0.092 mmol). 1H NMR (400 MHz, Chloroform-d) δ 7.68 – 7.62 (m, 2H), 7.18 – 7.13 (m, 2H), 6.61 (s, 1H), 6.57 (s, 1H), 6.54 (d, J = 15.8 Hz, 1H), 6.16 (dd, J = 15.8, 8.8 Hz, 1H), 3.85 (s, 3H), 3.83 (d, J = 8.8 Hz, 1H), 3.74 (s, 3H), 3.11 – 2.96 (m, 2H), 2.72 (dt, J = 16.0, 3.8 Hz, 1H), 2.58 (ddd, J = 10.8, 9.5, 4.2 Hz, 1H), 2.45 (s, 3H).

13C NMR (101 MHz, CDCl3) δ 147.97, 147.37, 137.84, 136.42, 132.74, 132.21, 128.37, 127.98, 126.65, 111.52, 111.02, 92.94, 68.51, 56.15, 56.03, 51.34, 44.28, 28.90. HR-ESIMS: m/z 436.0764 [M+H]+ (C20H23NO2+, calculated 436.0768).

4-(benzyloxy)-3-methoxybenzaldehyde. To a solution of vanillin (15.2 g, 100 mmol) in EtOH (125 ml) were added K2CO3 (20.7 g, 150 mmol) portionwise. Benzyl bromide (14.25 ml, 120 mmol) was added drop wise at 0 °C. The mixture was heated to 70 °C for 2.5 h. The solids were filtered off through a short plug of celite and eluted with EtOAc (150 ml). The solvents were removed under reduced pressure and the crude purified via recrystallization from ethanol. Filtration afforded the compound as cream white solids in 98% (23.6 g, 98 mmol). 1H NMR (400 MHz, CDCl3) δ 9.84 (s, 1H), 7.45 – 7.30 (m, 8H), 7.00 (d, J = 8.5 Hz)), 7.00 (d, 1H, J = 8.5 Hz)), 7.45-7.30 (m, 8H), 7.00 (d, 1H, J = 8.5 Hz)), 5.25 (s, 2H), 3.95 (s, 3H), 3.95 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 191.0, 153.7, 150.2, 136.1, 130.4, 128.9, 128.3, 127.3, 126.7, 112.5, 109.5, 71.0, 56.2. HR-ESIMS: m/z 265.0832 [M+Na]+ (C19H14NO3+, calculated 265.0835)
(E)-1-(benzyloxy)-2-methoxy-4-(2-nitrovinyl)benzene. To O-benzyl Vanillin (23.6 g, 97.2 mmol) in AcOH (70 ml) was added ammonium acetate (22.5 g, 291 mmol). The solution was purged with argon prior addition of nitromethane (26 ml, 490 mmol) was added. The solution was fitted with a reflux condenser and heated at 60 °C for 6.5 h. The reaction mixture was cooled to room temperature and partitioned between chloroform (300 ml) and water (150 ml). The phases were separated and the aqueous phase was extracted with chloroform (3*50 ml). The combined organic phases were washed with a saturated NaHCO₃ solution. The combined organic phases were dried over sodium sulphate and evaporated to dryness under reduced pressure yielding a yellow solid. The target compound was yielded from recrystallisation using EtOH:CHCl₃ (1:1) in 77% (21.4 g, 75.1 mmol).

1H NMR (400 MHz, Chloroform-d) δ 7.94 (d, J = 13.6 Hz, 1H), 7.51 (d, J = 13.6 Hz, 1H), 7.47 – 7.29 (m, 5H), 7.10 (dd, J = 8.3, 2.1 Hz, 1H), 7.02 (d, J = 2.1 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.22 (s, 2H), 3.93 (s, 3H).

13C NMR (100 MHz, CDCl₃) δ 152.1, 150.2, 139.4, 136.2, 135.4, 128.9, 128.4, 127.3, 124.5, 123.2, 113.6, 110.9, 71.0, 56.3.

HR-ESIMS: m/z 308.0892 [M+Na⁺], calculated 308.0893).

2-(4-(benzyloxy)-3-methoxyphenyl)ethan-1-amine hydrochloride. In an oven dried three necked round bottom flask on ice was drop wise THF (50 ml) added to lithium aluminium hydride (5.4 g, 142 mmol. Via cannulation was (E)-1-(benzyloxy)-2-methoxy-4-(2-nitrovinyl)benzene (10.15 g, 35.6 mmol) added from THF (180 ml) over 15 minutes. The reaction mixture was heated to 60 °C for 2.5 h. The reaction mixture was cooled on ice and quenched via drop wise addition of EtOAc (20 ml) and 2 M disodium tartrate (200 ml). The suspension was stirred for 30 minutes and extracted repeatedly with EtOAc. The combined organic phases were washed with brine and dried over sodium sulphate. The solvents were removed under reduced pressure. The crude was dissolved in MeOH and excess ethereal HCl was added (prepared from 37% HCl (aq) (25 ml, 0.30 mol) to Et₂O (150 ml) and dried over MgSO₄). The solids were filtered off washed with ether and dried under reduced pressure. The crude was recrystallised from MeOH affording the target compound as beige solids in 56% (5.81 g, 19.8 mmol).

1H NMR (400 MHz, MeOH-d₄) δ 7.45 – 7.41 (m, 2H), 7.38 – 7.3 (m, 2H), 7.32 – 7.26 (m, 1H), 6.96 – 6.91 (m, 2H), 6.77 (dd, J = 8.2, 2.1 Hz, 1H), 5.08 (s, 2H), 3.86 (s, 3H), 3.15 (t, J = 7.7 Hz, 2H), 2.90 (t, J = 7.7 Hz, 2H). 13C NMR (101 MHz, MeOD) δ 151.5, 148.7, 138.7, 131.5, 129.4, 128.9, 128.7, 122.1, 116.1, 114.1, 72.2, 56.6, 42.0, 34.2. HR-ESIMS: m/z 258.1485 [M+H]⁺ (C₁₆H₂₀NO₂⁺, calculated 258.1489).

3-Methoxytyramine hydrochloride (2a). To 2-(4-(benzyloxy)-3-methoxyphenyl)ethan-1-aminium (5.81 g, 19.8 mmol) in MeOH (225 ml) purged with argon was added 10% palladium on charcoal (200 mg, 0.19 mmol). A balloon with H₂ ws fitted and the reaction left over night. 1H
NMR indicated complete conversion. The catalyst was filtered off and rinsed with MeOH. The solvents were removed under reduced pressure affording a light yellow solid in 99% (4.00 g, 19.6 mmol). $^1$H NMR (400 MHz, Chloroform-$d$) δ 6.90 (s, 1H), 6.85 – 6.78 (m, 1H), 6.78 – 6.72 (m, 1H), 3.91 (s, 3H), 3.19 (t, $J = 7.7$ Hz, 2H), 2.92 (t, $J = 7.7$ Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 149.4, 146.9, 129.1, 122.3, 116.6, 113.4, 56.5, 42.2, 34.2. HR-ESIMS: $m/z$ 168.1019 [M+H]$^+$ (C$_9$H$_{14}$NO$_2^+$, calculated 168.1019).

1-(4-fluorophenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol. Synthesised in accordance to general BBr$_3$ demethylation. Purification via flash column chromatography using 15-20% MeOH in DCM yielded the target compound (9.5 mg, 0.0315 mmol) as pale yellow solids in 33%. $^1$H NMR (400 MHz, MeOH-$d_4$) δ 7.51 – 7.10 (m, 2H), 7.10 – 6.86 (m, 2H), 6.58 (s, 1H), 6.56 (s, 1H), 3.50 (t, $J = 5.4$ Hz, 1H), 3.24 – 3.15 (m, 1H), 2.74 (dddd, $J = 16.9$, 13.6, 10.0, 6.7 Hz, 4H), 2.58 (ddd, $J = 13.6$, 10.5, 5.3 Hz, 1H), 2.51 (s, 3H), 2.06 (ttdd, $J = 19.9$, 13.9, 10.9, 5.6 Hz, 2H). $^{19}$F NMR (377 MHz, MeOH-$d_4$) δ -121.6. $^{13}$C NMR (101 MHz, MeOD) δ 161.2 (d, $^1$J$_{CF} = 242$ Hz), 143.7, 143.3, 138.1 (d, $^4$J$_{CF} = 3$ Hz), 129.5, (d, $^3$J$_{CF} = 8$ Hz), 127.2, 124.4, 114.7, 114.4 (d, $^2$J$_{CF} = 21$ Hz), 113.3, 62.7, 47.7, 41.1, 36.0, 30.6, 24.4. HR-ESIMS: $m/z$ 302.1553 [M+H]$^+$ (C$_{18}$H$_{21}$FNO$_2^+$, calculated 302.1551)

(E)-1-(4-chlorostyryl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol. Synthesised in accordance to general BBr$_3$ demethylation. Purification via flash column chromatography using 15-20% MeOH in DCM yielded the target compound (3.9 mg, 12.3 µmol) in 12% as Yellow solids. $^1$H NMR (400 MHz, MeOH-$d_4$) δ 7.46 (d, $J = 8.2$ Hz, 2H), 7.35 (d, $J = 8.2$ Hz, 2H), 6.69 (d, $J = 15.7$ Hz, 1H), 6.57 (s, 1H), 6.54 (s, 1H), 6.14 (dd, $J = 15.8$, 8.9 Hz, 1H), 3.91 (d, $J = 8.9$ Hz, 1H), 3.13 (dt, $J = 11.7$, 4.6 Hz, 1H), 2.96 (ddd, $J = 15.6$, 10.0, 5.5 Hz, 1H), 2.76 – 2.58 (m, 2H), 2.47 (s, 3H). $^{13}$C NMR (101 MHz, MeOD) δ 145.6, 144.7, 136.7, 134.4, 134.3, 131.9, 129.8, 129.0, 127.5, 125.9, 116.0, 115.4, 69.7, 52.5, 44.1, 28.8. HR-ESIMS: $m/z$ 316.1099 [M+H]$^+$ (C$_{18}$H$_{19}$ClNO$_2^+$, calculated 316.1099)
1-(4-iodophenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol. Synthesised in accordance to general BBr₃ demethylation. Purification via flash column chromatography using 15-20% MeOH in DCM yielded the target compound (8 mg, 20 µmol) in 57% as off white solids. $^{13}$C NMR (101 MHz, MeOD) δ 143.9, 143.4, 142.0, 137.1, 130.2, 126.9, 124.3, 114.7, 113.3, 89.8, 62.7, 47.7, 41.1, 35.6, 30.9, 24.3. $^1$H NMR (400 MHz, MeOH-d₄) δ 7.63 (d, $J = 8.0$ Hz, 2H), 7.02 (d, $J = 8.0$ Hz, 2H), 6.59 (s, 1H), 6.57 (s, 1H), 3.55 (t, $J = 5.5$ Hz, 1H), 3.28 – 3.19 (m, 1H), 2.87 – 2.65 (m, 4H), 2.59 (dd, $J = 10.3$, 5.2 Hz, 1H), 2.54 (s, 3H), 2.07 (ddddd, $J = 30.9$, 14.0, 10.9, 5.6 Hz, 2H). HR-ESIMS: $m/z$ 410.0611 [M+H]$^+$ (C₁₈H₂₁INO₂$^+$, calculated 410.0612).

1-(4-chlorophenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol. Synthesised in accordance to general BBr₃ demethylation. Purification via flash column chromatography using 15–20% MeOH in DCM yielded the target compound (57 mg, 0.179 mmol) in 49% as yellow solids. $^1$H NMR (400 MHz, MeOH-d₄) δ 7.28 (d, $J = 8.4$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 2H), 6.59 (s, 1H), 6.56 (s, 1H), 3.51 (t, $J = 5.4$ Hz, 1H), 3.27 – 3.16 (m, 1H), 2.74 (ddddd, $J = 16.7$, 13.6, 8.7, 4.2 Hz, 4H), 2.59 (dd, $J = 13.6$, 10.5, 5.3 Hz, 1H), 2.52 (s, 3H), 2.16 – 1.96 (m, 2H). $^{13}$C NMR (101 MHz, MeOD) δ 145.2, 144.8, 142.5, 132.5, 131.0, 129.4, 128.7, 125.9, 116.1, 114.8, 64.1, 49.3, 42.6, 37.3, 32.2, 25.9. HR-ESIMS: $m/z$ 318.1256 [M+H]$^+$ (C₁₈H₂₁ClNO₂$^+$, calculated 318.1255).
Figure S5: Compounds that were inaccessible via general BBr₃ demethylation
(E)-1-(4-chlorostyryl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol (4g). To 3-methoxy-4-hydroxyphenethylamine hydrochloride (549 mg, 2.69 mmol) in EtOH (20 ml) was added 4-Cl-cinnamaldehyde (396 mg, 2.37 mmol) and triethylamine (0.40 ml; 2.87 mmol). The reaction mixture was evaporated to dryness under reduced pressure at 30 0C. The crude was redissolved and the process repeated 2 times. NMR indicated complete consumption of the aldehyde.

To a portion of the preformed imine mixture (292 mg, 0.560 mmol) was TFA (1.0 ml) added. The solution was thoroughly bubbled with argon and heated in a microwave reactor for 3.5 h at 90 0C followed by 1 hour at 100 0C. The pH of the reaction mixture was adjusted to 8-9 using sat. NaHCO3, left to stir for 30 minutes, and the aqueous phase extracted with DCM. The combined organic phases were washed with brine and evaporated to dryness under reduced pressure. Purification via flash column chromatography using 8% MeOH in DCM yielded the target compound as light brown solids in 8% (14 mg, 0.044 mmol). 1H NMR (400 MHz, MeOH-d4) δ 7.46 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 6.73 (s, 1H), 6.65 (d, J = 15.8 Hz, 1H), 6.59 (s, 1H), 6.34 (dd, J = 15.8, 8.1 Hz, 1H), 4.57 (d, J = 8.1 Hz, 1H), 3.86 (s, 3H), 3.28 (dt, J = 11.3, 5.3 Hz, 1H), 3.05 (ddd, J = 12.4, 8.3, 4.9 Hz, 1H), 2.97 – 2.84 (m, 1H), 2.78 (dt, J = 16.2, 5.2 Hz, 1H).

13C NMR (101 MHz, MeOD) δ 148.2, 145.8, 137.0, 134.3, 133.0, 132.9, 129.7, 129.4, 129.0, 126.8, 115.0, 113.1, 60.0, 56.4, 42.3, 29.1. HR-ESIMS: m/z 316.1099 [M+H]+ (C18H19ClNO2, calculated 316.1099)

(E)-6-methoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinolin-7-ol (4f). To 3,4-dimethoxyphenethylamine hydrochloride (549 mg, 2.69 mmol) in EtOH (20 ml) was added 4-Cl-cinnamaldehyde (396 mg, 2.37 mmol) and triethylamine (0.40 ml; 2.87 mmol). The reaction mixture was evaporated to dryness under reduced pressure at 30 0C. The crude was redissolved and the process repeated 2 times. NMR indicated complete consumption of the aldehyde. To a portion of the preformed imine mixture (292 mg, 0.560 mmol) was TFA (1.0 ml) added. The
solution was thoroughly bubbled with argon and heated in a microwave reactor for 15 min at 120 °C. The pH of the reaction mixture was adjusted to 8-9 using sat. NaHCO₃, left to stir for 30 minutes, and the aqueous phase extracted with DCM. The combined organic phases were washed with brine and evaporated to dryness under reduced pressure. The crude was purified using flash column chromatography. Column was performed using 8% MeOH in DCM affording target compound as light brown solids in 52% (95 mg 0.29 mmol). ^1H NMR (400 MHz, Chloroform-d) δ 8.19 – 8.13 (m, 2H), 7.53 – 7.45 (m, 2H), 6.65 (s, 1H), 6.63 (d, J = 16.1 Hz, 1H), 6.61 (s, 1H), 6.49 (dd, J = 15.8, 7.7 Hz, 1H), 4.61 (d, J = 7.6 Hz, 1H), 3.87 (s, 3H), 3.26 (dt, J = 12.1, 5.4 Hz, 1H), 3.08 (ddd, J = 12.3, 7.8, 4.8 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.72 (dt, J = 16.2, 5.2 Hz, 1H). ^13C NMR (101 MHz, CDCl₃) δ 147.1, 145.8, 144.0, 143.5, 137.1, 130.1, 128.7, 127.1, 126.5, 124.1, 113.3, 111.4, 58.9, 56.1, 41.7, 29.3. HR-ESIMS: m/z 327.1339 [M+H]^+ (C₁₈H₁₉N₂O₄^+), calculated 327.1339. >95% HPLC UV purity 230 nm.

(E)-6,7-dimethoxy-1-(4-(trifluoromethyl)styryl)-1,2,3,4-tetrahydroisoquinoline (4e). To 3,4-dimethoxyhenethylamine (220 µl, 1.3 mmol) in Et₂O (1 ml) without a magnetic stirrer bar was added 4-trifluoromethyl-cinnamaldehyde (200 mg, 1.0 mmol). Solvent was removed under reduced pressure at 40 °C at 30 mbar. A small sample was analysed via NMR analysis indicating complete consumption of aldehyde. A magnetic stirrer bar was fitted and TFA (2.0 ml) was added. The reaction mixture was purged with argon and heated in a microwave reactor (120 °C, 60 minutes, FHT). The reaction mixture was basified via addition of aqueous ammonia (10 ml) and diluted with EtOAc (20 ml). The phases were separated and the aqueous phase extracted with EtOAc (3*20 ml). The combined organic phases were washed with brine, dried over sodium sulphate and evaporated to dryness under reduced pressure. Purification via flash column chromatography using 2-5% MeOH in DCM yielded the target compound as yellow solids in 62% (224 mg, 0.616 mmol). ^1H NMR (400 MHz, Chloroform-d) δ 7.57 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 6.65 (s, 1H), 6.61 d, (J = 15.7 Hz, 1H), 6.58 (s, 1H), 6.44 (dd, J = 15.8, 7.7 Hz, 1H), 4.62 (d, J = 7.7 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.27 (dt, J = 12.1, 5.4 Hz, 1H), 3.07 (ddd, J = 12.3, 7.7, 4.8 Hz, 1H), 2.85 (ddd, J = 16.4, 8.0, 5.5 Hz, 1H), 2.73 (dt, J = 16.1, 5.2 Hz, 1H), 1.87 (s, 1H). ^19F NMR (377 MHz, Chloroform-d) δ -62.5. ^13C NMR (101 MHz, CDC₁₃) δ 147.9, 147.3, 140.4 (q, 1JC,F = 1 Hz), 135.0, 130.7, 129.4(q, 2JC,F = 32 Hz), 128.4, 127.2, 126.6, 125.5(q, 3JC,F = 3 Hz), 124.2 (q, 1JC,F = 272 Hz), 112.0, 110.4, 59.0, 56.0, 55.9, 41.5, 29.2. HR-ESIMS: m/z 364.1520 [M+H]^+ (C₂₀H₂₁F₃NO₂^+), calculated 364.1519. >95% HPLC UV purity 230 nm.
(E)-1-(4-chlorostyryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4b). To 3,4-dimethoxyphenethylamine (408 µl, 2.4 mmol) in EtOH (5 ml) without a magnetic stirrer bar was added 4-Cl-cinnamaldehyde (334 mg, 2.0 mmol). The reaction mixture was evaporated to dryness under reduced pressure at 50 °C and subsequently coevaporated with toluene (5 ml). NMR analysis indicated major conversion to the imine. The crude yellow solid was dissolved in TFA (1.22 ml, 16 mmol), purged with argon and heated in a microwave reactor (120 °C, 60 minutes, FHT). The reaction mixture was basified via addition of aqueous ammonia (pH 14) and diluted with EtOAc (20 ml). The phases were separated and the aqueous phase extracted with EtOAc (5*10 ml). The combined organic phases were dried over sodium sulphate and evaporated to dryness under reduced pressure. Purification via flash column chromatography using 6% MeOH in DCM yielded the target compound as orange solids in 73% (480 mg, 1.46 mmol). ¹H NMR (400 MHz, Chloroform-d) δ 7.35 – 7.25 (m, 4H), 6.62 (s, 1H), 6.58 (s, 1H), 6.53 (d, J = 15.8 Hz, 1H), 6.31 (dd, J = 15.8, 7.9 Hz, 1H), 4.58 (d, J = 7.9 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.27 (dt, J = 12.1, 5.4 Hz, 1H), 3.06 (m, 1H), 2.85 (m, 1H), 2.72 (dt, J = 16.1, 5.1 Hz, 1H), 1.98 (broad s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 148.0, 147.4, 135.5, 133.4, 133.0, 131.1, 128.9, 128.7, 127.8, 127.3, 112.0, 110.6, 59.2, 56.2, 56.0, 41.7, 29.3. HR-ESIMS: m/z 330.1256 [M+H]+ (C₂₀H₂₀ClNO₂⁺, calculated 330.1255). >95% HPLC UV purity 230 nm.

(E)-1-(4-fluorostyryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4b). To 3,4-dimethoxyphenethylamine (278 µl, 1.65 mmol) in EtOH (10 ml) without a magnetic stirrer bar was added 4-F-cinnamaldehyde (190 mg, 1.27 mmol). The reaction mixture was evaporated to dryness under reduced pressure at 40 °C at 30 mbar. Toluene (5 ml) was added and the solvent removed under reduced pressure. A magnetic stirrer bar was fitted and TFA (1.5 ml) added. The reaction mixture was purged with argon and heated in a microwave reactor (120 °C, 60 minutes, FHT). The reaction mixture was basified using aqueous ammonia (10 ml) and diluted with EtOAc (20 ml). The phases were separated and the aqueous phase extracted with EtOAc (3*20 ml). The combined organic phases were washed with brine, dried over sodium sulphate and evaporated to
dryness under reduced pressure. Purification via flash column chromatography using 2-5% MeOH in DCM yielded the target compound as pale yellow solids in 46% (183 mg, 0.58 mmol). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.42 – 7.31 (m, 2H), 7.04 – 6.96 (m, 2H), 6.62 (s, 1H), 6.59 (s, 1H), 6.54 (d, \(J = 15.8\) Hz, 1H), 6.25 (dd, \(J = 15.7, 7.9\) Hz, 1H), 4.57 (d, \(J = 7.9\) Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.27 (dt, \(J = 11.3, 5.4\) Hz, 1H), 3.06 (ddd, \(J = 12.3, 7.9, 4.8\) Hz, 1H), 2.90 – 2.79 (m, 1H), 2.71 (dt, \(J = 16.2, 5.2\) Hz, 1H), 1.94 (broad s, 1H). \(^{19}\)F NMR (377 MHz, Chloroform-\(d\)) \(\delta\) -114.5. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.5 (d, \(1\)J\(_{CF}\) = 247 Hz), 148.0, 147.4, 133.2 (d, \(4\)J\(_{CF}\) = 3 Hz), 131.16, 128.95, 132.11, 132.09, 128.1 (d, \(3\)J\(_{CF}\) = 8 Hz), 127.27, 131.16, 128.95, 132.11, 132.09, 128.1 (d, \(3\)J\(_{CF}\) = 8 Hz), 127.27, 115.6 (d, \(2\)J\(_{CF}\) = 22 Hz), 112.04, 110.64, 59.27, 56.17, 56.02, 41.72, 29.34. HR-ESIMS: \(m/z\) 314.1551 [M+H]\(^+\) (C\(_{19}\)H\(_{21}\)FNO\(_2\)^+, calculated 314.1551). >95% HPLC UV purity 230 nm.

(E)-6,7-dimethoxy-1-styryl-1,2,3,4-tetrahydroisoquinoline (4a). To 3,4-dimethoxyohenethylamine (170 µl, 1.0 mmol) in EtOH (5 ml) without a magnetic stirrer bar was added trans-cinnamaldehyde (126 µl, 1.0 mmol). The reaction mixture was evaporated to dryness under reduced pressure and subsequently coevaporated with toluene (5 ml). NMR analysis indicated complete conversion of aldehyde to the imine. A magnetic stirrer bar was fitted, TFA (1.5 ml) was added and the mixture purged with argon and heated in a microwave reactor (120 \(^\circ\)C, 60 minutes, FHT). The reaction mixture was basified using aqueous ammonia (5 ml) and diluted with EtOAc (10 ml). The phases were separated and the aqueous phase extracted with EtOAc (3*10 ml). The combined organic phases were washed with brine, dried over sodium sulphate and evaporated to dryness under reduced pressure. Purification via flash column chromatography using 5.5% MeOH in DCM yielded the target compound as yellow solids in 24% (71 mg, 0.24 mmol). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.29 – 7.24 (m, 2H), 7.21 – 7.15 (m, 2H), 7.13 – 7.07 (m, 1H), 6.48 (s, 1H), 6.47 (s, 1H), 6.46 (d, \(J = 15.8\) Hz, 1H), 6.20 (dd, \(J = 15.7, 8.0\) Hz, 1H), 4.46 (d, \(J = 7.9\) Hz, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 3.15 (dt, \(J = 12.0, 5.4\) Hz, 1H), 2.93 (ddd, \(J = 12.3, 8.0, 4.8\) Hz, 1H), 2.79 – 2.67 (m, 1H), 2.58 (dt, \(J = 16.1, 5.1\) Hz, 1H), 2.19 (broad s, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 148.0, 147.4, 137.0, 132.5, 132.1, 128.9, 128.7, 127.8, 127.1, 126.6, 112.0, 110.6, 59.3, 56.1, 56.0, 41.7, 29.2. HR-ESIMS: \(m/z\) 296.1647 [M+H]\(^+\) (C\(_{19}\)H\(_{22}\)NO\(_2\)^+, calculated 296.1645). 95% HPLC UV purity 230 nm.
(E)-6,7-dimethoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline (4c). To 3,4-dimethoxyohenethylamine (440 µl, 2.6 mmol) in EtOH (10 ml) without a magnetic stirrer bar was added 4-NO2-cinnamaldehyde (354 mg, 2.0 mmol). The reaction mixture was evaporated to dryness under reduced and subsequently coevaporated with toluene (5 ml). NMR analysis indicated complete conversion of aldehyde to the imine. A magnetic stirrer bar was fitted, TFA (1.5 ml) was added and the mixture purged with argon and heated in a microwave reactor (120 °C, 60 minutes, FHT). The reaction mixture was basified via addition of aqueous ammonia (10 ml) and diluted with EtOAc (20 ml). The phases were separated and the aqueous phase extracted with EtOAc (3×20 ml). The combined organic phases were washed with brine and evaporated to dryness under reduced pressure. Purification via flash column chromatography using 5.5% MeOH in DCM yielded the target compound as brown solids in 83% (563 mg, 1.65 mmol). 1H NMR (400 MHz, Chloroform-d) δ 8.21 – 8.14 (m, 2H), 7.55 – 7.49 (m, 2H), 6.64 (d, J = 15.7 Hz, 1H), 6.64 (s, 1H), 6.56 (s, 1H), 6.53 (q, J = 15.7, 7.5 Hz), 4.64 (d, J = 7.5 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.26 (dt, J = 11.7, 5.6 Hz, 1H), 3.08 (ddd, J = 12.2, 7.3, 4.9 Hz, 1H), 2.90 – 2.69 (broad s, 2H). 13C NMR (101 MHz, CDCl3) δ 148.2, 147.5, 147.1, 143.5, 137.4, 130.1, 128.0, 127.4, 127.1, 124.2, 112.2, 110.5, 58.9, 56.2, 56.1, 41.4, 29.3. HR-ESIMS: m/z 341.1498 [M+H]+ (C19H21N2O4+, calculated 314.1496) >95% HPLC UV purity 230 nm.

(R,E)-6,7-dimethoxy-1-(4-nitrostyryl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline. To Pyridine (0.5 ml) was added (above cmpd (O-acetyl mandelic acid salt thereof) (53 mg; 0.10 mmol) and tosyl chloride (29 mg; 0.15 mmol). The reaction was allowed to reach room temperature after 1 hour. The reaction mixture was diluted with EtOAc and washed with water, dilute HCl and saturated NaHCO3. The solvents were removed under reduced pressure and the crude purified via flash column chromatography (DCM) yielding yellow solids in 49% (24 mg, 0.049 mmol). 1H NMR (400 MHz, Chloroform-d) δ 8.17 – 8.09 (m, 2H), 7.69 – 7.62 (m, 2H), 7.40 – 7.33 (m, 2H), 7.20 – 7.12 (m, 2H), 6.54 (d, J = 15.3 Hz, 2H), 6.44 (d, J = 15.9 Hz, 1H), 6.37 (dd, J = 15.8, 5.6 Hz, 1H), 3.91 (dddd, J = 13.5, 6.2, 2.6, 1.0 Hz, 1H), 3.83 (d, J = 2.0 Hz, 6H), 3.35 (ddd, J = 13.5,
11.3, 4.4 Hz, 1H), 2.73 (ddd, \( J = 17.1, 11.3, 6.1 \) Hz, 1H), 2.58 (ddd, \( J = 16.3, 4.5, 2.5 \) Hz, 1H), 2.33 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 148.6, 147.9, 147.2, 143.5, 142.8, 137.8, 133.8, 130.5, 129.7, 127.30, 127.28, 126.0, 125.0, 124.0, 117.1, 110.5, 57.5, 56.2, 56.0, 39.8, 27.5, 21.6. HR-ESIMS: \( m/z \) 517.1404 [M+Na]+ (C\(_{26}\)H\(_{26}\)N\(_{2}\)O\(_{6}\)S\(^{+}\), calculated 517.1404).

**1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (1).** To 1-(4-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (200 mg, 0.58 mmol) in DMF (3 mL) was added a suspension of sodium hydride (58 mg, 1.45 mmol) and ethanethiol (104 \( \mu \)L, 1.45 mmol). The reaction mixture was thoroughly purged with argon and heated to 150 °C for 30 minutes. The reaction mixture was diluted with DCM and washed with water and brine. The organic phase was dried over sodium sulphate and solvents removed under reduced pressure. Purification via flash column chromatography using 7.5% MeOH and 0.6% EtOH in CHCl\(_3\) yielded a 81% 1:1 mix of regioisomers as yellow oil (153 mg, 0.44 mmol). Repeated chromatography (3 additional times) yielded **1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (1)** in 13% as yellow oil (24 mg, 0.072 mmol). Commercial compound was used for biology (Tocris) which had >95% HPLC UV purity 230 nm.

**E)-3-(4-nitrophenyl)acrylaldehyde (3c).** To p-NO\(_2\)-benzaldehyde (2.19 g, 14.5 mmol) under argon, on ice, was added acetaldehyde (6.6 mL, 118 mmol). The vigorously stirred suspension was allowed to reach room temperature and KOH (100 mg, 1.8 mmol) was added from MeOH (0.3 mL). Complete consumption of starting material was indicated using TLC analysis (20% EtOAc in hexanes). To the clear pale yellow solution was added Ac\(_2\)O (4.4 mL, 47 mmol) and the reaction mixture was heated at 120 degrees for one hour. The solution was cooled to room temperature and 1.25 M HCl (20 mL) was added. The reaction mixture was heated to refluxed for 30 minutes and left overnight at room temperature. The solids were filtered off and washed with water. The target compound was recrystallized from EtOH and obtained as yellow solids in 75% (1920 mg, 10.8 mmol). \(^1\)H NMR (400 MHz, Chloroform-\( d \)) \( \delta \) 9.78 (d, \( J = 7.4 \) Hz, 1H), 8.33 – 8.26 (m, 2H), 7.77 – 7.71 (m, 2H), 7.53 (d, \( J = 16.1 \) Hz, 1H), 6.81 (dd, \( J = 16.1, 7.4 \) Hz, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 192.9, 149.1, 149.0, 140.1, 131.9, 129.2, 124.5.
(E)-3-(4-chlorophenyl)acrylaldehyde (3b). To 4-Cl-benzaldehyde (3.09 g, 22 mmol) in MeOH (4.5 ml) on ice was first added acetaldehyde (1 ml, 17.8 mmol) and dropwise aqueous 300 mg/ml KOH (0.2 ml). The reaction mixture was allowed to reach room temperature and kept for 7 h. AcOH (1 ml) was added and the reaction mixture kept for 2 h. The solution was poured into water (50 ml) and extracted with Et₂O (4×25 ml). The combined organic phases were dried over Na₂SO₄ and the solvents removed under reduced pressure. Purification via flash column chromatography using 17% EtOAc in pentanes yielded the target compound in 21% as yellow solids (626 mg, 3.8 mmol). ¹H NMR (400 MHz, Chloroform-d) δ 9.70 (d, J = 7.6 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.42 (d, J = 16.0 Hz, 1H), 7.43 – 7.38 (m, 2H), f 6.68 (dd, J = 16.0, 7.6 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 193.4, 151.1, 137.4, 132.6, 129.7, 129.6, 129.1.

Chiral resolution

Chiral resolution of (R)- and (S)-1 was achieved successfully via co-crystallisation as diastereomeric salts with (R) and (S)-O-acetylmandelic acid, respectively. The absolute configuration was determined using X-ray⁶ diffraction on p-toluenesulfonyl amide 7a, synthesised to ease crystallisation. The enantiomerically pure derivatives of 1 were synthesised analogously via intermediates 5c and 6b (R and S) affording both enantiomers of 1 (R and S). Attempts aimed at chiral resolution using tartaric acid and 4c were unsuccessful likewise was attempts of chiral resolution using 4f and O-acetylmandelic acid.

![Chiral resolution diagram](image)

Figure S6: Synthetic strategy for a chiral resolution of 4c using co-crystallisation with (R)-O-acetylmandelic acid followed by a N-p-toluenesulfonyl conjugation, crystallisation and X-ray analysis of 7a.⁶

(R,E)-6,7-dimethoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline (same enantiomer as the compound used for X-ray analysis). To (E)-6,7-dimethoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline (1.33 g, 3.90 mmol) was added (R)-(−)-O-Acetylmandelic acid (794 mg,
4.09 mmol) and acetonitrile (56 ml). The reaction mixture was heated to reflux until clear. The reaction mixture was kept in room temperature for 2 days and the solvents removed with a needle fitted syringe. The solids were washed with cold acetonitrile affording pale yellow solids in 24% (493 mg, 0.92 mmol). The supernatant was evaporated to dryness and submitted to one more recrystallisation using a minimum amount of acetonitrile affording 12% more of target compound (257 mg, 0.481 mmol) adding up to 36% yield (750 mg (1.40 mmol). 1H NMR (400 MHz, Chloroform-d) δ 9.41 (broad s, 2H), 8.14 – 8.06 (m, 2H), 7.46 – 7.39 (m, 2H), 7.25 – 7.13 (m, 6H), 6.59 (s, 1H) 6.54 (d, J = 15.8 Hz, 2H), 6.39 (s, 1H), 6.35 (dd, 7.7, 15.8 Hz, 2H), 5.56 (s, 1H), 4.79 (d, J = 7.6 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.11 – 3.02 (m, 1H), 2.98 – 2.80 (m, 2H), 2.75 – 2.65 (m, 1H), 2.08 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 174.28, 170.86, 149.10, 148.18, 147.52, 142.19, 136.65, 135.10, 130.59, 128.40, 128.28, 127.88, 127.51, 124.80, 124.00, 122.71, 111.54, 110.21, 77.23, 56.69, 56.21, 56.11, 39.39, 25.43, 21.25. HR-ESIMS: m/z 341.1495 [M+H]+ (C19H21N2O4+, calculated 341.1496). α=−6.3 (2.3 mg)

(S,E)-6,7-dimethoxy-1-(4-nitrostyril)-1,2,3,4-tetrahydroisoquinoline. To (E)-6,7-dimethoxy-1-(4-nitrostyril)-1,2,3,4-tetrahydroisoquinoline (3.00 g, 8.81 mmol) was added (S)-(+) -O-Acetylmandelic acid (1.80 g, 9.25 mmol) and acetonitrile (127 ml). The reaction mixture was heated to reflux until clear. The reaction mixture was kept in room temperature for 2 days and the solvents removed with a needle fitted syringe. The solids were washed with cold acetonitrile affording pale yellow solids in 22% (1026 mg, 1.92 mmol). The supernatant was evaporated to dryness and submitted to one more recrystallisation using a minimum amount of acetonitrile affording 10% (457 mg, 0.855 mmol) adding up to 31% (1483 mg, 2.77 mmol). 1H NMR (400 MHz, Chloroform-d) δ 9.41 (broad s, 2H), 8.14 – 8.06 (m, 2H), 7.46 – 7.39 (m, 2H), 7.25 – 7.13 (m, 6H), 6.59 (s, 1H) 6.54 (d, J = 15.8 Hz, 2H), 6.39 (s, 1H), 6.35 (dd, 7.7, 15.8 Hz, 2H), 5.56 (s, 1H), 4.79 (d, J = 7.6 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 3.11 – 3.02 (m, 1H), 2.98 – 2.80 (m, 2H), 2.75 – 2.65 (m, 1H), 2.08 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 174.27, 170.85, 149.05, 148.15, 147.49, 142.23, 136.65, 134.95, 130.80, 128.40, 128.28, 127.87, 127.51, 124.88, 124.00, 122.71, 111.53, 110.19, 77.36, 56.75, 56.20, 56.11, 39.45, 25.43, 21.25. HR-ESIMS: m/z 341.1495 [M+H]+ (C19H21N2O4+, calculated 341.1496). α=3.6 (5.9 mg)
Enantiomerically enriched compounds were synthesized in accordance to the racemic analogue.

(R,E)-6,7-dimethoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline (5c).

*Synthesised in accordance to general reductive amination.* Flash column purification yielded the target compound in 96% yield (758 mg, 2.14 mmol) as fluffy yellow solids. $^1$H NMR (400 MHz, Chloroform- $d$) $\delta$ 8.22 – 8.14 (m, 2H), 7.58 – 7.49 (m, 2H), 6.68 (d, $J$ = 15.9 Hz, 1H), 6.63 (s, 1H), 6.54 (s, 1H), 6.35 (dd, $J$ = 15.9, 8.7 Hz, 1H), 3.91 (d, $J$ = 8.6 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.08 (ddd, $J$ = 11.2, 5.3, 4.0 Hz, 1H), 3.05 – 2.95 (m, 1H), 2.74 (dt, $J$ = 16.0, 4.1 Hz, 1H), 2.60 (ddd, $J$ = 11.2, 9.4, 4.2 Hz, 1H), 2.47 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 148.00, 147.30, 146.98, 143.15, 136.92, 130.83, 127.16, 126.93, 126.70, 124.06, 111.51, 110.84, 68.05, 56.06, 55.88, 50.92, 44.13, 28.64. HR-ESIMS: $m/z$ 355.1652 [M+H]$^+$ (C$_{20}$H$_{23}$N$_2$O$_4^+$, calculated 355.1652). $\alpha$ = 2.5 (4.5 mg).

(R)-4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl)aniline (6e).

*Synthesised in accordance to general hydrogenation.* Flash column purification yielded the target compound in 56% yield (398 mg, 1.20 mmol) as yellow oil. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.00 – 6.95 (m, 2H), 6.64 – 6.59 (m, 2H), 6.57 (s, 1H), 6.54 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.53 (d, $J$ = 53.2 Hz, 1H), 3.42 (t, $J$ = 5.5 Hz, 2H), 3.21 – 3.10 (m, 1H), 2.83 – 2.60 (m, 4H), 2.53 – 2.43 (m, 4H), 2.08 – 1.95 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 147.40, 147.36, 144.21, 132.94, 130.04, 129.29, 126.67, 115.36, 111.45, 110.30, 62.78, 56.12, 55.92, 48.14, 42.69, 37.22, 30.90, 25.47. HR-ESIMS: $m/z$ 327.2067 [M+H]$^+$ (C$_{20}$H$_{27}$N$_2$O$_2^+$, calculated 327.2067). $\alpha$ = -0.9 (23.8 mg).
(R)-1-(4-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline  (1).

Synthesised in accordance to general sandmeyer CuCl. Flash column purification yielded the target compound in 38% yield (10 mg, 0.0269 mmol) as yellow oil. $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.24 – 7.20 (m, 2H), 7.12 – 7.08 (m, 2H), 6.57 (s, 1H), 6.52 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.41 (t, $J$ = 5.4 Hz, 1H), 3.17 – 3.09 (m, 1H), 2.80 – 2.66 (m, 4H), 2.52 (dt, $J$ = 14.5, 7.7 Hz, 1H), 2.47 (s, 3H), 2.02 (td, $J$ = 8.2, 5.6 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 147.54, 147.51, 141.55, 131.42, 129.95, 129.73, 128.50, 126.99, 111.53, 110.19, 62.79, 56.21, 55.99, 48.33, 42.86, 36.97, 31.02, 25.65. HR-ESIMS: $m/z$ 346.1568 [M+H]$^+$ (C$_{20}$H$_{25}$ClNO$_2$, calculated 346.1568). $\alpha$=1.1 (3.2 mg)

(S,E)-6,7-dimethoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline  (5b).

Synthesised in accordance to general reductive amination. Flash column purification yielded the target compound in 99% yield (970 mg, 2.74 mmol) as yellow fluffy solids. $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 8.21 – 8.15 (m, 2H), 7.57 – 7.52 (m, 2H), 6.68 (d, $J$ = 15.8 Hz, 1H), 6.63 (s, 1H), 6.54 (s, 1H), 6.35 (dd, $J$ = 15.9, 8.7 Hz, 1H), 3.91 (d, $J$ = 8.6 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.09 (ddd, $J$ = 11.2, 5.3, 4.0 Hz, 1H), 3.05 – 2.95 (m, 1H), 2.74 (dt, $J$ = 16.1, 4.1 Hz, 1H), 2.60 (ddd, $J$ = 11.2, 9.4, 4.2 Hz, 1H), 2.47 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 148.15, 147.44, 147.13, 143.29, 137.09, 130.97, 127.31, 127.08, 126.85, 124.22, 111.65, 110.98, 68.22, 56.21, 56.04, 51.08, 44.29, 28.80. HR-ESIMS: $m/z$ 355.1652 [M+H]$^+$ (C$_{20}$H$_{23}$N$_2$O$_4$, calculated 355.1652). $\alpha$=3.6 (5.9 mg).
(S)-4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl)aniline  (6e).

*Synthesised in accordance to general hydrogenation.* Flash column purification yielded the target compound in 69% yield (625 mg, 1.88 mmol) as yellow oil. $^1$H NMR (400 MHz, Chloroform- $d$) $\delta$ 7.02 – 6.96 (m, 2H), 6.65 – 6.60 (m, 2H), 6.58 (s, 1H), 6.49 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.60 (t, $J = 5.7$ Hz, 1H), 3.32 – 3.22 (m, 1H), 2.94 – 2.80 (m, 2H), 2.75 (dt, $J = 17.4$, 6.4 Hz, 1H), 2.71 – 2.63 (m, 1H), 2.57 (dt, $J = 9.4$, 4.8 Hz, 1H), 2.53 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 147.88, 147.59, 144.38, 132.12, 129.37, 128.17, 125.14, 115.49, 111.43, 110.40, 62.59, 56.14, 55.97, 46.85, 41.63, 36.96, 31.30, 24.37. HR-ESIMS: $m/z$ 327.2067 [M+H]$^+$ (C$_{20}$H$_{27}$N$_2$O$_2$, calculated 327.2067). $\alpha$=1.0 (11.4 mg)

(S)-1-(4-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline  (6b).

*Synthesised in accordance to general sandmeyer CuCl.* Flash column purification yielded the target compound in 59% yield (184 mg, 0.532 mmol) as yellow oil. $^1$H NMR (400 MHz, Chloroform- $d$) $\delta$ 7.25 – 7.20 (m, 2H), 7.13 – 7.08 (m, 2H), 6.57 (s, 1H), 6.52 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.41 (t, $J = 5.4$ Hz, 1H), 3.18 – 3.09 (m, 1H), 2.80 – 2.65 (m, 4H), 2.52 (dt, $J = 13.2$, 7.0 Hz, 1H), 2.47 (s, 3H), 2.02 (td, $J = 8.2$, 5.5 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 147.50, 147.47, 141.54, 131.40, 129.94, 129.70, 128.49, 126.96, 111.47, 110.12, 62.77, 56.18, 55.97, 48.31, 42.86, 36.96, 31.00, 25.62. HR-ESIMS: $m/z$ 346.1568 [M+H]$^+$ (C$_{20}$H$_{25}$ClNO$_2$, calculated 346.1568). $\alpha$=1.6 (7.2 mg)

(S)-1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol  (1).

*Synthesised in accordance to racemic analogue* yielded 71% of a 1:1 mix of regioisomers as yellow oil (118 mg, 0.36 mmol). Repeated chromatography yielded (S)-1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (1), in 6% as yellow oil (10 mg, 0.030 mmol). $^1$H NMR (400 MHz, Chloroform- $d$) $\delta$ 7.25 – 7.20 (m, 2H), 7.14 – 7.07 (m, 2H), 6.64 (s, 1H), 6.48 (s, 1H), 3.83 (s, 3H), 3.40 (t, $J = 5.6$ Hz, 1H), 3.16 – 3.10 (m, 1H), 2.76 – 2.65 (m, 4H), 2.54 (ddd, $J = 14.1$, 9.1, 6.0 Hz, 1H), 2.46 (s, 3H), 2.06 – 1.96 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 145.21, 143.99, 141.53, 131.40, 129.95, 128.49, 127.60, 125.75, 114.36, 109.34, 62.82, 56.17, 48.06, 42.75, 37.12, 31.08, 25.22. HR-ESIMS: $m/z$ 332.1412 [M+H]$^+$ (C$_{19}$H$_{23}$ClNO$_2$, calculated 332.1412).
calculated 332.1412) α = -0.1 (4.2 mg). >95% HPLC UV purity 230 nm. NMR reveal <5% of the constitutional isomer.

(R)-1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (1)  
Synthesised in accordance to racemic analogue yielded 80% of a 1:1 mix of regioisomers as yellow oil (77 mg, 0.23 mmol). Repeated chromatography yielded (R)-1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (1). in 9% as yellow oil (9 mg, 0.027 mmol).  

Open chain analogues

4-(2-((3-((4-aminophenyl)propyl)amino)ethyl)-2-methoxyphenol. Synthesised in accordance to general hydrogenation. Purification via flash column chromatography using 8-15% MeOH in DCM yielded the target compound (64 mg, 0.20 mmol) in 71% as pale yellow oil.  

1H NMR (400 MHz, MeOH- d4) δ 6.96 – 6.91 (m, 2H), 6.76 (d, J = 2.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.69 – 6.64 (m, 2H), 6.61 (dd, J = 8.0, 2.0 Hz, 1H), 3.81 (s, 3H), 2.70 – 2.67 (m, 4H), 2.57 – 2.45 (m, 4H), 2.37 (s, 3H), 1.83 – 1.72 (m, 2H).  

13C NMR (101 MHz, MeOD) δ 149.0, 146.4, 146.0, 132.5, 132.0, 130.0, 122.1, 116.9, 116.3, 113.3, 60.2, 57.6, 56.4, 42.0, 33.6, 33.1, 29.2. HR-ESIMS: m/z 315.2068 [M+H]+ (C19H27N3O2+), calculated 315.2067)
(E)-2-methoxy-4-(2-((3-(4-nitrophenyl)allyl)amino)ethyl)phenol and 2-methoxy-4-(2-((3-(4-nitrophenyl)propyl)amino)ethyl)phenol. To imine synthesised in accordance to general imine formation (165 mg, 0.504 mmol) in 10:1 dichloroethane:MeOH (11 ml) was added sodium borohydride (38 mg, 1.0 mmol) and left to stir for 1 hour at room temperature. The reaction mixture was quenched with sat. NaHCO₃ and diluted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc the combined organic phases were washed with brine, dried over sodium sulfate and evaporated to dryness under reduced pressure. Purification via flash column chromatography using 8-12% MeOH in DCM yielded (E)-2-methoxy-4-(2-((3-(4-nitrophenyl)allyl)amino)ethyl)phenol in 32% (53 mg, 0.16 mmol) as yellow solids.

**1H NMR** (400 MHz, MeOH-d₄) δ 8.18 – 8.12 (m, 2H), 7.61 – 7.55 (m, 2H), 6.79 (d, J = 1.9 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.69 – 6.60 (m, 2H), 6.51 (d, J = 16.0, 6.3 Hz, 1H), 3.81 (s, 3H), 3.44 (dd, J = 6.3, 1.3 Hz, 2H), 2.85 (t, J = 7.7 Hz, 2H), 2.75 (t, J = 7.7 Hz, 2H). **13C NMR** (101 MHz, MeOD) δ 149.0, 148.2, 146.1, 144.9, 133.3, 132.2, 131.3, 128.1, 124.9, 122.1, 116.3, 113.3, 56.3, 51.9, 51.6, 36.2. HR-ESIMS: m/z 329.1495 [M+H]+ (C₁₈H₂₁N₂O₂⁺, calculated 329.1495) and 2-methoxy-4-(2-((3-(4-nitrophenyl)propyl)amino)ethyl)phenol in 5% (8 mg, 0.024 mmol) as brown solids. **1H NMR** (400 MHz, MeOH-d₄) δ 8.17 – 8.11 (m, 2H), 7.44 – 7.39 (m, 2H), 6.79 (d, J = 1.9 Hz, 1H), 6.72 (d, J = 7.4 Hz, 2H), 2.81 – 2.66 (m, 6H), 1.94 – 1.84 (m, 2H). **13C NMR** (101 MHz, MeOD) δ 151.0, 149.1, 147.8, 146.3, 131.5, 130.5, 124.6, 122.1, 116.3, 113.3, 56.4, 51.7, 49.4, 35.5, 34.0, 30.8. HR-ESIMS: m/z 331.1652 [M+H]+ (C₁₈H₂₃N₂O₄⁺, calculated 331.1652)

(E)-2-methoxy-4-(2-(methyl(3-(4-nitrophenyl)allyl)amino)ethyl)phenol. Synthesised in accordance to general reductive amination. Purification via flash column chromatography using 6% MeOH in DCM yielded the target compound in 92% (110 mg, 0.32 mmol) as brown solids. **1H NMR** (400 MHz, MeOH-d₄) δ 8.25 – 8.18 (m, 2H), 7.69 – 7.61 (m, 2H), 6.81 (d, J = 2.0 Hz, 1H), 6.76 – 6.65 (m, 3H), 6.62 – 6.52 (m, 1H), 3.83 (s, 3H), 2.82 – 2.75 (m, 2H), 2.75 – 2.66 (m, 2H), 2.41 (s, 3H). **13C NMR** (101 MHz, MeOD) δ 148.9, 148.3, 145.9, 144.8, 132.73, 132.72,
To 3-Methoxytyramine hydrochloride (143 mg, 0.70 mmol) in anhydrous MeOH (5 ml) was added 4-F-trans-cinnamaldehyde (105 mg, 0.70 mmol), triethylamine (98 µl, 0.70 mmol) and MgSO$_4$ (1.4 mmol, 169 mg) and left to stir overnight. The solids were filtered off through celite and diluted with dichloroethane (3 ml). On ice was added sodium borohydride (79 mg, 0.21 mmol, allowed to reach room temperature and kept for 30 minutes. The reaction mixture was quenched with sat. NaHCO$_3$ and diluted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate and evaporated to dryness under reduced pressure. Purification via flash column chromatography using 8-12% MeOH in DCM yielded the target compounds in 60% (127 mg, 0.42 mmol) as dark orange oil. $^1$H NMR (400 MHz, MeOH-d$_4$) $\delta$ 7.42 – 7.36 (m, 2H), 7.05 – 6.97 (m, 2H), 6.79 (d, $J = 1.9$ Hz, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 6.65 (d, $J = 8.0$ Hz), 6.53 (d, $J = 15.8$ Hz, 1H), 6.20 (dt, $J = 16.0$, 6.6 Hz, 1H), 3.81 (s, 3H), 3.40 (d, $J = 6.6$ Hz, 2H), 2.87 (t, $J = 7.2$ Hz, 2H), 2.75 (t, $J = 7.4$ Hz, 2H). $^{19}$F NMR (377 MHz, MeOD) $\delta$ -118.3. $^{13}$C NMR (101 MHz, MeOD) $\delta$ 162.2 (d, $^1$J$_{CF} = 246$ Hz), 147.6, 144.7, 133.2 (d, $^4$J$_{CF} = 3$ Hz), 131.4, 130.6, 127.7 (d, $^3$J$_{CF} = 8$ Hz), 125.7 (d, $^5$J$_{CF} = 3$ Hz), 120.7, 114.9, 114.8 (d, $^2$J$_{CF} = 22$ Hz), 111.9, 54.9, 50.5, 49.9, 34.5. HR-ESIMS: m/z 302.1551 [M+H]$^+$ (C$_{18}$H$_{21}$FNO$_2^+$, calculated 302.1551)
113.4, 59.9, 57.4, 56.4, 41.7, 33.5, 32.7, 28.5. **HR-ESIMS:** m/z 334.1569 [M+H]+ (C_{19}H_{25}ClNO_{2}^+, calculated 334.1568)

![Chemical structure](image)

**HR-ESIMS:** m/z 334.1569 [M+H]+ (C_{19}H_{25}ClNO_{2}^+, calculated 334.1568)

**(E)-4-(2-((3-(4-chlorophenyl)allyl)(methyl)amino)ethyl)-2-methoxyphenol.** *Synthesised in accordance to general reductive amination.* Purification via flash column chromatography using 8-15% MeOH in DCM yielded the target compound in 100% (22 mg, 0.066) as pale yellow oil. 

**1H NMR (400 MHz, MeOH-d_4)** δ 7.41 – 7.35 (m, 2H), 7.32 – 7.28 (m, 2H), 6.76 (d, J = 1.9 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.63 (dd, J = 8.0, 2.0 Hz, 1H), 6.56 (d, J = 15.7 Hz, 1H), 6.29 (dt, J = 15.9, 6.9 Hz, 1H), 3.79 (s, 3H), 3.27 (dd, J = 7.0, 1.4 Hz, 2H), 2.78 – 2.72 (m, 2H), 2.70 – 2.64 (m, 2H), 2.37 (s, 3H). 

**13C NMR (101 MHz, MeOD)** δ 149.0, 145.9, 136.9, 134.3, 133.9, 132.6, 129.7, 128.9, 127.4, 122.1, 116.2, 113.4, 60.5, 60.1, 56.3, 42.2, 33.7. 

**HR-ESIMS:** m/z 332.1412 [M+H]+ (C_{19}H_{23}ClNO_{2}^+, calculated 332.1412)

![Chemical structure](image)

**HR-ESIMS:** m/z 332.1412 [M+H]+ (C_{19}H_{23}ClNO_{2}^+, calculated 332.1412)

**(E)-4-(2-((3-(4-chlorophenyl)allyl)(methyl)amino)ethyl)-2-methoxyphenol.** To imine *synthesised in accordance to general imine formation* (100 mg, 0.1947 mmol) in 1:1 dichloroethane:MeOH (4 ml) was added on ice sodium borohydride (22 mg, 0.58 mmol) and allowed to reach room temperature and kept for 1 hour. The reaction mixture was quenched with sat. NaHCO_3 and diluted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc the combined organic phases were washed with brine, dried over sodium sulfate and evaporated to dryness under reduced pressure. Purification via flash column chromatography using 8-15% MeOH in DCM yielded the target compounds in 34% (21 mg, 0.066 mmol) as pale yellow solids. 

**1H NMR (400 MHz, MeOH-d_4)** δ 7.44 – 7.38 (m, 2H), 7.36 – 7.30 (m, 2H), 6.83 (d, J = 1.9 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.69 (dd, J = 8.0, 1.9 Hz, 1H), 6.59 (d, J = 15.9 Hz, 1H), 6.31 (dt, J = 15.7, 6.6 Hz, 1H), 3.85 (s, 3H), 3.48 (d, J = 6.6 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 2.80 (t, J = 7.4 Hz, 2H). 

**13C NMR (101 MHz, MeOD)** δ 149.1, 146.2, 136.9, 134.3, 133.1, 131.8, 129.7, 128.9, 127.8, 122.2, 116.3, 113.3, 60.5, 60.1, 56.3, 42.2, 33.7. **HR-ESIMS:** m/z 318.1255 [M+H]+ (C_{18}H_{21}ClNO_{2}^+, calculated 318.1255)
Pictet Spengler optimisation

Literature data suggest that electron rich cinnamic aldehydes produce low yields in combination with moderately activated phenethylamines (dimethylamino cinnamic aldehyde)\(^7\) which was in line with our findings in Table S5. Attempts cyclising cinnamic aldehyde and 3,4-dimethoxy phenethyl amine produced either complex reaction mixtures (formic acid reflux) or no yield refluxing TFA or pTsOH in refluxing PhMe. Following a Pictet-Spengler protocol described for aryl aldehydes,\(^8\) heating trans-cinnamaldehydes and 3,4-dimethoxyphenethylamine in TFA at 140 °C in a microwave reactor for 30 minutes produced low yield (14%) and a complicated reaction mixture. Decreasing the temperature to 120 °C and heating for 30 minutes showed unreacted starting materials on TLC analysis (data not shown), 60 minutes afforded 24% yield (Table S5 entry 5), enough to produce the desired compounds. Both neat TFA and TFA/PhMe mixtures produced comparable results, TFA was chosen as reaction solvent due to superior solubility properties. Increasing the reaction time and reducing the temperature increased the yield to a satisfactory 24%. The cyclisation reaction for the more activated p-Cl aldehyde analogue improved the yield to 36%. This is likely owing to a Meisenheimer transition complex intermediate. After observing that unreacted aldehyde (41%) was present after heating in TFA the reaction was further optimised by adding extra amine equivalents (0.2 – 0.3 eq.) thus enhancing the yield to 73% (Table S5 entry 7). Comparable satisfactory yields 83%, 46% and 62% were achieved for the p-NO\(_2\), p-F and p-CF\(_3\) substrates under standard conditions. Preliminary results performing the cyclisation reaction with N-methylated phenethylamines were unsuccessful (data not shown).

Table S5: Yields are isolated yields on 1-2 mmol scale. a = degradation, comp. mix, b = 41% aldehyde recovered

| Entry | Temp (°C) | Time | Heating | Acid     | R | Aldehyde:amine | Yield |
|-------|-----------|------|---------|----------|---|----------------|-------|
| 1     | 101       | 7h   | -       | COOH     | H | 1:1            | 0%\(^a\) |
| 2     | 72        | 4h   | -       | TFA      | H | 1:1            | 0%    |
| 3     | 111       | 4h   | -       | p-TsOH/PhMe | H | 1:1            | 0%    |
| 4     | 140       | 30 min | mw   | TFA      | H | 1:1            | 14%   |
| 5     | 120       | 60 min | mw   | TFA      | H | 1:1            | 24%   |
| 6     | 120       | 60 min | mw   | TFA      | Cl| 1:1            | 36%\(^b\) |
| 7     | 120       | 60 min | mw   | TFA      | Cl| 1:1.2          | 73%   |
| 8     | 120       | 60 min | mw   | TFA      | NO\(_2\)| 1:1.2          | 83%   |
| 9     | 120       | 60 min | mw   | TFA      | F | 1:1.3          | 46%   |
| 10    | 120       | 60 min | mw   | TFA      | CF\(_3\)| 1:1.3          | 62%   |
3-Methoxytyramine hydrochloride was conveniently prepared in excellent yields on gram scale avoiding the need of flash column chromatography via an improved literature protocol.9

Scheme XX: a) EtOH, K$_2$CO$_3$, BnBr b) MeNO$_2$, NH$_4$OAc, AcOH c) i) LAH, THF d) i) H$_2$ Pd(C) ii) Ethereal HCl

However constructing the desmethylated THIQ analogues proved more challenging. Initial attempts replicating the already developed conditions using the p-Cl analogue (Table S6 entry 1) gave 6% isolated yield compared to 36% for the guaiacol analogue and difficult to purify reaction mixture. As expected the guaiacol scaffold proved more sensitive than the veratrole scaffold but did not noticeably activate it for the P.S. ring closing reaction. Contrary to above, extra equivalents of aldehyde did not improve the conversion but resulted in complex reaction mixtures.

Attempts to perform the reaction under milder conditions by heating the isolated HCl salt of the corresponding imine in dry toluene at 120 °C were unfruitful likewise masking of the guaiacol phenol as a benzylether resulted in complex mixtures. Performing the reaction at lower temperatures to reduce degradation afforded even lower yields and higher temperatures resulted in complex mixtures. Reduction of time did not afford complete consumption of imine (data not shown). The p-Cl analogue was therefore assumed to be more easily available from a sandmeyer type reaction starting from the reduced p-NO$_2$ analogue. The more activated p-NO$_2$ aldehyde on the other hand afforded acceptable yields starting from the purified imine. The reaction was found to be completed after only 15 minutes. Attempts to perform the reaction at under ambient pressure at reflux using conventional heating gave low yield (6%, Table S6 entry 5).

Table S6: Ratio of amine to aldehyde was 1:1. a = precipitated imine was used as starting material; b = complex reaction mixture.

| Entry | temp | min | mw | solvent | Substrate | yield |
|-------|------|-----|----|---------|-----------|-------|
| 1     | 120  | 60  | yes| TFA     | X=OH, R= Cl | 6 %   |
| 2     | 110  | 60  | yes| TFA     | X=OH, R= Cl | 5 %   |
| 3     | 100  | 60  | yes| TFA     | X=OH, R= Cl | traces |
| 4     | 140  | 60  | yes| TFA     | X=OH, R= Cl | 0%$^b$ |
| 5     | 72   | 180 | no | TFA     | X=OH, R= NO$_2$$^a$ | 6 % |
|  |  |  |  |  |  |  |
|---|---|---|---|---|---|
| 6 | 120 | 15 | yes | TFA | X=OH, R= NO$_2^a$ | 59 % |
| 7 | 120 | 20 | yes | TFA | X=OH, R= NO$_2^a$ | 49 % |
Autoradiography

Figure S7: Autoradiographic image over rat brain using $[^3\text{H}]$Ro 04-5595 (25 nM, 4kBq) and (left = 5mM ZnCl$_2$, right = control), 50 mM TRIS-HCl pH 7.4. 5 + 5 Minutes washing at 0 degrees in buffer followed by a dip in deionised water.

Figure S8: Autoradiographic image over rat brain using $[^3\text{H}]$Ro 04-5595 (25 nM, 4kBq top and bottom 1000 nM, 4kBq), 50 mM TRIS-HCl pH 7.4. 5 + 5 Minutes washing at 0 degrees in buffer followed by a dip in deionised water.
Figure S9 $^1$H-NMR 4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl)aniline

Figure S10 $^{13}$C-NMR 4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl)aniline
Figure S11 $^1$H-NMR (E)-1-(4-aminostyryl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S12 $^{13}$C-NMR (E)-1-(4-aminostyryl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S13: $^{13}$C-NMR: 1-(4-aminophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S14: $^{13}$C-NMR: 1-(4-aminophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S15: $^1$H-NMR: 1-(4-fluorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

Figure S16: $^{13}$C-NMR: 1-(4-fluorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline
Figure S17: $^{19}$F-NMR: 1-(4-fluorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

Figure S18: $^1$H-NMR: 6,7-dimethoxy-2-methyl-1-(4-(trifluoromethyl)phenethyl)-1,2,3,4-tetrahydroisoquinoline
Figure S19: $^1^3$C-NMR: 6,7-dimethoxy-2-methyl-1-(4-(trifluoromethyl)phenethyl)-1,2,3,4-tetrahydroisoquinoline

Figure S20: $^{1^9}$F-NMR: 6,7-dimethoxy-2-methyl-1-(4-(trifluoromethyl)phenethyl)-1,2,3,4-tetrahydroisoquinoline
Figure S21: $^1$H-NMR: 1-(4-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

Figure S22: $^{13}$C-NMR: 1-(4-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline
Figure S23: $^1$H-NMR: 6-methoxy-1-phenethyl-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S24: $^{13}$C-NMR: 6-methoxy-1-phenethyl-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S25: $^1$H-NMR: 1-(4-chlorophenethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S26: $^{13}$C-NMR: 1-(4-chlorophenethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S27: $^1$H-NMR: (E)-4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)vinyl)aniline

Figure S28: $^1$H-NMR: (E)-4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)vinyl)aniline
Figure S29: $^{13}$C-NMR: (E)-4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)vinyl)aniline

Figure S30: $^1$H-NMR: (E)-6,7-dimethoxy-2-methyl-1-(4-(trifluoromethyl)styryl)-1,2,3,4-tetrahydroisoquinoline
Figure S31: $^{13}$C-NMR: (E)-6,7-dimethoxy-2-methyl-1-(4-(trifluoromethyl)styryl)-1,2,3,4-tetrahydroisoquinoline

Figure S32: $^{19}$F-NMR: (E)-6,7-dimethoxy-2-methyl-1-(4-(trifluoromethyl)styryl)-1,2,3,4-tetrahydroisoquinoline
Figure S33: ^1^H-NMR: (E)-1-(4-chlorostyryl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

Figure S34: ^13^C-NMR: (E)-1-(4-chlorostyryl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline
Figure S35: $^1$H-NMR: (E)-6,7-dimethoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline

Figure S36: $^{13}$C-NMR: (E)-6,7-dimethoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline
Figure S37: $^1$H-NMR: (E)-1-(4-fluorostyryl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

Figure S38: $^{13}$C-NMR: (E)-1-(4-fluorostyryl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline
Figure S39: $^{19}$F-NMR: (E)-1-(4-fluorostyryl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

Figure S40: $^1$H-NMR: (E)-1-(4-iodostyryl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline
Figure S41: $^{13}$C-NMR: (E)-1-(4-iodostyryl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

Figure S42: $^1$H-NMR: (E)-6-methoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S43: $^{13}$C-NMR: (E)-6-methoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S44: $^1$H-NMR: (E)-1-(4-chlorostyryl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S45: $^{13}$C-NMR: (E)-1-(4-chlorostyryl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S46: $^1$H-NMR: 6-methoxy-2-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S47: $^{13}$C-NMR: 6-methoxy-2-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S48: $^1$H-NMR: 1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S49: $^{13}$C-NMR: 1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S50: HSQC NMR for 1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol, synthesised via desymmetrisation.
Figure S51: HMBC NMR for 1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol, synthesised via desymmetrisation. Note how H8 couples to C1 and H5 couples to C4.
Figure S52: HMBC NMR for 1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol, synthesised via desymmetrisation. Protons H5 and -OCH3 couple to the same carbon (C6) and not to C7.
Figure S53: $^1$H-NMR: 1-(4-iodophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

Figure S54: $^1$H-NMR: 1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S55: $^{13}$C-NMR: 1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S56: $^{13}$C-NMR: 1-(4-iodophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline
Figure S57: $^1$H-NMR: 6,7-dimethoxy-2-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinoline

Figure S58: $^{13}$C-NMR: 6,7-dimethoxy-2-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinoline
Figure S59: $^1$H-NMR: 4-(benzyloxy)-3-methoxybenzaldehyde

Figure S60: $^{13}$C-NMR: 4-(benzyloxy)-3-methoxybenzaldehyde
Figure S61: $^1$H-NMR: (E)-1-(benzyloxy)-2-methoxy-4-(2-nitrovinyl)benzene

Figure S62: $^{13}$C-NMR: (E)-1-(benzyloxy)-2-methoxy-4-(2-nitrovinyl)benzene
Figure S63: $^1$H-NMR: 2-(4-(benzyloxy)-3-methoxyphenyl)ethan-1-amine hydrochloride

Figure S64: $^{13}$C-NMR: 2-(4-(benzyloxy)-3-methoxyphenyl)ethan-1-amine hydrochloride
Figure S65: $^1$H-NMR: 3-Methoxytyramine hydrochloride
Figure S66: $^1$H-NMR: 3-Methoxytyramine hydrochloride

Figure S67: $^{13}$C-NMR: 3-Methoxytyramine hydrochloride

Figure S68: $^1$H-NMR: 1-(4-fluorophenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol.
Figure S69: $^{13}$C-NMR: 1-(4-fluorophenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol.

Figure S70: $^{19}$F-NMR: 1-(4-fluorophenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol.
Figure S71: $^1$H-NMR: 1-(4-chlorophenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol

Figure S72: $^{13}$C-NMR: 1-(4-chlorophenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol
Figure S73: $^1$H-NMR: (E)-1-(4-chlorostyryl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol

Figure S74: $^{13}$C-NMR: (E)-1-(4-chlorostyryl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol
Figure S75: $^1$H-NMR: 1-(4-iodophenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol

Figure S76: $^{13}$C-NMR: 1-(4-iodophenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol
Figure S77: $^1$H-NMR: (E)-1-(4-chlorostyryl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S78: $^{13}$C-NMR: (E)-1-(4-chlorostyryl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S79: $^1$H-NMR: (E)-6-methoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S80: $^{13}$C-NMR: (E)-6-methoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S81: $^1$H-NMR: (E)-6,7-dimethoxy-1-(4-((trifluoromethyl)styryl)-1,2,3,4-tetrahydroisoquinoline

Figure S82: $^{13}$C-NMR: (E)-6,7-dimethoxy-1-(4-((trifluoromethyl)styryl)-1,2,3,4-tetrahydroisoquinoline
Figure S8: $^1$F-NMR: (E)-6,7-dimethoxy-1-((trifluoromethyl)styryl)-1,2,3,4-tetrahydroisoquinoline

Figure S84: $^1$H-NMR: (E)-1-(4-chlorostyryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline
Figure S85: $^{13}$C-NMR: (E)-1-(4-chlorostyryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

Figure S86: $^{13}$C-NMR: (E)-1-(4-fluorostyryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline
Figure S87: $^1$H-NMR: (E)-1-(4-fluorostyryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

Figure S88: $^{13}$C-NMR: (E)-1-(4-fluorostyryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline
Figure S89: $^1$H-NMR: (E)-6,7-dimethoxy-1-styryl-1,2,3,4-tetrahydroisoquinoline

Figure S90: $^{13}$C-NMR: (E)-6,7-dimethoxy-1-styryl-1,2,3,4-tetrahydroisoquinoline
Figure S91: $^1$H-NMR: (E)-6,7-dimethoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline

Figure S92: $^{13}$C-NMR: (E)-6,7-dimethoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline
Figure S93: $^1$H-NMR: (R,E)-6,7-dimethoxy-1-(4-nitrostyryl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline

Figure S94: $^{13}$C-NMR: (R,E)-6,7-dimethoxy-1-(4-nitrostyryl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline
Figure S95: $^1$H-NMR: (E)-3-(4-nitrophenyl)acrylaldehyde

Figure S96: $^{13}$C-NMR: (E)-3-(4-nitrophenyl)acrylaldehyde
Figure S97: $^1$H-NMR: (E)-3-(4-chlorophenyl)acrylaldehyde

Figure S98: $^{13}$C-NMR: (E)-3-(4-chlorophenyl)acrylaldehyde
Figure S99: $^1$H-NMR: 4-(2-((3-(4-aminophenyl)propyl)amino)ethyl)-2-methoxyphenol

Figure S100: $^{13}$C-NMR: 4-(2-((3-(4-aminophenyl)propyl)amino)ethyl)-2-methoxyphenol
Figure S101: $^1$H-NMR: (E)-2-methoxy-4-((2-(3-(4-nitrophenyl)allyl)amino)ethyl)phenol

Figure S102: $^{13}$C-NMR: (E)-2-methoxy-4-((2-(3-(4-nitrophenyl)allyl)amino)ethyl)phenol
Figure S103: $^1$H-NMR: 2-methoxy-4-((2-((3-(4-nitrophenyl)propyl)amino)ethyl)phenol

Figure S104: $^{13}$C-NMR: 2-methoxy-4-((2-((3-(4-nitrophenyl)propyl)amino)ethyl)phenol
Figure S105: $^1$H-NMR: (E)-2-methoxy-4-(2-(methyl(3-(4-nitrophenyl)allyl)amino)ethyl)phenol

Figure S106: $^{13}$C-NMR: (E)-2-methoxy-4-(2-(methyl(3-(4-nitrophenyl)allyl)amino)ethyl)phenol
Figure S107: $^1$H-NMR: (E)-4-(2-((3-(4-fluorophenyl)allyl)amino)ethyl)-2-methoxyphenol
Figure S108: $^{13}$C-NMR: (E)-4-(2-((3-(4-fluorophenyl)allyl)amino)ethyl)-2-methoxyphenol

Figure S109: $^{19}$F-NMR: (E)-4-(2-((3-(4-fluorophenyl)allyl)amino)ethyl)-2-methoxyphenol
Figure S110: $^1$H-NMR: 4-(2-((3-(4-chlorophenyl)propyl)(methyl)amino)ethyl)-2-methoxyphenol

Figure S111: $^{13}$C-NMR: 4-(2-((3-(4-chlorophenyl)propyl)(methyl)amino)ethyl)-2-methoxyphenol

Figure S112: $^1$H-NMR: (R,E)-6,7-dimethoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline
Figure S113: $^{13}$C-NMR: (R,E)-6,7-dimethoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline
Figure S114: $^1$H-NMR: (R,E)-6,7-dimethoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline

Figure S115: $^{13}$C-NMR: (R,E)-6,7-dimethoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline
Figure S116: $^1$H-NMR: (R)-4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydrossoquinolin-1-yl)ethyl)aniline

Figure S117: $^{13}$C-NMR: (R)-4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydrossoquinolin-1-yl)ethyl)aniline
Figure S118: $^1$H-NMR: (R)-1-(4-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

Figure S119: $^{13}$C-NMR: (R)-1-(4-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

Figure S120: $^1$H-NMR: (S,E)-6,7-dimethoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline
Figure S121: $^{13}$C-NMR: (S,E)-6,7-dimethoxy-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline

Figure S122: $^1$H-NMR: (S,E)-6,7-dimethoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline
Figure S123: $^1$C-NMR: (S,E)-6,7-dimethoxy-2-methyl-1-(4-nitrostyryl)-1,2,3,4-tetrahydroisoquinoline

Figure S124: $^1$H-NMR: (S)-4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl)aniline
Figure S125: $^{13}$C-NMR: (S)-4-(2-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl)aniline
Figure S126: $^1$H-NMR: (S)-1-(4-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline

Figure S127: $^{13}$C-NMR: (S)-1-(4-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline
Figure S128: $^1$H-NMR: (S)-1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S129: $^{13}$C-NMR: (S)-1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S130: $^1$H-NMR: (R)-1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol

Figure S131: $^{13}$C-NMR: (R)-1-(4-chlorophenethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol
Figure S132: Comparison of 1 produced via ethane thiolate mediated demethylation (top) and via Sandmeyer reaction (bottom).
Tritiation

Experiment performed by Tritec RC:

\[ ^{3}H \]Ro 04-5595. 3.48 mg (10.6 \, \mu \text{mol}) of starting material and 23.3 mg (29.0 \, \mu \text{mol}) Crabtree’s catalyst (Sigma-Aldrich 29590) were dissolved in dichloromethane (0.6 ml) (Sigma-Aldrich 270997). The orange solution was degassed three times at the high vacuum manifold and stirred under an atmosphere of tritium gas (9.1 Ci) for 16 h at room temperature. The maximum pressure was 796 mbar. The solvent was removed in vacuo, and labile tritium was exchanged by adding 0.7 ml of methanol (Fluka 65543), stirring the solution, and removing the solvent again under vacuo. This process was repeated two times. Finally, the well-dried solid was extracted with 5 ml of ethanol (Fluka 02860). The activity of the yellow crude product was 1.67 Ci (61.8 GBq). The RCP of the crude material was determined to 8% using the following HPLC system: Macherey + Nagel Nucleodur Gravity C18 (5 \, \mu \text{m}, 4.6 x 250 mm); solvents A: 20 mM NH4HCO3, pH 8.5, B: MeCN; gradient: 0 min 45% B; 30 min 45% B, 31 min 95% B; 35 min 95% B; 30 °C.

The crude material was subjected to preparative HPLC under the following conditions: Macherey + Nagel Nucleodur Gravity C18 (5 \, \mu \text{m}, 4.6 x 250 mm); solvents A: 20 mM NH4HCO3, pH 8.5, B: MeCN; isocratic 45% B; 254 nm; 4.7 ml/min; 25 °C. The target compound eluted at 22.3 min. The HPLC solvent mixture was reduced at the rotary evaporator and the material was isolated by solid phase extraction using a Phenomenex StrataX cartridge (3 ml, 100 mg), which was eluted with 5 ml of ethanol. The so obtained material (40.8 mCi; 1.51 GBq) was a mixture of desired product and unreacted starting material and was subjected to a further preparative HPLC purification. For purification of the compound, the following HPLC conditions were found to be suitable: Waters Sunfire C18, 5 \, \mu \text{m}, 10 x 250 mm; solvents A: water 0.1% TFA; B: MeOH; isocratic 47% B; 230 nm; 4.7 ml/min; 20 °C. The target compound eluted at 5.78 min (the retention time of the starting material was 4.90 min). The desired product was isolated from the HPLC solvent mixture by solid phase extraction. Therefore, the pH of the solution was set neutral with an aqueous solution of NaHCO3 (10%) and the volume of the solvent mixture was reduced at the rotary evaporator. Then the product was extracted with a Phenomenex StrataX cartridge (3 ml, 100 mg), which was eluted with 5 ml of ethanol. The extracted product showed a RCP of >99%. The SA was determined to be 28.1 Ci/mmol (1.04 TBq/mmol).
Certificate of Analysis

UV signal (reference)

Radio detector

S109
Figure S133: Certificate of analysis from Tritec for $[^3]$H$I$. 

| #  | Peak name | Rt.  | Area  | % Area |
|----|-----------|------|-------|--------|
| 1  |           | 8.87 | 77.00 | 0.46   |
| 2  |           | 9.22 | 73.50 | 0.44   |
| 3  | JEJ01     | 9.45 | 16675.50 | 99.11 |
| Sum|           |      | 16826.00 | 100.00|

RC TRITEC LTD.
Dr. Alexander Sele
Growing of crystal for X-ray

Crystals were grown from a small vial holding a methanolic solution of (R,E)-6,7-dimethoxy-1-(4-nitrostyryl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline. inside a larger vial containing hexanes, the closed system was set to equilibrate for one month at 5 degrees.

X-ray data

| Bond precision:  | \( C-C = 0.0030 \) A | Wavelength=0.71073 |
|------------------|-----------------------|---------------------|
| Cell:            | \( a=7.8427(4) \)     | \( b=12.7741(7) \)  | \( c=25.3725(12) \) |
|                  | \( \alpha=90 \)       | \( \beta=90 \)     | \( \gamma=90 \)   |
| Temperature:     | 100 K                 |                     |
| Volume           | 2541.9(2)             | 2541.9(2)           |
| Space group      | P 2 1 21 21           | P 2 1 21 21         |
| Hall group       | P 2ac 2ab             | P 2ac 2ab           |
| Moiety formula   | C26 H26 N2 O6 S, 0.898(C | C26 H26 N2 O6 S, 0.9(C H4 |
|                  | H4 O)                 | O)                  |
| Sum formula      | C26.90 H29.59 N2 O6.90 S | C26.90 H29.59 N2 O6.90 S |
| \( \text{Mr} \)  | 523.32                | 523.31              |
| \( \text{Dx}, g \text{ cm}^{-3} \) | 1.367                  | 1.367               |
| \( \text{Z} \)   | 4                     | 4                   |
| \( \text{Mx (mm}^{-1} \) | 0.177                  | 0.177               |
| \( \text{P000} \) | 1104.7                | 1105.0              |
| \( \text{P000}’ \) | 1105.70               |                     |
| \( h,k,l_{\text{max}} \) | 11,18,36              | 11,18,36            |
| \( \text{Nref} \) | 7786[ 4378]           | 7760                |
| \( \text{Tmin,Tmax} \) | 0.934,0.991           | 0.919,1.000         |
| \( \text{Tmin’} \) | 0.925                 |                      |

Correction method= # Reported T Limits: Tmin=0.919 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 1.77/1.00 \( \text{Theta(max)} = 30.529 \)
\( R(\text{reflections}) = 0.0406( 6775) \) \( \text{wr2(reflections)} = 0.1009( 7760) \)
\( S = 1.052 \) \( \text{Npar} = 342 \)
Crystal data
Chemical formula C$_{26}$H$_{38}$N$_2$O$_5$S$_2$·0.9(CH$_3$O)
$M_r$ 523.31
Crystal system, space group Orthorhombic, $P2_12_12_1$
Temperature (K) 100
$a$, $b$, $c$ (Å) 7.8427 (4), 12.7741 (7), 25.3725 (12)
$V$ (Å$^3$) 2541.9 (2)
Z 4
Radiation type Mo $\text{K}$α
$\mu$ (mm$^{-1}$) 0.18
Crystal size (mm) 0.44 × 0.32 × 0.05

Data collection
Diffractometer Bruker D8 Venture, CMOS detector
diffactometer
Absorption correction Multi-scan
$SADABS2014/5$ (Bruker, 2014/5) was used for absorption correction. $\omega R_1$(int) was 0.1142 before and
0.0485 after correction. The ratio of minimum to maximum transmission is 0.9188. The $\lambda$/$\sigma$ correction
factor is not present.
$T_{\text{min}}$, $T_{\text{max}}$ 0.919, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$]
reflections 26798, 7760, 6775
$R_{\text{int}}$ 0.039
$(\sin \theta/\lambda)_{\text{max}}$ (Å$^{-1}$) 0.715

Refinement
$R(|F|^2), wR_2(|F|), S$ 0.041, 0.101, 1.05
No. of reflections 7760
No. of parameters 342
H-atom treatment H atoms treated by a mixture of independent and constrained refinement
$\Delta$ρ$_{\text{max}}$, $\Delta$ρ$_{\text{min}}$ (e Å$^{-3}$) 0.36, −0.31

Absolute structure Flack x determined using 2646 quotients [$|I^+(+)I^-|/(\vert + I^-)\vert$] (Parsons, Flack and Wagner, Acta Cryst.
B69 (2013) 249-259).
Absolute structure parameter = 0.01 (2)

Computer programs: APEX2 v2014.11-0 (Bruker-AXS, 2016), SADABS v8.34A (Bruker-AXS, 2016), XT (Sheldrick, 2015a), XI (Sheldrick, 2015b),
Diamond v4.0.1 (Brandenburg, 2014), Olex2 (Dolomanov et al., 2009).

References
Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). J. Appl. Cryst. 42, 339–341.
Bruker-AXS (2016). APEX3. Version 2016.1-0. Madison, Wisconsin, USA.
Sheldrick, G. M. (2015a). Sheldrick. G. M., Acta Cryst. A2015. 71, 3–8.
Sheldrick, G. M. (2015b). Sheldrick. G. M., Acta Cryst. C2015. 71, 3–8.
Brandenburg, K. (2014). DIAMOND. Crystal Impact GbR, Bonn, Germany.
Computing details

Data collection: APEX2 v2014.11-0 (Bruker-AXS, 2016); cell refinement: APEX2 v2014.11-0 (Bruker-AXS, 2016); data reduction: SAINT v8.34A (Bruker-AXS, 2016); program(s) used to solve structure: XT (Sheldrick, 2015a); program(s) used to refine structure: XL (Sheldrick, 2015b); molecular graphics: Diamond v4.0.1 (Brandenburg, 2014); software used to prepare material for publication: Olex2 (Dolomanov et al., 2009).

(jj-177a)

Crystal data

C_{20}H_{12}N_{2}O_{6}S·0.9(CH_{2}O)
M_r = 523.31
Orthorhombic, P2_12_12
a = 7.8427 (4) Å
b = 12.7741 (7) Å
c = 25.3725 (12) Å
V = 2.541.9 (2) Å³
Z = 4
F(000) = 1165

Data collection

Bruker D8 Venture, CMOS detector diffractometer
Radiation source: microfocus sealed X-ray tube
Detector resolution: 10.4167 pixels mm⁻¹
θ and ϕ scans

Absorption correction: multi-scan SADABS2014/5 (Bruker,2014/5) was used for absorption correction. wR2( refl) was 0.1142 before and 0.0485 after correction. The R factor of minimum transmission is 0.9188. The R2 factor is not known.

T_max = 0.919, T_min = 1.000
26798 measured reflections
7760 independent reflections
6775 reflections with I > 2σ(I)
R_int = 0.039
θ_min = 30.5°, θ_max = 2.7°
h = −11→17
k = −18→18
l = −36→32

Refinement

Refinement on F²
Least-squares matrix: full
R[F² > 2σ(F²)] = 0.041
wR(F²) = 0.101
S = 1.05
7760 reflections
342 parameters
0 restraints
Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

w = 1/[σ²(F²) + (0.0532P)² + 0.4393P]
where P = (F² + 2F_c²)/3

(Δ/Δ) max = 0.001
Δρ max = 0.36 e Å⁻³
Δρ min = −0.31 e Å⁻³

Absolute structure: Flack x determined using 2646 quotients {{[I+]-[I−]}/([I+]+[I−])} (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).

Absolute structure parameter: −0.01 (2)
**Special details**

*Geometry.* All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

**Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)**

|   | x   | y   | z   | U(eq) / Å² | Occ. (<1) |
|---|-----|-----|-----|------------|-----------|
| S1 | 0.93122 (7) | 0.15395 (4) | 0.26916 (2) | 0.01716 (11) |           |
| O02 | 0.5652 (2) | 0.54425 (12) | 0.11008 (6) | 0.0199 (3) |           |
| O03 | 0.2953 (2) | 0.43133 (13) | 0.10555 (6) | 0.0242 (4) |           |
| O04 | 0.9414 (2) | 0.08137 (13) | 0.31235 (6) | 0.0252 (4) |           |
| O05 | 1.0803 (2) | 0.21158 (13) | 0.25403 (7) | 0.0259 (4) |           |
| O06 | 0.7532 (3) | 0.68451 (14) | 0.56546 (6) | 0.0311 (4) |           |
| N07 | 0.7869 (2) | 0.24019 (13) | 0.28464 (7) | 0.0151 (3) |           |
| N08 | 0.6925 (3) | 0.70385 (16) | 0.52195 (8) | 0.0256 (4) |           |
| C09 | 0.5562 (3) | 0.46527 (15) | 0.14666 (8) | 0.0160 (4) |           |
| O0A | 0.6089 (4) | 0.78253 (17) | 0.51278 (8) | 0.0565 (7) |           |
| C0B | 0.4909 (3) | 0.40253 (16) | 0.14372 (8) | 0.0175 (4) |           |
| C0C | 0.4982 (3) | 0.20019 (16) | 0.24988 (9) | 0.0176 (4) |           |
| H0A | 0.5244 | 0.1374 | 0.2285 | 0.021* |           |
| H0B | 0.3785 | 0.1945 | 0.2619 | 0.021* |           |
| C0D | 0.7687 (3) | 0.42696 (16) | 0.30522 (8) | 0.0167 (4) |           |
| H0D | 0.7361 | 0.4956 | 0.2949 | 0.020* |           |
| C0E | 0.7644 (3) | 0.48645 (17) | 0.39846 (8) | 0.0181 (4) |           |
| C0F | 0.6571 (3) | 0.36113 (15) | 0.21953 (7) | 0.0138 (4) |           |
| C0G | 0.6770 (3) | 0.44585 (16) | 0.18478 (8) | 0.0155 (4) |           |
| H0G | 0.7742 | 0.4899 | 0.1876 | 0.019* |           |
| C0H | 0.5163 (3) | 0.29628 (16) | 0.21575 (8) | 0.0148 (4) |           |
| C0I | 0.3912 (3) | 0.31875 (17) | 0.17767 (9) | 0.0176 (4) |           |
| H0I | 0.2928 | 0.2756 | 0.1753 | 0.021* |           |
| C0J | 0.7963 (3) | −0.01897 (16) | 0.22173 (9) | 0.0197 (4) |           |
| H0J | 0.7921 | −0.0490 | 0.2560 | 0.024* |           |
| C0K | 0.7169 (3) | 0.62798 (17) | 0.47936 (8) | 0.0190 (4) |           |
| C0L | 0.7915 (3) | 0.34613 (16) | 0.26201 (8) | 0.0147 (4) |           |
| H0L | 0.9062 | 0.3570 | 0.2456 | 0.018* |           |
| C0M | 0.8597 (3) | 0.08199 (16) | 0.21447 (8) | 0.0168 (4) |           |
| C0N | 0.7907 (3) | 0.40915 (17) | 0.35622 (8) | 0.0199 (4) |           |
| H0N | 0.8264 | 0.3410 | 0.3663 | 0.024* |           |
| C0O | 0.7191 (3) | 0.60421 (19) | 0.10911 (9) | 0.0245 (5) |           |
| H0C | 0.7171 | 0.6520 | 0.0789 | 0.037* |           |
| H0E | 0.8171 | 0.5570 | 0.1060 | 0.037* |           |
| H0F | 0.7287 | 0.6448 | 0.1418 | 0.037* |           |
| C0P | 0.8423 (3) | 0.47176 (18) | 0.44742 (9) | 0.0222 (5) |           |
| H0P | 0.9128 | 0.4118 | 0.4528 | 0.027* |           |
| C0Q | 0.8219 (3) | 0.54272 (18) | 0.48819 (3) | 0.0219 (5) |           |
| H0Q | 0.8776 | 0.5332 | 0.5210 | 0.026* |           |
| C0R | 0.6592 (3) | 0.57369 (17) | 0.39166 (9) | 0.0207 (4) |           |
| H0R | 0.6038 | 0.5842 | 0.3588 | 0.025* |           |
| C0S | 0.8632 (3) | 0.12693 (17) | 0.16441 (9) | 0.0212 (4) |           |
|        | 0.9053 | 0.1960 | 0.1596 | 0.025*  |
|--------|--------|--------|--------|---------|
| C00T   | 0.6152 (3) | 0.20206 (17) | 0.29790 (9) | 0.0172 (4) |
| H00H   | 0.5649 | 0.2479 | 0.3253 | 0.021*  |
| H00K   | 0.6239 | 0.1305 | 0.3127 | 0.021*  |
| C00U   | 0.7396 (3) | -0.0747 (17) | 0.17860 (9) | 0.0230 (5) |
| H00U   | 0.6975 | -0.1438 | 0.1834 | 0.028*  |
| C00V   | 0.6343 (3) | 0.64502 (18) | 0.43189 (8) | 0.0215 (4) |
| H00V   | 0.5624 | 0.7041 | 0.4271 | 0.026*  |
| C00W   | 0.1326 (3) | 0.3809 (2) | 0.10608 (11) | 0.0274 (5) |
| H00M   | 0.0611 | 0.4101 | 0.0780 | 0.041*  |
| H00O   | 0.0776 | 0.3926 | 0.1403 | 0.041*  |
| H00T   | 0.1476 | 0.3056 | 0.1003 | 0.041*  |
| C00X   | 0.8047 (3) | 0.06959 (19) | 0.12199 (9) | 0.0255 (5) |
| H00X   | 0.8066 | 0.0999 | 0.0878 | 0.031*  |
| C00Y   | 0.7429 (3) | -0.03216 (18) | 0.12832 (9) | 0.0242 (5) |
| O0AA   | 0.3239 (4) | 0.6627 (3) | 0.04825 (13) | 0.0794 (12) | 0.898 (6) |
| HOAA   | 0.333 (8) | 0.597 (5) | 0.035 (3) | 0.106*  | 0.898 (6) |
| C010   | 0.6819 (4) | -0.0941 (2) | 0.08128 (11) | 0.0363 (6) |
| H01A   | 0.7767 | -0.1352 | 0.0670 | 0.054*  |
| H01B   | 0.6394 | -0.0460 | 0.0542 | 0.054*  |
| H01C   | 0.5899 | -0.1413 | 0.0922 | 0.054*  |
| C011   | 0.1492 (5) | 0.6690 (3) | 0.05199 (14) | 0.0446 (9) | 0.898 (6) |
| H01D   | 0.1005 | 0.7181 | 0.0317 | 0.067*  | 0.898 (6) |
| H01E   | 0.1154 | 0.6666 | 0.0890 | 0.067*  | 0.898 (6) |
| H01F   | 0.1070 | 0.5934 | 0.0379 | 0.067*  | 0.898 (6) |

Atomic displacement parameters ($\AA^2$)

|        | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|--------|----------|----------|----------|----------|----------|----------|
| S01    | 0.0106 (2) | 0.0186 (2) | 0.0223 (2) | 0.00256 (19) | -0.0016 (2) | 0.0005 (2) |
| O002   | 0.0189 (8) | 0.0227 (7) | 0.0180 (7) | -0.0007 (6) | -0.0013 (7) | 0.0018 (6) |
| O003   | 0.0195 (8) | 0.0286 (8) | 0.0246 (8) | -0.0003 (7) | -0.0078 (7) | 0.0012 (7) |
| O004   | 0.0243 (9) | 0.0259 (8) | 0.0254 (8) | 0.0059 (7) | -0.0066 (7) | 0.0029 (6) |
| O005   | 0.0096 (7) | 0.0274 (8) | 0.0407 (10) | -0.0009 (6) | 0.0002 (7) | -0.0033 (7) |
| O006   | 0.0413 (11) | 0.0352 (10) | 0.0168 (8) | 0.0039 (8) | -0.0028 (8) | -0.0024 (7) |
| N007   | 0.0107 (8) | 0.0148 (7) | 0.0199 (8) | 0.0006 (6) | 0.0017 (7) | 0.0005 (6) |
| N008   | 0.0341 (12) | 0.0234 (9) | 0.0193 (9) | 0.0019 (9) | -0.0018 (8) | -0.0023 (7) |
| C009   | 0.0176 (10) | 0.0153 (8) | 0.0152 (9) | 0.0026 (8) | 0.0020 (8) | -0.0031 (7) |
| O00A   | 0.094 (2) | 0.0393 (11) | 0.0362 (11) | 0.0350 (13) | -0.0241 (12) | -0.0172 (9) |
| C00B   | 0.0136 (10) | 0.0209 (9) | 0.0181 (9) | 0.0022 (8) | -0.0024 (8) | -0.0054 (7) |
| C00C   | 0.0100 (9) | 0.0176 (9) | 0.0252 (10) | -0.0005 (8) | 0.0009 (8) | -0.0002 (8) |
| C00D   | 0.0157 (10) | 0.0152 (9) | 0.0192 (10) | -0.0018 (8) | -0.0015 (8) | -0.0025 (7) |
| C00E   | 0.0173 (11) | 0.0201 (10) | 0.0169 (9) | -0.0023 (8) | 0.0002 (8) | 0.0009 (7) |
| C00F   | 0.0116 (9) | 0.0153 (9) | 0.0145 (9) | 0.0009 (7) | 0.0013 (7) | -0.0036 (7) |
| C00G   | 0.0134 (10) | 0.0169 (9) | 0.0162 (9) | -0.0013 (7) | 0.0012 (7) | -0.0040 (7) |
| C00H   | 0.0116 (9) | 0.0154 (8) | 0.0174 (9) | 0.0005 (7) | 0.0026 (7) | -0.0040 (7) |
| C00I   | 0.0116 (10) | 0.0197 (10) | 0.0216 (10) | 0.0002 (7) | -0.0002 (8) | -0.0056 (8) |
| C00J   | 0.0167 (10) | 0.0181 (9) | 0.0242 (11) | 0.0014 (8) | 0.0033 (8) | 0.0044 (8) |
| C00K   | 0.0230 (11) | 0.0190 (9) | 0.0150 (9) | -0.0025 (8) | 0.0019 (8) | -0.0010 (7) |
| C00L   | 0.0121 (9) | 0.0157 (8) | 0.0163 (9) | -0.0021 (7) | 0.0007 (7) | -0.0002 (7) |
| C00M   | 0.0132 (9) | 0.0166 (9) | 0.0204 (10) | 0.0026 (8) | 0.0030 (8) | -0.0003 (7) |
|        |        |        |        |        |        |
|--------|--------|--------|--------|--------|--------|
| C00N   | 0.0212 | 0.0183 | 0.0201 | 0.0022 | -0.0017 |
| C00O   | 0.0258 | 0.0237 | 0.0239 | -0.0048 | -0.0013 |
| C00P   | 0.0267 | 0.0217 | 0.0183 | 0.0053 | -0.0015 |
| C00Q   | 0.0259 | 0.0247 | 0.0152 | 0.0000 | -0.0029 |
| C00R   | 0.0236 | 0.0208 | 0.0177 | -0.0064 | -0.0028 |
| C00S   | 0.0229 | 0.0161 | 0.0245 | -0.0064 | 0.00666 |
| C00T   | 0.0115 | 0.0178 | 0.0223 | -0.0014 | 0.00044 |
| C00U   | 0.0219 | 0.0164 | 0.0307 | -0.0007 | 0.0026 |
| C00V   | 0.0247 | 0.0191 | 0.0206 | 0.0022 | -0.0018 |
| C00W   | 0.0178 | 0.0285 | 0.0359 | -0.0002 | -0.0100 |
| C00X   | 0.0319 | 0.0236 | 0.0211 | 0.0046 | 0.0039 |
| C00Y   | 0.0240 | 0.0230 | 0.0256 | 0.0043 | 0.0002 |
| O0AA   | 0.057 | 0.083 | 0.072 | -0.0137 | -0.0220 |
| C010   | 0.0460 | 0.0307 | 0.0321 | 0.0024 | -0.0037 |
| C011   | 0.0542 | 0.0427 | 0.0369 | 0.0039 | -0.0026 |

**Geometric parameters (Å, °) for (ij-177a)**

|        |        |        |        |        |        |
|--------|--------|--------|--------|--------|--------|
| S01—O004 | 1.4376 | C00K—C00Q | 1.3434 | C00K—C00Q | 1.384 |
| S01—O005 | 1.4338 | C00K—C00V | 1.385 | C00K—C00Q | 1.384 |
| S01—N007 | 1.6277 | C00L—H00L | 1.000 | C00K—C00Q | 1.384 |
| S01—C00M | 1.757 | C00M—C00S | 1.394 | C00K—C00Q | 1.384 |
| C002—C009 | 1.373 | C00N—H00N | 0.950 | C00K—C00Q | 1.384 |
| C002—C00O | 1.430 | C00O—H00C | 0.980 | C00K—C00Q | 1.384 |
| C003—C00B | 1.367 | C00O—H00E | 0.980 | C00K—C00Q | 1.384 |
| C003—C00W | 1.429 | C00O—H00F | 0.980 | C00K—C00Q | 1.384 |
| C006—N008 | 1.227 | C00P—H00P | 0.950 | C00K—C00Q | 1.384 |
| N007—C00L | 1.470 | C00P—C00Q | 1.384 | C00K—C00Q | 1.384 |
| N007—C00T | 1.471 | C00Q—H00Q | 0.950 | C00K—C00Q | 1.384 |
| N008—O00A | 1.222 | C00R—H00R | 0.950 | C00K—C00Q | 1.384 |
| N008—C00K | 1.464 | C00R—C00V | 1.382 | C00K—C00Q | 1.384 |
| C009—C00B | 1.407 | C00S—H00S | 0.950 | C00K—C00Q | 1.384 |
| C009—C00G | 1.377 | C00S—C00X | 0.950 | C00K—C00Q | 1.384 |
| C00B—C00I | 1.381 | C00T—H00H | 0.9900 | C00K—C00Q | 1.384 |
| C00C—H00A | 0.9900 | C00T—H00K | 0.9900 | C00K—C00Q | 1.384 |
| C00C—H00B | 0.9900 | C00U—H00U | 0.9500 | C00K—C00Q | 1.384 |
| C00C—C00H | 1.509 | C00U—C00Y | 1.387 | C00K—C00Q | 1.384 |
| C00C—C00T | 1.526 | C00V—H00V | 0.9500 | C00K—C00Q | 1.384 |
| C00D—H00D | 0.9500 | C00W—H00M | 0.9800 | C00K—C00Q | 1.384 |
| C00D—C00L | 1.517 | C00W—H00C | 0.9800 | C00K—C00Q | 1.384 |
| C00D—C00N | 1.325 | C00W—H00T | 0.9800 | C00K—C00Q | 1.384 |
| C00E—C00N | 1.472 | C00X—H00X | 0.9500 | C00K—C00Q | 1.384 |
| C00E—C00P | 1.400 | C00X—C00Y | 1.397 | C00K—C00Q | 1.384 |
| C00E—C00R | 1.397 | C00Y—C010 | 1.510 | C00K—C00Q | 1.384 |
| C00F—C00G | 1.405 | C00A—H0AA | 0.91 | C00K—C00Q | 1.384 |
| C00F—C00H | 1.383 | C00A—C011 | 1.374 | C00K—C00Q | 1.384 |
| C00G—H00D | 0.9500 | C010—H01A | 0.9800 | C00K—C00Q | 1.384 |
| C00H—C00I | 1.407 | C010—H01B | 0.9800 | C00K—C00Q | 1.384 |
| C00H—H00I | 0.9500 | C010—H01C | 0.9800 | C00K—C00Q | 1.384 |
| C00H—H00J | 0.9500 | C011—H01D | 0.9800 | C00K—C00Q | 1.384 |
| Bond                  | Distance (Å) | Bond                  | Distance (Å) |
|-----------------------|--------------|-----------------------|--------------|
| C001—C00M             | 1.394 (3)    | C011—H01F             | 0.9800       |
| C001—C00U             | 1.379 (3)    |                       |              |
| O004—S01—N007         | 106.94 (10)  | C001—C00N—H00N        | 117.4        |
| O004—S01—C00M         | 106.41 (10)  | C001—C00N—H00N        | 117.4        |
| O005—S01—C00M         | 119.32 (10)  | C001—C00N—H00N        | 117.4        |
| O005—S01—N007         | 106.50 (9)   | O002—C00O—H00C        | 109.5        |
| O005—S01—C00M         | 108.52 (10)  | O002—C00O—H00E        | 109.5        |
| N007—S01—C00M         | 108.82 (9)   | O002—C00O—H00F        | 109.5        |
| C009—C002—C00O        | 116.68 (17)  | H00C—C00O—H00E        | 109.5        |
| C009—C003—C00W        | 117.03 (18)  | H00C—C00O—H00F        | 109.5        |
| C00L—N007—S01         | 120.76 (14)  | H00E—C00O—H00F        | 109.5        |
| C00L—N007—C00T        | 114.64 (16)  | C00E—C00O—H00P        | 119.3        |
| C00T—N007—S01         | 117.88 (14)  | C00Q—C00P—C00E        | 121.4 (2)    |
| O006—N008—C00K        | 118.68 (19)  | C00Q—C00P—H00P        | 119.3        |
| O00A—N008—C006        | 123.0 (2)    | C00K—C00Q—C00P        | 117.9 (2)    |
| O00A—N008—C008        | 118.3 (2)    | C00K—C00Q—H00Q        | 121.1        |
| O002—C009—C00B        | 115.16 (19)  | C00P—C00Q—H00Q        | 121.1        |
| O002—C009—C00G        | 124.9 (2)    | C00E—C00R—H00R        | 119.4        |
| C00G—C009—C00B        | 119.95 (19)  | C00V—C00R—C00E        | 121.2 (2)    |
| O003—C00B—C009        | 114.79 (19)  | C00V—C00R—H00R        | 119.4        |
| O003—C00B—C00I        | 125.8 (2)    | C00M—C00S—H00S        | 120.5        |
| C00I—C00B—C009        | 119.44 (19)  | C00X—C00S—C00M        | 119.0 (2)    |
| H00A—C00C—H00B        | 107.8        | C00X—C00S—H00S        | 120.5        |
| C00H—C00C—H00A        | 109.0        | N007—C00T—C00C        | 111.90 (17)  |
| C00H—C00C—H00B        | 109.0        | N007—C00T—H00H        | 109.2        |
| C00H—C00C—C00T        | 112.89 (17)  | N007—C00T—H00K        | 109.2        |
| C00T—C00C—H00A        | 109.0        | C00C—C00T—H00H        | 109.2        |
| C001—C00C—H00B        | 109.0        | C00C—C00T—H00K        | 109.2        |
| C00L—C00D—H00D        | 117.5        | H00H—C00T—H00K        | 107.9        |
| C00N—C00D—H00D        | 117.5        | C003—C00U—H00U        | 119.3        |
| C00N—C00D—C00L        | 125.00 (19)  | C003—C00U—C00Y        | 121.4 (2)    |
| C00P—C00E—C00N        | 119.6 (2)    | C00Y—C00U—H00U        | 119.3        |
| C00R—C00E—C00N        | 121.86 (19)  | C00K—C00V—H00V        | 120.9        |
| C00R—C00E—C00P        | 118.5 (2)    | C00R—C00V—C00K        | 118.2 (2)    |
| C00G—C00F—C00L        | 117.71 (17)  | C00R—C00Y—H00Y        | 120.9        |
| C00H—C00F—C00G        | 120.44 (18)  | O003—C00W—H00M        | 109.5        |
| C00H—C00F—C00L        | 121.82 (18)  | O003—C00W—H00O        | 109.5        |
| C009—C00G—C00F        | 120.20 (19)  | O003—C00W—H00T        | 109.5        |
| C009—C00G—H00G        | 119.9        | H00M—C00W—H00O        | 109.5        |
| C00F—C00G—H00G        | 119.9        | H00M—C00W—H00T        | 109.5        |
| C00F—C00H—C00C        | 121.49 (19)  | H00O—C00W—H00T        | 109.5        |
| C00F—C00H—C00I        | 118.84 (19)  | C00S—C00X—H00X        | 119.3        |
| C00I—C00H—C00C        | 119.62 (19)  | C00S—C00X—C00Y        | 121.3 (2)    |
| C00B—C00I—C00H        | 121.0 (2)    | C00Y—C00X—H00X        | 119.3        |
| C00B—C00I—H00I        | 119.5        | C00U—C00Y—C00X        | 118.5 (2)    |
| C00H—C00I—H00I        | 119.5        | C00U—C00Y—C010        | 121.0 (2)    |
| C00M—C00J—H00J        | 120.4        | C00X—C00Y—C010        | 120.5 (2)    |
| C00U—C00J—H00J        | 120.4        | C011—O0AA—H0AA        | 94 (4)       |
| C00U—C00J—C00M        | 119.2 (2)    | C00Y—C010—H01A        | 109.5        |
| C00Q—C00K—N008        | 118.71 (19)  | C00Y—C010—H01B        | 109.5        |
| Reaction                  | Energy (kcal/mol) |
|---------------------------|-------------------|
| COQ—COQ—COV              | 122.8 (2)         |
| COQV—COOK—N008           | 118.5 (2)         |
| N007—COO1—COOD           | 109.96 (16)       |
| N007—COOL—COOF           | 112.07 (16)       |
| N007—COOL—H00L           | 108.2             |
| COOD—COOL—COOF           | 110.17 (16)       |
| COOD—COOL—H00L           | 108.2             |
| COOF—COOL—H00L           | 108.2             |
| COOL—COOM—S01            | 119.57 (17)       |
| COOS—COOM—S01            | 119.85 (17)       |
| COO8—COOM—COOJ           | 120.6 (2)         |
| S01—N007—COOL—COOD      | -132.22 (16)      |
| S01—N007—COOL—COOF      | 104.89 (18)       |
| S01—N007—COOT—COOC      | -92.83 (18)       |
| S01—COOM—COOS—COOX      | -179.29 (18)      |
| OO02—COO9—CO09—CO03     | -1.4 (3)          |
| OO02—COO9—CO08—CO01     | 177.73 (18)       |
| OO02—COO9—CO09—CO0F      | -178.45 (18)      |
| OO03—CO0B—CO01—CO0H     | -179.8 (2)        |
| OO04—S01—N007—COOL      | 154.30 (15)       |
| OO04—S01—N007—CO0T      | -55.96 (17)       |
| OO04—S01—COOM—CO01J     | 11.8 (2)          |
| OO04—S01—COOM—CO0S      | -169.59 (18)      |
| O005—S01—N007—CO0L      | 25.68 (18)        |
| O005—S01—N007—CO0T      | 175.42 (15)       |
| O005—S01—COOM—CO0J      | 141.37 (17)       |
| O005—S01—COOM—CO0S      | -40.0 (2)         |
| O006—N008—CO0K—CO0Q      | -6.6 (3)          |
| O006—N008—CO0K—CO0V      | 173.7 (2)         |
| N007—S01—COOM—CO0J      | -103.12 (18)      |
| N007—S01—COOM—CO0S      | 75.5 (2)          |
| N008—CO0K—CO0Q—CO0P     | 179.9 (2)         |
| N008—CO0K—CO0V—CO0R      | 179.3 (2)         |
| CO09—CO0B—CO01—CO0H     | 1.1 (3)           |
| O00A—N008—CO0K—CO0Q     | 175.2 (3)         |
| O00A—N008—CO0K—CO0V     | -4.5 (4)          |
| CO0B—CO09—CO0G—CO0F     | 2.4 (3)           |
| CO0C—CO0H—CO01—CO0B     | -176.12 (19)      |
| CO0E—CO0P—CO0Q—CO0K     | 1.4 (4)           |
| CO0E—CO0R—CO0V—CO0K     | 0.1 (3)           |
| CO0F—CO0H—CO01—CO0B     | 1.4 (3)           |
| COOG—CO09—CO0B—O003     | 177.82 (18)       |
| COOG—CO09—CO0B—CO0I      | -3.0 (3)          |
| COOG—CO0F—CO0H—CO0C     | 175.42 (19)       |
| COOG—CO0F—CO0H—CO0I     | -2.0 (3)          |
| COOG—CO0F—CO0L—N007     | -162.44 (17)      |
| COOG—CO0F—CO0L—CO0D     | 74.8 (2)          |
| COOH—CO0C—CO0T—N007     | -42.3 (2)         |
Figure S134, ORTEP of 7a
Figure S135, ORTEP of 7a

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