Puckering the Planar Landscape of Fragments: Design and Synthesis of a 3D Cyclobutane Fragment Library

David J. Hamilton, Marieke Beemsterboer, Caroline M. Carter, Jasmina Elsayed, Rilana E. M. Huiberts, Hanna F. Klein, Peter O'Brien, Iwan J. P. de Esch, and Maikel Wijtmans*
Table of contents

Table S1 – Screening of various reducing agents S2
Table S2 – Physicochemical properties of the synthesised cyclobutane fragment library S3
Figure S1 – Nephelometry analysis S5
Experimental protocols S6
Safety warnings S6
Synthetic procedures S7
Figure S2 - 1D NOE explanation S26
Figures S3-S43 - Compound characterisation data S27
References S149
Table S1 – Screening of various reducing agents to afford the reduction of a key cyclobutanone intermediate of the n-butyl derivative. Diastereomeric ratios were determined by NMR analysis using the crude mixture in each case.

![Cyclobutanone intermediate](image)

| Reducing agent       | Conditions                                      | D.r. (cis:trans) of crude |
|----------------------|-------------------------------------------------|---------------------------|
| NaBH₄                | EtOH, rt, 2 h                                   | 2.8:1.0                   |
| LiBH₄                | THF/DCM (2:1), rt, 72 h                         | 2.2:1.0                   |
| (CH₃)₂SBH₃(S)-(CBS)ligand | THF, -20 °C to rt, 20 h                      | 1.6:1.0                   |
| (CH₃)₂SBH₃(R)-(CBS)ligand | THF, -20 °C to rt, 20 h                      | 1.3:1.0                   |
| 9-BBN                | 1) THF, 3 h<br>2) NaOH/H₂O₂, 0 °C to rt, 1 h   | 1.3:1.0                   |
Table S2 – Physicochemical properties of the synthesised cyclobutane fragment library. These values are the basis for Figures 4A and 4B of the main text.

| Compound | nRot | SlogP | TPSA (Å²) | MW (amu) | HBD | HBA | HAC | Fsp³ |
|----------|------|-------|-----------|---------|-----|-----|-----|------|
| 10a      | 5    | 2.44  | 44.3      | 260.4   | 3   | 3   | 19  | 0.63 |
| 10b      | 5    | 2.40  | 41.5      | 261.4   | 2   | 3   | 19  | 0.63 |
| 10c      | 5    | 2.18  | 52.5      | 235.3   | 3   | 3   | 17  | 0.57 |
| 10d      | 5    | 1.68  | 32.3      | 183.3   | 2   | 2   | 13  | 1.00 |
| 10e      | 5    | 2.75  | 32.3      | 255.3   | 2   | 2   | 18  | 0.57 |
| 10f      | 5    | 1.77  | 58.3      | 224.3   | 2   | 4   | 16  | 0.75 |
| 10g      | 5    | 2.17  | 45.2      | 234.3   | 2   | 3   | 17  | 0.64 |
| 11a      | 5    | 2.61  | 32.3      | 237.3   | 2   | 2   | 17  | 0.57 |
| 11b      | 5    | 2.78  | 32.3      | 233.4   | 2   | 2   | 17  | 0.60 |
| 11c      | 5    | 2.44  | 44.3      | 260.4   | 3   | 3   | 19  | 0.63 |
| 11d      | 5    | 2.75  | 32.3      | 255.3   | 2   | 2   | 18  | 0.57 |
| 11e      | 5    | 1.31  | 41.5      | 213.3   | 2   | 3   | 15  | 1.00 |
| 12a      | 5    | 2.82  | 49.3      | 273.8   | 2   | 3   | 17  | 0.58 |
| 12b      | 5    | 1.81  | 67.2      | 285.8   | 2   | 4   | 19  | 0.69 |
| 12c      | 5    | 1.76  | 49.3      | 223.3   | 2   | 2   | 16  | 0.77 |
| 12d      | 5    | 1.76  | 49.3      | 211.3   | 2   | 2   | 15  | 0.75 |
| 12e      | 5    | 2.76  | 49.3      | 267.8   | 2   | 2   | 18  | 0.50 |
| 12f      | 5    | 2.42  | 49.3      | 247.3   | 2   | 2   | 18  | 0.53 |
| 12g      | 5    | 1.64  | 62.2      | 252.3   | 2   | 3   | 18  | 0.54 |
| 12h      | 5    | 2.01  | 62.5      | 237.3   | 2   | 3   | 17  | 0.62 |
| 13a      | 5    | 2.82  | 49.3      | 273.8   | 2   | 3   | 17  | 0.58 |
| 13b      | 5    | 1.81  | 67.2      | 285.8   | 2   | 4   | 19  | 0.69 |
| 13c      | 5    | 1.64  | 62.2      | 252.3   | 2   | 3   | 18  | 0.54 |
| 13d      | 5    | 2.76  | 49.3      | 267.8   | 2   | 2   | 18  | 0.50 |
|     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|
| 13e | 5   | 2.56| 49.3| 265.3| 2   | 2   | 19  | 0.53|
| 13f | 5   | 1.45| 49.3| 199.3| 2   | 2   | 14  | 0.91|
| 13g | 5   | 2.01| 62.5| 237.3| 2   | 3   | 17  | 0.62|
| 13h | 5   | 2.42| 49.3| 247.3| 2   | 2   | 18  | 0.53|
| 13i | 5   | 2.31| 49.3| 257.3| 2   | 3   | 17  | 0.58|
| 13j | 5   | 0.84| 67.2| 237.3| 2   | 4   | 17  | 0.67|
| 14a | 5   | 1.80| 66.4| 287.4| 2   | 3   | 19  | 0.54|
| 14b | 5   | 0.76| 66.4| 233.3| 2   | 3   | 15  | 1.00|
| 14c | 5   | 1.97| 66.4| 283.4| 2   | 3   | 19  | 0.57|
Figure S1 - Nephelometry analysis of kaolin (control suspension) and of selected fragments at increasing concentrations in HBSS buffer containing 1% DMSO. Fragments tested comprise the ones with the lowest cLogD (0.28, 11e), the median cLogD (1.85, 11a), and the highest cLogD (2.82, diastereomers 12a and 13a). Data points represent the mean ± SD of values measured in triplo. The dotted horizontal line corresponds to 3 times the standard deviation of the average blank measurements and represents a cut-off above which aggregation is deemed to begin to occur.
Experimental protocols

General experimental synthetic section
All reagents have been purchased from commercial suppliers (primarily being Sigma-Aldrich and Combi blocks) and used without further purification. Et₂O, THF and DCM were dried by passing through an activated alumina column prior to use. All other solvents used were used as received unless otherwise stated. All reactions were performed under a N₂ atmosphere unless stated otherwise. Glassware was oven-dried for at least 16 h prior to use. All mole ratios of components in mixtures were determined by NMR analysis. TLC analyses were performed using Merck F254 aluminium-backed silica plates and visualized with 254 nm UV light or a KMnO₄ stain. Flash column chromatography was executed using Silicyle Siliaflash F60 silica gel and a Biotage Isolera one. All ¹H-NMR, ¹³C-NMR, COSY, HSQC, HMBC and 1D-NOE spectra were measured on a Bruker 300 MHz, Bruker Avance 400 MHz, Bruker Avance 500 MHz or Bruker Avance 600 MHz. The spectra were referenced to the internal solvent peak as follows: CDCl₃ (¹H = 7.26 ppm, ¹³C = 77.16 ppm), CD₂OD (¹H = 3.31 ppm, ¹³C = 49.00 ppm) and DMSO-d₆ (¹H = 2.50 ppm, ¹³C = 39.52 ppm) and peak multiplicities are designated as follows; s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; h, heptet; hept, heptet; m, multiplet; app, apparent; br s, broad singlet. In virtually all NMR analyses in CD₂OD, the NH and OH signals were not visible. HRMS data was collected using a Bruker microTOF-Q (ESQ). IUPAC names were adapted from ChemDraw Professional 19.0 (PerkinElmer). Purities were measured with the aid of analytical LC-MS using a Shimadzu LC-20AD liquid chromatography pump system with a Shimadzu SPDM20A diode array detector with the MS detection performed with a Shimadzu LC-MS-2010EV mass operating in both positive and negative ionisation mode. The column used was an XBridge (C18) 5 µm column (50 mm, 4.6 mm). The following solutions are used for the eluents. Solvent A: H₂O (+0.1% HCOOH) and solvent B: MeCN (+0.1% HCOOH). The eluent program used is as follows: flow rate: 1.0 mL/min, start 95% A in a linear gradient to 10% A over 4.5 min, hold 1.5 min at 10% A, in 0.5 min in a linear gradient to 95% A, hold 1.5 min at 95% A, hold 1.5 min at 95% A, total run time: 8.0 min. Compound purities were calculated as the percentage peak area of the analysed compound by UV detection at 254 nm, unless otherwise stated. In cases without reasonable 254 nm absorption, 200 nm, 210 nm or 230 nm was used instead and this is specified in each case. In the absence of a reasonable chromophore at these alternative wavelengths, qNMR measurements were carried out for final compounds according to a qNMR protocol using 1,3,5-trimethoxybenzene as internal standard.

Safety warnings:

[1] Cycloaddition with Cl₂COCI and alkynes
The reaction is potentially exothermic, depending on the substrate. The reaction setup involves a reflux condenser and internal thermometer, and each new portion of Cl₂COCI was added via dropping funnel when any visible reflux had subsided. When the solvent (especially when using Et₂O) started boiling violently, the reaction mixture was cooled by an ice bath for short periods of time.

[2] In situ generation of HN₃
Mixing NaN₃ and a strong acid will generate HN₃ (a highly toxic and colourless gas). Take necessary precautions and adjust the work-up (vide infra).

[3] Working with small-molecule azides
Organic azides with a low molecular weight carry a risk of explosion. Several rules have been established to estimate the risk. Take necessary precautions (vide infra).

[4] Working with reactive volatile electrophiles
Several of the compounds used as intermediates in this study (enones, dichloroenones) are expected to be (highly) volatile and are expected to be (highly) electrophilic. This leads to the potential risk of toxicity. Take necessary precautions and use face masks during steps that have increased risk of liberation of these compounds.

S6
Preparation of Zn-Cu
A procedure (adapted from Krepski and Hassner) was used. A suspension of Zn dust (10.0 g, 0.15 mol) in H$_2$O (40 mL) was stirred at rt for 15 min. CuSO$_4$.5H$_2$O (0.90 g, 3.6 mmol) was then added at once. The black suspension was stirred for an additional 45 min. The Zn-Cu was collected via filtration and was washed with H$_2$O (3x) and acetone (3x). The Zn-Cu was transferred to a vial and dried in a vacuum oven (40 °C) for at least 2 h prior to use.

4,4-dichloro-3-propylcyclobut-2-en-1-one (2)

A [2+2] cycloaddition (adapted from Amman et al.) was used. To a suspension of Zn-Cu (28.00 g, 0.22 mol) and pent-1-yne (5.00 g, 0.073 mol) in Et$_2$O (220 mL, 0.30 M) in an oven-dried 1 L three-necked flask, fitted with a reflux condenser, internal thermometer and dropping funnel, was added a solution of CCl$_3$COCl (16.5 mL, 0.15 mol) in Et$_2$O (25 mL) dropwise. The temperature was controlled by additional cooling with a cold-water bath such that the internal temperature was kept between 10-15 °C. After complete addition the solution was stirred at rt for 3 h before quenching the reaction mixture slowly with ice-cold water. The solids were filtered. Satd. aq. NaHCO$_3$ was added to the filtrate and the formed salts were filtered. The filtrate was washed with satd. aq. NaHCO$_3$ and brine. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. n-Pentane was added to the residue and the tarry materials were filtered. The filtrate was concentrated in vacuo and purified on silica gel using a gradient of 0-10% EtOAc/cHex to afford the product as a yellow solution (~5.40 g, ~30 mmol, ~41%) in cHex. Safety note – for both safety reasons and the suspected volatility of small dichlorocyclobutenones (vide supra), this compound was not evaporated to dryness at this stage. As a result, signals of cHex remain in the $^1$H and $^{13}$C NMR spectra and the yield was extrapolated from molar ratios by $^1$H NMR analysis.

$^1$H NMR (500 MHz, Chloroform-$d$) δ 6.22 (t, J = 1.6 Hz, 1H), 2.69 (td, J = 7.4, 1.6 Hz, 2H), 1.80 (app. h, J = 7.4 Hz, 2H), 1.08 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-$d$) δ 186.1, 179.6, 135.8, 92.1*, 28.4, 19.2, 14.0.

*Signal detected from HMBC analysis. No ionisation was observed for this compound.

3-propylcyclobut-2-en-1-one (3)

A reductive dechlorination (adapted from a procedure by Hekmatshoar et al.) was used. To a solution of dichloroenone 2 (~3.72 g, ~21 mmol) in THF (83 mL, 0.25 M) cooled with a cold-water bath was added a fresh suspension of Zn (5.43 g, 83.1 mmol) in satd. aq. NH$_4$Cl (42 mL). The ice bath was then removed and the mixture was stirred vigorously for 1 h. The solids were removed by filtration. The filtrate was diluted with Et$_2$O (150 mL) and the layers were separated. The organic layer was washed with water (x3), satd. aq. NaHCO$_3$ and brine. The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. Safety note – for both safety reasons and the suspected high volatility of small cyclobutenones (vide supra), this enone intermediate was not evaporated to dryness. Therefore, signals of the used solvents (cHex, Et$_2$O and THF) remain visible in both $^1$H
and $^{13}$C NMR spectra. The yield was extrapolated from molar ratios by $^1$H NMR analysis (~1.50 g, ~14 mmol, ~86%).

$^1$H NMR (500 MHz, Chloroform-d) δ 5.90 (s, 1H), 3.15 (s, 2H), 2.57 – 2.52 (m, 2H), 1.66 (app. h, $J = 7.4$ Hz, 2H), 1.01 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-d) δ 188.3, 181.4, 134.4, 50.8, 34.2, 19.7, 14.0. The reported analytical data are in accordance with the literature [9]. No ionisation was observed for this compound.

3-azido-3-propylcyclobutan-1-one (4)

\[
\begin{align*}
\text{nPr} & \quad \text{O} \\
\text{N}_3 & \quad \text{N}_3
\end{align*}
\]

To a suspension of NaN$_3$ (2.69 g, 41.4 mmol) in DCM (27.6 mL, 0.50 M with respect to enone 3) was added 37% aq. HCl (2.40 mL, 27.6 mmol) slowly. Safety note - the highly toxic HN$_3$ will form (vide supra). After vigorous stirring for 1 h at rt, enone 3 (~1.52 g, ~13.8 mmol) was added dropwise followed by Et$_3$N (0.38 mL, 2.76 mmol). The mixture turned orange and was stirred for 18 h overnight at rt. The mixture was diluted with water. The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with satd. aq. NaHCO$_3$ and brine. Safety note - the aqueous layers were treated with 40% aq. NaOH to neutralise any HN$_3$ before further processing as waste. The organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified over silica gel using a gradient of 0-15% EtOAc/cHex to afford the title compound (~1.28 g, ~8.4 mmol, ~61%) as a yellow solution in cHex. Safety note – for both safety reasons and the potential volatility of small organic azides (vide supra), the azidoketone intermediate was not evaporated to dryness. Therefore, signals of cHex remain in the $^1$H and $^{13}$C NMR spectra. The yield was extrapolated from molar ratios by $^1$H NMR analysis.

$^1$H NMR (500 MHz, Chloroform-d) δ 3.26 – 3.18 (m, 2H), 3.10 – 3.02 (m, 2H), 1.90 – 1.84 (m, 2H), 1.55 – 1.45 (m, 2H), 1.01 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-d) δ 203.0, 57.3, 56.7, 40.6, 18.5, 14.1. ESI-MS: m/z = 126 [M+H-N$_2$]$^+$ (loss of N$_2$ for azides in MS analyses is known [10])

3-azido-3-propylcyclobutan-1-ol (5, mixture of cis and trans isomers)

\[
\begin{align*}
\text{nPr} & \quad \text{OH} \\
\text{N}_3 & \quad \text{N}_3
\end{align*}
\]

To a solution of ketone 4 (2.63 g, 17.2 mmol) in EtOH (115 mL, 0.15 M), cooled with an ice-water bath, was added NaBH$_4$ (1.95 g, 51.5 mmol) portion wise. The water bath was removed and the reaction mixture was stirred for a further 2 h. The reaction mixture was quenched by addition of acetone (10 mL) and the volatiles were removed in vacuo. The residue was partitioned between H$_2$O (50 mL) and EtOAc (50 mL). The layers were separated. The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the title compound as a pale-yellow oil (2.18 g, 14.0 mmol, 82%) which did not require further purification. Safety note - although this compound could be evaporated to dryness due to expected reduced volatility, it was not heated extensively for safety reasons.
concerning small organic azides. A mixture of cis/trans azidocyclobutanol (which were not separable at this stage) was observed in an approximate ratio 0.7:0.3 cis:trans in CDCl₃ from ¹H NMR analysis. Stereochemistry was assigned by 1D NOE analysis on the crude sample. In the ¹H spectrum, all peaks for both isomers are reported, with overlapping signals being reported together and distinct signals reported separately. For ¹³C NMR analysis, all signals are reported.

¹H NMR (500 MHz, Chloroform-d) δ 4.49 (app. p, J = 6.9 Hz, 1H, major cis isomer), 4.11 (app. p, J = 6.9 Hz, 1H, major cis isomer), 2.55 – 2.47 (m, 2H), 2.14 (ddd, J = 10.0, 6.9, 3.0 Hz, 2H, major cis isomer), 2.03 – 1.95 (m, 2H, minor trans isomer), 1.72 – 1.66 (m, 2H, minor trans isomer), 1.52 – 1.46 (m, 2H, major cis isomer), 1.41 – 1.31 (m, 2H), 0.97 – 0.90 (m, 3H). ¹³C NMR (126 MHz, Chloroform-d) δ 62.8, 61.0, 60.6, 57.3, 43.0, 42.9, 42.6, 41.4, 17.6, 17.5, 14.3, 14.2. ESI-MS: m/z = 128 [M+H-N₂]⁺ (loss of N₂ for azides in MS analyses is known[10])

**Cis-3-azido-3-propylcyclobutyl benzoate (6) and trans-3-azido-3-propylcyclobutyl benzoate (7)**

![Chemical structures](image)

To a solution of cyclobutanol 5 (2.18 g, 14.0 mmol, mixture of cis and trans) in DCM (47 mL, 0.30 M) was added Et₃N (2.54 mL, 18.24 mmol) and DMAP (1.714 g, 14.03 mmol). The solution was cooled using a water-ice bath. BzCl (1.96 mL, 16.8 mmol) was added dropwise while stirring, after which the water-ice bath was removed and the reaction mixture was stirred for a further 18 h at rt. The reaction mixture was diluted with DCM (100 mL) and washed with 50% aq. citric acid solution (50 mL), water (50 mL) and brine (50 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified over silica gel using a gradient of 10-60% DCM/CHex to afford the cis isomer (2.28 g, 8.79 mmol, 63%) and the trans isomer (0.64 g, 2.47 mmol, 18%) as colourless oils which crystallised upon standing. Cis and trans stereochemistry was confirmed by 1D NOE analysis.

**Cis (6):** ¹H NMR (500 MHz, Chloroform-d) δ 8.06 – 8.03 (m, 2H), 7.60 – 7.55 (m, 1H), 7.48 – 7.43 (m, 2H), 5.03 (app. p, J = 7.1 Hz, 1H), 2.72 – 2.65 (m, 2H), 2.46 – 2.40 (m, 2H), 1.65 – 1.58 (m, 2H), 1.46 – 1.38 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-d) δ 166.2, 133.3, 129.9, 129.8, 128.6, 62.9, 58.7, 41.3, 40.1, 17.5, 14.3. LC-MS: RT = 5.74 min, 87% (254 nm), m/z = 232 [M+H-N₂]⁺ (loss of N₂ for azides in MS analyses is known[10])

**Trans (7):** ¹H NMR (500 MHz, Chloroform-d) δ 8.05 – 8.00 (m, 2H), 7.60 – 7.55 (m, 1H), 7.47 – 7.42 (m, 2H), 5.39 – 5.32 (m, 1H), 2.75 – 2.69 (m, 2H), 2.30 – 2.24 (m, 2H), 1.78 – 1.73 (m, 2H), 1.46 – 1.37 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-d) δ 166.1, 133.3, 130.0, 129.7, 128.6, 65.4, 62.0, 42.3, 40.5, 17.4, 14.2. LC-MS: RT = 5.76 min, 96% (254 nm), m/z = 232 [M+H-N₂]⁺ (loss of N₂ for azides in MS analyses is known[10])

**Cis-3-amino-3-propylcyclobutyl benzoate (8)**
To a solution cis-azole 6 (2.28 g, 8.79 mmol) in MeOH (88 mL, 0.10 M), flushed with N₂, was added 5% wt Pd/C (500 mg). Balloons of H₂ were placed on the flask, the atmosphere was flushed with H₂ for 10 min and the mixture was stirred vigorously at rt for 18 h. The mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo to obtain the title compound (1.93 g, 8.27 mmol, 94%) as a pale yellow oil.

$^1$H NMR (500 MHz, Methanol-$d_4$) δ 8.04 – 8.00 (m, 2H), 7.63 – 7.58 (m, 1H), 7.50 – 7.45 (m, 2H), 4.95 (app. p, J = 7.3 Hz, 1H), 2.66 – 2.58 (m, 2H), 2.16 – 2.09 (m, 2H), 1.58 – 1.51 (m, 2H), 1.46 – 1.38 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (126 MHz, Methanol-$d_4$) δ 167.6, 134.3, 131.4, 130.5, 129.6, 64.8, 60.7, 50.2, 46.9, 44.3, 44.1, 18.3, 14.9. LC-MS: RT = 3.29 min, 97% (230 nm), m/z = 234 ([M+H]$^+$). Cis stereochemistry was confirmed by 1D NOE analysis.

**Trans-3-amino-3-propylcyclobutyl benzoate (9)**

To a round-bottomed flask, flushed with N₂, containing a solution of trans-azole 7 (780 mg, 3.01 mmol) in MeOH (30 mL, 0.10 M), was added 5% wt Pd/C (200 mg). Balloons of H₂ were placed on the flask, the atmosphere was flushed with H₂ for 10 mins and the mixture was stirred vigorously at rt for 18 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo to obtain the title compound (635 mg, 2.72 mmol, 91%) as a pale-yellow solid.

$^1$H NMR (600 MHz, Chloroform-$d_4$) δ 8.05 – 8.01 (m, 2H), 7.57 – 7.53 (m, 1H), 7.46 – 7.41 (m, 2H), 5.42 (app. p, J = 6.9 Hz, 1H), 2.49 – 2.42 (m, 2H), 2.23 – 2.17 (m, 2H), 1.65 – 1.60 (m, 2H), 1.41 – 1.34 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). $^{13}$C NMR (151 MHz, Chloroform-$d_4$) δ 166.3, 133.0, 130.4, 129.7, 128.5, 66.3, 52.1, 46.1, 42.8, 17.1, 14.5. LC-MS: RT = 3.37 min, 98% (230 nm), m/z = 234 ([M+H]$^+$). Trans stereochemistry was confirmed by 1D NOE analysis.
General Procedure A – Reductive Amination

To a solution of cis- or trans-amine 8 or 9 (1.0 eq) in dry MeOH (0.30 M) containing a spatula of 3Å molecular sieves at rt was added the corresponding aldehyde (0.97 eq). The reaction mixture was stirred for 18 h. The mixture was cooled to 0 °C before portion wise addition of NaBH₄ (3.0 eq). The mixture was stirred for 2 min. The ice bath was removed and the reaction mixture was stirred for a further 1 h. The volatiles were removed in vacuo and the residue was partitioned between EtOAc and satd. aq. Na₂CO₃. The aqueous phase was extracted with DCM containing 5% CF₃CH₂OH. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was used in the next step without additional purification.

The combined organic layers were dried over anhydrous Na₂SO₄ between EtOAc and satd. aq. Na₂CO₃. The mixture was stirred for 2 h at rt. The volatiles were removed in vacuo and the residue was partitioned between EtOAc and satd. aq. Na₂CO₃. The aqueous phase was extracted with DCM containing 5% CF₃CH₂OH. The combined organic layers were dried over anhydrous Na₂SO₄ filtered and concentrated in vacuo. Purification was conducted as specified to afford the cyclobutanol product.

General Procedure B – Amide Formation

To a solution of the corresponding carboxylic acid (1.70 mmol) in DCM (0.30 M) containing a spatula of 3Å molecular sieves was added (COCl)₂ (2.04 mmol) and one drop of DMF. The reaction mixture was stirred at rt until the carboxylic acid was no longer observed (reaction progress was monitored by quenching a sample of reaction mixture with MeOH and conducting TLC analysis). The mixture was filtered and the filtrate concentrated in vacuo to afford the corresponding acid chloride, part of which was used directly in the amide-forming reaction without further analysis. The acid chloride (1.2 eq) and Et₃N (1.2 eq) were added to a solution of cis- or trans-amine 8 or 9 (1.0 eq) in DCM (0.30 M) containing a spatula of 3Å molecular sieves at 0 °C. The mixture was allowed to warm to rt and stirred for the specified time. The mixture was filtered and the filtrate was partitioned between EtOAc and satd. aq. Na₂CO₃. The aqueous phase was extracted with DCM containing 5% CF₃CH₂OH. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was used in the next step without additional purification. To a solution of crude benzoate ester in a 7:3 vol mixture of THF:MeOH (0.050 M) was added a suspension of LiOH.H₂O (4.0 eq) in H₂O (3.0 mL). The mixture was stirred for 2 h at rt. The volatiles were removed in vacuo and the residue was partitioned between EtOAc and satd. aq. Na₂CO₃. The aqueous phase was extracted with DCM containing 5% CF₃CH₂OH. The combined organic layers were dried over anhydrous Na₂SO₄ filtered and concentrated in vacuo. Purification was conducted as specified to afford the cyclobutanol product.

General Procedure C – Sulfonamide Formation

To a solution of cis- or trans-amine 8 or 9 (1.0 eq) in DCM (0.30 M) containing a spatula of 3Å molecular sieves at 0 °C was added the corresponding sulfonyl chloride (1.2 eq) and Et₃N (1.2 eq). The reaction mixture was allowed to warm to rt and stirred for the specified time. The mixture was filtered and the filtrate was partitioned between EtOAc and satd. aq. Na₂CO₃ solution. The aqueous phase was extracted with DCM containing 5% CF₃CH₂OH. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was used in the next step without additional purification. To a solution of crude benzoate ester in a 7:3 vol mixture of THF:MeOH (0.050 M) was added a suspension of LiOH.H₂O (4.0 eq) in H₂O (3.0 mL). The mixture was stirred for 2 h at rt. The volatiles were removed in vacuo and the residue was partitioned between EtOAc and satd. aq. Na₂CO₃. The aqueous phase was extracted with DCM containing 5% CF₃CH₂OH. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. Purification was conducted as specified to afford the cyclobutanol product.
Cis-3-((indolin-7-ylmethyl)amino)-3-propylcyclobutan-1-ol (10a)  
VUF25579

This compound was synthesised according to general procedure A using cis-amine 8 (152 mg, 0.65 mmol) and tert-butyl 7-formylindoline-1-carboxylate (156 mg, 0.63 mmol). Deprotection of the N-Boc group was performed by addition of TFA (0.50 mL) to a solution of the crude material in DCM (10 mL) and stirring for 16 h at rt. The volatiles were removed in vacuo and the residue partitioned between EtOAc and satd. aq. Na₂CO₃. The aqueous phase was extracted with DCM containing 5% CF₃CH₂OH. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified over silica gel using a gradient of 20-80% EtOAc/cHex (+2% Et₃N) to afford the title compound as a pale-yellow solid (52 mg, 0.20 mmol, 31%).

¹H NMR (600 MHz, Methanol-d₄) δ 7.02 (dd, J = 7.4, 1.4 Hz, 1H), 6.93 (app. d, J = 7.4 Hz, 1H), 6.68 (app. t, J = 8.4 Hz, 2H), 4.04 (app. p, J = 7.1 Hz, 1H), 3.54 (s, 2H), 3.50 (t, J = 8.4 Hz, 2H), 3.00 (t, J = 8.4 Hz, 2H), 2.35 (ddd, J = 11.6, 5.8, 2.3 Hz, 2H), 1.88 – 1.82 (m, 2H), 1.56 – 1.48 (m, 2H), 1.40 – 1.29 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H).

¹³C NMR (151 MHz, Methanol-d₄) δ 151.4, 131.4, 128.4, 124.5, 123.5, 120.6, 61.8, 53.0, 48.0, 44.6, 44.5, 40.6, 30.9, 18.1, 14.9. LC-MS: RT = 2.64 min, 99+% (254 nm), m/z = 261 ([M+H]⁺). HRMS calcd. for C₁₆H₂₅N₂O⁺ [M+H]⁺ = 261.1961, found 261.1950. Cis stereochemistry was confirmed by 1D NOE analysis.

Trans-3-(((2,3-dihydrobenzofuran-5-yl)methyl)amino)-3-propylcyclobutan-1-ol (10b)  
VUF25554

This compound was synthesised according to general procedure A using cis-amine 8 (150 mg, 0.64 mmol) and 2,3-dihydrobenzofuran-5-carboxaldehyde (92 mg, 0.62 mmol). The crude product was purified over silica gel using a gradient of 50-100% EtOAc/cHex to afford the title compound as a colourless crystalline solid (105 mg, 0.40 mmol, 63%).

¹H NMR (600 MHz, Methanol-d₄) δ 7.18 (d, J = 1.9 Hz, 1H), 7.04 (dd, J = 8.1, 1.9 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 4.51 (t, J = 8.7 Hz, 2H), 4.04 (app. p, J = 7.1 Hz, 1H), 3.50 (s, 2H), 3.18 (t, J = 8.7 Hz, 2H), 2.41 – 2.33 (m, 2H), 1.86 – 1.80 (m, 2H), 1.57 – 1.49 (m, 2H), 1.39 – 1.33 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ¹³C NMR (151 MHz, Methanol-d₄) δ 160.7, 133.2, 129.4, 128.6, 126.5, 109.8, 72.3, 61.8, 53.0, 47.6, 44.7, 40.6, 30.5, 18.1, 14.9. LC-MS: RT = 2.70 min, 99% (230 nm), m/z = 262 ([M+H]⁺). HRMS calcd. for C₁₆H₂₅N₂O⁺ [M+H]⁺ = 262.1802, found 262.1794. Cis stereochemistry was confirmed by 1D NOE analysis.

3-(((cis)-3-hydroxy-1-propylcyclobutyl)amino)methyl)phenol (10c)  
VUF25581
This compound was synthesised according to general procedure A using cis-amine 8 (170 mg, 0.73 mmol) and 3-hydroxybenzaldehyde (86 mg, 0.71 mmol). The crude product was purified over silica gel using a gradient of 0-15% MeOH/EtOAc to afford the title compound as a white solid (54 mg, 0.23 mmol, 32%).

$^1$H NMR (500 MHz, Methanol-d$_4$) δ 7.14 (app. t, $J$ = 7.9 Hz, 1H), 6.81 (app. dt, $J$ = 7.9, 2.0 Hz, 1H), 6.78 (app. t, $J$ = 2.0 Hz, 1H), 6.68 (ddd, $J$ = 7.9, 2.0, 1.0 Hz, 1H), 4.05 (app. p, $J$ = 7.1 Hz, 1H), 3.54 (s, 2H), 2.42 – 2.33 (m, 2H), 1.90 – 1.80 (m, 2H), 1.57 – 1.51 (m, 2H), 1.43 – 1.30 (m, 2H), 0.97 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (126 MHz, Methanol-d$_4$) δ 158.7, 142.2, 130.6, 120.8, 116.6, 115.1, 61.7, 53.2, 47.8, 44.5, 40.4, 18.0, 14.9. LC-MS: RT = 2.38 min, 97% (254 nm), m/z = 236 ([M+H]$^+$). HRMS calcd. for C$_{14}$H$_{22}$NO$_2$ $^{[M+H]}$ = 236.1645, found 236.1639. Cis stereochemistry was confirmed by 1D NOE analysis.

**Cis-3-((cyclopropylmethyl)amino)-3-propylcyclobutan-1-ol (10d)**

This compound was synthesised using a modified version of general procedure A using cis-amine 8 (150 mg, 0.64 mmol), cyclopropanecarbaldehyde (58 μL, 0.77 mmol) and AcOH (41 μL, 0.71 mmol). The crude product was purified over silica gel using a gradient of 15-100% EtOAc/cHex and 0-20% MeOH/EtOAc to afford the title compound as a yellow solid (55 mg, 0.30 mmol, 47%).

$^1$H NMR (500 MHz, Chloroform-d$_4$) δ 4.14 (tt, $J$ = 6.8, 5.2 Hz, 1H), 2.33 – 2.25 (m, 4H), 1.81 – 1.74 (m, 2H), 1.44 – 1.36 (m, 2H), 1.29 – 1.19 (m, 2H), 0.95 – 0.87 (m, 4H), 0.52 – 0.46 (m, 2H), 0.14 – 0.07 (m, 2H). $^{13}$C NMR (126 MHz, Chloroform-d$_4$) δ 62.2, 53.1, 47.4, 43.9, 39.2, 16.9, 14.6, 11.4, 3.7. Purity (qNMR): 97 %. HRMS calcd. for C$_{11}$H$_{22}$NO$^+$ [M+H]$^+$ = 184.1696, found 184.1689. Cis stereochemistry was confirmed by 1D NOE analysis.

**Cis-3-((3,4-difluorobenzyl)amino)-3-propylcyclobutan-1-ol (10e)**

This compound was synthesised according to general procedure A using cis-amine 8 (150 mg, 0.64 mmol) and 3,4-difluorobenzaldehyde (69 μL, 0.62 mmol). The crude product was purified over silica gel using a gradient of 10-70% EtOAc/cHex (+2% Et$_3$N) to afford the title compound as a pale-yellow gum (78 mg, 0.31 mmol, 48%).

$^1$H NMR (500 MHz, Methanol-d$_4$) δ 7.29 (ddd, $J$ = 11.7, 7.8, 2.1 Hz, 1H), 7.24 – 7.10 (m, 2H), 4.04 (app. p, $J$ = 7.1 Hz, 1H), 3.58 (s, 2H), 2.39 – 2.30 (m, 2H), 1.89 – 1.78 (m, 2H), 1.56 – 1.47 (m, 2H), 1.42 – 1.28 (m, 2H), 0.95 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (126 MHz, Methanol-d$_4$) δ 151.4 (dd, $J$ = 245.9, 12.7 Hz), 150.6 (dd, $J$ = 245.9, 12.7 Hz), 141.7, 139.2, 131.4, 129.2, 128.4, 127.2, 126.3, 124.5, 121.0, 117.0, 115.6, 114.5, 30.6, 24.0, 13.0.
139.3 (dd, \( J = 5.9, 3.6 \) Hz), 125.9 (dd, \( J = 5.9, 3.6 \) Hz), 118.4 (d, \( J = 17.3 \) Hz), 118.00 (d, \( J = 17.3 \) Hz), 61.7, 52.9, 46.8, 44.5, 40.7, 18.1, 14.9. LC-MS: RT = 2.73 min, 98% (254 nm), m/z = 256 ([M+H]+). HRMS calcd. for C_{14}H_{20}F_{2}NO+ [M+H]+ = 256.1507, found 256.1497. Cis stereochemistry was confirmed by 1D NOE analysis.

\textbf{Cis-3-(((5-methylisoxazol-3-yl)methyl)amino)-3-propylcyclobutan-1-ol (10f)}

\[\text{VUF25590}\]

This compound was synthesised according to general procedure A using cis-amine 8 (158 mg, 0.68 mmol) and 5-methyl-4,5-dihydroisoxazole-3-carbaldehyde (73 mg, 0.70 mmol). The crude product was purified over silica gel using a gradient of 40-100% EtOAc/CHex to afford the title compound as a light brown oil (64 mg, 0.29 mmol, 43%).

\[\text{\textsuperscript{1}H NMR (500 MHz, Chloroform-\textit{d})} \delta 6.03 (s, 1H), 4.12 (tt, \( J = 6.9, 5.5 \) Hz, 1H), 3.68 (s, 2H), 2.84 (br. s, 2H), 2.39 (s, 3H), 2.36 – 2.28 (m, 2H), 1.89 – 1.81 (m, 2H), 1.53 – 1.46 (m, 2H), 1.34 – 1.22 (m, 2H), 0.92 (t, \( J = 7.3 \) Hz, 3H). \text{\textsuperscript{13}C NMR (126 MHz, Chloroform-\textit{d})} \delta 169.7, 162.8, 101.4, 62.6, 54.1, 43.6, 39.2, 38.6, 16.9, 14.5, 12.4. LC-MS: RT = 2.26 min, 99+% (230 nm), m/z = 225 ([M+H]+). HRMS calcd. for C_{12}H_{21}N_{2}O_{2}+ [M+H]+ = 225.1598, found 225.1594. Cis stereochemistry was confirmed by 1D NOE analysis.

\textbf{Cis-3-(((5-methylisoxazol-3-yl)methyl)amino)-3-propylcyclobutan-1-ol (10g)}

\[\text{VUF25586}\]

This compound was synthesised according to general procedure A using cis-amine 8 (153 mg, 0.65 mmol) and 3-methylpicolinaldehyde (71 μL, 0.64 mmol). The crude product was purified over silica gel using a gradient of 0-10% MeOH/EtOAc (+1% Et3N) to afford the title compound as a pale yellow oil (59 mg, 0.25 mmol, 38%).

\[\text{\textsuperscript{1}H NMR (600 MHz, Chloroform-\textit{d})} \delta 8.36 (dd, \( J = 4.8, 1.7 \) Hz, 1H), 7.42 (dd, \( J = 7.7, 1.7 \) Hz, 1H), 7.07 (dd, \( J = 7.7, 4.8 \) Hz, 1H), 4.12 (tt, \( J = 7.0, 5.7 \) Hz, 1H), 3.74 (s, 2H), 2.99 (br. s, 2H), 2.37 – 2.32 (m, 2H), 2.31 (s, 3H), 1.94 – 1.88 (m, 2H), 1.54 – 1.49 (m, 2H), 1.37 – 1.30 (m, 2H), 0.92 (t, \( J = 7.3 \) Hz, 3H). \text{\textsuperscript{13}C NMR (151 MHz, Chloroform-\textit{d})} \delta 156.9, 146.4, 137.8, 131.1, 122.1, 62.5, 53.7, 45.0, 43.7, 39.9, 18.2, 17.1, 14.7. LC-MS: RT = 2.59 min, 99+% (254 nm), m/z = 235 ([M+H]+). HRMS calcd. for C_{14}H_{23}N_{2}O+ [M+H]+ = 235.1805, found 235.1808. Cis stereochemistry was confirmed by 1D NOE analysis.

\textbf{Trans-3-((3-fluorobenzyl)amino)-3-propylcyclobutan-1-ol (11a)}

\[\text{VUF25557}\]
This compound was synthesised according to general procedure A using cis-amine 8 (155 mg, 0.66 mmol) and 3-fluorobenzaldehyde (68 μL, 0.64 mmol). The crude product was purified over silica gel using a gradient of 20-70% EtOAc/CHex followed by reversed-phase C18 silica gel using a gradient of 0–100% MeCN/H2O (+0.1% HCOOH). MeCN was evaporated, solid Na2CO3 was added and extraction was performed with DCM containing 5% CF3CH2OH. The organic phase was dried with Na2SO4, filtered and concentrated in vacuo to afford the title compound as a pale-yellow oil (32 mg, 0.14 mmol, 21%).

1H NMR (500 MHz, Methanol-d4) δ 7.34 – 7.28 (m, 1H), 7.18 – 7.11 (m, 2H), 6.99 – 6.93 (m, 1H), 4.39 (tt, J = 7.5, 6.2 Hz, 1H), 3.59 (s, 2H), 2.35 – 2.28 (m, 2H), 1.81 – 1.75 (m, 2H), 1.68 – 1.63 (m, 2H), 1.36 – 1.28 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). 13C NMR (126 MHz, Methanol-d4) δ 164.34 (d, J = 243.9 Hz), 144.62, 131.05 (d, J = 8.2 Hz), 125.29 (d, J = 2.7 Hz), 116.17 (d, J = 21.3 Hz), 114.59 (d, J = 21.3 Hz), 63.46, 55.31, 47.45 (d, J = 1.8 Hz), 43.23, 42.36, 17.63, 14.82. LC-MS: RT = 2.57 min, 99+% (254 nm), m/z = 238 ([M+H]+). HRMS calc. for C12H12FNO+ [M+H]+ = 238.1602, found 238.1606. Trans stereochemistry was confirmed by 1D NOE analysis.

Trans-3-((3-methylbenzyl)amino)-3-propylcyclobutan-1-ol (11b)
VUF25580

This compound was synthesised according to general procedure A using trans-amine 9 (163 mg, 0.70 mmol) and 3-methylbenzaldehyde (80 μL, 0.68 mmol). The crude product was purified over silica gel using a gradient of 10-70% EtOAc/CHex to afford the title compound as a pale-yellow oil (34 mg, 0.15 mmol, 22%).

1H NMR (500 MHz, Methanol-d4) δ 7.19 (app. t, J = 7.5 Hz, 1H), 7.16 (s, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 4.39 (tt, J = 7.6, 6.1 Hz, 1H), 3.52 (s, 2H), 2.36 – 2.28 (m, 5H), 1.84 – 1.75 (m, 2H), 1.72 – 1.64 (m, 2H), 1.37 – 1.27 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). 13C NMR (126 MHz, Methanol-d4) δ 141.2, 139.1, 130.4, 129.4, 128.7, 126.7, 63.3, 55.3, 48.0, 43.2, 42.3, 21.4, 17.6, 14.8. LC-MS: RT = 2.76 min, 99+% (254 nm), m/z = 234 ([M+H]+). HRMS calc. for C12H12NO+ [M+H]+ = 234.1852, found 234.1854. Trans stereochemistry was confirmed by 1D NOE analysis.

Trans-3-((indolin-7-ylmethyl)amino)-3-propylcyclobutan-1-ol (11c)
VUF25552

This compound was synthesised according to general procedure A using trans-amine 9 (150 mg, 0.64 mmol) and tert-butyl 7-formylindoline-1-carboxylate (154 mg, 0.62 mmol). Deprotection of the N-Boc group was performed by addition of TFA (0.50 mL) to a solution of the crude material in DCM (10 mL) and stirring for 16 h at rt. The volatiles were removed in vacuo and the residue was partitioned between EtOAc and satd. aq. Na2CO3. The aqueous phase was extracted with DCM containing 5% CF3CH2OH. The organic layer was dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The crude product was purified over silica gel using a gradient of 40-100% EtOAc/CHex (+2% Et3N) to afford the title compound as a yellow oil (72 mg, 0.28 mmol, 44%).

1H NMR (500 MHz, Methanol-d4) δ 7.02 (d, J = 7.4 Hz, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.69 (app. t, J = 7.4 Hz, 1H), 4.36 (app. p, J = 7.0 Hz, 1H), 3.55 – 3.45 (m, 4H), 3.01 (t, J = 8.3 Hz, 2H), 2.38 – 2.28 (m, 2H), 1.81 – 1.73 (m, 2H), 1.72 – 1.61 (m, 2H), 1.36 – 1.25 (m, 3H), 0.96 (t, J = 7.3 Hz, 3H). 13C NMR (126 MHz, Methanol-d4) δ 150.4, 131.4,
128.3, 124.4, 123.8, 120.7, 63.7, 55.6, 48.0, 44.9, 43.3, 42.3, 30.9, 17.2, 14.2. LC-MS: RT = 2.43 min, 99+% (254 nm), m/z = 261 ([M+H]+). HRMS calc'd. for C_{16}H_{25}N_{2}O^{+} [M+H]+ = 261.1961, found 261.1960. Trans stereochemistry was confirmed by 1D NOE analysis.

Trans-3-((3,4-difluorobenzyl)amino)-3-propylcyclobutan-1-ol (11d)
VUF25587

This compound was synthesised according to general procedure A using trans-amine 9 (143 mg, 0.61 mmol) and 3,4-difluorobenzaldehyde (65 μL, 0.59 mmol). The crude product was purified over silica gel using a gradient of 0-70% EtOAc/chex (+1% Et3N) to afford the title compound as a colourless oil (81 mg, 0.32 mmol, 52%).

1H NMR (500 MHz, Chloroform-d) δ 7.21 (ddd, J = 11.4, 7.7, 2.0 Hz, 1H), 7.13 – 7.01 (m, 2H), 4.50 (app. p, J = 7.0 Hz, 1H), 3.54 (s, 2H), 2.34 – 2.26 (m, 2H), 1.79 – 1.71 (m, 2H), 1.65 – 1.58 (m, 2H), 1.32 – 1.21 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H).

13C NMR (151 MHz, Methanol-d4) δ 151.4 (dd, J = 245.4, 12.7 Hz), 150.6 (dd, J = 245.4, 12.7 Hz), 139.7 (app. t, J = 4.5 Hz), 125.7 (dd, J = 6.3, 3.5 Hz), 118.2 (d, J = 17.3 Hz), 117.9 (d, J = 17.3 Hz), 63.6, 55.2, 46.9, 43.3, 42.5, 17.6, 14.8. LC-MS: RT = 2.75 min, 99+% (254 nm), m/z = 256 ([M+H]+). HRMS calc'd. for C_{14}H_{20}F_{2}NO^{+} [M+H]+ = 256.1507, found 256.1500. Trans stereochemistry was confirmed by 1D NOE analysis.

Trans-3-(((3-methyloxetan-3-yl)methyl)amino)-3-propylcyclobutan-1-ol (11e)
VUF25551

This compound was synthesised according to general procedure A using trans-amine 9 (150 mg, 0.61 mmol) and 3-methyloxetane-3-carbaldehyde (59 mg, 0.59 mmol). The crude product was purified over silica gel using a gradient of 5-20% MeOH/EtOAc to afford the title compound as a colourless oil (55 mg, 0.26 mmol, 43%).

1H NMR (500 MHz, Methanol-d4) δ 4.46 (d, J = 5.8 Hz, 2H), 4.36 – 4.28 (m, 3H), 2.61 (s, 2H), 2.27 – 2.18 (m, 2H), 1.76 – 1.68 (m, 2H), 1.60 – 1.52 (m, 2H), 1.31 – 1.23 (m, 5H), 0.95 (t, J = 7.4 Hz, 3H). 13C NMR (126 MHz, Methanol-d4) δ 82.5, 63.9, 54.5, 50.9, 43.2, 42.4, 40.6, 22.3, 17.6, 14.8. HRMS calc'd. for C_{12}H_{22}NO^{+} [M+H]+ = 214.1802, found 214.1806. Purity (qNMR): 97%. Trans stereochemistry was confirmed by 1D NOE analysis.

3-chloro-N-((cis)-3-hydroxy-1-propylcyclobutyl)thiophene-2-carboxamide (12a)
VUF25569
This compound was synthesised according to general procedure B using cis-amine 8 (120 mg, 0.51 mmol) and 3-chlorothiophene-2-carboxyl chloride (112 mg, 0.62 mmol). The crude product was purified over silica gel using a gradient of 20-90% EtOAc/chex to afford the title compound as a colourless glass (83 mg, 0.30 mmol, 59%).

\[^{1}\text{H NMR (600 MHz, Methanol-d}_4\text{)} \delta 7.64 (d, J = 5.3 \text{ Hz}, 1H), 7.04 (d, J = 5.3 \text{ Hz}, 1H), 4.12 (\text{app. p, } J = 7.2 \text{ Hz}, 1H), 2.67 – 2.60 (m, 2H), 2.21 – 2.14 (m, 2H), 1.82 – 1.75 (m, 2H), 1.42 – 1.33 (m, 2H), 0.95 (t, J = 7.4 \text{ Hz}, 3H). \[^{13}\text{C NMR (151 MHz, Methanol-d}_4\text{)} \delta 161.4, 133.4, 130.2, 129.8, 125.5, 62.7, 51.2, 44.9, 41.1, 18.7, 14.7. \text{LC-MS: RT = 3.83 min, 99+\% (254 nm), } m/z = 274 ([M+H]^+). \text{HRMS calcd. for C}_{13}\text{H}_{12}\text{ClN}_2O_2^+ [M+H]^+ = 274.0663, found 274.0666. \text{Cis stereochemistry was confirmed by 1D NOE analysis.}

4-chloro-N-((cis)-3-hydroxy-1-propyclobutyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (12b)
VUF25556

This compound was synthesised according to general procedure B using cis-amine 8 (120 mg, 0.51 mmol) and 4-chloro-3-methyl-1-methyl-1H-pyrazole-5-carboxyl chloride (119 mg, 0.62 mmol). The crude product was purified over silica gel using a gradient of 40-100% EtOAc/chex to afford the title compound as a pale-yellow crystalline solid (95 mg, 0.33 mmol, 65%).

\[^{1}\text{H NMR (600 MHz, Methanol-d}_4\text{)} \delta 4.13 (\text{app. p, } J = 7.2 \text{ Hz}, 1H), 3.88 (s, 3H), 2.67 – 2.60 (m, 2H), 2.21 – 2.13 (m, 5H), 1.82 – 1.76 (m, 2H), 1.44 – 1.35 (m, 2H), 0.96 (t, J = 7.4 \text{ Hz}, 3H). \[^{13}\text{C NMR (151 MHz, Methanol-d}_4\text{)} \delta 159.5, 145.7, 135.9, 109.3, 62.7, 51.0, 44.8, 41.1, 38.9, 18.7, 14.7, 10.9. \text{LC-MS: RT = 3.60 min, 99+% (200 nm), } m/z = 224 ([M+H]^+). \text{HRMS calcd. for C}_{13}\text{H}_{12}\text{ClN}_2O_2^+ [M+H]^+ = 224.1645, found 224.1640. \text{Cis stereochemistry was confirmed by 1D NOE analysis.}

N-((cis)-3-hydroxy-1-propyclobutyl)cyclopent-3-ene-1-carboxamide (12c)
VUF25585

Procedure B was modified to take into account the low boiling point of cyclopent-3-ene-1-carboxylic acid. To a solution of cyclopent-3-ene-1-carboxylic acid (100 mg, 0.89 mmol) in DCM (2.5 mL) containing a spatula of 3Å molecular sieves was added (COCI) (71 μL, 0.65 mmol) at 0°C, followed by one drop of DMF. The ice bath was removed and the reaction mixture was stirred for a further 3 h at rt. A modified version of general procedure B was then followed in which Et\textsubscript{3}N (121 μL, 0.87 mmol) and cis-amine 8 (150 mg, 0.64 mmol) were used. The crude product was purified over silica gel using a gradient of 20-100% EtOAc/chex to afford the title compound as a pale-yellow crystalline solid (49 mg, 0.22 mmol, 34%).

\[^{1}\text{H NMR (600 MHz, Methanol-d}_4\text{)} \delta 5.63 (\text{app. br. s, } 2H), 4.06 (\text{app. p, } J = 7.3 \text{ Hz}, 1H), 3.01 – 2.92 (m, 1H), 2.58 – 2.49 (m, 6H), 2.05 – 1.98 (m, 2H), 1.70 – 1.64 (m, 2H), 1.32 – 1.23 (m, 2H), 0.92 (t, J = 7.4 \text{ Hz}, 3H). \[^{13}\text{C NMR (151 MHz, Methanol-d}_4\text{)} \delta 177.0, 129.9, 62.7, 49.8, 44.7, 44.1, 41.0, 37.8, 18.5, 14.7. \text{LC-MS: RT = 3.23 min, 99+% (200 nm), } m/z = 224 ([M+H]^+). \text{HRMS calcd. for C}_{13}\text{H}_{22}\text{NO}_2^+ [M+H]^+ = 224.1645, found 224.1640. \text{Cis stereochemistry was confirmed by 1D NOE analysis.}
This compound was synthesised according to general procedure B using cis-amine 8 (120 mg, 0.51 mmol) and (Z)-2-methylbut-2-enoic carbonyl chloride (73 mg, 0.62 mmol). The crude product was purified over silica gel using a gradient of 30-100% EtOAc/CHex to afford the title compound as a colourless glass (61 mg, 0.29 mmol, 57%). A mixture of Z/E alkenes was observed in an approximate ratio 7:3 in methanol-d4. In the 1H spectrum, all peaks for both alkene isomers are reported, with overlapping signals being reported together and distinct signals reported separately. For 13C NMR analysis, all signals are reported. 1H NMR (500 MHz, Methanol-d4) δ 6.28 (qq, J = 6.9, 1.5 Hz, 1H, minor E isomer), 5.49 (qq, J = 7.0, 1.6 Hz, 1H, major Z isomer), 4.11 – 4.04 (m, 1H), 2.62 – 2.52 (m, 2H), 2.10 – 2.01 (m, 2H), 1.84 (app. p, J = 1.6 Hz, 3H, major Z isomer), 1.79 (app. p, J = 1.2 Hz, 3H, minor E isomer), 1.76 – 1.67 (m, 5H), 1.36 – 1.24 (m, 2H), 0.96 – 0.89 (m, 3H). 13C NMR (126 MHz, Methanol-d4) δ 172.23, 171.40, 135.11, 133.66, 130.98, 126.03, 62.91, 62.84, 50.12, 44.89, 44.83, 41.18, 41.04, 20.88, 18.71, 18.68, 15.08, 14.72, 13.89, 12.50. LC-MS: (minor E isomer) 34 % (254 nm), RT = 3.05 min, 212 ([M+H]+); (major Z isomer) 67 % (254 nm), RT = 3.20 min, 212 ([M+H]+). HRMS calcd. for C12H22NO2+ [M+H]+ = 212.1645, found 212.1651. Cis stereochemistry was confirmed by 1D NOE analysis. E/Z stereochemistry was assigned by selective 1D NOE and decoupled 13C experiments.

3-chloro-N-((cis)-3-hydroxy-1-propylcyclobutyl)benzamide (12e)

This compound was synthesised according to general procedure B using cis-amine 8 (96 mg, 0.41 mmol) and 3-chlorobenzoyl chloride (86 mg, 0.49 mmol). The crude product was purified over silica gel using a gradient of 20-90% EtOAc to afford the title compound as a colourless oil (50 mg, 0.19 mmol, 46%).

1H NMR (600 MHz, Methanol-d4) δ 7.79 (app. t, J = 1.8 Hz, 1H), 7.71 (ddd, J = 7.8, 1.8, 1.1 Hz, 1H), 7.52 (ddd, J = 7.8, 1.8, 1.1 Hz, 1H), 7.43 (app. t, J = 7.8 Hz, 1H), 4.12 (app. p, J = 7.3 Hz, 1H), 2.69 – 2.62 (m, 2H), 2.18 – 2.11 (m, 2H), 1.81 – 1.75 (m, 2H), 1.38 – 1.29 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). 13C NMR (151 MHz, Methanol-d4) δ 167.2, 138.3, 135.5, 132.3, 131.1, 128.4, 126.6, 62.9, 50.8, 44.9, 41.1, 18.7, 14.7. LC-MS: RT = 3.84 min, 99+% (254 nm), m/z = 268 ([M+H]+). HRMS calcd. for C14H19ClNO2+ [M+H]+ = 212.1645, found 212.1651. Cis stereochemistry was confirmed by 1D NOE analysis.
This compound was synthesised according to general procedure B using cis-amine 8 (140 mg, 0.60 mmol) and 3-methylbenzoyl chloride (117 mg, 0.72 mmol). The crude product was purified over silica gel using a gradient of 10-50% EtOAc/cHex to afford the title compound as a white solid (72 mg, 0.29 mmol, 48%).

1H NMR (500 MHz, Methanol-d4) δ 7.62 – 7.57 (m, 1H), 7.58 – 7.55 (m, 1H), 7.36 – 7.28 (m, 2H), 4.64 (br. s, 1H), 4.12 (app. p, J = 7.3 Hz, 1H), 2.68 – 2.62 (m, 2H), 2.39 (s, 3H), 2.18 – 2.11 (m, 2H), 1.81 – 1.76 (m, 2H), 1.39 – 1.29 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H).

13C NMR (126 MHz, Methanol-d4) δ 169.1, 139.4, 136.3, 133.0, 129.4, 128.8, 125.4, 62.9, 50.6, 44.9, 41.1, 21.4, 18.7, 14.7. LC-MS: RT = 3.68 min, 99% (254 nm), m/z = 248 ([M+H]+). HRMS calcd. for C15H22NO2 + [M+H]+ = 248.1645, found 248.1636. Cis stereochemistry was confirmed by 1D NOE analysis.

VUF25584
N-((cis)-3-hydroxy-1-propylcyclobutyl)-3-methylbenzamide (12g)

This compound was synthesised according to general procedure B using cis-amine 8 (135 mg, 0.58 mmol) and 5-fluoronicotinoyl chloride (111 mg, 0.69 mmol). The crude product was purified over silica gel using a gradient of 10-30% MeOH/EtOAc to afford the title compound as a white solid (78 mg, 0.31 mmol, 53%).

1H NMR (500 MHz, Methanol-d4) δ 8.81 (app. t, J = 1.7 Hz, 1H), 8.61 (d, J = 2.8 Hz, 1H), 7.98 (ddd, J = 9.1, 2.8, 1.7 Hz, 1H), 4.14 (app. p, J = 7.2 Hz, 1H), 2.70 – 2.62 (m, 2H), 2.22 – 2.10 (m, 2H), 1.84 – 1.74 (m, 2H), 1.39 – 1.28 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H).

13C NMR (126 MHz, Methanol-d4) δ 169.14 (d, J = 1.4 Hz), 165.10 (d, J = 256.6 Hz), 149.55 (d, J = 4.2 Hz), 145.33 (d, J = 24.3 Hz), 138.23 (d, J = 3.3 Hz), 127.68 (d, J = 19.8 Hz), 67.04, 55.23, 49.00, 45.26, 22.97, 18.97. LC-MS: RT = 3.00 min, 99% (254 nm), m/z = 253 ([M+H]+). HRMS calcd. for C13H12FN2O2 + [M+H]+ = 253.1347, found 253.1335. Cis stereochemistry was confirmed by 1D NOE analysis.

VUF25591
N-((cis)-3-hydroxy-1-propylcyclobutyl)-2-methylfuran-3-carboxamide (12h)

This compound was synthesised according to general procedure B using cis-amine 8 (150 mg, 0.64 mmol) and 2-methylfuran-3-carbonyl chloride (111 mg, 0.77 mmol). The crude product was purified over silica gel using a gradient of 50-90% EtOAc/cHex to afford the title compound as a white solid (41 mg, 0.17 mmol, 27%).
1H NMR (500 MHz, Chloroform-d) δ 7.24 (d, J = 2.1 Hz, 1H), 6.35 (d, J = 2.1 Hz, 1H), 5.74 (br. s, 1H), 4.13 (dtt, J = 8.8, 7.4, 5.5 Hz, 1H), 3.49 (d, J = 8.8 Hz, 1H), 2.64 – 2.59 (m, 2H), 2.57 (s, 3H), 2.49 – 2.42 (m, 2H), 1.70 – 1.66 (m, 2H), 1.36 – 1.28 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). 13C NMR (126 MHz, Chloroform-d) δ 163.5, 157.0, 140.5, 116.0, 108.4, 62.0, 50.6, 44.2, 42.2, 17.5, 14.4, 13.7. LC-MS: RT = 3.34 min, 99+% (254 nm), m/z = 238 ([M+H]+). HRMS calcd. for C13H20NO3+ [M+H]+ = 238.1438, found 238.1447. Cis stereochemistry was confirmed by 1D NOE analysis.

3-chloro-N-[(trans)-3-hydroxy-1-propylcyclobutyl]thiophene-2-carboxamide (13a)

This compound was synthesised according to general procedure B using trans-amine 9 (157 mg, 0.64 mmol) and 3-chlorothiophene-2-carbonyl chloride (138 mg, 0.76 mmol). The crude product was purified over silica gel using a gradient of 20-80% EtOAc/cHex to afford the title compound as colourless needles (76 mg, 0.28 mmol, 44%).

1H NMR (600 MHz, Methanol-d4) δ 7.64 (d, J = 5.3 Hz, 1H), 7.04 (d, J = 5.3 Hz, 1H), 4.37 (app. p, J = 7.2 Hz, 1H), 2.76 – 2.66 (m, 2H), 2.01 – 1.95 (m, 2H), 1.93 – 1.86 (m, 2H), 1.37 – 1.29 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). 13C NMR (151 MHz, Methanol-d4) δ 162.3, 133.6, 130.1, 129.8, 125.4, 63.5, 54.2, 44.1, 42.6, 18.4, 14.6. LC-MS: RT = 3.78 min, 99+% (254 nm), m/z = 274 ([M+H]+). HRMS calcd. for C12H17ClNO2S+ [M+H]+ = 274.0663, found 274.0650. Trans stereochemistry was confirmed by 1D NOE analysis.

4-chloro-N-[(trans)-3-hydroxy-1-propylcyclobutyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (13b)

This compound was synthesised according to general procedure B using trans-amine 9 (160 mg, 0.69 mmol) and 4-chloro-3-methyl-1-methyl-1H-pyrazole-5-carbonyl chloride (159 mg, 0.82 mmol). The crude product was purified over silica gel using a gradient of 30-100% EtOAc/cHex to afford the title compound as a pale-yellow crystalline solid (102 mg, 0.36 mmol, 52%).

1H NMR (600 MHz, Methanol-d4) δ 4.37 (app. p, J = 7.2 Hz, 1H), 3.87 (s, 3H), 2.75 – 2.67 (m, 2H), 2.19 (s, 3H), 2.01 – 1.93 (m, 2H), 1.93 – 1.87 (m, 2H), 1.38 – 1.31 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). 13C NMR (151 MHz, Methanol-d4) δ 160.4, 145.7, 136.0, 109.4, 63.5, 54.0, 44.0, 42.5, 38.9, 18.4, 14.6, 10.9. LC-MS: RT = 3.55 min, 99+% (254 nm), m/z = 286 ([M+H]+). HRMS calcd. for C13H17ClNO2+ [M+H]+ = 286.1317, found 286.1307. Trans stereochemistry was confirmed by 1D NOE analysis.

6-fluoro-N-[(trans)-3-hydroxy-1-propylcyclobutyl]picolinamide (13c)

VUF25571
This compound was synthesised according to general procedure B using trans-amine 9 (160 mg, 0.65 mmol) and 6-fluoropyridine-2-carbonyl chloride (124 mg, 0.78 mmol). The crude product was purified over silica gel using a gradient of 20-100% EtOAc/cHex followed by reversed-phase C18 silica gel using a gradient of 0–100% MeCN/H2O (+0.1% HCOOH) to afford the title compound as a colourless oil (38 mg, 0.15 mmol, 23%).

$^1$H NMR (600 MHz, Methanol-$d_4$) δ 8.11 (app. q, $J = 7.8$ Hz, 1H), 7.97 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.26 (dd, $J = 7.8$, 1.8 Hz, 1H), 4.34 (app. p, $J = 7.1$ Hz, 1H), 2.81 – 2.76 (m, 2H), 2.04 – 1.99 (m, 2H), 1.94 – 1.90 (m, 2H), 1.33 – 1.26 (m, 2H), 0.92 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (151 MHz, Methanol-$d_4$) δ 164.49, 163.78 (d, $J = 268.4$ Hz), 150.09 (d, $J = 11.3$ Hz), 144.44 (d, $J = 7.8$ Hz), 120.50 (d, $J = 3.7$ Hz), 113.89 (d, $J = 36.5$ Hz), 63.44, 53.55, 43.93, 42.72, 18.30, 14.55. LC-MS: RT = 3.50 min, 99+% (254 nm), m/z = 253 ([M+H]+). HRMS calcd. for C13H17FN2NaO2+[M+Na]+ = 275.1166, found 275.1166.

Trans stereochemistry was confirmed by 1D NOE analysis.

3-chloro-$N$-((trans)-3-hydroxy-1-propylcyclobutyl)benzamide (13d)
VUF25572

This compound was synthesised according to general procedure B using trans-amine 9 (160 mg, 0.65 mmol) and 3-chlorobenzoyl chloride (136 mg, 0.78 mmol). The crude product was purified over silica gel using a gradient of 20-70% EtOAc/cHex followed by reversed-phase C18 silica gel using a gradient of 0–100% MeCN/H2O (+0.1% HCOOH) to afford the title compound as a colourless oil (40 mg, 0.15 mmol, 23%).

$^1$H NMR (600 MHz, Methanol-$d_4$) δ 7.79 (app. t, $J = 2.0$ Hz, 1H), 7.70 (app. dt, $J = 7.9$, 1.1 Hz, 1H), 7.52 (ddd, $J = 7.9$, 2.0, 1.1 Hz, 1H), 7.43 (app. t, $J = 7.9$ Hz, 1H), 4.32 (app. p, $J = 7.2$ Hz, 1H), 2.77 (ddd, $J = 10.3$, 7.2, 2.9 Hz, 2H), 1.97 (ddd, $J = 10.3$, 7.2, 2.9 Hz, 2H), 1.94 – 1.90 (m, 2H), 1.32 – 1.25 (m, 2H), 0.92 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (151 MHz, Methanol-$d_4$) δ 168.5, 138.5, 135.5, 132.3, 131.1, 128.4, 126.7, 63.6, 53.9, 43.8, 42.6, 18.4, 14.6. LC-MS: RT = 3.84 min, 99+% (254 nm), m/z = 268 ([M+H]+). HRMS calcd. for C14H19ClNO2+[M+H]+ = 268.1099, found 268.1090. Trans stereochemistry was confirmed by 1D NOE analysis.

2-fluoro-$N$-((trans)-3-hydroxy-1-propylcyclobutyl)-3-methylbenzamide (13e)
VUF25574

This compound was synthesised according to general procedure B using trans-amine 9 (160 mg, 0.65 mmol) and 2-fluoro-3-methylbenzoyl chloride (134 mg, 0.78 mmol). The crude product was purified over silica gel using a gradient of 20-70% EtOAc/cHex to afford the title compound as a colourless glass (81 mg, 0.31 mmol, 48%).

S21
\(^1\)H NMR (600 MHz, Methanol-\(d_4\)) \(\delta\) 7.39 – 7.36 (m, 1H), 7.36 – 7.32 (m, 1H), 7.12 (app. t, \(J = 7.6\) Hz, 1H), 4.34 (app. p, \(J = 7.2\) Hz, 1H), 2.75 – 2.70 (m, 2H), 2.31 (d, \(J = 2.0\) Hz, 3H), 1.98 – 1.89 (m, 4H), 1.37 – 1.29 (m, 2H), 0.94 (t, \(J = 7.4\) Hz, 3H). \(^{13}\)C NMR (151 MHz, Methanol-\(d_4\)) \(\delta\) 167.2, 159.4 (d, \(J = 247.2\) Hz), 134.7 (d, \(J = 5.3\) Hz), 128.3 (d, \(J = 2.8\) Hz), 126.8 (d, \(J = 18.1\) Hz), 125.0 (d, \(J = 16.0\) Hz), 125.0 (d, \(J = 4.1\) Hz), 125.0 (d, \(J = 16.0\) Hz), 125.0 (d, \(J = 2.8\) Hz), 125.0 (d, \(J = 18.1\) Hz), 125.0 (d, \(J = 16.0\) Hz), 125.0 (d, \(J = 4.1\) Hz), 63.6, 53.8, 44.0, 42.6, 18.3, 14.6, 14.5 (d, \(J = 4.5\) Hz). LC-MS: RT = 3.77 min, 99+% (254 nm), \(m/z\) = 266 ([M+H]+). HRMS calcd. for C\(_{15}\)H\(_{21}\)FNO\(_2\)\(^+\) [M+H]+ = 266.1551, found 266.1544. Trans stereochemistry was confirmed by 1D NOE analysis.

\textbf{N-\{(trans)-3-hydroxy-1-propylcyclobutyl\}isobutyramide (13f)}

\begin{center}
\includegraphics[width=0.2\textwidth]{figure1}
\end{center}

This compound was synthesised according to general procedure B using trans-amine 9 (160 mg, 0.65 mmol) and isobutyryl chloride (81 \(\mu\)L, 0.78 mmol). The crude product was purified over silica gel using a gradient of 30-100% EtOAc/CHex to afford the title compound as a colourless glass (56 mg, 0.28 mmol, 43%).

\(^1\)H NMR (500 MHz, Methanol-\(d_4\)) \(\delta\) 4.24 (app. p, \(J = 7.2\) Hz, 1H), 2.58 (ddd, \(J = 10.2, 7.2, 2.9\) Hz, 2H), 2.42 (hept, \(J = 6.9\) Hz, 1H), 1.85 (ddd, \(J = 10.2, 7.2, 2.9\) Hz, 2H), 1.81 – 1.76 (m, 2H), 1.37 – 1.29 (m, 2H), 0.90 (t, \(J = 7.4\) Hz, 3H). \(^{13}\)C NMR (126 MHz, Methanol-\(d_4\)) \(\delta\) 179.7, 63.6, 52.6, 44.0, 42.6, 36.3, 19.9, 18.3, 14.6. Purity (qNMR): 99%. HRMS calcd. for C\(_{11}\)H\(_{22}\)NO\(_2\)\(^+\) [M+H]+ = 200.1645, found 200.1653. Trans stereochemistry was confirmed by 1D NOE analysis.

\textbf{N-\{(trans)-3-hydroxy-1-propylcyclobutyl\}-2-methylfuran-3-carboxamide (13g)}

\begin{center}
\includegraphics[width=0.2\textwidth]{figure2}
\end{center}

This compound was synthesised according to general procedure B using trans-amine 9 (160 mg, 0.65 mmol) and 2-methylfuran-3-carbonyl chloride (112 mg, 0.78 mmol). The crude product was purified over silica gel using a gradient of 20-80% EtOAc/CHex followed by reversed-phase C18 silica gel using a gradient of 5-95% MeCN/H\(_2\)O (+0.1% HCOOH) to afford the title compound as a colourless glass (29 mg, 0.12 mmol, 19%).

\(^1\)H NMR (600 MHz, Methanol-\(d_4\)) \(\delta\) 7.33 (d, \(J = 1.9\) Hz, 1H), 6.72 (d, \(J = 1.9\) Hz, 1H), 4.30 (app. p, \(J = 7.2\) Hz, 1H), 2.73 (ddd, \(J = 10.2, 7.2, 2.7\) Hz, 2H), 2.49 (s, 3H), 1.94 (ddd, \(J = 10.2, 7.2, 2.7\) Hz, 2H), 1.91 – 1.87 (m, 2H), 1.31 – 1.25 (m, 2H), 0.92 (t, \(J = 7.4\) Hz, 3H). \(^{13}\)C NMR (151 MHz, Methanol-\(d_4\)) \(\delta\) 166.2, 157.6, 141.5, 117.5, 110.1, 63.7, 53.4, 44.0, 42.9, 18.4, 14.6, 13.5. LC-MS: RT = 3.32 min, 99+% (254 nm), \(m/z\) = 238 ([M+H]+). HRMS calcd. for C\(_{13}\)H\(_{20}\)NO\(_3\)\(^+\) [M+H]+ = 238.1438, found 238.1432. Trans stereochemistry was confirmed by 1D NOE analysis.

\textbf{N-\{(trans)-3-hydroxy-1-propylcyclobutyl\}-3-methylbenzamide (13h)}

\begin{center}
\includegraphics[width=0.2\textwidth]{figure3}
\end{center}

This compound was synthesised according to general procedure B using trans-amine 9 (160 mg, 0.65 mmol) and 3-methylbenzamide chloride (130 mg, 0.78 mmol). The crude product was purified over silica gel using a gradient of 20-80% EtOAc/CHex followed by reversed-phase C18 silica gel using a gradient of 5-95% MeCN/H\(_2\)O (+0.1% HCOOH) to afford the title compound as a colourless glass (28 mg, 0.12 mmol, 19%).
This compound was synthesised according to general procedure B using trans-amine 9 (130 mg, 0.53 mmol) and 3-methylbenzoyl chloride (98 mg, 0.63 mmol). The crude product was purified over silica gel using a gradient of 20-90% EtOAc/cHex followed by reversed-phase C18 silica gel using a gradient of 5-95% MeCN/H₂O (+0.1% HCOOH) to afford the title compound as a viscous colourless oil (40 mg, 0.16 mmol, 30%).

$^1$H NMR (600 MHz, Methanol-$_d_4$) $\delta$ 7.59 (br. s, 1H), 7.57 – 7.53 (m, 1H), 7.35 – 7.29 (m, 2H), 4.32 (app. p, $J$ = 7.2 Hz, 1H), 2.77 (ddd, $J$ = 10.3, 7.4, 2.8 Hz, 2H), 2.39 (s, 3H), 1.98 – 1.89 (m, 4H), 1.33 – 1.24 (m, 2H), 0.92 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (151 MHz, Methanol-$_d_4$) $\delta$ 170.4, 139.4, 136.6, 133.0, 129.4, 128.4, 125.4, 63.7, 53.7, 43.9, 42.7, 21.4, 18.4, 14.6. LC-MS: RT = 3.66 min, 99+% (254 nm), $m/z$ = 248 ([M+H]$^+$). HRMS calcd. for $C_{15}H_{22}NO_2$ $[M+H]^+$ = 248.1645, found 248.1639. Trans stereochemistry was confirmed by 1D NOE analysis.

5-fluoro-N-((trans)-3-hydroxy-1-propylcyclobutyl)thiophene-2-carboxamide (13i)

VUF25577

This compound was synthesised according to a modified version of general procedure B using trans-amine 9 (160 mg, 0.69 mmol) and 5-fluorothiophene-2-carboxylic chloride (120 mg, 0.82 mmol). The acid chloride formation was modified as follows: (COCl)$_2$ (2.04 mmol) was exchanged for S$_2$Cl$_2$ (8.50 mmol) and the solution was heated at reflux for 3 h at 40 °C. The ester hydrolysis step was modified by replacing MeOH with MeCN as solvent to avoid potential S$_2$Ar reactions by MeO$. After 2 h at rt, nBu$_4$NBr (25 mg, 0.077 mmol) was added and the mixture was stirred for a further 16 h at rt. The crude product was purified over silica gel using a gradient of 10-70% EtOAc/cHex to afford the title compound as a white solid (77 mg, 0.30 mmol, 43%).

$^1$H NMR (600 MHz, Methanol-$_d_4$) $\delta$ 7.44 (app. t, $J$ = 4.1 Hz, 1H), 6.58 (dd, $J$ = 4.1, 1.6 Hz, 1H), 4.30 (app. p, $J$ = 7.2 Hz, 1H), 2.74 (ddd, $J$ = 10.2, 7.2, 2.9 Hz, 2H), 1.94 (ddd, $J$ = 10.2, 7.2, 2.9 Hz, 2H), 1.90 – 1.84 (m, 2H), 1.33 – 1.22 (m, 2H), 0.91 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (151 MHz, Methanol-$_d_4$) $\delta$ 169.88 (d, $J$ = 292.2 Hz), 163.33 (d, $J$ = 1.5 Hz), 130.31 (d, $J$ = 3.1 Hz), 127.02 (d, $J$ = 4.7 Hz), 109.94 (d, $J$ = 11.8 Hz), 63.56, 53.91, 43.86, 42.83, 18.38, 14.58. LC-MS: RT = 3.63 min, 99+% (254 nm), $m/z$ = 258 ([M+H]$^+$). HRMS calcd. for $C_{12}H_{17}FNO_2$ $[M+H]^+$ = 258.0959, found 258.0947. Trans stereochemistry was confirmed by 1D NOE analysis.

$N$-((trans)-3-hydroxy-1-propylcyclobutyl)-1-methyl-1H-pyrazole-5-carboxamide (13j)

VUF25578

This compound was synthesised according to a modified version of general procedure B using trans-amine 9 (160 mg, 0.69 mmol) and 1-methyl-1H-pyrazole-5-carboxylic chloride (119 mg, 0.82 mmol). The acid chloride formation was modified as follows: (COCl)$_2$ (2.04 mmol) was exchanged for S$_2$Cl$_2$ (8.50 mmol) and the solution
was heated at reflux for 3 h at 40 °C. The crude product was purified over silica gel using a gradient of 20-90% EtOAc/cHex to afford the title compound as a colourless oil (80 mg, 0.34 mmol, 49%).

$^1$H NMR (600 MHz, Methanol-$d_4$) δ 7.43 (d, $J = 2.1$ Hz, 1H), 6.77 (d, $J = 2.1$ Hz, 1H), 4.31 (app. p, $J = 7.2$ Hz, 1H), 4.06 (s, 3H), 2.74 (ddd, $J = 10.3, 7.2, 2.9$ Hz, 2H), 1.96 (ddd, $J = 10.3, 7.2, 2.9$ Hz, 2H), 1.93 – 1.88 (m, 2H), 1.33 – 1.25 (m, 2H), 0.93 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (151 MHz, Methanol-$d_4$) δ 161.7, 138.5, 137.7, 108.4, 63.6, 53.8, 43.8, 42.7, 39.1, 18.4, 14.6. LC-MS: RT = 2.81 min, 99+% (254 nm), $m/z = 238 ([M+H]^+).$ HRMS calcd. for C$_{12}$H$_{20}$N$_3$O$_2$+ [M+H]$^+$ = 238.1550, found 238.1542. Trans stereochemistry was confirmed by 1D NOE analysis.

3-fluoro-$N$-[(cis)-3-hydroxy-1-propylcyclobutyl]benzenesulfonamide (14a)

This compound was synthesised according to general procedure C using cis-amine 8 (135 mg, 0.58 mmol) and 3-fluorobenzenesulfonyl chloride (92 µL, 0.69 mmol). The crude product was purified over silica gel using a gradient of 20-100% EtOAc/cHex to afford the title compound as a sticky white solid (21 mg, 0.073 mmol, 13%).

$^1$H NMR (600 MHz, Methanol-$d_4$) δ 7.70 (ddd, $J = 7.8, 1.6, 0.9$ Hz, 1H), 7.60 – 7.55 (m, 2H), 7.35 (app. tdd, $J = 8.5, 2.6, 0.9$ Hz, 1H), 3.96 (app. p, $J = 7.3$ Hz, 1H), 2.36 – 2.31 (m, 2H), 2.05 – 2.00 (m, 2H), 1.53 – 1.48 (m, 2H), 1.21 – 1.14 (m, 2H), 0.72 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (151 MHz, Methanol-$d_4$) δ 163.8 (d, $J = 249.0$ Hz), 147.4 (d, $J = 6.5$ Hz), 132.2 (d, $J = 3.2$ Hz), 123.8 (d, $J = 3.2$ Hz), 120.2 (d, $J = 21.5$ Hz), 114.9 (d, $J = 24.5$ Hz), 62.6, 52.1, 45.1, 42.4, 18.0, 14.2. LC-MS: RT = min, 99+% (254 nm), $m/z = 286 ([M-H]^-).$ HRMS calcd. for C$_{13}$H$_{19}$FNO$_3$S$^- [M+H]^- = 288.1064$, found 288.1051. Cis stereochemistry was confirmed by 1D NOE analysis.

$N$-[(cis)-3-hydroxy-1-propylcyclobutyl]cyclopropanesulfonamide (14b)

This compound was synthesised according to general procedure C using cis-amine 8 (135 mg, 0.58 mmol) and cyclopropanesulfonyl chloride (71 µL, 0.70 mmol). The crude product was purified over silica gel using a gradient of 40-100% EtOAc/cHex and 0-10% MeOH/EtOAc to afford the title compound as a colourless oil (23 mg, 0.10 mmol, 17%).

$^1$H NMR (600 MHz, Methanol-$d_4$) δ 4.04 (app. p, $J = 7.3$ Hz, 1H), 2.51 – 2.44 (m, 3H), 2.24 – 2.18 (m, 2H), 1.68 – 1.63 (m, 2H), 1.48 – 1.41 (m, 2H), 1.08 – 1.04 (m, 2H), 1.02 – 0.98 (m, 2H), 0.95 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (151 MHz, Methanol-$d_4$) δ 62.5, 51.8, 45.7, 43.1, 33.6, 18.2, 14.5, 6.5. Purity (qNMR): 97 %. HRMS calcd. for C$_{10}$H$_{19}$NNaO$_3$S$^- [M+Na]^+ = 256.0978$, found 256.0988. Cis stereochemistry was confirmed by 1D NOE analysis.

$N$-[(cis)-3-hydroxy-1-propylcyclobutyl]-4-methylbenzenesulfonamide (14c)

This compound was synthesised according to general procedure C using cis-amine 8 (135 mg, 0.58 mmol) and 4-methylbenzenesulfonyl chloride (71 µL, 0.70 mmol). The crude product was purified over silica gel using a gradient of 40-100% EtOAc/cHex and 0-10% MeOH/EtOAc to afford the title compound as a colourless oil (23 mg, 0.10 mmol, 17%).

$^1$H NMR (600 MHz, Methanol-$d_4$) δ 4.04 (app. p, $J = 7.3$ Hz, 1H), 2.51 – 2.44 (m, 3H), 2.24 – 2.18 (m, 2H), 1.68 – 1.63 (m, 2H), 1.48 – 1.41 (m, 2H), 1.08 – 1.04 (m, 2H), 1.02 – 0.98 (m, 2H), 0.95 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (151 MHz, Methanol-$d_4$) δ 62.5, 51.8, 45.7, 43.1, 33.6, 18.2, 14.5, 6.5. Purity (qNMR): 97 %. HRMS calcd. for C$_{15}$H$_{19}$NNaO$_3$S$^- [M+Na]^+ = 256.0978$, found 256.0988. Cis stereochemistry was confirmed by 1D NOE analysis.
This compound was synthesised according to general procedure C using cis-amine 8 (120 mg, 0.51 mmol) and 4-methylbenzenesulfonyl chloride (147 mg, 0.77 mmol). The crude product was purified over silica gel using a gradient of 20-100% EtOAc/cHex to afford the title compound as a white solid (53 mg, 0.19 mmol, 37%).

\[ ^1H \text{NMR (500 MHz, Methanol-}d_4) \delta 7.76 – 7.72 (m, 2H), 7.37 – 7.34 (m, 2H), 3.94 (app. p, J = 7.3 Hz, 1H), 2.42 (s, 3H), 2.33 – 2.25 (m, 2H), 2.06 – 1.96 (m, 2H), 1.52 – 1.44 (m, 2H), 1.24 – 1.10 (m, 2H), 0.70 (t, J = 7.3 Hz, 3H). \]

\[ ^{13}C \text{NMR (126 MHz, Methanol-}d_4) \delta 144.5, 142.2, 130.7, 128.1, 62.8, 52.1, 45.2, 42.4, 21.6, 18.1, 14.4. \]

LC-MS: RT = 3.86 min, 99+% (230 nm), m/z = 284 ([M+H]\(^+\)). HRMS calcd. for C_{14}H_{21}NNaO_3S\(^+\) [M+Na]\(^+\) = 306.1134, found 306.1143. Cis stereochemistry was confirmed by 1D NOE analysis.
1D NOE explanation

The relative stereochemistry of the 1-hydroxy group with respect to the 3-nitrogen substituent was determined using selective 1D Nuclear Overhauser Effect (NOE) analysis. In the case of both cis and trans isomers, the cyclobutane ring proton signal (CHOH) and the proton signal corresponding to the methylene unit of the n-propyl chain that is directly connected to the cyclobutane ring (CH₂CH₂CH₃) were selectively irradiated.

As a direct proof, in the case of cis stereochemistry, one would expect these two signals to interact with each other through space since they are on the same face of the cyclobutane ring. As an indirect proof, these two signals should also interact more strongly with the same equivalent protons of the cyclobutane ring (green) to which they have a cis relationship, compared to the equivalent protons of the cyclobutane ring (purple) to which they have a trans relationship.

In the case of trans stereochemistry, one would expect the absence of an NOE signal between the red and blue protons. However, to further support the stereochemistry an indirect proof may also be considered. The red and blue protons should interact more strongly with different equivalent protons of the cyclobutane ring (green vs purple) because the red and blue protons are cis to different protons of the cyclobutane ring (i.e. in the drawing the red proton is expected to interact stronger with the green proton and the blue proton is expected to interact stronger with the purple proton).

Figure S2 – Graphical explanation of the NOE analysis applied to the assignment of relative stereochemistry for synthesised cyclobutane fragments.
Compound characterisation data

Figure S3 - $^1$H and $^{13}$C NMR spectra of 4,4-dichloro-3-propylcyclobut-2-en-1-one (2)
Figure S4 - $^1$H and $^{13}$C NMR spectra of 3-propylcyclobut-2-en-1-one (3)
Figure S5 - $^1$H and $^{13}$C NMR spectra of 3-azido-3-propylcyclobutan-1-one (4)
Figure S6 - $^1$H and $^{13}$C NMR and selective 1D NOE NMR spectra of 3-azido-3-propylcyclobutan-1-ol (5, mixture of cis and trans isomers)
Figure S7 - $^1$H and $^{13}$C NMR and LCMS data of cis-3-azido-3-propylcyclobutyl benzoate (6)
Figure S8 - $^1$H and $^{13}$C NMR and LCMS data of *trans*-3-azido-3-propylcyclobutyl benzoate (7)
Figure S9 - $^1$H and $^{13}$C NMR and LCMS data of cis-3-amino-3-propylcyclobutyl benzoate (8)

\[ \text{cis-3-amino-3-propylcyclobutyl benzoate (8)} \]
Figure S10 - $^1$H and $^{13}$C NMR and LCMS data of *trans*-3-amino-3-propylcyclobutyl benzoate (9)
Figure S11 - $^1$H, $^{13}$C and 1D NOE NMR and LCMS data of *cis-3-(indolin-7-ylmethyl)amino)-3-propylcyclobutan-1-ol* (10a)
As a result of the low epsilon of the compound, the solvent front is amplified.
Figure S12 - \(^1\)H and \(^{13}\)C NMR and LCMS data of \textit{trans}-3-(((2,3-dihydrobenzofuran-5-yl)methyl)amino)-3-propylcyclobutan-1-ol (10b)
Figure S13 - $^1$H and $^{13}$C NMR and LCMS data of 3-(((cis)-3-hydroxy-1-propylcyclobutyl)amino)methyl]phenol (10c)
(As a result of the low epsilon of the compound, the solvent front is amplified)
Figure S14 - $^1$H and $^{13}$C NM and qNMR data of \textit{cis}-3-((cyclopropylmethyl)amino)-3-propylcyclobutan-1-ol (10d)
Figure S15 - $^1$H and $^{13}$C NMR and LCMS data of cis-3-((3,4-difluorobenzyl)amino)-3-propylcyclobutan-1-ol (10e)
(As a result of the low epsilon of the compound, the solvent front is amplified)
Figure S16 - $^1$H and $^{13}$C NMR and LCMS data of cis-3-((5-methylisoxazol-3-yl)methyl)amino)-3-propylcyclobutan-1-ol (10f)
As a result of the low epsilon of the compound, the solvent front is amplified.
Figure S17 - $^1$H and $^{13}$C NMR and LCMS data of cis-3-(((5-methylisoxazol-3-yl)methyl)amino)-3-propylcyclobutan-1-ol (10g)
Figure S18 - $^1$H and $^{13}$C NMR and LCMS data of trans-3-((3-fluorobenzyl)amino)-3-propylcyclobutan-1-ol (11a)
As a result of the low epsilon of the compound, the solvent front is amplified.
Figure S19 - $^1$H and $^{13}$C NMR and LCMS data of *trans*-3-((3-methylbenzyl)amino)-3-propylcyclobutan-1-ol (11b)
As a result of the low epsilon of the compound, the solvent front is amplified.
Figure S20 - $^1$H and $^{13}$C NMR and LCMS data of trans-3-((indolin-7-ylmethyl)amino)-3-propylcyclobutan-1-ol (11c)
Figure S21 - $^1$H and $^{13}$C NMR and LCMS data of trans-3-((3,4-difluorobenzyl)amino)-3-propylcyclobutan-1-ol (11d)
S81
Figure S22. $^1$H and $^{13}$C NMR and qNMR spectra of trans-3-(((3-methyloxetan-3-yl)methyl)amino)-3-propylcyclobutan-1-ol (11e)
Figure S23 - $^1$H and $^{13}$C NMR and LCMS data of 3-chloro-N-((cis)-3-hydroxy-1-propylcyclobutyl)thiophene-2-carboxamide (12a)
Figure S24 - $^1$H and $^{13}$C NMR and LCMS data of 4-chloro-N-((cis)-3-hydroxy-1-propylcyclobutyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (12b)
Figure S25 - $^1$H and $^{13}$C NMR and LCMS data of N-((cis)-3-hydroxy-1-propylcyclobutyl)cyclopent-3-ene-1-carboxamide (12c)
As a result of the low epsilon of the compound, the solvent front is amplified.
Figure S26 - $^1$H and $^{13}$C NMR and LCMS data of N-(cis)-3-hydroxy-1-propylcyclobutyl)-2-methylbut-2-enamide, 7:3 mixture of Z- and E-isomers (12d)
Figure S27 - $^1$H and $^{13}$C NMR and LCMS data of 3-chloro-N-((cis)-3-hydroxy-1-propylcyclobutyl)benzamide (12e)
Figure S28 - $^1$H and $^{13}$C NMR and LCMS data of $N$-((cis)-3-hydroxy-1-propylcyclobutyl)-3-methylbenzamide (12f)
Figure S29 - $^1$H and $^{13}$C NMR and LCMS data of $N$-(cis)-3-hydroxy-1-propylcyclobutyl)-3-methylbenzamide (12g)
Figure S30 - $^1$H and $^{13}$C NMR and LCMS data of $N$-((cis)-3-hydroxy-1-propylcyclobutyl)-2-methylfuran-3-carboxamide (12h)
(As a result of the low epsilon of the compound, the solvent front is amplified)
Figure S31 - $^1$H and $^{13}$C NMR and LCMS data of 3-chloro-N-(trans)-3-hydroxy-1-propylcyclobutyl)thiophene-2-carboxamide (13a)
Figure S32 - $^1$H and $^{13}$C NMR and LCMS data of 4-chloro-N-((trans)-3-hydroxy-1-propylcyclobutyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (13b)
Figure S33 - $^1$H, $^{13}$C and 1D NOE NMR and LCMS data of 6-fluoro-N-((trans)-3-hydroxy-1-propylcyclobutyl)picolinamide (13c)
Figure S34 - $^1$H and $^{13}$C NMR and LCMS data of 3-chloro-$N$-((trans)-3-hydroxy-1-propylcyclobutyl)benzamide (13d)
Figure S35 - $^1$H and $^{13}$C NMR and LCMS data of 2-fluoro-N-((trans)-3-hydroxy-1-propylcyclobutyl)-3-methylbenzamide (13e)
Figure S36 - $^1$H and $^{13}$C NMR and qNMR spectra of $N$-((trans)-3-hydroxy-1-propylcyclobutyl)isobutyramide (13f)
Figure S37 - $^1$H and $^{13}$C NMR and LCMS data of $N$-((trans)-3-hydroxy-1-propylcyclobutyl)-2-methylfuran-3-carboxamide (13g)
Figure S38 - $^1$H and $^{13}$C NMR and LCMS data of $N$-((trans)-3-hydroxy-1-propylcyclobutyl)-3-methylbenzamide (13h)
Figure S39 - $^1$H and $^{13}$C NMR and LCMS data of 5-fluoro-$N$-((trans)-3-hydroxy-1-propylcyclobutyl)thiophene-2-carboxamide (13i)
Figure S40 - $^1$H and $^{13}$C NMR and LCMS data of $N$-((trans)-3-hydroxy-1-propylcyclobutyl)-1-methyl-1H-pyrazole-5-carboxamide (13j)
Figure S41 - $^1$H and $^{13}$C NMR and LCMS data of 3-fluoro-N-((cis)-3-hydroxy-1-propylcyclobutyl)benzenesulfonamide (14a)
Figure S42 - $^1$H and $^{13}$C NMR and qNMR spectra of \textit{N-}((\textit{cis})-3-hydroxy-1-propylcyclobutyl)cyclopropanesulfonamide (14b)
Figure S43 - $^1$H and $^{13}$C NMR and LCMS data of $N$-((cis)-3-hydroxy-1-propylcyclobutyl)-4-methylbenzenesulfonamide (14c)
(As a result of the low epsilon of the compound, the solvent front is amplified)
References

[1] G. F. Pauli, S.-N. Chen, C. Simmler, D. C. Lankin, T. Gödecke, B. U. Jaki, J. B. Friesen, J. B. McAlpine, J. G. Napolitano, *J. Med. Chem.* **2014**, *57*, 9220–9231.

[2] “Information on Azide Compounds – Stanford Environmental Health & Safety,” can be found under https://ehs.stanford.edu/reference/information-azide-compounds, (accessed Nov 23, 2021)

[3] A. Claesson, A. Minidis, *Chem. Res. Toxicol.* **2018**, *31*, 389–411.

[4] A. F. Stepan, D. P. Walker, J. Bauman, D. A. Price, T. A. Baillie, A. S. Kalgutkar, M. D. Aleo, *Chem. Res. Toxicol.* **2011**, *24*, 1345–1410.

[5] A. Böhme, D. Thaens, A. Paschke, G. Schüürmann, *Chem. Res. Toxicol.* **2009**, *22*, 742–750.

[6] L. R. Krepski, A. Hassner, *J. Org. Chem.* **1978**, *43*, 3173–3179.

[7] A. A. Ammann, M. Rey, A. S. Dreiding, *Helv. Chim. Acta* **1987**, *70*, 321–328.

[8] R. Hekmatshoar, S. Sajadi, M. M. Heravi, *J. Chinese Chem. Soc.* **2008**, *55*, 616–618.

[9] R. L. Danheiser, S. K. Gee, *J. Org. Chem.* **1984**, *49*, 1672–1674.

[10] W. D. Crow, C. Wentrup, *Tetrahedron Lett.* **1967**, *8*, 4379–4384.