1,2-Dihydropyridazines as Versatile Synthetic Intermediates

Supporting Information

Thomas K. Britten, a Paul D. Kemmitt, b Nathan R. Halcovitch a and Susannah C. Coote a*

a Department of Chemistry, Lancaster University, Lancaster LA1 4YB, U.K.
b Medicinal Chemistry, Research and Early Development, Oncology R&D, AstraZeneca, Cambridge CB10 1XL, U.K.

1. Synthetic Procedures and Analytical Data of New Compounds
   1.1 General Information
   1.2 General Procedure for Thermal Isomerization of 1,2-Dihydropyridazines
   1.3 Synthetic Procedures

2. References for the Supporting Information

3. 1H/13C NMR Spectra of New Compounds

4. X-Ray Diffraction Data for 4b, 6, 8 and 10
1. Synthetic Procedures and Analytical Data of New Compounds

1.1 General Information

Reagents were purchased in the highest purity available from Acros Organics, Alfa Aesar or Sigma Aldrich. Anhydrous solvents used in reactions were purchased from Acros Organics equipped with AcroSeal™ and all other solvents used were of reagent grade. Reaction vessels were oven dried and cooled under an argon atmosphere prior to use and experiments were performed under argon gas. Reactions were monitored by thin-layer chromatography (TLC) and/or ¹H NMR spectroscopic analysis. Photochemical reactions were performed using a Rayonet RPR-100 Photochemical batch reactor.

Analytical TLC was carried out using Merck pre-coated aluminum-backed TLC silica gel plates (silica gel 60 F₂₅₄) and the plates were visualised by UV light (254 nm) and by staining with either potassium permanganate or aqueous acidic ammonium molybdate(IV). Normal phase flash column chromatography on silica gel was carried out using silica gel from VWR (40-63 microns).

¹H NMR spectroscopic data were obtained on either 300 or 400 MHz instruments and ¹³C(¹H) NMR data were obtained at 100 MHz (Bruker Ultrashield 400 Plus) at 298 K unless otherwise specified. The chemical shifts are reported in parts per million (δ) relative to residual CHCl₃ (δH = 7.26 ppm) and CDCl₃ (δC = 77.16 ppm, central line), residual d₅-DMSO (δH = 2.50 ppm) and d₆-DMSO (δC = 39.52 ppm, central line). The assignment of the signals in the ¹H and ¹³C NMR spectra was achieved through 2D-NMR techniques: COSY, HSQC and HMBC. Coupling constants (J) are quoted in Hertz. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. Melting points were performed on a Sanyo Gallenkamp capillary melting point apparatus and are uncorrected. High resolution mass spectrometry data were recorded using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Shimadzu LCMS-IT-TOF mass spectrometer. UV/Vis spectra were recorded using an Agilent Cary 60 UV-Vis spec spectrophotometer. For X-ray crystallography a suitable crystal was selected and mounted on a Mitegen loop using Paratone-N oil on a SuperNova, Dual, Cu at zero, AtlasS2 diffractometer. The crystal was kept at 100.2(5) K during data collection. Using Olex2,¹ the structure was solved with the ShelXT structure solution program using direct methods and refined with the ShelXL refinement package using least squares minimisation.²,³ Figures and tables were prepared using Olex2 software.¹

1,2-Dihydropyridazine starting materials were synthesized according to our previous publication.⁴

1.2 General Procedure for Thermal Isomerization of 1,2-Dihydropyridazines

A solution of 1,2-dihydropyridazine (1.0 eq) in o-xylene (0.4-0.5 M) was heated at reflux for 5 hours under argon. The reaction mixture was purified directly by flash column chromatography using an appropriate solvent system, as described for each individual procedure. Note: 2-Aminopyrroles must be stored in the freezer under an inert atmosphere in order to prevent degradation.
1.3 Synthetic Procedures

**Methyl 2-[(methoxycarbonyl)amino]-1H-pyrrole-1-carboxylate 2a**

\[
\begin{align*}
\text{Using the general procedure, a solution of 1,2-dihydropyridazine 1a (520 mg, 2.62 mmol) in o-xylene (5 mL) was heated at reflux for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 100% hexane→9:1) gave 2-aminopyrrole 2a (320 mg, 1.61 mmol, 62%) as a white solid.} \\
R_f (Hexane-EtOAc, 2:1) = 0.35 \\
\text{m.p.} = 46-47 \degree C \\
{^1}H \text{ NMR (400 MHz, CDCl}_3); \delta 9.05 (\text{br s, 1H, NH}), 6.85 (dd, J = 3.6, 1.8 Hz, 1H, H1), 6.42-6.32 (br m, 1H, H3), 6.13 (t, J = 3.6 Hz, 1H, H2), 3.95 (s, 3H, H8), 3.77 (s, 3H, H6). \\
{^{13}}C \text{ NMR (100 MHz, CDCl}_3); \delta 153.1 (C5), 152.4 (C7), 130.5 (C4), 114.0 (C1), 111.6 (C2), 98.4 (C3), 54.2 (C8), 52.6 (C6). \\
\text{FTIR (ATR) } \nu (\text{cm}^{-1}); 3349 (\text{NH}), 2950, 1724 (\text{C=O}). \\
\text{HRMS (APCI): } m/z \text{ calculated for: C}_{8}H_{10}N_{2}O_{4} [\text{M+H}]^{+} 199.0713, \text{ found 199.0712.}
\end{align*}
\]

**Ethyl 2-[(ethoxycarbonyl)amino]-1H-pyrrole-1-carboxylate 2b**

\[
\begin{align*}
\text{Using the general procedure, a solution of 1,2-dihydropyridazine 1b (562 mg, 2.48 mmol) in o-xylene (5 mL) was heated at reflux for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 100% hexane→14:1) gave 2-aminopyrrole 2b (481 mg, 2.13 mmol, 86%) as a pale yellow oil.} \\
R_f (Hexane-EtOAc, 1:1) = 0.57 \\
{^1}H \text{ NMR (400 MHz, CDCl}_3); \delta 9.08 (\text{br s, 1H, NH}), 6.87 (dd, J = 3.6, 1.8 Hz, 1H, H1), 6.42-6.31 (br m, 1H, H3), 6.13 (t, J = 3.6 Hz, 1H, H2), 4.40 (q, J = 7.1 Hz, 2H, H9), 4.22 (q, J = 7.1 Hz, 2H, H6), 1.41 (t, J = 7.1 Hz, 3H, H10), 1.30 (t, J = 7.1 Hz, 3H, H7).
\end{align*}
\]
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 152.8 (C5), 152.0 (C8), 130.8 (C4), 113.9 (C1), 111.5 (C2), 98.2 (C3), 63.8 (C9), 61.6 (C6), 14.7 (C7), 14.3 (C10).

\(^1\)H NMR (400 MHz, d\(_6\)-DMSO) δ 8.92 (br s, 1H, NH), 7.07 (dd, \(J = 3.6, 1.9\) Hz, 1H, H1), 6.15 (t, \(J = 3.6\) Hz, 1H, H2), 6.10-6.06 (br m, 1H, H3), 4.32 (q, \(J = 7.1\) Hz, 2H, H9), 4.08 (q, \(J = 7.1\) Hz, 2H, H6), 1.30 (t, \(J = 7.1\) Hz, 3H, H10), 1.20 (t, \(J = 7.1\) Hz, 3H, H7).

\(^{13}\)C NMR (100 MHz, d\(_6\)-DMSO) δ 154.1 (C5), 150.0 (C8), 128.1 (C4), 117.3 (C1), 110.1 (C2), 105.3 (C3), 63.4 (C9), 60.6 (C6), 14.5 (C7), 13.9 (C10).

FTIR (ATR) ν (cm\(^{-1}\)): 3345 (NH), 3145 (NH), 2980, 1718 (C=O).

HRMS (ESI): \(m/z\) calculated for: C\(_{10}\)H\(_{14}\)N\(_2\)O\(_4\) [M+H\(^+\)] 227.1026, found 227.1024.

**Important NOE Contacts (d\(_6\)-DMSO):**

\[\text{Isopropyl 2-(isopropoxycarbonylamino)-1H-pyrrole-1-carboxylate 2c}\]

Using the general procedure, a solution of 1,2-dihydropyridazine 1c (906 mg, 3.56 mmol) in \(\sigma\)-xylene (10 mL) was heated at reflux for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 100% hexane→14:1) gave 2-aminopyrrole 2c (818 mg, 3.22 mmol, 90%) as yellow oil. 

\(R_f\) (Hexane-EtOAc, 2:1) = 0.58

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 9.08 (br s, 1H, NH), 6.85 (dd, \(J = 3.6, 1.8\) Hz, 1H, H1), 6.40-6.32 (br m, 1H, H3), 6.12 (t, \(J = 3.5\) Hz, 1H, H2), 5.16 (sept, \(J = 6.2\) Hz, 1H, H9), 5.00 (sept, \(J = 6.2\) Hz, 1H, H6), 1.39 (d, \(J = 6.2\) Hz, 6H, H10), 1.29 (d, \(J = 6.2\) Hz, 6H, H7).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 152.4 (C5), 151.6 (C8), 131.0 (C4), 113.8 (C1), 111.3 (C2), 98.0 (C3), 72.3 (C9), 69.1 (C6), 22.2 (C7), 21.9 (C10).

FTIR (ATR) ν (cm\(^{-1}\)): 3366 (NH), 2982, 1720 (C=O).

HRMS (APCI): \(m/z\) calculated for: C\(_{12}\)H\(_{18}\)N\(_2\)O\(_4\) [M+Na\(^+\)] 277.1159, found 277.1154.
**tert-Butyl 2-(tert-butoxycarbonylamino)pyrrole-1-carboxylate 2d**

Using the general procedure, a solution of 1,2-dihydropyridazine 1d (304 mg, 1.08 mmol) in o-xylene (3 mL) was heated at reflux for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 100% hexane→9:1) gave 2-aminopyrrole 2d (33 mg, 0.12 mmol, 11%) as a brown oil and 2-aminopyrrole S1 (56 mg, 0.31 mmol, 28%) as a brown film.

**2-Aminopyrrole 2d**

\[ \begin{align*}
\text{R}_f \text{ (Hexane-EtOAc, 2:1)} & = 0.58 \\
^1\text{H NMR (400 MHz, CDCl}_3\text{)} & : \delta 9.00 \text{ (br s, 1H, NH), 6.79 (dd, J = 3.5, 1.8 Hz, 1H, H1), 6.35-6.29 (br m, 1H, H3), 6.08 (t, J = 3.5 Hz, 1H, H2), 1.59 (s, 9H, H7 or H10), 1.50 (s, 9H, H7 or H10).} \\
^13\text{C NMR (100 MHz, CDCl}_3\text{)} & : \delta 151.8 (C5), 150.8 (C8), 131.2 (C4), 113.9 (C1), 110.8 (C2), 97.5 (C3), 84.8 (C6 or C9), 80.6 (C6 or C9), 28.5 (C7 or C10), 28.1 (C7 or C10). \\
\text{FTIR (ATR) } \nu \text{ (cm}^{-1}) & : 3366 (\text{NH}), 2982, 1720 (\text{C=O)}. \\
\text{HRMS (APCI): } m/z \text{ calculated for: C}_{12}\text{H}_{18}\text{N}_2\text{O}_4 [M+Na}^+ & 277.1159, \text{ found } 277.1154.
\end{align*} \]

**2-Aminopyrrole S1**

\[ \begin{align*}
\text{R}_f \text{ (Hexane-EtOAc, 2:1)} & = 0.50 \\
^1\text{H NMR (400 MHz, CDCl}_3\text{)} & : \delta 9.60 \text{ (br s, 1H, NH\text{A}), 7.26 (br s, 1H, NH\text{b}), 6.50-6.45 (m, 1H, H1), 6.07 (m, 1H, H2), 5.61-5.51 (m, 1H, H3), 1.52 (s, 9H, H7).} \\
^13\text{C NMR (100 MHz, CDCl}_3\text{)} & : \delta 153.4 (C5), 128.1 (C4), 112.1 (C1), 107.0 (C2), 92.5 (C3), 81.1 (C6), 28.4 (C). \\
\text{FTIR (ATR) } \nu \text{ (cm}^{-1}) & : 3452 (\text{NH}), 3314 (\text{NH}), 2980, 1679 (\text{C=O}).
\end{align*} \]

S5
HRMS (ESI): m/z calculated for: C_{9}H_{14}N_{2}O_{2} [M+H]^+ 183.1128, found 183.1127.

Important NOE Contacts:

\[
\text{Isopropyl 2-(isoproxy carbonylamino)-5-methoxycarbonyl-1H-pyrrole-1-carboxylate 2e}
\]

A solution of 1,2-dihydropyridazine 1e (100 mg, 0.32 mmol) in o-xylene (2 mL) was heated at 130 °C for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-Et_{2}O, 2:1) gave 2-aminopyrrole 2e (79 mg, 0.25 mmol, 79%) as a colourless oil.

R_{f} (hexane-Et_{2}O, 2:1) = 0.28

^1H NMR (400 MHz, CDCl_{3}); δ 8.81 (br s, 1H, NH), 6.88 (dd, J = 3.5, 0.5 Hz, 1H, H3), 6.36 (br d, J = 3.5, 1H, H2), 5.14 (sept, J = 6.3 Hz, 1H, H7 or H10), 4.99 (sept, J = 6.2 Hz, 1H, H7 or H10), 3.78 (s, 3H, OMe), 1.36 (d, J = 6.3 Hz, 6H, H8 or H11), 1.29 (d, J = 6.2 Hz, 6H, H8 or H11).

^{13}C NMR (100 MHz, CDCl_{3}); δ 160.9 (C5), 152.0 and 151.5 (C6 and C9), 136.0 (C1), 123.0 (C2), 118.9 (C4), 97.2 (C3), 73.9 and 69.8 (C7 and C10), 22.1 and 21.5 (C8 and C11).

FTIR (ATR) ν (cm\(^{-1}\)): 3367 (NH), 2983, 2948, 1719 (C=O), 1531, 1357, 1344, 1305, 1279, 1195, 1179, 1100, 1002, 754.

HRMS (ESI): m/z calculated for: C_{14}H_{20}N_{2}O_{6} [M+H]^+ 313.1394, found 313.1400.

Diisopropyl naphthalene-1,4-diylbiscarbamate 4a
CsF (79 mg, 0.52 mmol, 3.0 eq) was added in one portion to a stirred solution of 2-aminopyrrole 2c (44 mg, 0.17 mmol, 2.1 eq) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (20 µL, 0.08 mmol, 1.0 eq) in MeCN (0.8 mL) at room temperature under argon, then heated at 40 °C for 2.5 hours. The reaction mixture was cooled to room temperature, filtered through Celite and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave diamine 4a (20 mg, 0.06 mmol, 74%) as a white solid. 

$R_f$ (Hexane-EtOAc, 2:1) = 0.26

m.p. = 187-189 °C (decomposition)

$^1$H NMR (400 MHz, d$_6$-DMSO); δ 9.37 (br s, 2H, NH), 8.02 (br dd, $J = 6.5, 3.3$ Hz, 2H, H5), 7.54 (br dd, $J = 6.5, 3.3$ Hz, 2H, H2), 4.91 (sept, $J = 6.2$ Hz, 2H, H7), 1.28 (br d, $J = 6.2$ Hz, 12H, H8).

$^{13}$C NMR (100 MHz, d$_6$-DMSO); δ 154.7 (C6), 131.1 (C1), 128.7 (C3), 125.8 (C5), 123.1 (C4), 121.4 (C2), 67.6 (C7), 22.0 (C8).

FTIR (ATR) ν (cm$^{-1}$): 3263 (NH), 2974, 1737 (C=O), 1690 (C=O).

HRMS (ESI): m/z calculated for: C$_{18}$H$_{22}$N$_2$O$_4$ [M+Na]$^+$ 353.1472, found 353.1458.

Dimethyl acetylenedicarboxylate (31 µL, 0.25 mmol, 1.1 eq) was added in one portion to a stirred solution of 2-aminopyrrole 2c (58 mg, 0.23 mmol, 1.0 eq) in PhMe (3.0 mL). The reaction was heated at 60 °C for 18 hours, then cooled to room temperature and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave p-phenylenediamine derivative 4b (59 mg, 0.15 mmol, 65%) as a yellow solid.

$R_f$ (Hexane-EtOAc, 2:1) = 0.4

m.p. = 118-120 °C

$^1$H NMR (400 MHz, CDCl$_3$); δ 8.42 (br s, 2H, NH), 8.31 (s, 2H, H2), 4.99 (sept, $J = 6.3$ Hz, 2H, H7), 3.87 (s, 6H, H5), 1.29 (d, $J = 6.3$ Hz, 12H, H8).

$^{13}$C NMR (100 MHz, CDCl$_3$); δ 167.9 (C4), 153.4 (C6), 133.6 (C1), 124.7 (C2), 119.4z (C3), 69.3 (C7), 53.0 (C5), 22.2 (C8).

FTIR (ATR) ν (cm$^{-1}$): 3343 (NH), 3308 (NH), 2984, 1720 (C=O ester), 1705 (C=O carbamate).

HRMS (APCI): m/z calculated for: C$_{18}$H$_{24}$N$_2$O$_8$ [M-H]$^-$ 395.1460, found 395.1454.
Diisopropyl 3,6-dihydroxy-3,6-dihydropyridazine-1,2-dicarboxylate 6

\[
\begin{align*}
\text{m-CPBA (76 mg, 0.44 mmol, 1.1 eq) was added in one portion to a stirred solution of 1,2-}
\text{dihydropyridazine 1c (100 mg, 0.39 mmol, 1.0 eq) in MeCN (1 mL) at 0 °C under argon. The reaction}
\text{mixture was stirred at room temperature for 44 hours, then the solvent was removed under reduced}
\text{pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent:}
\text{hexane-EtOAc, 3:1–2:1–1:1) gave diol trans-6 (63 mg, 0.22 mmol, 56%) as a colourless oil, which}
\text{became an off-white solid upon standing.}
\text{Rf (Hexane-EtOAc, 1:1) = 0.11}
\text{m.p. = 108-110 °C}
\text{H NMR (400 MHz, 328 K, CDCl}_3\text{): δ 6.03-5.98 (m, 2H, H2 and H3), 5.94-5.85 (br m, 2H, H1 and H4),}
\text{4.97 (sept, J = 6.3 Hz, 2H, H6 and H9), 1.26 (br d, J = 6.3 Hz, 12H, H7 and H10).}
\text{C NMR (100 MHz, 328 K, CDCl}_3\text{): δ 154.6 (C5/C8), 127.6 (C2/C3), 72.4 (C1/C4), 70.9 (C6/C9), 22.1}
\text{and 22.0 (C7/C10).}
\text{FTIR (ATR) ν (cm}^{-1}\text{): 3416 (OH), 2982, 1679 (C=O).}
\text{HRMS (ESI): m/z calculated for: C12H20N2O6 [M+Na]^+ 311.1214, found 311.1199.}
\end{align*}
\]

Diisopropyl 3,6-bis[(4-methylbenzene-1-sulfonyl)amino]-3,6-dihydropyridazine-1,2-
dicarboxylate 8

\[
\begin{align*}
\text{Cu(OTf)}_2\text{ (14 mg, 0.04 mmol, 0.1 eq) was added to a stirred solution of PhI=NTs (294 mg, 0.79 mmol,}
\text{2.0 eq) and 1,2-dihydropyridazine 1c (100 mg, 0.39 mmol, 1.0 eq) in MeCN (2 mL) at room temperature}
\text{under argon. The resulting mixture was stirred at room temperature for 1 hour, then evaporated under}
\text{reduced pressure to give the crude product. Purification by flash column chromatography on silica gel}
\text{(eluent Et}_2\text{O) gave trans-9 (145 mg, 0.24 mmol, 62%) as a white solid.}
\text{Rf (Et}_2\text{O) = 0.52}
\end{align*}
\]
m.p. = 203-205 °C (decomposition)
The \(^1\)H/\(^{13}\)C NMR spectra of 8 are complex, with several species present at room temperature. Upon heating, full coalescence is not observed until 408 K (at which temperature significant degradation is also observed), thus \(^1\)H NMR data is given at 378 K, and spectra are provided at both 298 K and 378 K. For \(^{13}\)C NMR, data and spectra are given at 298 K and at 388 K (at which temperature C3 is barely visible):

\(^1\)H NMR (400 MHz, 378 K, d\textsubscript{6}-DMSO); δ 8.16 (d, J = 8.5 Hz, 2H, NH), 7.75 (d, J = 8.1 Hz, 4H, H7), 7.32 (d, J = 8.1 Hz, 4H, H8), 5.79 (br d, J = 8.4 Hz, 2H, H2), 5.73-5.68 (m, 2H, H1), 4.73 (sept, J = 6.2 Hz, 2H, H4), 2.38 (s, 6H, H10), 1.12 (d, J = 6.2 Hz, 6H, H5), 1.07 (d, J = 6.2 Hz, 6H, H5).

\(^{13}\)C NMR (100 MHz, 388 K, d\textsubscript{6}-DMSO; δ 152.5 (C3), 141.6 (C6), 139.1 (C9), 128.5 (C7), 125.9 (C8), 125.6 (C2), 69.1 (C4), 58.5 (C1), 20.9, 20.7 and 20.2 (C5).

FTIR (ATR) ν (cm\(^{-1}\)): 3248 (NH), 2982, 2935, 1687 (C=O), 1407, 1385 (S=O), 1318, 1288, 1157 (S=O), 1107, 1046, 908, 814, 747.

**Diisopropyl 3,4-dihydroxy-3,4-dihydropyridazine-1,2-dicarboxylate 9**

\[ \text{HO} \]
\[ \overset{\text{N}}{\text{N}} \]
\[ \overset{\text{O}}{\text{O}} \]

NMO (140 mg, 1.20 mmol, 3.0 eq) was added in one portion to a stirred solution of 1,2-dihydropyridazine 1c (102 mg, 0.40 mmol, 1.0 eq) and OsO\(_4\) (2.5% w/v in \(^1\)BuOH, 0.2 mL, 0.02 mmol, 0.05 eq) in acetone:H\(_2\)O (8:1, 4.5 mL) at room temperature under argon, then stirred at room temperature for 17 hours. The reaction mixture was diluted with a saturated aqueous solution of Na\(_2\)S\(_2\)O\(_3\) (5 mL) and extracted with CH\(_2\)Cl\(_2\) (5 x 5 mL). The combined organic layers were dried (MgSO\(_4\)) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1→1:1) gave the minor product diastereoisomer (24 mg, 0.08 mmol, 21%) as a white solid, and the major product diastereoisomer (66 mg, 0.23 mmol, 57%), as a colourless oil.

**Minor diastereoisomer:**

\[ \text{OH} \]
\[ \overset{\text{N}}{\text{N}} \]
\[ \overset{\text{O}}{\text{O}} \]

\(R_1\) (Hexane-EtOAc, 1:1) = 0.14

m.p. = 104-106°C
$^1$H NMR (400 MHz, d$_6$-DMSO, 348 K); δ 6.81-6.44 (br m, 2H, H$_4$ and OH), 5.51-5.38 (br m, 1H, H$_1$), 4.99-4.93 (br m, 1H, OH), 4.87-4.71 (br m, 3H, H$_3$, H$_6$ and H$_9$), 4.10-4.04 (br m, 1H, H$_2$), 1.24-1.19 (m, 12H, H$_7$ and H$_{10}$).

$^{13}$C NMR (100 MHz, d$_6$-DMSO, 348 K): Spectrum could not be obtained due to epimerisation at this temperature over the length of the experiment. At 298 K, the spectrum is very complex.

FTIR (ATR) ν (cm$^{-1}$): 3424 (OH), 2980, 1687 (C=O).

HRMS (APCI): m/z calculated for: C$_{12}$H$_{20}$N$_2$O$_6$ [M+Na]$^+$ 311.1214, found 311.1199.

Major diastereoisomer:

$R_f$ (Hexane-EtOAc, 1:1) = 0.08

$^1$H NMR (400 MHz, d$_6$-DMSO, 298 K); δ 7.02-6.71 (br m, 1H, H$_4$), 6.54-6.21 (br m, 1H, OH), 5.60-5.45 (br m, 1H, H$_1$), 5.13-4.99 (br m, 2H, OH and H$_3$), 4.87-4.77 (br m, 2H, H$_6$ and H$_9$), 4.31-3.65 (br m, 1H, H$_2$), 1.26-1.14 (m, 12H, H$_7$ and H$_{10}$).

$^1$H NMR (400 MHz, d$_6$-DMSO, 348 K); δ 6.95 (br d, J = 7.6 Hz, 0.9H, H$_4$), 6.77 (br d, J = 7.9 Hz, 0.1H, H$_4$), 6.11 (br s, 1H, OH), 5.68-5.48 (br m, 1H, H$_1$), 5.08-4.99 (br m, 1H, H$_3$), 4.91-4.77 (br m, 3H, H$_6$, H$_9$ and OH), 3.73 (br d, J = 5.2 Hz, 1H, H$_2$), 1.35-1.09 (m, 12H, H$_7$ and H$_{10}$).

$^{13}$C NMR (100 MHz, d$_6$-DMSO, 298 K; additional peaks present due to multiple species present); δ 153.7-151.0 (C$_5$ or C$_8$), 127.5-123.8 (C$_4$), 107.1-105.3 (C$_3$), 80.5-79.0 (C$_1$), 70.9-68.9 (C$_6$ or C$_9$), 63.8-62.7 (C$_2$), 22.0-21.6 (C$_7$ or C$_{10}$).

FTIR (ATR) ν (cm$^{-1}$): 3422 (OH), 2984, 1702 (C=O), 1649 (C=O).

HRMS (APCI): m/z calculated for: C$_{12}$H$_{20}$N$_2$O$_6$ [M+Na]$^+$ 311.1214, found 311.1199.

Diisopropyl 3,3,8,8-tetrachloro-5,6-diazatricyclo[5.1.0.0$^{2,4}$]octane-5,6-dicarboxylate trans-10

An aqueous solution of NaOH (50% w/v, 5 mL) was added dropwise to a solution of 1,2-dihydropyridazine 1c (101 mg, 0.40 mmol, 1.0 eq) and tetrabutylammonium chloride (11 mg, 0.04 mmol, 0.1 eq) in CHCl$_3$ (10 mL) at room temperature under argon, then stirred at room temperature for 3 hours. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl (10 mL) and the organic
layer was separated. The aqueous layer was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 7:1→4:1) gave tricycle trans-10 (117 mg, 0.28 mmol, 71%) as an off-white sticky solid.

Rᵣ (Hexane-EtOAc, 2:1) = 0.44

m.p. = 118-120 °C

The ¹H/¹³C NMR spectra of 10 are complex, with three species apparent at room temperature:

¹H NMR (400 MHz, CDCl₃); δ 5.04-4.94 (m, 2H, H₈/H₁₁), 3.63-3.54 (m, 2H, H₁/H₆), 2.15-2.11 (m, 2H, H₃/H₄), 1.35-1.23 (m, 12H, H₉/H₁₂).

¹³C NMR (100 MHz, CDCl₃); δ 153.5, 153.3, 153.2 (C₇/C₁₀), 71.5, 71.3, 71.1 (C₈/C₁₁), 63.1, 63.0, 62.8 (C₂/C₅), 42.5, 42.2, 41.8 (C₁/C₆), 26.1, 26.0, 25.8 (C₃/C₄), 22.3, 22.0, 21.8 (C₉/C₁₂).

FTIR (ATR) ν (cm⁻¹): 2978, 2926, 1757 (C=O), 1724 (C=O).

HRMS (APCI): m/z calculated for: C₁₄H₁₈N₂O₄Cl₄ [M+H]^⁺ 419.0093, found 419.0079.
2. References for the Supporting Information


$^{1}H$ NMR (400 MHz, CDCl$_3$)

NHCO$_2$Me

$\text{N-N}^{\text{CO$_2$Me}}$

$2\text{a}$
$^{13}$C NMR (101 MHz, CDCl$_3$)

![Chemical structure](2a)

- 153.13
- 152.36
- 130.54
- 113.97
- 111.64
- 54.24
- 52.65

S14
$^{1\text{H}}$NMR (400 MHz, CDCl$_3$)

NHCO$_2$Pr

$\text{N-CO}_2$Pr

$2c$
$^{13}$C NMR (101 MHz, CDCl$_3$)

\[ \text{N} \text{HCO}_2\text{Pr} \]

\[ \text{N} - \text{CO}_2\text{Pr} \]

$2c$
\textsuperscript{1}H NMR (400 MHz, CDCl$_3$)

NHCO$_2$Bu

\begin{align*}
\text{N} & \quad \text{CO$_2$Bu} \\
2d & 
\end{align*}
$^{13}$C NMR (101 MHz, CDCl$_3$)

$\text{NHCO}_2^\text{Bu}$

$\text{N-CO}_2^\text{Bu}$

2d
$^{1}H$ NMR (400 MHz, CDCl$_3$)

\[
\text{MeO}_2C\text{N} \begin{array}{c}
\text{H} \\
\text{CO}_2\text{Pr}
\end{array} \text{NHCO}_2\text{Pr} \\
\text{CO}_2\text{Pr}
\]

2e
$^{13}$C NMR (101 MHz, CDCl$_3$)

$2e$
$\text{H NMR (298 K, 400 MHz, } d_6\text{-DMSO)}$

$$\text{NHCO}_2\text{Pr}$$

$\text{NHCO}_2\text{Pr}$

$\text{1H NMR (298 K, 400 MHz, } d_6\text{-DMSO)}$

$\text{NHCO}_2\text{Pr}$

$\text{NHCO}_2\text{Pr}$
$^{13}$C NMR (298 K, 101 MHz, $d_6$-DMSO)

![Carbon-13 NMR spectrum of compound 4a](image)

-154.66
-137.08
-125.76
-123.08
-121.44
-67.56
-22.04
$^1$H NMR (298 K, 400 MHz, CDCl$_3$)

![NMR Spectrum Image]

Chemical shifts (ppm): 6.01, 6.00, 5.90, 5.02, 4.99, 4.97, 4.96, 4.94, 4.90
$^{13}$C NMR (298 K, 101 MHz, CDCl$_3$)
$^{1}H$ NMR (298 K, 400 MHz, $d_{6}$-DMSO)
$^1$H NMR (378 K, 400 MHz, $d_6$-DMSO)
$^{13}$C NMR (298 K, 101 MHz, $d_6$-DMSO)

![Chemical Structure]

1. $-153.44$
2. $-142.36$
3. $-139.42$
4. $-129.24$
5. $-126.47$
6. $-69.39$
7. $-58.30$
8. $21.48$
9. $21.18$
10. $20.92$

S27
$^{13}$C NMR (388 K, 101 MHz, $d_6$-DMSO)
$^1$H NMR (298 K, 101 MHz, $d_6$-DMSO)
major diastereoisomer

\[
\begin{align*}
\text{HO} & \quad \text{CO}_2\text{iPr} \\
\text{OH} & \quad \text{CO}_2\text{iPr}
\end{align*}
\]
$^{1}$H NMR (348 K, 400 MHz, $d_6$-DMSO)
major diastereoisomer

\[
\begin{align*}
\text{HO} & \quad \text{N} - \text{CO}_2\text{Pr} \\
\text{N} - \text{CO}_2\text{Pr} & \quad \text{OH}
\end{align*}
\]
$^{13}$C NMR (298 K, 101 MHz, $d_6$-DMSO)

major diastereoisomer

\[ \begin{align*}
\text{N} & \quad \text{CO}_2\text{iPr} \\
\text{OH} & \\
\text{HO} & \quad \text{N} \quad \text{CO}_2\text{iPr}
\end{align*} \]
$^{13}$C NMR (348 K, 101 MHz, $d_6$-DMSO)

major diastereoisomer
$^1$H NMR (348 K, 400 MHz, $d_6$-DMSO)

minor diastereoisomer
$^1$H NMR (298 K, 400 MHz, CDCl$_3$)
$^{13}$C NMR (298 K, 101 MHz, CDCl$_3$)
3. X-Ray Diffraction Data for 4b, 6, 8 and 10

X-Ray Crystal Structure Data for 4b (CCDC 1973034)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>pre_MC201; CCDC1973034</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C₁₈H₂₆N₂O₈</td>
</tr>
<tr>
<td>Formula weight</td>
<td>396.39</td>
</tr>
<tr>
<td>Temperature/K</td>
<td>292.52(10)</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁/n</td>
</tr>
<tr>
<td>a/Å</td>
<td>9.8453(3)</td>
</tr>
<tr>
<td>b/Å</td>
<td>7.5243(2)</td>
</tr>
<tr>
<td>c/Å</td>
<td>26.0993(11)</td>
</tr>
<tr>
<td>α/°</td>
<td>90</td>
</tr>
<tr>
<td>β/°</td>
<td>98.958(3)</td>
</tr>
<tr>
<td>γ/°</td>
<td>90</td>
</tr>
<tr>
<td>Volume/Å³</td>
<td>1909.82(11)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>ρ.calcd/g/cm³</td>
<td>1.379</td>
</tr>
<tr>
<td>μ/mm⁻¹</td>
<td>0.924</td>
</tr>
<tr>
<td>F(000)</td>
<td>840.0</td>
</tr>
<tr>
<td>Crystal size/mm³</td>
<td>0.203 × 0.036 × 0.024</td>
</tr>
</tbody>
</table>
Radiation CuKα (λ = 1.54184)

2Θ range for data collection/° 9.206 to 147.368

Index ranges -12 ≤ h ≤ 11, -9 ≤ k ≤ 6, -31 ≤ l ≤ 31

Reflections collected 13128

Independent reflections 3805 [Rint = 0.0411, Rsigma = 0.0393]

Data/restraints/parameters 3805/0/259

Goodness-of-fit on F² 1.045

Final R indexes [I>=2σ(I)] R₁ = 0.0384, wR₂ = 0.0876

Final R indexes [all data] R₁ = 0.0512, wR₂ = 0.0933

Largest diff. peak/hole / e Å⁻³ 0.28/-0.26

X-Ray Crystal Structure Data for 6 (CCDC 1973032)

Identification code SC106; CCDC1973032

Empirical formula C₁₂H₂₀N₂O₆

Formula weight 288.30

Temperature/K 100

Crystal system monoclinic

Space group P2₁/c

a/Å 10.0193(3)
b/Å 14.8599(4)
c/Å 9.9341(3)
$\alpha/^{\circ}$ 90
$\beta/^{\circ}$ 110.451(3)
$\gamma/^{\circ}$ 90
Volume/$\text{Å}^3$ 1385.83(7)
Z 4
$\rho_{\text{calc}}$ g/cm$^3$ 1.382
$\mu$ mm$^{-1}$ 0.942
F(000) 616.0
Crystal size/mm$^3$ 0.218 × 0.092 × 0.07
Radiation CuK$\alpha$ ($\lambda$ = 1.54184)
2$\Theta$ range for data collection/$^{\circ}$ 9.42 to 153.318
Index ranges -12 ≤ h ≤ 12, -18 ≤ k ≤ 18, -10 ≤ l ≤ 12
Reflections collected 9374
Independent reflections 2863 [R(int) = 0.0287, R(sigma) = 0.0238]
Data/restraints/parameters 2863/0/187
Goodness-of-fit on $F^2$ 1.073
Final R indexes [I $\geq$ 2$\sigma$(I)] $R_1$ = 0.0399, w$R_2$ = 0.1049
Final R indexes [all data] $R_1$ = 0.0420, w$R_2$ = 0.1065
Largest diff. peak/hole / e Å$^{-3}$ 0.38/-0.30

X-Ray Crystal Structure Data for 8 (CCDC 1973033)
Identification code  SC105; CCDC1973033
Empirical formula  C_{26}H_{34}NaO_{8}S_{2}
Formula weight  594.69
Temperature/K  140.00(10)
Crystal system  monoclinic
Space group  P2_1/c
a/Å  13.00210(10)
b/Å  17.5123(2)
c/Å  14.0169(2)
α/°  89.4160(18)
β/°  113.1200(10)
γ/°  90
Volume/Å³  2935.27(6)
Z  4
ρ_{calc} g/cm³  1.346
μ/μm⁻¹  2.102
F(000)  1256.0
Crystal size/mm³  0.224 × 0.162 × 0.065
Radiation  CuKα (λ = 1.54184)
2Θ range for data collection/°  7.392 to 153.548
Index ranges  -9 ≤ h ≤ 16, -20 ≤ k ≤ 21, -17 ≤ l ≤ 16
Reflections collected  23871
Independent reflections  6111 [R_{int} = 0.0360, R_{sigma} = 0.0321]
Data/restraints/parameters  6111/2/375
Goodness-of-fit on F²  1.070
Final R indexes [I>=2σ (I)]  R₁ = 0.0395, wR₂ = 0.1072
Final R indexes [all data]  R₁ = 0.0437, wR₂ = 0.1113
Largest diff. peak/hole / e Å⁻³  0.30/-0.52
X-Ray Crystal Structure Data for 10 (CCDC 1973035)

Identification code: SC105; CCDC1973035
Empirical formula: C_{28}H_{36}Cl_{8}N_{4}O_{8}
Formula weight: 840.21
Temperature/K: 100.00(10)
Crystal system: triclinic
Space group: P-1
a/Å: 10.2631(2)
b/Å: 11.9194(3)
c/Å: 15.8919(4)
α/°: 89.4160(18)
β/°: 89.8269(18)
γ/°: 77.4429(18)
Volume/Å³: 1897.44(7)
Z: 2
ρ_{calc}/g/cm³: 1.471
μ/mm⁻¹: 5.859
F(000): 864.0
Crystal size/mm³: 0.433 × 0.247 × 0.18
Radiation: CuKα (λ = 1.54184)
2Θ range for data collection/°: 7.6 to 152.966
Index ranges: -11 ≤ h ≤ 12, -14 ≤ k ≤ 15, -19 ≤ l ≤ 20
Reflections collected: 29243
Independent reflections: 7879 [R_{int} = 0.0347, R_{sigma} = 0.0205]
Data/restraints/parameters: 7879/0/441
Goodness-of-fit on $F^2$ 1.175

Final R indexes [$|I| \geq 2\sigma (I)$] $R_1 = 0.0470$, $wR_2 = 0.1223$

Final R indexes [all data] $R_1 = 0.0473$, $wR_2 = 0.1224$

Largest diff. peak/hole / e Å$^{-3}$ 0.61/-0.38
1,2-Dihydropyridazines as Versatile Synthetic Intermediates

Supporting Information

Thomas K. Britten, a Paul D. Kemmitt, b Nathan R. Halcovitch a and
Susannah C. Coote a

a Department of Chemistry, Lancaster University, Lancaster LA1 4YB, U.K.
b Medicinal Chemistry, Research and Early Development, Oncology R&D, AstraZeneca, Cambridge
CB10 1XL, U.K.

1. Synthetic Procedures and Analytical Data of New Compounds S2
   1.1 General Information S2
   1.2 General Procedure for Thermal Isomerization of 1,2-Dihydropyridazines S2
   1.3 Synthetic Procedures S3
2. References for the Supporting Information S12
3. 1H/13C NMR Spectra of New Compounds S13
4. X-Ray Diffraction Data for 4b, 6, 8 and 10 S36
1. Synthetic Procedures and Analytical Data of New Compounds

1.1 General Information

Reagents were purchased in the highest purity available from Acros Organics, Alfa Aesar or Sigma Aldrich. Anhydrous solvents used in reactions were purchased from Acros Organics equipped with AcroSeal™ and all other solvents used were of reagent grade. Reaction vessels were oven dried and cooled under an argon atmosphere prior to use and experiments were performed under argon gas. Reactions were monitored by thin-layer chromatography (TLC) and/or ^1H NMR spectroscopic analysis. Photochemical reactions were performed using a Rayonet RPR-100 Photochemical batch reactor.

Analytical TLC was carried out using Merck pre-coated aluminum-backed TLC silica gel plates (silica gel 60 F254) and the plates were visualised by UV light (254 nm) and by staining with either potassium permanganate or aqueous acidic ammonium molybdate(IV). Normal phase flash column chromatography on silica gel was carried out using silica gel from VWR (40-63 microns).

^1H NMR spectroscopic data were obtained on either 300 or 400 MHz instruments and ^13C(^1H) NMR data were obtained at 100 MHz (Bruker Ultrashield 400 Plus) at 298 K unless otherwise specified. The chemical shifts are reported in parts per million (δ) relative to residual CHCl₃ (δH = 7.26 ppm) and CDCl₃ (δC = 77.16 ppm, central line), residual d₅-DMSO (δH = 2.50 ppm) and d₆-DMSO (δC = 39.52 ppm, central line). The assignment of the signals in the ^1H and ^13C NMR spectra was achieved through 2D-NMR techniques: COSY, HSQC and HMBC. Coupling constants (J) are quoted in Hertz. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. Melting points were performed on a Sanyo Gallenkamp capillary melting point apparatus and are uncorrected. High resolution mass spectrometry data were recorded using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Shimadzu LCMS-IT-TOF mass spectrometer. UV/Vis spectra were recorded using an Agilent Cary 60 UV-Vis spec spectrophotometer. For X-ray crystallography a suitable crystal was selected and mounted on a Mitegen loop using Paratone-N oil on a SuperNova, Dual, Cu at zero, AtlasS2 diffractometer. The crystal was kept at 100.2(5) K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using direct methods and refined with the ShelXL refinement package using least squares minimisation. Figures and tables were prepared using Olex2 software.

1,2-Dihydropyridazine starting materials were synthesized according to our previous publication.

1.2 General Procedure for Thermal Isomerization of 1,2-Dihydropyridazines

A solution of 1,2-dihydropyridazine (1.0 eq) in o-xylene (0.4-0.5 M) was heated at reflux for 5 hours under argon. The reaction mixture was purified directly by flash column chromatography using an appropriate solvent system, as described for each individual procedure. Note: 2-Aminopyrroles must be stored in the freezer under an inert atmosphere in order to prevent degradation.
1.3 Synthetic Procedures

**Methyl 2-[(methoxycarbonyl)amino]-1H-pyrrole-1-carboxylate 2a**

Using the general procedure, a solution of 1,2-dihydropyridazine 1a (520 mg, 2.62 mmol) in o-xylene (5 mL) was heated at reflux for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 100% hexane→9:1) gave 2-aminopyrrole 2a (320 mg, 1.61 mmol, 62%) as a white solid.

R<sub>f</sub> (Hexane-EtOAc, 2:1) = 0.35

m.p. = 46-47 °C

1H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.05 (br s, 1H, NH), 6.85 (dd, J = 3.6, 1.8 Hz, 1H, H1), 6.42-6.32 (br m, 1H, H3), 6.13 (t, J = 3.6 Hz, 1H, H2), 3.95 (s, 3H, H8), 3.77 (s, 3H, H6).

13C NMR (100 MHz, CDCl<sub>3</sub>): δ 153.1 (C5), 152.4 (C7), 130.5 (C4), 114.0 (C1), 111.6 (C2), 98.4 (C3), 54.2 (C8), 52.6 (C6).

FTIR (ATR) ν (cm<sup>-1</sup>): 3349 (NH), 2950, 1724 (C=O).

HRMS (APCI): m/z calculated for: C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup> 199.0713, found 199.0712.

**Ethyl 2-[(ethoxycarbonyl)amino]-1H-pyrrole-1-carboxylate 2b**

Using the general procedure, a solution of 1,2-dihydropyridazine 1b (562 mg, 2.48 mmol) in o-xylene (5 mL) was heated at reflux for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 100% hexane→14:1) gave 2-aminopyrrole 2b (481 mg, 2.13 mmol, 86%) as a pale yellow oil.

R<sub>f</sub> (Hexane-EtOAc, 1:1) = 0.57

1H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.08 (br s, 1H, NH), 6.87 (dd, J = 3.6, 1.8 Hz, 1H, H1), 6.42-6.31 (br m, 1H, H3), 6.13 (t, J = 3.6 Hz, 1H, H2), 4.40 (q, J = 7.1 Hz, 2H, H9), 4.22 (q, J = 7.1 Hz, 2H, H6), 1.41 (t, J = 7.1 Hz, 3H, H10), 1.30 (t, J = 7.1 Hz, 3H, H7).
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 152.8 (C\(_5\)), 152.0 (C\(_8\)), 130.8 (C\(_4\)), 113.9 (C\(_1\)), 111.5 (C\(_2\)), 98.2 (C\(_3\)), 63.8 (C\(_9\)), 61.6 (C\(_6\)), 14.7 (C\(_7\)), 14.3 (C\(_{10}\)).

\(^1\)H NMR (400 MHz, \(d_6\)-DMSO) \(\delta\) 8.92 (br s, 1H, NH), 7.07 (dd, \(J = 3.6, 1.9\) Hz, 1H, H\(_1\)), 6.15 (t, \(J = 3.6\) Hz, 1H, H\(_2\)), 6.10-6.06 (br m, 1H, H\(_3\)), 4.32 (q, \(J = 7.1\) Hz, 2H, H\(_9\)), 4.08 (q, \(J = 7.1\) Hz, 2H, H\(_6\)), 1.30 (t, \(J = 7.1\) Hz, 3H, H\(_7\)), 1.20 (t, \(J = 7.1\) Hz, 3H, H\(_{10}\)).

\(^{13}\)C NMR (100 MHz, \(d_6\)-DMSO) \(\delta\) 154.1 (C\(_5\)), 150.0 (C\(_8\)), 128.1 (C\(_4\)), 117.3 (C\(_1\)), 110.1 (C\(_2\)), 105.3 (C\(_3\)), 63.4 (C\(_9\)), 60.6 (C\(_6\)), 14.5 (C\(_7\)), 13.9 (C\(_{10}\)).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)): 3345 (NH), 3145 (NH), 2980, 1718 (C=O).

HRMS (ESI): \(m/z\) calculated for \(C_{10}H_{14}N_2O_4\) [M+H]\(^+\) 227.1026, found 227.1024.

**Important NOE Contacts (\(d_6\)-DMSO):**

![Diagram showing NOE contacts](image)

**Isopropyl 2-(isopropoxycarbonylamino)-1H-pyrrole-1-carboxylate 2c**

Using the general procedure, a solution of 1,2-dihydropyridazine 1c (906 mg, 3.56 mmol) in \(o\)-xylene (10 mL) was heated at reflux for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 100% hexane\(\rightarrow\)14:1) gave 2-aminopyrrole 2c (818 mg, 3.22 mmol, 90%) as yellow oil.

\(R_f\) (Hexane-EtOAc, 2:1) = 0.58

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.08 (br s, 1H, NH), 6.85 (dd, \(J = 3.6, 1.8\) Hz, 1H, H\(_1\)), 6.40-6.32 (br m, 1H, H\(_3\)), 6.12 (t, \(J = 3.5\) Hz, 1H, H\(_2\)), 5.16 (sept, \(J = 6.2\) Hz, 1H, H\(_9\)), 5.00 (sept, \(J = 6.2\) Hz, 1H, H\(_6\)), 1.39 (d, \(J = 6.2\) Hz, 6H, H\(_{10}\)), 1.29 (d, \(J = 6.2\) Hz, 6H, H\(_7\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 152.4 (C\(_5\)), 151.6 (C\(_8\)), 131.0 (C\(_4\)), 113.8 (C\(_1\)), 111.3 (C\(_2\)), 98.0 (C\(_3\)), 72.3 (C\(_9\)), 69.1 (C\(_6\)), 22.2 (C\(_7\)), 21.9 (C\(_{10}\)).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)): 3366 (NH), 2982, 1720 (C=O).

HRMS (APCI): \(m/z\) calculated for \(C_{12}H_{16}N_2O_4\) [M+Na]\(^+\) 277.1159, found 277.1154.
**tert-Butyl 2-(tert-butoxycarbonylamino)pyrrole-1-carboxylate 2d**

Using the general procedure, a solution of 1,2-dihydropyridazine 1d (304 mg, 1.08 mmol) in o-xylene (3 mL) was heated at reflux for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 100% hexane→9:1) gave 2-aminopyrrole 2d (33 mg, 0.12 mmol, 11%) as a brown oil and 2-aminopyrrole S1 (56 mg, 0.31 mmol, 28%) as a brown film.

**2-Aminopyrrole 2d**

$R_f$ (Hexane-EtOAc, 2:1) = 0.58

$^1$H NMR (400 MHz, CDCl$_3$); δ 9.00 (br s, 1H, NH), 6.79 (dd, $J$ = 3.5, 1.8 Hz, 1H, H1), 6.35-6.29 (br m, 1H, H3), 6.08 (t, $J$ = 3.5 Hz, 1H, H2), 1.59 (s, 9H, H7 or H10), 1.50 (s, 9H, H7 or H10).

$^{13}$C NMR (100 MHz, CDCl$_3$); δ 151.8 (C5), 150.8 (C8), 131.2 (C4), 113.9 (C1), 110.8 (C2), 97.5 (C3), 84.8 (C6 or C9), 80.6 (C6 or C9), 28.5 (C7 or C10), 28.1 (C7 or C10).

FTIR (ATR) ν (cm$^{-1}$): 3366 (NH), 2982, 1720 (C=O).

HRMS (APCI): $m/z$ calculated for: C$_{12}$H$_{18}$N$_2$O$_4$ [M+Na]$^+$ 277.1159, found 277.1154.

**2-Aminopyrrole S1**

$R_f$ (Hexane-EtOAc, 2:1) = 0.50

$^1$H NMR (400 MHz, CDCl$_3$); δ 9.60 (br s, 1H, NH$_A$), 7.26 (br s, 1H, NH$_B$), 6.50-6.45 (m, 1H, H1), 6.07 (m, 1H, H2), 5.61-5.51 (m, 1H, H3), 1.52 (s, 9H, H7).

$^{13}$C NMR (100 MHz, CDCl$_3$); δ 153.4 (C5), 128.1 (C4), 112.1 (C1), 107.0 (C2), 92.5 (C3), 81.1 (C6), 28.4 (C).

FTIR (ATR) ν (cm$^{-1}$): 3452 (NH), 3314 (NH), 2980, 1679 (C=O).
HRMS (ESI): m/z calculated for: C_{9}H_{14}N_{2}O_{2} [M+H]^+ 183.1128, found 183.1127.

**Important NOE Contacts:**

![Diagram showing NOE Contacts](image)

**Isopropyl 2-(isopropoxycarbonylamino)-5-methoxycarbonyl-1H-pyrrole-1-carboxylate 2e**

A solution of 1,2-dihydropyridazine 1e (100 mg, 0.32 mmol) in o-xylene (2 mL) was heated at 130 °C for 5 hours. Purification by flash column chromatography on silica gel (eluent: hexane-Et_{2}O, 2:1) gave 2-aminopyrrole 2e (79 mg, 0.25 mmol, 79%) as a colourless oil.

Theoretical Rf (hexane-Et_{2}O, 2:1) = 0.28
1H NMR (400 MHz, CDCl_{3}); δ 8.81 (br s, 1H, NH), 6.88 (dd, J = 3.5, 0.5 Hz, 1H, H3), 6.36 (br d, J = 3.5, 1H, H2), 5.14 (sept, J = 6.3 Hz, 1H, H7 or H10), 4.99 (sept, J = 6.2 Hz, 1H, H7 or H10), 3.78 (s, 3H, OMe), 1.36 (d, J = 6.3 Hz, 6H, H8 or H11), 1.29 (d, J = 6.2 Hz, 6H, H8 or H11).

13C NMR (100 MHz, CDCl_{3}); δ 160.9 (C5), 152.0 and 151.5 (C6 and C9), 136.0 (C1), 123.0 (C2), 118.9 (C4), 97.2 (C3), 73.9 and 69.8 (C7 and C10), 22.1 and 21.5 (C8 and C11).

FTIR (ATR) ν (cm⁻¹): 3367 (NH), 2983, 2948, 1719 (C=O), 1531, 1357, 1344, 1305, 1279, 1195, 1179, 1100, 1002, 754.

HRMS (ESI): m/z calculated for: C_{14}H_{20}N_{2}O_{6} [M+H]^+ 313.1394, found 313.1400.

**Diisopropyl naphthalene-1,4-diylbiscarbamate 4a**

![Diagram showing structure](image)
CsF (79 mg, 0.52 mmol, 3.0 eq) was added in one portion to a stirred solution of 2-aminopyrrole 2c (44 mg, 0.17 mmol, 2.1 eq) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (20 µL, 0.08 mmol, 1.0 eq) in MeCN (0.8 mL) at room temperature under argon, then heated at 40 °C for 2.5 hours. The reaction mixture was cooled to room temperature, filtered through Celite and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave diamine 4a (20 mg, 0.06 mmol, 74%) as a white solid.

$R_f$ (Hexane-EtOAc, 2:1) = 0.26
m.p. = 187-189 °C (decomposition)

$^1$H NMR (400 MHz, $d_6$-DMSO); δ 9.37 (br s, 2H, NH), 8.02 (br dd, $J = 6.5$, 3.3 Hz, 2H, H4), 7.54 (br dd, $J = 6.5$, 3.3 Hz, 2H, H5) 7.51-7.49 (m, 2H, H2), 4.91 (sept, $J = 6.2$ Hz, 2H, H7), 1.28 (br d, $J = 6.2$ Hz, 12H, H8).

$^{13}$C NMR (100 MHz, $d_6$-DMSO); δ 154.7 (C6), 131.1 (C1), 128.7 (C3), 125.8 (C5), 123.1 (C4), 121.4 (C2), 67.6 (C7), 22.0 (C8).

FTIR (ATR) ν (cm$^{-1}$): 3263 (NH), 2974, 1737 (C=O), 1690 (C=O).

HRMS (ESI): $m/z$ calculated for: C$_{18}$H$_{22}$N$_2$O$_4$ [M+Na]$^+$ 353.1472, found 353.1458.

**Dimethyl 3,6-bis(isopropoxycarbonylamino)benzene-1,2-dicarboxylate 4b**

Dimethyl acetylenedicarboxylate (31 µL, 0.25 mmol, 1.1 eq) was added in one portion to a stirred solution of 2-aminopyrrole 2c (58 mg, 0.23 mmol, 1.0 eq) in PhMe (3.0 mL). The reaction was heated at 60 °C for 18 hours, then cooled to room temperature and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave p-phenylenediamine derivative 4b (59 mg, 0.15 mmol, 65%) as a yellow solid.

$R_f$ (Hexane-EtOAc, 2:1) = 0.4

m.p. = 118-120 °C

$^1$H NMR (400 MHz, CDCl$_3$); δ 8.42 (br s, 2H, NH), 8.31 (s, 2H, H2), 4.99 (sept, $J = 6.3$ Hz, 2H, H7), 3.87 (s, 6H, H5), 1.29 (d, $J = 6.3$ Hz, 12H, H8).

$^{13}$C NMR (100 MHz, CDCl$_3$); δ 167.9 (C4), 153.4 (C6), 133.6 (C1), 124.7 (C2), 119.4z (C3), 69.3 (C7), 53.0 (C5), 22.2 (C8).

FTIR (ATR) ν (cm$^{-1}$): 3343 (NH), 3308 (NH), 2984, 1720 (C=O ester), 1705 (C=O carbamate).

HRMS (APCI): $m/z$ calculated for: C$_{18}$H$_{24}$N$_2$O$_8$ [M-H]$^-$ 395.1460, found 395.1454.
Diisopropyl 3,6-dihydroxy-3,6-dihydropyridazine-1,2-dicarboxylate 6

\[
\begin{align*}
\text{OH} & \quad \text{N} \\
7 & \quad 6 \\
\text{N} & \quad \text{O} \\
4 & \quad 3 \\
\text{OH} & \quad \text{O} \\
10 & \quad 9
\end{align*}
\]

\(m\text{-CPBA} \ (76 \text{ mg}, 0.44 \text{ mmol}, 1.1 \text{ eq})\) was added in one portion to a stirred solution of 1,2-dihydropyridazine 1c \((100 \text{ mg}, 0.39 \text{ mmol}, 1.0 \text{ eq})\) in MeCN \((1 \text{ mL})\) at 0 °C under argon. The reaction mixture was stirred at room temperature for 44 hours, then the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 3:1→2:1→1:1) gave diol trans-6 \((63 \text{ mg}, 0.22 \text{ mmol}, 56\%)\) as a colourless oil, which became an off-white solid upon standing.

\(R_f\) (Hexane-EtOAc, 1:1) = 0.11

m.p. = 108-110 °C

\(^1\text{H NMR}\) (400 MHz, 328 K, CDCl\(_3\)); \(\delta\) 6.03-5.98 (m, 2H, H2 and H3), 5.94-5.85 (br m, 2H, H1 and H4), 4.97 (sept, \(J = 6.3 \text{ Hz}\), 2H, H6 and H9), 1.26 (br d, \(J = 6.3 \text{ Hz}\), 12H, H7 and H10).

\(^{13}\text{C NMR}\) (100 MHz, 328 K, CDCl\(_3\)); \(\delta\) 154.6 (C5/C8), 127.6 (C2/C3), 72.4 (C1/C4), 70.9 (C6/C9), 22.1 and 22.0 (C7/C10).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)): 3416 (OH), 2982, 1679 (C=O).

HRMS (ESI): \(m/z\) calculated for: \(\text{C}_{12}\text{H}_{20}\text{N}_{2}\text{O}_6[\text{M+Na}]^+\) 311.1214, found 311.1199.

Diisopropyl 3,6-bis[(4-methylbenzene-1-sulfonyl)amino]-3,6-dihydropyridazine-1,2-dicarboxylate 8

\[
\begin{align*}
\text{O} & \quad \text{N} \\
7 & \quad 6 \\
\text{O} & \quad \text{N} \\
4 & \quad 3 \\
\text{O} & \quad \text{N} \\
10 & \quad 9
\end{align*}
\]

\(\text{Cu(OTf)}_2\) \((14 \text{ mg}, 0.04 \text{ mmol}, 0.1 \text{ eq})\) was added to a stirred solution of Phl=NTs \((294 \text{ mg}, 0.79 \text{ mmol}, 2.0 \text{ eq})\) and 1,2-dihydropyridazine 1c \((100 \text{ mg}, 0.39 \text{ mmol}, 1.0 \text{ eq})\) in MeCN \((2 \text{ mL})\) at room temperature under argon. The resulting mixture was stirred at room temperature for 1 hour, then evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent Et\(_2\)O) gave trans-9 \((145 \text{ mg}, 0.24 \text{ mmol}, 62\%)\) as a white solid.

\(R_f\) (Et\(_2\)O) = 0.52
m.p. = 203-205 °C (decomposition)

The \(^1\)H/\(^{13}\)C NMR spectra of 8 are complex, with several species present at room temperature. Upon heating, full coalescence is not observed until 408 K (at which temperature significant degradation is also observed), thus \(^1\)H NMR data is given at 378 K, and spectra are provided at both 298 K and 378 K. For \(^{13}\)C NMR, data and spectra are given at 298 K and at 388 K (at which temperature C3 is barely visible):

\(^1\)H NMR (400 MHz, 378 K, d\textsubscript{6}-DMSO): \(\delta\) 8.16 (d, \(J = 8.5\) Hz, 2H, NH), 7.75 (d, \(J = 8.1\) Hz, 4H, H7), 7.32 (d, \(J = 8.1\) Hz, 4H, H8), 5.79 (br d, \(J = 8.4\) Hz, 2H, H2), 5.73-5.68 (m, 2H, H1), 4.73 (sept, \(J = 6.2\) Hz, 2H, H4), 2.38 (s, 6H, H10), 1.12 (d, \(J = 6.2\) Hz, 6H, H5), 1.07 (d, \(J = 6.2\) Hz, 6H, H5).

\(^{13}\)C NMR (100 MHz, 388 K, d\textsubscript{6}-DMSO): \(\delta\) 152.5 (C3), 141.6 (C6), 139.1 (C9), 128.5 (C7), 125.9 (C8), 125.6 (C2), 69.1 (C4), 58.5 (C1), 20.9, 20.7 and 20.2 (C5).

FTIR (ATR) \(\nu\) (cm\(^{-1}\)): 3248 (NH), 2982, 2935, 1687 (C=O), 1407, 1385 (S=O), 1318, 1288, 1157 (S=O), 1107, 1046, 908, 814, 747.

### Diisopropyl 3,4-dihydroxy-3,4-dihydropyridazine-1,2-dicarboxylate 9

NMO (140 mg, 1.20 mmol, 3.0 eq) was added in one portion to a stirred solution of 1,2-dihydropyridazine 1c (102 mg, 0.40 mmol, 1.0 eq) and OsO\(_4\) (2.5% w/v in \(^t\)BuOH, 0.2 mL, 0.02 mmol, 0.05 eq) in acetone:H\(_2\)O (8:1, 4.5 mL) at room temperature under argon, then stirred at room temperature for 17 hours. The reaction mixture was diluted with a saturated aqueous solution of Na\(_2\)S\(_2\)O\(_3\) (5 mL) and extracted with CH\(_2\)Cl\(_2\) (5 x 5 mL). The combined organic layers were dried (MgSO\(_4\)) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-ETOAc, 4:1→2:1→1:1) gave the minor product diastereoisomer (24 mg, 0.08 mmol, 21%) as a white solid, and the major product diastereoisomer (66 mg, 0.23 mmol, 57%), as a colourless oil.

#### Minor diastereoisomer:

\(R_f\) (Hexane-ETOAc, 1:1) = 0.14

m.p. = 104-106°C
$^1$H NMR (400 MHz, $d_6$-DMSO, 348 K); δ 6.81-6.44 (br m, 2H, H4 and OH), 5.51-5.38 (br m, 1H, H1), 4.99-4.93 (br m, 1H, OH), 4.87-4.71 (br m, 3H, H3, H6 and H9), 4.10-4.04 (br m, 1H, H2), 1.24-1.19 (m, 12H, H7 and H10).

$^{13}$C NMR (100 MHz, $d_6$-DMSO, 348 K): Spectrum could not be obtained due to epimerisation at this temperature over the length of the experiment. At 298 K, the spectrum is very complex.

FTIR (ATR) ν (cm$^{-1}$): 3424 (OH), 2980, 1687 (C=O).

HRMS (APCI): m/z calculated for: C$_{12}$H$_{20}$N$_2$O$_6$ [M+Na]$^+$ 311.1214, found 311.1199.

Major diastereoisomer:

![Chemical Structure]

$R_f$ (Hexane-EtOAc, 1:1) = 0.08

$^1$H NMR (400 MHz, $d_6$-DMSO, 298 K); δ 7.02-6.71 (br m, 1H, H4), 6.54-6.21 (br m, 1H, OH), 5.60-5.45 (br m, 1H, H1), 5.13-4.99 (br m, 2H, OH and H3), 4.87-4.77 (br m, 2H, H6 and H9), 3.71-3.65 (br m, 1H, H2), 1.26-1.14 (m, 12H, H7 and H10).

$^1$H NMR (400 MHz, $d_6$-DMSO, 348 K); δ 6.95 (br d, $J = 7.6$ Hz, 0.9H, H4), 6.77 (br d, $J = 7.9$ Hz, 0.1H, H4), 6.11 (br s, 1H, OH), 5.68-5.48 (br m, 1H, H1), 5.08-4.99 (br m, 1H, H3), 4.91-4.77 (br m, 3H, H6, H9 and OH), 3.73 (br d, $J = 5.2$ Hz, 1H, H2), 1.35-1.09 (m, 12H, H7 and H10).

$^{13}$C NMR (100 MHz, $d_6$-DMSO, 298 K; additional peaks present due to multiple species present); δ 153.7-151.0 (C5 or C8), 127.5-123.8 (C4), 107.1-105.3 (C3), 80.5-79.0 (C1), 70.9-68.9 (C6 or C9), 63.8-62.7 (C2), 22.0-21.6 (C7 or C10).

FTIR (ATR) ν (cm$^{-1}$): 3422 (OH), 2984, 1702 (C=O), 1649 (C=O).

HRMS (APCI): m/z calculated for: C$_{12}$H$_{20}$N$_2$O$_6$ [M+Na]$^+$ 311.1214, found 311.1199.

Diisopropyl 3,3,8,8-tetrachloro-5,6-diazatricyclo[5.1.0.0$^{2,4}$]octane-5,6-dicarboxylate trans-10

![Chemical Structure]

An aqueous solution of NaOH (50% w/v, 5 mL) was added dropwise to a solution of 1,2-dihydropyridazine 1c (101 mg, 0.40 mmol, 1.0 eq) and tetrabutylammonium chloride (11 mg, 0.04 mmol, 0.1 eq) in CHCl$_3$ (10 mL) at room temperature under argon, then stirred at room temperature for 3 hours. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl (10 mL) and the organic...
layer was separated. The aqueous layer was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried (MgSO$_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (elucent: hexane-EtOAc, 7:1→4:1) gave tricycle trans-10 (117 mg, 0.28 mmol, 71%) as an off-white sticky solid. 
$R_f$ (Hexane-EtOAc, 2:1) = 0.44
m.p. = 118-120 °C

The $^1$H/$^{13}$C NMR spectra of 10 are complex, with three species apparent at room temperature:
$^1$H NMR (400 MHz, CDCl$_3$); δ 5.04-4.94 (m, 2H, H8/H11), 3.63-3.54 (m, 2H, H1/H6), 2.15-2.11 (m, 2H, H3/H4), 1.35-1.23 (m, 12H, H9/H12).
$^{13}$C NMR (100 MHz, CDCl$_3$); δ 153.5, 153.3, 153.2 (C7/C10), 71.5, 71.3, 71.1 (C8/C11), 63.1, 63.0, 62.8 (C2/C5), 42.5, 42.2, 41.8 (C1/C6), 26.1, 26.0, 25.8 (C3/C4), 22.3, 22.0, 21.8 (C9/C12).
FTIR (ATR) ν (cm$^{-1}$): 2978, 2926, 1757 (C=O), 1724 (C=O).
HRMS (APCI): m/z calculated for: C$_{14}$H$_{18}$N$_2$O$_2$Cl$_4$ [M+H]$^+$ 419.0093, found 419.0079.
2. References for the Supporting Information


H NMR (400 MHz, CDCl₃)

\[ \text{NHCO}_2\text{Me} \]

\[ \text{N-CO}_2\text{Me} \]

\[ 2a \]
$^{13}$C NMR (101 MHz, CDCl$_3$)
\[ \text{H NMR (400 MHz, CDCl}_3) \]

\[ \text{CO}_2\text{Pr} \]

\[ \text{NHCO}_2\text{Pr} \]

\[ \text{2c} \]
$^{13}$C NMR (101 MHz, CDCl$_3$)

$\text{NHCOC}_2\text{Pr}$

$\text{N-COC}_2\text{Pr}$

$2c$
$^{1}H$ NMR (400 MHz, CDCl$_3$)

NHCO$_2$Bu

N-CO$_2$Bu

2d
$^{13}$C NMR (101 MHz, CDCl$_3$)

$\text{NHCO}_2^t\text{Bu}$

$\text{N-CO}_2^t\text{Bu}$

$2d$
\[ \text{H NMR (400 MHz, CDCl}_3 \text{)} \]

\[
\text{Me}_2\text{C} - \text{N} - \text{NHCO}_2\text{Pr} \\
\text{CO}_2\text{Pr}
\]

$2e$
$^{13}$C NMR (101 MHz, CDCl$_3$)

![NMR spectrum](image.png)

- 160.92
- 159.01
- 148.78
- 128.88
- 73.40
- 57.32
- 22.00

2e
$^{1}$H NMR (298 K, 400 MHz, d$_6$-DMSO)
$^{13}$C NMR (298 K, 101 MHz, $d_6$-DMSO)

$\text{NHCO}_2\text{Pr}$

4a

$\text{NHCO}_2\text{Pr}$
$^1$H NMR (298 K, 400 MHz, CDCl$_3$)
$^{13}$C NMR (298 K, 101 MHz, CDCl$_3$)

![Chemical Structure](image)

-154.62, -127.56, 70.90, 22.06
$^{1}H$ NMR (298 K, 400 MHz, $d_6$-DMSO)

![NMR spectrum image]

Chemical shifts labeled:
- 8.62
- 7.71
- 7.33
- 5.64
- 5.71
- 5.72
- 5.65
- 4.70
- 4.68
- 4.64
- 4.59
- 1.03
- 0.94
- 0.92

Peaks at specific ppm values.
$^1$H NMR (378 K, 400 MHz, $d_6$-DMSO)
$^{13}$C NMR (298 K, 101 MHz, $d_6$-DMSO)

$$\text{NHTs} \quad \text{CO}_2\text{Pr} \quad \text{NHTs}$$

$$\text{NHTs} \quad \text{CO}_2\text{Pr} \quad \text{NHTs}$$
$^{13}$C NMR (388 K, 101 MHz, $d_6$-DMSO)

![NMR spectrum of compound 8](image)

-152.47, -141.65, -139.13, -128.50, -128.52, -125.63, -69.10, -58.48, -20.90, -20.68, -20.15
$^{1}$$H$ NMR (298 K, 101 MHz, $d_6$-DMSO)

major diastereoisomer
$^{1}$H NMR (348 K, 400 MHz, $d_6$-DMSO)

major diastereoisomer

![Chemical structure image]
$^{13}$C NMR (298 K, 101 MHz, $d_6$-DMSO)

major diastereoisomer

\[
\begin{align*}
\text{HO} & \quad \text{N-CO}_2\text{Pr} \\
\text{N-CO}_2\text{Pr} & \quad \text{HO}
\end{align*}
\]
\[ ^{13}\text{C} \text{NMR (348 K, 101 MHz, } d_6-\text{DMSO)} \]

major diastereoisomer

\[
\begin{align*}
\text{OH} & \quad \text{CO}_2\text{Pr} \\
\text{HO} & \quad \text{N} \quad \text{CO}_2\text{Pr} \\
& \quad \text{N} \quad \text{CO}_2\text{Pr}
\end{align*}
\]
$^{1}H$ NMR (348 K, 400 MHz, $d_{6}$-DMSO)

minor diastereoisomer

$\text{OH}$

$\text{HO}$_N$\text{CO}_2^i\text{Pr}$

$\text{HO}$_N$\text{CO}_2^i\text{Pr}$
$\text{H NMR (298 K, 400 MHz, CDCl}_3$)$\text{)}$
$^{13}$C NMR (298 K, 101 MHz, CDCl$_3$)

N N

CO$_2$Pr

CO$_2$Pr

Cl Cl

Cl Cl
3. X-Ray Diffraction Data for 4b, 6, 8 and 10

X-Ray Crystal Structure Data for 4b (CCDC 1973034)

Identification code: pre_MC201; CCDC1973034
Empirical formula: C_{18}H_{24}N_{2}O_{8}
Formula weight: 396.39
Temperature/K: 292.52(10)
Crystal system: monoclinic
Space group: P2₁/n
a/Å: 9.8453(3)
b/Å: 7.5243(2)
c/Å: 26.0993(11)
α/°: 90
β/°: 98.958(3)
γ/°: 90
Volume/Å³: 1909.82(11)
Z: 4
ρ_cal:g/cm³: 1.379
μ/mm⁻¹: 0.924
F(000): 840.0
Crystal size/mm³: 0.203 × 0.036 × 0.024
Radiation  
CuKα (λ = 1.54184)

2θ range for data collection/° 9.206 to 147.368

Index ranges  
-12 ≤ h ≤ 11, -9 ≤ k ≤ 6, -31 ≤ l ≤ 31

Reflections collected  13128

Independent reflections  3805 [R_{int} = 0.0411, R_{sigma} = 0.0393]

Data/restraints/parameters  3805/0/259

Goodness-of-fit on F²  1.045

Final R indexes [I>=2σ (I)]  R₁ = 0.0384, wR₂ = 0.0876

Final R indexes [all data]  R₁ = 0.0512, wR₂ = 0.0933

Largest diff. peak/hole / e Å⁻³ 0.28/-0.26

X-Ray Crystal Structure Data for 6 (CCDC 1973032)

Identification code  SC106; CCDC1973032

Empirical formula  C₁₂H₂₀N₂O₆

Formula weight  288.30

Temperature/K  100

Crystal system  monoclinic

Space group  P2₁/c

a/Å  10.0193(3)

b/Å  14.8599(4)

c/Å  9.9341(3)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha/^\circ$</td>
<td>90</td>
</tr>
<tr>
<td>$\beta/^\circ$</td>
<td>110.451(3)</td>
</tr>
<tr>
<td>$\gamma/^\circ$</td>
<td>90</td>
</tr>
<tr>
<td>Volume/$\text{Å}^3$</td>
<td>1385.83(7)</td>
</tr>
<tr>
<td>$Z$</td>
<td>4</td>
</tr>
<tr>
<td>$\rho_{\text{calc}}$/$\text{g/cm}^3$</td>
<td>1.382</td>
</tr>
<tr>
<td>$\mu$/$\text{mm}^{-1}$</td>
<td>0.942</td>
</tr>
<tr>
<td>$F(000)$</td>
<td>616.0</td>
</tr>
<tr>
<td>Crystal size/$\text{mm}^3$</td>
<td>0.218 $\times$ 0.092 $\times$ 0.07</td>
</tr>
<tr>
<td>Radiation</td>
<td>CuK$\alpha$ ($\lambda = 1.54184$)</td>
</tr>
<tr>
<td>$2\Theta$ range for data collection/$^\circ$</td>
<td>9.42 to 153.318</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-12 $\leq$ h $\leq$ 12, -18 $\leq$ k $\leq$ 18, -10 $\leq$ l $\leq$ 12</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>9374</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2863 [R(int) = 0.0287, R(sigma) = 0.0238]</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>2863/0/187</td>
</tr>
<tr>
<td>Goodness-of-fit on $F^2$</td>
<td>1.073</td>
</tr>
<tr>
<td>Final R indexes [I$\geq$2$\sigma$(I)]</td>
<td>$R_1 = 0.0399$, $wR_2 = 0.1049$</td>
</tr>
<tr>
<td>Final R indexes [all data]</td>
<td>$R_1 = 0.0420$, $wR_2 = 0.1065$</td>
</tr>
<tr>
<td>Largest diff. peak/hole / e Å$^{-3}$</td>
<td>0.38/-0.30</td>
</tr>
</tbody>
</table>

**X-Ray Crystal Structure Data for 8 (CCDC 1973033)**

![Crystal structure diagram](image)
<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>SC105; CCDC1973033</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C_{26}H_{34}N_{4}O_{8}S_{2}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>594.69</td>
</tr>
<tr>
<td>Temperature/K</td>
<td>140.00(10)</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2_1/c</td>
</tr>
<tr>
<td>a/Å</td>
<td>13.00210(10)</td>
</tr>
<tr>
<td>b/Å</td>
<td>17.5123(2)</td>
</tr>
<tr>
<td>c/Å</td>
<td>14.0169(2)</td>
</tr>
<tr>
<td>α/°</td>
<td>89.4160(18)</td>
</tr>
<tr>
<td>β/°</td>
<td>113.1200(10)</td>
</tr>
<tr>
<td>γ/°</td>
<td>90</td>
</tr>
<tr>
<td>Volume/Å³</td>
<td>2935.27(6)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>ρ_{calc}/g/cm³</td>
<td>1.346</td>
</tr>
<tr>
<td>μ/μm⁻¹</td>
<td>2.102</td>
</tr>
<tr>
<td>F(000)</td>
<td>1256.0</td>
</tr>
<tr>
<td>Crystal size/mm³</td>
<td>0.224 \times 0.162 \times 0.065</td>
</tr>
<tr>
<td>Radiation</td>
<td>CuKα (λ = 1.54184)</td>
</tr>
<tr>
<td>2Θ range for data collection/°</td>
<td>7.392 to 153.548</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-9 ≤ h ≤ 16, -20 ≤ k ≤ 21, -17 ≤ l ≤ 16</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>23871</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>6111 [R_{int} = 0.0360, R_{sigma} = 0.0321]</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>6111/2/375</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.070</td>
</tr>
<tr>
<td>Final R indexes [I&gt;=2σ (I)]</td>
<td>R_1 = 0.0395, wR_2 = 0.1072</td>
</tr>
<tr>
<td>Final R indexes [all data]</td>
<td>R_1 = 0.0437, wR_2 = 0.1113</td>
</tr>
<tr>
<td>Largest diff. peak/hole / e Å⁻³</td>
<td>0.30/-0.52</td>
</tr>
</tbody>
</table>
### X-Ray Crystal Structure Data for 10 (CCDC 1973035)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>SC105; CCDC1973035</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C_{28}H_{36}Cl_{8}N_{4}O_{8}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>840.21</td>
</tr>
<tr>
<td>Temperature/K</td>
<td>100.00(10)</td>
</tr>
<tr>
<td>Crystal system</td>
<td>triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P-1</td>
</tr>
<tr>
<td>a/Å</td>
<td>10.2631(2)</td>
</tr>
<tr>
<td>b/Å</td>
<td>11.9194(3)</td>
</tr>
<tr>
<td>c/Å</td>
<td>15.8919(4)</td>
</tr>
<tr>
<td>α/°</td>
<td>89.4160(18)</td>
</tr>
<tr>
<td>β/°</td>
<td>89.8269(18)</td>
</tr>
<tr>
<td>γ/°</td>
<td>77.4429(18)</td>
</tr>
<tr>
<td>Volume/Å³</td>
<td>1897.44(7)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>ρ_{calc}/g/cm³</td>
<td>1.471</td>
</tr>
<tr>
<td>μ/mm⁻¹</td>
<td>5.859</td>
</tr>
<tr>
<td>F(000)</td>
<td>864.0</td>
</tr>
<tr>
<td>Crystal size/mm³</td>
<td>0.433 × 0.247 × 0.18</td>
</tr>
<tr>
<td>Radiation</td>
<td>CuKα (λ = 1.54184)</td>
</tr>
<tr>
<td>2Θ range for data collection/°</td>
<td>7.6 to 152.966</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-11 ≤ h ≤ 12, -14 ≤ k ≤ 15, -19 ≤ l ≤ 20</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>29243</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>7879 [R_{int} = 0.0347, R_{sigma} = 0.0205]</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>7879/0/441</td>
</tr>
</tbody>
</table>
Goodness-of-fit on $F^2$ 1.175

Final R indexes [$l \geq 2\sigma (l)$] $R_1 = 0.0470$, $wR_2 = 0.1223$

Final R indexes [all data] $R_1 = 0.0473$, $wR_2 = 0.1224$

Largest diff. peak/hole / e Å$^{-3}$ 0.61/-0.38