Electronic supplementary information

Pd-catalysed oxidative carbonylation of α-amino amides to hydantoins under mild conditions

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1. General information

All reagents were used as received from commercial sources without further purification. All solvents were dried over activated 4 Å molecular sieves for 24 h. All reactions were analyzed by TLC and by GC using a 30 m SE-30 capillary column. Flash column chromatography was performed on silica gel 60 (70–230 mesh). Melting points were measured with an Electrothermal apparatus and are uncorrected. Electron impact mass spectra [m/z, relative intensity (%)] were determined with a GC-MS apparatus at 70 eV ionization energy, optical purity was analyzed using Agilent CP-Chirasil 25 m column. IR spectra were run on PerkinElmer Spectrum Two spectrometer paired with a Diamond Smart Orbit accessory. Specific rotation angles were measured with polarimeter PerkinElmer 341. HRMS spectra were obtained with LTQ Orbitrap XL Thermo. Unless otherwise indicated NMR spectra were recorded on Bruker AVANCE 400 and JEOL 600MHz ECZ600R spectrometers in deuterated chloroform, using the solvent residual signals as internal reference (7.26 and 77.00 ppm, respectively for $^1$H and $^{13}$C), or deuterated dimethyl sulfoxide (2.50 and 39.52 ppm, respectively for $^1$H and $^{13}$C). Chemical shifts ($\delta$) and coupling constants (J) are given in ppm and in Hz, respectively.

2. Experimental procedures

2.1 General procedure for the synthesis of amino acid amides 1a-h, 1n, 1o, 1q-t

A 10 mL Schlenk tube was charged with the amino acid methyl ester hydrochloride (2 mmol) and an amine (8 mmol) under N$_2$. The Schlenk tube was sealed and the mixture was stirred at 60°C for 72 h. The crude mixture was transferred to a 50 mL flask and the excess of amine was removed under vacuum (in case of high-boiling amines the evaporation step was skipped). The residue was washed with brine and extracted with ethyl acetate (3x10 mL). The organic phase was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was then purified by silica gel column chromatography (ethyl acetate/hexane/methanol (5:10:1)) to afford the pure amino acid amide 1.
2.2 General procedure for the synthesis of amino acid amides 1i-k, 1l, 1p[1]

\[
\text{Ph-N=CH}_{2} + 
\begin{array}{c}
\text{R-} \\
\text{NH}_{2}
\end{array}
\xrightarrow{\text{Cul, K}_{2}\text{CO}_3}
\text{Ph-N=CH-NH}_{2}
\]

A literature procedure has been followed for the synthesis of amino acid amides 1i-k, 1l, 1p[1]

2.3 Synthesis of the amino acid amides 1v

To a solution of 1a (330 mg, 1.5 mmol) in dry MeOH (8.0 mL), benzaldehyde (0.158 mL, 1.55 mmol) and acetic acid (2 mL) were added. The reaction mixture was stirred at room temperature for 10 min and cooled to 0 °C, then NaBH(OAc)$_3$ (650 mg, 3 mmol) was added portionwise. After stirring at room temperature for additional 4 h, the solvent was evaporated, and the residue was extracted with ethyl acetate and washed with brine. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane/methanol (5:15:1)).

2.4 Synthesis of methyl L-phenylalanylglycinate 1u[2]

\[
\text{Bn-} \begin{array}{c}
\text{O} \\
\text{HN}
\end{array}
\xrightarrow{\text{HOBt, EDC.HCl}}
\text{Bn-} \begin{array}{c}
\text{O} \\
\text{HN}
\end{array} \text{CO}_2\text{Me}
\]

N-Boc-phenylalanine (292 mg, 1.1 mmol) and HOBt (203 mg, 1.5 mmol) were dissolved in cooled at 0°C DMF (10 mL) and maintained under stirring for 15 minutes. To the resulting solution methyl glycinate hydrochloride (125 mg, 1.0 mmol), EDC·HCl (287 mg, 1.5 mmol), and, 5 minutes later, TEA (0.67 mL, 5 mmol) were added. The reaction mixture was stirred at room temperature for 24 hours and monitored by TLC until the complete consume of methyl
glycinate. The mixture was filtered through a pad of SiO$_2$, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using ethyl acetate/hexane (2:3) mixture as eluent. The obtained colourless oil (317 mg, 0.94 mmol) was dissolved in 3 mL of DCM, and TFA (0.72 mL, 9.4 mmol) was added dropwise to the solution. After stirring for 8 hours at room temperature, the excess of TFA was removed under reduced pressure, the residue was dissolved in ethyl acetate (3 mL), and potassium carbonate (414 mg, 3 mmol) was added. The solution was then filtered through a pad of SiO$_2$ and concentrated under vacuo. The product (219 mg, 93% yield) did not require any further purification.

2.5 Synthesis of urea 5a (Scheme 2b)

\[
\text{Ph-CH$_2$-CH(NH$_2$)-CH$_2$-NH$_2$ Bu} + \text{PhNCO} \rightarrow \text{Ph-CH$_2$-CH(NH$_2$)-CH$_2$-NH$_2$ Bu}
\]

In a 25 ml Schlenk tube, 1a (66 mg, 0.3 mmol) was dissolved in dry acetonitrile (3 mL) under N$_2$. Phenyl isocyanate was added (0.033 mL, 0.3 mmol), and the mixture was stirred for 1h. Solvent evaporation afforded 5a in quantitative yield, and no further purification was required.

2.6 PdI$_2$/KI oxidative carbonylation of amino amide 1a

A 45 mL stainless steel autoclave was charged with substrate 1a (110 mg, 0.5 mmol), PdI$_2$ (2-5 mol%), KI (20-100%) and the solvent (5 mL). The autoclave was sealed and pressurized with CO and air, heated at 70-115 °C (oil bath) under stirring for 18 h. Then the autoclave was cooled, degassed and opened. The mixture was passed through a pad of Celite®, and the solvent was removed in vacuo affording product 3a in quantitative yield.
**Table S1.** PdI₂/KI-catalysed oxidative carbonylation of 1a.[a]

<table>
<thead>
<tr>
<th>N</th>
<th>PdI₂, mol%</th>
<th>KI, mol%</th>
<th>p(CO), bar</th>
<th>p(air), bar</th>
<th>T, °C</th>
<th>Solvent</th>
<th>Yield 3a[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>20</td>
<td>16</td>
<td>4</td>
<td>115</td>
<td>1,4-dioxane</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>20</td>
<td>16</td>
<td>4</td>
<td>100</td>
<td>1,4-dioxane</td>
<td>84%</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>20</td>
<td>16</td>
<td>4</td>
<td>80</td>
<td>1,4-dioxane</td>
<td>92%</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>20</td>
<td>4</td>
<td>16</td>
<td>80</td>
<td>1,4-dioxane</td>
<td>94%</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>50</td>
<td>4</td>
<td>16</td>
<td>80</td>
<td>1,4-dioxane</td>
<td>99%</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>50</td>
<td>8</td>
<td>2</td>
<td>80</td>
<td>1,4-dioxane</td>
<td>99%</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>50</td>
<td>8</td>
<td>2</td>
<td>70</td>
<td>1,4-dioxane</td>
<td>99%</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>50</td>
<td>8</td>
<td>2</td>
<td>70</td>
<td>MeCN</td>
<td>93%</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>50</td>
<td>8</td>
<td>2</td>
<td>70</td>
<td>DME</td>
<td>88%</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>100</td>
<td>16</td>
<td>4</td>
<td>80</td>
<td>DMF</td>
<td>94%</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1a (0.5 mmol), PdI₂ (2-5 mol%), KI (20-50), solvent (5 mL), CO/air (reported pressure measured at 25 °C), 45 ml autoclave, 18h. [b] Isolated yield.

2.7 Pd-catalysed oxidative carbonylation of amino amides 1a-r to hydantoins 2a-r

A 25 mL Schlenk tube was charged with a solution of amino acid amide 1 (0.3 mmol) in glacial acetic acid (3 mL), palladium acetate (6.7 mg, 0.03 mmol) and TEMPO (104 mg, 0.66 mmol) under N₂. The tube was sealed and the mixture was stirred for 5 minutes at 80 °C. Then, the tube was evacuated and filled with carbon monoxide gas using a balloon (1 atm of CO). The reaction was kept at 80 °C under stirring for 2-6 h. The crude reaction mixture was cooled down to room temperature and passed through a Celite® path. Acetic acid was evaporated under reduced pressure at 60 °C and the residue was neutralized with K₂CO₃ powder (400 mg, 2.9 mmol), dissolved in ethyl acetate (5 mL) and filtered. The product was purified by silica gel column chromatography (ethyl acetate/dichloromethane (1:8)).
3. Table S2

Additional experiments for optimisation study of Pd(OAc)$_2$-catalysed carbonylation of amino amides 1a to hydantoin 2a.\[^a\]

![Chemical structure of 1a, 2a, 3a, 4a, and 2b](image)

<table>
<thead>
<tr>
<th>N</th>
<th>T (°C)</th>
<th>Oxidant (equiv)</th>
<th>co-oxidant</th>
<th>Solvent</th>
<th>Yield (%) 2a[^b]</th>
<th>Yield (%) 3a[^b]</th>
<th>Yield (%) 4a[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120</td>
<td>BQ (2)</td>
<td>-</td>
<td>AcOH</td>
<td>74</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>DDQ (2)</td>
<td>-</td>
<td>AcOH</td>
<td>66</td>
<td>-</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>AgOTf (2)</td>
<td>air</td>
<td>AcOH</td>
<td>62</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>AgNO$_3$ (2)</td>
<td>air</td>
<td>AcOH</td>
<td>23</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>120</td>
<td>Cu(OAc)$_2$ (0.5)</td>
<td>air</td>
<td>AcOH</td>
<td>37</td>
<td>-</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>120</td>
<td>BQ (2)</td>
<td>-</td>
<td>AcOH + DMF (1:1)</td>
<td>62</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>BQ (1.2)</td>
<td>-</td>
<td>AcOH + MeCN (1:1)</td>
<td>81</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>BQ (1.2)</td>
<td>-</td>
<td>AcOH + MeCN (1:10)</td>
<td>61</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>80</td>
<td>TEMPO (0.1)</td>
<td>Na$_2$S$_2$O$_8$ (2 eq)</td>
<td>AcOH</td>
<td>11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
<td>TEMPO (0.3)</td>
<td>Urea-hydrogen peroxide (3 eq)</td>
<td>AcOH</td>
<td>19</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>80</td>
<td>TEMPO (1.2)</td>
<td>-</td>
<td>AcOH</td>
<td>51</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\[^a\] Reaction conditions: 1a (0.5 mmol), Pd(OAc)$_2$ (10 mol%), solvent (5 mL), 6 h. \[^b\] Isolated yield.
4. Figure S1

Gas chromatogram and mass spectrum of (S)-2a
5. Figure S2

Gas chromatogram and mass spectrum of \((\text{rac})-2a\)
6. Enantiomeric excess of selected amino amides 1 and hydantoin 2

Gas chromatogram and mass spectrum of (S)-1a

Gas chromatogram and mass spectrum of (rac)-1a
Gas chromatogram and mass spectrum of (S)-1d

Gas chromatogram and mass spectrum of (S)-2d
Gas chromatogram and mass spectrum of (S)-1i

Gas chromatogram and mass spectrum of (S)-2i
Gas chromatogram and mass spectrum of (S)-1q

Gas chromatogram and mass spectrum of (S)-2q
Gas chromatogram and mass spectrum of (S)-1u

Gas chromatogram and mass spectrum of (S)-2u
7. Characterizations

(S)-2-amino-N-butyl-3-phenylpropanamide (1a)

![Chemical structure](image)

Colourless oil (414 mg, 94% yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.32-7.20 (m, 5H), 3.59 (br s, 2H), 3.25-3.22 (m, 3H), 2.70 (dd, $J = 13.7$, 9.1 Hz, 1H), 1.65-1.42 (m, 3H), 1.35-1.24 (m, 2H), 0.91 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 174.2, 138.0, 129.3 (2C), 128.6 (2C), 126.7, 56.4, 41.1, 38.8, 31.6, 20.0, 13.7; HRMS (ESI) m/z calculated for C$_{13}$H$_{20}$N$_2$O [M+H]$^+$: 221.1468, found: 221.1466; IR (ATR diamond, neat): $\nu$ 3299.8, 3063.5, 3027.6, 2956.9, 2929.4, 2871.3, 2358.9, 2337.9, 1647.2, 1522.3, 1454.0, 741.7, 698.8 cm$^{-1}$.

(S)-2-amino-N-methyl-3-phenylpropanamide (1b)

![Chemical structure](image)

Colourless solid (328 mg, 92% yield); m.p. 58.5-60.6°C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.37 (br s, 1H), 7.30–7.09 (m, 5H), 3.55 (br s, 1H), 3.19 (dd, $J = 13.6$, 3.9 Hz, 1H), 2.73 (d, $J = 5.0$ Hz, 3H), 2.63 (dd, $J = 13.7$, 9.2 Hz, 1H), 1.57 (br s, 2H); IR (ATR diamond, neat): $\nu$ 3372, 3344, 2939, 2914, 2876, 1644, 1522, 1455, 1439, 744, 698 cm$^{-1}$.

(S)-2-amino-N-hexyl-3-phenylpropanamide (1c)

![Chemical structure](image)

Light yellow solid (432 mg, 87% yield); m.p. 39.2-39.6°C; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.30–7.22 (m, 3H), 7.17 (d, $J = 6.7$ Hz, 2H), 5.99 (s, 1H), 4.21 (dd, $J = 4.2$, 1.2 Hz, 1H), 3.38 (dd, $J = 7.9$, 7.0 Hz, 2H), 3.22 (dd, $J = 14.0$, 3.9 Hz, 1H), 2.87 (dd, $J = 14.0$, 8.0 Hz, 1H), 1.43 (t, $J = 7.1$ Hz, 2H), 1.29–1.13 (m, 6H), 0.86 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.2, 138.1, 129.3 (2C), 128.6 (2C), 126.7, 56.5, 41.2, 39.1, 31.5, 29.6, 26.6, 22.6, 14.0; HRMS (ESI) m/z calculated for C$_{15}$H$_{24}$N$_2$O [M+H]$^+$: 249.1961, found: 249.1660; IR (ATR diamond, neat): $\nu$ 3304.1, 2956.8, 2921.4, 2987.6, 1638.4, 1545.8, 1491.0, 1453.8, 744.2, 697.2 cm$^{-1}$.

S14
(S)-N-allyl-2-amino-3-phenylpropanamide (1d) [7]

\[
\begin{align*}
&\text{Colourless oil (384 mg, 94% yield); }^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.50 - 7.18 \text{ (m, 6H), 5.83} \\
&\text{ (ddt, } J = 17.3, 10.7, 5.6 \text{ Hz, 1H), 5.21 - 5.09} \text{ (m, 2H), 3.90} \text{ (td, } J = 5.8, 1.6 \text{ Hz, 2H), 3.64} \text{ (dd, } J = 9.3, 4.1 \text{ Hz, 1H), 3.29} \text{ (dd, } J = 13.7, 4.1 \text{ Hz, 1H), 2.73} \text{ (dd, } J = 13.7, 9.3 \text{ Hz, 1H), 1.41} \text{ (br s, 2H); }^1\text{C NMR (101 MHz, CDCl}_3\text{): } \delta 174.0, 137.9, 134.3, 129.3 (2C), 128.7 (2C), 126.8, 116.1, 56.5, 41.5, 41.1; \text{ HRMS (ESI) } m/z \text{ calculated for C}_{12}\text{H}_{16}\text{N}_2\text{O}[M+H]^+: 205.1335, \text{ found: 205.1334; IR (ATR diamond, neat): } \nu 3299.1, 3082.8, 3027.2, 2919.3, 1652.5, 1640.9, 1517.3, 1496.0, 1453.8, 1254.5, 989.9, 918.2, 743.6, 699.7 \text{ cm}^{-1}.}
\end{align*}
\]

(S)-2-amino-N-benzyl-3-phenylpropanamide (1e) [8]

\[
\begin{align*}
&\text{Colourless oil (437 mg, 86% yield); }^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.64 \text{ (t, } J = 5.8 \text{ Hz, 1H), 7.41 - 7.22} \text{ (m, 10H), 4.47} \text{ (dd, } J = 5.9, 4.0 \text{ Hz, 2H), 3.80 - 3.63} \text{ (m, 1H), 3.33} \text{ (dd, } J = 13.7, 4.2 \text{ Hz, 1H), 2.79} \text{ (dd, } J = 13.7, 9.1 \text{ Hz, 1H), 1.61} \text{ (br s, 2H).}
\end{align*}
\]

(S)-2-amino-N-(4-methylbenzyl)-3-phenylpropanamide (1f)

\[
\begin{align*}
&\text{Yellow solid (488 mg, 91% yield); m.p. 70.1-71.5°C; }^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.59 \text{ (s, 1H), 7.37 - 7.09} \text{ (m, 9H), 4.41} \text{ (dd, } J = 5.9, 2.6 \text{ Hz, 2H), 3.67} \text{ (s, 1H), 3.30} \text{ (dd, } J = 13.7, 4.2 \text{ Hz, 1H), 2.79} \text{ (dd, } J = 13.7, 8.9 \text{ Hz, 1H), 2.36} \text{ (s, 3H), 1.64} \text{ (s, 2H); }^1\text{C NMR (100 MHz, CDCl}_3\text{): } \delta 174.0, 137.9, 137.0, 135.4, 129.4 (2C), 129.3 (2C), 128.7 (2C), 127.8 (2C), 126.8, 56.5, 42.9, 41.0, 21.1; \text{ HRMS (ESI) } m/z \text{ calculated for C}_{17}\text{H}_{20}\text{N}_2\text{O}[M+H]^+: 269.1648, \text{ found: 269.1650; IR (ATR diamond, neat): } \nu 3284.9, 3022.7, 2915.4, 2857.7, 1637.5, 1530.2, 1515.0, 1493.1, 743.3, 697.1 \text{ cm}^{-1}.}
\end{align*}
\]
(S)-2-amino-N-(4-fluorobenzyl)-3-phenylpropanamide (1g)\(^8\)

![Chemical structure of (S)-2-amino-N-(4-fluorobenzyl)-3-phenylpropanamide (1g)](image)

Yellow solid (501 mg, 92% yield); m.p. 59.4-60.0°C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.60 (br s, 1H), 7.29 (t, \(J = 7.4\) Hz, 2H), 7.26-7.21 (m, 1H), 7.20 – 7.15 (m, 4H), 6.97 (t, \(J = 8.6\) Hz, 2H), 4.38 (qd, \(J = 14.8, 6.0\) Hz, 2H), 3.64 (dd, \(J = 9.1, 4.3\) Hz, 1H), 3.25 (dd, \(J = 13.7, 4.2\) Hz, 1H), 2.75 (dd, \(J = 13.7, 9.0\) Hz, 1H), 1.42 (br s, 2H); \(^13\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 174.2, 162.2 (d, \(J_{C,F} = 245.5\) Hz), 137.9, 134.3 (d, \(J_{C,F} = 3.2\) Hz), 129.5, 129.4, 128.8, 126.9, 115.52 (d, \(J_{C,F} = 21.5\) Hz), 56.5, 42.5, 41.1; HRMS (ESI) \(m/z\) calculated for C\(_{16}\)H\(_{17}\)FN\(_2\)O [M+H]\(^+\): 273.1398, found: 273.1395; IR (ATR diamond, neat): \(\nu\) 3350.2, 3297.0, 3271.2, 1654.1, 1601.7, 1526.3, 1507.3, 1220.8, 723.5, 703.2 cm\(^{-1}\).

(S)-2-amino-N-phenethyl-3-phenylpropanamide (1h)

![Chemical structure of (S)-2-amino-N-phenethyl-3-phenylpropanamide (1h)](image)

Yellow solid (494 mg, 92% yield); m.p. 58.6-60.7°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.40 (d, \(J = 5.9\) Hz, 1H), 7.35 – 7.11 (m, 10H), 3.51 (dq, \(J = 19.9, 6.7\) Hz, 3H), 3.22 (dd, \(J = 13.7, 4.1\) Hz, 1H), 2.78 (t, \(J = 7.1\) Hz, 2H), 2.69 (dd, \(J = 13.6, 9.1\) Hz, 1H), 1.33 (br s, 2H); \(^13\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 174.2, 139.0, 137.9, 129.3 (2C), 128.8 (2C), 128.7 (2C), 128.5 (2C), 126.8, 126.4, 56.5, 41.1, 40.3, 35.8; HRMS (ESI) \(m/z\) calculated for C\(_{17}\)H\(_{20}\)N\(_2\)O [M+H]\(^+\): 269.1648, found: 269.1649; IR (ATR diamond, neat): \(\nu\) 3360.5, 3331.3, 3062.4, 3026.7, 2918.8, 1644.4, 1522.9, 1494.2, 1453.8, 740.9, 695.7 cm\(^{-1}\).

(S)-2-amino-N,3-diphenylpropanamide (1i)\(^{11}\)

![Chemical structure of (S)-2-amino-N,3-diphenylpropanamide (1i)](image)

Colourless solid (374 mg, 78% yield); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.44 (s, 1H), 7.66 – 7.58 (m, 2H), 7.42 – 7.23 (m, 7H), 7.13 (t, \(J = 7.4\) Hz, 1H), 3.77 (dd, \(J = 9.5, 4.0\) Hz, 1H), 3.41 (dd, \(J = 13.8, 3.9\) Hz, 1H), 2.82 (dd, \(J = 13.8, 9.5\) Hz, 1H), 1.61 (s, 2H).
(S)-2-amino-3-phenyl-N-(p-tolyl)propanamide (1j) \(^1\)

![Chemical Structure Image]

Colourless solid (532 mg, 75% yield); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.37 (br s, 1H), 7.50 (m, 2H), 7.35–7.24 (m, 5H), 7.18–7.06 (m, 2H), 3.83–3.63 (m, 1H) 3.47–3.31 (dd, \(J = 14, 4.8\) Hz, 1H), 2.88–2.73 (m ,1H), 2.35 (s, 3H), 1.56 (br s, 2H).

(S)-2-amino-3-phenyl-N-(4-methoxyphenyl)propanamide (1k) \(^9,10\)

![Chemical Structure Image]

Colourless solid (516 mg, 77% yield); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.26 (br s, 1H), 7.55–7.52 (m, 2H), 7.25–7.04 (m, 7H), 3.38–3.35 (m, 1H), 3.23 (m, 4H), 2.82–2.76 (br s, 1H).

(S)-2-amino-N-(3,4-dicyanophenyl)-3-phenylpropanamide (1l)

![Chemical Structure Image]

Light green oil (69 mg, 33% yield); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 10.03 (br s, 1H), 8.21 (d, \(J = 2.2\) Hz, 1H), 7.88 (dd, \(J = 8.6, 2.2\) Hz, 1H), 7.72 (d, \(J = 8.5\) Hz, 1H), 7.36–7.30 (m, 2H), 7.39–7.24 (m, 1H), 7.24–7.19 (m, 2H), 3.78 (dd, \(J = 9.3, 4.0\) Hz, 1H), 3.32 (dd, \(J = 13.9, 4.1\) Hz, 1H), 2.83 (dd, \(J = 13.9, 9.2\) Hz, 1H), 1.61 (br s, 2H); \(^13\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 173.5, 156.0, 142.2, 136.9, 134.6, 129.3 (2C), 129.1 (2C), 127.4, 123.4, 122.8, 117.0, 115.6, 115.3, 110.0, 56.7, 40.3; HRMS (ESI) \(m/z\) calculated for C\(_{17}\)H\(_{14}\)N\(_4\)O [M+H]\(^+\): 290.1168, found: 290.1164; IR (ATR diamond, neat): \(\nu\) 3385.8, 3265.1, 3028.3, 2923.5, 2230.9, 1693.9, 1597.3, 1568.7, 1497.2, 1407.5, 1315.3, 1253.1, 1187.7, 1098.4, 906.4, 837.9, 727.5, 699.7 cm\(^{-1}\).

(S)-2-amino-N-butyl-3-(4-hydroxyphenyl)propanamide (1n) \(^7\)
Colourless solid (455 mg, 96% yield); m.p. 140.7-141.2°C; \(^1\)H NMR (600 MHz, DMSO): \(\delta\) 7.71 (t, \(J = 5.8\) Hz, 1H), 6.99 – 6.87 (m, 2H), 6.68 – 6.55 (m, 2H), 3.26 (dd, \(J = 7.8, 5.5\) Hz, 1H), 3.05 – 2.91 (m, 2H), 2.73 (dd, \(J = 13.4, 5.5\) Hz, 1H), 2.52 – 2.47 (m, 1H), 2.37 (d, \(J = 5.5\) Hz, 1H), 1.35 – 1.22 (m, 2H), 1.22 – 1.08 (m, 2H), 0.80 (t, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (151 MHz, DMSO): \(\delta\) 174.4, 156.3, 130.7 (2C), 129.0, 115.4 (2C), 56.9, 40.8, 38.5, 31.7, 20.0, 14.2; HRMS (ESI) \(m/z\) calculated for \(\text{C}_{13}\text{H}_{20}\text{N}_{2}\text{O}_{2}\) [M+H]: 237.1598, found: 237.1560; IR (ATR diamond, neat): \(\nu\) 3338.5, 3322.0, 3281.5, 2952.1, 2925.8, 2871.7, 2854.0, 2669.3, 2585.8, 1635.9, 1554.8, 1455.4, 1381.2, 1250.4, 1098.8, 996.6, 825.1, 700.0, 557.8 cm\(^{-1}\).

\((S)-2\text{-amino-N-benzyl-3-(4-hydroxyphenyl)propanamide (1o)}\) \(^{[10]}\)

Colourless solid (496 mg, 92% yield); m.p. 144.5-145.3°C; \(^1\)H NMR (600 MHz, DMSO): \(\delta\) 9.25 – 9.03 (m, 1H), 8.23 (t, \(J = 6.1\) Hz, 1H), 7.32 – 7.11 (m, 3H), 7.14 – 7.03 (m, 2H), 7.00 – 6.89 (m, 2H), 6.68 – 6.56 (m, 2H), 4.22 (dd, \(J = 50.0, 15.1, 6.0\) Hz, 2H), 3.34 (dd, \(J = 7.7, 5.8\) Hz, 1H), 2.77 (dd, \(J = 13.4, 5.7\) Hz, 1H), 2.53 (dd, \(J = 13.4, 7.7\) Hz, 1H), 1.94 – 1.69 (m, 2H); \(^{13}\)C NMR (151 MHz, DMSO): \(\delta\) 174.9, 156.3, 140.0, 130.8 (2C), 129.1 (2C), 128.7 (2C), 127.7, 127.2, 115.5 (2C), 57.1, 42.4, 41.0; HRMS (ESI) \(m/z\) calculated for \(\text{C}_{16}\text{H}_{18}\text{N}_{2}\text{O}_{2}\) [M+H]: 271.1441, found: 271.1440; IR (ATR diamond, neat): \(\nu\) 3334.3, 3276.5, 2950.1, 2926.6, 2856.5, 2669.3, 2580.7, 1636.3, 1542.9, 1515.2, 1453.9, 1243.6, 1098.9, 998.2, 825.5, 696.7, 536.8 cm\(^{-1}\).

\((S)-2\text{-amino-N-(3-fluorophenyl)-3-(4-hydroxyphenyl)propanamide (1p)}\)

Light yellow waxy solid (139 mg, 50% yield); \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.51 (dt, \(J = 11.2, 2.2\) Hz, 1H), 7.30 – 7.17 (m, 2H), 7.09 – 7.01 (m, 2H), 6.81 (tdd, \(J = 8.3, 2.6, 1.1\) Hz, 1H), 6.77 – 6.71 (m, 2H), 4.93 (br s, 1H), 3.64 (dd, \(J = 7.2, 6.4\) Hz, 1H), 2.99 (dd, \(J = 13.6, 6.4\) Hz, 1H).
Hz, 1H), 2.86 – 2.75 (dd, J = 13.6, 7.2 Hz, 1H); \(^{13}\)C NMR (101 MHz, CD\(_3\)OD): \(\delta\) 173.9, 164.0, 161.6, 156.0, 139.8, 139.6, 130.1 (2C), 129.9, 129.8, 127.8, 115.4, 115.3, 115.1 (2C), 110.5, 110.2, 107.1, 106.8, 57.1, 47.5, 47.3, 47.1, 40.4; HRMS (ESI) \(m/z\) calculated for C\(_{15}\)H\(_{15}\)FN\(_2\)O\(_2\) \([\text{M+H}]^+\): 274.1118, found: 258.1117; IR (ATR diamond, neat): \(\nu\) 3270.2, 3029.1, 2920.7, 2397.7, 1667.5, 1610.0, 1551.4, 1512.7, 1491.7, 1443.0, 1423.3, 1249.9, 954.7, 858.3, 814.4, 774.9, 678.4 cm\(^{-1}\).

(S)-2-amino-N,3-dimethylbutanamide (1q)\[^{[11]}\]

![Structure](image)

Colourless oil (234 mg, 90% yield); \(^1\)H NMR (400 MHz, DMSO): \(\delta\) 7.94 (br s, 1H), 3.78 (s, 2H), 3.05 (d, \(J = 5.4\) Hz, 1H), 2.61 (d, \(J = 4.6\) Hz, 3H), 1.89 (pd, \(J = 6.9, 5.4\) Hz, 1H), 0.87 (d, \(J = 6.9\) Hz, 3H), 0.81 (d, \(J = 6.8\) Hz, 3H); \(^{13}\)C NMR (101 MHz, DMSO): \(\delta\) 173.8, 60.0, 31.6, 25.8, 19.7, 17.9; HRMS (ESI) \(m/z\) calculated for C\(_6\)H\(_{14}\)N\(_2\)O \([\text{M+H}]^+\): 131.1179, found: 131.1176; IR (ATR diamond, neat): \(\nu\) 3265.3, 3084.0, 2962.4, 2901.5, 2876.8, 1641.9, 1563.0, 1466.5, 1410.9, 1371.8, 1301.1, 1251.2, 1160.9, 1056.7, 977.8, 885.7, 586.7 cm\(^{-1}\).

(S)-2-amino-N-butyl-3-methylbutanamide (1r)

![Structure](image)

Colourless oil (320 mg, 93% yield); \(^1\)H NMR (400 MHz, DMSO): \(\delta\) 7.99 (br t, 1H), 3.92 (s, 2H), 3.20 – 2.93 (m, 3H), 1.99 – 1.80 (m, 1H), 1.45 – 1.34 (m, 2H), 1.28 (dp, \(J = 9.0, 7.0\) Hz, 2H), 0.87 (dt, \(J = 7.3, 3.9\) Hz, 6H), 0.82 (d, \(J = 6.8\) Hz, 3H); \(^{13}\)C NMR (101 MHz, DMSO): \(\delta\) 173.0, 59.9, 38.5, 31.7, 31.6, 20.0, 19.7, 17.9, 14.1; HRMS (ESI) \(m/z\) calculated for C\(_9\)H\(_{20}\)N\(_2\)O \([\text{M+H}]^+\): 173.1648, found: 173.1650; IR (ATR diamond, neat): \(\nu\) 3675.4, 3280.3, 3071.0, 2958.6, 2931.4, 2872.7, 1642.8, 1531.5, 1465.2, 1370.7, 1299.9, 1242.0, 1076.3, 980.0, 868.1 cm\(^{-1}\).

(S)-2-amino-N-butylpropanamide (1s)

![Structure](image)
Colourless oil (252 mg, 88% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.37 (t, J = 6.0 Hz, 1H), 3.47 (qt, J = 6.9, 2.6 Hz, 1H), 3.23 – 3.10 (m, 2H), 2.12 (d, J = 6.6 Hz, 2H), 1.52 – 1.35 (m, 2H), 1.35 – 1.21 (m, 5H), 0.94 – 0.77 (m, 3H);¹³C NMR (101 MHz, CDCl₃): δ 175.2, 50.6, 38.7, 31.6, 21.5, 20.0, 13.7; HRMS (ESI) m/z calculated for C₁₇H₁₆N₂O [M+H]⁺: 287.1333, found: 287.1336; IR (ATR diamond, neat): ν 3287.2, 3082.6, 2959.3, 2931.4, 2873.0, 1643.6, 1536.2, 1455.7, 1368.8, 1259.0, 1229.0, 1130.0, 1074.3, 956.8, 856.4, 665.4 cm⁻¹.

(R)-2-amino-N-butyl-3-(1H-indol-3-yl)propanamide (1t) [¹²]

Colourless solid (471 mg, 91% yield); ¹H NMR (600 MHz, DMSO): δ 10.80 (s, 1H), 7.75 (d, J = 5.7 Hz, 1H), 7.52 (dd, J = 7.9, 2.8 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.02 (dd, J = 8.1, 6.9, 1.3 Hz, 1H), 6.93 (td, J = 7.4, 6.9, 1.1 Hz, 1H), 3.43 – 3.35 (m, 1H), 3.07 – 2.94 (m, 3H), 2.72 (dd, J = 14.1, 8.1 Hz, 1H), 2.08 – 1.71 (m, 2H), 1.34 – 1.24 (m, 2H), 1.22 – 1.11 (m, 2H), 0.80 (s, 3H).

Methyl L-phenylalanylglycinate (1u) [¹²]

Colourless oil (221 mg, 94% yield); ¹H NMR (400 MHz, CD₃OD) δ 7.41 – 7.26 (m, 5H), 4.98 (br s, 1H), 4.23 (dd, J = 7.7, 6.4 Hz, 1H), 4.00 (s, 2H), 3.74 (s, 3H), 3.28 (dd, J = 14.1, 6.4 Hz, 1H), 3.13 (dd, J = 14.1, 7.8 Hz, 1H);¹³C NMR (101 MHz, CD₃OD) δ 170.2, 169.1, 134.2, 129.2 (2C), 128.7 (2C), 127.4, 54.3, 51.5, 40.6, 37.1.

(S)-2-(benzylamino)-N-butyl-3-phenylpropanamide (1v)
S21

Colourless solid (395 mg, 85% yield); m.p. 58.6-61.4°C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39 – 7.22 (m, 7H), 7.22 – 7.16 (m, 2H), 7.14 – 7.04 (m, 2H), 3.72 (d, $J$ = 13.3 Hz, 1H), 3.59 (d, $J$ = 13.3 Hz, 1H), 3.51 – 3.18 (m, 5H), 2.78 (dd, $J$ = 13.8, 9.2 Hz, 1H), 1.48 (ddd, $J$ = 14.3, 7.6, 5.0 Hz, 2H), 1.41 – 1.25 (m, 2H), 0.94 (t, $J$ = 7.3 Hz, 3H); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39 – 7.22 (m, 7H), 7.22 – 7.16 (m, 2H), 7.14 – 7.04 (m, 2H), 3.72 (d, $J$ = 13.3 Hz, 1H), 3.59 (d, $J$ = 13.3 Hz, 1H), 3.51 – 3.18 (m, 5H), 2.78 (dd, $J$ = 13.8, 9.2 Hz, 1H), 1.48 (ddd, $J$ = 14.3, 7.6, 5.0 Hz, 2H), 1.41 – 1.25 (m, 2H), 0.94 (t, $J$ = 7.3 Hz, 3H); $^1$C NMR (100 MHz, CDCl$_3$): $\delta$ 173.2, 138.9, 137.3, 129.1 (2C), 128.8 (2C), 128.9 (2C), 128.0 (2C), 127.3, 126.9, 63.2, 52.6, 39.2, 38.8, 31.7, 20.1, 13.8; HRMS (ESI) $m/z$ calculated for C$_{20}$H$_{26}$N$_2$O [M+H]$^+$: 311.2118, found: 311.2115; IR (ATR diamond, neat): $\nu$ 3314.7, 3286.1, 3059.7, 3027.0, 2958.4, 2930.0, 2872.9, 1626.5, 1542.3, 1496.1, 1472.2, 1453.2, 1301.1, 1126.4, 750.1, 740.0, 695.0 cm$^{-1}$.

(S)-5-benzyl-3-butylimidazolidine-2,4-dione (2a) [13]

$\begin{array}{c}
\text{\includegraphics[width=0.2\textwidth]{image1.png}}
\end{array}$

Colourless solid (62 mg, 84% yield); $[\alpha]_D^{27}$ 72.52° (c 0.3, MeOH); $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.30-7.21 (m, 3H), 7.21-7.13 (m, 2H), 6.21 (s, 1H), 4.21 (ddd, $J$ = 7.8, 3.9, 1.2 Hz, 1H), 3.47-3.29 (m, 2H), 3.21 (dd, $J$ = 14.0, 4.0 Hz, 1H), 2.89 (dd, $J$ = 14.0, 7.7 Hz, 1H), 1.46-1.37 (m, 2H), 1.19-1.09 (m, 2H), 0.86 (t, $J$ = 7.4 Hz, 3H).

(S)-5-benzyl-3-methylimidazolidine-2,4-dione (2b) [14]

$\begin{array}{c}
\text{\includegraphics[width=0.2\textwidth]{image2.png}}
\end{array}$

Colourless solid (56 mg, 91% yield); $[\alpha]_D^{27}$ 87.75° (c 0.3, MeOH); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.31 – 7.20 (m, 3H), 7.17 (m, 2H), 6.08 (s, 1H), 4.21 (ddd, $J$ = 8.8, 3.9, 1.2 Hz, 1H), 3.25 (dd, $J$ = 14.0, 3.8 Hz, 1H), 2.91 (s, 3H), 2.86 – 2.78 (m, 1H).

(S)-5-benzyl-3-hexylimidazolidine-2,4-dione (2c) [15]

$\begin{array}{c}
\text{\includegraphics[width=0.2\textwidth]{image3.png}}
\end{array}$

S21
Colourless solid (58 mg, 71% yield); $[\alpha]_D^{23} = -58.81^\circ$ (c 0.3, MeOH); $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.30 – 7.22 (m, 3H), 7.17 (d, $J = 6.7$ Hz, 2H), 5.99 (s, 1H), 4.21 (dd, $J = 4.2$, 1.2 Hz, 1H), 3.38 (dd, $J = 7.9$, 7.0 Hz, 2H), 3.22 (dd, $J = 14.0$, 3.9 Hz, 1H), 2.87 (dd, $J = 14.0$, 8.0 Hz, 1H), 1.43 (t, $J = 7.1$ Hz, 2H), 1.29 – 1.13 (m, 6H), 0.86 (t, $J = 7.0$ Hz, 3H).

(S)-3-allyl-5-benzylimidazolidine-2,4-dione (2d)

Colourless solid (39 mg, 85% yield); $[\alpha]_D^{20} = -69.6^\circ$ (c 0.3, MeOH); m.p. 94.5-95.3°C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38 – 7.24 (m, 3H), 7.20 (dd, $J = 7.7$, 1.8 Hz, 2H), 6.33 (s, 1H), 5.68 (ddt, $J = 17.1$, 10.2, 5.6 Hz, 1H), 5.11 (dp, $J = 10.3$, 1.3 Hz, 1H), 5.02 (dq, $J = 17.1$, 1.5 Hz, 1H), 4.28 (ddd, $J = 7.8$, 4.0, 1.3 Hz, 1H), 4.13 – 3.95 (m, 2H), 3.26 (dd, $J = 14.0$, 3.9 Hz, 1H), 2.94 (dd, $J = 14.0$, 7.9 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.8, 157.1, 135.0, 130.9, 129.5, 128.8, 127.4, 117.6, 58.4, 40.5, 37.8; HRMS (ESI) $m/z$ calculated for C$_{13}$H$_{14}$N$_{2}$O$_2$ [M+H]$^+$: 231.1288, found: 231.1289; IR (ATR diamond, neat): $\nu$ 3284.7, 2926.2, 1750.3, 1697.5, 1542.2, 1421.5, 1355.7, 1334.7, 1142.0, 1094.8, 964.5, 700.2 cm$^{-1}$.

(S)-3,5-dibenzylimidazolidine-2,4-dione (2e)$^{[13,14,15]}$

Colourless solid (76 mg, 90% yield); $[\alpha]_D^{27} = -36.18^\circ$ (c 0.3, MeOH); $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.29 – 7.07 (m, 10H), 6.43 (s, 1H), 4.63 – 4.48 (m, 2H), 4.22 (dd, $J = 7.6$, 5.3 Hz, 1H), 3.18 (dd, $J = 14.1$, 4.0 Hz, 1H), 2.89 (dd, $J = 14.0$, 7.7 Hz, 1H).

(S)-5-benzyl-3-(4-methylbenzyl)imidazolidine-2,4-dione (2f)
Colourless solid (78 mg, 88% yield); [α]$_D^{23}$ $–38.40^\circ$ (c 0.3, MeOH); m.p. 125.6-127.1°C; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.30-7.27 (m, 3H), 7.19-7.17 (m, 4H), 7.11-7.10 (m, 2H), 5.50 (br s, 1H), 4.58 (d, J = 6.5 Hz, 2H), 4.25 (ddd, J = 8.7, 3.8, 1.2 Hz, 1H), 3.28 (dd, J = 13.9, 3.8 Hz, 1H), 2.85 (dd, J = 13.9, 8.7 Hz, 1H), 2.34 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 172.7, 156.6, 137.6, 135.2, 132.8, 129.3 (2C), 129.2 (2C), 128.9 (2C), 128.4 (2C), 127.4, 58.4, 41.9, 37.9, 21.2; HRMS (ESI) m/z calculated for C$_{18}$H$_{18}$N$_2$O$_2$ [M+H]$^+$: 295.1441, found: 295.1442; IR (ATR diamond, neat): ν 3240.0, 3031.0, 2922.4, 1769.6, 1707.0, 1446.7, 1349.2, 1196.8, 906.8, 725.2 cm$^{-1}$.

($S$)-5-benzyl-3-(4-fluorobenzyl)imidazolidine-2,4-dione (2g) $^{[15]}$

![Chemical structure of 2g](image)

Colourless solid (80 mg, 89% yield); [α]$_D^{23}$ $–15.49^\circ$ (c 0.4, MeOH); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.18-7.02 (m, 7H), 6.88-6.83 (m, 2H), 5.29 (br s, 1H), 4.43 (dd, J = 15.0, 11.5 Hz, 2H), 4.18 (ddt, J = 7.6, 4.1, 1.1 Hz, 1H), 3.11 (ddd, J = 14.0, 4.0, 1.3 Hz, 1H), 2.83 (ddd, J = 14.0, 7.5, 1.1 Hz, 1H).

($S$)-5-benzyl-3-phenethylimidazolidine-2,4-dione (2h) $^{[16]}$

![Chemical structure of 2h](image)

Colourless solid (75 mg, 85% yield); [α]$_D^{27}$ $–89.90^\circ$ (c 0.3, MeOH); m.p. 126.1-126.4°C; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.26-7.09 (m, 10H), 5.78 (br s, 1H), 4.09 (ddd, J = 8.8, 3.8, 1.1 Hz, 1H), 3.66-3.52 (m, 2H), 3.13 (ddd, J = 13.9, 3.8 Hz, 1H), 2.74-2.63 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 172.9, 157.0, 137.8, 135.3, 128.3 (2C), 129.0 (2C), 128.9 (2C), 128.6 (2C), 127.5, 126.7, 58.2, 38.6, 38.0, 33.8; HRMS (ESI) m/z calculated for C$_{18}$H$_{18}$N$_2$O$_2$ [M+H]$^+$: 295.1441, found: 295.1443; IR (ATR diamond, neat): ν 3286.0, 2985.3, 1764.3, 1683.3, 1453.2, 1423.6, 1355.5, 1130.1, 749.0, 726.0, 696.4 cm$^{-1}$.

($S$)-5-benzyl-3-phenylimidazolidine-2,4-dione (2i) $^{[15,16]}$
Colourless solid (68 mg, 85% yield); \([\alpha]^{27}_D\) –109.72° (c 0.3, MeOH); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.37-7.08 (m, 10H), 6.55 (br s, 1H), 4.30 (ddd, \(J = 7.1, 4.0, 1.2\) Hz, 1H), 3.16 (dd, \(J = 13.9, 4.1\) Hz, 1H), 2.99 (dd, \(J = 13.9, 7.0\) Hz, 1H).

\((S)-5\)-benzyl-3-(p-tolyl)imidazolidine-2,4-dione (2j)

Colourless solid (78 mg, 93% yield); \([\alpha]^{23}_D\) –163.89° (c 0.3, MeOH); m.p. 124.9-127.0°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.38 – 7.22 (m, 7H), 7.06 (dd, \(J = 8.4, 2.0\) Hz, 2H), 6.55 (d, \(J = 7.6\) Hz, 1H), 4.40 (ddd, \(J = 7.1, 4.0, 1.1\) Hz, 1H), 3.26 (dt, \(J = 13.9, 3.7\) Hz, 1H), 3.17 – 3.01 (m, 1H), 2.39 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 172.3, 156.7, 138.5, 134.7, 129.8 (2C), 129.6 (2C), 128.8 (2C), 128.6, 127.5, 126.2 (2C), 58.1, 37.8, 21.2; HRMS (ESI) \(m/z\) calculated for C\(_{17}\)H\(_{16}\)N\(_2\)O\(_2\) [M+H]\(^+\): 281.1285, found: 281.1283; IR (ATR diamond, neat): \(\nu\) 3325.0, 3116.2, 2920.0, 2848.8, 1774.8, 1711.8, 1513.1, 1404.3, 1358.1, 1162.8, 818.1, 746.8, 695.4 cm\(^{-1}\).

\((S)-5\)-benzyl-3-(4-methoxyphenyl)imidazolidine-2,4-dione (2k) \(^{15}\)

Colourless solid (76 mg, 86% yield); \([\alpha]^{27}_D\) –143.07° (c 0.3, MeOH); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.38 – 7.30 (m, 3H), 7.27 – 7.21 (m, 2H), 7.09 – 7.03 (m, 2H), 7.00 – 6.92 (m, 2H), 6.76 (s, 1H), 4.39 (ddd, \(J = 6.8, 4.1, 1.2\) Hz, 1H), 3.83 (s, 3H), 3.24 (dd, \(J = 13.9, 4.1\) Hz, 1H), 3.10 (dd, \(J = 13.9, 6.7\) Hz, 1H).

\((S)-4\)-(4-benzyl-2,5-dioxoimidazolidin-1-yl)phthalonitrile (2l)
Yellow solid (10 mg, 13% yield); \([\alpha]_D^{20} = -101.3^\circ\) (c 0.1, MeOH); m.p. 165.1-167.2°C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.96 – 7.91 (m, 1H), 7.89 – 7.81 (m, 2H), 7.37 – 7.28 (m, 3H), 7.21 (dt, \(J = 6.1, 1.6\) Hz, 2H), 6.06 (br s, 1H), 4.48 (dd, \(J = 7.9, 3.9, 1.2\) Hz, 1H), 3.34 (dd, \(J = 14.0, 3.9\) Hz, 1H), 3.05 (dd, \(J = 14.0, 7.8\) Hz, 1H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 181.7, 170.8, 154.0, 141.5, 136.3, 134.2, 134.1, 129.5, 129.4 (2C), 129.2 (2C), 129.1, 128.1, 116.8, 115.0, 114.7, 114.3, 58.1, 38.1; HRMS (ESI) \(m/z\) calculated for C\(_{18}\)H\(_{12}\)N\(_4\)O\(_2\) [M+H]\(^+\): 316.3200, found: 316.3197; IR (ATR diamond, neat): \(\nu\) 3327.9, 3116.2, 3030.2, 2925.7, 2853.0, 2235.3, 1784.7, 1720.1, 1599.4, 1494.2, 1392.7, 1348.1, 1186.1, 1160.7, 1112.8, 1030.1, 907.7, 841.6, 727.7 cm\(^{-1}\).

\((\text{rac})-5\)-Benzyimidazolidine-2,4-dione (2m)\(^{[16]}\)

Colourless solid (43 mg, 75% yield); \(^1\)H NMR (400 MHz, DMSO): \(\delta\) 10.43 (s, 1H), 7.93 (s, 1H), 7.35 – 7.13 (m, 5H), 4.39 – 4.29 (m, 1H), 2.93 (dd, \(J = 5.0, 3.7\) Hz, 2H); \(^{13}\)C NMR (101 MHz, DMSO): \(\delta\) 180.4, 162.4, 140.9, 135.0, 133.3, 131.9, 63.6, 41.7.

\((S)-3\)-butyl-5-(4-hydroxybenzyl)imidazolidine-2,4-dione (2n)

Light yellow solid (70 mg, 89% yield); \([\alpha]_D^{23} = -50.81^\circ\) (c 0.3, MeOH); m.p. 173.5-174.2°C; \(^1\)H NMR (400 MHz, DMSO): \(\delta\) 9.21 (s, 1H), 8.26 – 8.03 (m, 1H), 7.07 – 6.85 (m, 2H), 6.71 – 6.53 (m, 2H), 4.27 (d, \(J = 1.1\) Hz, 1H), 3.14 (d, \(J = 18.5\) Hz, 2H), 2.84 (dd, \(J = 4.6, 2.2\) Hz, 2H), 1.29 – 1.08 (m, 2H), 1.03 – 0.82 (m, 2H), 0.75 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (101 MHz, DMSO): \(\delta\) 174.0, 157.1, 156.7, 131.2 (2C), 125.3, 115.2 (2C), 57.6, 37.5, 35.9, 29.9, 19.5, 14.0; HRMS (ESI) \(m/z\) calculated for C\(_{14}\)H\(_{18}\)N\(_2\)O\(_3\) [M+H]\(^+\): 263.1690, found: 262.1689; IR (ATR diamond, neat): ν 3315.5, 3115.7, 3031.4, 2924.4, 2854.1, 2235.3, 1789.3, 1716.9, 1599.4, 1494.2, 1392.7, 1348.1, 1187.6, 1160.9, 1112.3, 1030.1, 907.8, 841.6, 727.5 cm\(^{-1}\).
(S)-3-benzyl-5-(4-hydroxybenzyl)imidazolidine-2,4-dione (2o)

Light yellow solid (83 mg, 94% yield); $[\alpha]_{D}^{23} -19.71^\circ$ (c 0.3, MeOH); m.p. 149.4-150.2°C; $^1$H NMR (600 MHz, DMSO): $\delta$ 9.29 (s, 1H), 8.28 (s, 1H), 7.17 – 7.13 (m, 3H), 6.91 (d, $J = 8.5$ Hz, 2H), 6.72 – 6.64 (m, 2H), 6.63 – 6.56 (m, 2H), 4.44 – 4.22 (m, 3H), 2.92 – 2.78 (m, 2H); $^{13}$C NMR (151 MHz, DMSO): $\delta$ 173.9, 156.9, 156.8, 136.8, 131.5 (2C), 128.7 (2C), 127.4, 126.9 (2C), 125.4, 115.5 (2C), 58.0, 41.2, 35.7; HRMS (ESI) m/z calculated for C$_{17}$H$_{16}$N$_2$O$_3$ [M+H]$^+$: 296.1234, found: 296.1233; IR (ATR diamond, neat): ν 3304.8, 3190.2, 3028.7, 2926.8, 1742.6, 1689.1, 1613.9, 1448.7, 1204.9, 1175.0, 1081.3, 864.0, 824.1, 766.0, 566.5 cm$^{-1}$.

(S)-3-(3-fluorophenyl)-5-(4-hydroxybenzyl)imidazolidine-2,4-dione (2p)

Colourless solid (60 mg, 67% yield); $[\alpha]_{D}^{20} -92.3^\circ$ (c 0.2, MeOH); m.p. 150.0-151.5°C; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.40 (td, $J = 8.2$, 6.3 Hz, 1H), 7.15 – 7.04 (m, 3H), 6.90 (ddd, $J = 8.0$, 1.9, 1.0 Hz, 1H), 6.84 (dt, $J = 9.8$, 2.3 Hz, 1H), 6.79 – 6.71 (m, 2H), 4.88 (br s, 2H) 4.46 (dd, $J = 4.5$ Hz, $J = 4.5$ Hz, 1H), 3.15 – 3.01 (m, 2H); $^{13}$C NMR (101 MHz, CD$_3$OD) $\delta$ 173.1, 163.6, 161.2, 156.5, 156.3, 133.2, 133.1, 130.8 (2C), 129.9, 129.8, 125.0, 122.2, 114.8 (2C), 114.7, 114.5, 113.6, 113.4, 58.0, 36.0; HRMS (ESI) m/z calculated for C$_{16}$H$_{13}$FN$_2$O$_3$ [M+H]$^+$: 300.0910, found: 300.0913; IR (ATR diamond, neat): ν 3260.9, 2426.2, 1771.9, 1599.0, 1600.4, 1514.0, 1492.1, 1422.2, 1348.8, 1238.6, 1185.9, 1166.8, 1015.1, 802.0, 781.5, 735.6 cm$^{-1}$.

(S)-3-butyl-5-isopropylimidazolidine-2,4-dione (2q)
Colourless oil (52 mg, 88% yield); [α]D20 36.91° (c 0.3, MeOH); 1H NMR (400 MHz, CDCl3): δ 6.71 (s, 1H), 3.93 (dd, J = 3.7, 1.1 Hz, 1H), 3.59 – 3.40 (m, 2H), 2.28-2.20 (m, 1H), 1.66 – 1.49 (m, 2H), 1.41 – 1.27 (m, 2H), 1.06 (d, J = 7.0 Hz, 3H), 0.99 – 0.87 (m, 6H); 13C NMR (101 MHz, CDCl3): δ 173.7, 158.7, 62.3, 38.3, 30.2, 30.1, 20.0, 18.8, 15.9, 13.6; HRMS (ESI) m/z calculated for C10H18N2O2 [M+H]+: 199.1441, found: 199.1440; IR (ATR diamond, neat): ν 3662.0, 3283.9, 2961.3, 2934.6, 2874.9, 1770.9, 1696.4, 1449.4, 1421.1, 1353.1, 1294.6, 1200.1, 1103.5, 1042.3, 922.1, 765.2, 624.1 cm⁻¹.

(S)-5-isopropyl-3-methylimidazolidine-2,4-dione (2r)

Colourless solid (34 mg, 72% yield); [α]D20 59.80° (c 0.3, MeOH); m.p. 127.1-128.6°C; 1H NMR (400 MHz, CDCl3): δ 6.68 (s, 1H), 3.95 (dd, J = 3.9, 1.2 Hz, 1H), 3.01 (s, 3H), 2.29-2.20 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); 13C NMR (101 MHz, CDCl3): δ 173.7, 158.6, 62.6, 30.2, 24.4, 18.8, 16.1; HRMS (ESI) m/z calculated for C7H12N2O2 [M+H]+: 157.0972, found: 157.0972; IR (ATR diamond, neat): ν 3283.6, 2966.0, 2874.7, 1745.7, 1693.8, 1470.0, 1392.2, 1355.2, 1305.7, 1280.3, 1197.4, 1143.9, 1115.1, 1100.2, 1041.6, 947.3, 832.6, 761.5, 719.9 cm⁻¹.

(S)-3-butyl-5-methylimidazolidine-2,4-dione (2s)

Colourless oil (37 mg, 73% yield); [α]D20 3299.8° (c 0.3, MeOH); 1H NMR (400 MHz, CDCl3): δ 6.66 (s, 1H), 4.08 (qd, J = 6.9, 1.0 Hz, 1H), 3.49 (td, J = 7.2, 1.5 Hz, 2H), 1.67 – 1.53 (m, 2H), 1.45 (d, J = 7.0 Hz, 3H), 1.41 – 1.26 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); 13C NMR (101 MHz, CDCl3): δ 174.9, 158.0, 52.8, 38.4, 30.1, 19.9, 17.6, 13.6; HRMS (ESI) m/z calculated for C8H14N2O2 [M+H]+: 171.1128, found: 171.1126; IR (ATR diamond, neat): ν 3299.8,
2959.1, 2935.1, 2874.0, 1771.7, 1449.4, 1421.2, 1370.9, 1344.4, 1321.6, 1200.9, 1133.8, 1045.4, 936.2, 772.0, 594.5 cm\(^{-1}\).

\((R)-5-((1H\text{-indol}-3-yl)methyl)-3\text{-butylimidazolidine-2,4-dione (2t)}\)

Brown solid (35 mg, 41% yield); \([\alpha]_D^{20} +2.6^\circ\) (c 0.1, MeOH); m.p. 129.0-130.8\(^\circ\)C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.26 (s, 1H), 7.61 (dt, \(J = 7.9, 1.0\) Hz, 1H), 7.35 (dt, \(J = 8.2, 0.9\) Hz, 1H), 7.22 (ddd, \(J = 8.2, 7.0, 1.2\) Hz, 1H), 7.13 (ddd, \(J = 8.0, 7.0, 1.1\) Hz, 1H), 7.00 (d, \(J = 1.9\) Hz, 1H), 6.07 (s, 1H), 4.26 (ddd, \(J = 8.1, 3.8, 1.0\) Hz, 1H), 3.50 – 3.31 (m, 3H), 3.07 (dd, \(J = 14.8, 8.1\) Hz, 1H), 1.40 (p, \(J = 7.4\) Hz, 2H), 1.27 – 1.11 (m, 2H), 0.86 (t, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 173.8, 157.8, 136.2, 127.1, 123.3, 122.4, 119.9, 118.7, 111.4, 109.3, 57.8, 38.4, 29.9, 27.9, 19.8, 13.6; HRMS (ESI) \(m/z\) calculated for C\(_{16}\)H\(_{19}\)N\(_3\)O\(_2\) [M+H]\(^+\): 286.1550, found: 286.1553; IR (ATR diamond, neat): \(\nu\) 3313.6, 2956.6, 2929.3, 2879.6, 1767.4, 1692.8, 1452.5, 1422.1, 1341.9, 1232.6, 1096.5, 739.5, 553.1 cm\(^{-1}\).

\(\text{Methyl (S)-2-(4-benzyl-2,5-dioxoimidazolidin-1-yl)acetate (2u)}\)

Colourless solid (30 mg, 38% yield); \([\alpha]_D^{20} -94.5^\circ\) (c 0.2, MeOH); m.p. 132.9-135.4\(^\circ\)C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.39 – 7.30 (m, 2H), 7.34 – 7.26 (m, 1H), 7.26 – 7.18 (m, 2H), 5.96 (br s, 1H), 4.34 (ddd, \(J = 9.4, 3.8, 1.2\) Hz, 1H), 4.22 (d, \(J = 1.0\) Hz, 2H), 3.77 (s, 3H), 3.34 (dd, \(J = 14.0, 3.8\) Hz, 1H), 2.88 (dd, \(J = 13.9, 9.3\) Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.6, 167.4, 156.1, 135.4, 129.2 (2C), 129.0 (2C), 127.5, 58.8, 52.7, 39.2, 38.0; HRMS (ESI) \(m/z\) calculated for C\(_{13}\)H\(_{14}\)N\(_2\)O\(_4\) [M+H]\(^+\): 262.0954, found: 262.0950; IR (ATR diamond, neat): \(\nu\) 3232.1, 3108.9, 3031.5, 2954.5, 1774.6, 1716.3, 1498.8, 1455.4, 1431.9, 1344.6, 1221.7, 1157.4, 1084.9, 924.6, 729.0 cm\(^{-1}\).

\(2,2'\text{-}(\text{carbonylbis(azanediyl)}\text{bis(N-butyl-3-phenylpropanamide) (3a)}}\)
Colourless solid (116 mg, quant. yield); m.p. 210.5-211.7°C; $^1$H NMR (400 MHz, DMSO): $\delta$ 7.76 (t, $J = 5.6$ Hz, 2H), 7.33 – 7.11 (m, 10H), 6.33 (d, $J = 8.3$ Hz, 2H), 4.27 (td, $J = 7.8$, 6.2 Hz, 2H), 3.03 (dt, $J = 13.1$, 6.6 Hz, 2H), 2.95 (dt, $J = 12.7$, 6.2 Hz, 2H), 2.85 (dd, $J = 13.5$, 6.2 Hz, 2H), 2.73 (dd, $J = 13.6$, 7.6 Hz, 2H), 1.37 – 1.24 (m, 4H), 1.24 – 1.10 (m, 4H), 0.82 (t, $J = 7.2$ Hz, 6H); $^{13}$C NMR (101 MHz, DMSO): $\delta$ 171.8 (2C), 157.1, 138.3 (2C), 129.7 (4C), 128.4 (4C), 126.6 (2C), 54.9 (2C), 39.3 (2C), 38.5 (2C), 31.5 (2C), 19.9 (2C), 14.1 (2C); HRMS (ESI) $m/z$ calculated for C$_{27}$H$_{38}$N$_{4}$O$_{3}$ [M+H]$^+$: 467.3017, found: 467.3014; IR (ATR diamond, neat): $\nu$ 3381.2, 3280.0, 2960.8, 2934.8, 2885.3, 1632.6, 1548.6, 1495.0, 1449.2, 1372.9, 1283.7, 1225.6, 1077.6, 1031.9, 740.2, 701.2, 615.5 cm$^{-1}$.

$(S)$-N-buty1-3-phenyl-2-(3-phenylureido)propanamide (5a)

Colourless solid (101 mg, quant. yield); m.p. 181.7-183.1°C; $^1$H NMR (400 MHz, DMSO): $\delta$ 8.66 (s, 1H), 8.05 (t, $J = 5.6$ Hz, 1H), 7.39 – 7.15 (m, 9H), 6.89 (t, $J = 7.3$ Hz, 1H), 6.36 (d, $J = 8.3$ Hz, 1H), 4.47 (td, $J = 7.8$, 5.9 Hz, 1H), 3.18 – 2.91 (m, 3H), 2.84 (dd, $J = 13.6$, 7.5 Hz, 1H), 1.44 – 1.28 (m, 2H), 1.28 – 1.15 (m, 2H), 0.85 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (101 MHz, DMSO): $\delta$ 171.6, 155.0, 140.8, 138.0, 129.8 (2C), 129.1 (2C), 128.5 (2C), 126.7, 121.6, 117.9 (2C), 54.4, 39.6, 38.6, 31.6, 20.0, 14.1; HRMS (ESI) $m/z$ calculated for C$_{20}$H$_{25}$N$_{3}$O$_{2}$ [M+H]$^+$: 340.2020, found: 340.2017; IR (ATR diamond, neat): $\nu$ 3279.3, 3089.2, 3062.7, 2957.2, 2929.4, 2870.3, 1634.0, 1544.3, 1497.3, 1440.9, 1312.2, 1225.9, 1030.9, 742.6, 691.6, 503.0 cm$^{-1}$. 

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8. References

9. Copy of NMR Spectra
1b

[Chemical structure]
1d
$^{1}g$
The image contains a chemical structure labeled as 2a, along with a 1D NMR spectrum. The spectrum shows peaks at various ppm values, indicating the chemical shifts of different protons or other nuclei in the molecule. The peaks are labeled with their corresponding ppm values, which are crucial for identifying the specific chemical structures and their environments in the compound.
The image shows an NMR spectrum with chemical shifts at various ppm values. The spectrum is labeled with the structure of compound 2m. The chemical shifts are:

- 180.41 ppm
- 162.35 ppm
- 140.86 ppm
- 133.30 ppm
- 131.87 ppm
- 63.61 ppm
- 41.65 ppm

The spectrum is labeled with f1 (ppm) on the x-axis and is used to identify the chemical shifts of the protons in the molecule.