A Simple Base-Mediated Amidation of Aldehydes with Azides

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**General:** All reagents and solvents were purchased from commercial sources and used without further purification. All reactions were run under an Argon atmosphere unless otherwise indicated. Prior to use of solvents in reactions, they were purified by passing the degassed solvents through a column of activated alumina and transferred by an oven-dried syringe or cannula. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F$_{254}$). $^1$H NMR and $^{13}$C NMR were recorded on a Varian Inova 400 (400 MHz) or a Bruker Avance DPX-250 (250 MHz) instrument. The HRMS data were measured on an Agilent 1100 Series MSD/TOF with electrospray ionization.

The azides 1a, $^{1}$b, $^{2}$d, $^{3}$e, $^{4}$f, $^{5}$l, $^{6}$j, $^{7}$l, $^{8}$l, and an aldehyde 2n$^{9}$ were synthesized as previously reported in the literature. The $t$-BuOK (sublimed grade) was purchased from Sigma Aldrich.
1. Synthesis of azides:

1.1 1-(azidomethyl)-3-(trifluoromethyl)benzene (1c):

To a solution of 1-(bromomethyl)-3-(trifluoromethyl)benzene (1.0 g, 4.18 mmol) in DMSO (15 mL), was added sodium azide (326 mg, 5.0 mmol, 1.2 eq) and the resulting reaction mixture was stirred overnight at 70 °C. The reaction was then treated with H₂O (40 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL x 3), dried with Na₂SO₄ and concentrated under reduced pressure. The azide 1c was then obtained by flash chromatography. Yield = 76%. Rₐ = 0.31 in hexanes. ¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.55 (m, 2H), 7.51 – 7.48 (m, 2H), 4.42 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 136.74, 131.48, 131.42 (q, J = 32.5 Hz), 129.53, 125.25 (q, J = 3.7 Hz), 124.94 (q, J = 3.7 Hz), 124.12 (q, J = 272.4 Hz), 54.31 ppm.

1.2 5-(azidomethyl)-6-chlorobenzo[d][1,3]dioxole (1g):

The azide 1g was prepared following the procedure described for the synthesis of azide 1c. Yield = 73%. Rₐ = 0.62 in hexanes : EtOAc = 5:1. ¹H NMR (400 MHz, CDCl₃) δ 6.86 (s, 1H), 6.82 (s, 1H), 5.98 (s, 2H), 4.36 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 148.47, 147.14, 126.41, 126.12, 110.29, 109.85, 102.22, 52.35 ppm.
1.3 2-(azidomethyl)-1,1'-biphenyl (1h):

![Chemical structure of 1h](image)

The azide 1h was synthesized following the procedure described for the synthesis of azide 1c. Yield = 83%. R$_f$ = 0.22 in hexanes. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.47 – 7.43 (m, 2H), 7.42 – 7.37 (m, 4H), 7.36 – 7.30 (m, 3H), 4.28 (s, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 142.42, 140.45, 132.99, 130.64, 129.76, 129.39, 128.53, 127.99, 127.65, 52.80 ppm.

1.4 2-azido-1-(4-benzylpiperidin-1-yl)ethanone (1k):

![Chemical structure of 1k](image)

The azide 1k was prepared following the procedure described for the synthesis of azide 1c, starting from 1-(4-benzylpiperidin-1-yl)-2-chloroethanone.$^{10}$ Yield = 54%. R$_f$ = 0.3 in hexanes : EtOAc = 2:1. $^1$H NMR (250 MHz, CDCl$_3$) δ 7.36 – 7.09 (m, 5H), 4.58 (d, $J$ = 13.3 Hz, 1H), 3.92 (s, 2H), 3.61 (d, $J$ = 13.7 Hz, 1H), 3.05 – 2.87 (m, 1H), 2.67 – 2.47 (m, 3H), 1.90 – 1.65 (m, 3H), 1.19 (q, $J$ = 11.8 Hz, 2H) ppm. $^{13}$C NMR (63 MHz, CDCl$_3$) δ 165.20, 139.61, 128.95, 128.20, 125.98, 50.47, 45.11, 42.66, 42.31, 37.83, 32.18, 31.43 ppm. HRMS (ESI) calcd for C$_{14}$H$_{18}$N$_4$O [M+H]$^+$: 259.1553, found: 259.1557
2. Screening of various non-nucleophilic bases for amidation:

Following additional bases were screened using benzyl azide (1a) and benzaldehyde (2a) as substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Reaction Temp.</th>
<th>Yield (%)$^a$</th>
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<tbody>
<tr>
<td>1</td>
<td>DABCO</td>
<td>DMF</td>
<td>rt</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>TEA</td>
<td>DMF</td>
<td>rt</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>DMAP</td>
<td>DMF</td>
<td>rt</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2,6-lutidine</td>
<td>DMF</td>
<td>rt</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>NaH</td>
<td>DMF</td>
<td>rt</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>t-BuLi</td>
<td>THF</td>
<td>-78 °C to rt$^b$</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>LDA</td>
<td>THF</td>
<td>-78 °C to rt$^b$</td>
<td>10</td>
</tr>
</tbody>
</table>

General reaction conditions: 1a (0.5 mmol), 2a (0.6 mmol), base (0.75 mmol), solvent (2.5 mL), 15 min; $^a$ Isolated yield based on 1a; $^b$ warmed up to rt over 1 h.

3. Synthesis of amides:

**General Procedure:** To a mixture of the azide (0.5 mmol) and an aldehyde (0.6 mmol, 1.2 eq) in DMF (2.5 mL) at room temperature, t-BuOK (1.0 or 2.0 mmol, 2 or 4 eq) was carefully added and bubbling was observed immediately. After the completion of reaction, (monitored by TLC) water (10 mL) was added and the pH was adjusted to 7.0 using saturated NH₄Cl solution. The reaction mixture was extracted with EtOAc (20 mL × 2) and the combined organic layers were washed with brine (30 mL × 3), dried with Na₂SO₄ and concentrated under reduced pressure. The product was purified by flash chromatography.
3.1 *N*-benzylbenzamide (3aa):

Yield = 72%. Rf = 0.41 in hexanes : EtOAc = 2:1. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.78 (d, $J = 7.6$ Hz, 2H), 7.46 – 7.37 (m, 2H), 7.31 (t, $J = 7.6$ Hz, 2H), 7.28 – 7.20 (m, 4H), 4.52 (d, $J = 5.8$ Hz, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.68, 138.49, 134.37, 131.39, 128.59, 128.43, 127.68, 127.30, 127.16, 43.87 ppm. HRMS (ESI) calcd for C$_{14}$H$_{13}$NO [M+H]$^+$: 212.1070, found: 212.1068

3.2 *N*-benzyl-4-methoxybenzamide (3ab):

Yield = 81%. Rf = 0.31 in hexanes : EtOAc = 2:1. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.74 (d, $J = 8.7$ Hz, 2H), 7.35 – 7.18 (m, 5H), 7.07 (s, 1H), 6.84 – 6.77 (m, 2H), 4.52 (d, $J = 5.8$ Hz, 2H), 3.76 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.16, 162.19, 138.74, 128.99, 128.65, 127.79, 127.35, 126.75, 113.71, 55.41, 43.94 ppm. HRMS (ESI) calcd for C$_{15}$H$_{15}$NO$_2$ [M+H]$^+$: 242.1176, found: 242.1172

3.3 *N*-benzyl-3-methoxybenzamide (3ac):

Yield = 81%. Rf = 0.35 in hexanes : EtOAc = 2:1. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38 – 7.36 (m, 1H), 7.32 (d, $J = 0.5$ Hz, 1H), 7.32 – 7.29 (m, 3H), 7.29 – 7.28 (m, 1H), 7.28 – 7.24 (m, 2H), 7.03 – 6.97 (m, 1H), 6.61 (s, 1H), 4.59 (d, $J = 5.7$ Hz, 2H), 3.80 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.42, 159.99, 138.35, 136.02, 129.71,
128.91, 128.03, 127.74, 118.89, 117.92, 112.57, 55.59, 44.29 ppm. HRMS (ESI) calcd for C₁₅H₁₅NO₂ [M+H]⁺: 242.1176, found: 242.1175

3.4 N-benzyl-2-methoxybenzamide (3ad):

Yield = 45%. Rf = 0.39 in hexanes : EtOAc = 2:1. ¹H NMR (400 MHz, CDCl₃) δ 8.22 (dd, J = 7.8, 1.8 Hz, 2H), 7.43 – 7.37 (m, 1H), 7.36 – 7.28 (m, 4H), 7.27 – 7.21 (m, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 4.66 (d, J = 5.7 Hz, 2H), 3.83 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 165.33, 157.48, 138.77, 132.79, 132.20, 128.57, 127.42, 127.16, 121.19, 111.37, 55.87, 43.66 ppm. HRMS (ESI) calcd for C₁₅H₁₅NO₂ [M+H]⁺: 242.1176, found: 242.1177

3.5 N-benzyl-3-methylbenzamide (3ae):

Yield = 75%. Rf = 0.51 in hexanes : EtOAc = 2:1. ¹H NMR (400 MHz, CDCl₃) δ 7.67 – 7.56 (m, 3H), 7.29 – 7.16 (m, 7H), 4.51 (d, J = 5.9 Hz, 2H), 2.28 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 167.84, 138.57, 138.06, 134.31, 132.01, 128.43, 128.19, 127.86, 127.55, 127.11, 124.14, 43.71, 21.17 ppm. HRMS (ESI) calcd for C₁₅H₁₅NO [M+H]⁺: 226.1226, found: 226.1230
3.6 N-benzyl-4-(methylthio)benzamide (3af):

Yield = 83%. Rf = 0.37 in hexanes : EtOAc = 2:1. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.71 – 7.67 (m, 2H), 7.34 – 7.25 (m, 5H), 7.23 – 7.20 (m, 2H), 6.42 (s, 1H), 4.61 (d, \(J = 5.7\) Hz, 2H), 2.48 (s, 3H) ppm. \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.00, 143.65, 138.44, 130.63, 128.92, 128.05, 127.74, 127.57, 125.58, 44.25, 15.21 ppm. HRMS (ESI) calcd for C\(_{15}\)H\(_{15}\)NOS [M+H]\(^+\): 258.0947, found: 258.0951

3.7 N-benzyl-[1,1'-biphenyl]-4-carboxamide (3ag):

Yield = 74%. Rf = 0.49 in hexanes : EtOAc = 2:1. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.86 (d, \(J = 7.1\) Hz, 2H), 7.58 (t, \(J = 6.5\) Hz, 4H), 7.44 (t, \(J = 6.4\) Hz, 2H), 7.41 – 7.22 (m, 6H), 6.96 (s, 1H), 4.62 (d, \(J = 4.5\) Hz, 2H) ppm. \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.34, 144.40, 140.11, 138.48, 133.18, 129.04, 128.87, 128.47, 128.12, 127.99, 127.73, 127.31, 44.23 ppm. HRMS (ESI) calcd for C\(_{20}\)H\(_{17}\)NO [M+H]\(^+\): 288.1383, found: 288.1384

3.8 N-benzyl-1-naphthamide (3ah):

Yield = 67%. Rf = 0.49 in hexanes : EtOAc = 2:1. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.24 (d, \(J = 7.7\) Hz, 1H), 7.80 (d, \(J = 8.1\) Hz, 2H), 7.51 – 7.40 (m, 3H), 7.34 – 7.21 (m, 6H), 6.85 (s, 1H), 4.52 (d, \(J = 5.8\) Hz, 2H) ppm. \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 169.49,
138.34, 134.19, 133.62, 130.51, 130.18, 128.68, 128.26, 127.75, 127.43, 126.99, 126.33, 125.46, 125.00, 124.62, 43.85 ppm. HRMS (ESI) calcd for C_{18}H_{15}NO [M+H]^+: 262.1226, found: 262.1224

3.9 *N*-benzylbenzo[\textit{d}][\textit{1,3}]dioxole-5-carboxamide (3ai):

\begin{center}
\includegraphics[width=1in]{image}
\end{center}

Yield = 86%. R\text{f} = 0.32 in hexanes : EtOAc = 2:1. \textit{\textsuperscript{1}}H NMR (400 MHz, CDCl\textsubscript{3}) \text{\textdelta} 7.32 – 7.26 (m, 7H), 6.76 (dd, \textit{\textit{J}} = 8.0, 0.5 Hz, 1H), 6.52 (s, 1H), 5.97 (s, 2H), 4.56 (d, \textit{\textit{J}} = 5.7 Hz, 2H) ppm. \textit{\textsuperscript{13}}C NMR (101 MHz, CDCl\textsubscript{3}) \text{\textdelta} 166.84, 150.49, 148.11, 138.48, 128.89, 128.76, 128.01, 127.69, 121.76, 108.12, 107.86, 101.83, 44.28 ppm. HRMS (ESI) calcd for C\textsubscript{15}H\textsubscript{13}NO\textsubscript{3} [M+H]^+: 256.0968, found: 256.0966

3.10 *N*-benzyl-4-(dimethylamino)benzamide (3aj):

\begin{center}
\includegraphics[width=1in]{image}
\end{center}

Yield = 83%. R\text{f} = 0.26 in hexanes : EtOAc = 2:1. \textit{\textsuperscript{1}}H NMR (400 MHz, CDCl\textsubscript{3}) \text{\textdelta} 7.68 (d, \textit{\textit{J}} = 9.0 Hz, 2H), 7.35 – 7.25 (m, 5H), 6.64 (d, \textit{\textit{J}} = 9.0 Hz, 2H), 6.26 (s, 1H), 4.61 (d, \textit{\textit{J}} = 5.7 Hz, 2H), 2.99 (s, 6H) ppm. \textit{\textsuperscript{13}}C NMR (101 MHz, CDCl\textsubscript{3}) \text{\textdelta} 167.44, 152.63, 139.05, 128.81, 128.63, 128.01, 127.49, 121.25, 111.21, 44.04, 40.27 ppm. HRMS (ESI) calcd for C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O [M+H]^+: 255.1492, found: 255.1500
3.11 N-benzylfuran-2-carboxamide (3ak):

![Chemical structure](image)

Yield = 86%. Rf = 0.48 in hexanes : EtOAc = 1:1. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 (s, 1H), 7.30 – 7.18 (m, 4H), 7.06 (d, $J$ = 3.2 Hz, 2H), 6.43 – 6.37 (m, 1H), 4.53 (d, $J$ = 5.9 Hz, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 158.39, 147.89, 143.96, 138.17, 128.58, 127.73, 127.39, 114.18, 111.99, 42.99 ppm. HRMS (ESI) calcd for C$_{12}$H$_{11}$NO$_2$ [M+H]$^+$: 202.0863, found: 202.0862

3.12 N-benzyl-5-bromo-1-methyl-1H-indole-3-carboxamide (3al):

![Chemical structure](image)

Yield = 72%. Rf = 0.25 in hexanes : EtOAc = 1:1. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.19 – 8.16 (m, 1H), 7.51 (s, 1H), 7.36 – 7.25 (m, 6H), 7.16 – 7.13 (m, 1H), 6.22 (s, 1H), 4.63 (d, $J$ = 5.8 Hz, 2H), 3.71 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 164.69, 138.99, 136.00, 132.47, 128.90, 127.97, 127.60, 127.56, 125.78, 123.53, 115.27, 111.51, 110.43, 43.65, 33.59 ppm. HRMS (ESI) calcd for C$_{17}$H$_{15}$BrN$_2$O [M+H]$^+$: 343.0441, found: 343.0440

3.13 N-benzyl-4-chlorobenzamide (3am):

![Chemical structure](image)

Yield = 80%. Rf = 0.55 in hexanes : EtOAc = 2:1. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.70 (d, $J$ = 8.5 Hz, 2H), 7.38 – 7.25 (m, 7H), 6.54 (s, 1H), 4.59 (d, $J$ = 5.7 Hz, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.53, 138.17, 137.98, 132.95, 129.02, 128.63,
128.10, 127.90, 44.41 ppm. HRMS (ESI) calcd for C_{14}H_{12}ClNO [M+H]^+: 246.0680, found: 246.0678

3.14 N-benzyl-4-cyanobenzamide (3an):

\[
\begin{align*}
\text{Yield} &= 37\%. \ R_f = 0.35 \text{ in hexanes : EtOAc } = 2:1. \ \text{ } ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \ \delta \ 7.83 \\
&= (d, \ J = 8.4 \text{ Hz, 2H}), 7.62 (d, \ J = 8.4 \text{ Hz, 2H}), 7.33 - 7.25 (m, 5H), 7.00 (s, 1H), 4.56 \\
&= (d, \ J = 5.7 \text{ Hz, 2H}) \text{ ppm. } ^13C \text{ NMR} (101 \text{ MHz, CDCl}_3) \ \delta \ 165.85, 138.36, 137.75, \\
&= 132.49, 128.95, 127.93, 127.91, 118.14, 115.10, 44.37 \text{ ppm. HRMS (ESI) calcd for } \\
C_{15}H_{12}N_2O [M+H]^+: 237.1022, \text{ found: 237.1023}
\end{align*}
\]

3.15 N-benzylecinnamamide (3ao):

\[
\begin{align*}
\text{Yield} &= 19\%. \ R_f = 0.38 \text{ in hexanes : EtOAc } = 2:1. \ \text{ } ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \ \delta \ 7.63 \\
&= (d, \ J = 15.6 \text{ Hz, 1H}), 7.43 (dd, \ J = 6.4, 2.8 \text{ Hz, 2H}), 7.35 - 7.22 (m, 8H), 6.52 (s, 1H), \\
&= 6.47 (d, \ J = 15.6 \text{ Hz, 1H}), 4.50 (d, \ J = 5.8 \text{ Hz, 2H}) \text{ ppm. } ^13C \text{ NMR} (101 \text{ MHz, CDCl}_3) \\
&= \delta \ 166.14, 141.36, 138.40, 134.97, 129.79, 128.92, 128.83, 128.16, 127.95, 127.62, \\
&= 120.80, 43.93 \text{ ppm. HRMS (ESI) calcd for } C_{16}H_{15}NO [M+H]^+: 238.1226, \text{ found: 238.1223}
\end{align*}
\]

3.16 N-(2-chlorobenzyl)benzamide (3ba):

\[
\begin{align*}
\text{Yield} &= 78\%. \ R_f = 0.5 \text{ in hexanes : EtOAc } = 2:1. \ \text{ } ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \ \delta \ 7.78 \\
&= -7.74 (m, 2H), 7.49 - 7.33 (m, 5H), 7.23 - 7.18 (m, 2H), 6.75 (s, 1H), 4.69 (d, \ J =
\end{align*}
\]
6.0 Hz, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.55, 135.79, 134.42, 133.84, 131.76, 130.48, 129.73, 129.17, 128.75, 127.32, 127.17, 42.20 ppm. HRMS (ESI) calcd for C$_{14}$H$_{12}$ClNO [M+H]$^+$: 246.0680, found: 246.0677

3.17 $N$-(3-(trifluoromethyl)benzyl)benzamide (3ca):

$$\text{F}_3\text{C}-\text{C}_6\text{H}_4-\text{N}=\text{C}(\text{H})-\text{O}$$

Yield = 52%. R$_f$ = 0.37 in hexanes : EtOAc = 2:1. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.80 – 7.75 (m, 2H), 7.57 – 7.46 (m, 4H), 7.45 – 7.37 (m, 3H), 6.75 (s, 1H), 4.65 (d, $J$ = 5.9 Hz, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.79, 139.56, 134.21, 131.96, 131.37 (q, $J$ = 1.3 Hz), 131.22 (q, $J$ = 32.2 Hz), 129.42, 128.85, 127.19, 124.70 – 124.50 (m, two quartets being merged, $J$ = 3.8 Hz), 124.20 (q, $J$ = 272.4 Hz), 43.73 ppm. HRMS (ESI) calcd for C$_{15}$H$_{12}$F$_3$NO [M+H]$^+$: 280.0944, found: 280.0949

3.18 $N$-((6-chloropyridin-3-yl)methyl)benzamide (3da):

$$\text{C}_6\text{H}_4\text{N}^{+} - \text{Cl}^-$$

Yield = 65%. R$_f$ = 0.33 in hexanes : EtOAc = 1:1. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.24 (s, 1H), 7.77 – 7.72 (m, 2H), 7.61 (dd, $J$ = 8.2, 2.4 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.40 – 7.34 (m, 2H), 7.21 (d, $J$ = 8.2 Hz, 1H), 7.08 (s, 1H), 4.53 (d, $J$ = 6.0 Hz, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.96, 150.68, 149.07, 138.83, 133.88, 133.37, 132.06, 128.82, 127.19, 124.48, 40.85 ppm. HRMS (ESI) calcd for C$_{13}$H$_{11}$ClN$_2$O [M+H]$^+$: 247.0633, found: 247.0635
3.19 \( N \)-(3-methylbenzyl)benzamide (3ea):

\[
\begin{align*}
\text{Yield} &= 58\%. \quad R_f = 0.45 \text{ in hexanes : EtOAc = 2:1. } ^1H \text{ NMR (400 MHz, CDCl}_3) \delta 7.80 - 7.76 (m, 2H), 7.50 - 7.44 (m, 1H), 7.42 - 7.36 (m, 2H), 7.24 - 7.19 (m, 1H), 7.15 - 7.06 (m, 3H), 6.58 (s, 1H), 4.57 (d, } J = 5.7 \text{ Hz, 2H), 2.32 (s, 3H) ppm. } ^{13}C \text{ NMR (101 MHz, CDCl}_3) \delta 167.49, 138.63, 138.30, 134.59, 131.65, 128.83, 128.83, 128.71, 128.49, 127.16, 125.10, 44.27, 21.55 \text{ ppm. HRMS (ESI) calcd for C}_{15}H_{15}NO [M+H]^+: 226.1226, found: 226.1231}
\end{align*}
\]

3.20 \( N \)-(3-methoxybenzyl)benzamide (3fa):

\[
\begin{align*}
\text{Yield} &= 75\%. \quad R_f = 0.32 \text{ in hexanes : EtOAc = 2:1. } ^1H \text{ NMR (400 MHz, CDCl}_3) \delta 7.80 - 7.75 (m, 2H), 7.51 - 7.44 (m, 1H), 7.42 - 7.36 (m, 2H), 7.27 - 7.22 (m, 1H), 6.93 - 6.86 (m, 2H), 6.81 (dd, } J = 8.2, 2.5 \text{ Hz, 1H), 6.60 (s, 1H), 4.58 (d, } J = 5.7 \text{ Hz, 2H), 3.77 (s, 3H) ppm. } ^{13}C \text{ NMR (101 MHz, CDCl}_3) \delta 167.56, 160.09, 139.98, 134.53, 131.70, 129.97, 128.74, 127.15, 120.26, 113.65, 113.17, 55.41, 44.23 \text{ ppm. HRMS (ESI) calcd for C}_{15}H_{15}NO_2 [M+H]^+: 242.1176, found: 242.1179}
\end{align*}
\]

3.21 \( N\)-((6-chlorobenzo[d][1,3]dioxol-5-yl)methyl)benzamide (3ga):

\[
\begin{align*}
\text{Yield} &= 77\%. \quad R_f = 0.4 \text{ in hexanes : EtOAc = 2:1. } ^1H \text{ NMR (400 MHz, CDCl}_3) \delta 7.77 - 7.73 (m, 2H), 7.49 - 7.43 (m, 1H), 7.41 - 7.35 (m, 2H), 6.91 (s, 1H), 6.80 (s, 1H), 6.70 (s, 1H), 5.92 (s, 2H), 4.57 (d, } J = 6.0 \text{ Hz, 2H) ppm. } ^{13}C \text{ NMR (101 MHz, CDCl}_3)
\end{align*}
\]
δ 167.56, 147.91, 147.04, 134.39, 131.77, 129.03, 128.75, 127.16, 125.61, 110.30, 110.03, 102.03, 42.08 ppm. HRMS (ESI) calcd for C_{13}H_{12}ClNO_3 [M+H]^+: 290.0578, found: 290.0583

3.22 N-(1,1'-biphenyl)-2-ylmethyl)benzamide (3ha):

\[
\text{Yield = 78\%. } \text{Rf} = 0.53 \text{ in hexanes : EtOAc = 2:1. } ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta \text{ 7.63 - 7.60 (m, 2H), 7.49 - 7.40 (m, 4H), 7.38 - 7.32 (m, 7H), 7.29 - 7.26 (m, 1H), 6.26 (s, 1H), 4.61 (d, } J = 5.6 \text{ Hz, 2H) ppm. } ^{13}\text{C NMR (101 MHz, CDCl}_3\text{)} \delta \text{ 167.20, 141.89, 140.95, 135.61, 134.51, 131.57, 130.44, 129.15, 129.03, 128.67, 128.65, 128.03, 127.73, 127.58, 127.02, 42.27 ppm. HRMS (ESI) calcd for C}_{20}\text{H}_{17}\text{NO [M+H]^+: 288.1383, found: 288.1383}
\]

3.23 N-(naphthalen-1-ylmethyl)benzamide (3ia):

\[
\text{Yield = 60\%. } \text{Rf} = 0.47 \text{ in hexanes : EtOAc = 2:1. } ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta \text{ 8.07 - 8.04 (m, 1H), 7.89 - 7.85 (m, 1H), 7.81 (d, } J = 8.1 \text{ Hz, 1H), 7.75 - 7.71 (m, 2H), 7.55 - 7.45 (m, 3H), 7.45 - 7.39 (m, 2H), 7.38 - 7.32 (m, 2H), 6.48 (s, 1H), 5.05 (d, } J = 5.3 \text{ Hz, 2H) ppm. } ^{13}\text{C NMR (101 MHz, CDCl}_3\text{)} \delta \text{ 167.36, 134.46, 134.09, 133.58, 131.68, 131.66, 128.98, 128.91, 128.71, 127.15, 127.04, 126.91, 126.22, 125.59, 123.68, 42.54 ppm. HRMS (ESI) calcd for C}_{18}\text{H}_{15}\text{NO [M+H]^+: 262.1226, found: 262.1225}
\]
3.24 \(N\)-(2-oxo-2-(4-phenylpiperazin-1-yl)ethyl)benzamide (3ja):

Yield = 56\%. R\(_f\) = 0.17 in hexanes : EtOAc = 1:1. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.86 – 7.81 (m, 2H), 7.52 – 7.46 (m, 1H), 7.45 – 7.39 (m, 2H), 7.35 (s, 1H), 7.30 – 7.25 (m, 2H), 6.93 – 6.88 (m, 3H), 4.28 (d, \(J\) = 4.0 Hz, 2H), 3.83 – 3.79 (m, 2H), 3.62 – 3.58 (m, 2H), 3.21 – 3.15 (m, 4H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.38, 166.74, 150.89, 134.05, 131.85, 129.47, 128.74, 127.26, 121.02, 116.99, 49.77, 49.53, 44.58, 42.22, 41.90 ppm. HRMS (ESI) calcd for C\(_{19}\)H\(_{21}\)N\(_3\)O\(_2\) [M+H]+: 324.1707, found: 324.1716

3.25 tert-butyl 4-(2-benzamidoacetyl)piperazine-1-carboxylate (3ka):

Yield = 45\%. R\(_f\) = 0.12 in hexanes : EtOAc = 1:1. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.83 – 7.76 (m, 2H), 7.46 (ddd, \(J\) = 6.4, 3.7, 1.3 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.31 (s, 1H), 4.22 (d, \(J\) = 4.0 Hz, 2H), 3.63 – 3.56 (m, 2H), 3.48 – 3.37 (m, 6H), 1.43 (s, 9H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.39, 166.95, 154.55, 133.94, 131.85, 128.71, 127.23, 80.70, 44.45, 42.05, 41.89, 28.50 ppm. HRMS (ESI) calcd for C\(_{18}\)H\(_{25}\)N\(_3\)O\(_4\) [M+Na]+: 370.1737, found: 370.1738
3.26 \( N-(2-(4\text{-benzylpiperidin-1-yl})-2\text{-oxoethyl})\text{benzamide (3la):} \)

Yield = 76\%. R\(_f\) = 0.14 in hexanes : EtOAc = 2:1. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.86 – 7.81 (m, 2H), 7.51 – 7.46 (m, 1H), 7.45 – 7.37 (m, 3H), 7.31 – 7.24 (m, 2H), 7.23 – 7.17 (m, 1H), 7.14 – 7.10 (m, 2H), 4.62 – 4.52 (m, 1H), 4.29 – 4.12 (m, 2H), 3.80 – 3.70 (m, 1H), 2.96 (tt, \(J = 15.6, 8.0\) Hz, 1H), 2.65 – 2.52 (m, 3H), 1.84 – 1.67 (m, 3H), 1.26 – 1.11 (m, 2H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.30, 166.26, 139.79, 134.13, 131.73, 129.20, 128.67, 128.51, 127.22, 126.31, 44.85, 42.97, 42.69, 41.85, 38.24, 32.36, 31.73 ppm. HRMS (ESI) calcd for C\(_{21}H_{24}N_2O_2\) [M+H]\(^+\): 337.1911, found: 337.1904

4. Experiment involving benzaldehyde-\(\alpha\)-d\(_1\): 

All the spectral data (\(^1\)H, \(^{13}\)C, and \(^2\)H NMR) is included (see pages 78 – 80). From the \(^1\)H NMR spectroscopy, 50\% deuterium incorporation was observed (see page 78). HRMS (ESI) calcd for C\(_{14}H_{12}DNO\) [M+H]\(^+\): 213.1133, found: 213.1132

(Note: \(^1\)H NMR spectrum was recorded on a Agilent Technologies Direct Drive 500 MHz instrument with a cryogenic triple resonance (TR) 5mm indirect detection probe, while \(^{13}\)C and \(^2\)H NMR spectra were recorded on a Varian Inova 400 MHz instrument.)
References:


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F₃C₄H₂N₃
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D
O

\[
\begin{align*}
\text{f1 (ppm)} & = 7.32, 7.31, 7.42, 7.43, 7.45, 7.46, 7.53, 7.80, 7.81, 7.82
\end{align*}
\]