Electronic Supporting Information

Copper-catalyzed oxidative cleavage of Passerini and Ugi adducts in basic medium yielding α-ketoamides

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Table of Contents

1. Optimization studies for oxidative cleavage of Ugi adducts
2. Labeling experiments
3. Kinetic Isotope Effect (KIE) measurement by independent reactions
4. References
5. Copies of $^1$H and $^{13}$C NMR spectra
1. Optimization studies for oxidative cleavage of Ugi adducts

Table S1. Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Additive (mol %)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>2a: yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>4a: yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>----</td>
<td>THF</td>
<td>12</td>
<td>5</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>CuI (5)</td>
<td>THF</td>
<td>2</td>
<td>11</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>CuI (10)</td>
<td>THF</td>
<td>2</td>
<td>50</td>
<td>35</td>
<td>60</td>
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<tr>
<td>4</td>
<td>NaH</td>
<td>CuI (20)</td>
<td>THF</td>
<td>2</td>
<td>15</td>
<td>5</td>
<td>20</td>
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<tr>
<td>5</td>
<td>NaH</td>
<td>CuI (20)</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>2</td>
<td>20</td>
<td>15</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>NaH</td>
<td>CuI (20)</td>
<td>DMF</td>
<td>4</td>
<td>90</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>KO‘Bu</td>
<td>----</td>
<td>THF</td>
<td>12</td>
<td>75</td>
<td>41</td>
<td>52</td>
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<tr>
<td>8</td>
<td>KO‘Bu</td>
<td>CuI (5)</td>
<td>THF</td>
<td>2</td>
<td>11</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>KO‘Bu</td>
<td>CuI (10)</td>
<td>THF</td>
<td>2</td>
<td>81</td>
<td>50</td>
<td>67</td>
</tr>
<tr>
<td>10</td>
<td>KO‘Bu</td>
<td>CuI (20)</td>
<td>THF</td>
<td>2</td>
<td>83</td>
<td>65</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>KO‘Bu</td>
<td>CuI (20)</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>0.5</td>
<td>100</td>
<td>81</td>
<td>53</td>
</tr>
<tr>
<td>12</td>
<td>KO‘Bu</td>
<td>CuI (20)</td>
<td>DMSO</td>
<td>4</td>
<td>30</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>KO‘Bu</td>
<td>CuI (20)</td>
<td>DMF</td>
<td>4</td>
<td>93</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>KO‘Bu</td>
<td>CuI (20)</td>
<td>THF</td>
<td>0.5</td>
<td>5</td>
<td>trace</td>
<td>trace</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction Conditions: 1a (0.1 mmol), base (0.3 mmol), CuI in solvent (2.0 mL) at rt under oxygen balloon.

<sup>b</sup>Under argon. *Isolated yields.
2. Labeling Experiments

a) Preparation of 4-Methoxybenzaldehyde-\(\alpha\)-D

\[
\text{RuHCl(CO)(PPh}_3\text{)}_3 (5 \text{ mol\%}) \quad \text{D}_2\text{O (5 equiv)} \\
\text{PhMe, 100°C, 30 min} \\
\text{4-Methoxybenzaldehyde-\(\alpha\)-D} \\
(79\% \text{ yield, 55\% D})
\]

4-Methoxybenzaldehyde-\(\alpha\)-D was synthesized according to reported procedure.\(^1\) 4-Methoxybenzaldehyde (100.0 mg, 0.734 mmol) and RuHCl(CO)(PPh\(_3\))\(_3\) (34.9 mg, 0.036 mmol, 5 mol \%) were dissolved in toluene (3.0 ml) in an oven-dried screw-cap vial. D\(_2\)O (0.07 ml, 3.670 mmol) was then added and the vial was sparged with argon and capped. The resulting solution was heated to 100 °C and stirred for 30 minutes. On completion of the reaction, the solvent was removed \textit{in vacuo} and crude was purified by column chromatography to afford \textit{4-Methoxybenzaldehyde-\(\alpha\)-D} as colourless oil (80.0 mg, 79\% yield, 55\% D); \(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.89 – 7.80 (m, 2H), 7.04 – 6.98 (m, 2H), 3.89 (s, 3H); residual formyl proton: \(\delta\) 9.89.

b) Preparation of the deuterated Passerini adduct D-1d

\[
\text{H}_2\text{O, rt, 12 h} \\
\text{D-1d} \\
(27\% \text{ yield, 65\% D})
\]

Equimolar mixture of 4-Methoxybenzaldehyde-\(\alpha\)-D (200.0 mg, 1.45 mmol), benzoic acid (194.5 mg, 1.59 mmol) and tert-butyl isocyanide (0.16 ml, 1.45 mmol) in water was stirred at room temperature for 12 h. After completion of the reaction (based on TLC), reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. Aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate followed by evaporation of solvent \textit{in vacuo}. The crude was
purified by silica gel column chromatography to afford the deuterium-labeled Passerini adduct D-1d as a white sticky solid (134.0 mg, 27% yield, 65% D); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.07 (dt, $J$ = 8.5, 1.6 Hz, 2H), 7.63 – 7.56 (m, 1H), 7.50 – 7.41 (m, 4H), 6.95 – 6.87 (m, 2H), 5.96 (s, 1H), 3.80 (s, 3H), 1.37 (s, 9H); Residual formyl proton: $\delta$ 6.17.

c) Preparation of $^{18}$O-labeled benzaldehyde

$^{18}$O-labeled benzaldehyde was synthesized according to reported procedure.$^2$ Sodium (0.05 g, 2.17 mmol) was added to $^{18}$O-labeled water (98% H$_2^{18}$O, 0.75 mL) in a flask followed by the addition of benzyl chloride (0.5 mL, 4.34 mmol). The mixture was heated to 95 °C and then heated at reflux for 48 h with continuous stirring. The product was purified by column chromatography to yield the $^{18}$O-labeled benzyl alcohol (0.2 g, 1.8 mmol, 83% yield). To a solution of the $^{18}$O-labeled benzyl alcohol (0.2 g, 1.8 mmol) in anhydrous dichloromethane (20.0 mL) under nitrogen, Dess-Martin periodinane (0.99 g, 2.34 mmol) was added at 0 °C, and the resulting mixture was stirred at room temperature for 30 minutes. On completion of the reaction (progress monitored by TLC analysis), the reaction was quenched by the slow addition of NaHCO$_3$/Na$_2$S$_2$O$_3$ solution, and the mixture was vigorously stirred for 30 minutes. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with brine and dried with anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure to afford the $^{18}$O-labeled benzaldehyde in quantitative yield.
d) **Preparation of $^{18}$O-labeled benzoic acid**

$^{18}$O-labeled benzoic acid was synthesized according to reported procedure.\(^3\) \(\alpha,\alpha,\alpha\)-trichlorotoluene (2.5 g, 12.5 mmol) and \(\text{H}_2^{18}\text{O}\) (1.0 g, 50.0 mmol) were heated at 120 °C in a sealed tube for 24 h. The reaction mixture was concentrated *in vacuo* to remove excess water and HCl, then a solution of NaOH (0.15 M, 75 mL) was added to the crude mixture. The aqueous phase was washed with ethyl acetate, acidified with an aqueous HCl (1 N) solution and extracted with dichloromethane. The combined organic layers were dried upon anhydrous Na\(_2\)SO\(_4\), filtered, concentrated *in vacuo* to afford $^{18}$O-enriched benzoic acid (1.5 g, yield: 99%) as white solid.

e) **Procedure for the synthesis of $^{18}$O-labeled Passerini adduct $^{18}$O-1b.**

Equimolar mixture of $^{18}$O-labeled benzaldehyde (200.00 mg, 1.85 mmol), $^{18}$O-labeled benzoic acid (233.29 mg, 1.85 mmol) and tert-butyl isocyanide (0.21 mL, 1.85 mmol) in anhydrous dichloromethane was stirred at room temperature for 12 h under nitrogen. After completion of the reaction (based on TLC), reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution. Aqueous layer was extracted with dichloromethane and the combined organic layers were dried over anhydrous sodium sulfate followed by evaporation of solvent *in vacuo*. The crude was purified by silica
gel column chromatography to afford the $^{18}$O-labeled Passerini adduct $^{18}$O-1b (240.00 mg, 40.8%). Isotopic distribution amounted to 70.92% $^{18}$O/$^{18}$O/$^{18}$O and 29.08% $^{18}$O/$^{18}$O/$^{16}$O respectively (Figure S1).

2-(tert-butylamino)-2-(oxo-$^{18}$O)-1-phenylethyl benzoate-$^{18}$O$_2$ ($^{18}$O-1b): White solid (240.0 mg, 41%); m.p: 140 °C; R$_f$: 0.32 (30% EtOAc in hexane); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.12 – 8.06 (m, 2H), 7.64 – 7.57 (m, 1H), 7.55 – 7.44 (m, 4H), 7.43 – 7.34 (m, 3H), 6.22 (s, 1H), 5.99 (s, 1H), 1.37 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 167.3, 164.8, 135.9, 133.5, 129.7, 129.4, 128.9, 128.7, 128.6, 127.4, 76.0, 51.6, 28.7; HRMS (ESI): calcd. for C$_{19}$H$_{22}$N$_1$$^{18}$O$_3$ [M+H]$^+$: 318.1727, found: 318.1717.

Figure S1: HRMS Spectrum of $^{18}$O-1b
f) Procedure for the oxidative cleavage of $^{18}$O-1b.

To the solution of $^{18}$O-1b (193.0 mg, 0.608 mmol) in dry THF was added KO'Bu (204.7 mg, 1.82 mmol) and CuI (23.1 mg, 20 mol %) at room temperature and the reaction vessel was flushed with O$_2$. The resulting reaction mixture was stirred at room temperature. After completion of the reaction (based on TLC) in 10 minutes, the reaction mixture was quenched with water and the crude product was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo and the crude was purified by silica gel column chromatography to afford $\alpha$-ketoamide $^{18}$O-2b (34.0 mg, 27%). The aqueous layer was acidified with HCl solution up to pH 2-3, followed by extraction with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo to afford the $^{18}$O-labeled benzoic acid $^{18}$O-2b' (29.0 mg, 38%). HRMS analysis revealed that the $\alpha$-ketoamide $^{18}$O-2b (having only C-1 oxygen labeled) has m/z = 208.1217, while the $^{18}$O-labeled benzoic acid has m/z = 127.9792. This indicates that the oxygen at C-2 position of the $\alpha$-ketoamide $^{18}$O-2b is coming from molecular oxygen. On the contrary, this experiment also confirmed the incorporation of only one $^{16}$O oxygen atom in the $\alpha$-ketoamide $^{18}$O-2b. For $\alpha$-ketoamide $^{18}$O-2b, isotopic distribution amounted to 90.9% $^{16}$O/$^{18}$O and 9.09% $^{16}$O/$^{16}$O (Figure S2). For the acid $^{18}$O-2b', isotopic distribution amounted to 51.02% $^{18}$O/$^{18}$O, 23.98% $^{18}$O/$^{16}$O and 25% $^{16}$O/$^{16}$O (Figure S3).
Figure S2: HRMS Spectrum of $^{18}\text{O}-2b$

calc. [M+H]$^+$: 208.1223  
Found: 208.1217

Figure S3: HRMS Spectrum of $^{18}\text{O}-2b'$

calc. [M+H]$^+$: 123.0446  
Found: 123.0797

calc. [M+H]$^+$: 125.0489  
Found: 125.9875

S8
3. Kinetic Isotope Effect (KIE) measurement by independent reactions

![Chemical Structures](image)

The aerobic oxidative cleavage of substrate 1d and D-1d (65% D-enriched) were carried out in parallel under the standard reaction conditions to study the kinetic isotopic effect (KIE). To the solutions of 1d (100.0 mg, 0.29 mmol) and D-1d (100.0 mg, 0.29 mmol) in dry THF, KO’Bu (98.6 mg, 0.87 mmol) and CuI (11.1 mg, 0.058 mmol) were added at room temperature and the reaction vessel was flushed with O2. The resulting reaction mixtures were stirred at room temperature. KIE value was determined by comparison of rates of formation of α-ketoamide by LCMS analysis. Aliquots (25 μL) were periodically removed to provide the following conversions as determined by LCMS analysis. K_H/K_D was calculated to be 3.14.

**Table S2. % Formation vs time table.**

<table>
<thead>
<tr>
<th>t (min)</th>
<th>1d (%)</th>
<th>3</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.67</td>
<td>14.09</td>
<td>15.79</td>
<td>18.93</td>
</tr>
<tr>
<td>D-1d# (%)</td>
<td>3.71</td>
<td>4.52</td>
<td>5.08</td>
<td>5.58</td>
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</tbody>
</table>

#The product formation was calibrated by multiplying with 0.65 taking into the account that only 65% substrate was D-labeled.
4. References:


5. Copies of $^1$H and $^{13}$C NMR Spectra

**Figure S5: $^1$H NMR of compound 1a**

![1H NMR spectrum of compound 1a](image)

(CDC$_3$, 300 MHz)

**Figure S6: $^{13}$C NMR of compound 1a**

![13C NMR spectrum of compound 1a](image)

(CDC$_3$, 75 MHz)
Figure S7: $^1$H NMR of compound 1b

Figure S8: $^{13}$C NMR of compound 1b
Figure S9: $^{1}$H NMR of compound 1c

![Figure S9: $^{1}$H NMR of compound 1c](image)

Figure S10: $^{13}$C NMR of compound 1c

![Figure S10: $^{13}$C NMR of compound 1c](image)
Figure S11: $^1$H NMR of compound 1d

(CDC$_3$, 400 MHz)

Figure S12: $^{13}$C NMR of compound 1d

(CDC$_3$, 125 MHz)
Figure S13: $^1$H NMR of compound 1e

Figure S14: $^{13}$C NMR of compound 1e
Figure S15: $^1$H NMR of compound 1f

![Figure S15: $^1$H NMR of compound 1f](image)

Figure S16: $^{13}$C NMR of compound 1f

![Figure S16: $^{13}$C NMR of compound 1f](image)
Figure S17: $^1$H NMR of compound 1g

Figure S18: $^{13}$C NMR of compound 1g
Figure S19: $^1$H NMR of compound 1h

Figure S20: $^{13}$C NMR of compound 1h
Figure S21: $^1$H NMR of compound 1i

Figure S22: $^{13}$C NMR of compound 1i
Figure S23: $^1$H NMR of compound 1j

Figure S24: $^{13}$C NMR of compound 1j
**Figure S25:** $^1$H NMR of compound 1k

![1H NMR spectrum of compound 1k](image1)

(CDC$_3$, 300 MHz)

**Figure S26:** $^{13}$C NMR of compound 1k

![$^{13}$C NMR spectrum of compound 1k](image2)

(CDC$_3$, 75 MHz)
Figure S27: $^1$H NMR of compound 11

Figure S28: $^{13}$C NMR of compound 11
Figure S29: $^1$H NMR of compound 1m

(CDCl$_3$, 300 MHz)

Figure S30: $^{13}$C NMR of compound 1m

(CDCl$_3$, 75 MHz)
Figure S31: $^1$H NMR of compound 1n

Figure S32: $^{13}$C NMR of compound 1n
Figure S33: $^1$H NMR of compound 2a

![H NMR Spectrum](image)

(CDC$_3$, 400 MHz)

Figure S34: $^{13}$C NMR of compound 2a

![C NMR Spectrum](image)

(CDC$_3$, 100 MHz)
Figure S35: $^1$H NMR of compound 2b

![NMR谱图](image)

Figure S36: $^{13}$C NMR of compound 2b

![NMR谱图](image)
Figure S37: $^1$H NMR of compound 2c

Figure S38: $^{13}$C NMR of compound 2c
Figure S39: $^1$H NMR of compound 2d

![NMR spectrum of compound 2d (CDCl$_3$, 400 MHz)](image)

Figure S40: $^{13}$C NMR of compound 2d

![NMR spectrum of compound 2d (CDCl$_3$, 100 MHz)](image)
Figure S41: $^1$H NMR of compound 2e

![H NMR spectrum of compound 2e]

Figure S42: $^{13}$C NMR of compound 2e

![C NMR spectrum of compound 2e]
**Figure S43:** $^1$H NMR of compound 2f

![Figure S43](image)

**Figure S44:** $^{13}$C NMR of compound 2f

![Figure S44](image)
Figure S45: $^1$H NMR of compound 2g

![$^1$H NMR of compound 2g](image)

Figure S46: $^{13}$C NMR of compound 2g

![$^{13}$C NMR of compound 2g](image)
Figure S47: $^1$H NMR of compound 2h

![H NMR spectrum](image1)

Figure S48: $^{13}$C NMR of compound 2h

![C NMR spectrum](image2)
**Figure S49:** $^1$H NMR of compound 2i

![H NMR spectrum](image1)

**Figure S50:** $^{13}$C NMR of compound 2i

![C NMR spectrum](image2)
Figure S51: $^1$H NMR of compound 2j

Figure S52: $^{13}$C NMR of compound 2j
Figure S53: $^1$H NMR of compound 2k

![NMR spectrum of compound 2k](image)

Figure S54: $^{13}$C NMR of compound 2k

![NMR spectrum of compound 2k](image)
Figure S55: $^1$H NMR of compound 2k'

(CDC$_3$, 300 MHz)

Figure S56: $^{13}$C NMR of compound 2k'

(CDC$_3$, 75 MHz)
Figure S57: $^1$H NMR of compound 2i'

![H NMR spectrum of 2i'](image)

(CDCl$_3$, 300 MHz)

Figure S58: $^{13}$C NMR of compound 2i'

![C NMR spectrum of 2i'](image)

(CDCl$_3$, 75 MHz)
Figure S59: $^1$H NMR of compound 2m'

Figure S60: $^{13}$C NMR of compound 2m'
Figure S61: $^1$H NMR of compound 2n

![1H NMR spectrum of compound 2n](image)

(CDC$_2$H, 400 MHz)

Figure S62: $^{13}$C NMR of compound 2n

![$^{13}$C NMR spectrum of compound 2n](image)

(CDCl$_3$, 75 MHz)
Figure S63: $^1$H NMR of compound 2o

(CDC$_3$, 400 MHz)

Figure S64: $^{13}$C NMR of compound 2o

(CDC$_3$, 100 MHz)
Figure S65: $^1$H NMR of compound 2p

![$^1$H NMR spectrum of 2p](image)

(CDC$_3$, 300 MHz)

Figure S66: $^{13}$C NMR of compound 2p

![$^{13}$C NMR spectrum of 2p](image)

(CDC$_3$, 75 MHz)
Figure S67: $^1$H NMR of compound 2q

Figure S68: $^{13}$C NMR of compound 2q
**Figure S69:** $^1$H NMR of compound 2r

![H NMR spectrum of 2r](image)

(CDCl$_3$, 300 MHz)

**Figure S70:** $^{13}$C NMR of compound 2r

![C NMR spectrum of 2r](image)

(CDCl$_3$, 75 MHz)
**Figure S71:** $^1$H NMR of compound 2s

![$^1$H NMR of compound 2s](image)

**Figure S72:** $^{13}$C NMR of compound 2s

![$^{13}$C NMR of compound 2s](image)
Figure S73: $^1$H NMR of compound 2t

![1H NMR spectrum of compound 2t]

Figure S74: $^{13}$C NMR of compound 2t

![$^{13}$C NMR spectrum of compound 2t]
Figure S75: $^1$H NMR of compound 2u

(CDCl$_3$, 400 MHz)

Figure S76: $^{13}$C NMR of compound 2u

(CDCl$_3$, 125 MHz)
Figure S77: $^1$H NMR of compound 2v

Figure S78: $^{13}$C NMR of compound 2v
Figure S79: $^1$H NMR of compound 2w

Figure S80: $^{13}$C NMR of compound 2w
Figure S81: $^1$H NMR of compound 2x

![1H NMR spectrum of 2x](image_url)

Figure S82: $^{13}$C NMR of compound 2x

![13C NMR spectrum of 2x](image_url)
Figure S83: $^1$H NMR of compound 2y

![1H NMR spectrum of 2y](image)

(CDC$_3$, 300 MHz)

Figure S84: $^{13}$C NMR of compound 2y

![13C NMR spectrum of 2y](image)

(CDC$_3$, 75 MHz)
Figure S85: $^1$H NMR of compound 2z

Figure S86: $^{13}$C NMR of compound 2z
Figure S87: $^1$H NMR of compound 2aa

![NMR spectrum of 2aa](image1)

Figure S88: $^{13}$C NMR of compound 2aa

![NMR spectrum of 2aa](image2)
**Figure S89:** $^1$H NMR of compound 2ab

![H NMR spectrum of compound 2ab](image)

(CDC$_2$, 500 MHz)

**Figure S90:** $^{13}$C NMR of compound 2ab

![C NMR spectrum of compound 2ab](image)

(CDC$_2$, 125 MHz)
Figure S91: $^1$H NMR of compound 2ac

![Figure S91: $^1$H NMR of compound 2ac](image)

Figure S92: $^{13}$C NMR of compound 2ac

![Figure S92: $^{13}$C NMR of compound 2ac](image)
**Figure S93**: $^1$H NMR of compound 2ad

![1H NMR of compound 2ad](image)

(DMSO, 300 MHz)

**Figure S94**: $^{13}$C NMR of compound 2ad

![13C NMR of compound 2ad](image)

(DMSO, 75 MHz)
Figure S95: $^1$H NMR of compound 2ae

![H NMR spectrum](image)

(CDC$_3$, 300 MHz)

Figure S96: $^{13}$C NMR of compound 2ae

![C NMR spectrum](image)

(CDC$_3$, 75 MHz)
Figure S97: $^1$H NMR of compound 3a

![$^1$H NMR spectrum of 3a](image)

(CDC$_3$, 300 MHz)

Figure S98: $^{13}$C NMR of compound 3a

![$^{13}$C NMR spectrum of 3a](image)

(CDC$_3$, 75 MHz)
Figure S99: $^1$H NMR of compound 3b

Figure S100: $^{13}$C NMR of compound 3b
Figure S101: $^1$H NMR of compound 3c

![Figure S101](image)

Figure S102: $^{13}$C NMR of compound 3c

![Figure S102](image)
Figure S103: $^1$H NMR of compound 3d

![Figure S103: $^1$H NMR of compound 3d](image)

Figure S104: $^{13}$C NMR of compound 3d

![Figure S104: $^{13}$C NMR of compound 3d](image)
Figure S105: $^1$H NMR of compound 3e

![H NMR spectrum of 3e](image1)

(CDC$_3$, 400 MHz)

Figure S106: $^{13}$C NMR of compound 3e

![C NMR spectrum of 3e](image2)

(CDC$_3$, 75 MHz)
Figure S107: $^1$H NMR of compound 3f

Figure S108: $^{13}$C NMR of compound 3f
Figure S109: $^1$H NMR of compound 3g

![NMR Spectrum of Compound 3g (H NMR)](image)

Figure S110: $^{13}$C NMR of compound 3g

![NMR Spectrum of Compound 3g (C NMR)](image)
Figure S111: $^1$H NMR of compound 3h

![Figure S111: $^1$H NMR of compound 3h](image)

(CDC$_3$, 400 MHz)

Figure S112: $^{13}$C NMR of compound 3h

![Figure S112: $^{13}$C NMR of compound 3h](image)

(CDC$_3$, 100 MHz)
Figure S113: $^1$H NMR of compound 3i

![1H NMR spectrum of compound 3i](image)

(CDC$_3$, 400 MHz)

Figure S114: $^{13}$C NMR of compound 3i

![$^{13}$C NMR spectrum of compound 3i](image)

(CDC$_3$, 125 MHz)
Figure S115: $^1$H NMR of compound 3j

Figure S116: $^{13}$C NMR of compound 3j
Figure S117: $^1$H NMR of compound 3k

![H NMR spectrum of compound 3k](image)

(CDCl$_3$, 500 MHz)

Figure S118: $^{13}$C NMR of compound 3k

![C NMR spectrum of compound 3k](image)

(CDCl$_3$, 125 MHz)
**Figure S119:** $^1$H NMR of compound 3l

(CDCl$_3$, 400 MHz)

**Figure S120:** $^{13}$C NMR of compound 3l

(CDCl$_3$, 75 MHz)
Figure S121: $^1$H NMR of compound 3m

Figure S122: $^{13}$C NMR of compound 3m
**Figure S123:** $^1$H NMR of compound 3n

![$^1$H NMR of compound 3n](image)

**Figure S124:** $^{13}$C NMR of compound 3n

![$^{13}$C NMR of compound 3n](image)
Figure S125: $^1$H NMR of compound 3o

Figure S126: $^{13}$C NMR of compound 3o
Figure S127: $^1$H NMR of compound 3p

![$^1$H NMR of compound 3p](image)

Figure S128: $^{13}$C NMR of compound 3p

![$^{13}$C NMR of compound 3p](image)
Figure S129: $^1$H NMR of compound 3q

![H NMR of compound 3q](image1)

(CDC$_3$, 300 MHz)

Figure S130: $^{13}$C NMR of compound 3q

![C NMR of compound 3q](image2)

(CDC$_3$, 100 MHz)
Figure S131: $^1$H NMR of compound 3r

![Figure S131: $^1$H NMR of compound 3r](image)

Figure S132: $^{13}$C NMR of compound 3r

![Figure S132: $^{13}$C NMR of compound 3r](image)
**Figure S133**: $^1$H NMR of compound 3s

![NMR spectrum of compound 3s (1H)](image)

**Figure S134**: $^{13}$C NMR of compound 3s

![NMR spectrum of compound 3s (13C)](image)
Figure S135: $^1$H NMR of compound 3t

Figure S136: $^{13}$C NMR of compound 3t
Figure S137: $^1$H NMR of compound 3u

![NMR spectrum of compound 3u in CDCl₃ at 400 MHz](image)

Figure S138: $^{13}$C NMR of compound 3u

![NMR spectrum of compound 3u in CDCl₃ at 100 MHz](image)
Figure S139: $^1$H NMR of compound 4a

![Figure S139: $^1$H NMR of compound 4a](image)

Figure S140: $^{13}$C NMR of compound 4a

![Figure S140: $^{13}$C NMR of compound 4a](image)
Figure S141: $^1$H NMR of compound 4b

(CDCl₃, 400 MHz)

Figure S142: $^{13}$C NMR of compound 4b

(CDCl₃, 100 MHz)
**Figure S143:** $^1$H NMR of compound 4c

![$^1$H NMR spectrum of compound 4c](image)

(CDC$_3$, 400 MHz)

**Figure S144:** $^{13}$C NMR of compound 4c

![$^{13}$C NMR spectrum of compound 4c](image)

(CDC$_3$, 100 MHz)
Figure S145: $^1$H NMR of compound 4d

Figure S146: $^{13}$C NMR of compound 4d
Figure S147: $^1$H NMR of compound 5a

(DMSO, 400 MHz)

Figure S148: $^{13}$C NMR of compound 5a

(DMSO, 125 MHz)
**Figure S149:** $^1$H NMR of compound 5b

![Figure S149: $^1$H NMR of compound 5b](image)

(DMSO, 400 MHz)

**Figure S150:** $^{13}$C NMR of compound 5b

![Figure S150: $^{13}$C NMR of compound 5b](image)

(DMSO, 100 MHz)
Figure S151: $^1$H NMR of compound 5c

![Figure S151: $^1$H NMR of compound 5c](image.png)

Figure S152: $^{13}$C NMR of compound 5c

![Figure S152: $^{13}$C NMR of compound 5c](image.png)
Figure S153: $^1$H NMR of compound 6a

Figure S154: $^{13}$C NMR of compound 6a
Figure S155: $^1$H NMR of compound 6b

Figure S156: $^{13}$C NMR of compound 6b
Figure S157: $^1$H NMR of compound 6c

Figure S158: $^{13}$C NMR of compound 6c
**Figure S159:** $^1$H NMR of compound 8a

![1H NMR spectrum of compound 8a](image)

(CDCl$_3$, 300 MHz)

**Figure S160:** $^{13}$C NMR of compound 8a

![13C NMR spectrum of compound 8a](image)

(CDCl$_3$, 75 MHz)
**Figure S161:** $^1$H NMR of compound 9b

![Figure S161: $^1$H NMR of compound 9b](image)

**Figure S162:** $^{13}$C NMR of compound 9b

![Figure S162: $^{13}$C NMR of compound 9b](image)
**Figure S163:** $^1$H NMR of compound 10

![1H NMR of compound 10](image)

**Figure S164:** $^{13}$C NMR of compound 10

![13C NMR of compound 10](image)
Figure S165: $^1$H NMR of compound 11a

(DMSO, 400 MHz)

Figure S166: $^{13}$C NMR of compound 11a

(DMSO, 125 MHz)
Figure S167: $^1$H NMR of compound 11b

(CDCl$_3$+DMSO, 300 MHz)

Figure S168: $^{13}$C NMR of compound 11b

(CDCl$_3$+DMSO, 75 MHz)
Figure S169: $^1$H NMR of compound 11c

Figure S170: $^{13}$C NMR of compound 11c
Figure S171: $^1$H NMR of compound 11d

(CDCl$_3$, 500 MHz)

Figure S172: $^{13}$C NMR of compound 11d

(CDCl$_3$, 75 MHz)
Figure S173: $^1$H NMR of compound 11e

(DMSO, 300 MHz)

Figure S174: $^{13}$C NMR of compound 11e

(DMSO, 75 MHz)
Figure S175: $^1$H NMR of compound 11f

Figure S176: $^{13}$C NMR of compound 11f
Figure S177: $^1$H NMR of 4-Methoxybenzaldehyde-$\alpha$-D

Figure S178: $^1$H NMR of compound D-1d
Figure S179: $^1$H NMR of compound $^{18}$O-1b

![Figure S179: $^1$H NMR of compound $^{18}$O-1b](image)

Figure S180: $^{13}$C NMR of compound $^{18}$O-1b

![Figure S180: $^{13}$C NMR of compound $^{18}$O-1b](image)