Electronic Supplementary Material (ESI) for Chemical Communications


# Gold-Catalyzed Amide Synthesis from Aldehydes and Amines in Aqueous Medium

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# Supporting Information

## General Experimental Section.

Chemicals purchased from commercial sources were used without further purification. $H_2{}^{18}O$ was purchased from Meryer. Flash column chromatography was performed using silica gel 60 (230-400 mesh ASTM) with ethyl acetate/n-hexane as eluent. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on Varian AS-400 or Varian AS-500 spectrometer. Chemical shifts (ppm) were referenced to TMS. Mass spectra were measured using a Q-TOF 2 ™ mass spectrometer with a ESI source (Waters-Micromass, Manchester, UK).

## LC–MS Analysis of Oligosaccharides.

LC-MS analyses were performed by using the a hydrid Q-TOF mass spectrometry (QSTAR, API, USA) in the positive ion mode. Mobile-phase A was made of 0.5% formic acid in Milli-Q® water. The CapLC® system (Perkinelmer series 200 mixer, USA) was equipped with a Poroshell 300SB-C18 column (1.0 mm ID × 75 mm, 5μm) with ZORBAX Poroshell guard column (1.0 mm ID × 17 mm, 5 μm) (Agilent-Technologies Inc., Wilmington, United States of America). Mobile-phase B was made of 0.5% formic acid in acetonitrile. 5 μl of sample was injected with a flow rate of 40 μl/min at room temperature. The grandient program was set to 3% B for 0-3 min, followed by a linear gradient to 80% B in 4-30 min and 3% B in 31-45 min. The mass spectrometer was monitored over a *m*/*z* range of 200-1000.

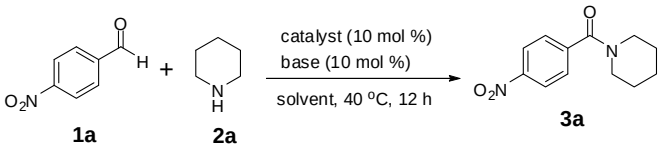
## Calculation of Aldehyde Conversion

The crude reaction mixture of aldehyde-containing oligosaccharides (aldehyde) and modified oligosaccharides (product) was subjected to LC-MS analysis with elution time of 45 min. The aldehyde conversion was determined by measuring the relative peak intensities of aldehyde and product in the mass spectrum as follows:

$$\textit{Aldehyde Conversion (\%)} = \left(1 - \frac{\textit{Relative Peak Intensity of Aldehyde}}{\textit{Relative Peak Intensities of Aldehyde and Product}}\right) \text{X } 100\%$$

**General Procedure for $KAuCl_4$-Catalyzed Amide Synthesis.** A mixture of aldehyde (0.2 mmol), amine (0.4 mmol), $KAuCl_4$ (0.02 mmol), and $K_2CO_3$ (0.02 mmol) in $CH_3CN/H_2O$ (1:1, 1 mL) was stirred at 40 °C for 12 h. The reaction mixture was allowed to cool to room temperature, treated with water (5 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using ethyl acetate-hexane as eluent.

**Table S1**. Studies on Reaction Conditions of Catalytic Synthesis of Amide **3a** from *p*-Nitrobenzaldehyde **1a** and Piperidine **2a**[a]




**1a** **2a** **3a**

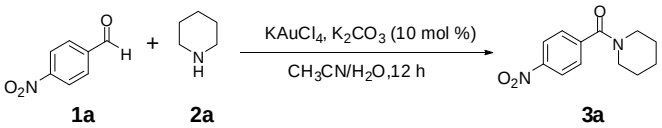
| Entry | Catalyst | Base | Solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $KAuCl_4$ | $K_2CO_3$ | $CH_3CN/H_2O$ | 85 |
| 2 | - | $K_2CO_3$ | $CH_3CN/H_2O$ | 0 |
| 3[c] | $KAuCl_4$ | $K_2CO_3$ | $CH_3CN/H_2O$ | 30 |
| 4 | AuCl | $K_2CO_3$ | $CH_3CN/H_2O$ | 79 |
| 5 | [Au(C^N)$Cl_2$] | $K_2CO_3$ | $CH_3CN/H_2O$ | trace |
| 6 | $PPh_3AuCl$ | $K_2CO_3$ | $CH_3CN/H_2O$ | trace |
| 7 | $KAuCl_4$ | $K_2CO_3$ | $THF/H_2O$ | 42 |
| 8 | $KAuCl_4$ | $K_2CO_3$ | $CH_3OH/H_2O$ | 35 |
| 9 | $KAuCl_4$ | $K_2CO_3$ | *t*-$BuOH/H_2O$ | 66 |
| 10 | $KAuCl_4$ | $K_2CO_3$ | $H_2O$ | trace |
| 11 | $KAuCl_4$ | $K_2CO_3$ | $CH_3CN$ | trace |
| 12 | $KAuCl_4$ | $K_2CO_3$ | THF | trace |
| 13 | $KAuCl_4$ | $K_2CO_3$ | toluene | trace |
| 14 | $KAuCl_4$ | - | $CH_3CN/H_2O$ | 37 |
| 15 | $KAuCl_4$ | $Na_2CO_3$ | $CH_3CN/H_2O$ | 25 |
| 16 | $KAuCl_4$ | $CaCO_3$ | $CH_3CN/H_2O$ | 44 |
| 17 | $KAuCl_4$ | $NaHCO_3$ | $CH_3CN/H_2O$ | 60 |
| 18 | $KAuCl_4$ | $Cs_2CO_3$ | $CH_3CN/H_2O$ | 61 |
| 19 | $KAuCl_4$ | $Et_3N$ | $CH_3CN/H_2O$ | 44 |

[a] All reactions were carried out with **1a** (0.2 mmol), **2a** (0.4 mmol, 2 equiv), $KAuCl_4$ (10 mol %), $K_2CO_3$ (10 mol %) in $CH_3CN/H_2O$ (1:1, 1 mL) for 12 h. [b] Isolated yield.

As shown in Table S1, the coupling reaction of *p*-nitrobenzaldehyde **1a** (1 equiv) and piperidine **2a** (2 equiv) in the presence of $KAuCl_4$ (10 mol %) and $K_2CO_3$ (10 mol

%) in $CH_3CN/H_2O$ (1:1) at 40 °C for 12 h was conducted (entry 1). It was found that amide **3a** was obtained in 85% isolated yield with complete conversion while no amide product was detected without $KAuCl_4$ (entry 2). Using 2 mol % of $KAuCl_4$, amide **3a** was obtained with 30% yield (entry 3). Comparable yield (79%) was found when AuCl (10 mol %) was used as the catalyst (entry 4). Only a trace amount of aldehyde conversion was observed for $[Au(C^N)Cl_2]$ (N^CH = 2-phenylpyridine) and $PPh_3AuCl$ (entries 5 and 6). Poor conversion (10%) was found for $RuCl_3$ (10 mol%). Other metal catalysts (10 mol %) including CuBr, $CuBr_2$, CuI, $AgNO_3$, $MnSO_4 \cdot 3H_2O$, $Zn(OTf)_2$ and $Yb(OTf)_3$ gave no conversion (data not shown). These findings indicated that $KAuCl_4$ is effective to catalyze the amide synthesis from aldehydes and amines. The amide synthesis reactions could be performed in various solvent systems ($THF/H_2O$, $CH_3OH/H_2O$, and *t*-$BuOH/H_2O$) with 35–66% yield (entries 7–9). Yet, no product was obtained when the reaction was conducted in $H_2O$ only, presumably due to the poor solubility of aldehyde (entry 10). Without $H_2O$, only a trace amount of aldehyde conversion was found (entries 11–13). Without $K_2CO_3$, lower conversion yield (37%) was obtained (entry 1 vs entry 14). The presence of base is important for the reaction conversion and yield (entry 14 vs entries 15–19).

**Table S2**. Studies on Reaction Conditions of Catalyst Loading and Reaction Temperature of $KAuCl_4$-Catalyzed Amide Synthesis from Aldehyde **1a** and Piperidine **2a**[a]



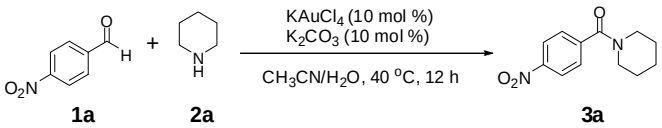

**1a** **2a** **3a**

| Entry | Catalyst Loading (mol%) | temperature | yield (%)[c] |
|---|---|---|---|
| 1 | 10 | 25 °C | – |
| **2** | **10** | **40 °C** | **85** |
| 3 | 5 | 40 °C | 56 |
| 4 | 2 | 40 °C | 30 |
| 5 | 1 | 40 °C | 15 |
| 6 | 0.5 | 40 °C | 10 |
| 7 | 10 | 60 °C | 60 |
| 8 | 5 | 60 °C | 54 |
| 9 | 2 | 60 °C | 25 |
| 10[c] | 1 | 60 °C | 61 |
| 11 | 0.5 | 60 °C | 12 |
| 12 | 5 | 80 °C | 57 |
| 13 | 2 | 80 °C | 36 |
| 14 | 1 | 80 °C | 49 |
| 15 | 0.5 | 80 °C | 48 |

[a] All reactions were carried out with **1a** (0.2 mmol), **2a** (0.4 mmol, 2 equiv), $KAuCl_4$, $K_2CO_3$ (10 mol %) in $CH_3CN/H_2O$ (1:1, 1 mL) for 12 h. [b] Isolated yield. [c] **1a** (1.0 mmol), **2a** (2.0 mmol, 2 equiv), $KAuCl_4$ (1 mol %), $K_2CO_3$ (10 mol %) in $CH_3CN/H_2O$ (1:1, 2 mL) for 12 h.

We conducted a detailed study on catalyst loading and reaction temperature of $KAuCl_4$-catalyzed synthesis of amide **3a**; with 0.5 mol % $KAuCl_4$, **3a** was obtained with 48% yield when the reaction was carried out at 80 °C (Table S2).

**Table S3**. Studies on Effect of the Ratio of $CH_3CN$ to $H_2O$[a]

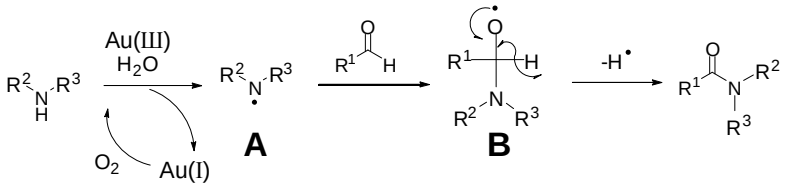



| Entry | $CH_3CN$ (mL) | $H_2O$ (mL) | Conversion (%) [b] |
|---|---|---|---|
| 1 | 0.9 | 0.1 | 10 |
| 2 | 0.8 | 0.2 | 11 |
| 3 | 0.6 | 0.4 | 98 |
| **4** | **0.5** | **0.5** | **100** |
| 5 | 0.4 | 0.6 | 95 |
| 6 | 0.2 | 0.8 | 5 |

[a] All reactions were carried out with **1a** (0.2 mmol), **2a** (0.4 mmol, 2 equiv), $KAuCl_4$ (10 mol %), $K_2CO_3$ (10 mol %) in $CH_3CN/H_2O$ (1 mL) for 12 h. [b] Determined by $^1H$ NMR analysis of the crude reaction mixture.

We further examined the effect of the ratio of $CH_3CN$ to $H_2O$, the highest conversion was obtained in a 1:1 solvent system (Table S3).

**Proposed Reaction Mechanism**

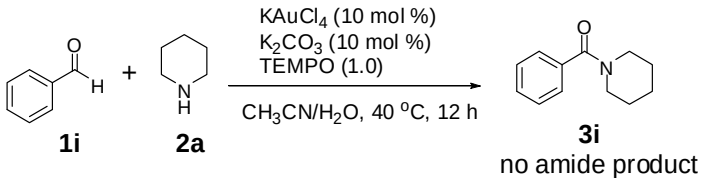



A reaction mechanism for the gold-catalyzed amide synthesis from aldehydes and amines in aqueous medium is proposed on the basis of mechanistic studies.

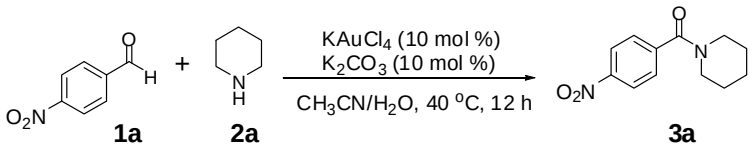
Aminyl radical (**A**) is generated from the reaction between amine and Au(III) ion in aqueous medium. The reaction of **A** with aldehyde gives alkoxy radical (**B**) which affords amide as the product via loss of hydrogen radical. Oxygen acts as the oxidant for the re-oxidation of Au(I) to Au(III) ion to complete the catalytic cycle.

**[I] <u>Aminyl radical (A)</u>**

As shown in Scheme S1a, addition of radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) to the coupling reaction of benzaldehyde **1i** and piperidine **2a** significantly suppressed the reaction. Significant reduction in product yield (from 85% to 2% and 5%) were found when the radical scavengers (TEMPO/1,1-diphenylethylene) were added into the reaction of *p*-nitrobenzaldehyde **1a** and piperidine **2a** (Scheme S1b). These results suggested that radical species would be involved in the amide synthesis reaction. Generation of aminyl radicals through the reaction of amines with gold ions[1] and in gold(III)/gold(I) redox processes in aqueous medium have been reported.[2] Thus, generation of aminyl radical (**A**) from the reaction between amine and Au(III) ion in aqueous medium is suggested.




Scheme S1a




(i): no radical scavenger, 85% isolated yield
(ii): TEMPO (1.0 equiv.), 2% isolated yield
(iii): 1,1-Diphenylethylene (1.0 equiv.), 5% isolated yield

Scheme S1b

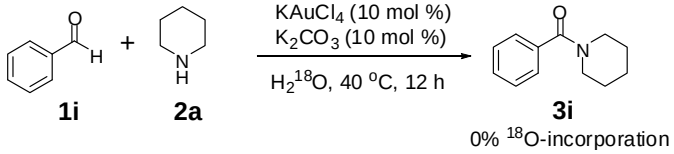
References:

1. (a) M. Aslam, L. Fu, M. Su, K. Vijayamohanan and V. P. Dravid, *J. Mater. Chem.*, 2004, **14**, 1795; (b) S. K. Bhargava, J. M. Booth, S. Agrawal, P. Coloe and G. Kar, *Langmuir* 2005, **21**, 5949; (c) J. D. S. Newman and G. J. Blanchard, *Langmuir* 2006, **22**, 5882.

2. (a) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180; (b) A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2005, **44**, 6990; (c) X. Yao, C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 6884.

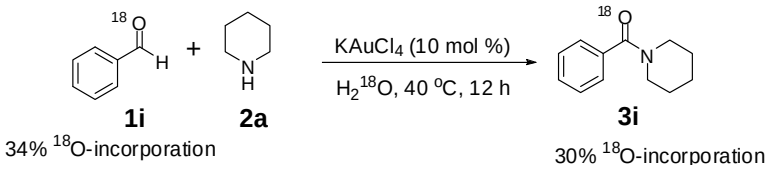
## [II] Alkoxy radical (B)

The coupling reaction of **1i** and **2a** was conducted in $H_2{}^{18}O$ (Scheme S1c). No $^{18}O$-incorporation was detected in the product amide **3i** by ESI-MS analysis, indicating that the carbonyl oxygen atom of the amide did not come from $H_2{}^{18}O$.



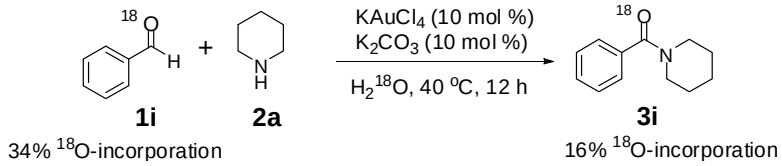

Scheme S1c

The reaction of benzaldehyde **1i** (34% $^{18}O$-incorporation) and **2a** was conducted in $H_2{}^{18}O$ (Scheme S1d). The product amide **3i** with 30% $^{18}O$-incorporation was found by ESI-MS analysis, indicating that the amide carbonyl oxygen atom originated from aldehyde.



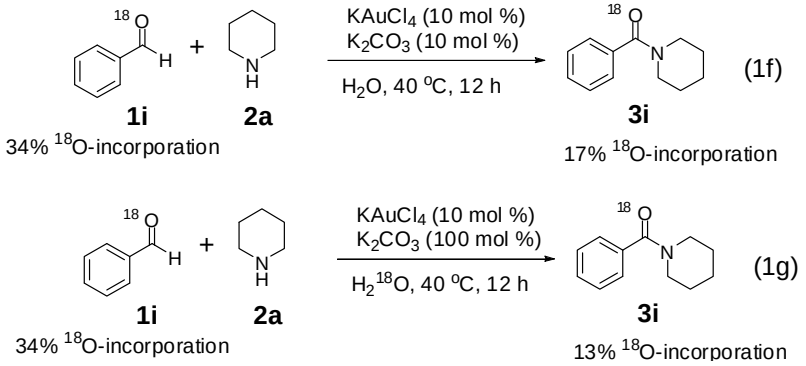

Scheme S1d

When the reaction was conducted in the presence of potassium carbonate (10 mol %), 16% $^{18}$O-incorporation in **3i** was found (Scheme S1e).



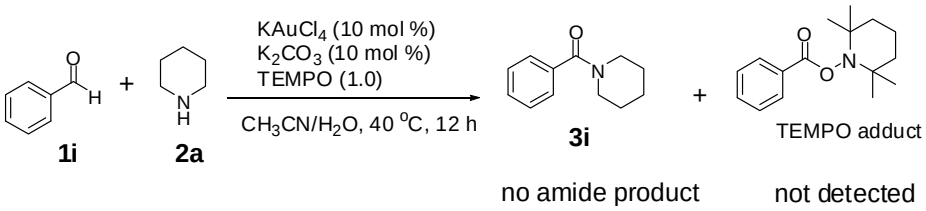

Scheme S1e

Through a number of control experiments, we noticed that the $^{18}$O-label loss of amide (17-21%) was attributed to the presence of potassium carbonate, (Scheme S1f-1g). $^{18}$O-label loss in the presence of potassium carbonate was also observed in the amide synthesis reaction by Johnston and coworkers.[3]




Scheme S1f-1g

Addition of TEMPO (1 equivalent) gave no amide formation (Scheme S1h). No formation of TEMPO adduct by $^{1}$H NMR and chromatography analysis suggested that acyl radical would not be generated under the reaction conditions.[4]




Scheme S1h

In this connection, alkoxy radical (**B**) generated from the reaction of aminyl radical (**A**) and aldehyde is suggested.

References:

3. J. P. Shackleford, B. Shen, and J. N. Johnston, *PNAS,* 2012, **109**, 44.

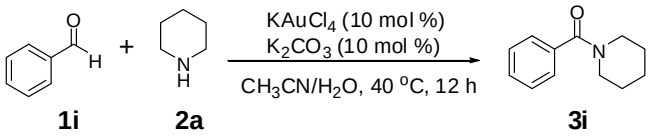
4. Z, Liu, J. Zhang, S. Chen, E. Shi, Y. Xu and X. Wan, *Angew. Chem., Int. Ed*., 2012, DOI: 10.1002/anie.201108763.

## [III] Oxygen as the oxidant

We performed the reaction between benzaldehyde **1i** and piperidine **2a** in air, and the amide product **3i** was obtained in 50% isolated yield (Condition A, Scheme S1i).

When the reaction was carried out under $N_2$ atmosphere, **3i** was found in 5% isolated yield indicating oxygen in air is important (Condition B).

Under oxygen atmosphere (balloon), no amide product was detected (Condition C). This would be attributed to the oxidation of aminyl radical species by oxygen.[5, 6]




Condition A: air, 50% isolated yield
Condition B: $N_2$ atmosphere, 5% isolated yield
Condition C: $O_2$ (balloon), no amide product was detected

Scheme S1i

In this regard, oxygen acting as an oxidant for the oxidation of Au(I) to Au(III) is suggested.[7]

References:

5. J. H. Horner, F. N. Martinez, O. M. Musa, M. Newcomb and H. E. Shahin, *J. Am. Chem. Soc*., 1995, **117**, 11124.

6. M. Jonsson, D. D. M. Wayner and J. Lusztyk, *J. Phys. Chem*., 1996, **100**, 17539.

7. (a) G. B. Shul'pin, A. E. Shilov, G. Süss-Fink, *Tetrahedron Lett*, 2001, **42**, 7253; (b) A. Corma, I. Domíguez, A. Doménech, V. Fornés, C. J. Gómez-García, T. Ródenas and M. J. Sabater, *J. Catal*., 2009, **265**, 238; (c) J. Xie, H. Li, J. Zhou, Y. Cheng and C. Zhu, *Angew. Chem., Int. Ed*., 2012, **124**, 1252.

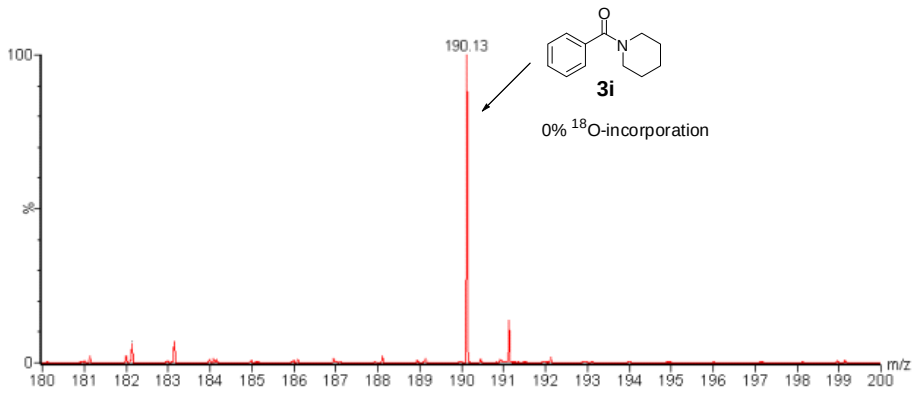



**Figure S1a** ESI-MS spectrum of 0% $^{18}$O-incorporation (Scheme S1c).

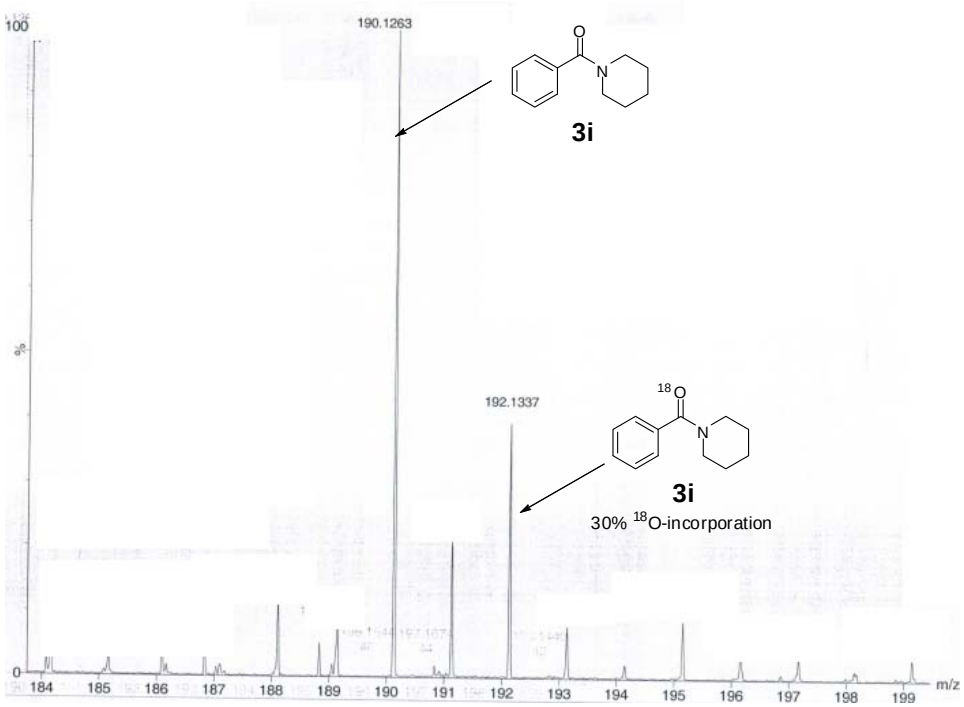



**Figure S1b** ESI-MS spectrum of 30% $^{18}$O-incorporation (Scheme S1d).

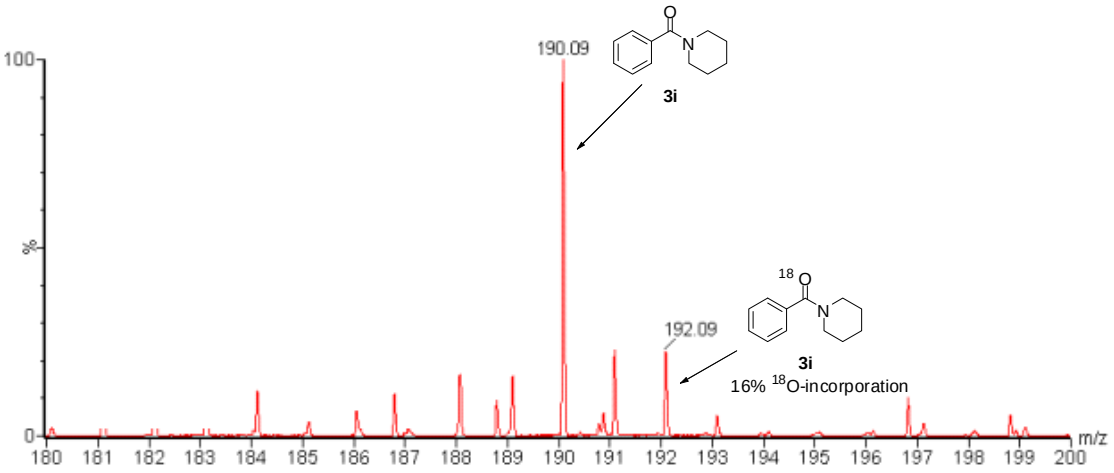



**Figure S1c** ESI-MS spectrum of 16% $^{18}$O-incorporation (Scheme S1e).

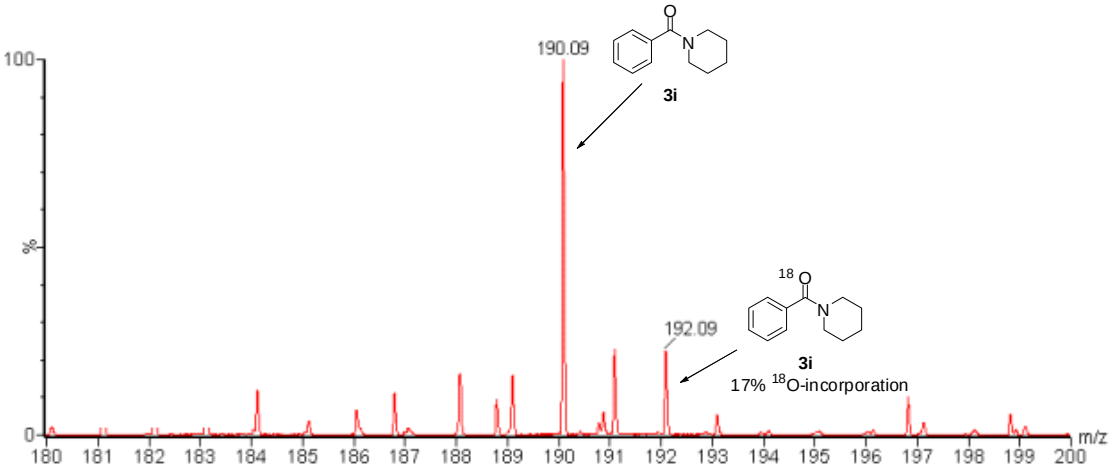



**Figure S1d** ESI-MS spectrum of 17% $^{18}$O-incorporation (Scheme S1f).

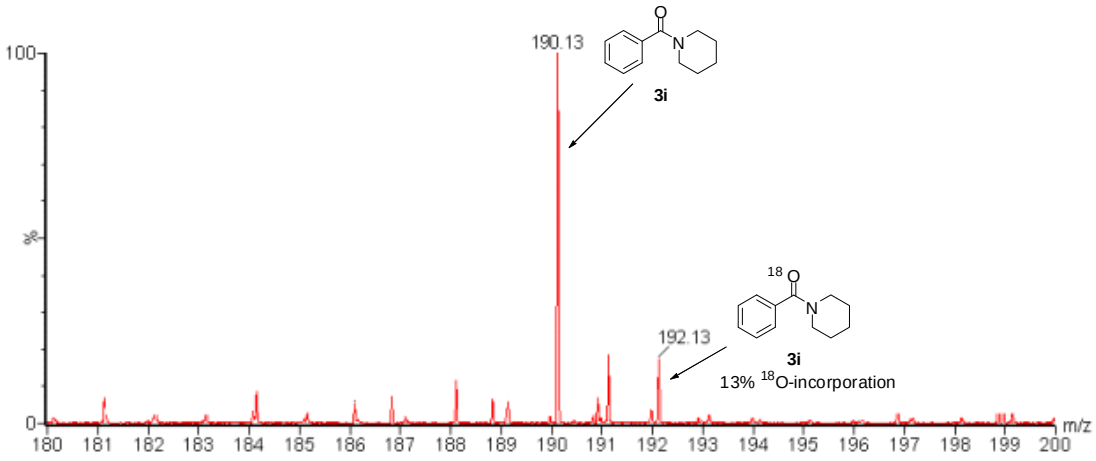
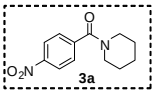
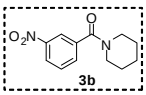



**Figure S1e** ESI-MS spectrum of 13% $^{18}$O-incorporation (Scheme S1g).

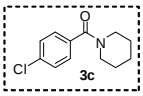
## Characterization data of the amide products 3a-6c



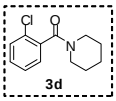

**(4-nitrophenyl)(piperidin-1-yl)methanone (3a)**.[8] Yellow solid; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.5; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 3.73 (br s, 2H), 3.29 (br s, 2H), 1.71 (br s, 4H), 1.53 (br s, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.1, 148.4, 142.9, 128.0, 124.0, 48.8, 43.4, 26.7, 25.7, 24.6 ppm; MS (ESI) *m*/*z* 235 $[M+H]^+$.



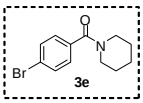

**(3-nitrophenyl)(piperidin-1-yl)methanone (3b)**. Yellow solid; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.5; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.26-8.28 (m, 2H), 7.72 (dt, *J* = 7.5, 1,5 Hz, 1H), 7.59 (td, *J* = 7.5, 1,0 Hz, 1H), 3.73 (br s, 2H), 3.33 (br s, 2H), 1.71 (br s, 4H), 1.55 (br s, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.8, 148.2, 138.3, 133.1, 130.0, 124.4, 122.3, 49.1, 43.6, 26.7, 25.7, 24.6 ppm; MS (ESI) *m*/*z* 235 $[M+H]^+$; HRMS (ESI) for $C_{12}H_{15}N_2O_3$ $[M+H]^+$ calcd: 235.1083, found: 235.1078.



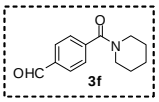

**(4-chlorophenyl)(piperidin-1-yl)methanone (3c)**.[8] Colorless oil; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.6; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.64 (br s, 2H), 3.28 (br s, 2H), 1.63 (br s, 4H), 1.47 (br s, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.4, 135.6, 135.1, 128.8, 128.6, 49.0, 43.5, 26.7, 25.9, 24.7 ppm; MS (ESI) *m*/*z* 224 $[M+H]^+$.



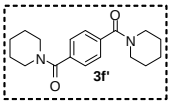

**(2-chlorophenyl)(piperidin-1-yl)methanone (3d)**. Yellow oil; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.6; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38-7.40 (m, 1H), 7.26-7.33 (m, 3H), 3.70-3.81 (m, 2H), 3.13-3.24 (m, 2H), 1.66-1.68 (m, 5H), 1.46 (br s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.9, 136.7, 130.6, 130.1, 129.8, 127.8, 127.3, 48.1, 42.8, 26.6, 25.8, 24.7 ppm; MS (ESI) *m*/*z* 224 $[M+H]^+$; HRMS (ESI) for $C_{12}H_{15}NOCl$ $[M+H]^+$ calcd: 224.0842, found: 224.0831.



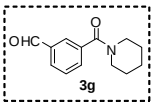

**(4-bromophenyl)(piperidin-1-yl)methanone (3e)**.[9] White solid; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.6; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 3.67 (br s, 2H), 3.31 (br s, 2H); 1.66 (br s, 4H), 1.50 (br s, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.4, 135.6, 131.8, 128.8, 123.8, 49.0, 43.4, 26.7, 25.9, 24.7 ppm; MS (ESI) *m*/*z* 268 $[M+H]^+$.



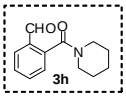

**4-(piperidine-1-carbonyl)benzaldehyde (3f)**.[10] Colorless oil; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.4; $^1$H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.88 (d, *J* = 8.0, 2H), 7.50 (d, *J* = 8.0, 2H), 3.68 (br s, 2H), 3.24 (br s, 2H), 1.64 (br s, 4H), 1.47 (br s, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 191.7, 169.0, 142.5, 136.9, 130.1, 127.6, 48.9, 43.3, 26.8, 25.8, 24.7 ppm; MS (ESI) *m*/*z* 218 $[M+H]^+$.



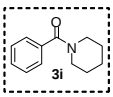

**1,4-phenylenebis(piperidin-1-ylmethanone) (3f')**. Yellow solid; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.2; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 4H), 3.67 (br s, 4H), 3.32 (br s, 4H), 1.67 (br s, 8H), 1.47 (br s, 4H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.8, 137.7, 127.1, 49.0, 43.3, 26.7, 25.8, 24.7 ppm; MS (ESI) *m*/*z* 301 $[M+H]^+$; HRMS (ESI) for $C_{18}H_{24}N_2O_2$ $[M+H]^+$ calcd: 301.1872, found: 301.1875.




**3-(piperidine-1-carbonyl)benzaldehyde (3g)**.[11] Colorless oil; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.4; $^1$H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.91-7.94 (m, 1H), 7.67 (dt, *J* = 1.5, 3.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 3.74 (br s, 2H), 3.34 (br s, 2H), 1.70 (br s, 4H), 1.54 (br s, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 191.6, 169.0, 137.7, 136.6, 132.9, 130.6, 129.5, 128.2, 49.0, 43.5, 26.8, 25.8, 24.7 ppm; MS (ESI) *m*/*z* 218 $[M+H]^+$.

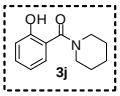



**2-(piperidine-1-carbonyl)benzaldehyde (3h)**.[12] Colorless oil; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.4; $^1$H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.93-7.95 (m, 1H), 7.62-7.65 (dt, *J* = 1.5, 3.0 Hz, 1H), 7.53-7.56 (m, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 3.79 (t, *J* = 6.0 Hz, 2H), 3.14 (t, *J* = 5.5 Hz, 2H), 1.65-1.71 (m, 4H), 1.43-1.46 (m, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 190.7, 167.9, 139.5, 134.4, 133.0, 130.2, 129.4, 127.1, 48.3, 42.9, 26.4, 25.7, 24.7 ppm; MS (ESI) *m*/*z* 218 $[M+H]^+$.

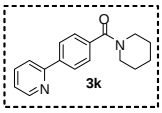



**phenyl(piperidin-1-yl)methanone (3i)**.[8] Colorless oil; analytical TLC (silica gel 60) (30% EtOAc in hexane) $R_f$ = 0.6; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 5H), 3.69 (br s, 2 H), 3.31 (br s, 2H), 1.65 (br s, 4H), 1.47 (br s, 2H) ppm; $^{13}$C NMR (100 MHz,

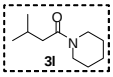
$CDCl_3$) δ 170.5, 136.7, 129.5, 128.6, 126.9, 49.0, 43.3, 26.8, 25.9, 24.8 ppm; MS (ESI) *m*/*z* 190 $[M+H]^+$.



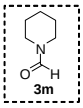

**(2-hydroxyphenyl)(piperidin-1-yl)methanone (3j)**.[13] Yellow solid; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.5; $^1$H NMR (500 MHz, $CDCl_3$) δ 9.68 (br s, 1H), 7.32-7.29 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 3.65 (t, *J* = 6.0 Hz, 4H), 1.63-1.72 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.0, 159.2, 132.5, 128.4, 118.6, 118.2, 117.7, 47.1, 26.3, 24.7; MS (ESI) *m*/*z* 206 $[M+H]^+$.



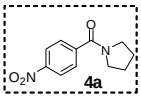

**piperidin-1-yl(4-(pyridin-2-yl)phenyl)methanone (3k)**. White solid; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.2; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.69-8.71 (m, 1H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.73-7.79 (m, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.25-7.28 (m, 1H), 3.73 (br s, 2H), 3.37 (br s, 2H), 1.70 (br s, 4H), 1.69 (br s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.2, 156.9, 150.0, 140.6, 137.1, 137.0, 127.5, 127.2, 122.7, 120.9, 49.0, 43.4, 26.7, 25.9, 24.8; MS (ESI) *m*/*z* 267 $[M+H]^+$; HRMS (ESI) for $C_{17}H_{19}N_2O$ $[M+H]^+$ calcd: 267.1497, found: 267.1491.



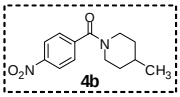

**3-methyl-1-(piperidin-1-yl)butan-1-one (3l)**. Colorless oil; analytical TLC (silica gel 60) (60% EtOAc in hexane) $R_f$ = 0.2; $^1$H NMR (500 MHz, $CDCl_3$) δ 3.48 (br s, 4H), 2.21 (d, *J* = 7.0 Hz, 2H), 2.04-2.14 (m, 1H), 1.62-1.65 (m, 2H), 1.51-1.56 (m, 4H) 0.96 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ171.4, 42.1, 31.1, 26.3, 26.2, 24.7, 22.9; MS (ESI) *m*/*z* 170 $[M+H]^+$; HRMS (ESI) for $C_{10}H_{20}NO$ $[M+H]^+$ calcd:170.1545, found: 170.1542.



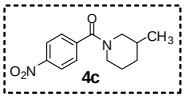

**1-formylpiperidine (3m)**.[14] Colorless oil; analytical TLC (silica gel 60) (60% EtOAc in hexane) $R_f$ = 0.2; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 3.44 (t, *J* = 5.5 Hz, 2H), 3.27 (t, *J* = 5.5 Hz, 2H), 1.63-1.67 (m, 2H), 1.48-1.57 (m, 4H); MS (ESI) *m*/*z* 114 $[M+H]^+$.




**(4-nitrophenyl)(pyrrolidin-1-yl)methanone (4a)**.[8] Yellow crystal; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.6; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 3.67 (t, *J* = 7.0 Hz, 2H), 3.39 (t, *J* = 6.5 Hz, 2H), 1.98-2.03 (m, 2H), 1.90-1.96 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.4, 148.5, 143.2, 128.2, 123.7, 49.4, 46.4, 26.4, 24.4; MS (ESI) *m*/*z* 221$[M+H]^+$.

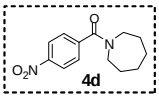



**4-methylpiperidin-1-yl(4-nitrophenyl)methanone (4b)**. Yellow solid; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.6; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 2H), 4.68 (br, 1H), 3.56 (br, 1H), 3.05 (br, 1H), 2.82 (br, 1H), 1.60-1.80 (m, 3H), 1.08-1.27 (m, 2H), 0.98 (d, *J* = 6.5Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.1, 148.4, 142.9, 128.0, 124.0, 48.1, 42.8, 34.9, 33.9, 31.3, 21.8; MS (ESI) *m*/*z* 249 $[M+H]^+$; HRMS (ESI) for $C_{13}H_{17}N_2O_3$ $[M+H]^+$ calcd: 249.1239, found: 249.1230.

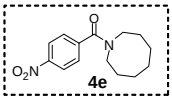



**3-methylpiperidin-1-yl(4-nitrophenyl)methanone (4c)**. Yellow oil; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.6; $^{11}$H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 4.50 (d, *J* = 12.0 Hz, 1H), 3.40-3.45 (m, 1H), 2.83-2.90 (m, 1H), 2.46-2.70 (m, 1H), 1.16-1.88 (m, 5H), 0.92 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR: (100 MHz, $CDCl_3$) δ 168.1, 148.4, 142.9, 128.0, 124.0, 55.3, 49.7/48.4, 33.1, 32.2/31.3, 26.2/24.8, 19.2/18.9; MS (ESI) *m*/*z* 249 $[M+H]^+$; HRMS

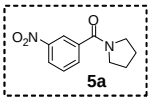
(ESI) for $C_{13}H_{17}N_2O_3$ $[M+H]^+$ calcd: 249.1239, found: 249.1234.



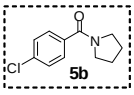

**azepan-1-yl(4-nitrophenyl)methanone (4d)**. Yellow crystal; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.5; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.0 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 3.71 (t, *J* = 5.5 Hz, 2H), 3.32 (t, *J* = 5.0 Hz, 2H), 1.84-1.87 (m, 2H) 1.58-1.66 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.4, 148.3, 143.7, 127.7, 124.1, 48.9, 46.7, 29.6, 27.9, 27.3, 26.7; MS (ESI) *m*/*z* 249 $[M+H]^+$; HRMS (ESI) for $C_{13}H_{17}N_2O_3$ $[M+H]^+$ calcd: 249.1239, found: 249.1234.




**azocan-1-yl(4-nitrophenyl)methanone (4e)**. Yellow oil; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.5; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.0 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 3.64 (t, *J* = 5.5 Hz, 2H), 3.27 (br s, 2H), 1.89 (br s, 2H), 1.62 (s, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.2, 148.2, 144.0, 127.6, 124.1, 51.2, 47.1, 27.1, 26.6, 26.3, 25.7, 24.3; MS (ESI) *m*/*z* 263 $[M+H]^+$; HRMS (ESI) for $C_{14}H_{19}N_2O_3$ $[M+H]^+$ calcd: 263.1396, found: 263.1387.

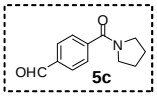



**(3-nitrophenyl)(pyrrolidin-1-yl)methanone (5a)**. Yellow crystal; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.6; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.24-8.28 (m, 1H), 7.86 (d, *J* = 6.5 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 3.68 (t, *J* = 7.0 Hz, 2H), 3.43 (t, *J* = 6.5 Hz, 2H), 1.96-2.02 (m, 2H), 1.89-1.94 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.2, 148.2,138.9, 133.4, 129.8, 124.8, 122.4, 49.8, 46.7, 26.6, 24.6; MS (ESI) *m*/*z* 221 $[M+H]^+$; HRMS (ESI) for $C_{11}H_{13}N_2O_3$ $[M+H]^+$ calcd: 221.0926, found: 221.0919.

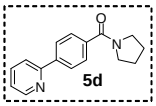



**(4-chlorophenyl)(pyrrolidin-1-yl)methanone (5b)**.[8] Colorless oil; analytical TLC ( silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.5; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47

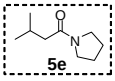
(d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 3.64 (t, *J* = 7.0 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 1.93-1.99 (m, 2H), 1.86-1.91 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.8, 136.0, 135.8, 128.9, 128.7, 49.8, 46.5, 26.6, 24.6; MS (ESI) *m*/*z* 210 $[M+H]^+$.



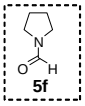

**4-(pyrrolidine-1-carbonyl)benzaldehyde (5c)**. Colorless oil; analytical TLC (silica gel 60) (60% EtOAc in hexane) $R_f$ = 0.5; $^1$H NMR (500 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.0, 2H), 3.69 (t, *J* = 7.0 Hz, 2H), 3.40 (t, *J* = 6.5 Hz, 2H), 1.96-2.02 (m, 2H), 1.88-1.94 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 191.7, 168.5, 143.0, 137.2, 129.9, 127.9, 49.6, 46.4, 26.6, 24.6; MS (ESI) *m*/*z* 204 $[M+H]^+$; HRMS (ESI) for $C_{12}H_{14}NO_2$ $[M+H]^+$ calcd: 204.1025, found: 204.1020.




**4-(Pyridin-2-yl)phenyl(pyrrolidin-1-yl)methanone (5d)**. Yellow solid; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.3; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.75-8.77 (m, 1H), 8.09 (dd, *J* = Hz, 2H), 7.81-7.85 (m, 2H), 7.69 (dd, *J* = 6.5, 2.0 Hz, 2H), 7.30-7.33 (m, 1H), 3.73 (t, *J* = 7.0 Hz, 2H), 3.52 (t, *J* = 7.0 Hz, 2H ), 2.03-2.06 (m, 2H), 1.93-1.97 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.6, 156.8, 150.0, 140.9, 137.8, 137.1, 127.8, 127.0, 122.7, 120.9, 49.8, 46.5, 26.6, 24.7; MS (ESI) *m*/*z* 253 $[M+H]^+$; HRMS (ESI) for $C_{16}H_{17}N_2O$ $[M+H]^+$ calcd: 252.1263, found: 252.1260.

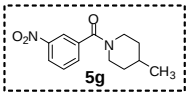



**3-methyl-1-(pyrrolidin-1-yl)butan-1-one (5e)**. Colorless oil; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.3; $^1$H NMR (500 MHz, $CDCl_3$) δ 3.45 (t, *J* = 7.0 Hz, 2H), 3.40 (t, *J* = 6.5 Hz, 2H), 2.12-2.20 (m, 3H), 1.90-1.95 (m, 2H), 1.80-1.86 (m, 2H), 0.95 (d, *J* = 6.5 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.4, 47.0, 45.7, 43.9, 26.3, 25.7, 24.6, 22.9; MS (ESI) *m*/*z* 156 $[M+H]^+$; HRMS (ESI) for $C_9H_{18}NO$ $[M+H]^+$ calcd: 155.1310, found: 155.1308.



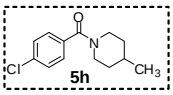
5f

**pyrrolidine-1-carbaldehyde (5f)**.[14] Colorless oil; analytical TLC (silica gel 60) (60% EtOAc in hexane) $R_f$ = 0.2; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 3.48 (t, *J* = 6.5 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 1.85-1.93 (m, 4H).



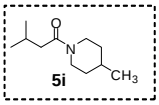
5g

**4-methylpiperidin-1-yl(3-nitrophenyl)methanone (5g)**. Colorless oil; analytical TLC (silica gel 60) (60% EtOAc in hexane) $R_f$ = 0.3; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.24-8.26 (m, 2H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 4.67 (br, 1H), 3.61 (br, 1H), 3.05 (br, 1H), 2.80 (br, 1H), 1.64-1.79 (m, 3H), 1.09-1.25 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.8, 148.3, 138.3, 133.1, 129.9, 124.4, 122.2, 48.4, 42.9, 34.9, 33.9, 31.3, 21.8; MS (ESI) *m/z* 249 $[M+H]^+$; HRMS (ESI) for $C_{13}H_{17}N_2O_3$ $[M+H]^+$ calcd: 249.1239, found: 249.1230.



5h

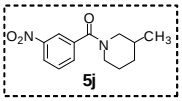
**4-chlorophenyl(4-methylpiperidin-1-yl)methanone (5h)**. Colorless oil; analytical TLC (silica gel 60) (60% EtOAc in hexane) $R_f$ = 0.3; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 1H), 4.62 (br s, 1H), 3.64 (br s, 1H), 2.84 (br d, 2H), 1.57-1.73 (m, 3H), 1.06-1.24 (m, 2H), 0.94 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.4, 135.6, 135.1, 128.9, 128.6, 48.3, 42.8, 34.9, 34.0, 31.4, 21.9; MS (ESI) *m/z* 238 $[M+H]^+$; HRMS (ESI) for $C_{13}H_{17}NOCl$ $[M+H]^+$ calcd: 238.0999 found: 238.0994.



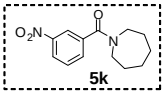
5i

**3-methyl-1-(4-methylpiperidin-1-yl)butan-1-one (5i)**. Colorless oil; analytical TLC (silica gel 60) (60% EtOAc in hexane) $R_f$ = 0.2; $^1$H NMR (500 MHz, $CDCl_3$) δ 4.58-4.61 (m, 1H), 3.82-3.85 (m, 1H), 2.98 (dt, *J* = 13.0, 2.5 Hz, 1H), 2.52 (dt, *J* = 13.0, 2.5 Hz, 1H), 2.21 (dd, *J* = 7.0, 3.0 Hz, 2H), 2.09-2.14 (m, 1H), 1.57-1.69 (m, 3H), 1.03-1.12 (m, 2H), 0.94-0.97 (m, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.1,

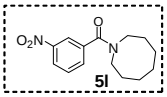
46.4, 42.5, 42.2, 35.1, 34.2, 31.4, 26.1, 23.0, 22.9, 21.9; MS (ESI) *m/z* 184 $[M+H]^+$; HRMS (EI) for $C_{11}H_{21}NO$ $[M+H]^+$ calcd: 184.1623 found: 184.1630.



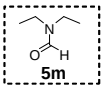

**3-methylpiperidin-1-yl(3-nitrophenyl)methanone (5j)**. Colorless oil; analytical TLC (silica gel 60) (60% EtOAc in hexane) $R_f$ = 0.2; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.5 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 4.51 (br s, 1H), 3.45-3.56 (m, 1H), 2.84-3.02 (m, 1H), 2.46-2.73 (m, 1H), 1.45-1.90 (m, 4H), 1.17-1.24 (m, 1H), 0.98 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ167.8, 148.3, 138.3, 133.1, 129.9, 124.4, 122.2, 55.3, 49.9/48.6, 43.1, 32.2/31.3, 26.2/24.8, 19.2/18.9; MS (ESI) *m/z* 249 $[M+H]^+$; HRMS (ESI) for $C_{13}H_{17}N_2O_3$ $[M+H]^+$ calcd: 249.1239, found: 249.1230.



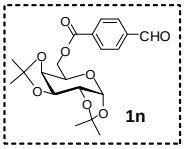

**azepan-1-yl(3-nitrophenyl)methanone (5k)**. Colorless oil; analytical TLC (silica gel 60) (60% EtOAc in hexane) $R_f$ = 0.2; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.25-8.27 (m, 2H), 7.73 (d, *J* = 6.5 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 3.70 (t, *J* = 5.5 Hz, 2H), 3.37 (t, *J* = 5.5 Hz, 2H), 1.85-1.89 (m, 2H), 1.61-1.67 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.1, 148.3, 139.1, 132.9, 130.0, 124.2, 122.0, 50.1, 46.8, 29.7, 28.0, 27.4, 26.7; MS (ESI) *m/z* 249 $[M+H]^+$; HRMS (EI) for $C_{13}H_{17}N_2O_3$ $[M+H]^+$ calcd: 249.1239, found: 249.1235.



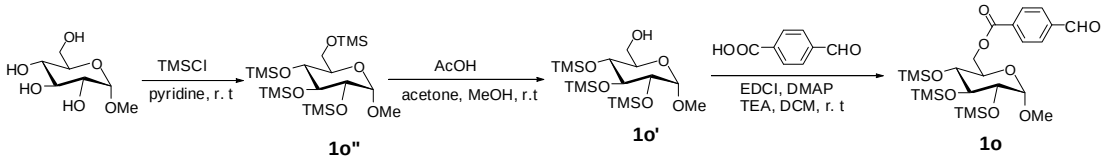

**azocan-1-yl(3-nitrophenyl)methanone (5l)**. Colorless oil; analytical TLC (silica gel 60) (60% EtOAc in hexane) $R_f$ = 0.2; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.24-8.26 (m, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 3.65 (t, *J* = 6.0 Hz, 2H), 3.32 (s, 2H), 1.89 (s, 2H), 1.62 (s, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.9, 148.2, 139.3, 132.7, 130.0, 124.1, 121.8, 51.4, 47.2, 27.1, 26.7, 26.4, 25.7, 24.3; MS (ESI) *m/z* 263 $[M+H]^+$; HRMS (ESI) for $C_{14}H_{19}N_2O_3$ $[M+H]^+$ calcd: 263.1396, found: 263.1383.




***N,N*-diethylformamide (5m)**.[14] Colorless oil; analytical TLC (silica gel 60) (60% EtOAc in hexane) $R_f$ = 0.2; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 3.33 (q, *J* = 14.5, 7.5 Hz, 2H), 3.27 (q, *J* = 14.5, 7.5 Hz, 2H), 1.17 (t, *J* = 7.0 Hz, 3H), 1.11 (t, *J* = 7.0 Hz, 3H).

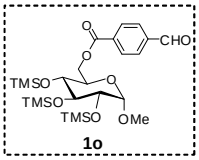



**Compound 1n**. To a solution of 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (0.262 g, 1.0 mmol), 4-formylbenzoic acid (0.150 g, 1.0 mmol), EDC·HCl (0.192 g, 1.0 mmol) and DMAP (0.01 g, 0.1 mmol) in $CH_2Cl_2$ (15 mL) was added triethylamine (1 mL). After stirring at room temperature for overnight, the reaction mixture was diluted with $CH_2Cl_2$ (20 mL) and washed with 5% HCl aqueous solution (3×10 mL), $NaHCO_3$ saturated aqueous solution (3×10 mL), and brine (3×10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was concentrated. The residue was purified by flash column chromatography (30% EtOAc in hexane) to give **1n** as a colorless oil. Yield: 92%. $^1$H NMR (500 MHz, $CDCl_3$) *δ* 10.1 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2H), 5.58 (d, *J* = 5.0 Hz, 1H), 4.67 (dd, *J* = 7.5 Hz, 2.5 Hz, 1H), 4.57 (dd, *J* = 11.5 Hz, 4.5 Hz, 1H), 4.48 (dd, *J* = 11.5 Hz, 8.0 Hz, 1H), 4.34-4.48 (m, 2H), 4.19-4.22 (m, 1H), 1.49-1.53 (2s, 6H), 1.35-1.37 (2s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 191.8, 165.6, 139.4, 135.2, 130.5, 129.7, 109.9, 109.0, 96.5, 71.3, 70.9, 70.7, 66.3, 64.7, 26.2, 26.2, 25.1, 24.7; ESI-MS m/z 393 $[M+H]^+$; HRMS (ESI) for $C_{20}H_{25}O_8$ $[M+H]^+$ calcd: 393.1471, found: 393.1475.



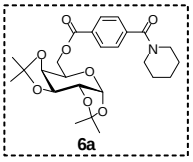

**Compound 1o'**. To a solution of **1o"**[15] (0.173 g, 3.0 mmol) in acetone (7 mL) and MeOH (10 mL) was added acetic acid (0.4 mL, 6.0 mmol) dropwise at 0 °C. After

stirring at room temperature for 2 h. The solvent was concentrated in vacuo. The residue was purified by flash column chromatography (50% EtOAc in hexane) to give **1o'** as a white solid. Yield: 50%. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.62 (d, $J$ = 3.5, 1H), 3.75-3.79 (m, 2H), 3.7 (dd, $J$ = 12.0, 5.0 Hz, 1H), 3.57-3.60 (m, 1H), 3.46-3.49 (m, 2H), 3.36 (s, 3H), 0.16-0.18 (3s, 27H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 100.2, 75.0, 74.0, 72.2, 71.8, 62.1, 55.1, 1.53, 1.27, 0.73; ESI-MS m/z 411 $[M+H]^+$; HRMS (ESI) for $C_{16}H_{39}O_6Si_3$ $[M+H]^+$ calcd: 411.1976, found: 411.1981.



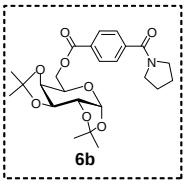
**1o**

**Compound 1o**. To a solution of **1o'** (0.412 g, 1.0 mmol), 4-formylbenzoic acid (0.150 g, 1.0 mmol), EDC·HCl (0.193 g, 1.0 mmol) and DMAP (0.01 g, 0.1 mmol) in $CH_2Cl_2$ (15 mL) was added triethylamine (1 mL). After stirring at room temperature for overnight, the reaction mixture was diluted with $CH_2Cl_2$ (20 mL) and washed with 5% HCl aqueous solution (3×10 mL), $NaHCO_3$ saturated aqueous solution (3×10 mL), and brine (3×10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was concentrated. The residue was purified by flash column chromatography (20% EtOAc in hexane) to give **1o** as a colorless oil. Yield: 92%. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.1 (s, 1H), 8.22 (d, $J$ = 8.0 Hz, 2H), 7.98 (d, $J$ = 7.5 Hz, 2H), 4.63-4.69 (m, 2H), 4.38 (dd, $J$ = 11.5 Hz, 5.5 Hz, 1H), 3.88-3.91 (m, 1H), 3.82 (t, $J$ = 9.0 Hz, 1H), 3.54-3.59 (m, 2H), 3.38 (s, 3H), 0.16-0.18 (3s, 27H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 191.7, 165.6, 139.5, 135.2, 130.4, 129.8, 100.0, 109.0, 75.4, 74.0, 72.8, 69.7, 65.0, 55.1, 1.58, 1.21, 0.79; ESI-MS m/z 543 $[M+H]^+$; HRMS (ESI) for $C_{24}H_{43}O_8Si_3$ $[M+H]^+$ calcd: 543.2187, found: 543.2200.

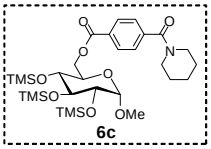

**6a**

**Compound 6a**. White solid; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.4; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.07 (d, $J$ = 8.5 Hz, 2H), 7.43 (d, $J$ = 8.5 Hz, 2H), 5.55 (d, $J$ = 5.0 Hz, 1H), 4.65 (dd, $J$ = 7.5 Hz, 2.5 Hz, 1H), 4.50 (dd, $J$ = 11.5 Hz,

5.0 Hz, 1H), 4.43 (dd, *J* = 11.5 Hz, 8.0 Hz, 1H), 4.30-4.35 (m, 2H), 4.16-4.19 (m, 1H), 3.70 (br, 2H), 3.27 (br, 2H), 1.67 (br, 4H), 1.47-1.50 (m, 8H), 1.33 (d, *J* = 11.0 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.4, 166.0, 141.2, 131.0, 130.1, 127.0, 110.0, 109.0, 96.6, 71.4, 70.9, 70.7, 66.4, 64.4, 26.3, 26.2, 25.2, 24.8, 24.7; ESI-MS m/z 476 $[M+H]^+$; HRMS (ESI) for $C_{25}H_{34}NO_8$ $[M+H]^+$ calcd: 476.2206, found: 476.2210.




**Compound 6b**. Yellow solid; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.2; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.07 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 5.55 (d, *J* = 5.0 Hz, 1H), 4.64 (dd, *J* = 7.5, 2.0 Hz, 1H), 4.53 (dd, *J* = 11.5 Hz, 5.0 Hz, 1H), 4.41-4.45 (m, 1H), 4.31-4.35 (m, 2H), 4.16-4.19 (m, 1H), 3.64 (t, *J* = 7.0 Hz, 2H), 3.36 (t, *J* = 6.5 Hz, 2H), 1.93-1.99 (m, 2H), 1.85-1.90 (m, 2H), 1.46-1.50 (2s, 6H), 1.32-1.34 (2s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.9, 166.0, 141.7, 131.3, 130.0, 127.3, 110.0, 109.0, 96.5, 66.4, 64.4, 49.7, 46.5, 31.8, 26.6, 26.2, 26.1, 25.2, 24.7, 24.6, 22.9; ESI-MS m/z 461 $[M+H]^+$; HRMS (ESI) for $C_{24}H_{32}NO_8$ $[M+H]^+$ calcd: 476.2206, found: 476.2210.




**Compound 6c**. White solid; analytical TLC (silica gel 60) (50% EtOAc in hexane) $R_f$ = 0.3; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.08 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 4.62-4.65 (m, 2H), 4.34 (dd, *J* = 11.5 Hz, 5.5 Hz, 1H), 3.85-3.89 (m, 1H), 3.81 (t, *J* = 8.5 Hz, 1H), 3.72 (br, 2H), 3.52-3.59 (m, 2H), 3.36 (s, 3H), 3.29 (br, 2H), 1.51-1.69 (m, 6H), 1.64-1.71 (3s, 27H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.4, 165.9, 141.3, 131.1, 130.0, 127.0, 100.0, 75.4, 74.0, 72.9, 69.7, 64.6, 55.1, 24.7, 1.57, 1.21, 0.79; ESI-MS m/z 626 $[M+H]^+$; HRMS (ESI) for $C_{29}H_{52}NO_8Si_3$ $[M+H]^+$ calcd: 626.2922, found: 626.2930.

**Procedure for Modification of D-Raffinose Aldeheyde 1p with Secondary amines 2**. A solution of D-raffinose aldehyde **1p**[16] (10 mM ) and **2** (5 equiv.) in the presence of $KAuCl_4$ (50 mol%) and $K_2CO_3$ (10 mol%) in $H_2O$ was kept at 40 °C for 12 h. The crude reaction mixture was centrifuged. The clear liquor was taken out for determination of aldehyde conversion by LC-MS.

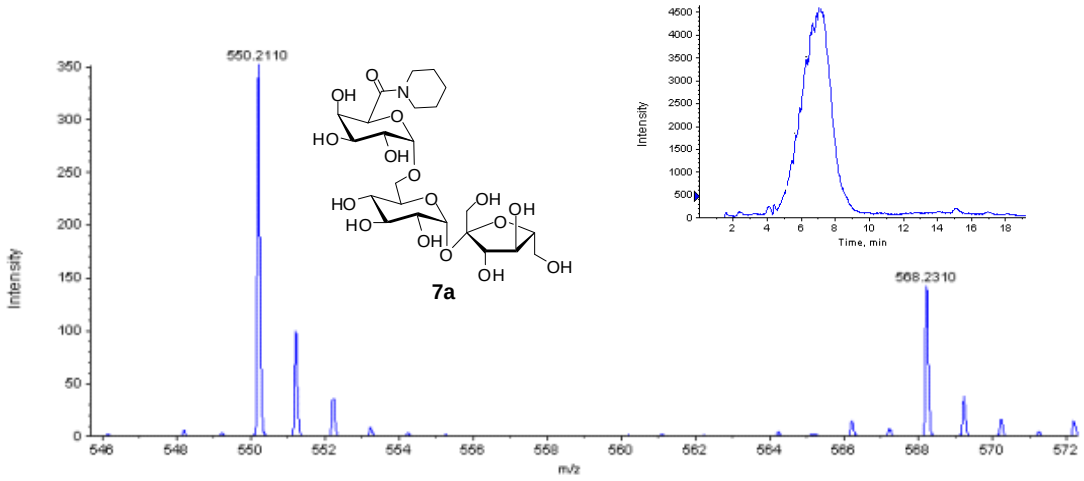



**Figure S2** MS spectrum of **7a** ($[M\text{-}2H_2O+H]^+$ = m/z 550.21, $[M\text{-}H_2O+H]^+$ = m/z 568.23) and the XIC chromatogram of **7a** at = 7.0 min (inset).

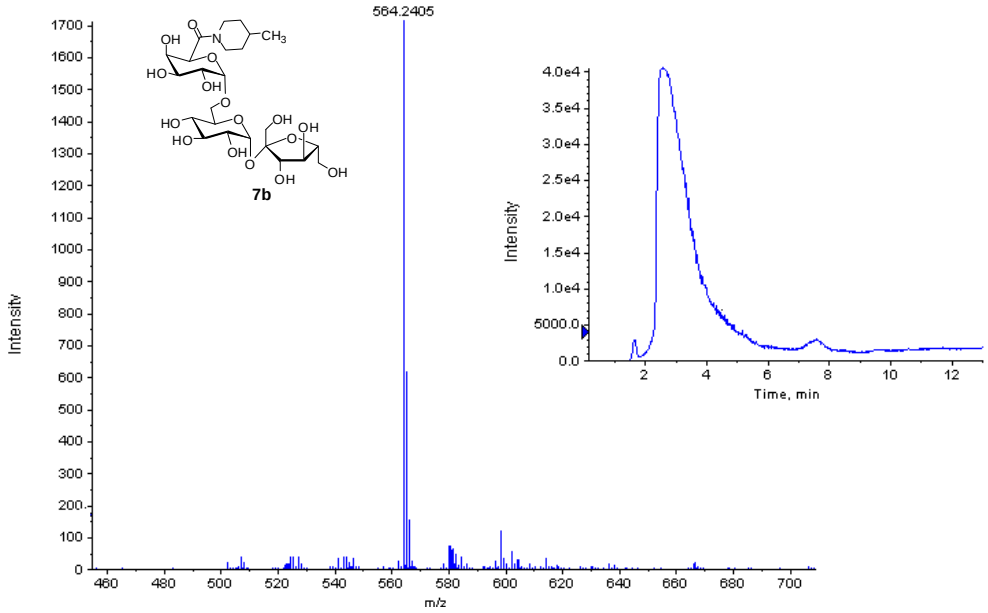



**Figure S3** MS spectrum of **7b** ($[M\text{-}2H_2O+H]^+$ = m/z 564.24) and the XIC chromatogram of **7b** at = 3.2 min (inset).

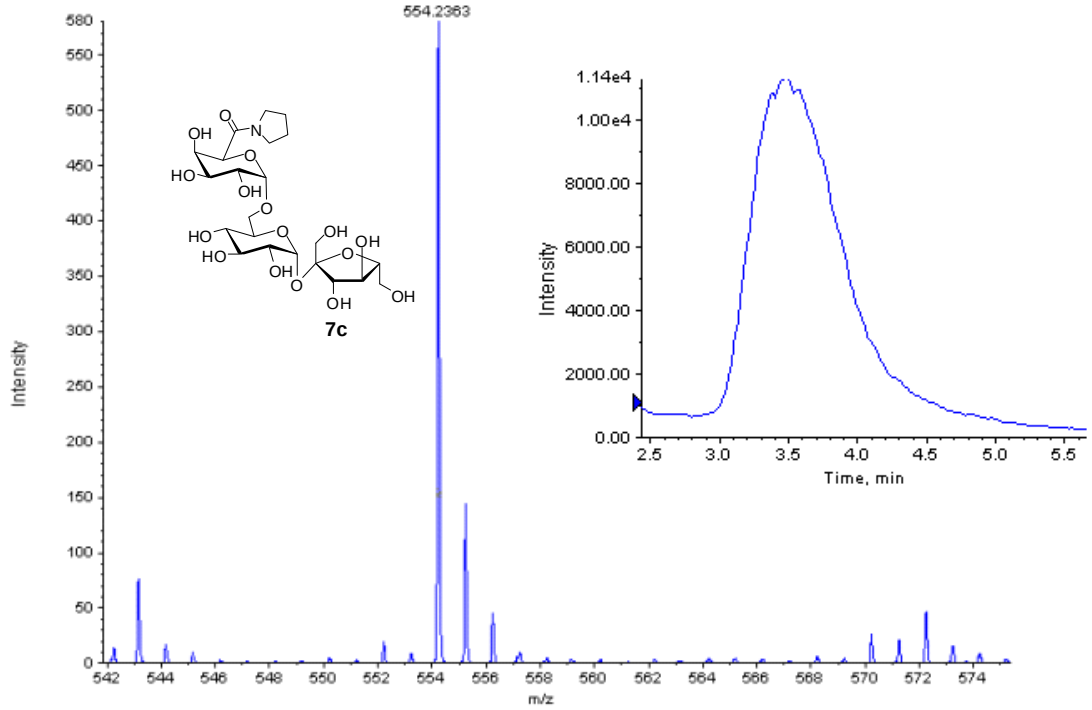



**Figure S4** MS spectrum of **7c** ($[M\text{-}H_2O+H]^+$ = m/z 554.24) and the XIC chromatogram of **7c** at = 3.5 min (inset).

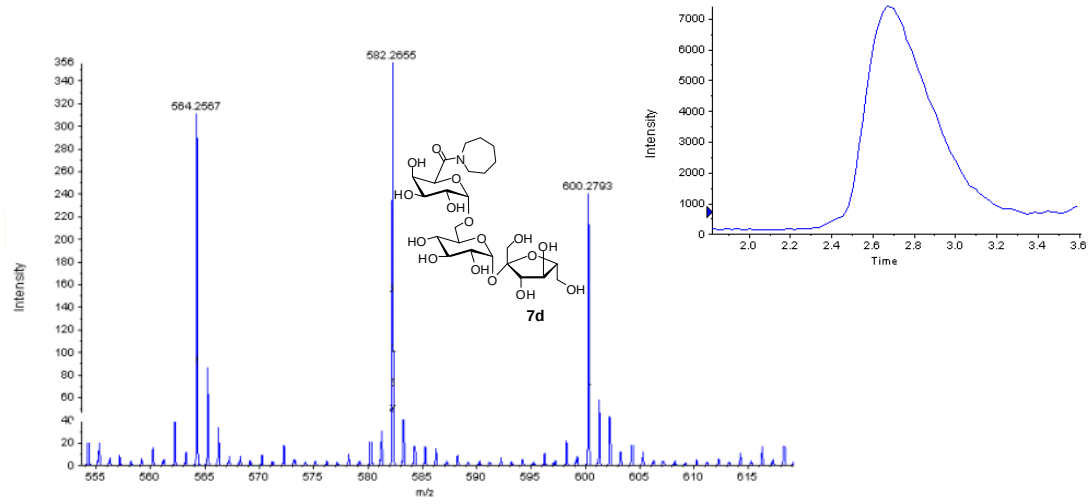



**Figure S5** MS spectrum of **7d** ($[M\text{-}2H_2O+H]^+$ = m/z 564.25, $[M\text{-}H_2O+H]^+$ = m/z 582.27, $[M+H]^+$ = m/z 600.28) and the XIC chromatogram of **7d** at = 2.8 min (inset).

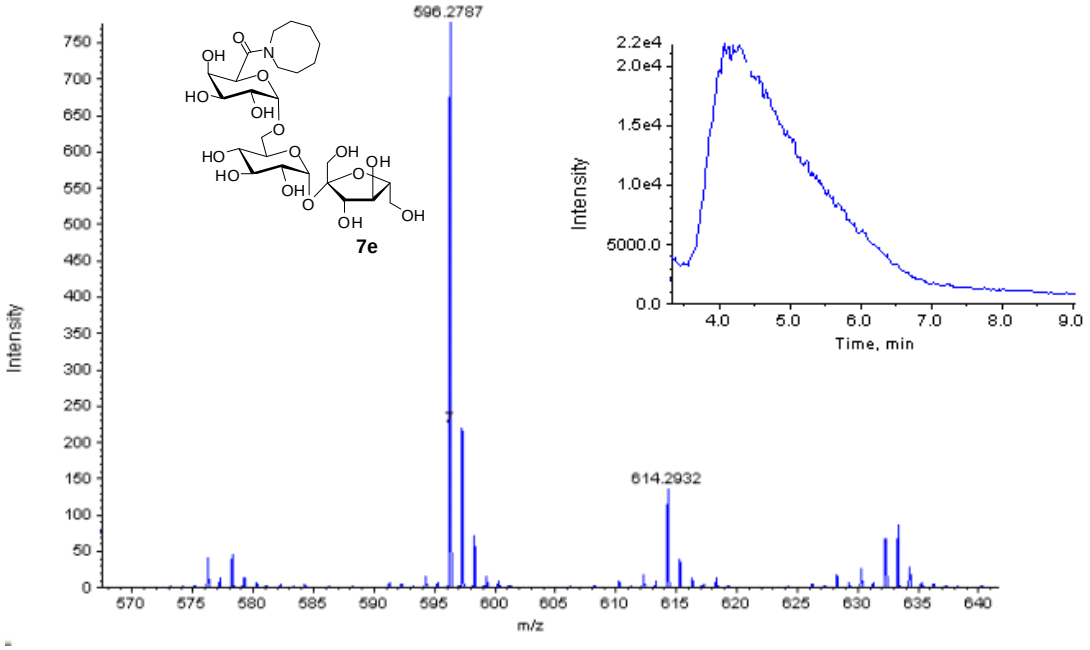



**Figure S6** MS spectrum of **7e** ($[M\text{-}H_2O+H]^+$ = m/z 596.27, $[M+H]^+$ = m/z 614.29 and the XIC chromatogram of **7e** at = 4.5 min (inset).

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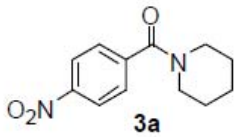
$^{1}$H NMR

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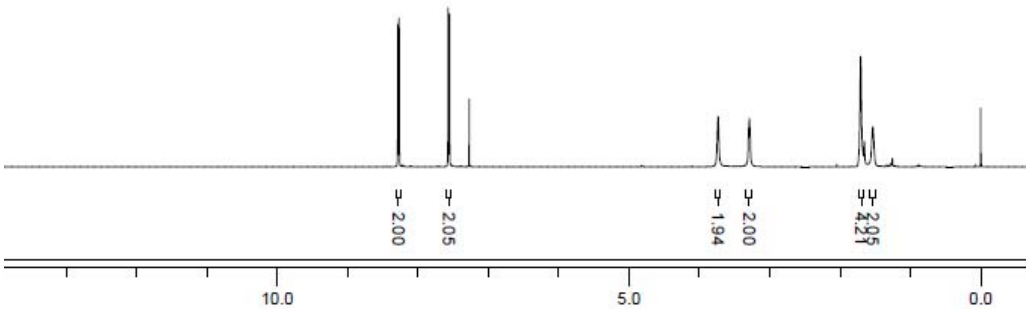


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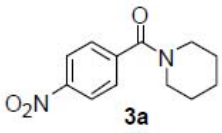


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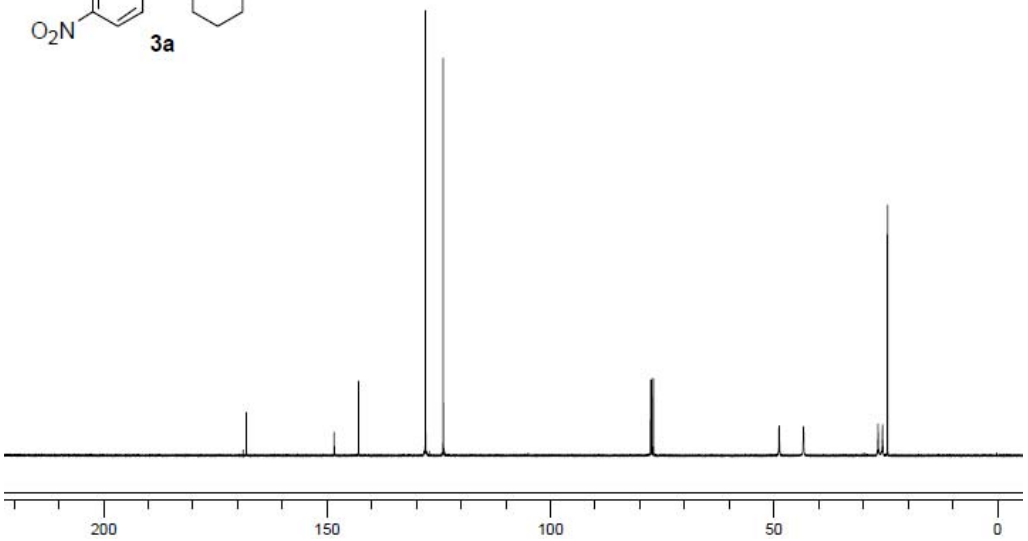

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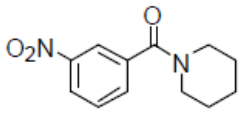


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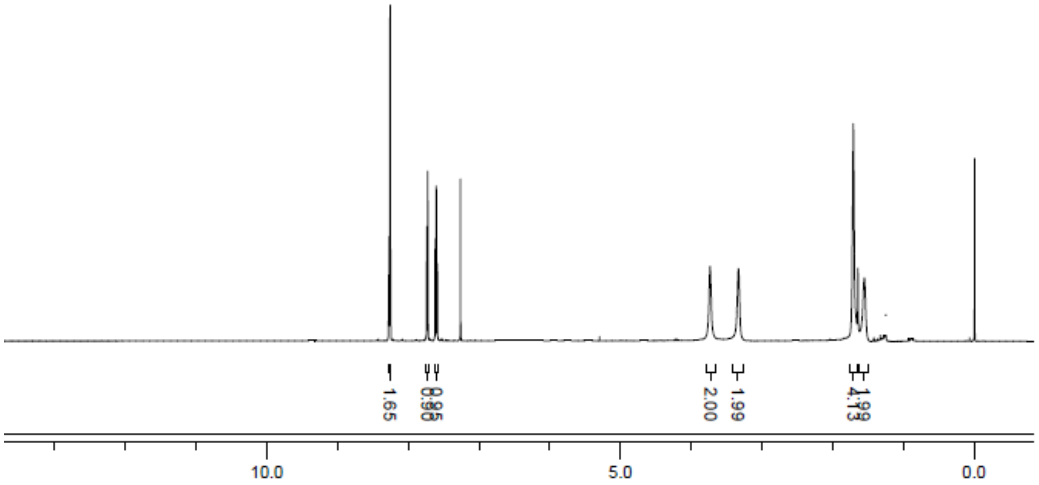


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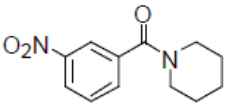


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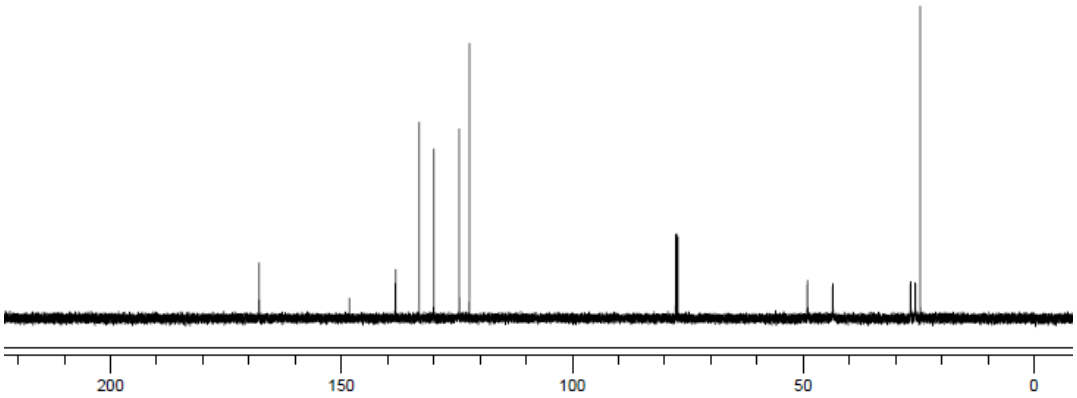

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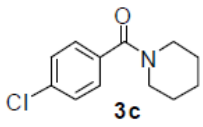


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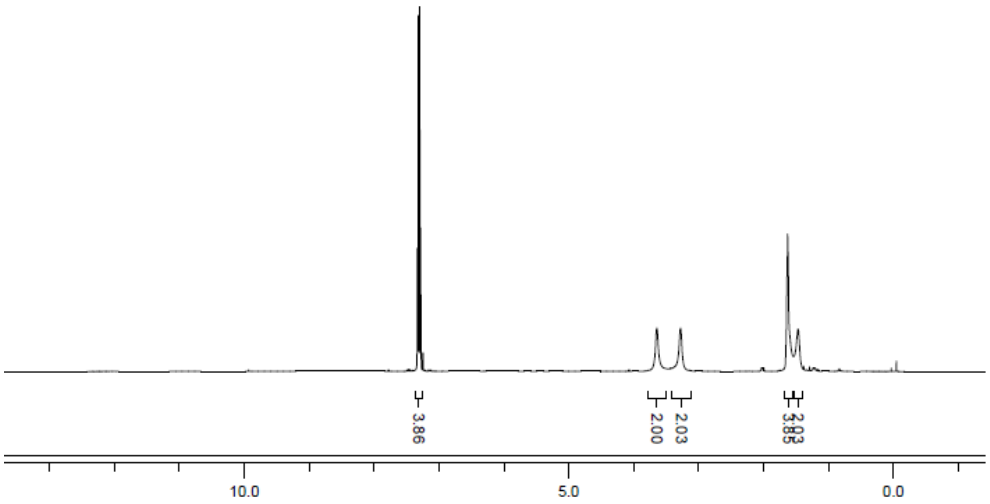


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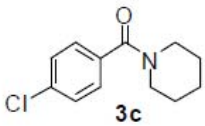


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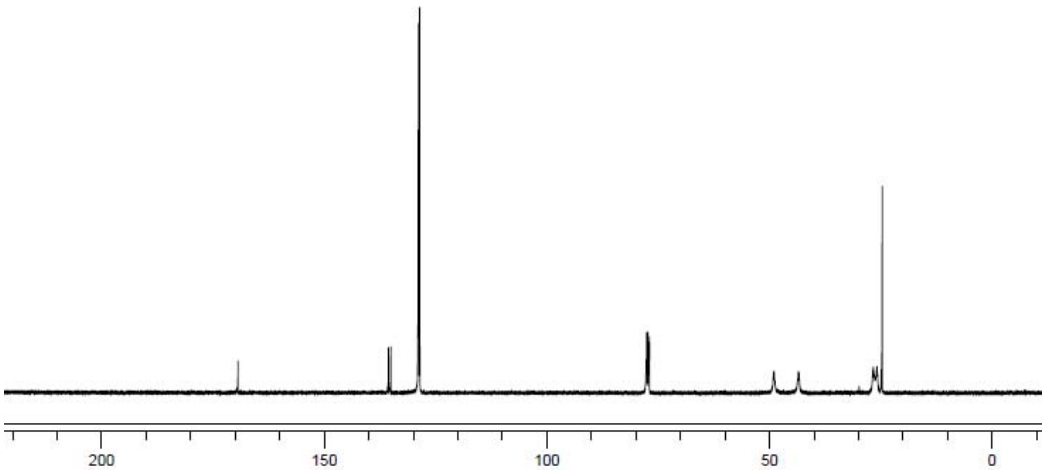

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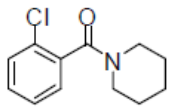


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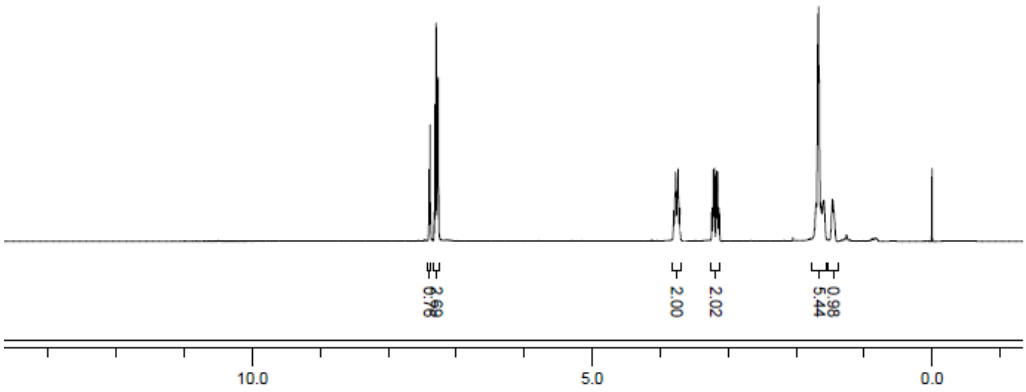


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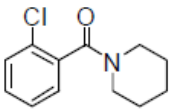


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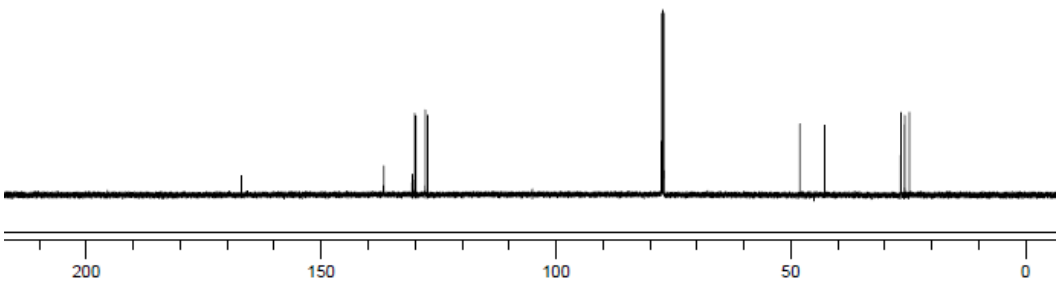

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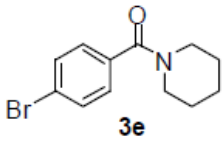


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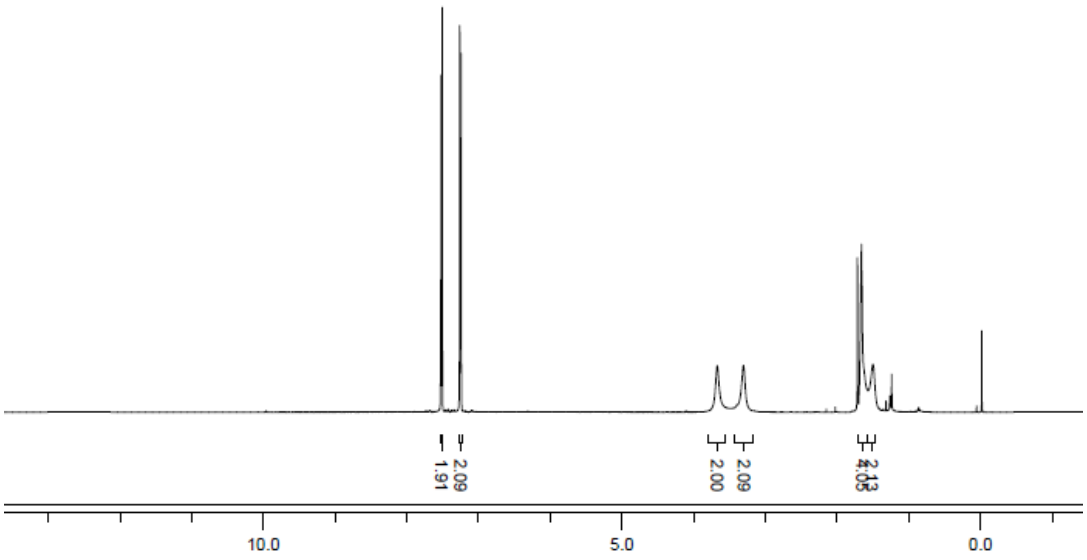


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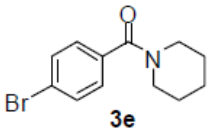


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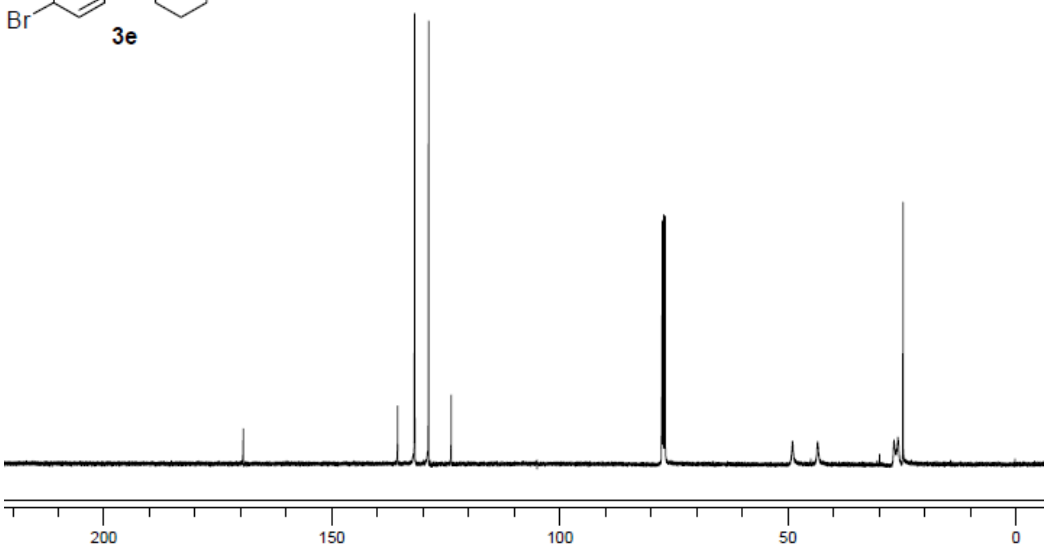

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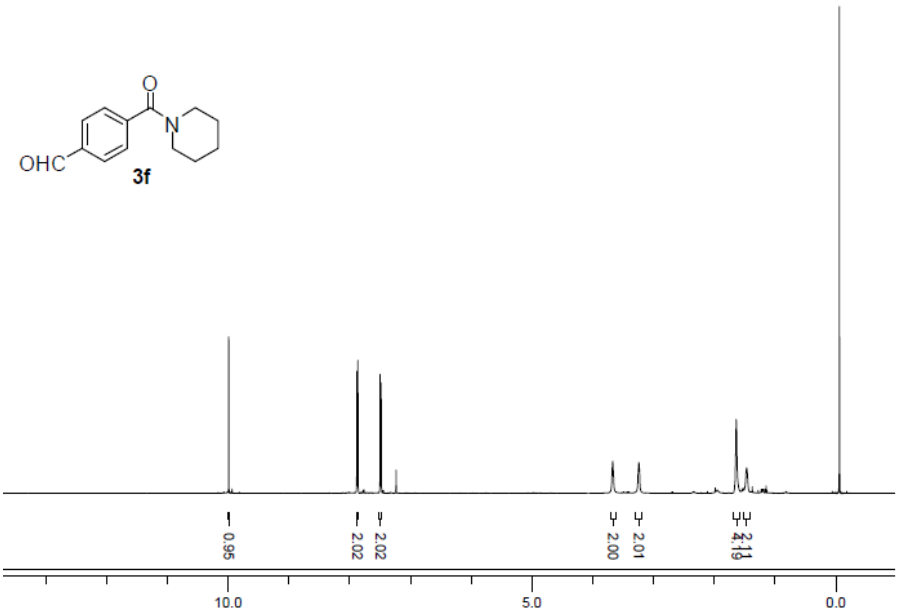


3f

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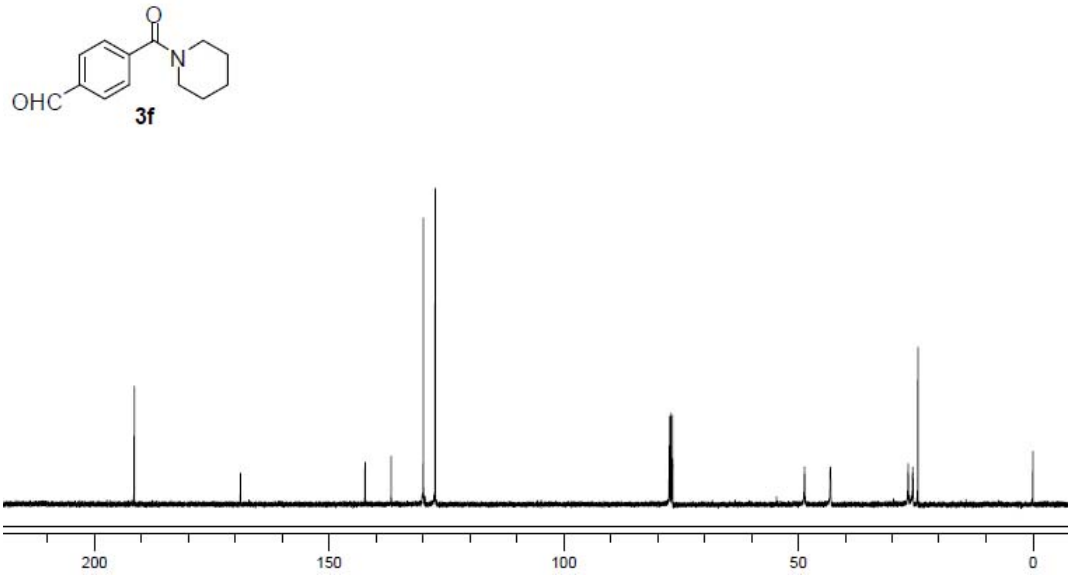


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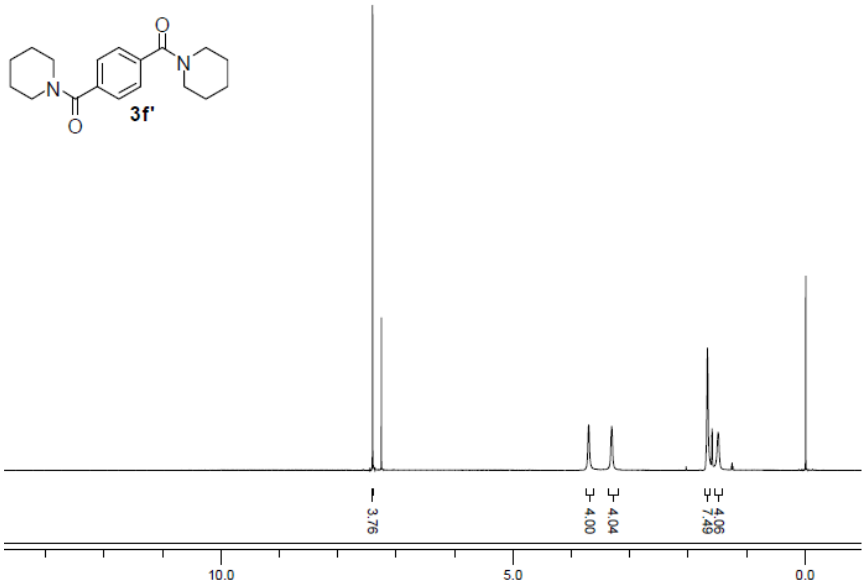


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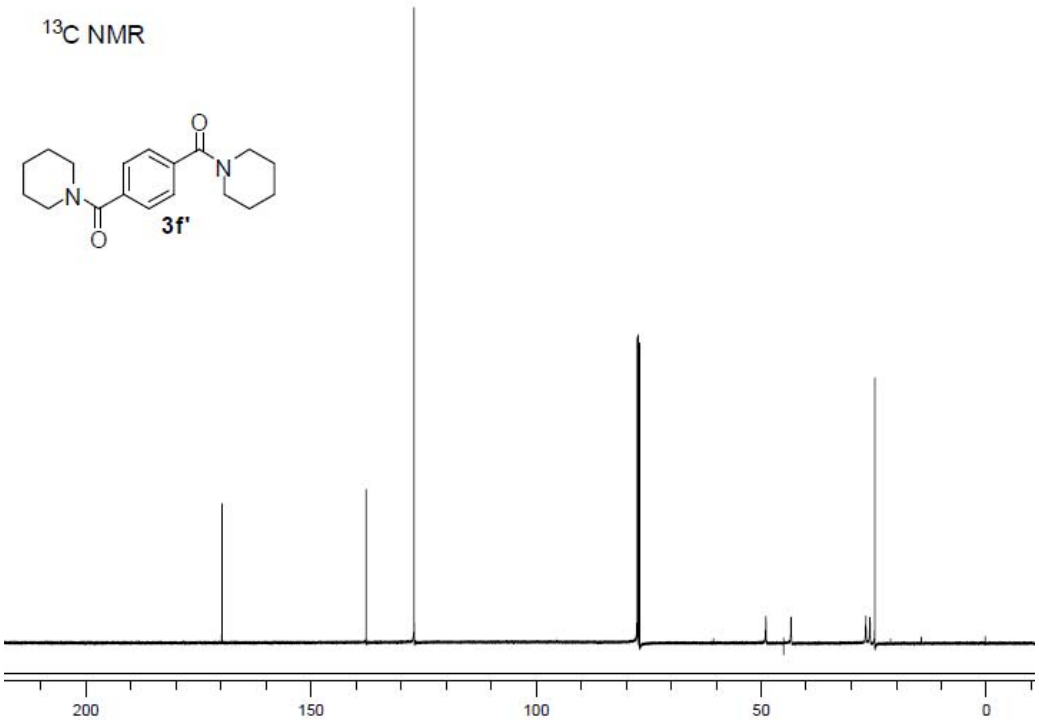

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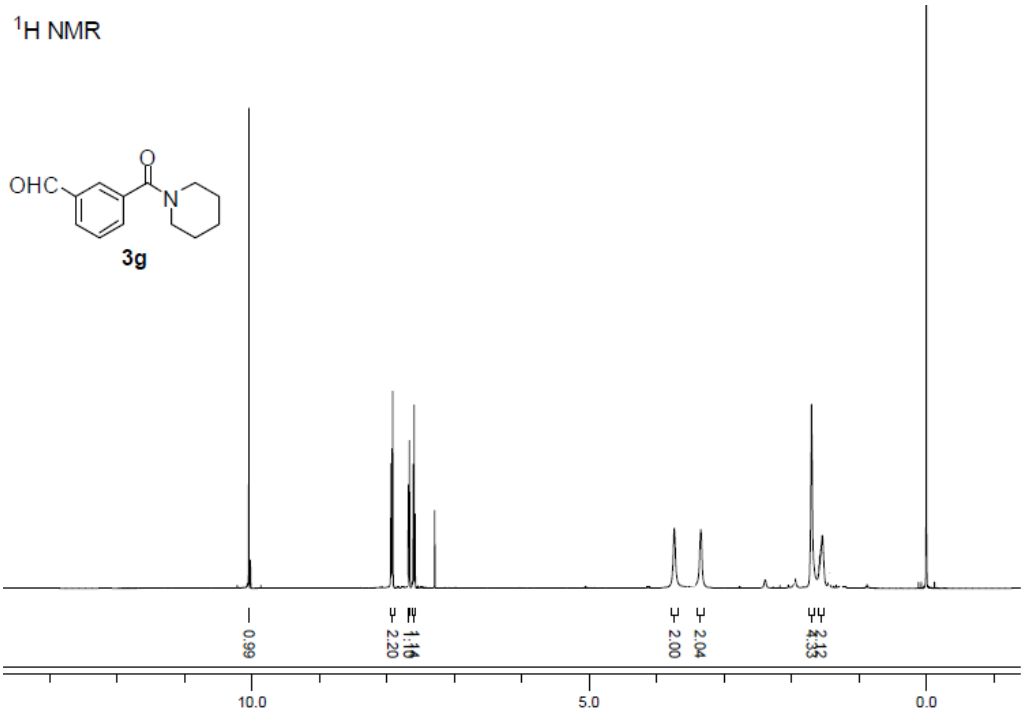


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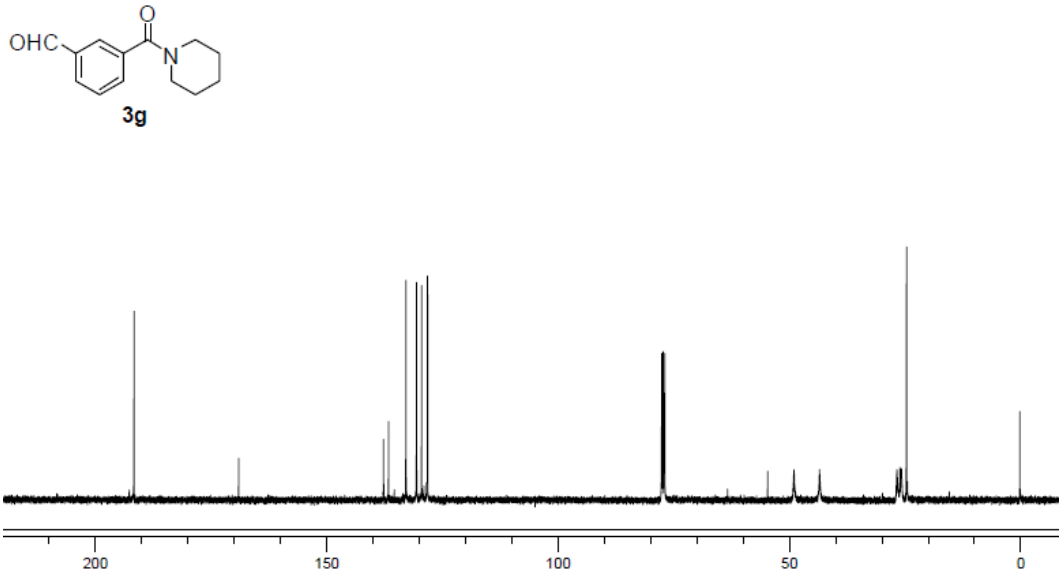


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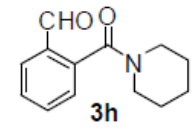


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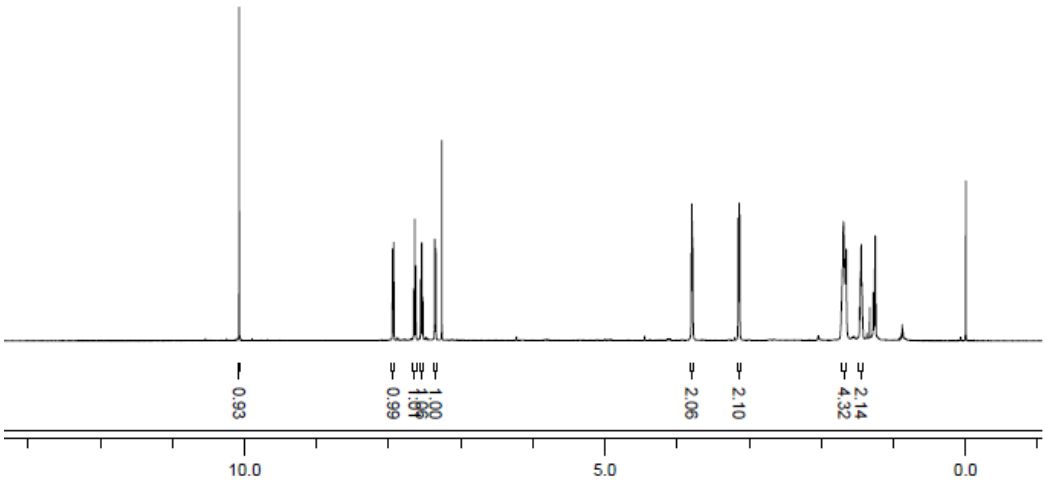


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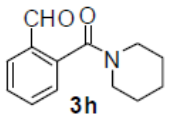


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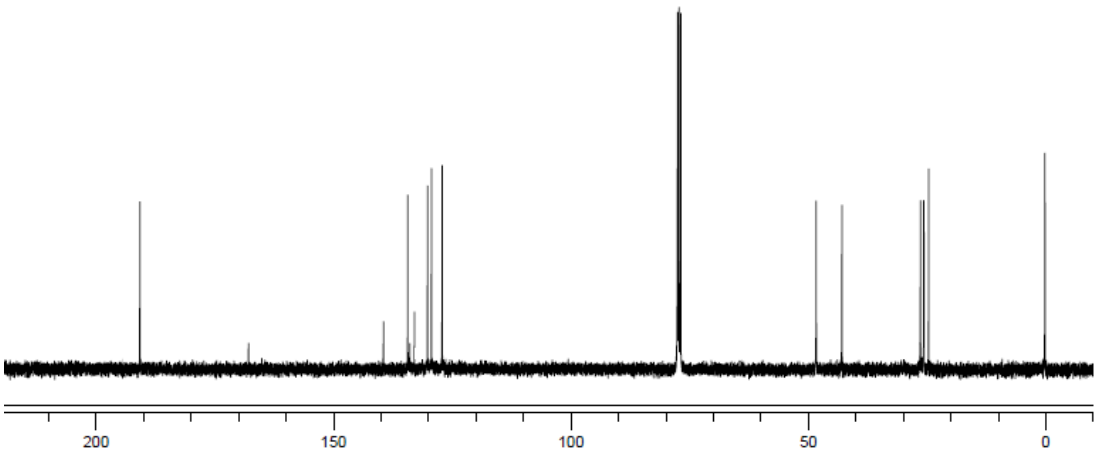

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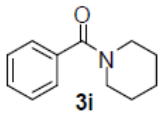

**3i**




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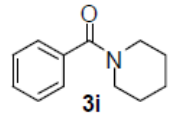

**3i**

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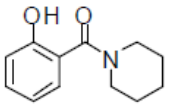


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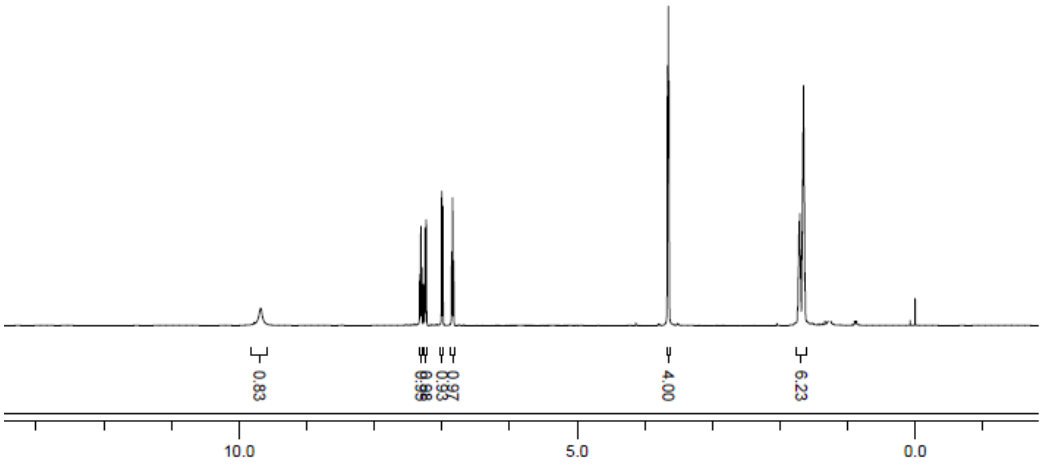


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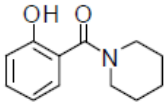


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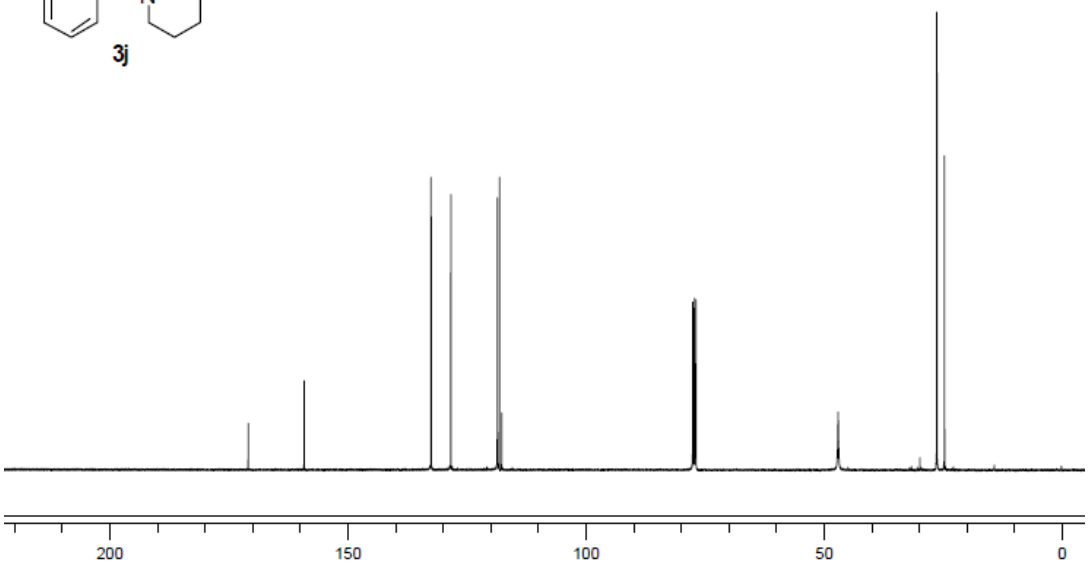

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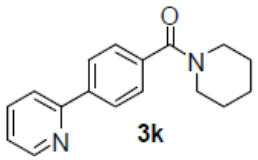


**3k**




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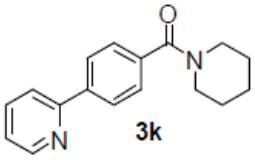


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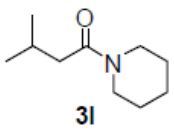

**3l**




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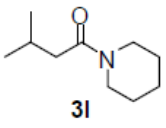

**3l**

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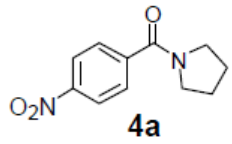
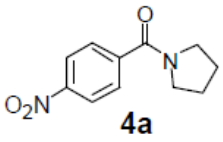



**4a**




$^{13}$C NMR




**4a**

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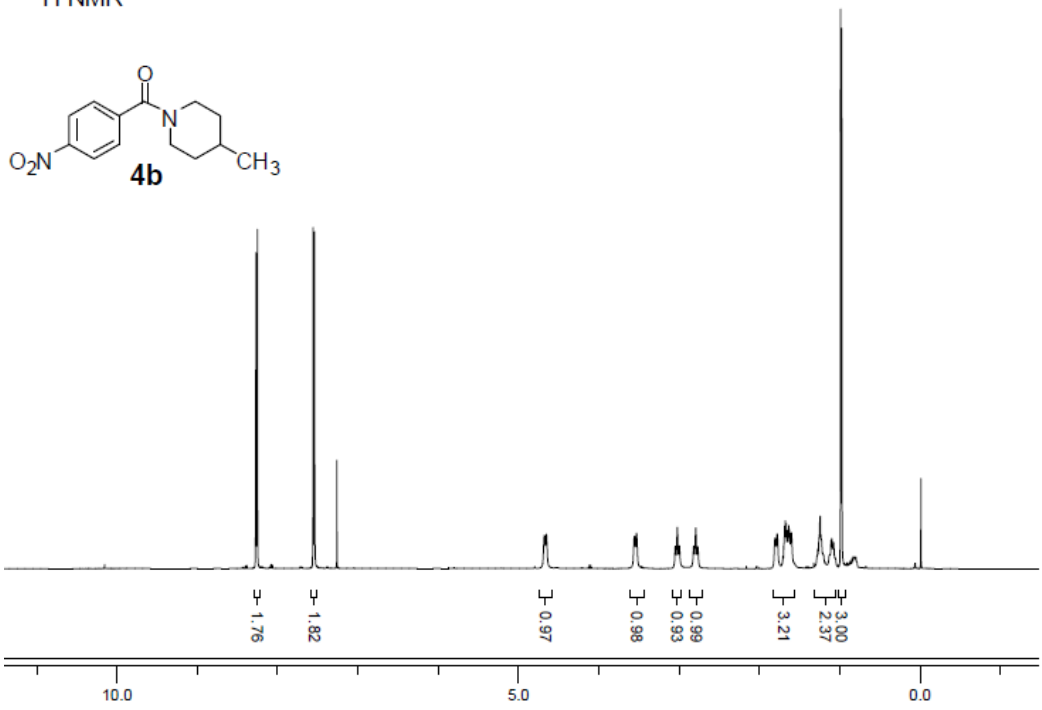


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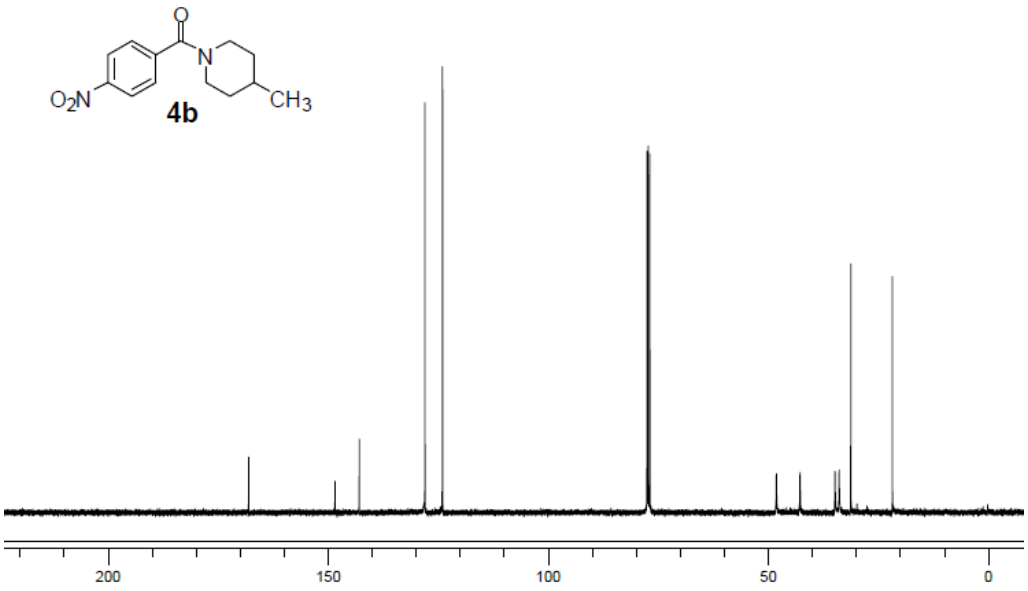
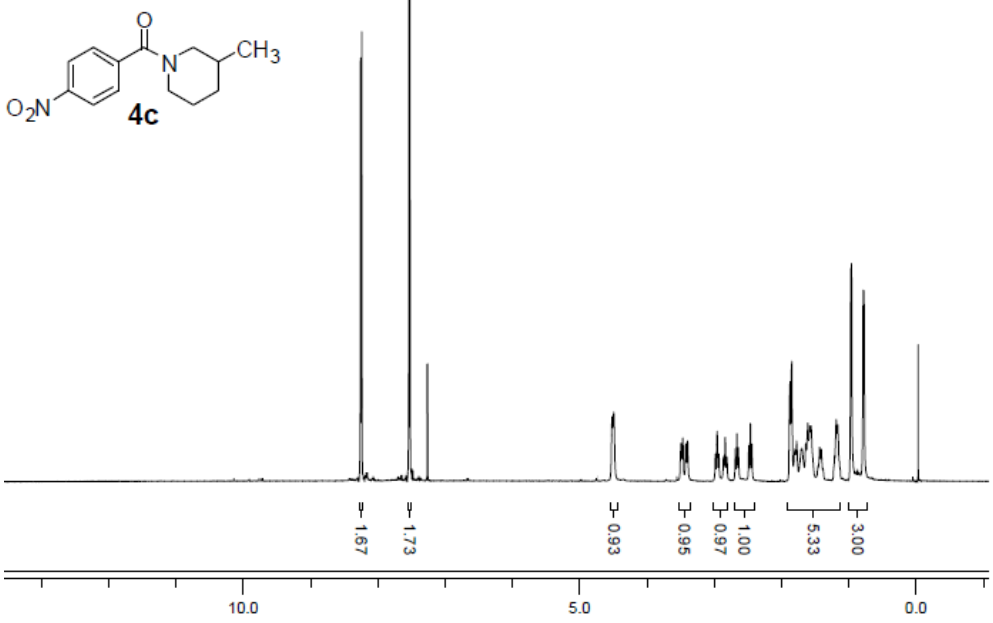
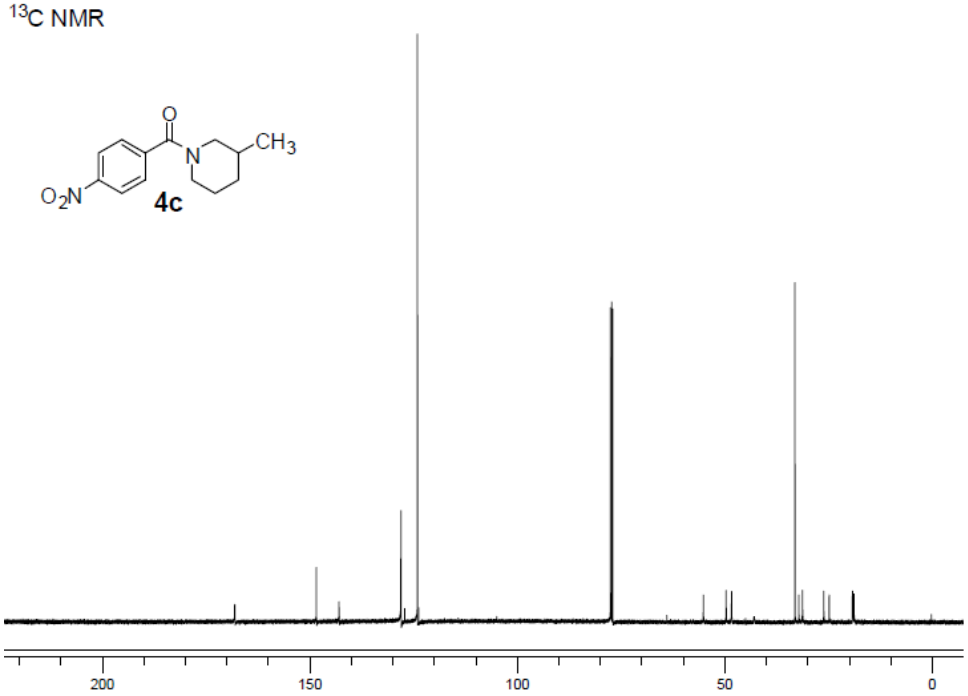


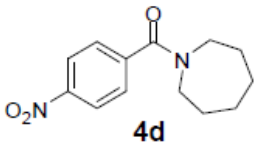
$^1$H NMR




$^{13}$C NMR



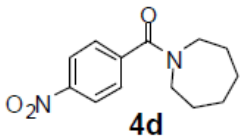
$^1$H NMR



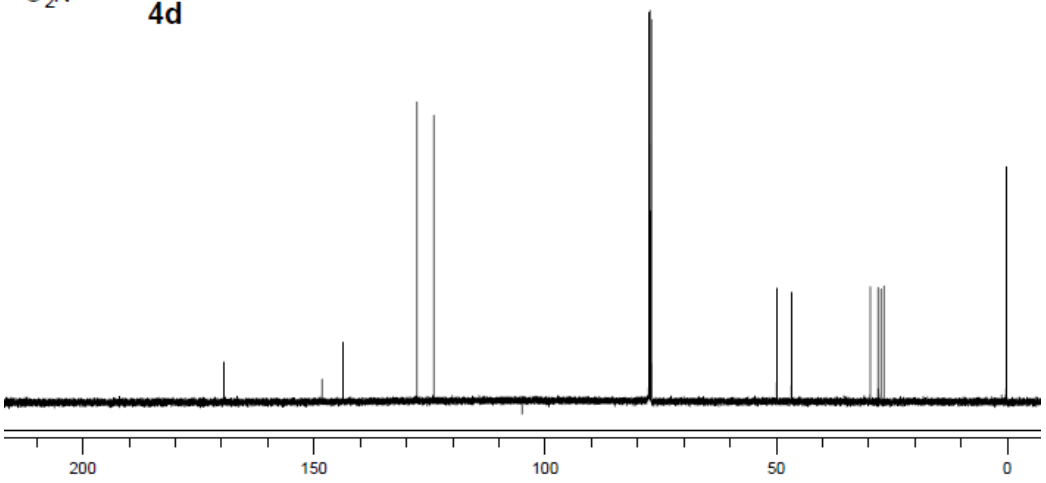

**4d**



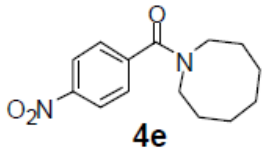

$^{13}$C NMR




**4d**



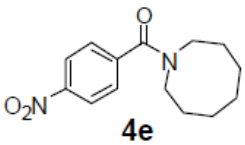
$^1$H NMR



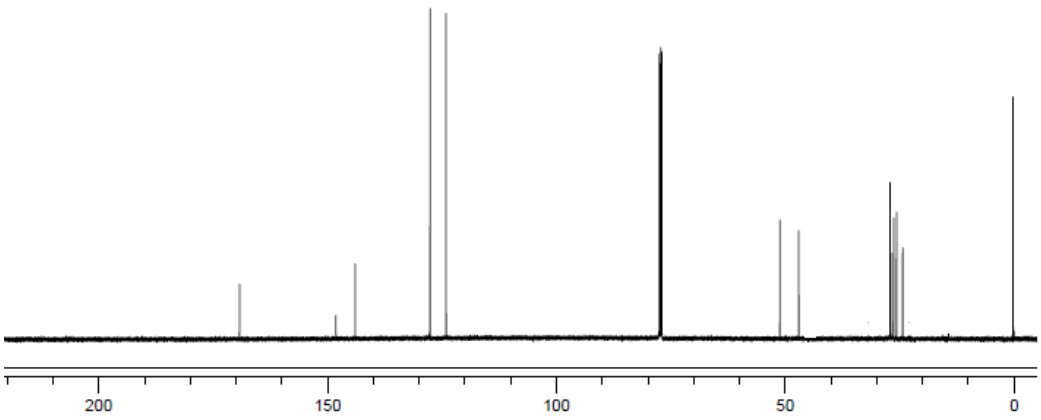
**4e**



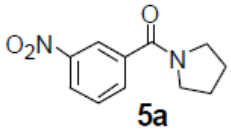

$^{13}$C NMR



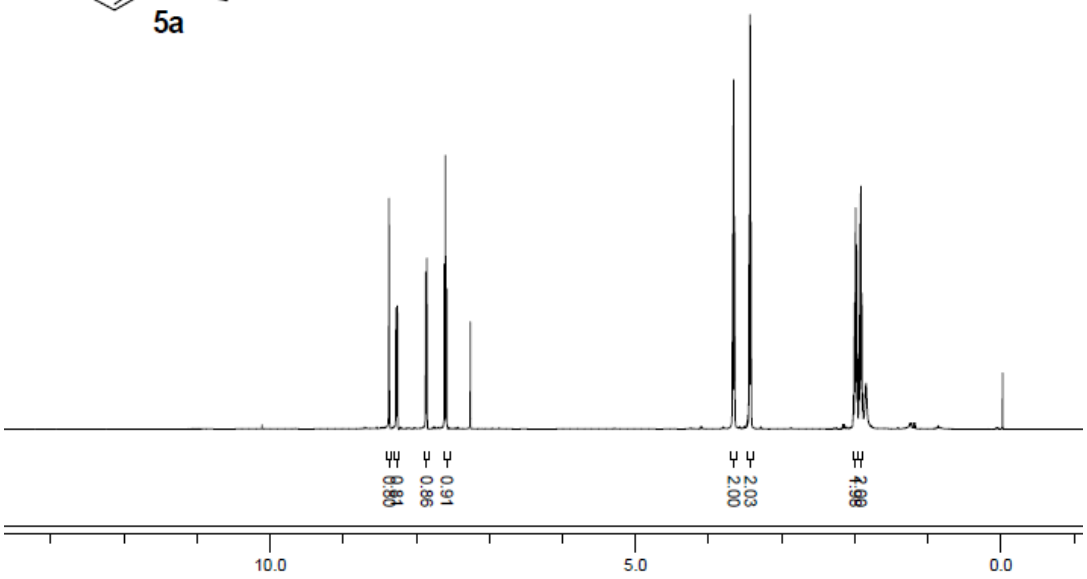
**4e**



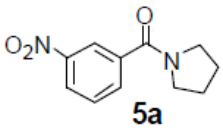
$^{1}$H NMR



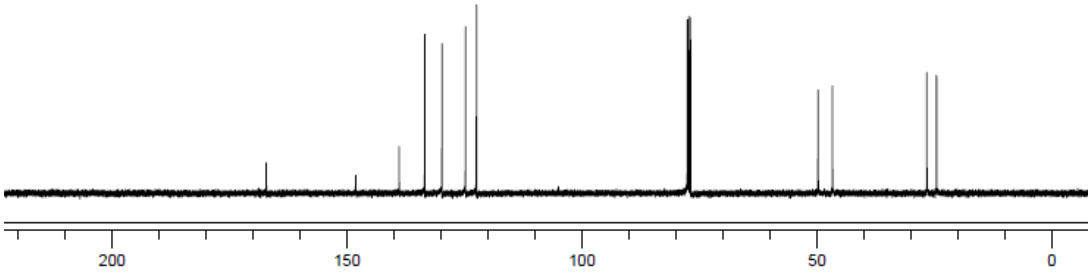
**5a**



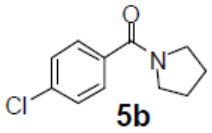

$^{13}$C NMR



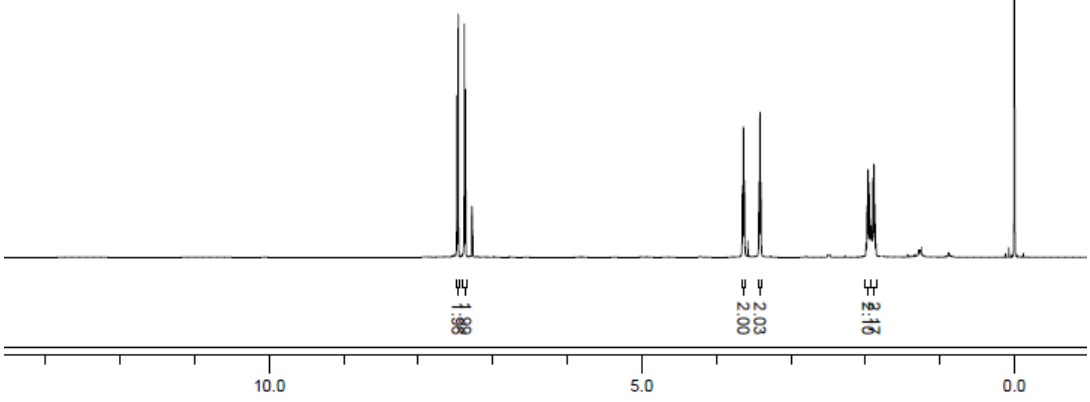
**5a**



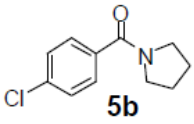
$^{1}$H NMR




**5b**

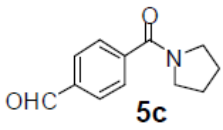



$^{13}$C NMR




**5b**

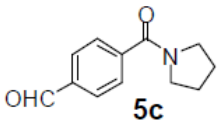
$^{1}$H NMR



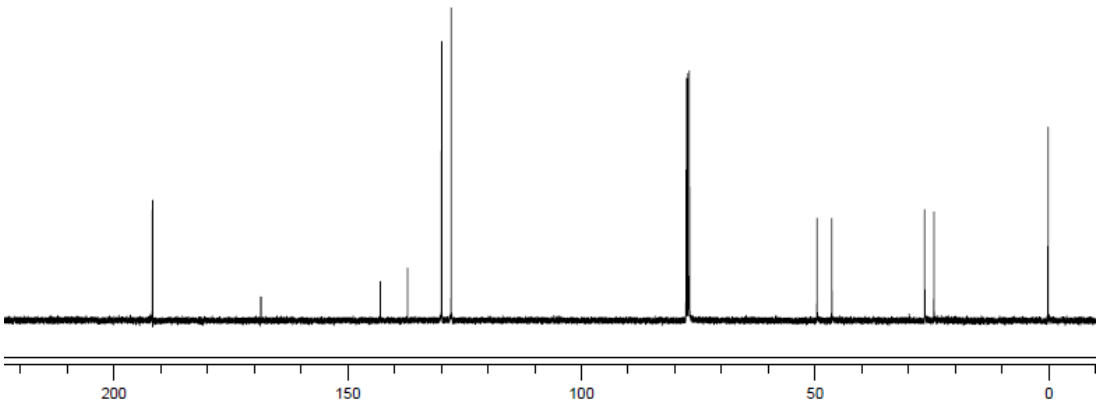

**5c**



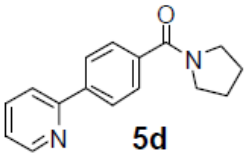

$^{13}$C NMR



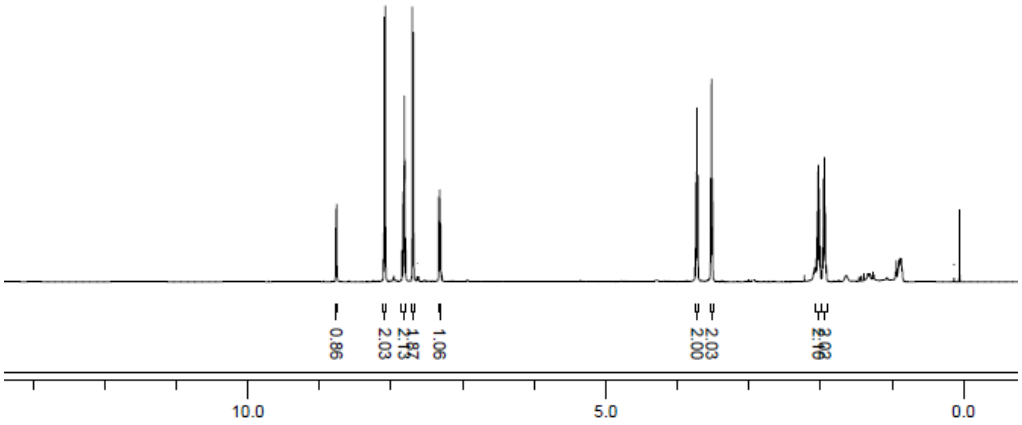

**5c**



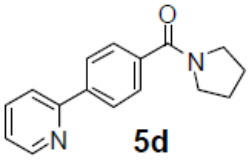
$^{1}$H NMR



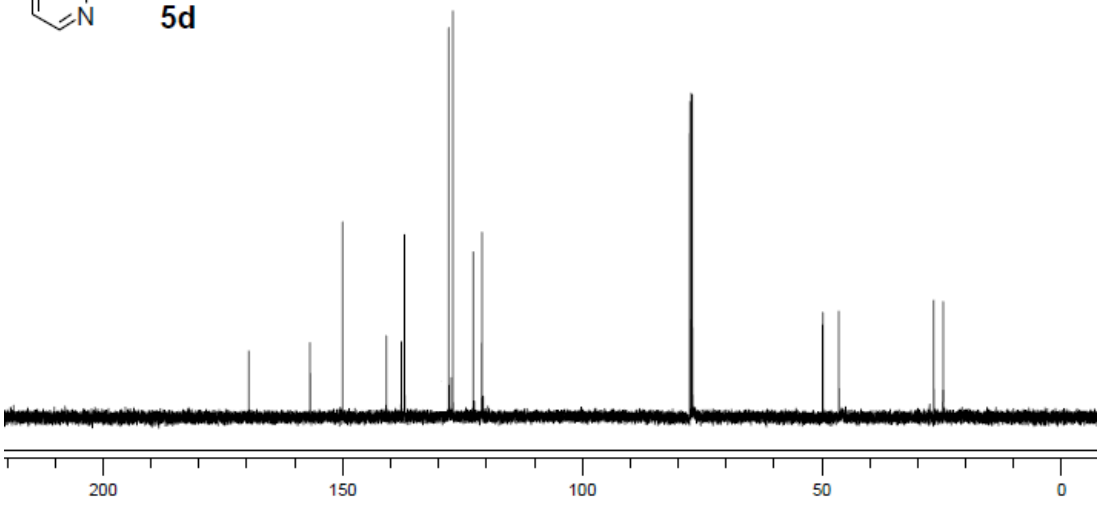

**5d**



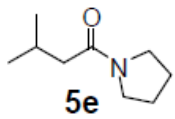

$^{13}$C NMR




**5d**



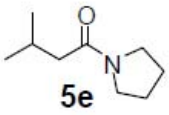
$^{1}$H NMR



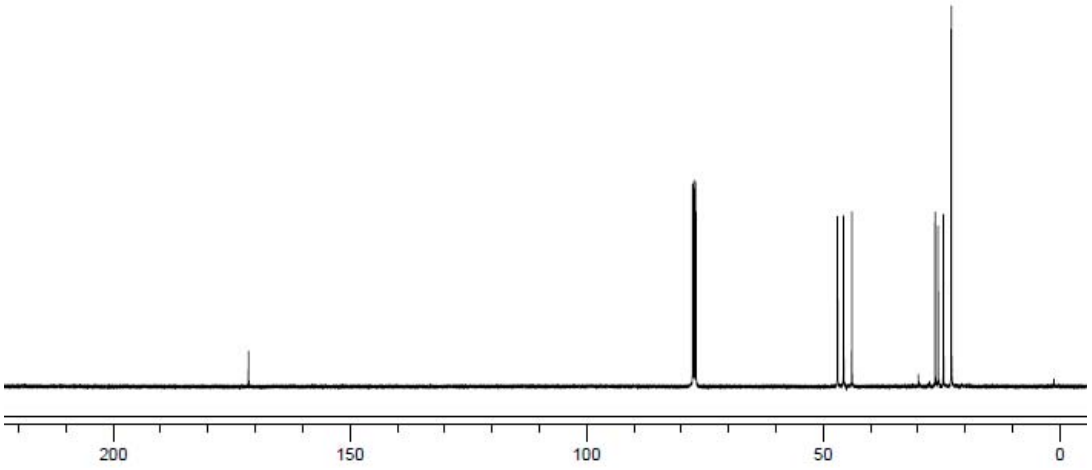

**5e**



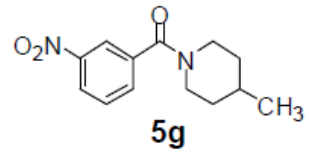

$^{13}$C NMR




**5e**



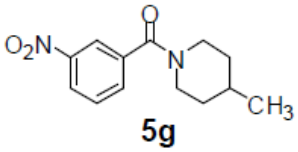
$^1$H NMR



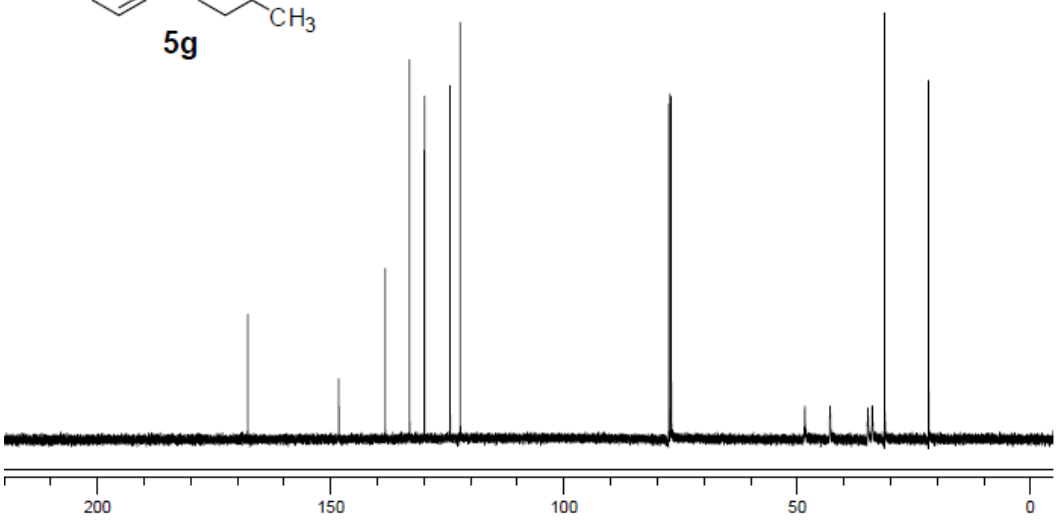
**5g**



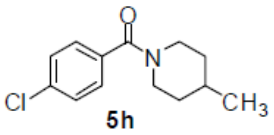

$^{13}$C NMR



**5g**



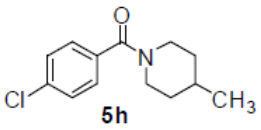
$^1$H NMR




**5h**

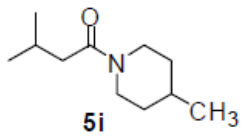



$^{13}$C NMR




**5h**

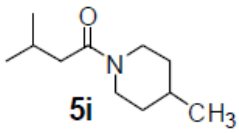
$^{1}$H NMR




**5i**

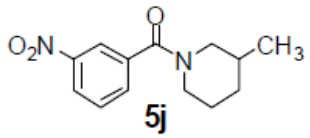



$^{13}$C NMR

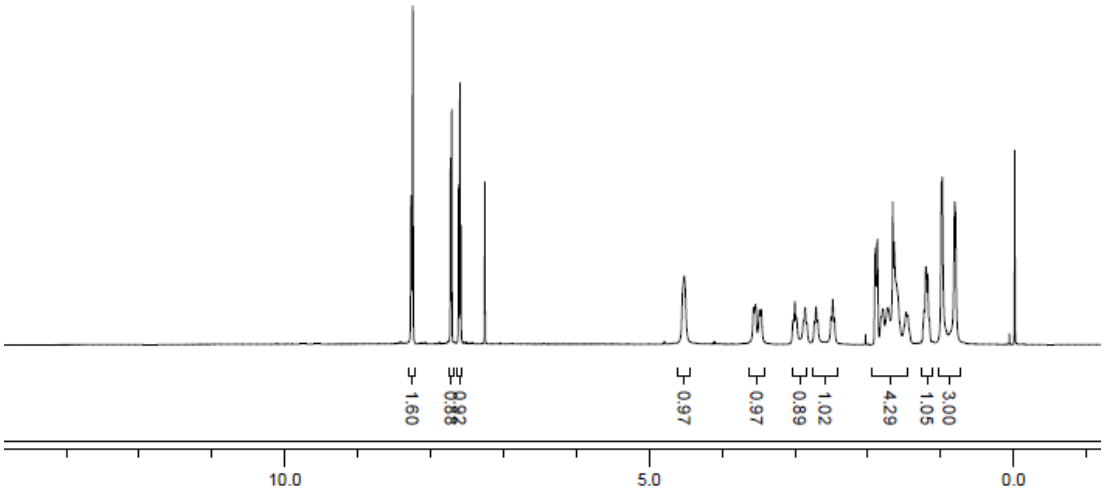



**5i**

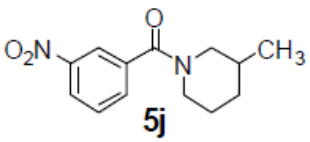
$^{1}$H NMR




**5j**

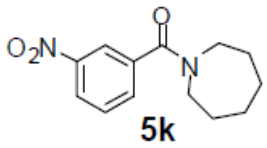



$^{13}$C NMR




**5j**

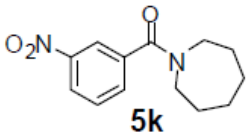
$^{1}$H NMR



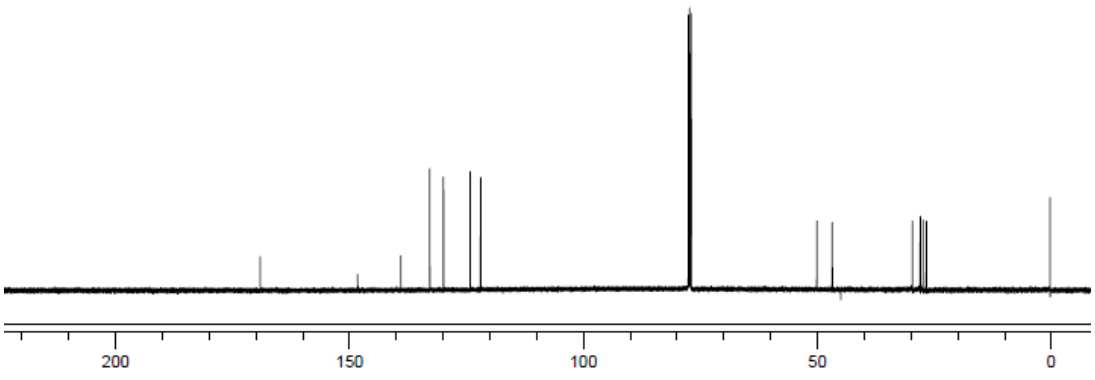
**5k**



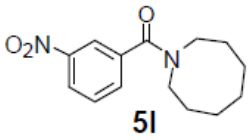

$^{13}$C NMR



**5k**



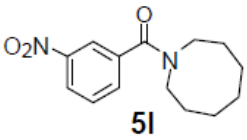
$^{1}$H NMR



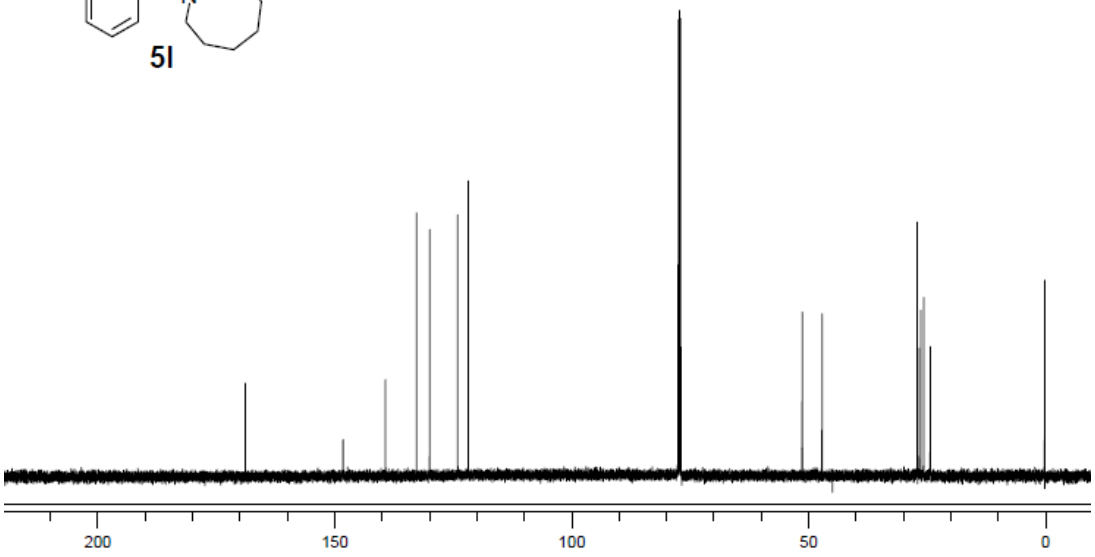
**5l**



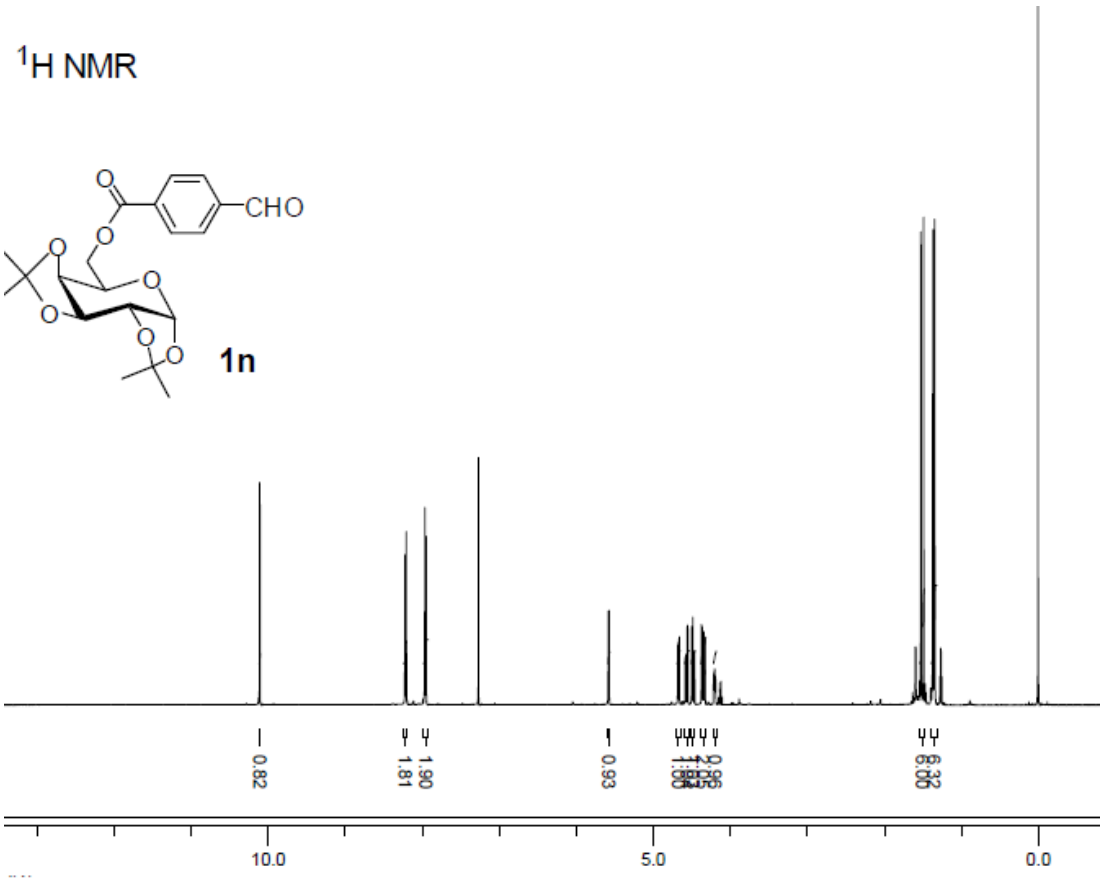

$^{13}$C NMR



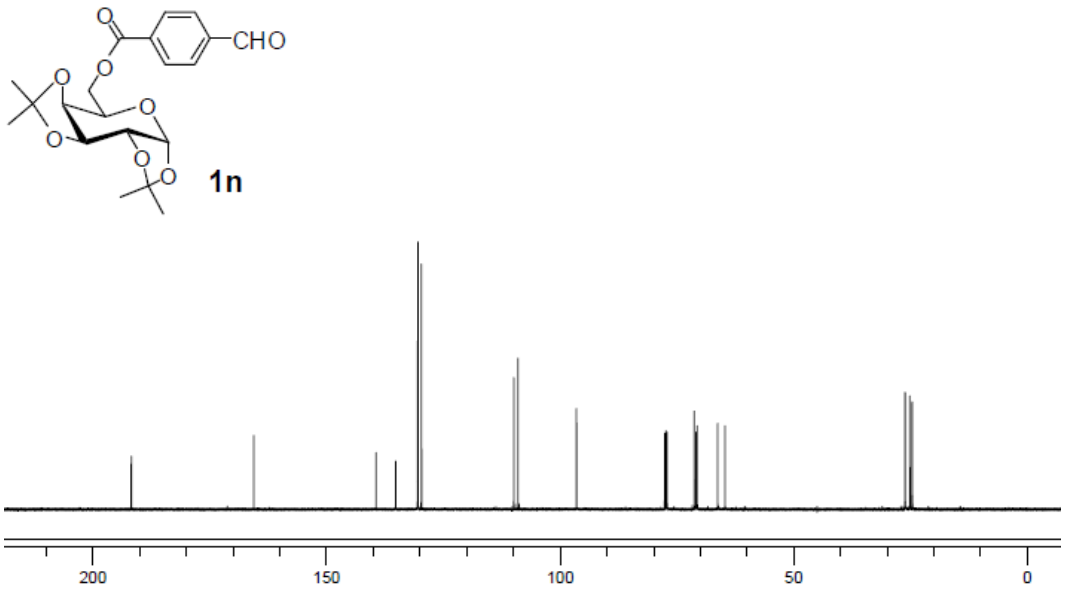
**5l**



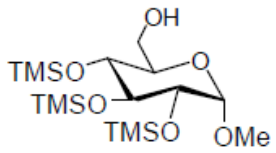
$^{1}$H NMR




$^{13}$C NMR



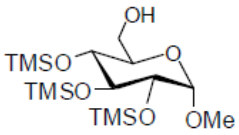
$^{1}$H NMR




**1o'**

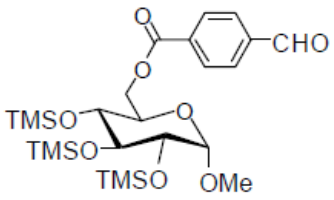



$^{13}$C NMR




**1o'**

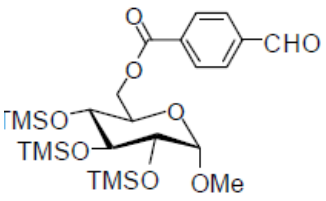
$^{1}$H NMR




**1o**

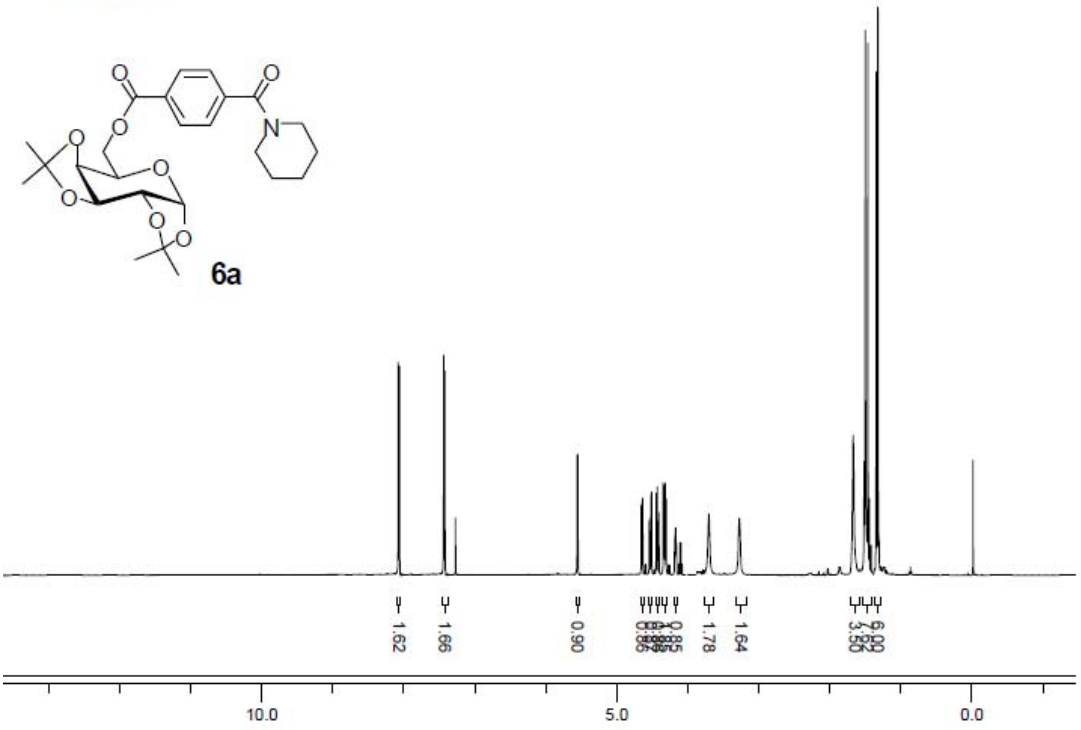



$^{13}$C NMR

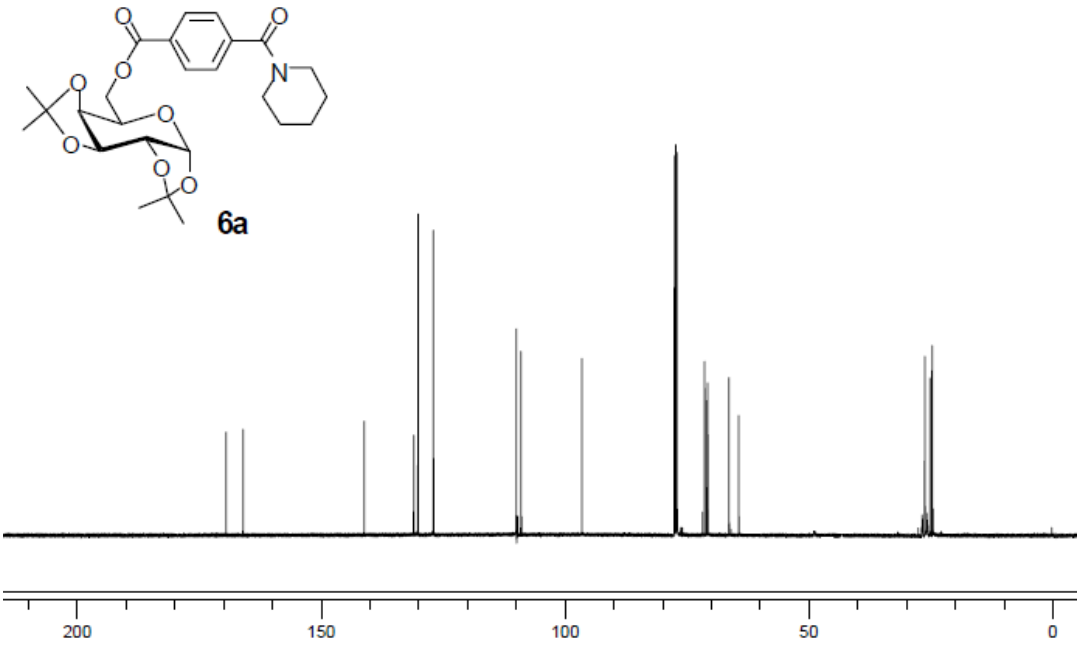



**1o**

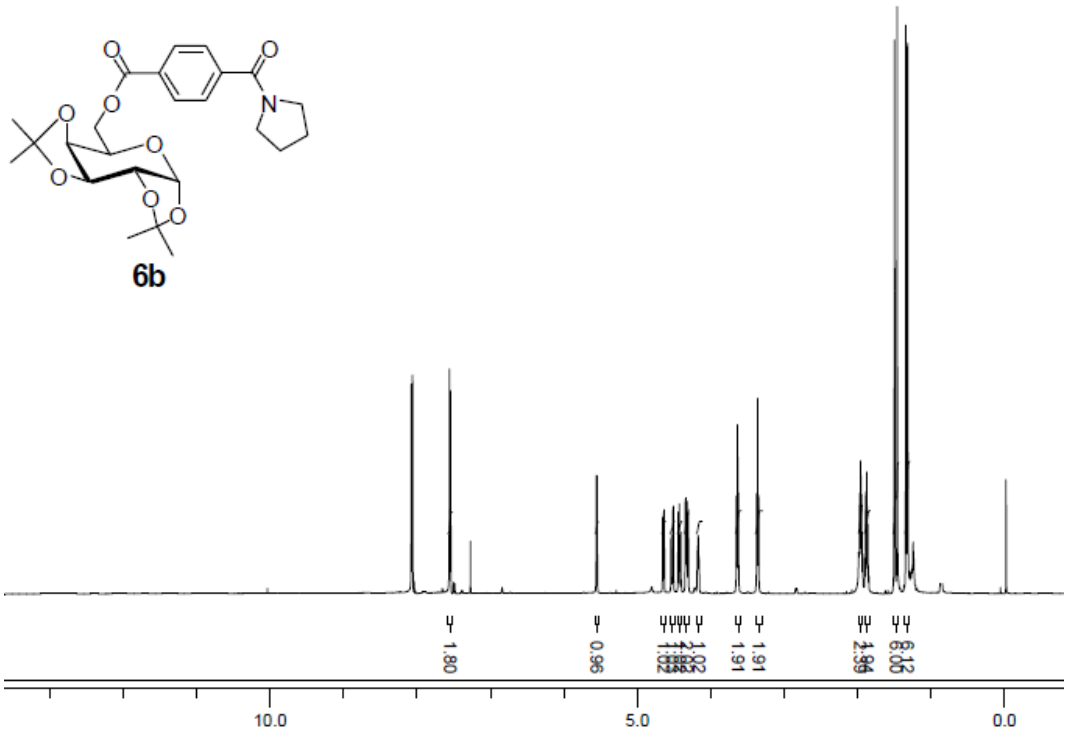
$^{1}$H NMR



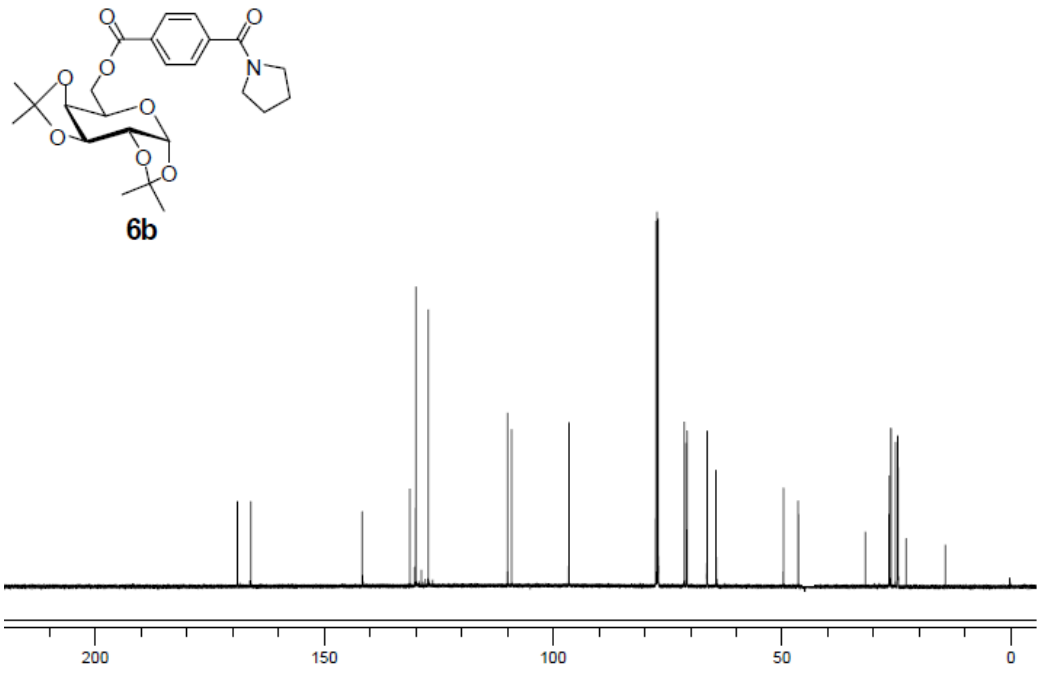

$^{13}$C NMR



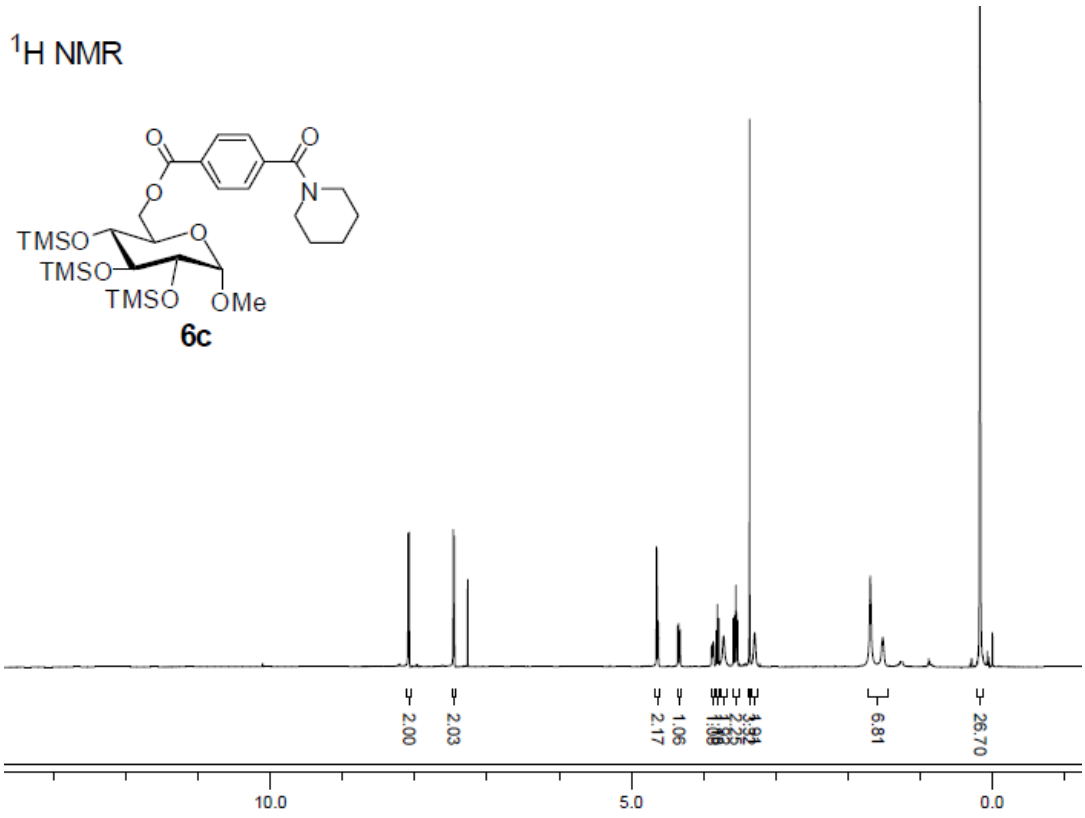
$^{1}$H NMR




$^{13}$C NMR

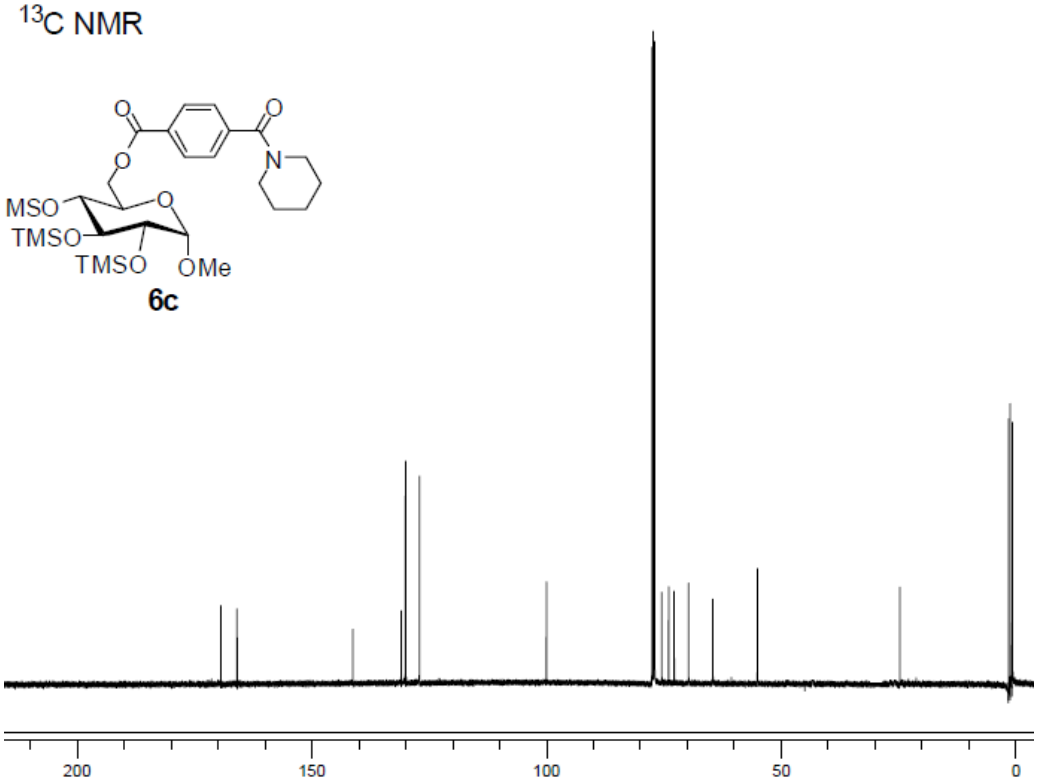


$^{1}$H NMR




**6c**

$^{13}$C NMR




**6c**