Supporting information

for

Gas-Liquid Tubular Continuous-Flow Pd-catalysed Aminocarbonylation Process for Scalable Synthesis of Carboxamides

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Contents

1. Reagents and solvents. The iodoalkene substrates (**1**,[1] **2**,[2,3] **3**,[2,3] **6**,[4] **7**,[5]) were synthesized according to the modified Barton's method.[6,7] The haloarene substrates (iodobenzene (**4**) (>99%) and 1-bromo-4-iodobenzene (**5**) (98%)) as well as heptan-1-amine (>99%) (**c**), 1-methylpiperazine (**b**) (99%), L-phenylalanine methyl ester hydrochloride (**d**) (98%), and *N*-Boc-ethylenediamine (99%) (**f**) were purchased from Sigma-Aldrich. Piperidine (>99%) (**a**) and palladium(II) acetate (99.98%) were acquired from ThermoFisher. Xantphos (>97%) was purchased from Apollo Scientific. Nortropinone hydrochloride (>98%) (**e**) was purchased from TCI. Carbon monoxide (99.997%) was purchased from Praxair Portugal. All reagents were used as received from the supplier, without any further purification. The solvents (toluene, *N,N*-dimethylformamide and triethylamine) were dried and purified by standard methods.[8] Air and moisture sensitive reagents and solvents were manipulated using Schlenk techniques.

2. Instrumentation. Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker Avance III 400 MHz spectrometer (400.13 for ^{1}H and 100.62 MHz for ^{13}C) and recorded in deuterated chloroform (chloroform-d). The signal of the residual non-deuterated solvent was used as chemical shift standard (7.26 ppm for ^{1}H NMR and 77.2 ppm for ^{13}C NMR). Gas chromatography was carried out in an Agilent-7820 apparatus equipped with a nonpolar HP-5 capillary column (5% diphenyl- and 95% dimethylpolysiloxane), with 30 m length and 0.32 mm internal diameter, using N_2 as carrier gas, and a flame ionization detector (FID). The GC-MS analysis was carried out using a HP chromatograph equipped with a HP-5 column (5% diphenyl/95% dimethylpolysiloxane), with 30 m length, 0.25 mm ID and 0.25 μm coating), coupled with a HP mass selective detector 5975. Continuous-flow reactions were performed on a *Vapourtec E-series* apparatus, equipped with PFA tubing (1 mm ID). Its configuration consisted of two V3 peristaltic pumps, a tubular reactor (10 mL, 1 mm ID) and a manually adjustable back-pressure regulator (BPR). An inert gas kit was used to introduce the reagents/solvents of Flask A under a nitrogen flow. Carbon monoxide was introduced using a pressurized vessel (Bottle B) containing CO (99%), connected to a V3 pump, through a manual mass flow controller, and mixed with the liquid reagents in a T-mixer, before entering the tubular reactor.

3. General procedure of continuous-flow palladium-catalyzed aminocarbonylation reactions. In a typical experiment, a solution of haloalkene or haloarene substrate (8.0×10^{-4} mol, 0.2 M), the amine nucleophile (1.6×10^{-3} mol, 0.4 M), Pd(OAc)$_2$ (1.6×10^{-5} mol, 0.004 M), xantphos (2.0×10^{-5} mol, 0.005 M) and triethylamine (2.4×10^{-3} mol, 0.6 M) in 4 mL of toluene (or DMF) was prepared under inert atmosphere. This solution (Flask A, Scheme S1) was pumped along with carbon monoxide (Bottle B), through a 10 mL tubular reactor, thermostated at 80 or 100 °C, using an A to B volumetric ratio of 1:3 (flow rate $_A$ = 0.3 mL min^{-1}; flow rate $_B$ = 1.0 mL; residence time = 10 min, system total gas pressure = 2-3 bar), and the reaction's crude mixture

was collected at the steady state. The crude was dissolved in dichloromethane (10 mL) and washed with water (3×10 mL). Then, the organic phase was dried with anhydrous sodium sulfate, and the solvent was removed under vacuum. Finally, column chromatography was carried out using silica gel or aluminum oxide (grade II) as stationary phases and selected mixtures of eluents, to afford the desired carboxamide products.
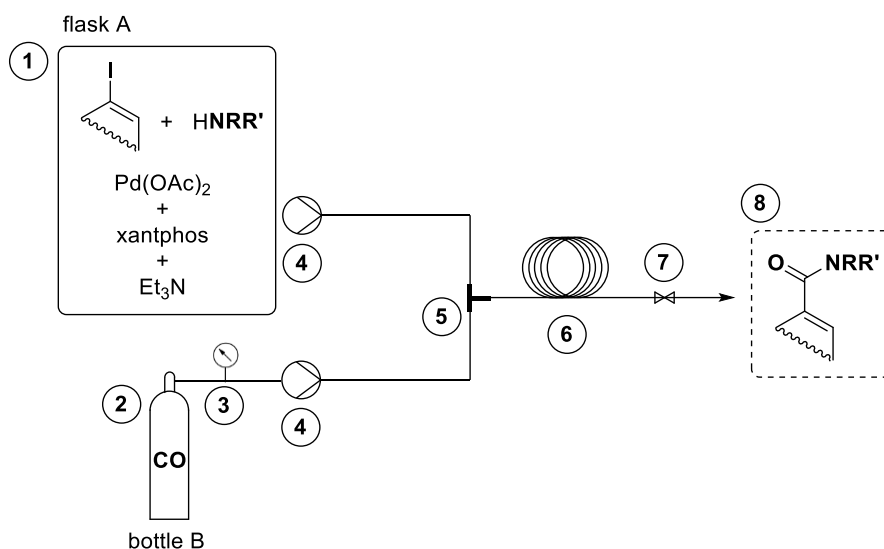
Scheme S1. Home-made system set-up of continuous-flow Pd-catalyzed aminocarbonylation: (1) Flask A with toluene solution of reagents and catalyst; (2) CO steel-bottle; (3) manual pressure regulator valve; (4) V3 pump system; (5) T-mixer; (6) tubular reactor; (7) back-pressure regulator; (8) reaction output (collecting valve).

4. Batch synthesis of 6a. The evaluation of the 17-iodo-androst-16-ene aminocarbonylation under batch conditions was carried out in a 40 mL stainless-steel autoclave. The catalyst precursor Pd(OAc)$_2$ (0.02 mmol) and ligand xantphos (0.025 mmol) were placed in a glass beaker, inside the autoclave and the reactor was connected to a high-pressure gas line and purged 3x with CO/vacuum cycles. Then, a solution of trimethylamine (6 mmol), 17-iodoandrost-16-ene (1 mmol) and piperidine (2 mmol) in 5 mL of solvent (DMF or toluene) was introduced into the autoclave via cannula. The autoclave was then pressurized with CO (1 bar) and the reaction proceeded at 100 °C, under magnetic stirring. After the desired reaction time, the autoclave was cooled, and slowly depressurized, the reaction mixture was analysed by GC-MS.

Table S1. Batch aminocarbonylation reaction of 17-iodo-androst-16-ene using piperidine as nuchleophile[a)]

Entry	Solvent	Reaction time [h]	Conversion [b)] [%]
1	Toluene	0.5	2
2		1	4
3		2	47
4		4	67
5		6	77
6		24	78
7	DMF	0.5	100

a) Reaction conditions: 1 mmol 17-iodoandrost-16-ene, 2 mmol piperidine, 0.02 mmol Pd(OAc)$_2$, 0.025 mmol Xantphos, 0.84 mL triethylamine, solvent: 5 mL, 1 bar CO, reaction temperature 100 °C.
b) Determined by GC-MS.

5. Characterization of compounds

The spectroscopic data (^{1}H NMR and MS) of carboxamide products **1a**,[9] **1d,**[1] **4a**[10] **4b**,[11] **4c,**[10] **4d,**[12] **5a**,[13] **5b**,[14] **7a**,[15] **8a**,[16] **9f**[17] were in good agreement with that reported in the literature and is presented below. Compounds **1b**, **1c**, **2Ba**, **3a**, and **6a** are new compounds and their spectroscopic data (^{1}H NMR, ^{13}C NMR and MS) is also presented below.

Cyclohex-1-en-1-yl(piperidin-1-yl)methanone (**1a**)

Isolated yield: 139.2 mg (90%), yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.71-5.69 (1H, *m*), 3.43 (4H, *brs*), 2.14–2.09 (2H, *m*), 2.06–2.00 (2H, *m*), 1.66–1.55 (6H, *m*), 1.51–1.45 (2H, *m*).

EI-MS (m/z, rel. int.): 193 (100, [M$^+$]), 178 (10), 164 (88), 150 (84), 136 (31), 109 (84), 81 (100), 53 (27).
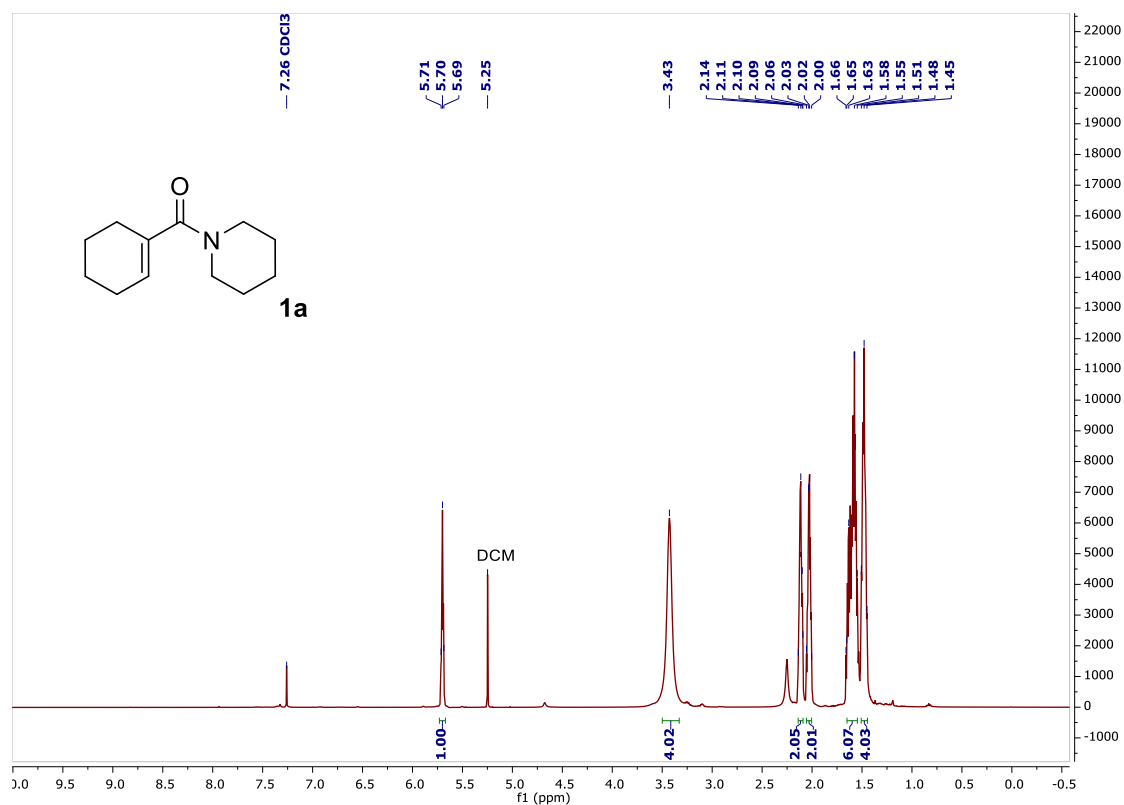
Figure S1. ^{1}H-NMR spectrum for **1a** in CDCl$_3$.
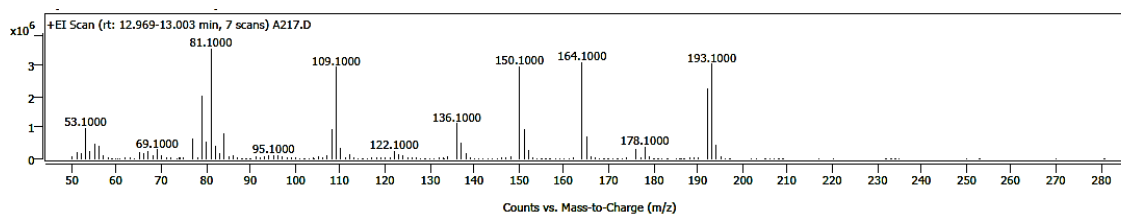
Figure S2. EI-MS spectrum for **1a**.

N-heptylcyclohex-1-ene-1-carboxamide (**1b**)

Isolated yield: 151.9 mg (85%), yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.61–6.58 (1H, *m*), 5.66 (1H, *brs*), 3.31–3.26 (2H, *m*), 2.24–2.19 (2H, *m*), 2.17–2.12 (2*H*, *m*), 1.70–1.64 (2H, *m*), 1.61–1.55 (2H, *m*), 1.53–1.48 (2H, *m*), 1.32–1.25 (8H, *m*), 0.87 (3H, *t*, *J* = 6.9 Hz).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 168.7, 133.4, 133.2, 39.7, 31.9, 29.8, 29.1, 27.1, 25.5, 24.5, 22.7, 22.3, 21.7, 14.2.

HRMS (ESI): m/z calcd. for C$_{14}$H$_{26}$NO$^+$ [M+H]$^+$: 224.2009, found: 224.2003.

EI-MS (m/z, rel. int.): 223 (24, [M$^+$]), 194 (10), 180 (10), 166 (21), 152 (15), 139 (42), 124 (6), 109 (100), 81 (43), 53 (10).
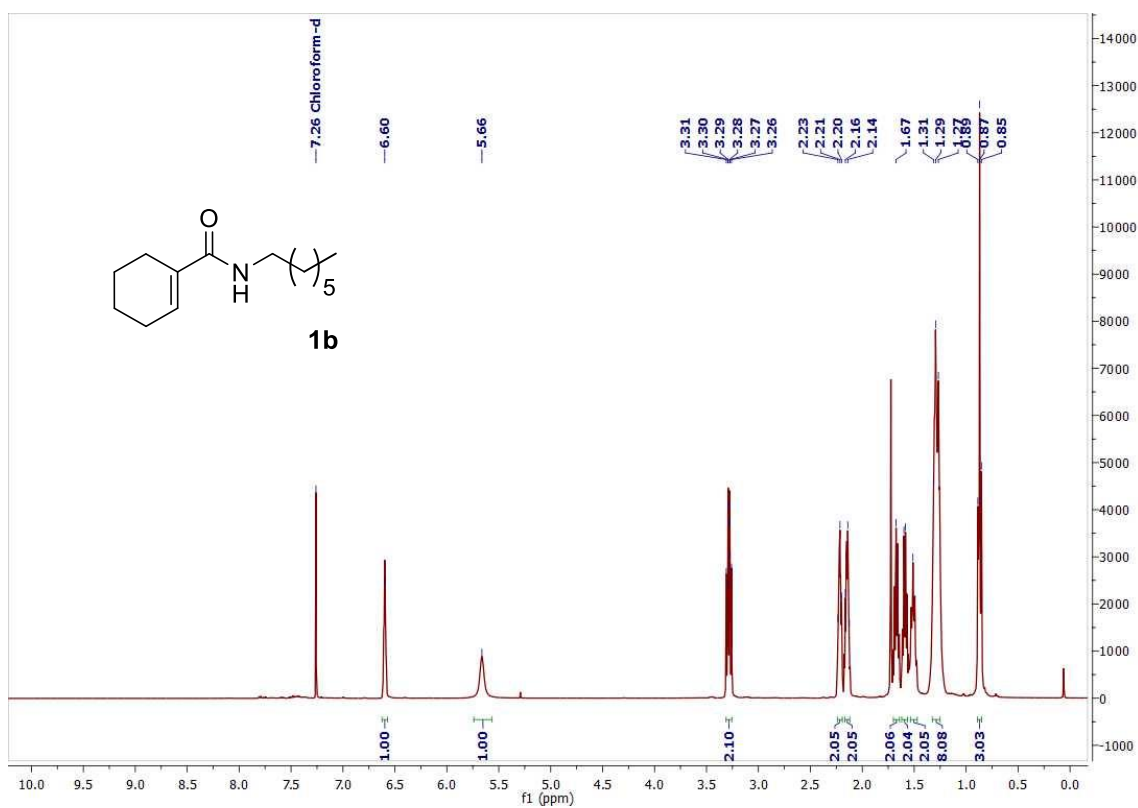
Figure S3. ^{1}H-NMR spectrum for **1b** in CDCl$_3$.
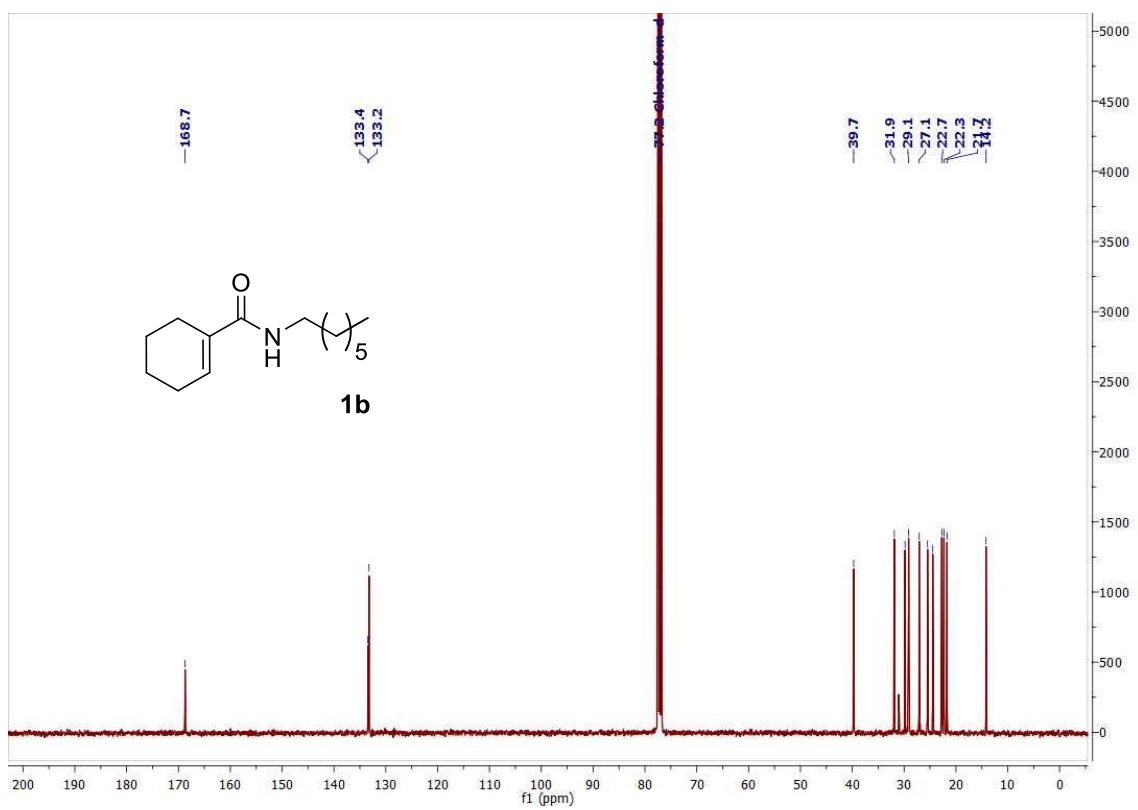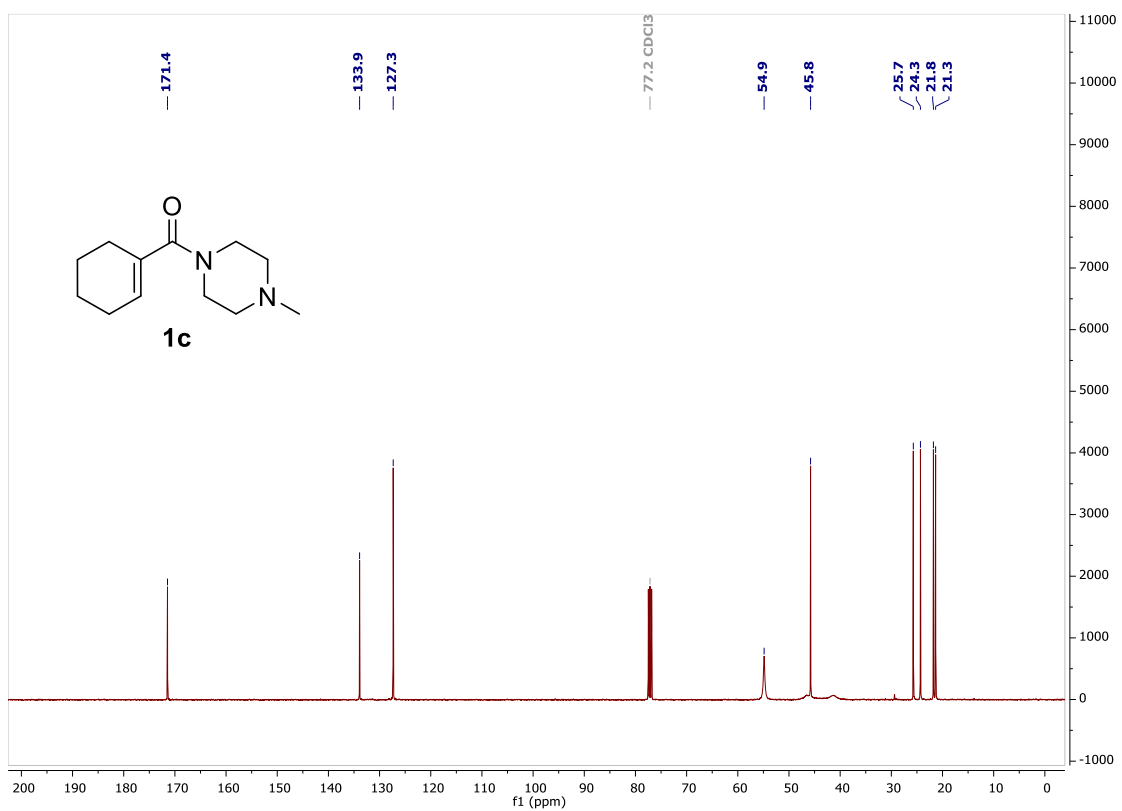

Figure S4. ^{13}C-NMR spectrum for **1b** in CDCl$_3$.
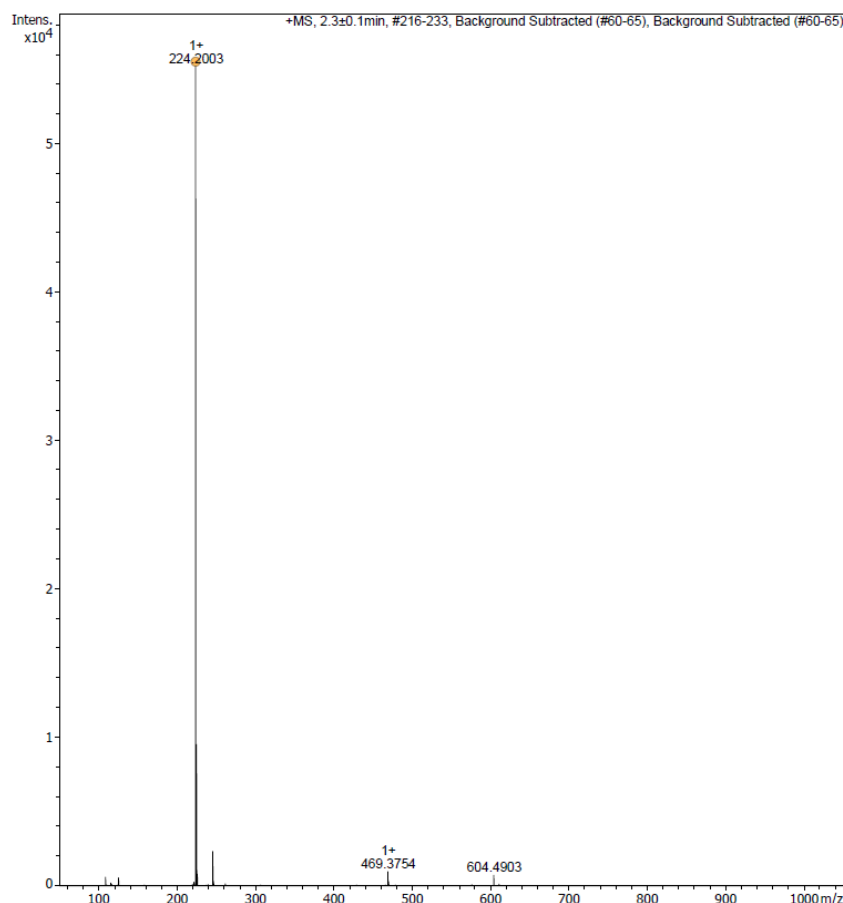
Figure S5. HRMS(ESI) spectrum for **1b**.
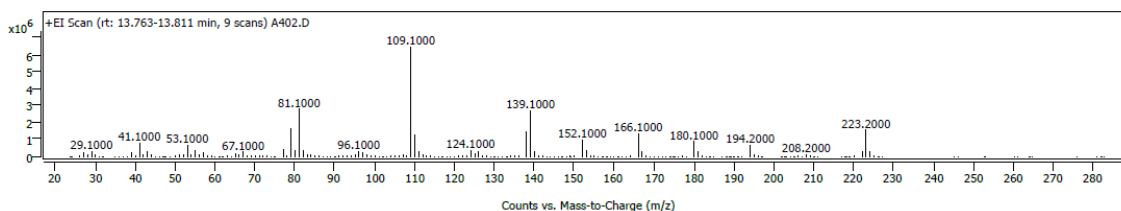
Figure S6. EI-MS spectrum for **1b**.

Cyclohex-1-en-1-yl(4-methylpiperazin-1-yl)methanone (**1c**)

Isolated yield: 135.0 mg (81%), yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.62–5.58 (1H, *m*), 3.40 (4H, *brs*), 2.19 (4H, *t*, *J* = 5.1 Hz,), 2.11 (3H, *s*), 2.02–1.98 (2H, *m*), 1.93–1.89 (2H, *m*), 1.54–1.48 (2H, *m*), 1.47–1.41 (2H, *m*).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 171.4, 133.9, 127.3, 54.9, 48.5, 25.7, 24.3, 21.8, 21.3.

HRMS (ESI): m/z calcd. for C$_{12}$H$_{21}$N$_2$O$^+$ [M+H]$^+$: 209.1648, found: 209.1644.

EI-MS (m/z, rel. int.): 208 (37, [M$^+$]),164 (10), 136 (13), 109 (18), 99 (44), 83 (47), 81 (20) 79 (23), 77 (10), 70 (100), 58 (26), 56 (35), 53 (13), 42 (23).
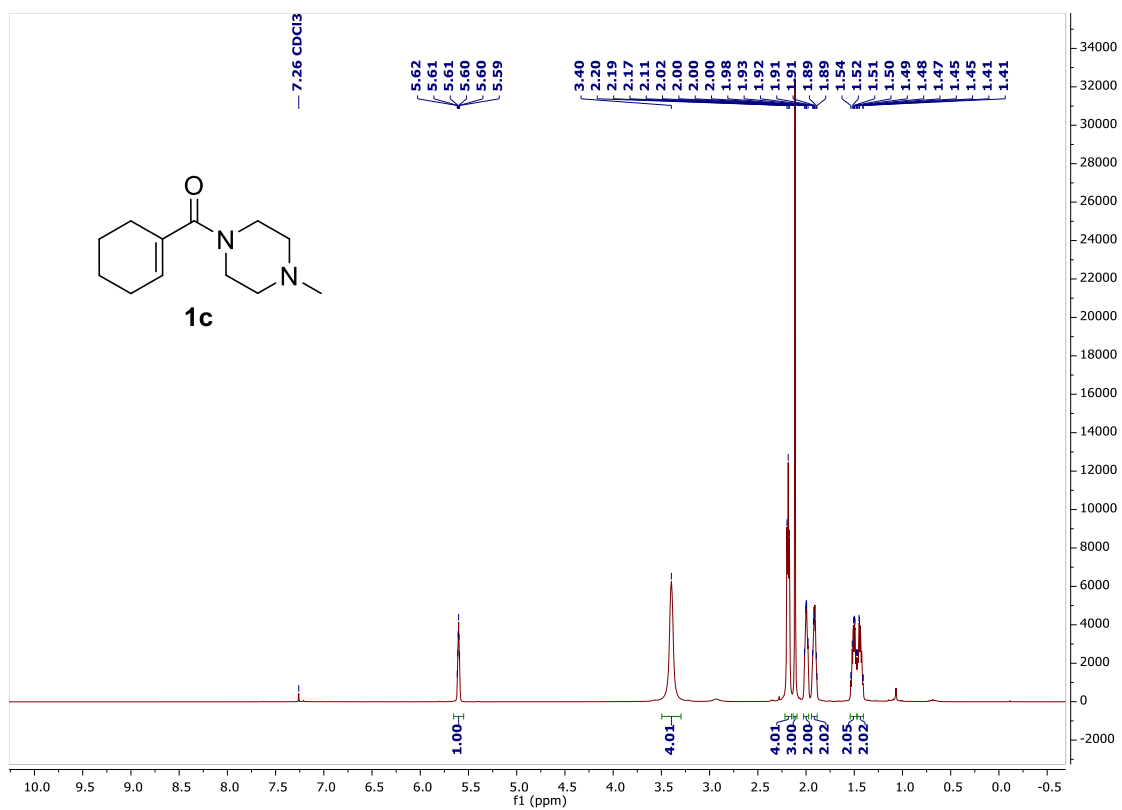
Figure S7. ^{1}H-NMR spectrum for **1c** in CDCl$_3$.

Figure S8. ^{13}C-NMR spectrum for **1c** in CDCl$_3$.
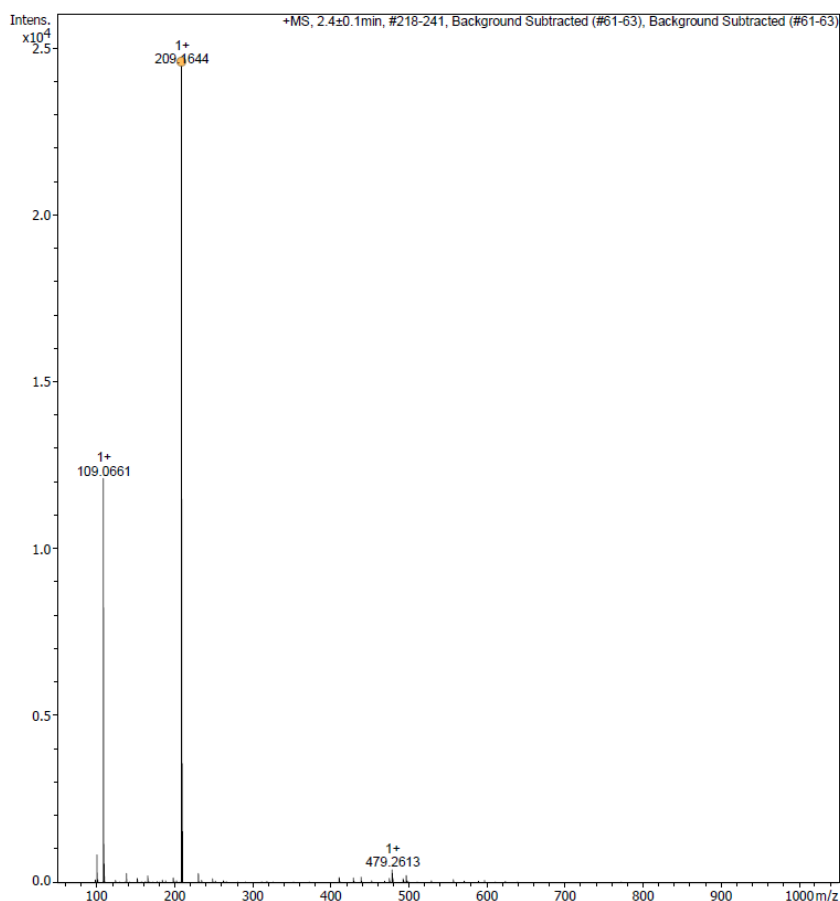
Figure S9. HRMS(ESI) spectrum for **1c**.
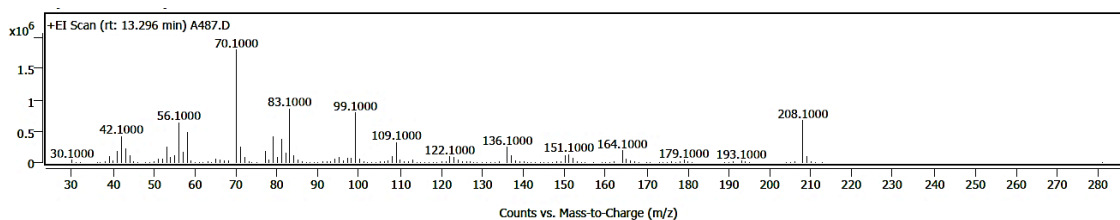
Figure S10. EI-MS spectrum for **1c**.

(cyclohex-1-ene-1-carbonyl)phenylalanine methyl ester (**1d**)

Isolated yield: 126.5 mg (55%), yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.24-7.17 (3H, *m*), 7.03-7.02 (2H, *m*), 6.55-6.53 (1H, *m*), 6.04 (1H, *d, J* = 7.2 Hz), 4.86 (1H, *dt*, *J* = 7.5, 5.7 Hz), 3.65 (3H, *s*), 3.11 (1H, *dd*, *J* = 13.8, 5.8 Hz), 3.06 (1H, *dd*, *J* = 13.8, 5.8 Hz), 2.18–2.14 (1H, *m*), 2.10–2.05 (*3H, m*), 1.62–1.54 (2H, *m*), 1.51–1.48 (2H, *m*).

EI-MS (m/z, rel. int.): 287 (7, [M$^+$]), 228 (7), 162 (70), 125 (19), 109 (100), 91 (19), 81 (45), 53 (12).
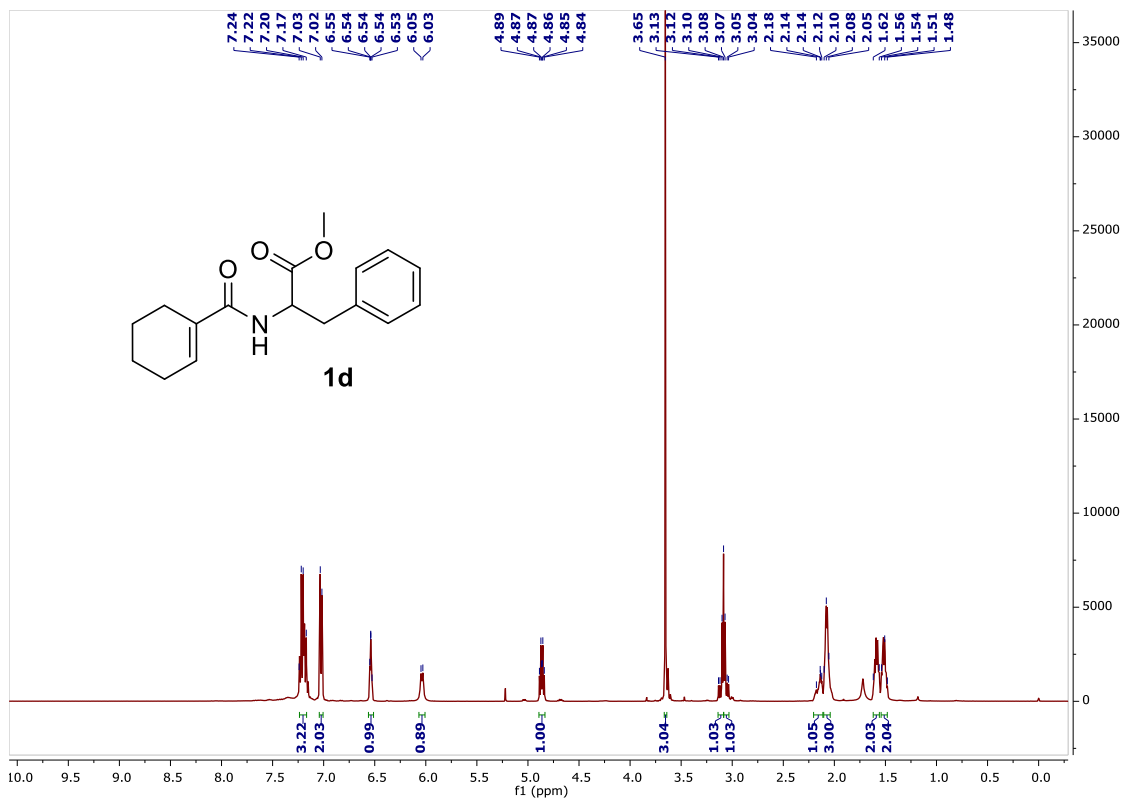
Figure S11. ^{1}H-NMR spectrum for **1d** in CDCl$_3$.
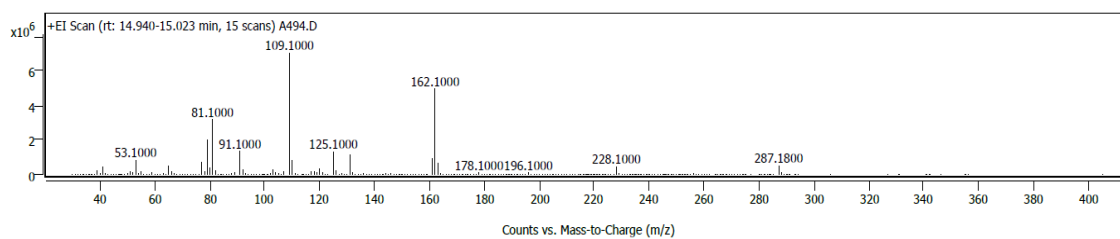
Figure S12. EI-MS spectrum for **1d**.

(2-methylcyclohex-1-en-1-yl)(piperidin-1-yl)methanone (**2Aa**)

EI-MS (m/z, rel. int.): 193 (100), 178 (11), 164 (95), 150 (89), 136 (31), 109 (77), 81 (87), 55 (11), 41 (25).
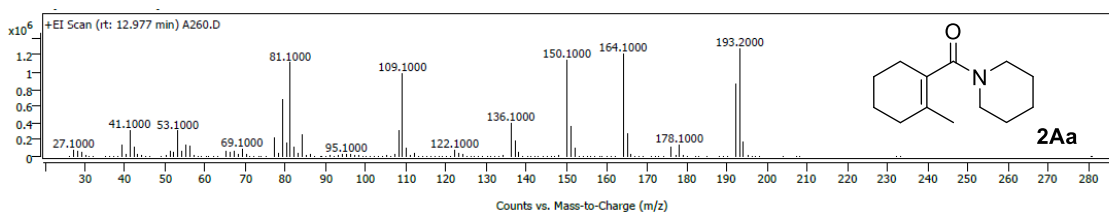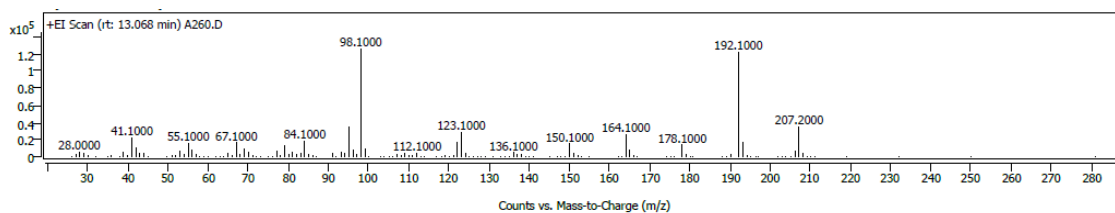

Figure S13. EI-MS spectrum for **2Aa**.

(6-methylcyclohex-1-en-1-yl)(piperidin-1-yl)methanone (**2Ba**)

Isolated yield: 24.9 mg (75%), yellowish oil (93% purity)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.64–5.62 (1H, *m*), 3.45 (4H, *brs*), 2.55–2.50 (1H, *m*), 2.03–1.98 (2H, *m*), 1.81–1.74 (*1H, m*), 1.63–1.56 (4H, *m*), 1.34 (4H, *brs*), 1.26–0.94 (1H, *m*), 0.92 (3H, *d*, *J* = 7.1 Hz).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 171.3, 139.3, 126.4, 30.8, 30.5, 24.9, 24.7, 20.1, 19.4.

HRMS (ESI): m/z calcd. for C$_{13}$H$_{22}$NO$^+$ [M+H]$^+$: 208.1696, found: 208.1691.

EI-MS (m/z, rel. int.): 207 (27, [M$^+$]), 192 (97), 178 (11), 164 (21), 150 (12), 123 (23), 98 (100), 84 (14), 67 (13), 55 (13), 41 (18).
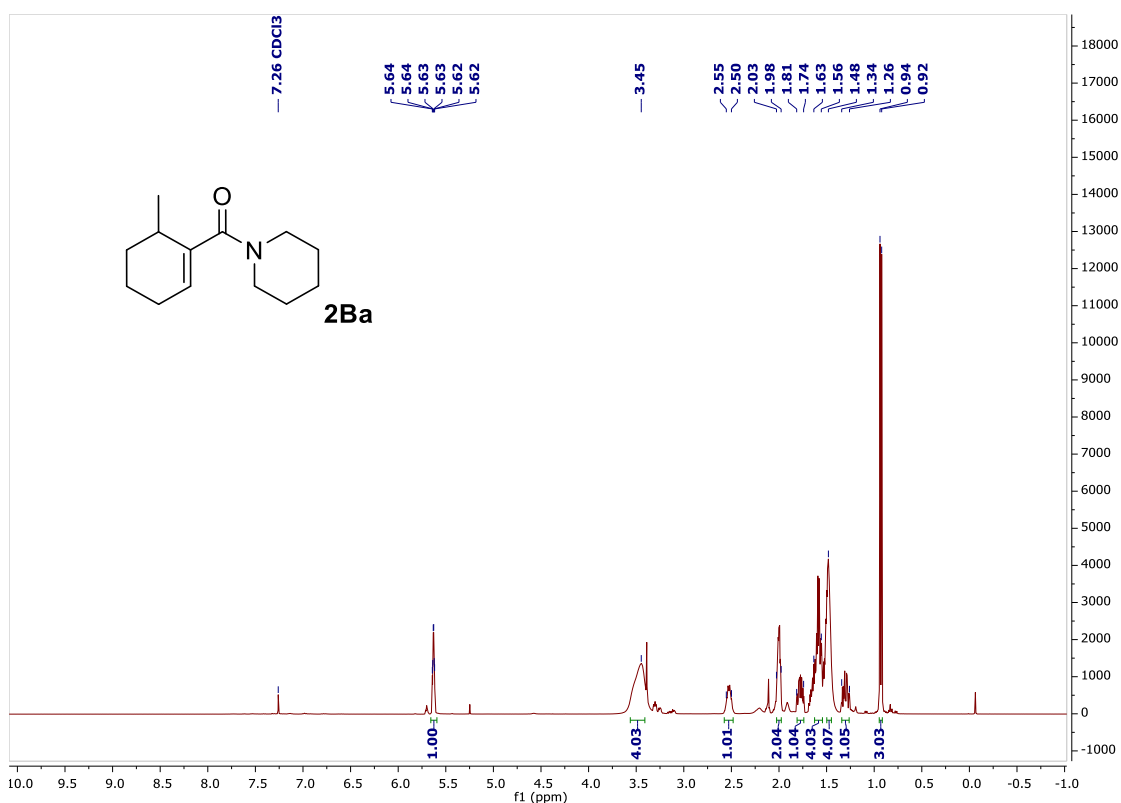
Figure S14. ^{1}H-NMR spectrum for **2Ba** in CDCl$_3$.
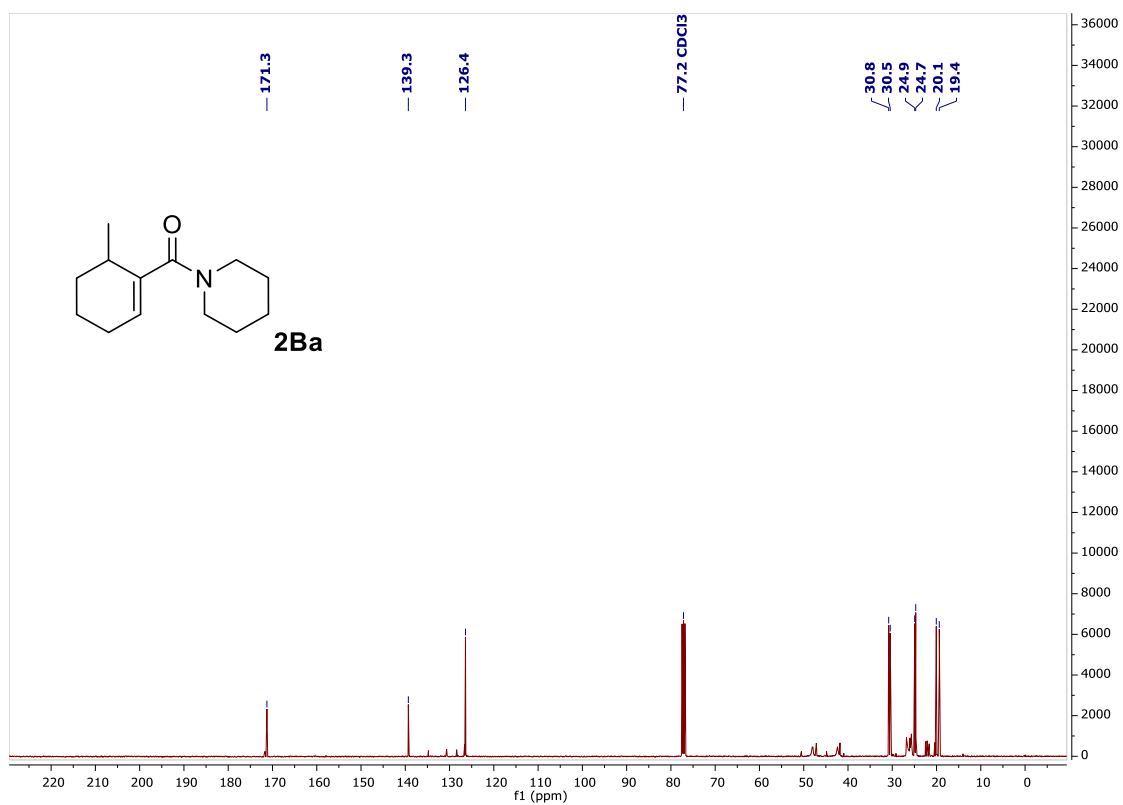
Figure S15. ^{13}C-NMR spectrum for **2Ba** in CDCl$_3$.
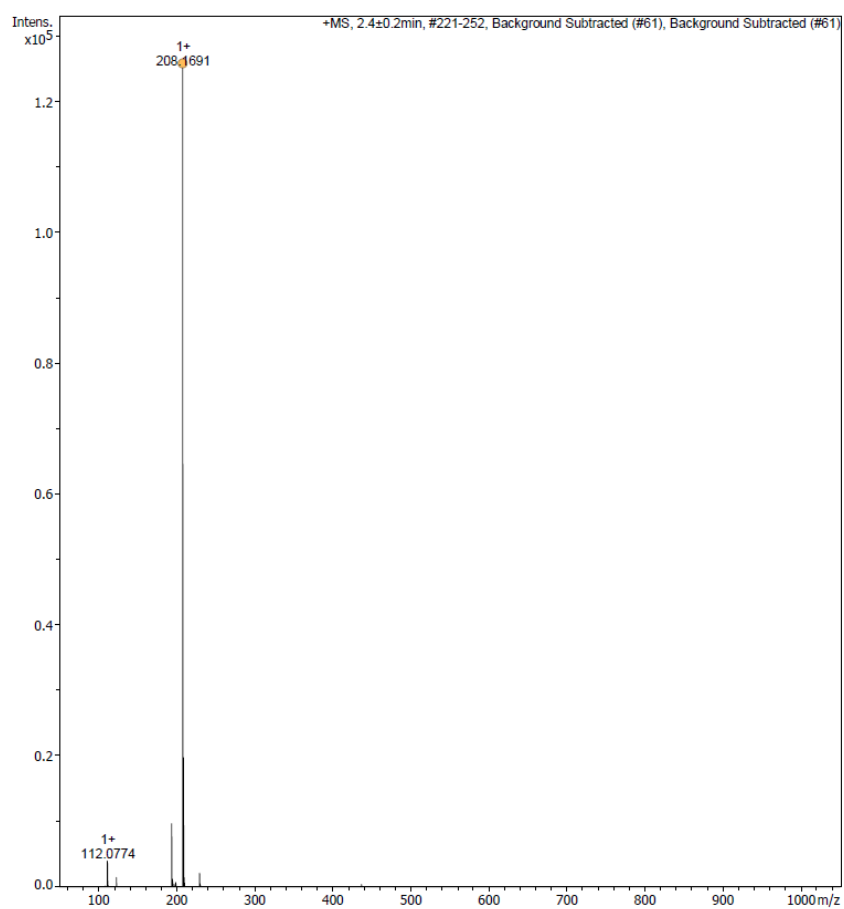
Figure S16. HRMS(ESI) spectrum for **2Ba**.

Figure S17. EI-MS spectrum for 2**Ba**.

(4-(tert-butyl)cyclohex-1-en-1-yl)(piperidin-1-yl)methanone (**3a**)

Isolated yield: 1.68 g (90%), yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.75 (1H, *s*), 3.46 (4H, *brs*), 2.33–2.06 (3H, *m*), 1.94–1.78 (2H, *m*), 1.68–1.58 (2H, *m*), 1.57–1.47 (4H, *m*), 1.35–l.14 (2H, *m*), 0.85 (9H, *s*).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 171.9, 134.6, 127.1, 43.5, 32.3, 27.8, 27.2, 26.5, 24.8, 23.7.

HRMS (ESI): m/z calcd. for C$_{16}$H$_{28}$NO$^+$ [M+H]$^+$: 250.2165, found: 250.2167.

EI-MS (m/z, rel. int.): 249 (45, [M$^+$]), 234 (19), 192(100), 164 (28), 150 (18). 136 (9), 107 (17), 81 (16), 57 (17).
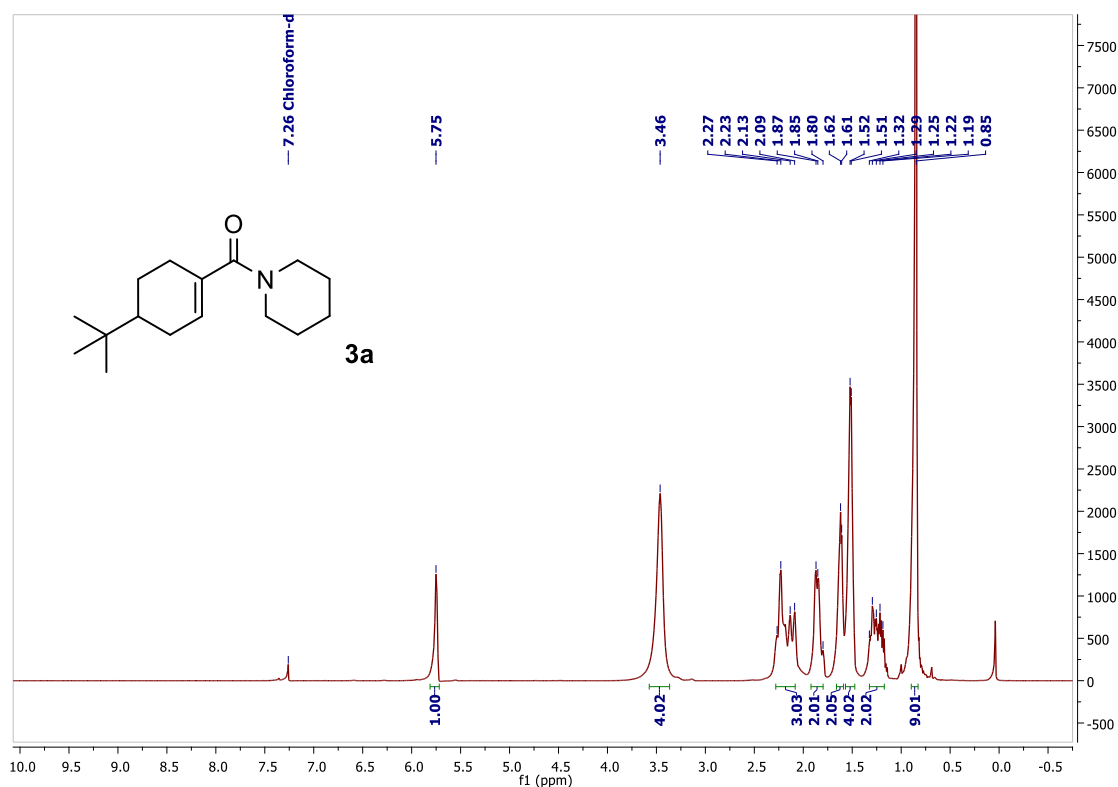
Figure S18. ^{1}H-NMR spectrum for **3a** in CDCl$_3$.
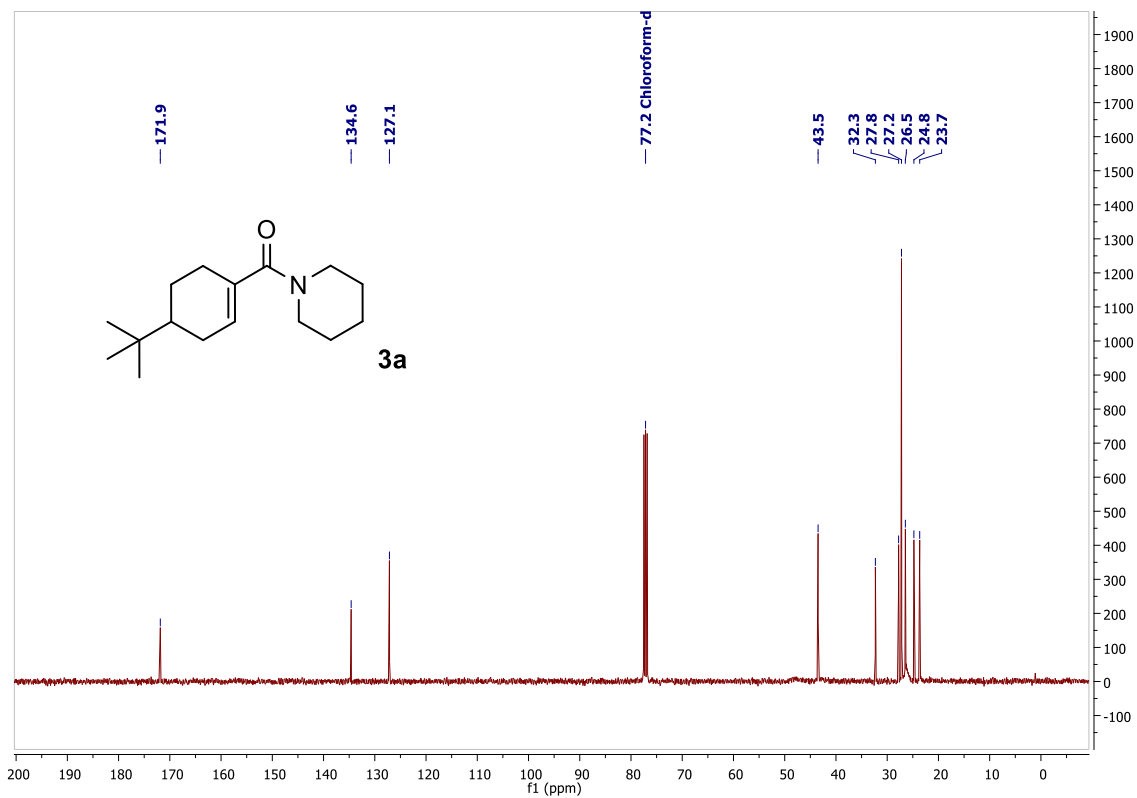
Figure S19. ^{13}C-NMR spectrum for **3a** in CDCl$_3$.
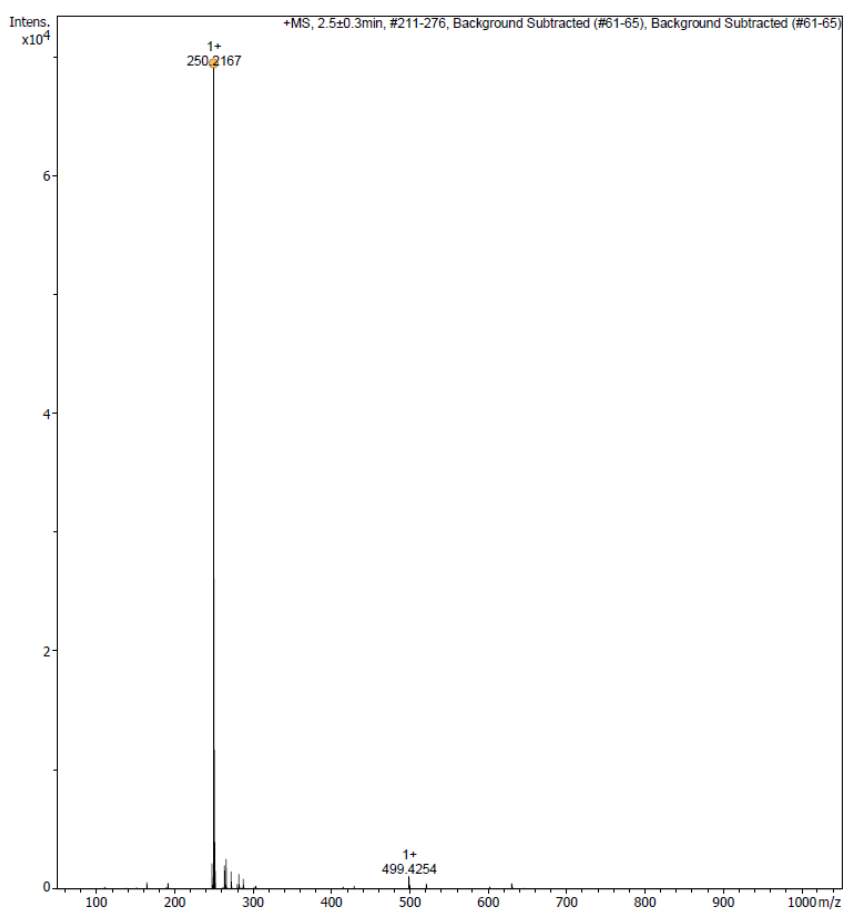
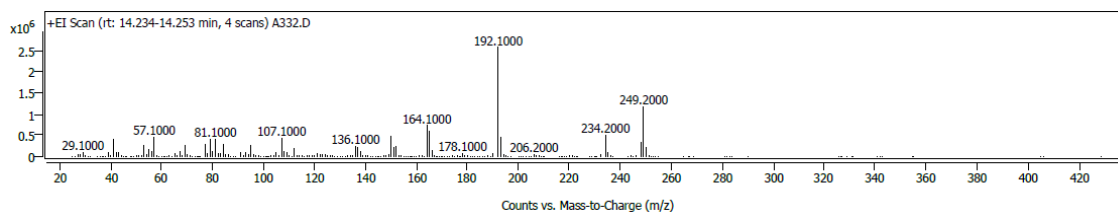**Figure S20.** HRMS(ESI) spectrum for **3a**.

Figure S21. EI-MS spectrum for **3a**.

Phenyl(piperidin-1-yl)methanone (**4a**)

Isolated yield: 1.2 g (93%), yellowish oil,

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.75 (1H, *s*), 3.46 (4H, *brs*), 2.33–2.06 (3H, *m*), 1.94–1.78 (2H, *m*), 1.68–1.58 (2H, *m*), 1.57–1.47 (4H, *m*), 1.35–l.14 (2H, *m*), 0.85 (9H, *s*).

EI-MS (m/z, rel. int.): 188 (100, [M$^+$]), 105 (95), 84 (8), 77 (64), 51 (14).
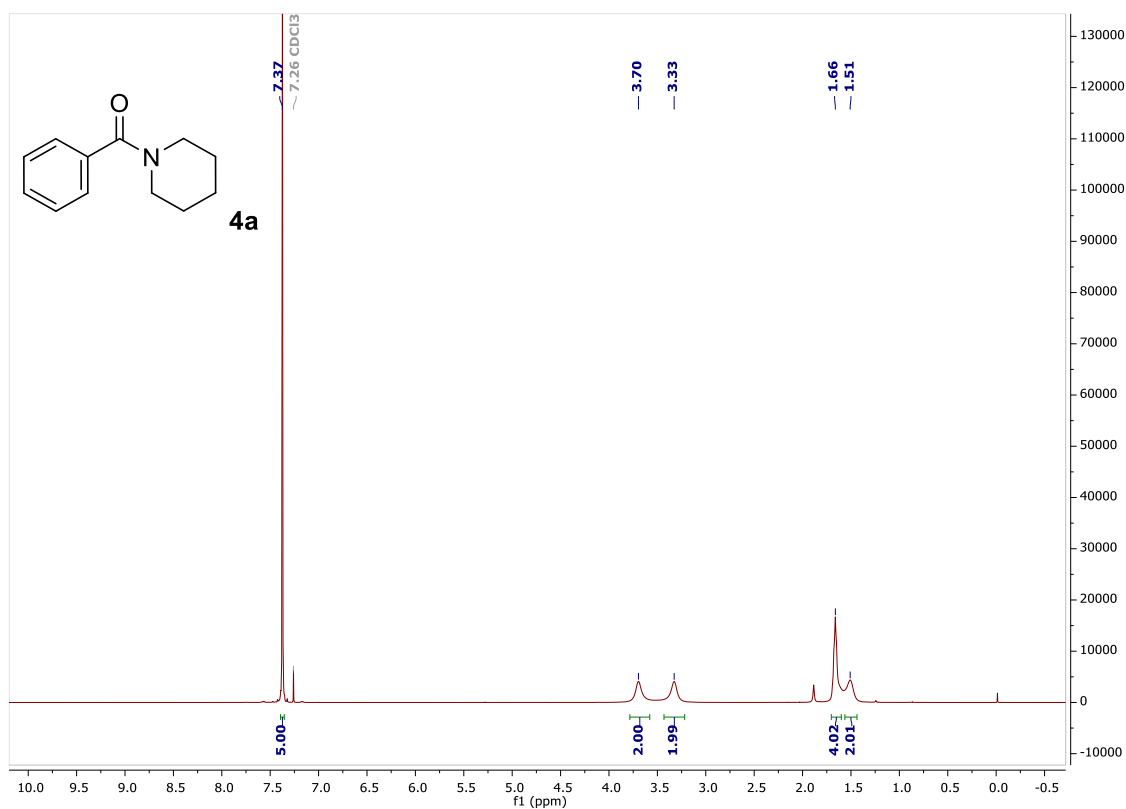
Figure S22. ^{1}H-NMR spectrum for **4a** in CDCl$_3$.
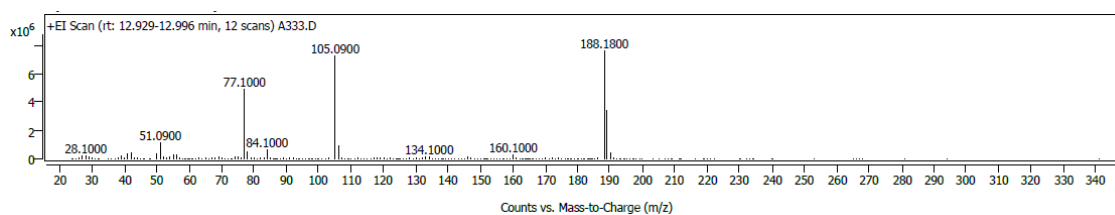
Figure S23. EI-MS spectrum for **4a**.

N-heptylbenzamide (**4b**)

Isolated yield: 157.9 mg (90%), yellowish oil,

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.77–7.74 (2H, *m*), 7.51–7.41 (3H, *m*), 6.08 (1H, *brs*), 3.48–3.43 (2H, *m*), 1.64–1.57 (2H, *m*), 1.40-1.25 (8H, *m*), 1.32, 0.89 (3H, *t*, *J* = 6.8 Hz).

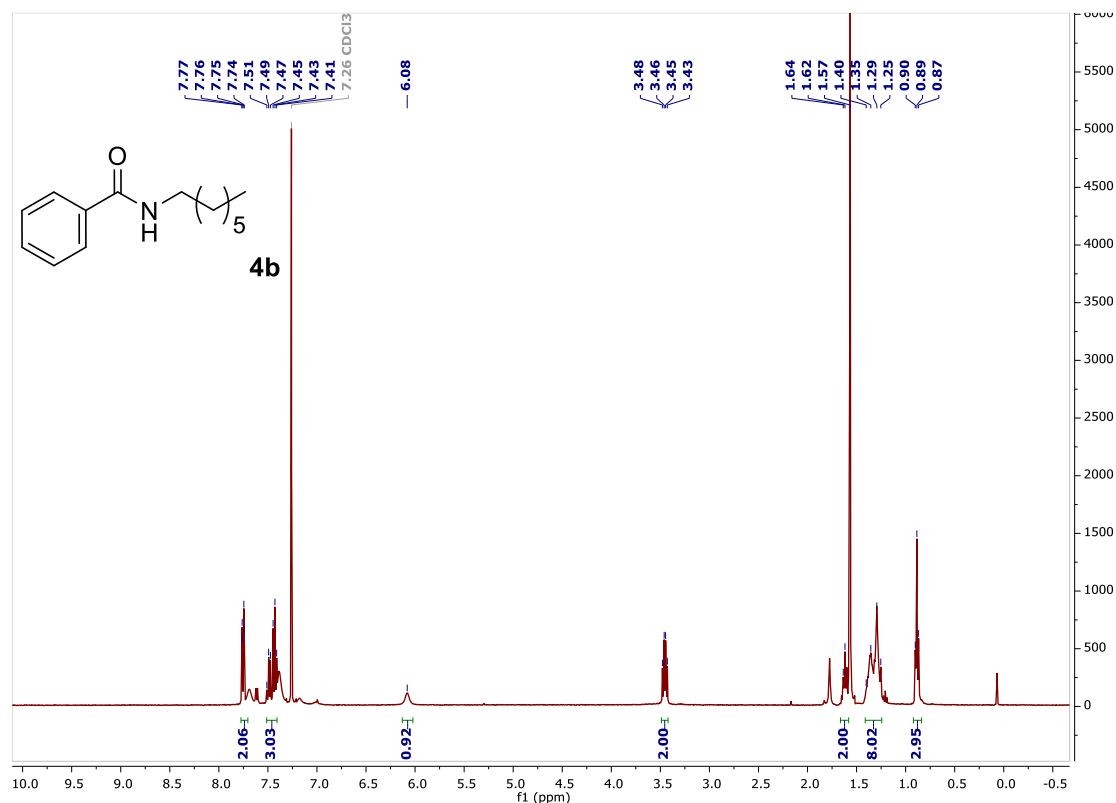EI-MS (m/z, rel. int.): 219 (9, [M$^+$]), 176 (13), 162 (17), 148 (18), 134 (44), 105 (100), 77 (56), 51 (9).

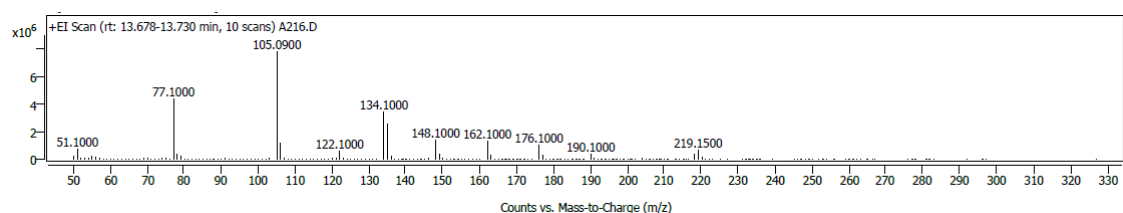

Figure S24. ^{1}H-NMR spectrum for **4b** in CDCl$_3$.

Figure S25. EI-MS spectrum for **4b**.

(4-methylpiperazin-1-yl)(phenyl)methanone (**4c**)

Isolated yield: 130.7 mg (80%), yellowish oil,

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.38 (5H, *s*), 3.78 (2H, *brs*), 3.41 (2H, *brs*), 2.46 (2H, *brs*), 2.32 (2H, *brs*), 2.29 (3H, *s*).

EI-MS (m/z, rel. int.): δ = 204 (17, [M$^+$]), 160 (21), 146 (5), 105 (55), 99 (38), 83 (41), 77 (56), 70 (100), 58 (33), 56 (33) 42 (21).

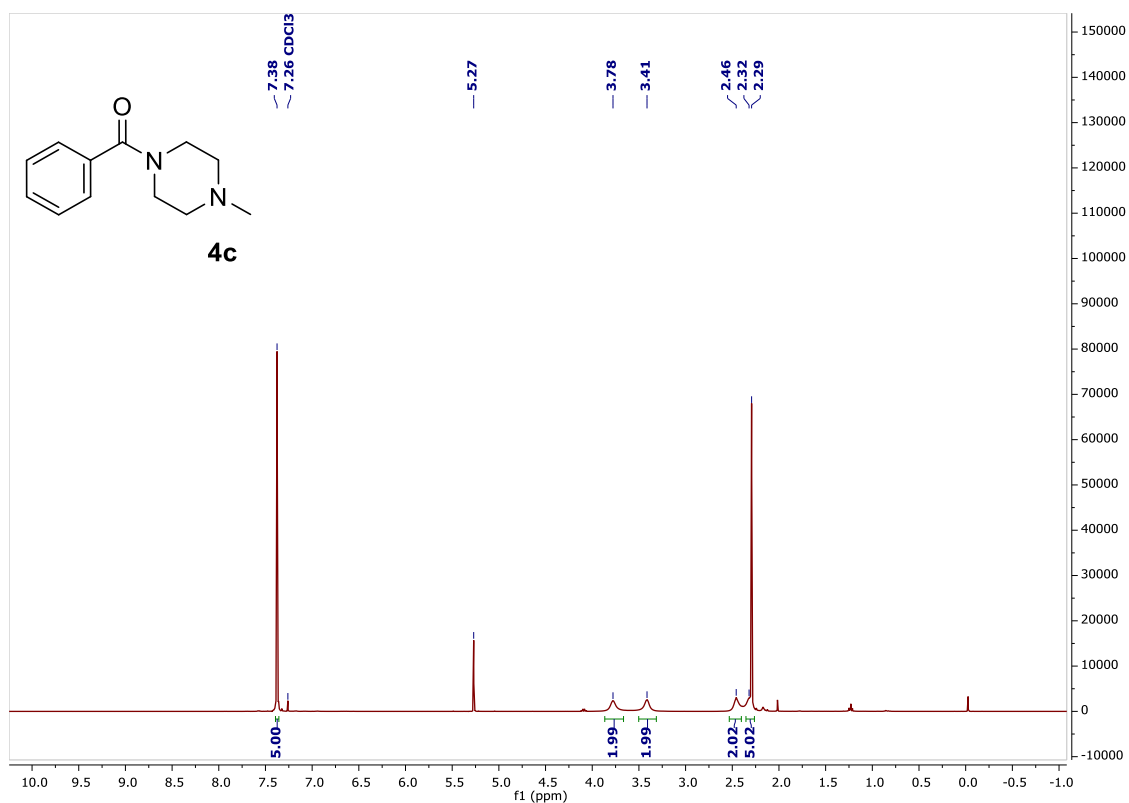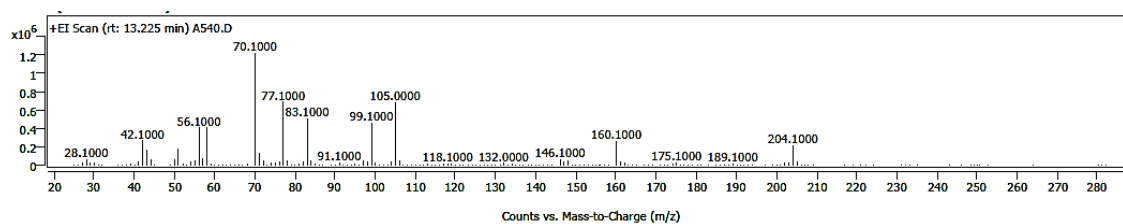**Figure S26.** ^{1}H-NMR spectrum for **4c** in CDCl$_3$.

Figure S27. EI-MS spectrum for **4c**.

Methyl benzoylphenylalaninate (**4d**)

Isolated yield: 158.6 mg (70%), yellowish oil,

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.66-7.64 (2H, *m*), 7.45-7.41 (1H, *m*) 7.36-7.33 (2H, *m*), 7.24-7.18 (3H, *m*), 7.07-7.05 (2H, *m*), 6.54 (1H, *d, J* = 7.2 Hz), 5.02 (1H, *dt*, *J* = 7.5, 5.6 Hz), 3.69 (3H, *s*), 3.22 (1H, *dd*, *J* = 13.8, 5.8 Hz), 3.15 (1H, *dd*, *J* = 13.8, 5.8 Hz).

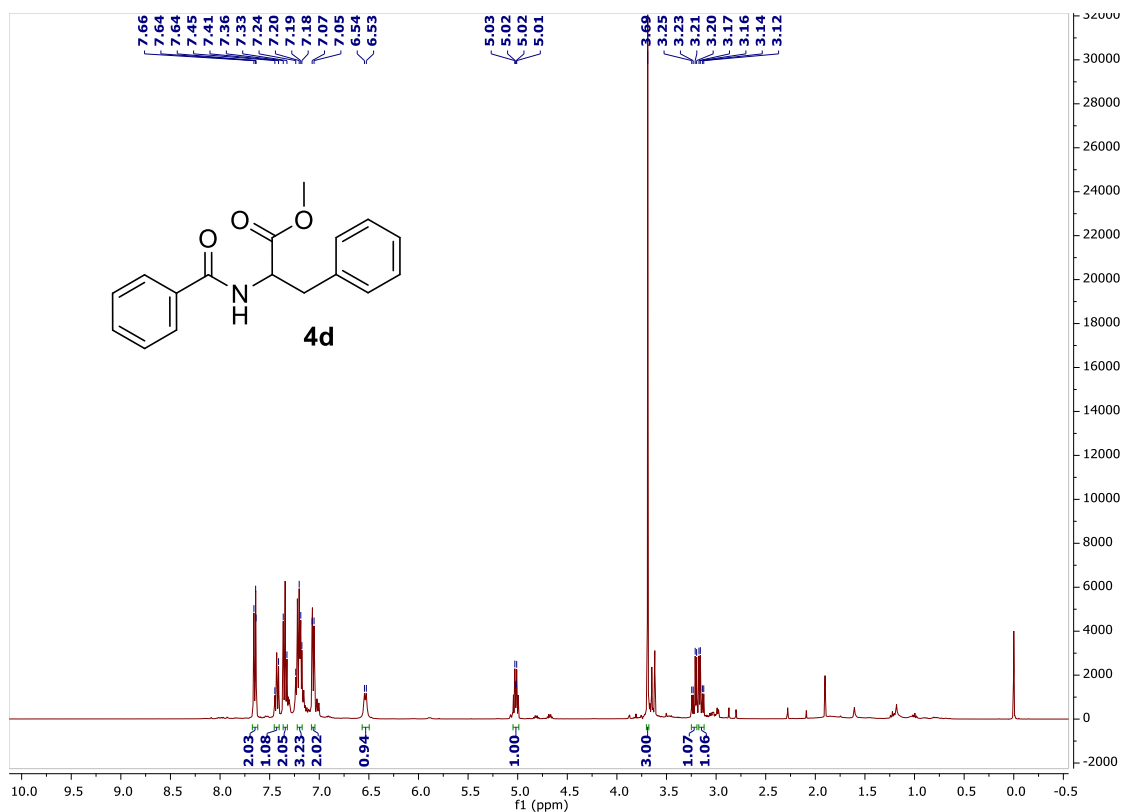EI-MS (m/z, rel. int.): 224 (10), 162 (92), 131 (22), 105 (100), 91 (21), 77 (65), 51 (12).
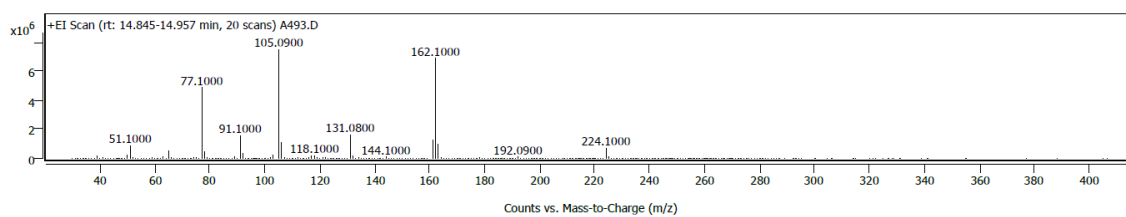
Figure S28. ^{1}H-NMR spectrum for **4d** in CDCl$_3$.

Figure S29. EI-MS spectrum for **4d**.

(4-bromophenyl)(piperidin-1-yl)methanone (**5a**)

Isolated yield: 130.9 mg (61%), yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$): 7.53 (2H, *d*, J = 8.4 Hz), 7.27 (2H, *d*, J = 8.4 Hz) 3.69 (2H, *brs*), 3.32 (2H, *brs*), 1.68 (4H, *brs*), 1.52 (2H, *brs*).

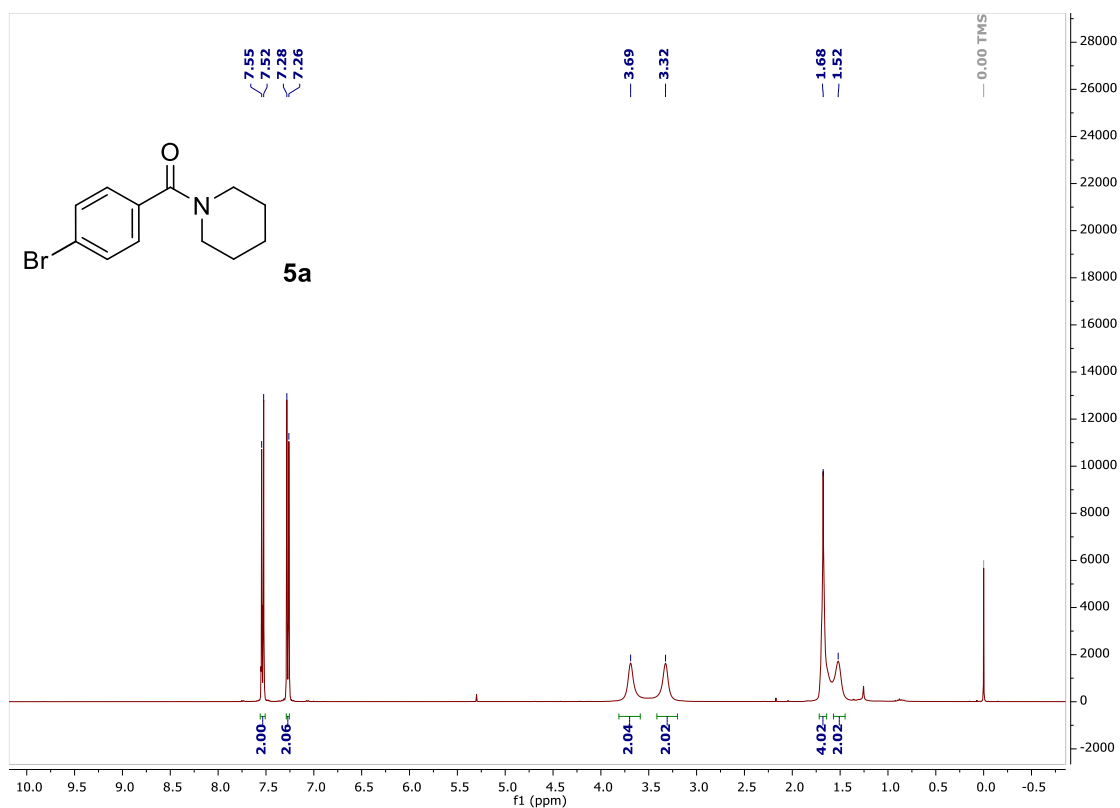EI-MS (m/z, rel. int.): 266 (100, [M$^+$]), 183 (82), 155 (32), 104 (10), 76 (22).
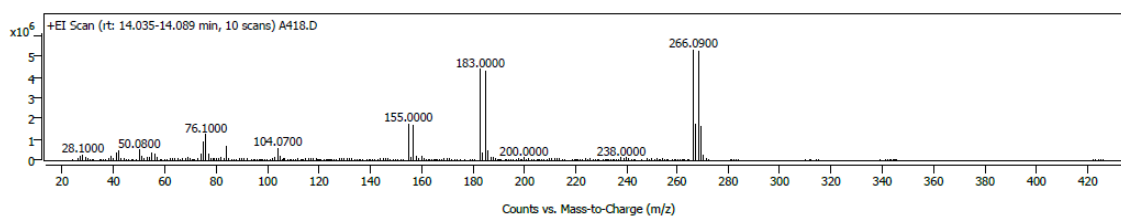
Figure S30. ^{1}H-NMR spectrum for **5a** in CDCl$_3$.

Figure S31. EI-MS spectrum for **5a**.

4-bromo-N-heptylbenzamide (**5b**)

Isolated yield: 205.2 mg (86%), yellowish oil,

^{1}H NMR (400 MHz, CDCl$_3$): 7.64–7.61 (2H, *m*), 7.56–7.54 (2H, *m*), 6.16 (1H, *brs*), 3.42 (2H, *dt*, J = 7.3, 5.8 Hz), 1.59 (2H, *q*, J = 7.2, 6.8 Hz), 1.33–1.25 (8H, *m*), 0.88 (3H, *t*, *J* = 6.3 Hz).

EI-MS (m/z, rel. int.): 297 (6, [M$^+$], 254 (9), 240 (7), 226 (9), 212 (24), 183 (100), 155 (23), 104 (10), 76 (14), 55 (4).
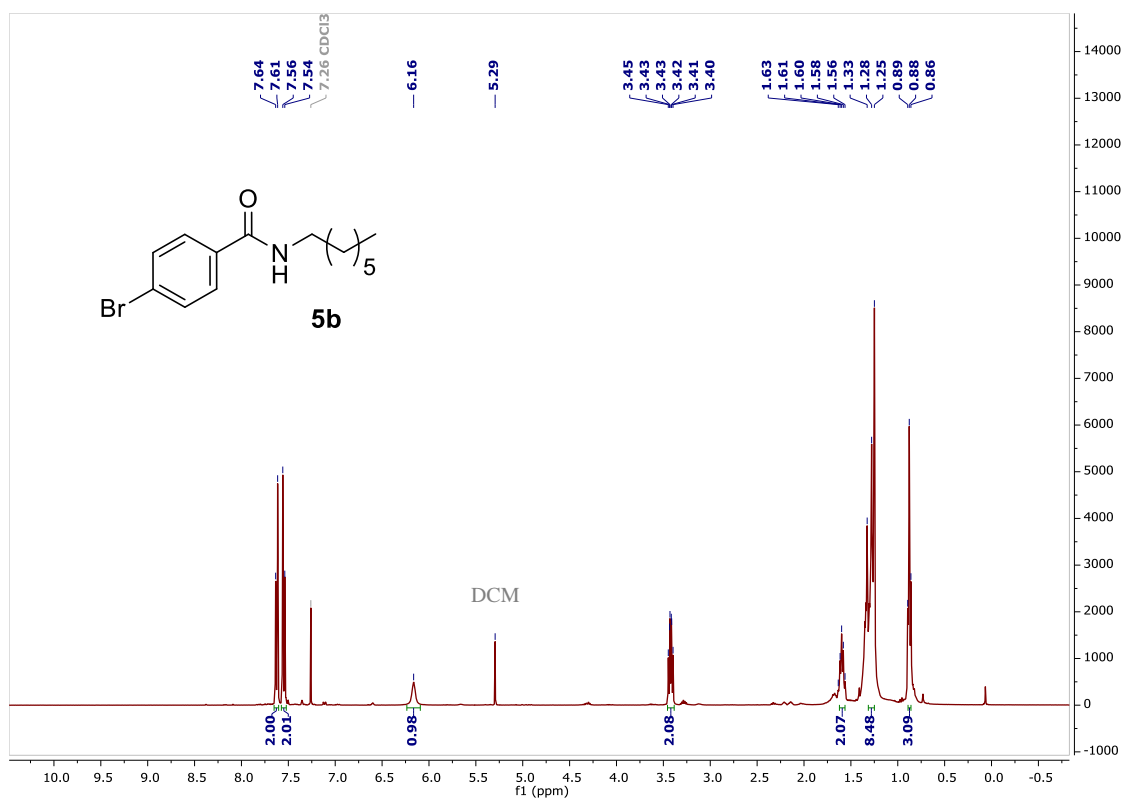
Figure S32. ^{1}H-NMR spectrum for **5b** in CDCl$_3$.
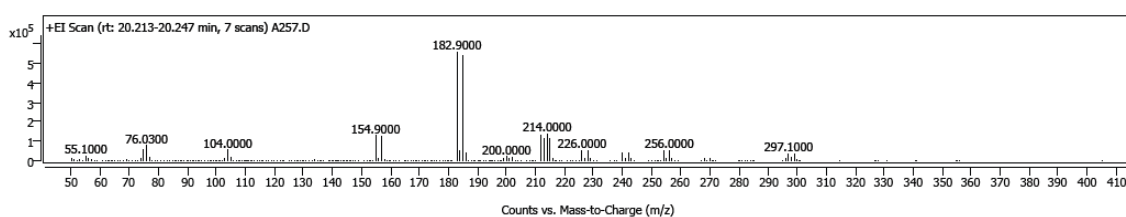

Figure S33. EI-MS spectrum for **5b**.

8-(4-bromobenzoyl)-8-azabicyclo[3.2.1]octan-3-one (**5e**)

Isolated yield: 184.9 mg (75%), yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$/MeOD): δ = 7.58 (2H, *d*, *J* = 8.4 Hz), 7.41 (2H, *d*, *J* = 8.4 Hz), 5.03 (1H, *brs*), 4.36 (1H, *brs*) 2.92 (1H, *brs*), 2.46 (2H, *brs*), 2.35 (1H, *brs*) 2.16 (2H, *d*, *J* = 7.2 Hz) 1.76 (2H, *d*, *J* = 8.2 Hz).

^{13}C NMR (400 MHz, CDCl$_3$/MeOD): δ = 207.2, 168.0, 134.4, 132.1, 129.0, 125.2, 70.7, 29.8.

HRMS (ESI): m/z calcd. for C$_{14}$H$_{15}$BrNO$_2^+$ [M+H]$^+$: 308.0281, found: 308.0291.

EI-MS (m/z, rel. int.): 307 (13, [M$^+$]), 280 (3), 250 (10), 183 (100), 155 (31), 124 (76), 104 (9), 76 (18), 50 (6).
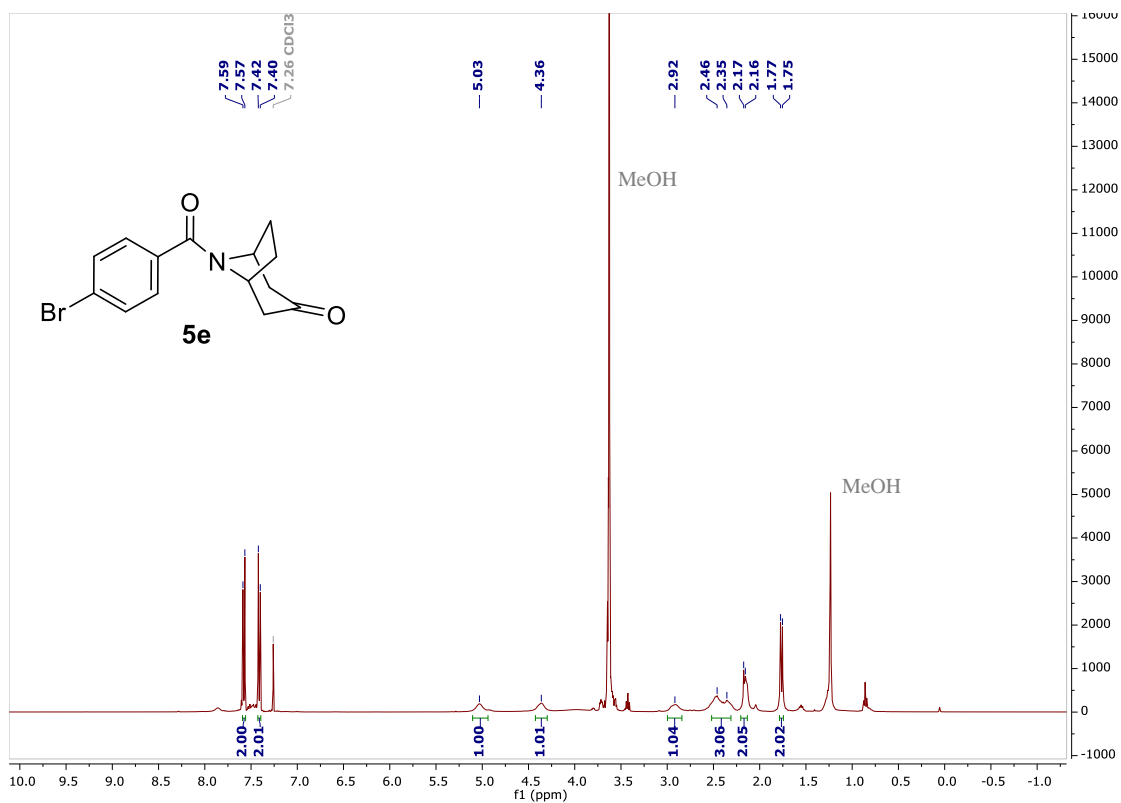
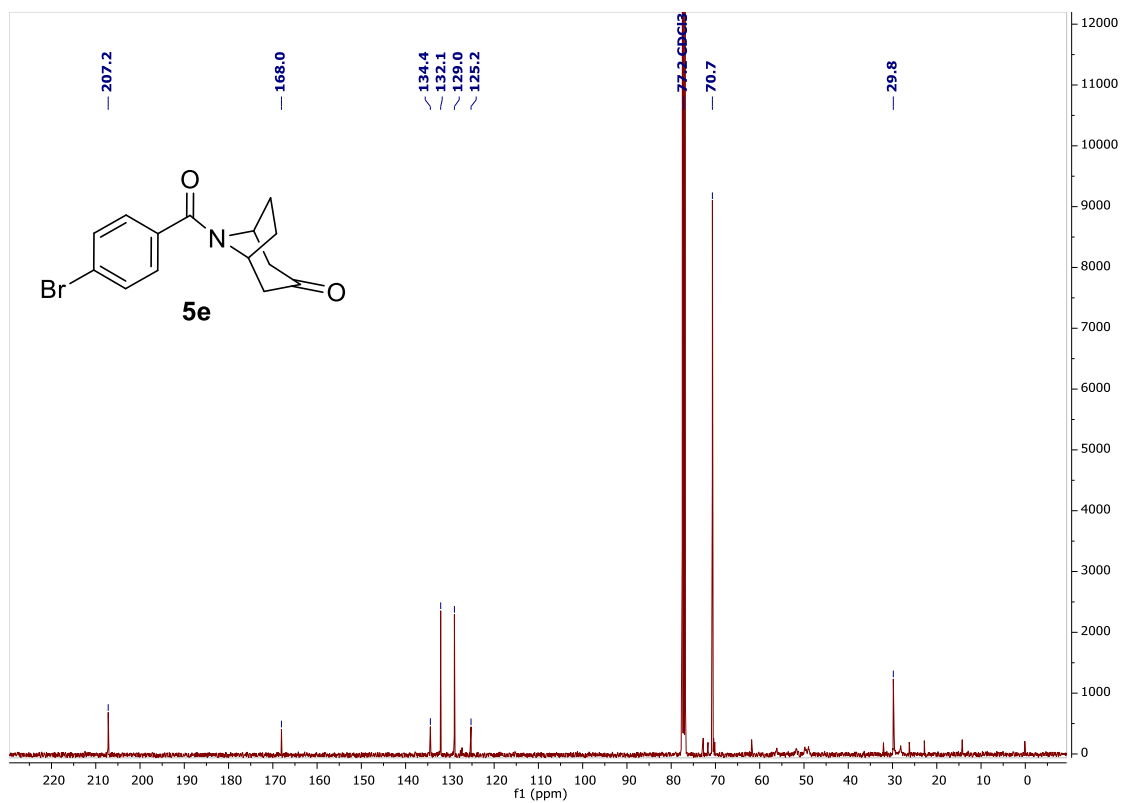**Figure S34.** ^{1}H-NMR spectrum for **5e** in CDCl$_3$/MeOD.

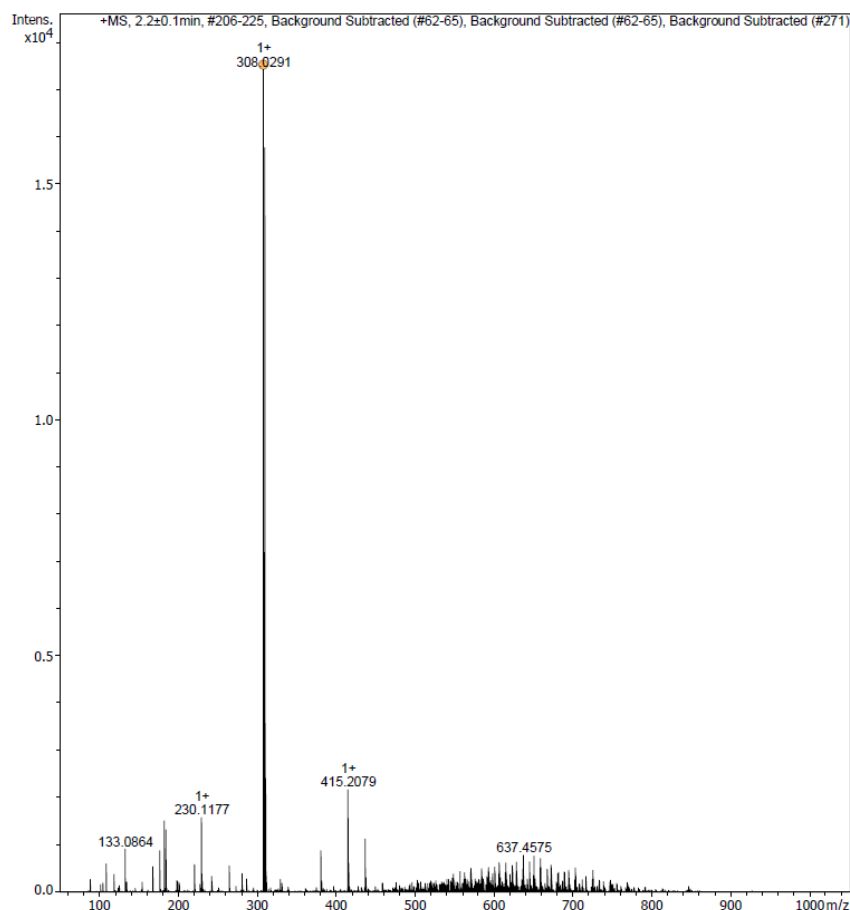**Figure S35.** ^{13}C-NMR spectrum for **5e** in CDCl$_3$/MeOD.

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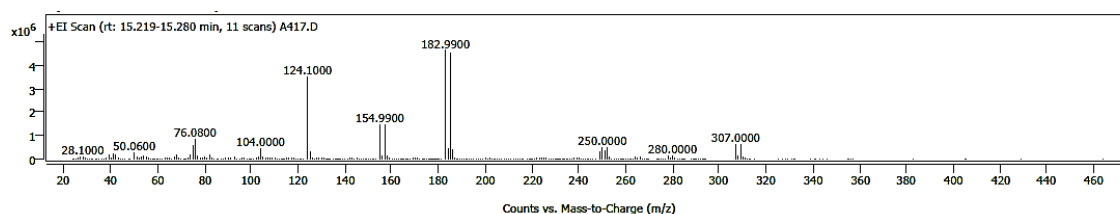**Figure S36.** HRMS(ESI) spectrum for **5e**.

Figure S37. EI-MS spectrum for **5e**.

17-(N,N-penta-1,5-diylcarbamoyl)-5α-androst-16-ene (**6a**)

Isolated yield: 81.3 mg (55%), yellowish oil

^{1}H NMR (400 MHz, CDCl$_3$): δ = 5.69–5.68 (1H, *m*), 3.55 (4H, *brs*) 2.23-2.17 (1H, *m*), 2.02-1.95 (1H, *m*), 1.81-1.79 (1H, *m*), 1.70-1.58 (8H, *m*), 1.52 (4H, *brs*) 1.47-1.37 (3H, *m*) 1.35-1.32 (2H, *m*) 1.29-1.25 (2H, *m*) 1.22 (2H, *m*), 1.04 (3H, *s*), 1.00-0.83 (3H, *m*), 0.81 (3H, *s*), 0.80-0.73 (1H, *m*).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 168.3, 149.4, 129.5, 57.0, 55.4, 48.9, 47.5, 38.7, 36.7, 34.5, 34.0, 32.3, 29.2, 29.1, 26.9, 24.9, 22.3, 20.7, 17.0, 12.3.

HRMS (ESI): m/z calcd. for C$_{25}$H$_{40}$NO$^+$ [M+H]$^+$: 370.3104, found: 370.3111.

EI-MS (m/z, rel. int.): 369 (51, [M$^+$]), 354 (100), 285 (5), 257 (9), 178 (12), 151 (10), 121 (10), 112 (23), 91 (14), 69 (15), 41 (10).
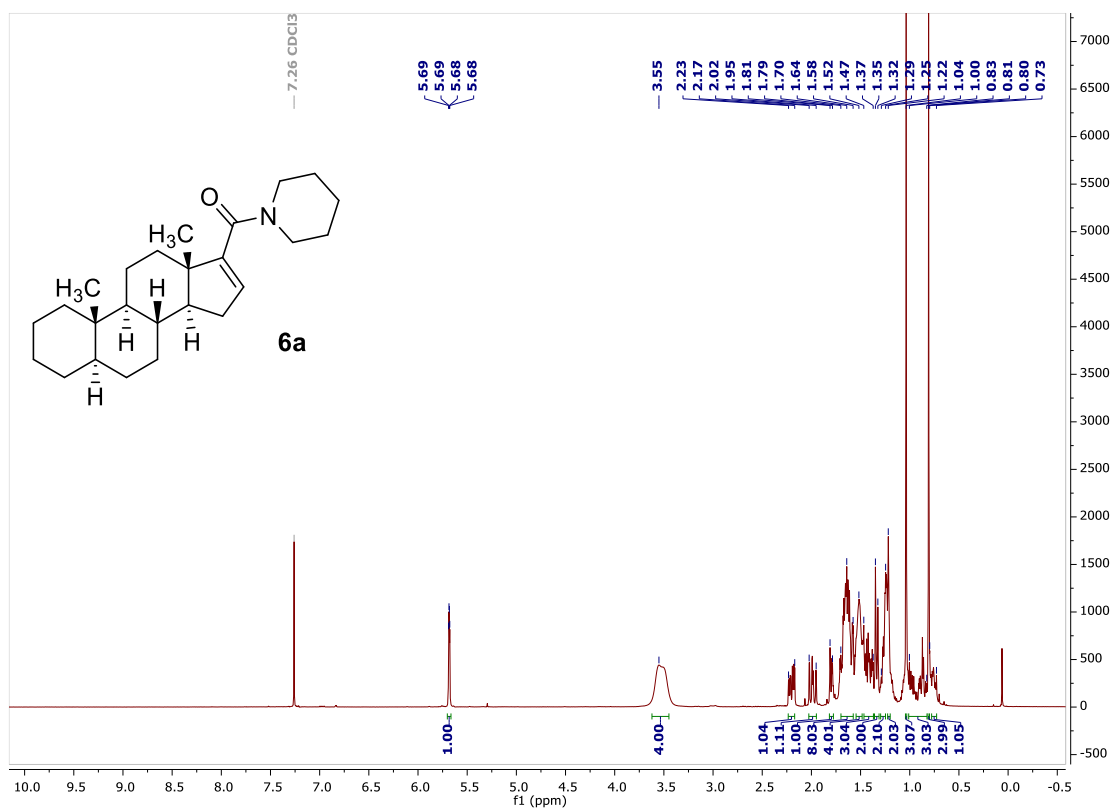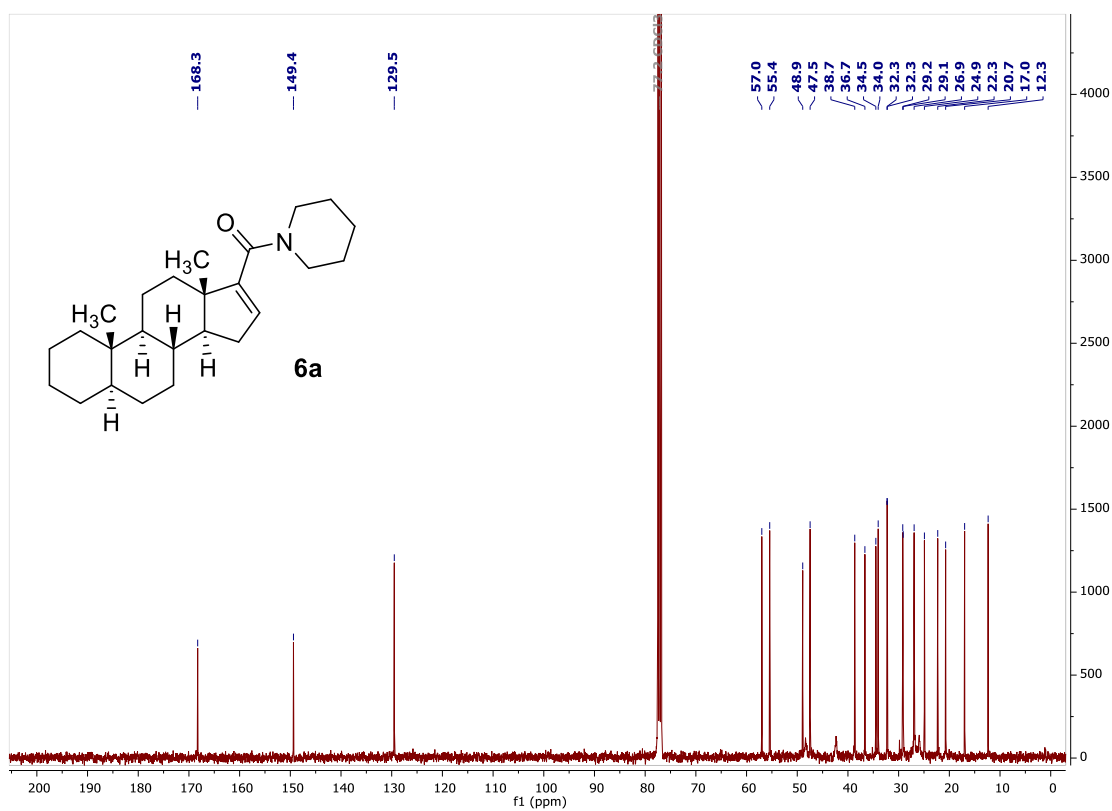
Figure S38. ^{1}H-NMR spectrum for **6a** in CDCl$_3$.

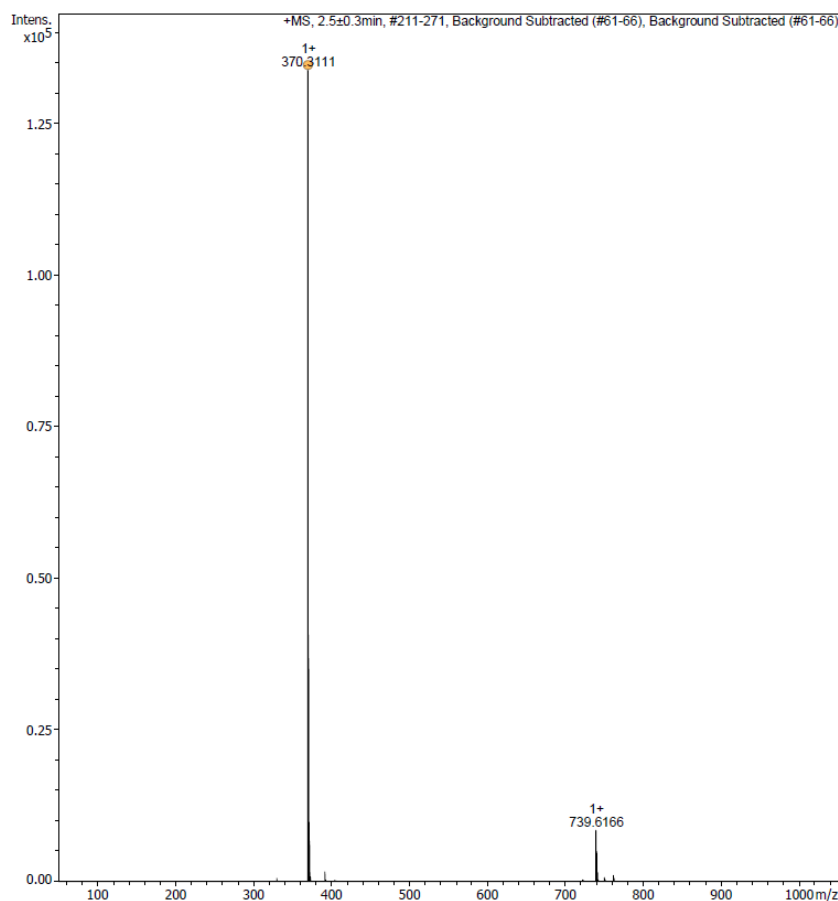**Figure S39.** ^{13}C-NMR spectrum for **6a** in CDCl$_3$.

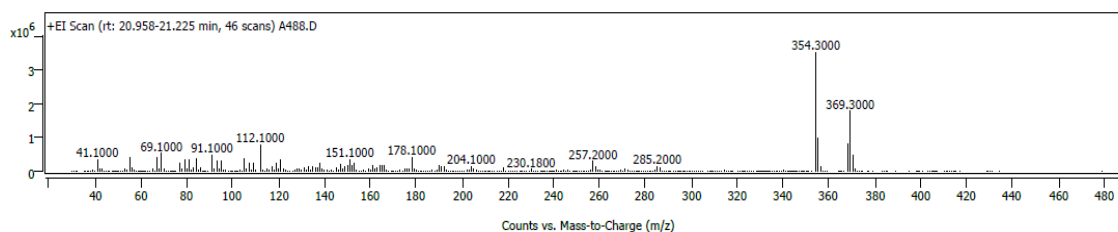**Figure S40.** HRMS(ESI) spectrum for **6a**.

Figure S41. EI-MS spectrum for **6a**.

3-Methoxy-17-[(N,N-(1',5'-pentandiyl)-carboxamido)]-13α-estra-1,3,5(10),16-tetraene (**7a**)

Isolated yield: 78.9 mg (52%), yellowish oil

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.19 (1H, *d*, *J* = 8.6 Hz), 6.71 (1H, *dd*, *J* = 8.6, 2.8 Hz), 6.64 (1H, *d*, *J* = 2.8 Hz), 5.75 (1H, *dd*, *J* = 3.2, 1.6 Hz), 3.78 (3H, *s*), 3.57 (4H, *brs*), 3.93-2.84 (2H, *m*), 2.36-2.10 (1H, *m*), 1.99-192 (2H, *m*), 1.76-1.47 (11H, *m*), 1.08 (3H, *s*).

EI-MS (m/z, rel. int.): 379 (100, [M$^+$]), 364 (95), 218 (13), 193 (13), 187 (20), 178 (10), 173 (38), 171 (19), 165 (10), 160 (17), 147 (30), 138 (12), 121 (22), 112 (26), 91 (19), 69 (13).
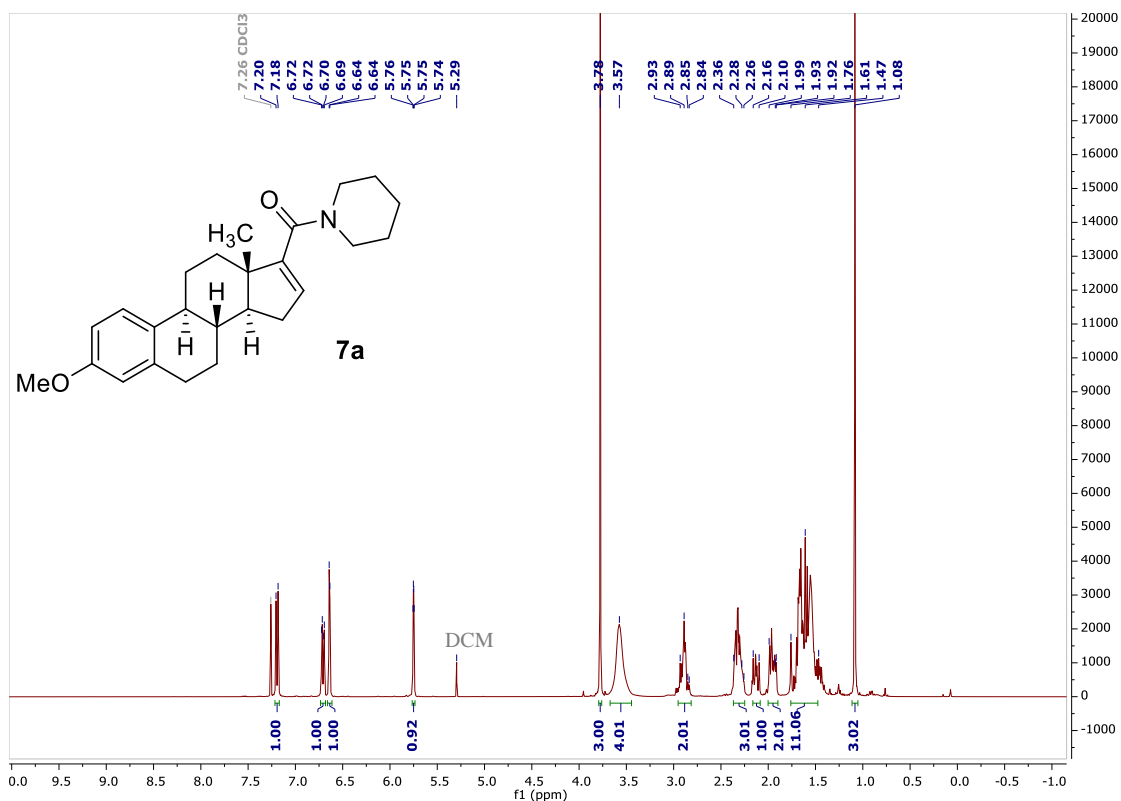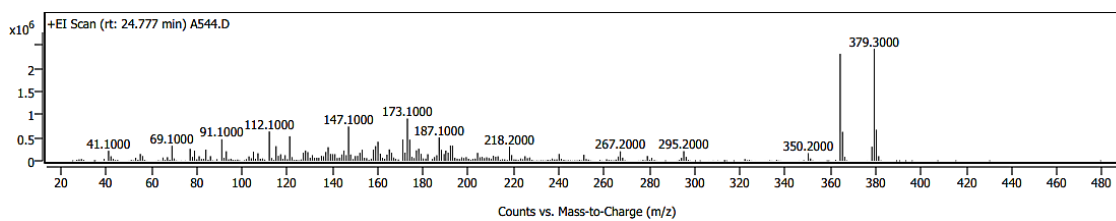
Figure S42. ^{1}H-NMR spectrum for **7a** in CDCl$_3$.

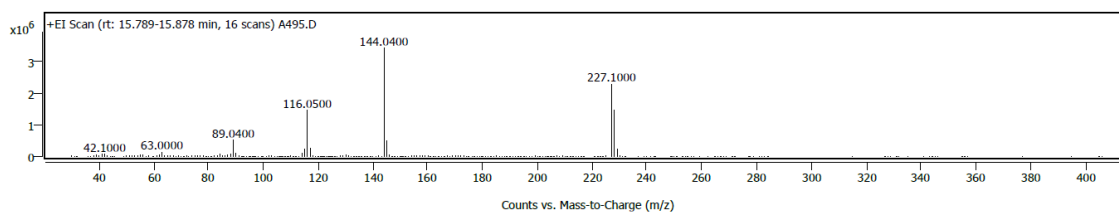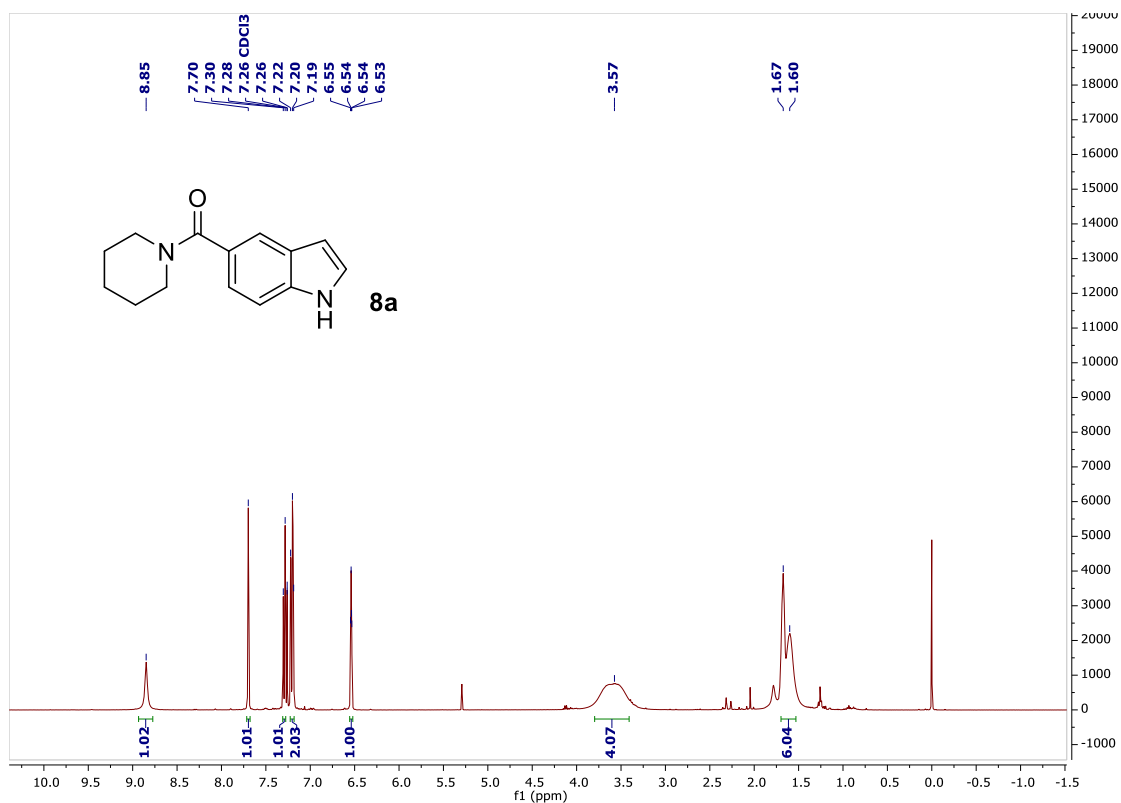**Figure S43.** EI-MS spectrum for **7a**.

(1H-indol-5-yl)(piperidin-1-yl)methanone (**8a**)

Isolated yield: 146.0 mg (80%), yellowish oil

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.85 (1H, *brs*), 7.70 (1H, *s*), 7.29 (1H, *d*, J = 8.4 Hz), 7.22-7.19 (2H, *m*), 6.55-6.53 (1H, *m*), 3.57 (4H, *brs*), 1.67 (2H, *brs*) 1.60 (4H, *brs*).

EI-MS (m/z, rel. int.): 227 (67, [M$^+$]), 144 (100), 116 (42), 89 (15), 63 (4).

Figure S44. ^{1}H-NMR spectrum for **8a** in CDCl$_3$.

Figure S45. EI-MS spectrum for **8a**.

tert-butyl (2-(6-chloronicotinamido)ethyl)carbamate (**9f**)

Isolated yield: 177.1 mg (74%), yellowish oil

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.84 (1H, *d*, *J* = 2.3 Hz), 8.13 (1H, *dd*, J = 8.3, 2.4 Hz), 7.74 (1H, *brs*), 7.40 (1H, *d*, *J* = 8.3 Hz) 5.01 (1H, *brs*), 3.58-3.54 (2H, *m*), 3.44-3.40 (2H, *m*), 1.43 (9H, *s*).

EI-MS (m/z, rel. int.): 226 (9) 182 (10), 170 (63), 159 (10), 157 (30), 140 (100) 135 (30), 112 (38), 85 (14), 76 (16), 57 (90), 41 (28), 30 (26).
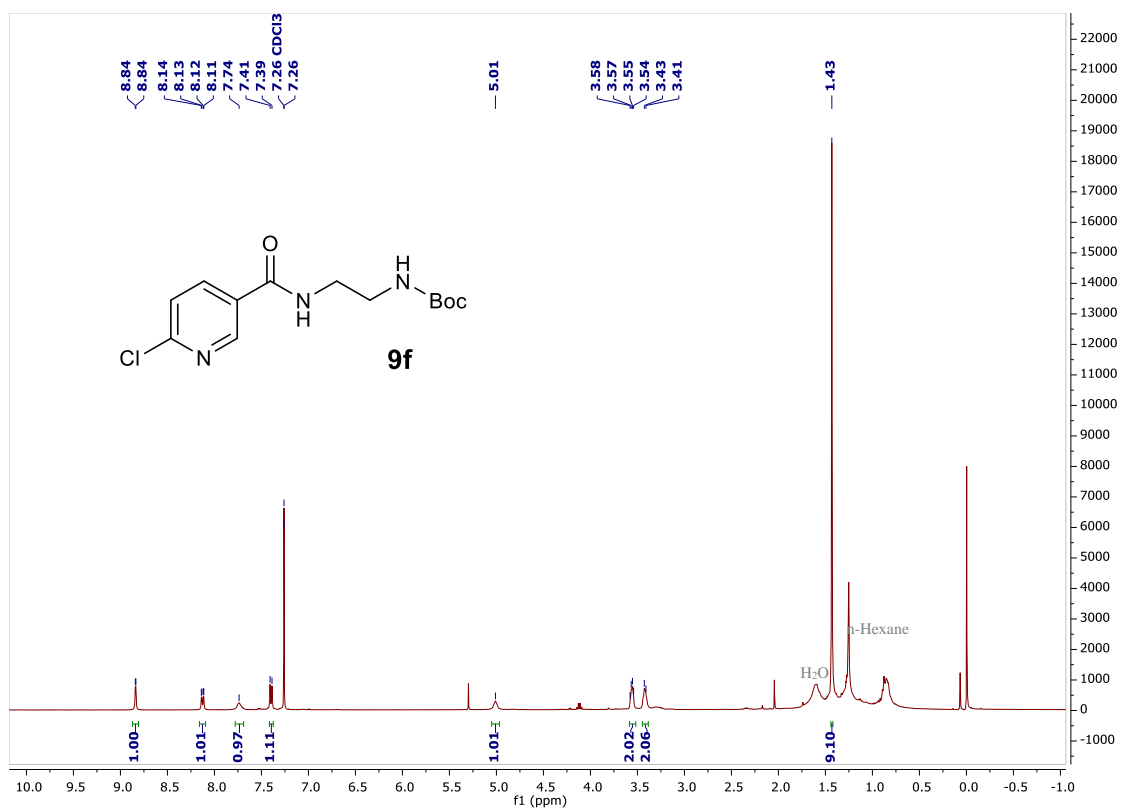
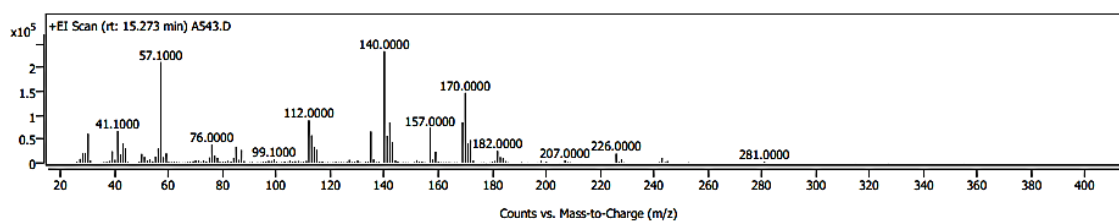**Figure S46.** ^{1}H-NMR spectrum for **9f** in CDCl$_3$.

Figure S47. EI-MS spectrum for **9f**.

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