Supporting information

for

A two-step continuous synthesis of α-ketoamide and α-amino ketones from 2° benzylic alcohols using hydrogen peroxide as an economical and benign oxidant

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1. General experimental information

Reagents and solvents: Commercially available reagents were used without any further purification. All organic solvents were also of reagent grade quality without any further purification.

Chromatography: Flash column chromatography was performed using silicycle silica gel (200-300 mesh).

Analytical thin-layer chromatography (TLC) was performed on 0.2 mm coated silica gel plates (HSGF 254) and visualized using a UV lamp (254 nm or 365 nm).

Nuclear Magnetic Resonance Spectroscopy:

^{1}H NMR was recorded on magnet system 400'54 ascend purchased from Bruker Biospin AG. ^{1}H NMR spectra chemical shifts (δ) are reported in parts per million (ppm) referenced to TMS (0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, m = multiplet, br = broad), coupling constant (J) in Hertz (Hz), and integration.

^{13}C NMR spectra chemical shifts (δ) are reported in parts per million (ppm) were referenced to carbon resonances in the NMR solvent ($CDCl_3$, δ = 77.23 ppm).

ESI-MS spectra were recorded on Agilent Q-TOF 6520.

2. General material information for continuous-flow setups

Parts information for continuous-flow system:

(1), Slit plate mixer LH25 (Hastelloy C) purchased from Ehrfeld Mikrotechnik BTS GmbH.

(2), The coil reactors and connecting tubes are PFA tubes purchased from Upchurch Scientific.

(3), Syringe pumps were purchased from Harvard Apparatus.

As shown in Figure S1, the PFA tubing reactor (ID=0.05 cm, length=1000 cm, volume=1.962 mL) was connected to two syringes respectively via the slit plate mixer. The syringe pumps were used to infuse the liquid reagent into the mixer and the reactor. The modest temperature was kept by the oil bath.

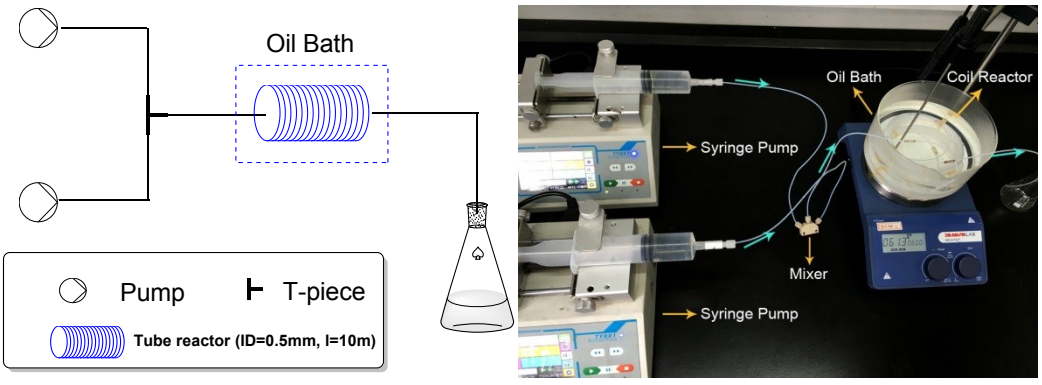


Figure S1: Flow parts connections in coil reactor

3. experimental details of a, b, c, d, e in table 1

3.1 experimental details of a in table 1

The reaction was carried out using a 25 mL round bottom flask charged with DL-1-phenethylalcohol (1 mmol, 0.1221 g, 1 eq), 1-oxa-4-azacyclohexane (3 mmol, 0.2614 g, 3 eq), potassium iodide (0.2 mmol, 0.0332 g, 0.2 eq), sulfuric acid (98%, 0.2 mmol, 0.0200 g, 0.2 eq), hydrogen peroxide (30% aq, 6 mmol, 0.6802 g, 6 eq), DMF (3 mL) and a magnetic stir bar. The reaction mixture was stirred at 70℃ for 24h.

3.2 experimental details of b in table 1

The reaction was carried out using a 25 mL round bottom flask charged with DL-1-phenethylalcohol (1 mmol, 0.1221 g,1 eq), 1-oxa-4-azacyclohexane (3 mmol, 0.2614 g, 3 eq), potassium iodide (0.2 mmol, 0.0332 g, 0.2 eq), sulfuric acid (98%, 0.2 mmol, 0.0200 g, 0.2 eq), DMF (3 mL) and a magnetic stir bar. Then a solution of hydrogen peroxide (H_2O_2 (30% aq, 6 mmol, 0.6802 g, 6 eq) in DMF (1.5 mL)) was added into the reaction mixture slowly with the help of springe pump within 12 h. the mixture was stirred for another 12 h.

3.3 Experimental details of c in table 1.

A solution of DL-1-phenethylalcohol (1 mmol, 0.1221 g, 1,eq), potassium iodide (0.2 mmol, 0.0332 g, 0.2 eq), sulfuric acid (98%, 0.2 mmol, 0.0200 g, 0.2 eq) and hydrogen peroxide (2 mmol, 0.2267 g, 2 eq) in DMF (1.5 mL) was stirred at 70℃. After 12h, 1-oxa-4-azacyclohexane (3 mmol, 0.2614 g, 3 eq) was added in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (30% aq, 4 mmol, 0.4535 g, 4 eq) in DMF (1.5 mL) was syringed addition within 2h. The mixture was stirred for another 1h.

3.4 Experimental details of d in table 1.

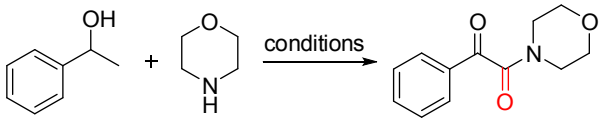
One vial was placed a 15 mL DMF solution of the DL-1-phenethylalcohol (10 mmol, 1.2207 g, 1 eq) and 1-oxa-4-azacyclohexane (30 mmol, 2.6136 g, 3 eq). Another vial was placed a 14.5 mL DMF solution of hydrogen peroxide (30% aq, 60 mmol, 6.8020 g, 6 eq), sulphuric acid (98%, 2 mmol, 0.2001 g, 0.2 eq) and potassium iodide (2 mmol, 0.3320 g, 0.2 eq). 0.5 mL H_2O was added to dissolve the potassium iodide. The reaction streams were introduced to the PFA tube reactor at a preheated temperature of 70℃ through the mixer. The flow rates of reagent and oxidant were both 0.327 mL/min (residence time was 3 min). The reaction mixture was collected in a vial through the segment of PTA tube.

3.5 Experimental details of e in table 1.

One vial was placed a 15 mL DMF solution of the DL-1-phenethylalcohol (10 mmol, 1.2207 g, 1 eq). Another vial was placed a 14.5 mL DMF solution of hydrogen peroxide (30% aq, 20 mmol, 2.2673 g, 2 eq), sulphuric acid (98%, 2 mmol, 0.2001 g, 0.2 eq) and potassium iodide (2 mmol, 0.3320 g, 0.2 eq). 0.5 mL H_2O was added to dissolve the potassium iodide. The reaction streams were introduced to the PFA tube reactor at a preheated temperature of 70℃ through the mixer. The flow rates of reagent and oxidant were both 0.327 mL/min (residence time was 3 min). The reaction mixture was collected in a vial through the segment of PTA tube. 3 mL reaction mixture was taken and 1-oxa-4-azacyclohexane (3 mmol, 0.2614 g, 3 eq) was added in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (30%

aq, 4 mmol, 0.4535 g, 4 eq) in DMF (1.5 mL)) was added slowly within 2h using springe pump. The mixture was stirred for another 1h.

4. Table S1: the equiv. of potassium iodide screening for two-step continuous flow synthesis of α-ketoamide[a]

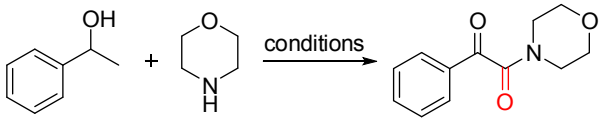


1a 2a 3a

Entry	Equiv. of potassium iodide	Yield (%)
1	0.2	95
2	0.15	93
3	0.1	94
4	0.05	94

[a]reaction conditions: 1a (1.0 mmol, 0.1221 g), 2a (3.0 mmol, 0.2614 g), KI, H_2O_2(30% aq, 6 mmol, 0.6802 g), H_2SO_4 (98%, 0.2 mmol, 0.0200 g), DMF, T (60℃), 3min+3h.

5. Table S2: the equiv. of sulfuric acid screening for two-step continuous flow synthesis of α-ketoamide[a]

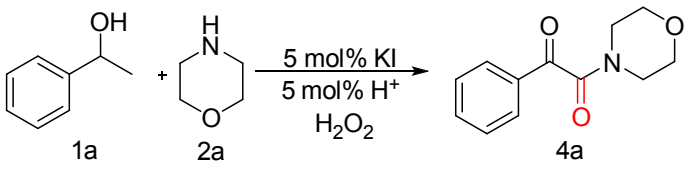


1a 2a 3a

Entry	Equiv. of sulfuric acid	Yield (%)
1	0.2	95
2	0.15	95
3	0.1	92
4	0.05	94

[a]reaction conditions: 1a (1.0 mmol, 0.1221 g), 2a (3.0 mmol, 0.2614 g), KI (0.05 mmol, 0.0083 g), H_2O_2 (30% aq, 6 mmol, 0.6802 g), H_2SO_4(98%), DMF, T (60℃), 3min+3h.

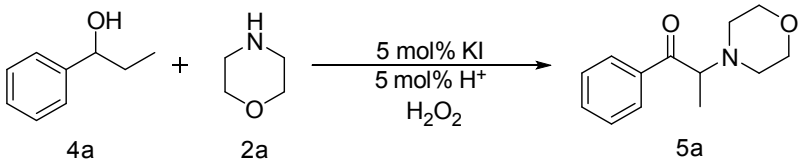
6. Table S3: the equiv. of oxidant screening for two-step continuous flow synthesis of α-ketoamide[a]



Entry	Equiv. of oxidant	Yield (%)
1	6 (2+4)	95
2	5.8 (2+3.8)	92
3	5.6(2+3.6)	93
4	5.4(2+3.4)	82

reaction conditions: 1a (1.0 mmol, 0.1221 g), 2a (3.0 mmol, 0.2614 g), KI (0.05 mmol, 0.0083 g), H_2O_2(30% aq), H_2SO_4 (98% 0.05 mmol, 0.0050 g), DMF, T (60℃), 3min+3h.

7. Table S4: the equiv. of oxidant screening for two-step continuous flow synthesis of α-amino ketones[a]



Entry	Equiv. of oxidant	Yield (%)
1	6 (2+4)	91
2	5 (2+3)	92
3	4 (2+2)	88
4	3.5(2+1.5)	85
5	3 (2+1)	65

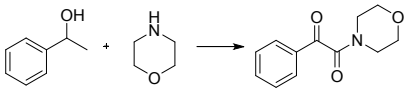
[a]reaction conditions: 4a (1.0 mmol, 0.1361 g), 2a (3.0 mmol, 0.2614 g), KI (0.05 mmol, 0.0083 g), H_2O_2(30% aq), H_2SO_4 (98%, 0.05 mmol, 0.0050 g), DMF, T (60℃), 3min+3h.

8. General experimental details for the synthesis of α-ketoamides

One vial was placed a 15 mL DMF solution of the specific benzylic alcohol (10 mmol, 1 eq). Another vial was placed a 14.5 mL DMF solution of hydrogen peroxide (30% aq, 20 mmol, 2.2673 g, 2 eq), sulphuric acid (98%, 0.5 mmol, 0.0500 g, 0.05 eq) and potassium iodide (0.5 mmol, 0.0830 g, 0.05 eq). 0.5 mL H_2O was added to dissolve the potassium iodide. The reaction streams were introduced to the PFA tube reactor at a preheated temperature of 60℃ through the mixer. The flow rates of reagent and oxidant were both 0.327 mL/min (residence time was 3 min). The reaction mixture was collected in a vial through the segment of PTA tube. 3 mL reaction mixture was taken and amine (3 mmol, 3 eq) was added in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (30% aq, 3.6 mmol, 0.4081 g in DMF (1.5 mL)) was added slowly within 2h using springe pump. After the TLC revealed that

the full conversion of staring material was consumed, the reaction mixture was cooled and diluted with ethyl acetate (30 mL). The crude product was washed with brine (30 mL) and water (30 mL). The separated organic layer was dried over by anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane/ethyl acetate to afford the desired product.

8.1



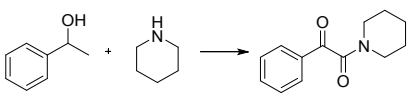
8.1.1small scale

One vial was placed a 15 mL DMF solution of the DL-1-Phenethylalcohol (10 mmol, 1.2207 g, 1 eq). Another vial was placed a 14.5 mL DMF solution of hydrogen peroxide (30% aq, 20 mmol, 2.2673 g, 2 eq), sulphuric acid (98%, 0.5 mmol, 0.0500 g, 0.05 eq) and potassium iodide (0.5 mmol, 0.0830 g, 0.05 eq). 0.5 mL H_2O was added to dissolve the potassium iodide. The reaction streams were introduced to the PFA tube reactor at a preheated temperature of 60℃ through the mixer. The flow rates of reagent and oxidant were both 0.327 mL/min (residence time was 3 min). The reaction mixture was collected in a vial through the segment of PTA tube. 3 mL reaction mixture was taken and 1-oxa-4-azacyclohexane (3 mmol, 0.2614 g, 3 eq) was added in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (30% aq, 3.6 mmol, 0.4081 g in DMF (1.5 mL)) was added slowly within 2h using springe pump. After another 1h, the reaction mixture was cooled and diluted with ethyl acetate (30mL). The crude product was washed with brine (30 mL) and water (30 mL). The separated organic layer was dried over by anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane/ethyl acetate (10:1) to afford the desired product.

8.1.2scale up to gram degree

One vial was placed a 15 mL DMF solution of the DL-1-Phenethylalcohol (10 mmol, 1.2207 g, 1 eq). Another vial was placed a 14.5 mL DMF solution of hydrogen peroxide (30% aq, 20 mmol, 2.2673 g, 2 eq), sulphuric acid (98%, 0.5 mmol, 0.0500 g, 0.05 eq) and potassium iodide (0.5 mmol, 0.0830 g, 0.05 eq). 0.5 mL H_2O was added to dissolve the potassium iodide. The reaction streams were introduced to the PFA tube reactor at a preheated temperature of 60℃ through the mixer. The flow rates of reagent and oxidant were both 0.327 mL/min (residence time was 3 min). The reaction mixture was collected in a vial through the segment of PTA tube. 25 mL reaction mixture was taken and 1-oxa-4-azacyclohexane (25 mmol, 2.1780 g, 3 eq) was added in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (30% aq, 30 mmol 3.4010 g in DMF (12.5 mL)) was added slowly within 2h using springe pump. After another 1h, the reaction mixture was cooled and diluted with ethyl acetate (80 mL). The crude product was washed with brine (80 mL) and water (80 mL). The separated organic layer was dried over by anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane/ethyl acetate (10:1) to afford the desired product with 88% isolated yield.

8.2



8.2.1small scale

One vial was placed a 15 mL DMF solution of the DL-1-Phenethylalcohol (10 mmol, 1.2207 g, 1 eq). Another vial was placed a 14.5 mL DMF solution of hydrogen peroxide (30% aq, 20 mmol, 2.2673 g, 2 eq), sulphuric acid (98%, 0.5 mmol, 0.0500 g, 0.05 eq) and potassium iodide (0.5 mmol, 0.0830 g, 0.05 eq). 0.5 mL H_2O was added to dissolve the potassium iodide. The reaction streams were introduced to the PFA tube reactor at a preheated temperature of 60℃ through the mixer. The flow rates of reagent and oxidant were both 0.327 mL/min (residence time was 3 min). The reaction mixture was collected in a vial through the segment of PTA tube. 3 mL reaction mixture was taken and piperidine (3 mmol, 0.2553 g, 3 eq) was added in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (30% aq, 3.6 mmol, 0.4081 g in DMF (1.5 mL)) was added slowly within 2h using springe pump. After another 1h, the reaction mixture was cooled and diluted with ethyl acetate (30 mL). The crude product was washed with brine (30 mL) and water (30 mL). The separated organic layer was dried over by anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane/ethyl acetate (10:1) to afford the desired product.

8.2.2scale up to gram degree

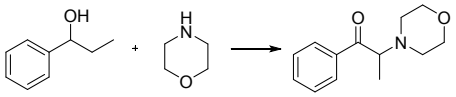
One vial was placed a 15 mL DMF solution of the DL-1-Phenethylalcohol (10 mmol, 1.2207 g, 1 eq). Another vial was placed a 14.5 mL DMF solution of hydrogen peroxide (30% aq, 20 mmol, 2.2673 g, 2 eq), sulphuric acid (98%, 0.5 mmol, 0.0500 g, 0.05 eq) and potassium iodide (0.5 mmol, 0.0830 g, 0.05 eq). 0.5 mL H_2O was added to dissolve the potassium iodide. The reaction streams were introduced to the PFA tube reactor at a preheated temperature of 60℃ through the mixer. The flow rates of reagent and oxidant were both 0.327 mL/min (residence time was 3 min). The reaction mixture was collected in a vial through the segment of PTA tube. 25 mL reaction mixture was taken and piperidine (25 mmol, 2.1272 g, 3 eq) was added in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (30% aq, 30 mmol, 3.4010 g in DMF (12.5 mL)) was added slowly within 2h using springe pump. After another 1h, the reaction mixture was cooled and diluted with ethyl acetate (80 mL). The crude product was washed with brine (80 mL) and water (80 mL). The separated organic layer was dried over by anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane/ethyl acetate (10:1) to afford the desired product with 84% isolated yield.

9. General experimental details for the synthesis of α-amino ketones

One vial was placed a 15 mL DMF solution of the specific benzylic alcohol (10 mmol, 1 eq). Another vial was placed a 14.5 mL DMF solution of hydrogen peroxide (30% aq, 20 mmol, 2.2673 g, 2 eq), sulphuric acid (98%, 0.5 mmol, 0.0500 g, 0.05 eq) and potassium iodide (0.5 mmol, 0.0830 g, 0.05 eq). 0.5 mL H_2O was added to dissolve the potassium iodide. The reaction streams were introduced to the PFA tube reactor at a preheated temperature of 60℃ through the mixer. The flow rates of reagent and oxidant were both 0.327 mL/min (residence time was 3 min). The reaction mixture was collected in a vial through the segment of PTA tube. 3 mL reaction mixture was taken and amine (3 mmol, 3 eq) was added

in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (30% aq, 1.5 mmol, 0.1700 g) in DMF (1.5 mL)) was added slowly within 2h using springe pump. After the TLC revealed that the full conversion of staring material was consumed, the reaction mixture was cooled and diluted with ethyl acetate (30 mL). The crude product was washed with brine (30 mL) and water (30 mL). The separated organic layer was dried over by anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane/ethyl acetate to afford the desired product.

9.1



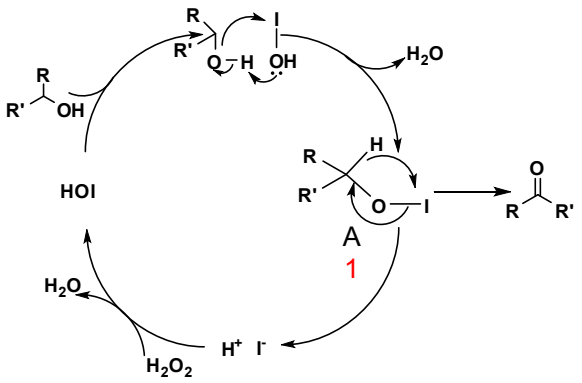
9.1.1small scale

One vial was placed a 15 mL DMF solution of 1-phenyl-1-propanol (10 mmol, 1.3609 g, 1 eq). Another vial was placed a 14.5 mL DMF solution of hydrogen peroxide (30% aq, 20 mmol, 2.2673 g, 2 eq), sulphuric acid (98%, 0.5 mmol, 0.0500 g, 0.05 eq) and potassium iodide (0.5 mmol, 0.0830 g, 0.05 eq). 0.5 mL H_2O was added to dissolve the potassium iodide. The reaction streams were introduced to the PFA tube reactor at a preheated temperature of 60℃ through the mixer. The flow rates of reagent and oxidant were both 0.327 mL/min (residence time was 3 min). The reaction mixture was collected in a vial through the segment of PTA tube. 3 mL reaction mixture was taken and 1-oxa-4-azacyclohexane (3 mmol, 0.2614 g, 3 eq) was added in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (30% aq, 1.5 mmol, 0.1700 g) in DMF (1.5 mL)) was added slowly within 2h using springe pump. After another 0.25h, the reaction mixture was cooled and diluted with ethyl acetate (30 mL). The crude product was washed with brine (30 mL) and water (30 mL). The separated organic layer was dried over by anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane/ethyl acetate (10:1) to afford the desired product.

9.1.2scale up to gram degree

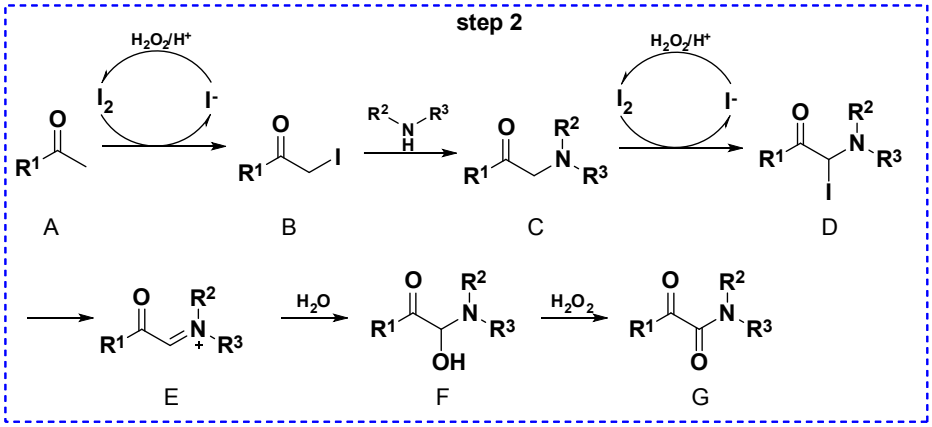
One vial was placed a 15 mL DMF solution of 1-phenyl-1-propanol (10 mmol, 1.3609 g, 1 eq). Another vial was placed a 14.5 mL DMF solution of hydrogen peroxide (30% aq, 20 mmol, 2.2673 g, 2 eq), sulphuric acid (98%, 0.5 mmol, 0.0500 g, 0.05 eq) and potassium iodide (0.5 mmol, 0.0830 g, 0.05 eq). 0.5 mL H_2O was added to dissolve the potassium iodide. The reaction streams were introduced to the PFA tube reactor at a preheated temperature of 60℃ through the mixer. The flow rates of reagent and oxidant were both 0.327 mL/min (residence time was 3 min). The reaction mixture was collected in a vial through the segment of PTA tube. 25 mL reaction mixture was taken and 1-oxa-4-azacyclohexane (25 mmol, 2.1780 g, 3 eq) was added in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (30% aq, 12.5 mmol, 1.4171 g) in DMF (12.5 mL)) was added slowly within 2h using springe pump. After another 0.25h, the reaction mixture was cooled and diluted with ethyl acetate (80 mL). The crude product was washed with brine (80 mL) and water (80 mL). The separated organic layer was dried over by anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane/ethyl acetate (10:1) to afford the desired product with 86 % isolated yield.

10. Proposed mechanism



Scheme S2: Proposed mechanism of step 1

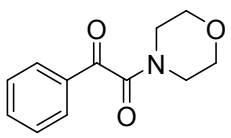
Initially, I^- was oxidized to form the hydroiodic acid in the presence of acid and hydrogen peroxide. The generated hydroiodic acid subsequently reacted with the corresponding hydroxyl group to form the hypoiodite intermediate 1, which yielded the corresponding carbonyl compounds via α-hydrogen elimination. Brnsted acid and I^- were reformatted to maintain the system circularly.



Scheme S3: Proposed mechanism of step 2

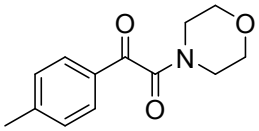
As listed in figure S2, the oxidative amidation of acetophenones was likely to undergo the processes of iodination (A-B), nucleophilic substitution by amine (B-C), iodination (C-D), ionization (D-E), hydrolysis (E-F) and oxidation (F-G).

11. ^1H and ^{13}C NMR spectra of new compounds

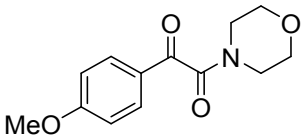


1-morpholino-2-phenylethane-1,2-dione (3a)[1]: Yellow solid (210.3 mg, 96% yield); ^1H NMR

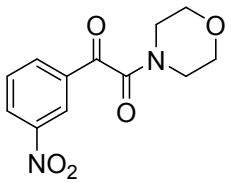
(400 MHz, CDCl3) δ 7.95 (d, J = 7.3 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 3.78 (br, s, 4H), 3.67 – 3.60 (m, 2H), 3.40 – 3.33 (m, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 191.29, 165.59, 135.08, 133.20, 129.82, 129.24, 66.88, 66.81, 46.41, 41.76; HRMS (TOF) m/z [M + Na]$^+$ Calcd for $C_{12}H_{13}NO_3$ 242.0788 found 242.0783.



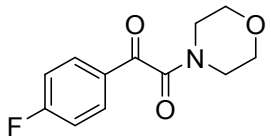
1-morpholino-2-(*p*-tolyl)ethane-1,2-dione (3b)[2]: Yellow solid (226.1 mg, 97% yield); ^{1}H NMR (400 MHz, CDCl3) δ 7.83 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 3.77 (br, s, 4H), 3.64 – 3.60 (m, 2H), 3.37 – 3.33 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 190.98, 165.75, 146.36, 130.73, 129.90, 129.86, 66.82, 66.74, 46.34, 41.64, 22.00; HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{13}H_{15}NO_3$ 234.1125 found 234.1106.



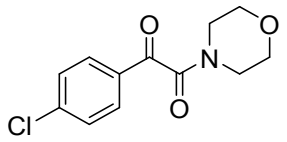
1-(4-methoxyphenyl)-2-morpholinoethane-1,2-dione (3d): Yellow solid (134.5 mg, 54% yield); ^{1}H NMR (400 MHz, CDCl3) δ 7.89 (t, J = 12.9 Hz, 2H), 6.94 (t, J = 12.3 Hz, 2H), 3.88 – 3.79 (m, 3H), 3.73 (d, J = 25.3 Hz, 4H), 3.60 (t, J = 10.4 Hz, 2H), 3.33 (t, J = 10.7 Hz, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 189.91, 165.89, 165.11, 132.23, 126.24, 114.51, 66.86, 66.76, 55.76, 46.38, 41.64; HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{13}H_{15}NO_4$ 250.1074 found 250.1072.



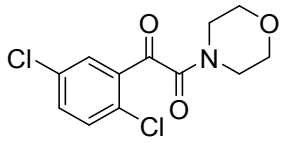
1-morpholino-2-(3-nitrophenyl)ethane-1,2-dione (3e)[1]: Yellow solid (258.8mg, 98% yield); ^{1}H NMR (400 MHz, CDCl3) δ 8.78 (t, J = 1.8 Hz, 1H), 8.48 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 8.34 – 8.27 (m, 1H), 7.74 (t, J = 8.0 Hz, 1H), 3.83 – 3.79 (m, 4H), 3.72 – 3.67 (m, 2H), 3.46 – 3.42 (m, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 188.25, 164.00, 148.73, 135.24, 134.66, 130.48, 128.96, 124.64, 66.85, 66.74 46.48, 42.10; HRMS (TOF) m/z [M + Na]$^+$ Calcd for $C_{12}H_{12}N_2O_5$ 287.0638 found 287.0623.



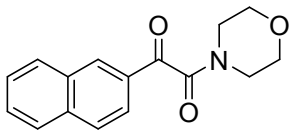
1-(4-fluorophenyl)-2-morpholinoethane-1,2-dione (3f)[1]: Yellow solid (227.6 mg, 96% yield); ^{1}H NMR (400 MHz, CDCl3) δ 8.06 – 7.95 (m, 2H), 7.19 (t, J = 8.5 Hz, 2H), 3.79 (s, 4H), 3.70 – 3.62 (m, 2H), 3.43 – 3.34 (m, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 189.50, 166.94 (d, J=256.7), 165.22, 132.69 (d, J=9.8), 129.75 (d, J=2.8), 116.70, 116.48, 66.89, 66.79, 46.44, 41.84; HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{12}H_{12}FNO_3$ 238.0874 found 238.0876.



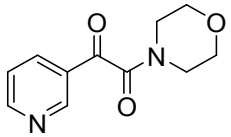
1-(4-chlorophenyl)-2-morpholinoethane-1,2-dione (3g)[3]: Yellow solid (245.4 mg, 97% yield); ^{1}H NMR (400 MHz, CDCl3) δ 7.98 – 7.85 (m, 2H), 7.56 – 7.46 (m, 2H), 3.82 – 3.74 (m, 4H), 3.69 – 3.63 (m, 2H), 3.42 – 3.34 (m, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 188.83, 164.04, 140.76, 130.61, 130.18, 128.64, 65.88, 65.79, 45.43, 40.85; HRMS (TOF) m/z [M + Na]$^+$ Calcd for $C_{12}H_{12}ClNO_3$ 276.0398 found 276.0374.



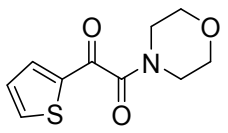
1-(2,5-dichlorophenyl)-2-morpholinoethane-1,2-dione (3h): Yellow solid (266.9 mg, 93% yield); ^{1}H NMR (400 MHz, CDCl3) δ 7.73 (d, J = 8.5 Hz, 1H), 7.39 (dd, J = 9.4, 7.7 Hz, 1H), 7.34 – 7.25 (m, 1H), 3.74 – 3.61 (m, 6H), 3.47 (d, J = 3.9 Hz, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 187.39, 163.81, 134.03, 133.29, 132.93, 130.92, 130.90, 130.67, 65.38, 65.33, 45.28, 41.13; HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{12}H_{11}Cl_2NO_3$ 288.0189 found 288.0165.



1-morpholino-2-(naphthalen-2-yl)ethane-1,2-dione (3i): Yellow solid (263.7 mg, 98% yield); ^{1}H NMR (400 MHz, CDCl3) δ 8.46 (s, 1H), 8.04 – 7.86 (m, 4H), 7.61 (dt, J = 28.4, 7.3 Hz, 2H), 3.84 (s, 4H), 3.72 – 3.61 (m, 2H), 3.47 – 3.36 (m, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 191.34, 165.70, 136.54, 133.16, 132.53, 130.53, 130.02, 129.66, 129.30, 128.08, 127.35, 123.68, 66.87, 66.82, 46.47, 41.83; HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{16}H_{15}NO_3$ 270.1125 found 270.1140.

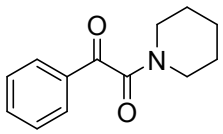


1-morpholino-2-(pyridin-3-yl)ethane-1,2-dione (3k)[1]: Yellow solid (202.5 mg, 92% yield); ^{1}H NMR (400 MHz, CDCl3) δ 9.07 (s, 1H), 8.81 – 8.75 (m, 1H), 8.19 (dd, J = 8.0, 2.0 Hz, 1H), 7.46 – 7.37 (m, 1H), 3.72 (s, 4H), 3.63 – 3.58 (m, 2H), 3.38 – 3.33 (m, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 189.45, 164.13, 154.80, 151.17, 136.73, 128.77, 123.92, 66.68, 66.55, 46.25, 41.79; HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{11}H_{12}N_2O_3$ 221.0921 found 221.0928.

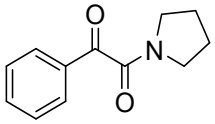


1-morpholino-2-(thiophen-2-yl)ethane-1,2-dione (3l)[4]: Yellow oil (2115 mg, 94% yield); ^{1}H NMR (400 MHz, CDCl3) δ 7.81 (ddd, J = 5.9, 4.4, 1.0 Hz, 2H), 7.17 (dd, J = 4.8, 4.0 Hz, 1H), 3.78 – 3.71 (m, 4H), 3.69 – 3.62 (m, 2H), 3.51 – 3.44 (m, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 182.90,

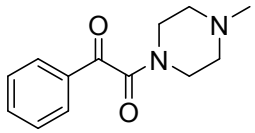
164.41, 140.36, 136.87, 136.37, 128.82, 66.89, 66.70, 46.52, 42.03; HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{10}H_{11}NO_3S$ 226.0532 found 226.0552.



1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione (3m)[5]: Yellow solid (206.2 mg, 95% yield); ^{1}H NMR (400 MHz, CDCl3) δ 7.92 (d, J = 1.4 Hz, 2H), 7.65 – 7.59 (m, 1H), 7.49 (t, J = 7.7 Hz, 2H), 3.69 (s, 2H), 3.31 – 3.23 (m, 2H), 1.71 – 1.64 (m, 4H), 1.57 – 1.47 (m, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 192.05, 165.54, 134.74, 133.36, 129.65, 129.09, 47.12, 42.24, 26.29, 25.54, 24.47; HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{13}H_{15}NO_2$ 218.1184 found 218.1184.

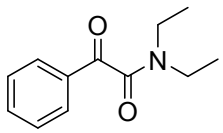


1-phenyl-2-(pyrrolidin-1-yl)ethane-1,2-dione (3n)[4]: Yellow solid (195.0 mg, 96% yield); ^{1}H NMR (400 MHz, CDCl3) δ 8.05 – 7.94 (m, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 3.64 (t, J = 6.8 Hz, 2H), 3.40 (t, J = 6.2 Hz, 2H), 2.00 – 1.87 (m, 4H); HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{12}H_{13}NO_2$ 204.1019 found 204.1026.

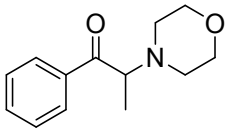


One vial was placed a 15 mL DMF solution of DL-1-phenethylalcohol (10 mmol, 1 eq). Another vial was placed a 14.5 mL DMF solution of hydrogen peroxide (30%, 20 mmol, 2 eq), sulphuric acid (98%, 0.5 mmol, 0.05 eq) and potassium iodide (0.5 mmol, 0.05 eq). 0.5 mL H_2O was added to dissolve the potassium iodide. The reaction streams were introduced to the PFA tube reactor at a preheated temperature of 60℃ through the mixer. The flow rates of reagent and oxidant were both 0.327 mL/min (residence time was 3 min). The reaction mixture was collected in a vial through the segment of PTA tube. 3 mL reaction mixture was taken and 1-methylpiperazine (3 mmol, 3 eq) was added in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (3.6 mmol) in DMF (1.5 mL)) was added slowly within 2h using springe pump. After the TLC revealed that the full conversion of staring material was completed, the reaction mixture was cooled and diluted with dichloromethane (30mL). The crude product was washed with brine (30mL) and water (30mL). The separated organic layer was dried over by anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane/ethyl acetate/triethylamine to afford the desired product.

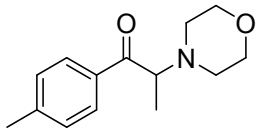
1-(4-methylpiperazin-1-yl)-2-phenylethane-1,2-dione (3o)[6]: Yellow solid (220.5 mg, 95% yield); ^{1}H NMR (400 MHz, CDCl3) δ 7.96 – 7.87 (m, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 3.82 – 3.71 (m, 2H), 3.39 – 3.28 (m, 2H), 2.51 – 2.45 (m, 2H), 2.36 – 2.32 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 191.54, 165.44, 134.88, 133.16, 129.69, 129.11, 54.95, 54.49, 46.04, 45.81, 41.20; HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{13}H_{16}N_2O_2$ 233.1285 found 233.1281.



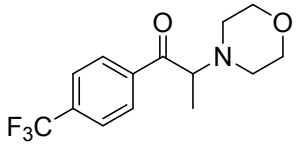
N,N-diethyl-2-oxo-2-phenylacetamide (3p)[2]: Yellow solid (168.2 mg,82% yield); ^{1}H NMR (400 MHz, CDCl3) δ 7.97 – 7.85 (m, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 3.53 (q, J = 7.2 Hz, 2H), 3.21 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 191.66, 166.80, 134.64, 133.28, 129.64, 129.01, 42.16, 38.85, 14.14, 12.87; HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{12}H_{15}NO_2$ 206.1176 found 206.1191.



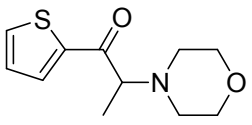
2-morpholino-1-phenylpropan-1-one (5a) [7]: pale yellow solid (210.3 mg, 96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.05 (m, 2H), 7.57 – 7.51 (m, 1H), 7.41-7.46 (m, 2H), 4.06 (q, *J* = 6.8 Hz, 1H), 3.71 – 3.62 (m, 4H), 2.65 – 2.52 (m, 4H), 1.28 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.18 (s), 135.18 (s), 132.03 (s), 127.78 (s), 127.41 (s), 66.14 (s), 63.75 (s), 49.05 (s), 10.61 (s); HRMS (TOF) m/z [M + Na]$^+$ Calcd for $C_{13}H_{17}NO_2$ 242.1151 found 242.1182.



1-propanone, 1-(4-methylphenyl)-2-(4-morpholinyl) (5b): yellow solid (219.2 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.03 (q, *J* = 6.8 Hz, 1H), 3.72 – 3.62 (m, 4H), 2.65 – 2.50 (m, 4H), 2.40 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.85 (s), 142.86 (s), 132.64 (s), 128.12 (s), 127.91 (s), 66.15 (s), 63.70 (s), 49.13 (s), 20.63 (s),10.92 (s); HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{14}H_{19}NO_2$ 234.1489 found 234.1490.

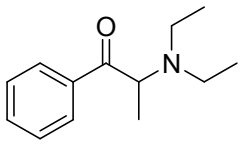


2-morpholino-1-(4-(trifluoromethyl)phenyl)propan-1-one (5e)[7]: yellow solid (272.7 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 4.04 (q, *J* = 6.8 Hz, 1H), 3.71 – 3.61 (m, 4H), 2.64 – 2.52 (m, 4H), 1.29 (d, *J* = 6.8 Hz, 3H); HRMS (TOF) m/z [M + Na]$^+$ Calcd for $C_{14}H_{16}NO_2F_3$ 310.1025 found 310.1055.

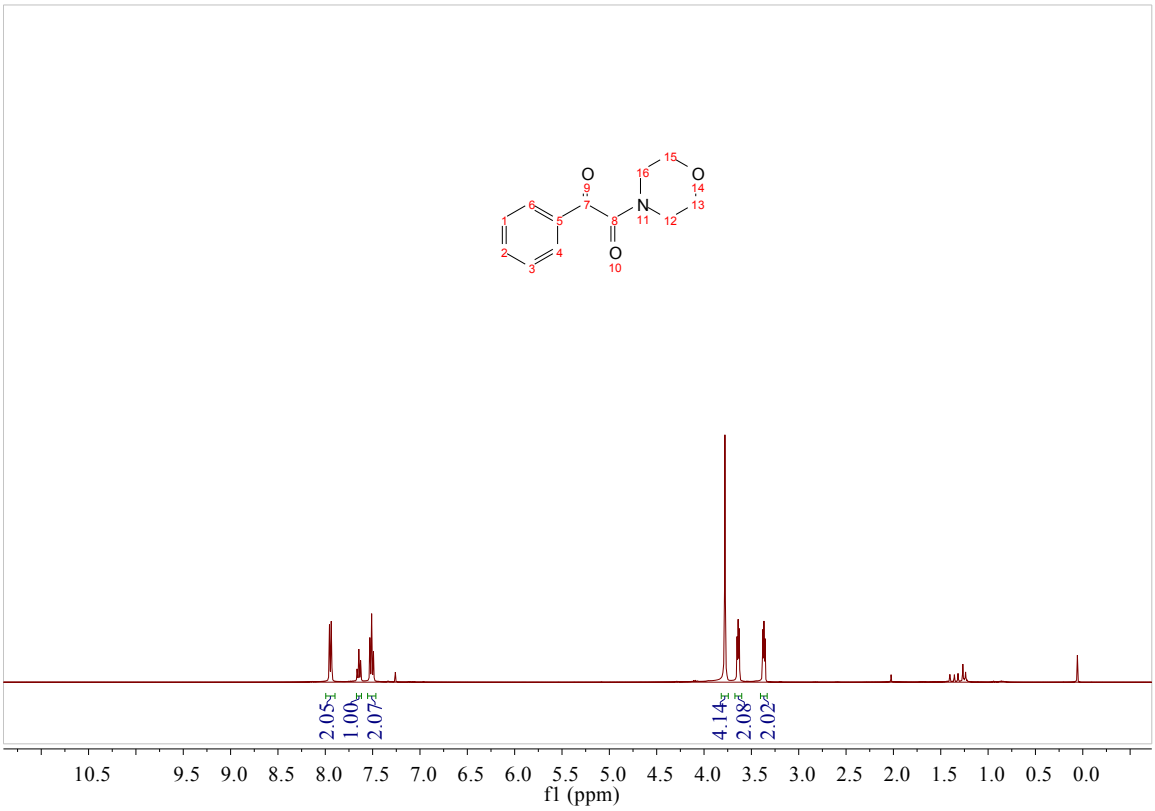


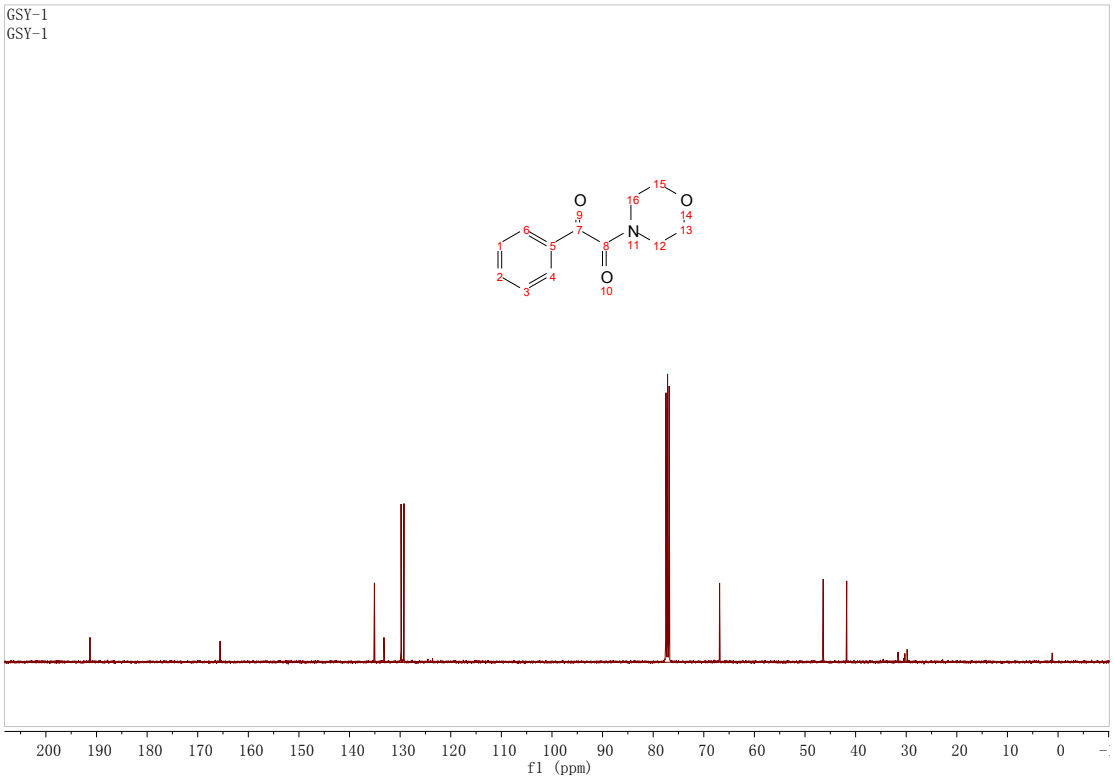
1-propanone, 2-(4-morpholinyl)-1-(2-thienyl) (5g) [7]: yellow solid (198.1 mg, 88%); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.59 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.10 (dd, *J* = 4.9, 3.9 Hz, 1H), 3.75 – 3.68 (m, 5H), 2.66 – 2.60 (m, 2H), 2.58 – 2.52 (m, 2H), 1.29 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.91 (s), 139.76 (s), 132.93 (s), 132.40 (s), 126.47 (s), 66.65 (s), 65.86 (s), 49.33 (s), 11.10 (s); HRMS (TOF) m/z $[M + Na]^+$ Calcd for $C_{11}H_{15}NO_2S$ 248.0716 found 248.0767.



2-(benzyl(2,2-dimethoxyethyl)amino)-1-phenylpropan-1-one (5j)[7]: pale yellow liquid (86.2 mg, 42%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.07 (m, 2H), 7.54 – 7.49 (m, 1H), 7.45 – 7.40 (m, 2H), 4.38 (q, *J* = 6.7 Hz, 1H), 2.66 – 2.52 (m, 4H), 1.23 (d, *J* = 6.7 Hz, 3H), 1.01 (t, *J* = 7.1 Hz, 6H); HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{13}H_{19}NO$ 206.1539 found 206.1628.

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GSY-1
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O
O
N
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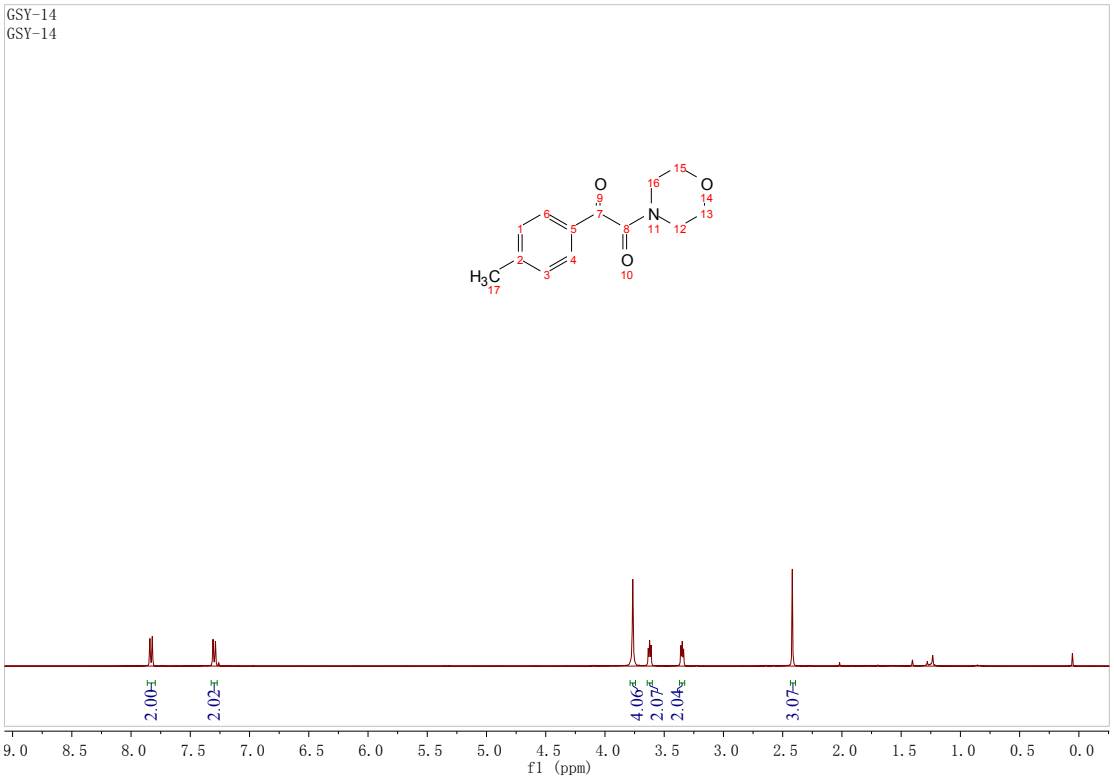
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2.02
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2.07
2.04
3.07
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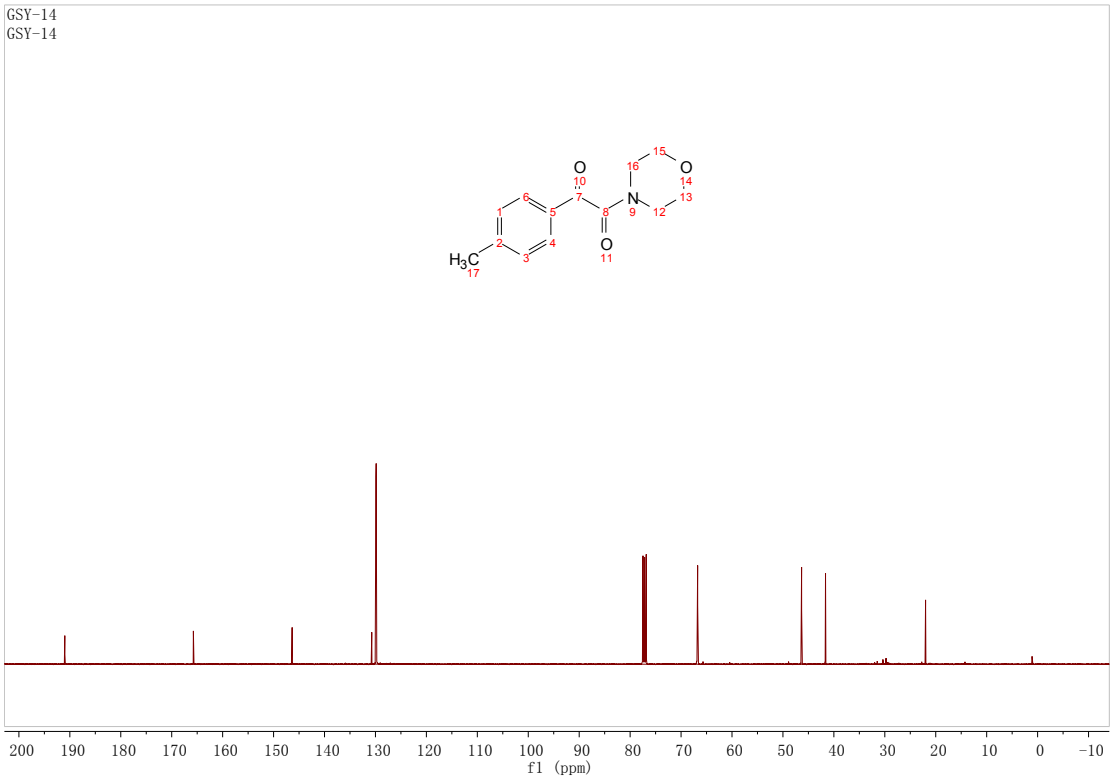
f1 (ppm)


GSY-14
GSY-14
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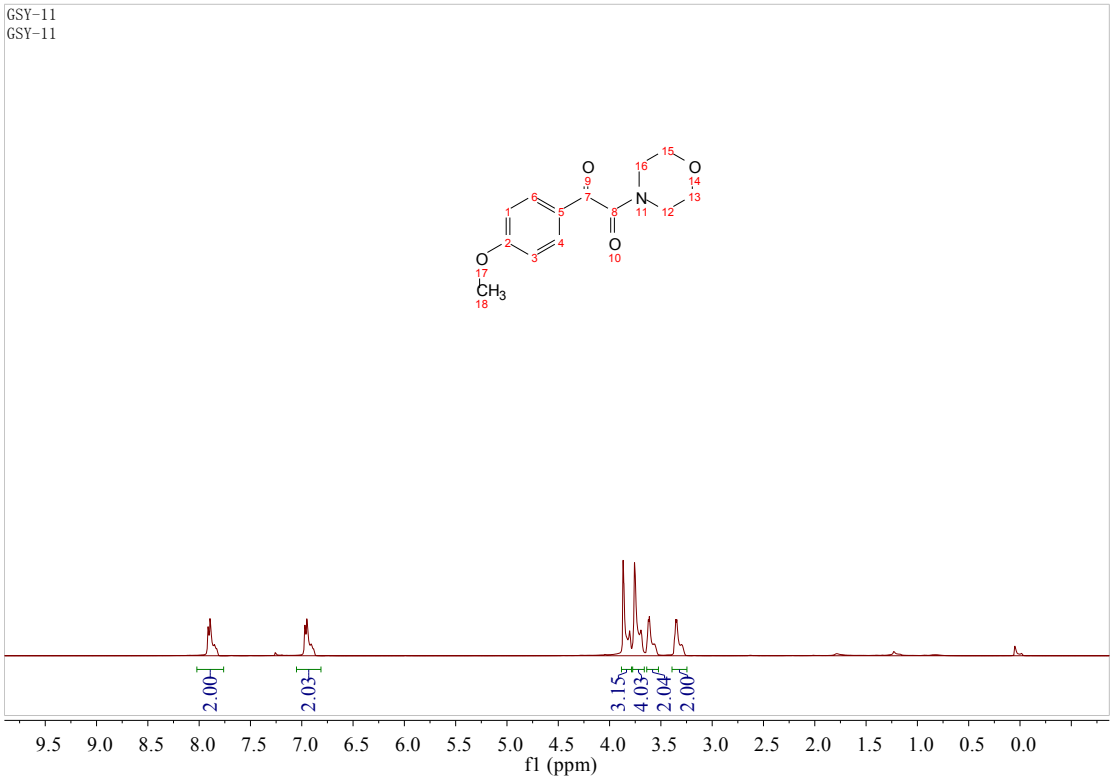
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GSY-11
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3.15
4.03
2.04
2.00
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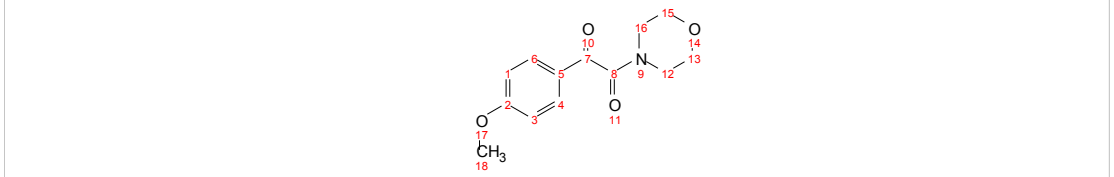
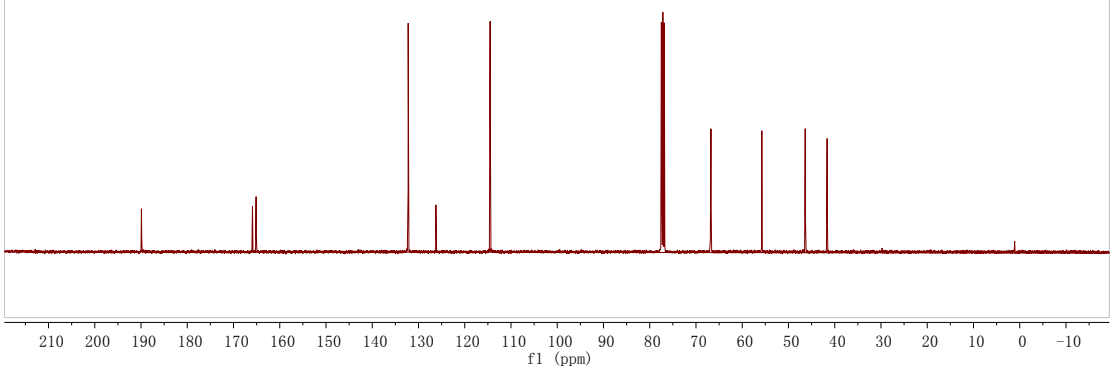
f1 (ppm)

GSY-11
GSY-11

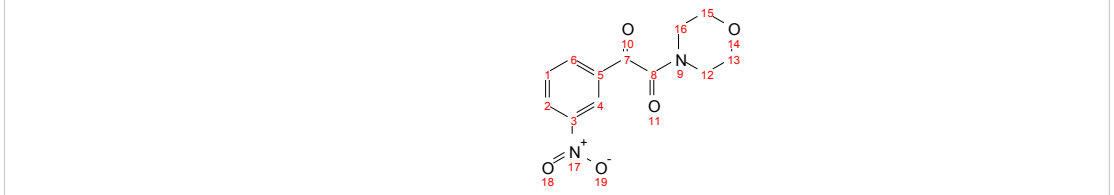


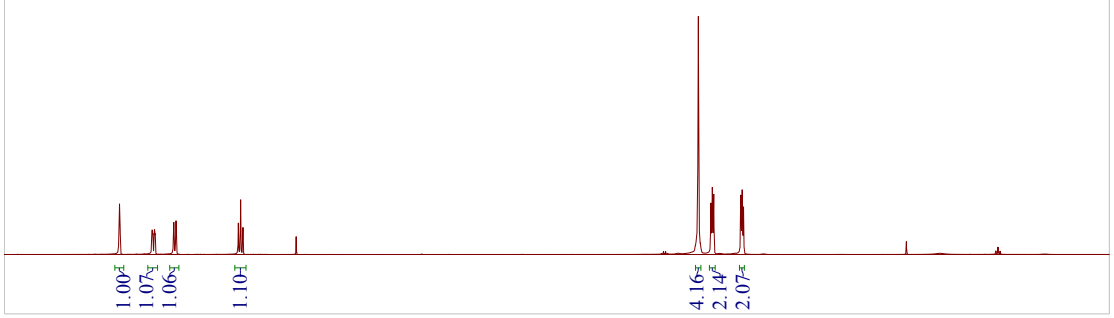


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

f1 (ppm)

GSY-3
GSY-3

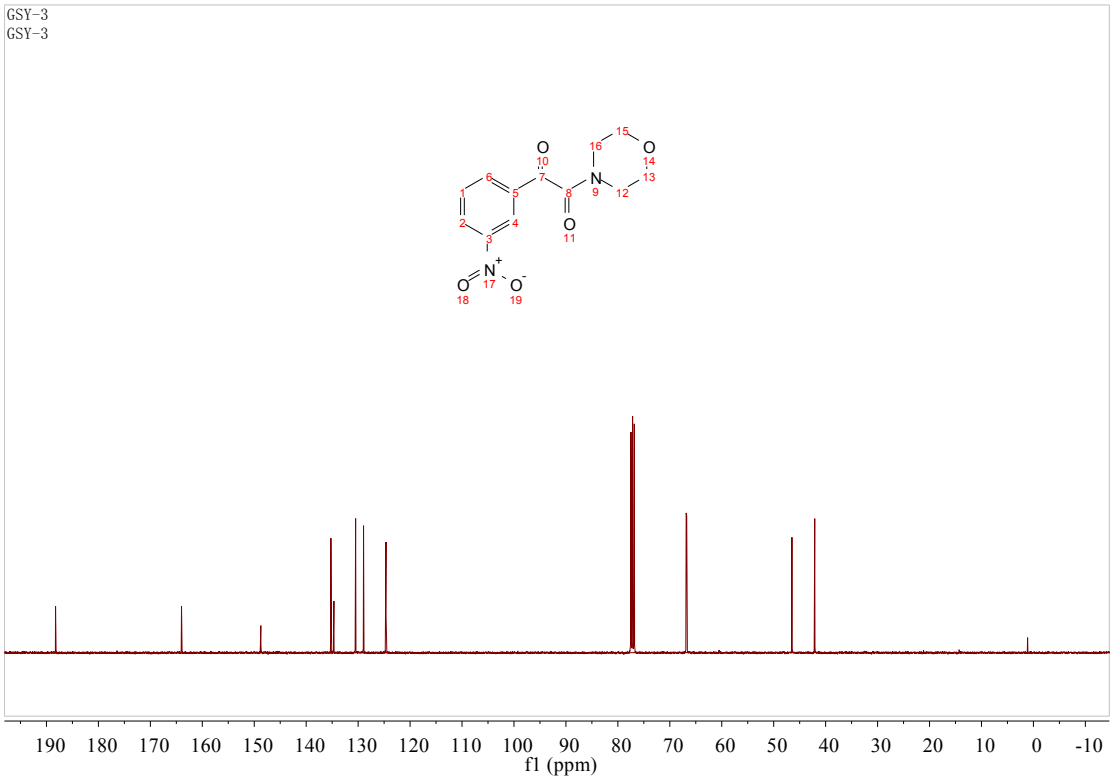


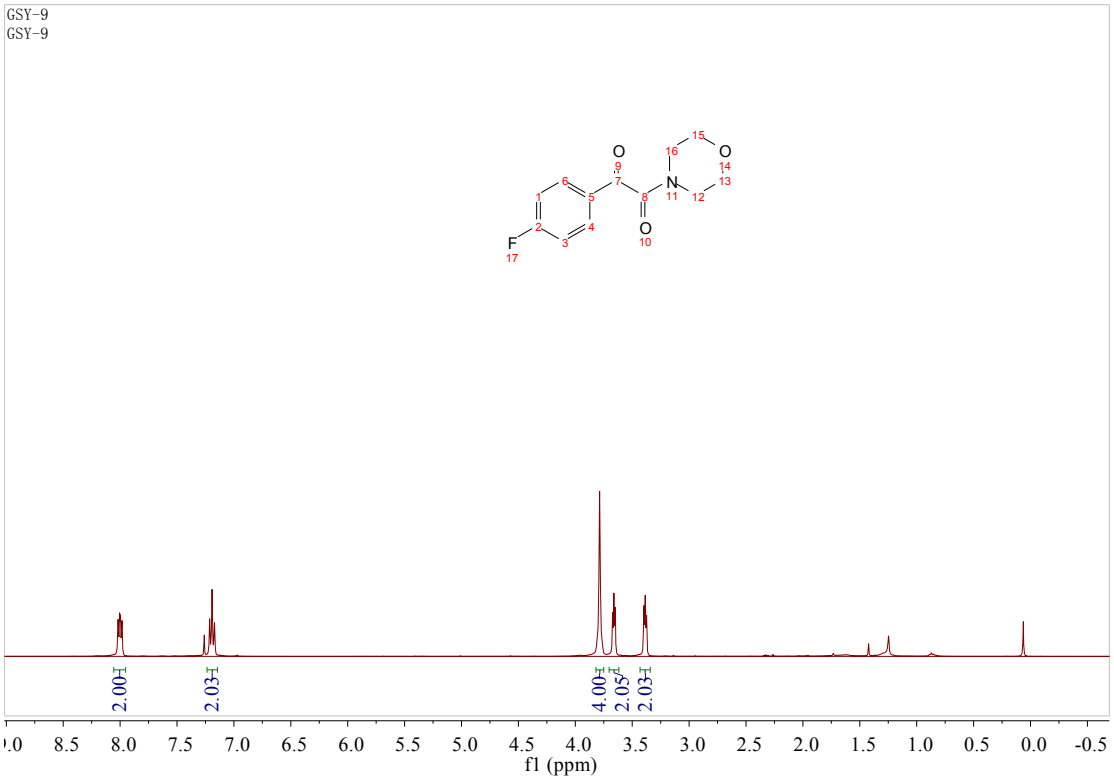


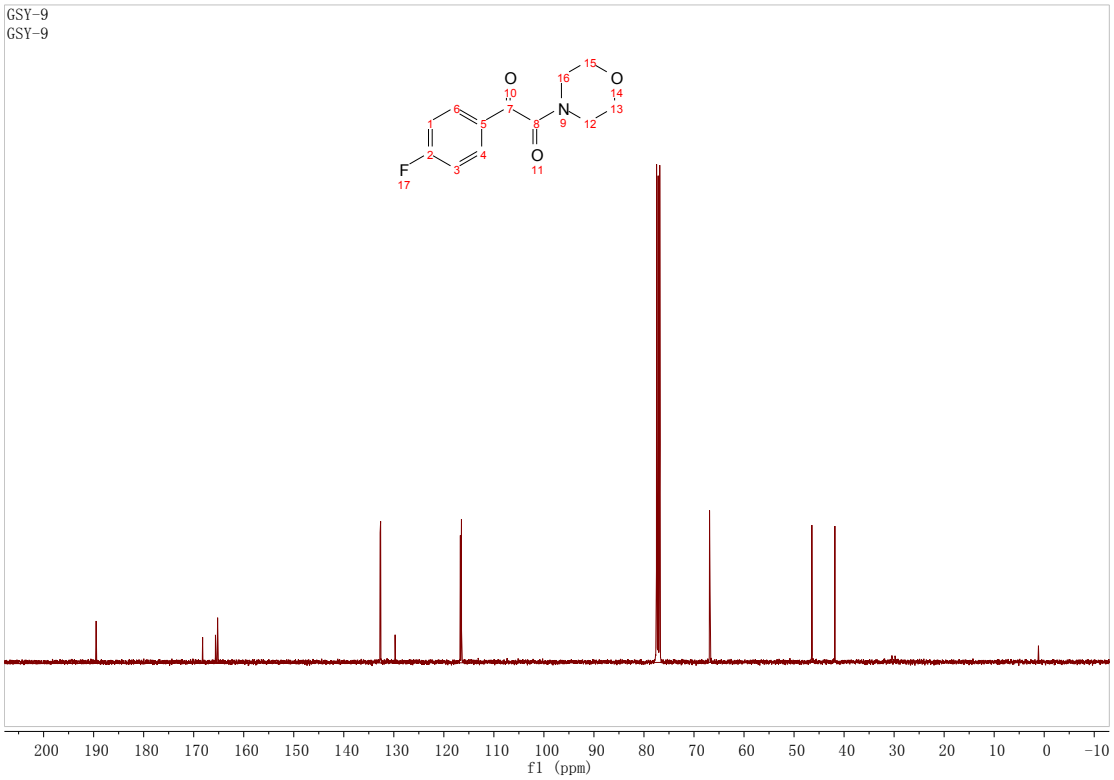
1.00 1.07 1.06 1.10 4.16 2.14 2.07

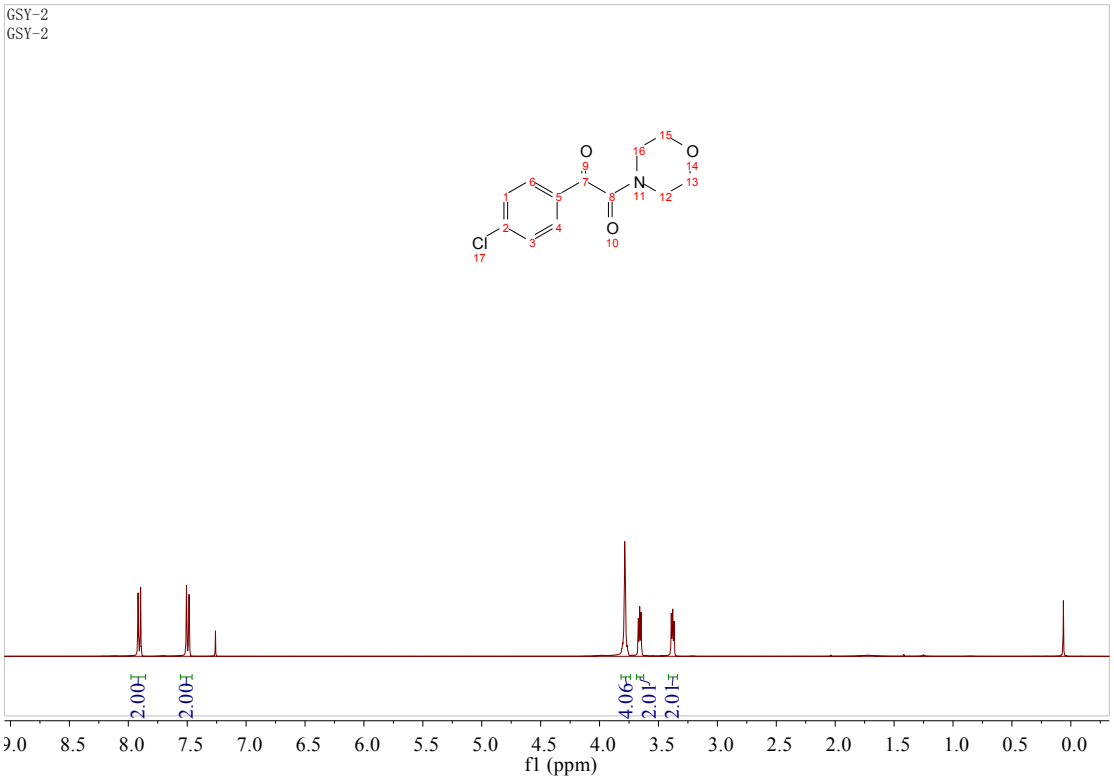
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

f1 (ppm)

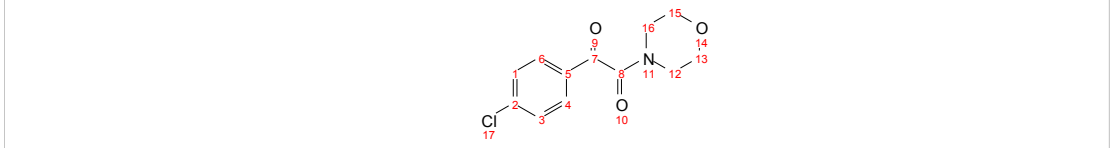

GSY-3
GSY-3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

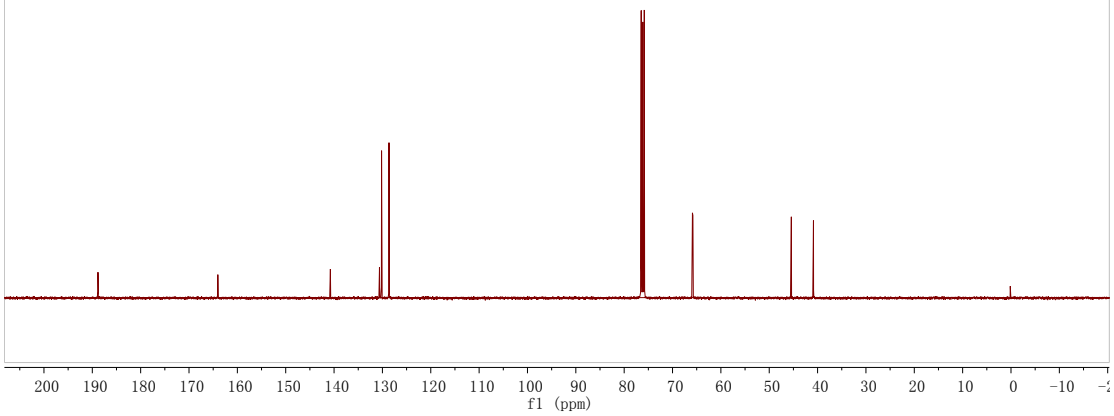

GSY-9
GSY-9
2.00
2.03
4.00
2.05
2.03
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


GSY-9
GSY-9
f1 (ppm)


GSY-2
GSY-2
2.00
2.00
4.06
2.01
2.01
f1 (ppm)

GSY-2
GSY-2

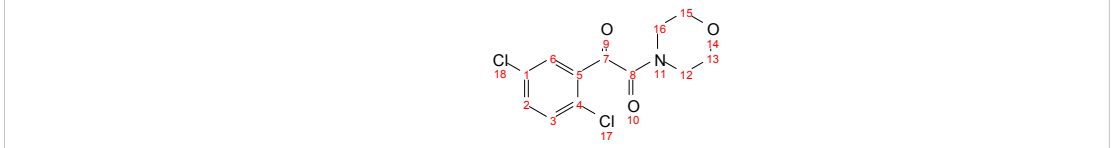


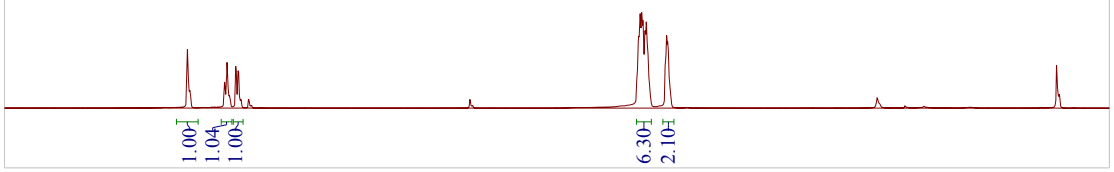


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

f1 (ppm)

GSY-8
GSY-8

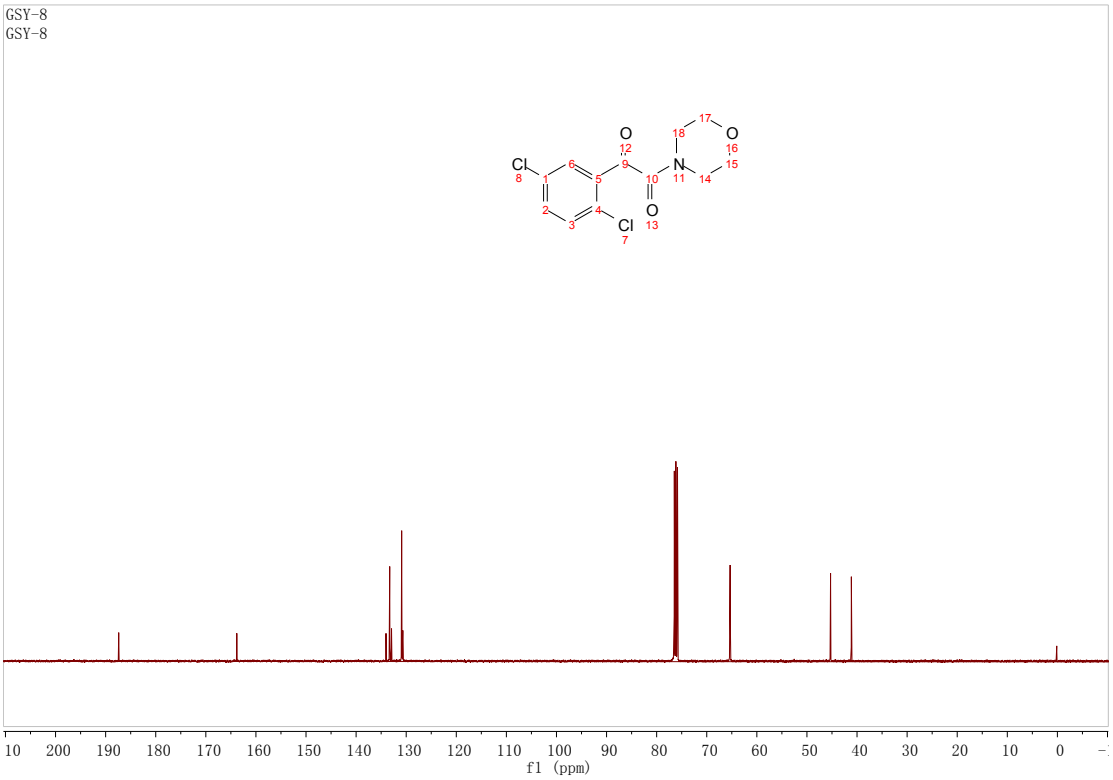




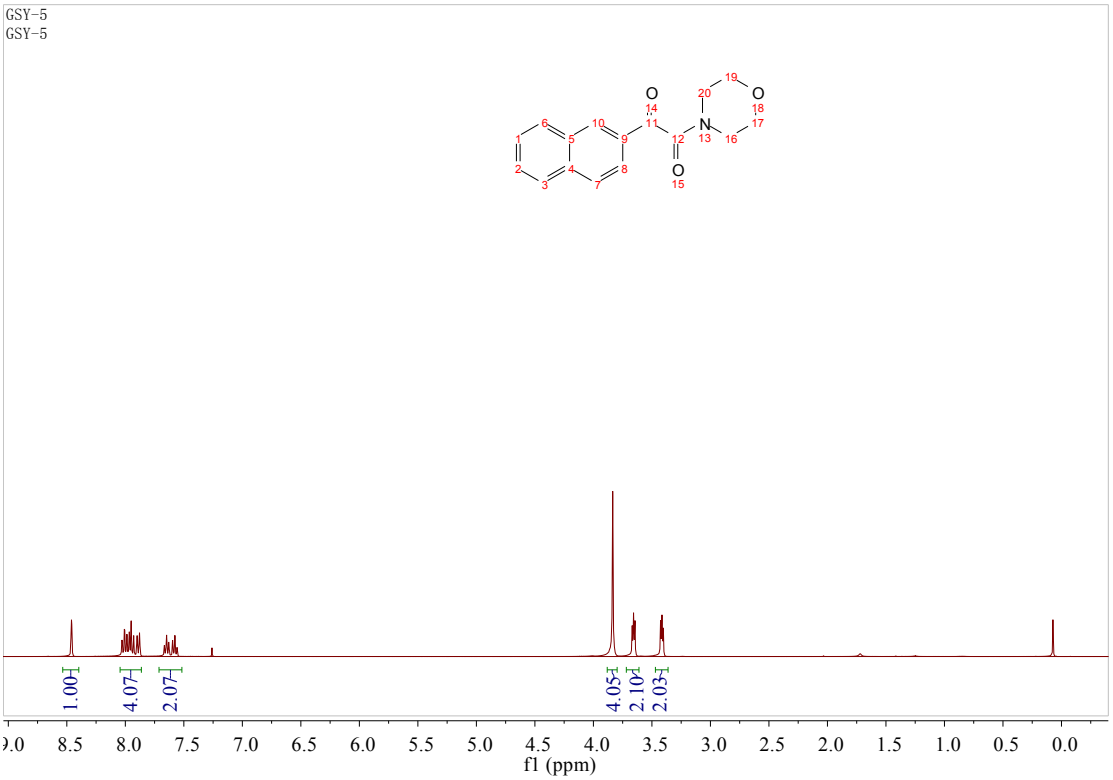
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

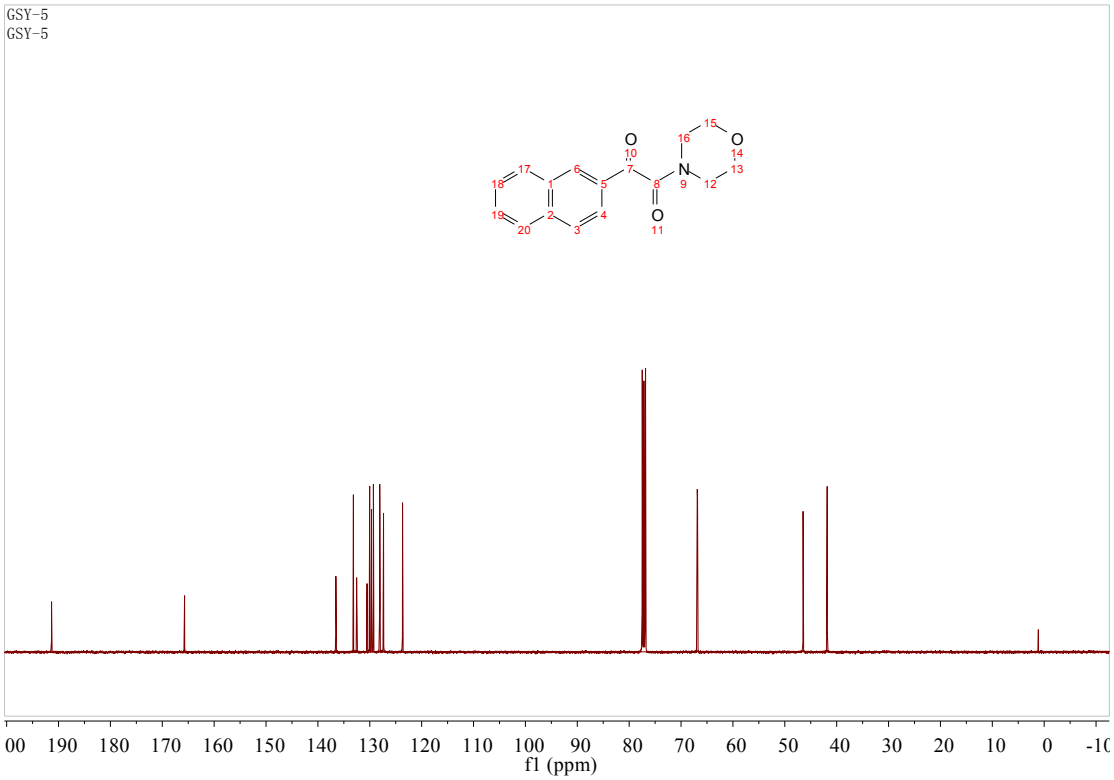
f1 (ppm)

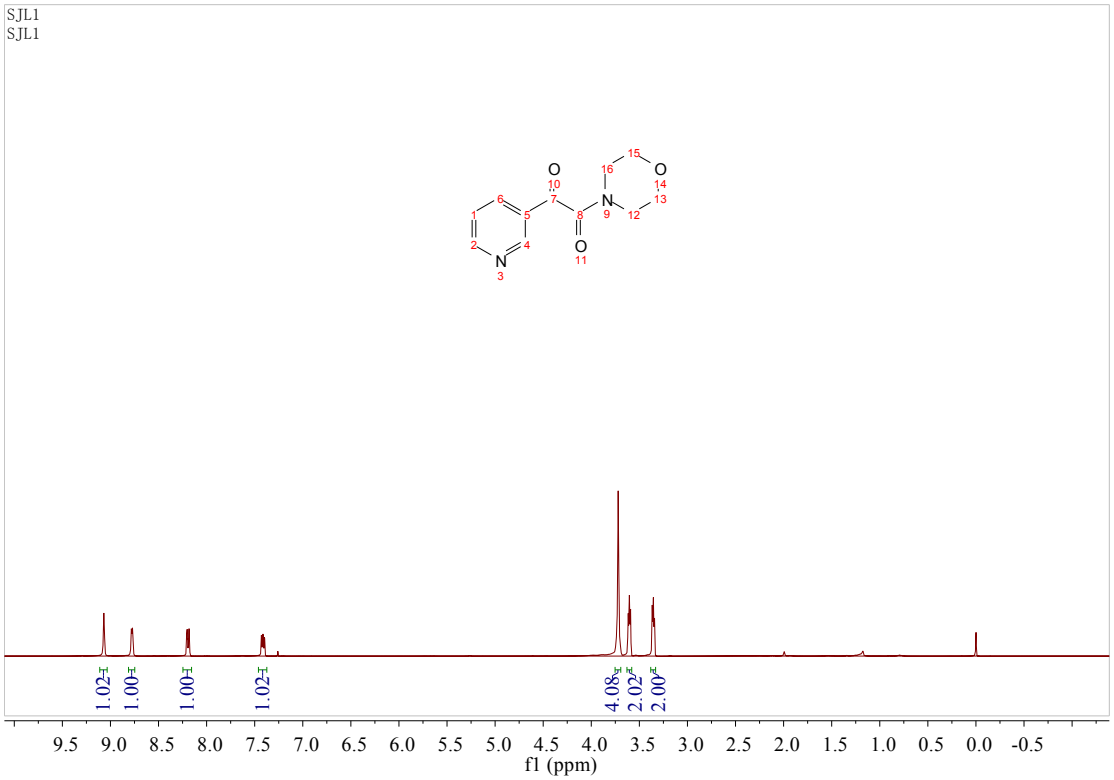
GSY-8
GSY-8



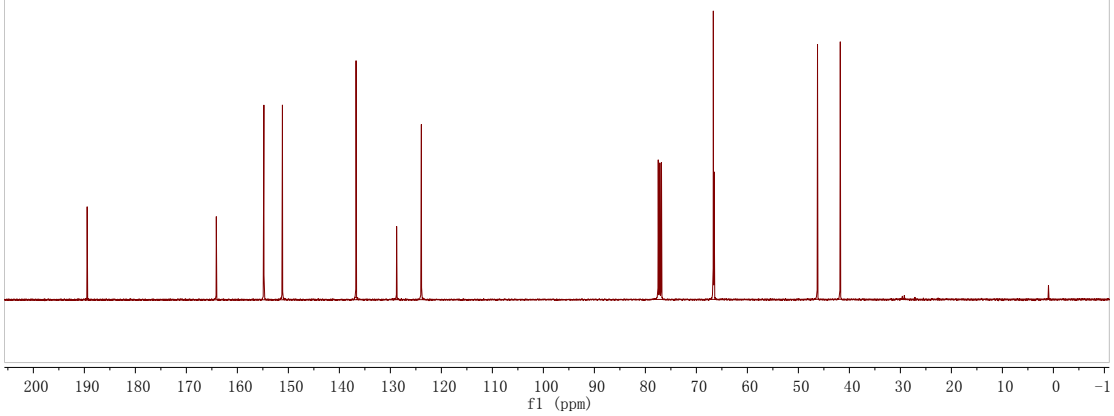
GSY-5
GSY-5




GSY-5
GSY-5
f1 (ppm)


SJL1
SJL1
1.02
1.00
1.00
1.02
4.08
2.02
2.00
f1 (ppm)

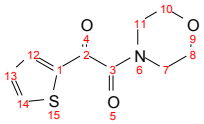
GSY-26
GSY-26

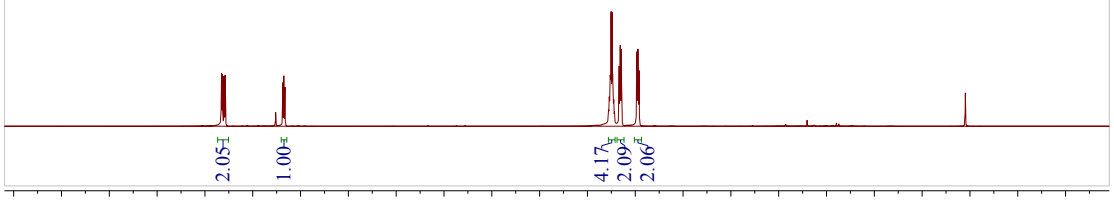


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1

f1 (ppm)

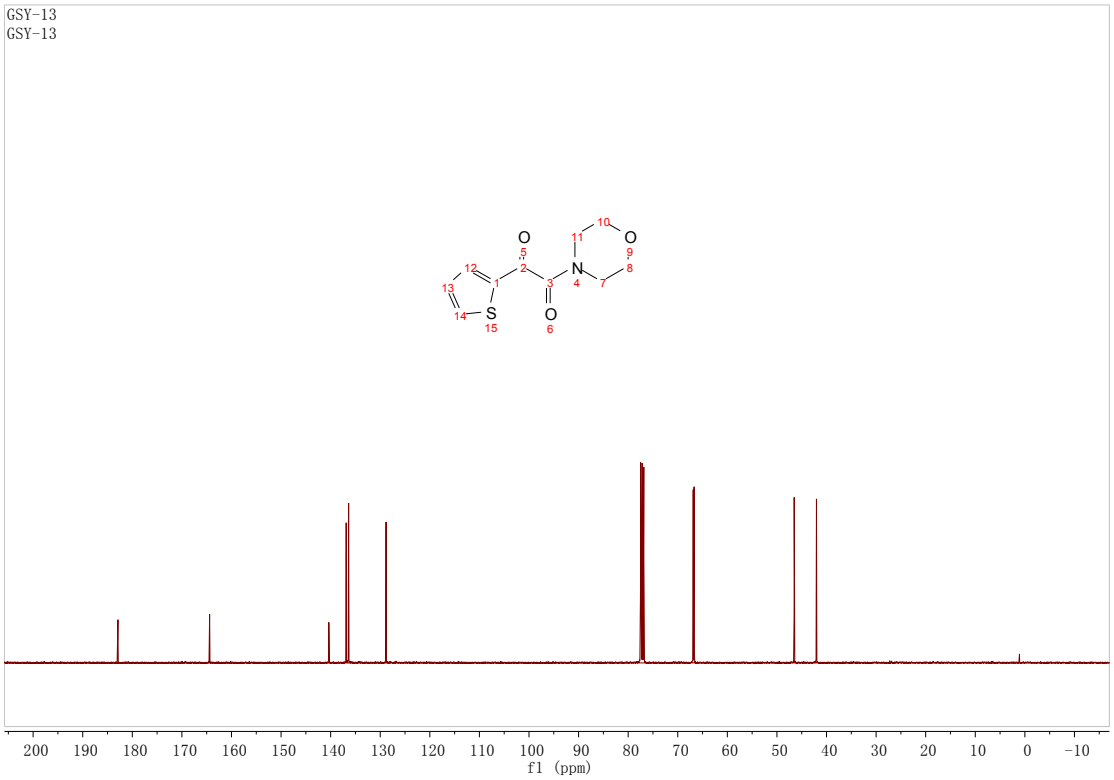
GSY-13
GSY-13

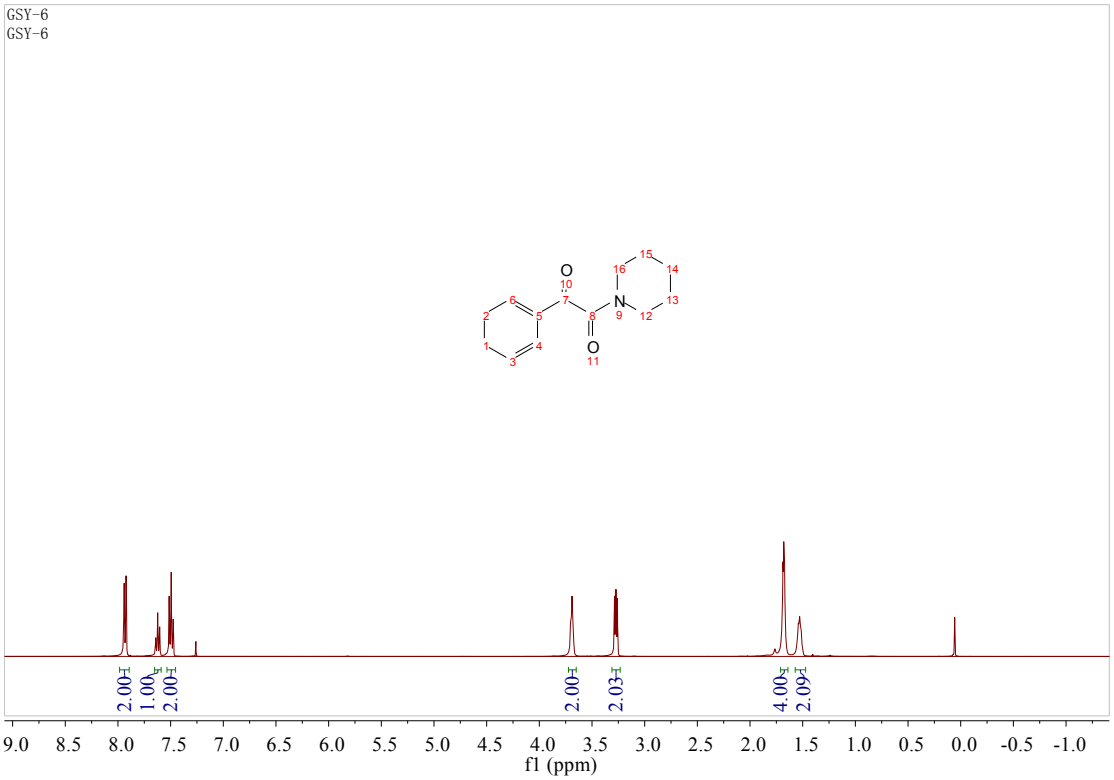




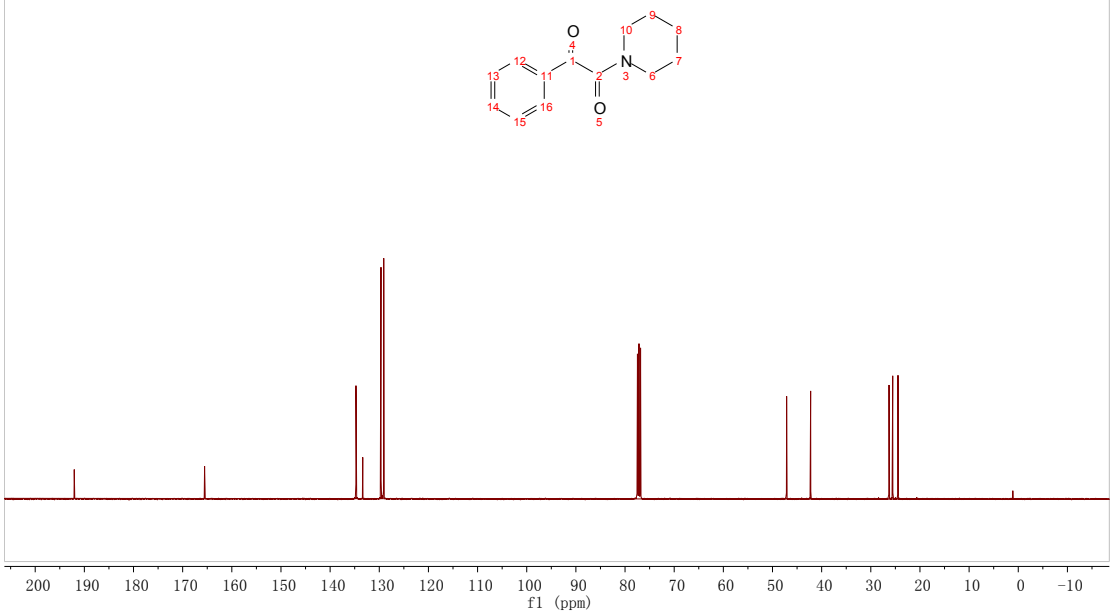
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

f1 (ppm)

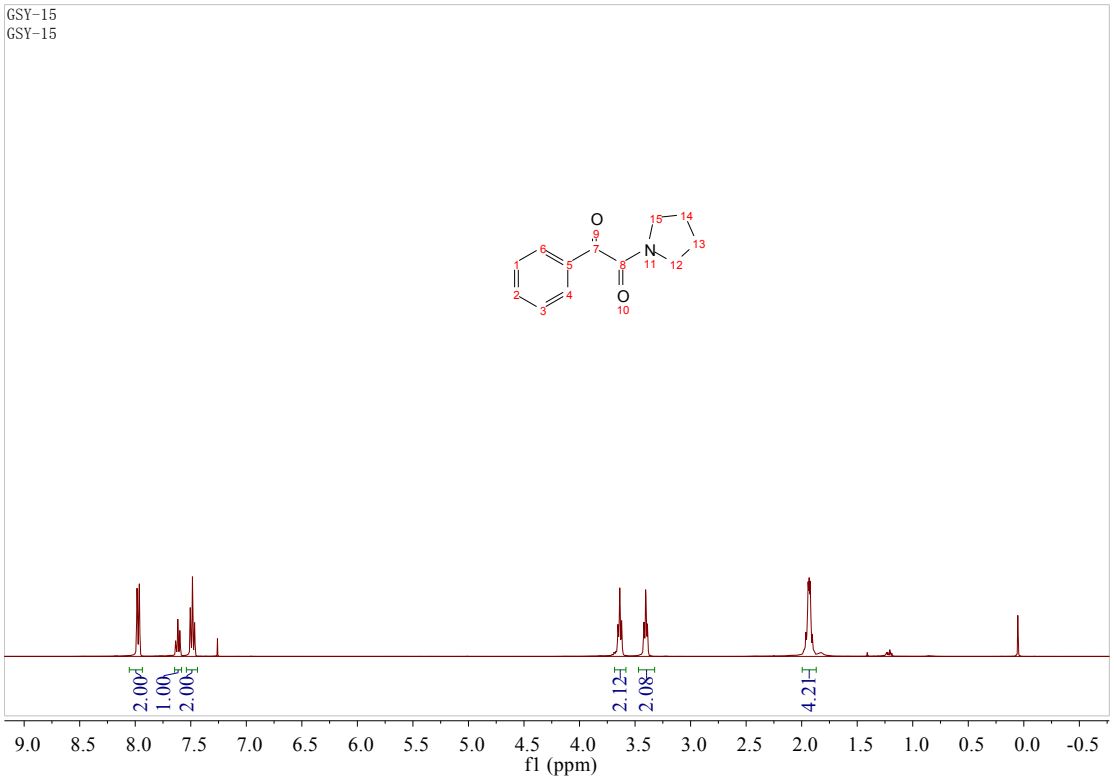

GSY-13
GSY-13
f1 (ppm)

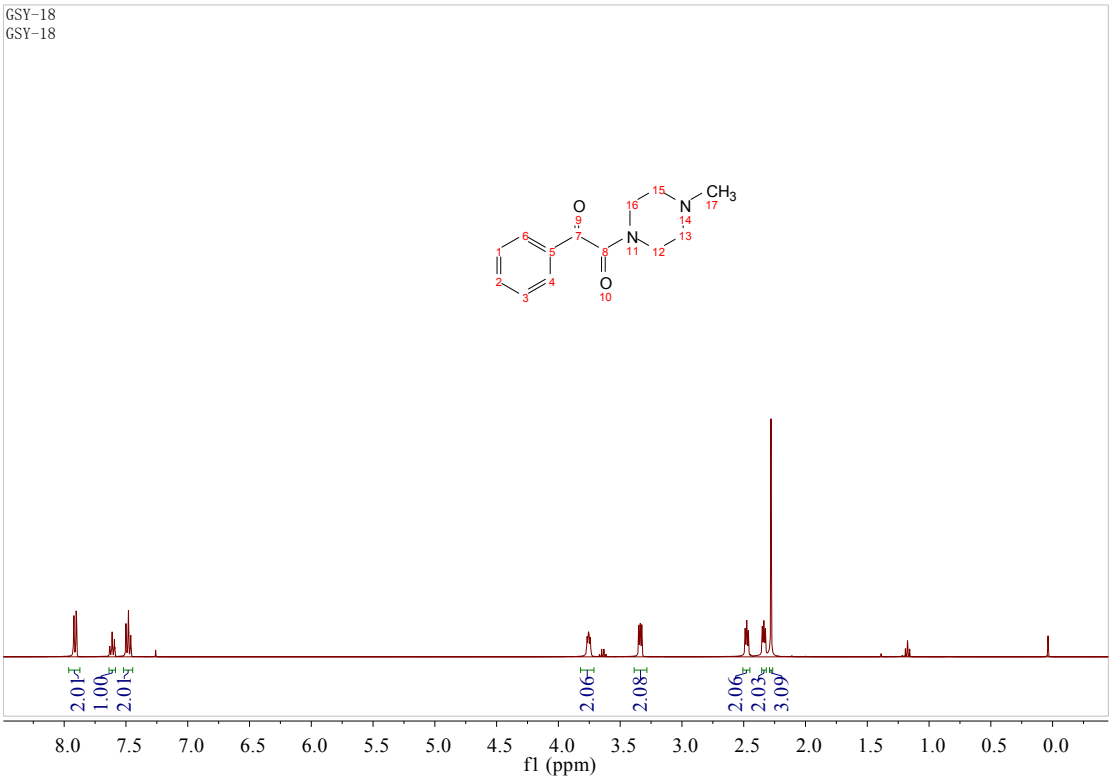

GSY-6
GSY-6
2.00
1.00
2.00
2.00
2.03
4.00
2.09
f1 (ppm)

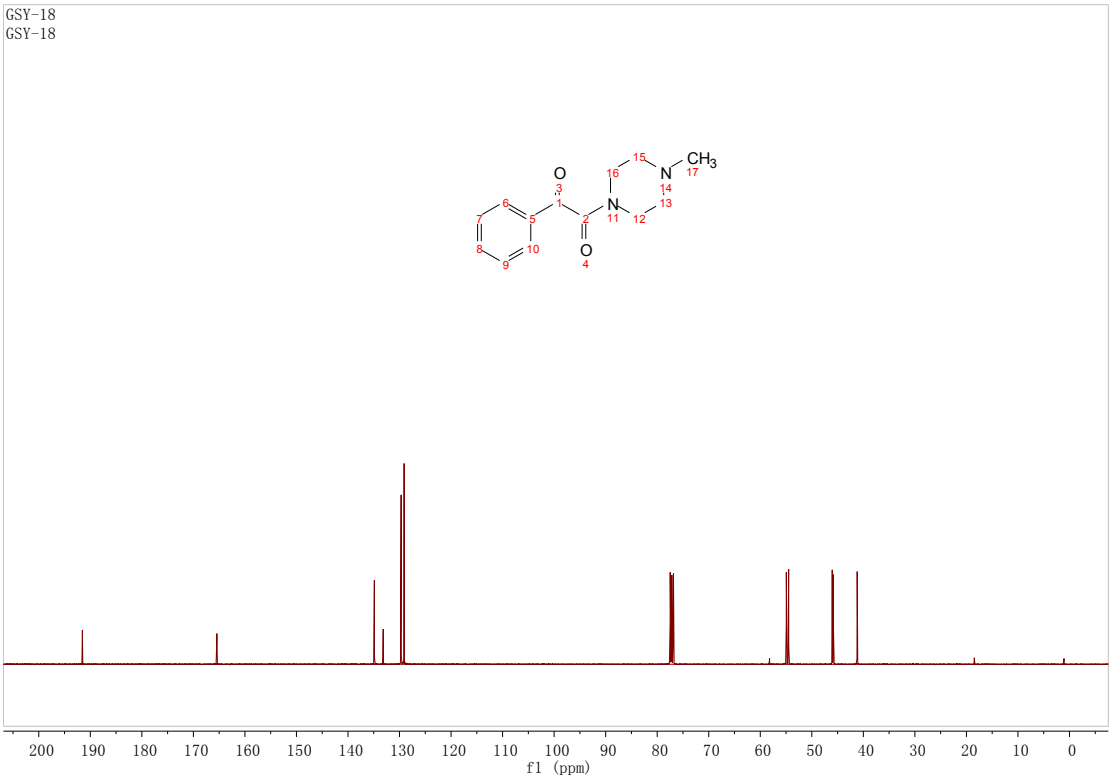
GSY-6
GSY-6

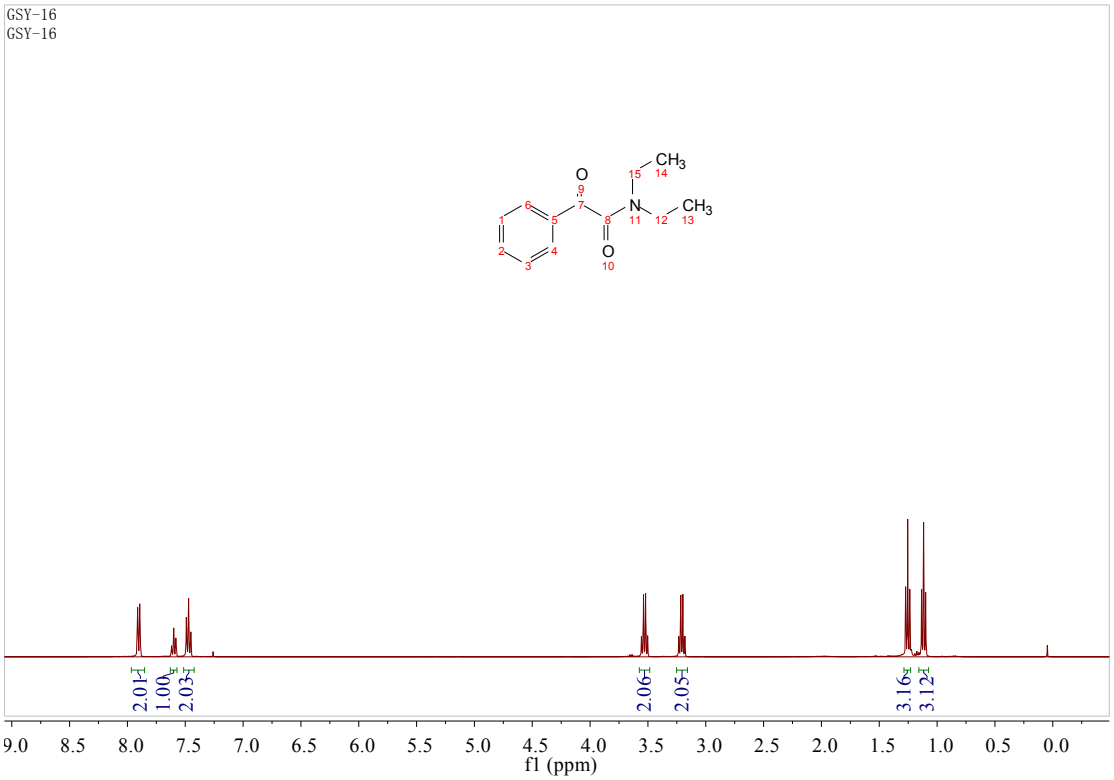


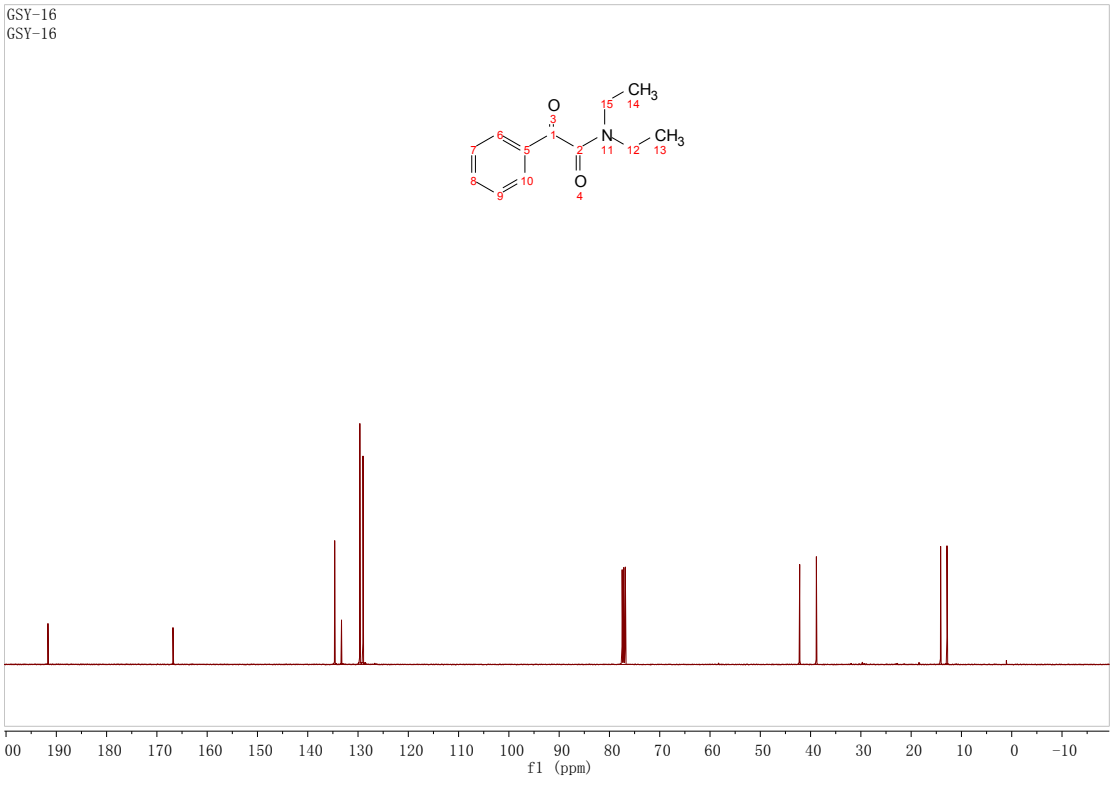
GSY-15
GSY-15



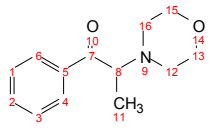

GSY-18
GSY-18
2.01
1.00
2.01
2.06
2.08
2.06
2.03
3.09
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

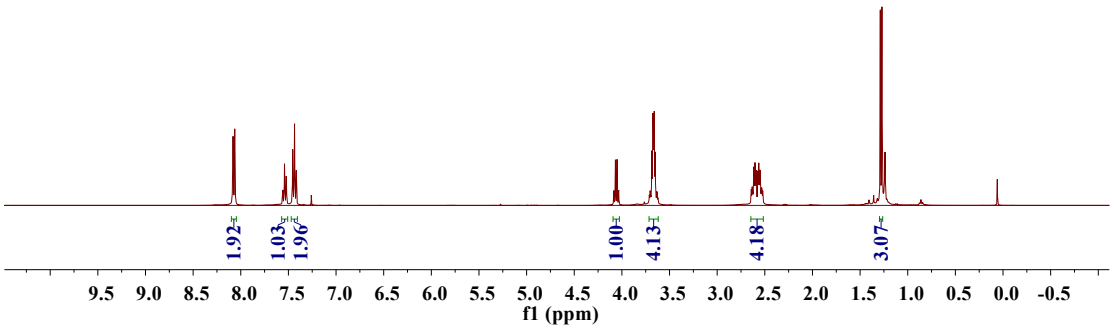

GSY-18
GSY-18
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


GSY-16
GSY-16
2.01
1.00
2.03
2.06
2.05
3.16
3.12
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

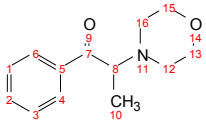

GSY-16
GSY-16
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

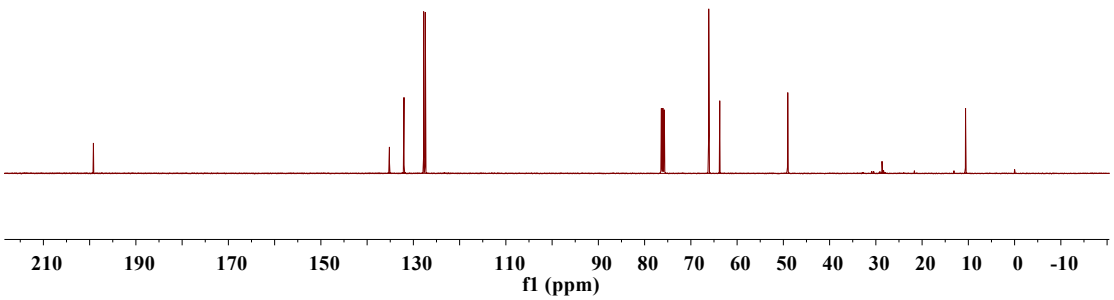
LCK-59
LCK-59



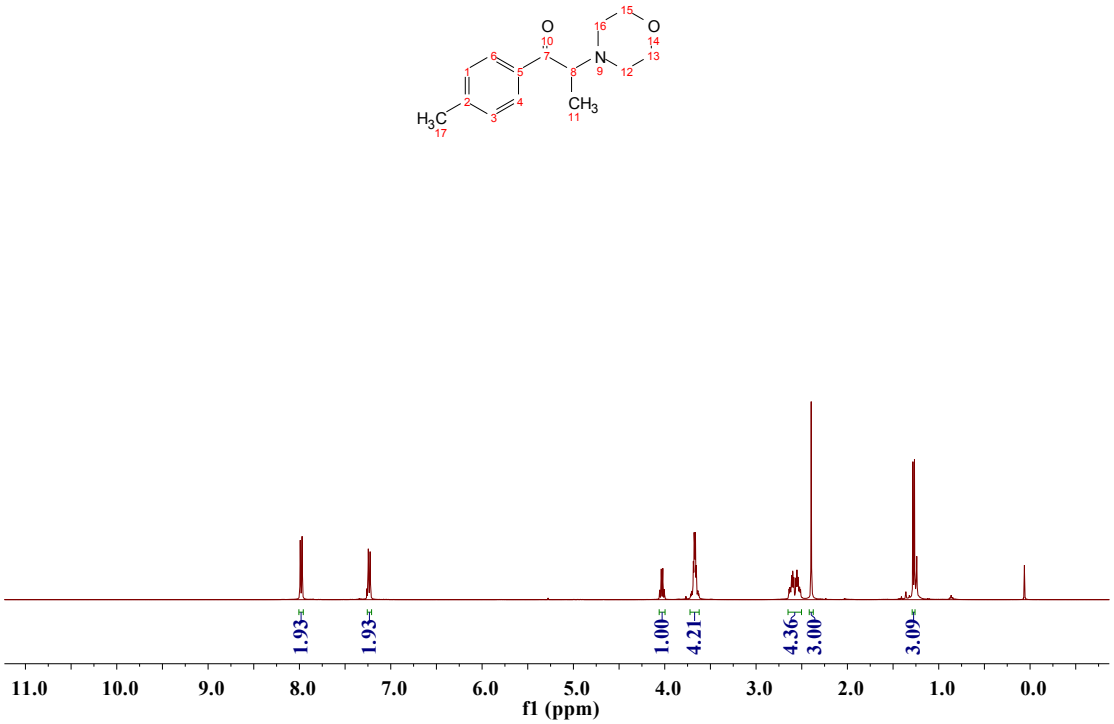


LCK-59
LCK-59

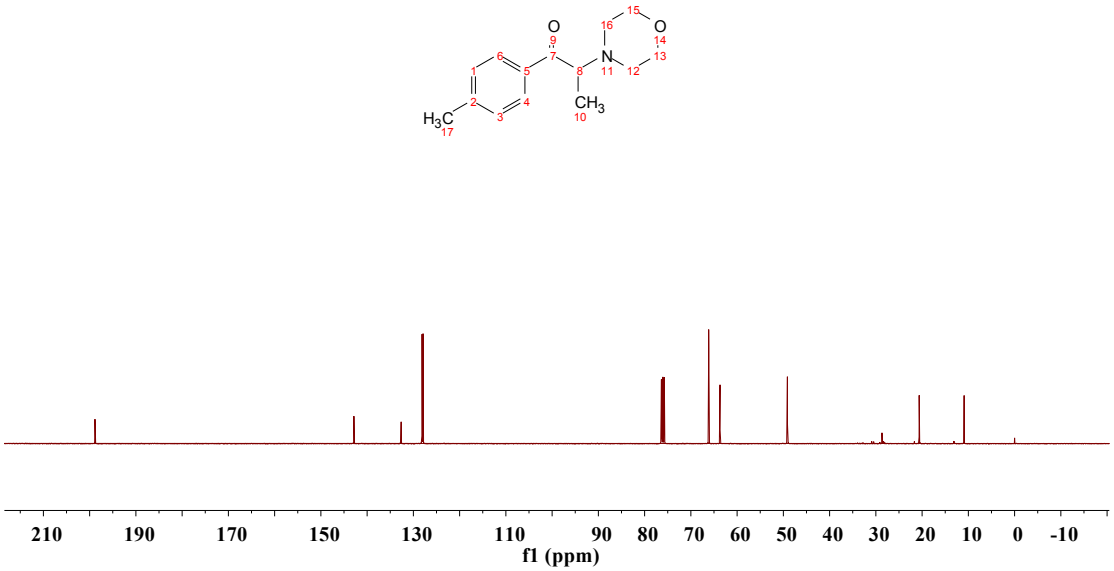




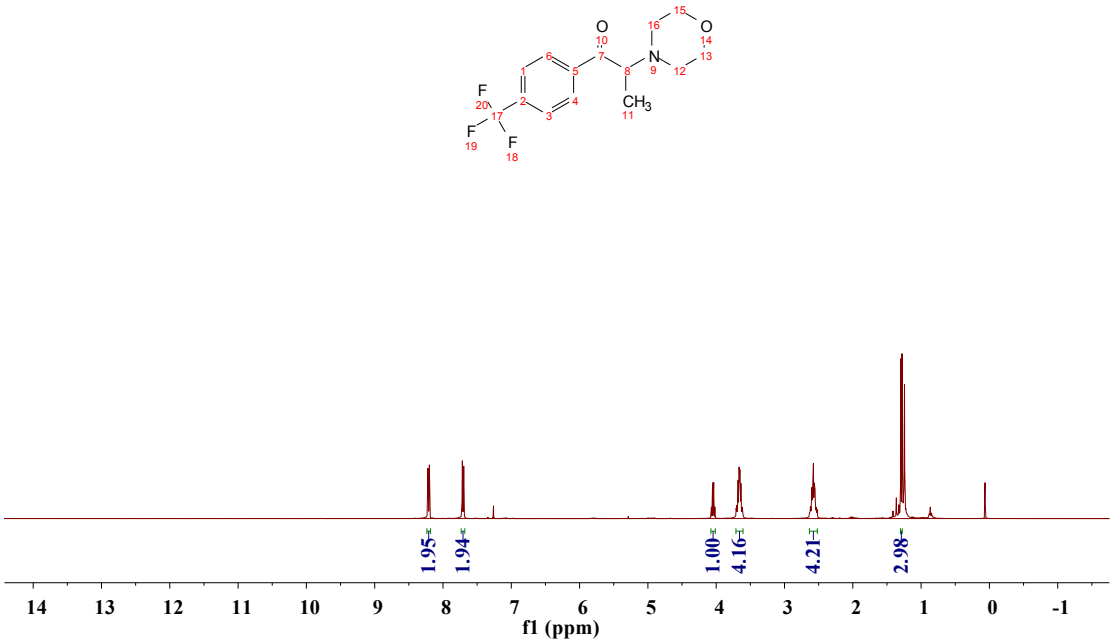
LCK-60
LCK-60



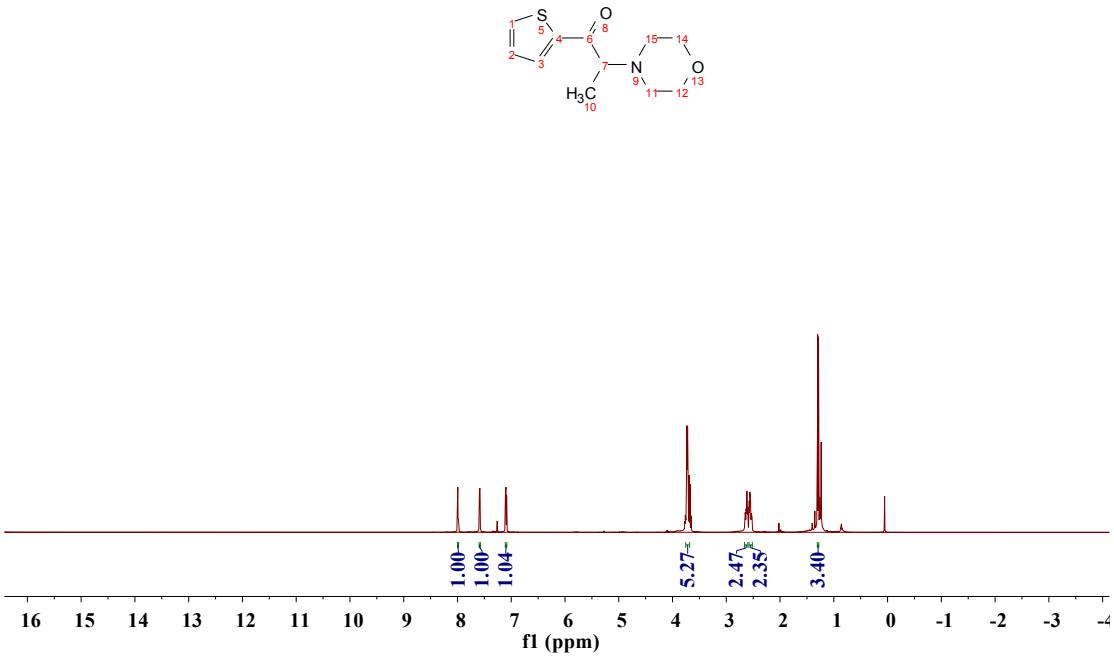
LCK-60
LCK-60



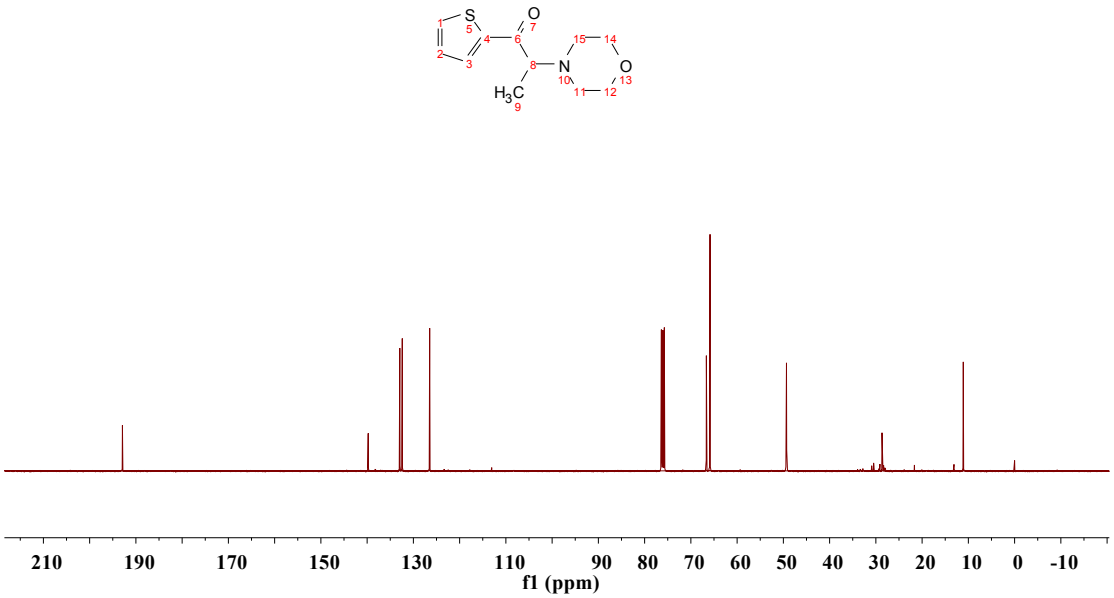
LCK-57
LCK-57



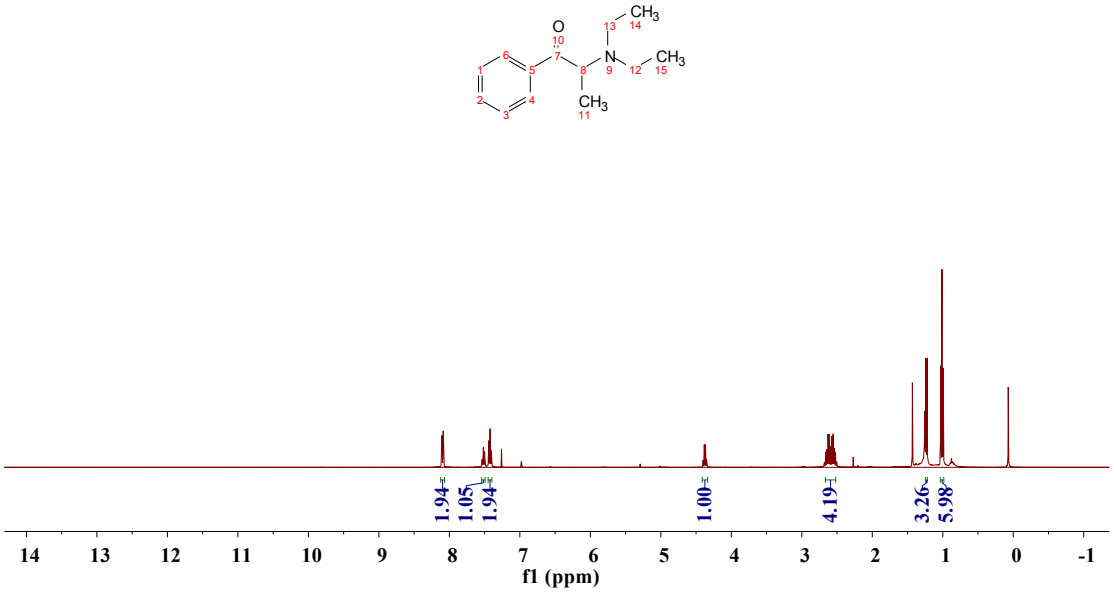
LCK-58
LCK-58



LCK-58
LCK-58



LCK-56
LCK-56



12. References

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