Supporting Information For Enzymatic process of Morita-Baylis-Hillman (MBH) reaction in Microflow system

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Full experimental details, characterization data and copies of NMR spectra

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[1]. General information

Reaction solvents were obtained commercially and used without further purification. Commercial reagents were used as received. *Novozym* 435 was purchased from Sigma-Aldrich (Germany, China). **^{1}H/^{13}C NMR** spectra were recorded on a 400′54 Ascend purchased from Bruker Biospin AG, operating at 400/100 MHz, respectively.

[2]. Reaction Optimizations

Table S1. Effect of the catalyst on the conversion rate of the MBH reaction [a]

Entry	Amides	β- cyclodextrin	Conversion [b] (%)
1	4eq	0.01eq	84
2	4eq	0.0075eq	70
3	4eq	0.0125eq	75
4	3eq	0.01eq	76
5	2eq	0.01eq	64
6	5eq	0.01eq	79
7	6eq	0.01eq	80

[a] Reaction conditions:**1a** (0.5 mmol), 40℃, flow rate 0.13 mL/min, catalyst, solvent: methylbenzene (3 mL) + **2a** (1 mL). [b] Conversion calculated by ^{1}H NMR.

[3]. Other unsuccessful alkene substrate

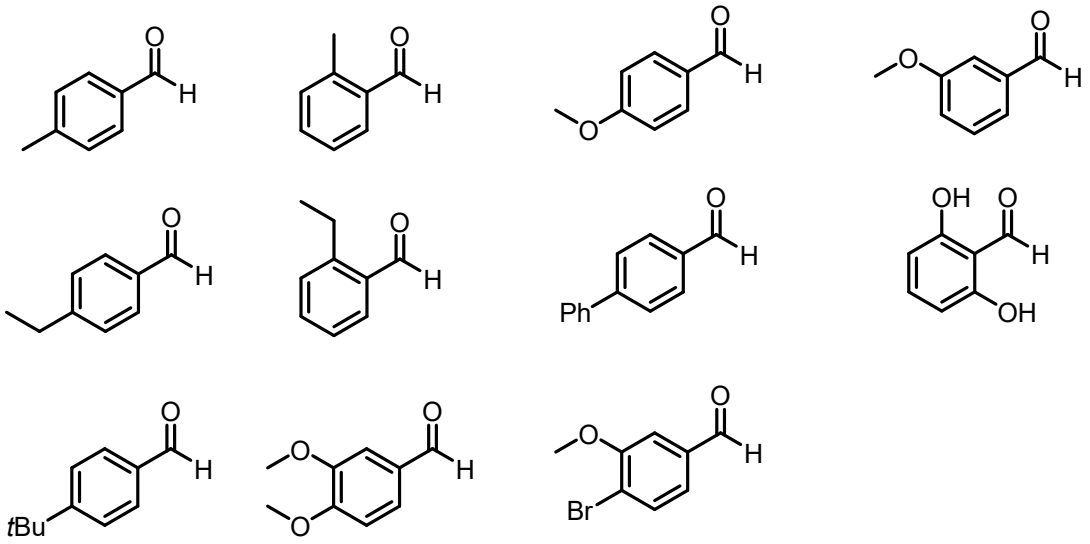
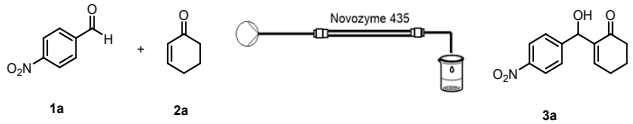


Figure S1. Some aldehydes which cannot react with cyclohexanone

[4]. Calculation of Space-Time Yield (STY)

The space-time yield (STY) in continuous flow reactions was calculated as follows:



$$STY = \frac{Substrate\ concentration\ (M) \times Yield\ (\%) \times Flow\ rate\left(\frac{L}{h}\right) \times MW\left(\frac{g}{mol}\right)}{Reactor\ volume\ (L) \times 100}$$

$$= \frac{\frac{0.5}{3}M \times 67\% \times \frac{0.13 \times 10^{-3}L}{\frac{1}{60}h} \times 151.12\frac{g}{mol}}{3 \times 10^{-3}L \times 100} = 0.439\ g \cdot L^{-1} \cdot h^{-1}$$

The STY in batch reactions was calculated as follows:

$$STY = \frac{Substrate\ concentration\ (M) \times Yield\ (\%) \times MW\left(\frac{g}{mol}\right)}{Reaction\ time\ (h) \times 100}$$

$$= \frac{\frac{0.5}{5}M \times 51\% \times 151.12\frac{g}{mol}}{75h \times 100} = 0.001\ g \cdot L^{-1} \cdot h^{-1}$$

[5]. Experimental section

General procedure 1 for compound 3 in the microflow system

70 mg *Novozym* 435 into an enzyme column and the column residence volume was 3ml, 0.5 mmol benzaldehyde (**1**), 0.01 mmol *β*- cyclodextrin, 2 mmol nicotinamide and 1 ml cyclohexanone (**2a**) were added into 3 ml methylbenzene, and then the solution was placed into syringe. The flow rate of syringe was 0.13 ml/min. The temperature of the water bath was set to 40℃. The residence time was 16 min, The reaction liquid was collected. And, the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain product**.**

General procedure 2 for compound 5 in the microflow system

70 mg Novozyme 435 into an enzyme column and the column residence volume was 3ml, 0.5 mmol benzaldehyde (**1**), 0.01 mmol *β*- cyclodextrin, 2 mmol nicotinamide and 1 ml 2-cyclopenten-1-one (**4**) were added into 3 ml methylbenzene, and then the solution was placed into syringe. The flow rate of syringe was 0.1 ml/min. The temperature of the water bath was set to 40℃. The residence time was 31 min, The reaction liquid was collected. And, the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain product**.**

General scale up procedure for the synthesis of compound 3a in the microflow system

70 mg *Novozym* 435 into an enzyme packed column and the column residence volume was 3 ml, 10 mmol 4-nitrobenzaldehyde (**1a**), 0.1 mmol *β*- cyclodextrin, 10 mmol nicotinamide and 12 ml cyclohexanone (**2a**) were added into 10 ml methylbenzene, and then the solution was placed into syringe. The flow rate of syringe was 0.13 ml/min. The temperature of the water bath was set to 40℃. The reaction liquid was collected. And, the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain product **3a**.

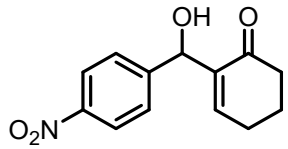
Synthesis of compound 3 in batch

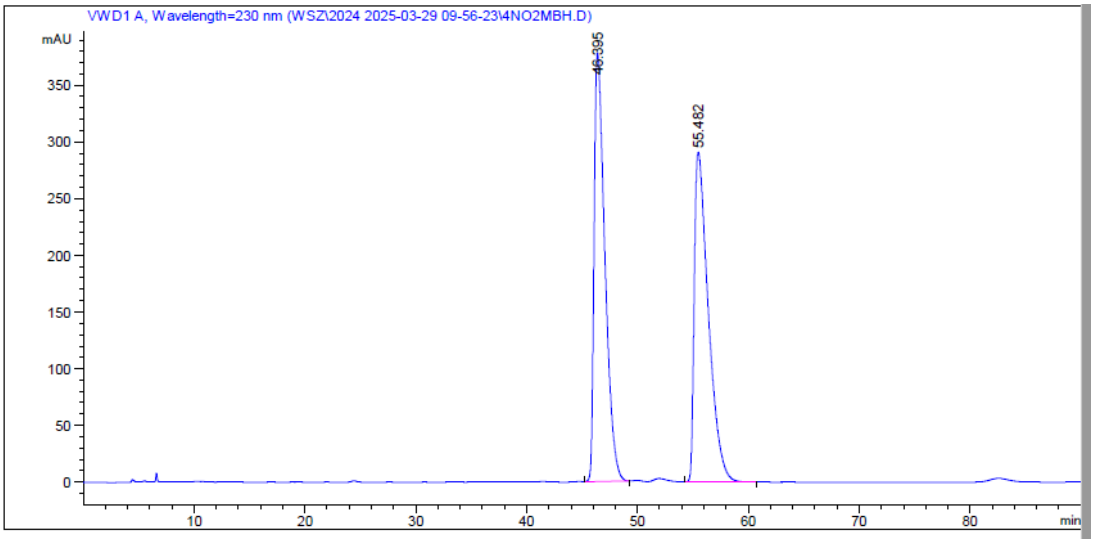
0.5 mmol benzaldehyde (**1**), 0.01 mmol *β*- cyclodextrin, 2 mmol nicotinamide and 1 ml cyclohexanone (**2a**) were added into 5 mL methylbenzene and 8 mg *Novozym* 435 in batch. After stirring for 75 h in air at 55°C. Then reaction solution was collected. And, the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain product.

Synthesis of compound 5a in batch

0.5 mmol benzaldehyde (**1**), 0.01 mmol *β*- cyclodextrin, 2 mmol nicotinamide and 1 ml 2-cyclopenten-1-one (**2a**) were added into 5 mL methylbenzene and 8 mg *Novozym* 435 in batch. After stirring for 96 h in air at 60°C. Then reaction solution was collected. And, the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain product **5**.

[6]. Analytical data of products



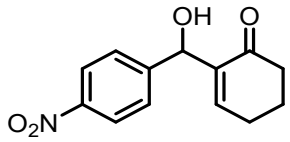


Signal 1: VWD1 A, Wavelength=230 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %	Name
1	46.395	BB	1.0201	2.56333e4	50.0484	?
2	55.482	BB	1.2961	2.55838e4	49.9516	?

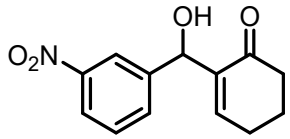
Chiral HPLC report of **3a**: racemate. Determined by HPLC with a Chiralcel OJ-H column (hexane/*i*PrOH = 90/10, 0.7 mL/min, 230 nm, t_1 = 46.395 min, t_2 = 55.482 min.

2-[Hydroxy(4-nitrophenyl)methyl]-2-cyclohexen-1-one (3a)



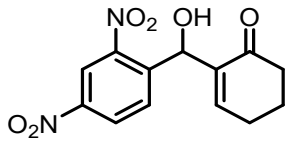
Following the general procedure 1, use 4-Nitrobenzaldehyde,**3a** (83 mg, 0.335 mmol, 67%) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.06 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 6.82 (t, J = 4.1 Hz, 1H), 5.53 (s, 1H), 3.79 (s, 1H), 2.35 (dd, J = 8.7, 4.6 Hz, 4H), 1.91 (p, J = 6.1 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 199.96, 149.72, 148.29, 147.09, 140.26, 127.18, 123.45, 71.36, 38.37, 25.78, 22.37. Known compound, spectroscopic data matched those previously reported.[1]

2-[Hydroxy(3-nitrophenyl)methyl]-2-cyclohexen-1-one (3b)



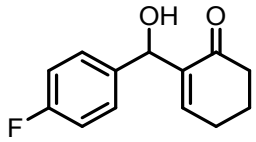
Following the general procedure 1, use 3-Nitrobenzaldehyde,**3b** (72 mg, 0.29mmol, 58%) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.14 (s, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 6.81 (t, J = 4.1 Hz, 1H), 5.53 (s, 1H), 3.65 (s, 1H), 2.38 (t, J = 6.7 Hz, 4H), 1.94 (p, J = 6.2 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 199.13, 147.24, 147.17, 143.31, 139.15, 131.60, 128.21, 121.41, 120.30, 70.69, 37.41, 24.76, 21.38. Known compound, spectroscopic data matched those previously reported.[1]

2-[(2,4-Dinitrophenyl)hydroxymethyl]-2-cyclohexen-1-one (3c)



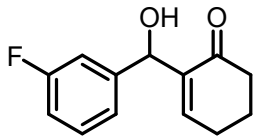
Following the general procedure 1, use 2,4-dinitrobenzaldehyde,**3c** (91 mg, 0.31mmol, 62%) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.65 (d, J = 2.3 Hz, 1H), 8.39 (dd, J = 8.7, 2.3 Hz, 1H), 8.03 (d, J = 8.7 Hz, 1H), 6.66 (t, J = 4.1 Hz, 1H), 6.17 (s, 1H), 3.97 – 3.90 (m, 1H), 2.42 – 2.30 (m, 5H), 1.93 (td, J = 12.6, 11.3, 5.1 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 198.44, 147.19, 146.83, 146.01, 142.72, 138.04, 129.70, 126.11, 118.88, 65.99, 37.08, 24.76, 21.26. Known compound, spectroscopic data matched those previously reported.[2]

2-[(4-Fluorophenyl)hydroxymethyl]-2-cyclohexen-1-one (3d)



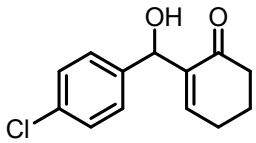
Following the general procedure 1, use 4-fluorobenzaldehyde,**3d** (53 mg, 0.24mmol, 48%) was obtained as a slightly yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.24 (dd, J = 8.6, 5.5 Hz, 2H), 6.93 (t, J = 8.7 Hz, 2H), 6.68 (t, J = 4.1 Hz, 1H), 5.45 (s, 1H), 3.32 (s, 1H), 2.39 – 2.29 (m, 4H), 1.91 (p, J = 6.2 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 199.34, 161.10 (d, *J* = 245.4 Hz), 146.32, 139.93, 136.49, 127.09, 114.20, 113.99, 70.75, 37.50, 24.71, 21.46.**^{19}F NMR** (376 MHz, Chloroform-d) δ -115.24. Known compound, spectroscopic data matched those previously reported.[1]

2-[(3-Fluorophenyl)hydroxymethyl]-2-cyclohexen-1-one (3e)



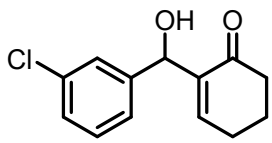
Following the general procedure 1, use 3-fluorobenzaldehyde,**3e** (44 mg, 0.2mmol, 40%) was obtained as a slightly yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.23 – 7.16 (m, 1H), 7.05 – 6.97 (m, 2H), 6.86 (td, J = 8.4, 2.5 Hz, 1H), 6.71 (t, J = 4.1 Hz, 1H), 5.44 (s, 1H), 3.59 (s, 1H), 2.33 (dq, J = 10.5, 5.8, 5.3 Hz, 4H), 1.90 (p, J = 6.1 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 199.23, 161.83 (d, *J* = 245.6 Hz), 146.69, 143.64, 139.61, 128.78, 121.02, 113.23 (d, *J* = 21.1 Hz), 112.33 (d, *J* = 22.2 Hz), 70.76, 70.74, 37.45, 24.72, 21.42. **^{19}F NMR** (376 MHz, Chloroform-d) δ -113.03. Known compound, spectroscopic data matched those previously reported.[3]

2-[(4-Chlorophenyl)hydroxymethyl]-2-cyclohexen-1-one (3f)



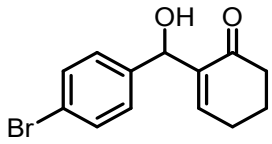
Following the general procedure 1, use 4-chlorobenzaldehyde,**3f** (46 mg, 0.195mmol, 39%) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.18 (s, 4H), 6.71 (t, J = 3.9 Hz, 1H), 5.41 (s, 1H), 3.74 (s, 1H), 2.29 (dq, J = 9.6, 5.7, 5.3 Hz, 4H), 1.87 (p, J = 6.3 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 199.04, 146.40, 139.77, 139.61, 131.98, 127.32, 126.87, 70.18, 70.16, 37.40, 24.69, 21.42. Known compound, spectroscopic data matched those previously reported.[1]

2-[(3-Chlorophenyl)hydroxymethyl]-2-cyclohexen-1-one (3g)



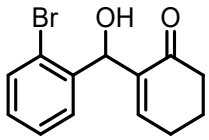
Following the general procedure 1, use 3-chlorobenzaldehyde,**3g** (41 mg, 0.175mmol, 35%) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.26 (s, 1H), 7.14 (q, J = 5.5, 5.0 Hz, 3H), 6.71 (t, J = 4.1 Hz, 1H), 5.41 (s, 1H), 3.64 (s, 1H), 2.32 (dt, J = 11.9, 5.9 Hz, 4H), 1.89 (p, J = 6.2 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 200.19, 147.76, 144.10, 140.59, 134.20, 129.57, 127.56, 126.55, 124.68, 71.65, 38.47, 25.76, 22.45. Known compound, spectroscopic data matched those previously reported.[3]

2-[(4-Bromophenyl)hydroxymethyl]-2-cyclohexen-1-one (3h)



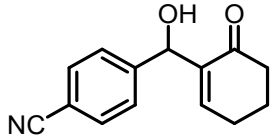
Following the general procedure 1, use 2-bromobenzaldehyde,**3h** (41 mg, 0.145mmol, 29%) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.36 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.69 (t, J = 4.1 Hz, 1H), 5.40 (s, 1H), 3.60 (s, 1H), 2.32 (ddd, J = 13.4, 9.0, 5.7 Hz, 4H), 1.89 (p, J = 6.1 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 199.18, 146.50, 139.93, 139.68, 130.32, 127.19, 120.25, 70.59, 37.44, 24.71, 21.42. Known compound, spectroscopic data matched those previously reported.[1]

2-[(2-Bromophenyl)hydroxymethyl]-2-cyclohexen-1-one (3i)



Following the general procedure 1, use 2-bromobenzaldehyde,**3i** (27 mg, 0.095mmol, 19%) was obtained as a white solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.57 – 7.51 (m, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.08 (td, J = 7.8, 1.4 Hz, 1H), 6.38 (t, J = 4.1 Hz, 1H), 5.83 (s, 1H), 3.67 (d, J = 4.0 Hz, 1H), 2.43 (dt, J = 7.8, 3.5 Hz, 2H), 2.26 (p, J = 4.8 Hz, 2H), 1.92 (p, J = 7.1, 6.6 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 199.56, 147.09, 139.08, 138.50, 131.56, 127.96, 127.52, 126.55, 121.65, 69.56, 37.40, 24.80, 21.45. Known compound, spectroscopic data matched those previously reported.[1]

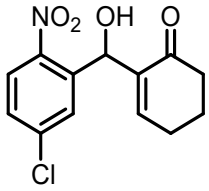
4-[Hydroxy(6-oxo-1-cyclohexen-1-yl)methyl]benzonitrile (3j)



Following the general procedure 1, use 4-formylbenzonitrile,**3j** (62 mg, 0.275mmol, 55%) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.53 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 6.77 (t, J = 4.1 Hz, 1H), 5.49 (s, 1H), 3.64 (s, 1H), 2.35 (q, J = 6.2, 5.2 Hz, 4H), 1.92 (p, J = 6.2 Hz, 2H). **^{13}C NMR** (101 MHz,

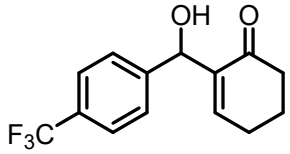
Chloroform-d) δ 199.01, 147.06, 146.52, 139.26, 131.09, 126.05, 117.83, 110.03, 70.71, 37.39, 24.75, 21.37. Known compound, spectroscopic data matched those previously reported.[2]

2-[(5-Chloro-2-nitrophenyl)hydroxymethyl]-2-cyclohexen-1-one (3k)



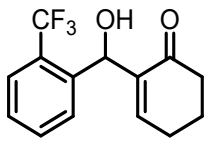
Following the general procedure 1, use 5-chloro-2-nitrobenzaldehyde,**3k** (77 mg, 0.275mmol, 55%) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.85 (d, J = 8.7 Hz, 1H), 7.76 (d, J = 2.2 Hz, 1H), 7.34 (dd, J = 8.7, 2.3 Hz, 1H), 6.54 (t, J = 4.1 Hz, 1H), 6.14 (s, 1H), 3.75 (s, 1H), 2.41 (dt, J = 8.5, 4.0 Hz, 2H), 2.30 (q, J = 5.3 Hz, 2H), 1.93 (h, J = 6.1 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 199.63, 147.30, 146.09, 140.13, 139.54, 138.95, 129.23, 128.47, 126.10, 66.87, 38.19, 25.74, 22.38. MS: calculated for C13H12ClNO4 $[M + H]^+$ m/z 282.0528, found: 282.0526.

2-[Hydroxy[4-(trifluoromethyl)phenyl]methyl]-2-cyclohexen-1-one (3l)



Following the general procedure 1, use 4-(trifluoromethyl)benzaldehyde,**3l** (61 mg, 0.225mmol, 45%) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.49 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 6.72 (t, J = 4.1 Hz, 1H), 5.49 (s, 1H), 3.56 (s, 1H), 2.32 (p, J = 6.2, 5.4 Hz, 4H), 1.89 (p, J = 6.2 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 199.20, 146.88, 144.99, 139.55, 128.51 (q, J = 32 Hz), 125.69, 124.19 (q, J = 4 Hz), 123.16 (q, J = 270 Hz), 70.74, 37.41, 24.72, 21.38.**^{19}F NMR** (376 MHz, Chloroform-d) δ -62.45. Known compound, spectroscopic data matched those previously reported.[4]

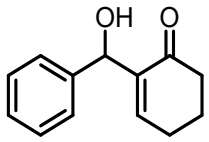
2-[Hydroxy[2-(trifluoromethyl)phenyl]methyl]-2-cyclohexen-1-one (3m)



Following the general procedure 1, use 2-(trifluoromethyl)benzaldehyde,**3m** (55 mg, 0.205mmol, 41%) was obtained as a yellow solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.69 (d, J = 7.8 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.34 (t, J = 7.6 Hz, 1H), 6.21 (t, J = 4.1 Hz, 1H), 5.98 (s, 1H), 3.37 (d, J = 50.9 Hz, 1H), 2.46 – 2.39 (m, 2H), 2.24 (q, J = 4.9 Hz, 2H), 1.91 (p, J = 6.1 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 199.50, 147.03, 139.98, 138.29, 131.07, 127.84, 126.73, 126.59 (q, J = 30 Hz), 124.68 (q, J = 6 Hz), 123.14 (q, J = 273 Hz), 66.23, 37.39, 24.75, 21.43.**^{19}F NMR** (376 MHz,

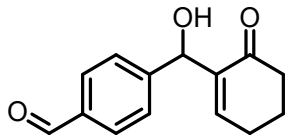
Chloroform-d) δ -58.83. Known compound, spectroscopic data matched those previously reported.[5]

2-(Hydroxy phenylmethyl)-2-cyclohexen-1-one (3n)



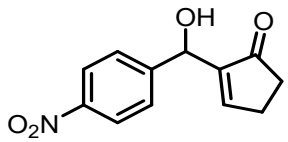
Following the general procedure 1, use benzaldehyde,**3n** (55 mg, 0.205mmol, 41%) was obtained as a colorless oil. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.27 (q, J = 4.5, 3.6 Hz, 4H), 7.21 – 7.16 (m, 1H), 6.67 (t, J = 4.1 Hz, 1H), 5.48 (s, 1H), 3.48 – 3.38 (m, 1H), 2.34 (ddd, J = 25.0, 8.9, 5.5 Hz, 4H), 1.92 (p, J = 6.1 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 199.42, 146.39, 140.63, 140.02, 127.28, 126.46, 125.43, 71.48, 37.54, 24.73, 21.48. Known compound, spectroscopic data matched those previously reported.[1]

4-[Hydroxy(6-oxo-1-cyclohexen-1-yl)methyl]benzaldehyde (3o)



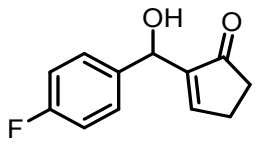
Following the general procedure 1, use terephthalaldehyde,**3o** (55 mg, 0.205mmol, 41%) was obtained as a colorless oil. **^{1}H NMR** (400 MHz, Chloroform-d) δ 9.89 (s, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 6.76 (t, J = 4.1 Hz, 1H), 5.53 (s, 1H), 3.51 (s, 1H), 2.35 (p, J = 6.2, 5.5 Hz, 4H), 1.92 (p, J = 6.2 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 199.10, 191.06, 147.95, 146.95, 139.47, 134.53, 128.78, 125.95, 70.96, 37.42, 24.76, 21.39. Known compound, spectroscopic data matched those previously reported.[6]

2-[Hydroxy(4-nitrophenyl)methyl]-2-cyclopenten-1-one (4a)



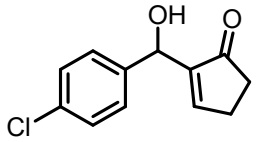
Following the general procedure 2, use 4-Nitrobenzaldehyde,**4a** (59 mg, 0.255mmol, 51%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.14 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.25 (s, 1H), 5.60 (s, 1H), 3.65 (s, 1H), 2.59 – 2.54 (m, 2H), 2.41 (dd, J = 3.8, 2.1 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 209.36, 159.95, 148.55, 147.47, 146.71, 127.11, 123.74, 68.97, 35.16, 26.87. Known compound, spectroscopic data matched those previously reported.[1]

2-[(4-Fluorophenyl)hydroxymethyl]-2-cyclopenten-1-one(4b)



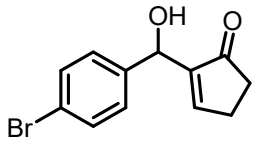
Following the general procedure 2, use 4-fluorobenzaldehyde,**4b** (46 mg, 0.225mmol, 45%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.27 (dd, J = 8.5, 5.5 Hz, 2H), 7.22 – 7.19 (m, 1H), 6.95 (t, J = 8.7 Hz, 2H), 5.44 (s, 1H), 3.55 (s, 1H), 2.54 – 2.49 (m, 2H), 2.39 – 2.34 (m, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 208.58, 161.3, 158.46, 146.70, 136.18, 127.09, 114.29, 68.12, 34.23, 25.65. **^{19}F NMR** (376 MHz, Chloroform-d) δ -114.59. Known compound, spectroscopic data matched those previously reported.[7]

2-[(4-Chlorophenyl)hydroxymethyl]-2-cyclopenten-1-one(4c)



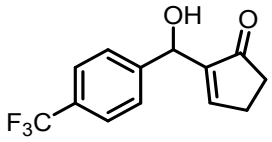
Following the general procedure 2, use 4-chlorobenzaldehyde,**4c** (44 mg, 0.2mmol, 40%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.67 (s, 1H), 7.39 (s, 4H), 5.80 (s, 1H), 5.33 (s, 1H), 2.59 (s, 2H), 2.36 (ddd, J = 8.7, 5.5, 2.8 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 207.73, 159.65, 148.92, 142.91, 132.00, 128.77, 128.44, 67.28, 35.37, 26.69. Known compound, spectroscopic data matched those previously reported.[3]

2-[(4-Bromophenyl)hydroxymethyl]-2-cyclopenten-1-one(4d)



Following the general procedure 2, use 4-bromobenzaldehyde,**4d** (39 mg, 0.145mmol, 29%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.41 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 4.1 Hz, 2H), 5.45 (s, 1H), 2.89 (s, 1H), 2.56 – 2.51 (m, 2H), 2.42 – 2.37 (m, 2H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 208.57, 158.51, 146.30, 139.31, 130.59, 127.07, 120.72, 68.27, 34.20, 25.68. Known compound, spectroscopic data matched those previously reported.[3]

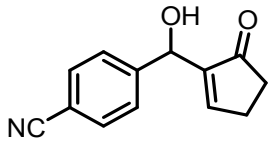
2-[Hydroxy[4-(trifluoromethyl)phenyl]methyl]-2-cyclopenten-1-one(4e)



Following the general procedure 2, use 4-(trifluoromethyl)benzaldehyde,**4e** (42 mg, 0.165mmol, 33%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.53 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 6.8 Hz, 1H), 5.54 (s, 1H),

3.67 (s, 1H), 2.56 – 2.51 (m, 2H), 2.38 (dd, *J* = 5.8, 2.6 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 208.53, 158.79, 146.14, 144.30, 128.95, 125.60, 124.43, 121.72, 68.16, 34.17, 25.74. Known compound, spectroscopic data matched those previously reported.[8]

4-[Hydroxy(5-oxo-1-cyclopenten-1-yl)methyl]benzonitrile(4f)



Following the general procedure 2, use 4-formylbenzonitrile,**4f** (50 mg, 0.235mmol, 47%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.27 (s, 1H), 5.53 (s, 1H), 3.80 (s, 1H), 2.58 – 2.52 (m, 2H), 2.41 – 2.36 (m, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 208.32, 159.02, 145.90, 145.81, 131.30, 125.99, 117.74, 110.41, 67.88, 34.15, 25.82. Known compound, spectroscopic data matched those previously reported.[2]

[7]. Reference

1. Shi, M.; Liu, X.-G., Asymmetric Morita-Baylis-Hillman reaction of arylaldehydes with 2-cyclohexen-1-one catalyzed by chiral bis(thio)urea and DABCO. *ORGANIC LETTERS* **2008,** *10* (6), 1043-1046.
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3. Nakayama, Y.; Gotanda, T.; Ito, K., Asymmetric Morita–Baylis–Hillman reactions of 2-cyclohexen-1-one catalyzed by chiral biaryl-based bis(thiourea) organocatalysts. *Tetrahedron Letters* **2011,** *52* (47), 6234-6237.
4. Sohtome, Y.; Takemura, N.; Takagi, R.; Hashimoto, Y.; Nagasawa, K., Thiourea-catalyzed Morita–Baylis–Hillman reaction. *Tetrahedron* **2008,** *64* (40), 9423-9429.
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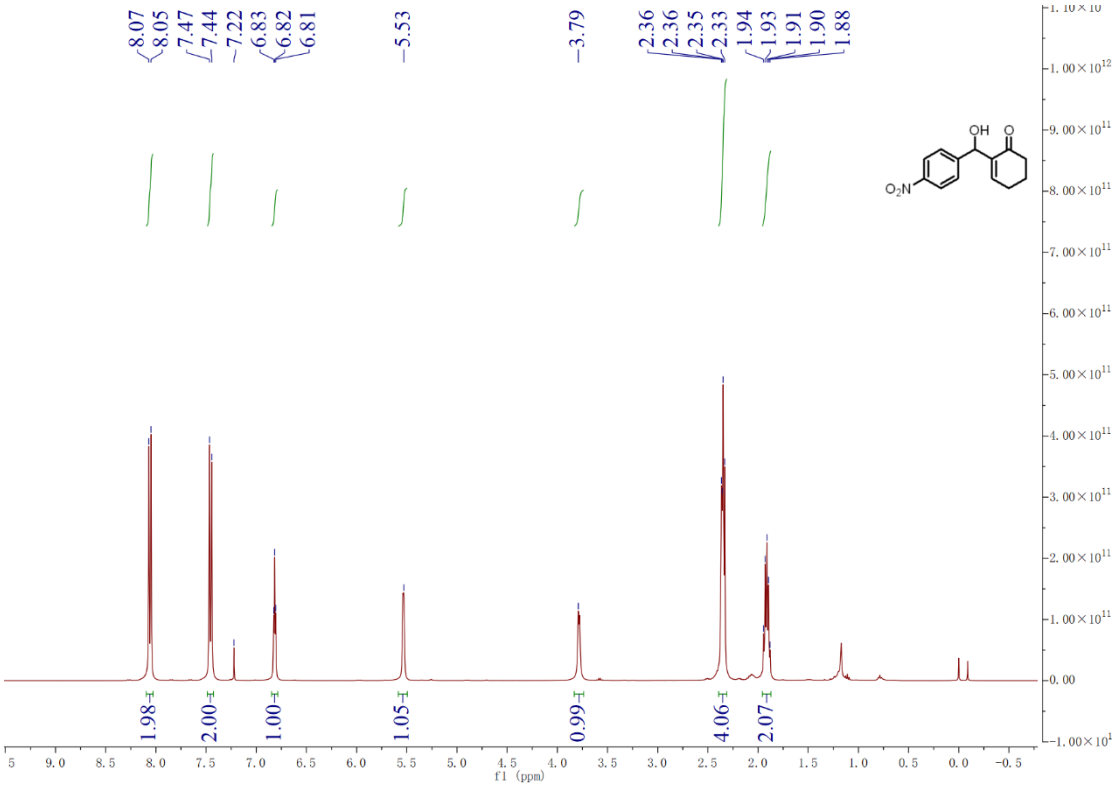
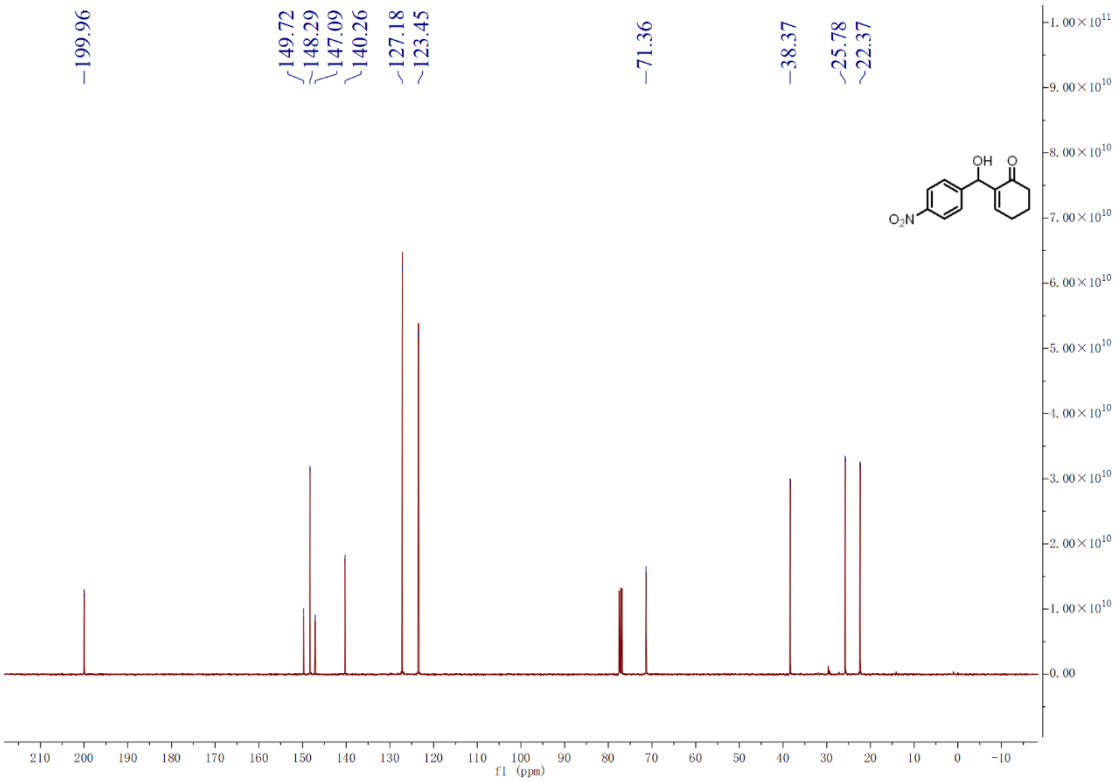
6. Verdier, R. A. T.; Mikkelsen, J. H.; Lindhardt, A. T., Studying the Morita-Baylis-Hillman Reaction in Continuous Flow Using Packed Bed Reactors. *Organic Process Research & Development* **2018,** *22* (11), 1524-1533.
7. Yang, Y.; Shang, H.; Li, X.; Zhu, K.; Luan, Y., The synthesis of a copper metal-organic framework Cu3TDPAT and its application in a Morita-Baylis-Hillman (MBH) reaction. *Applied Organometallic Chemistry* **2022,** *36* (3), e6566.
8. Bugarin, A.; Connell, B. T., MgI2-accelerated enantioselective Morita–Baylis–Hillman reactions of cyclopentenone utilizing a chiral DMAP catalyst. *Chemical Communications* **2010,** *46* (15), 2644-2646.

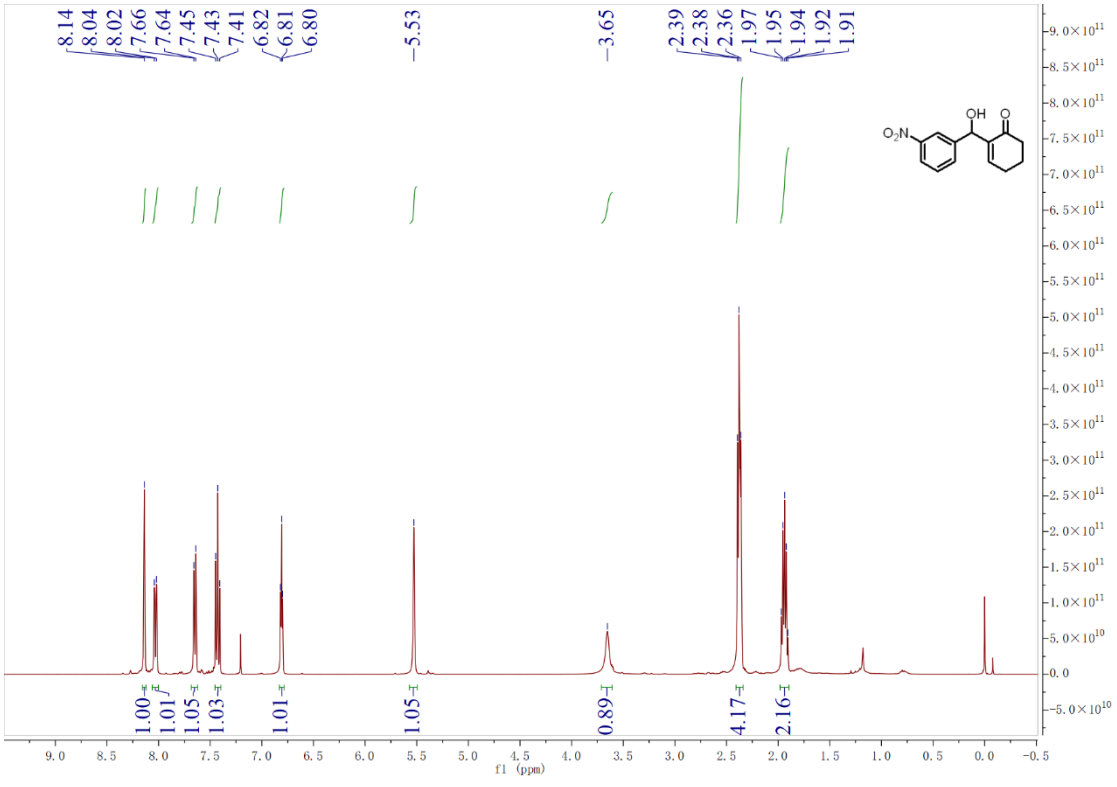
[8]. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra

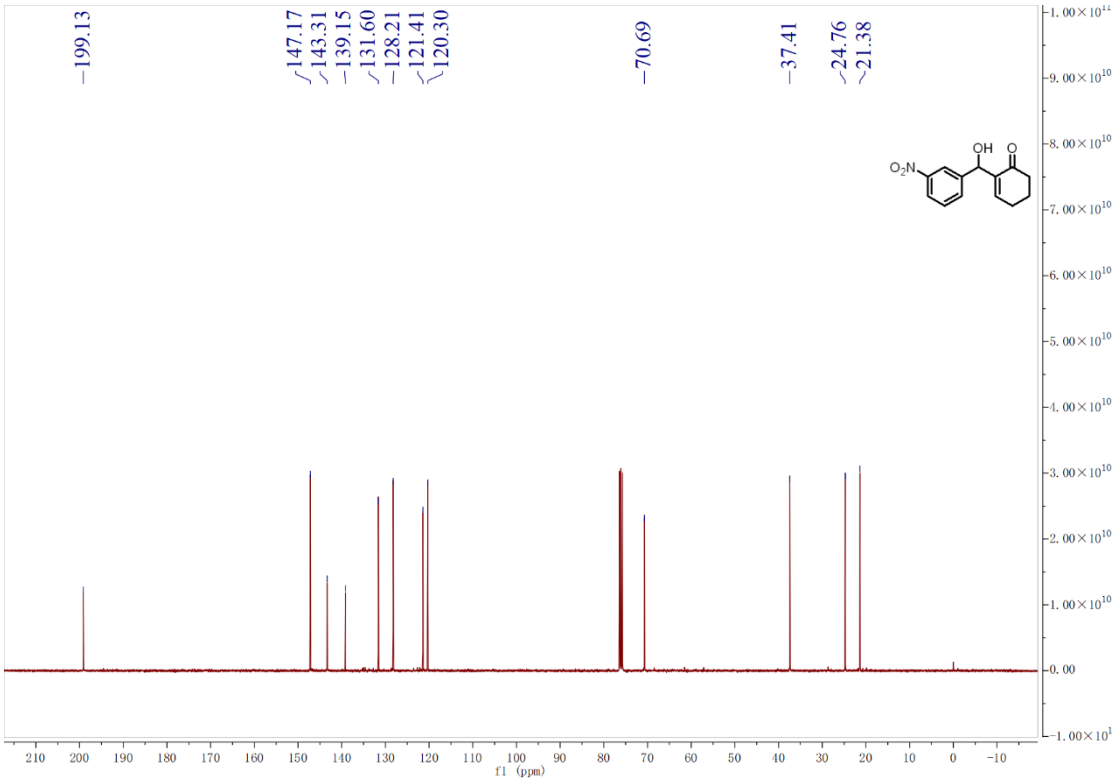
(**3a**) 2-[Hydroxy(4-nitrophenyl)methyl]-2-cyclohexen-1-one



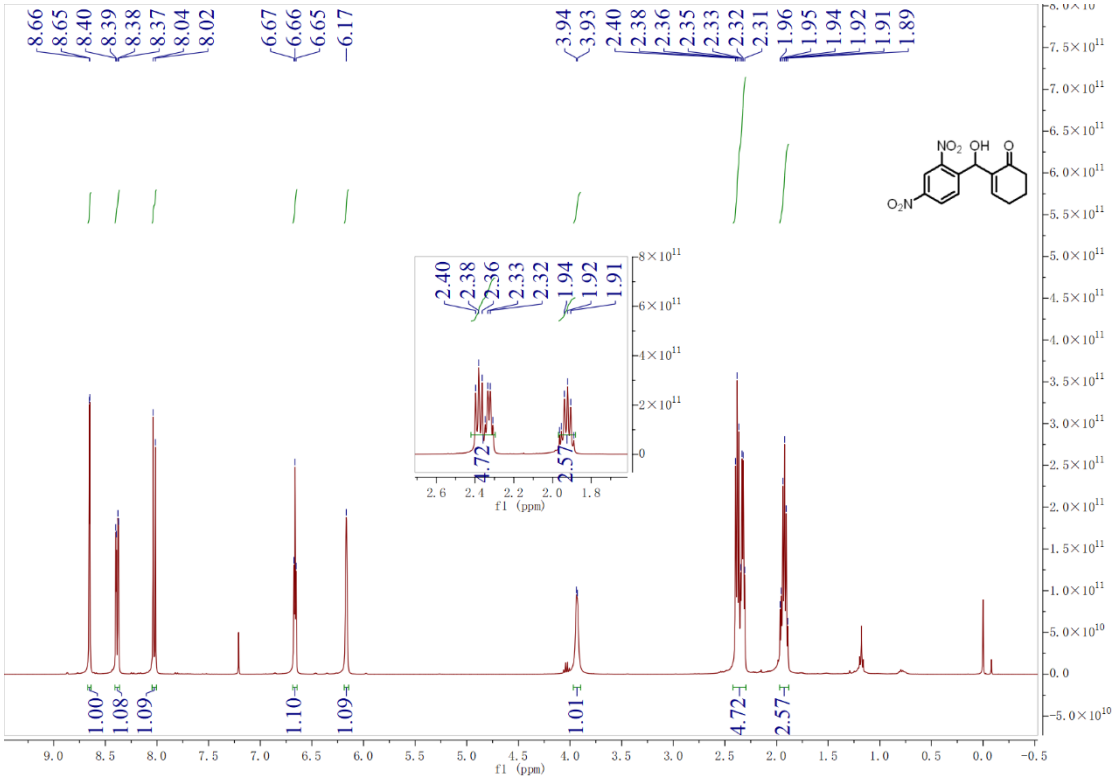


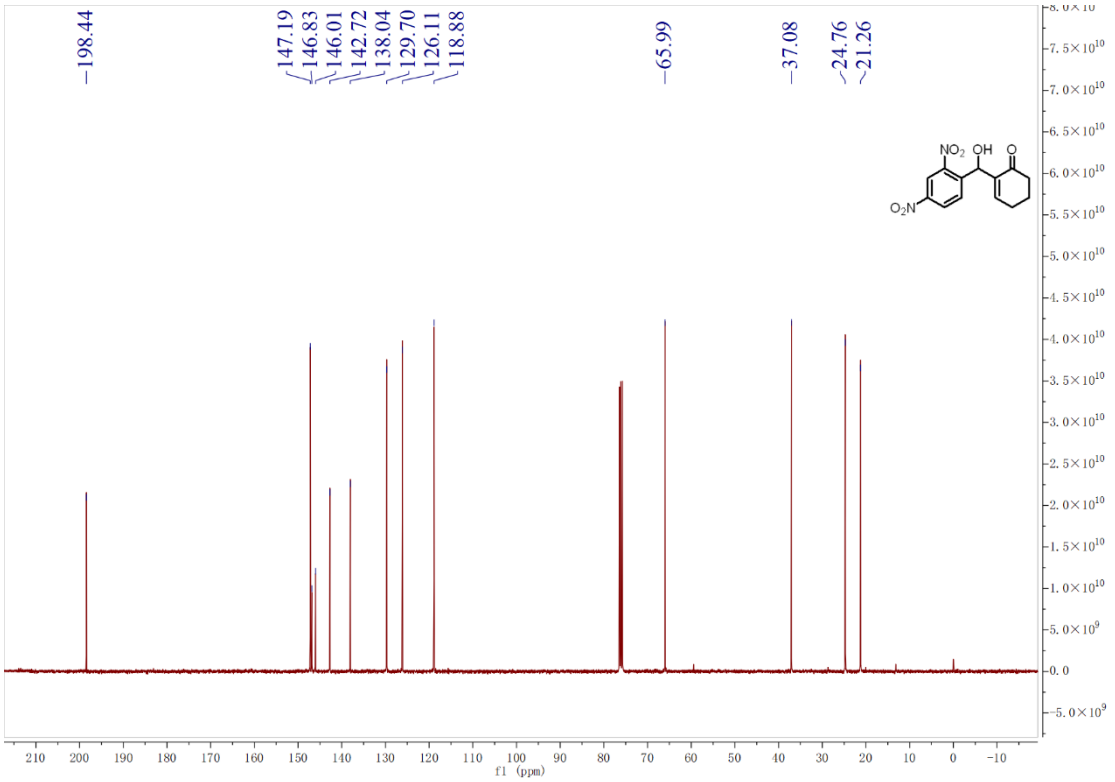
(**3b**) 2-[Hydroxy(3-nitrophenyl)methyl]-2-cyclohexen-1-one



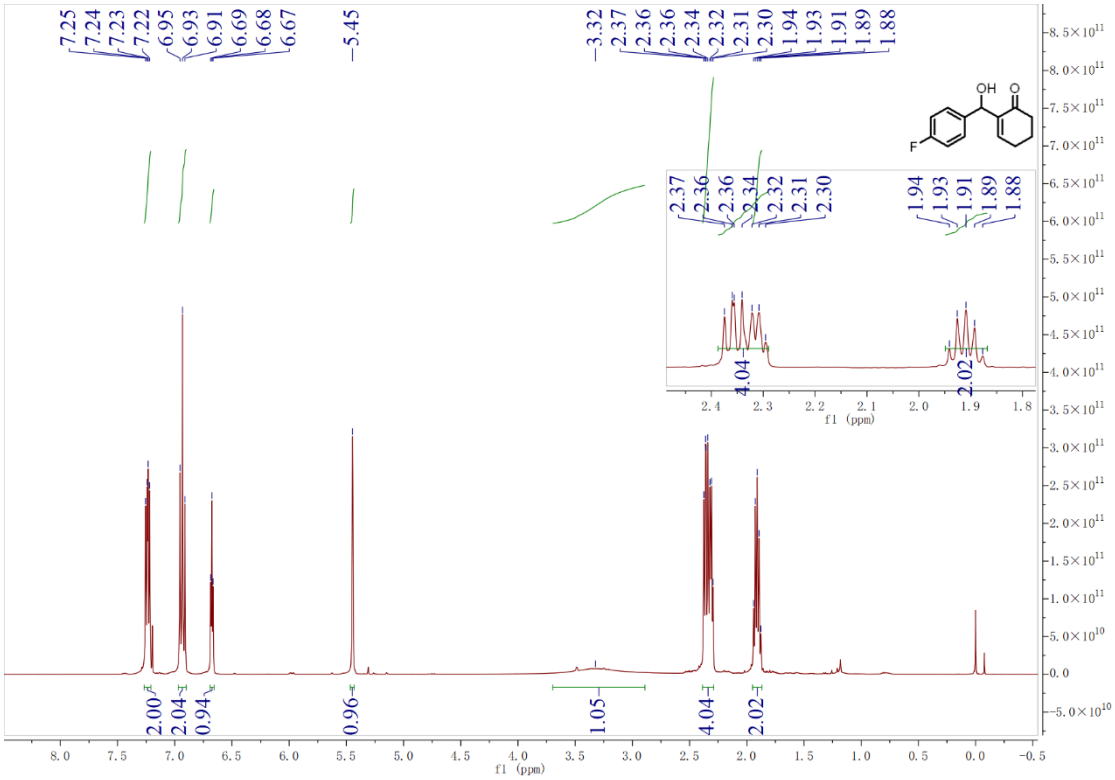


(**3c**) 2-[(2,4-Dinitrophenyl)hydroxymethyl]-2-cyclohexen-1-one





(**3d**) 2-[(4-Fluorophenyl)hydroxymethyl]-2-cyclohexen-1-one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2.36
2.34
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2.30
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1.91
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O
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2.04
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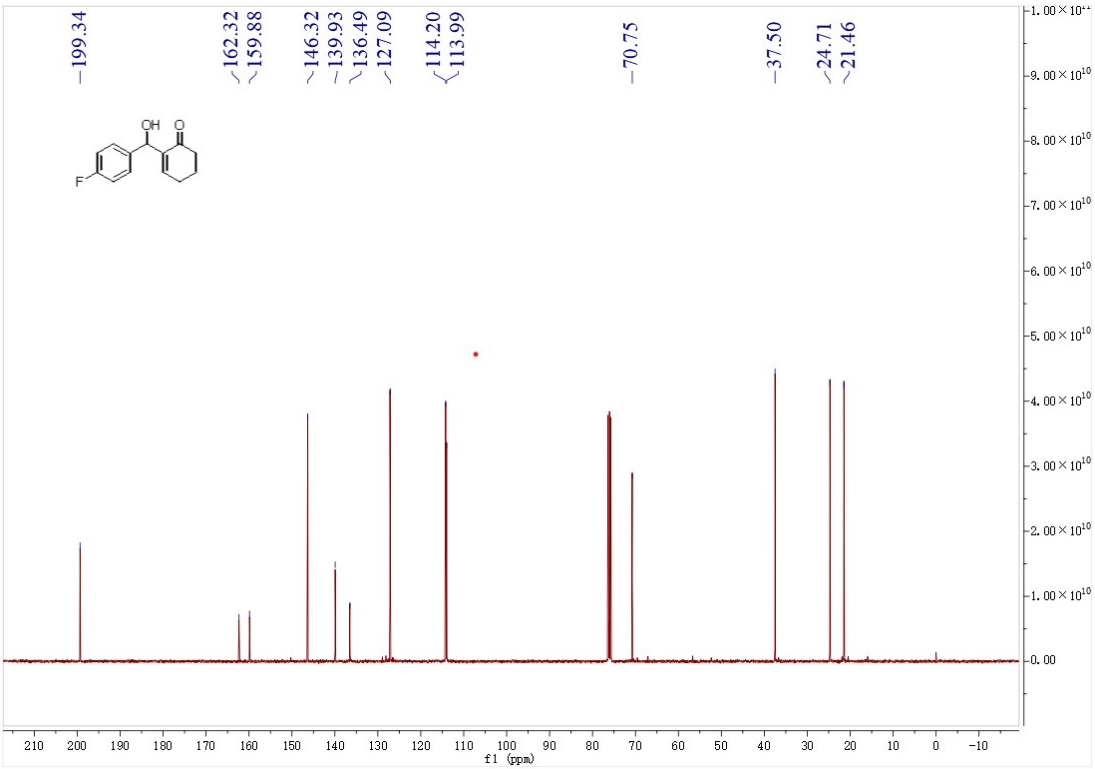
4.04
2.02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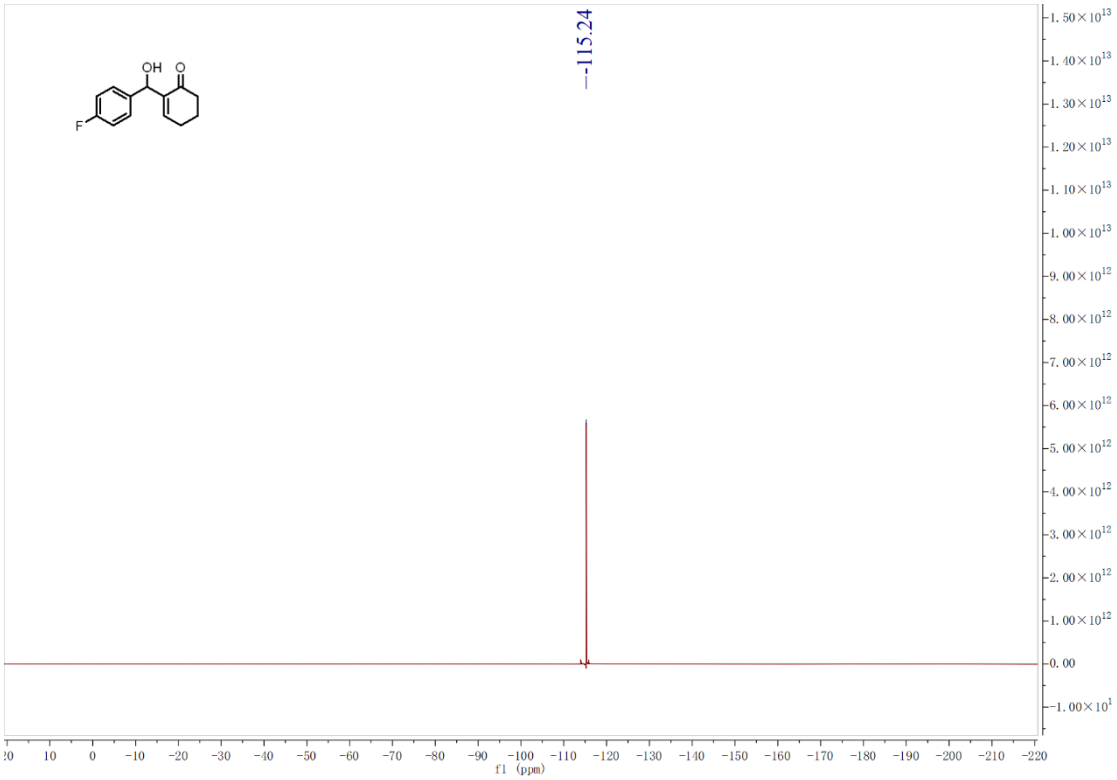
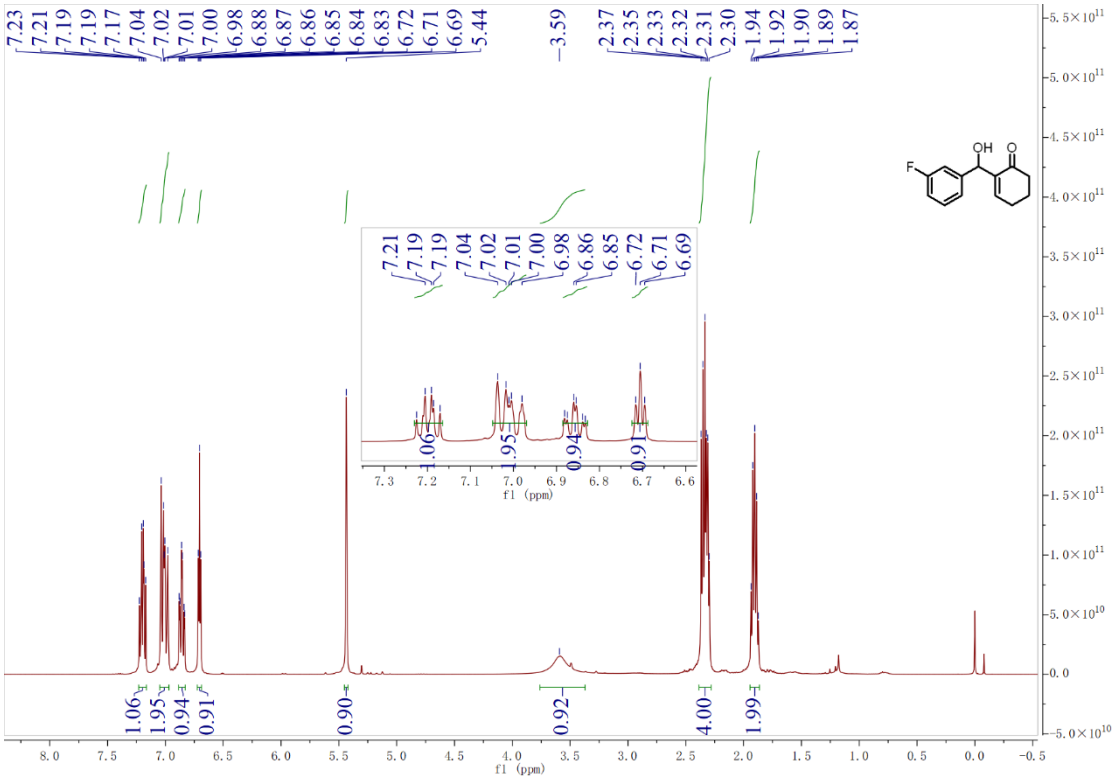
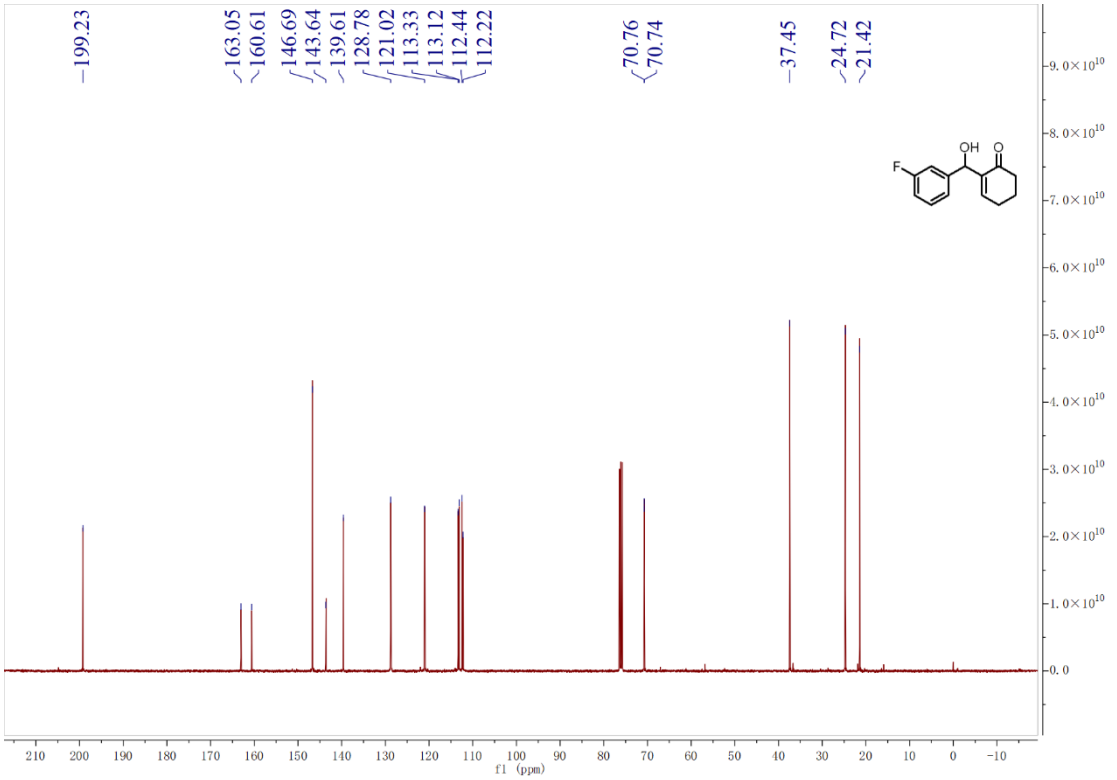
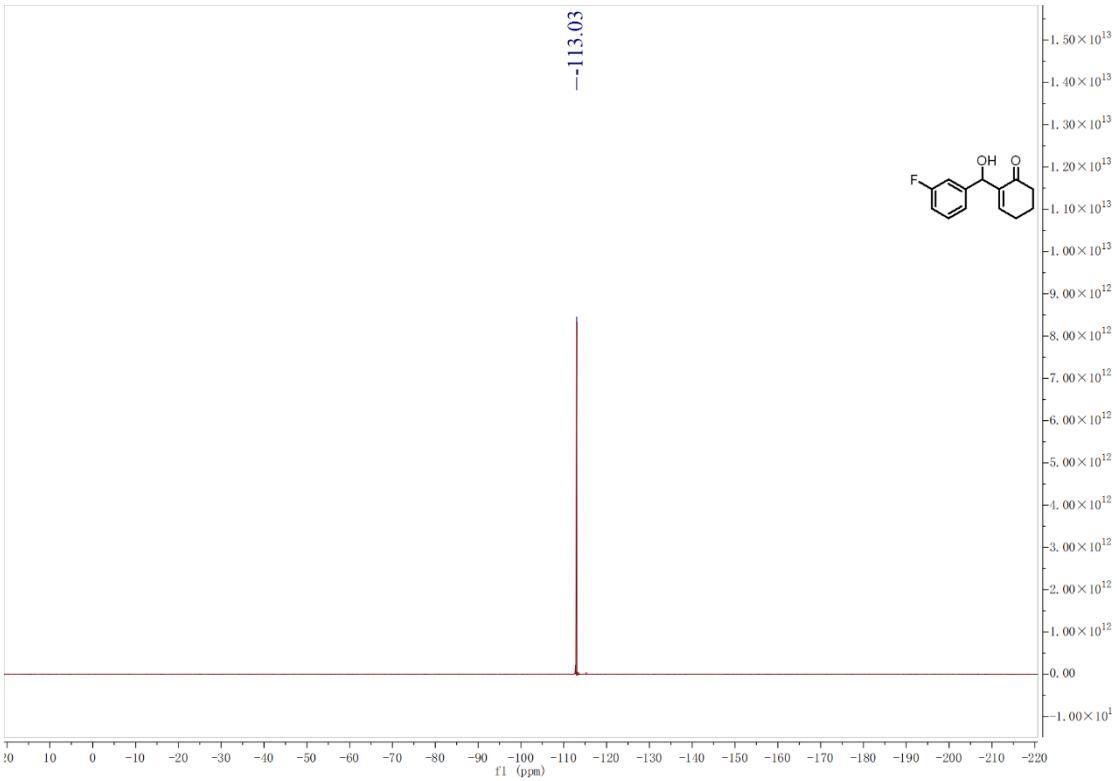
OH
O
F
f1 (ppm)



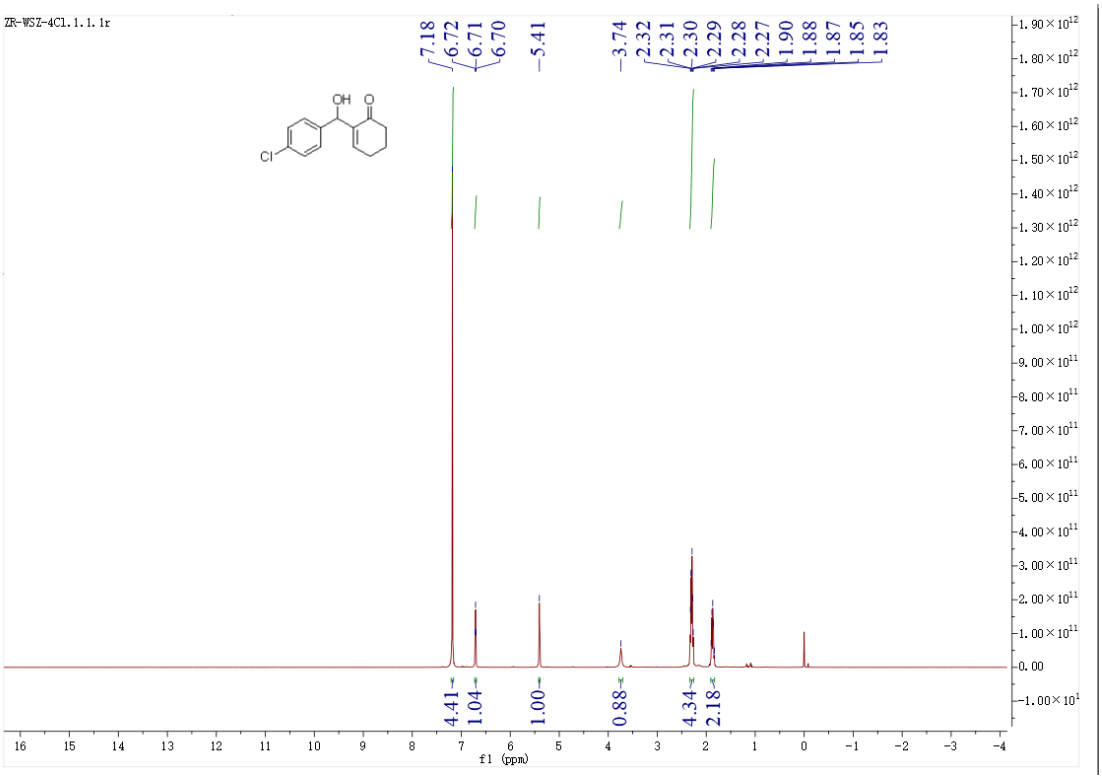
(**3e**) 2-[(3-Fluorophenyl)hydroxymethyl]-2-cyclohexen-1-one

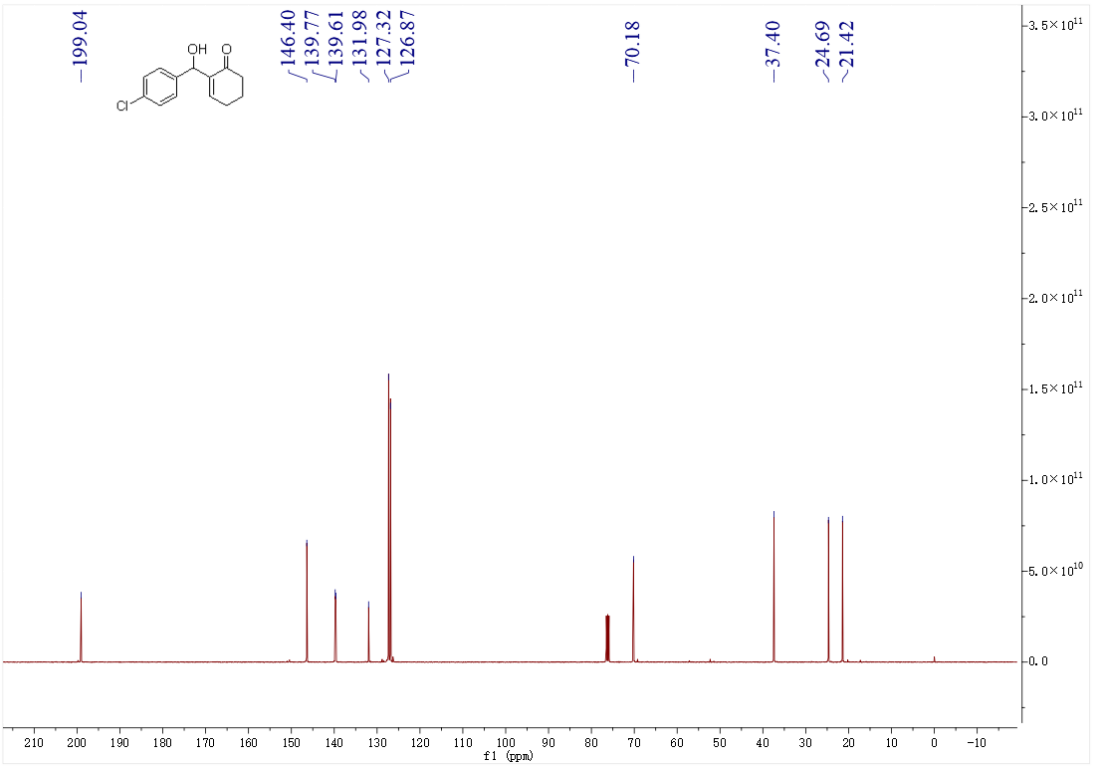




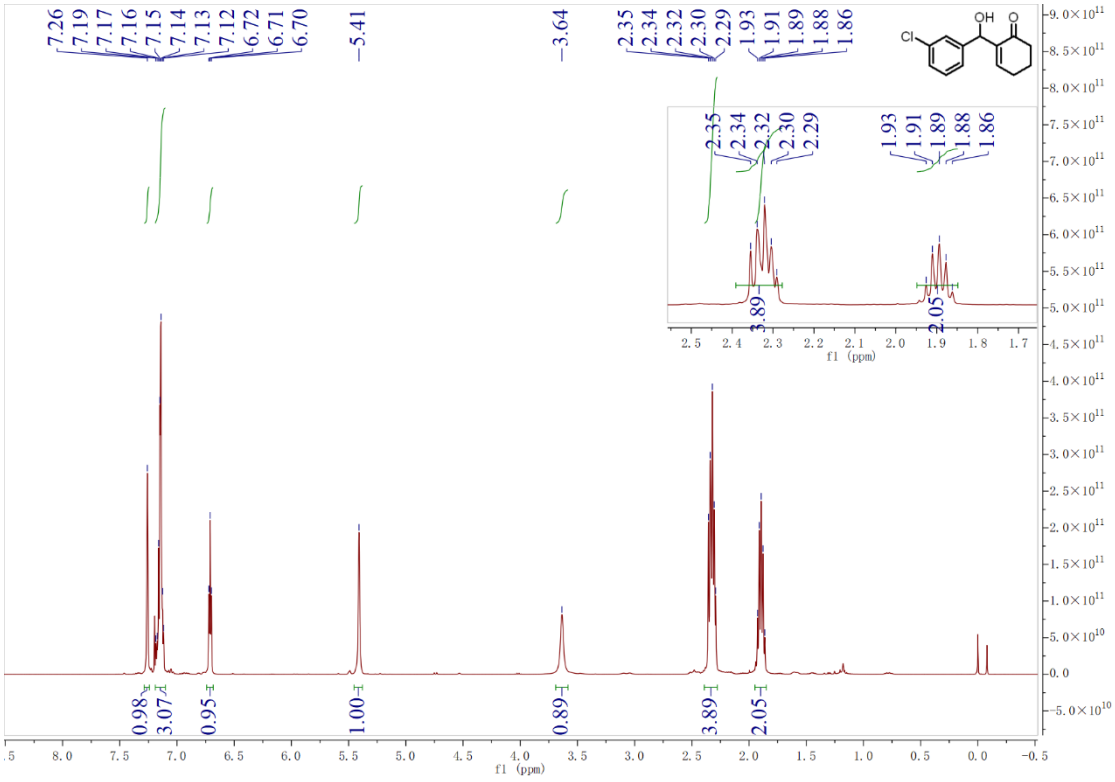


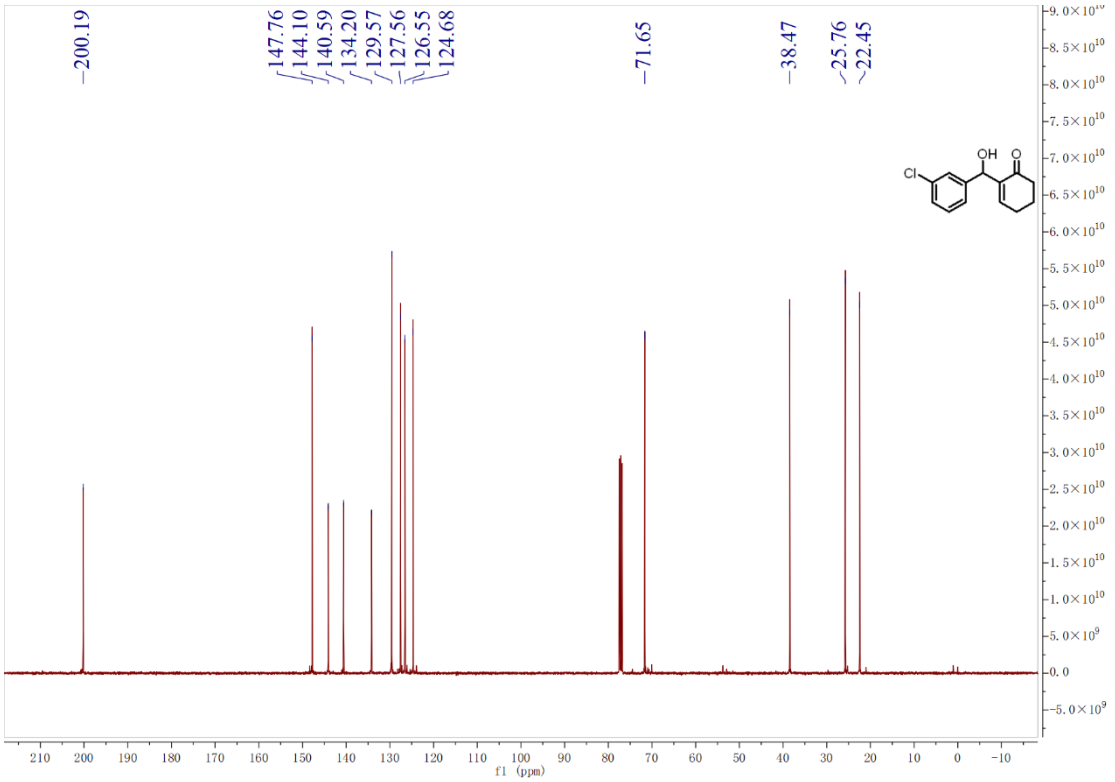
(**3f**) 2-[(4-Chlorophenyl)hydroxymethyl]-2-cyclohexen-1-one



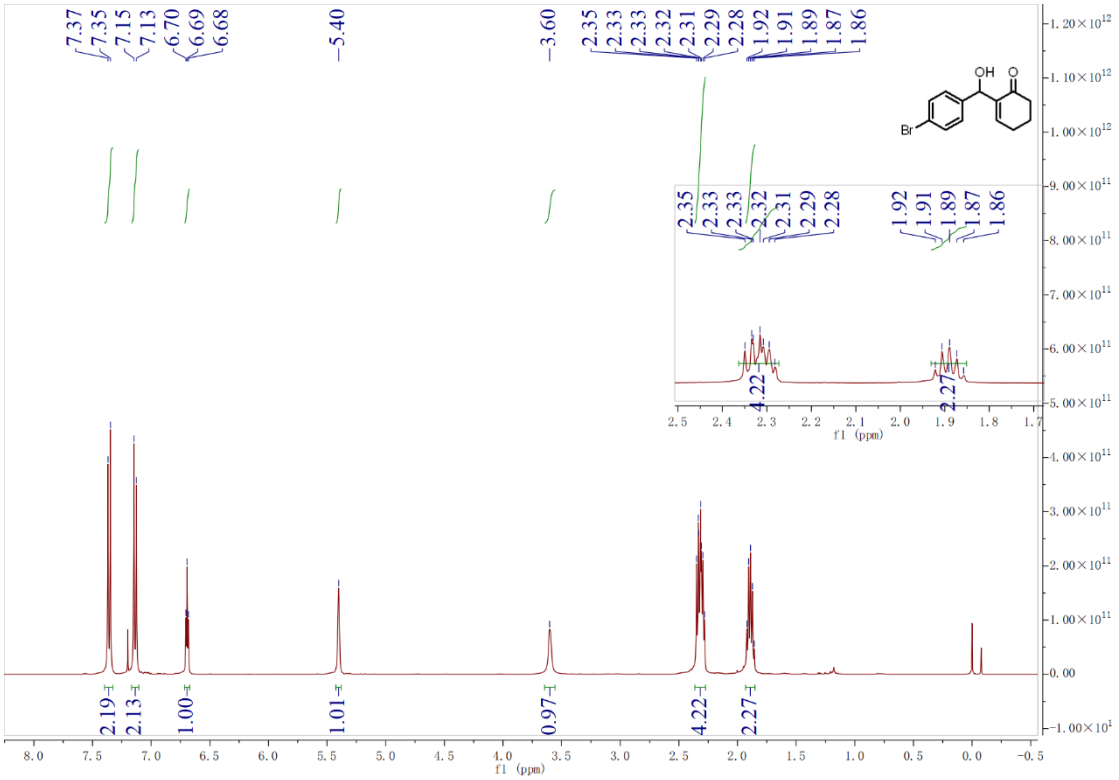


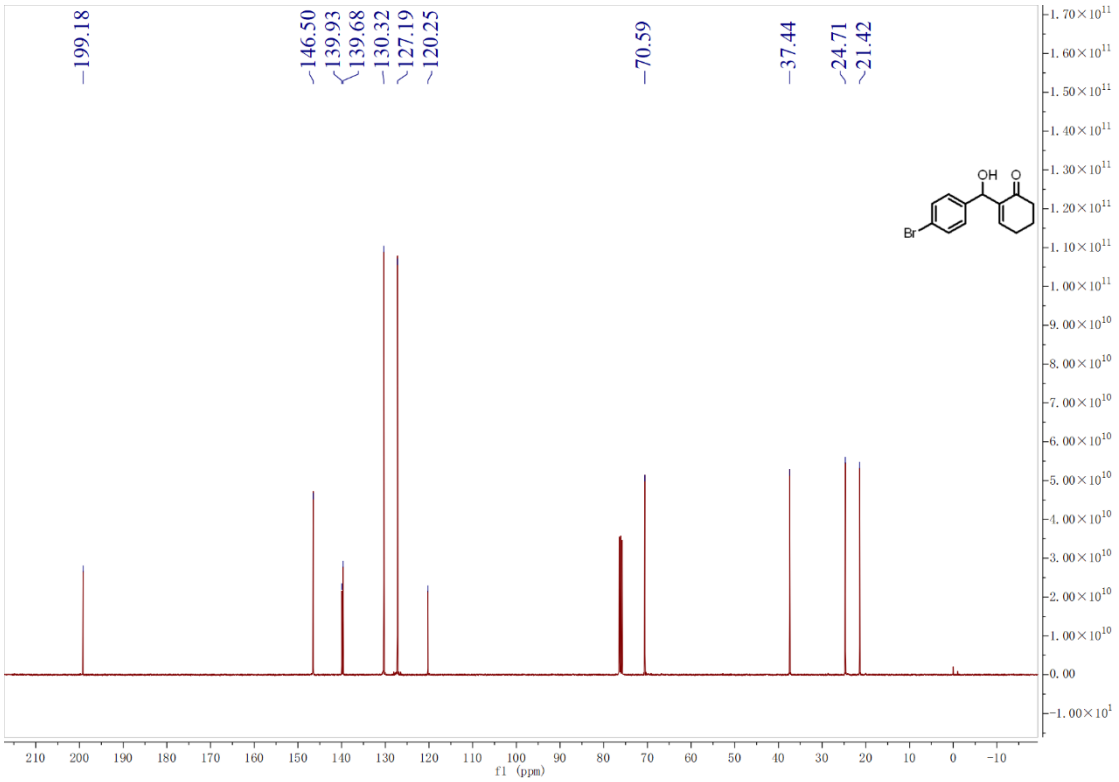
(**3g**) 2-[(3-Chlorophenyl)hydroxymethyl]-2-cyclohexen-1-one



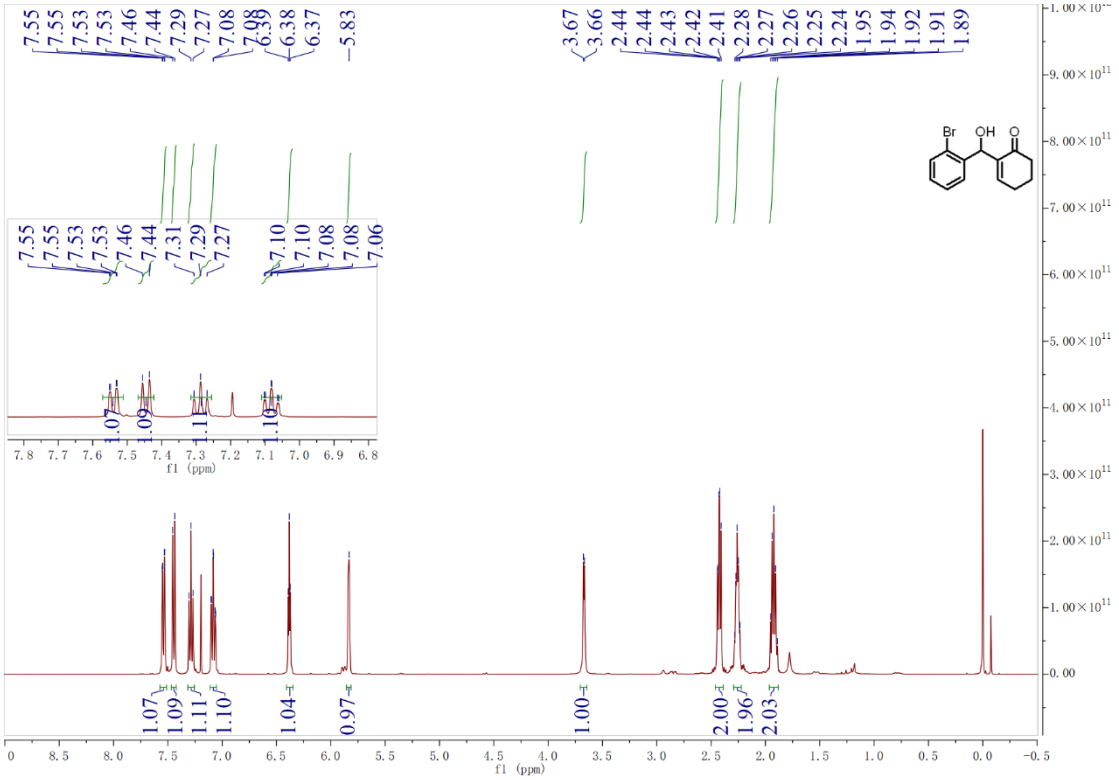


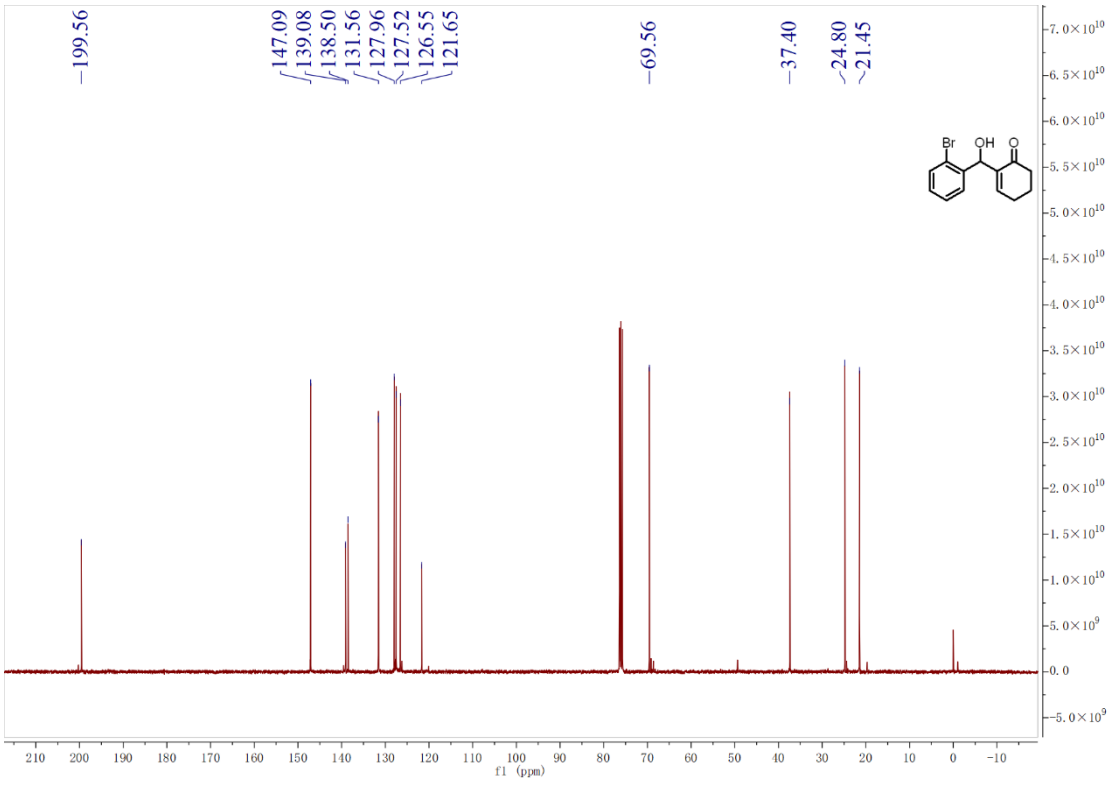
(**3h**) 2-[(4-Bromophenyl)hydroxymethyl]-2-cyclohexen-1-one



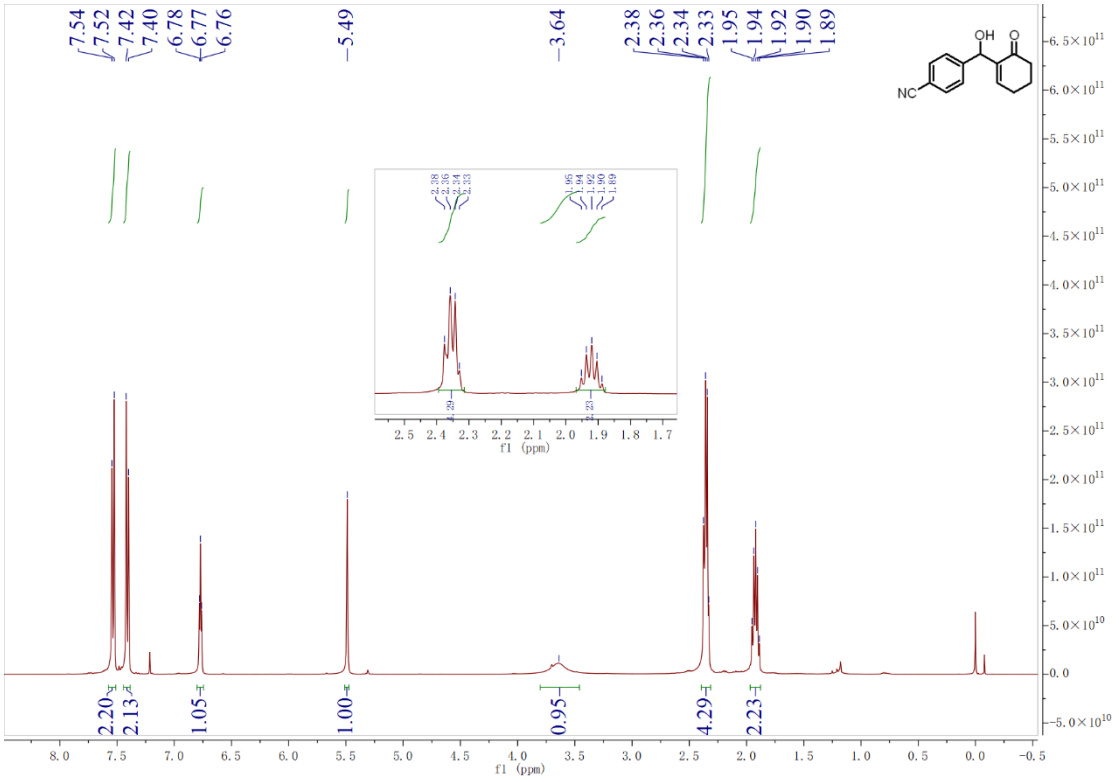


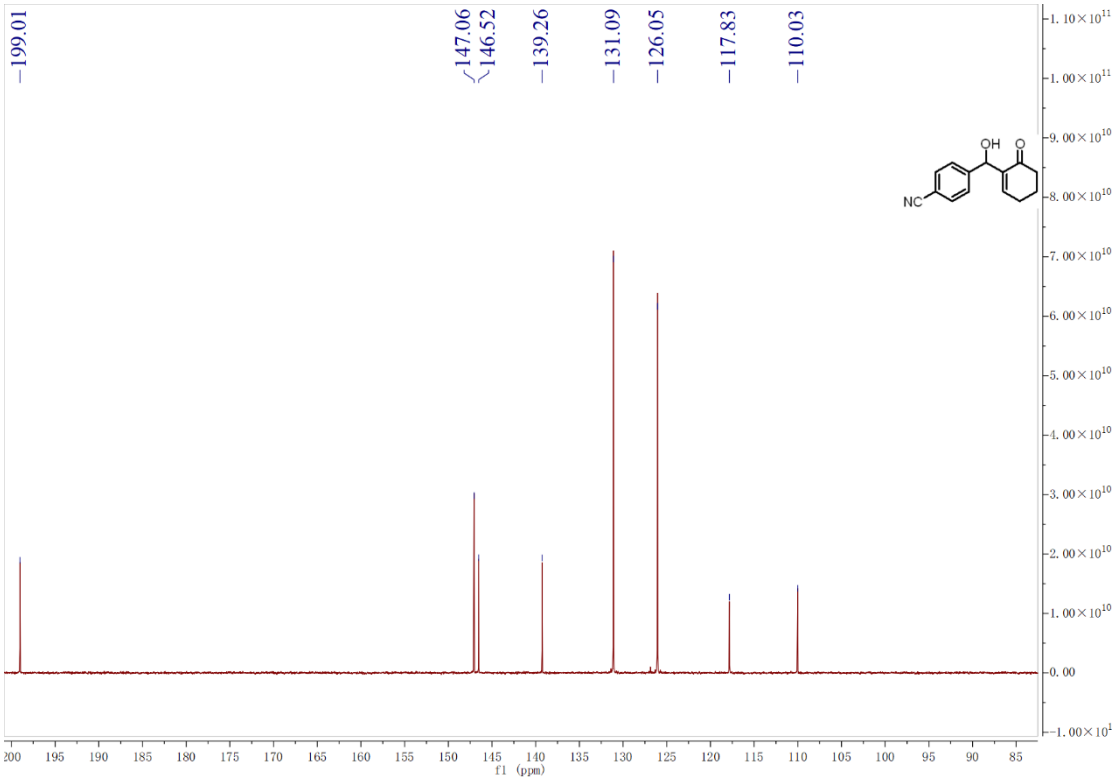
(**3i**) 2-[(2-Bromophenyl)hydroxymethyl]-2-cyclohexen-1-one



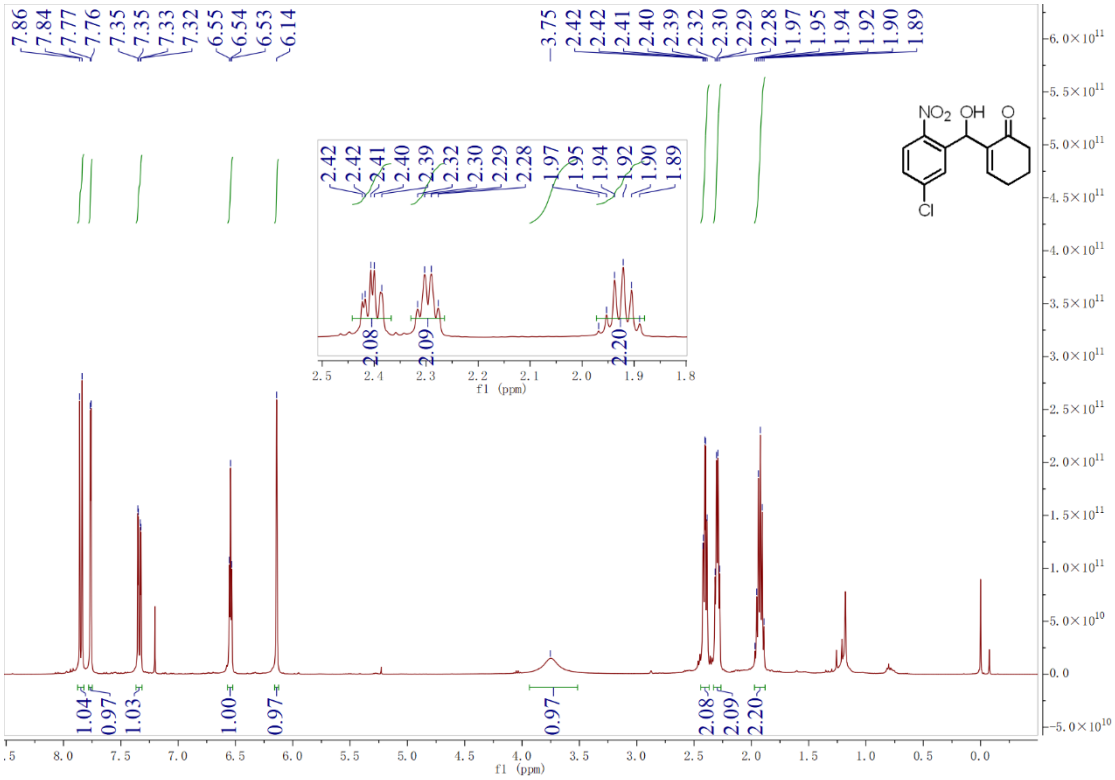


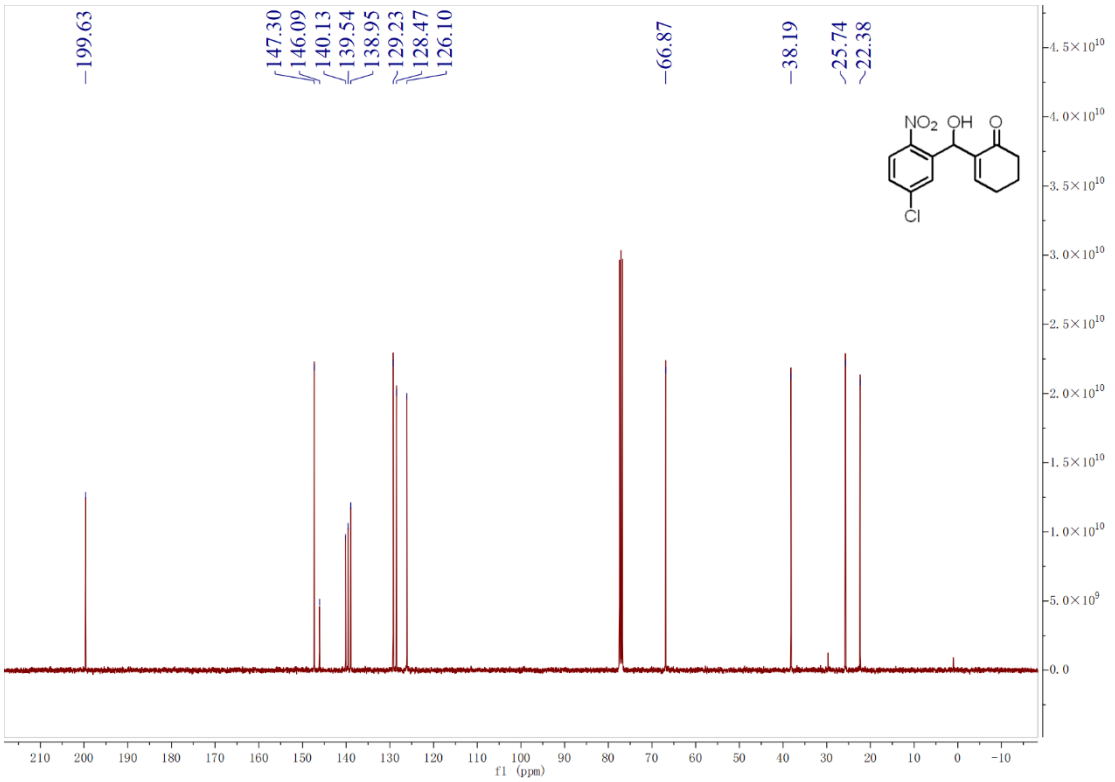
(**3j**) 4-[Hydroxy(6-oxo-1-cyclohexen-1-yl)methyl]benzonitrile



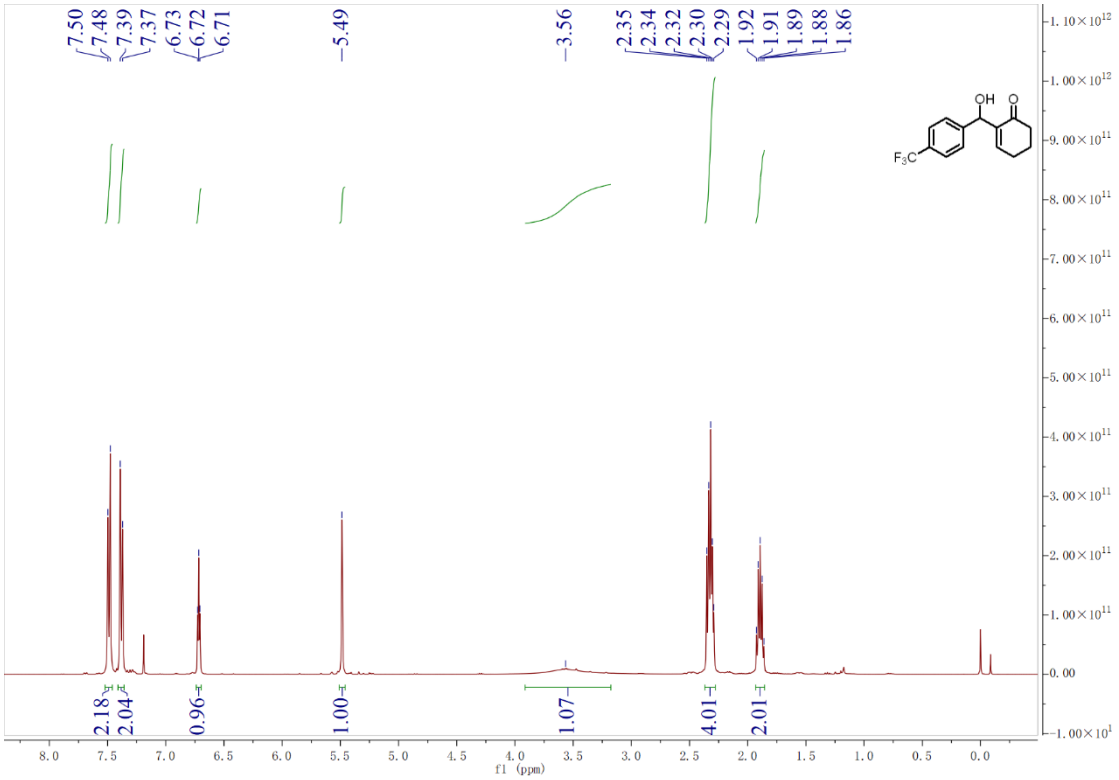


(**3k**) 2-[(5-Chloro-2-nitrophenyl)hydroxymethyl]-2-cyclohexen-1-one





(3l) 2-[Hydroxy[4-(trifluoromethyl)phenyl]methyl]-2-cyclohexen-1-one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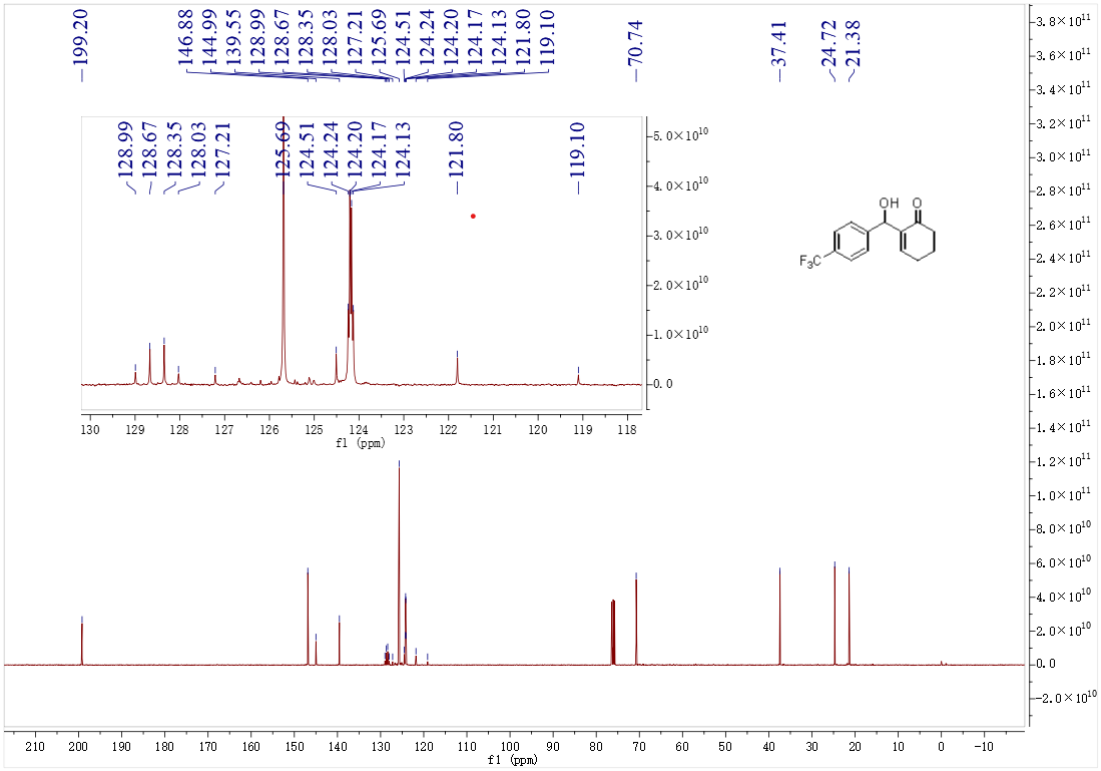
f1 (ppm)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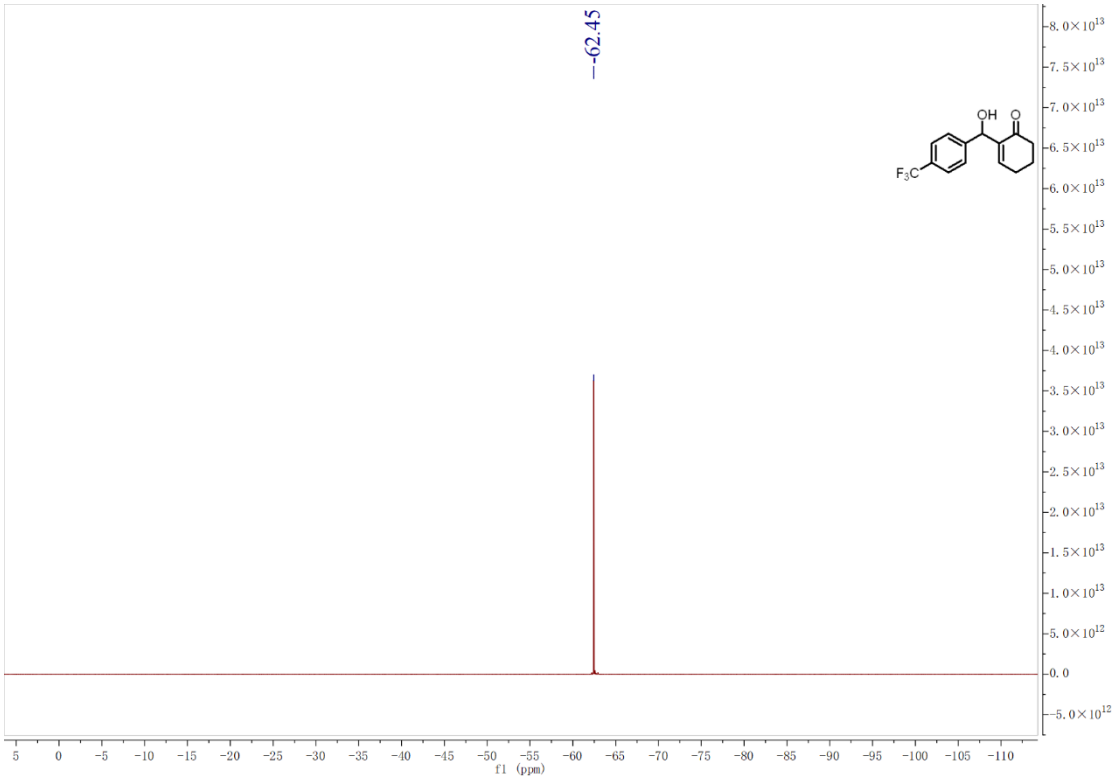
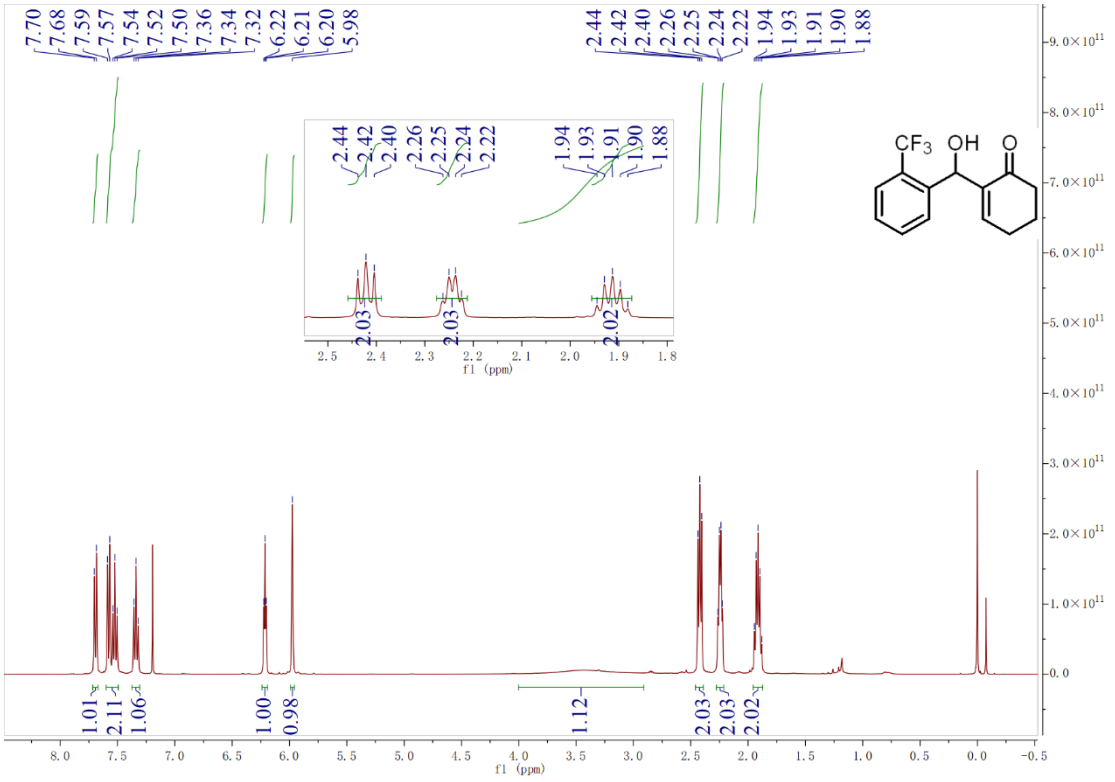
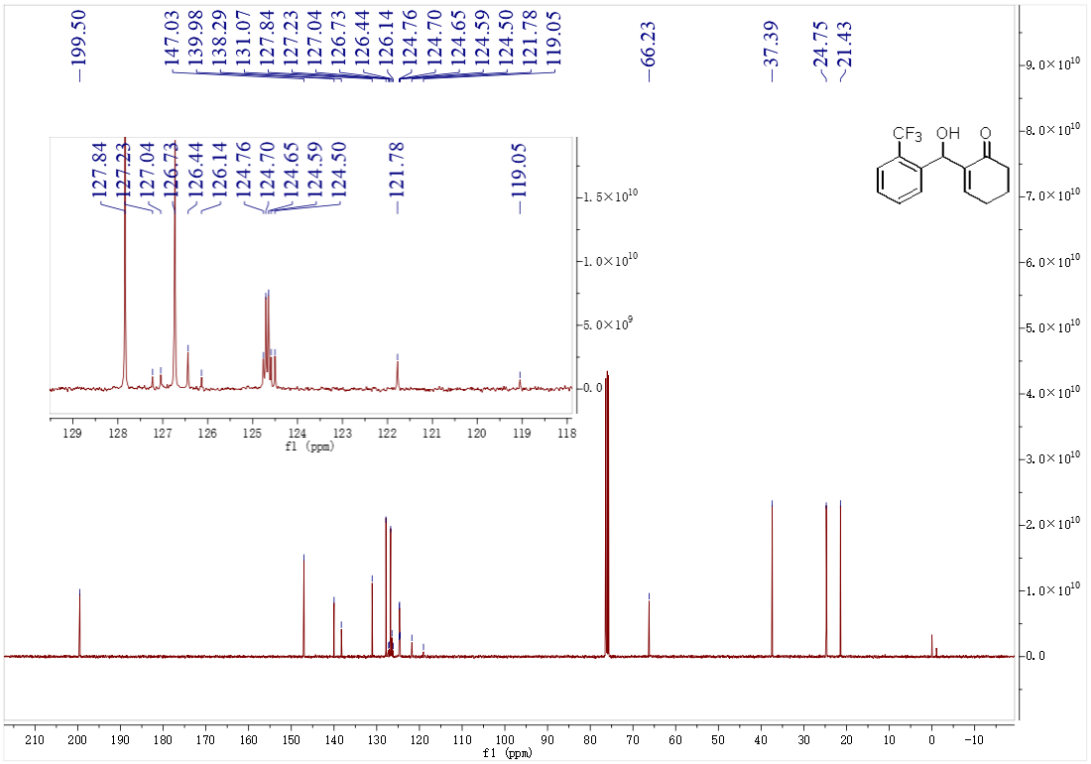
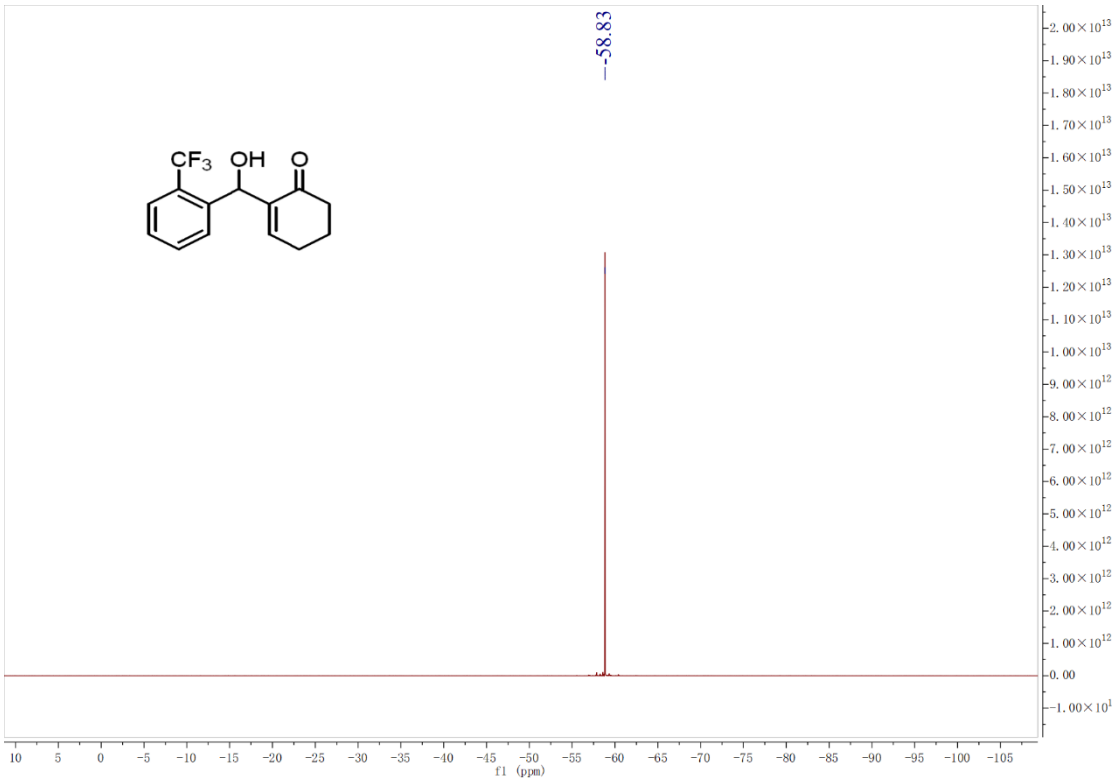
124.13
121.80
119.10
70.74
37.41
24.72
21.38
OH
O
F3C
f1 (ppm)



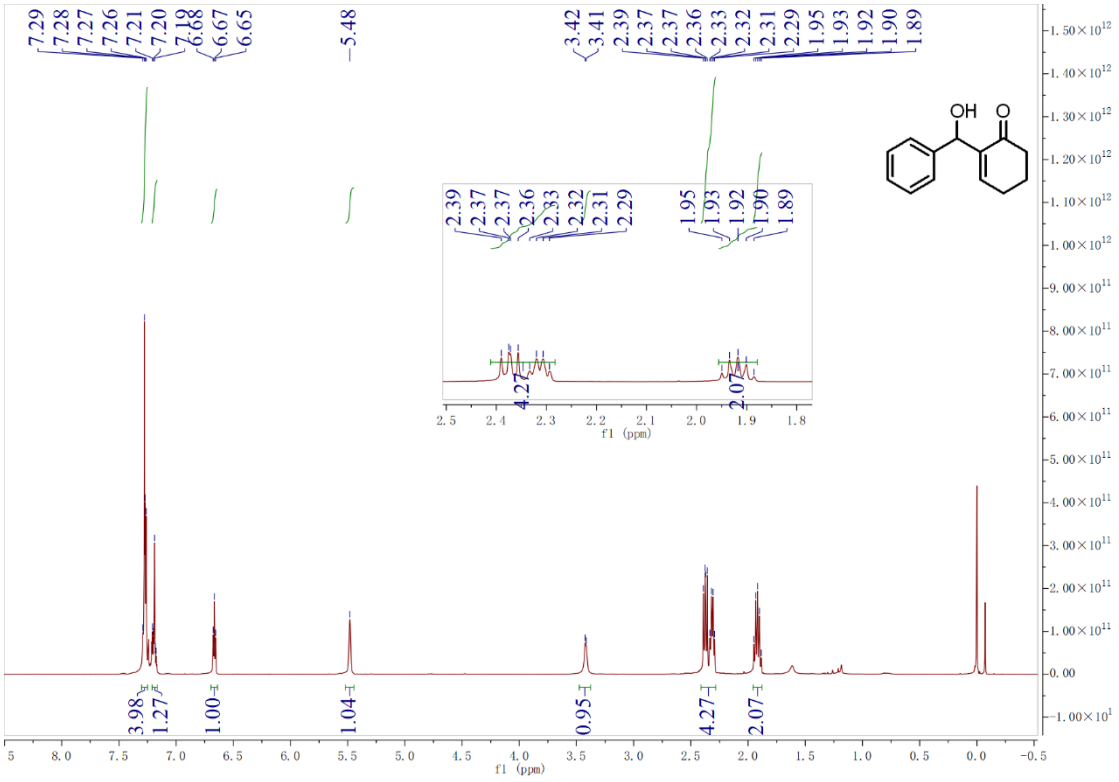
(**3m**) 2-[Hydroxy[2-(trifluoromethyl)phenyl]methyl]-2-cyclohexen-1-one

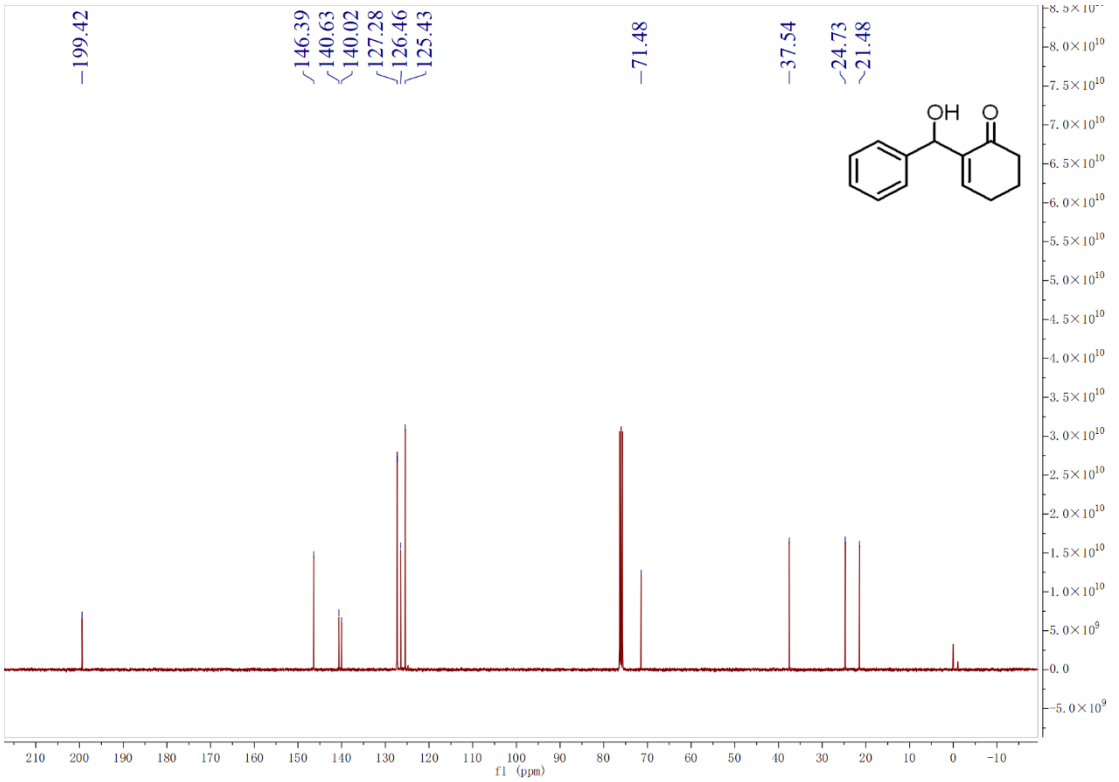




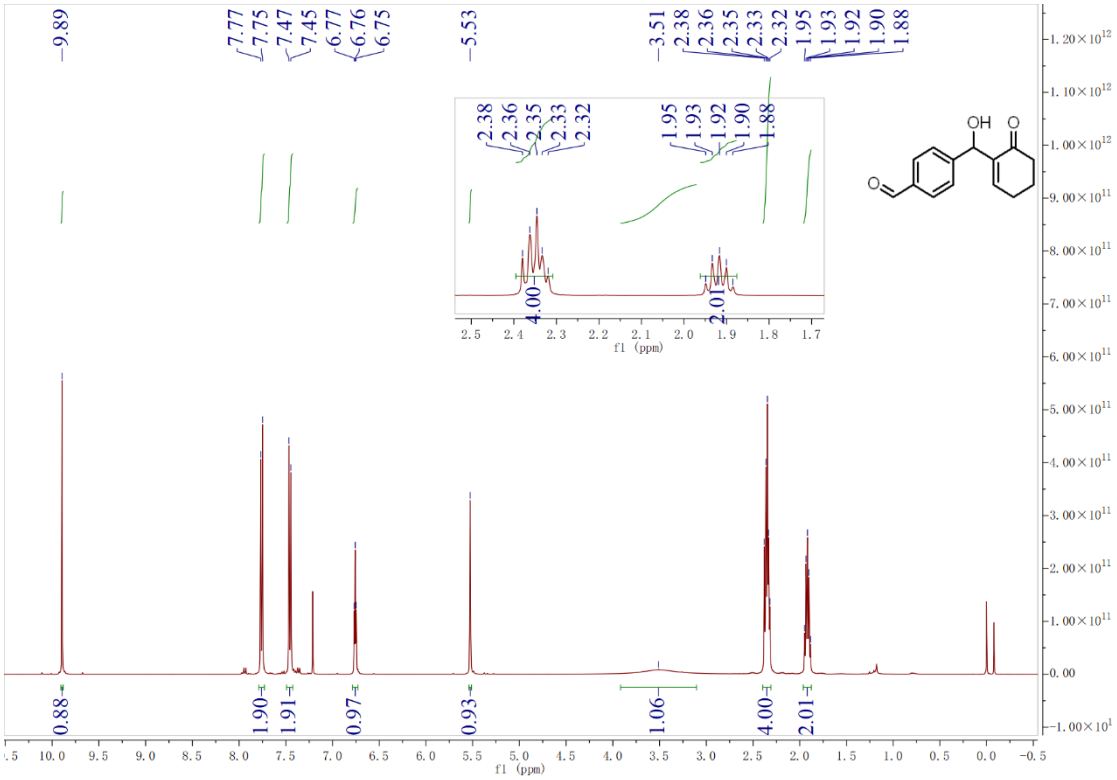


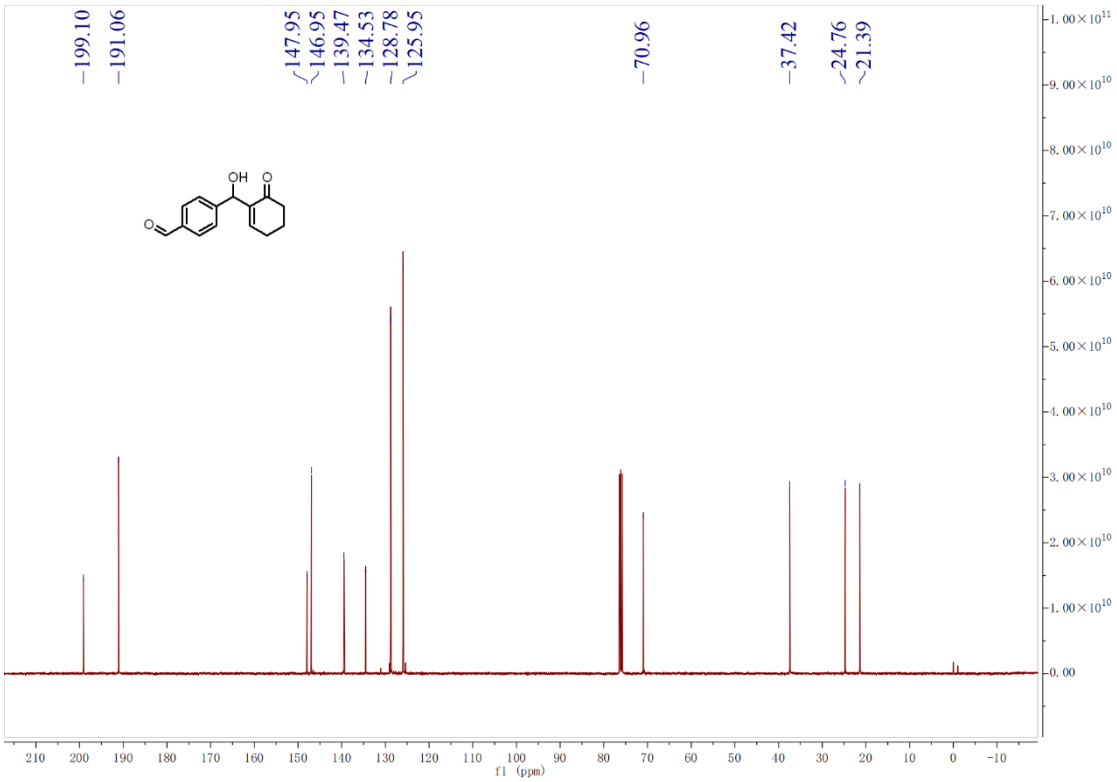
(**3n**) 2-(Hydroxyphenylmethyl)-2-cyclohexen-1-one



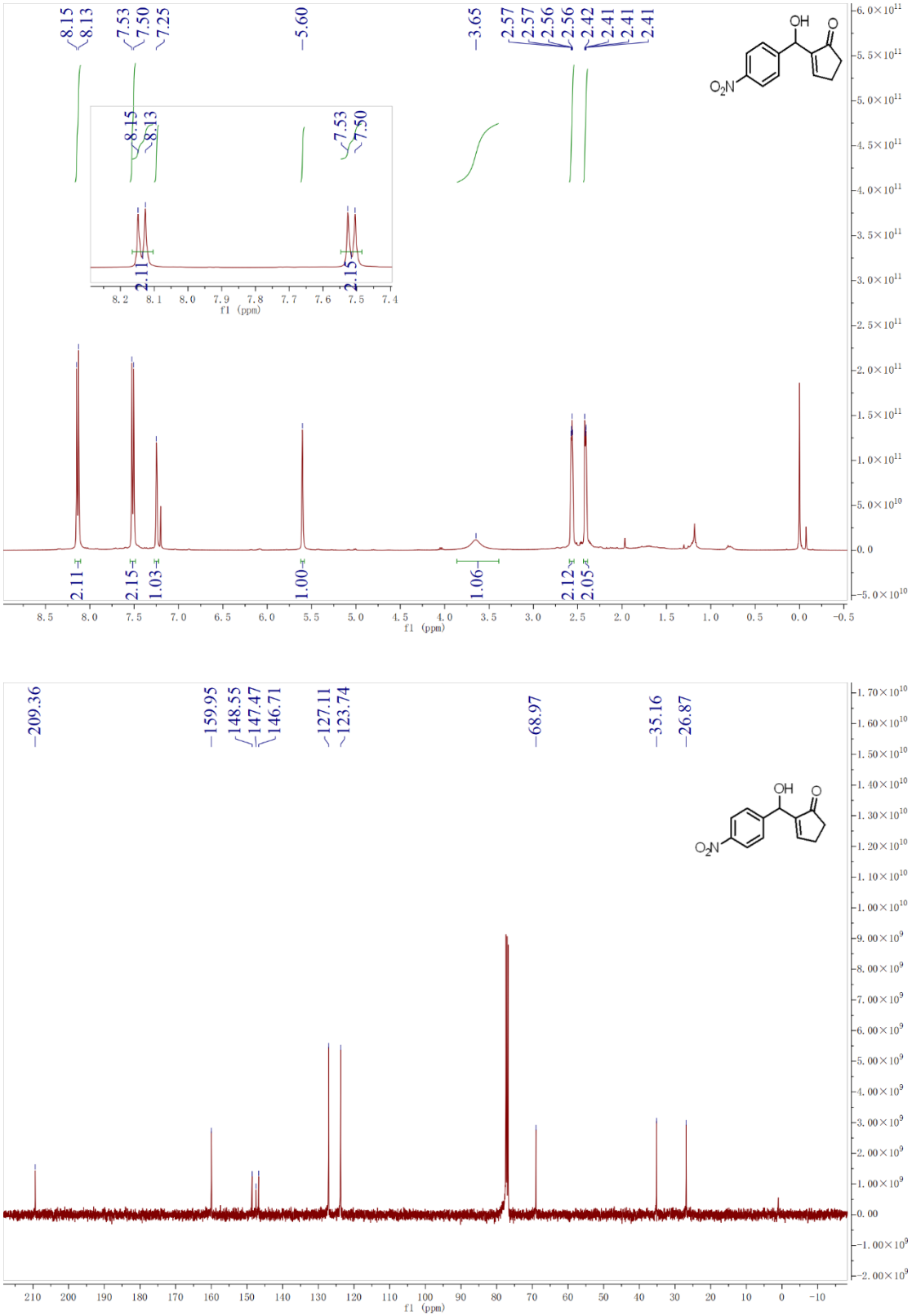


(**3o**) 4-[Hydroxy(6-oxo-1-cyclohexen-1-yl)methyl]benzaldehyde

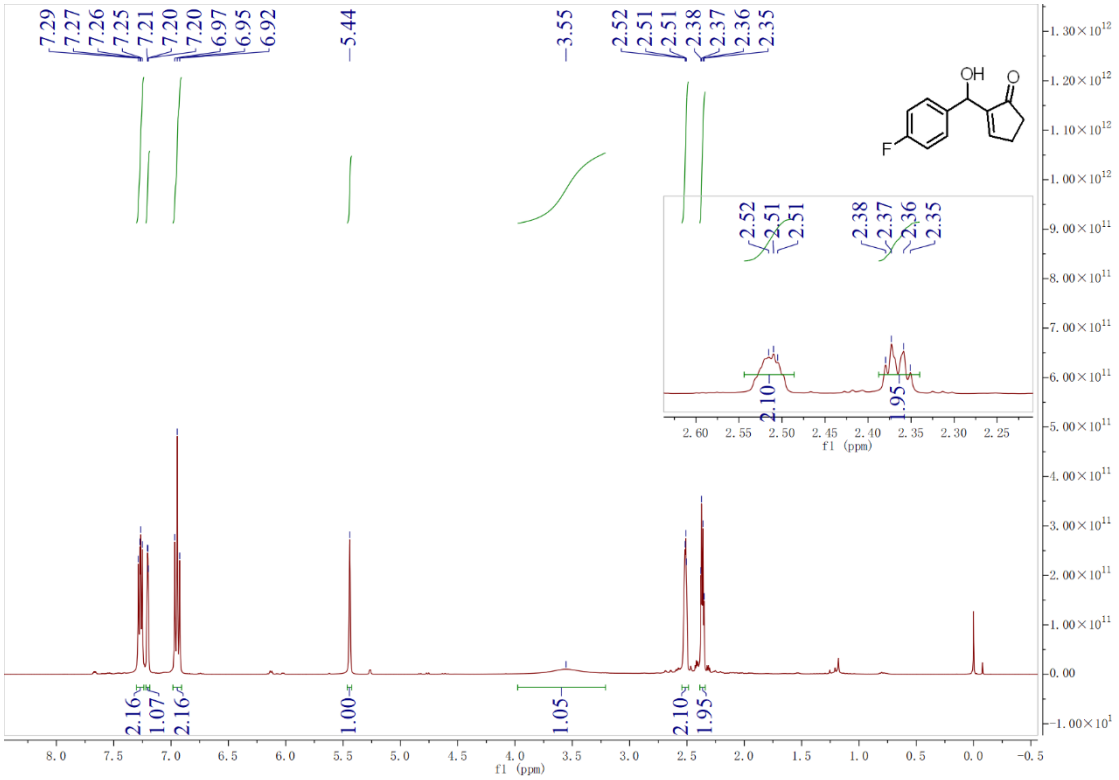


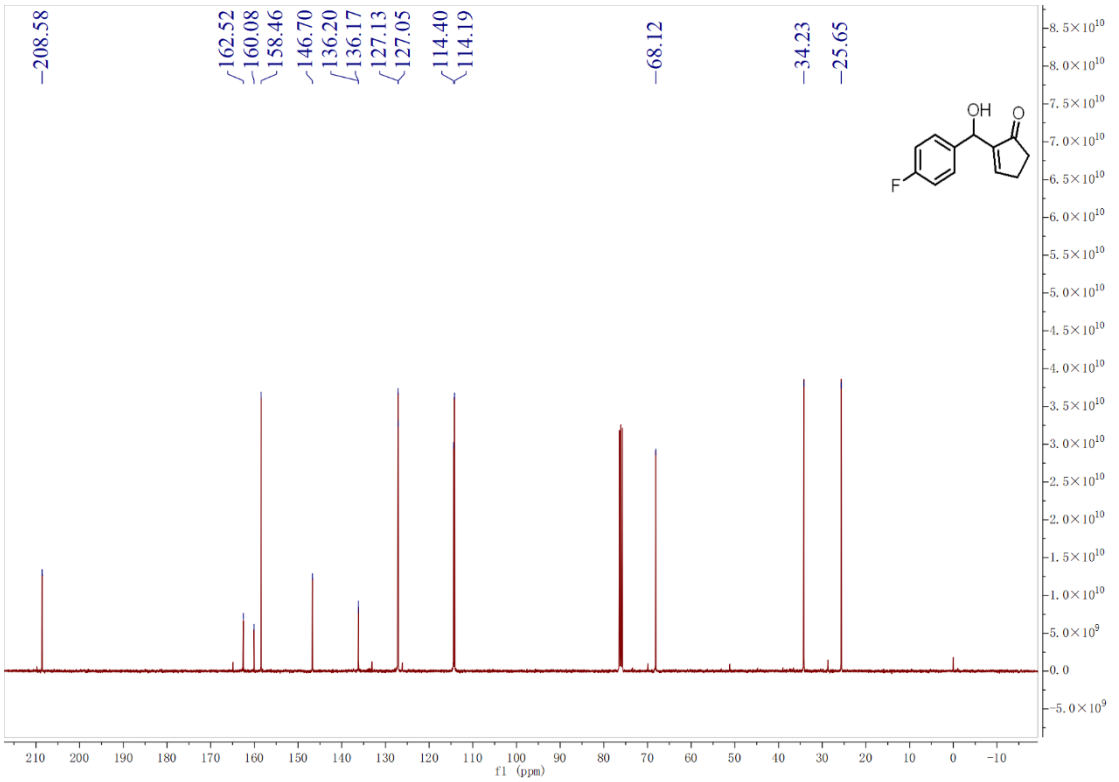


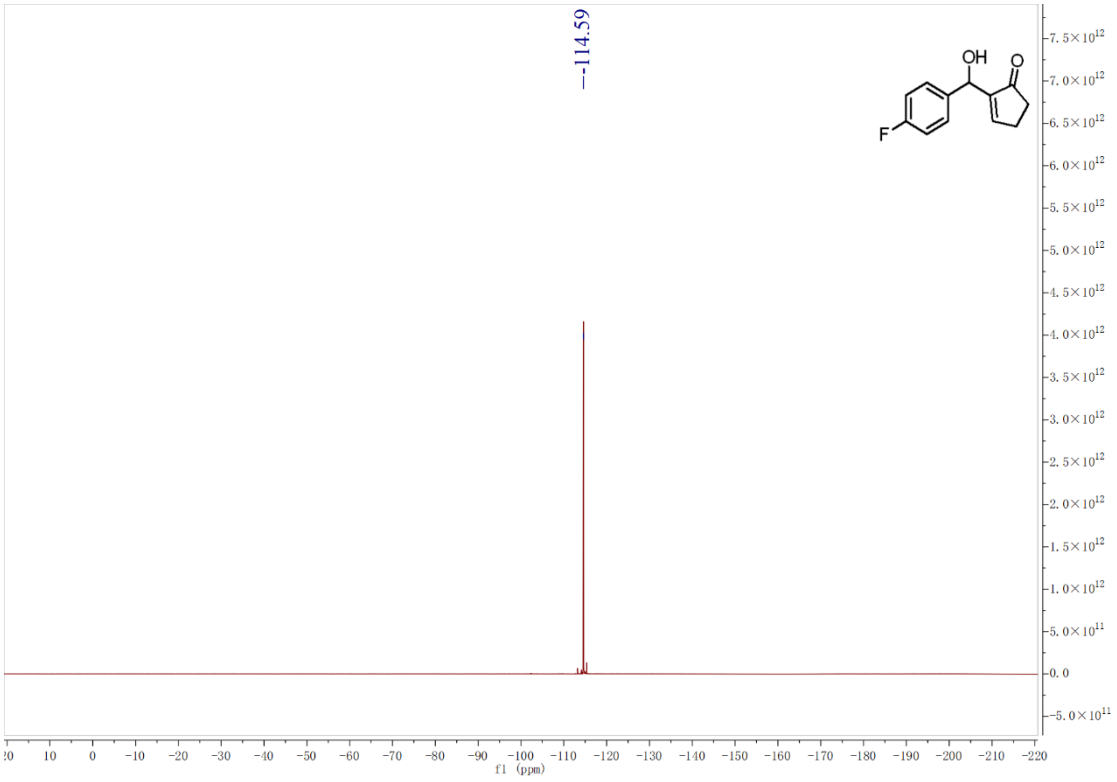
(**5a**) 2-[Hydroxy(4-nitrophenyl)methyl]-2-cyclopenten-1-one



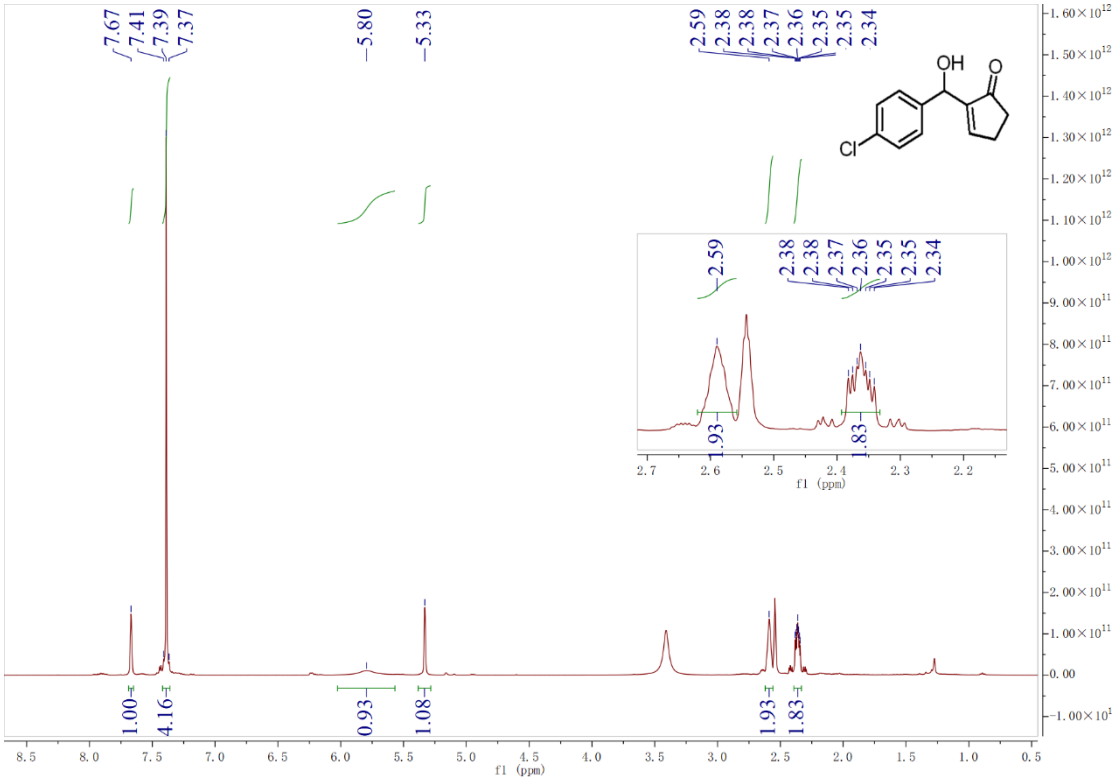
(**5b**) 2-[(4-Fluorophenyl)hydroxymethyl]-2-cyclopenten-1-one

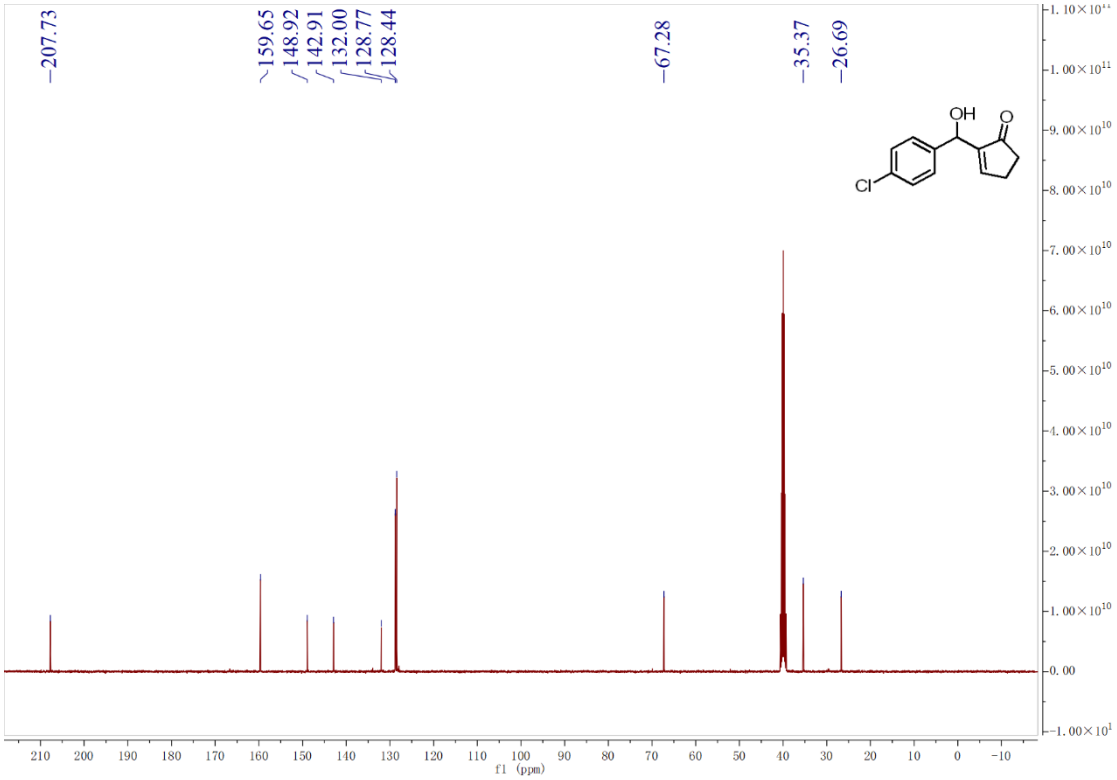

7.29
7.27
7.26
7.25
7.21
7.20
7.20
6.97
6.95
6.92
5.44
3.55
2.52
2.51
2.51
2.38
2.37
2.36
2.35
OH
O
F
2.16
1.07
2.16
1.00
1.05
2.10
1.95
f1 (ppm)


208.58
162.52
160.08
158.46
146.70
136.20
136.17
127.13
127.05
114.40
114.19
68.12
34.23
25.65
OH
O
F
f1 (ppm)

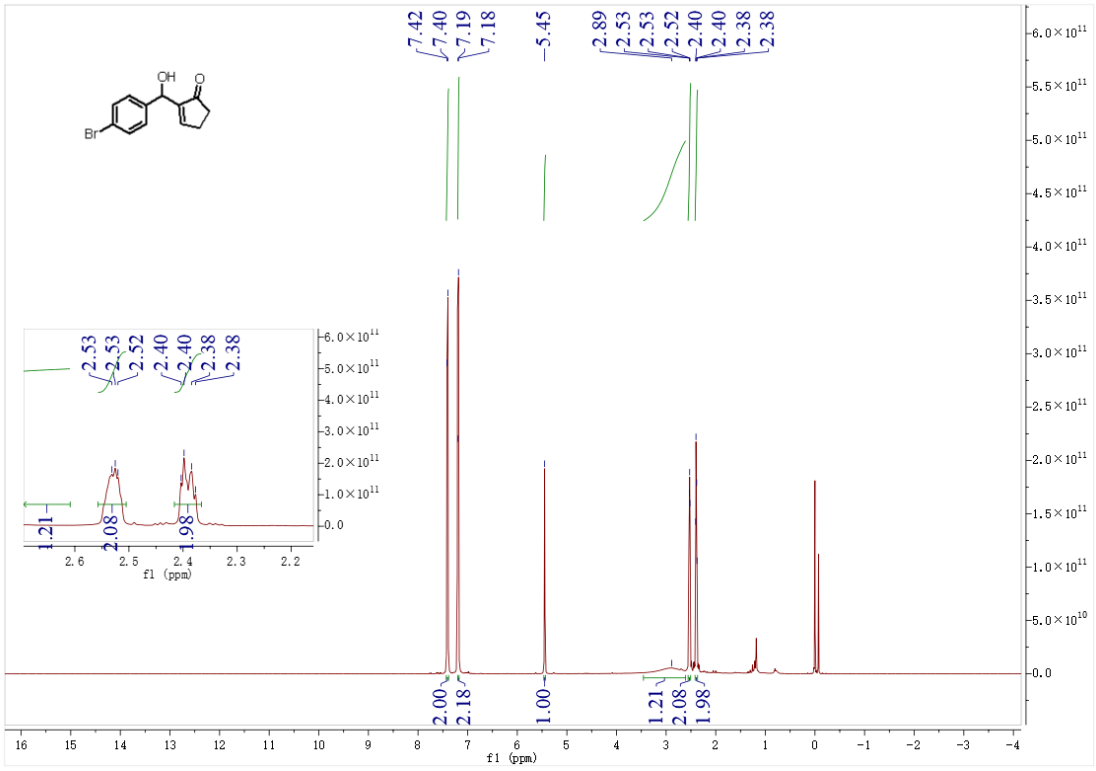


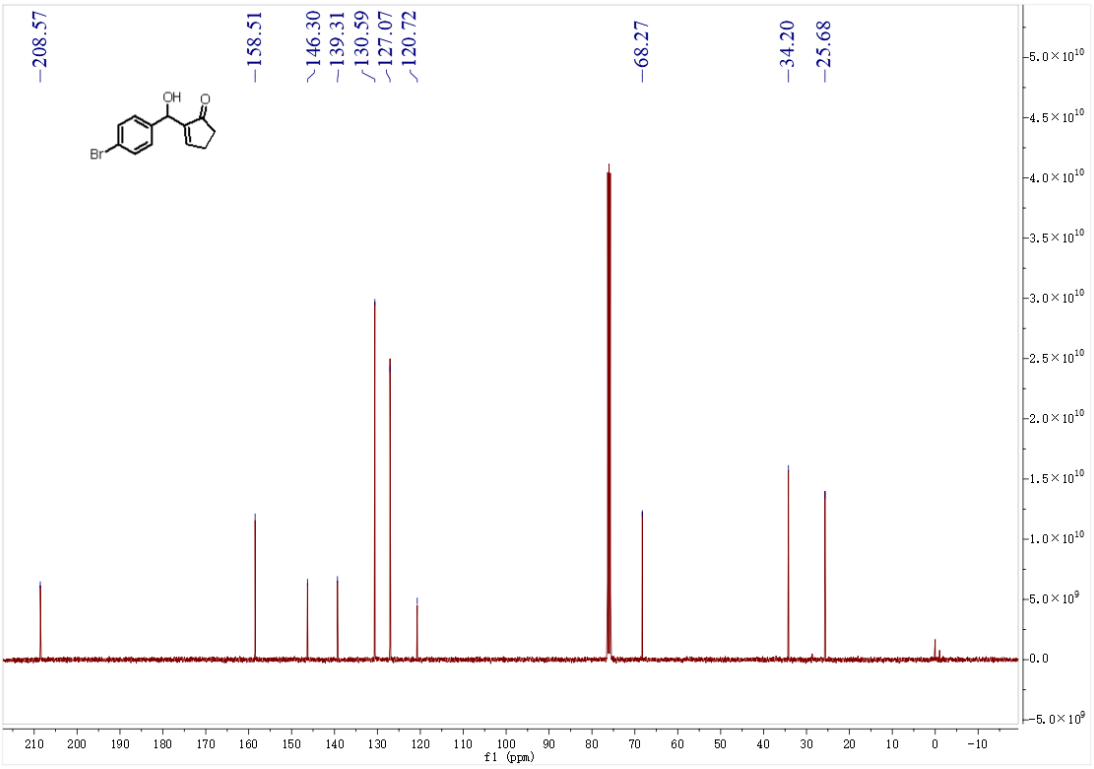
(**5c**) 2-[(4- Chlorophenyl)hydroxymethyl]-2-cyclopenten-1-one



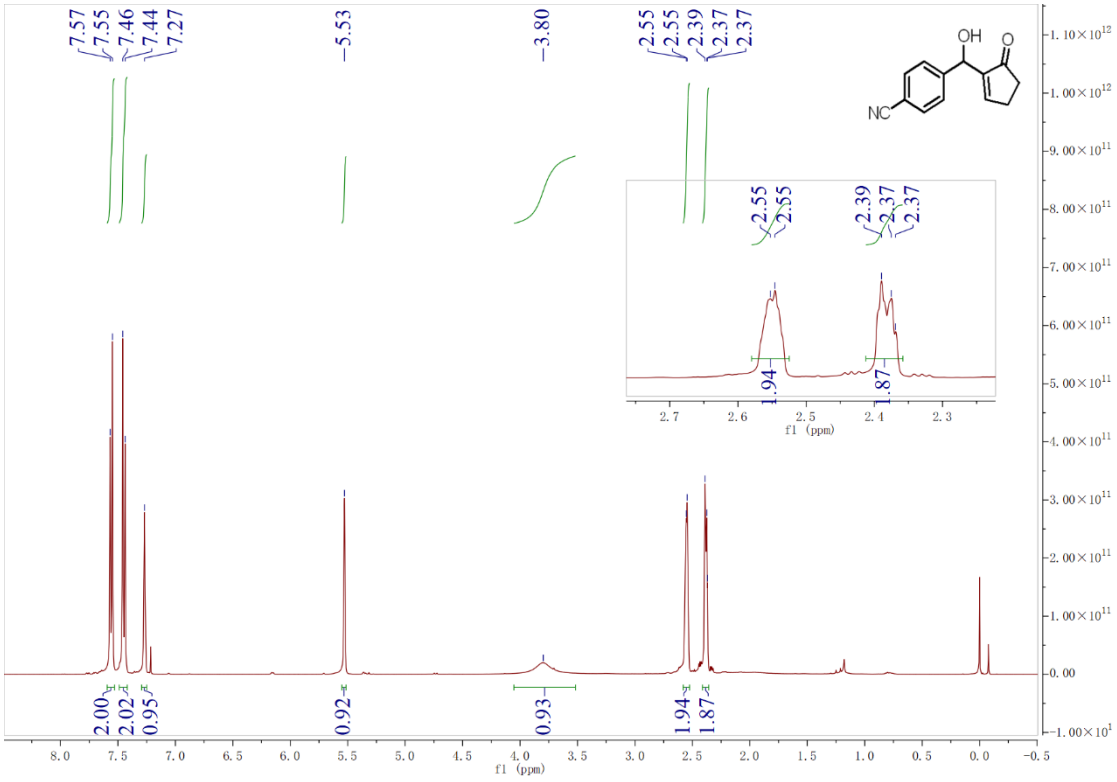


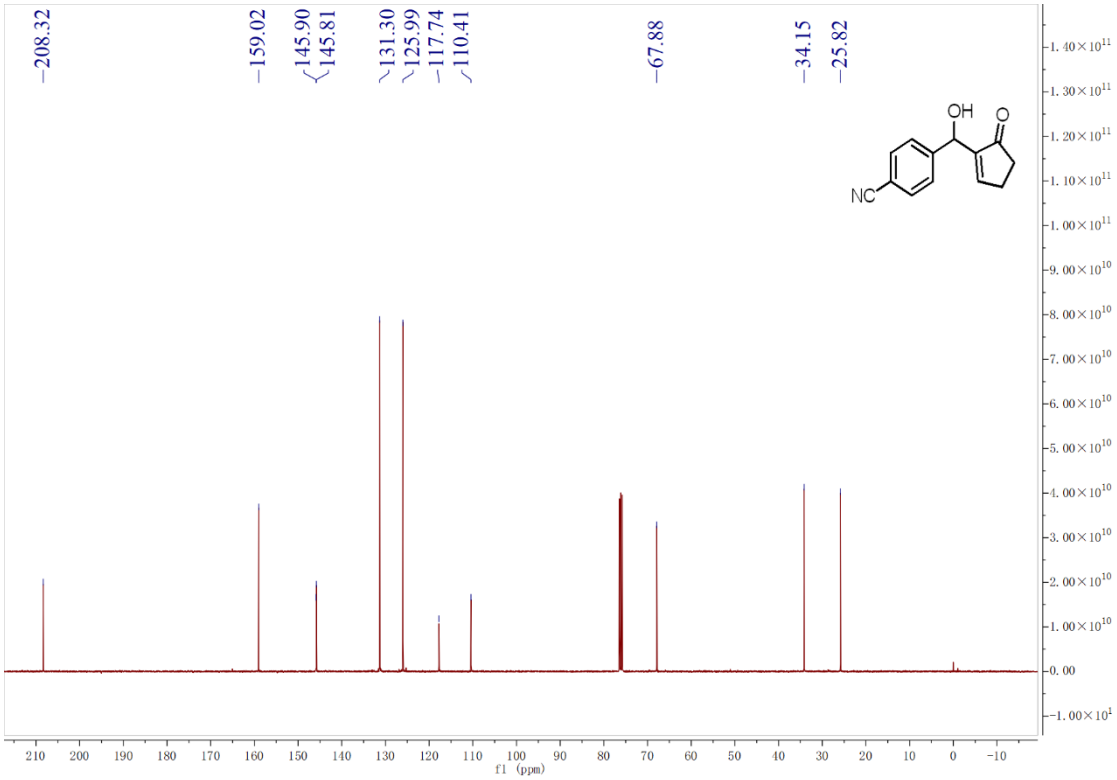
(**5d**) 2-[(4- Bromophenyl)hydroxymethyl]-2-cyclopenten-1-one





(5e) 4-[Hydroxy(5-oxo-1-cyclopenten-1-yl)methyl]benzonitrile





[9]. General Material Information for Continuous-flow Enzyme Reactor

Fig. S2 the diagram of continuous-flow Enzyme reactor