Photo-induced Tungsten-catalyzed Cascade Synthesis of Pyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate and its Reaction Mechanism

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Supporting Information

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General Information

All chemicals, unless otherwise noted, were purchased from commercial sources and used without further purification. All solvents for reactions and measurements were purified by standard methods. ^{1}H and proton-decoupled ^{13}C NMR spectra were recorded respectively on Brucker 400 M or 500 M spectrometers. ^{19}F NMR spectra were recorded respectively on Brucker 400 M spectrometers. ^{1}H NMR and ^{13}C NMR chemical shifts (δ) were determined relative to TMS at δ 0.0 ppm. Coupling constants (*J*) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All reactions were monitored by TLC or ^{1}H NMR analysis. Flash column chromatography was carried out using 300–400 mesh silica-gel at medium pressure.

High resolution mass spectra were recorded using a Q Exactive mass spectrometer (Thermo Fisher Scientific, USA. Gas chromatography-mass spectrometry (GC-MS) analyses were performed with an Agilent Technologies 7890A Network GC System equipped with an Agilent Technologies 5975C Network Mass Selective Detector (MSD).

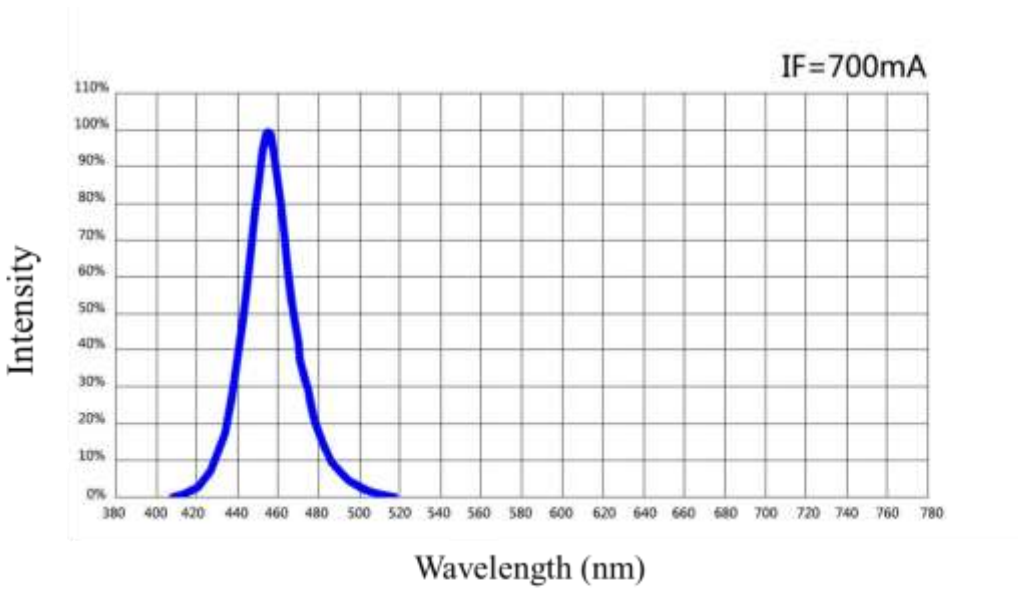
Unless stated otherwise, visible light irradiation was performed using 24 W 450 nm LEDs (3 W × 8) under O_2 atmosphere. All the reaction vessels used are the ordinary borosilicate glass test tubes. The illumination instruments were purchased from Hefei Hanhai Star Technology Co. Ltd. The photoreactor model is JH-3B14P45-T2A-M455, light 24 W (3 W × 8)). In all the reactions, the filters were not used.

All the substrates were purchased from Bide Pharmatech. Co., Ltd., Energy Chemical, Titan Chemical Co. Ltd or prepared according to previous literatures.[1]

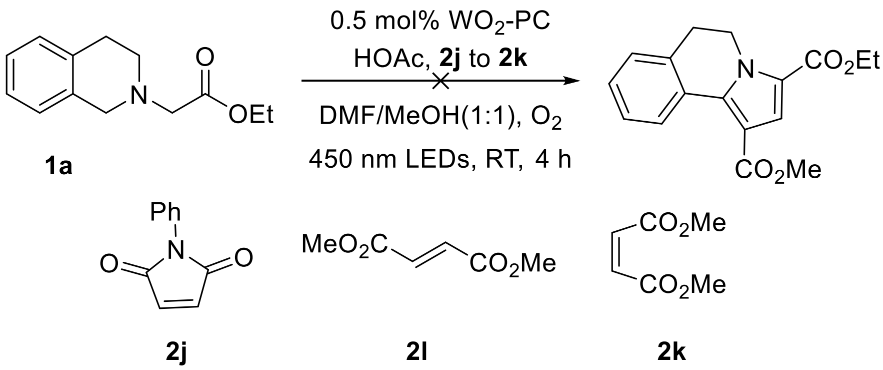
Figure S1. Reaction setup with cooling by running water.

Figure S2. the distance from the light source to the irradiation vessel. The distance is about 3 mm from light source

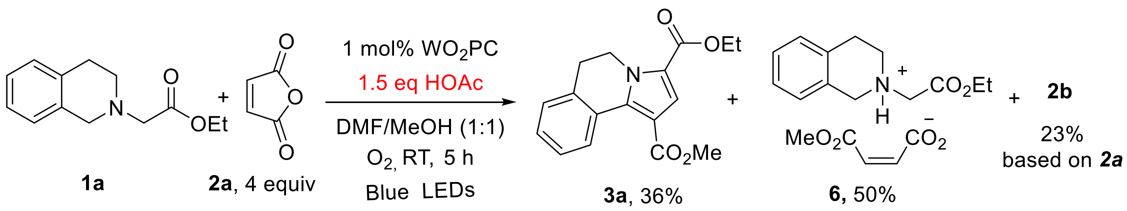
Firgue S3. Wavelength of peak intensity and broadband source



Scheme S1: Unsuccessful results.

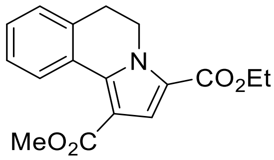


Mechanistic experiments



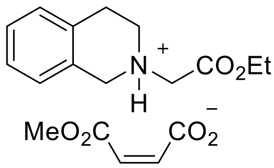
In a 20 mL reaction tube with a magnetic stirring bar, dihydroisoquinoline derivative (219.0 mg, 1.0 mmol), maleic anhydride (392.2 mg, 4.0 mmol, 4 equiv) and WO_2PC (5.0 mg, 0.5 mol%) were dissolved in DMF/MeOH (v/v; 5 mL/5 mL). The test tube was screwed with a stopper. The mixture was purged with oxygen for fifteen minutes. Then the mixture was irradiated at room temperature with 450 nm LEDs for 5 h. Water (10 mL) was added, then the mixture was extracted with EtOAc (15 mL) three times. The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash column chromatography (PE:EA = 10:1 to 1:1) to give the product **3a** (108.1 mg, 36%), **6** (176.2 mg, 50%) and **2b** (120.4 mg, 23%).

3-Ethyl 1-methyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (3a)[2]



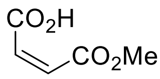
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 7.8 Hz, 1 H), 7.51 (s, 1 H), 7.36 (t, J = 7.5 Hz, 1 H), 7.32 (t, J = 7.4 Hz, 1 H), 7.26 (d, J = 7.3 Hz, 1 H), 4.62 (t, J = 6.6 Hz, 2 H), 4.34 (q, J = 7.1 Hz, 2 H), 3.88 (s, 3 H), 3.04 (t, J = 6.6 Hz, 2 H), 1.40 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 160.9, 137.9, 134.1, 128.9, 128.5, 127.3, 127.1, 127.0, 121.3, 121.2, 111.9, 60.4, 51.5, 42.3, 29.5, 14.4 ppm. HRMS (ESI) Calcd for $[C_{17}H_{17}NO_4 + H]^+$: 300.1230, found: 300.1230.

Ion-pair intermediate 6

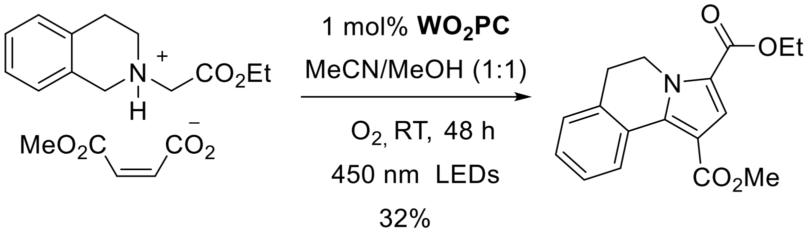


^{1}H NMR (500 MHz, $CDCl_3$) δ 10.32 (br, 1 H), 7.19 – 7.12 (m, 3 H), 7.04 (d, J = 6.7 Hz, 1 H), 6.35 (d, J = 12.2 Hz, 1 H), 6.11 (d, J = 12.2 Hz, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 4.08 (s, 2 H), 3.73 (s, 3 H), 3.66 (s, 2 H), 3.20 (t, J = 6.1 Hz, 2 H), 3.02 (t, J = 6.0 Hz, 2 H), 1.29 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.74, 168.06, 166.77, 135.24, 132.70, 131.85, 128.77, 126.86, 126.71, 126.21, 126.17, 61.20, 56.69, 53.69, 52.30, 49.66, 27.22, 14.17 ppm.

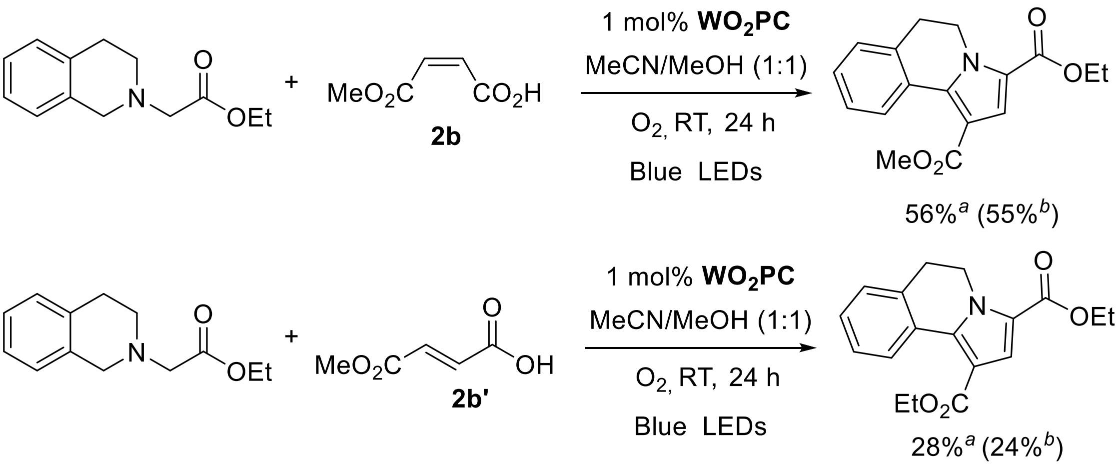
Monoester maleate 2b



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (br, 1 H), 6.34 (d, J = 12.2 Hz, 1 H), 6.15 (d, J = 12.2 Hz, 1 H), 3.75 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.96, 166.79, 134.50, 126.97, 52.43 ppm.



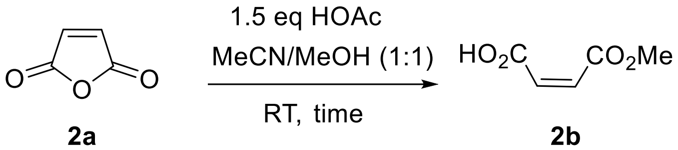
In a 10 mL reaction tube with a magnetic stirring bar, ion-pair intermediate (96.9 mg, 0 .28 mmol) and WO_2PC (1.4 mg, 0.5 mol%) were dissolved in MeCN/MeOH (v/v; 1 mL/1 mL). The test tube was screwed with a stopper. The mixture was purged with oxygen for fifteen minutes. Then the mixture was irradiated at room temperature with 450 nm LEDs for 48 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (PE:EA = 10:1) to give the product **3a** (26.5 mg, 32%).



[a]yields were determinded by ^1H NMR using dibromomethane as internal standard;
[b]isolated yield

In a 10 mL reaction tube with a magnetic stirring bar, dihydroisoquinoline derivative (65.8 mg, 0.30 mmol), *(Z)*-4-methoxy-4-oxobut-2-enoic acid (**2b**) or *(E)*-4-methoxy-4-oxobut-2-enoic acid (**2b'**) (156.1 mg, 1.2 mmol, 4 equiv) and WO_2PC (1.5 mg, 0.5 mol%) were dissolved in MeCN/MeOH (v/v; 1.5 mL/1.5 mL). The test tube was screwed with a stopper. The mixture was purged with oxygen for fifteen minutes. Then the mixture was irradiated at room temperature with 450 nm LEDs for 24 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (PE:EA = 10:1) to give the product **3a** in 55% or 24% yields.

Table S1: The formation of *(Z)*-4-methoxy-4-oxobut-2-enoic acid (**2b**)

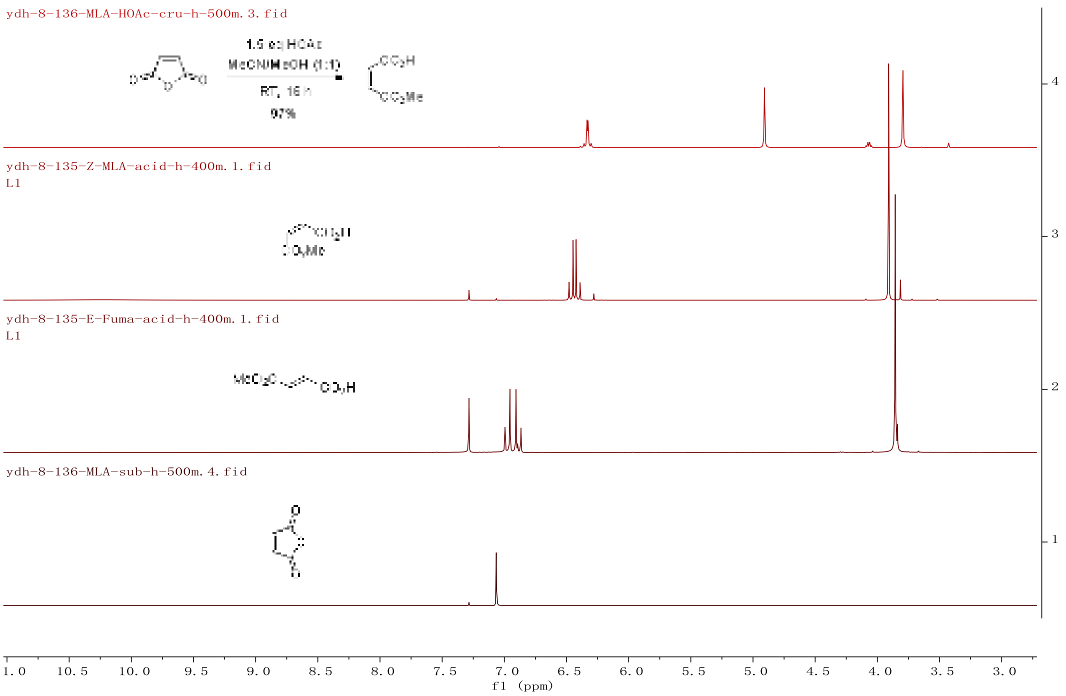


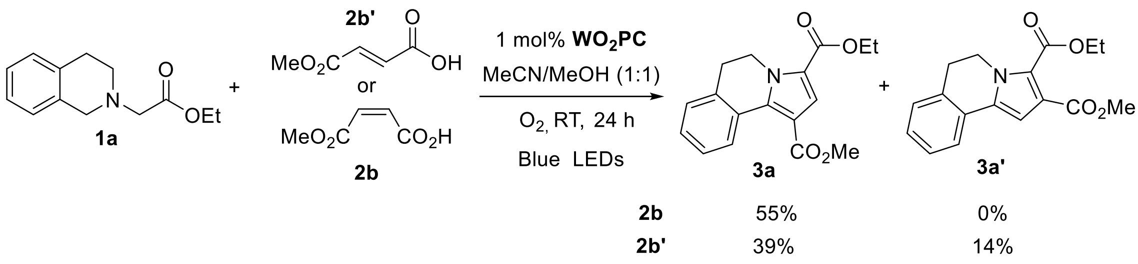
2a **2b**

Entry	Time	Substrate	Product
1	0.5 h	63%	36%
2	1 h	24%	76%
3	4 h	12%	88%
4	16 h	1%	97%[a]

[a]yields were determinded by ^{1}H NMR using CH_2Br_2 as internal standard.

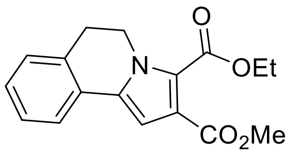
Figure S4. Reaction progress detected by ^{1}H NMR.



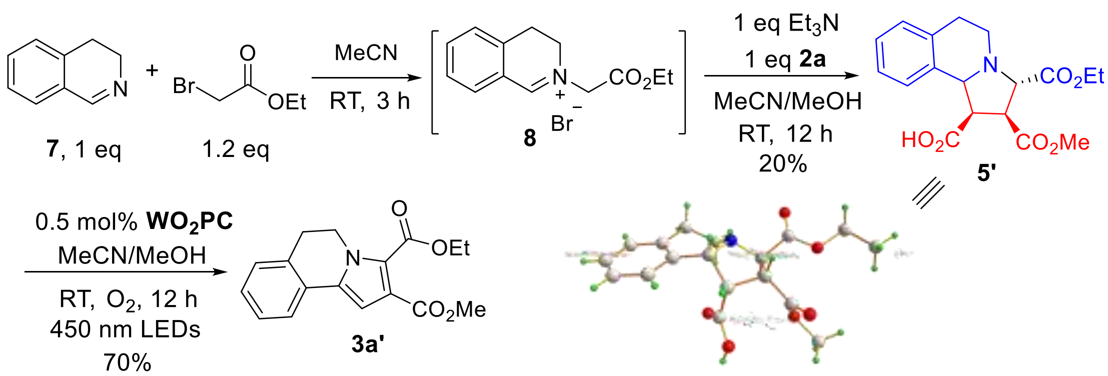


In a 10 mL reaction tube with a magnetic stirring bar, dihydroisoquinoline derivative (65.5 mg, 0.20 mmol), Monomethyl fumarate **2b′** or Monomethyl maleate **2b** (56.0 mg, 0.4 mmol, 2.0 equiv) and WO_2PC (1.0 mg, 0.5 mol%) were dissolved in DMF (3 mL). The test tube was screwed with a stopper. The mixture was purged with oxygen for fifteen minutes. Then the mixture was irradiated at room temperature with 450 nm LEDs for 24 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (PE:EA = 10:1) to give the product **3a** and **3a′.**

3-Ethyl 2-methyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-2,3-dicarboxylate (3a′)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.4 Hz, 1 H), 7.35 – 7.25 (m, 1 H), 7.25 (d, *J* = 4.1 Hz, 2 H), 4.48 (t, *J* = 6.6 Hz, 2 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 3.88 (s, 3 H), 3.10 (t, *J* = 6.7 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.44, 161.21, 133.39, 131.48, 127.92, 127.79, 127.43, 123.65, 121.34, 106.17, 61.11, 51.83, 42.67, 28.77, 14.15 ppm. HRMS (ESI) Calcd for $[C_{17}H_{17}NO_4 + H]^+$: 314.1387, found: 314.1393.

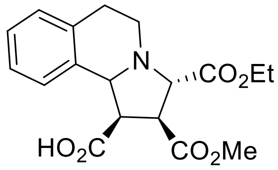


In a 10 mL reaction tube with a magnetic stirring bar, 3,4-dihydroisoquinoline **7** (51.8 mg, 0.39 mmol) and ethyl 2-bromoacetate (65.9 mg, 0.39 mmol) were dissolved in MeCN (2 mL).

The mixture was stirred at room temperature for 3 h. Maleic anhydride (38.7 mg, 0.39 mmol, 1 equiv), trimethylamine (40.0 mg, 0.39 mmol) and MeOH (2 mL) were added. The mixture was. The mixture was stirred at room temperature for 12 h. The mixture was extracted with DCM (15 mL) three times. The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash column chromatography (PE:EA = 1:1, DCM : MeOH = 10:1) to give the product **5′** (27.4 mg, 20%).

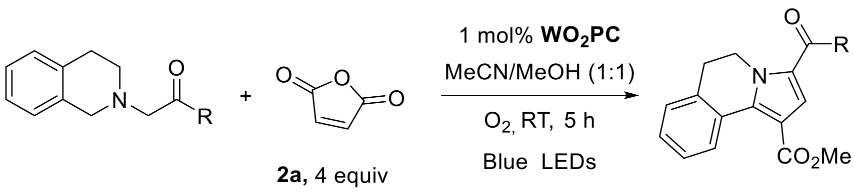
In a 10 mL reaction tube with a magnetic stirring bar, **5′** (12.4 mg, 0.035 mmol) and WO_2PC (0.5 mg, 0.5 mol%) were dissolved in MeCN/MeOH (0.5/0.5 mL). The reaction tube was screwed with a stopper. The mixture was purged with oxygen for fifteen minutes. Then the mixture was irradiated at room temperature with 450 nm LEDs for 12 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (PE:EA = 10:1) to give the product **3a′** (7.5 mg, 70%).

(1R,2S,3S)-3-(ethoxycarbonyl)-2-(methoxycarbonyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline-1-carboxylic acid (**5′**)



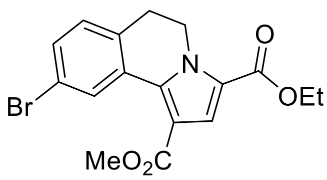
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.12 (m, 4 H), 4.68 (d, J = 4.5 Hz, 1 H), 4.52 (d, J = 5.6 Hz, 1 H), 4.28 (qd, J = 7.2, 4.5 Hz, 2 H), 3.89 – 3.82 (m, 2 H), 3.75 (s, 3 H), 3.45 – 3.28 (m, 1 H), 3.22 – 2.95 (m, 2 H), 2.93 – 2.72 (m, 1 H), 1.35 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.35, 170.19, 134.24, 132.29, 128.92, 127.34, 126.62, 126.33, 63.79, 62.67, 61.68, 52.82, 50.80, 49.23, 44.68, 28.96, 14.31 ppm. HRMS (ESI) Calcd for $[C_{18}H_{21}NO_6 + H]^+$: 348.1442, found: 348.1448.

General procedure for tungsten catalyzed decarboxylative aromatization with 3a as an example



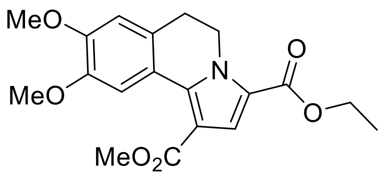
In a 10 mL reaction tube with a magnetic stirring bar, dihydroisoquinolines derivatives (0.30 mmol), maleic anhydride (1.20 mmol, 4 equiv) and WO_2PC (0.5 mol%) were dissolved in MeCN/MeOH (v/v; 2 mL/2 mL). The test tube was screwed with a stopper. The mixture was purged with oxygen for fifteen minutes. Then the mixture was irradiated at room temperature with 450 nm LEDs for 5 h. Water (10 mL) was added, then the mixture was extracted with EtOAc (15 mL) three times. The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash column chromatography (PE:EA = 20:1 to 10:1) to give the product..

3-Ethyl 1-methyl 9-bromo-5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (3b)



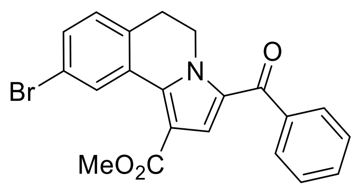
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1 H), 7.48 (s, 1 H), 7.40 (d, J = 8.0 Hz, 1 H), 7.11 (d, J = 8.0 Hz, 1 H), 4.59 (t, J = 6.6 Hz, 2 H), 4.31 (q, J = 7.1 Hz, 2 H), 3.87 (s, 3 H), 2.96 (t, J = 6.6 Hz, 2 H), 1.38 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.64, 160.80, 136.12, 132.75, 131.56, 131.24, 128.93, 128.80, 121.60, 121.40, 120.68, 112.56, 60.50, 51.62, 42.19, 29.01, 14.39 ppm. HRMS (ESI) Calcd for $[C_{17}H_{16}BrNO_4 + H]^+$: 378.0335 , found: 378.0338.

3-Ethyl 1-methyl 8,9-dimethoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate （3c）



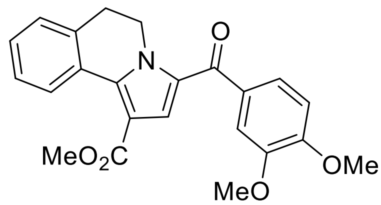
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 7.51 (s, 1 H), 6.75 (s, 1 H), 4.61 (t, J = 6.6 Hz, 2 H), 4.32 (q, J = 7.1 Hz, 2 H), 3.99 (s, 3 H), 3.94 (s, 3 H), 3.87 (s, 3 H), 2.98 (t, J = 6.7 Hz, 2 H), 1.39 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.09, 161.00, 149.37, 147.49, 138.29, 127.25, 121.65, 120.69, 119.84, 112.14, 110.93, 110.19, 60.30, 56.15, 55.95, 51.47, 42.45, 28.98, 14.41 ppm. HRMS (ESI) Calcd for $[C_{19}H_{21}NO_6 + H]^+$: 360.1442 , found: 360.1440.

Methyl 3-benzoyl-9-bromo-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate (3d)



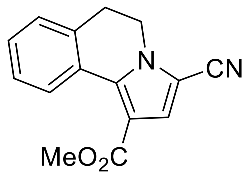
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.73 (d, *J* = 2.0 Hz, 1H), 7.88 – 7.86 (m, 2H), 7.63 (tt, *J* = 6.9, 1.2 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.49 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.29 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 4.69 (t, *J* = 6.6 Hz, 2H), 3.88 (s, 3H), 3.06 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.25, 163.50, 138.00, 136.47, 132.35, 131.16, 130.96, 130.53, 128.29, 128.03, 127.86, 127.57, 127.34, 124.93, 119.68, 111.73, 50.64, 41.68, 28.05 ppm. HRMS (ESI) Calcd for $[C_{21}H_{16}BrNO_3 + H]^+$: 410.0386, found: 410.0388.

Methyl 3-(3,4-dimethoxybenzoyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate (3e)



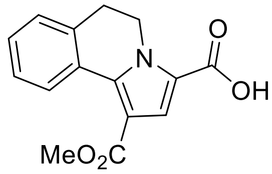
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.59 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.41 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.37 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 4.65 (t, *J* = 6.7 Hz, 2H), 4.02 (s, 3H), 4.00 (s, 3H), 3.88 (s, 3H), 3.11 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.96, 164.97, 152.73, 148.97, 138.94, 134.67, 131.87, 129.27, 128.97, 128.73, 127.44, 127.04, 126.87, 125.12, 124.13, 111.99, 111.74, 109.93, 56.14, 56.09, 51.52, 42.88, 29.61 ppm. HRMS (ESI) Calcd for $[C_{23}H_{21}NO_5 + H]^+$: 392.1492, found: 392.1494.

Methyl 3-cyano-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate (3f)



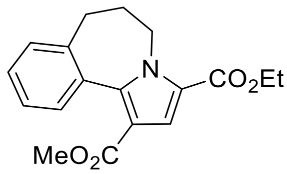
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.3 Hz, 1H), 7.35 (td, *J* = 7.3, 1.7 Hz, 2H), 7.32 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.30 – 7.29 (m, 2H), 4.30 (t, *J* = 6.8 Hz, 2H), 3.95 (s, 3H), 3.20 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.75, 134.90, 130.99, 128.70, 128.35, 127.85, 126.76, 124.47, 123.89, 112.19, 106.69, 105.90, 51.99, 43.23, 28.35. HRMS (ESI) Calcd for $[C_{15}H_{12}N_2O_2 + Na]^+$: 275.0791, found: 275.0795.

1-(Methoxycarbonyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylic acid (3g)



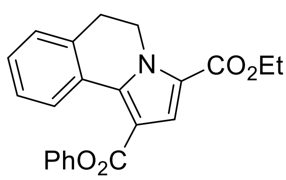
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (dd, J = 5.2, 3.2 Hz, 1H), 7.34 – 7.29 (m, 3H), 4.52 (t, J = 6.3 Hz, 2H), 3.76 (s, 3H), 3.00 (t, J = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.36, 166.81, 141.78, 139.59, 134.04, 133.05, 132.75, 131.80, 131.74, 127.14, 125.30, 116.26, 56.53, 47.22, 33.75 ppm. HRMS (ESI) Calcd for $[C_{15}H_{13}NO_4 + Na]^+$: 294.0737, found: 294.0741.

3-Ethyl 1-methyl 6,7-dihydro-5H-benzo[c]pyrrolo[1,2-a]azepine-1,3-dicarboxylate (3h)



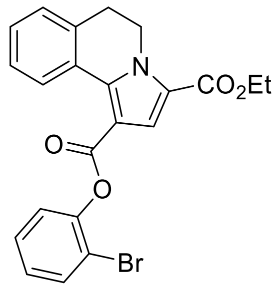
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71 – 7.67 (m, 1 H), 7.52 (s, 1 H), 7.40 – 7.36 (m, 2 H), 7.30 – 7.26 (m, 1 H), 5.24 (br, 1 H), 4.34 (q, J = 7.1 Hz, 2 H), 3.77 (br, 3 H), 3.42 (br, 1 H), 2.68 (br, 1 H), 2.50 (br, 2 H), 2.09 (br, 1 H), 1.41 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 164.36, 161.03, 143.47, 139.24, 131.63, 130.09, 129.55, 128.53, 126.01, 121.65, 119.78, 111.89, 60.32, 51.13, 43.24, 32.28, 30.33, 14.41 ppm. HRMS (ESI) Calcd for $[C_{18}H_{19}NO_4 + H]^+$: 314.1387, found: 314.1389.

3-Ethyl 1-phenyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (3i)



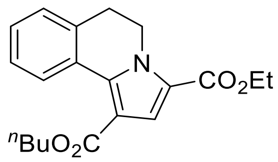
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.58 – 8.55 (m, 1 H), 7.76 (s, 1 H), 7.47 (d, J = 7.6 Hz, 1 H), 7.45 (d, J = 7.7 Hz), 7.33 (m, 2 H), 7.31 – 7.28 (m, 2 H), 7.27 – 7.22 (m, 2 H), 4.68 (t, J = 6.6 Hz, 2 H), 4.38 (q, J = 7.1 Hz, 2 H), 3.08 (t, J = 6.6 Hz, 2 H), 1.43 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 163.01, 160.91, 150.92, 139.07, 134.15, 129.46, 129.24, 128.81, 127.32, 127.08, 126.84, 125.67, 122.00, 121.83, 121.45, 111.04, 60.55, 42.46, 29.47, 14.44 ppm. HRMS (ESI) Calcd for $[C_{22}H_{19}NO_4 + H]^+$: 362.1387 , found: 362.1387.

1-(2-Bromophenyl) 3-ethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (3j)



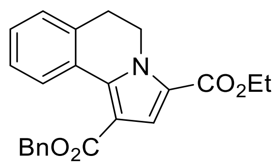
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.55 (m, 1 H), 7.82 (s, 1 H), 7.68 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.40 (td, *J* = 7.7, 1.5 Hz, 1 H), 7.33 (d, *J* = 3.4 Hz, 11 H), 7.32 (d, *J* = 3.5 Hz, 1 H）7.30 – 7.27 (m, 2 H), 7.18 (td, *J* = 7.8, 1.5 Hz, 1 H), 4.69 (t, *J* = 6.6 Hz, 2 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 3.08 (t, *J* = 6.7 Hz, 2 H), 1.43 (t, *J* = 7.1 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.96, 160.88, 148.51, 139.41, 134.12, 133.35, 129.32, 128.74, 128.48, 127.31, 127.19, 127.13, 126.75, 124.24, 121.94, 121.59, 116.82, 110.30, 60.56, 42.50, 29.42, 14.44 ppm. HRMS (ESI) Calcd for $[C_{22}H_{18}BrNO_4 + H]^+$: 440.0492, found: 440.0496.

1-Butyl 3-ethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (3k)



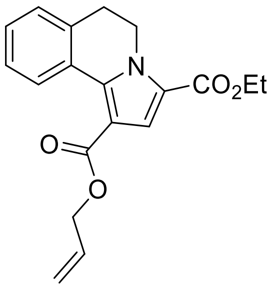
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.50 (s, 1 H), 7.36 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.31 (td, *J* = 7.4, 1.5 Hz, 1 H), 7.26 (d, *J* = 6.5 Hz, 1 H), 4.62 (t, *J* = 6.6 Hz, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 4.30 (t, *J* = 6.6 Hz, 2 H), 3.04 (t, *J* = 6.6 Hz, 2 H).1.79 – 1.74 (m, 2 H), 1.53 – 1.40 (m, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 1.00 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.65, 160.99, 137.77, 134.06, 128.87, 128.56, 127.27, 127.13, 126.92, 121.27, 121.08, 112.37, 64.19, 60.38, 42.36, 30.87, 29.50, 19.34, 14.44, 13.83 ppm. HRMS (ESI) Calcd for $[C_{20}H_{23}NO_4 + H]^+$: 342.1700, found: 342.1702.

1**-Benzyl 3-ethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (3l)**



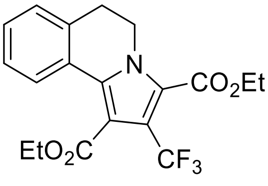
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 – 8.45 (m, 1 H), 7.55 (s, 1 H), 7.49 (d, *J* = 7.1 Hz, 2 H), 7.42 (t, *J* = 7.3 Hz, 2 H), 7.37 (d, *J* = 7.2 Hz, 1 H), 7.35 – 7.29 (m, 2 H), 7.29 – 7.23 (m, 1 H), 5.36 (s, 2 H), 4.63 (t, *J* = 6.5 Hz, 2 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 3.04 (t, *J* = 6.6 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.28, 160.95, 138.08, 136.44, 134.09, 128.95, 128.61, 128.56, 128.26, 128.10, 127.29, 127.04, 126.97, 121.40, 121.19, 111.89, 65.98, 60.41, 42.38, 29.48, 14.45 ppm. HRMS (ESI) Calcd for $[C_{23}H_{21}NO_4 + H]^+$: 376.1543, found: 376.1542.

1-Allyl 3-ethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (3m)



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.54 (s, 1 H), 7.36 (td, *J* = 7.6, 1.5 Hz, 1 H), 7.32 (td, *J* = 7.4, 1.4 Hz, 1 H), 7.27 (d, *J* = 7.2 Hz, 1 H), 6.11 – 6.03 (m, 1 H), 5.42 (dd, *J* = 17.2, 1.5 Hz, 1 H), 5.30 (dd, *J* = 10.4, 1.3 Hz, 1 H), 4.81 (dt, *J* = 5.7, 1.4 Hz, 1 H), 4.63 (t, *J* = 6.5 Hz, 2 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 3.04 (t, *J* = 6.6 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.12, 160.96, 138.03, 134.08, 132.63, 128.95, 128.56, 127.29, 127.05, 126.97, 121.36, 121.16, 118.01, 111.88, 64.94, 60.39, 42.36, 29.48, 14.43 ppm. HRMS (ESI) Calcd for $[C_{19}H_{19}NO_4 + H]^+$: 326.1387, found: 326.1386.

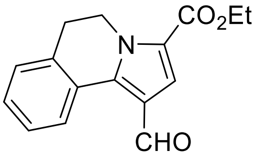
Diethyl 2-(trifluoromethyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (3n)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.65 (m, 1 H), 7.32 – 7.30 (m, 2 H), 7.27 (d, *J* = 5.0 Hz, 1 H), 4.53 (t, *J* = 6.6 Hz, 2 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 3.08 (t, *J* = 6.6 Hz, 2 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.47; ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.84, 160.15, 133.15, 131.61, 128.83, 127.91, 127.51, 126.28, 125.32, 122.36 (q, *J* = 268.7 Hz), 121.13 (q, *J* = 3.2 Hz), 117.51 (q, *J* = 36.8 Hz), 113.28

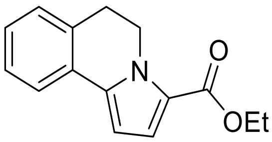
(q, J = 2.6 Hz), 61.97, 61.65, 42.77, 28.98, 13.87, 13.77 ppm. HRMS (ESI) Calcd for $[C_{19}H_{18}F_3NO_4 + H]^+$: 382.1261, found: 382.1263.

Ethyl 1-formyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (3o)



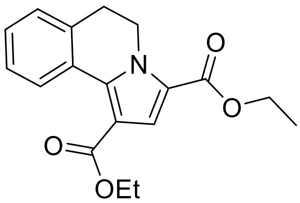
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1 H), 8.09 (d, J = 6.7, 1.9 Hz, 1 H), 7.54 (s, 1 H), 7.47 – 7.36 (m, 2 H), 7.34 (d, J = 6.5 Hz, 1 H), 4.67 (t, J = 6.6 Hz, 2 H), 4.36 (q, J = 7.1 Hz, 2 H), 3.10 (t, J = 6.6 Hz, 2 H), 1.41 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.53, 160.94, 139.07, 134.15, 129.56, 127.95, 127.81, 127.62, 126.84, 122.77, 121.66, 120.00, 60.61, 42.28, 29.11, 14.37 ppm. HRMS (ESI) Calcd for $[C_{16}H_{15}NO_3 + H]^+$: 270.1125, found: 270.1125.

Ethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (3p)[3]



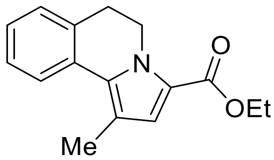
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 7.5 Hz, 1 H), 7.33 – 7.26 (m, 1 H), 7.26 – 7.20 (m, 2 H), 7.05 (d, J = 4.1 Hz, 1 H), 6.56 (d, J = 4.1 Hz, 1 H), 4.66 (t, J = 6.8 Hz, 2 H), 4.33 (q, J = 7.1 Hz, 2 H), 3.10 (t, J = 6.8 Hz, 2 H), 1.39 (t, J = 7.1 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.44, 136.07, 131.76, 128.42, 127.90, 127.41, 127.18, 123.65, 122.15, 118.25, 104.43, 59.86, 42.21, 28.97, 14.52 ppm. HRMS (ESI) Calcd for $[C_{15}H_{15}NO_2 + H]^+$: 242.1176, found: 242.1176.

Diethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (3q)[4]



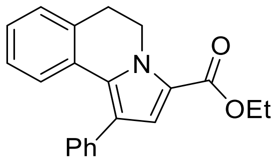
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, J = 7.7, 1.7 Hz, 1 H), 7.51 (s, 1 H), 7.36 (td, J = 7.7, 1.8 Hz, 1 H), 7.32 (td, J = 7.5, 1.7 Hz, 1 H), 7.26 (d, J = 7.1 Hz, 1 H), 4.62 (t, J = 6.6 Hz, 2 H), 4.35 (q, J = 7.1 Hz, 2 H), 4.34 (q, J = 7.1 Hz, 2 H), 3.04 (t, J = 6.6 Hz, 2 H), 1.42 (t, J = 7.1 Hz, 3 H), 1.40 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.57, 160.99, 137.76, 134.08, 128.88, 128.55, 127.29, 127.13, 126.91, 121.33, 121.08, 112.36, 60.37, 60.25, 42.35, 29.49, 14.44, 14.42 ppm. HRMS (ESI) Calcd for $[C_{18}H_{19}NO_4 + H]^+$: 314.1387, found: 314.1387.

Ethyl 1-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (3r)



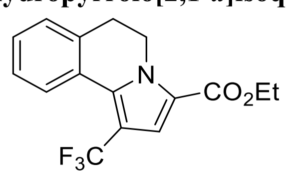
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 1 H), 7.33 (td, *J* = 7.5, 1.6 Hz, 1 H), 7.26 (m, 1 H), 7.12 (td, *J* = 7.3, 1.1 Hz, 1 H), 6.87 (s, 1 H), 4.62 (t, *J* = 6.6 Hz, 2 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 3.04 (t, *J* = 6.6 Hz, 2 H), 2.40 (s, 3 H), 1.38 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.38, 133.00, 131.99, 129.55, 127.90, 126.98, 126.65, 124.41, 119.89, 116.66, 59.77, 42.01, 29.82, 14.52, 14.00 ppm. HRMS (ESI) Calcd for $[C_{16}H_{17}F_3NO_2 + H]^+$: 256.1332, found: 256.1333.

Ethyl 1-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (3s)



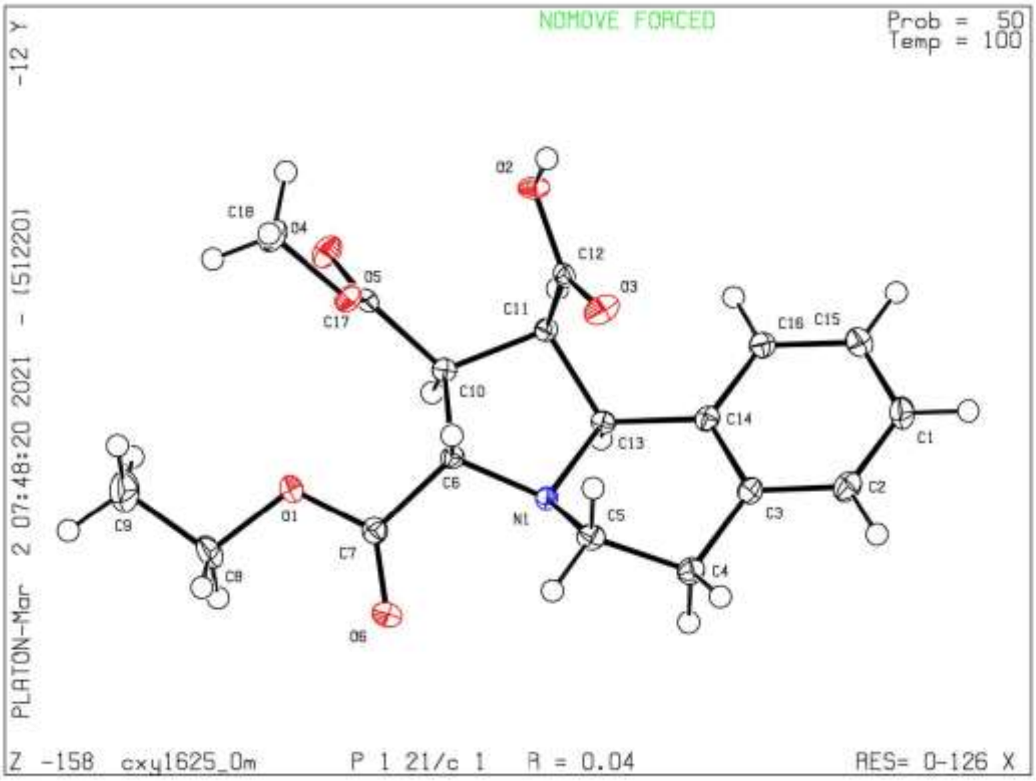
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.2, 1.3 Hz, 2 H), 7.40 (t, *J* = 7.3 Hz, 2 H), 7.36 – 7.30 (m, 2 H), 7.26 (d, *J* = 7.4 Hz, 1 H), 7.17 (td, *J* = 7.4, 1.1 Hz, 1 H), 7.05 (s, 1 H), 7.04 (t, J = 8.6 Hz, 1 H), 4.66 (t, *J* = 6.5 Hz, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 3.12 (t, *J* = 6.6 Hz, 2 H).1.40 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.40, 136.50, 133.26, 131.24, 129.08, 128.53, 128.49, 127.80, 127.23, 126.71, 126.58, 125.31, 122.94, 121.14, 119.34, 59.98, 42.39, 29.66, 14.51 ppm. HRMS (ESI) Calcd for $[C_{21}H_{19}NO_2 + H]^+$: 318.1489, found: 318.1489.

Ethyl 1-(trifluoromethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (4a)[1e]



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 7.1 Hz, 1 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 7.18 (d, *J* = 7.7 Hz, 1 H), 7.17 (s, 1 H), 4.56 (t, *J* = 6.6 Hz, 2 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 2.96 (t, *J* = 6.7 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -55.70; ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.70, 132.52, 132.32 (q, *J* = 3.5 Hz), 127.67, 126.78, 126.48, 125.45, 125.15 (q, J = 4.3 Hz), 122.73 (q, J = 267.1 Hz), 119.82, 116.03 (q, J = 4.4 Hz), 109.49 (q, J = 37.3 Hz), 59.40, 41.25, 28.19, 13.34 ppm.

X-ray of 5´ (CCDC Number: 2079259)

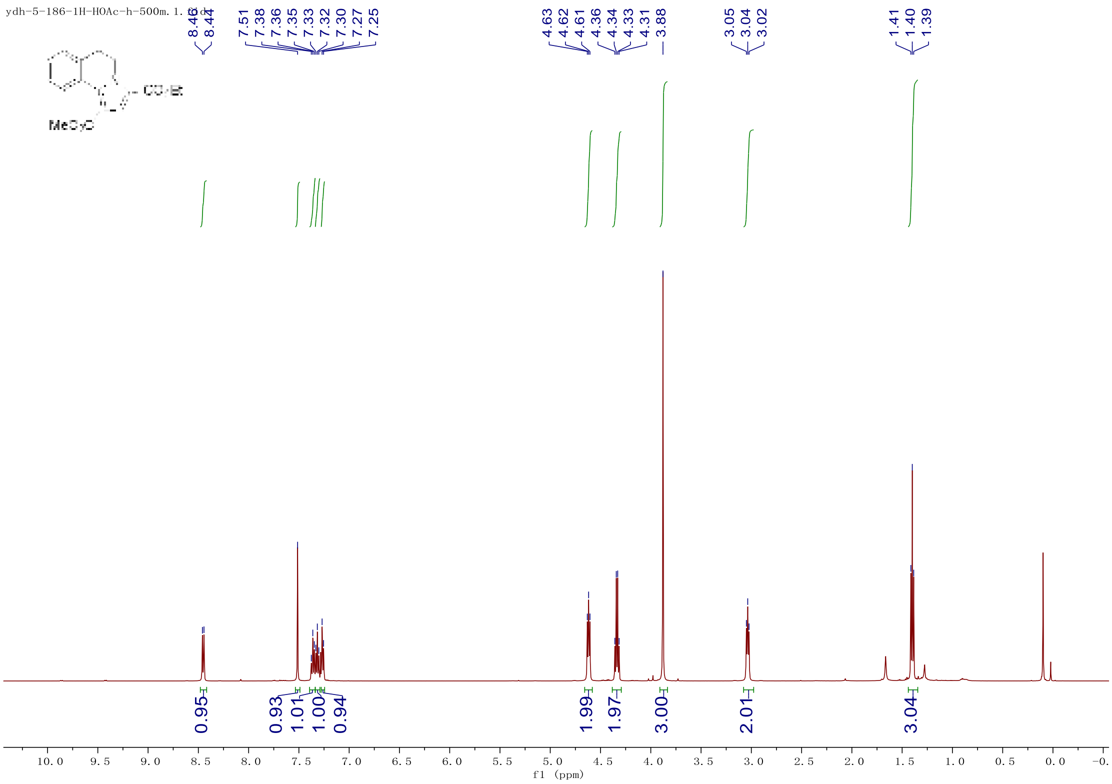


Reference:

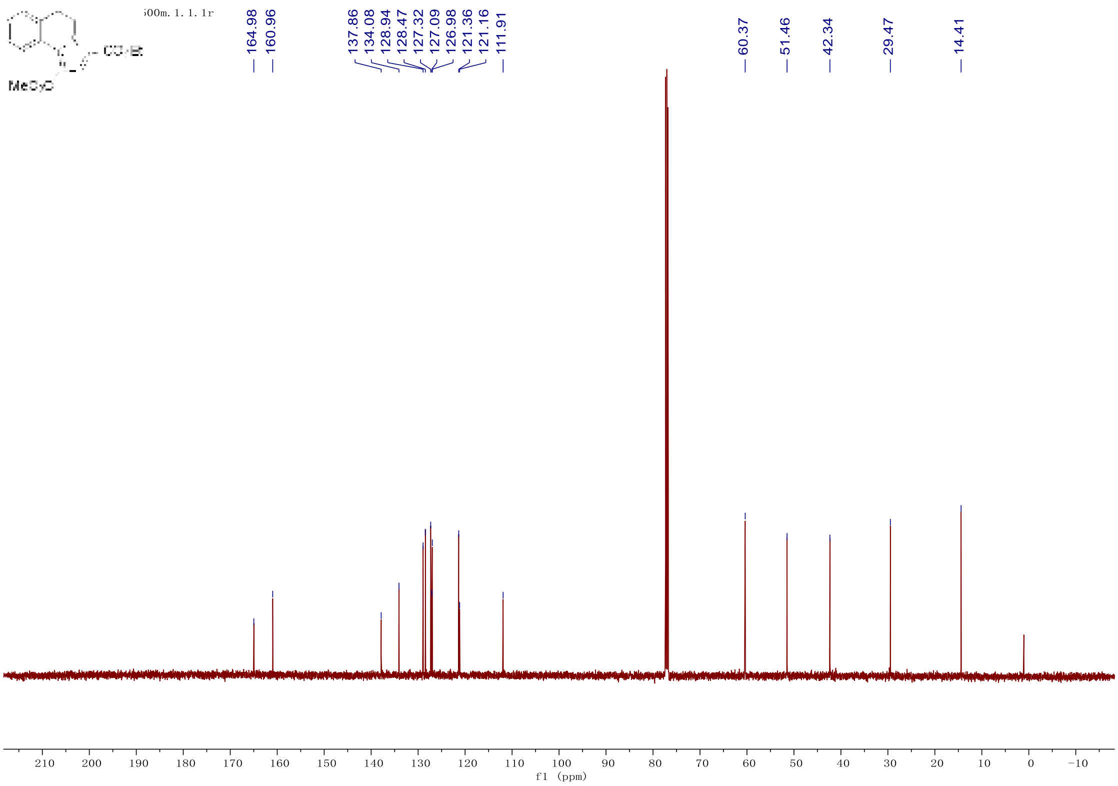
1. (a) M. Matziari, M. Nasopoulou and A. Yiotakis, *Org. Lett.* **2006, *8***, 2317; (b) J. Magalhães, N. Franko, G. Annunziato, M. Pieroni, R. Benoni, A. Nikitjuka, A. Mozzarelli, S. Bettati, A. Karawajczyk, , A. Jirgensons, B. Campanini and G. Costantino, *J. Enzyme Inhib. Med. Chem.* 2019, ***34***, 31; (c) J. C. de Mendonça Cavalcanti, M. O. Fonseca Goulart, E. Léonel and J.-Y. Nédélec, *Tetrahedron Lett.*, 2002, **43**, 6343; (d) H.-Y. Zhou, L.-Q. Fei, J.-L. Zhang, Y.-M. Pan and H.-T. Tang, *Adv. Synth. Catal.*, 2023, **365**, 1591; (e) Yu, D. Yu; Liu, Y. and C.-M. Che, Org. Chem. Front., 2022, **9**, 2779.
2. C. Yu, Y. Zhang, S. Zhang, H. Li and W. Wang, *Chem. Commun.* 2011, ***47***, 1036.
3. S. M. Allin, W. R. Bowman, M. R. J. Elsegood, V. McKee, R. Karim and S. S. Rahman, *Tetrahedron* **2005,** *61*, 2689.
4. A. Fujiya, M. Tanaka, E. Yamaguchi, N. Tada and A. Itoh, *J. Org. Chem.* 2016, ***81***, 7262.

NMR Spectra

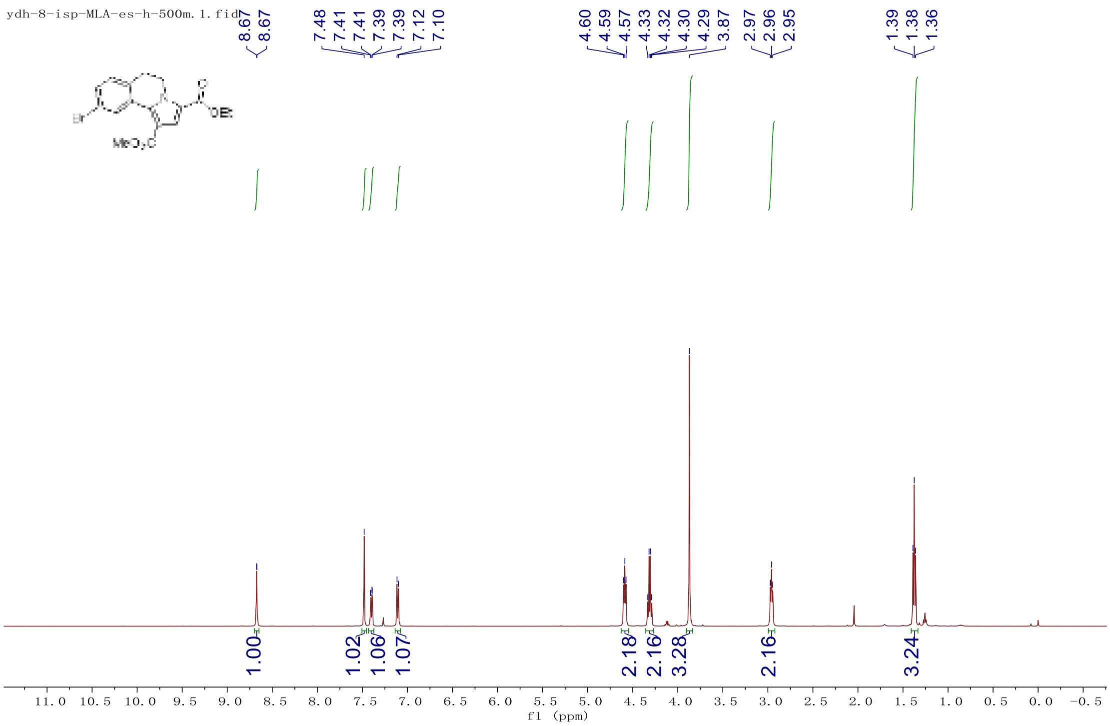
^{1}H NMR of 3a



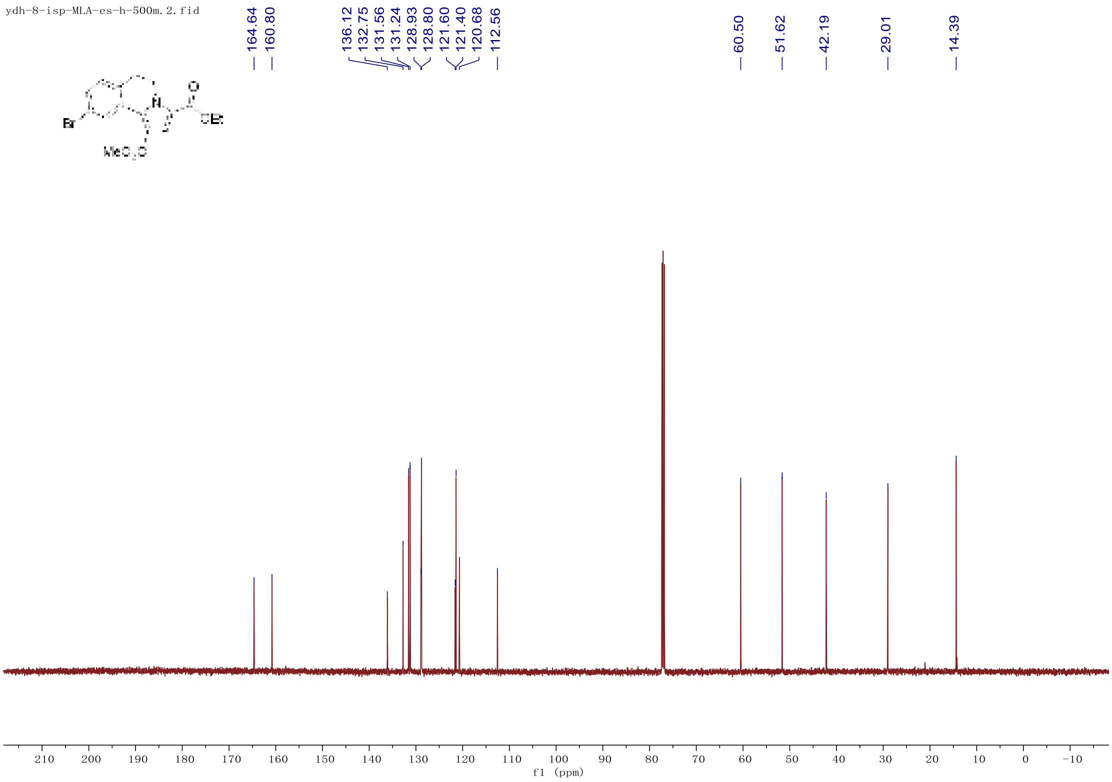
^{13}C NMR of 3a



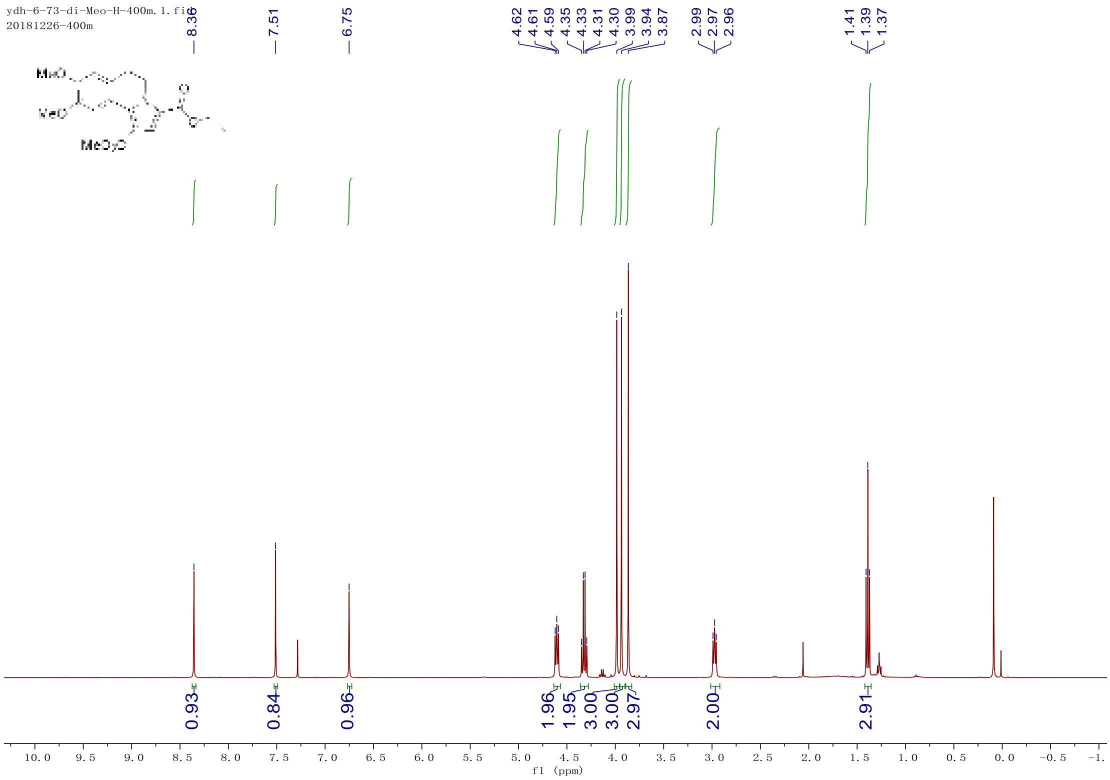
^{1}H NMR of 3b



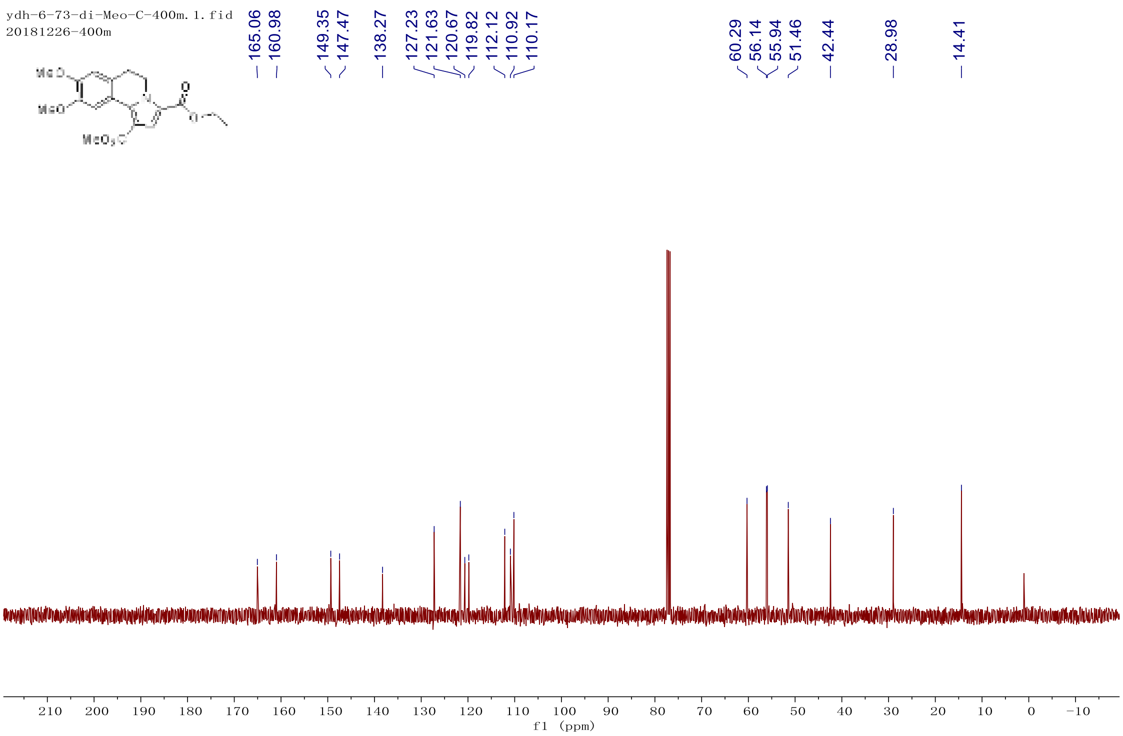
^{13}C NMR of 3b



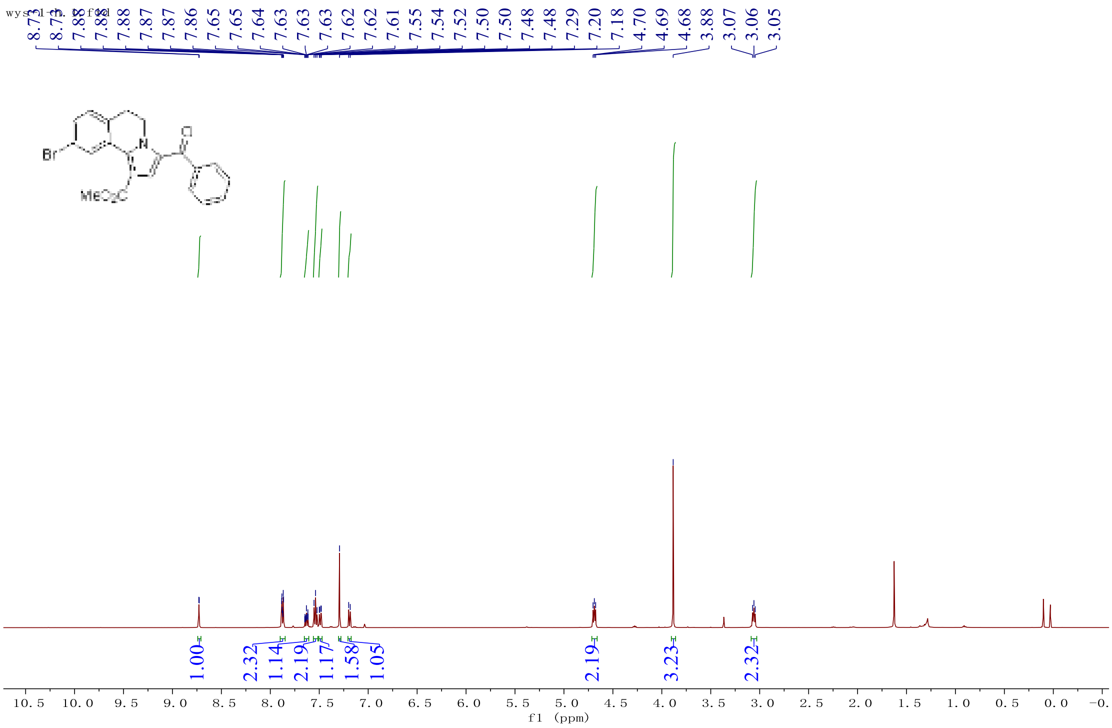
[1]H NMR of 3c



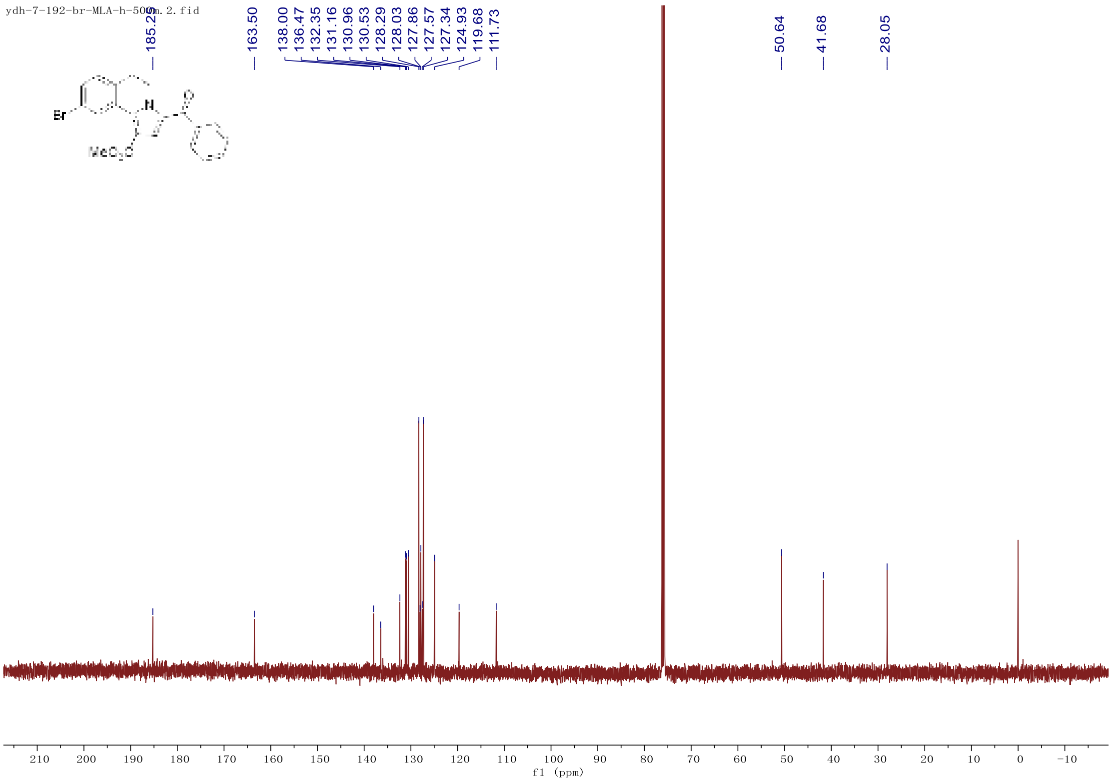
[13]C NMR of 3c



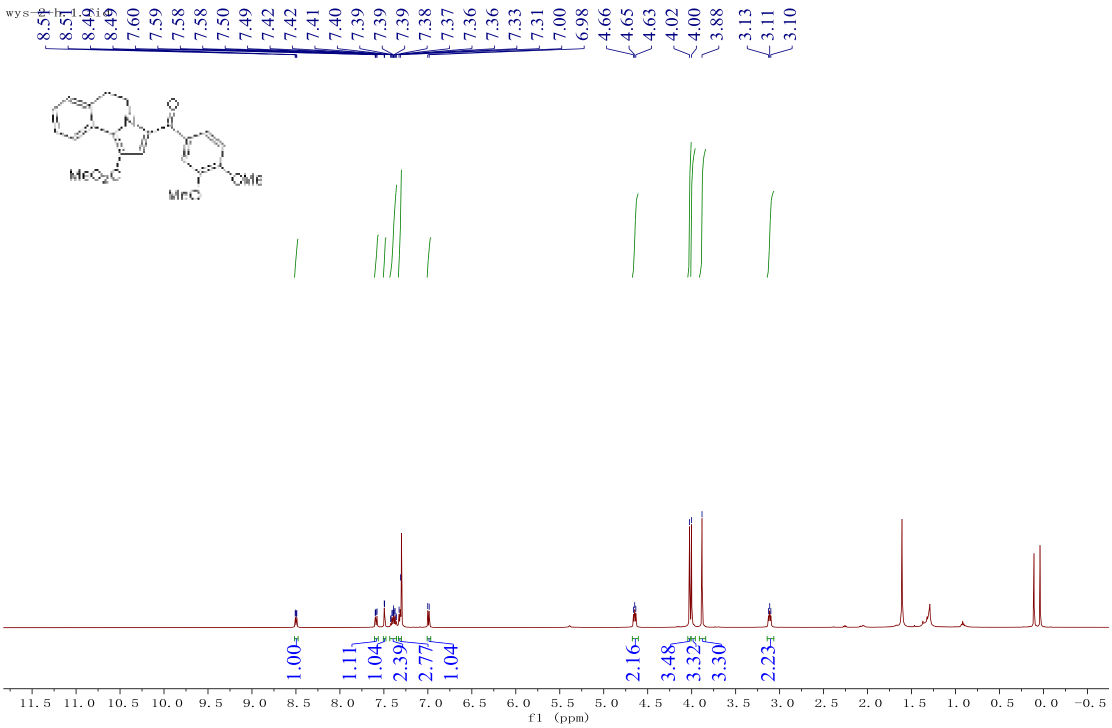
[1]H NMR of 3d



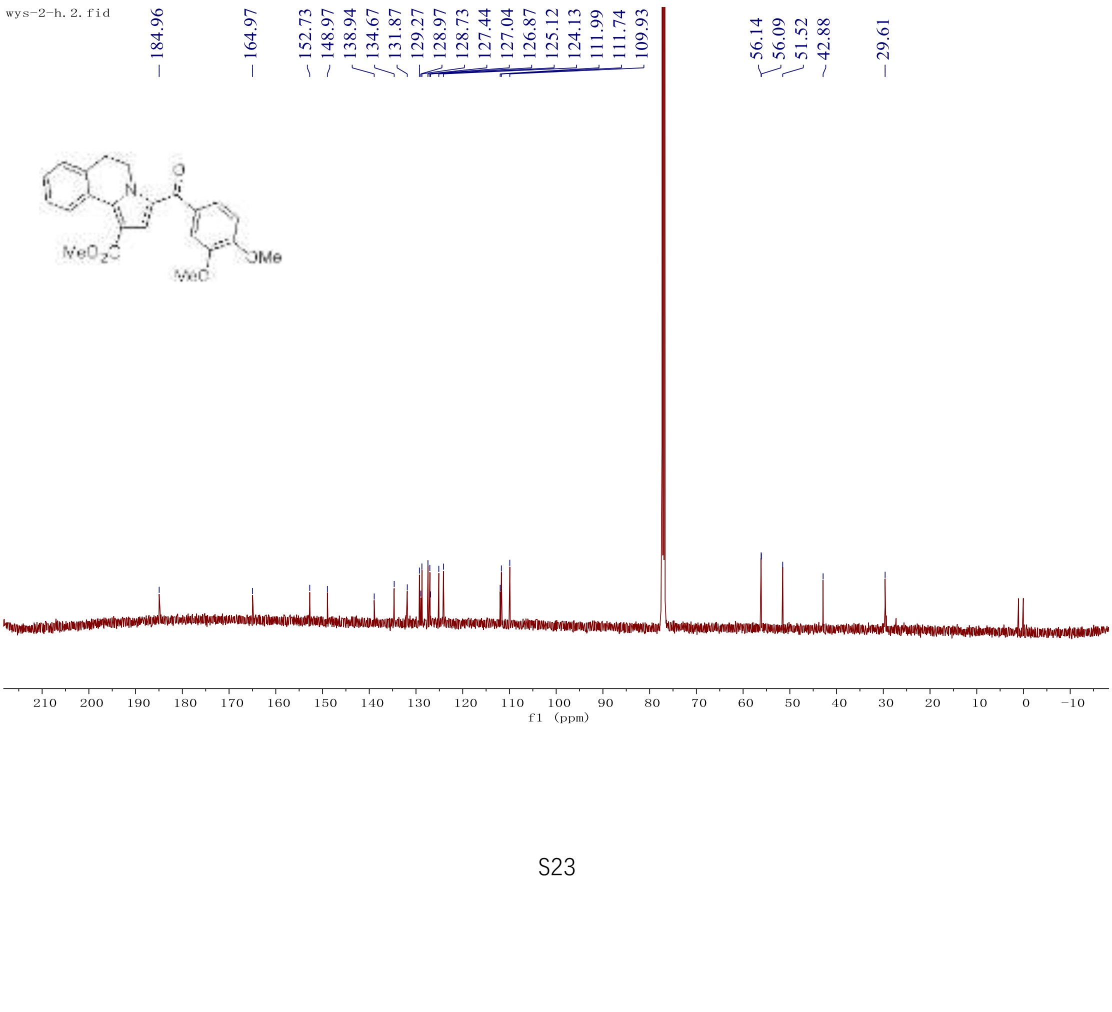
[13]C NMR of 3d



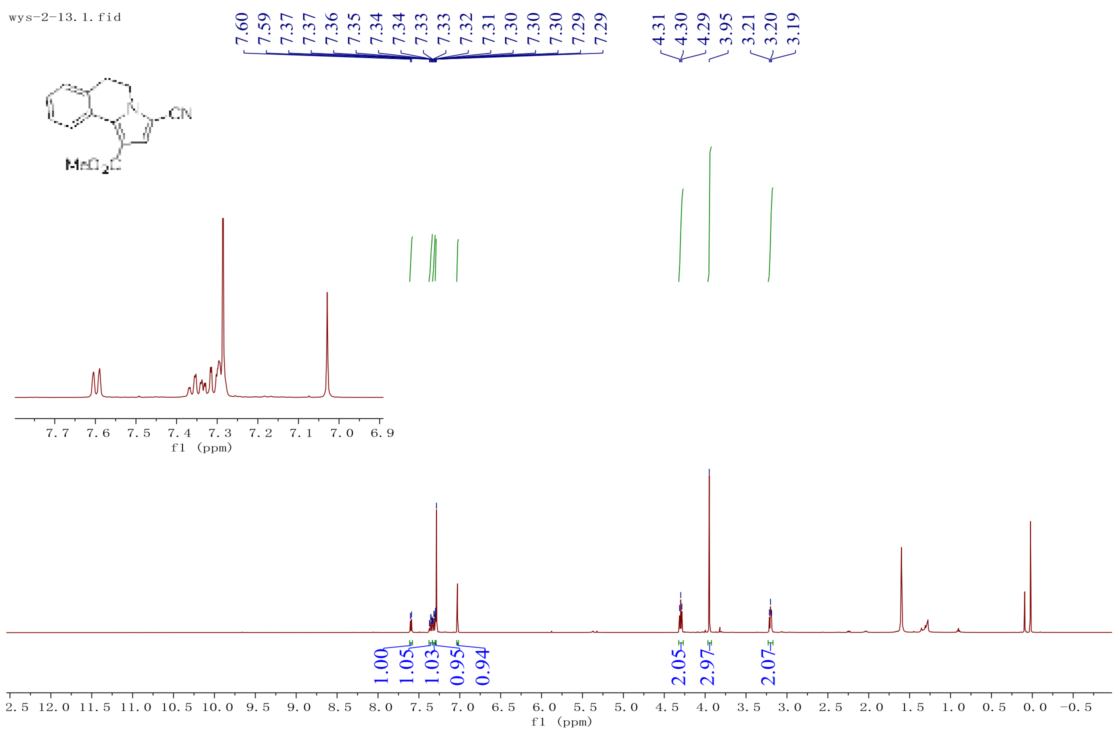
^{1}H NMR of 3e



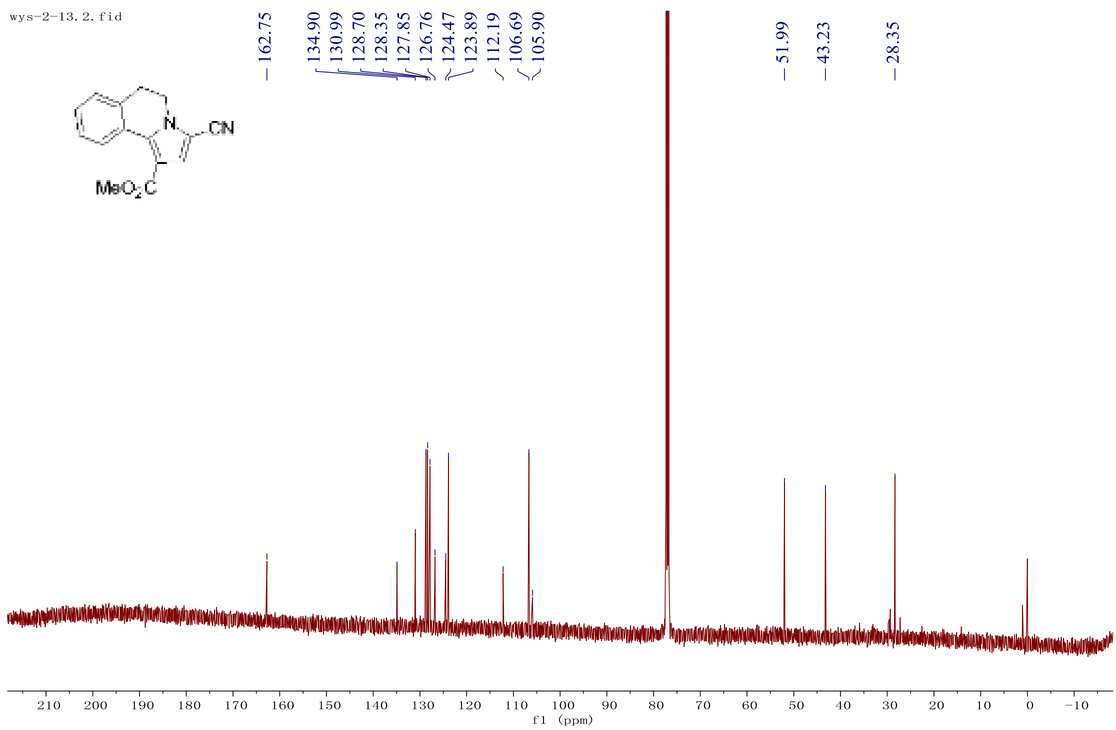
^{13}C NMR of 3e



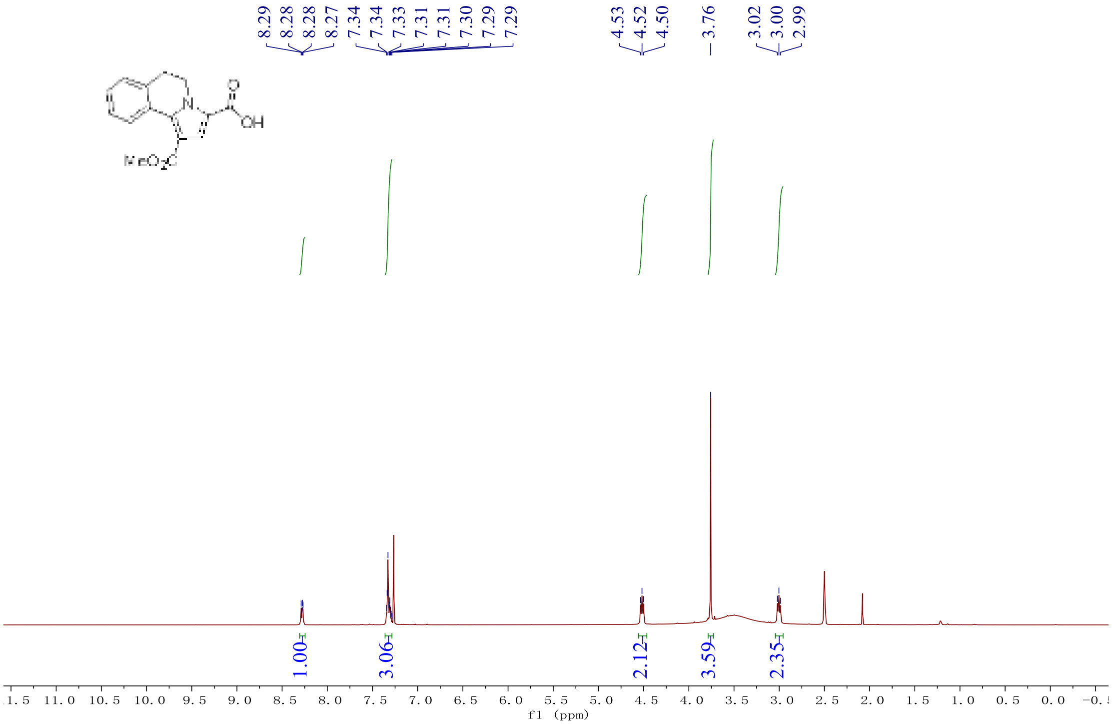
[1]H NMR of 3f



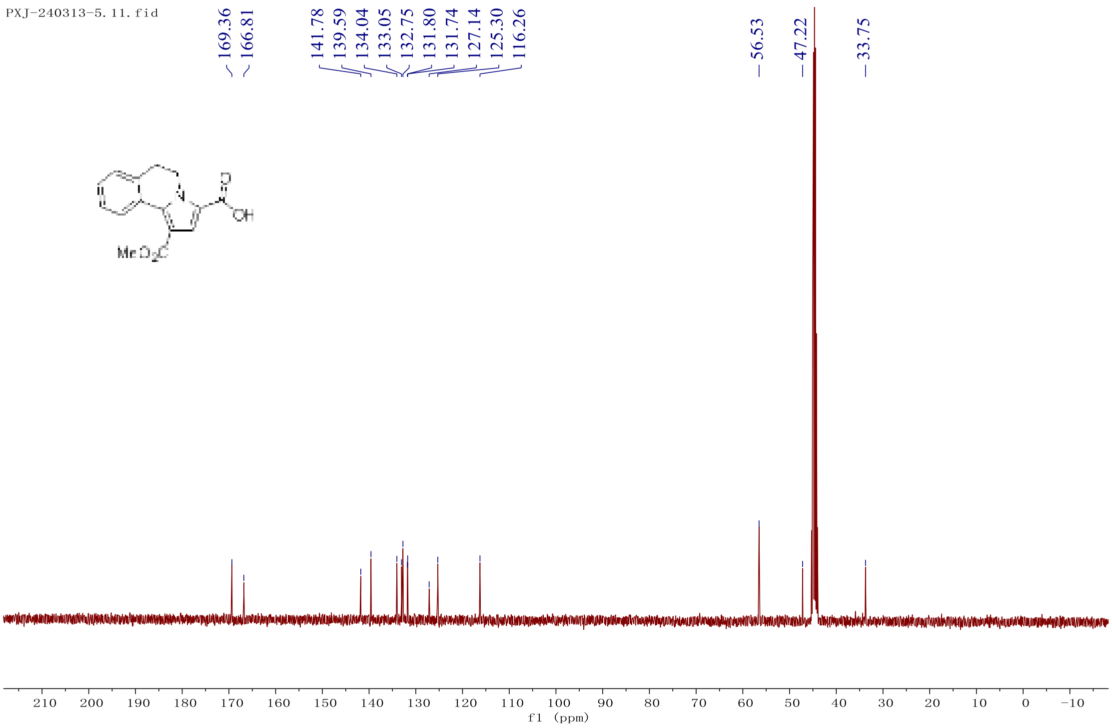
[13]C NMR of 3f



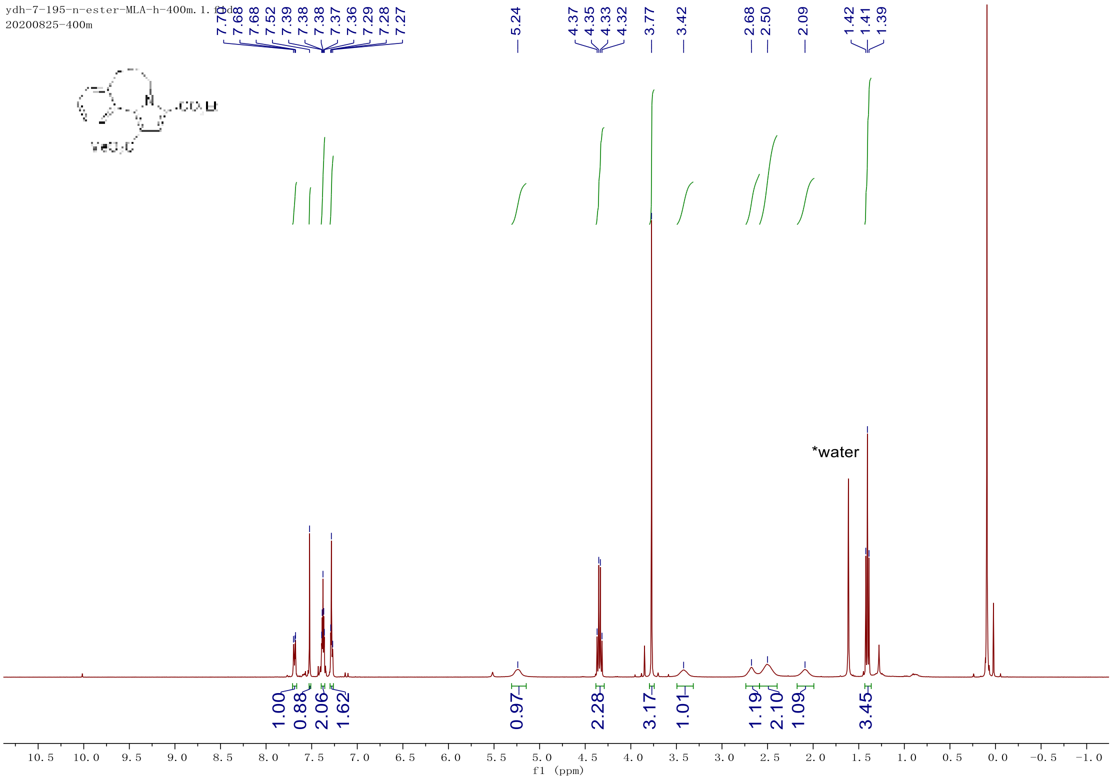
^{1}H NMR of 3g



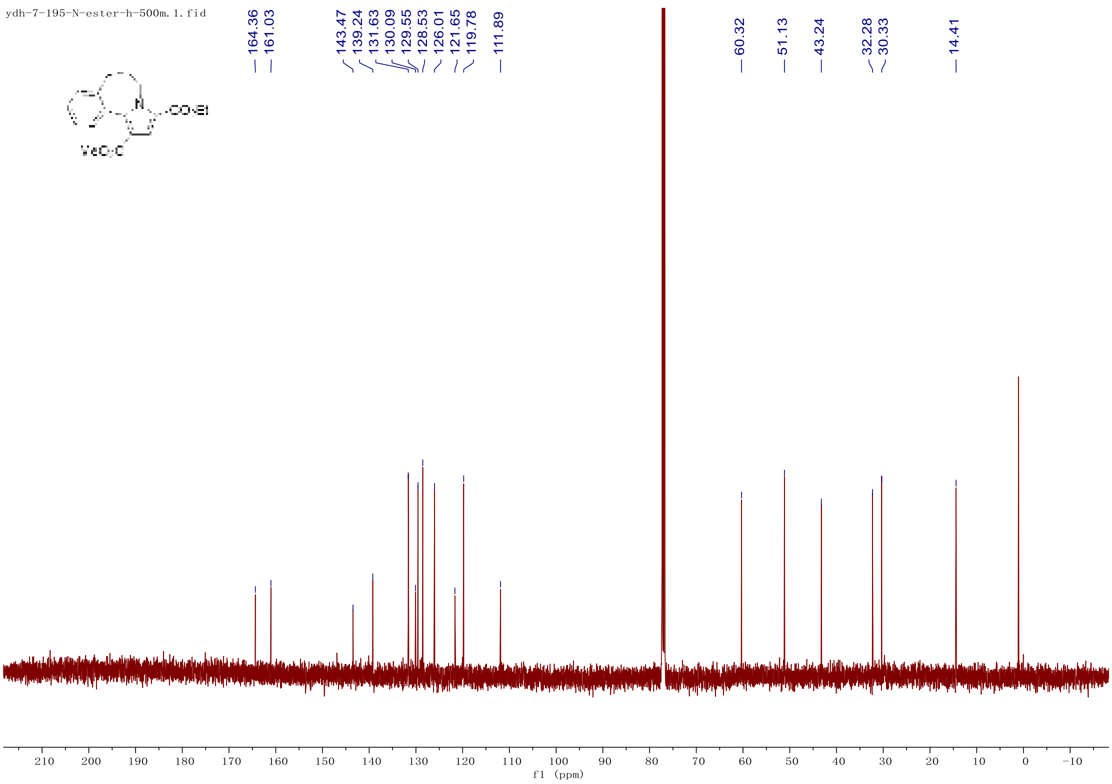
^{13}C NMR of 3g



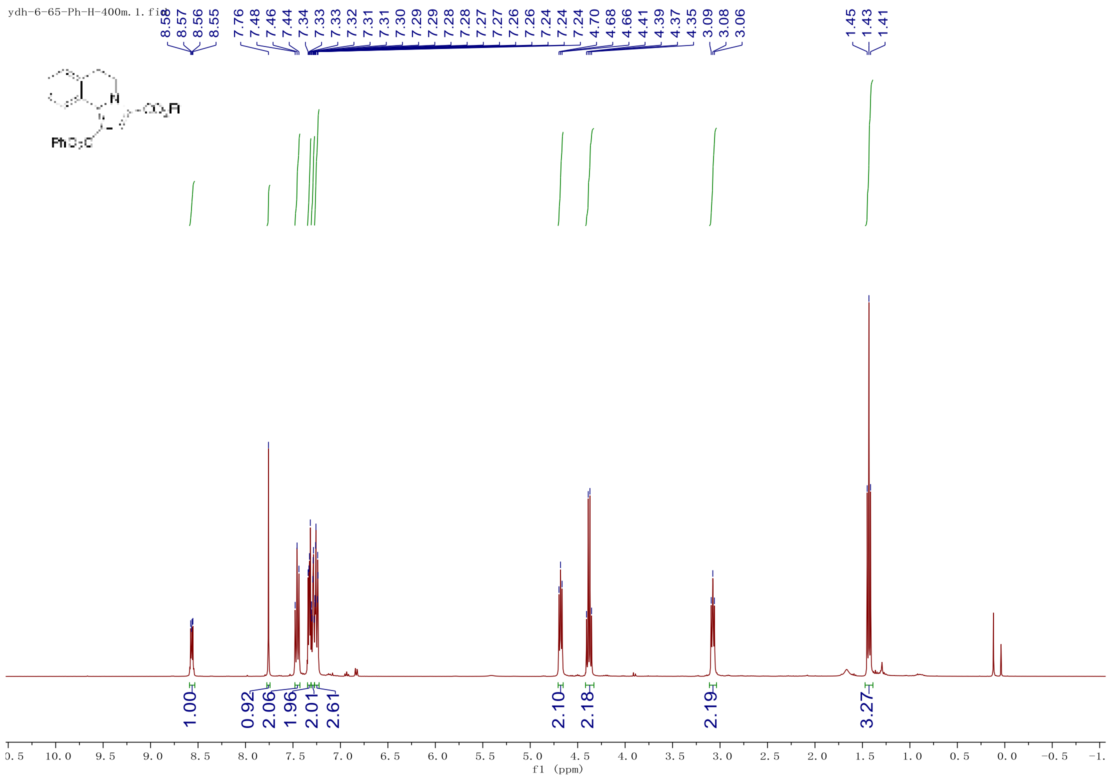
^{1}H NMR of 3h



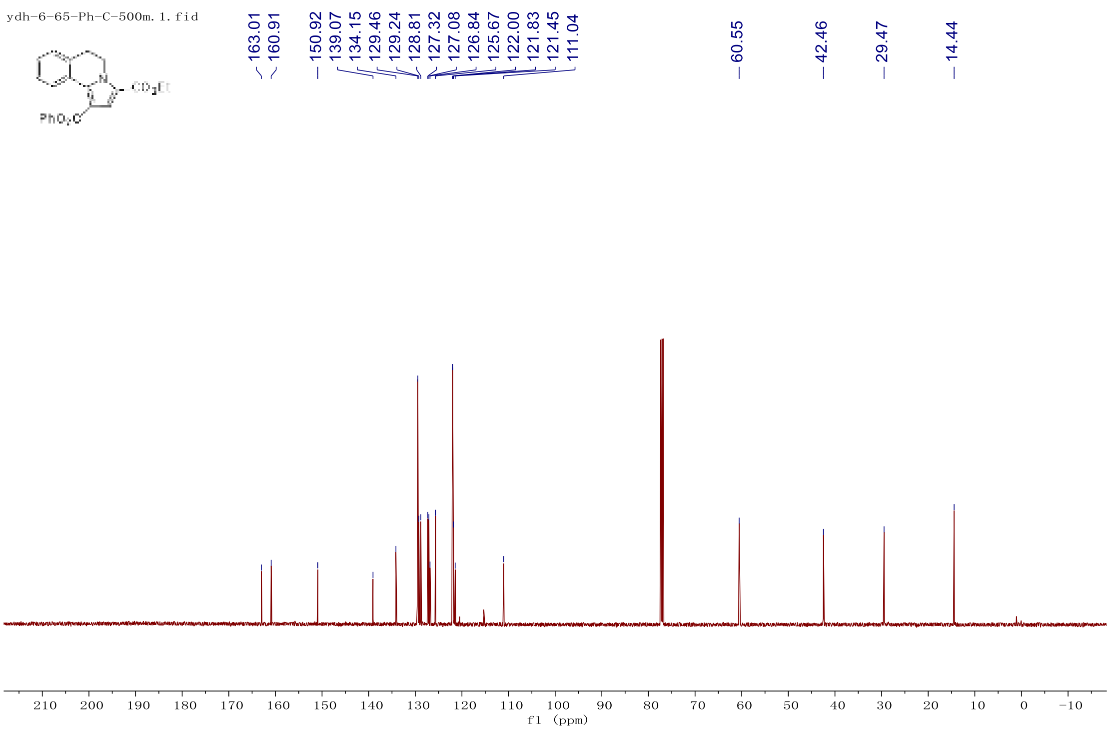
^{13}C NMR of 3h



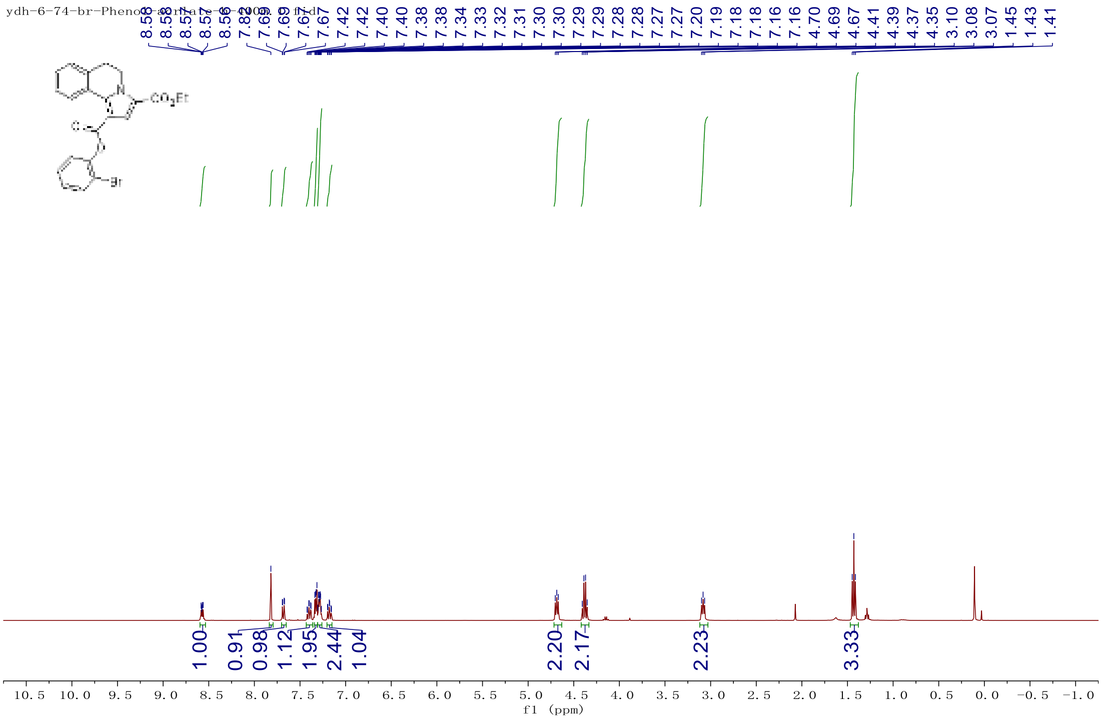
^{1}H NMR of 3i



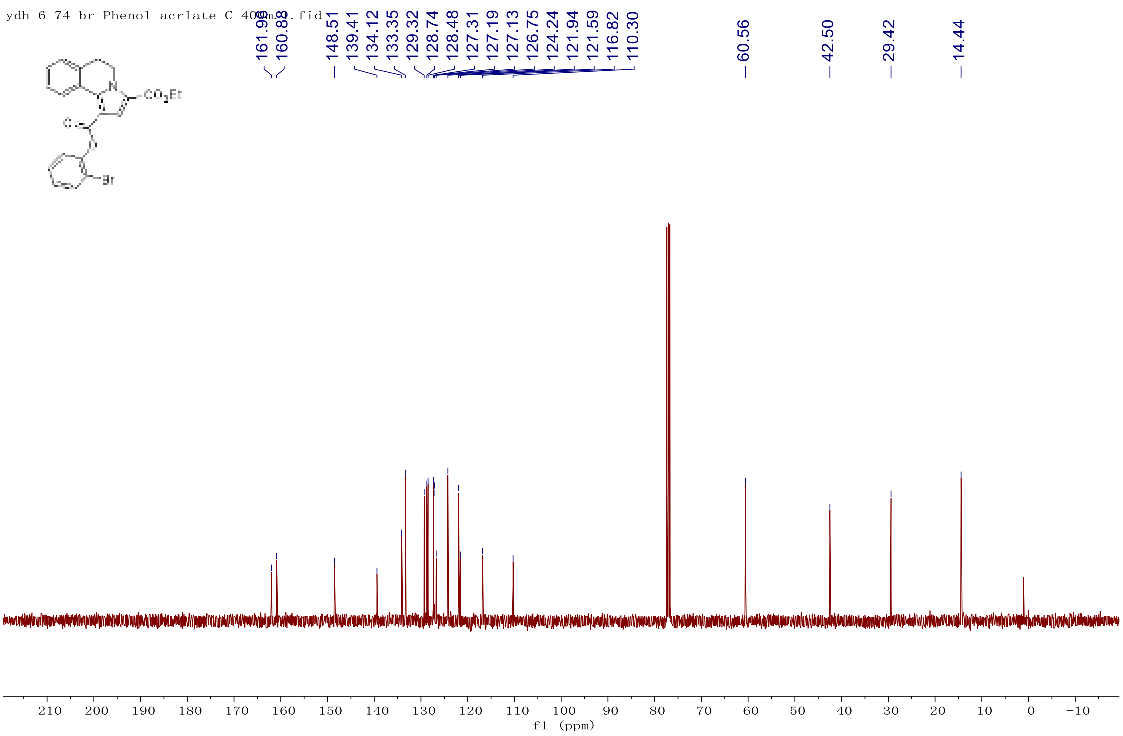
^{13}C NMR of 3i



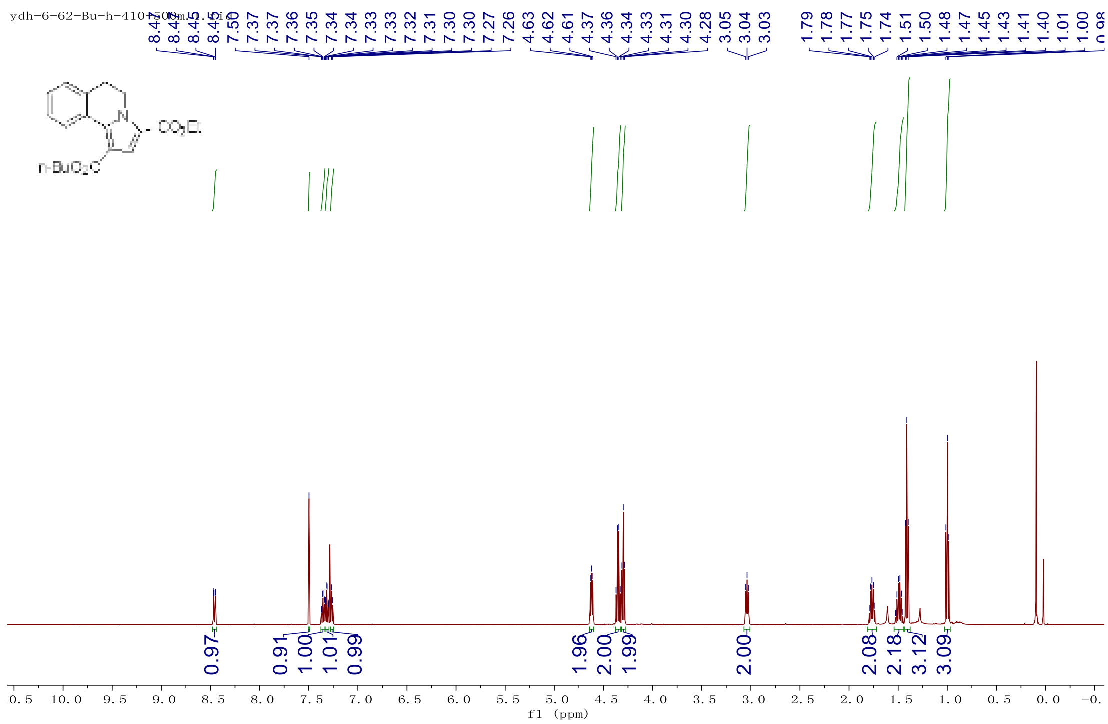
^{1}H NMR of 3j



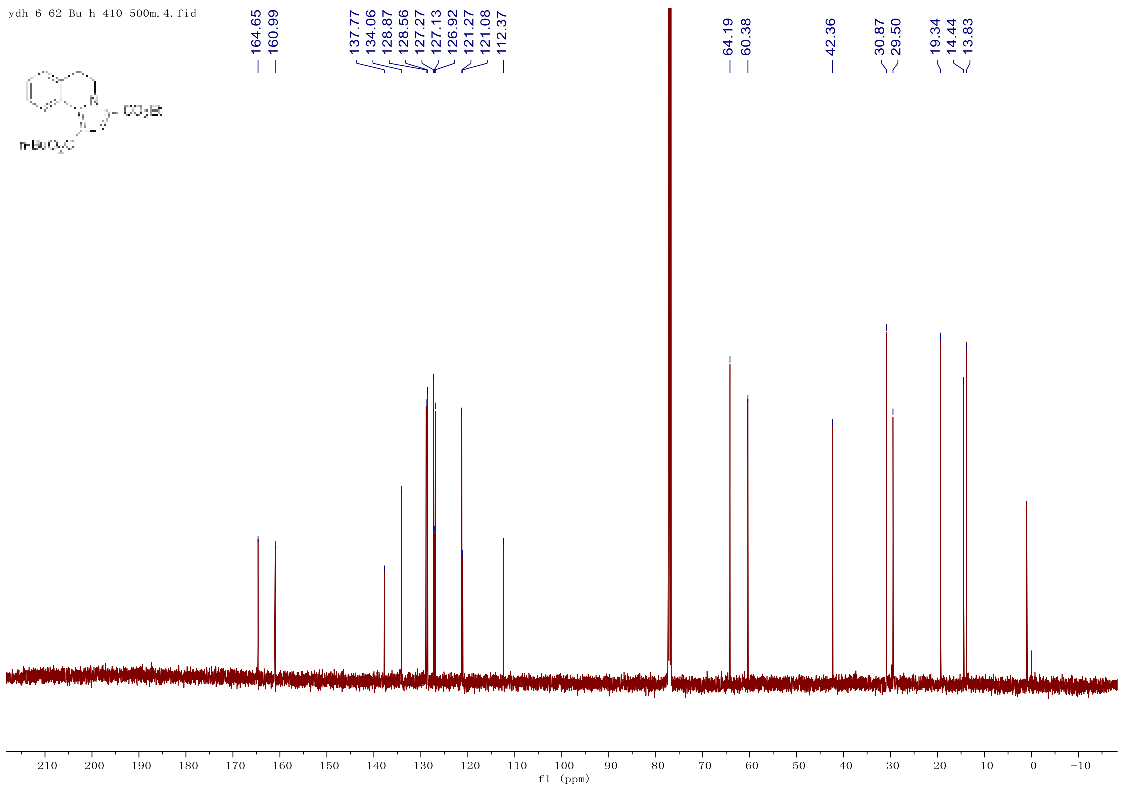
^{13}C NMR of 3j



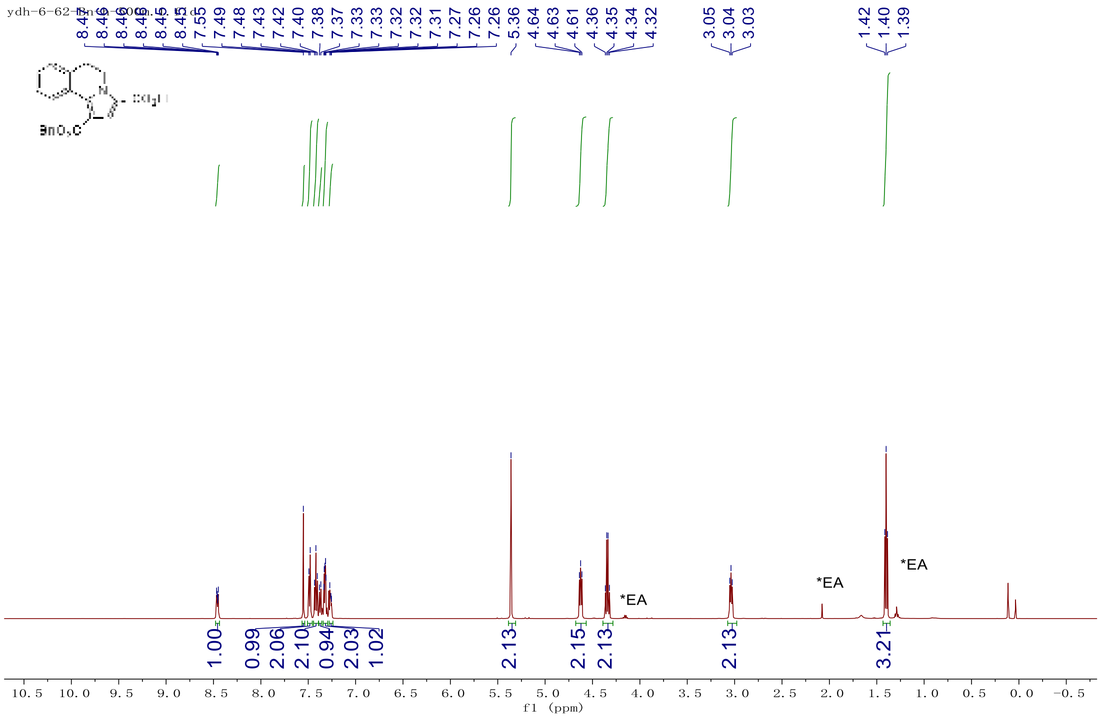
^{1}H NMR of 3k



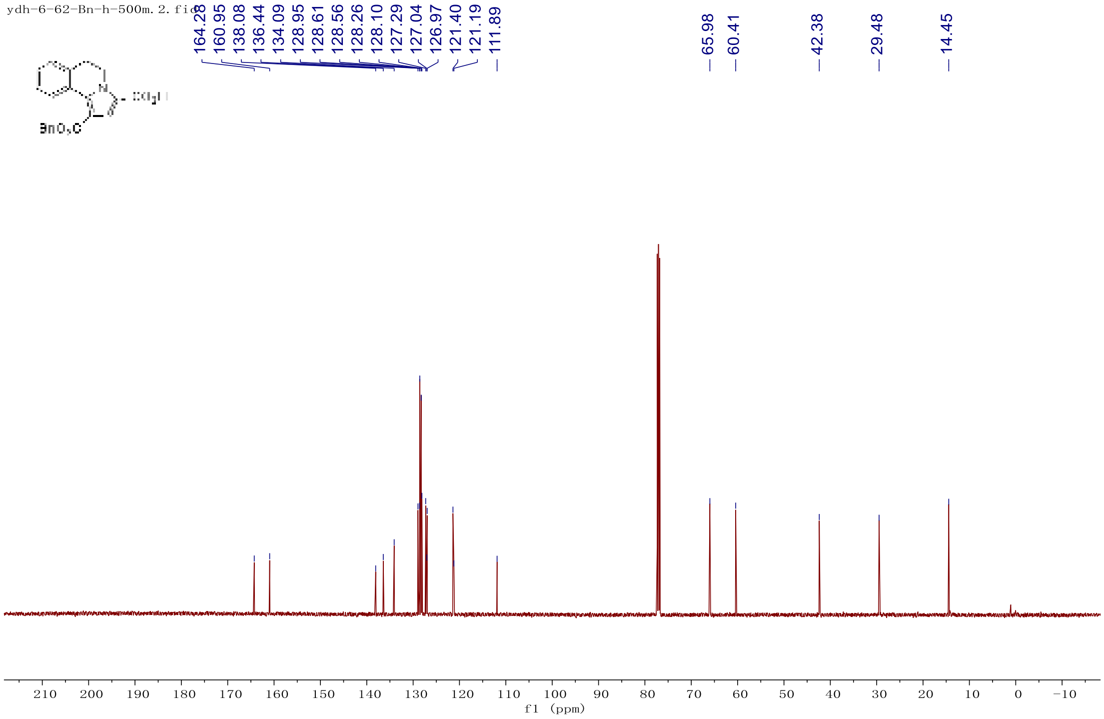
^{13}C NMR of 3k



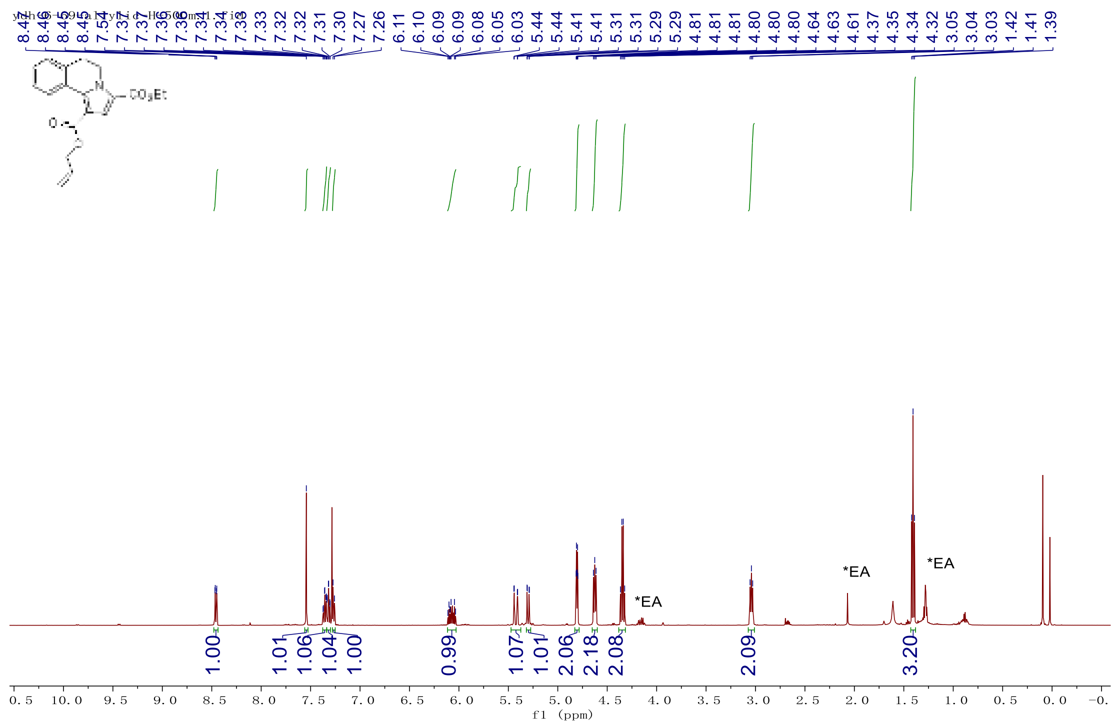
^{1}H NMR of 3l



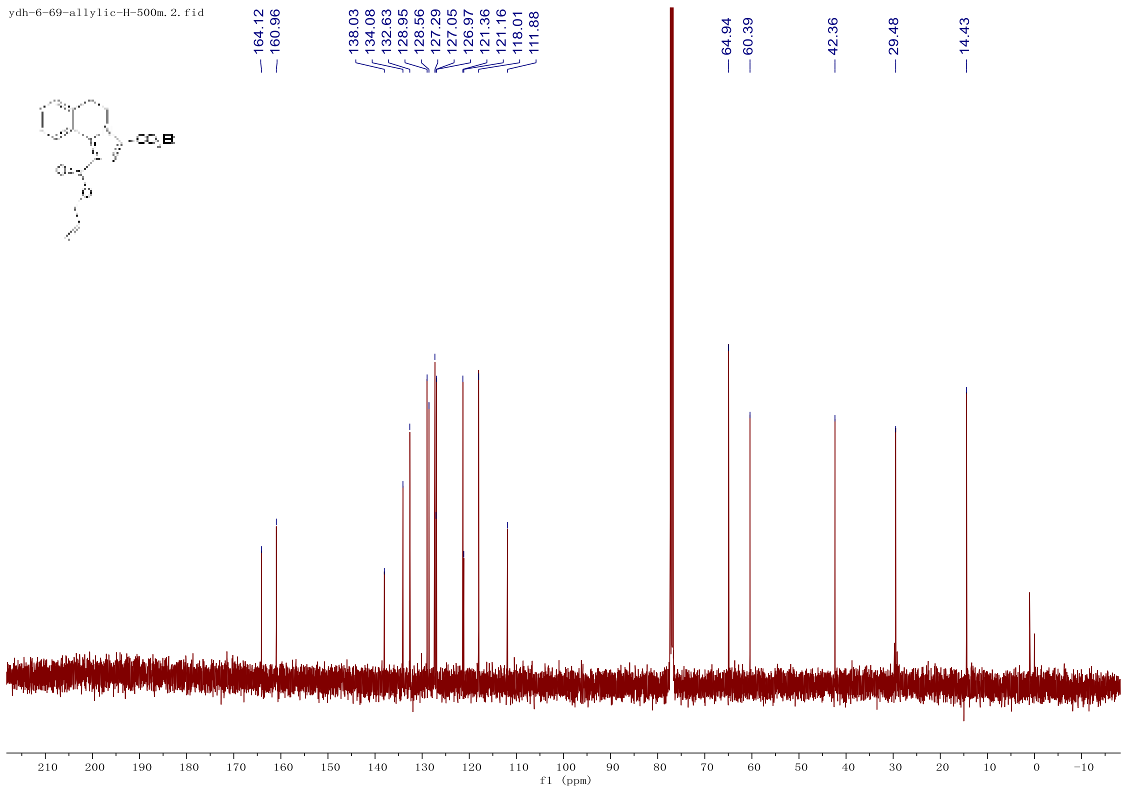
^{13}C NMR of 3l



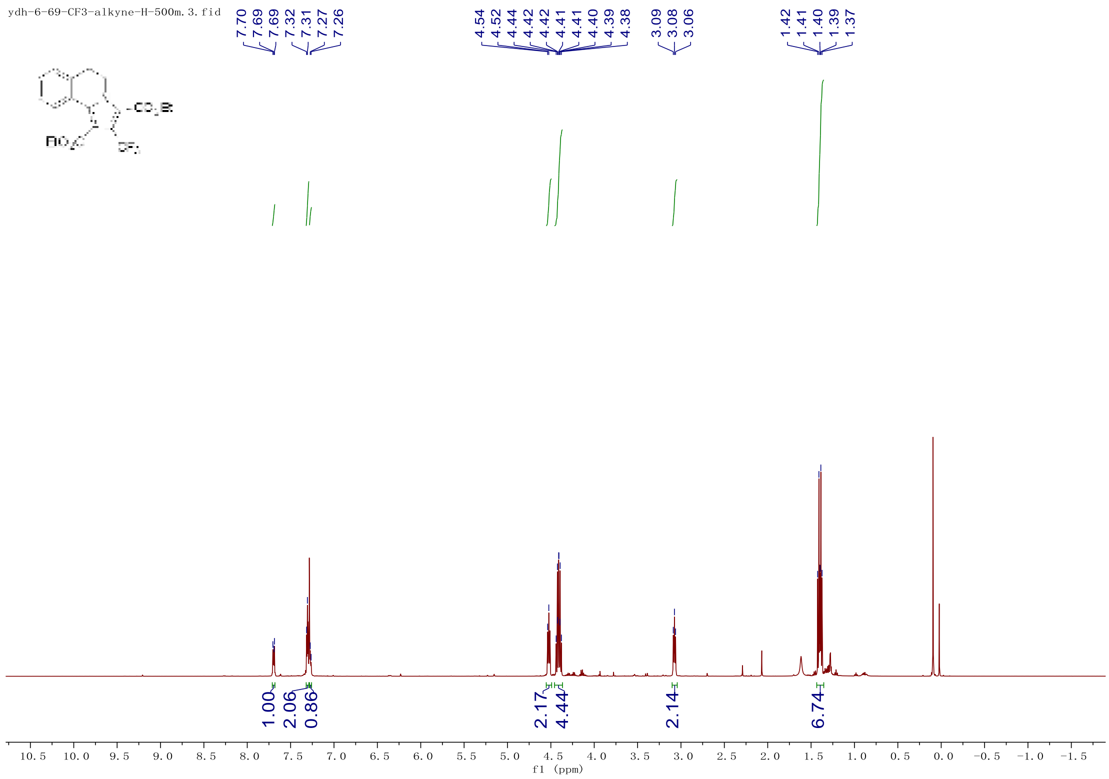
^{1}H NMR of 3m



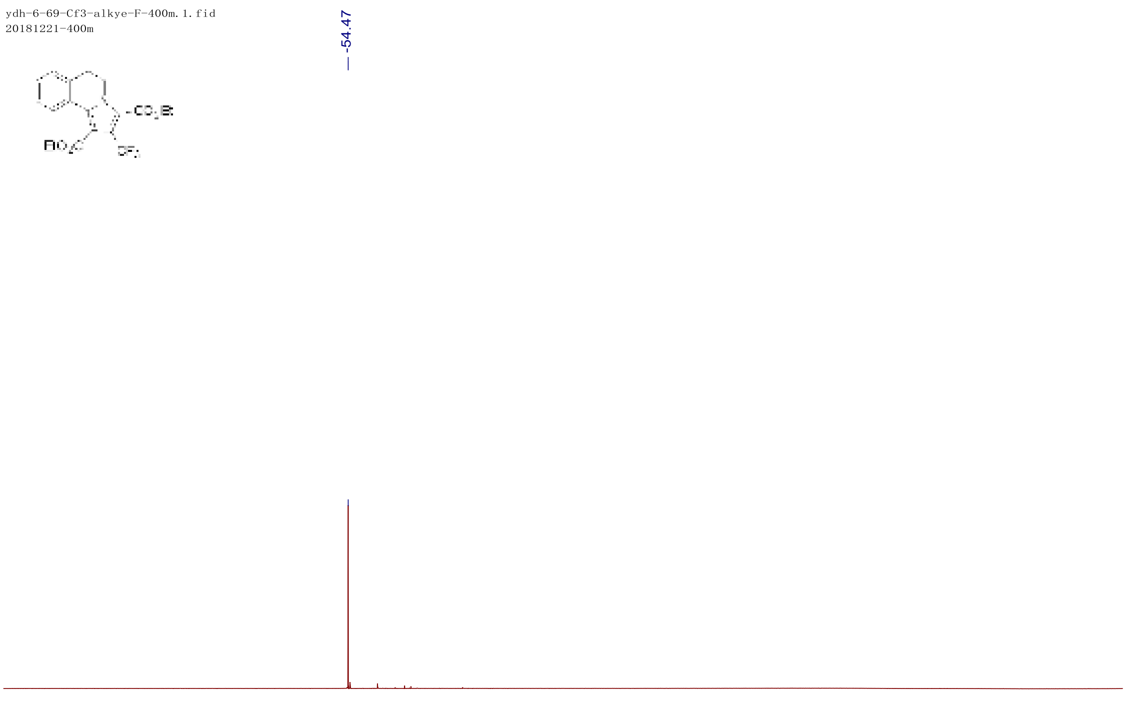
^{13}C NMR of 3m



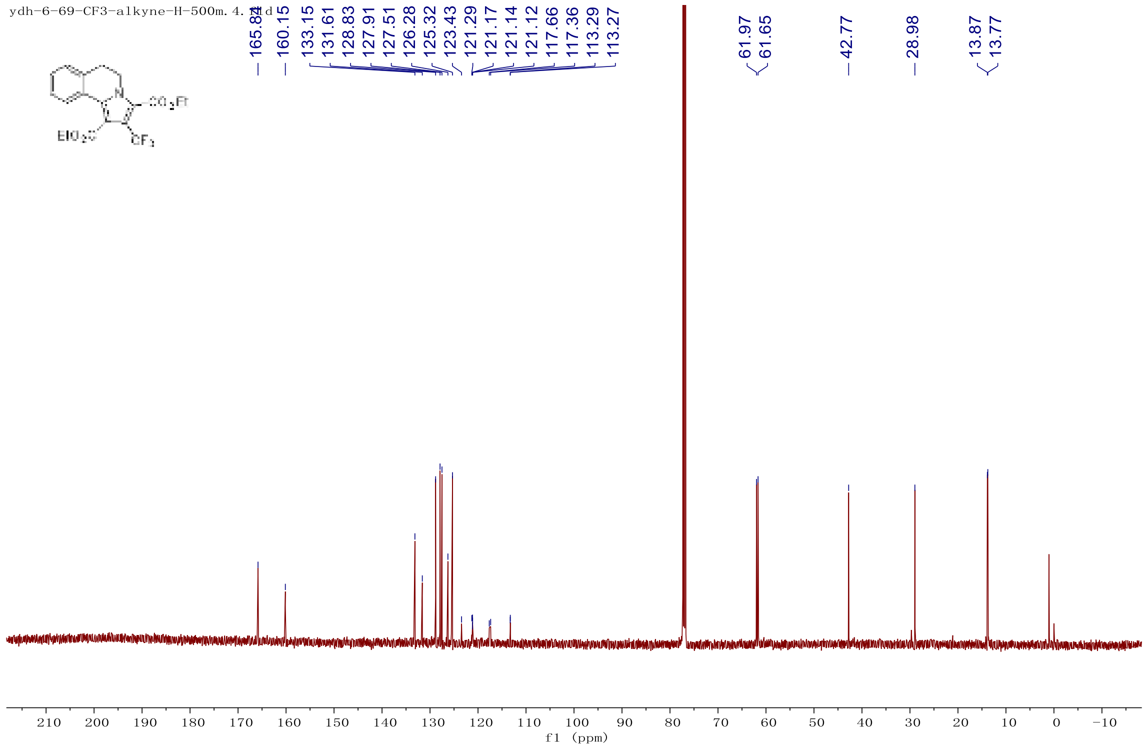
^{1}H NMR of 3n



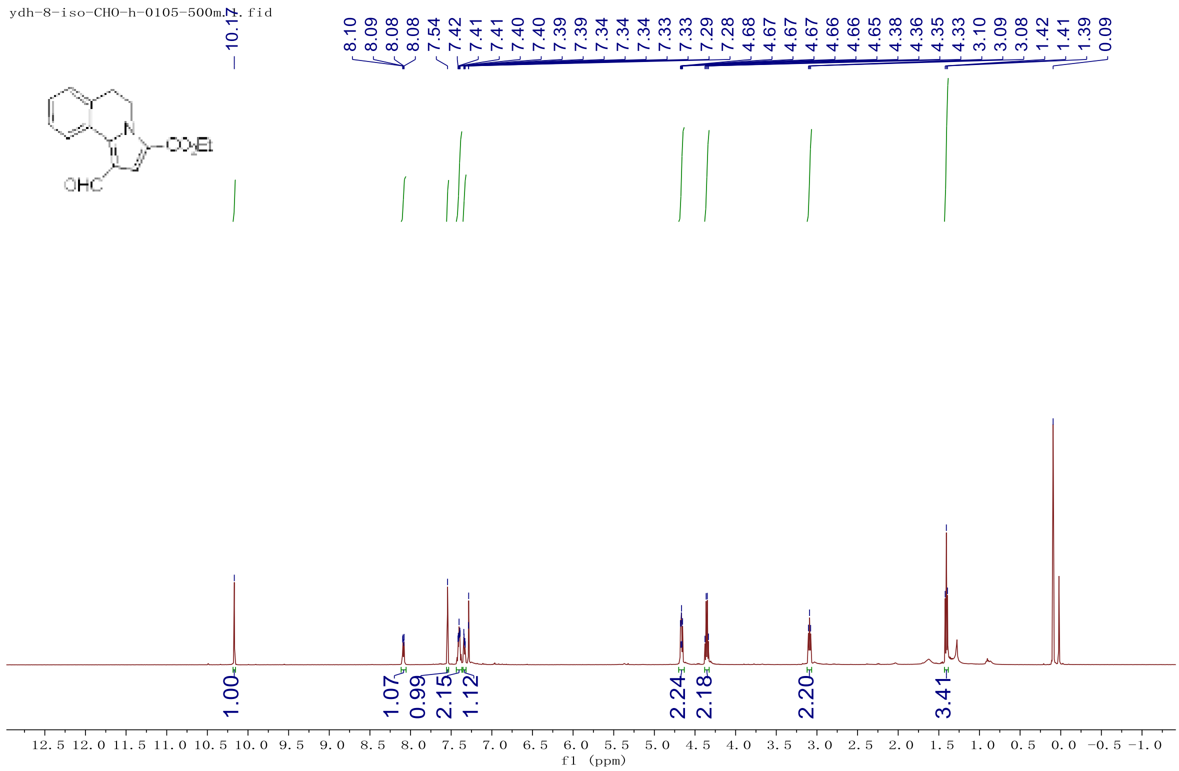
^{19}F NMR of 3n



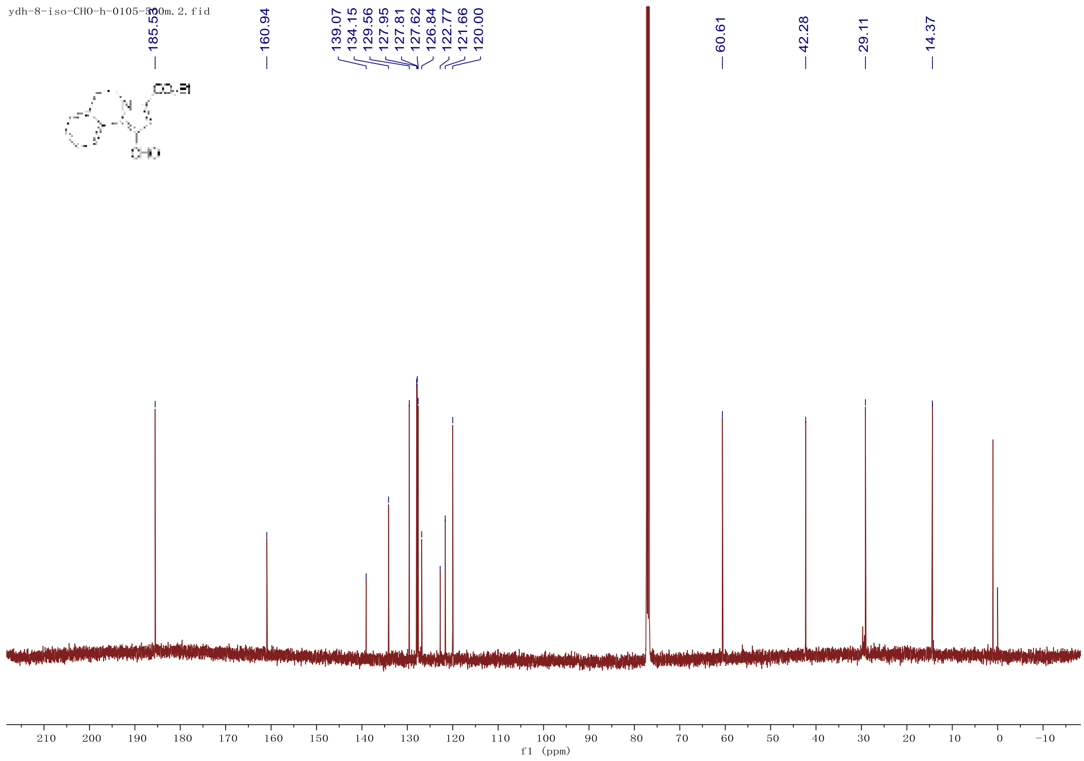
^{13}C NMR of 3n



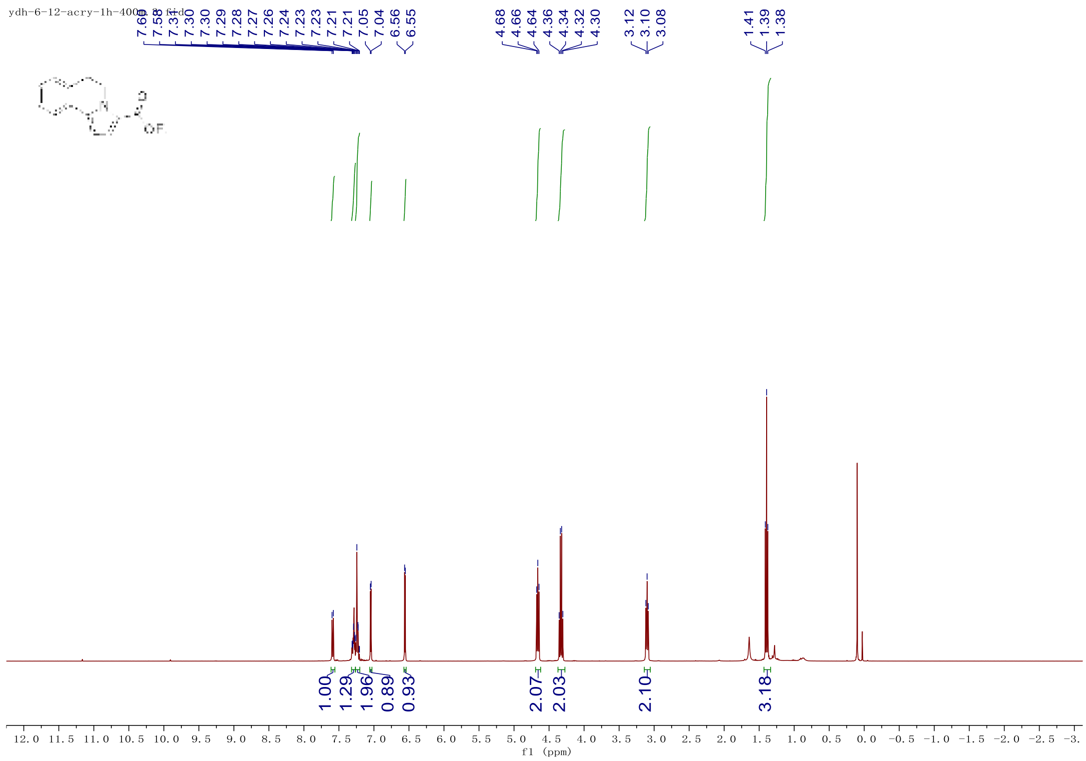
^{1}H NMR of 3o



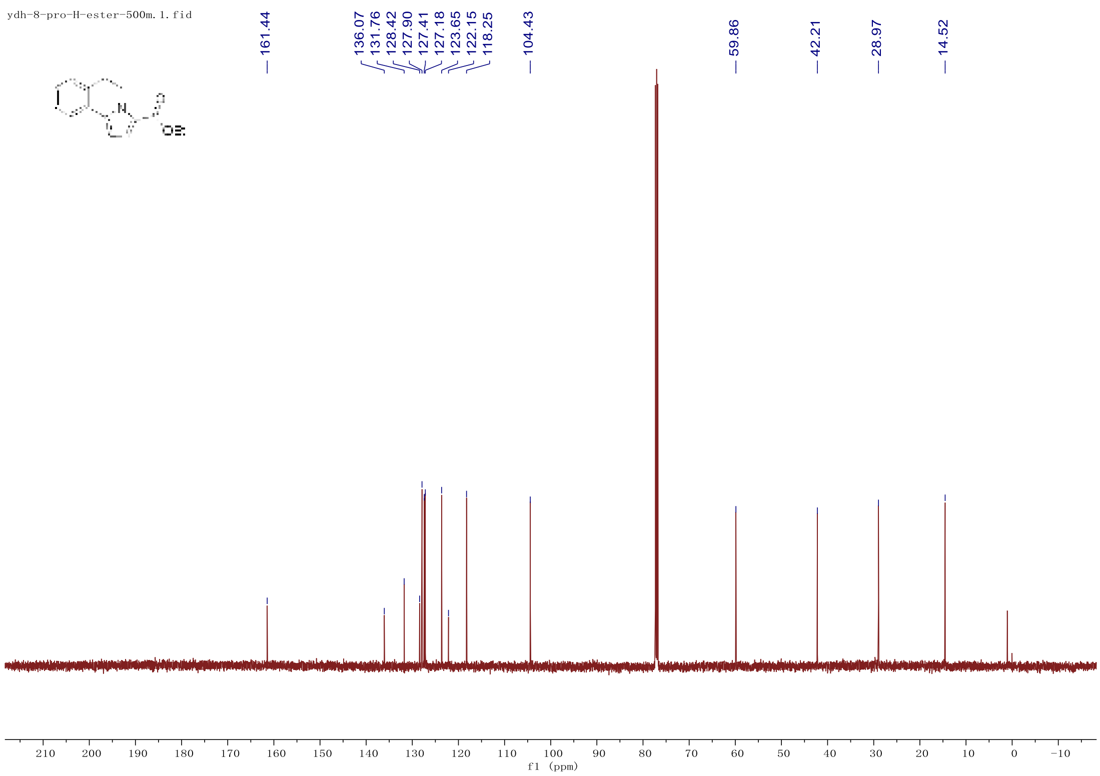
^{13}C NMR of 3o



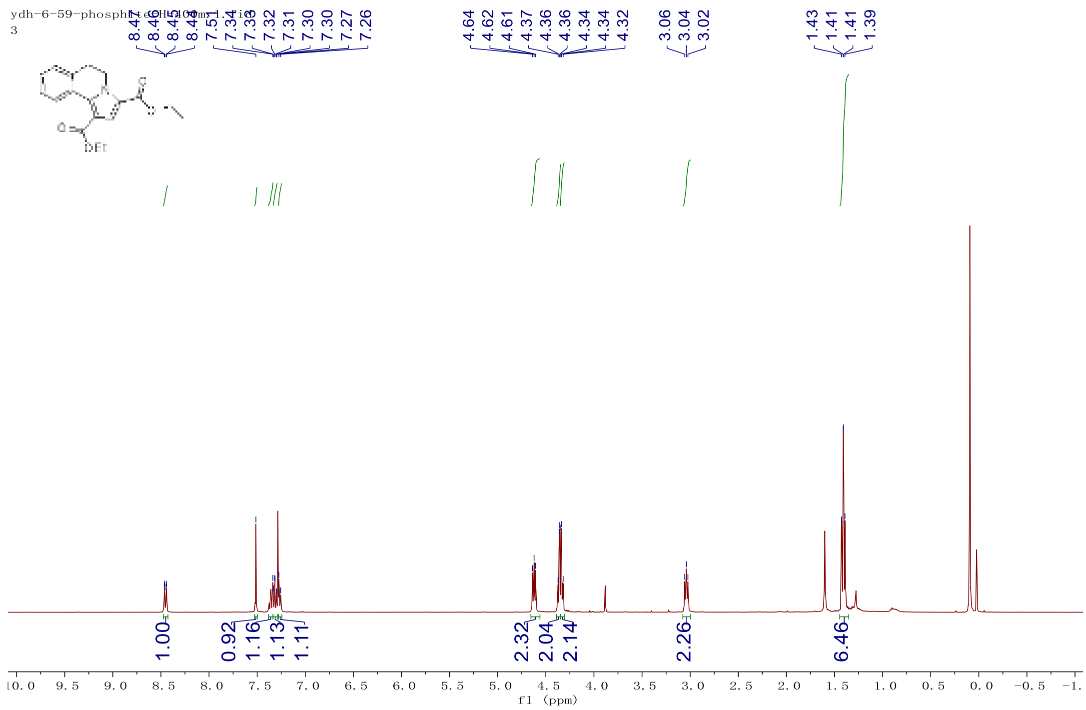
^{1}H NMR of 3p



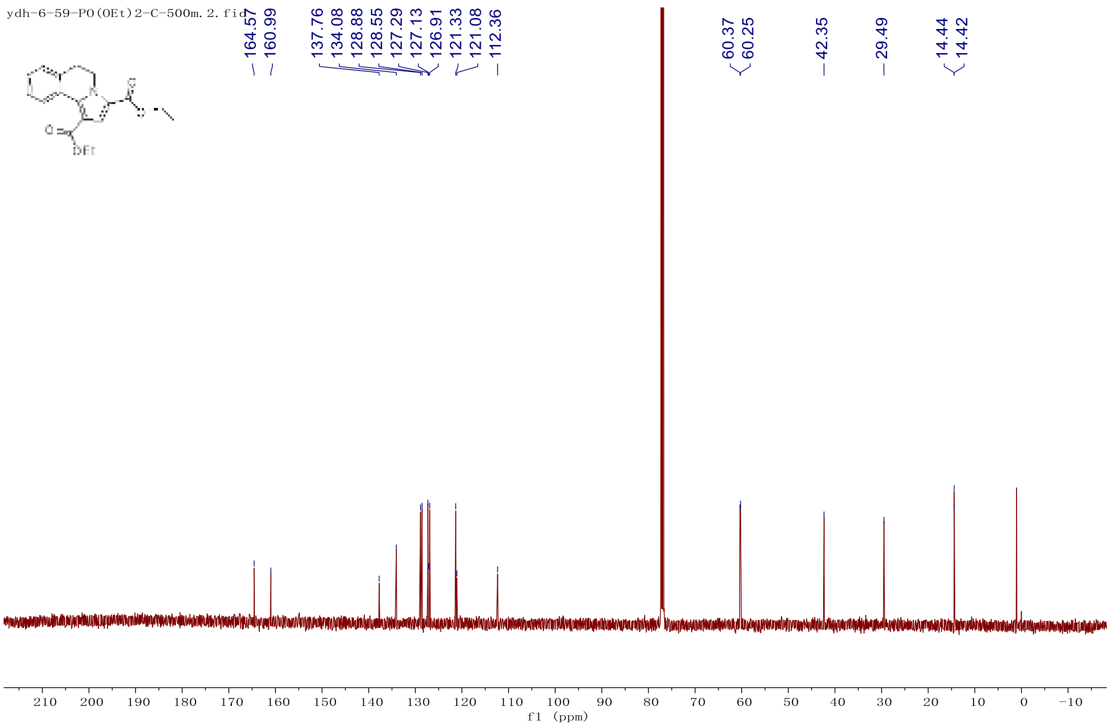
^{13}C NMR of 3p



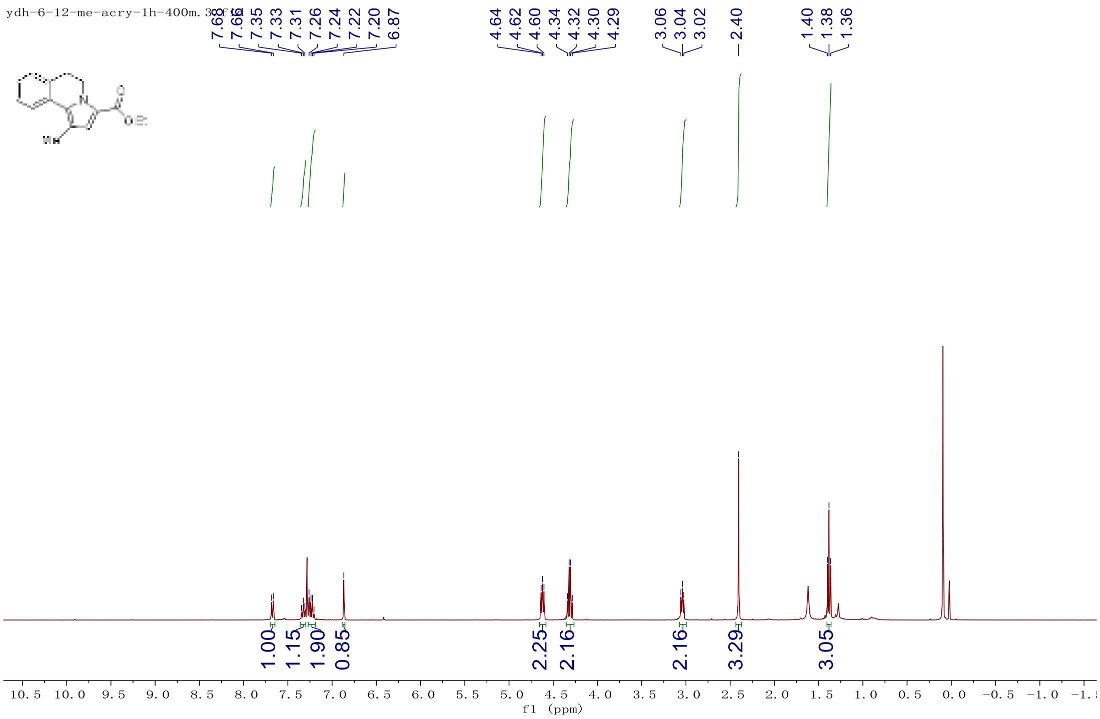
^{1}H NMR of 3q



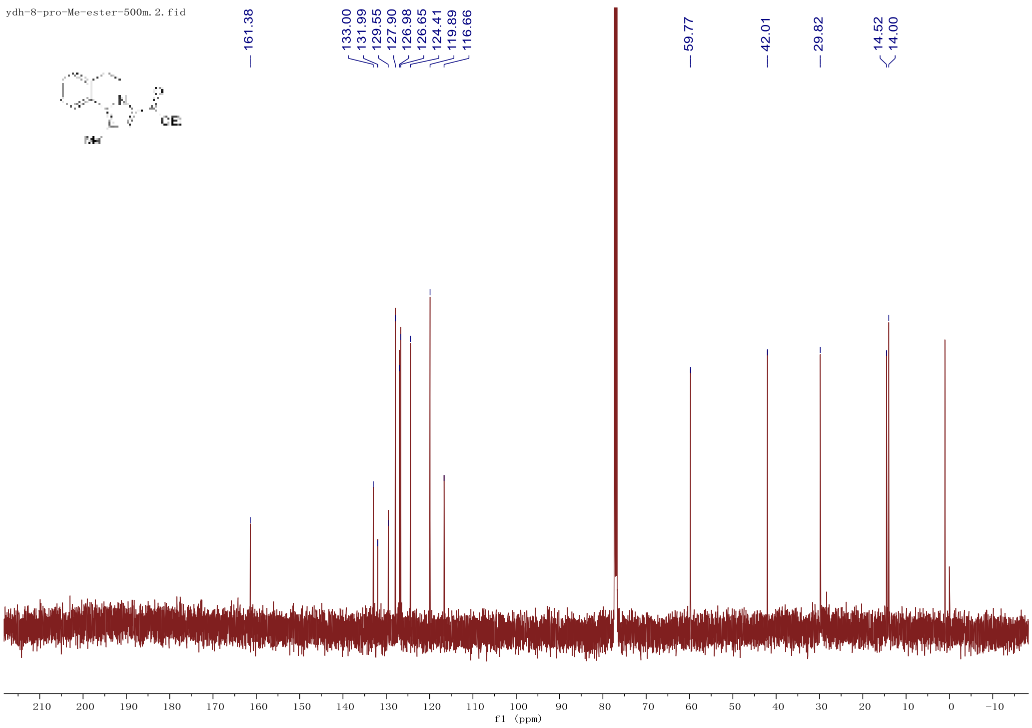
^{13}C NMR of 3q



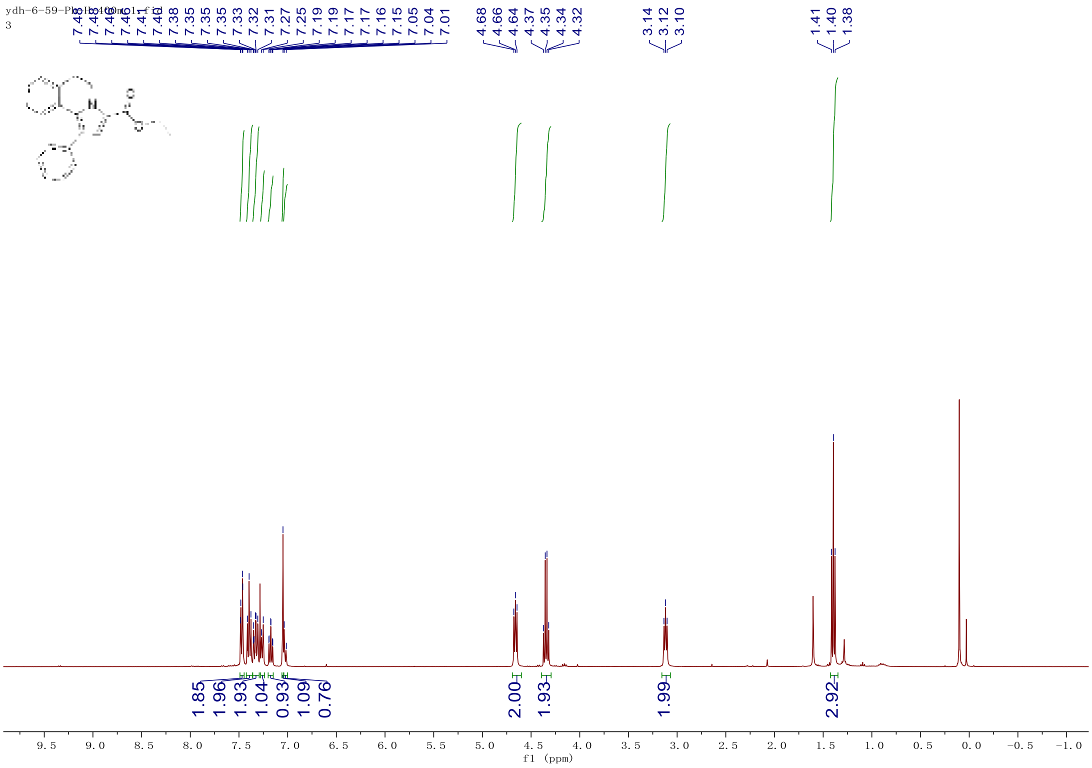
^{1}H NMR of 3r



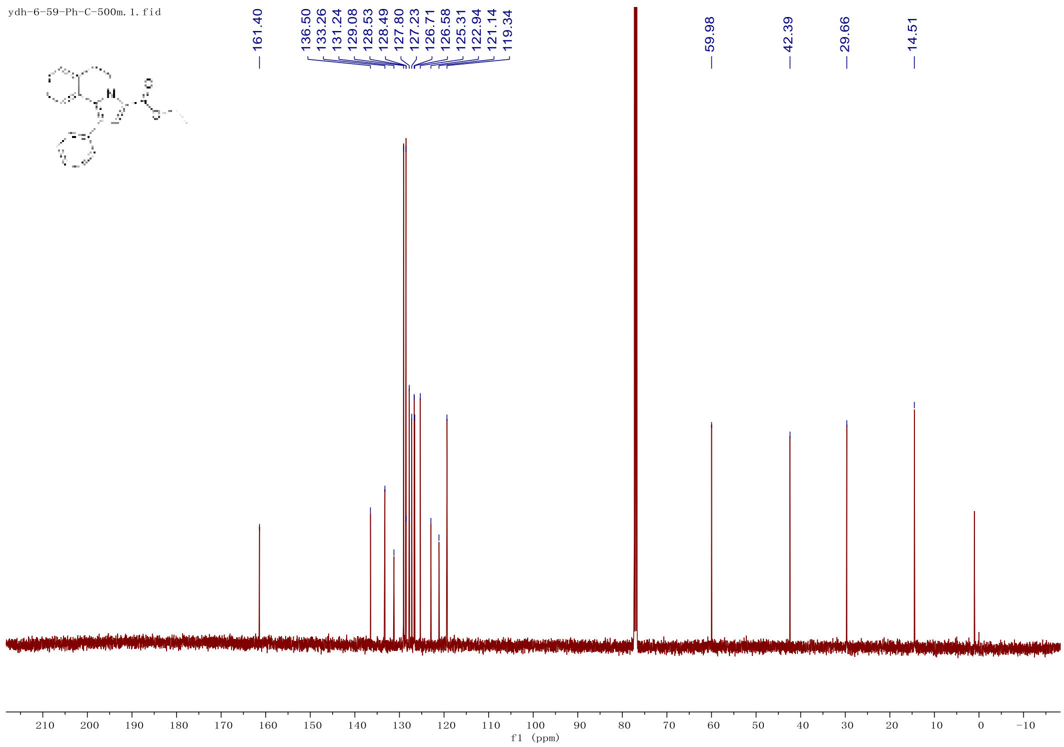
^{13}C NMR of 3r



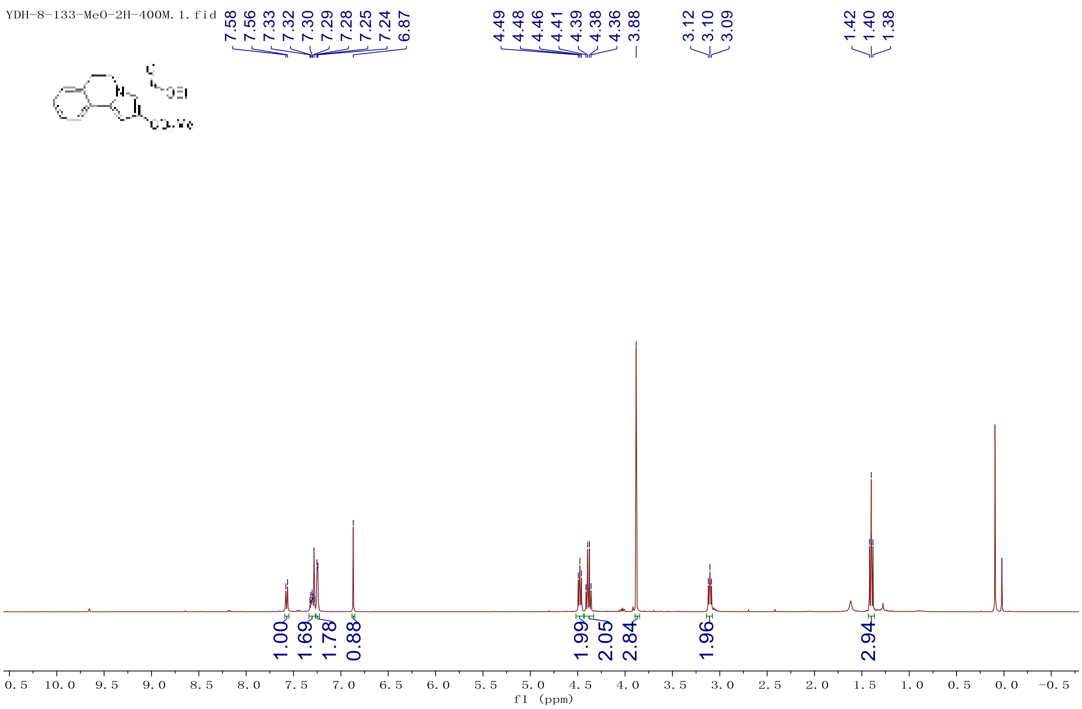
^{1}H NMR of 3s



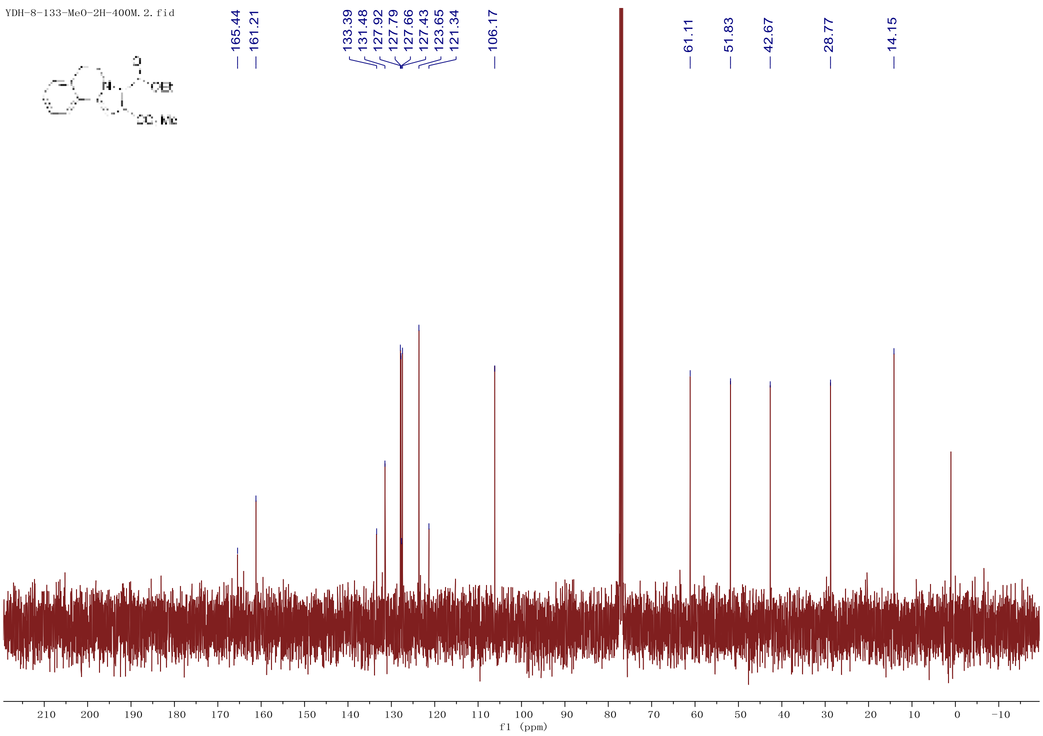
^{13}C NMR of 3s



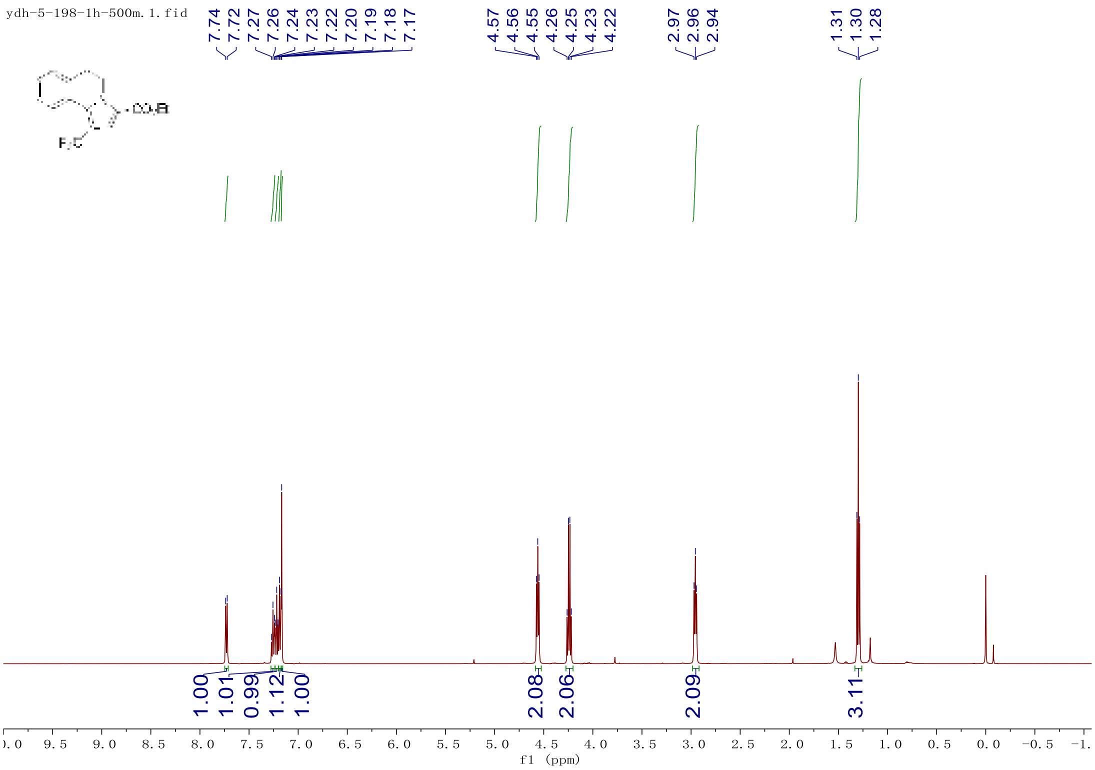
^{1}H NMR of 3a´



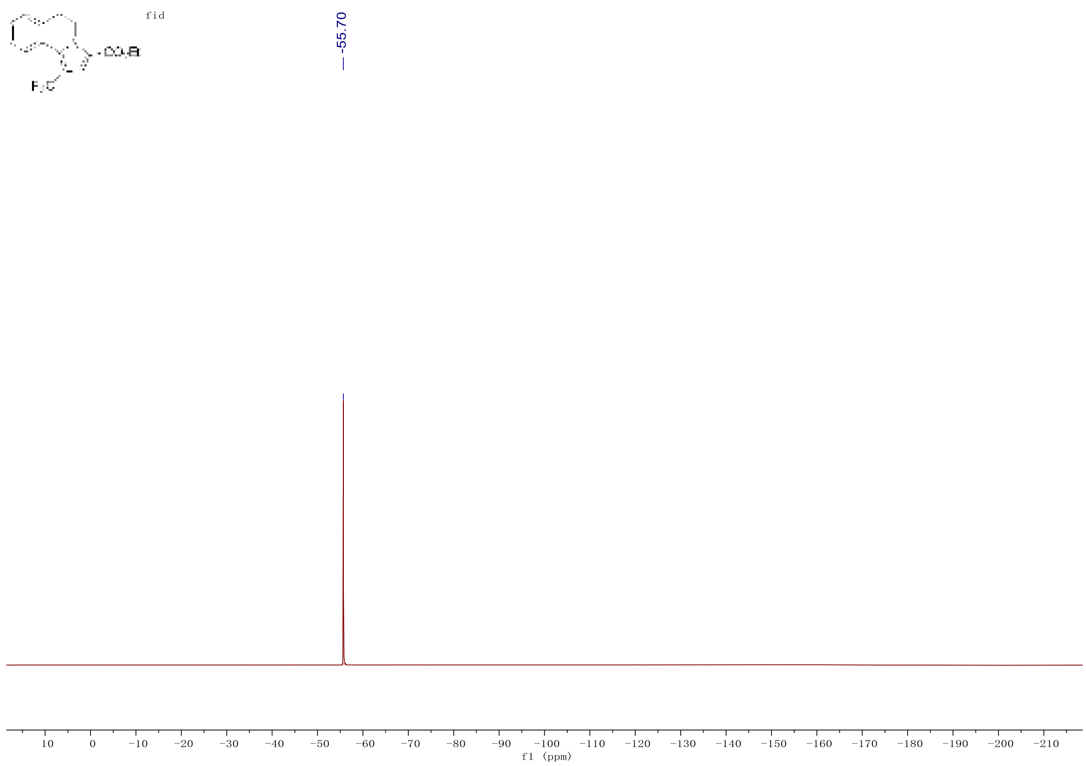
^{13}C NMR of 3a′



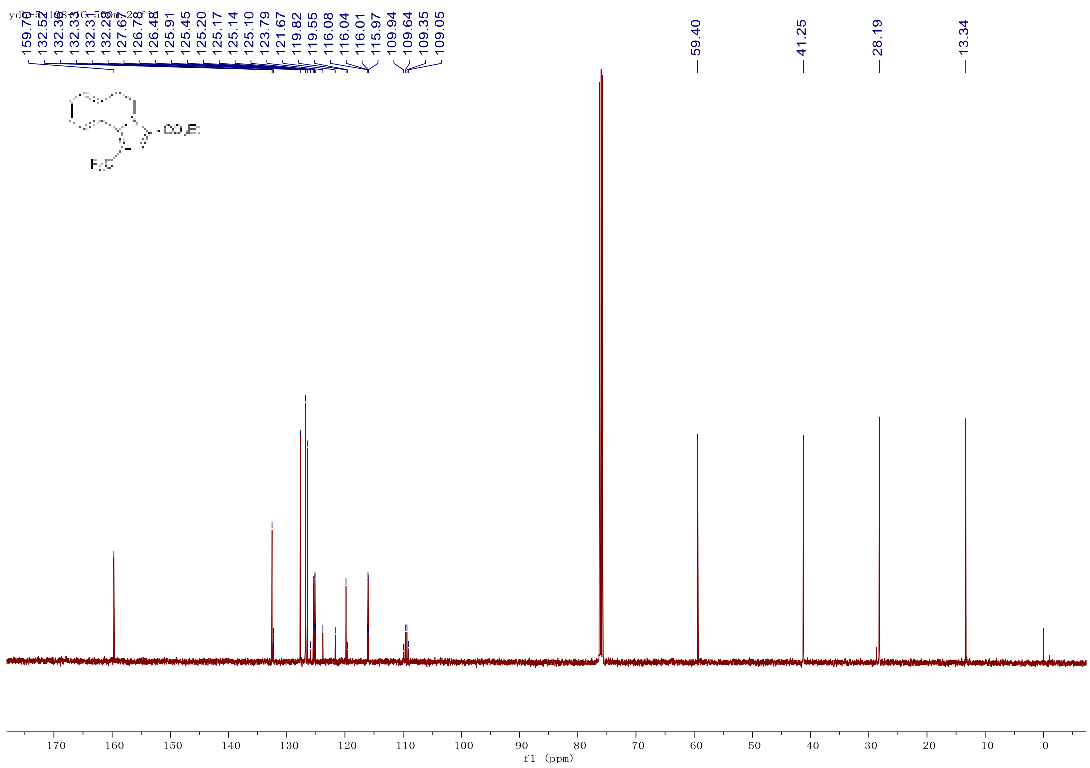
^{1}H NMR of 4a



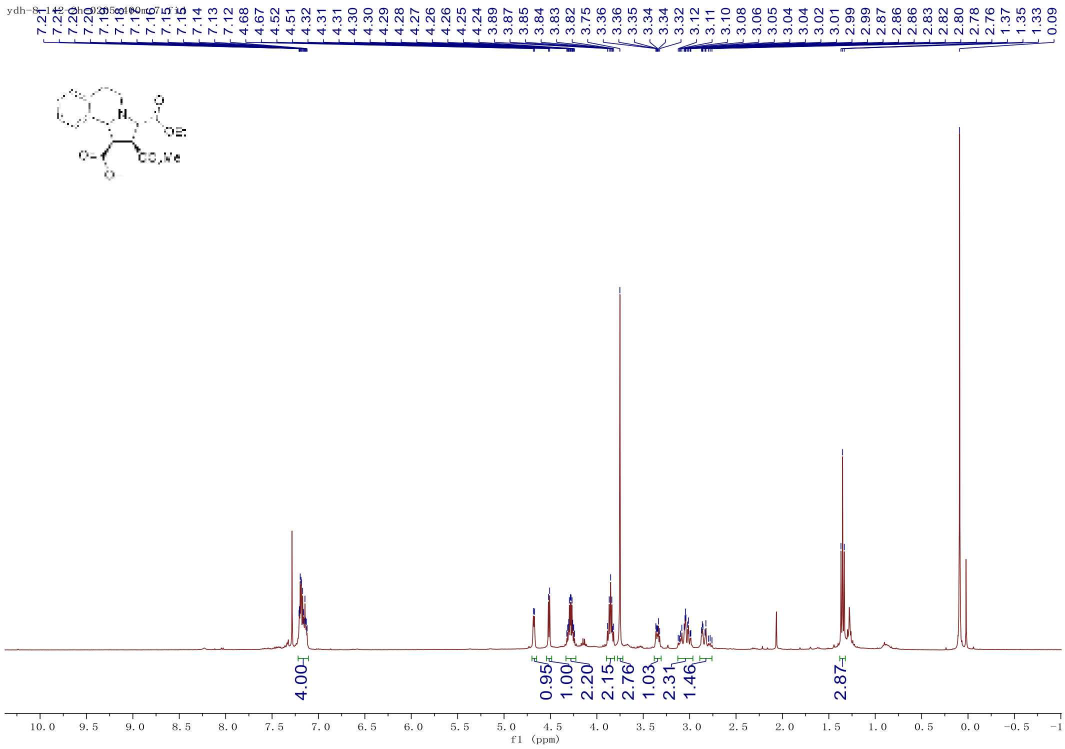
^{19}F NMR of 4a



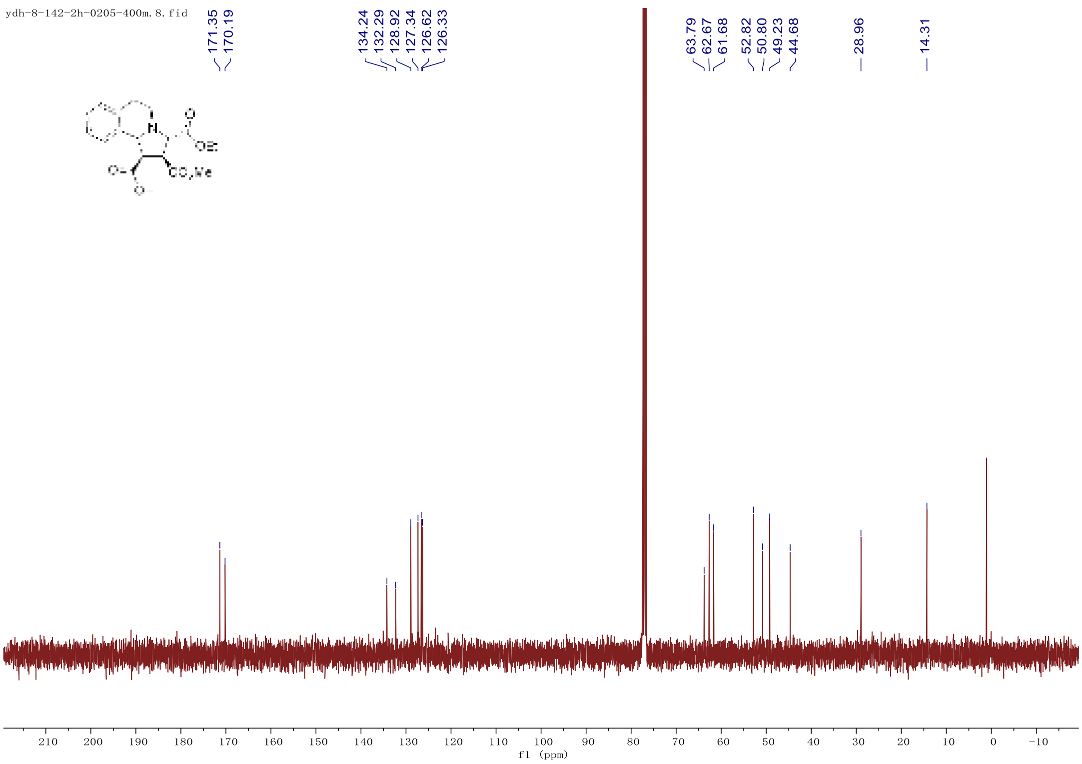
^{13}C NMR of 4a



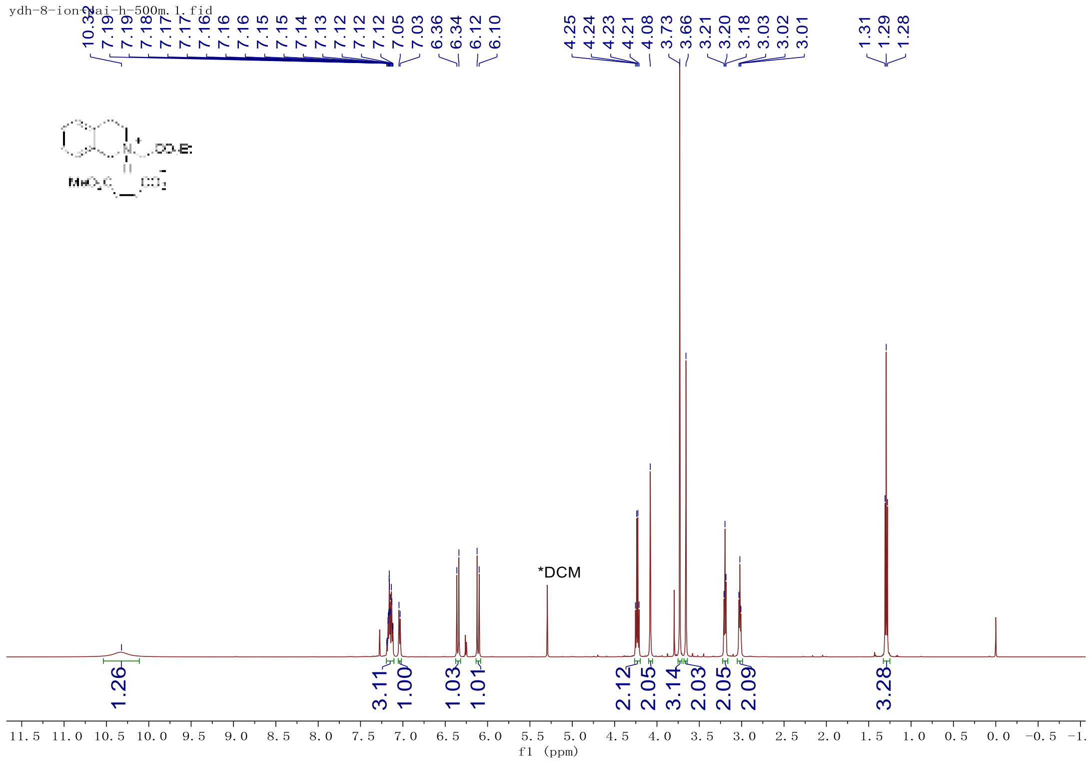
^{1}H NMR of 5′



^{13}C NMR of 5′



^{1}H NMR of 6



^{13}C NMR of 6