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Highly Efficient Synthesis of Polysubstituted 1,2-Dihydroquinolines via Cascade Reaction of α-Ketoesters with Arylamines Mediated by Iodine

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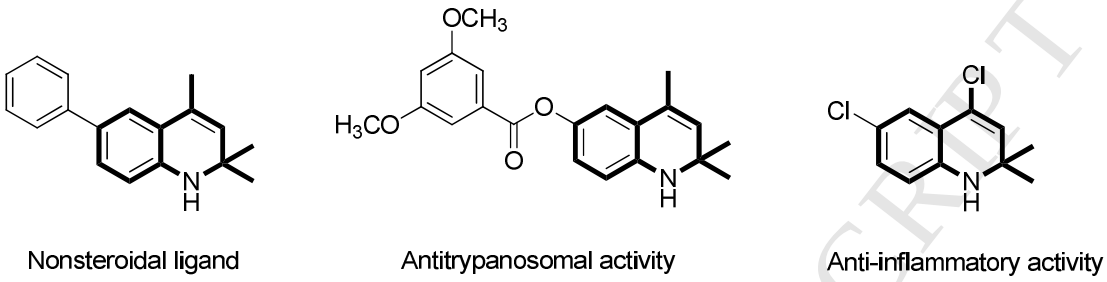
Abstract An efficient strategy enabling the construction of polysubstituted 1,2-dihydroquinoline derivatives mediated by the commercially available, economical, and environmentally benign iodine (3 mol %) under mild conditions was developed. Various arylamines and α-ketoesters could participate in this cascade reaction, and the desired products were obtained in excellent yields up to 98%.

Keywords Polysubstituted 1,2-dihydroquinoline; α-Ketoester; Arylamine; Iodine; Cascade reaction

1. Introduction

Dihydroquinolines and their derivatives are ubiquitous skeletons in pharmaceuticals, [1-3] synthetic intermediates, [4] and natural products. [5-7] Among these, 2,4-multisubstituted-1,2-dihydroquinoline derivative frameworks are important heterocycles found in a wide range of bioactive and pharmacological compounds (**Scheme 1**). [2,8,9] As a result, considerable efforts were directed toward the development of efficient methods for their synthesis. Many high-efficiency catalytic methods were revealed, such as the cascade

reaction of anilines with alkynes catalyzed by transition metals, [10-13] the condensation reaction of anilines with ketones catalyzed by scandium triflate, silicotungstic acid, [14,15] the allylation of quinolines mediated by indium and [16] etc.



Scheme 1 Representative bioactive or pharmacological multisubstituted dihydroquinolines.

Recently, a novel domino reaction of pyruvate with arylamine has been proposed to construct 2,4-multisubstituted-1,2-dihydroquinoline derivatives. Kumar et al. first used the domino reaction of α-ketoesters and arylamines in the formation of 2,4-multisubstituted-1,2-dihydroquinolines via variants of the Mannich and aryl C(sp^2)-H bond functionalization procedures employing $AuCl_3$ and $AgSbF_6$ in the presence of acetonitrile and ethanol. [17] Subsequently, Ji et al. presented the same tandem reaction catalyzed by indium triflate and HNO_3 respectively. [18,19] The cascade reaction of pyruvates with arylamines was also reported by Yi and coworkers using a complex catalytic system of fluorous hydrazine-1,2-bis(carbothioate) and N-chlorosuccinimide. [20] Among the reported approaches, some used expensive metal catalysts, strong corrosive acid, or multiple step synthesized catalysts. These drawbacks limited their wide application in industry and academia. Therefore, development of a highly efficient, environmentally friendly, commercially available and cheap catalyst to realize this important transformation is still desirable. Herein, we report another Mannich and aryl C(sp^2)-H bond functionalization

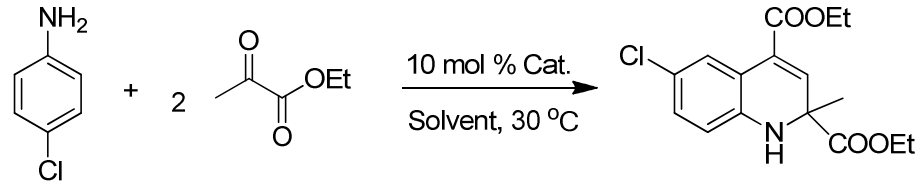
conversion for efficient synthesis of 2,4-multisubstituted-1,2-dihydroquinoline derivatives using iodine as an easily available, economical, and environmentally benign catalyst.

2. Results and discussion

The cascade reaction was carried out using *p*-chloroaniline and ethyl pyruvate as a model reaction. In initial investigation, various catalysts such as pyrrolidine, proline, [BMIm]HSO_4, [BMIm]Ac, and I_2 were screened in MeCN at 30 ^oC. As can be seen from the summarized results in **Table 1**, only iodine could promote the model reaction, giving the desired product in a moderate yield of 62% (**Table 1**, entry 5). Therefore, we chose iodine as the catalyst for the cascade reaction. Then solvent screening was performed to identify the optimal conditions (**Table 1**, entries 5-13). The reaction media played an important role in the model reaction. Among the tested organic solvents, the highest yield of 62% was obtained in MeCN at 30 ^oC (**Table 1**, entry 5). When the reaction was performed in EtOH, ethyl acetate, MTBE, or solvent-free respectively, the yields were slightly inferior to the results in MeCN. The reaction in MeOH and THF only gave product in low yields of 10% and 20% respectively (**Table 1**, entries 9 and 11). We did not get the desired product in water (**Table 1**, entry 7), and only a low yield of 20% was obtained in water/EtOH (1:1) (**Table 1**, entry 8). Thus, MeCN was chosen as the solvent for the further investigation.

Table 1

The screening of catalysts and solvents[a]



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

Entry	Catalyst	Solvent	Yield[b] (%)
1	pyrrolidine	MeCN	--
2	proline	MeCN	--
3	[BMIm]HSO_4	MeCN	--
4	[BMIm]Ac	MeCN	--
5	I_2	MeCN	62
6	I_2	EtOH	54
7	I_2	H_2O	--
8	I_2	EtOH/H_2O (1:1)	20
9	I_2	MeOH	10
10	I_2	ethyl acetate	60
11	I_2	THF	20
12	I_2	MTBE	41
13	I_2	none	52

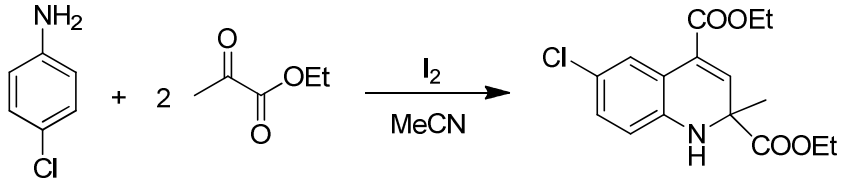
[a] The reaction was carried out using **1a** (0.3 mmol), **2a** (1.8 mmol) and catalyst (10 mol %) in solvent (0.5 mL) at 30 °C for 2 d.

[b] Isolated yield after silica gel chromatography.

Next, the effects of temperature, molar ratio of substrates and catalyst loading on the model cascade reaction were investigated (**Table 2**). As the reaction temperature increased from 30 °C to 50 °C, the yields increased from 62% to 94% (**Table 2**, entries 1-3), thus 50 °C was a desired temperature for this reaction. Then, the molar ratio (**1a:2a**) was investigated. The yields were improved by increasing **2a** from 2 to 3 equivalents (**Table 2**, entries 6 and 7). Further increasing the equivalents of **2a** could not enhance the yields notably (**Table 2**, entries 8 and 9). Therefore, the 1:3 molar ratio of *p*-chloroaniline to ethyl pyruvate was selected as the optimal conditions. Moreover, the I_2 loading was tested from 1 mol % to 10 mol % (**Table 2**, entries 10-14 and 7). The satisfactory yield of 96% was obtained when only 3 mol % of I_2 was applied (**Table 2**, entry 12). Thus, the optimized catalyst loading was set as 3 mol % for further investigation.

Table 2

Optimization of reaction parameters[a]



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

Entry	I_2 loading	T (^oC)	Molar ratio (**1a:2a)**	Yield[b] (%)
1	I_2（10%）	30	1:6	62[c]
2	I_2（10%）	40	1:6	70
3	I_2（10%）	50	1:6	94
4	I_2（10%）	60	1:6	95
5	I_2（10%）	70	1:6	93
6	I_2（10%）	50	1:2	89
7	I_2（10%）	50	1:3	94
8	I_2（10%）	50	1:4	94
9	I_2（10%）	50	1:5	97
10	I_2（1%）	50	1:3	86
11	I_2（2%）	50	1:3	88
12	I_2（3%）	50	1:3	96
13	I_2（4%）	50	1:3	95
14	I_2（5%）	50	1:3	97

[a] Unless otherwise indicated, the reaction was carried out using **1a** (0.3 mmol), **2a** and I_2 in MeCN (0.5 mL) for 16 h.

[b] Isolated yield after silica gel chromatography.

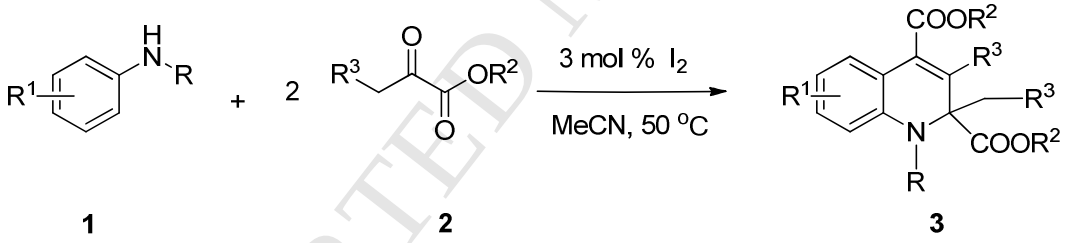
[c] The reaction time was 2 d.

In order to explore the scope and generality of this iodine-mediated cascade reaction, various aromatic amines and ketoesters were tested under the optimized conditions (**Table 3**). A wide range of substrates could effectively participate in the reaction. Aromatic amines bearing either electron-donating or electron-withdrawing groups could react with ethyl pyruvate and methyl pyruvate giving desired products. For example, good to excellent yields were obtained with non-substituted aromatic amine and substituted aromatic amines containing -Cl, -Br, -OMe, -Me, or -OH (**Table 3**, **3a**-**3g** and **3k**-**3p**). However, bearing a strong electro-withdrawing -NO_2 group, *p*-nitroaniline afforded the desired product **3h** in 97% yield in the presence of 10 mol % of I_2 at 80

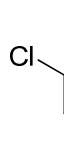
^{o}C (**Table 3**, **3h**). The substituent position of arylamine did not obviously affect the yields. For instance, both *m*- and *p*- bromoaniline gave good to excellent yields with ethyl pyruvate and methyl pyruvate (**Table 3, 3b, 3c, 3l** and **3m**). It was remarkable that 1-aminonaphthalene and indoline were successfully introduced to this reaction, and complex tricyclic dihydroquinolines could be prepared in yields of 43-75% when reacting with ethyl pyruvate and methyl pyruvate (**Table 3, 3i, 3j, 3q** and **3r**). Besides pyruvates, ethyl 2-oxohexanoate and ethyl 2-oxo-4-phenylbutyrate also could be used as α-ketoesters to react with *p*-chloroaniline, and the desired products were obtained in yields of 26% and 21% respectively, in the presence of 10 mol % of I_2 at 80 ^{o}C (**Table 3, 3s and 3t**).

Table 3

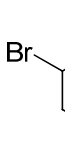
Iodine-mediated cascade reaction of various aromatic amines and α-ketoesters [a,b]



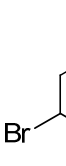
1 **2** **3**



3a 12 h (95%)

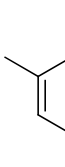


3b 19 h (98%)

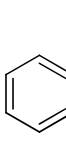


3c 12 h (95%)

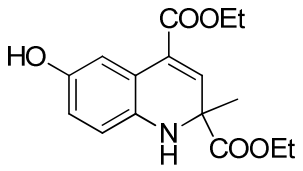
3d 19 h (91%)



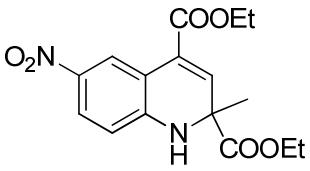
3e 12 h (98%)



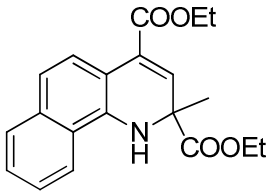
3f 19 h (70%)



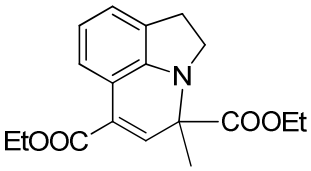
3g 19 h (66%)



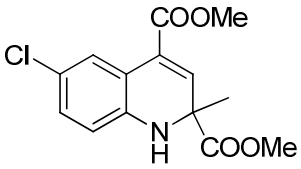
3h 19 h (20%)
16 h (97%) [c]



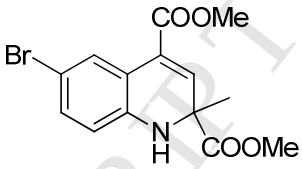
3i 12 h (44%)



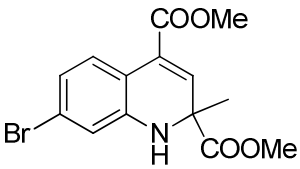
3j 12 h (43%) [d]



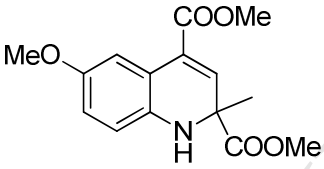
3k 12 h (85%)



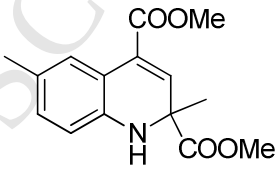
3l 12 h (88%)



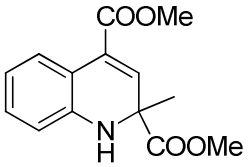
3m 13 h (93%)



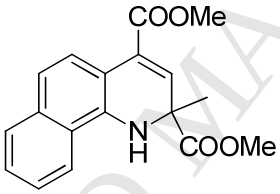
3n 19 h (58%)



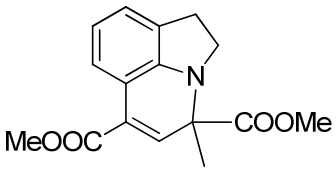
3o 12 h (94%)



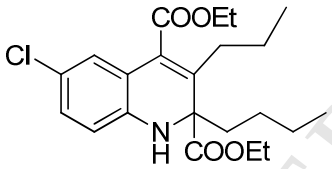
3p 13 h (97%)



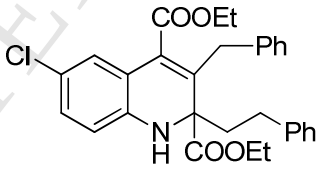
3q 19 h (75%)



3r 12 h (61%) [e]



3s 38h (26%) [c]



3t 48h (21%) [c]

[a] Unless otherwise indicated, the reaction was carried out using arylamine (0.3 mmol), pyruvate (0.9 mmol) and I_2 (3 mol %) in MeCN (0.5 mL) at 50 °C.

[b] Isolated yield after silica gel chromatography.

[c] I_2 (10 mol %); 80 °C.

[d] I_2 (10 mol %); MeCN (2.0 mL); 60 °C.

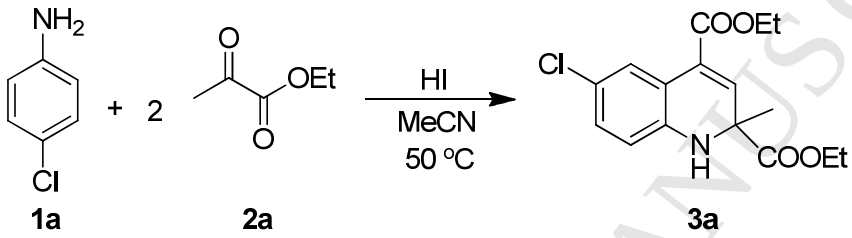
[e] MeCN (1.0 mL); 80 °C.

It is well known that acid can catalyze the cascade reaction of α-ketoesters with arylamines.[18,21] Regarding the role of iodine in the reaction, it is possible that trace amount of HI was generated during the reaction, which might be the actual catalyst for this tandem process. Thus,

some controlled experiments were performed by using different amounts of HI (**Table 4**). It can be seen that even 0.1 mol % of HI was sufficient to catalyze the model reaction of *p*-chloroaniline and ethyl pyruvate giving the product in a good yield of 86% at 50 ^{o}C after 12 h (**Table 4**, entry 2). Therefore, we speculated that the trace amount of HI generated from I_2 during the reaction may be responsible for the cascade reaction.

Table 4

Control experiments using hydrogen iodide as a catalyst [a]



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

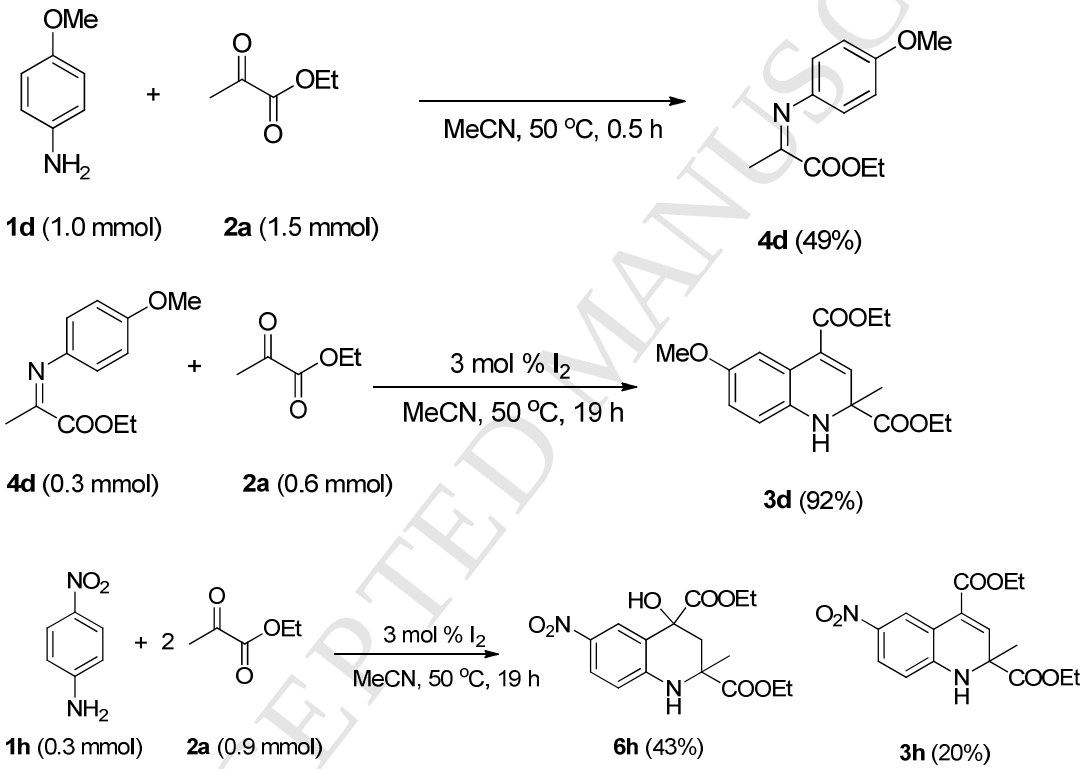
Entry	HI loading (mol %)	Yield[b] (%)
1	0	0
2	0.1	86
3	0.5	95
4	1	95
5	2	97
6	3	96

[a] The reaction was carried out using **1a** (0.3 mmol), **2a** (0.9 mmol) in MeCN (0.5 mL) at 50 ^{o}C for 12 h.

[b] Isolated yield after silica gel chromatography.

Finally, based on the previous reports[18-21] and some control experiments, we inferred that the cascade reaction may be catalyzed by trace amount of HI generated from I_2 during the reaction, and this tandem process followed a reaction pathway similar to Brønsted acid-catalyzed cascade reaction of α-ketoesters with arylamines proposed by Ji et al. [18] The process includes the formation of intermediate imine, the Mannich reaction between α-ketoester and the imine**,** the intramolecular aryl C(sp^2)-H bond functionalization, and the elimination of water. The formation of intermediate imine could be confirmed by isolating the imine **4d** from control experiment in which **1d** reacted

with **2a** in the absence of catalyst (**Scheme 2**). And the reaction pathway through intermediate imine could be further verified by the control experiment in which imine **4d** instead of same equivalent of arylamine **1d** and pyruvate **2a** was used to react directly with another pyruvate **2a** giving the desired product **3d** (**Scheme 2**). Moreover, the formation of un-dehydrated intermediate was proved by isolating **6h** from the reaction of **1h** with **2a** under the optimized conditions (**Scheme 2**).



Scheme 2 Control experiments.

Yields refer to isolated products after silica gel chromatography.

3. Conclusion

An economical and environmentally benign iodine-mediated cascade reaction between α-ketoesters and aromatic amines to prepare polysubstituted 1,2-dihydroquinolines was developed under mild conditions. A series of substituted dihydroquinolines including complex tricyclic dihydroquinolines could be conveniently obtained from simple and readily available starting

materials. This protocol avoids the use of exorbitant metallic reagents, strong corrosive acids, and complex catalysts prepared by multi-step synthesis. In the present method only 3 mol % of iodine could promote the reaction effectively, and a wide range of arylamines could participate in this cascade reaction with ethyl pyruvate or methyl pyruvate. Besides pyruvates, α-ketoesters ethyl 2-oxohexanoate and ethyl 2-oxo-4-phenylbutyrate also could be used in this reaction. These advantages provide a potential possibility for application in industry and academia.

4. Experimental section

4.1 General

The NMR spectra were recorded with TMS as the internal standard in $CDCl_3$ on a Bruker 300 MHz instrument at room temperature. All reactions were monitored by thin-layer chromatography (TLC) with Haiyang GF254 silica gel plates. Flash column chromatography was carried out using 200-300 mesh silica gel at increased pressure. All chemical reagents and solvents were purchased from commercial vendors. They were used without any further purification.

4.2 Experiments

General procedure for the iodine-mediated cascade reaction of α-ketoesters and arylamines:

A round-bottomed flask was charged with arylamine (0.3 mmol), pyruvate (0.9 mmol), iodine (3 mol %) and MeCN (0.50 mL). The resultant mixture was stirred for a specified time at 50 °C. Upon completion of the reaction (monitored by TLC), the solvents were removed by rotary evaporation and the mixture was purified by column chromatography, eluted with petroleum ether and ethyl acetate to afford the desired product.

4.3 Characterization Data

4.3.1 Diethyl 6-chloro-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3a**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.55 (s, 3H), 4.11-4.26 (m, 2H), 4.30-4.37 (m, 2H), 4.53 (brs, 1H), 6.56 (d, J = 8.5 Hz, 1H), 6.74 (s, 1H), 7.02 (dd, J = 2.4, 8.5 Hz, 1H), 7.86 (d, J = 2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2, 27.2, 58.5, 61.2, 61.9, 115.2, 117.6, 123.2, 126.3, 127.4, 129.2, 133.9, 141.1, 165.2, 173.5. [18-20]

4.3.2 Diethyl 6-bromo-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3b**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.54 (s, 3H), 4.13-4.25 (m, 2H), 4.29-4.36 (m, 2H), 4.58 (brs, 1H), 6.52 (d, J = 8.5 Hz, 1H), 6.72 (s, 1H), 7.15 (dd, J = 2.0, 8.5 Hz, 1H), 7.99 (d, J = 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2, 27.2, 58.5, 61.2, 61.9, 110.3, 115.6, 118.1, 127.2, 129.1, 132.0, 133.8, 141.6, 165.2, 173.4. [20]

4.3.3 Diethyl 7-bromo-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3c**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.53 (s, 3H), 4.13-4.26 (m, 2H), 4.27-4.34 (m, 2H), 4.63 (brs, 1H), 6.68 (d, J = 1.3 Hz, 1H), 6.77 (d, J = 1.8 Hz, 1H), 6.80 (dd, J = 1.9, 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2, 27.4, 58.6, 61.1, 62.0, 115.3, 116.7, 121.3, 123.2, 127.6, 127.9, 132.8, 143.8, 165.4, 173.4. [18,19]

4.3.4 Diethyl 6-methoxy-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3d**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.54 (s, 3H), 3.75 (s, 1H), 4.11-4.25 (m, 2H), 4.29-4.37 (m, 2H), 4.38 (brs, 1H), 6.60 (d, J = 8.6 Hz, 1H), 6.71 (dd, J

= 2.7, 8.7 Hz, 1H), 6.75 (s, 1H), 7.49 (d, *J* = 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2, 26.7, 55.6, 58.5, 61.0, 61.7, 111.4, 115.1, 116.2, 117.5, 128.1, 134.1, 136.7, 152.5, 165.7, 174.1. [18-20]

4.3.5 Diethyl 2,6-dimethyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3e**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.53 (s, 3H), 2.23 (s, 3H), 4.11-4.24 (m, 2H), 4.29-4.36 (m, 2H), 4.43 (brs, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.65 (s, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2, 20.7, 27.0, 58.4, 60.9, 61.7, 114.2, 116.6, 126.7, 127.7, 128.4, 130.1, 132.7, 140.3, 165.9, 174.0. [19,20]

4.3.6 Diethyl 2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3f**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.47 (s, 3H), 4.05-4.18 (m, 2H), 4.22-4.29 (m, 2H), 4.46 (brs, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 6.59 (s, 1H), 6.65 (t, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.4 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2, 27.3, 58.4, 61.0, 61.8, 114.2, 116.5, 118.5, 126.4, 128.4, 129.5, 132.5, 142.6, 165.8, 173.9. [18-20]

4.3.7 Diethyl 6-hydroxy-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3g**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.54 (s, 3H), 4.11-4.24 (m, 2H), 4.27-4.33 (m, 2H), 5.67 (brs, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 6.63 (dd, *J* = 2.7, 8.5 Hz, 1H), 6.74 (s, 1H), 7.44 (d, *J* = 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.1, 26.6, 58.5, 61.2, 61.8, 113.2, 115.3, 116.8, 117.6, 127.9, 134.4, 136.4, 148.5, 165.8, 174.4. [18]

4.3.8 Diethyl 2-methyl-6-nitro-1,2-dihydroquinoline-2,4-dicarboxylate (**3h**). Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.60 (s, 3H),

4.17-4.29 (m, 2H), 4.32-4.39 (m, 2H), 5.35 (brs, 1H), 6.58 (d, *J* = 8.9 Hz, 1H), 6.76 (s, 1H), 7.96 (dd, *J* = 2.3, 8.9 Hz, 1H), 8.82 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.1, 28.4, 59.2, 61.6, 62.4, 113.1, 114.4, 123.4, 126.0, 126.7, 133.3, 138.9, 147.9, 164.7, 172.4. [18]

4.3.9 Diethyl 2-methyl-1,2-dihydrobenzo[h]quinoline-2,4-dicarboxylate (**3i**). Reddish brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.62 (s, 3H), 4.16-4.28 (m, 2H), 4.34-4.41 (m, 2H), 5.36 (brs, 1H), 6.68 (d, *J* = 1.6 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 7.44-7.47 (m, 2H), 7.73-7.77 (m, 1H), 7.85-7.88 (m, 1H), 7.91 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2, 27.2, 58.6, 61.1, 61.9, 111.3, 117.7, 120.0, 122.2, 124.0, 125.1, 126.4, 128.5, 129.3, 130.1, 134.2, 137.9, 166.2, 173.9. [19,20]

4.3.10 Diethyl 4-methyl-2,4-dihydro-1H-pyrrolo[3,2,1-ij]quinoline-4,6-dicarboxylate (**3j**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.56 (s, 3H), 2.88-3.09 (m, 2H), 3.43-3.52 (m, 2H), 4.06-4.13 (m, 2H), 4.20-4.28 (m, 2H), 6.35 (s, 1H), 6.50 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2, 22.6, 28.1, 47.4, 60.9, 61.4, 63.3, 112.7, 117.7, 123.5, 125.0, 126.3, 128.1, 133.3, 148.2, 165.5, 171.4. [19]

4.3.11 Dimethyl 6-chloro-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3k**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 3H), 3.74 (s, 3H), 3.86 (s, 3H), 4.58 (brs, 1H), 6.56 (d, *J* = 8.5 Hz, 1H), 6.74 (s, 1H), 7.02 (dd, *J* = 2.3, 8.5 Hz, 1H), 7.86 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 52.2, 52.9, 58.6, 115.2, 117.5, 123.3, 126.3, 127.1, 129.3, 134.0, 141.1, 165.5, 174.1. [18]

4.3.12 Dimethyl 6-bromo-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3l**). Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54 (s, 3H), 3.73 (s, 3H), 3.84 (s, 3H), 4.60 (brs, 1H), 6.50 (d, *J* = 8.5 Hz, 1H), 6.71 (s, 1H), 7.14 (dd, *J* = 2.1, 8.5 Hz, 1H), 7.97 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 52.2, 52.9, 58.5, 110.4, 115.6, 117.9, 127.0, 129.0, 132.2, 134.0, 141.5, 165.5, 174.0. [20]

4.3.13 Dimethyl 7-bromo-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3m**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 4.65 (brs, 1H), 6.70 (s, 1H), 6.78 (d, *J* = 1.8 Hz, 1H), 6.82 (dd, *J* = 1.9, 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.5, 52.1, 52.9, 58.6, 115.1, 116.7, 121.4, 123.3, 127.4, 127.9, 132.9, 143.7, 165.7, 174.0. [18,19]

4.3.14 Dimethyl 6-methoxy-2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3n**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 3H), 3.73 (s, 3H), 3.75 (s, 3H), 3.86 (s, 3H), 4.36 (brs, 1H), 6.58 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 2.8, 8.7 Hz, 1H), 6.75 (s, 1H), 7.50 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.8, 52.0, 52.7, 55.7, 58.5, 111.5, 115.1, 116.2, 117.4, 127.8, 134.2, 136.6, 152.5, 166.0, 174.7. [18]

4.3.15 Dimethyl 2,6-dimethyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3o**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54 (s, 3H), 2.23 (s, 3H), 3.72 (s, 3H), 3.85 (s, 3H), 4.44 (brs, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.66 (s, 1H), 6.90 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 27.1, 52.0, 52.7, 58.4, 114.2, 116.4, 126.7, 127.8, 128.2, 130.3, 132.9, 140.2, 166.2, 174.6. [19,20]

4.3.16 Dimethyl 2-methyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3p**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 3H), 3.72 (s, 3H), 3.85 (s, 3H), 4.57 (brs, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.66 (s, 1H), 6.72 (t, *J* = 7.4Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.79 (dd, *J* = 0.9, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 52.0, 52.7, 58.5, 114.2, 116.3, 118.6, 126.4, 128.2, 129.6, 132.7, 142.6, 166.1, 174.4. [18]

4.3.17 Dimethyl 2-methyl-1,2-dihydrobenzo[h]quinoline-2,4-dicarboxylate (**3q**). Reddish brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (s, 3H), 3.77 (s, 3H), 3.90 (s, 3H), 5.36 (brs, 1H), 6.70 (d, *J* = 1.5 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.44-7.47 (m, 2H), 7.74-7.78 (m, 1H), 7.85-7.89 (m, 1H), 7.90 (d, *J* = 8.8Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 52.1, 52.9, 58.6, 111.1, 117.8, 120.0, 122.2, 124.0, 125.2, 126.4, 128.6, 129.0, 130.3, 134.2, 137.9, 166.5, 174.5. [19,10]

4.18 Dimethyl 4-methyl-2,4-dihydro-1H-pyrrolo[3,2,1-ij]quinoline-4,6-dicarboxylate (**3r**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (s, 3H), 2.98-3.14 (m, 2H), 3.50-3.62 (m, 2H), 3.71 (s, 3H), 3.84 (s, 3H), 6.42 (s, 1H), 6.57 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8, 28.1, 47.4, 51.9, 52.5, 63.3, 112.5, 117.8, 123.5, 125.2, 126.4, 127.8, 133.3, 148.0, 165.8, 171.8. [19]

4.3.19 Diethyl 2-butyl-6-chloro-3-propyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3s**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87-0.95 (m, 6H), 1.23-1.44 (m, 10H), 1.44-1.55 (m, 2H), 1.88-1.93 (m, 2H), 2.20-2.37 (m, 2H), 4.12-4.23 (m, 2H), 4.31-4.41 (m, 3H), 6.52 (d, *J* = 4.2 Hz, 1H), 6.89-7.00 (m, 1H), 7.24-7.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.0, 14.2, 14.6, 22.7, 23.3, 25.8, 32.9, 36.0, 61.2, 61.7, 64,8, 114.7, 119.2, 124.1, 122.9, 128.5, 129.0, 136.0, 140.1, 167.9, 172.8. [19]

4.3.20 Diethyl 3-benzyl-6-chloro-2-phenethyl-1,2-dihydroquinoline-2,4-dicarboxylate (**3t**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ =1.11 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 2.13-2.21 (m, 2H), 2.52-2.57 (m, 2H), 3.71-3.84 (m, 4H), 4.12-4.25 (m, 2H), 4.42 (brs, 1H), 6.48 (d, J = 4.2 Hz, 1H), 6.99-7.01 (m, 3H), 7.15-7.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 13.9, 30.0, 36.2, 37.8, 61.4, 61.9, 64.9, 115.2, 118.9, 119.7, 121.9, 123.1, 124.5, 126.1, 126.4, 128.2, 128.2, 128.4, 128.7, 129.1, 131.1, 132.4, 137.8, 140.0, 140.8, 167.6, 171.8. [19]

4.3.21 (Z)-ethyl 2-((4-methoxyphenyl)imino)propanoate (**4d**). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, J = 7.1 Hz, 3H), 2.14 (s, 3H), 3.81 (s, 3H), 4.36-4.43 (m, 2H), 6.80 (d, J = 28.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 21.4, 62.0, 68.8, 105.7, 118.6, 128.2, 134.4, 154.5, 158.6, 167.7, 171.6. [19]

4.3.22 Diethyl 4-hydroxy-2-methyl-6-nitro-1,2,3,4-tetrahydroquinoline-2,4-dicarboxylate (**6h**). Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.60 (s, 3H), 2.36 (d, J = 13.8 Hz, 1H), 2.74 (d, J = 15.2 Hz, 1H), 3.70 (brs, 1H), 4.12-4.19 (m, 2H), 4.30-4.37 (m, 2H), 5.36 (brs, 1H), 6.67 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 2.3 Hz, 1H), 8.00 (dd, J = 2.4, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 27.1, 41.2, 55.6, 61.7, 63.0, 72.0, 114.6, 119.8, 124.2, 125.9, 138.4, 148.9, 174.2. [19]

Acknowledgements

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Graphical Abstract

Highly Efficient Synthesis of Polysubstituted 1,2-Dihydroquinolines via Cascade Reaction of α-Ketoesters with Arylamines Mediated by Iodine

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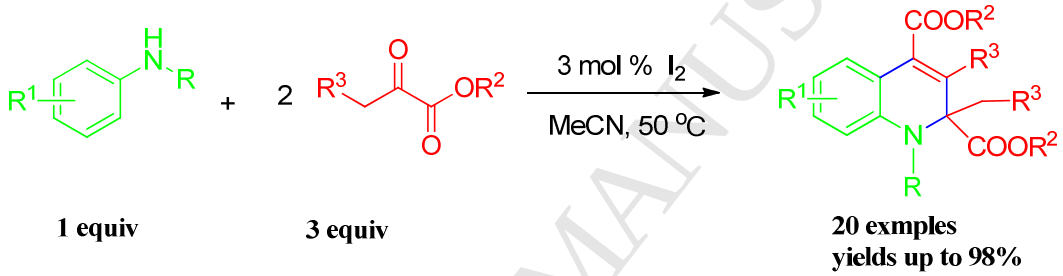

1 equiv **3 equiv** **20 exmples yields up to 98%**

Supporting Information

Highly Efficient Synthesis of Polysubstituted 1,2-Dihydroquinolines via Cascade Reaction of α-Ketoesters with Arylamines Mediated by Iodine

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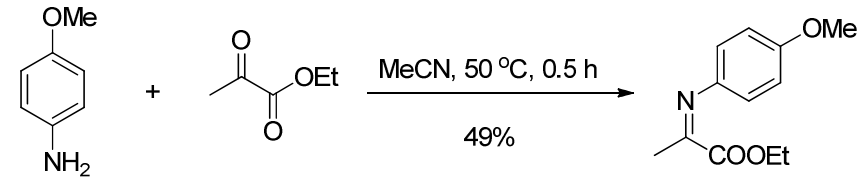
Table of Contents

1. Experiments

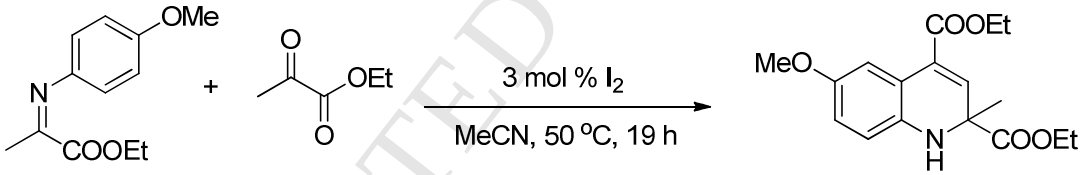
1.1 The reaction of 1d and 2a in the absence of catalyst:



1d (1.0 mmol) **2a** (1.5 mmol) **4d**

A round-bottomed flask was charged with *p*-methoxyaniline **1d** (1.0 mmol), ethyl pyruvate **2a** (1.5 mmol), and MeCN (1.5 mL). The resultant mixture was stirred at 50 °C for 0.5 h. Then the solvents were removed by rotary evaporation to provide a crude product, which was purified by flash chromatography on aluminium oxide (petroleum ether/ethyl acetate, 15:1) to give imine **4d** (109 mg, 49%) as yellow oil.

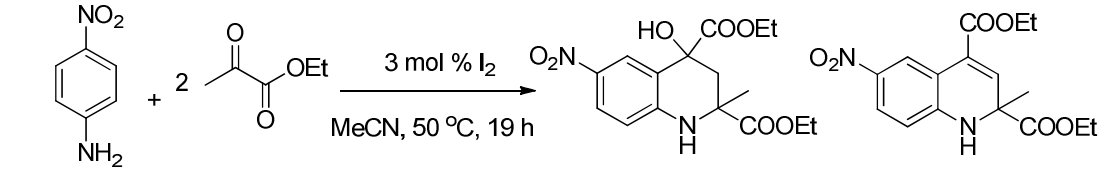
1.2 The reaction of imine 4d with 2a:



4d (0.3 mmol) **2a** (0.6 mmol) **3d** (92%)

A round-bottomed flask was charged with imine **4d** (0.3 mmol), ethyl pyruvate **2a** (0.6 mmol), iodine (3 mol %), and MeCN (0.5 mL). The reaction mixture was stirred at 50 °C for 19 h. After completion of the reaction, the solvents were removed by rotary evaporation to provide a crude product, which was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) to give the desired product **3d** (92%) as yellow oil.

1.3 The reaction of *p*-nitroaniline 1h with ethyl pyruvate 2a:



1h (0.3 mmol) **2a** (0.9 mmol) **6h** (43%) **3h** (20%)

A round-bottomed flask was charged with *p*-nitroaniline **1h** (0.3 mmol), ethyl pyruvate **2a** (0.9 mmol), iodine (3 mol %) and MeCN (0.50 mL). The resultant mixture was stirred at 50 °C for 18 h. The mixture was purified by column chromatography, eluted with petroleum ether and ethyl acetate (5:1-3:1) to afford **6h** (45 mg, 43%) and **3h** (20 mg, 20%).

1.4 The time course of the iodine-mediated cascade reaction

The time course of the iodine-mediated cascade reaction was investigated (**Figure S1**). The yield increased as the reaction time prolonged and reached its peak (95%) at 12 h.

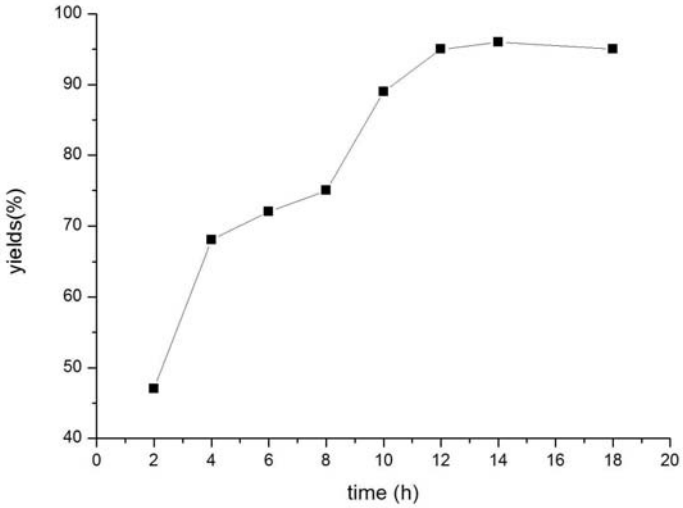
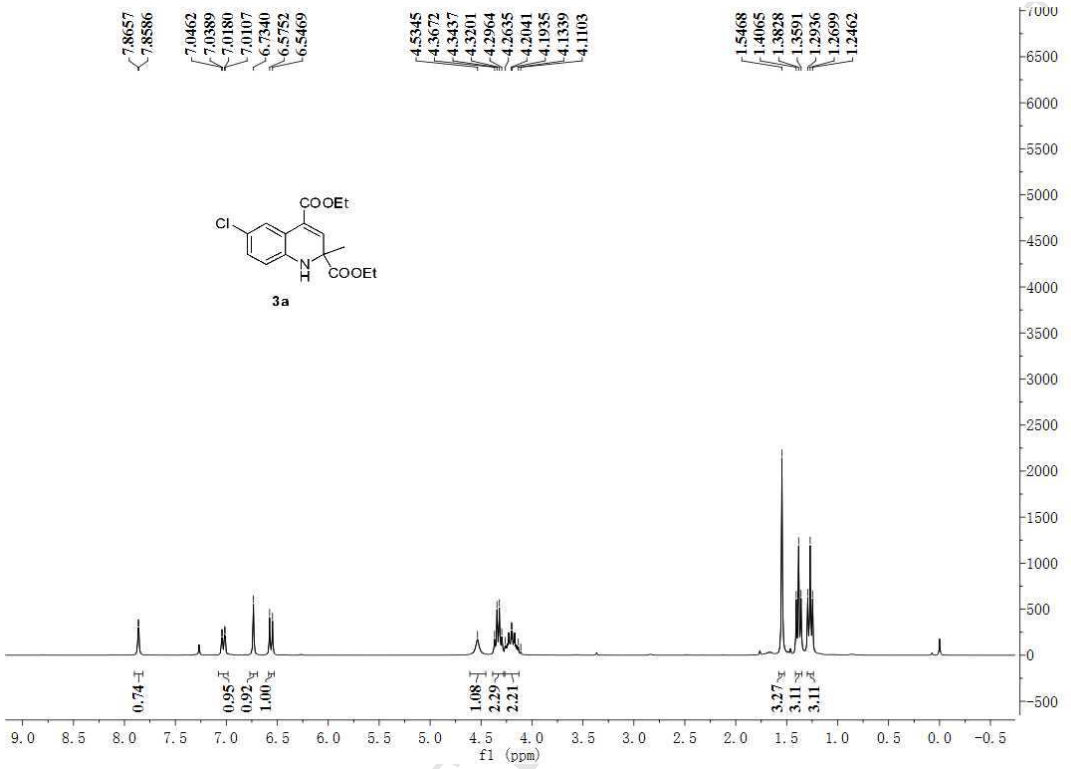
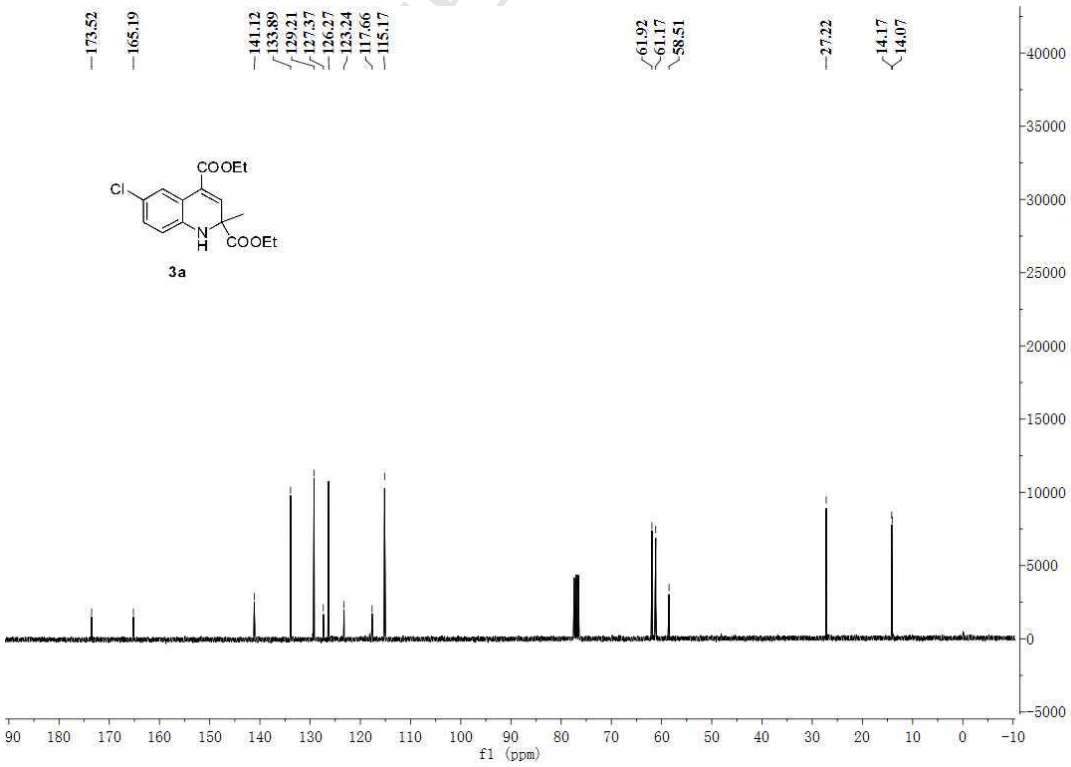


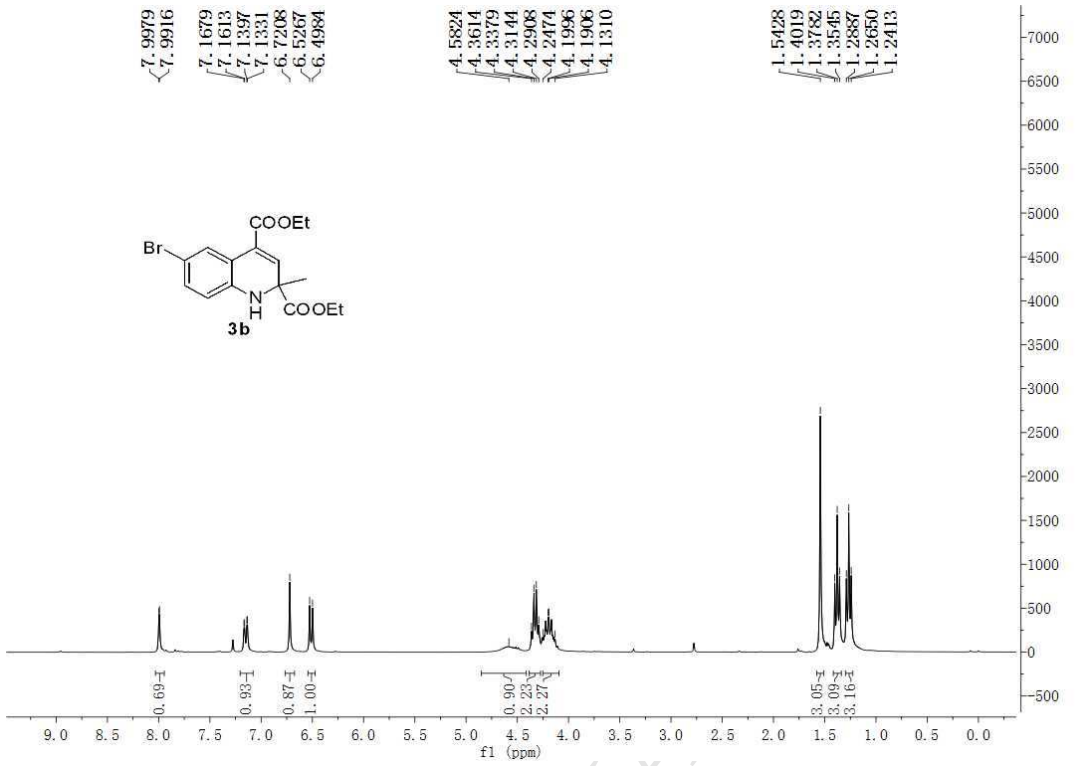
Figure S1. Time course of the reaction.[a]

[a] The reaction was carried out using *p*-chloroaniline (0.3 mmol), ethyl pyruvate (0.9 mmol) and I_2 (3 mol %) in MeCN (0.5 mL) at 50 °C. The yield refers to isolated product after silica gel chromatography.

2. The ^{1}H and ^{13}C NMR Spectra of the Products



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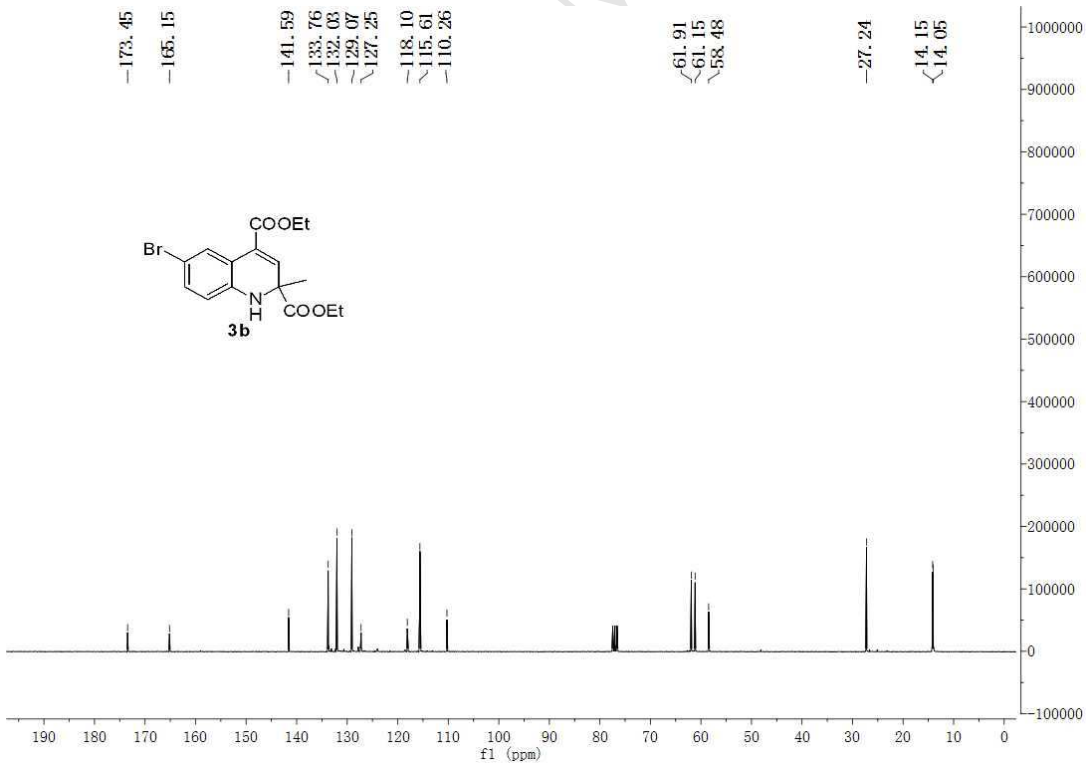
7.1679
7.1613
7.1397
7.1331
6.7208
6.5267
6.4984
4.5824
4.3614
4.3379
4.3144
4.2908
4.2474
4.1996
4.1906
4.1310
1.5428
1.4019
1.3782
1.3545
1.2887
1.2650
1.2413
COOEt
Br
N
H
COOEt
3b
0.69
0.93
0.87
1.00
0.90
2.23
2.27
3.05
3.09
3.16
f1 (ppm)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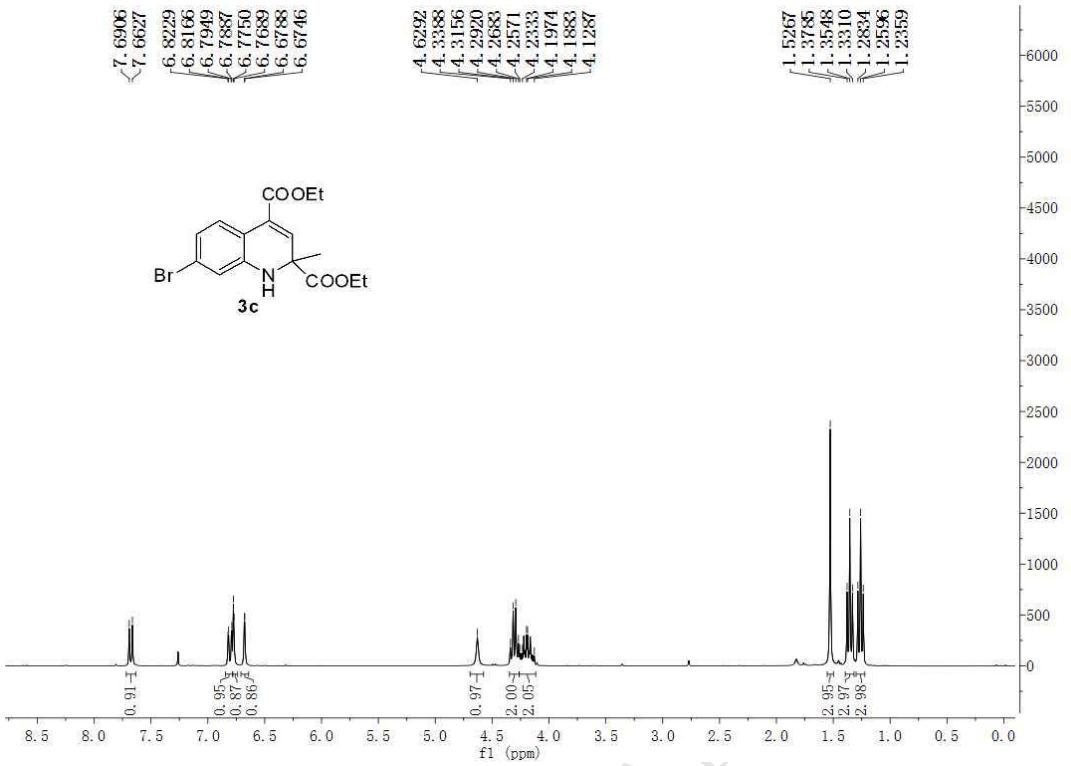
141.59
133.76
132.03
129.07
127.25
118.10
115.61
110.26
61.91
61.15
58.48
27.24
14.15
14.05
COOEt
Br
N
H
COOEt
3b
f1 (ppm)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6.6746
4.6292
4.3388
4.3156
4.2920
4.2683
4.2571
4.2333
4.1974
4.1883
4.1287
1.5267
1.3785
1.3548
1.3310
1.2834
1.2596
1.2359
COOEt
Br
N
H
COOEt
3c
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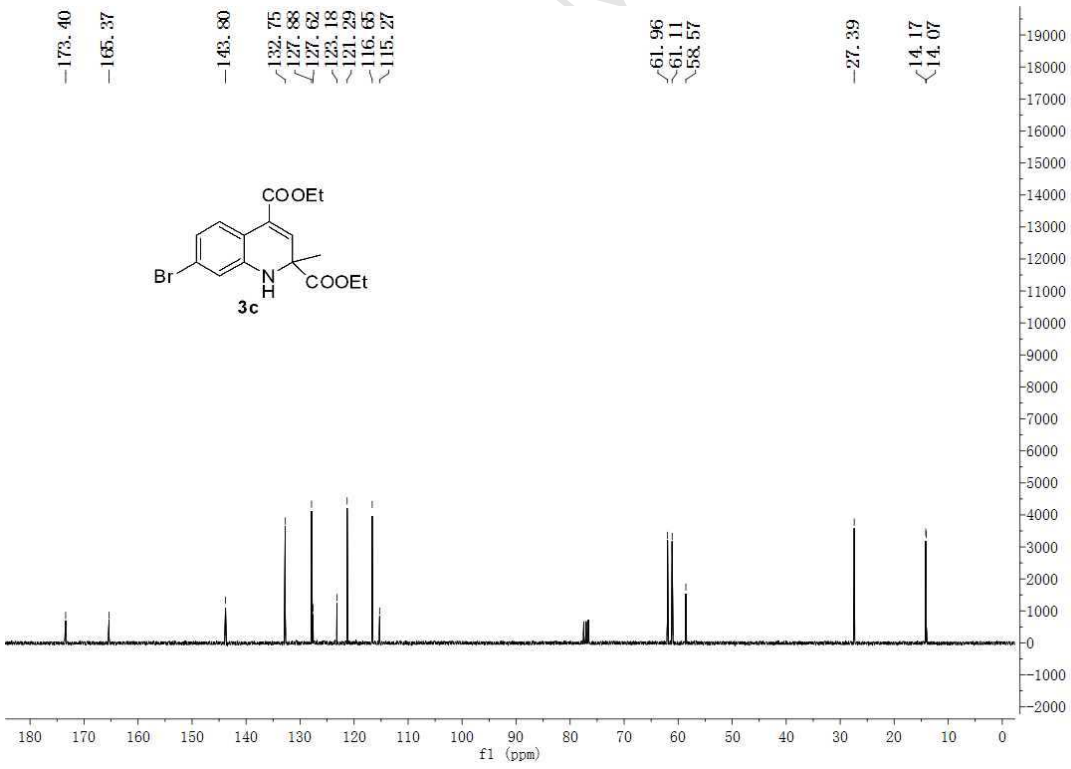
0.95
0.87
0.86
0.97
2.00
2.05
2.95
2.97
2.98
f1 (ppm)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127.62
123.18
121.29
116.65
115.27
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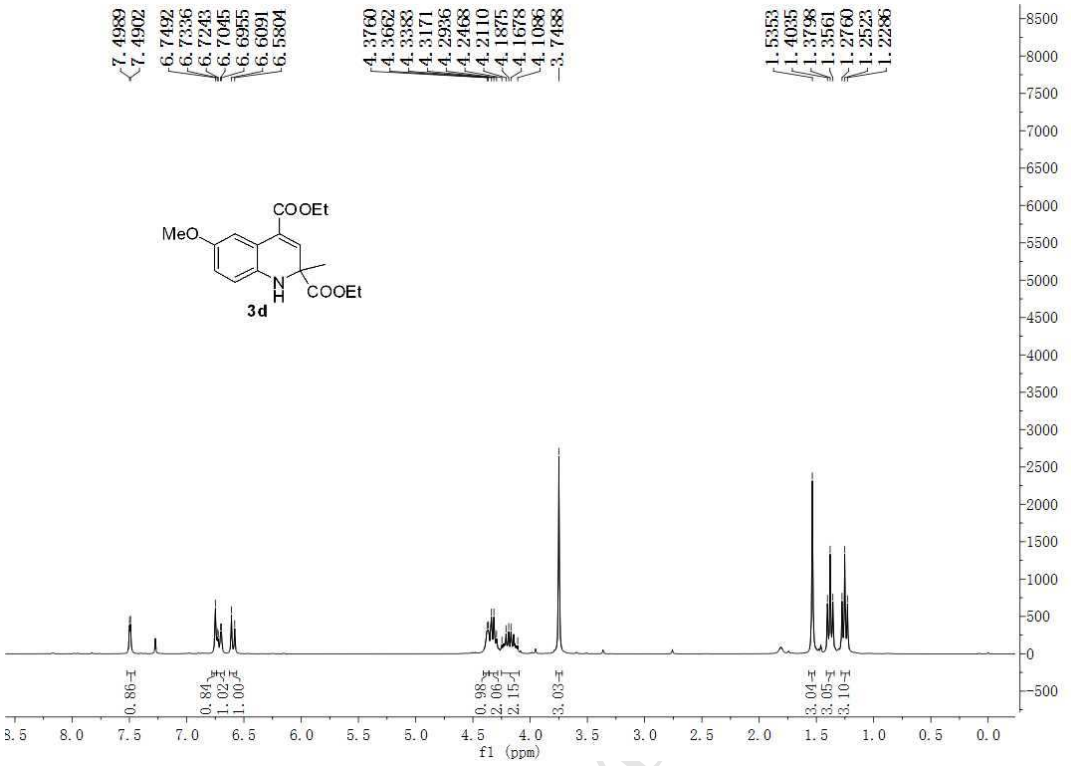
58.57
27.39
14.17
14.07
COOEt
Br
N
H
COOEt
3c
f1 (ppm)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6.7045
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6.6091
6.5804
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4.3662
4.3383
4.3171
4.2936
4.2468
4.2110
4.1875
4.1678
4.1086
3.7488
1.5353
1.4035
1.3798
1.3561
1.2760
1.2523
1.2286
COOEt
MeO
N
H
COOEt
3d
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1.00
0.98
2.06
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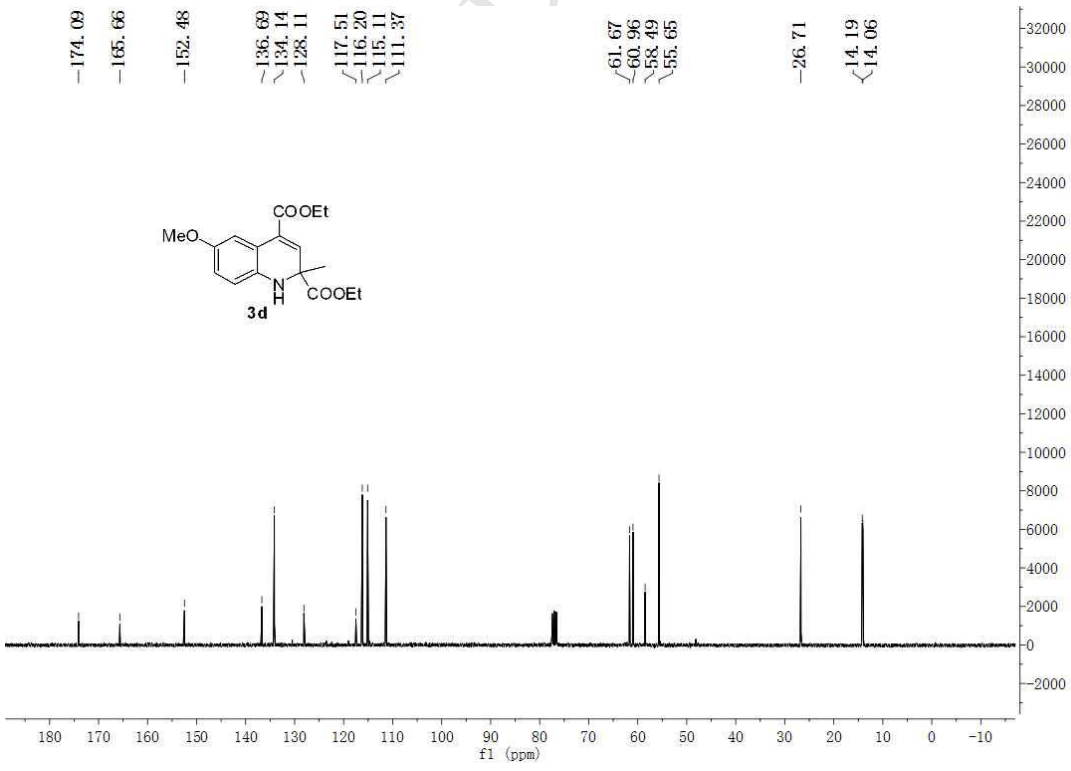
3.03
3.04
3.05
3.10
f1 (ppm)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128.11
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116.20
115.11
111.37
61.67
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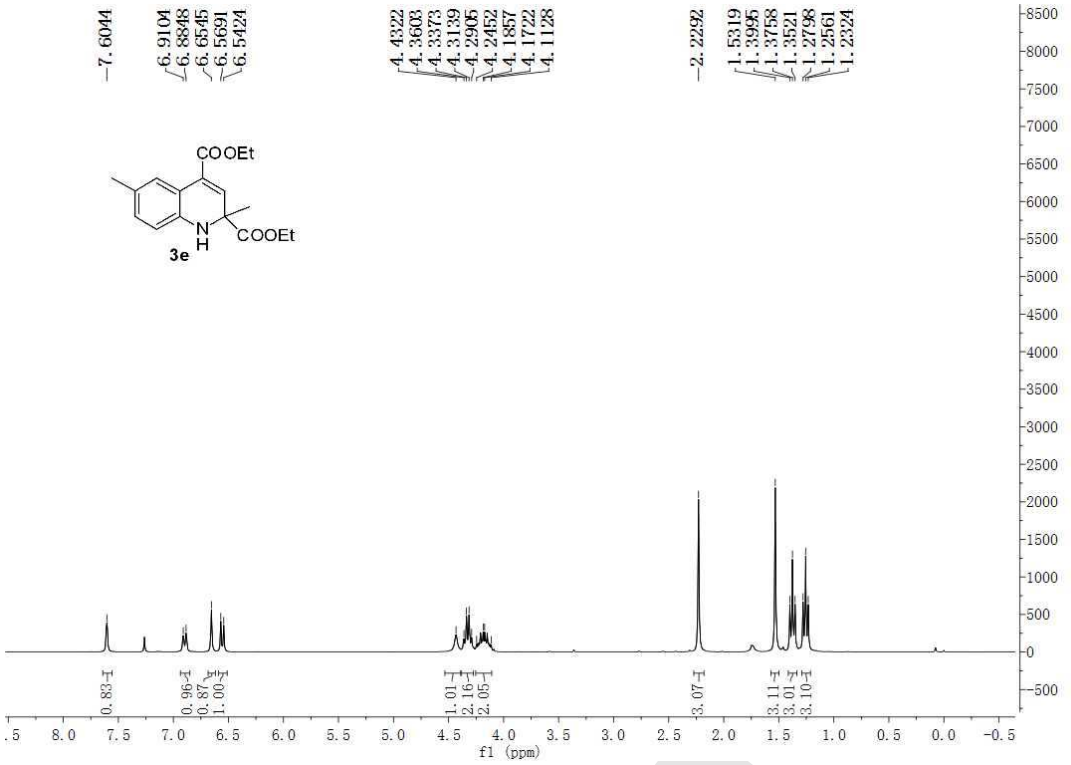
58.49
55.65
26.71
14.19
14.06
COOEt
MeO
N
H
COOEt
3d
f1 (ppm)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4.3373
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4.2905
4.2452
4.1857
4.1722
4.1128
2.2292
1.5319
1.3995
1.3758
1.3521
1.2798
1.2561
1.2324
COOEt
COOEt
N
H
3e
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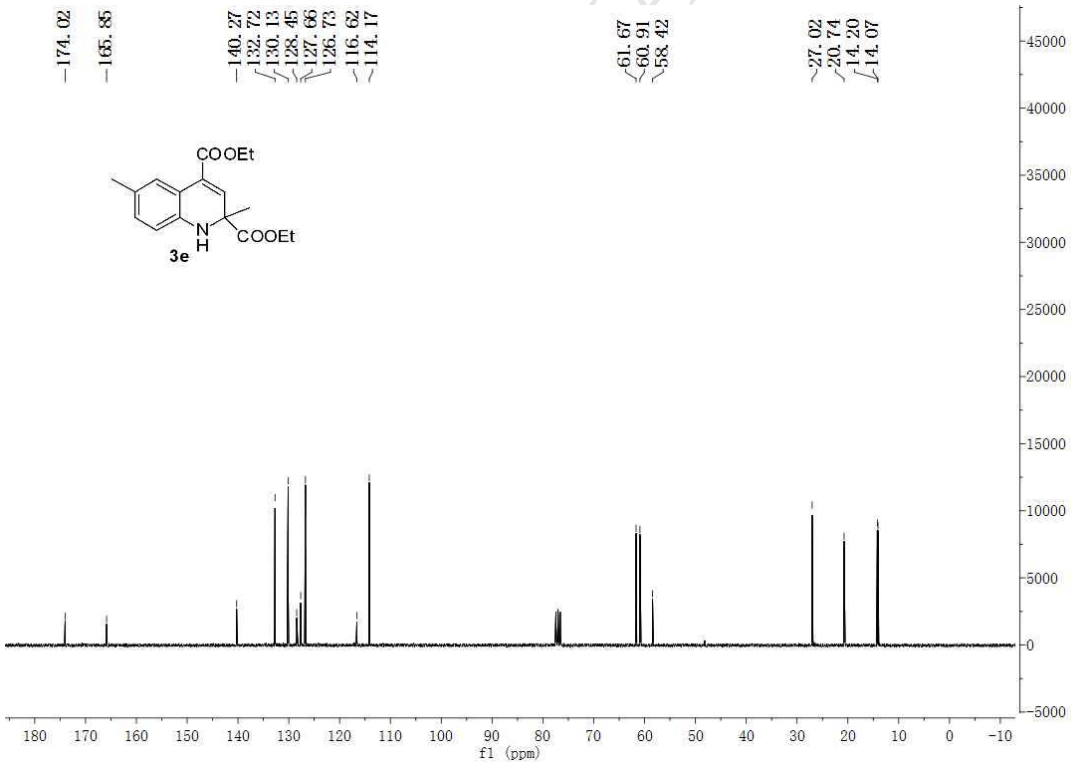
1.01
2.16
2.05
3.07
3.11
3.01
3.10
f1 (ppm)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128.45
127.66
126.73
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114.17
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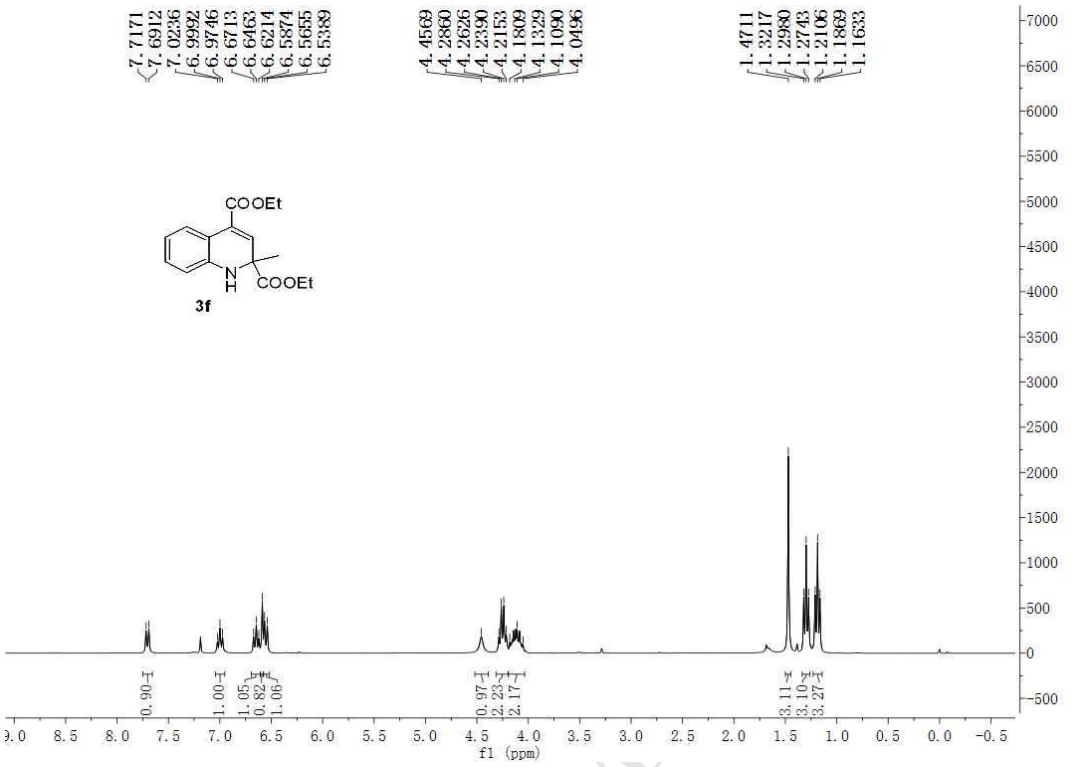
14.20
14.07
COOEt
COOEt
N
H
3e
f1 (ppm)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6.5389
4.4569
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4.2626
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4.2153
4.1809
4.1329
4.1090
4.0496
1.4711
1.3217
1.2980
1.2743
1.2106
1.1869
1.1633
COOEt
COOEt
3f
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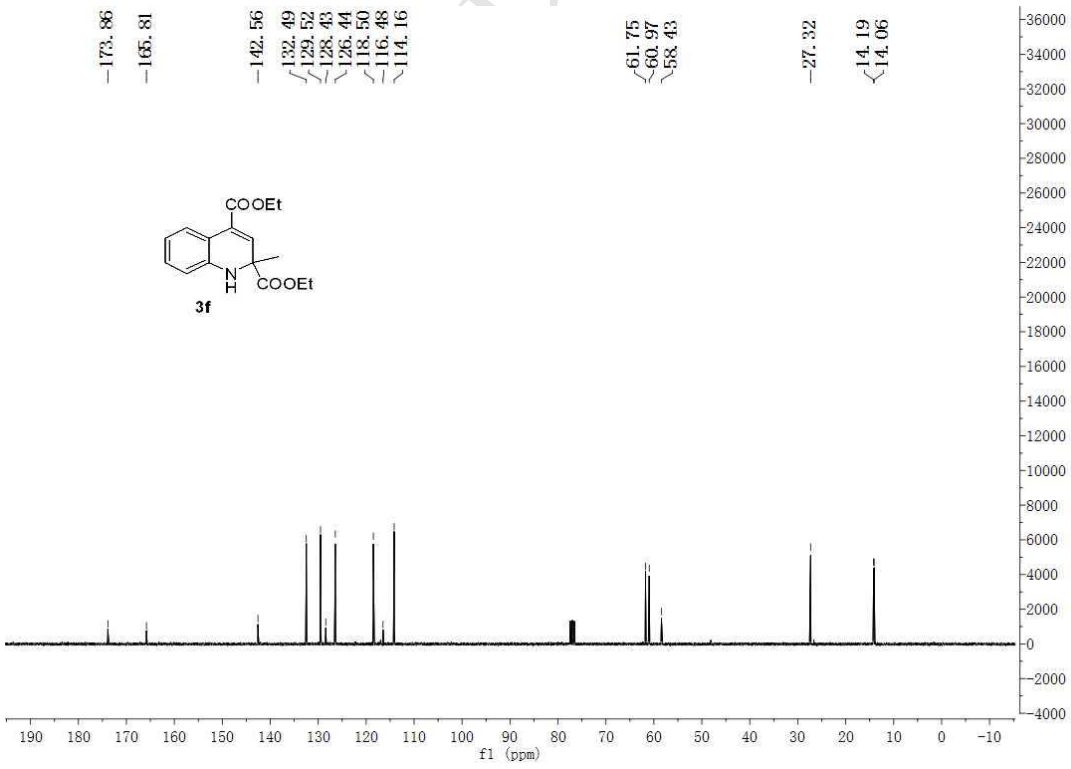
0.82
1.06
0.97
2.23
2.17
3.11
3.10
3.27
f1 (ppm)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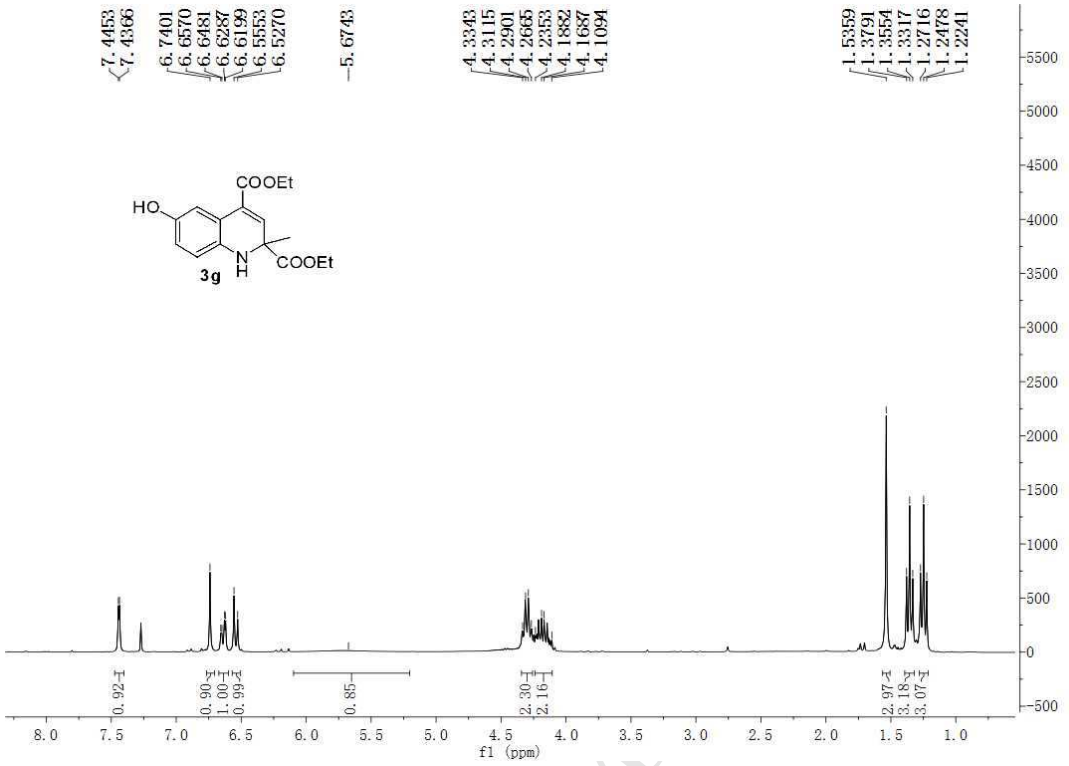
58.43
27.32
14.19
14.06
COOEt
COOEt
3f
f1 (ppm)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6.5270
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4.3115
4.2901
4.2665
4.2353
4.1882
4.1687
4.1094
1.5359
1.3791
1.3554
1.3317
1.2716
1.2478
1.2241
COOEt
HO
N
H
COOEt
3g
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0.99
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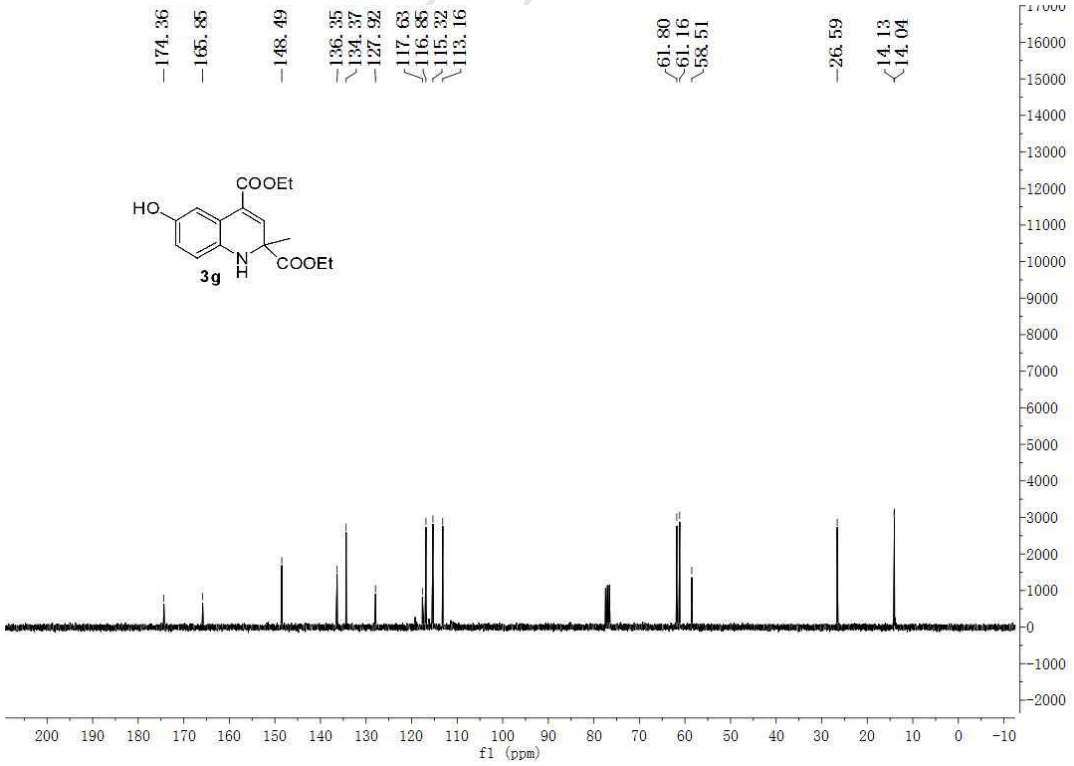
2.97
3.18
3.07
f1 (ppm)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117.63
116.85
115.32
113.16
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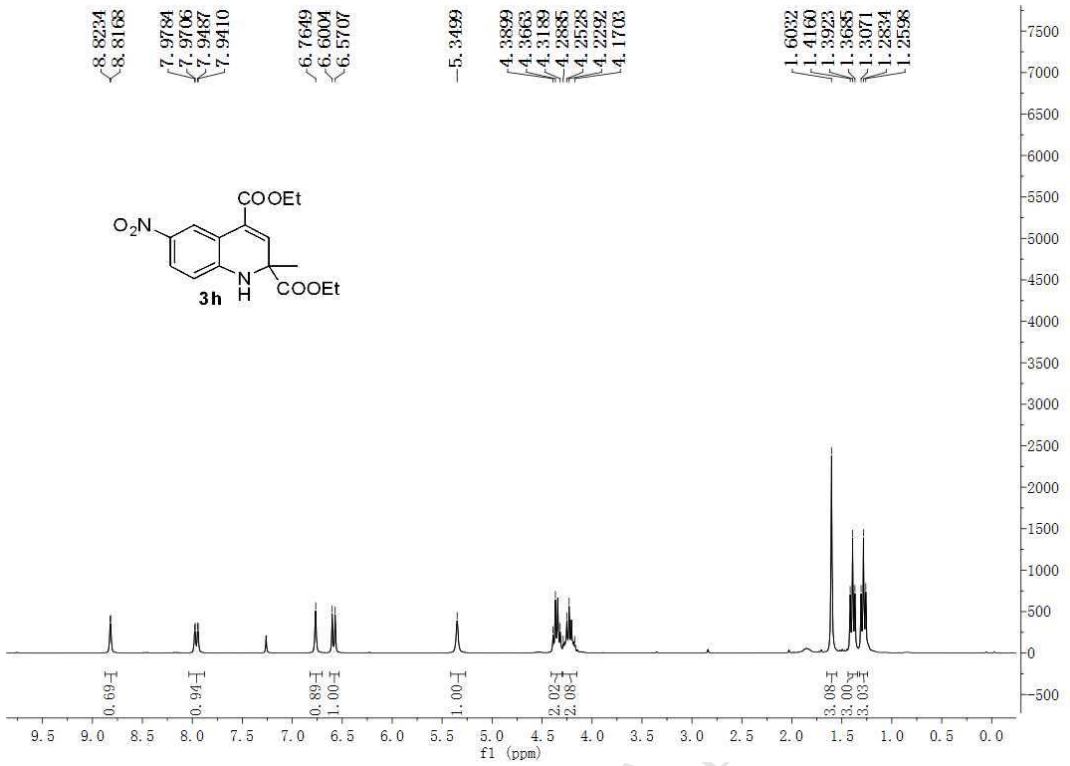
58.51
26.59
14.13
14.04
COOEt
HO
N
H
COOEt
3g
f1 (ppm)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7.9410
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4.3899
4.3663
4.3189
4.2885
4.2528
4.2292
4.1703
1.6032
1.4160
1.3923
1.3685
1.3071
1.2834
1.2598
COOEt
O2N
N
H
COOEt
3h
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0.89
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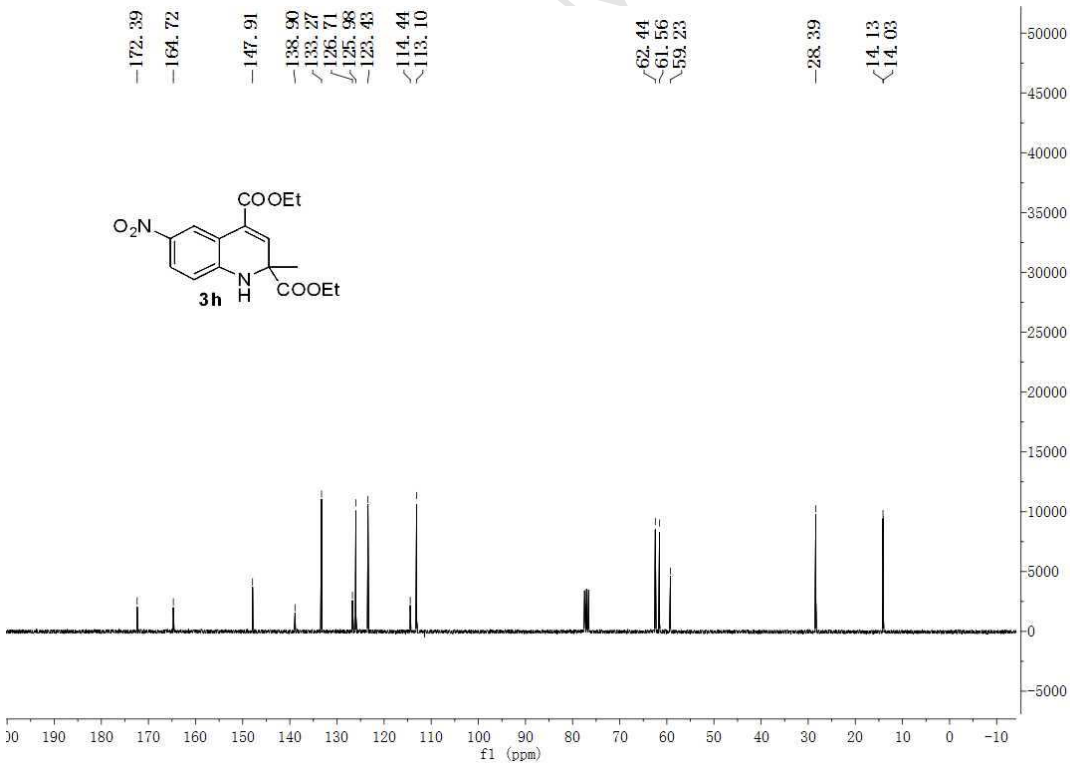
1.00
2.02
2.08
3.08
3.00
3.03
f1 (ppm)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113.10
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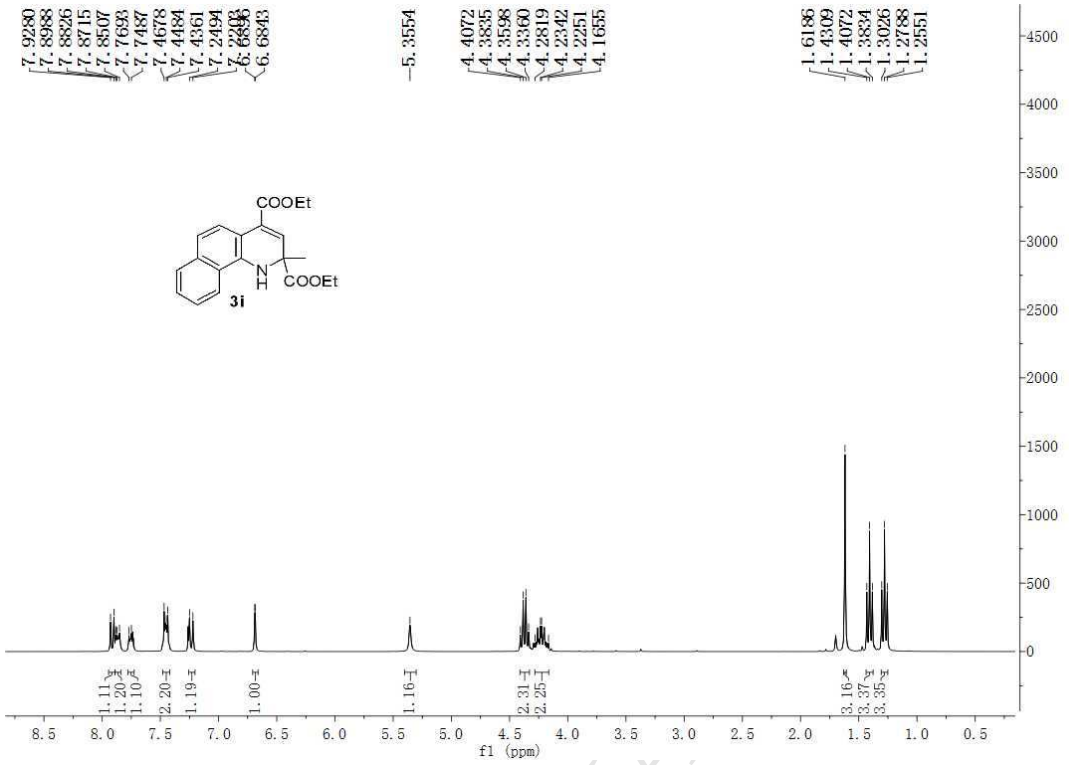
28.39
14.13
14.03
COOEt
O2N
N
H
COOEt
3h
f1 (ppm)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4.2819
4.2342
4.2251
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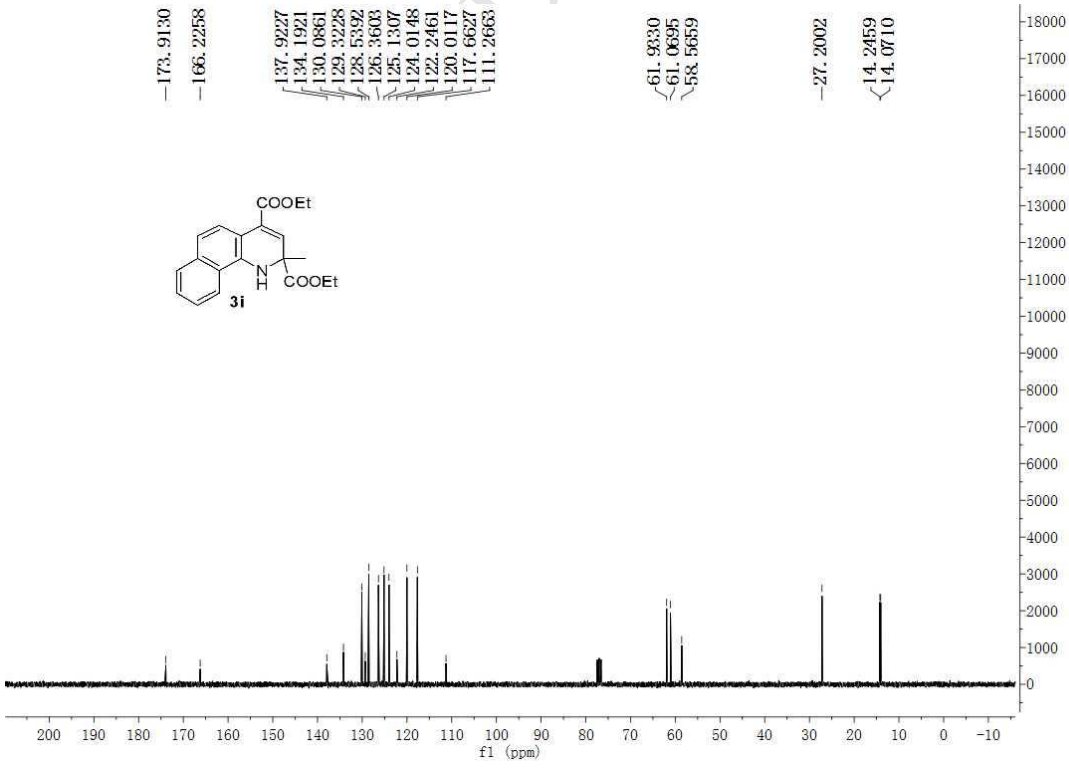
COOEt
3i
f1 (ppm)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122.2461
120.0117
117.6627
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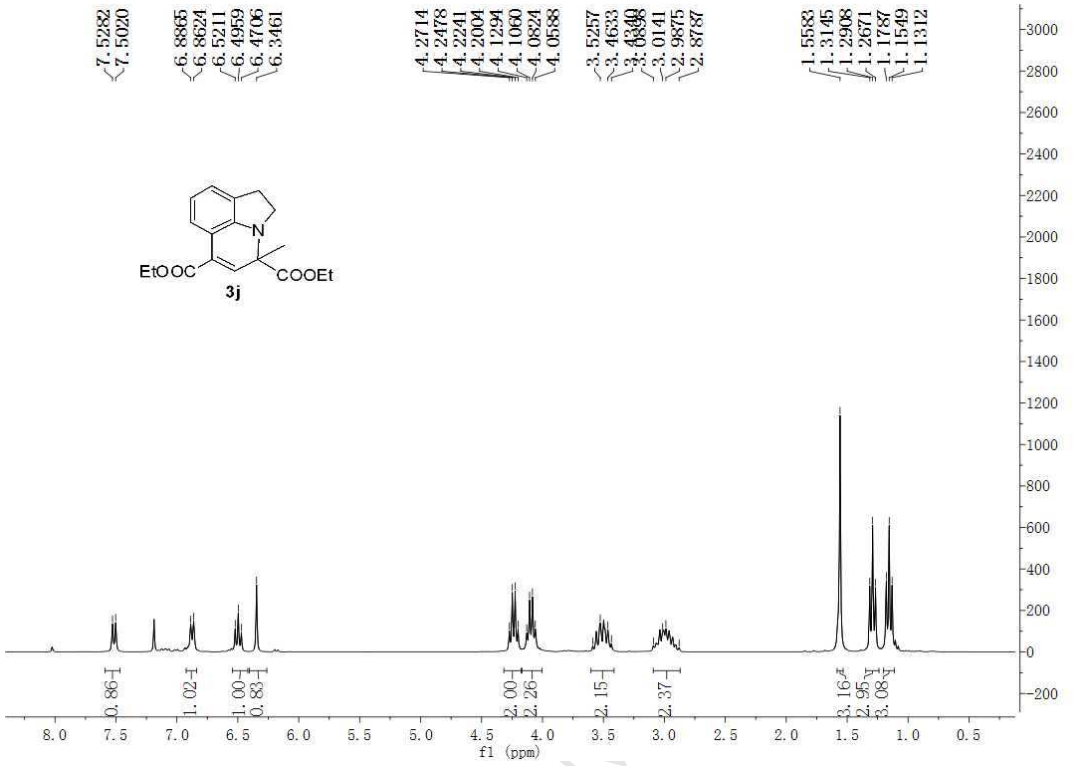
3i
f1 (ppm)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2.8787
1.5583
1.3145
1.2908
1.2671
1.1787
1.1549
1.1312
EtOOC
COOEt
3j
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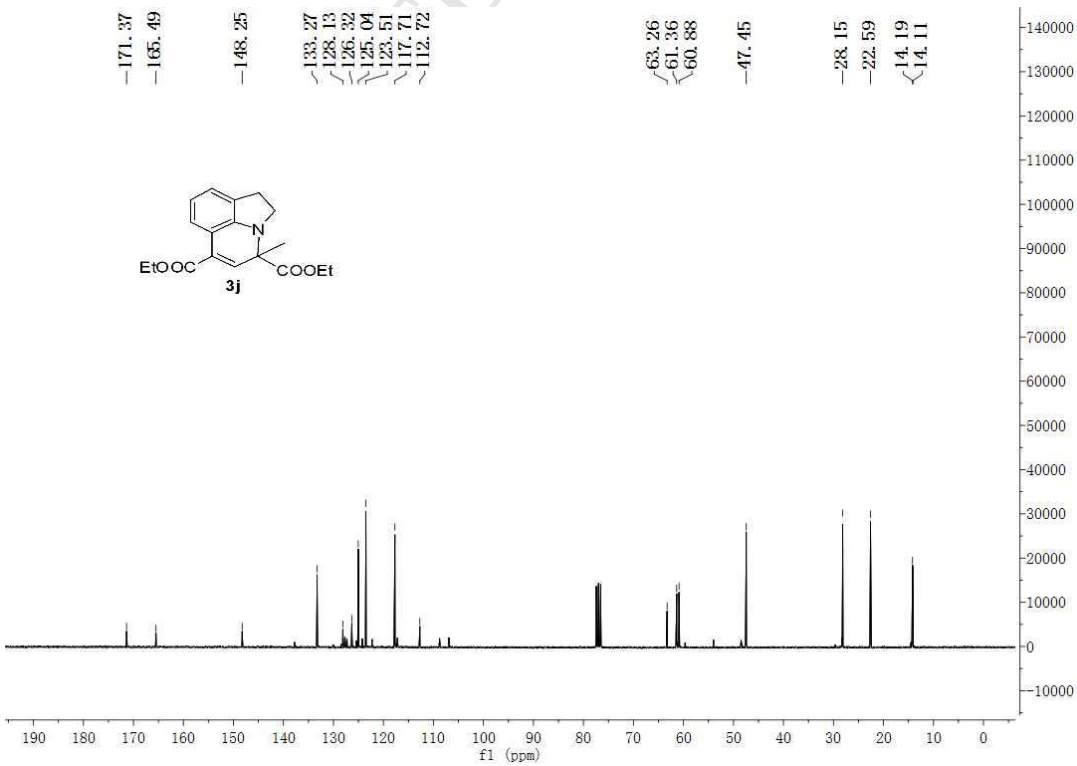
3.08
f1 (ppm)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112.72
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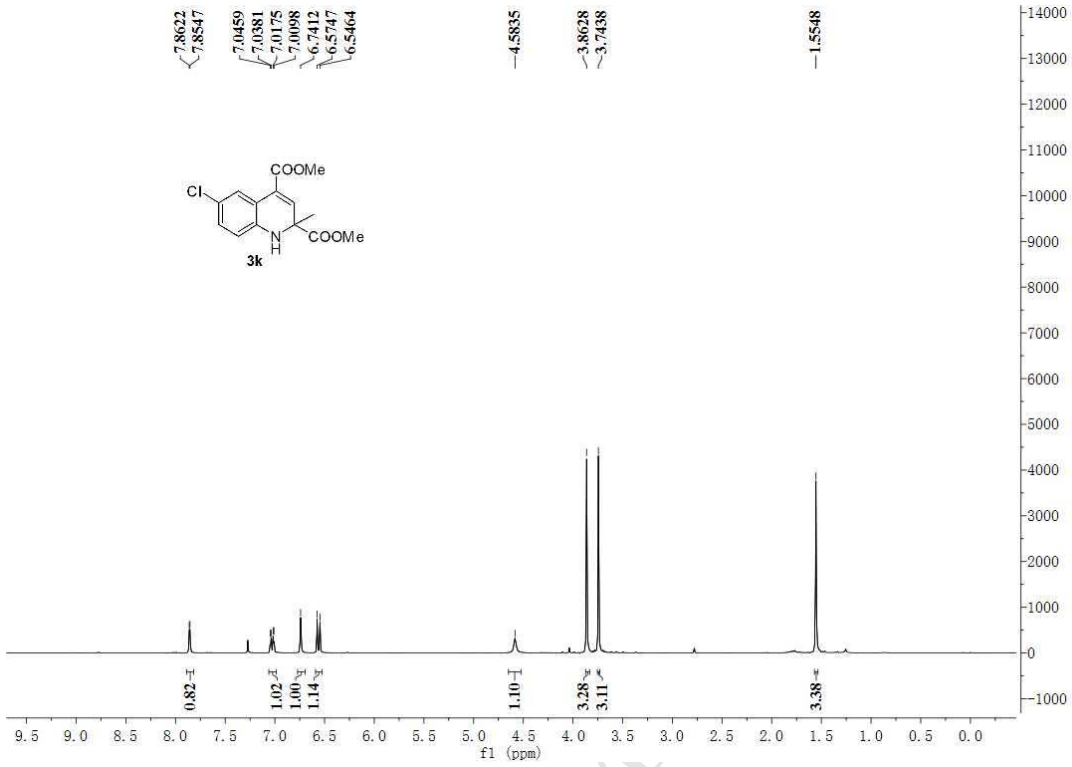
47.45
28.15
22.59
14.19
14.11
EtOOC
COOEt
3j
f1 (ppm)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3.8628
3.7438
1.5548
COOMe
Cl
COOMe
N
H
3k
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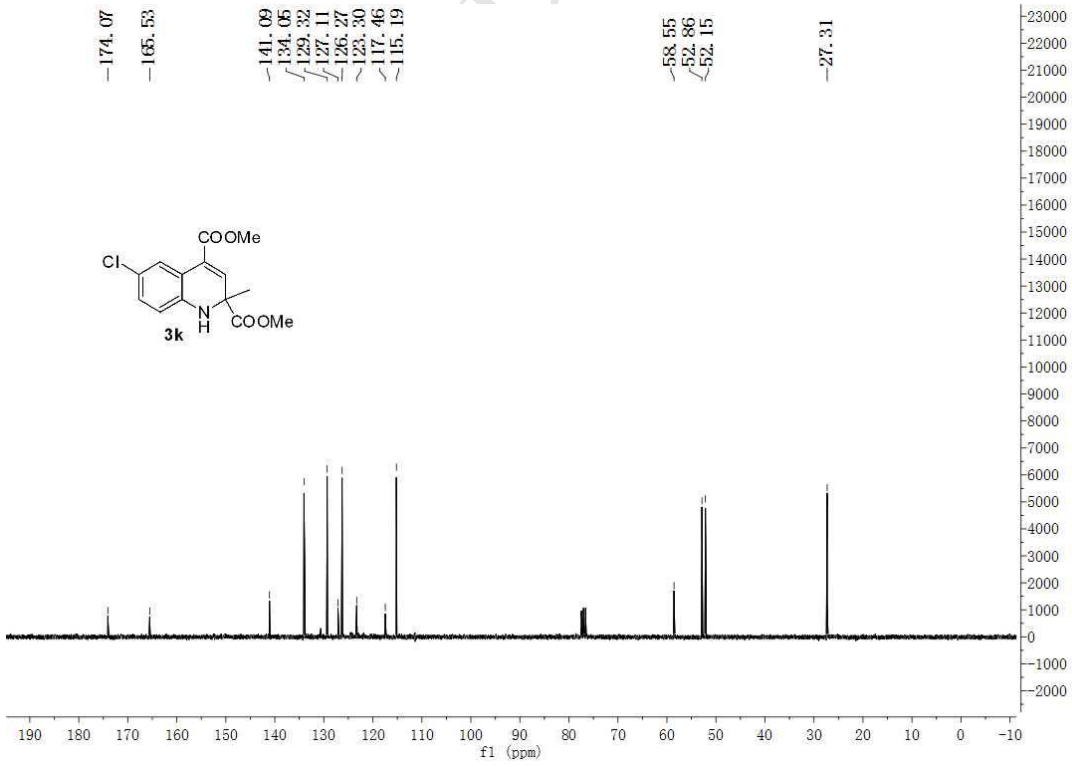
3.11
3.38
f1 (ppm)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126.27
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117.46
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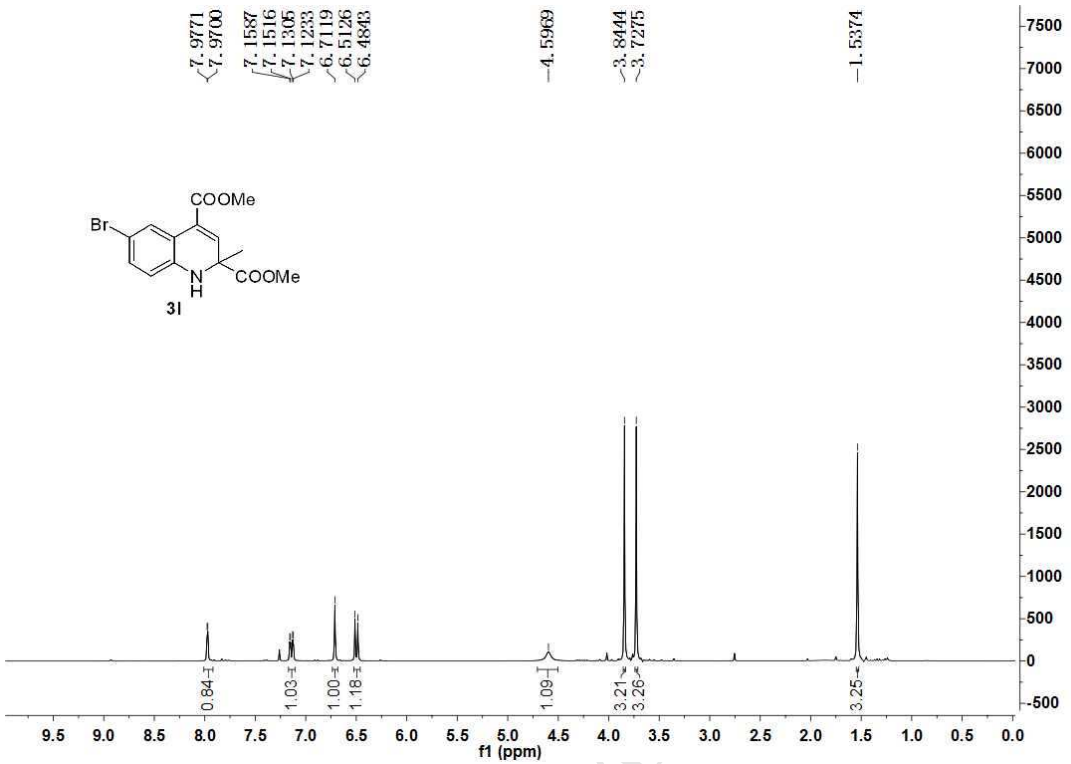
27.31
COOMe
Cl
COOMe
N
H
3k
f1 (ppm)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3.7275
1.5374
COOMe
Br
N
H
COOMe
3l
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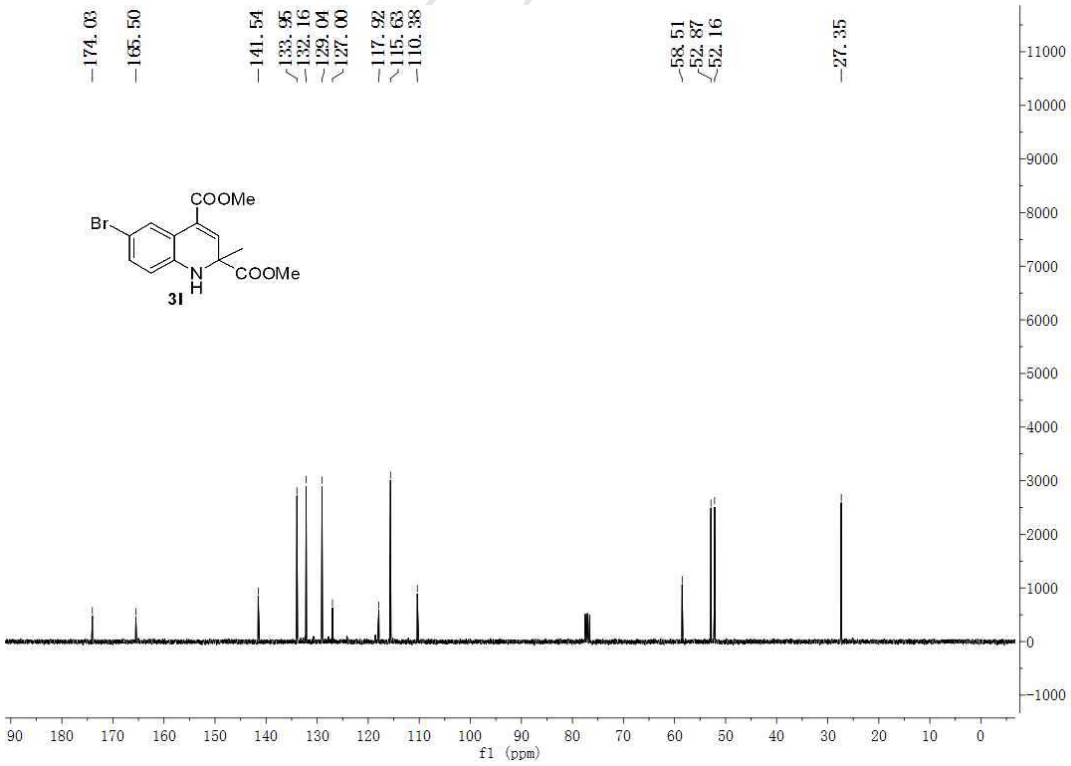
1.00
1.18
1.09
3.21
3.26
3.25
f1 (ppm)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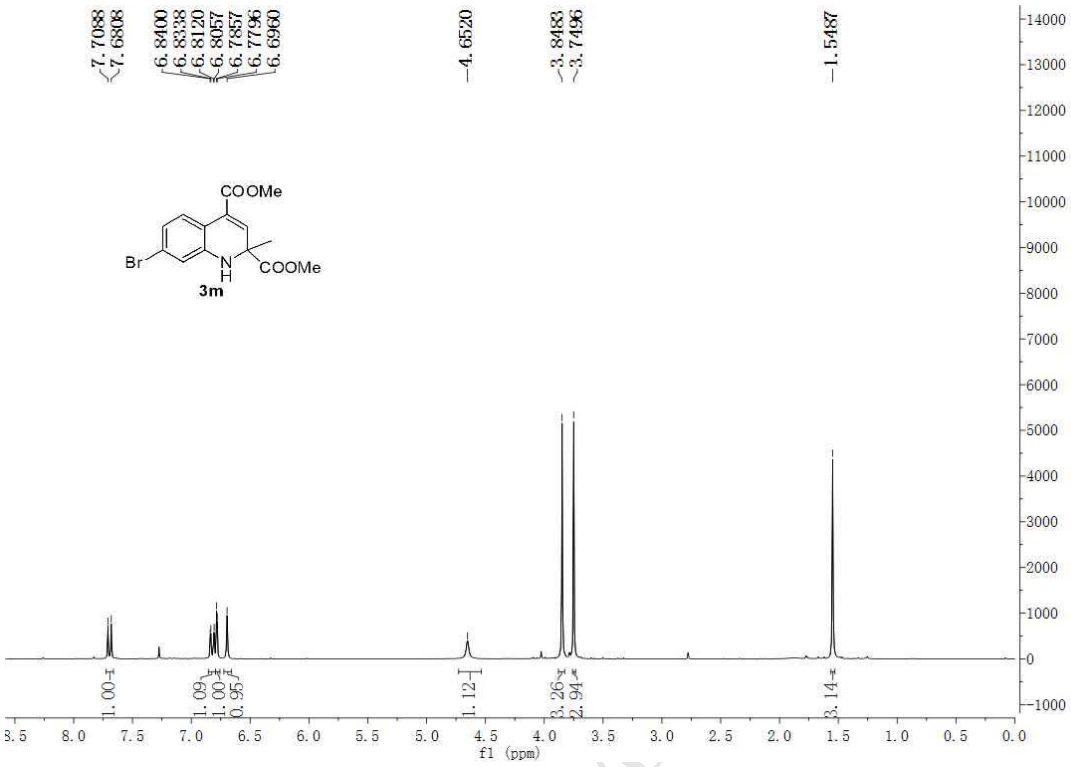
COOMe
Br
N
H
COOMe
3l
f1 (ppm)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3.7496
1.5487
COOMe
Br
N
H
COOMe
3m
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1.09
1.00
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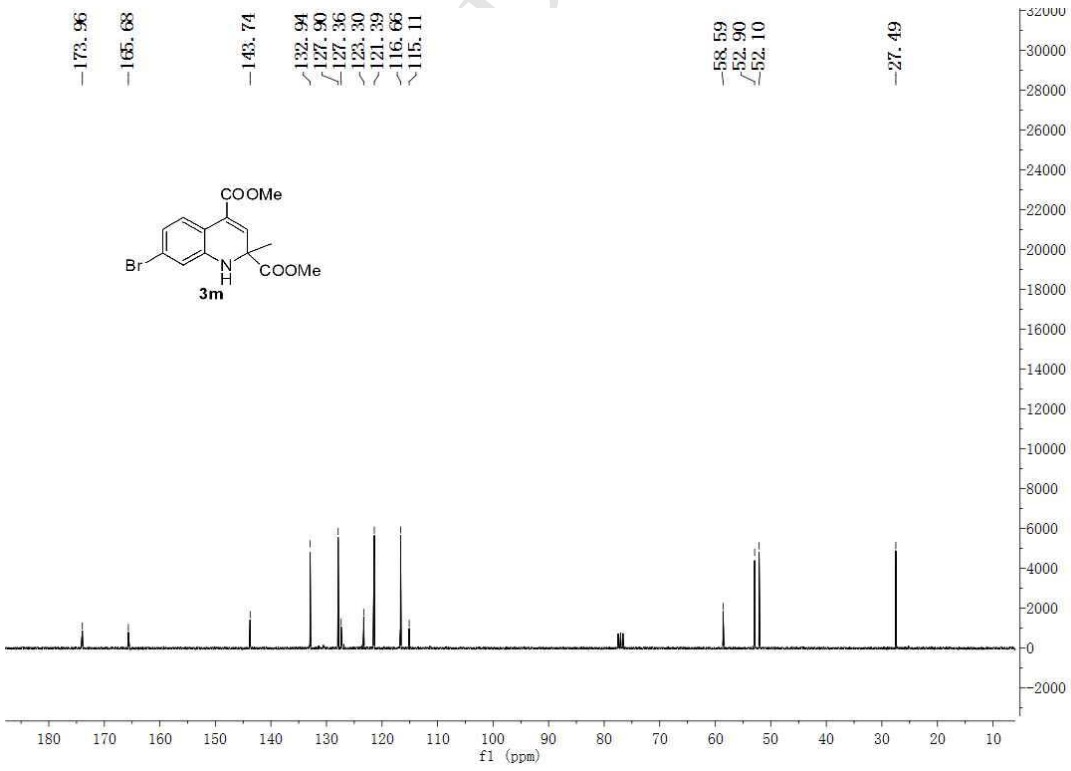
1.12
3.26
2.94
3.14
f1 (ppm)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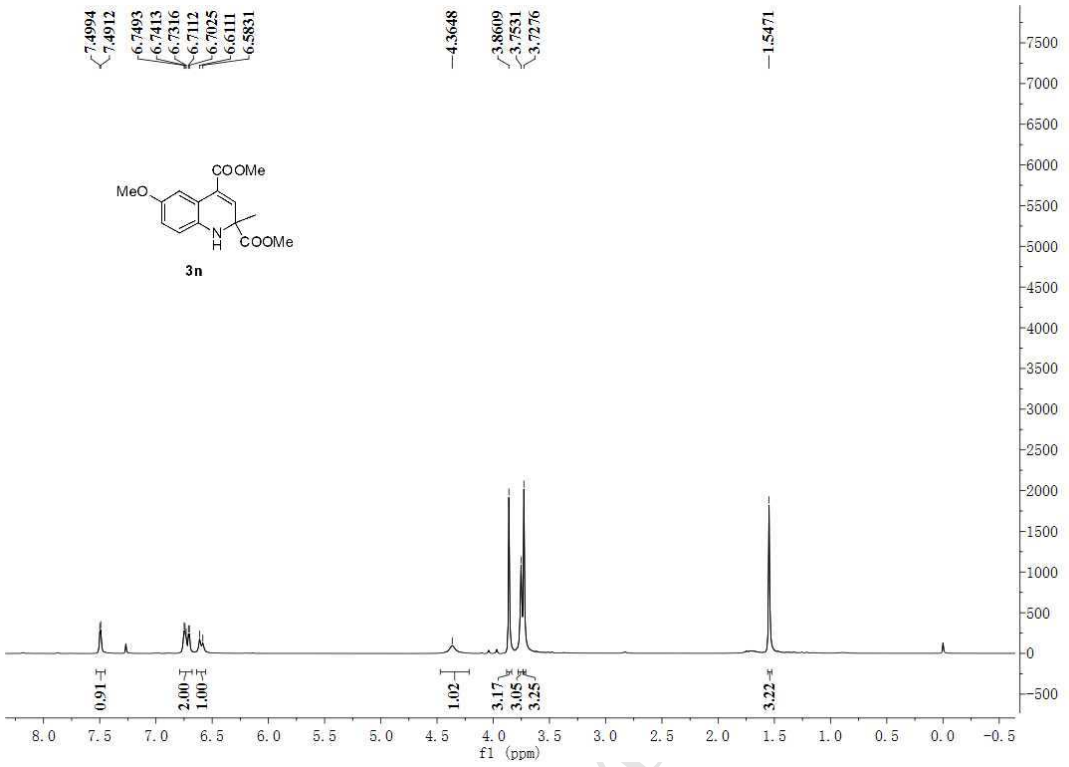
123.30
121.39
116.66
115.11
58.59
52.90
52.10
27.49
COOMe
Br
N
H
COOMe
3m
f1 (ppm)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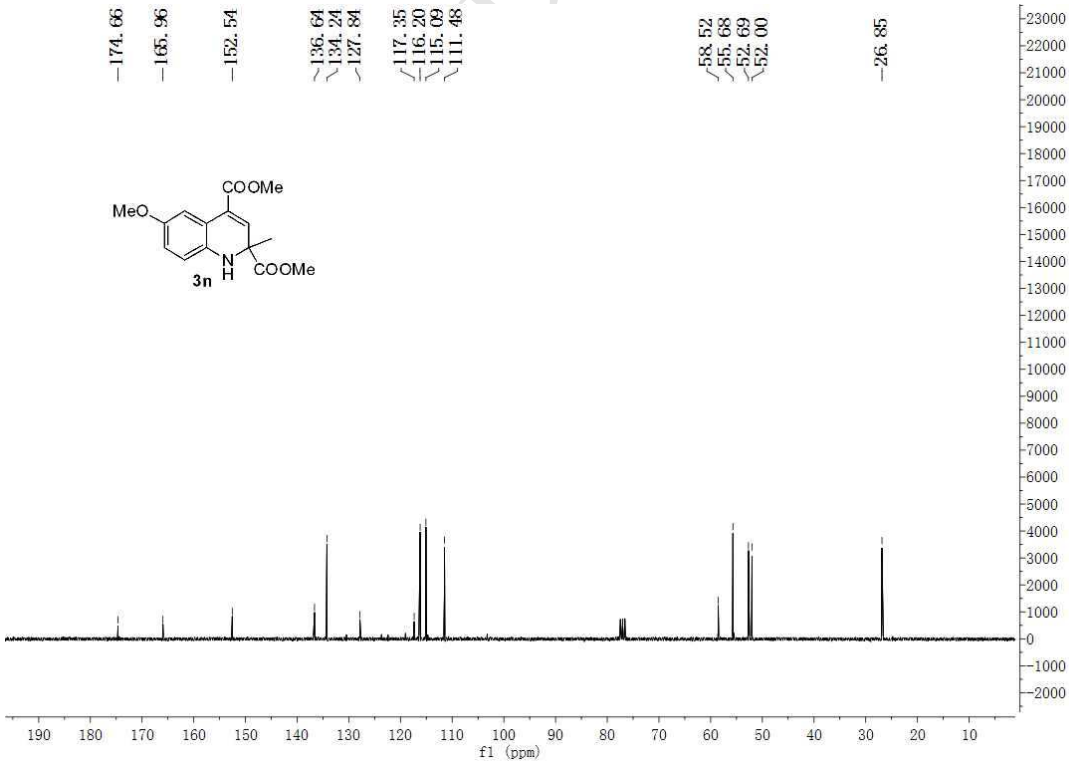
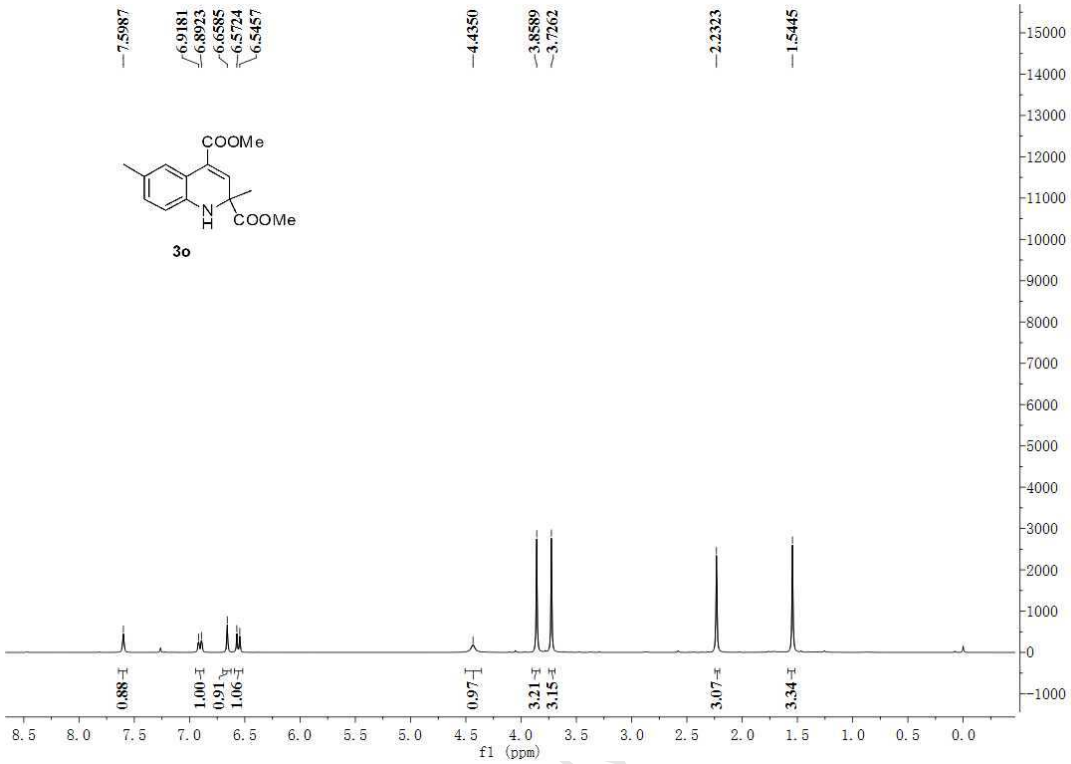
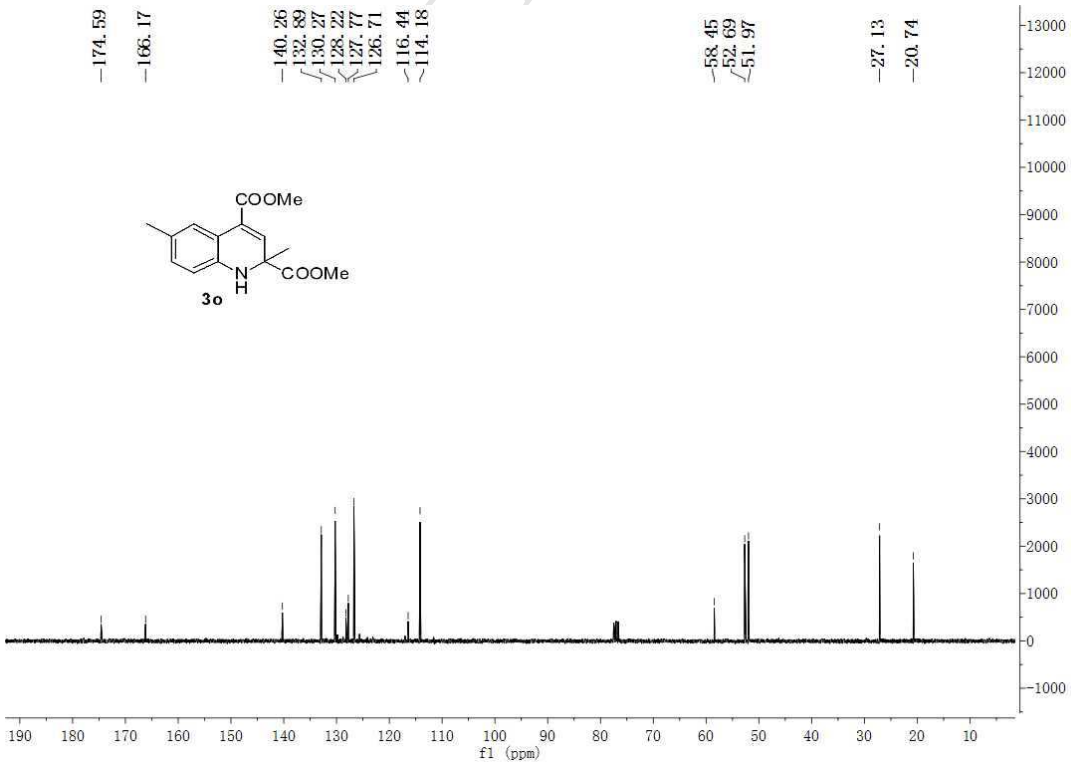
7.4912
6.7493
6.7413
6.7316
6.7112
6.7025
6.6111
6.5831
4.3648
3.8609
3.7531
3.7276
1.5471
COOMe
MeO
COOMe
3n
0.91
2.00
1.00
1.02
3.17
3.05
3.25
3.22
f1 (ppm)


174.66
165.96
152.54
136.64
134.24
127.84
117.35
116.20
115.09
111.48
58.52
55.68
52.69
52.00
26.85
COOMe
MeO
COOMe
3n
f1 (ppm)


7.5987
6.9181
6.8923
6.6585
6.5724
6.5457
4.4350
3.8589
3.7262
2.2323
1.5445
COOMe
COOMe
3o
0.88
1.00
0.91
1.06
0.97
3.21
3.15
3.07
3.34
f1 (ppm)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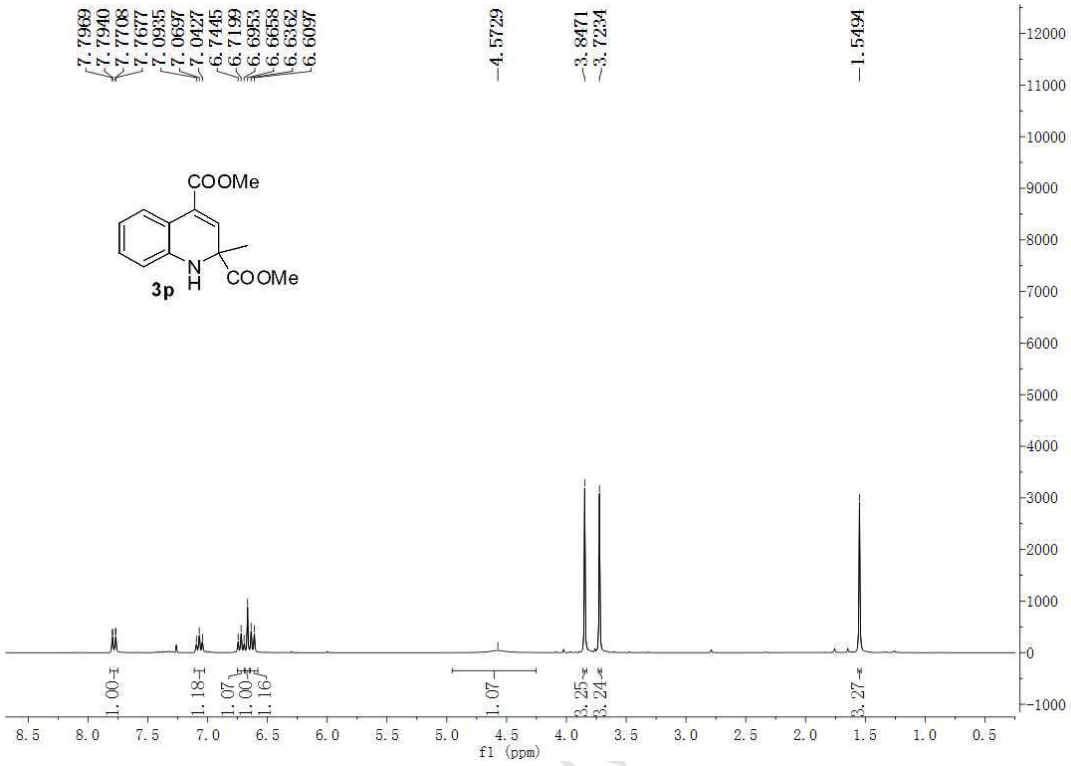
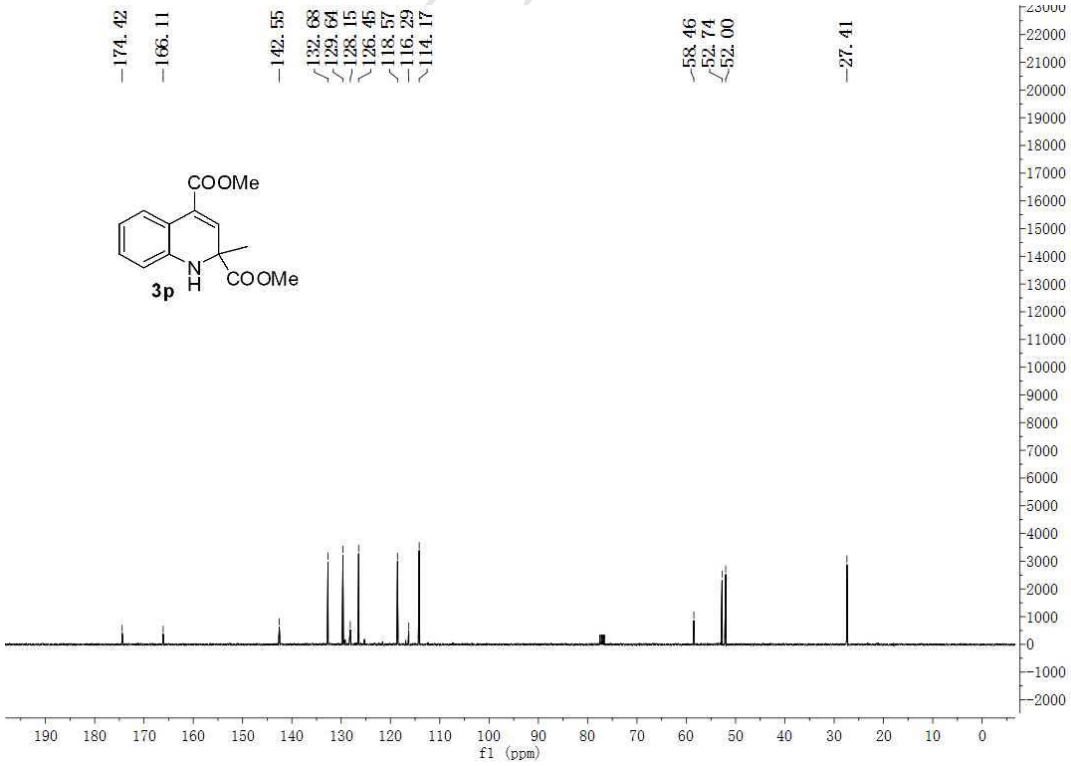
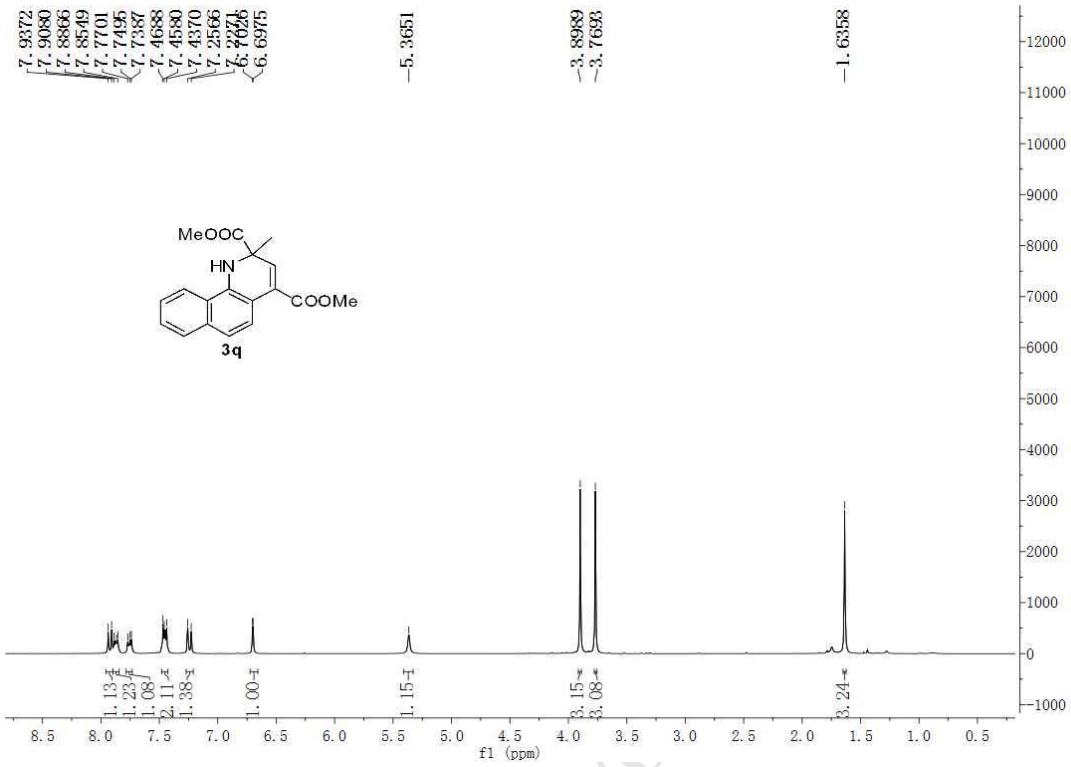
166.17
140.26
132.89
130.27
128.22
127.77
126.71
116.44
114.18
58.45
52.69
51.97
27.13
20.74
COOMe
COOMe
3o
f1 (ppm)


7.7969
7.7940
7.7708
7.7677
7.0935
7.0697
7.0427
6.7445
6.7199
6.6953
6.6658
6.6362
6.6097
4.5729
3.8471
3.7234
1.5494
COOMe
N
H
COOMe
3p
1.00
1.18
1.07
1.00
1.16
1.07
3.25
3.24
3.27
f1 (ppm)


174.42
166.11
142.55
132.68
129.64
128.15
126.45
118.57
116.29
114.17
58.46
52.74
52.00
27.41
COOMe
N
H
COOMe
3p
f1 (ppm)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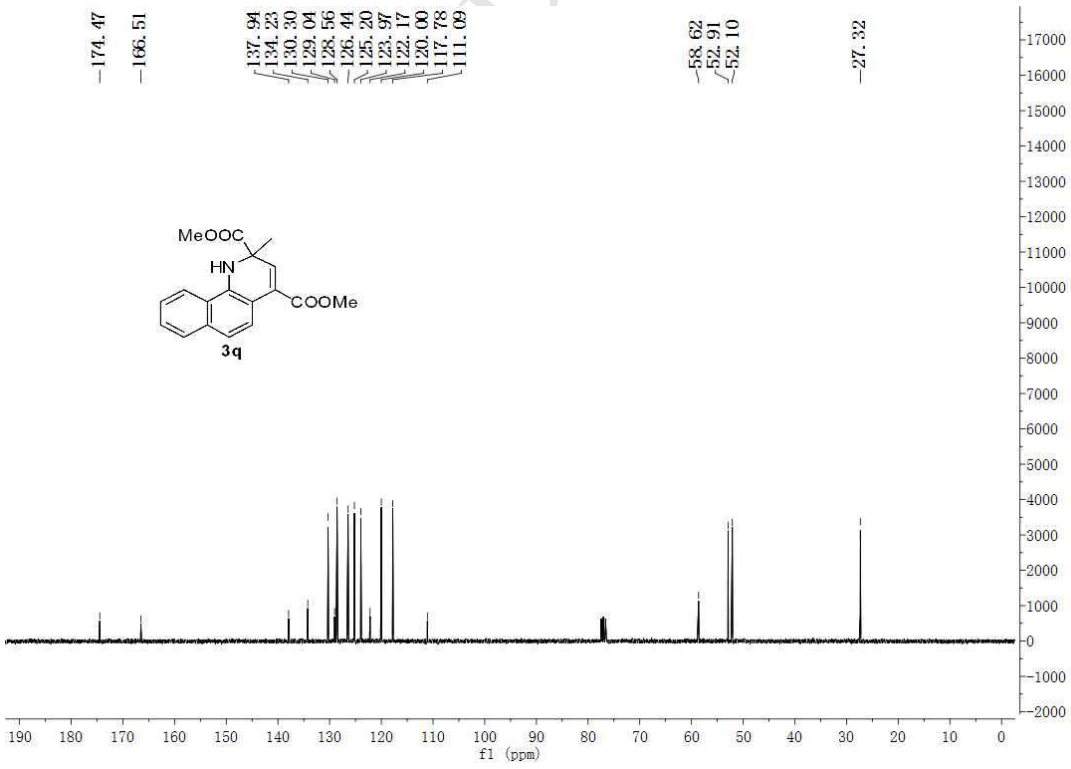
7.8866
7.8549
7.7701
7.7495
7.7387
7.4688
7.4580
7.4370
7.2566
5.3651
3.8989
3.7693
1.6358
MeOOC
HN
COOMe
3q
1.13
1.23
1.08
2.11
1.38
1.00
1.15
3.15
3.08
3.24
f1 (ppm)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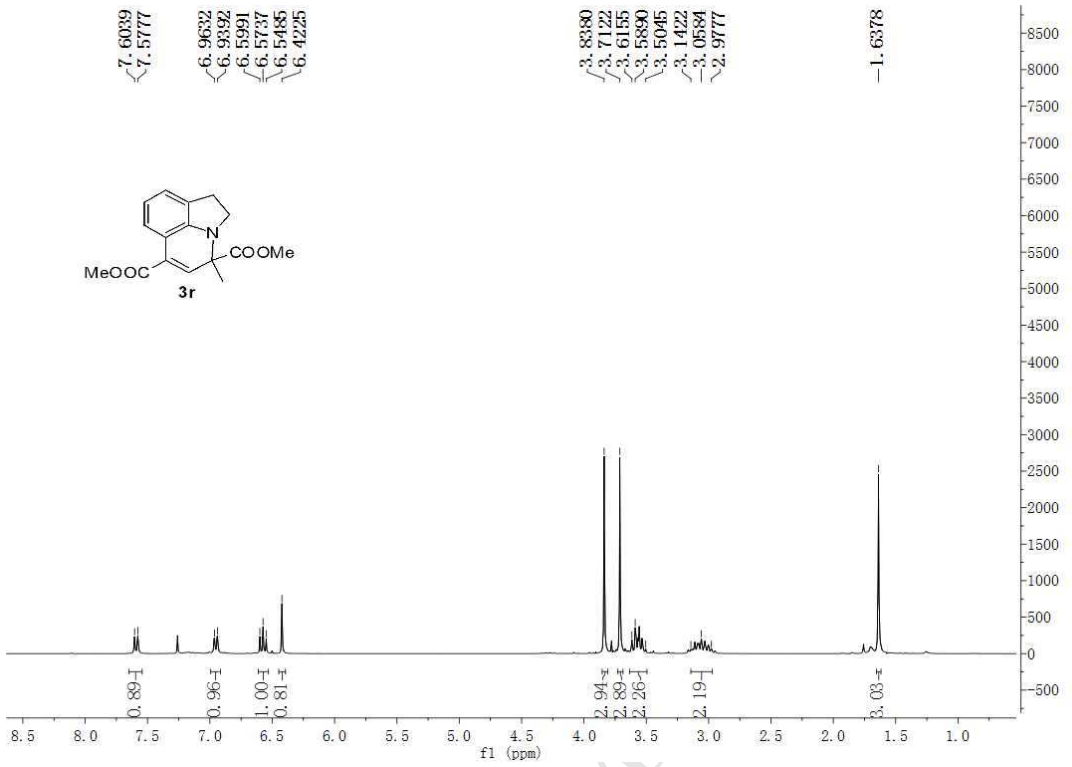
166.51
137.94
134.23
130.30
129.04
128.56
126.44
125.20
123.97
122.17
120.00
117.78
111.09
58.62
52.91
52.10
27.32
MeOOC
HN
COOMe
3q
f1 (ppm)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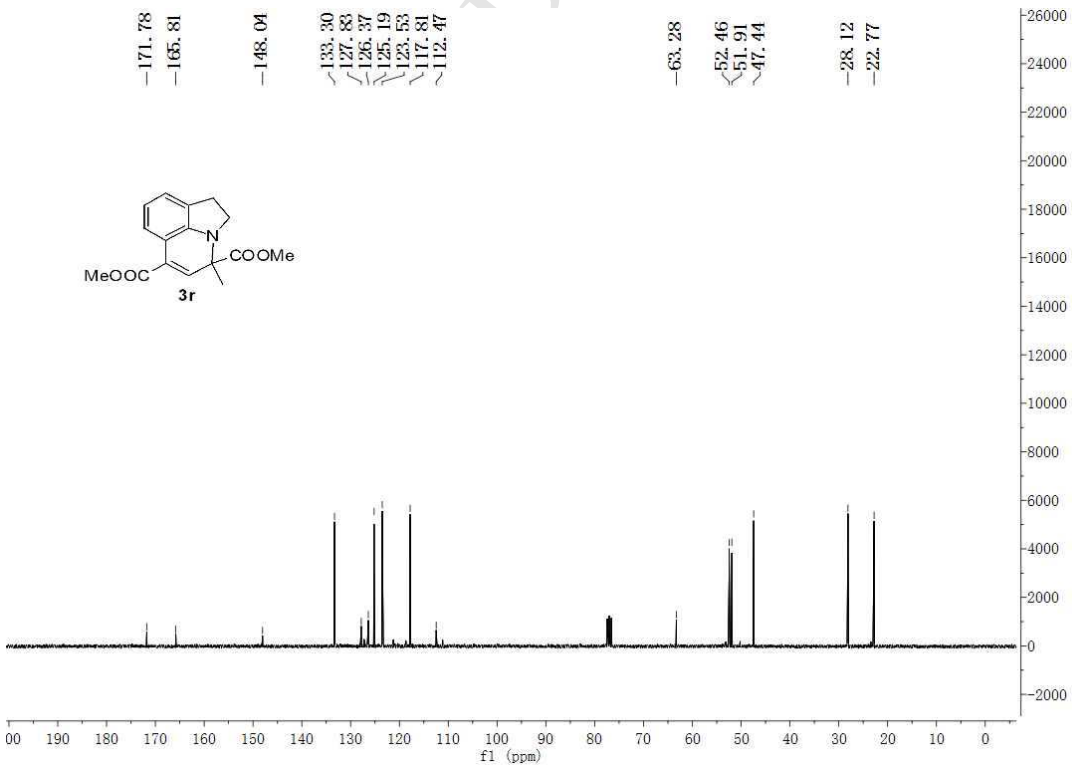
7.5777
6.9632
6.9392
6.5991
6.5737
6.5485
6.4225
3.8380
3.7122
3.6155
3.5890
3.5045
3.1422
3.0584
2.9777
1.6378
MeOOC
COOMe
3r
0.89
0.96
1.00
0.81
2.94
2.89
2.26
2.19
3.03
f1 (ppm)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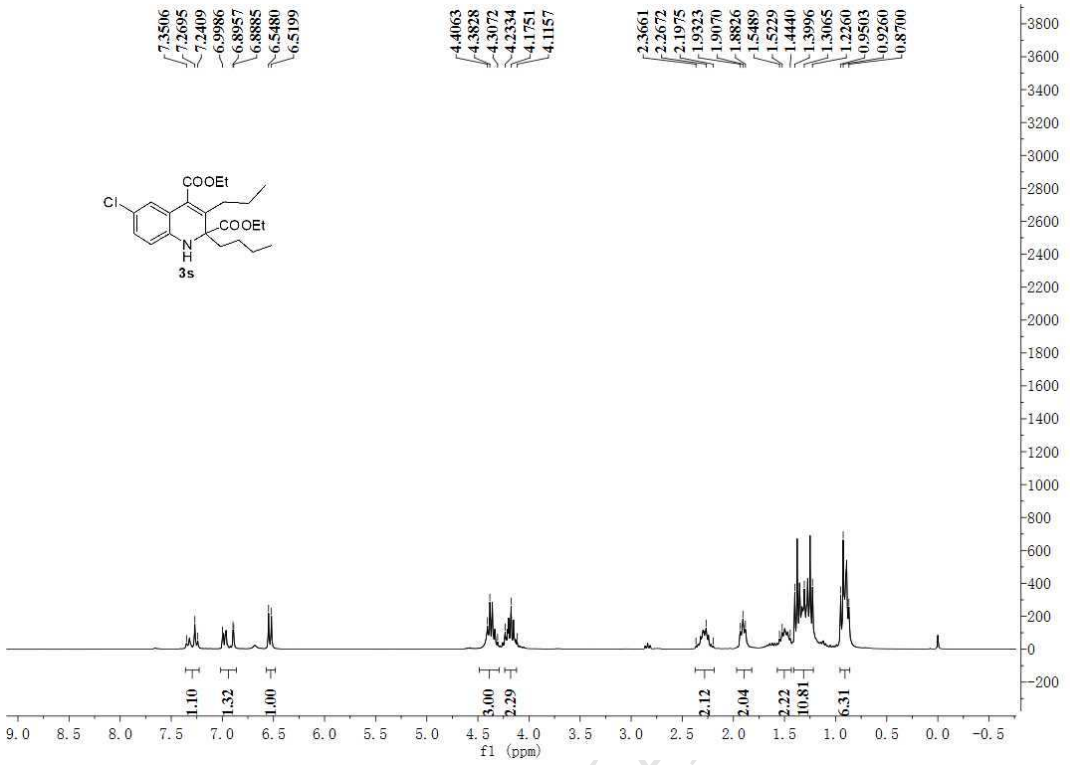
165.81
148.04
133.30
127.83
126.37
125.19
123.53
117.81
112.47
63.28
52.46
51.91
47.44
28.12
22.77
MeOOC
COOMe
3r
f1 (ppm)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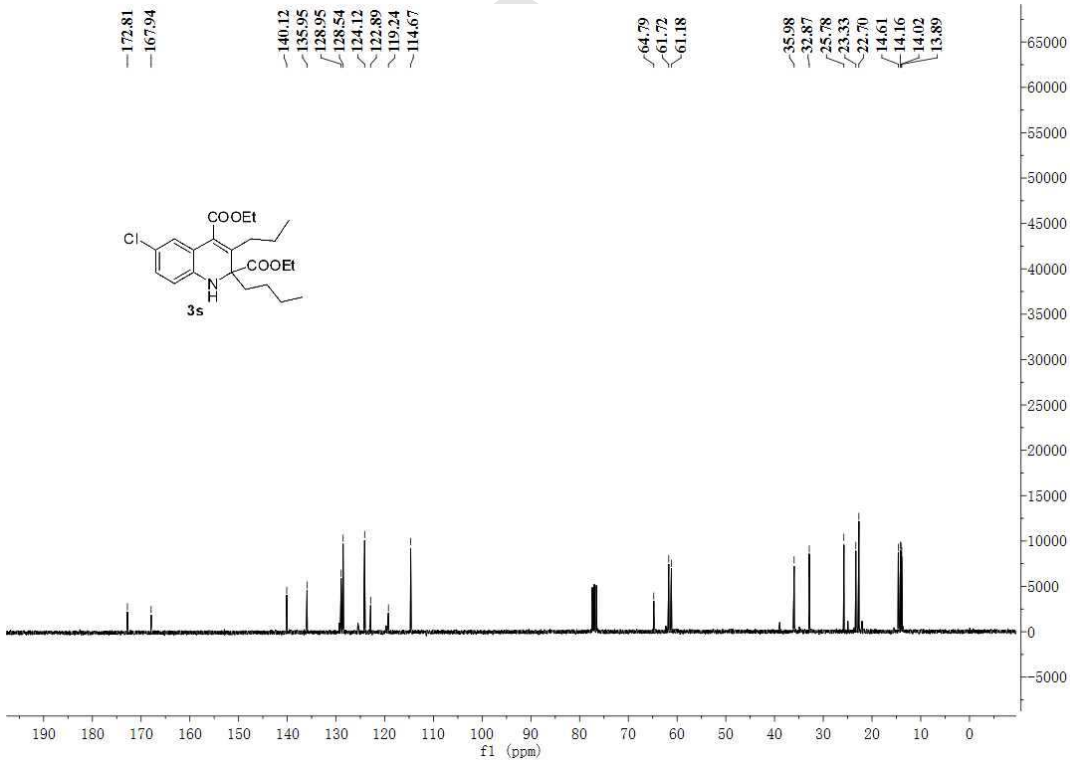
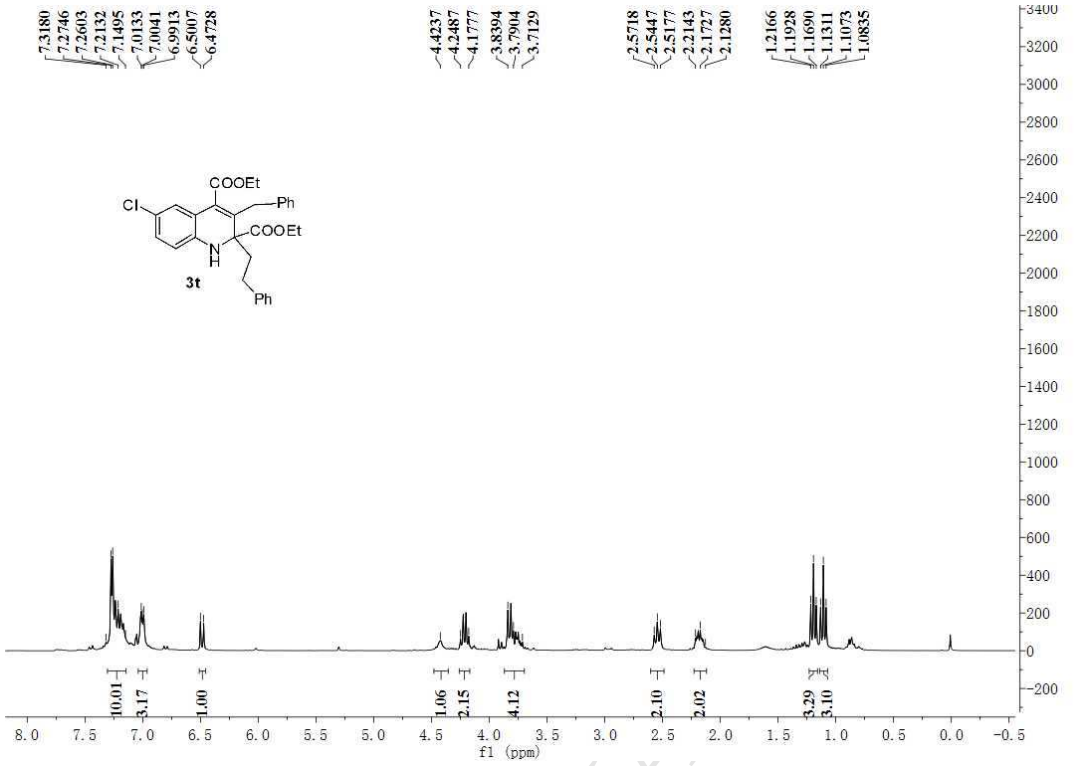
7.2409
6.9986
6.8957
6.8885
6.5480
6.5199
4.4063
4.3828
4.3072
4.2334
4.1751
4.1157
2.3661
2.2672
2.1975
1.9323
1.9070
1.8826
1.5489
1.5229
1.4440
1.3996
1.3065
1.2260
0.9503
0.9260
0.8700
COOEt
Cl
COOEt
N
H
3s
1.10
1.32
1.00
3.00
2.29
2.12
2.04
2.22
10.81
6.31
f1 (ppm)


172.81
167.94
140.12
135.95
128.95
128.54
124.12
122.89
119.24
114.67
64.79
61.72
61.18
35.98
32.87
25.78
23.33
22.70
14.61
14.16
14.02
13.89
COOEt
Cl
COOEt
N
H
3s
f1 (ppm)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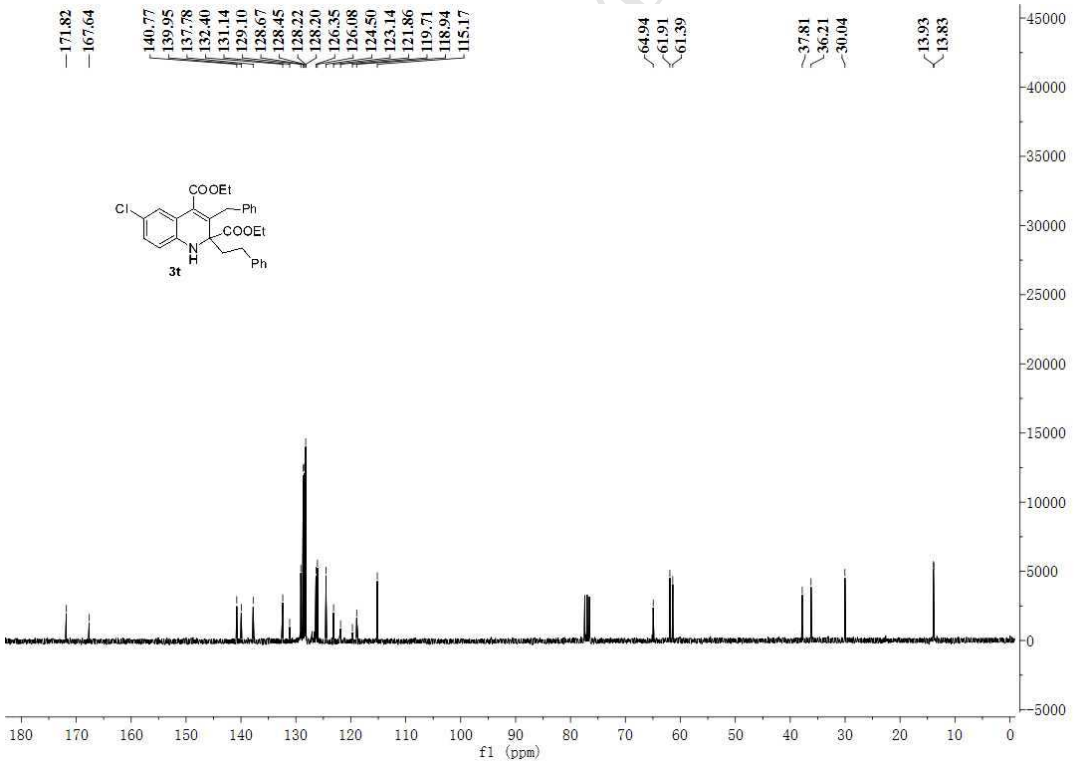
7.2746
7.2603
7.2132
7.1495
7.0133
7.0041
6.9913
6.5007
6.4728
4.4237
4.2487
4.1777
3.8394
3.7904
3.7129
2.5718
2.5447
2.5177
2.2143
2.1727
2.1280
1.2166
1.1928
1.1690
1.1311
1.1073
1.0835
COOEt
Ph
Cl
COOEt
N
H
3t
Ph
10.01
3.17
1.00
1.06
2.15
4.12
2.10
2.02
3.29
3.10
f1 (ppm)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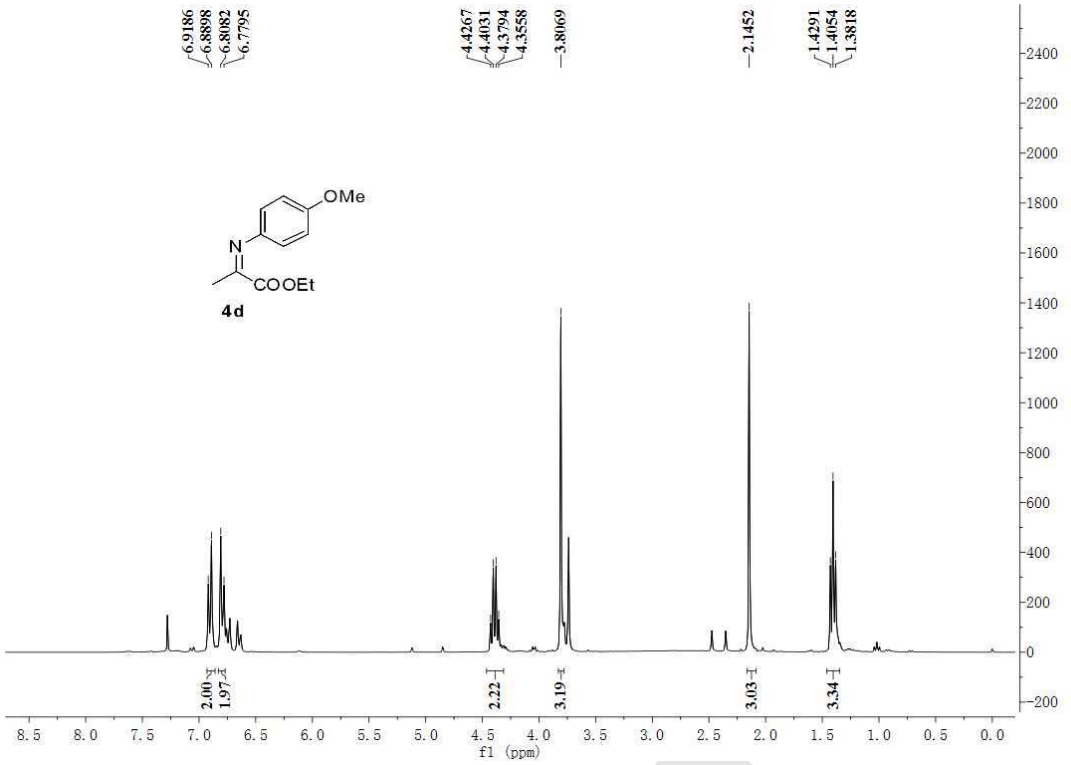
140.77
139.95
137.78
132.40
131.14
129.10
128.67
128.45
128.22
128.20
126.35
126.08
124.50
123.14
121.86
119.71
118.94
115.17
64.94
61.91
61.39
37.81
36.21
30.04
13.93
13.83
COOEt
Ph
Cl
COOEt
N
H
3t
Ph
f1 (ppm)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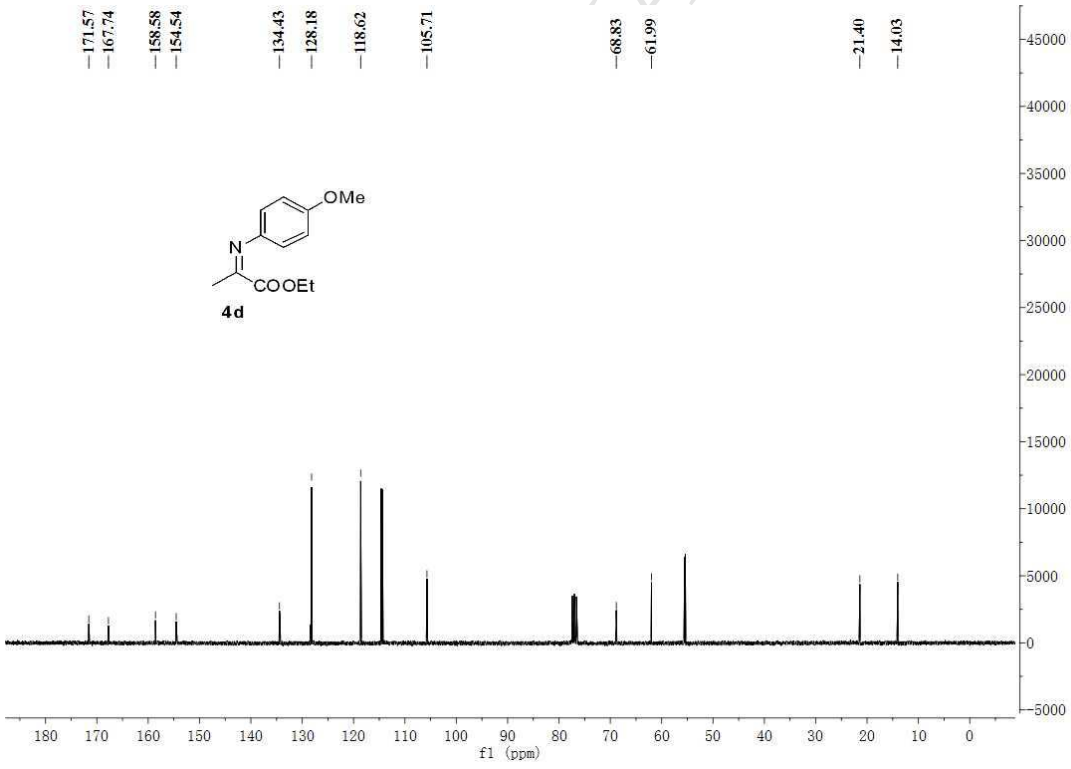
6.8082
6.7795
4.4267
4.4031
4.3794
4.3558
3.8069
2.1452
1.4291
1.4054
1.3818
OMe
N
COOEt
4d
2.00
1.97
2.22
3.19
3.03
3.34
f1 (ppm)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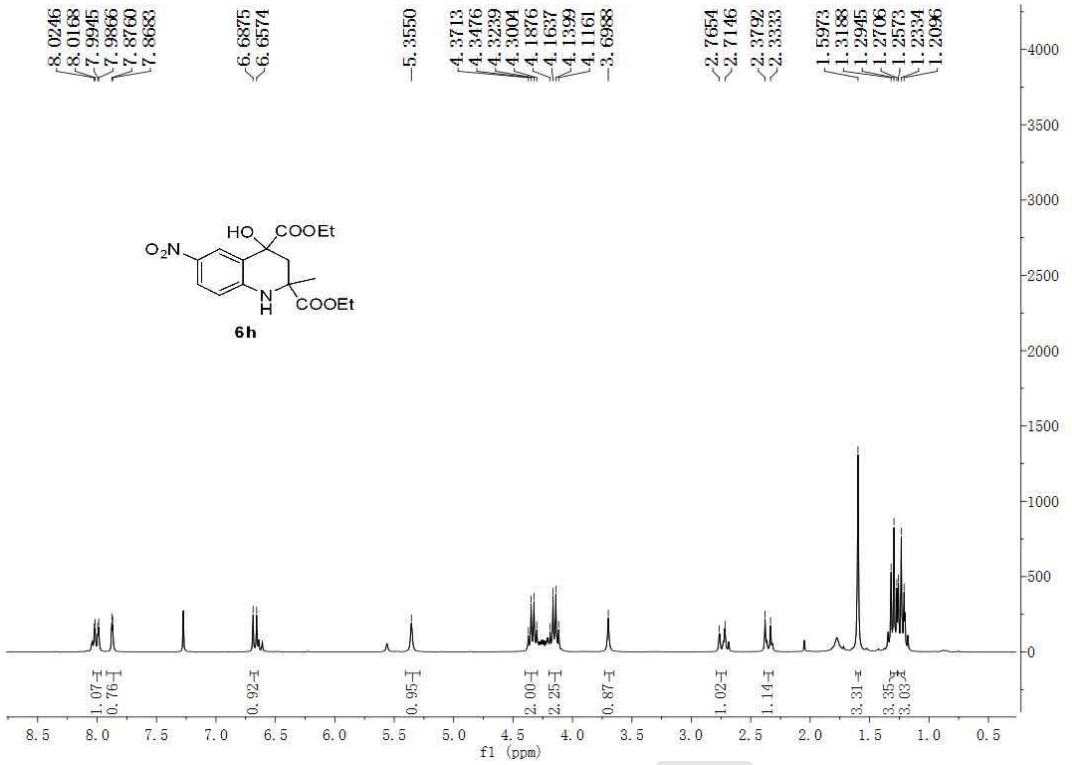
167.74
158.58
154.54
134.43
128.18
118.62
105.71
68.83
61.99
21.40
14.03
OMe
N
COOEt
4d
f1 (ppm)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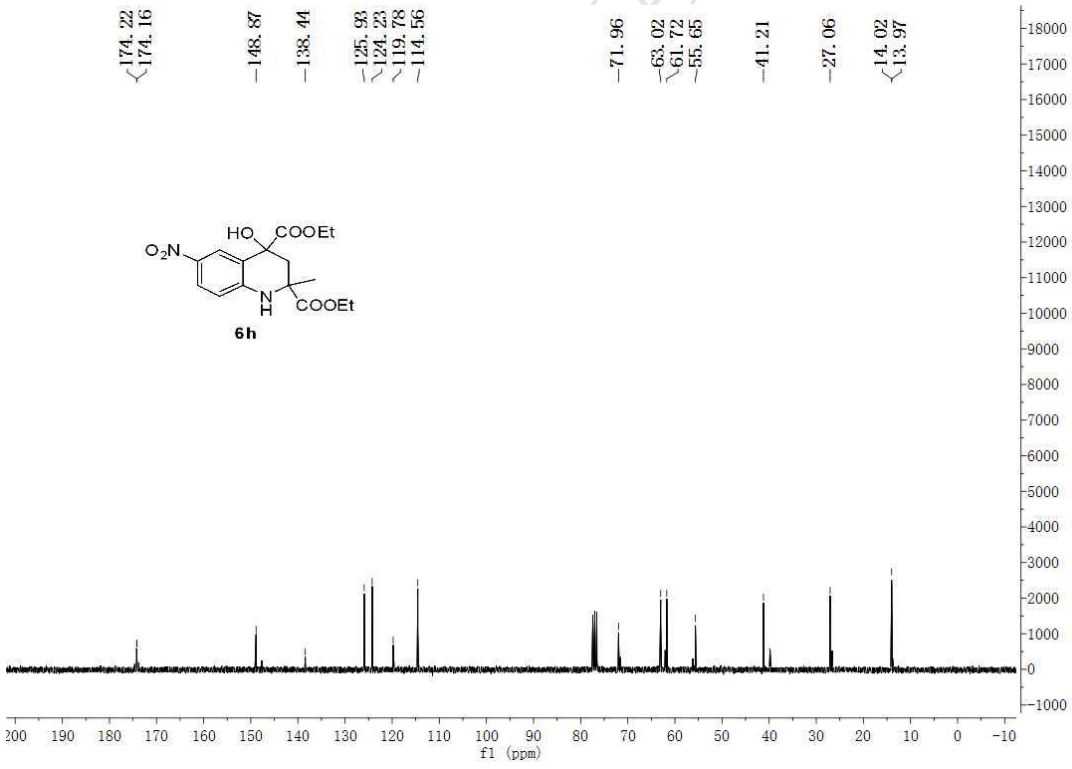
7.9866
7.8760
7.8683
6.6875
6.6574
5.3550
4.3713
4.3476
4.3239
4.3004
4.1876
4.1637
4.1399
4.1161
3.6988
2.7654
2.7146
2.3792
2.3333
1.5973
1.3188
1.2945
1.2706
1.2573
1.2334
1.2096
HO
COOEt
O2N
N
H
COOEt
6h
1.07
0.76
0.92
0.95
2.00
2.25
0.87
1.02
1.14
3.31
3.35
3.03
f1 (ppm)


174.22
174.16
148.87
138.44
125.93
124.23
119.78
114.56
71.96
63.02
61.72
55.65
41.21
27.06
14.02
13.97
HO
COOEt
O2N
N
H
COOEt
6h
f1 (ppm)