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Graphical Abstract

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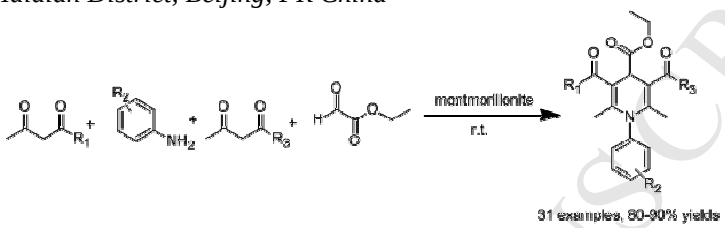

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Multicomponent reactions leading to symmetric and asymmetric multi-substituted 1, 4-dihydropyridines on montmorillonite

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ABSTRACT

Highly functionalized multi-substituted symmetric and asymmetric 1,4-dihydropyridines were concisely synthesized in moderate to good yields via one-pot multicomponent reactions (MCRs) of β-dicarbonyl compounds, aldehydes and amines at room temperature on montmorillonite. The merits of this method include the environmentally friendly reaction conditions, simple operation, broad substrate, satisfied yields and the reuse of the montmorillonite.

1. Introduction

The 1,4-dihydropyridine (DHP) scaffold is not only a very useful reducing agent[1,2] and synthetic intermediates,[3,4] but also an important pharmacophore found in a large number of biologically active[5,6] and potential therapeutic compounds.[7] Their pharmacological activities include calcium channel blockers,[8] multidrug-resistance (MDR) reversing agents,[9,10] radioprotection,[11] HIV protease inhibition,[12] cocaine dependent regulator,[13] TGFβ signal inhibitors[14] etc. Based on the existed experimental and SAR studies of DHP derivatives,[15] most of the researches were focused on *N*-unsubstituted DHPs. However, the *N*-substituted DHPs with biological activity are attracted more attention recently. For example, *N*-acyloxy DHPs (**Fig. 1**, **a**)[16] and *N*-substituted cage dimeric DHPs (**Fig. 1**, **b**)[17] were synthesized as P-gloycoprotein-mediated MDR-reversing agents, *N*-aryl substituted DHPs were verified as sirtuin activators and inhibitors (**Fig. 1**, **c**),[18] and 1-phenyl-4-glycosyl-dihydropyridines were prepared as potent antileishmanial agents (**Fig. 1**, **d**).[19]

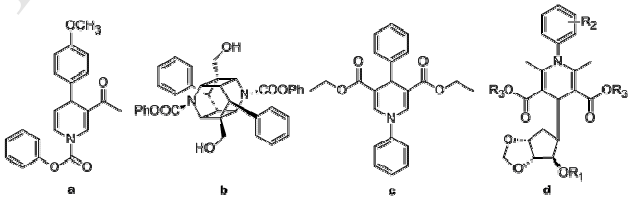

Figure 1. Representative *N*-substituted DHPs with biological activities

Hantzsch DHPs synthesis is one of the most broadly used methods for the preparation of DHPs. In order to improve the efficiency of Hantzsch DHPs synthesis, different catalysts have been explored and many of them exhibited excellent catalytic activity,[20-23] such as L-proline,[24] S-Valin,[25] $Yb(OTf)_3$,[26] I_2,[27] TBAHS,[28] HOAc,[29] Et_3N,[30] DBU,[31] Py[32] and so on. Furthermore, along with the development of environmental consciousness in chemical research and industry, solvent-free reaction, microwave method,[29,30,31] "grindstone chemistry" technique[33] and some efficient attempts have been used to build dihydropyridine scaffold.[34,35] However, some drawbacks still exist, such as the use

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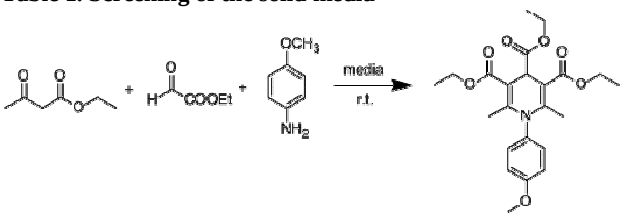
of expensive or toxic catalyst, high reaction temperature, low yields or finite scope of substrates. Especially, the research on the synthesis of *N*-substituted DHPs is usually ignored.[36] Recently, Yan *et al.* reported an efficient multicomponent synthesis of *N*-substituted DHPs in EtOH.[37] As our continuing efforts to develop reactions in solid media,[38] we here report a practical synthesis of highly functionalized multi-substituted symmetric and asymmetric DHPs using montmorillonite K10 as solid-phase.

2. Results and discussion

Initially, the reaction of ethyl acetoacetate, ethyl glyoxalate and 4-methoxyaniline was chosen as a model to examine the effect of different solid media on the reaction (**Table 1)**. To our delight, montmorillonite K10, as the best one among the screened six kinds of solid media, *i.e.* alkaline, acid and neutral Al_2O_3, silica gel, bentonite and montmorillonite K10, could generate the product in high yield (**Table 1**, entry 7, yield 82%) comparing to the solvent free system (**Table 1**, entry 1, yield 48%). Optimization for using amount of the montmorillonite K10 revealed that the best yield could be obtained when 0.75g montmorillonite K10 was used under the experimental scale (**Table 1**, entry 9, yield 86%) .

Table 1. Screening of the solid media[a]



Entry	Media	Media loading (g)	Yield (%)[b]
1	Solvent-free	--	48
2	Alkaline Al_2O_3	1	41
3	Acid Al_2O_3	1	28
4	Neutral Al_2O_3	1	33
5	Silica gel	1	52
6	Bentonite	1	72
7	Montmorillonite K10	1	82
8	Montmorillonite K10	0.5	74
9	Montmorillonite K10	0.75	86
10	Montmorillonite K10	1.5	85

[a] The reaction was conducted with ethyl acetoacetate (1 mmol), ethyl glyoxalate (0.5 mmol) and amine(0.5mmol) for 12h at r. t..

[b] Isolated yields.

Having optimized the reaction conditions for the model system (**Table 1**, entry 9), the structurally diverse substrates were chosen to explore the scope and limitations of this protocol. As shown in **Table 2**, most scanned reactants afforded the corresponding DHPs in moderate to excellent yields. It was found that the steric hindrance of substrates influenced the reaction yields significantly. For example, when para or meta position of aniline was substituted, whatever it is electron-withdrawing group or electron-donating group, the reaction were performed smoothly (**Table 2**, entries 1-4). Whereas, ortho substituted aniline wouldn't occur the reaction (**Table 2**, entry 5). Similarly, among all examined aromatic aldehydes (**Table 2**, entries 7-12), para substituted aromatic aldehydes gained higher yields compare to ortho substituted aromatic aldehydes. Also, tert-butyl 3-oxobutanoate, which owned bulky ester group, provided the lowest yield among the five tested esters (**Table 2**, entry 16, yield 65%). Moreover, when acetylacetone was used to replace *β*-carbonyl esters to react with ethyl glyoxalate and different aromatic aldehydes (**Table 2**, entries 18-24), the reactions were much easier to carry out, even aryl amine with strong electron-withdrawing group could achieve the moderate yield (**Table 2**, entry 24, yield 51%).

Next, based on the mechanism of DHPs synthesis, we envisaged that this protocol should be applied in the synthesis of asymmetric 1,4-dihydropyridines by choosing different *β*-dicarbonyl compounds and tandem multicomponent reactions (MCRs). Therefore, four-component tandem reactions of 1,3-diacetone, *β*-carbonyl ester, ethyl glyoxalate and 4-methoxyaniline were investigated under the optimized reaction conditions and the results are shown in **Table 3**. As expected, all asymmetric 1,4-dihydropyridine derivatives could be obtained in moderate to good yields through mixing the starting materials successively.

Finally, recyclability of montmorillonite K10 was examined through the reaction of ethyl acetoacetate, ethyl glyoxalate and 4-methoxyaniline in montmorillonite K10. As showed in **Table 4**, montmorillonite K10 can be easily recovered and reused at least 5 times without any significant loss of activity. Besides, the satisfied result was also obtained when the reaction was amplified to 5 times.

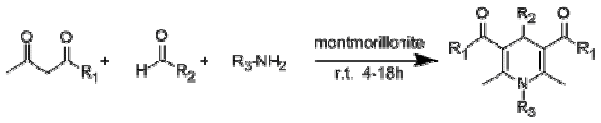
Table 4. Recycle of the montmorillonite

Entry	Recycle times	Yield (%)
1	0	86
2	1	85
3	2	85
4	3	81
5	4	78

3. Conclusion

In conclusion, we have developed an efficient method for the synthesis of both symmetric and asymmetric 1, 4-dihydro-pyridine derivatives from the MCRs of *β*-dicarbonyl compounds with aldehyde and amine at room temperature by utilizing montmorillonite K10 as solid media. The advantages of this method include the environmentally friendly reaction conditions, simple operation, broad substrate scope, satisfied yields and reused montmorillonite K10. Thus, this method will be widely applied in the synthesis of diverse substituted 1, 4-dihydropyridine derivatives.

Table 2. Synthesis of the symmetric DHPs[a]



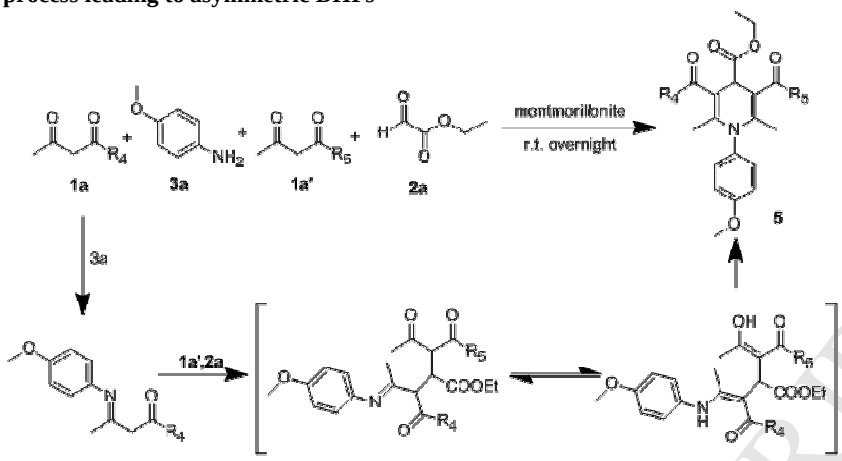
1 2 3 4

Entry	R_1	R_2	R_3	Product	Yield(%)[b]
1	OEt	COOEt	4-CH_3Ph	4a	71
2	OEt	COOEt	Ph	4b	78
3	OEt	COOEt	4-ClPh	4c	77
4	OEt	COOEt	3-ClPh	4d	70
5	OEt	COOEt	2-ClPh	4e	0
6	OEt	COOEt	3,5-$(CH_3)_2$Ph	4f	70
7	OEt	4-NO_2Ph	4-CH_3OPh	4g	82
8	OEt	4-ClPh	4-CH_3OPh	4h	76
9	OEt	Ph	4-CH_3OPh	4i	74
10	OEt	4-CH_3Ph	4-CH_3OPh	4j	75
11	OEt	2-CNPh	4-CH_3OPh	4k	65
12	OEt	2-thienyl	4-CH_3OPh	4l	85
13	OMe	COOEt	4-CH_3OPh	4m	89
14	OEt	COOEt	4-CH_3OPh	4n	86
15	i-PrO	COOEt	4-CH_3OPh	4o	81
16	t-BuO	COOEt	4-CH_3OPh	4p	65
17	OBz	COOEt	4-CH_3OPh	4q	76
18	Me	COOEt	4-CH_3OPh	4r	90
19	Me	COOEt	4-CH_3Ph	4s	86
20	Me	COOEt	Ph	4t	90
21	Me	COOEt	4-ClPh	4u	83
22	Me	COOEt	3-ClPh	4v	80
23	Me	COOEt	3,5-$(CH_3)_2$Ph	4w	77
24	Me	COOEt	3-CF_3Ph	4x	51
25	Ph	COOEt	4-CH_3OPh	4y	83

[a] The reaction was conducted with one pot method.

[b] Isolated yields.

Table 3. The tandem process leading to asymmetric DHPs[a]



Entry	R_4	R_5	Product[b]	Yield(%)[c]
1	Me	OMe	5a	78
2	Me	OEt	5b	76
3	Me	i-PrO	5c	76
4	Me	t-BuO	5d	69
5	Ph	Me	5e	85
6	Ph	OMe	5f	78
7	Ph	OEt	5g	78

[a] The reaction is conducted with tandem MCRs.

[b] These products are mixture of enantiomers.

[c] Isolated yields.

4. Experimental section

4.1. General experimental

Unless otherwise stated, all reagents were purchased from commercial suppliers (Aladdin) and were used without further purification. Melting point data were recorded on an X-4 micro-melting point instrument. NMR spectra were recorded on a Bruker ACF 500 (400MHz ^{1}H, 100MHz ^{13}C), the spectra were recorded in $CDCl_3$ as a solvent at room temperature. HRMS was performed on a Bruker-APEX IV. Column chromatography was performed on silica gel (200-300 mesh).

4.2. General procedure for the synthesis of symmetric DHPs

A mixture of *β*-dicarbonyl compound **1** (1 mmol), amine **3** (0.5 mmol), aldehyde **2** (0.5 mmol) and the montmorillonite K-10 (0.75 g) was added into a small test tube and magnetically stirred at room temperature until the reaction was completed (TLC, 4-18h). The mixture was added ethyl acetate (5 mL), stirred and filtered. The filtrate was concentrated and the residue was recrystallized in ethyl acetate/petroleum ether or purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the corresponding products. The filter (montmorillonite K10) could be reused after dried and ground.

4.2.1. Triethyl 2,6-dimethyl-1-p-tolyl-1,4-dihydro-pyridine-3,4,5-tricarboxylate(4a).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 4.87 (s, 1H), 4.22 (dd, *J* = 13.9, 7.0 Hz, 4H), 4.14 (m, 2H), 2.39 (s, 3H), 2.05 (s, 6H), 1.30 (t, *J* = 7.2 Hz, 6H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.88, 167.56, 149.01, 138.67, 137.48, 130.08, 129.97, 100.98, 60.60, 60.10, 40.06, 21.15, 18.20, 14.33, 14.25. HRMS (ESI): m/z calcd for $C_{23}H_{30}NO_6$ $[M+H]^+$: 416.20676. Found: 416.20722.

4.2.2. Triethyl 2,6-dimethyl-1-phenyl-1,4-dihydro-pyridine-3,4,5-tricarboxylate(4b).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.2 Hz, 3H), 7.20 (dd, *J* = 7.8, 1.5 Hz, 2H), 4.88 (s, 1H), 4.23 (dt, *J* = 10.8, 3.7 Hz, 4H), 4.15 (m, 2H), 2.05 (s, 6H), 1.31 (t, *J* = 7.1 Hz, 6H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.84, 167.52, 148.76, 140.21, 130.46, 129.37, 128.69, 101.20, 60.63, 60.14, 40.10, 18.21, 14.32, 14.24. HRMS (ESI): m/z calcd for $C_{22}H_{27}NO_6$ $[M+H]^+$: 402.19111. Found: 402.19084.

4.2.3. Triethyl 1-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate(4c).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 4.86 (s, 1H), 4.23 (m, 4H), 4.15 (dd, *J* = 14.0, 6.9 Hz, 2H), 2.05 (s, 6H), 1.31 (t, *J* = 7.1 Hz, 6H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.80, 167.34, 148.35, 138.76, 134.75, 131.82, 129.66, 101.81, 60.72, 60.24, 40.11, 18.14, 14.30, 14.23. HRMS (ESI): m/z calcd for $C_{22}H_{26}ClNNaO_6$ $[M+Na]^+$: 458.13409. Found: 458.13408.

4.2.4. Triethyl 1-(3-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate(4d).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.1 Hz, 2H), 7.25 (s, 1H), 7.13 (d, *J* = 7.1 Hz, 1H), 4.86 (s, 1H), 4.22 (m, 4H), 4.15 (m, 2H), 2.06 (s, 6H), 1.31 (t, *J* = 7.1 Hz, 6H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.68, 167.32, 148.15, 141.40, 135.04, 130.77, 130.26, 129.15, 128.93, 101.92,

60.75, 60.25, 40.15, 18.14, 14.29, 14.22. HRMS (ESI): m/z calcd for $C_{22}H_{26}ClNNaO_6$ $[M+Na]^+$: 458.13409. Found: 458.13404.

4.2.5. Triethyl 1-(3,5-dimethylphenyl)-2,6-dimethyl -1,4-dihydropyridine-3,4,5-tricarboxylate(4f).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.79 (s, 2H), 4.88 (s, 1H), 4.23 (dd, *J* = 14.1, 7.1 Hz, 4H), 4.16 (m, 2H), 2.34 (s, 6H), 2.07 (s, 6H), 1.32 (t, *J* = 7.1 Hz, 6H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.96, 167.64, 148.94, 139.92, 139.12, 130.26, 127.90, 100.79, 60.60, 60.08, 58.45, 40.11, 21.15, 18.26, 14.34. HRMS (ESI): m/z calcd for C24H32NO6 $[M+H]^+$: 430.22241. Found: 430.22355; m/z calcd for $C_{24}H_{31}NNaO_6$ $[M+Na]^+$: 452.20436. Found: 452.20513.

4.2.6. Diethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate(4g).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.00 (dd, *J* = 21.9, 8.8 Hz, 4H), 5.24 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 4H), 3.88 (s, 3H), 2.10 (s, 6H), 1.26 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.60, 159.57, 154.60, 148.68, 132.54, 130.92, 129.98, 128.32, 123.45, 114.68, 104.66, 60.22, 55.55, 39.18, 18.73, 14.28. HRMS (ESI): m/z calcd for $C_{26}H_{29}N_2O_7$ $[M+H]^+$: 481.19693. Found: 481.19664.

4.2.7. Diethyl 4-(4-chlorophenyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate(4h).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.00 (dd, *J* = 23.5, 8.7 Hz, 4H), 5.24 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 4H), 3.87 (s, 3H), 2.10 (s, 6H), 1.26 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.60, 159.58, 154.63, 148.70, 146.43, 132.54, 130.94, 128.34, 123.46, 114.69, 104.66, 60.22, 55.55, 39.19, 18.74, 14.28. HRMS (ESI): m/z calcd for $C_{26}H_{29}ClNO_5$ $[M+H]^+$: 470.17288. Found: 470.17336.

4.2.8. Diethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate(4i).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.4 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.16 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 4H), 3.86 (s, 3H), 2.08 (s, 6H), 1.27 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.18, 159.37, 147.78, 147.17, 133.03, 129.53, 128.85, 128.02, 127.51, 126.14, 114.48, 105.80, 59.94, 55.50, 38.77, 18.58, 14.26. HRMS (ESI): m/z calcd for $C_{26}H_{30}NO_5$ $[M+H]^+$: 436.21185. Found: 436.21189.

4.2.9. Diethyl 1-(4-methoxyphenyl)-2,6-dimethyl-4-p-tolyl-1,4-dihydropyridine-3,5-dicarboxylate(4j).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 5.11 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 4H), 3.87 (s, 3H), 2.34 (s, 3H), 2.08 (s, 6H), 1.28 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.21, 159.33, 147.69, 144.28, 135.58, 133.07, 130.98, 128.78, 127.39, 114.46, 105.87, 59.94, 55.52, 38.32, 21.10, 18.64, 14.30. HRMS (ESI): m/z calcd for $C_{27}H_{32}NO_5$ $[M+H]^+$: 450.22750. Found: 450.22849.

4.2.10. Diethyl 4-(2-cyanophenyl)-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate(4k).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 6.99 (m, 4H), 5.19 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 4H), 3.88 (s, 3H), 2.09 (s, 6H), 1.26 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.66, 159.55, 152.55, 148.53, 132.59, 131.98, 128.32, 119.24, 114.65, 109.88, 104.75, 60.17, 55.54, 39.30, 29.69, 18.70, 14.27. HRMS (ESI): m/z calcd for $C_{27}H_{29}N_2O_5$ $[M+H]^+$: 461.20710. Found: 461.20733.

4.2.11. Diethyl 4-(furan-2-yl)-1-(4-methoxyphenyl) -2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate(4l).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.28 (m, 1H), 6.04 (d, *J* = 3.0 Hz, 1H), 5.27 (s, 1H), 4.20 (m, 4H), 3.85 (s, 3H), 2.09 (s, 6H), 1.30 (t, *J* = 7.2Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.75, 159.37, 158.68, 149.17, 140.95, 133.01, 131.31, 114.39, 110.05, 104.27, 102.86, 59.98, 55.48, 32.93, 18.29, 14.31.HRMS (ESI): m/z calcd for $C_{24}H_{28}NO_6$ $[M+H]^+$: 426.19111. Found: 426.19063.

4.2.12. 4-Ethyl 3,5-dimethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate(4m).

Yellow crystal, mp: 101.6-103.1 ℃, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.87 (s, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 6H), 2.07 (s, 6H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.59, 167.91, 159.47, 149.68, 132.61, 131.26, 114.45, 100.70, 60.68, 55.48, 51.40, 39.91, 18.15, 14.20. HRMS (ESI): m/z calcd for $C_{21}H_{26}NO_7$ $[M+H]^+$: 404.10738. Found: 404.17082.

4.2.13. Triethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate(4n).

Yellow crystal, mp: 108.2-109.5 ℃, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.87 (s, 1H), 4.23 (q, *J* = 7.2 Hz, 4H), 4.15 (q, *J* = 7.2Hz, 2H), 3.85 (s, 3H), 2.06 (s, 6H), 1.31 (t, *J* = 7.2 Hz, 6H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.90, 167.56, 159.42, 149.27, 132.77, 131.32, 114.41, 101.10, 60.60, 60.11, 55.49, 40.08, 18.17, 14.32, 14.24. HRMS (ESI): m/z calcd for $C_{23}H_{30}NO_7$ $[M+H]^+$: 432.20168. Found: 432.20124.

4.2.14. 4-Ethyl 3,5-diisopropyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate(4o).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.15 – 5.02 (m, 2H), 4.86 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 2.05 (s, 6H), 1.32 – 1.26 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.06, 167.12, 159.38, 148.87, 132.86, 131.37, 114.37, 101.45, 67.37, 60.55, 55.48, 40.23, 22.01, 21.87, 18.13, 14.29. HRMS (ESI): m/z calcd for $C_{25}H_{34}NO_7$ $[M+H]^+$:460.23298. Found:460.23410.

4.2.15. 3,5-Di-tert-butyl 4-ethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate(4p).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 4.80 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 2.02 (s, 6H), 1.51 (s, 18H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.15, 166.94, 159.30, 148.28, 133.01, 131.44, 114.31, 102.42, 79.94, 60.47, 55.46, 40.86, 28.23, 17.99, 14.37. HRMS (ESI): m/z calcd for $C_{27}H_{38}NO_7$ $[M+H]^+$: 488.26428. Found: 488.26451

4.2.16. 3,5-Dibenzyl 4-ethyl 1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4,5-tricarboxylate(4q).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 4H), 7.37 – 7.30 (m, 6H), 7.11 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.22 (dd, *J* = 29.4, 12.8 Hz, 4H), 5.04 (s, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 2.10 (s, 6H), 1.13 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.79, 167.09, 159.49, 150.16, 136.60, 132.58, 131.24, 128.38, 127.75, 127.67, 114.47, 100.72,

65.91, 60.71, 55.50, 39.90, 18.25, 14.10. HRMS (ESI): m/z calcd for $C_{33}H_{34}NO_7$ $[M+H]^+$: 556.23298. Found: 556.23300.

4.2.17. Ethyl 3,5-diacetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (4r).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.72 (s, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 2.40 (s, 6H), 2.01 (s, 6H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.97, 172.98, 159.57, 148.49, 132.29, 131.08, 114.55, 110.25, 61.09, 55.50, 40.97, 30.14, 18.88, 14.18. HRMS (ESI): m/z calcd for $C_{21}H_{26}NO_5$ $[M+H]^+$: 372.18055. Found: 372.18063.

4.2.18. Ethyl 3,5-diacetyl-2,6-dimethyl-1-p-tolyl-1,4-dihydropyridine-4-carboxylate(4s).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 4.72 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 6H), 2.38 (s, 3H), 2.00 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.96, 172.95, 148.21, 138.95, 137.06, 130.09, 129.81, 110.15, 61.07, 40.97, 30.15, 21.14, 18.92, 14.18. HRMS (ESI): m/z calcd for $C_{21}H_{26}NO_4$ $[M+H]^+$: 356.18563. Found: 356.18629.

4.2.19. Ethyl 3,5-diacetyl-2,6-dimethyl-1-phenyl-1,4-dihydropyridine-4-carboxylate(4t).

Yellow solid, mp: 77.2-79.9℃, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 6.6 Hz, 3H), 7.17 (d, *J* = 7.7 Hz, 2H), 4.74 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 6H), 2.01 (s, 6H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.95, 172.92, 147.95, 139.79, 130.20, 129.51, 128.93, 110.27, 61.12, 41.00, 30.16, 18.92, 14.19. HRMS (ESI): m/z calcd for $C_{20}H_{24}NO_4$ $[M+H]^+$: 342.16998. Found: 342.17043.

4.2.20. Ethyl 3,5-diacetyl-1-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate(4u).

Yellow solid, mp: 79,5-81.1℃, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 4.70 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 6H), 1.99 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.88, 172.81, 147.49, 138.31, 134.96, 131.59, 129.76, 110.64, 61.20, 40.99, 30.11, 18.81, 14.17. HRMS (ESI): m/z calcd for $C_{20}H_{23}ClNO_4$ $[M+H]^+$: 376.13101. Found: 376.13125.

4.2.21. Ethyl 3,5-diacetyl-1-(3-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate(4v).

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.22 (s, 1H), 7.12 (d, *J* = 9.0 Hz, 1H), 4.72 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 6H), 2.02 (s, 6H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.96, 172.77, 147.31, 140.98, 135.19, 130.55, 130.40, 129.38, 128.71, 110.75, 61.27, 41.04, 30.15, 18.85, 14.18. HRMS (ESI): m/z calcd for $C_{20}H_{23}ClNO_4$ $[M+H]^+$: 376.13101. Found: 376.13143.

4.2.22. Ethyl 3,5-diacetyl-1-(3,5-dimethylphenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (4w).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.77 (s, 2H), 4.75 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 6H), 2.35 (s, 6H), 2.04 (s, 6H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.06, 173.04, 148.16, 139.54, 139.32, 130.51, 127.65, 110.01, 61.10, 41.01, 30.18, 21.17, 19.03, 14.20. HRMS (ESI): m/z calcd for $C_{22}H_{28}NO_4$ $[M+H]^+$: 370.20128. Found: 370.20193.

4.2.23. Ethyl 3,5-diacetyl-2,6-dimethyl-1-(3-(trifluoromethyl)phenyl)-1,4-dihydropyridine-4-carboxylate(4x).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.48 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 4.74 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 6H), 2.00 (s, 6H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.00, 172.73, 147.07, 140.54, 133.92, 132.41, 130.29, 127.34, 127.30, 127.27, 127.23, 125.96, 125.92, 125.89, 125.85, 111.03, 61.34, 41.12, 30.13, 18.87, 14.15. HRMS (ESI): m/z calcd for $C_{21}H_{23}F_3NO_4$ $[M+H]^+$: 410.15737. Found: 410.15811.

4.2.24. Ethyl 3,5-dibenzoyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (4y).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.1 Hz, 4H), 7.50 (t, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 4H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.67 (s, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 1.67 (s, 6H), 1.14 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.06, 172.66, 159.50, 145.46, 139.82, 132.50, 131.95, 131.17, 128.82, 128.53, 114.48, 109.29, 60.96, 55.50, 44.03, 19.69, 14.02. HRMS (ESI): m/z calcd for $C_{31}H_{30}NO_5$ $[M+H]^+$: 496.21185. Found: 496.21119.

4.3. General procedure for the synthesis of asymmetric DHPs

A mixture of *β*-dicarbonyl compound **1a** (0.5mmol), amine **3a** (0.5mmol) and the montmorillonite K-10 (0.75g) was added into a small test tube and magnetically stirred at room temperature for 6h, then the other *β*-dicarbonyl compound **1a'** (0.5mmol) and aldehyde **2a** (0.5mmol) was added and stirred overnight. The mixture was added ethyl acetate (5 mL), stirred and filtered. The filtrate was concentrated and the residue was recrystallized in ethyl acetate/petroleum ether or purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the corresponding product. The filter (montmorillonite K10) could be reused after dried and ground.

4.3.1. 4-Ethyl 3-methyl 5-acetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate(5a).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 4.76 (s, 1H), 4.14 (qd, J = 7.1, 2.5 Hz, 2H), 3.82 (s, 3H), 3.74 (s, 3H), 2.41 (s, 3H), 2.08 (s, 3H), 1.97 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ198.89, 173.18, 167.66, 159.48, 150.14, 148.03, 132.38, 131.16, 114.47, 109.42, 100.59, 60.94, 55.48, 51.53, 40.71, 29.87, 18.68, 18.18, 14.19. HRMS (ESI): m/z calcd for $C_{21}H_{26}NO_6$ $[M+H]^+$: 388.17546. Found: 388.17661.

4.3.2. Diethyl 5-acetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate (5b).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 4.78 (s, 1H), 4.17 (m, 4H), 3.83 (s, 3H), 2.41 (s, 3H), 2.08 (s, 3H), 1.98 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.88, 173.29, 167.23, 159.48, 149.71, 148.12, 132.47, 131.18, 114.46, 109.38, 101.06, 60.88, 60.23, 55.47, 40.81, 29.81, 18.67, 18.14, 14.32, 14.20. HRMS (ESI): m/z calcd for $C_{22}H_{28}NO_6$ $[M+H]^+$: 402.19111. Found: 402.19233.

4.3.3. 4-Ethyl 3-isopropyl 5-acetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate(5c).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 5.08 (m, 1H), 4.76 (s, 1H), 4.14 (qd, J = 7.1, 3.2 Hz, 2H), 3.83 (s, 3H), 2.41 (s, 3H), 2.07 (s, 3H), 1.98 (s, 3H), 1.26 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.88, 173.37, 166.78, 159.45, 149.29, 148.25, 132.50, 131.20, 114.43, 109.27, 101.51, 67.58, 60.86, 55.48, 40.87, 29.84, 22.03, 21.91,

18.72, 18.14, 14.24. HRMS (ESI): m/z calcd for $C_{23}H_{30}NO_6$ $[M+H]^+$: 416.20676. Found: 416.20738.

4.3.4. 3-tert-Butyl 4-ethyl 5-acetyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate(5d).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.75 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 2.43 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.52 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.85, 173.45, 166.66, 159.43, 148.50, 148.40, 132.62, 131.26, 114.42, 109.03, 102.86, 80.42, 60.84, 55.48, 41.22, 29.80, 28.28, 18.74, 18.09, 14.27. HRMS (ESI): m/z calcd for $C_{24}H_{32}NO_6$ $[M+H]^+$: 430.22241. Found: 430.22320.

4.3.5. Ethyl 3-acetyl-5-benzoyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate(5e).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.0 Hz, 2H), 7.52 (t, J = 6.1 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.13 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 4.67 (s, 1H), 4.16 (qd, J = 7.1, 2.0 Hz, 2H), 3.85 (s, 3H), 2.38 (s, 3H), 2.11 (s, 3H), 1.60 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.47, 196.79, 172.87, 159.55, 149.20, 145.78, 139.79, 132.35, 132.08, 131.10, 128.89, 128.56, 114.52, 110.25, 108.46, 61.10, 55.51, 42.59, 29.97, 29.69, 19.81, 18.88, 14.15. HRMS (ESI): m/z calcd for $C_{26}H_{28}NO_5$ $[M+H]^+$: 434.19620. Found: 434.19650.

4.3.6. 4-Ethyl 3-methyl 5-benzoyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate(5f).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.1 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.74 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 2.17 (s, 3H), 1.58 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.33, 173.01, 167.88, 159.47, 150.72, 143.67, 139.16, 132.58, 132.18, 131.22, 128.97, 128.53, 114.47, 110.14, 99.10, 60.82, 55.49, 51.42, 51.34, 42.33, 29.69, 19.24, 18.30, 18.17, 14.09. HRMS (ESI): m/z calcd for $C_{26}H_{28}NO_6$ $[M+H]^+$: 450.19111. Found: 450.19231.

4.3.7. Diethyl 5-benzoyl-1-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate (5g).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.1 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 4.75 (s, 1H), 4.17 (qd, J = 7.1, 3.0 Hz, 2H), 4.08 (q, J = 6.7 Hz, 2H), 3.83 (s, 3H), 2.16 (s, 3H), 1.57 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.31, 173.17, 167.40, 159.44, 150.38, 143.78, 139.19, 132.63, 132.16, 131.23, 128.98, 128.50, 114.45, 109.99, 99.53, 77.40, 77.08, 76.76, 60.76, 60.01, 55.48, 42.37, 19.32, 18.26, 14.30, 14.10. HRMS (ESI): m/z calcd for $C_{27}H_{30}NO_6$ $[M+H]^+$: 463.20676. Found: 464.20783.

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Supplementary Material

The original data of ^{1}H NMR and ^{13}C NMR of all products are supplied. The supplementary data files are to be used as an aid for the refereeing of the paper only.

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Supporting Information

Multicomponent reaction leading to symmetric and asymmetric highly functionalized multi-substituted 1, 4-dihydropyridines on montmorillonite

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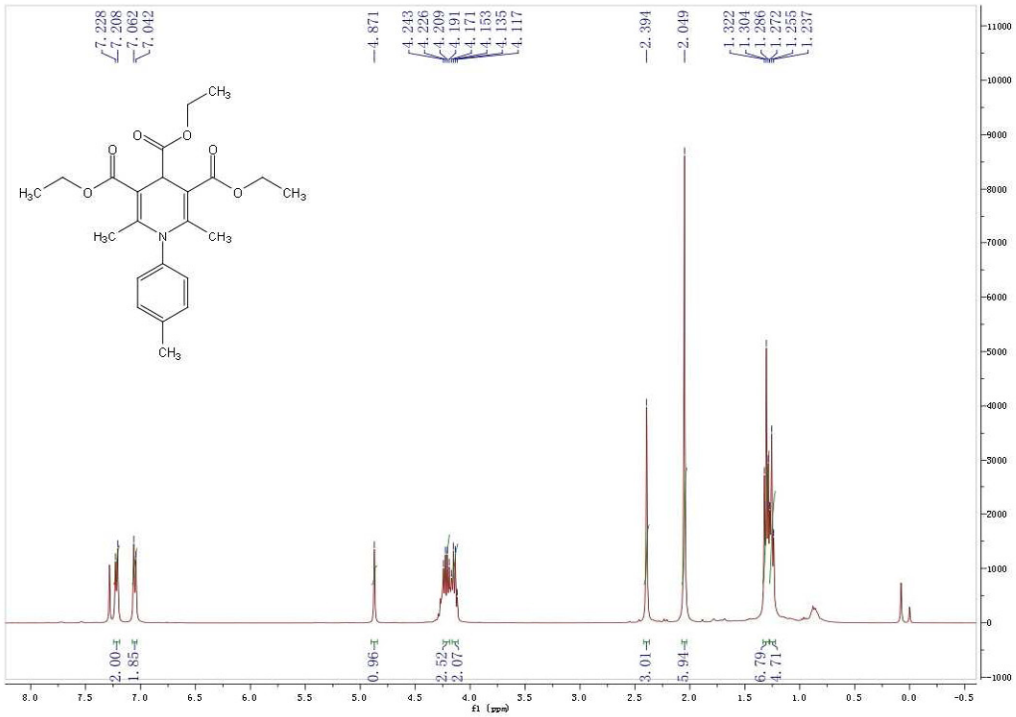
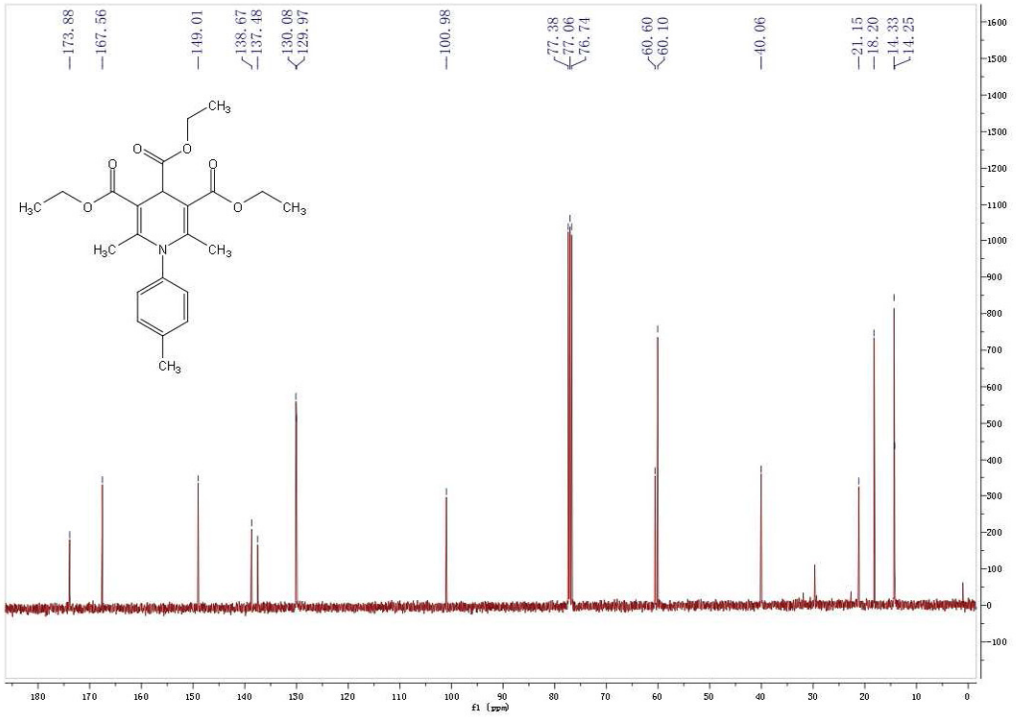
NMR spectra for all compounds

4a





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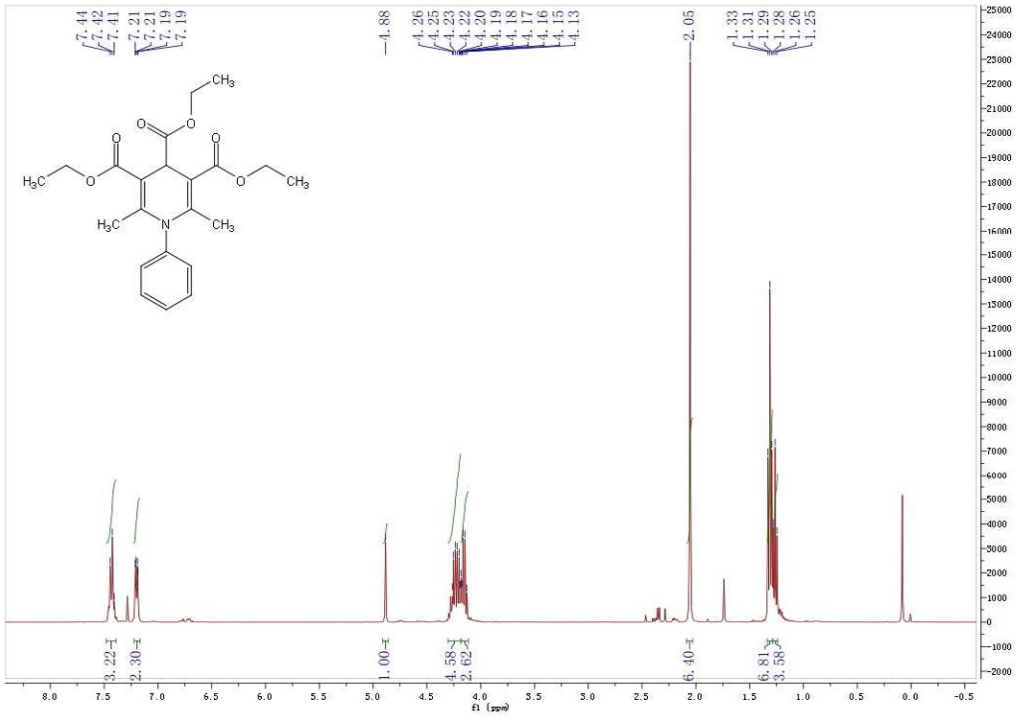
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4.17
4.16
4.15
4.13
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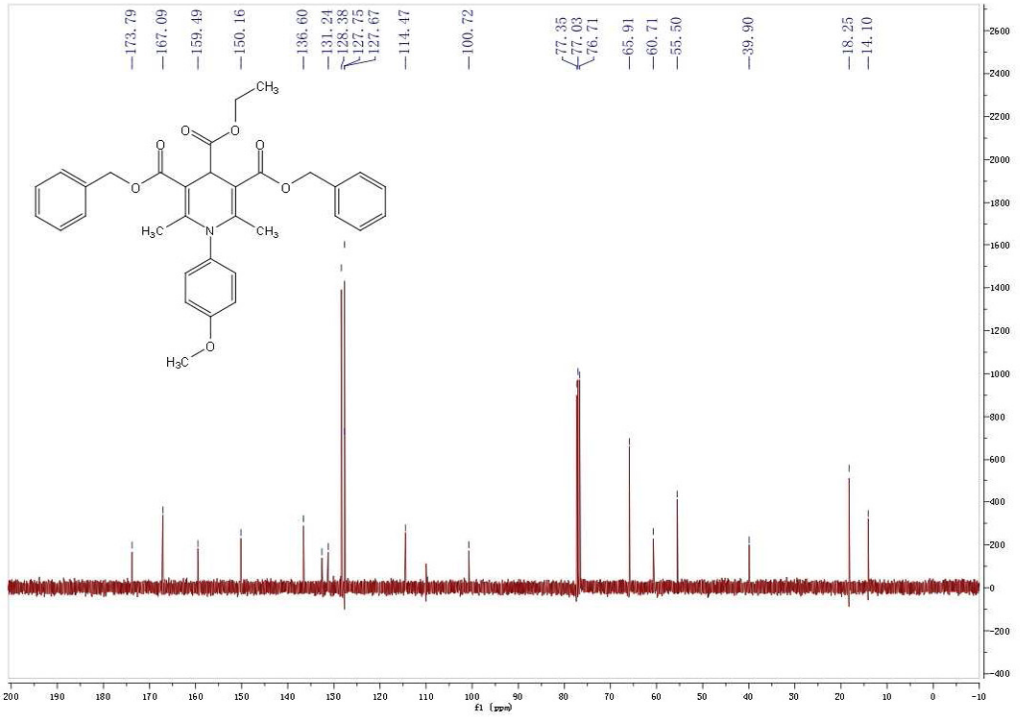
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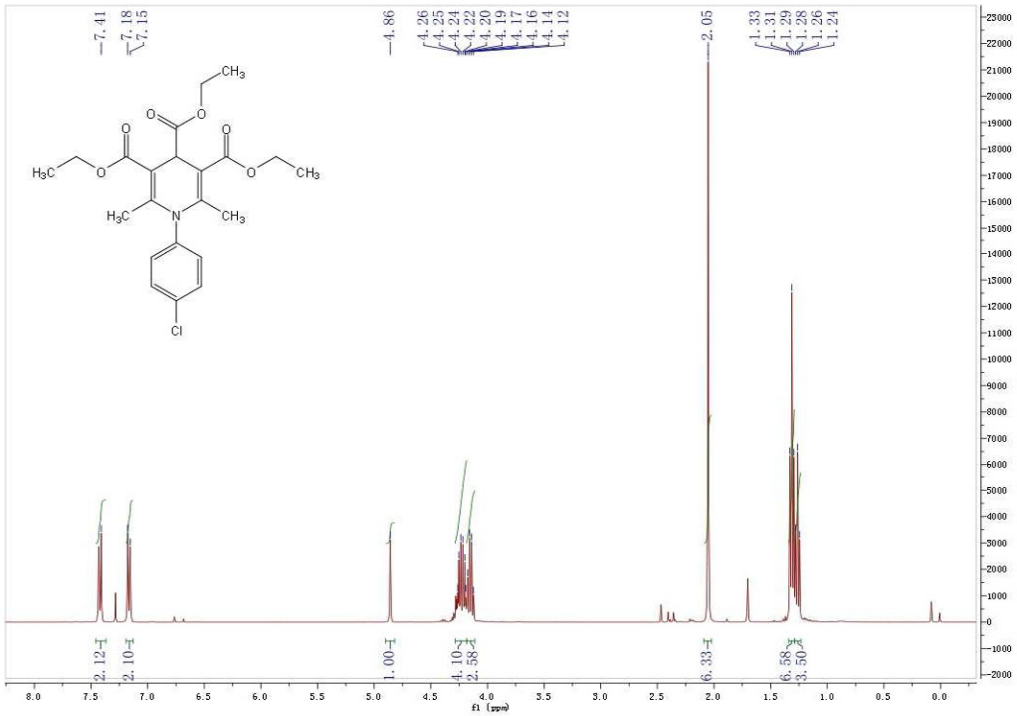
4c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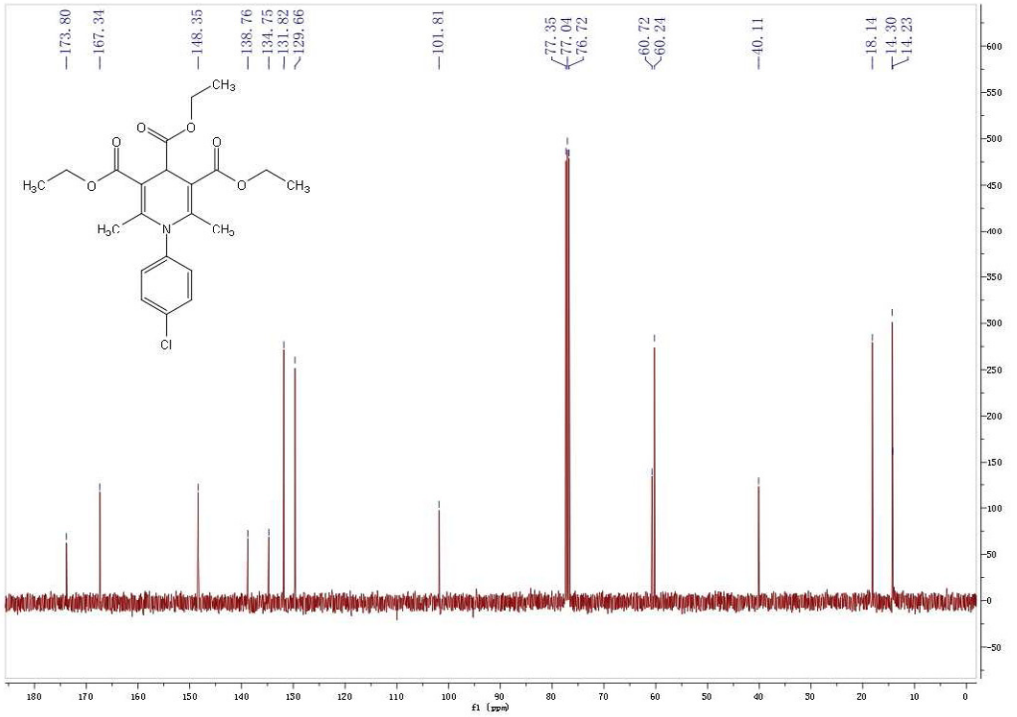
f1 (ppm)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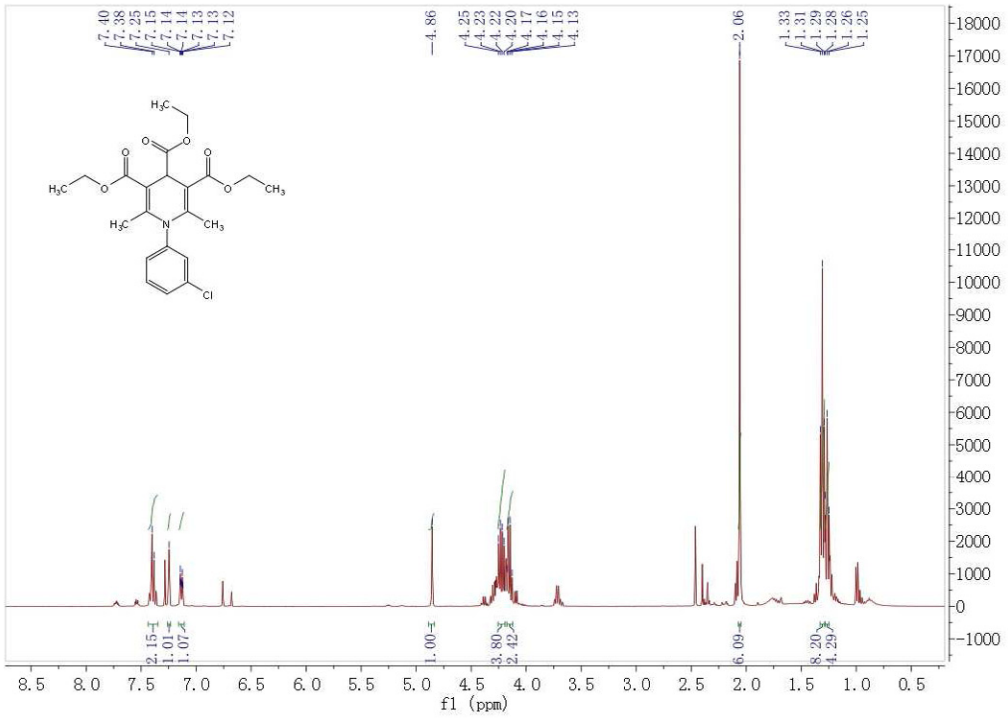
4d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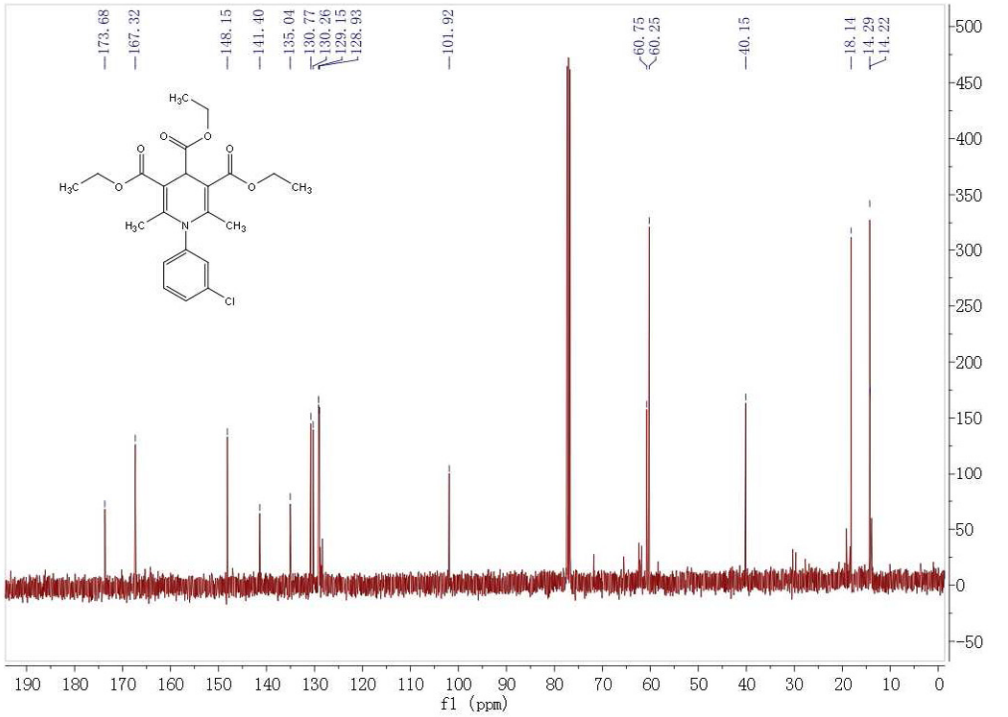
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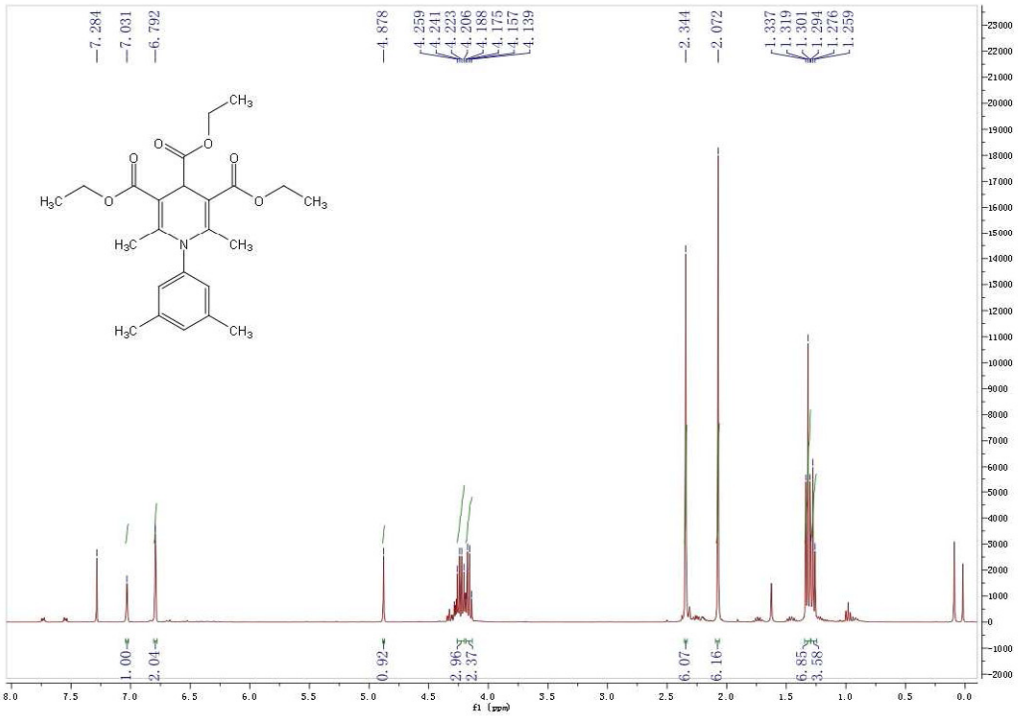
f1 (ppm)

4f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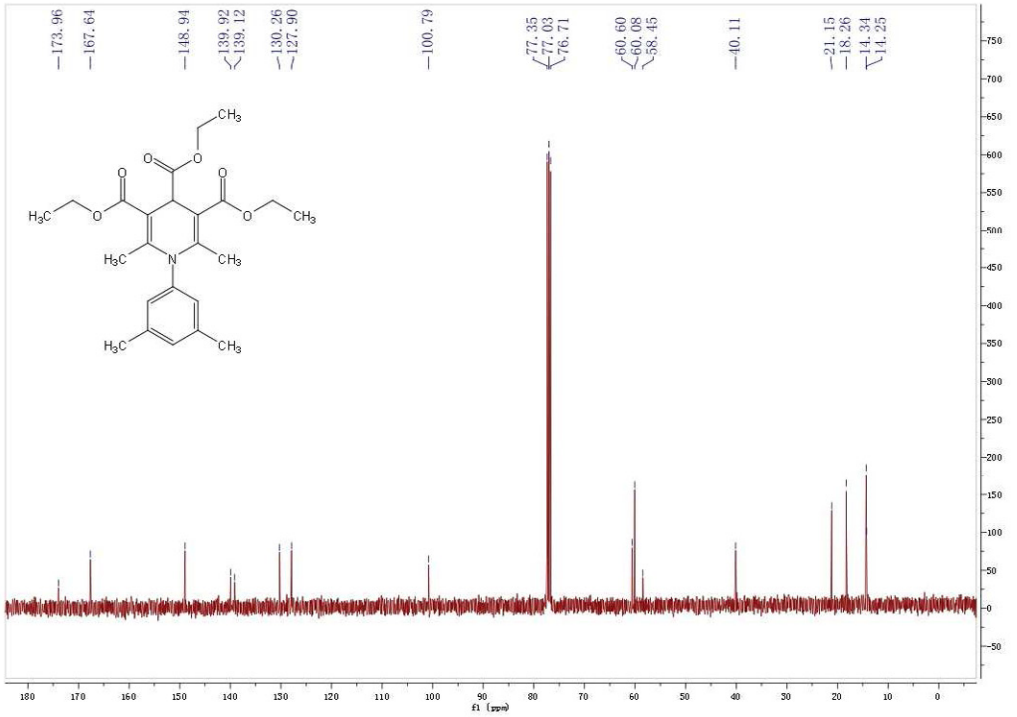
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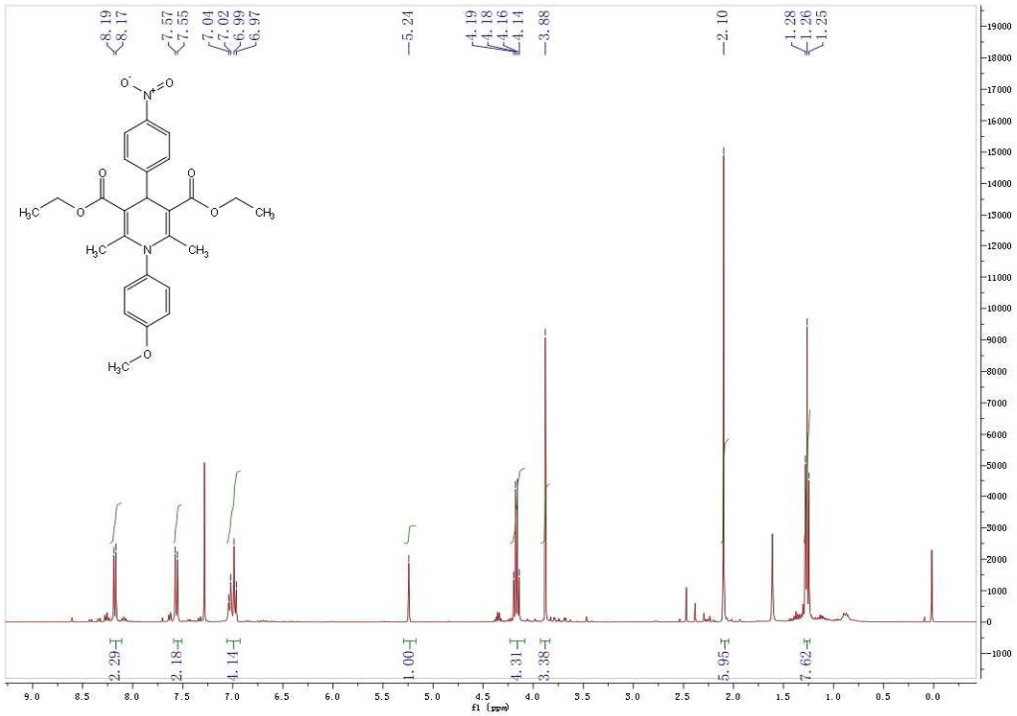
4g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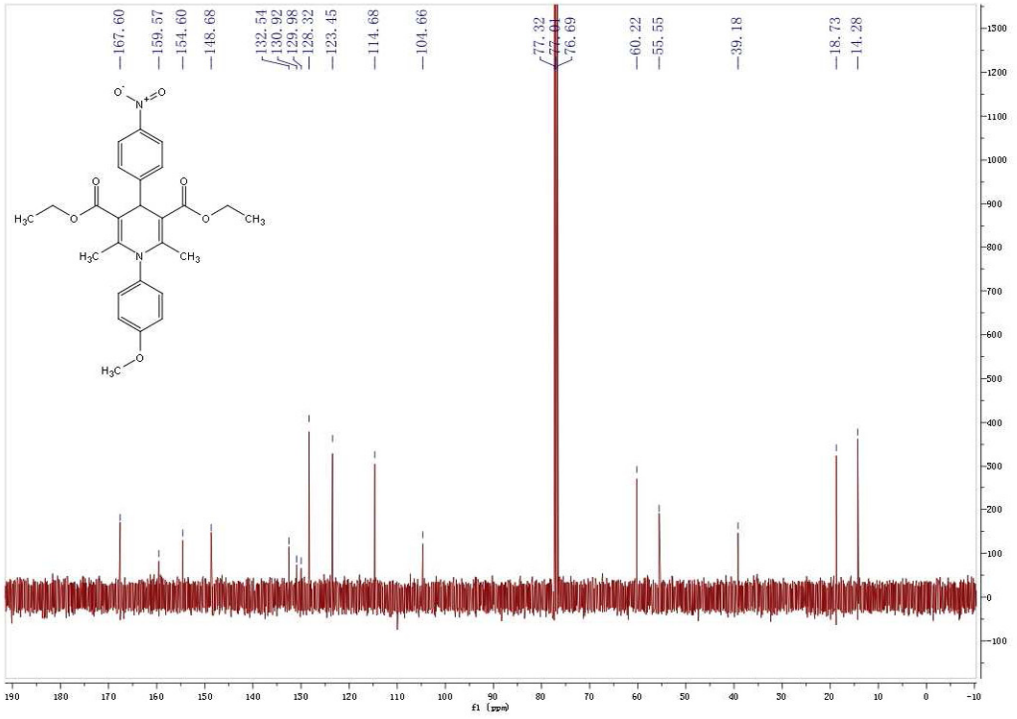
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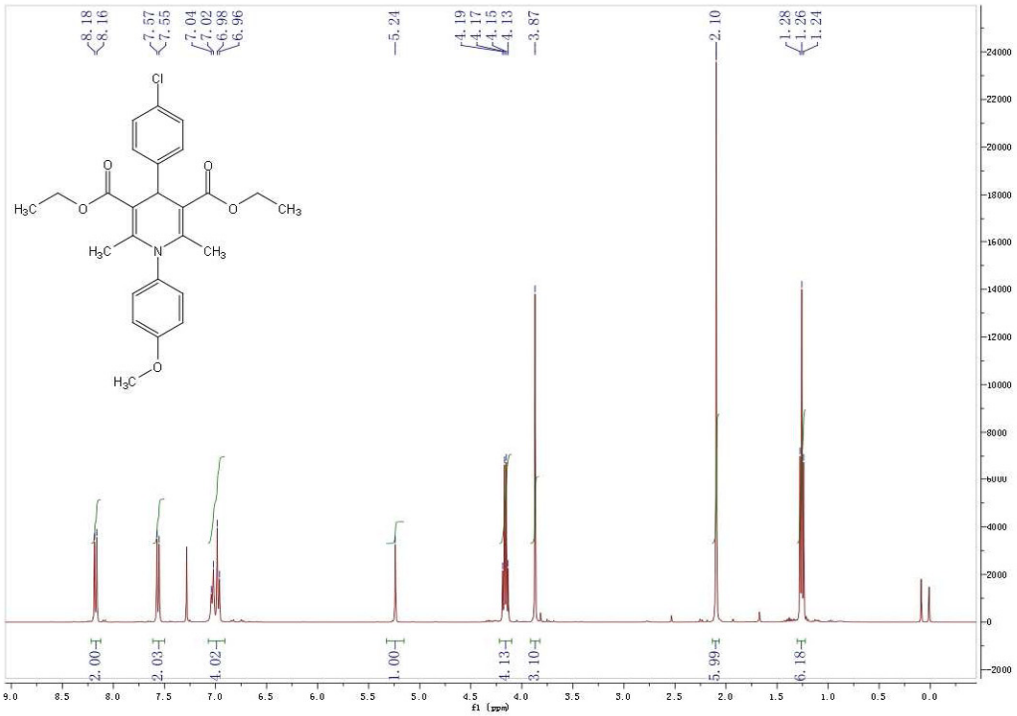
4h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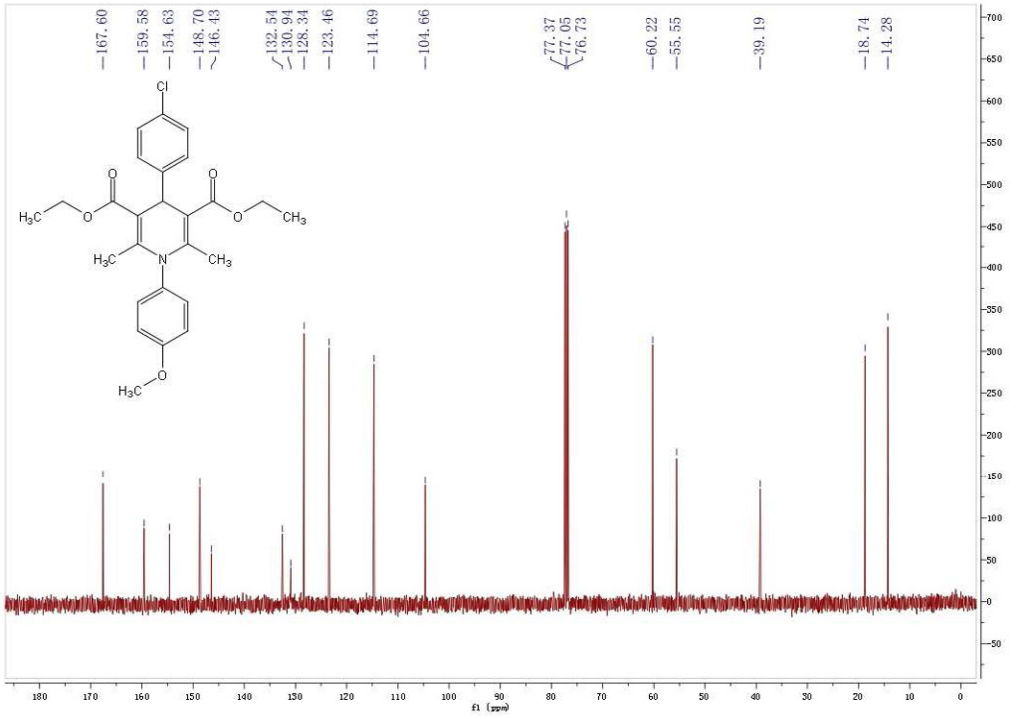
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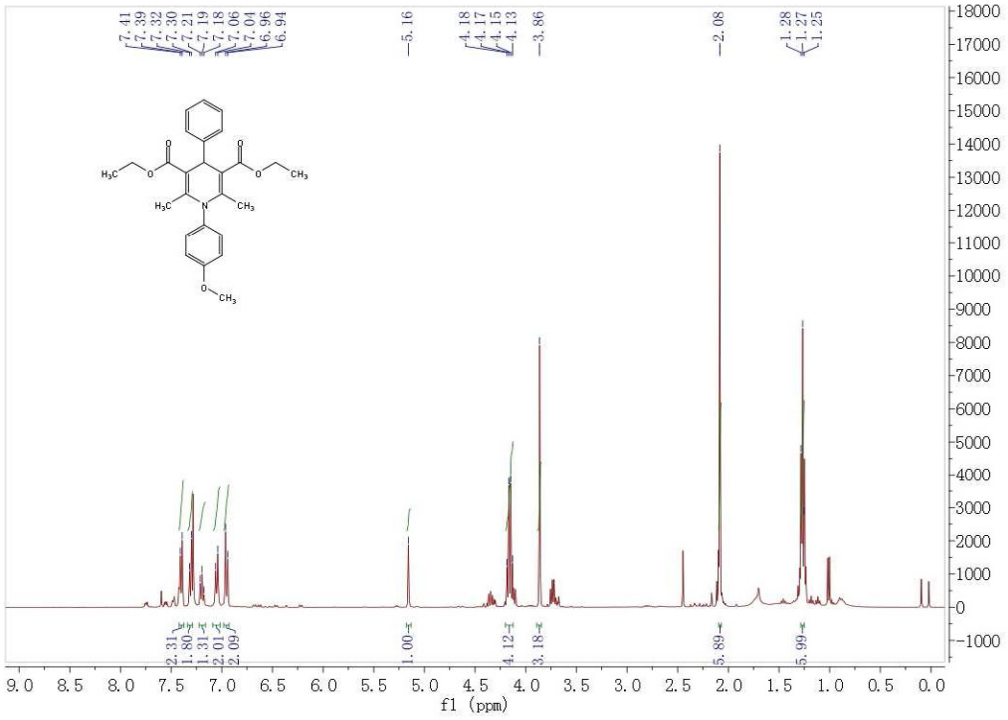
4i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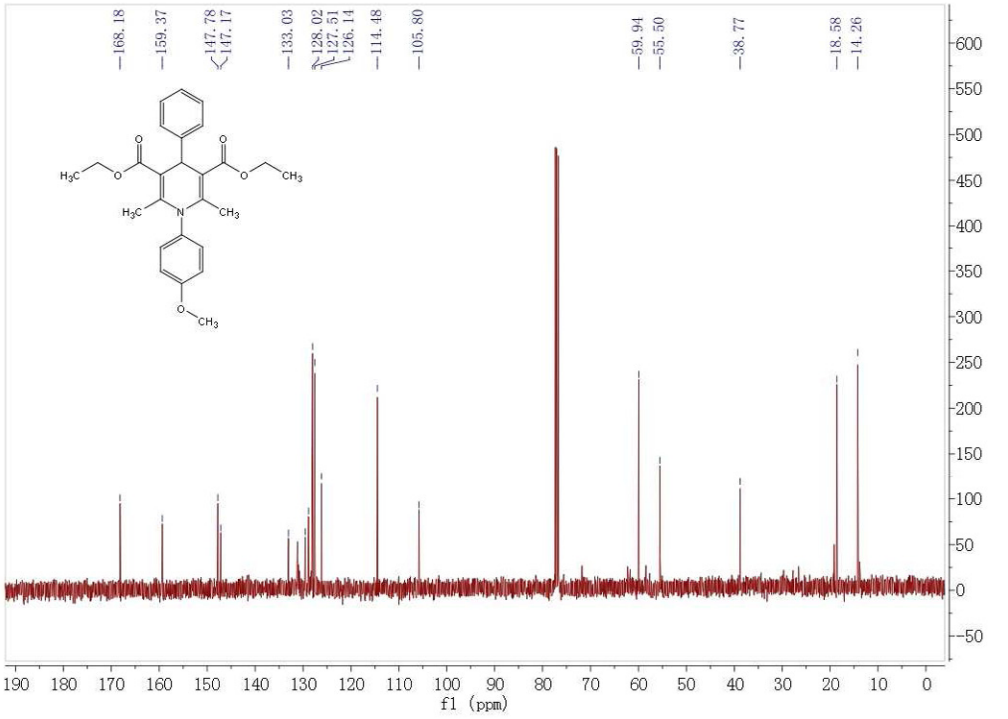
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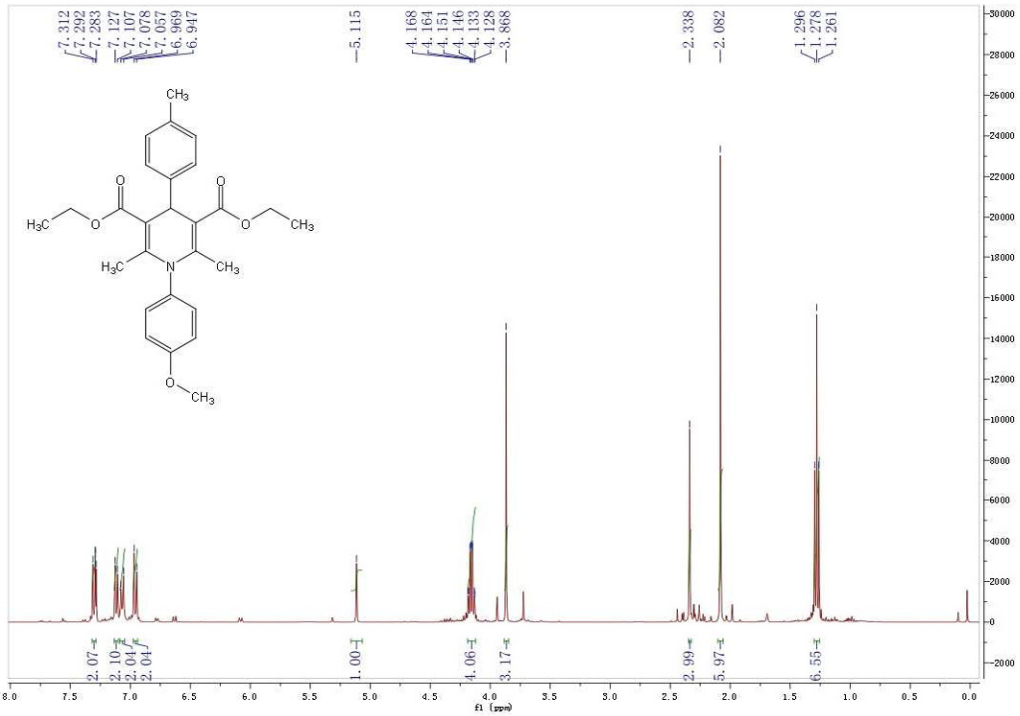
4j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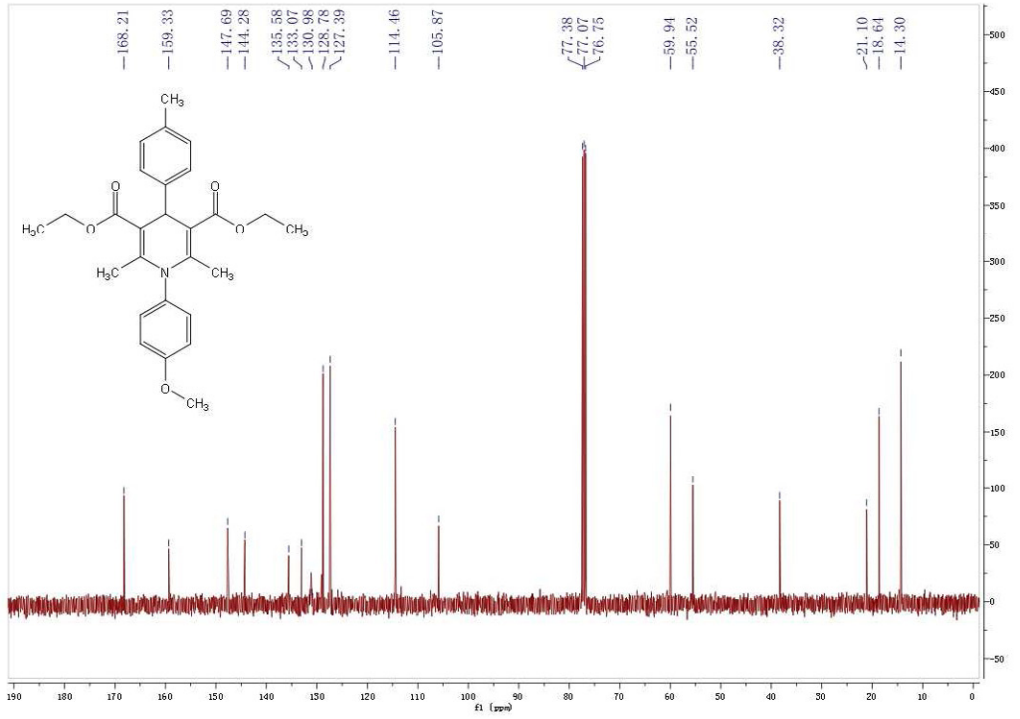
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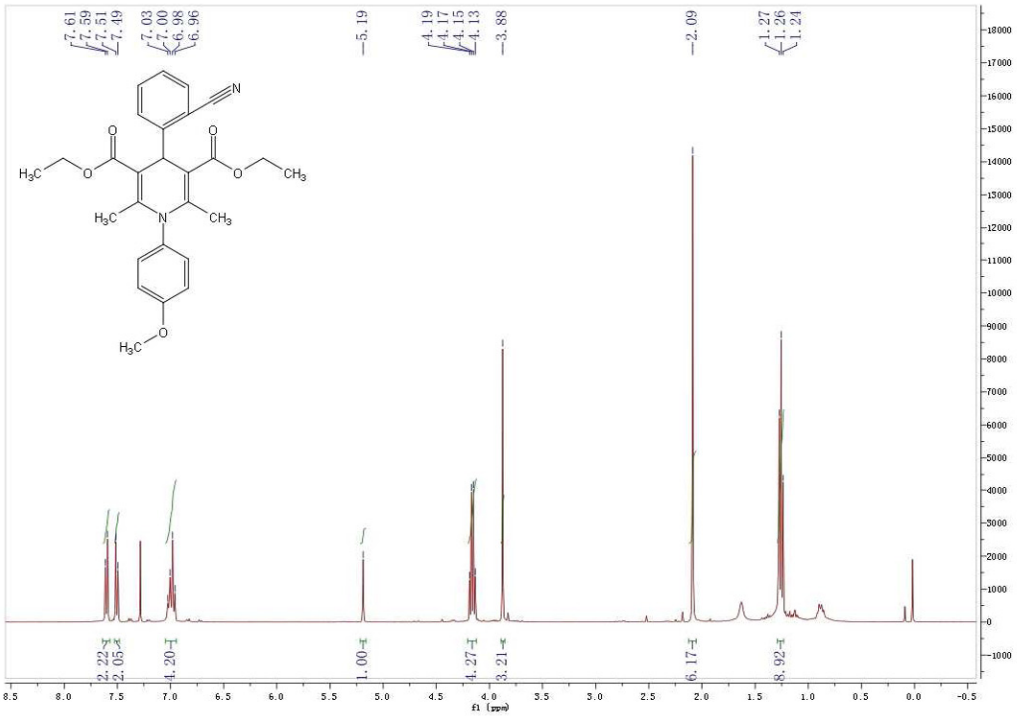
4k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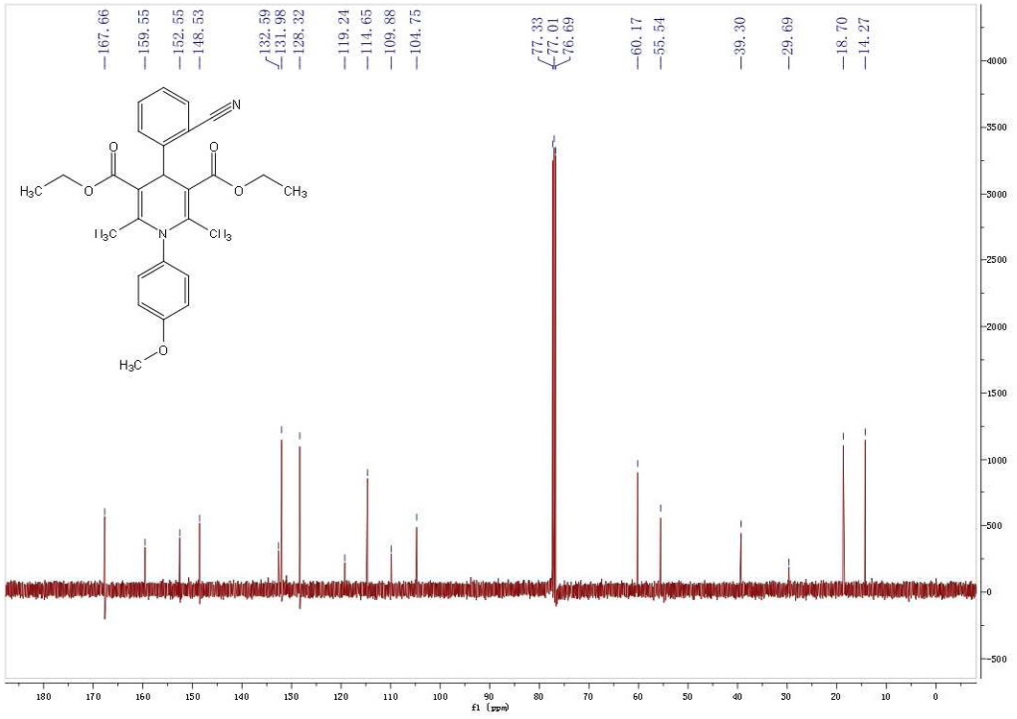
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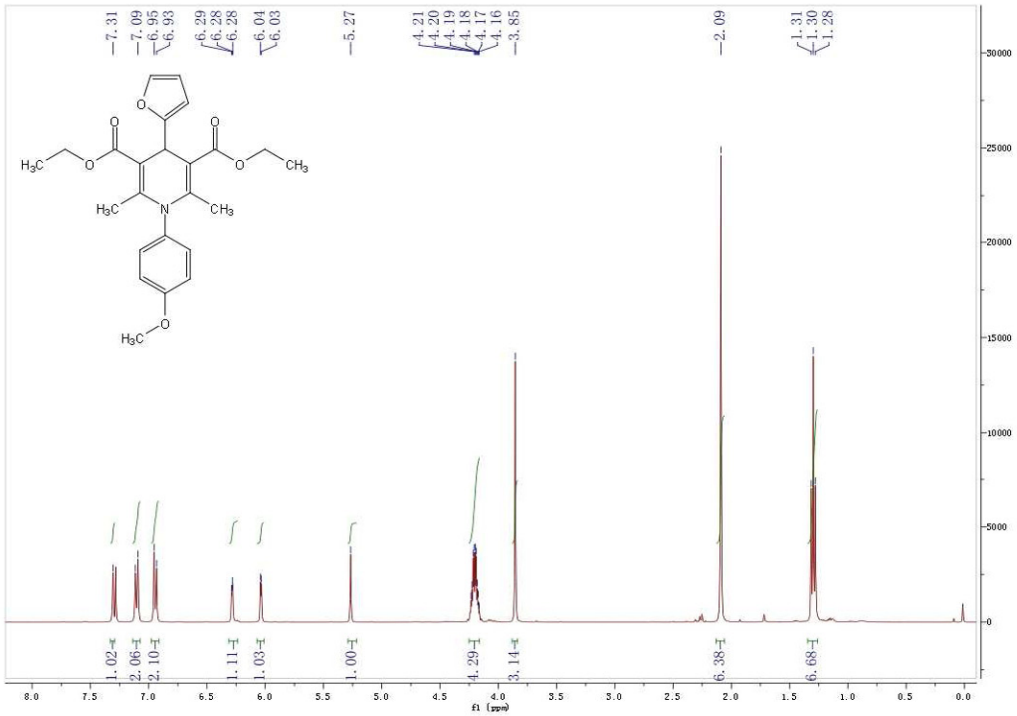
4l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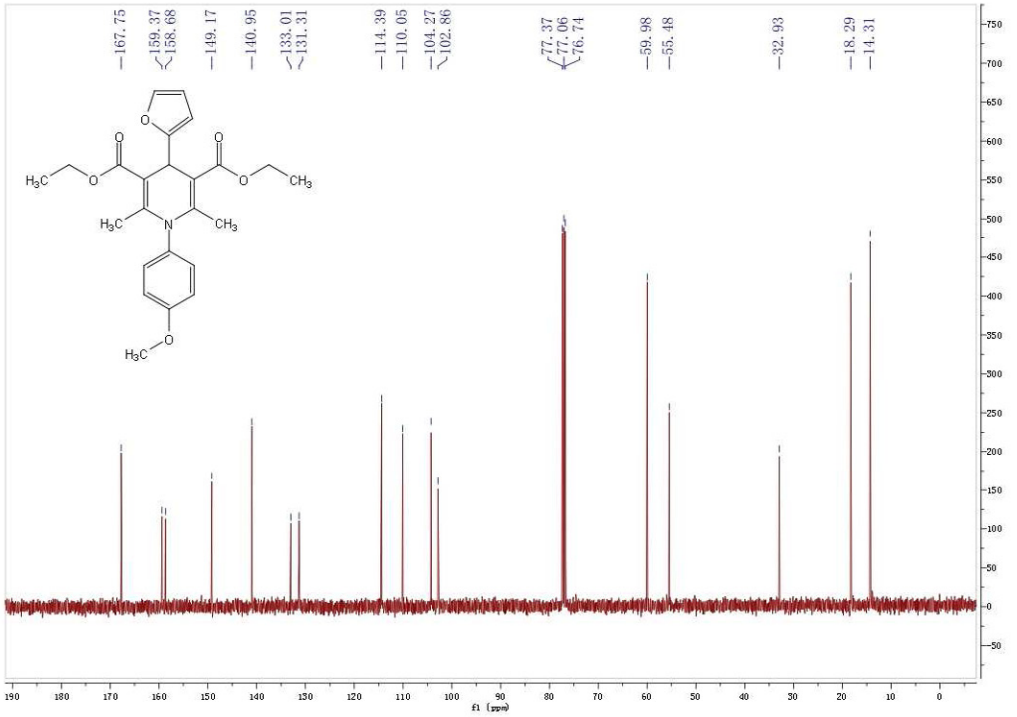
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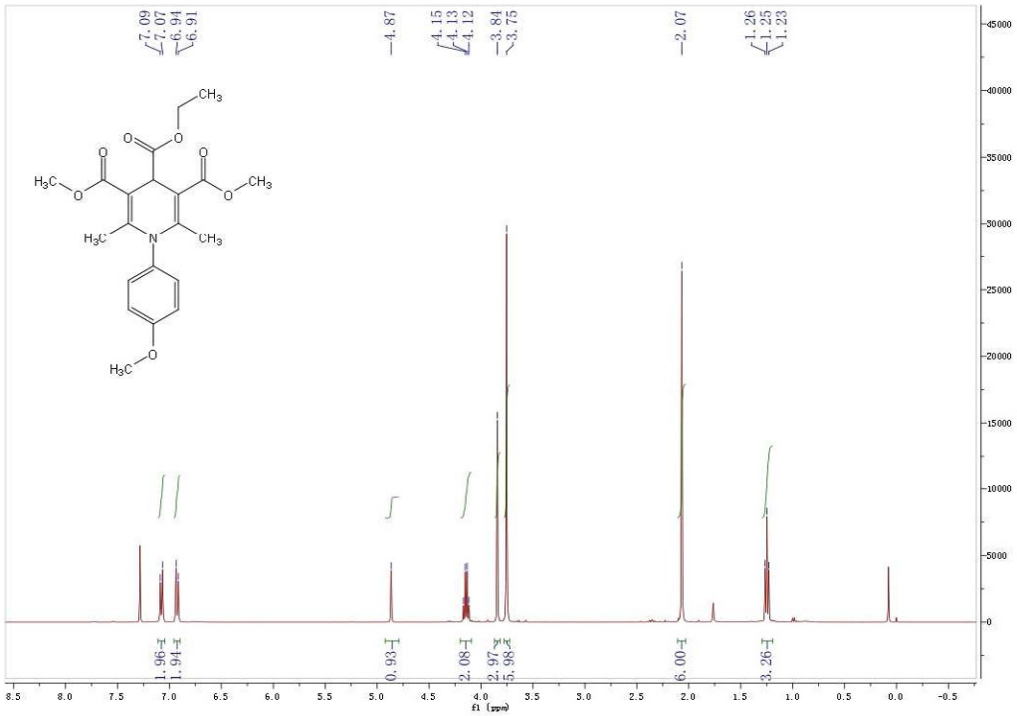
4m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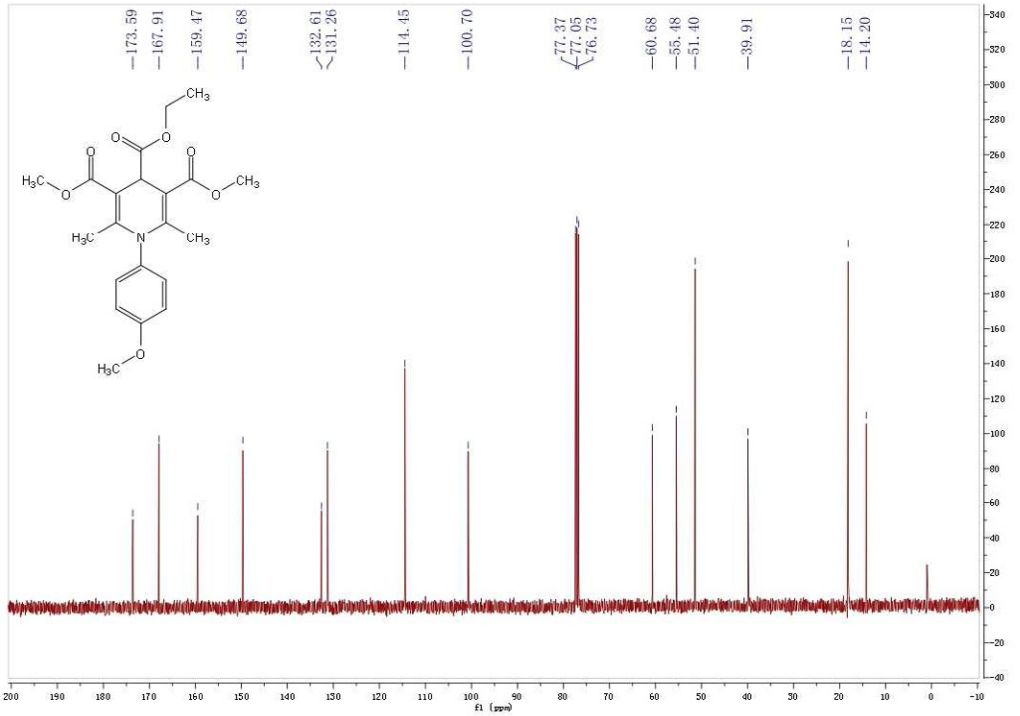
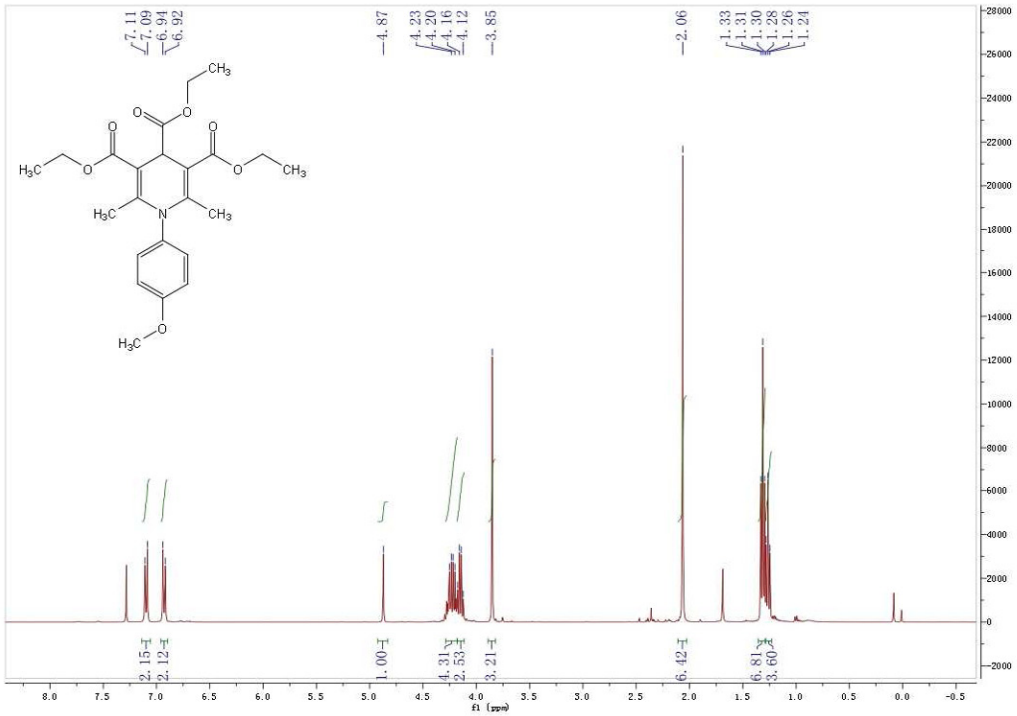
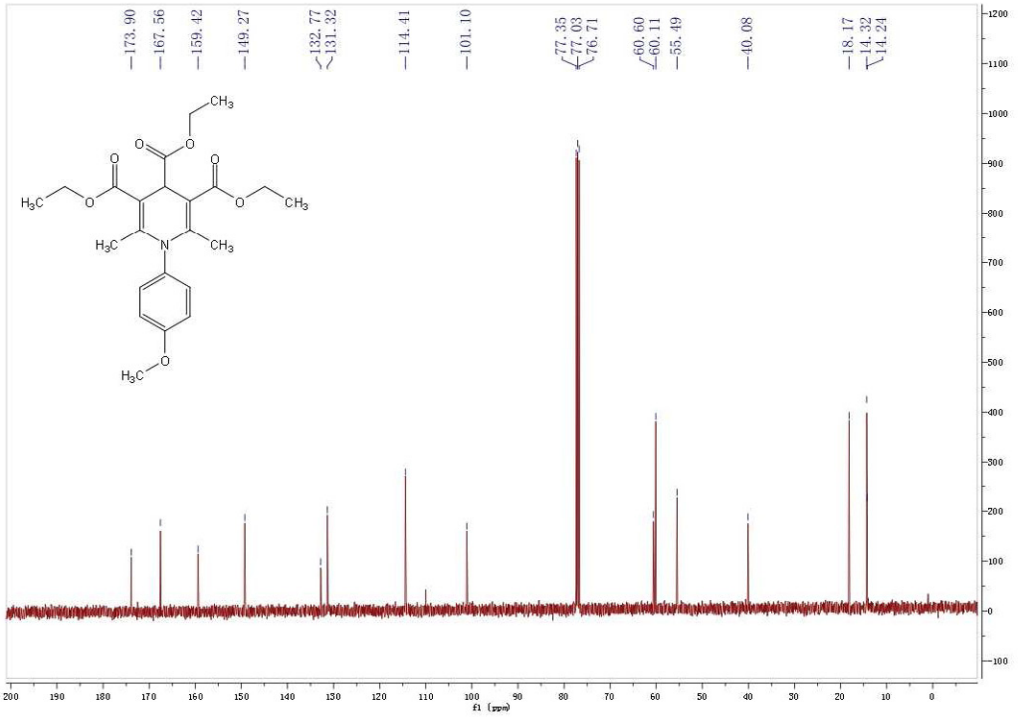
3.75
2.07
1.26
1.25
1.23
1.96
1.94
0.93
2.08
2.97
5.98
6.00
3.26
f1 (ppm)

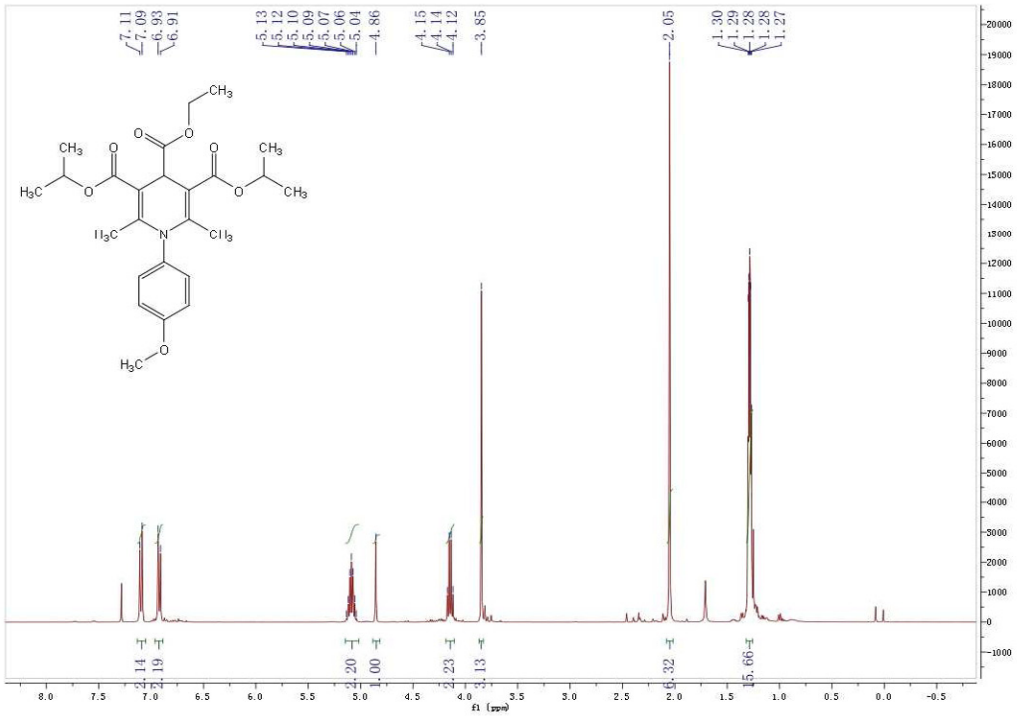

173.59
167.91
159.47
149.68
132.61
131.26
114.45
100.70
77.37
77.05
76.73
60.68
55.48
51.40
39.91
18.15
14.20
f1 (ppm)

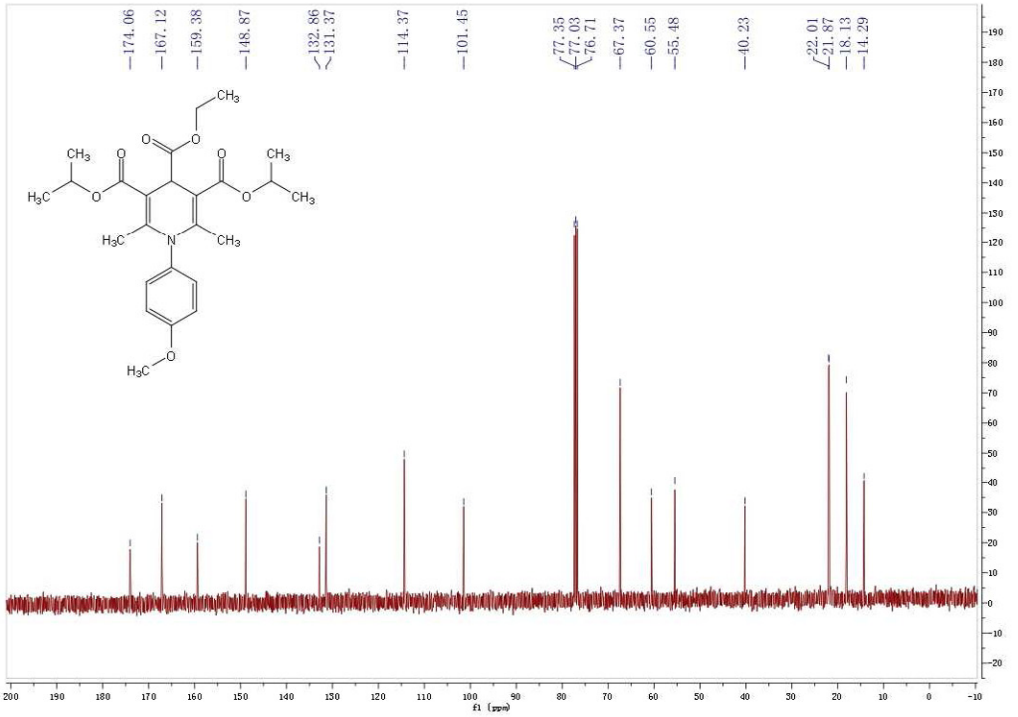
4n


7.11
7.09
6.94
6.92
4.87
4.23
4.20
4.16
4.12
3.85
2.06
1.33
1.31
1.30
1.28
1.26
1.24
2.15
2.12
1.00
4.31
2.53
3.21
6.42
6.81
3.60
f1 (ppm)

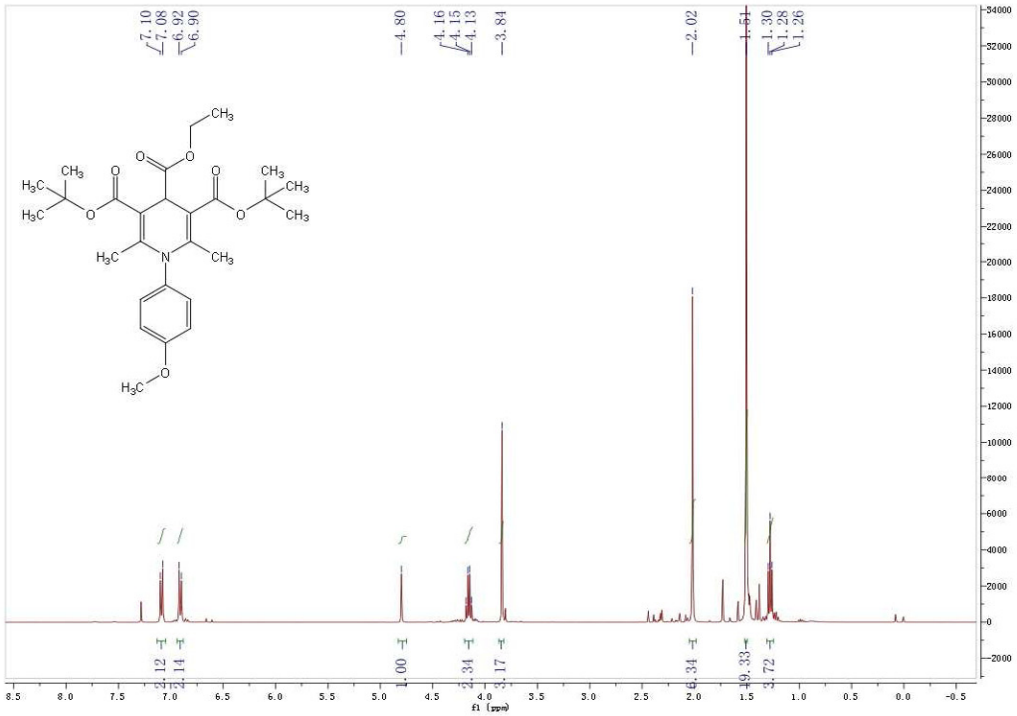

173.90
167.56
159.42
149.27
132.77
131.32
114.41
101.10
77.35
77.03
76.71
60.60
60.11
55.49
40.08
18.17
14.32
14.24
f1 (ppm)

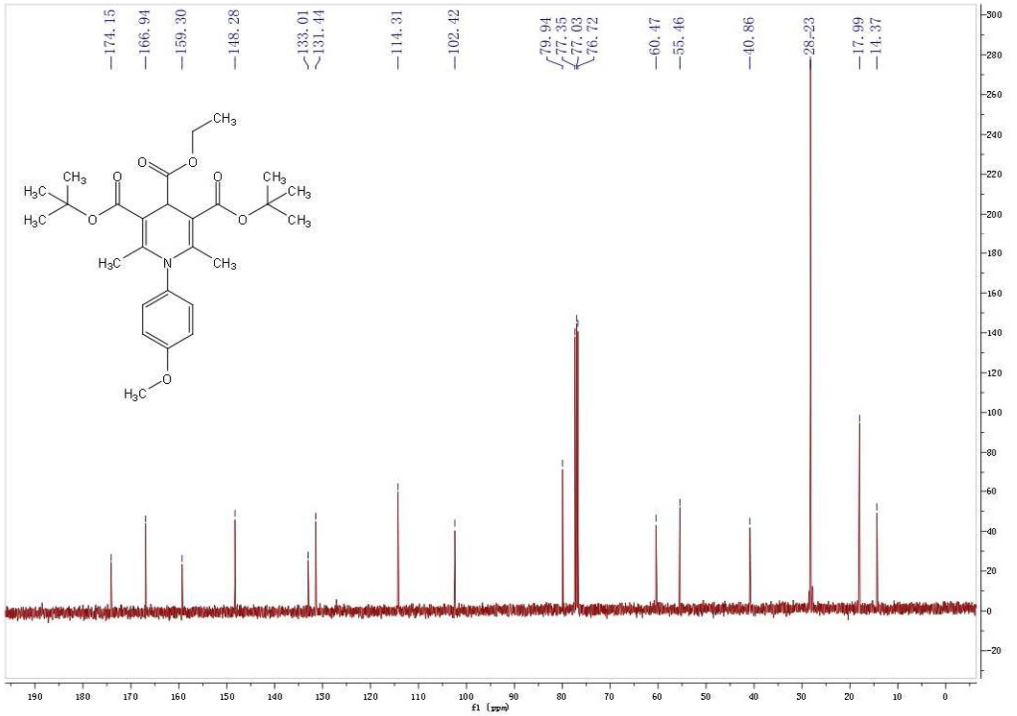
4o


7.11
7.09
6.93
6.91
5.13
5.12
5.10
5.09
5.07
5.06
5.04
4.86
4.15
4.14
4.12
3.85
2.05
1.30
1.29
1.28
1.28
1.27
14
19
20
00
23
13
32
66
f1 (ppm)

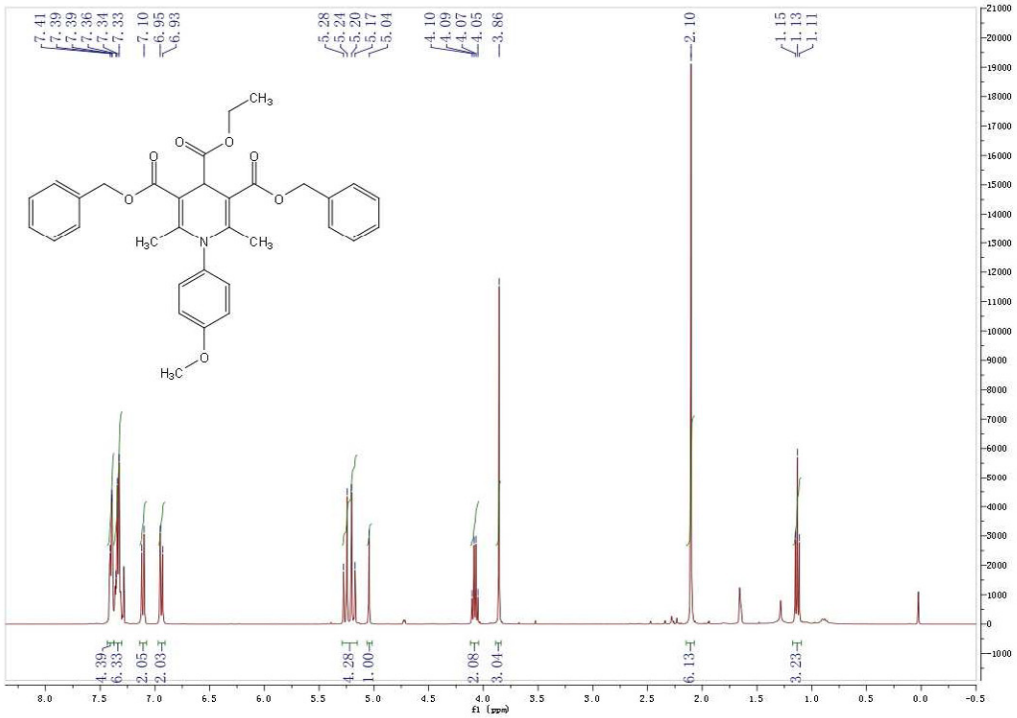

174.06
167.12
159.38
148.87
132.86
131.37
114.37
101.45
77.35
77.03
76.71
67.37
60.55
55.48
40.23
22.01
21.87
18.13
14.29
f1 (ppm)

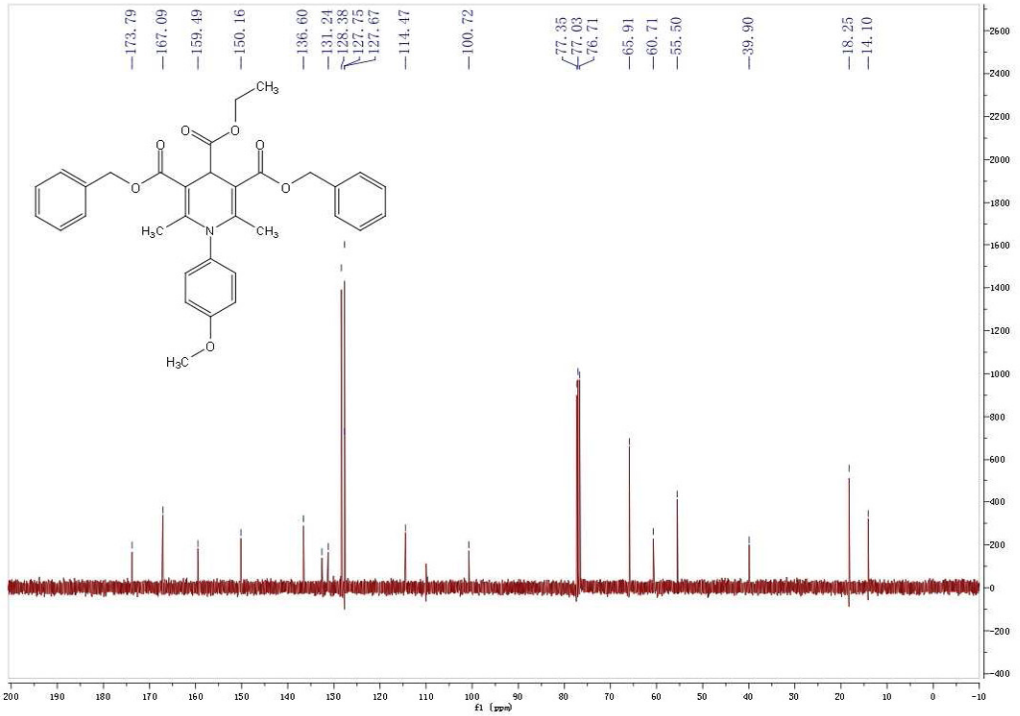
4p


7.10
7.08
6.92
6.90
4.80
4.16
4.15
4.13
3.84
2.02
1.61
1.30
1.28
1.26
2.12
2.14
1.00
2.34
3.17
6.34
19.33
3.72
f1 (ppm)

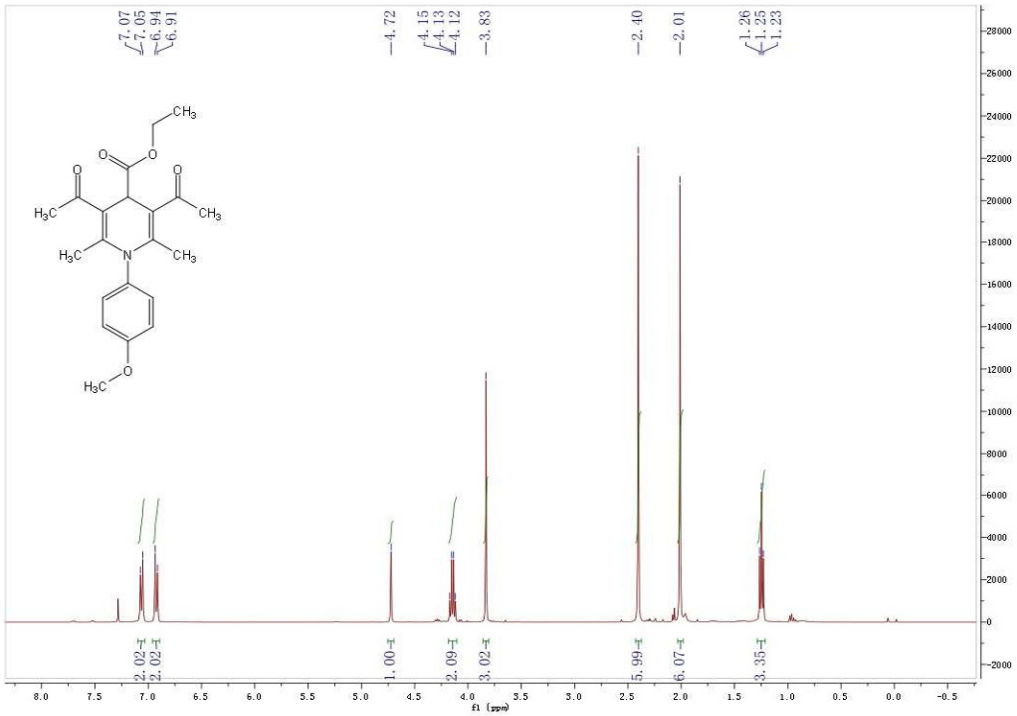

174.15
166.94
159.30
148.28
133.01
131.44
114.31
102.42
79.94
77.35
77.03
76.72
60.47
55.46
40.86
28.23
17.99
14.37
f1 (ppm)

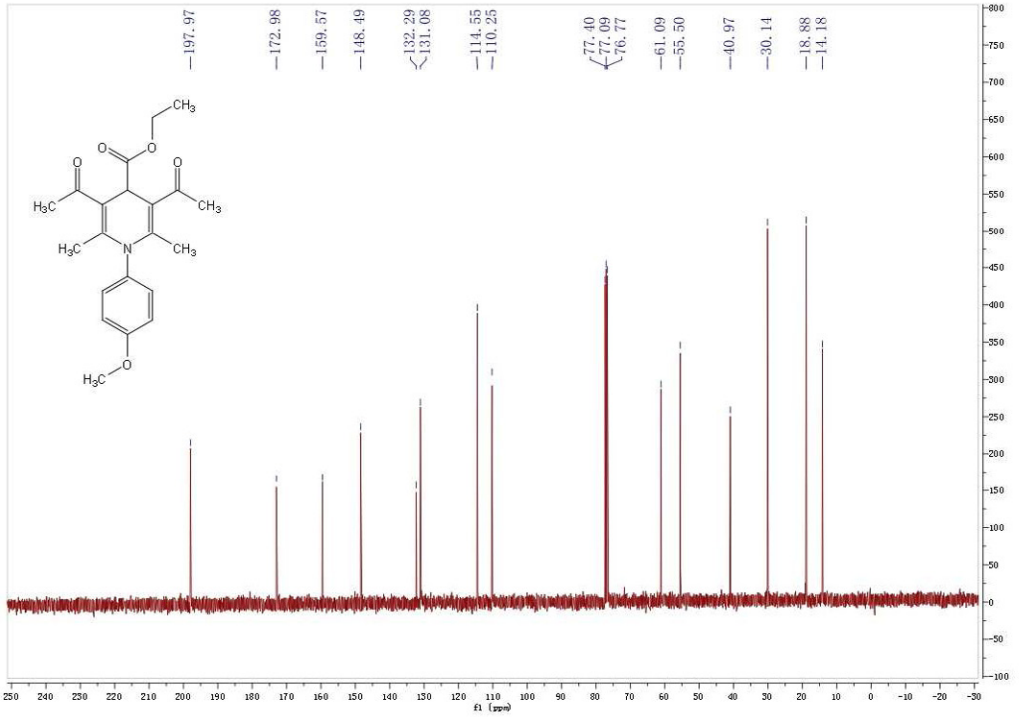
4q


7.41
7.39
7.39
7.36
7.34
7.33
7.10
6.95
6.93
5.28
5.24
5.20
5.17
5.04
4.10
4.09
4.07
4.05
3.86
2.10
1.15
1.13
1.11
4.39
6.33
2.05
2.03
4.28
1.00
2.08
3.04
6.13
3.23
f1 (ppm)

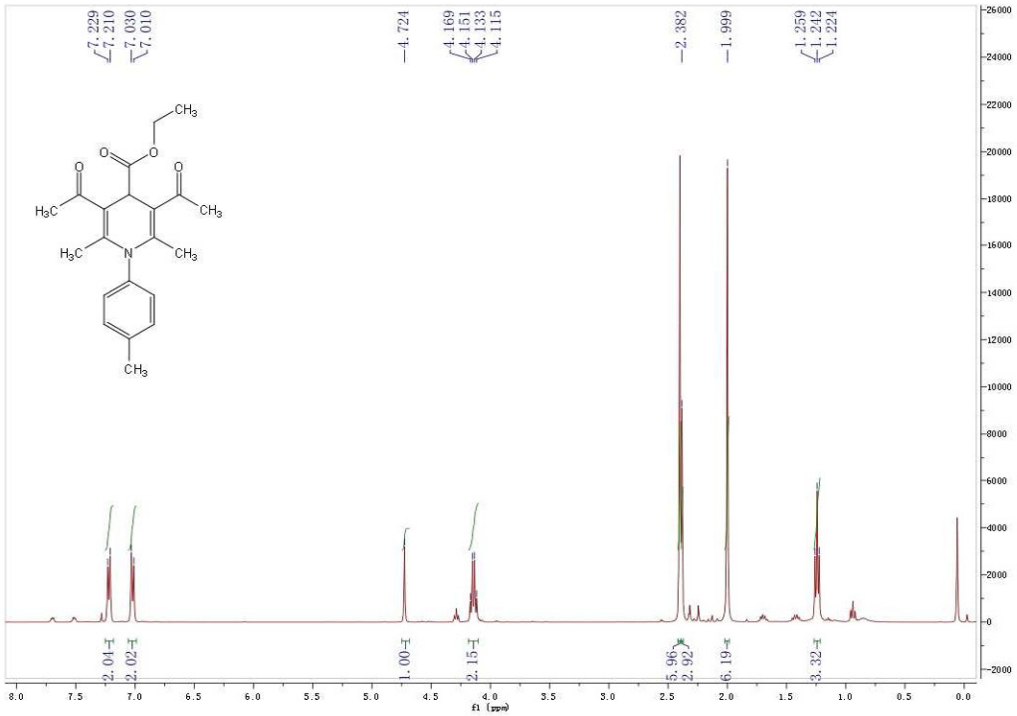

173.79
167.09
159.49
150.16
136.60
131.24
128.38
127.75
127.67
114.47
100.72
77.35
77.03
76.71
65.91
60.71
55.50
39.90
18.25
14.10
f1 (ppm)

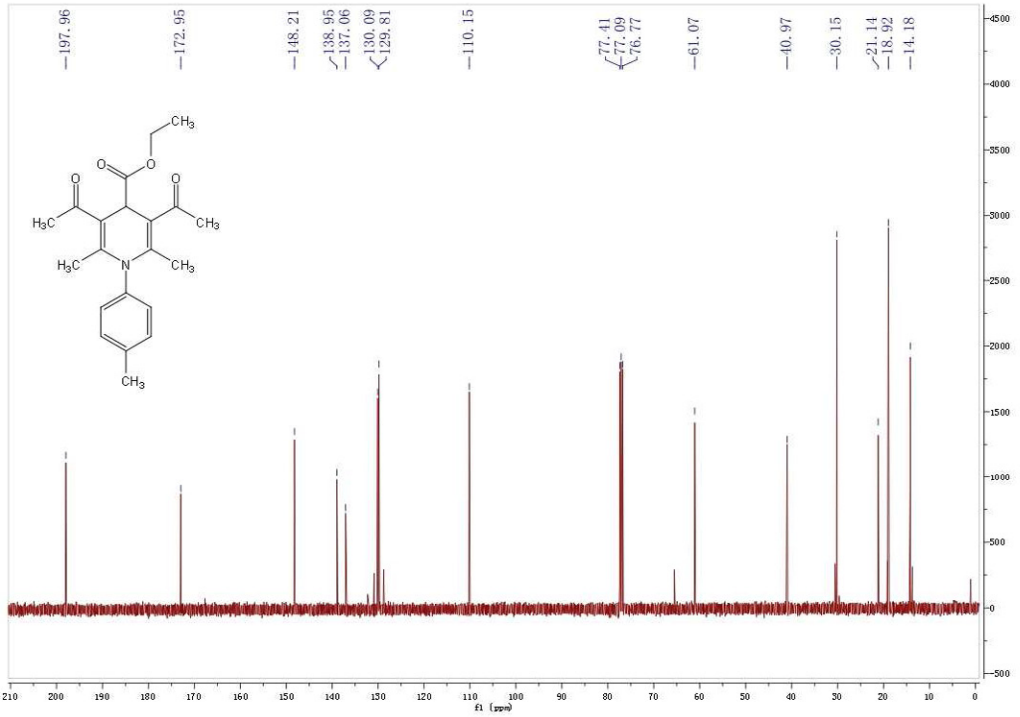
4r


7.07
7.05
6.94
6.91
4.72
4.15
4.13
4.12
3.83
2.40
2.01
1.26
1.25
1.23
2.02
2.02
1.00
2.09
3.02
5.99
6.07
3.35
f1 (ppm)

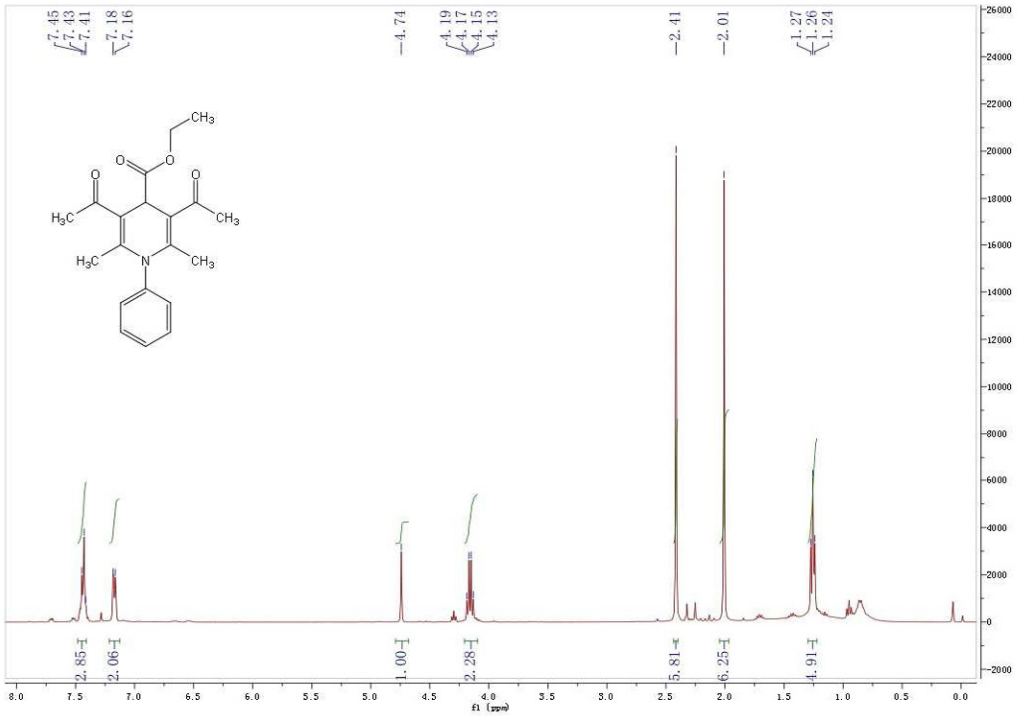

197.97
172.98
159.57
148.49
132.29
131.08
114.55
110.25
77.40
77.09
76.77
61.09
55.50
40.97
30.14
18.88
14.18
f1 (ppm)

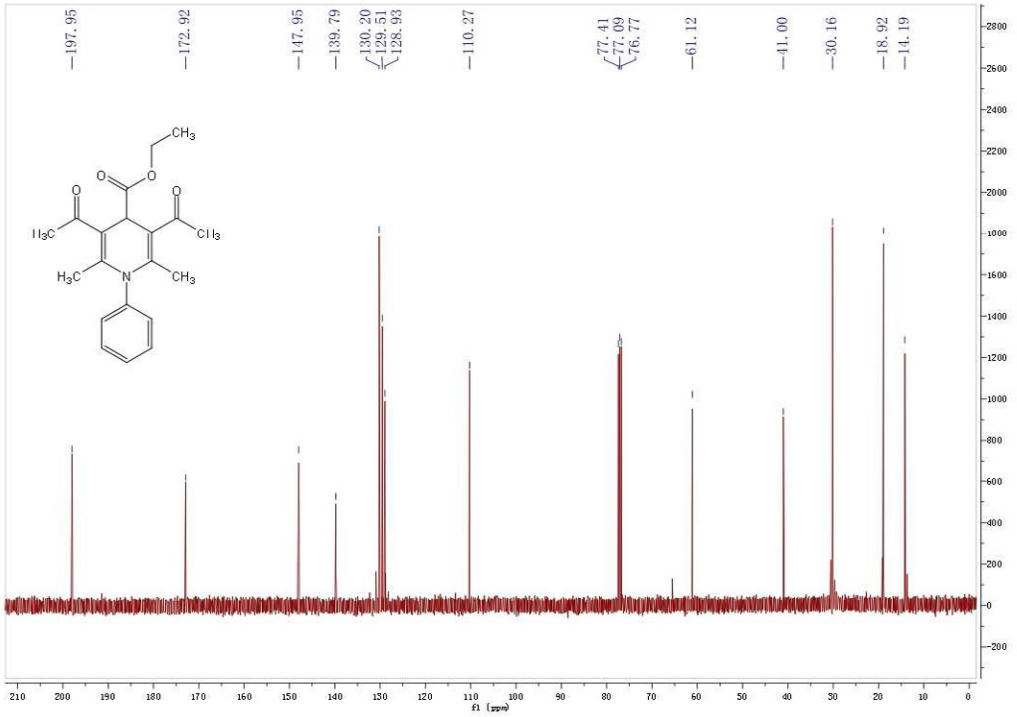
4s


7.229
7.210
7.030
7.010
4.724
4.169
4.151
4.133
4.115
2.382
1.999
1.259
1.242
1.224
2.04
2.02
1.00
2.15
5.96
2.92
6.19
3.32
f1 (ppm)

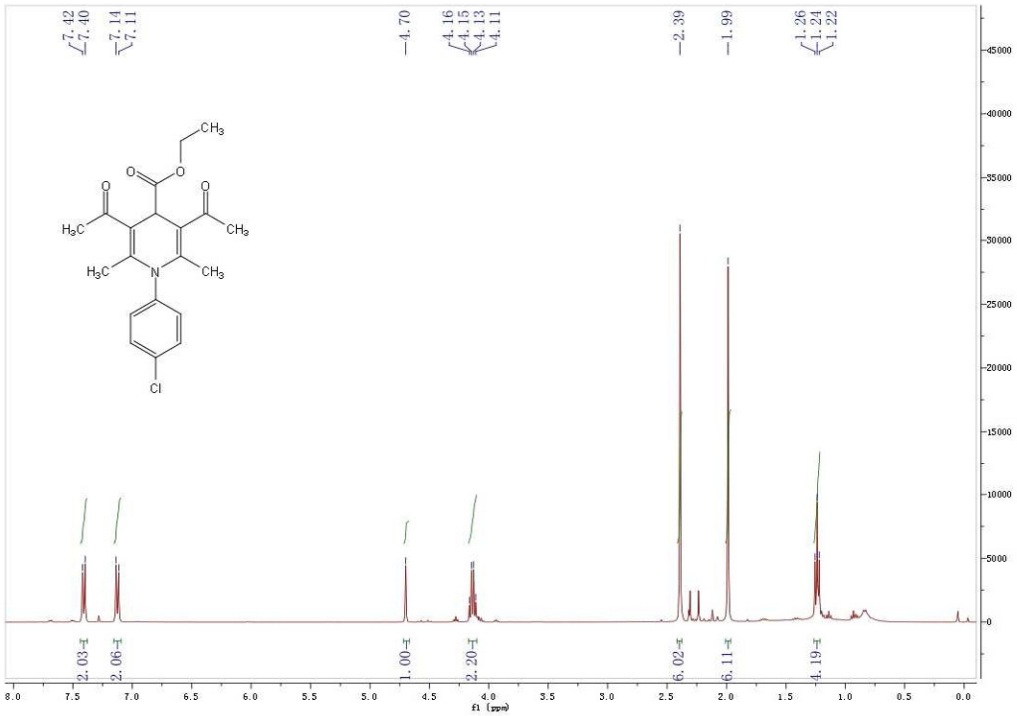

197.96
172.95
148.21
138.95
137.06
130.09
129.81
110.15
77.41
77.09
76.77
61.07
40.97
30.15
21.14
18.92
14.18
f1 (ppm)

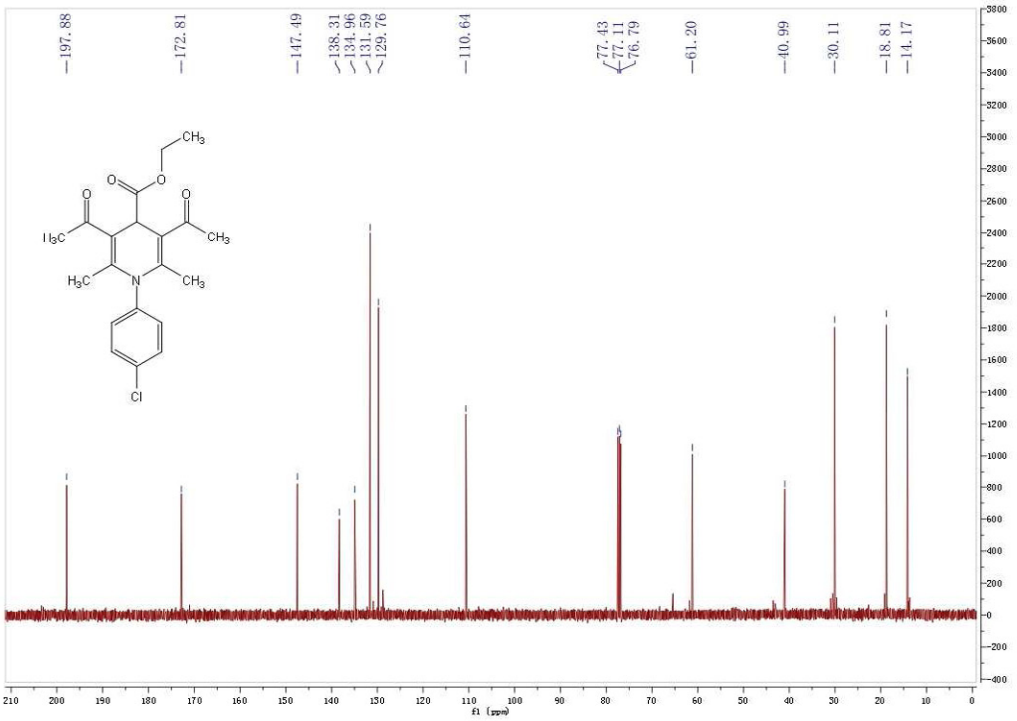
4t


7.45
7.43
7.41
7.18
7.16
4.74
4.19
4.17
4.15
4.13
2.41
2.01
1.27
1.26
1.24
2.85
2.06
1.00
2.28
5.81
6.25
4.91
f1 (ppm)

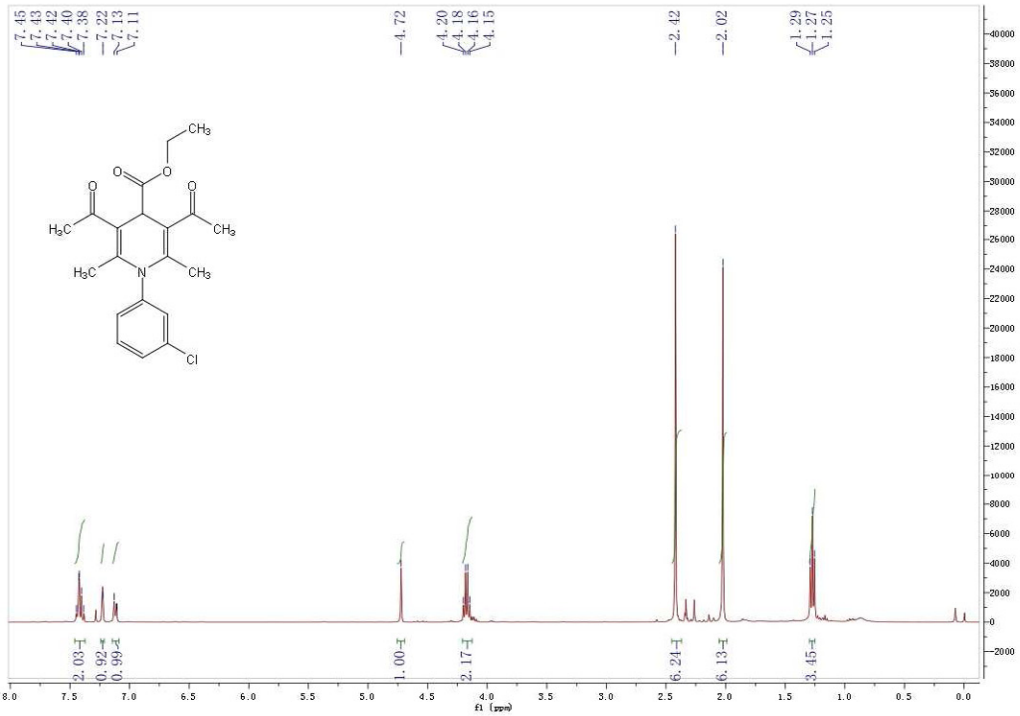

197.95
172.92
147.95
139.79
130.20
129.51
128.93
110.27
77.41
77.09
76.77
61.12
41.00
30.16
18.92
14.19
f1 (ppm)

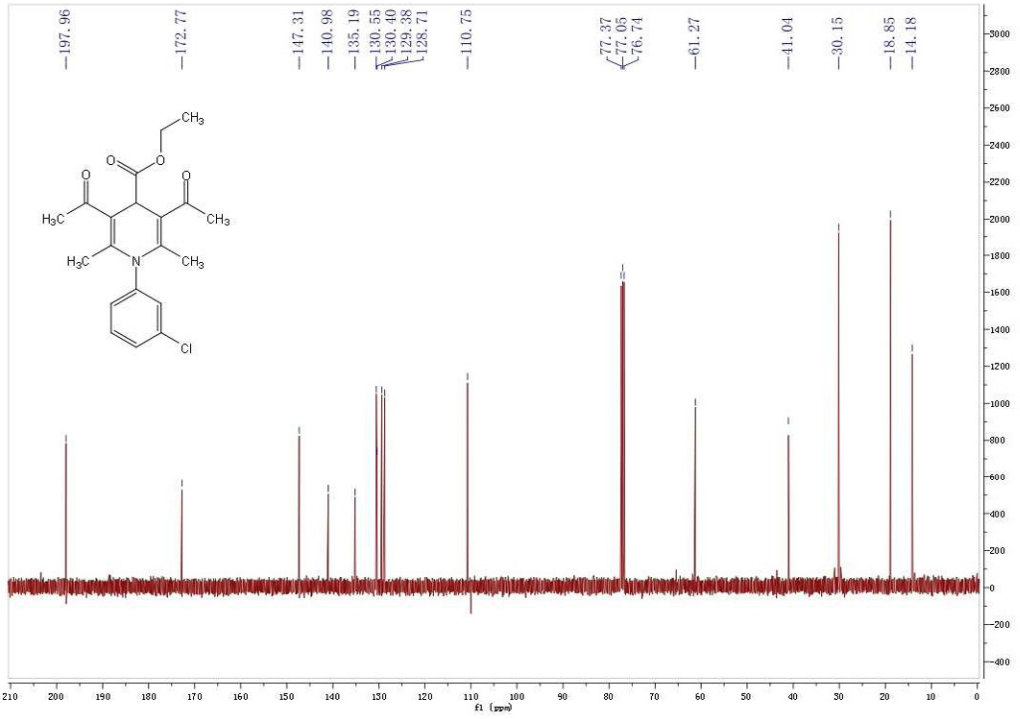
4u


7.42
7.40
7.14
7.11
4.70
4.16
4.15
4.13
4.11
2.39
1.99
1.26
1.24
1.22
2.03
2.06
1.00
2.20
6.02
6.11
4.19
f1 (ppm)

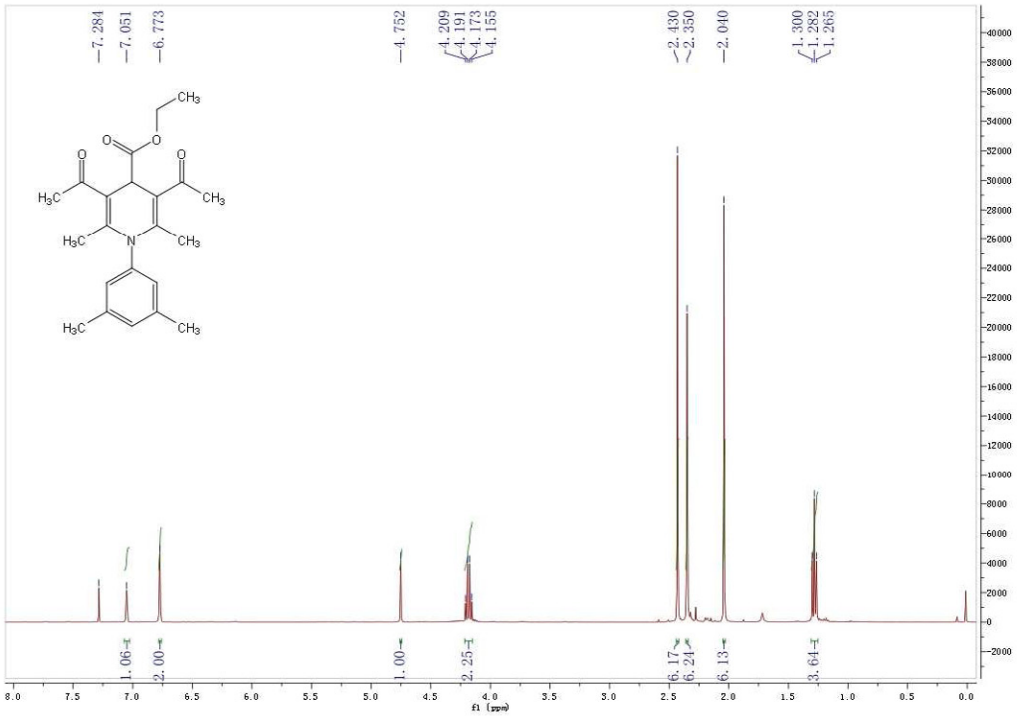

197.88
172.81
147.49
138.31
134.96
131.59
129.76
110.64
77.43
77.11
76.79
61.20
40.99
30.11
18.81
14.17
f1 (ppm)

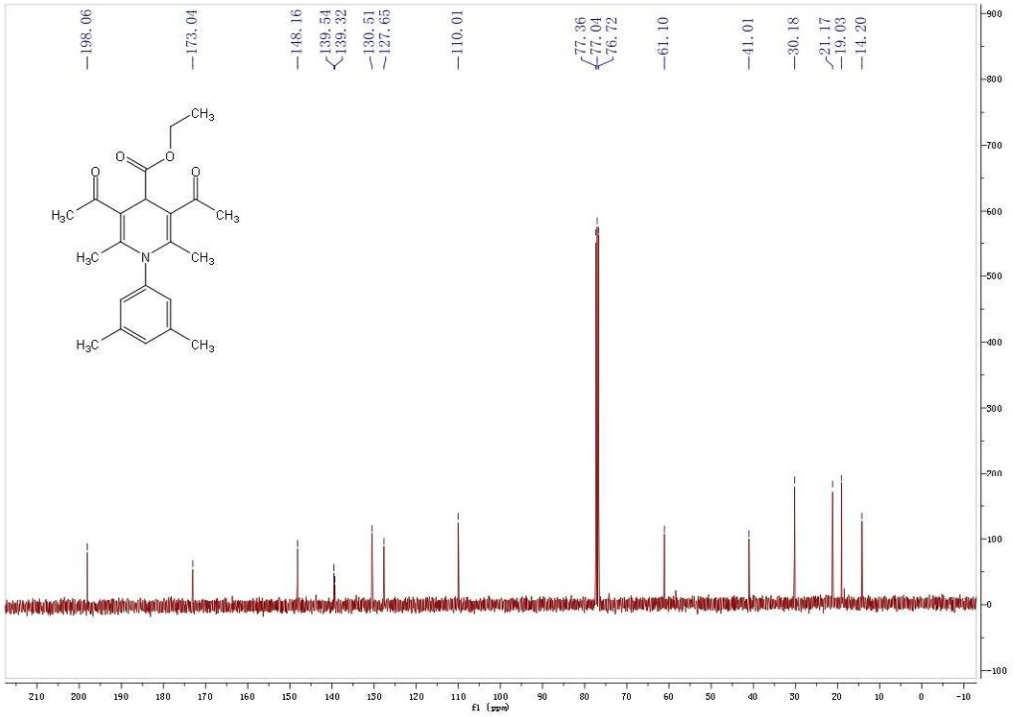
4v


7.45
7.43
7.42
7.40
7.38
7.22
7.13
7.11
4.72
4.20
4.18
4.16
4.15
2.42
2.02
1.29
1.27
1.25
2.03
0.92
0.99
1.00
2.17
6.24
6.13
3.45
f1 (ppm)

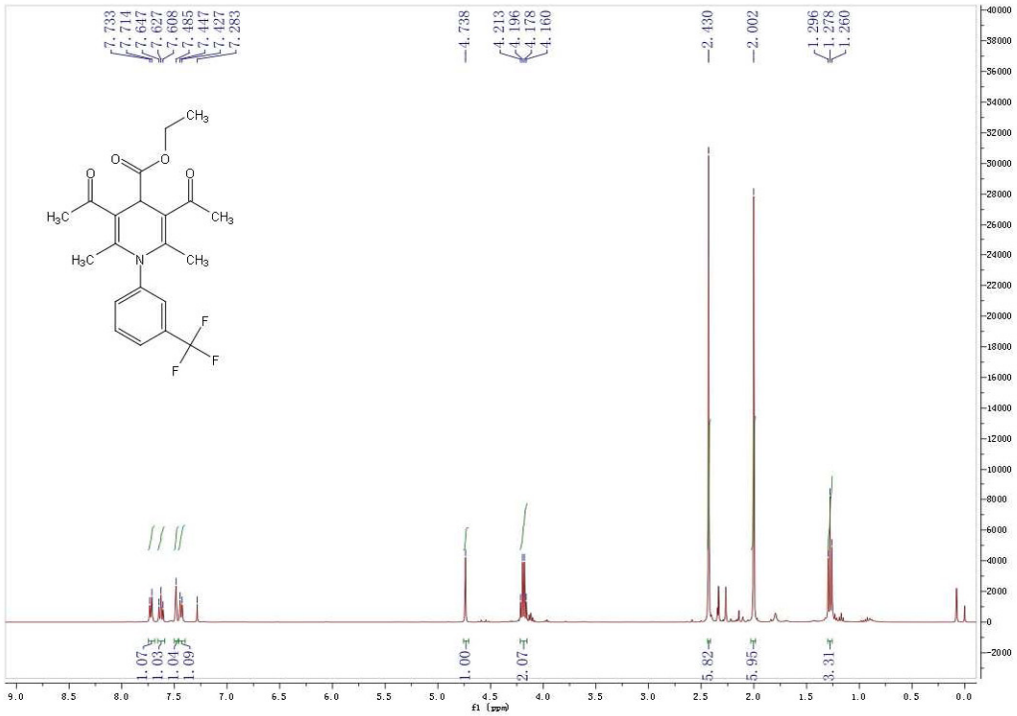

197.96
172.77
147.31
140.98
135.19
130.55
130.40
129.38
128.71
110.75
77.37
77.05
76.74
61.27
41.04
30.15
18.85
14.18
f1 (ppm)

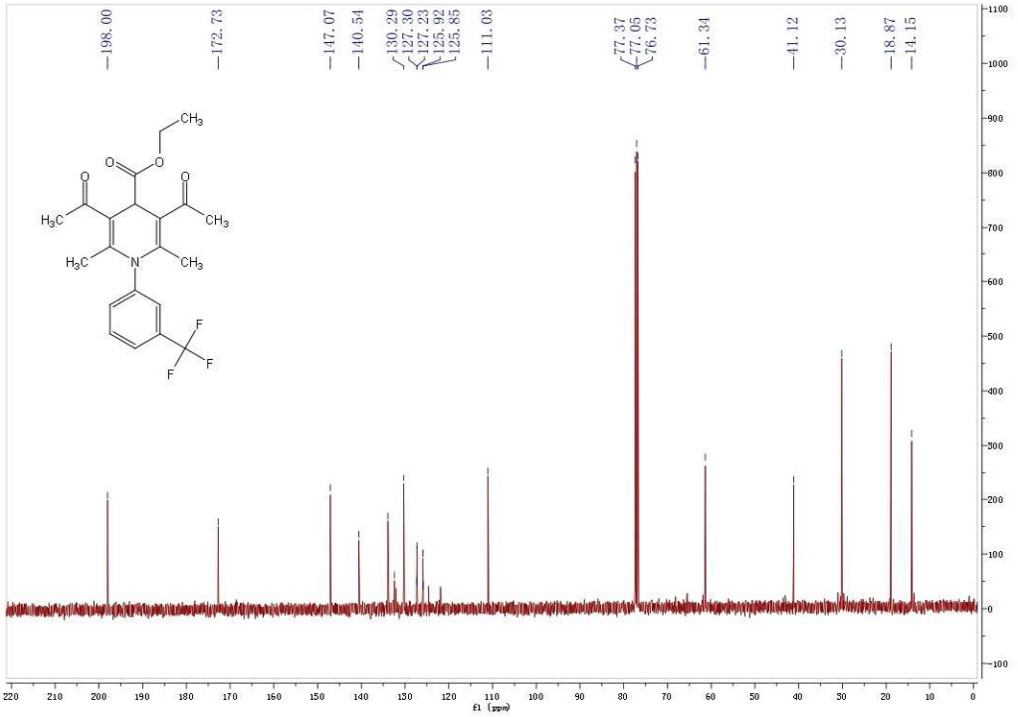
4w


7.284
7.051
6.773
4.752
4.209
4.191
4.173
4.155
2.430
2.350
2.040
1.300
1.282
1.265
1.06
2.00
1.00
2.25
6.17
6.24
6.13
3.64
f1 (ppm)

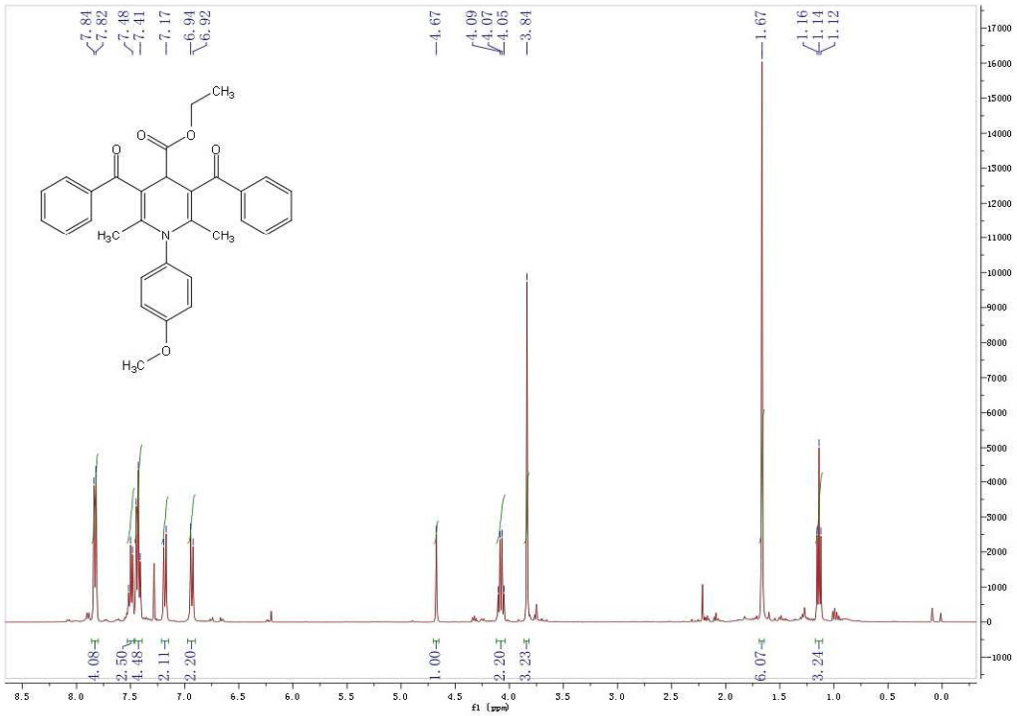

198.06
173.04
148.16
139.54
139.32
130.51
127.65
110.01
77.36
77.04
76.72
61.10
41.01
30.18
21.17
19.03
14.20
f1 (ppm)

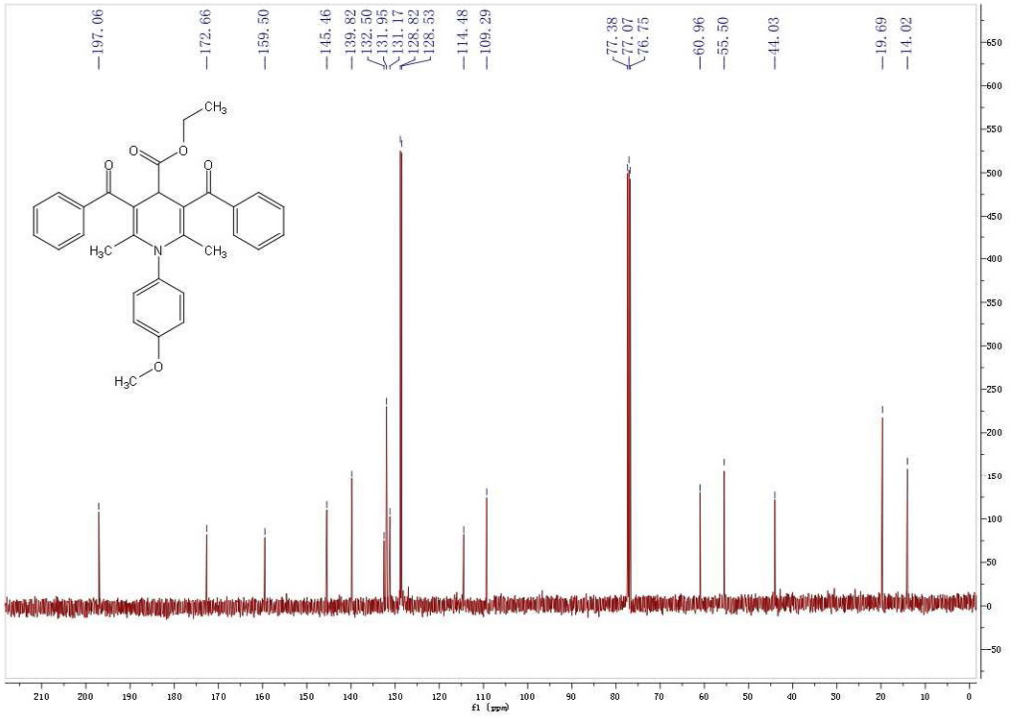
4x


7.733
7.714
7.647
7.627
7.608
7.485
7.447
7.427
7.283
4.738
4.213
4.196
4.178
4.160
2.430
2.002
1.296
1.278
1.260
1.07
1.03
1.04
1.09
1.00
2.07
5.82
5.95
3.31
f1 (ppm)

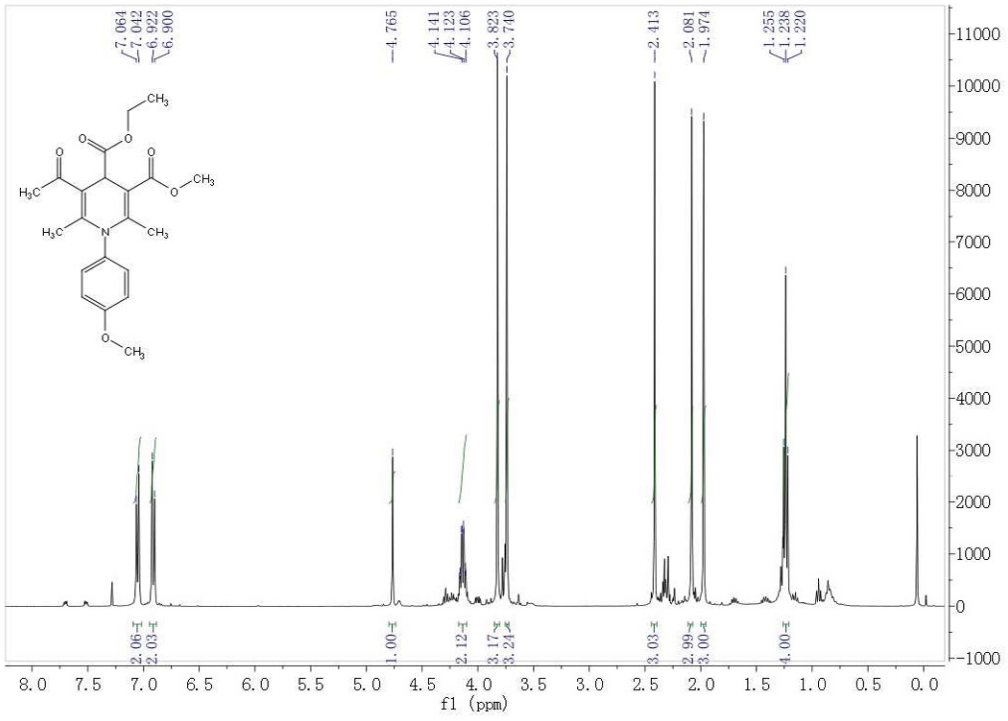

198.00
172.73
147.07
140.54
130.29
127.30
127.23
125.92
125.85
111.03
77.37
77.05
76.73
61.34
41.12
30.13
18.87
14.15
f1 (ppm)

4y


7.84
7.82
7.48
7.41
7.17
6.94
6.92
4.67
4.09
4.07
4.05
3.84
1.67
1.16
1.14
1.12
4.08
2.50
4.48
2.11
2.20
1.00
2.20
3.23
6.07
3.24
f1 (ppm)


197.06
172.66
159.50
145.46
139.82
132.50
131.95
131.17
128.82
128.53
114.48
109.29
77.38
77.07
76.75
60.96
55.50
44.03
19.69
14.02
f1 (ppm)

5a


7.064
7.042
6.922
6.900
4.765
4.141
4.123
4.106
3.823
3.740
2.413
2.081
1.974
1.255
1.238
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2.06
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1.00
2.12
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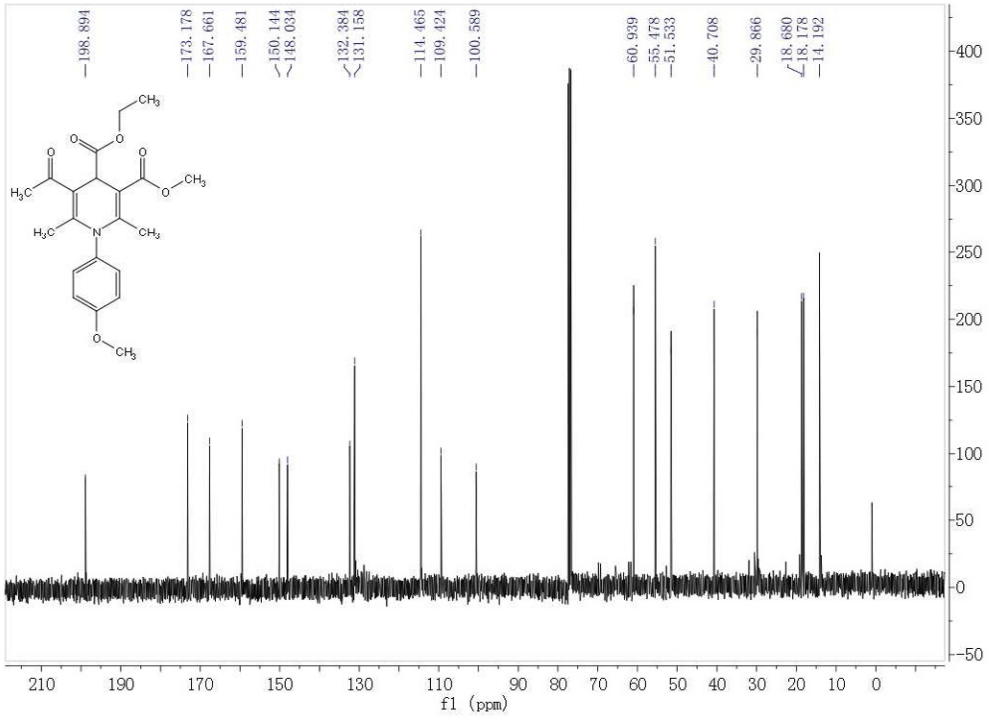
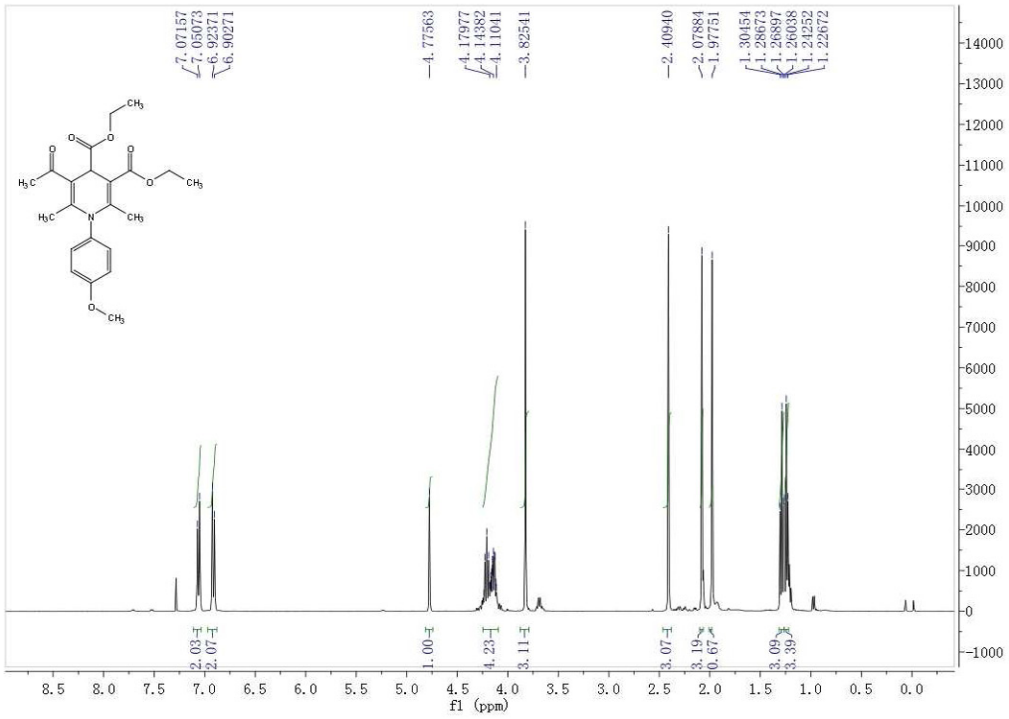
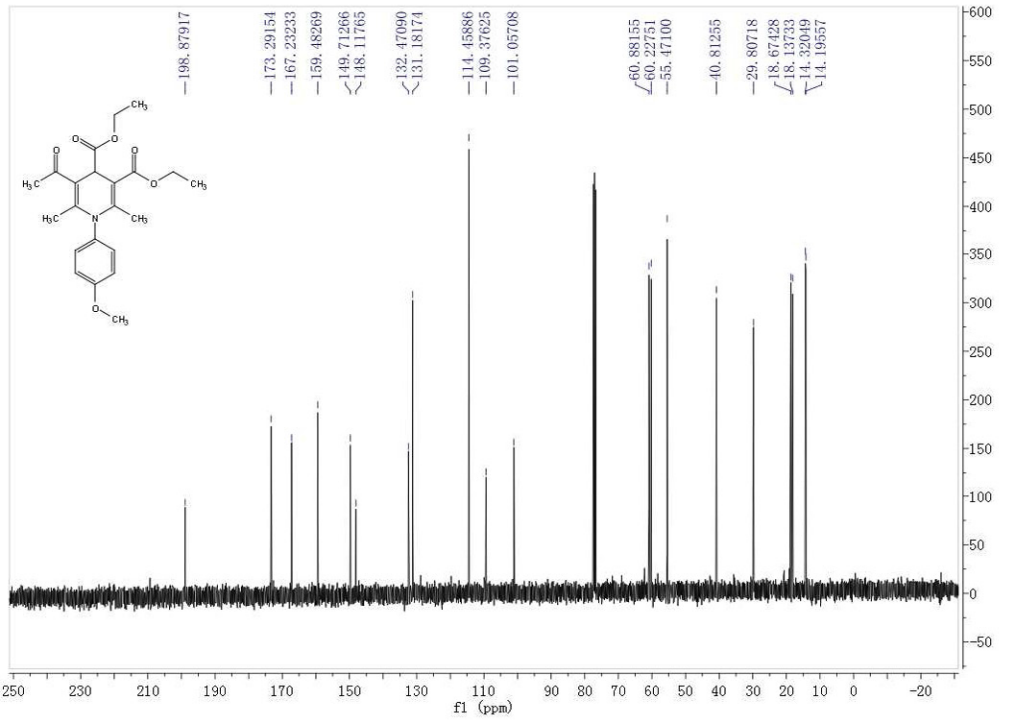
3.24
3.03
2.99
3.00
4.00
f1 (ppm)

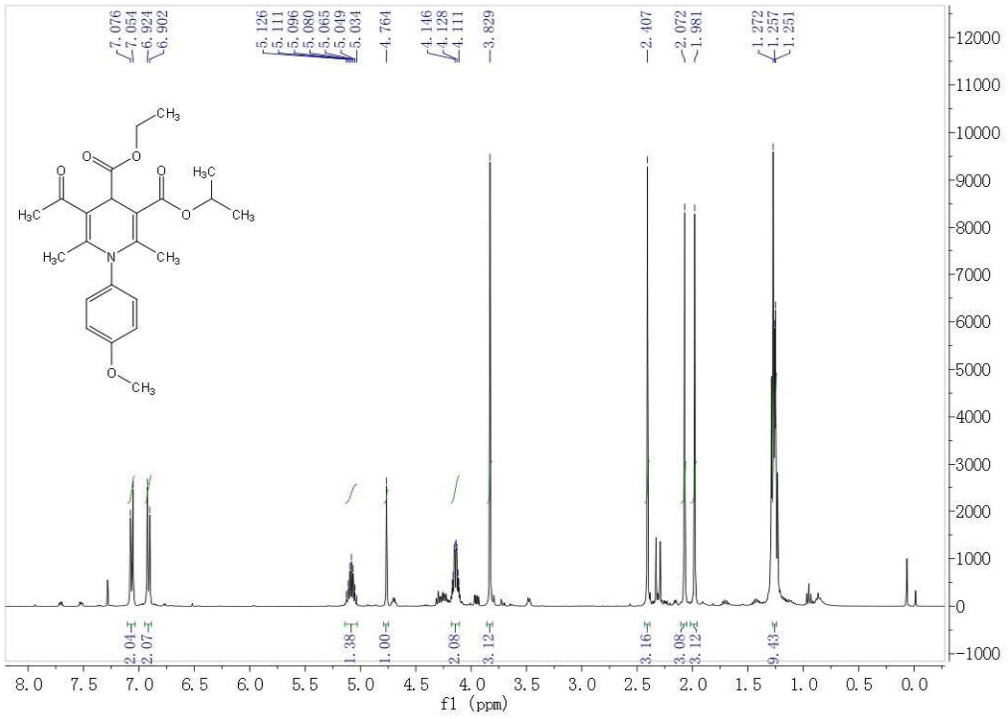

198.894
173.178
167.661
159.481
150.144
148.034
132.384
131.158
114.465
109.424
100.589
60.939
55.478
51.533
40.708
29.866
18.680
18.178
14.192
f1 (ppm)

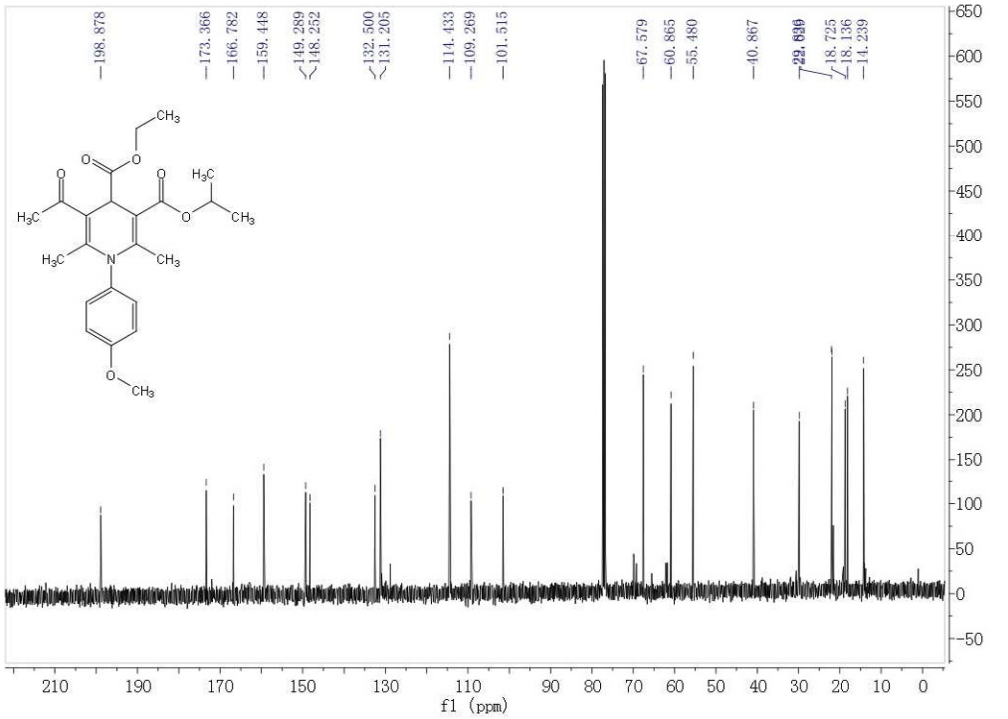
5b


7.07157
7.05073
6.92371
6.90271
4.77563
4.17977
4.14382
4.11041
3.82541
2.40940
2.07884
1.97751
1.30454
1.28673
1.26897
1.26038
1.24252
1.22672
2.03
2.07
1.00
4.23
3.11
3.07
3.19
0.67
3.09
3.39
f1 (ppm)

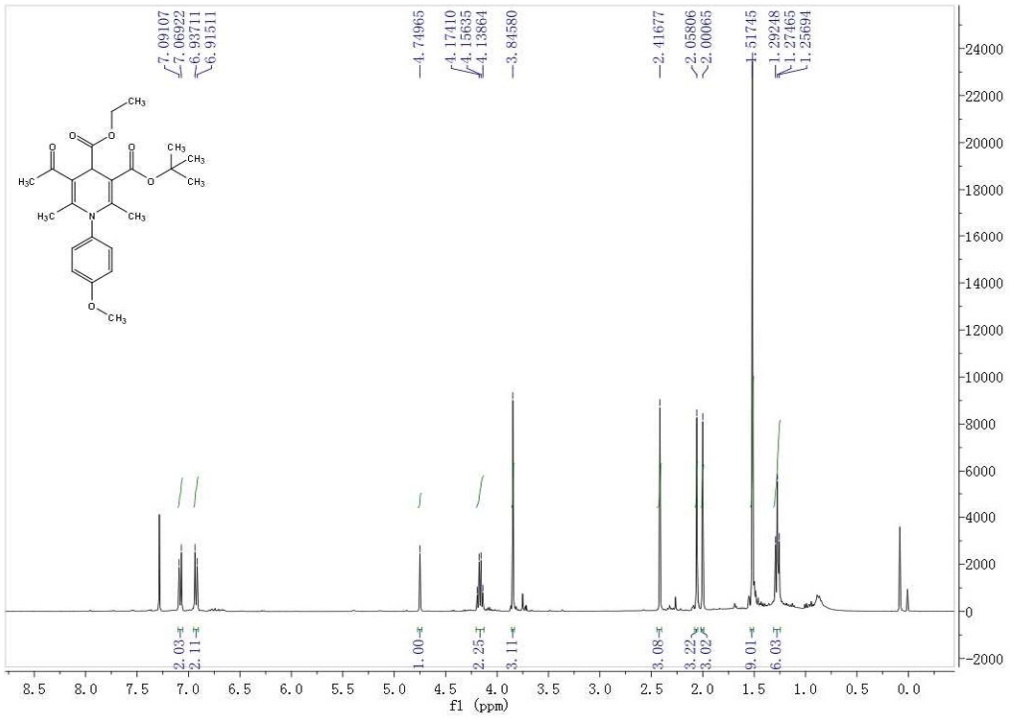

198.87917
173.29154
167.23233
159.48269
149.71266
148.11765
132.47090
131.18174
114.45886
109.37625
101.05708
60.88155
60.22751
55.47100
40.81255
29.80718
18.67428
18.13733
14.32049
14.19557
f1 (ppm)

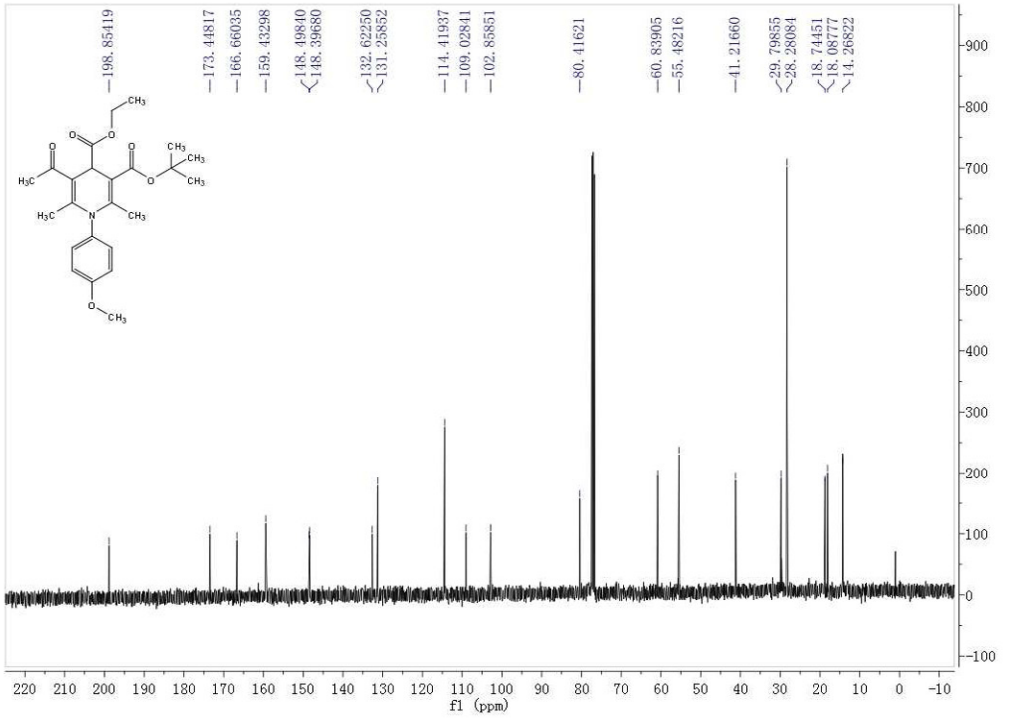
5c


7.076
7.054
6.924
6.902
5.126
5.111
5.096
5.080
5.065
5.049
5.034
4.764
4.146
4.128
4.111
3.829
2.407
2.072
1.981
1.272
1.257
1.251
2.04
2.07
1.38
1.00
2.08
3.12
3.16
3.08
3.12
9.43
f1 (ppm)

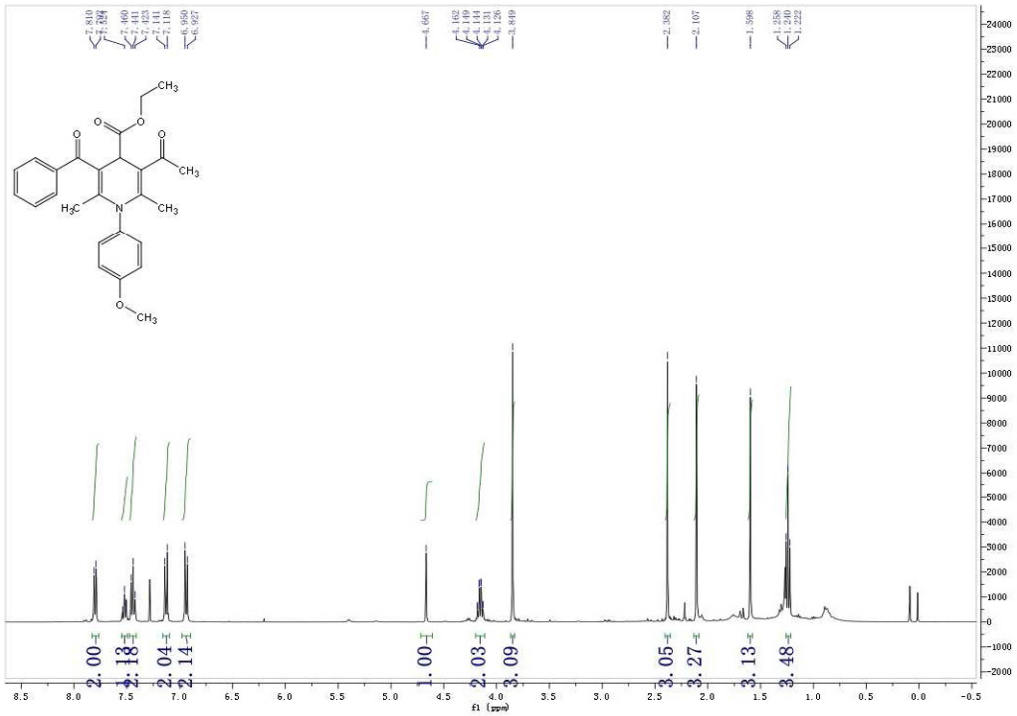

198.878
173.366
166.782
159.448
149.289
148.252
132.500
131.205
114.433
109.269
101.515
67.579
60.865
55.480
40.867
29.636
18.725
18.136
14.239
f1 (ppm)

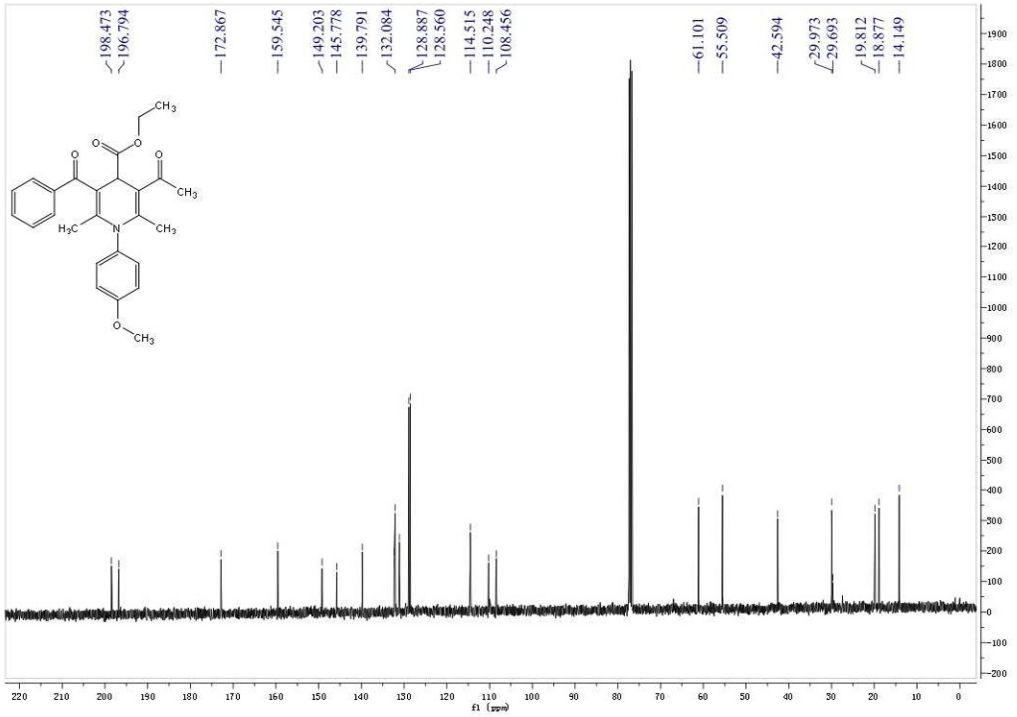
4d


7.09107
7.06922
6.93711
6.91511
4.74965
4.17410
4.15635
4.13864
3.84580
2.41677
2.05806
2.00065
1.51745
1.29248
1.27465
1.25694
2.03
2.11
1.00
2.25
3.11
3.08
3.22
3.02
9.01
6.03
f1 (ppm)

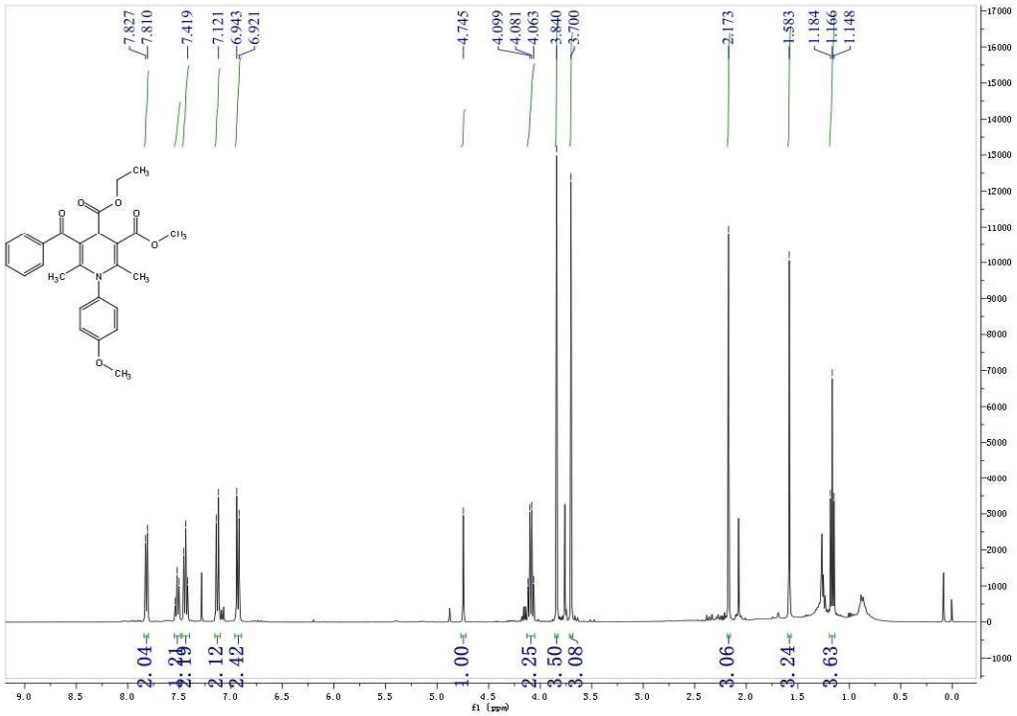

198.85419
173.44817
166.66035
159.43298
148.49840
148.39680
132.62250
131.25852
114.41937
109.02841
102.85851
80.41621
60.83905
55.48216
41.21660
29.79855
28.28084
18.74451
18.08777
14.26822
f1 (ppm)

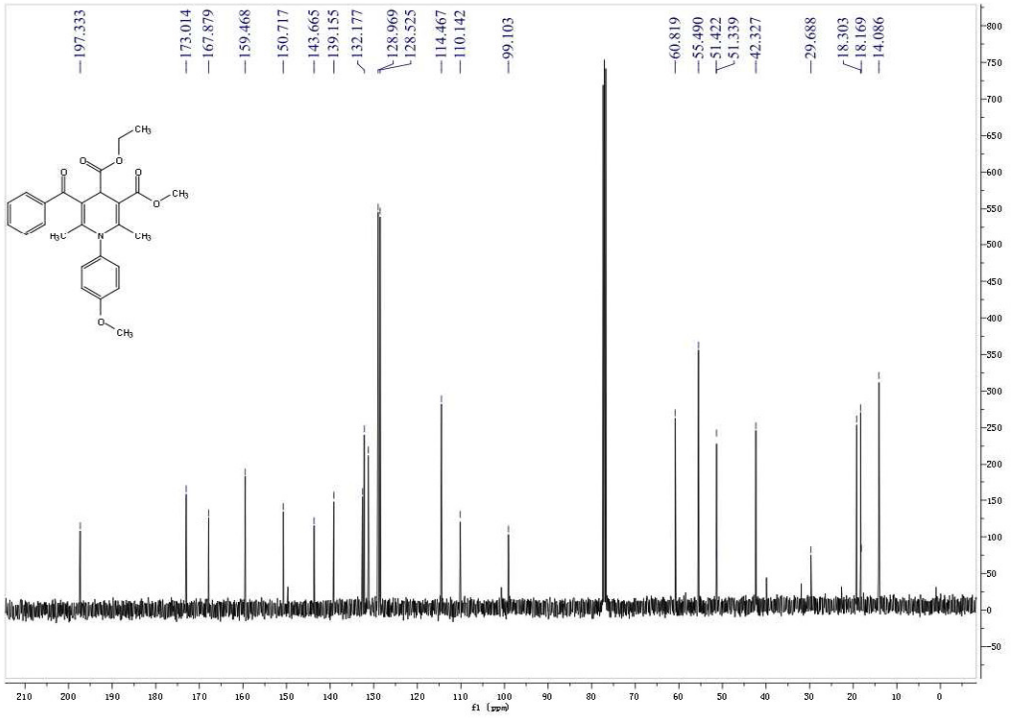
4e



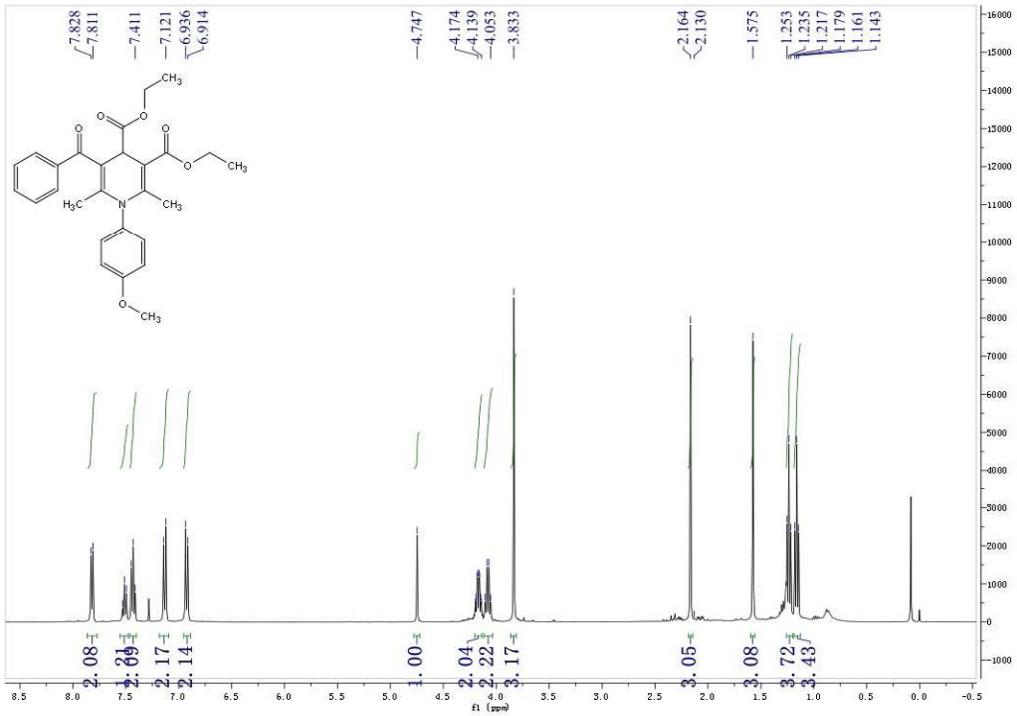


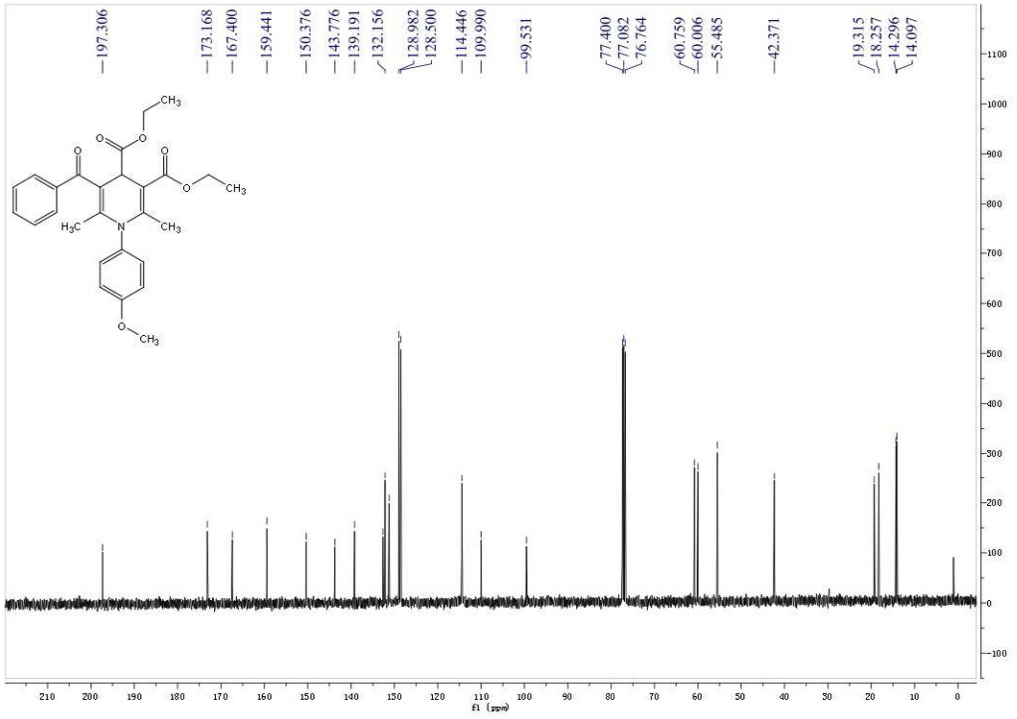
4f


7.827
7.810
7.419
7.121
6.943
6.921
4.745
4.099
4.081
4.063
3.840
3.700
2.173
1.583
1.184
1.166
1.148
2.04
2.21
2.19
2.12
2.42
1.00
2.25
3.50
3.08
3.06
3.24
3.63
f1 (ppm)


197.333
173.014
167.879
159.468
150.717
143.665
139.155
132.177
128.969
128.525
114.467
110.142
99.103
60.819
55.490
51.422
51.339
42.327
29.688
18.303
18.169
14.086
f1 (ppm)

4g


7.828
7.811
7.411
7.121
6.936
6.914
4.747
4.174
4.139
4.053
3.833
2.164
2.130
1.575
1.253
1.235
1.217
1.179
1.161
1.143
2.08
1.21
2.09
2.17
2.14
1.00
2.04
2.22
3.17
3.05
3.08
3.72
3.43
f1 (ppm)


197.306
173.168
167.400
159.441
150.376
143.776
139.191
132.156
128.982
128.500
114.446
109.990
99.531
77.400
77.082
76.764
60.759
60.006
55.485
42.371
19.315
18.257
14.296
14.097
f1 (ppm)