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Primary-secondary Diamines Catalyzed Michael Reaction to Generate Chiral Fluorinated Quaternary Carbon through Enamine Activation

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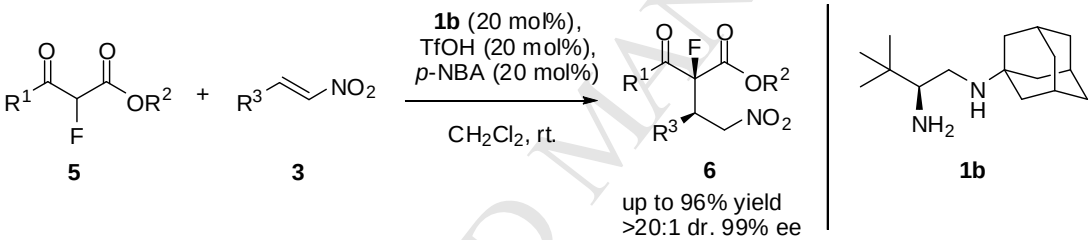

Primary-secondary Diamines Catalyzed Michael Reaction to Generate Chiral Fluorinated Quaternary Carbon Centers

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KEYWORDS: *organocatalysis, primary amine catalyst, Michael addition, chiral fluorinated quaternary carbon*

ABSTRACT: Asymmetric Michael reactions of α-fluoro-β-ketoesters to nitroolefins have been achieved by using readily accessible primary-secondary diamines as the organocatalysts through enamine activation mode, affording the useful Michael adducts bearing chiral fluorinated quaternary carbon in good yields, with high diastereoselectivities and enantioselectivities (up to 87% yield, >20 : 1 d.r. and 99% ee).

1. Introduction

Developing novel methods for synthesizing fluorine-containing compounds has become a fascinating field in organic chemistry due to the great potentials of these compounds in medicinal and pharmaceutical applications [1]. During the last decade, great progress has been made for the preparation of stereogenic fluorinated carbon using electrophilic fluorinating agents mediated by metal or organocatalysts.[2] Alternatively, another strategy using pre-fluorinated nucleophiles in asymmetric C-C bond formation reaction also attracts chemists due to its mild reaction conditions and diverse applications. Many studies have been focused on the organocatalysis in asymmetric reaction of monofluorinated nucleophiles addition to various electrophiles, which has been an ideal solution to the construction of chiral fluorinated moieties.[3] Remarkably, Michael reactions of fluorine-containing β-ketoesters with nitroolefins are important as the products could be readily converted to synthetically useful compounds. Three groups so far have reported related reactions respectively using cinchona derivatives or chiral thiourea (both are tertiary amines) as organocatalysts.[4] The primary amine, which could be a potential HOMO rising activation catalyst with α-fluoro-β-ketoesters is still unknown in the literature.

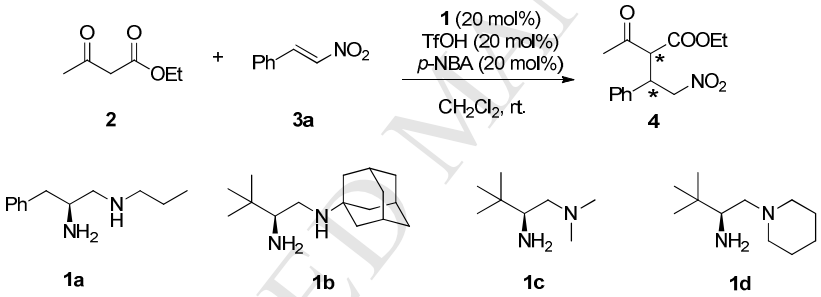
Chiral primary amines have emerged as powerful organocatalysts in a variety of reactions during the last ten years. They usually showed good compatibility and reactivity with ketone moieties. Various types of carbon-carbon or carbon-hetero bond formation reactions such as Aldol reaction, Michael addition had been achieved by using chiral primary amine under iminium and enamine activation modes.[5] However, enamine activation is still a challenging subject in the primary amine catalysis, since cleavage of the N-H bond of the iminium competes with the loss of an α-proton during the conversion step from iminium to enamine.[5c] By summarizing the literature, the key solution to this problem is to promote the elimination of the α-proton and to stabilize the enamine intermediate formed at the same time. The amino acid derived primary-secondary diamines developed by our group have proved to be powerful catalysts in iminium catalysis.[6] It is expected that these powerful catalysts could also be effective in the challenging enamine activation. Although great progress has been made

by primary-tertiary diamine catalyst in enamine activation derived from *Cinchona alkaloids*, chiral diamines or amino acids,[7] to the best of our knowledge, no primary-secondary diamine catalyst has been reported in related reaction via enamine activation. On this context, *β*-ketoesters were selected as effective nucleophiles in the addition to nitroolefins to first attempt this reaction.

2. Results and discussion

Initially, reaction of ethyl acetoacetate **2** with *trans*-*β*-nitrostyrene **3a** was chosen as the model to evaluate the potential enamine activation catalysis in the presence of primary-secondary diamines **1** (Table 1). The *L*-Phenylalanine derived primary-secondary diamine catalyst **1a**, which usually worked well in Michael addition by iminium activation only gave trace of the product in a complicated mixture (Table 1, entry 1). Previous studies indicated steric effect of the catalyst usually plays a crucial role in the reaction and indeed a sterically hindered catalyst **1b** derived from *tert*-leucine and amantadine gave satisfactory yield and enantioselectivity (Table 1, entry 2). Primary-tertiary diamines were also examined and high ee value could be obtained under the catalysis of **1c**. However, these catalysts were proved to be less active revealed by the low yield and long reaction time (Table 1, entries 3 and 4). Both reactions catalyzed by **1b** and **1c** gave the products with poor diastereoselectivities, which may be due to the enolization of the products. We postulate that the problem could be solved by using fluorine substituted *β*-ketoesters since the quaternary carbon generated would prevent the enolization. So ethyl 2-fluoro-3-oxobutanoate **5a** was used instead of **2** as nucleophile and the optimization details are shown in table 2.

Table 1. Investigation of catalysts [a]



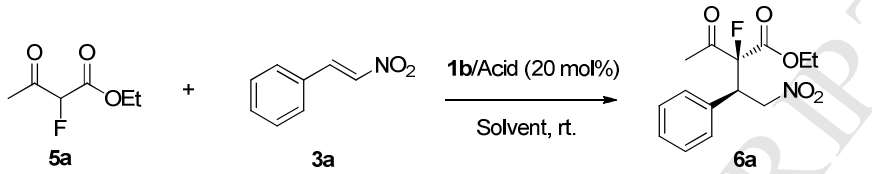
Entry	Cat	Time (h)	Yield (%)[b]	Dr [c]	Ee (%) [d]
1	**1a**	12	trace [e]	n.d.	n.d.
2	**1b**	12	87	56 : 44	95/97
3	**1c**	48	46	58 : 42	94/95
4	**1d**	72	n.r.	n.d.	n.d.

[a] Unless otherwise specified, the reaction was carried out with **2** (0.1 mmol), **3a** (0.12 mmol), cat. **1** (0.02 mmol), trifluoromethanesulfonic acid (TfOH) (0.02 mmol) and *p*-nitrobenzoic acid (*p*-NBA) (0.02 mmol) in CH_2Cl_2 (1.5 mL) at room temperature. [b] Sum of diastereoisomers. [c] Determined by ^1H NMR spectroscopy of crude mixture. [d] Determined by chiral HPLC analysis. [e] The reaction was complicated.

Acid additives usually play important role in primary amine catalysis [6, 7]. We firstly investigated the amount of acid used. Without acid additive, though the reaction could happen, the yield, diastereoselectivity and enantioselectivity of the product were very poor (Table 2, entry 1). No reaction occurred when 20 mol% of the acid was added, while 40 mol% of the acid additive in this reaction promoted the reaction to give the desired product in good yield and enantioselectivity (Table 2, entries 2-6). No enolization happened with this product so the diastereoselectivity was largely improved to 9 : 1. A combination of strong acid/weak acid (1 : 1, molar ratio) was also tried, which gave the product with the highest ee and dr value in the presence of the mixed

trifluoromethanesulfonic acid (TfOH) and *p*-nitrobenzoic acid (*p*-NBA) (Table 2, entries 7-12). Further optimization of the reaction conditions such as solvent or catalyst loading gave no improved result (Table 2, entries 13-15). Thus, the optimum reaction conditions were determined to be the primary-secondary diamine catalyst **1b** (20 mol%) in the presence of TfOH (20 mol%) and *p*-NBA (20 mol%) in CH_2Cl_2 at room temperature.

Table 2. Optimization of the reaction conditions [a]



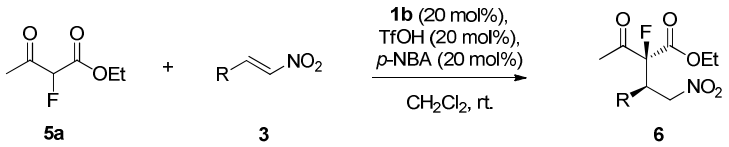
Entry	Acid	Time (h)	Yield (%)[b]	Dr [c]	Ee (%)[d]
1	No Acid	72	60	1.5 : 1	47.0
2	TfOH	72	trace	n.d.	n.d.
3	TfOH (40 mol%)	12	90	9 : 1	87.1
4	*p*-NBA	72	trace	n.d.	n.d.
5	*p*-NBA (40 mol%)	24	72	9 : 1	79.5
6	TFA (40 mol%)	12	90	10 : 1	94.2
7	TfOH/*p*-NBA	24	87	12 : 1	98.5
8	TfOH/*o*-NBA	24	65	4 : 1	92.0
9	TfOH/*m*-NBA	24	88	9 : 1	90.5
10	TfOH/$PhCO_2H$	72	n.r.	n.d.	n.d.
11	TfOH/L-Boc-Phe-OH	12	90	8 : 1	95.8
12	TfOH/D-Boc-Phe-OH	12	89	10 : 1	91.0
13 [e]	TfOH/*p*-NBA	24	75	10 : 1	92.5
14 [f]	TfOH/*p*-NBA	12	90	4 : 1	97.5
15 [g]	TfOH/*p*-NBA	48	76	12 : 1	92.0

[a] Unless otherwise specified, the reaction was carried out with **3a** (0.12 mmol), **5a** (0.1 mmol), **1b** (20 mol%) and acid (20 mol%) in CH_2Cl_2 (1.5 mL) at room temperature. [b] Isolated yields. [c] Determined by ^1H NMR spectroscopy of crude mixture. [d] The ee value of major diastereomer, determined by chiral HPLC analysis. [e] Toluene was used as solvent. [f] THF was used as solvent. [g] **1b**/Acid (10%) was used.

With the optimized condition in hand, the scope of the Michael reaction was explored and the results were summarized in Table 3 and Table 4. In general, the nitroethylenes with different aryl, heteroaryl or alkyl substituted group worked quite well in this reaction. The products were exclusively formed in good yields, with high to excellent diastereoselectivities and enantioselectivities. It should be noted that, under this catalytic system, the diastereoselectivity has been improved a lot compared to the reported results[4] probably due to the interaction between the catalyst and substrate changed from hydrogen-bonding to covalent bond. Specifically, Substrates with either electron-donating or withdrawing group on the phenyl gave the products with satisfactory results (Table 3, entries 2-4). Bromo-substitution on the *ortho*, *meta* or *para*-position of phenyl group also worked well under this catalyst system in spite of *ortho* substitution made the reaction a little slowly (Table 3, entries 5-7). The alkyl substitute on the nitroethylenes also participated in the reaction and afforded the corresponding products with good yields and high stereoselectivities (Table 3, entries 12-13). It

seemed that steric effects with the substitution have some impact on the yield of the reaction. When bulky group on nitroolefins was used, the reaction was slow and the yield decreased sharply (Table 3, entries 6, 10, 11 and 14).

Table 3. Scope of electrophile in Michael reaction [a]

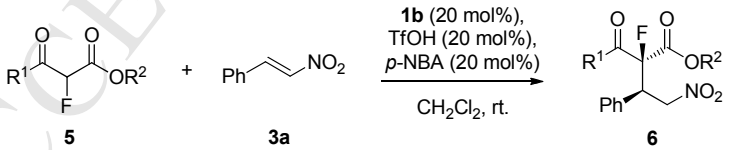


5a + **3** → **6**

Entry	R	**6**	Yield (%)[b]	Dr [c]	Ee (%)[d]
1	Ph	**6a**	87	12 : 1	98.5
2	4-Me-Ph	**6b**	78	8 : 1	98.5
3	4-OMe-Ph	**6c**	83	>20 : 1	98.0
4	4-CF_3-Ph	**6d**	93	>20 : 1	97.0
5	4-Br-Ph	**6e**	96	>20 : 1	97.0
6	2-Br-Ph	**6f**	72	12 : 1	98.0
7	3-Br-Ph	**6g**	78	>20 : 1	98.4
8	2-Furyl	**6h**	84	11 : 1	93.9
9	2-Thienyl	**6i**	83	9 : 1	97.7
10	1-Naphthyl	**6j**	33	>20 : 1	96.8
11	2-Naphthyl	**6k**	67	6 : 1	97.9
12	PhC_2H_4	**6l**	76	>20 : 1	98.1
13	*n*-Pentyl	**6m**	68	>20 : 1	97.4
14	cyclohexyl	**6n**	20	>20 : 1	89.6

[a] Unless otherwise specified, the reaction was carried out with **5** (0.1 mmol), **3** (0.12 mmol), **1b** (0.02 mmol), TfOH (0.02 mmol) and *p*-NBA (0.02 mmol) in CH_2Cl_2 (1.5 mL) at room temperature. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy of crude mixture. [d] The ee value of major diastereomer, determined by chiral HPLC analysis.

Table 4. Scope of Nucleophile in Michael reaction [a]



5 + **3a** → **6**

Entry	R^1	R^2	**6**	Yield (%)[b]	Dr [c]	Ee (%) [d]
1	*n*-Propyl	Et	**6o**	36	9 : 1	92.2
2	Ph	Et	--	trace	n.d.	n.d.
3	Me	Me	**6p**	80	> 20:1	97.5
4	Me	*t*-Bu	**6q**	77	> 20:1	97.9
5	Me	Bn	**6r**	87	> 20:1	99.5
6[e]	Me	*t*-Bu	**6s**	82	> 20:1	98.3

[a] Unless otherwise specified, the reaction was carried out with **5** (0.1 mmol), **3** (0.12 mmol), **1b** (0.02 mmol), TfOH (0.02 mmol) and *p*-NBA (0.02 mmol) in CH_2Cl_2 (1.5 mL) at room temperature. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy of crude mixture. [d] The ee value of major diastereomer, determined by chiral HPLC analysis. [e] 1-Bromo-4-(2-nitrovinyl)benzene **3e** was used instead of **3a**.

Next, the scope and limitation of α-fluoro-*β*-ketoesters were investigated. Extending the carbon chain of the ketone side led to a sharply decreasing in yield but still with a high dr and ee value (Table 4, entry 1). When R^1 was replaced to phenyl group, the reaction could not proceed (Table 4, entry 2). Various substituted esters on R^2 were also evaluated. The reactions worked quite well to give each diastereomer exclusively (Table 4, entries 3-5). Notably, when **3e** instead of **3a** was used, excellent results was also obtained and we were able to obtain an X-ray crystal structure of product **6s** [8]. The absolute configuration of **6s** was determined to be (*2S, 3R*) and the configuration of other products was determined by analogy (Figure 1).

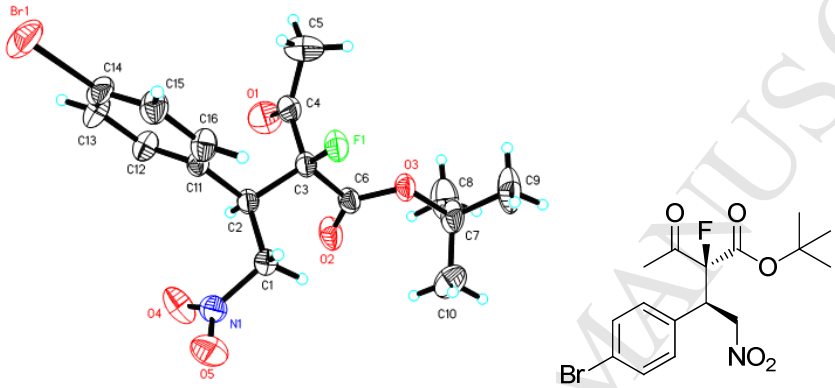
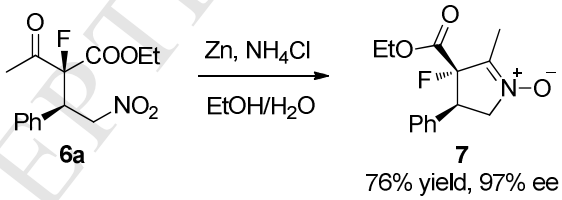


Figure 1: crystal structure of 6s.

The product can be readily converted into synthetically useful chiral pyrrolidine or lactam scaffolds according to the known literalities.[4a, 4b] Besides, they can also be transformed to highly functionalized fluorinated chiral pyrroline-N-oxide by a simple reduction step (Scheme 1).



Scheme 1. Transformation of 6a.

To gain some insight into the mechanism of the reaction, the ^{19}F NMR experiments were performed to tracing the process of the reaction. From the spectrum of ^{19}F NMR (Figure 2), the signal of ketone **5a** (A) and its enolate (B) were first determined. When the catalyst **1b** was added, the balance moved to enolization. After adding the TfOH and *p*-NBA, the signal of enamine intermediate (C) could be observed. Then the signal of product (D) emerged after **3a** was added, which was increasing with the reaction ongoing. Besides, the ^{1}H NMR experiments were also performed and we can get some important information to show the existence of H-bonding (see supporting information). These results suggested the enamine activation during the reaction and the effect of hydrogen-bond.

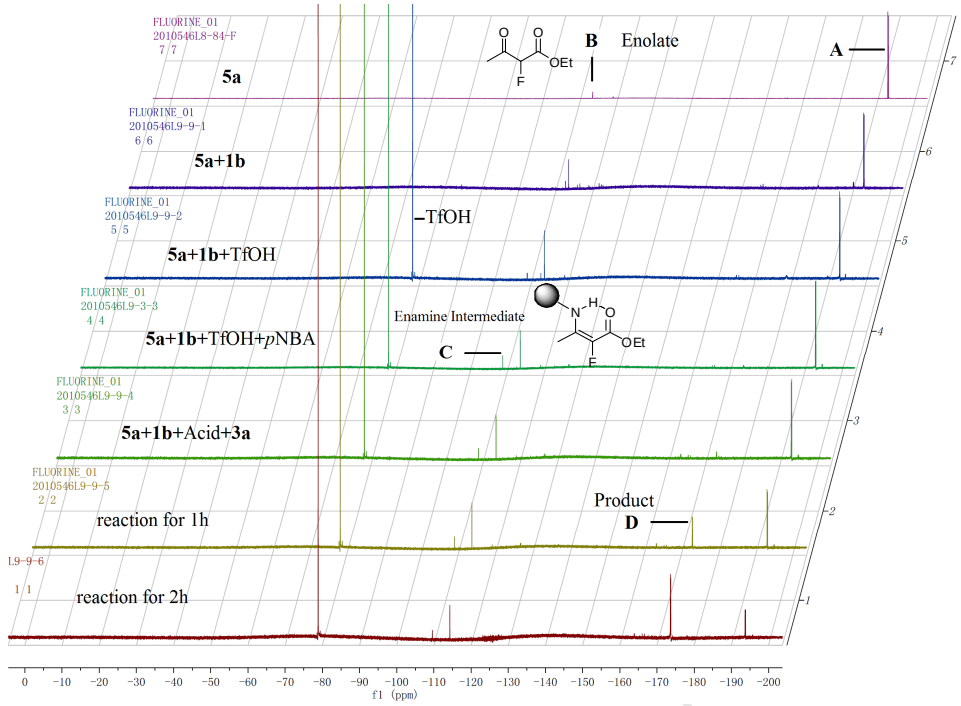


Figure 2: Monitoring the reaction by ^{19}F NMR.

Based on the observation, a bifunctional enamine mechanism similar to those previously proposed for primary-tertiary diamine catalysts in the enamine activation may be invoked to explain the observed stereochemical results.[7] We presume that the primary amine moiety of the catalyst **1b** activates the *β*-ketoester **5** *via* the formation of an enamine intermediate which is stabilized by an intramolecular H-bond. The secondary amine activates the electrophilic nitroolefins by H-bond at the same time. The *Si*-face of the electrophilic nitroolefins is shielded by the bulky group of catalyst driving the nucleophilic enamine to attack the *Re*-face of the nitroolefins. The acid additive may facilitate the elimination of the *α*-H of iminium ion to form enamine and stabilize the enamine intermediate by intramolecular H-bond (Figure 3).

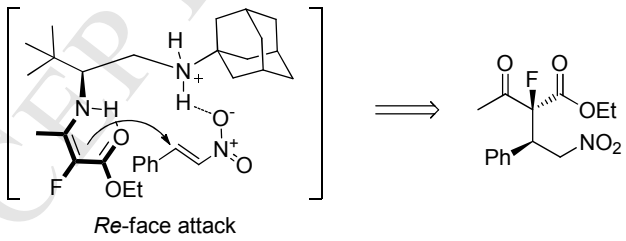


Figure 3: Possible transition state of the reaction.

3. Conclusions

We have developed a novel approach of asymmetric Michael reaction of *α*-fluoro-*β*-ketoesters with nitroalkenes, using our amino acid derived primary-secondary diamine catalyst, to construct the chiral fluorinated quaternary carbon. Remarkably, this primary-secondary catalyst has been proved to be quite effective in enamine activation with the *β*-ketoesters. The easily prepared catalyst and convenient protocol enable improvement in the Michael reaction to afford the product under mild condition with good yield, high diastereoselectivity and enantioselectivity. Efforts are being focused on further application of this catalyst system to the related reactions.

4. Experiment section

4.1 General

Chemicals and solvents were purchased from commercial suppliers and purified by standard techniques. The ^{1}H NMR spectra were recorded on a Bruker DRX 400 MHz. All chemical shifts (δ) are given in ppm. Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on a Bruker DRX 400 MHz. The ^{19}F NMR spectra were recorded on a Bruker DRX 400 MHz. HPLC analysis was carried out on WATERS equipment using a chiral column. Melting points were determined on a SGW X-4 and were uncorrected. Optical rotations were measured on a JASCOP-1010 Polarimeter at λ = 589 nm. Mass spectra analysis was performed on API 200 LC/MS system (Applied Biosystems Co. Ltd.).

Primary-secondary diamines catalysts **1a**[6a] and **1b**[6a], primary-tertiary diamines catalysts **1c**[9] and **1d**[9] were prepared following the known literature. Procedures and all physical data were in agreement with the literature.

4.2 General procedure for the Michael addition of *α*-fluoro-*β*-ketoesters with nitroolefins.

Catalyst **1b** (5.0 mg, 0.02 mmol) was added to the solution of Trifluoromethanesulfonic acid (1.7 μL, 0.02 mmol) and 4-nitrobenzoic acid (3.2 mg, 0.02 mmol) in CH_2Cl_2 (1.5 mL). Then *α*-fluoro-*β*-ketoester **5** (0.1 mmol) and nitroolefin **3** (0.12 mmol) were added. The reaction mixture was stirred at room temperature for 12-72 h. Water (3 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (2×3 mL) and the combined organic phases were washed with brine, dried by Na_2SO_4, filtered and concentrated. The crude products were purified by silica gel column chromatography to afford the pure product **6**.

4.3 Characterization Data for the Michael adducts.

Ethyl 2-acetyl-4-nitro-3-phenylbutanoate **4**

Colorless oil; Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.12 (m, 5H), 4.78-4.75 (m, 0.8H), 4.68 (d, *J* = 6.4 Hz, 1.2H), 4.19-4.04 (m, 2.5H), 3.97-3.87 (m, 1.5H), 2.23 (s, 1.7H), 1.99 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 1.3H), 0.98 (t, *J* = 7.2 Hz, 1.7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 200.3, 167.5, 166.9, 136.4, 136.3, 129.1, 128.9, 128.3, 128.2, 128.0, 127.9, 77.0, 76.7, 62.2, 61.9, 61.7, 42.5, 42.3, 30.3, 30.1, 14.0, 13.6; ESI-MS (m/z): 302.1 ($M+Na^+$); ee: 95/ 97%; (HPLC conditions: Chiralcel AD-H, 20 ^{o}C, 214 nm, 95 : 5 hexane/*i*-PrOH, 1.0 mL/min; (major diastereomer) t_{major} = 18.9 min, t_{minor} = 12.9 min, (minor diastereomer) t_{major} = 20.5 min, t_{minor} = 35.6 min)

(*2S, 3R*)-ethyl 2-acetyl-2-fluoro-4-nitro-3-phenylbutanoate **6a** [4a]

Colorless oil; Yield: 87%; $[\alpha]_D^{25}$ = -5.42 (*c* 0.75, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 4.86-4.84 (m, 2H), 4.63-4.52 (m, 1H), 4.33 (dq J_1 = 0.8 Hz, J_2 = 7.2 Hz, 2H), 1.87 (d, *J* = 5.6 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2 (d, $J_{C\text{-}F}$ = 28.6 Hz), 164.5 (d, $J_{C\text{-}F}$ = 25.0 Hz), 132.4, 129.5 (d, $J_{C\text{-}F}$ = 1.6 Hz), 129.0, 128.9, 100.5 (d, $J_{C\text{-}F}$ = 206.5 Hz), 75.2 (d, $J_{C\text{-}F}$ = 4.6 Hz), 63.6, 47.1 (d, $J_{C\text{-}F}$ = 17.4 Hz), 26.4, 13.9 (d, $J_{C\text{-}F}$ = 30.0 Hz); ESI-MS (m/z): 320.1 ($M+Na^+$);The ee value of major product was 98.5 %. (The major and minor isomers could be separated by column chromatography. But only the HPLC chromatogram of the major isomer is shown below for the minor isomer could not be obtained.) (HPLC-separation conditions: Chiralcel OD-H, 20 ^{o}C, 214 nm, 80 : 20 hexane/*i*-PrOH, 0.6 mL/min; t_{major} = 24.6 min, t_{minor} = 15.1 min)

(*2S, 3R*)-ethyl-2-acetyl-2-fluoro-4-nitro-3-(*p*-tolyl) butanoate **6b** [4a]

Colorless oil; Yield: 78%; $[\alpha]_D^{25}$ = 3.24 (*c* 1.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.04 (m, 4H), 4.76-4.74 (m, 2H), 4.52-4.40 (m, 1H), 4.26 (dq J_1 = 1.2 Hz, J_2 = 7.2 Hz, 2H), 2.24 (s, 3H), 1.82 (d, *J* = 5.6 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3 (d, $J_{C\text{-}F}$ = 28.8 Hz), 164.5 (d, $J_{C\text{-}F}$ = 25.0 Hz), 138.8, 129.7 (d, $J_{C\text{-}F}$ = 7.6 Hz), 129.3 (d, $J_{C\text{-}F}$ = 1.5 Hz), 129.2, 100.5 (d, $J_{C\text{-}F}$ = 206.6 Hz), 75.3 (d, $J_{C\text{-}F}$ = 4.5 Hz), 63.6, 46.8 (d, $J_{C\text{-}F}$ = 18.3 Hz), 26.5, 21.1, 13.9; ESI-MS (m/z):

311.1 ($M+H^+$); The ee value of major product was 98.5 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^oC, 214 nm, 80 : 20 hexane/*i*-PrOH, 0.7 mL/min; t_{major} = 16.4 min, t_{minor} = 12.7 min)

(*2S*, *3R*)-ethyl 2-acetyl-2-fluoro-3-(4-methoxyphenyl)-4-nitrobutanoate **6c** [4a]

Colorless oil; Yield: 83%; $[\alpha]_D^{23}$ = -11.09 (*c* 1.25, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.19-7.12 (m, 2H), 6.79-6.76 (m, 2H), 4.73 (d, *J* = 7.2 Hz, 2H), 4.51-4.40 (m, 1H), 4.26 (dq J_1 = 1.2 Hz, J_2 = 7.2 Hz, 2H), 1.82 (d, *J* = 5.6 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4 (d, J_{C-F} = 28.8 Hz), 164.5 (d, J_{C-F} = 25.8 Hz), 159.8, 130.6 (d, J_{C-F} = 2.5 Hz), 124.0, 114.4, 100.6 (d, J_{C-F} = 205.7 Hz), 75.4 (d, J_{C-F} = 5.3 Hz), 63.5, 55.2, 46.5 (d, J_{C-F} = 18.2 Hz), 26.5, 13.9; ESI-MS (m/z): 350.1 ($M+Na^+$); The ee value of major product was 98.0 %. (HPLC-separation conditions: Chiralcel AS-H, 20 ^oC, 214 nm, 80 : 20 hexane/*i*-PrOH, 0.6 mL/min; t_{major} = 30.7 min, t_{minor} = 27.9 min)

(*2S*, *3R*)-ethyl 2-acetyl-2-fluoro-4-nitro-3-(4-(trifluoro-methyl)phenyl)butanoate **6d**

Colorless oil; Yield: 93%; $[\alpha]_D^{27}$ = 5.51 (*c* 1.45, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 4.0 Hz, 2H), 4.80-4.78 (m, 2H). 4.66-4.55 (m, 1H), 4.28 (dq J_1 = 1.2 Hz, J_2 = 7.2 Hz, 2H), 1.87 (d, *J* = 5.6 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7 (d, J_{C-F} = 28.8 Hz), 164.1 (d, J_{C-F} = 25.1 Hz), 136.7, 130.0 (d, J_{C-F} = 2.3 Hz), 129.6 (dd, J_{C-F} = 277.9 Hz), 126.0 (d, J_{C-F} = 3.8 Hz), 125.9 (d, J_{C-F} = 3.8 Hz), 100.3 (d, J_{C-F} = 207.3 Hz), 74.9 (d, J_{C-F} = 4.6 Hz), 63.9, 46.7 (d, J_{C-F} = 18.2 Hz), 26.3, 14.0 (d, J_{C-F} = 19.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.98 (s, 3F), -172.60 (dq, J_1 = 3.76 Hz, J_2 = 30.08 Hz, 1F); ESI-MS (m/z): 388.1 ($M+Na^+$); HRMS Calc. $C_{15}H_{15}F_4NO_5Na_1$ ($M+Na^+$) 388.0779 Found: 388.0774; The ee value of major product was 97.0 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^oC, 214 nm, 90 : 10 hexane/*i*-PrOH, 1.0 mL/min; t_{major} = 34.8 min, t_{minor} = 12.0 min)

(*2S*, *3R*)-ethyl 2-acetyl-3-(4-bromophenyl)-2-fluoro-4-nitrobutanoate **6e** [4a]

Colorless oil; Yield: 96%; $[\alpha]_D^{26}$ = 1.29 (*c* 1.4, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.39 (m, 2H), 7.12-7.10 (m, 2H), 4.77-4.69 (m, 2H), 4.55-4.43 (m, 1H), 4.26 (dq J_1 = 1.6 Hz, J_2 = 7.2 Hz, 2H), 1.87 (d, *J* = 5.6 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8 (d, J_{C-F} = 29.7 Hz), 164.2 (d, J_{C-F} = 25.0 Hz), 132.3, 131.5, 131.1 (d, J_{C-F} = 2.3 Hz), 123.3, 100.3 (d, J_{C-F} = 206.5 Hz), 75.0 (d, J_{C-F} = 5.3 Hz), 63.8, 46.5 (d, J_{C-F} = 18.2 Hz), 26.5, 13.9; ESI-MS (m/z): 398.0 ($M+Na^+$); The ee value of major product was 97.0 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^oC, 214 nm, 80 : 20 hexane/*i*-PrOH, 0.7 mL/min; t_{major} = 27.2 min, t_{minor} = 17.0 min)

(*2S*, *3R*)-ethyl 2-acetyl-3-(2-bromophenyl)-2-fluoro-4-nitrobutanoate **6f**

Colorless oil; Yield: 72%; $[\alpha]_D^{26}$ = 7.63 (*c* 1.1, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.29-7.25 (m, 1H), 7.13-7.01 (m, 1H), 5.33-5.22 (m, 1H), 4.86-4.82 (m, 1H), 4.70-4.64 (m, 1H), 4.32-4.24 (m, 2H), 1.93 (d, *J* = 4.8 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7 (d, J_{C-F} = 26.5 Hz), 164.4 (d, J_{C-F} = 25.1 Hz), 134.1, 133.0 (d, J_{C-F} = 1.5 Hz), 130.4, 128.8, 128.1, 126.5, 100.0 (d, J_{C-F} = 206.5 Hz), 75.2 (d, J_{C-F} = 6.1 Hz), 63.8, 44.6 (dd, J_1 = 2.3 Hz, J_2 = 18.3 Hz), 26.2, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -171.15 (d, *J* = 30.08 Hz, 1F); ESI-MS (m/z): 398.0 ($M+Na^+$); HRMS Calc. $C_{14}H_{15}Br_1F_1NO_5Na_1$ ($M+Na^+$) 398.0015 Found: 398.0009; The ee value of major product was 98.0 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^oC, 214 nm, 80 : 20 hexane/*i*-PrOH, 0.7 mL/min; t_{major} = 21.9 min, t_{minor} = 14.2 min)

(2S, *3R*)-ethyl 2-acetyl-3-(3-bromophenyl)-2-fluoro-4-nitrobutanoate **6g** [4a]

Colorless oil; Yield: 78%; $[\alpha]_D^{26}$ = -13.88 (*c* 1.1, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H), 7.19-7.12 (m, 2H), 4.54-4.43 (m, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.89 (d, *J* = 5.6 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8 (d, J_{C-F} = 28.8 Hz), 164.2 (d, J_{C-F} = 25.3 Hz), 134.8, 132.3 (d, J_{C-F} = 2.3 Hz), 132.2, 130.5, 128.3 (d, J_{C-F} = 2.3 Hz), 123.0, 100.3 (d, J_{C-F} = 206.5 Hz), 75.0 (d, J_{C-F} = 5.3 Hz), 63.8, 46.5 (d, J_{C-F} = 18.2 Hz), 26.5, 13.9; ESI-MS (m/z): 398.0 ($M+Na^+$); The ee value of major product was 98.4 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^oC, 214 nm, 80 : 20 hexane/*i*-PrOH, 0.7 mL/min; t_{major} = 22.2 min, t_{minor} = 13.5 min)

(*2S, 3S*)-ethyl 2-acetyl-2-fluoro-3-(furan-2-yl)-4-nitrobutanoate **6h** [4a]

Colorless oil; Yield: 84%; $[\alpha]_D^{26}$ = -2.33 (*c* 0.6, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 1.2 Hz, 1H), 6.27-6.12 (m, 2H), 4.85-4.78 (m, 1H), 4.74-4.64 (m, 2H), 4.25 (dq J_1 = 0.8 Hz, J_2 = 7.2 Hz, 2H), 1.99 (d, *J* = 5.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9 (d, J_{C-F} = 28.8 Hz), 164,1 (d, J_{C-F} = 25.1 Hz), 146.2, 143.5, 110.9, 110.8, 99.2 (d, J_{C-F} = 206.2 Hz), 73.2 (d, J_{C-F} = 4.6 Hz), 63.7, 41.3 (d, J_{C-F} = 19.8 Hz), 25.8, 13.9; ESI-MS (m/z): 310.0 ($M+Na^+$); The ee value of major product was 93.9%. (HPLC-separation conditions: Chiralcel AS-H, 20 ^{o}C, 214 nm, 80 : 20 hexane/*i*-PrOH, 0.6 mL/min; t_{major} = 15.1 min, t_{minor} = 16.4 min)

(*2S, 3R*)-ethyl 2-acetyl-2-fluoro-4-nitro-3-(thiophen-2-yl) butanoate **6i** [4a]

Colorless oil; Yield: 83%; $[\alpha]_D^{25}$ = 2.58 (*c* 1.25, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.19 (m, 1H), 6.96-6.88 (m, 2H), 4.93-4.82 (m, 1H), 4.76-4.65 (m, 2H), 4.26 (dq J_1 = 1.2 Hz, J_2 = 7.2 Hz, 2H), 1.97 (d, *J* = 5.6 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8 (d, J_{C-F} = 28.9 Hz), 164,1 (d, J_{C-F} = 25.0 Hz), 133.6 (d, J_{C-F} = 1.6 Hz), 129.2, 127.2, 126.9 (d, J_{C-F} = 1.5 Hz), 99.0 (d, J_{C-F} = 206.5 Hz), 76.2 (d, J_{C-F} = 4.6 Hz), 63.7, 43.0 (d, J_{C-F} = 19.0 Hz), 26.3, 13.9; ESI-MS (m/z): 326.0 ($M+Na^+$); The ee value of major product was 97.7 %. (HPLC-separation conditions: Chiralcel AS-H, 20 ^{o}C, 214 nm, 80 : 20 hexane/*i*-PrOH, 0.7 mL/min; t_{major} = 12.1 min, t_{minor} = 14.2 min)

(*2S, 3R*)-ethyl 2-acetyl-2-fluoro-3-(naphthalen-1-yl)-4-nitrobutanoate **6j**

Colorless oil; Yield: 33%; $[\alpha]_D^{26}$ = -2.19 (*c* 0.35, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.61-7.37 (m, 4H), 5.63-5.52 (m, 1H), 4.97-4.80 (m, 2H), 4.33-4.27 (m, 2H), 1.72 (d, *J* = 6.2 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5 (d, J_{C-F} = 28.9 Hz), 164.6, 134.0, 131.7, 129.8, 129.5, 128.8, 127.2, 126.3, 126.1, 126.0, 124.9, 123.2, 100.5 (d, J_{C-F} = 207.3 Hz), 76.0 (d, J_{C-F} = 6.1 Hz), 63.7, 39.9 (d, J_{C-F} = 17.4 Hz), 26.3, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -172.05 (dd, J_1 = 3.76 Hz, J_2 = 30.08 Hz, 1F); ESI-MS (m/z): 370.1 ($M+Na^+$); HRMS Calc. $C_{18}H_{18}F_1NO_5Na_1$ ($M+Na^+$) 370.1061 Found: 370.1061; The ee value of major product was 96.8 %. (HPLC-separation conditions: Chiralcel AS-H, 20 ^{o}C, 214 nm, 80 : 20 hexane/*i*-PrOH, 0.7 mL/min; t_{major} = 13.6 min, t_{minor} = 12.3 min)

(*2S, 3R*)-ethyl 2-acetyl-2-fluoro-3-(naphthalen-2-yl)-4-nitrobutanoate **6k**

Colorless oil; Yield: 67%; $[\alpha]_D^{26}$ = -6.81 (*c* 1.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.69 (m, 4H), 7.45-7.33 (m, 3H), 4.93-4.82 (m, 2H), 4.75-4.63 (m, 1H), 4.29 (dq J_1 = 1.2 Hz, J_2 = 7.2 Hz, 2H), 1.78 (d, *J* = 5.6 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1 (d, J_{C-F} = 23.8 Hz), 164.5 (d, J_{C-F} = 25.0 Hz), 133.1 (d, J_{C-F} = 6.0 Hz), 129.8, 129.4, 129.4, 128.9, 128.1, 127.6, 126.8, 126.6, 126.3, 126.3, 100.7 (d, J_{C-F} = 207.0 Hz), 75.4(d, J_{C-F} = 4.5 Hz), 63.7, 47.3 (d, J_{C-F} = 18.2 Hz), 26.5, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -172.62 (dd, J_1 = 3.76 Hz, J_2 = 30.08 Hz, 1F); ESI-MS (m/z): 370.1 ($M+Na^+$); HRMS Calc. $C_{18}H_{18}F_1NO_5Na_1$ ($M+Na^+$) 370.1061 Found: 370.1058; The ee value of major product was 97.9 %. (HPLC-separation conditions: Chiralcel AS-H, 20 ^{o}C, 214 nm, 90 : 10 hexane/*i*-PrOH, 0.7 mL/min; t_{major} = 18.7 min, t_{minor} = 14.6 min)

(*2S, 3R*)-ethyl 2-acetyl-2-fluoro-3-(nitromethyl)-5-phenylpentanoate **6l**

Colorless oil; Yield: 76%; $[\alpha]_D^{26}$ = 12.43 (*c* 0.85, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.13 (m, 5H), 4.67-4.64 (m, 1H), 4.47-4.43 (m, 1H), 4.26 (q *J* = 7.2 Hz, 2H), 3.42-3.29 (m, 1H), 2.78-2.60 (m, 2H), 2.31 (d, *J* = 5.2 Hz, 3H), 1.84-1.75 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2 (d, J_{C-F} = 28.8 Hz), 164.7 (d, J_{C-F} = 25.1 Hz), 140.1, 128.6, 128.3, 126.5, 100.9 (d, J_{C-F} = 202.3 Hz), 74.3 (d, J_{C-F} = 3.8 Hz), 63.4, 41.0 (d, J_{C-F} = 21.2 Hz), 33.1, 29.9 (d, J_{C-F} = 2.2 Hz), 26.2, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -171.16 (dd, J_1 = 3.76 Hz, J_2 = 26.32 Hz, 1F); ESI-MS (m/z): 348.1 ($M+Na^+$); HRMS Calc. $C_{16}H_{20}F_1NO_5Na_1$ ($M+Na^+$) 348.1218 Found: 348.1224; The ee value of major product was 98.1 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^{o}C, 214 nm, 90 : 10 hexane/*i*-PrOH, 0.8 mL/min; t_{major} = 20.3 min, t_{minor} = 18.2 min)

(*2S, 3R*)-ethyl 2-acetyl-2-fluoro-3-(nitromethyl)octanoate **6m** [4a]

Colorless oil; Yield: 68%; $[\alpha]_D^{26}$ = 26.45 (*c* 0.7, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63-4.58 (m, 1H), 4.41-4.36 (m, 1H), 4.26 (q *J* = 7.2 Hz, 2H), 3.35-3.25 (m, 1H), 2.35 (d, *J* = 5.6 Hz, 3H), 1.47-1.23 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4 (d, J_{C-F} = 28.8 Hz), 164.7 (d, J_{C-F} = 25.8 Hz), 101.0 (d, J_{C-F} = 201.9 Hz), 74.4 (d, J_{C-F} = 3.0 Hz), 63.3, 41.3 (d, J_{C-F} = 20.5 Hz), 31.4 (d, J_{C-F} = 2.5 Hz), 27.8 (d, J_{C-F} = 2.2 Hz), 26.4 (d, J_{C-F} = 3.0 Hz), 22.3, 13.8 (d, J_{C-F} = 8.3 Hz); ESI-MS (m/z): 314.1 ($M+Na^+$); The ee value of major product was 97.4 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^{o}C, 214 nm, 95 : 5 hexane/*i*-PrOH, 0.5 mL/min; t_{major} = 19.3 min, t_{minor} = 13.0 min)

(*2S, 3R*)-ethyl 2-acetyl-3-cyclohexyl-2-fluoro-4-nitrobutanoate **6n**

Colorless oil; Yield: 19%; $[\alpha]_D^{25}$= 5.00 (*c* 0.30, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (dq J_1 = 4.8 Hz, J_2 = 14.4 Hz, 2H), 4.23 (dq J_1 = 1.6 Hz, J_2 = 7.2 Hz, 2H), 3.42-3.31 (m, 1H), 2.37 (d, *J* = 5.6 Hz, 3H), 1.76-1.64 (m, 6H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.33-0.84 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3 (d, J_{C-F} = 28.8 Hz), 164.9 (d, J_{C-F} = 25.8 Hz), 102.0 (d, J_{C-F} = 205.0 Hz), 72.2 (d, J_{C-F} = 3.8 Hz), 63.4, 45.9 (d, J_{C-F} = 19.8 Hz), 38.5, 31.9, 29.7, 28.6 (d, J_{C-F} = 3.8 Hz), 26.3, 26.2, 25.8, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -169.30 (dd, J_1 = 3.76 Hz, J_2 = 30.08 Hz, 1F); ESI-MS (m/z): 326.0 ($M+Na^+$); HRMS Calc. $C_{14}H_{22}F_1NO_5Na_1$ ($M+Na^+$) 326.1374 Found: 326.1378; The ee value of major product was 89.6 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^{o}C, 214 nm, 90 : 10 hexane/*i*-PrOH, 0.8 mL/min; t_{major} = 8.6 min, t_{minor} = 7.6 min)

(*S*)-ethyl 2-fluoro-2-((*R*)-2-nitro-1-phenylethyl)-3-oxohexanoate **6o**

Colorless oil; Yield: 36%; $[\alpha]_D^{26}$ = -5.84 (*c* 0.35, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 4.86-4.84 (m, 2H), 4.65-4.53 (m, 1H), 4.33 (dq J_1 = 1.6 Hz, J_2 = 6.8 Hz, 2H), 2.44-2.35 (m, 1H), 1.93-1.84 (m, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.23-1.12 (m, 2H), 0.59 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2 (d, J_{C-F} = 27.3 Hz), 164.6 (d, J_{C-F} = 25.1 Hz), 132.5, 129.6 (d, J_{C-F} = 2.3 Hz), 128.9 (d, J_{C-F} = 6.1 Hz), 100.7 (d, J_{C-F} = 204.3 Hz), 75.3 (d, J_{C-F} = 5.3 Hz), 63.5, 47.2 (d, J_{C-F} = 8.2 Hz), 40.3, 15.6 (d, J_{C-F} = 2.3 Hz), 13.9, 13.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -175.82 (d, *J* = 30.08 Hz, 1F); ESI-MS (m/z): 348.1 ($M+Na^+$); HRMS Calc. $C_{16}H_{20}F_1NO_5Na_1$ ($M+Na^+$) 348.1218 Found: 348.1234; The ee value of major product was 92.2 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^{o}C, 214 nm, 90 : 10 hexane/*i*-PrOH, 0.9 mL/min; t_{major} = 21.7 min, t_{minor} = 11.0 min)

(*2S, 3R*)-methyl 2-acetyl-2-fluoro-4-nitro-3-phenylbutanoate **6p** [4a]

Colorless oil; Yield: 80%; $[\alpha]_D^{26}$ = -24.50 (*c* 0.9, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 4.86-4.84 (m, 2H), 4.63-4.51 (m, 1H), 3.58 (s, 3H), 1.86 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2 (d, J_{C-F} = 28.8 Hz), 164.9 (d, J_{C-F} = 25.1 Hz), 132.3, 129.5 (d, J_{C-F} = 2.3 Hz), 129.1, 129.0, 100.5 (d, J_{C-F} = 206.5 Hz), 75.1 (d, J_{C-F} = 5.3 Hz), 54.0, 47.2 (d, J_{C-F} = 18.2 Hz), 26.4; ESI-MS (m/z): 306.0 ($M+Na^+$); The ee value of major product was 97.5 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^{o}C, 214 nm, 90 : 10 hexane/*i*-PrOH, 0.8 mL/min; t_{major} = 33.8 min, t_{minor} = 16.0 min)

(*2S, 3R*)-*tert*-butyl 2-acetyl-2-fluoro-4-nitro-3-phenylbutanoate **6q**

White solid; Yield: 77%; mp: 129-135^{o}C $[\alpha]_D^{26}$ = -2.38 (*c* 1.5, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 5H), 4.84-4.83 (m, 2H), 4.57-4.45 (m, 1H), 1.84 (d, *J* = 5.2 Hz, 3H), 1.50 (s, 9H); ESI-MS (m/z): 348.1 ($M+Na^+$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5 (d, J_{C-F} = 28.9 Hz), 163.4 (d, J_{C-F} = 24.3 Hz), 132.7, 129.5 (d, J_{C-F} = 2.3 Hz), 128.9, 128.8, 128.8, 100.7 (d, J_{C-F} = 205.0 Hz), 85.6, 75.5 (d, J_{C-F} = 4.6 Hz), 47.1 (d, J_{C-F} = 18.2 Hz), 27.7, 26.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -171.93 (dq, J_1 = 3.76 Hz, J_2 = 30.08 Hz, 1F); ESI-MS (m/z): 348.1 ($M+Na^+$); HRMS Calc. $C_{16}H_{20}F_1NO_5Na_1$ ($M+Na^+$) 348.1218 Found: 348.1222; The ee value of major product was 97.9 %. (HPLC-separation conditions: Chiralcel AS-H, 20 ^{o}C, 214 nm, 90 : 10 hexane/*i*-PrOH, 0.6 mL/min; t_{major} = 10.6 min, t_{minor} = 9.5 min)

(*2S, 3R*)-benzyl 2-acetyl-2-fluoro-4-nitro-3-phenylbutanoate **6r**

White solid; Yield: 77%; mp: 108-112^{o}C; $[\alpha]_D^{26}$ = -6.10 (*c* 1.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.26 (m, 10H), 5.29 (q, *J* = 12.0 Hz, 2H), 4.82-4.76 (m, 1H), 4.67-4.52 (m, 2H), 1.85 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9 (d, J_{C-F} = 28.8 Hz), 164.3 (d, J_{C-F} = 25.8 Hz), 134.0, 132.2, 129.5, 129.5, 129.1, 129.0, 128.9, 128.8, 128.5, 100.5 (d, J_{C-F} = 206.9 Hz), 75.0 (d, J_{C-F} = 4.5 Hz), 68.9, 47.3 (d, J_{C-F} = 18.2 Hz), 26.42; ^{19}F NMR (376 MHz, $CDCl_3$) δ -172.96 (dq, J_1 = 3.76 Hz, J_2 = 30.08 Hz, 1F); ESI-MS (m/z): 382.1 ($M+Na^+$); HRMS Calc. $C_{19}H_{18}F_1NO_5Na_1$ ($M+Na^+$) 382.1061 Found: 382.1059; The ee value of major product was 99.5 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^{o}C, 214 nm, 80 : 20 hexane/*i*-PrOH, 0.8 mL/min; t_{major} = 37.7 min, t_{minor} = 15.1 min)

(2S, 3R)-tert-butyl 2-acetyl-3-(4-bromophenyl)-2-fluoro-4-nitrobutanoate **6s**

White solid; Yield: 85%; mp: 140-146^{o}C; $[\alpha]_D^{26}$ = 6.56 (*c* 1.25, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2H), 7.17-7.15 (m, 2H), 4.80-4.74 (m, 2H), 4.55-4.43 (m, 1H), 1.90 (d, *J* = 6.0 Hz, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2 (d, J_{C-F} = 29.6 Hz), 163.1 (d, J_{C-F} = 25.1 Hz), 132.2, 131.8, 131.2 (d, J_{C-F} = 2.3 Hz), 123.2, 100.5 (d, J_{C-F} = 205.0 Hz), 85.9, 75.3 (d, J_{C-F} = 4.6 Hz), 46.4 (d, J_{C-F} = 18.3 Hz), 27.6, 26.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -171.97 (dq, J_1 = 3.76 Hz, J_2 = 30.08 Hz, 1F); ESI-MS (m/z): 426.0 ($M+Na^+$); HRMS Calc. $C_{16}H_{19}Br_1F_1NO_5Na_1$ ($M+Na^+$) 426.0323 Found: 426.0312; The ee value of major product was 98.3 %. (HPLC-separation conditions: Chiralcel OD-H, 20 ^{o}C, 214 nm, 90 : 10 hexane/*i*-PrOH, 0.8 mL/min; t_{major} = 8.2 min, t_{minor} = 10.7 min)

4.4 Transformation of the Michael adduct 6a to prepare 7.

To a solution of **6a** (30 mg, 0.1 mmol) in EtOH (2 mL) and water (2 mL), NH_4Cl (22 mg, 0.4 mmol) were added and the mixture was cold to 0^{o}C. Then Zn power (13 mg, 0.2 mmol) was added in one portion and the mixture were stirred at 0^{o}C for 3h. The reaction mixture was filtered and the filtrate was evaporated in vacuo to remove EtOH. The residue were extracted CH_2Cl_2 (2×4 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated. Crude products were purified by silica gel column chromatography (Hexane : EtOAc = 2 : 1) to afford the pure product **7** 18.4 mg, yield: 69.2%.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5H), 4.52-4.48 (m, 2H), 4.08 (dt, J_1 = 8.4 Hz, J_2 = 24.8 Hz, 1H), 3.81-3.90 (m, 2H), 2.08 (m, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 140.3, 133.2, 128.9, 128.6, 127.8, 103.1 (d, J_{C-F} = 198.2 Hz), 64.2, 62.4, 48.1 (d, J_{C-F} = 22.8 Hz), 13.6, 9.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -145.22 (ddt, J_1 = 3.01 Hz, J_2 = 7.53 Hz, J_3 = 24.82 Hz, 1F); ESI-MS (m/z): 266.1 ($M+H^+$); HRMS Calc. $C_{14}H_{17}O_3NF$ ($M+H^+$) 266.1187 Found: 266.1184; 97.2% ee. (HPLC-separation conditions: Chiralcel OD-H, 20 ^{o}C, 214 nm, 90 : 10 hexane/*i*-PrOH, 0.8 mL/min; t_{major} = 8.2 min, t_{minor} = 10.7 min)

Supplementary data

^{1}H NMR experiments to tracing the reaction, copies of NMR spectra and HPLC traces for the isolated products and Crystal data and structure of **6s**. Supplementary data associated with this article can be found in the online version, at http://

Acknowledgment

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8. CCDC 1045691 [(2*S*, 3*R*)-**6s**] contains the supplymentary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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Primary-secondary Diamines Catalyzed Michael Reaction to Generate Chiral Fluorinated Quaternary Carbon

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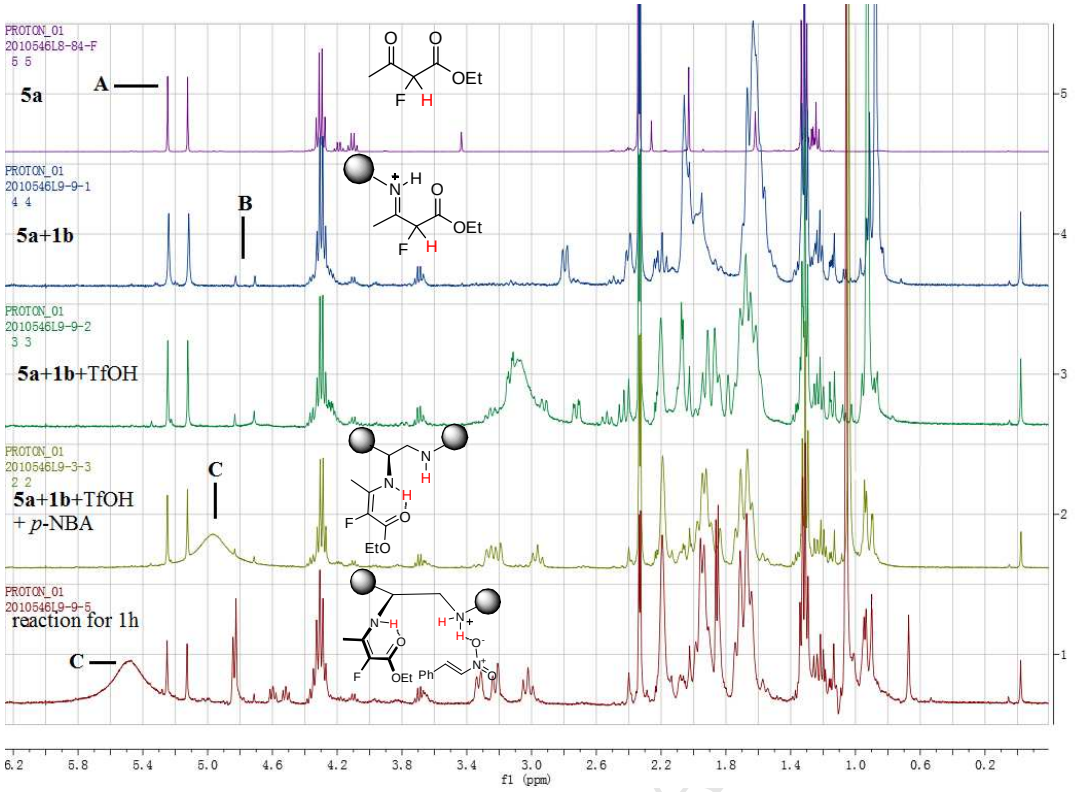
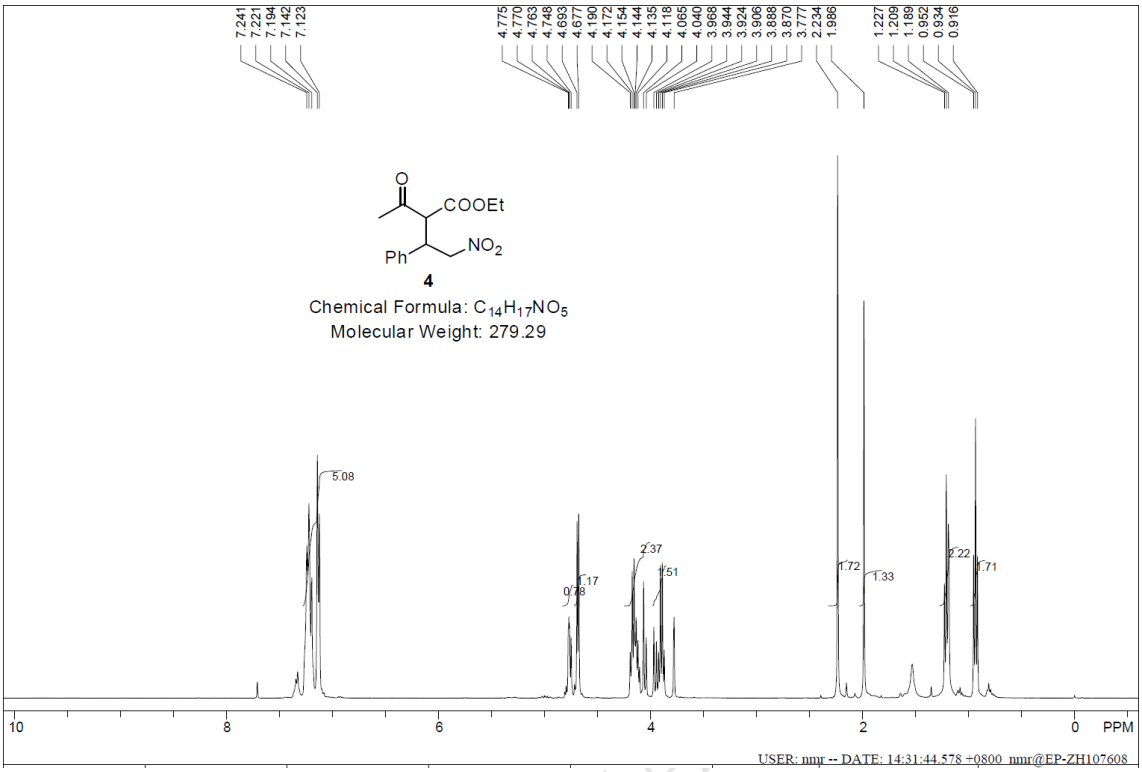
Supporting information

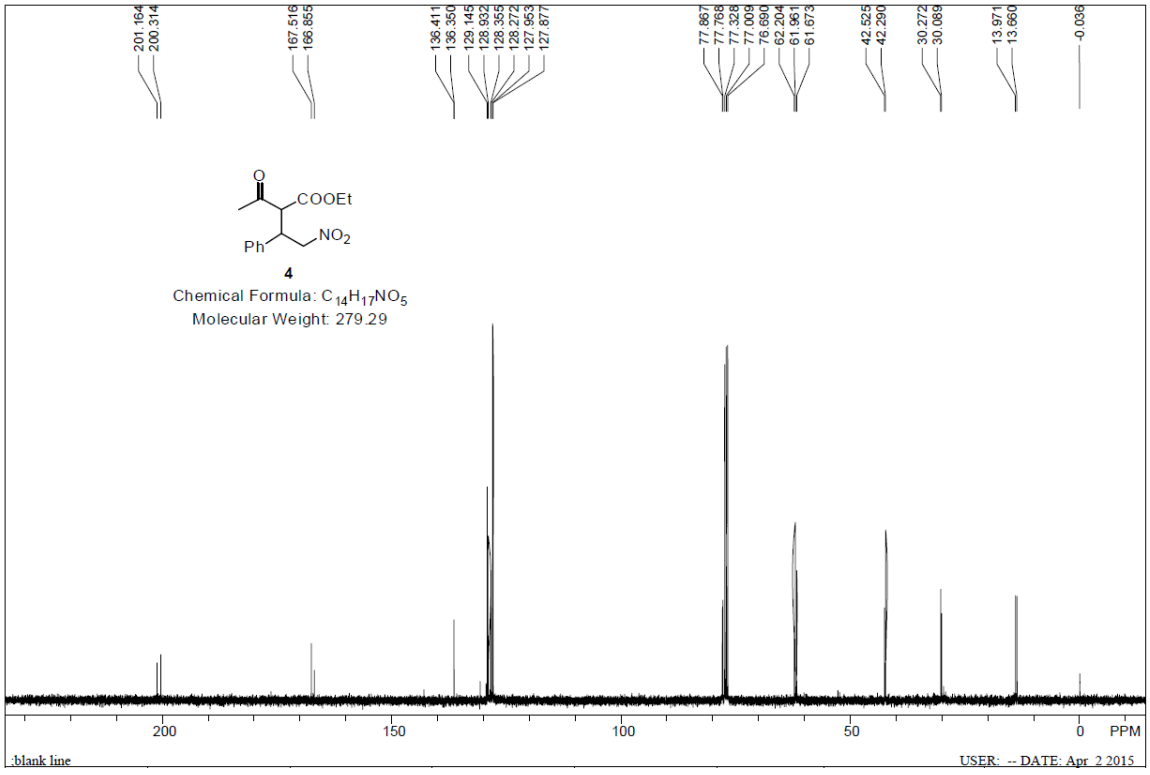
^{1}H NMR experiments to tracing the reaction.

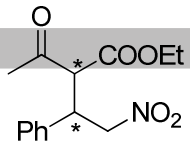


When catalyst **1b** was added to the solution of **5a**, the iminium signal (B) was observed. after the acids were added, the NH_2 signal of catalyst (C) at δ 2 ppm moved to δ 5 ppm, which indicated the existence of H-bonding. When the electrophilic **3a** was added, the broad peak of NH moved to the low field further, which demonstrated the H-bond interaction between the catalyst and electrophile.

Copies of NMR spectra and HPLC traces







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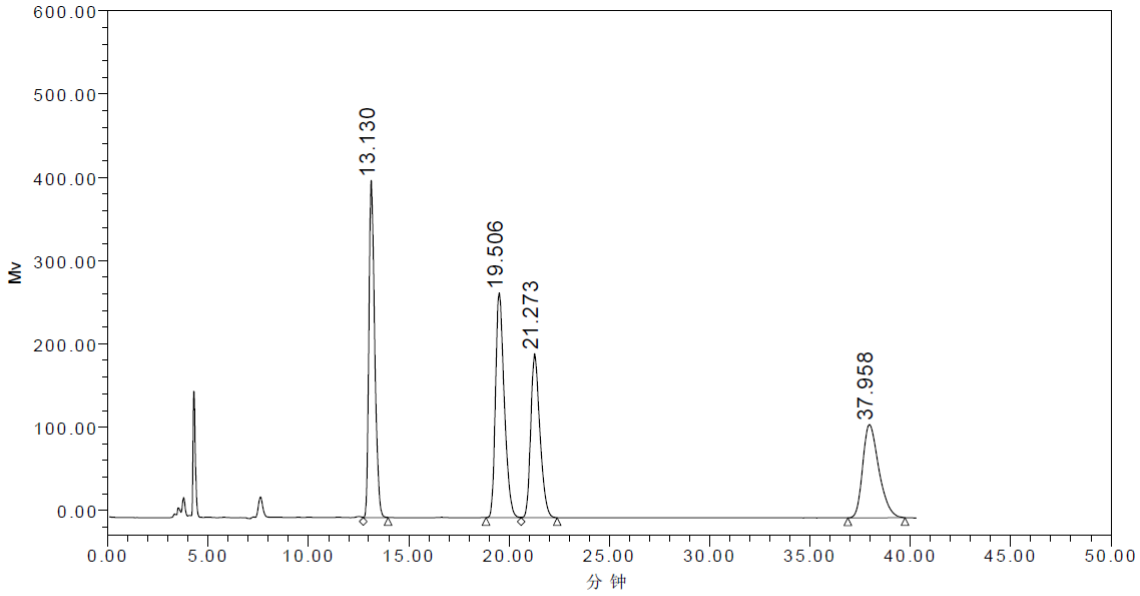

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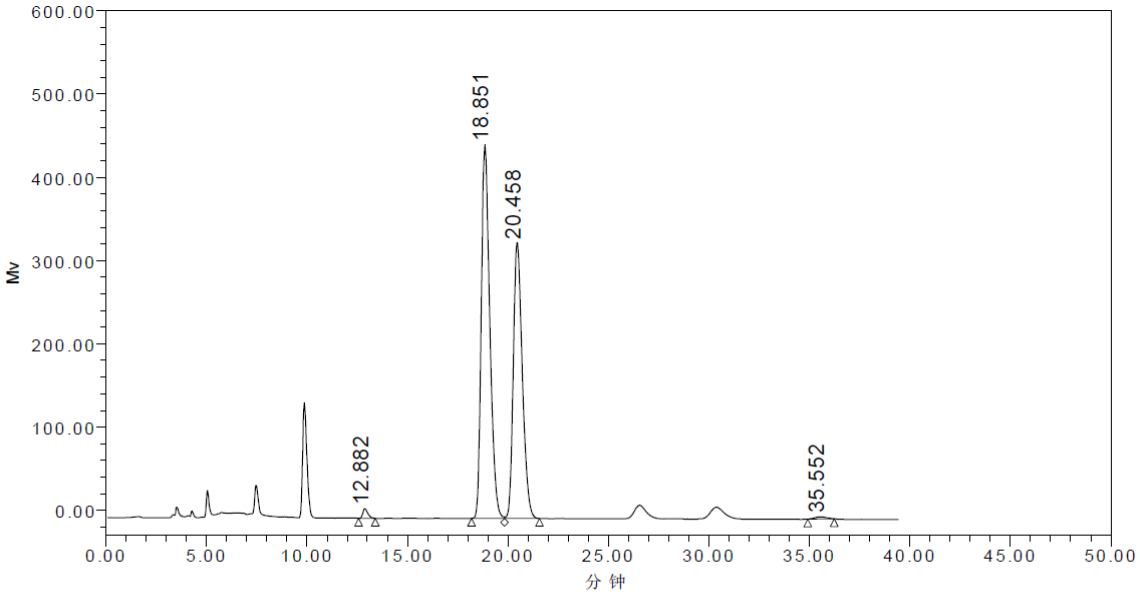

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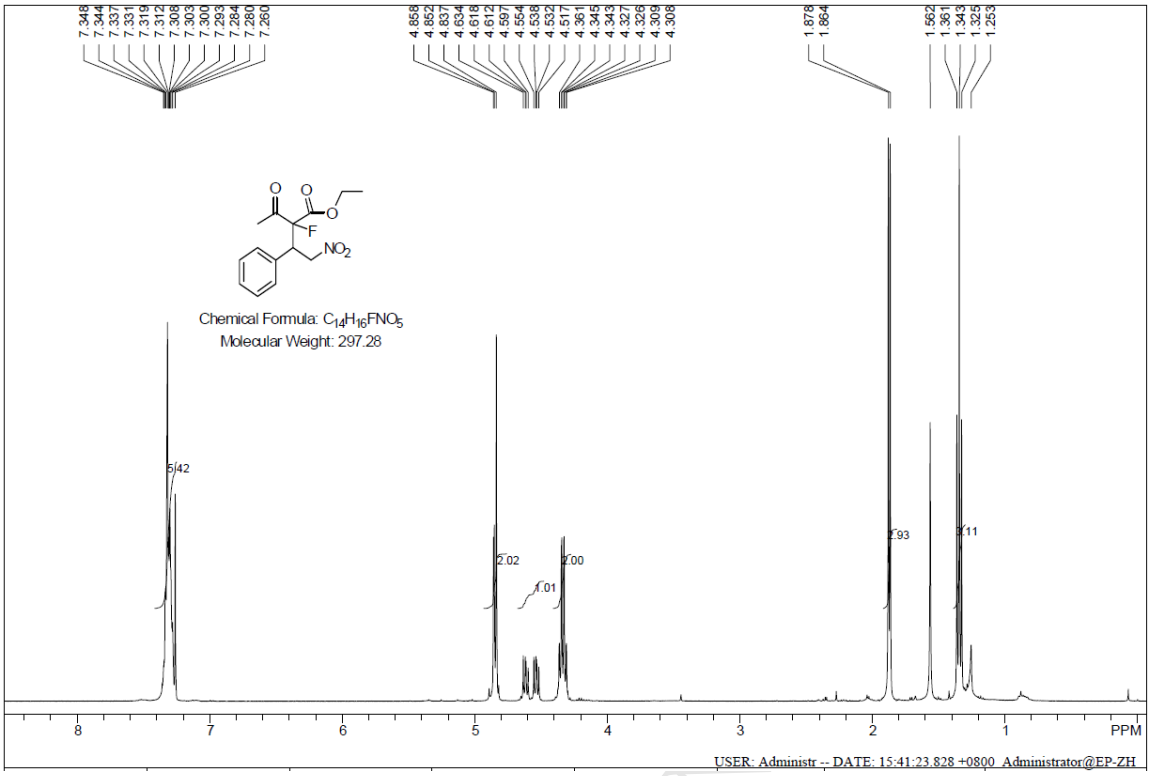
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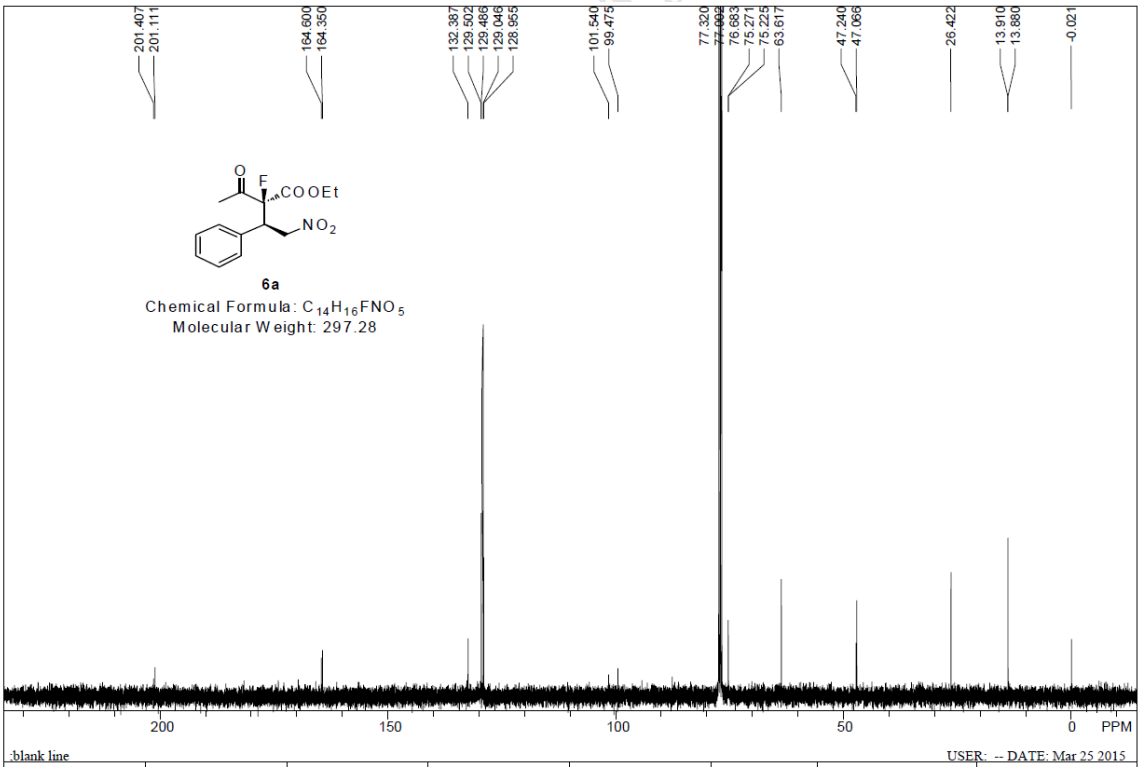
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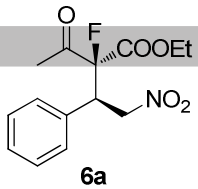

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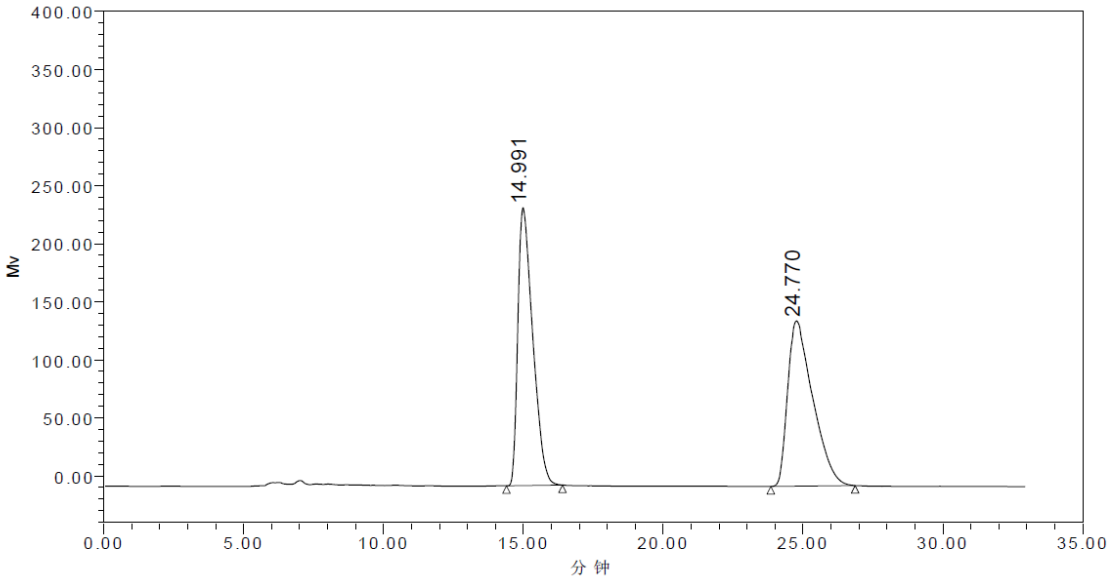

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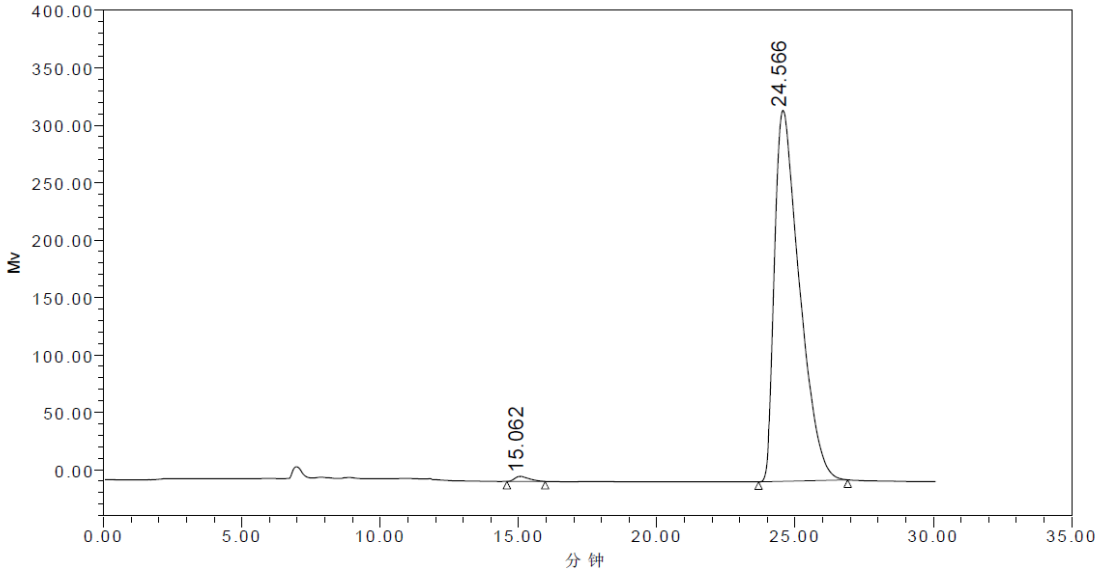

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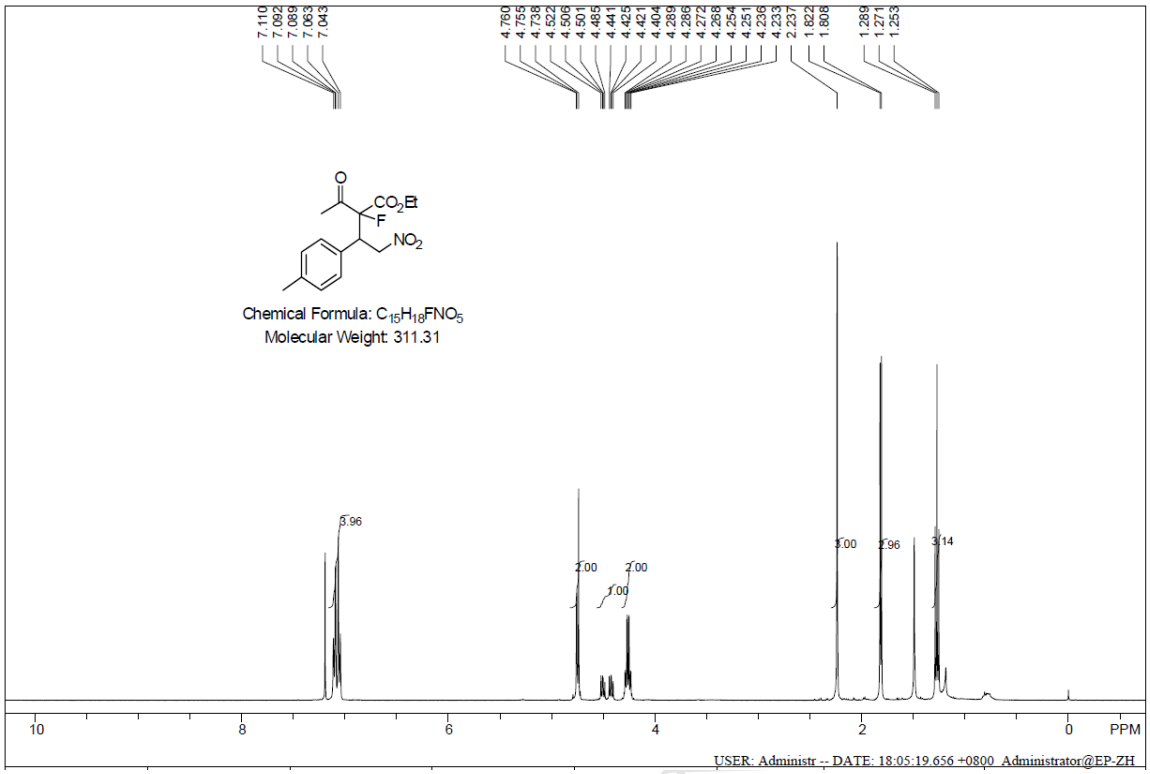
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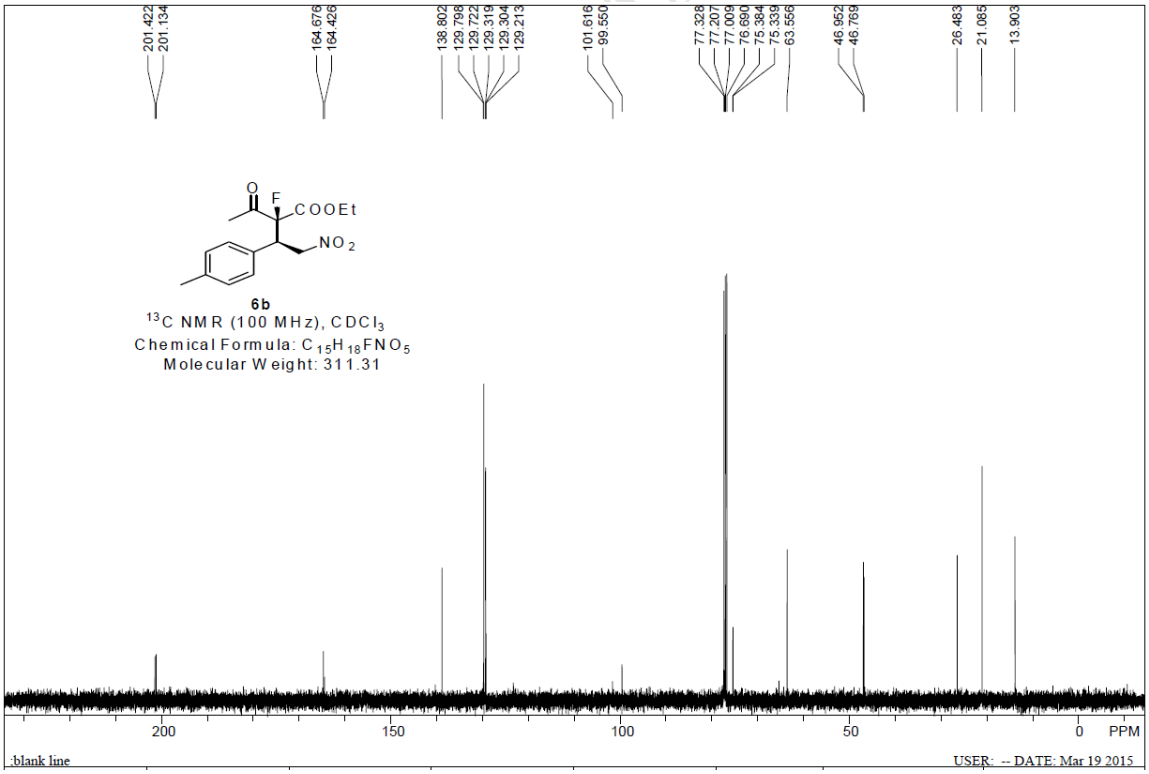
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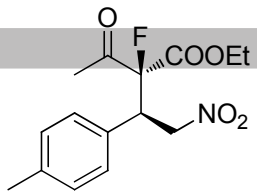

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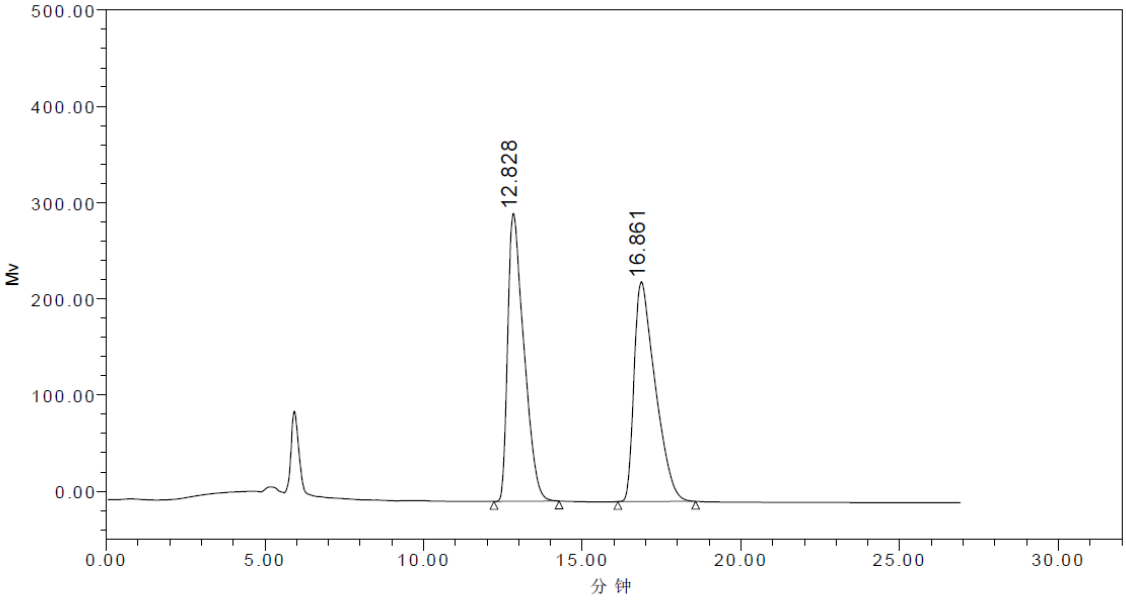

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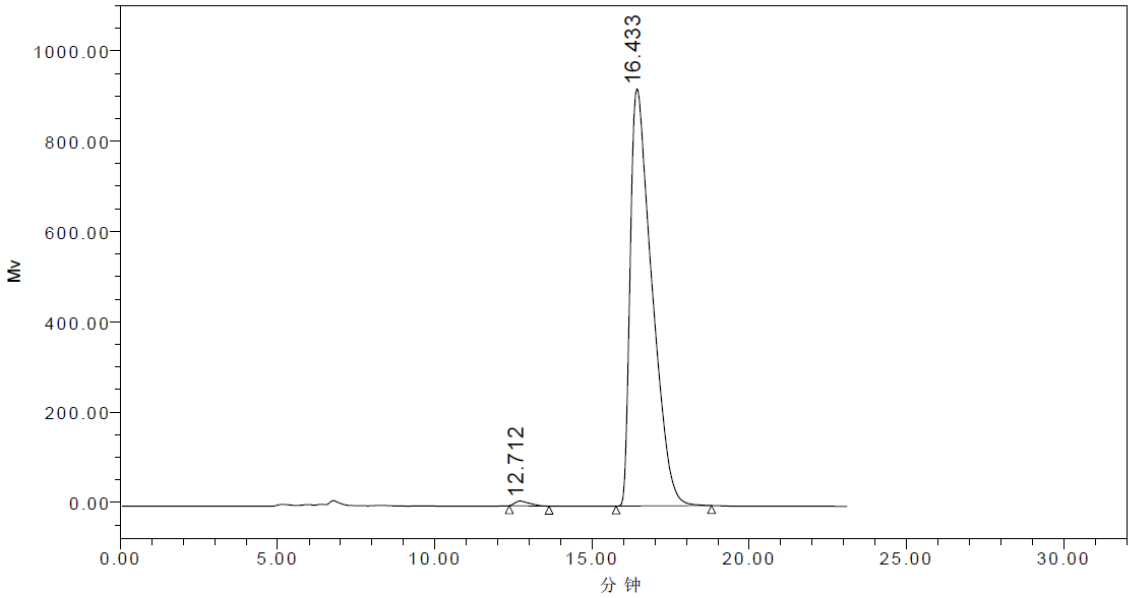

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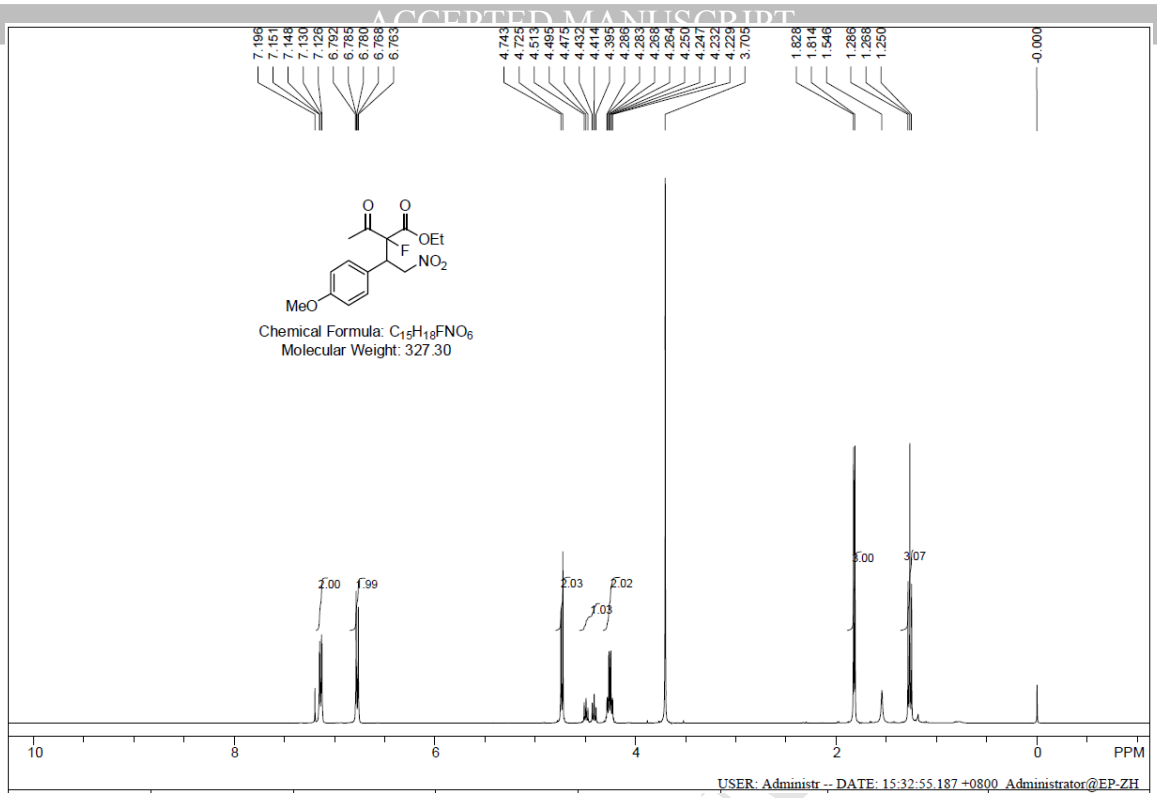

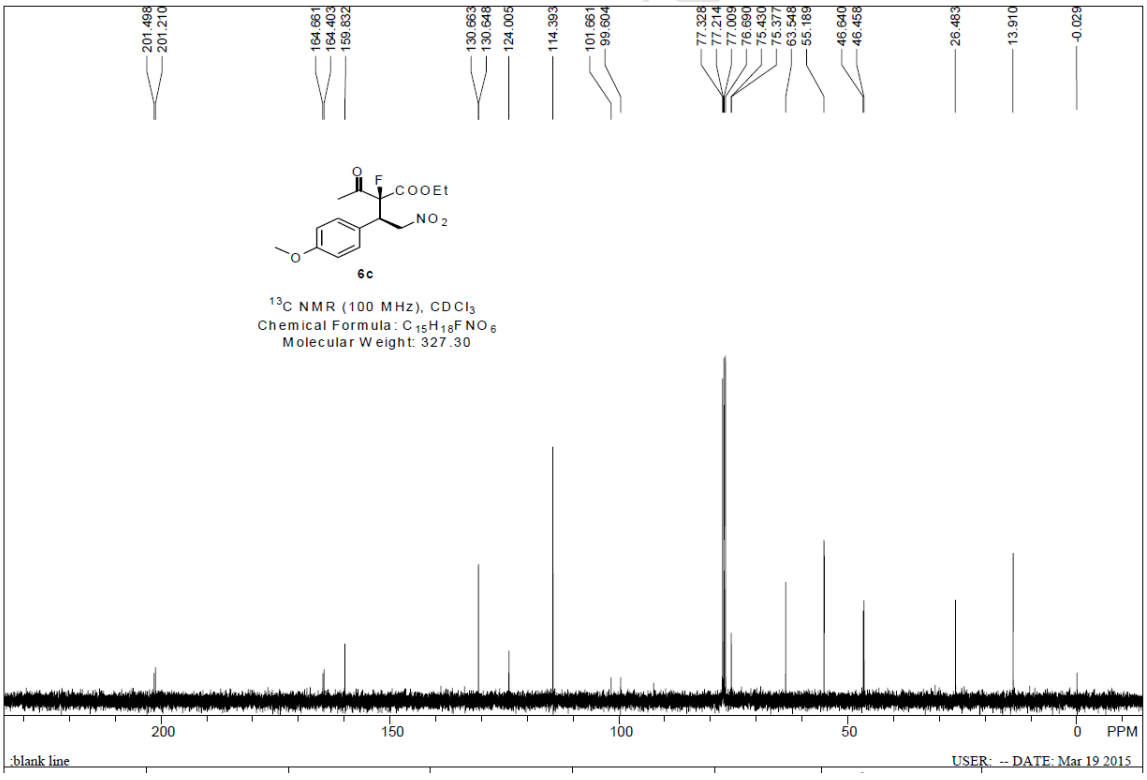

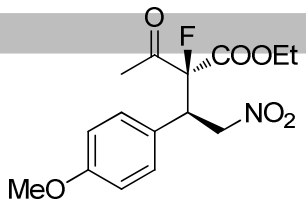

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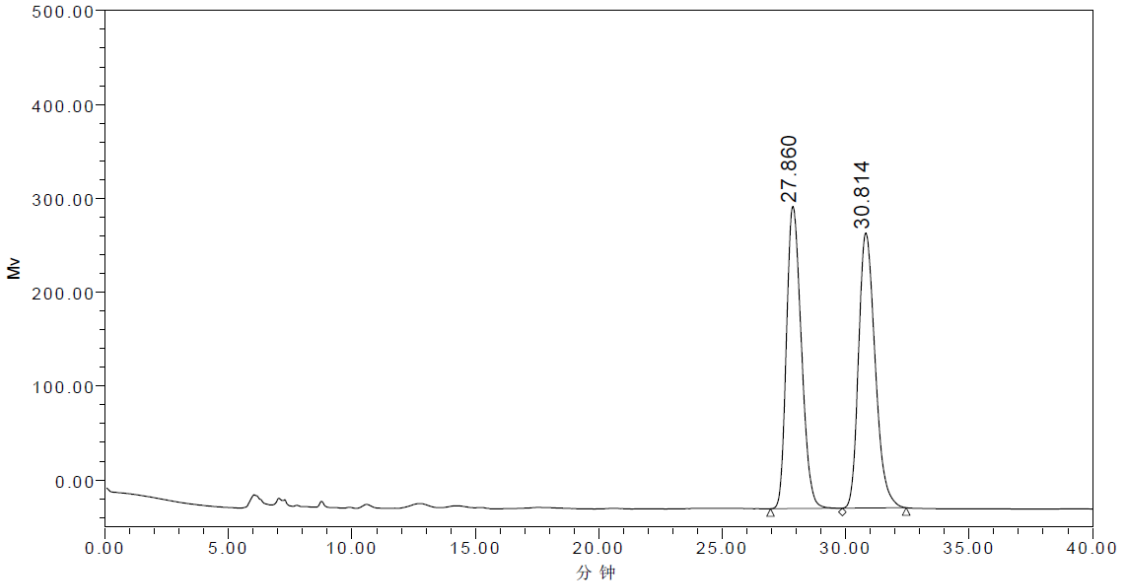

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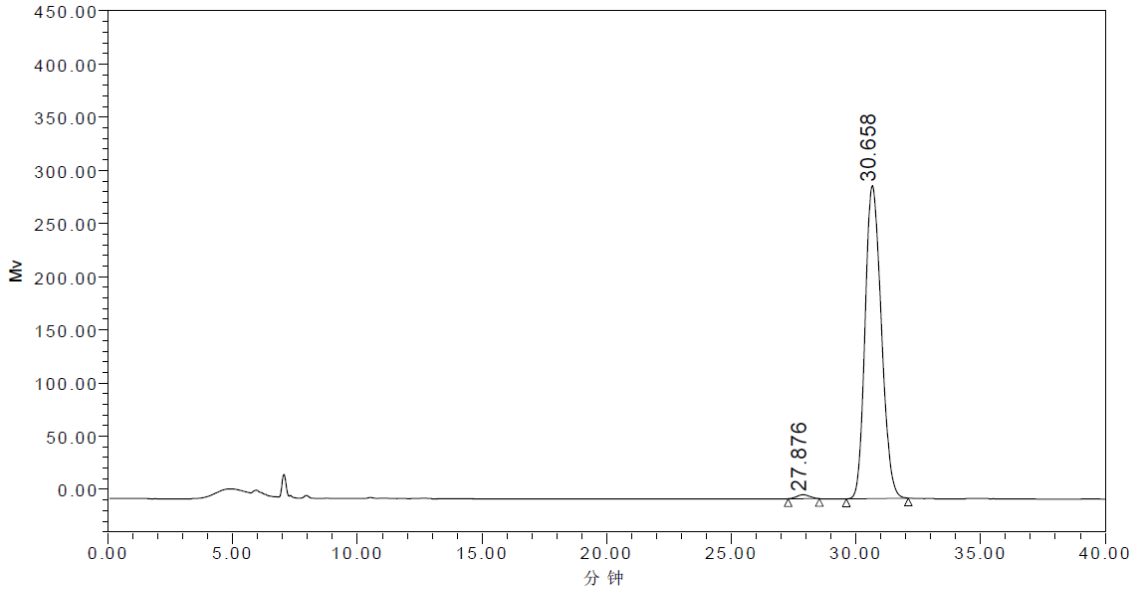

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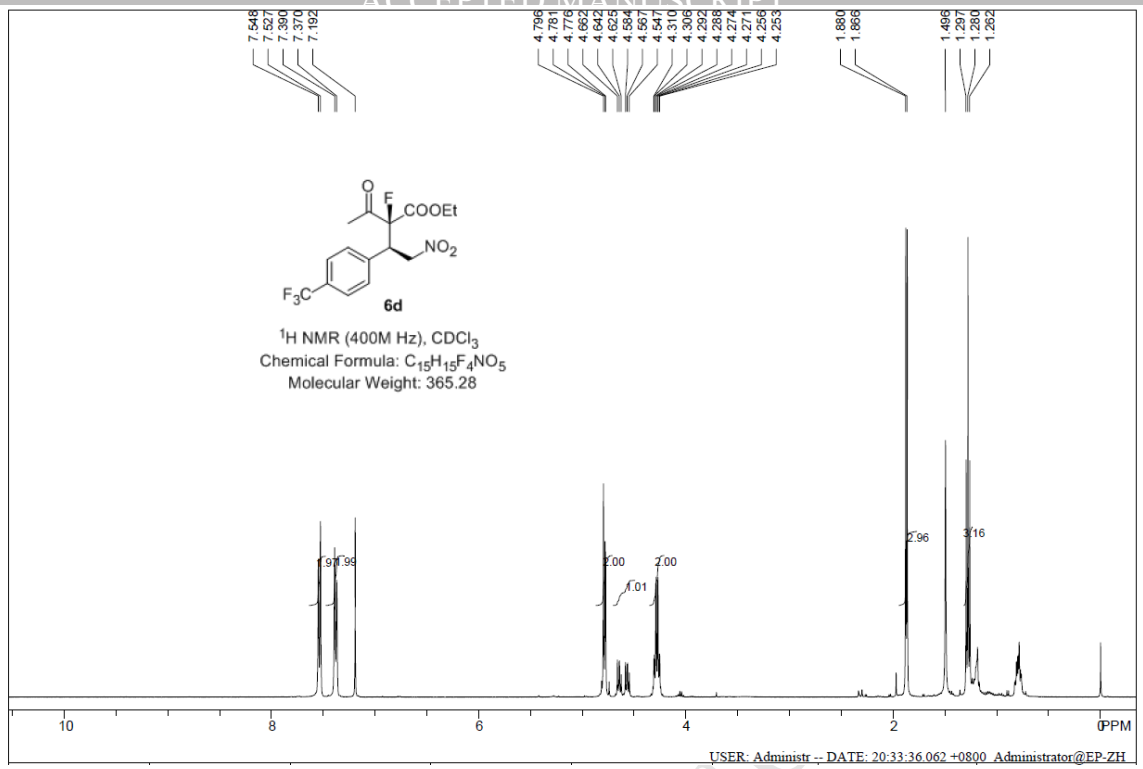
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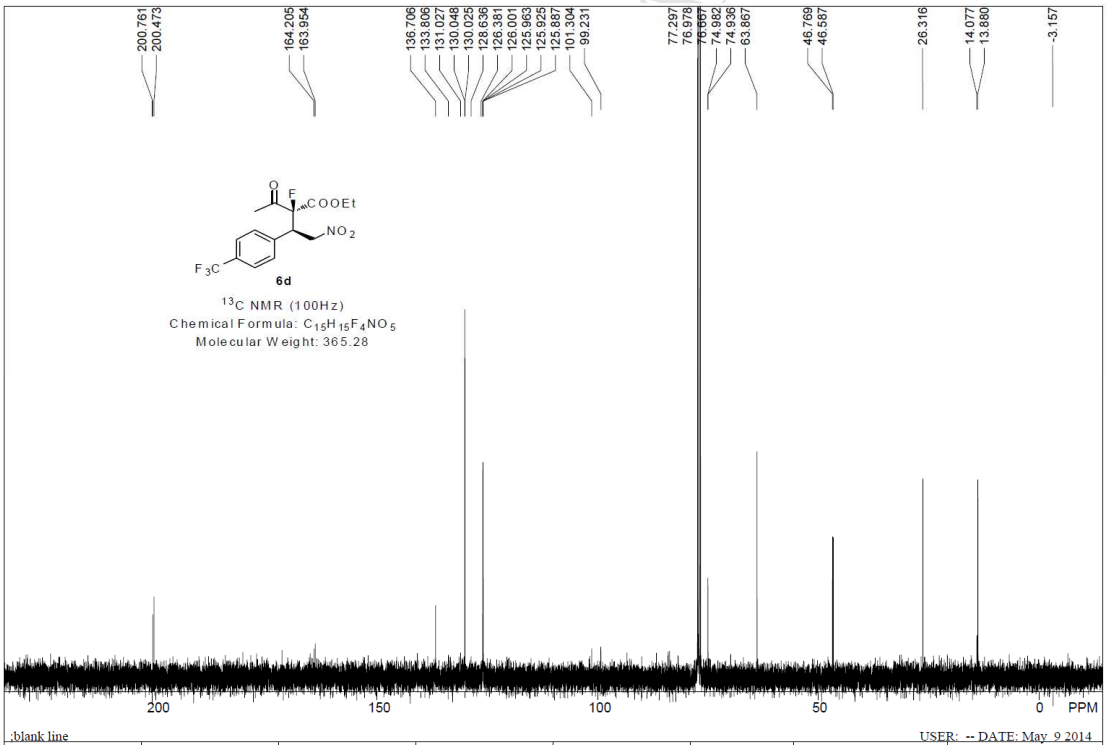
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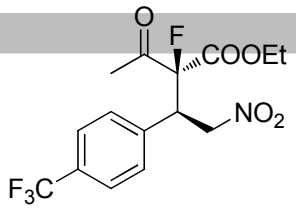

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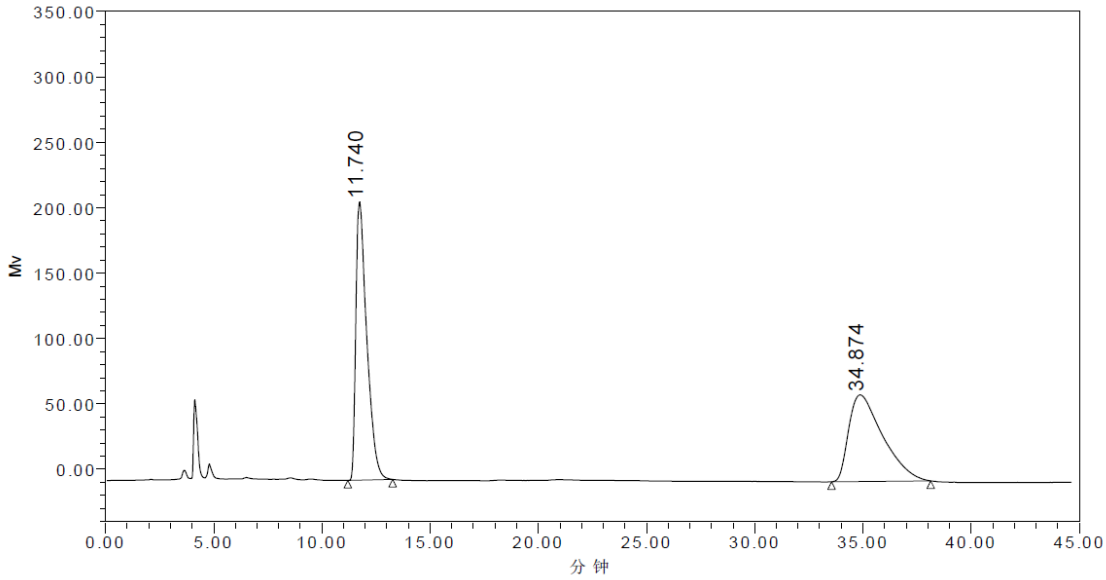

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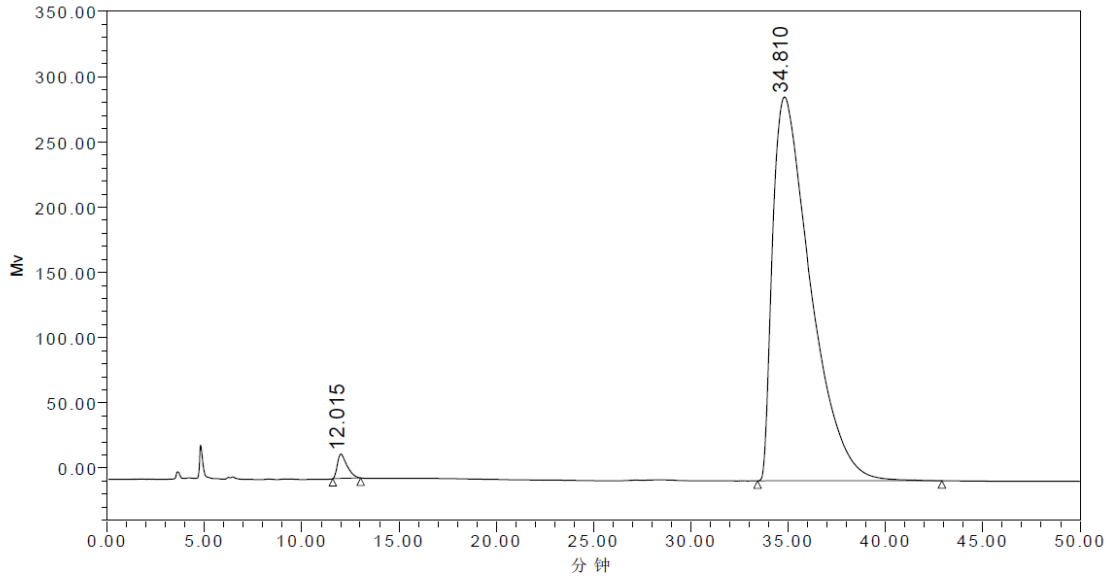

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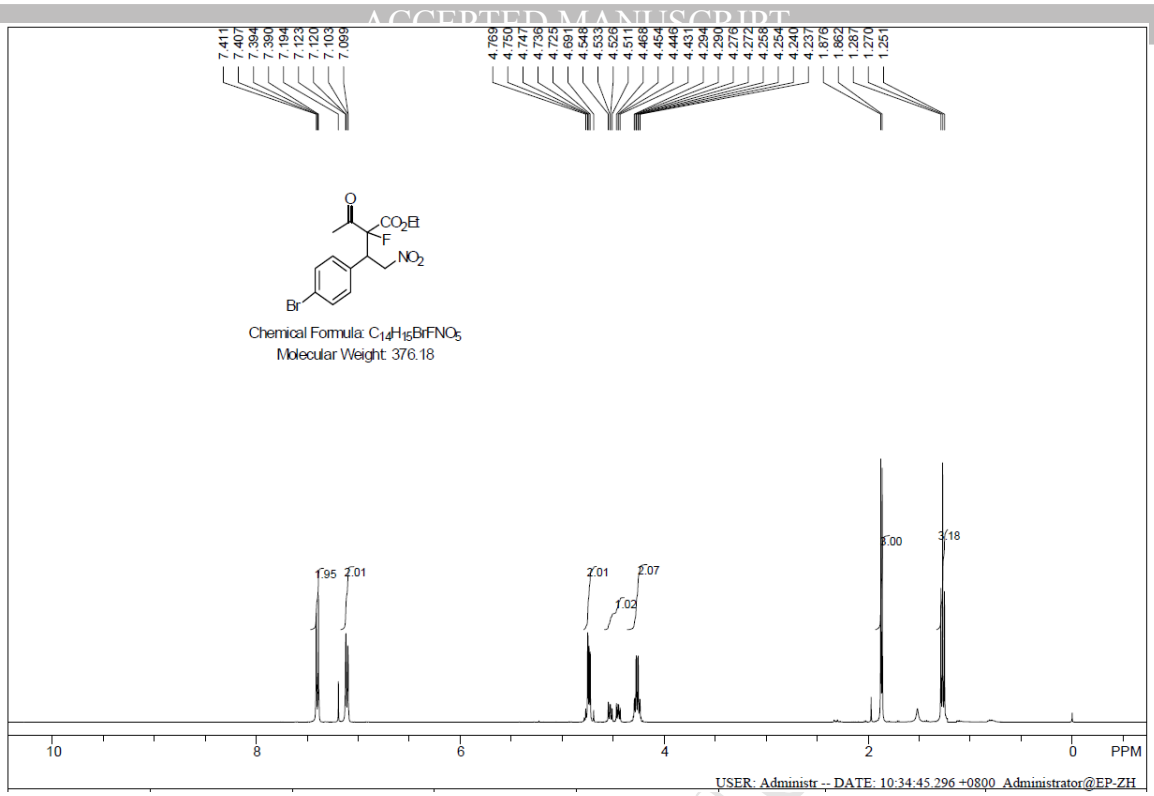

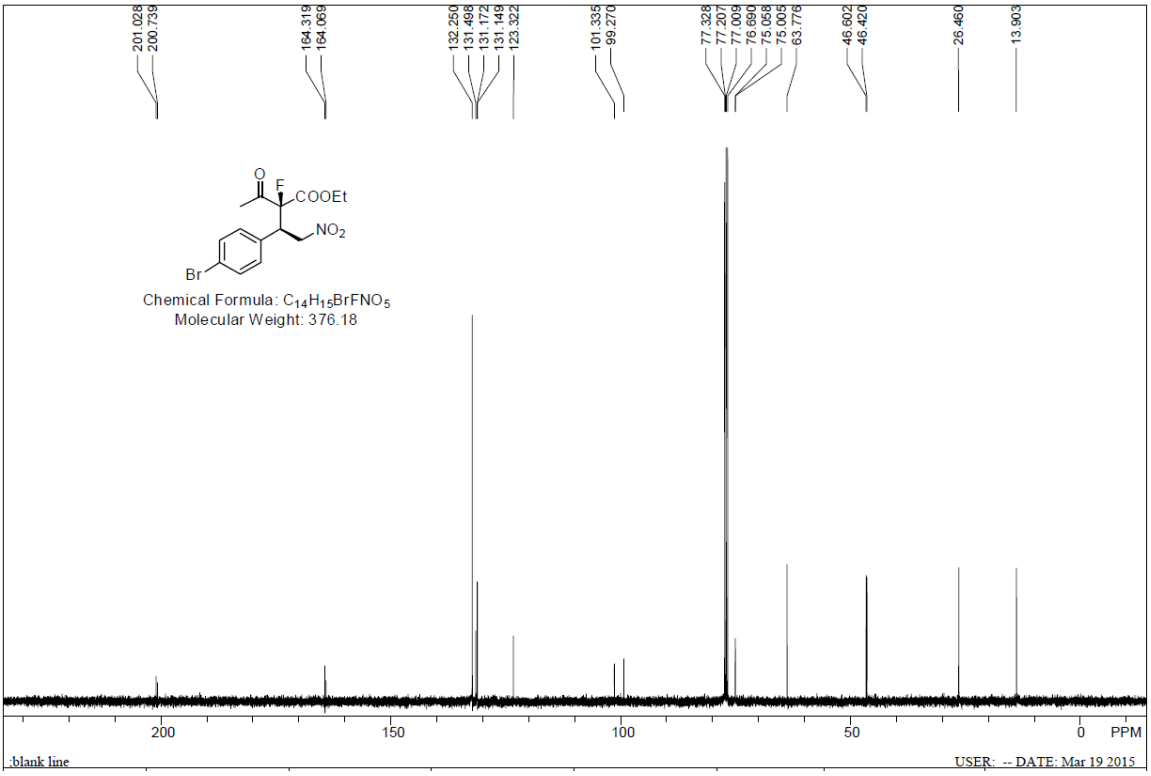

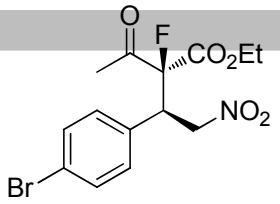

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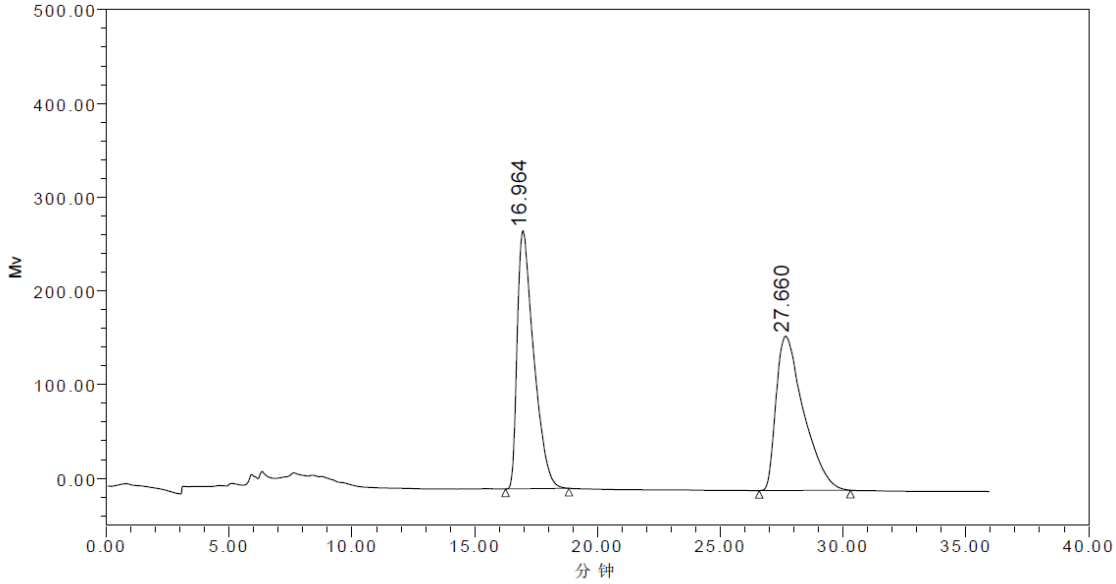

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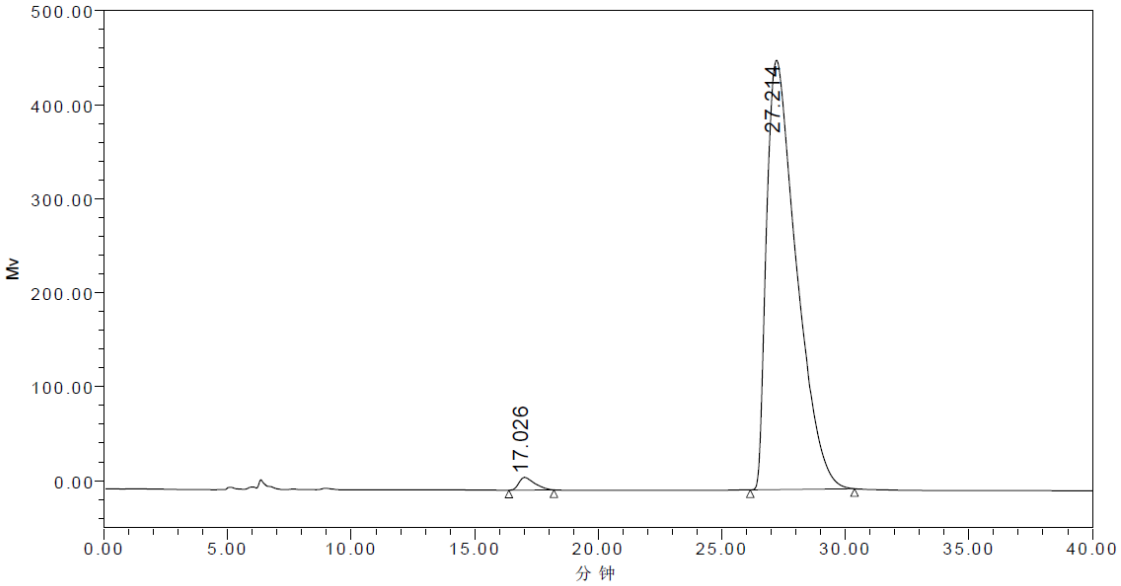

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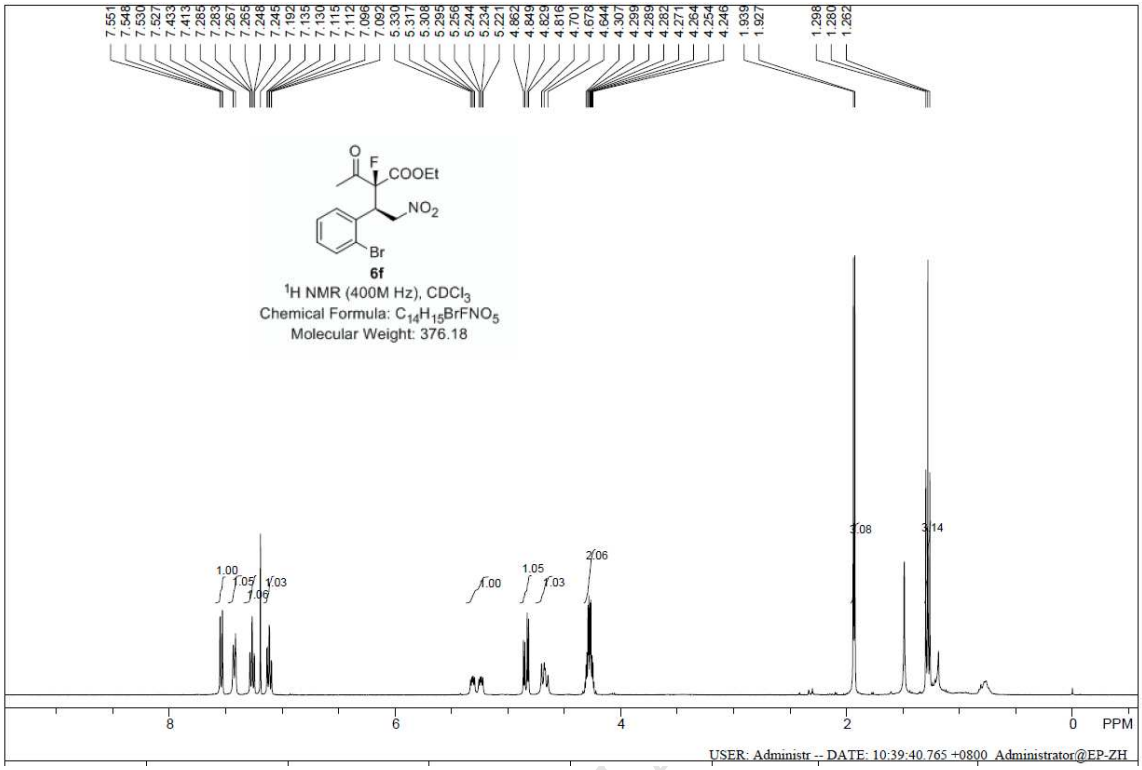
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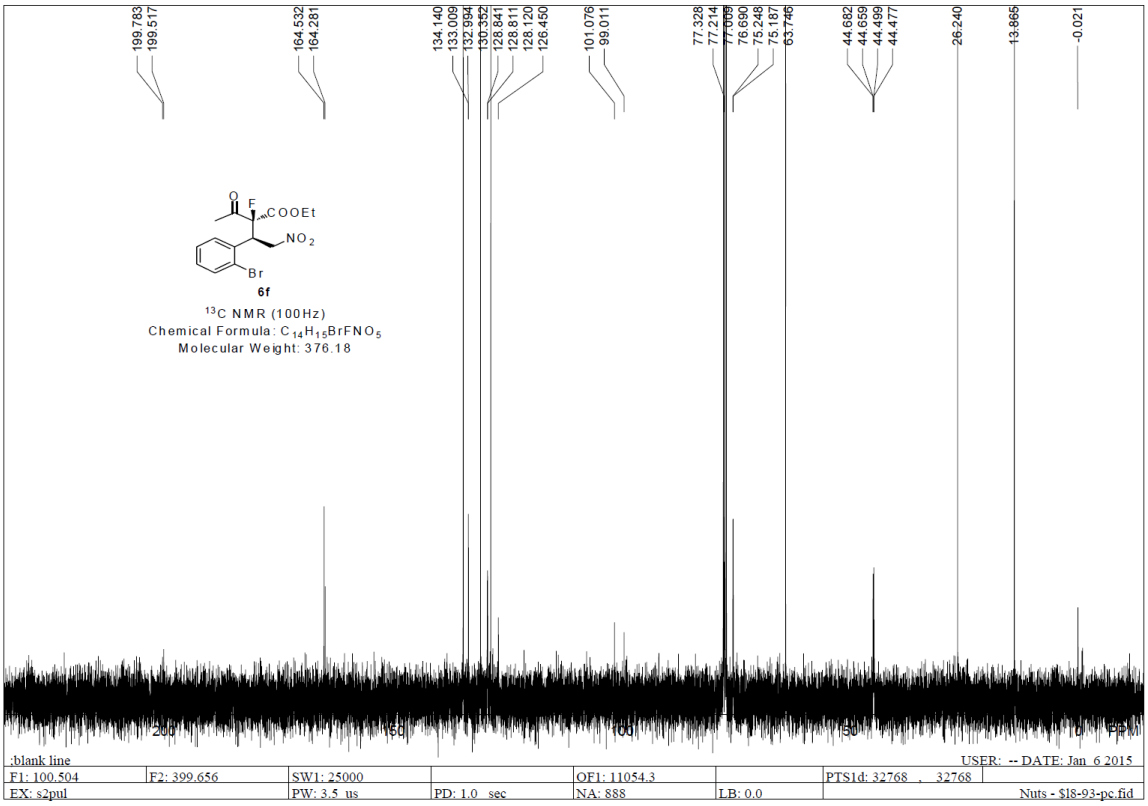
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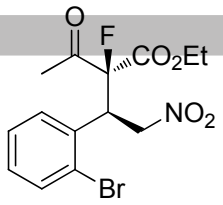

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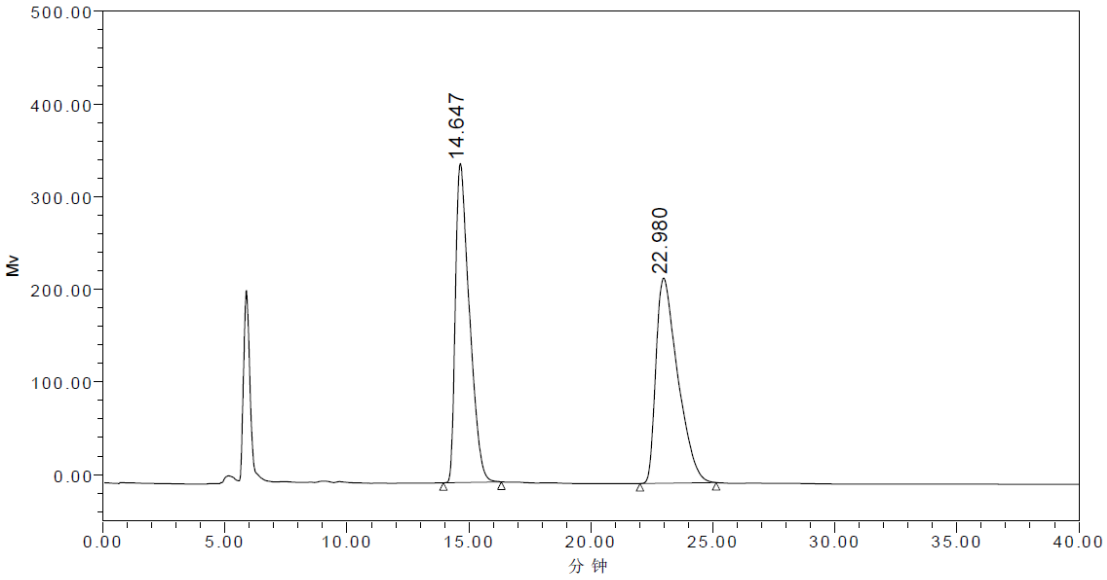

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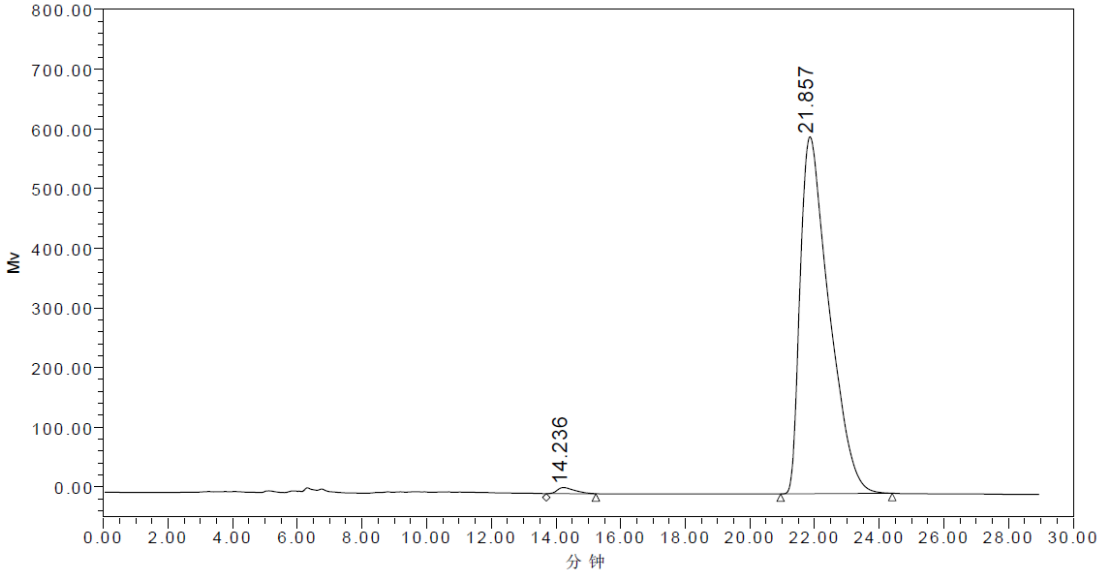

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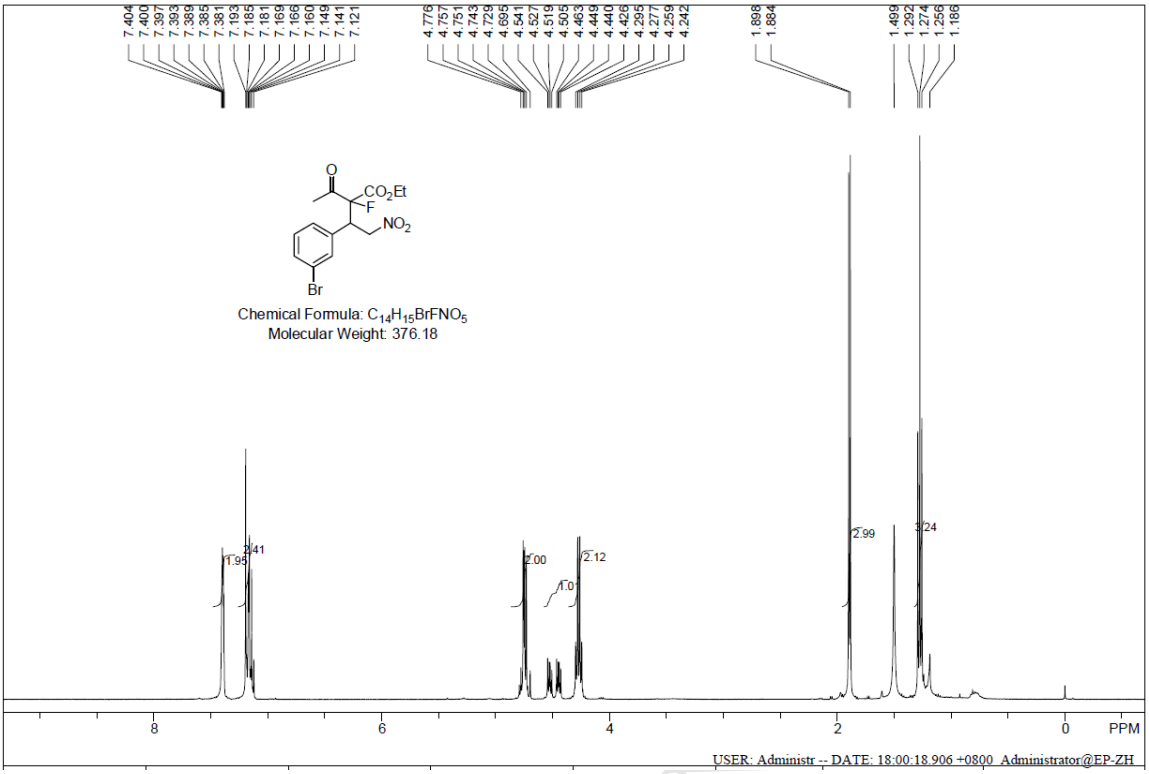
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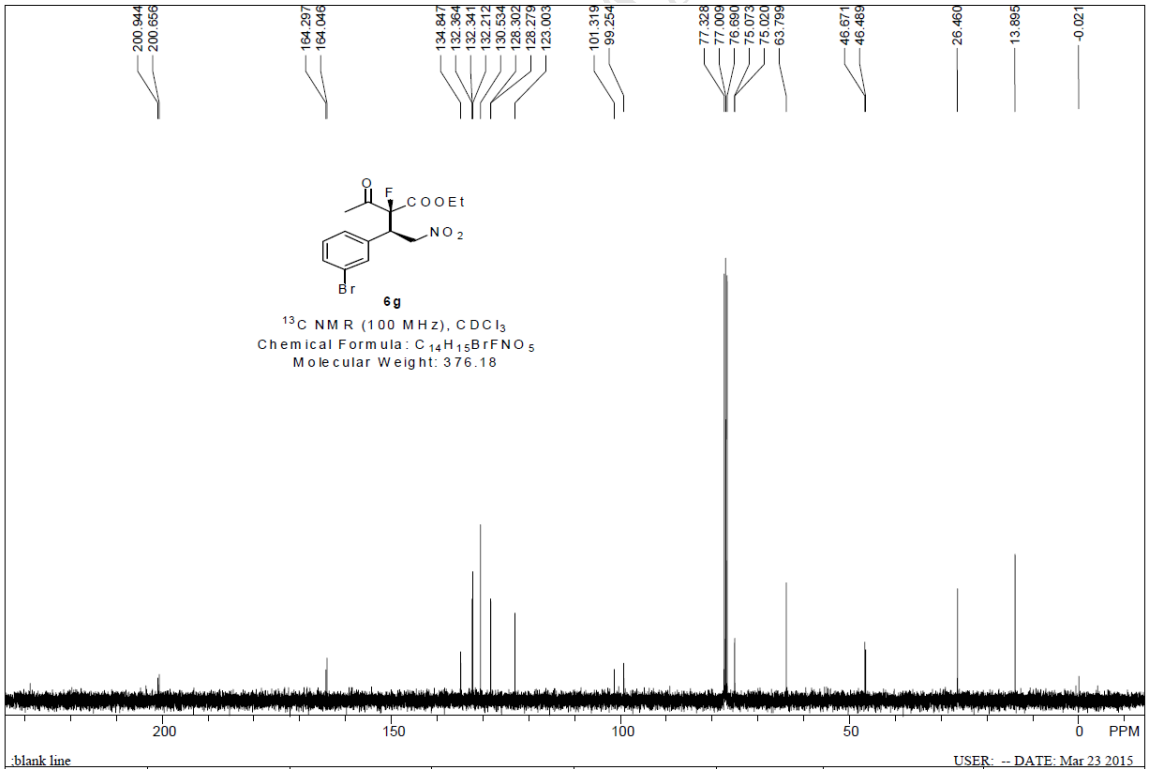
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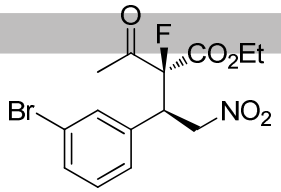

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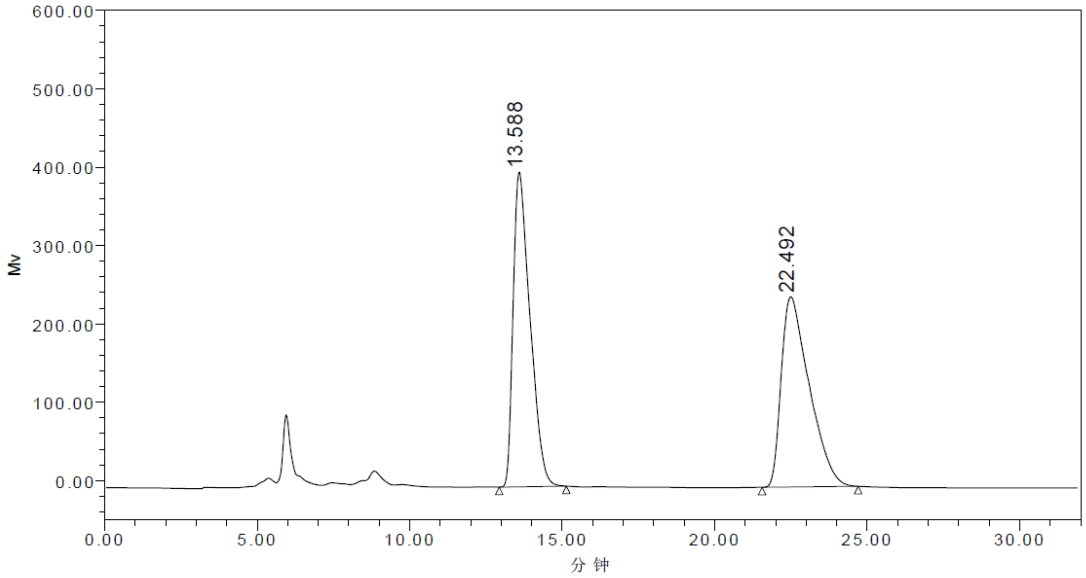

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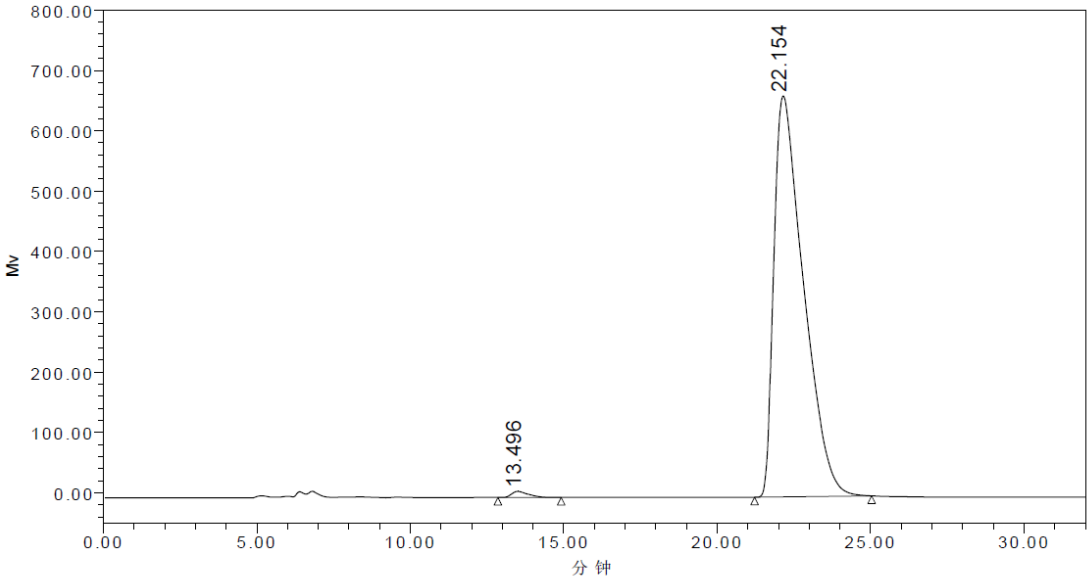

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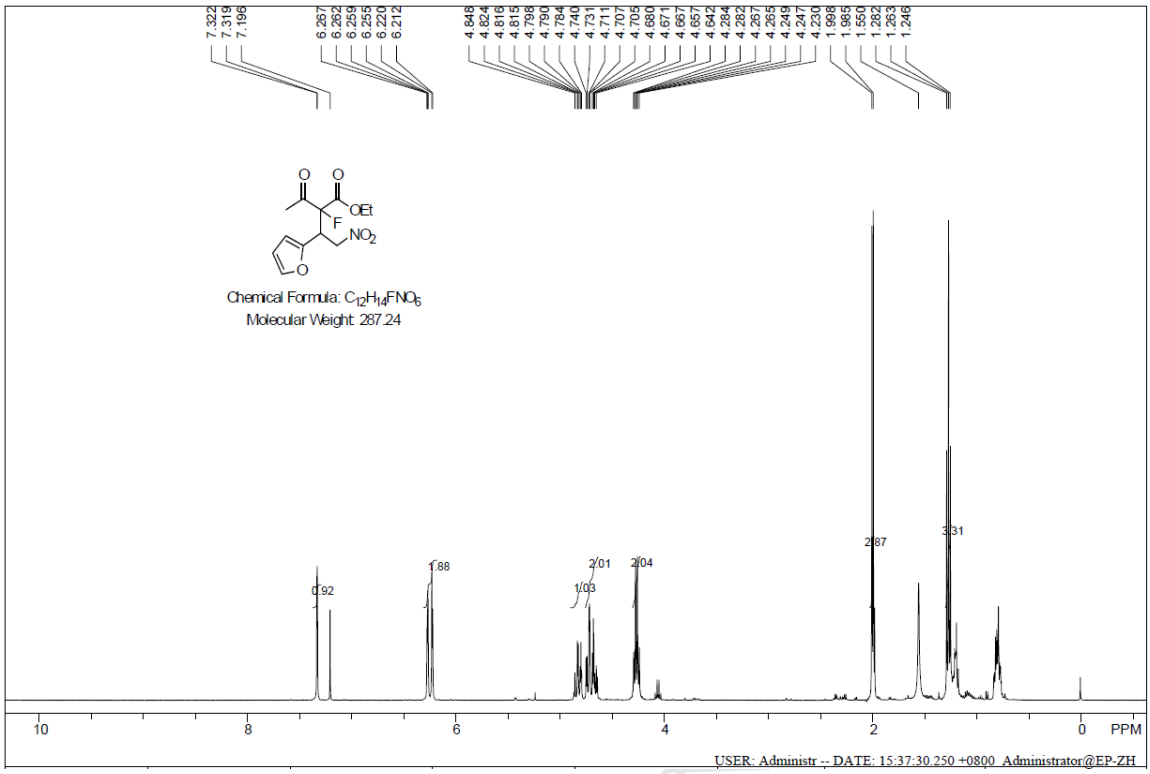
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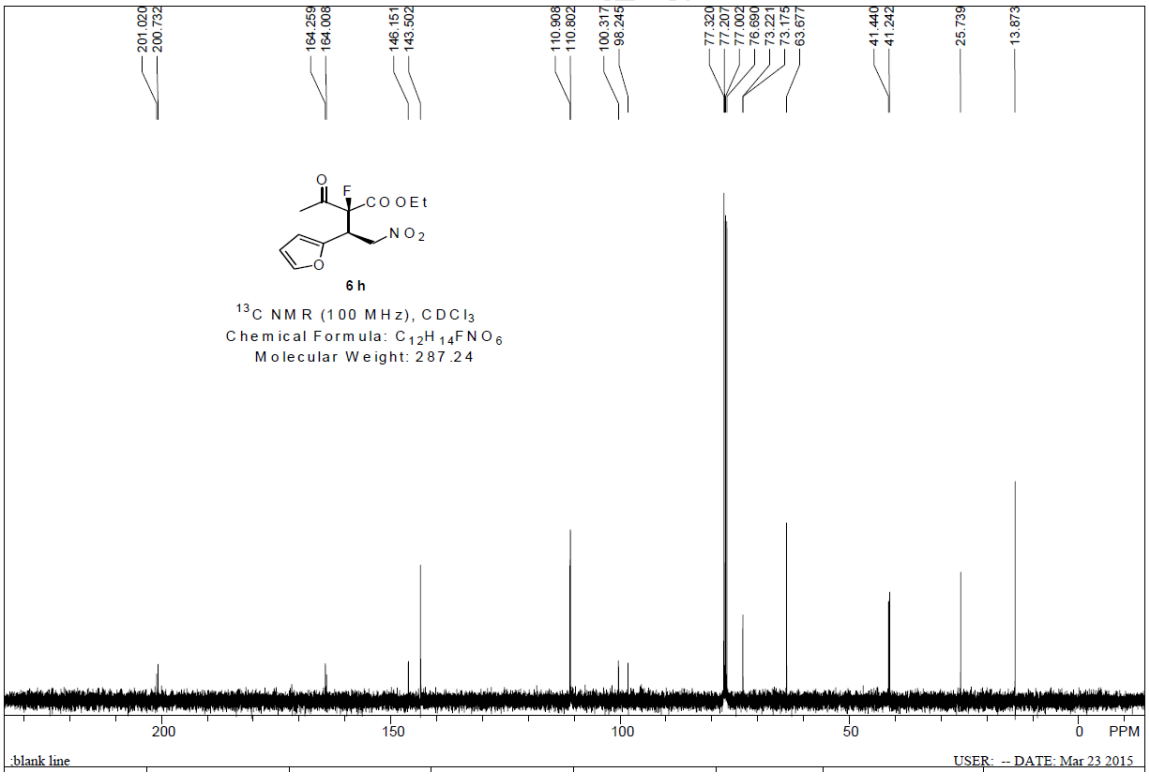
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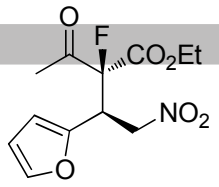

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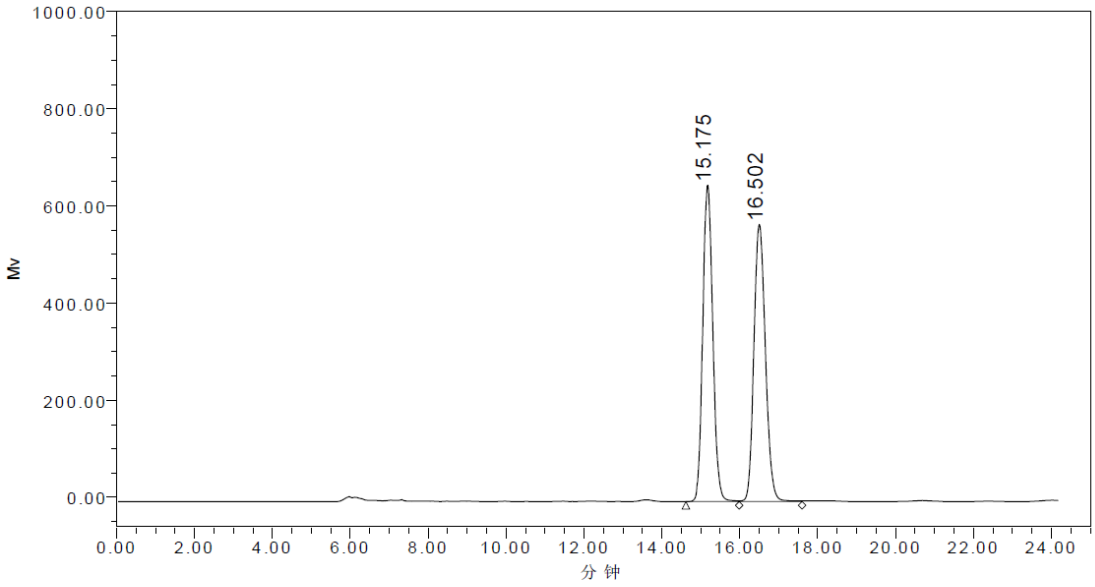

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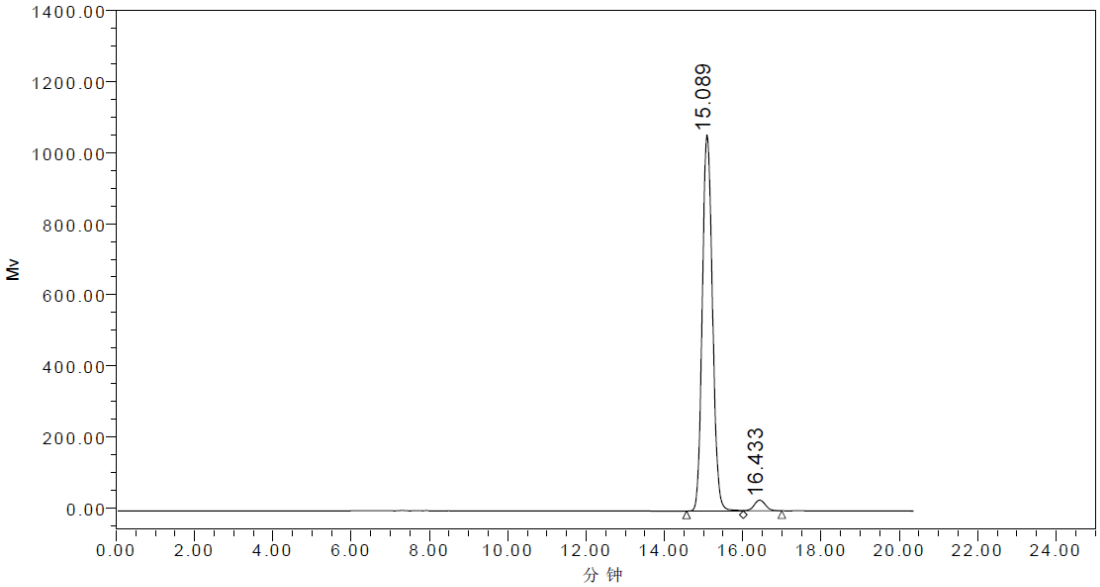

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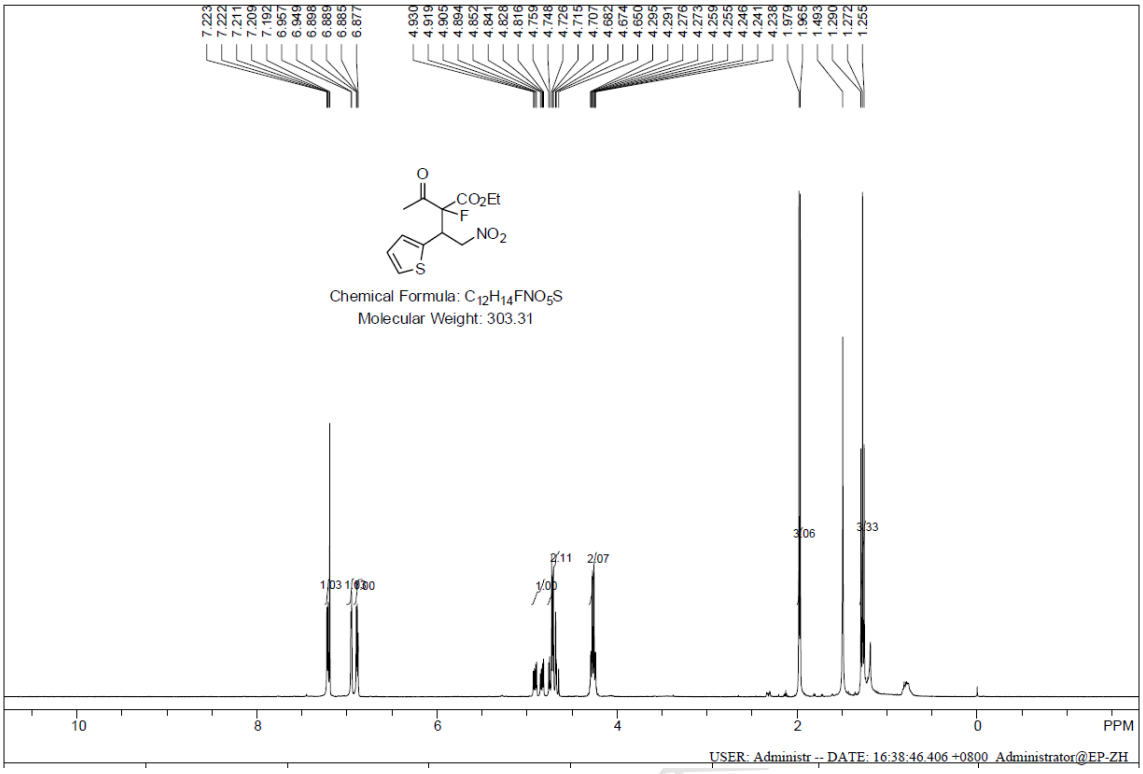
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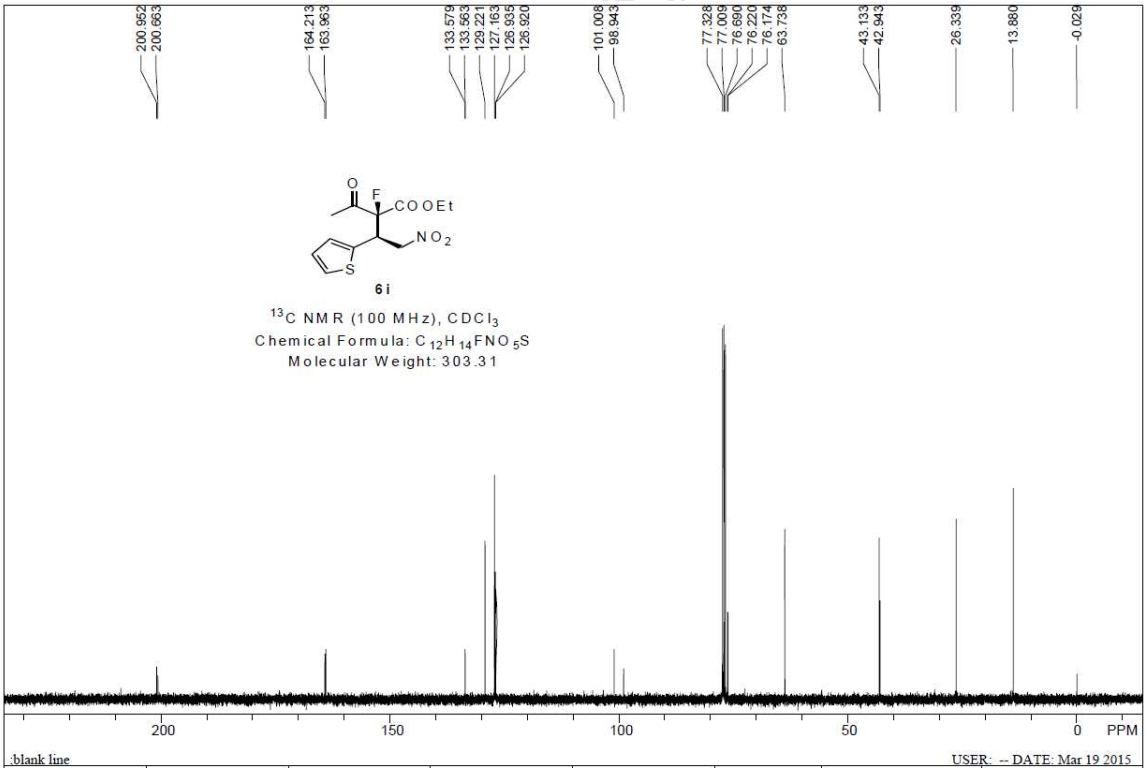
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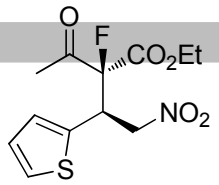

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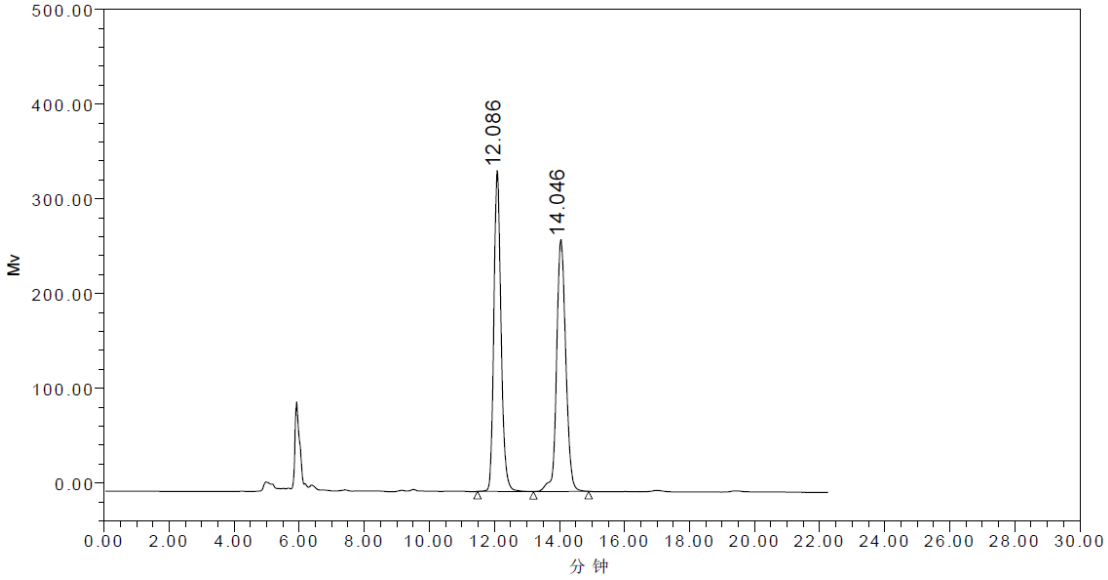

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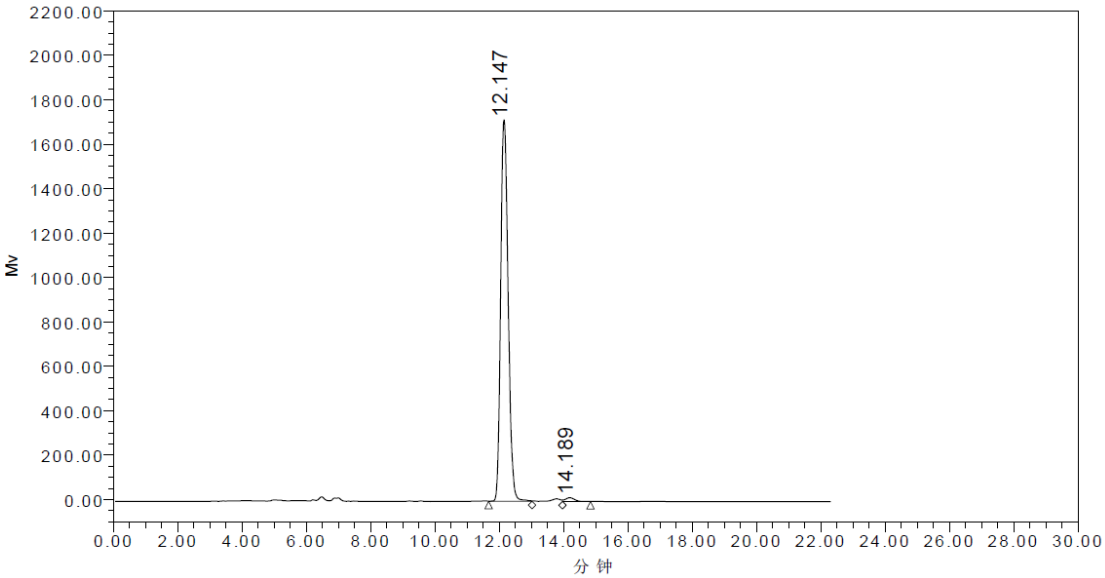

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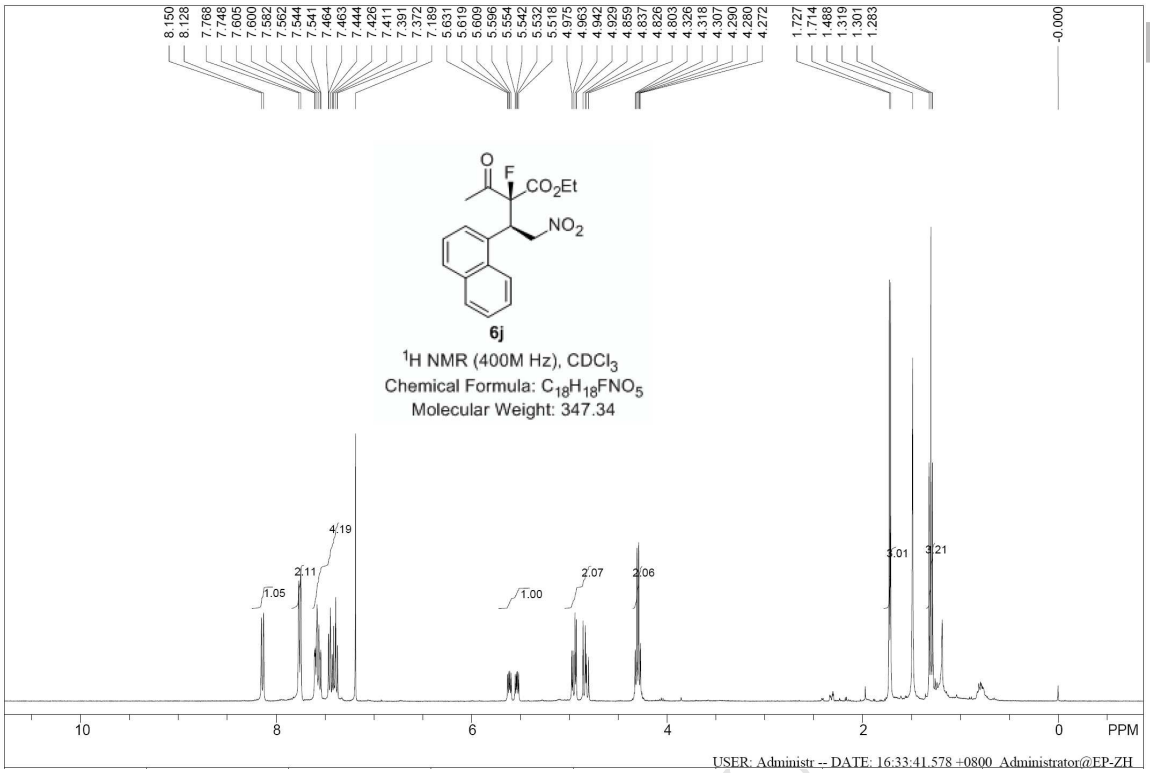
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Molecular Weight: 347.34
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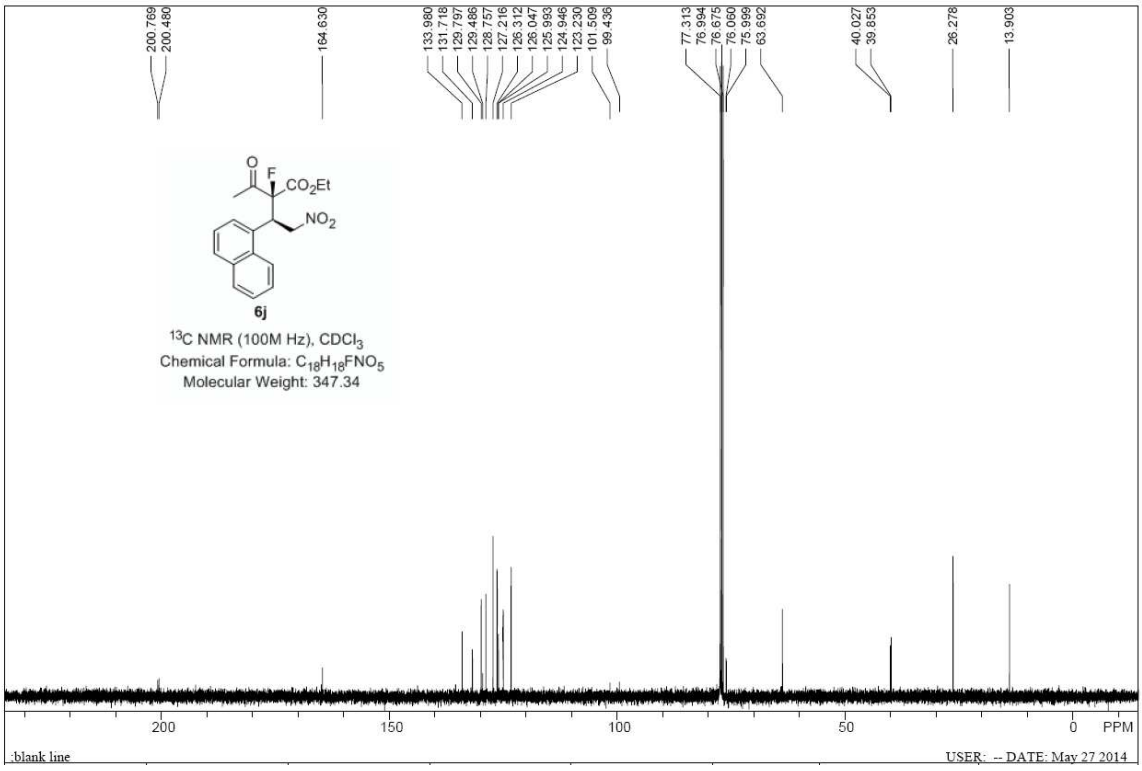
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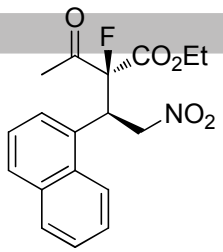

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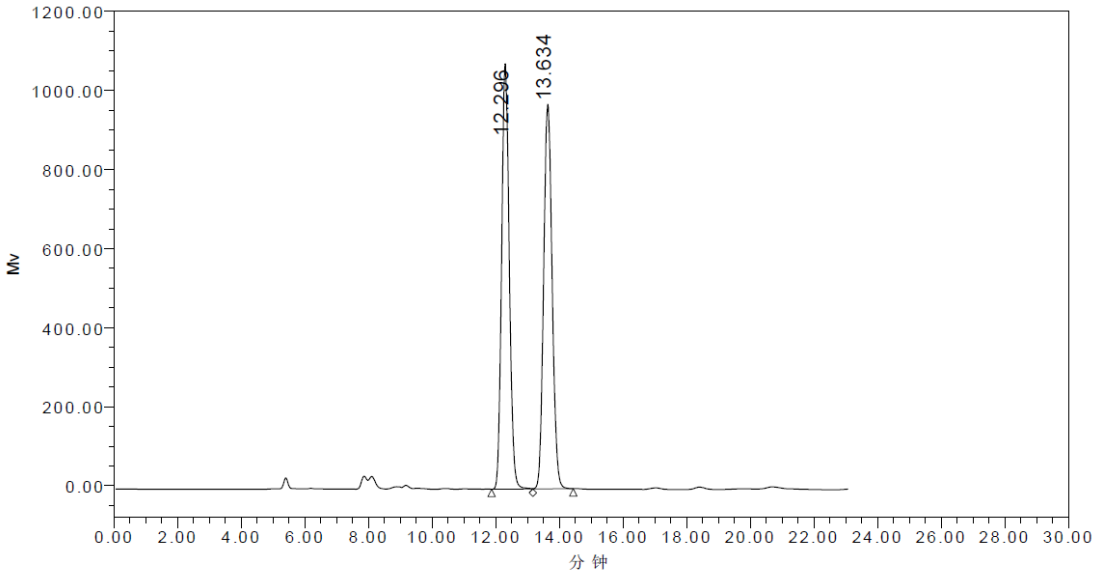

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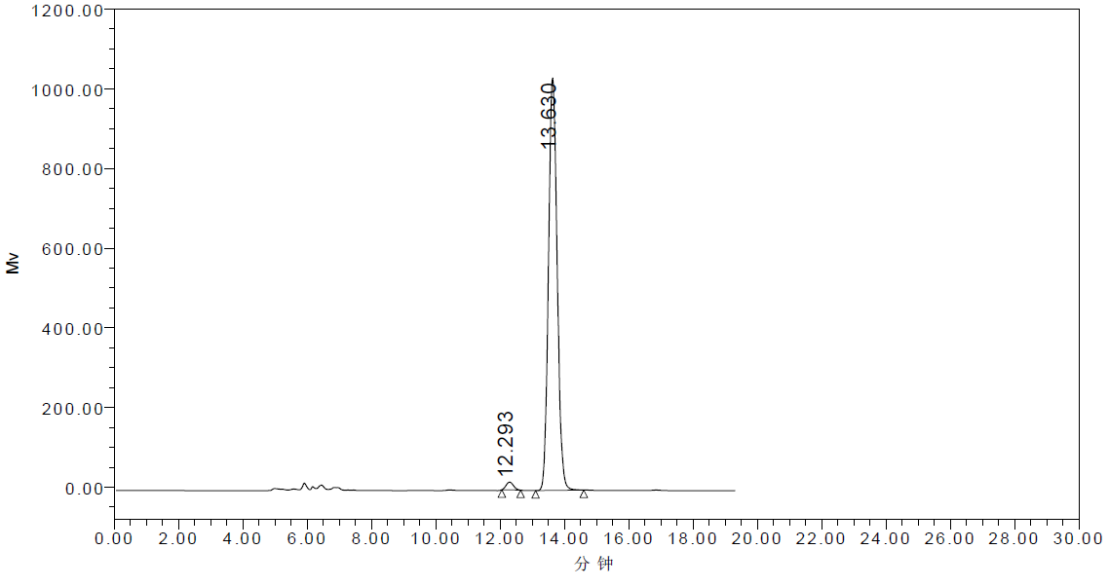

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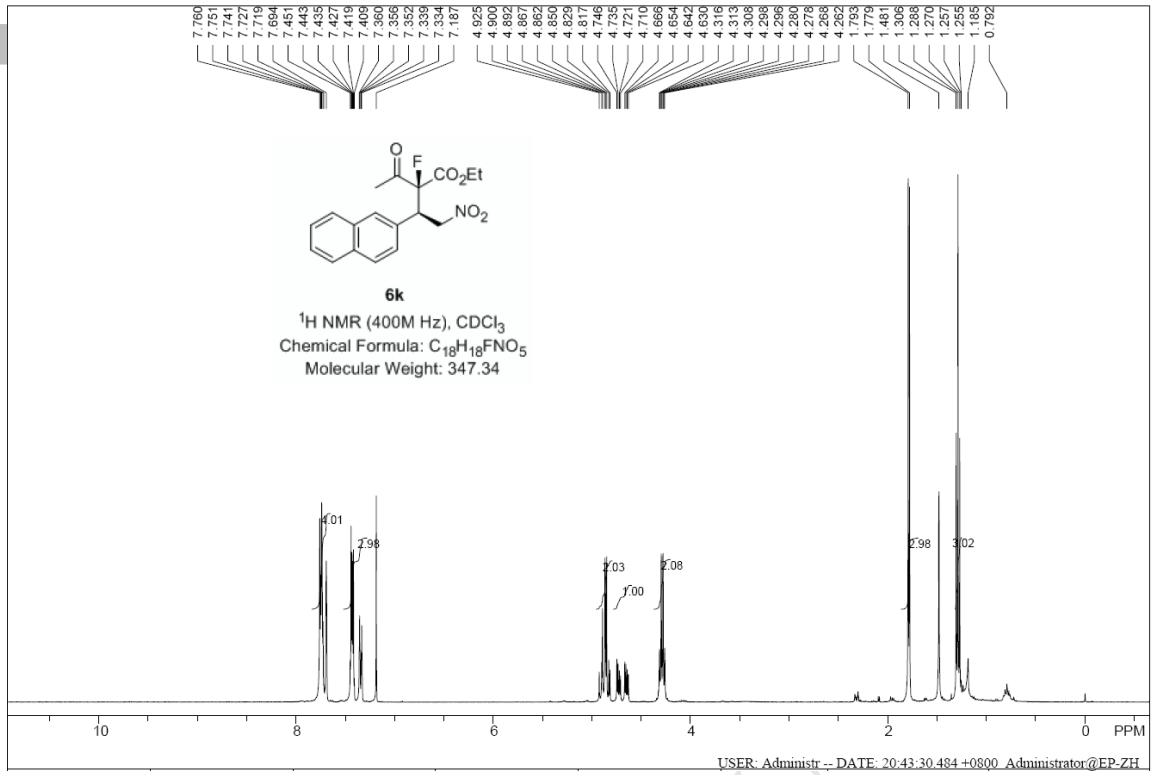
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Chemical Formula: C18H18FNO5
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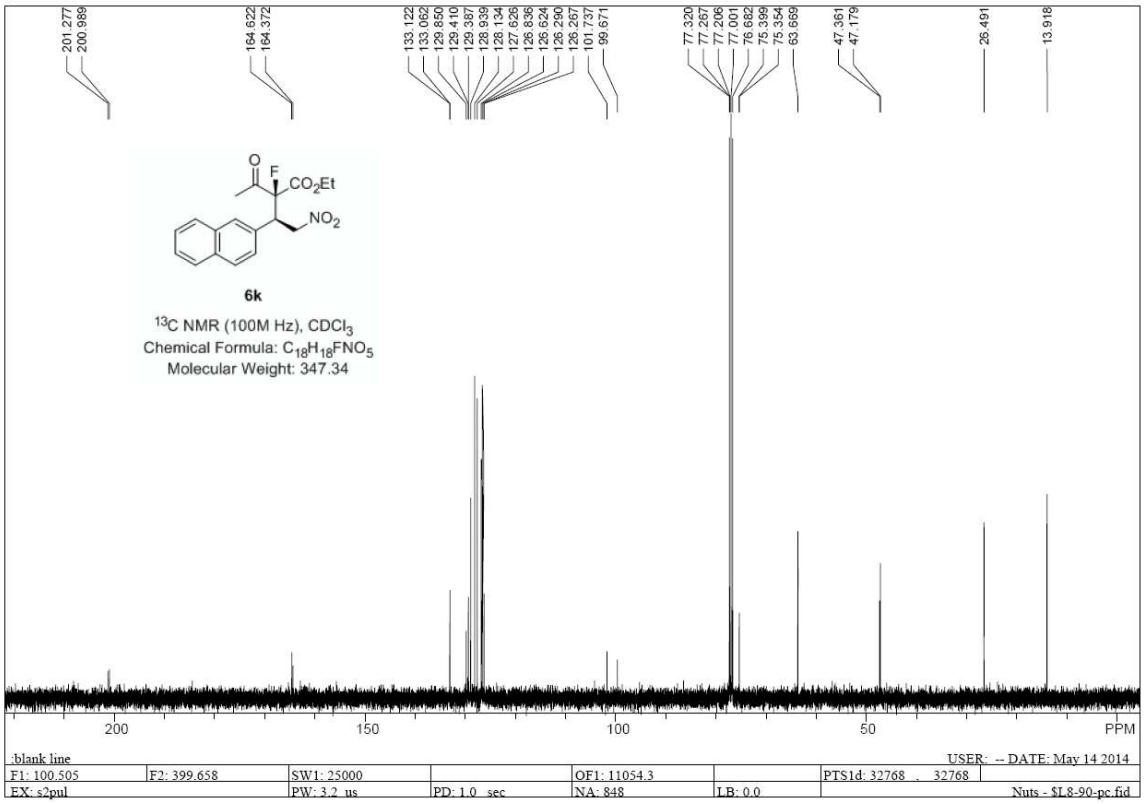
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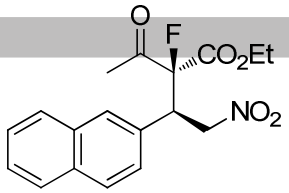

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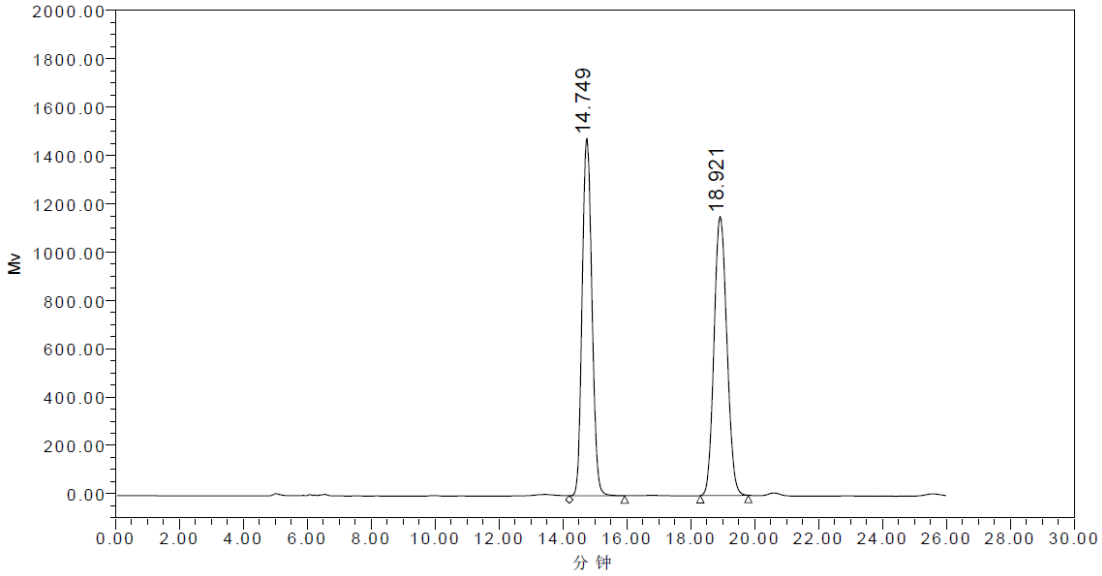

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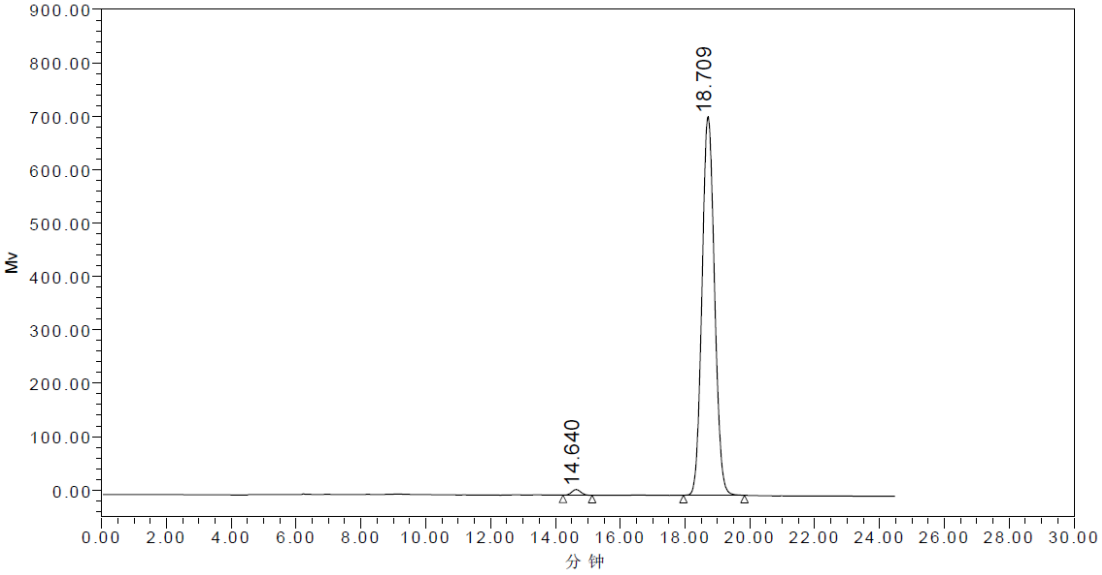

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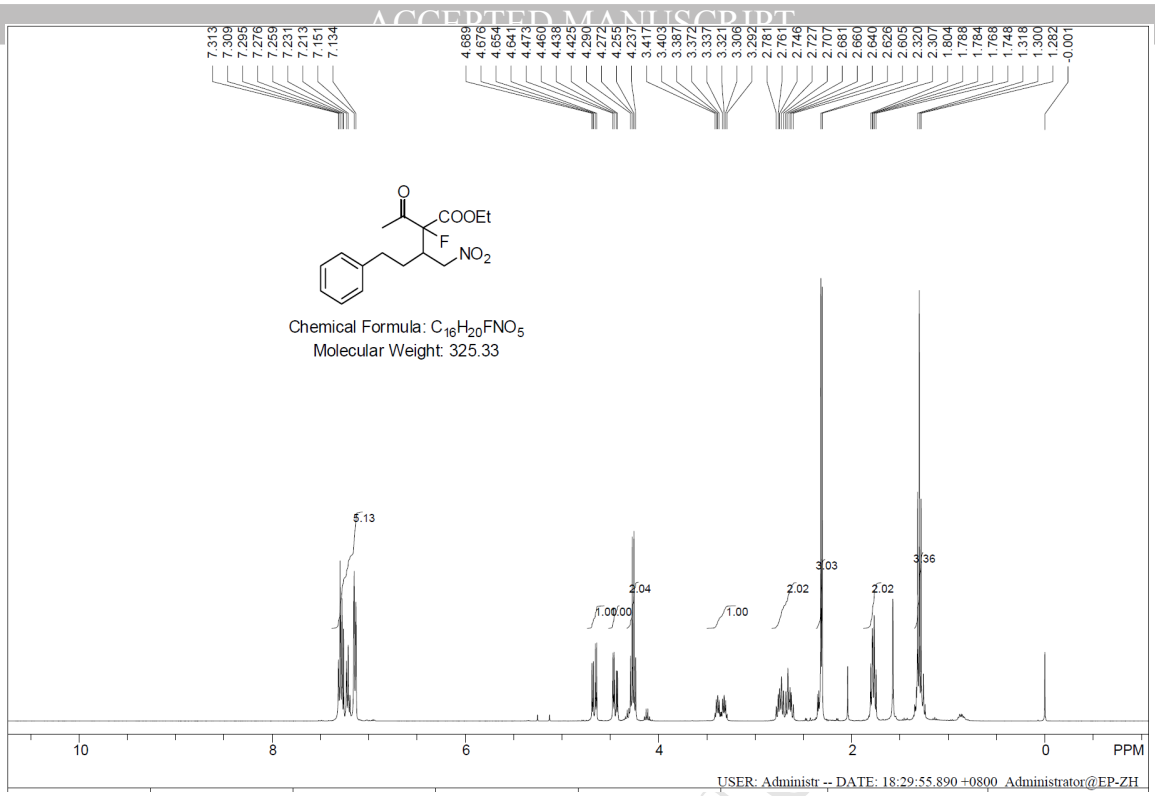

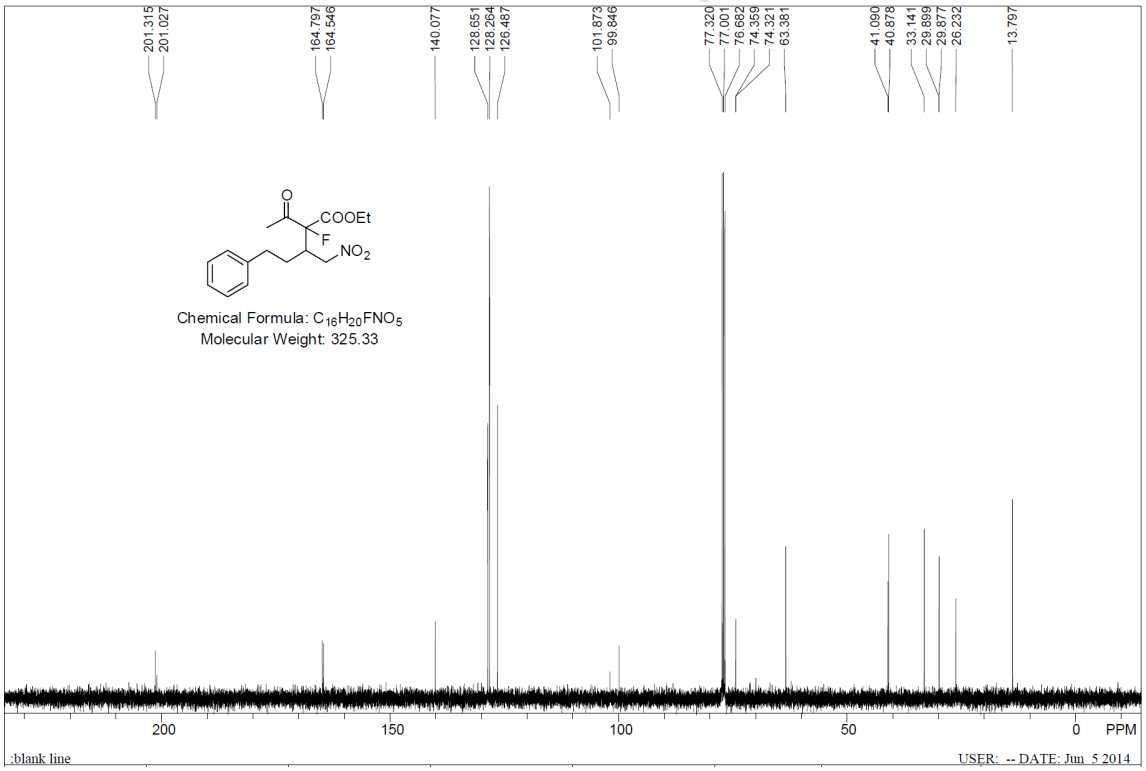

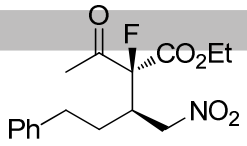

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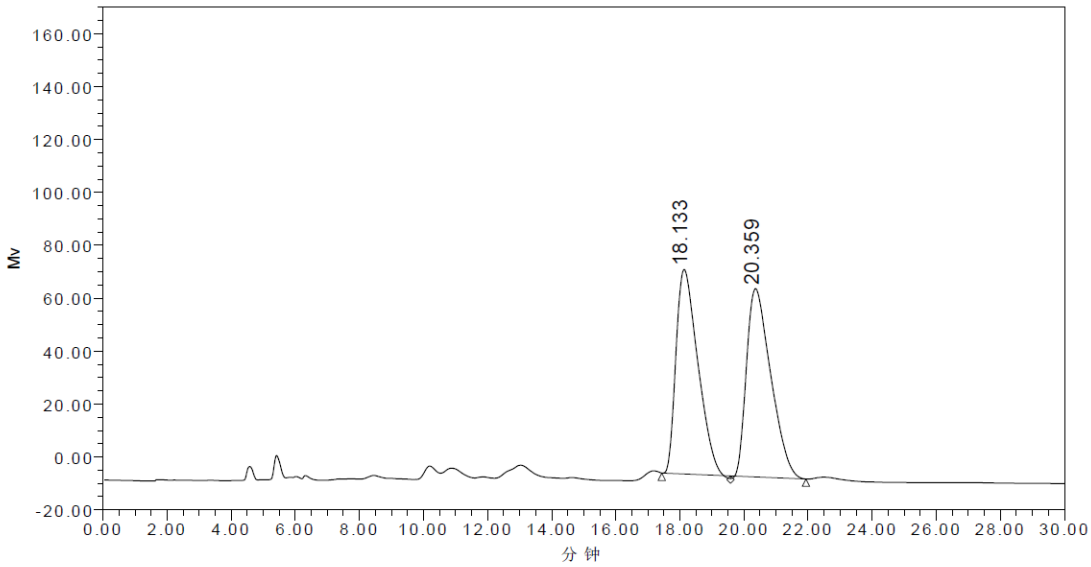

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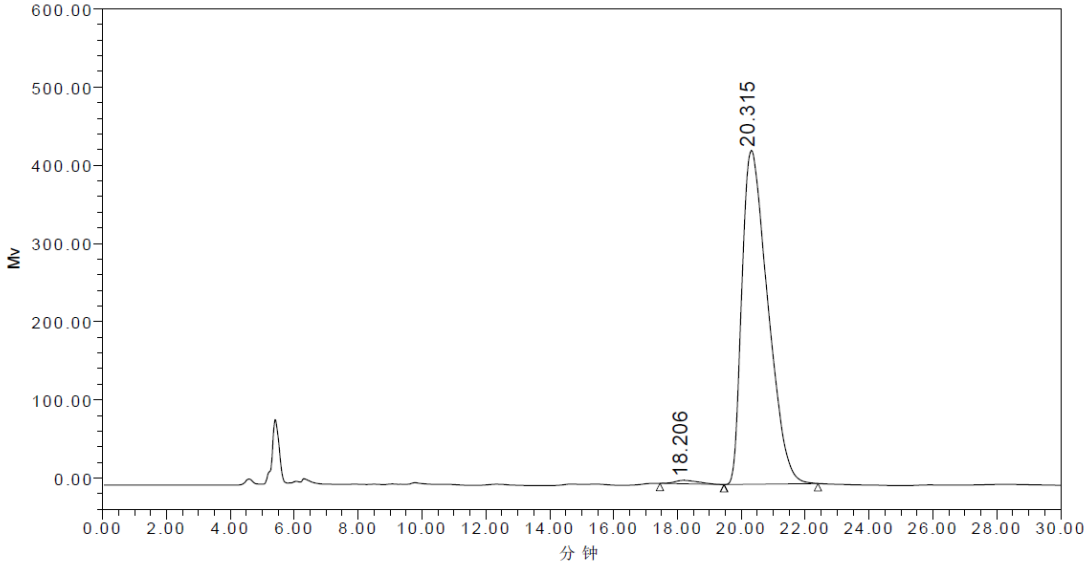

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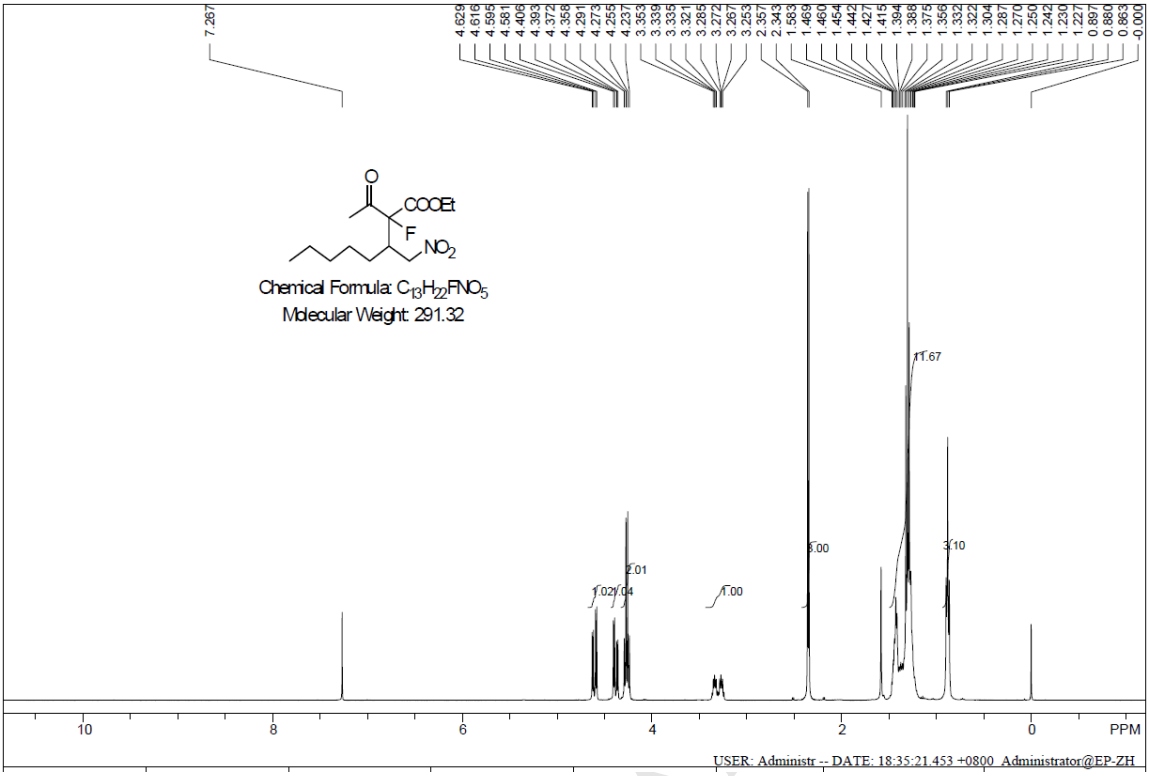
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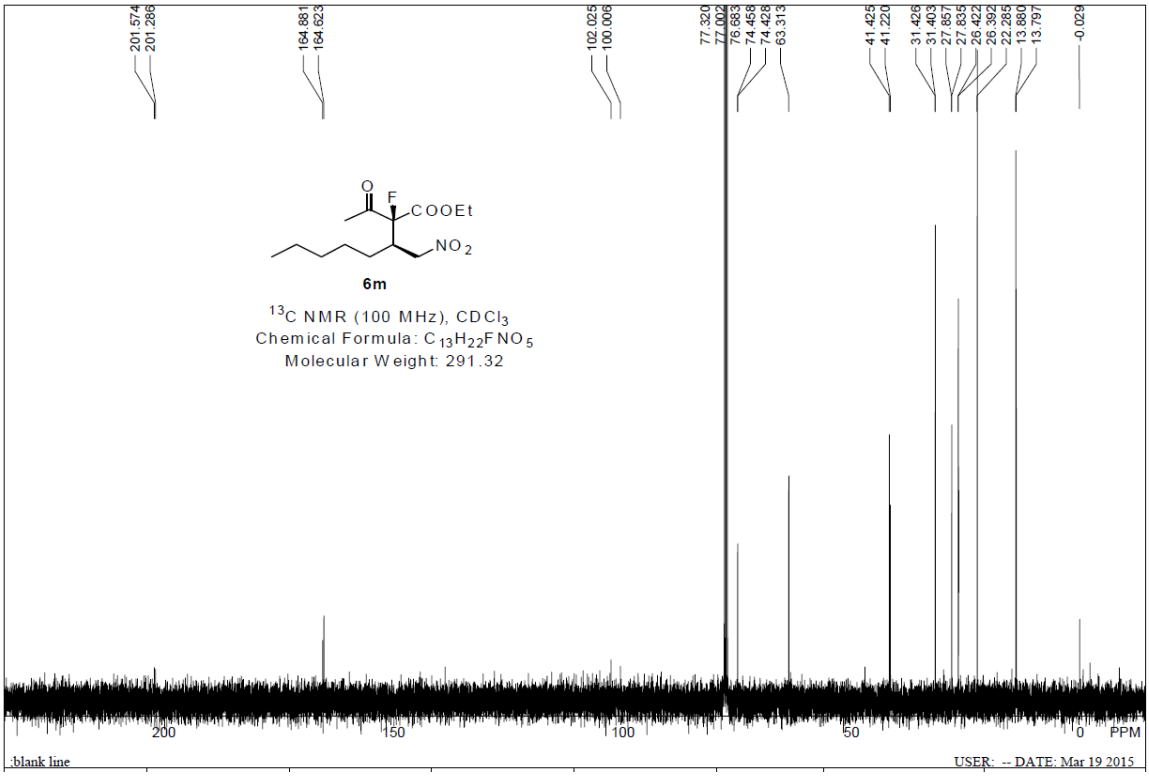
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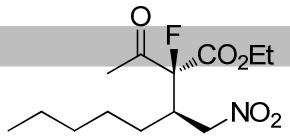

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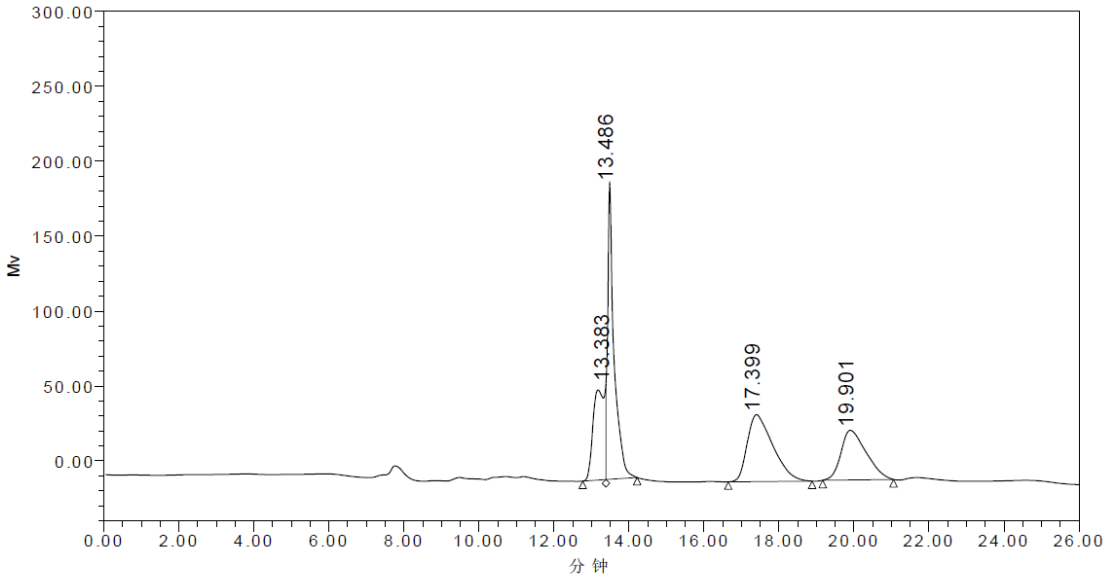

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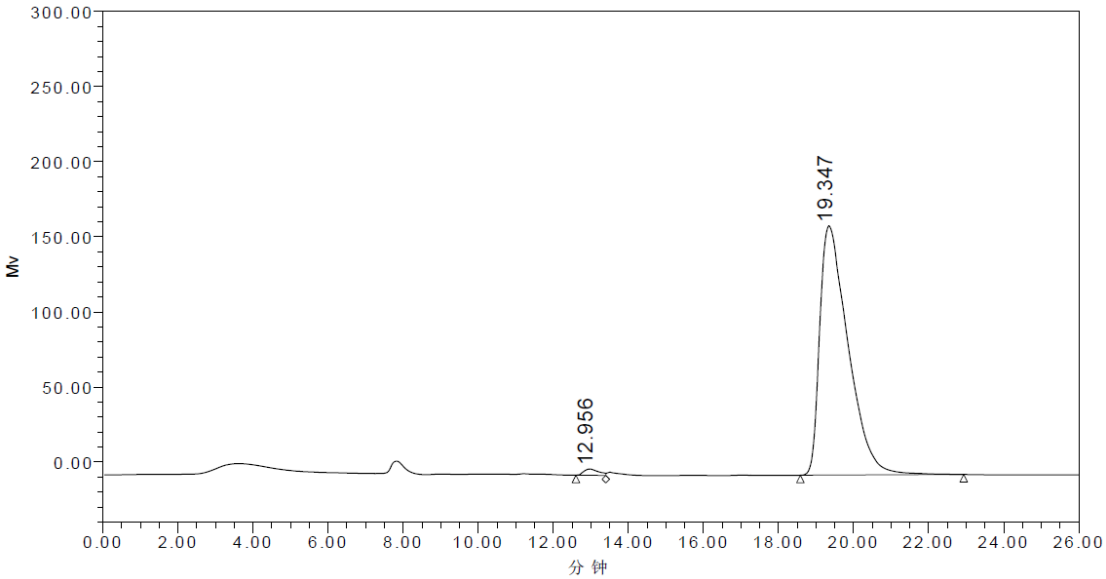

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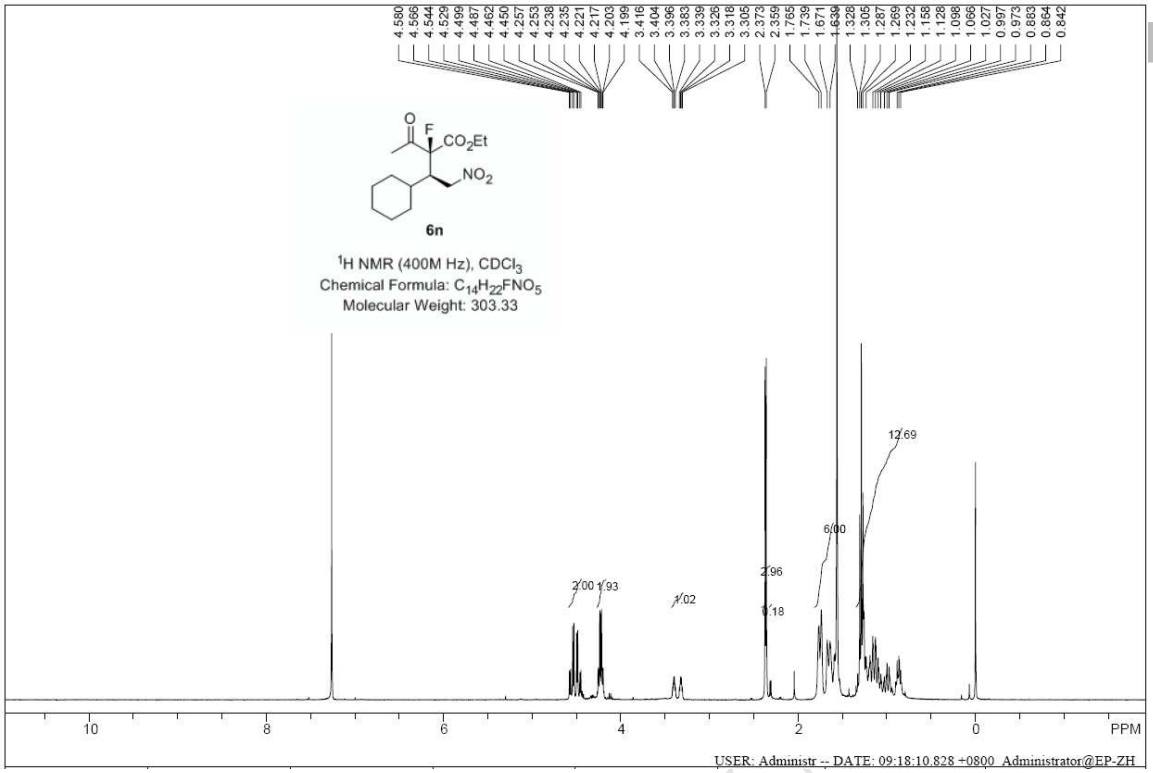
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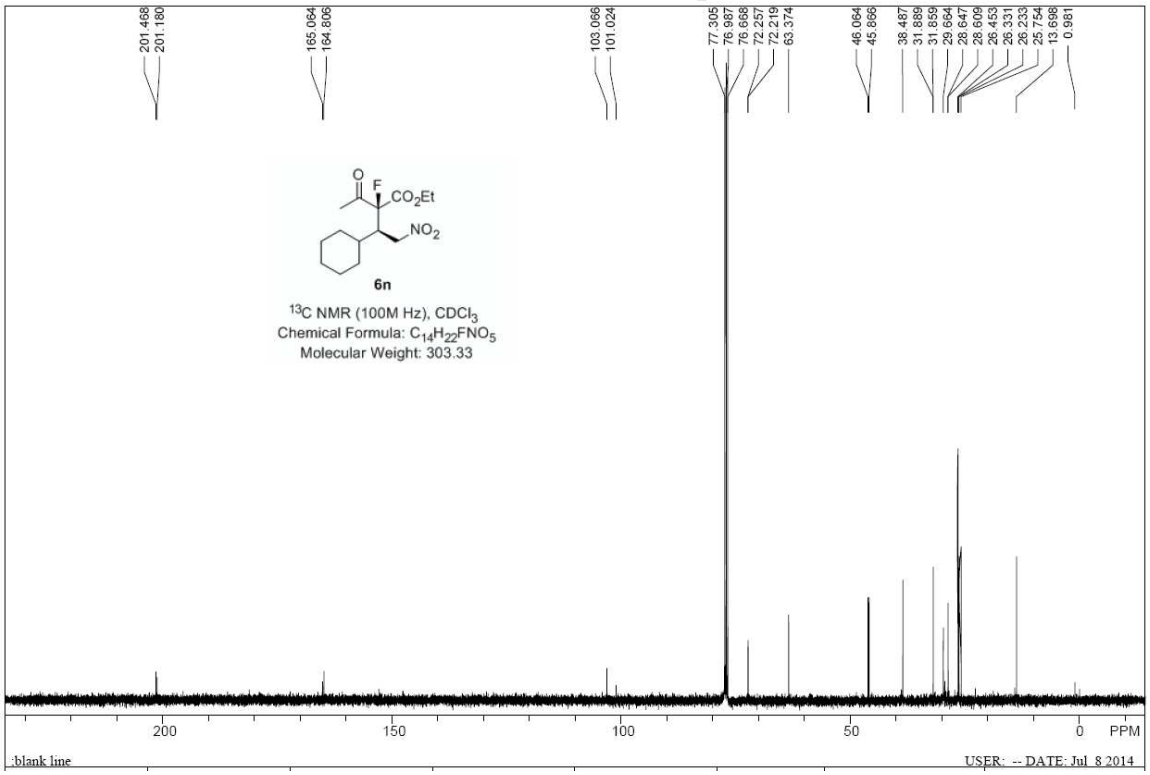
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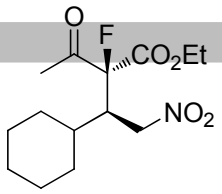

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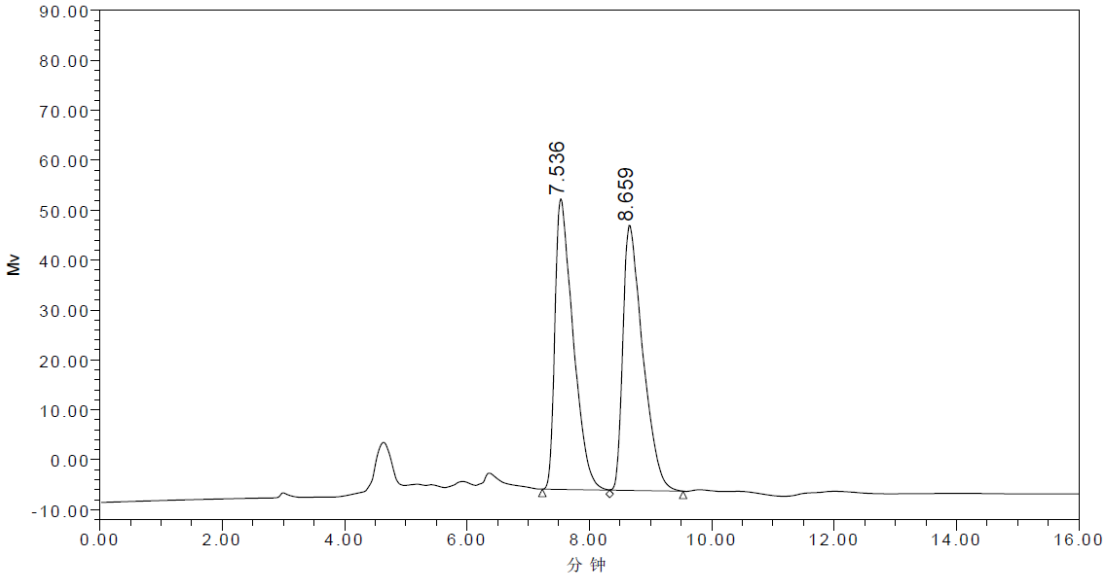

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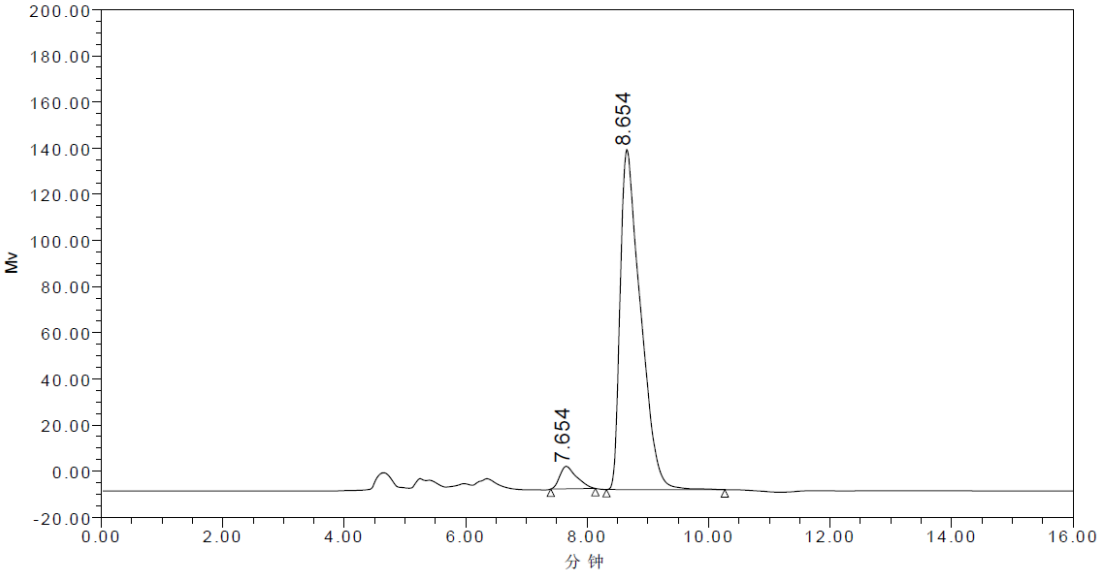

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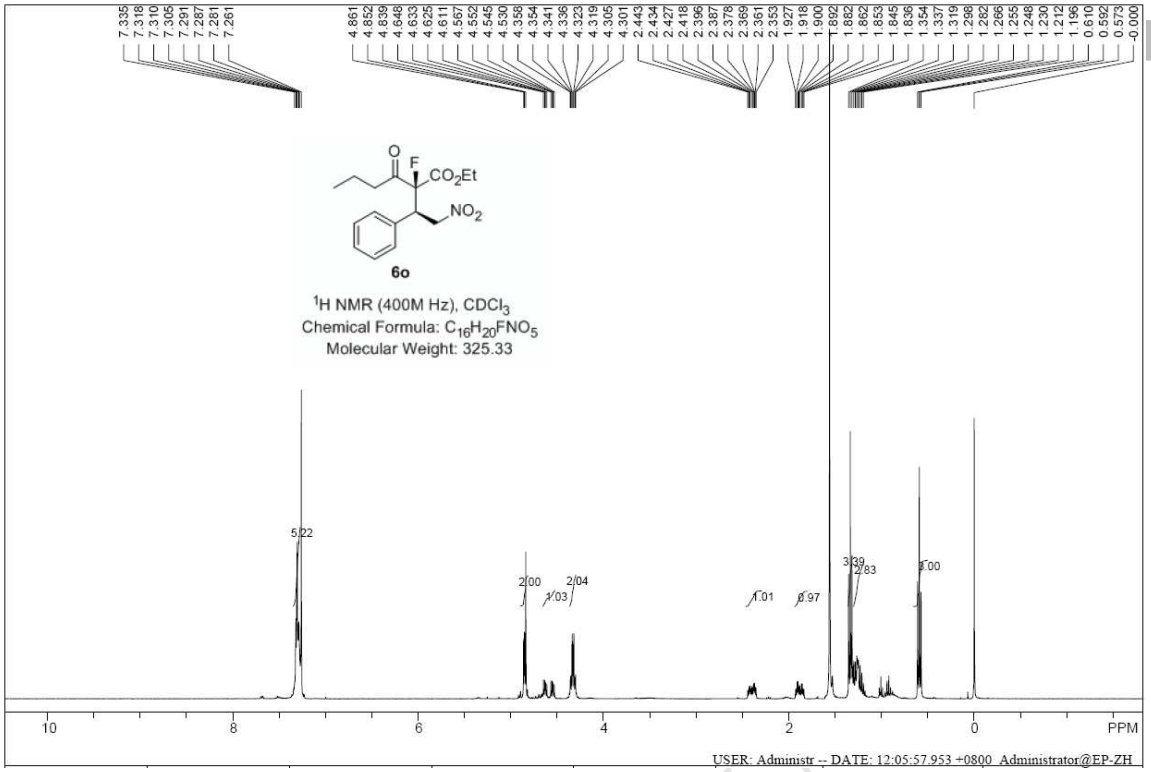
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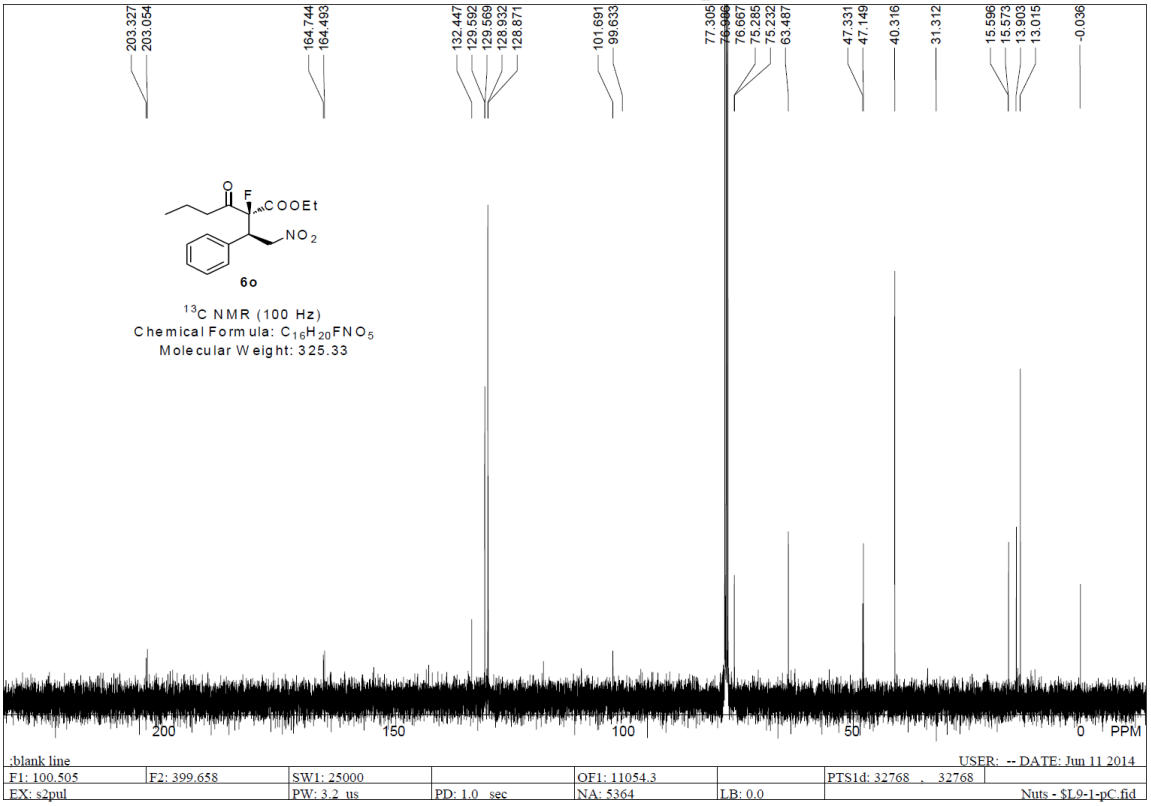
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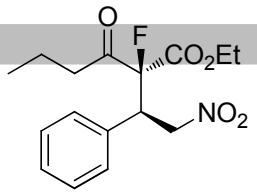

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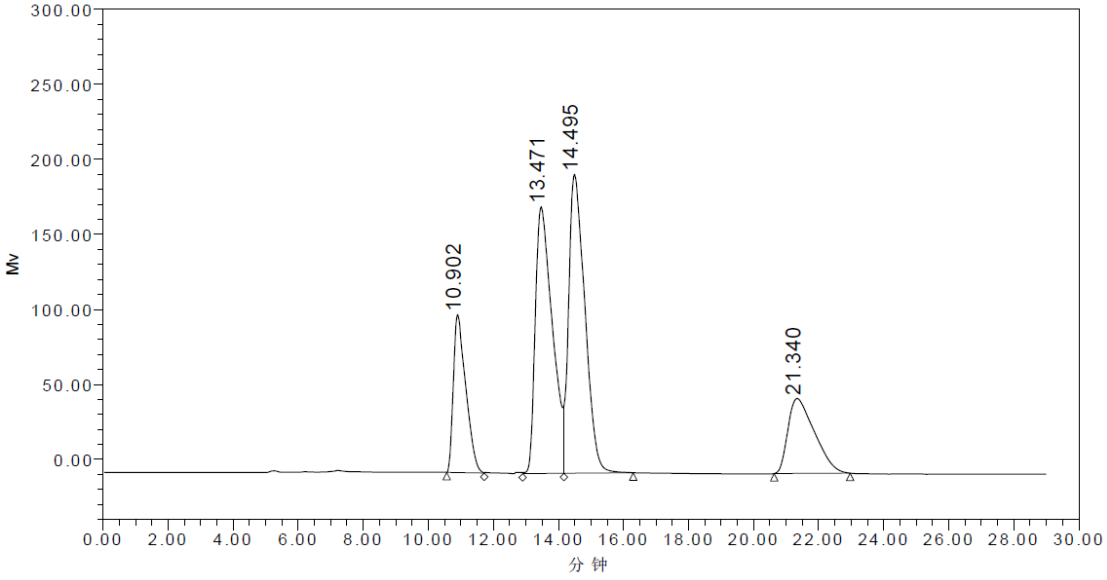

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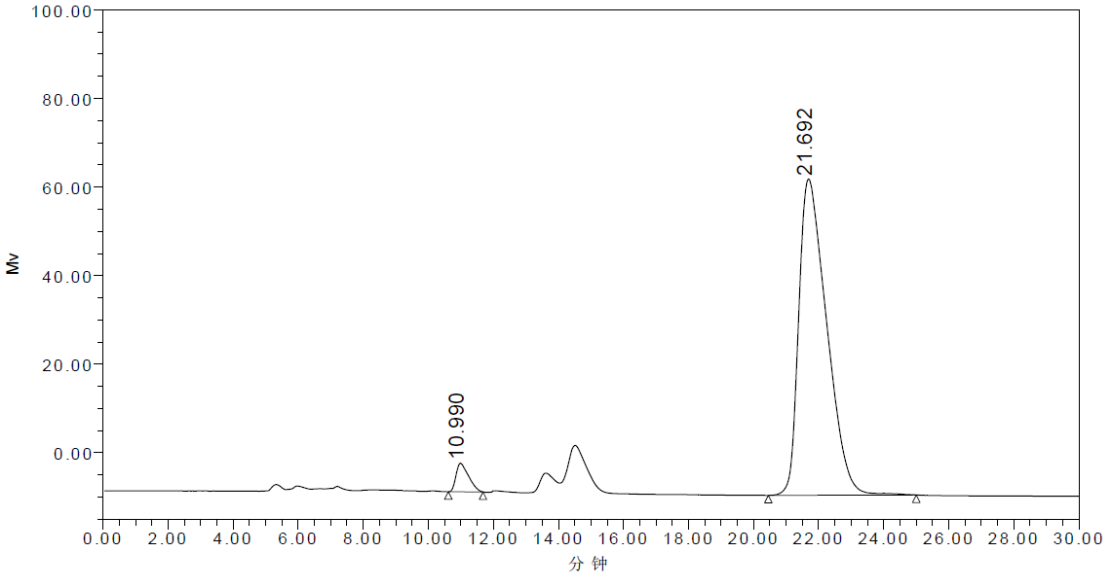

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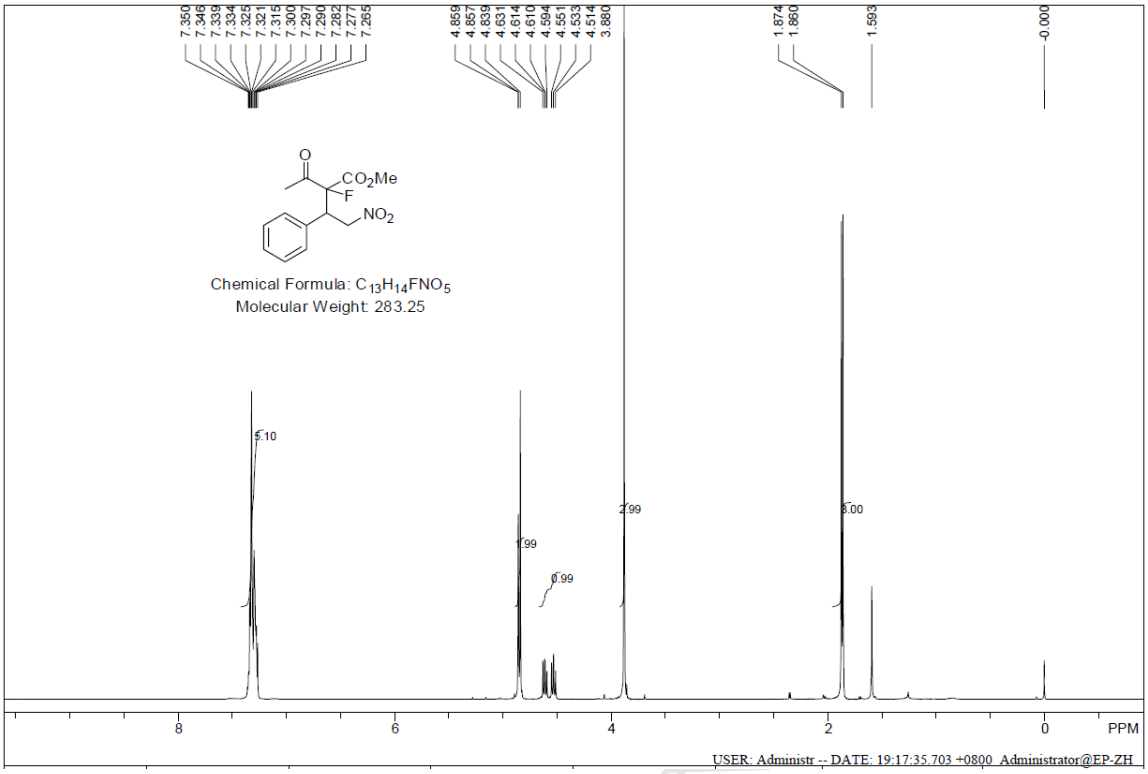
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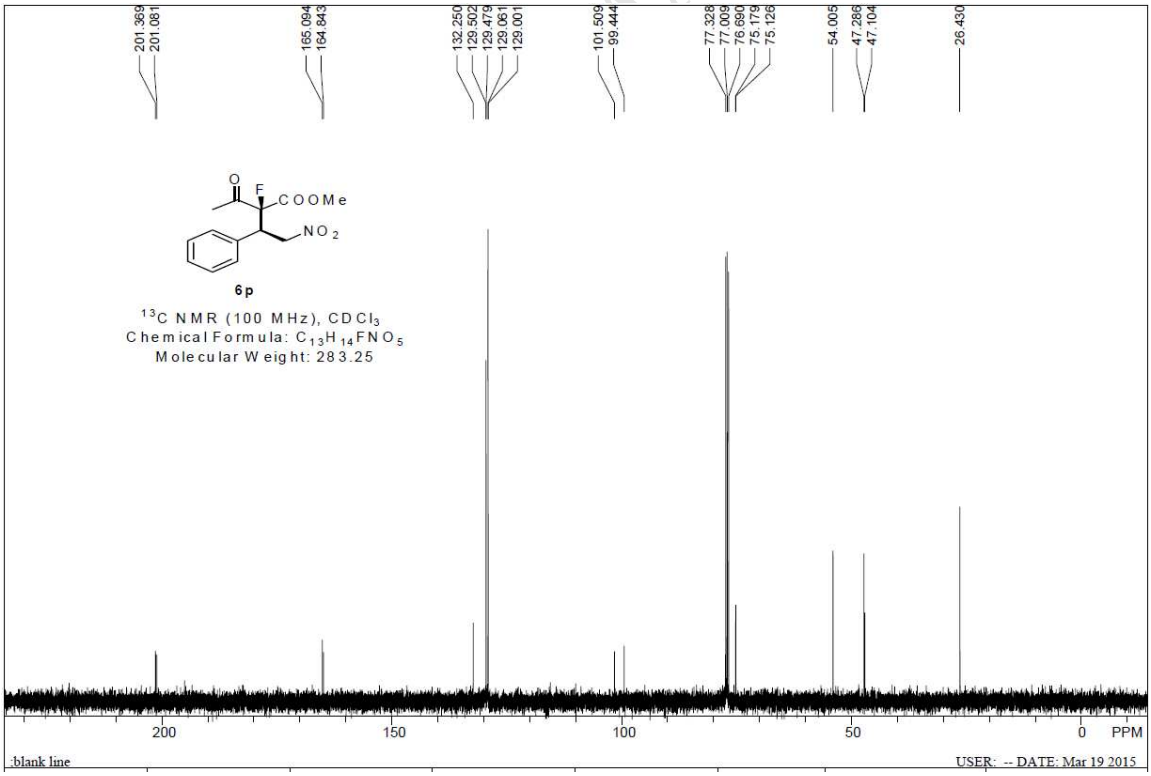
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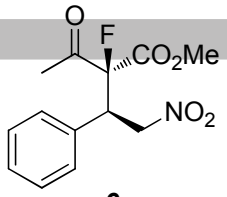

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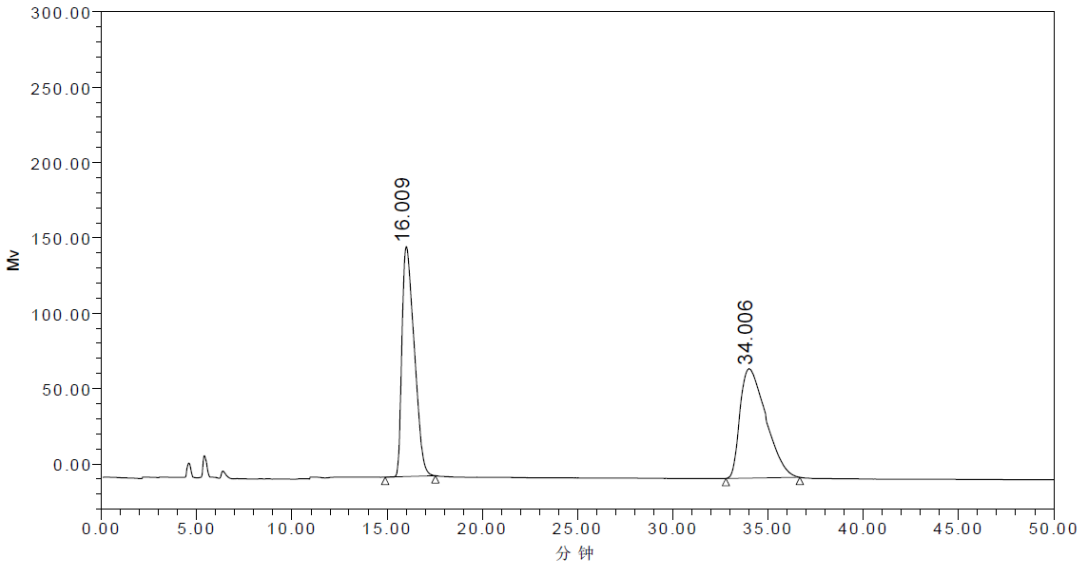

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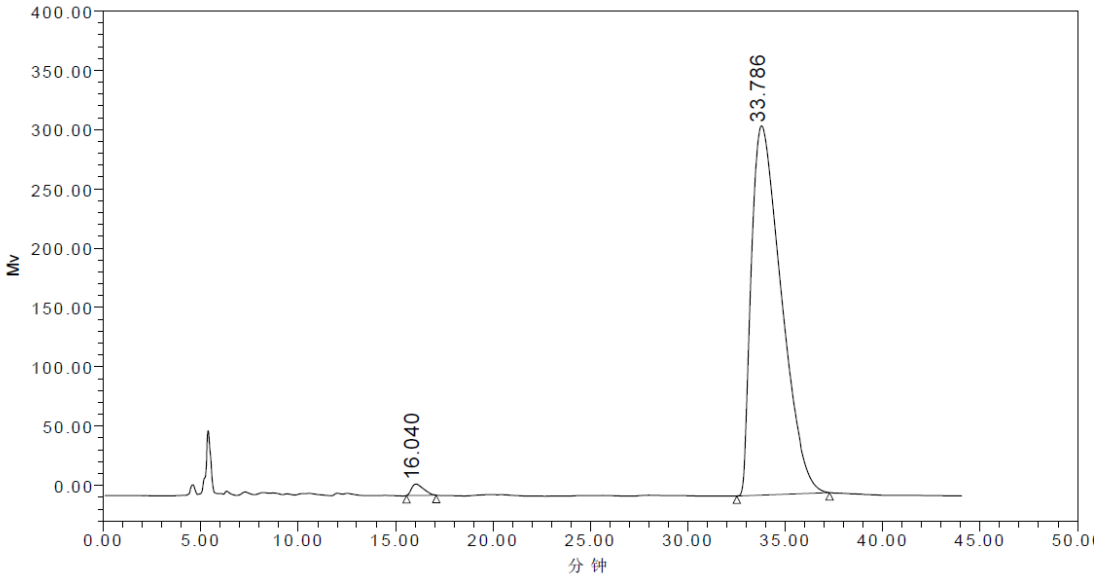

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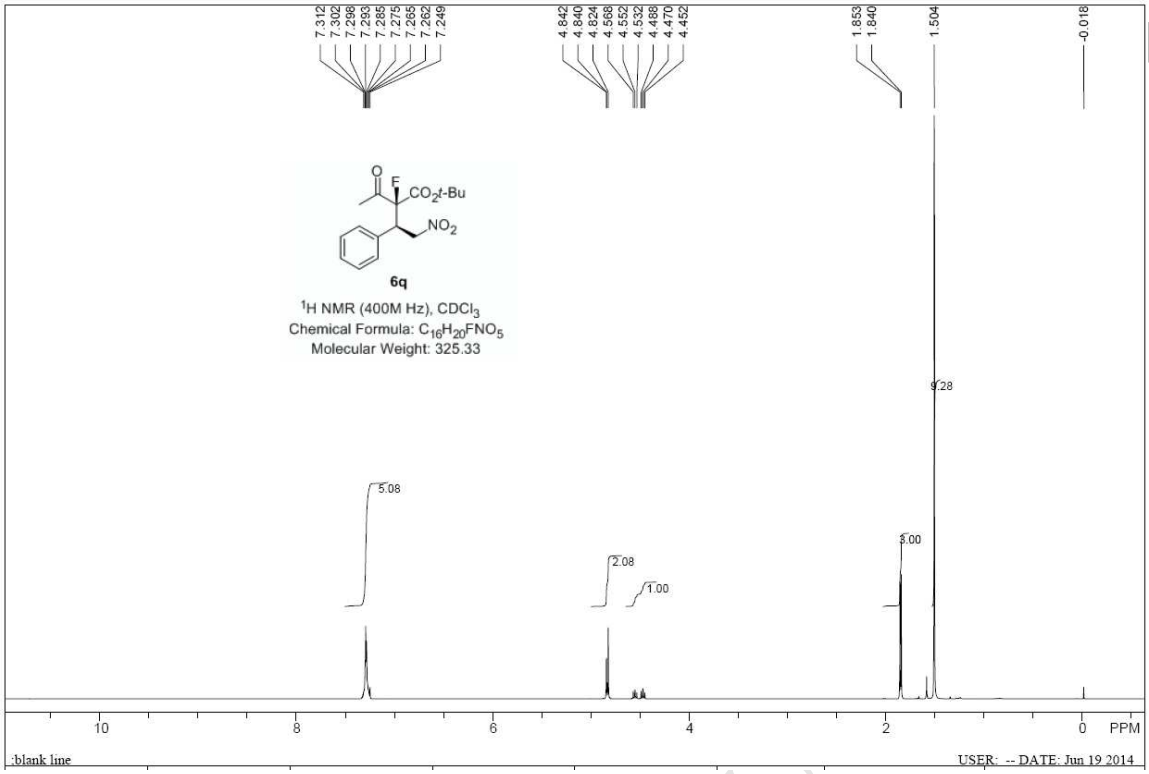
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4.552
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4.470
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CO2t-Bu
NO2
6q
1H NMR (400M Hz), CDCl3
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Molecular Weight: 325.33
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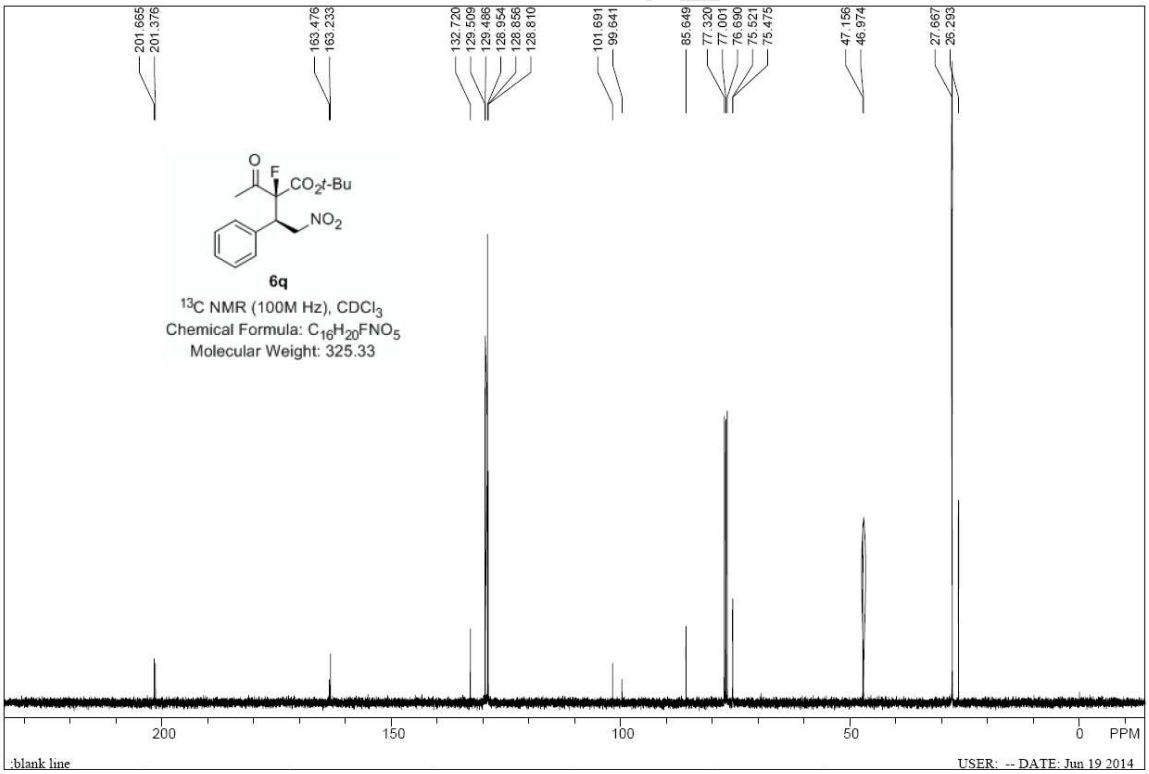
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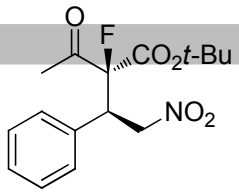

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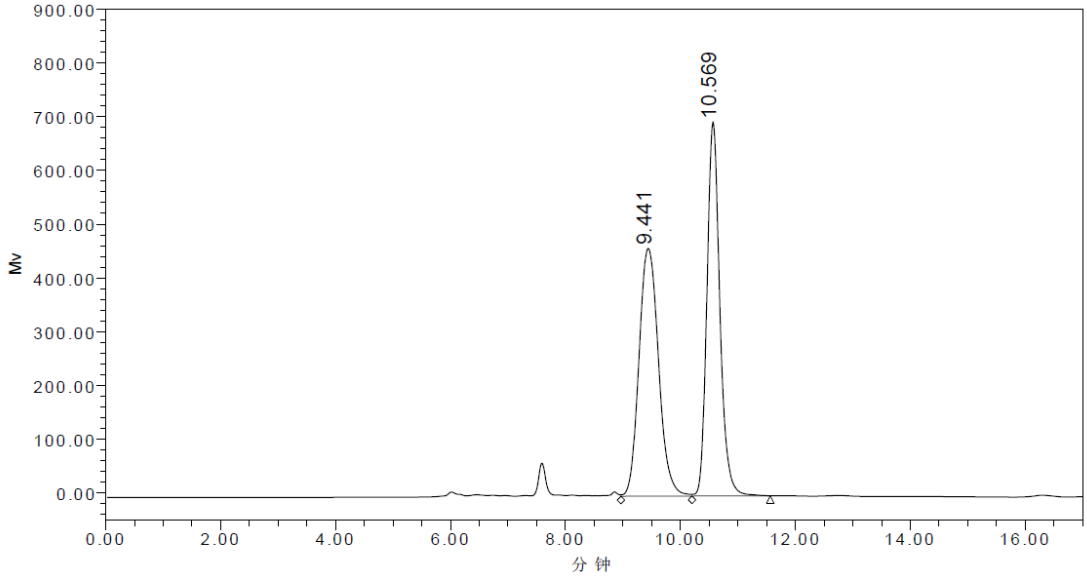

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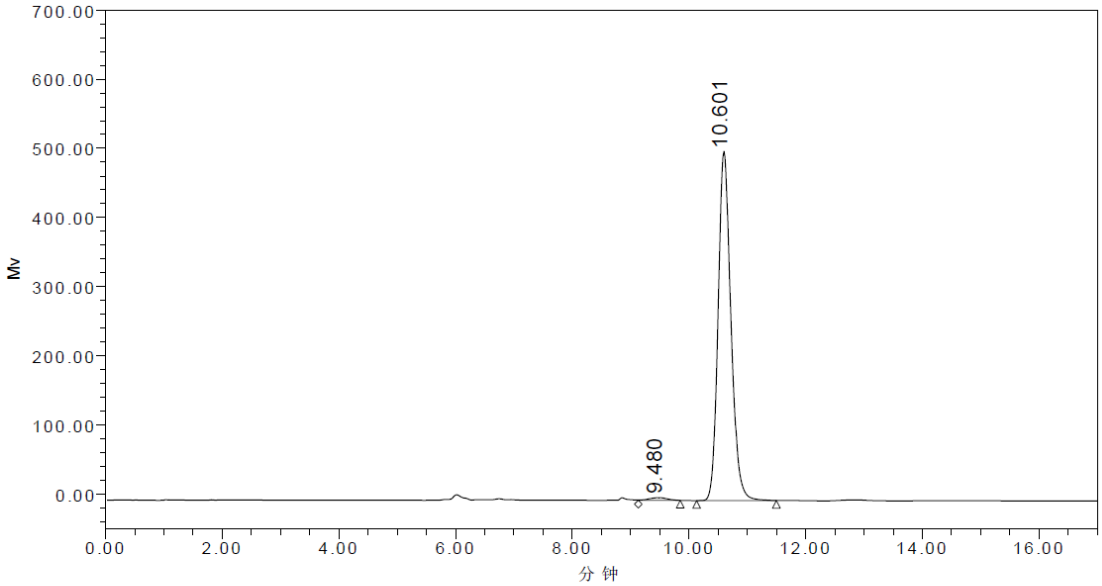

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1	9.480	84896	1.09	3917
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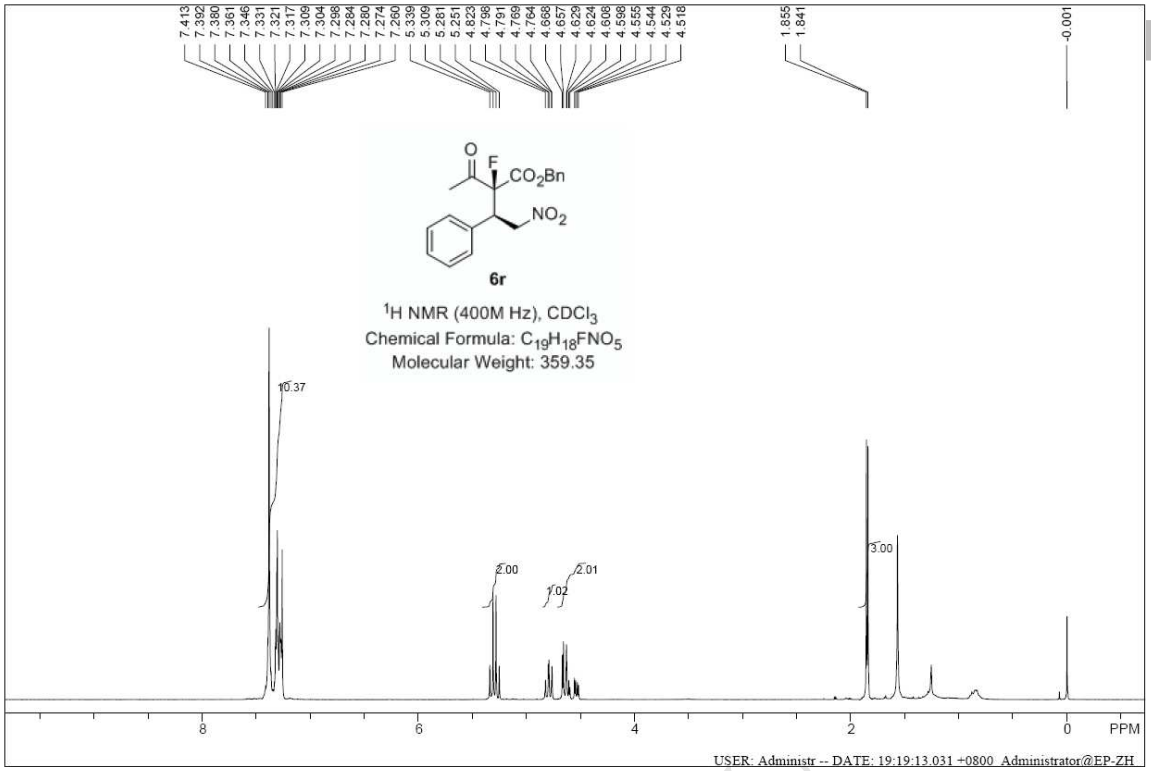
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5.281
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Chemical Formula: C19H18FNO5
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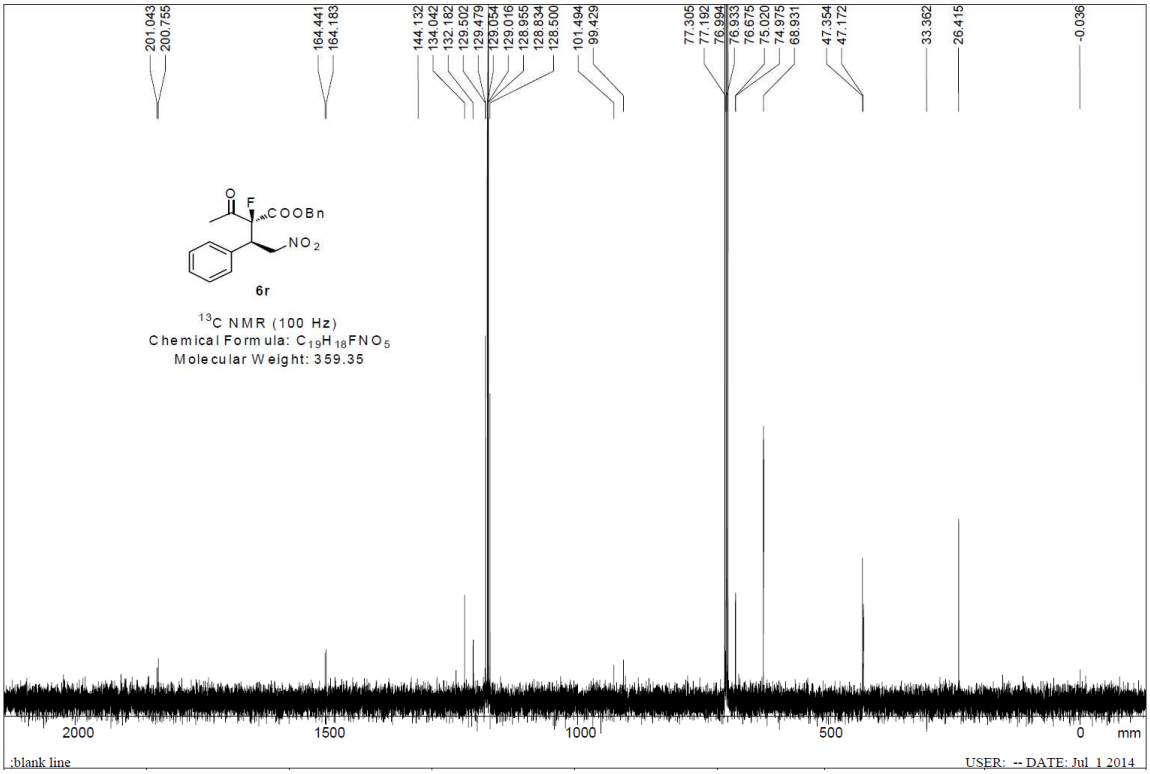
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77.305
77.192
76.994
76.933
76.675
75.020
74.975
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Chemical Formula: C19H18FNO5
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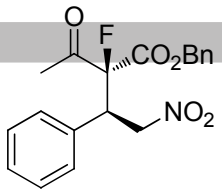

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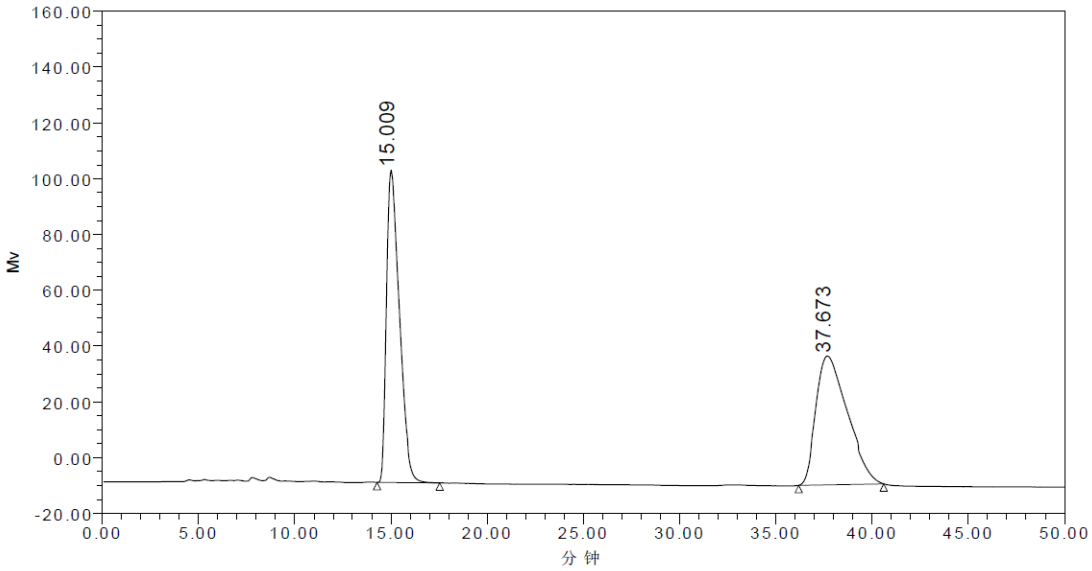

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1	15.009	5232539	49.87	111931
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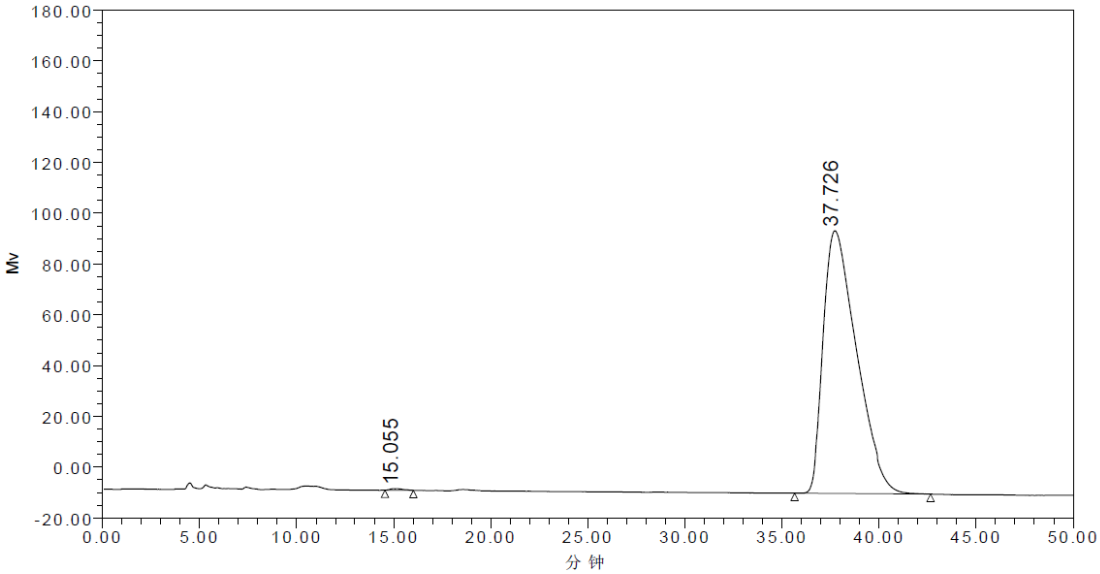

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1	15.055	28561	0.23	650
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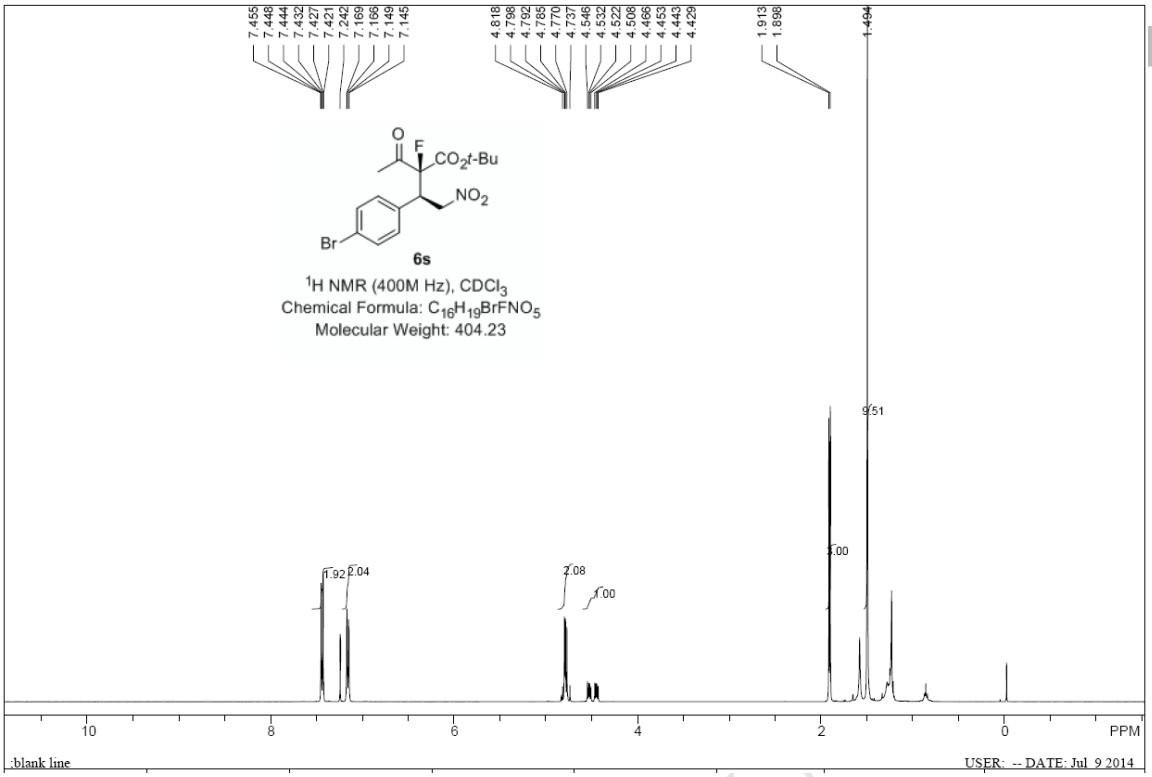
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4.532
4.522
4.508
4.466
4.453
4.443
4.429
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CO2t-Bu
NO2
Br
6s
1H NMR (400M Hz), CDCl3
Chemical Formula: C16H19BrFNO5
Molecular Weight: 404.23
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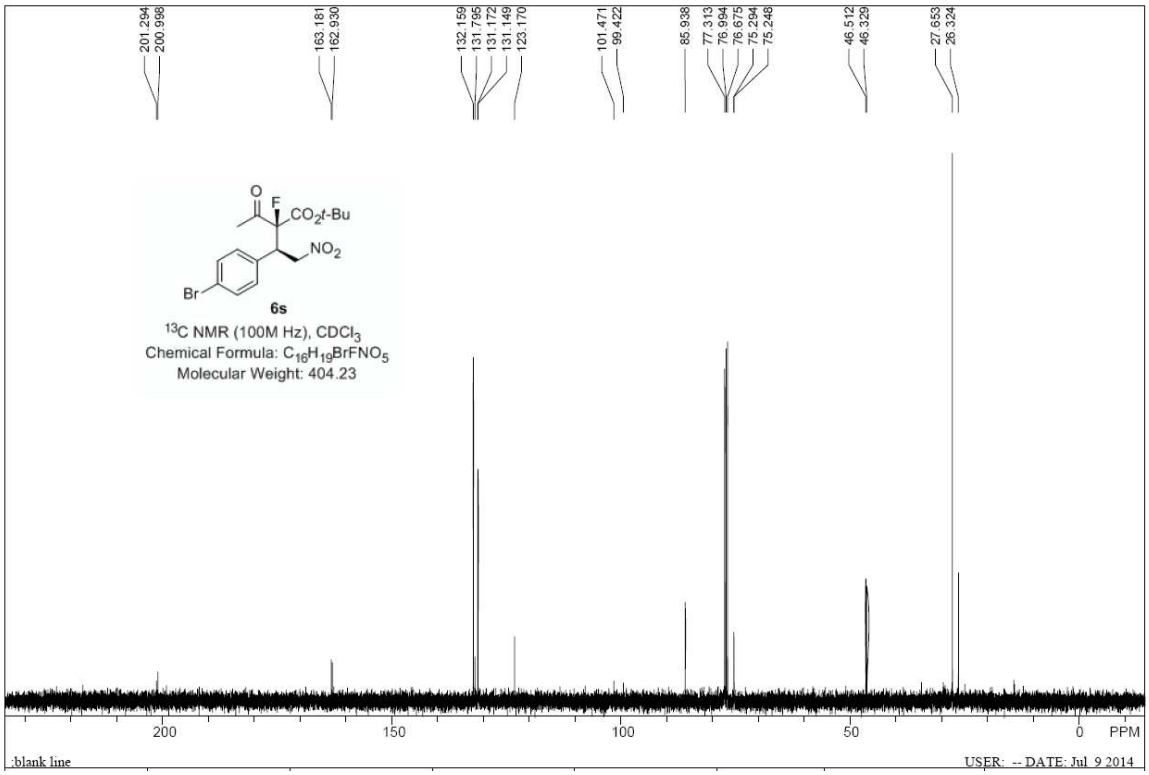
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76.994
76.675
75.294
75.248
46.512
46.329
27.653
26.324
O
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CO2t-Bu
NO2
Br
6s
13C NMR (100M Hz), CDCl3
Chemical Formula: C16H19BrFNO5
Molecular Weight: 404.23
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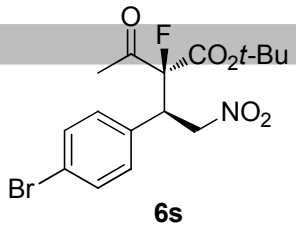

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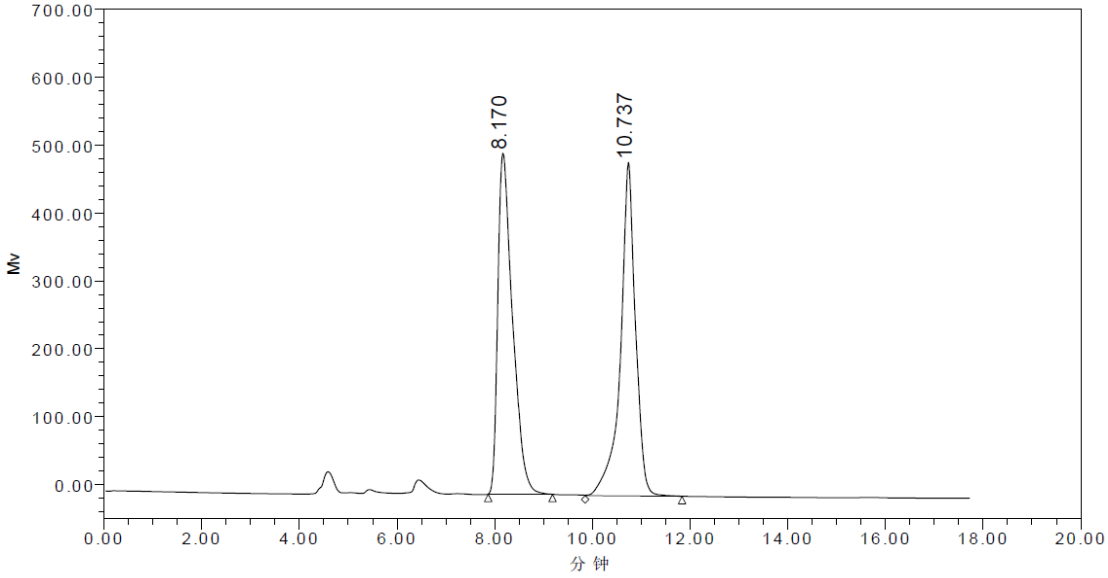

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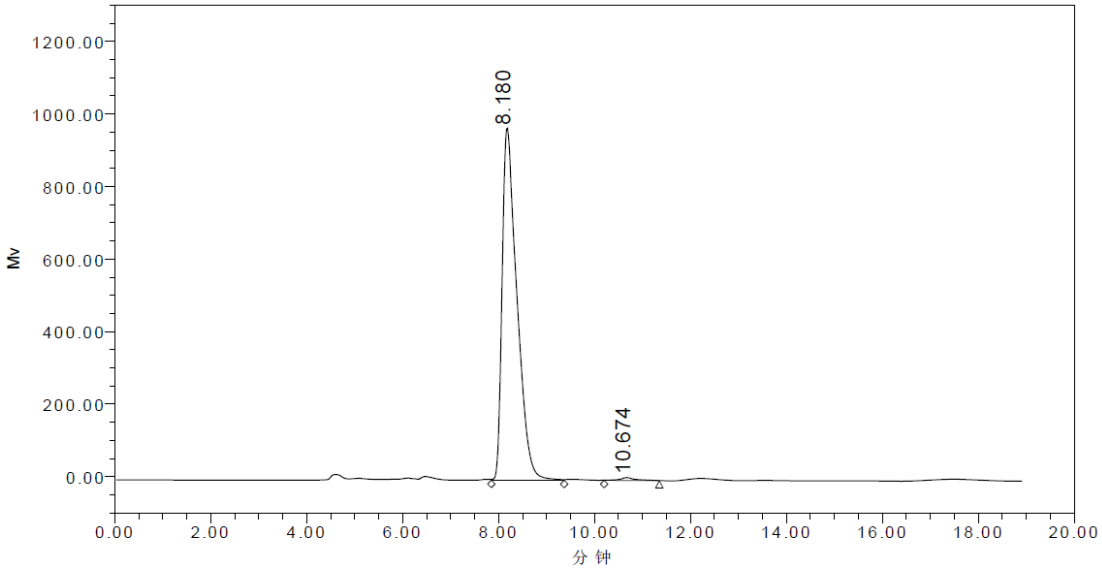
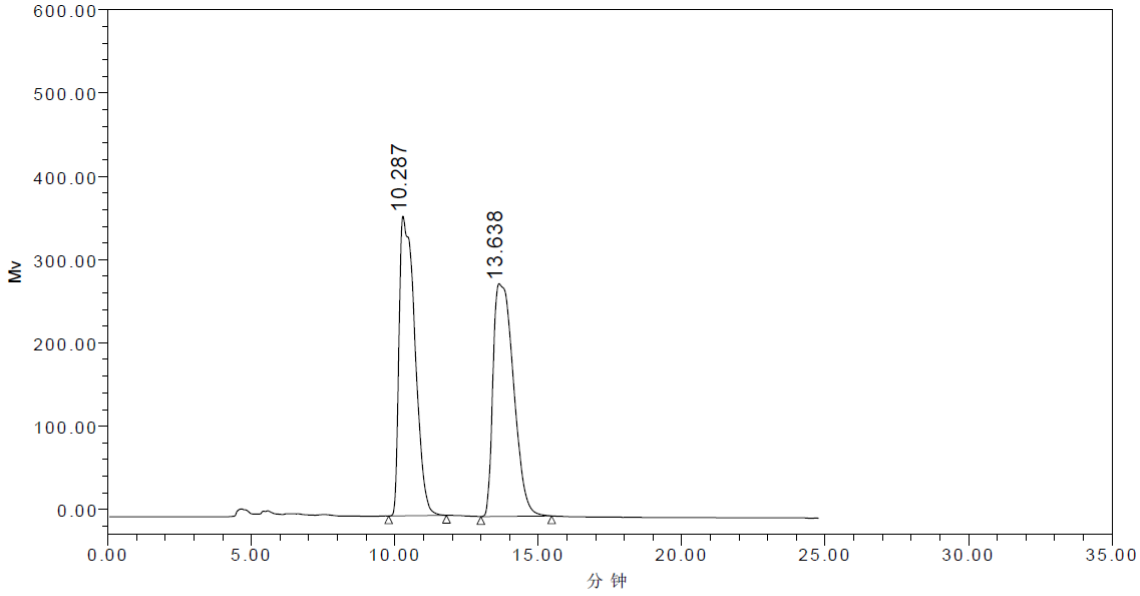
2	10.737	10490242	49.98	491239

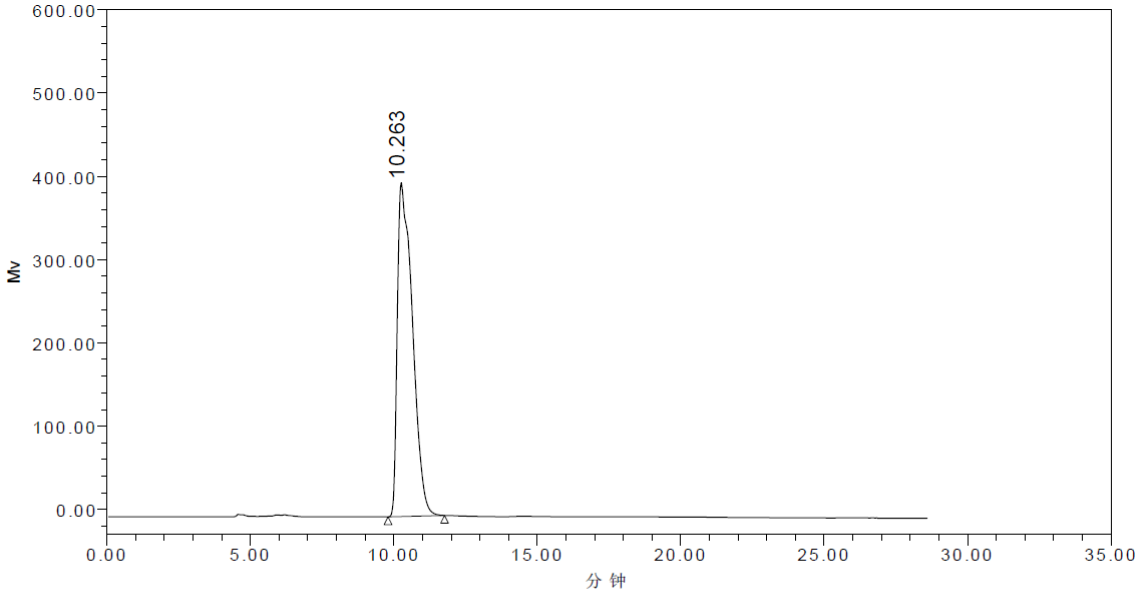


	RT	Area	% Area	Height
1	8.180	20763246	99.13	972130
2	10.674	182235	0.87	8132

Recycled crystal of **6s**



	RT	Area	% Area	Height
1	10.287	13799728	49.91	360170
2	13.638	13851774	50.09	279564



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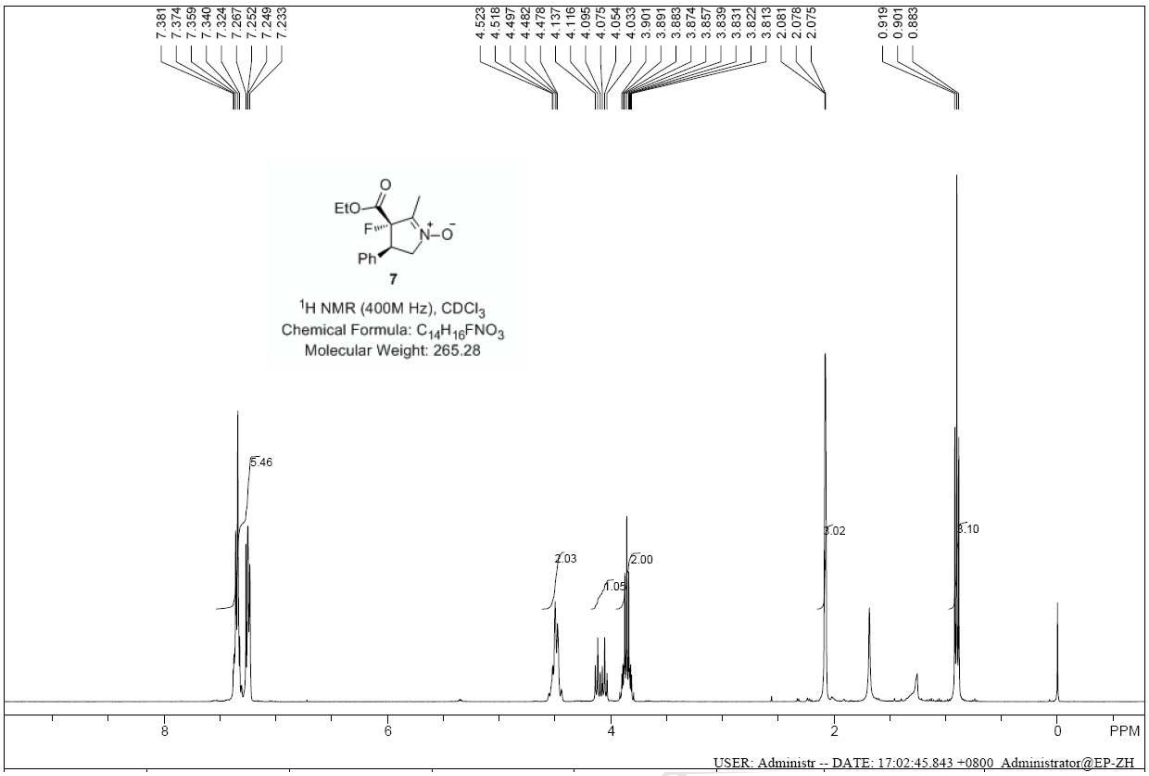
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3.874
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Molecular Weight: 265.28
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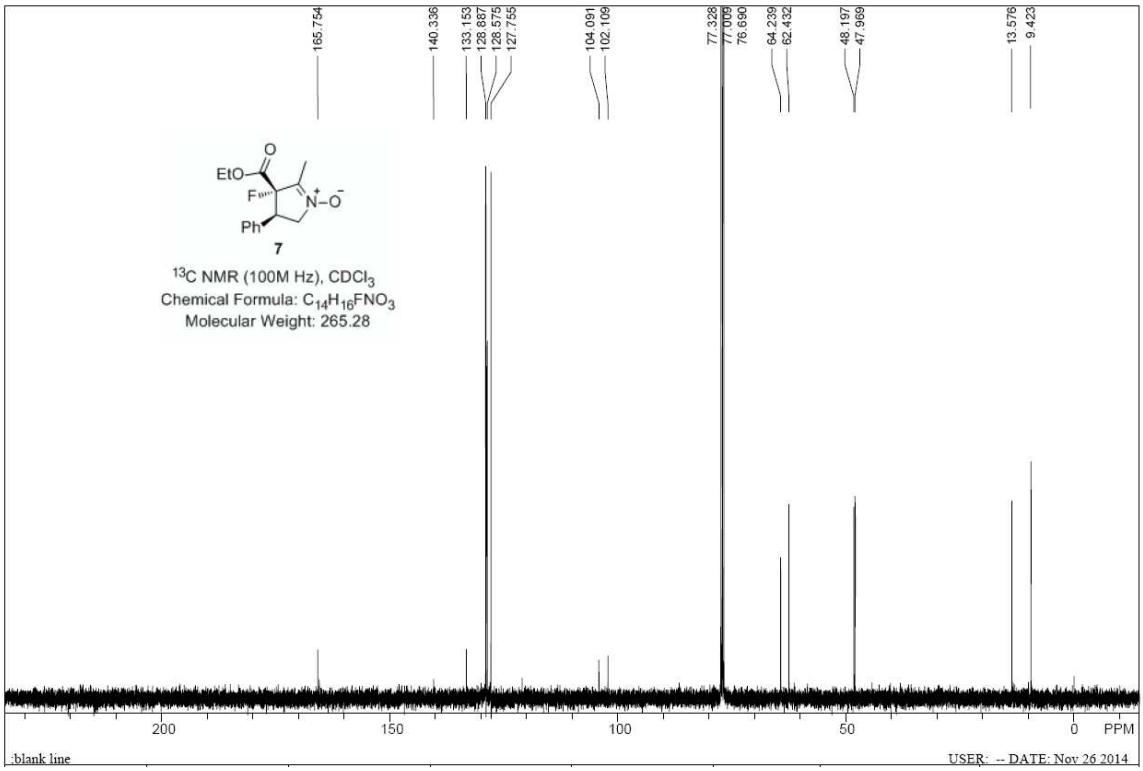
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102.109
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76.690
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N+
O−
Ph
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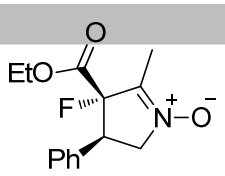

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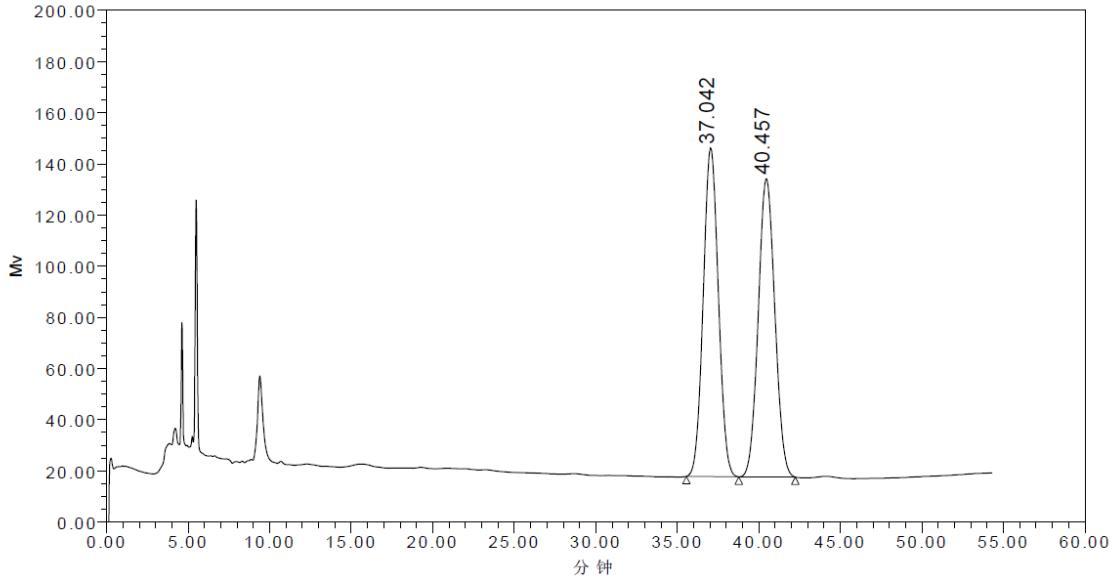

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1	37.042	8289141	50.12	128406
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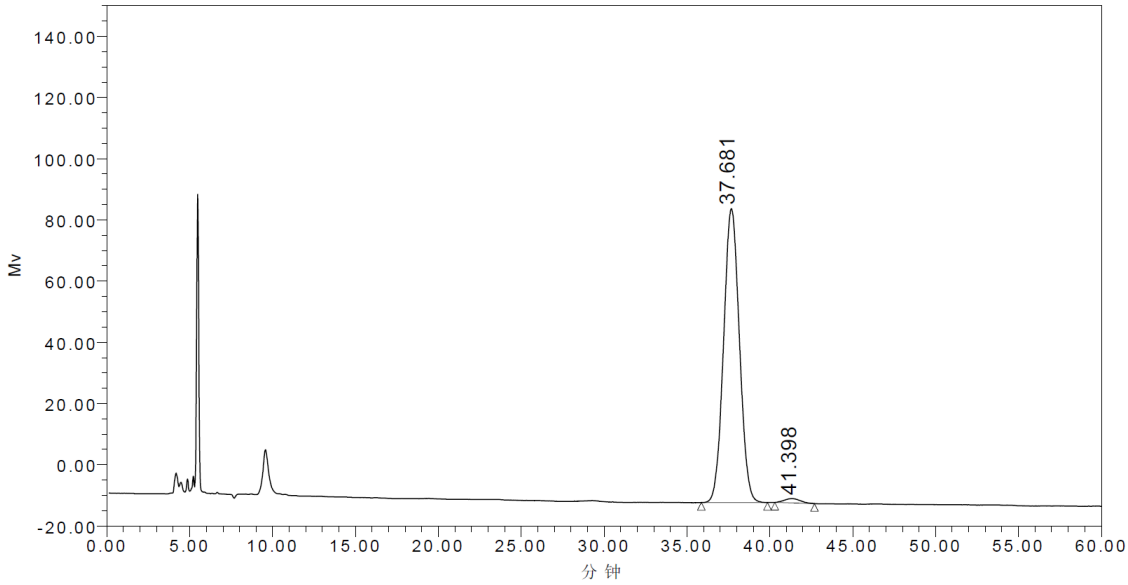

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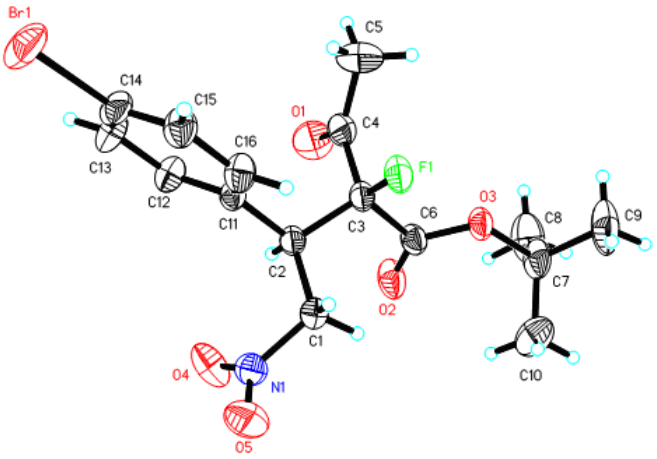
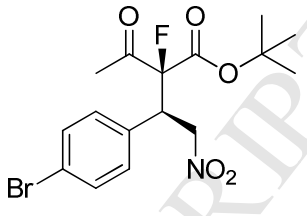
2	41.398	91470	1.41	1377

Crystal data and structure of 6s





6s

Table 1. Crystal data and structure refinement for cd214428.

Identification code	cd214428	
Empirical formula	C16 H19 Br F N O5	
Formula weight	404.23	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Trigonal	
Space group	P 32	
Unit cell dimensions	a = 10.384(7) Å	α= 90°.
	b = 10.384(7) Å	β= 90°.
	c = 15.286(15) Å	γ = 120°.
Volume	1427(2) Å^3	
Z	3	
Density (calculated)	1.411 Mg/m^3	
Absorption coefficient	2.192 mm^{-1}	
F(000)	618	
Crystal size	0.211 x 0.154 x 0.123 mm^3	
Theta range for data collection	2.265 to 25.979°.	
Index ranges	-12<=h<=12, -12<=k<=8, -18<=l<=18	
Reflections collected	8607	
Independent reflections	3716 [R(int) = 0.0588]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7457 and 0.5707	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3716 / 1 / 222	
Goodness-of-fit on F^2	0.910	

Final R indices [I>2sigma(I)]	R1 = 0.0403, wR2 = 0.0846
R indices (all data)	R1 = 0.0663, wR2 = 0.0926
Absolute structure parameter	0.024(9)
Largest diff. peak and hole	0.341 and -0.206 e.Å^{-3}