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Recyclable Organocatalysis of One-pot Michael/Mannich/Lactamization Sequence for Asymmetric Synthesis of Fluorinated Poly-substituted 2-Piperidinones

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Biochemistry Honors Thesis Presented

By

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Abstract:

2-piperidinone (δ-lactam), a bio-interesting nitrogen-containing six-membered ring compound, has attracted much interest from researchers both in synthetic and medicinal chemistry. Polysubstituted piperidine derivatives, such as the δ-lactam, serve as a synthon for numerous biologically relevant structures and pharmaceutical agents. A novel one-pot asymmetric Michael/Mannich/Lactamization sequence promoted by recyclable fluorous bifunctional cinchona alkaloid–thiourea organocatalysts is introduced for the synthesis of polysubstituted 2-piperidinones bearing four contiguous stereocenters, one of which is a fluorinated quaternary chiral center with excellent stereoselectivities (ee up to >99%, dr up to >20:1).

Introduction:

Ever since their discovery, heterocyclic compounds have been widely synthesized as the building blocks for numerous natural products and pharmaceuticals. Among the bio-interesting nitrogen-containing six-membered heterocycles, 2-piperidinone (δ-lactam) has especially attracted much attention both in synthetic and medicinal chemistry. Polysubstituted piperidine derivatives, such as chiral 2-piperidinones,[1] serve as substructures for numerous biologically relevant structures and pharmaceutical agents. Examples of compounds containing the δ-lactam moiety include natural products awajanomycin **1**,[2] tedanalactam **2**,[3] and meloscine **3** (Figure 1).[4] Other biologically active compounds containing δ-lactam are MDM2 inhibitor AM-8553 **4**,[5] prostaglandin agonists **5,**[6] and HIV protease inhibitors **6** (Figure 1).[7] In the synthetic endeavor of drugs and more natural products, chiral polysubstituted 2-piperidinone has been utilized as an efficient fundamental adduct for the synthesis of antimalarial (+)-febrifugine, antibiotic and anesthetic prosopis alkaloid (+)-prosophylline, and clinical agent (+)-CP-99,994, which is involved in several biological mechanisms such as neurogenic inflammation, pain transmission, and regulation of the immune response.[8] With its extensive use as a synthon for the synthesis of medicinally interesting compounds, further developments of novel asymmetric syntheses of polysubstituted 2-piperidinones are a highly desirable topic of study in both synthetic and medicinal chemistry.

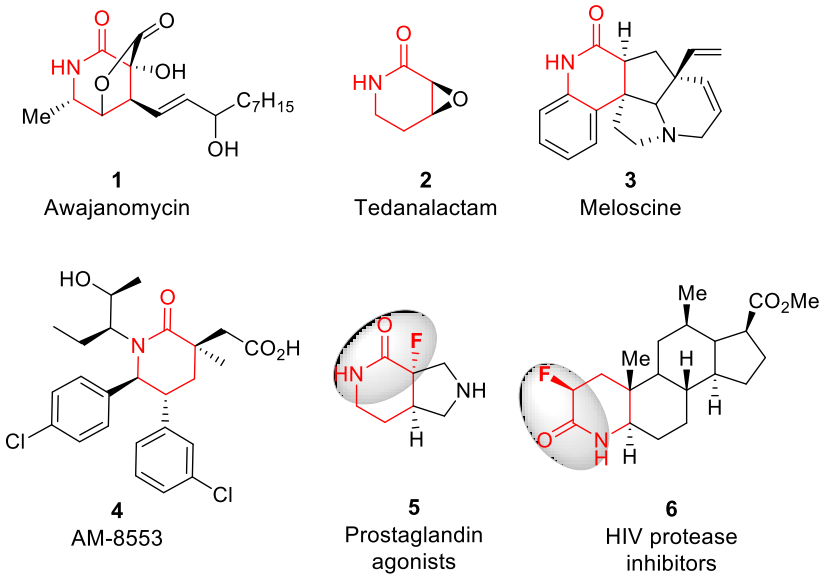
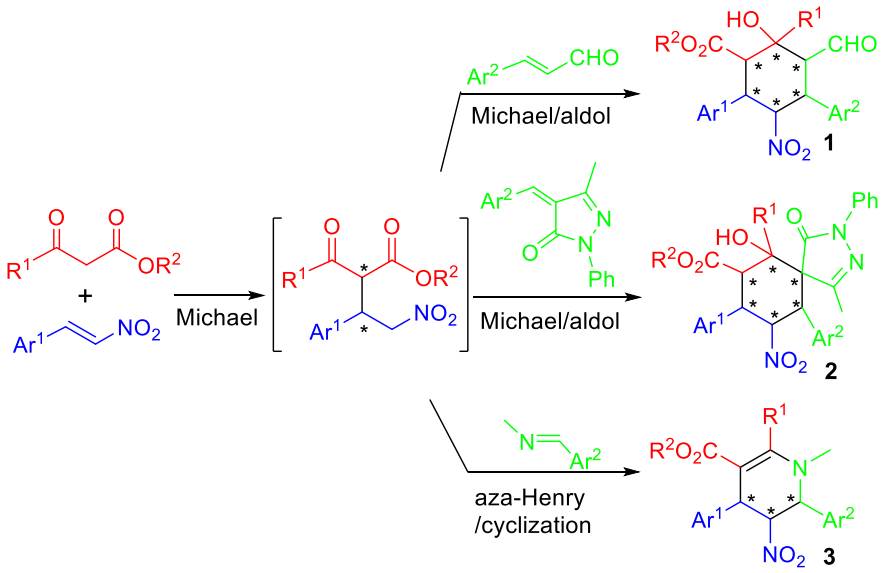


Figure 1. Biologically active 2-piperidinones

Organocatalysis is becoming an increasingly important tool for asymmetric synthesis, as it possesses the capability to construct complex frameworks with multiple stereogenic centers in a highly stereoselective manner from simple substrates. Compared to metal catalysis, organocatalysis has the advantages of being free from toxic heavy metals, having mild reaction conditions, and possessing easy structural modifications. However, high catalyst loading (up to 20 mol%) coupled with the difficulty in catalyst recovery is the major drawback of organocatalysis. Appropriately, organocatalyst recycling is highly desirable. Among related organocascade catalyses, the Michael-initiated cascade reactions play a significant role in the sequence, in which the chiral Michael adducts could efficiently serve as synthons for subsequent reactions of Michael, Aldol, Darzen, Mannich, Henry or for triple cascade reactions like Michael-aldol, Michael-Henry and Mannich-Cyclization.[9]

In the development of organocatalytic asymmetric synthesis of 6-membered carbon and nitrogen-containing heterocycles,[9] there have been numerous reports detailing such reactions. Recently, bis-nucleophilic 1, 3-dicarbonyl compounds were found to be versatile Michael donors

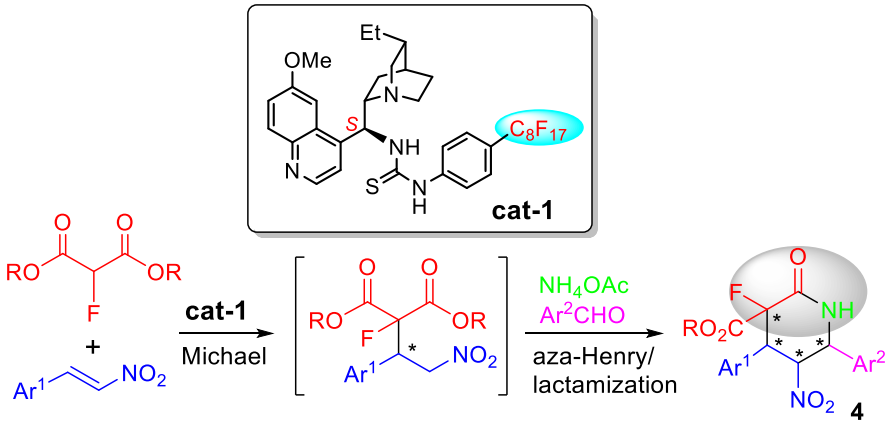
for nitroolefines resulting in Michael adducts that are capable of undergoing intermolecular triplecascade reactions to afford polysubstituted compounds with multiple stereogenic centers.[9],[10] The Enders group, in 2012, were the first to introduce a series of highly diastereo- and enantioselective one-pot 1,3-dicarbonyl compounds-initiated cascade reactions[10] that entailed a consecutive three-component sequence, such as the Michael/Michael/aldol sequence, for the synthesis of hexasubstituted cyclohexanols **1**[11] and spirocyclohexanepyrazolones **2** (Scheme 1).[12] In 2014, P. Chauhan and coworkers also introduced a Michael/aza-Henry/cyclization sequence to make tetrahydropyridines **3**.[13] Some other compounds that were created using cascade reactions involving Michael, Mannich, Henry, and Aldol reactions[14] are



Scheme 1. Previous work by Enders group.

dihydropyridinones,[15] piperidinones,[16] and dihydroquinolinones.[17] To the best of our knowledge, the asymmetric synthesis of chiral polysubstituted 2-piperidinones via Michael-initiated reactions between 1, 3-dicarbonyl compounds and nitroolefines followed by intermolecular cascade reactions is not known. With organofluorine chemistry also being an

active topic in medicinal and agricultural chemistry,[18] we would like to introduce here a recyclable fluorous organocatalyst-catalysed one-pot Michael/aza-Henry/lactamization sequence for the synthesis of fluorinated 2-piperidinones **4** bearing four stereogenic centers (scheme 2).



Scheme 2. 1,3-Dicarbonyl compounds for asymmetric cascade reactions

Atom and step economic one-pot synthesis, toxic transition metal-free organocatalysis, and catalyst recycling are important green synthetic techniques. As part of our continuous efforts to develop recyclable fluorous organocatalysts[19] for the asymmetric synthesis of organofluorine compounds,[20] we have recently reported one-pot fluorination and Michael addition reactions for the synthesis of α-fluorinated and alkylated 1,3-dicarbonyl compounds.[20c] The reactions were promoted by fluorous bifunctional cinchona alkaloid–thiourea organocatalyst **cat-1**, which was recovered by fluorous solid-phase extraction (F-SPE) with >98% purity. Since the fluorinated carbon of the 1,3-dicarbonyl compounds is more nucleophilic and thus favourable for the Michael addition, we envisioned that such compounds could be used in the development of Michael/aza-Henry/lactamization sequence for the synthesis of fluorinated 2-piperidinones.

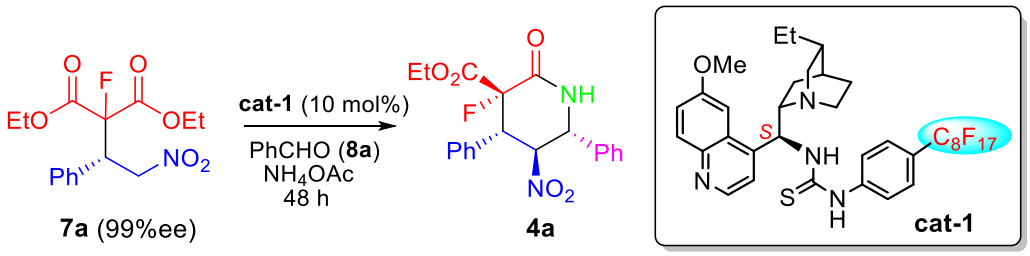
Experimental Method:

A solution of fluorous catalysts (0.025 mmol) in toluene (0.5 mL) and trans-*β*-nitrostyrene (0.25, mmol) was stirred at room temperature for 20 min., and then fluorinated 1,3-diester (0.3 mmol) was added. The reaction mixture was stirred for 24 h followed by the addition of ethanol (1 mL), benzaldehyde (0.25 mmol), NH_4OAc (0.3 mmol) as well as 4 drops of piperidine. The reaction mixture was stirred for 24 h at 40 ^oC. The purification by Yamazen AI-580 flash column system with Agela silica gel columns ($EtOAc/CH_2Cl_2$) afforded fluorinated 2-piperidinone.

The chemicals and solvents used for the reactions were purchased from commercial sources and used as received. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Varian NMR spectrometer. The ratios of the diastereomers were determined by ^1H NMR. Only the peaks from the major diastereomer are given below. LC-MS was performed on the Agilent 2100 system with a C_{18} column for separation. Mass spectra were recorded in APCI (atmospheric pressure chemical ionization). Flash chromatography separations were performed on Yamazen system with Agela silica gel columns. High-resolution mass spectrometry (HRMS) was performed using an ESI-TOF/MS instrument.

Results and discussion:

Table 1. Optimization of aza-Henry and lactamization reactions [a]



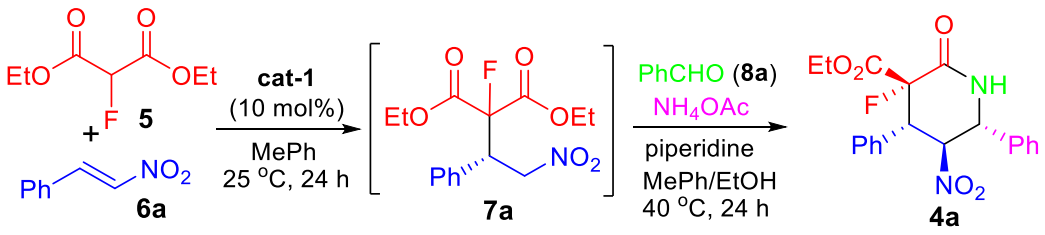
Entry	Base (equiv)	Solvent	T (°C)	Yield (%)[b]	dr[c]	ee (%)[d]
1	K_2CO_3 (0.5)	EtOH	25	trace	ND	ND
2	Cs_2CO_3 (0.5)	EtOH	25	trace	ND	ND
3	NaOH (0.5)	EtOH	25	23	5:5:1	ND
4	piperidine (0.5)	EtOH	25	42	6:1	98
5	piperidine (0.5)	EtOH	40	72	6:1	98
6	piperidine (0.25)	EtOH	40	36	6:1	98
7	piperidine (0.75)	EtOH	40	68	6:1	98
8	piperidine (0.5)	EtOH	0	75	1.25:1	93(89)[e]
9	piperidine (0.5)	EtOH	60	75	1.25:1	ND
10	piperidine (0.5)	MePh	40	27	5:1	98
11	piperidine (0.5)	CH_2Cl_2	40	12	ND	ND
12	piperidine (0.5)	MeCN	40	10	ND	ND
13[f]	piperidine (0.5)	EtOH	40	68	5:3:1	25

[a] Reaction of 0.25 mmol **7a** in 1.0 mL of solvent, 1:1:1.2 of **7a:8a**:NH_4OAc. [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Determined by HPLC on Venusil Chiral OD-H column with 90:10 hexane/*i*-PrOH as the eluent. [e] ee of the minor diastereoisomer. [f] Without catalyst

By following our previous study on the asymmetric Michael addition between α-fluoro β-ketoesters and nitroalkenes in the presence of recyclable fluorous thiourea catalysts, we synthesized the Michael adduct **7a**. We first explored the asymmetric aza-Henry and sequential lactamization reactions using enantiomerically pure Michael adduct **7a** (99% ee),[20a,b] benzaldehyde **8a**, and NH_4OAc as substrates and previously reported recyclable fluorous bifunctional cinchona alkaloid–thiourea **cat-1** as a catalyst (Table 1).[20c] During our initial study and condition optimization, it was found that carbonates (entry 1 and 2) could not serve as effective bases to promote this cascade reaction and a more basic NaOH afforded the product to only 23% yield after 48 h with three diastereomers in a ratio of 5:5:1

(entry 3). When piperidine was screened, a product with an excellent 98% ee and a good 6:1 dr was achieved with 42% yield (entry 4) making it an effective choice of base for the reactions. When the effects of temperature were examined in entries 4, 5, 8, and 9, reactions at lower temperatures (25 ^{o}C) led to reduced yields, but good disatereoselectivity (6:1) (Table 1, entry 4), while higher temperatures (50 or 60 ^{o}C) increased product yields to 75% but decreased the diastereomeric ratios to 1.25:1 (entries 8 and 9). It was found that a moderate temperature of 40 ^{o}C (entry 5) could give both good stereoselectivities and yield. A reaction with MePh as a solvent gave the product in high dr and ee but low yield (entry 10). Further optimization for solvents indicated that EtOH was the best choice and the desired product was obtained in excellent diastereo- and enantioselectivities (entry 4). A control reaction without using a catalyst afforded 68% product yield, but gave three diastereomeric products (5:3:1) in low ee (25%) (entry 13). After screening bases (K_2CO_3, Cs_2CO_3, NaOH, and piperidine), solvents (EtOH, MePh, CH_2Cl_2, and MeCN), and reaction temperatures (25-60 ^{o}C), we found that the reaction with 0.5 equiv. of piperidine as a base and EtOH as a solvent at 40 ^{o}C for 48 h gave fluorinated 2-piperidinone **4a** in 72% yield with a good diastereoselectivity (6:1) and excellent enantioselectivity (98% ee) (Table 1, entry 5).

Table 2. Optimization of Michael/aza-Henry/lactamization reactions [a]



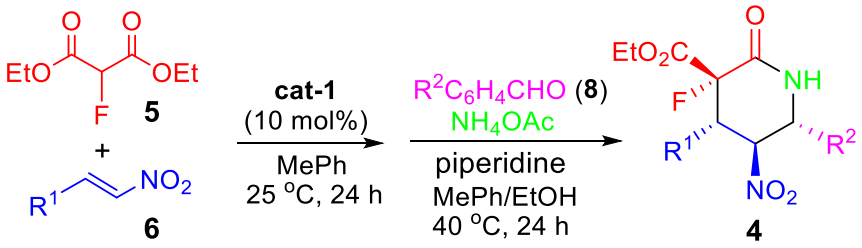
Entry	**5**:**6a**	MePh /EtOH[b]	Yield (%)[c]	dr[d]	ee (%)[e]
1	1:1	1:0	22	5:1	98
2	1:1	1:0.5	39	5:1	98
3	1:1	1:1	47	6:1	99
4	1:1	1:1.5	65	6:1	99
5	1:1	1:2	67	6:1	99
6	1:1	1:2.5	65	6:1	99
7	1.25:1	1:2	72	6:1	99
8	1.5:1	1:2	78	6:1	99
9	2:1	1:2	69	6:1	99

[a] Reaction of 0.25 mmol of **6a** in 0.5 mL of MePh. [b] Ratio of solvents for the 2nd reaction. [c] Yield of isolated product **4a**. [d] Determined by ^{1}H NMR.[e] Determined by HPLC on Venusil Chiral OD-H column with 90:10 hexane/*i*-PrOH as the eluent

With the optimized reaction conditions for the successful aza-Henry and sequential lactamization reactions, we started to develop an organocatalytic asymmetric one-pot process for the synthesis of 2-piperidinones by combining the aza-Henry reaction with the Michael addition of the fluorinated dicarbonyl compounds to the nitroalkenes.[20c] Commercially available 2-fluoro-1,3-diester **5** was used as the Michael donor and the same fluorous bifunctional cinchona alkaloid–thiourea **cat-1** was used as a catalyst for the cascade reactions. The solvent for the one-pot reaction had to be modified because while MePh was effective for the Michael addition,[20c] EtOH displayed the best results for the aza-Henry reaction. We found that after the Michael reaction was carried out in MePh, EtOH could be added to the reaction mixture for the sequential aza-Henry reaction. The best ratio of solvents was 1:2 MePh:EtOH (Table 2, entry 8) and the best ratio of reactants was

1.5:1:1:1.2 **5:6a**:PhCHO:NH_4OAc for the one-pot cascade reactions. The time for the aza-Henry and lactamization reactions could be reduced from 48 h to 24 h.

Table 3. Scope of one-pot Michael/aza-Henry/lactamization reactions [a, b]

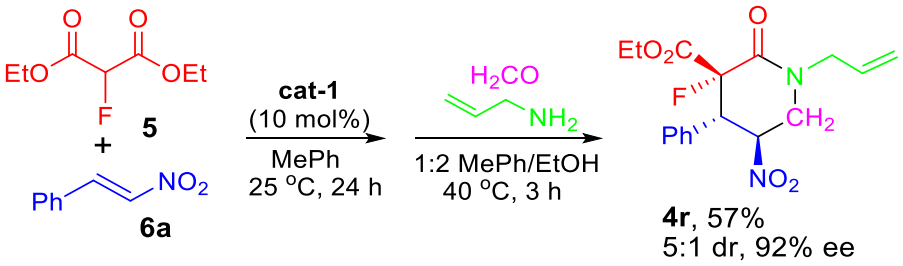


Entry	Product	R^1	R^2	Yield (%)[c]	dr[d]	ee (%)[e]
1	**4a**	C_6H_5	H	78	6:1	99
2	**4b**	C_6H_5	4-F	85	8:1	98
3	**4c**	C_6H_5	4-Br	87	10:1	96
4	**4d**	C_6H_5	4-NO_2	83	10:1	96
5	**4e**	C_6H_5	4-CF_3	85	15:1	97
6	**4f**	C_6H_5	4-^{t}butyl	35	4:1	97
7	**4g**	C_6H_5	4-OMe	30	4:1	95
8	**4h**	C_6H_5	2,3-Cl	55	3.5:1	90
9	**4i**	C_6H_5	4-F,3-OMe	62	2:1	93(90)[f]
10	**4j**	3-ClC_6H_4	H	65	3:1	90
11	**4k**	4-BrC_6H_4	H	68	3.5:1	93
12	**4l**	4-MeC_6H_4	H	55	5:1	95
13	**4m**	4-$OMeC_6H_4$	H	69	3:1	91(90)[f]
14	**4n**	2-Furyl	H	62	3.5:1	99(99)[f]
15	**4o**	4-BrC_6H_4	4-Br	67	4:1	99
16	**4p**	4-$OMeC_6H_4$	4-Br	65	3:1	98(99)[f]

[a] Reaction of 0.25 mmol of **6** in 0.5 mL of MePh. [b] Add 1.0 mL of EtOH for the aza-Henry reaction, 1.5:1:1:1.2 of **5:6:8**:NH_4OAc. [c] Yield of isolated product. [d] Determined by ^1H NMR. [e] Determined by HPLC on Chiral column with hexane/*i*-PrOH as the eluent. [f] ee of the minor diastereoisomer

A variety of nitroalkenes **6**, as well as benzaldehydes **8** were tested to explore the scope of the one-pot Michael/aza-Henry/lactamization reactions (Table 3). The employment of both electron-donating and -withdrawing (entries 2-9) groups at the *para*-position of the aryl rings in benzaldehydes showed little effect on the enantioselectivities of the products. Benzaldehydes with electron-withdrawing groups (F, Br, NO_2, CF_3) at the *para*-position gave products **4b-e** in 83-87% yields with >8:1 dr and >96% ee (Table 3, entries 2-5). These higher product yields may be attributed to easy formation of imines

of theses aldehydes with NH_4OAc. On the contrary, benzaldehydes with an electron-donating group, such as *t*-Bu and OMe or disubstituted groups, gave products **4f-i** with reduced yields (30-62%) and dr (2:1 to 4:1) due to unfavourable electronic and steric effects (Table 3, entries 6-9). Reactions with nitroalkenes bearing different R^1 groups resulted in the desired products **4j-m** in good and consistent yields (55-69%) and dr (3:1 to 3.5:1) (entries 10-13), while keeping excellent ee values. Furthermore, a reaction with a nitroalkene bearing a furyl ring gave product **4n** in good yield and enantioselectivity (entry 14). Similar results were obtained from the reactions with 4-bromobenzaldehyde and other substituted nitroalkenes (entries 15-16). A reaction using formaldehyde and vinyl amine was also attempted. Highly reactive formaldehyde reduced the time for the aza-Henry reaction to 3 h and gave *N*-vinylated 2-piperidinone **4r** in 57% yield with a good dr and ee (Scheme 3).



Scheme 3. One-pot synthesis of **4r**

The relative configuration of the final products was determined by NOE contacts between the concerning hydrogen atoms, whereas the absolute configuration of the four stereogenic centers of 2-piperidinone products was assigned by investigating the configurations of related Michael addition and 6-membered products reported in literature[15]-[17],[21] and also by obtaining the single X-ray crystal structure of **4c** (Figure 2).

In the Michael/aza-Henry/lactamization reaction process, fluorous **cat-1** with a (S)-C9 stereogenic center induces the formation of a (S)-2 stereogenic center in the Michael addition product (Scheme 4). This compound undergoes the aza-Henry reaction with benzaldehyde and NH_4OAc to form compound **5** and is then cyclized to form 2-piperidinone **4** bearing four contiguous stereogenic centers. The results in Table 3 and Scheme 2 indicated that fluorous **cat-1** is a good catalyst that is responsible for excellent product stereoselectivities.

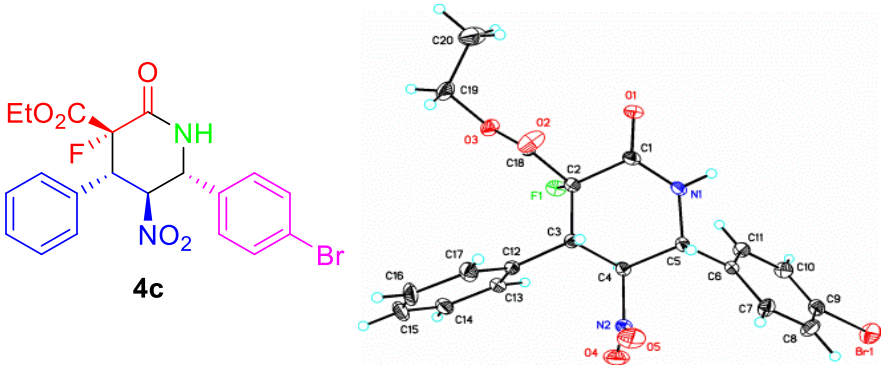
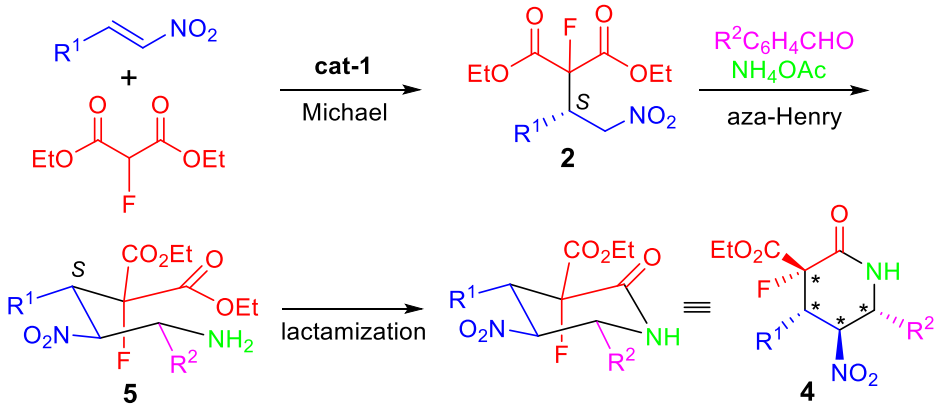


Figure 2. X-ray crystal structure of **4c**



Scheme 4. Stereochemistry of the one-pot reactions

We tested the efficiency of fluorous catalyst recovery by performing fluorous solid-phase extraction (F-SPE).[22] After the completion of the reaction, the concentrated reaction mixture was loaded onto a fluorous silica gel cartridge. The cartridge was first eluted with 80:20 MeOH/H_2O for the product and other non-fluorous components. The fluorous catalyst remained on the cartridge until it was eluted with MeOH. The catalyst was recovered in 94% yield and 98% purity, and could be reused without further purification.

Conclusion:

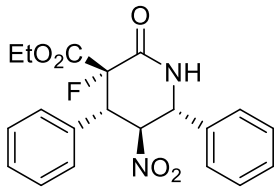
Using recyclable fluorous bifunctional cinchona alkaloid–thiourea as a catalyst, which was recovered in 94% yield and 98% purity, a protocol optimized with green techniques was introduced for the one-pot asymmetric synthesis of 2-piperidinone. In summary, we have developed a recyclable fluorous bifunctional cinchona alkaloid–thiourea promoted one-pot asymmetric Michael/Mannich/Lactamization triple cascade reaction of fluorinated 1,3-dicarbonyl compounds, β-nitro-olefins, aldehydes and amines to provide potentially bioactive fluorinated poly-substituted 2-piperidinones in very good yields and up to high diastereo- and excellent enantioselectivities.

Acknowledgements:

We thank Sanofi Genzyme Undergraduate Research Fellowship, Joseph P. Healey Research Grant, UMB Center for Green Chemistry for support.

Analytical Data of Products:

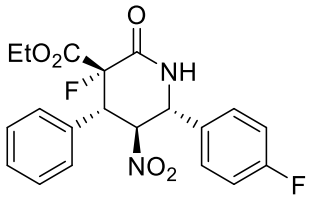
Ethyl -3-fluoro-5-nitro-2-oxo-4,6-diphenylpiperidine-3-carboxylate (4a):



4a

White solid, yield: 32 mg (78%), 6:1 dr, 99% ee. The enantiomeric excess was determined by HPLC on on Venusil Chiral OD-H with hexane/*i*-PrOH (90:10) as the eluent. Flow rate: 1.0 mL/min, λ = 254 nm: t_{minor} = 28.90 min, t_{major} = 16.90 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.28 (s, 1H), 7.47–7.28 (m, 8H), 7.26–7.11 (m, 2H), 5.53 (d, J = 3.7 Hz, 1H), 5.43 (t, J = 3.6 Hz, 1H), 4.57 (dd, J = 33.0, 3.4 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.11 (t, J = 7.1 Hz, 3H). ^{19}F (282 MHz, CDCl3): δ 162.88 ppm. MS (ACPI) m/z: 416.1 (M+1). HRMS (ESI): calcd. for $C_{20}H_{19}FN_2O_5[M+Na]^+$ 409.1176; found 409.1170.

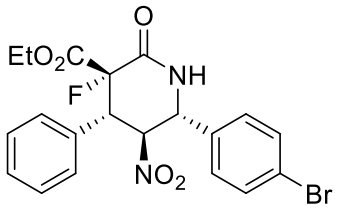
Ethyl 3-fluoro-6-(4-fluorophenyl)-5-nitro-2-oxo-4-phenylpiperidine-3-carboxylate (4b):



4b

White solid, yield: 34 mg (85%), 8:1 dr, 98% ee. The enantiomeric excess was determined by HPLC on on Venusil Chiral OD-H with hexane/*i*-PrOH (80:20) as the eluent. Flow rate: 1.0 mL/min, λ = 254 nm: t_{minor} = 11.66 min, t_{major} = 8.50 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.19 (m, 7H), 7.13 (d, J=4.6 Hz, 2H), 6.10 (s, 1H), 5.35 (t, J = 9.1 Hz, 1H), 5.21 (d, J = 9.9 Hz, 1H), 4.39 (dd, J = 30.6, 12.3 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.91, 50.19, 50.44, 59.93, 62.98, 87.71, 116.75, 117.04, 128.81, 128.92, 129.03, 129.17, 129.59, 215.98 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ 110.22, 162.80 ppm. MS (ACPI) m/z: 405.1 (M+1).

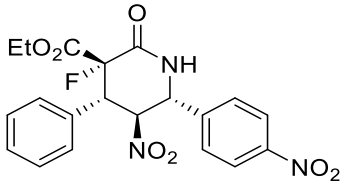
Ethyl 6-(4-bromophenyl)-3-fluoro-5-nitro-2-oxo-4-phenylpiperidine-3-carboxylate (4c):



4c

White solid, yield: 40 mg (87%), 10:1 dr, 96% ee. The enantiomeric excess was determined by HPLC on on Venusil Chiral OD-H with hexane/*i*-PrOH (90:10) as the eluent. Flow rate: 1.0 mL/min, λ = 254 nm: t_{minor} = 25.62 min, t_{major} = 19.97 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J = 11.1 Hz, 2H), 7.38 – 7.04 (m, 7H), 6.46 (s, 1H), 5.35 (t, J = 9.1 Hz, 1H), 5.17 (d, J = 9.9 Hz, 2H), 4.37 (dd, J = 30.7, 12.4 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.81, 49.85, 50.37, 59.92, 63.04, 87.72, 124.82, 128.46, 129.02, 129.59, 132.90, 133.96, 162.63, 164.43, 178.44, 215.96 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ 162.83 ppm.MS (ACPI) m/z: 467.1 (M+1). HRMS (ESI): calcd. for $C_{20}H_{18}BrFN_2O_5[M+Na]^+$ 487.0281; found 487.0293.

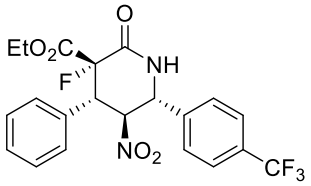
Ethyl 3-fluoro-5-nitro-6-(4-nitrophenyl)-2-oxo-4-phenylpiperidine-3-carboxylate (4d):



4d

White solid yield: 35 mg (83%), 10:1 dr, 96% ee. The enantiomeric excess was determined by HPLC on on Venusil Chiral OD-H with hexane/*i*-PrOH (90:10) as the eluent. Flow rate: 1.0 mL/min, λ = 254 nm: t_{minor} = 97.22 min, t_{major} = 67.28 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.45 – 7.04 (m, 5H), 6.76 (s, 1H), 5.45–5.15 (m, 2H), 4.59–4.26 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.96, 201.71, 141.94, 129.76, 129.12, 128.08, 124.99, 87.65, 63.22, 60.03, 50.30, 50.05, 13.97 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ 163.09 ppm MS (ACPI) m/z: 432.1 (M+1)

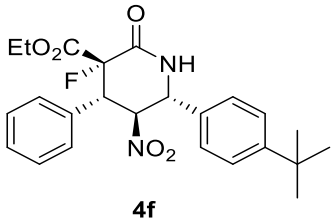
Ethyl3-fluoro-5-nitro-2-oxo-4-phenyl-6-(4-(trifluoromethyl)phenyl)piperidine-3-carboxylate (4e):



4e

White solid, yield: 38 mg (85%), 15:1 dr, 97% ee. The enantiomeric excess was determined by HPLC on on Venusil Chiral OD-H with hexane/*i*-PrOH (90:10) as the eluent. Flow rate: 1.0 mL/min, λ = 254 nm: t_{minor} = 26.56 min, t_{major} = 12.73 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.40–7.10 (m, 5H), 5.44–5.11 (m, 2H), 4.40 (dd, J = 30.7, 11.7 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.58, 164.25, 163.10, 162.81, 129.66, 129.37, 129.14, 129.11, 129.06, 127.41, 126.72, 126.67, 88.05, 63.30, 60.31, 50.34, 50.10, 13.84 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -63.75, -163.34 ppm. MS (ACPI) m/z 455.1 (M+1)

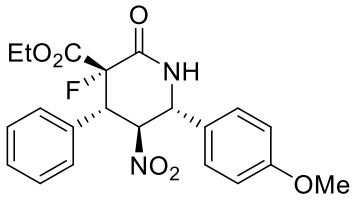
Ethyl 6-(4-(tert-butyl)phenyl)-3-fluoro-5-nitro-2-oxo-4-phenylpiperidine-3-carboxylate (4f):



4f

White solid, yield: 15 mg (35%), 4:1 dr, 97% ee. The enantiomeric excess was determined by HPLC on on Venusil Chiral OD-H with hexane/*i*-PrOH (90:10) as the eluent. Flow rate: 1.0 mL/min, λ = 254 nm: t_{minor} = 19.42 min, t_{major} = 13.77 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.44 (d, J = 8.3 Hz, 2H), 7.34–7.06 (m, 7H), 6.91 (s, 1H), 5.80 (dd, J = 12.3, 6.2 Hz, 1H), 5.48–5.18 (m, 1H), 4.42 (dd, J = 30.9, 12.3 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.31 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.90, 163.54, 153.13, 131.11, 130.28, 128.93, 128.62, 128.60, 126.99, 126.53, 126.17, 125.86, 83.69, 62.98, 57.03, 44.76, 44.52, 34.70, 31.16, 13.92.ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -63.75, -163.50 ppm MS (ACPI) m/z: 443.1 (M+1)

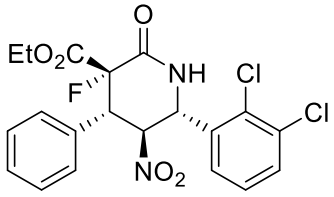
Ethyl 3-fluoro-6-(4-methoxyphenyl)-5-nitro-2-oxo-4-phenylpiperidine-3-carboxylate (4g):



4g

White solid, yield: 12 mg (30%), 4:1 dr, 95% ee. The enantiomeric excess was determined by HPLC on on Venusil Chiral OD-H with hexane/*i*-PrOH (85:15) as the eluent. Flow rate: 1.0 mL/min, λ = 254 nm: t_{minor} = 52.40 min, t_{major} = 25.26 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.21 (m, 7H), 6.95 (d, J = 8.7 Hz, 2H), 6.00 (s, 1H), 5.35 (t, J = 9.1 Hz, 1H), 5.16 (d, J = 10.1 Hz, 1H) 4.38 (dd, J = 30.7, 12.4 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.69, 129.49, 129.16, 128.98, 128.22, 118.72, 114.53, 63.21, 60.59, 55.13, 50.30, 13.82, 8.01 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -163.09 ppm MS (ACPI) m/z: 417.1 (M+1)

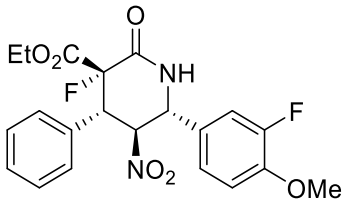
Ethyl 6-(2,3-dichlorophenyl)-3-fluoro-5-nitro-2-oxo-4-phenylpiperidine-3-carboxylate (4h):



4h

Colorless oil, yield: 25 mg (55%), 3.5:1 dr, 90% ee. The enantiomeric excess was determined by HPLC on Venusil Chiral OD-H with hexane/*i*-PrOH (80:20) as the eluent. Flow rate: 1.0 mL/min, λ = 254nm: t_{minor} = 13.62 min, t_{major} = 11.28 min. ^{1}H NMR (300 MHz, CDCl3) δ 7.57 (dd, J = 7.8, 1.7 Hz, 1H), 7.49–7.15 (m, 7H), 6.30 (s, 1H), 5.84 (d, J = 10.0 Hz, 1H), 5.70–5.46 (m, 1H) , 4.42 (dd, J = 31.0, 12.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.15, 201.46, 132.45, 129.80, 129.32, 129.29, 129.24, 128.71, 86.00, 63.21, 57.57, 50.34, 50.10, 13.99 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -164.16 ppm. MS (ACPI) m/z: 456.1 (M+1).

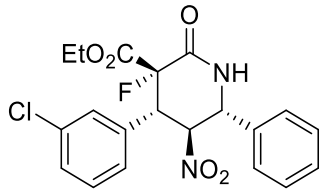
Ethyl 3-fluoro-6-(3-fluoro-4-methoxyphenyl)-5-nitro-2-oxo-4-phenylpiperidine-3-carboxylate (4i):



4i

White solid, yield: 27 mg (62%), 2:1 dr, 93% ee. The enantiomeric excess was determined by HPLC on on Venusil Chiral OD-H with hexane/*i*-PrOH (95:5) as the eluent. Flow rate: 1.0 mL/min, λ = 254 nm: t_{minor} = 25.02 min, t_{major} = 6.36 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.22 (m, 5H), 7.11 (dd, J = 10.7, 8.3 Hz, 1H), 7.02–6.74 (m, 2H), 5.45–5.22 (m, 1H), 5.17 (dd, J = 9.9, 2.7 Hz, 1H), 4.37 (dd, J = 30.8, 12.4 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 1.13 (t, J = 7.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.57, 163.09, 155.16, 152.21, 129.57, 129.49, 129.12, 129.01, 128.56, 119.60, 119.50, 117.13, 116.88, 111.37, 87.70, 63.03, 60.39, 56.42, 50.41, 50.16, 13.86 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -131.85, -132.67, -162.56, -164.68 ppm. MS (ACPI) m/z: 435.1 (M+1).

Ethyl 3-fluoro-6-(3-fluoro-4-methoxyphenyl)-5-nitro-2-oxo-4-phenylpiperidine-3-carboxylate (4i):

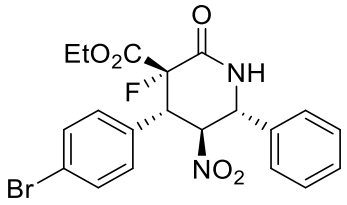


4j

White solid, yield: 27 mg (65%), 3:1 dr, 90% ee. The enantiomeric excess was determined by HPLC on on Venusil Chiral OD-H with hexane/*i*-PrOH (90:10) as the eluent. Flow rate: 1.0 mL/min, λ = 254 nm: t_{minor} = 31.12 min, t_{major} = 23.62 min. ^{1}H NMR (300 MHz, CDCl3) δ 7.50–7.40 (m, 3H), 7.33 (dd, J = 6.7, 2.8 Hz, 2H), 7.29–7.23 (m, 2H), 7.23–7.16 (m, 1H), 7.14–7.06 (m, 1H), 6.55 (s, 1H), 5.79 (dd, J = 12.3, 6.2 Hz, 1H), 5.43 (d, 1H), 4.59 – 4.14 (m, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.88, 133.16, 130.51, 130.23, 129.95, 129.51,

129.38, 129.32, 128.94, 127.66, 127.19, 126.74, 126.72, 83.46, 63.29, 57.29, 44.53, 44.28, 13.97.ppm ^{19}F NMR (282 MHz, CDCl3): δ -163.19 ppm. MS (ACPI) m/z: 421.1 (M+1).

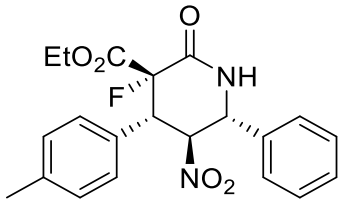
Ethyl 4-(4-bromophenyl)-3-fluoro-5-nitro-2-oxo-6-phenylpiperidine-3-carboxylate (4k):



4k

White solid, yield: 32 mg (68%), 3.5:1 dr, 93% ee. The enantiomeric excess was determined by HPLC on Venusil Chiral OD-H with hexane/*i*-PrOH (80:20) as the eluent. Flow rate: 0.6 mL/min, λ = 254nm: t_{minor} = 22.54 min, t_{major} = 13.57 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, J = 8.5, 5.5 Hz, 5H), 7.32 (dd, J = 6.7, 2.6 Hz, 2H), 7.08 (d, J = 8.3 Hz, 2H), 6.78 (s, 1H), 5.77 (dd, J = 12.4, 6.3 Hz, 1H), 5.41 (d, J = 6.5 Hz, 1H) , 4.54 – 4.08 (m, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.32, 133.09, 132.62, 129.78, 129.62, 129.31, 129.21, 128.66, 124.82, 87.90, 63.23, 60.37, 50.56, 50.31, 14.07.ppm ^{19}F NMR (282 MHz, $CDCl_3$): δ -164.83 ppm. MS (ACPI) m/z: 466.1 (M+1).

Ethyl 3-fluoro-5-nitro-2-oxo-6-phenyl-4-(p-tolyl)piperidine-3-carboxylate (4l):

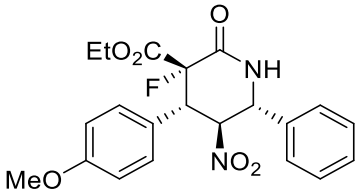


4l

White solid, yield: 22 mg (55%), 5:1 dr, 95% ee. The enantiomeric excess was determined by HPLC on Venusil Chiral OD-H with hexane/*i*-PrOH (85:15) as the eluent. Flow rate: 0.5 mL/min, λ = 254nm: t_{minor} = 13.38 min, t_{major} = 10.54 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.41 (m, 2H), 7.35–7.28 (m, 2H), 7.07 (s, 5H), 5.78 (dd, J = 12.4, 6.2 Hz, 1H), 5.39 (d, J = 5.8 Hz, 1H), 4.56– 4.11 (m, 3H) , 1.21 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.80, 133.53, 129.94, 129.65, 129.17, 128.42, 127.81, 127.24, 118.50, 83.76,

62.96, 57.18, 44.37, 44.12, 21.06, 13.92 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -164.85 ppm MS (ACPI) m/z: 401.1 (M+1).

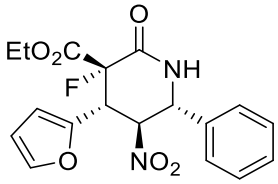
Ethyl 3-fluoro-4-(4-methoxyphenyl)-5-nitro-2-oxo-6-phenylpiperidine-3-carboxylate (4m):



4m

White solid, yield: 28 mg (69%), 3:1 dr, 91% ee. The enantiomeric excess was determined by HPLC on Venusil Chiral OD-H with hexane/*i*-PrOH (90:10) as the eluent. Flow rate: 1 mL/min, λ = 254nm: t_{minor} = 45.22 min, t_{major} = 39.45 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (dd, J = 6.5, 3.6 Hz, 2H, 7.39 – 7.29 (m, 2H), 7.21 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 6.31 (s, 1H), 5.32 (dd, J = 12.2, 10.1 Hz, 1H), 5.18 (dd, J = 9.9, 2.7 Hz, 1H), 4.47 – 4.10 (m, 3H), 3.76 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.65, 163.18, 162.88, 160.42, 135.43, 130.51, 129.83, 127.19, 127.00, 121.58, 114.55, 88.36, 63.13, 60.85, 55.37, 49.95, 49.70, 14.17. ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -163.30.MS (ACPI) m/z : 417.1 (M+1)..

Ethyl 3-fluoro-4-(furan-2-yl)-5-nitro-2-oxo-6-phenylpiperidine-3-carboxylate (4n):

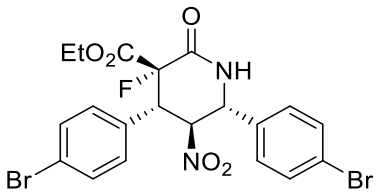


4n

White solid, yield: 23 mg (62%), 3.5:1 dr, 99% ee. The enantiomeric excess was determined by HPLC on Venusil Chiral OD-H with hexane/i-PrOH (95:5) as the eluent. Flow rate: 1 mL/min, λ = 254nm: t_{minor} = 24.66 min, t_{major} = 22.90 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (dd, J = 8.3, 4.9 Hz, 4H), 7.36–7.27 (m, 2H), 6.40 (s, 1H), 6.33 – 6.29 (m, 1H), 6.23 (d, J = 3.3 Hz, 1H), 5.76 (dd, J = 11.8, 6.1 Hz, 1H), 5.40 (d, J = 5.8 Hz, 1H), 4.65 (dd, J = 29.2, 11.9 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.55, 201.27, 143.95, 143.40, 134.78, 130.46, 129.68, 126.89, 110.81, 86.64, 73.17, 63.32, 60.41, 44.36, 41.60 ppm.

^{19}F NMR (282 MHz, $CDCl_3$): δ -161.22, -170.03. MS (ACPI) m/z: 377.1 (M+1). HRMS (ESI): calcd. for $C_{18}H_{17}FN_2O_6[M+Na]^+$ 399.0968; found 399.0978.

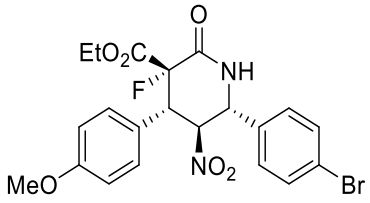
Ethyl 4,6-bis(4-bromophenyl)-3-fluoro-5-nitro-2-oxopiperidine-3-carboxylate (4o):



4o

White solid, yield: 36 mg (67%), 4:1 dr, 99% ee. The enantiomeric excess was determined by HPLC on Venusil Chiral OD-H with hexane/*i*-PrOH (90:10) as the eluent. Flow rate: 1 mL/min, λ = 254nm: t_{minor} = 49.20min, t_{major} =22.47 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 7.29 – 7.01 (m, 5H), 5.32 – 5.21 (m, 1H), 5.16 (dd, J = 8.7, 3.8 Hz, 1H), 4.35 (dd, J = 30.4, 12.2 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.78, 164.57, 162.66, 133.87, 132.91, 132.49, 132.30, 132.24, 130.70, 130.21, 128.80, 128.43, 124.82, 124.03, 87.53, 63.24, 60.05, 49.80, 49.55, 13.93. ^{19}F NMR (282 MHz, $CDCl_3$): δ -163.05, -164.70 ppm. MS (ACPI) m/z: 545.1 (M+1). HRMS (ESI): calcd. for $C_{20}H_{17}Br_2FN_2O_5[M+Na]^+$ 564.9386; found 564.9384.

Ethyl 6-(4-bromophenyl)-3-fluoro-4-(4-methoxyphenyl)-5-nitro-2-oxopiperidine-3-carboxylate (4p):

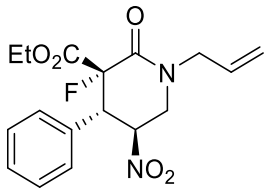


4p

Colorless oil, yield: 28 mg (65%), 3:1 dr, 98% ee. The enantiomeric excess was determined by HPLC on Venusil Chiral OD-H with hexane/*i*-PrOH (90:10) as the eluent. Flow rate: 1 mL/min, λ = 254nm: t_{minor} = 30.16 min, t_{major} = 20.45 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.35 (s, 1H) , 5.76 (dd, J = 12.4, 6.3 Hz, 1H), 5.38 (dd, J = 6.3, 3.1 Hz, 1H), 4.47 – 4.15 (m, 3H), 1.24 (t, J =

7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.22, 132.91, 132.55, 132.47, 130.34, 129.80, 129.61, 128.80, 128.45, 124.61, 121.23, 118.54, 114.41, 87.97, 63.02, 60.12, 55.20, 49.71, 49.47, 13.97. ^{19}F NMR (282 MHz, $CDCl_3$): δ -165.28 ppm. MS (ACPI) m/z: 435.1 (M+1).

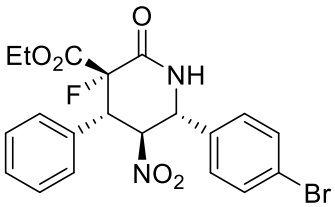
Ethyl 1-allyl-3-fluoro-5-nitro-2-oxo-4-phenylpiperidine-3-carboxylate (4q):



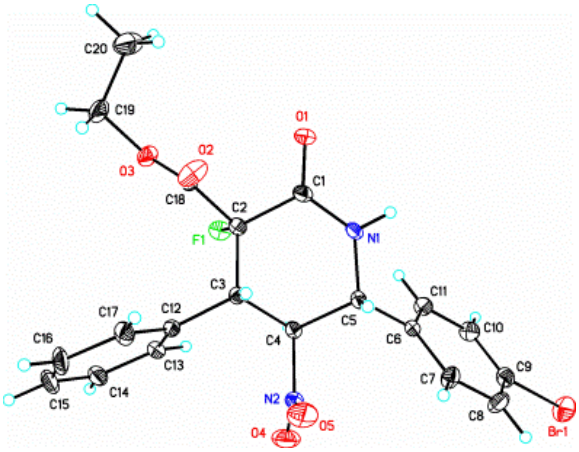
4q

Colorless oil, 20 mg (57%), 5:1 dr, 92% ee. The enantiomeric excess was determined by HPLC on Regis (R,R)-Whelk-O1 with hexane/*i*-PrOH (80:20) as the eluent. Flow rate: 1 mL/min, λ = 254nm: t_{minor} = 12.34 min, t_{major} = 9.52 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62–7.03 (m, 5H), 5.79 (ddd, J = 12.5, 10.4, 5.3 Hz, 1H), 5.45 (ddd, J = 11.4, 8.4, 6.2 Hz, 1H), 5.32 (dd, J = 21.1, 5.5 Hz, 2H), 4.43 – 4.11 (m, 3H), 4.10 – 3.82 (m, 4H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.16, 130.95, 130.37, 129.27, 129.19, 129.01, 128.10, 120.15, 81.29, 62.81, 49.64, 49.41, 48.39, 13.87. ^{19}F NMR (282 MHz, $CDCl_3$): δ -158.92, -165.17 ppm. MS (ACPI) m/z: 351.1 (M+1). HRMS (ESI): calcd. for $C_{17}H_{19}FN_2O_5[M+H]^+$ 351.1356; found 351.1354.

X-Ray Report of 4c:



4c



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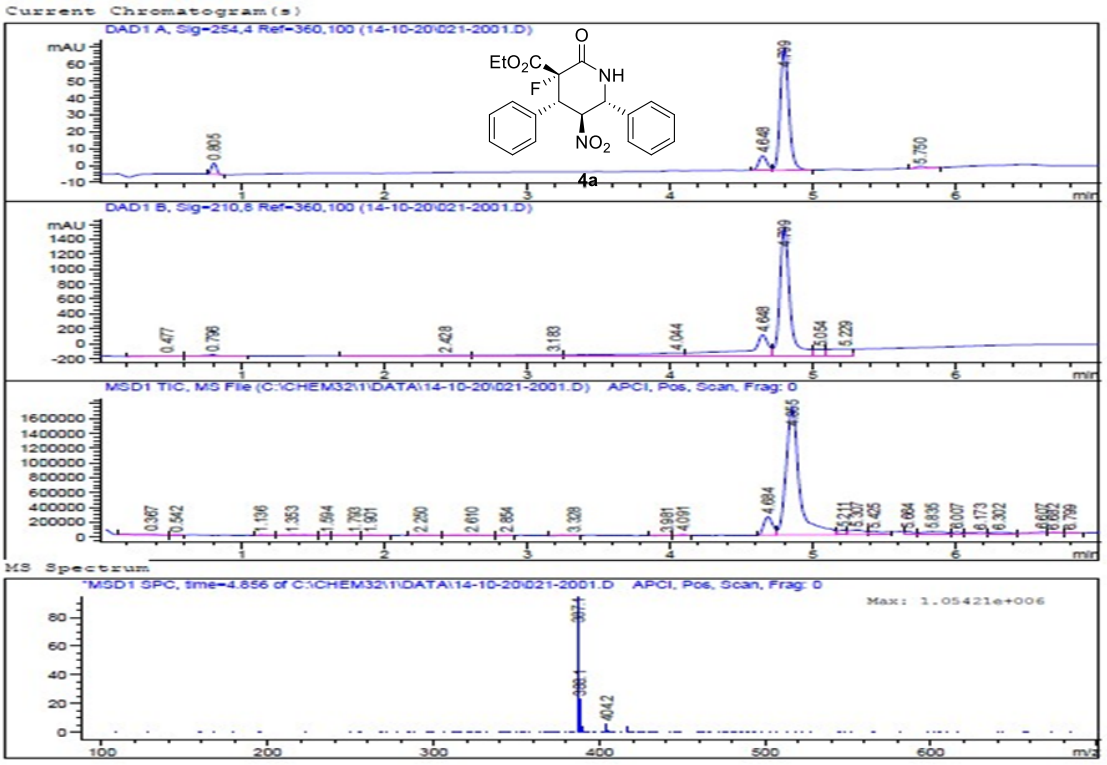
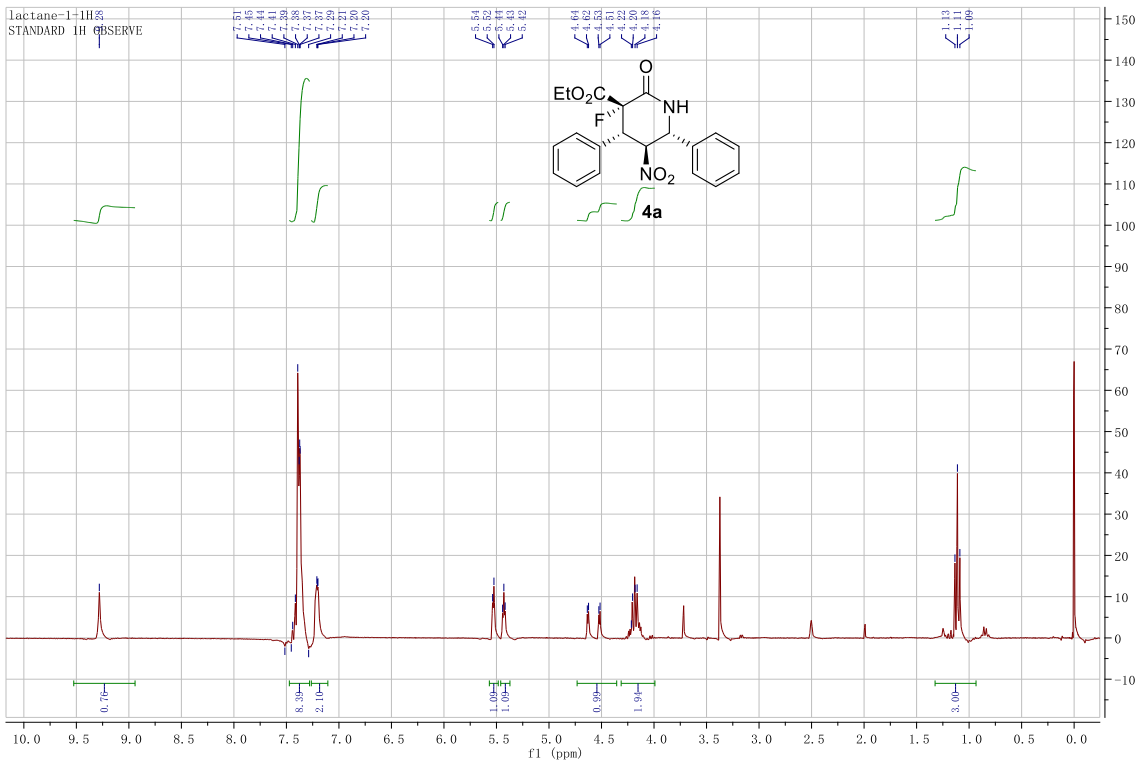
Cell	a=22.744(3) b=7.5503(4) c=16.0634(18) α=90 β=131.075(18) γ=90	
Temperature	173K	
	Calculated	Reported
Volumn	2079.5(7)	2079.5(6)
Space group	C 2	C 1 2 1
Hall group	C 2y	C 2y
Moiety formula	C_{20} H_{18} Br F N_2 O_5	C_{20} H_{18} Br F N_2 O_5
Sum formula	C_{20} H_{18} Br F N_2 O_5	C_{20} H_{18} Br F N_2 O_5
Mr	465.26	465.27
Dx,g cm^{-3}	1.486	1.486
Z	4	4
Mu (mm^{-1})	3.073	3.073
F000	944.0	944.0
F000'	944.14	
h,k,lmax	27,9,19	27,9,19
Nref	4027[2174]	2972
Tmin,Tmax	0.541,0.782	0.398,1.000
Tmin'	0.232	

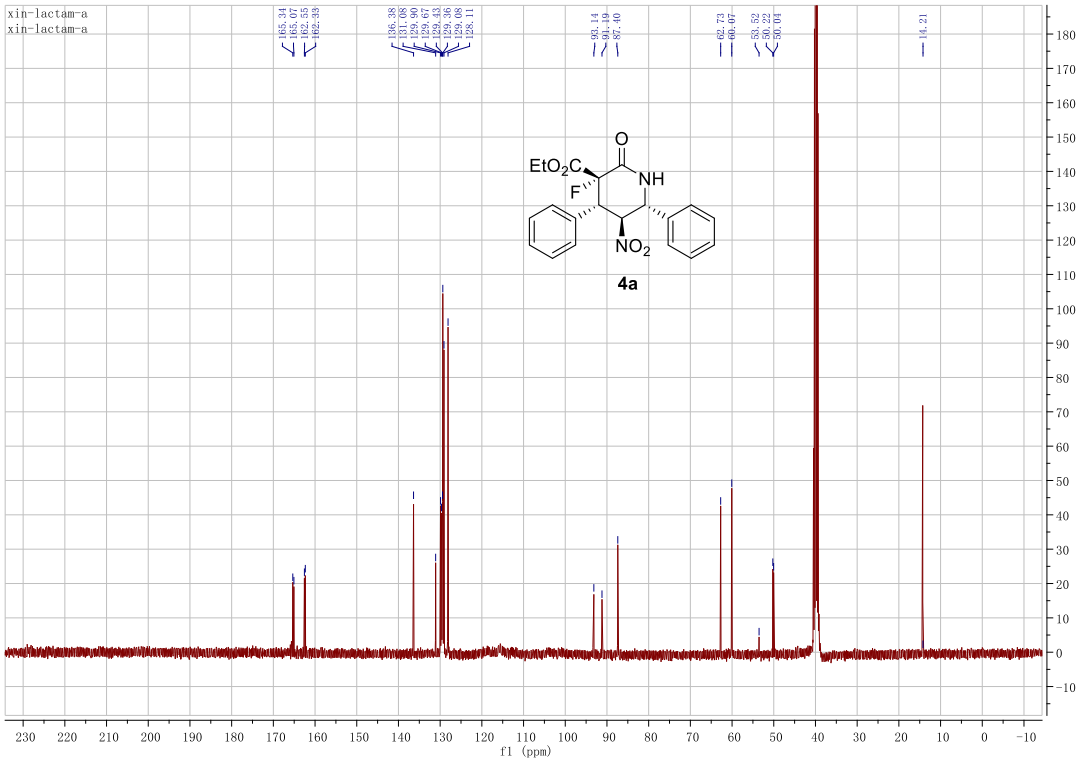
Data completeness= 1.37/0.74 Theta(max)= 71.104
R(reflections)= 0.0511(2872) wR2(reflections)= 0.1329(2972)
S = 1.079 Npar= 264

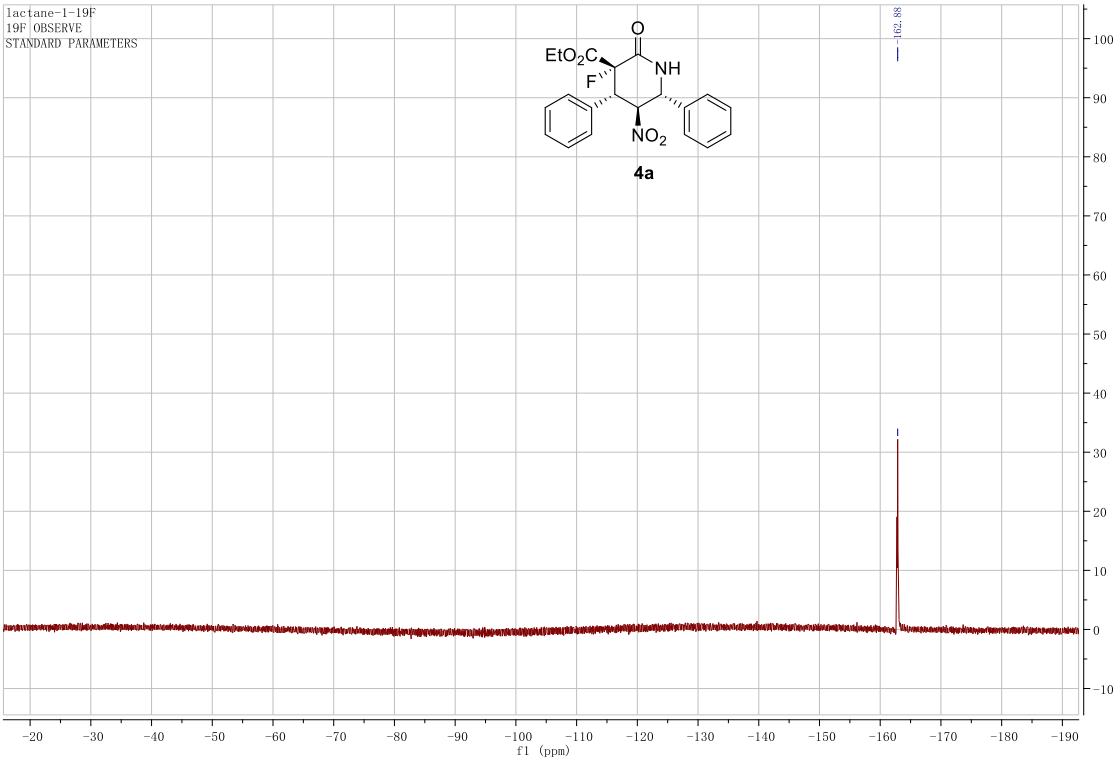
Crystallographic data (excluding structural factors) for compound **4c** also has been deposited at the Cambridge Crystallographic Data Centre under the deposition number CCDC 1043112.

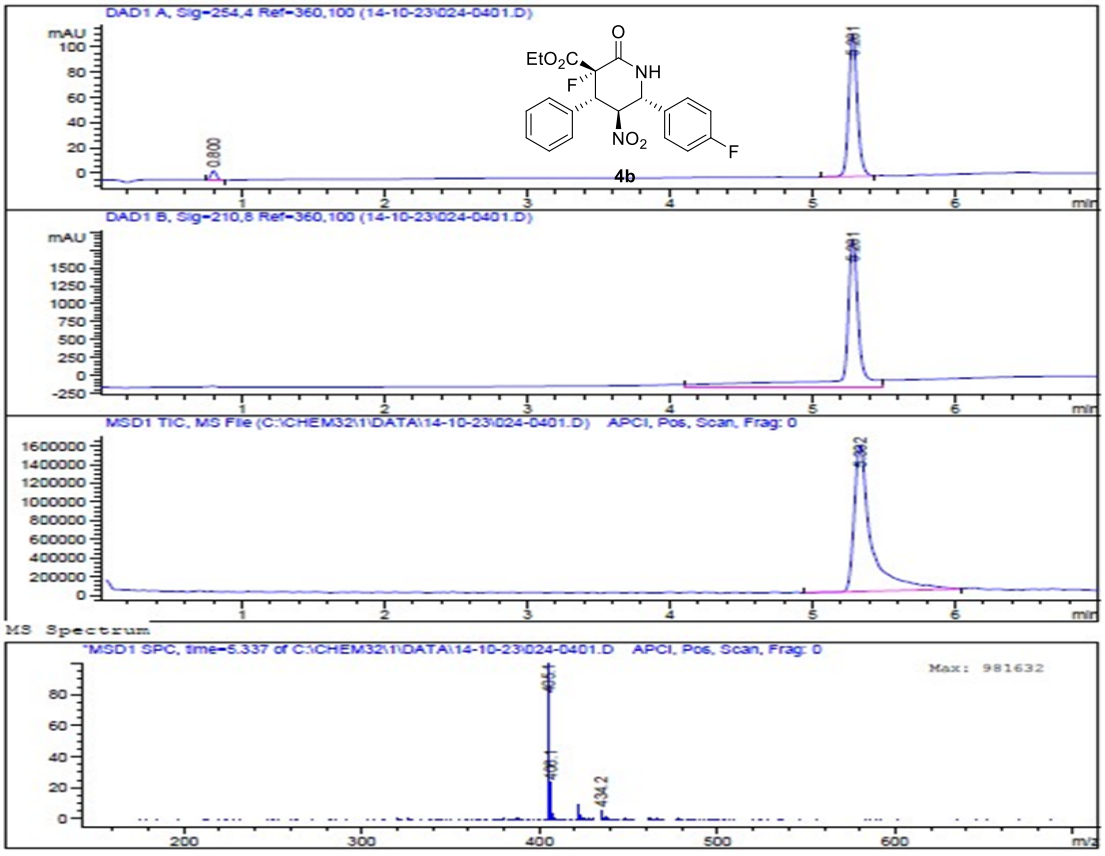
LC-MS, ^{1}H, ^{13}C, ^{19}F NMR Spectra of Products:

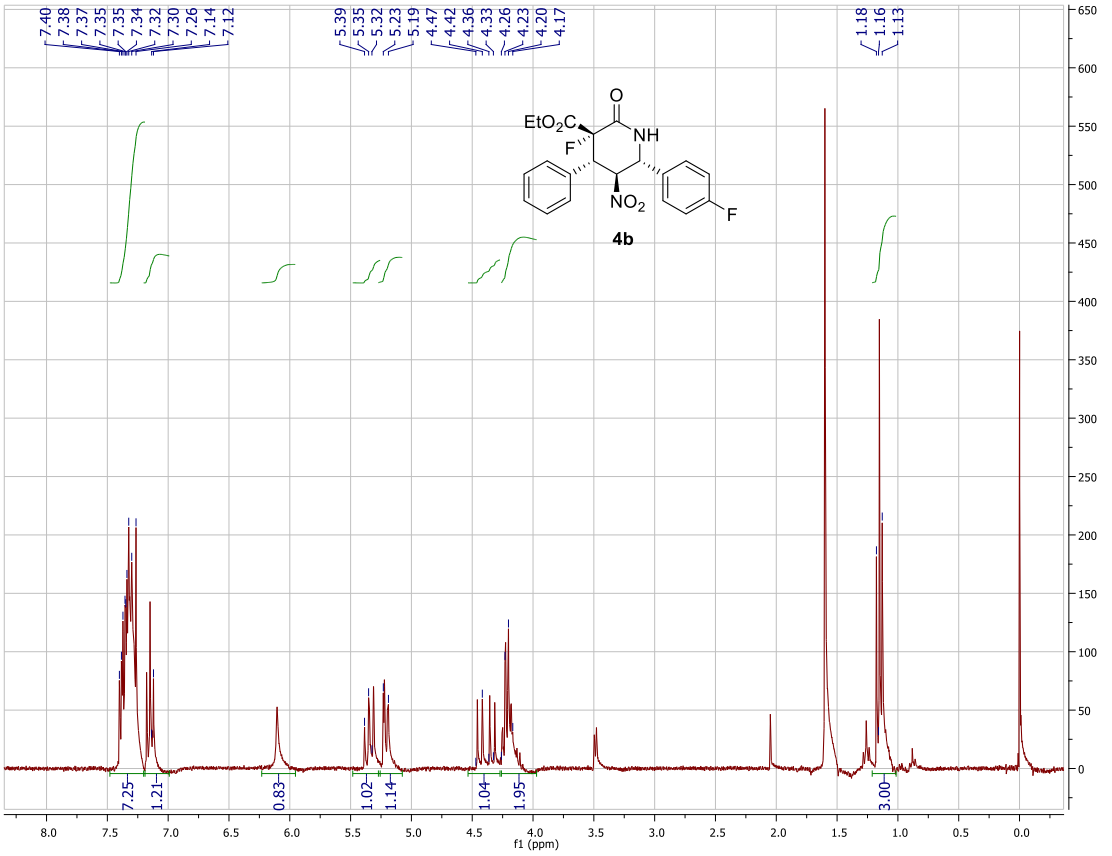


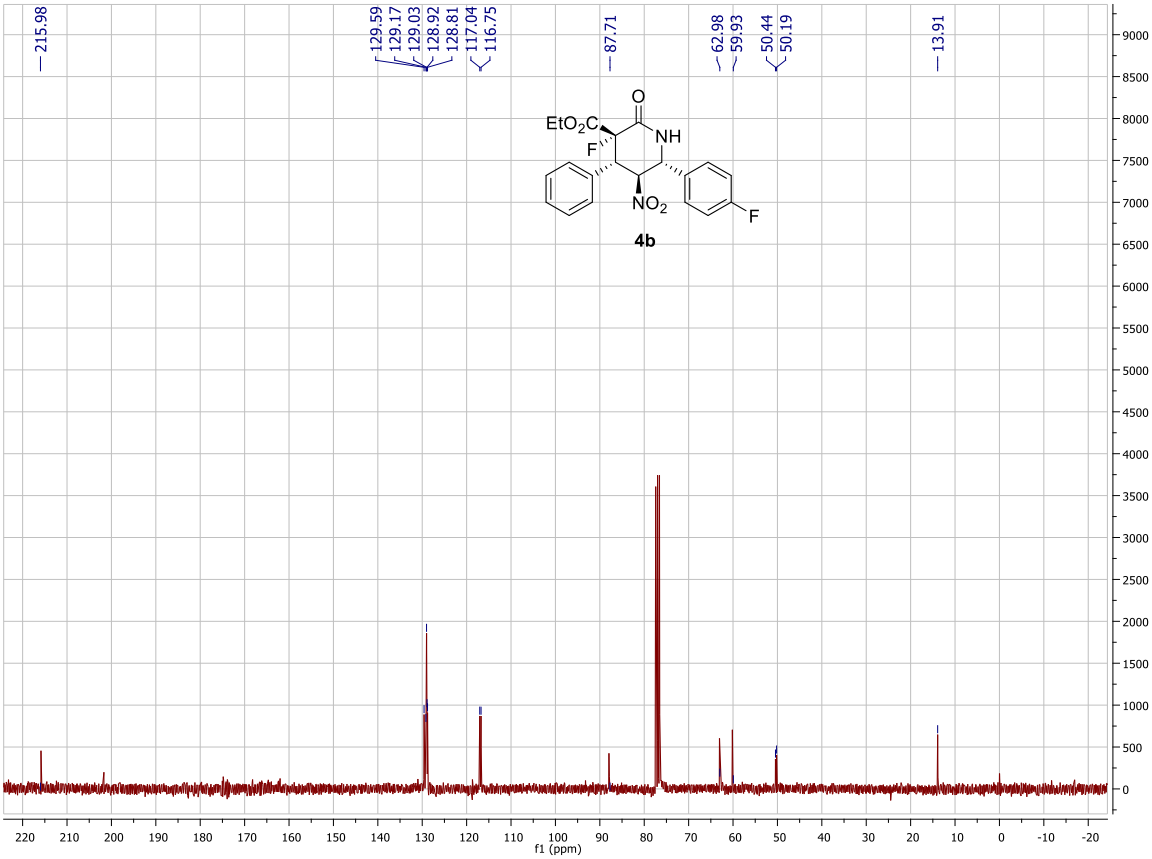


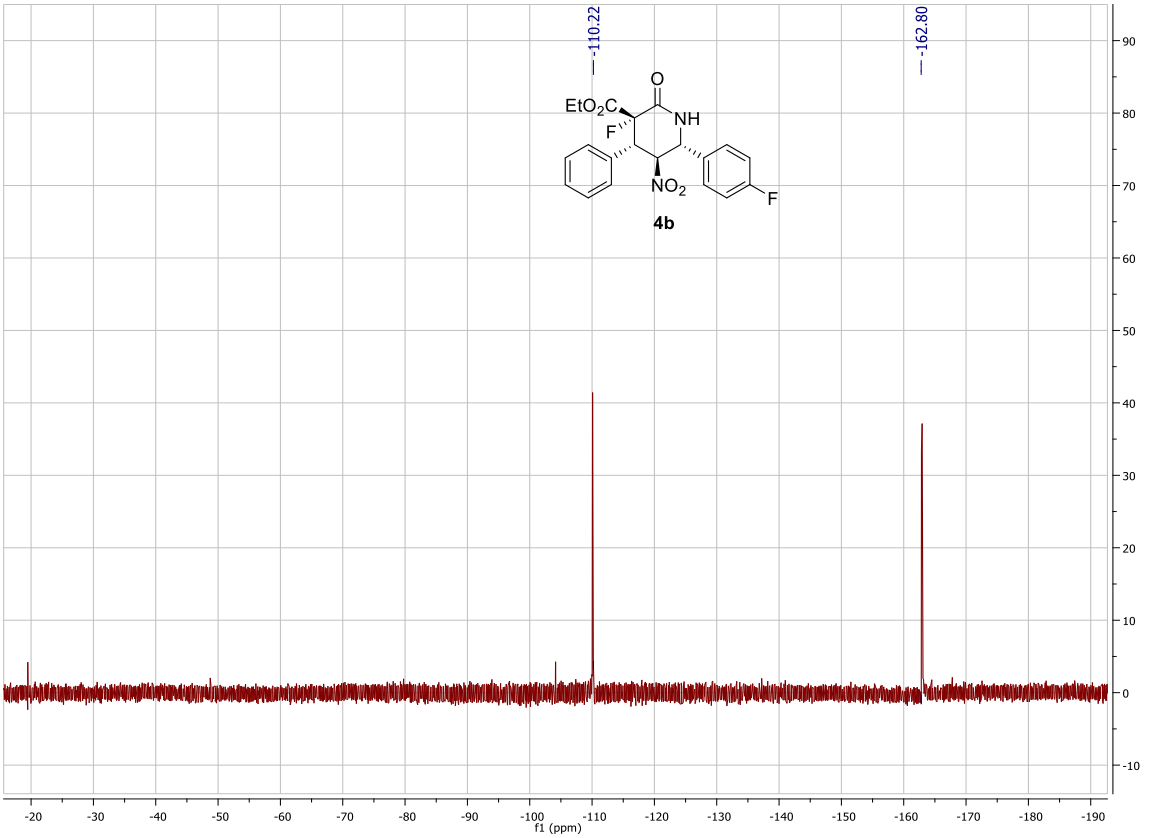

xin-lactam-a
xin-lactam-a
165.34
165.07
162.55
162.39
138.38
131.08
129.90
129.67
129.43
129.06
128.08
128.11
93.14
91.49
87.40
62.73
60.07
53.52
50.22
50.04
14.21
EtO2C
F
O
NH
NO2
4a
f1 (ppm)

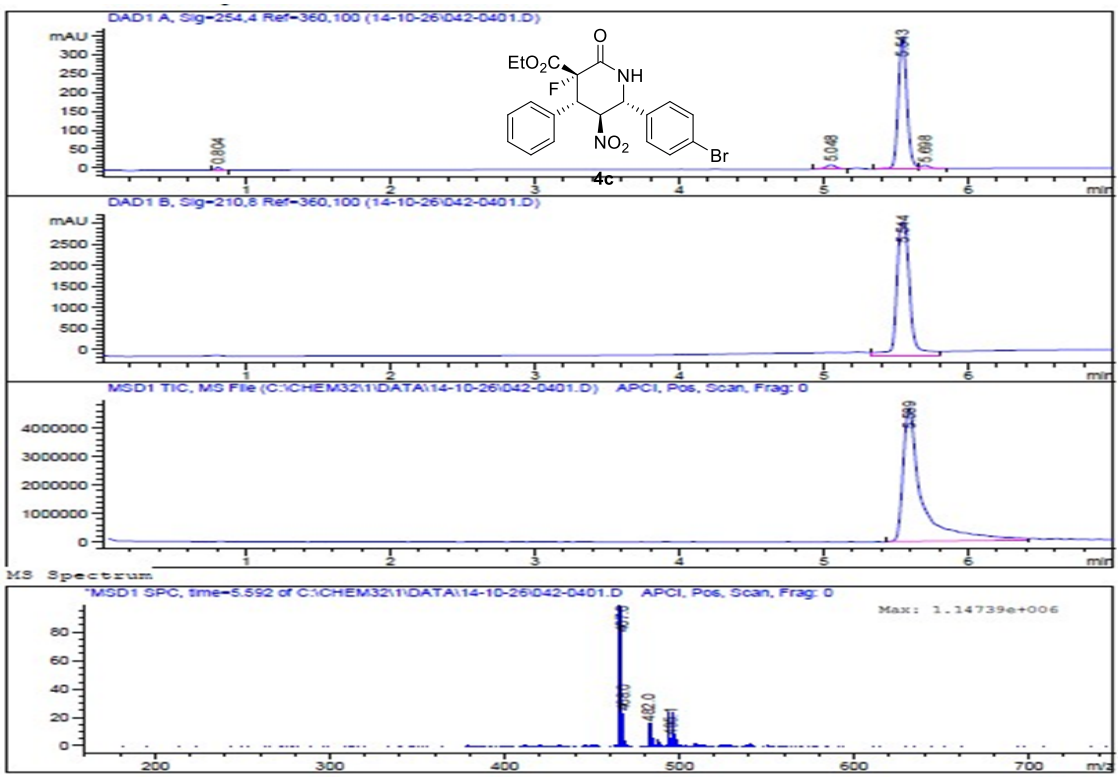

lactane-1-19F
19F OBSERVE
STANDARD PARAMETERS
-162.88
EtO2C
F
O
NH
NO2
4a
f1 (ppm)

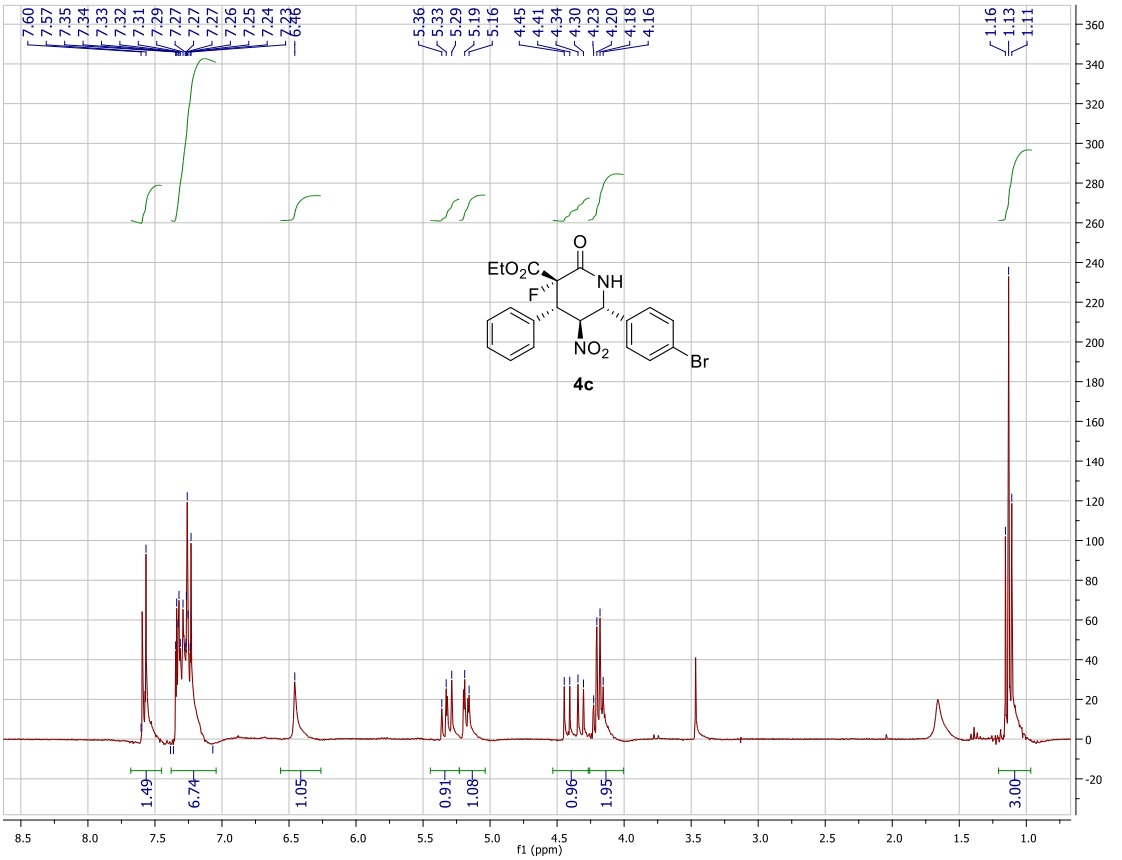

DAD1 A, Sig=254,4 Ref=360,100 (14-10-23\024-0401.D)
mAU
min
DAD1 B, Sig=210,8 Ref=360,100 (14-10-23\024-0401.D)
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-10-23\024-0401.D) APCI, Pos, Scan, Frag: 0
MS Spectrum
MSD1 SPC, time=5.337 of C:\CHEM32\1\DATA\14-10-23\024-0401.D APCI, Pos, Scan, Frag: 0
Max: 981632
4b

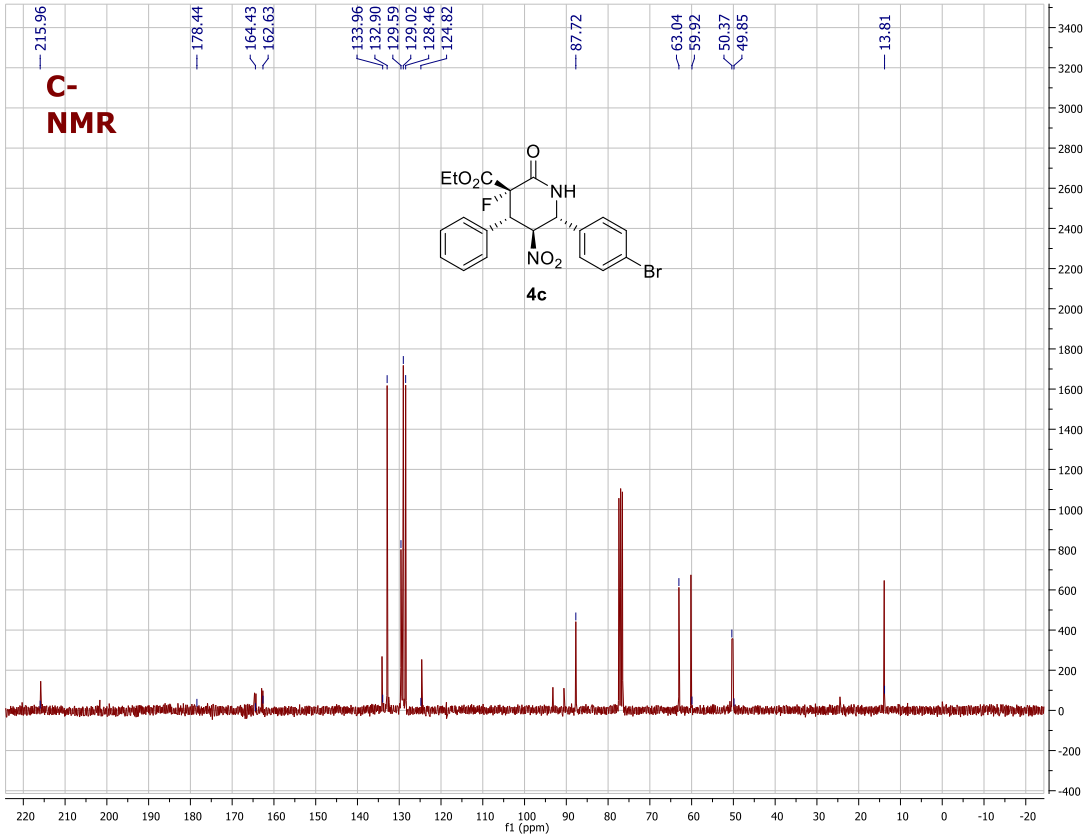

4b
f1 (ppm)

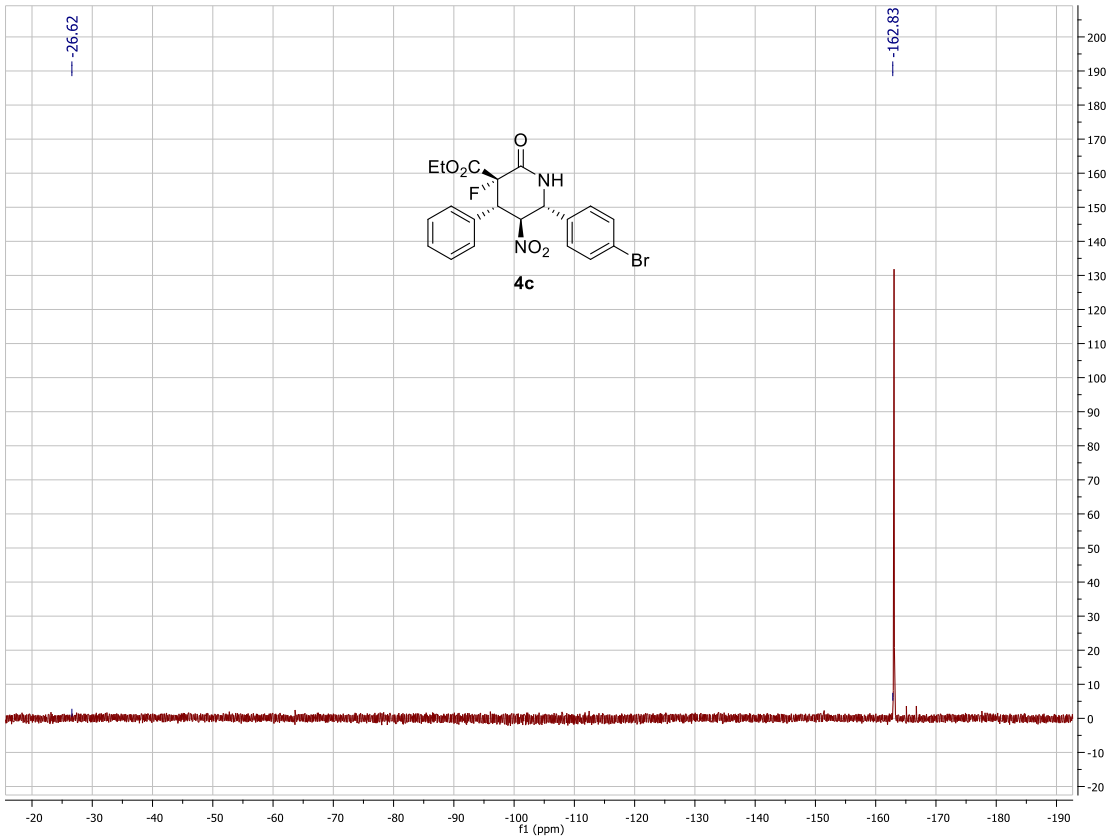

215.98
129.59
129.17
129.03
128.92
128.81
117.04
116.75
87.71
62.98
59.93
50.44
50.19
13.91
EtO2C
F
O
NH
NO2
F
4b
f1 (ppm)

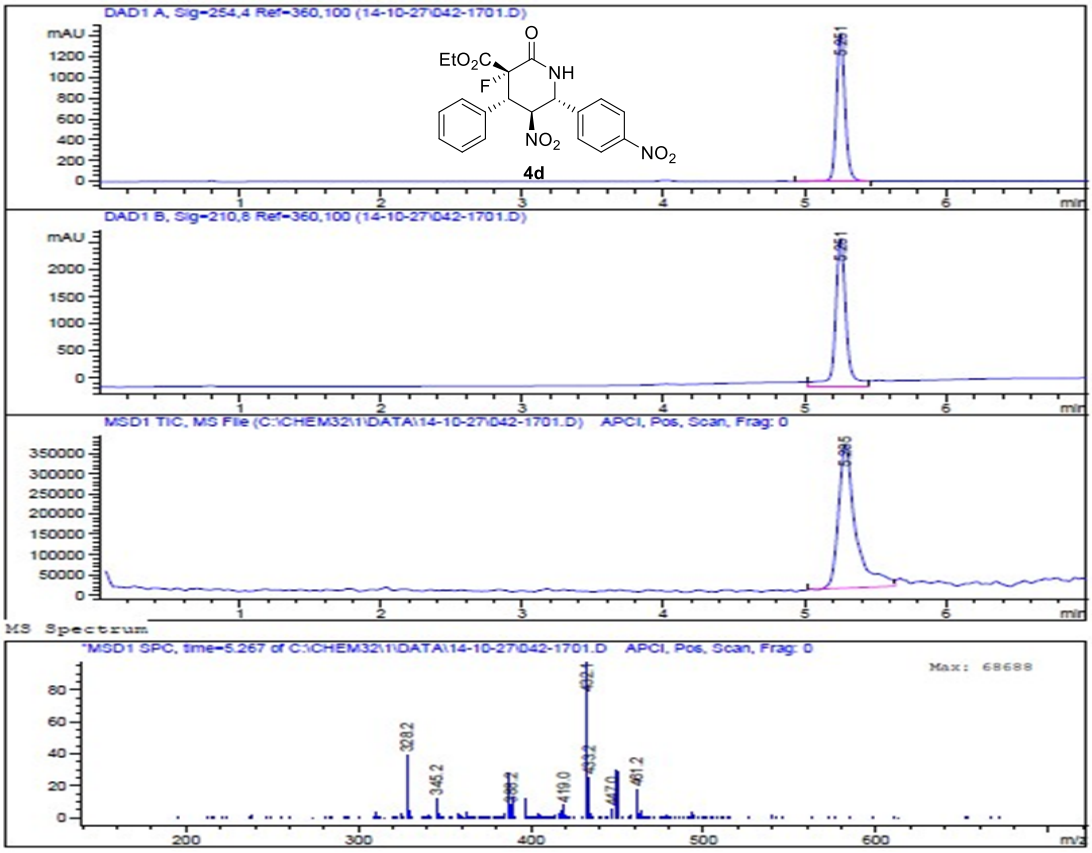

-110.22
-162.80
EtO2C
F
O
NH
NO2
F
4b
f1 (ppm)

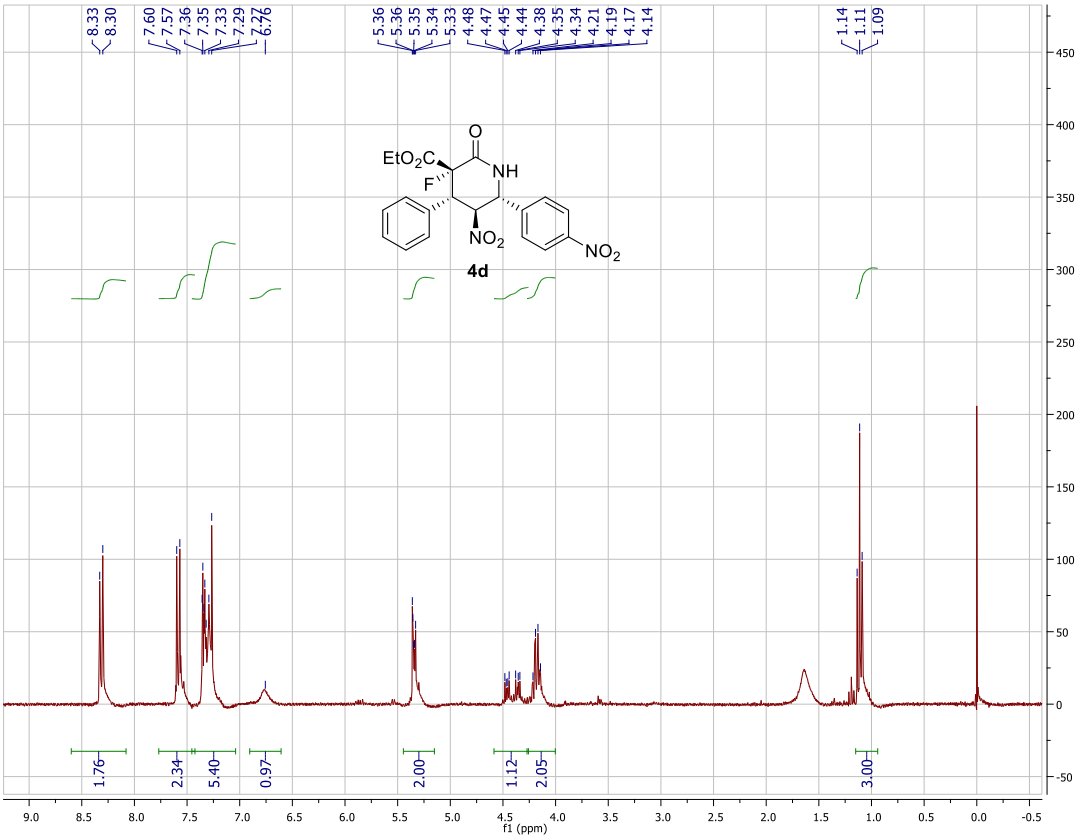

DAD1 A, Sig=254,4 Ref=360,100 (14-10-26\042-0401.D)
mAU
min
DAD1 B, Sig=210,8 Ref=360,100 (14-10-26\042-0401.D)
mAU
min
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-10-26\042-0401.D) APCI, Pos, Scan, Frag: 0
min
MS Spectrum
*MSD1 SPC, time=5.592 of C:\CHEM32\1\DATA\14-10-26\042-0401.D APCI, Pos, Scan, Frag: 0
Max: 1.14739e+006
m/z
EtO2C
F
O
NH
NO2
Br
4c

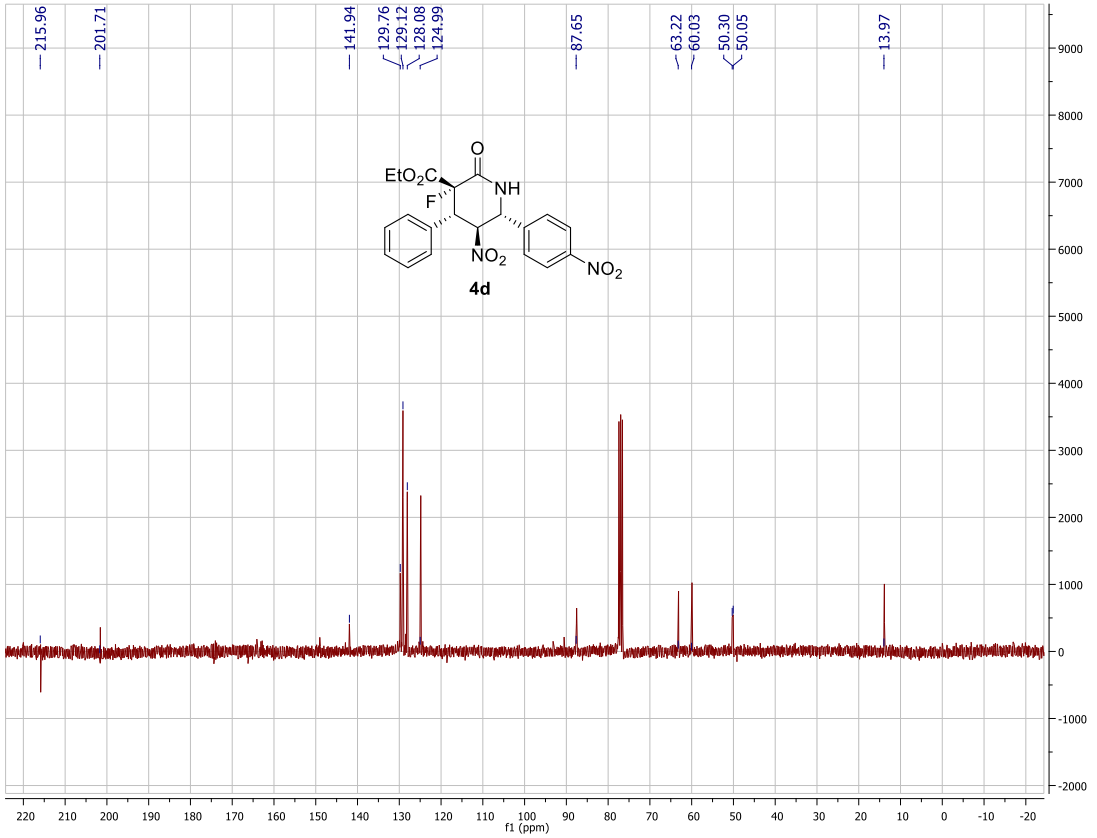

7.60
7.57
7.35
7.34
7.33
7.32
7.31
7.29
7.27
7.27
7.27
7.26
7.25
7.24
7.23
6.46
5.36
5.33
5.29
5.19
5.16
4.45
4.41
4.34
4.30
4.23
4.20
4.18
4.16
1.16
1.13
1.11
EtO2C
F
O
NH
NO2
Br
4c
1.49
6.74
1.05
0.91
1.08
0.96
1.95
3.00
f1 (ppm)

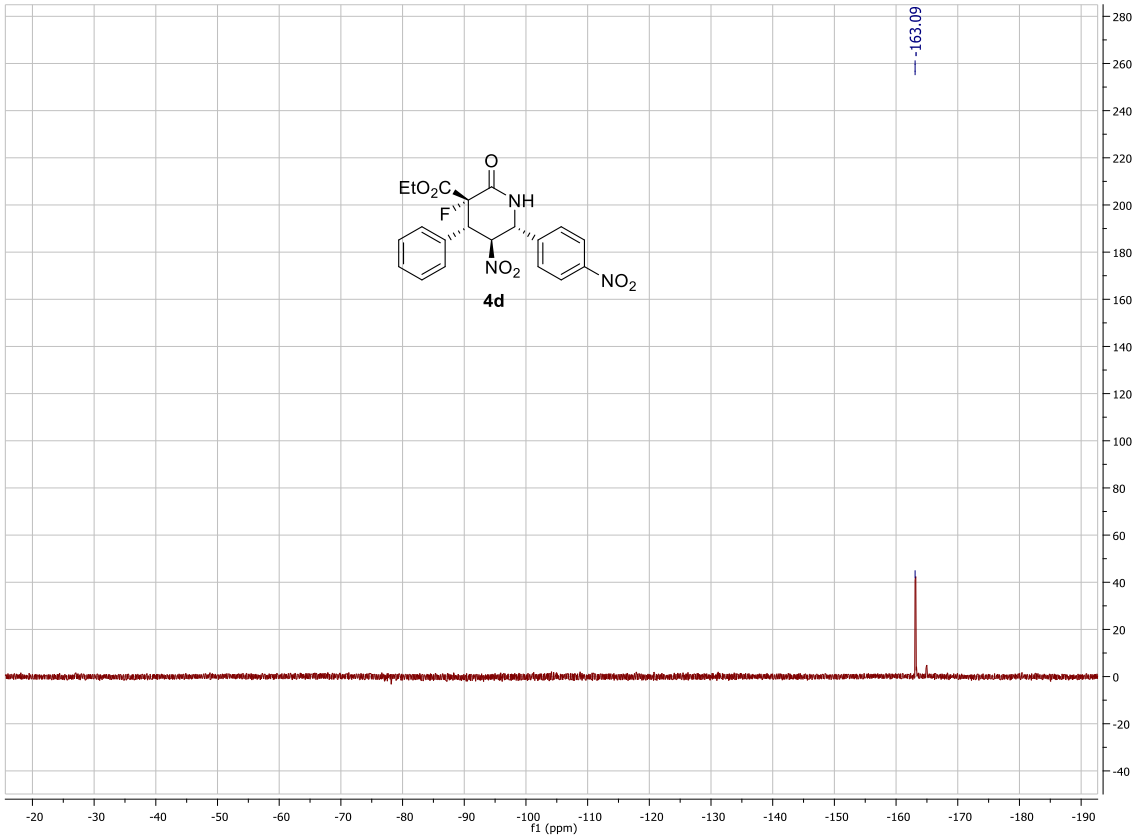

C-
NMR
215.96
178.44
164.43
162.63
133.96
132.90
129.59
129.02
128.46
124.82
87.72
63.04
59.92
50.37
49.85
13.81
EtO2C
F
O
NH
NO2
Br
4c
f1 (ppm)

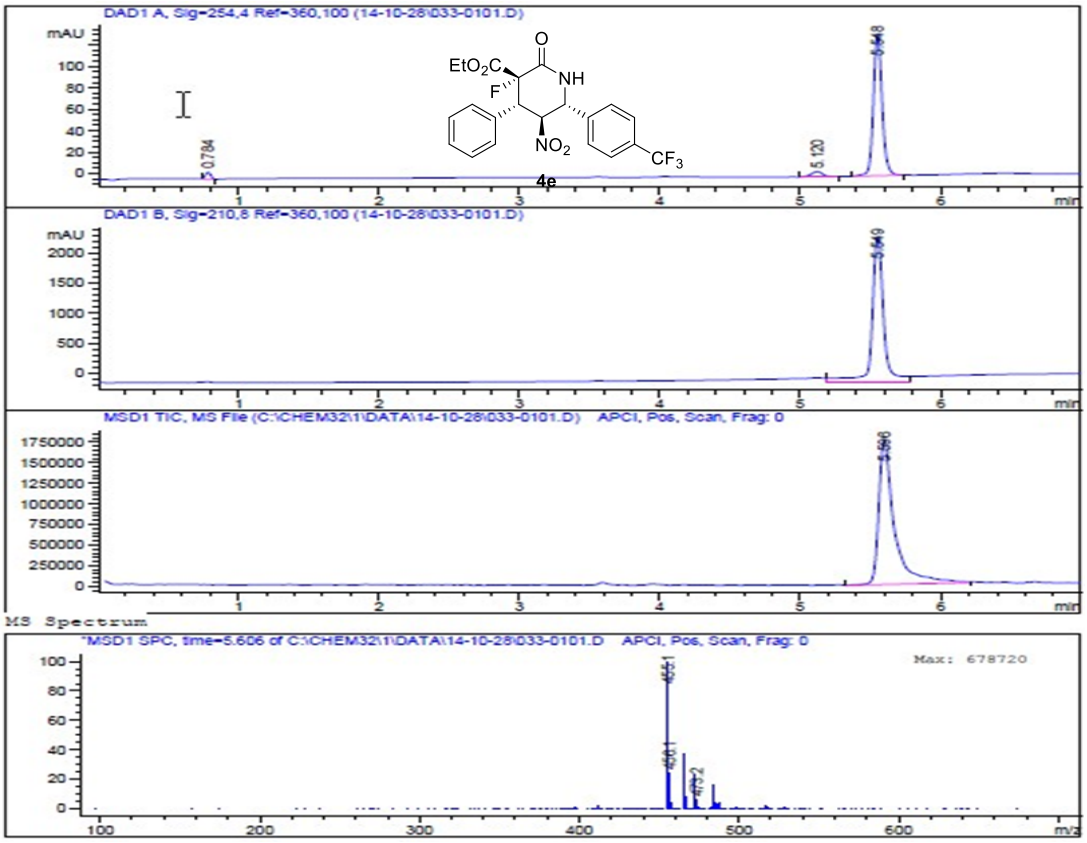

-26.62
-162.83
EtO2C
F
O
NH
NO2
Br
4c
f1 (ppm)

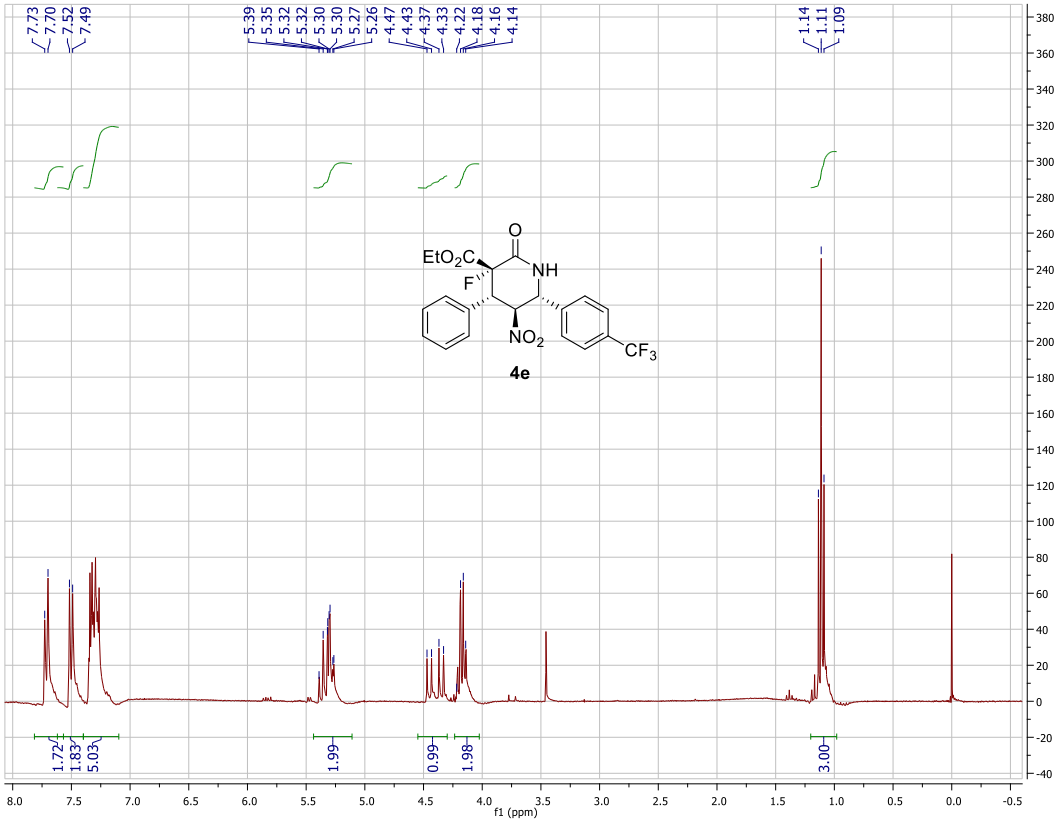

DAD1 A, Sig=254,4 Ref=360,100 (14-10-27\042-1701.D)
mAU
min
DAD1 B, Sig=210,8 Ref=360,100 (14-10-27\042-1701.D)
mAU
min
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-10-27\042-1701.D) APCI, Pos, Scan, Frag: 0
min
MS Spectrum
*MSD1 SPC, time=5.267 of C:\CHEM32\1\DATA\14-10-27\042-1701.D APCI, Pos, Scan, Frag: 0
Max: 68688
m/z
4d

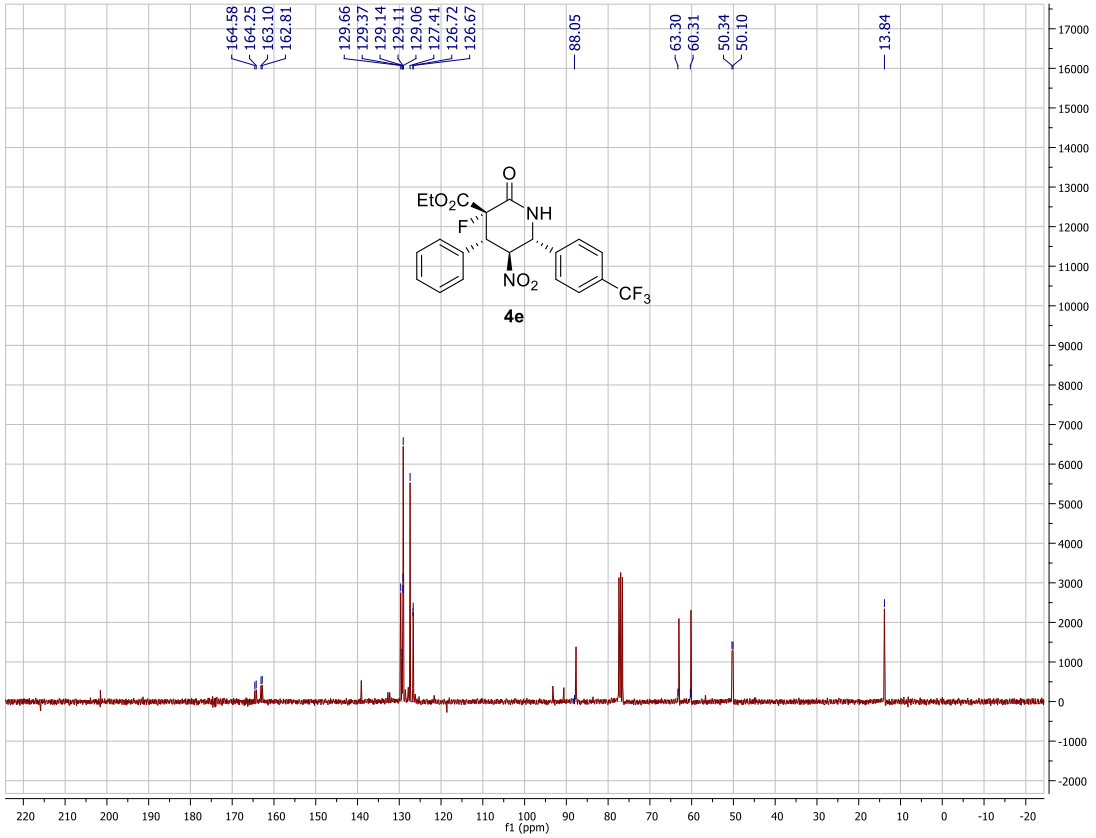

8.33
8.30
7.60
7.57
7.36
7.35
7.33
7.29
7.27
6.76
5.36
5.36
5.35
5.34
5.33
4.48
4.47
4.45
4.44
4.38
4.35
4.34
4.21
4.19
4.17
4.14
1.14
1.11
1.09
4d
1.76
2.34
5.40
0.97
2.00
1.12
2.05
3.00
f1 (ppm)

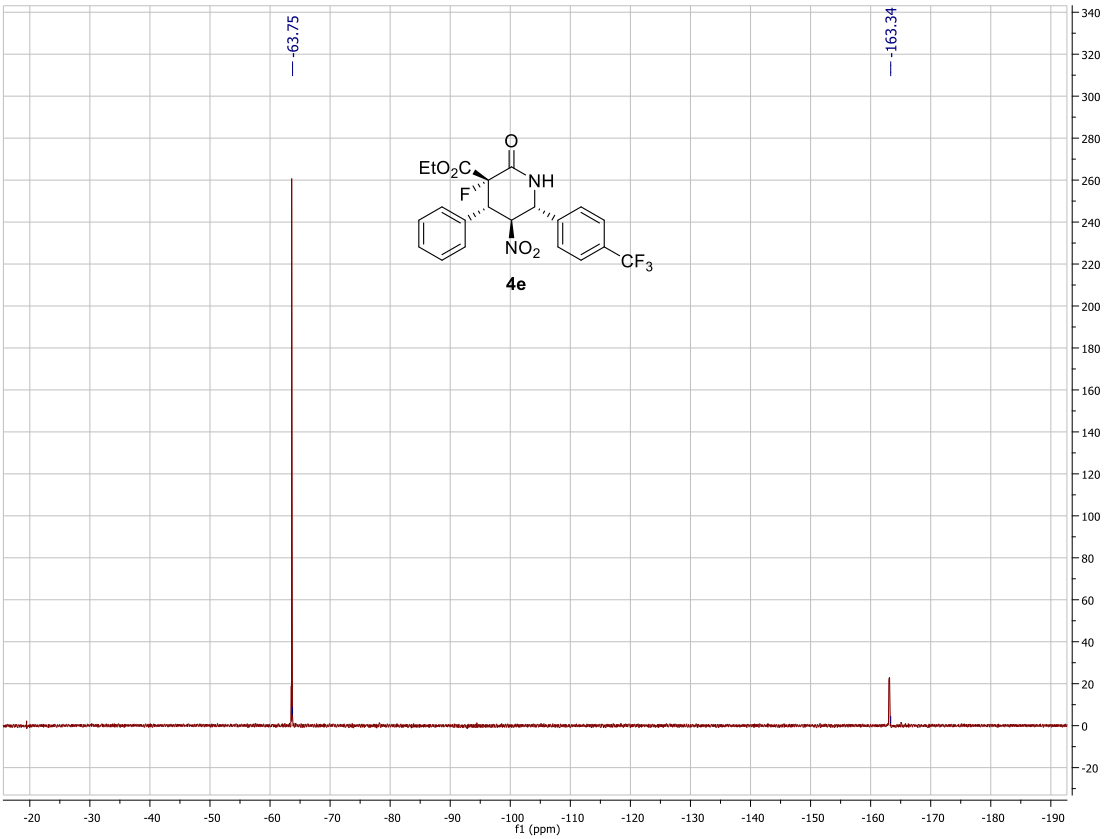

215.96
201.71
141.94
129.76
129.12
128.08
124.99
87.65
63.22
60.03
50.30
50.05
13.97
EtO2C
O
NH
F
NO2
NO2
4d
f1 (ppm)

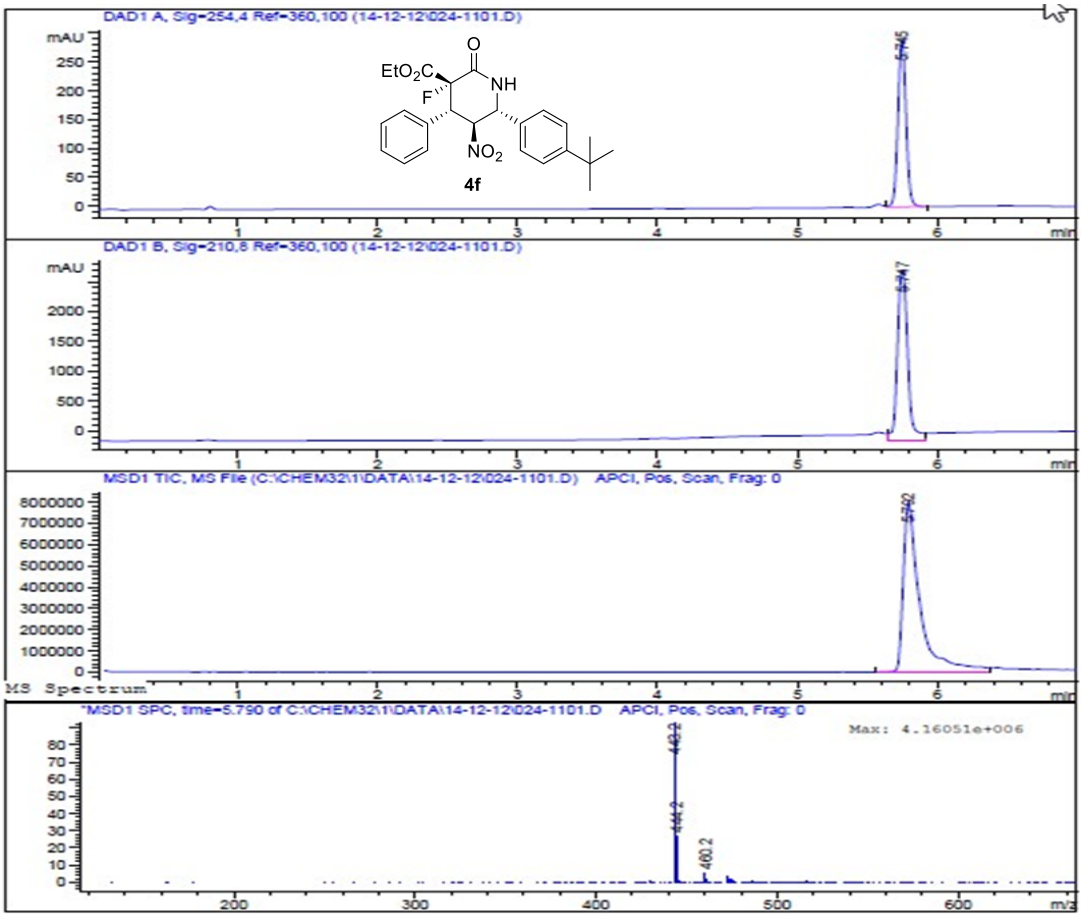

-163.09
EtO2C
O
NH
F
NO2
NO2
4d
f1 (ppm)


DAD1 A, Sig=254,4 Ref=360,100 (14-10-28\033-0101.D)
mAU
0.784
5.120
5.648
min
4e
DAD1 B, Sig=210,8 Ref=360,100 (14-10-28\033-0101.D)
mAU
5.649
min
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-10-28\033-0101.D) APCI, Pos, Scan, Frag: 0
5.606
min
MS Spectrum
*MSD1 SPC, time=5.606 of C:\CHEM32\1\DATA\14-10-28\033-0101.D APCI, Pos, Scan, Frag: 0
Max: 678720
466.1
m/z


7.73
7.70
7.52
7.49
5.39
5.35
5.32
5.32
5.30
5.30
5.27
5.26
4.47
4.43
4.37
4.33
4.22
4.18
4.16
4.14
1.14
1.11
1.09
4e
1.72
1.83
5.03
1.99
0.99
1.98
3.00
f1 (ppm)


164.58
164.25
163.10
162.81
129.66
129.37
129.14
129.11
129.06
127.41
126.72
126.67
88.05
63.30
60.31
50.34
50.10
13.84
O
EtO2C
NH
F
NO2
CF3
4e
f1 (ppm)


-63.75
-163.34
O
EtO2C
NH
F
NO2
CF3
4e
f1 (ppm)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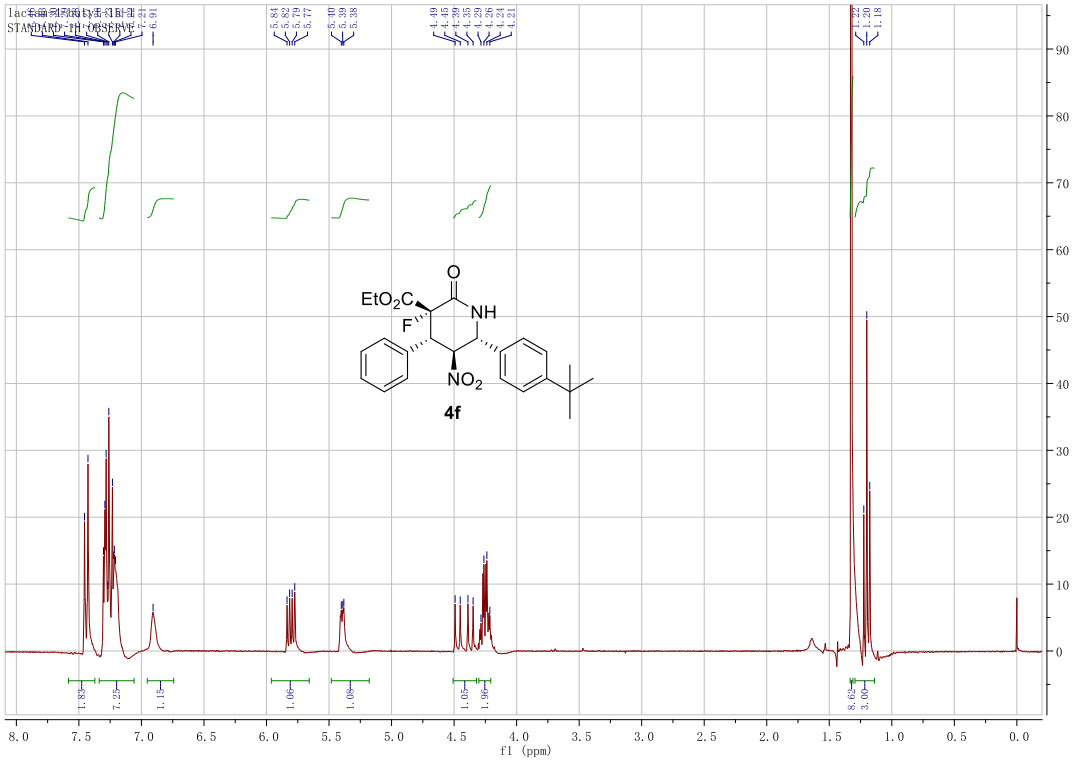
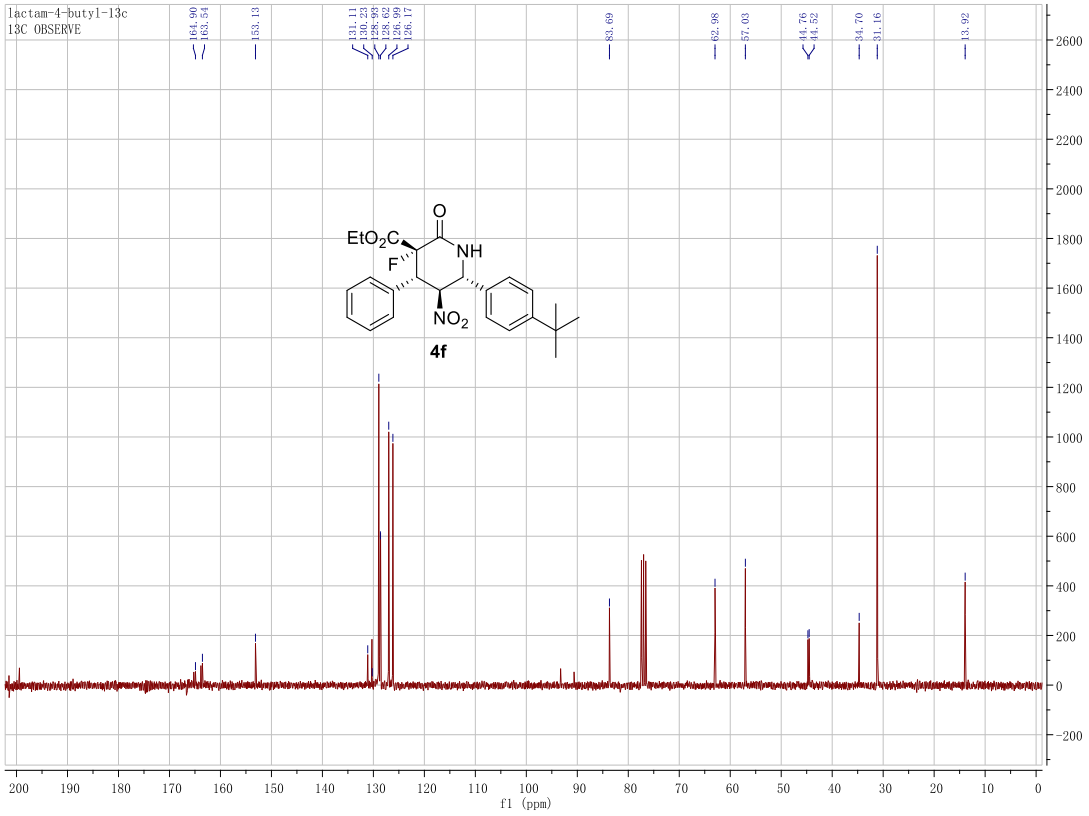
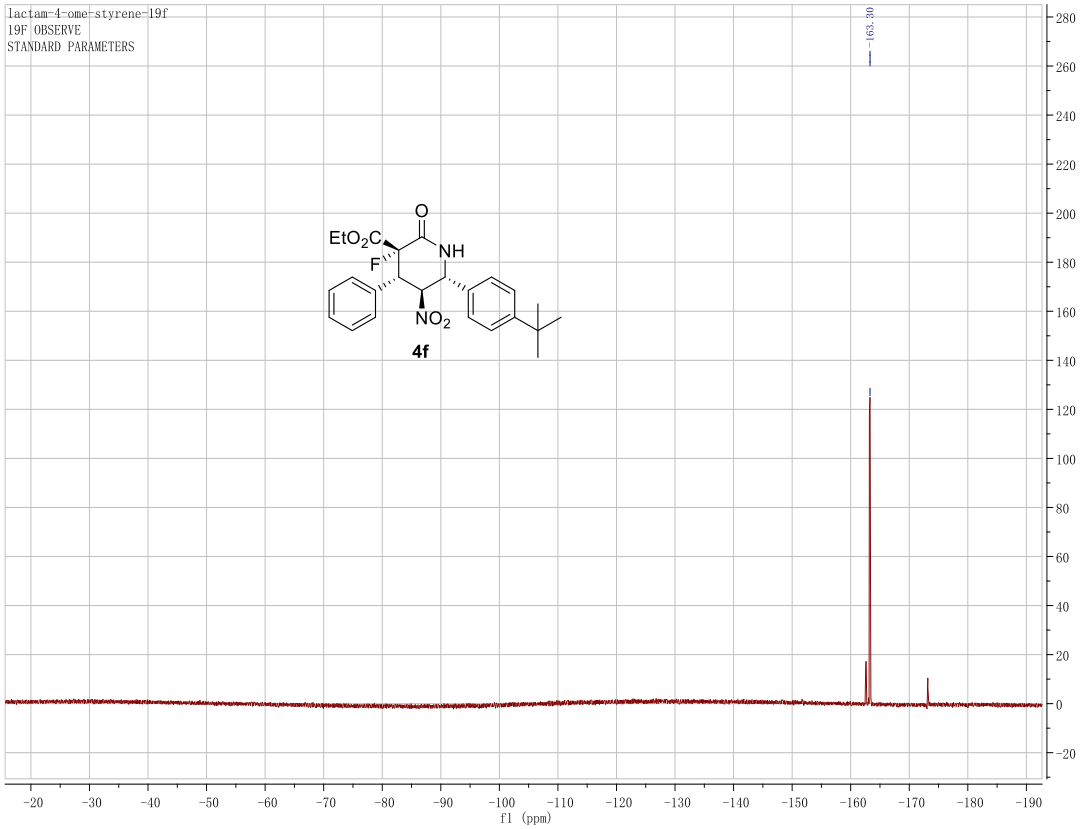
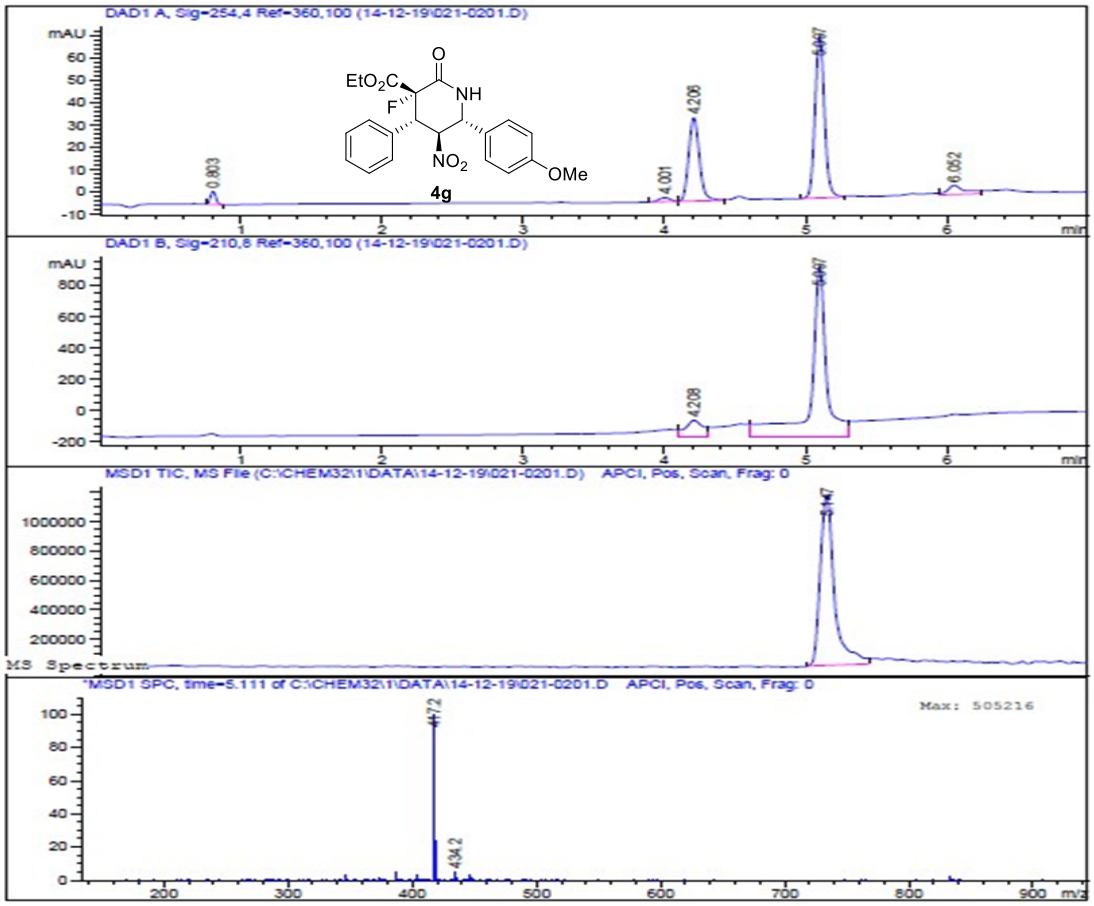
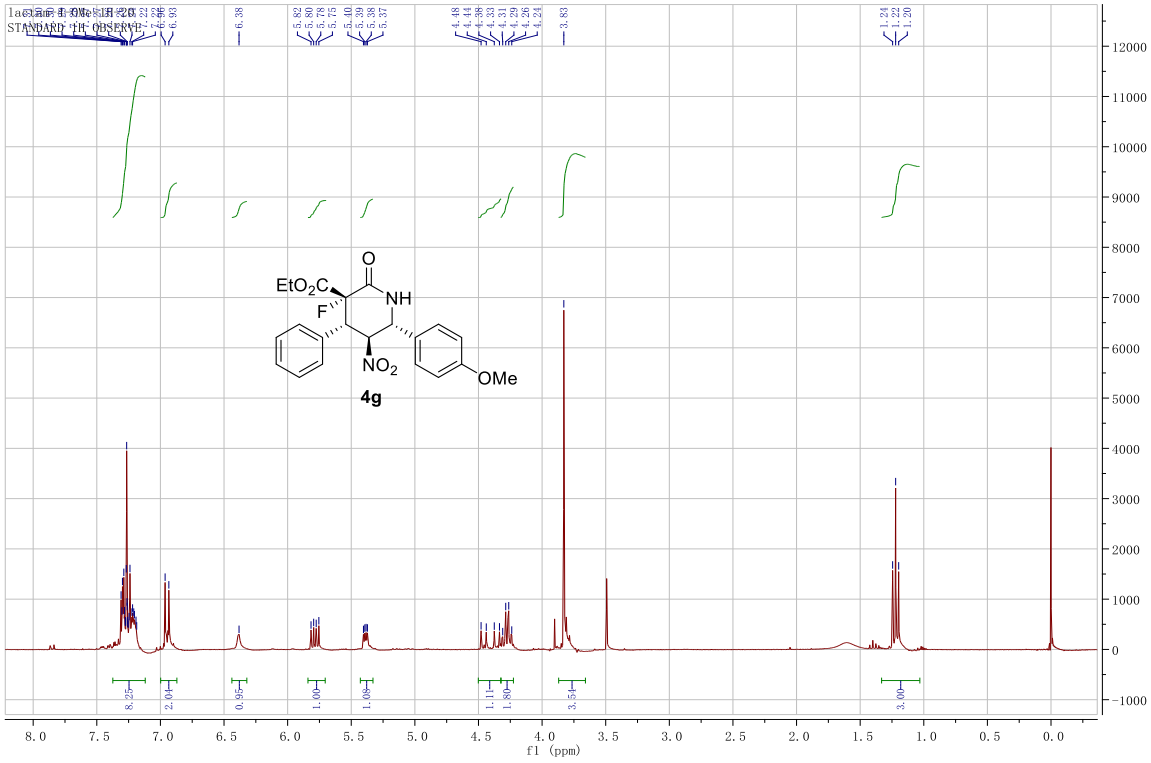
mAU
5.745
DAD1 B, Sig=210,8 Ref=360,100 (14-12-12\024-1101.D)
mAU
5.747
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-12-12\024-1101.D) APCI, Pos, Scan, Frag: 0
5.792
MS Spectrum
*MSD1 SPC, time=5.790 of C:\CHEM32\1\DATA\14-12-12\024-1101.D APCI, Pos, Scan, Frag: 0
Max: 4.16051e+006
462.2
444.2
460.2
m/z
4f

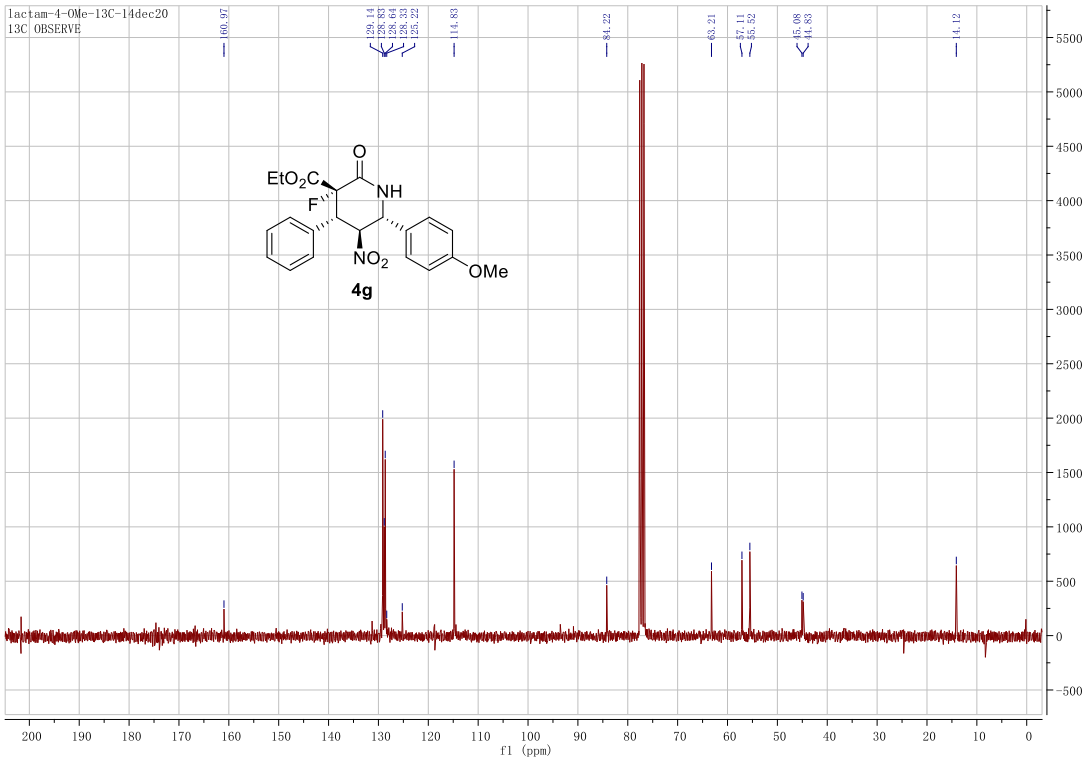

4f
f1 (ppm)

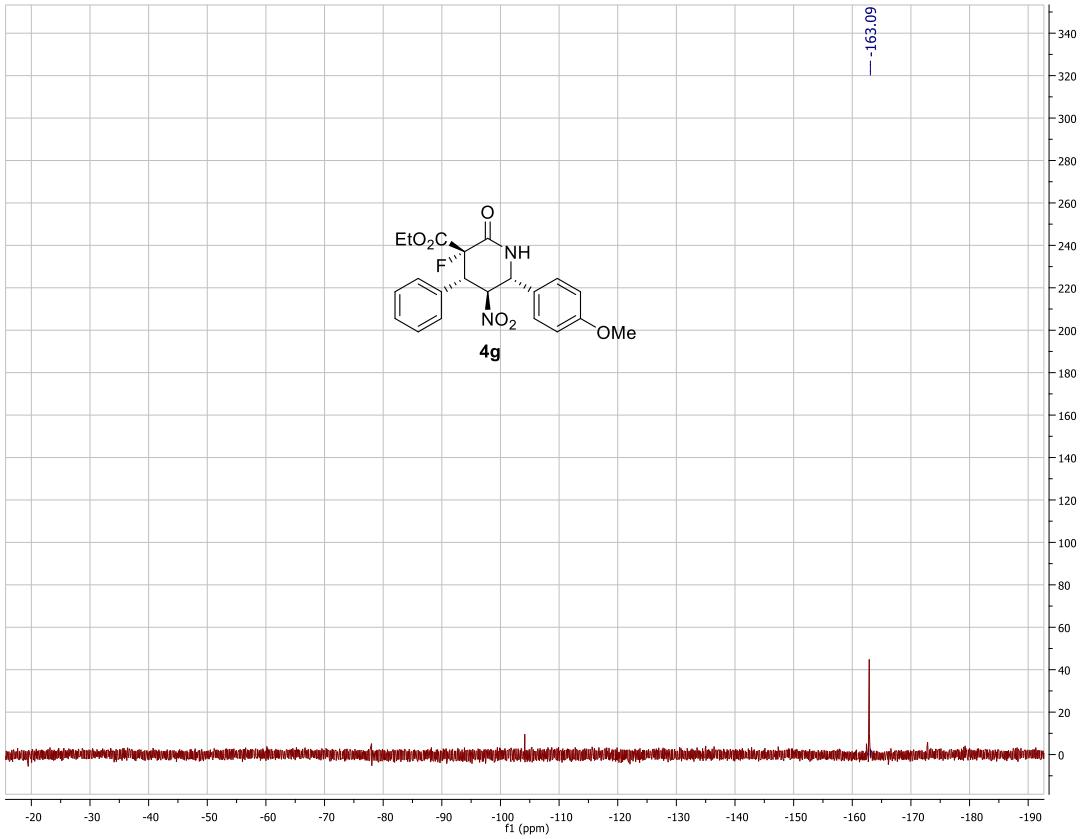

lactam-4-butyl-13c
13C OBSERVE
164.90
163.54
153.13
131.11
130.23
128.93
128.62
126.99
126.17
83.69
62.98
57.03
44.76
44.52
34.70
31.16
13.92
EtO2C
F
O
NH
NO2
4f
f1 (ppm)

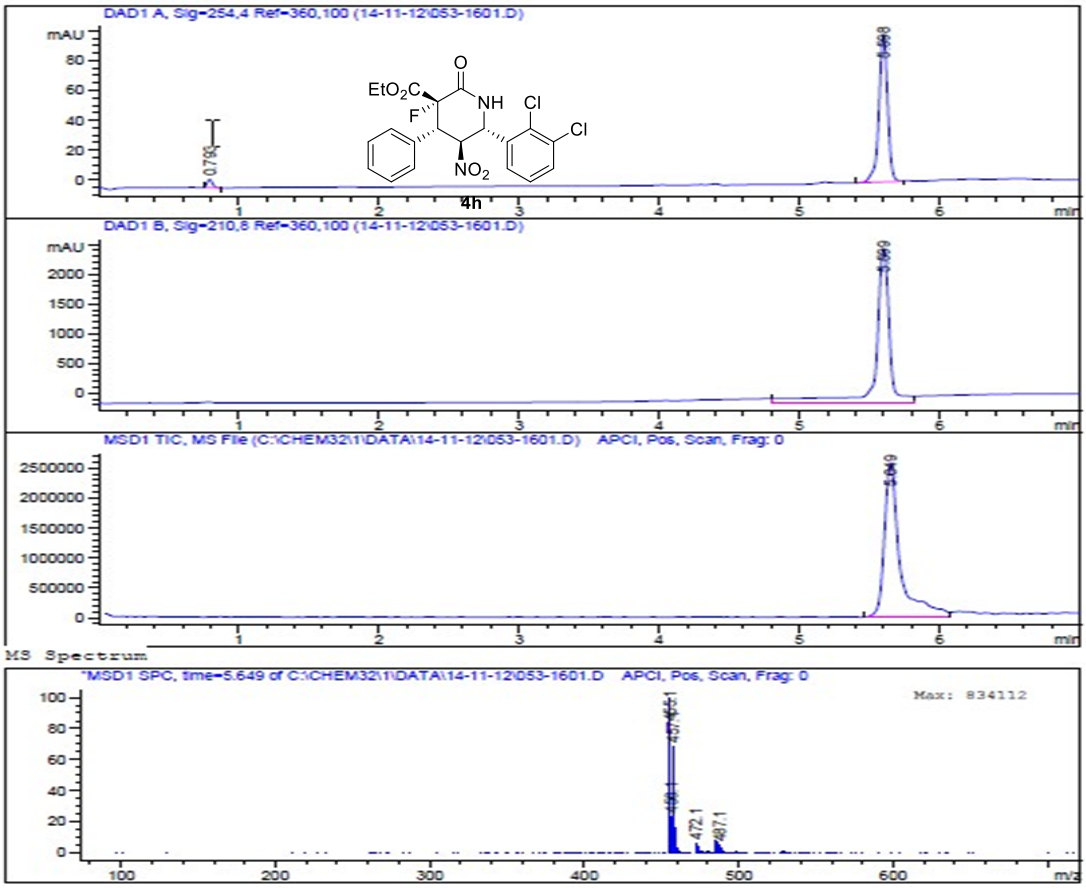

lactam-4-ome-styrene-19f
19F OBSERVE
STANDARD PARAMETERS
-163.30
EtO2C
F
O
NH
NO2
4f
f1 (ppm)

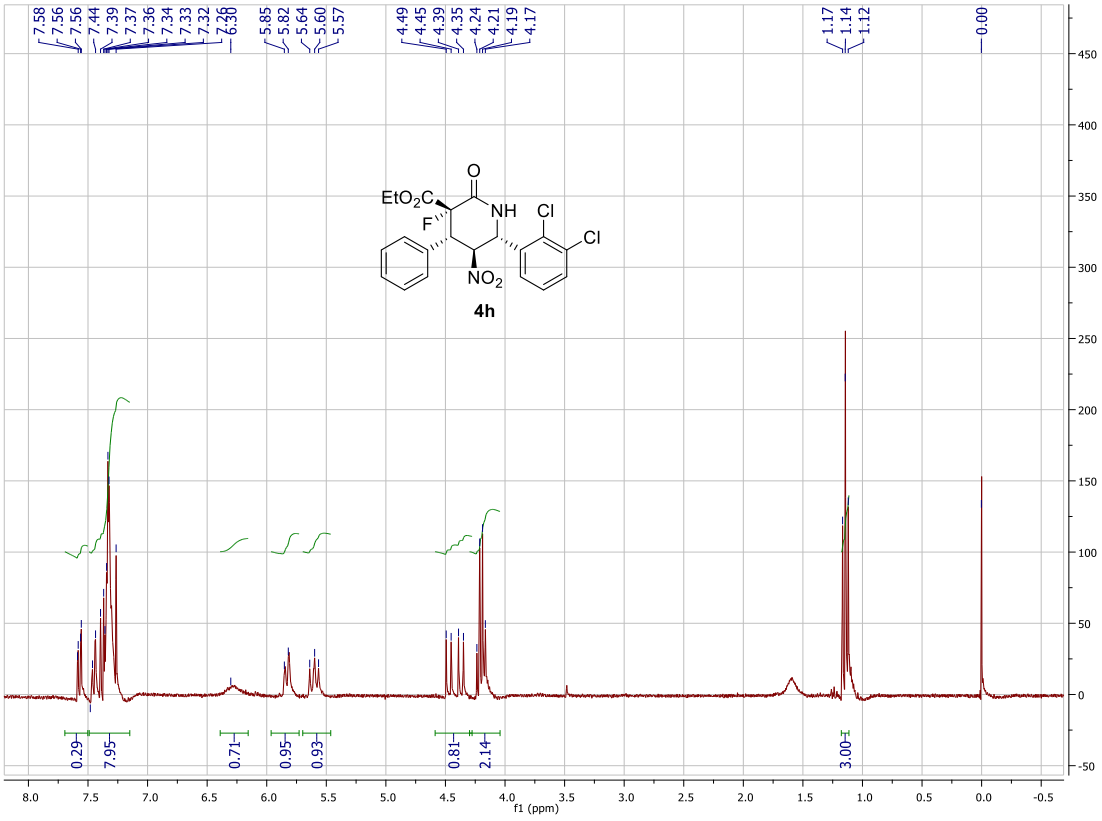

DAD1 A, Sig=254,4 Ref=360,100 (14-12-19\021-0201.D)
mAU
min
4g
DAD1 B, Sig=210,8 Ref=360,100 (14-12-19\021-0201.D)
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-12-19\021-0201.D) APCI, Pos, Scan, Frag: 0
MS Spectrum
*MSD1 SPC, time=5.111 of C:\CHEM32\1\DATA\14-12-19\021-0201.D APCI, Pos, Scan, Frag: 0
Max: 505216
m/z

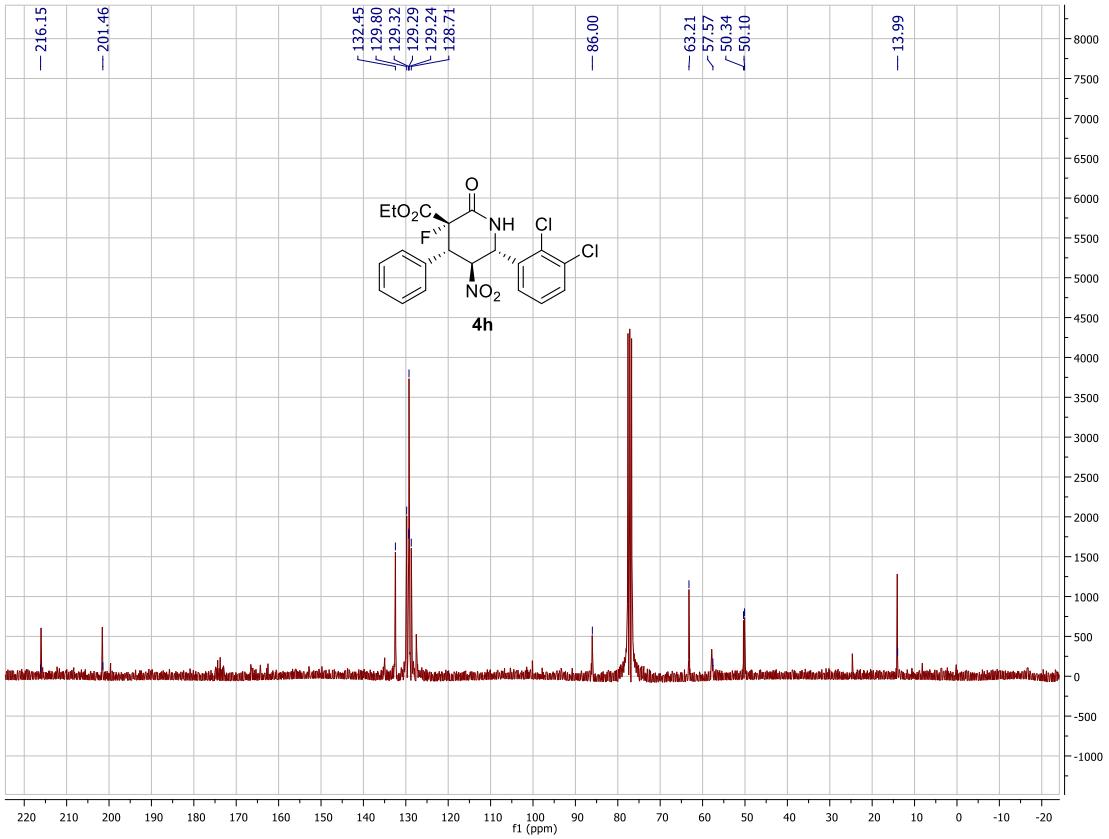

STANDARD 1H OBSERVE
4g
f1 (ppm)

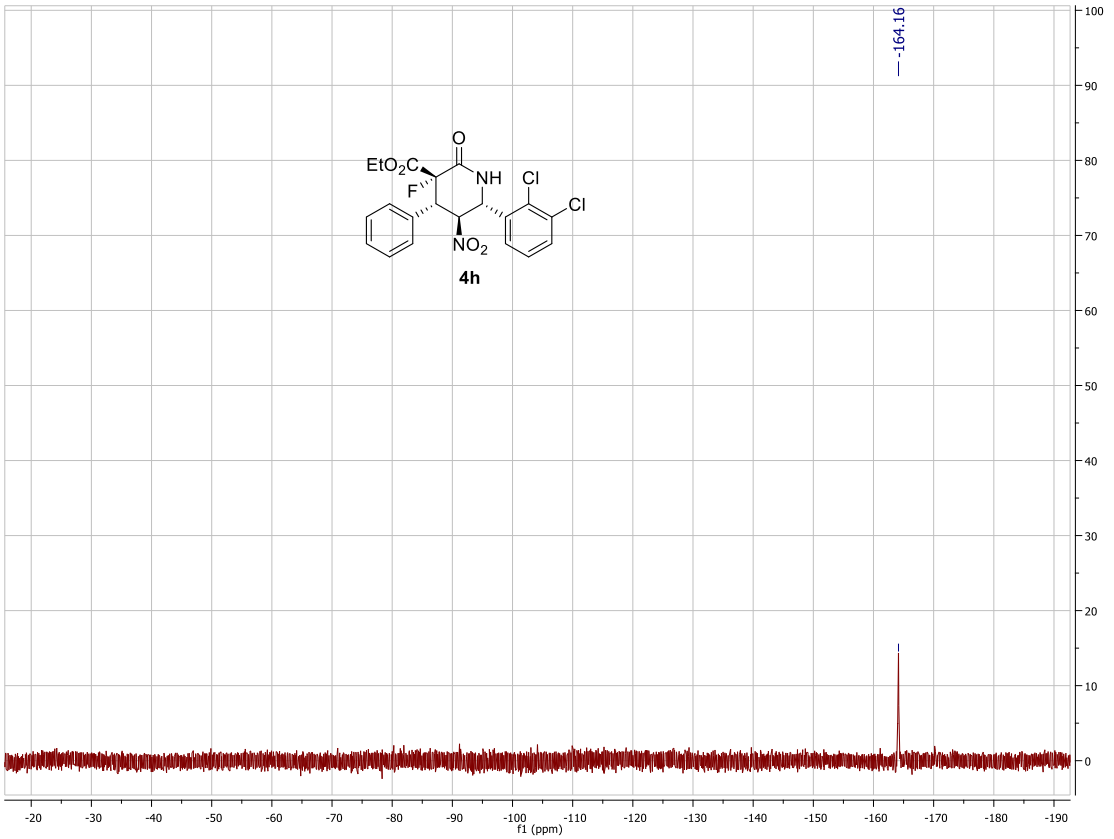

lactam-4-OMe-13C-14dec20
13C OBSERVE
160.97
129.14
128.83
128.64
128.53
125.22
114.83
84.22
63.21
57.11
55.52
45.08
41.83
14.12
EtO2C
O
NH
F
NO2
OMe
4g
f1 (ppm)

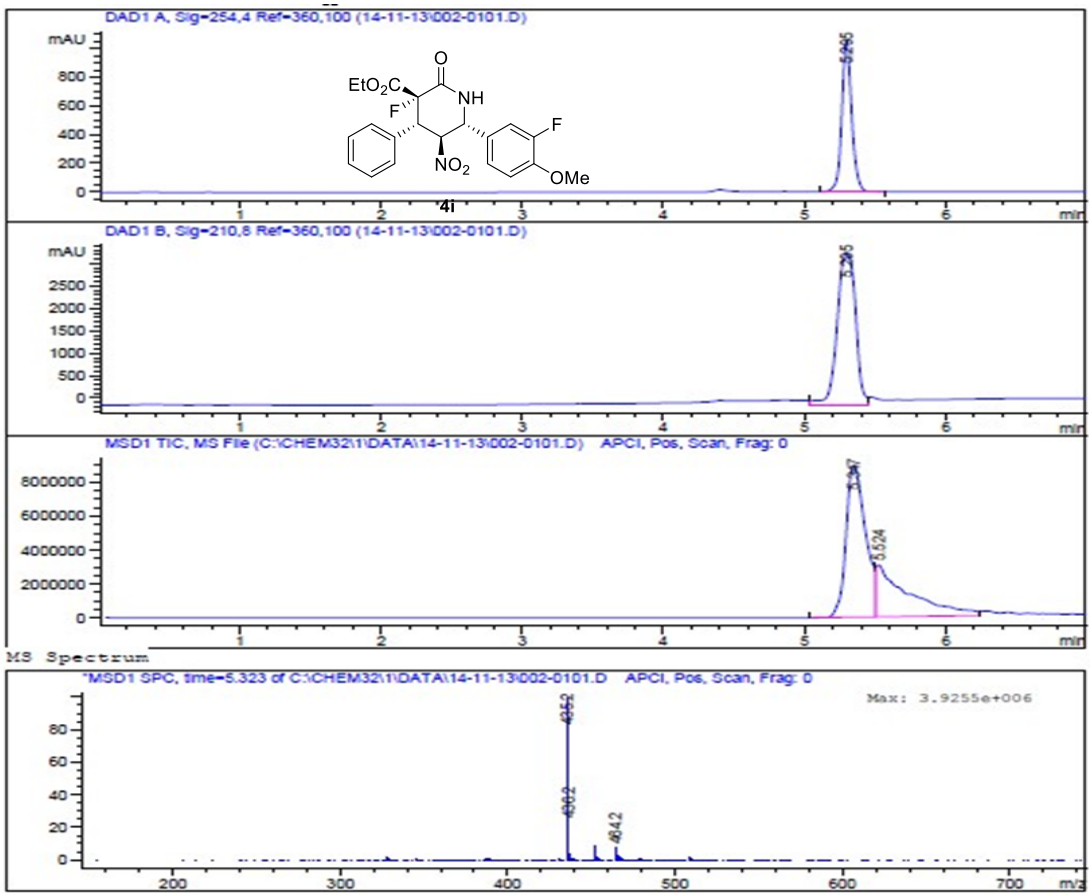

-163.09
EtO2C
O
NH
F
NO2
OMe
4g
f1 (ppm)

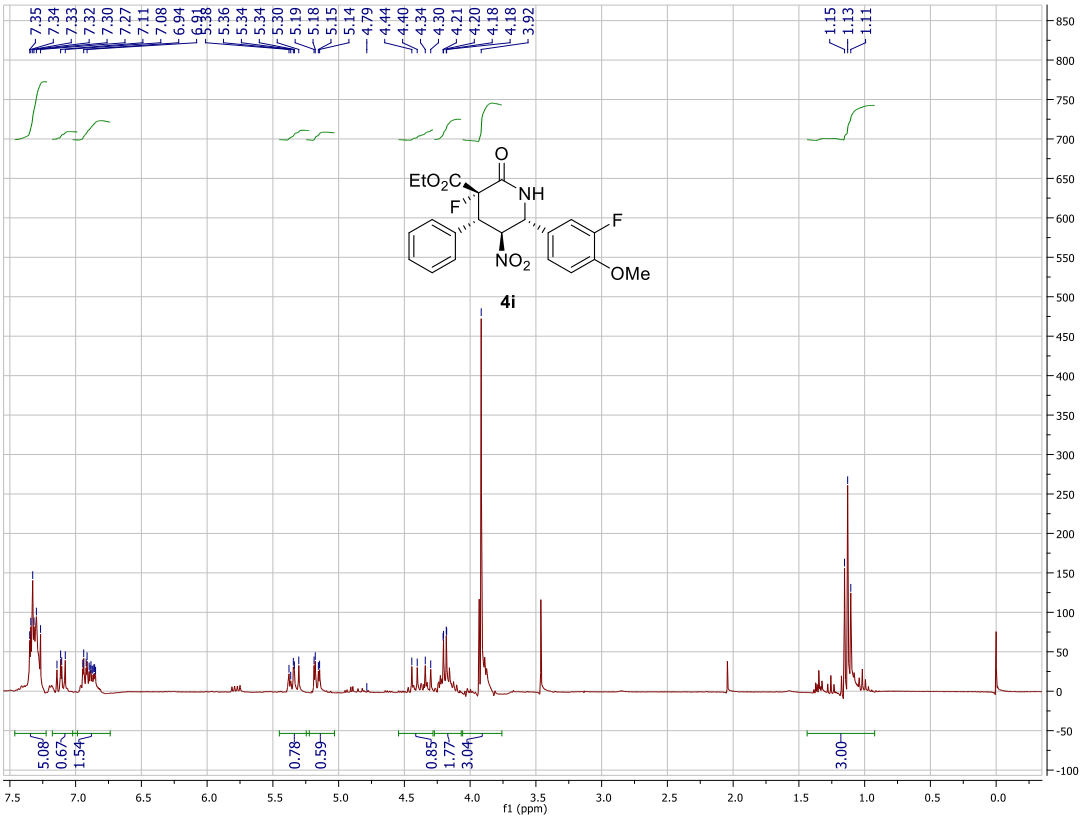

DAD1 A, Sig=254,4 Ref=360,100 (14-11-12\053-1601.D)
mAU
min
DAD1 B, Sig=210,8 Ref=360,100 (14-11-12\053-1601.D)
mAU
min
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-11-12\053-1601.D) APCI, Pos, Scan, Frag: 0
min
MS Spectrum
*MSD1 SPC, time=5.649 of C:\CHEM32\1\DATA\14-11-12\053-1601.D APCI, Pos, Scan, Frag: 0
Max: 834112
m/z
4h

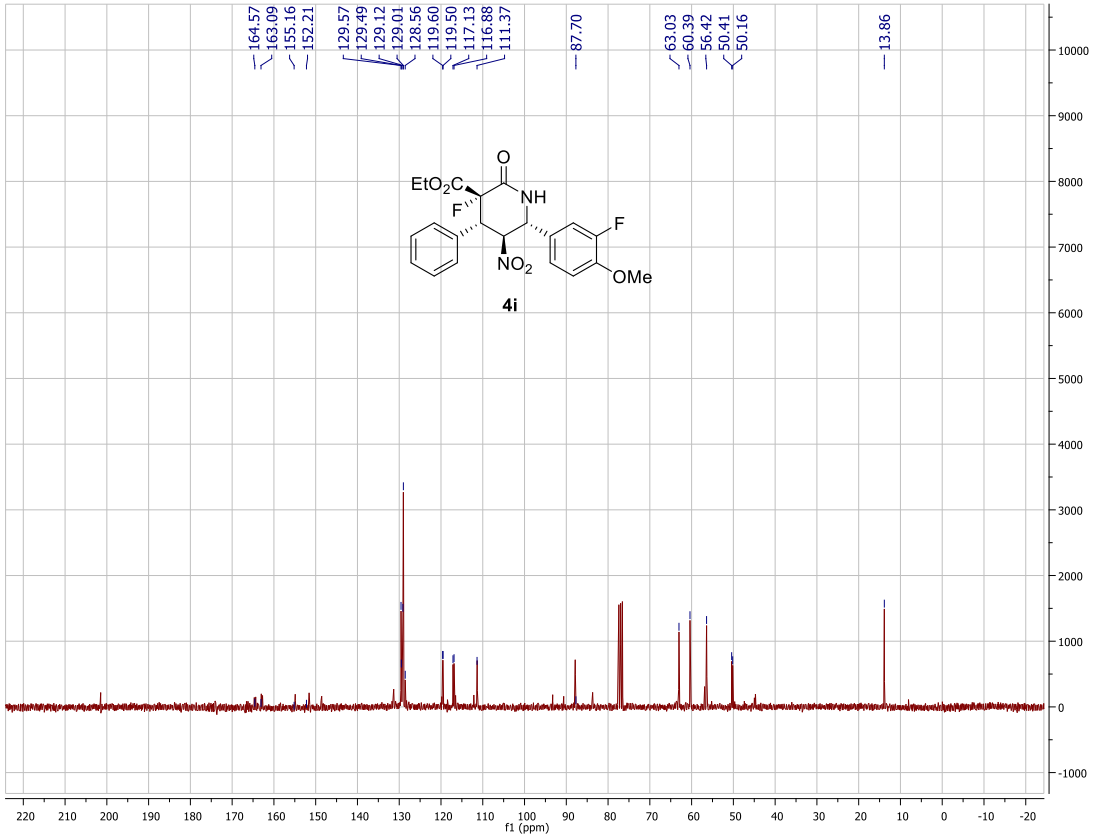

4h
f1 (ppm)

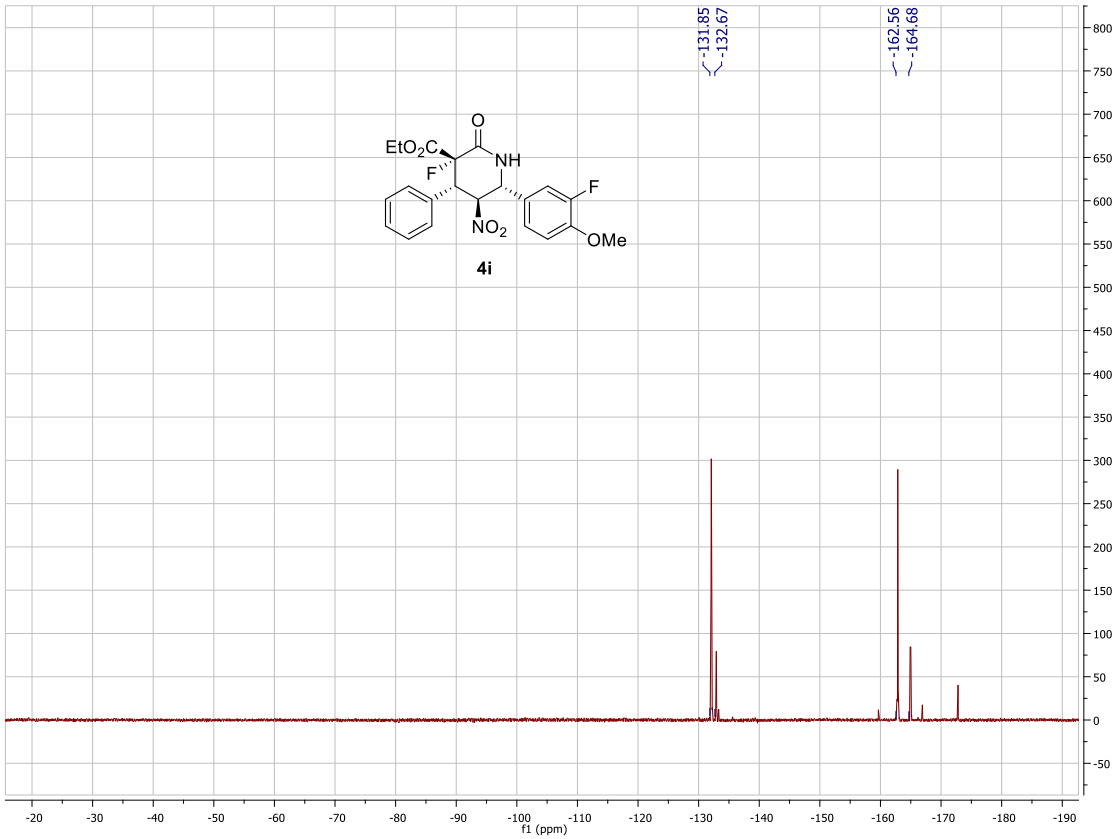

216.15
201.46
132.45
129.80
129.32
129.29
129.24
128.71
86.00
63.21
57.57
50.34
50.10
13.99
O
EtO2C
F
NH
Cl
Cl
NO2
4h
f1 (ppm)

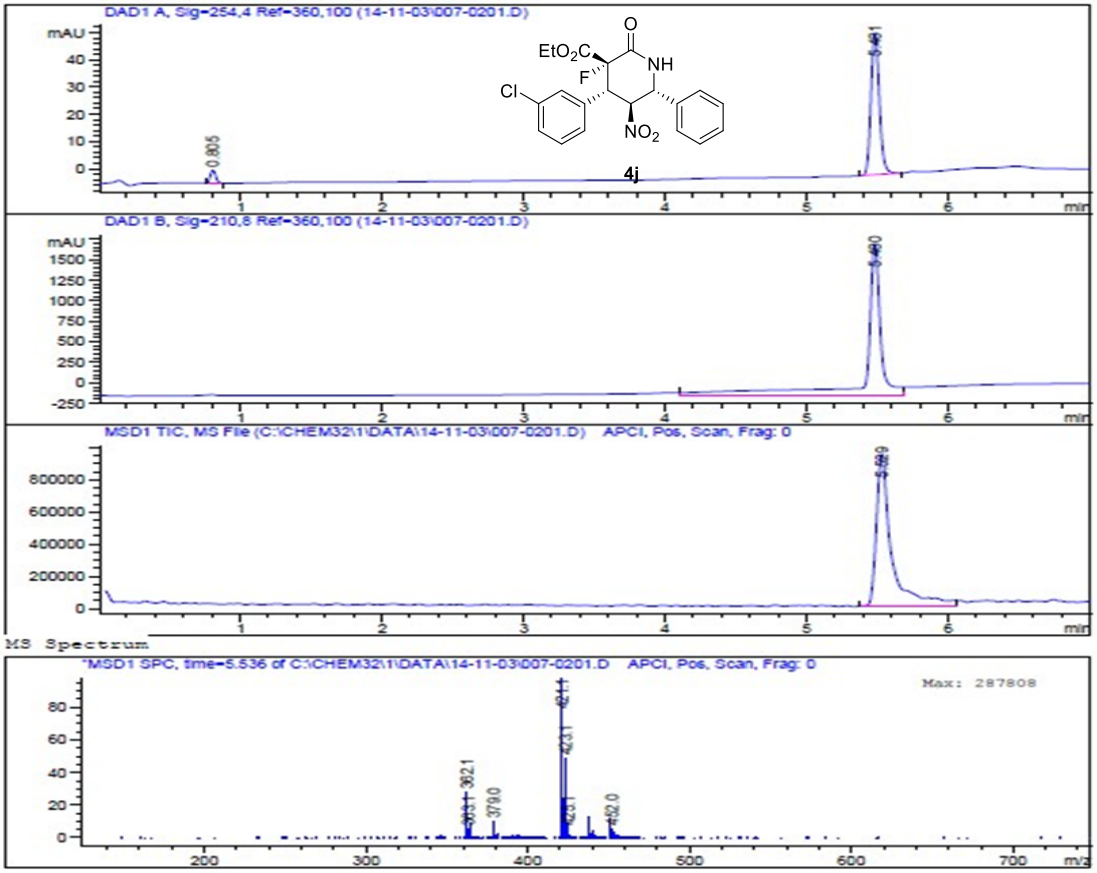

-164.16
O
EtO2C
F
NH
Cl
Cl
NO2
4h
f1 (ppm)

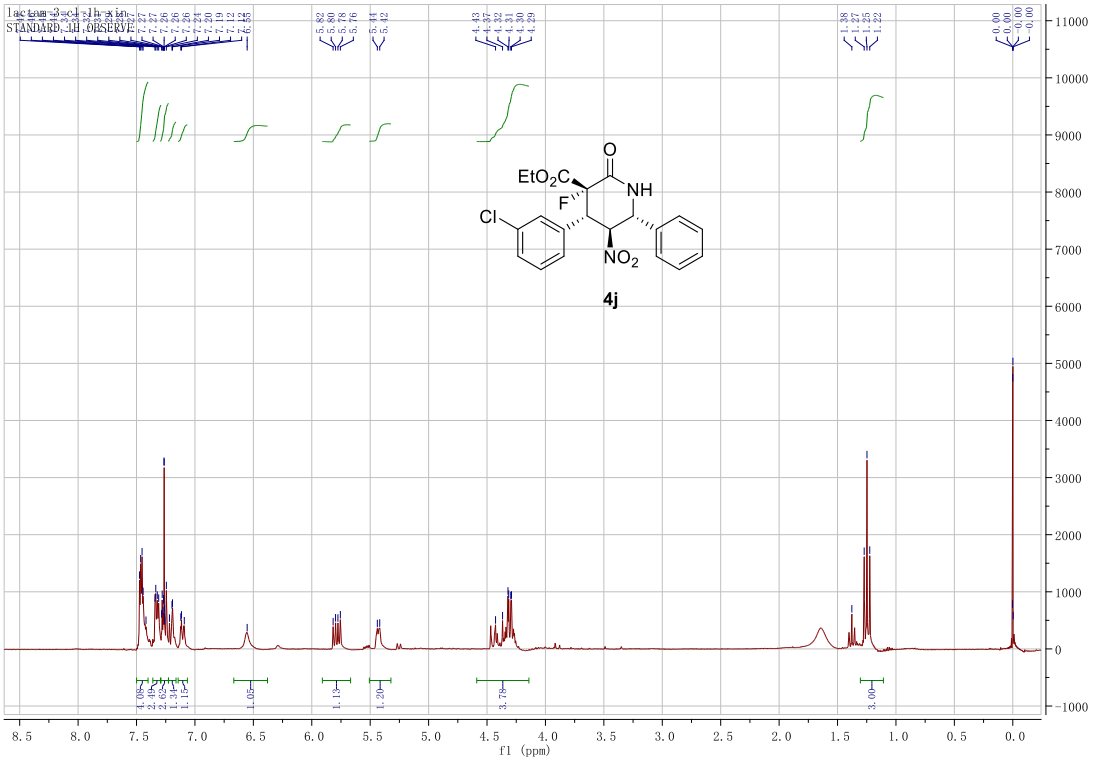

DAD1 A, Sig=254,4 Ref=360,100 (14-11-13\002-0101.D)
mAU
min
DAD1 B, Sig=210,8 Ref=360,100 (14-11-13\002-0101.D)
mAU
min
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-11-13\002-0101.D) APCI, Pos, Scan, Frag: 0
5.524
MS Spectrum
*MSD1 SPC, time=5.323 of C:\CHEM32\1\DATA\14-11-13\002-0101.D APCI, Pos, Scan, Frag: 0
Max: 3.9255e+006
m/z

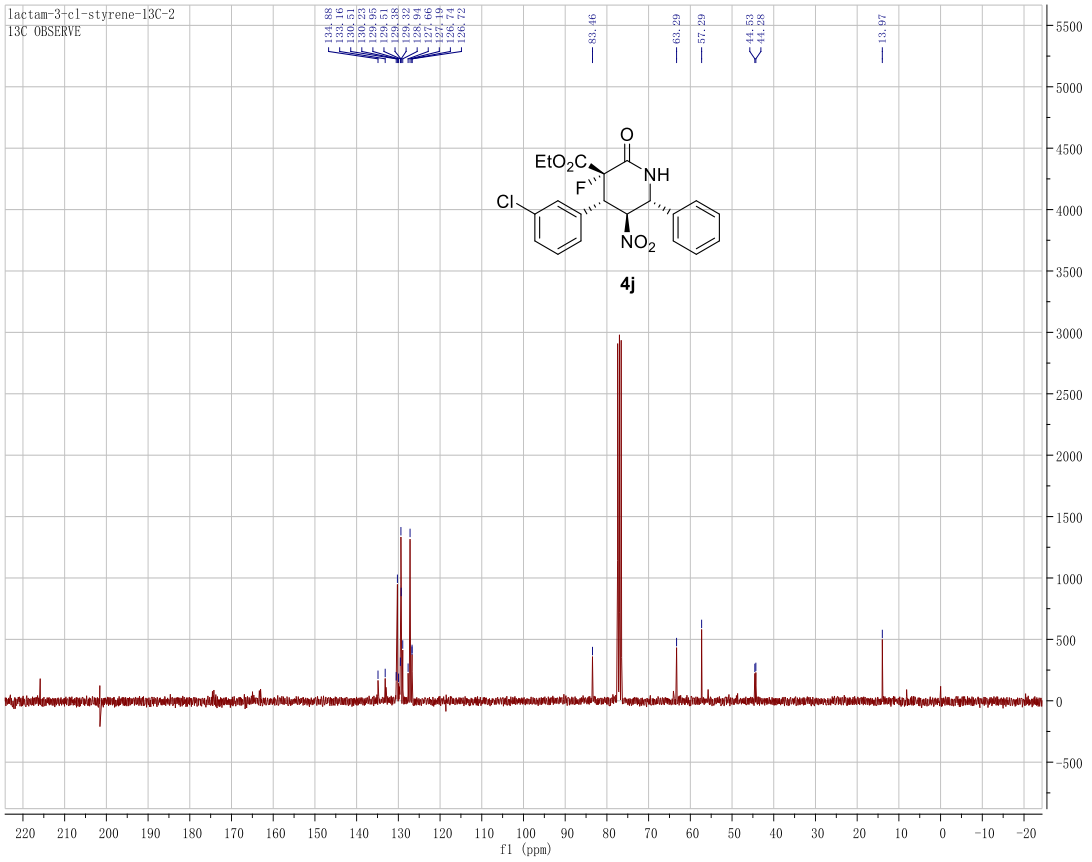

4i
f1 (ppm)

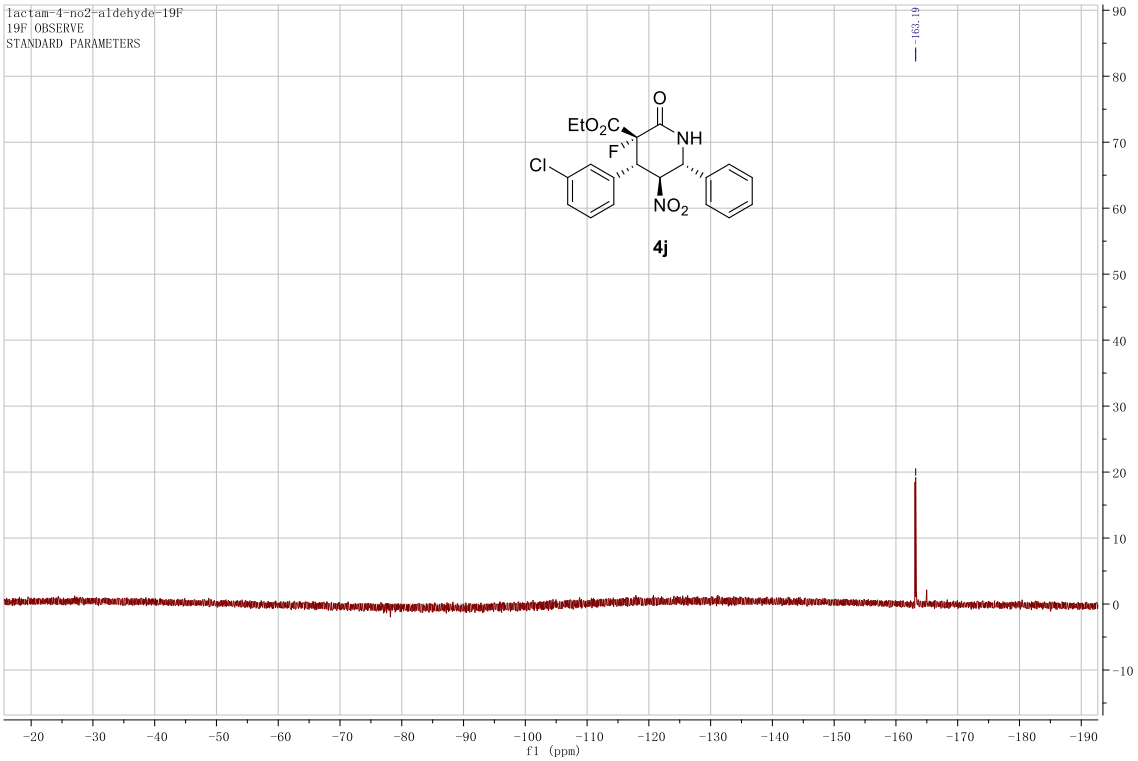

164.57
163.09
155.16
152.21
129.57
129.49
129.12
129.01
128.56
119.60
119.50
117.13
116.88
111.37
87.70
63.03
60.39
56.42
50.41
50.16
13.86
EtO2C
O
NH
F
NO2
F
OMe
4i
f1 (ppm)

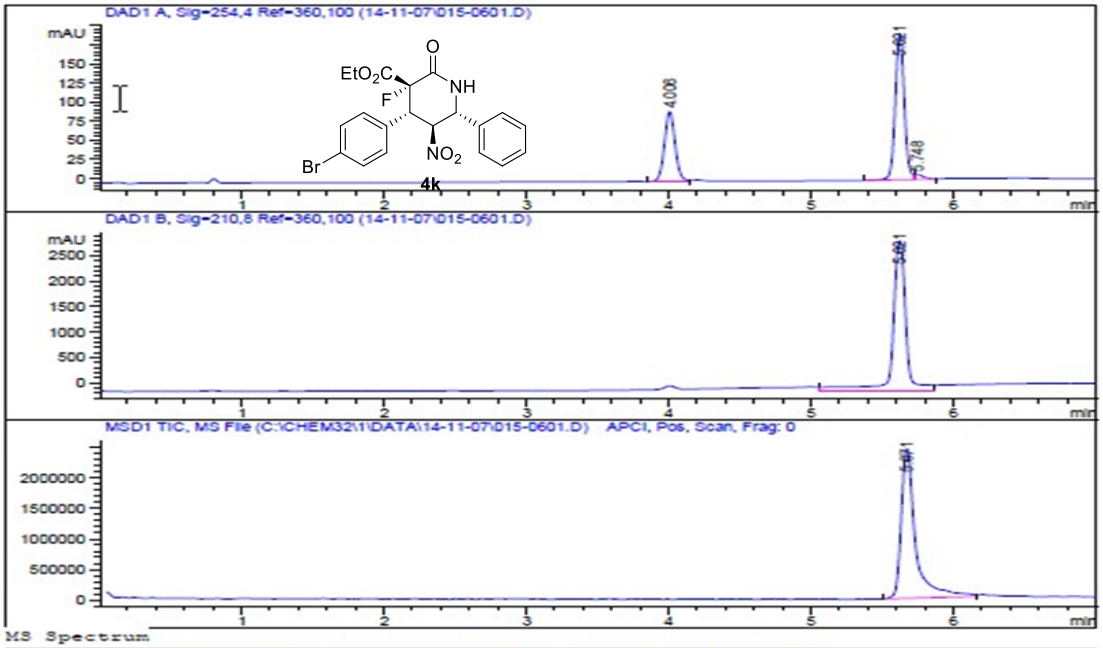

-131.85
-132.67
-162.56
-164.68
EtO2C
O
NH
F
NO2
F
OMe
4i
f1 (ppm)

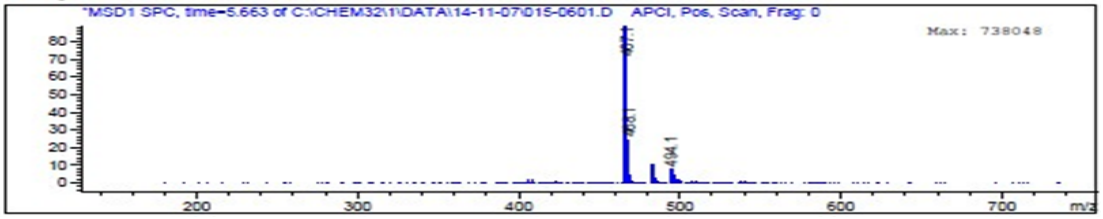

DAD1 A, Sig=254,4 Ref=360,100 (14-11-03\007-0201.D)
mAU
0.805
5.461
min
DAD1 B, Sig=210,8 Ref=360,100 (14-11-03\007-0201.D)
mAU
5.460
min
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-11-03\007-0201.D) APCI, Pos, Scan, Frag: 0
5.539
min
MS Spectrum
*MSD1 SPC, time=5.536 of C:\CHEM32\1\DATA\14-11-03\007-0201.D APCI, Pos, Scan, Frag: 0
Max: 287808
362.1
379.0
421.1
423.1
442.0
m/z
EtO2C
O
NH
F
Cl
NO2
4j

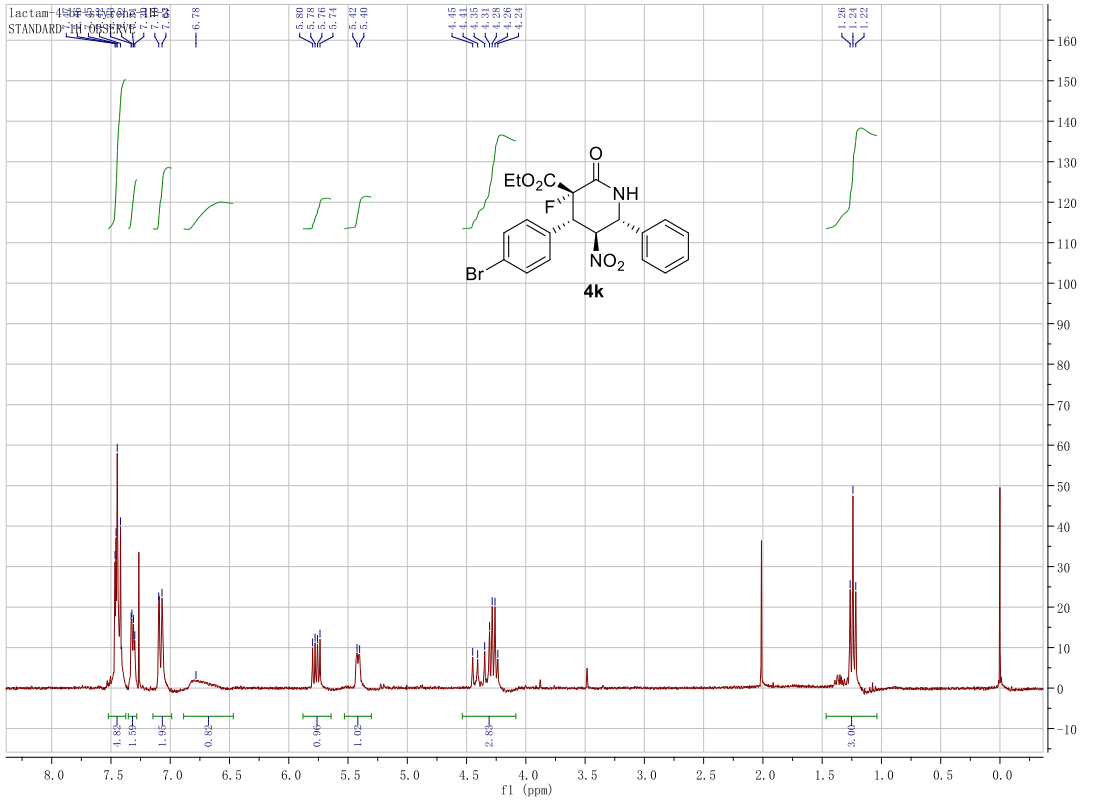

EtO2C
O
NH
F
Cl
NO2
4j
f1 (ppm)

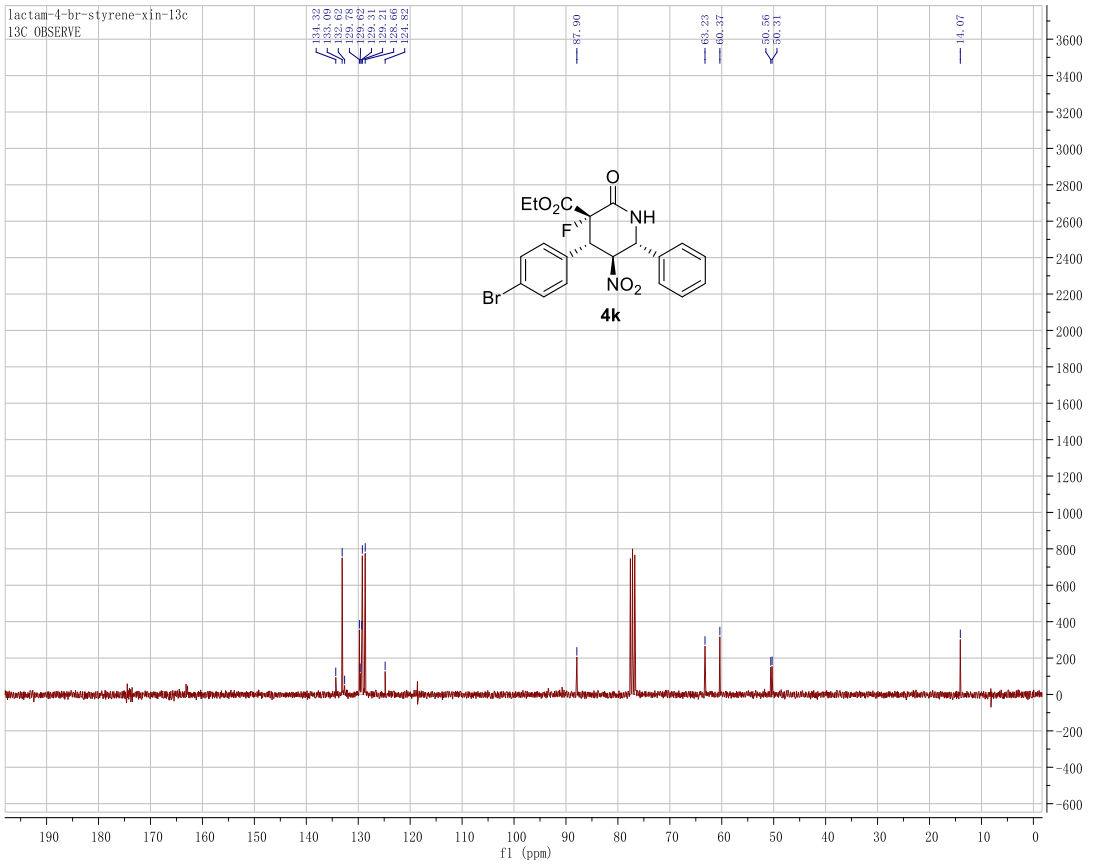

lactam-3-cl-styrene-13C-2
13C OBSERVE
134.88
133.16
130.51
130.23
129.95
129.51
129.38
128.32
128.04
127.66
127.49
126.74
126.72
83.46
63.29
57.29
44.53
44.28
13.97
O
EtO2C
NH
F
Cl
NO2
4j
f1 (ppm)

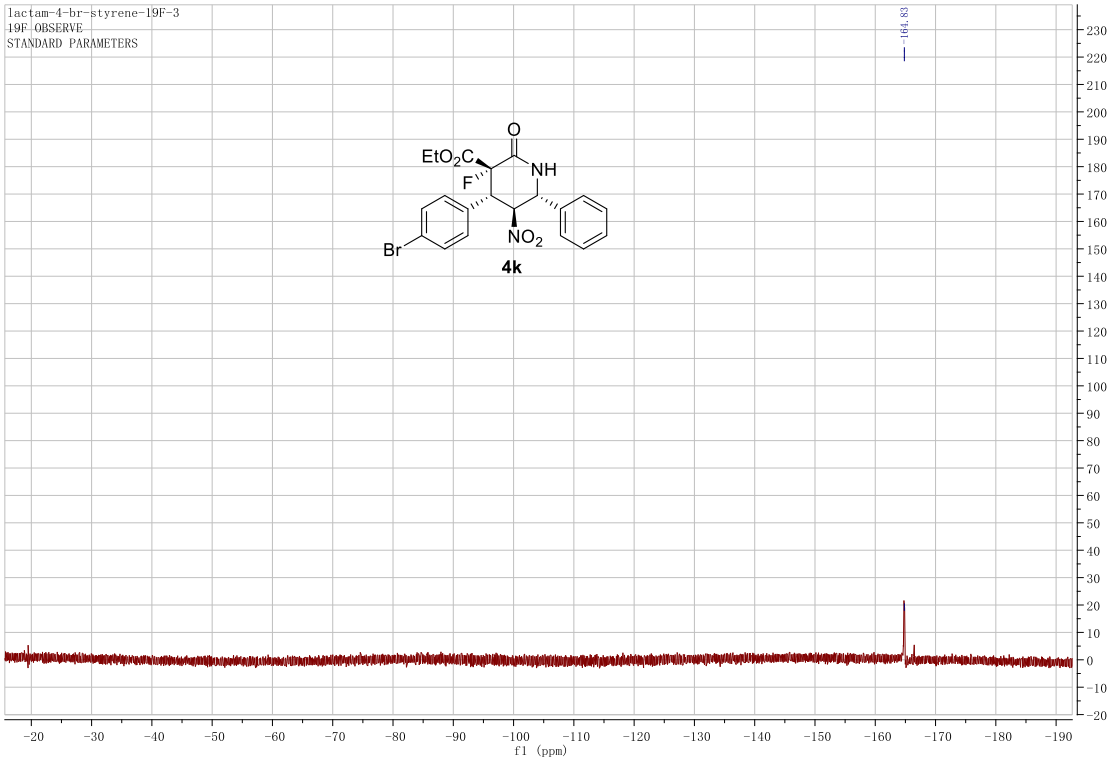

lactam-4-no2-aldehyde-19F
19F OBSERVE
STANDARD PARAMETERS
-163.19
O
EtO2C
NH
F
Cl
NO2
4j
f1 (ppm)

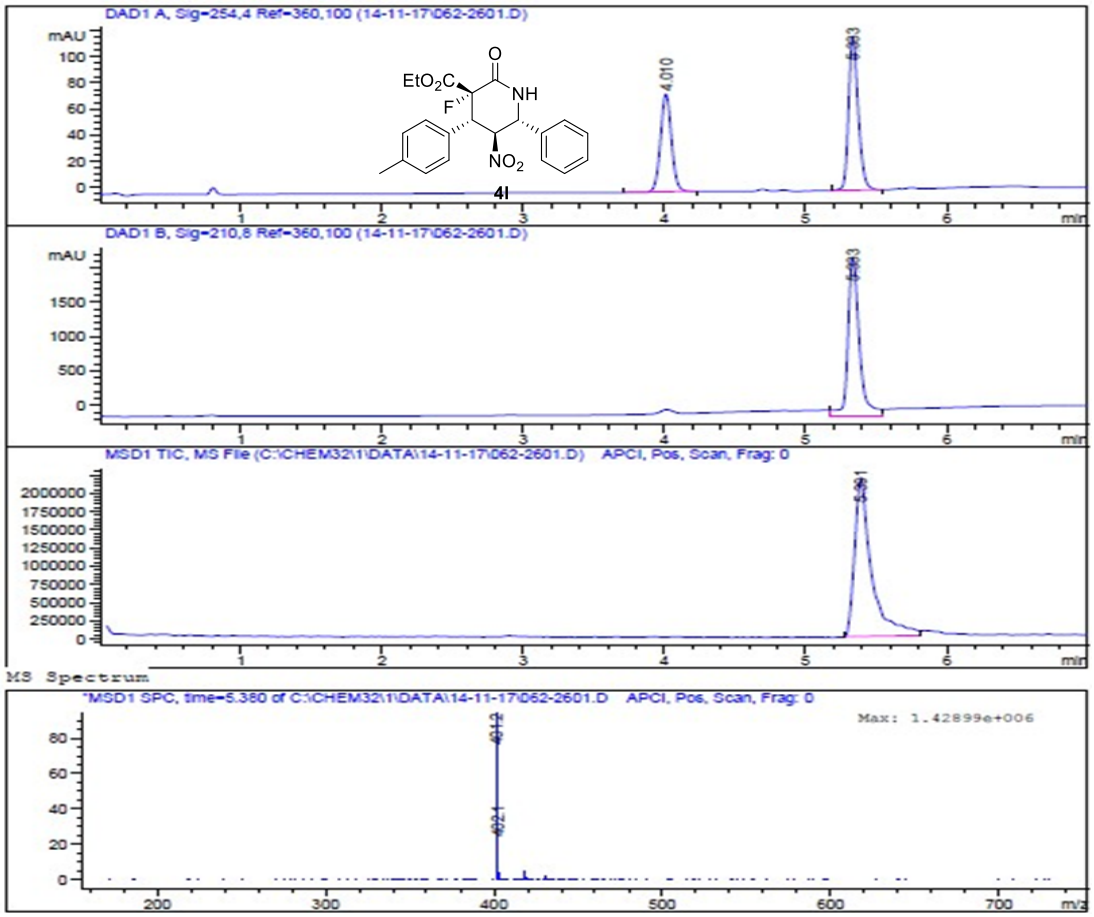

DAD1 A, Sig=254,4 Ref=360,100 (14-11-07\015-0601.D)
mAU
4.008
5.748
min
DAD1 B, Sig=210,8 Ref=360,100 (14-11-07\015-0601.D)
mAU
min
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-11-07\015-0601.D) APCI, Pos, Scan, Frag: 0
min

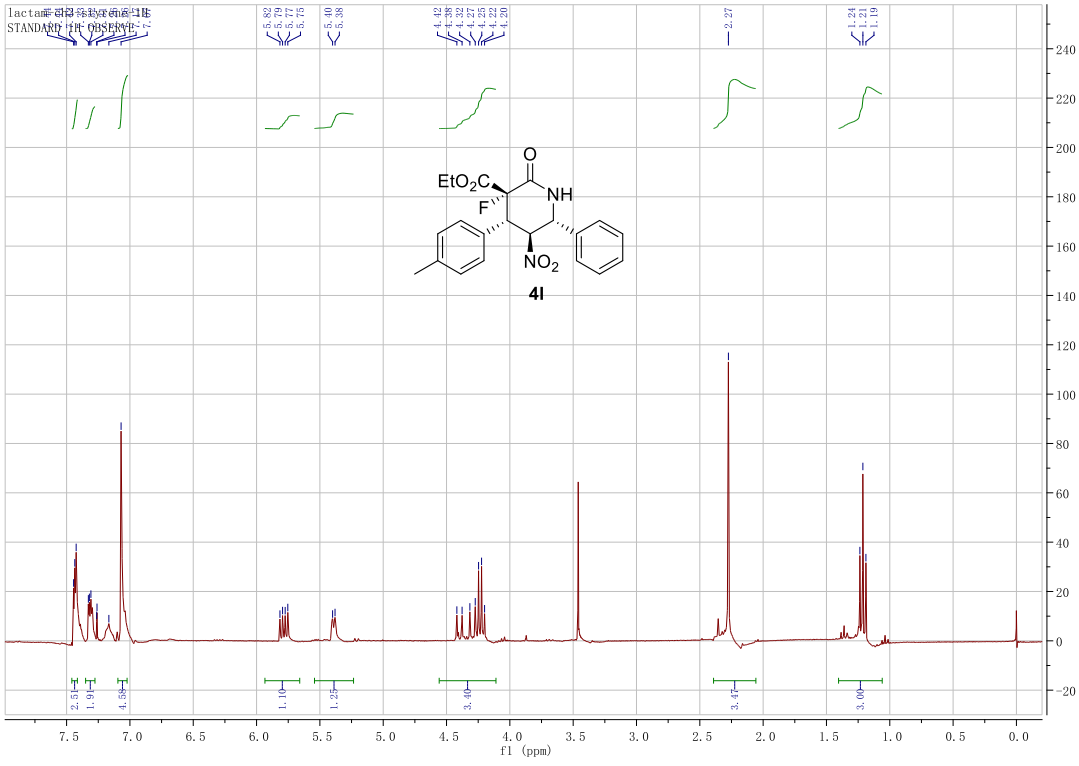

MS Spectrum
*MSD1 SPC, time=5.663 of C:\CHEM32\1\DATA\14-11-07\015-0601.D APCI, Pos, Scan, Frag: 0
Max: 738048
m/z

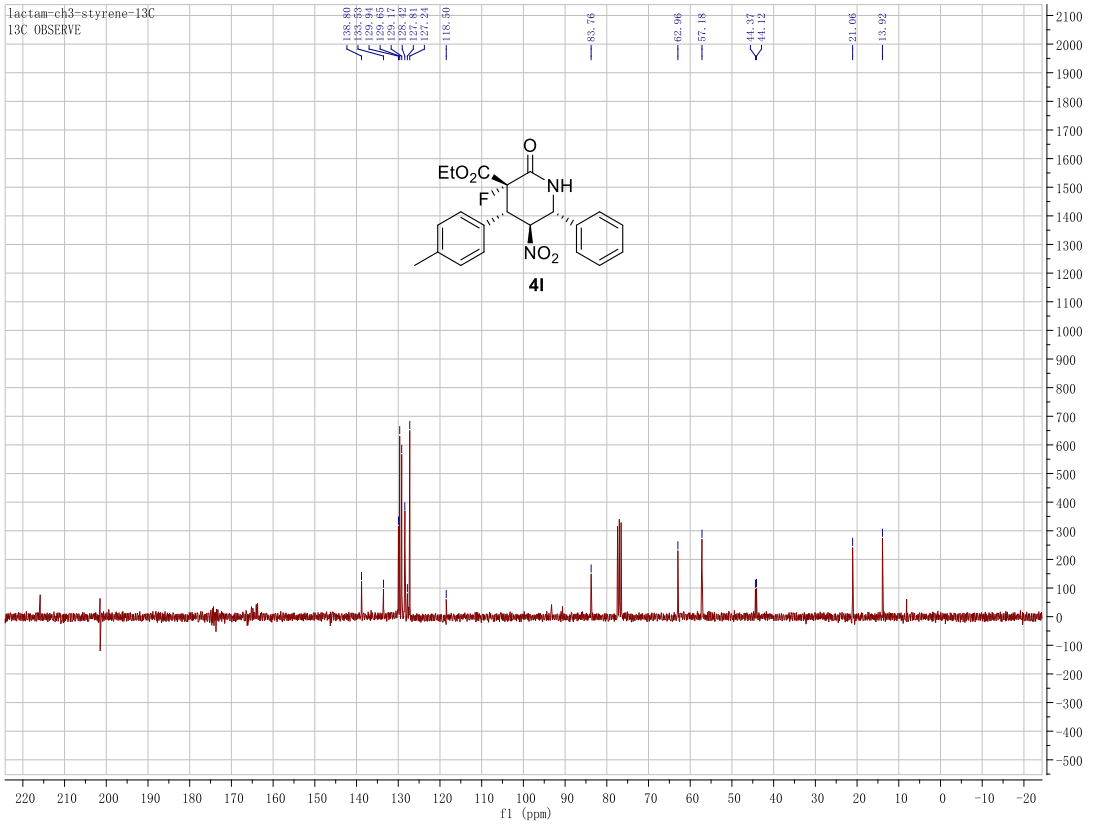

f1 (ppm)

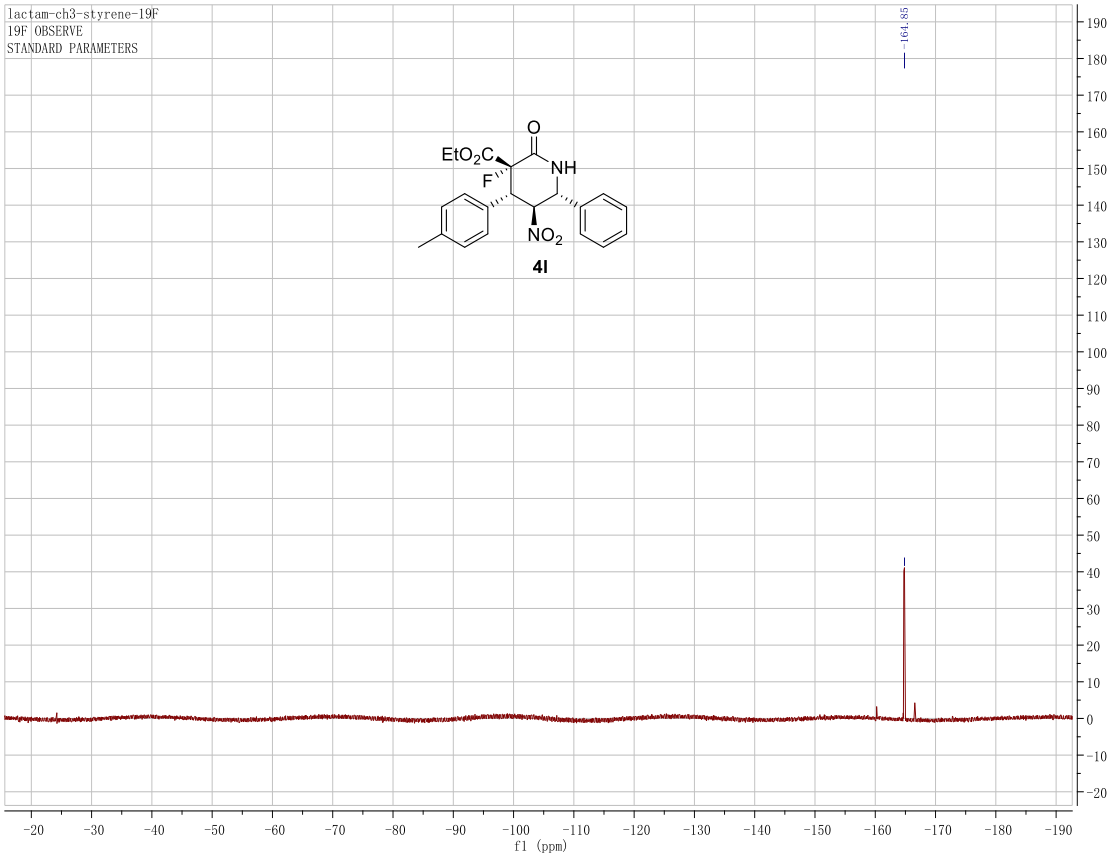

lactam-4-br-styrene-xin-13c
13C OBSERVE
134.32
133.09
132.62
129.78
129.42
129.31
129.21
128.66
124.02
87.90
63.23
60.37
50.56
50.31
14.07
O
EtO2C
F
NH
NO2
Br
4k
f1 (ppm)

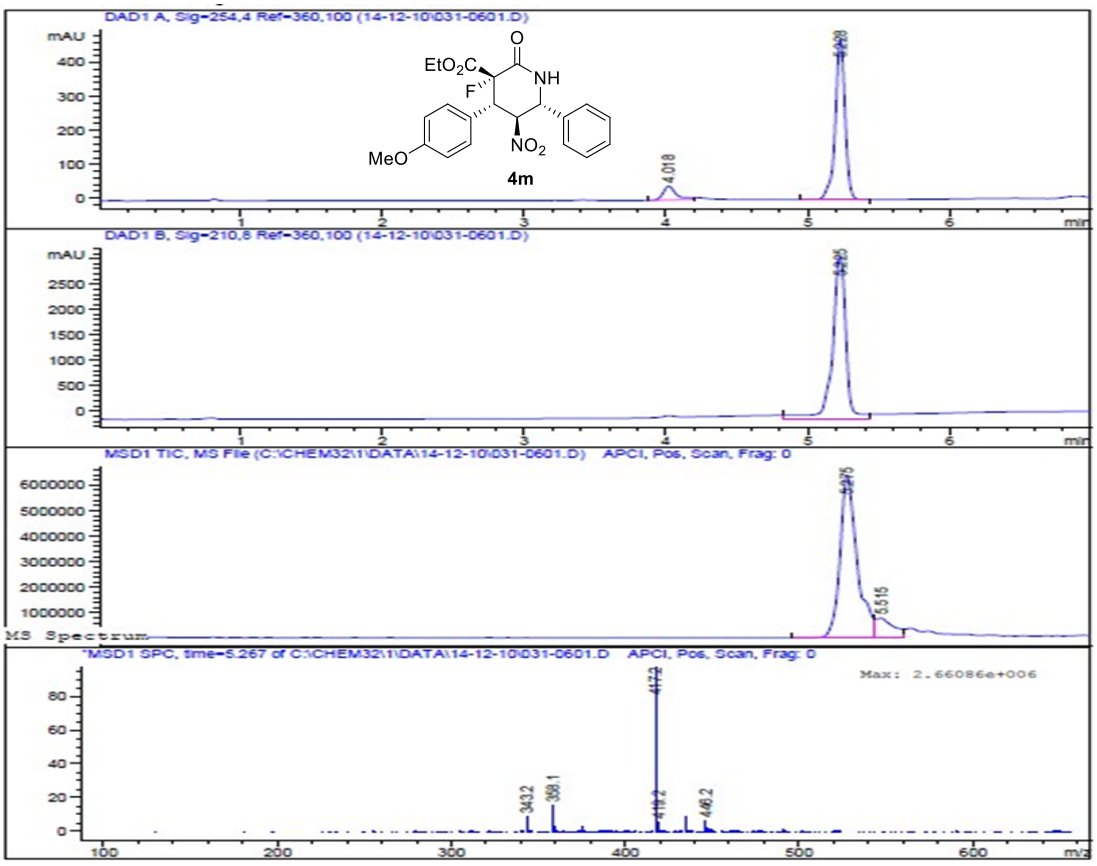

lactam-4-br-styrene-19F-3
19F OBSERVE
STANDARD PARAMETERS
164.83
O
EtO2C
F
NH
NO2
Br
4k
f1 (ppm)

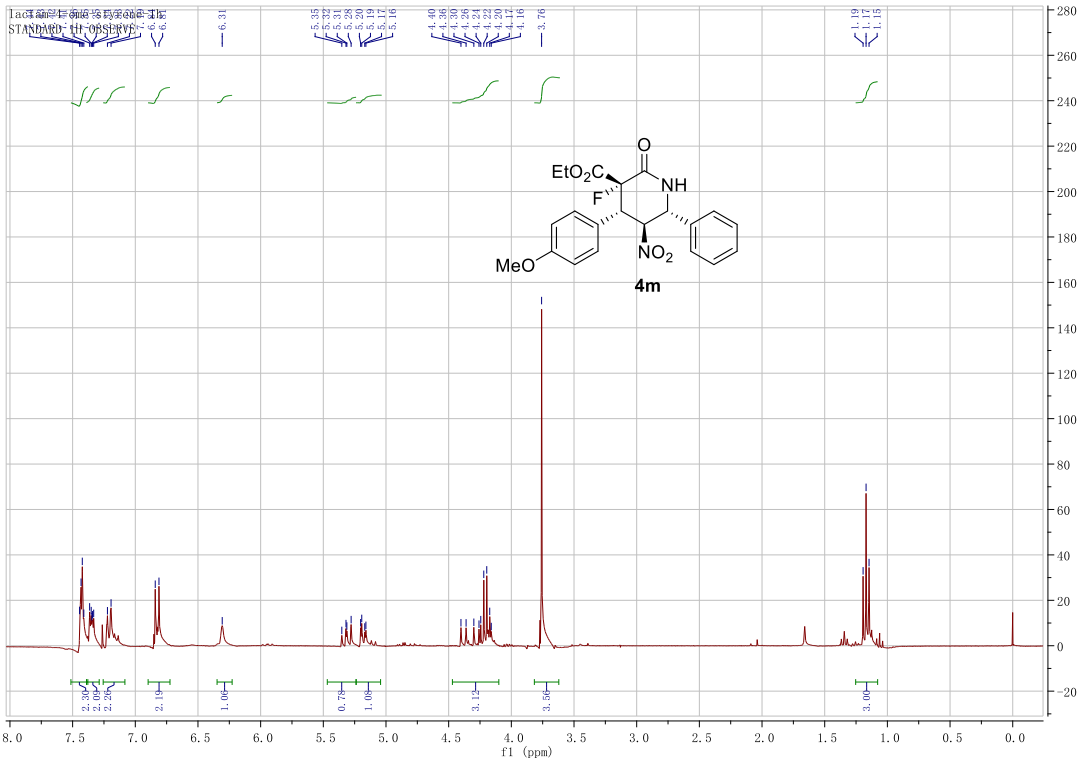

DAD1 A, Sig=254,4 Ref=360,100 (14-11-17\062-2601.D)
mAU
4.010
5.393
min
DAD1 B, Sig=210,8 Ref=360,100 (14-11-17\062-2601.D)
mAU
5.393
min
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-11-17\062-2601.D) APCI, Pos, Scan, Frag: 0
5.381
min
MS Spectrum
*MSD1 SPC, time=5.380 of C:\CHEM32\1\DATA\14-11-17\062-2601.D APCI, Pos, Scan, Frag: 0
Max: 1.42899e+006
4012
4021
m/z

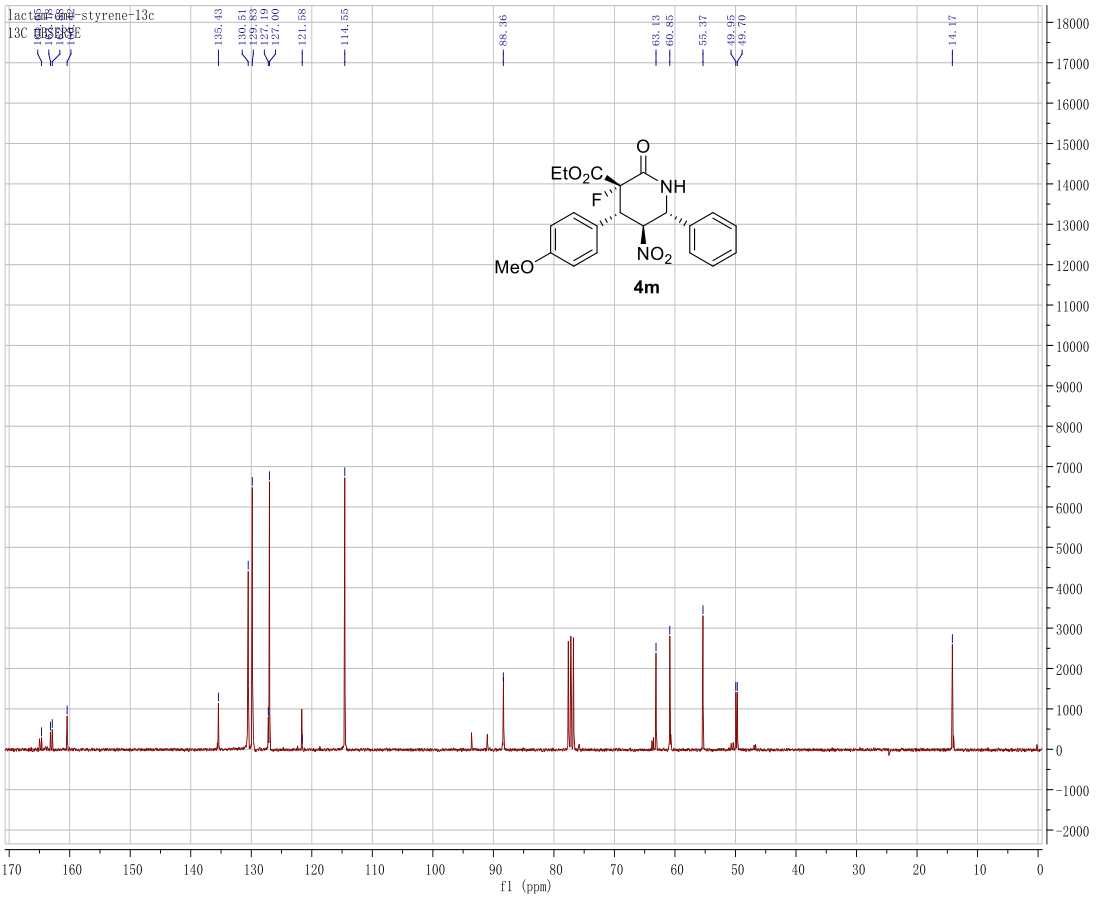

STANDARD 1H OBSERVE
5.82
5.79
5.77
5.75
5.40
5.38
4.42
4.38
4.32
4.27
4.25
4.22
4.20
2.27
1.24
1.21
1.19
f1 (ppm)

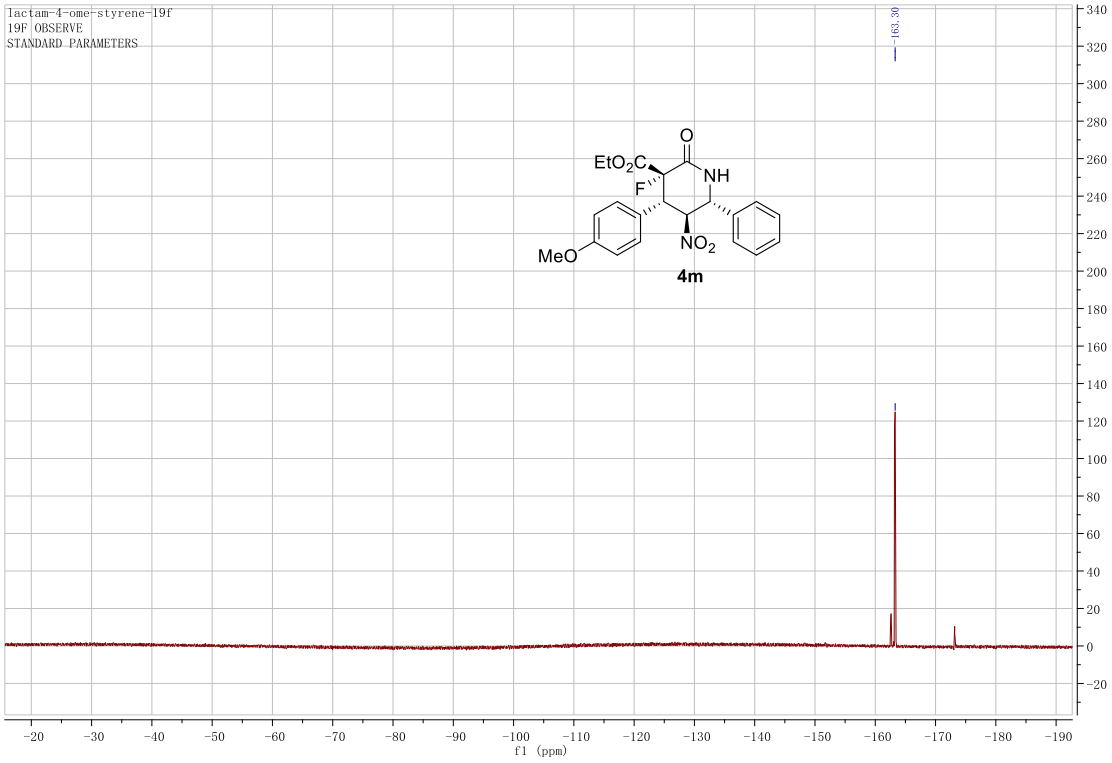

lactam-ch3-styrene-13C
13C OBSERVE
138.80
133.53
129.94
129.65
129.17
128.47
127.81
127.24
118.50
83.76
62.96
57.18
44.37
44.12
21.06
13.92
O
EtO2C
NH
F
NO2
4l
f1 (ppm)

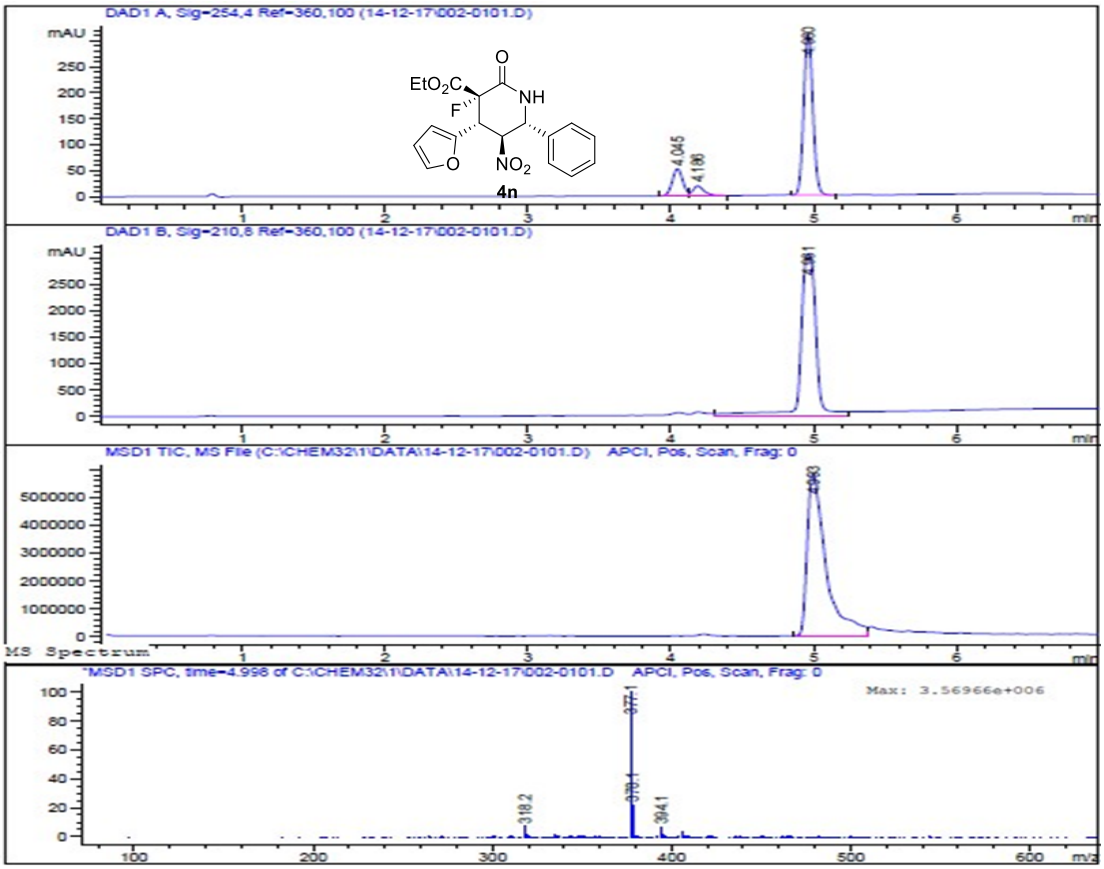

lactam-ch3-styrene-19F
19F OBSERVE
STANDARD PARAMETERS
-164.85
O
EtO2C
NH
F
NO2
4l
f1 (ppm)

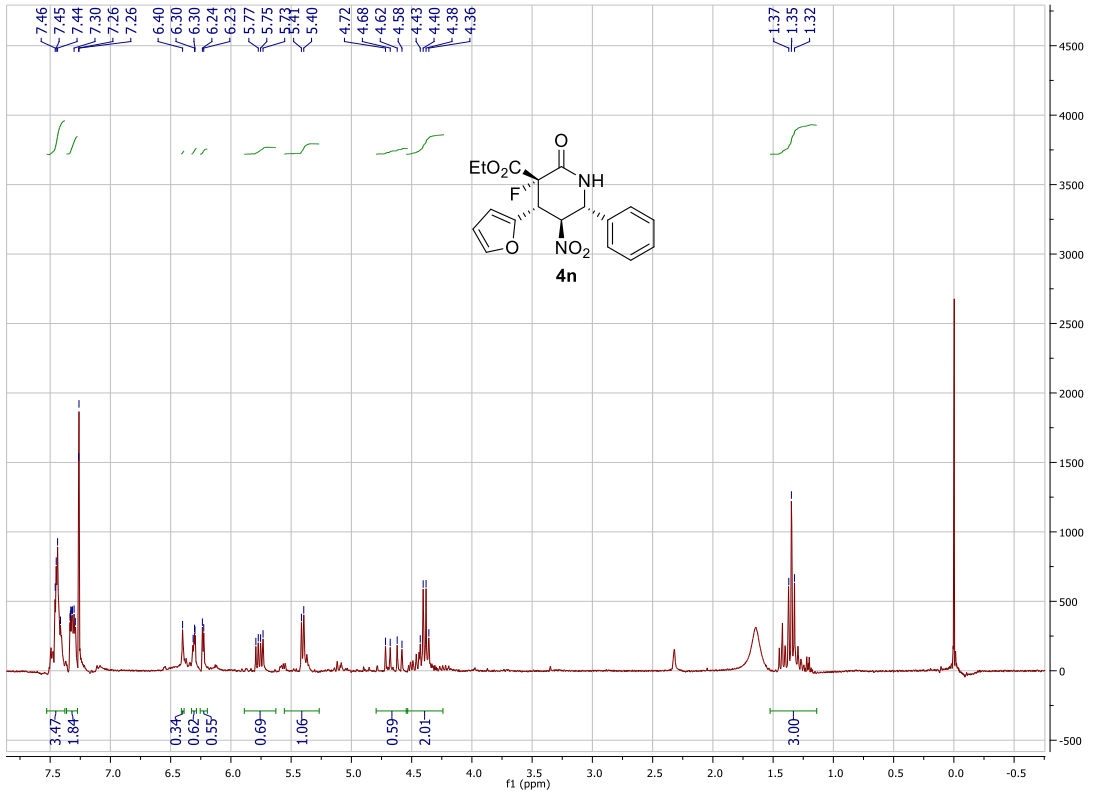

DAD1 A, Sig=254,4 Ref=360,100 (14-12-10\031-0601.D)
mAU
4.018
DAD1 B, Sig=210,8 Ref=360,100 (14-12-10\031-0601.D)
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-12-10\031-0601.D) APCI, Pos, Scan, Frag: 0
5.515
MS Spectrum
*MSD1 SPC, time=5.267 of C:\CHEM32\1\DATA\14-12-10\031-0601.D APCI, Pos, Scan, Frag: 0
Max: 2.66086e+006
343.2
388.1
410.2
446.2
min
m/z

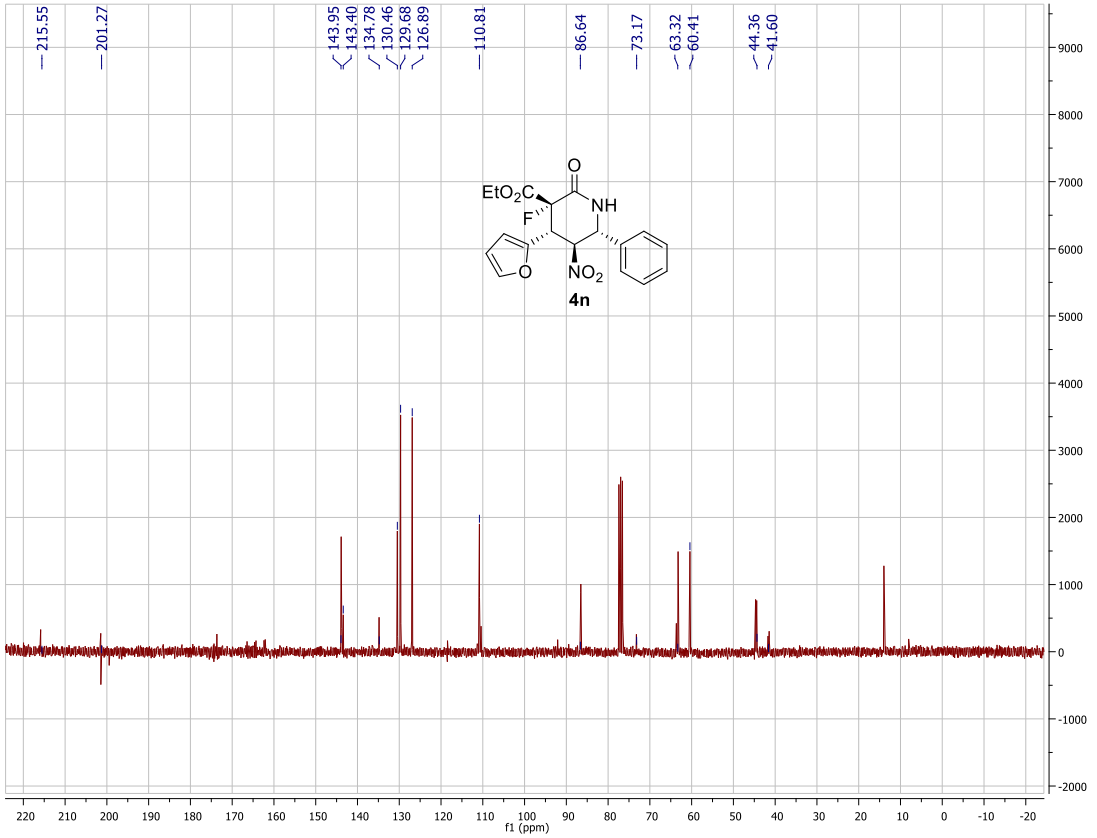

f1 (ppm)

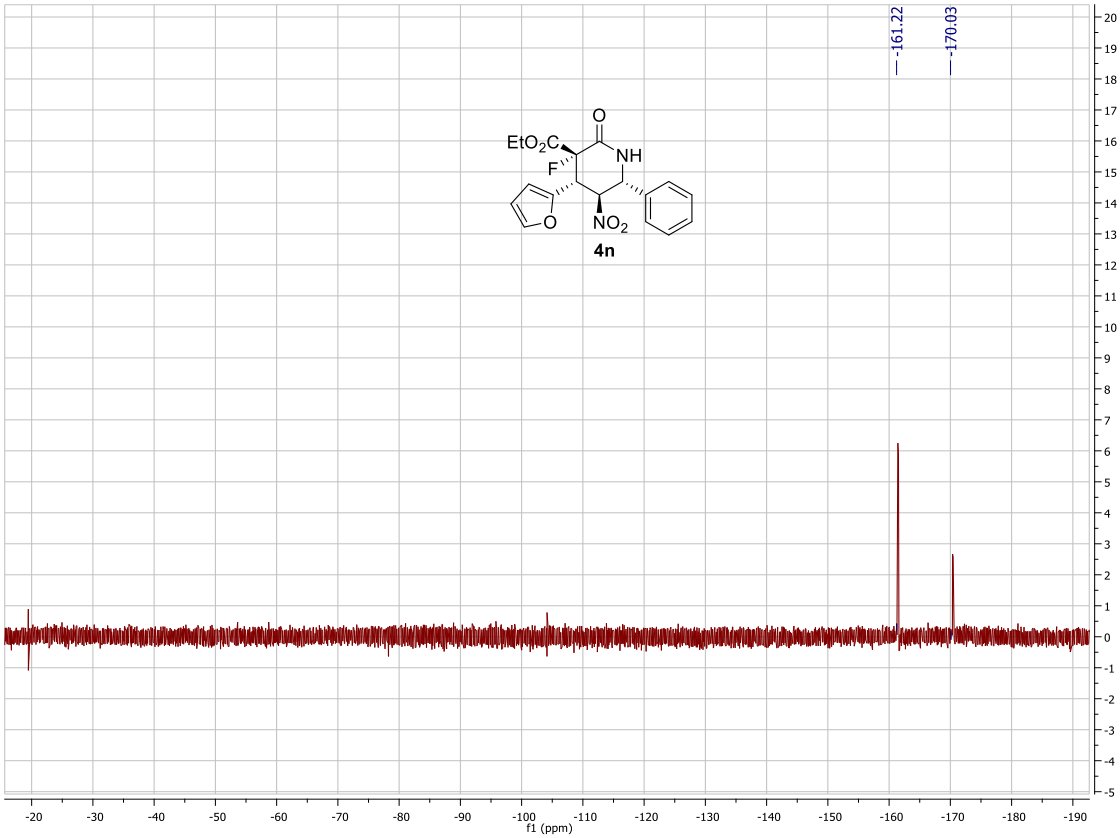

lactam-4-ome-styrene-13c
13C OBSERVE
135.43
130.51
129.83
127.19
127.00
121.58
114.55
88.36
63.43
60.45
55.37
49.95
49.70
14.17
EtO2C
O
NH
F
NO2
MeO
4m
f1 (ppm)

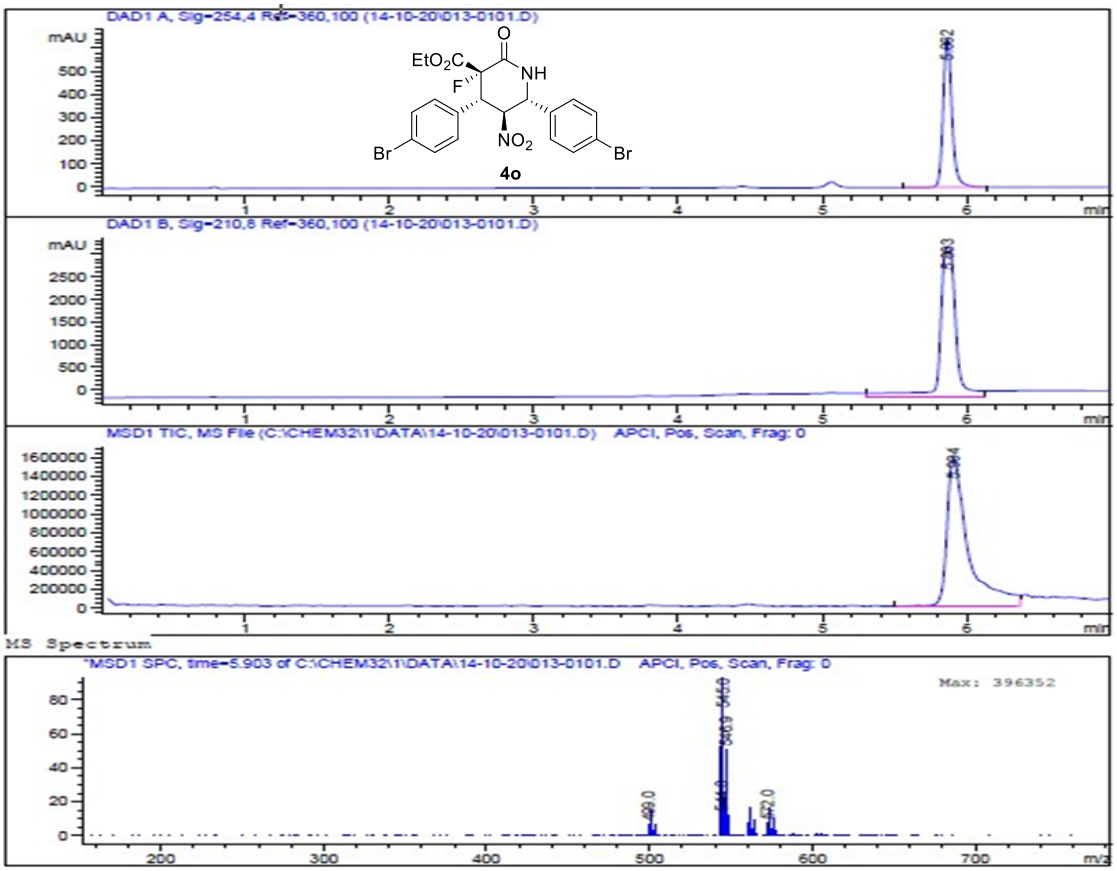

lactam-4-ome-styrene-19f
19F OBSERVE
STANDARD PARAMETERS
-163.30
EtO2C
O
NH
F
NO2
MeO
4m
f1 (ppm)

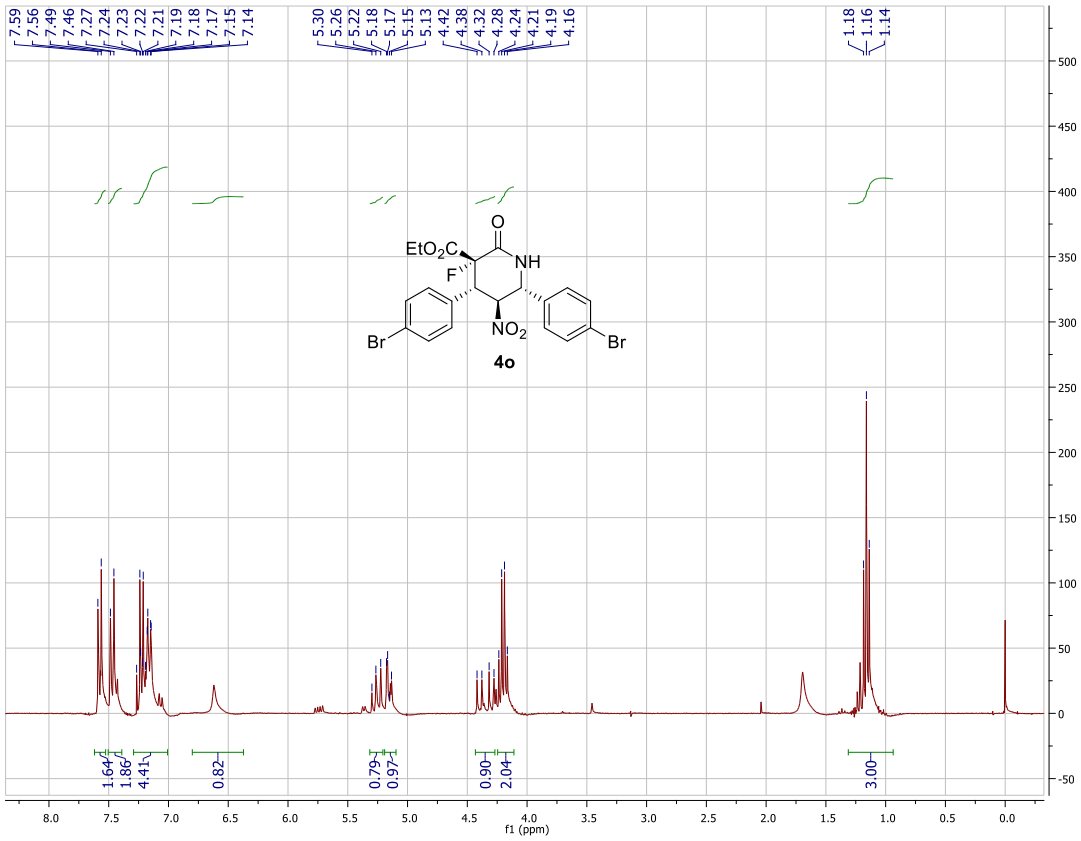

DAD1 A, Sig=254,4 Ref=360,100 (14-12-17\002-0101.D)
mAU
4.045
4.186
DAD1 B, Sig=210,8 Ref=360,100 (14-12-17\002-0101.D)
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-12-17\002-0101.D) APCI, Pos, Scan, Frag: 0
MS Spectrum
*MSD1 SPC, time=4.998 of C:\CHEM32\1\DATA\14-12-17\002-0101.D APCI, Pos, Scan, Frag: 0
Max: 3.56966e+006
377.1
318.2
394.1
min
m/z

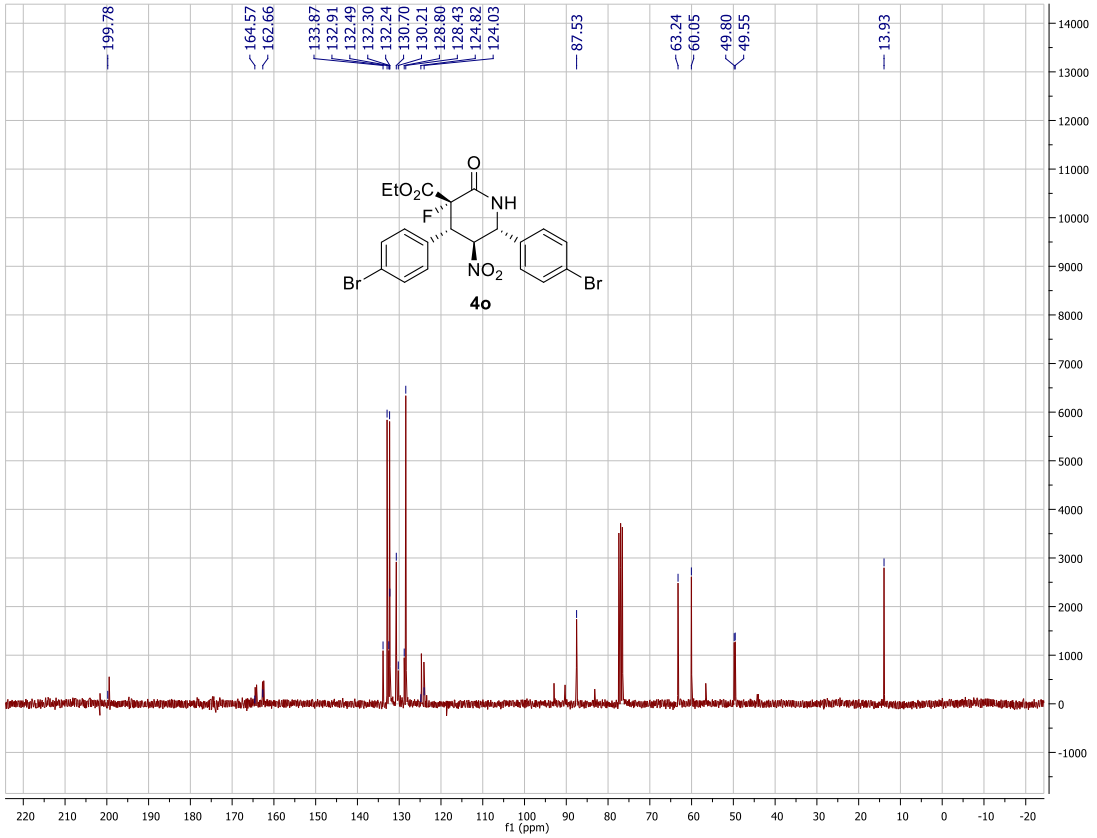

7.46
7.45
7.44
7.30
7.26
7.26
6.40
6.30
6.30
6.24
6.23
5.77
5.75
5.43
5.41
5.40
4.72
4.68
4.62
4.58
4.43
4.40
4.38
4.36
1.37
1.35
1.32
4n
3.47
1.84
0.34
0.62
0.59
0.69
1.06
0.59
2.01
3.00
f1 (ppm)

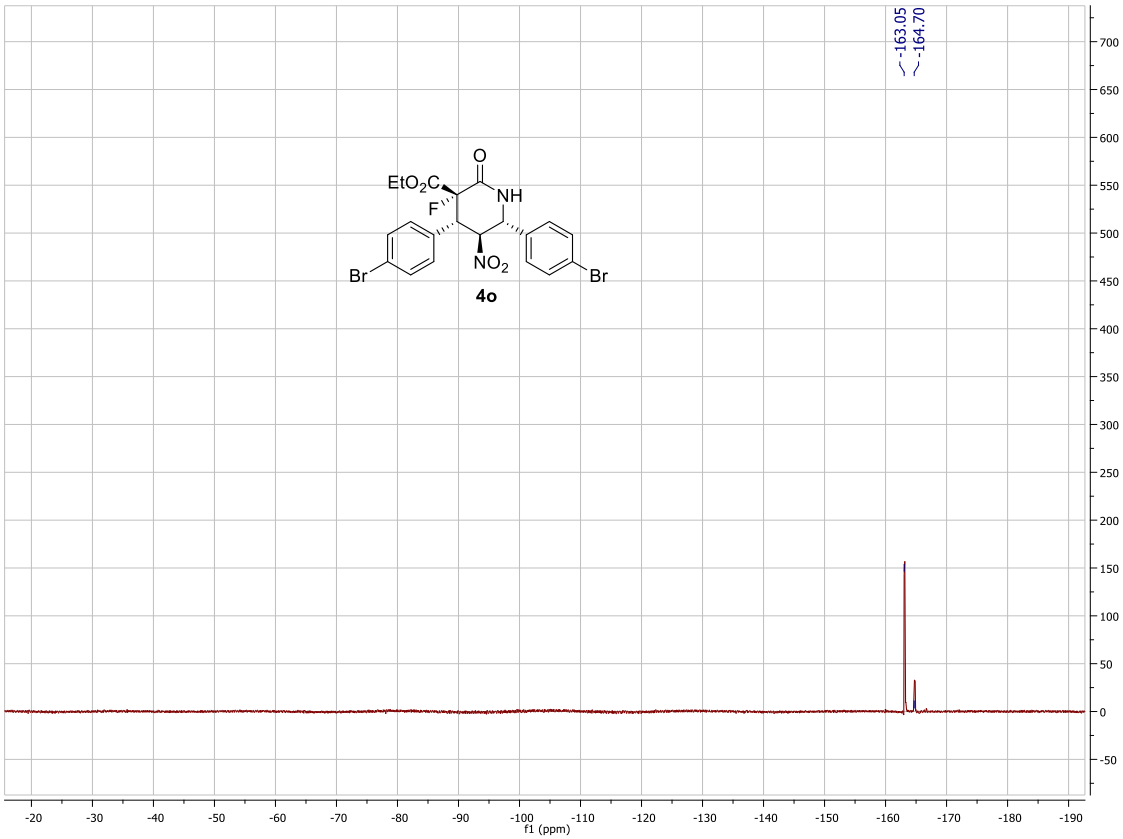

215.55
201.27
143.95
143.40
134.78
130.46
129.68
126.89
110.81
86.64
73.17
63.32
60.41
44.36
41.60
EtO2C
F
O
NH
O
NO2
4n
f1 (ppm)

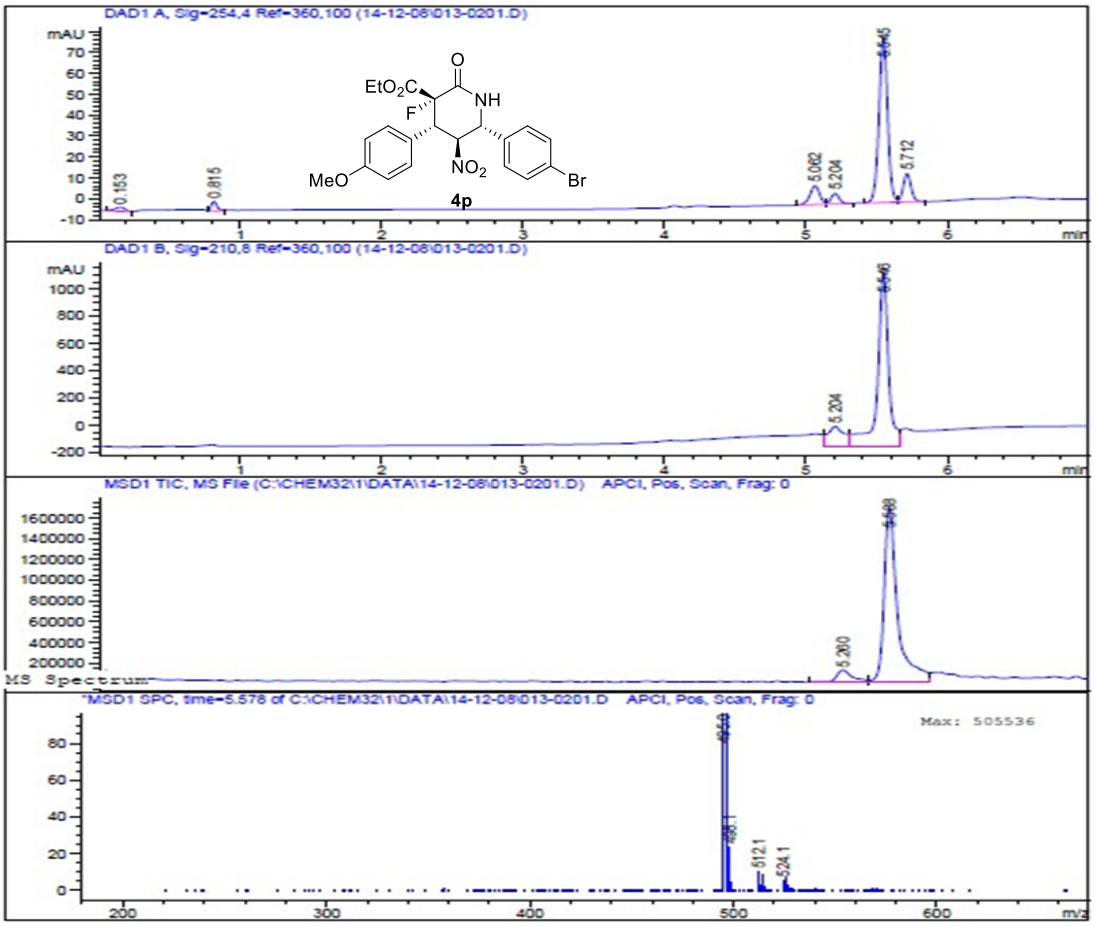

-161.22
-170.03
EtO2C
F
O
NH
O
NO2
4n
f1 (ppm)

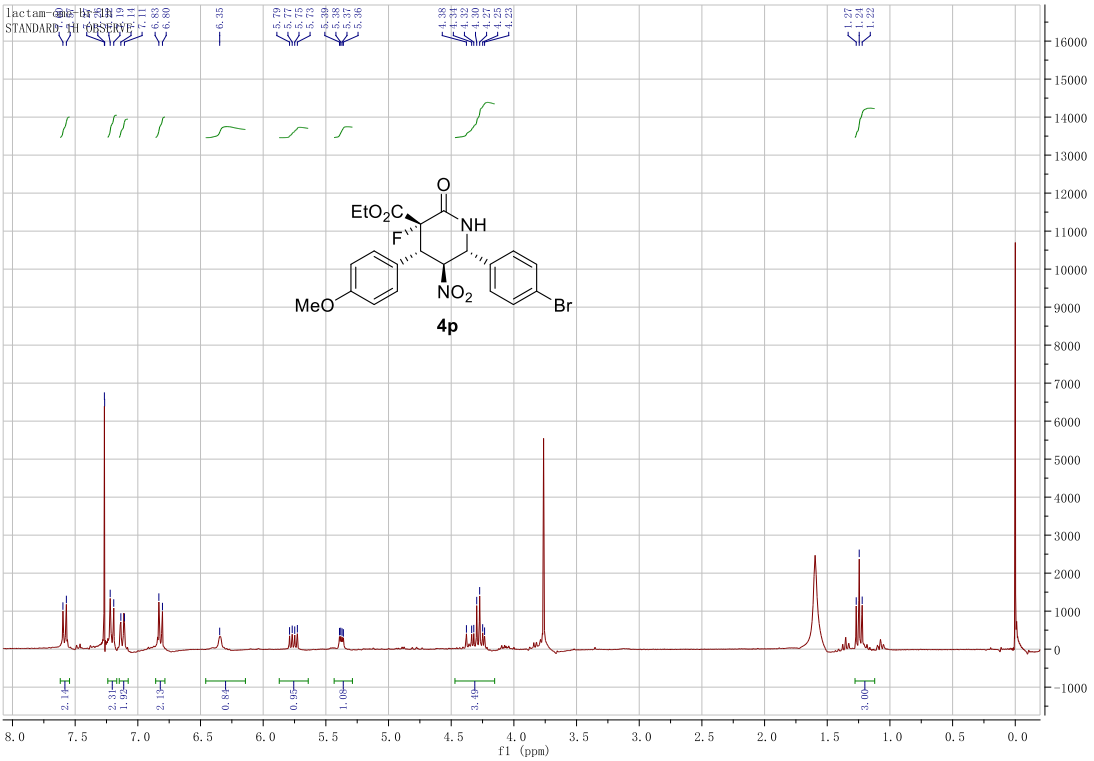

DAD1 A, Sig=254,4 Ref=360,100 (14-10-20\013-0101.D)
mAU
min
DAD1 B, Sig=210,8 Ref=360,100 (14-10-20\013-0101.D)
mAU
min
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-10-20\013-0101.D) APCI, Pos, Scan, Frag: 0
min
MS Spectrum
*MSD1 SPC, time=5.903 of C:\CHEM32\1\DATA\14-10-20\013-0101.D APCI, Pos, Scan, Frag: 0
Max: 396352
m/z

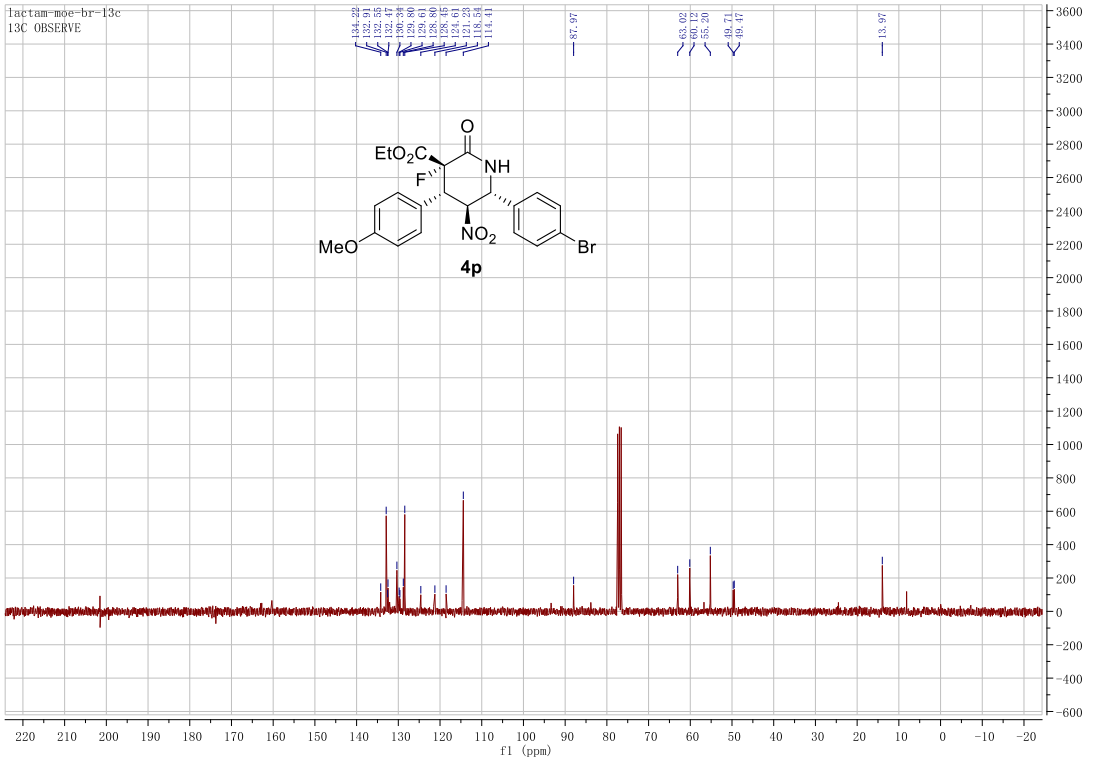

7.59
7.56
7.49
7.46
7.27
7.24
7.23
7.22
7.21
7.19
7.18
7.17
7.15
7.14
5.30
5.26
5.22
5.18
5.17
5.15
5.13
4.42
4.38
4.32
4.28
4.24
4.21
4.19
4.16
1.18
1.16
1.14
1.64
1.86
4.41
0.82
0.79
0.97
0.90
2.04
3.00
f1 (ppm)

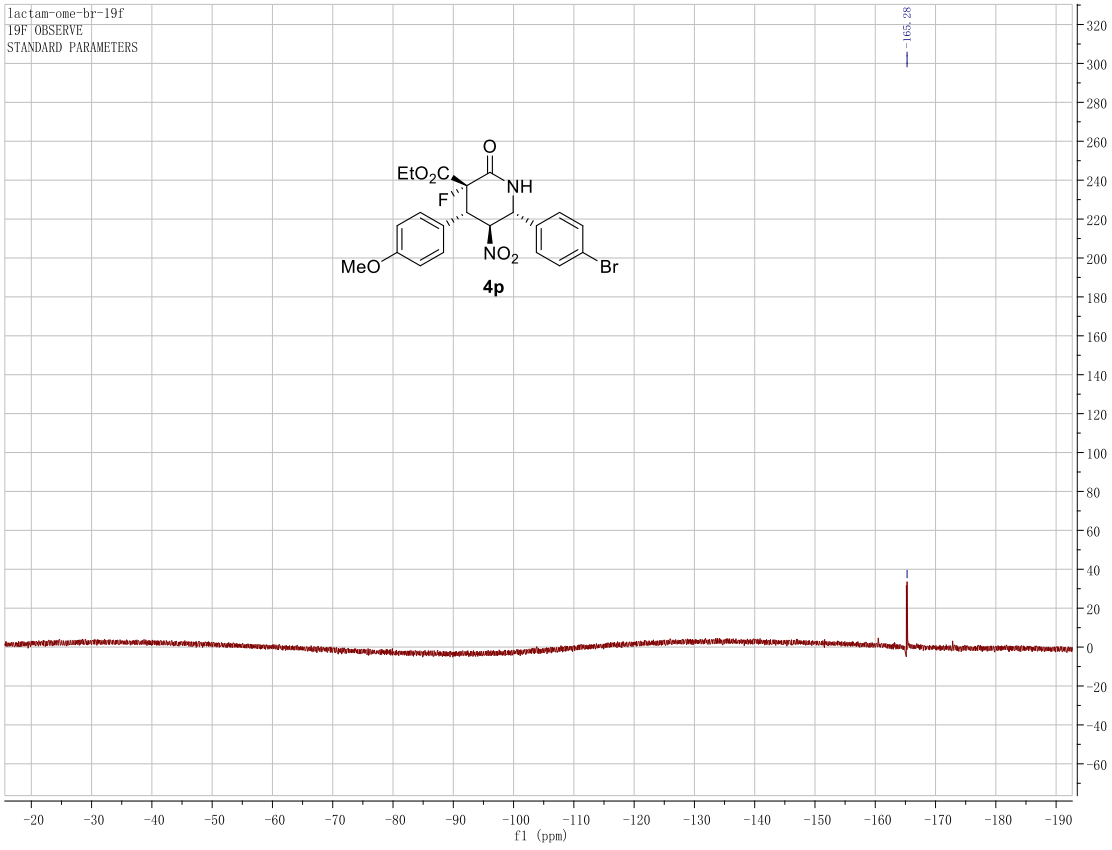

199.78
164.57
162.66
133.87
132.91
132.49
132.30
132.24
130.70
130.21
128.80
128.43
124.82
124.03
87.53
63.24
60.05
49.80
49.55
13.93
O
EtO2C
NH
F
NO2
Br
Br
4o
f1 (ppm)

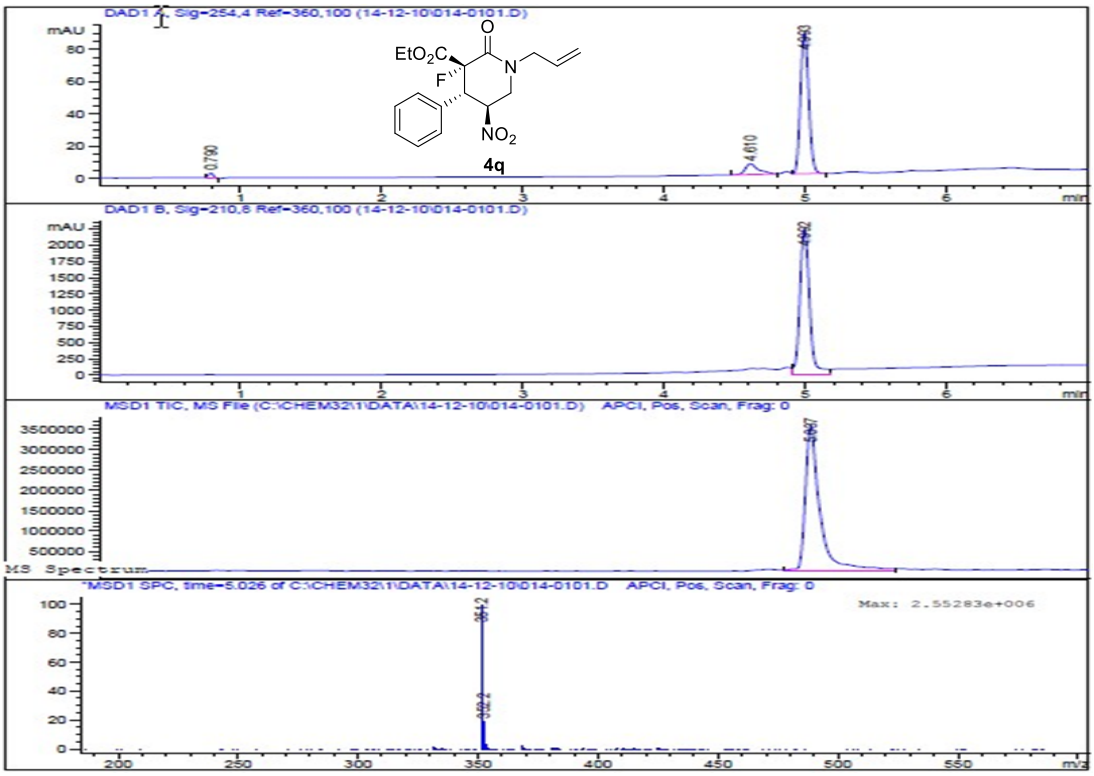

-163.05
-164.70
O
EtO2C
NH
F
NO2
Br
Br
4o
f1 (ppm)

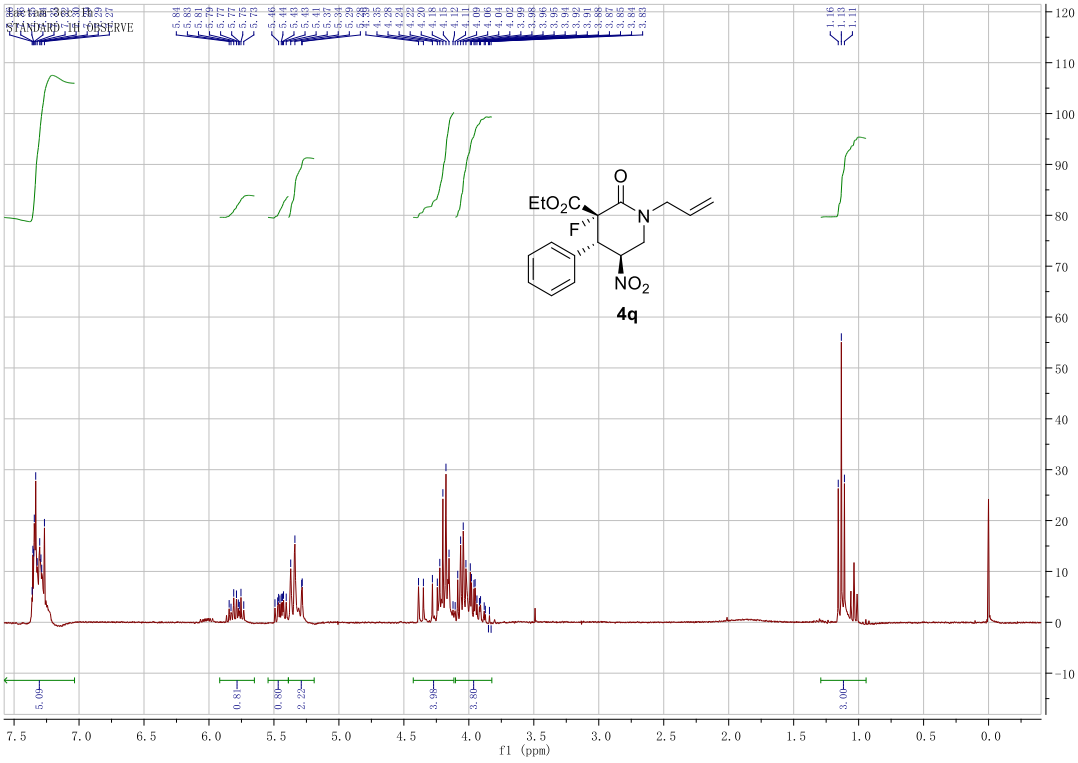

DAD1 A, Sig=254,4 Ref=360,100 (14-12-08\013-0201.D)
mAU
0.153
0.815
5.062
5.204
5.645
5.712
min
DAD1 B, Sig=210,8 Ref=360,100 (14-12-08\013-0201.D)
mAU
5.204
5.646
min
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-12-08\013-0201.D) APCI, Pos, Scan, Frag: 0
5.200
5.588
MS Spectrum
*MSD1 SPC, time=5.578 of C:\CHEM32\1\DATA\14-12-08\013-0201.D APCI, Pos, Scan, Frag: 0
Max: 505536
468.1
512.1
524.1
m/z
O
EtO2C
NH
F
NO2
MeO
Br
4p

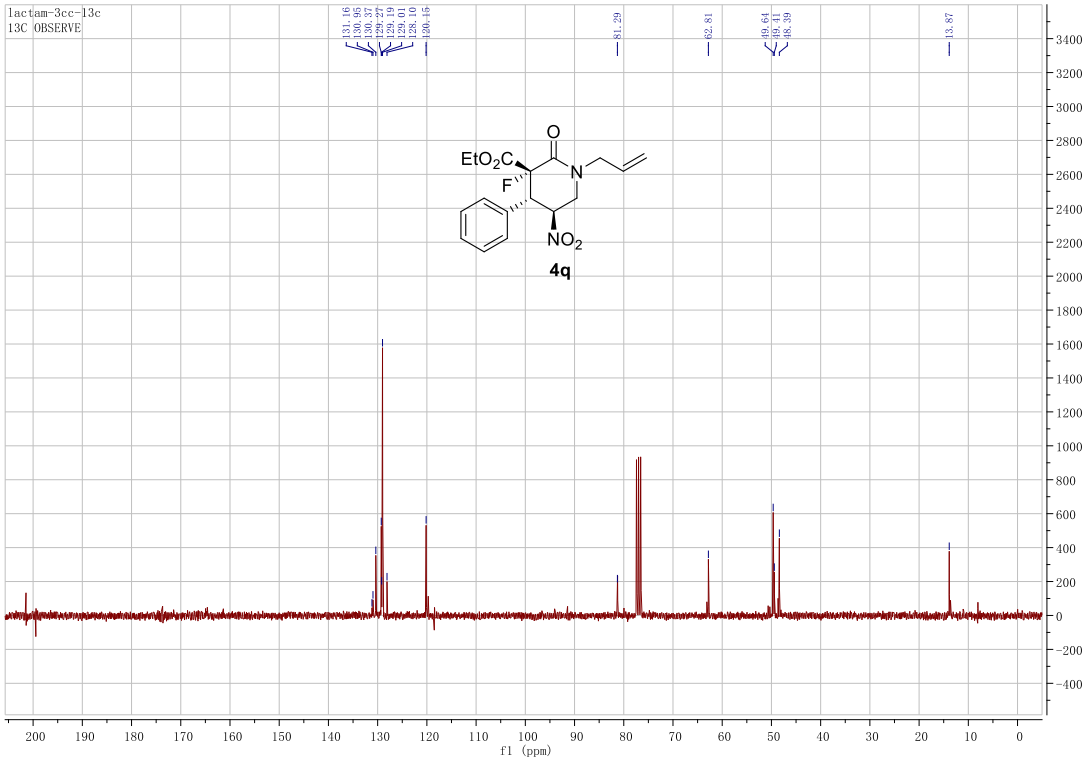

O
EtO2C
NH
F
NO2
MeO
Br
4p
f1 (ppm)

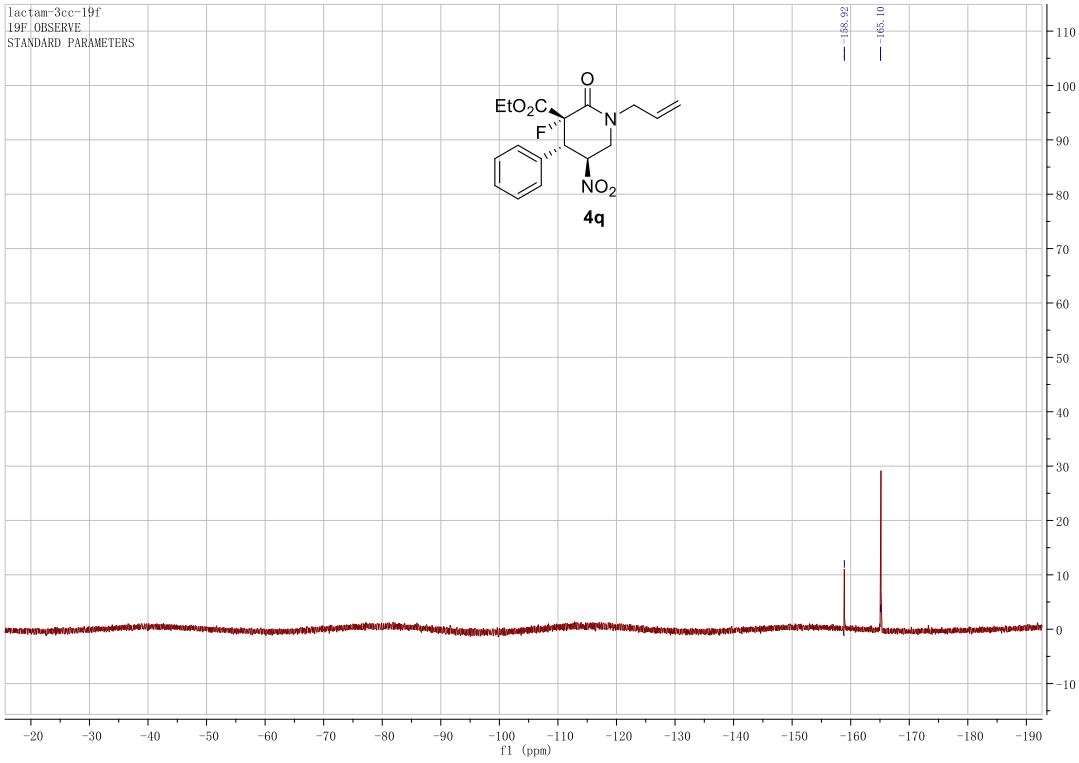

lactam-moe-br-13c
13C OBSERVE
134.22
132.91
132.45
132.47
130.34
129.80
129.61
128.80
128.45
124.61
121.23
116.54
114.41
87.97
63.02
60.12
55.20
49.71
48.47
13.97
EtO2C
F
O
NH
NO2
MeO
Br
4p
f1 (ppm)


lactam-ome-br-19f
19F OBSERVE
STANDARD PARAMETERS
-165.28
EtO2C
F
O
NH
NO2
MeO
Br
4p
f1 (ppm)

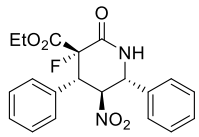

DAD1 A, Sig=254,4 Ref=360,100 (14-12-10\D14-0101.D)
mAU
EtO2C
F
N
NO2
4q
0.790
4.610
min
DAD1 B, Sig=210,8 Ref=360,100 (14-12-10\D14-0101.D)
MSD1 TIC, MS File (C:\CHEM32\1\DATA\14-12-10\D14-0101.D) APCI, Pos, Scan, Frag: 0
MS Spectrum
*MSD1 SPC, time=5.026 of C:\CHEM32\1\DATA\14-12-10\D14-0101.D APCI, Pos, Scan, Frag: 0
Max: 2.55283e+006
m/z


EtO2C
F
N
NO2
4q
f1 (ppm)

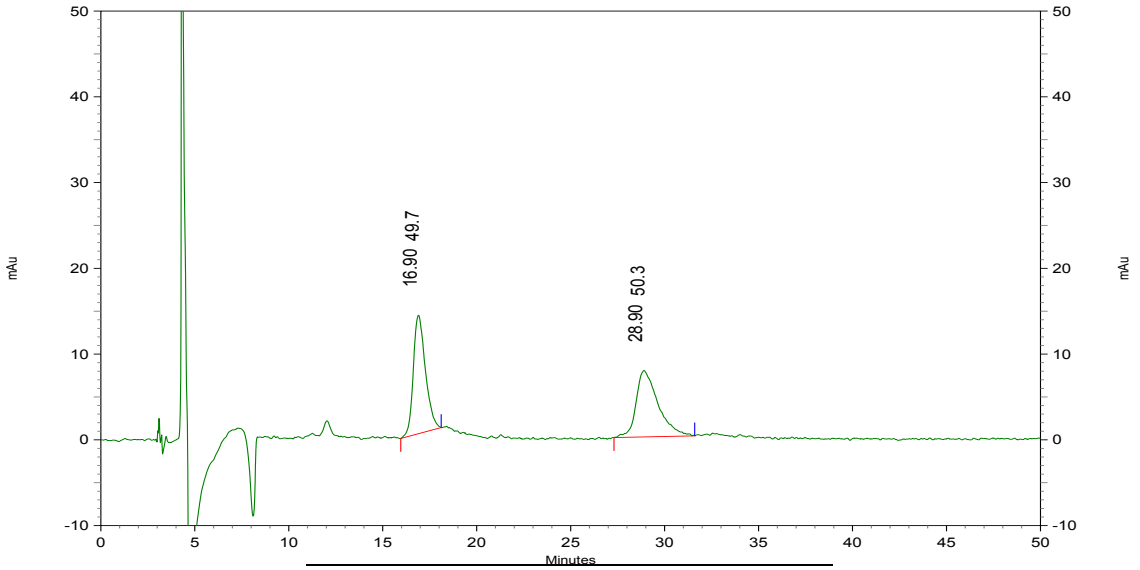

lactam-3cc-13c
13C OBSERVE
131.16
130.95
130.37
129.27
129.19
129.01
128.10
120.46
81.29
62.81
49.64
49.41
48.39
13.87
O
EtO2C
F
N
NO2
4q
f1 (ppm)


lactam-3cc-19f
19F OBSERVE
STANDARD PARAMETERS
158.92
165.10
O
EtO2C
F
N
NO2
4q
f1 (ppm)

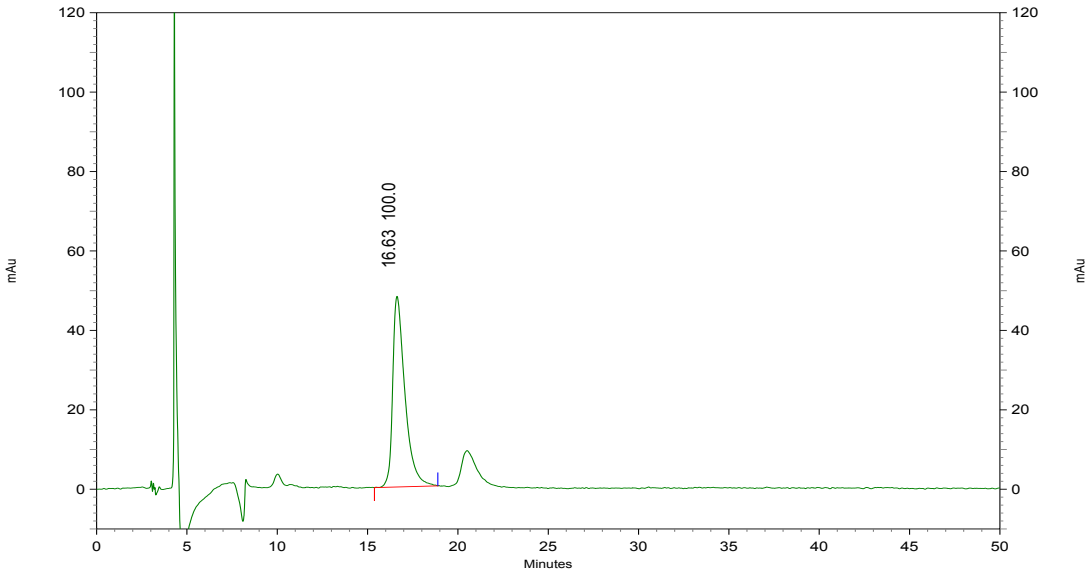
Chiral LC of Products:



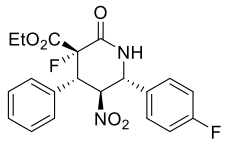
4a



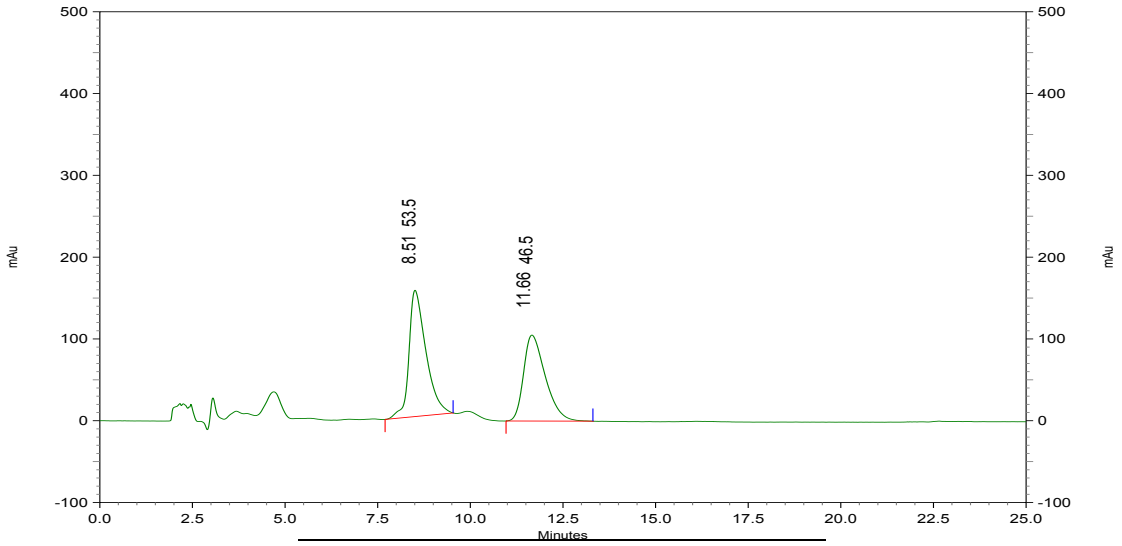
Time	Area %	Height %
16.900	49.66	64.05
28.900	50.34	35.95



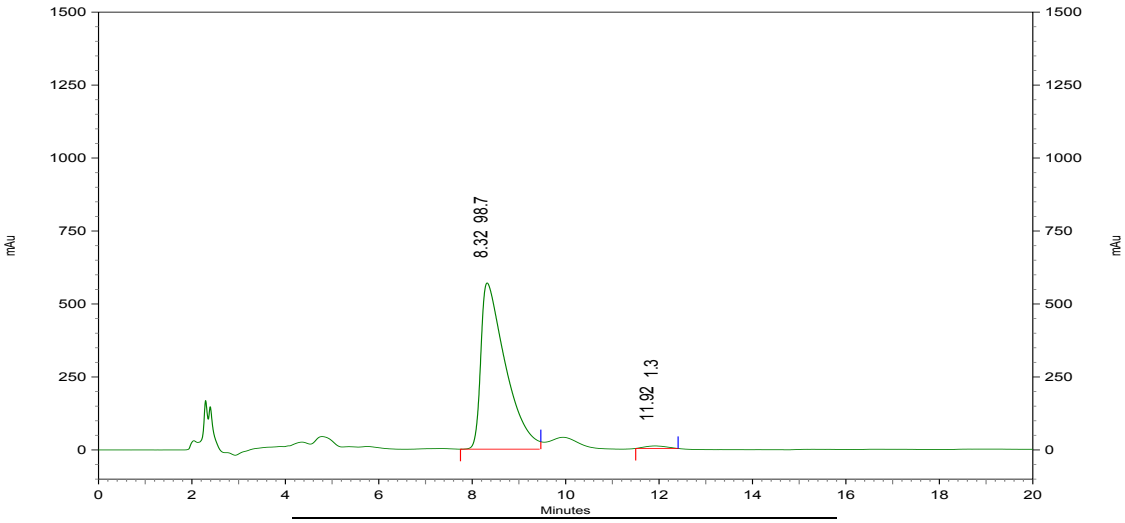
Time	Area %	Height %
16.628	100.00	100.00



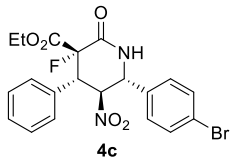
4b



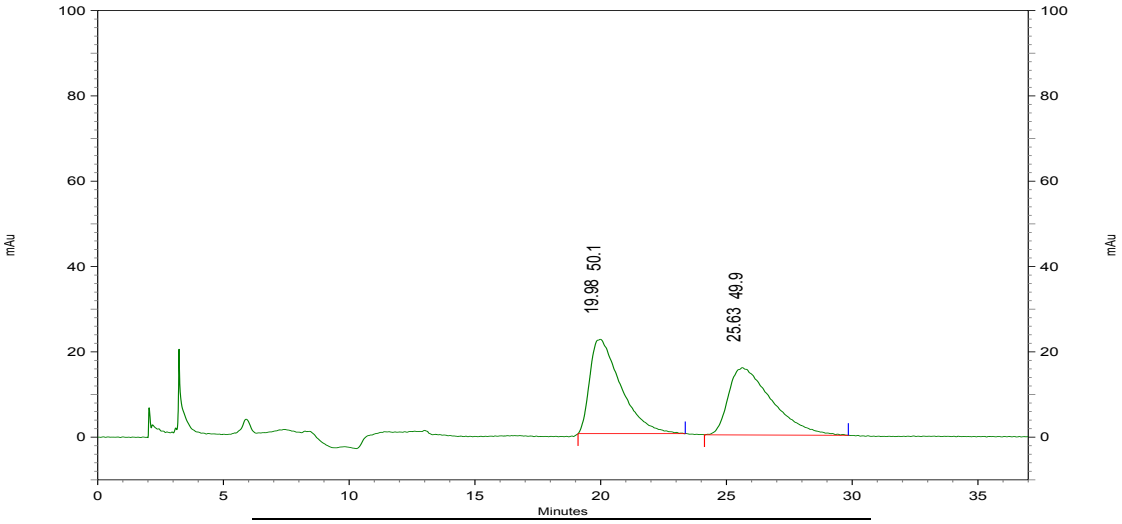
Time	Area %	Height %
8.508	53.52	59.51
11.664	46.48	40.49



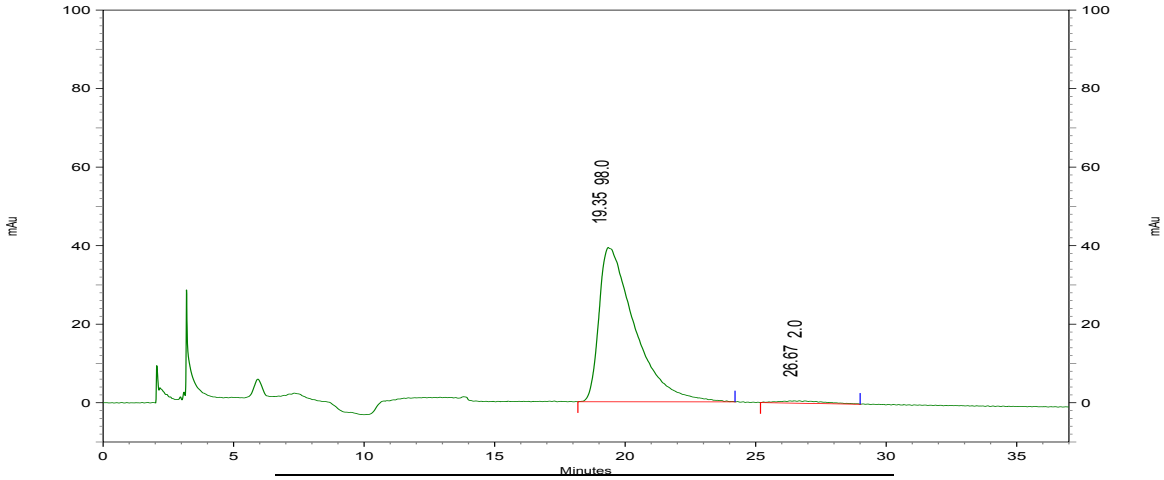
Time	Area %	Height %
8.320	98.70	98.52
11.920	1.30	1.48



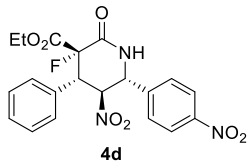
4c



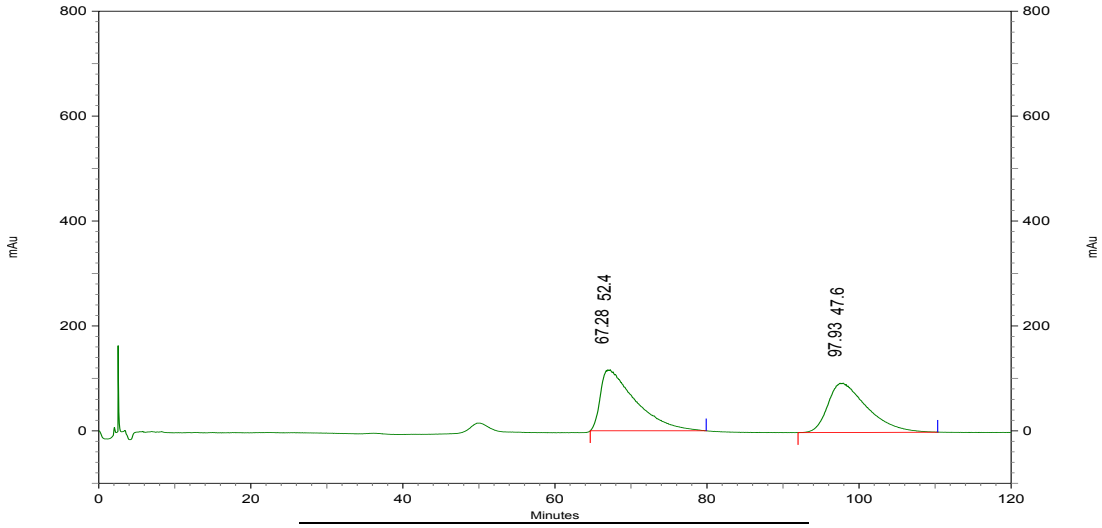
Time	Area %	Height %
19.976	50.11	58.36
25.628	49.89	41.64



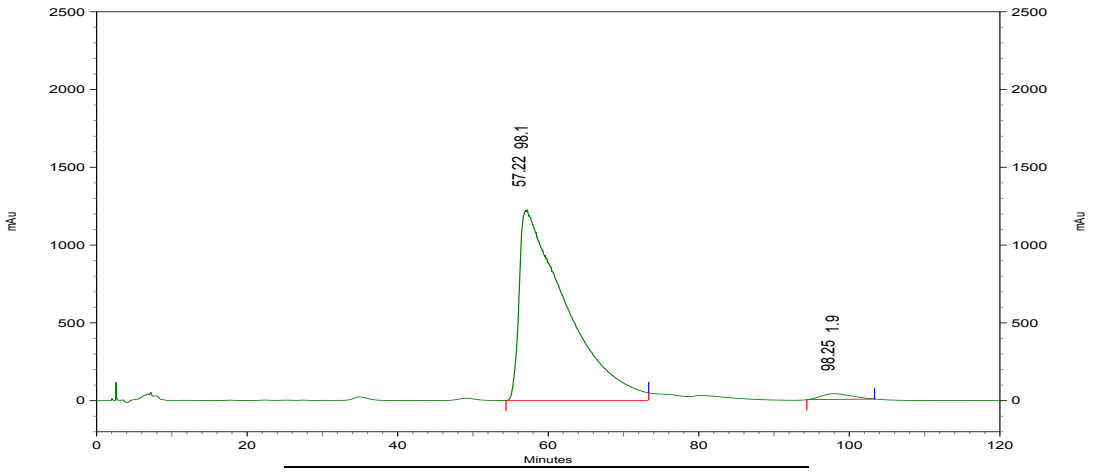
Time	Area %	Height %
19.352	98.02	98.42
26.672	1.98	1.58



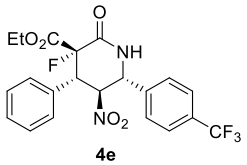
4d



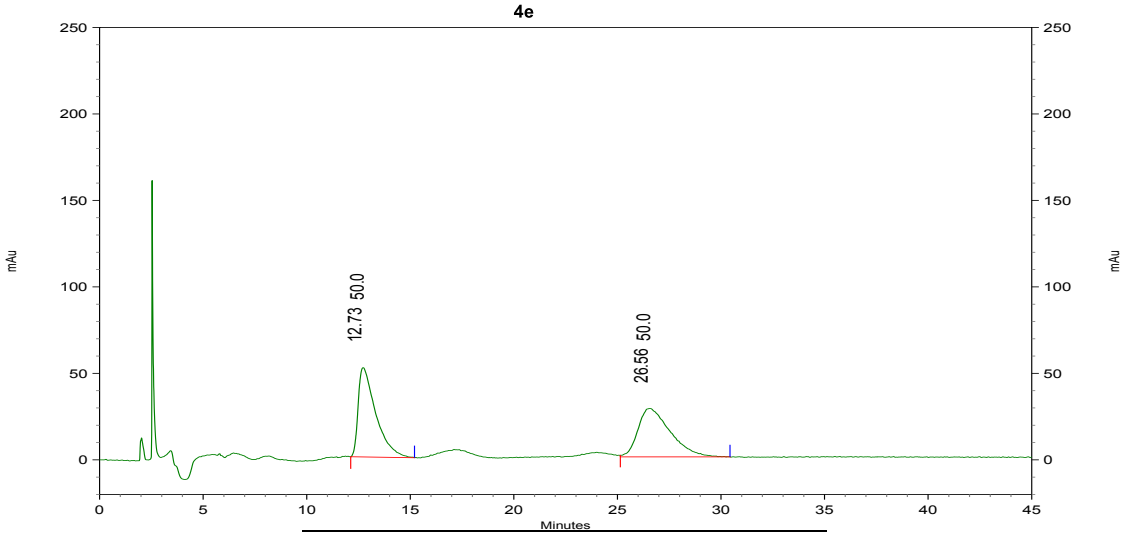
Time	Area %	Height %
67.280	52.40	55.30
97.932	47.60	44.70



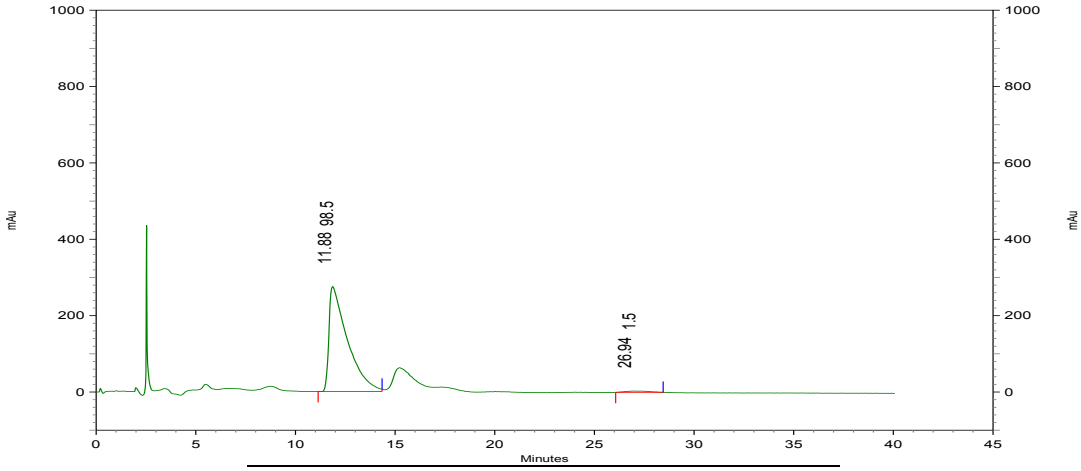
Time	Area %	Height %
57.224	98.08	97.09
98.252	1.92	2.91



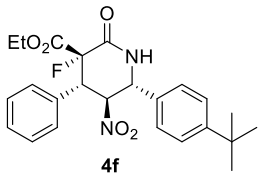
4e



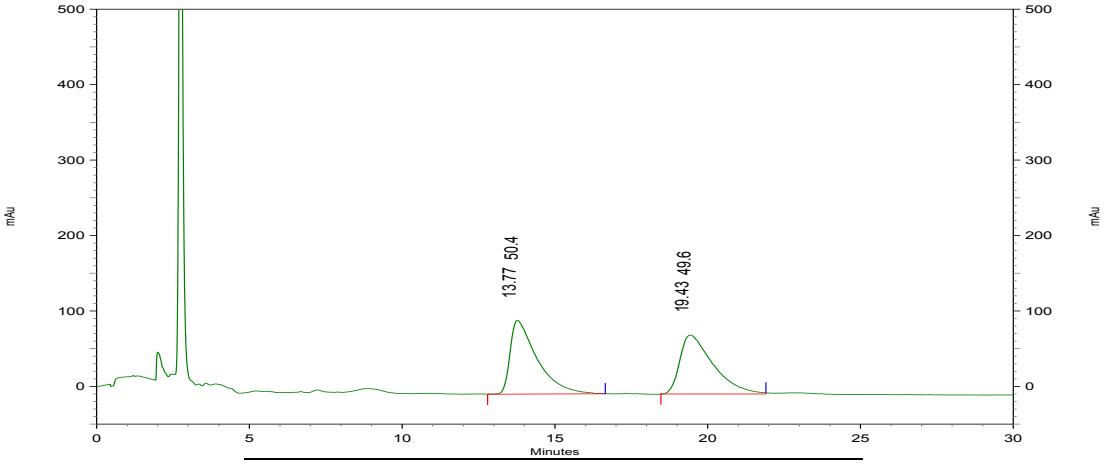
Time	Area %	Height %
12.732	49.78	56.39
26.567	50.22	43.61



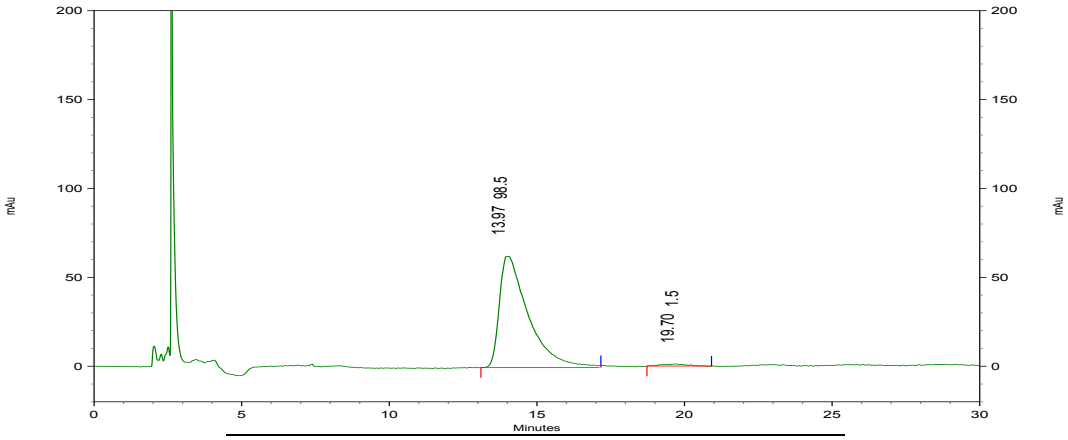
Time	Area %	Height %
11.876	98.54	98.79
26.936	1.46	1.21



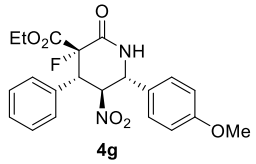
4f



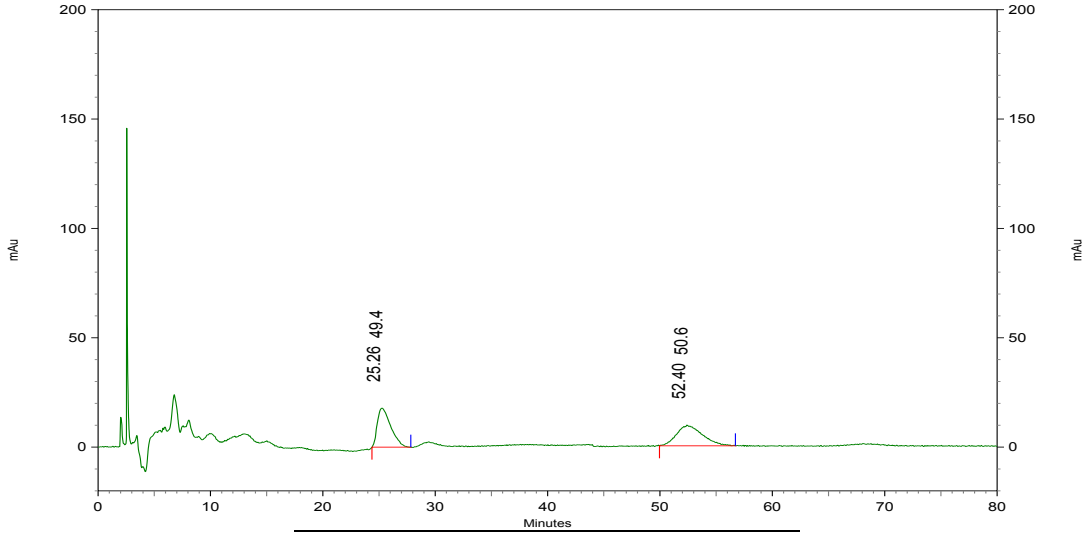
Time	Area %	Height %
13.772	50.35	55.59
19.428	49.65	44.41



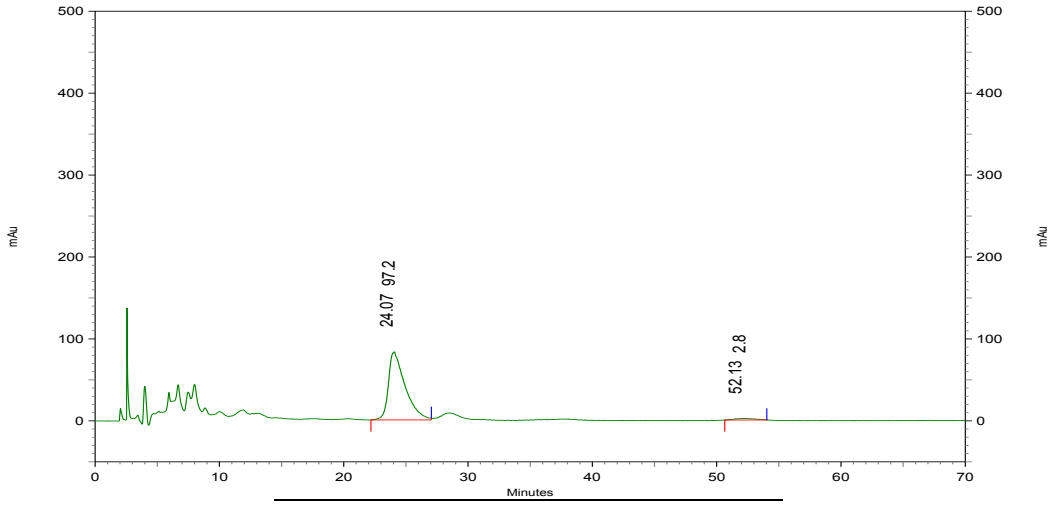
Time	Area %	Height %
13.968	98.51	98.12
19.700	1.49	1.88



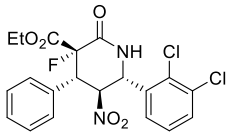
4g



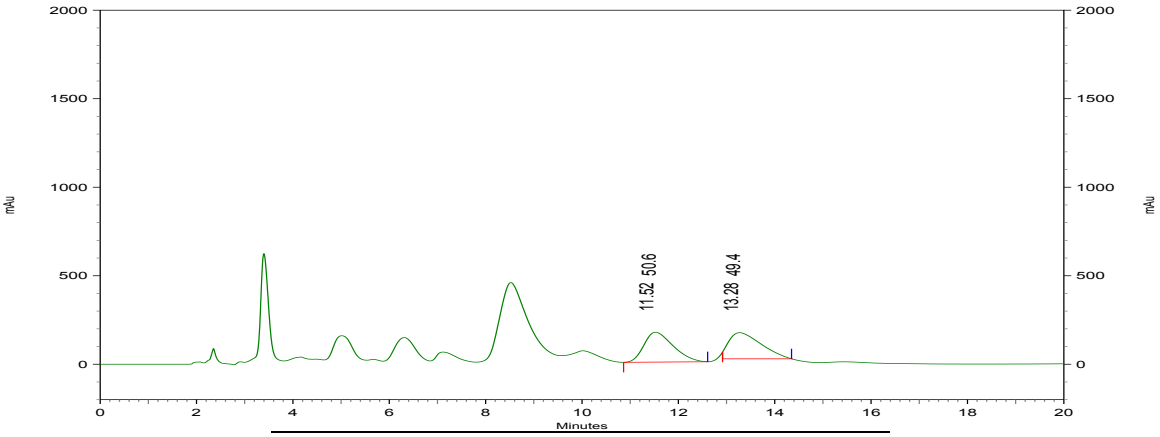
Time	Area %	Height %
25.264	49.41	65.21
52.404	50.59	34.79



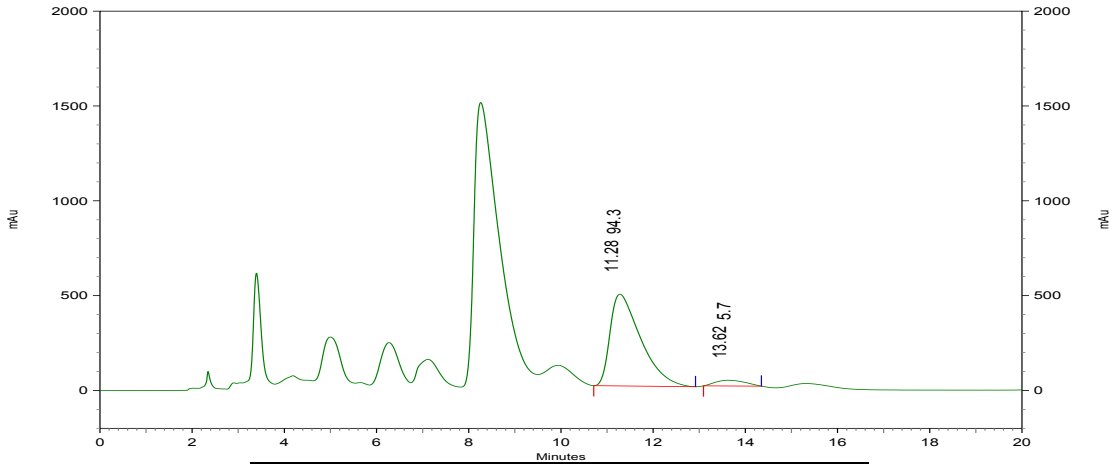
Time	Area %	Height %
24.072	97.19	97.53
52.132	2.81	2.47



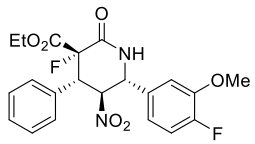
4h



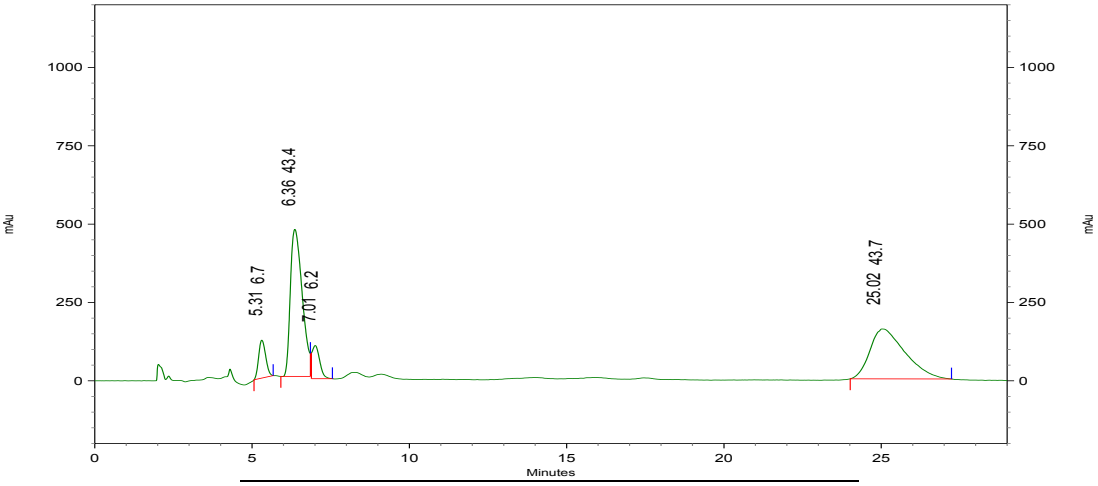
Time	Area %	Height %
11.524	50.63	53.33
13.276	49.37	46.67



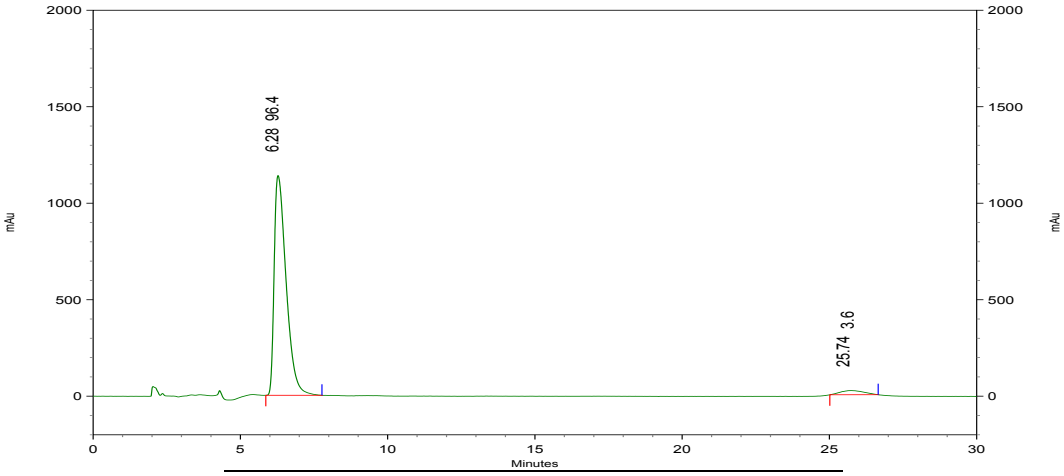
Time	Area %	Height %
11.280	94.30	94.14
13.620	5.70	5.86



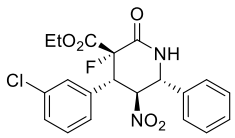
4i



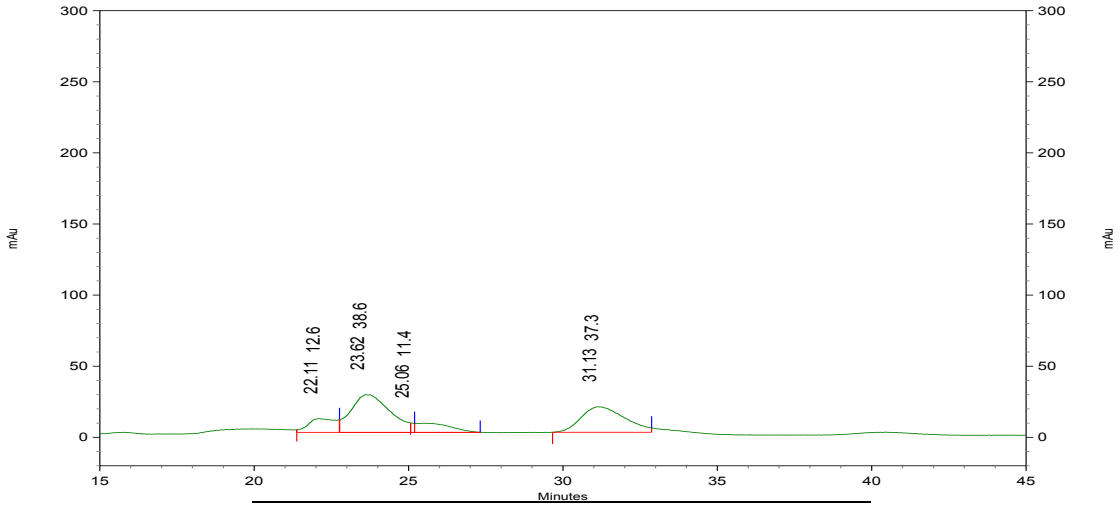
Time	Area %	Height %
5.308	6.66	14.14
6.360	43.43	54.86
7.008	6.18	12.38
25.020	43.74	18.62



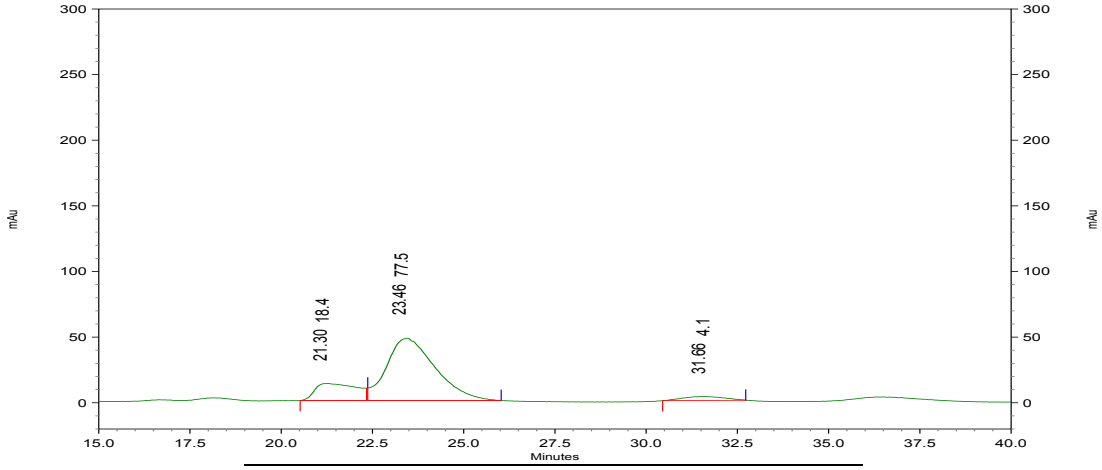
Time	Area %	Height %
6.280	96.38	98.14
25.744	3.62	1.86



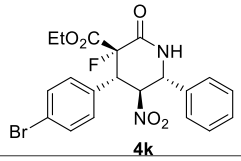
4j



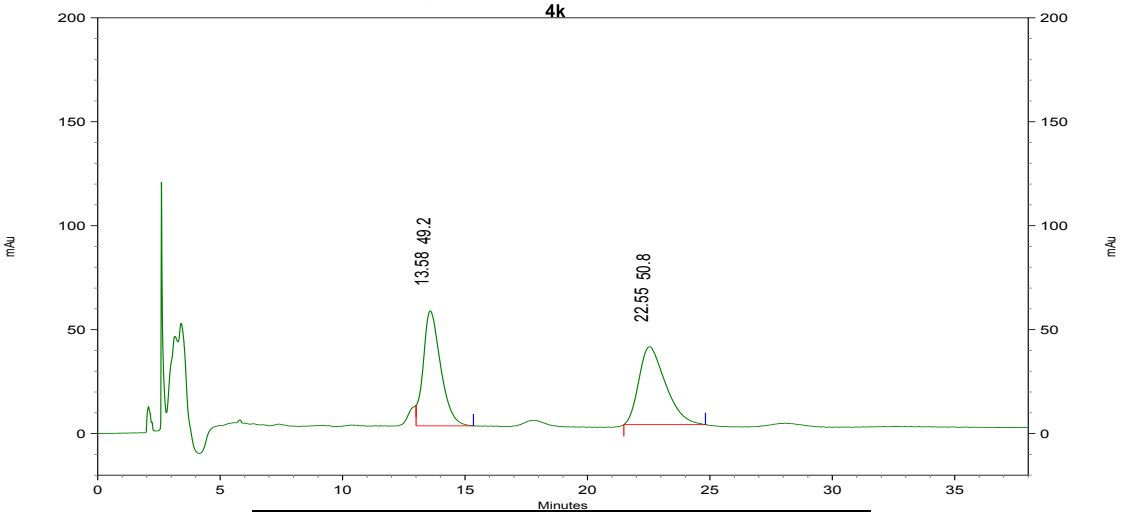
Time	Area %	Height %
22.108	12.65	15.87
23.624	38.63	43.71
25.064	11.44	10.86
31.128	37.28	29.57



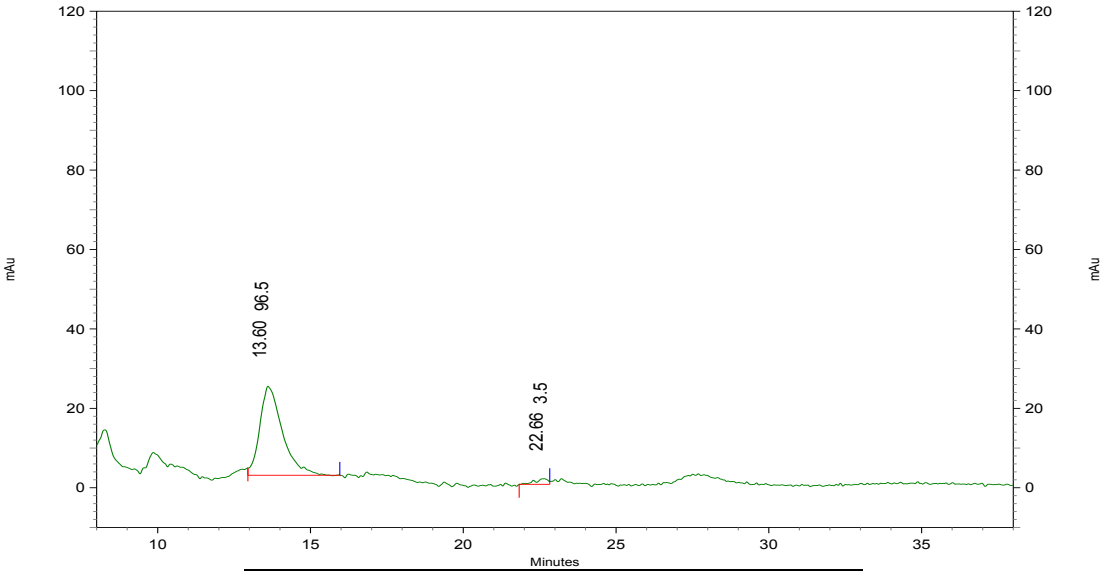
Time	Area %	Height %
21.296	18.39	20.38
23.460	77.52	75.02
31.664	4.09	4.60



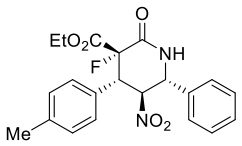
4k



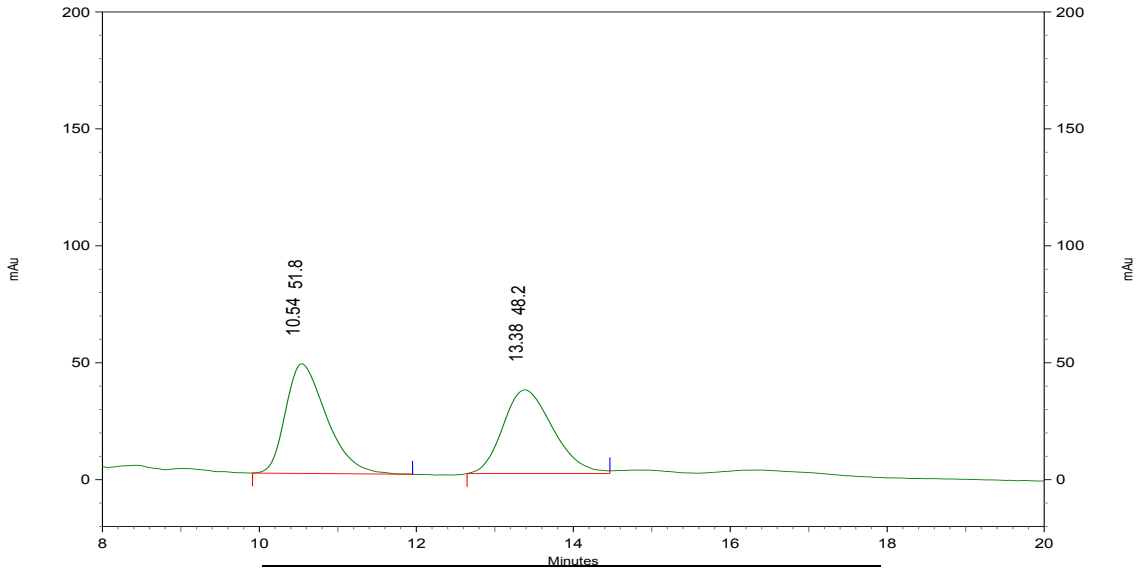
Time	Area %	Height %
13.576	49.18	59.64
22.548	50.82	40.36



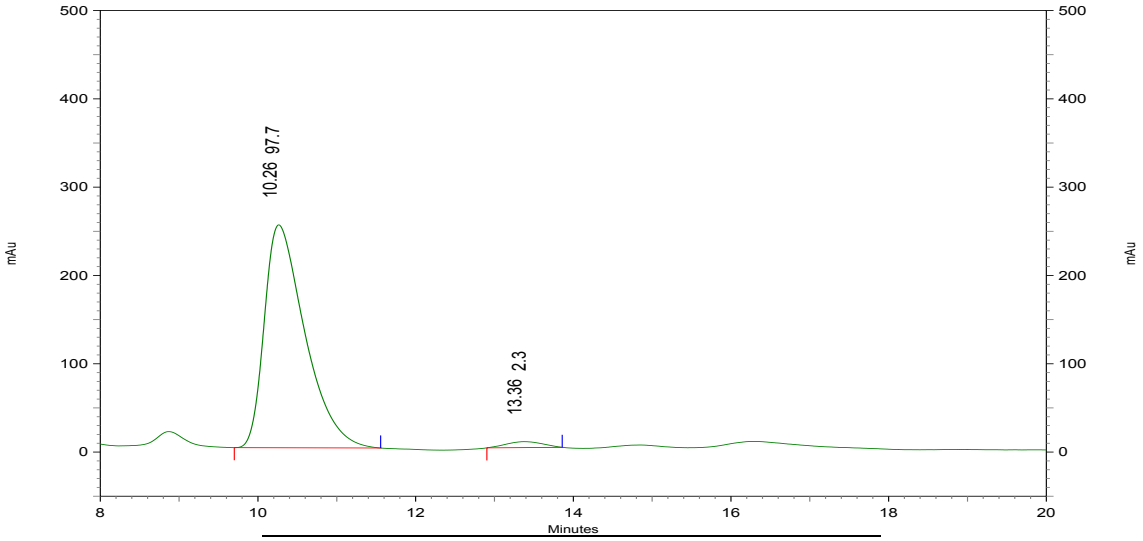
Time	Area %	Height %
13.604	96.55	94.04
22.656	3.45	5.96



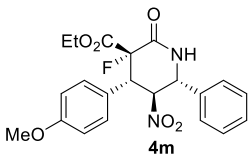
4l



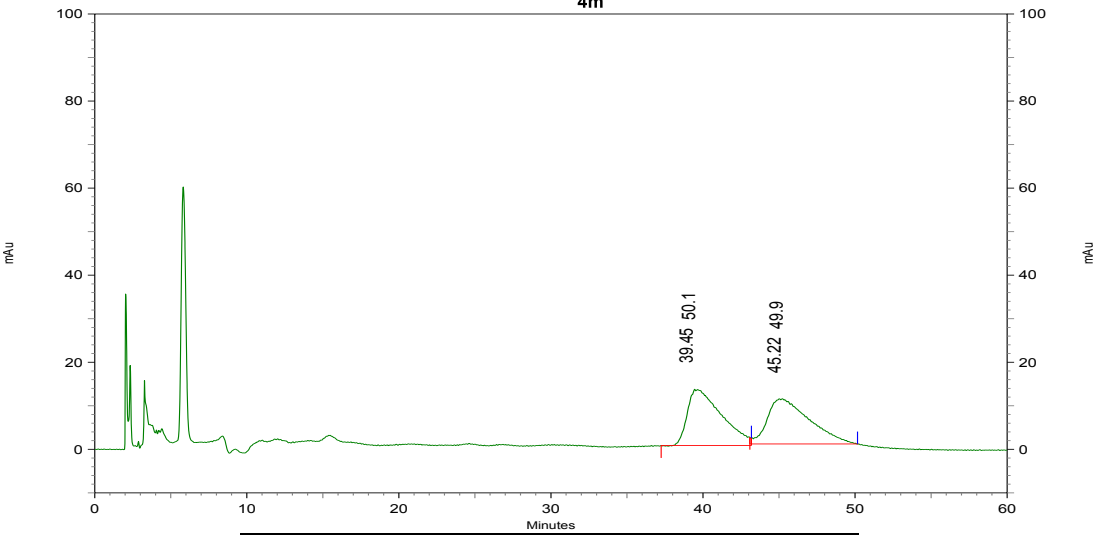
Time	Area %	Height %
10.540	51.76	56.70
13.380	48.24	43.30



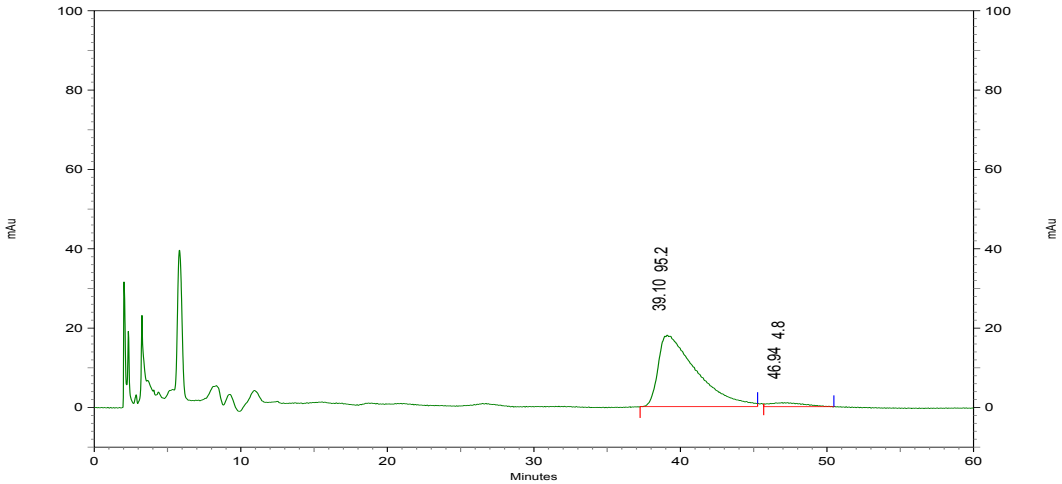
Time	Area %	Height %
10.264	97.68	97.42
13.364	2.32	2.58



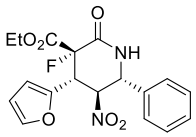
4m



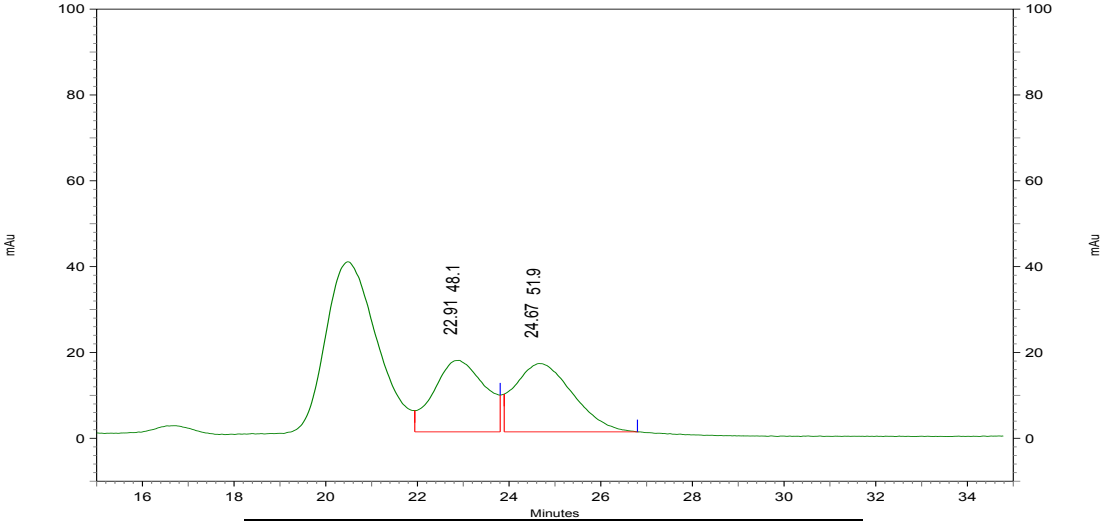
Time	Area %	Height %
39.452	50.13	55.45
45.224	49.87	44.55



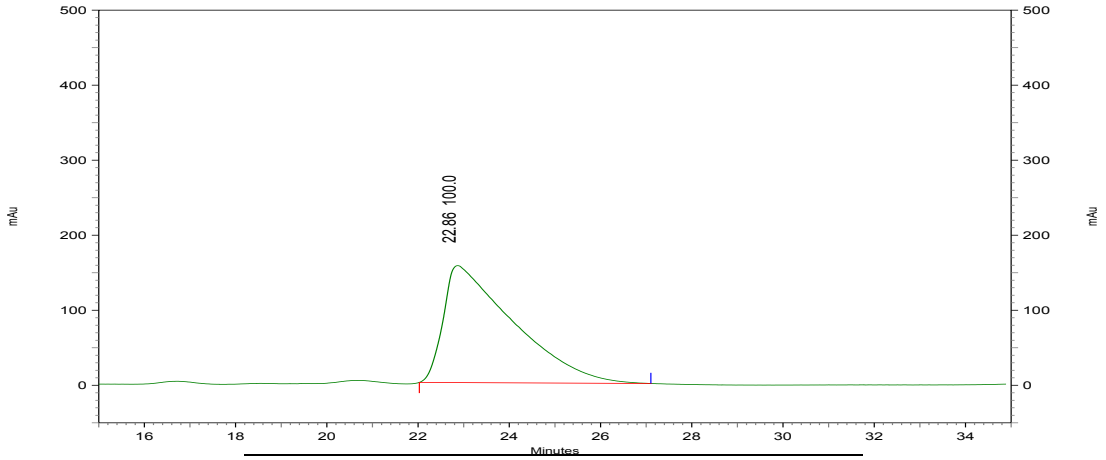
Time	Area %	Height %
39.096	95.20	94.57
46.940	4.80	5.43



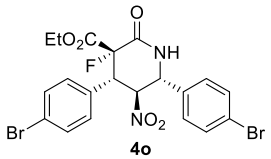
4n



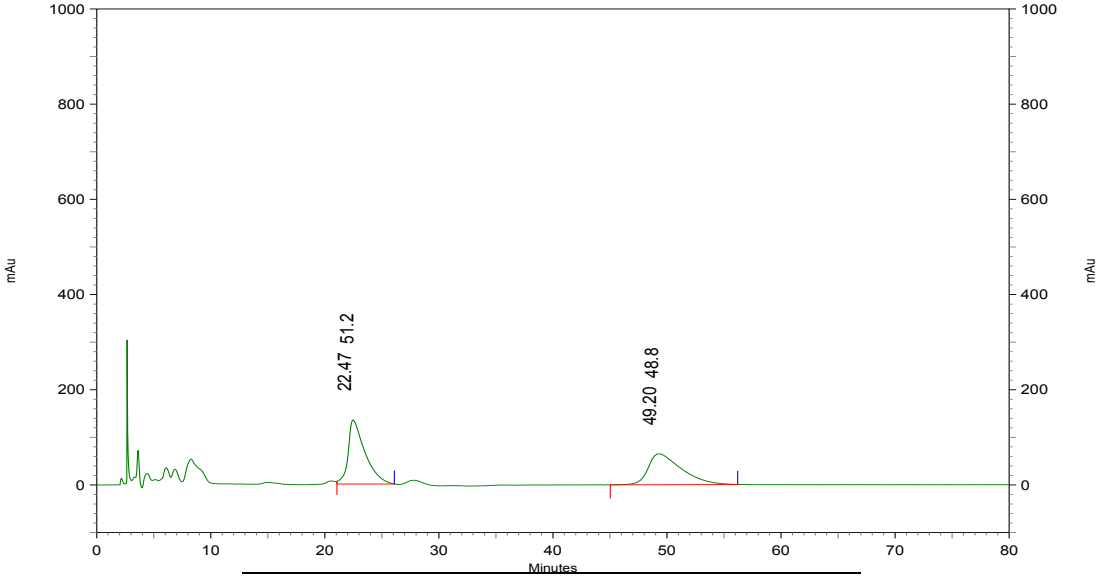
Time	Area %	Height %
22.908	48.11	51.16
24.668	51.89	48.84



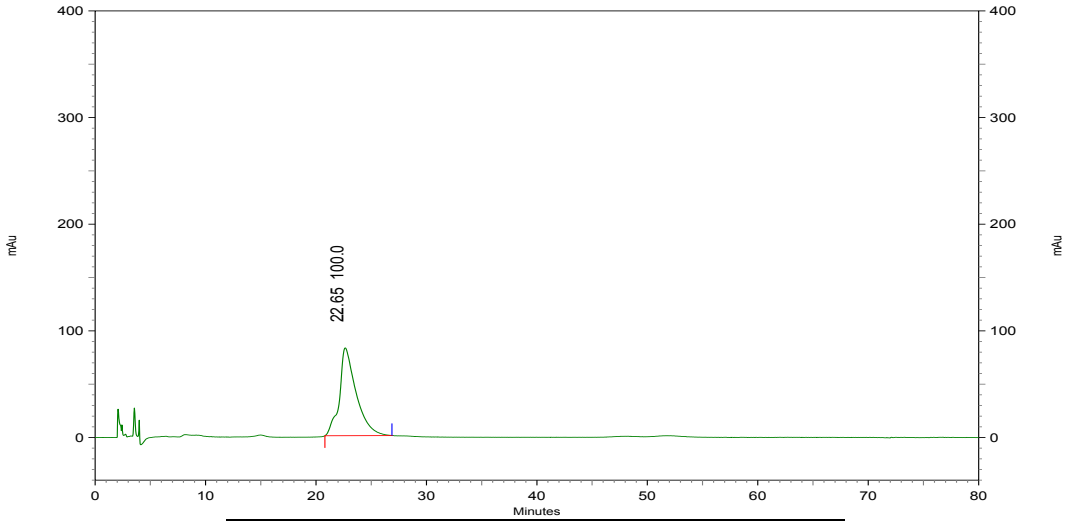
Time	Area %	Height %
22.864	100.00	100.00



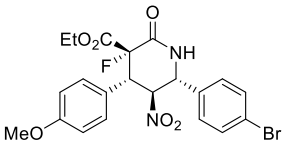
4o



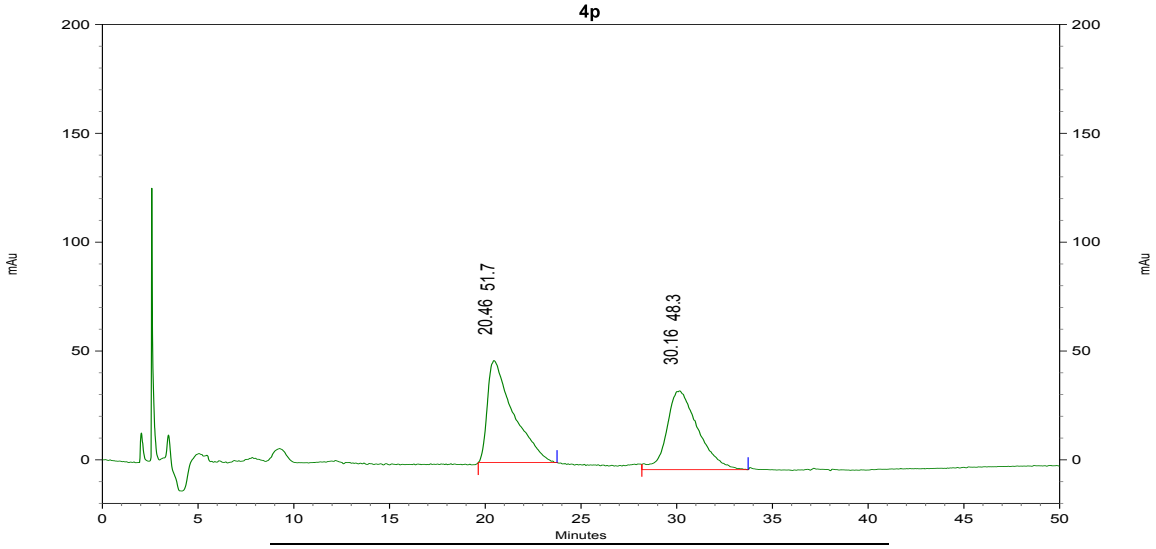
Time	Area %	Height %
22.472	51.23	67.47
49.200	48.77	32.53



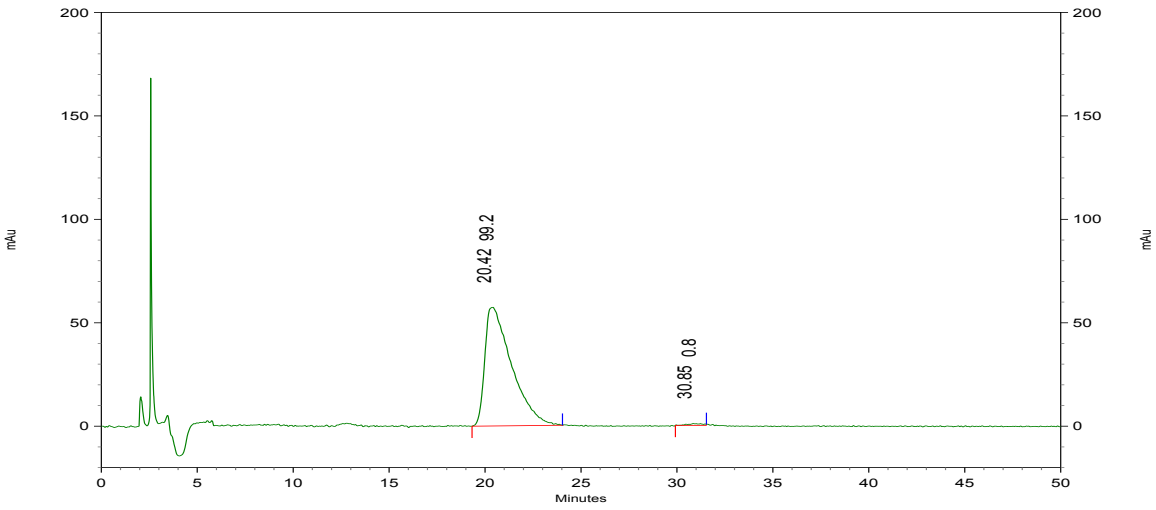
Time	Area %	Height %
22.648	100.00	100.00



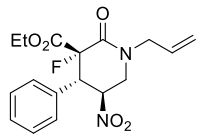
4p



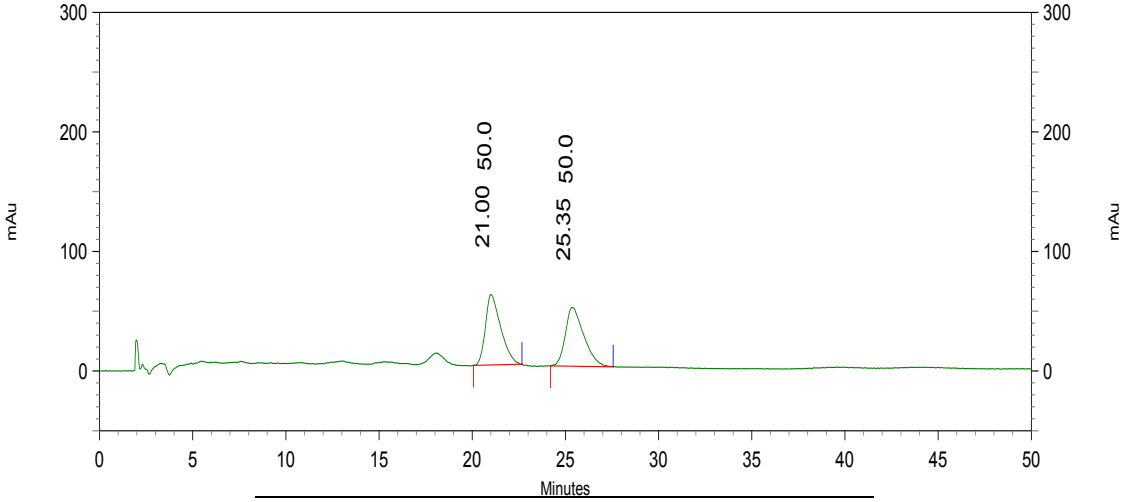
Time	Area %	Height %
20.456	51.66	56.39
30.160	48.34	43.61



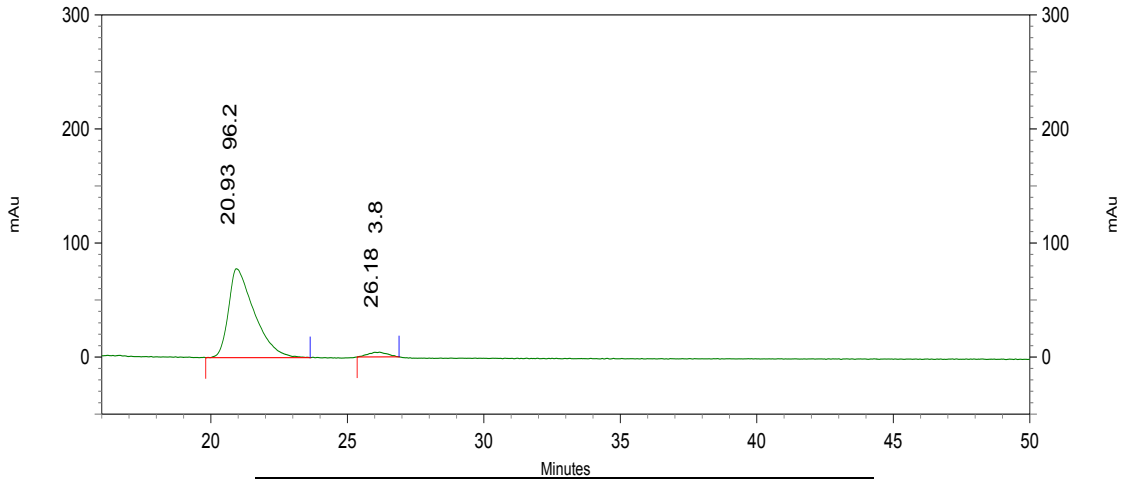
Time	Area %	Height %
20.420	99.17	98.51
30.852	0.83	1.49



4q



Time	Area %	Height %
9.520	50.87	55.40
12.340	49.13	44.60



Time	Area %	Height %
20.928	96.23	94.94
26.180	3.77	5.06

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