Supporting Information

Carbene-Catalyzed Imine Reductive Reaction: A New Application of Breslow Intermediate

Hui Zhu[a]#, Han Xiao[a]#, Lihe Wang[a], Bo Jiang[a], Qingyun Wang[a], Shuquan Wu[a]*, and Pengcheng Zheng[a]*

[a] Center for Industrial Catalysis & Cleaning Process Development, School of Chemical Engineering, Guizhou Minzu University, Guiyang Huaxi District, 550025, China.

* E-mail: wusq0708@163.com

* E-mail: zhengpc1986@163.com

#These authors contributed equally to this work.

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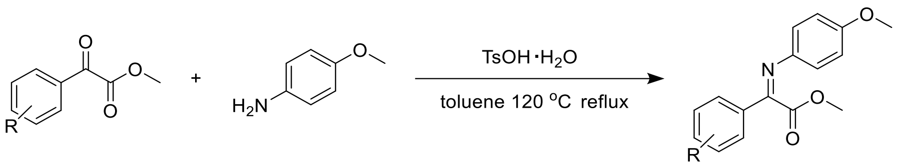
I. General information

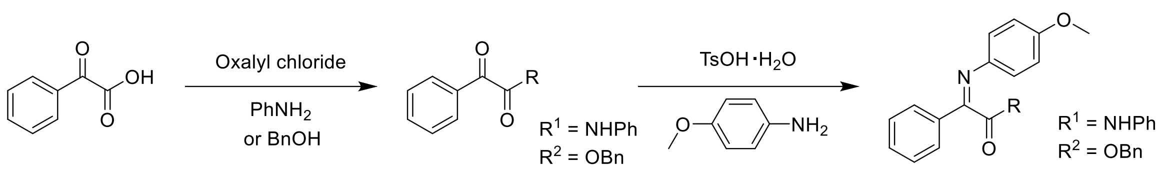
Commercially available materials and dry solvents purchased from Energy Chemical and Bidepharm were used as received. Unless otherwise specified, all reactions were prepared using 10 mL Schlenk tube under N_2 atmosphere using Schlenk techniques. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker (AVANCE NEO 400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (AVANCE NEO 400MHz, 101 MHz for ^{13}C NMR) spectrometer. Fluorine (^{19}F) nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker (AVANCE NEO 400 MHz, 376 MHz for ^{19}F NMR) spectrometer. High resolution mass spectrometer analysis (HRMS) was performed on Waters Xevo G2-S QTof mass spectrometer. The structure of the substrates and products were determined by X-ray crystallography (Bruker D8 quest). The gas chromatography mass spectrometry (GC-MS) analyses were measured on Agilent systems, 7890B-5975C GC/MSD model. The determination of er was performed via chiral phase HPLC analysis using Shimadzu LC-20AD HPLC workstation. Chiralcel brand chiral columns from Daicel Chemical Industries were used with models ID in 4.6 x 250 mm size. The melting points (m.p.) of the title compounds were determined by SGW®X-4B apparatus from Shanghai INESA Physics-Optical Instrument Co.,Ltd. (Shanghai, China). Optical rotations were measured on a Insmark IP-digi300/1 Polarimeter in a 1 dm cuvette at 25 °C. The concentration (c) is given in g/100 mL. Analytical thin-layer chromatography (TLC) was carried out pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

II. Supplementary methods

Preparation of substrates

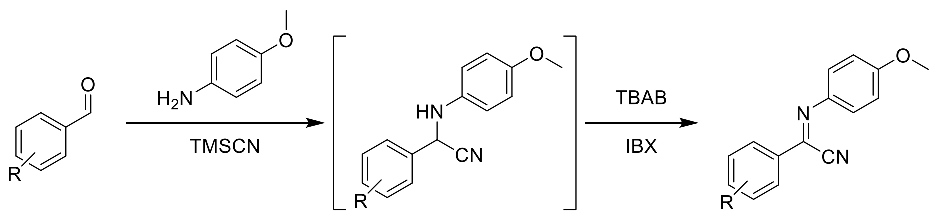


To a solution of para-anisidine (2.5 g, 20.0 mmol) in toluene (30.0 mL), tosic acid monohydrate (350 mg, 2.0 mmol) was added. To this solution was added methyl benzoylformate (2.8 mL, 20.0 mmol). The solution was then heated at reflux with azeotropic removal of water under air (Dean-Stark conditions) for 2 h. The reaction process was detected by TLC. then the product was isolated by column chromatography (petroleum ether/ethyl acetate 10/1) to afford α-keto amides. Spectral data agreed with those reported previously by Zhang et al[1].

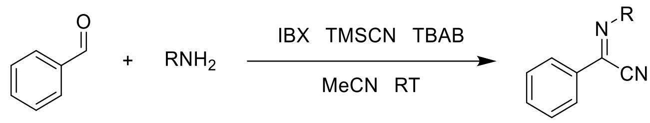


To a solution of α-keto acids (3.0 g, 20.0 mmol) and 1 drop of DMF in dry DCM (30.0 mL) was added oxalyl chloride (2.0 mL, 24.0 mmol) dropwise, and the yellow mixture was left to stir at room temperature for 3 h. Then evaporate the solvent under vacuum conditions, then add aniline (1.8 mL, 20.0 mmol), DMAP (6.1 mg, 0.1 mmol) and Et_3N (5.6 mL, 40.0 mmol) in dry THF (20.0 mL) at 0 °C. The mixture was left to stir at room temperature for 12 h. The aqueous layer was extracted with EA (2 × 80.0 mL) and wash with saturated sodium chloride, dry over anhydrous sodium sulfate, then the product was isolated by column chromatography (petroleum ether/ethyl acetate 5/1) to afford α-keto amides.

And then to a solution of α-keto amides (2.0 g, 8.9 mmol) in toluene (30.0 mL), tosic acid monohydrate (169.0 mg, 0.9 mmol) was added. Para-anisidine (1.3 g, 10.7 mmol) was added to the solution. Then, the solution was heated at reflux with azeotropic removal of water under air (Dean-Stark conditions) for 2 h. The reaction process was detected by TLC. The mixture was then cooled, then the product was isolated by column chromatography (petroleum ether/ethyl acetate 5/1) to afford imine as yellow solid. Spectral data agreed with those reported previously by Yoda et al[2].

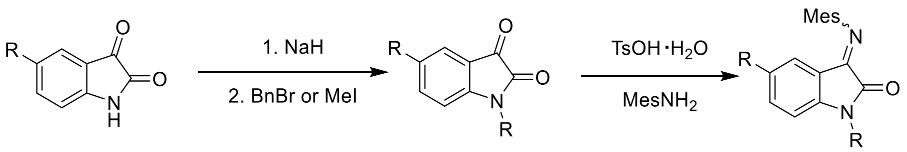


To a solution of benzaldehyde (1.7 mL, 30.0 mmol), para-anisidine (3.7 g, 30.0 mmol) and I_2 (0.8 g, 3 mmol) in MeCN (100.0 mL) was added TMSCN (4.1 mL, 33.0 mmol) at room temperature, and the mixture was then stirred for 1h. Then the IBX (9.2 g, 33.0 mmol) and tetrabutylammonium bromide (10.6 g, 33.0 mmol) were added (under water bath if necessary) and stirring was maintained at room temperature. After the reaction was monitored by TLC, the reaction mixture was then filtered over celite and concentrated. The crude product was purified by flash chromatograph on silica gel (eluent: petroleum ether/ethyl acetate = 50/1) to afford the cyanimide. Spectral data agreed with those reported previously by Zhu et al[3].

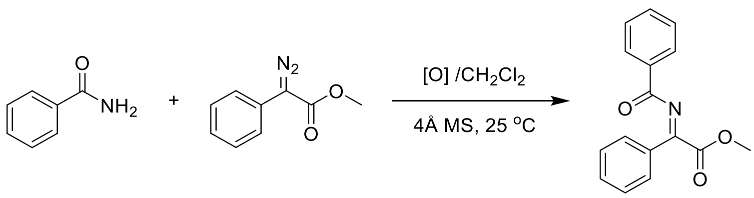


To a solution of benzaldehyde (0.5 mL, 5.0 mmol), alkyl amines (5.0 mmol) and TMSCN (0.7 mL, 5.5 mmol) in acetonitrile (5.0 mL) were added IBX (1.5 g, 5.5 mmol) and tetrabutylammonium bromide (1.77 g, 5.5 mmol) at room temperature, and stirring was maintained at room temperature. After the reaction was completed as monitored by TLC, the reaction mixture was then filtered over celite and concentrated. The crude product was purified by flash chromatograph on silica gel (eluent: petroleum ether/ethyl acetate = 50/1) to afford the cyanimide. Spectral data agreed with those reported previously by Liu et al[4].

Synthesis method of product **indole-imine**



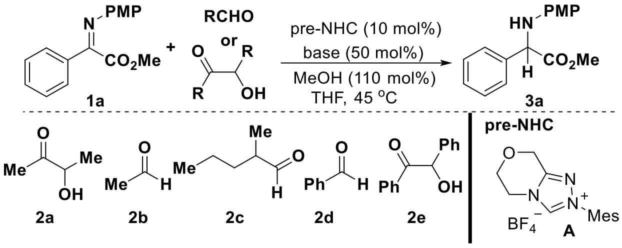
Add a 60% dispersion of NaH, in mineral oil (1.4 g, 35.3 mmol) to a solution of isatin (4.0 g, 27.2 mmol) in DMF (80.0 mL) and cool at 0 °C. Stir for 30 min at 0 °C. Add methyl iodide (2.0 mL, 36.2 mmol) or benzyl bromide (3.9 mL, 36.2 mmol), allow the reaction at 25 °C and stir for 12 h. Add a saturated solution of NH_4Cl (40.0 mL) and extract the mixture with EtOAc (3 x 50.0 mL). Wash the combined organic layers with brine, dry over Na_2SO_4 and concentrate in vacuo. Purify the crude by chromatography on silica gel (25% EtOAc in petroleum ether). And then to a solution of N-METHYLISATIN (2.0 g, 12.4 mmol) in toluene (30.0 mL), tosic acid monohydrate (236.0 mg, 1.2 mmol) was added. To this solution was added Trimethylaniline (2.09 mL, 14.9 mmol). The solution was then heated at reflux with azeotropic removal of water under air (Dean-Stark conditions) for 2 h. The reaction process was detected by TLC. The crude product was purified by flash chromatograph on silica gel (eluent: petroleum ether/ethyl acetate = 5/1) to afford indole-imine as red solid. Spectral data agreed with those reported previously by Davidovich et al[5].



A suspension of $Rh_2(OAc)_4$ (11 mg, 0.5 mol%), the amide (0.61 g, 5 mmol), fresh dried 4Å MS (3.00 g), and DDQ (1.36 g, 6 mmol) in 30.0 mL CH_2Cl_2 was warmed to reflux. Then the diazo compound (0.97 g, 5.5 mmol) in 5.0 mL CH_2Cl_2 was added to the suspension over 1 h via a syringe pump. After completion of the addition, the reaction mixture was stirred for another 0.5 h. The crude products were filtered through Cleanert Alumina (N) and concentrated. The residue was purified by column chromatography on silica gel coated with a dry ice jacket eluting with CH_2Cl_2 (1% triethylamine) to get **1P** 1.0 g (75% yield). Spectral data agreed with those reported previously by Hu et al[6].

Initial studies and condition optimization for the synthesis of 3a

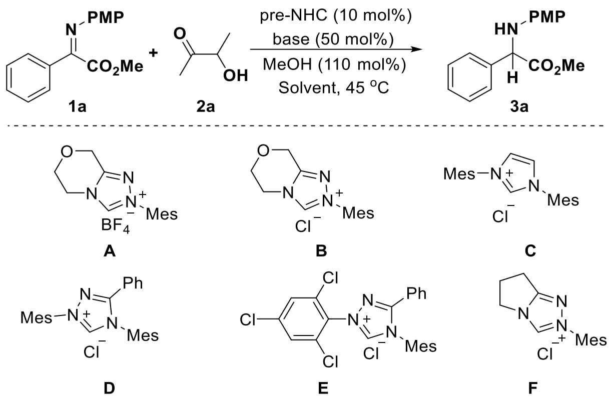
Supplementary Table S1. Optimization of reductants [a]



entry	reducing agent	base	solvent	yield(%)[b]
1	**2a**	K_2CO_3	THF	72
2	**2b**	K_2CO_3	THF	8
3	**2c**	K_2CO_3	THF	nr
4	**2d**	K_2CO_3	THF	15
5	**2e**	K_2CO_3	THF	15
6[c]	**2a**	K_2CO_3	THF	45
7[d]	**2b**	K_2CO_3	THF	32
7[e]	**2b**	K_2CO_3	THF	65

[a]Unless otherwise specified, the reactions were carried out using **1a** (0.50 mmol), **2a** (0.50 mmol), **2b-2d** (1.00 mmol), **2e** (0.50 mmol) base (0.25 mmol), alcohol (0.55 mmol), pre-NHC (0.05 mmol, 10 mol%), solvent (2.00 mL) at 45°C for 8 h under N_2, PMP = 4-Methoxyphenyl. [b]Isolated yield of **3a**. [c]**2a** (0.25 mmol) for 24 h. [d]**2b** (0.50 mmol) for 24 h. [e]**2b** (1.00 mmol) for 24 h.

Supplementary Table S2. The effects of catalysts, bases, solvents on the reaction outcome[a]



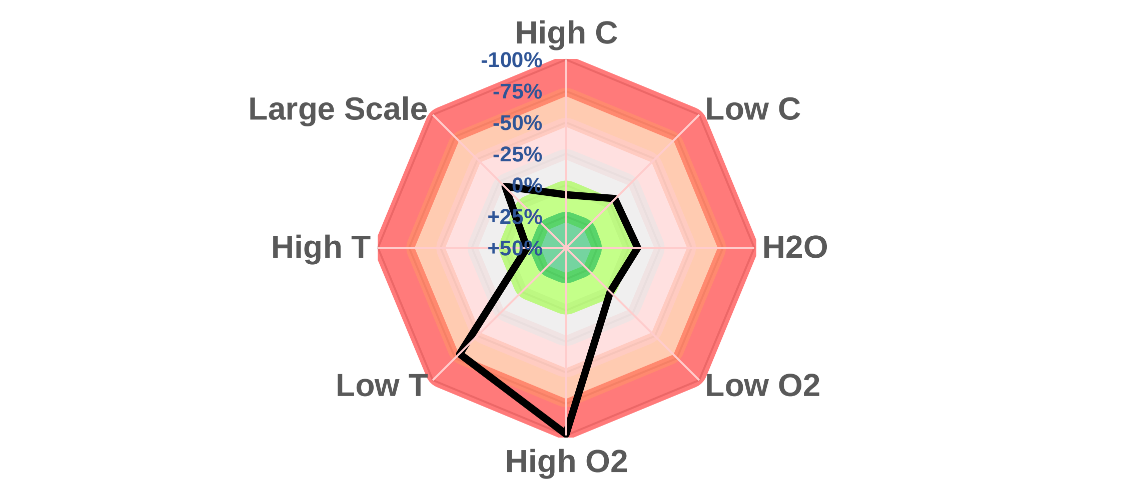
entry	pre-NHC	base	solvent	yield(%)[b]
1	**A**	K_2CO_3	THF	72
2	**B**	K_2CO_3	THF	69
3	**C**	K_2CO_3	THF	nr
4	**D**	K_2CO_3	THF	42
5	**E**	K_2CO_3	THF	nr
6	**F**	K_2CO_3	THF	58
7	**A**	Na_2CO_3	THF	nr
8	**A**	Cs_2CO_3	THF	72
9	**A**	NaOAc	THF	nr
10	**A**	Et_3N	THF	nr
11	**A**	DIPEA	THF	nr
12	**A**	DMAP	THF	nr
13	**A**	DBU	THF	35
14	**A**	K_2CO_3	EA	81
15	**A**	K_2CO_3	$CHCl_3$	60
16	**A**	K_2CO_3	DCM	47
17	**A**	K_2CO_3	DMF	62
18	**A**	K_2CO_3	MeCN	56
19	**A**	K_2CO_3	Toluene	99
20[c]	**A**	K_2CO_3	Toluene	96
21[d]	**A**	K_2CO_3	Toluene	91
22[e]	**A**	K_2CO_3	Toluene	55

[a]Unless otherwise specified, the reactions were carried using **1a** (0.50 mmol), **2a** (0.60 mmol), base (0.25 mmol), alcohol (0.60 mmol), pre-NHC (0.05 mmol, 10 mol%), solvent (2.00 mL) at 45 °C for 8 h under N_2. [b]Isolated yield of **3a**. [c]The pre-NHC (5 mol%). [d]The pre-NHC (2 mol%). [e]The pre-NHC (1 mol%). nr = no reaction.

Supplementary Table S3. Sensitivity screen[a]7

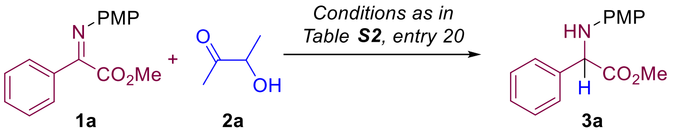
Variation	Lower Point	Center Point[a]	Higher Point
Concentration	V_{rxn} - 50% V_{rxn}	STANDARD CONDITIONS	V_{rxn} + 50% V_{rxn}
H_2O level	-		+H_2O; V_{H2O} = 1% V_{rxn}
O_2 level	-		Open in air
Temperature	T – 20 °C		T + 20 °C
Scale	-		$n \cdot 75$
Σ reactions	2		5

[a]Unless otherwise specified, the reactions were carried using **1a** (0.50 mmol), **2a** (0.60 mmol), base (0.25 mmol), alcohol (0.60 mmol), pre-NHC (0.05 mmol, 10 mol%), solvent (2.00 mL) at 25 °C for 8 h under N_2. [b]Isolated yield of **3a**.



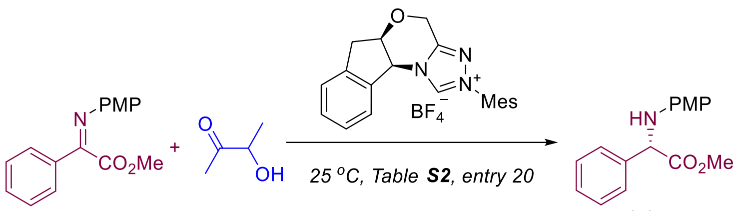
General procedure for the catalytic reactions

General procedure for the catalytic reduction reaction of imine 1a



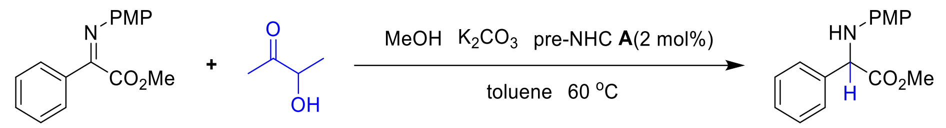
To a dry 10 ml Schlenk reaction tube equipped with a magnetic stir bar was added **1a** (134.6 mg, 0.5 mmol), pre-NHC **A** (8.3 mg, 25.0 μmol), and K_2CO_3 (34.6 mg, 0.25 mmol). The Schlenk tube was then closed with septum, evacuated and refilled with N_2, freshly distilled anhydrous toluene (2.0 mL), acetoin (52.3 μL, 0.6 mmol), and methanol (24.3 μL, 0.6 mmol), was added. The mixture was stirred at 45 °C for 8 h. After completion of the reaction monitored by TLC, solvent was removed under reduced pressure and the residue was purified via column chromatography on silica gel with petroleum ether/ethyl acetate (10/1) as eluent to afford the products **3a** (130.1 mg, 479.5 μmol, 96% yield).

Synthetic transformations of products (*S*)-3a:



To a dry Schlenk reaction tube equipped with a magnetic stir bar was added **1a** (26.7 mg, 0.10 mmol,), pre-NHC **G** (8.4 mg, 0.02 mmol), and K_2CO_3 (6.9 mg, 0.05 mmol). The Schlenk tube was then closed with septum, evacuated and refilled with N_2, freshly distilled anhydrous toluene (2.0 mL), acetoin (13 μL, 0.15 mmol), and methanol (6 μL, 0.15 mmol), was added. The mixture was stirred at 25 °C for 10 h. After completion of the reaction monitored by TLC, solvent was removed under reduced pressure and the residue was purified via column chromatography on silica gel with petroleum ether/ethyl acetate (10/1) as eluent to afford the products **(*S*)-3a** (26.0 mg, 95.8 μmol, 96% yield).

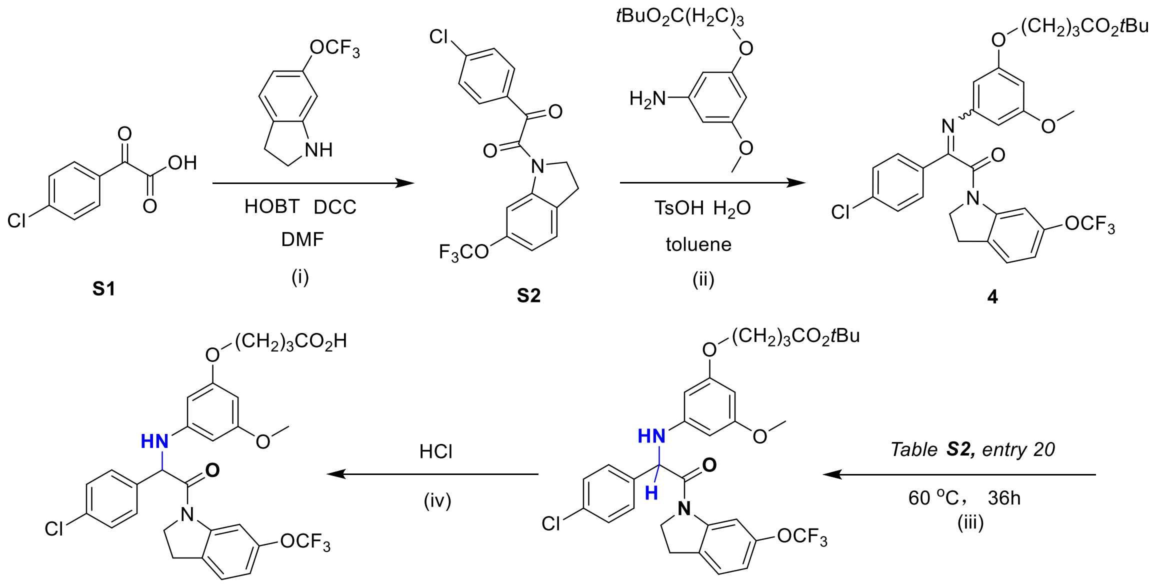
Scale-up synthesis of 3a:



1a (10.0 g, 37.1 mmol) **2** (3.6 ml, 40.9 mmol) **3a** 80% yield

To a dry 200 ml Schlenk reaction tube equipped with a magnetic stir bar was added **1a** (10.0 g, 37.1 mmol), pre-NHC **A** (245.9 mg, 0.7 mmol), and K_2CO_3 (2.6 g, 18.6 mmol). The Schlenk tube was then closed with septum, evacuated and refilled with N_2, freshly distilled anhydrous toluene (80.0 mL), acetoin (3.6 mL, 40.9 mmol), and methanol (1.7 mL, 40.9 mmol), was added. The mixture was stirred at 60 °C for 8 h. After completion of the reaction monitored by TLC, solvent was removed under reduced pressure and the residue was purified via column chromatography on silica gel with petroleum ether/ethyl acetate (10/1) as eluent to afford the products **3a** (8.1 g, 29.7 mmol, 80% yield).

Synthesis of JNJ-A07.



1-(4-chlorophenyl)-2-(6-(trifluoromethoxy)indolin-1-yl)ethane-1,2-dione (S2)

S1 (2.0 g, 10.8 mmol) and 6-(trifluoromethoxy) indoline (2.2 g, 10.8 mmol) were dissolved in DMF. Then, HOBT (1.8 g, 13.0 mmol) was added to the mixture followed by DCC (2.7 g, 13.0 mmol) added in portions. The reaction was stirred at room temperature overnight until completion. The reaction mixture was then quenched with water and extracted with EA. The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to afford **S2** (3.3 g, 9.1 mmol, yield: 85%).

tert-butyl 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethylidene)amino)-5-methoxyphenoxy)butanoate (4)

To a solution of tert-butyl 4-(3-amino-5-methoxyphenoxy)butanoate (0.8 g, 2.7 mmol) in toluene (30.0 mL), tosic acid monohydrate (51.0 mg, 270.0 μmol) was added. To this solution was added 1-(4-chlorophenyl)-2-(6-(trifluoromethoxy)indolin-1-yl)ethane-1,2-dione (1.0 g, 2.7 mmol). The solution was then heated at reflux with azeotropic removal of water under air (Dean-Stark conditions) for 6 h. The mixture was then cooled. The crude residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to afford **4** as a yellow oil (349.3 mg, 551.8 μmol, yield: 20%).

2-((3-((3-(tert-butylperoxy)but-3-en-1-yl)oxy)-5-methoxyphenyl)amino)-2-(4-chlorophenyl)-1-(6-((trifluoromethyl)peroxy)indolin-1-yl)ethan-1-one (5)

To a dry 10 ml Schlenk reaction tube equipped with a magnetic stir bar was added **6** (316.5 mg, 0.5 mmol), pre-NHC **A** (8.3 mg, 25.0 μmol), and K_2CO_3 (34.6 mg, 0.25 mmol). The Schlenk tube was then closed with septum, evacuated and refilled with N_2, freshly distilled anhydrous toluene (2.0 mL), acetoin (61.7 μL, 0.7 mmol), and methanol (28.4 μL, 0.7 mmol), was added. The mixture was stirred at 60 ℃ for 36 h. After completion of the reaction monitored by TLC, solvent was removed under reduced pressure and the residue was purified via column chromatography on silica gel with petroleum ether/ethyl acetate (5/1) as eluent to afford the products **5** (305.0 mg, 480.3 μmol, yield: 96%).

4-(3-((1-(4-Chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy) butanoic acid (JNJ-A07)[8]

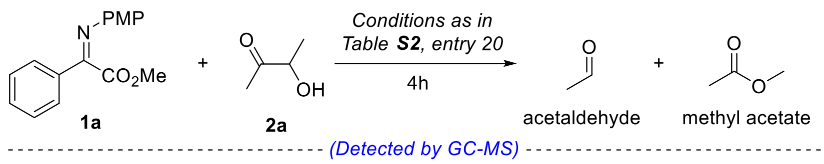
A solution of 4 (2.4 g, 3.8 mmol) in 4 M HCl in dioxane (24.0 mL) was stirred at 5 °C for 3 h and at room temperature for 3 h. The precipitate was filtered off and dried to afford 4-(3-((1-(4-chlorophenyl)-2-oxo2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)butanoic acid as an HCl salt.

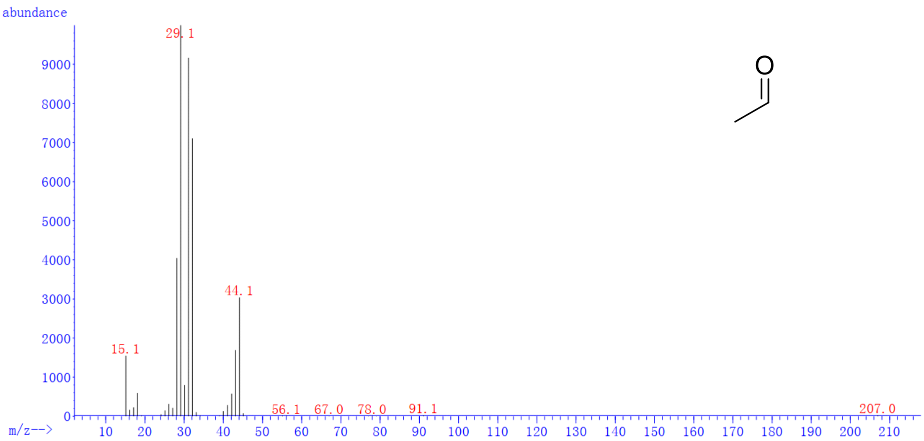
III. Supplementary Discussion

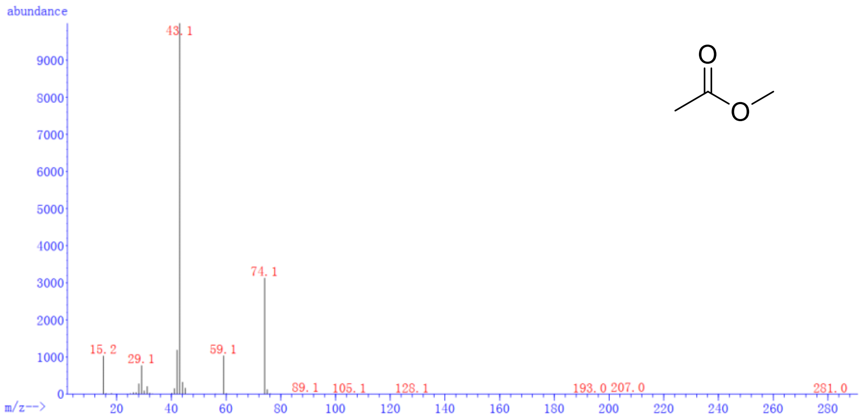
Mechanistic study experiments: GC-MS analysis and HRMS analysis

GC-MS analysis of reaction systems

To a dry 10 ml Schlenk reaction tube equipped with a magnetic stir bar was added **1a** (134.6 mg, 0.5 mmol), pre-NHC **A** (8.3 mg, 25.0 μmol), and K_2CO_3 (34.6 mg, 0.25 mmol). The Schlenk tube was then closed with septum, evacuated and refilled with N_2, freshly distilled anhydrous toluene (2.0 mL), acetoin (52.3 μL, 0.6 mmol), and methanol (24.3 μL, 0.6 mmol), was added. The mixture was stirred at 45 °C for 4 h. During the subsequent reaction process, 200.0 μL of the reaction system was taken out and diluted in 800.0 μL of toluene solution at regular intervals which was determined by Gas chromatography mass spectrometry (GC-MS).






abundance
9000
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20
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15.2
29.1
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89.1
105.1
128.1
193.0
207.0
281.0
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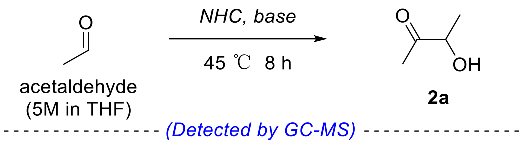
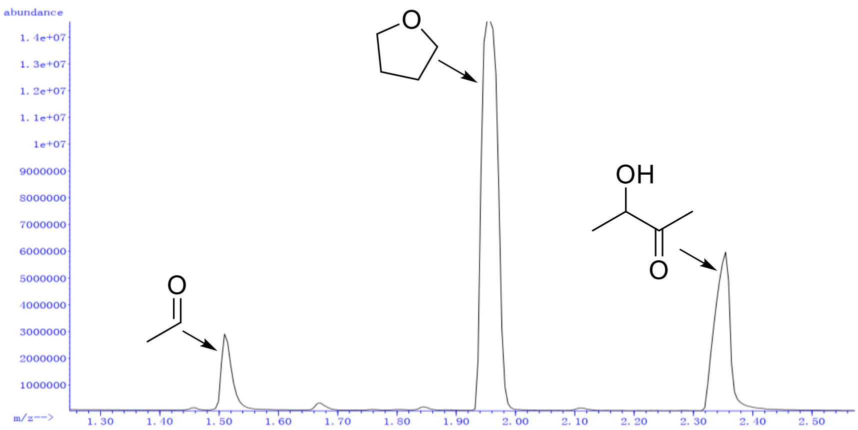
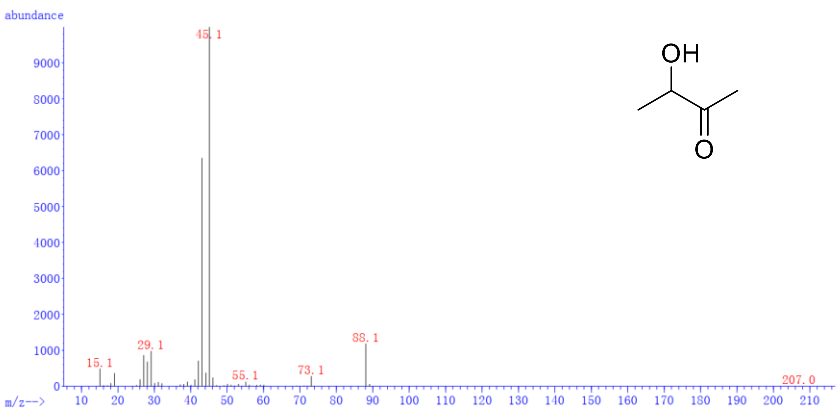
O

To a dry 10 ml Schlenk reaction tube equipped with a magnetic stir bar was added pre-NHC **A** (8.3 mg, 25.0 μmol), and K_2CO_3 (34.6 mg, 0.25 mmol). The Schlenk tube was then closed with septum, evacuated and refilled with N_2, freshly distilled anhydrous toluene (2.0 mL), acetaldehyde (200.0 μL, 5M in THF, 1.0 mmol), was added. The mixture was stirred at 45 °C for 8 h. During the subsequent reaction process, 200.0 μL of the reaction system was taken out and diluted in 800.0 μL of toluene solution at regular intervals which was determined by Gas chromatography mass spectrometry (GC-MS).

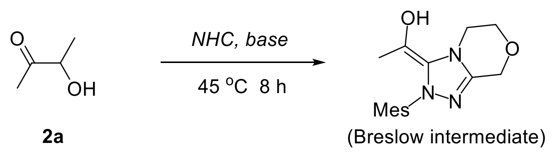


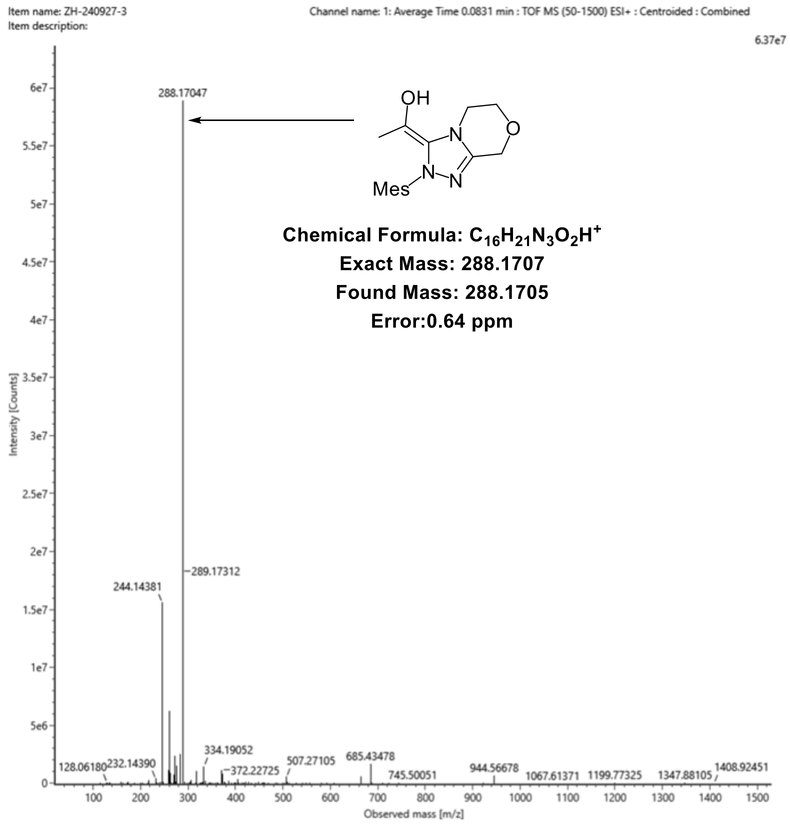




HRMS analysis of reaction systems

To a dry 10 ml Schlenk reaction tube equipped with a magnetic stir bar was added pre-NHC **A** (8.3 mg, 25.0 µmol), and K_2CO_3 (34.6 mg, 0.25 mmol). The Schlenk tube was then closed with septum, evacuated and refilled with N_2, freshly distilled anhydrous toluene (2.0 mL), acetoin (52.3 µL, 0.6 mmol), was added. The mixture was stirred at 45 °C for 8 h. And then high-resolution mass spectrometry (HRMS) analysis of crude mixtures.

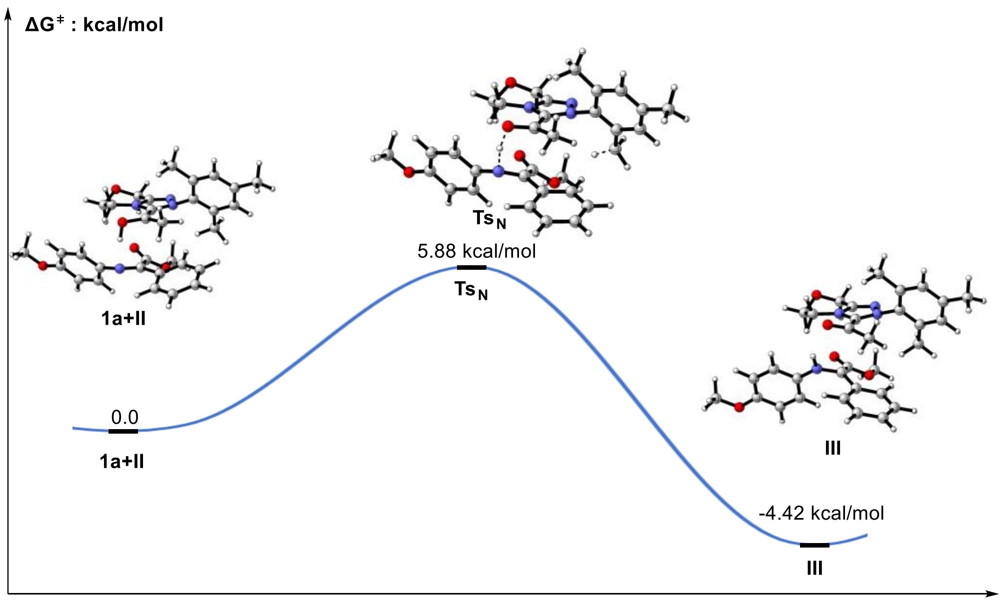


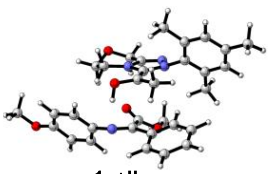


Computational details

The initial cluster structures were optimized using global hybrid functional M062X-D3 with Karlsruhe-family double-ζ valence def2-SVP basis set for all atoms as implemented in Gaussian 16[9]. Single point (SP) corrections were performed using M062X-D3 functional and def2-TZVPP basis set for all atoms. Minima and transition structures on the potential energy surface (PES) were confirmed as such by harmonic frequency analysis, showing respectively zero and one imaginary frequency. The implicit IEFPCM continuum solvation model for Toluene solvent was used to account for the effect of solvent on the potential energy surface. Gibbs energies were evaluated at 318.15 K, which was used in the experiments, using a quasi-RRHO treatment of vibrational entropies. Vibrational entropies of frequencies below 100 cm^{-1} were obtained according to a free rotor description, using a smooth damping function to interpolate between the two limiting descriptions. The thermal energy terms associated with various thermal motions of the molecule were calculated from the frequency analysis output using Shermo[10]. Noncovalent interactions were analyzed by using Multiwfn[11]. The three-dimensional structures were illustrated by using VMD[12,13] and CYLview20[14].

The hydride of the Breslow intermediate transferred to the N atom of iminoester





1a+II

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H	2.41288900	3.16452500	-0.62794200
C	1.22638500	4.93686000	-0.94129300

H	1.84953900	5.27602400	-1.76732200
C	0.12814900	5.68607400	-0.50809600
C	-0.63020900	5.22671200	0.58145000
H	-1.46233700	5.84105600	0.92646600
C	-0.31945800	4.02801700	1.19761300
H	-0.90786000	3.68913800	2.05273400
C	0.47573500	7.35851200	-2.14459800
H	1.52299300	7.55830200	-1.86522800
H	-0.00225300	8.29774400	-2.44236800
H	0.45968900	6.65870200	-2.99625600
C	0.86140100	0.03308000	2.61126200
C	1.95844800	0.31766700	3.43667800
H	2.37355600	1.32582300	3.42640200
C	2.50551600	-0.67036700	4.25208100
H	3.35630700	-0.43367100	4.89263100
C	1.96653100	-1.95735700	4.25093800
H	2.39672700	-2.73228300	4.88720300
C	0.87950600	-2.25064800	3.42637900
H	0.46684900	-3.26098000	3.39563200
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H	-3.71726600	1.26597500	1.49658300
H	-3.77712000	-0.31629600	2.35909000
H	-3.28665300	-0.23779300	0.62450800
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C	-1.65537600	-0.40819300	-2.03789000
C	0.07629400	1.32498700	-2.42766500
C	-1.12238300	2.14575000	-2.88215200

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O	-2.05098200	1.35402400	-3.59347000
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N	-0.39338600	0.08327100	-1.83852700
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N	-0.62385200	-1.89212600	-0.92459600
C	-0.34387200	-3.25532200	-0.65361700
C	-1.04097000	-3.91363900	0.37219800
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C	-0.69440100	-5.23614600	0.66817800
C	0.92505600	-5.25349800	-1.09892500
C	0.30118800	-5.91507400	-0.03542500
H	-1.22601800	-5.74952800	1.47417500
H	1.66907500	-5.78583000	-1.69775000
C	1.24047100	-3.27912000	-2.63314700
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H	2.04099600	-2.58402500	-2.33929900
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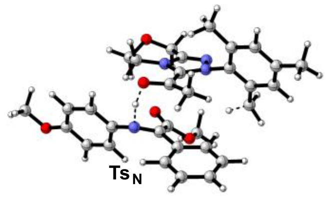
H	-2.14195400	-2.16359300	1.01062000
H	-2.17082100	-3.52603500	2.17244000
C	0.69456600	-7.32223100	0.33040500
H	1.62015700	-7.32573300	0.92660300
H	0.88129000	-7.92796600	-0.56710300
H	-0.08714300	-7.81389200	0.92409200
C	2.30975400	-1.73553800	0.25506900
H	1.69219600	-2.57198800	0.59723100
H	3.13571800	-2.14073200	-0.35639200
H	2.76536800	-1.27242700	1.14711400
H	0.74644100	1.09632000	-3.27220300
H	-0.78593500	2.94374000	-3.55571300



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H	1.64015200	2.23913400	-0.12460100
C	0.58236000	4.11401500	0.00257900
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C	-1.04237900	4.27118300	1.77909200
H	-1.77986900	4.86921900	2.31593400
C	-0.74969900	2.97748300	2.17252800
H	-1.25285200	2.54796600	3.04110400
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H	0.98401500	6.82182000	-0.54550700
H	-0.52750700	7.74551200	-0.80653700
H	-0.27407600	6.18921200	-1.65493700
C	0.24087500	-0.89532400	3.44110100
C	1.40966400	-0.51377700	4.12273300
H	1.86985100	0.44016700	3.86568900
C	1.97017300	-1.32818800	5.10448100
H	2.87615400	-1.00438100	5.61959400
C	1.37695400	-2.54655300	5.43176500
H	1.81486000	-3.18611600	6.19956800
C	0.21649700	-2.93988500	4.76248900
H	-0.25353200	-3.89684600	4.99725800
C	-0.34382400	-2.12858100	3.78188800
H	-1.23108300	-2.46913100	3.25576400
C	-1.70859900	0.05790000	2.00125600
C	-3.90048800	-0.59371000	2.48570900
H	-4.26697400	0.44067500	2.45731100
H	-4.41793500	-1.16469700	3.26297900
H	-4.06670900	-1.05621400	1.50031000
N	0.57747700	0.92610800	1.89885200

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O	-2.14884000	0.67128200	1.05345800
O	-2.52136400	-0.62506300	2.82267300
H	1.24529900	0.30742300	0.94072600
O	1.33608500	-0.41818600	0.05454700
C	0.65076500	-1.48468800	0.40552800
C	-3.55774500	-0.53820800	-1.99523600
C	-2.52670200	-1.33114600	-1.24701700
C	-0.86375300	0.49094900	-1.53674800
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H	-4.13717600	-1.20495200	-2.64480900
H	-0.34381000	1.05745700	-0.76248900
H	-2.63163000	1.64298100	-1.12002500
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N	-2.66334100	-2.51072700	-0.73945300
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C	-0.18667600	-4.77602300	-0.52344900
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H	0.87953500	-4.90869700	-2.38600600
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H	-2.99113800	-4.36758600	3.09117100
C	0.06370100	-8.04844300	1.42411600
H	0.97294000	-7.97552800	2.04048600

H	0.30316400	-8.68003300	0.55804100
H	-0.70555200	-8.55342200	2.02249900
C	1.38398000	-2.55820400	1.15962400
H	0.73111800	-3.24156800	1.71195800
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III

C	0.36928500	0.76519400	1.07545800
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C	1.25526100	5.28375900	-0.65445500
H	1.79076400	5.87647100	-1.39545400
C	0.32831700	5.87225200	0.20708100
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H	-1.04240200	5.53733800	1.82056000
C	-0.07054600	3.70488300	1.22531800
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C	0.65201200	8.02525400	-0.71501300
H	1.74490000	8.03007600	-0.56256600
H	0.26613000	9.03915300	-0.55953800
H	0.44365200	7.71774600	-1.75420500
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C	2.21239200	0.65321000	2.72625200
H	2.69194100	1.45626300	2.16720700
C	2.86095500	0.11105600	3.83258000
H	3.84121300	0.49840200	4.11783100
C	2.27029000	-0.91092900	4.57444300
H	2.77810600	-1.33927000	5.43962200
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H	0.52156400	-2.16320600	4.75483600
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H	-3.37648900	-0.45515000	0.22082000
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O	-1.52412400	1.36733400	-0.22519100
O	-1.84230800	0.03658700	1.53796700
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C	-2.72828400	0.12661200	-3.12705200
C	-1.74392300	-0.69493800	-2.35093700
C	-0.00069400	1.06750400	-2.64147000
C	-1.18621000	1.86145700	-3.17099000
H	-3.38017100	0.64404400	-2.39839900
H	-3.34207100	-0.52627800	-3.75871800
H	0.49883600	1.61623200	-1.84040400
H	-1.72925500	2.30577700	-2.32331100
O	-2.04662400	1.03966100	-3.93724000
N	-1.92359200	-1.86066600	-1.80545500
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C	-1.09547700	-4.00207900	0.37770100
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C	-0.74649400	-5.30021700	0.75154200
C	0.77969600	-5.47796600	-1.09721700
C	0.19774100	-6.04661700	0.03927100
H	-1.22888900	-5.74008100	1.62751500
H	1.49248400	-6.06138100	-1.68444800
C	1.07907000	-3.60534700	-2.76479600

H	0.33253800	-3.06231400	-3.36266500
H	1.49739600	-4.40544300	-3.38727600
H	1.89785000	-2.90381700	-2.53808200
C	-2.13046500	-3.21665900	1.12846900
H	-3.05844400	-3.14538800	0.54051600
H	-1.78493700	-2.19112000	1.31487100
H	-2.36220500	-3.69527600	2.08780400
C	0.58358200	-7.42781800	0.49562300
H	1.35156300	-7.37015500	1.28216000
H	0.99555100	-8.02076500	-0.33092300
H	-0.27883700	-7.96235100	0.91534300
C	1.97051400	-1.91357200	0.32342100
H	1.17106300	-2.26104800	0.98705200
H	2.43809200	-2.78590600	-0.16049300
H	2.73124400	-1.39297300	0.91977800
H	0.71833100	0.82175200	-3.43398400
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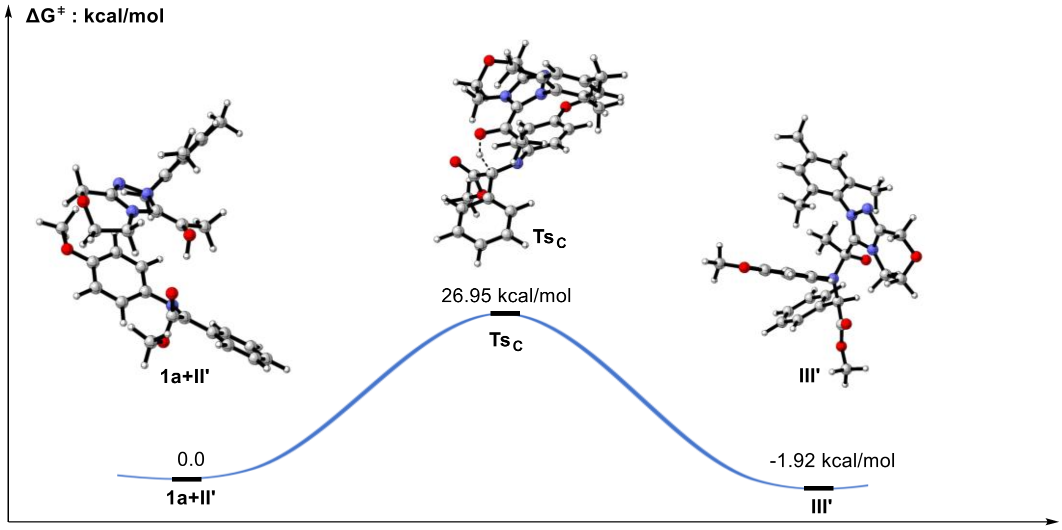
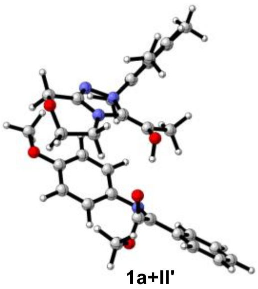
The hydride of the Breslow intermediate transferred to the C atom of iminoester





1a+II'

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C	-1.54050100	-2.83716500	-3.11938600
C	-0.73671300	-2.52890900	-1.88445400
C	-0.08887700	-0.30682700	-2.80948200
C	-1.22631200	-0.63499900	-3.76914000
H	-2.61619600	-2.71951400	-2.89407900
H	-1.35723100	-3.87353500	-3.42890700
H	-0.28708000	0.64453000	-2.28990300
H	-2.20227300	-0.43437000	-3.28897700
O	-1.16456400	-1.98635300	-4.16945900
N	-0.65774200	-3.24217200	-0.81710800
N	0.00051200	-1.37617500	-1.83335700
C	0.62356200	-1.33530600	-0.58067300
N	0.17968600	-2.51421500	0.04609900
C	1.00553600	-3.28374900	0.91986100
C	0.46600300	-3.70154100	2.14691400
C	2.31158900	-3.63754900	0.54341800

C	1.26604500	-4.44557400	3.01377600
C	3.08438800	-4.36866900	1.45199200
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H	4.10262800	-4.64776100	1.16773400
C	2.87297400	-3.27345200	-0.80574900
H	2.10516500	-3.35368200	-1.58847500
H	3.70515900	-3.94117100	-1.06363600
H	3.23857300	-2.23547800	-0.82342900
C	-0.94791600	-3.33713200	2.50744700
H	-1.64837900	-3.68649300	1.73405600
H	-1.05890800	-2.24385400	2.57751300
H	-1.23498900	-3.77720800	3.47049500
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H	3.91021900	-4.85563600	4.39335200
H	4.26068700	-6.06639500	3.14449600
H	2.85945700	-6.27381600	4.22580700
C	1.92486500	-0.29031000	1.30921400
H	1.33208600	-0.92450100	1.98245600
H	2.98306700	-0.59282400	1.40768100
H	1.84826300	0.75169600	1.66543000
C	-0.18818500	3.51368200	0.72382200
C	-1.62432900	1.64561000	0.58639900
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C	-2.38263000	-0.65862400	0.41837300
H	-2.32067200	-1.68599800	0.77145700
C	-3.18286000	-0.32209900	-0.67770500
C	-3.22248300	1.00717600	-1.12442000
H	-3.88938300	1.25868000	-1.95012500
C	-2.45328800	1.97929000	-0.49994700
H	-2.53329600	3.01784100	-0.82661000
C	-4.16457000	-2.47763800	-0.75321700
H	-3.23162100	-3.06071800	-0.68744900
H	-4.88262700	-3.00308300	-1.39241200
H	-4.59028700	-2.36298300	0.25661100
C	0.59821900	4.48248700	1.52647300

C	0.58949200	4.37957800	2.92558900
H	-0.01178100	3.59457100	3.38455600
C	1.33775600	5.26054000	3.69651700
H	1.32583000	5.17373200	4.78385500
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C	2.11963500	6.36194400	1.69356400
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C	1.36813600	5.48148900	0.91673900
H	1.38531100	5.58381500	-0.16969500
C	-0.09619100	3.64474500	-0.78814800
C	-0.69073500	4.88740600	-2.67452300
H	0.34713300	4.95998000	-3.02335400
H	-1.23546800	5.81284200	-2.87740700
H	-1.17618400	4.03445000	-3.16704400
N	-0.83217300	2.56922800	1.28355900
O	-3.94628900	-1.21482000	-1.34933200
O	0.49304900	2.85671500	-1.48579600
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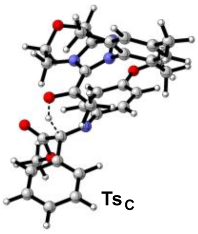

Ts_C

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C	0.57268500	-2.12317000	-2.97438900
C	0.56753300	0.34752400	-3.27947400
C	-0.03034000	-0.03291700	-4.62418900
H	-0.79639500	-2.59621400	-4.54285100
H	0.87364500	-3.17067600	-4.80891600
H	-0.05206600	1.09067500	-2.76702000

H	-1.11892900	-0.20399600	-4.52451900
O	0.59183300	-1.18310200	-5.15750700
N	0.79650400	-3.01485300	-2.05941900
N	0.61849400	-0.86046700	-2.45271300
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N	0.99220700	-2.28595100	-0.92474800
C	1.42026500	-2.97141100	0.26216400
C	0.46327300	-3.45616600	1.15332600
C	2.79954100	-3.11661400	0.45195100
C	0.93179000	-4.12181600	2.28978400
C	3.21688400	-3.78588600	1.60122500
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H	4.28751300	-3.90614500	1.78393400
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H	4.80091000	-2.68222800	-0.21781100
H	3.59439000	-1.43335800	-0.64654300
C	-1.00044200	-3.21133800	0.91399500
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H	-1.24030400	-2.14147500	1.03644900
H	-1.61426800	-3.78224900	1.62139200
C	2.78292200	-5.03571900	3.74604300
H	3.63069900	-4.51445500	4.21145600
H	3.12707700	-6.04523400	3.47426000
H	1.98603000	-5.14104900	4.49311500
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H	0.76464600	-0.74835200	1.66703200
H	2.50162700	-0.65322600	1.25907700
H	1.63429300	0.80776200	1.77441600
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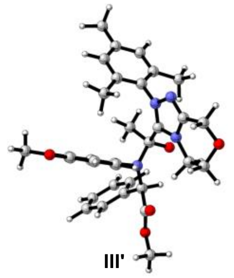

III'

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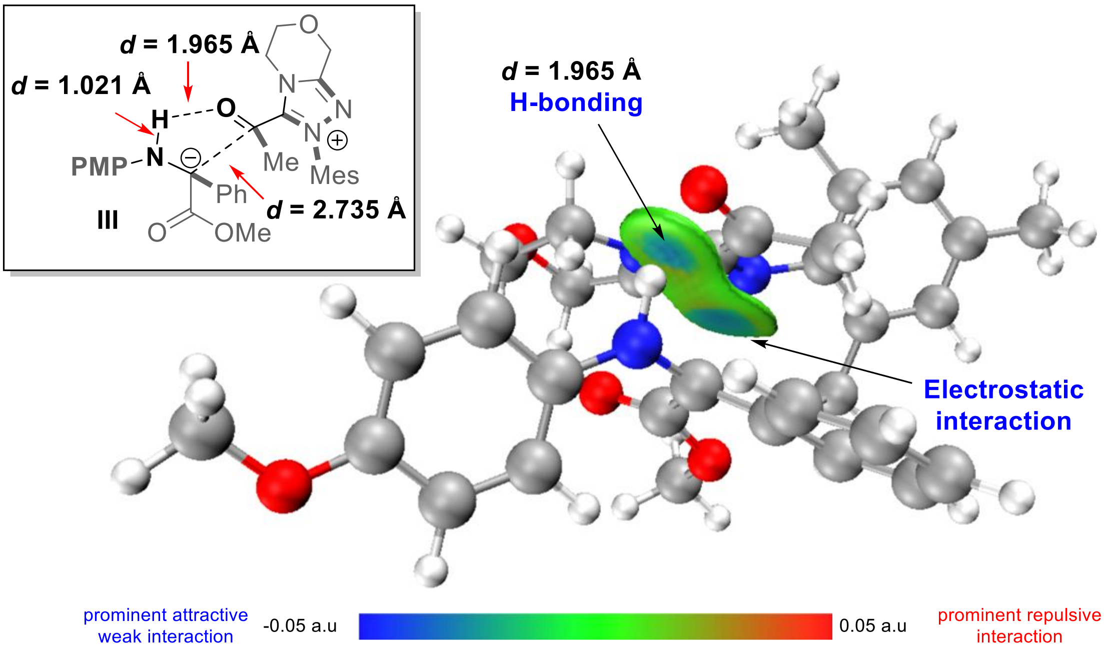
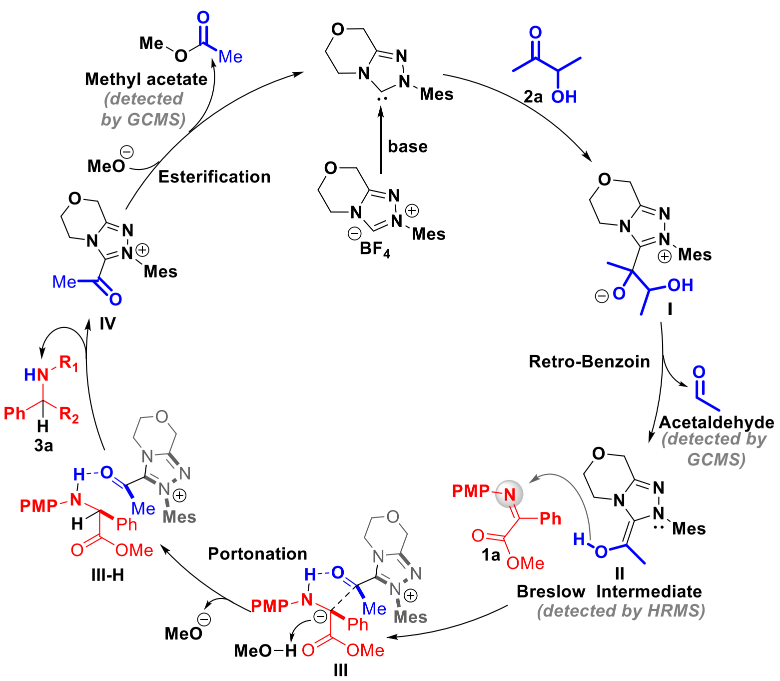
Non-covalent interaction analysis of complex III

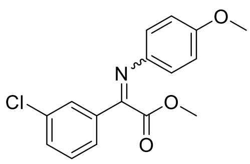


Postulated reaction mechanism



IV. Characterization of substrates and products

Characterization of substrates



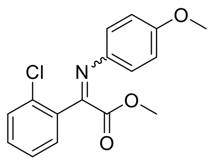
methyl 2-(3-chlorophenyl)-2-((4-methoxyphenyl)imino)acetate (1h)

93:7 mixture of geometric isomers. Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 20 / 1). yellow solid, 75% yield, 4.6 g, m. p. 48.7-51.4 ℃.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 – 7.88 (m, 1H), 7.72 – 7.66 (m, 1H), 7.48 – 7.43 (m, 1H), 7.41 – 7.34 (m, 1H), 6.96 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 3.80 (s, 3H), 3.70 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 165.7, 157.7, 157.4, 142.6, 135.9, 134.9, 131.5, 129.9, 127.7, 126.1, 121.3, 114.3, 55.4, 52.2.

HRMS (ESI, m/z): Mass calcd. for $C_{16}H_{14}ClNO_3H^+$ $[M+H]^+$: 304.0735, found: 304.0727.



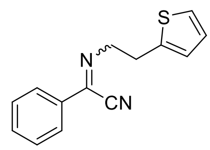
methyl 2-(2-chlorophenyl)-2-((4-methoxyphenyl)imino)acetate (1k)

88:12 mixture of geometric isomers. Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 20 / 1). yellow solid, 81% yield, 4.9 g, m. p. 54.3-55.7 ℃.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 – 7.37 (m, 1H), 7.33 – 7.27 (m, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.97 (dd, J = 7.6, 1.7 Hz, 1H), 6.78 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 3.94 (s, 3H), 3.73 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 164.4, 158.1, 156.3, 140.8, 134.0, 132.9, 130.5, 129.9, 129.5, 126.9, 123.3, 113.8, 55.3, 53.4.

HRMS (ESI, m/z): Mass calcd. for $C_{16}H_{14}ClNO_3H^+$ $[M+H]^+$: 304.0735, found: 304.0727.



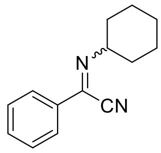
N-(2-(thiophen-2-yl)ethyl)benzimidoyl cyanide (1w)

89:11 mixture of geometric isomers. Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 20 / 1). Yellow solid, 72% yield, 0.9 g, m. p. 63.3-65.4 ℃.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01 (d, J = 7.7 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.50 (d, J = 7.7 Hz, 2H), 7.20 – 7.14 (m, 1H), 6.98 – 6.91 (m, 1H), 6.92 – 6.87 (m, 1H), 4.24 (t, J = 6.7 Hz, 2H), 3.36 (t, J = 6.7 Hz, 2H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 142.4, 141.2, 133.4, 132.3, 128.9, 127.7, 126.9, 125.6, 124.2, 109.5, 59.7, 30.8.

HRMS (ESI, m/z): Mass calcd. for $C_{14}H_{12}N_2SH^+$ $[M+H]^+$: 241.0794, found: 241.0793.



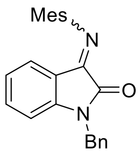
N-cyclohexylbenzimidoyl cyanide (1x)

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 100 / 1). Colorless oil, 88% yield, 0.8 g.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 – 7.93 (m, 2H), 7.52 – 7.39 (m, 3H), 3.97 – 3.81 (m, 1H), 1.88 – 1.58 (m, 7H), 1.49 – 1.40 (m, 2H), 1.35 – 1.24 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 139.1, 133.8, 131.9, 128.8, 127.6, 109.8, 67.4, 33.5, 25.5, 24.1.

HRMS (ESI, m/z): Mass calcd. for $C_{14}H_{16}N_2H^+$ $[M+H]^+$: 213.1386, found: 213.1381.



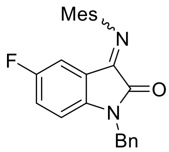
1-benzyl-3-(mesitylimino)indolin-2-one (1y)

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 4 / 1). red solid, 68% yield, 6.6 g, m. p. 156.5-157.3 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.26 (m, 6H), 7.22 (td, J = 7.8, 1.3 Hz, 1H), 6.92 (s, 2H), 6.77 – 6.68 (m, 2H), 6.42 (dd, J = 7.8, 1.3 Hz, 1H), 5.02 (s, 2H), 2.33 (s, 3H), 2.02 (s, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 163.2, 155.0, 146.5, 145.7, 135.2, 134.0, 133.8, 129.1, 128.9, 127.9, 127.5, 125.2, 124.1, 123.3, 116.7, 110.1, 44.0, 20.8, 17.8.

HRMS (ESI, m/z): Mass calcd. for $C_{18}H_{18}N_2OH^+$ $[M+H]^+$: 279.1492, found: 279.1505.



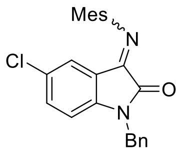
1-benzyl-5-fluoro-3-(mesitylimino)indolin-2-one (1z)

92:8 mixture of geometric isomers. Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 4 / 1). red solid, 59% yield, 6.0 g, m.p. 127.3-128.1 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.33 (m, 4H), 7.33 – 7.29 (m, 1H), 6.98 – 6.91 (m, 3H), 6.69 – 6.63 (m, 1H), 6.19 – 6.07 (m, 1H), 5.01 (s, 2H), 2.33 (s, 3H), 2.02 (s, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 163.0, 158.8 (d, J = 242.4 Hz), 154.5, 154.4, 145.2, 142.5 (d, J = 2.1 Hz), 134.9, 134.3, 129.3, 129.0, 128.1, 127.4, 123.8, 120.3 (d, J = 24.3 Hz), 117.1 (d, J = 8.0 Hz), 112.6 (d, J = 25.8 Hz), 110.94 (d, J = 7.9 Hz), 44.2, 20.8, 17.8.

HRMS (ESI, m/z): Mass calcd. for $C_{24}H_{21}FN_2OH^+$$[M+H]^+$: 373.1711, found: 373.1716.



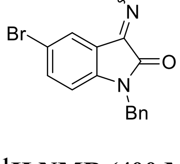
1-benzyl-5-chloro-3-(mesitylimino)indolin-2-one (1aa)

89:11 mixture of geometric isomers. Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 4 / 1). red solid, 47% yield, 5.0 g, m. p. 152.2-154.8 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.30 (m, 5H), 7.20 (dd, J = 8.4, 2.2 Hz, 1H), 6.94 (s, 2H), 6.66 (d, J = 8.4 Hz, 1H), 6.36 (d, J = 2.2 Hz, 1H), 5.01 (s, 2H), 2.34 (s, 3H), 2.02 (s, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 162.7, 154.0, 145.3, 144.9, 134.7, 134.4, 133.6, 129.3, 129.1, 128.6, 128.1, 127.4, 125.2, 123.8, 117.5, 111.2, 44.2, 20.8, 17.9.

HRMS (ESI, m/z): Mass calcd. for $C_{24}H_{21}ClN_2OH^+$ $[M+H]^+$: 389.1415, found: 389.1413.



1-benzyl-5-bromophenyl-3-(mesitylimino)indolin-2-one (1ab)

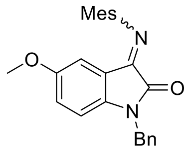
89:11 mixture of geometric isomers. Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 4 / 1). red solid, 56% yield, 6.6 g, m. p. 158.7-161.8 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 – 7.28 (m, 6H), 6.95 (s, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.48 (d, J = 2.0 Hz, 1H), 5.01 (s, 2H), 2.34 (s, 3H), 2.01 (s, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 162.6, 153.8, 145.3, 145.3, 136.5, 134.7, 134.4, 129.2, 129.1, 128.1, 128.0, 127.4, 123.9, 117.9, 115.9, 111.7, 44.1, 20.8, 17.9.

HRMS (ESI, m/z): Mass calcd. for $C_{24}H_{21}BrN_2OH^+$ $[M+H]^+$: 433.0910, found: 433.0915.

1-benzyl-3-(mesitylimino)-5-methoxyindolin-2-one (1ac)



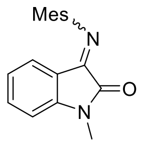
90:10 mixture of geometric isomers. Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 4 / 1). red solid, 70% yield, 7.3 g, m. p. 129.2-130.4 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.27 (m, 5H), 6.93 (s, 2H), 6.76 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.60 (d, *J* = 8.6 Hz, 1H), 5.96 (d, *J* = 2.7 Hz, 1H), 4.99 (s, 2H), 3.44 (s, 3H), 2.31 (s, 3H), 2.03 (s, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 163.2, 155.8, 155.4, 145.7, 140.1, 135.3, 133.9, 129.1, 129.0, 128.9, 127.9, 127.4, 124.1, 119.0, 117.2, 111.2, 110.7, 55.4, 44.1, 20.8, 17.9.

HRMS (ESI, m/z): Mass calcd. for $C_{25}H_{24}N_2O_2H^+$ [M+H]$^+$: 385.1911, found: 385.1909.

3-(mesitylimino)-1-methylindolin-2-one (1ad)

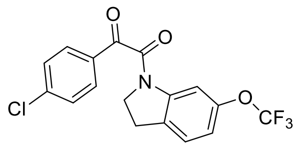


92:8 mixture of geometric isomers. Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 5 / 1). red solid, 85% yield, 6.4 g, m. p. 162.7-164.8 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 (t, *J* = 7.7 Hz, 1H), 6.91 (s, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.76 (t, *J* = 7.7 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 3.31 (s, 3H), 2.32 (s, 3H), 1.98 (s, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 163.18, 155.13, 147.27, 145.69, 134.09, 133.78, 129.06, 125.16, 124.08, 123.30, 116.54, 109.03, 26.31, 20.85, 17.79.

HRMS (ESI, m/z): Mass calcd. for $C_{18}H_{18}N_2OH^+$ [M+H]$^+$: 279.1492, found: 279.1505.



1-(4-chlorophenyl)-2-(6-(trifluoromethoxy)indolin-1-yl)ethane-1,2-dione (S2)

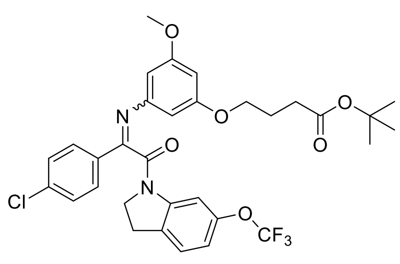
Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10/ 1). White solid, 85% yield, 3.3 g, m.p. 130.6-132.6 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.20 (d, *J* = 1.2 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.12 (t, *J* = 8.4 Hz, 2H), 3.19 (t, *J* = 8.4 Hz, 2H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 188.2, 163.2, 148.6 (d, *J* = 2.3 Hz), 142.8, 141.7, 131.5, 131.0, 130.4, 129.5, 125.3, 120.5 (q, *J* = 257.2 Hz), 111.2, 48.8, 27.7.

^{19}F NMR (376 MHz, CDCl$_3$) δ -57.9.

HRMS (ESI, m/z): Mass calcd. for $C_{17}H_{11}ClF_3NO_3H^+$ [M+H]$^+$: 370.0452, found: 370.0452.



tert-butyl 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethylidene)amino)-5-methoxyphenoxy)butanoate (4)

74:26 mixture of geometric isomers. Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10/ 1). Yellow oil. 20% yield, 349 mg.

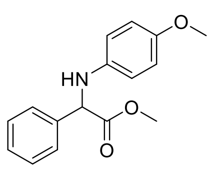
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07 (s, 1H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.30 – 6.26 (m, 2H), 6.17 – 6.13 (m, 1H), 4.07 – 3.86 (m, 1H), 3.86 – 3.78 (m, 2H), 3.62 (s, 3H), 3.59 – 3.52 (m, 1H), 3.01 – 2.86 (m, 1H), 2.85 – 2.76 (m, 1H), 2.29 – 2.25 (m, 2H), 1.96 – 1.89 (m, 2H), 1.35 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.4, 164.4, 161.1, 160.6, 160.4, 160.1, 149.9, 148.4, 142.4, 138.2, 132.5, 132.2, 132.2, 130.4, 129.6, 129.4, 129.2, 125.3, 120.5 (q, J = 257.2 Hz), 117.5, 110.7, 99.6, 99.3, 99.0, 80.3, 67.1, 55.3, 48.3, 31.9, 28.5, 27.4, 24.6.

^{19}F NMR (376 MHz, CDCl$_3$) δ -57.9.

HRMS(ESI, m/z): Mass calcd. for $C_{32}H_{32}ClF_3N_2O_6Na^+$ $[M+Na]^+$: 655.1793, found: 655.1788.

Characterization of products



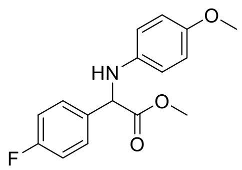
methyl 2-((4-methoxyphenyl)amino)-2-phenylacetate (3a)[15]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 96% yield, 130 mg, m.p. 103.0-104.2 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 – 7.43 (m, 1H), 7.39 – 7.26 (m, 2H), 6.71 (d, J = 8.9 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 5.02 (d, J = 5.2 Hz, 1H), 4.66 (d, J = 5.2 Hz, 1H), 3.71 (s, 2H), 3.69 (s, 2H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.6, 152.5, 140.2, 137.8, 128.8, 128.3, 127.3, 114.9, 114.8, 61.6, 55.7, 52.7.

HRMS (ESI, m/z): Mass calcd. for $C_{16}H_{17}NO_3Na^+$ $[M+Na]^+$: 294.1101, found: 294.1091.



methyl 2-(4-fluorophenyl)-2-((4-methoxyphenyl)amino)acetate (3b)[15]

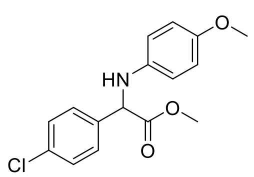
Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 92% yield, 133 mg, m.p. 94.0-95.7 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 – 7.42 (m, 2H), 7.07 – 6.99 (m, 2H), 6.71 (d, J = 9.0 Hz, 2H), 6.50 (d, J = 9.0 Hz, 2H), 4.99 (s, 1H), 4.80 - 4.55 (br, 1H), 3.71 (s, 3H), 3.69 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.4, 162.7 (d, J = 247.1 Hz), 152.6, 138.8, 133.6 (d, J = 3.4 Hz) , 128.9 (d, J = 8.2 Hz), 115.8 (d, J = 21.7 Hz), 114.9, 114.8, 60.9, 54.8, 52.8.

^{19}F NMR (376 MHz, CDCl$_3$) δ -113.9.

HRMS (ESI, m/z): Mass calcd. for $C_{16}H_{16}FNO_3Na^+$$[M+Na]^+$: 312.1006, found: 312.0997.



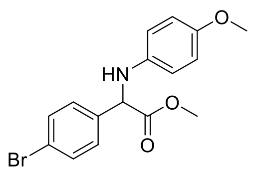
methyl 2-(4-chlorophenyl)-2-((4-methoxyphenyl)amino)acetate (3c)[15]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). Pale yillow oil, 95% yield, 145 mg.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.9 Hz, 2H), 6.49 (d, J = 8.9 Hz, 2H), 4.98 (d, J = 5.5 Hz, 1H), 4.69 (d, J = 5.5 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.1, 152.7, 139.8, 136.4, 134.1, 129.1, 128.7, 114.9, 114.8, 61.0, 55.7, 52.9.

HRMS(ESI, m/z): Mass calcd. for $C_{16}H_{16}ClNO_3Na^+$ $[M+Na]^+$: 328.0711, found: 328.0698.



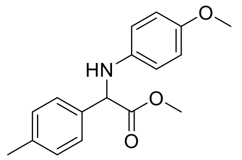
methyl 2-(4-bromophenyl)-2-((4-methoxyphenyl)amino)acetate (3d)[15]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 95% yield, 167 mg, m.p. 77.2-78.9 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.9 Hz, 2H), 6.49 (d, J = 8.9 Hz, 2H), 4.97 (d, J = 5.4 Hz, 1H), 4.70 (d, J = 5.4 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 171.8, 152.6, 139.7, 137.0, 132.0, 129.0, 122.2, 114.9, 114.8, 61.0, 55.7, 52.9.

HRMS(ESI, m/z): Mass calcd. for $C_{16}H_{16}BrNO_3Na^+$[M+Na]$^+$: 350.0386, found: 350.03811.



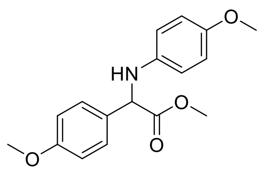
methyl 2-((4-methoxyphenyl)amino)-2-(p-tolyl)acetate (3e)[15]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 88% yield, 126 mg, m.p. 58.9-61.7 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.71 (d, J = 8.9 Hz, 2H), 6.52 (d, J = 8.9 Hz, 2H), 4.98 (s, 1H), 4.72 – 4.52 (br, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.8, 152.5, 140.3, 138.1, 134.9, 129.6, 127.2, 114.9, 114.8, 61.4, 55.7, 52.7, 21.2.

HRMS(ESI, m/z): Mass calcd. for $C_{16}H_{17}NO_3Na^+$[M+Na]$^+$: 308.1258, found: 308.1255.



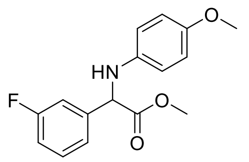
methyl 2-(4-methoxyphenyl)-2-((4-methoxyphenyl)amino)acetate (3f)[15]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 89% yield, 135 mg, m.p. 87.5-88.6 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.9 Hz, 2H), 6.53 (d, J = 8.9 Hz, 2H), 4.96 (s, 1H),4.75 – 4.38 (br, 1H) 3.78 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.9, 159.6, 152.5, 140.3, 129.8, 128.4, 114.9, 114.8, 114.3, 61.0, 55.7, 55.3, 52.7.

HRMS(ESI, m/z): Mass calcd. for $C_{17}H_{19}NO_4Na^+$[M+Na]$^+$: 324.1207, found: 324.1202.



methyl 2-(3-fluorophenyl)-2-((4-methoxyphenyl)amino)acetate (3g)[15]

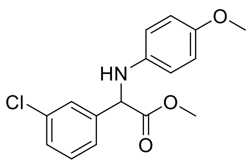
Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 92% yield, 133 mg, m.p. 74.1-75.8 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34 – 7.25 (m, 2H), 7.24 – 7.18 (m, 1H), 7.03 – 6.93 (m, 1H), 6.71 (d, J = 8.9 Hz, 2H), 6.50 (d, J = 8.9 Hz, 2H), 5.00 (s, 1H), 4.85 – 4.55 (br, 1H), 3.71 (s, 3H), 3.68 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 171.9, 163.1 (d, J = 247.0 Hz), 152.7, 140.6 (d, J = 6.8 Hz), 139.8, 130.4 (d, J = 8.4 Hz) , 123.0 (d, J = 3.0 Hz), 115.3 (d, J = 21.2 Hz), 114.9, 114.8, 114.3 (d, J = 22.5 Hz), 61.2, 61.2, 55.7, 52.9.

^{19}F NMR (376 MHz, CDCl$_3$) δ -112.2.

HRMS (ESI, m/z): Mass calcd. for $C_{16}H_{16}FNO_3Na^+$ $[M+Na]^+$, 290.1187; found: 290.1186.



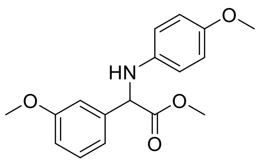
methyl 2-(3-chlorophenyl)-2-((4-methoxyphenyl)amino)acetate (3h)[16]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). Pale green oil, 94% yield, 143 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.43 – 7.36 (m, 1H), 7.32 – 7.26 (m, 2H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.52 (d, *J* = 8.9 Hz, 2H), 4.99 (s, 1H), 4.85 –4.62 (br, 1H), 3.74 (s, 3H), 3.71 (s, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 171.9, 152.7, 140.1, 139.8, 134.8, 130.1, 128.5, 127.5, 125.5, 114.9, 114.8, 61.2, 55.7, 52.9.

HRMS (ESI, m/z): Mass calcd. for $C_{16}H_{16}ClNO_3H^+$ $[M+H]^+$, 306.08914; found 306.0881.



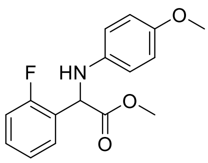
methyl 2-(3-methoxyphenyl)-2-((4-methoxyphenyl)amino)acetate (3i)[15]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). Pale yellow oil, 88% yield, 133 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 1H), 7.10 – 7.01 (m, 2H), 6.85 – 6.80 (m, 1H), 6.71 (d, *J* = 8.9 Hz, 2H), 6.52 (d, *J* = 8.9 Hz, 2H), 4.98 (s, 1H), 4.78 –4.53 (br, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 160.1, 152.6, 140.3, 139.5, 129.9, 119.7, 114.9, 114.8, 113.8, 112.9, 61.7, 55.7, 55.3, 52.8.

HRMS(ESI, m/z): Mass calcd. for $C_{17}H_{19}NO_4Na^+[M+Na]^+$: 324.1207, found: 324.1205.



methyl 2-(2-fluorophenyl)-2-((4-methoxyphenyl)amino)acetate (3j)[15]

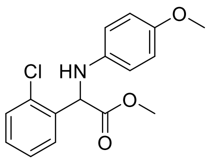
Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 95% yield, 137 mg, m.p. 81.7-83.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.38 (m, 1H), 7.30 – 7.24 (m, 1H), 7.14 – 7.05 (m, 2H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.56 (d, *J* = 8.9 Hz, 2H), 5.38 (d, *J* = 6.2 Hz, 1H), 4.69 (d, *J* = 6.2 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 160.8 (d, *J* = 247.2 Hz), 152.8, 139.8, 129.9 (d, *J* = 8.3 Hz), 128.3 (d, *J* = 3.1 Hz), 125.4 (d, *J* = 13.8 Hz), 124.7 (d, *J* = 3.6 Hz), 115.8 (d, *J* = 21.8 Hz), 114.8, 55.6, 54.7 (d, *J* = 3.0 Hz), 52.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ -118.5.

HRMS(ESI, m/z): Mass calcd. for $C_{16}H_{16}FNO_3Na^+[M+Na]^+$: 290.1187, found: 290.1189.



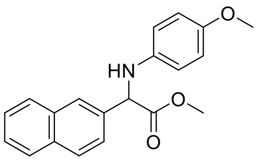
methyl 2-(2-chlorophenyl)-2-((4-methoxyphenyl)amino)acetate (3k)[17]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 20 / 1). Pale yellow oil, 82% yield, 125 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 1H), 7.44 – 7.37 (m, 1H), 7.27 – 7.18 (m, 2H), 6.71 (d, *J* = 9.0 Hz, 2H), 6.54 (d, *J* = 9.0 Hz, 2H), 5.54 (s, 1H), 4.84 – 4.71 (br, 1H), 3.72 (s, 3H), 3.69 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.1, 152.7, 141.4, 137.0, 134.2, 123.0, 129.4, 128.3, 127.5, 114.9, 114.8, 58.0, 55.7, 52.9.

HRMS(ESI, m/z): Mass calcd. for $C_{16}H_{16}ClNO_3Na^+$[M+Na]$^+$: 328.0711, found: 328.0698.



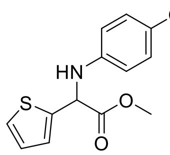
methyl 2-((4-methoxyphenyl)amino)-2-(naphthalen-2-yl)acetate (3l)[15]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 92% yield, 148 mg, m.p. 92.3-95.6 ℃.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 (d, *J* = 1.9 Hz, 1H), 7.83 – 7.76 (m, 3H), 7.58 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.47 – 7.40 (m, 2H), 6.69 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 8.9 Hz, 2H), 5.16 (d, *J* = 5.4 Hz, 1H), 4.82 (d, *J* = 5.4 Hz, 1H), 3.67 (s, 3H), 3.64 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.6, 152.6, 140.3, 135.5, 133.5, 133.3, 128.8, 128.2, 127.8, 126.6, 126.4, 126.4, 125.1, 114.9, 61.9, 55.7, 52.8.

HRMS(ESI, m/z): Mass calcd. for $C_{20}H_{19}NO_3Na^+$ [M+Na]$^+$: 344.1257, found: 344.1253.



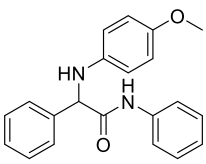
methyl 2-((4-methoxyphenyl)amino)-2-(thiophen-2-yl)acetate (3m)[18]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). yellow oil, 92% yield, 128 mg.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.24 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.12 (dd, *J* = 3.5, 1.3 Hz, 1H), 6.98 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.75 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 2H), 5.28 (s, 1H), 4.83 – 4.43 (br, 1H), 3.77 (s, 3H), 3.72 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 171.7, 153.0, 141.5, 140.0, 127.1, 125.7, 125.5, 115.3, 114.0, 57.8, 55.6, 52.9.

HRMS (ESI, m/z): Mass calcd. for $C_{14}H_{16}NO_3SNa^+$ [M+Na]$^+$, 278.0845; found: 278.0848.



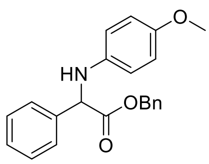
2-((4-methoxyphenyl)amino)-N,2-diphenylacetamide (3n)[19]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 5 / 1). White solid, 85% yield, 141 mg, m.p. 132.1-134.5 ℃.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.91 (s, 1H), 7.56 – 7.49 (m, 2H), 7.51 – 7.44 (m, 2H), 7.42 – 7.31 (m, 3H), 7.31 – 7.26 (m, 2H), 7.13 – 7.02 (m, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 4.74 (s, 1H), 4.40 – 4.05 (br, 1H), 3.73 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 169.9, 153.6, 141.3, 138.6, 137.4, 129.3, 129.0, 128.8, 127.4, 124.6, 119.9, 115.4, 115.0, 66.2, 56.4.

HRMS (ESI, m/z): Mass calcd. for $C_{21}H_{20}N_2O_2Na^+$ [M+Na]$^+$, 355.1417; found 355.1410.



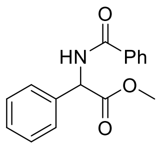
benzyl 2-((4-methoxyphenyl)amino)-2-phenylacetate (3o)[20]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). Pale yellow oil, 83% yield, 145 mg.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 – 7.44 (m, 2H), 7.38 – 7.24 (m, 6H), 7.20 – 7.10 (m, 2H), 6.70 (d, *J* = 8.9 Hz, 2H), 6.52 (d, *J* = 8.9 Hz, 2H), 5.21 – 5.07 (m, 2H), 5.07 (s, 1H), 4.85 – 4.45 (br, 1H), 3.69 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 172.0, 152.6, 140.2, 137.7, 135.4, 128.9, 128.5, 128.0, 127.9, 127.5, 114.9, 114.8, 67.2, 61.8, 55.7.

HRMS (ESI, m/z): Mass calcd. for $C_{22}H_{21}NO_3H^+$ $[M+H]^+$, 348.1594; found: 348.1587.



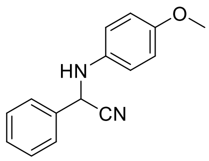
methyl 2-benzamido-2-phenylacetate (3p)[21]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate= 5 / 1). White solid, 95% yield, 128 mg, m.p. 72.4-74.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.79 (m, 2H), 7.55 – 7.47 (m, 1H), 7.48 – 7.39 (m, 4H), 7.42 – 7.29 (m, 3H), 7.17 (d, *J* = 7.0 Hz, 1H), 5.78 (d, *J* = 7.0 Hz, 1H), 3.77 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 166.6, 136.6, 133.6, 131.9, 129.0, 128.6, 127.3, 127.2, 56.8, 52.9.

HRMS (ESI, m/z): Mass calcd. for $C_{16}H_{15}NO_3Na^+$ $[M+Na]^+$, 292.0944; found: 292.0940.



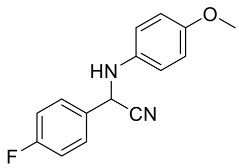
2-((4-methoxyphenyl)amino)-2-phenylacetonitrile (3q)[22]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 85% yield, 101 mg, m.p. 114.5-116.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 2H), 7.47 – 7.36 (m, 3H), 6.82 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.9 Hz, 2H), 5.31 (s, 1H), 3.95 – 3.75 (br, 1H), 3.74 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 138.7, 134.2, 129.4, 129.3, 127.3, 118.6, 116.3, 115.0, 55.7, 51.5.

HRMS (ESI, m/z): Mass calcd. for $C_{14}H_{14}NO^+$ $[M-CN^-]^+$, 212.1070; found: 212.1070.



2-(4-fluorophenyl)-2-((4-methoxyphenyl)amino)acetonitrile (3r)[22]

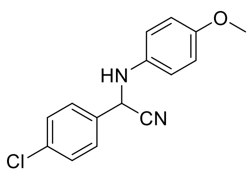
Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 82% yield, 105 mg, m.p. 101.2-102.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H), 7.13 – 7.05 (m, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.72 (d, *J* = 8.9 Hz, 2H), 5.29 (s, 1H), 3.95 – 3.77 (br, 1H), 3.73 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2 (d, *J* = 249.1 Hz), 154.1, 138.5, 130.1 (d, *J* = 3.1 Hz), 129.2 (d, *J* = 8.2 Hz), 118.5, 116.5, 116.2 (d, *J* = 21.8 Hz), 115.0, 55.6, 50.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.7.

HRMS (ESI, m/z): Mass calcd. for $C_{14}H_{13}FNO^+$ $[M-CN^-]^+$, 230.0976; found: 230.0978.



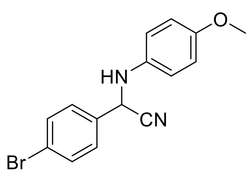
2-(4-chlorophenyl)-2-((4-methoxyphenyl)amino)acetonitrile (3s)[22]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 81% yield, 110 mg, m.p. 61.2-63.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.71 (d, *J* = 8.9 Hz, 2H), 5.30 (d, *J* = 9.1 Hz, 1H), 3.86 (d, *J* = 9.1 Hz, 1H), 3.74 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 138.2, 135.5, 132.7, 129.4, 128.6, 118.1, 116.6, 115.0, 55.6, 51.1.

HRMS (ESI, m/z): Mass calcd. for $C_{14}H_{13}ClNO^+$ $[M-CN^-]^+$, 246.0680; found: 246.0679.



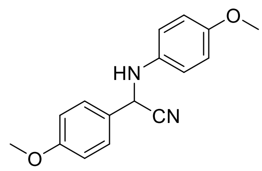
2-(4-bromophenyl)-2-((4-methoxyphenyl)amino)acetonitrile (3t)[22]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 83% yield, 132 mg, m.p. 82.2-87.2 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 9.0 Hz, 2H), 5.28 (s, 1H), 3.95 – 3.79 (br, 1H), 3.74 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 154.9, 138.3, 133.2, 132.5, 128.9, 124.3, 118.7, 116.6, 115.0, 55.6, 51.1.

HRMS (ESI, m/z): Mass calcd. for $C_{14}H_{13}BrNO^{+}$ $[M-CN^{-}]^{+}$, 290.0175; found: 290.0166.



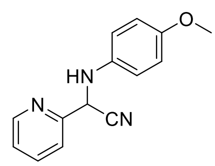
2-(4-methoxyphenyl)-2-((4-methoxyphenyl)amino)acetonitrile (3u)[22]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 83% yield, 112 mg, m.p. 92.7-94.2 ℃.

^{1}H NMR (400 MHz, CDCl$_3$ δ 7.47 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.73 (d, *J* = 9.0 Hz, 2H), 5.25 (d, *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 3.80 – 3.74 (br, 1H), 3.74 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 160.4, 154.1, 138.7, 128.6, 126.2, 118.7, 116.3, 115.0, 114.6, 55.7, 55.4, 51.0.

HRMS (ESI, m/z): Mass calcd. for $C_{15}H_{16}NO_2^{+}$ $[M-CN^{-}]^{+}$, 242.1176; found: 242.1174.



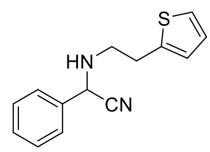
2-((4-methoxyphenyl)amino)-2-(pyridin-2-yl)acetonitrile (3v)

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 3 / 1). yellow oil, 61% yield, 73 mg.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.66 (d, *J* = 4.9 Hz, 1H), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.34 (dd, *J* = 7.7, 4.9 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 2H), 5.40 (s, 1H), 4.85 – 4.71 (br, 1H), 3.75 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 154.0, 152.5, 149.9, 138.5, 137.7, 124.3, 122.2, 118.2, 116.4, 115.0, 55.6, 52.2.

HRMS (ESI, m/z): Mass calcd. for $C_{14}H_{14}N_3OH^{+}$ $[M+H]^{+}$, 240.1131; found: 240.1122.



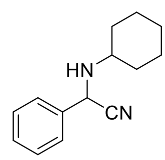
2-phenyl-2-((2-(thiophen-2-yl)ethyl)amino)acetonitrile (3w)

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 10 / 1). White solid, 81% yield, 98 mg, m.p. 78.6-80.2 ℃.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 – 7.45 (m, 2H), 7.46 – 7.32 (m, 3H), 7.16 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.86 (dd, *J* = 3.5, 1.1 Hz, 1H), 4.82 (s, 1H), 3.18 – 2.95 (m, 4H), 1.76 – 1.61 (br, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 141.5, 134.6, 129.1, 129.1, 129.0, 127.3, 126.9, 125.3, 124.0, 118.7, 54.4, 48.3, 30.1.

HRMS (ESI, m/z): Mass calcd. for $C_{13}H_{14}NS^{+}$ $[M-CN^{-}]^{+}$: 216.0841, found: 216.0839.



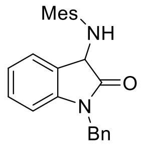
2-(cyclohexylamino)-2-phenylacetonitrile (3x)[23]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 20 / 1). Colorless oil, 69% yield, 74 mg.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.46 (m, 2H), 7.42 – 7.29 (m, 3H), 4.81 (s, 1H), 2.91 – 2.78 (m, 1H), 1.98 (d, J = 12.6 Hz, 1H), 1.82 – 1.68 (m, 3H), 1.62 (d, J = 12.6 Hz, 1H), 1.44 – 1.08 (m, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 135.7, 129.0, 128.9, 127.3, 119.4, 54.8, 51.6, 33.8, 31.9, 26.0, 24.7, 24.3.

HRMS (ESI, m/z): Mass calcd. for $C_{14}H_{18}N_2H^+$ [M+H]$^+$, 215.1543; found: 215.1537.



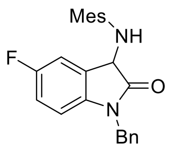
2H-Indol-2-one, 3- 2,4,6-trimethyl-Benzenamine-1,3-dihydro-1-benzyl (3y)

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 4 / 1). White solid, 92% yield, 164 mg, m.p. 117.1-119.2 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.25 (m, 5H), 7.22 – 7.13 (m, 2H), 6.96 (t, J = 7.5 Hz, 1H), 6.87 (s, 2H), 6.75 (d, J = 7.8 Hz, 1H), 4.96 (d, J = 15.4 Hz, 1H), 4.82 (d, J = 15.4 Hz, 2H) 3.41 (d, J = 7.4 Hz, 1H), 2.30 (s, 6H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 176.1, 143.4, 140.4, 135.9, 132.2, 130.1, 129.7, 129.0, 128.8, 127.9, 127.7, 127.6, 124.5, 122.2, 109.1, 59.7, 43.8, 21.6, 18.1.

HRMS(ESI, m/z): Mass calcd. for $C_{24}H_{24}N_2ONa^+$ [M+Na]$^+$: 377.1624 , found: 377.1626.



5-Fluoro-2H-Indol-2-one, 3- 2,4,6-trimethyl-Benzenamine-1,3-dihydro-1-benzyl (3z)

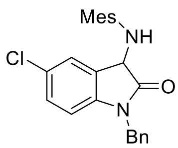
Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 4 / 1). White solid, 92% yield, 172 mg, m.p. 124.7-126.4 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.22 (m, 5H), 6.87 (d, J = 7.8 Hz, 4H), 6.69 – 6.61 (m, 1H), 4.94 (d, J = 15.6 Hz, 1H), 4.80 (d, J = 16.0 Hz, 2H), 3.57 – 3.25 (br, 1H), 2.30 (s, 6H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 175.8,159.2 (d, J = 241.3 Hz), 140.5, 138.7 (d, J = 2.1 Hz), 135.6, 132.6, 130.3, 129.8,129.5 (d, J = 8.0 Hz) , 128.9, 127.9, 127.5, 115.3 (d, J = 23.5 Hz), 113.0 (d, J = 25.0 Hz), 109.7 (d, J = 8.0 Hz), 59.0, 43.9, 20.7, 18.6.

^{19}F NMR (376 MHz, CDCl$_3$) δ -120.2.

HRMS(ESI, m/z): Mass calcd. for $C_{24}H_{23}FN_2ONa^+$ [M+Na]$^+$: 397.1687 , found: 397.1675.



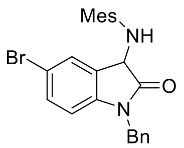
5-Chloro-2H-Indol-2-one, 3- 2,4,6-trimethyl-Benzenamine-1,3-dihydro-1-benzyl (3aa)

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 4 / 1). White solid, 95% yield, 186 mg, m.p. 107.1-110.1 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.26 (m, 5H), 7.21 – 7.13 (m, 2H), 6.88 (s, 2H), 6.70 – 6.61 (m, 1H), 4.94 (d, J = 15.5 Hz, 1H), 4.80 (d, J = 15.5 Hz, 1H), 4.77 (s, 1H), 3.71 – 3.11 (br, 1H), 2.31 (s, 6H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 175.6, 141.3, 140.5, 135.4, 132.6, 130.2, 129.8, 129.5, 128.9, 128.9, 128.2, 127.9, 127.5, 125.4, 110.1, 58.9, 43.9, 20.7, 18.6.

HRMS(ESI, m/z): Mass calcd. for $C_{24}H_{23}ClN_2ONa^+$ [M+Na]$^+$: 413.1391 , found: 413.1378.



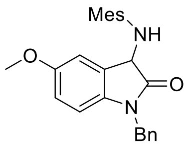
5-Bromo-2H-Indol-2-one, 3- 2,4,6-trimethyl-Benzenamine-1,3-dihydro-1-benzyl (3ab)

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 4 / 1). White solid, 92% yield, 200 mg, m.p. 112.9-115.1 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 – 7.26 (m, 7H), 6.88 (s, 2H), 6.62 (d, *J* = 8.2 Hz, 1H), 4.92 (d, *J* = 15.6 Hz, 1H), 4.80 (d, *J* = 15.6 Hz, 2H), 3.45 – 3.33 (br, 1H), 2.31 (s, 6H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 175.5, 141.9, 140.5, 135.4, 132.6, 131.9, 130.2, 129.9, 129.8, 128.9, 128.2, 127.9, 127.5, 115.4, 110.6, 58.8, 43.9, 20.7, 18.6.

HRMS(ESI, m/z): Mass calcd. for $C_{24}H_{23}BrN_2ONa^+$ [M+Na]$^+$: 457.0886, found: 457.0866.



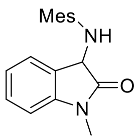
5-Methoxy-2H-Indol-2-one, 3- 2,4,6-trimethyl-Benzenamine-1,3-dihydro-1-benzyl (3ac)

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 4 / 1). White solid, 90% yield, 173 mg, m.p. 134.8-138.3 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 – 7.19 (m, 5H), 6.86 (s, 2H), 6.74 (d, *J* = 2.6 Hz, 1H), 6.69 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 4.91 (d, *J* = 15.5 Hz, 1H), 4.78 (d, *J* = 12.7 Hz, 2H), 3.65 (s, 3H), 3.55 – 3.18 (br, 1H), 2.30 (s, 6H), 2.25 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 175.7, 156.0, 140.8, 136.2, 135.9, 132.3, 130.2, 129.0, 129.1, 128.8, 127.7, 127.5, 113.6, 112.0, 109.6, 59.1, 55.7, 43.9, 20.7, 18.7.

HRMS(ESI, m/z): Mass calcd. for $C_{25}H_{26}N_2O_2Na^+$ [M+Na]$^+$: 409.1886 , found: 409.1889.



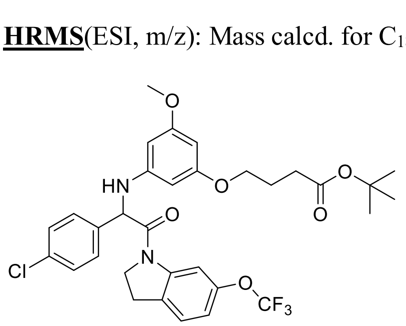
2H-Indol-2-one,3-2,4,6-trimethyl-Benzenamine-1,3-dihydro-1-methyl (3ad)

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 4 / 1). White solid, 92% yield, 129 mg, m.p. 124.1-126.3 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 (t, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 7.3 Hz, 1H), 6.98 (td, *J* = 7.5, 1.0 Hz, 1H), 6.86 (s, 2H), 6.83 (d, *J* = 7.8 Hz, 1H), 4.72 (s, 1H), 3.43 – 3.24 (br, 1H), 3.21 (s, 3H), 2.28 (s, 6H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 175.9, 143.7, 141.0, 133.1, 132.1, 130.0, 129.7, 129.1, 128.1, 124.8, 122.7, 108.2, 58.9, 26.3, 20.7, 18.7.

HRMS(ESI, m/z): Mass calcd. for $C_{18}H_{20}N_2ONa^+$ [M+Na]$^+$: 303.1468, found: 303.1475.



tert-butyl 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy) butanoate (5)[8]

Purification by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 5/ 1). White solid, 96% yield, 305 mg, m.p. 110.9-113.2 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.18 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 5.86 (t, *J* = 2.1 Hz, 1H), 5.81 (dt, *J* = 6.5, 2.1 Hz, 2H), 5.29 (d, *J* = 7.5 Hz, 1H), 5.16 (d, *J* = 7.5 Hz, 1H), 4.29 (td, *J* = 10.4, 6.0 Hz, 1H), 3.9 6 (dt, *J* = 10.4, 5.2 Hz, 1H), 3.89

(t, J = 6.2 Hz, 2H), 3.70 (s, 3H), 3.27 – 3.03 (m, 2H), 2.39 (t, J = 7.3 Hz, 2H), 2.01 (p, J = 6.7 Hz, 2H), 1.44 (s, 9H).

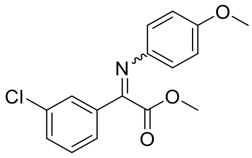
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 168.8, 161.6, 161.0, 148.6, 147.6, 143.8, 135.6, 134.4, 129.6, 129.4, 129.3, 121.8 (q, J = 228.0 Hz)., 117.0, 116.9, 111.10, 92.9, 92.6, 91.0, 80.4, 66.7, 59.6, 55.1, 48.3, 32.0, 28.1, 27.6, 24.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -57.8.

HRMS(ESI, m/z): Mass calcd. for $C_{32}H_{34}ClF_3N_2O_6H^+$ $[M+H]^+$: 635.2130, found: 635.2127.

V. Supplementary Figures

^{1}H NMR, ^{13}C NMR, ^{19}F NMR. spectra



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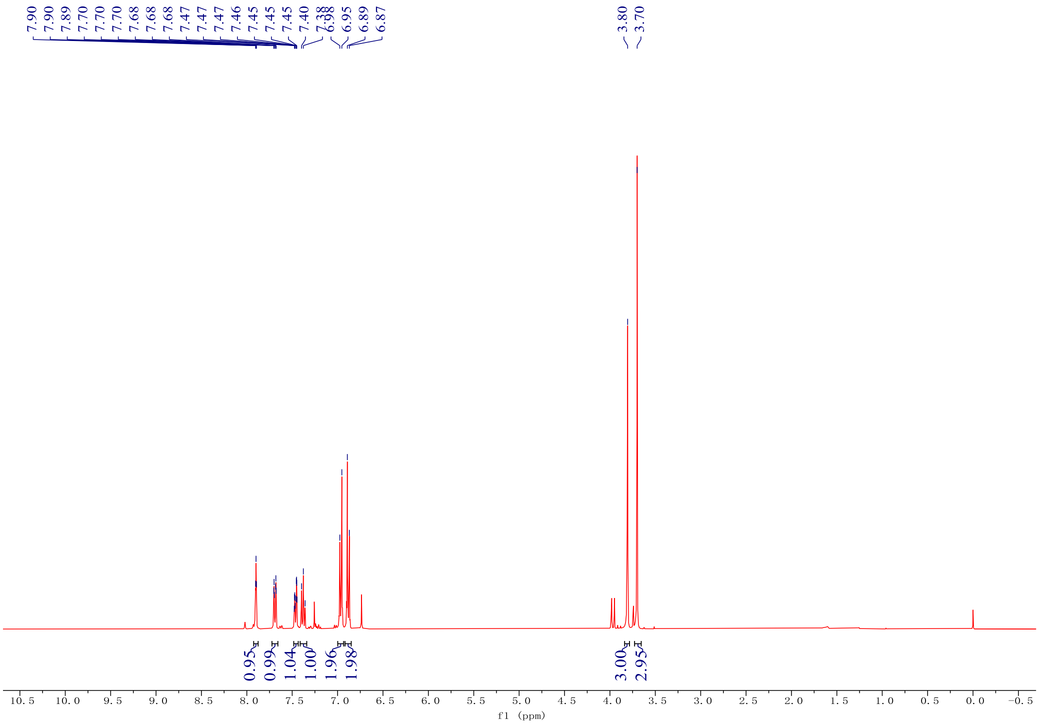

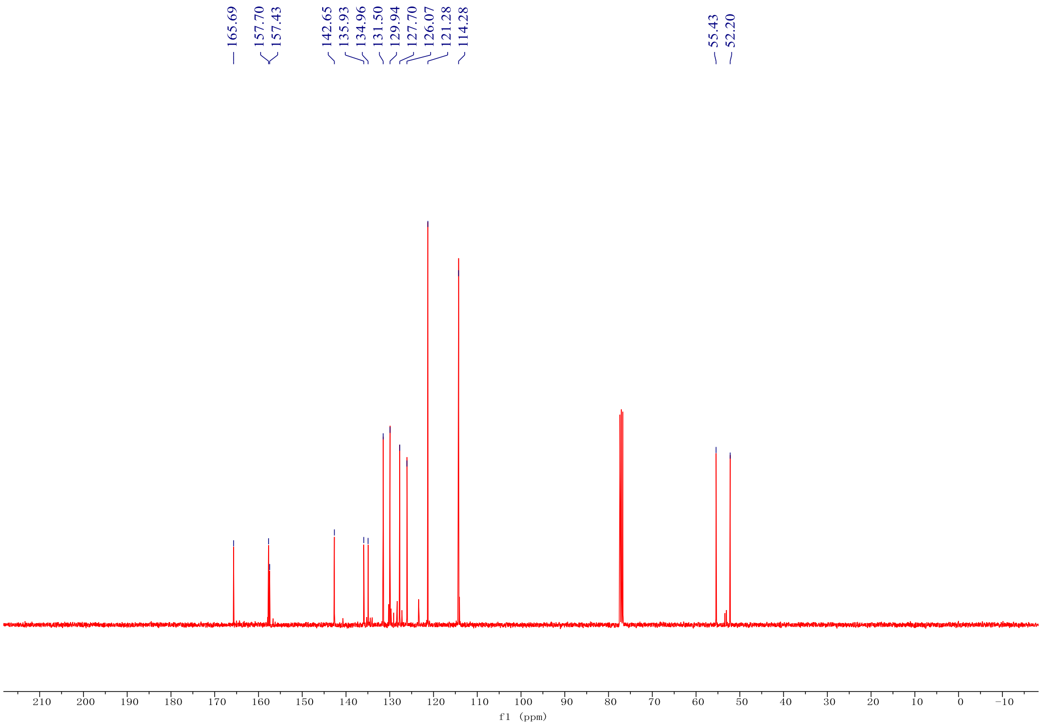

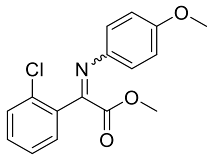
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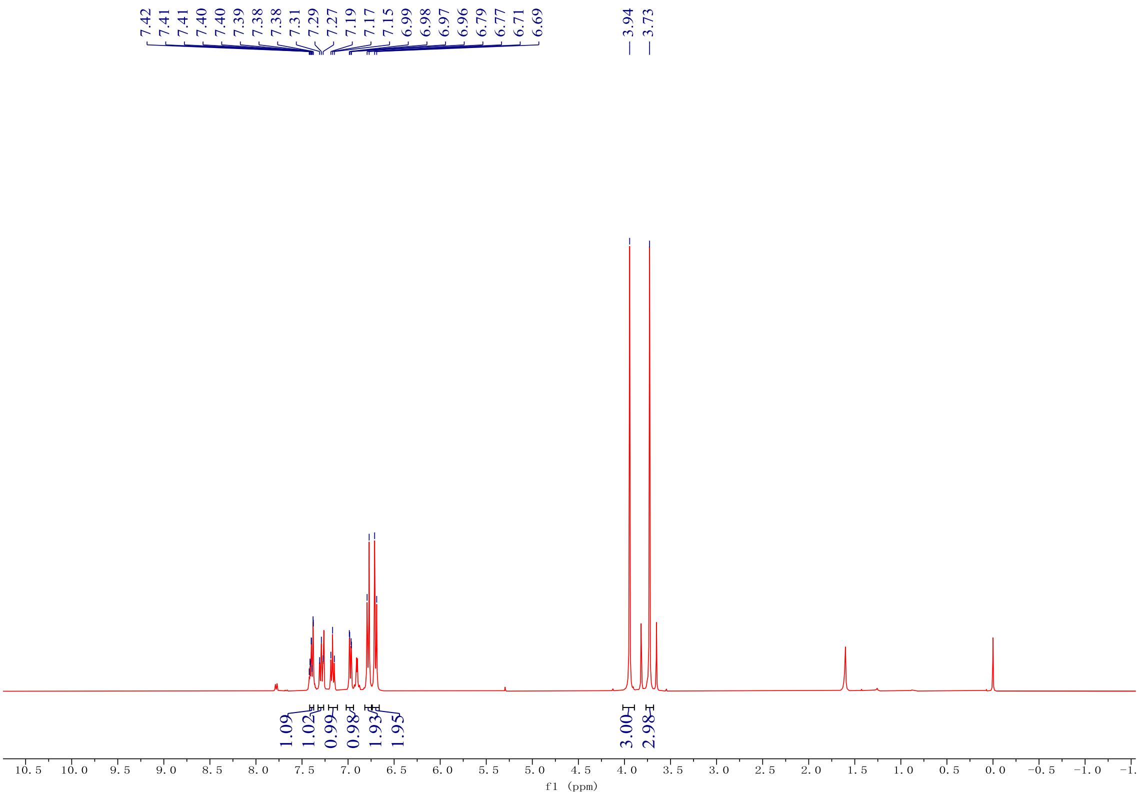
O

1k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6.98
6.97
6.96
6.79
6.77
6.71
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0.99
0.98
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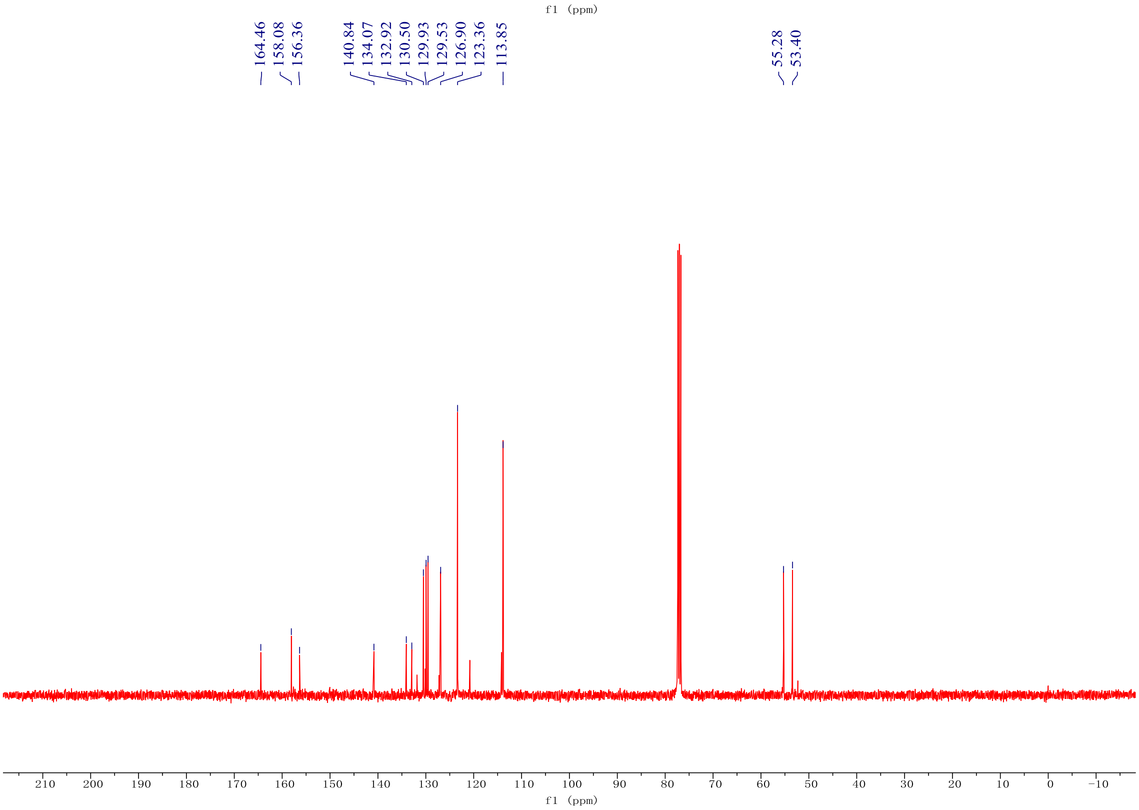
2.98
f1 (ppm)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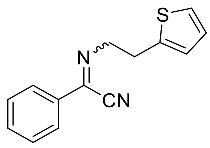
f1 (ppm)



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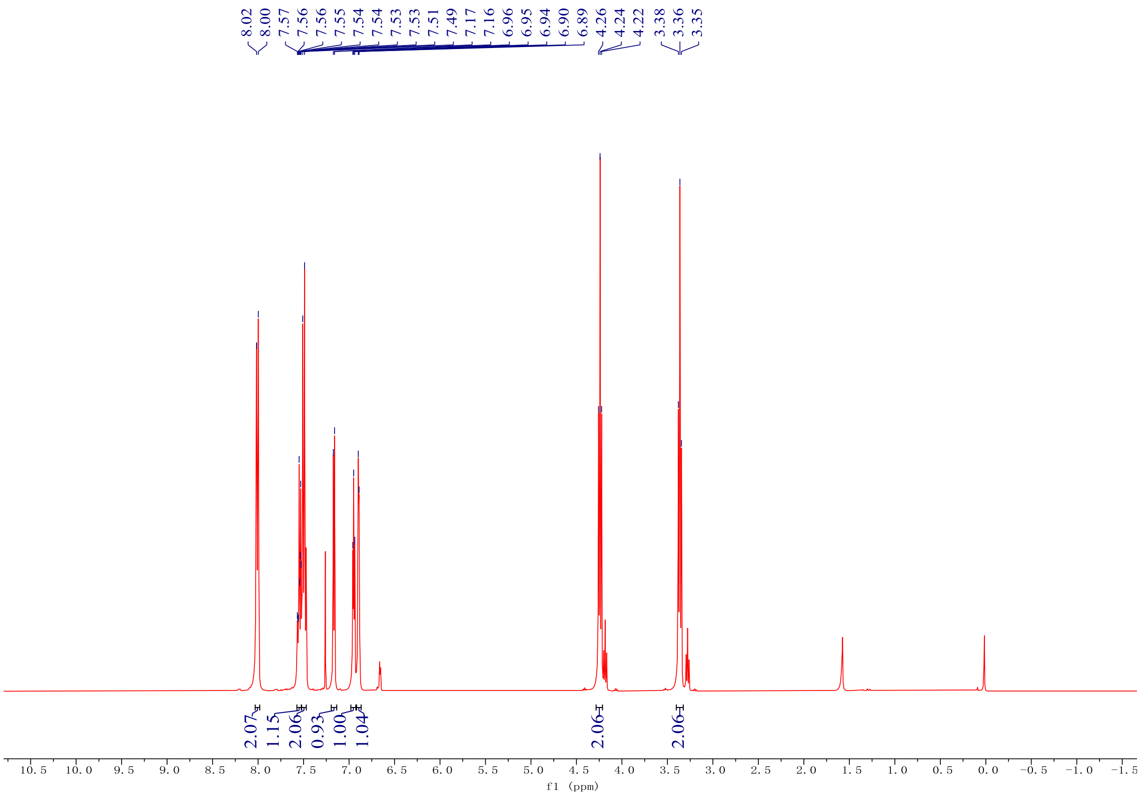
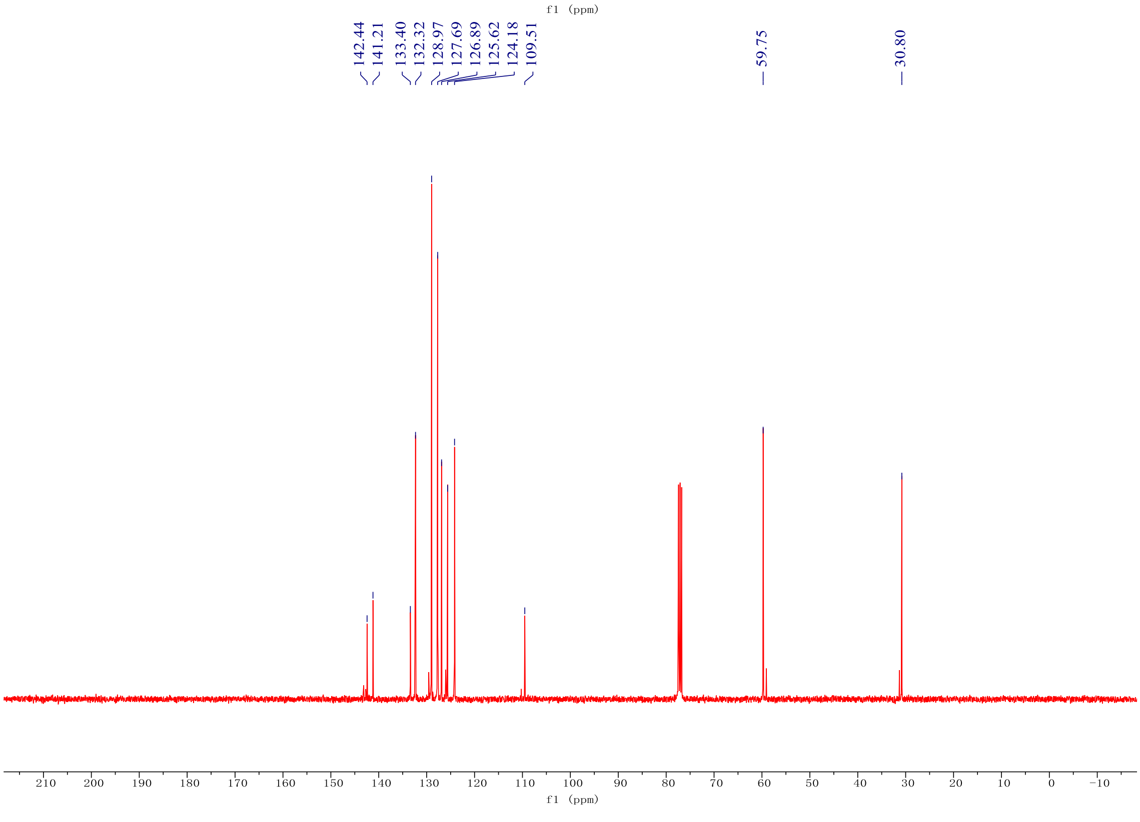
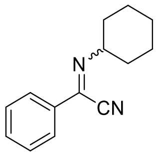
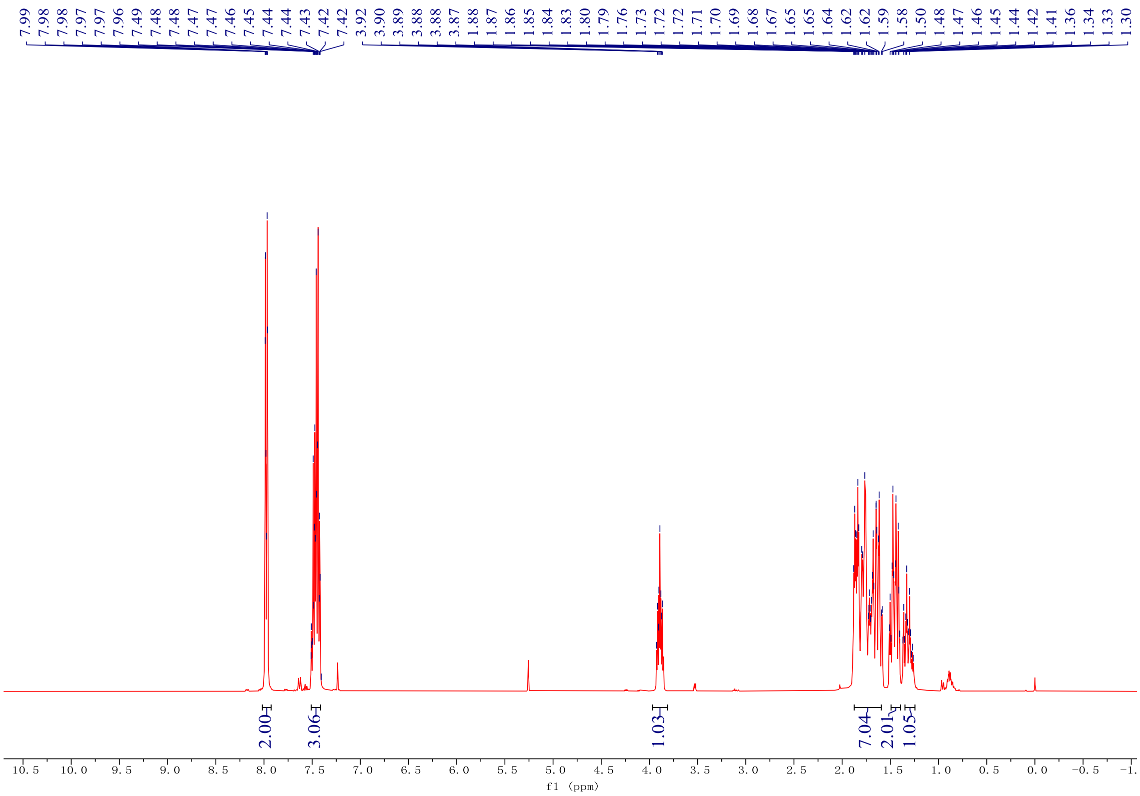





N
CN

1x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3.87
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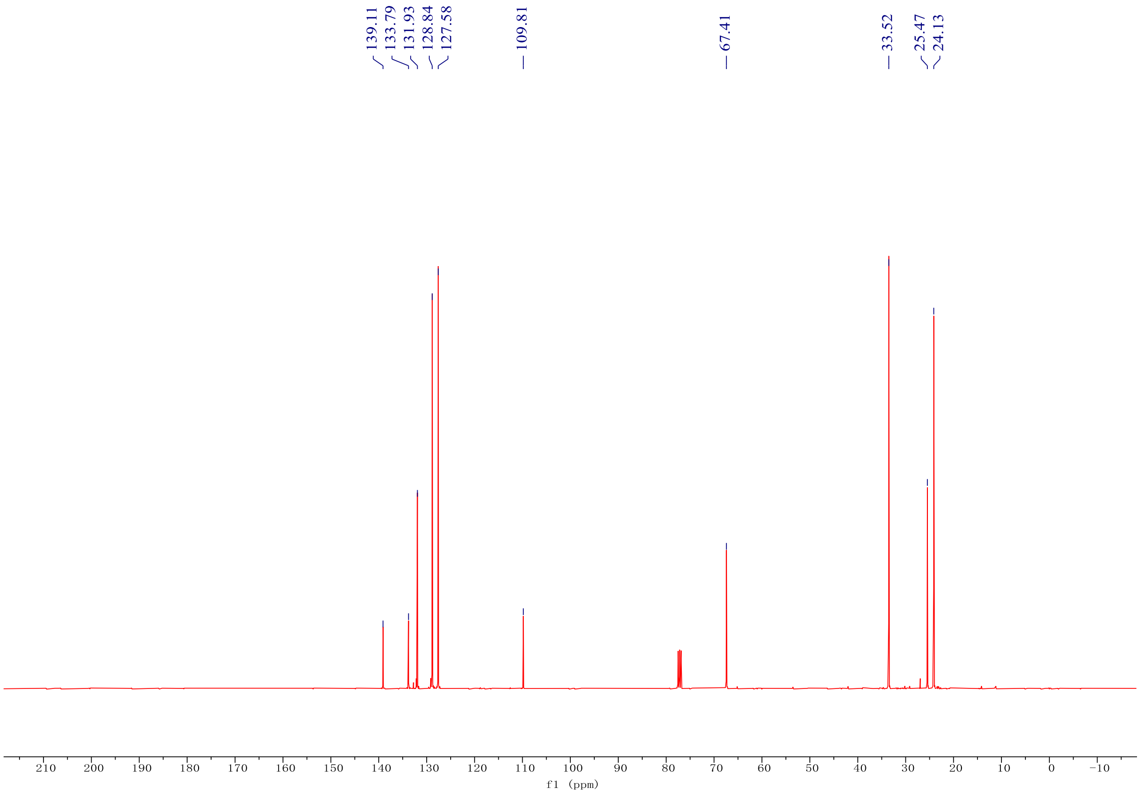
f1 (ppm)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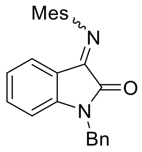
f1 (ppm)



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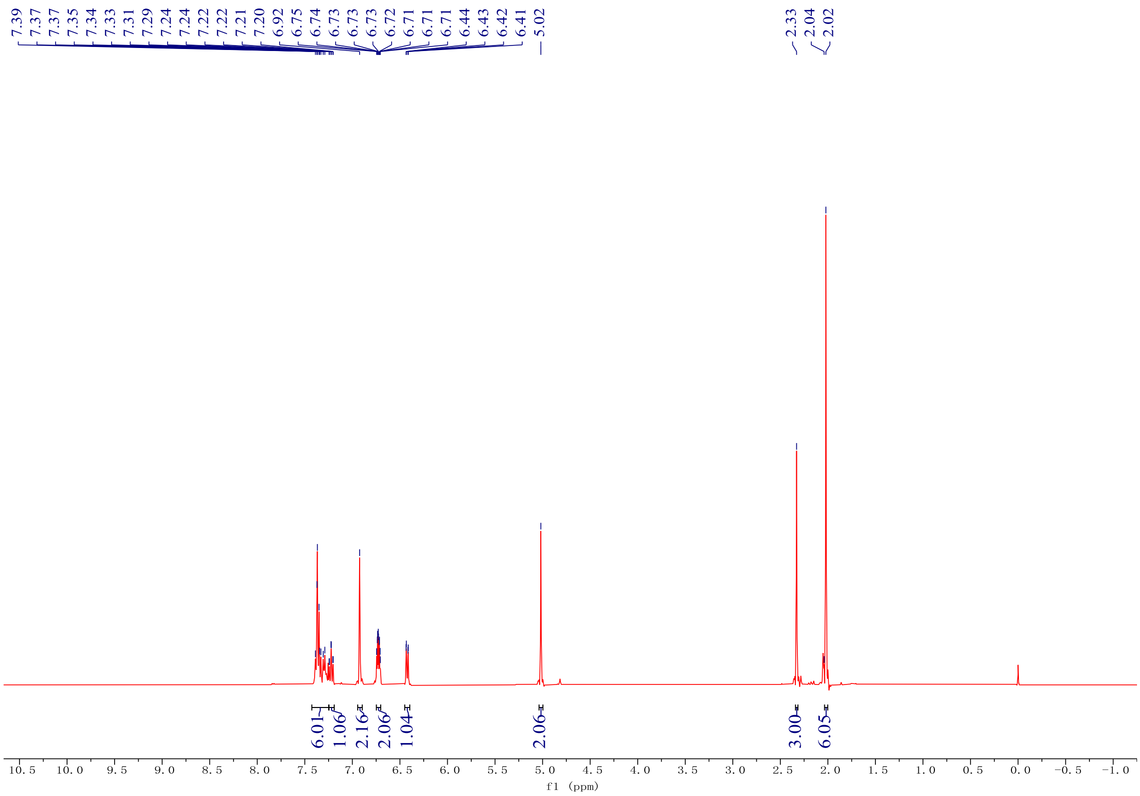
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6.74
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6.71
6.71
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6.42
6.41
5.02
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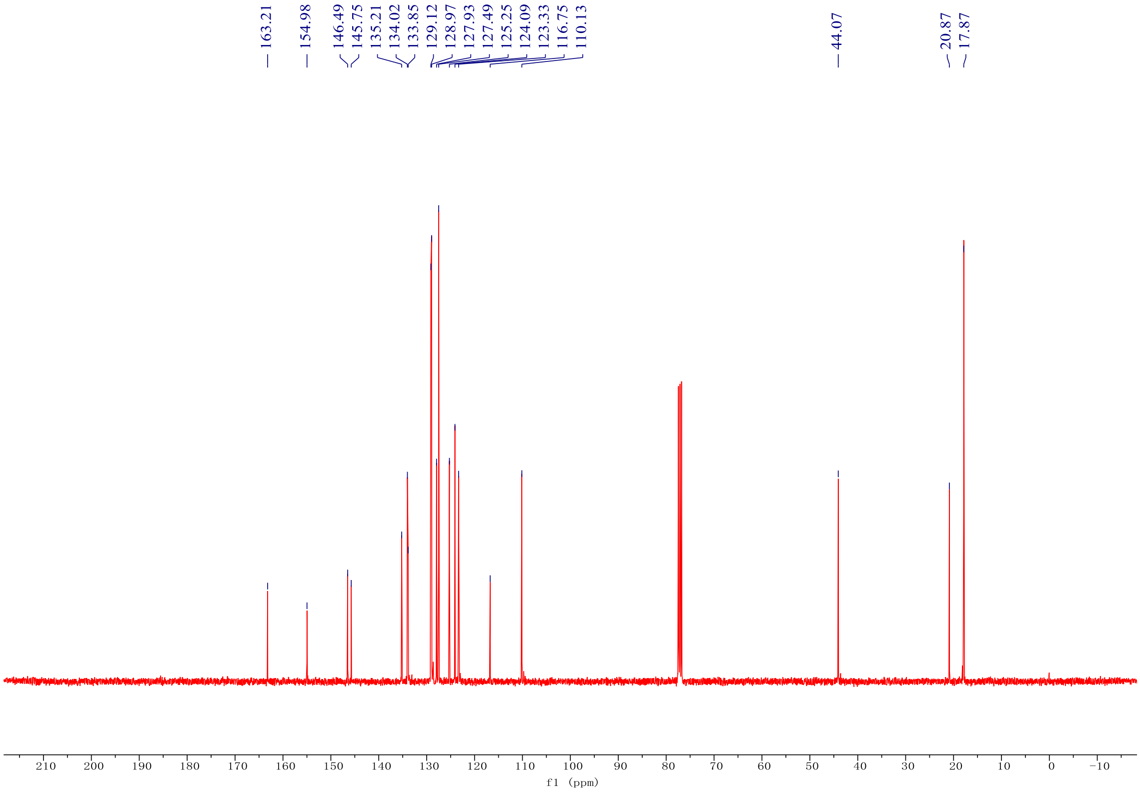
f1 (ppm)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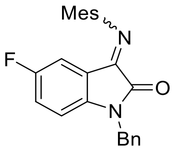
17.87
f1 (ppm)



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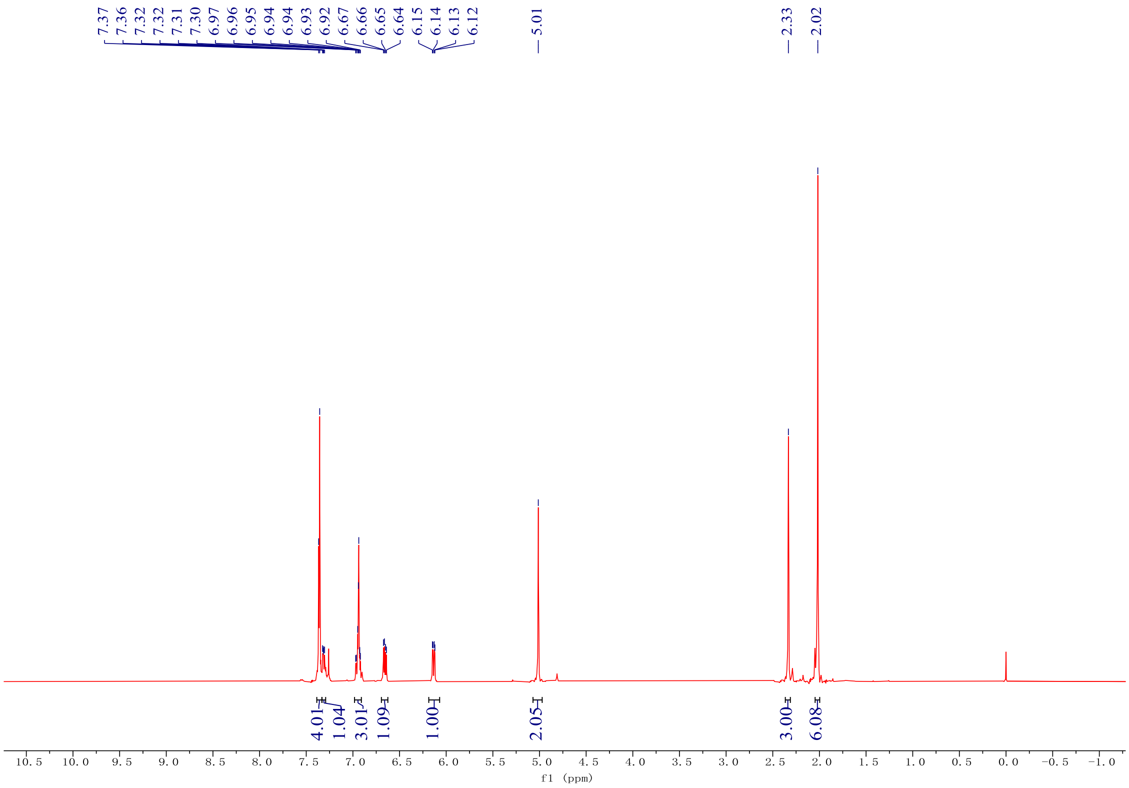

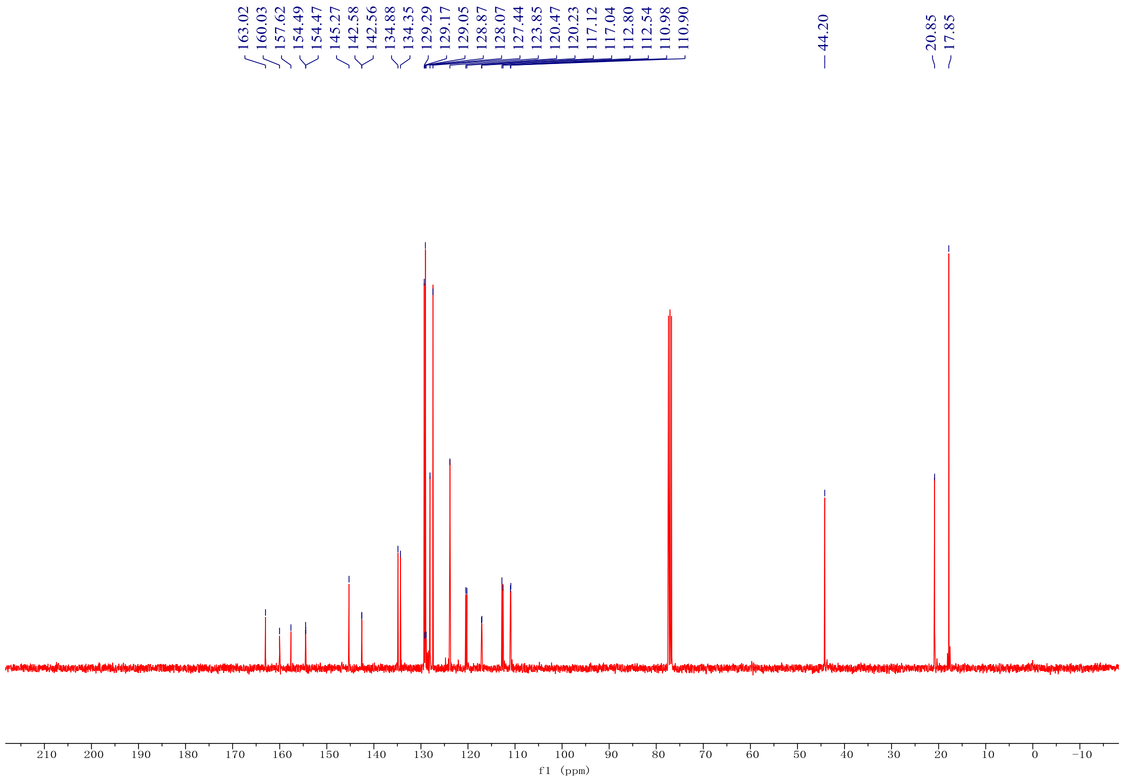

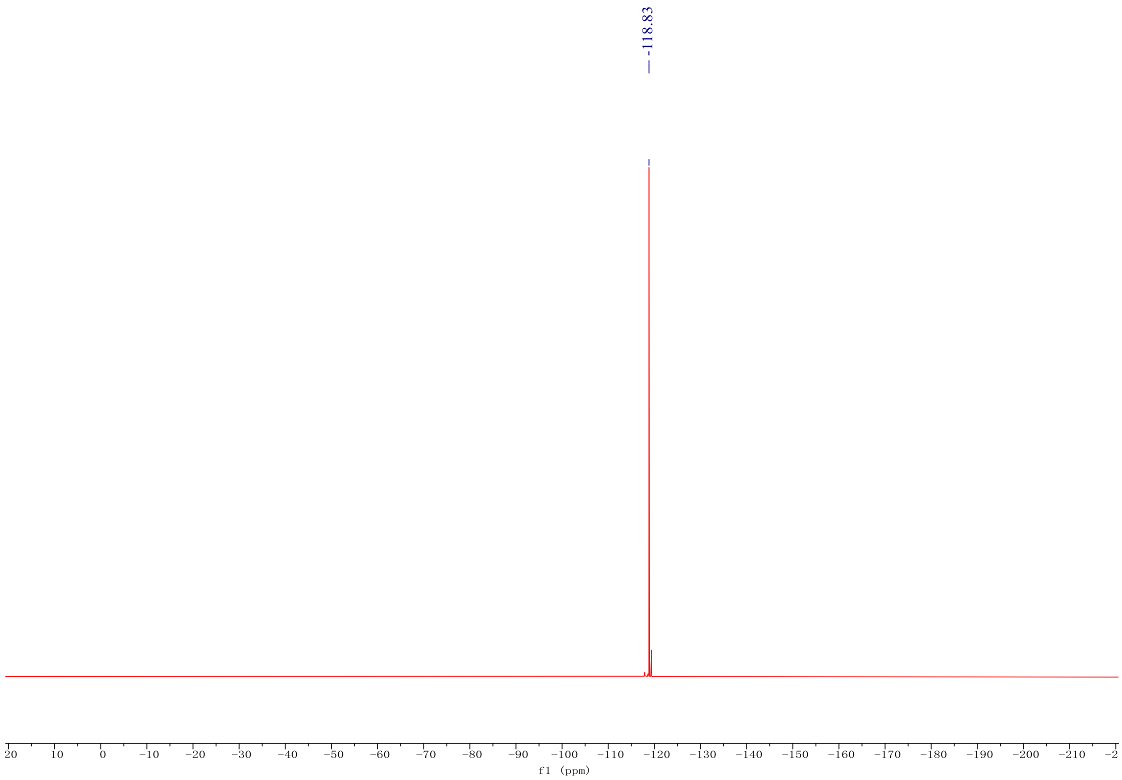
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-140
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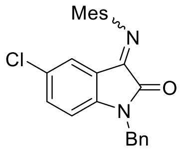
-160
-170
-180
-190
-200
-210
-2
f1 (ppm)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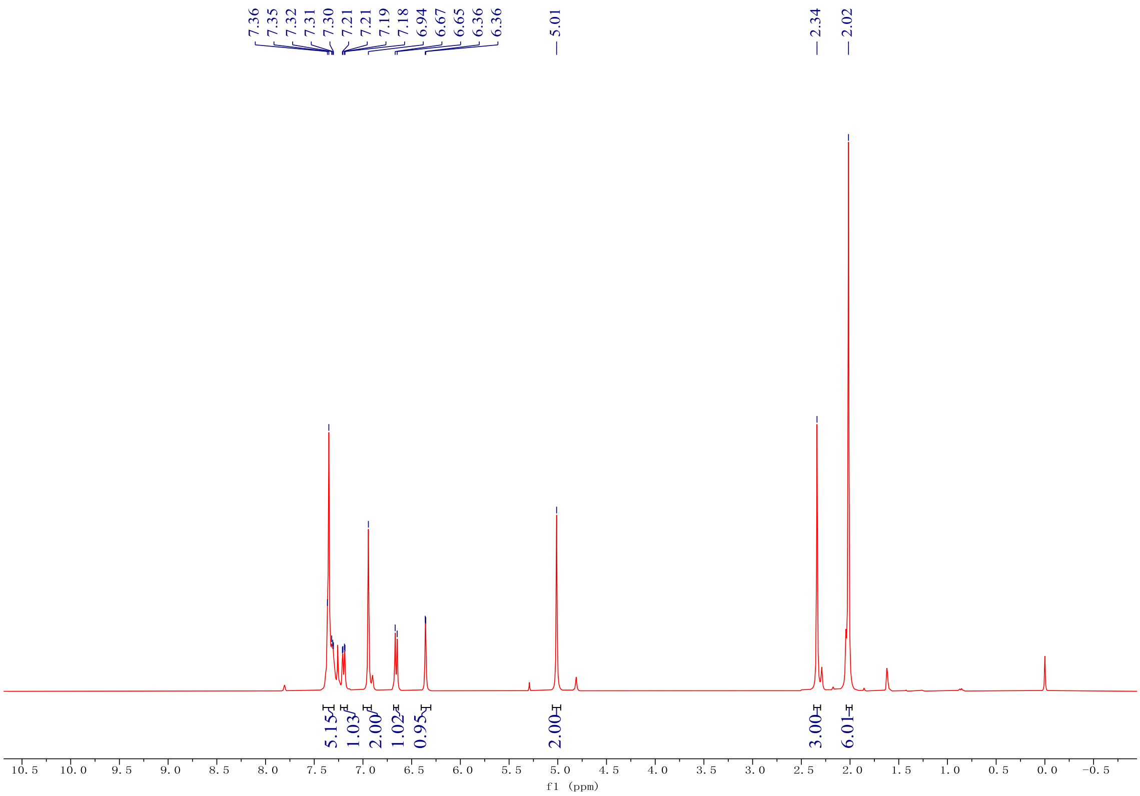
Cl
O
N
Bn

1aa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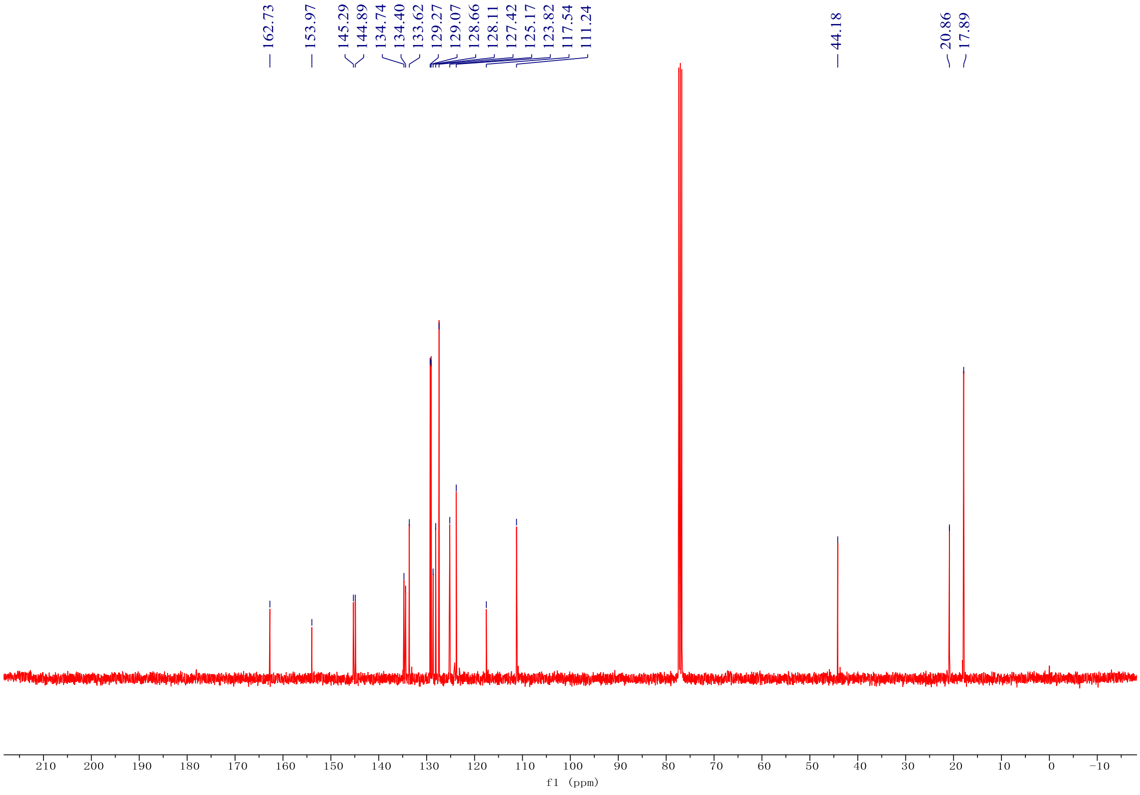
f1 (ppm)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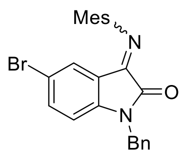
44.18
20.86
17.89
f1 (ppm)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Br
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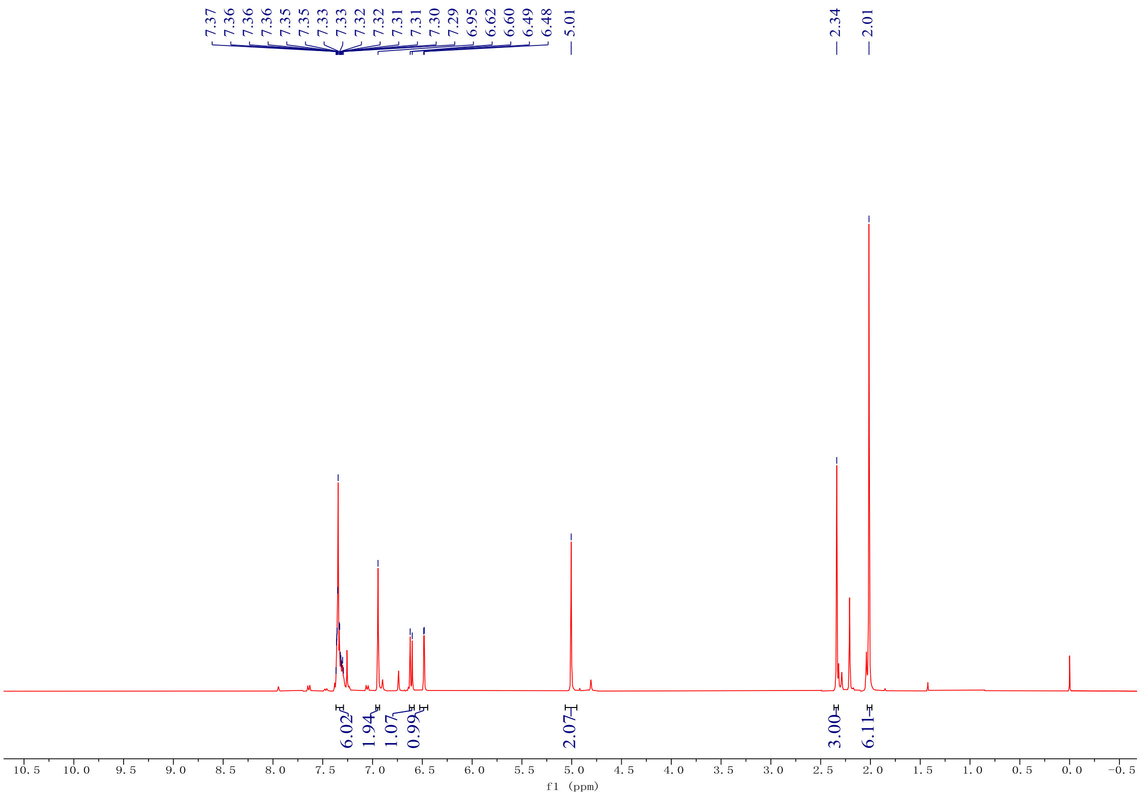
N
Bn

1ab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6.62
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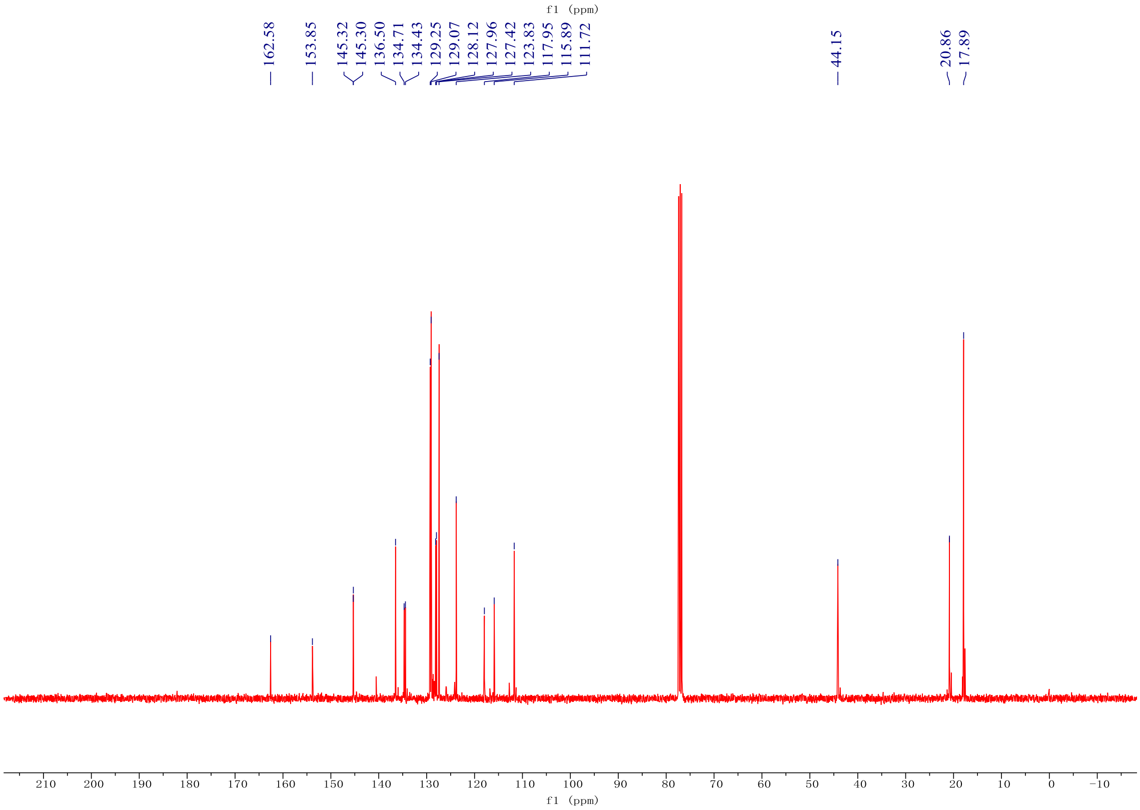
6.49
6.48
5.01
2.34
2.01
6.02
1.94
1.07
0.99
2.07
3.00
6.11
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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128.12
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127.42
123.83
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115.89
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44.15
20.86
17.89
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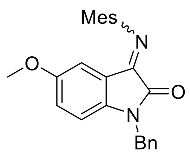
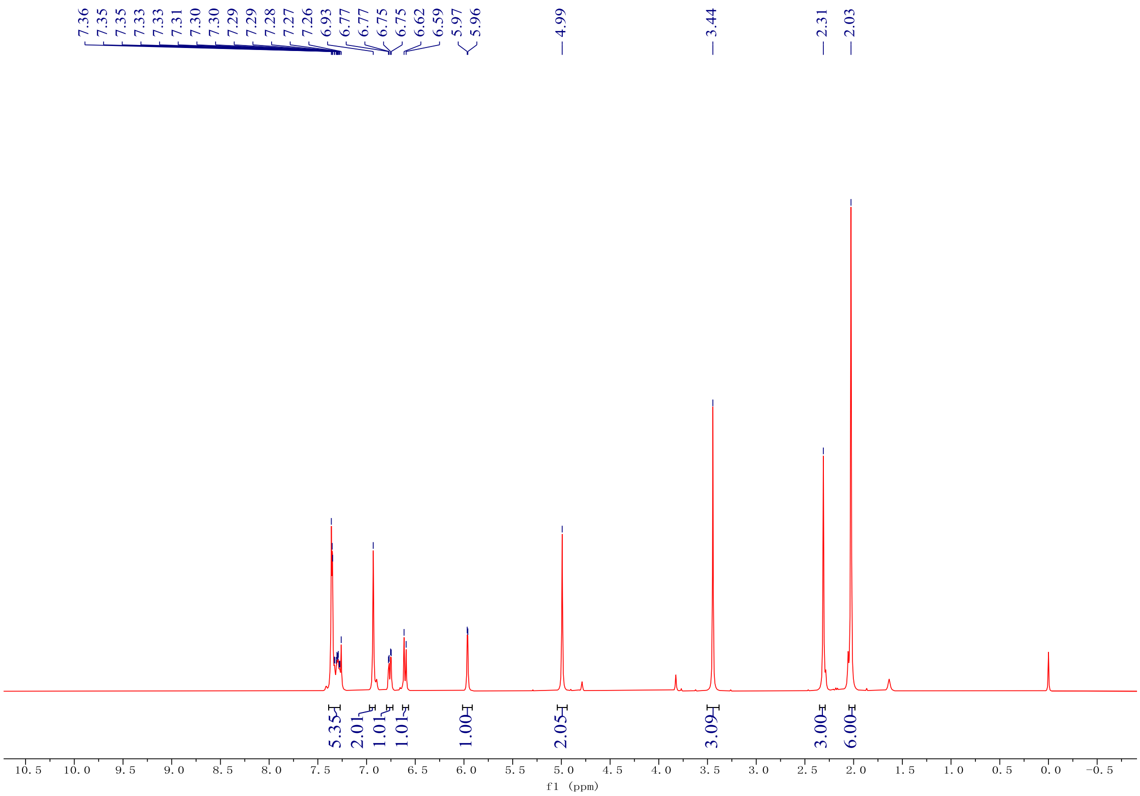
f1 (ppm)


Mes
N
O
O
N
Bn

1ac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6.75
6.75
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5.97
5.96
4.99
3.44
2.31
2.03
5.35
2.01
1.01
1.01
1.00
2.05
3.09
3.00
6.00
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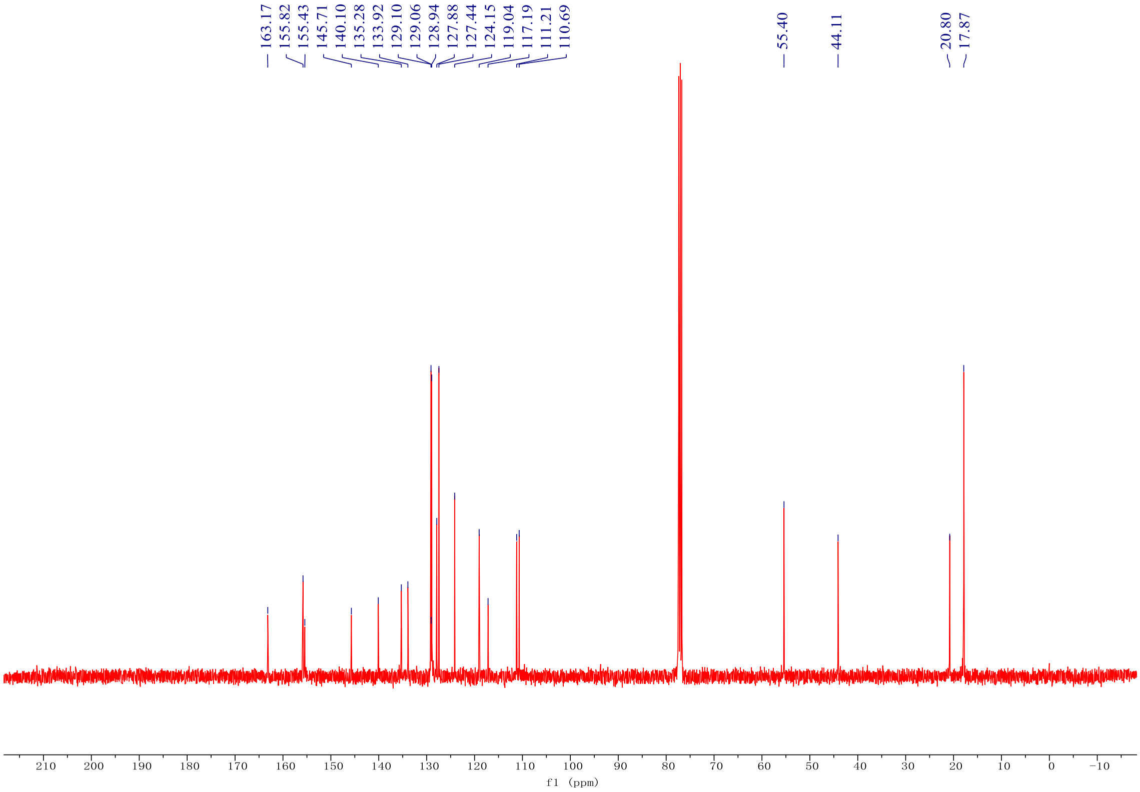
f1 (ppm)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20.80
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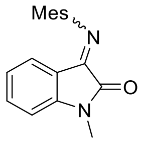

Mes
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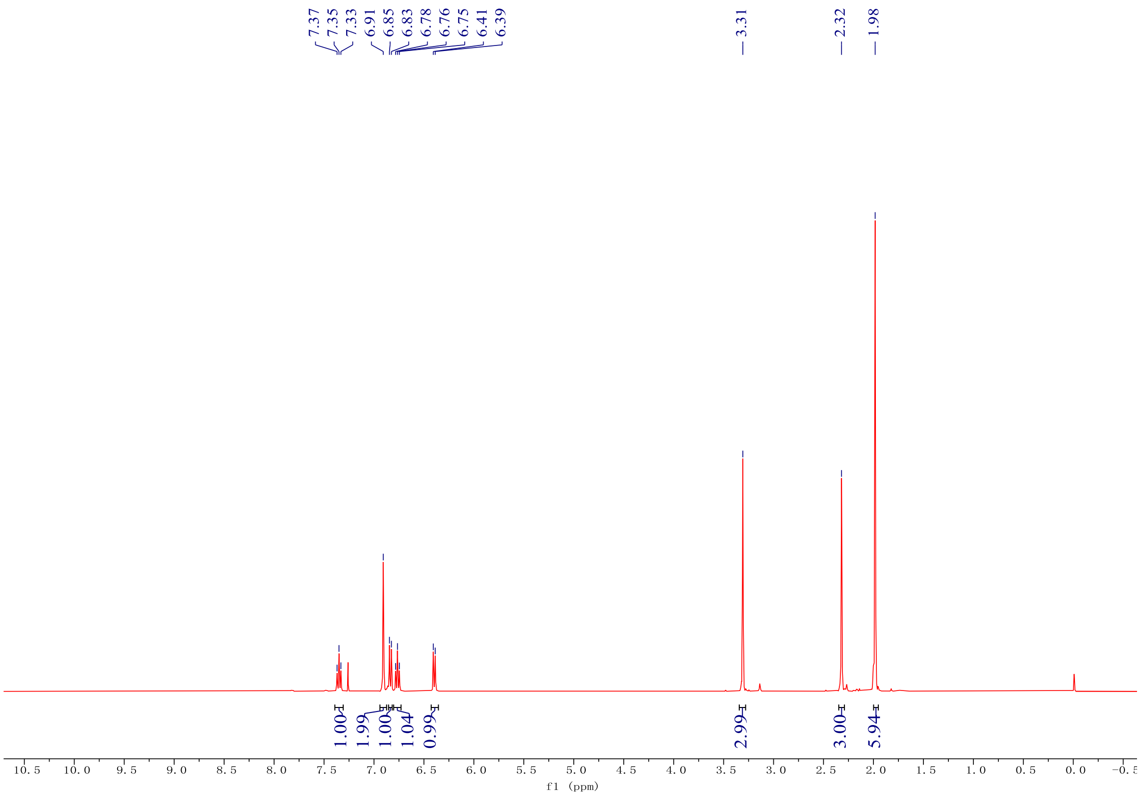
O
N

1ad



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2.32
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1.99
1.00
1.04
0.99
2.99
3.00
5.94
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
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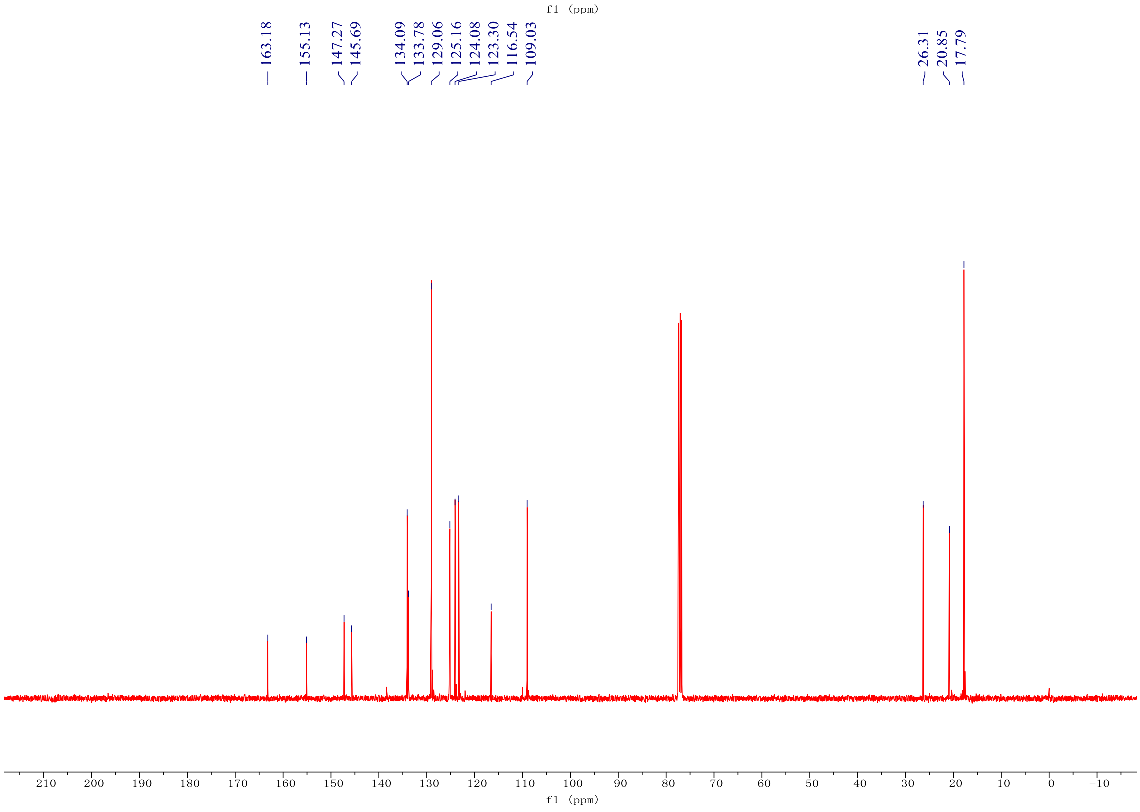

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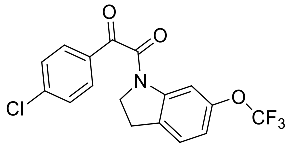

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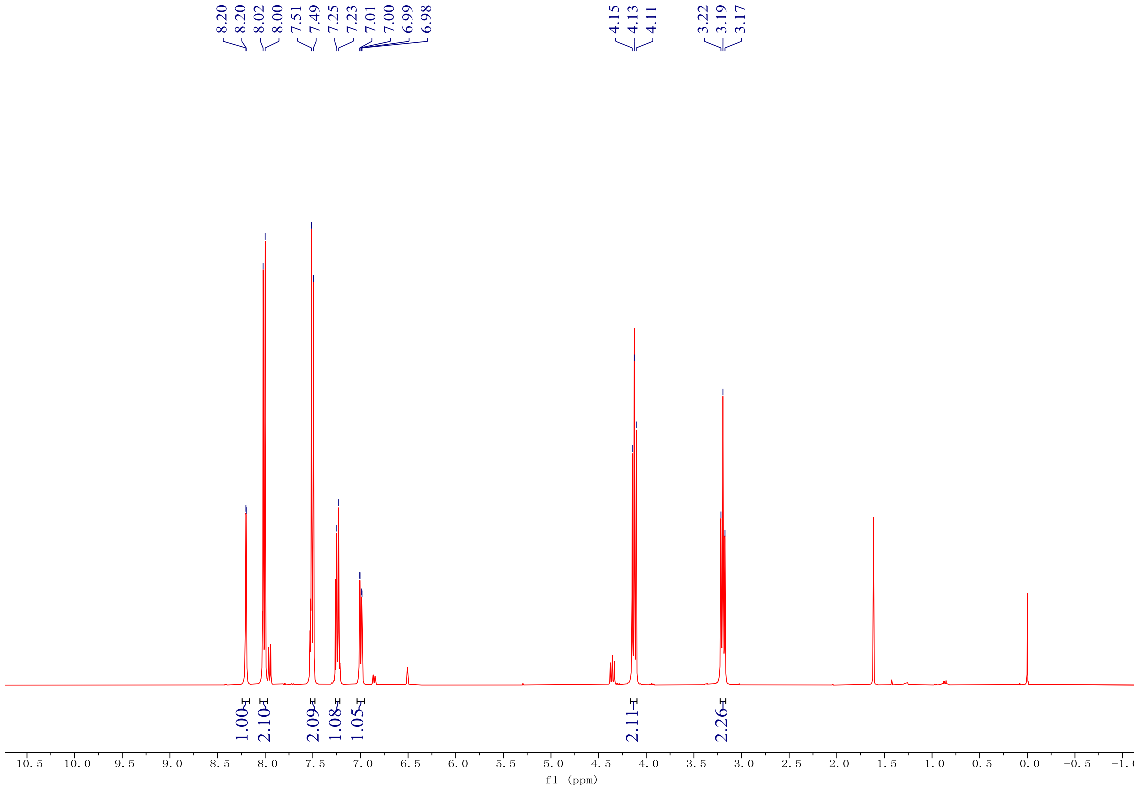
N
Cl
O
CF3

S2



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7.01
7.00
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4.13
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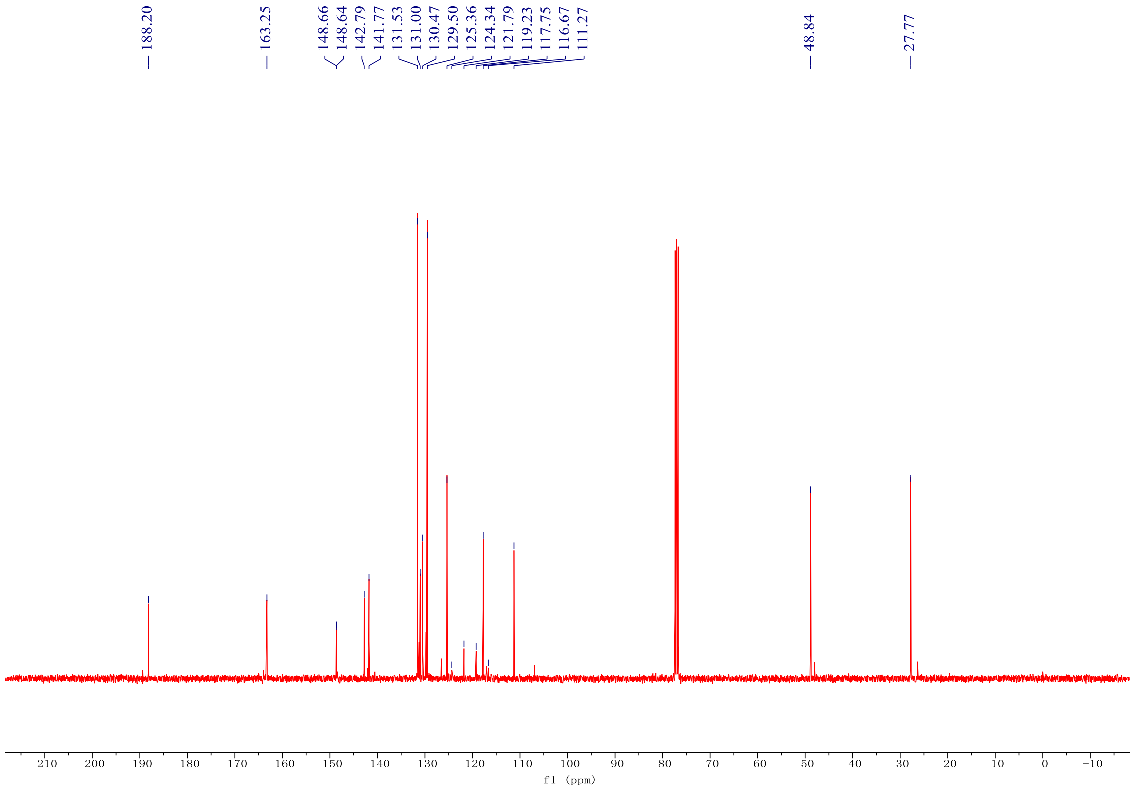

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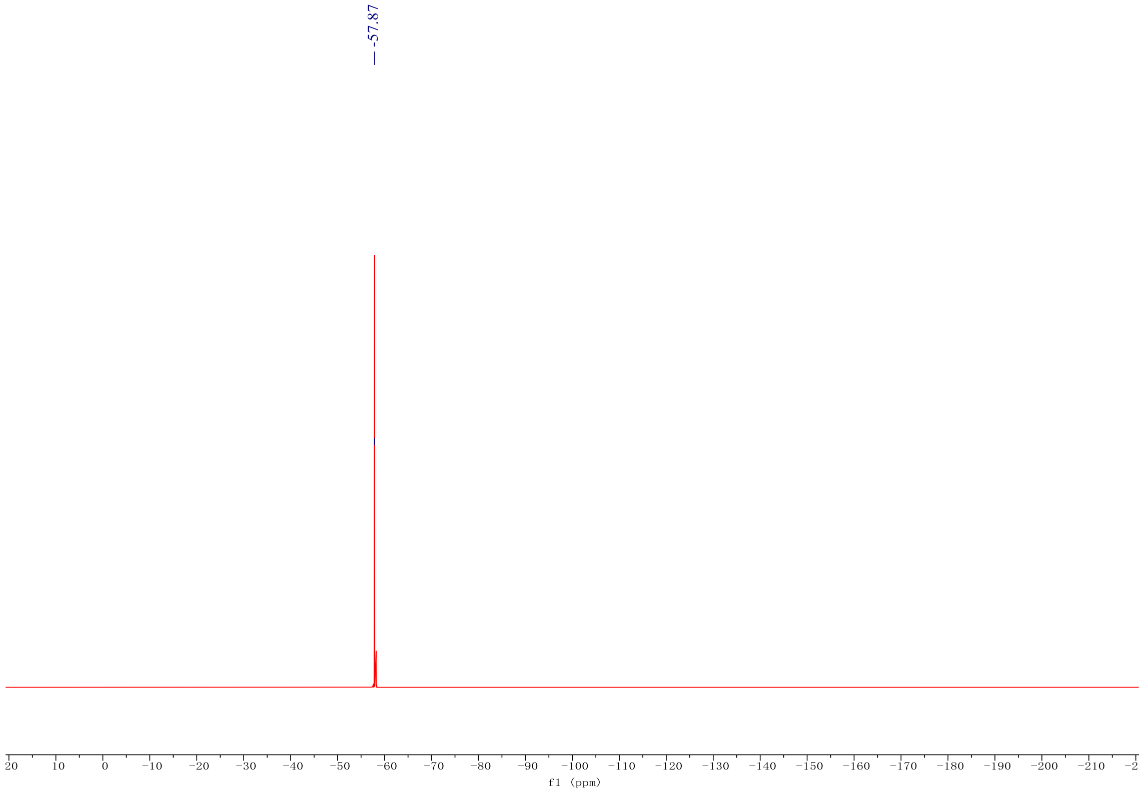
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-150
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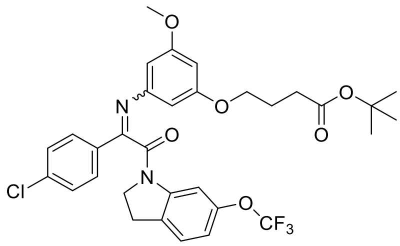
f1 (ppm)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O
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O
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Cl
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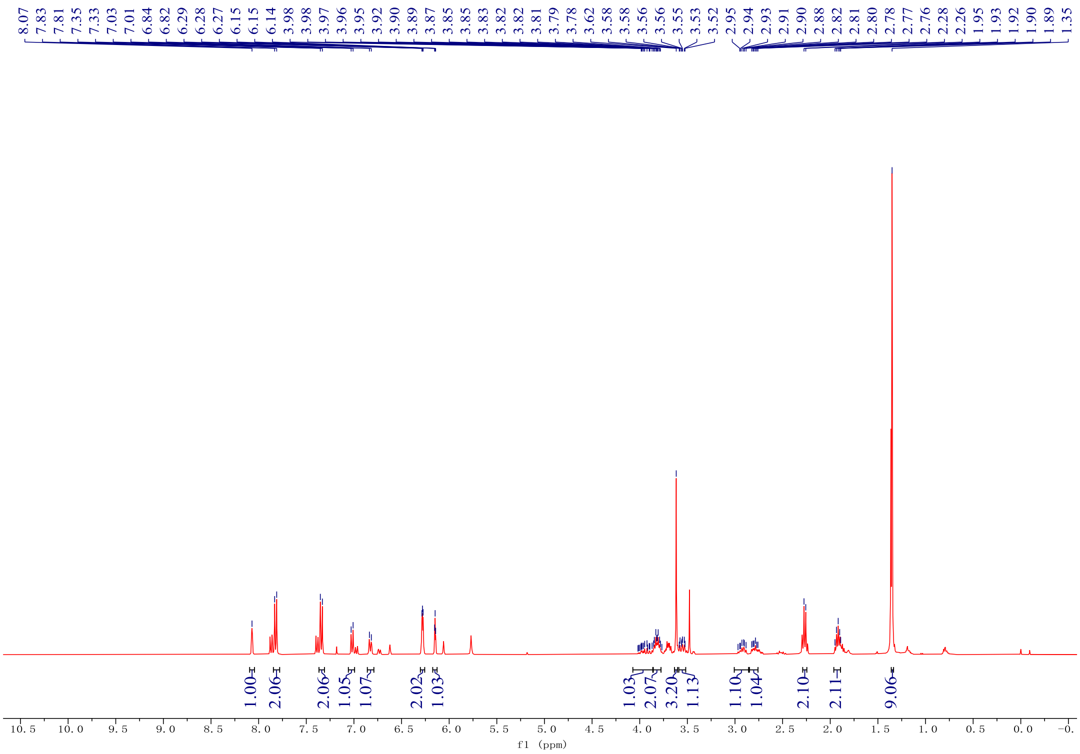
O
CF3

4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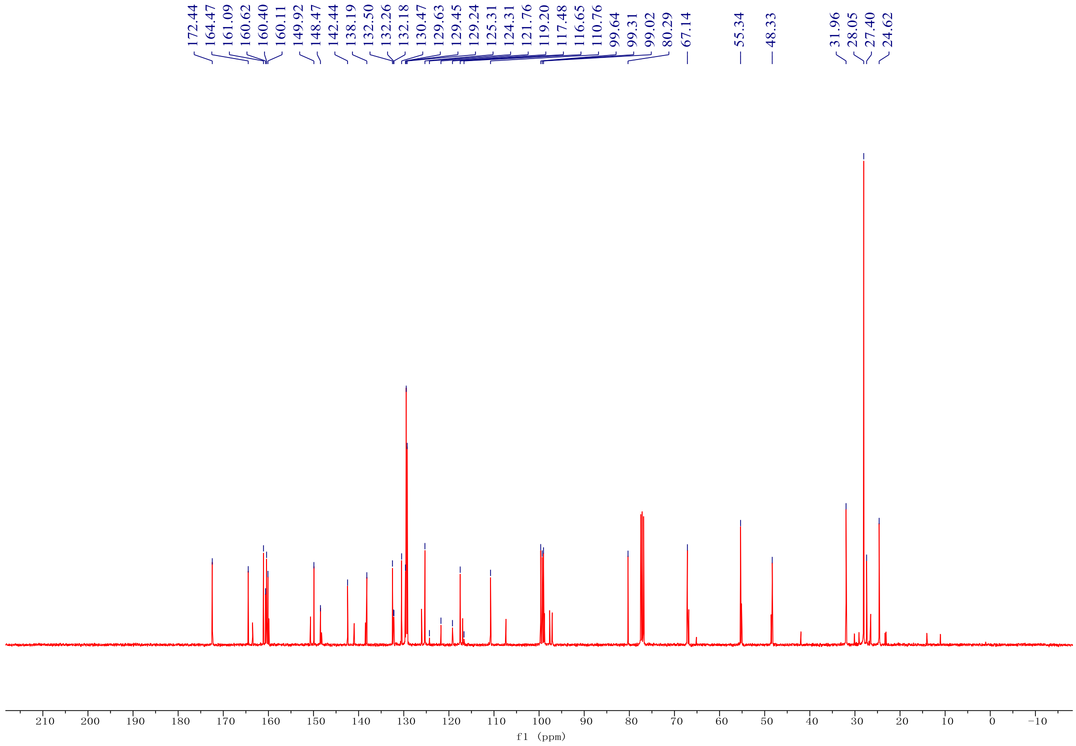
f1 (ppm)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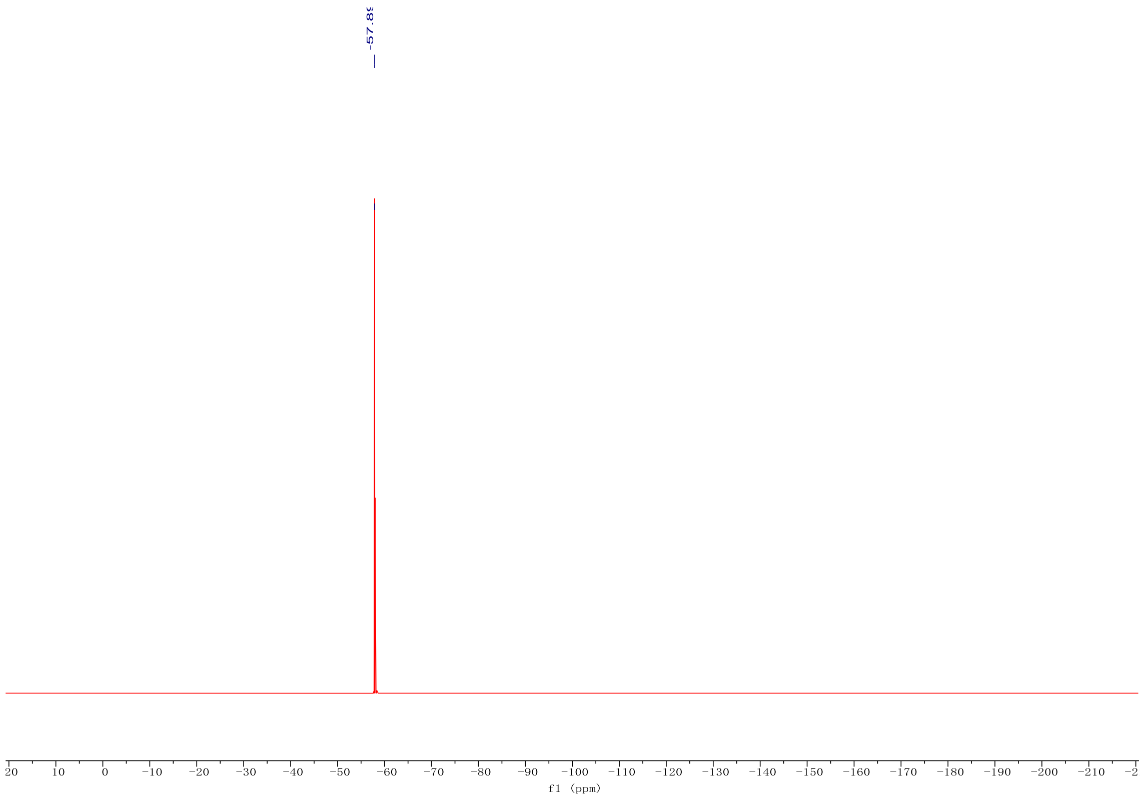
f1 (ppm)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-180
-190
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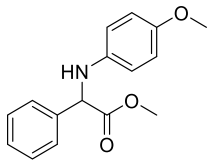
-210
f1 (ppm)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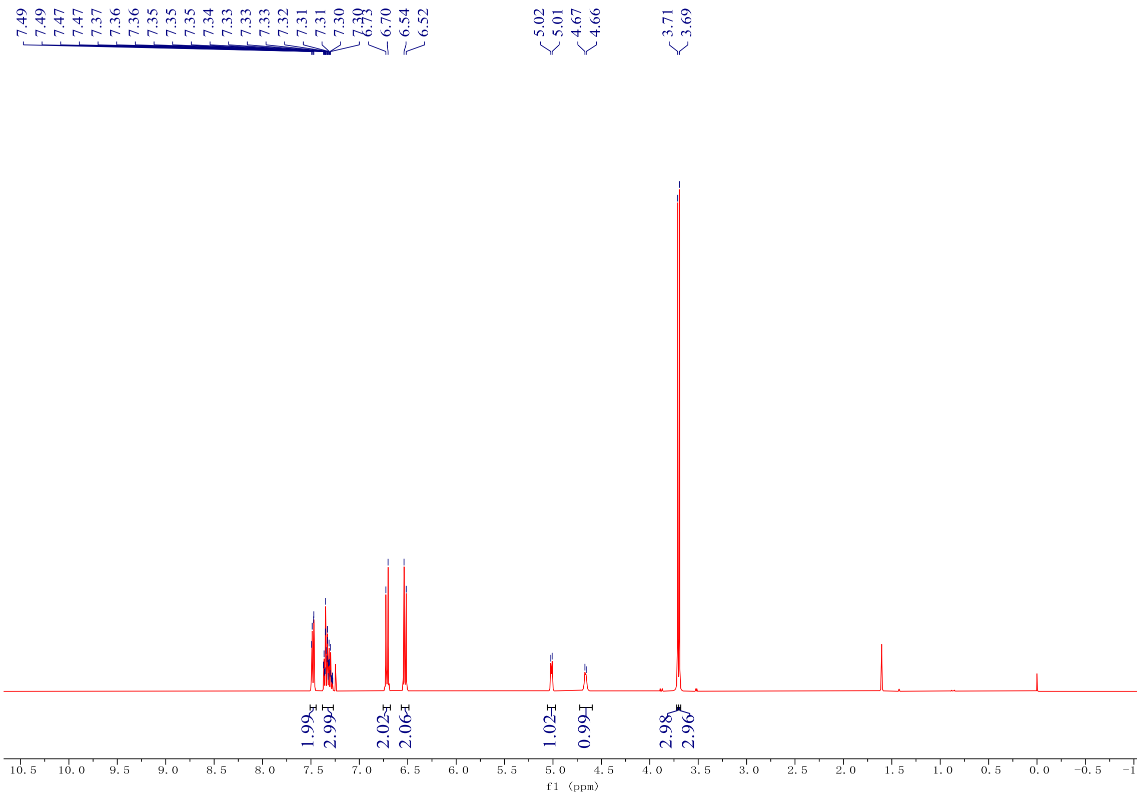
3a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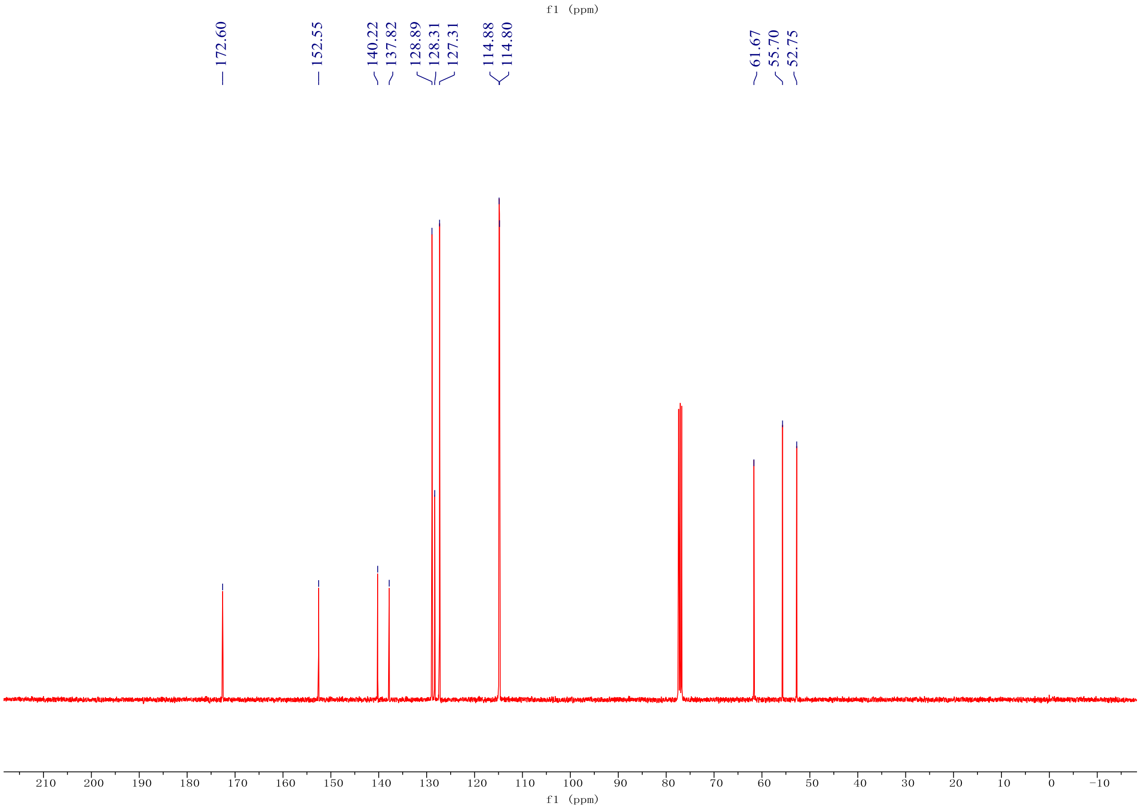
3.71 3.69
1.99 2.99 2.02 2.06 1.02 0.99 2.98 2.96
f1 (ppm)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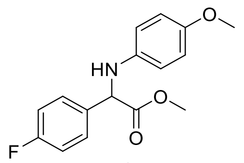
f1 (ppm)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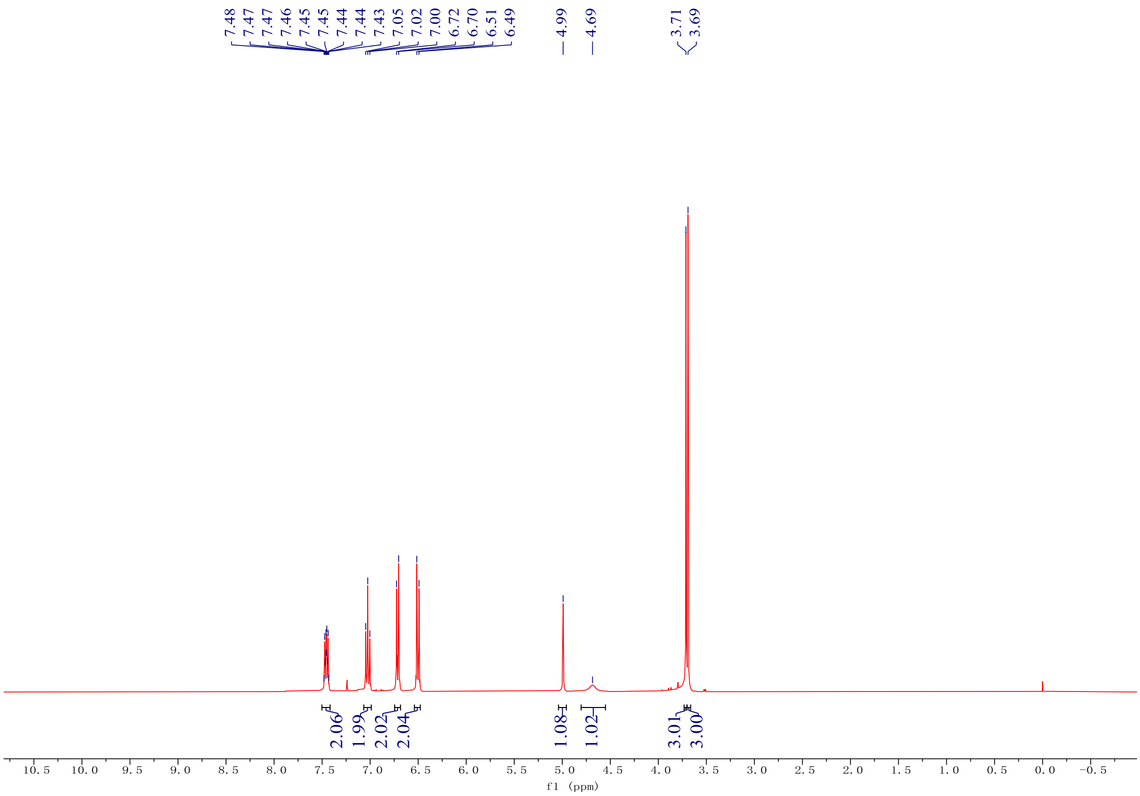
O
F

3b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4.69
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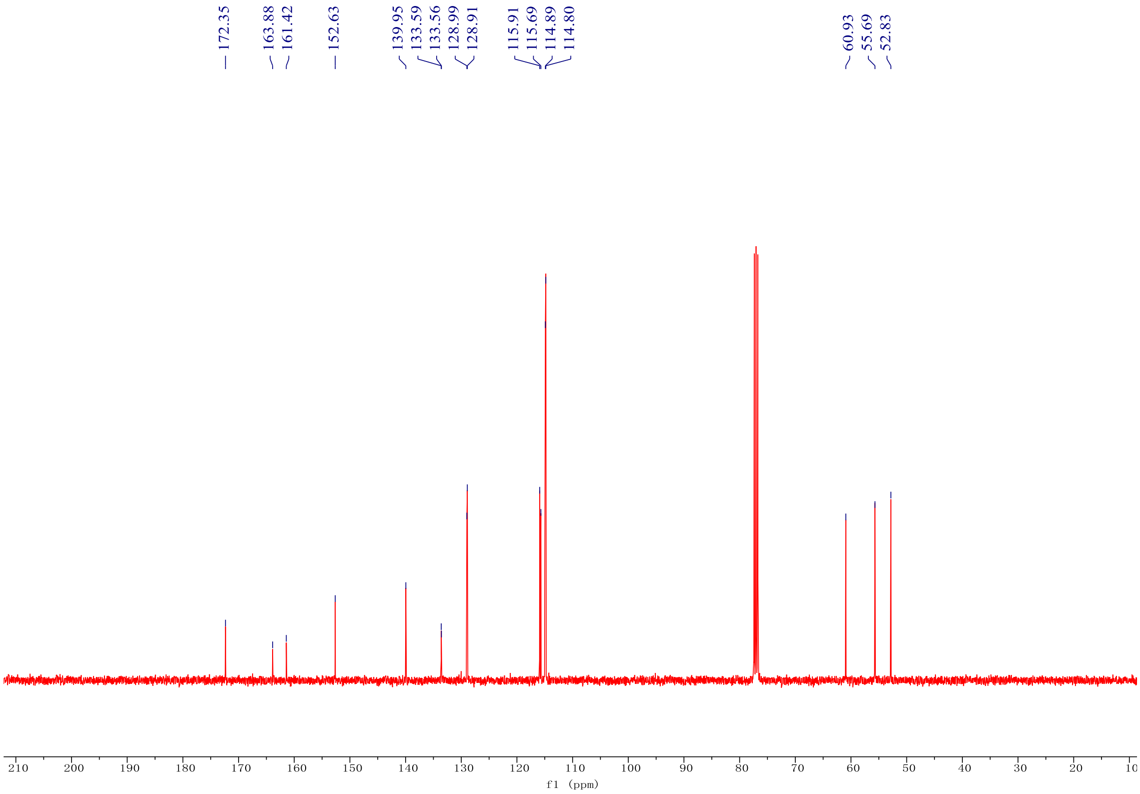
3.69
2.06
1.99
2.02
2.04
1.08
1.02
3.01
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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60.93
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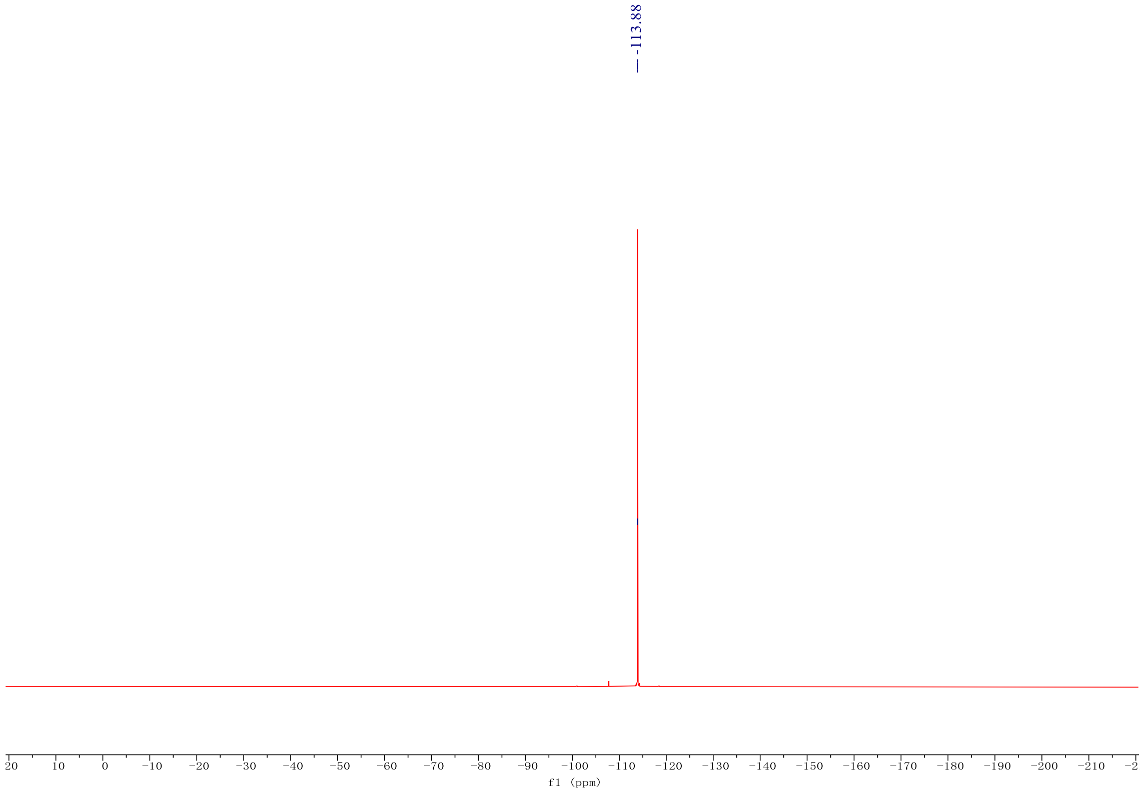
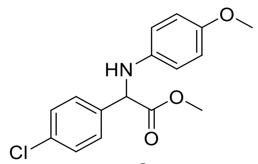
52.83
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-113.88
20 10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190 −200 −210 −2
f1 (ppm)



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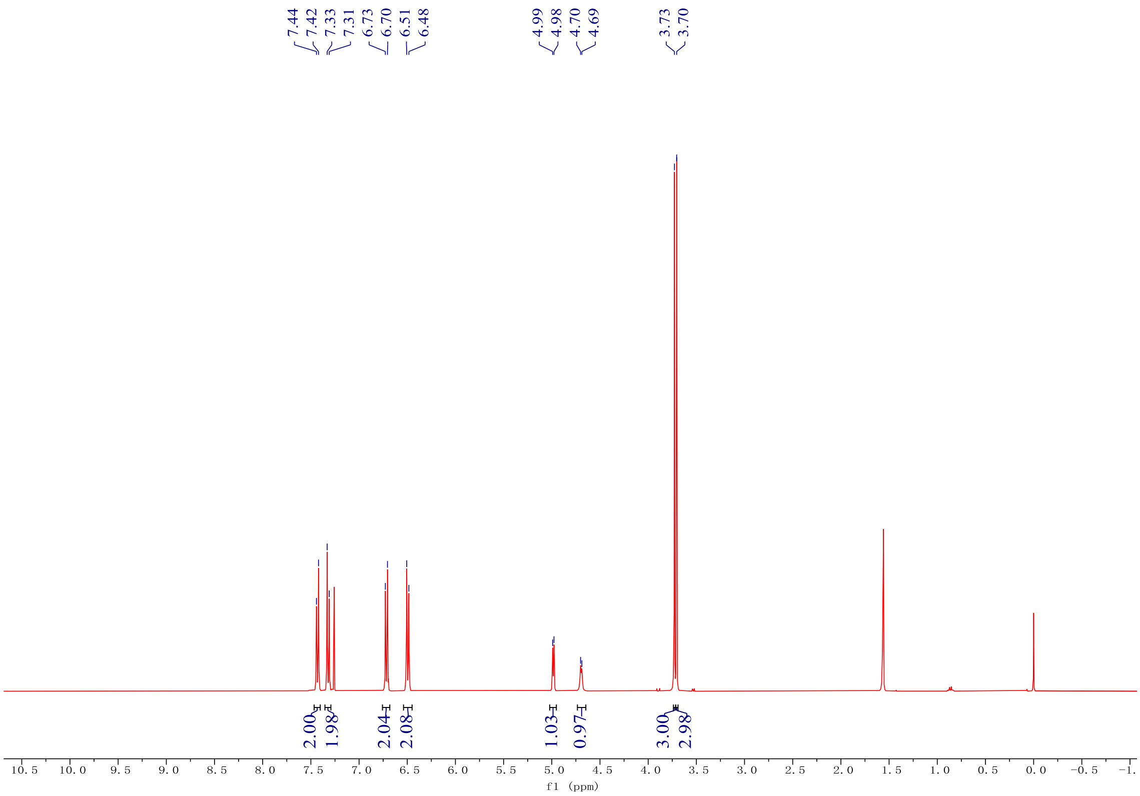

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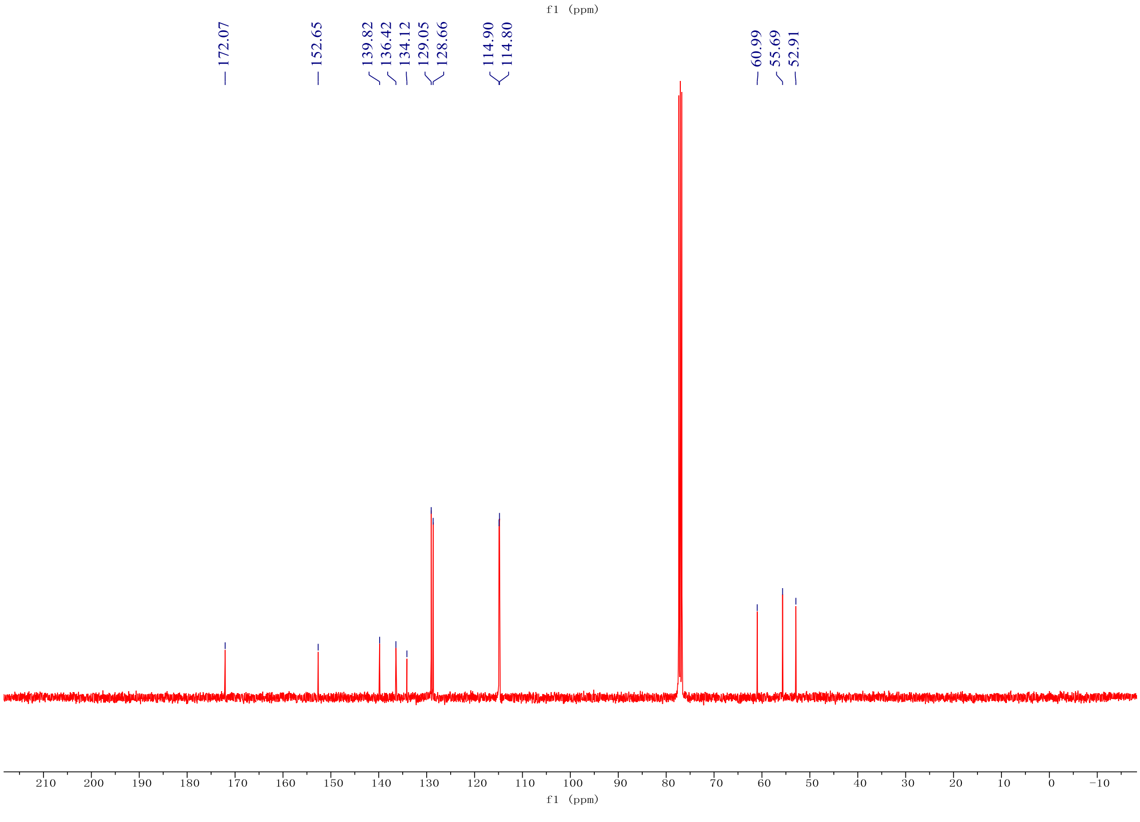
2.00
1.98
2.04
2.08
1.03
0.97
3.00
2.98
f1 (ppm)



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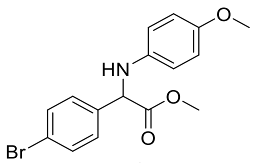
52.91
f1 (ppm)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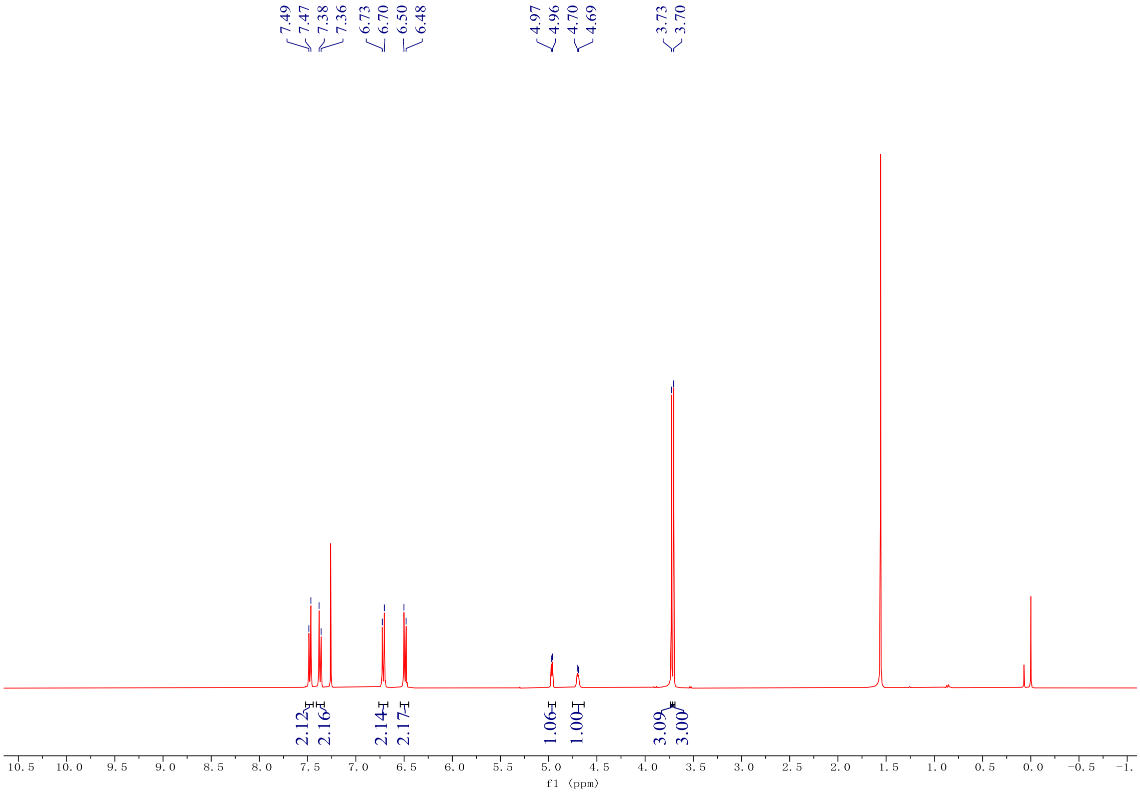
O
O
Br

3d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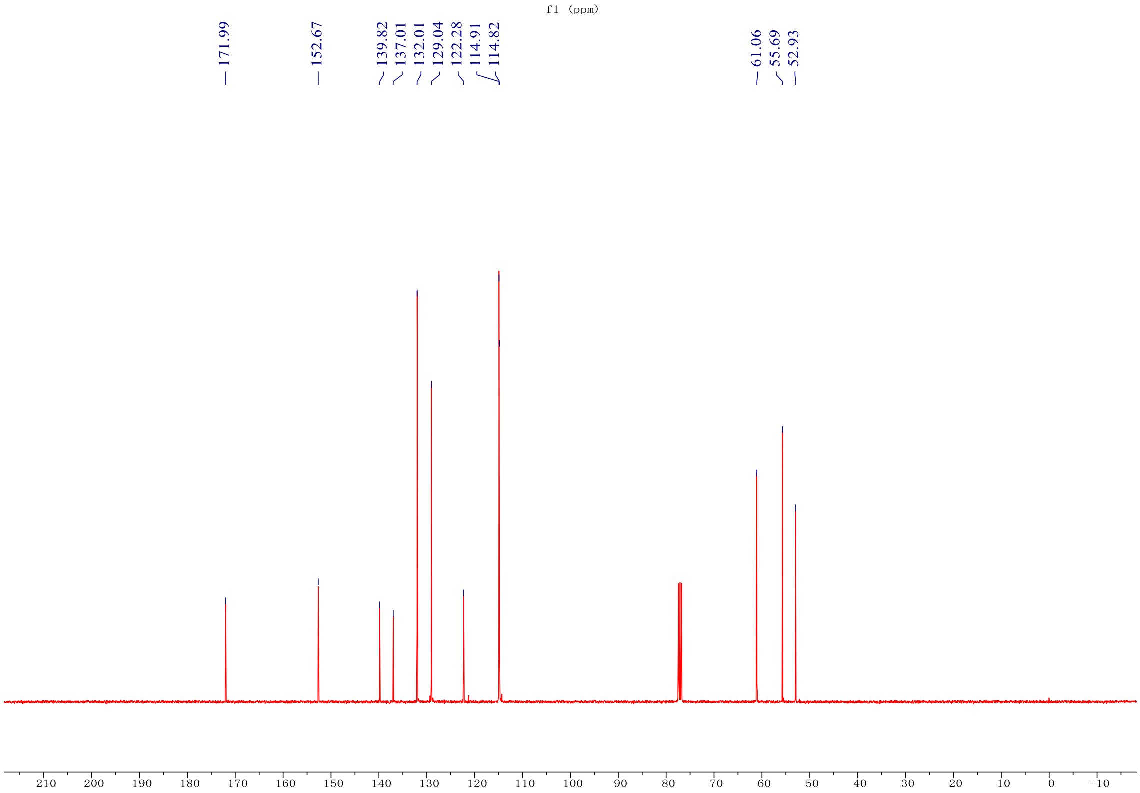
4.96
4.70
4.69
3.73
3.70
2.12
2.16
2.14
2.17
1.06
1.00
3.09
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)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129.04
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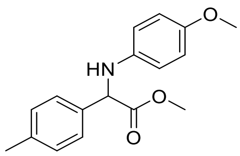
61.06
55.69
52.93
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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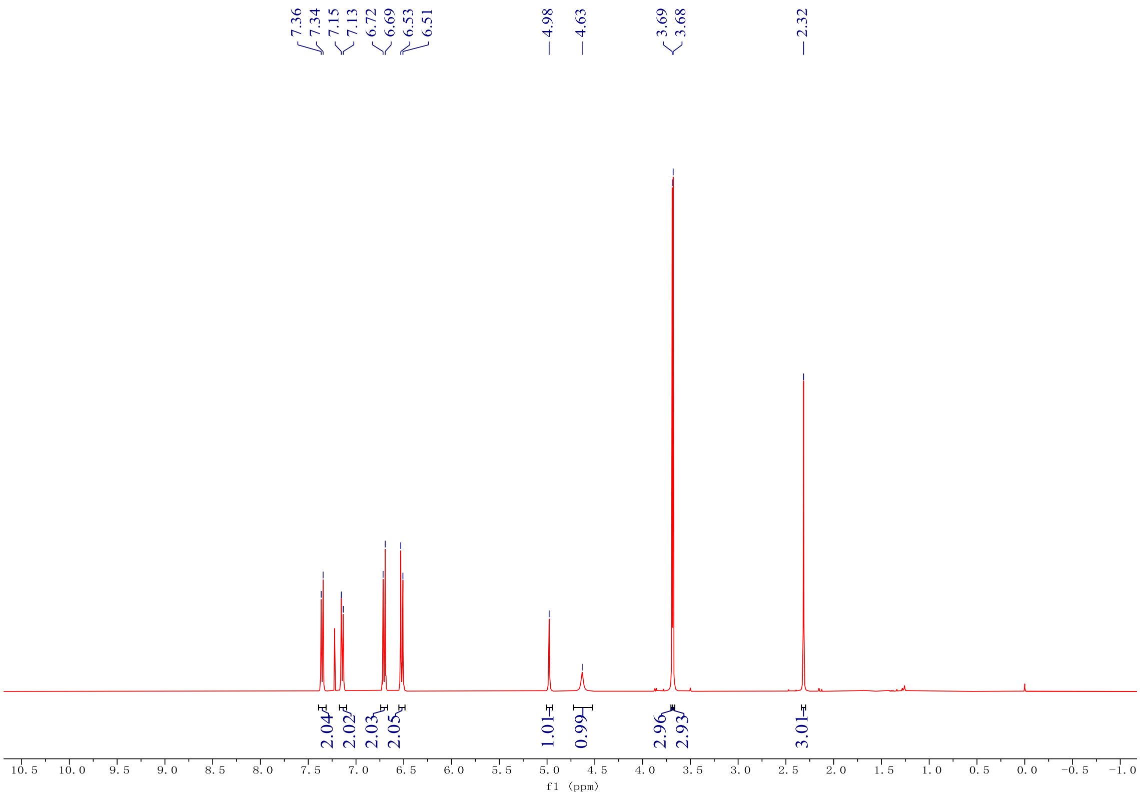
O

3e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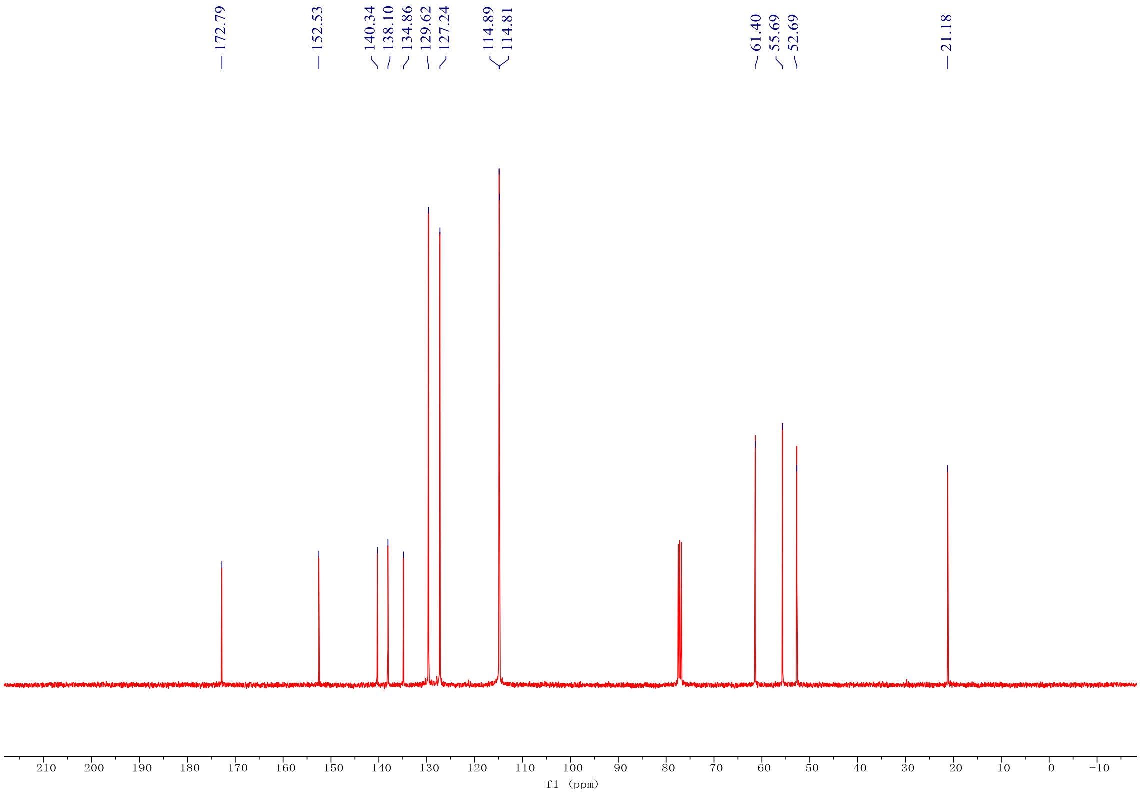
4.63
3.69
3.68
2.32
2.04
2.02
2.03
2.05
1.01
0.99
2.96
2.93
3.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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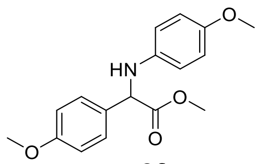
f1 (ppm)



HN
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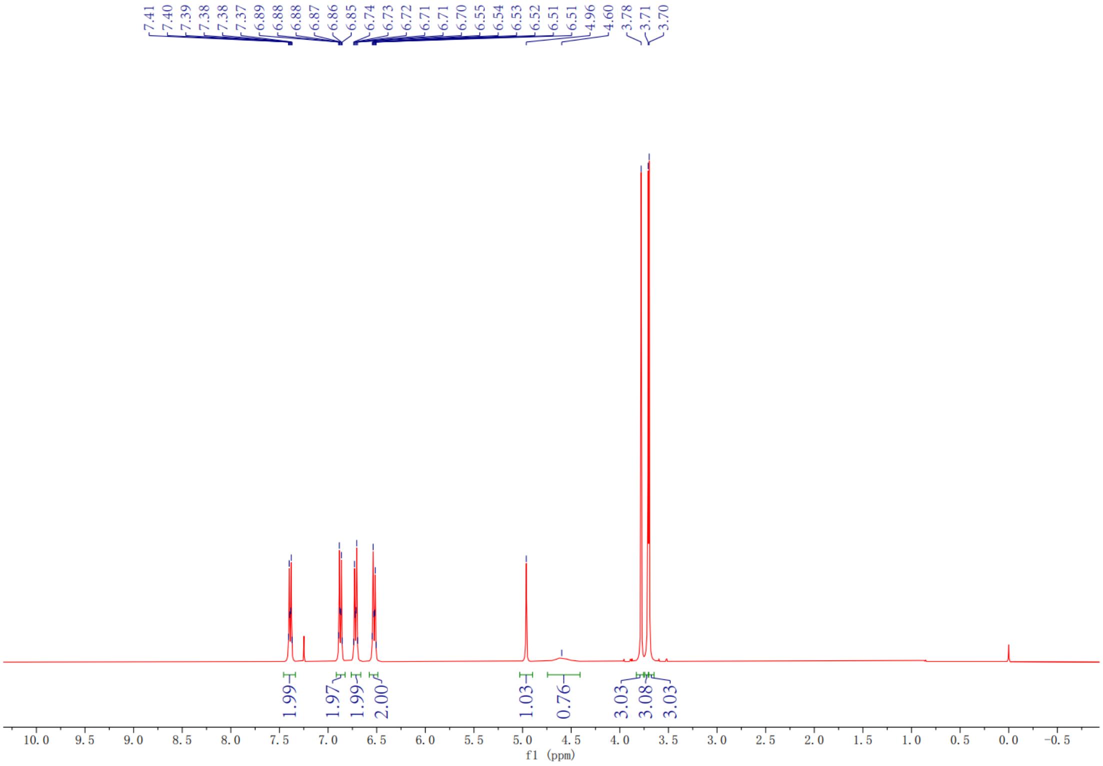
O
O
O

3f



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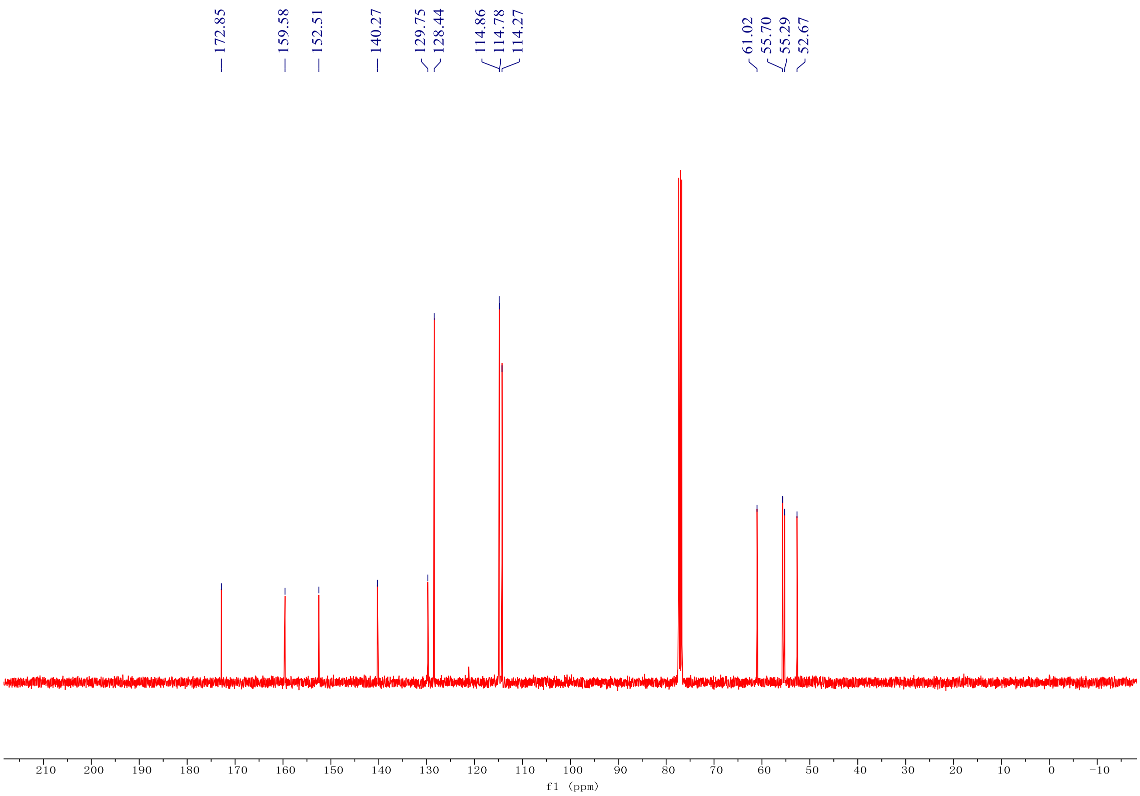
1.99 1.97 1.99 2.00 1.03 0.76 3.03 3.08 3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



172.85 159.58 152.51 140.27 129.75 128.44 114.86 114.78 114.27 61.02 55.70 55.29 52.67
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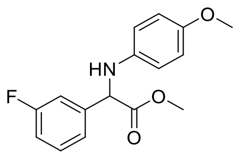
f1 (ppm)



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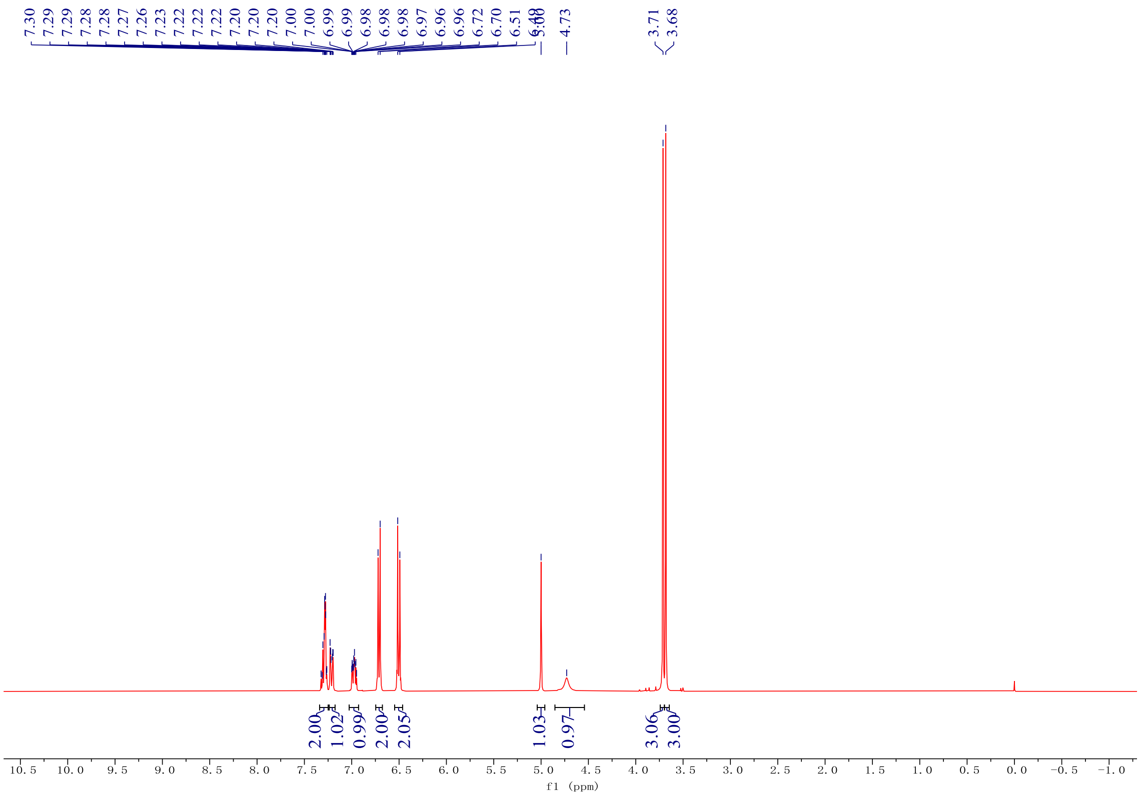

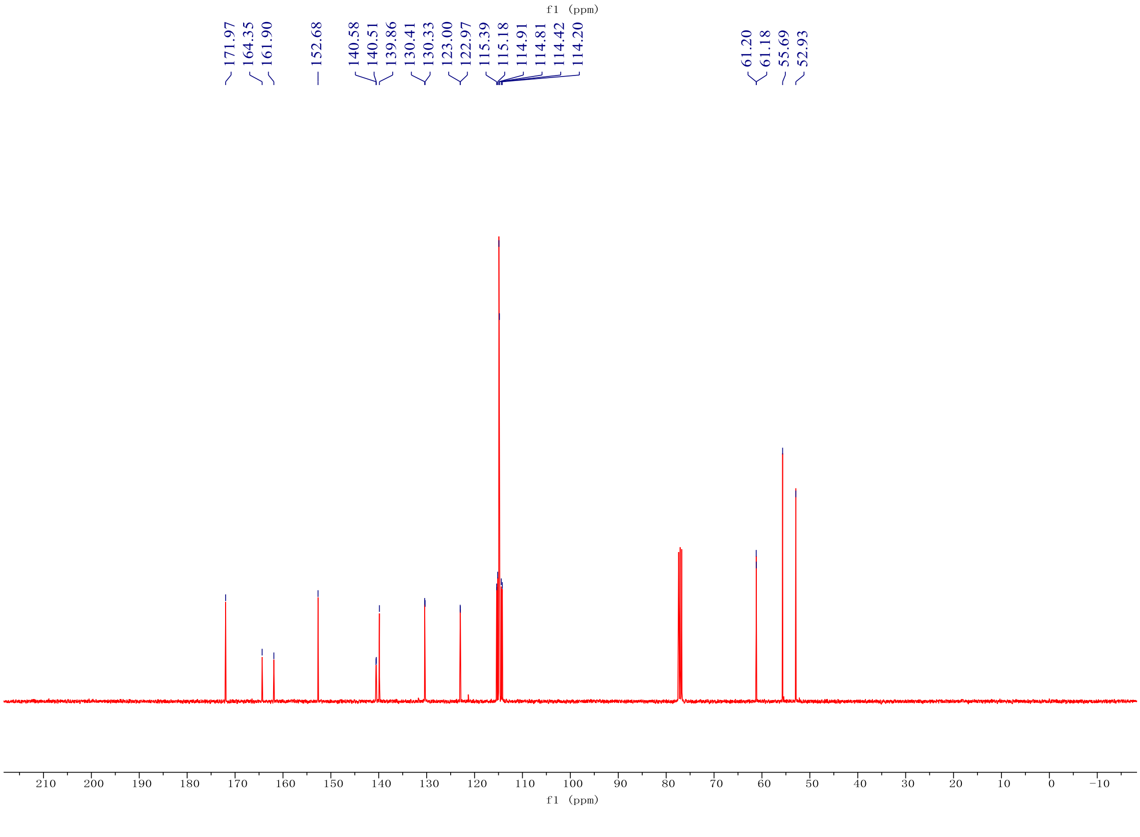

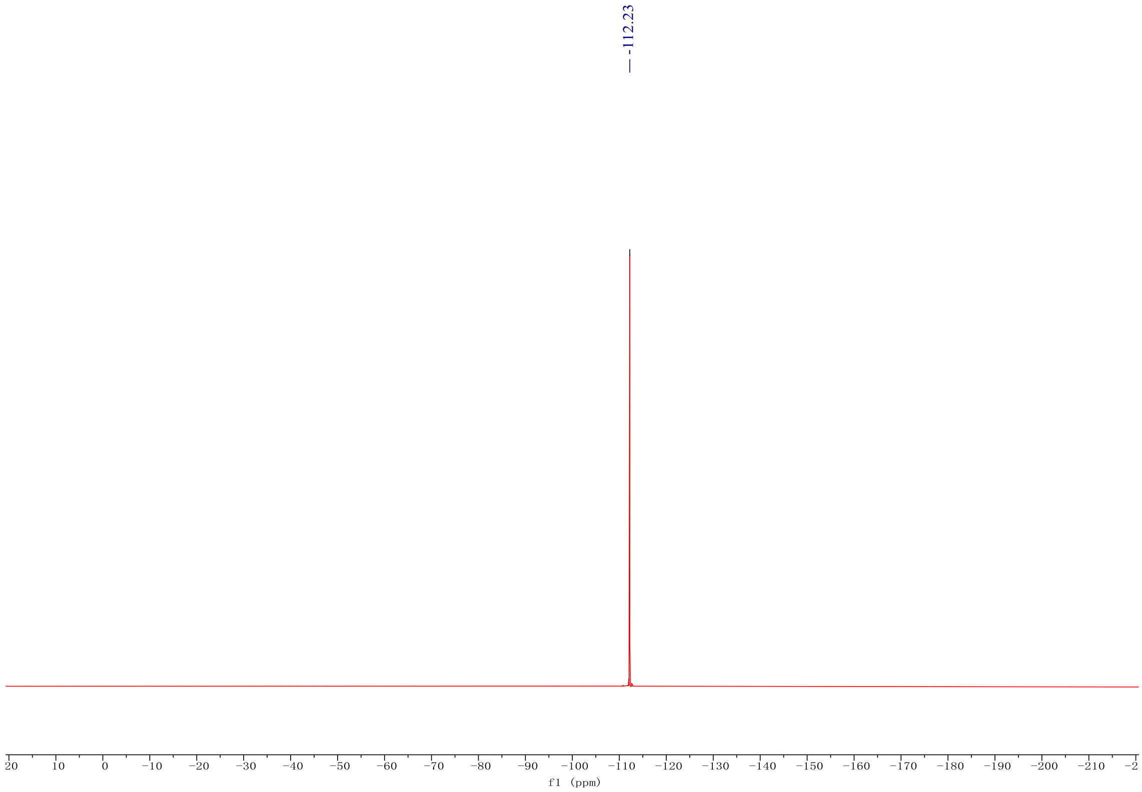

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-100
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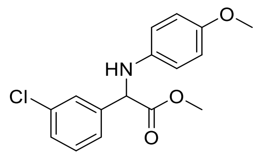
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)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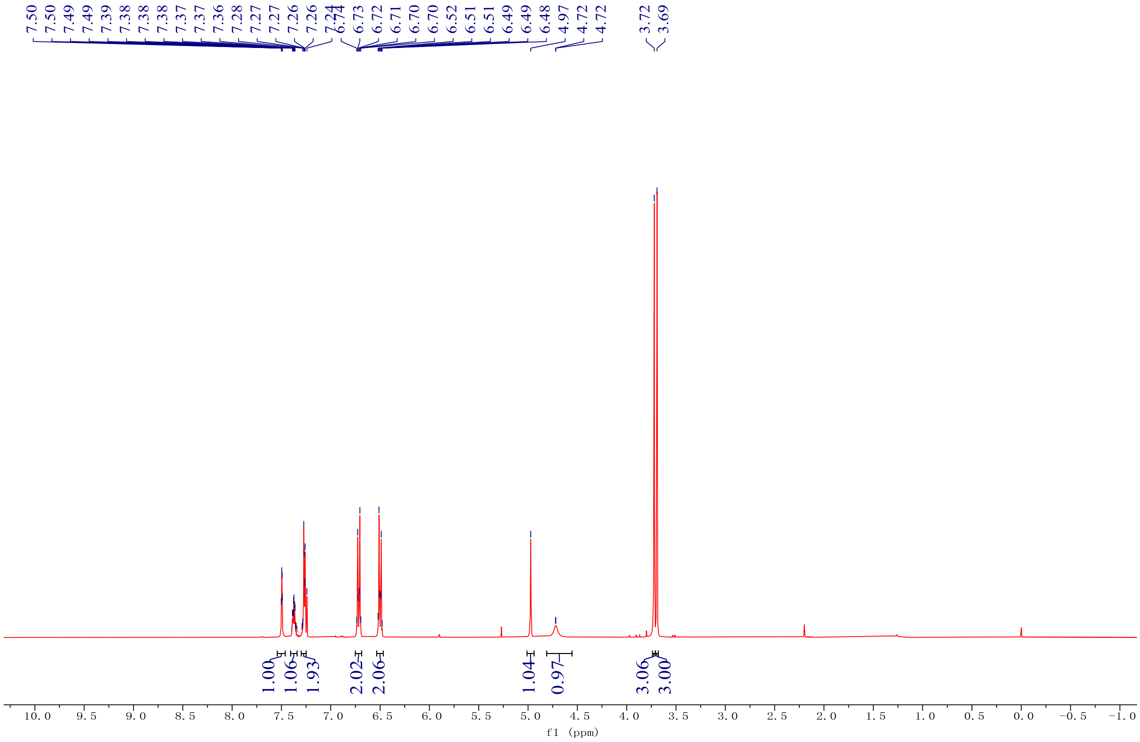
Cl
O
O

3h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6.51
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6.48
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4.72
4.72
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2.06
1.04
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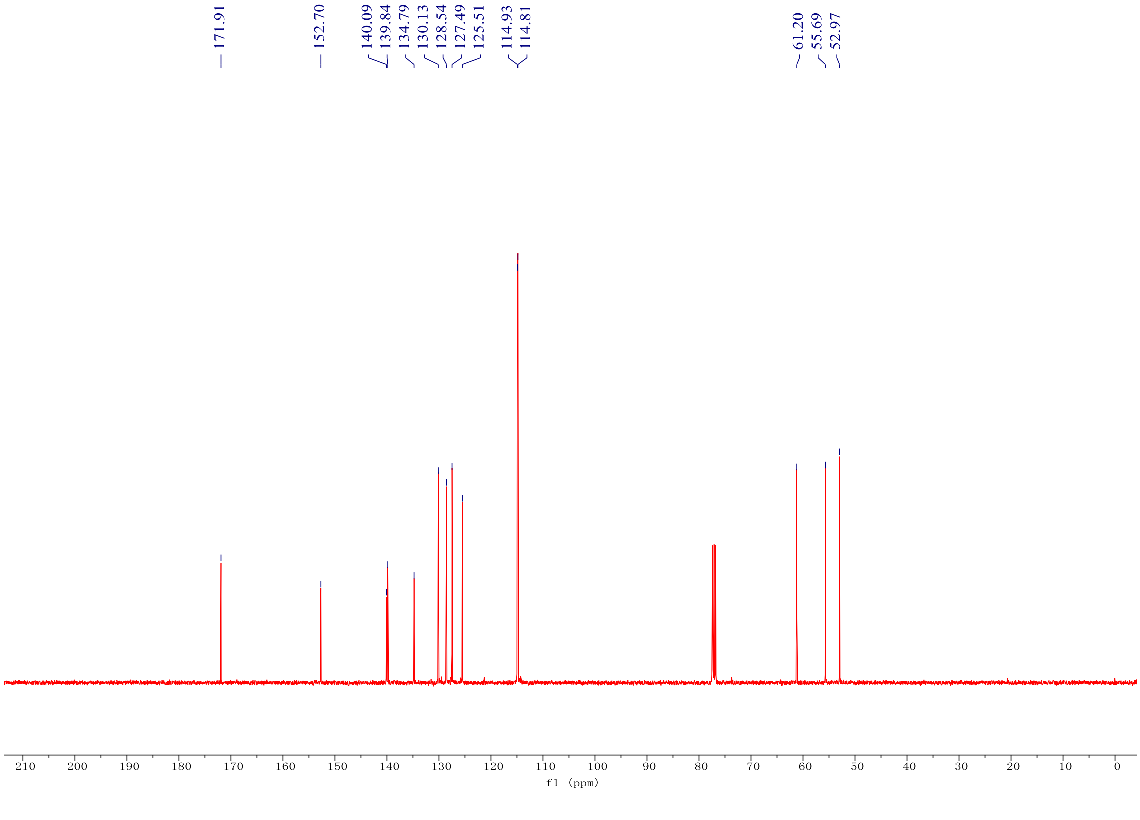
3.06
3.00
f1 (ppm)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61.20
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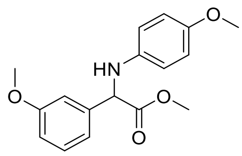
52.97
f1 (ppm)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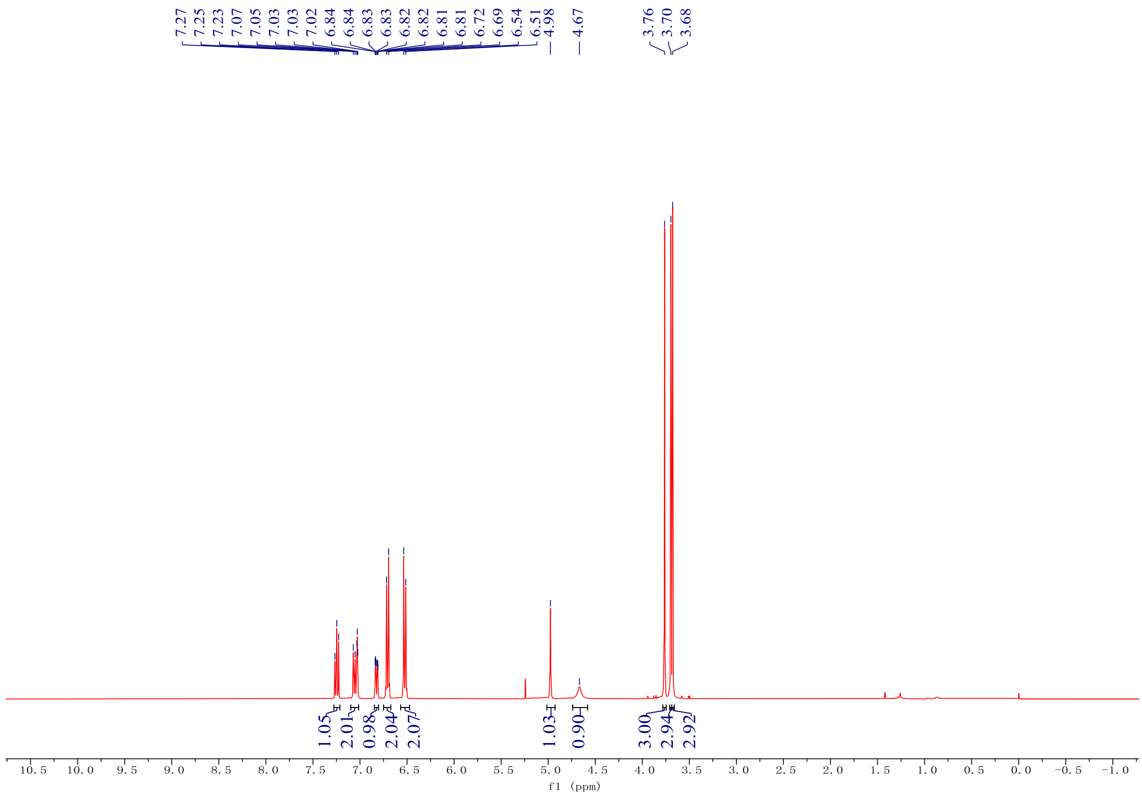
O
O
O

3i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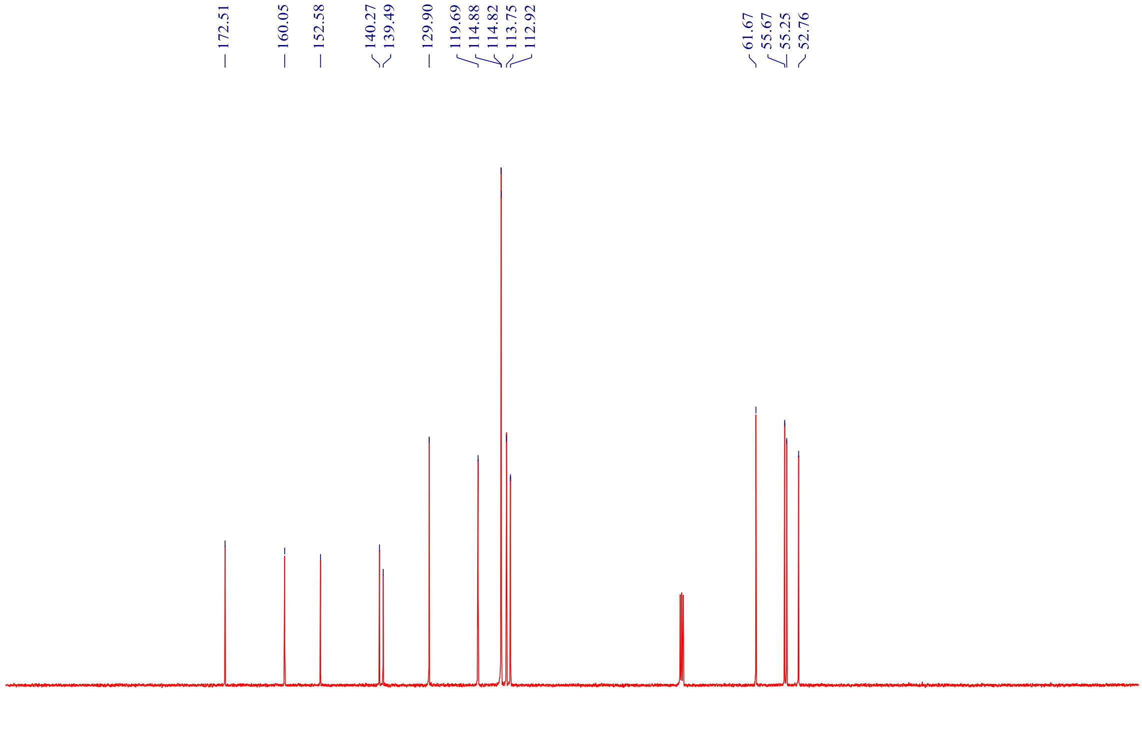
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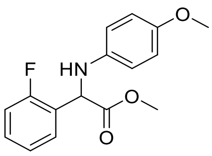

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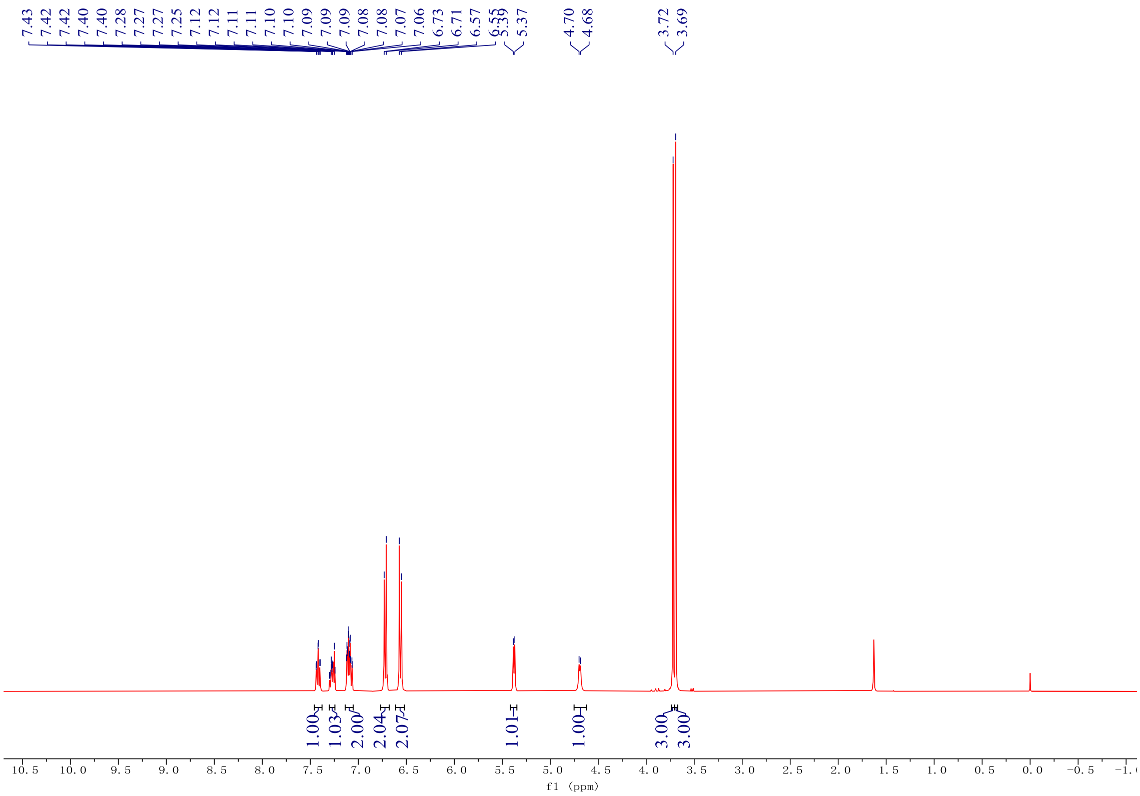

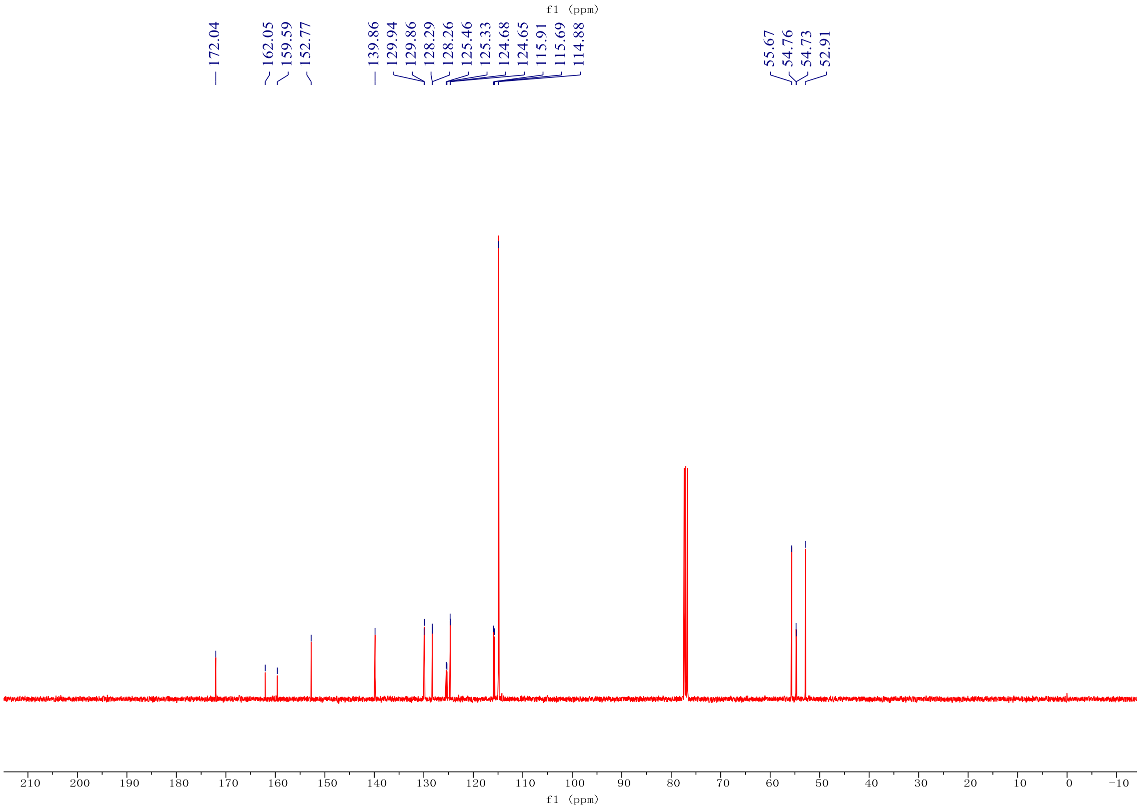

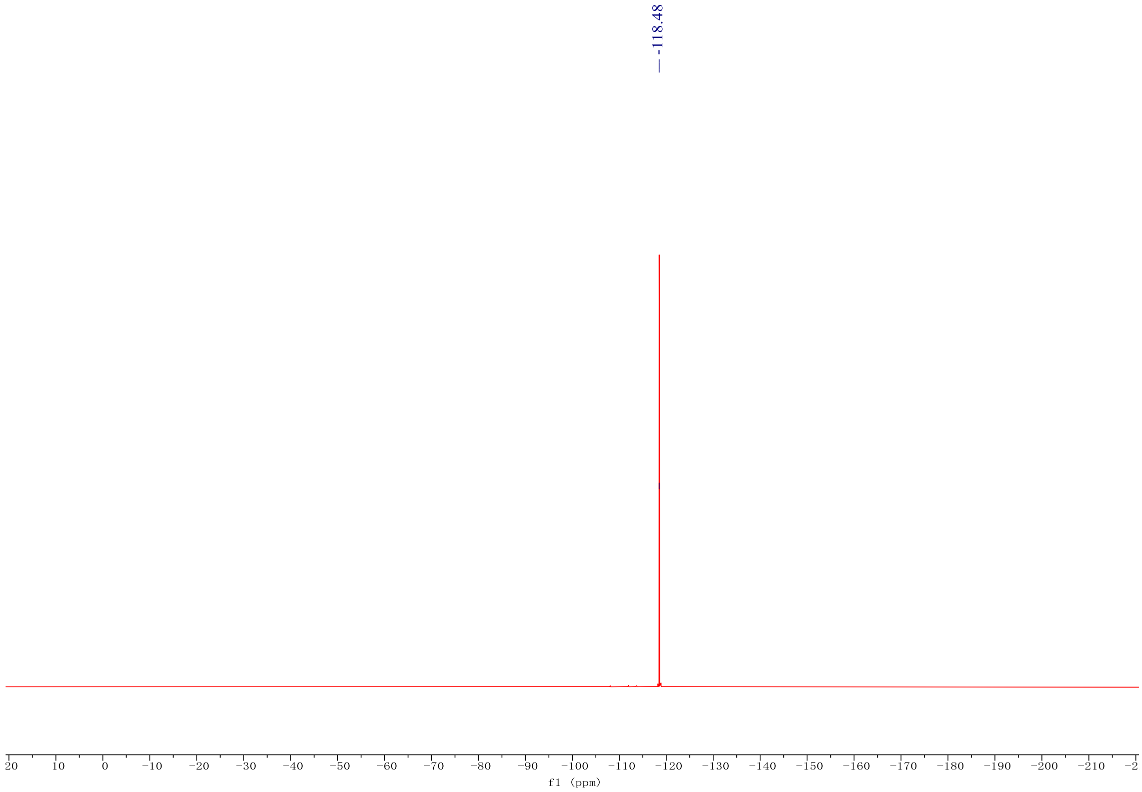
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-210
-2
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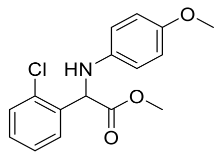

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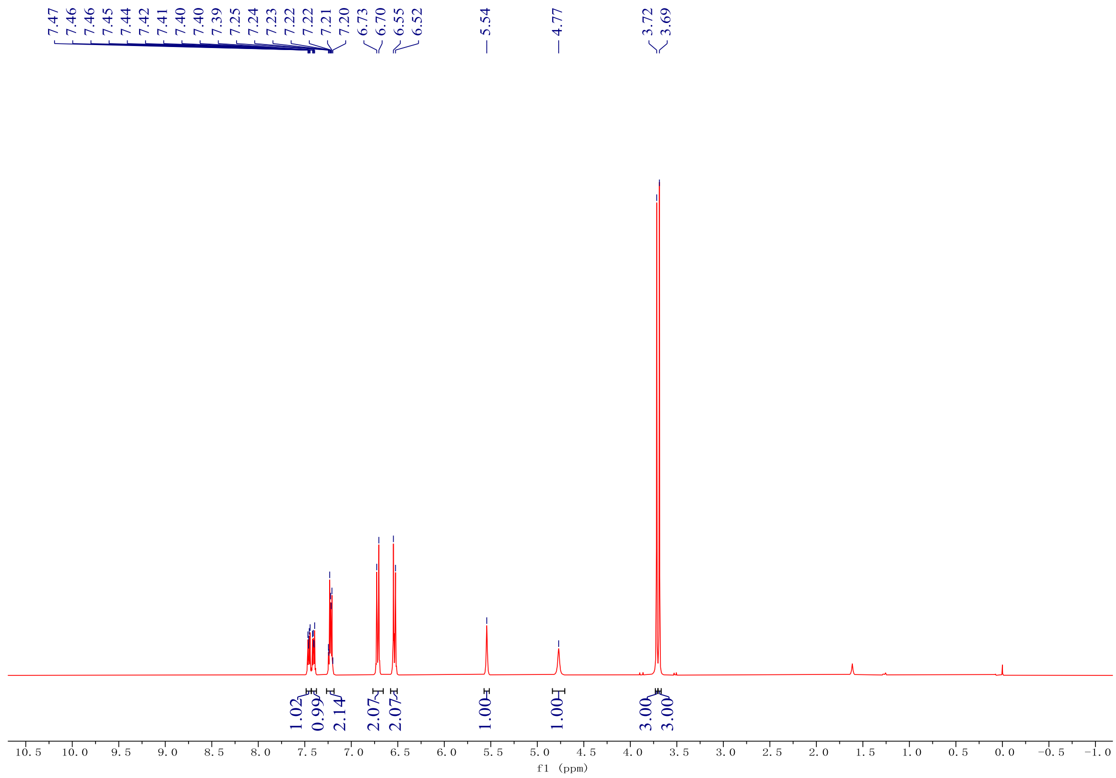

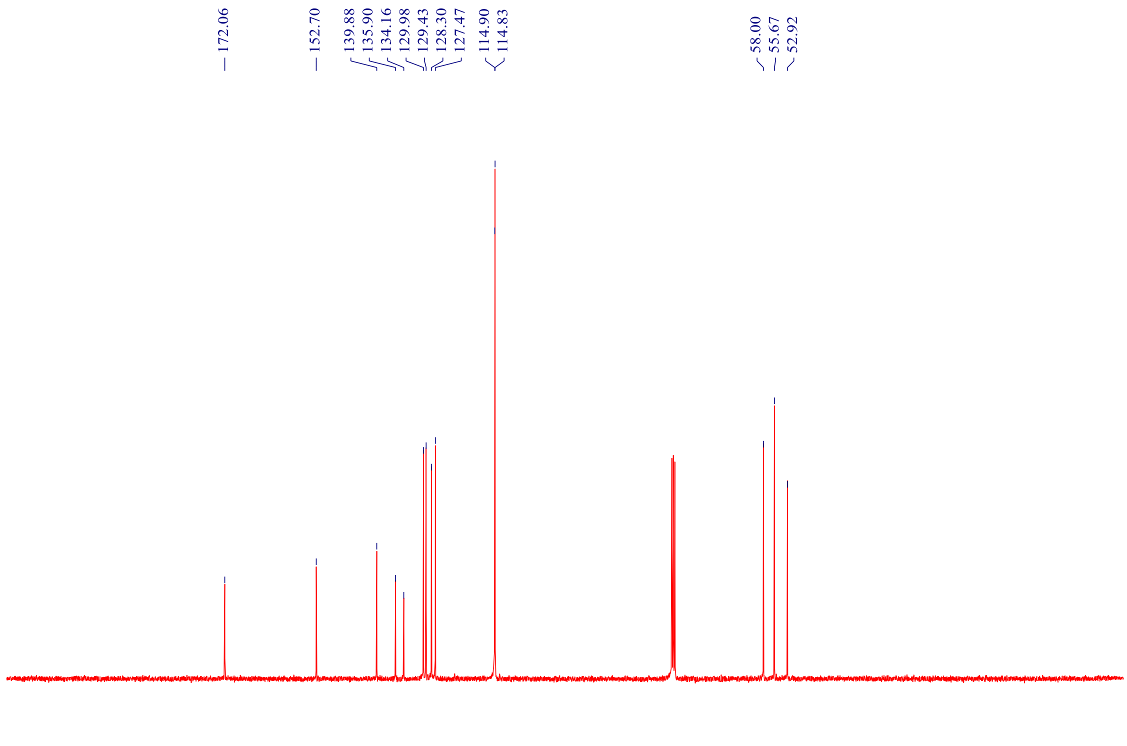

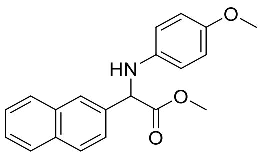
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O
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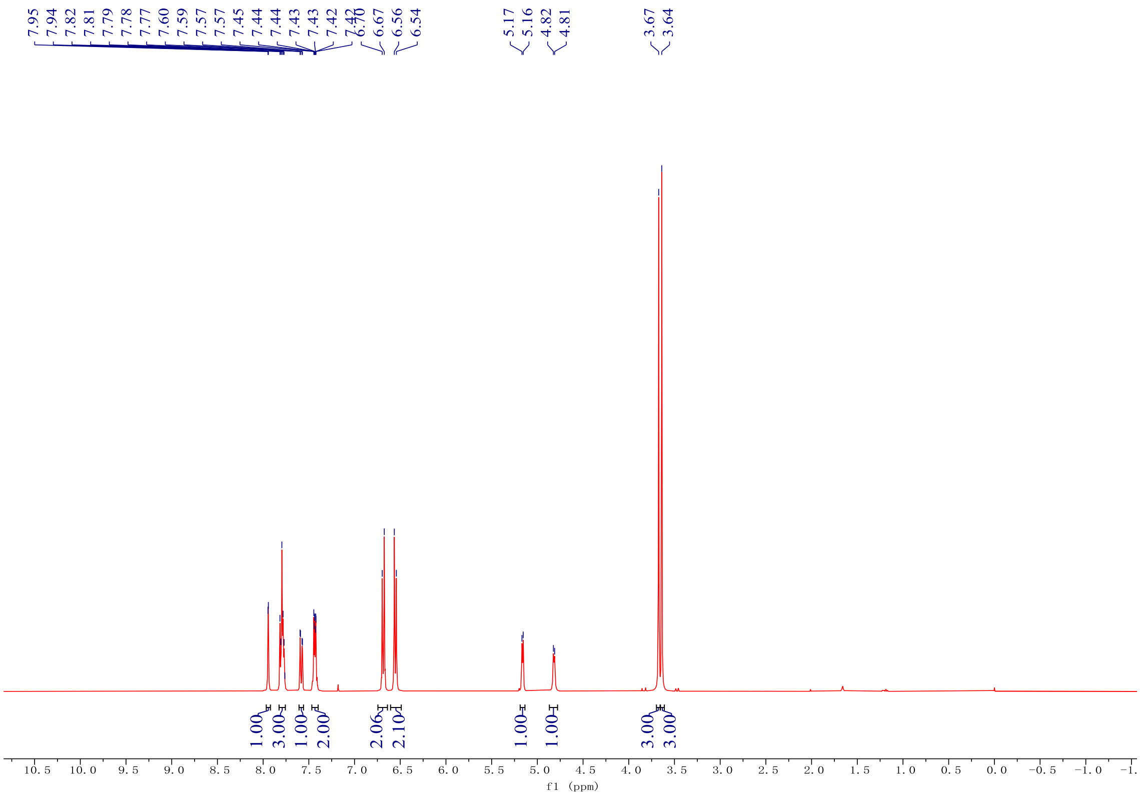
3l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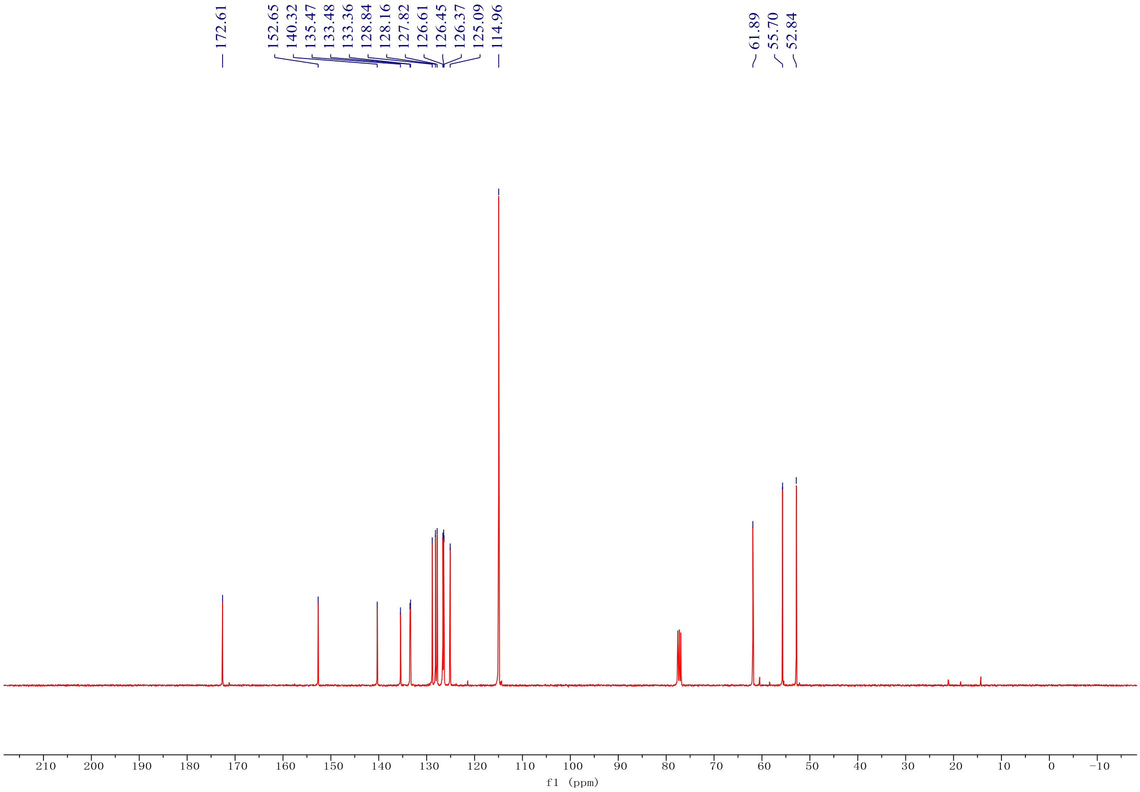
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.
f1 (ppm)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55.70
52.84
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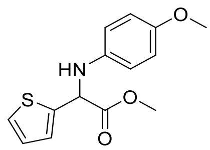
f1 (ppm)



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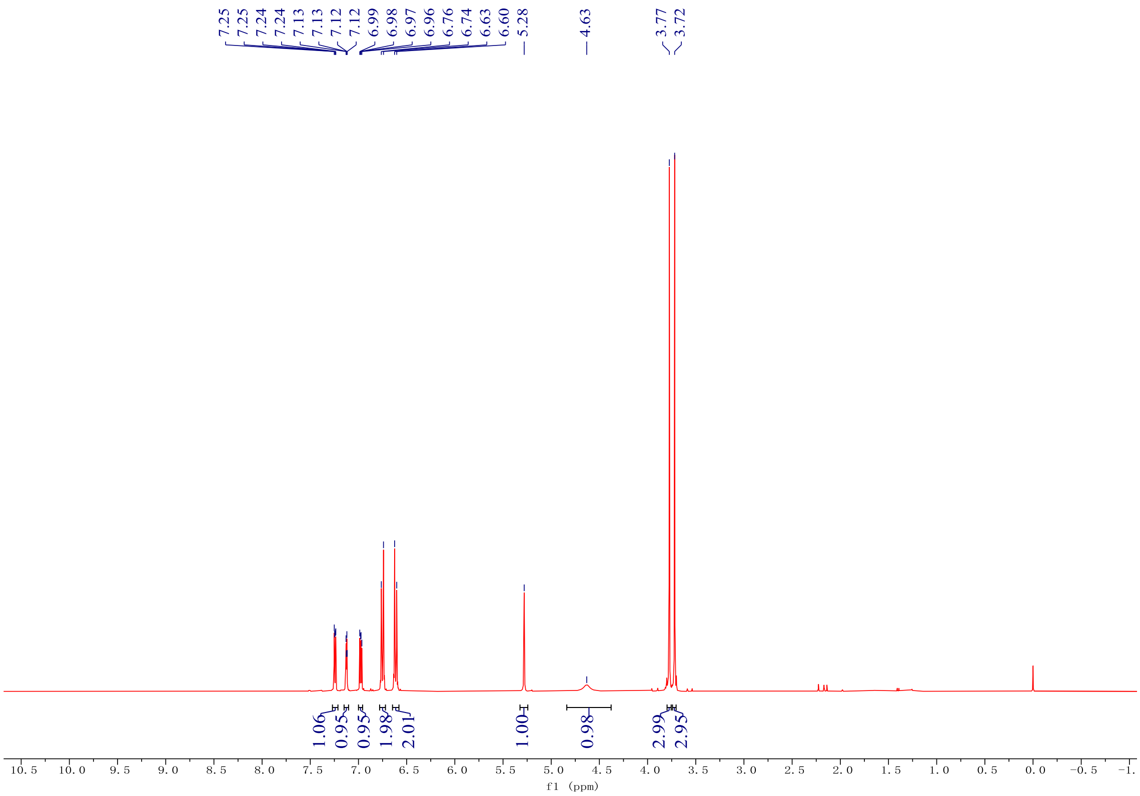
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6.74
6.63
6.60
5.28
4.63
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1.98
2.01
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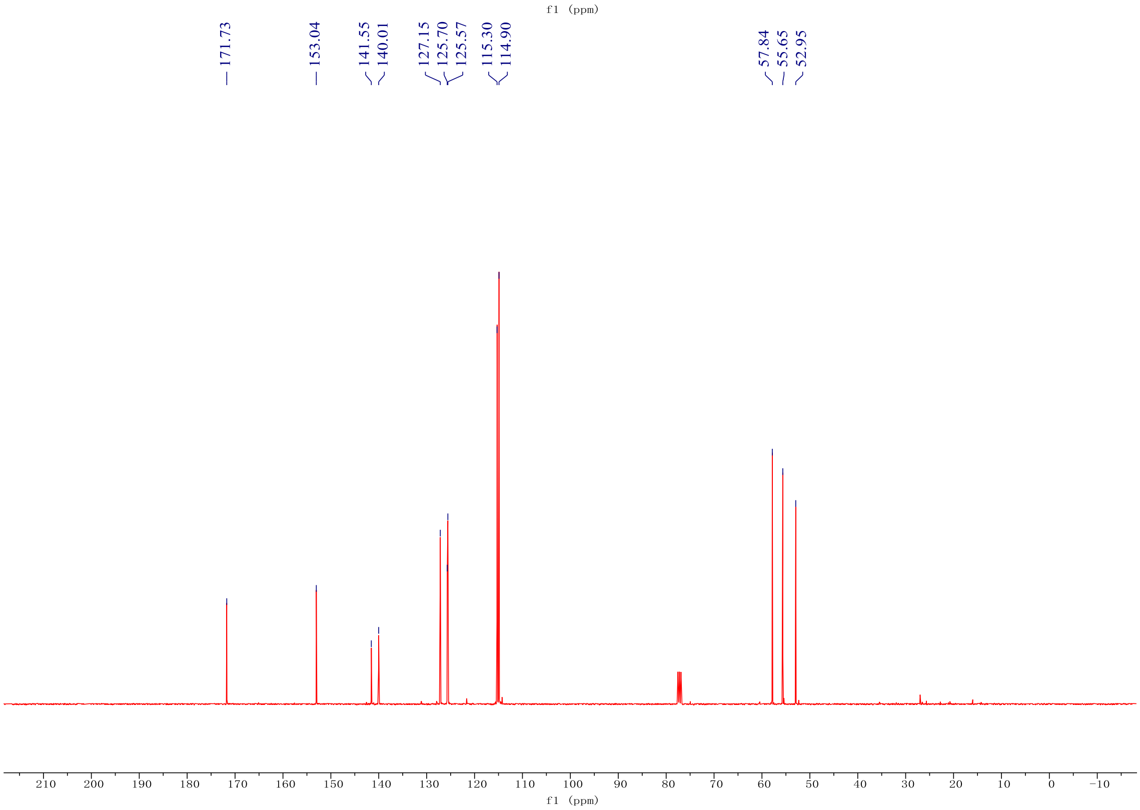
0.98
2.99
2.95
f1 (ppm)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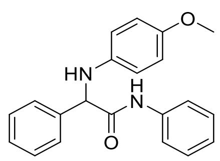
f1 (ppm)



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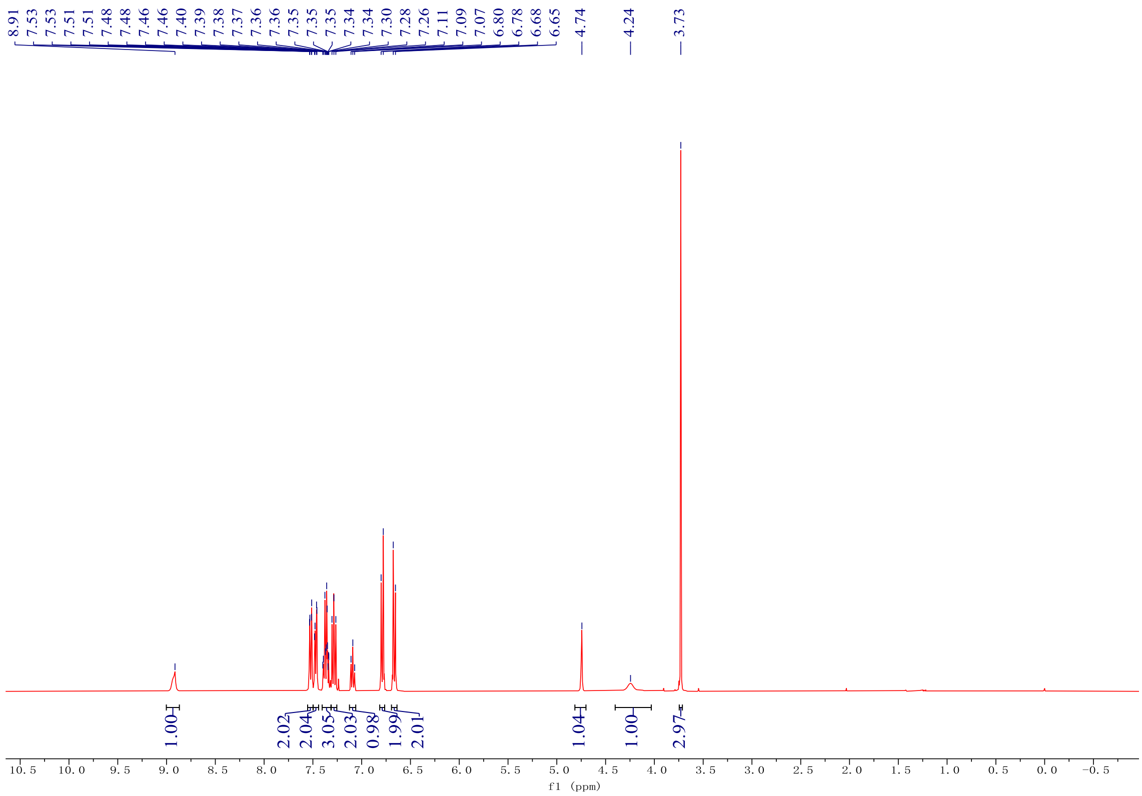
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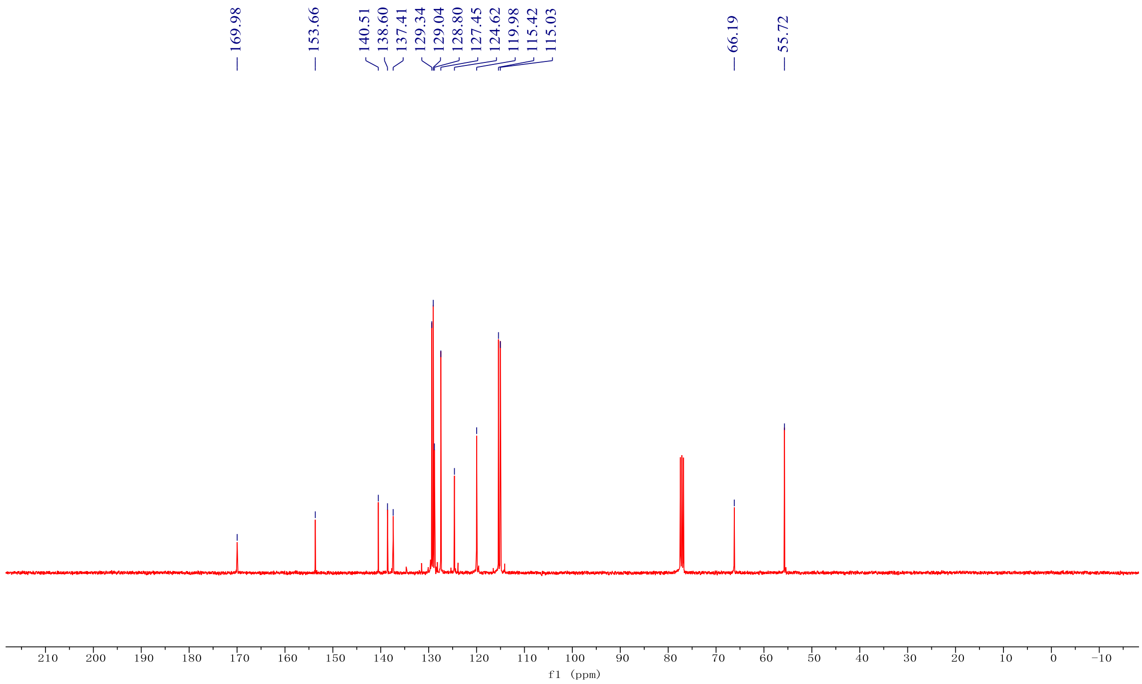
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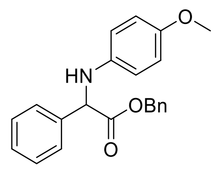
f1 (ppm)



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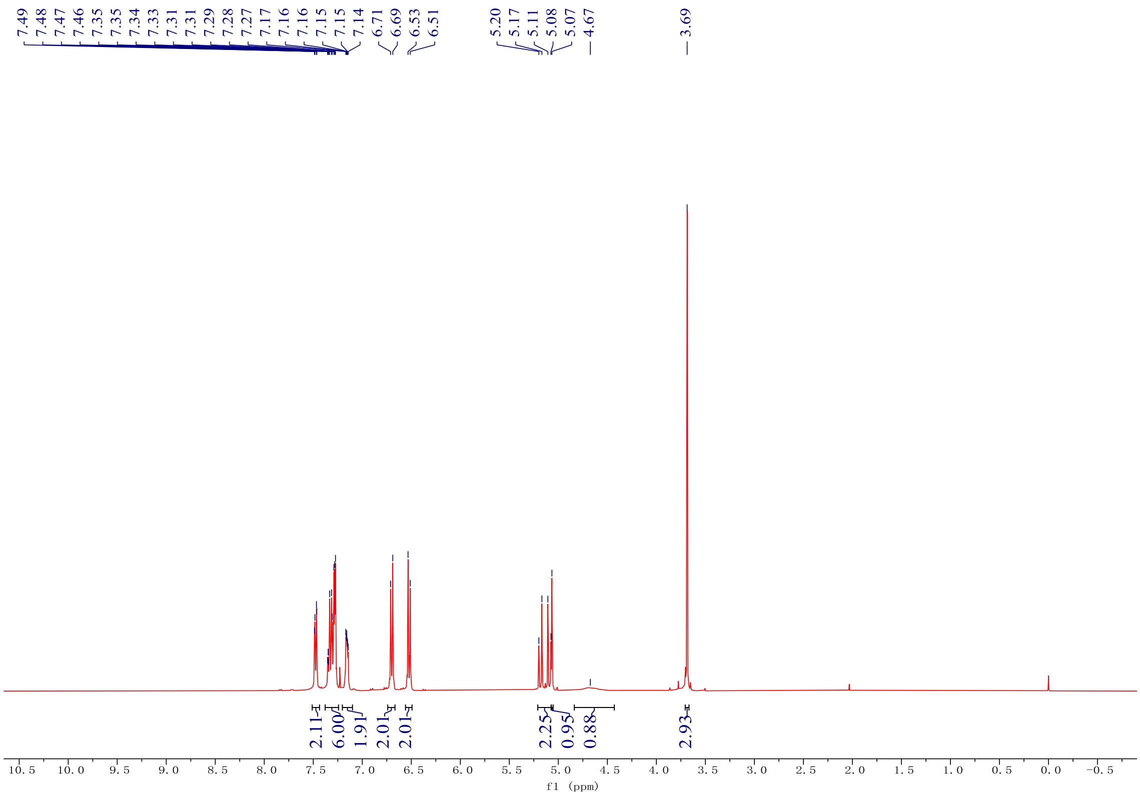
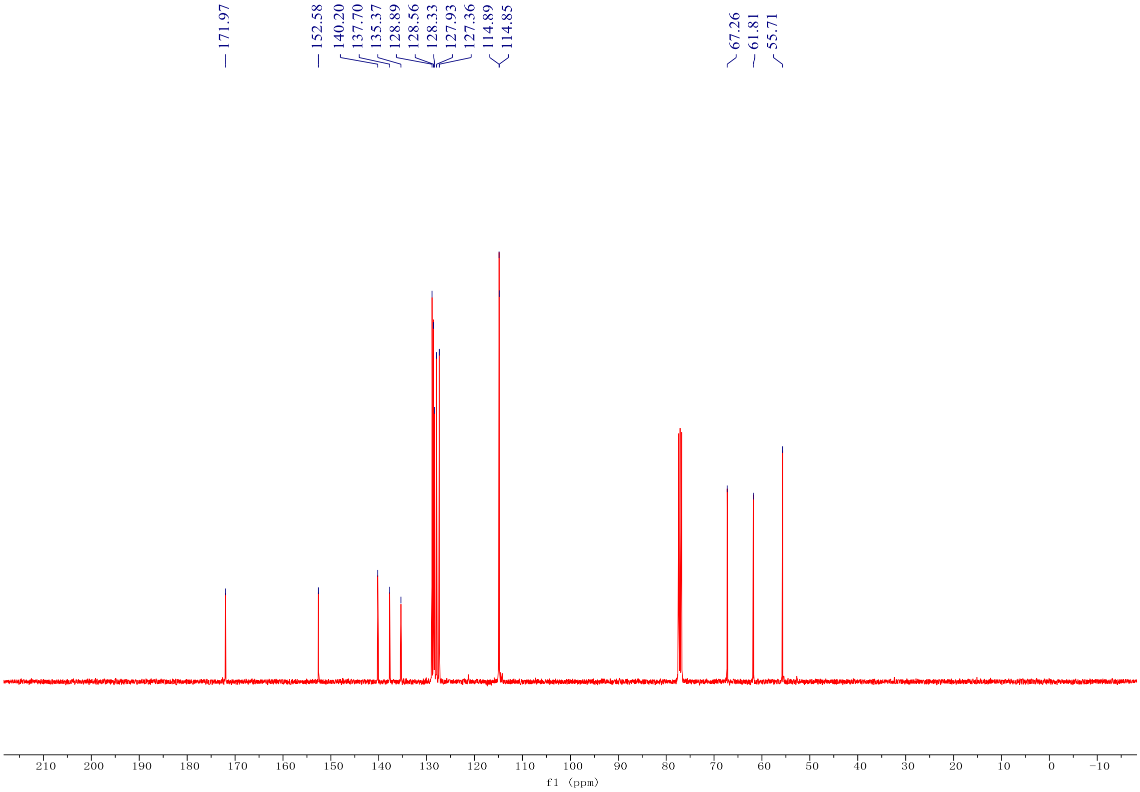
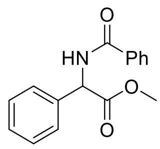
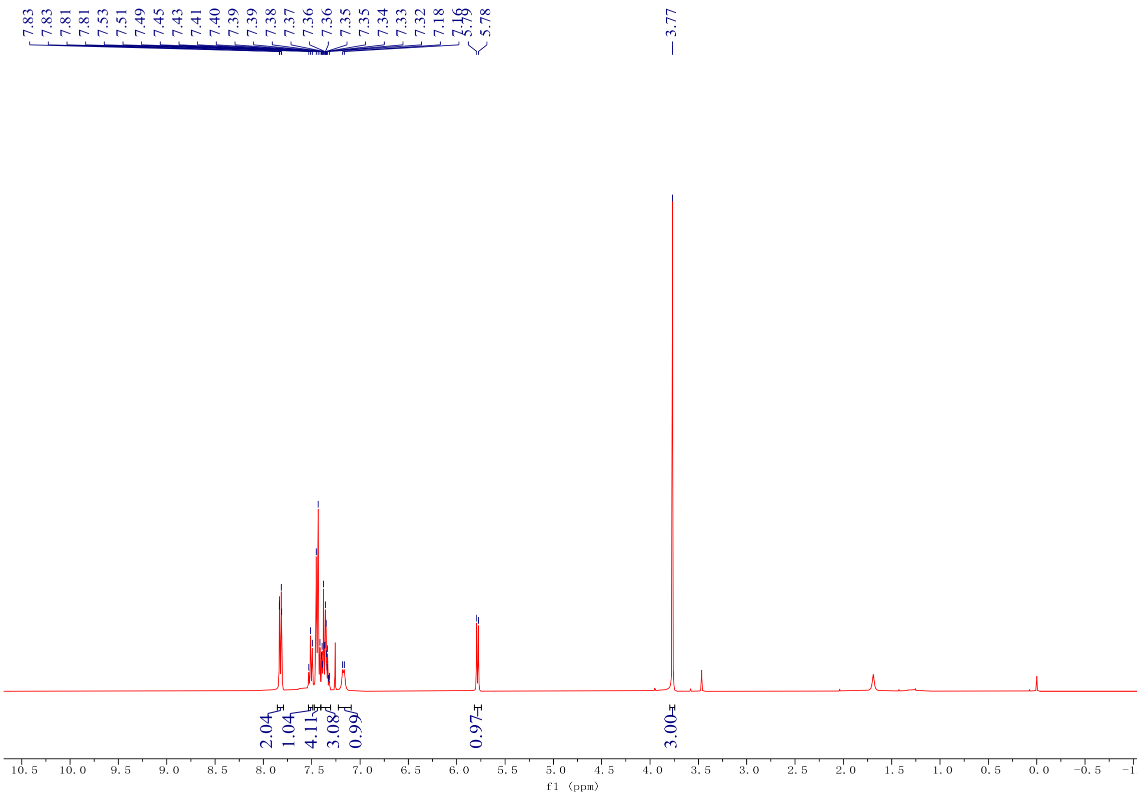





O
HN
Ph
O
O

3p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7.40
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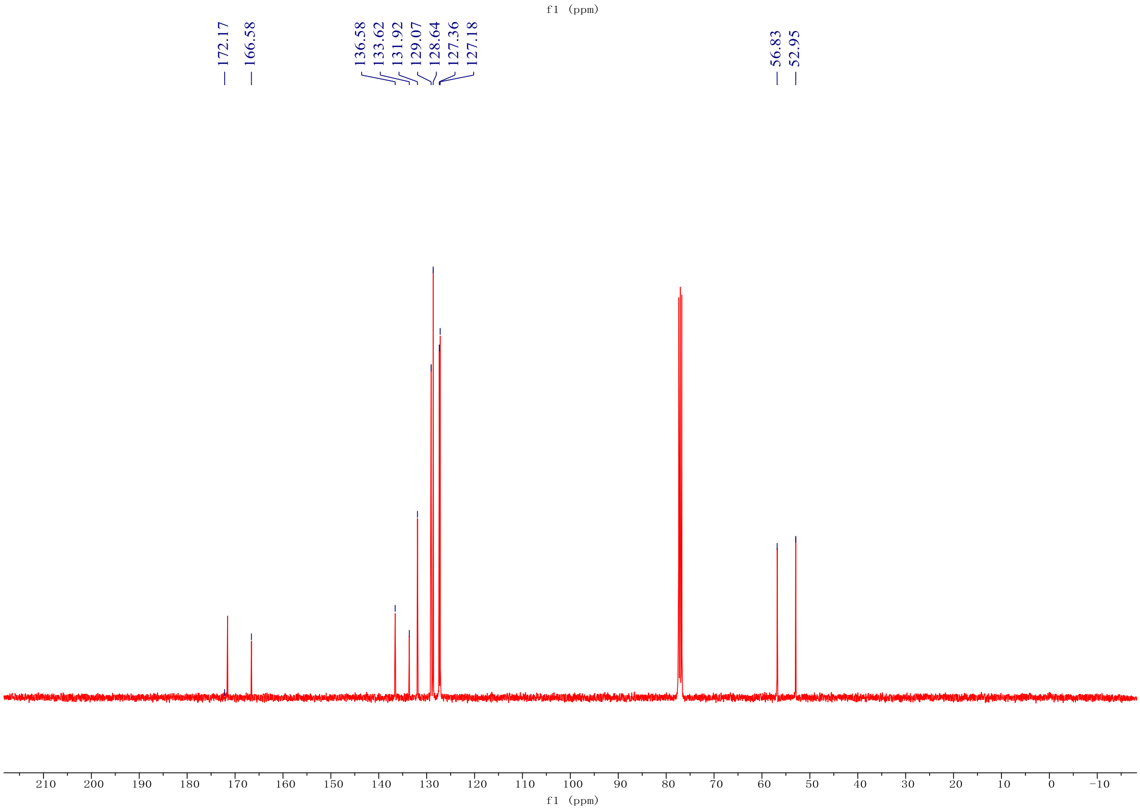
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.32
7.18
7.16
5.79
5.78
3.77
2.04
1.04
4.11
3.08
0.99
0.97
3.00
f1 (ppm)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129.07
128.64
127.36
127.18
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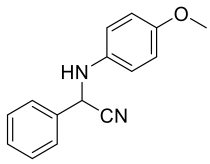
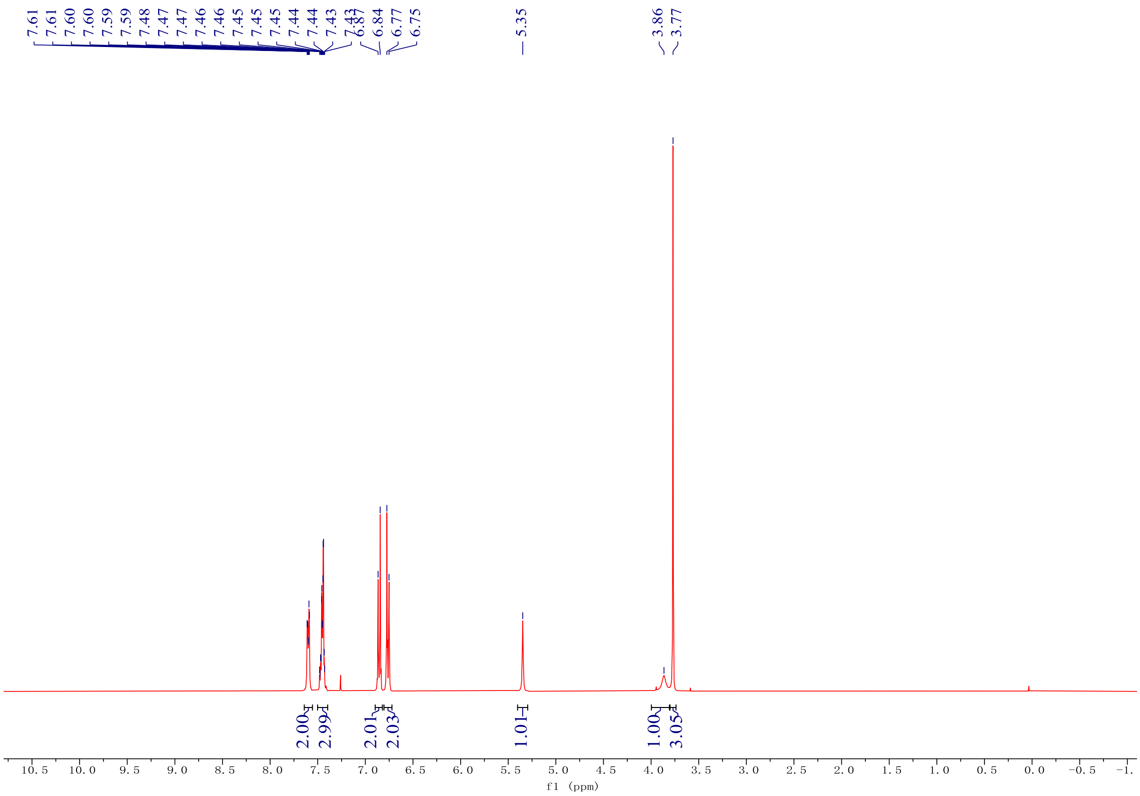
52.95
f1 (ppm)


HN
CN
O

3q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7.47
7.47
7.46
7.46
7.45
7.45
7.45
7.44
7.44
7.43
7.43
6.87
6.84
6.77
6.75
5.35
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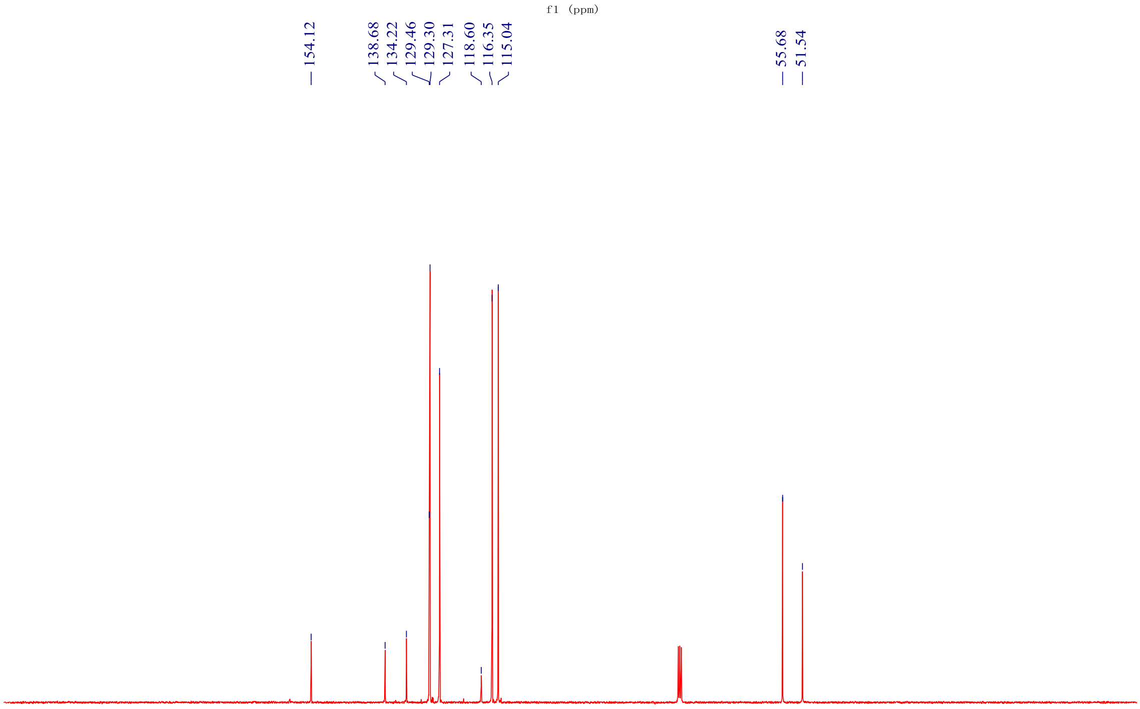
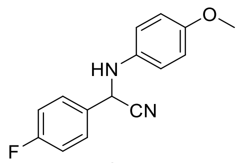
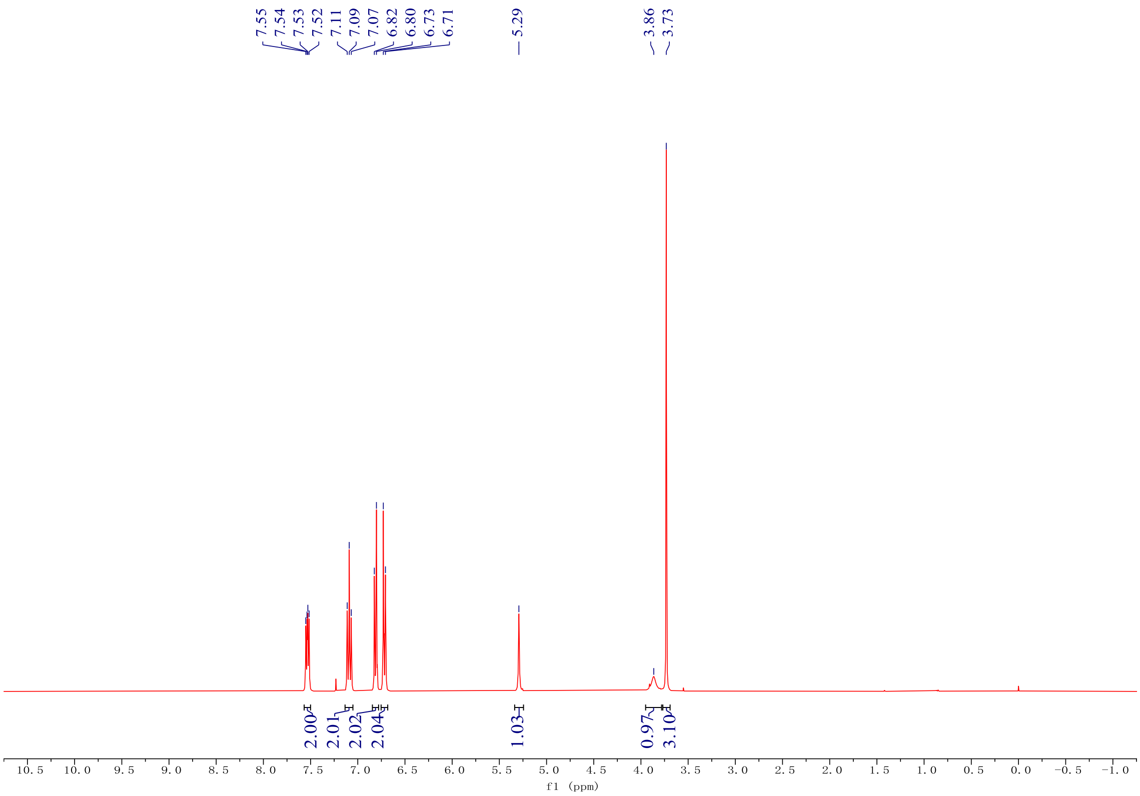
3.77
2.00
2.99
2.01
2.03
1.01
1.00
3.05
f1 (ppm)


154.12
138.68
134.22
129.46
129.30
127.31
118.60
116.35
115.04
55.68
51.54
f1 (ppm)



3r



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7.54
7.53
7.52
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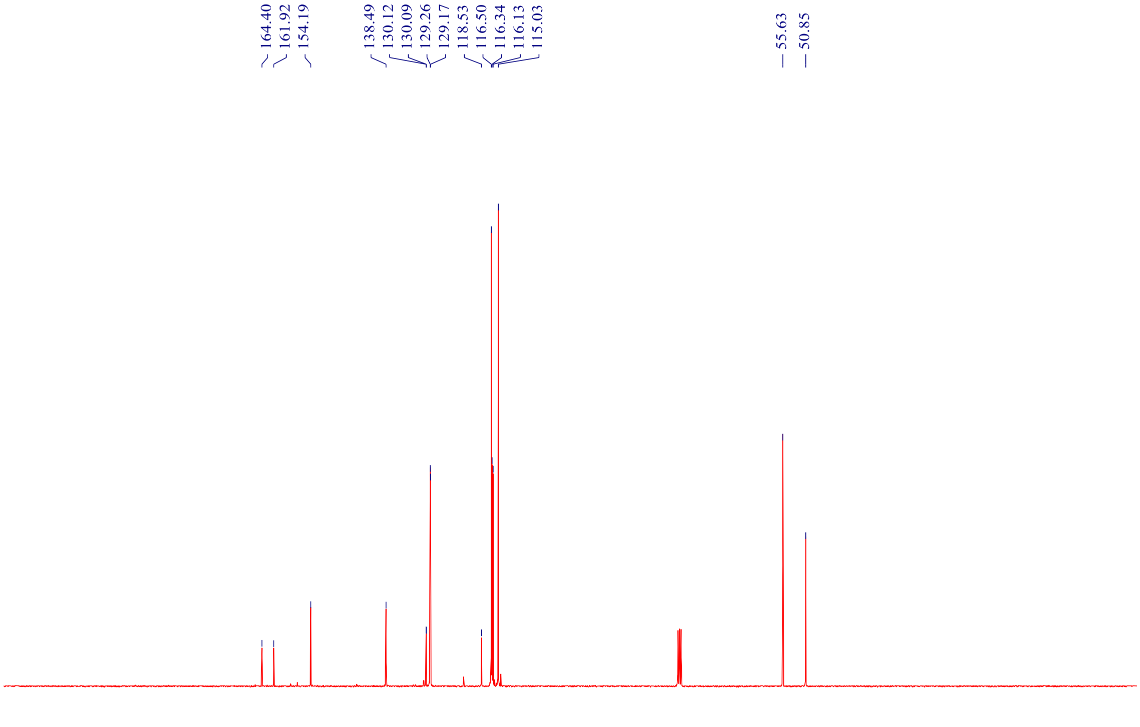
7.09
7.07
6.82
6.80
6.73
6.71
5.29
3.86
3.73
2.00
2.01
2.02
2.04
1.03
0.97
3.10
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)



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154.19
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130.09
129.26
129.17
118.53
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116.34
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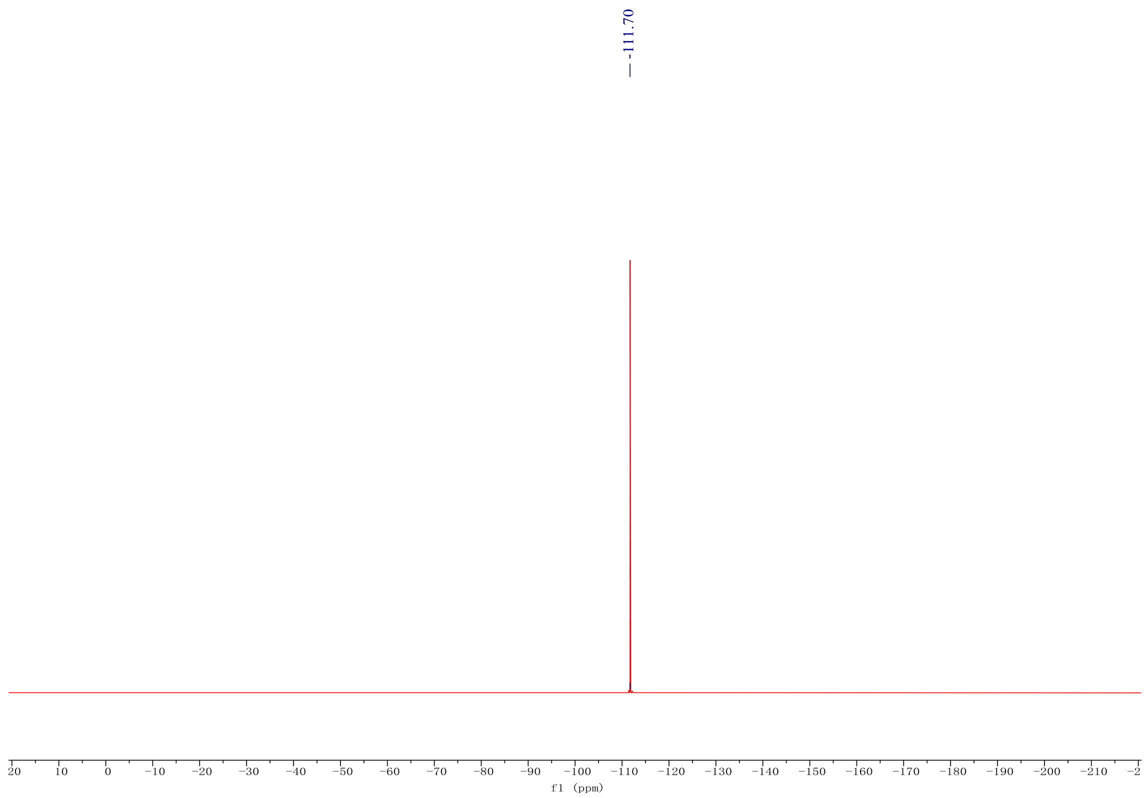
115.03
55.63
50.85
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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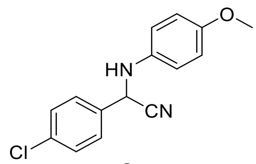
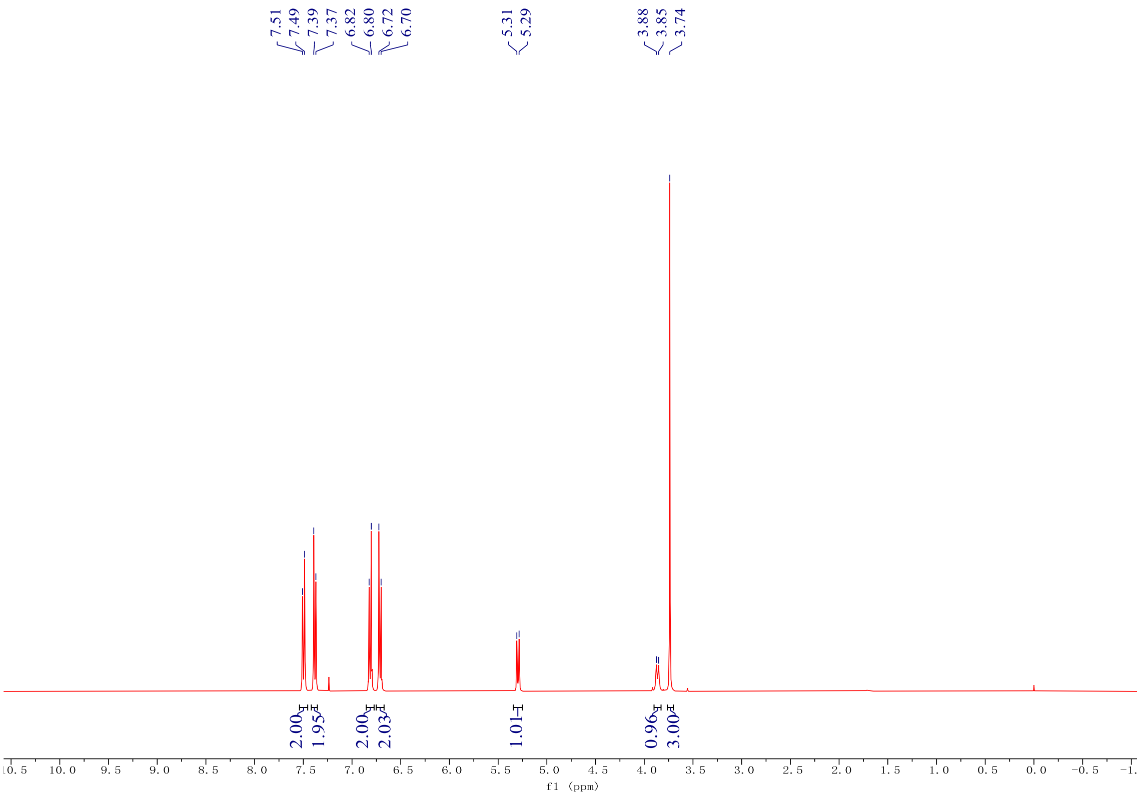
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -2
f1 (ppm)



O
HN
CN
Cl

3s



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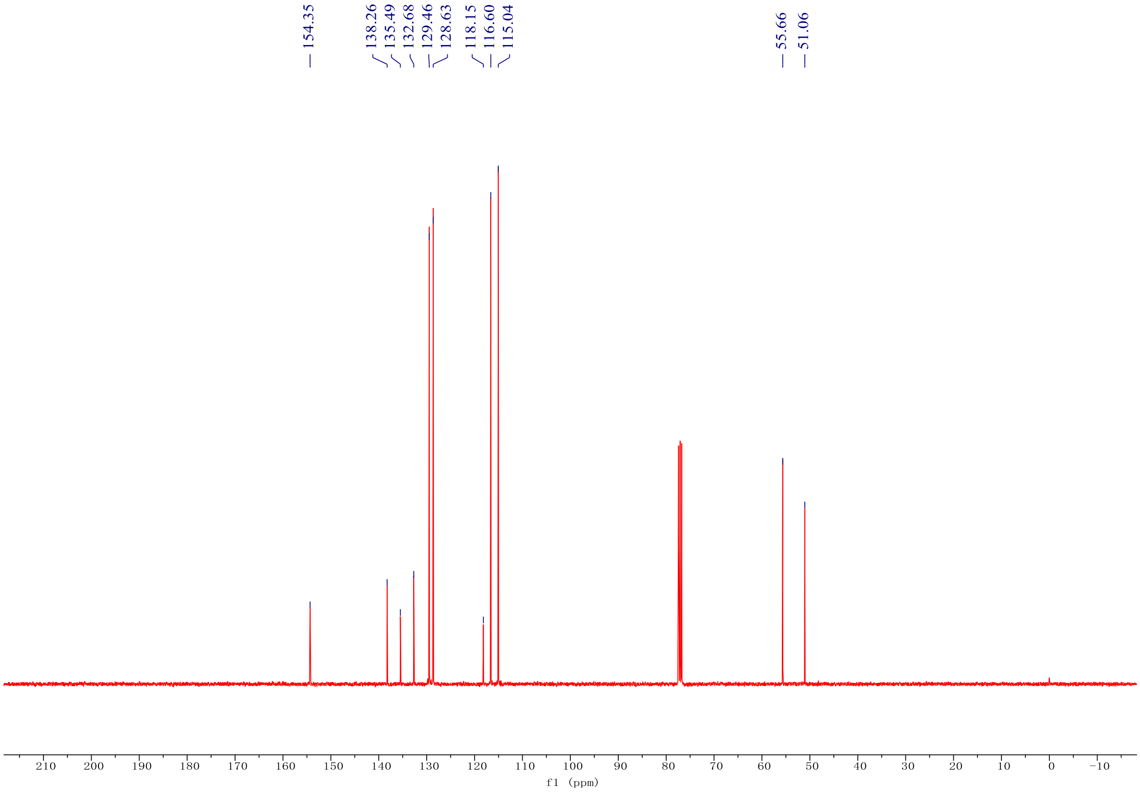
7.37
6.82
6.80
6.72
6.70
5.31
5.29
3.88
3.85
3.74
2.00
1.95
2.00
2.03
1.01
0.96
3.00
f1 (ppm)



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138.26
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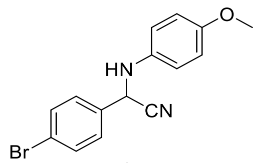
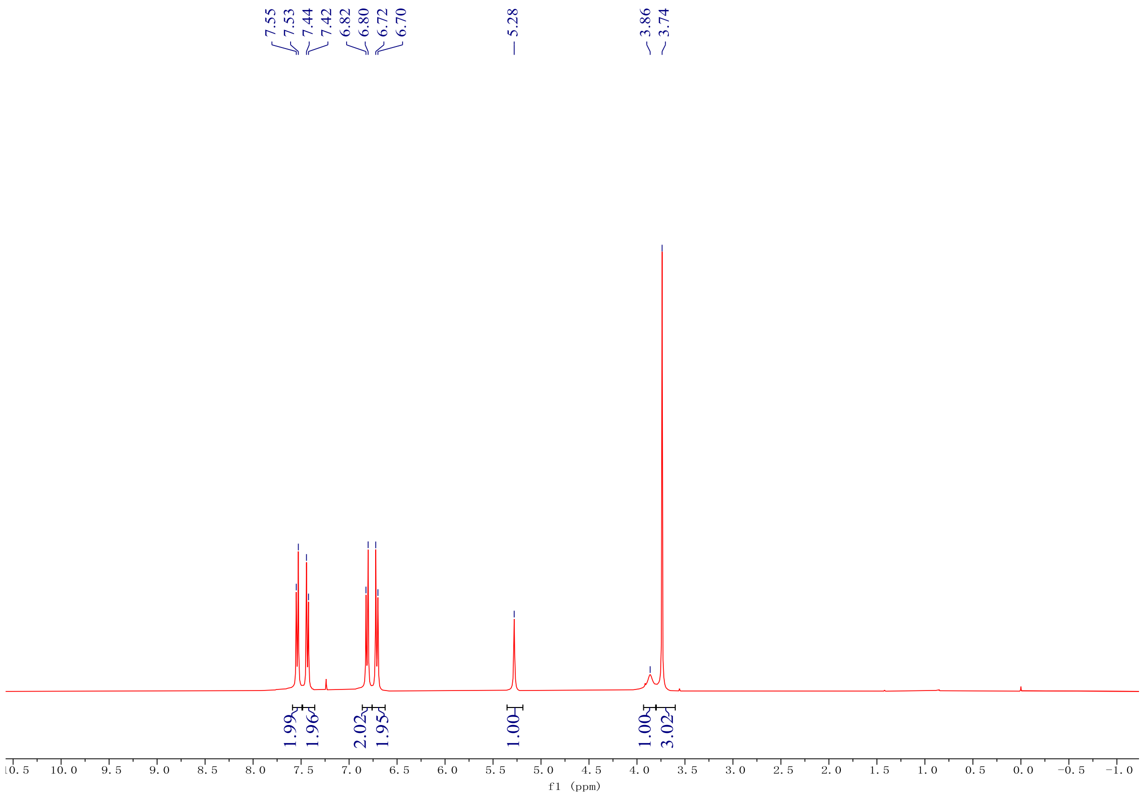
132.68
129.46
128.63
118.15
116.60
115.04
55.66
51.06
f1 (ppm)


O
HN
CN
Br

3t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7.42
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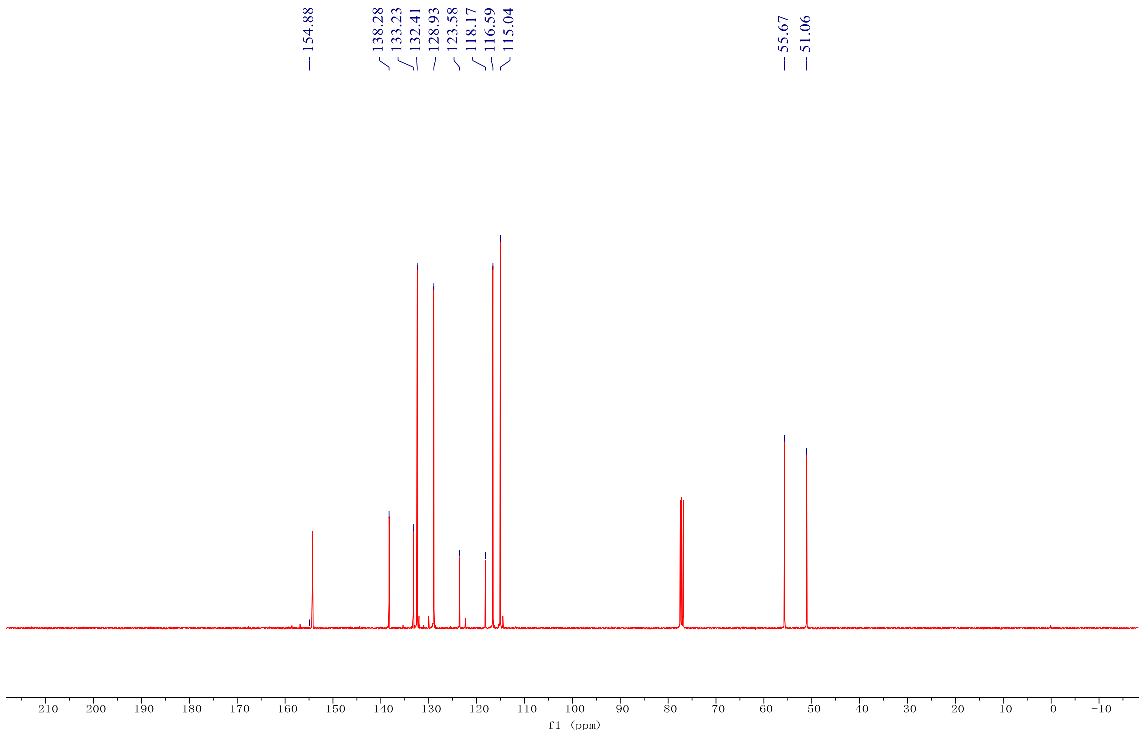
6.80
6.72
6.70
5.28
3.86
3.74
1.99
1.96
2.02
1.95
1.00
1.00
3.02
f1 (ppm)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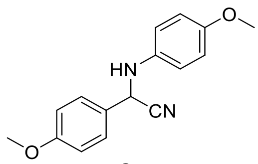
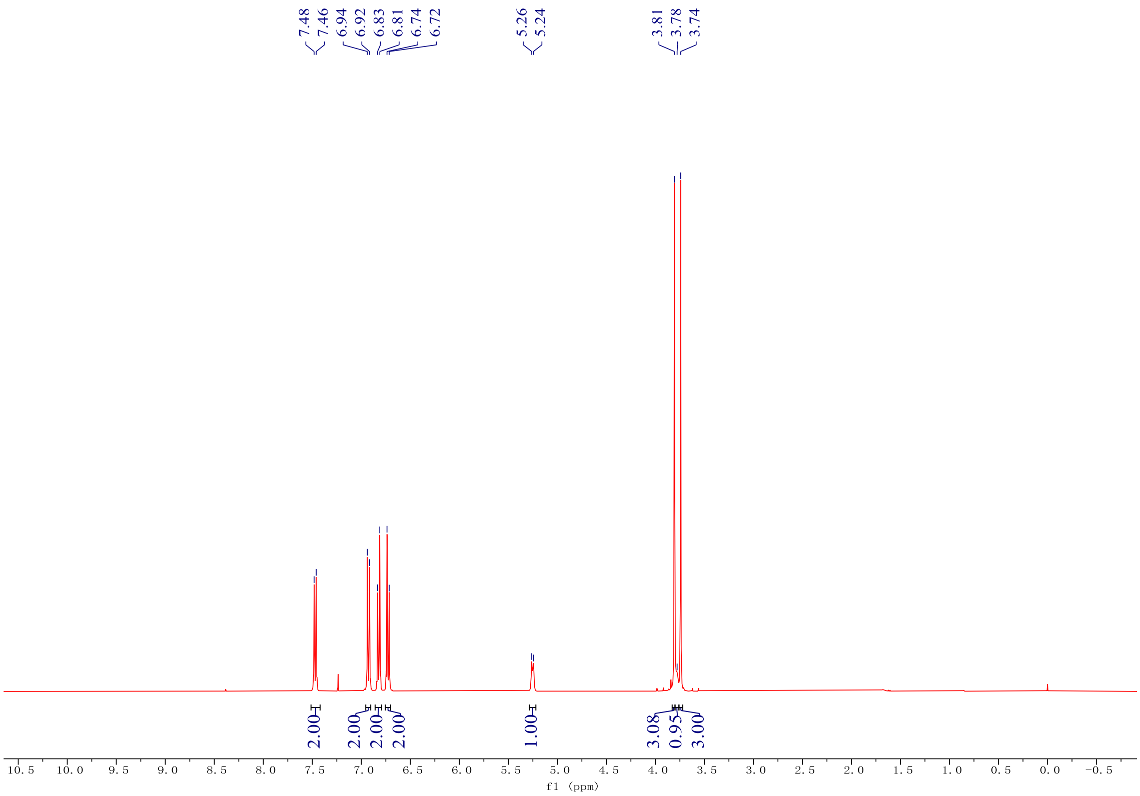
123.58
118.17
116.59
115.04
55.67
51.06
f1 (ppm)


HN
CN
O
O

3u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7.46
6.94
6.92
6.83
6.81
6.74
6.72
5.26
5.24
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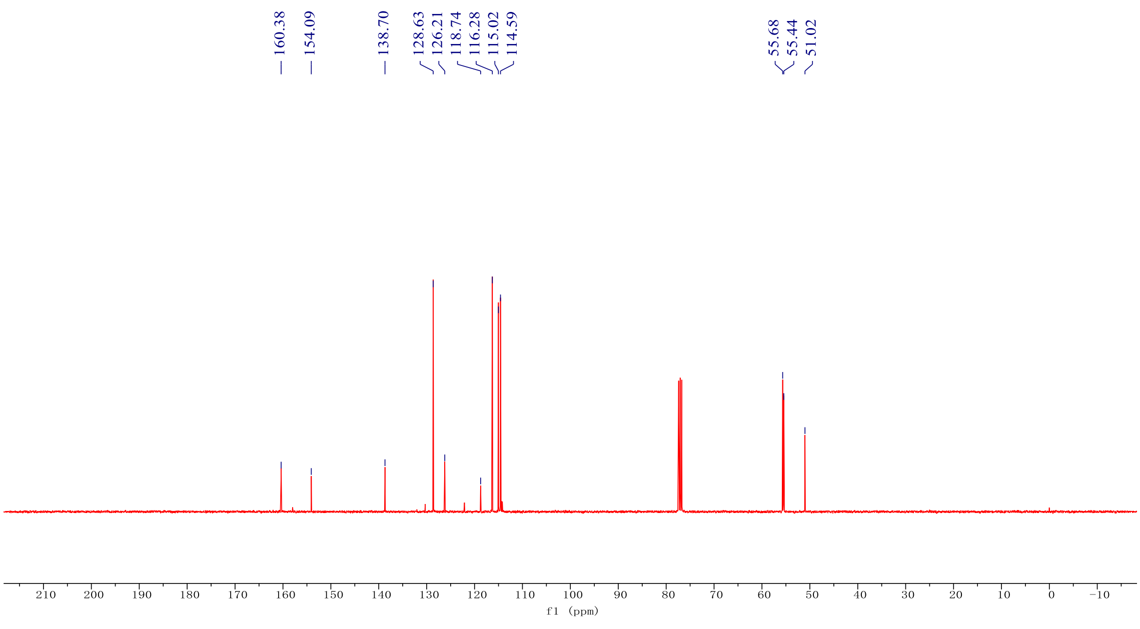
3.78
3.74
2.00
2.00
2.00
2.00
1.00
3.08
0.95
3.00
f1 (ppm)


160.38
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115.02
114.59
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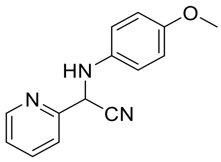
55.44
51.02
f1 (ppm)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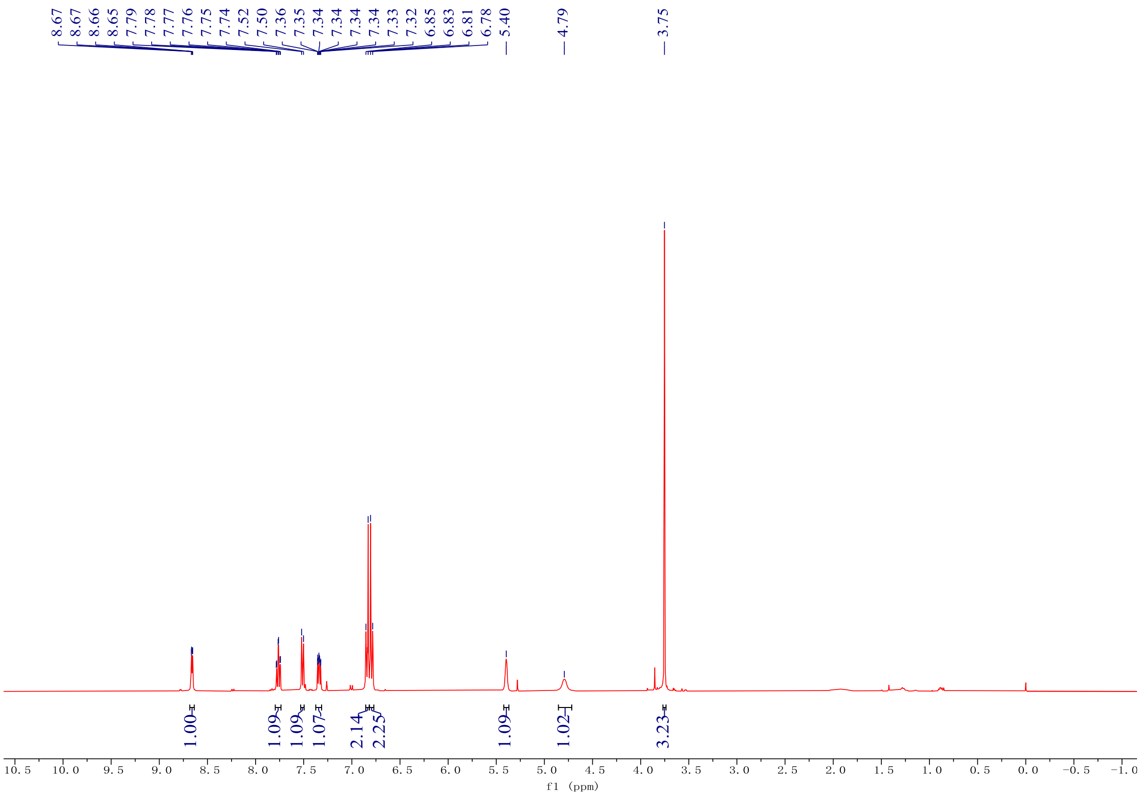
CN
O

3v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7.34
7.34
7.34
7.33
7.32
6.85
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6.81
6.78
5.40
4.79
3.75
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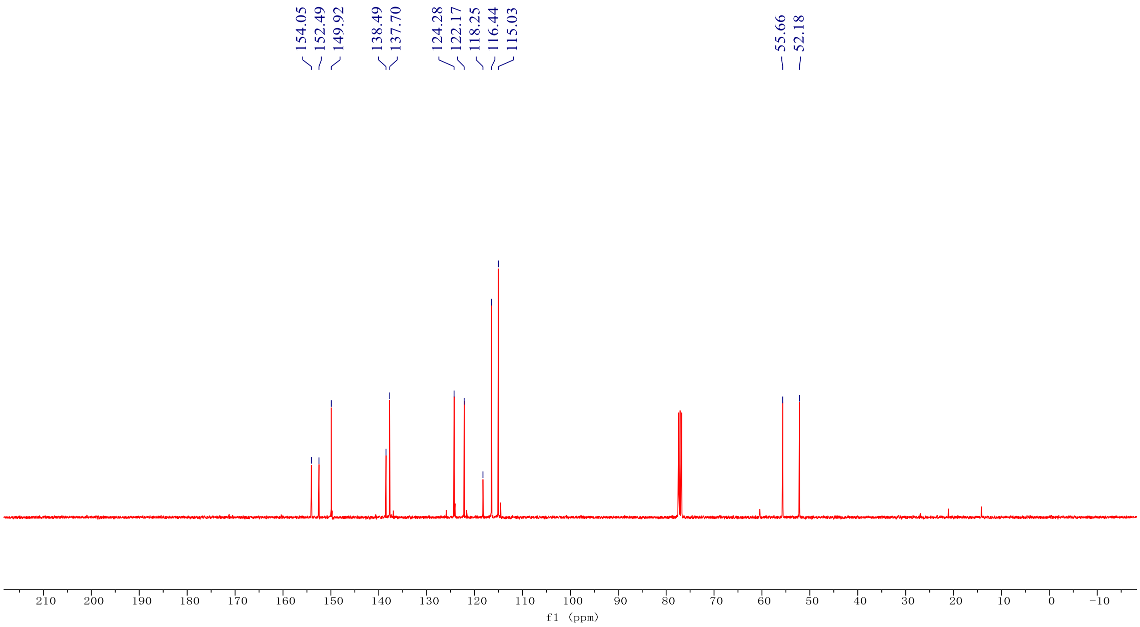
1.07
2.14
2.25
1.09
1.02
3.23
f1 (ppm)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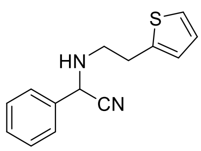
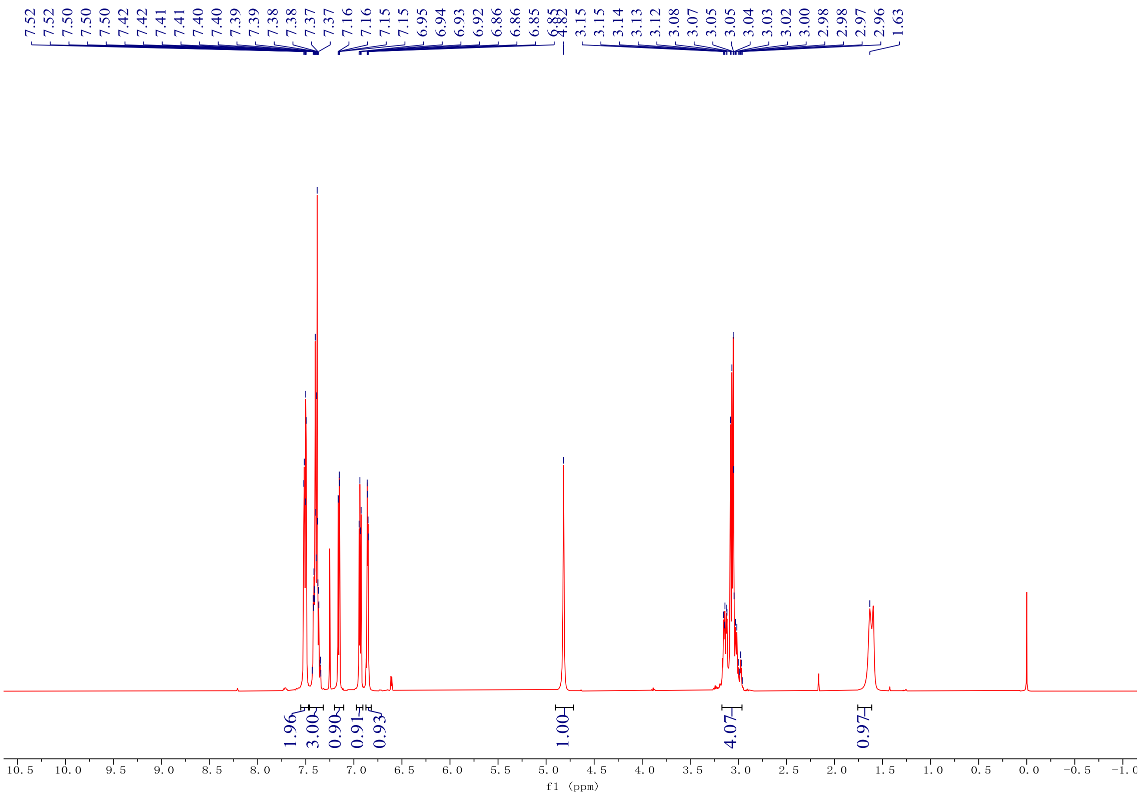
52.18
f1 (ppm)


HN
S
CN

3w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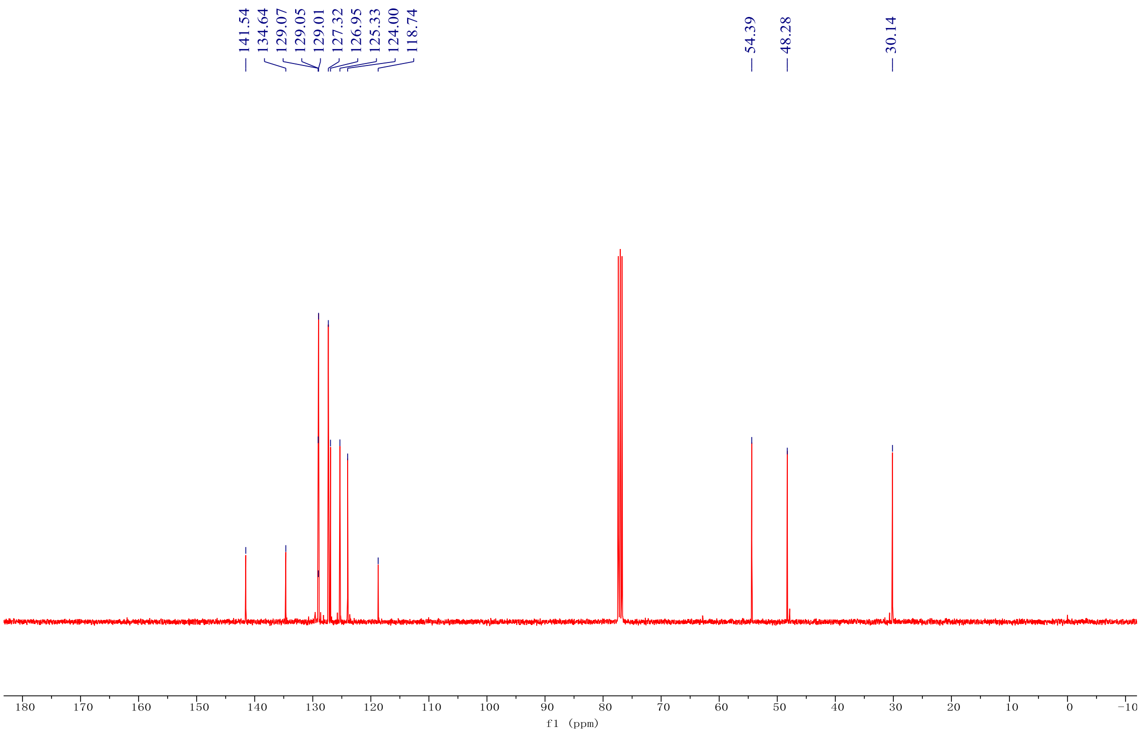
1.96 3.00 0.90 0.91 0.93 1.00 4.07 0.97
f1 (ppm)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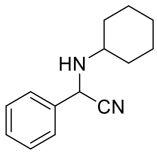
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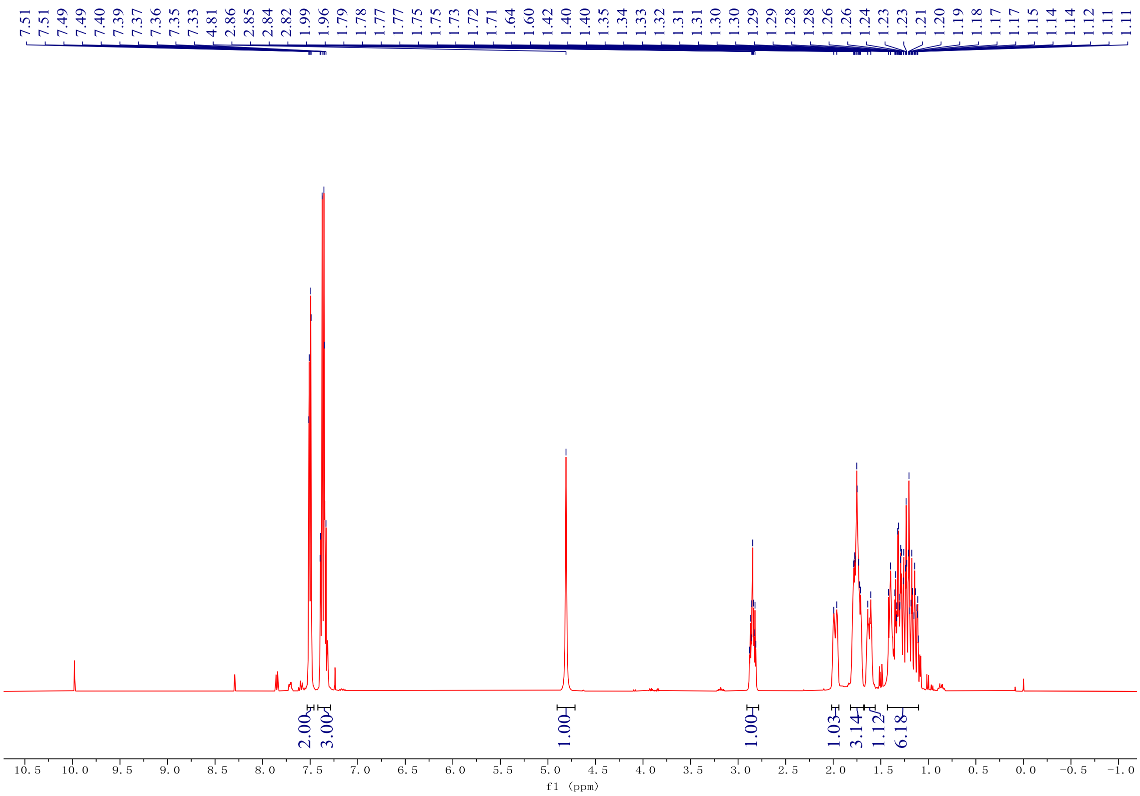
CN

3x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2.00
3.00
1.00
1.00
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3.14
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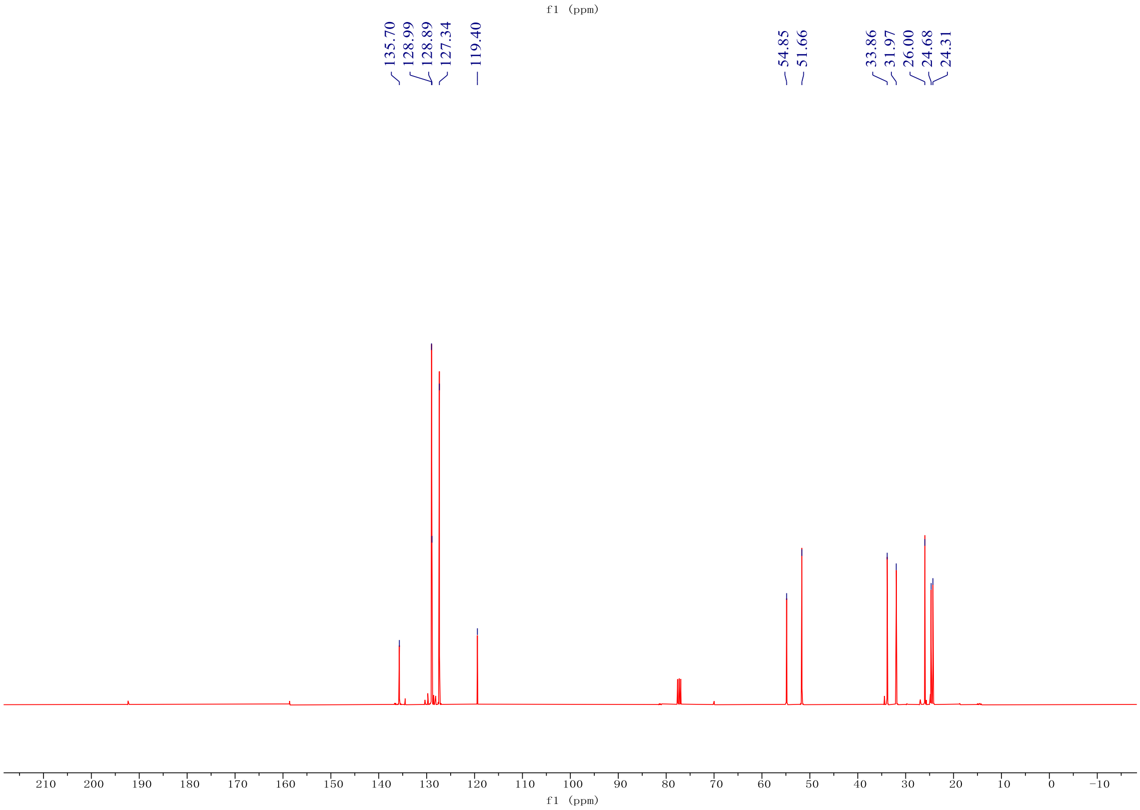
6.18
f1 (ppm)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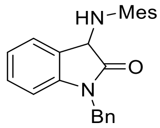

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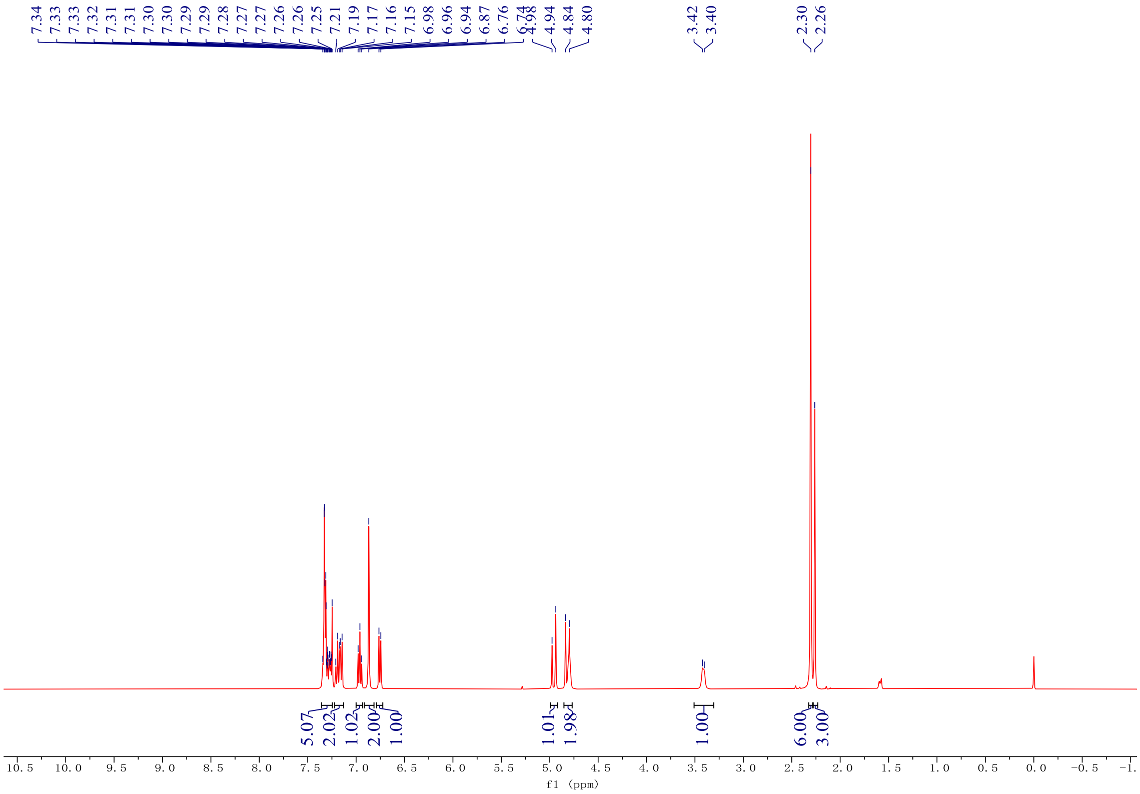
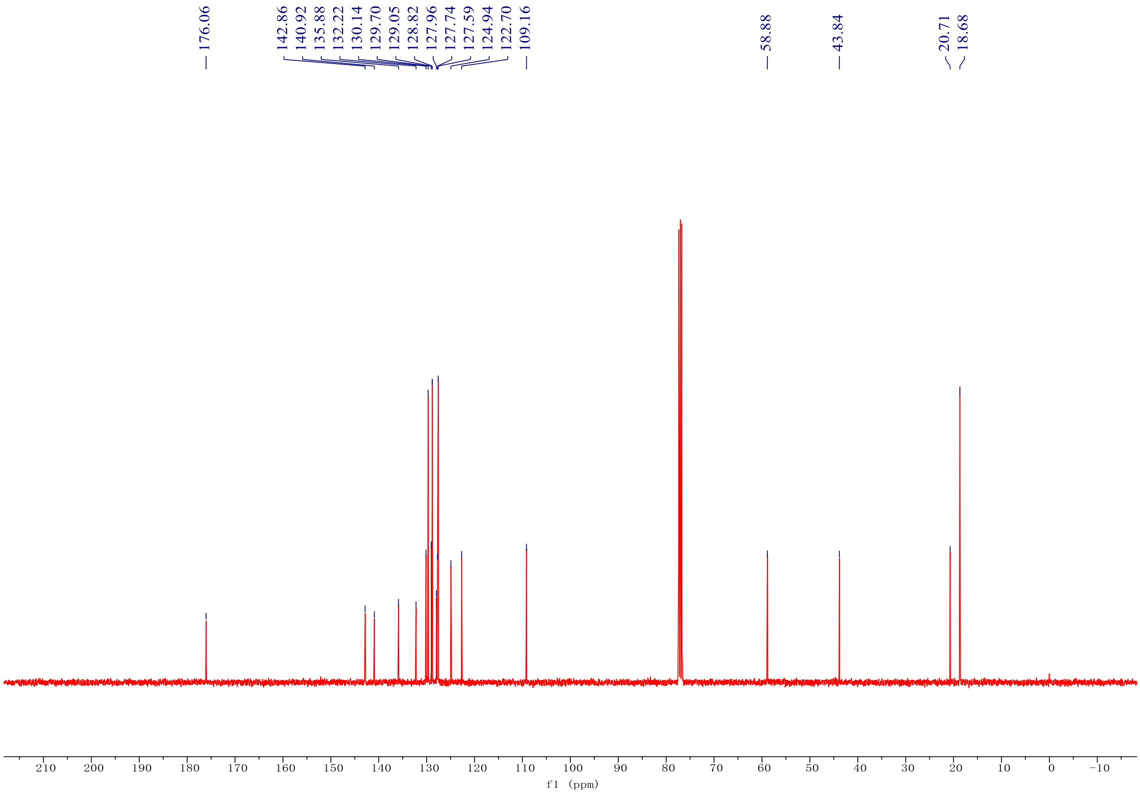
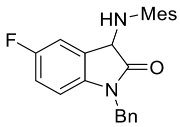
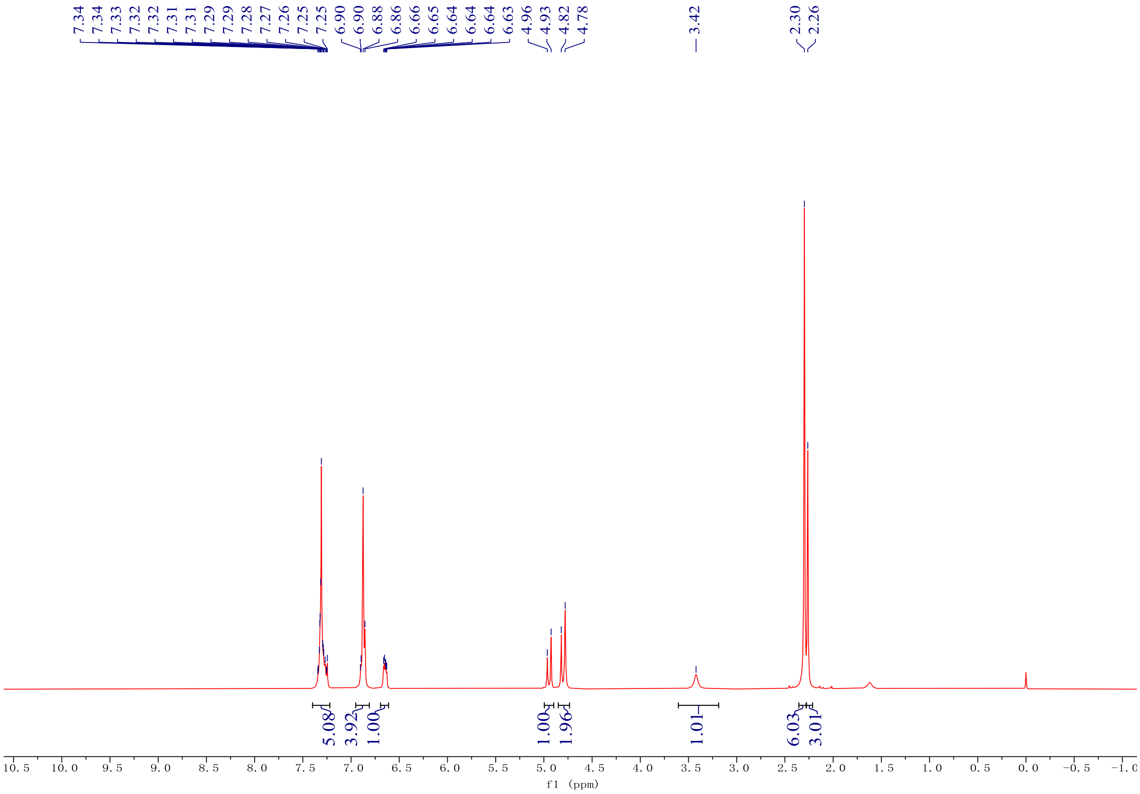





HN–Mes
F
O
N
Bn

3z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4.78
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1.00
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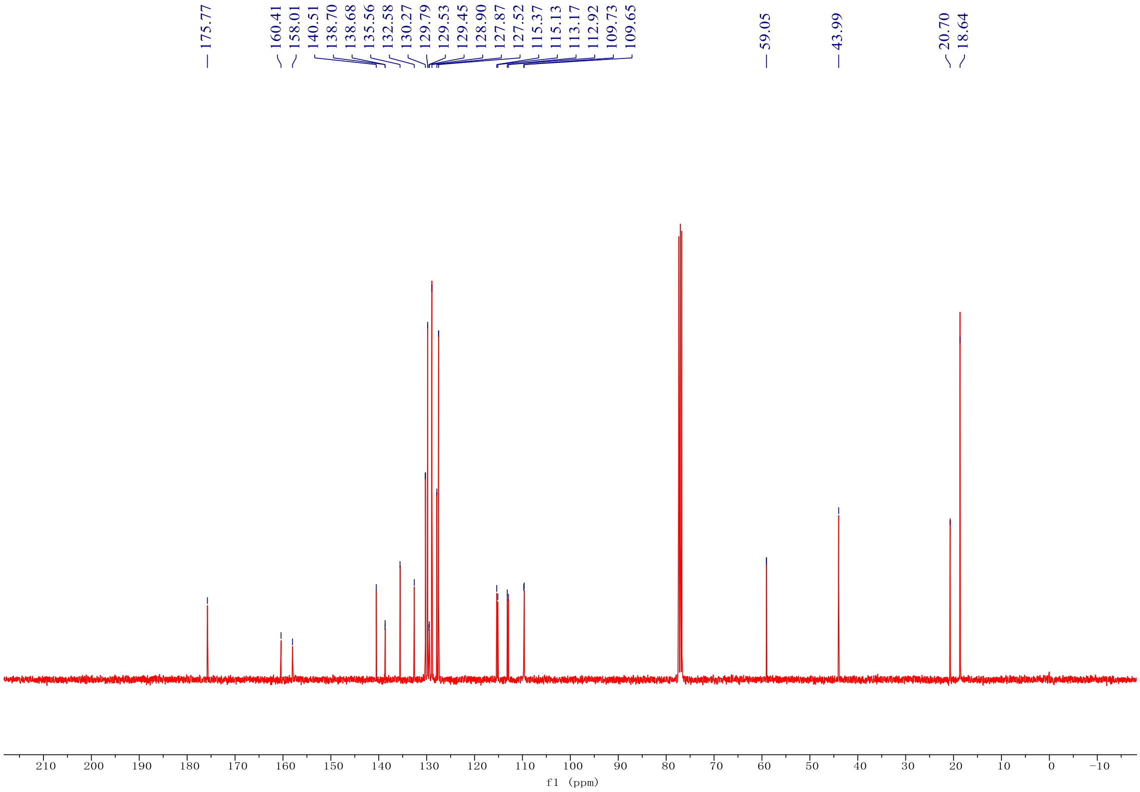
1.01
6.03
3.01
f1 (ppm)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128.90
127.87
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109.65
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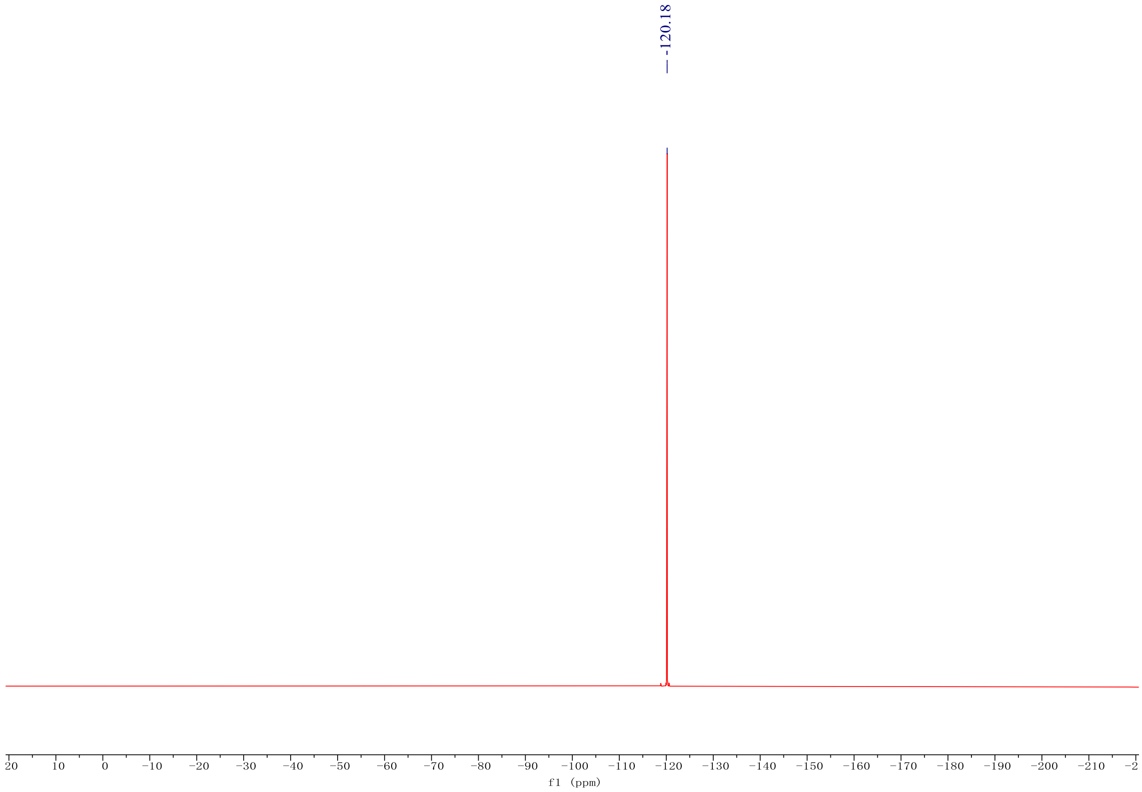
43.99
20.70
18.64
f1 (ppm)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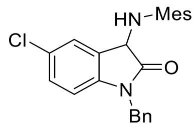
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Mes
Cl
O
N
Bn

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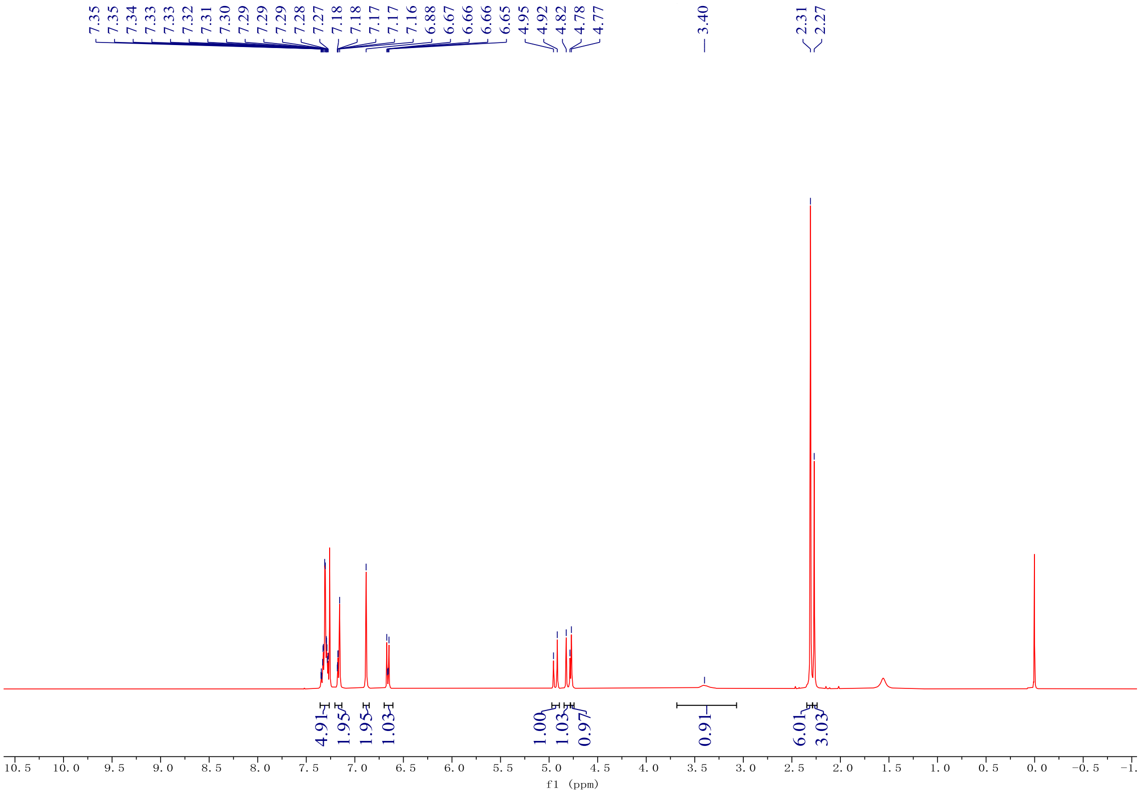
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6.66
6.65
4.95
4.92
4.82
4.78
4.77
3.40
2.31
2.27
4.91
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1.95
1.03
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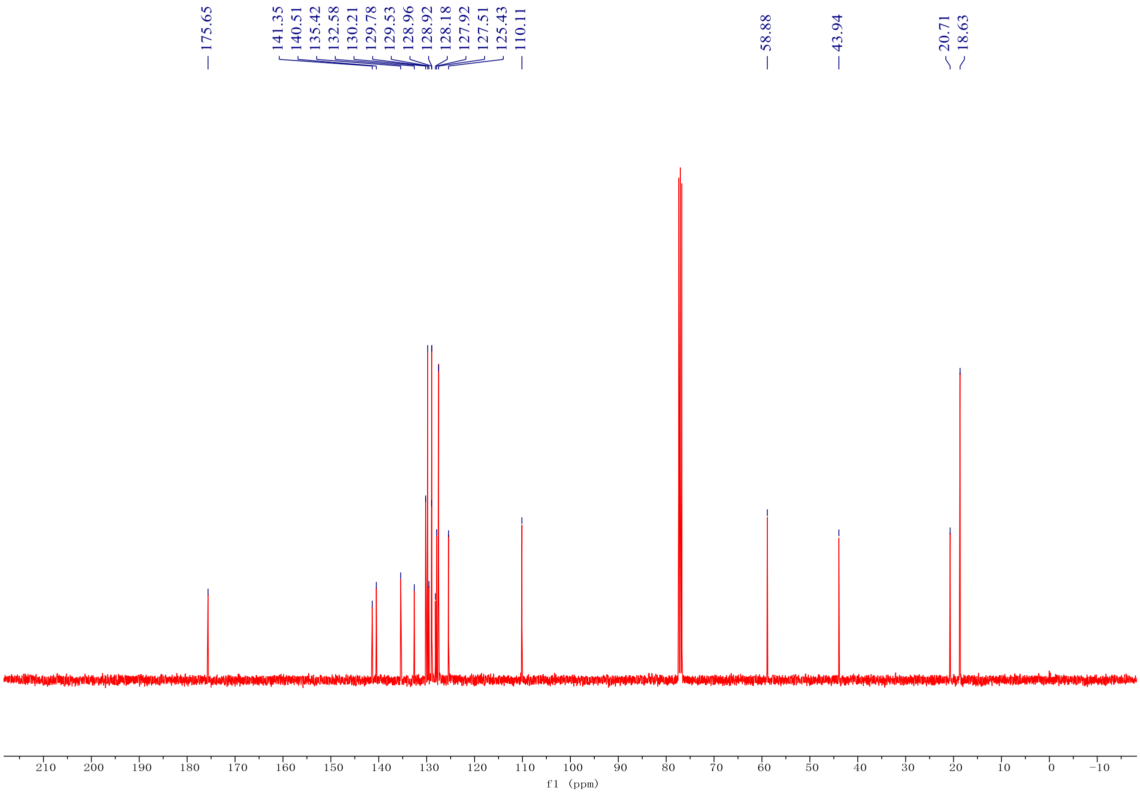
1.03
0.97
0.91
6.01
3.03
f1 (ppm)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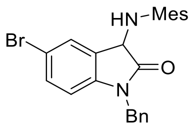
18.63
f1 (ppm)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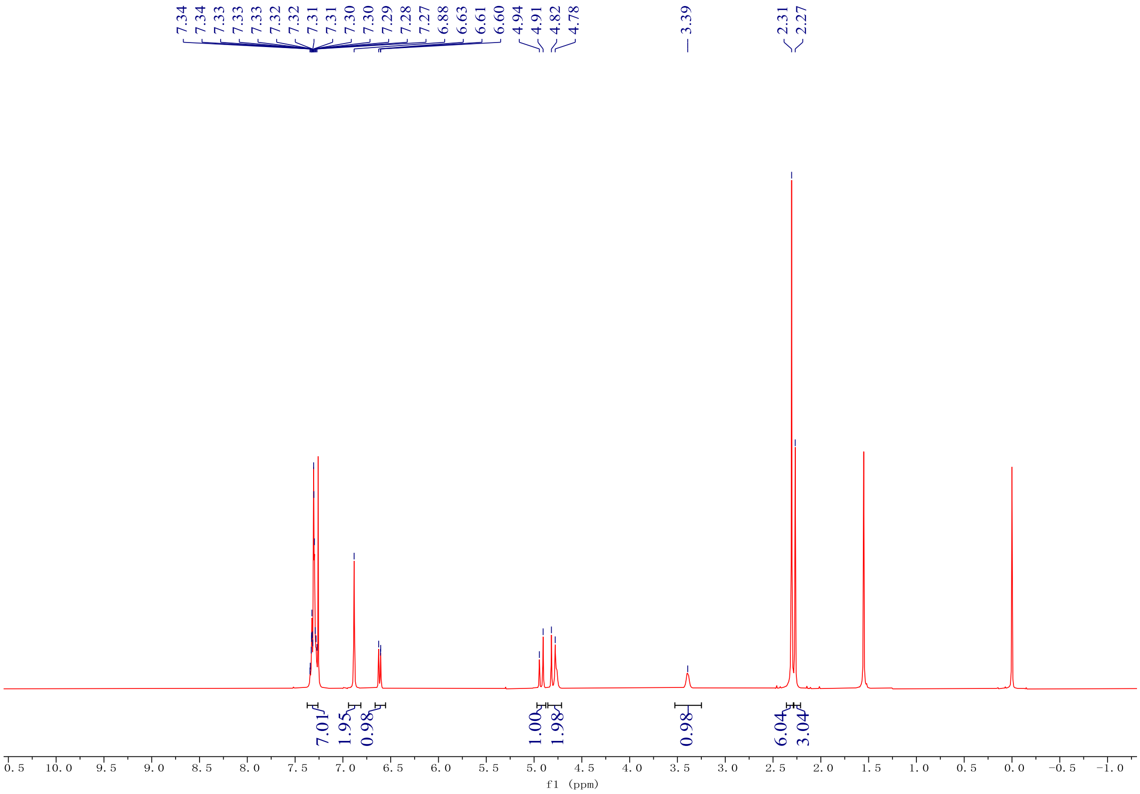
Mes
Br
O
N
Bn

3ab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6.63
6.61
6.60
4.94
4.91
4.82
4.78
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1.00
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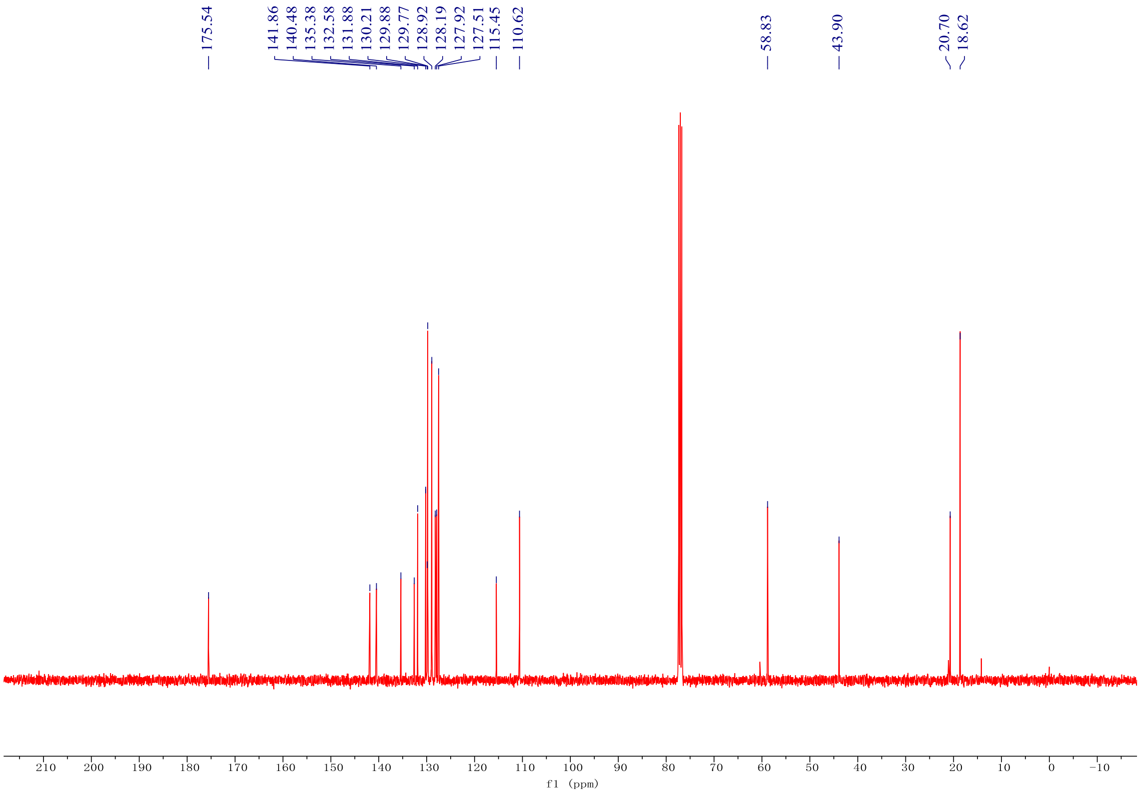
3.04
f1 (ppm)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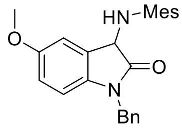
18.62
f1 (ppm)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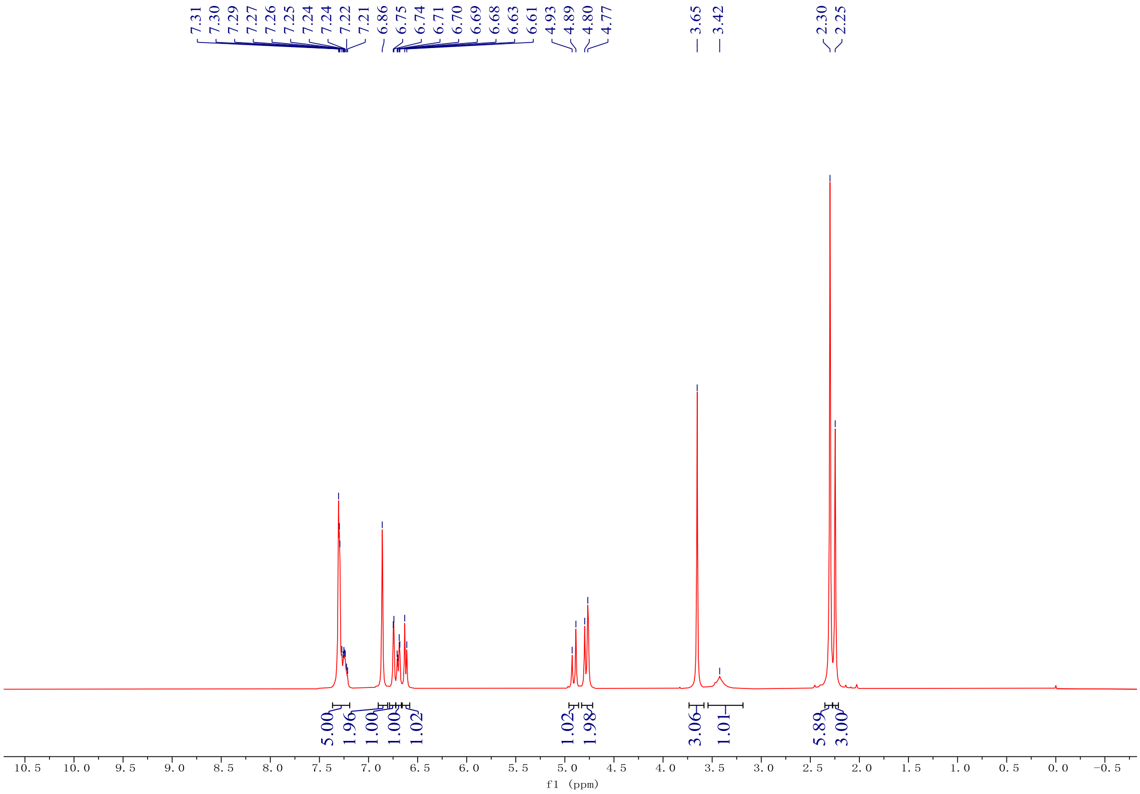
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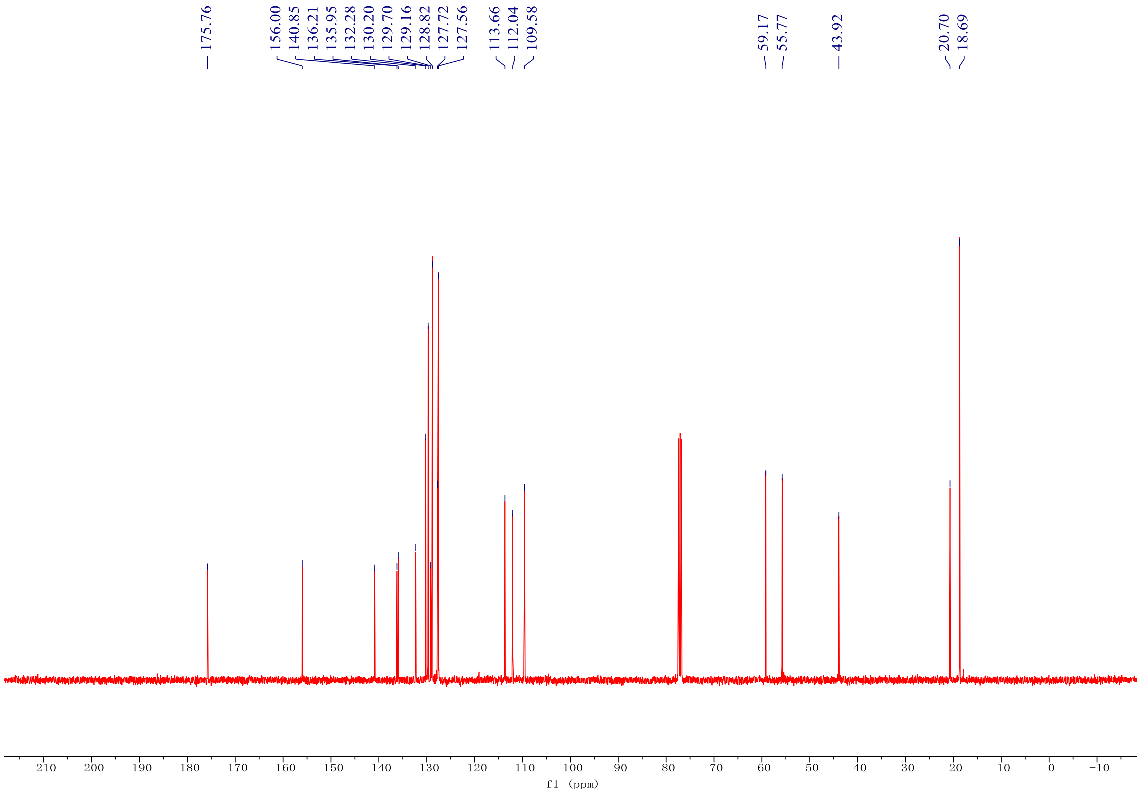
6.70
6.69
6.68
6.63
6.61
4.93
4.89
4.80
4.77
3.65
3.42
2.30
2.25
5.00
1.96
1.00
1.00
1.02
1.02
1.98
3.06
1.01
5.89
3.00
f1 (ppm)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136.21
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132.28
130.20
129.70
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128.82
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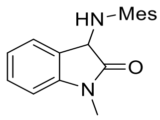
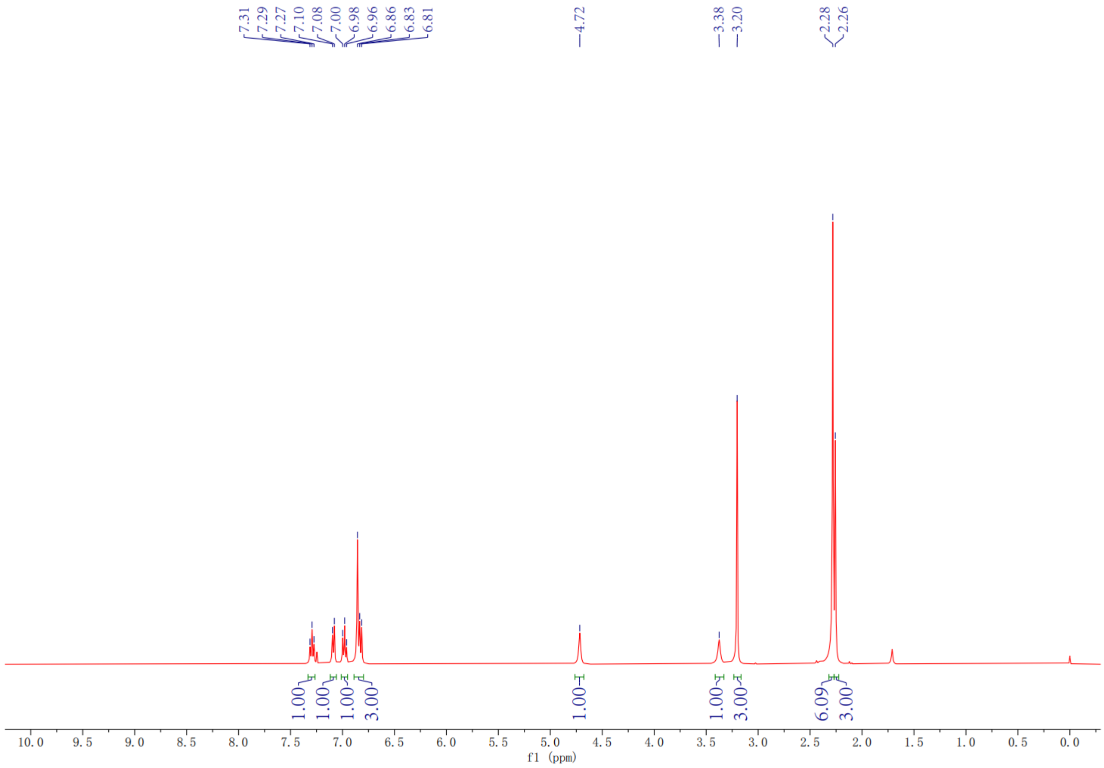
113.66
112.04
109.58
59.17
55.77
43.92
20.70
18.69
f1 (ppm)


HN
Mes
N
O

3ad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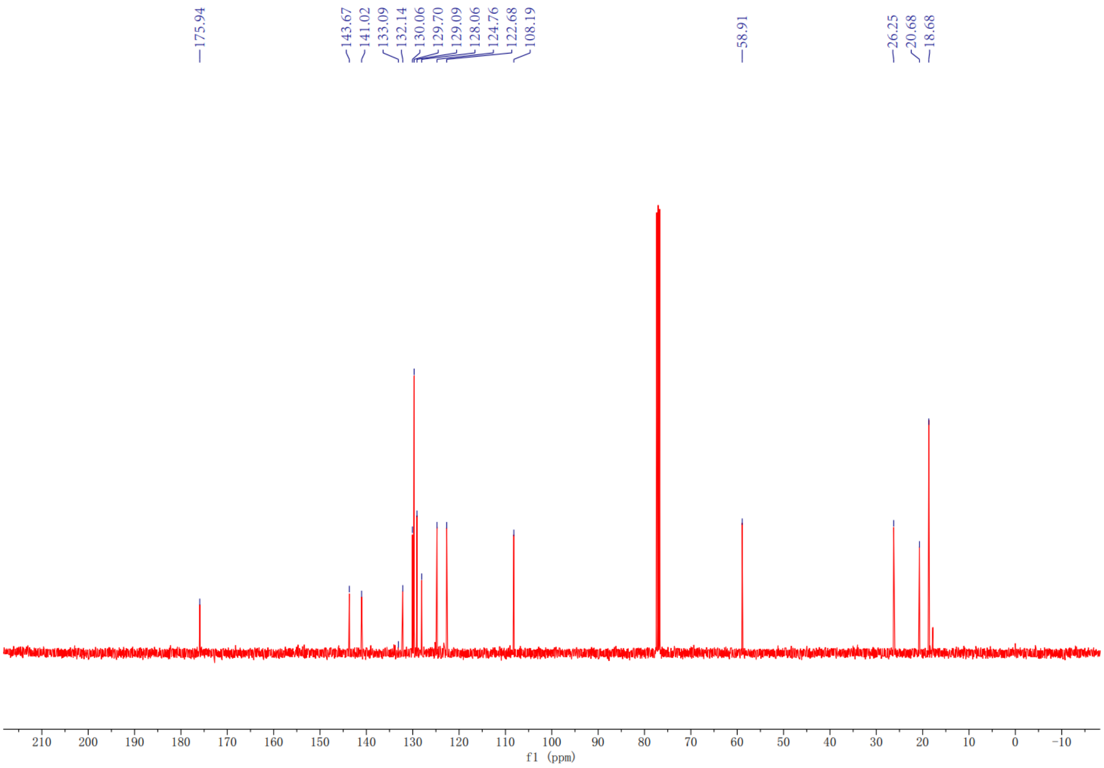
6.83
6.81
4.72
3.38
3.20
2.28
2.26
1.00
1.00
1.00
3.00
1.00
1.00
3.00
6.09
3.00
f1 (ppm)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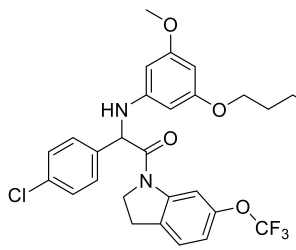
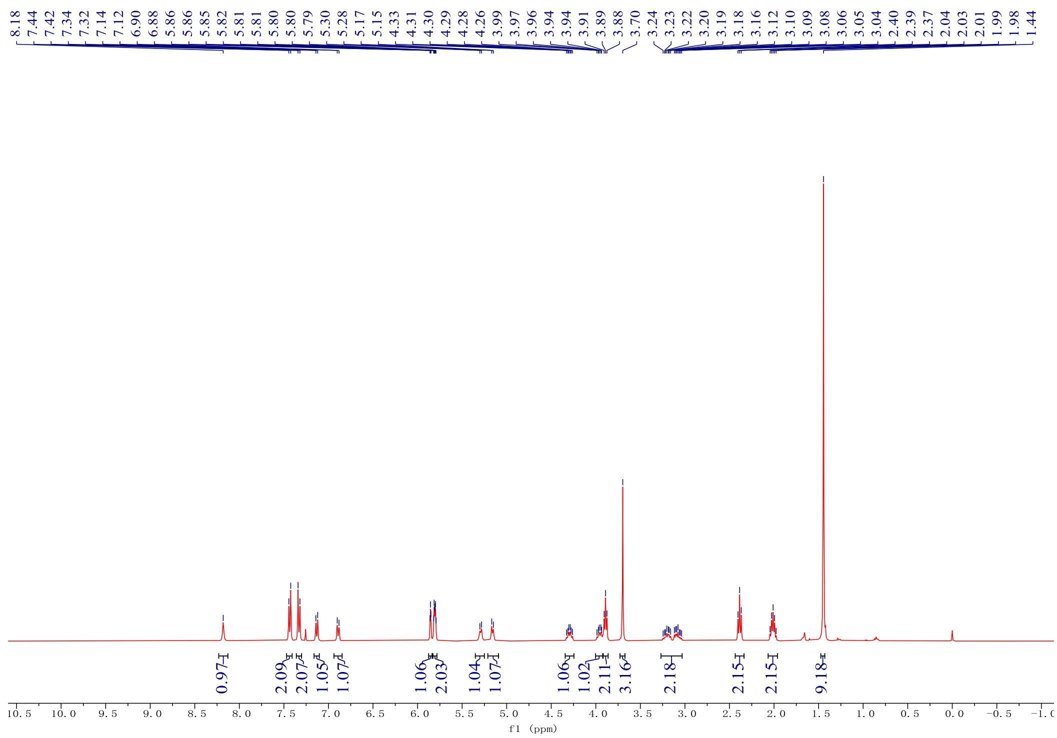
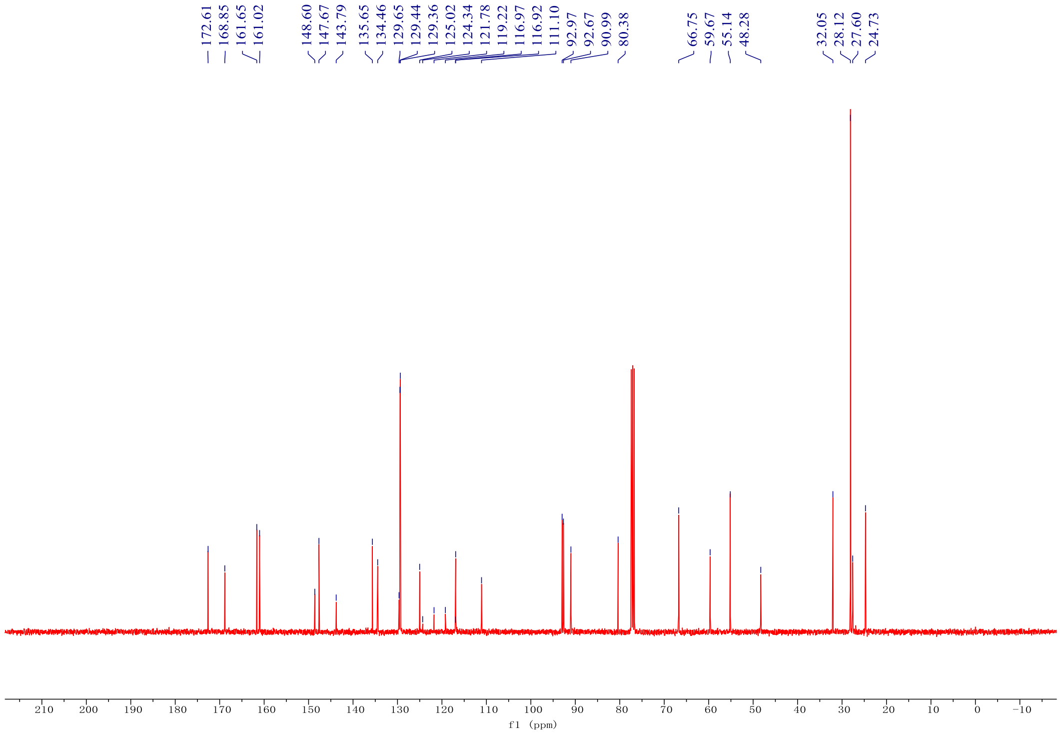
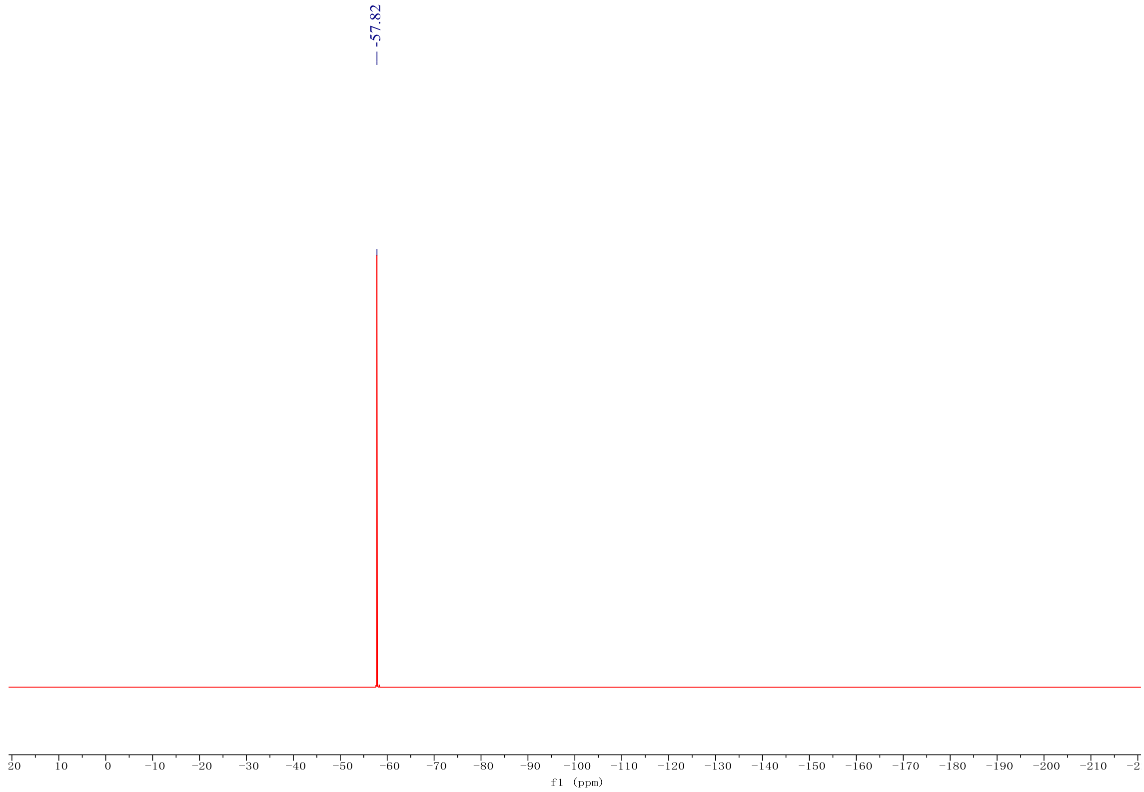
130.06
129.70
129.09
128.06
124.76
122.68
108.19
58.91
26.25
20.68
18.68
f1 (ppm)



5



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−140
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−160
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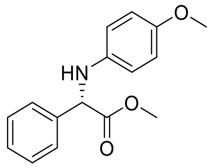
−180
−190
−200
−210
−2
f1 (ppm)

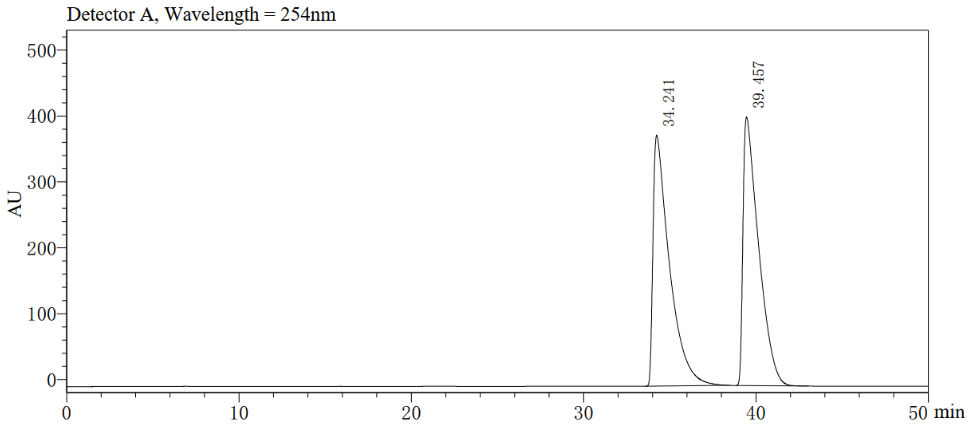
HPLC spectra



(*S*)-3a

[α]$^{25}_{D}$ = +78.9 (c = 0.1 in $CHCl_3$).

HPLC analysis (Chiralcel ID; 30 °C, IPA/Hexane = 10/90, 0.5 mL/min, 254 nm), Rt_1 (minor) = 34.4 min, Rt_2 (major) =39.0 min; 74:26 er.



	RT	Area	%Height	%Area
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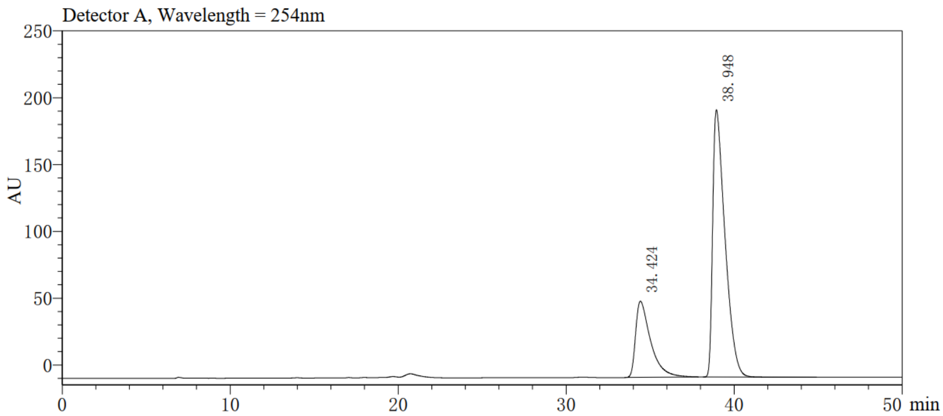
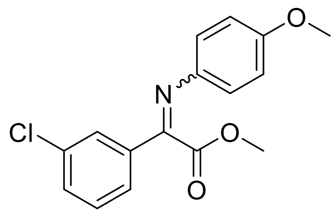
2	39. 457	25619315	51. 691	50. 269
		50964481	100. 000	100. 000



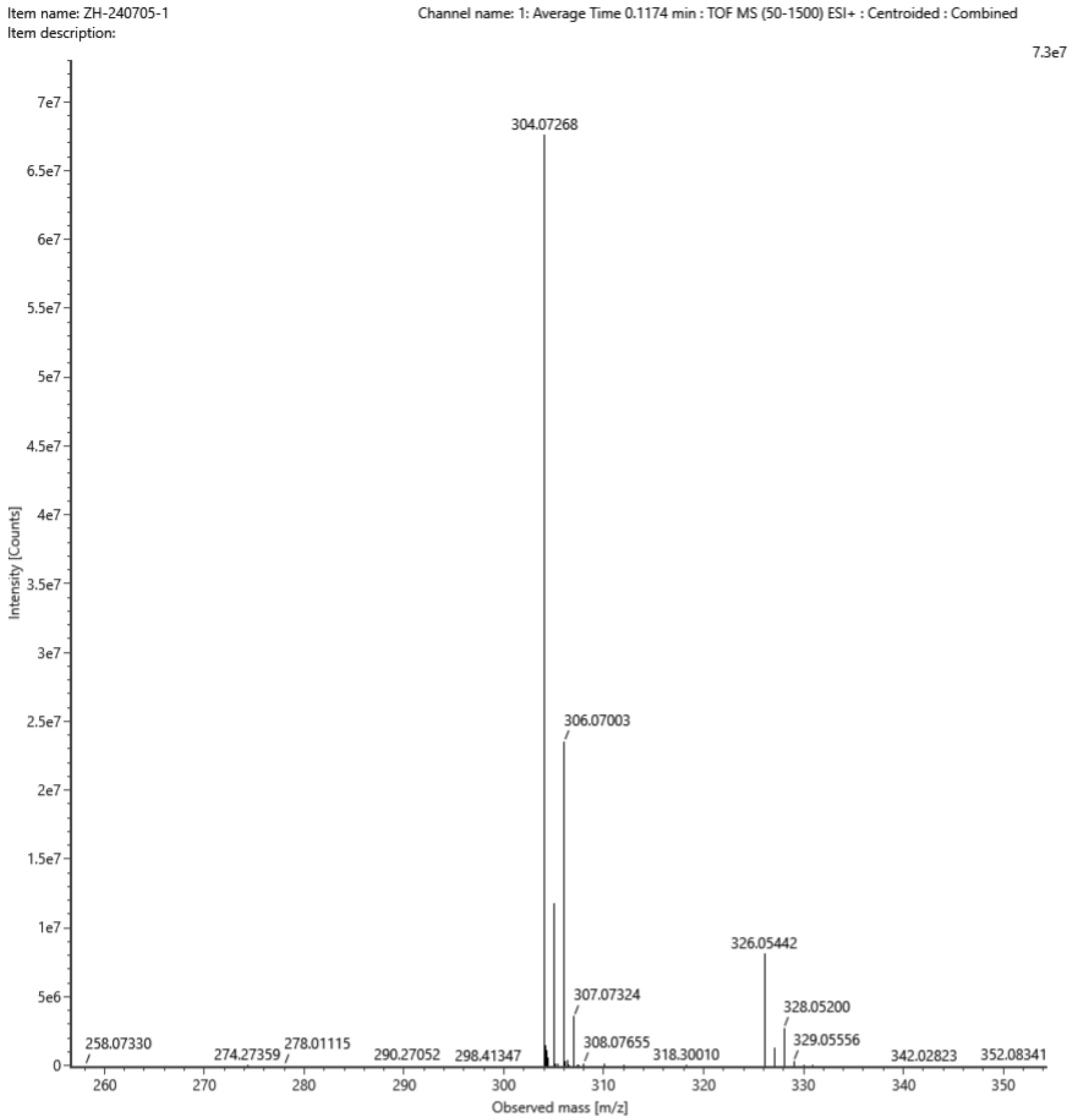
	RT	Area	%Height	%Area
1	34. 424	3550128	22. 215	25. 833
2	38. 948	10192341	77. 785	74. 167
		13742470	100. 000	100. 000

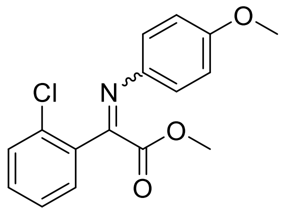
High resolution mass spectra



1h

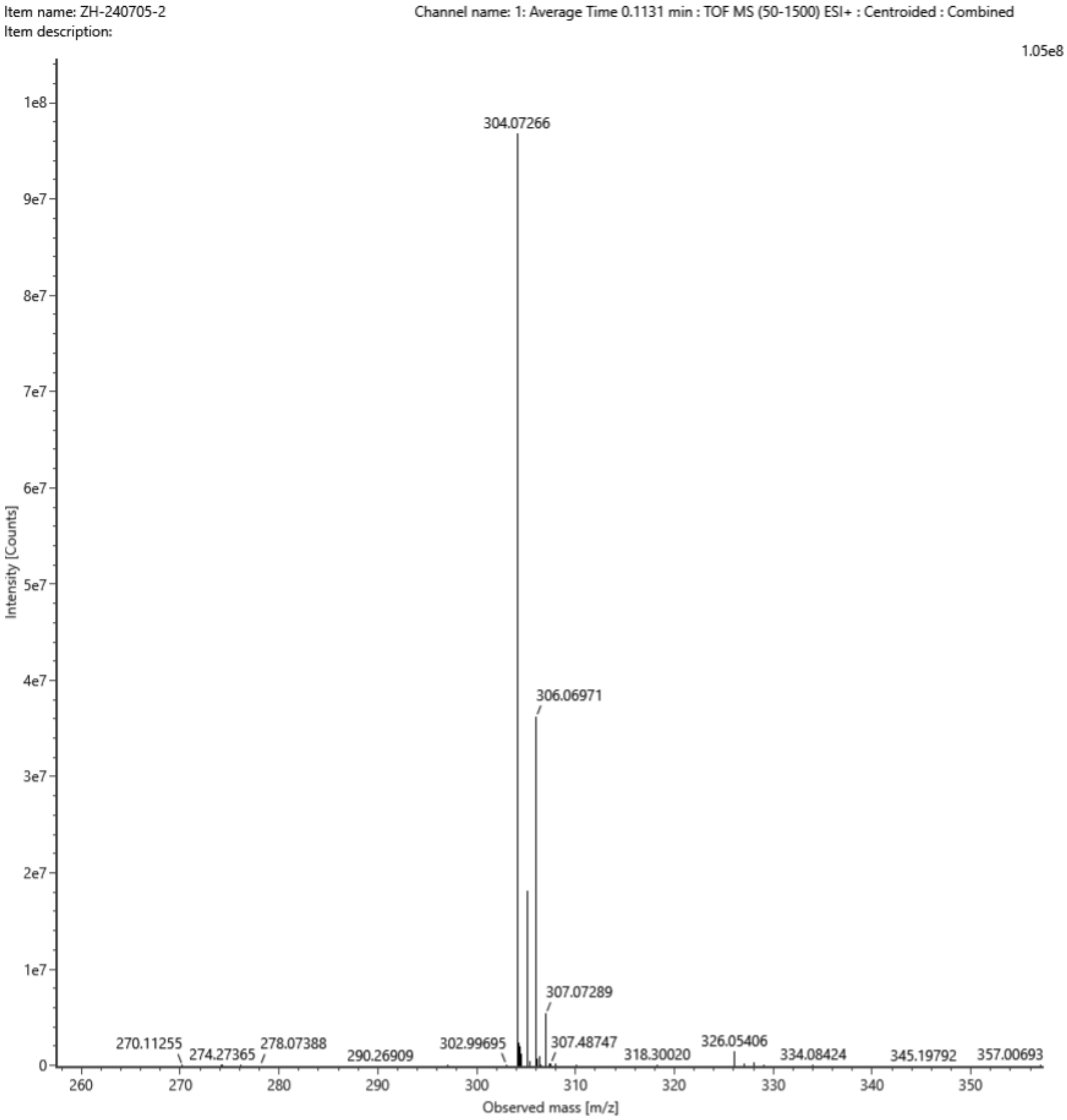
Composition	i-FIT(%)	Exact Mass	Found	Error (ppm)
$C_{16}H_{14}ClNO_3H^+$	100.000000	304.0735	304.0727	-2.6300

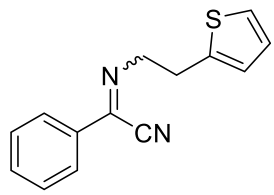




1K

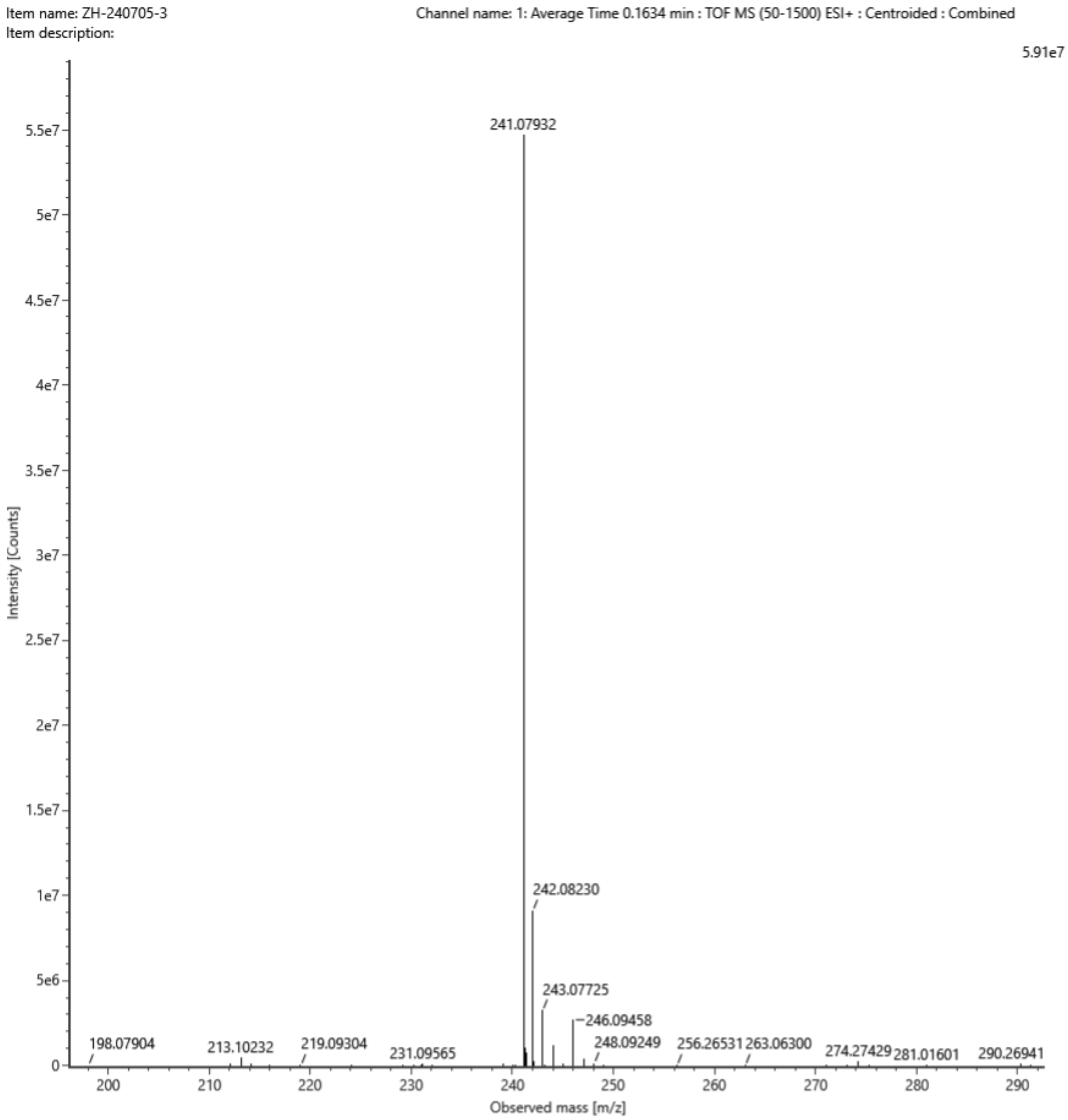
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{16}H_{14}ClNO_3H^+$	100.000000	304.0735	304.0727	-2.6300

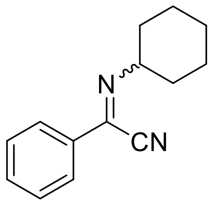




1w

Composition	**i-FIT(%)**	**Exact Mass**	**Found**	**Error (PPM)**
$C_{14}H_{12}N_2SH^+$	100.000000	241.0794	241.0793	-0.4148



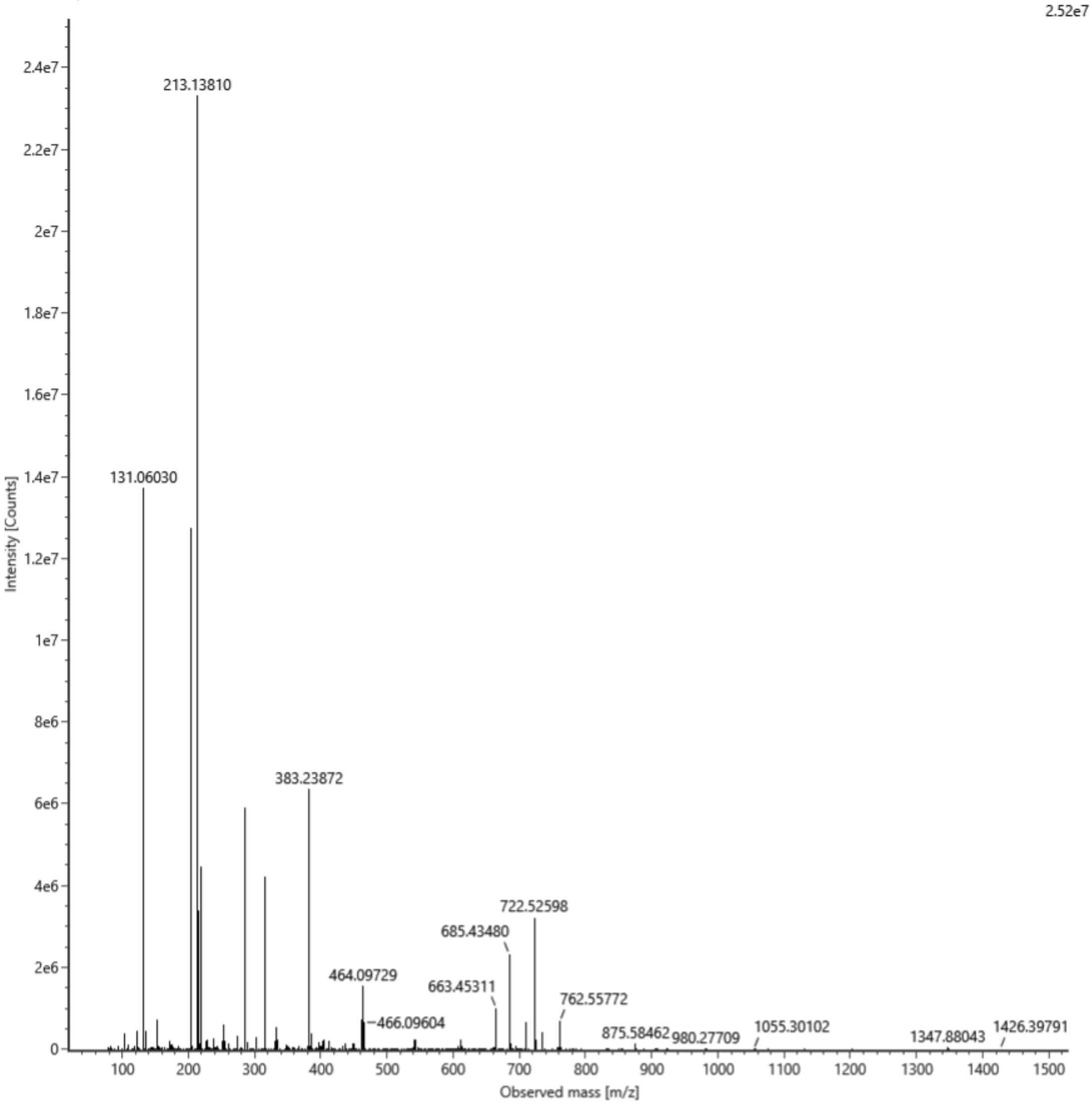


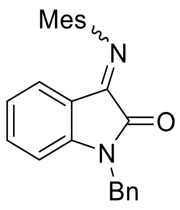
1x

Composition	**i-FIT(%)**	**Exact Mass**	**Found**	**Error (PPM)**
$C_{14}H_{16}N_2H^+$	100.000000	213.1386	231.1381	-2.1632

Item name: ZH-240912-3
Item description:

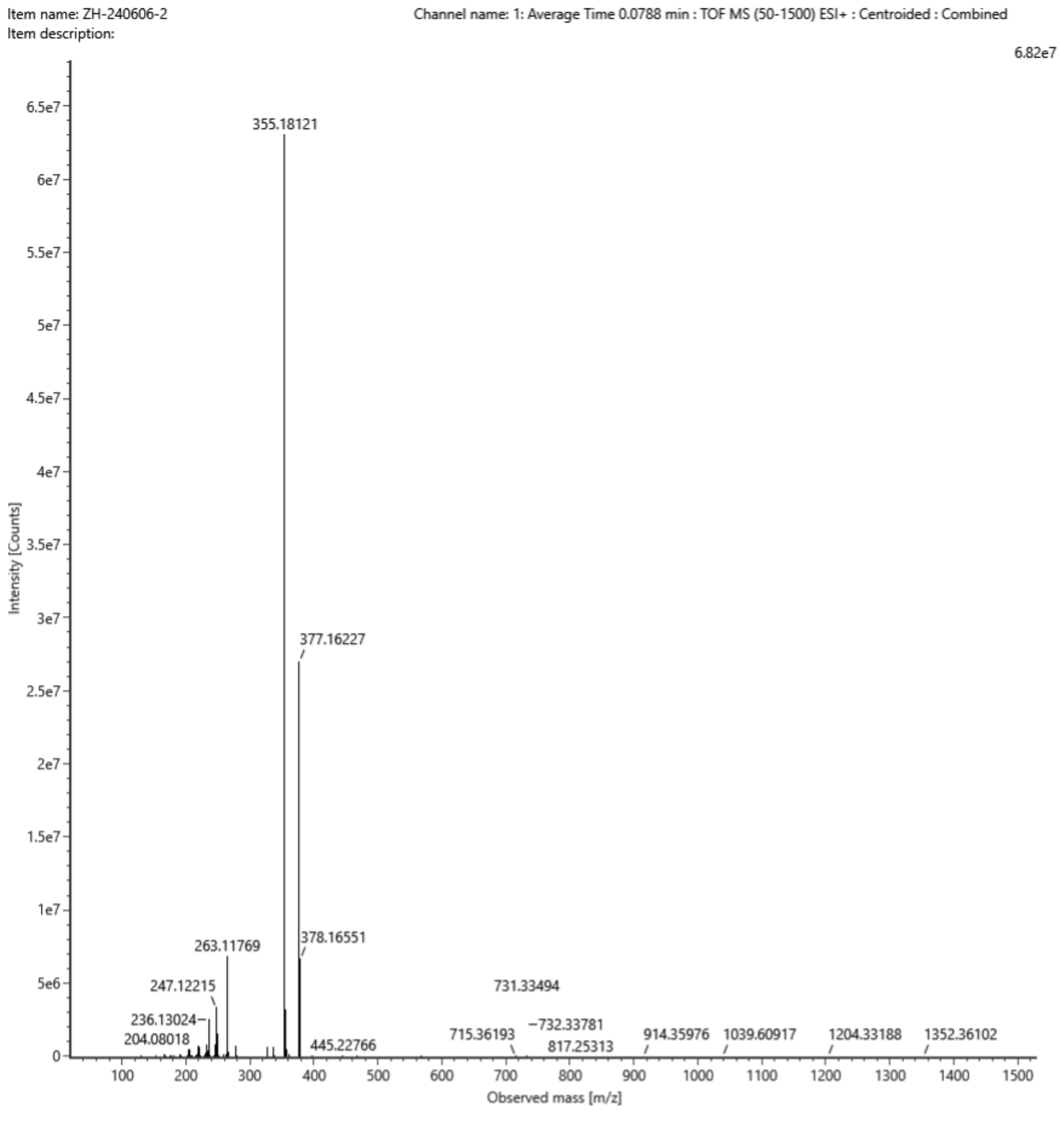
Channel name: 1: Average Time 0.1977 min : TOF MS (50-1500) ESI+ : Centroided : Combined

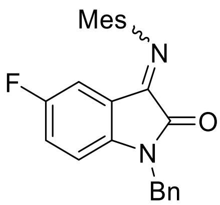




1y

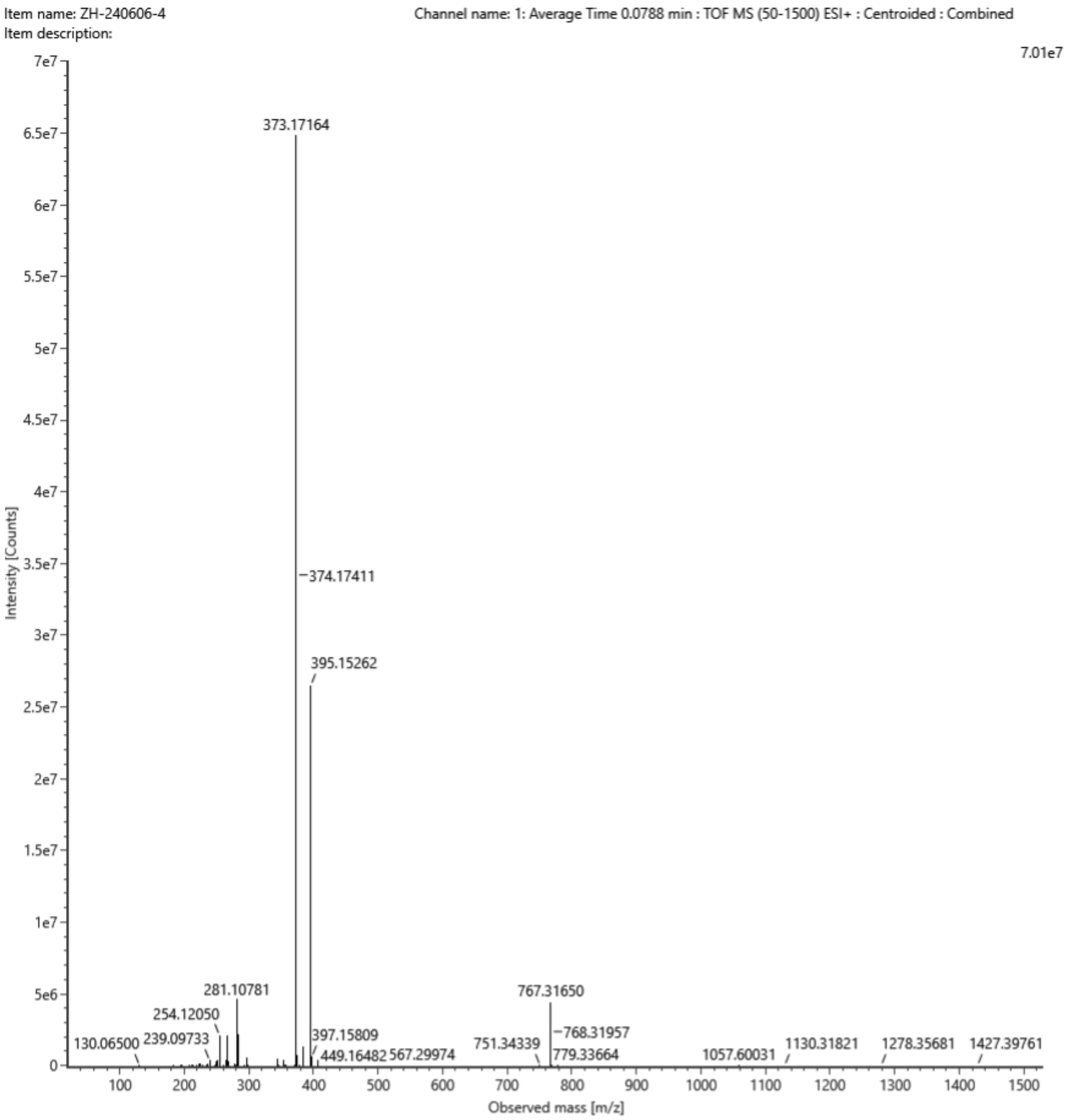
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{24}H_{22}N_2OH^+$	100.000000	355.1805	355.1812	1.9708

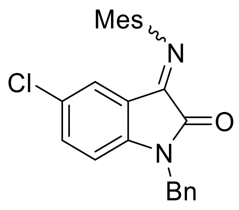




1z

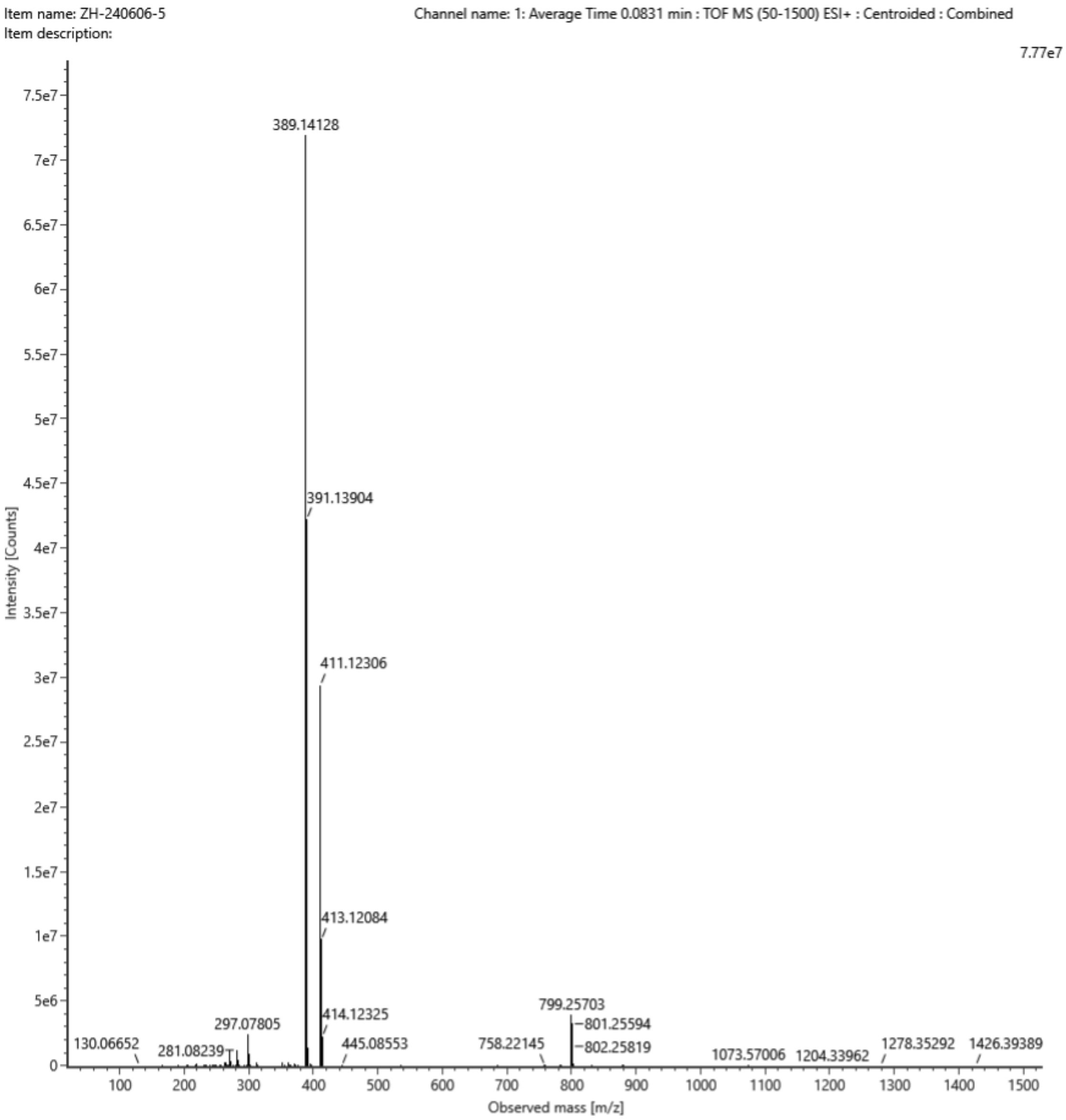
Composition	**i-FIT(%)**	**Exact Mass**	**Found**	**Error (PPM)**
$C_{24}H_{21}FN_2OH^+$	100.000000	373.1711	373.1716	1.3399

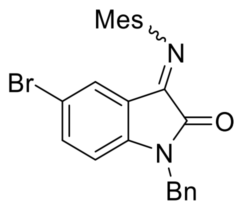




1aa

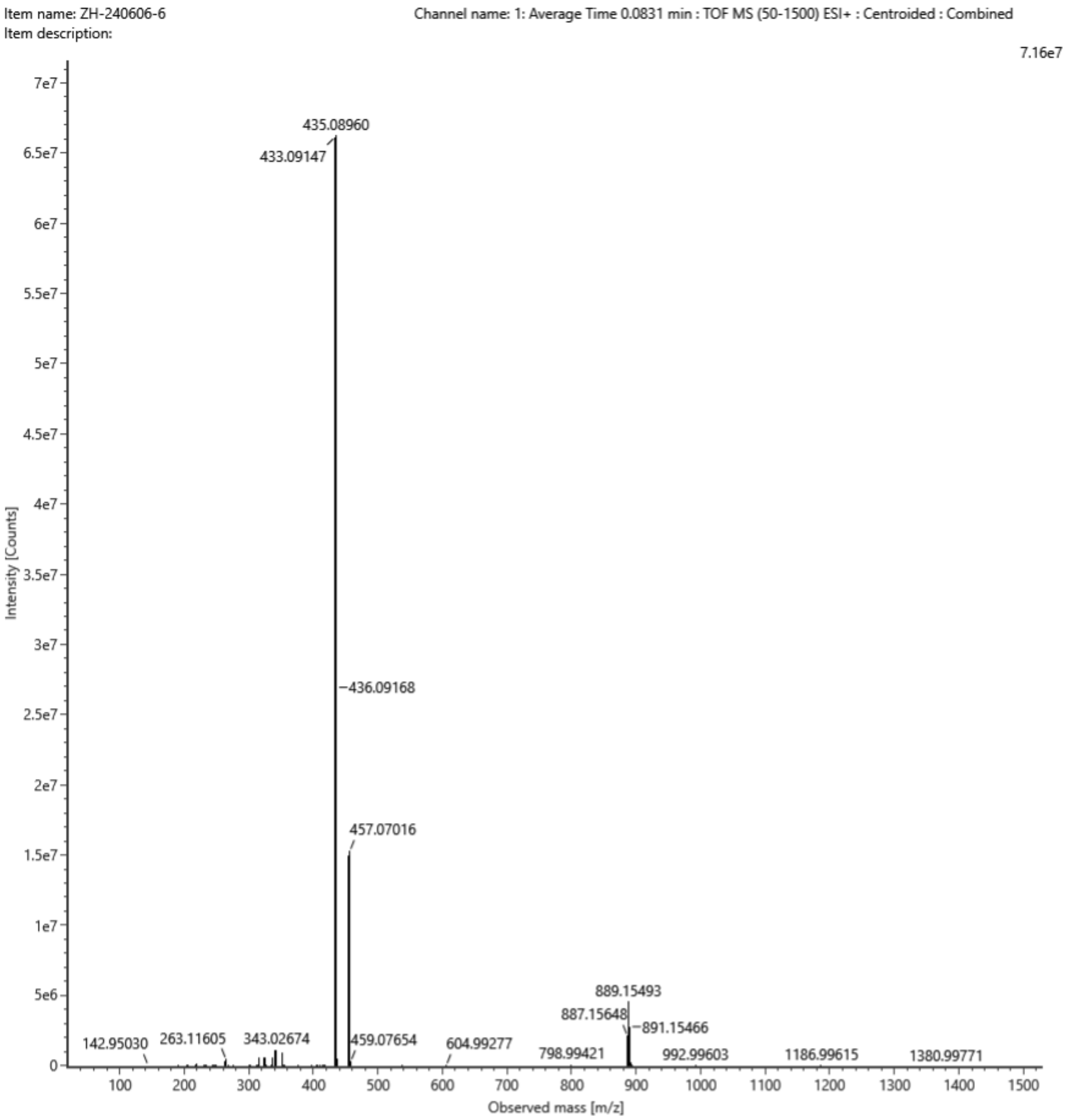
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{24}H_{21}ClN_2OH^+$	100.000000	389.1415	389.1413	-0.5140

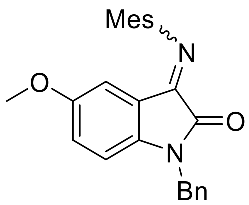




1ab

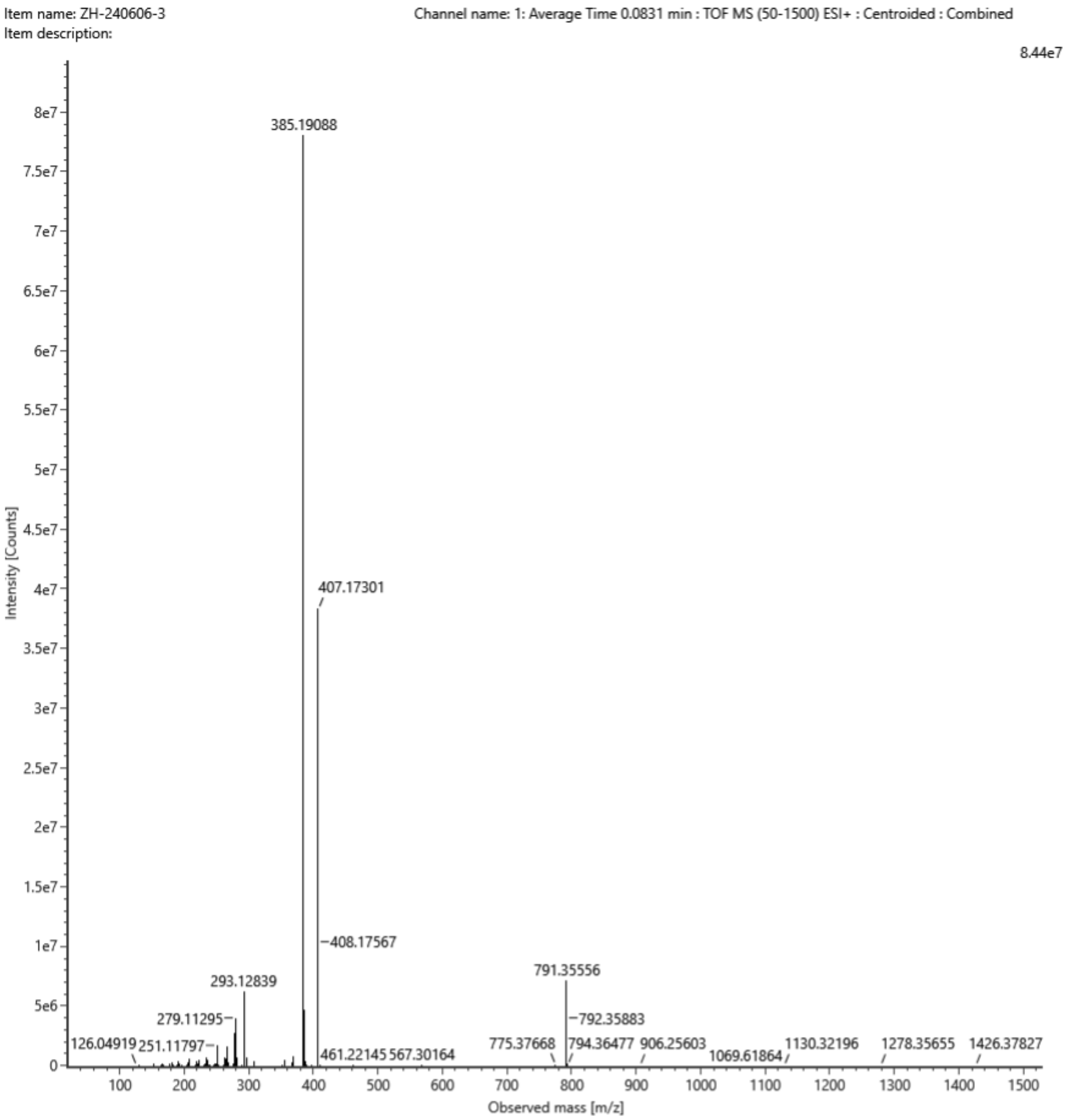
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{24}H_{21}BrN_2OH^+$	100.000000	433.0910	433.0915	1.1545

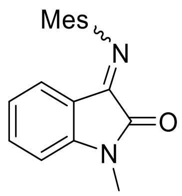




1ac

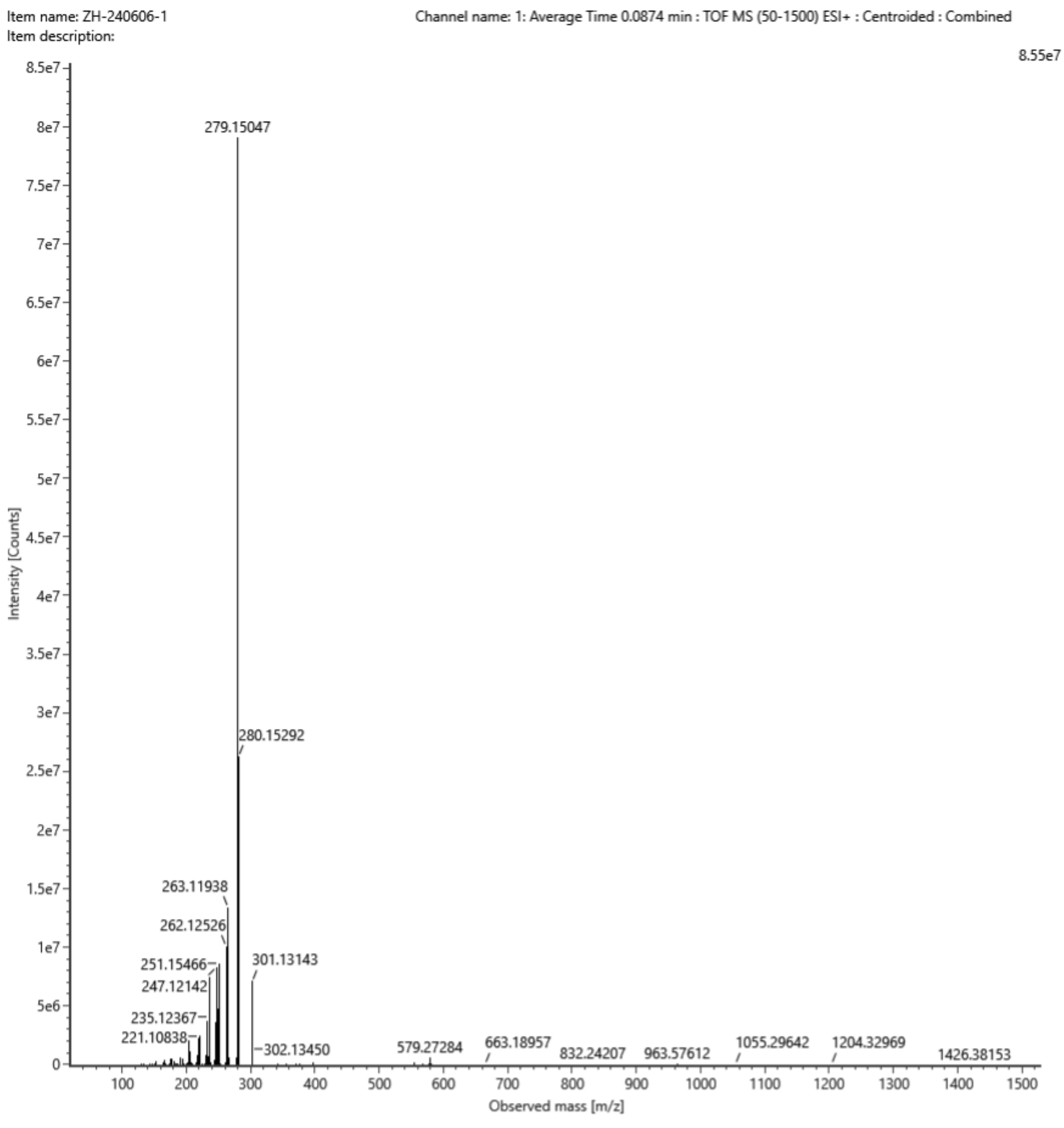
Composition	**i-FIT(%)**	**Exact Mass**	**Found**	**Error (PPM)**
$C_{25}H_{23}N_2O_2H^+$	100.000000	385.1911	385.1909	-0.5192

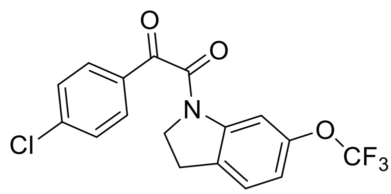




1ad

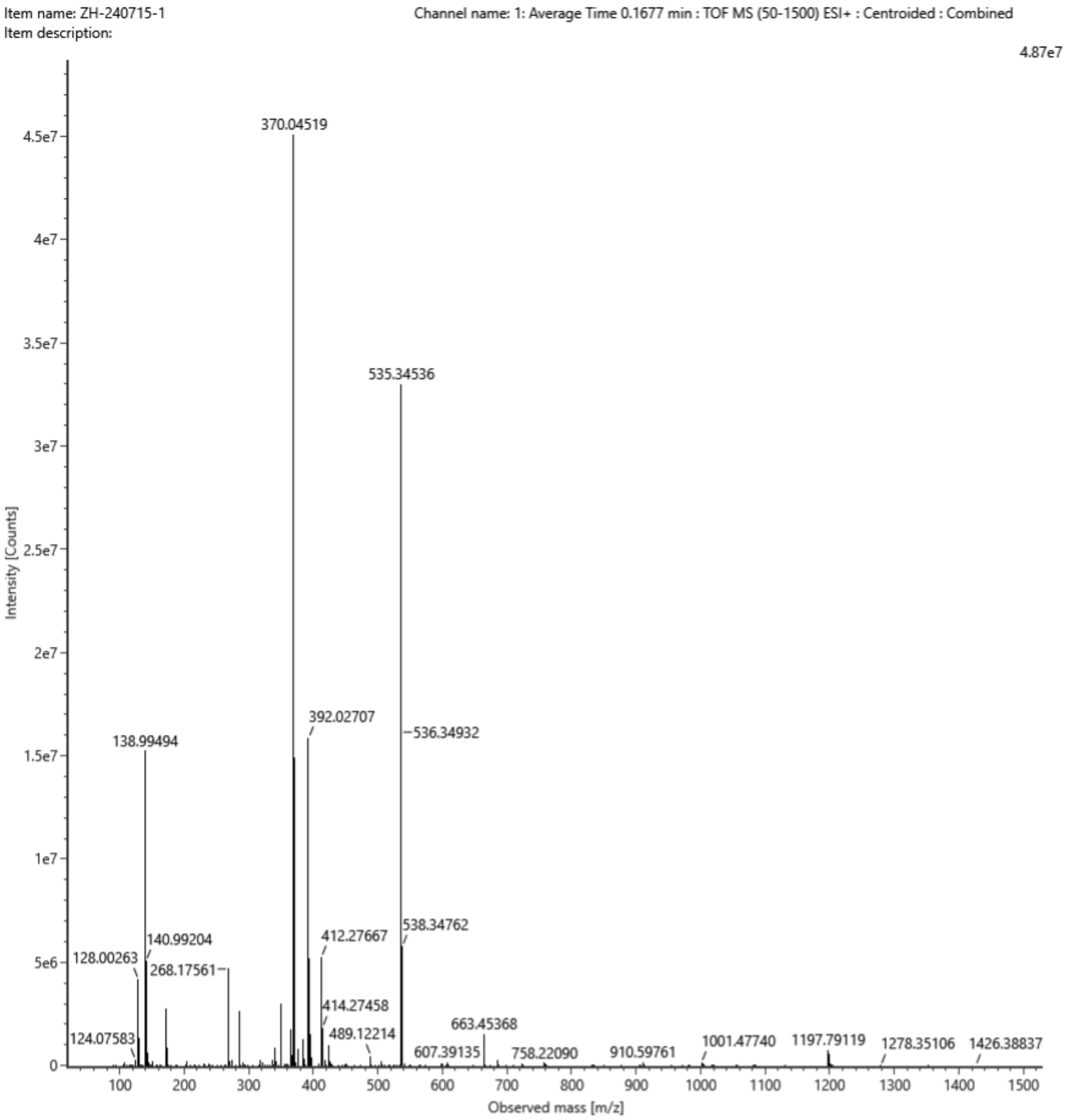
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{18}H_{18}N_2OH^+$	100.000000	279.1492	279.1505	4.6570

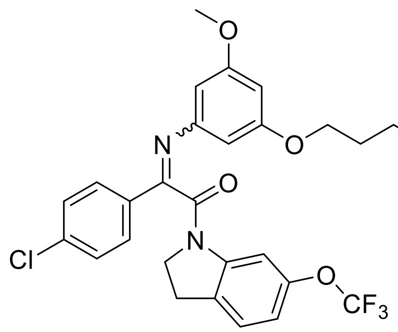




S2

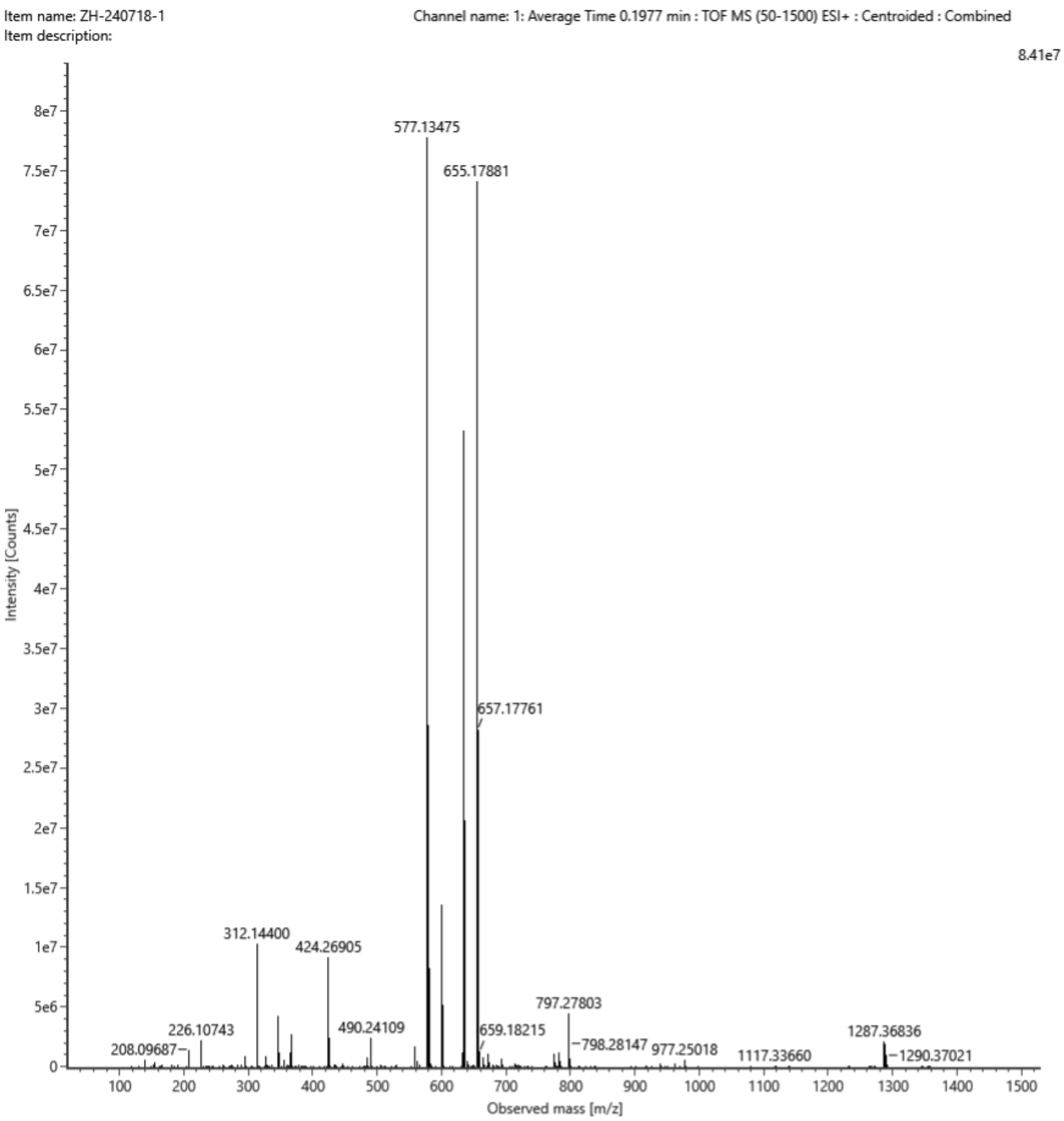
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{17}H_{11}ClF_3NO_3H^+$	100.000000	370.0452	370.0452	0.0000

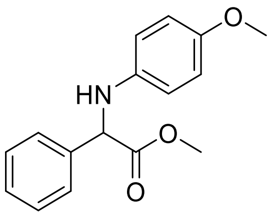




4

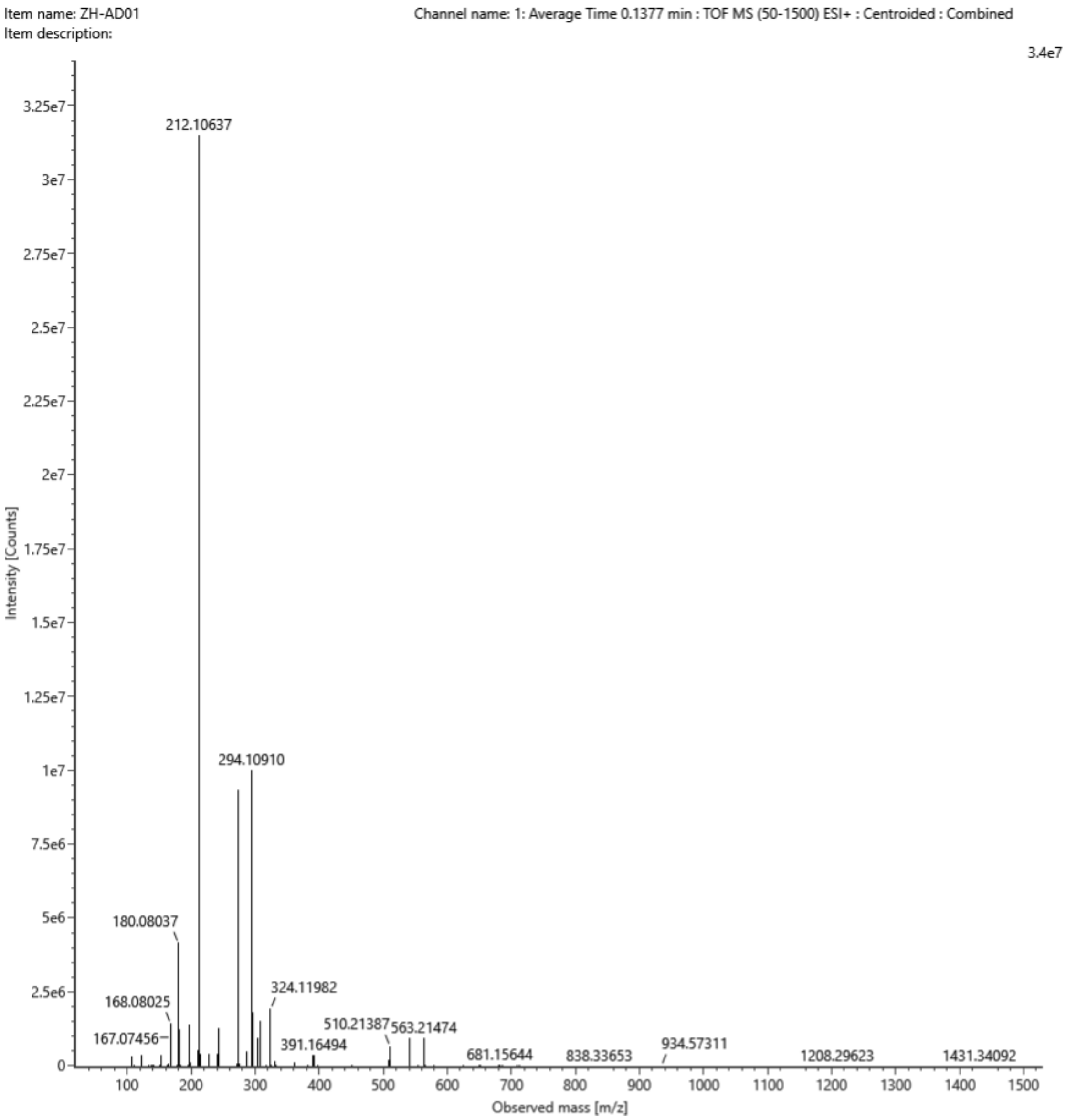
Composition	**i-FIT(%)**	**Exact Mass**	**Found**	**Error (PPM)**
$C_{32}H_{32}ClF_{3}N_{2}O_{6}Na^{+}$	100.000000	655.1793	655.1788	-0.7631

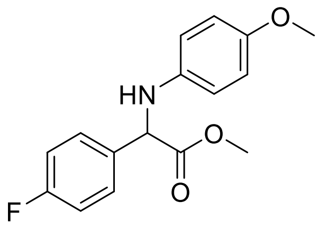




3a

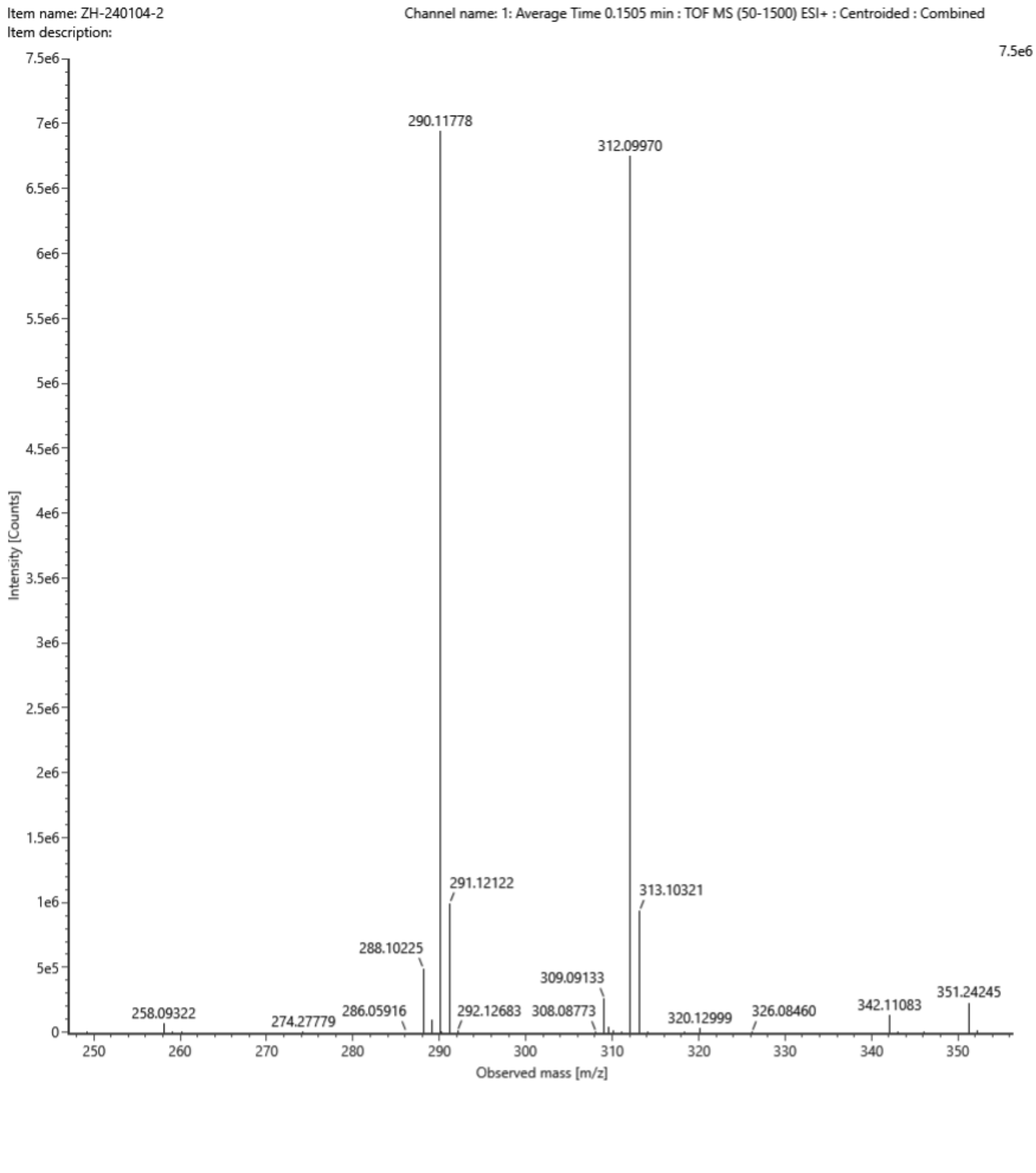
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{16}H_{17}NO_3Na^+$	100.000000	294.1101	294.1091	-3.4001

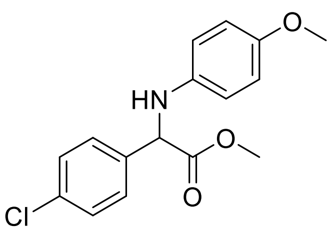




3b

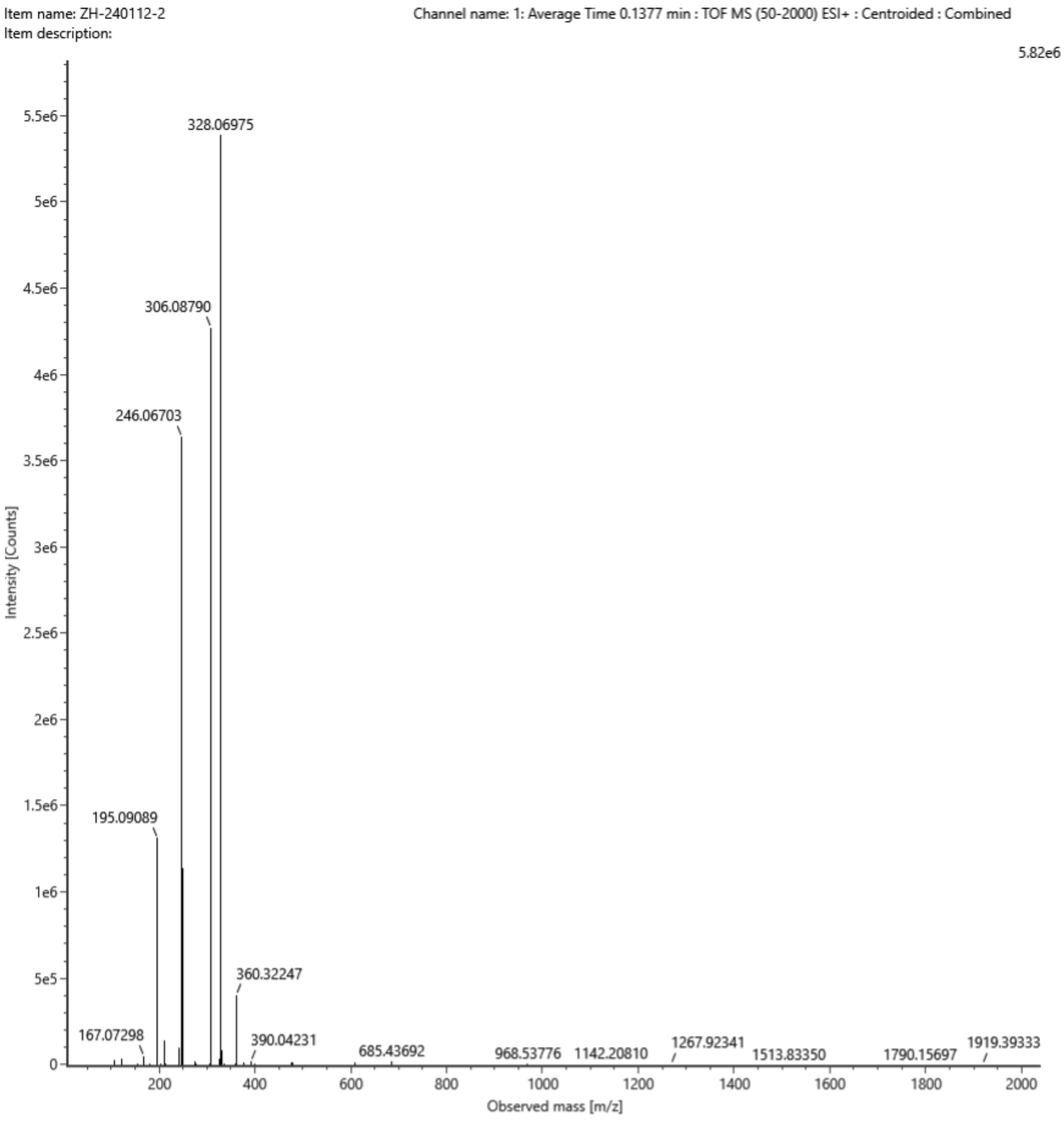
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{16}H_{16}FNO_3Na^+$	100.000000	312.1006	312.0997	-2.8837

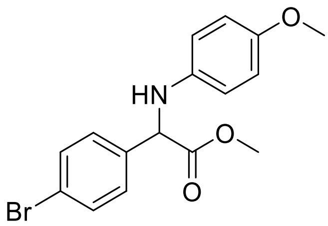




3c

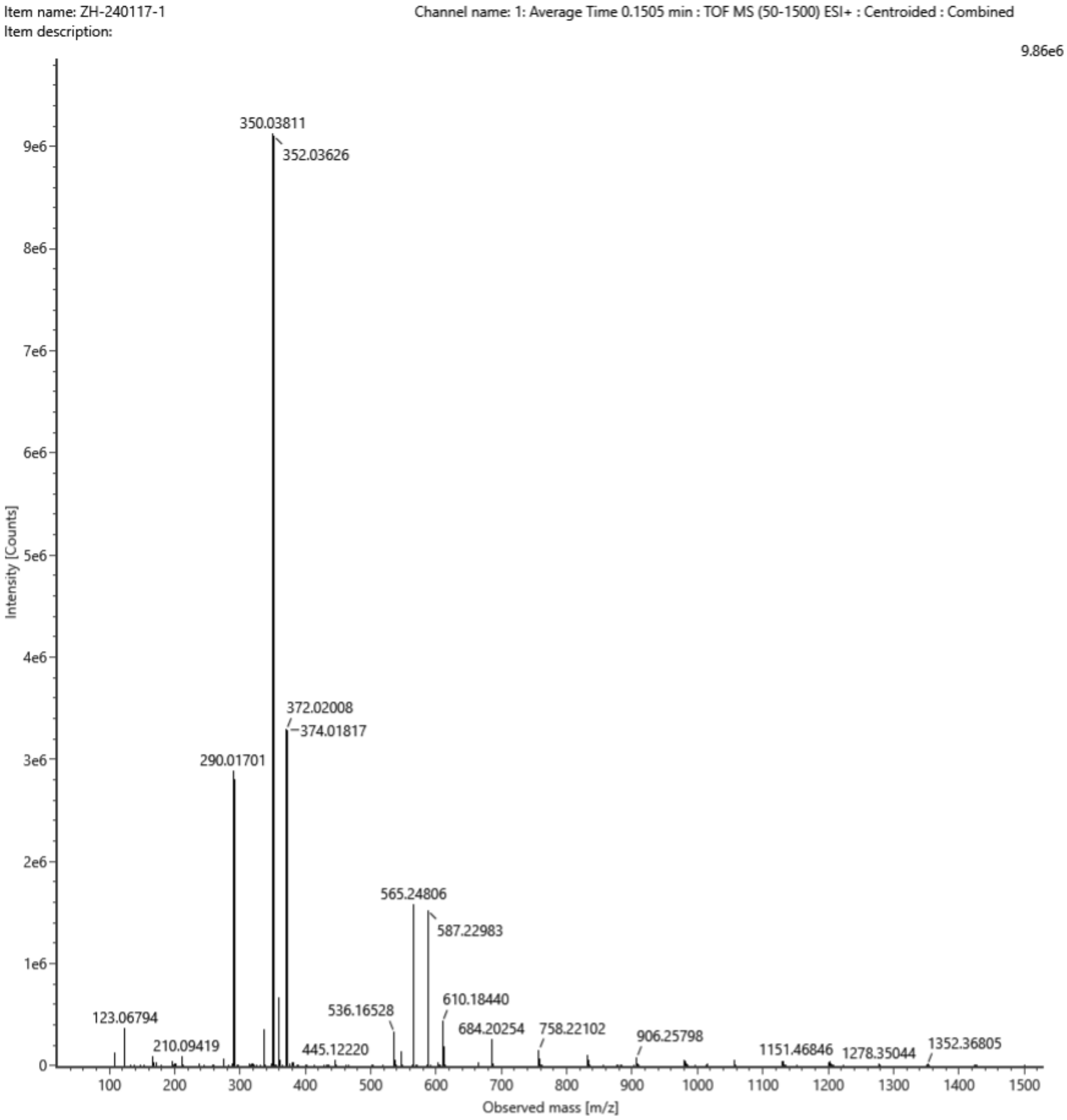
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{16}H_{16}ClNO_3Na^+$	100.000000	328.0711	328.0698	-3.9626

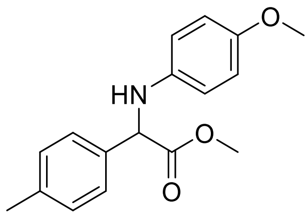




3d

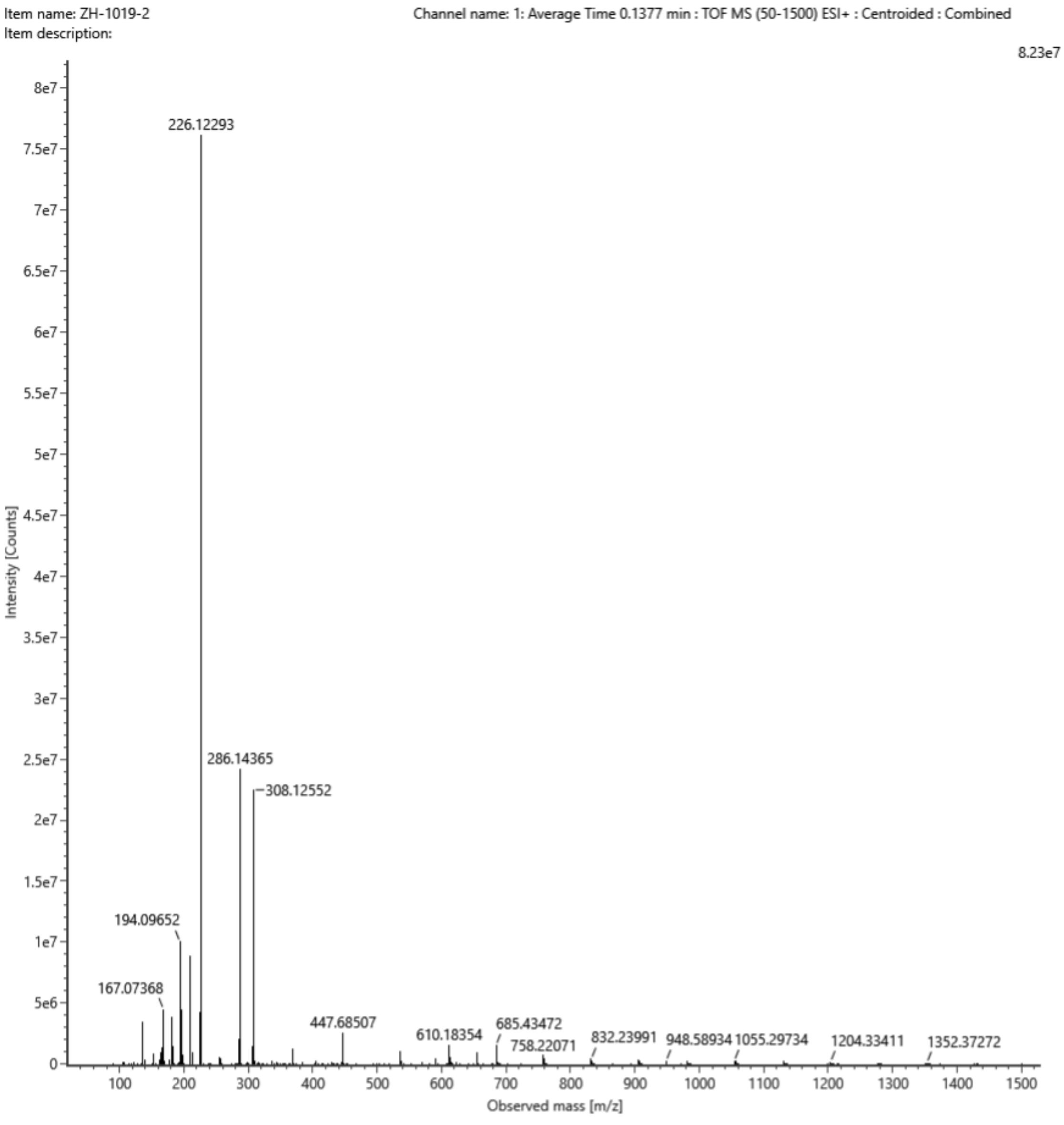
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{16}H_{16}BrNO_3Na^+$	100.000000	350.0386	350.0381	-1.4284

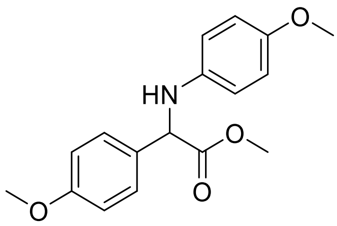




3e

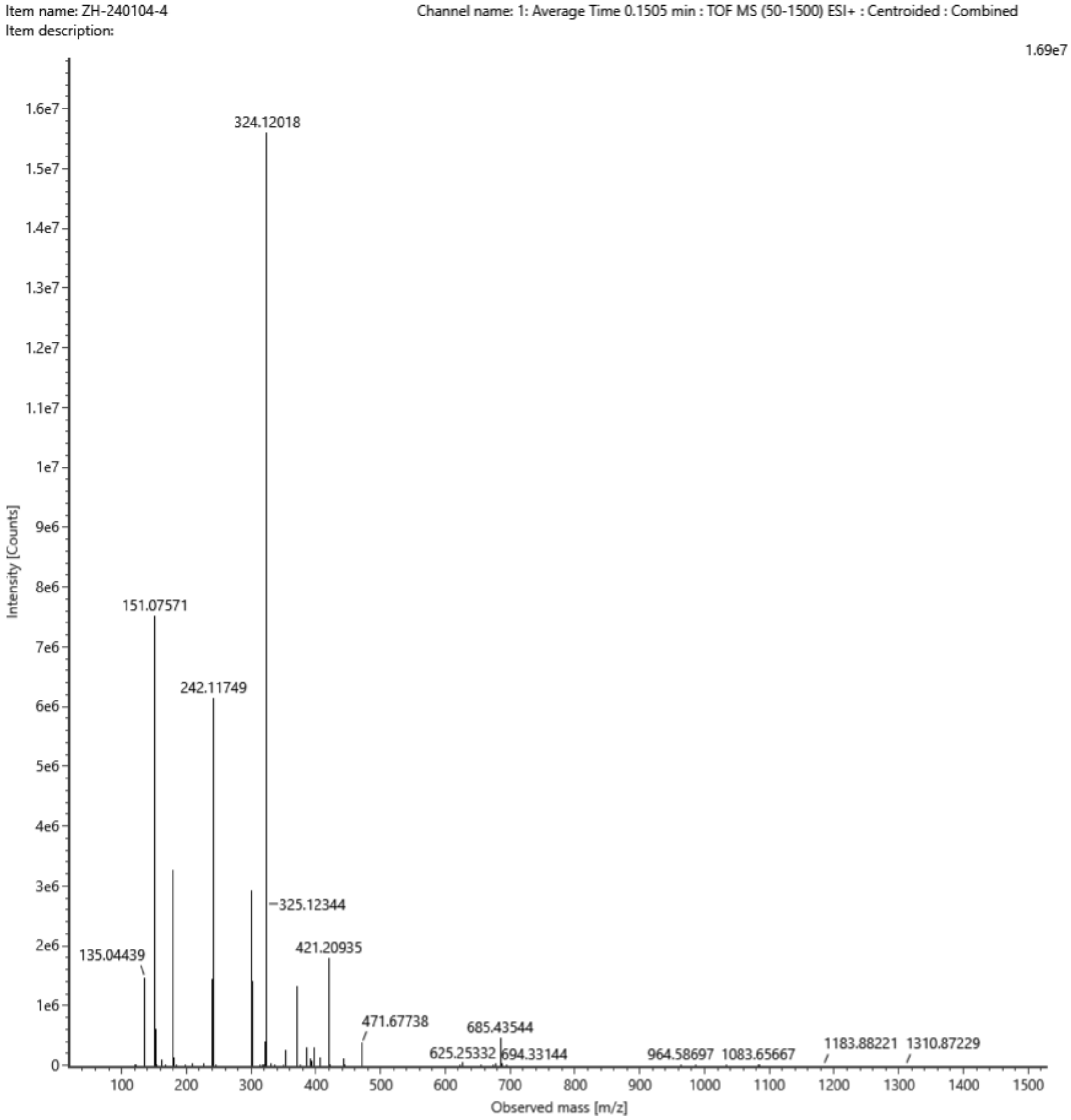
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{17}H_{19}NO_3Na^+$	100.000000	308.1258	308.1255	-0.9736

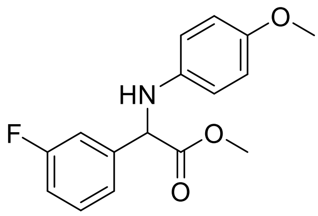




3f

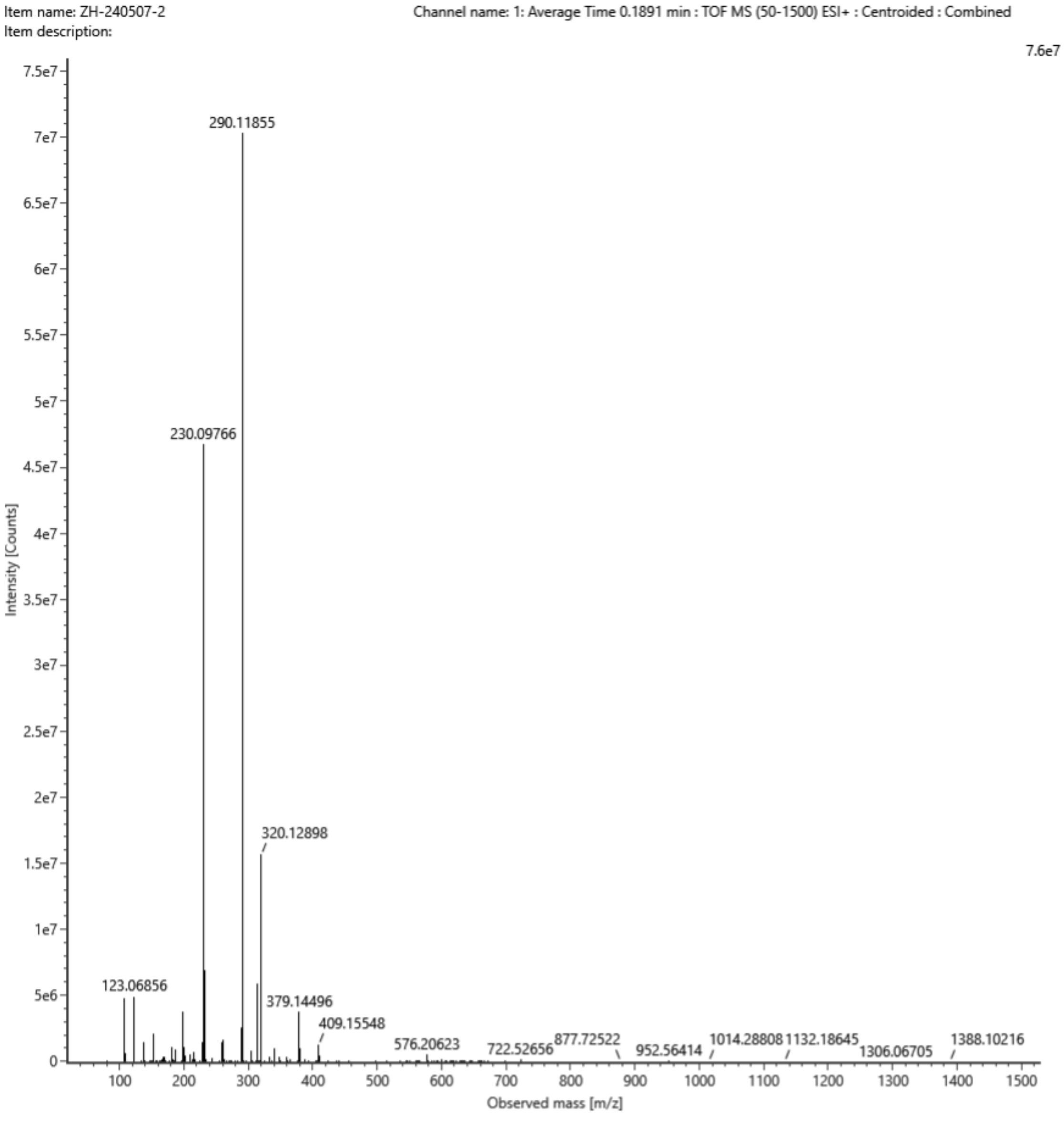
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{17}H_{19}NO_4Na^+$	100.000000	324.1206	324.1202	-1.2341

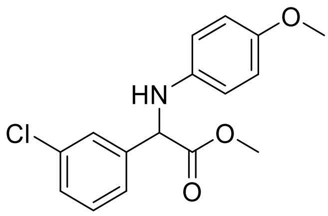




3g

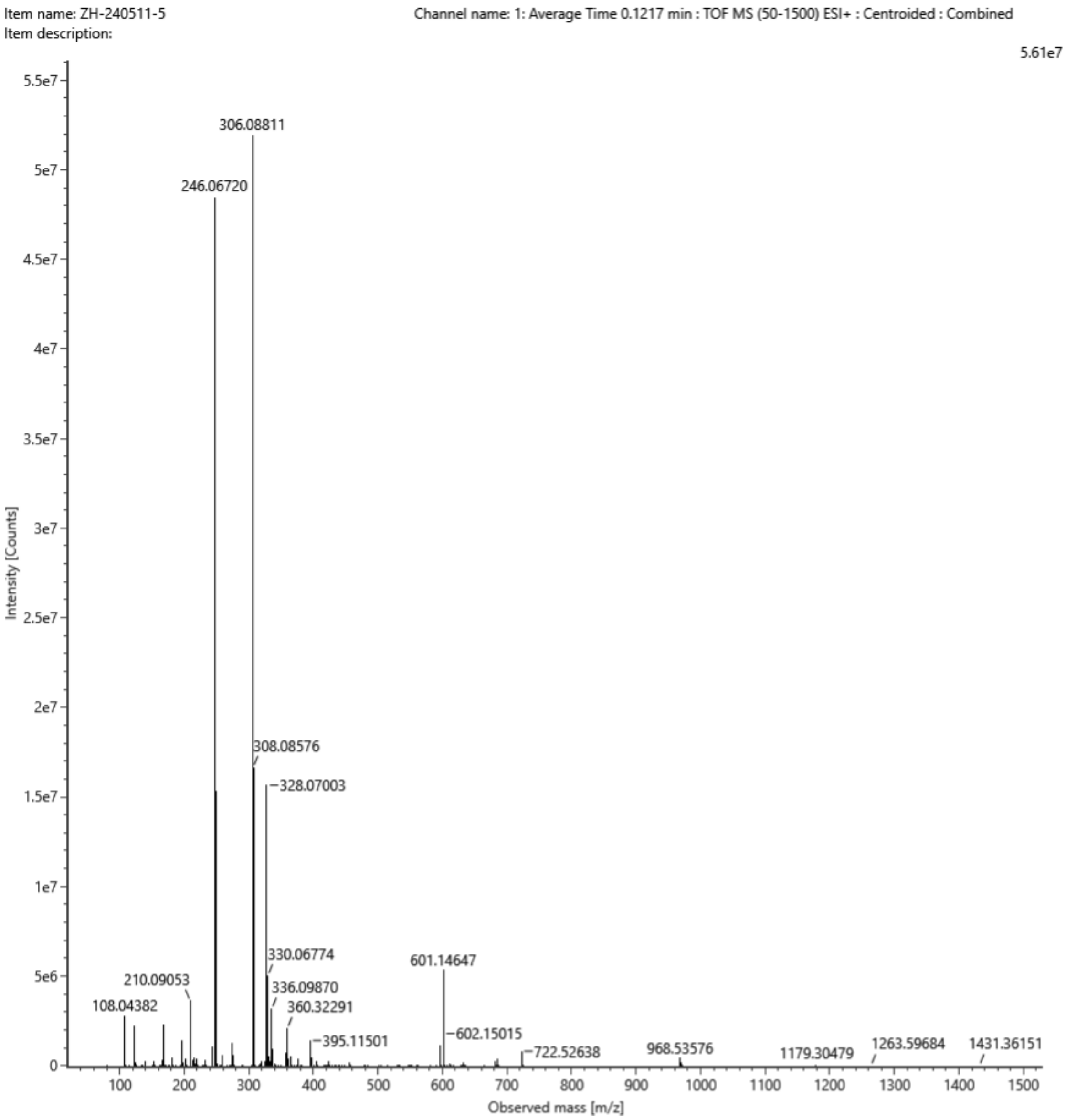
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{16}H_{16}FNO_3Na^+$	100.000000	290.1187	290.1186	-0.3447

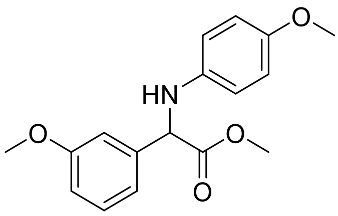




3h

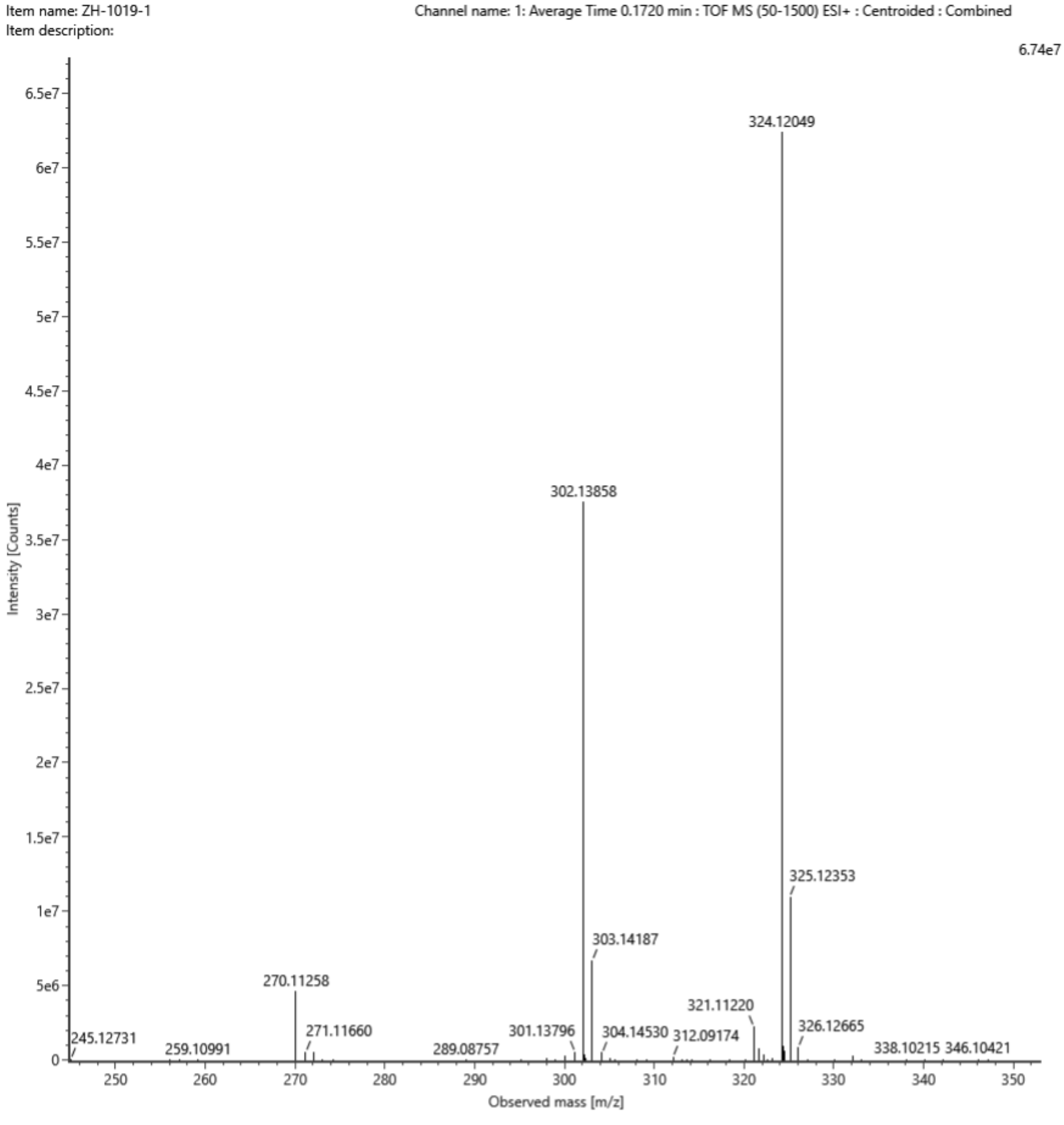
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{16}H_{16}ClNO_3Na^+$	100.000000	306.0891	306.0881	-3.2670

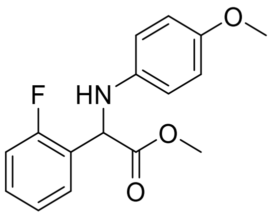




3i

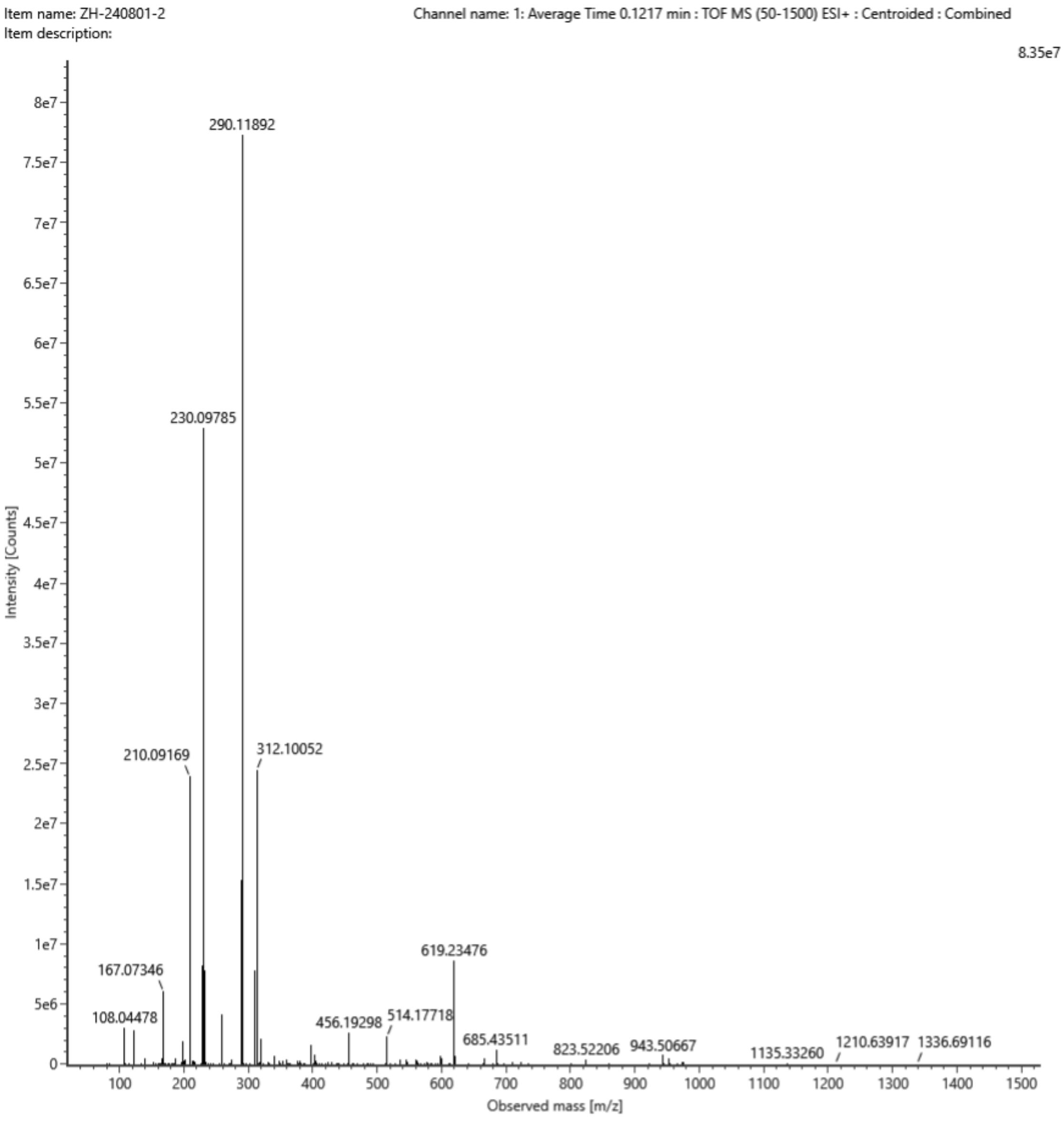
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{17}H_{19}NO_4Na^+$	100.000000	324.1206	324.1205	-0.3085

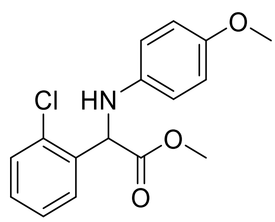




3j

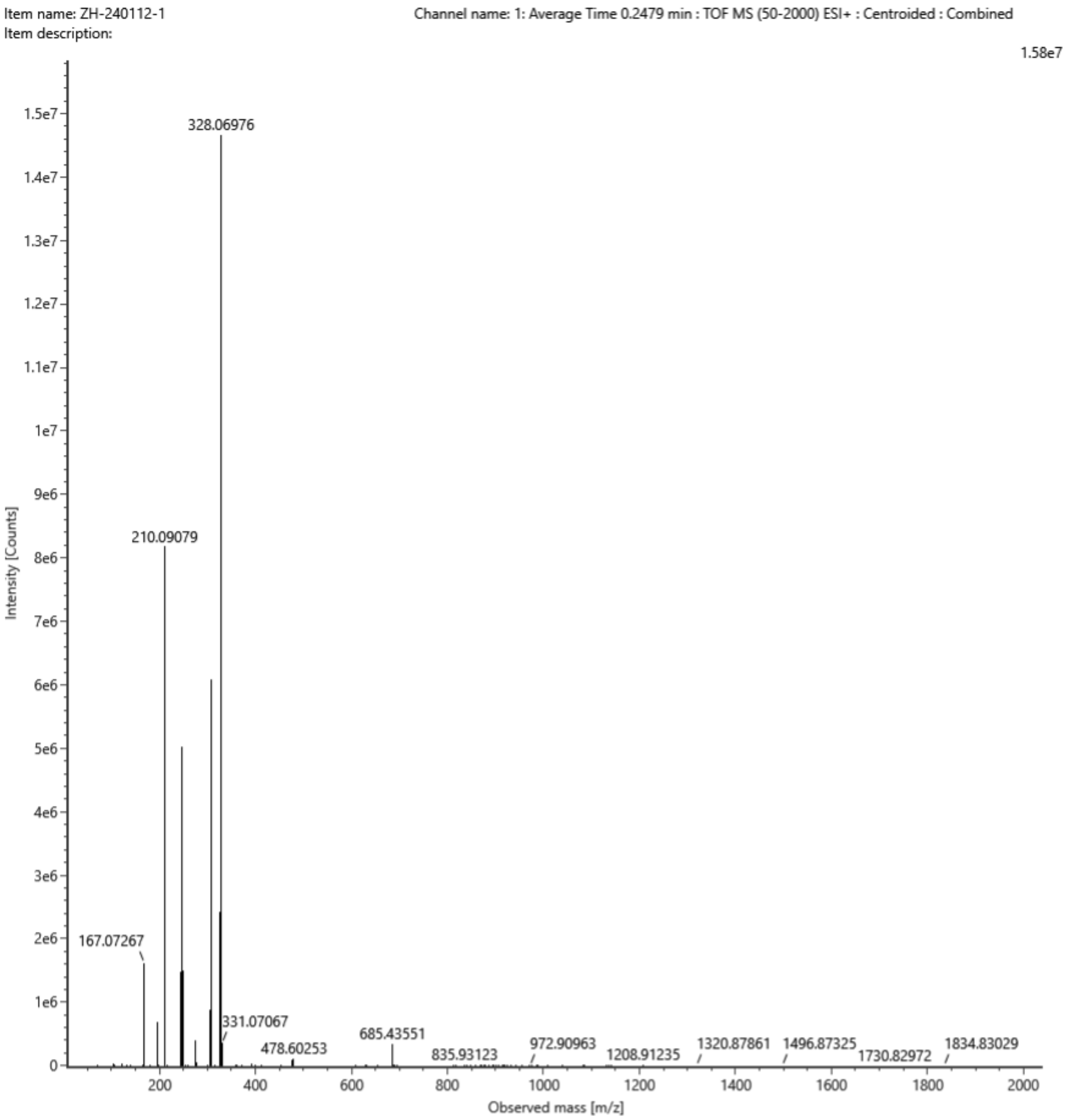
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{16}H_{16}FNO_3Na^+$	100.000000	290.1187	290.1189	0.6894

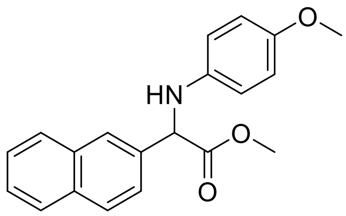




3k

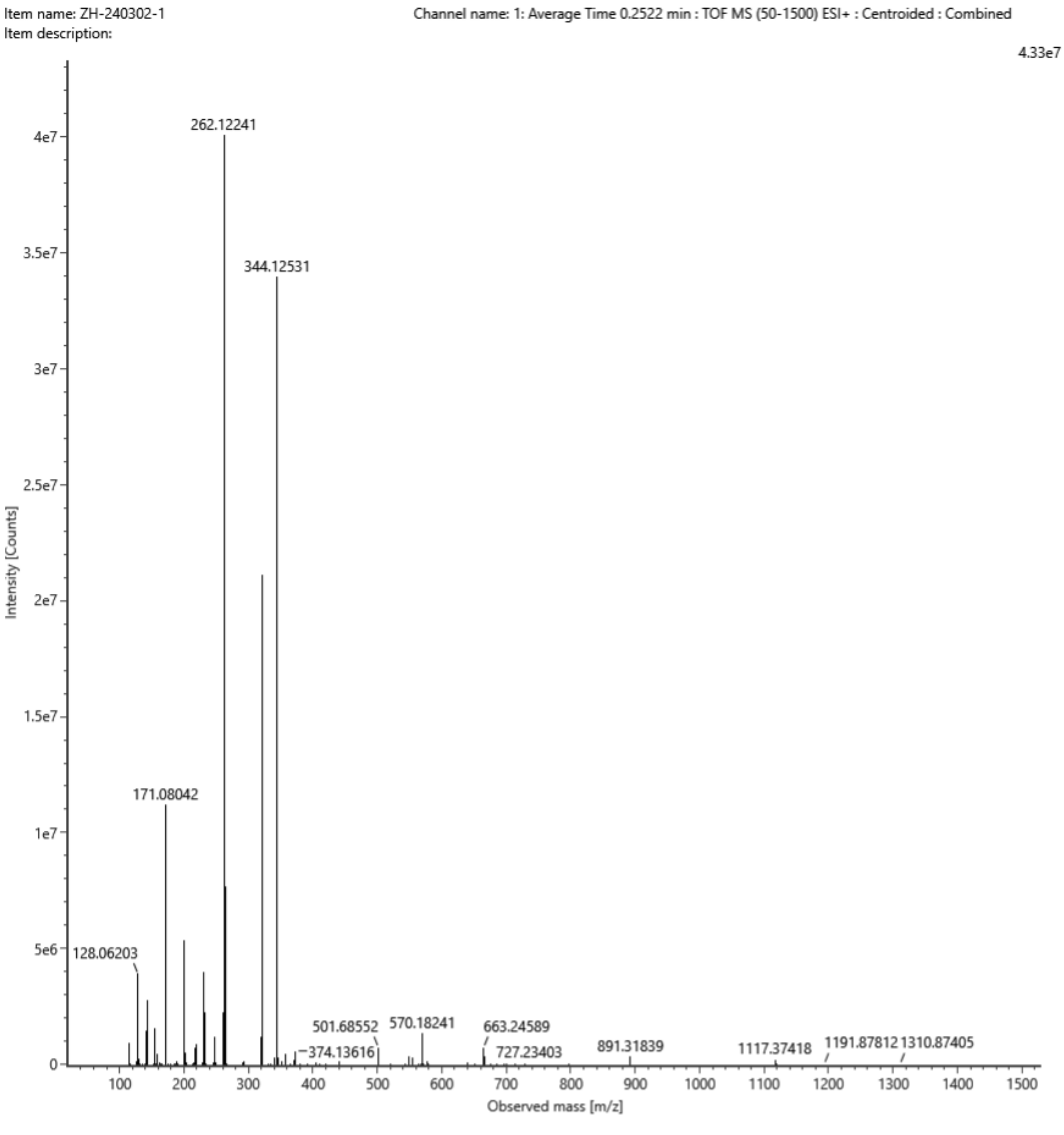
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{16}H_{16}ClNO_3Na^+$	100.000000	328.0711	328.0698	-3.9626

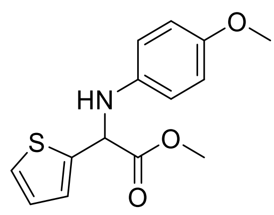




3l

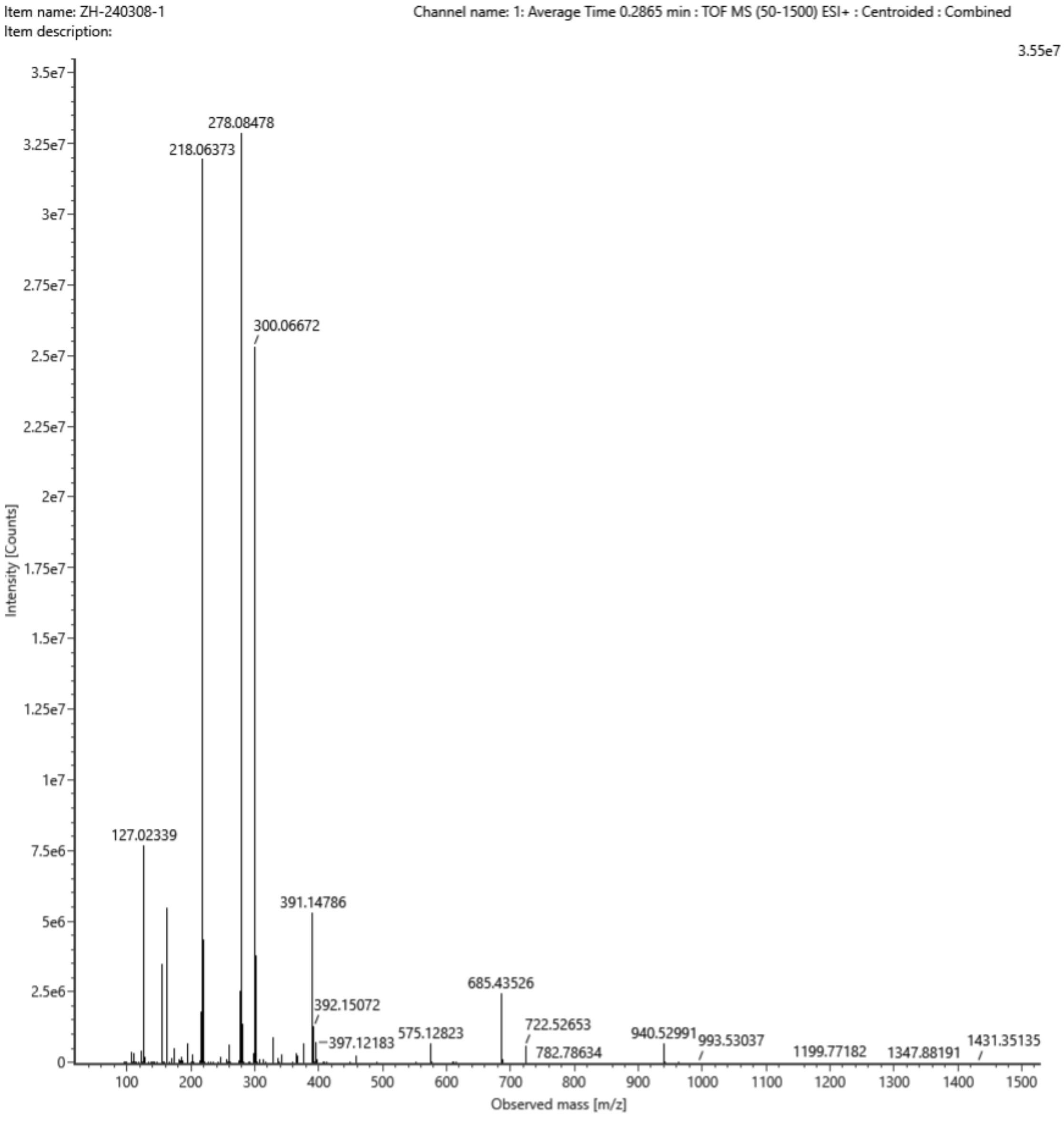
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{20}H_{19}NO_3Na^+$	100.000000	344.1257	344.1253	-1.1624

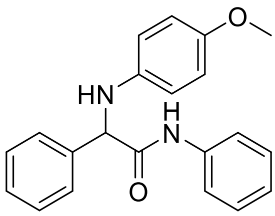




3m

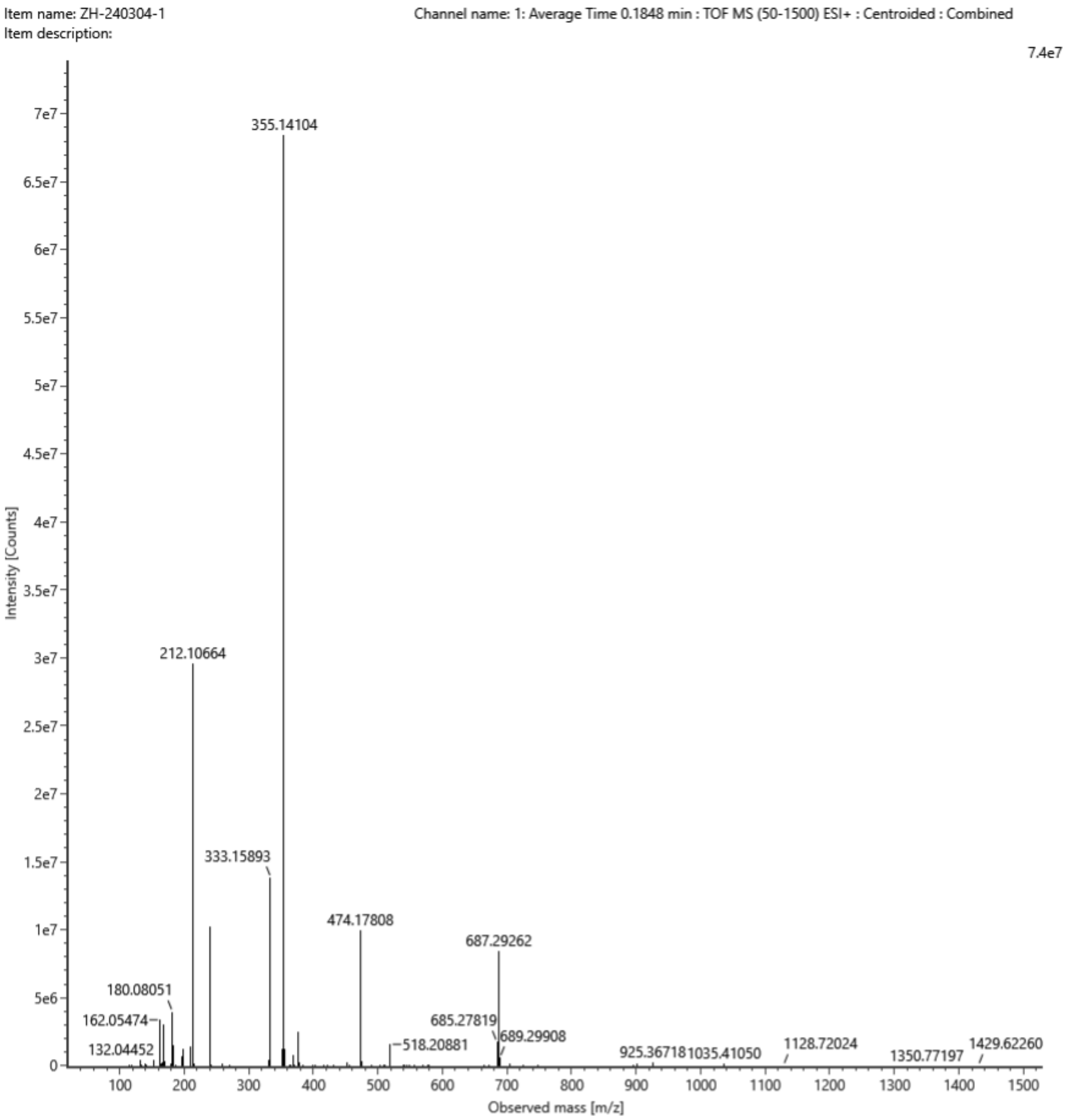
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{14}H_{15}NO_3Na^+$	100.000000	300.0665	300.0667	0.6665

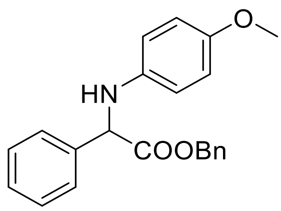




3n

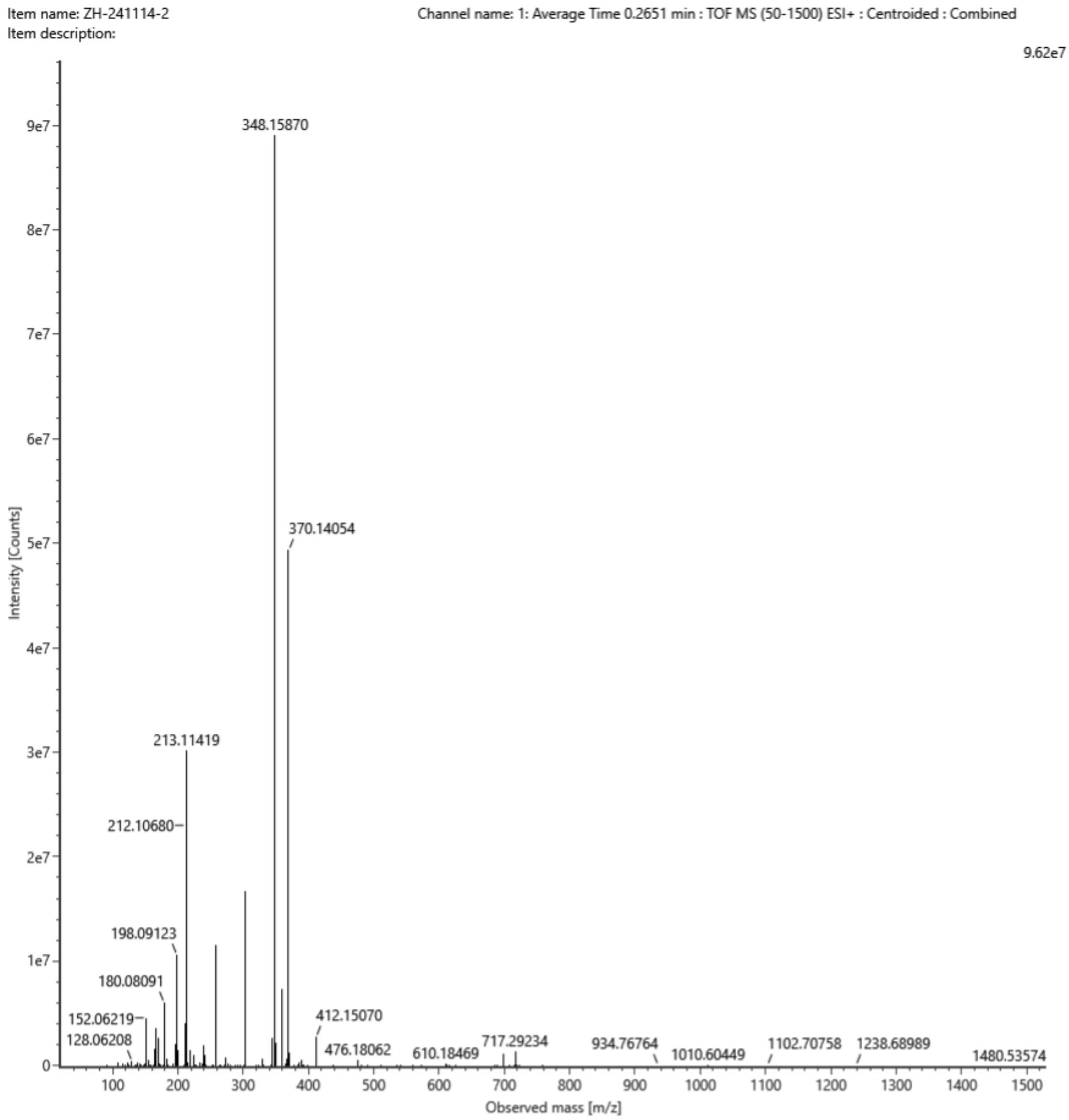
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{21}H_{20}N_2O_2Na^+$	100.000000	355.1417	355.1410	-1.9710

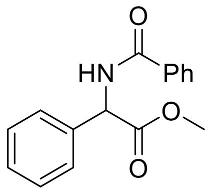




3o

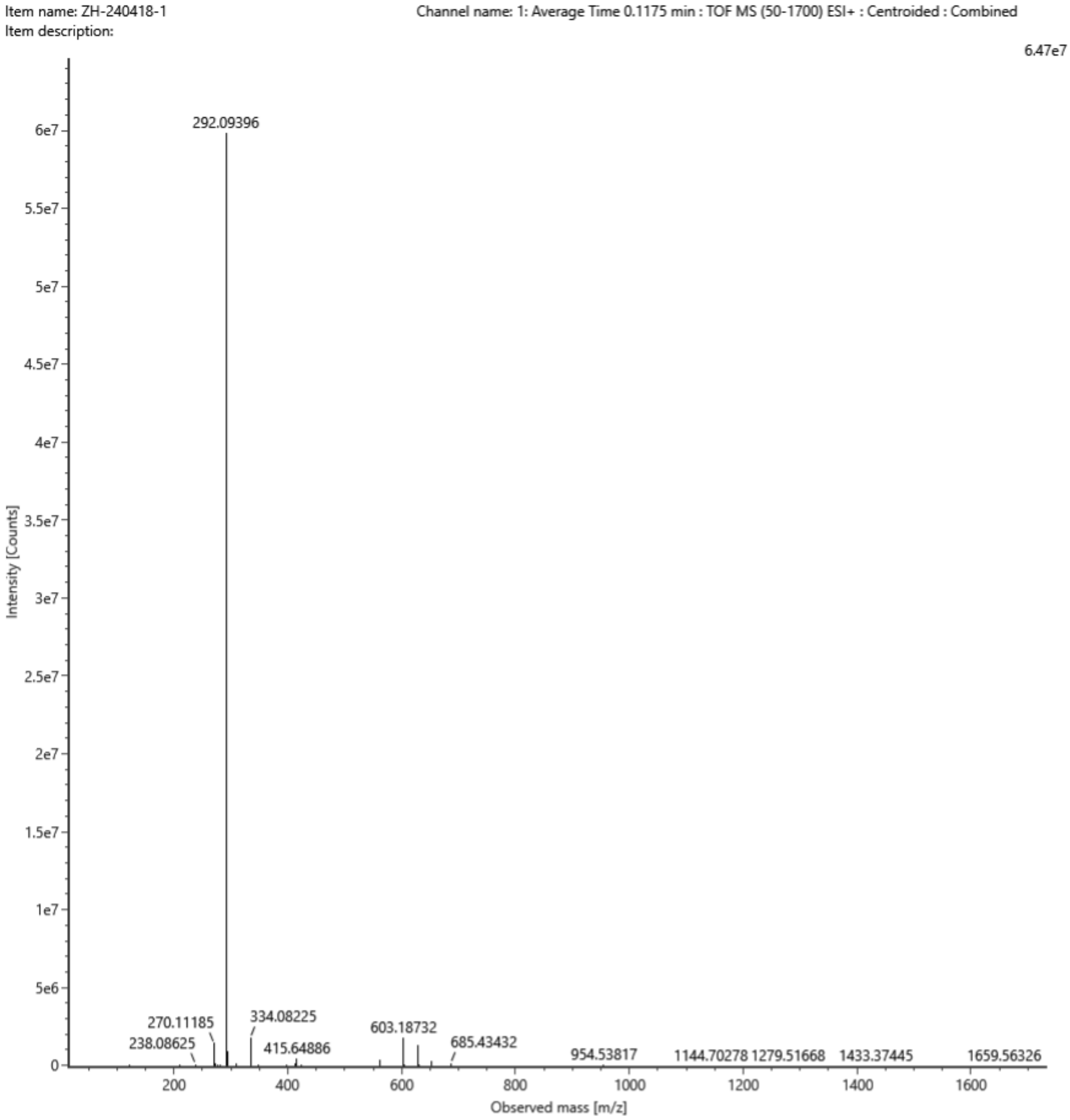
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{22}H_{21}NO_3Na^+$	100.000000	348.1594	348.1587	-2.0106

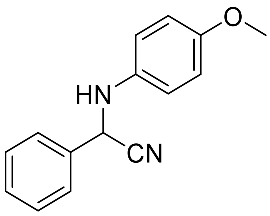




3p

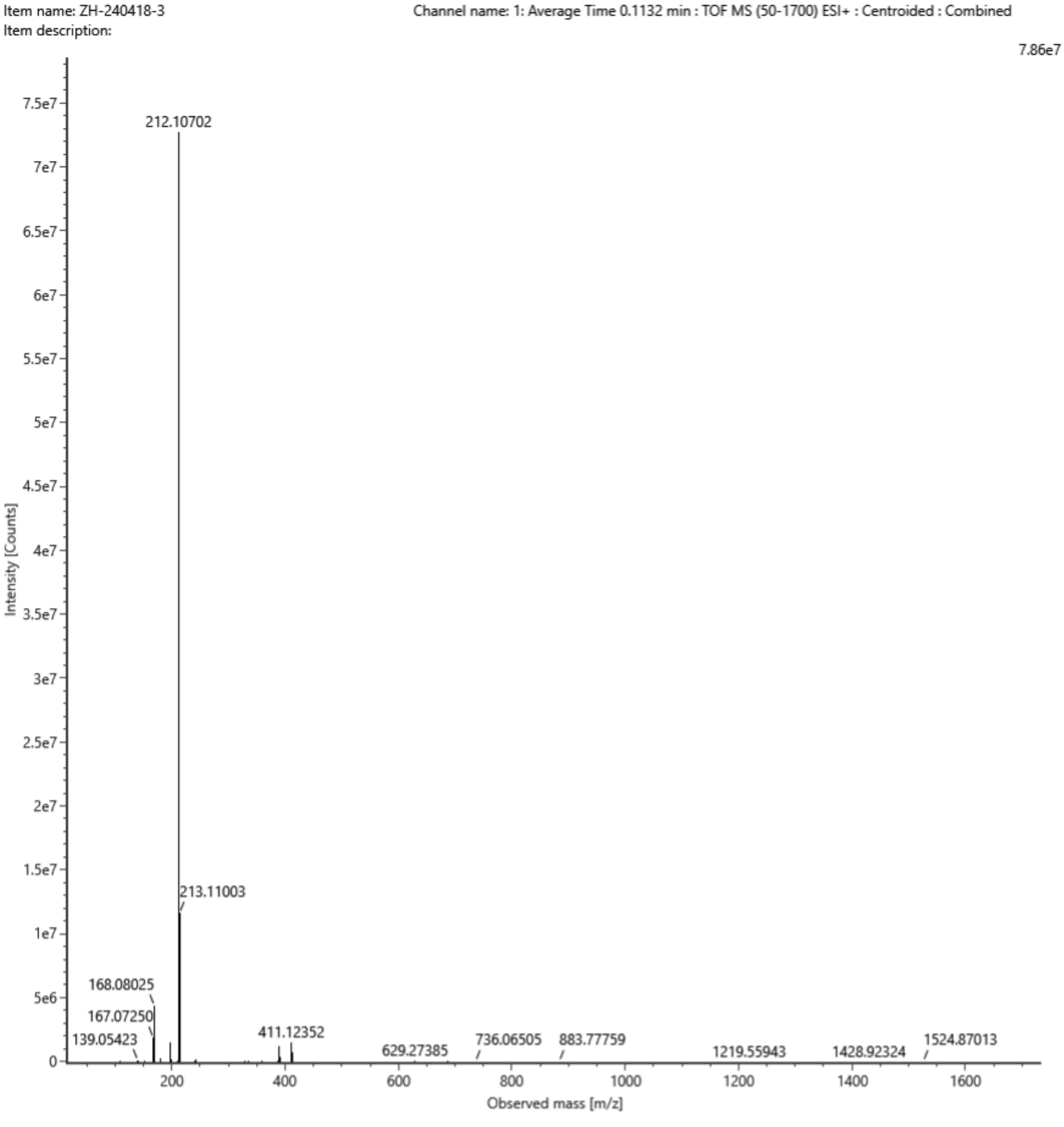
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{16}H_{15}NO_3Na^+$	100.000000	292.0945	292.0940	-1.7118

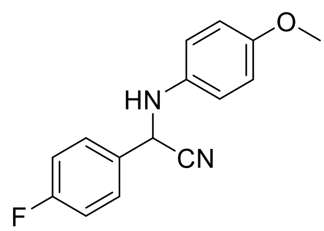




3q

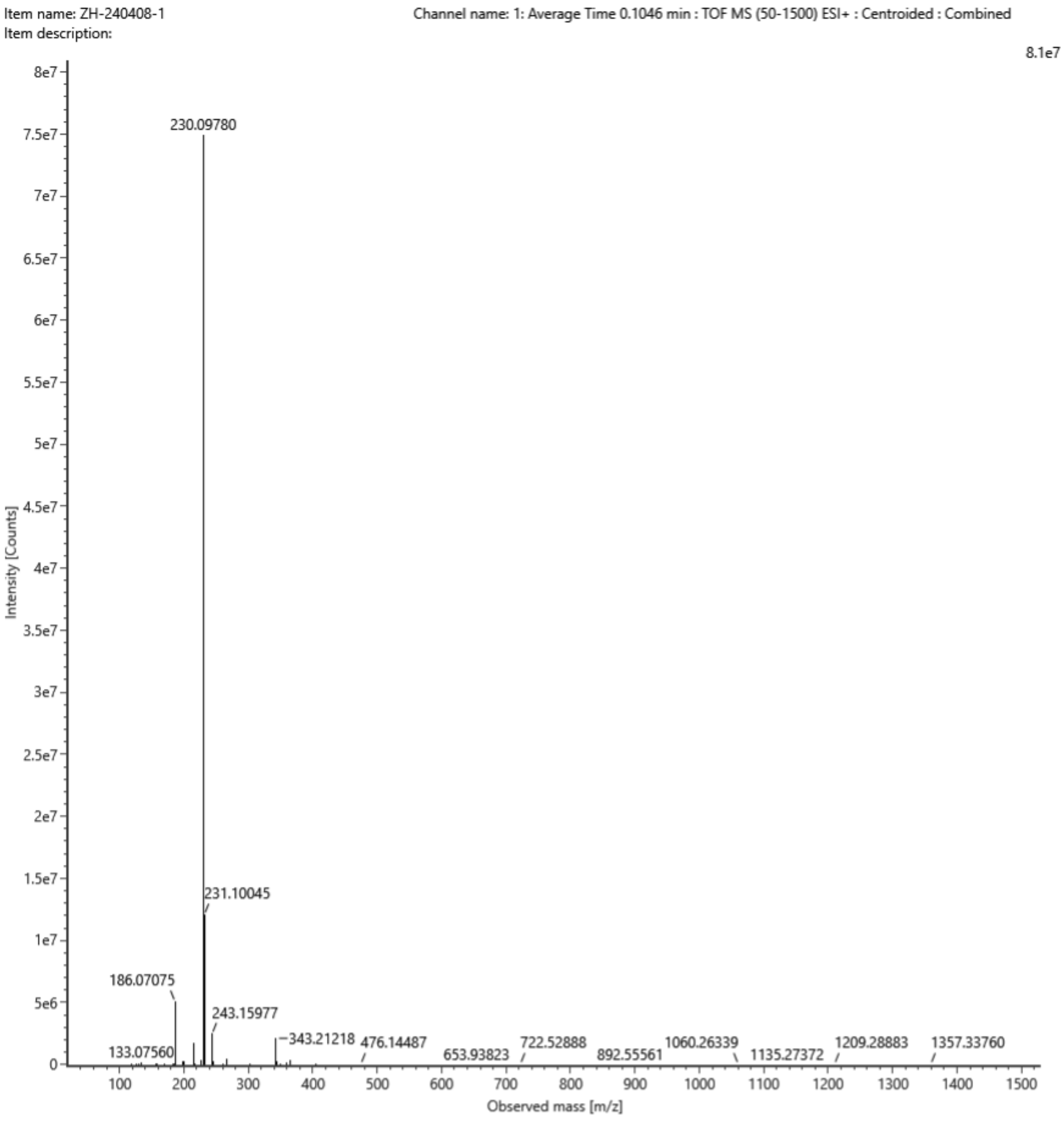
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{14}H_{14}NO^{+}$	100.000000	212.1070	212.1070	0.0000

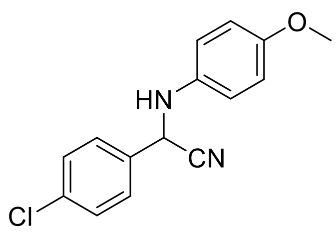




3r

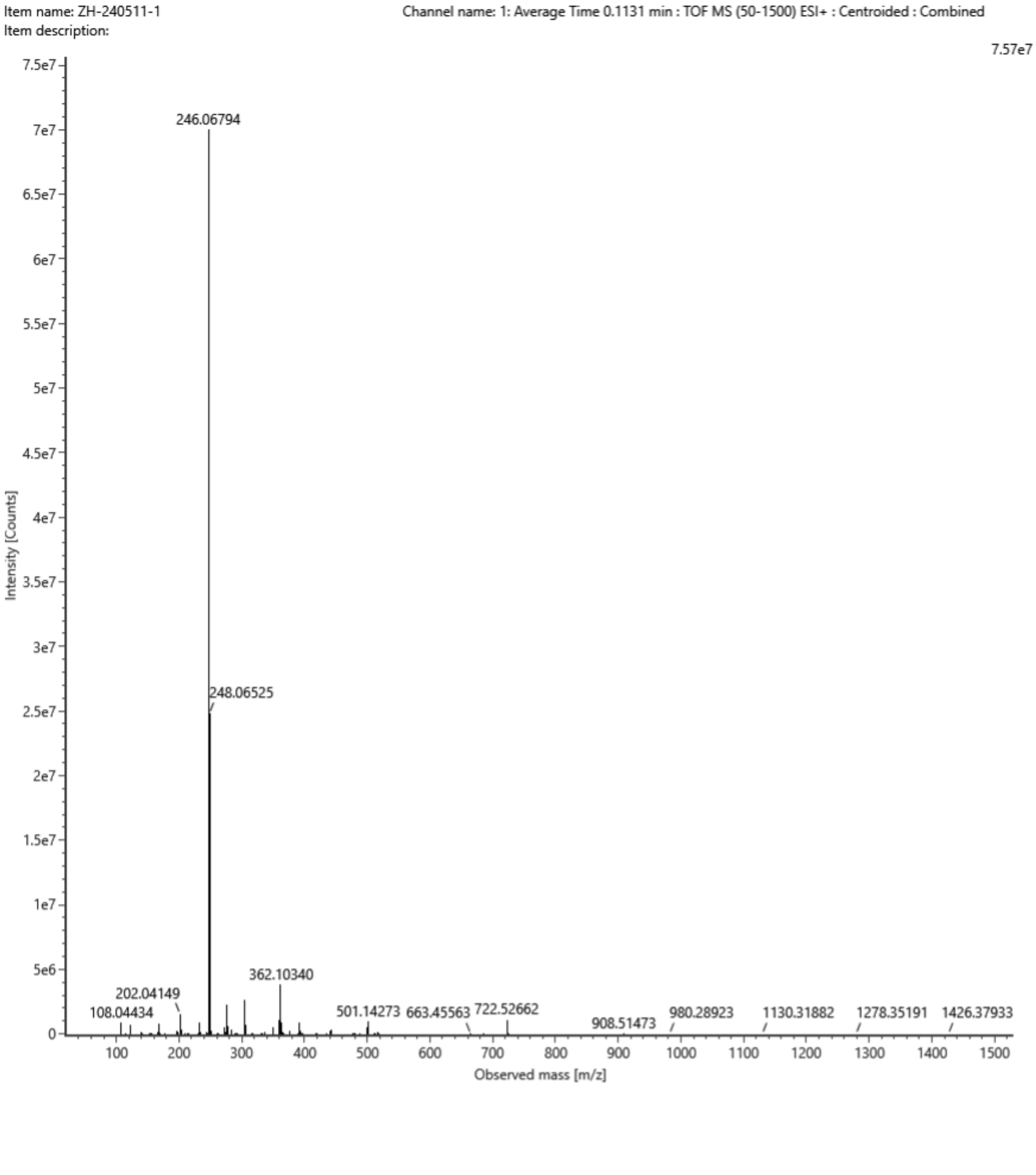
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{14}H_{13}FNO^{+}$	100.000000	230.0976	230.0978	0.8692

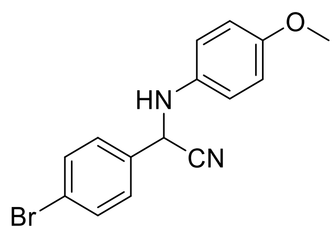




3s

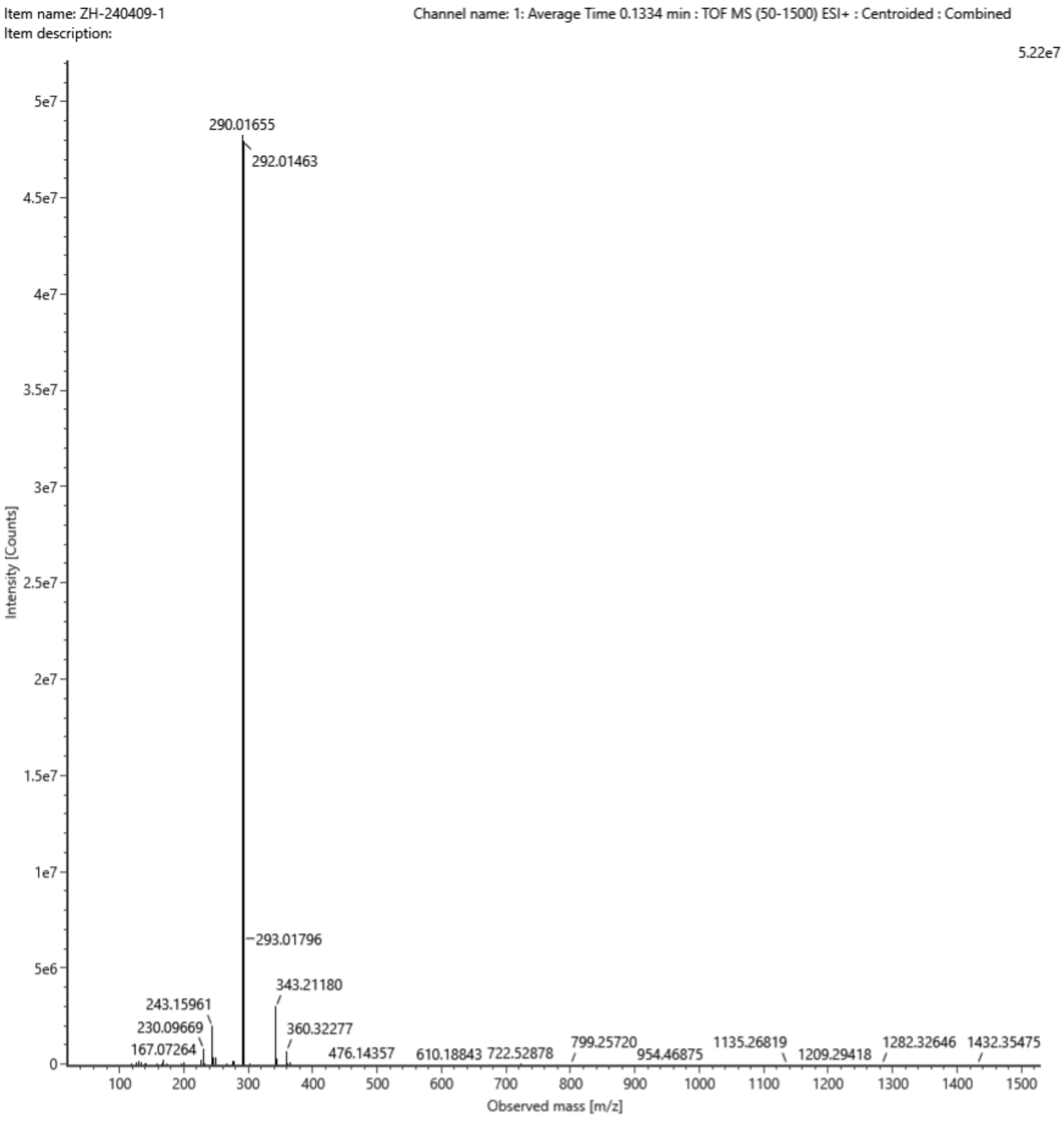
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{14}H_{13}ClNO^+$	100.000000	246.0680	246.0679	-0.4064

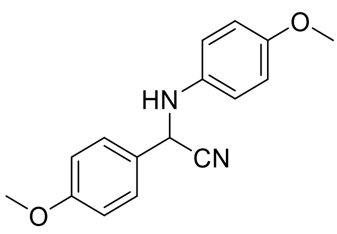




3t

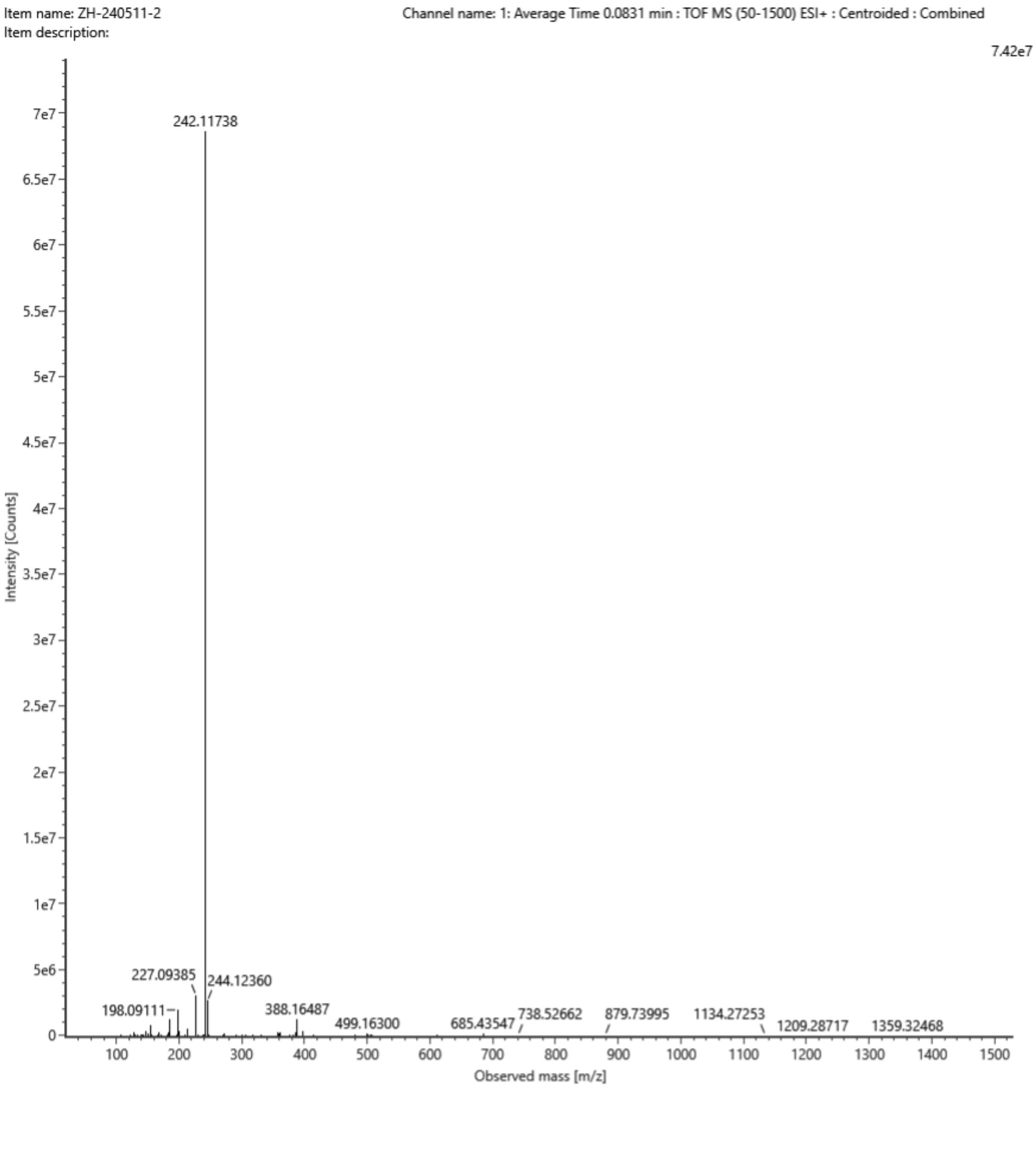
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{14}H_{13}BrNO^{+}$	100.000000	290.0175	290.0166	-3.1033

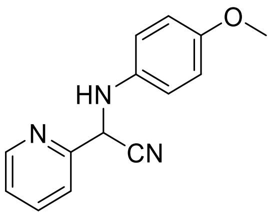




3u

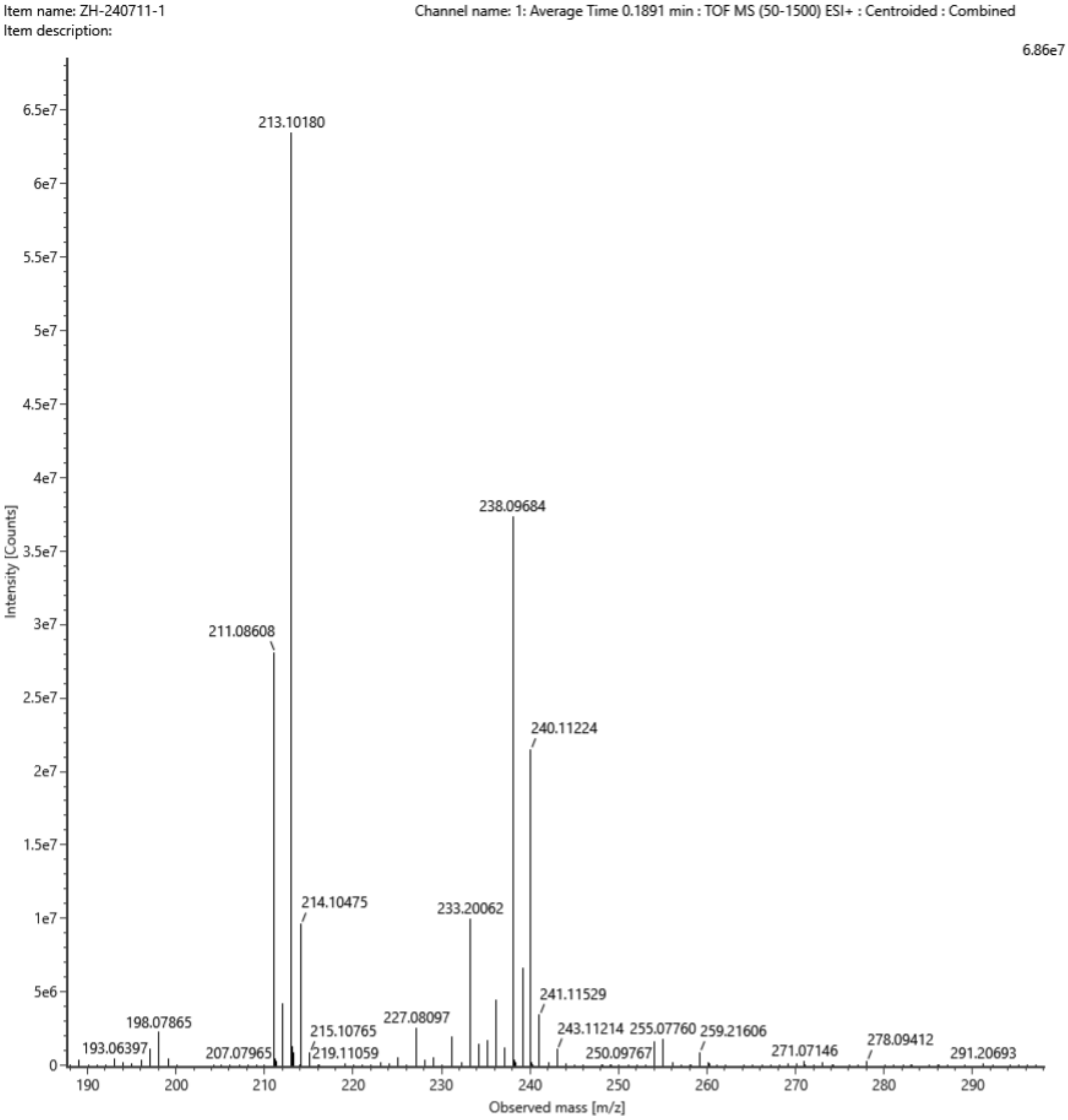
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{15}H_{16}NO_2^+$	100.000000	242.1176	242.1174	-0.8260

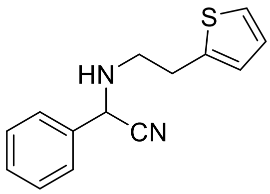




3v

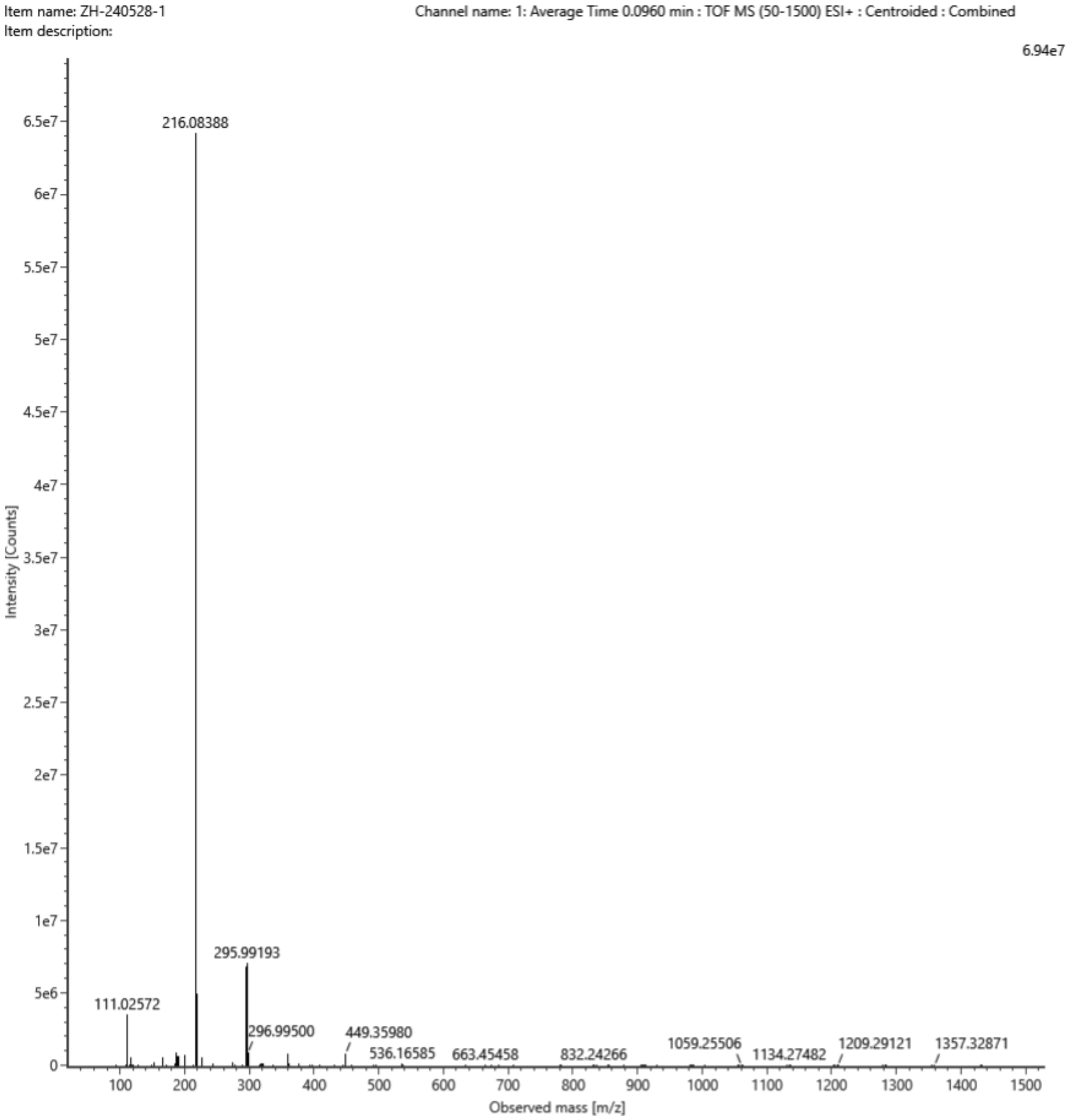
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{14}H_{14}N_3OH^+$	100.000000	240.1131	240.1122	-3.7482

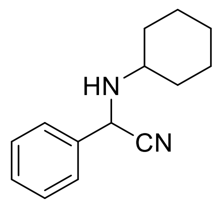




3w

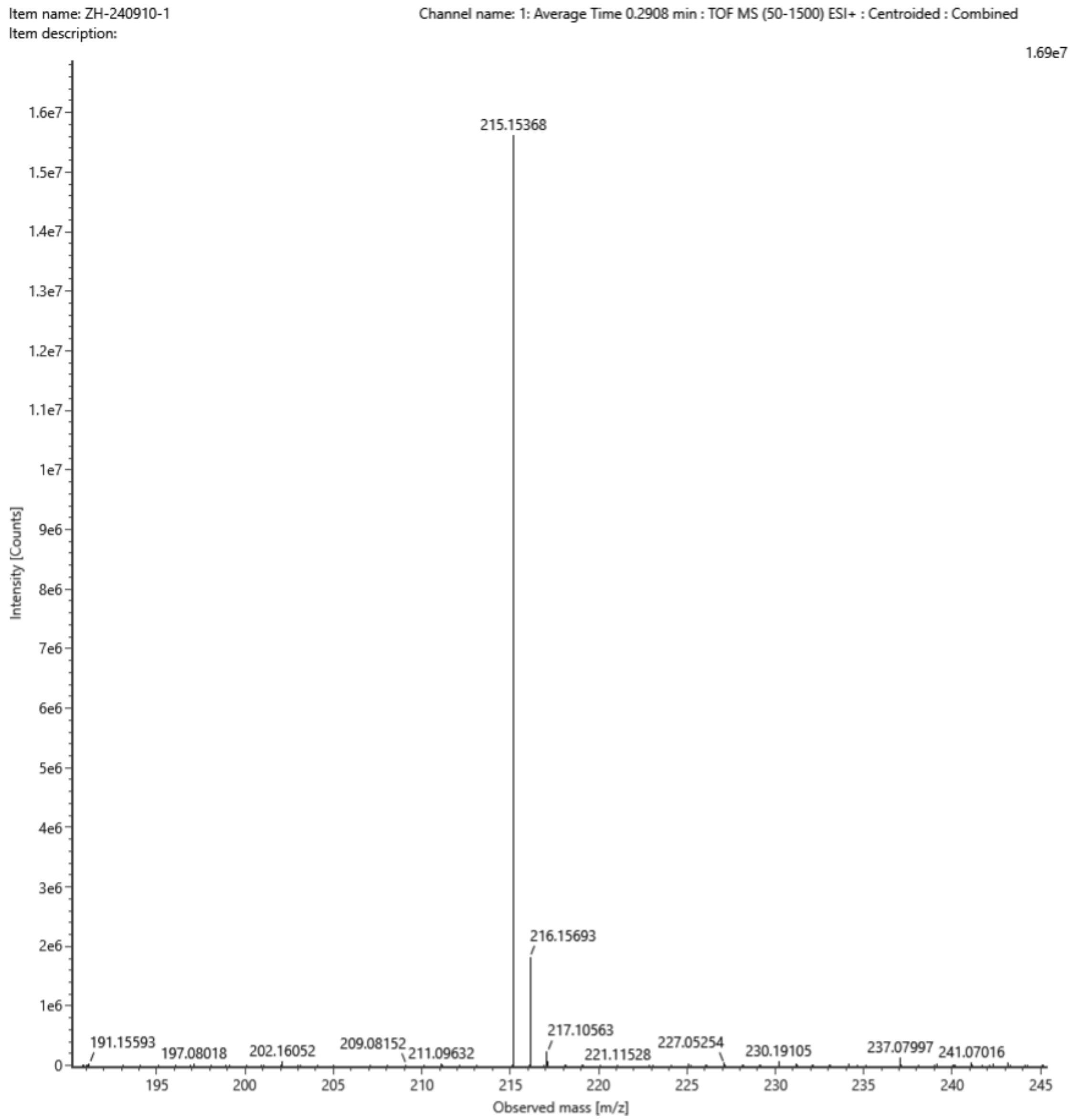
Composition	**i-FIT(%)**	**Exact Mass**	**Found**	**Error (PPM)**
$C_{13}H_{14}NS^{+}$	100.000000	216.0841	216.0839	-0.9256

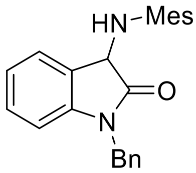




3x

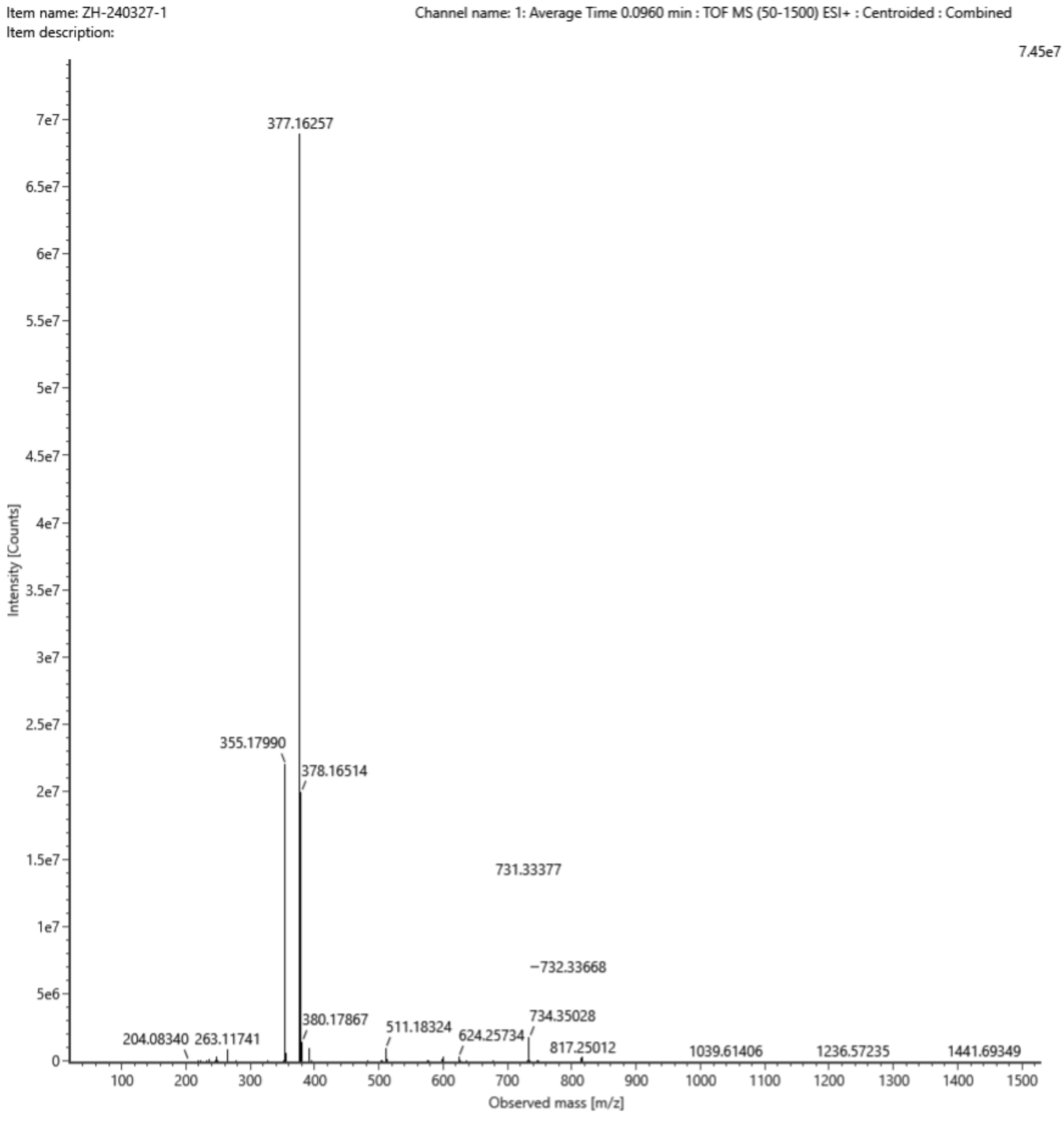
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{14}H_{18}N_2H^+$	100.000000	215.1543	215.1537	-2.7887

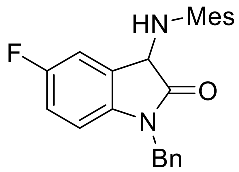




3y

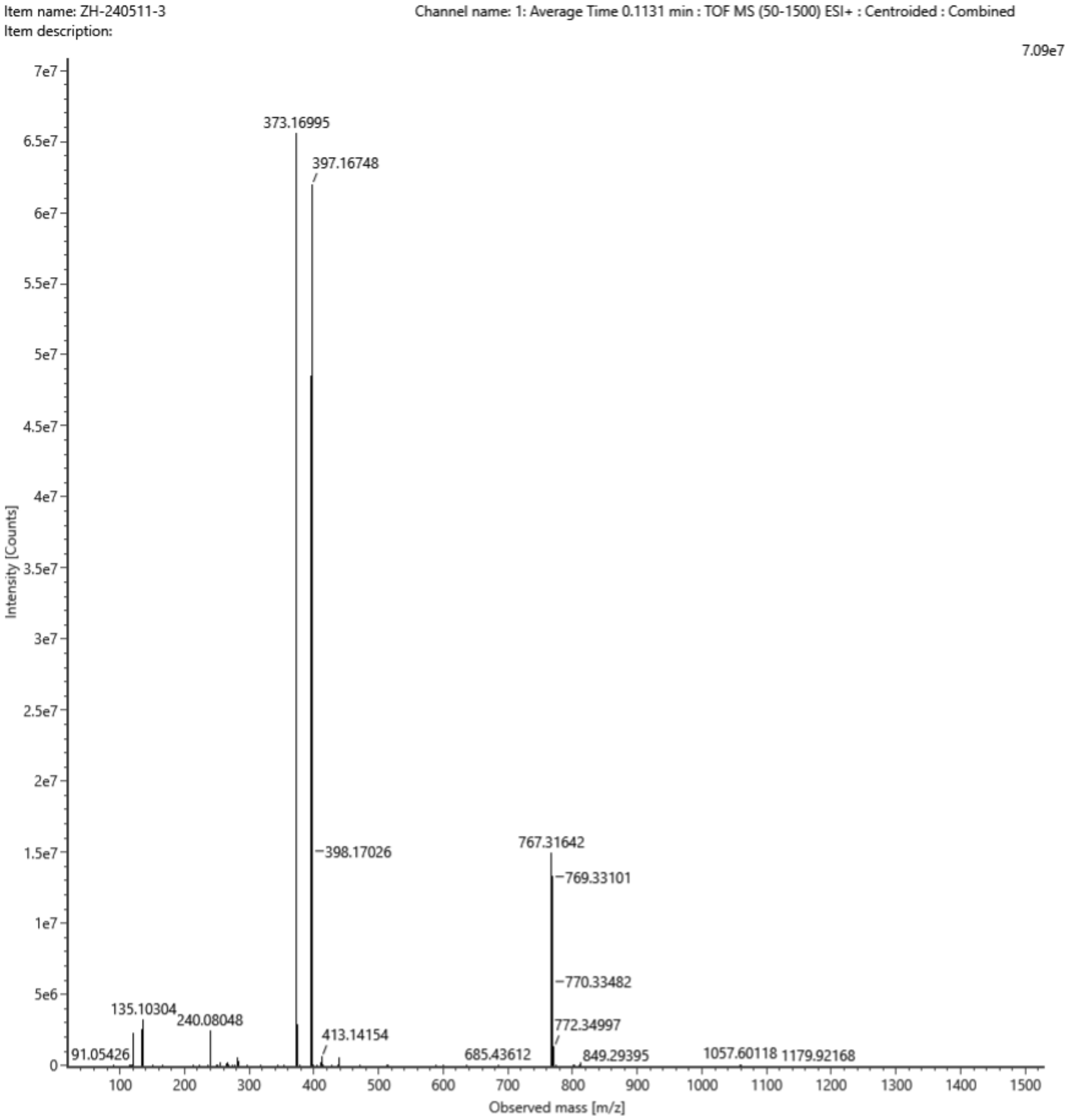
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{24}H_{24}N_2ONa^+$	100.000000	377.1624	377.1626	0.5303

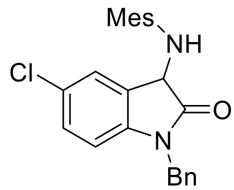




3z

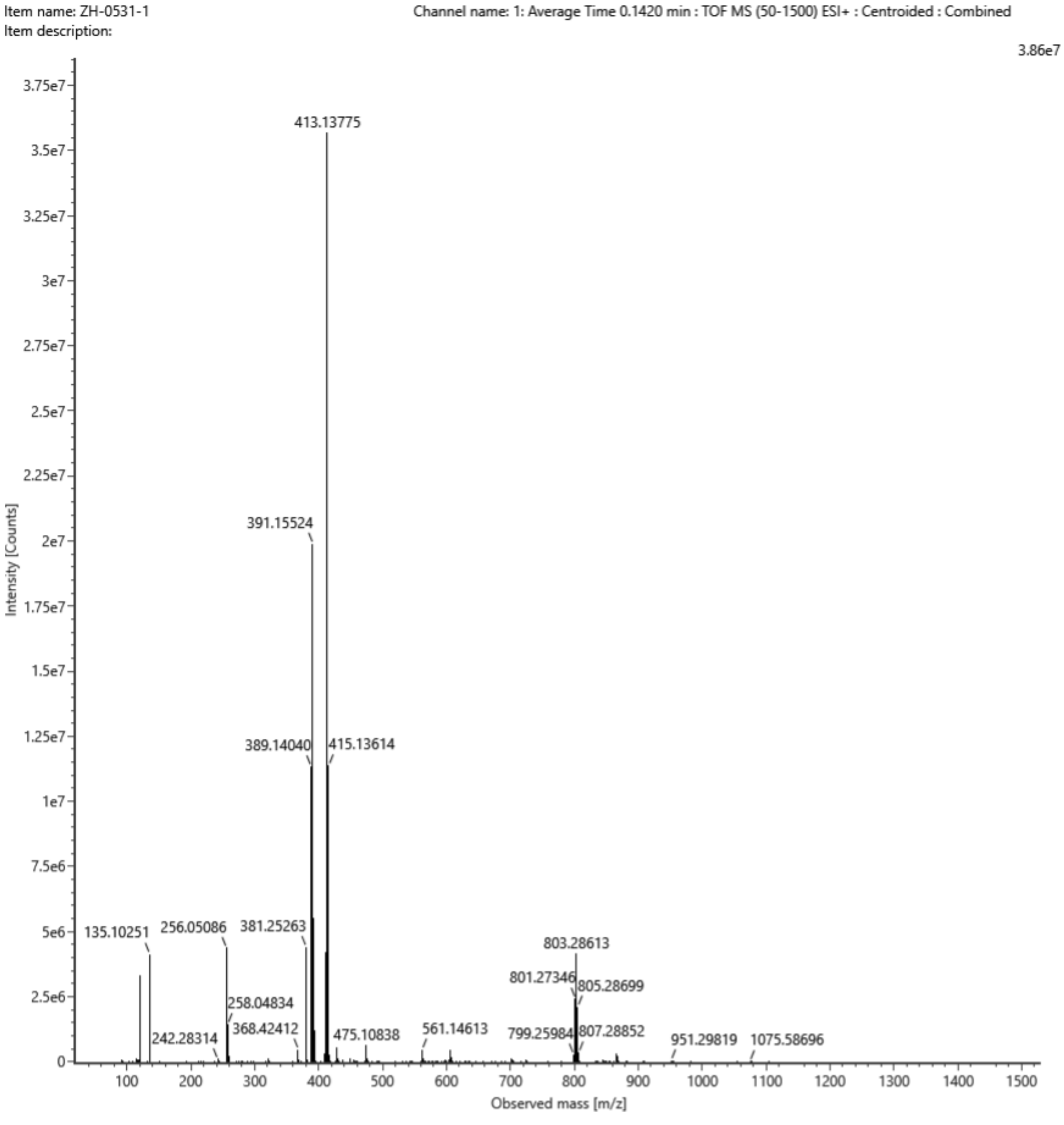
Composition	**i-FIT(%)**	**Exact Mass**	**Found**	**Error (PPM)**
$C_{24}H_{23}FN_2ONa^+$	100.000000	397.1687	397.1675	-3.0214

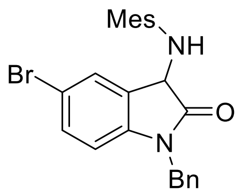




3aa

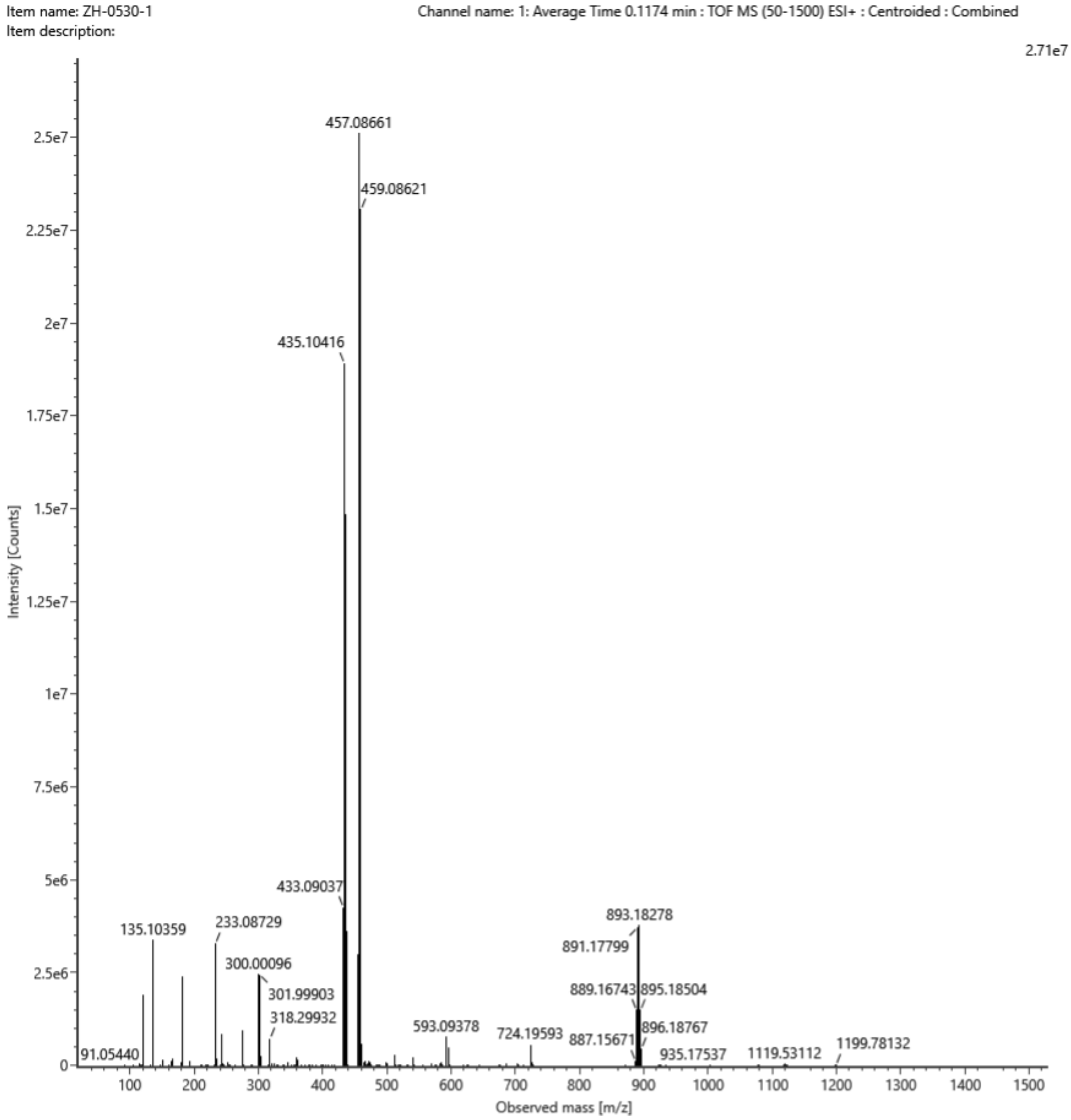
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{24}H_{23}ClN_2ONa^+$	100.000000	413.1391	413.1378	-3.1466

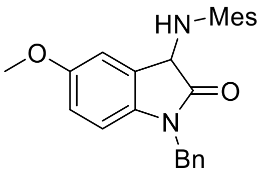




3ab

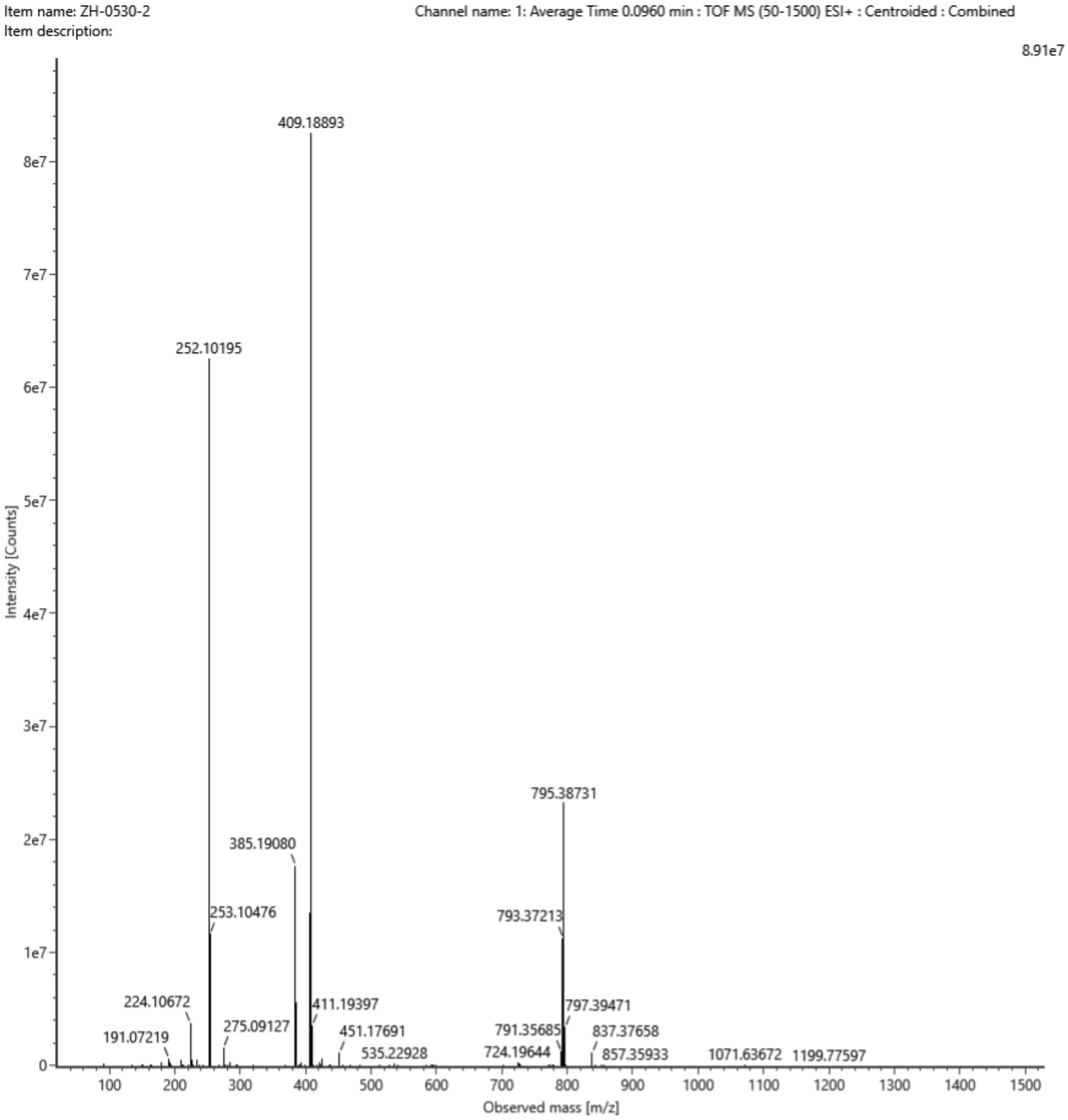
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{24}H_{23}BrN_2ONa^+$	100.000000	457.0886	457.0866	-4.3755

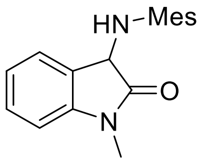




3ac

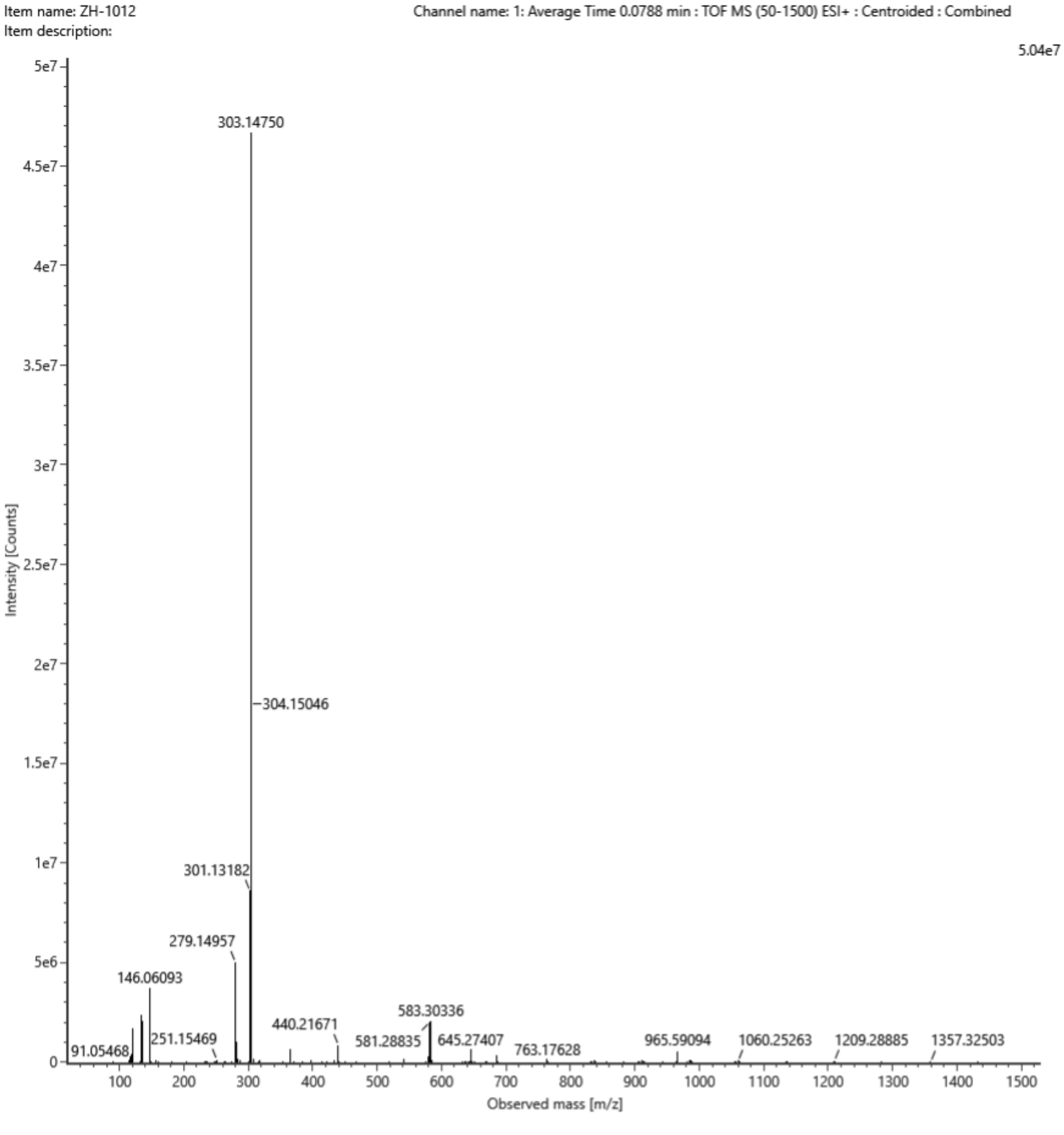
Composition	**i-FIT(%)**	**Exact Mass**	**Found**	**Error (PPM)**
$C_{25}H_{26}N_2O_2Na^+$	100.000000	409.1886	409.1889	0.7332

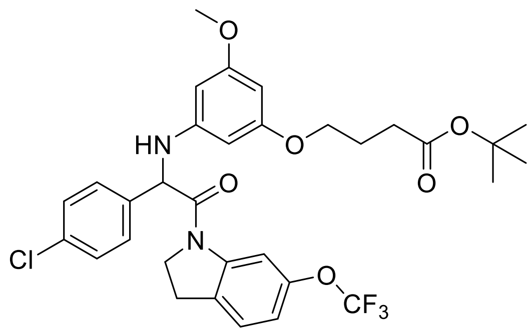




3ad

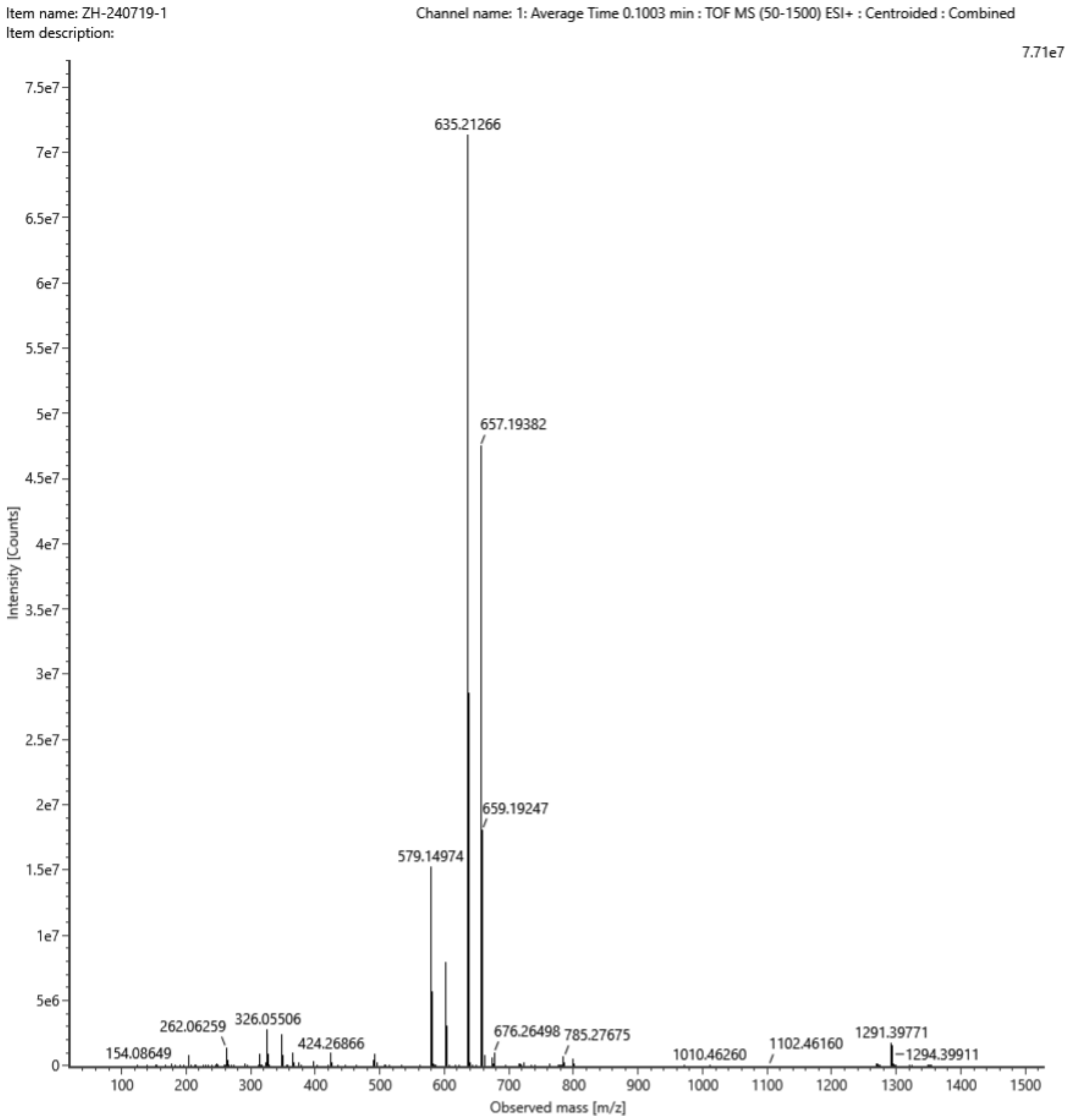
Composition	i-FIT(%)	Exact Mass	Found	Error (PPM)
$C_{18}H_{20}N_2ONa^+$	100.000000	303.1468	303.1475	2.3091





5

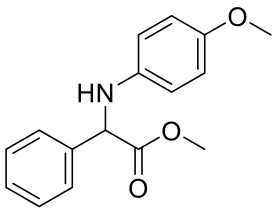
Composition	**i-FIT(%)**	**Exact Mass**	**Found**	**Error (PPM)**
$C_{32}H_{34}ClF_3N_2O_6H^+$	100.000000	635.2130	635.2127	-0.4723



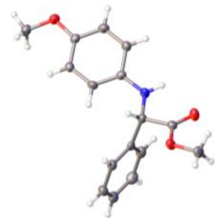
X-ray crystallography

The colorless block crystals of compounds **3a** and **(*S*)-3a** were obtained by vaporization of a petroleum ether / dichloromethane solution. The absolute stereochemistry was determined by the X-ray diffraction. These crystals were deposited in the Cambridge Crystallographic Data Centre and assigned.
www.ccdc.cam.ac.uk/data request/cif.

Supplementary Table S3. X-ray crystallographic analysis of 3a.



3a



CCDC: 2247204

Bond precision: C-C = 0.0071 A   Wavelength=1.54178

Cell:	a=14.1888(16)	b=9.7914(11)	c=10.6811(13)
	alpha=90	beta= 107.956(5)	gamma=90
Temperature:	273 K		

	Calculated	Reported
Volume	1411.6(3)	1411.6(3)
Space group	C c	C 1 c 1
Hall group	C -2yc	C -2yc
Moiety formula	C16 H17 N O3	C16 H17 N O3
Sum formula	C16 H17 N O3	C16 H17 N O3
Mr	271.31	271.30
Dx,g cm-3	1.277	1.277
Z	4	4
Mu (mm-1)	0.718	0.718
F000	576.0	576.0
F000’	577.79	
h, k, lmax	17,12,13	17,12,13
Nref	2788[1397]	2369
Tmin, Tmax	0.842,0.931	0.960, 1.000
Thin’	0.806	

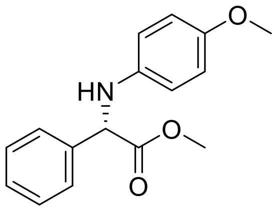
Correction method= Not given

Data completeness= 1.70/0.85   Theta(max)= 72.304

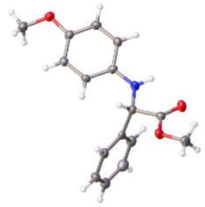
R(reflections)= 0.0726(2139)   wR2(reflections)= 0.2138(2369)

S = 1.117   Npar= 186

Supplementary Table S4. X-ray crystallographic analysis of (*S*)-3a.



(s)-3a



CCDC: 2271403

Bond precision: C-C = 0.0025 A   Wavelength=1.54184

Cell:	a=5.6574(2)	b=9.8640(3)	c=12.4816(4)
	alpha=90	beta=96.154(3)	gamma=90
Temperature:	115 K		

	Calculated	Reported
Volume	692.52(4)	692.52(4)
Space group	P 21	P 1 21 1
Hall group	P 2yb	P 2yb
Moiety formula	C16 H17 N O3	C16 H17 N O3
Sum formula	C16 H17 N O3	C16 H17 N O3
Mr	271.31	271.31
Dx,g cm-3	1.301	1.301
Z	2	2
Mu (mm-1)	0.732	0.732
F000	288.0	288.0
F000’	288.90	
h, k, lmax	6,11,14	6,11,14
Nref	2434[1294]	2375
Tmin, Tmax	0.877,0.909	0.960,1.000
Thin’	0.780	

Correction method= # Reported T Limits: Tmin=0.960 Tmax=1.000

AbsCorr = MULTI-SCAN

Data completeness= 1.84/0.98	Theta(max)= 66.270	
R(reflections)= 0.0347(2252)		wR2(reflections)= 0.0859(2375)
S = 1.076	Npar=352	

VI. Reference

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