

## Electronic Supplementary Information (ESI)

### New Transient Directing Group: *Diethoxyethyl-L-Proline* Facilitate *ortho*-Arylation at Aryl-Amines/-Amino acids via Pd-Catalyzed C(sp<sup>2</sup>)-H Activation

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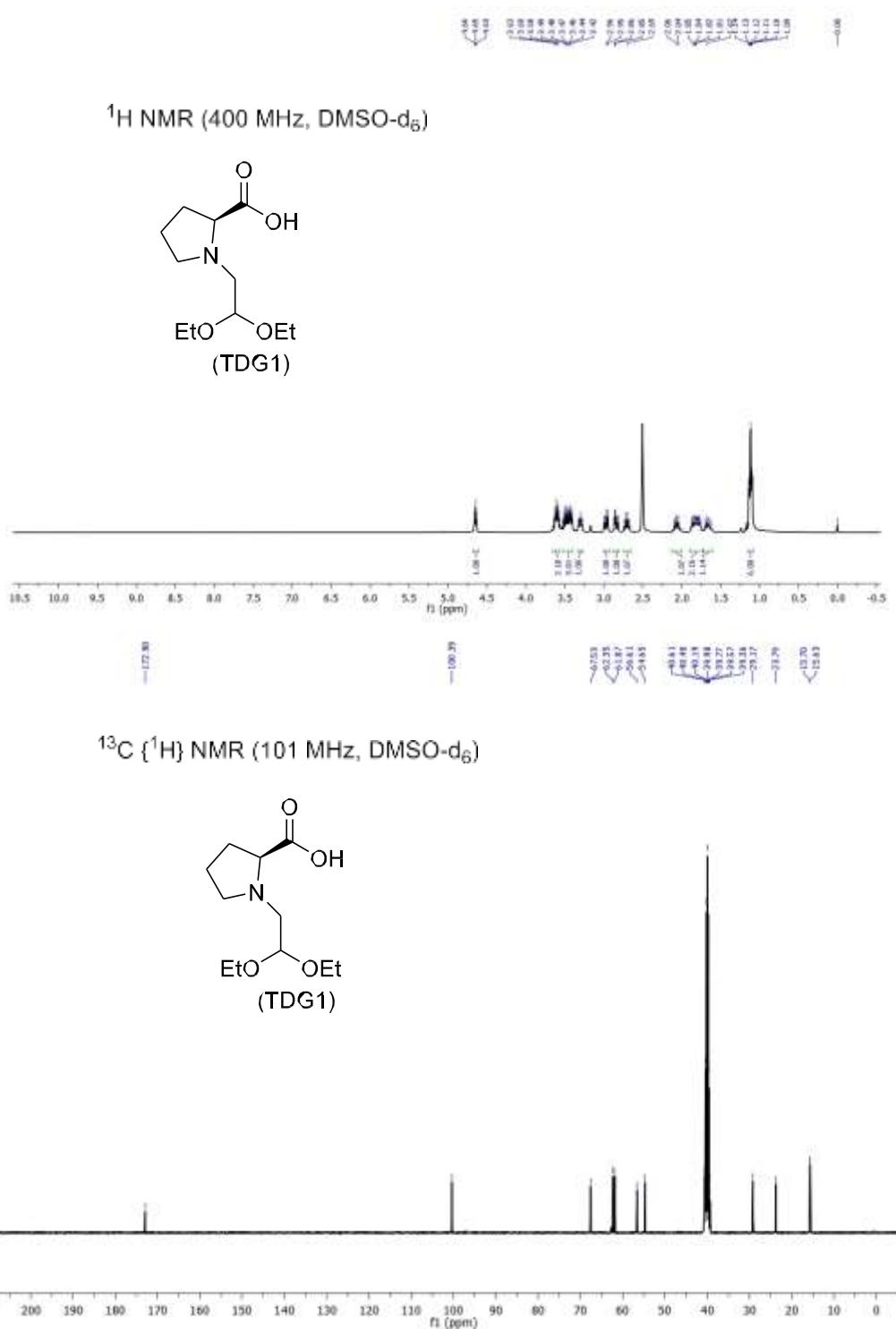
1. Optimization of Reaction Conditions

**Table S1. Solvent Optimization of mono-o-arylation of amine in different solvent**

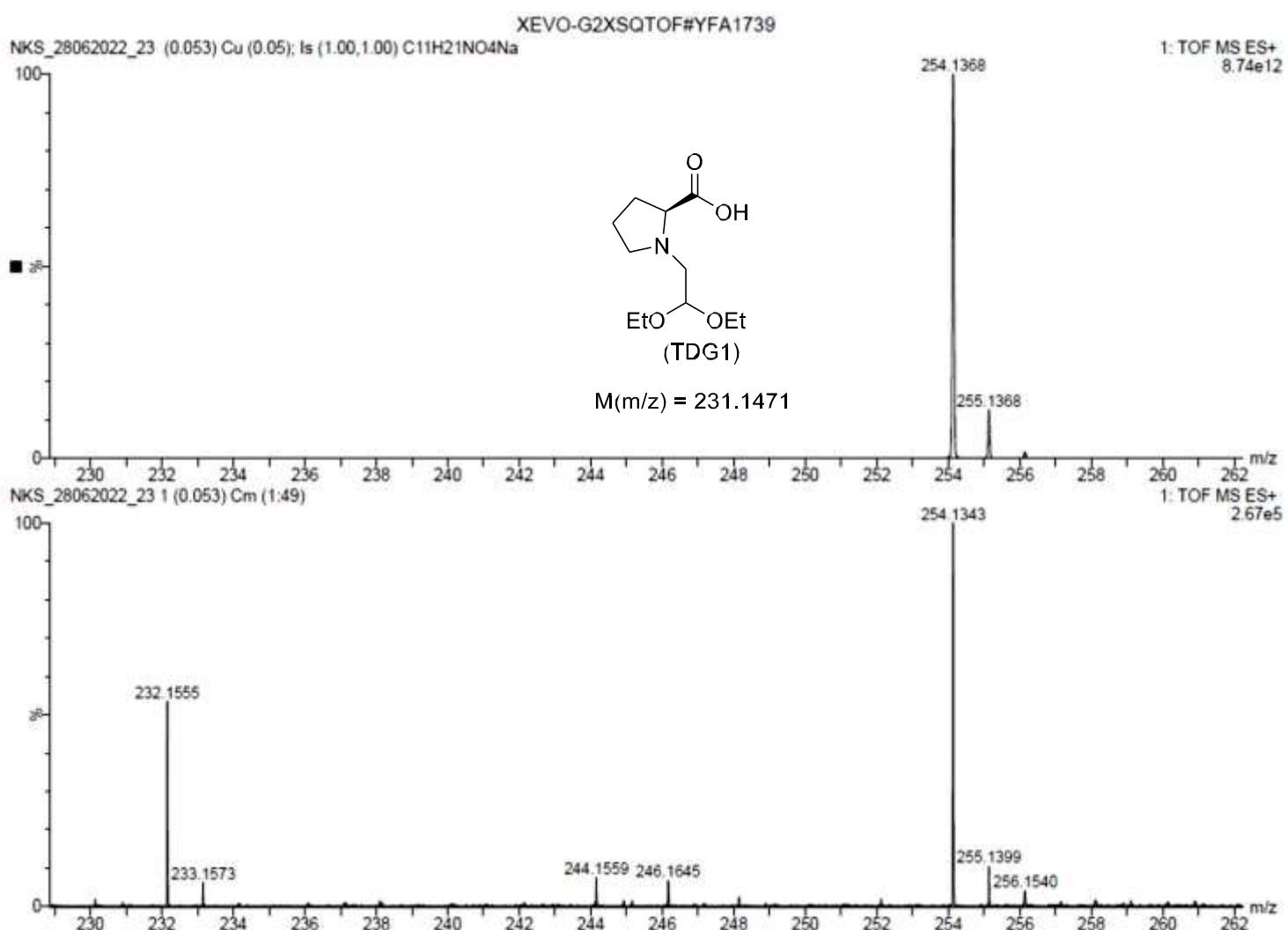
Entry	Solvent	Ag Salt	Time (h)	Temp.	Yield (%) (m:d)	
					1(a)	2(a)
1.	HFIP	AgTFA	20	90	71:9	
2.	1,2-DCE	AgTFA	20	90	trace	
3.	AcOH	AgTFA	20	90	37	
4.	DMF	AgTFA	20	90	n.d	
5.	ACN	AgTFA	20	90	n.d	
6.	DMA	AgTFA	20	90	n.d	
7.	TFE	AgTFA	20	90	51	
8.	t-Butanol	AgTFA	20	90	n.d	
9.	THF	AgTFA	20	90	n.d	
10.	1,4-Dioxane	AgTFA	20	90	n.d	
11.	Isopropanol	AgTFA	20	90	n.d	
12.	HFIP	AgSbF <sub>6</sub>	20	90	7	
13.	HFIP	CF <sub>3</sub> SO <sub>3</sub> Ag	20	90	13	
14.	HFIP	AgPF <sub>6</sub>	20	90	trace	

Reaction Conditions: - (i) 1a (1.0 eq.), 4-Iodobenzene (2.0 eq.), Pd (OAc)<sub>2</sub> (10 mol%), Ag Salt (2.0 eq.), TDG1 (20 mol%), HFIP (1ml.), 90 °C, 20 h (ii) (Boc)<sub>2</sub>O (1.1 eq.), Et<sub>3</sub>N (3 eq.), DCM, rt, 1.5h.

## 2. ESI-HRMS and NMR Characterization.



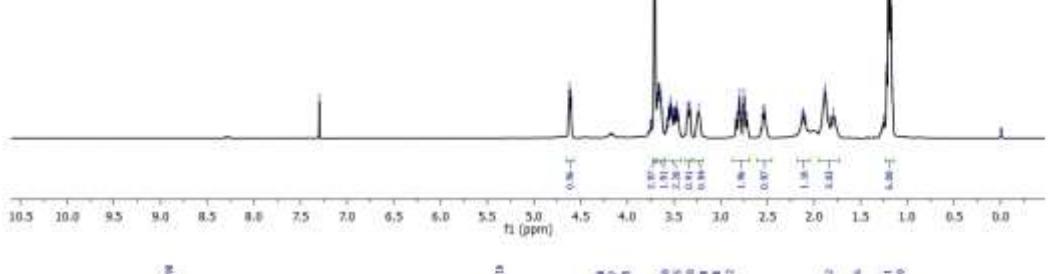
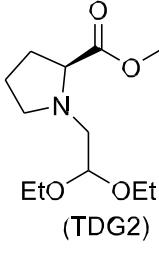
**Fig. S1**  $^1\text{H}$ ,  $^{13}\text{C}$  { $^1\text{H}$ } NMR Spectra of TDG1.

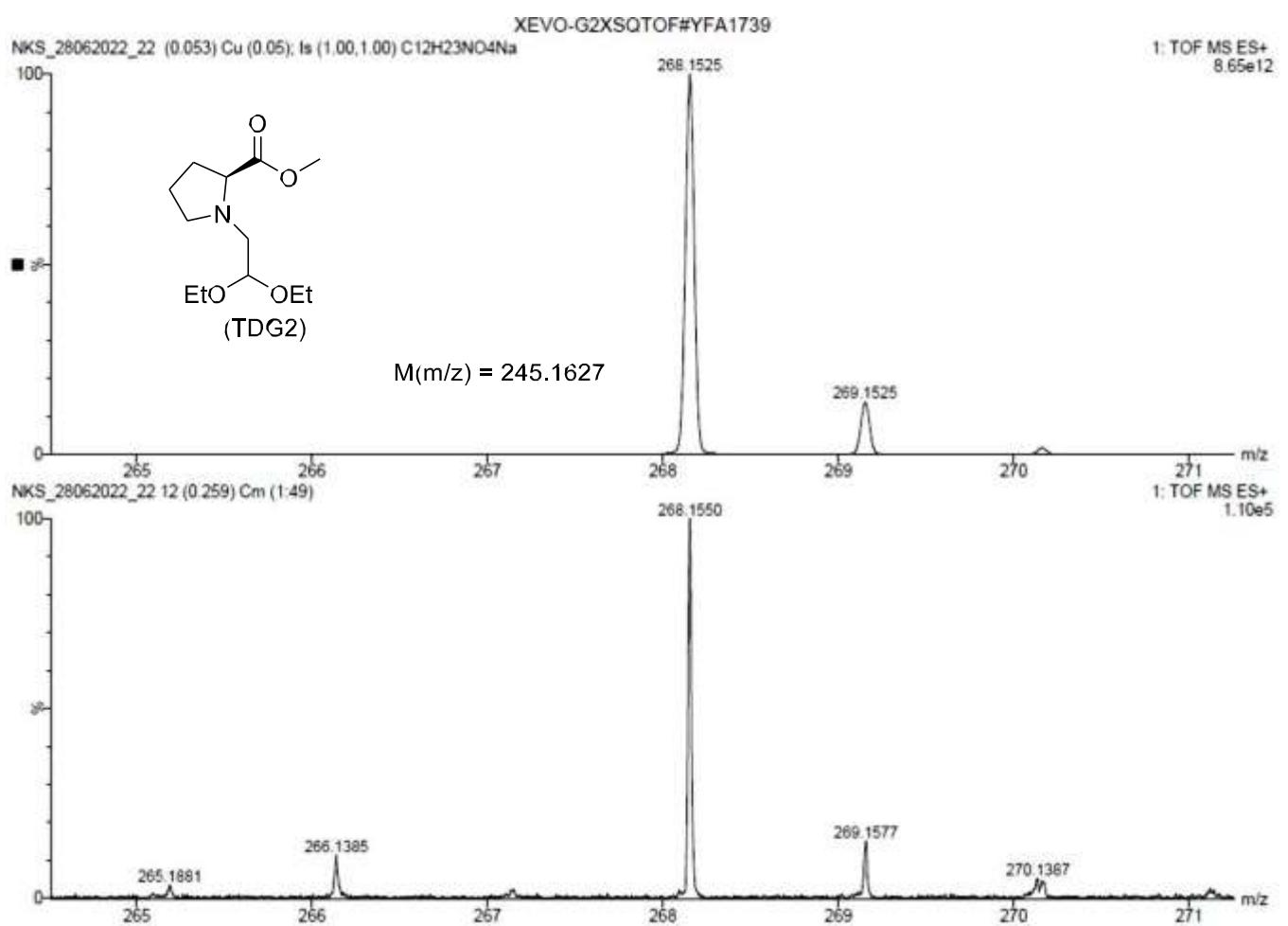


**Fig. Fig. S2 ESI-HRMS Spectra of TDG 1.**

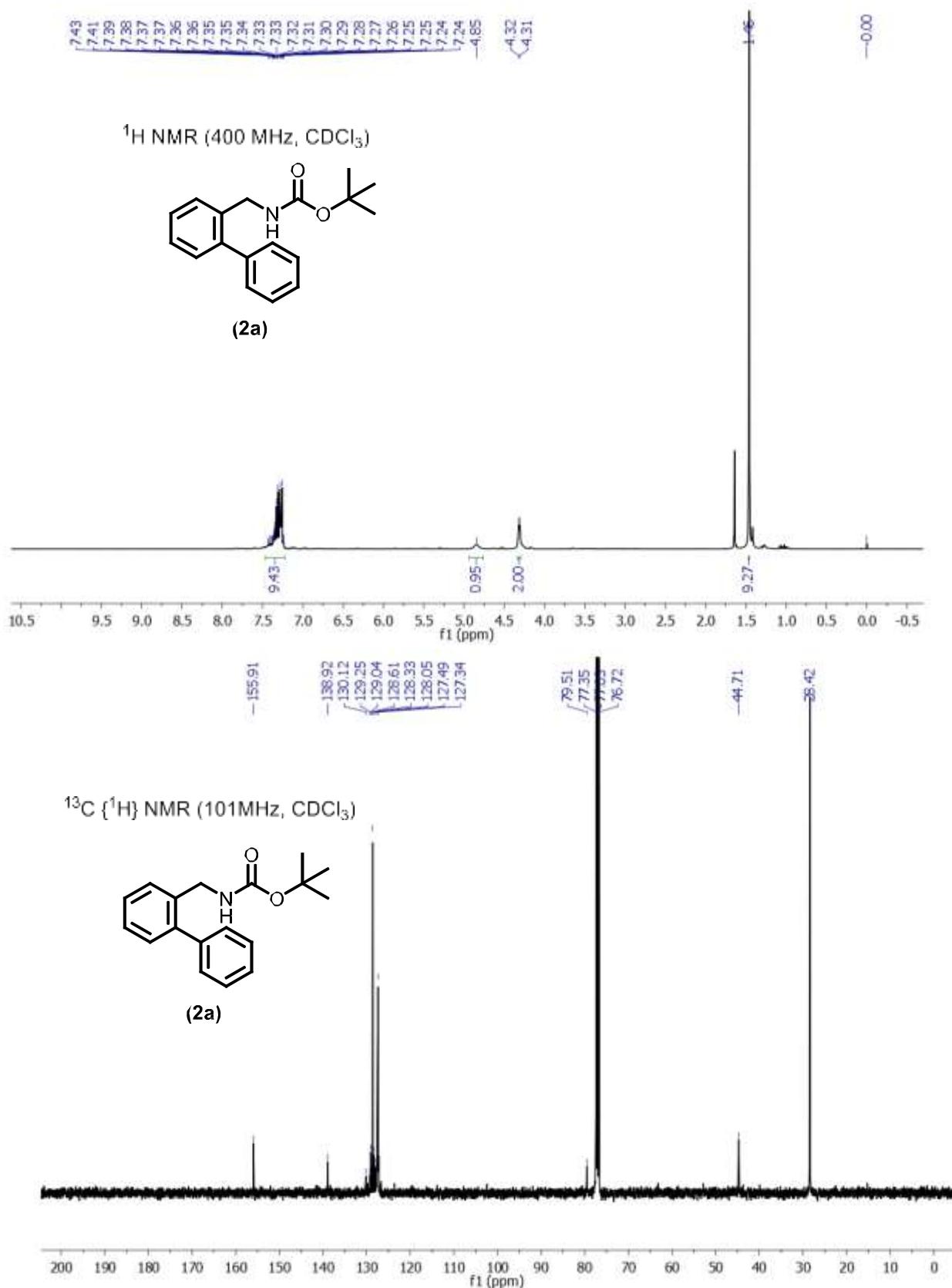
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<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

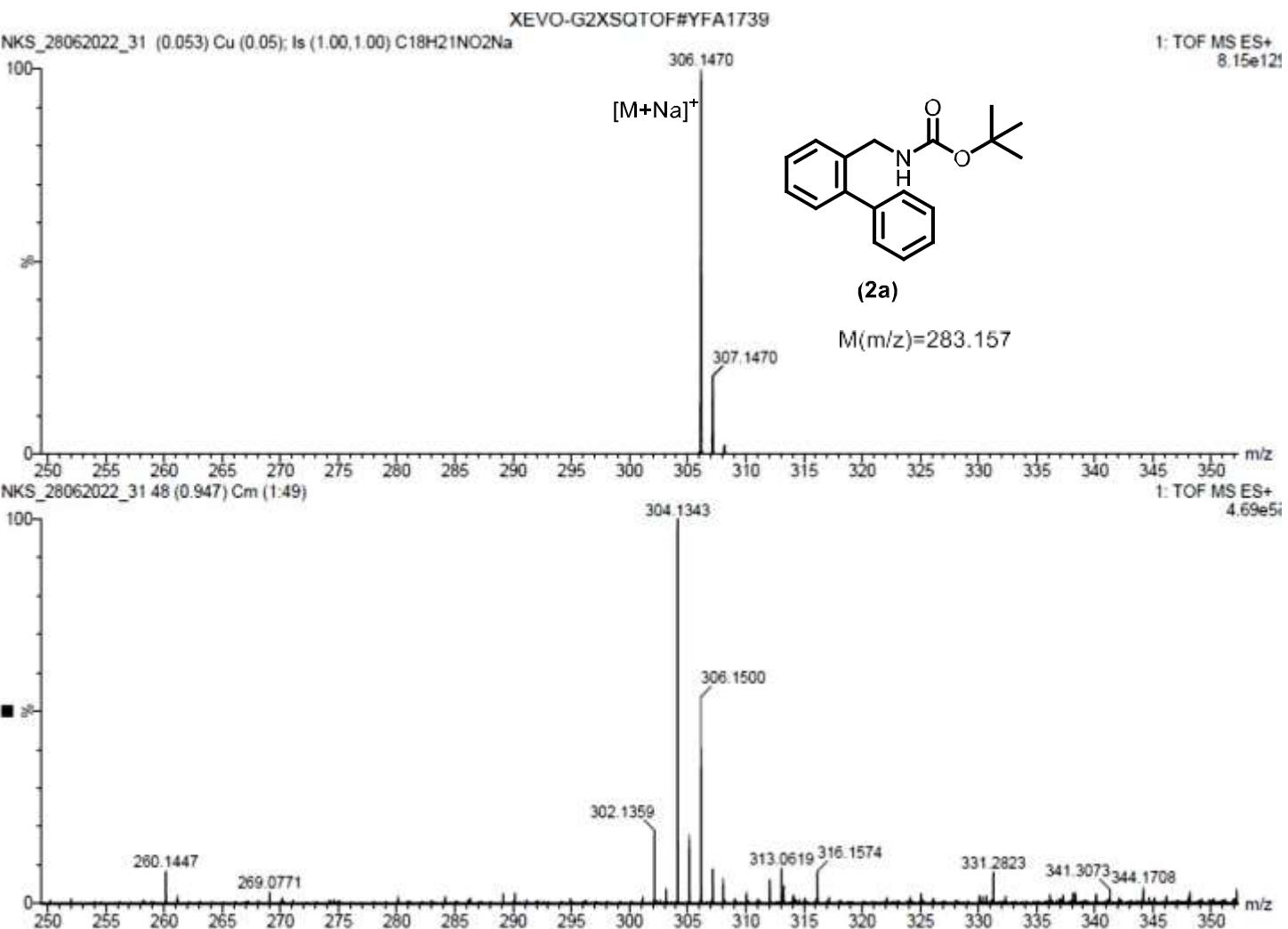




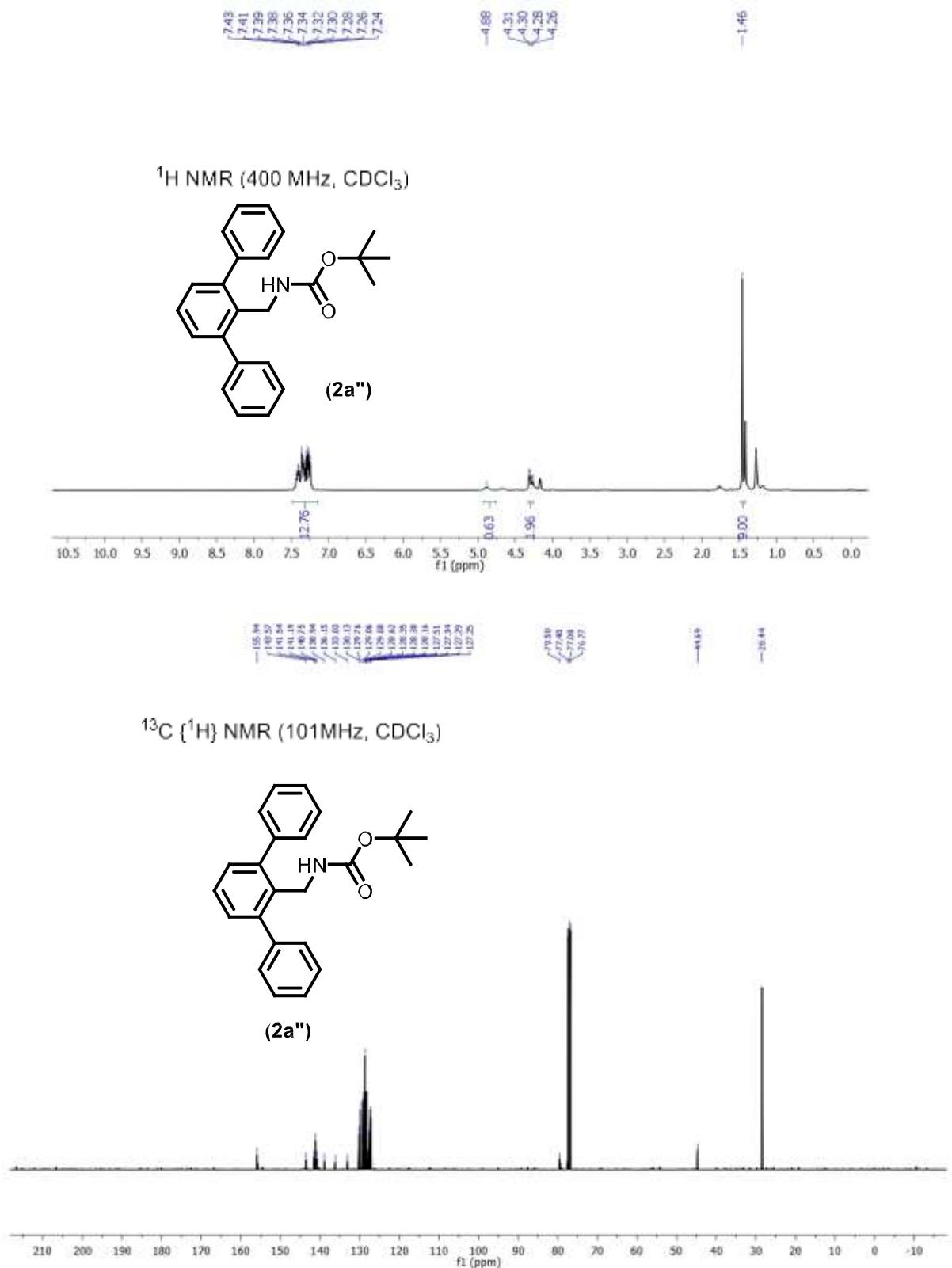
**Fig. S4 ESI-HRMS Spectra of TDG2.**



**Fig. S5** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H} NMR Spectra of compound 2a.



**Fig. S6** ESI-HRMS Spectra of compound **2a**.



**Fig. S7**  $^1\text{H}$ ,  $^{13}\text{C}$  { $^1\text{H}$ } NMR Spectra of compound **2a**

## Display Report

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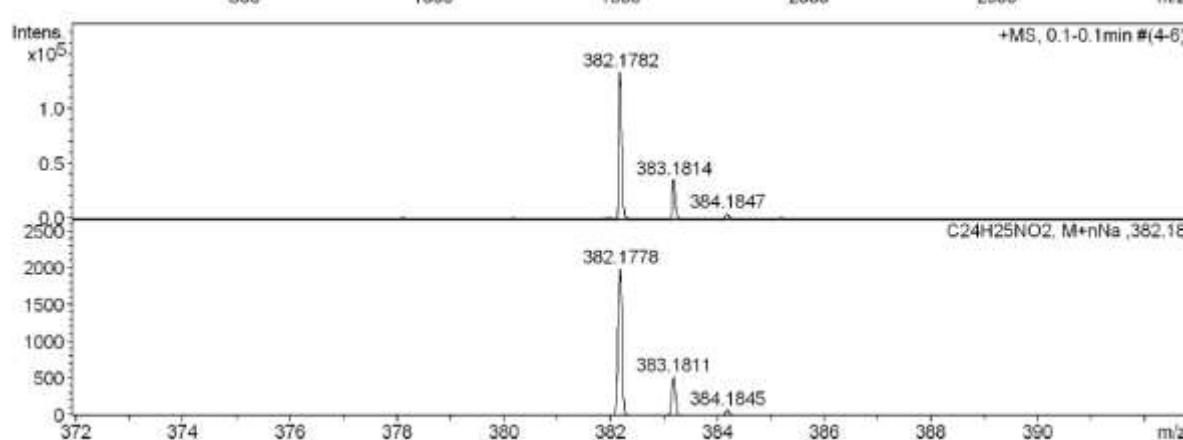
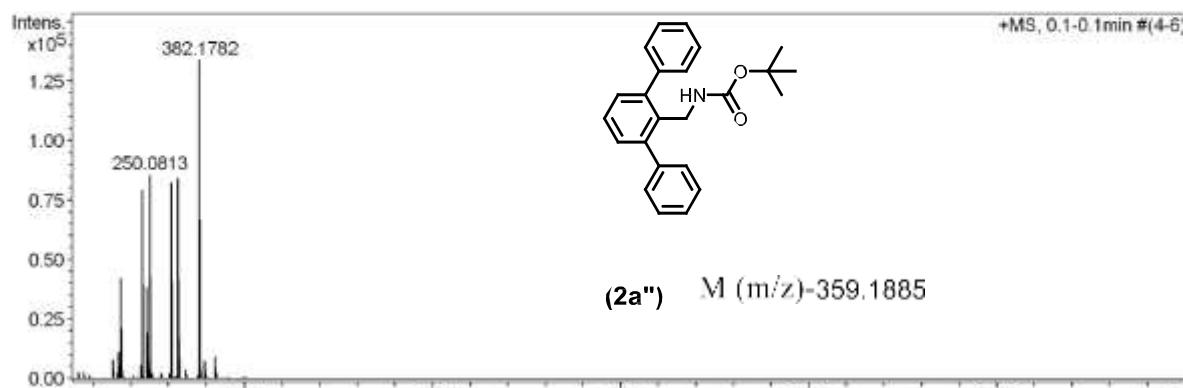
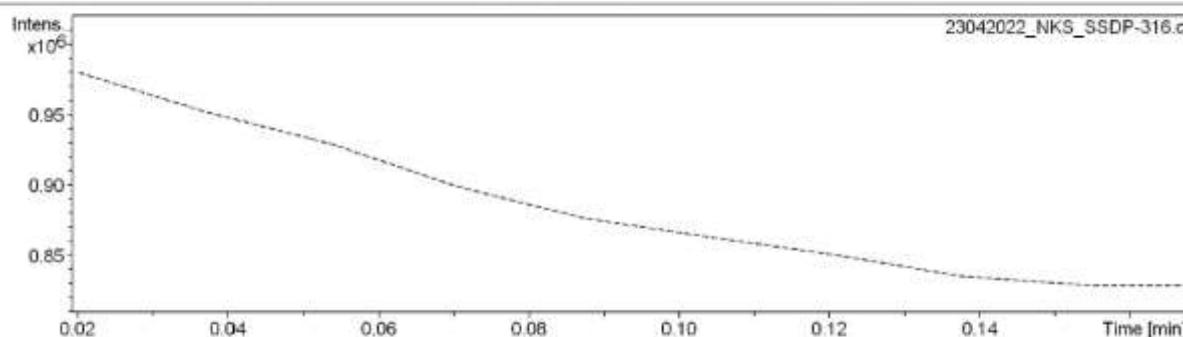
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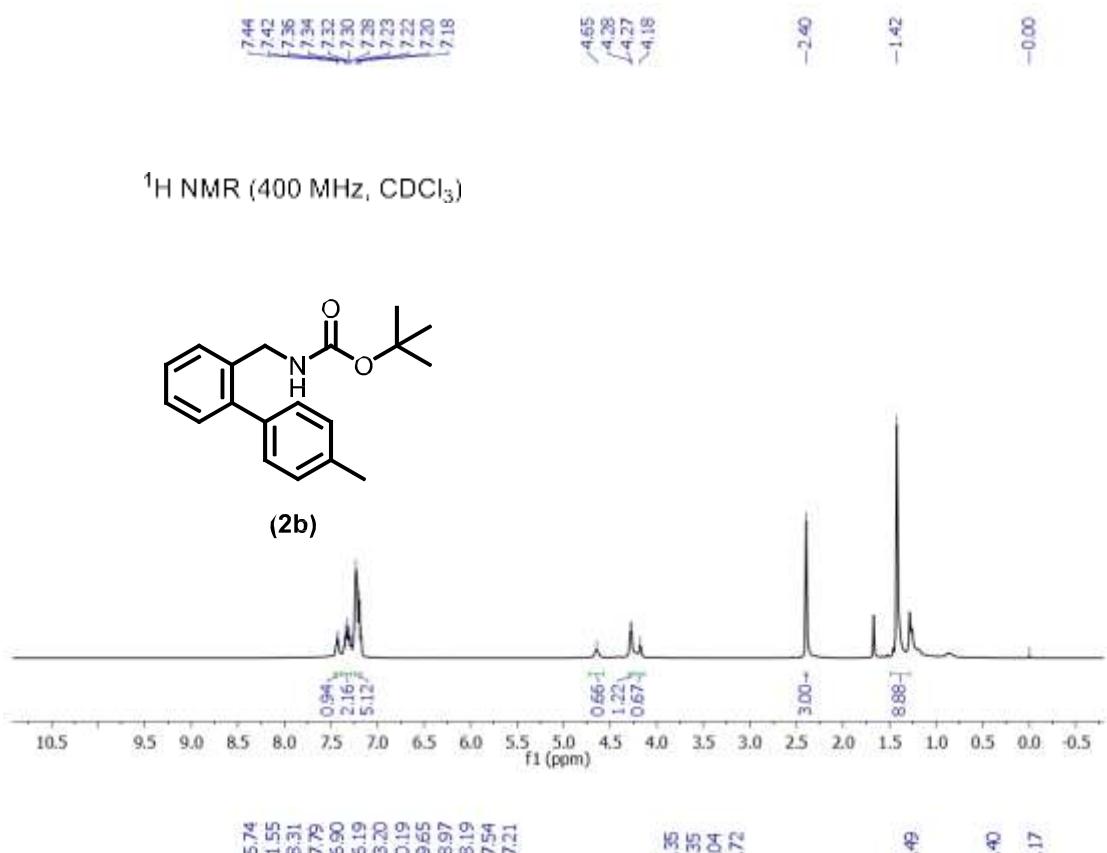
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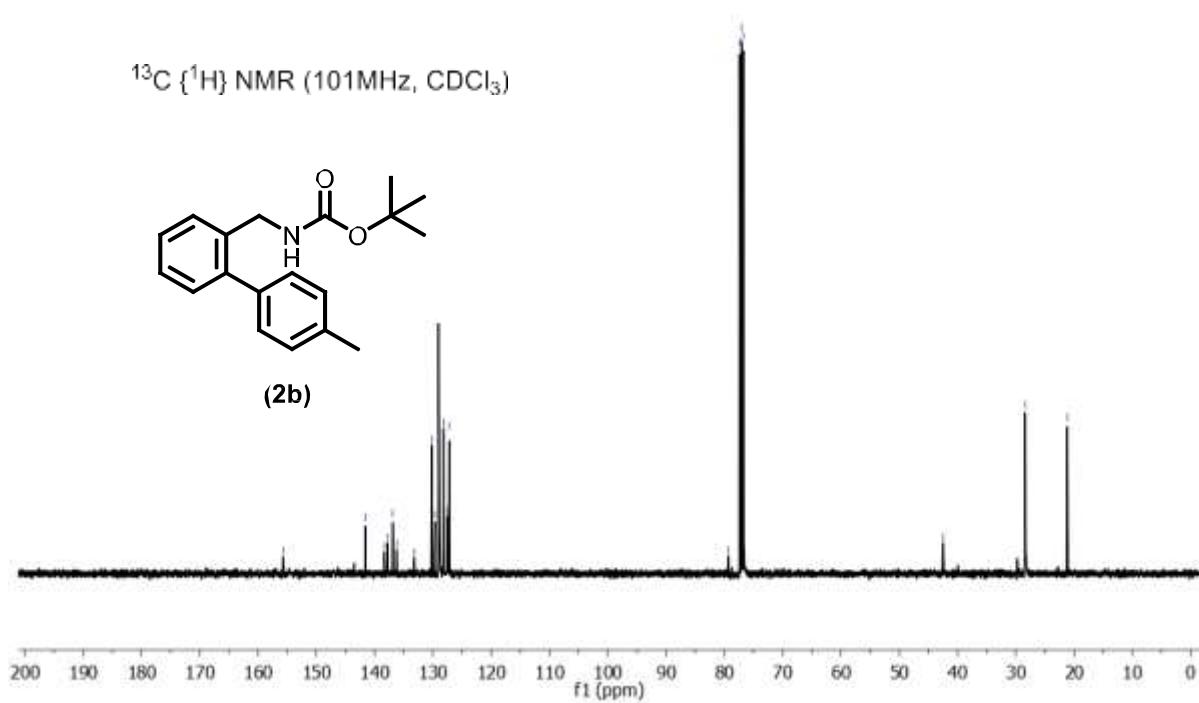


**Fig. S8 ESI-HRMS Spectra of compound 2a''**

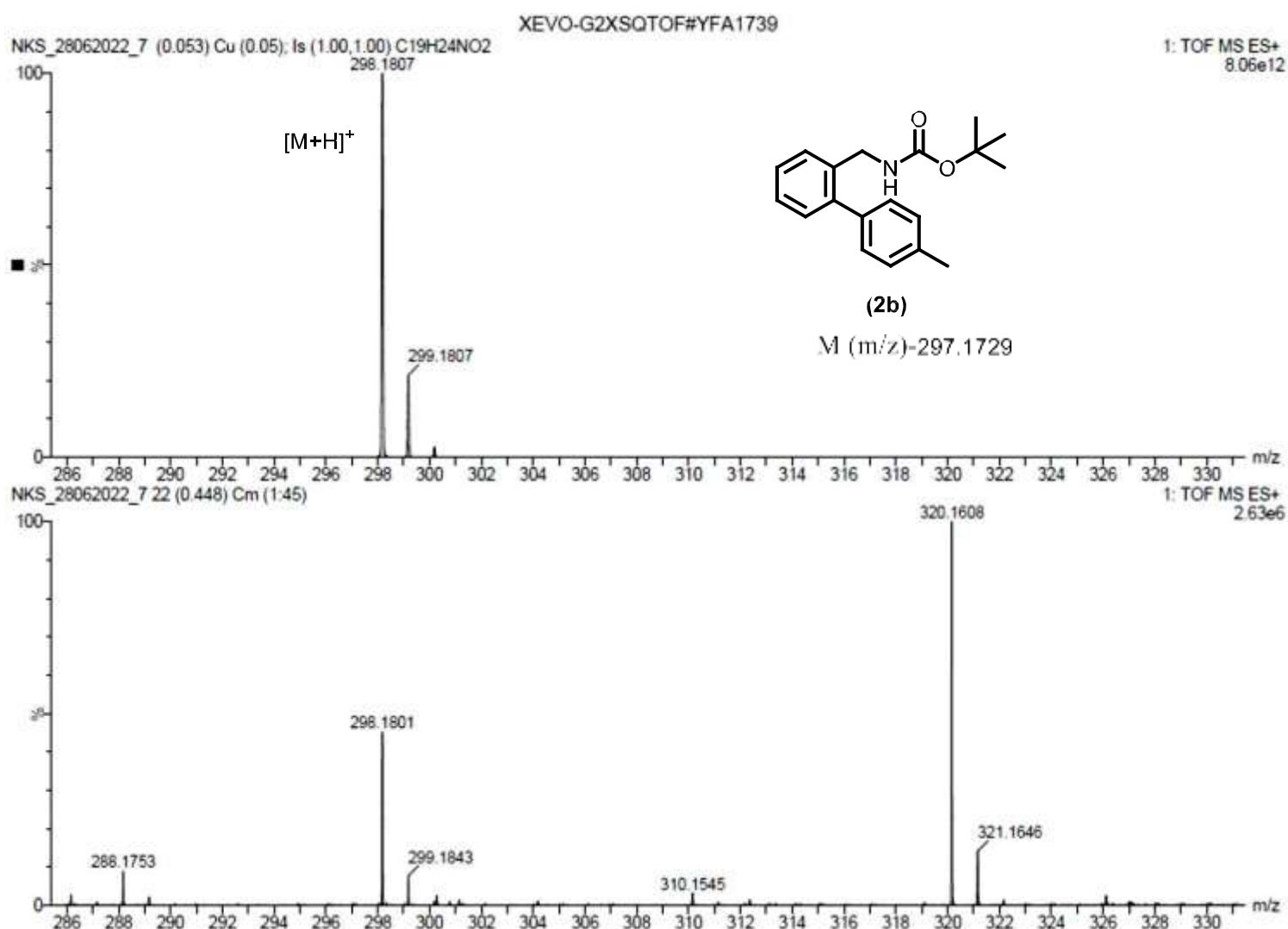
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C} \{^1\text{H}\}$  NMR (101MHz,  $\text{CDCl}_3$ )

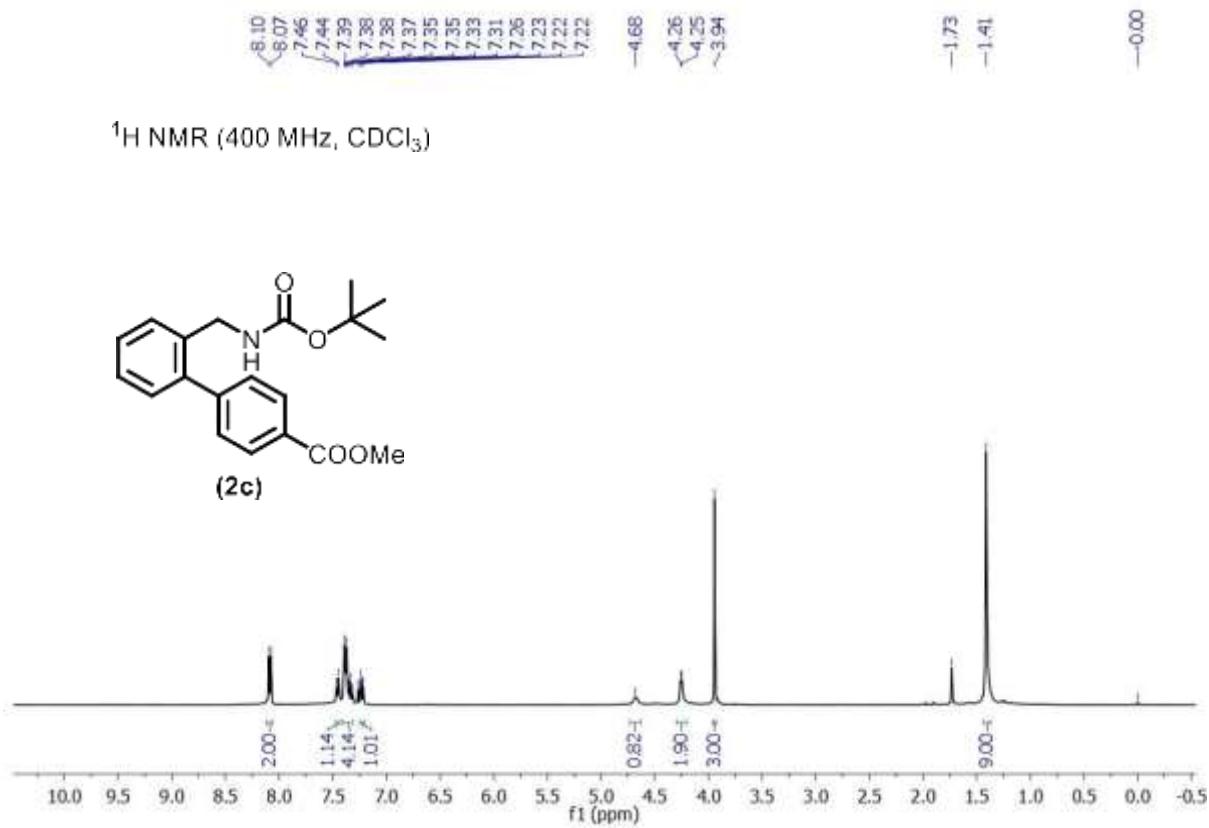


**Fig. S9**  $^1\text{H}$ ,  $^{13}\text{C} \{^1\text{H}\}$  NMR Spectra of compound **2b**.

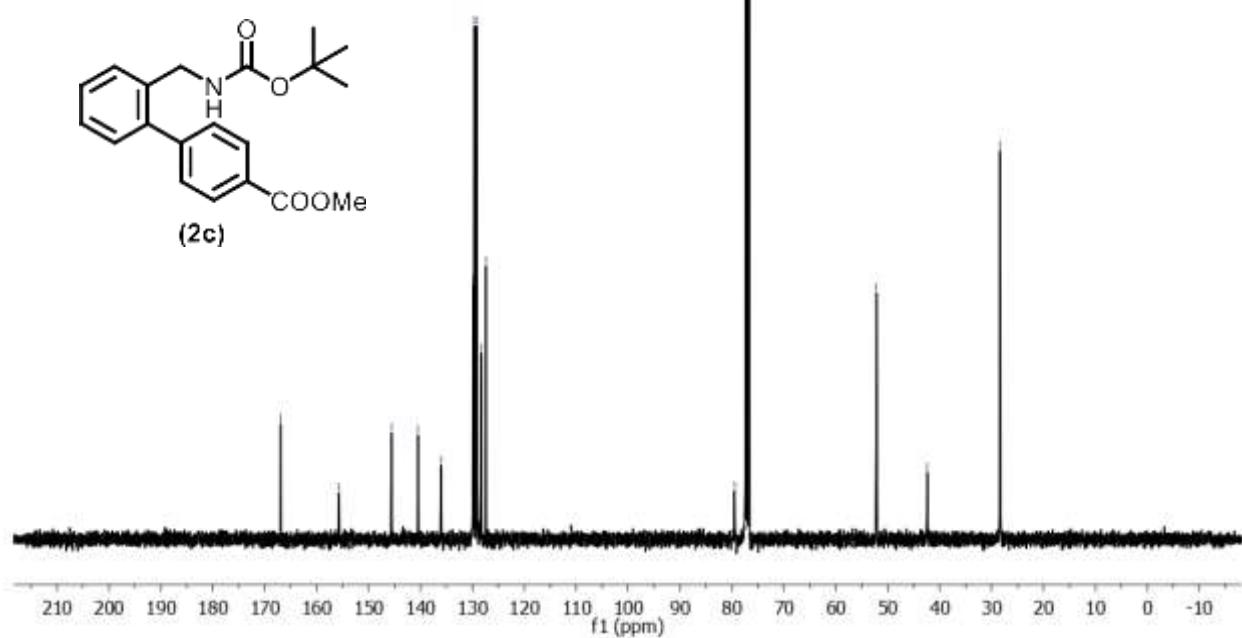


**Fig. S10 ESI-HRMS Spectra of compound 2b.**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C} \{^1\text{H}\}$  NMR (101MHz,  $\text{CDCl}_3$ )



**Fig. S11**  $^1\text{H}$ ,  $^{13}\text{C} \{^1\text{H}\}$  NMR Spectra of compound **2c**.

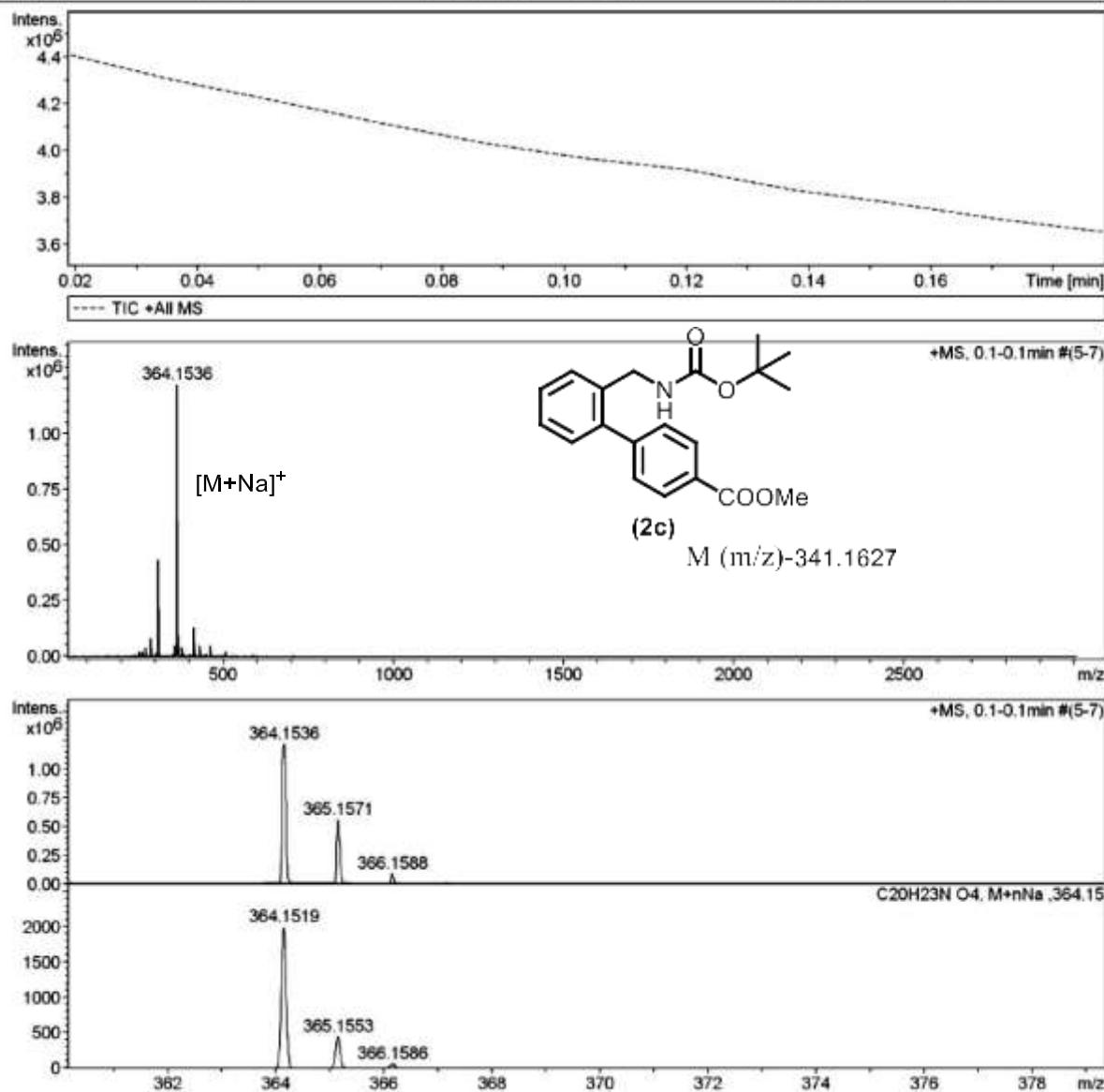
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Comment			

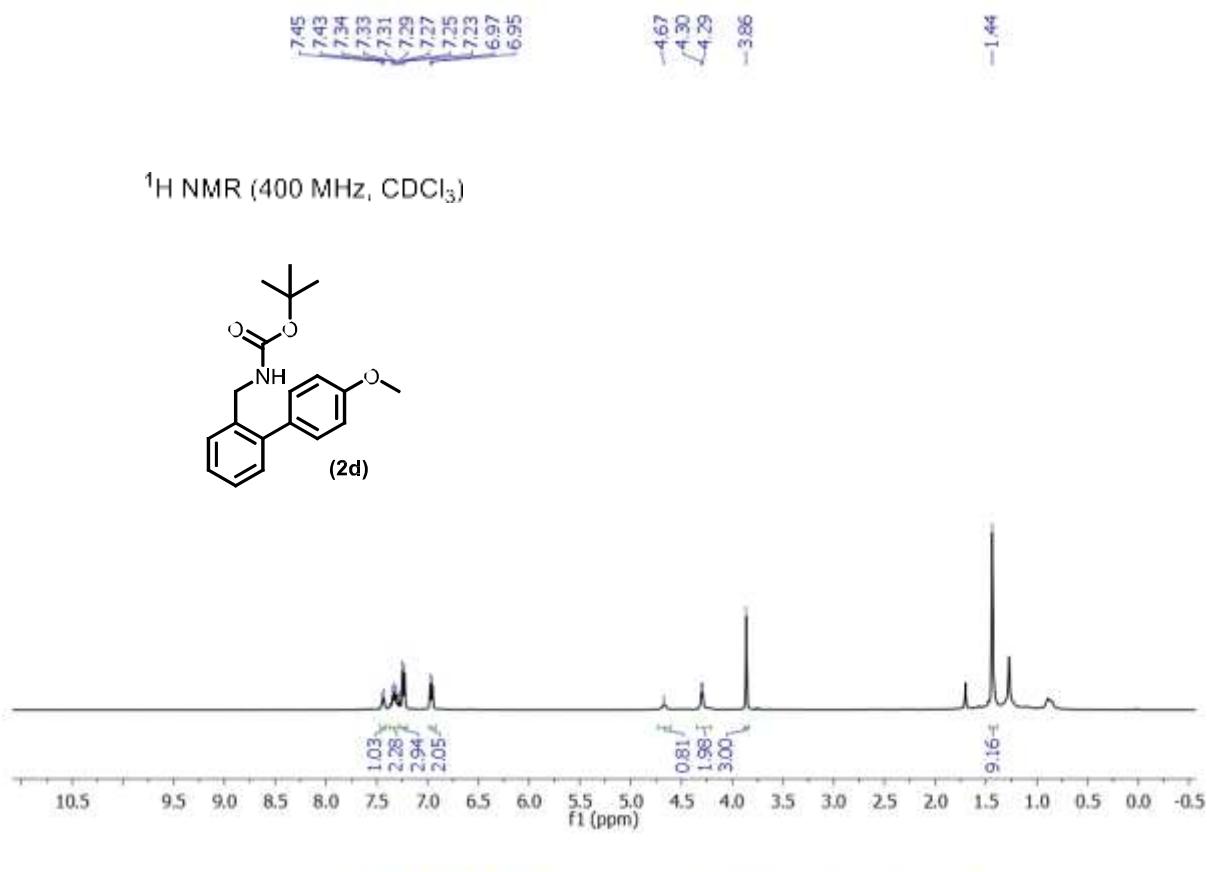
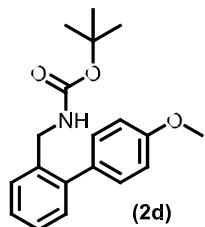
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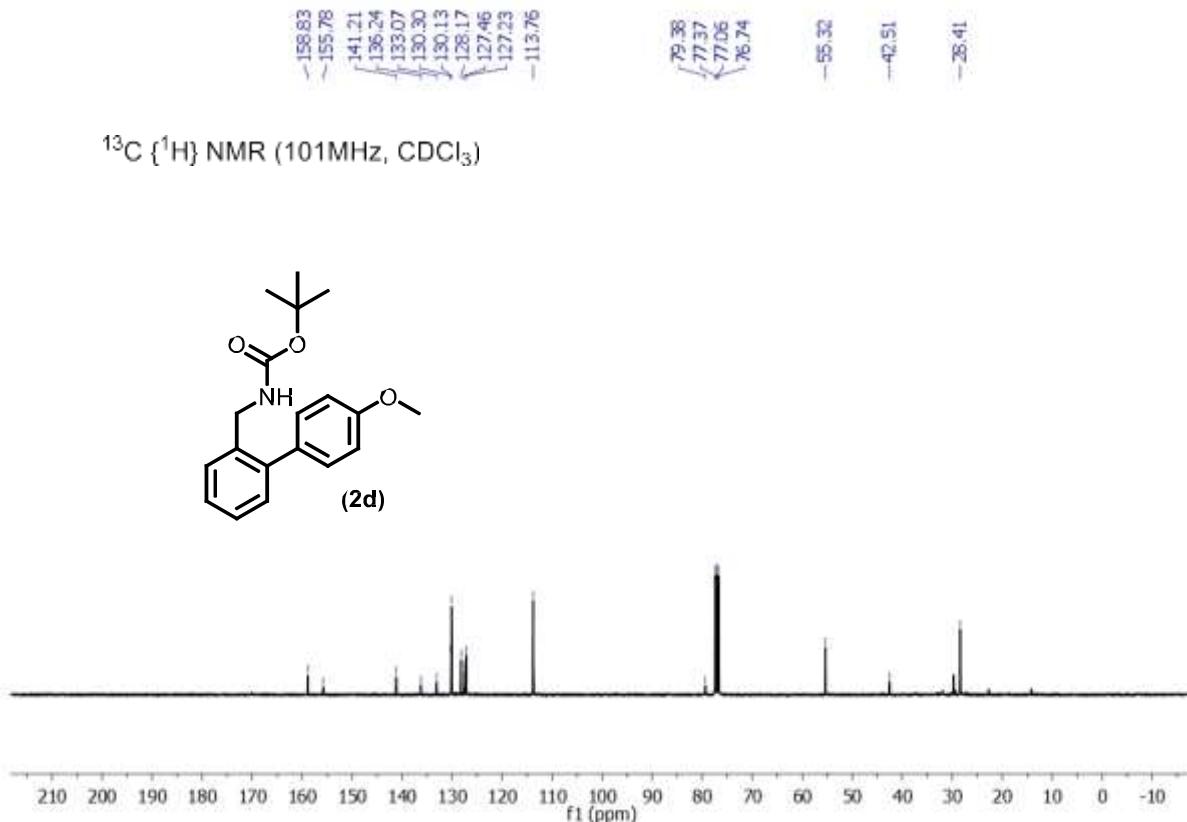
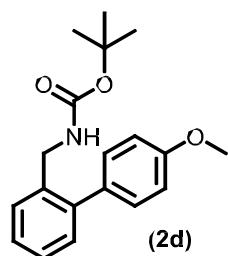


**Fig. S12 ESI-HRMS Spectra of compound 2c.**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C} \{^1\text{H}\}$  NMR (101MHz,  $\text{CDCl}_3$ )



**Fig. S13**  $^1\text{H}$ ,  $^{13}\text{C} \{^1\text{H}\}$  NMR Spectra of compound 2d.

## Display Report

**Analysis Info**

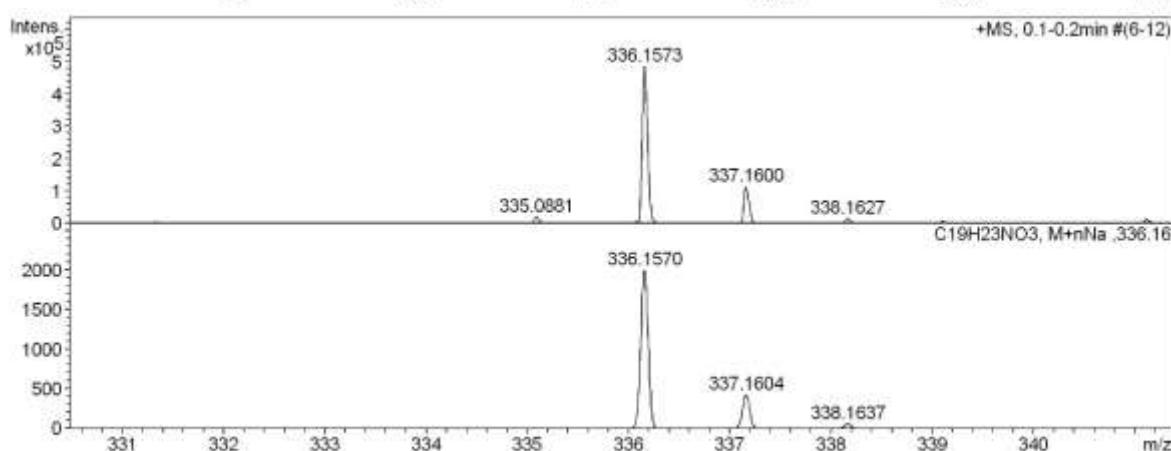
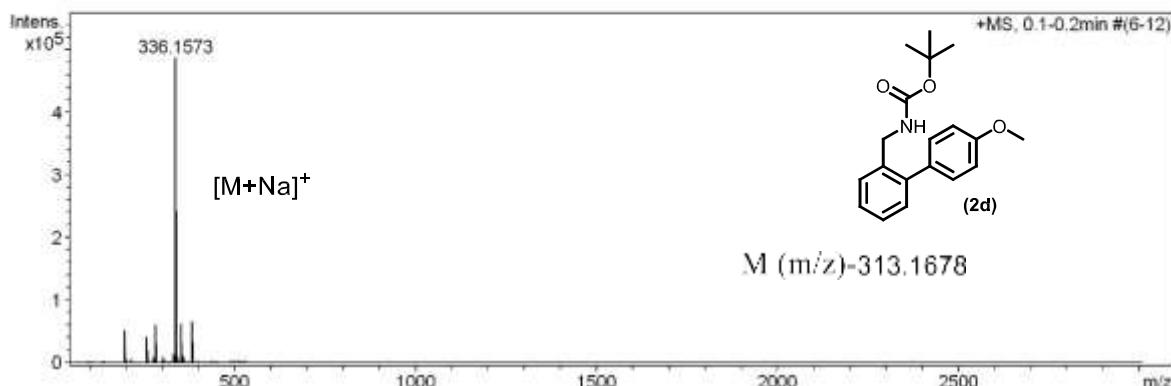
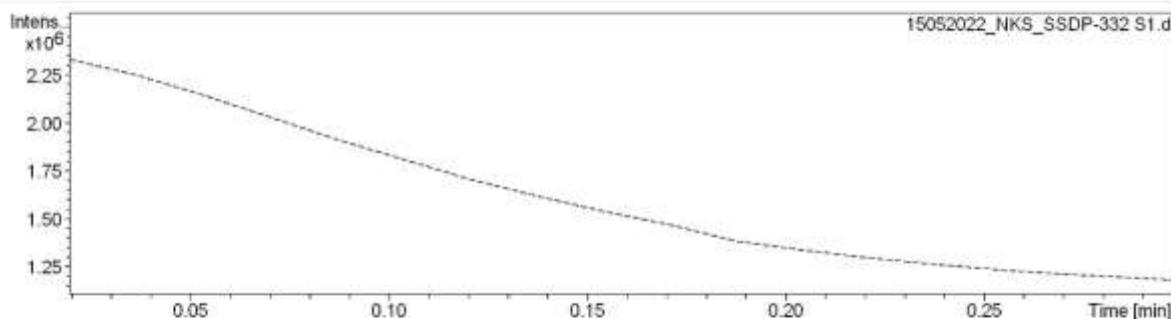
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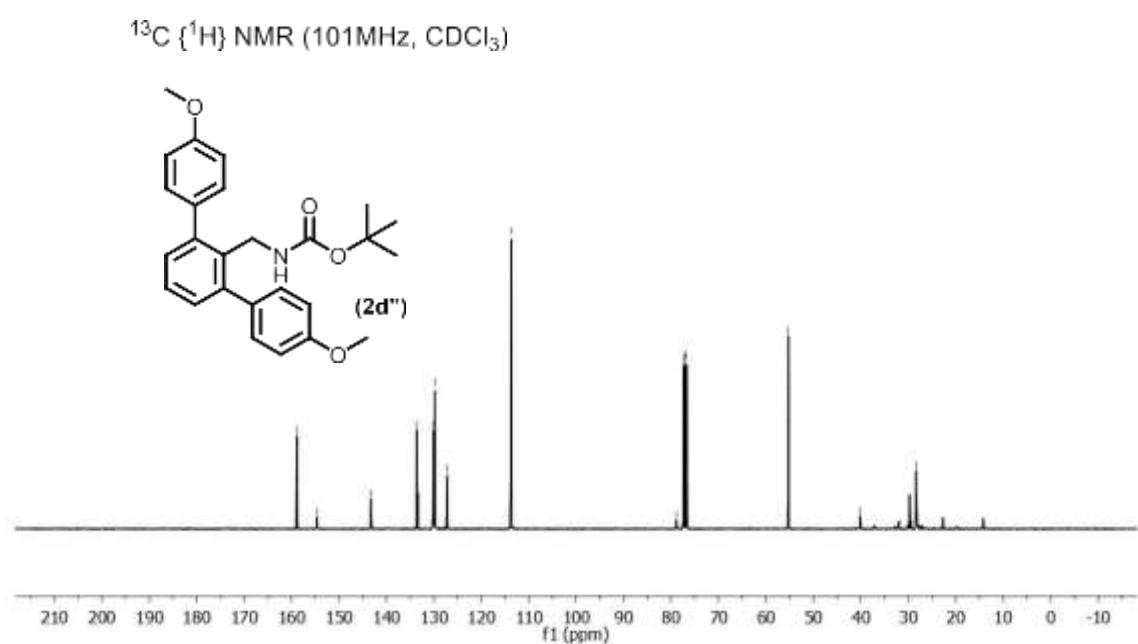
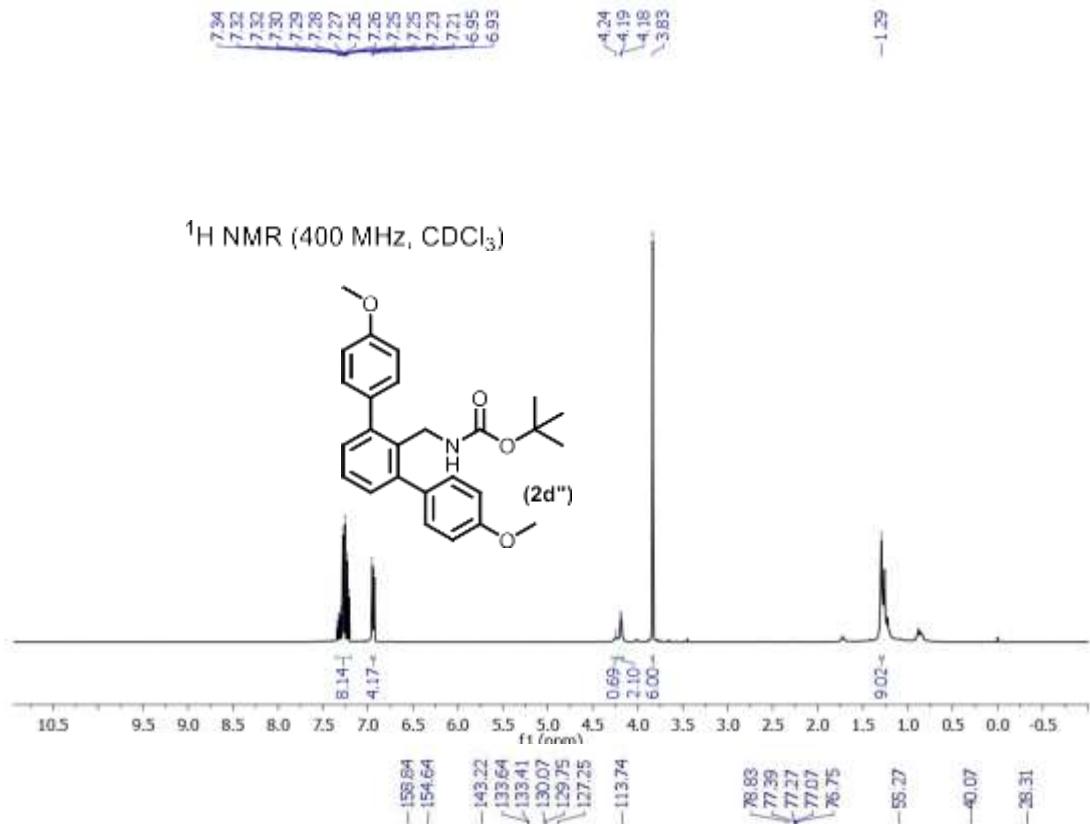
 Operator Amit S.Sahu  
 Instrument micrOTOF-Q II 10337

**Acquisition Parameter**

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Scan End	3000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



**Fig. S14 ESI-HRMS Spectra of compound 2d.**



**Fig. S15** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H} NMR Spectra of compound 2d''.

## Display Report

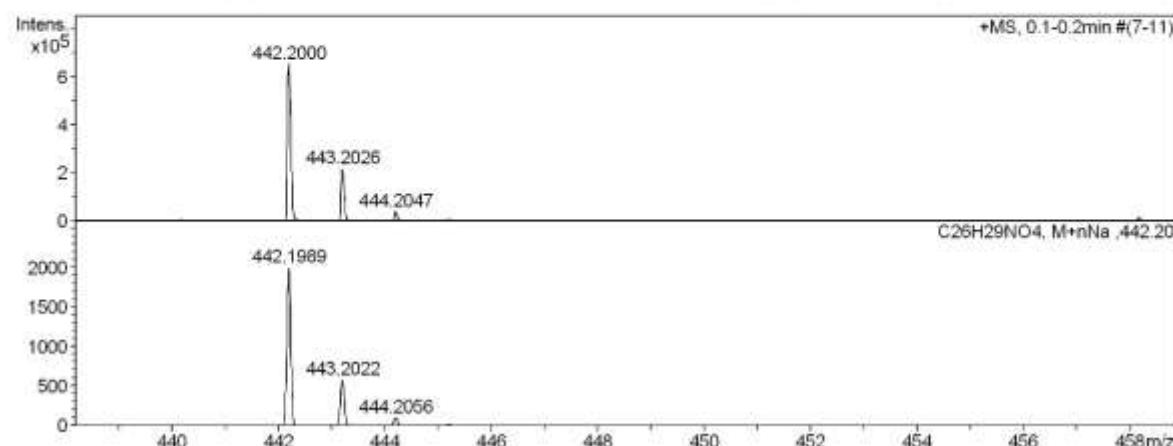
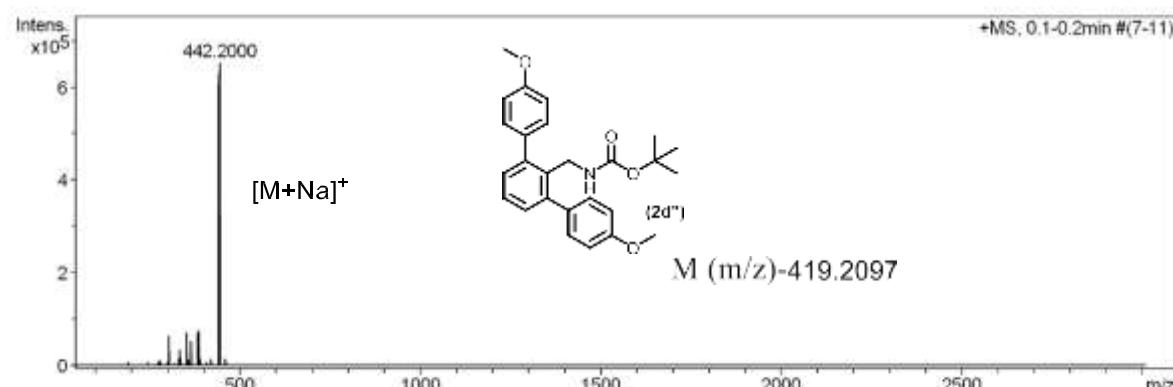
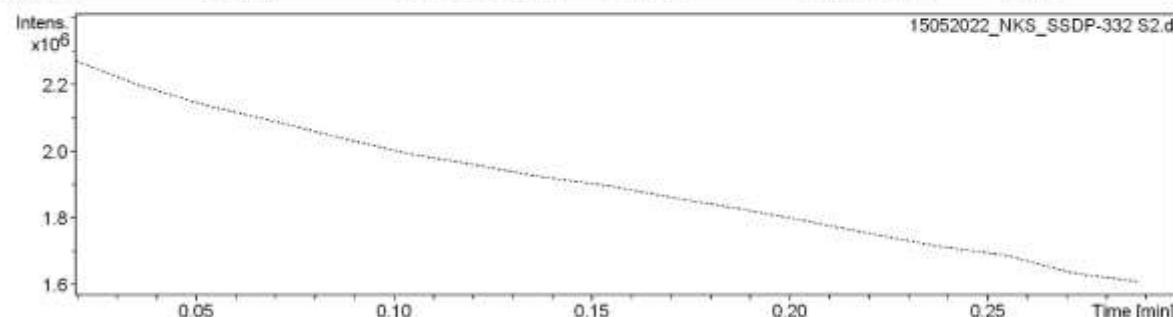
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 Instrument micrOTOF-Q II 10337

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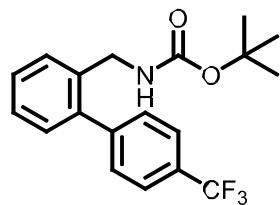
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Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



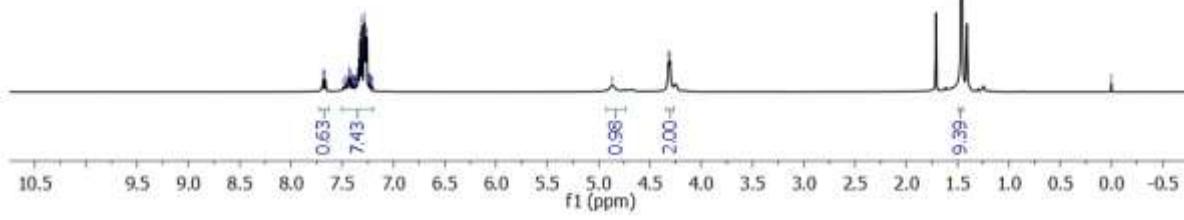
**Fig. S16 ESI-HRMS Spectra of compound 2d”.**



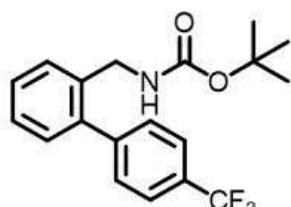
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



(2e)

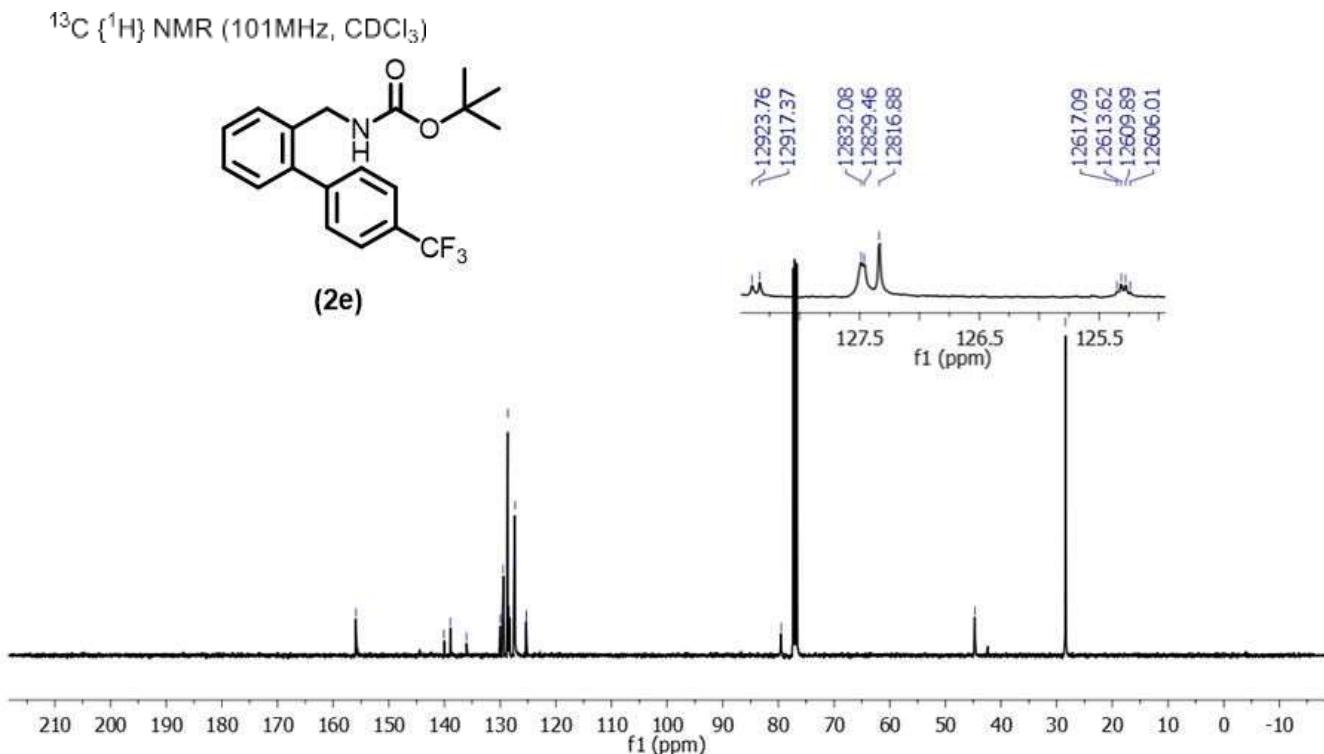


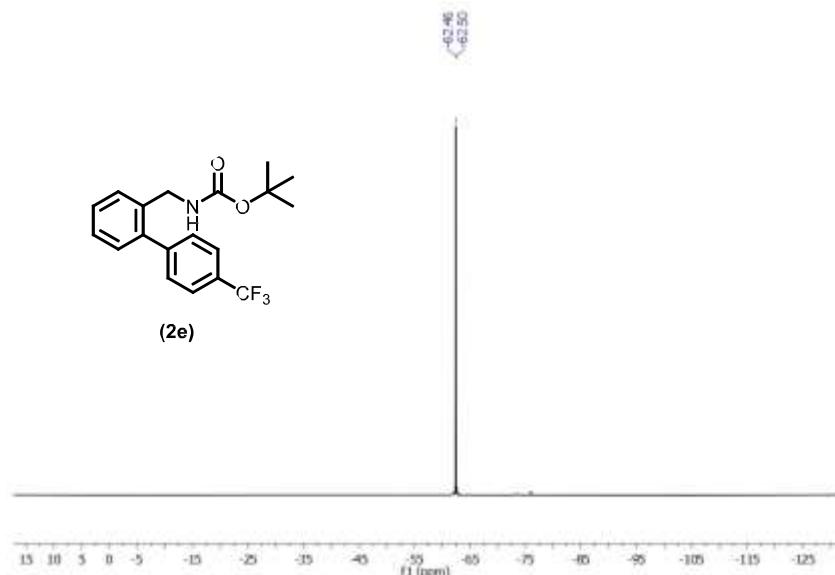
<sup>13</sup>C {<sup>1</sup>H} NMR (101MHz, CDCl<sub>3</sub>)



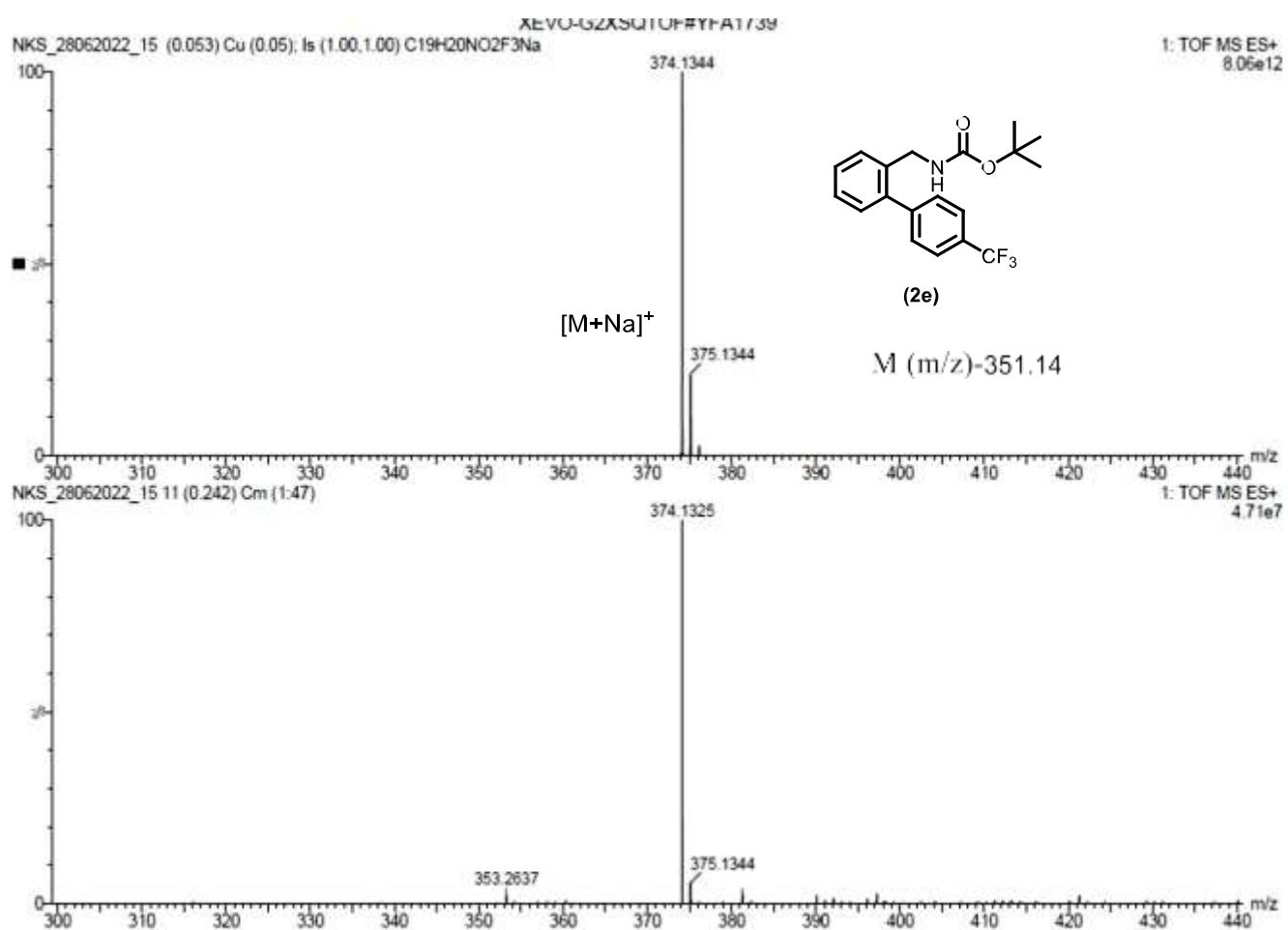
(2e)

-155.93  
 -140.08  
 -138.92  
 -136.02  
 -130.15  
 -129.96  
 -129.43  
 -128.61  
 -128.40  
 -128.33  
 -127.49  
 -127.46  
 -127.33  
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 -125.31  
 -125.28  
 -125.24  
 -79.51  
 -44.70  
 -28.42

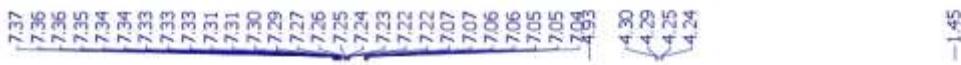




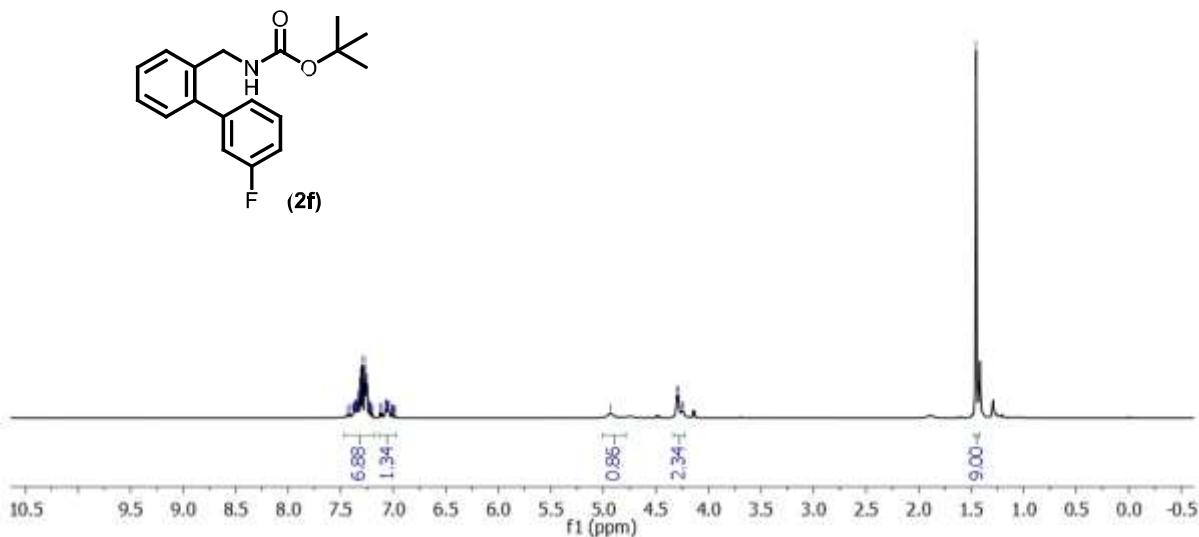
**Fig. S17**  $^1\text{H}$ ,  $^{13}\text{C}$  { $^1\text{H}$ },  $^{19}\text{F}$  NMR Spectra of compound **2e**.



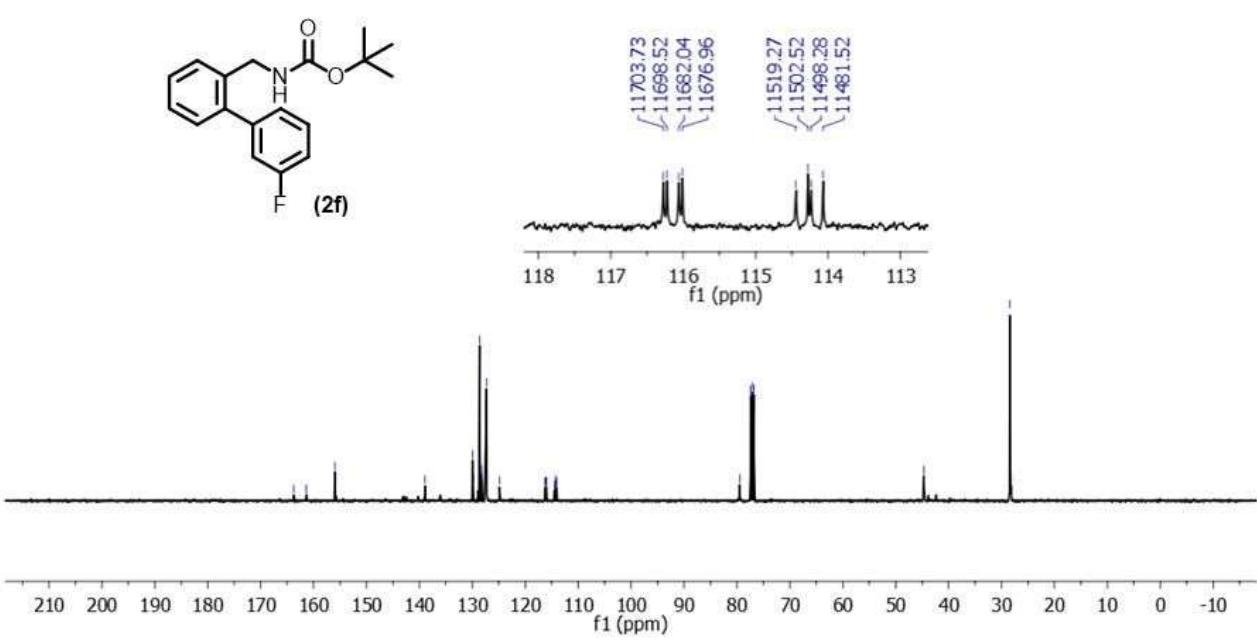
**Fig. S18** ESI-HRMS Spectra of compound **2e**.

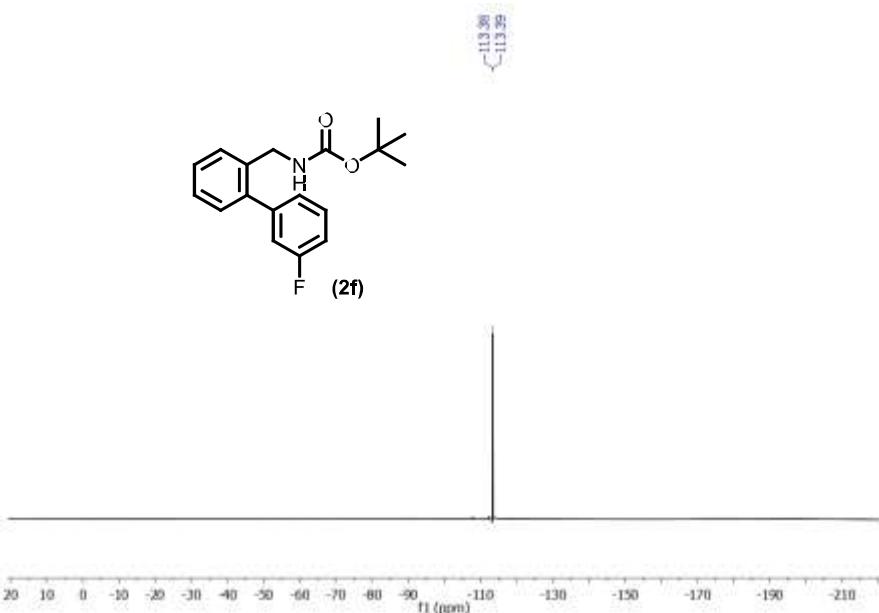


$^1\text{H}$  NMR ( $400 \text{ MHz}, \text{CDCl}_3$ )

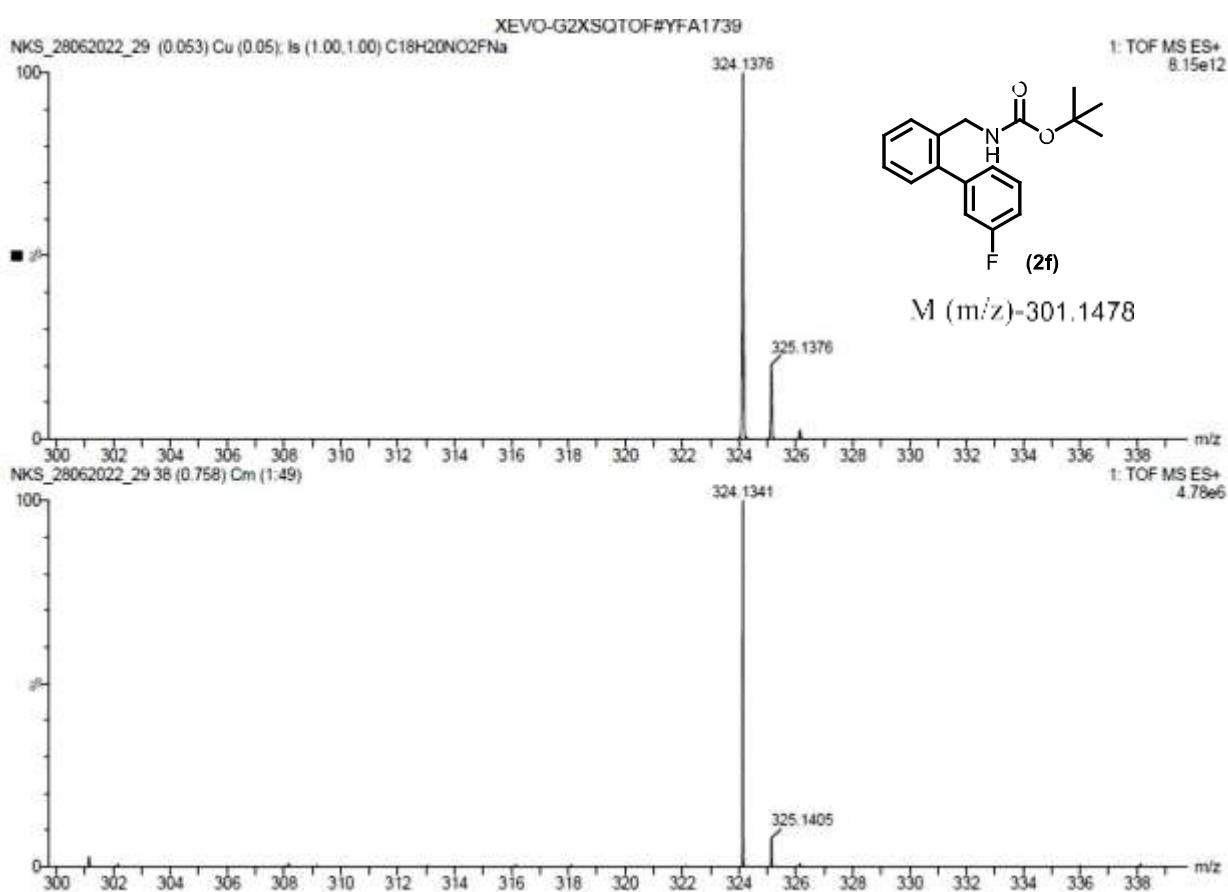


$^{13}\text{C} \{^1\text{H}\}$  NMR ( $101 \text{ MHz}, \text{CDCl}_3$ )



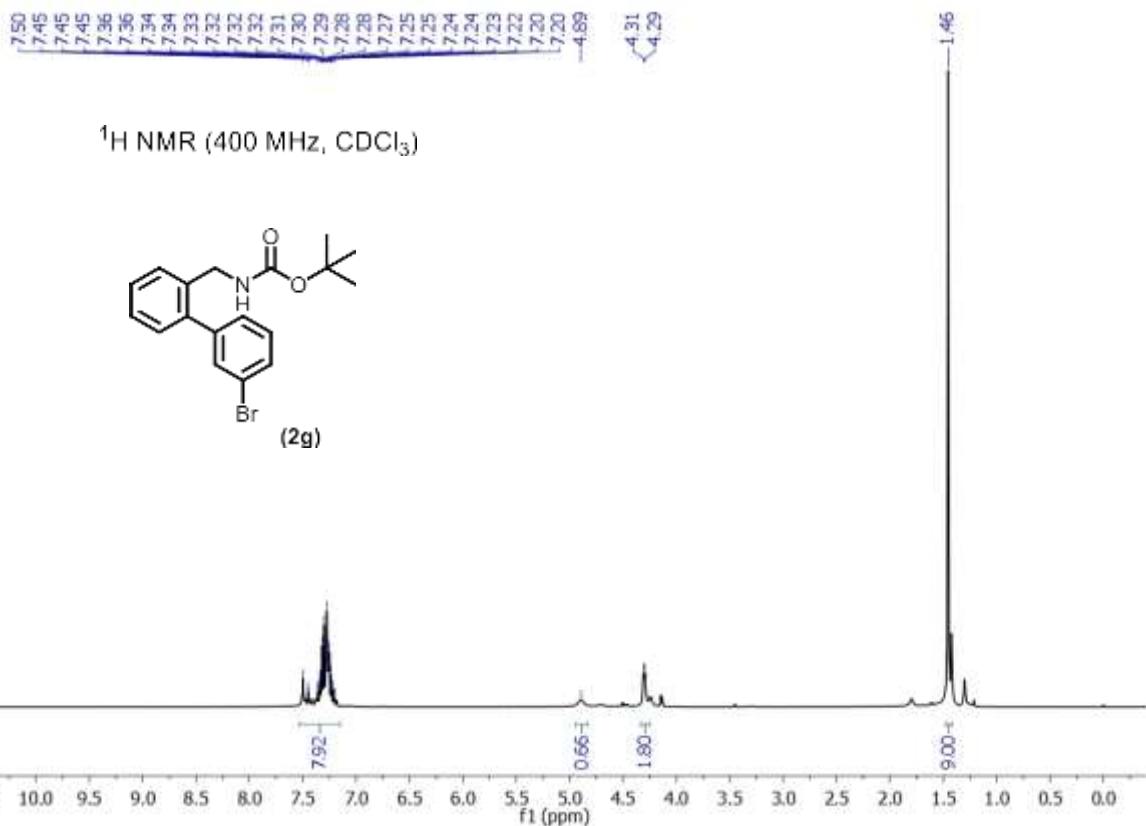


**Fig. S19** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, <sup>19</sup>F NMR Spectra of compound **2f**.

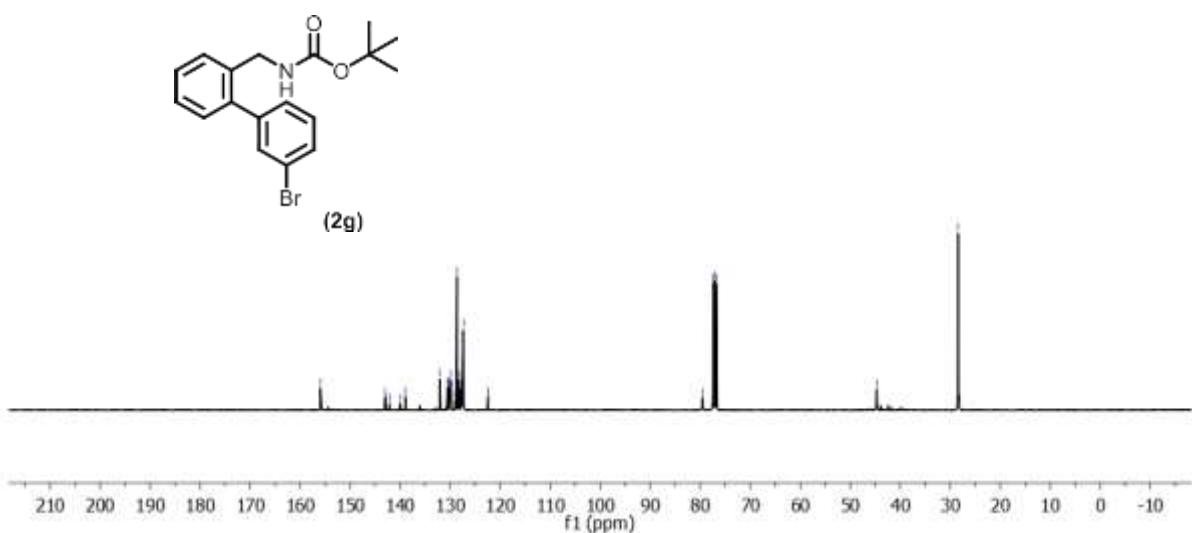


**Fig. S20** ESI-HRMS Spectra of compound **2f**.

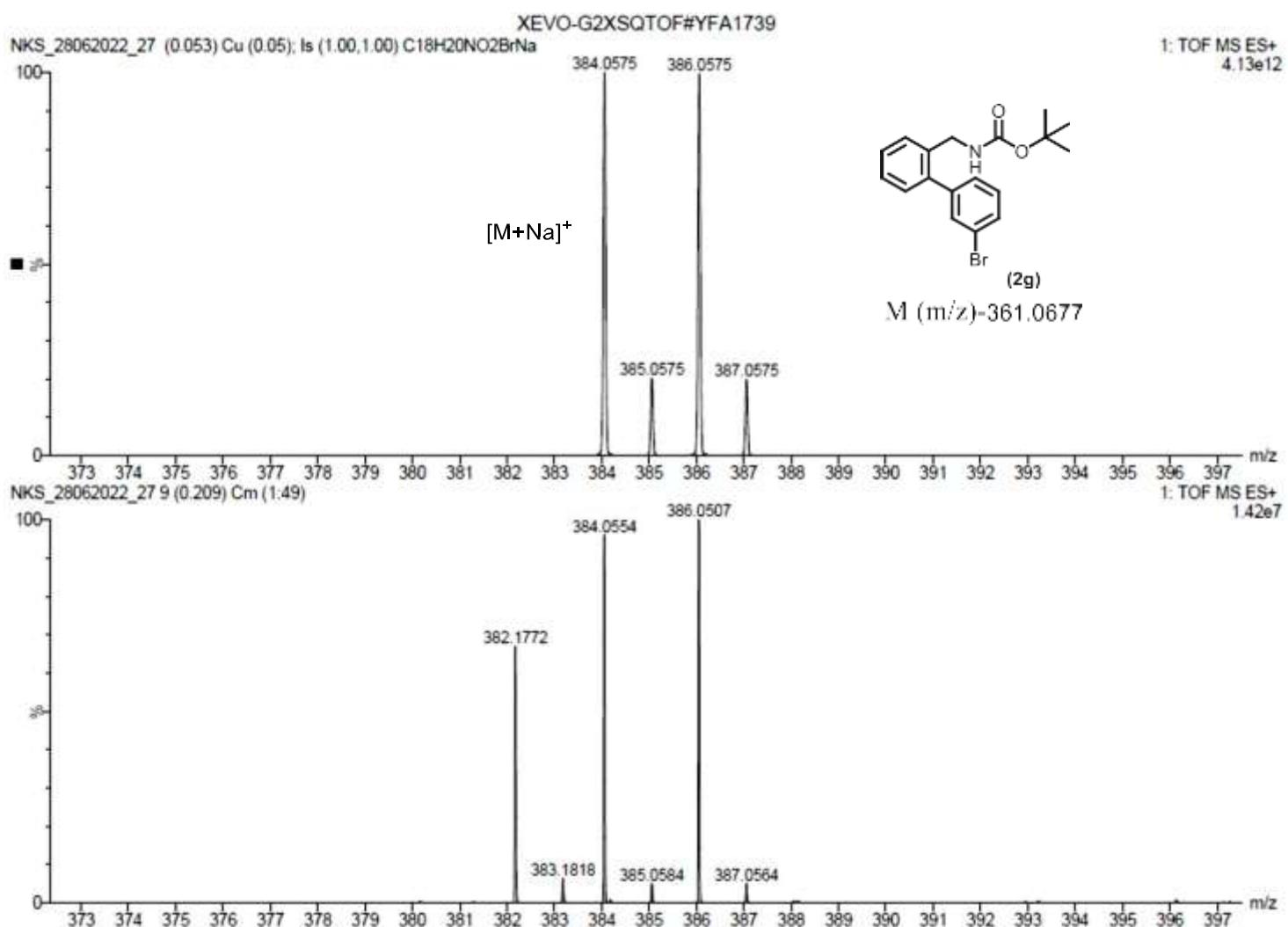
[M+Na]<sup>+</sup>



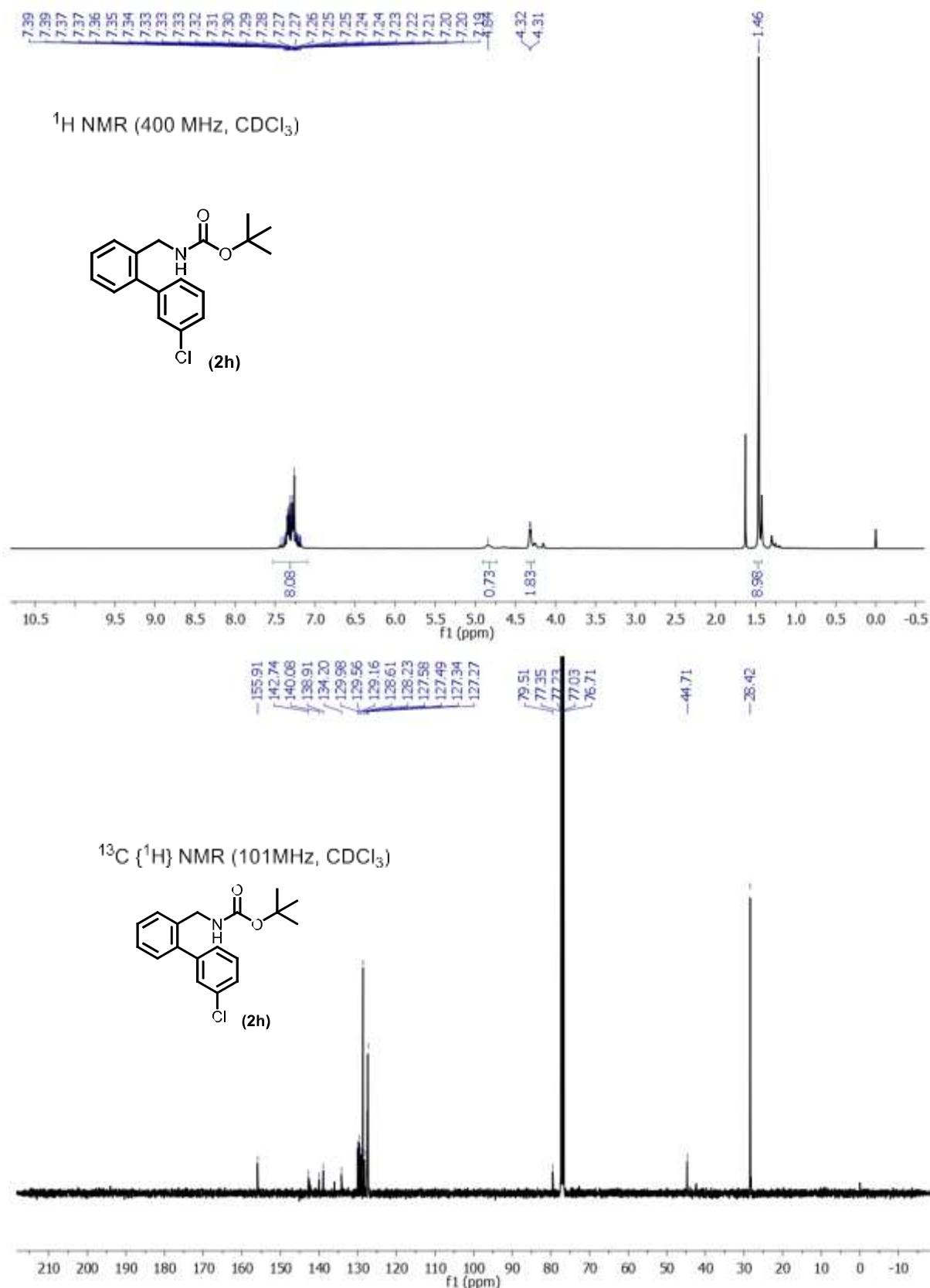
<sup>13</sup>C {<sup>1</sup>H} NMR (101MHz, CDCl<sub>3</sub>)



**Fig. S21** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound **2g**.



**Fig. S22 ESI-HRMS Spectra of compound 2g.**



**Fig. S23**  $^1\text{H}$ ,  $^{13}\text{C}$  { $^1\text{H}$ }, NMR Spectra of compound **2h**.

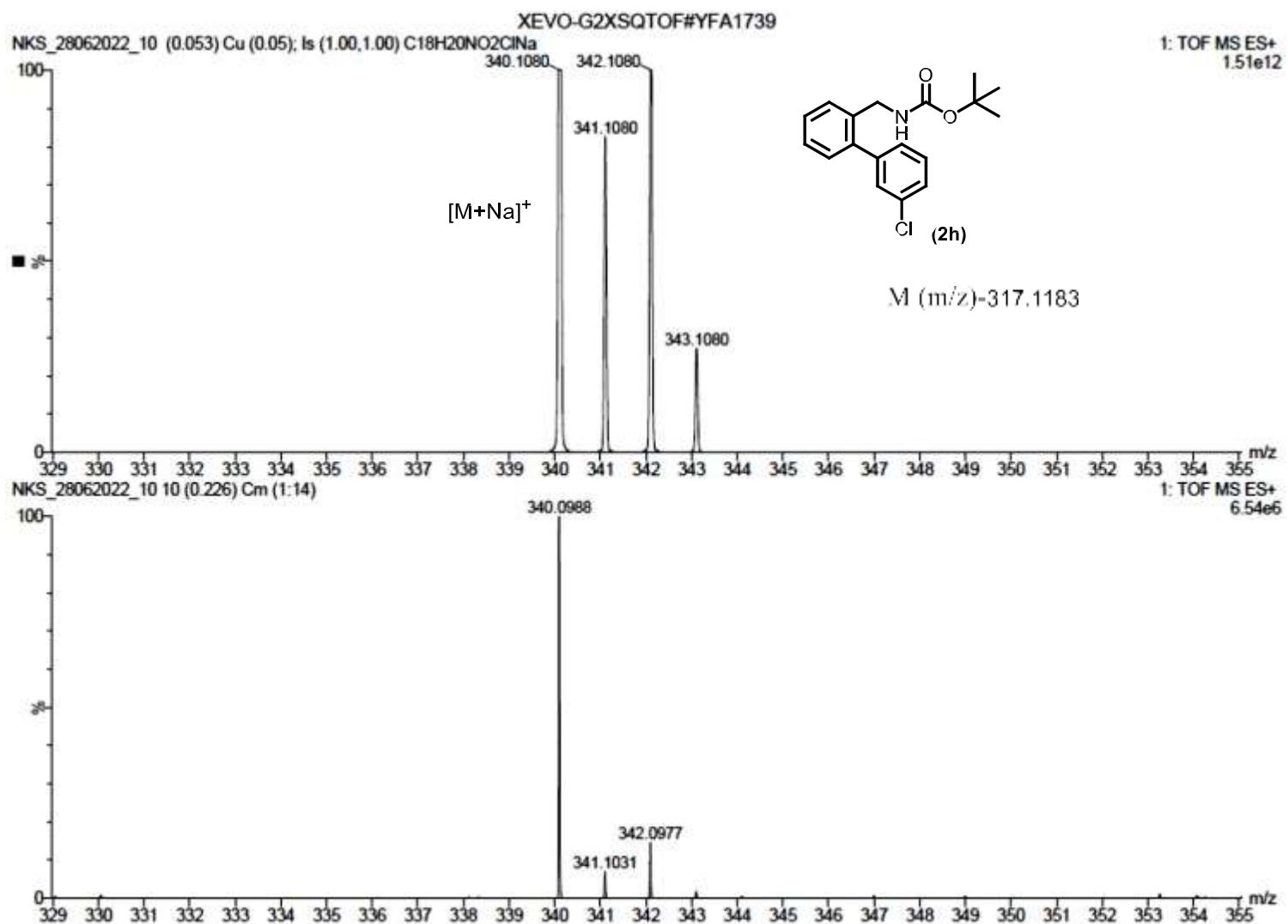
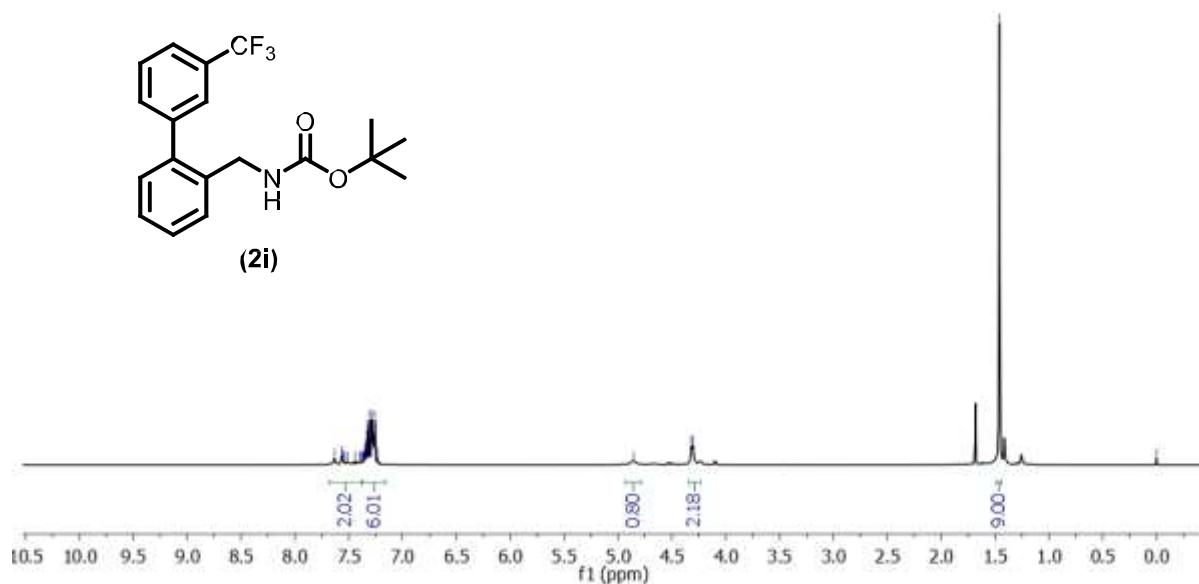
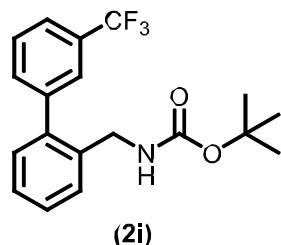


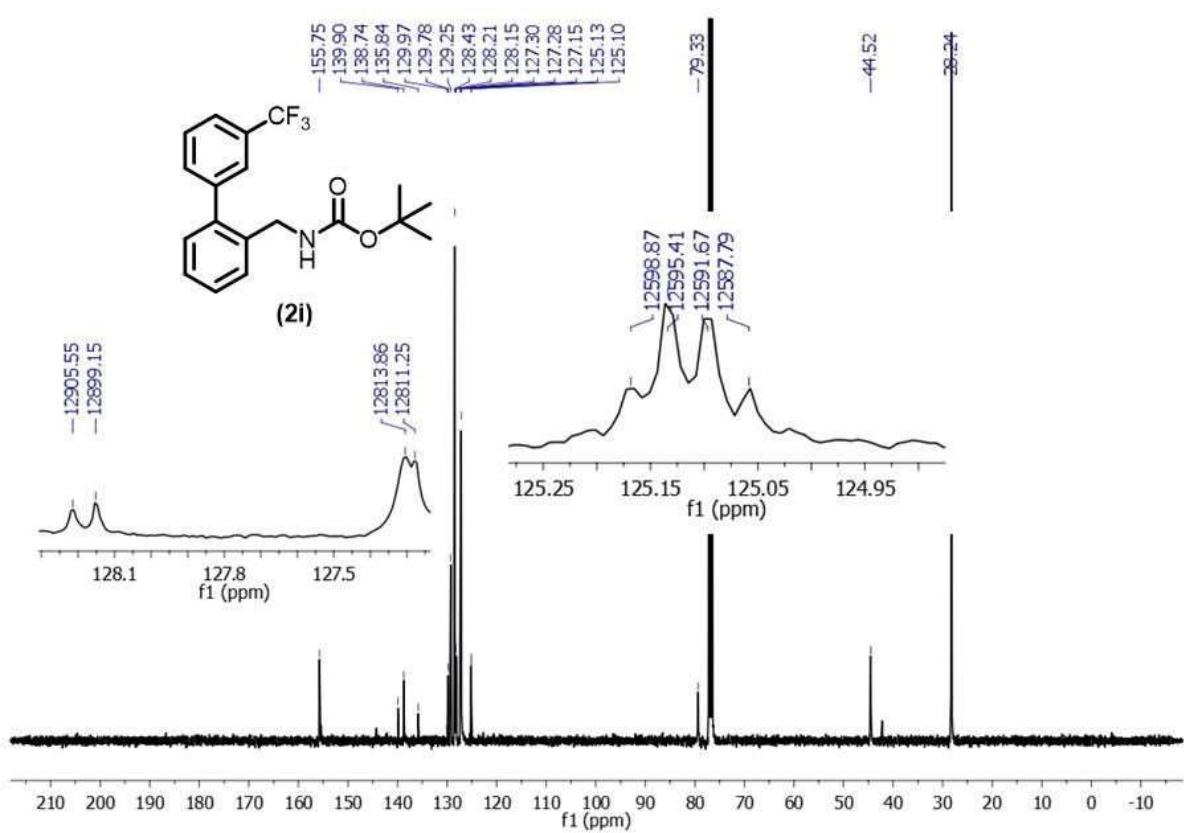
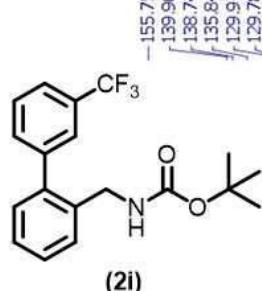
Fig. S24 ESI-HRMS Spectra of compound 2h.



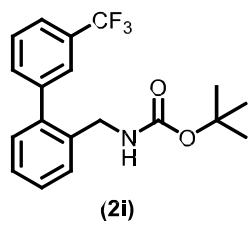
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



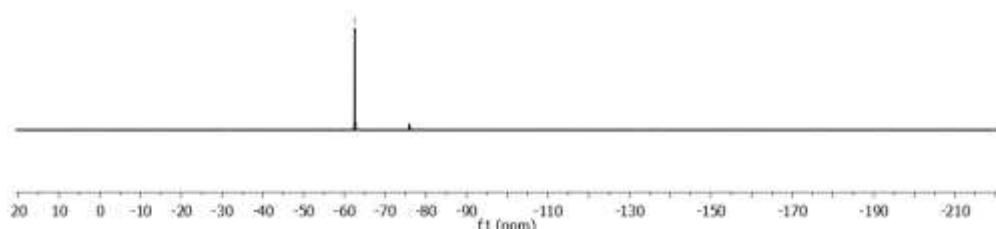
$^{13}\text{C}$  { $^1\text{H}$ } NMR (101MHz,  $\text{CDCl}_3$ )



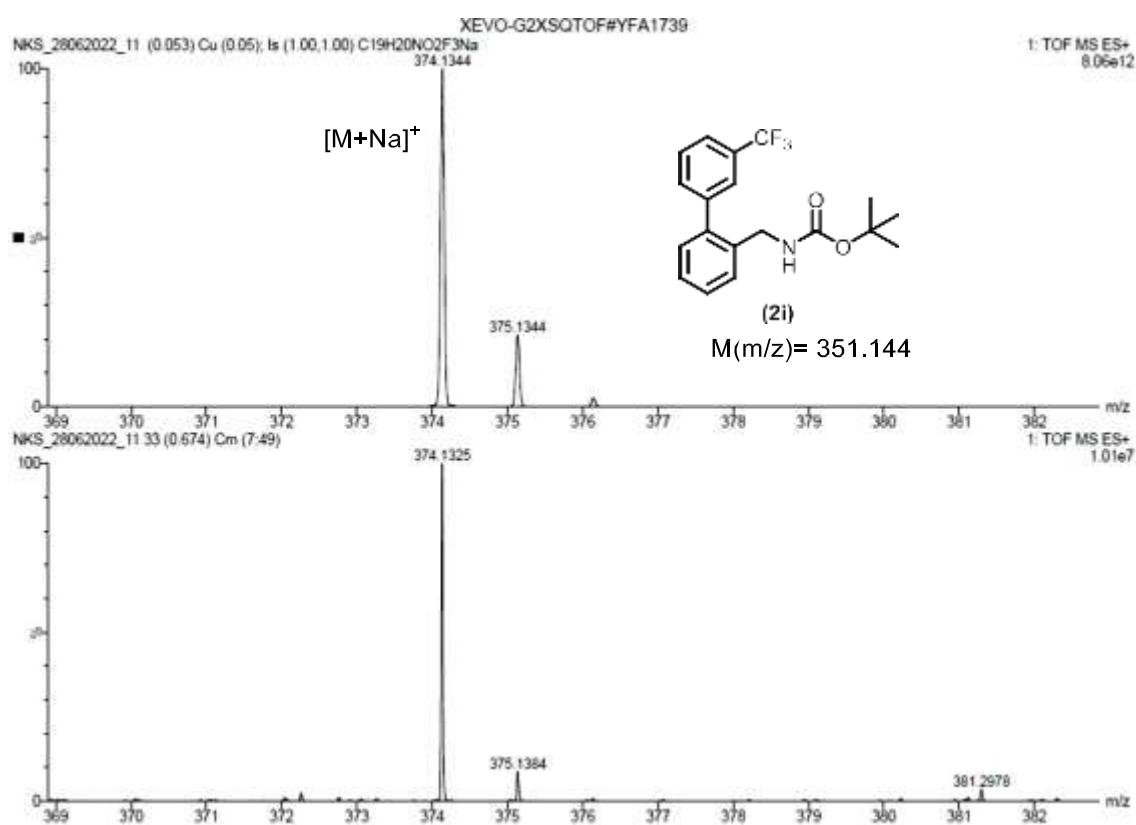
SDP-345A  
19F



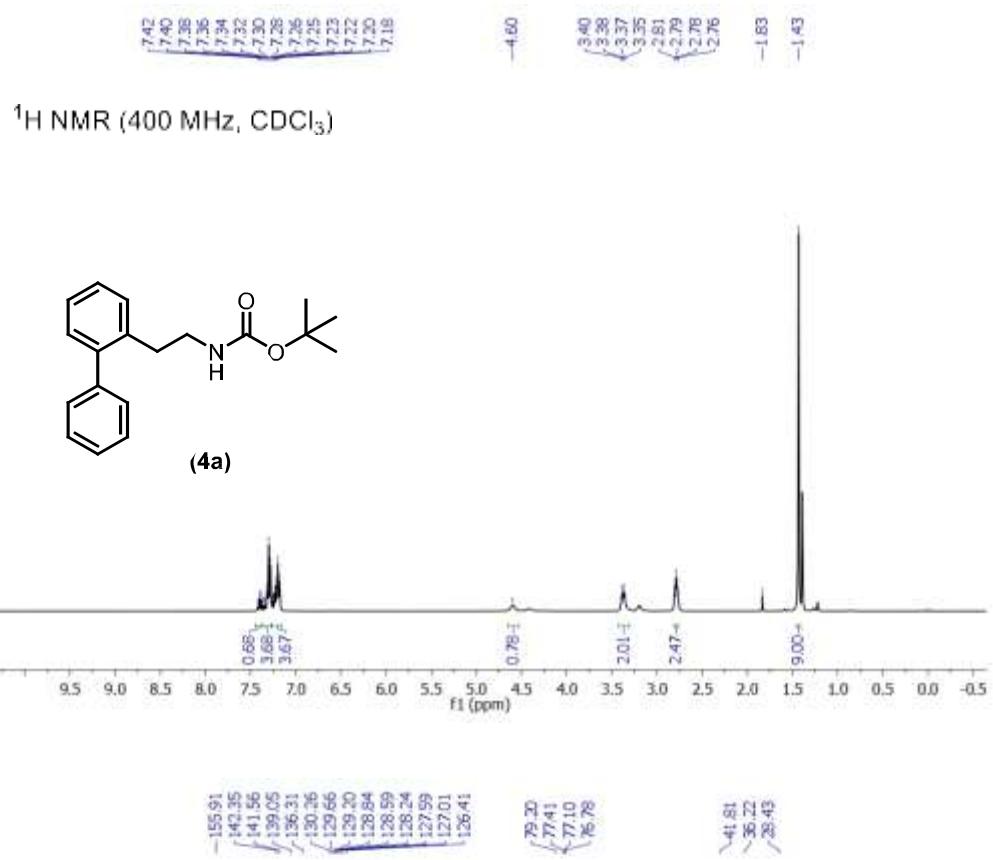
(**2i**)



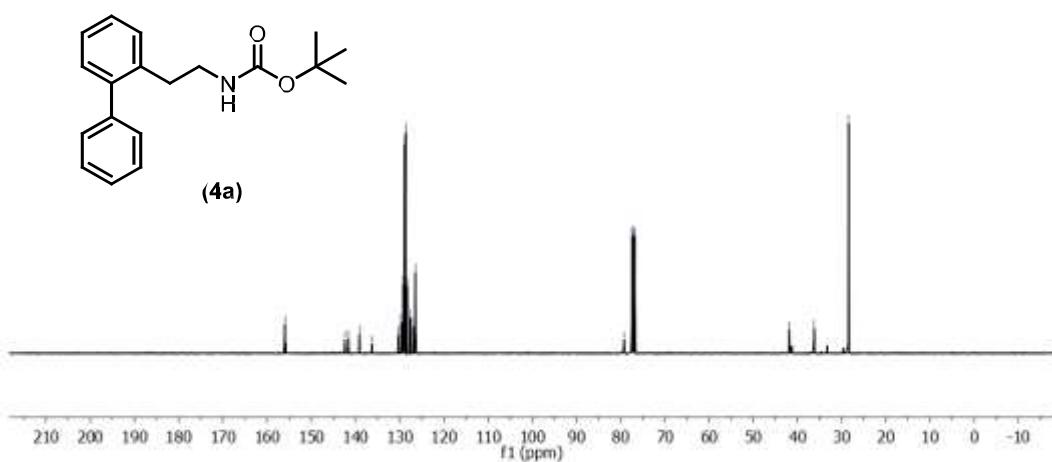
**Fig. S25**  $^1\text{H}$ ,  $^{13}\text{C}$  { $^1\text{H}$ }, NMR Spectra of compound **2i**



**Fig. S26** ESI-HRMS Spectra of compound **2i**.



<sup>13</sup>C {<sup>1</sup>H} NMR (101MHz, CDCl<sub>3</sub>)



**Fig. S27** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound 4a.

## Display Report

**Analysis Info**

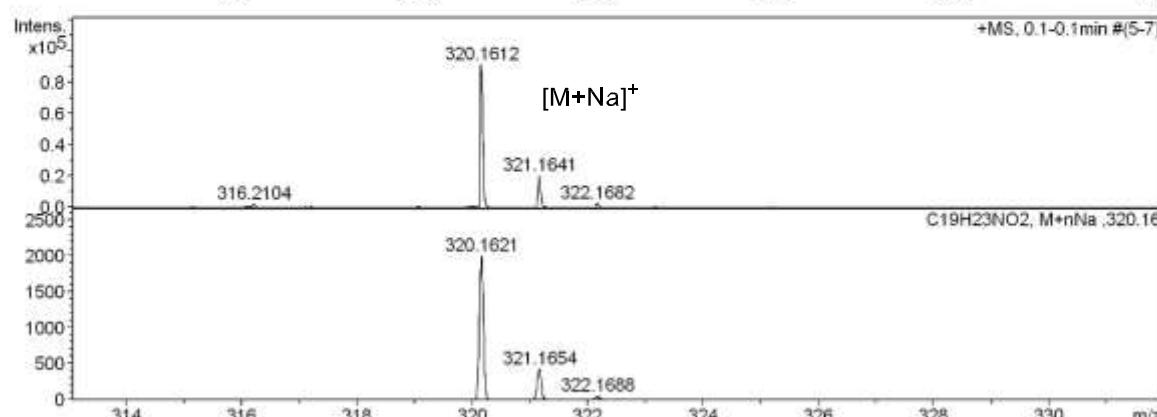
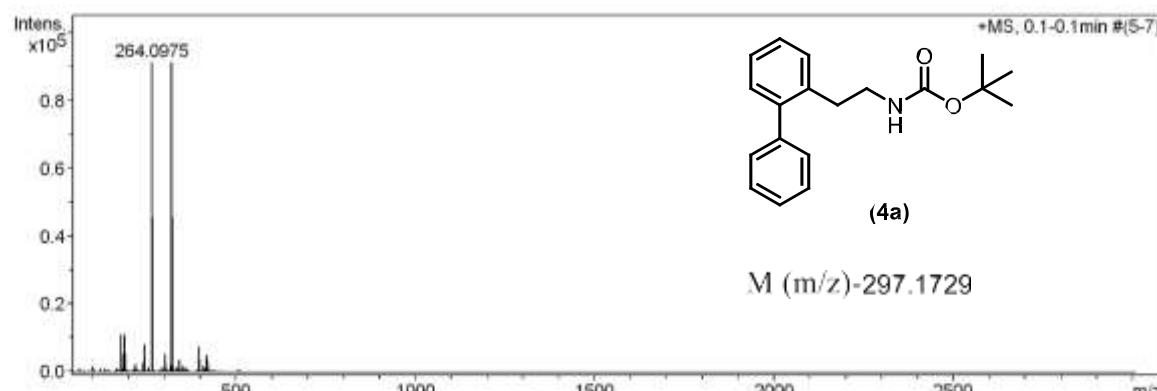
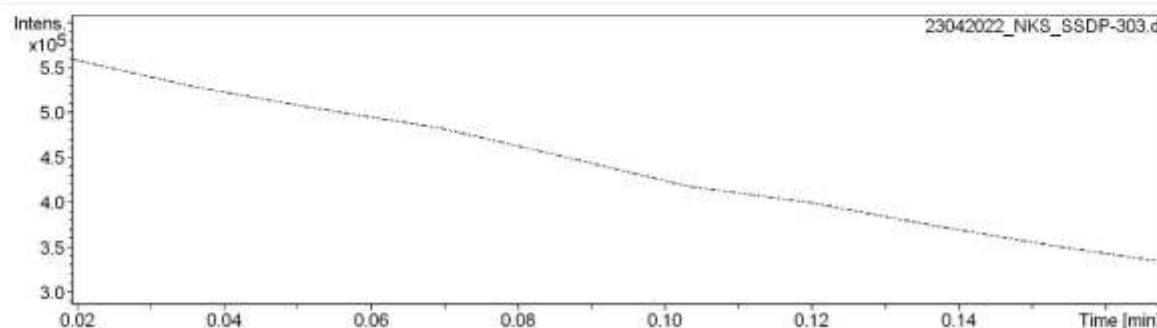
Analysis Name D:\Data\APR-2022\NKS\23042022\_NKS\_SSDP-303.d  
 Method Pos\_tune\_low\_05122019.m  
 Sample Name Tmix-131118  
 Comment

Acquisition Date 4/23/2022 8:45:33 PM

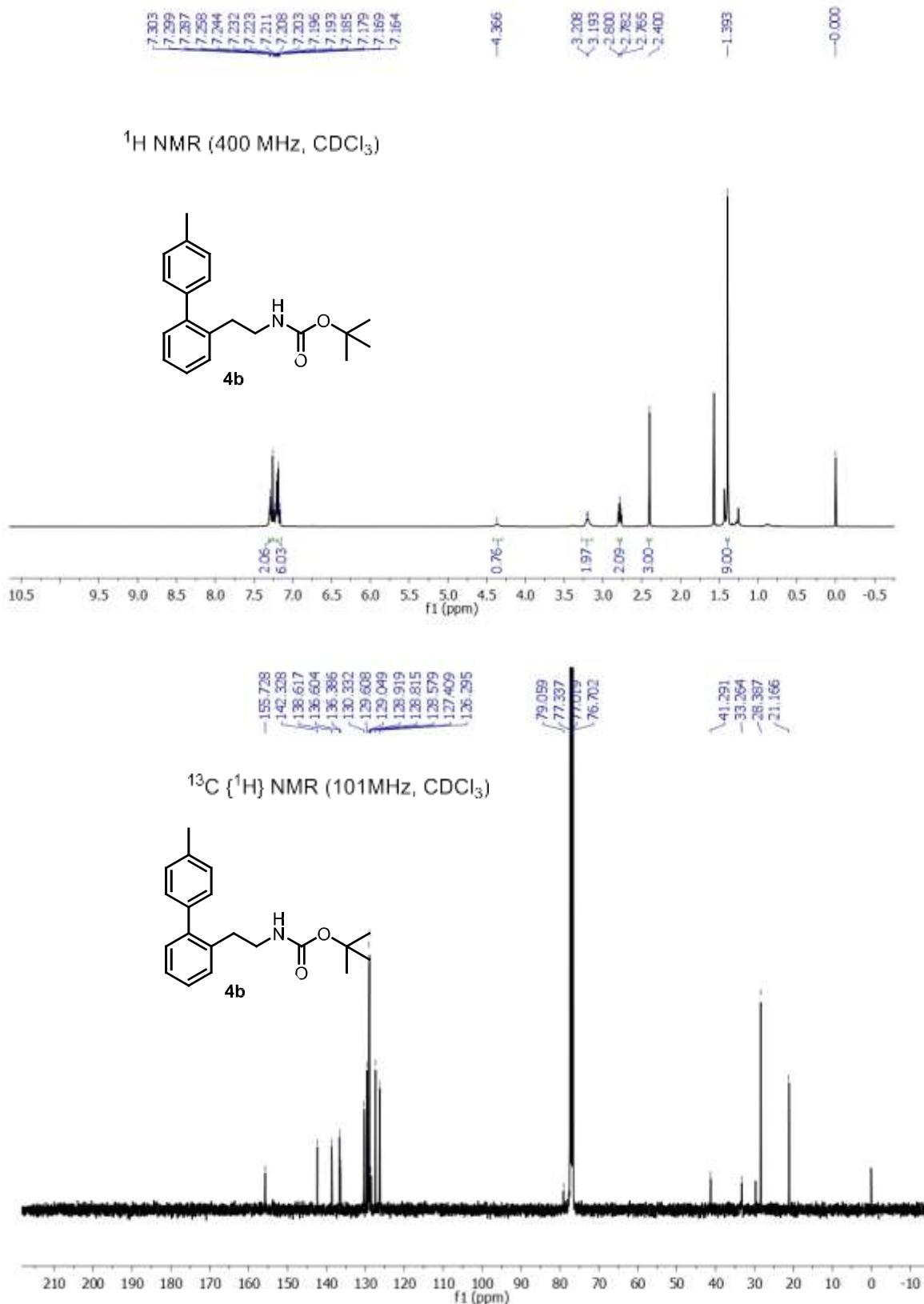
 Operator PRAKASH BEHERA  
 Instrument micrOTOF-Q II 10337

**Acquisition Parameter**

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Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



**Fig. S28 ESI-HRMS Spectra of compound 4a.**



**Fig. S29** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound **4b**

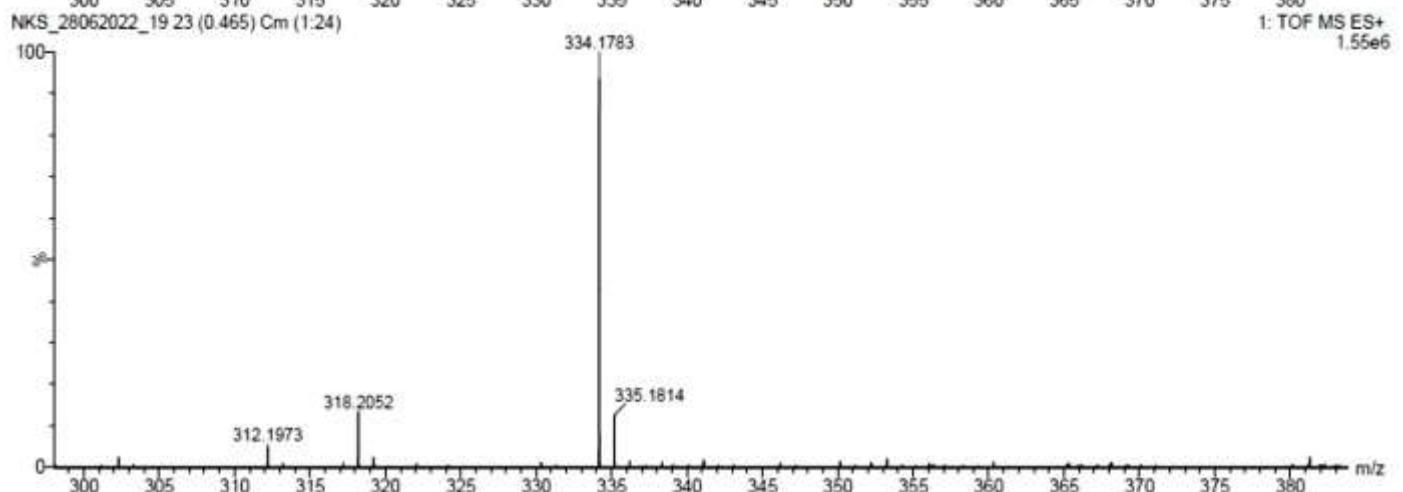
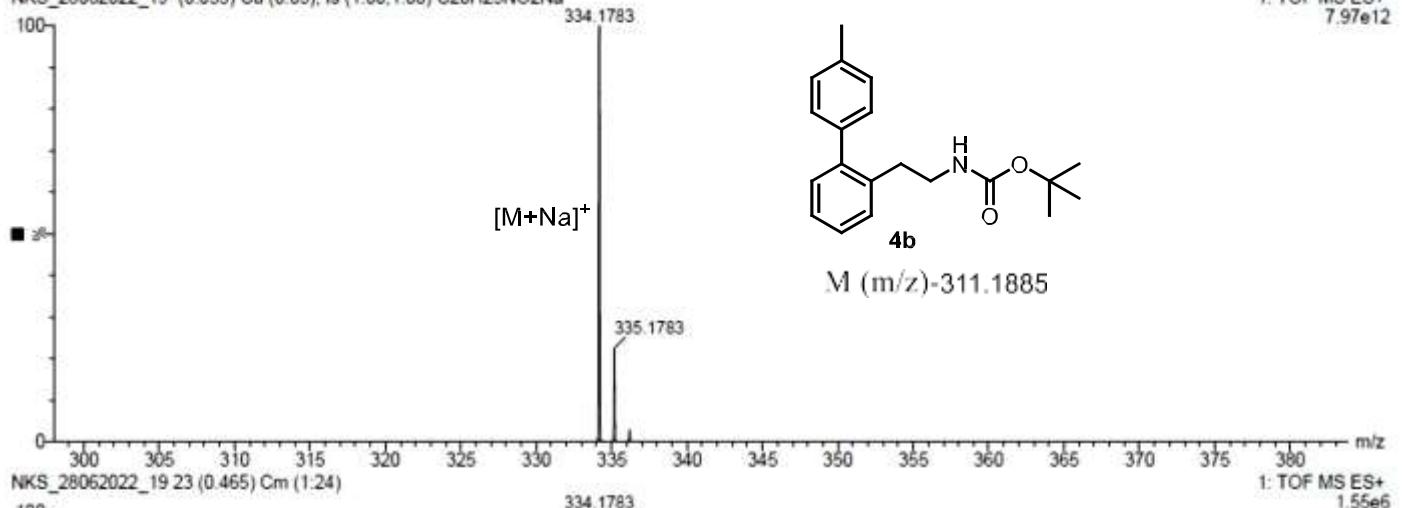
NKS\_SSDP\_317

28-Jun-2022  
23:25.56

XEVO-G2XSQTOF#YFA1739

NKS\_28062022\_19 (0.053) Cu (0.05); ls (1.00,1.00) C<sub>20</sub>H<sub>25</sub>NO<sub>2</sub>Na

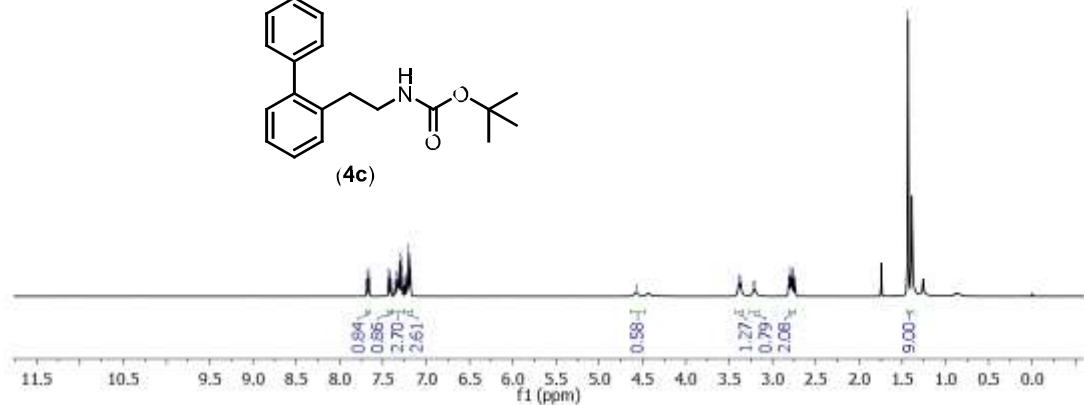
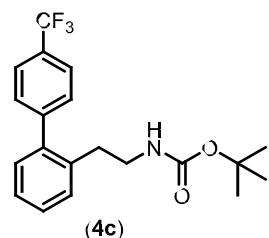
1: TOF MS ES+  
7.97e12



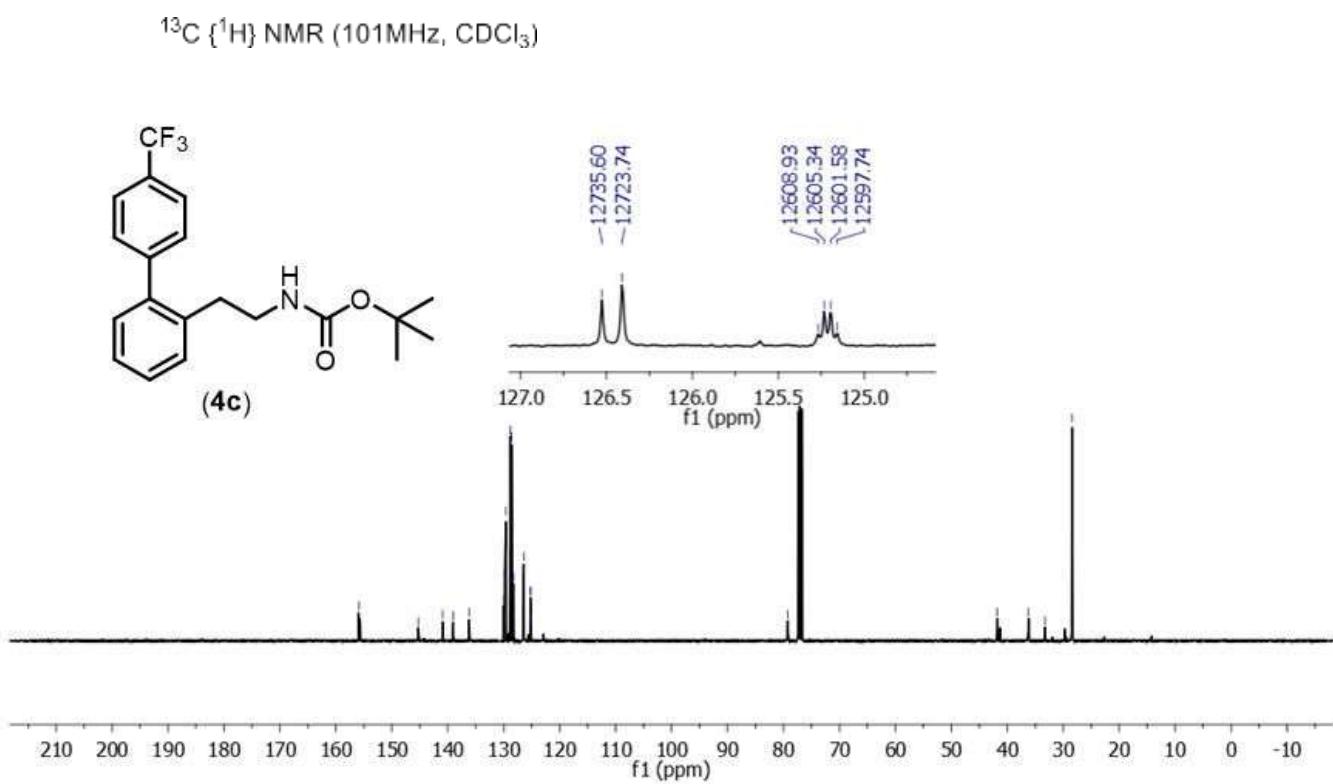
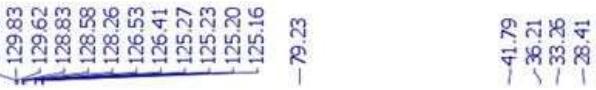
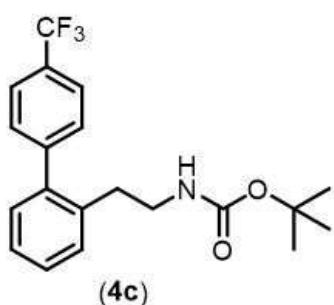
**Fig. S30 ESI-HRMS Spectra of compound 4b.**

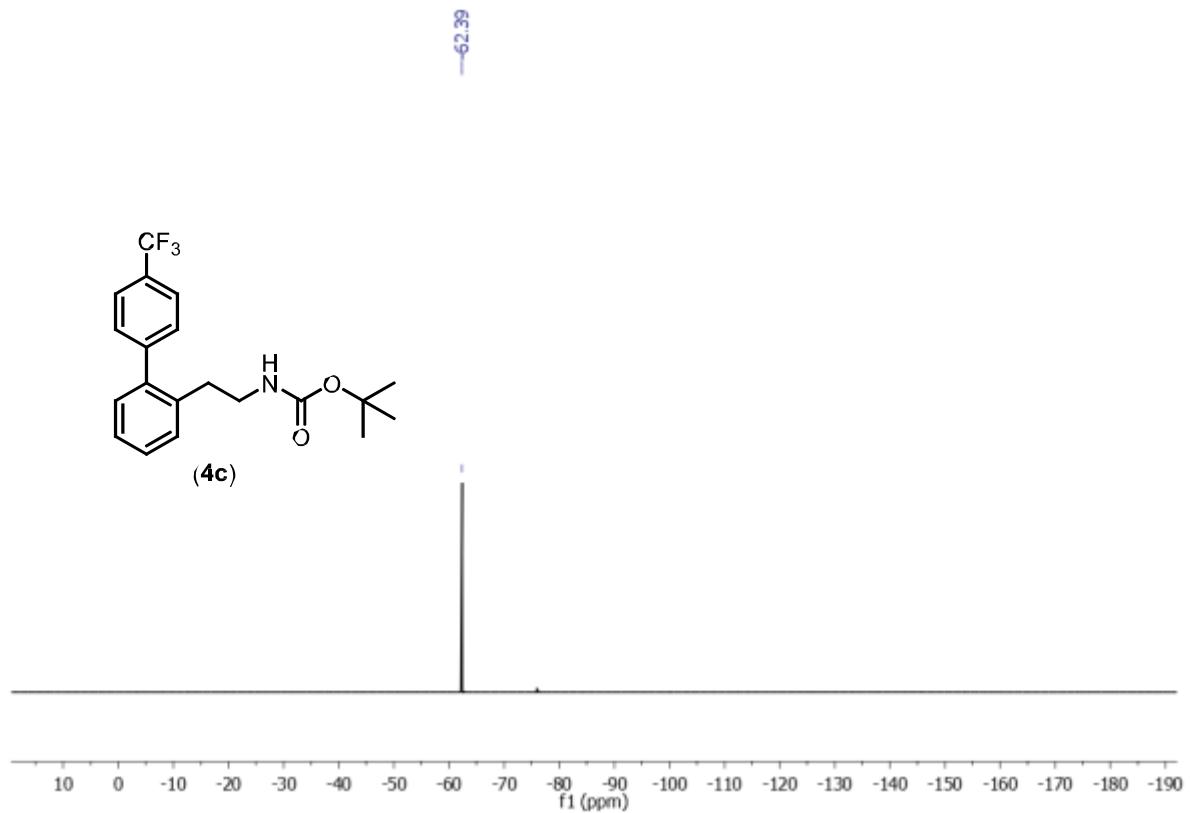


<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



$^{13}\text{C}$  { $^1\text{H}$ } NMR (101MHz,  $\text{CDCl}_3$ )





**Fig. S31**  $^1\text{H}$ ,  $^{13}\text{C}$  { $^1\text{H}$ },  $^{19}\text{F}$  NMR Spectra of compound **4c**.

## Display Report

**Analysis Info**

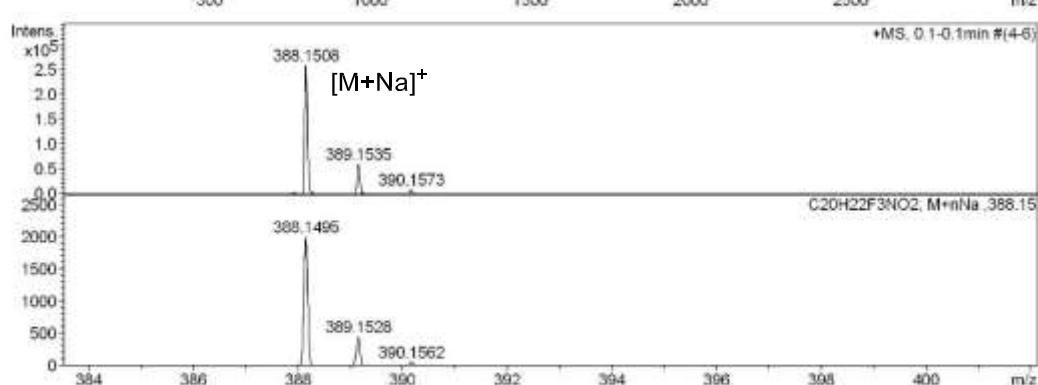
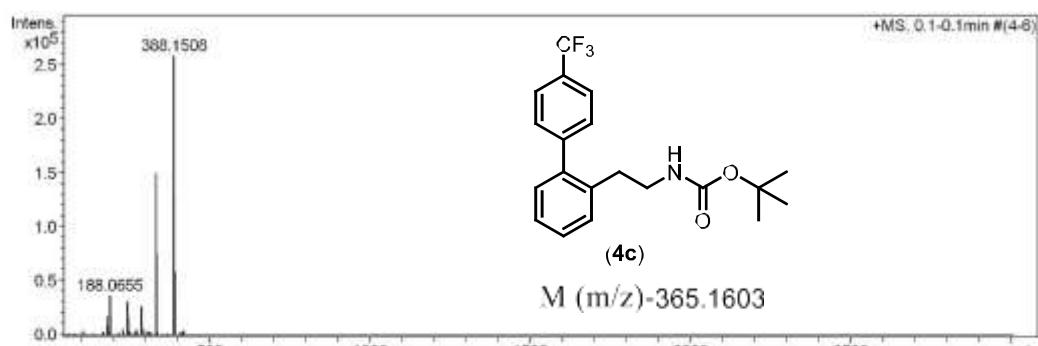
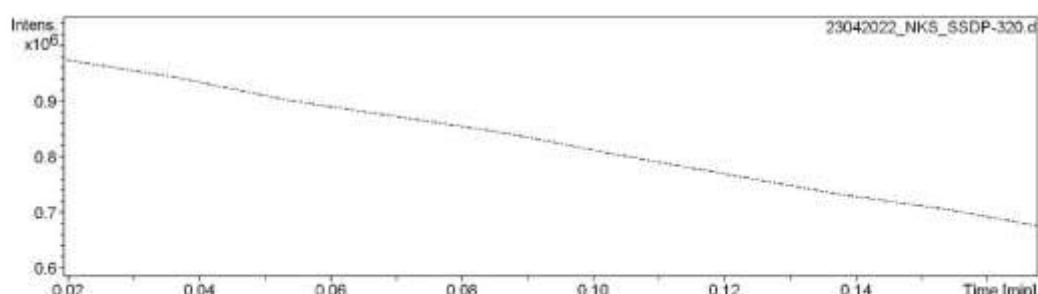
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 Comment:

Acquisition Date: 4/23/2022 8:51:09 PM

 Operator: PRAKASH BEHERA  
 Instrument: micrOTOF-Q II 10337

**Acquisition Parameter**

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.5 Bar
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Scan End	3000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

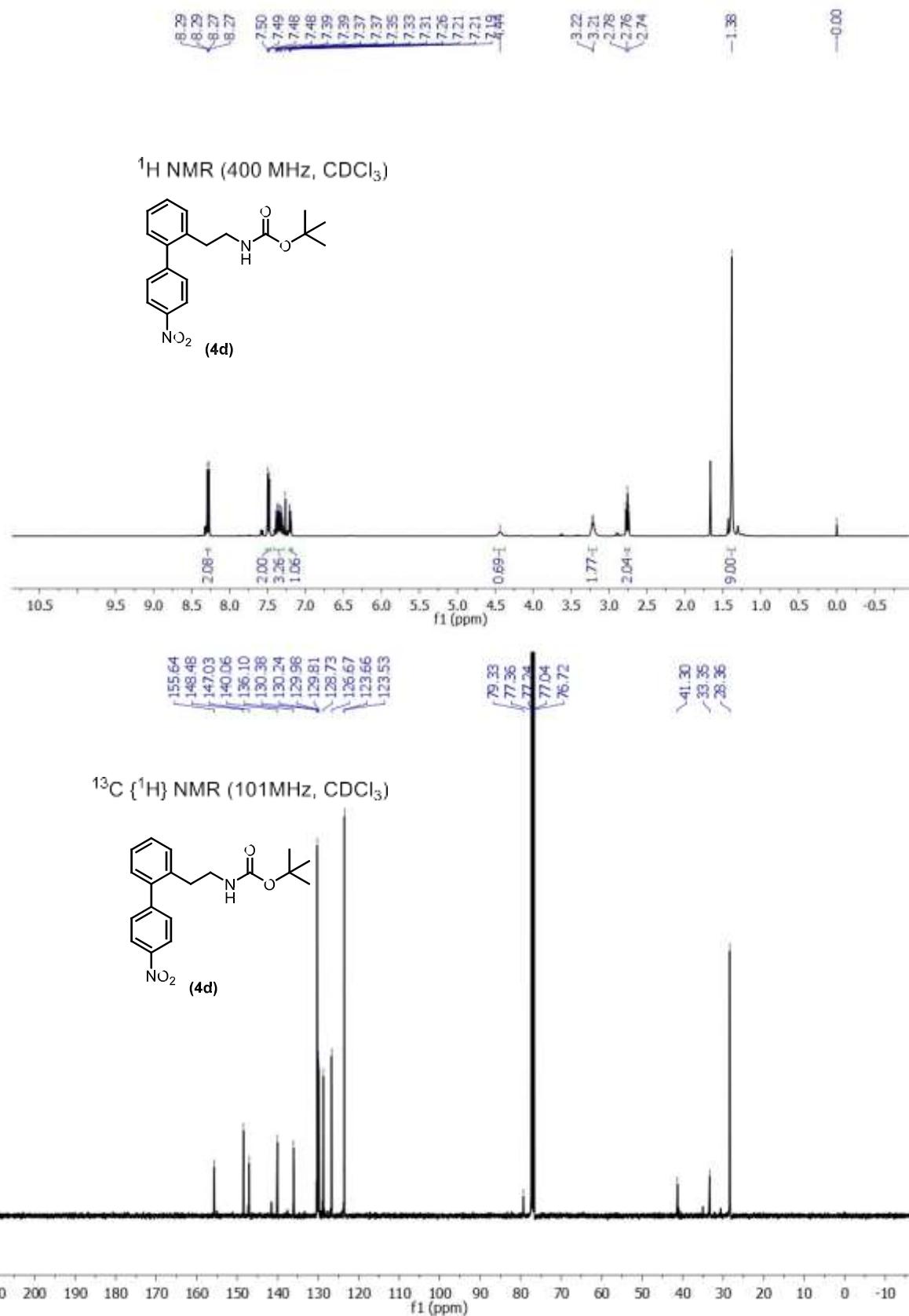


Bruker Compass DataAnalysis 4.0

printed: 4/23/2022 8:53:29 PM

Page 1 of 1

**Fig. S32 ESI-HRMS Spectra of compound 4c.**



**Fig. S33** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound 4d.

## Display Report

**Analysis Info**

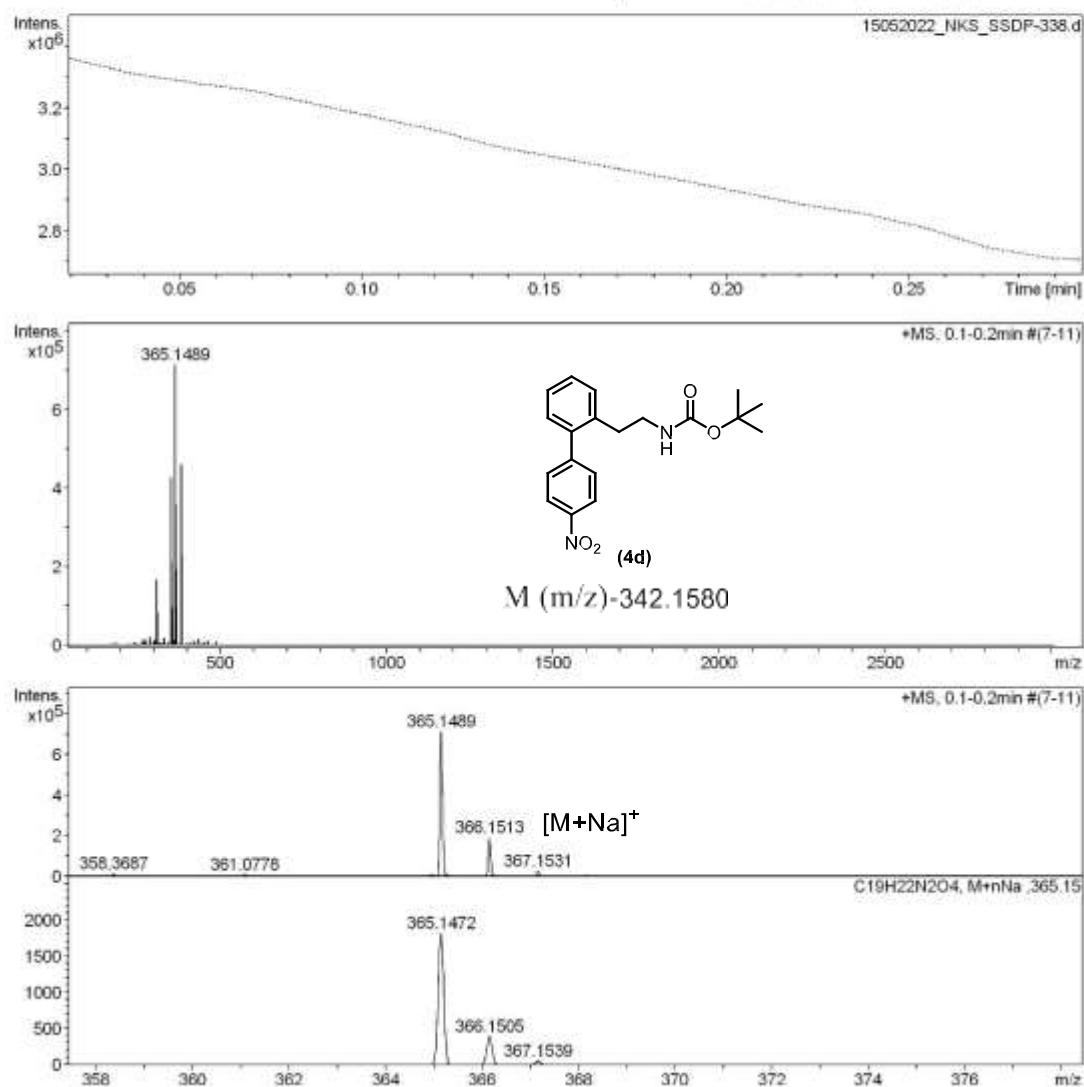
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 Comment:

Acquisition Date: 5/15/2022 11:24:09 PM

 Operator: Amit S.Sahu  
 Instrument: micrOTOF-Q II 10337

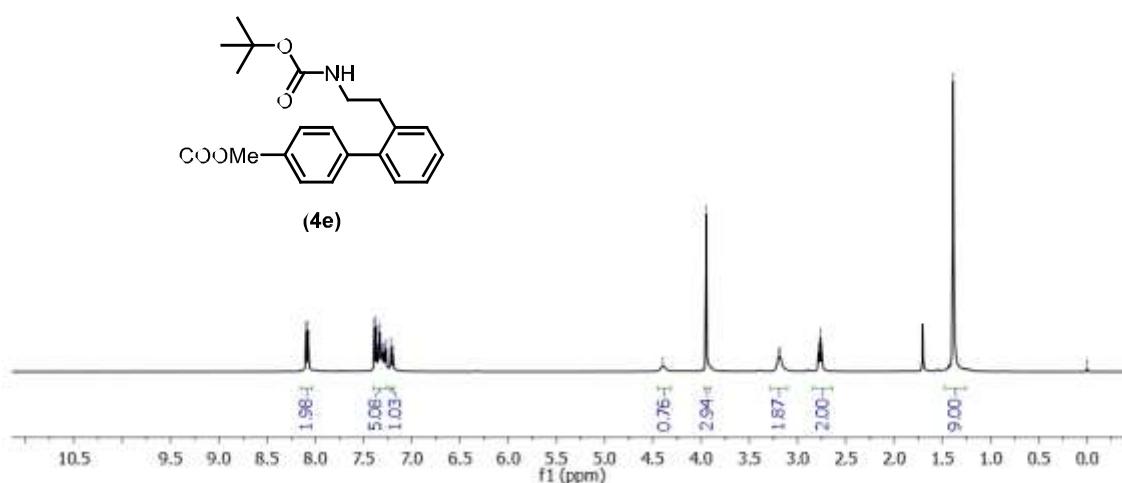
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Scan End	3000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

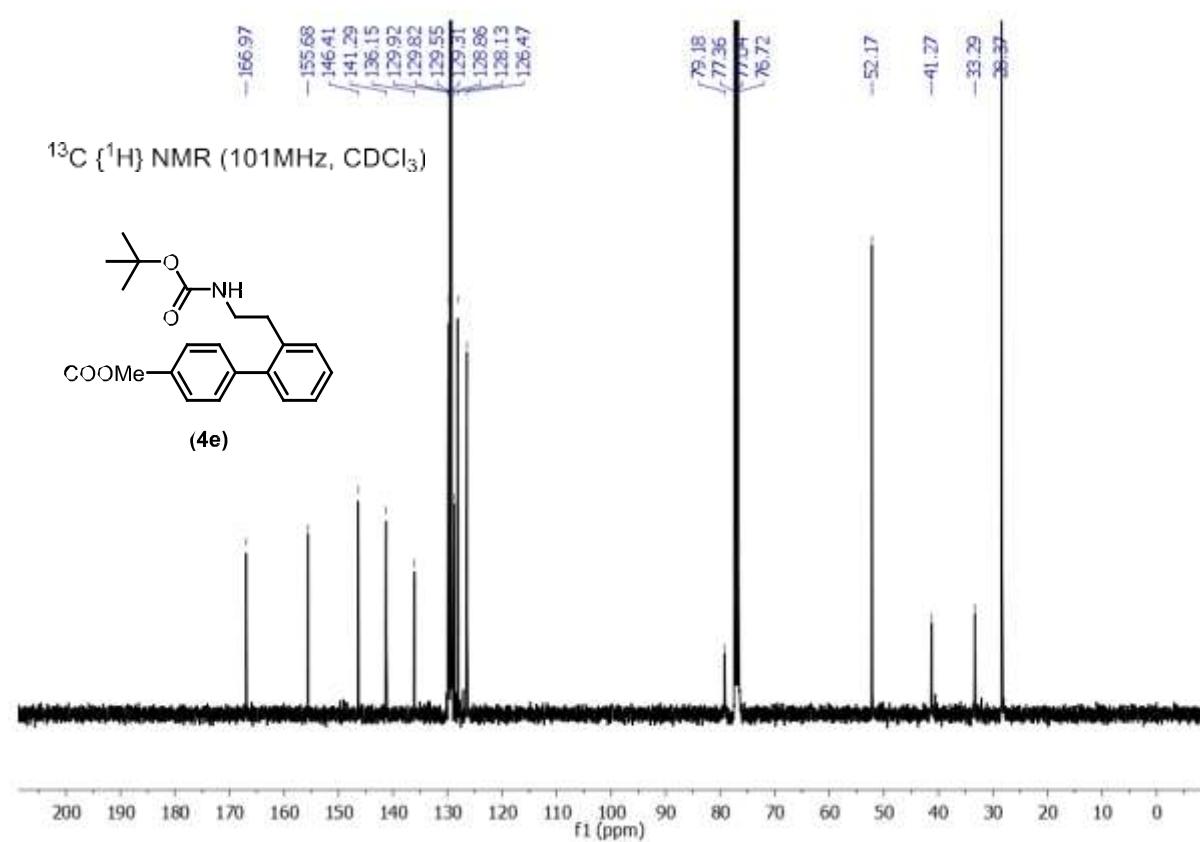


**Fig. S34 ESI-HRMS Spectra of compound 4d.**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C} \{^1\text{H}\}$  NMR (101MHz,  $\text{CDCl}_3$ )



**Fig. S35**  $^1\text{H}$ ,  $^{13}\text{C} \{^1\text{H}\}$ , NMR Spectra of compound **4e**.

## Display Report

**Analysis Info**

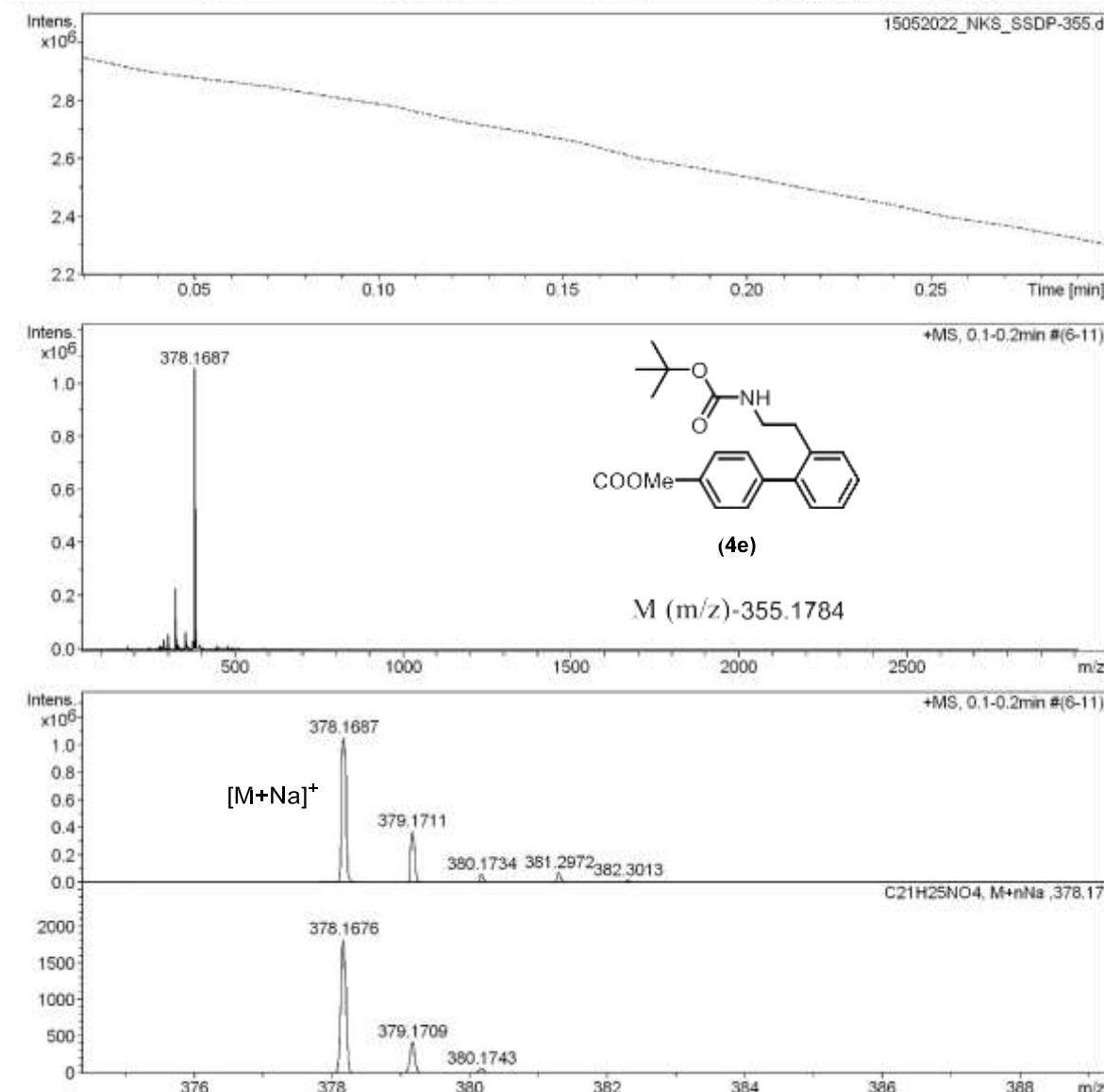
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 Comment

Acquisition Date 5/15/2022 11:37:41 PM

 Operator Amit S.Sahu  
 Instrument micrOTOF-Q II 10337

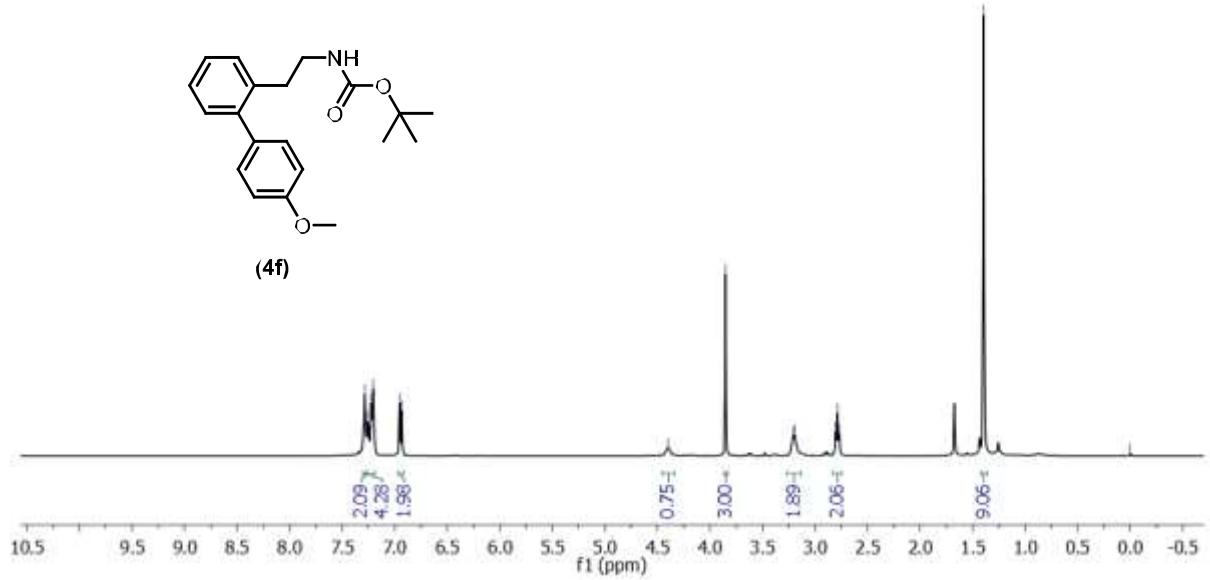
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Scan End	3000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste

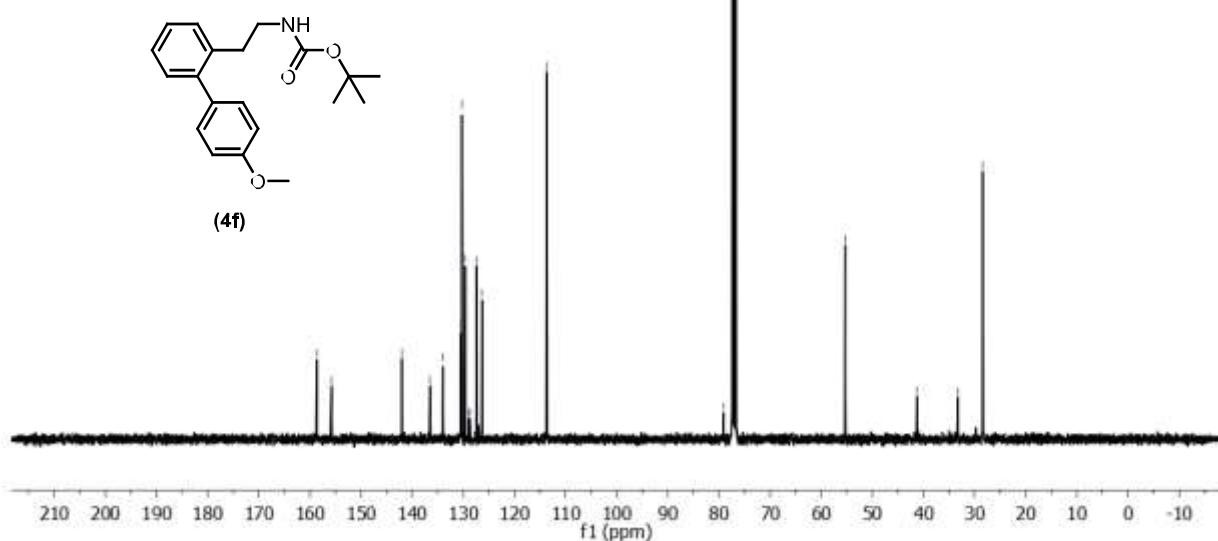


**Fig. S36** ESI-HRMS Spectra of compound **4e**.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C} \{^1\text{H}\}$  NMR (101MHz,  $\text{CDCl}_3$ )



**Fig. S37**  $^1\text{H}$ ,  $^{13}\text{C} \{^1\text{H}\}$ , NMR Spectra of compound **4f**.

## Display Report

**Analysis Info**

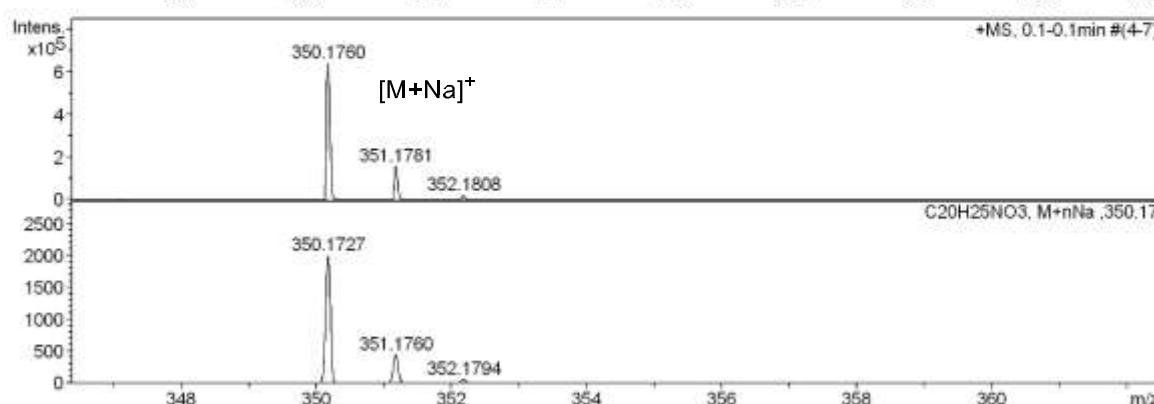
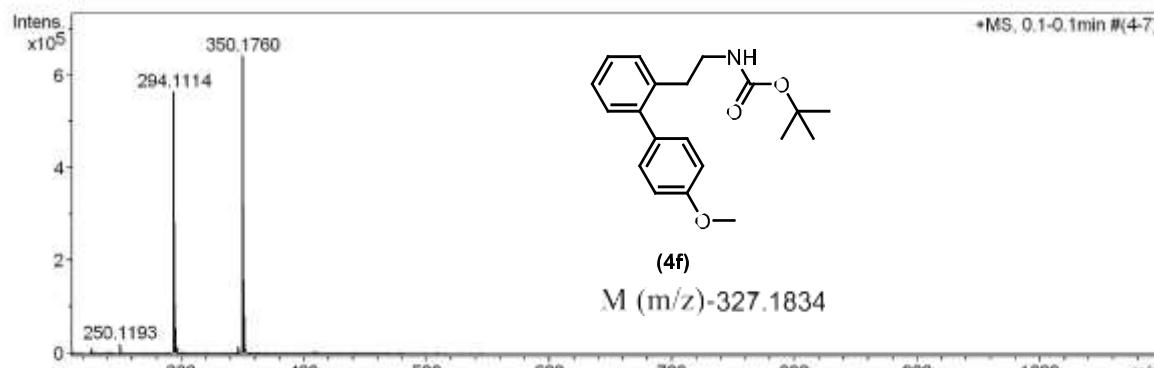
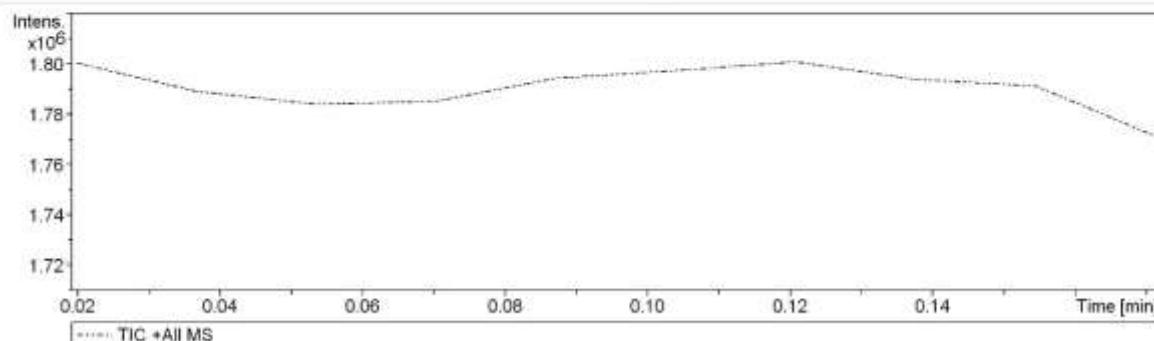
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 Sample Name Tmix-131118  
 Comment

Acquisition Date 4/23/2022 8:32:43 PM

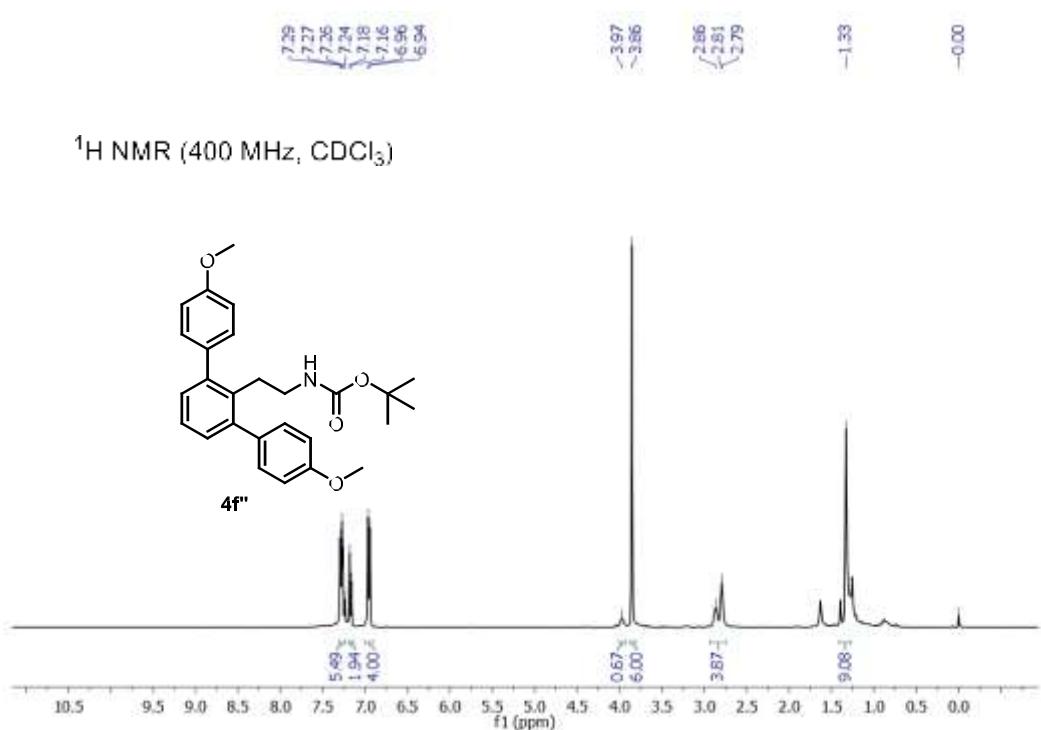
 Operator PRAKASH BEHERA  
 Instrument micrOTOF-Q II 10337

**Acquisition Parameter**

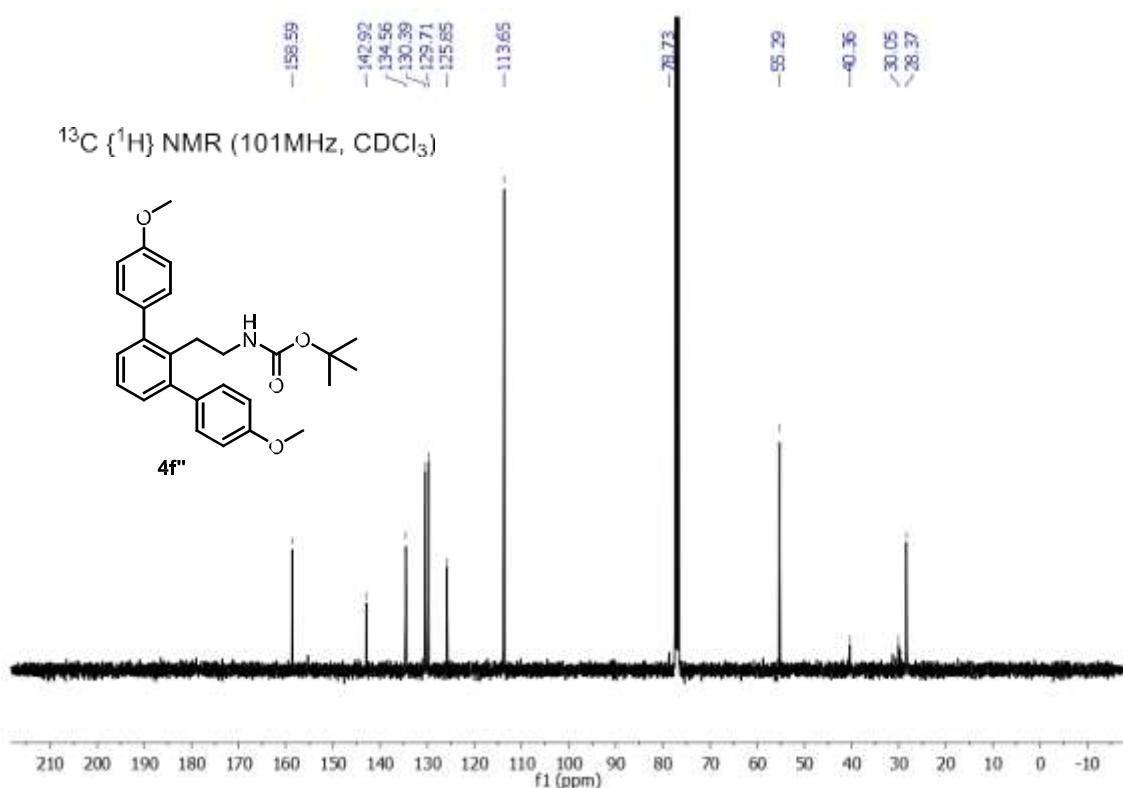
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Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste


**Fig. S38 ESI-HRMS Spectra of compound 4f.**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C} \{^1\text{H}\}$  NMR (101MHz,  $\text{CDCl}_3$ )



**Fig. S39**  $^1\text{H}$ ,  $^{13}\text{C} \{^1\text{H}\}$ , NMR Spectra of compound  $4f''$ .

## Display Report

**Analysis Info**

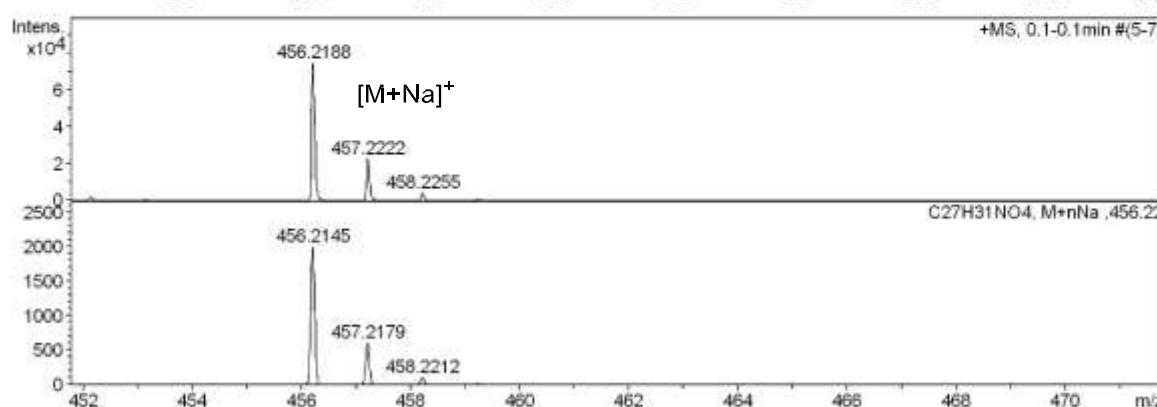
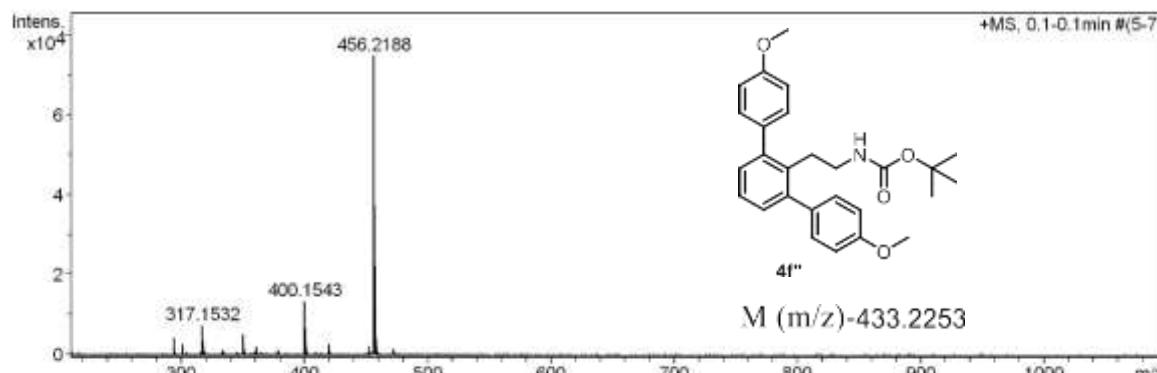
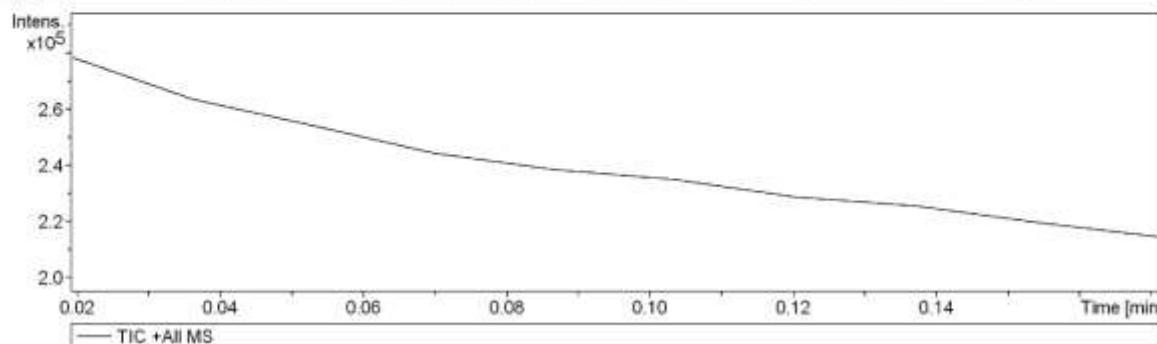
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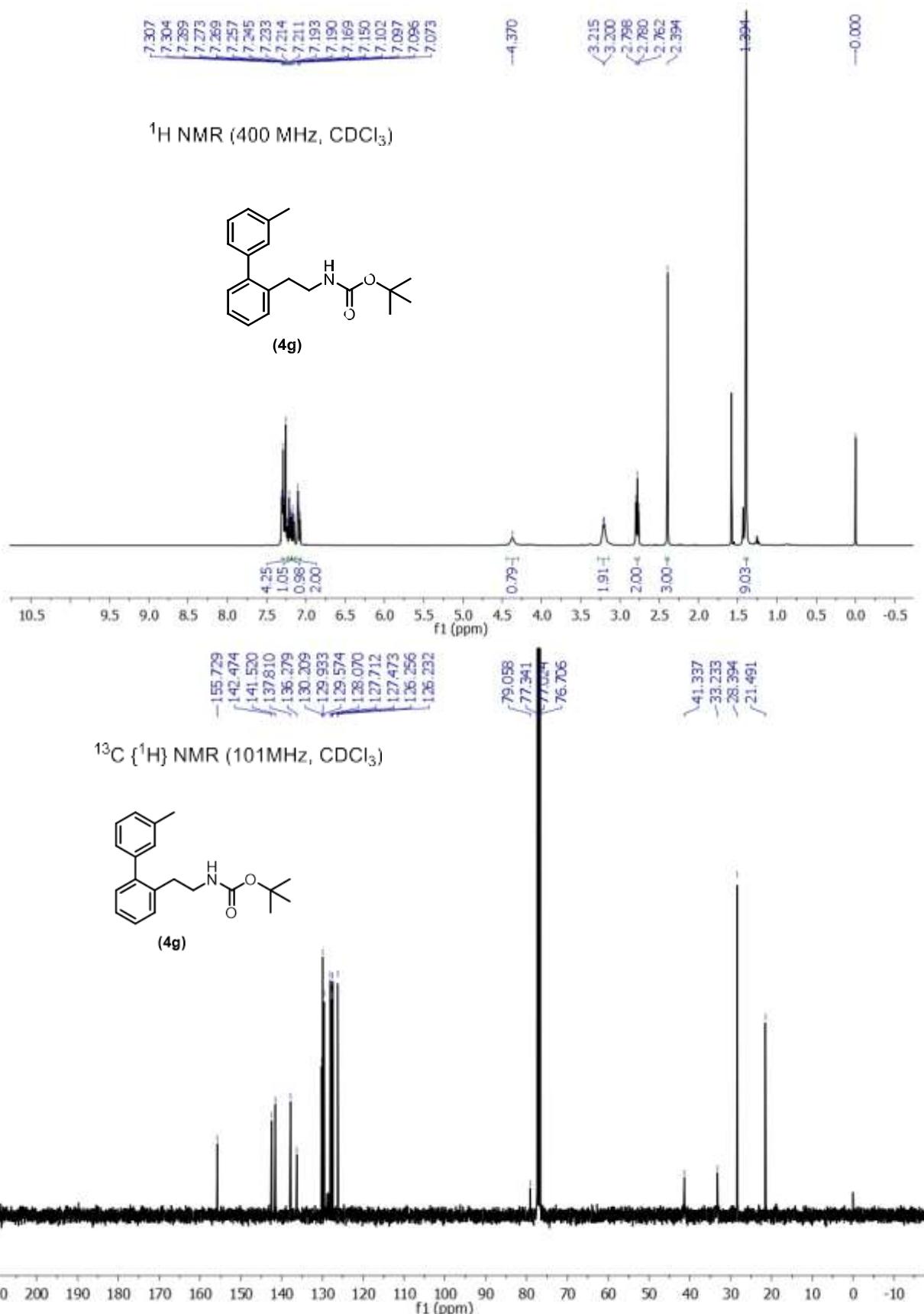
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 Operator: PRAKASH BEHERA  
 Instrument: micrOTOF-Q II 10337

**Acquisition Parameter**

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Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste


**Fig. S40 ESI-HRMS Spectra of compound 4f'.**



**Fig. S41** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound 4g.

## Display Report

**Analysis Info**

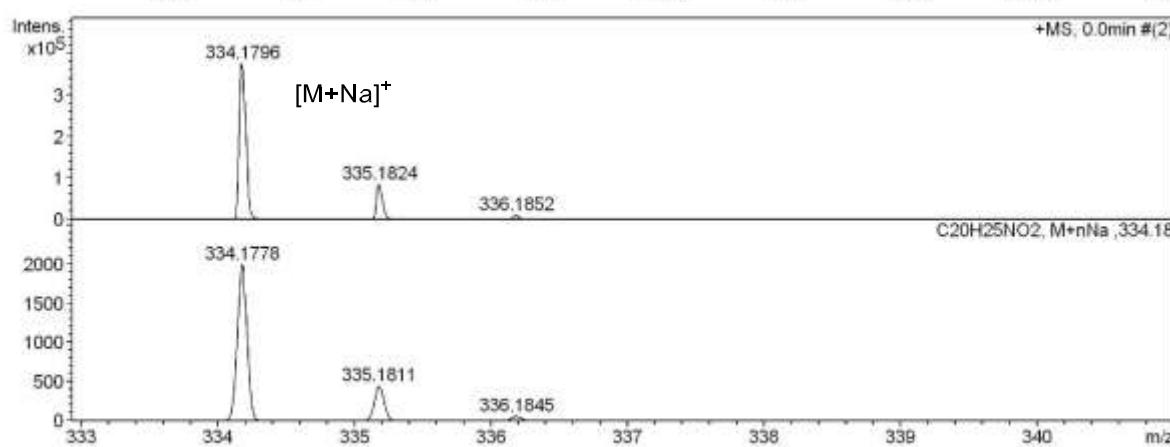
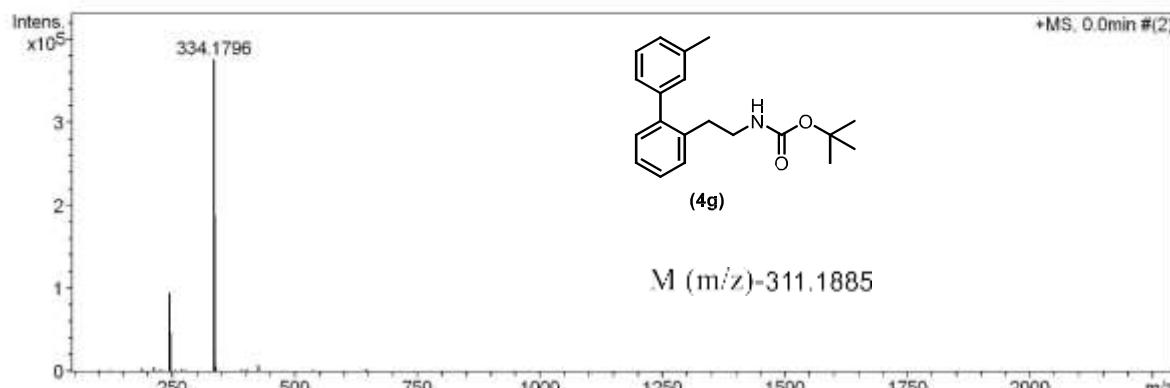
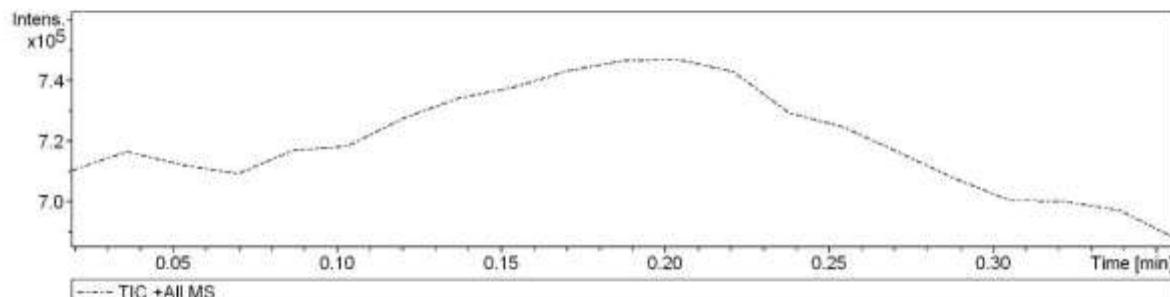
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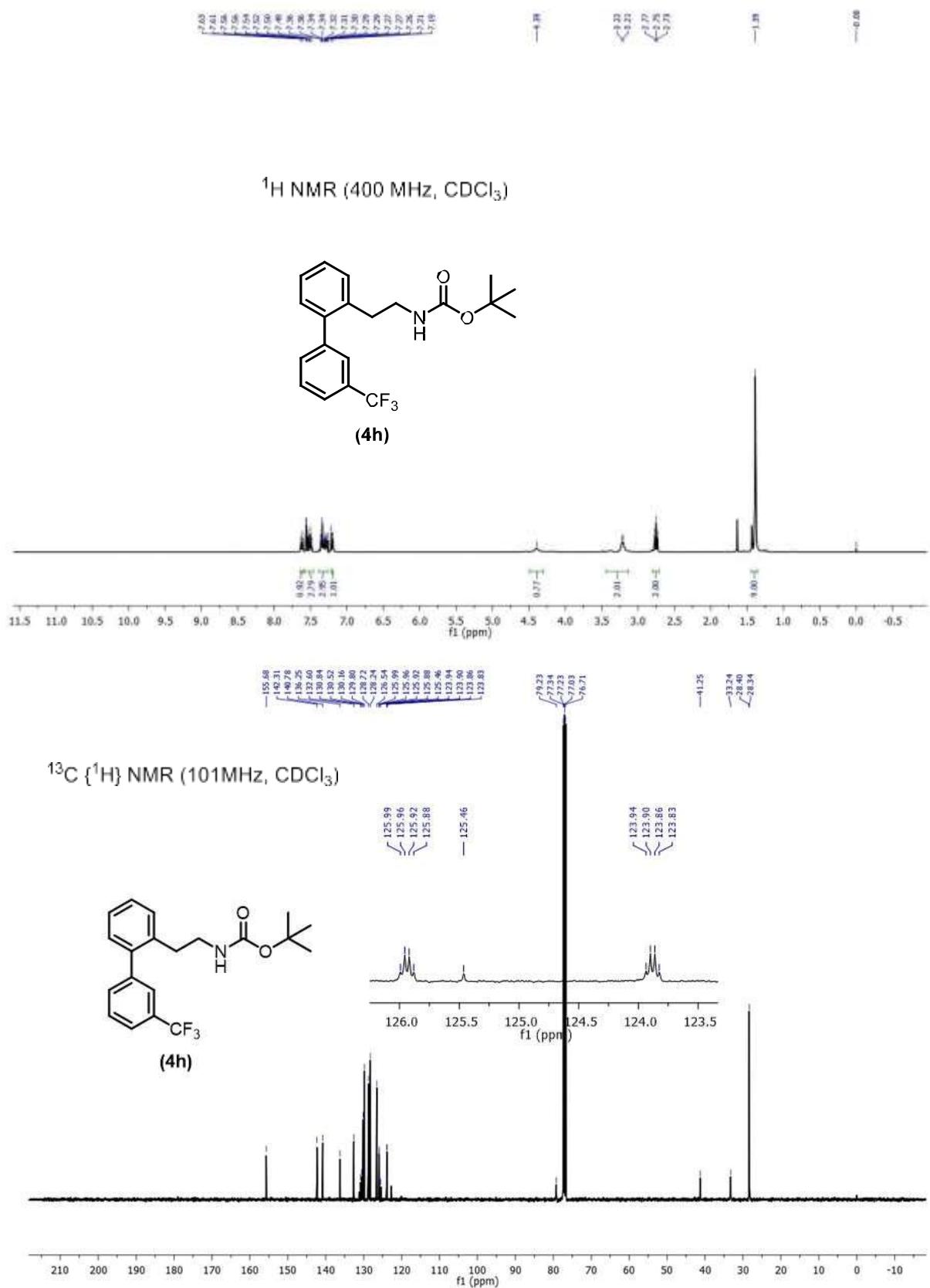
 Operator: PRAKASH BEHERA  
 Instrument: micrOTOF-Q II 10337

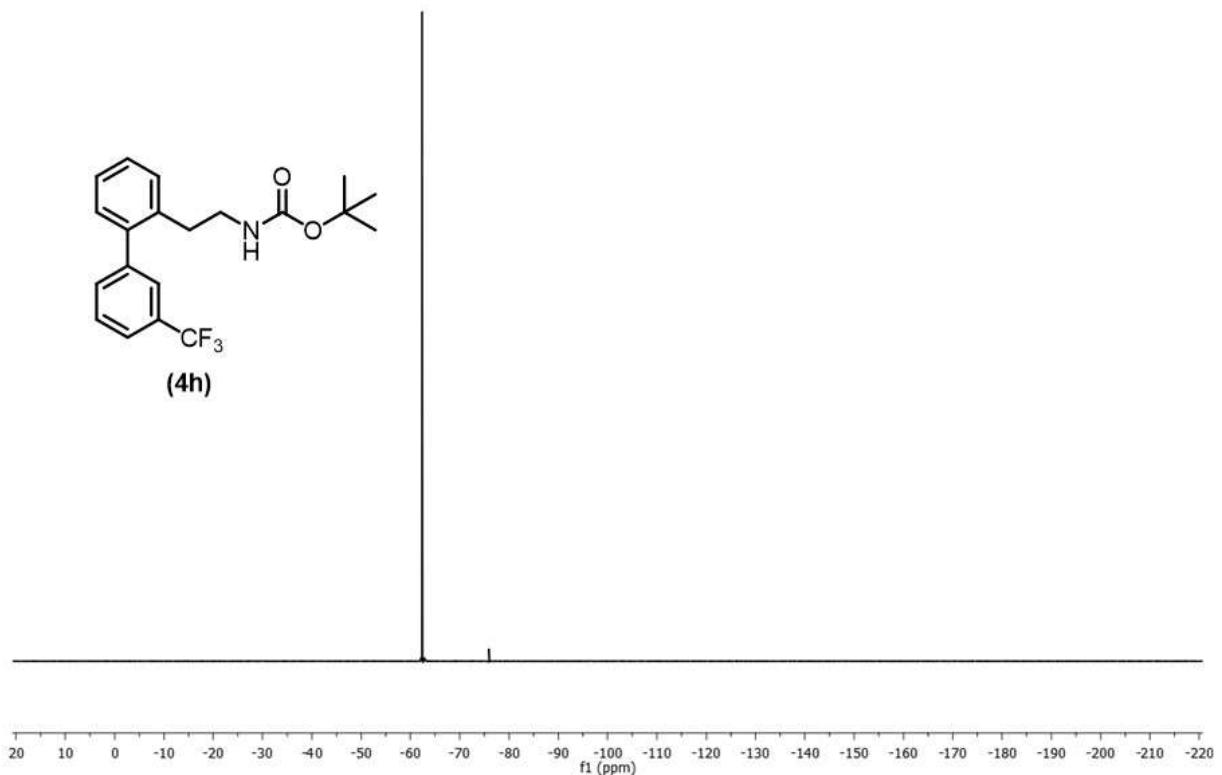
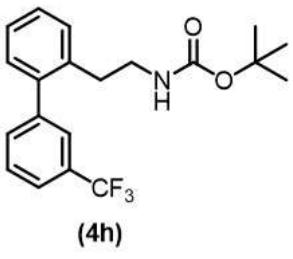
**Acquisition Parameter**

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



**Fig. S42 ESI-HRMS Spectra of compound 4g.**





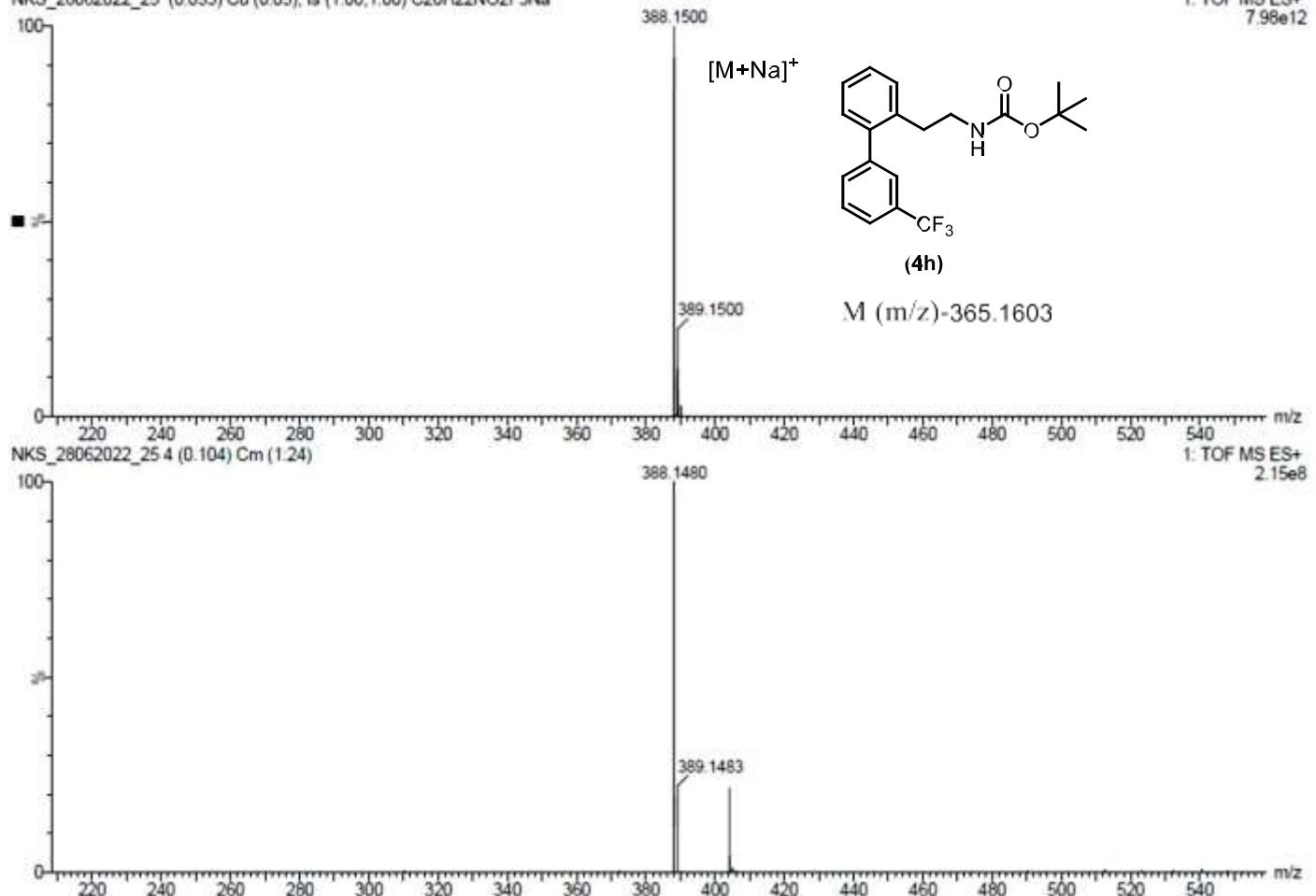
**Fig. S43**  $^1\text{H}$ ,  $^{13}\text{C}$  { $^1\text{H}$ }, and  $^{19}\text{F}$ NMR Spectra of compound **4h**.

NKS\_SSDP\_342

29-Jun-2022  
01:16:51

XEVO-G2XSQTOF#YFA1739

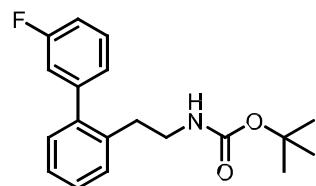
NKS\_28062022\_25 (0.053) Cu (0.05); ls (1.00,1.00) C20H22NO2F3Na

1: TOF MS ES+  
7.98e12

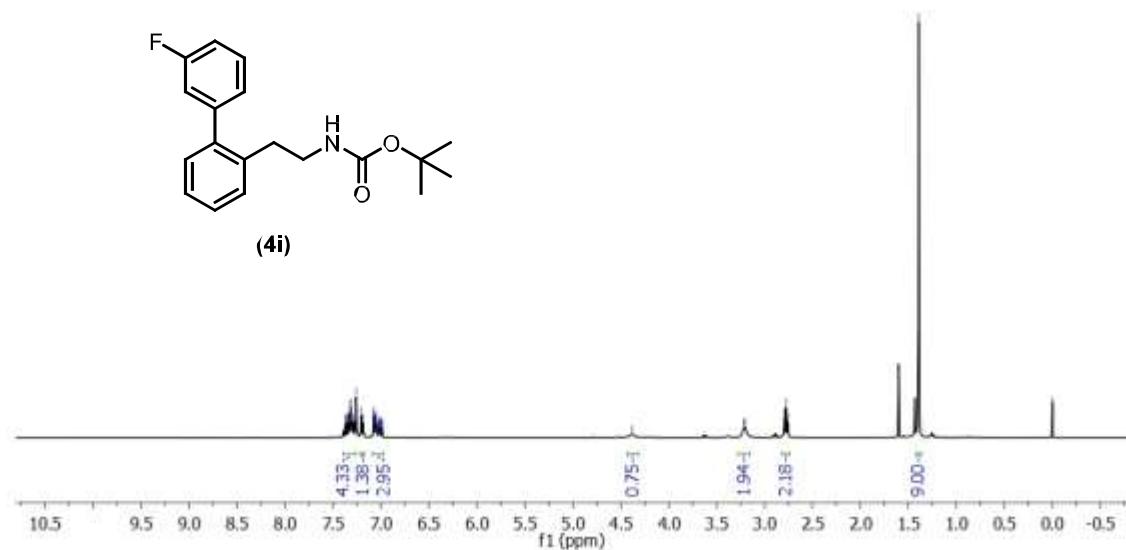
**Fig. S44** ESI-HRMS Spectra of compound **4h**.



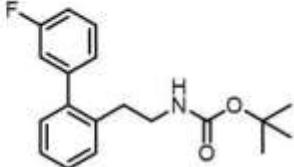
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



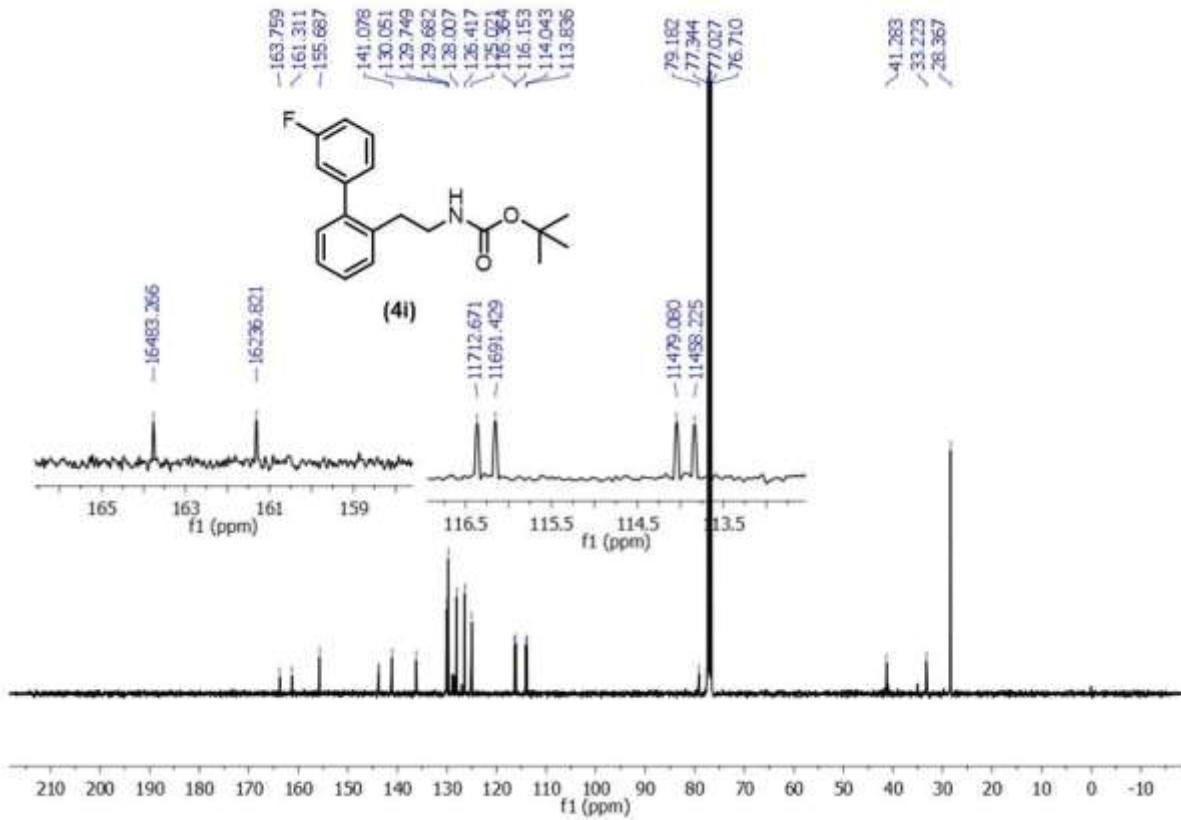
(4i)

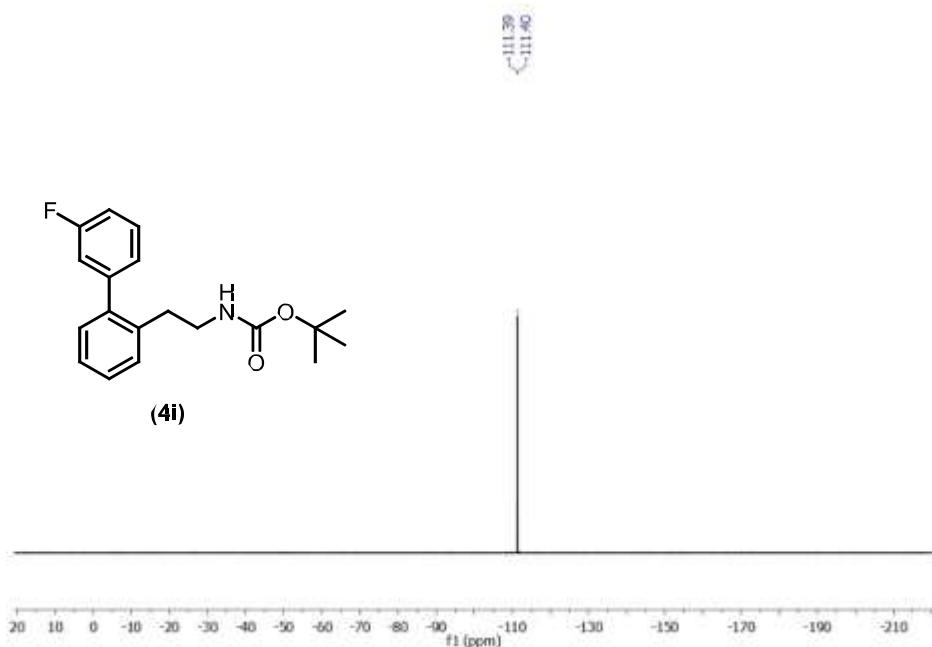


$^{13}\text{C}$  { $^1\text{H}$ } NMR (101MHz,  $\text{CDCl}_3$ )

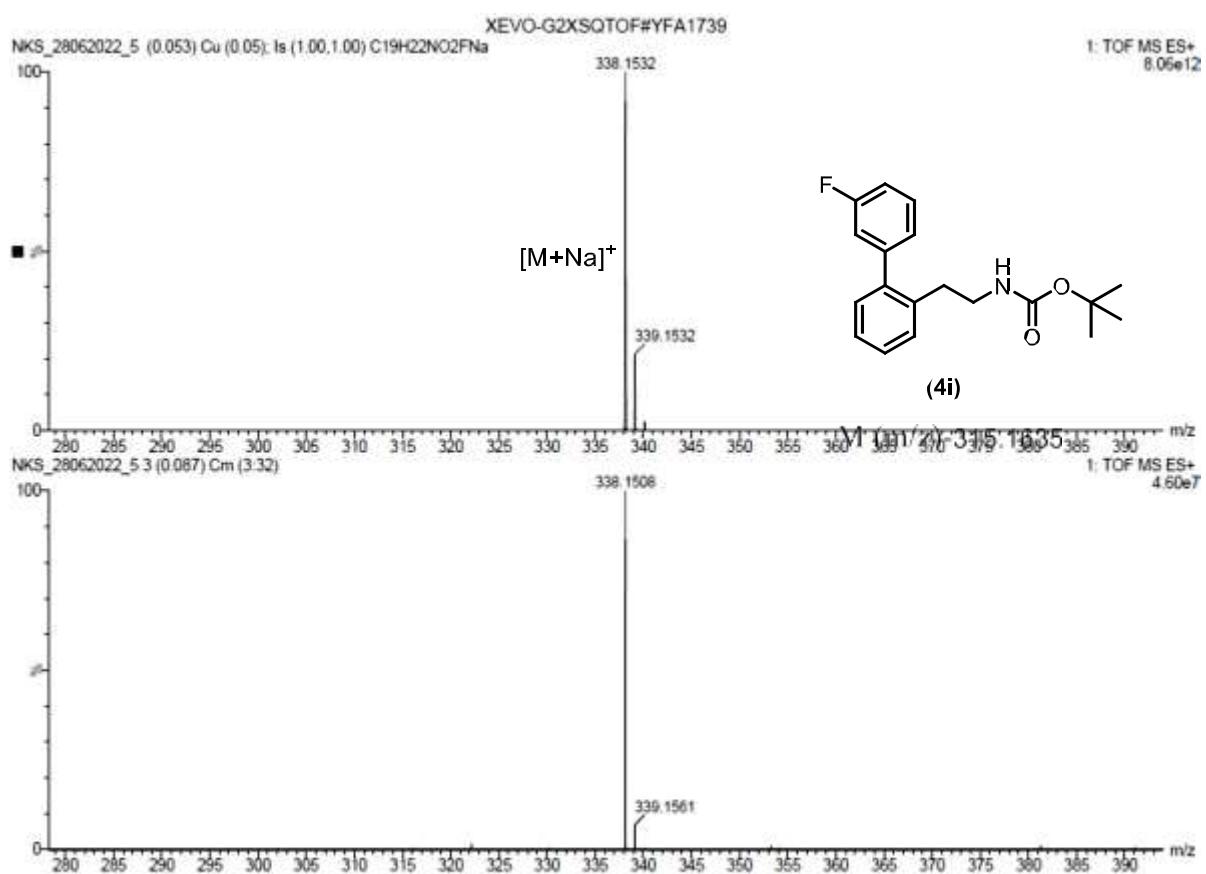


(41)





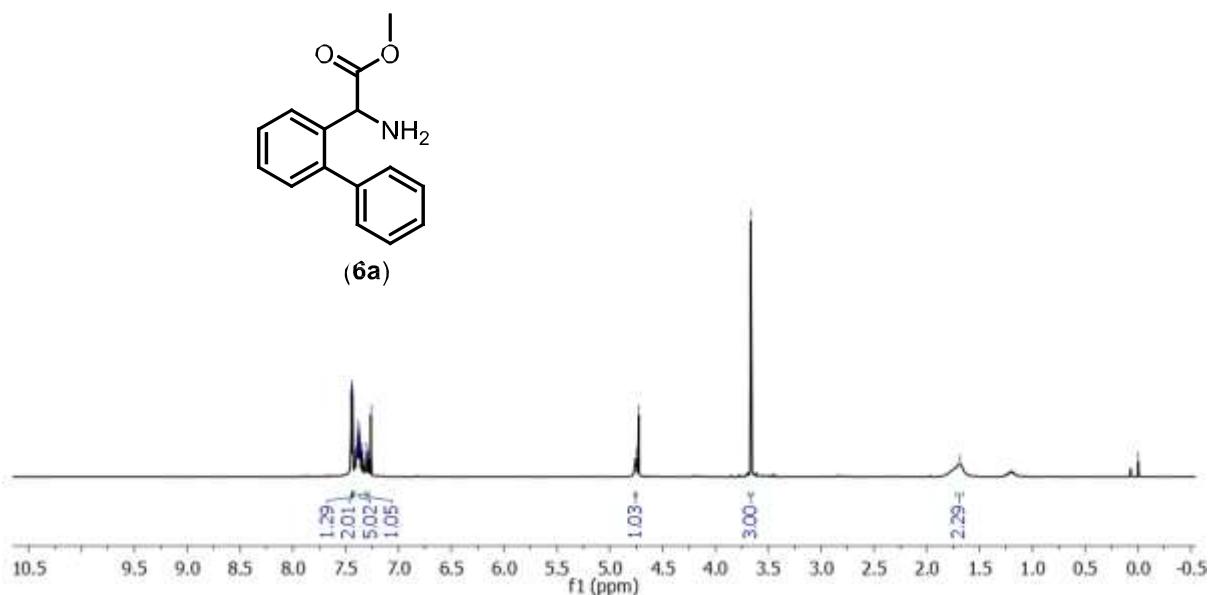
**Fig. S45** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, <sup>19</sup>F NMR Spectra of compound **4i**.



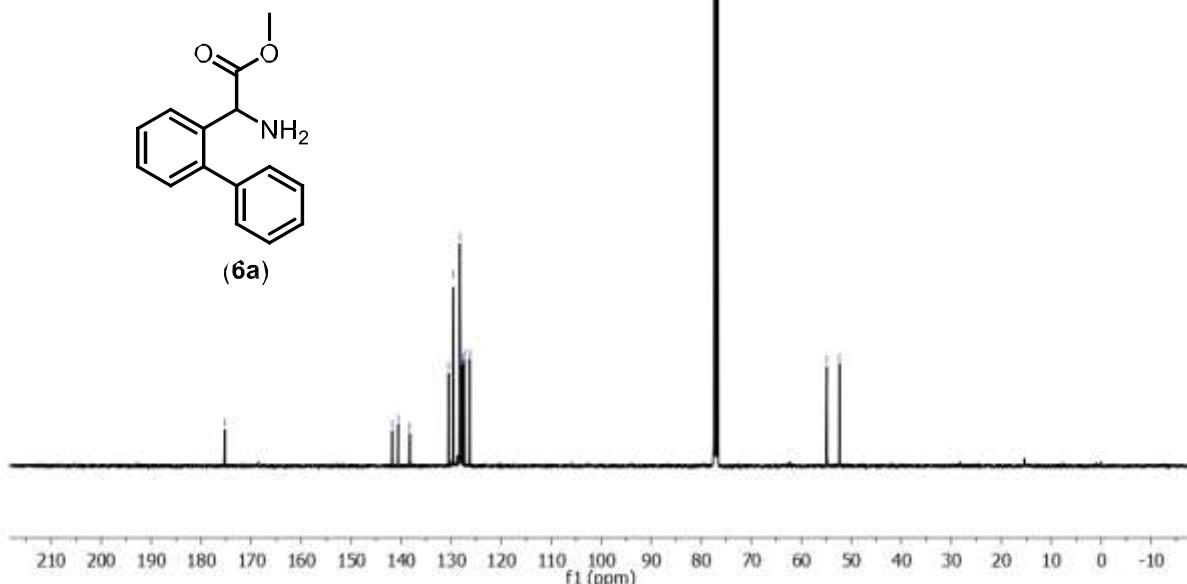
**Fig. S46** ESI-HRMS Spectra of compound **4i**.



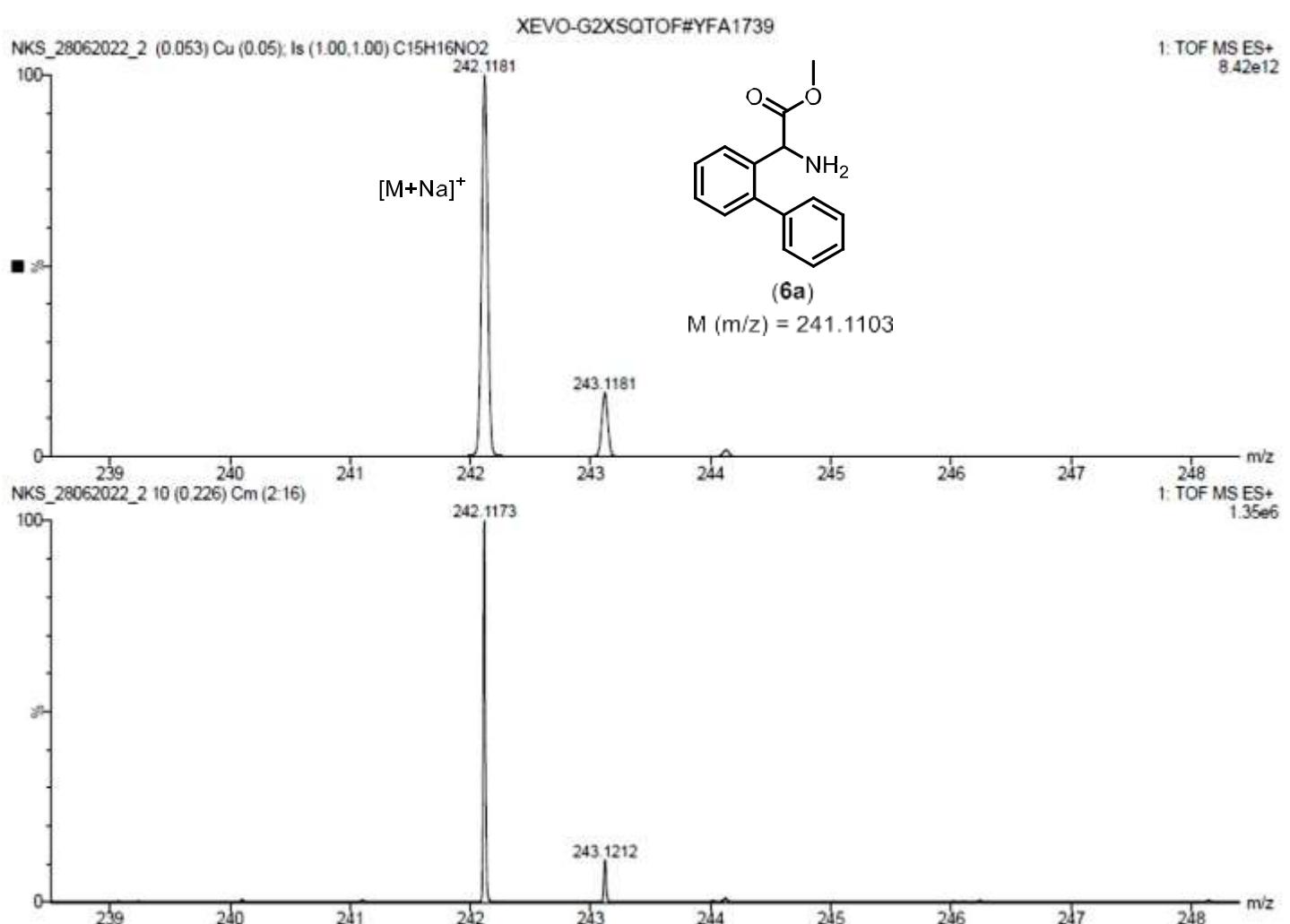
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



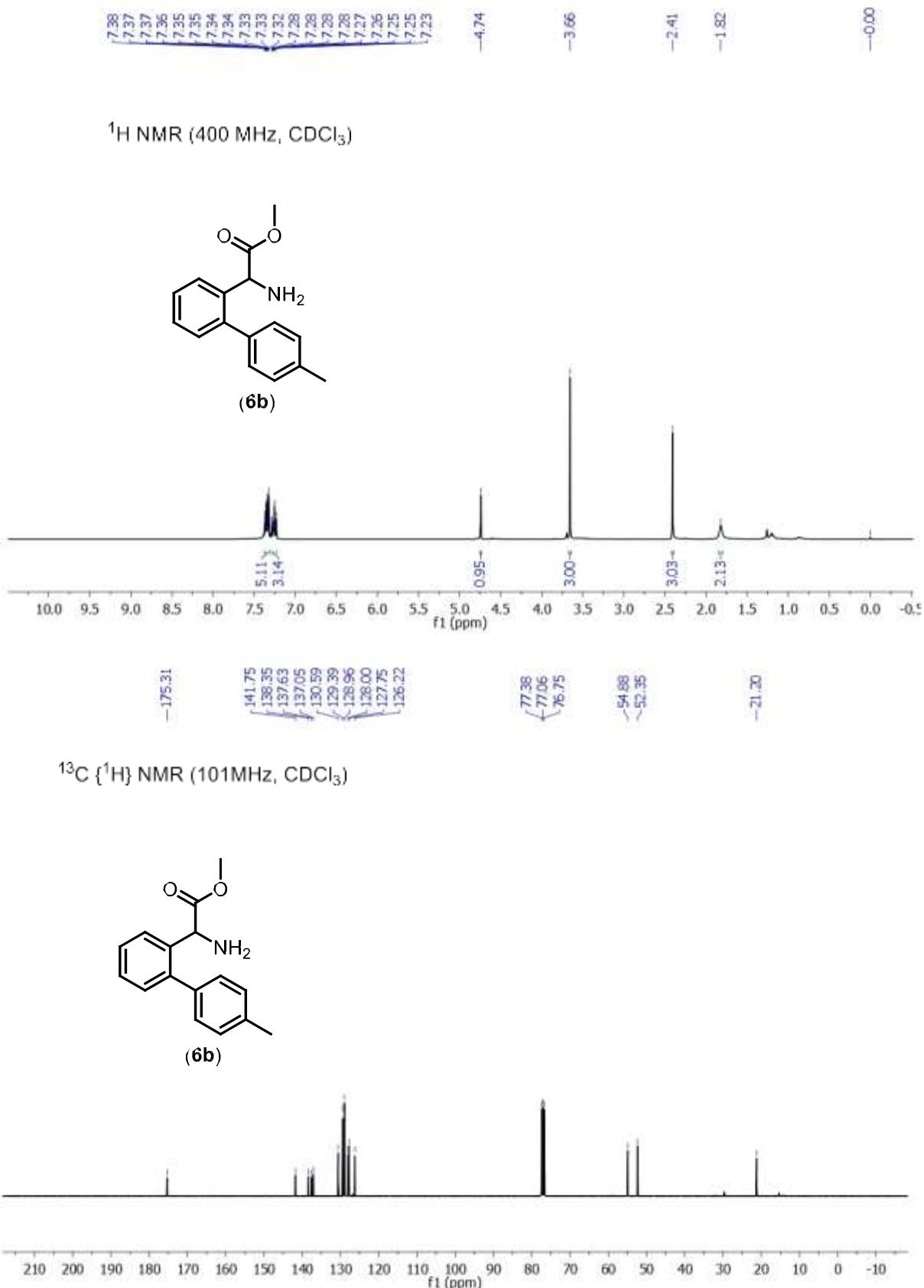
<sup>13</sup>C {<sup>1</sup>H} NMR (101MHz, CDCl<sub>3</sub>)



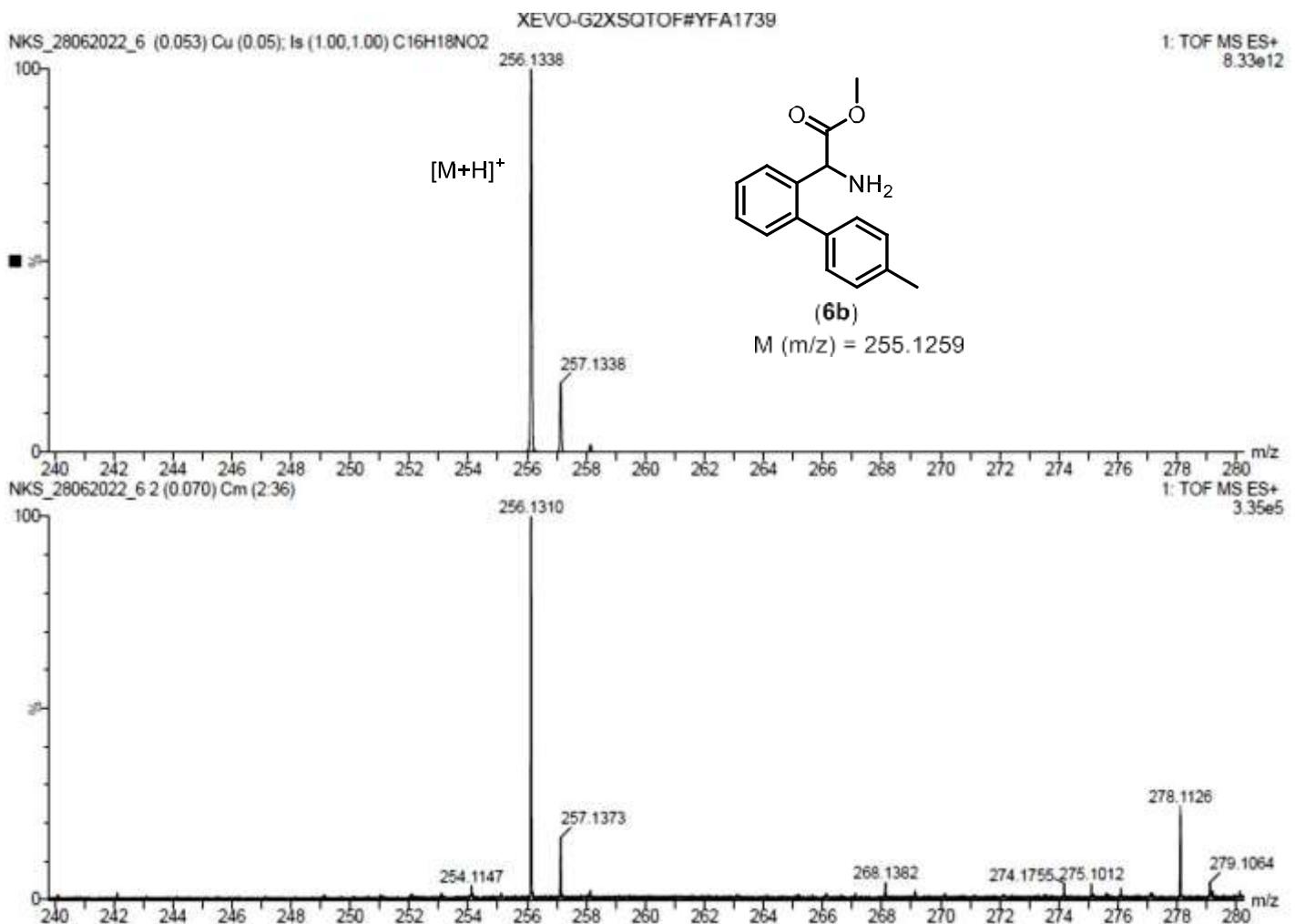
**Fig. S47** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound **6a**.



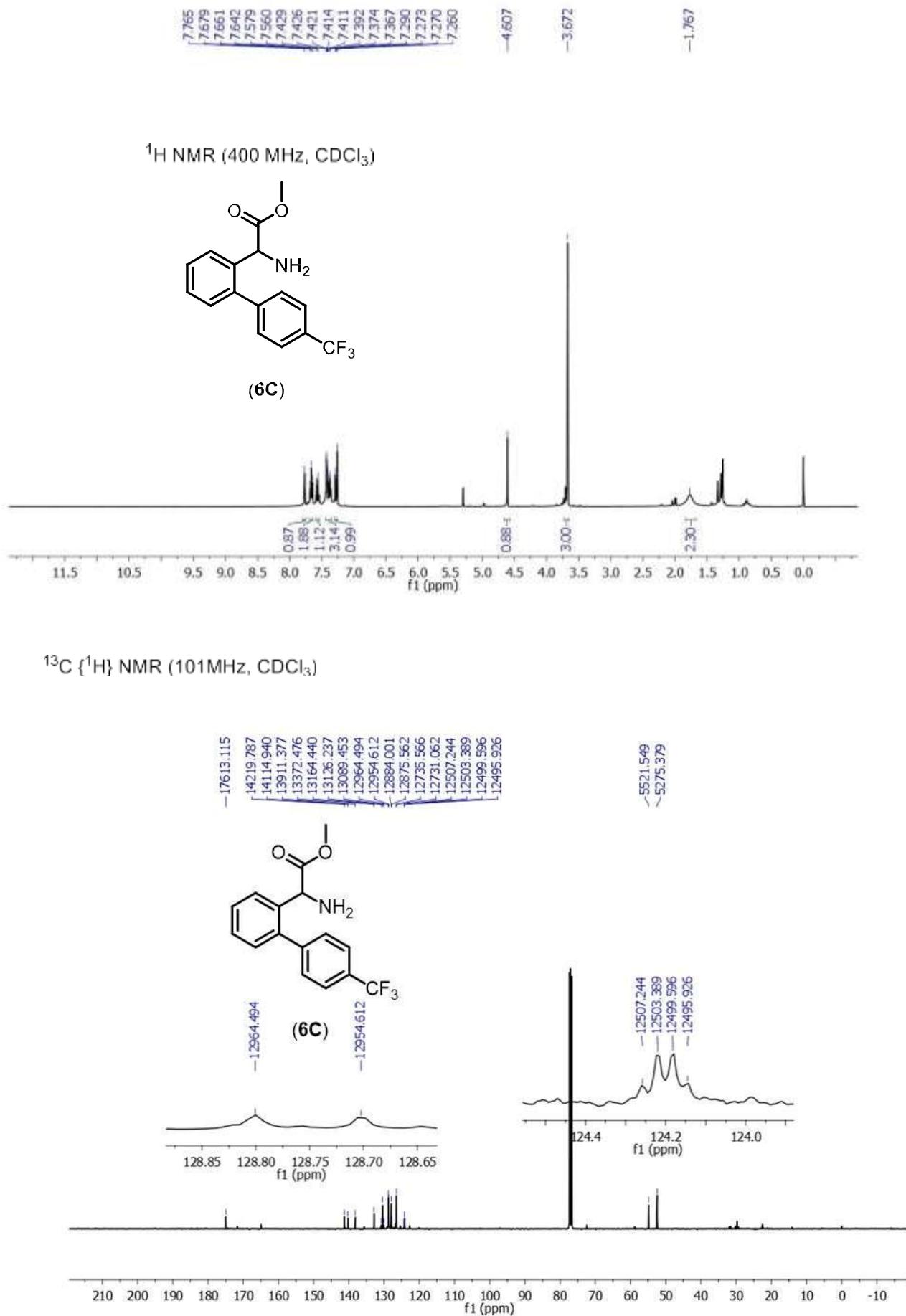
**Fig. S48 ESI-HRMS Spectra of compound 6a.**

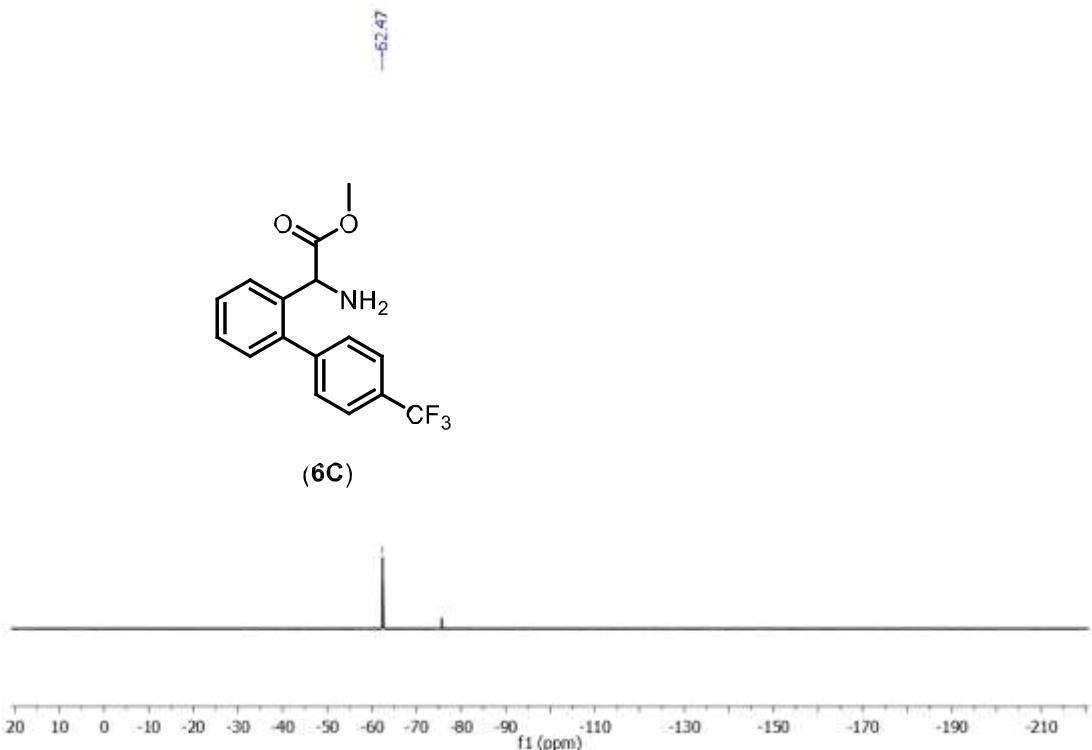


**Fig. S49** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound 6b.

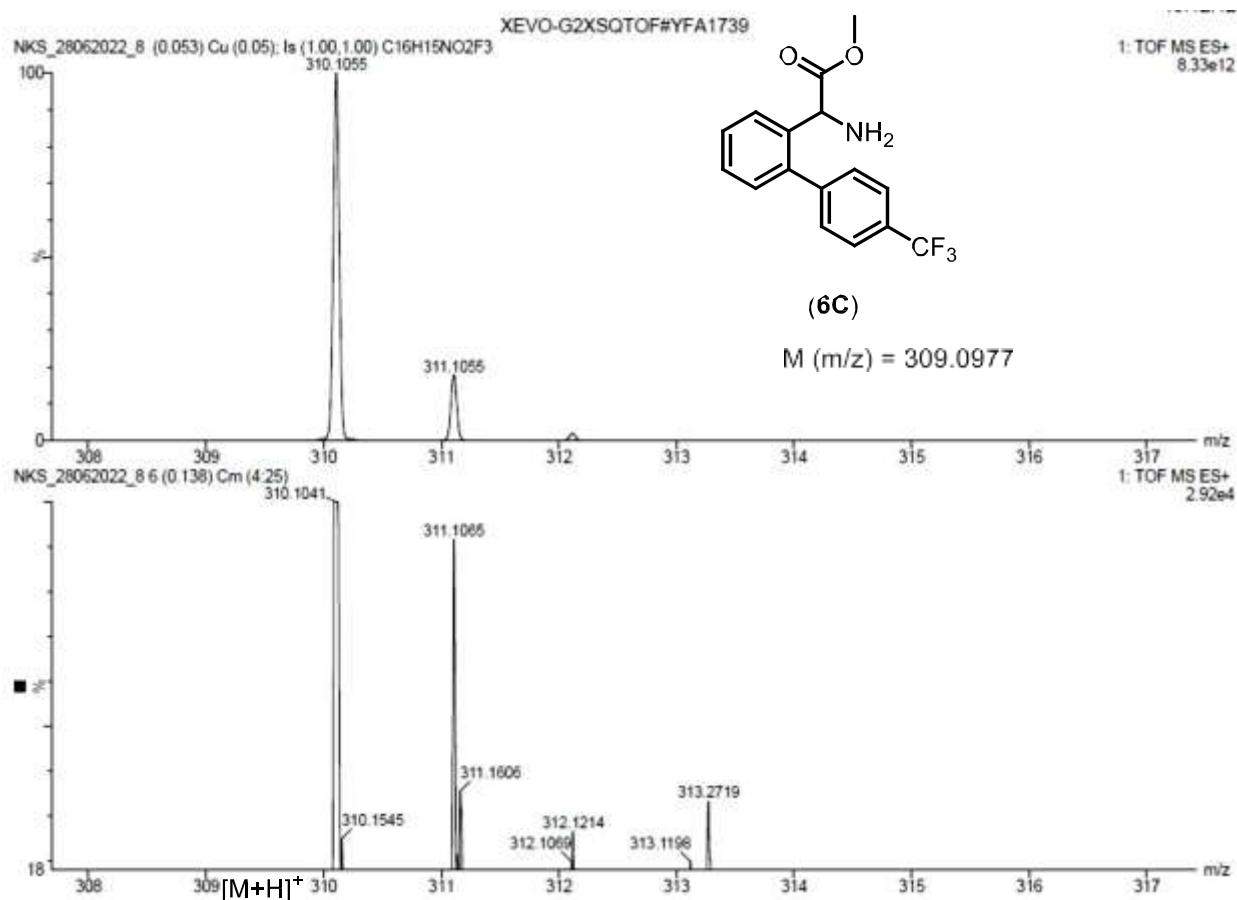


**Fig. S50 ESI-HRMS Spectra of compound 6b.**

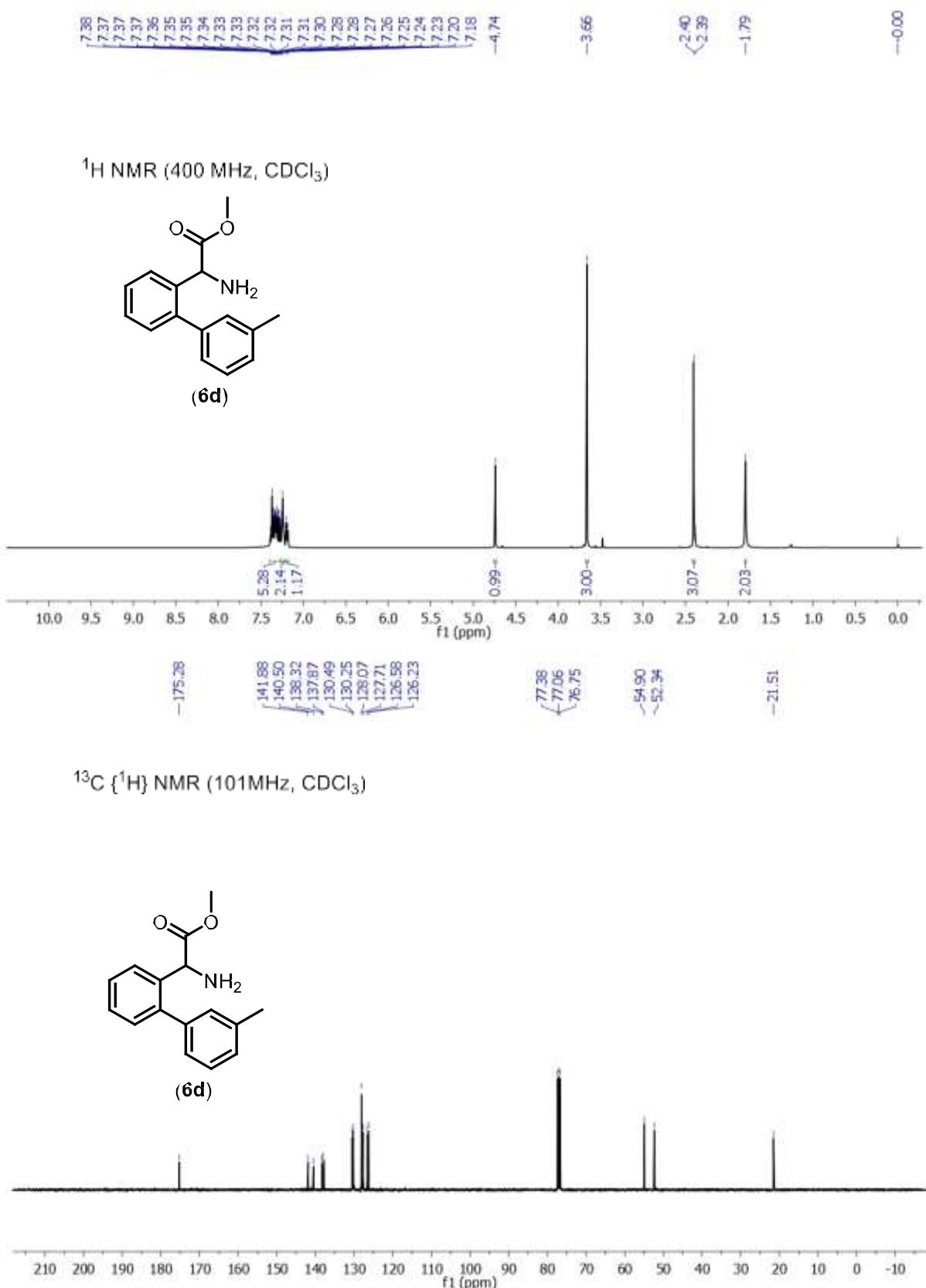




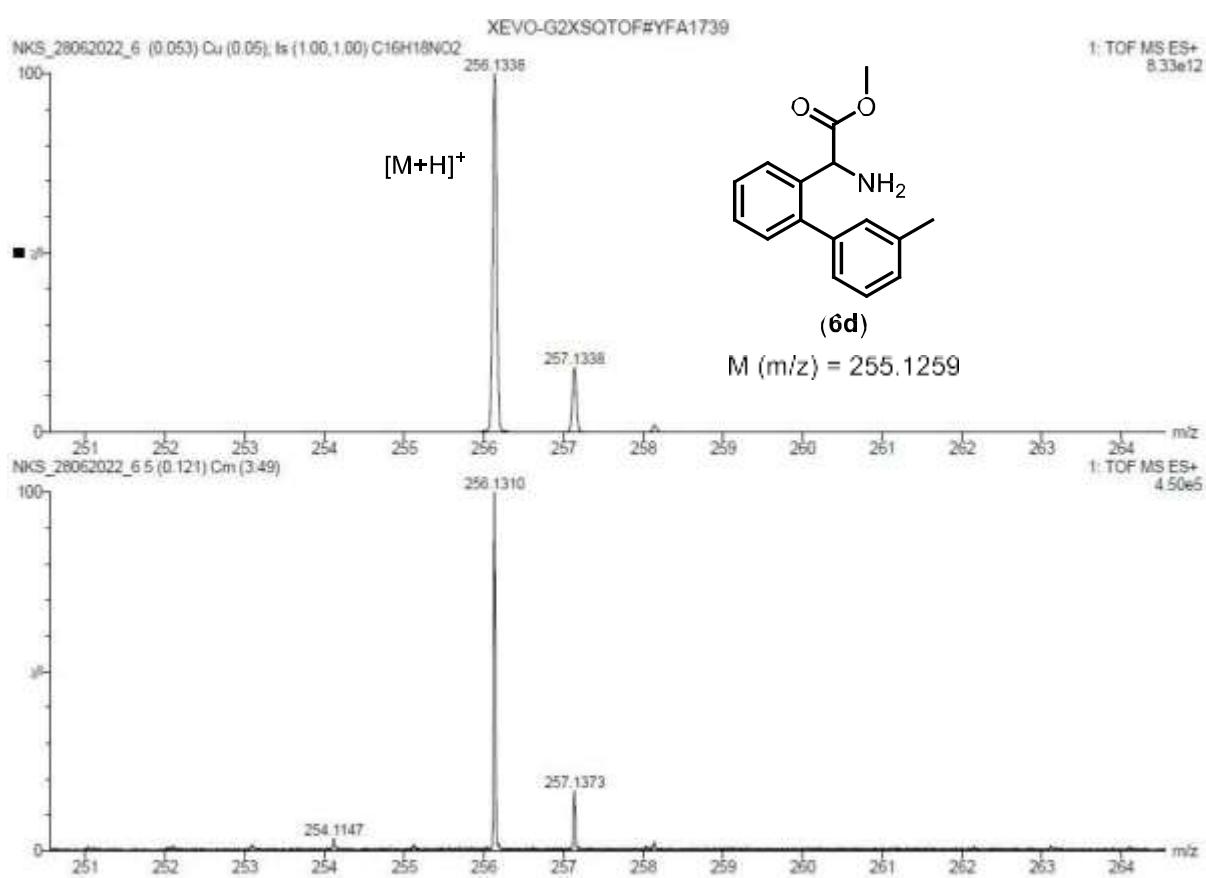
**Fig. S51**  $^1\text{H}$ ,  $^{13}\text{C}$  { $^1\text{H}$ },  $^{19}\text{F}$  NMR Spectra of compound **6c**.



**Fig.S52** ESI-HRMS Spectra of compound **6c**.

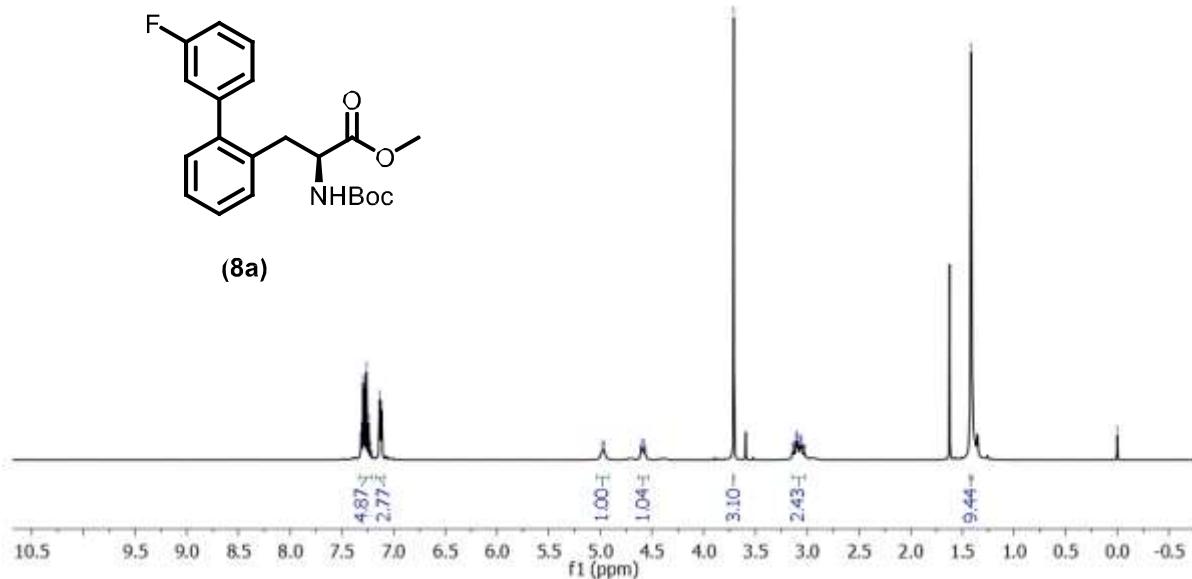


**Fig. S53**  $^1\text{H}$ ,  $^{13}\text{C}$  { $^1\text{H}$ }, NMR Spectra of compound **6d**.

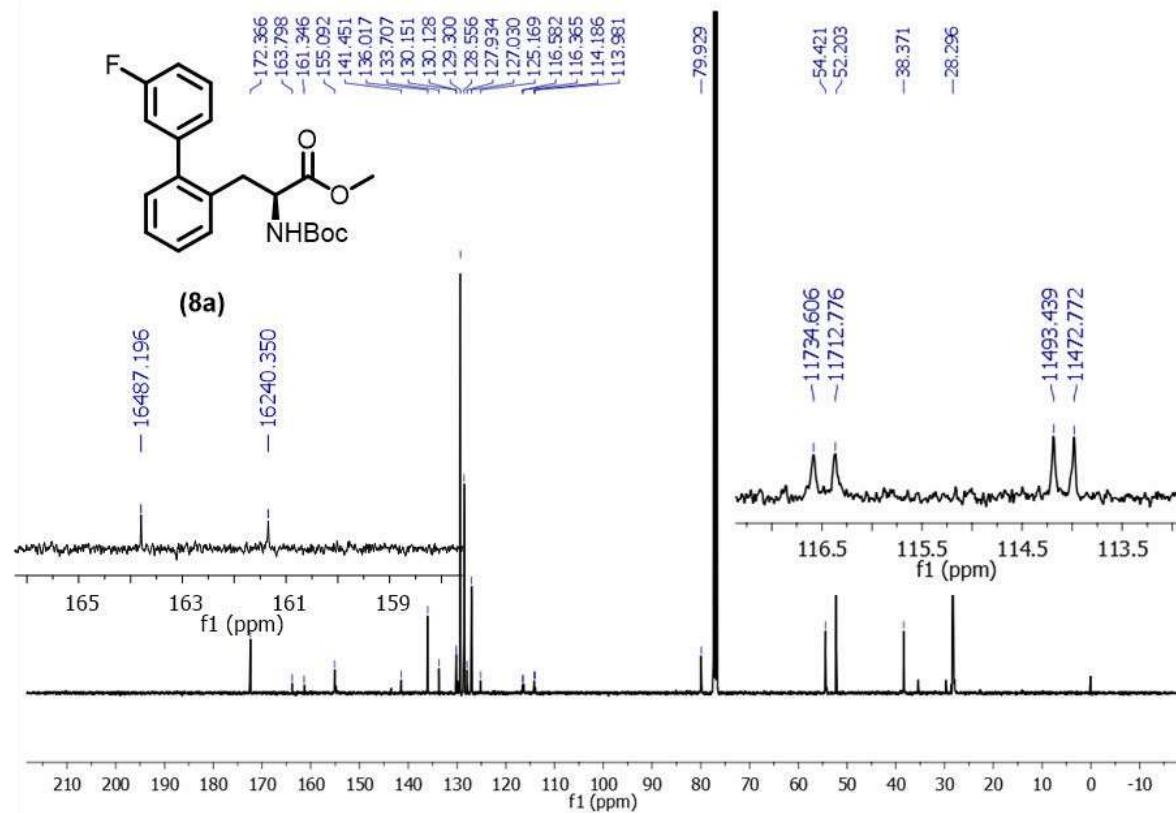


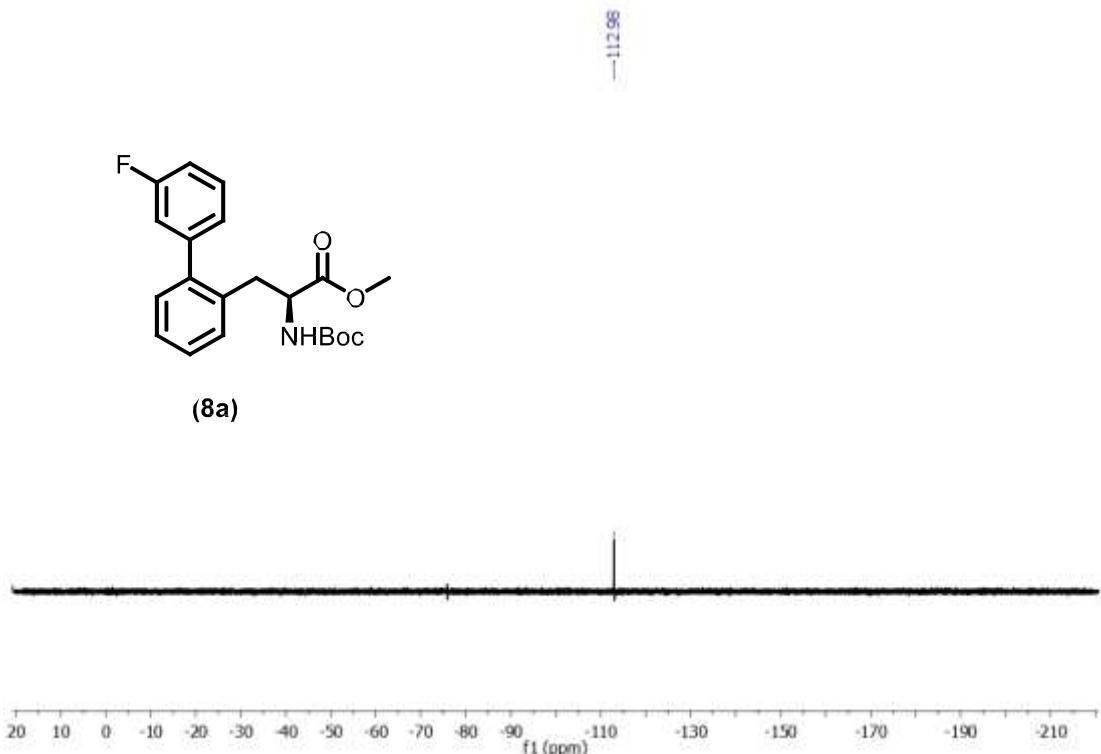
**Fig. S54 ESI-HRMS Spectra of compound 6d.**

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

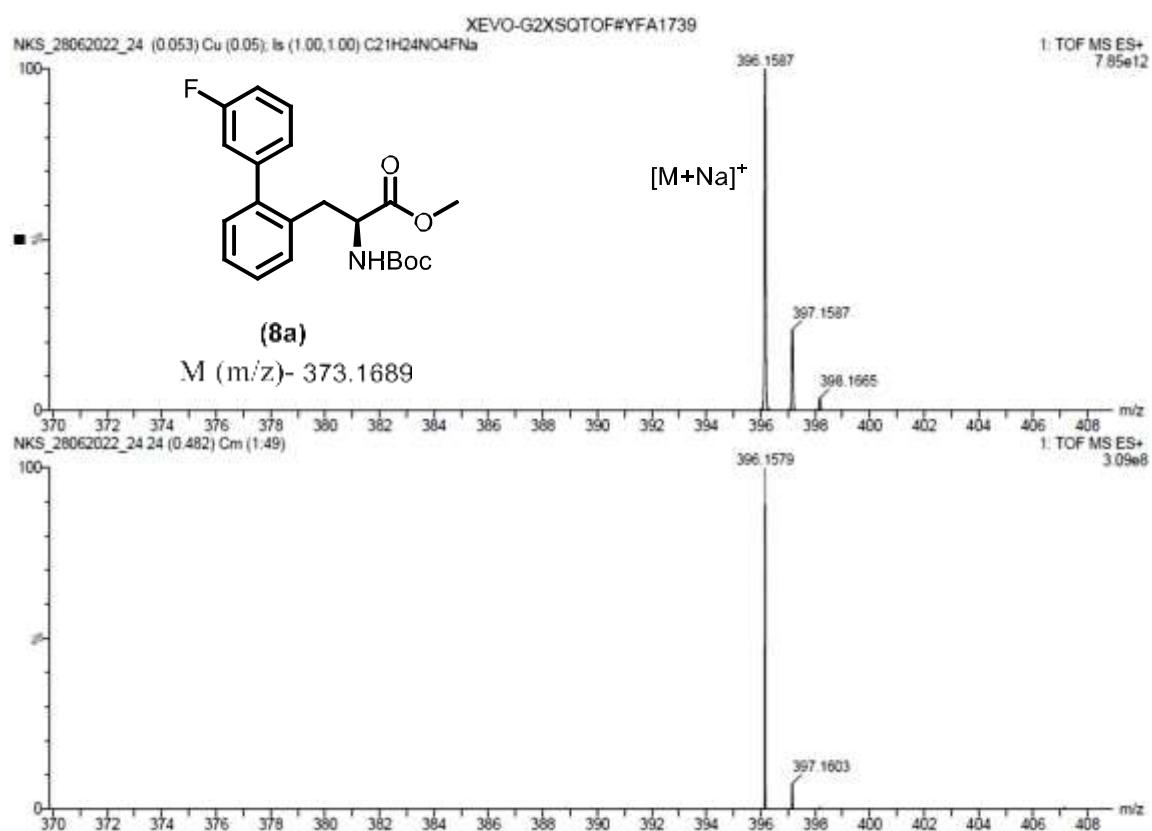


$^{13}\text{C} \{^1\text{H}\}$  NMR (101MHz,  $\text{CDCl}_3$ )





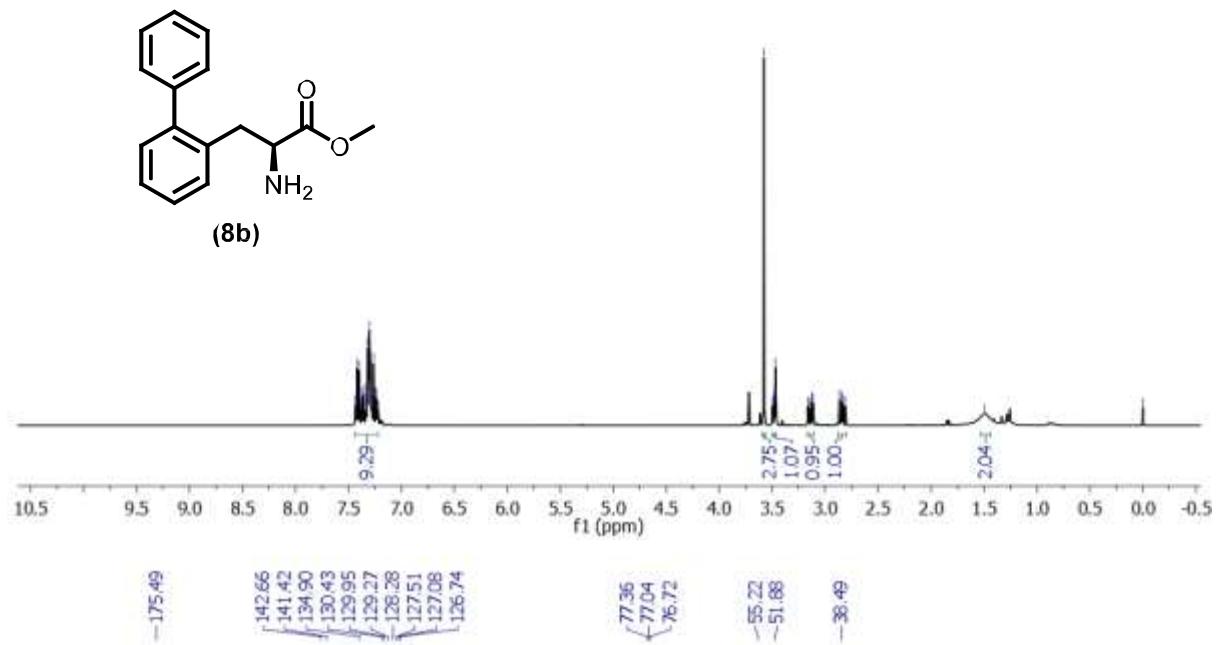
**Fig. S55**  $^1\text{H}$ ,  $^{13}\text{C}$  { $^1\text{H}$ }, NMR Spectra of compound **8a**.



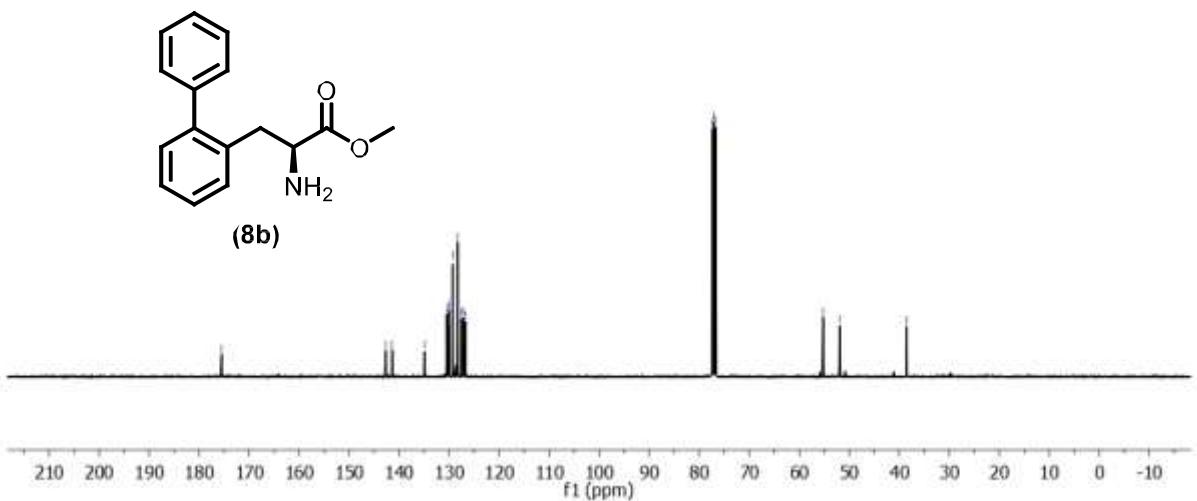
**Fig. S56** ESI-HRMS Spectra of compound **8a**.



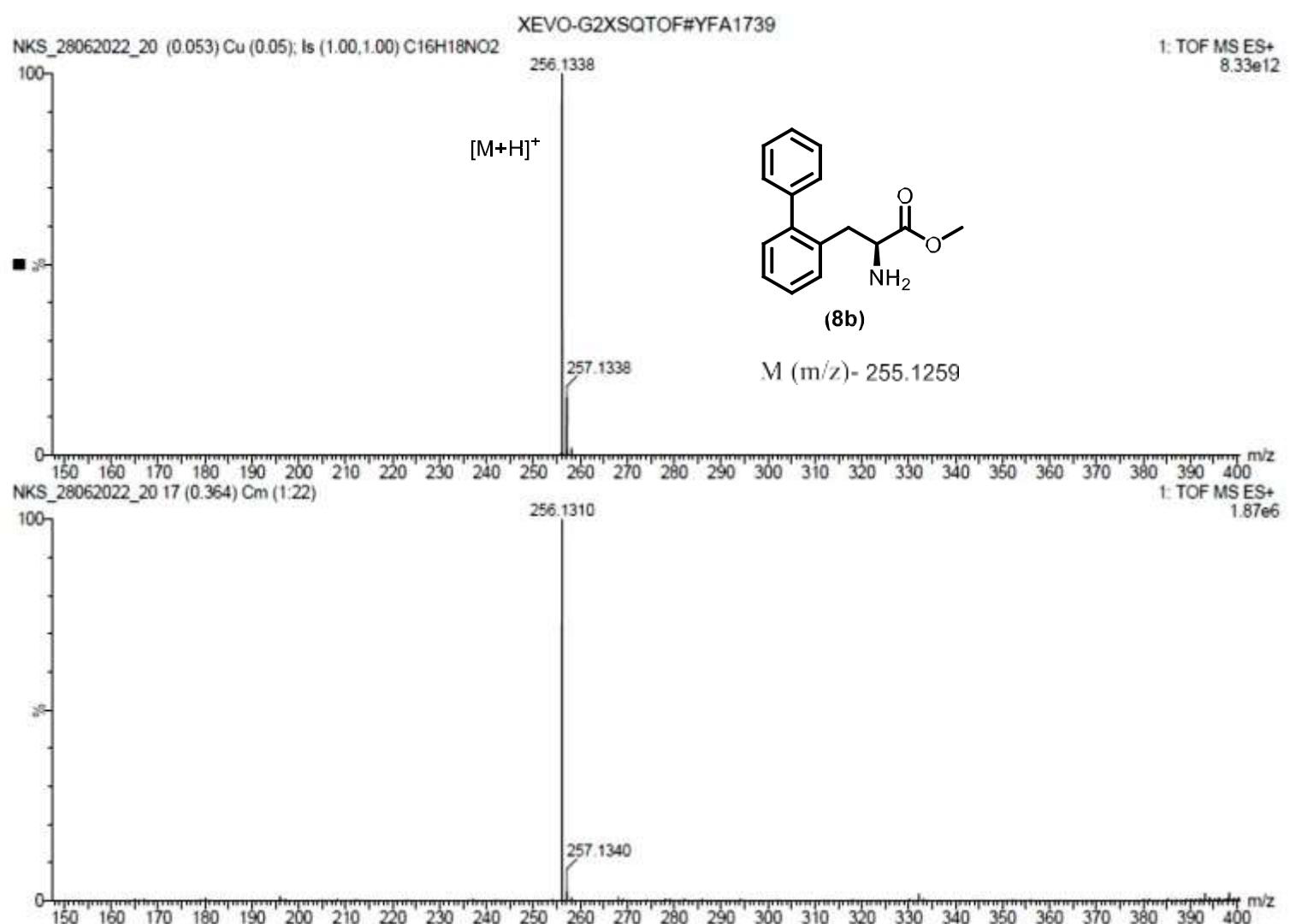
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



<sup>13</sup>C {<sup>1</sup>H} NMR (101MHz, CDCl<sub>3</sub>)



**Fig. S57** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound **8b**.



**Fig. S58 ESI-HRMS Spectra of compound 8b.**

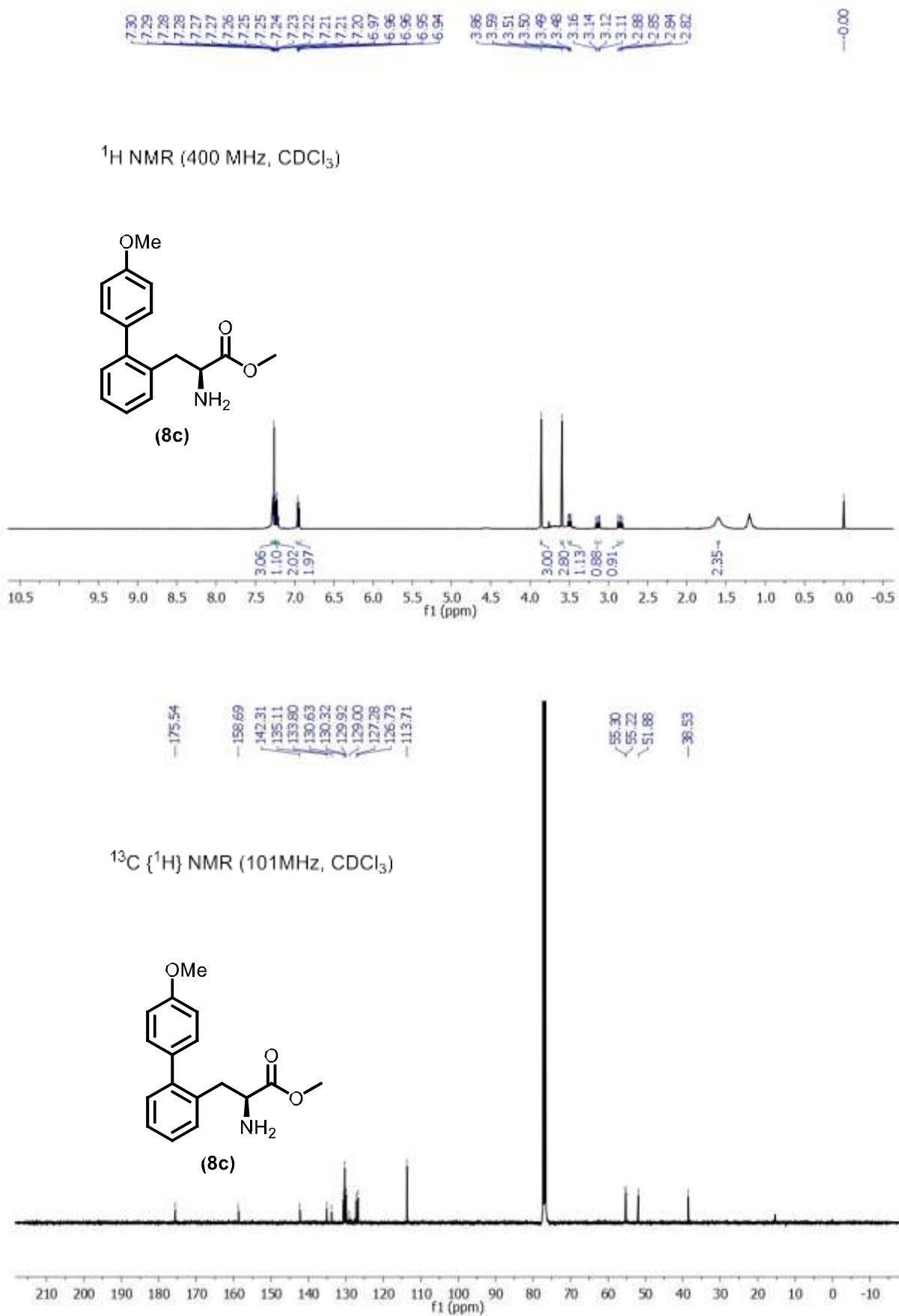
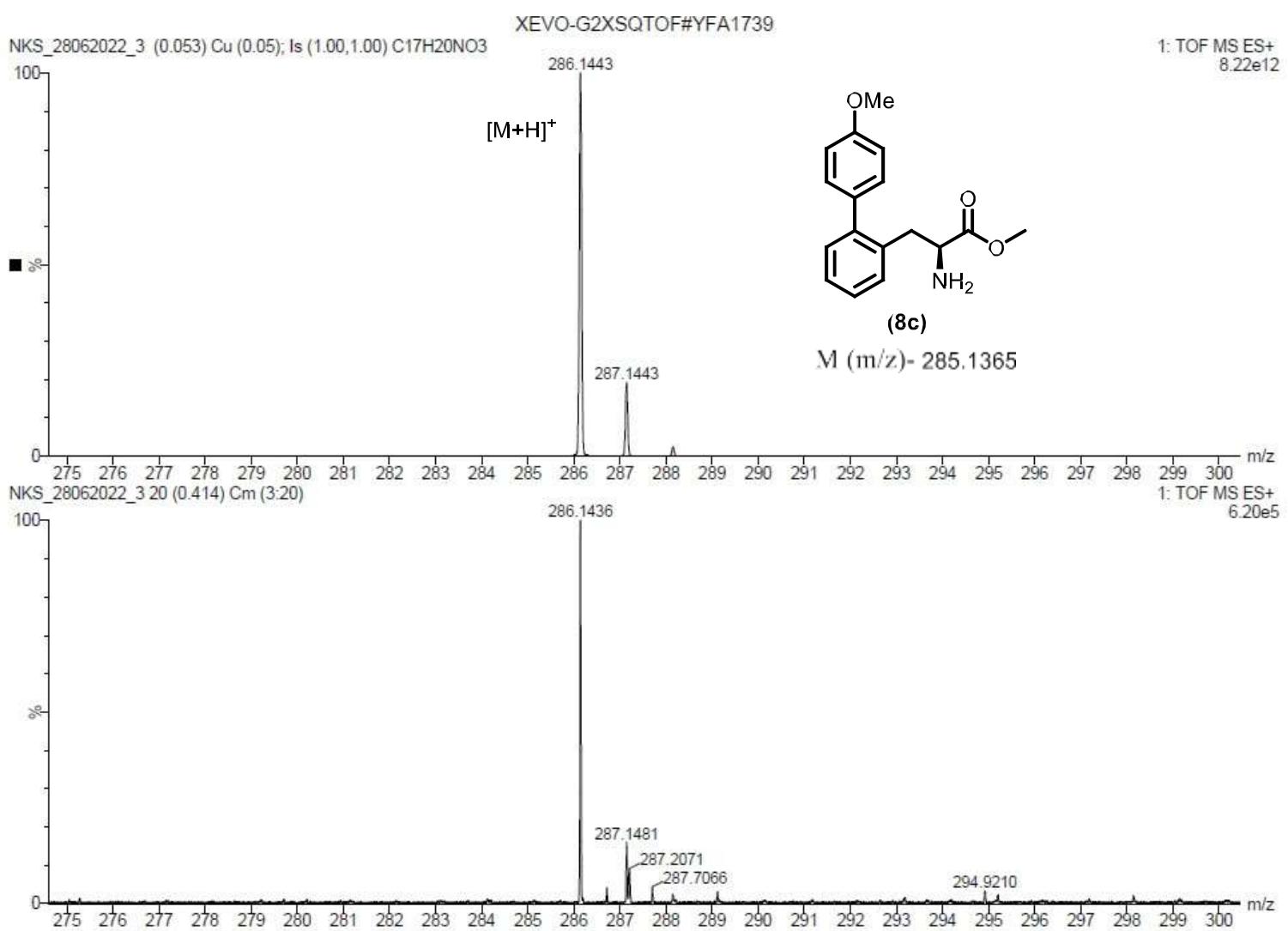
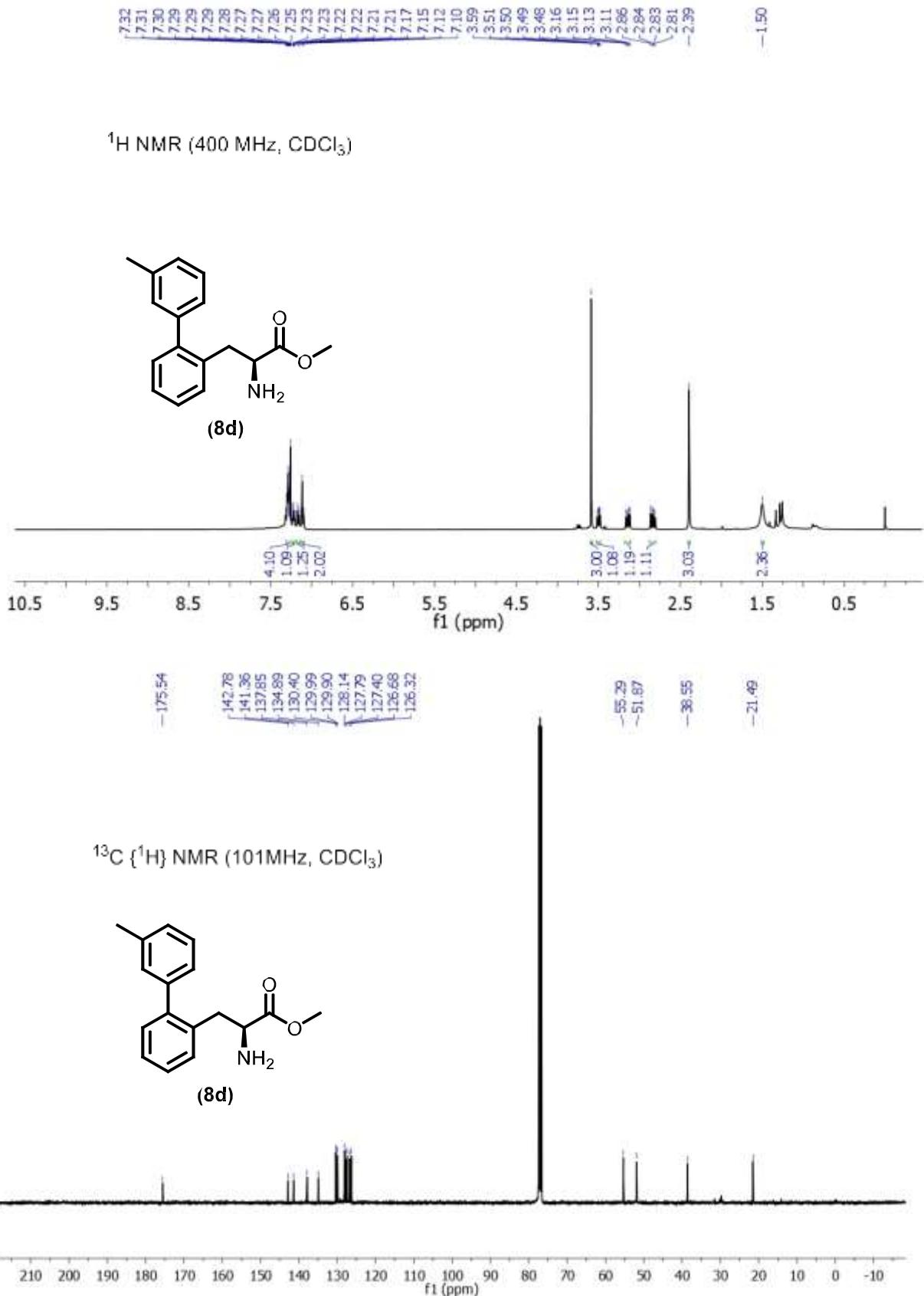
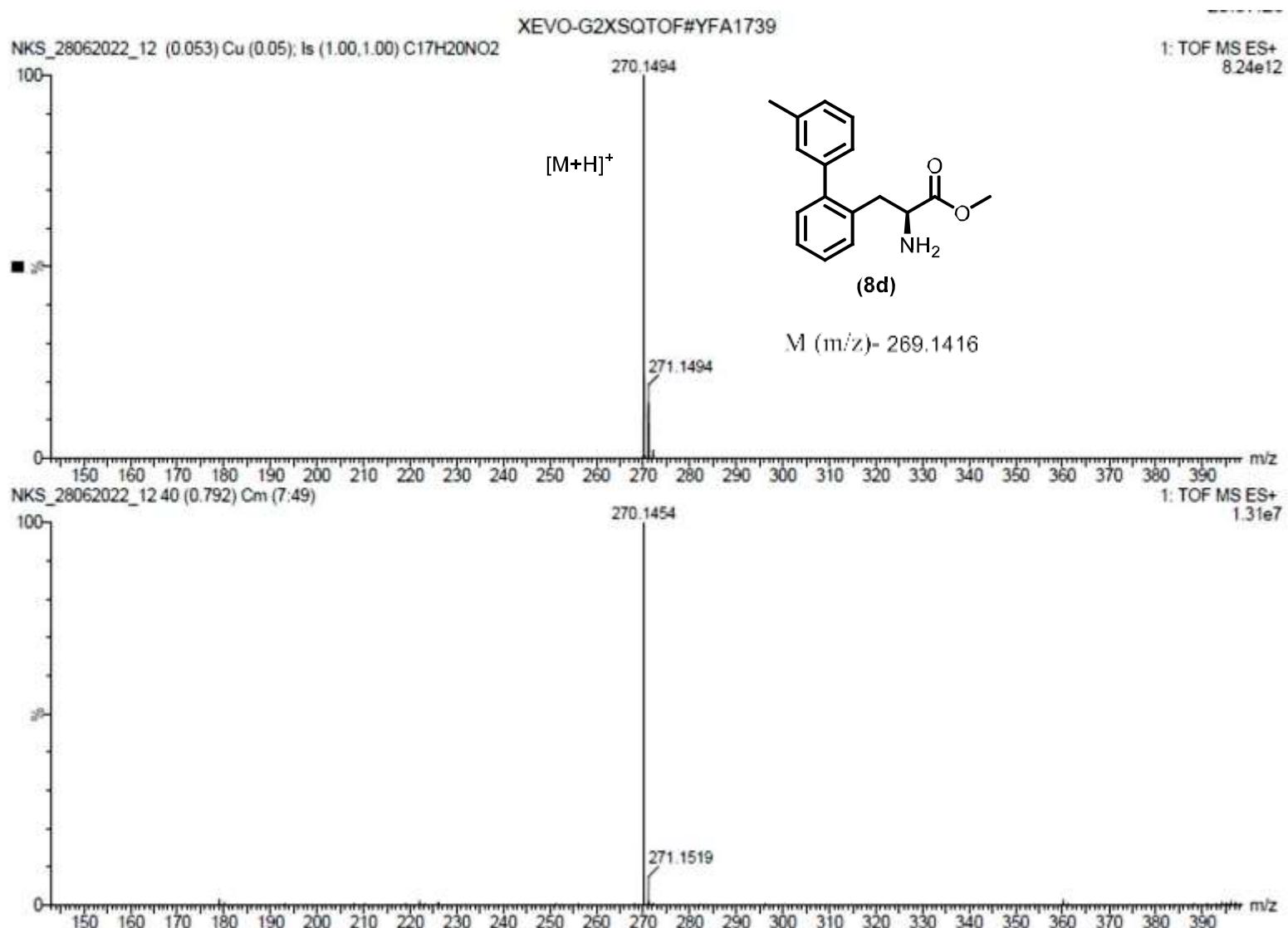


Fig. S59 <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound 8c.

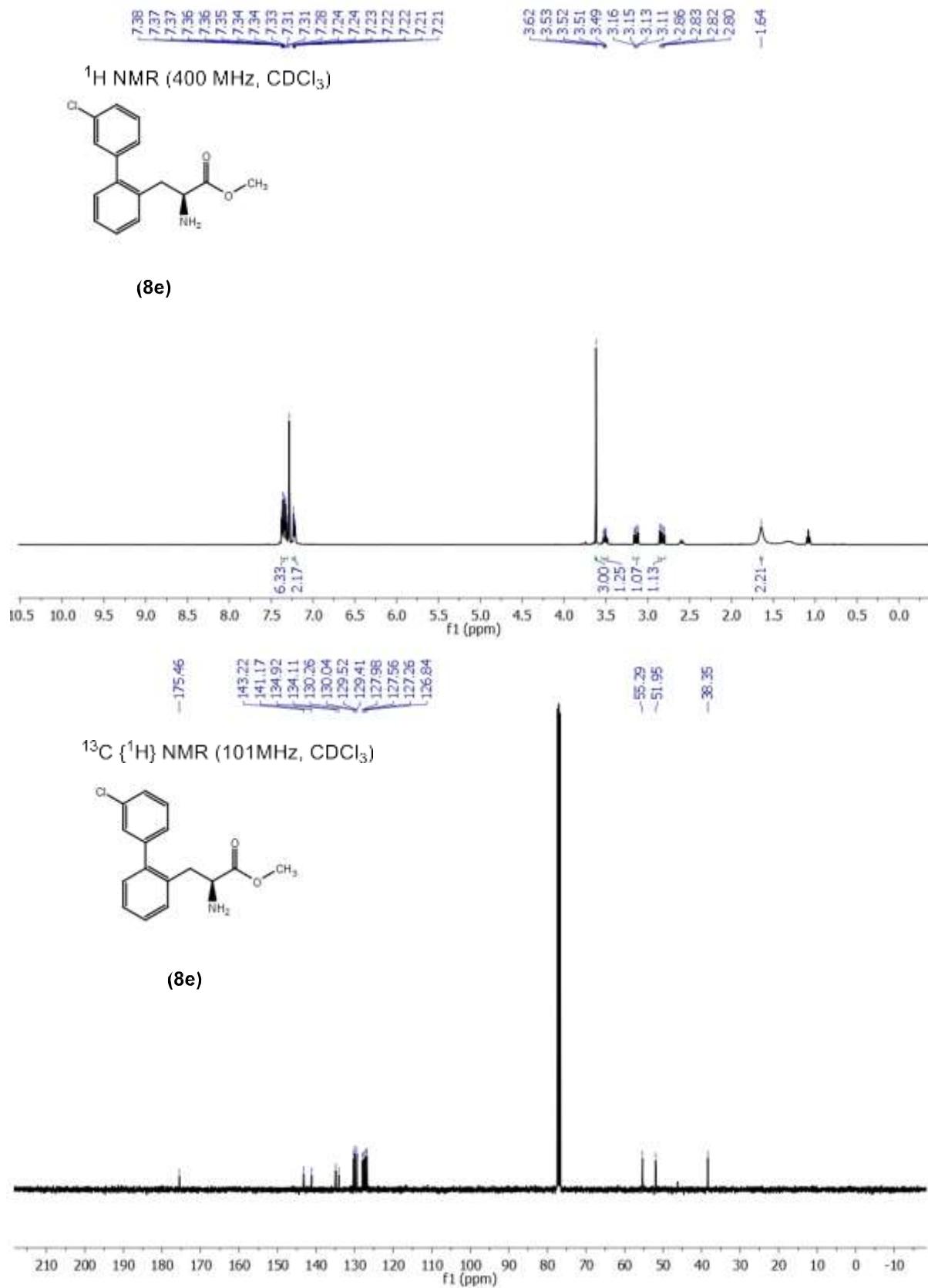


**Fig. S60 ESI-HRMS Spectra of compound 8c.**

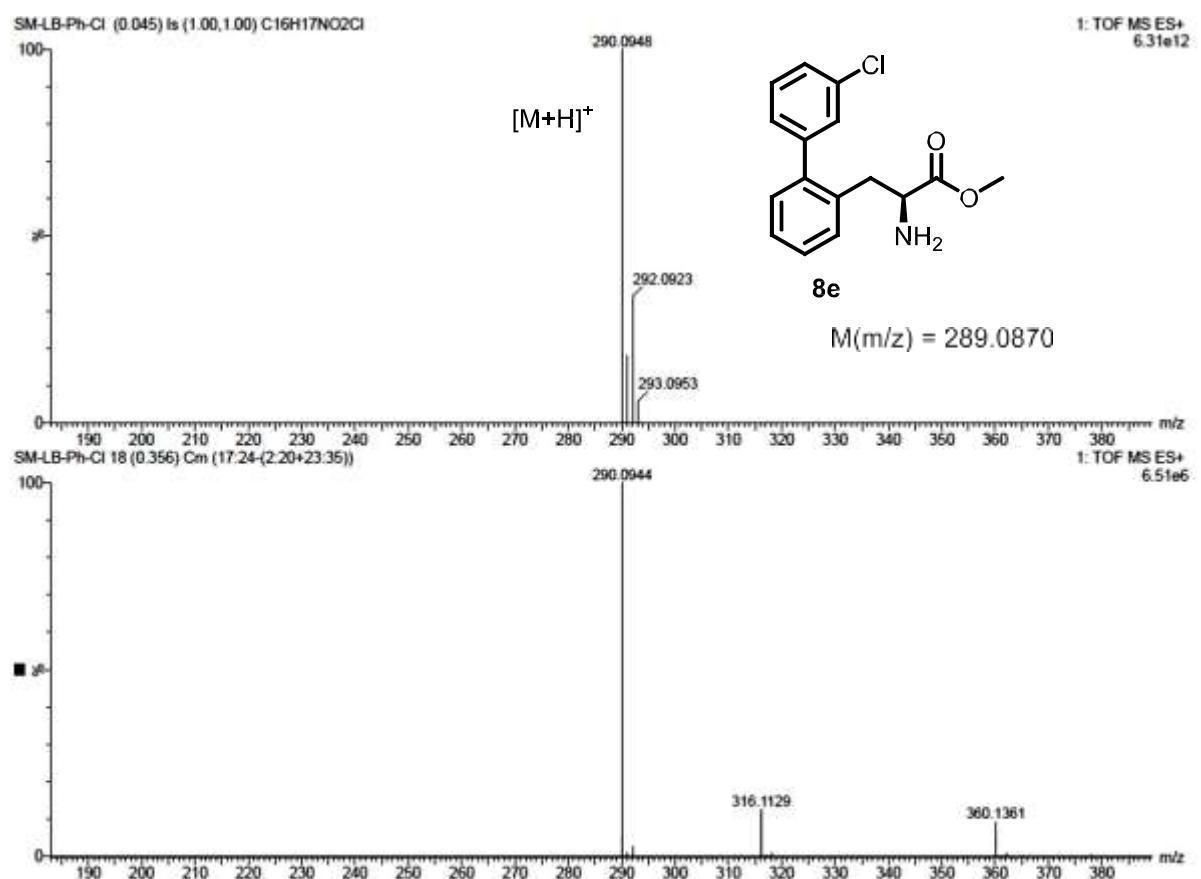




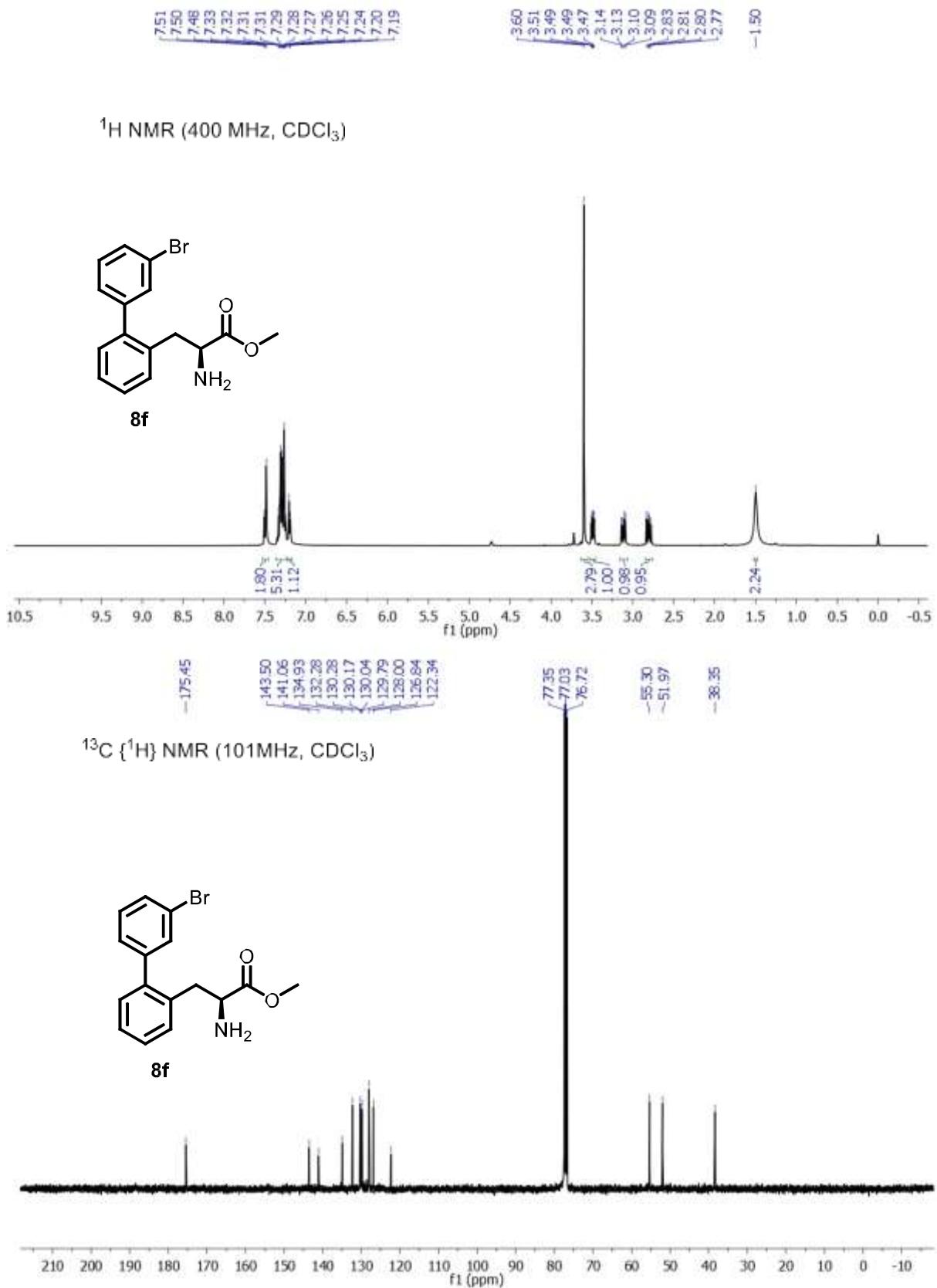
**Fig. S62 ESI-HRMS Spectra of compound 8d.**



**Fig. S63** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound 8e.

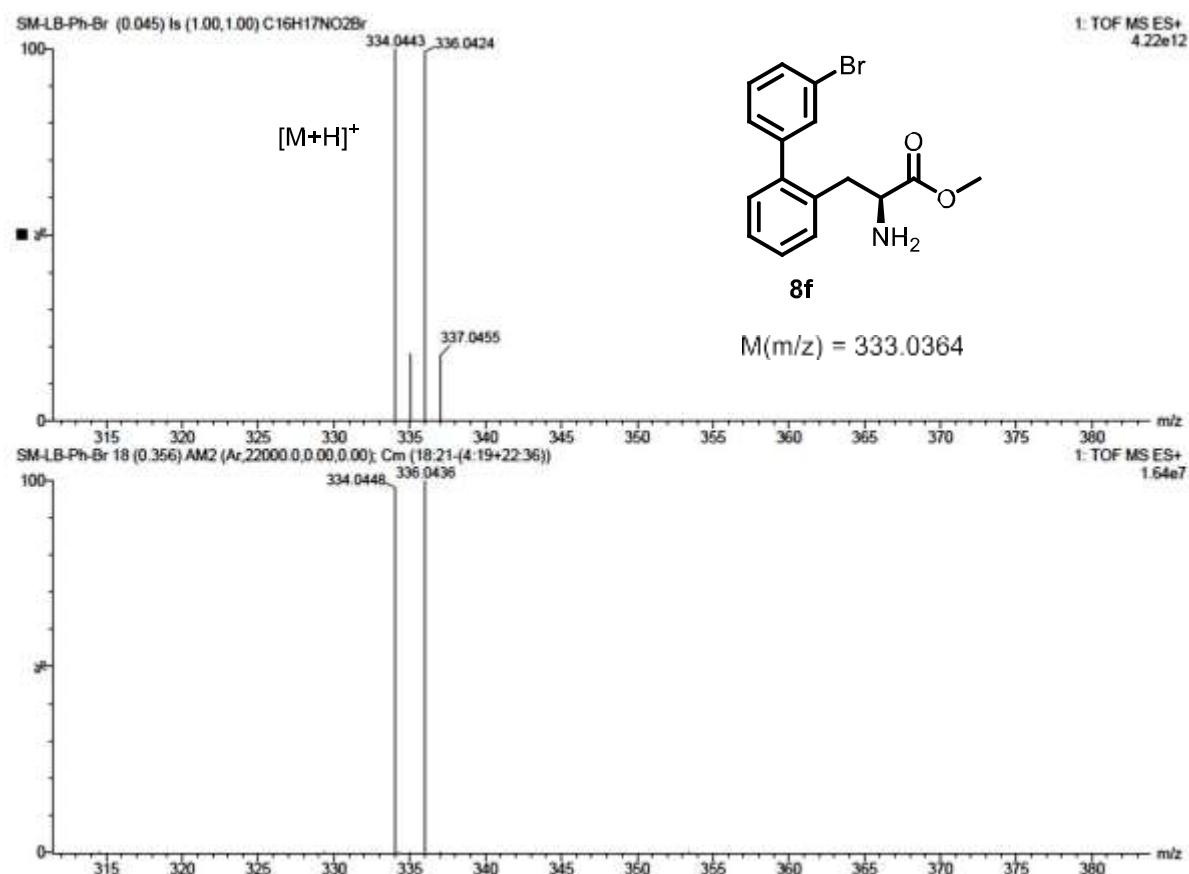


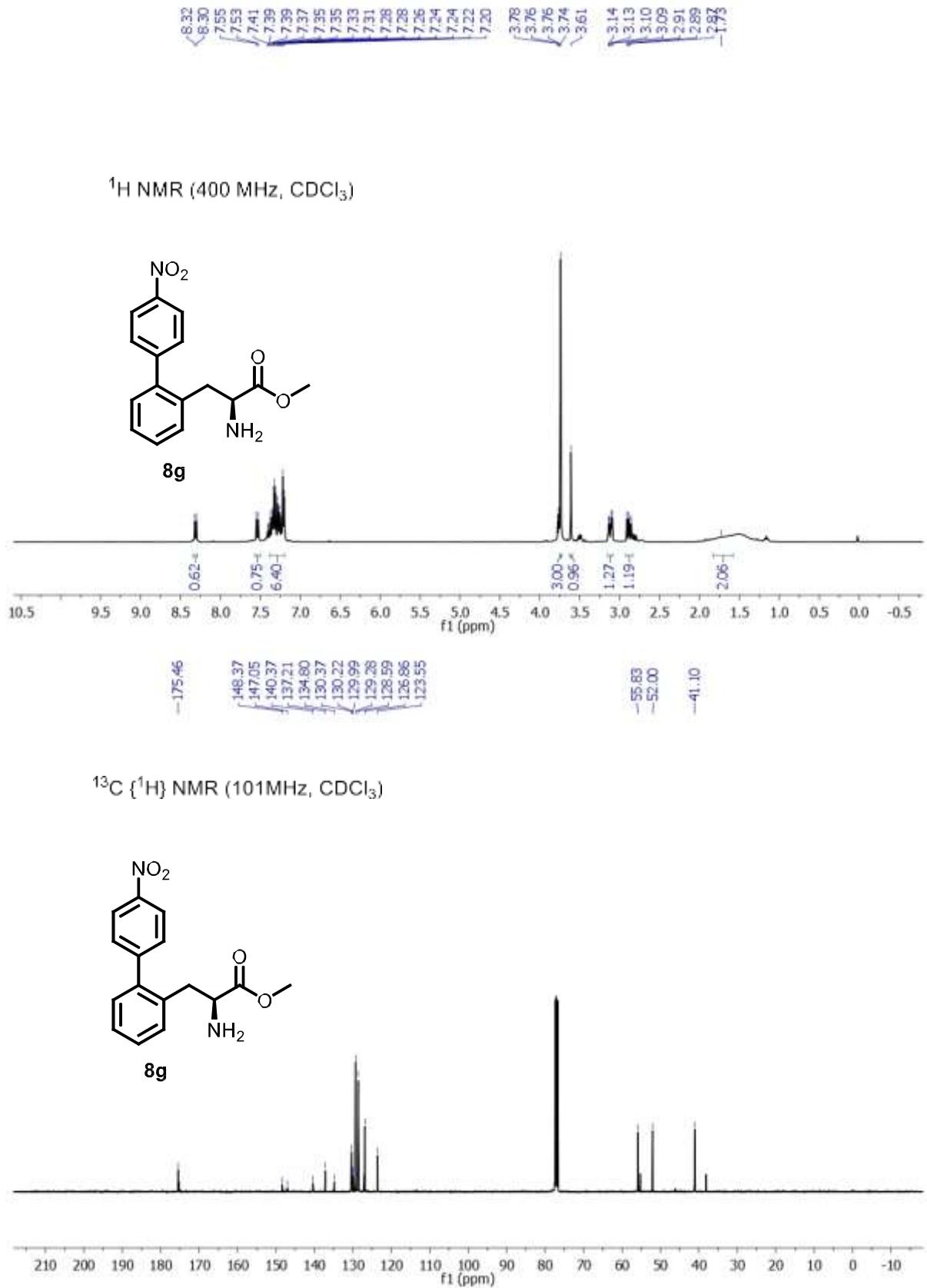
**Fig. S64 ESI-HRMS Spectra of Compound 8e.**



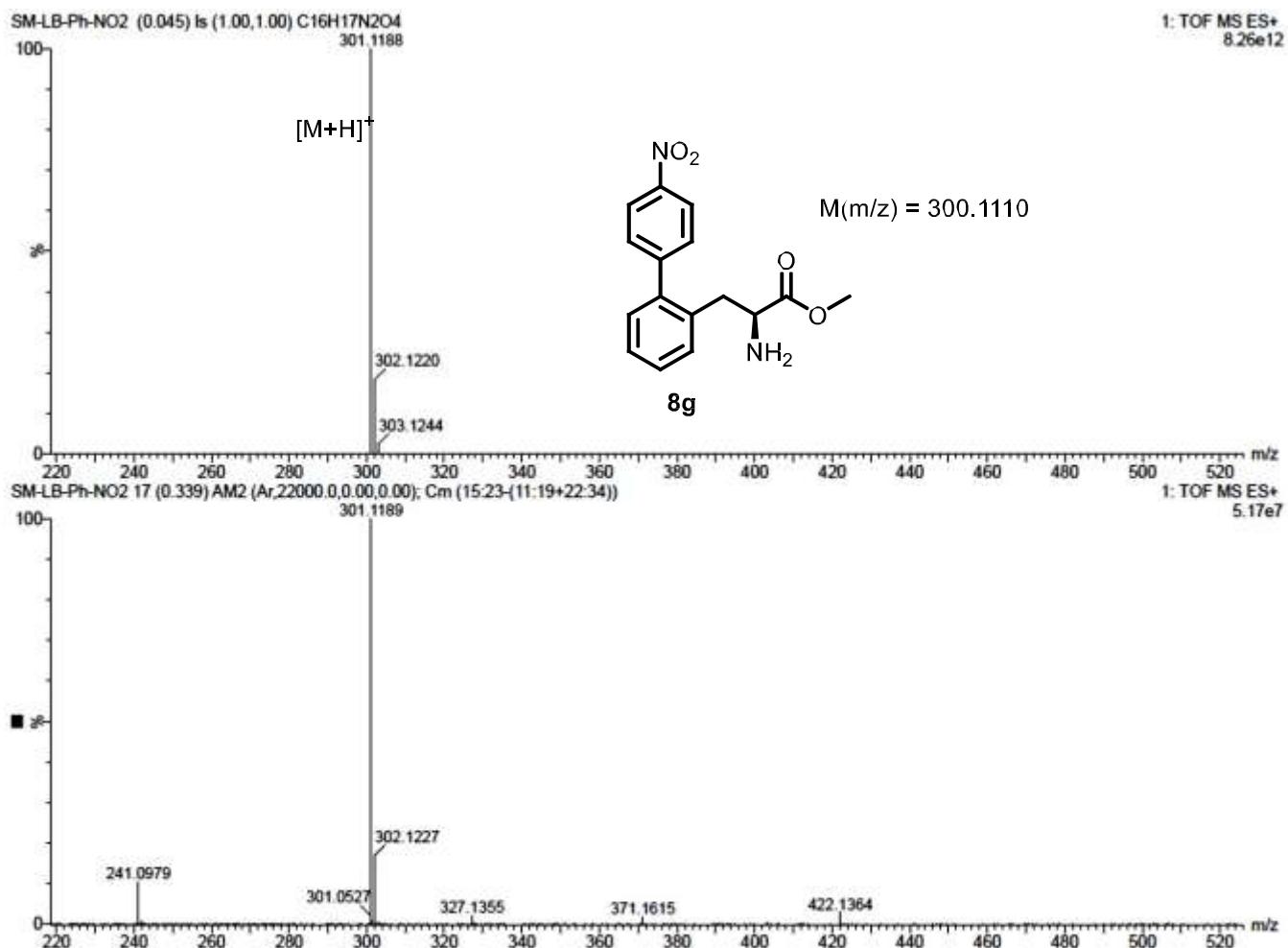
**Fig. S65** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound 8f.

**Fig. S66 ESI-HRMS Spectra of Compound 8f.**



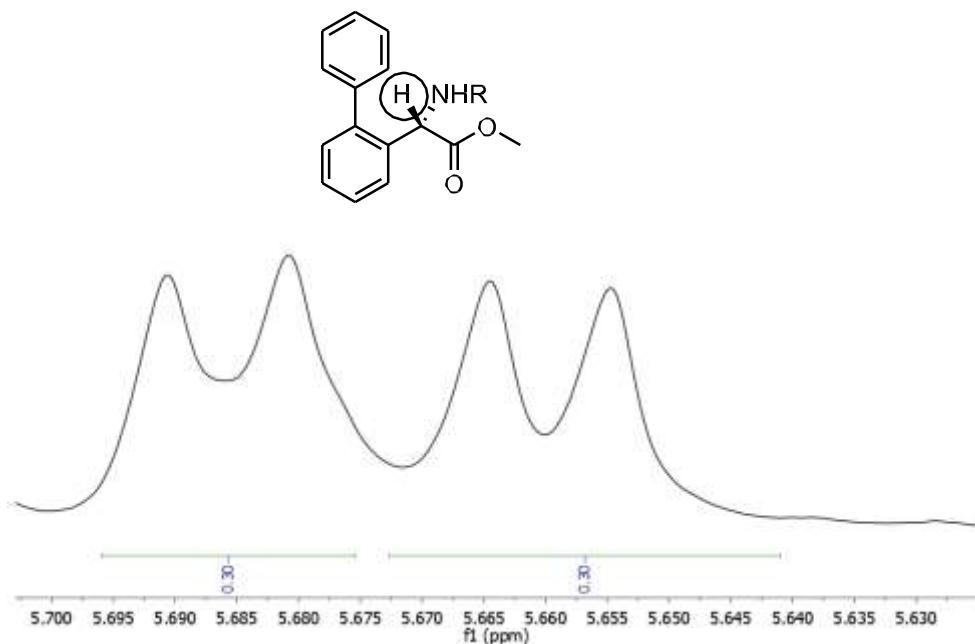


**Fig. S67** <sup>1</sup>H, <sup>13</sup>C {<sup>1</sup>H}, NMR Spectra of compound 8g.

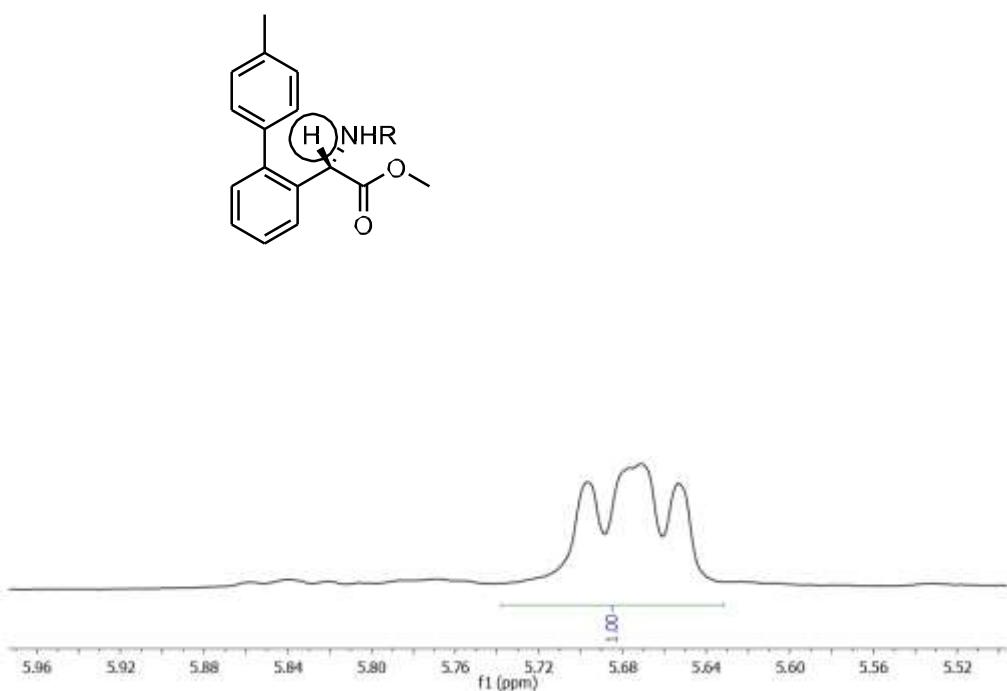


**Fig. S68** ESI-HRMS Spectra of Compound 8g.

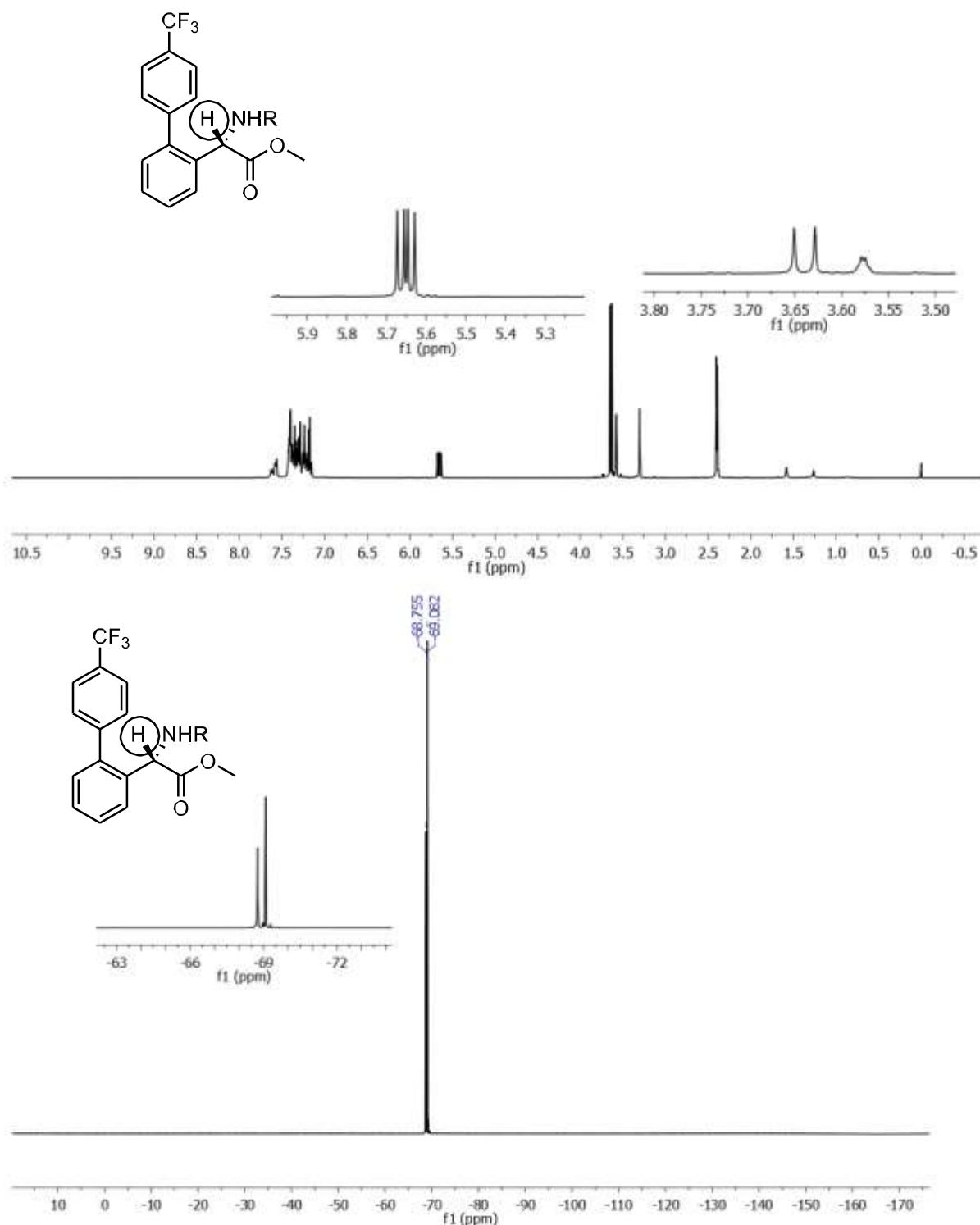
3.  $^1\text{H}$ , NMR Spectra of compound Mosher Amides



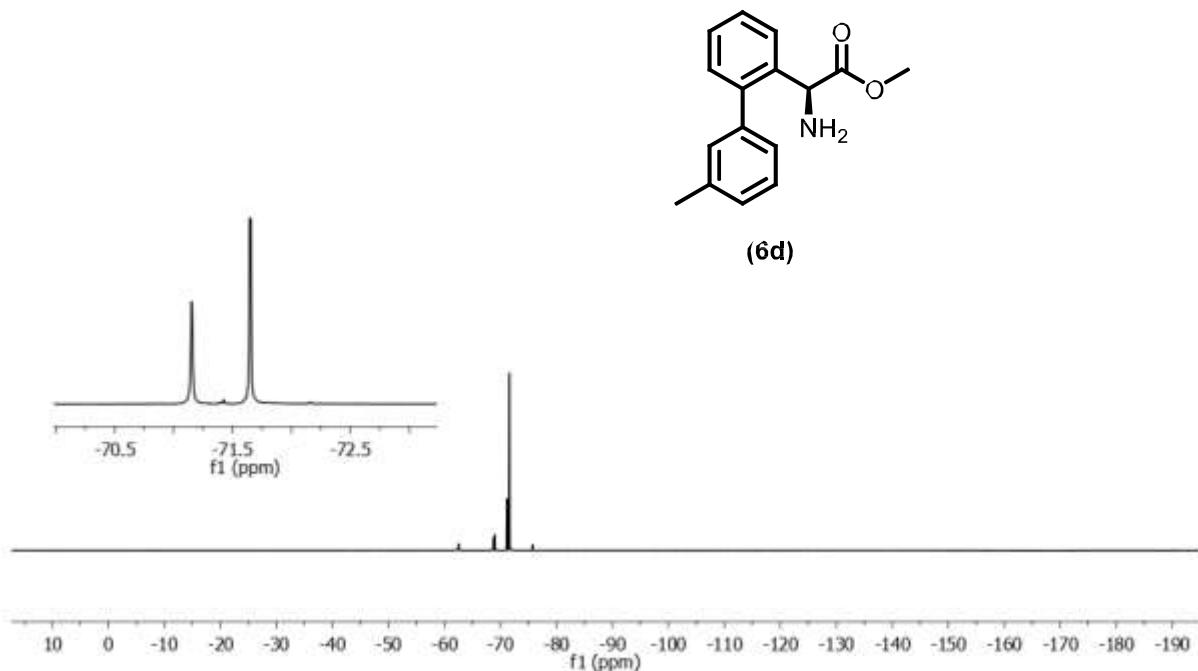
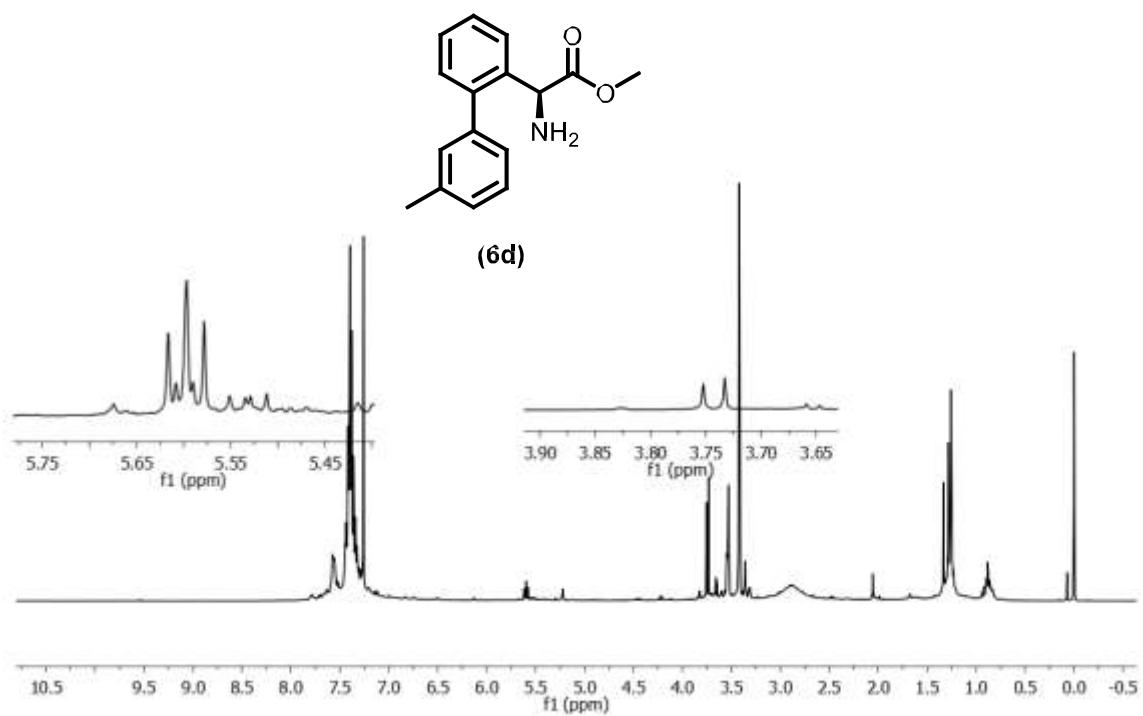
**Fig. S69**  $^1\text{H}$ , NMR Spectra of compound 6a-Mosher Amide (Area of interest blown up) ee-0%.



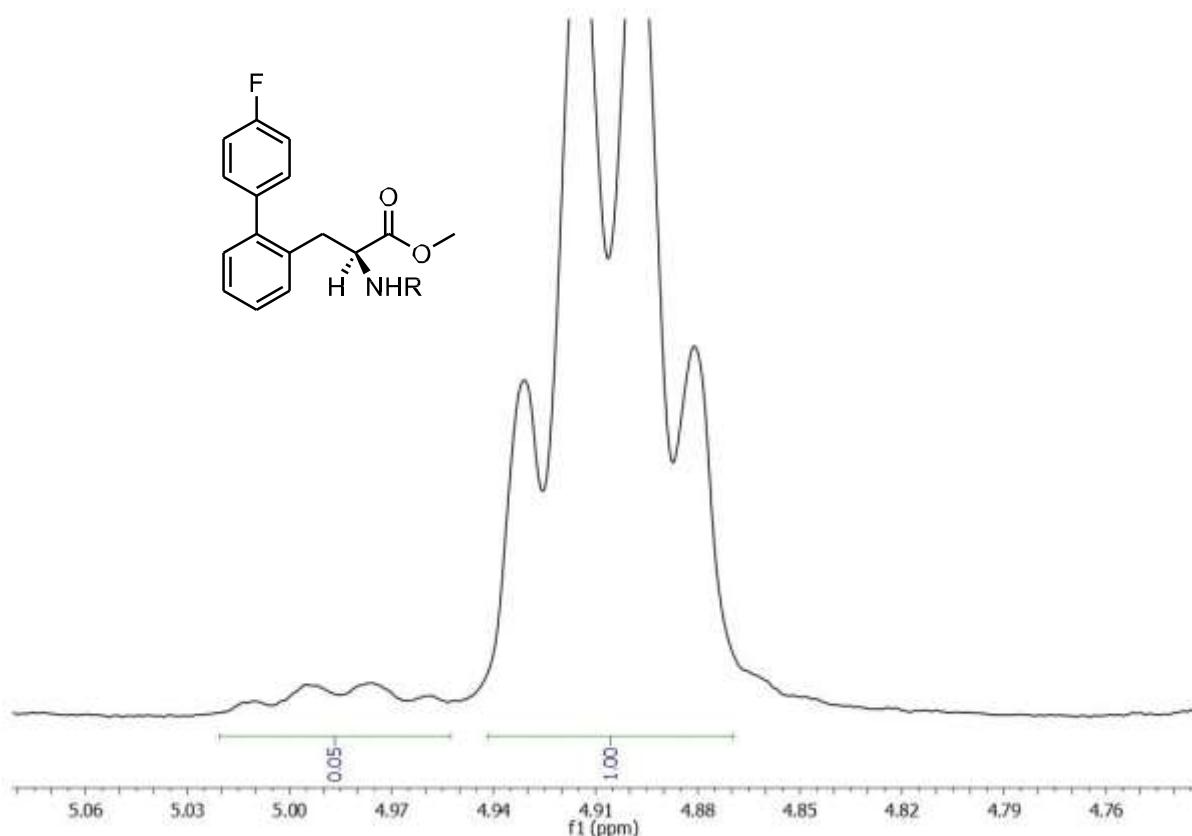
**Fig. S70**  $^1\text{H}$ , NMR Spectra of compound 6b-Mosher Amide (Area of interest blown up) ee 0%.



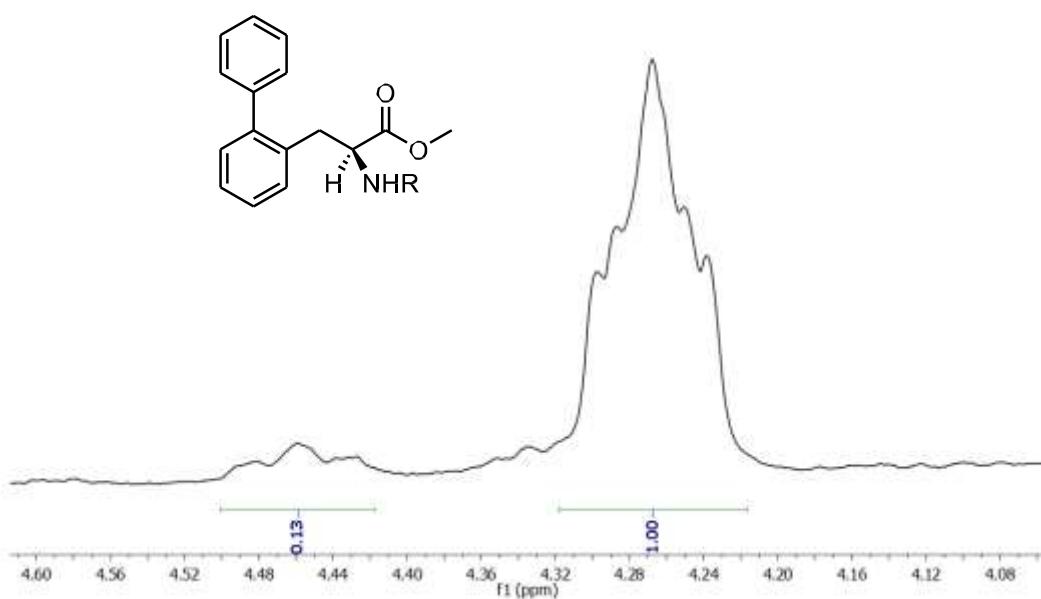
**Fig. S71**  $^1\text{H}$ ,  $^{19}\text{F}$  NMR Spectra of compound 6C-Mosher Amide (Area of interest blown up) ee-0%.



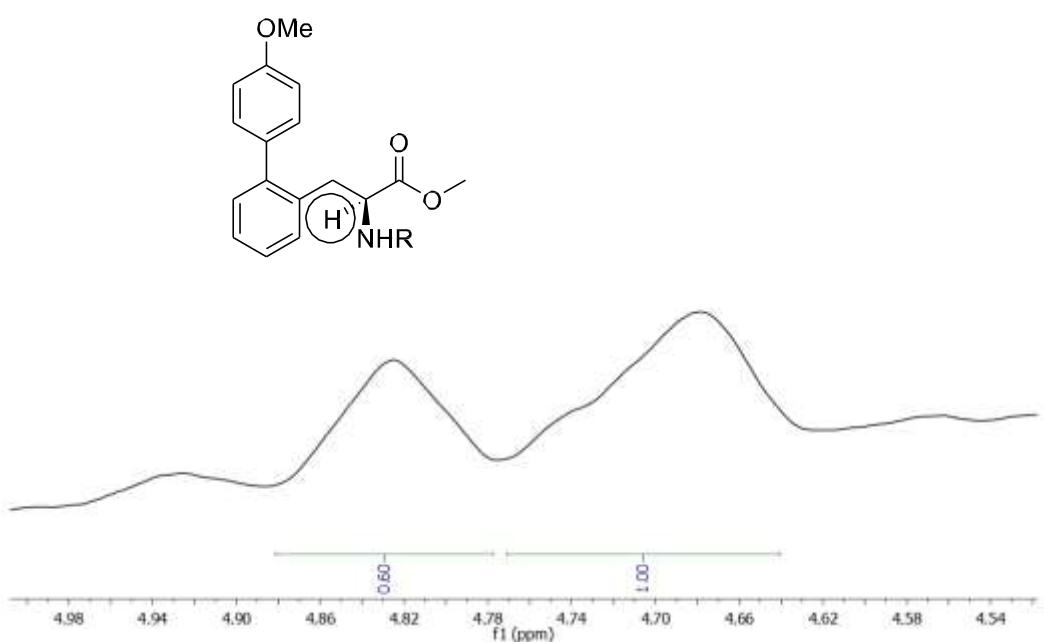
**Fig. S72**  $^1\text{H}$ ,  $^{19}\text{F}$  NMR Spectra of compound **6d-Mosher Amide** (Area of interest blown up)  
ee-0%.



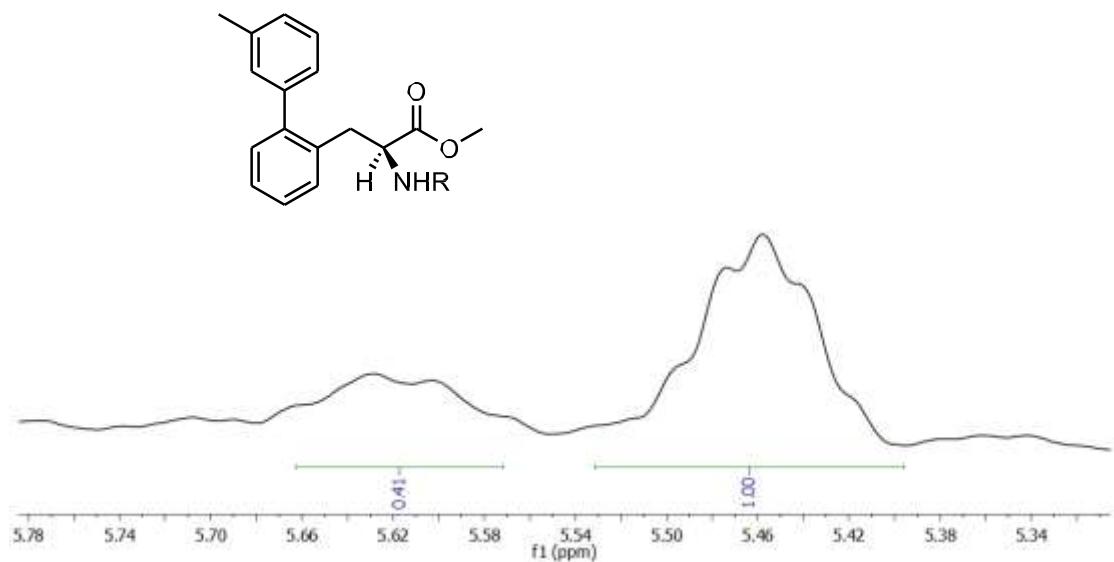
**Fig. S73**  $^1\text{H}$ , NMR Spectra of compound **8a**-Mosher Amide (Area of interest blown up) ee-90%



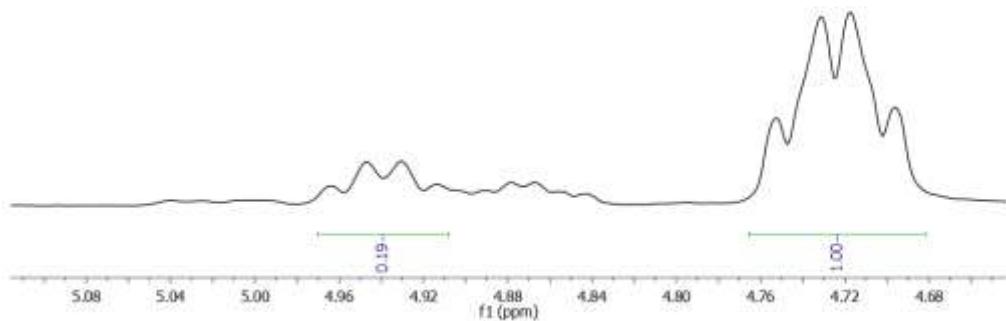
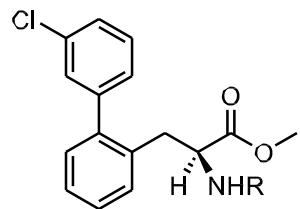
**Fig. S74**  $^1\text{H}$ , NMR Spectra of compound **8b**-Mosher Amide (Area of interest blown up) ee-77%.



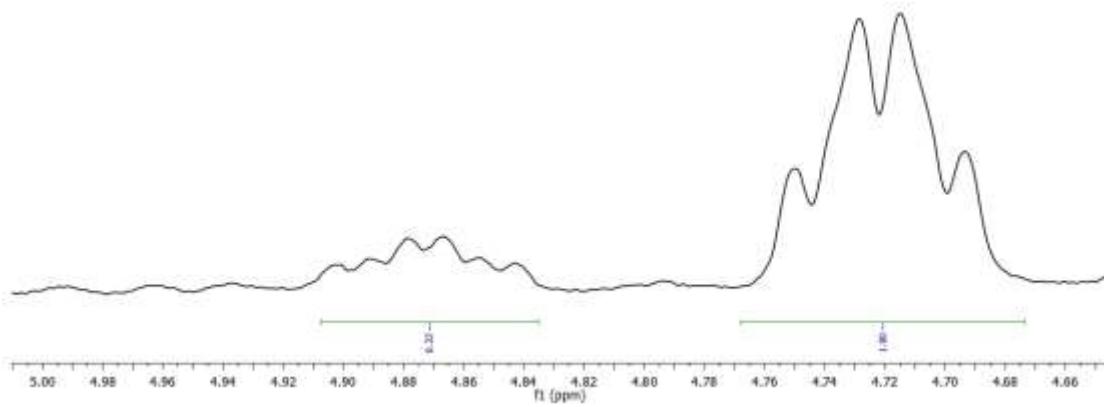
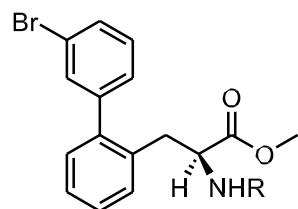
**Fig. S75**  $^1\text{H}$ , NMR Spectra of compound **8b**-Mosher Amide (Area of interest blown up) ee-25%.



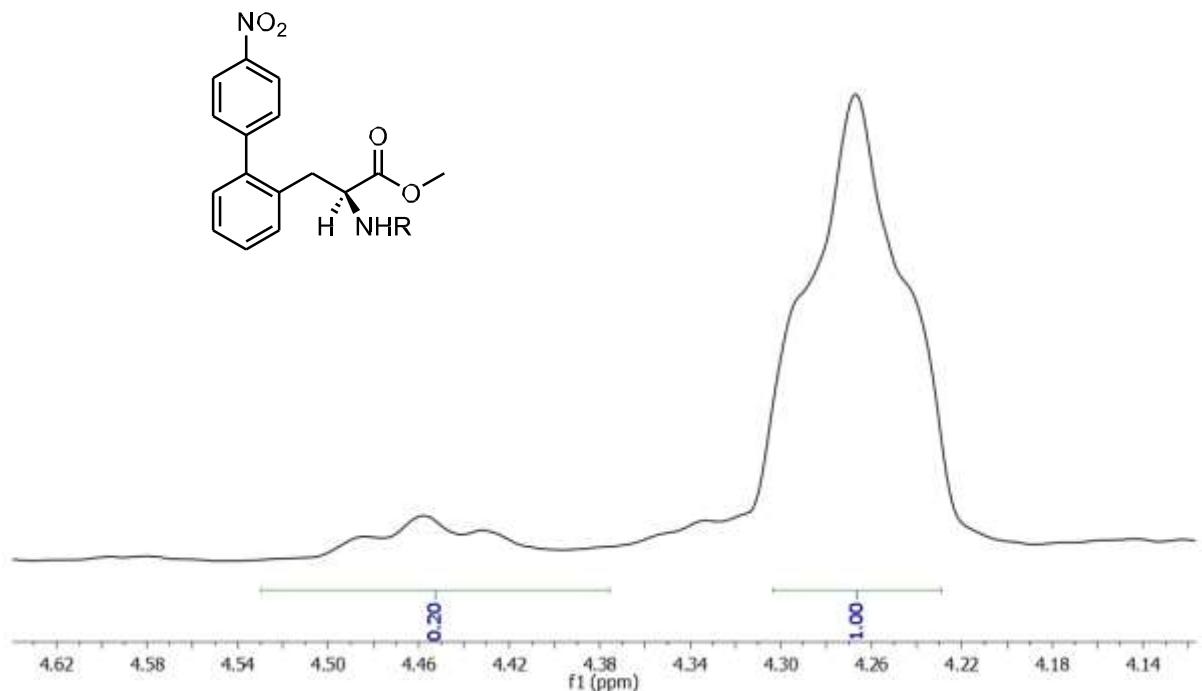
**Fig. S76**  $^1\text{H}$ , NMR Spectra of compound **8d**-Mosher Amide (Area of interest blown up) ee-41%.



**Fig. S77** <sup>1</sup>H NMR Spectra of compound **8e-Mosher Amide** (Area of interest blown up) ee-68%.



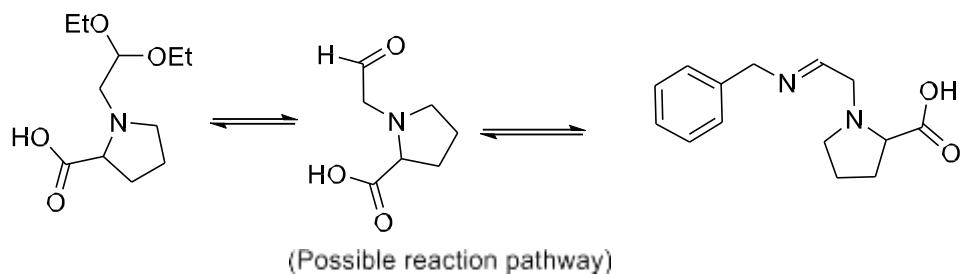
**Fig. S78**  $^1\text{H}$ , NMR Spectra of compound **8f-Mosher Amide** (Area of interest blown up) ee-64%.



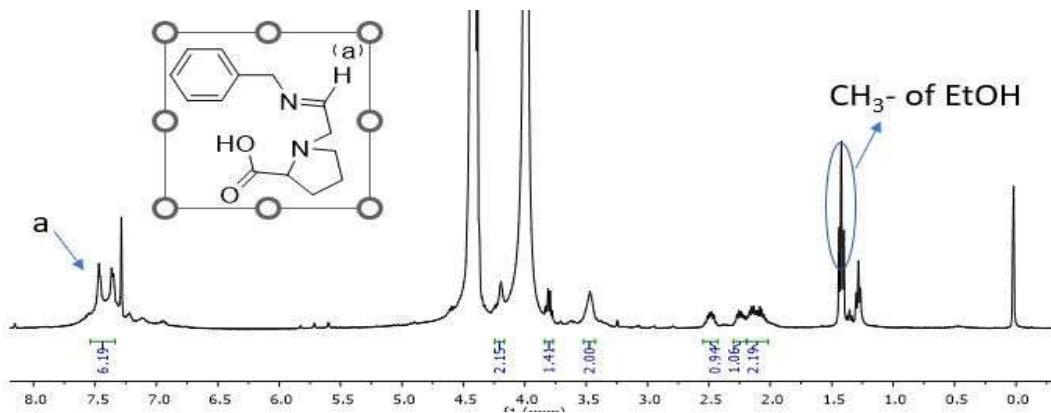
**Fig. S79**  $^1\text{H}$ , NMR Spectra of compound **8g-Mosher Amide** (Area of interest blown up) ee-66%.

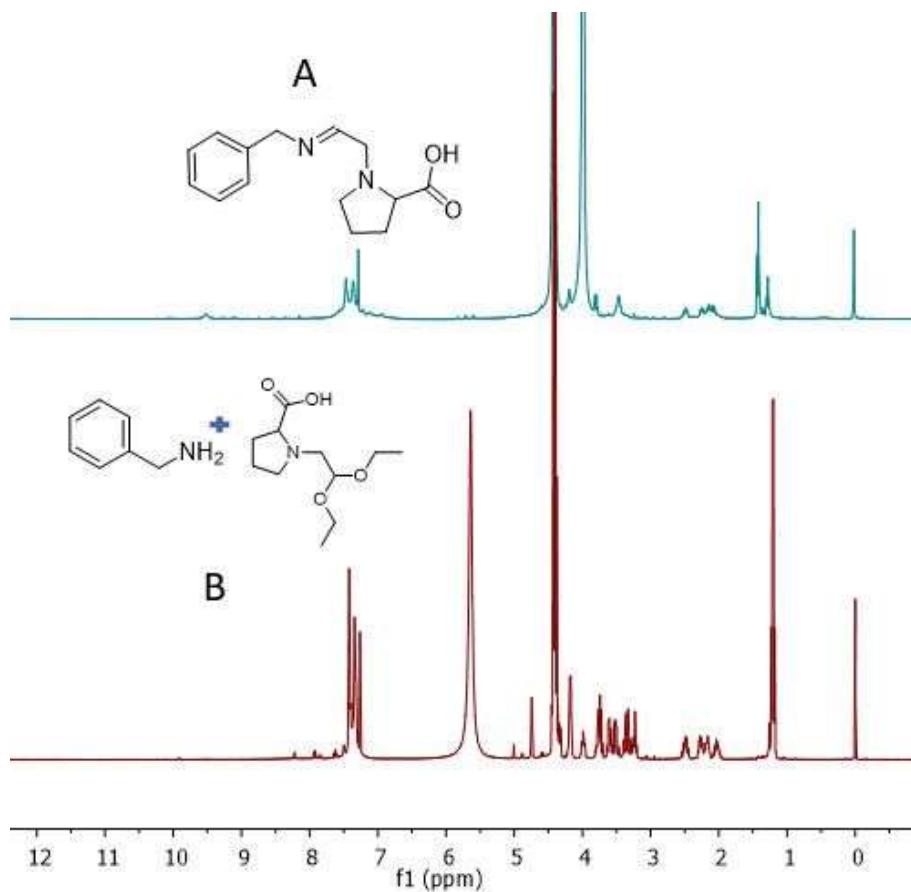
#### 4. Crude NMR analysis of imine formation

In a sealed tube both benzyl amine and diethoxy ethyl proline (DEP) was taken and heated at 90<sup>0</sup>C. After 1h reaction mixture was concentrated and taken for NMR in CDCl<sub>3</sub>. From crude NMR analysis a triplet of 3 proton is clearly showing dissociation of -OEt group from DEP and 1 extra proton in aromatic region due to formation of imine. Formation of aldehyde intermediate was confirmed by HRMS spectrometry.



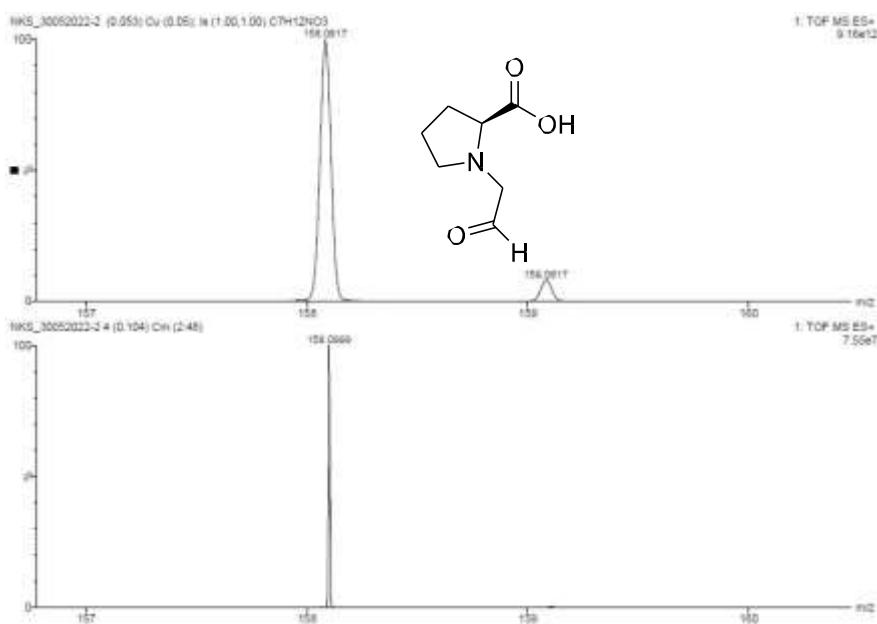
(2-oxoethyl)-L-proline





(i)A- After 1h of heating at 90°C (ii) B- Just after mixing both reagents.

**Fig. S80** <sup>1</sup>H NMR Spectral co-relation study of imine formation.



**Fig. S81** ESI-HRMS Spectra of (2-oxoethyl) L-proline.