

Electronic Supplementary Information for

**Organocatalytic Multicomponent Reaction for the Acquisition of a Potent and Selective Inhibitor of mPTPB, a Virulence Factor of Tuberculosis**

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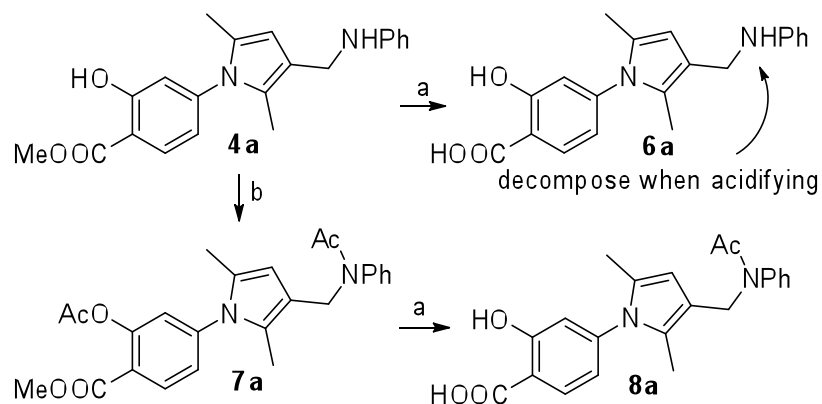
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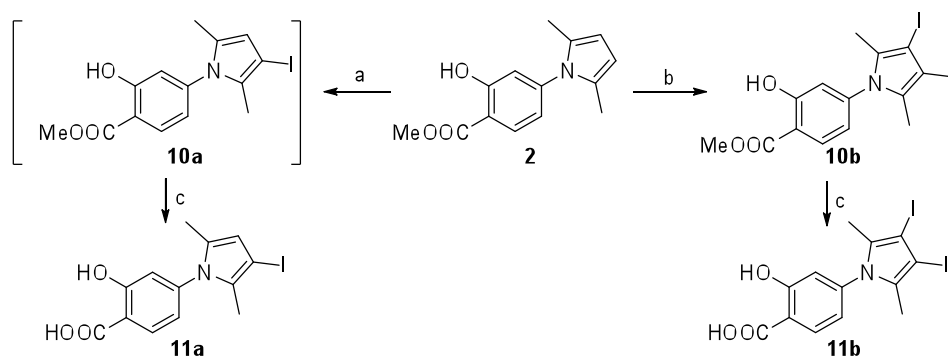
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Table S1. Complete list of optimization of reaction conditions

entry	solvent	catalyst	time	ratio of 4a/5/2, %	yield of 4a %	yield of 5 %
1	DMSO	HOAc (20 mol%)	24 h	no reaction		
2	DMF	HOAc (20 mol%)	24 h	no reaction		
3	THF	HOAc (20 mol%)	24 h	no reaction		
4	MeCN	HOAc (20mol%)	24 h	13/8/79		
5	Et <sub>2</sub> O	HOAc (20 mol%)	24 h	13/6/81		
6	toluene	HOAc (20 mol%)	24 h	no reaction		
7	MeOH	HOAc (20 mol%)	24 h	9/8/91		
8	CH <sub>2</sub> Cl <sub>2</sub>	HOAc (20 mol%)	24 h	52//22/26		
9	CHCl <sub>3</sub>	HOAc (20 mol%)	24 h	48//15/37		
10	CH <sub>2</sub> Cl <sub>2</sub>	4-F-PhCO <sub>2</sub> H(20 mol%)	24 h	47/5/48		
11	CH <sub>2</sub> Cl <sub>2</sub>	Proline (20 mol%)	24 h	7/0/93		
12	CH <sub>2</sub> Cl <sub>2</sub>	TFA (20 mol%)	24 h	decomposition		
13	CH <sub>2</sub> Cl <sub>2</sub>	2 M HCl (20 mol%)	24 h	26/4/70		
14	CH <sub>2</sub> Cl <sub>2</sub>	4-Me-PhCO <sub>2</sub> H(20 mol%)	24 h	28/13/59		
15	CH <sub>2</sub> Cl <sub>2</sub>	3-F-5-CF <sub>3</sub> -PhCO <sub>2</sub> H(20 mol%)	24 h	50/25/25		
16	CH <sub>2</sub> Cl <sub>2</sub>	3,5-(CF <sub>3</sub> ) <sub>2</sub> -PhCO <sub>2</sub> H(20 mol%)	24 h	46/17/37		
17	CH <sub>2</sub> Cl <sub>2</sub>	MeOCH <sub>2</sub> CO <sub>2</sub> H (20 mol%)	24 h	45/36/19		
18	CH <sub>2</sub> Cl <sub>2</sub>	PhCH <sub>2</sub> CO <sub>2</sub> H (20 mol%)	24 h	23/10/67		
19	CH <sub>2</sub> Cl <sub>2</sub>	Cyc.C <sub>6</sub> H <sub>11</sub> CO <sub>2</sub> H (20 mol%)	24 h	13/10/77		
20	CH <sub>2</sub> Cl <sub>2</sub>	PTSA (20 mol%)	24 h	21/5/74		
21	CH <sub>2</sub> Cl <sub>2</sub>	(3,5-(CF <sub>3</sub> ) <sub>2</sub> -PhNH) <sub>2</sub> CS (20 mol%)	24 h	no reaction		
22	CH <sub>2</sub> Cl <sub>2</sub>	diphenic acid (20 mol%)	24 h	47/23/30		
23	CH <sub>2</sub> Cl <sub>2</sub>	HOAc (100 mol%)	24 h	59//17/24		
24	CHCl <sub>3</sub>	HOAc (100 mol%)	24 h	44/11/45		
25	CH <sub>2</sub> Cl <sub>2</sub>	HOAc (100 mol%)	24 h	45/9/46	85	
26	CH <sub>2</sub> Cl <sub>2</sub>	MeOCH <sub>2</sub> CO <sub>2</sub> H (100 mol%)	48 h	0/100/0		75

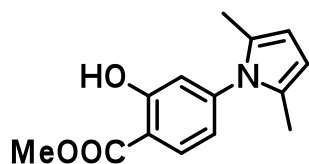


**Scheme S1.** Strategy to obtain stable hydrolyzed compound **8a**. a. 10% LiOH, MeOH, rt, 2 h, 95% yield. b. Ac<sub>2</sub>O (3 equiv.), DMAP (0.1 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, rt, 2 h, 95% yield.

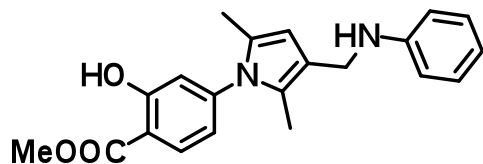


**Scheme S2.** Synthesis of **10a**, **10b**, **11a**, **11b**. a. I<sub>2</sub> (2.2 equiv.), NaHCO<sub>3</sub> (3 equiv.), ether, rt, 24 h, 60% yield. b. ICl (2.2 equiv.), NaHCO<sub>3</sub> (3 equiv.), ether, rt, 24 h, 70% yield. c. 10% LiOH, MeOH, rt, 2 h, 95% yield.

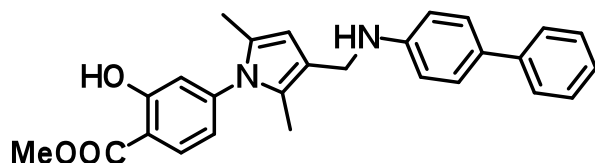
## Characterizations of compounds **2**, **4a-4l**, **5**, **10a**, **10b**



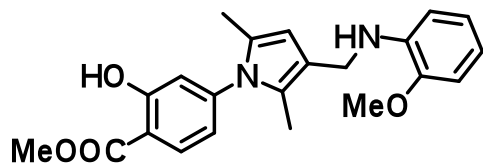
**2.**  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ) 10.91 (s, 1H), 7.93 (d,  $J = 8.5$  Hz, 1H), 6.86 (d,  $J = 2.0$  Hz, 1H), 6.76-6.74 (m, 1H), 5.91 (s, 2H), 3.99 (s, 3H), 2.08 (s, 6H). ESI-MS Calcd. for  $\text{C}_{14}\text{H}_{16}\text{NO}_3$  ( $\text{M}+\text{H}^+$ ):  $m/z$  246.1; found 246.0.



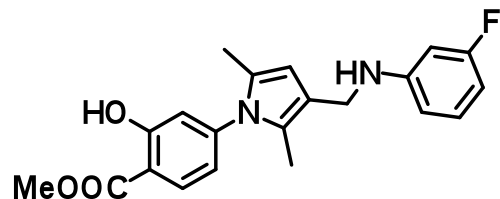
**4a.**  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ) 10.93 (s, 1H), 7.94 (d,  $J = 8.4$  Hz, 1H), 7.22-7.19 (m, 2H), 6.85 (d,  $J = 2.0$  Hz, 1H), 6.75-6.68 (m, 4H), 5.99 (s, 1H), 4.08 (s, 2H), 3.99 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 162.1, 148.6, 145.3, 130.6, 129.2, 128.0, 125.8, 119.2, 117.2, 117.1, 117.1, 112.6, 111.7, 107.6, 52.5, 40.6, 12.8, 10.7. ESI-MS Calcd. for  $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_3$  ( $\text{M}+\text{H}^+$ ):  $m/z$  349.2; found 349.2.



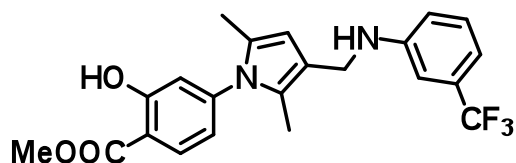
**4b.**  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ) 10.92 (s, 1H), 7.94 (d,  $J = 8.5$  Hz, 1H), 7.55 (d,  $J = 7.7$  Hz, 2H), 7.47 (d,  $J = 8.6$  Hz, 2H), 7.39 (t,  $J = 7.9$  Hz, 2H), 7.26-7.23 (m, 1H), 6.86 (d,  $J = 1.9$  Hz, 1H), 6.76-6.73 (m, 3H), 6.00 (s, 1H), 4.12 (s, 2H), 3.98 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 162.1, 148.0, 145.2, 141.3, 130.6, 130.0, 128.6, 128.0, 127.9, 126.2, 125.9, 125.8, 119.2, 117.1, 117.1, 112.9, 111.7, 107.6, 52.5, 40.6, 12.8, 10.7. ESI-MS Calcd. for  $\text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_3$  ( $\text{M}+\text{H}^+$ ):  $m/z$  425.2; found 425.0.



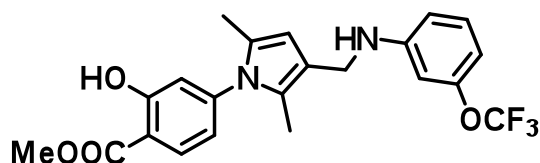
**4d.**  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ) 10.92 (s, 1H), 7.94 (d,  $J = 8.5$  Hz, 1H), 6.93-6.92 (m, 1H), 6.90 (d,  $J = 8.5$  Hz, 1H), 6.88-6.74 (m, 3H), 6.70-6.67 (m, 1H), 6.02 (s, 1H), 4.10 (s, 2H), 4.00 (s, 3H), 3.84 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 162.1, 146.8, 145.4, 138.6, 130.6, 127.8, 125.8, 121.3, 119.3, 117.3, 117.1, 116.2, 111.6, 109.8, 109.3, 107.8, 55.3, 52.5, 40.3, 12.9, 10.8. ESI-MS Calcd. for  $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}^+$ ):  $m/z$  379.1663; found 379.1671.



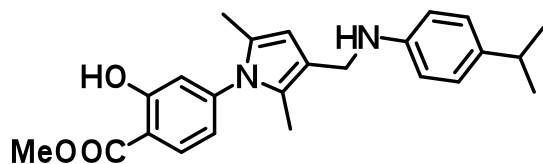
**4e.**  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ) 10.93 (s, 1H), 7.95 (d,  $J = 8.4$  Hz, 1H), 7.11 (dd,  $J = 14.9, 8.0$  Hz, 1H), 6.86 (d,  $J = 2$  Hz, 1H), 6.75-6.73 (m, 1H), 6.43-6.35 (m, 3H), 5.97 (s, 1H), 4.01 (s, 2H), 4.00 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 165.1, 163.2, 162.1, 150.3, 150.3, 145.2, 130.7, 130.2, 130.1, 128.1, 125.9, 119.2, 117.1, 116.7, 111.8, 108.5, 107.5, 103.5, 103.3, 99.3, 99.0, 52.5, 40.5, 12.8, 10.7. ESI-MS Calcd. for  $\text{C}_{21}\text{H}_{20}\text{FN}_2\text{O}_3$  ( $\text{M}+\text{H}^+$ ):  $m/z$  367.1463; found 367.1469.



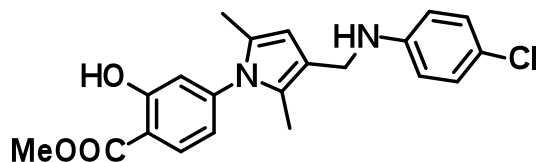
4f.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 10.93 (s, 1H), 7.95 (d,  $J = 8.5$  Hz, 1H), 7.27 (d,  $J = 5.0$  Hz, 1H), 6.94 (d,  $J = 7.7$  Hz, 1H), 6.87-6.86 (m, 2H), 6.81-6.79 (m, 1H), 6.76-6.674 (m, 1H), 5.98 (s, 1H), 4.10 (s, 2H), 4.00 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H). ESI-MS Calcd. for  $\text{C}_{22}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_3$  ( $\text{M}-\text{H}^+$ ):  $m/z$  417.1432; found 417.1442.



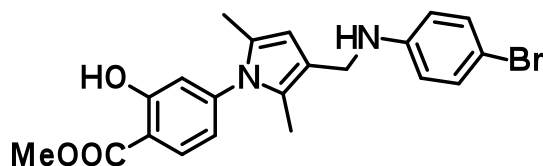
4g.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 10.93 (s, 1H), 7.95 (d,  $J = 8.4$  Hz, 1H), 7.06 (d,  $J = 8.5$  Hz, 2H), 6.86 (d,  $J = 1.9$  Hz, 1H), 6.76-6.73 (m, 1H), 6.63-6.62 (m, 2H), 5.98 (s, 1H), 4.06 (s, 2H), 4.00 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 162.1, 147.4, 145.2, 140.2, 130.7, 128.1, 125.9, 122.4, 119.2, 117.1, 116.8, 112.8, 111.8, 107.5, 52.5, 40.8, 12.8, 10.7. ESI-MS Calcd. for  $\text{C}_{22}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_4$  ( $\text{M}-\text{H}^+$ ):  $m/z$  434.1465; found 434.1392.



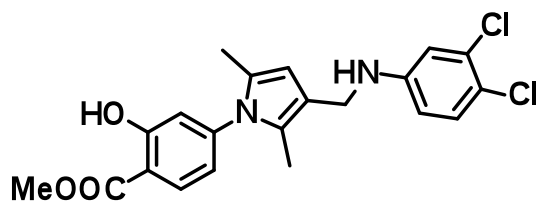
4h.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 10.92 (s, 1H), 7.94 (d,  $J = 8.4$  Hz, 1H), 7.09-7.08 (m, 2H), 6.86 (d,  $J = 2.0$  Hz, 1H), 6.76-6.74 (m, 1H), 6.66-6.64 (m, 2H), 5.99 (s, 1H), 4.07 (s, 2H), 4.00 (s, 3H), 2.83 (p,  $J = 6.9$  Hz, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 162.1, 146.7, 145.3, 137.7, 130.6, 127.9, 127.0, 125.8, 119.2, 117.4, 117.1, 112.7, 111.6, 107.6, 52.5, 40.9, 33.2, 24.3, 12.8, 10.7. ESI-MS Calcd. for  $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_3$  ( $\text{M}-\text{H}^+$ ):  $m/z$  391.2109; found 391.2036.



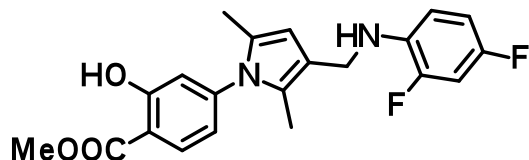
4i.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 10.93 (s, 1H), 7.94 (d,  $J = 8.4$  Hz, 1H), 7.14 (dd,  $J = 6.8, 2.1$  Hz, 2H), 6.85 (d,  $J = 1.9$  Hz, 1H), 6.74 (dd,  $J = 8.4, 2.0$  Hz, 1H), 6.60-6.58 (m, 2H), 5.97 (s, 1H), 4.05 (s, 2H), 4.00 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 162.1, 147.1, 145.2, 130.6, 129.0, 128.1, 125.8, 121.6, 119.2, 117.1, 116.8, 113.7, 111.7, 107.4, 52.5, 40.7, 12.8, 10.7. ESI-MS Calcd. for  $\text{C}_{21}\text{H}_{21}\text{ClN}_2\text{O}_3$  ( $\text{M}-\text{H}^+$ ):  $m/z$  383.1168; found 383.1168.



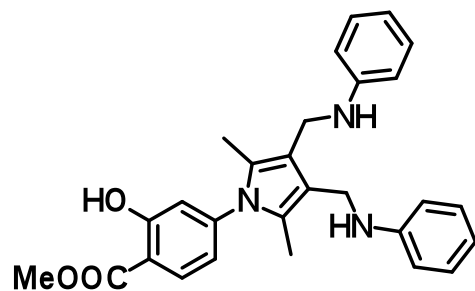
4j.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 10.92 (s, 1H), 7.93 (d,  $J = 8.4$  Hz, 1H), 7.26 (d,  $J = 8.8$  Hz, 2H), 6.84 (d,  $J = 2.0$  Hz, 1H), 6.73 (dd,  $J = 8.4, 2.0$  Hz, 1H), 6.54 (d,  $J = 8.8$  Hz, 2H), 5.96 (s, 1H), 4.03 (s, 2H), 3.99 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 162.1, 147.5, 145.2, 131.8, 130.6, 128.1, 125.8, 119.2, 117.1, 116.8, 114.2, 111.7, 108.6, 107.4, 52.5, 40.6, 12.8, 10.7. ESI-MS Calcd. for  $\text{C}_{21}\text{H}_{21}\text{BrN}_2\text{O}_3$  ( $\text{M}-\text{H}^+$ ):  $m/z$  427.0663; found 427.0660.



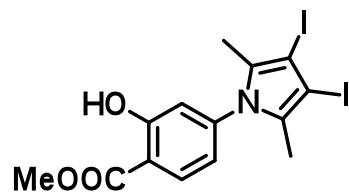
**4k.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 10.93 (s, 1H), 7.94 (d,  $J = 8.4$  Hz, 1H), 7.19(d,  $J = 8.7\text{Hz}$ , 1H), 6.85 (t,  $J = 2.1$  Hz, 1H), 6.75-6.73(m, 2H), 6.48 (dd,  $J = 8.8, 2.8\text{Hz}$ , 1H), 5.95 (s, 1H), 4.03 (s, 2H), 4.00 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H). ESI-MS Cacl. for  $\text{C}_{21}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_3$  ( $\text{M}-\text{H}^+$ ):  $m/z$  417.0778; found 417.0783.



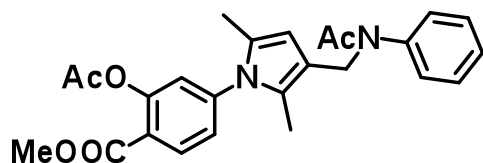
**4l.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 10.92 (s, 1H), 7.94 (d,  $J = 8.4$  Hz, 1H), 6.86 (d,  $J = 2.0$  Hz, 1H), 6.81-6.71(m, 4H), 5.98 (s, 1H), 4.08 (s, 2H), 4.00 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H). ESI-MS Cacl. for  $\text{C}_{21}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_3$  ( $\text{M}-\text{H}^+$ ):  $m/z$  385.1369; found 385.1368.



**5.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 10.94 (s, 1H), 7.96 (d,  $J = 8.4$  Hz, 1H), 7.19-7.16 (m, 4H), 6.86 (d,  $J = 2.0$  Hz, 1H), 6.76-6.65(m, 8H), 4.13 (s, 4H), 4.00 (s, 3H), 2.08 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 162.2, 148.5, 145.1, 130.7, 129.3, 129.2, 126.1, 119.4, 118.6, 117.6, 117.3, 116.6, 115.1, 113.2, 111.9, 52.6, 39.2, 10.7. ESI-MS Cacl. for  $\text{C}_{28}\text{H}_{28}\text{N}_3\text{O}_3$  ( $\text{M}-\text{H}^+$ ):  $m/z$  454.2; found 454.0.

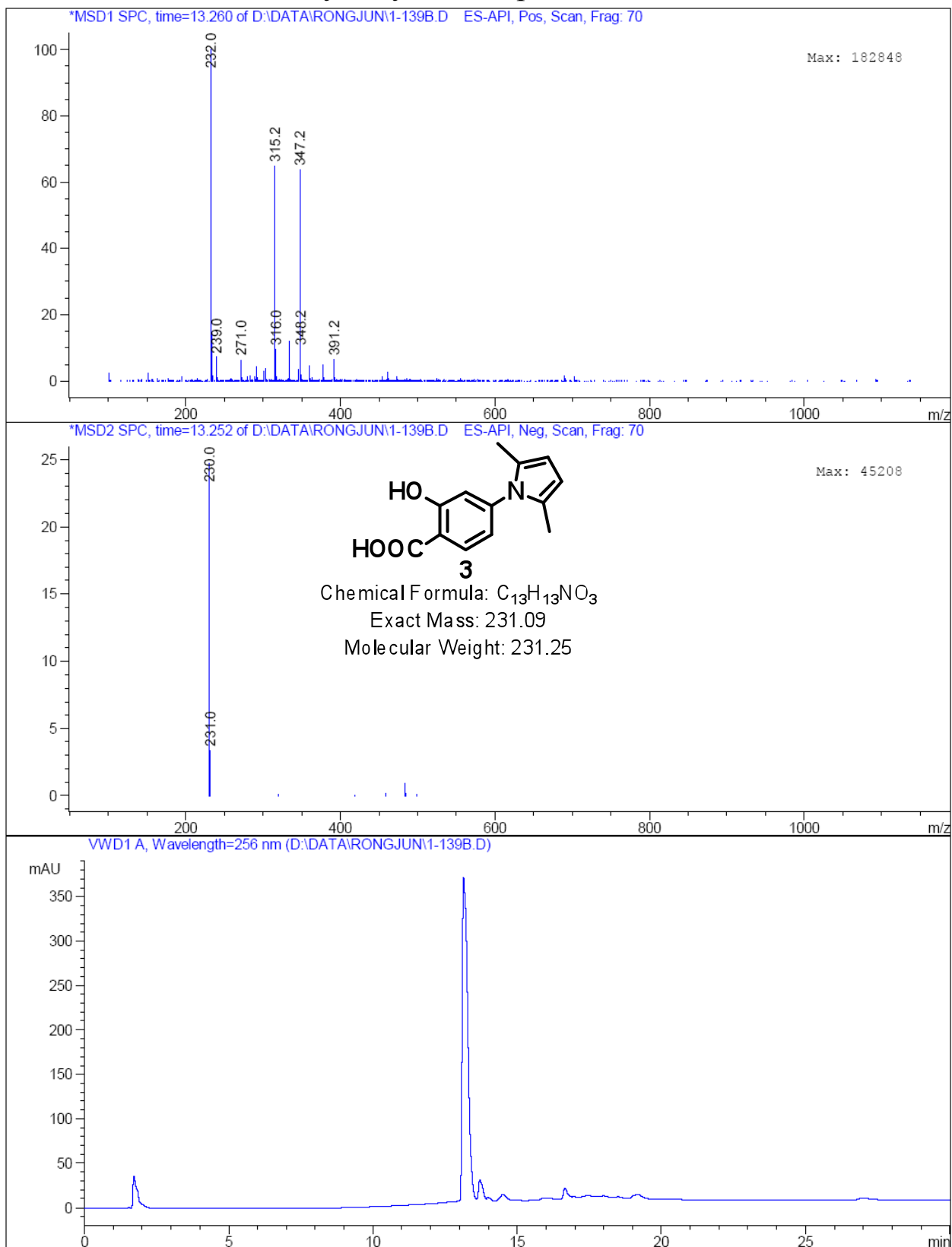


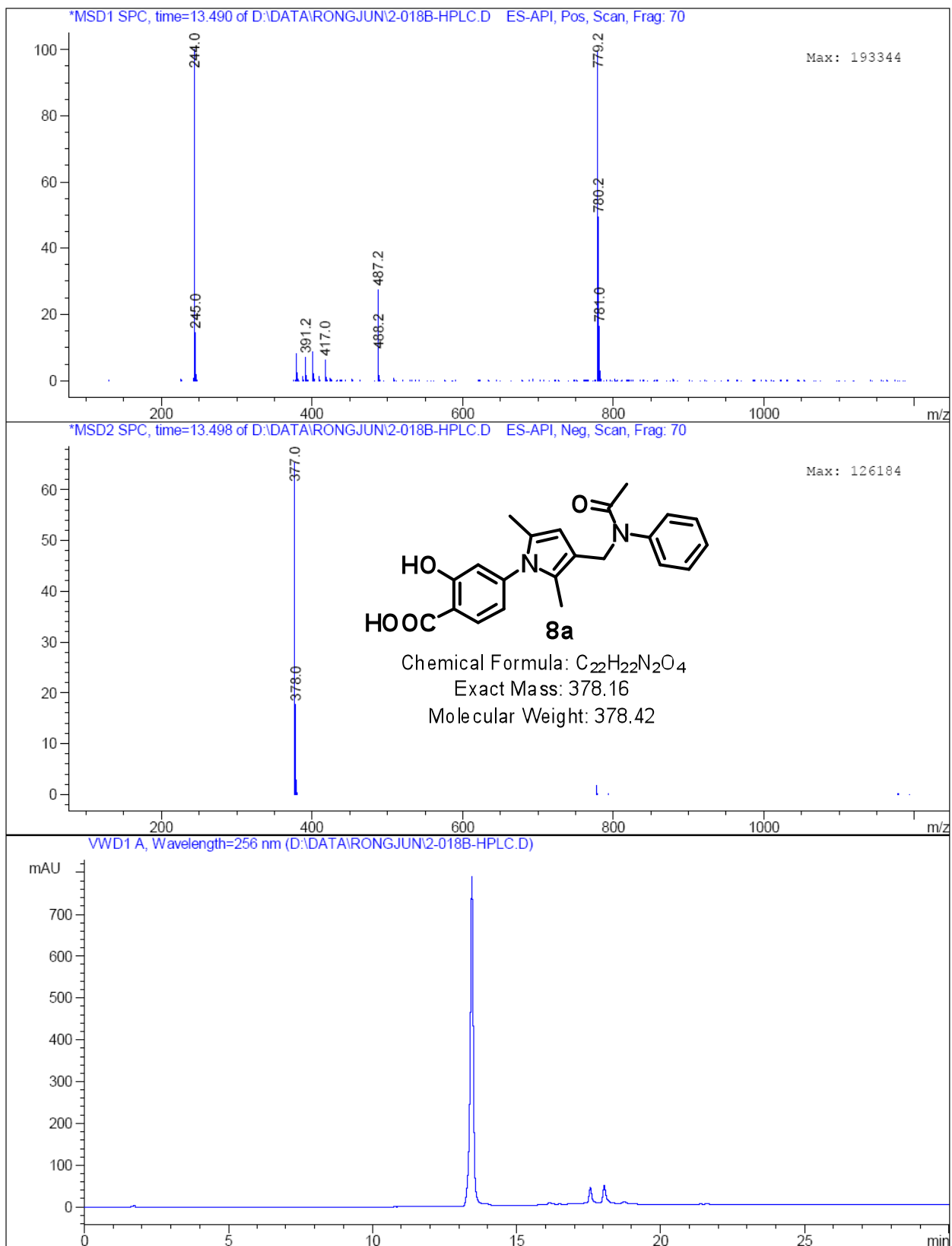
**10b.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 10.95 (s, 1H), 7.95 (d,  $J = 8.4$  Hz, 1H), 6.79 (d,  $J = 2.0$  Hz, 1H), 6.69-6.63 (m, 1H), 4.00 (s, 3H), 2.15 (s, 6H). ESI-MS Cacl. for  $\text{C}_{14}\text{H}_{13}\text{I}_2\text{NO}_3$  ( $\text{M}-\text{H}^+$ ):  $m/z$  495.9; found 496.0.



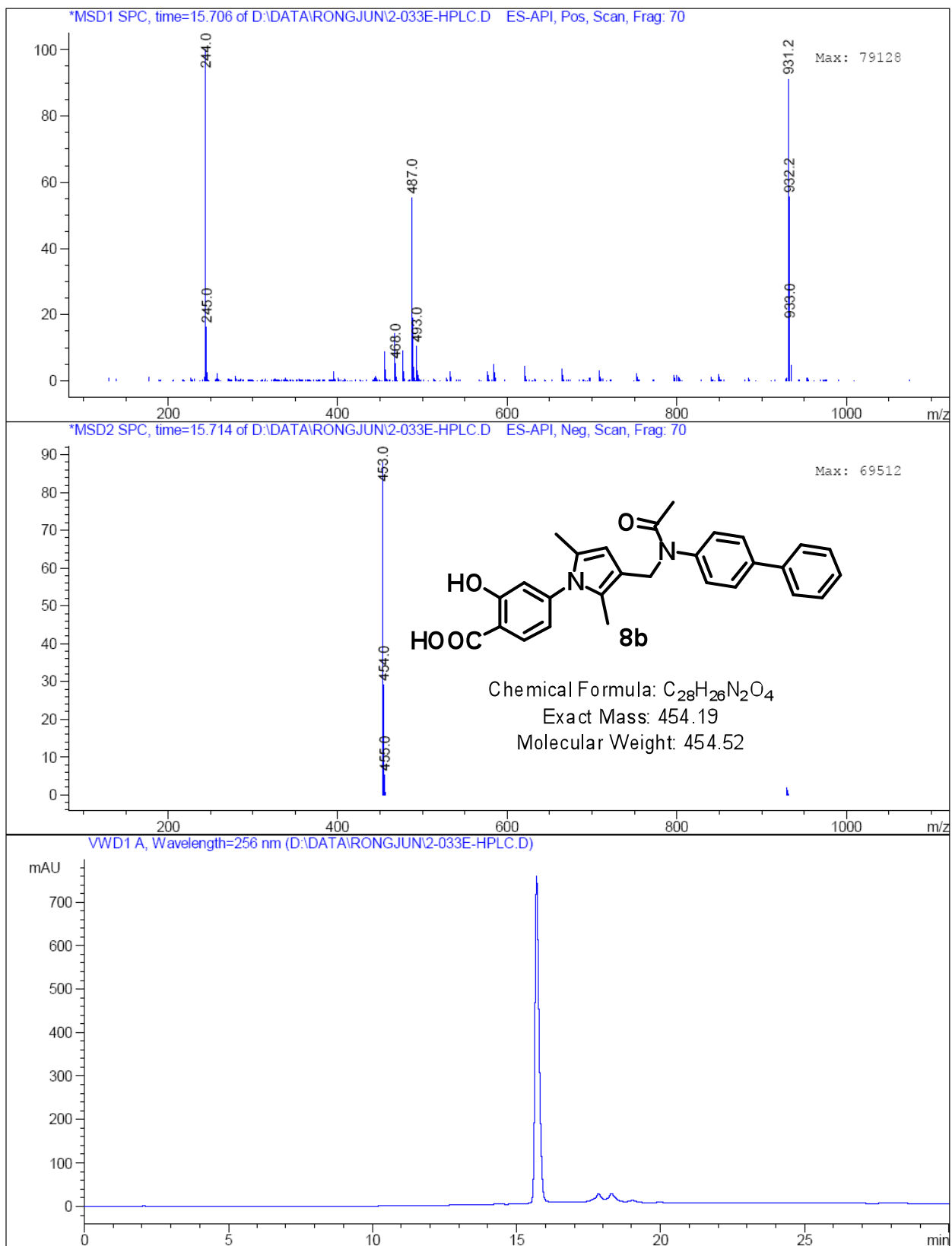
**7a.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 8.06 (d,  $J = 8.3$  Hz, 1H), 7.37-7.31 (m, 3H), 7.06-7.03 (m, 3H), 6.87 (d,  $J = 3.8$  Hz, 1H), 5.85 (s, 1H), 4.69 (s, 2H), 3.89 (s, 3H), 2.35 (s, 3H), 2.00 (s, 3H), 1.83 (s, 3H), 1.66 (s, 3H). ESI-MS Cacl. for  $\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_5$  ( $\text{M}+\text{H}^+$ ):  $m/z$  435.2; found 435.0.

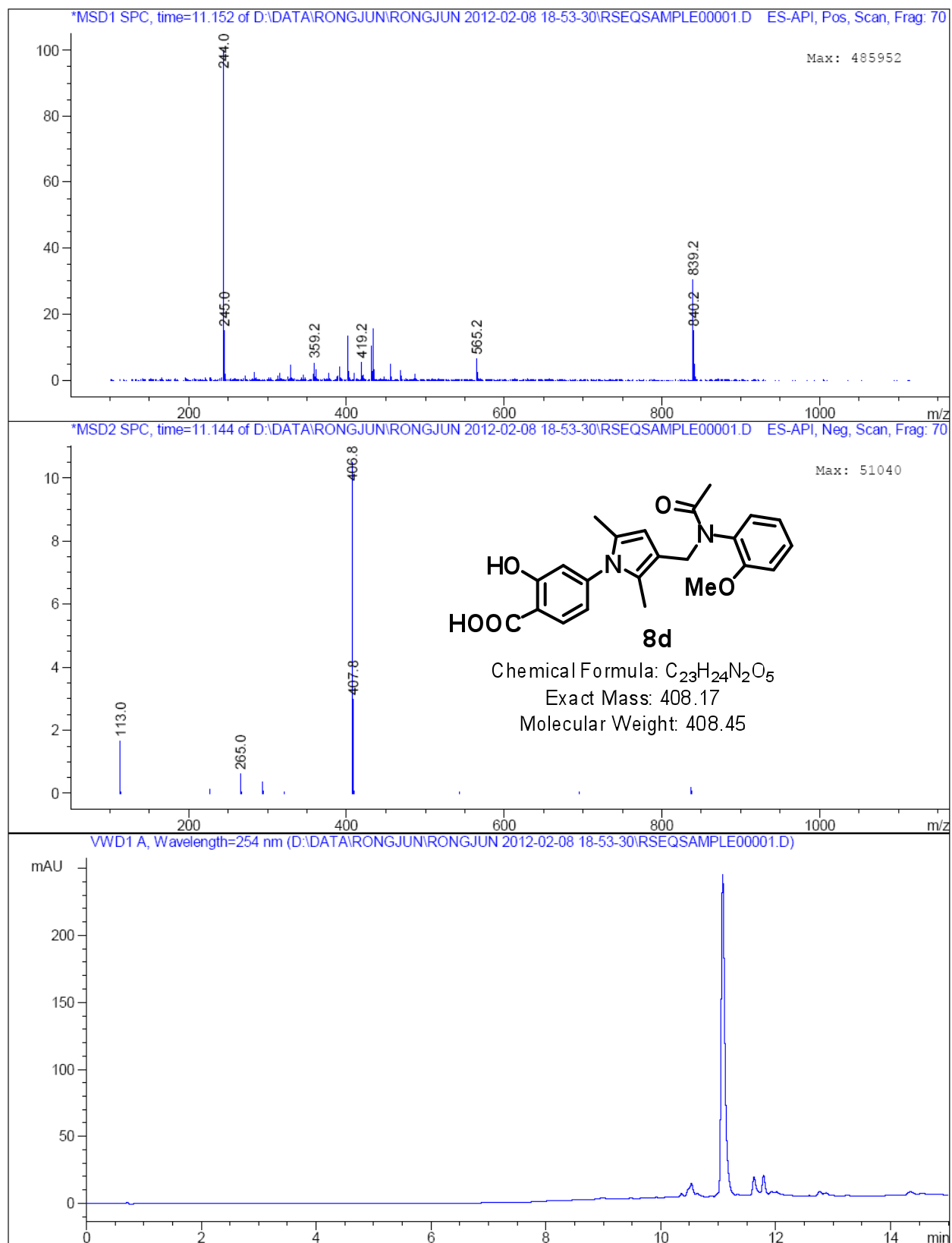
## LC-MS studies of hydrolyzed compounds **3**, **8a-8l**, **9**, **11a**, **11b**

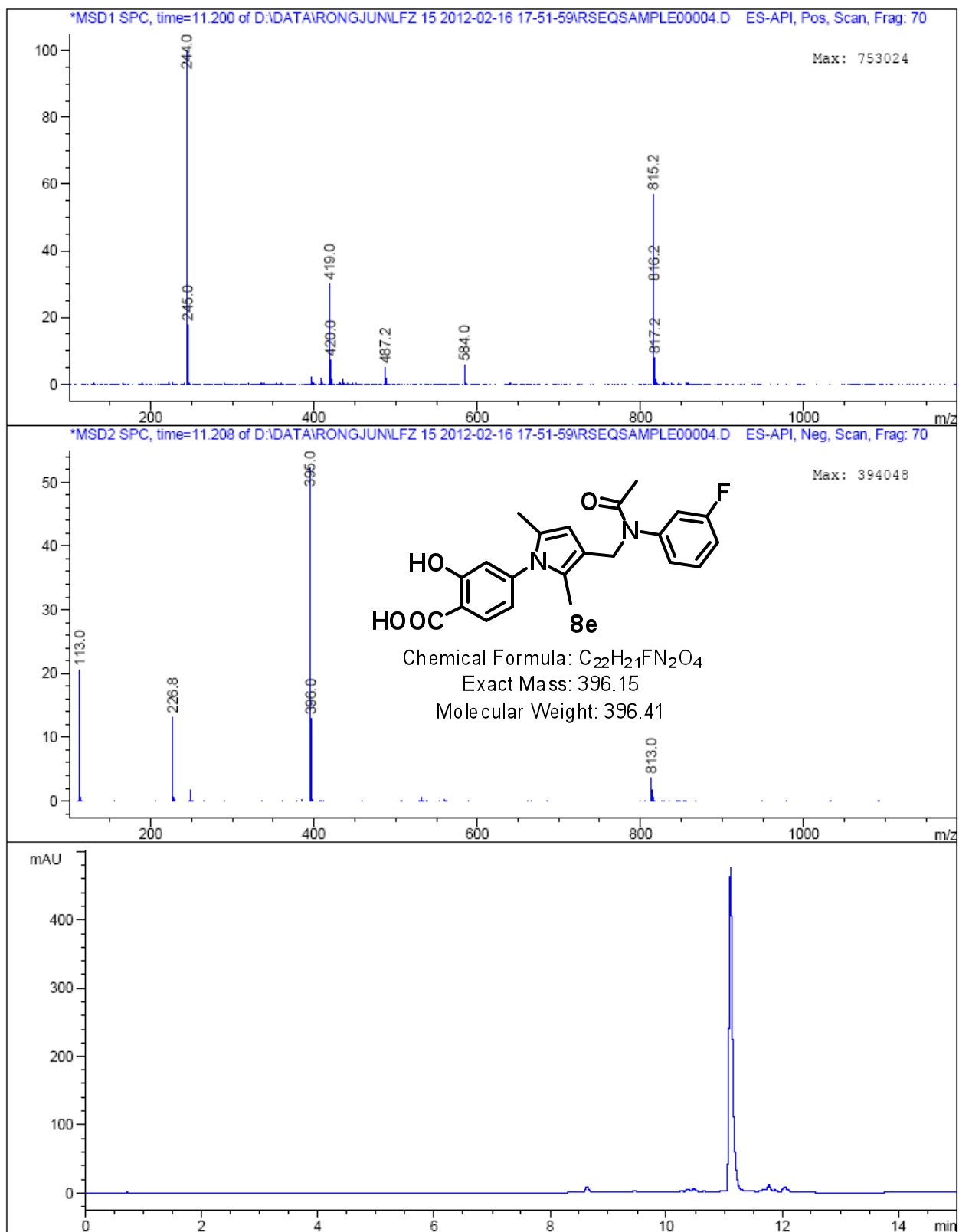


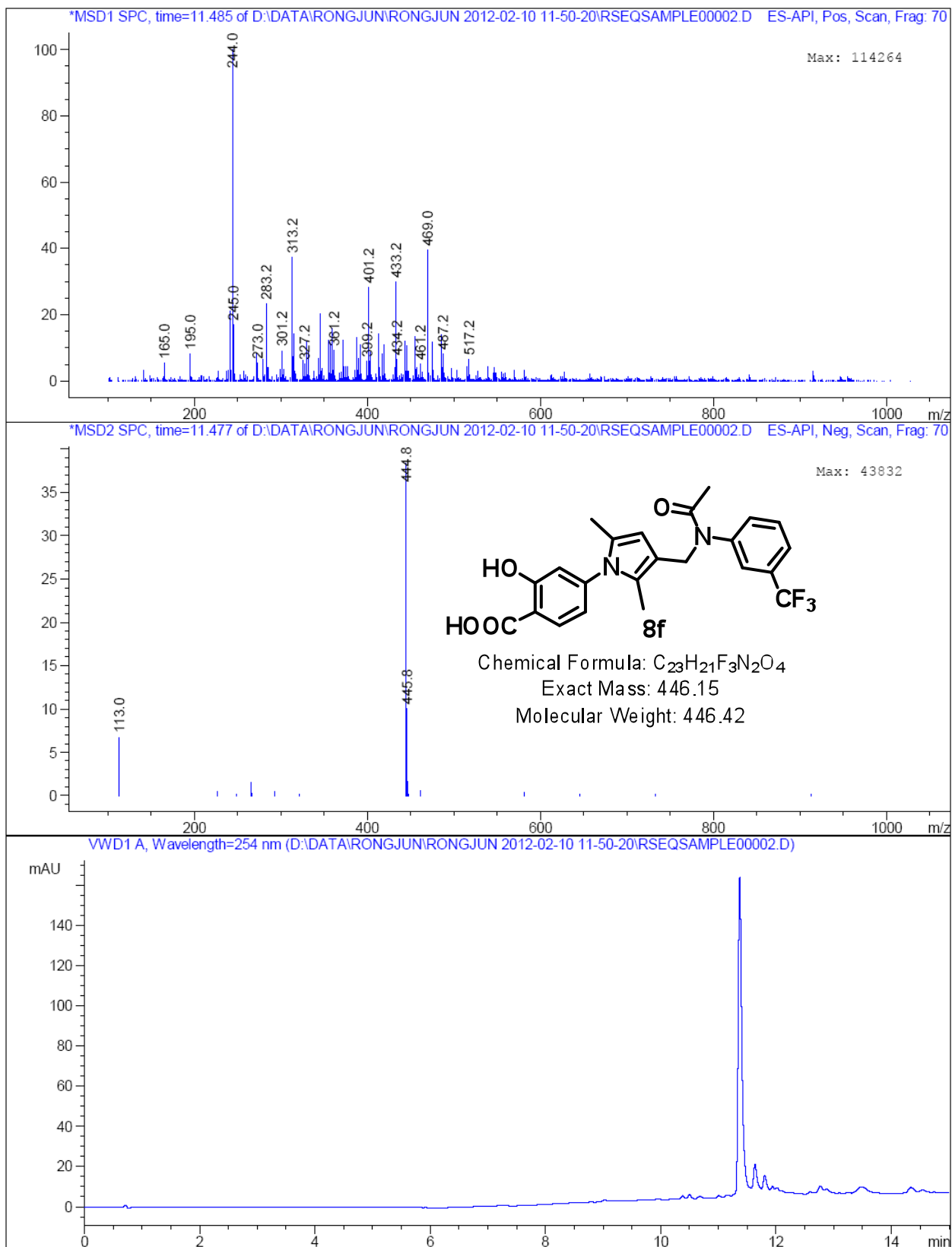


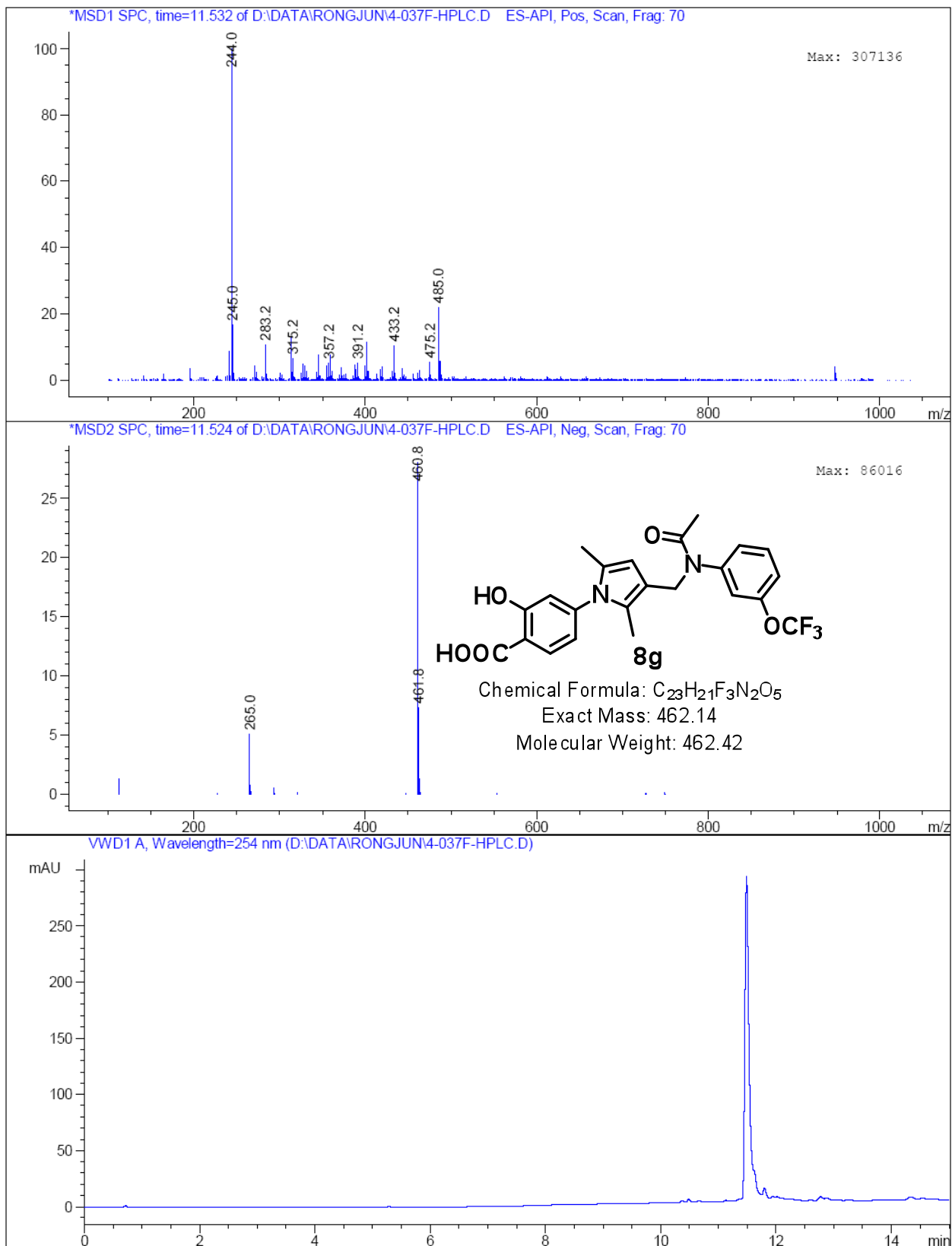


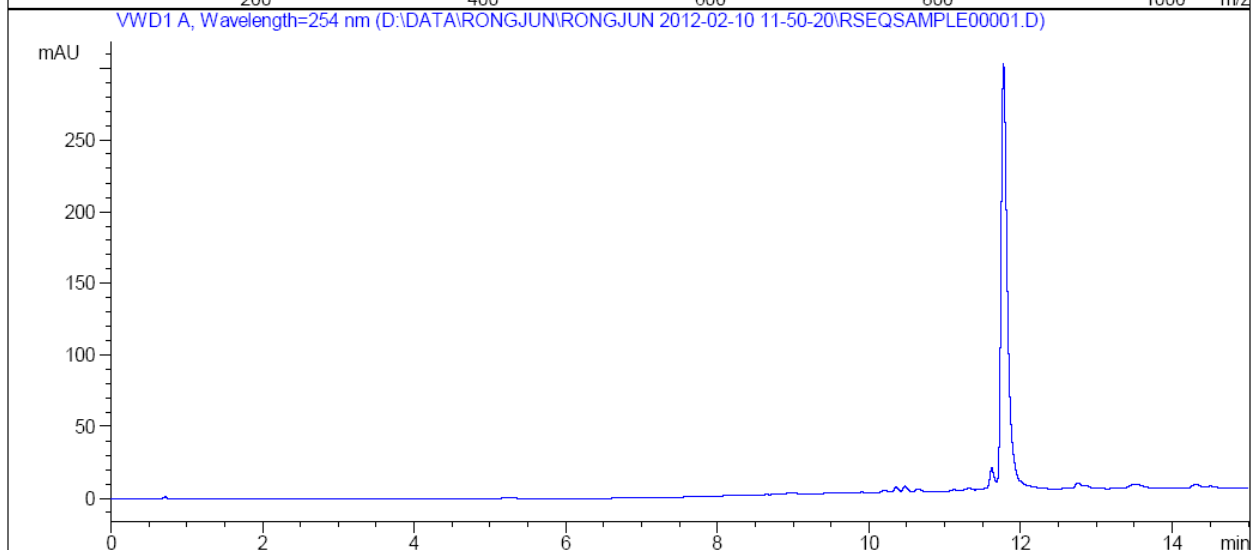
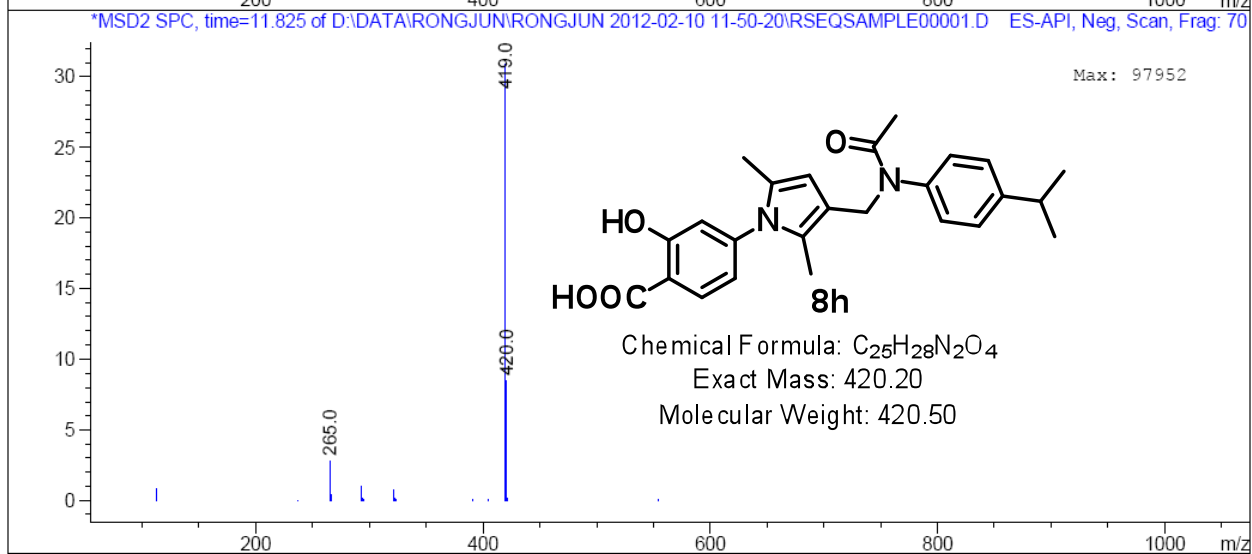
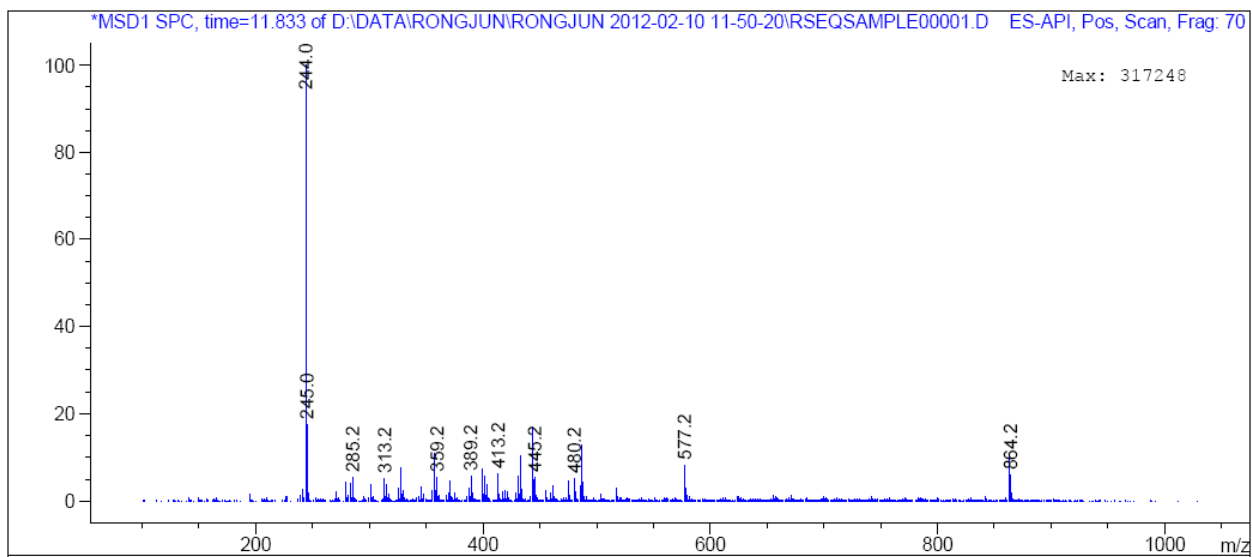


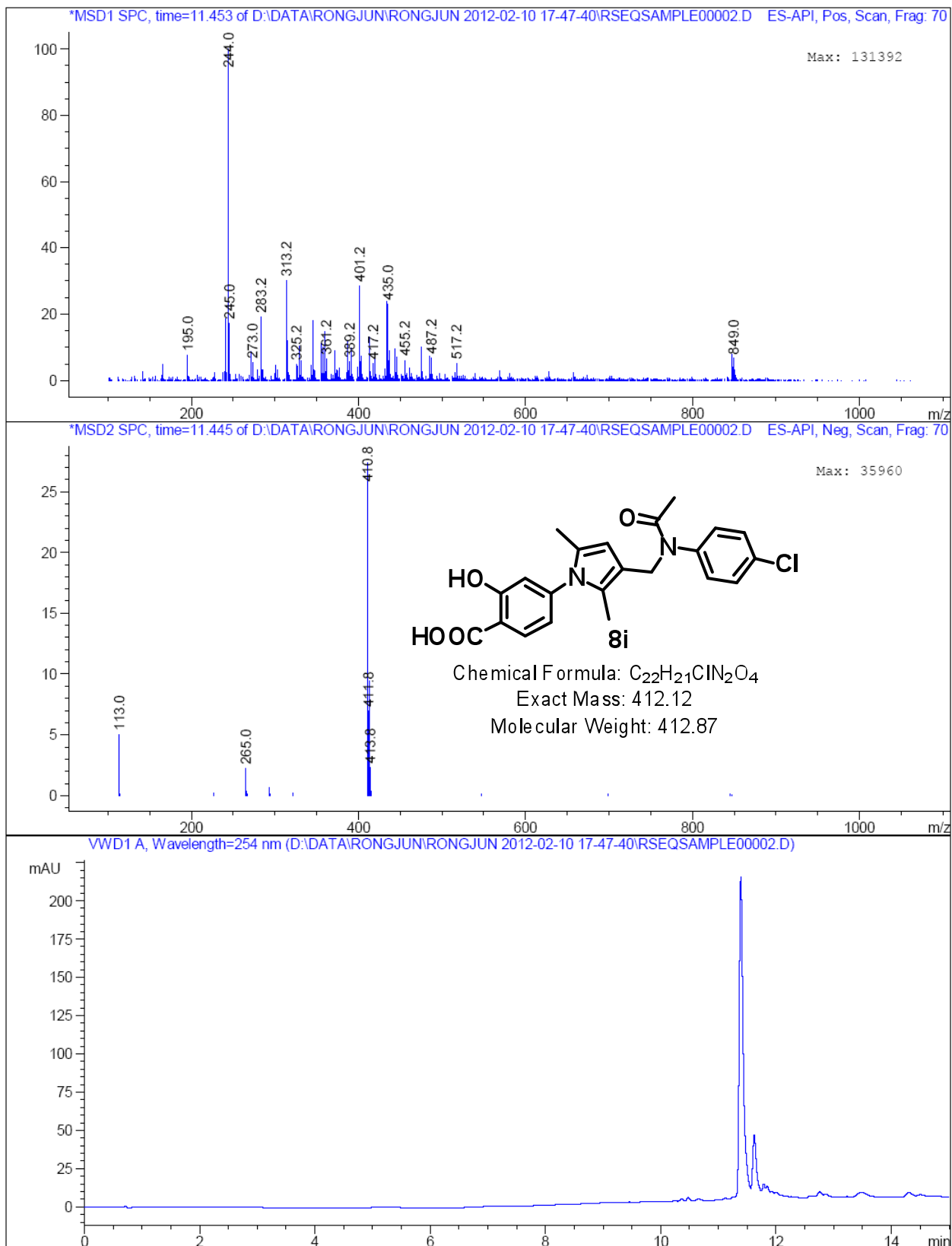


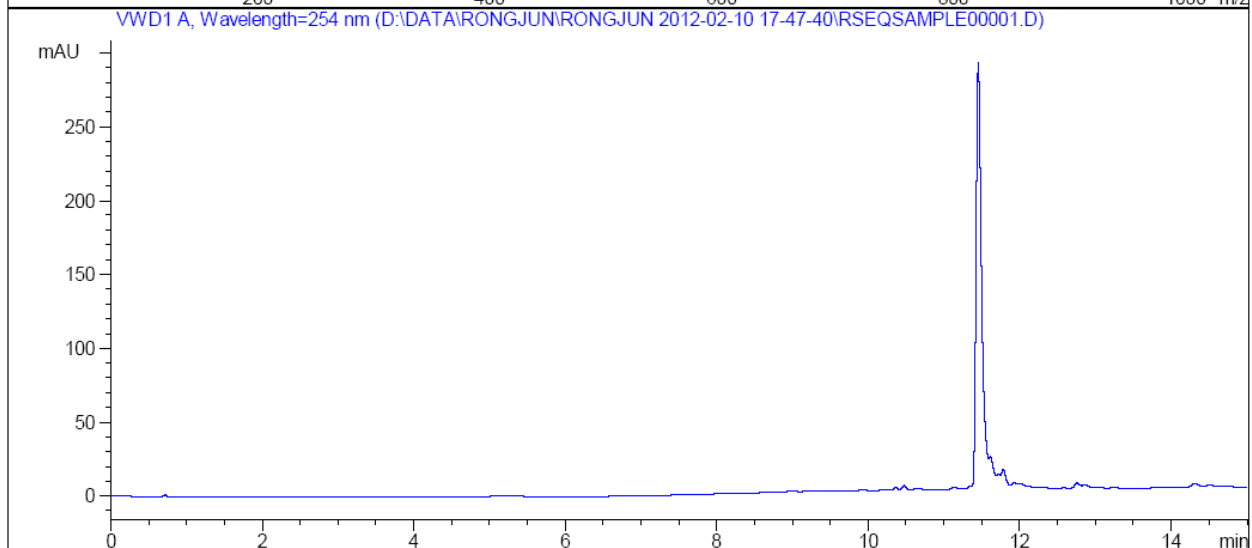
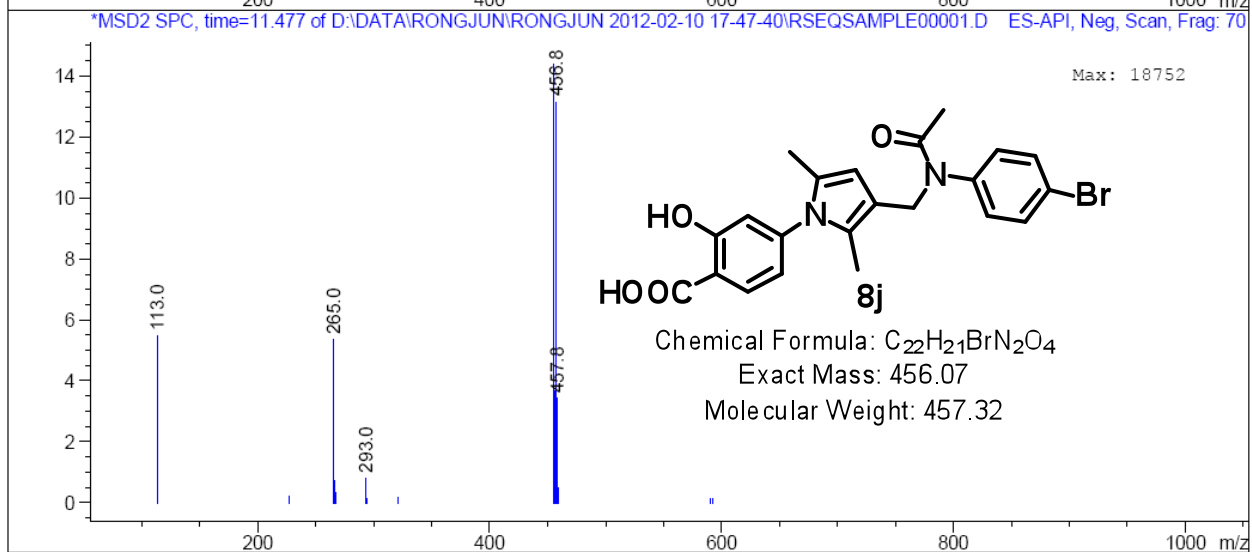
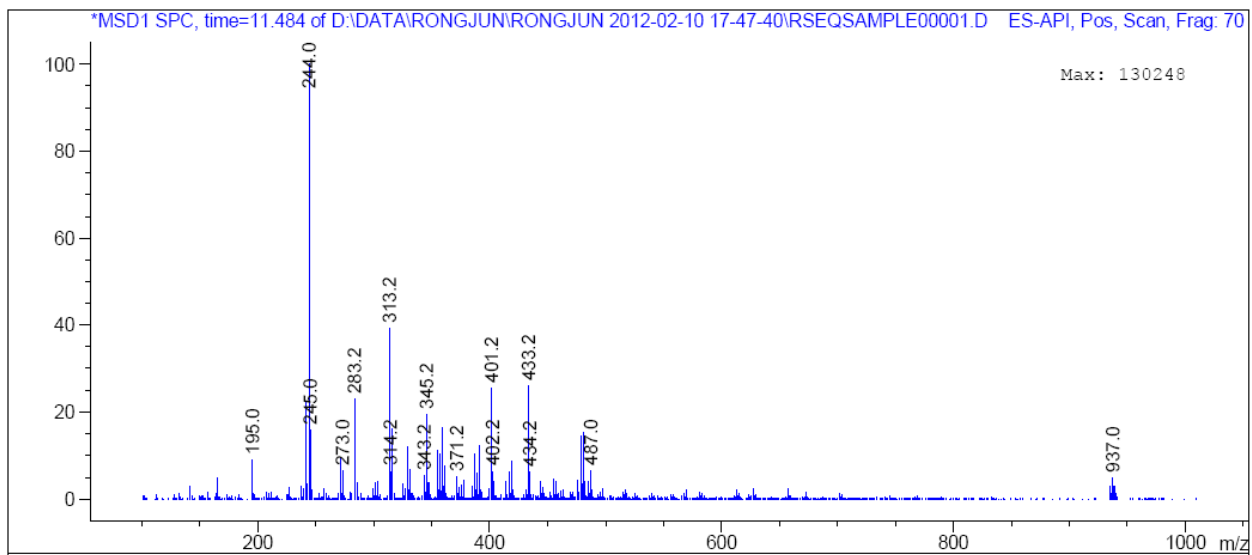




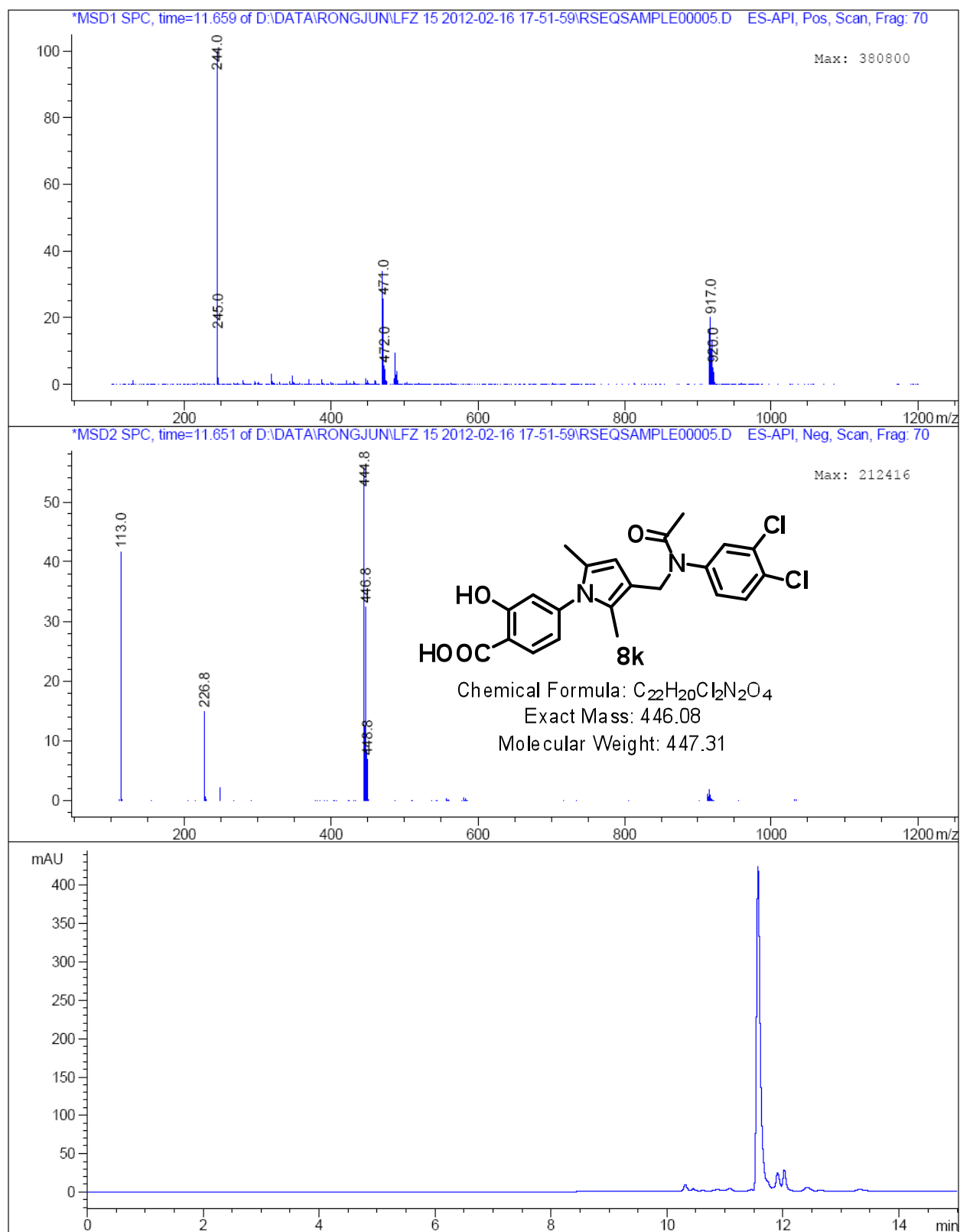


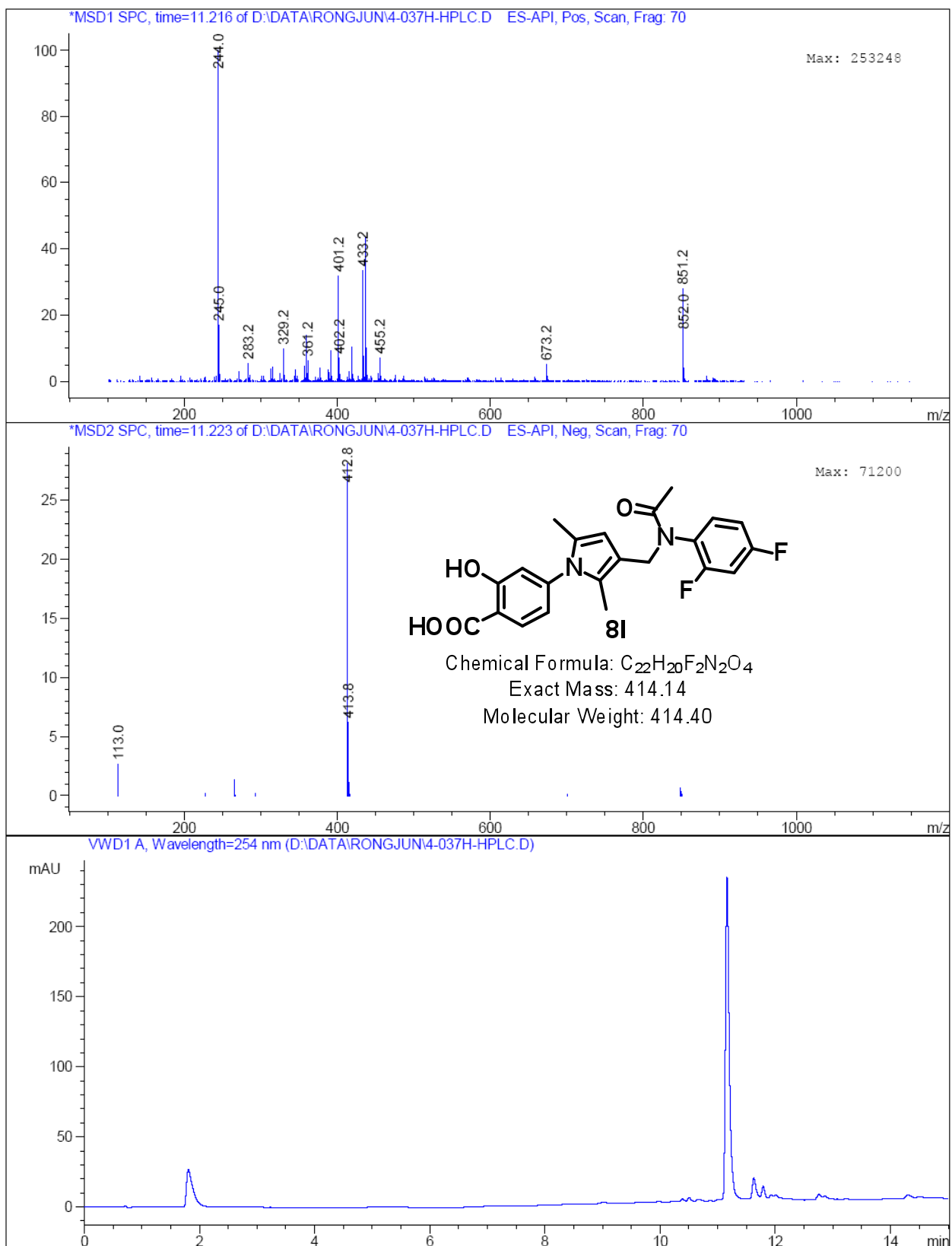


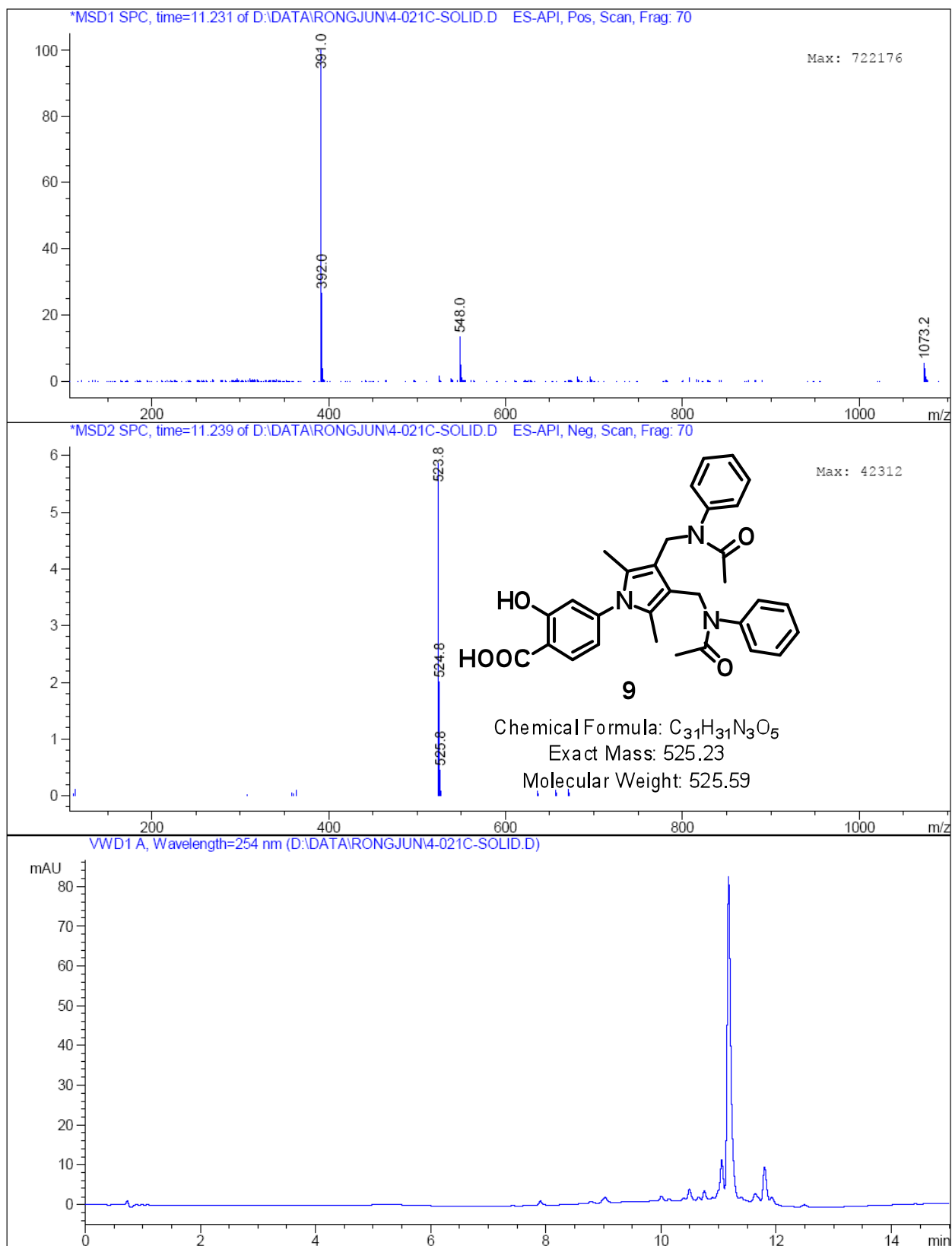


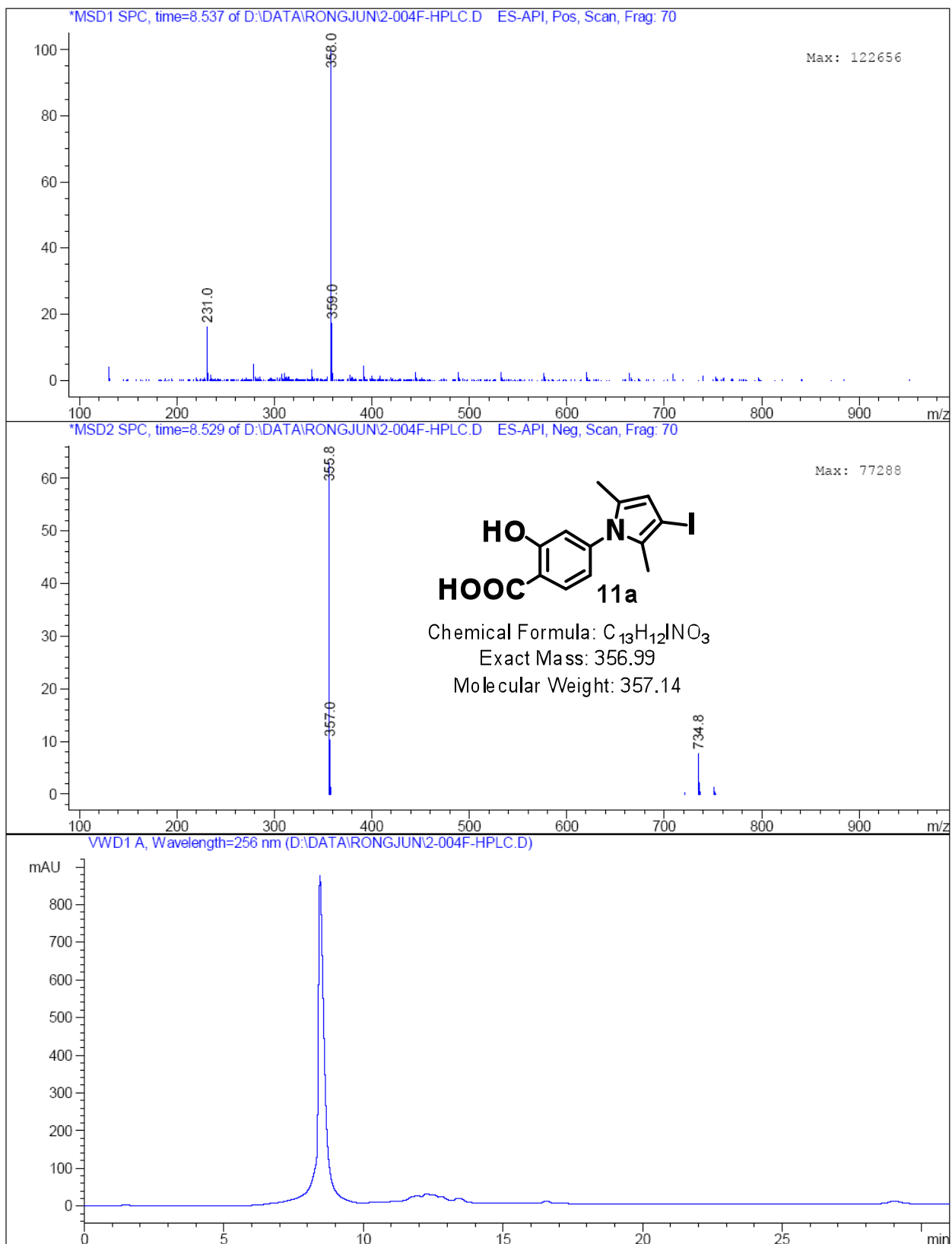


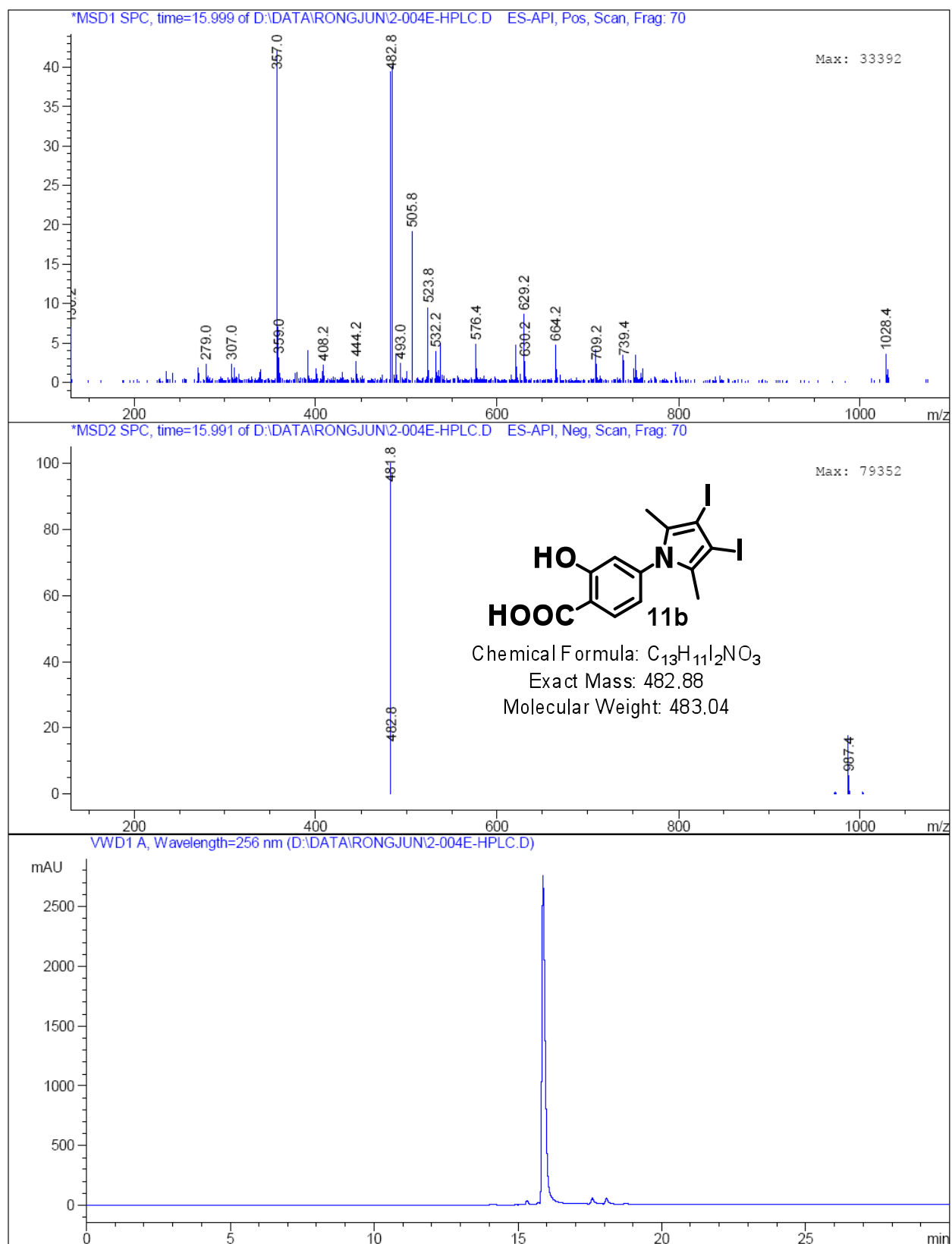




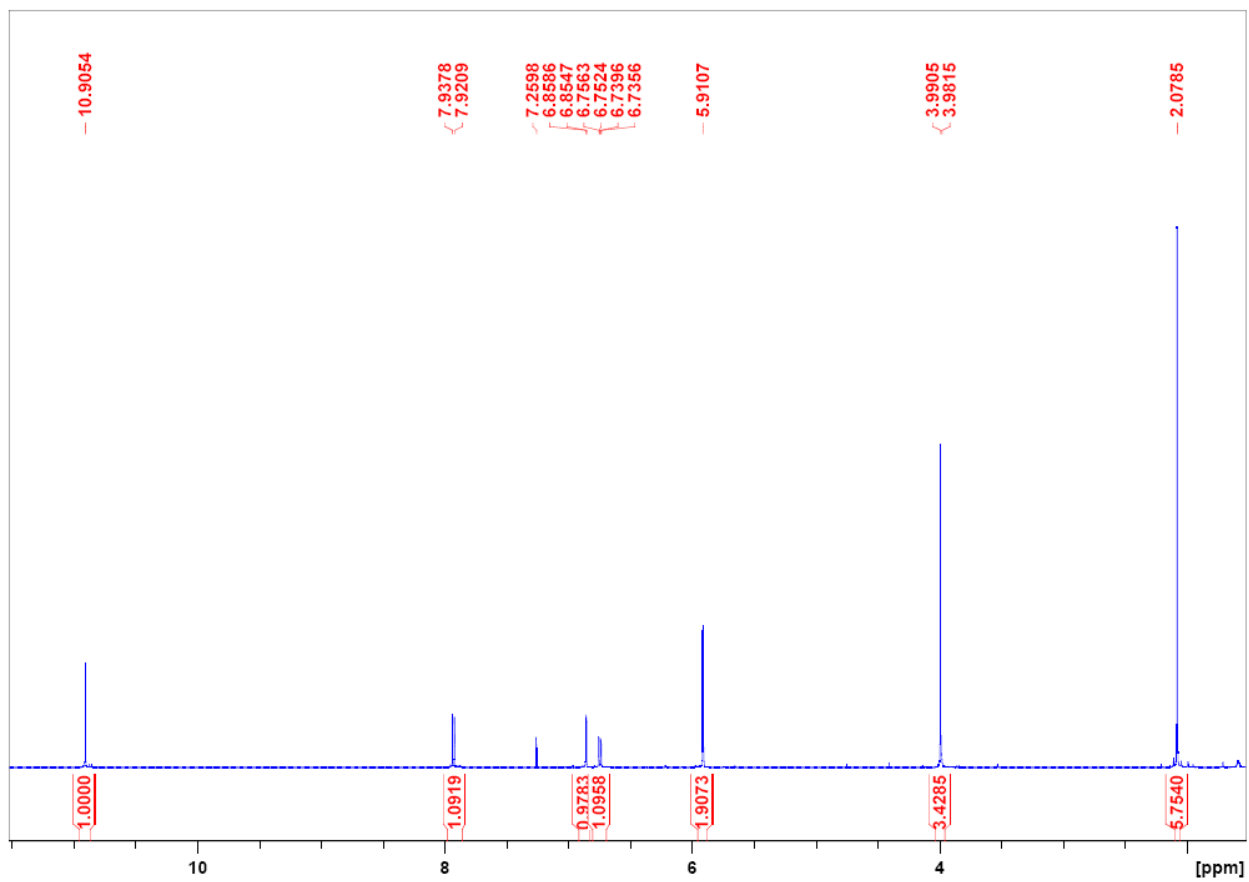
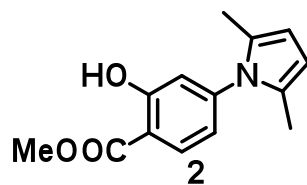


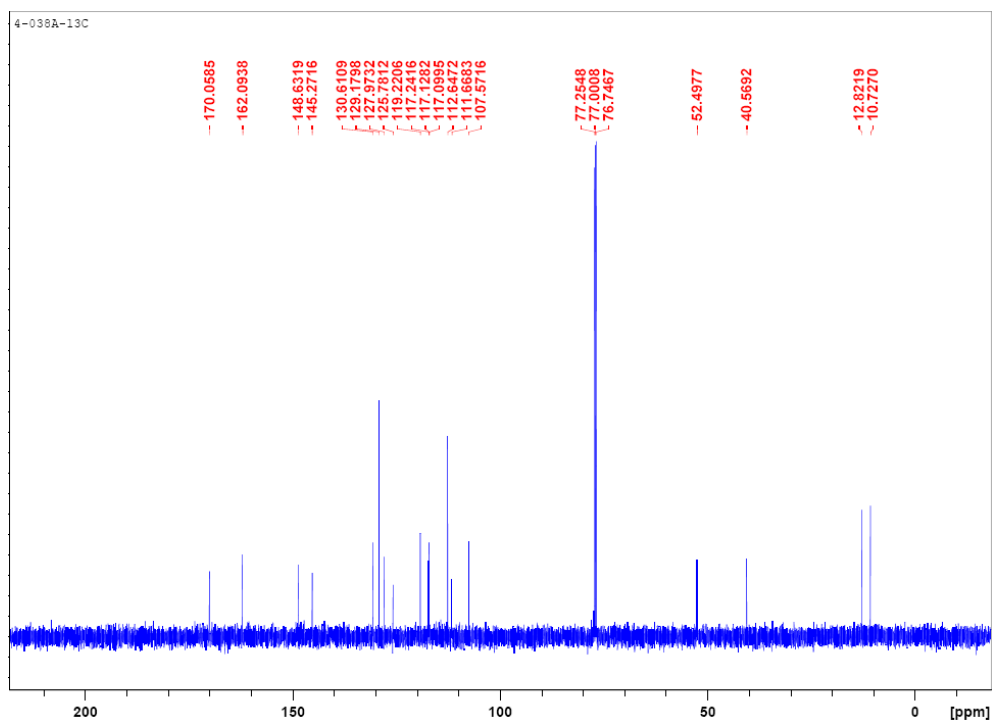
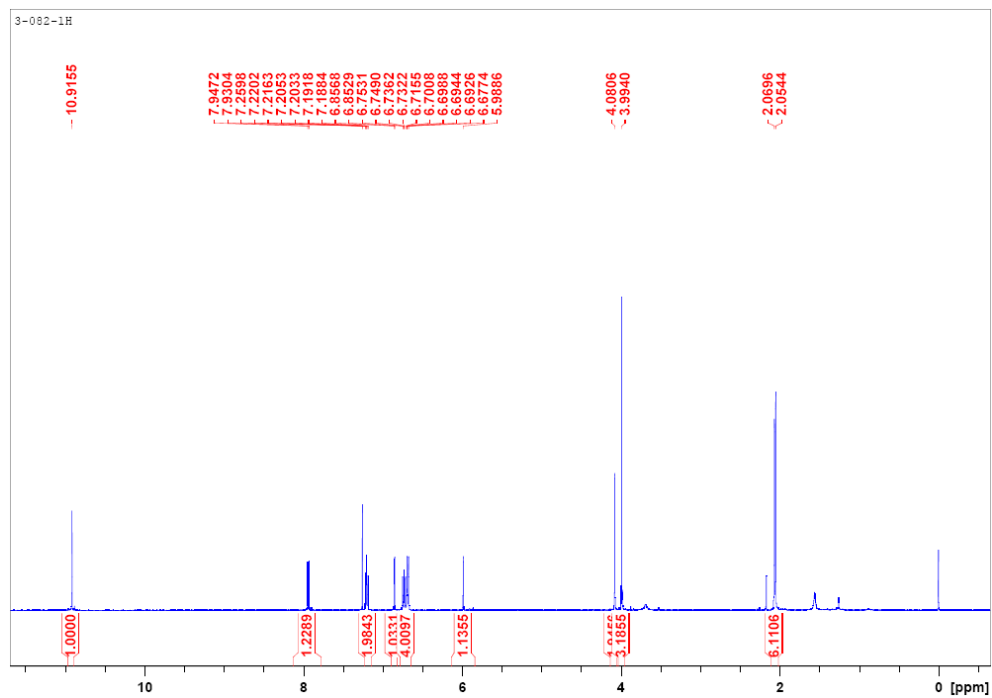
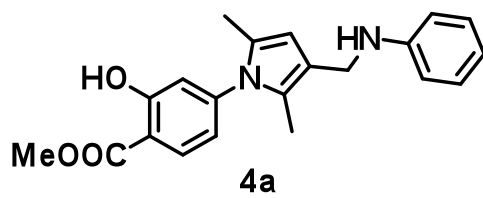


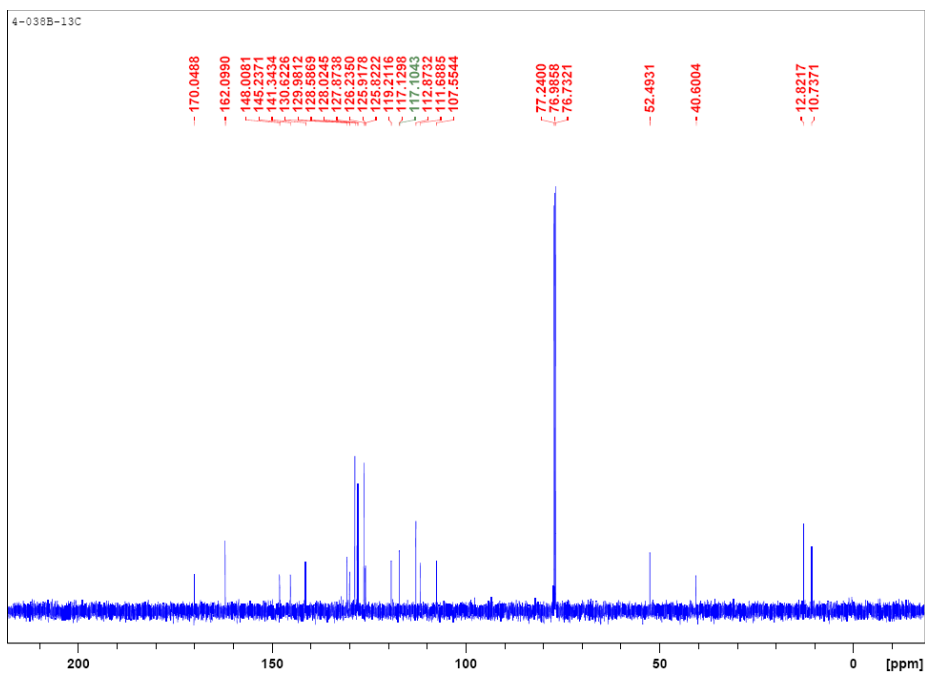
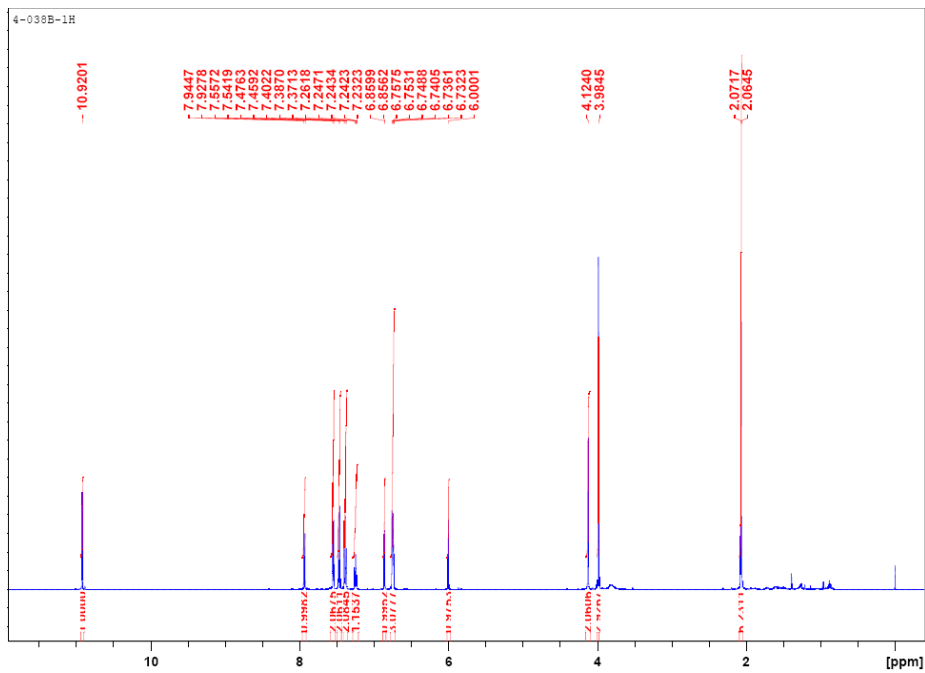
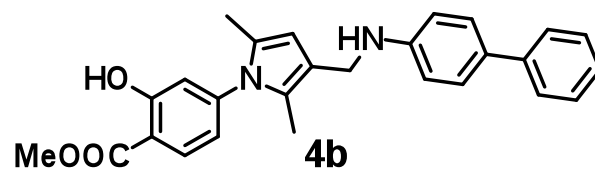




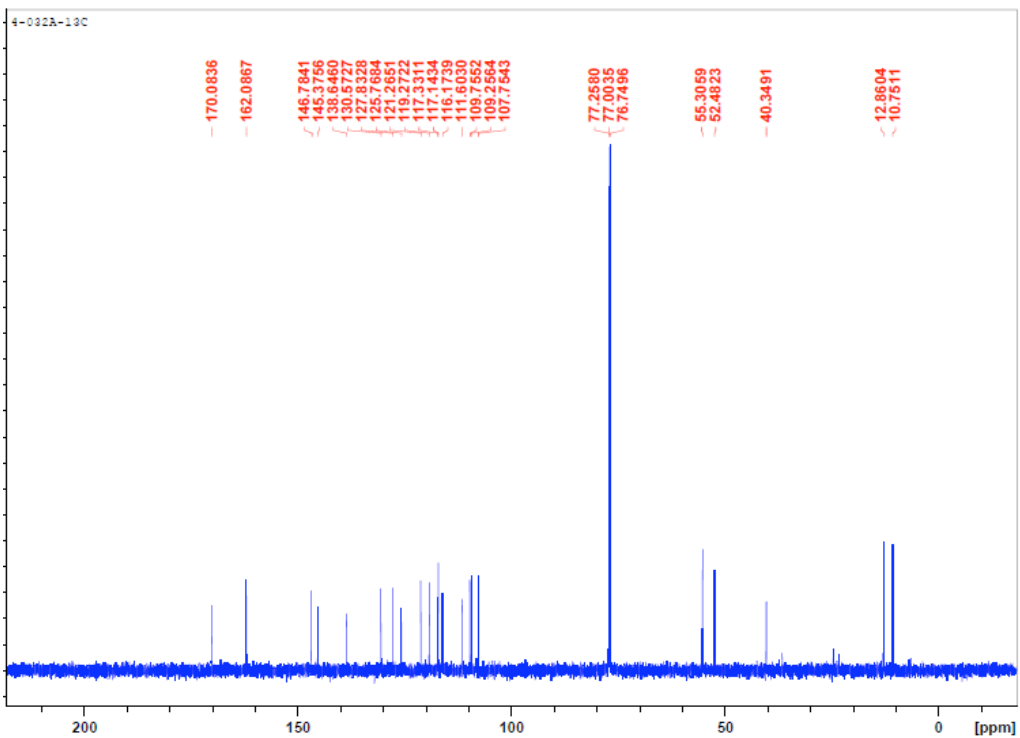
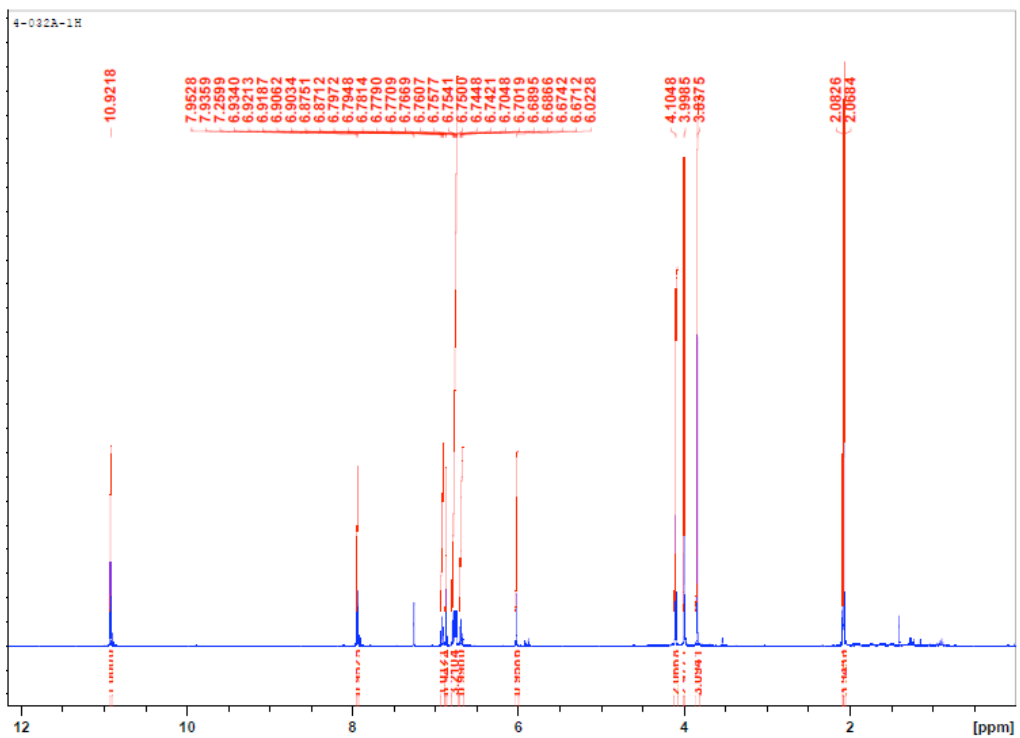
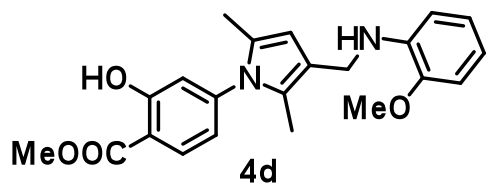
## Copies of $^1\text{H}$ and $^{13}\text{C}$ NMR Spectra of compounds **2**, **4a-4l**, **5**, **7a**, **10b**

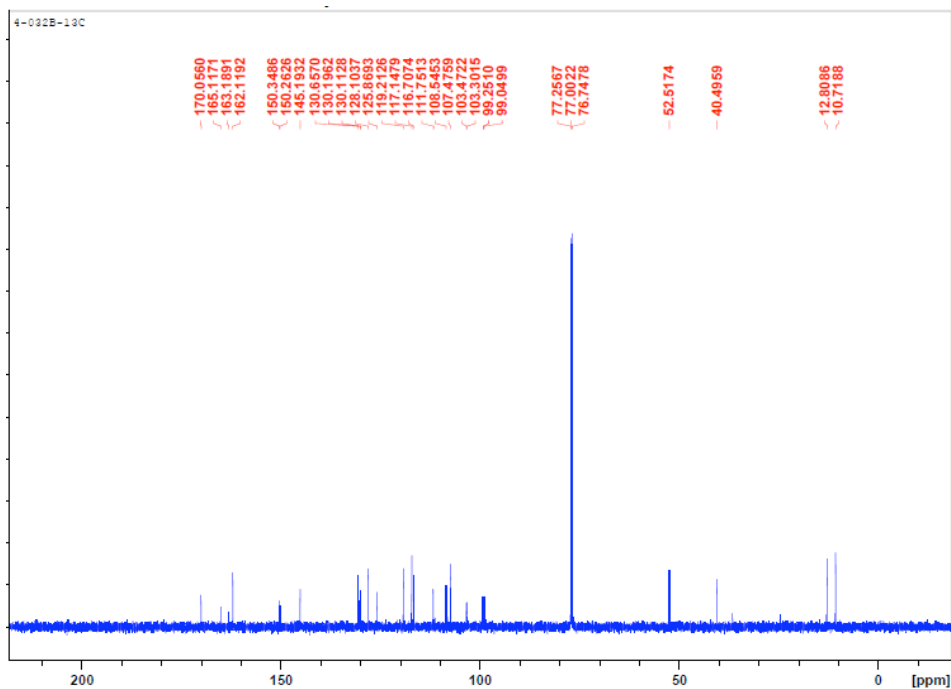
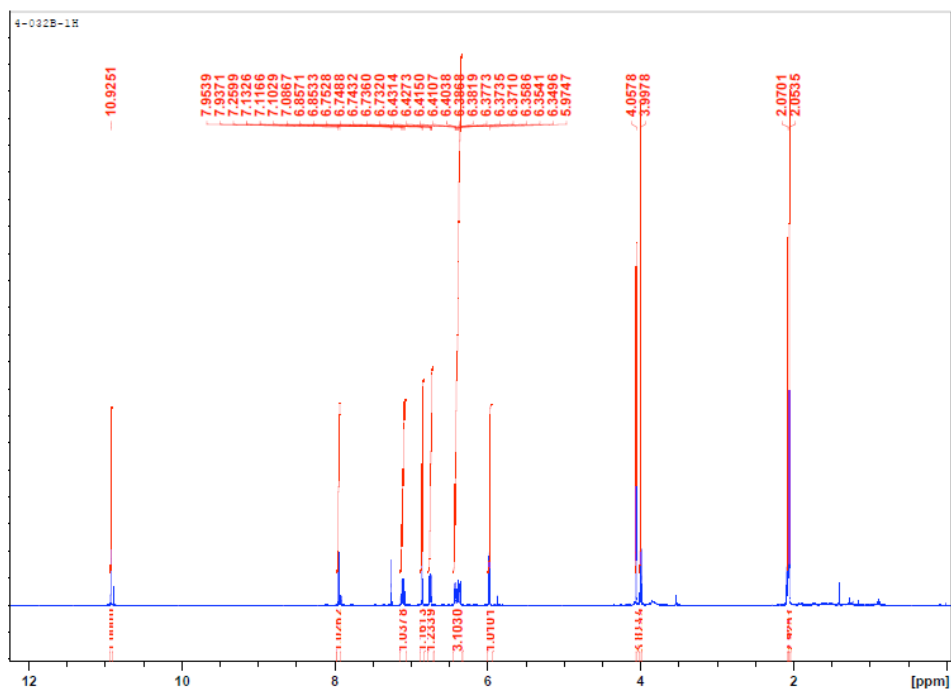
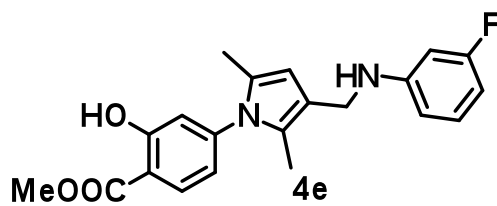


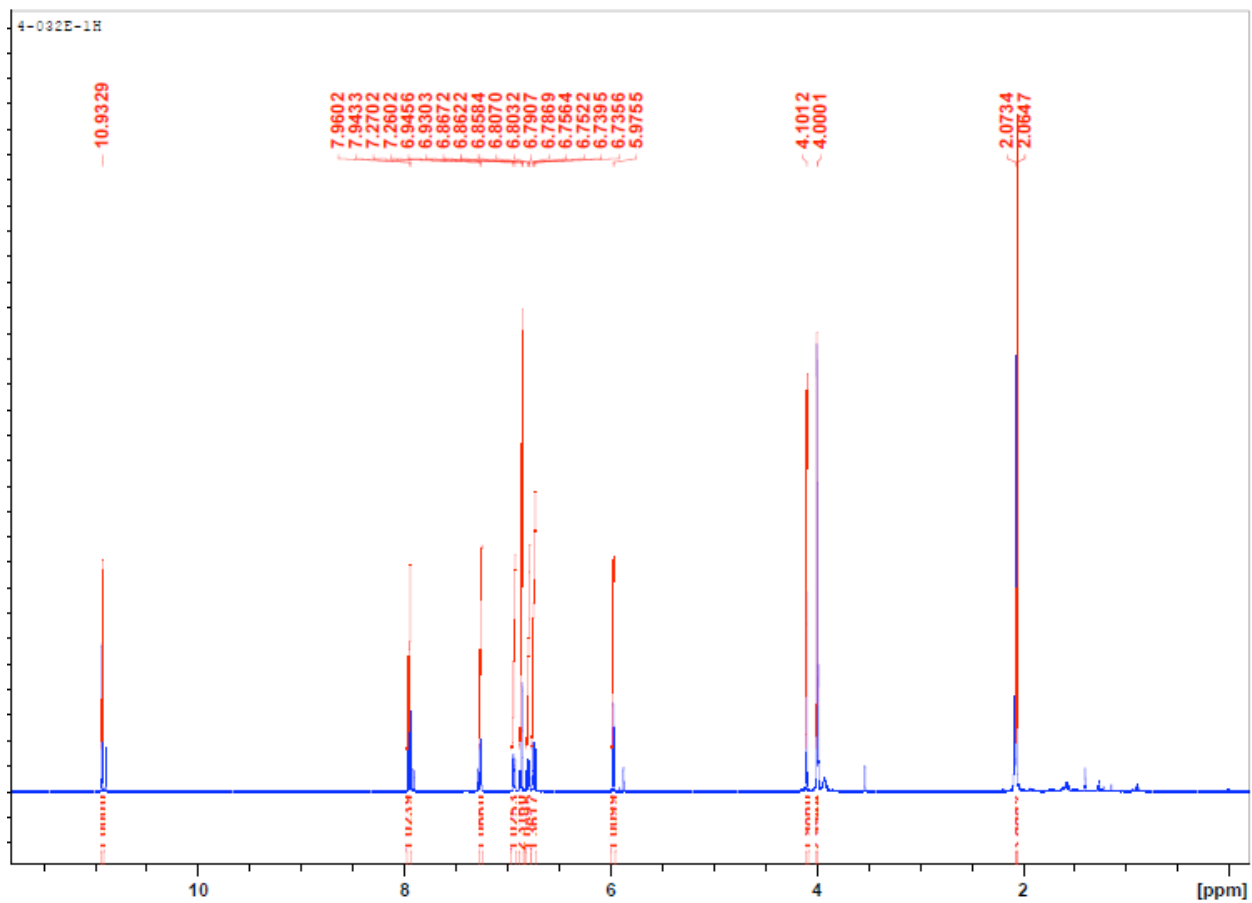
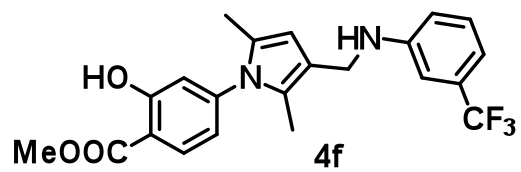


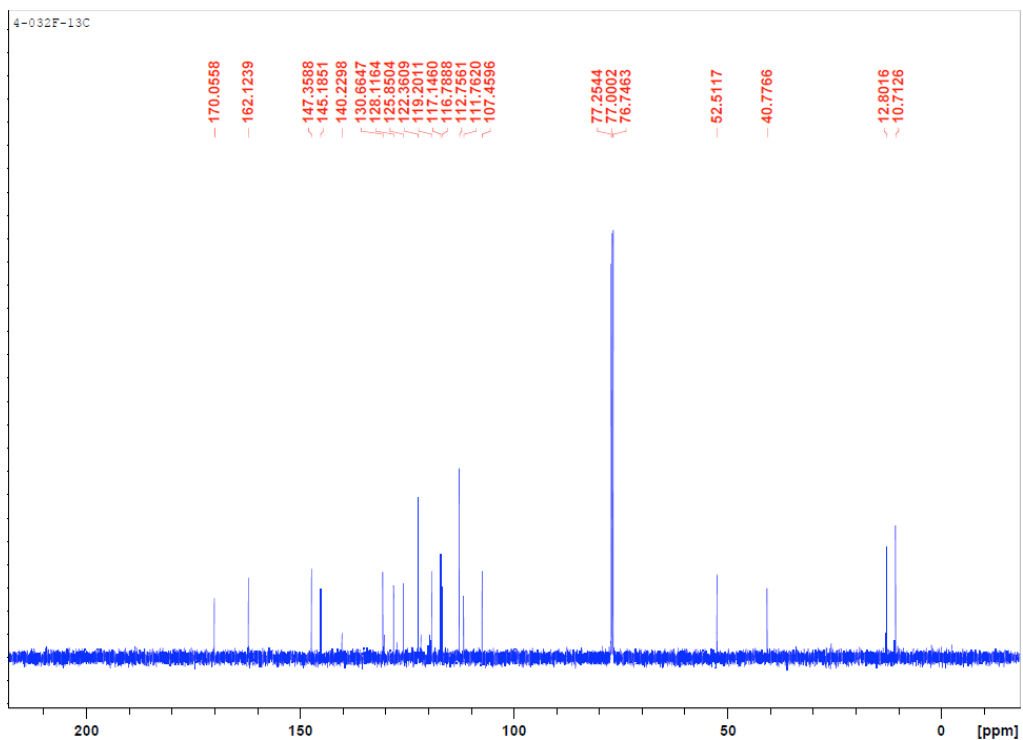
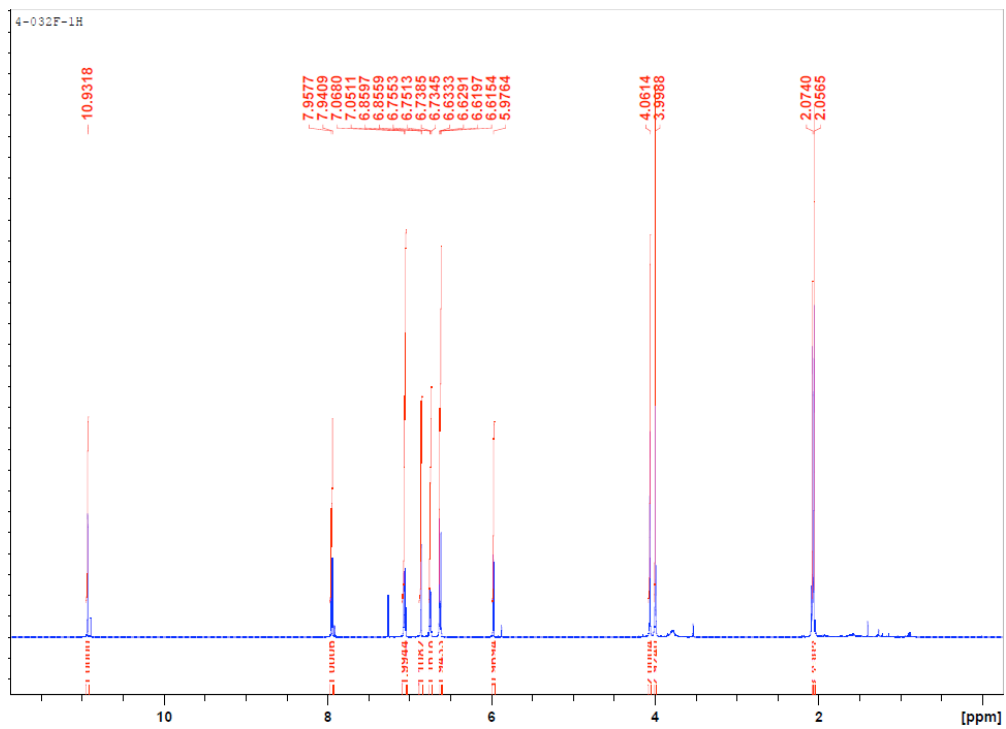
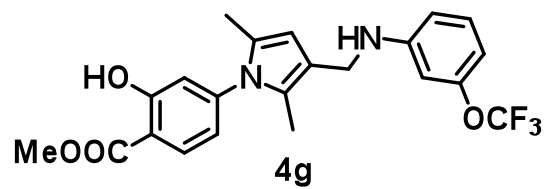


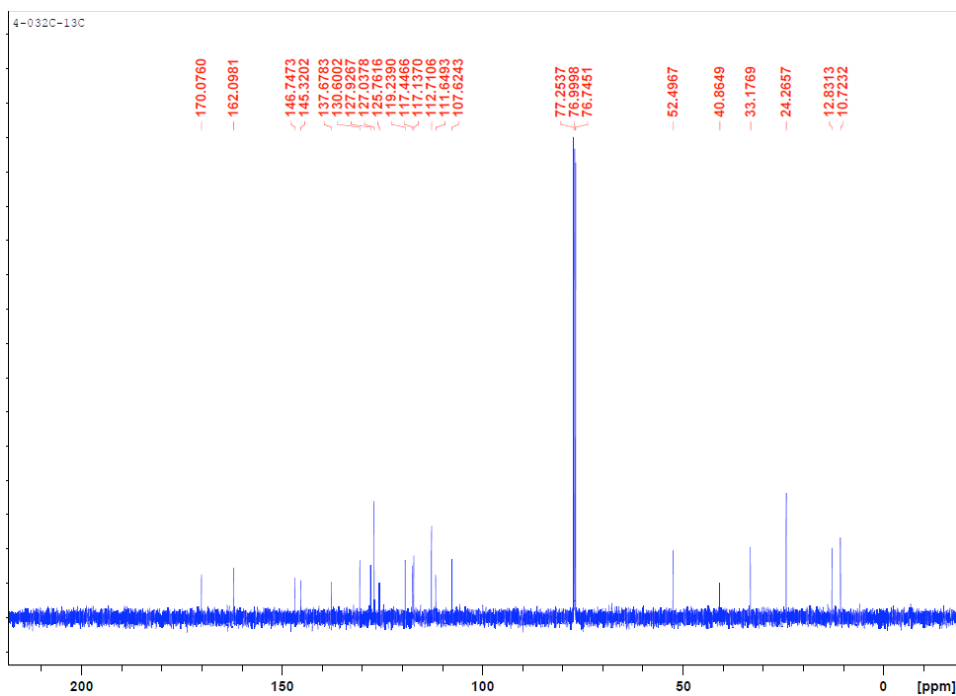
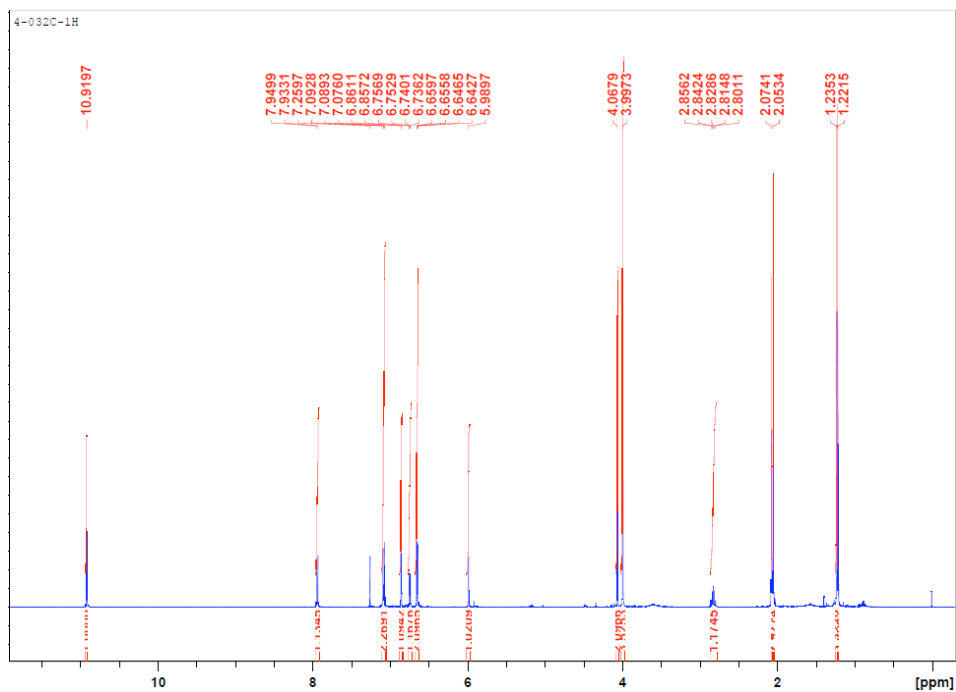
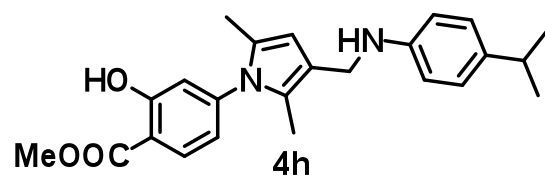


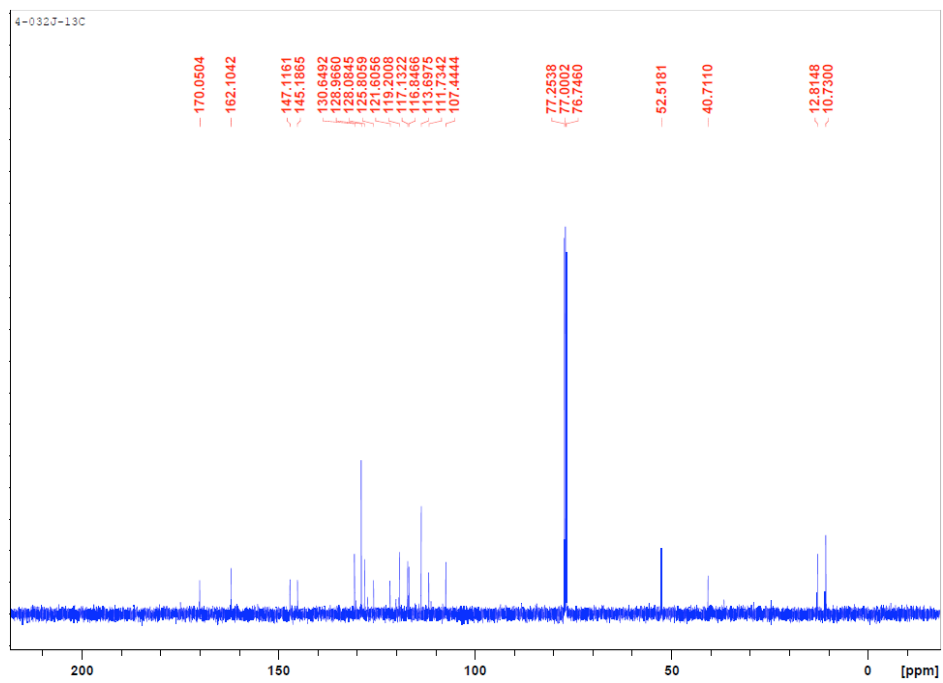
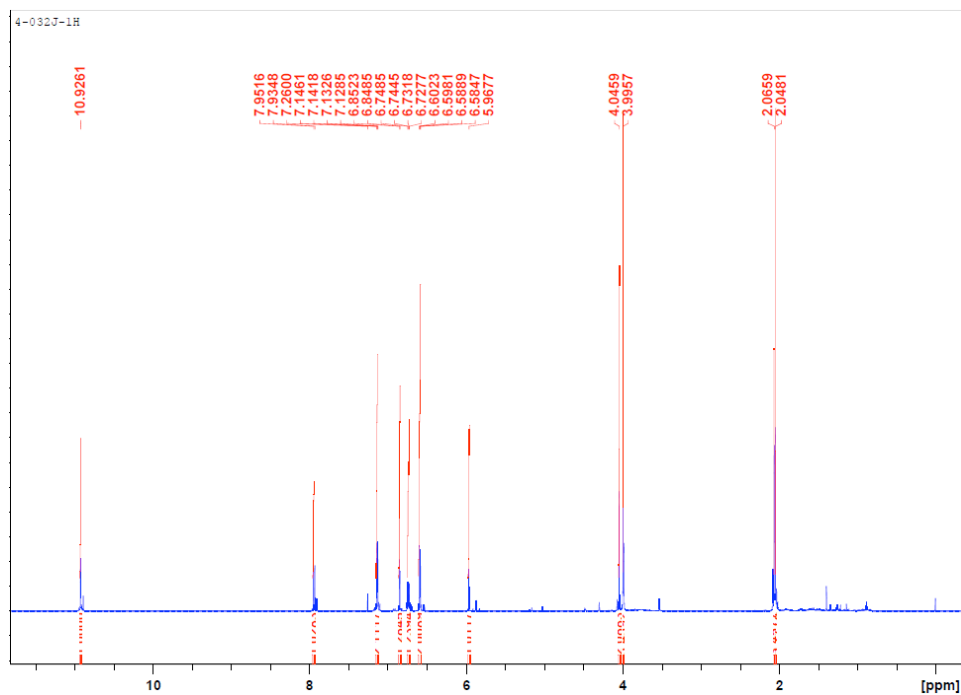
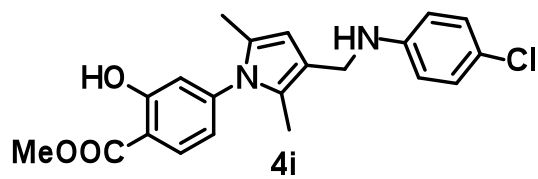


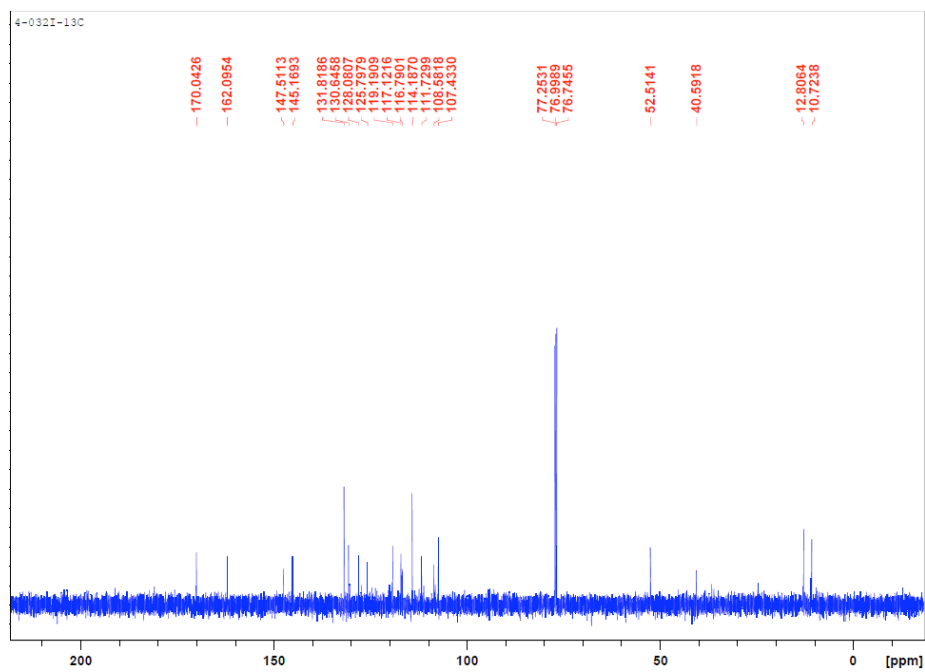
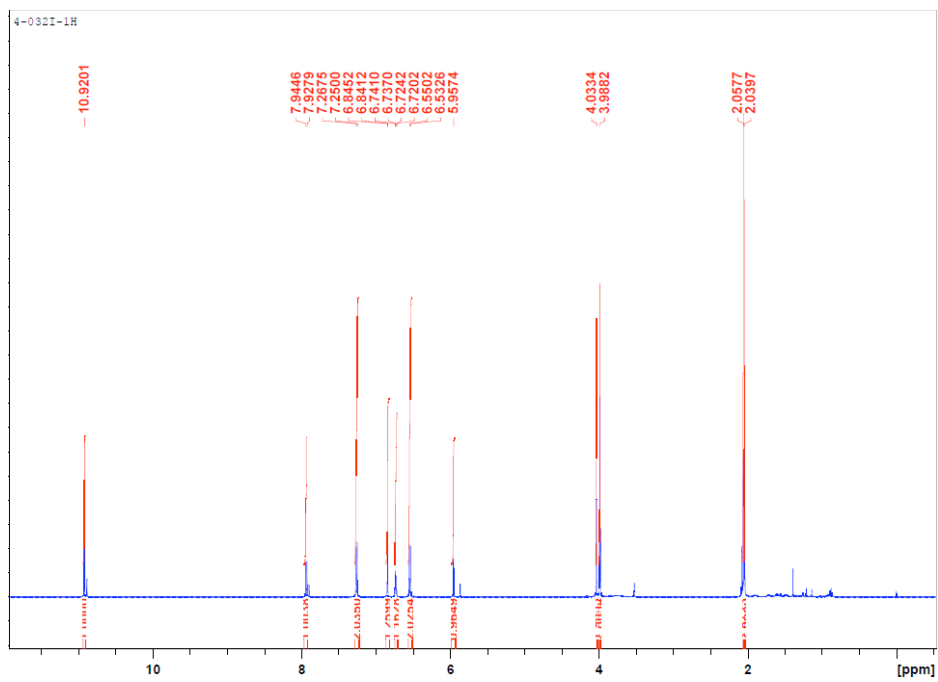
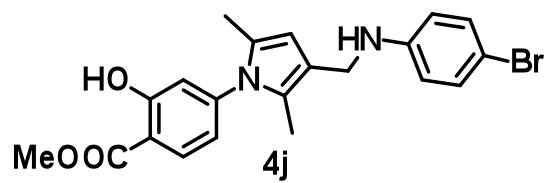


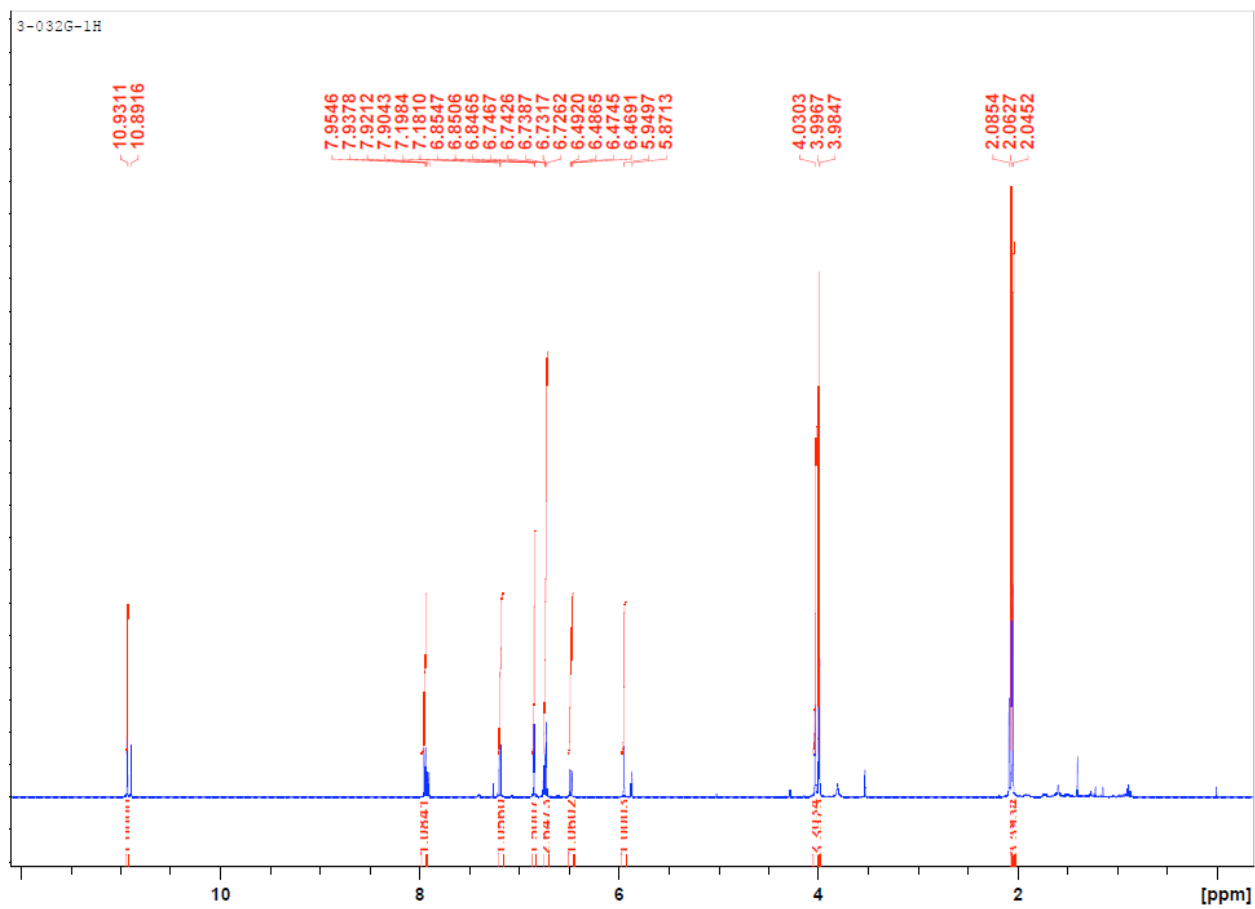
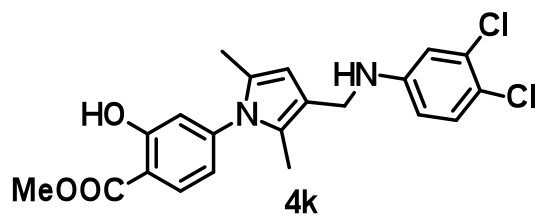




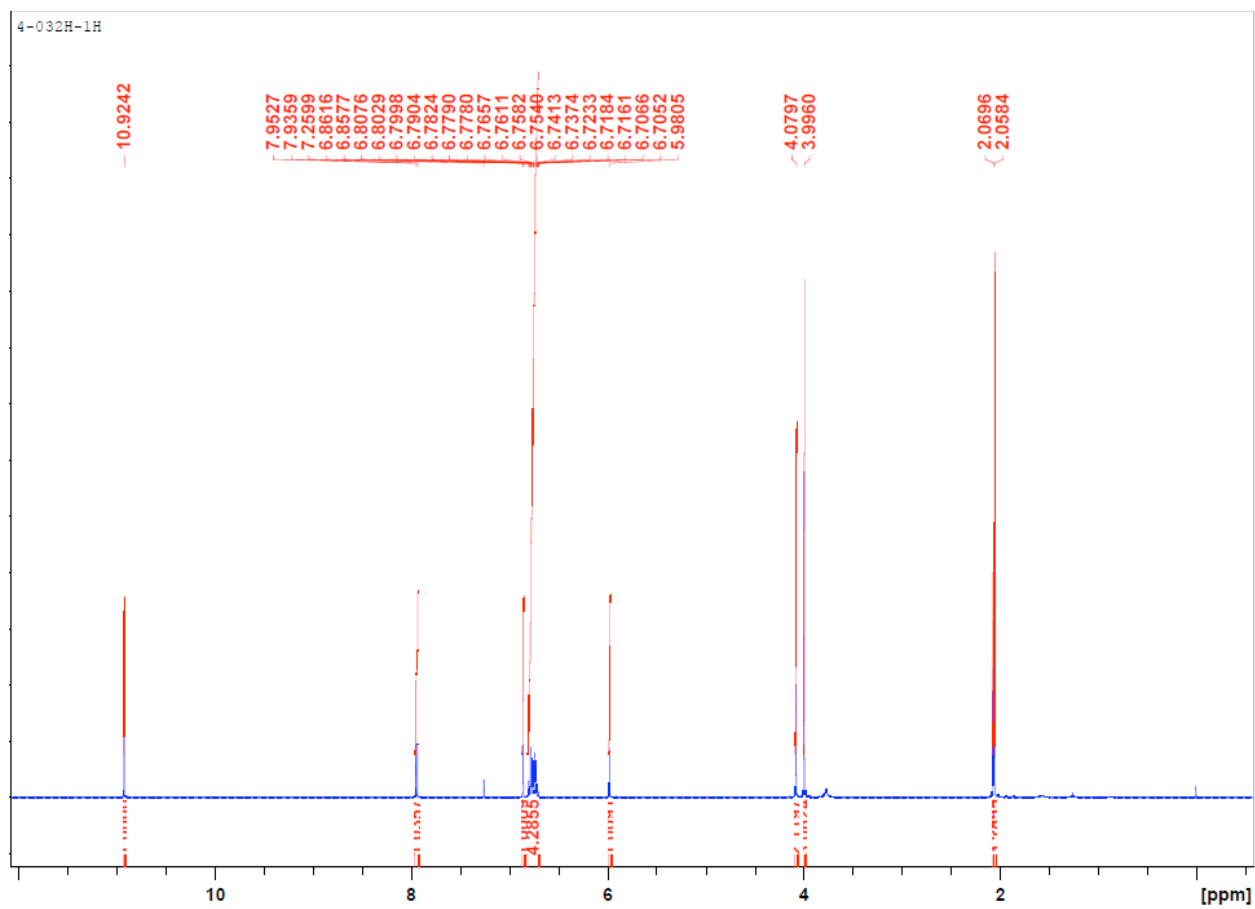
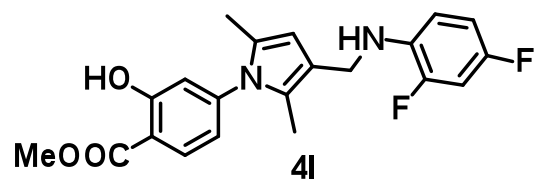


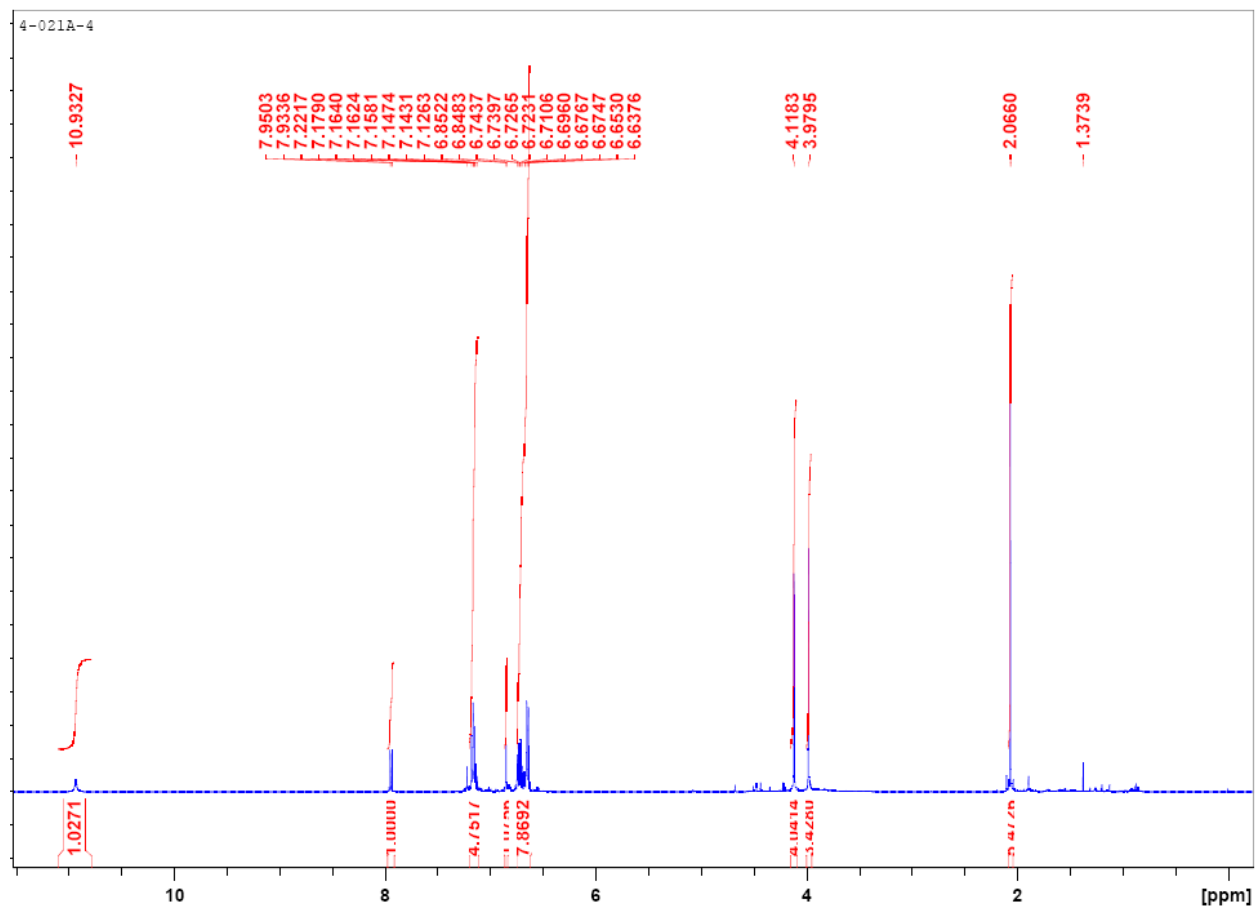
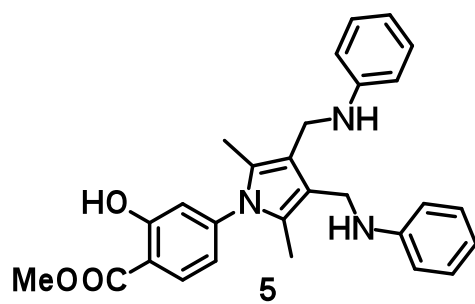


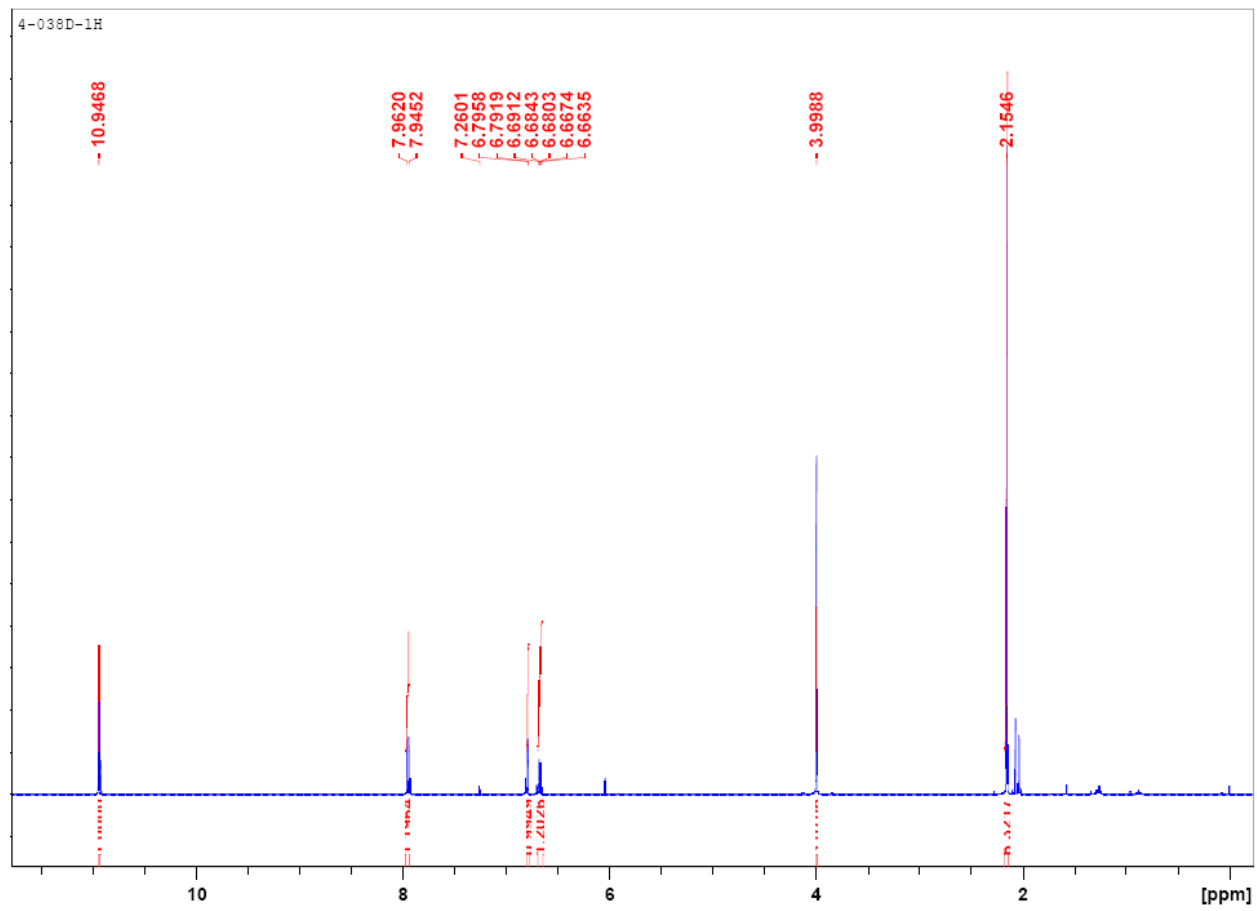
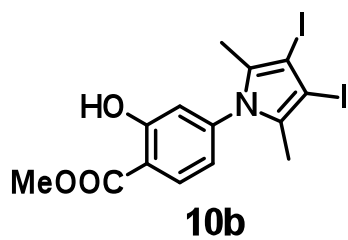


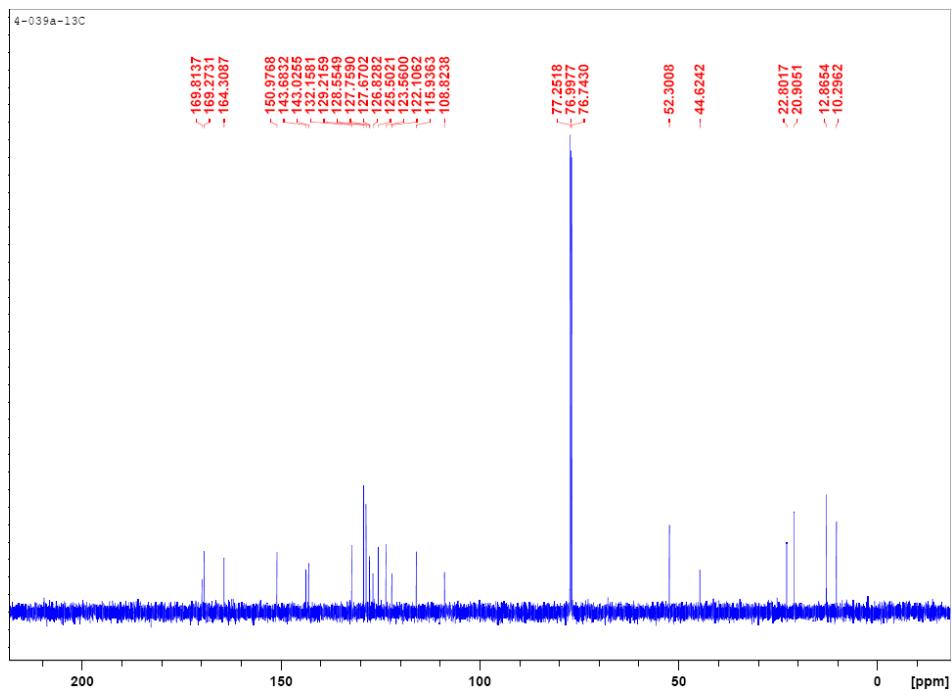
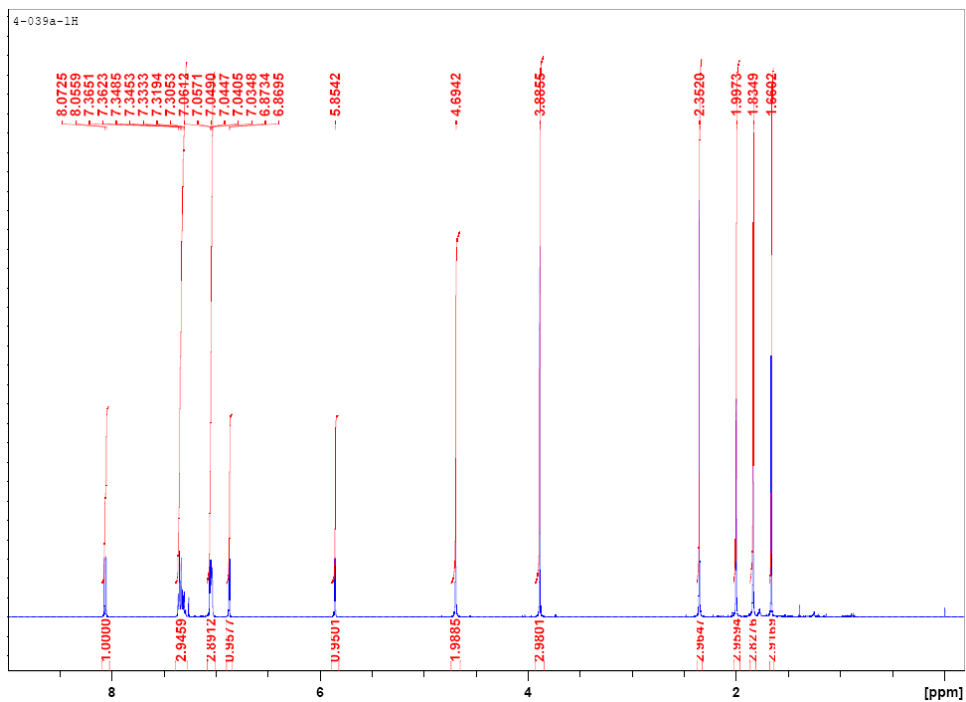
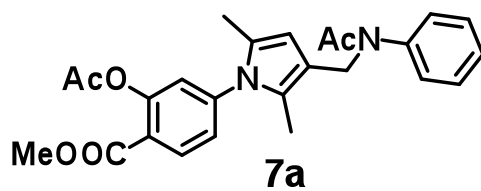












## Inhibition studies for all compounds

The inhibition assays were performed on 96-well plates at 25°C in 50 mM 3,3-dimethylglutarate buffer, pH 7.0, containing 1 mM EDTA with an ionic strength of 0.15 M adjusted by NaCl. The reaction was started by the addition of 50 µl of the enzyme to 150 µl of reaction mixture containing *p*-nitrophenyl phosphate (*p*NPP) and various concentrations of the inhibitor [final concentration of mPTPB: 20 nM, final concentration of *p*NPP: 3 mM (the  $K_m$  value)]. The reaction was quenched after 10 min by the addition of 50 µl of 5 N NaOH. The absorbance at 405 nm was detected by a Spectra MAX340 microplate spectrophotometer (Molecular Devices).  $IC_{50}$  values were calculated by fitting the absorbance at 405nm *versus* inhibitor concentration to the following equation:

$$AI/A0=IC_{50}/(IC_{50}+[I])$$

where AI is the absorbance at 405 nm of the sample in the presence of inhibitor; A0 is the absorbance at 405 nm in the absence of inhibitor; and [I] is the concentration of the inhibitor.

Expression and purification of recombinant mPTPB were described previously.<sup>1</sup>

[1] B. Zhou, Y. He, X. Zhang, J. Xu, Y. Luo, Y. Wang, S. G. Franzblau, Z. Yang, R. J. Chan, Y. Liu, J. Zheng, Z.-Y. Zhang, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 4573-4578.