

Supporting Information

Synthesis of Indolizines from Pyridinium Salts and Ethyl

Bromodifluoroacetate

Xiaoya Hou,[†] Sen Zhou,[†] Yuli Li,[†] Minjie Guo,^{*,‡} Wentao Zhao,[†] Xiangyang Tang,[†] and Guangwei Wang^{*,†}

[†]*Tianjin Key Laboratory of Molecular Optoelectronic Science, Department of Chemistry, School of Science, Tianjin University, Tianjin 300072, P. R. China*

[‡]*Institute for Molecular Design and Synthesis, School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, P. R. China*

*Email: wanggw@tju.edu.cn.

Table of Contents

1. General information.....	S2
2. Optimization of the reaction conditions for the synthesis of 2 and study of substrate scope.....	S2
3. Optimization of the reaction conditions for the synthesis of 5 and study of substrate scope....	S6
4. Mechanistic studies.....	S8
5. Experimental procedure and characterization of 1f	S13
6. Representative procedure I and characterization of 2a-2p , 2a-Me and 3a-Me	S14
7. Representative procedure II and characterization of 5a-5p , 6 and 7	S23
8. References.....	S33
9. ¹ H NMR, ¹⁹ F NMR, ¹³ C NMR, and HRMS spectra.....	S34

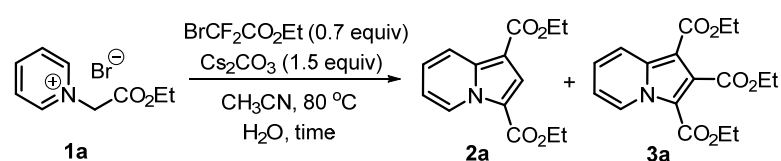
1. General information.

All experiments were carried out under an argon atmosphere with dry solvents in flame-dried glassware unless otherwise noted. Toluene, THF, DMSO, CH₂Cl₂, and acetonitrile (CH₃CN) were dried and distilled by the standard methods. Other commercially available reagents were purchased and used without further purification, unless otherwise stated. Flash chromatographic separations were carried out on 200-300 mesh silica gel. Reactions were monitored by TLC and GC analysis of reaction aliquots. GC analyses were performed on an Agilent 7890 Gas Chromatography instrument using a HP-5 capillary column (30 m × 0.32 mm, 0.5 μm film) with mesitylene as the internal standard. ¹H, ¹⁹F, and ¹³C NMR spectra were recorded in deuterated solvents on a Bruker AVANCE III or JNM-ECZ600R spectrometer and calibrated using residual undeuterated solvent (CDCl₃ at 7.26 ppm ¹H NMR, 77.16 ppm ¹³C NMR, DMSO-*d*₆ at 2.50 ppm ¹H NMR, 39.52 ppm ¹³C NMR). Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectrometry (HRMS) were recorded on a QTOF mass analyzer with electrospray ionization (ESI) through a Waters G2-XS QTOF. Melting points were measured in a X-6 Micro Melting Point Apparatus purchased from Beijing TECH Instrumental Company.

Pyridinium salts **1a-1p** and **4a-4p** were synthesized from the corresponding pyridines and ethyl bromoacetates according to the reported procedure.^{1,2}

2. Optimization of the reaction conditions for the synthesis of **2** and study of substrate scope.

Table S1. Optimization of reaction Conditions for the synthesis of **2a.^a**



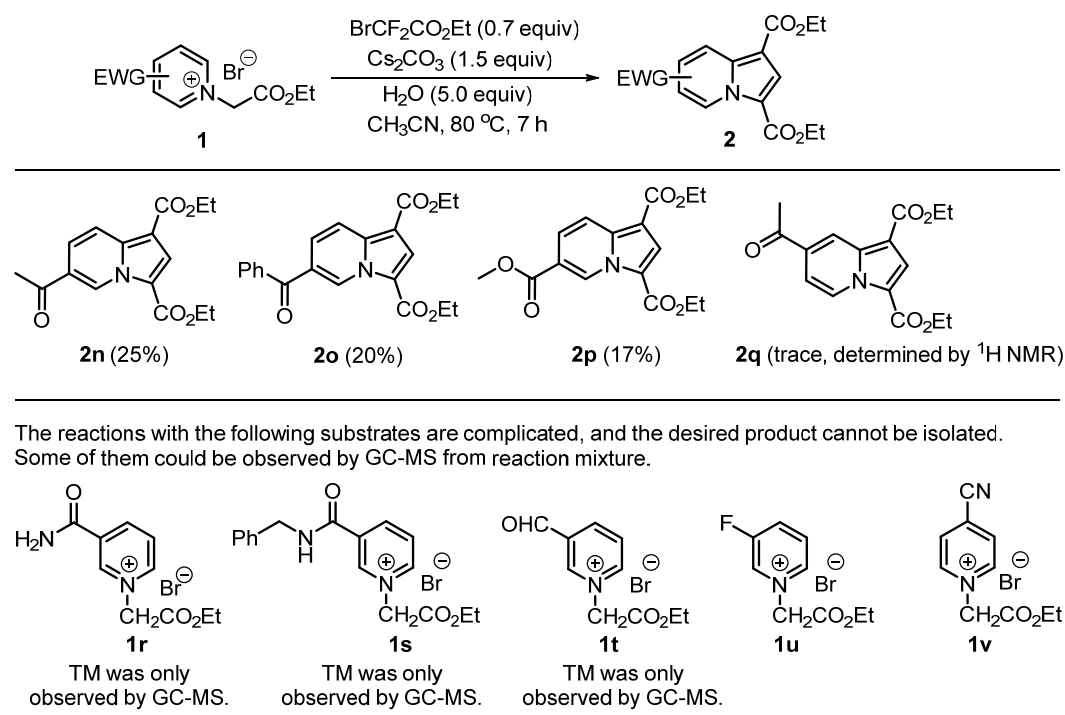
entry	H ₂ O (equiv)	time (h)	2a (%) ^a	3a (%) ^a
1	5.0	5	90	0
2	5.0	7	94	0
3	5.0	16	95	2
4	3.0	7	64	1
5	10.0	7	62	0

^aReaction conditions: **1a** (0.5 mmol), BrCF₂CO₂Et (0.7 equiv, 0.35 mmol), Cs₂CO₃ (1.5 equiv, 0.75 mmol) in CH₃CN (2.0 mL) under an argon atmosphere. Yields were determined by GC analysis with mesitylene as internal standard.

(a) Discussion on electron-withdrawing substituents on pyridine ring.

We tested several pyridinium salts with electron-withdrawing groups on pyridine ring, but the resulting yields were much lower than the substrates with electron-donating groups. As shown in Scheme S1, the 3-EWG (CH₃CO-, PhCO-, and CO₂CH₃-) substituted products (**2n**, **2o**, **2p**) can be isolated in low yields and 4-CH₃CO-substituted product (**2q**) was isolated in only trace amount. For compounds **1r-1v**, the reactions are messy and no desired products can be isolated.

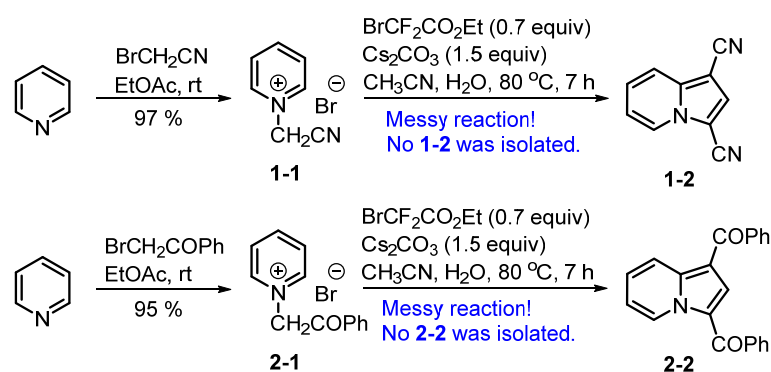
Scheme S1. Reactions of pyridinium salts with electron-withdrawing substituents on pyridine ring.



(b) Discussion on other substituents on nitrogen atom of pyridine.

We have synthesized Py+CH₂CN and Py+CH₂C(O)Ph with high yield as shown below in Scheme S2. However, different from the Py+CH₂CO₂Et salt, the reactions of Py+CH₂CN and Py+CH₂C(O)Ph both did not proceed well. TLC indicated messy reactions under the current reaction conditions and no desired products **1-2** and **2-2** can be isolated. The possible reason is that the ketone and nitrile groups have stronger electron withdrawing ability than the ester group. Therefore the corresponding carbon anions display low reactivity toward further reaction steps.

Scheme S2. The reactions of N-CH₂CN or N-CH₂C(O)Ph pyridinium salt with BrCF₂CO₂Et.



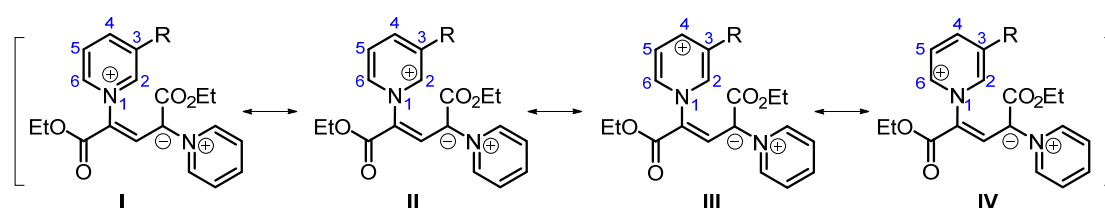
(c) Discussion on regioselectivity of *m*-substituted pyridinium salts.

The C2 or C6-selectivity for *m*-substituted pyridinium salts is controlled by the properties of substituents. When *m*-substitution is an electron-withdrawing group, the reaction proceeds selectively at C6 position which is sterically favored; when *m*-substitution is an electron-donating group, the reaction proceeds selectively at C2 position which is electronically favored. These different patterns could be explained as follows.

Based on the proposed mechanism, the key step toward the formation of products **2** is the nucleophilic attack of carbon anion to C2 or C6 position of pyridinium, which is dependent on both electronic and steric effects (Scheme S3). When R is EWG, it can impose electron-withdrawing effect through both conjugation effect and inductive effect, and the conjugation effect dominates. Both C2 and C6 are electrophilic enough to react with nucleophiles and therefore C6 is favored due to less steric hindrance.

When R is EDG such as RO group, although it can impose comparable electron-donating effect on both C2 and C6 position through conjugation, the inductive electron-withdrawing effect on C2 is much larger than C6 since the inductive effect decreases rapidly with the increasing of distance. Combining the above two factors, the C6 position is less electrophilic than C2 position when R is EDG, leading to C2 selectivity for *m*-substituted pyridinium salts.

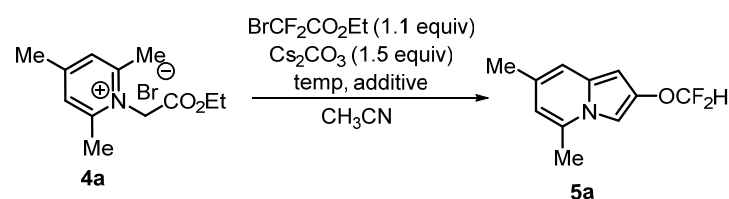
Scheme S3. Resonance structures of 3-substituted pyridinium salt and the comparison of electrophilicities between C2 and C6.



3. Optimization of the reaction conditions for the synthesis of **5** and study of substrate scope.

1-(2-Ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide (**4a**) was used as the substrates to optimize the reaction conditions (Table S2) for synthesis of difluoroalkylated indolizines. We directly used the best known conditions for compounds **2** to synthesize the **5a**, but the yield was only 70% (entry 1). Fortunately, the yield increased to 99% when the water was removed (entry 2). Then, we screened a range of temperatures (entries 2-4). Finally, the following reaction parameters were chosen as the optimized conditions: Cs₂CO₃ (1.5 equiv.) as the base at 50 °C in CH₃CN for 7 hours under argon atmosphere.

Table S2. Optimization of reaction conditions for the synthesis of **5a.^a**



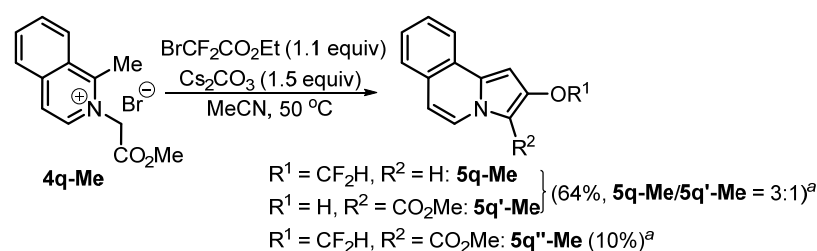
entry	additive (equiv)	temp (°C)	5a (%) ^a
1	H ₂ O (5.0)	80	70
2	-	80	99
3	-	50	99
4	-	r.t.	45

^aReaction conditions: **4a** (0.5 mmol), BrCF₂CO₂Et (1.1 equiv., 0.55 mmol), Cs₂CO₃ (1.5 equiv., 0.75 mmol) in CH₃CN (2 mL) for 7 h under an argon atmosphere. Isolated yields.

(a) Discussion on electron-withdrawing substituents on 2-methylpyridine ring.

For the scope of 2-methylpyridinium ylides, we also tested the 3-bromo-2,6-dimethylpyridinium salt and 4-bromo-2,6-dimethylpyridinium salt, but no expected products were obtained due to the decomposition of pyridinium salts. The 2-methylpyridines with other electron-withdrawing substituents are difficult to prepare and the commercially available ones are also very expensive. From the perspective of synthetic value, we did not make further attempts. It is noteworthy that when we subject isoquinolinium salt under above conditions, **5q-Me** was obtained together with **5q'-Me** and **5q''-Me**.

Scheme S4. Reaction of 2-methylisoquinolinium salt.



^aIsolated yields. The ratio was determined by ¹H NMR analysis.

2-(Difluoromethoxy)pyrrolo[2,1-a]isoquinoline (5q-Me) and Methyl 2-hydroxypyrrolo[2,1-a]isoquinoline-3-carboxylate (5q'-Me). To a 25 mL Schlenk tube was added Cs₂CO₃ (489 mg, 1.5 mmol) and 2-(2-methoxy-2-oxoethyl)-1-methylisoquinolin-2-ium bromide (**4q-Me**) (296 mg, 1.0 mmol) under argon. Then CH₃CN (4 mL) and ethyl bromodifluoroacetate (141 μL, 1.1 mmol) were added subsequently. The resultant mixture was heated to 50 °C (oil bath). After stirring for 7 hrs and monitored by TLC, the reaction was cooled to room

temperature. The reaction mixture was diluted with EtOAc and filtered with a pad of Celite. The filtrate was concentrated, and the residue was purified with silica gel chromatography (Petroleum ether/EtOAc = 30:1) to give the title compounds as light yellow liquid **5q-Me** + **5q'-Me** (151 mg, 64% yield). **5q-Me** ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.54 (d, J = 7.4 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.42 – 7.32 (m, 1H), 7.11 (s, 1H), 6.81 – 6.72 (m, 2H), 6.53 (t, J = 74.7 Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -81.94 (d, J = 74.7 Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{13}\text{H}_{10}\text{F}_2\text{NO}^+ [\text{M} + \text{H}^+]$: 234.0725, found: 234.0729. **5q'-Me** ^1H NMR (400 MHz, CDCl_3) δ 9.22 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.1 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.00 (s, 1H), δ 6.99 (d, J = 2.6 Hz, 1H), 3.94 (s, 3H). HRMS (ESI): m/z calcd. for $\text{C}_{14}\text{H}_{12}\text{NO}_3^+ [\text{M} + \text{H}^+]$: 242.0812, found: 242.0811. Mixture of **5q'-Me** and **5q-Me**. ^{13}C NMR (101 MHz, CDCl_3) δ 161.9, 140.7 (t, J = 3.7 Hz), 135.5, 128.0, 127.9, 127.7, 127.6, 127.4, 127.1, 126.9, 126.8, 126.2, 125.6, 125.2, 124.9, 124.2, 123.2, 122.1, 120.7, 116.4 (t, J = 261.6 Hz), 116.3, 112.7, 111.3, 103.9, 101.2, 91.8, 51.3.

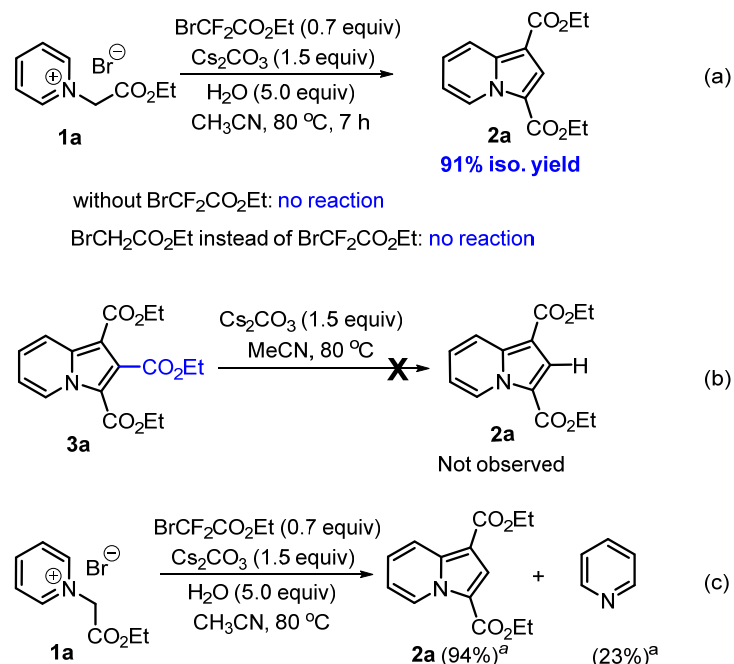
Methyl 2-(difluoromethoxy)pyrrolo[2,1-a]isoquinoline-3-carboxylate (5q''-Me**).**

The title compound was prepared according to the above procedure. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 15:1) to give the title compound as light yellow gum (29 mg, 10% yield). ^1H NMR (400 MHz, CDCl_3) δ 9.21 (d, J = 7.6 Hz, 1H), 8.15 – 7.98 (m, 1H), 7.71 – 7.63 (m, 1H), 7.61 – 7.46 (m, 2H), 7.07 (d, J = 7.6 Hz, 1H), 6.85 (s, 1H), 6.66 (t, J = 74.2 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 161.3, δ 145.6 (t, J = 3.8 Hz), 132.9, 128.3, 128.2, 128.0, 127.2, 124.7, 124.3, 123.3, 116.5 (t, J = 262.0 Hz), 113.1, 101.4, 93.0, 51.5. ^{19}F NMR (376 MHz, CDCl_3) δ -82.81 (d, J = 74.3 Hz, F). HRMS (ESI): m/z calcd. for Chemical Formula: $\text{C}_{15}\text{H}_{12}\text{F}_2\text{NO}_3^+ [\text{M} + \text{H}^+]$: 292.0780, found: 292.0786.

4. Mechanistic studies.

(a) Control experiments for indolizine 2.

Scheme S5. Control experiments for indolizine 2.

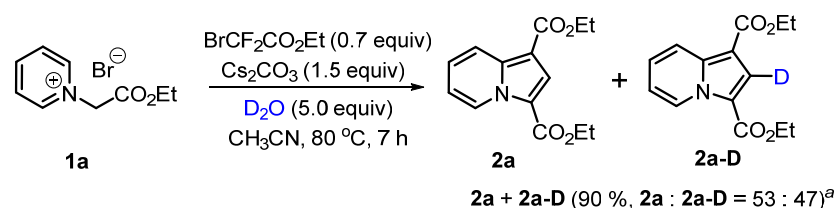


^aYield and ratio were determined by GC analysis with mesitylene as an internal standard.

2a may be derived from decarboxylation of **3a**. So we subject **3a** under the optimized reaction conditions, but without BrCF₂CO₂Et. The results show that no **2a** is formed, which indicates that **2a** is not the decarboxylation product of **3a**, and they are formed through two independent reaction pathways.

For selective synthesis of **2**, the water might serve as proton mediator that promotes the proton transfer from **B** to **C** in Scheme 5, thus improving the regioselectivity and yield of **2**. When D₂O was used instead of H₂O, deuterated product **2a-D** can be obtained (Scheme S6). The hydrogen signal at C2 position is still observed due to the heavy humidity in the lab and the absolute anhydrous reaction conditions is difficult to achieve in the current stage.

Scheme S6. Deuterium experiment.

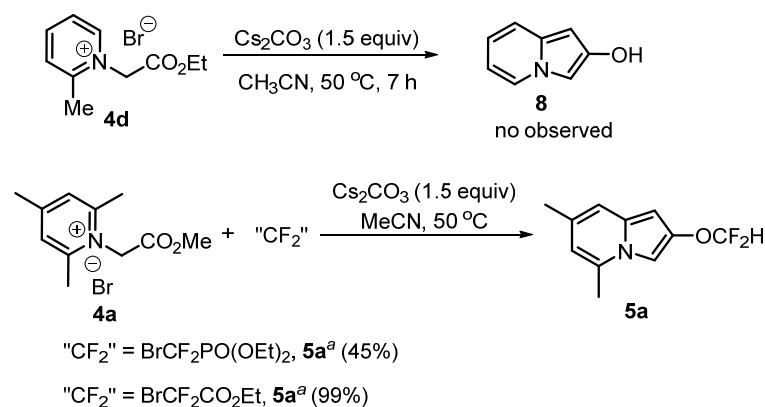


^aIsolated yields. The ratio was determined by ¹H NMR analysis.

Synthesis of Diethyl indolizine-1,3-dicarboxylate (2a-D).^[3] To a 25 mL Schlenk tube was added Cs₂CO₃ (489 mg, 1.5 mmol) and 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (**1a**) (246 mg, 1.0 mmol) under argon. Then CH₃CN (4 mL), ethyl bromodifluoroacetate (90 μ L, 0.7 mmol), and D₂O (92 μ L, 5.0 mmol) were added subsequently. The resultant mixture was heated to 80 °C (oil bath). After stirring for 7 hrs and monitored by TLC, the reaction was cooled to room temperature. The reaction mixture was diluted with EtOAc and filtered with a pad of Celite. The filtrate was concentrated, and the residue was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the desired products **2a** and **2a-D** as off-white solid (118 mg, 90% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.50 (d, J = 7.1 Hz, 1H), 8.31 (d, J = 9.0 Hz, 1H), 7.97 (s, 0.53 H), 7.29 (t, J = 8.0 Hz, 1H), 6.96 (t, J = 6.9 Hz, 1H), 4.40 – 4.30 (m, 4H), 1.49 – 1.32 (m, 6H).

(b) Control experiments for indolizine 5.

Scheme S7. Control experiments for indolizine 5.



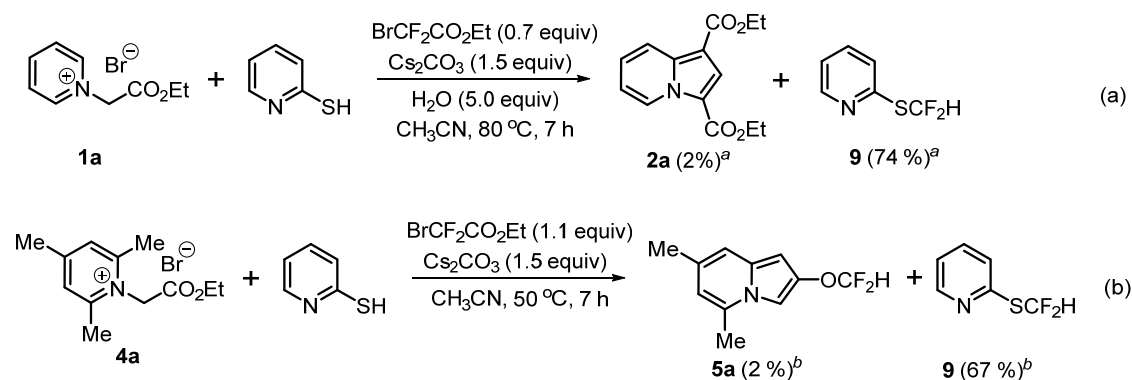
^aIsolated yields.

When the **4d** was treated under the optimized condition in the absence of BrCF₂CO₂Et, no **8** was afforded. When we use BrCF₂PO(OEt)₂ instead of BrCF₂CO₂Et as CF₂ carbene precursor, Chichibabin-like cyclization product **5a** can be isolated in 45% yield, while the isolation yield was 99% when BrCF₂CO₂Et was used.

(c) Carbene trap experiments.

2-Mercaptopyridine, which can trap difluorocarbene as literature reported,^[6] was added under the standard reaction conditions. And it severely inhibited the progress of reactions, with **2a** getting 2% yield and **5a** getting 2% yield (Scheme S1). The 2-((difluoromethyl)thio)pyridine was obtained as a major product. This proved that the reaction proceeds through the difluorocarbene intermediate.

Scheme S8. Carbene trap experiments.



^aYields and ratio were determined by GC analysis with mesitylene as an internal standard. ^bYields and ratio were determined by isolated yields.

2-((Difluoromethyl)thio)pyridine (9).^[6] To a 25 mL Schlenk tube was added Cs₂CO₃ (489 mg, 1.5 mmol), 2-mercaptopyridine (111 mg, 1.0 mmol) and 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide (**4a**) (288 mg, 1.0 mmol) under argon. Then CH₃CN (4 mL) and ethyl bromodifluoroacetate (141 μL, 1.1 mmol) were added subsequently. The resultant mixture was heated to 50 °C (oil bath). After stirring for 7 hrs and monitored by TLC, the reaction was cooled to room temperature. The reaction mixture was diluted with EtOAc and filtered with a pad of Celite. The filtrate was concentrated, and the residue was purified with silica gel chromatography (Petroleum ether/EtOAc = 30:1) to give the desired product **9** as yellow oil (108 mg, 67% yield). ¹H NMR (600 MHz, CDCl₃) δ 8.46 (d, *J* = 4.7 Hz, 1H), 7.69 (t, *J* = 56.3 Hz, 1H), 7.57 (td, *J* = 7.8, 1.8 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.12 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 153.2 (t, *J* = 3.7 Hz), 150.1, 137.2, 124.3 (t, *J* = 2.5 Hz), 121.8, 121.4 (t, *J* = 271.0 Hz). ¹⁹F NMR (564 MHz, CDCl₃) δ -96.19 (d, *J* = 50.9 Hz, 2F).

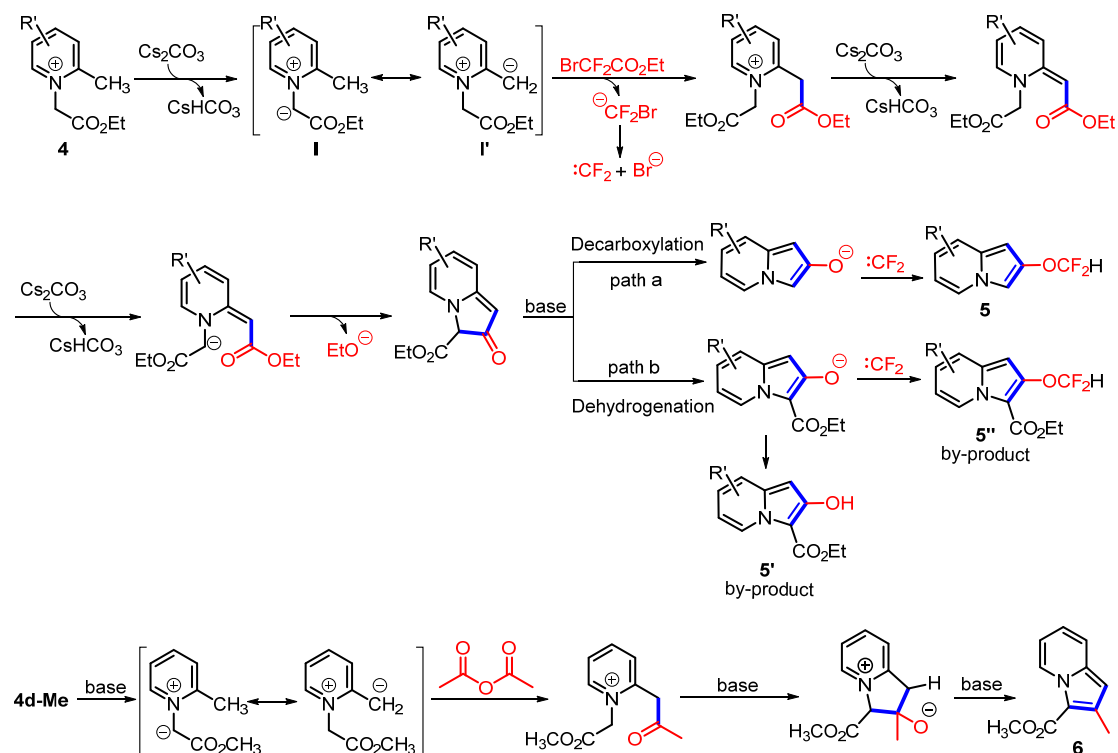
(d) Other possible mechanisms.

According to the Scheme S7, when ethyl bromodifluoroacetate was replaced by the bromodifluorophosphate, the yield of **5a** is halved. When **4q-Me** was subjected to the conditions in Scheme 3, **5q-Me** was obtained together with **5q'-Me** and **5q''-Me**. All of these experiments shed light on the other possible mechanism of this reaction.

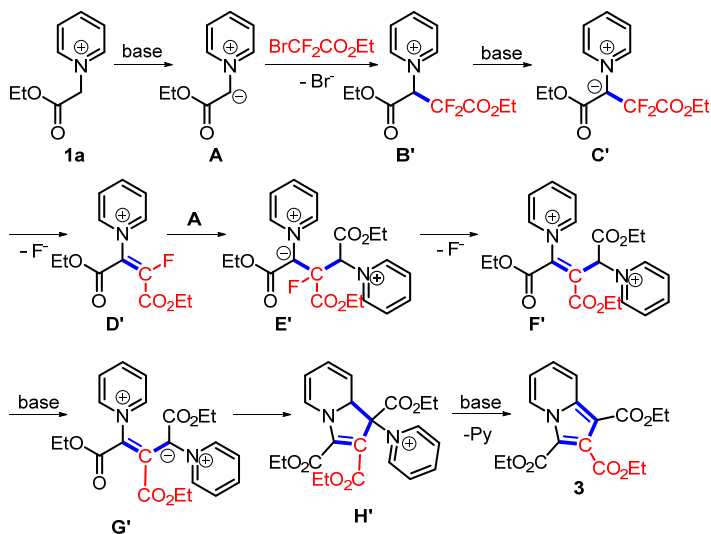
Based on previous reports and the experimental observations, other plausible reaction mechanisms for the synthesis of indolizines derivatives **3** and **5** as well as the byproducts were proposed in Scheme S9. For the formation of **2**, we suspect that the most steric hindered ester of triester **3** might be labile to hydrolysis and decarboxylation to give diester **2** as major product. However, when we treat the byproduct **3a** under basic condition, no **2a** was formed with **3a** being intact (Scheme S5 (b)). Therefore, compound **2a** might be afforded through the route shown in Scheme 5 in manuscript.

Scheme S9. Possible pathways to generate compounds **5**, **5'**, **5''**, **6** and **3**

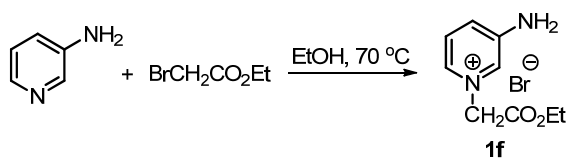
Possible pathways of the formation of **5**, **5'**, **5''**, and **6**



Possible pathways of the formation of by-product **3**

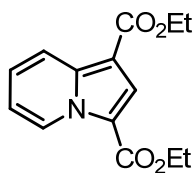


5. Experimental procedure and characterization of **1f**.



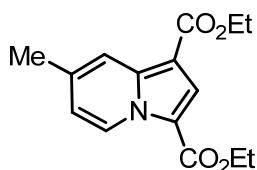
3-Amino-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (1f). To a solution of 3-aminopyridine (188 mg, 2 mmol) in ethanol (1 mL) at room temperature was added ethyl bromoacetate (0.24 mL, 2.2 mmol), and the mixture was heated to 70 °C. After stirring for 12 hrs and monitored by TLC, the reaction was cooled to room temperature. The ethanol was distilled under reduced pressure, and ethyl acetate was added to the residue to precipitate the brown solid **1f** (506 mg, 97% yield). m.p. 147-150 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 8.13 (d, J = 5.7 Hz, 1H), 8.09 (s, 1H), 7.81 – 7.74 (m, 1H), 7.73 – 7.67 (m, 1H), 6.79 (s, 2H), 5.53 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 166.5, 148.4, 132.5, 130.0, 128.1, 127.6, 62.2, 60.2, 14.0. HRMS (ESI): m/z calcd. for $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_2^+$ [$\text{M} - \text{Br}^-$]: 181.0972, found: 181.0968.

6. Representative procedure I and characterization of **2a-2p**, **2a-Me**, and **3a-Me**.



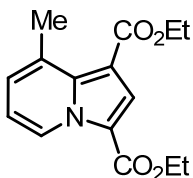
Synthesis of Diethyl indolizine-1,3-dicarboxylate (2a).^[3] *Representative Procedure*

I. To a 25 mL Schlenk tube was added Cs₂CO₃ (489 mg, 1.5 mmol) and 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (**1a**) (246 mg, 1.0 mmol) under air and then evacuated and backfilled with argon (3 times). Then CH₃CN (4 mL), ethyl bromodifluoroacetate (90 μL, 0.7 mmol) and H₂O (90 μL, 5.0 mmol) were added subsequently. The resultant mixture was heated to 80 °C (oil bath). After stirring for 7 hrs and monitored by TLC, the reaction was cooled to room temperature. The reaction mixture was diluted with EtOAc and filtered with a pad of Celite. The filtrate was concentrated, and the residue was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the desired product **2a** as off-white solid (119 mg, 91% yield). When the reaction was run in a 5 mmol (1.24 g of **1a**) scale, the isolated yield was 90% (1.17 g of **2a**). m.p. 128-132 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.41 (d, *J* = 6.9 Hz, 1H), 8.22 (d, *J* = 8.9 Hz, 1H), 7.88 (s, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.86 (t, *J* = 6.8 Hz, 1H), 4.45 – 4.18 (m, 4H), 1.53 – 1.16 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 163.2, 160.2, 138.1, 126.9, 124.6, 123.2, 118.6, 113.8, 113.4, 104.3, 59.3, 59.0, 13.6, 13.6.

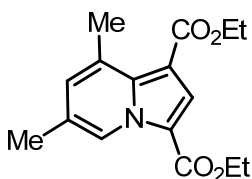


Diethyl 7-methylindolizine-1,3-dicarboxylate (2b).^[3] The title compound was prepared according to *Representative Procedure I* except that 1-(2-ethoxy-2-oxoethyl)-4-methylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as off-white solid (76 mg, 55% yield). m.p. 77-80 °C. ¹H NMR (400 MHz, CDCl₃) δ

9.36 (d, $J = 7.2$ Hz, 1H), 8.10 (s, 1H), 7.92 (s, 1H), 6.83 – 6.75 (m, 1H), 4.42 – 4.30 (m, 4H), 2.43 (s, 3H), 1.44 – 1.35 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.5, 161.3, 139.7, 137.1, 127.4, 124.4, 118.3, 117.0, 114.3, 103.9, 60.3, 59.9, 21.5, 14.7, 14.6. HRMS (ESI): m/z calcd. for $\text{C}_{15}\text{H}_{18}\text{NO}_4^+$ [$\text{M} + \text{H}^+$]: 276.1230, found: 276.1235.

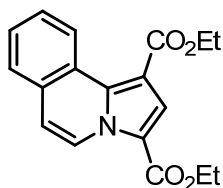


Diethyl 8-methylindolizine-1,3-dicarboxylate (2c).^[3] The title compound was prepared according to *Representative Procedure I* except that 1-(2-ethoxy-2-oxoethyl)-3-methylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as light yellow solid (117 mg, 83% yield). m.p. 70-74 °C. ^1H NMR (400 MHz, CDCl_3) δ 9.46 (d, $J = 7.0$ Hz, 1H), 7.98 (s, 1H), 7.01 (d, $J = 7.0$ Hz, 1H), 6.84 (t, $J = 7.0$ Hz, 1H), 4.42 – 4.25 (m, 4H), 2.76 (s, 1H), 1.44 – 1.37 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.3, 161.2, 138.2, 130.2, 126.8, 126.2, 125.9, 119.0, 114.3, 107.3, 60.3, 22.7, 14.6.

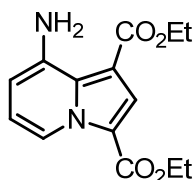


Diethyl 6,8-dimethylindolizine-1,3-dicarboxylate (2d). The title compound was prepared according to *Representative Procedure I* except that 1-(2-ethoxy-2-oxoethyl)-3,5-dimethylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as light yellow viscous oil (64 mg, 44% yield). ^1H NMR (400 MHz, CDCl_3) δ 9.29 (s, 1H), 7.94 (s, 1H), 6.90 (s, 1H), 4.45 – 4.19 (m, 4H), 2.74 (s, 3H), 2.31 (s, 3H), 1.53 – 1.33 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.3, 161.3, 137.0, 130.0, 129.4, 126.0,

124.0, 123.9, 113.7, 106.9, 60.2, 22.0, 18.3, 14.6. HRMS (ESI): m/z calcd. for $C_{16}H_{20}NO_4^+$ $[M + H^+]$: 290.1387, found: 290.1396.

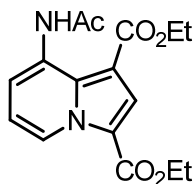


Diethyl pyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (2e)^[4] The title compound was prepared according to *Representative Procedure I* except that 2-(2-ethoxy-2-oxoethyl)isoquinolin-2-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as light yellow solid (77 mg, 49% yield). m.p. 124-127 °C. 1H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, J = 8.1 Hz, 1H), 9.36 (d, J = 7.5 Hz, 1H), 8.02 (s, 1H), 7.73 – 7.67 (m, 1H), 7.67 – 7.53 (m, 2H), 7.15 (d, J = 7.5 Hz, 1H), 4.51 – 4.33 (m, 4H), 1.53 – 1.38 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 161.2, 136.0, 129.8, 128.9, 127.9, 127.8, 126.8, 125.3, 125.1, 124.4, 116.0, 115.0, 109.7, 60.6, 60.6, 14.6, 14.6.

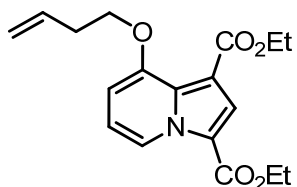


Diethyl 8-aminoindolizine-1,3-dicarboxylate (2f). The title compound was prepared according to *Representative Procedure I* except that 3-amino-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as light yellow solid (79 mg, 57% yield). m.p. 115-119 °C. 1H NMR (600 MHz, $DMSO-d_6$) δ 8.82 (d, J = 6.7 Hz, 1H), 7.76 (s, 1H), 7.01 (s, 2H), 6.95 (t, J = 6.0 Hz, 1H), 6.50 (d, J = 8.4 Hz, 0H), 4.30 (q, J = 6.0, 2H), 4.27 (q, J = 6.0, 2H), 1.32 (t, J = 6.0, 3H), 1.32 (t, J = 6.0, 3H). ^{13}C NMR (151 MHz, $DMSO-d_6$) δ 164.8, 160.1,

140.6, 130.2, 124.3, 117.0, 115.7, 113.9, 105.3, 104.7, 60.4, 60.0, 14.3, 14.2. HRMS (ESI): m/z calcd. for $C_{14}H_{17}N_2O_4^+$ [$M + H^+$]: 277.1183, found: 277.1184.

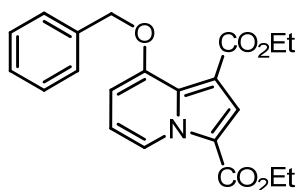


Diethyl 8-acetamidindolizine-1,3-dicarboxylate (2g). The title compound was prepared according to *Representative Procedure I* except that 3-acetamido-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as light yellow solid (87 mg, 55% yield). m.p. 152-157 °C. 1H NMR (400 MHz, $CDCl_3$) δ 12.52 (s, 1H), 9.25 (d, $J = 6.9$ Hz, 1H), 8.50 (d, $J = 7.8$ Hz, 1H), 7.93 (s, 1H), 6.93 (t, $J = 7.4$ Hz, 1H), 4.42 – 4.29 (m, 4H), 2.25 (s, 3H), 1.51 – 1.35 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 166.9, 160.8, 131.9, 131.6, 125.8, 123.0, 115.5, 115.2, 114.1, 104.7, 61.4, 60.6, 25.0, 14.6, 14.5. HRMS (ESI): m/z calcd. for $C_{16}H_{19}N_2O_5^+$ [$M + H^+$]: 319.1288, found: 319.1294.

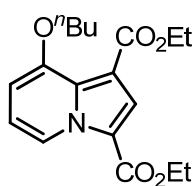


Diethyl 8-(but-3-en-1-yloxy)indolizine-1,3-dicarboxylate (2h). The title compound was prepared according to *Representative Procedure I* except that 3-(but-3-en-1-yloxy)-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as yellow viscous oil (108 mg, 65% yield). 1H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, $J = 6.9$ Hz, 1H), 7.86 (s, 1H), 6.82 (t, $J = 7.3$ Hz, 1H), 6.55 (d, $J = 7.7$ Hz, 1H), 6.05 – 5.89 (m, 1H), 5.24 – 5.16 (m, 1H), 5.14 – 5.07 (m, 1H), 4.43 – 4.29 (m, 4H), 4.14 (t, $J = 6.8$ Hz, 2H), 2.67 (q, $J = 6.8$ Hz, 2H), 1.47 – 1.33 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 161.2, 151.1, 134.4, 130.9, 124.7, 120.9, 117.4, 115.0,

114.1, 107.8, 103.5, 68.5, 60.4, 60.4, 33.5, 14.7, 14.6. HRMS (ESI): m/z calcd. for $C_{18}H_{22}NO_5^+$ [$M + H^+$]: 332.1492, found: 332.1498.

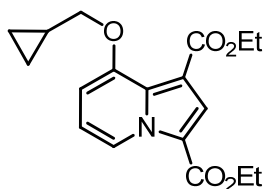


Ethyl 8-(benzyloxy)-1-((ethylperoxy)methyl)indolizine-3-carboxylate (2i). The title compound was prepared according to *Representative Procedure I* except that 3-(benzyloxy)-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as light yellow solid (136 mg, 74% yield). m.p. 97-100 °C. 1H NMR (400 MHz, $CDCl_3$) δ 9.19 (d, J = 6.9 Hz, 1H), 7.89 (s, 1H), 7.51 (t, J = 10.8 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 6.78 (t, J = 7.3 Hz, 1H), 6.59 (d, J = 7.7 Hz, 1H), 5.24 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 161.2, 150.6, 136.3, 130.7, 128.6, 128.1, 127.5, 124.6, 121.1, 115.0, 113.9, 107.9, 104.3, 70.8, 60.5, 60.3, 14.6, 14.4. HRMS (ESI): m/z calcd. for $C_{21}H_{22}NO_5^+$ [$M + H^+$]: 368.1492, found: 368.1500.

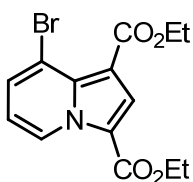


Diethyl 8-butoxyindolizine-1,3-dicarboxylate (2j). The title compound was prepared according to *Representative Procedure I* except that 3-butoxy-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as light yellow solid (130 mg, 78% yield). m.p. 96-98 °C. 1H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, J = 6.9 Hz, 1H), 7.85 (s, 1H), 6.80 (t, J = 8.0 Hz, 1H), 6.53 (d, J = 8.0 Hz,

1H), 4.41 – 4.27 (m, 4H), 4.08 (t, $J = 8.0$ Hz, 2H), 1.94 – 1.81 (m, 2H), 1.60 – 1.47 (m, 2H), 1.44 – 1.32 (m, 6H), 0.98 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.0, 161.2, 151.3, 130.9, 124.5, 120.7, 114.9, 114.1, 107.7, 103.1, 68.7, 60.4, 60.3, 31.1, 19.3, 14.6, 14.6, 13.9. HRMS (ESI): m/z calcd. for $\text{C}_{18}\text{H}_{24}\text{NO}_5^+$ [$\text{M} + \text{H}^+$]: 334.1649, found: 334.1648.

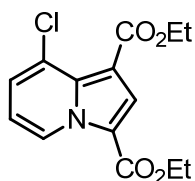


Diethyl 8-(cyclopropylmethoxy)indolizine-1,3-dicarboxylate (2k). The title compound was prepared according to *Representative Procedure I* except that 3-(cyclopropylmethoxy)-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as yellow gum (129 mg, 78% yield). ^1H NMR (400 MHz, CDCl_3) δ 9.18 (d, $J = 6.9$ Hz, 1H), 7.87 (s, 1H), 6.81 (t, $J = 7.2$ Hz, 1H), 6.54 (d, $J = 7.7$ Hz, 1H), 4.57 – 4.31 (m, 4H), 3.97 (d, $J = 6.6$ Hz, 2H), 1.47 – 1.31 (m, 7H), 0.75 – 0.55 (m, 2H), 0.50 – 0.37 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.3, 161.3, 151.1, 131.0, 124.6, 120.9, 114.9, 114.1, 107.9, 104.0, 73.9, 60.5, 60.3, 14.7, 14.6, 10.2, 3.5. HRMS (ESI): m/z calcd. for $\text{C}_{18}\text{H}_{22}\text{NO}_5^+$ [$\text{M} + \text{H}^+$]: 332.1492, found: 332.1491.

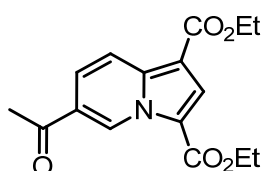


Diethyl 8-bromoindolizine-1,3-dicarboxylate (2l)^[3] The title compound was prepared according to *Representative Procedure I* except that 3-bromo-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as brown viscous oil (84 mg, 49% yield). ^1H NMR (400 MHz, CDCl_3) δ 9.58 (d, $J =$

7.0 Hz, 1H), 7.92 (s, 1H), 7.49 (d, $J = 7.4$ Hz, 1H), 6.78 (t, $J = 7.2$ Hz, 1H), 4.50 – 4.30 (m, 4H), 1.46 – 1.31 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 164.0, 160.9, 134.6, 129.9, 126.9, 125.5, 114.8, 113.9, 112.3, 109.1, 61.0, 60.7, 14.6, 14.5. HRMS (ESI): m/z calcd. for $\text{C}_{14}\text{H}_{15}\text{BrNO}_4^+$ [$\text{M} + \text{H}^+$]: 340.0179, found: 340.0179.

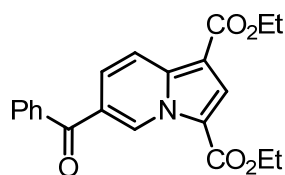


Diethyl 8-chloroindolizine-1,3-dicarboxylate (2m). The title compound was prepared according to *Representative Procedure I* except that 3-chloro-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as brown viscous oil (77 mg, 52% yield). ^1H NMR (400 MHz, CDCl_3) δ 9.52 (d, $J = 8.0$ Hz, 1H), 7.93 (s, 1H), 7.28 (d, $J = 8.0$ Hz, 1H), 6.85 (t, $J = 8.0$ Hz, 1H), 4.44 – 4.30 (m, 4H), 1.43 – 1.33 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.6, 160.8, 134.0, 126.3, 126.0, 125.6, 125.3, 115.0, 113.5, 108.2, 60.7, 60.6, 14.4, 14.4. HRMS (ESI): m/z calcd. for $\text{C}_{14}\text{H}_{15}\text{ClNO}_4^+$ [$\text{M} + \text{H}^+$]: 296.0684, found: 296.0695.

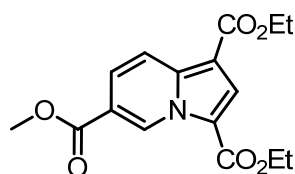


Diethyl 6-acetylindolizine-1,3-dicarboxylate (2n). The title compound was prepared according to *Representative Procedure I* except that 3-acetyl-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as yellow gum (38 mg, 25% yield). ^1H NMR (400 MHz, CDCl_3) δ 10.23 (s, 1H), 8.33 (d, $J = 8.0$ Hz, 1H), 8.05 (s, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 4.47 – 4.26 (m, 4H), 2.67 (s, 3H), 1.48 – 1.37 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 195.1, 163.9, 161.2, 139.5,

131.7, 126.0, 125.4, 123.5, 119.5, 116.2, 106.8, 60.9, 60.4, 26.3, 14.7, 14.6. HRMS (ESI): m/z calcd. for $C_{16}H_{18}NO_5^+$ [$M + H^+$]: 304.1179, found: 304.1182.

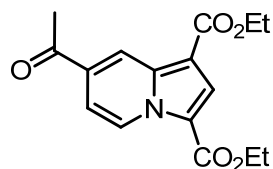


Diethyl 6-benzoylindolizine-1,3-dicarboxylate (2o). The title compound was prepared according to *Representative Procedure I* except that 3-benzoyl-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as yellow gum (37 mg, 20% yield). 1H NMR (600 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.41 (d, $J = 10.2$ Hz, 1H), 8.07 (s, 1H), 7.85 (d, $J = 7.1$ Hz, 2H), 7.82 (d, $J = 9.3$ Hz, 1H), 7.65 (t, $J = 8.0$ Hz, 1H), 7.55 (t, $J = 7.7$ Hz, 2H), 4.41 (q, $J = 7.1$ Hz, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 1.44 (t, $J = 7.1$ Hz, 3H), 1.37 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.6, 164.0, 161.0, 139.3, 137.2, 133.1, 133.0, 129.9, 128.8, 126.0, 125.4, 125.2, 119.6, 116.4, 106.6, 60.8, 60.4, 14.7, 14.5. HRMS (ESI): m/z calcd. for $C_{21}H_{20}NO_5^+$ [$M + H^+$]: 366.1336, found: 366.1338.

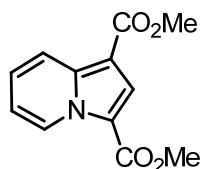


Diethyl 6-benzoylindolizine-1,3-dicarboxylate (2p). The title compound was prepared according to *Representative Procedure I* except that 1-(2-ethoxy-2-oxoethyl)-3-(methoxycarbonyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as yellow gum (27 mg, 17% yield). 1H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.33 (d, $J = 9.4$ Hz, 1H), 8.05 (s, 1H), 7.83 (d, $J = 10.8$ Hz, 1H), 4.48 – 4.34 (m, 4H), 3.97 (s, 3H), 1.49 – 1.38 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4,

163.9, 161.0, 139.5, 131.8, 125.8, 124.9, 119.2, 118.3, 116.0, 106.4, 60.8, 60.4, 52.6, 14.6, 14.6. HRMS (ESI): m/z calcd. for $C_{16}H_{18}NO_6^+$ $[M + H^+]$: 320.1129, found: 320.1137.

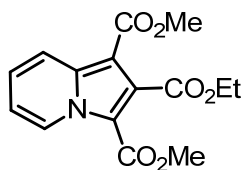


Diethyl 7-acetyllindolizine-1,3-dicarboxylate (2q).^[3] The title compound was prepared according to *Representative Procedure I* except that 4-acetyl-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as yellow gum (~1.0 mg, <5% yield). 1H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, J = 7.4 Hz, 1H), 8.94 (s, 1H), 8.03 (s, 1H), 7.52 (dd, J = 7.4, 2.0 Hz, 1H), 4.46 – 4.37 (m, 4H), 2.70 (s, 3H), 1.46 – 1.39 (m, 6H). The 1H NMR spectrum is consistent with literature.^[3]



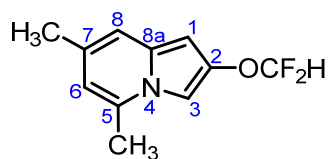
Dimethyl indolizine-1,3-dicarboxylate (2a-Me).^[5] The title compound was prepared according to *Representative Procedure I* except that 1-(2-methoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide and without H_2O . The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give the title compound as white solid (20 mg, 17% yield). m.p. 187-190 °C. 1H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, J = 7.1 Hz, 1H), 8.32 (d, J = 9.0 Hz, 1H), 7.97 (s, 1H), 7.31 (t, J = 8.0 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H). ^{13}C NMR

(101 MHz, CDCl₃) δ 164.7, 161.7, 139.2, 128.0, 125.8, 124.5, 119.7, 114.6, 114.6, 105.1, 51.5, 51.3.



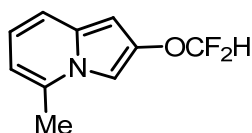
2-Ethyl 1,3-dimethyl indolizine-1,2,3-tricarboxylate (3a-Me). The title compound was prepared according to *Representative Procedure I* except that 1-(2-methoxy-2-oxoethyl)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide and without H₂O. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 5:1) to give the title compound as light yellow gum (17 mg, 11% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.53 (d, *J* = 7.1 Hz, 1H), 8.35 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 165.9, 163.5, 160.7, 138.1, 131.0, 128.1, 126.9, 120.1, 115.6, 111.9, 103.1, 62.0, 51.9, 51.6, 14.4. HRMS (ESI): *m/z* calcd. for Chemical Formula: C₁₅H₁₅NNaO₆⁺ [*M* + Na⁺]: 328.0792, found: 328.0799.7.

7. Representative procedure II and characterization of 5a-5p, 6 and 7.

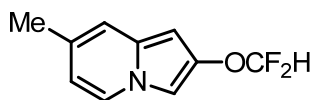


2-(Difluoromethoxy)-5,7-dimethylindolizine (5a). *Representative Procedure II.* To a 25 mL Schlenk tube was added Cs₂CO₃ (489 mg, 1.5 mmol) and 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide (**4a**) (288 mg, 1.0 mmol) under air and then evacuated and backfilled with argon (3 times). Then CH₃CN (4 mL) and ethyl bromodifluoroacetate (141 μ L, 1.1 mmol) were added subsequently. The resultant mixture was heated to 50 °C (oil bath). After stirring for 7

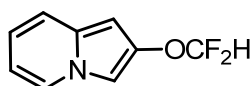
hrs and monitored by TLC, the reaction was cooled to room temperature. The reaction mixture was diluted with EtOAc and filtered with a pad of Celite. The filtrate was concentrated, and the residue was purified with silica gel chromatography (Petroleum ether/EtOAc = 20:1) to give the desired product **5a** as light brown oil (209 mg, 99% yield). When the reaction was run in a 4 mmol (1.15 g of **4a**) scale, the isolated yield was 92% (778 mg of **5a**). ^1H NMR (400 MHz, CDCl_3) δ 6.83 (s, 1H, H8), 6.79 (s, 1H, H3), 6.37 (t, $J = 76.0$ Hz, 1H, CF₂H), 6.09 (s, 1H, H6), 6.02 (s, 1H, H1), 2.23 (s, 3H, 5-CH₃), 2.11 (s, 3H, 7-CH₃). ^{13}C NMR (101 MHz, CDCl_3) δ 142.6 (t, $J = 3.5$ Hz, C2), 132.5 (C5), 131.9 (C8a), 128.9 (C7), 116.6 (t, $J = 260.6$ Hz, (CF₂H)), 114.6 (C8), 112.8 (C6), 97.6 (C3), 89.0 (C1), 21.0 (7-CH₃), 18.4 (5-CH₃). ^{19}F NMR (564 MHz, CDCl_3) δ -81.59 (d, $J = 73.5$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{11}\text{H}_{12}\text{F}_2\text{NO}^+$ [$\text{M} + \text{H}^+$]: 212.0881, found: 212.0888.



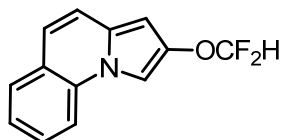
2-(Difluoromethoxy)-5-methylindolizine (5b). The title compound was prepared according to *Representative Procedure II* except that 1-(2-ethoxy-2-oxoethyl)-2,6-dimethylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as yellow oil (191 mg, 97% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.29 (d, $J = 8.9$ Hz, 1H), 7.08 (s, 1H), 6.85 - 6.79 (m, 1H), 6.58 (t, $J = 76.0$ Hz, 1H), 6.46 (d, $J = 6.7$ Hz, 1H), 6.36 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 142.4 (t, $J = 3.0$ Hz), 133.0, 131.6, 116.5 (t, $J = 261.6$ Hz), 118.7, 116.4, 110.1, 98.7, 90.5, 18.8. ^{19}F NMR (564 MHz, CDCl_3) δ -81.77 (d, $J = 75.3$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{10}\text{H}_{10}\text{F}_2\text{NO}^+$ [$\text{M} + \text{H}^+$]: 198.0725, found: 198.0727.



2-(Difluoromethoxy)-7-methylindolizine (5c). The title compound was prepared according to *Representative Procedure II* except that 1-(2-ethoxy-2-oxoethyl)-2,4-dimethylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as yellow oil (120 mg, 61% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, $J = 7.0$ Hz, 1H), 7.08 (s, 1H), 7.03 (s, 1H), 6.51 (t, $J = 72.0$ Hz, 1H), 6.34 (d, $J = 8.5$ Hz, 1H), 6.10 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 142.3 (t, $J = 3.5$ Hz), 131.2, 128.5, 124.8, 116.8, 116.5 (t, $J = 261.6$ Hz), 113.4, 100.6, 88.5, 21.1. ^{19}F NMR (376 MHz, CDCl_3) δ -81.91 (d, $J = 74.9$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{10}\text{H}_{10}\text{F}_2\text{NO}^+ [\text{M} + \text{H}^+]$: 198.0725, found: 198.0732.

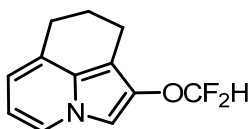


2-(Difluoromethoxy)indolizine (5d). The title compound was prepared according to *Representative Procedure II* except that 1-(2-ethoxy-2-oxoethyl)-2-methylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as light yellow oil (82 mg, 45% yield). ^1H NMR (600 MHz, CDCl_3) δ 7.82 (d, $J = 7.9$ Hz, 1H), 7.28 (d, $J = 9.0$ Hz, 1H), 7.17 (s, 1H), 6.73 (t, $J = 8.0$ Hz, 1H), 6.51 (t, $J = 6.8$ Hz, 1H), 6.50 (t, $J = 74.7$ Hz, 1H), 6.23 (s, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 142.1 (t, $J = 3.0$ Hz), 130.9, 125.3, 118.7, 118.2, 116.3 (t, $J = 259.7$ Hz), 110.8, 101.6, 90.0. ^{19}F NMR (376 MHz, CDCl_3) δ -82.10 (d, $J = 74.8$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_9\text{H}_8\text{F}_2\text{NO}^+ [\text{M} + \text{H}^+]$: 184.0568, found: 184.0576.

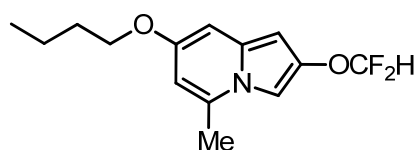


2-(Difluoromethoxy)pyrrolo[1,2-a]quinoline (5e). The title compound was prepared according to *Representative Procedure II* except that

1-(2-ethoxy-2-oxoethyl)-2-methylquinolin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as light yellow oil (149 mg, 64% yield). ^1H NMR (600 MHz, CDCl_3) δ 7.76 (d, J = 8.4 Hz, 1H), 7.66 (s, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.51 (t, J = 7.1 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 9.3 Hz, 1H), 7.07 (d, J = 9.3 Hz, 1H), 6.53 (t, J = 74.6 Hz, 1H), 6.35 (s, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 141.4 (t, J = 3.7 Hz), 133.0, 129.1, 129.0, 128.2, 123.8, 123.6, 120.2, 118.3, 116.4 (t, J = 261.6 Hz), 114.1, 101.2, 94.4. ^{19}F NMR (376 MHz, CDCl_3) δ -81.97 (d, J = 74.7 Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{13}\text{H}_{10}\text{F}_2\text{NO}^+$ [$\text{M} + \text{H}^+$]: 234.0725, found: 234.0735.

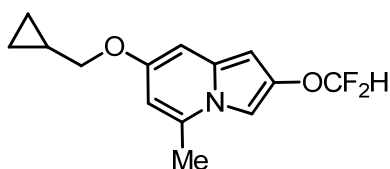


1-(Difluoromethoxy)-8,9-dihydro-7H-pyrrolo[3,2,1-ij]quinoline (5f). The title compound was prepared according to *Representative Procedure II* except that 1-(2-ethoxy-2-oxoethyl)-5,6,7,8-tetrahydroquinolin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as light yellow oil (221 mg, 99% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, J = 6.9 Hz, 1H), 7.08 (s, 1H), 6.49 (t, J = 76.0 Hz, 1H), 6.42 (t, J = 6.7 Hz, 1H), 6.33 (d, J = 6.5 Hz, 1H), 2.89 – 2.75 (m, 4H), 2.30 – 1.69 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 138.17 (t, J = 3.0 Hz), 130.1, 129.0, 121.9, 116.5 (t, J = 260.4 Hz), 111.5, 111.4, 101.1, 101.0, 27.8, 23.2, 20.7. ^{19}F NMR (376 MHz, CDCl_3) δ -81.23 (d, J = 75.0 Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{12}\text{H}_{12}\text{F}_2\text{NO}^+$ [$\text{M} + \text{H}^+$]: 224.0881, found: 224.0886.

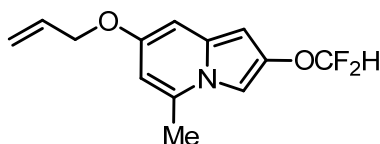


7-Butoxy-2-(difluoromethoxy)-5-methylindolizine (5g). The title compound was prepared according to *Representative Procedure II* except that

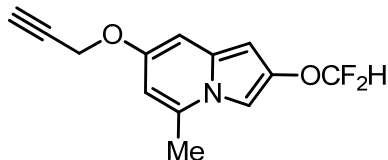
4-butoxy-1-(2-ethoxy-2-oxoethyl)-2,6-dimethylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as yellow oil (189 mg, 70% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.88 (s, 1H), 6.54 (d, $J = 76.0$ Hz, 1H), 6.53 (d, $J = 2.1$ Hz, 1H), 6.21 (d, $J = 1.3$ Hz, 1H), 6.13 (s, 1H), 3.94 (t, $J = 6.5$ Hz, 2H), 2.40 (s, 3H), 1.94 – 1.67 (m, 2H), 1.66 – 1.37 (m, 2H), 1.04 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 152.8, 142.8 (t, $J = 3.6$ Hz), 134.6, 132.4, 116.6 (t, $J = 259.5$ Hz), 105.3, 96.5, 94.0, 88.7, 67.6, 31.2, 19.4, 18.4, 13.9. ^{19}F NMR (376 MHz, CDCl_3) δ -81.63 (d, $J = 75.1$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{14}\text{H}_{18}\text{F}_2\text{NO}_2^+$ [$\text{M} + \text{H}^+$]: 270.1300, found: 270.1305.



7-(Cyclopropylmethoxy)-2-(difluoromethoxy)-5-methylindolizine (5h). The title compound was prepared according to *Representative Procedure II* except that 4-(cyclopropylmethoxy)-1-(2-ethoxy-2-oxoethyl)-2,6-dimethylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as yellow oil (166 mg, 62% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.86 (s, 1H), 6.51 (t, $J = 76.0$ Hz, 1H), 6.48 (d, $J = 2.2$ Hz, 1H), 6.23 (d, $J = 1.4$ Hz, 1H), 6.09 (s, 1H), 3.77 (d, $J = 6.9$ Hz, 2H), 2.40 (s, 3H), 1.35 – 1.21 (m, 1H), 0.80 – 0.52 (m, 2H), 0.43 – 0.32 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 152.6, 142.7 (t, $J = 3.6$ Hz), 134.6, 132.2, 116.5 (t, $J = 259.6$ Hz), 105.3, 96.6, 94.1, 88.7, 72.6, 18.5, 10.1, 3.3. ^{19}F NMR (376 MHz, CDCl_3) δ -81.70 (d, $J = 75.1$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_2\text{NO}_2^+$ [$\text{M} + \text{H}^+$]: 268.1144, found: 268.1150.

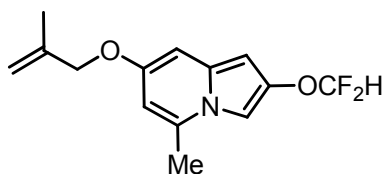


7-(Allyloxy)-2-(difluoromethoxy)-5-methylindolizine (5i). The title compound was prepared according to *Representative Procedure II* except that 4-(allyloxy)-1-(2-ethoxy-2-oxoethyl)-2,6-dimethylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as yellow oil (162 mg, 64% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.88 (s, 1H), 6.52 (s, 1H), 6.51 (t, $J = 76.0$ Hz, 1H), 6.23 (s, 1H), 6.12 (s, 1H), 6.11 – 6.00 (m, 1H), 5.50 – 5.38 (m, 1H), 5.35 – 5.27 (m, 1H), 4.50 (d, $J = 5.3$ Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 152.1, 142.8 (t, $J = 3.7$ Hz), 134.7, 133.0, 132.1, 117.9, 116.5 (t, $J = 260.6$ Hz), 105.2, 96.8, 94.6, 89.0, 68.7, 18.6. ^{19}F NMR (376 MHz, CDCl_3) δ -81.75 (d, $J = 75.0$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{13}\text{H}_{14}\text{F}_2\text{NO}_2^+ [\text{M} + \text{H}^+]$: 254.0987, found: 254.0995.

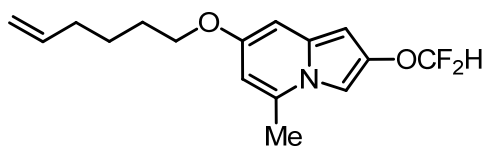


2-(Difluoromethoxy)-5-methyl-7-(prop-2-yn-1-yloxy)indolizine (5j). The title compound was prepared according to *Representative Procedure II* except that 1-(2-ethoxy-2-oxoethyl)-2,6-dimethyl-4-(prop-2-yn-1-yloxy)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as yellow oil (176 mg, 70% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.89 (d, $J = 0.6$ Hz, 1H), 6.63 (d, $J = 2.3$ Hz, 1H), 6.53 (t, $J = 76.0$ Hz, 1H), 6.21 (d, $J = 2.3$ Hz, 1H), 6.16 (s, 1H), 4.65 (d, $J = 2.4$ Hz, 2H), 2.57 (t, $J = 2.4$ Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 151.0, 142.7 (t, $J = 3.6$ Hz), 134.9, 131.7, 116.4 (t, $J = 259.9$ Hz), 104.8, 97.0, 95.1, 89.4, 78.3, 75.9, 55.7,

18.5. ^{19}F NMR (376 MHz, CDCl_3) δ -81.78 (d, J = 74.9 Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{13}\text{H}_{12}\text{F}_2\text{NO}_2^+$ [$\text{M} + \text{H}^+$]: 252.0831, found: 252.0835.

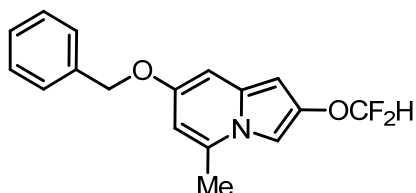


2-(Difluoromethoxy)-5-methyl-7-((2-methylallyl)oxy)indolizine (5k). The title compound was prepared according to *Representative Procedure II* except that 1-(2-ethoxy-2-oxoethyl)-2,6-dimethyl-4-((2-methylallyl)oxy)pyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as light yellow oil (198 mg, 74% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.90 (s, 1H), 6.55 (s, 1H), 6.55 (t, J = 76.0 Hz, 1H), 6.26 (d, J = 1.4 Hz, 1H), 6.15 (s, 1H), 5.16 (s, 1H), 5.06 (s, 1H), 4.43 (s, 2H), 2.41 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 152.3, 142.8 (t, J = 3.5 Hz), 140.6, 134.6, 132.1, 116.5 (t, J = 259.6 Hz), 112.8, 105.2, 96.6, 94.6, 88.9, 71.5, 19.4, 18.4. ^{19}F NMR (376 MHz, CDCl_3) δ -81.62 (d, J = 75.1 Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_2\text{NO}_2^+$ [$\text{M} + \text{H}^+$]: 268.1144, found: 268.1150.

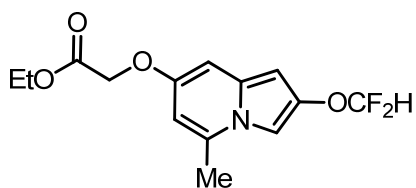


2-(Difluoromethoxy)-7-(hex-5-en-1-yloxy)-5-methylindolizine (4l). The title compound was prepared according to *Representative Procedure II* except that 1-(2-ethoxy-2-oxoethyl)-4-(hex-5-en-1-yloxy)-2,6-dimethylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as yellow oil (207 mg, 70% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.88 (s, 1H), 6.54 (t, J = 75.2 Hz, 1H), 6.52 (d, J = 1.9 Hz, 1H), 6.21 (s, 1H), 6.12 (s, 1H), 5.88 (m, 1H), 5.15 – 5.05 (m, 1H), 5.03 (d, J = 10.2 Hz, 1H), 3.94 (t, J = 6.4 Hz, 2H), 2.41 (s, 3H), 2.17 (q, J = 7.2 Hz, 2H), 1.87 – 1.80

(m, 2H), 1.64 – 1.57 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 152.7, 142.8 (t, $J = 3.6$ Hz), 138.6, 134.6, 132.3, 116.5 (t, $J = 260.6$ Hz), 114.9, 105.2, 96.5, 94.0, 88.7, 67.6, 33.5, 28.6, 25.4, 18.5. ^{19}F NMR (376 MHz, CDCl_3) δ -81.64 (d, $J = 75.1$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{16}\text{H}_{20}\text{F}_2\text{NO}_2^+$ [$\text{M} + \text{H}^+$]: 296.1457, found: 296.1469.

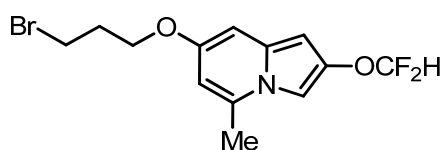


7-(Benzyloxy)-2-(difluoromethoxy)-5-methylindolizine (5m). The title compound was prepared according to *Representative Procedure II* except that 4-(benzyloxy)-1-(2-ethoxy-2-oxoethyl)-2,6-dimethylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as yellow oil (197 mg, 65% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.50-7.35 (m, 5H), 6.90 (s, 1H), 6.62 (d, $J = 2.1$ Hz, 1H), 6.53 (t, $J = 76.0$ Hz, 1H), 6.30 (d, $J = 1.3$ Hz, 1H), 6.14 (s, 1H), 5.04 (s, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 152.3, 142.8 (t, $J = 3.6$ Hz), 136.7, 134.8, 132.1, 128.7, 128.2, 127.6, 116.5 (t, $J = 259.8$ Hz), 105.3, 96.8, 94.8, 89.1, 69.9, 18.6. ^{19}F NMR (376 MHz, CDCl_3) δ -81.72 (d, $J = 75.0$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{17}\text{H}_{16}\text{F}_2\text{NO}_2^+$ [$\text{M} + \text{H}^+$]: 304.1144, found: 304.1149.

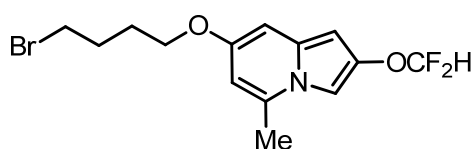


Ethyl 2-((2-(difluoromethoxy)-5-methylindolizin-7-yl)oxy)acetate (5n). The title compound was prepared according to *Representative Procedure II* except that 4-(2-ethoxy-2-oxoethoxy)-1-(2-ethoxy-2-oxoethyl)-2,6-dimethylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as light yellow oil (221

mg, 74% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.85 (s, 1H), 6.51 (t, $J = 76.0$ Hz, 1H), 6.42 (d, $J = 2.3$ Hz, 1H), 6.24 (d, $J = 1.5$ Hz, 1H), 6.09 (s, 1H), 4.54 (s, 2H), 4.26 (q, $J = 7.1$ Hz, 2H), 2.35 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 168.5, 151.3, 142.7 (t, $J = 3.5$ Hz), 134.9, 131.5, 116.4 (t, $J = 259.7$ Hz), 104.6, 96.9, 94.5, 89.3, 65.0, 61.4, 18.3, 14.0. ^{19}F NMR (376 MHz, CDCl_3) δ -81.87 (d, $J = 75.0$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_2\text{NO}_4^+$ [$\text{M} + \text{H}^+$]: 300.1042, found: 300.1046.

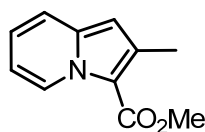


7-(3-Bromopropoxy)-2-(difluoromethoxy)-5-methylindolizine (5o). The title compound was prepared according to *Representative Procedure II* except that 4-(3-bromopropoxy)-1-(2-ethoxy-2-oxoethyl)-2,6-dimethylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum ether/EtOAc = 20:1) to give the title compound as yellow oil (190 mg, 57% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.88 (s, 1H), 6.54 (s, 1H), 6.51 (t, $J = 76.0$ Hz, 1H), 6.19 (s, 1H), 6.12 (s, 1H), 4.07 (t, $J = 5.8$ Hz, 2H), 3.60 (t, $J = 6.4$ Hz, 2H), 2.42 (s, 3H), 2.37 – 2.26 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 152.3, 142.8 (t, $J = 3.3$ Hz), 134.8, 132.1, 116.5 (t, $J = 259.9$ Hz), 105.0, 96.8, 94.3, 89.1, 65.3, 32.2, 30.0, 18.6. ^{19}F NMR (376 MHz, CDCl_3) δ -81.78 (d, $J = 75.0$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{13}\text{H}_{15}\text{BrF}_2\text{NO}_2^+$ [$\text{M} + \text{H}^+$]: 334.0249, found: 334.0258.

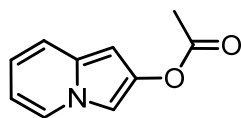


7-(4-Bromobutoxy)-2-(difluoromethoxy)-5-methylindolizine (5p). The title compound was prepared according to *Representative Procedure II* except that 4-(4-bromobutoxy)-1-(2-ethoxy-2-oxoethyl)-2,6-dimethylpyridin-1-ium bromide was used instead of 1-(2-ethoxy-2-oxoethyl)-2,4,6-trimethylpyridin-1-ium bromide. The crude product was purified by silica gel column chromatography (Petroleum

ether/EtOAc = 20:1) to give the title compound as yellow oil (164 mg, 47% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.87 (s, 1H), 6.51 (t, $J = 76.0$ Hz, 1H), 6.50 (s, 1H), 6.18 (s, 1H), 6.11 (s, 1H), 3.96 (t, $J = 6.0$ Hz, 2H), 3.49 (t, $J = 6.6$ Hz, 2H), 2.41 (s, 3H), 2.07 (m, 2H), 1.95 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 152.4, 142.7 (t, $J = 3.5$ Hz), 134.7, 132.2, 116.5 (t, $J = 259.8$ Hz), 105.1, 96.7, 94.1, 89.0, 66.8, 33.5, 29.6, 27.8, 18.6. ^{19}F NMR (376 MHz, CDCl_3) δ -81.75 (d, $J = 75.0$ Hz, 2F). HRMS (ESI): m/z calcd. for $\text{C}_{14}\text{H}_{17}\text{BrF}_2\text{NO}_2^+ [\text{M} + \text{H}^+]$: 348.0405, found: 348.0413.



Ethyl 2-methylindolizine-3-carboxylate (6)^[8]. To a 25 mL Schlenk tube was added Cs_2CO_3 (489 mg, 1.5 mmol) and 1-(2-methoxy-2-oxoethyl)-2-methylpyridin-1-ium bromide (**4d-Me**) (246 mg, 1.0 mmol) under argon. Then CH_3CN (4 mL) and acetic anhydride (105 μL , 1.1 mmol) were added subsequently. The resultant mixture was heated to 50 $^\circ\text{C}$ (oil bath). After stirring for 7 hrs and monitored by TLC, the reaction was cooled to room temperature. The reaction mixture was diluted with EtOAc and filtered with a pad of Celite. The filtrate was concentrated, and the residue was purified with silica gel chromatography (Petroleum ether/EtOAc = 30:1) to give the desired product **6** as yellow oil (64 mg, 34% yield). ^1H NMR (400 MHz, CDCl_3) δ 9.44 (d, $J = 7.2$ Hz, 1H), 7.36 (d, $J = 8.8$ Hz, 1H), 7.97 (t, $J = 7.8$ Hz, 1H), 6.72 (t, $J = 6.9$ Hz, 1H), 6.31 (s, 1H), 3.92 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.9, 137.3, 134.8, 127.8, 122.0, 117.8, 112.1, 112.0, 103.7, 50.8, 15.2.



Indolizin-2-yl acetate (7). According to the above steps, except that 80 $^\circ\text{C}$ was used instead of 50 $^\circ\text{C}$. The crude product was purified with silica gel chromatography (Petroleum ether/EtOAc = 30:1) to give the title compound as brown oil (89 mg, 51% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, $J = 6.9$ Hz, 1H), 7.45 (s, 1H), 7.30 (d, $J = 9.0$ Hz, 1H), 6.71 (t, $J = 8.3$ Hz, 1H), 6.49 (t, $J = 6.8$ Hz, 1H), 6.30 (s, 1H), 2.32 (s,

3H). ^{13}C NMR (101 MHz, CDCl_3) δ 168.6, 141.4, 130.1, 125.3, 118.7, 117.8, 110.4, 102.8, 90.6, 21.2. HRMS (ESI): m/z calcd. for $\text{C}_{10}\text{H}_{10}\text{NO}_2^+$ [$\text{M} + \text{H}^+$]: 176.0706, found: 176.0706.

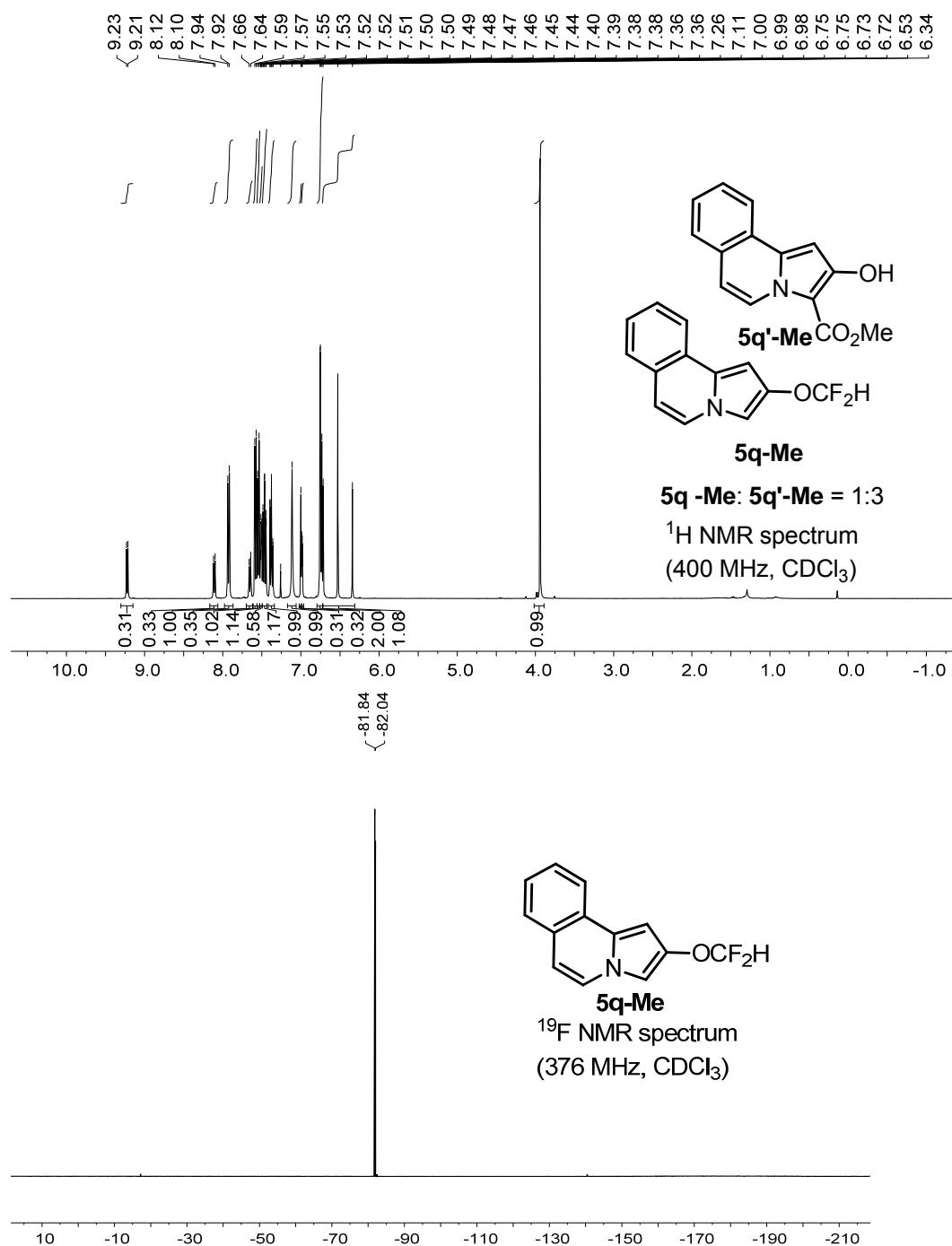
8. References.

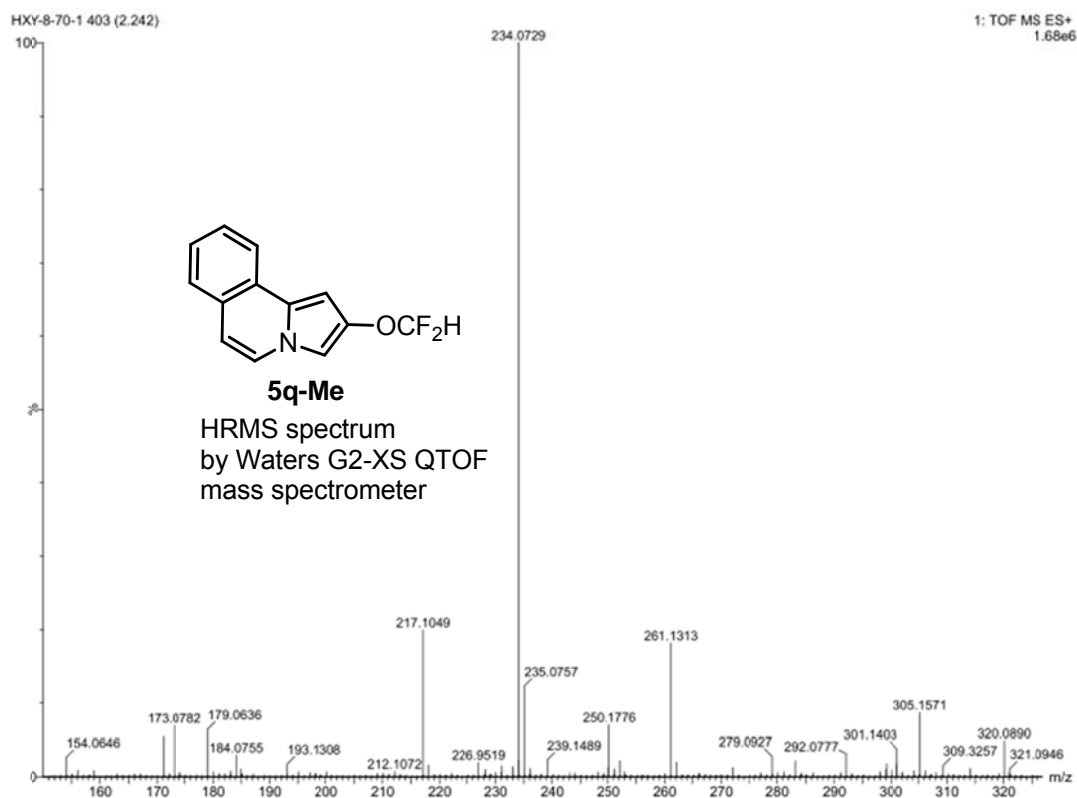
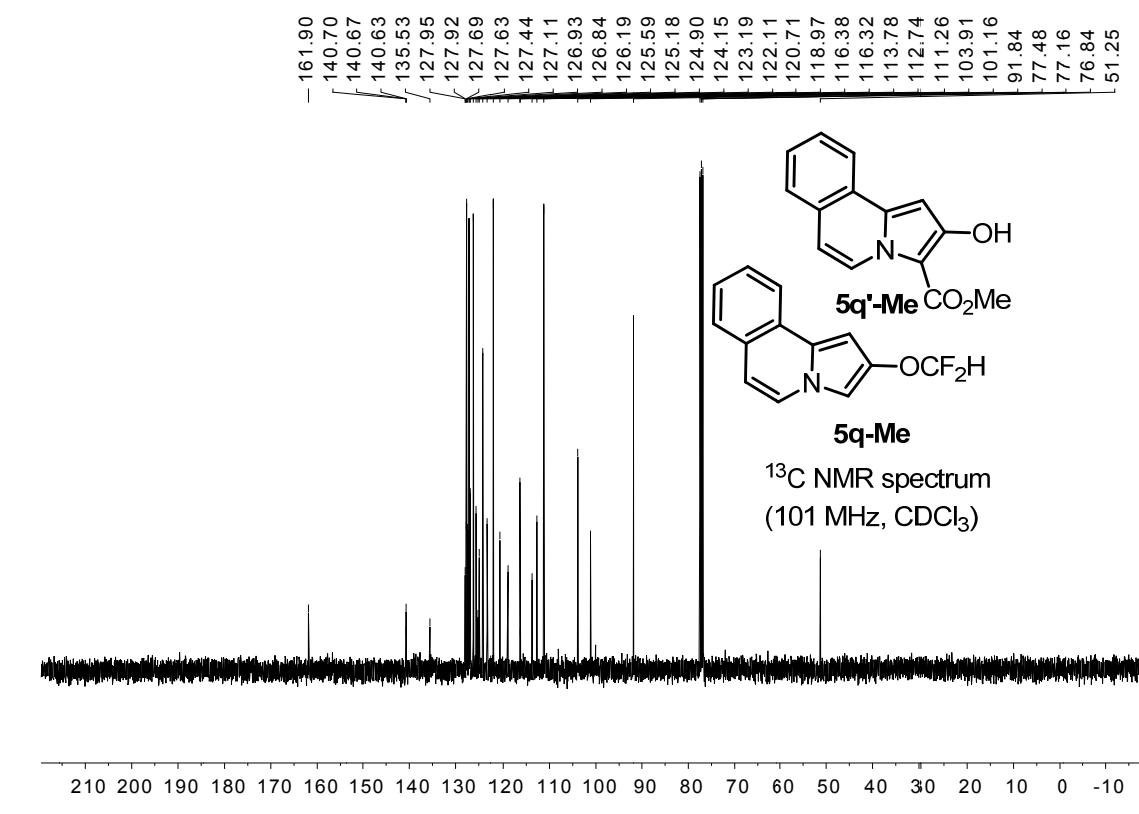
- [1] Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teplý, F.; Meghani, P.; Kočovský, P. Synthesis of New Chiral 2,2'-Bipyridine Ligands and Their Application in Copper-Catalyzed Asymmetric Allylic Oxidation and Cyclopropanation. *J. Org. Chem.* **2003**, *68*, 4727-4742.
- [2] Ezquerra, J.; Alvarez-Builla, J. 2-Methylpyridinium ylide as 1,4-Dinucleophiles. II. Westphal Condensation with Substituted Pyridinium Substrates. *J. Heterocyclic Chem.* **1986**, *23*, 1151-1157.
- [3] Douglas, T.; Pordea, A.; Dowden, J. Iron-Catalyzed Indolizine Synthesis from Pyridines, Diazo Compounds, and Alkynes. *Org. Lett.* **2017**, *19*, 6396-6399.
- [4] Zhang, X.; Lu, G. P.; Xu, Z. B.; Cai, C. Facile Synthesis of Indolizines via 1,3-Dipolar Cycloadditions in [Omim]Br: The Promotion of the Reaction through Noncovalent Interactions. *ACS Sustainable Chem. Eng.* **2017**, *5*, 9279-9285.
- [5] Yue, G.; Wan, Y.; Song, S.; Yang, G.; Chen, Z. Synthesis of a Library of Benzoindolizines Using Poly(ethylene glycol) as Soluble Support. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 453-458.
- [6] Heine, N. B.; Studer, A. Radical Difluoromethylation of Thiols with (Difluoromethyl)triphenylphosphonium Bromide. *Org. Lett.* **2017**, *19*, 4150-4153.
- [7] (a) Kakehi, A.; Ito, S.; Watanabe, K.; Kitagawa, M.; Takeuchi, S.; Hashimoto, T. Preparation of New Nitrogen-Bridged Heterocycles. Synthesis and Some Reactions of 2,3-Dihydroindolizin-2-one Derivatives. *J. Org. Chem.* **1980**, *45*, 5100-5104. (b) Kostik, E. I.; Abiko, A.; Oku, A. Chichibabin Indolizine Synthesis Revisited: Synthesis of Indolizinones by Solvolysis of 4-Alkoxy carbonyl-3-oxotetrahydroquinolizinium Ylides. *J. Org. Chem.* **2001**, *66*, 2618-2623.
- [8] Ceder, O.; Sharif, M. R. The Reaction of Indolizines with Esters of Orthoformic Acid: Synthesis of Tris-indolizine Molecular Propellers. *Chem. Ber.* **1987**, *120*, 239-242.

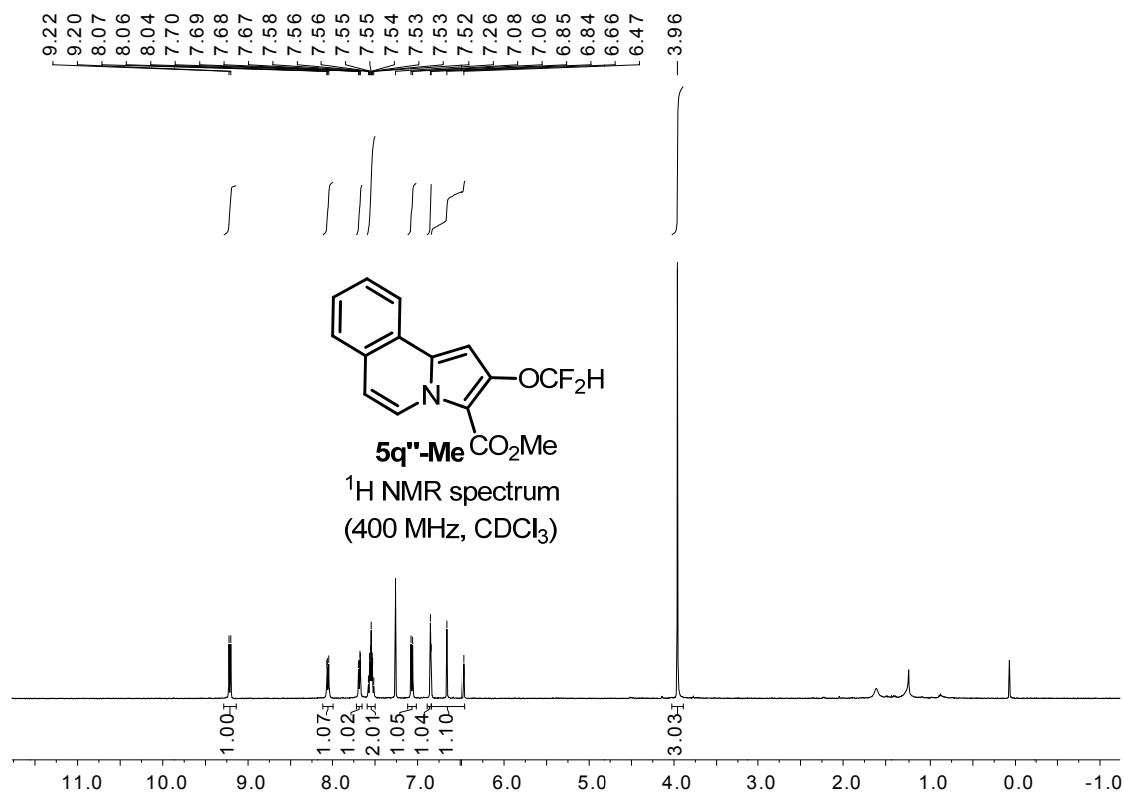
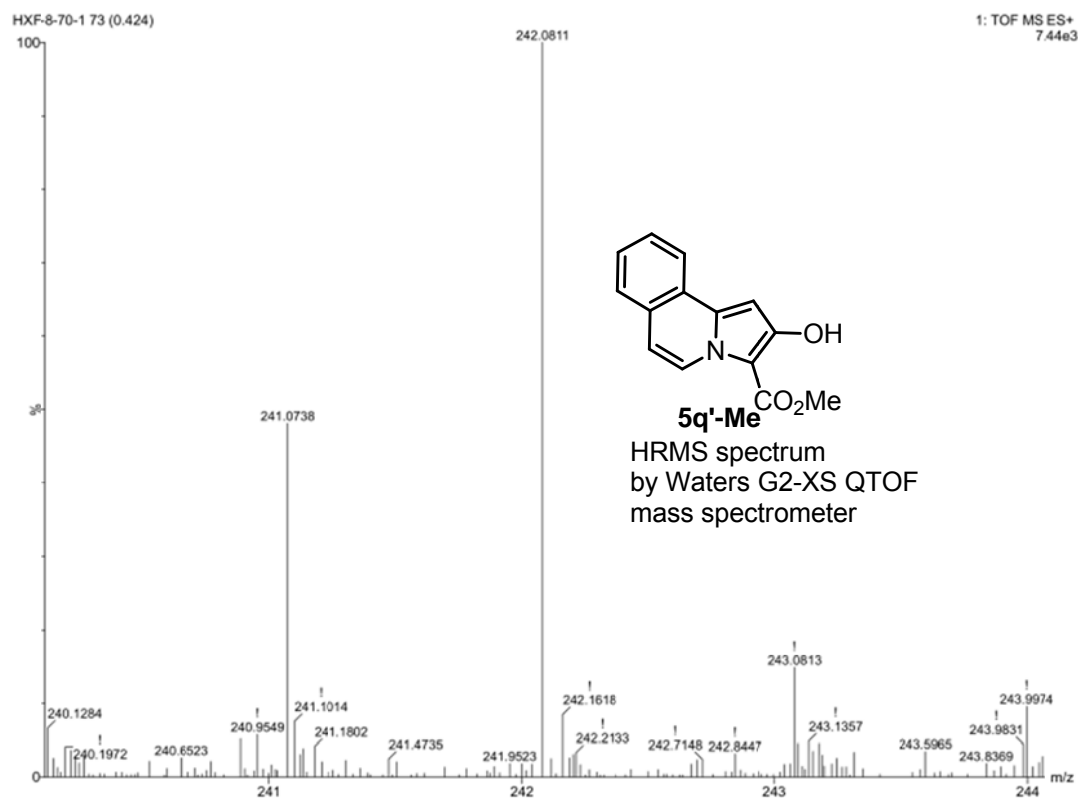
9. ^1H NMR, ^{19}F NMR, ^{13}C NMR, and HRMS spectra.

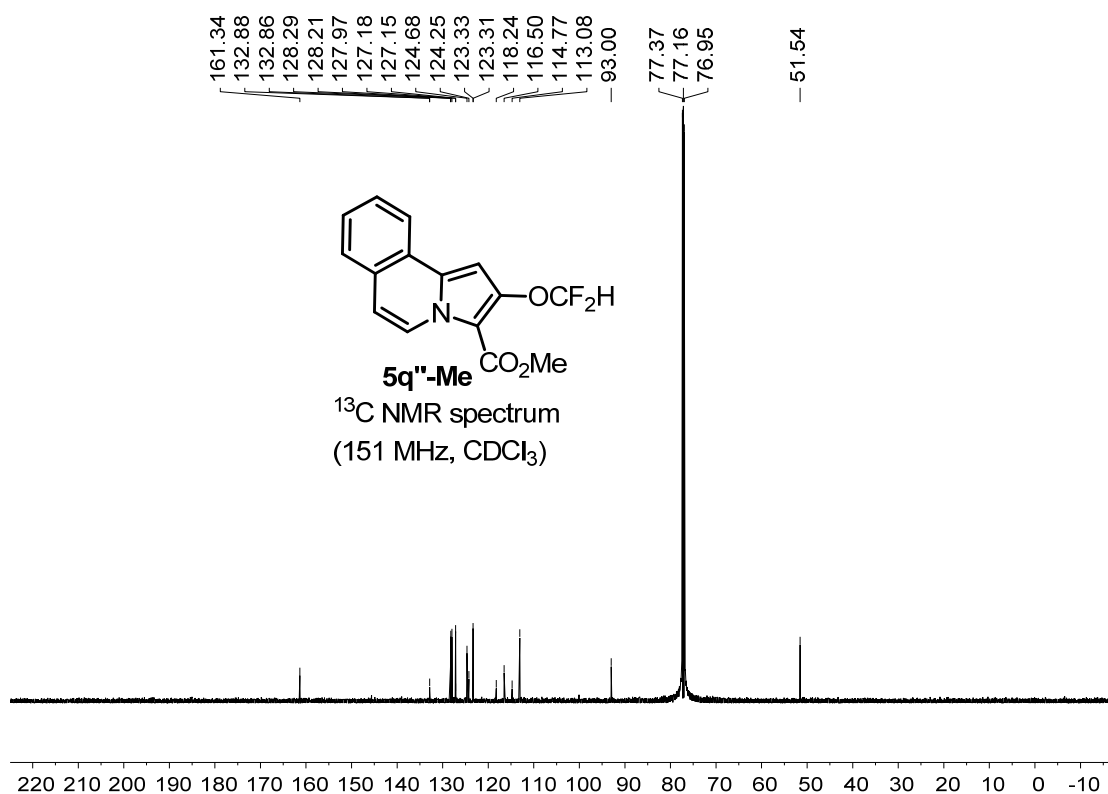
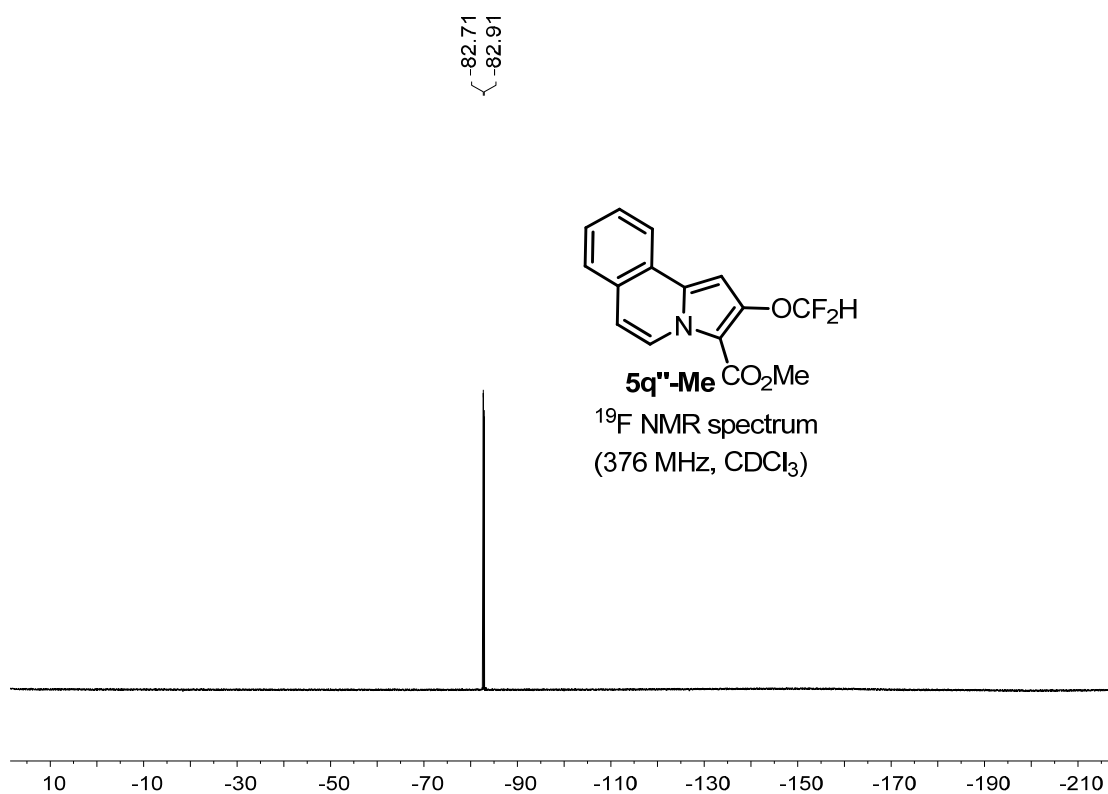
Note: The 2-difluoromethoxylated indolizines in this article were easily deteriorated and could not be dried for a long time, so peaks of ^1H NMR containing petroleum ether and ethyl acetate were normal. The 1,3-diester substituted indolizines in this article were solids or viscous oil and easily encapsulated ethyl acetate and petroleum ether, so some spectra had peaks of ethyl acetate and petroleum ether.

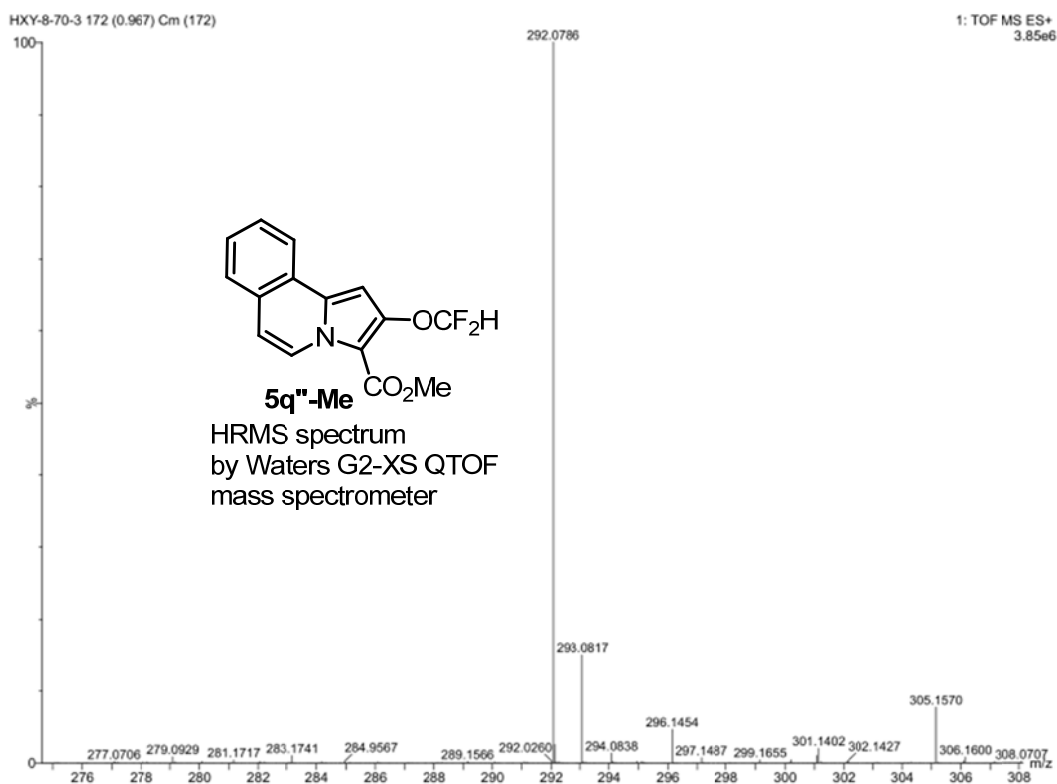
(a) ^1H NMR, ^{13}C NMR, and HRMS spectra of scope studies.



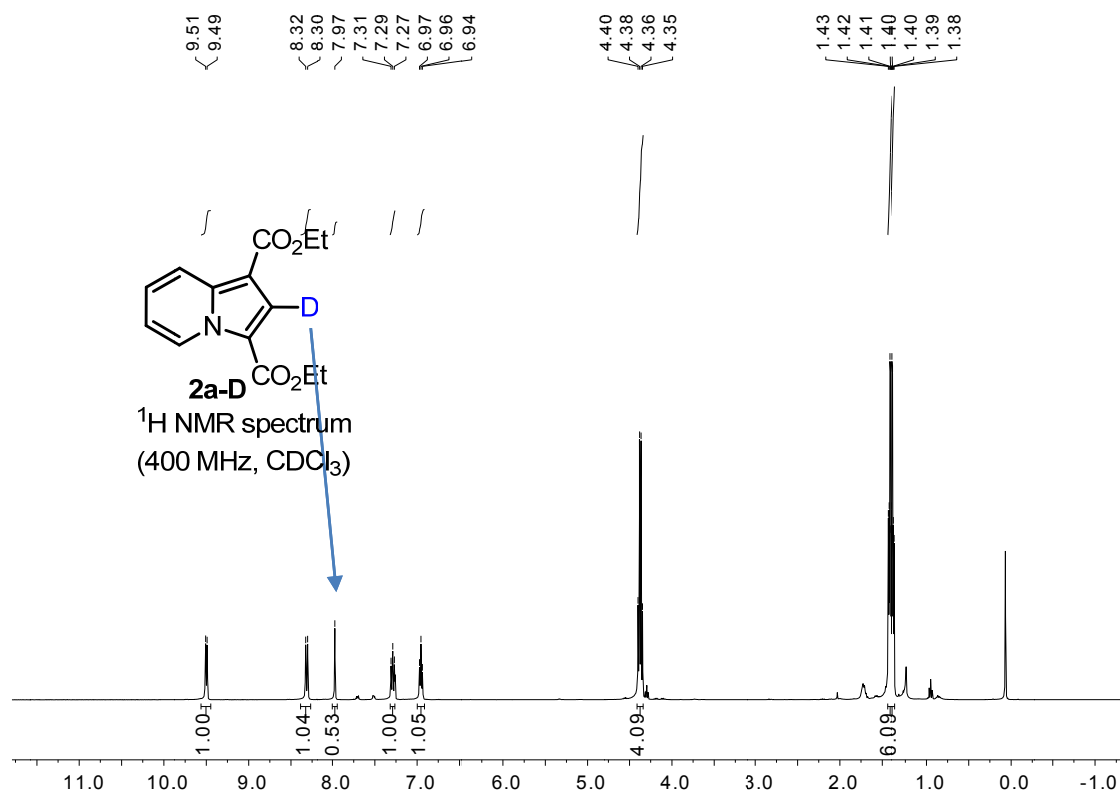


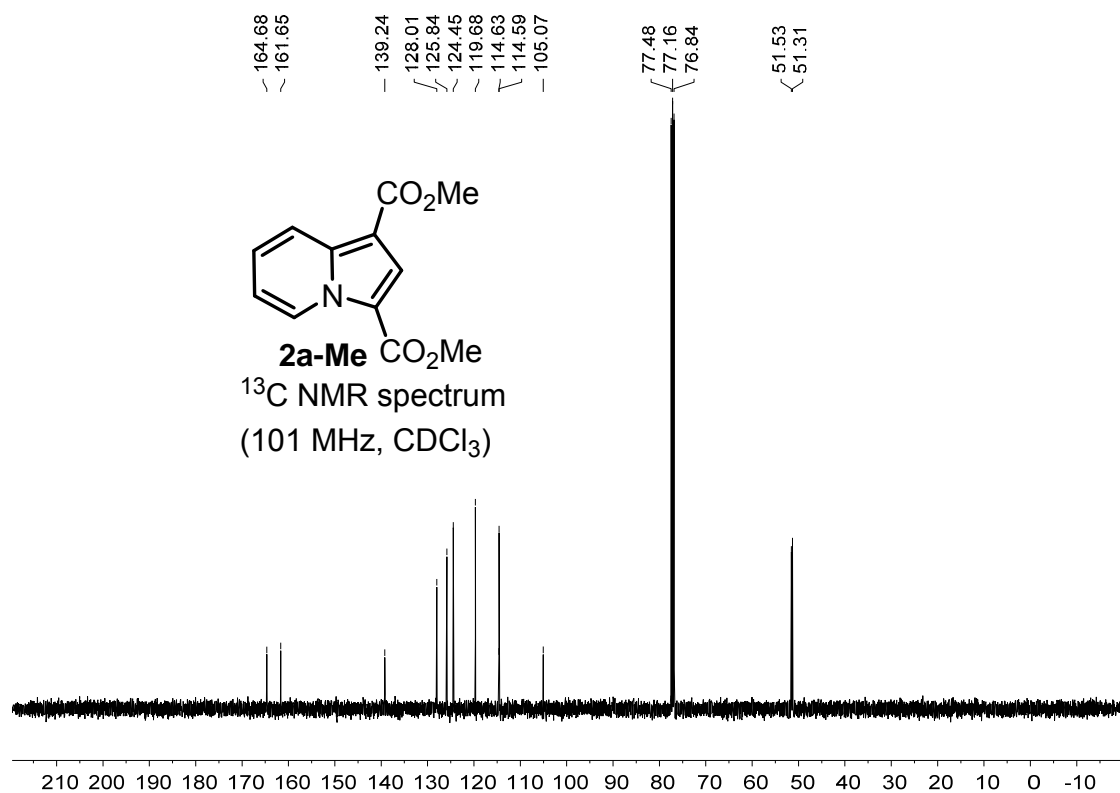
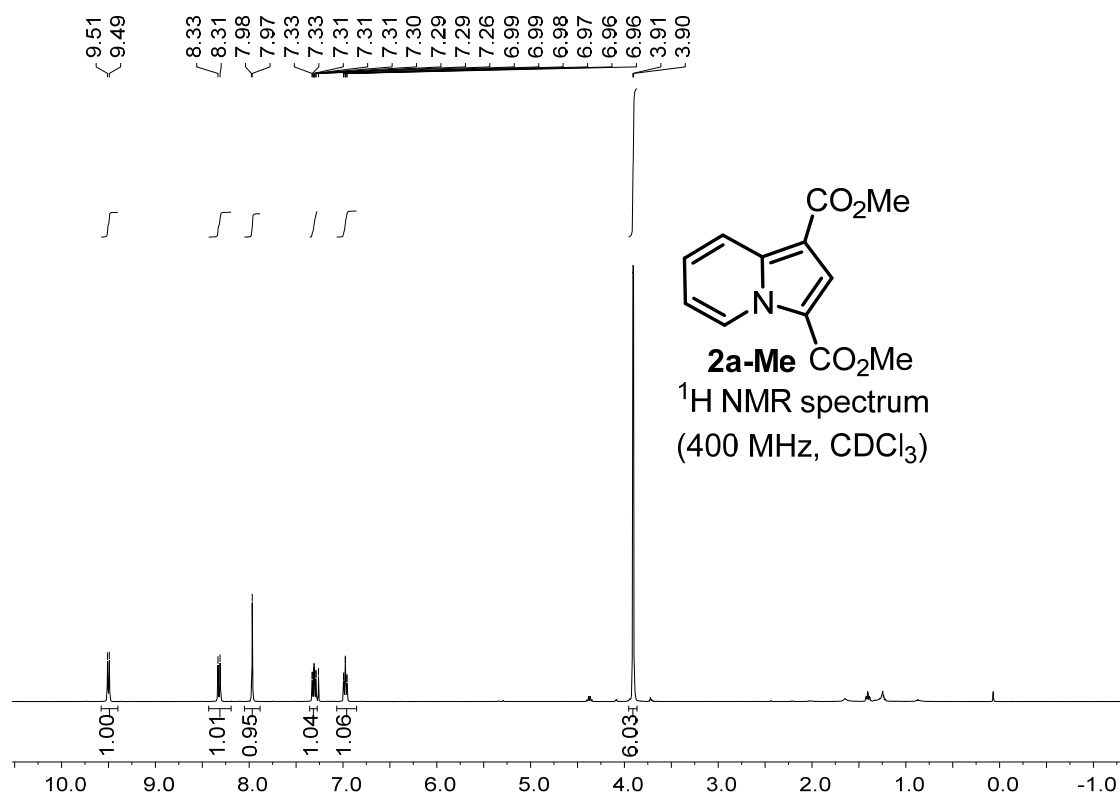


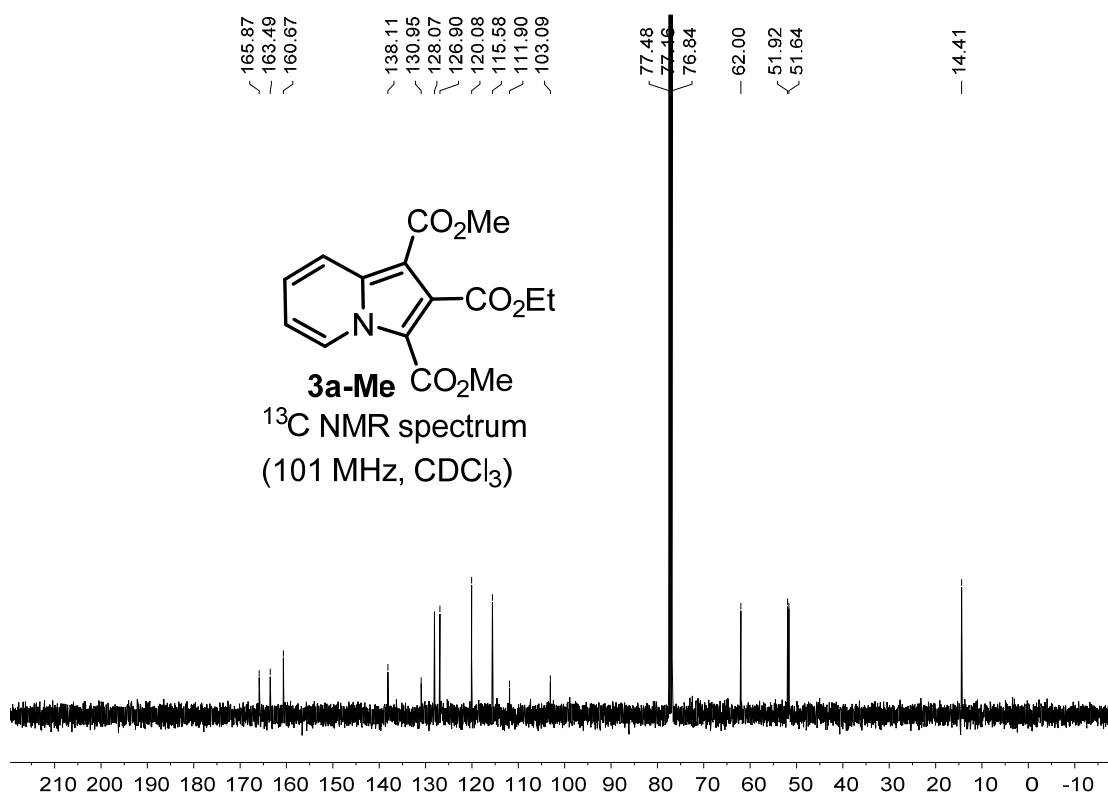
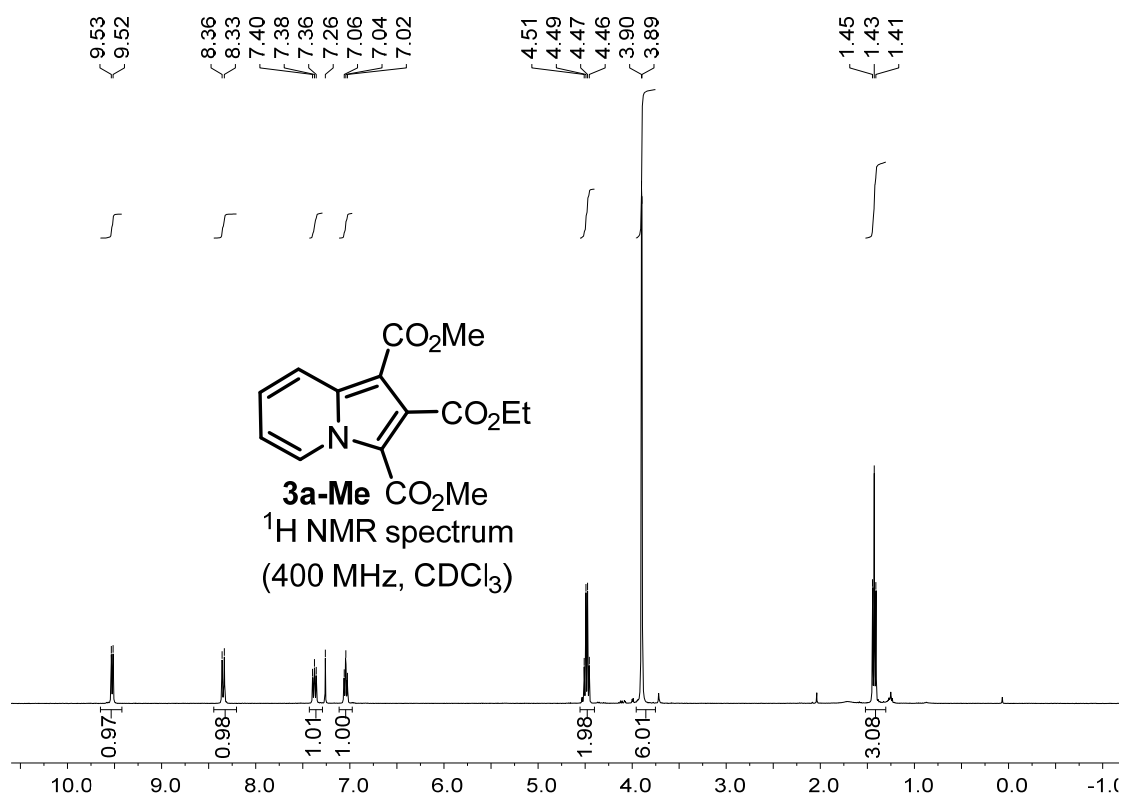


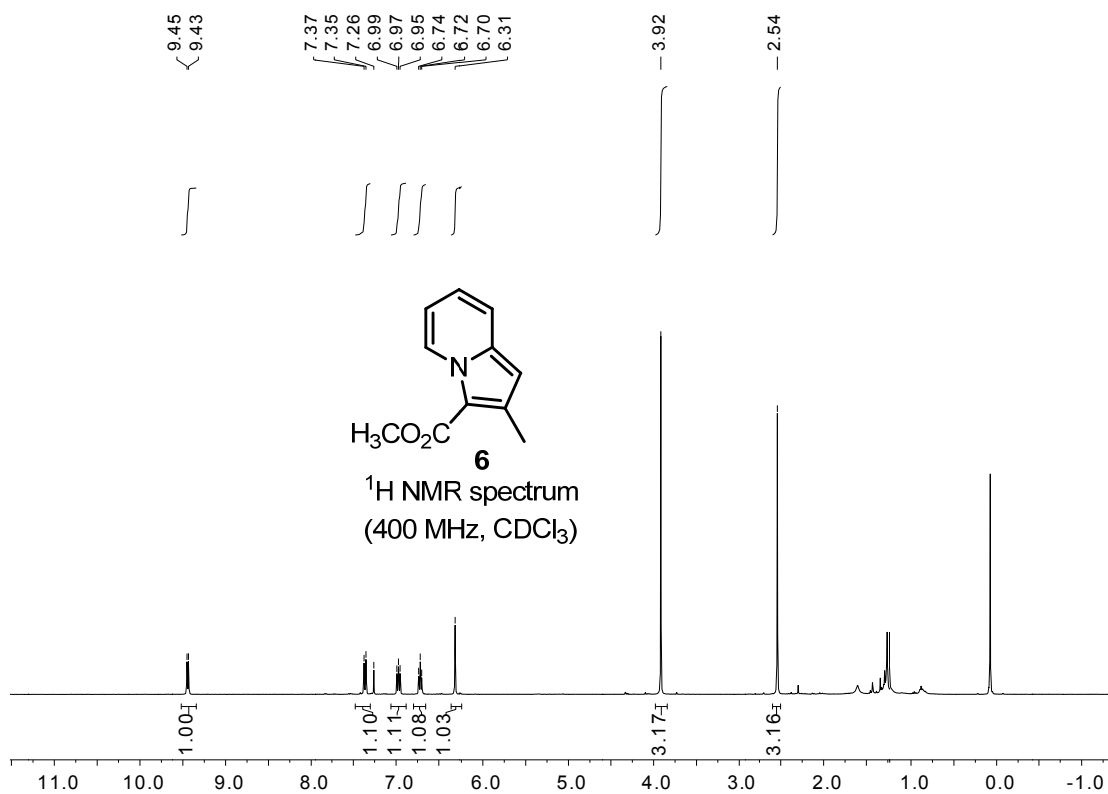
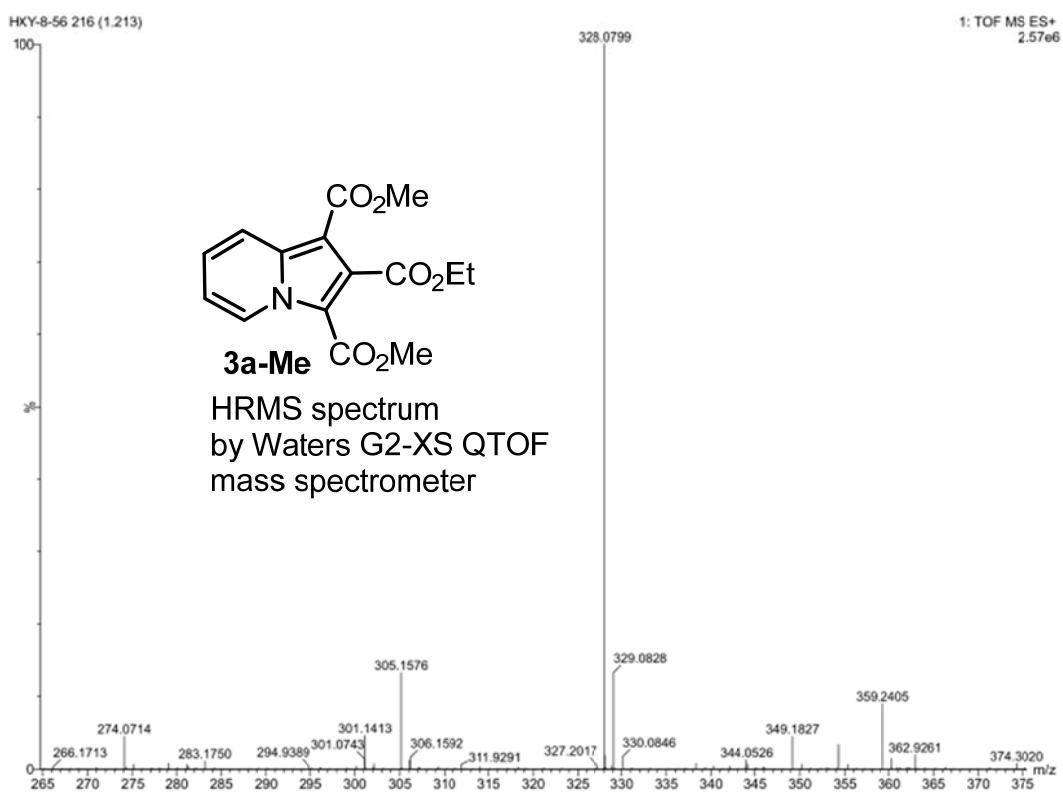


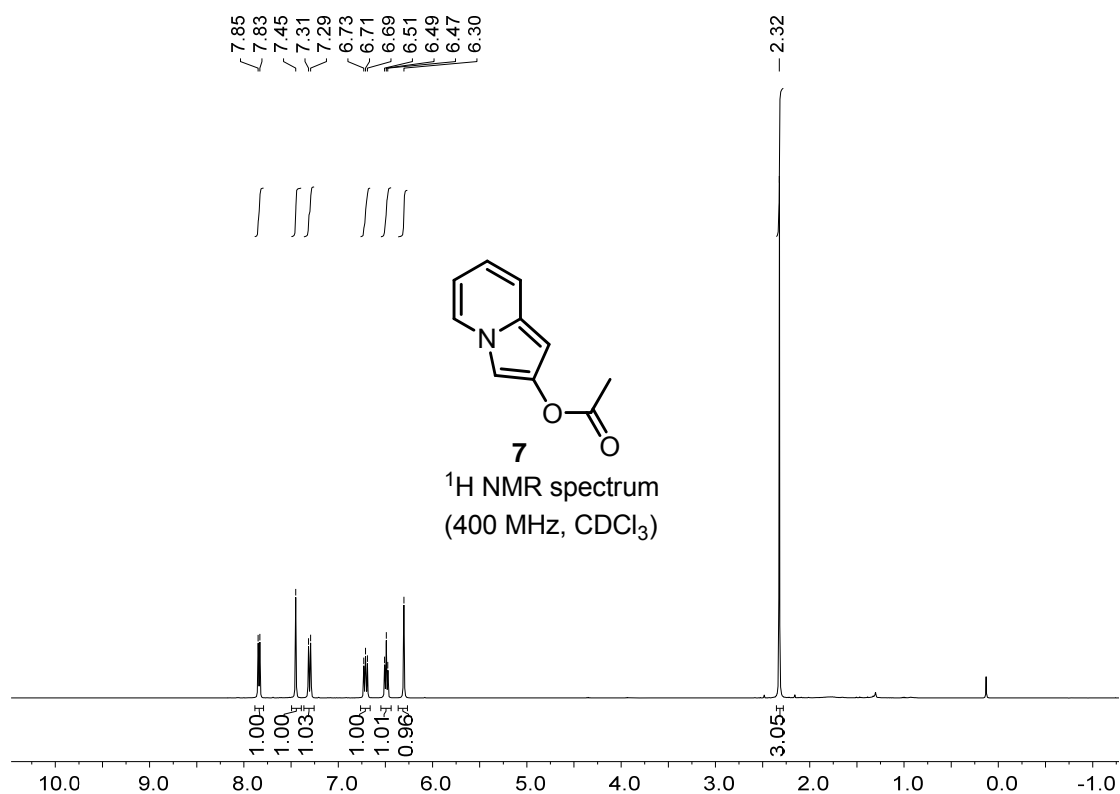
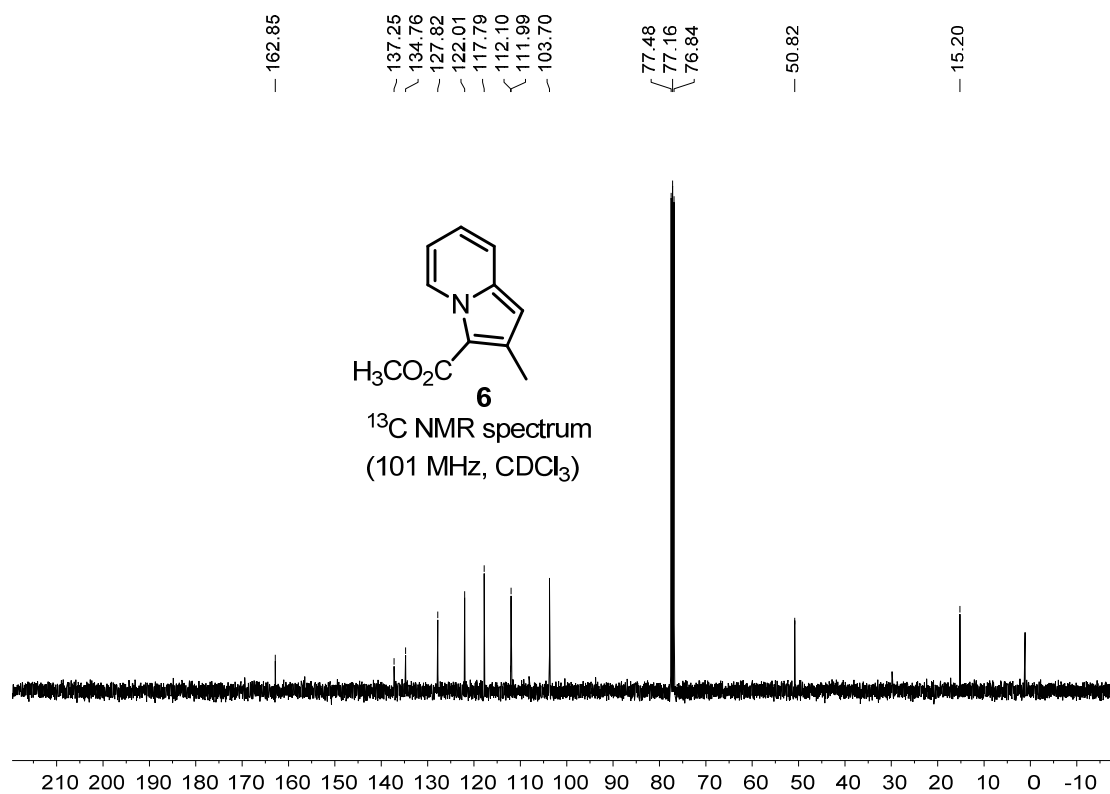
(b) ^1H NMR, ^{13}C NMR, ^{19}F NMR, and HRMS spectra of Mechanistic studies.

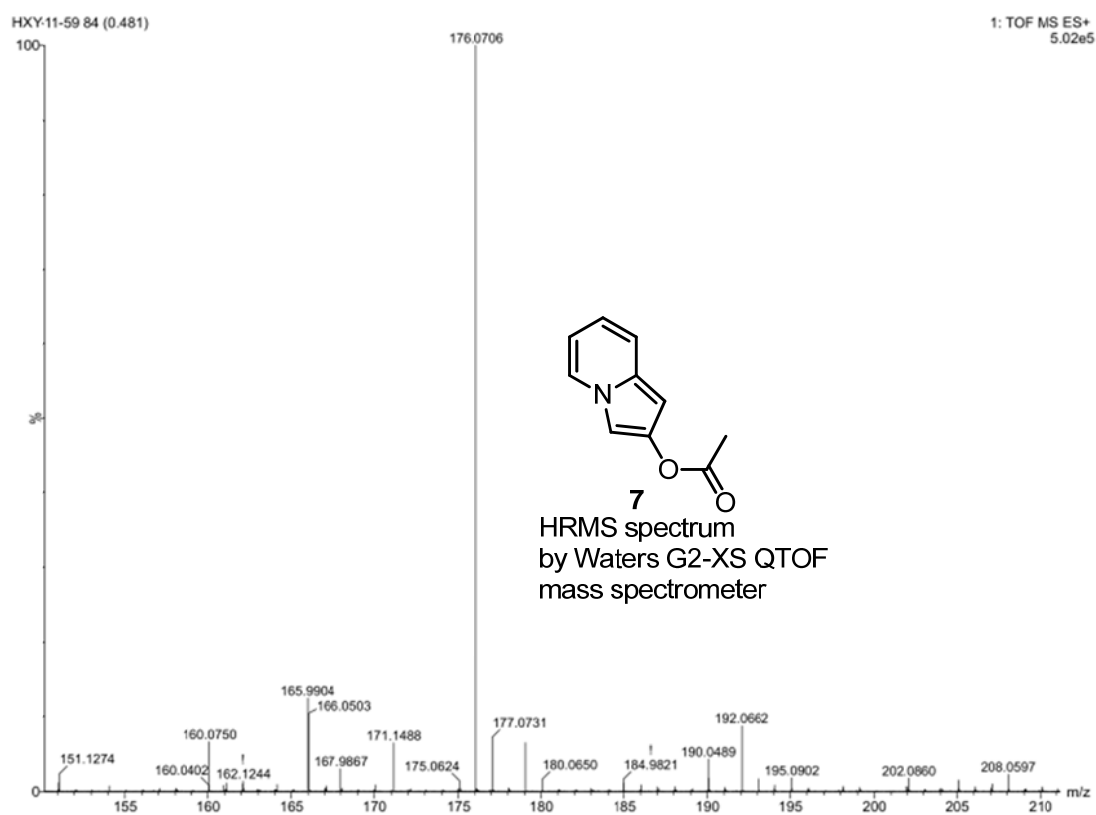
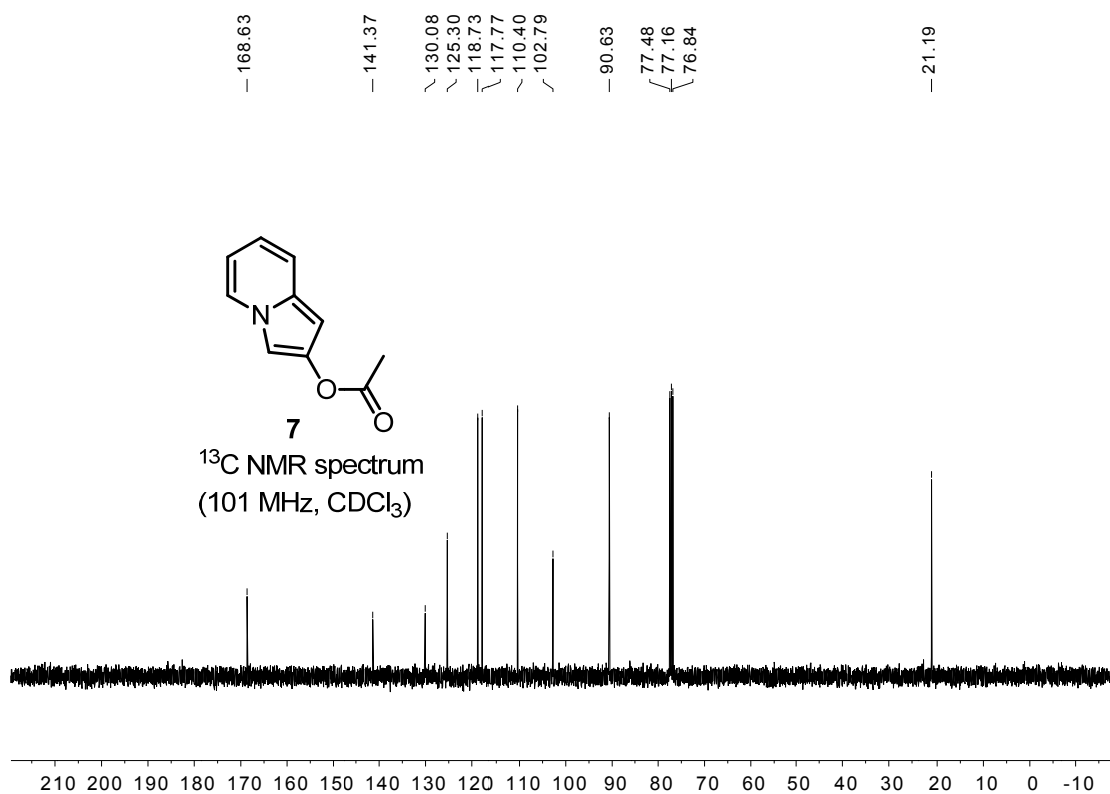


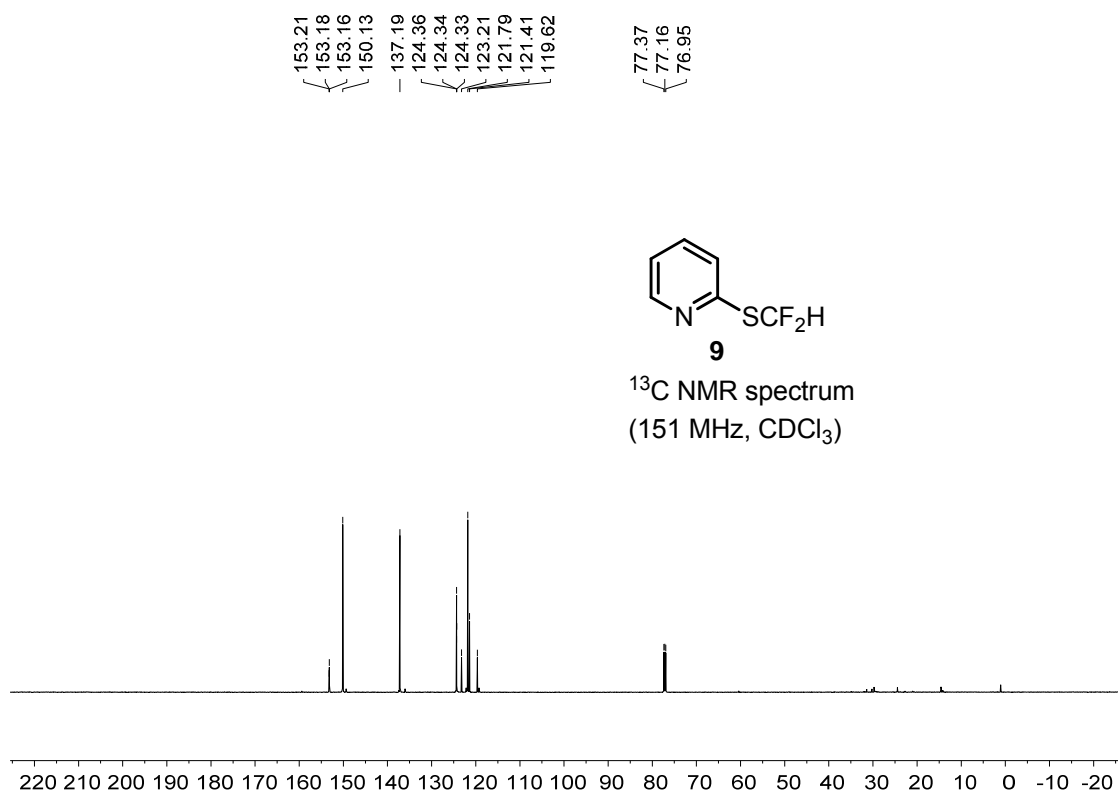
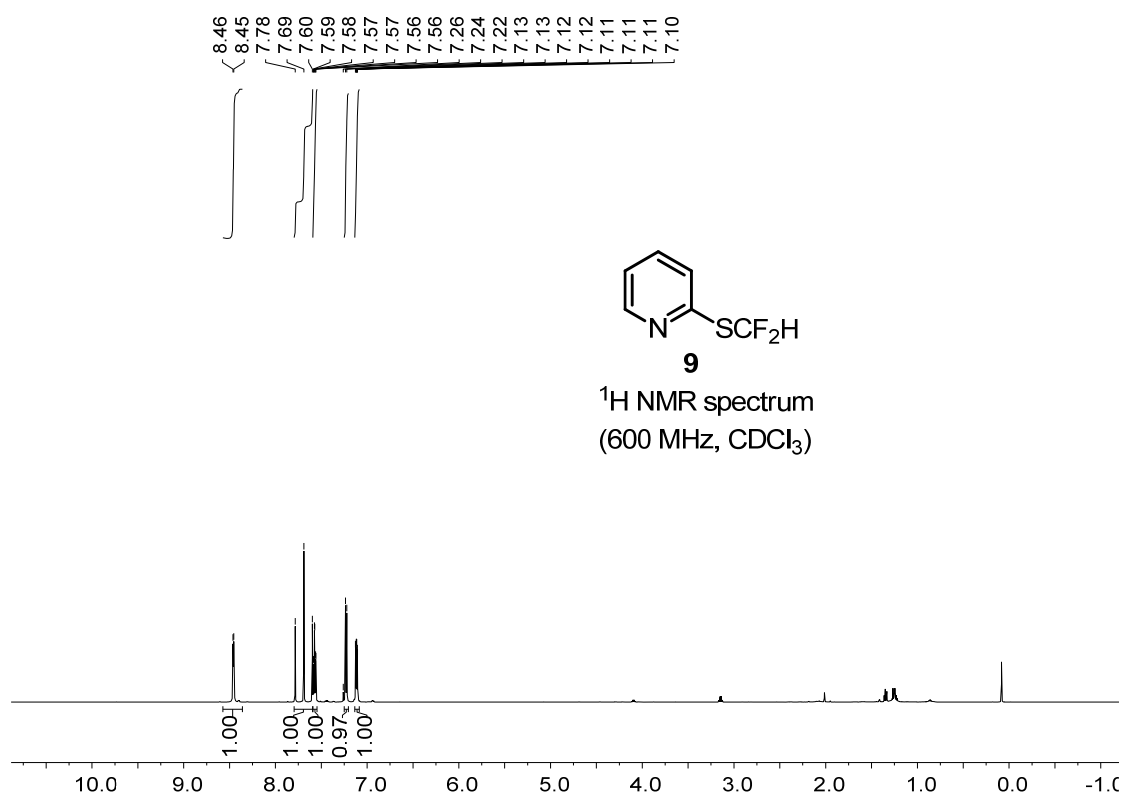


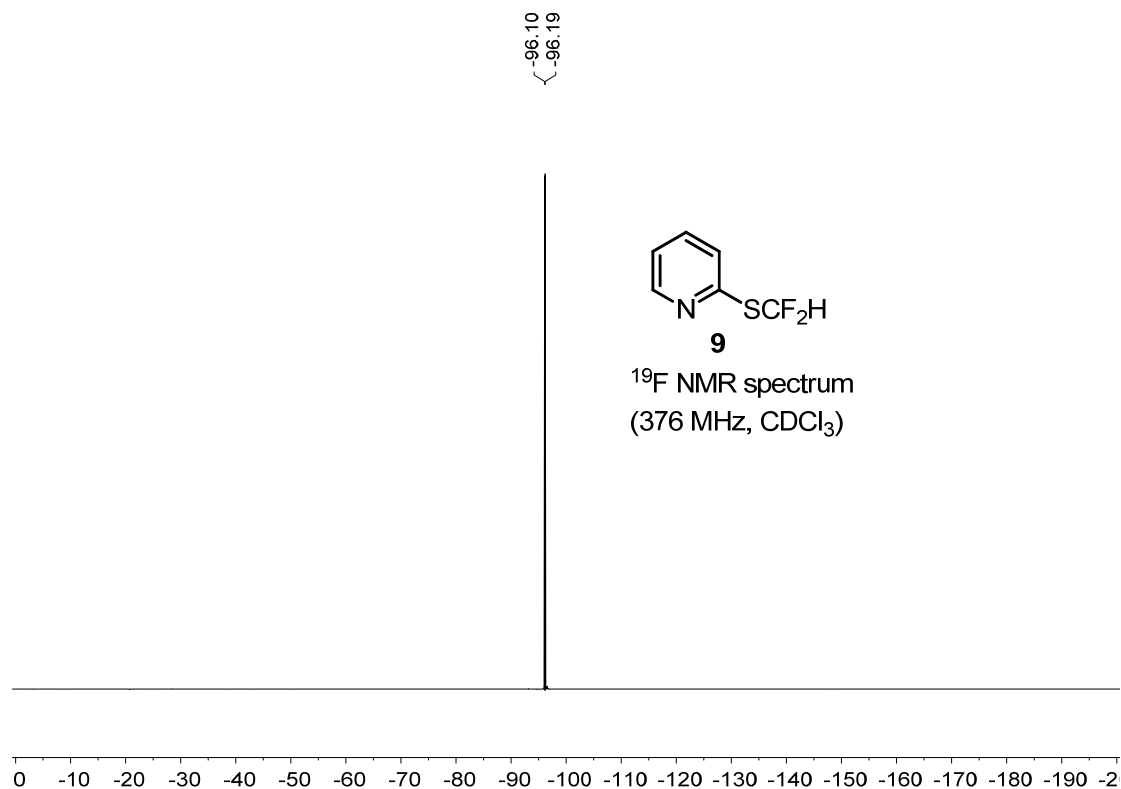




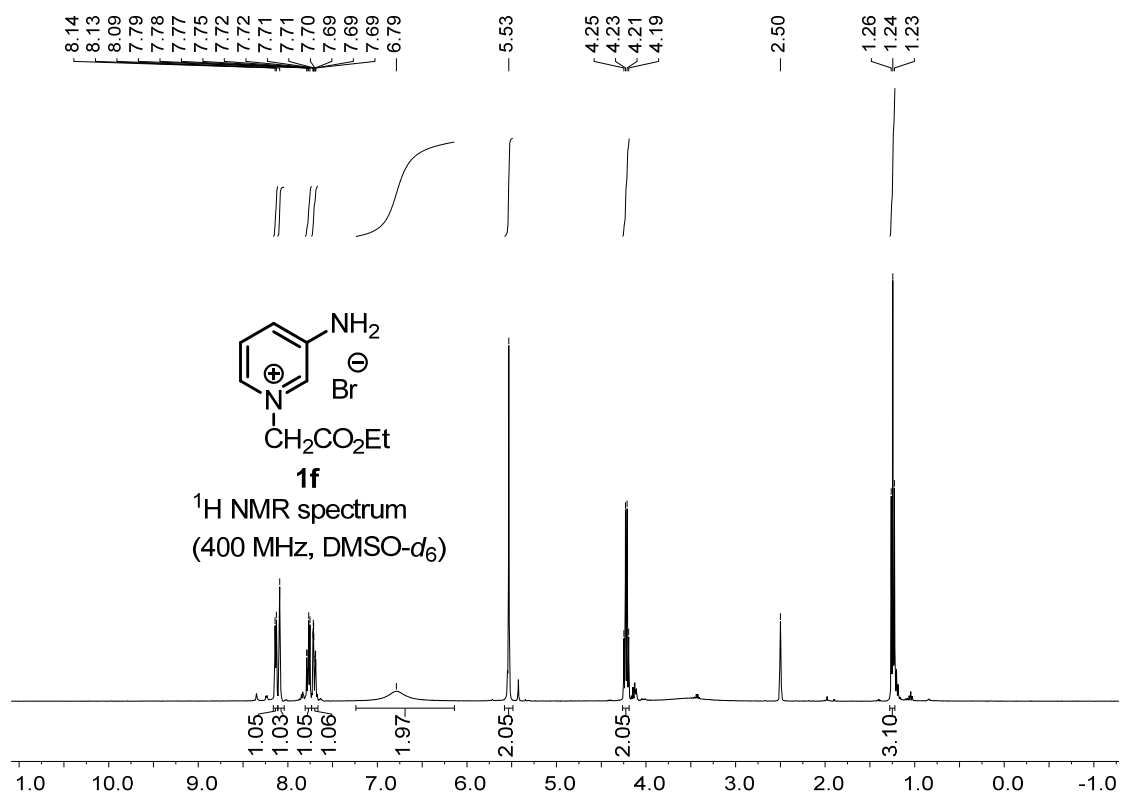


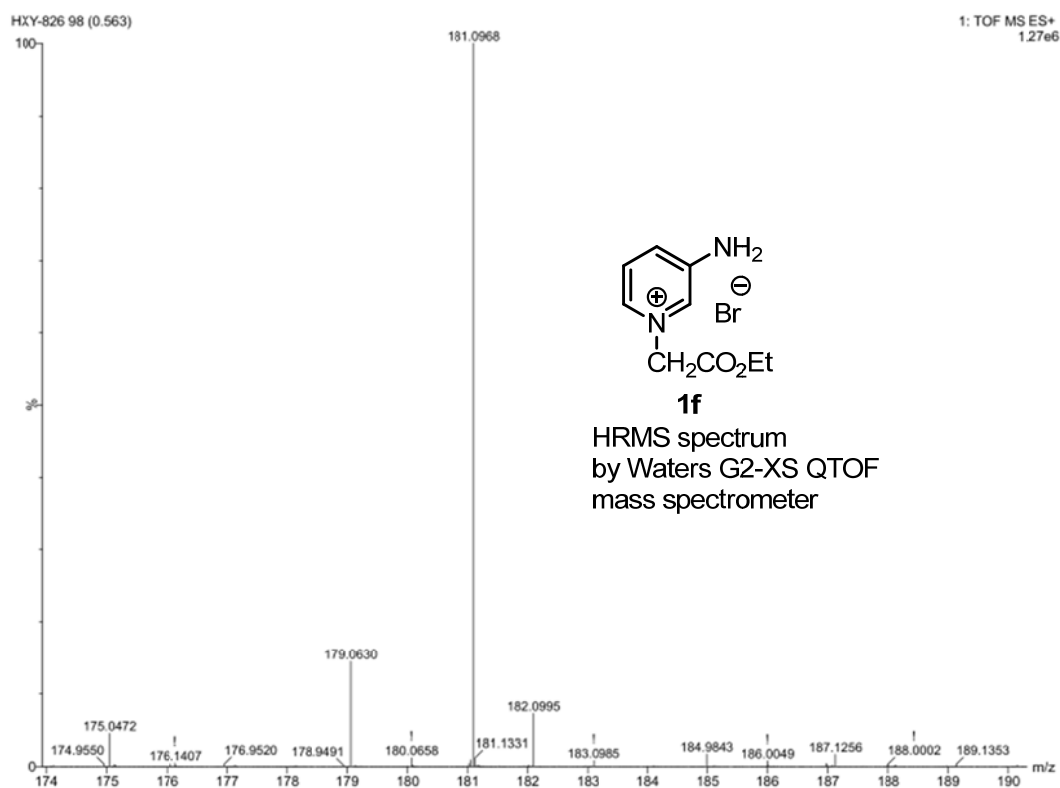
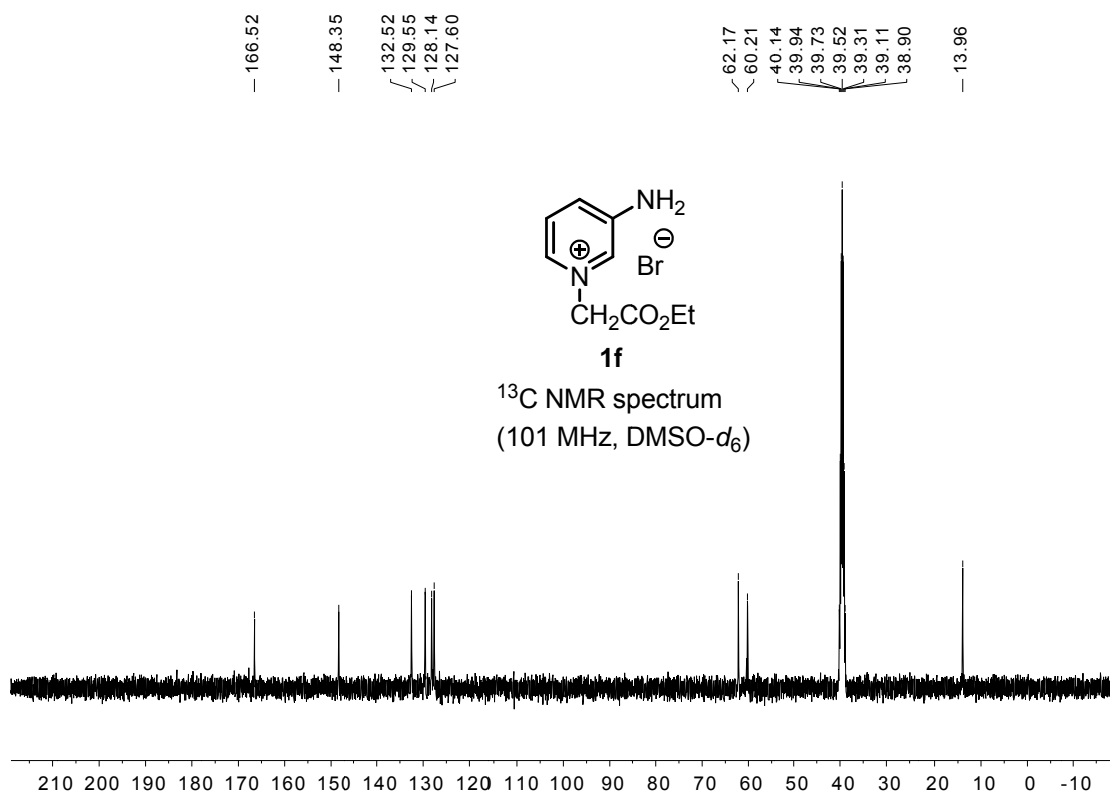




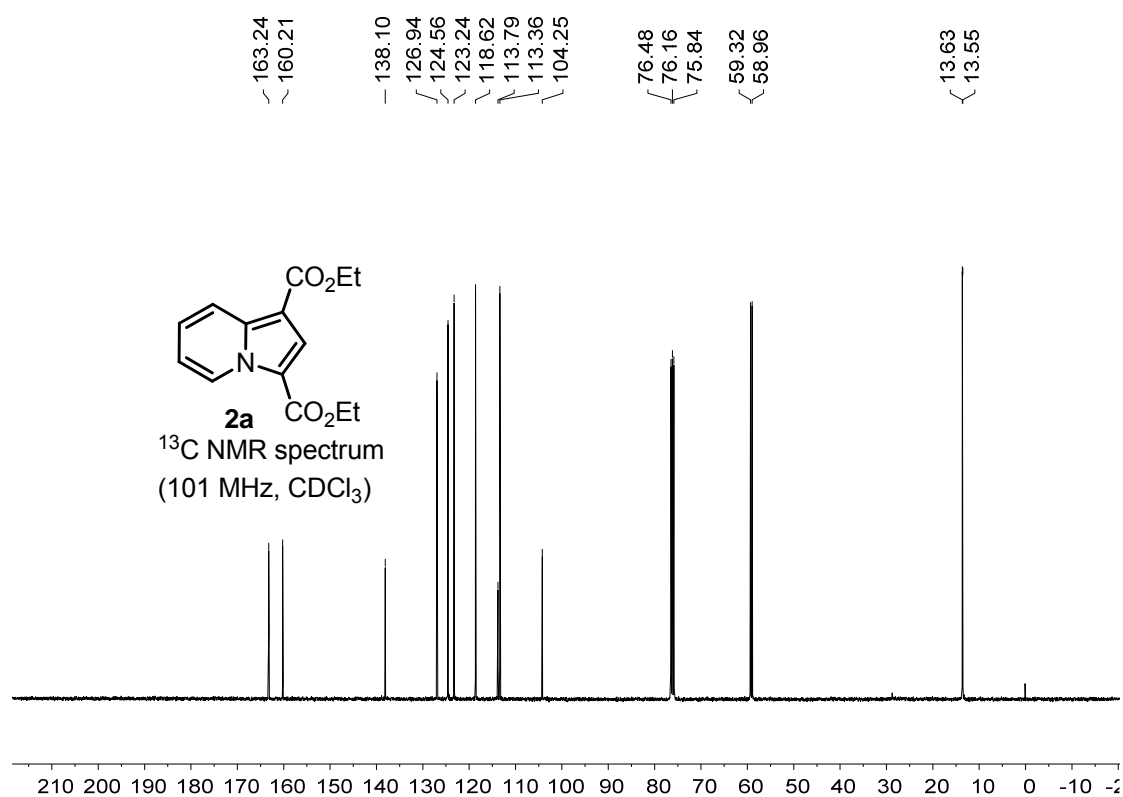
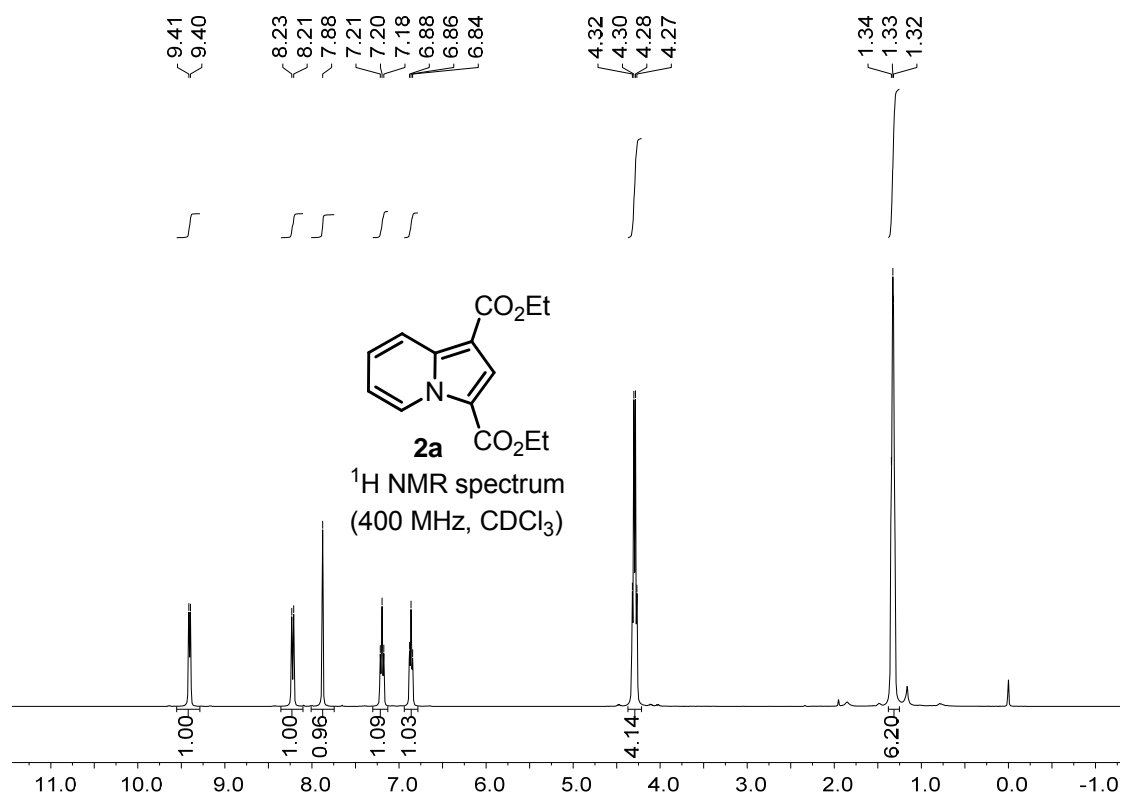


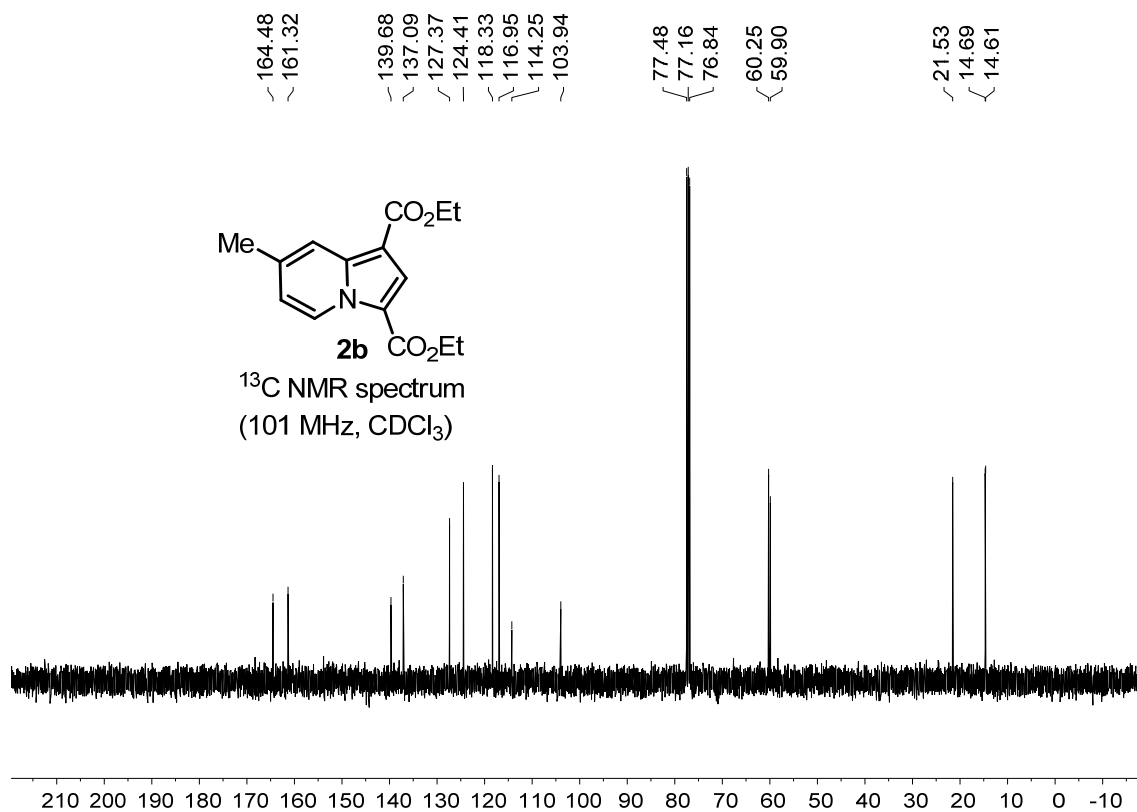
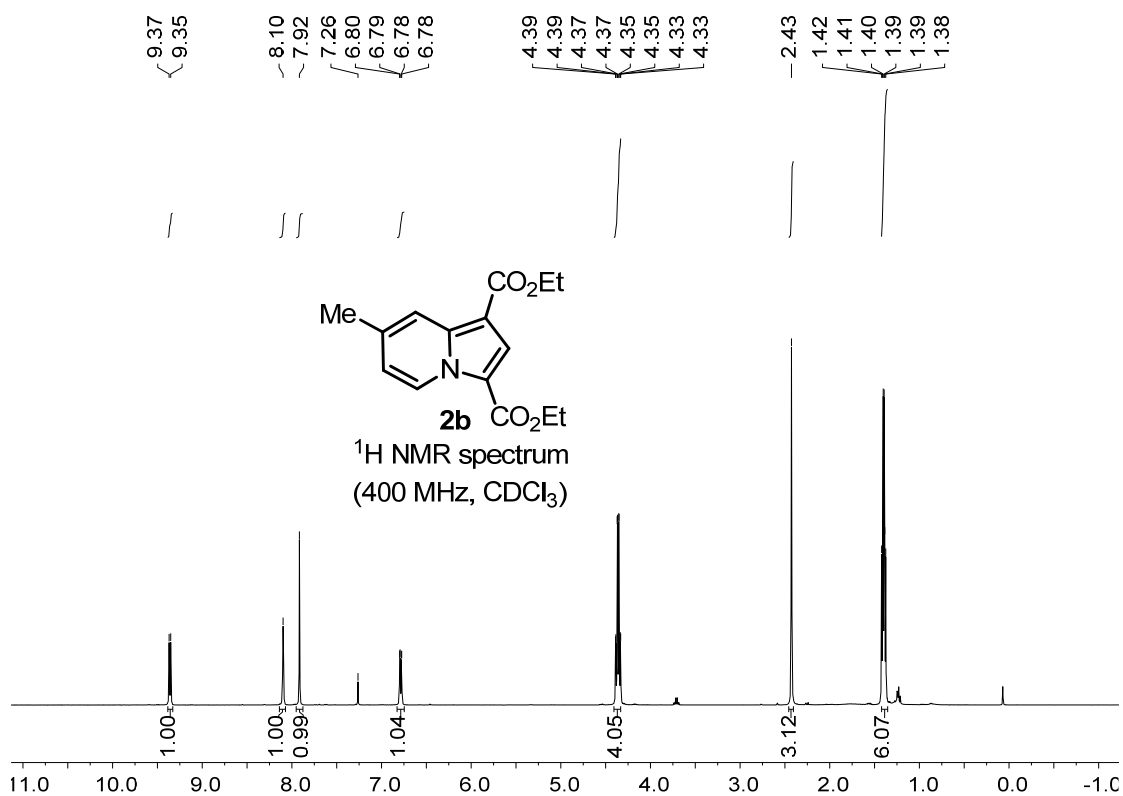
(c) ^1H NMR, ^{13}C NMR, and HRMS spectra of **1f**.

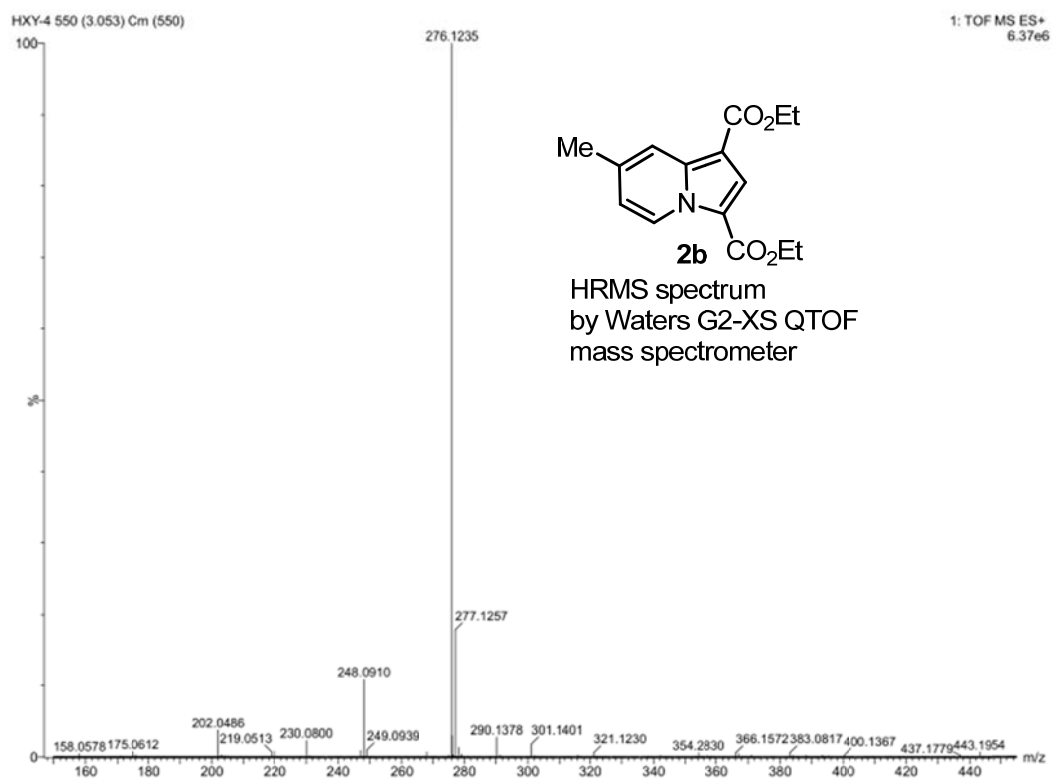


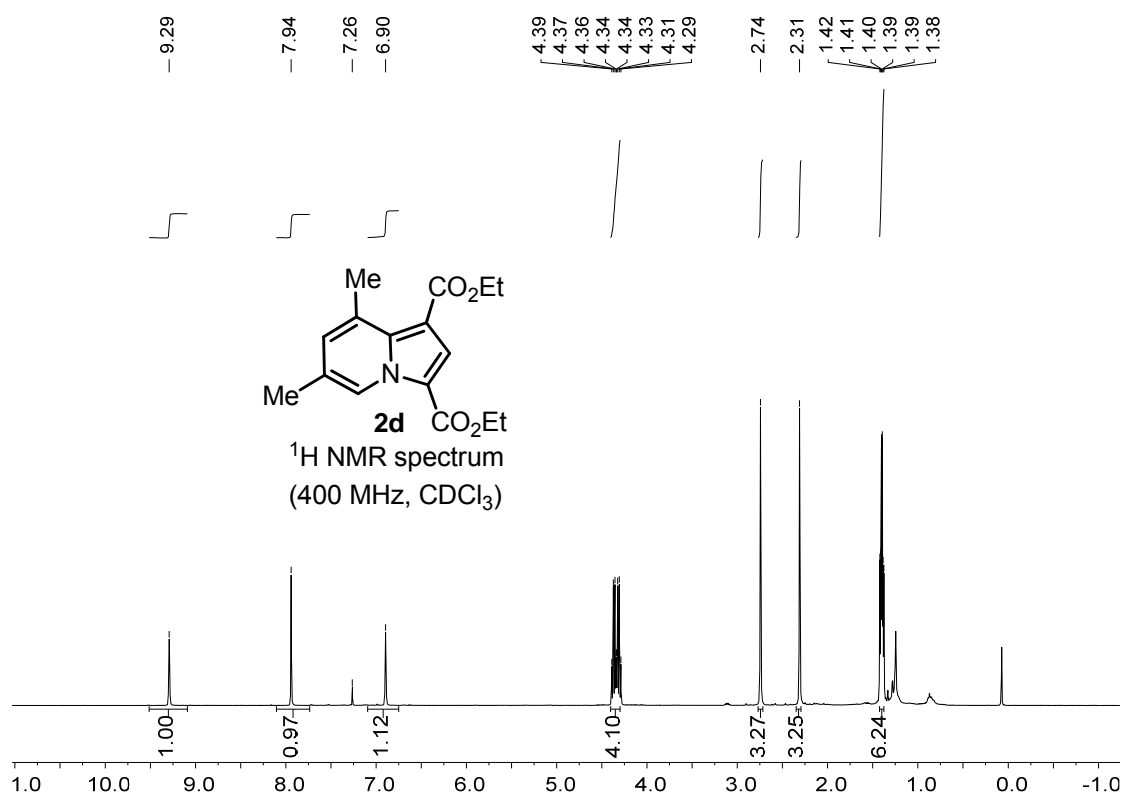
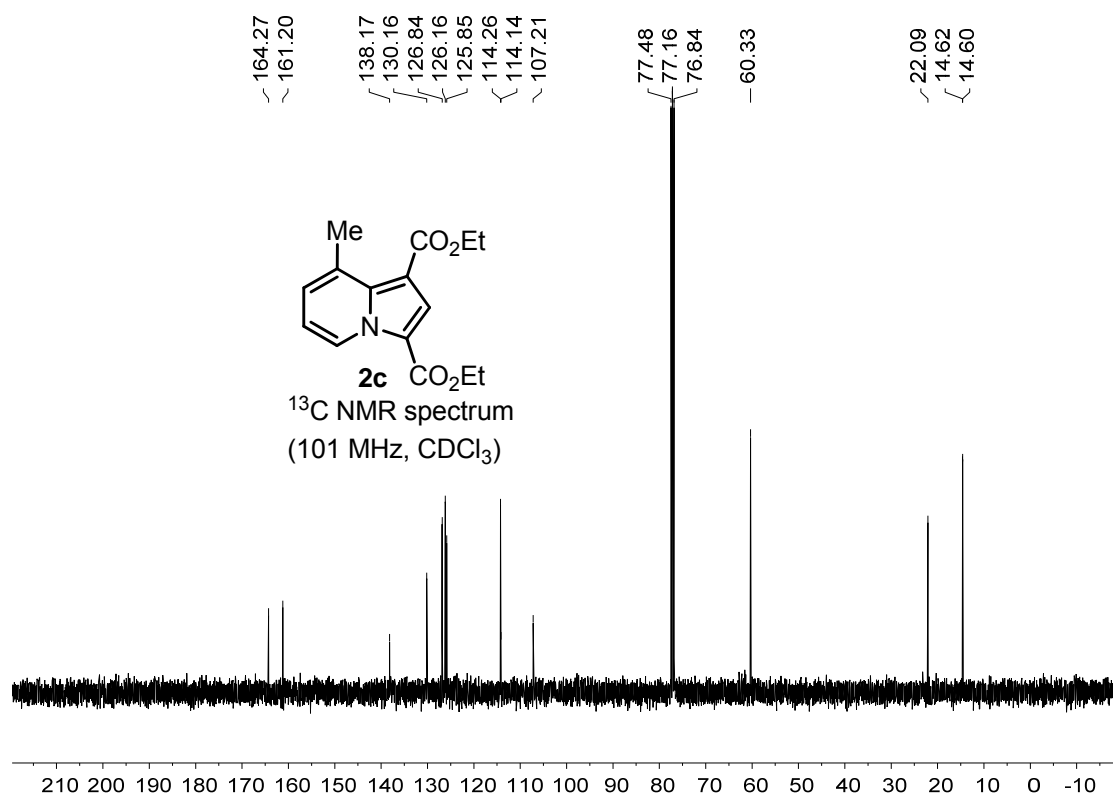


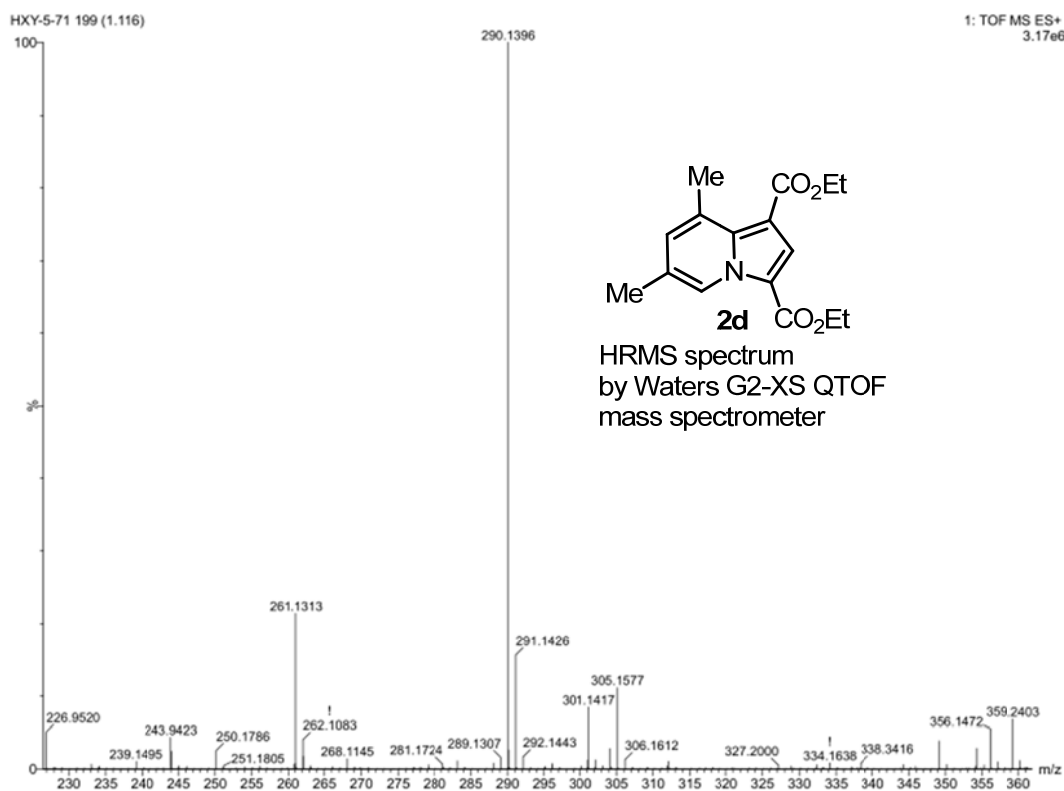
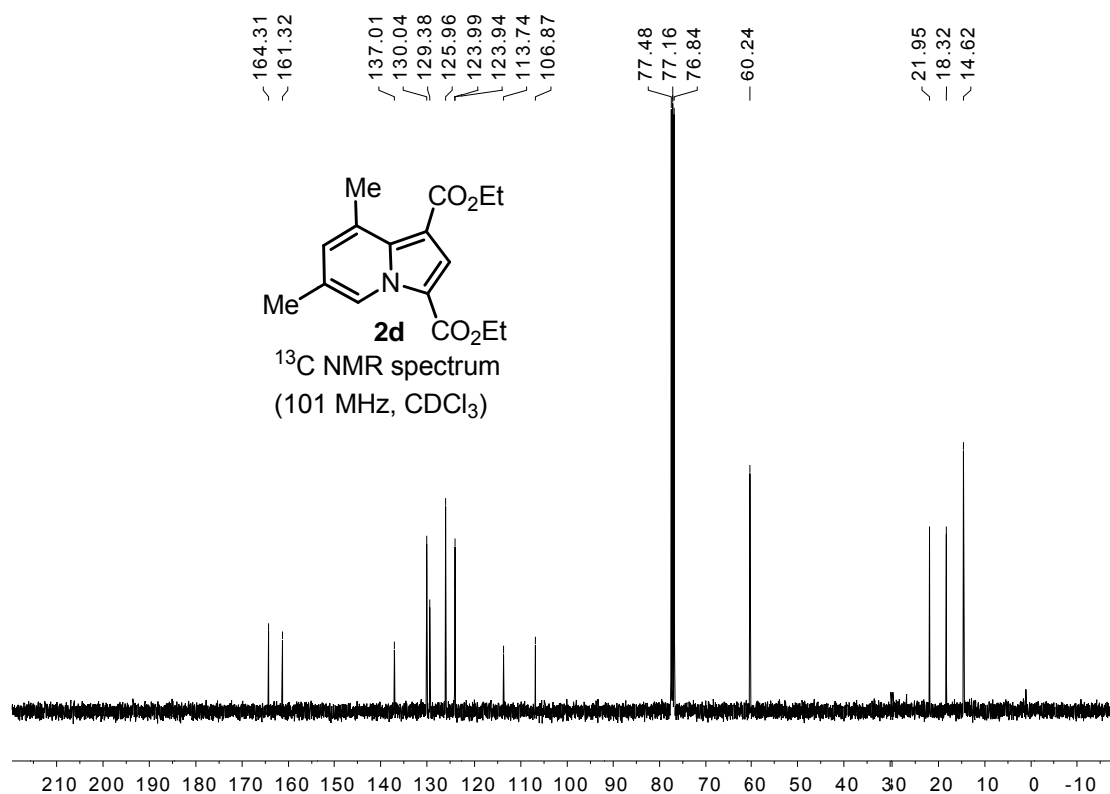
(d) ¹H NMR, ¹³C NMR, and HRMS spectra of **2**.

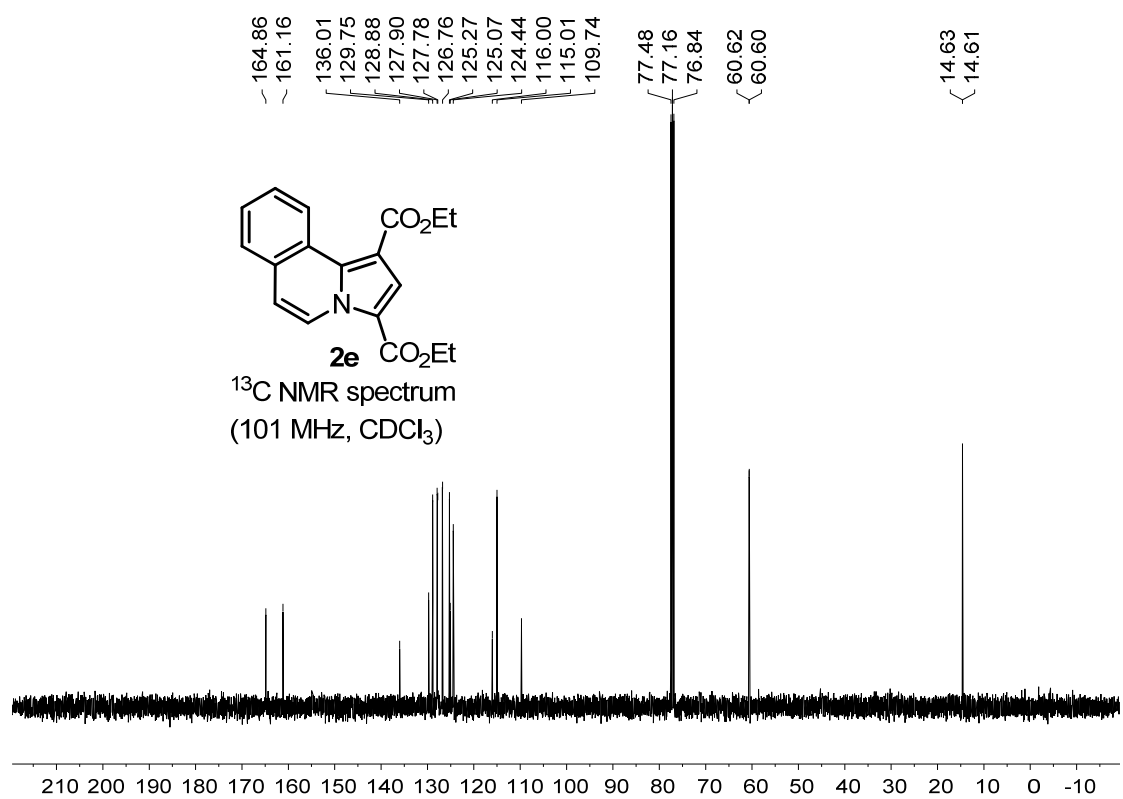
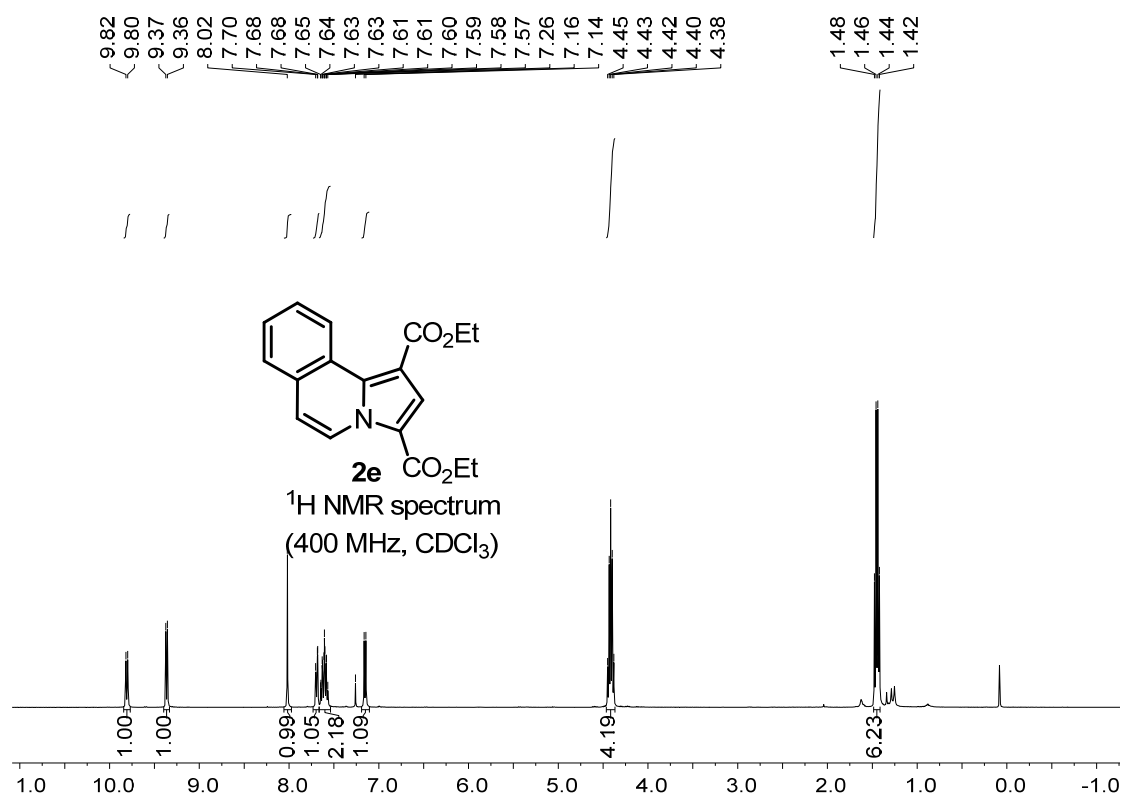


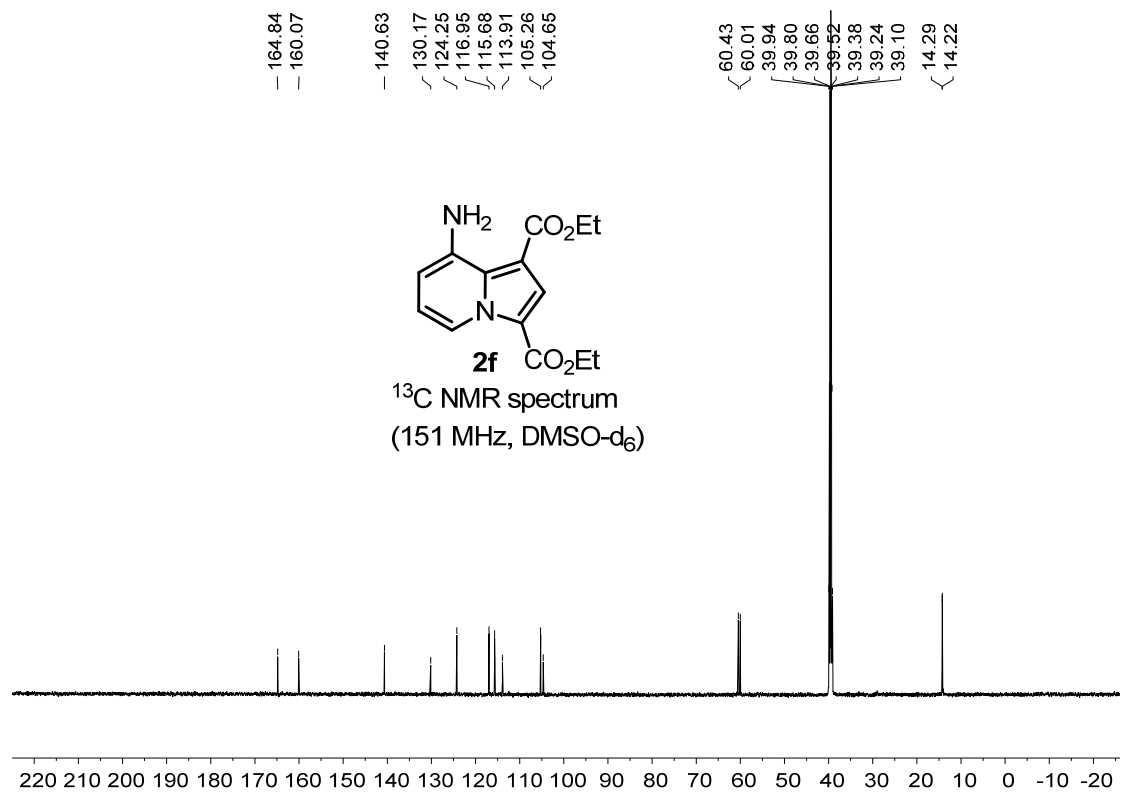
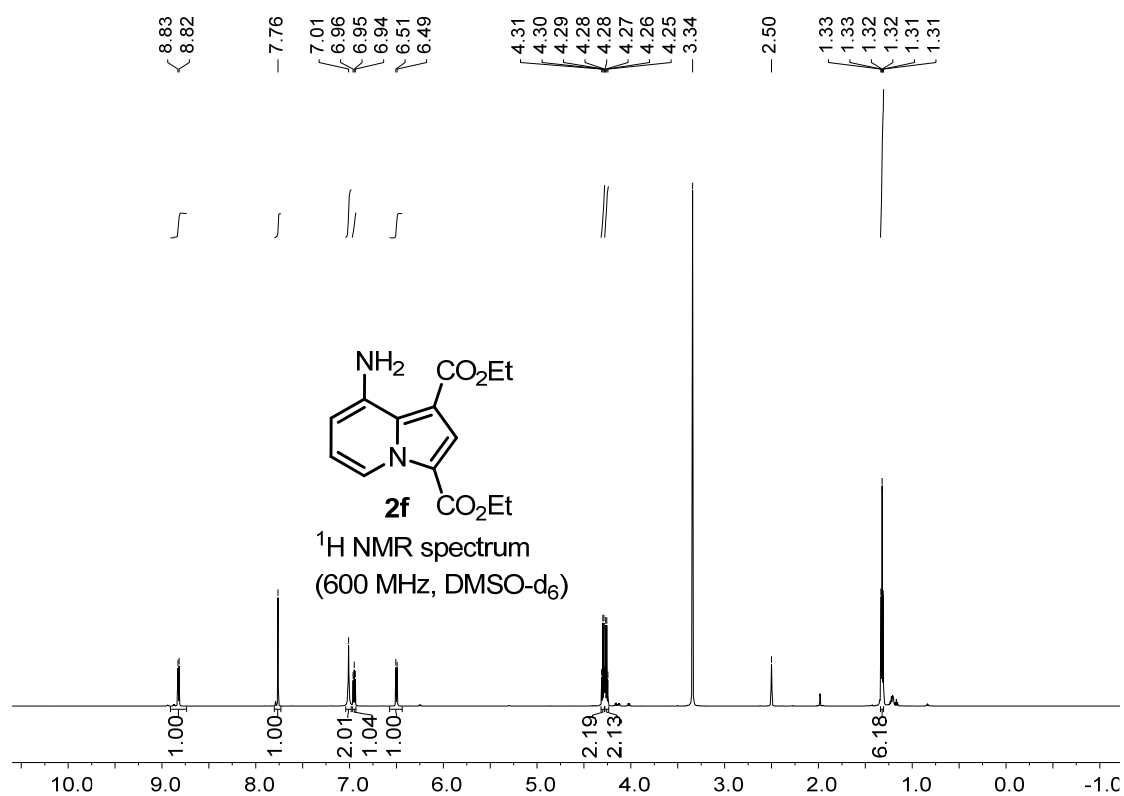


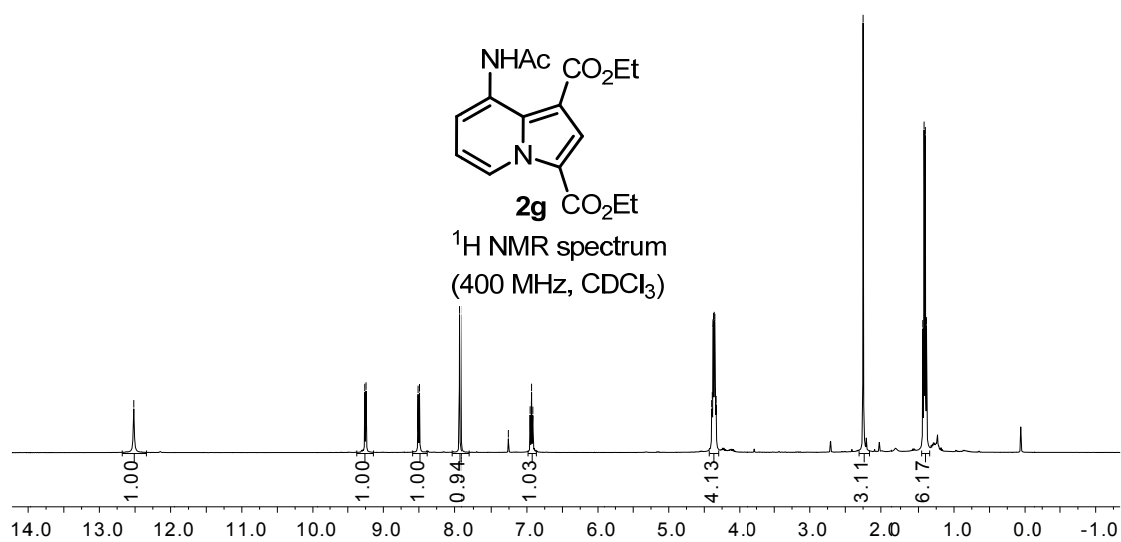
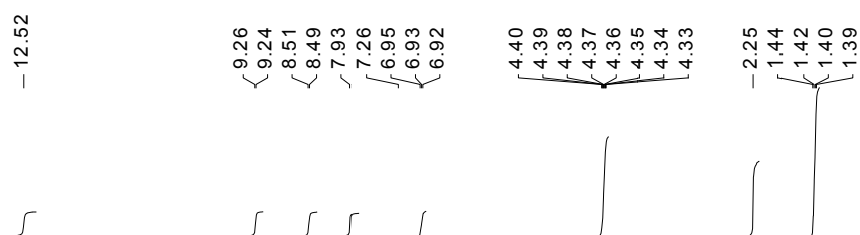
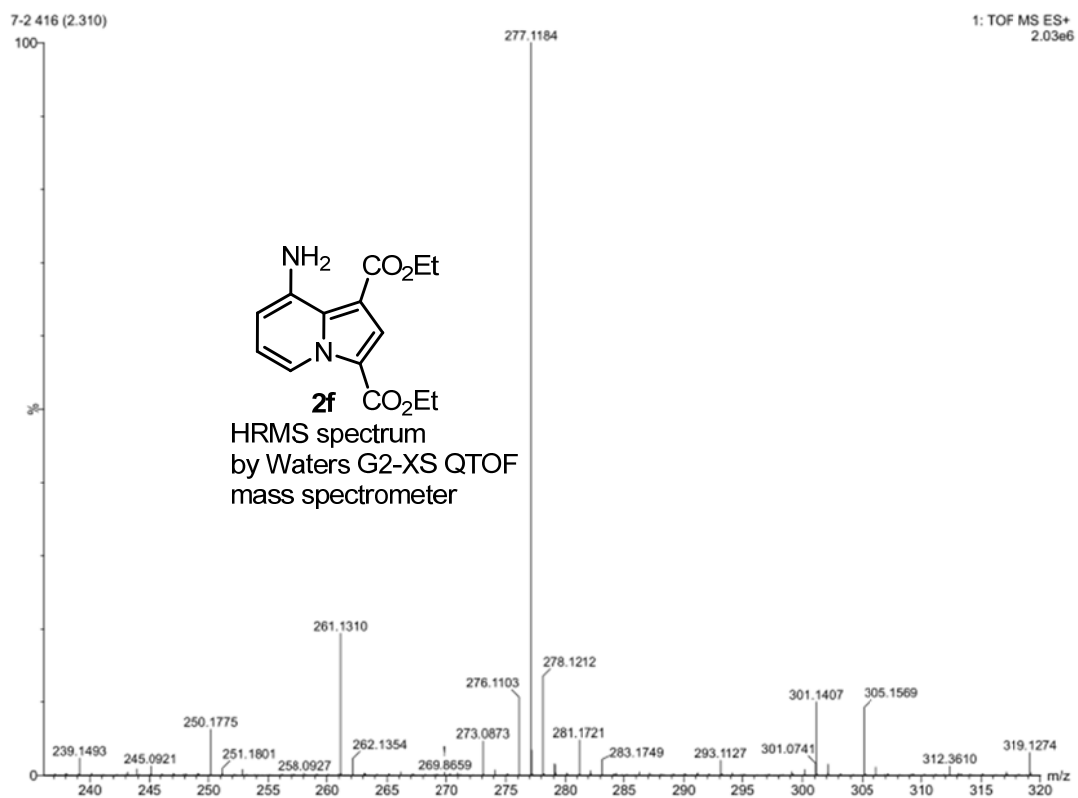


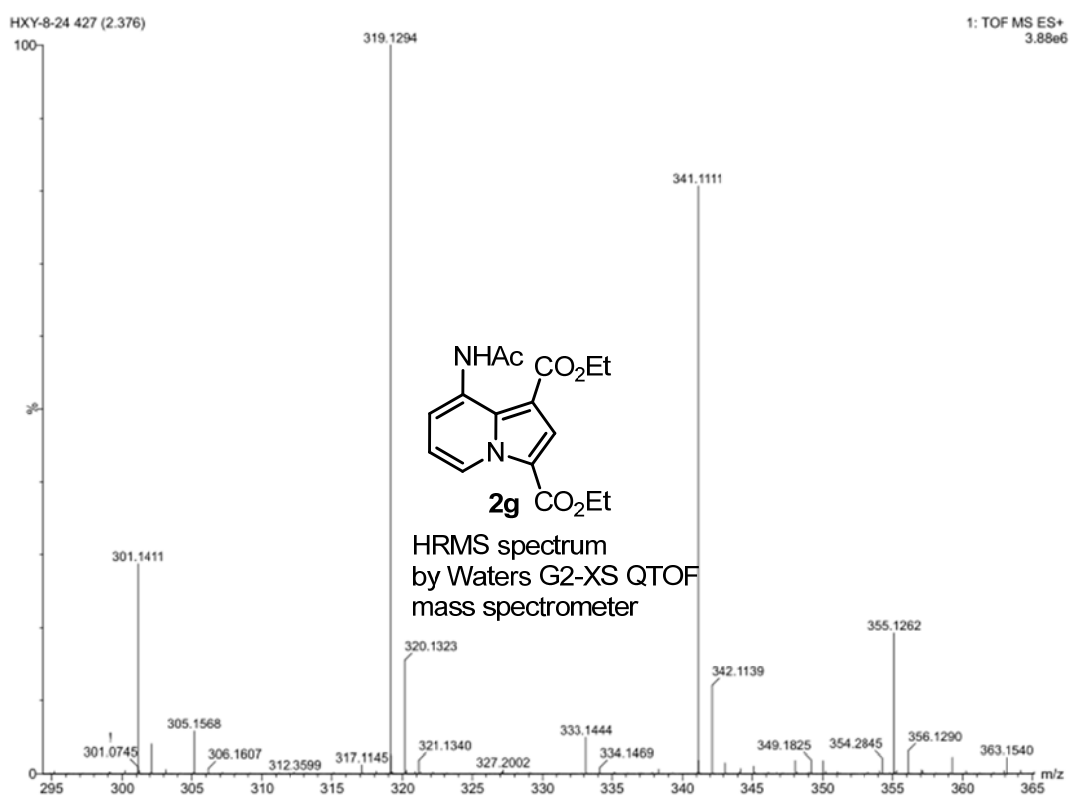
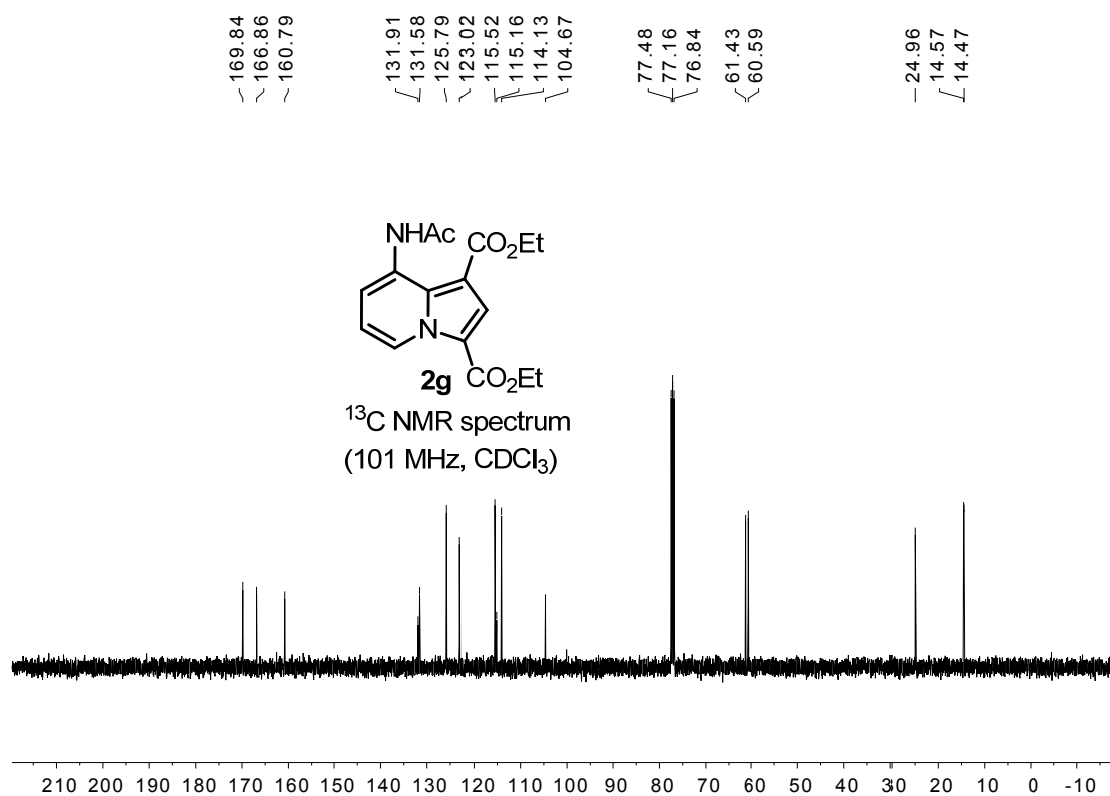


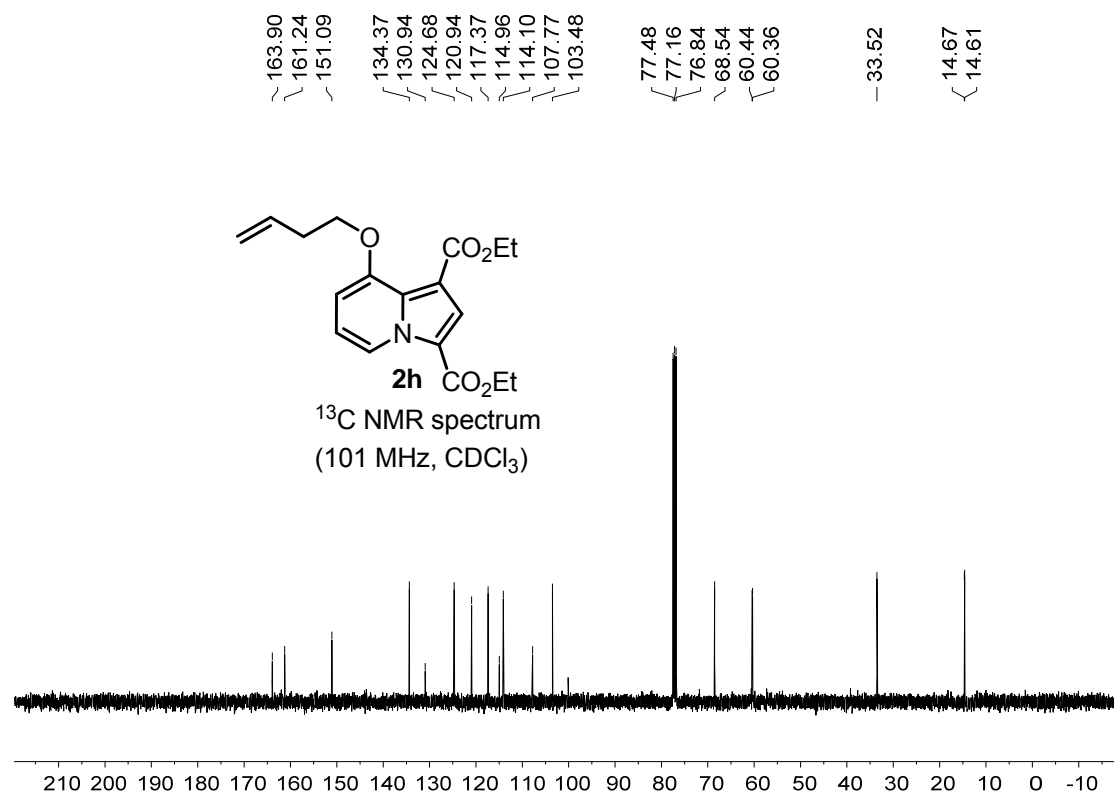
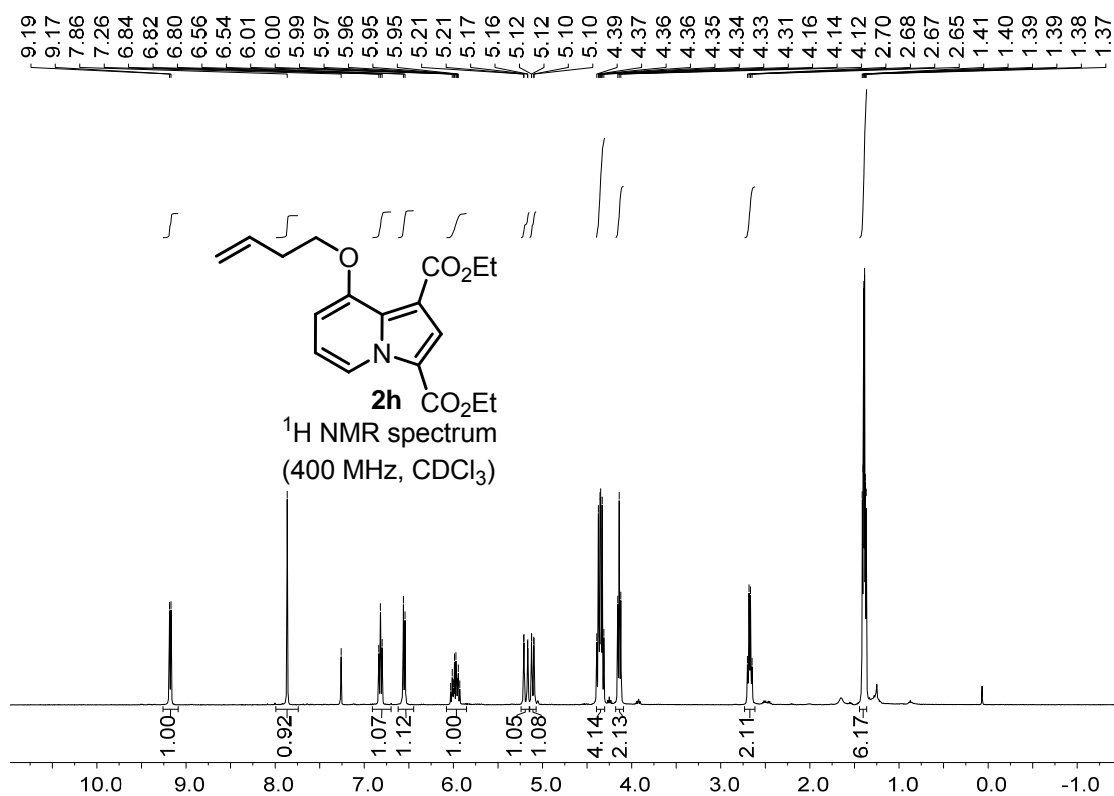


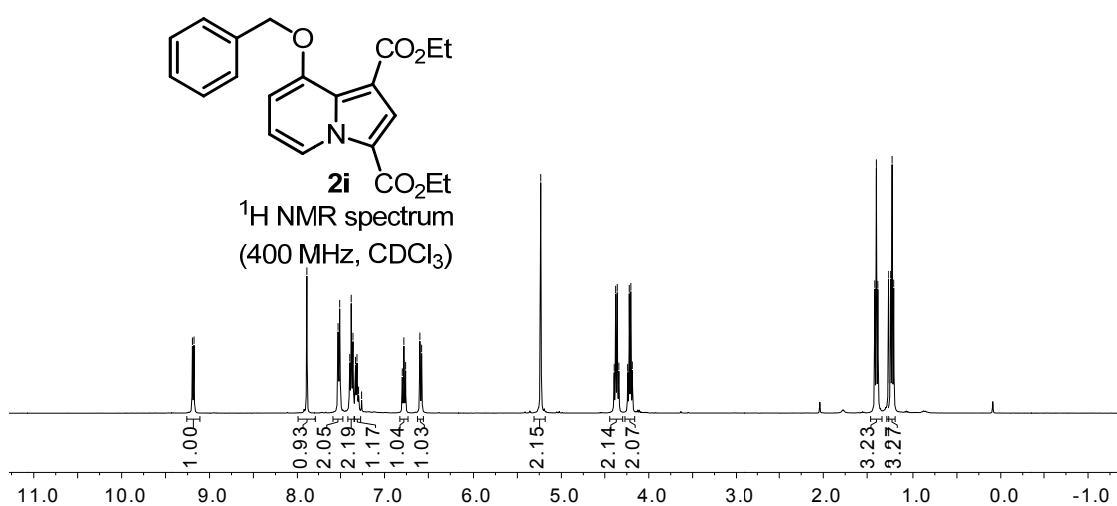
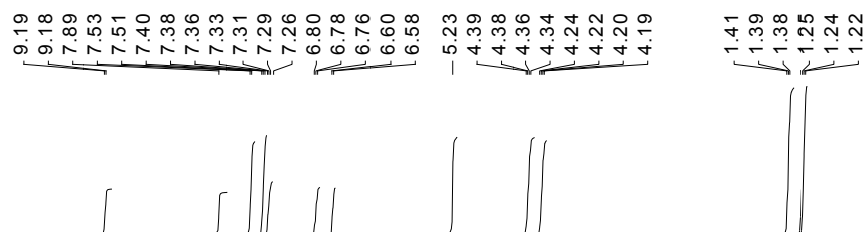
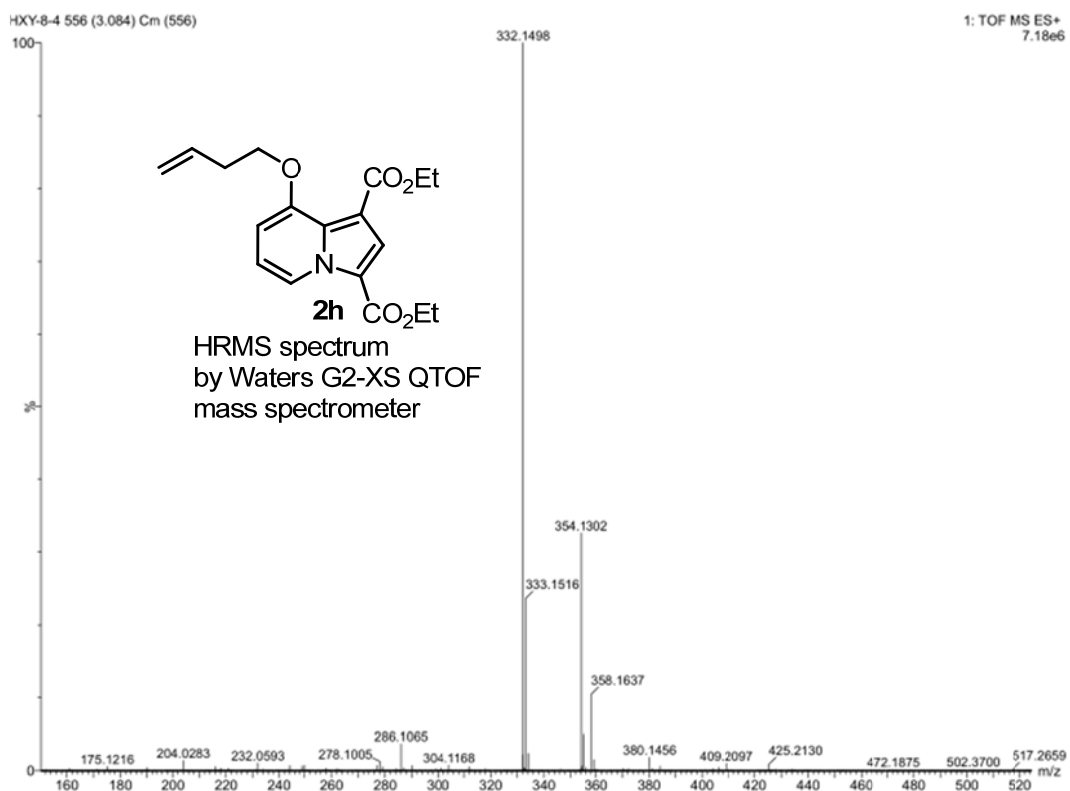


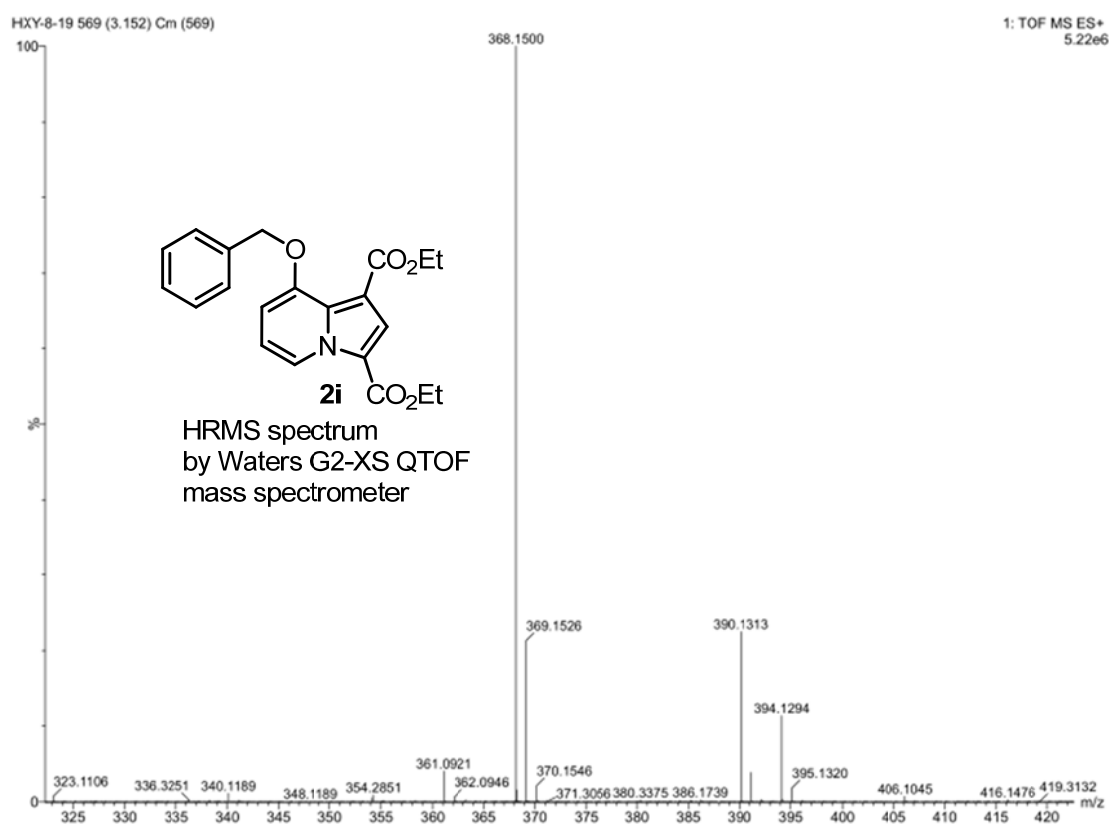
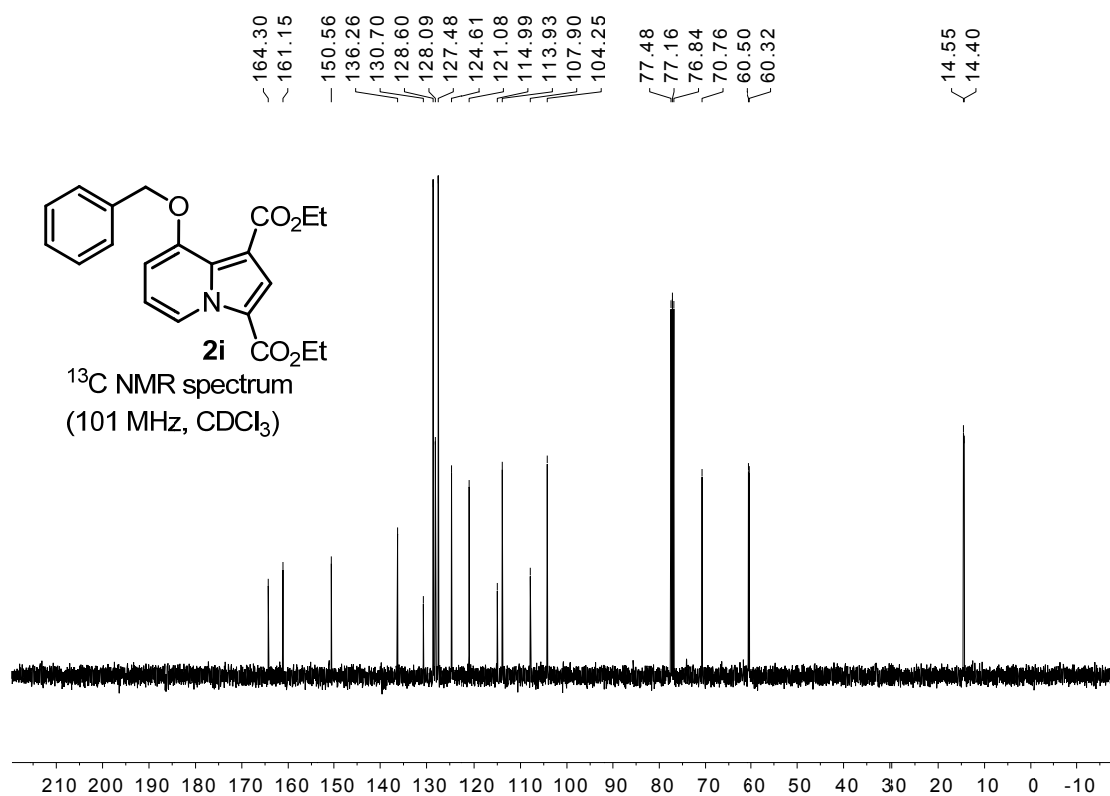


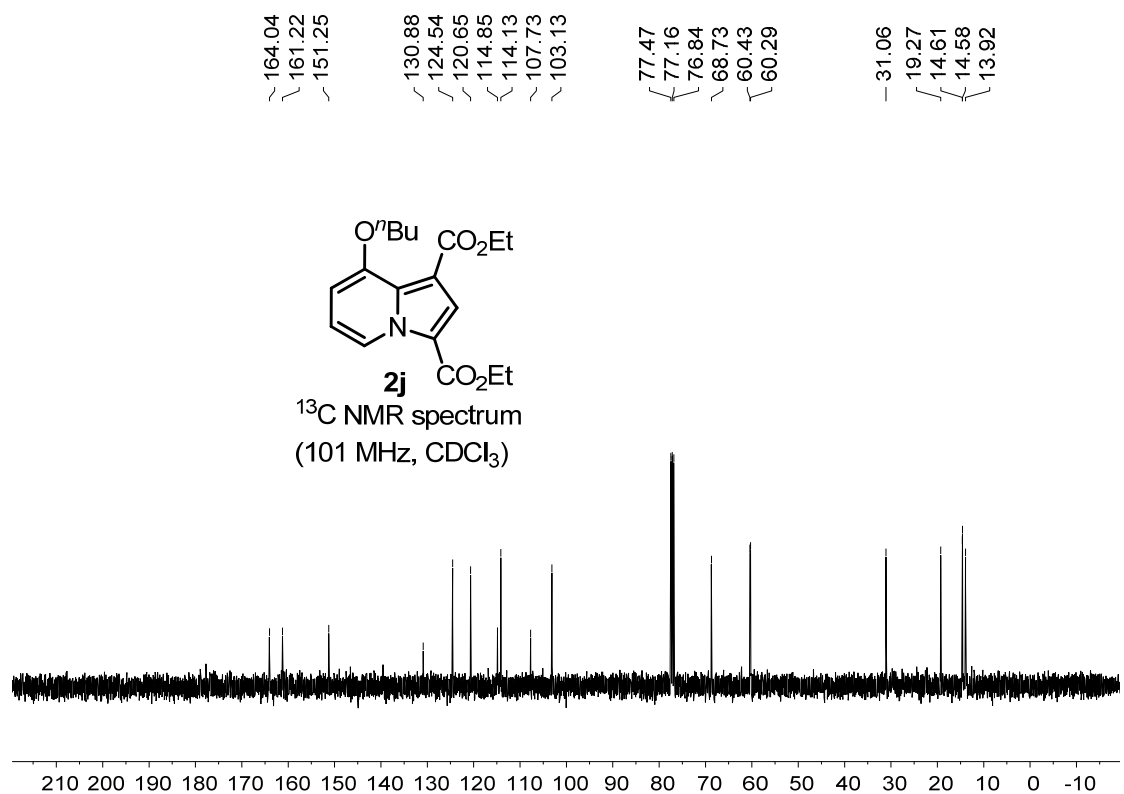
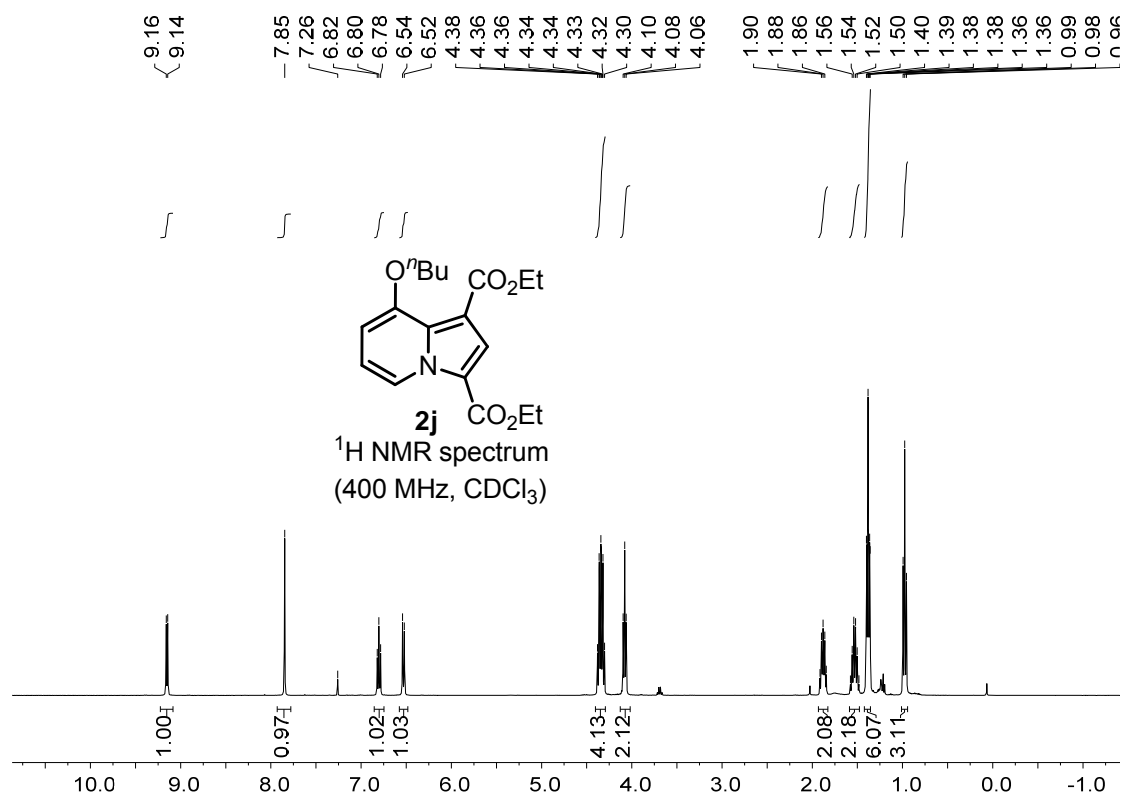


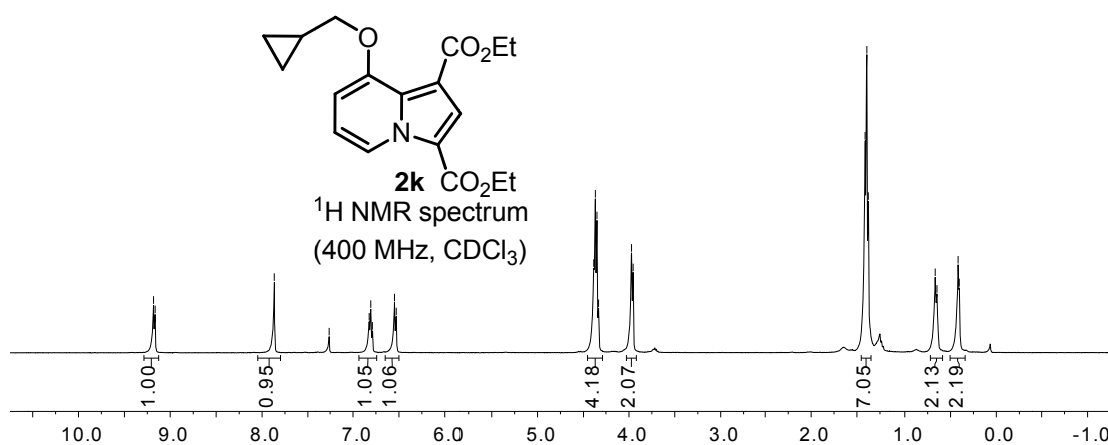
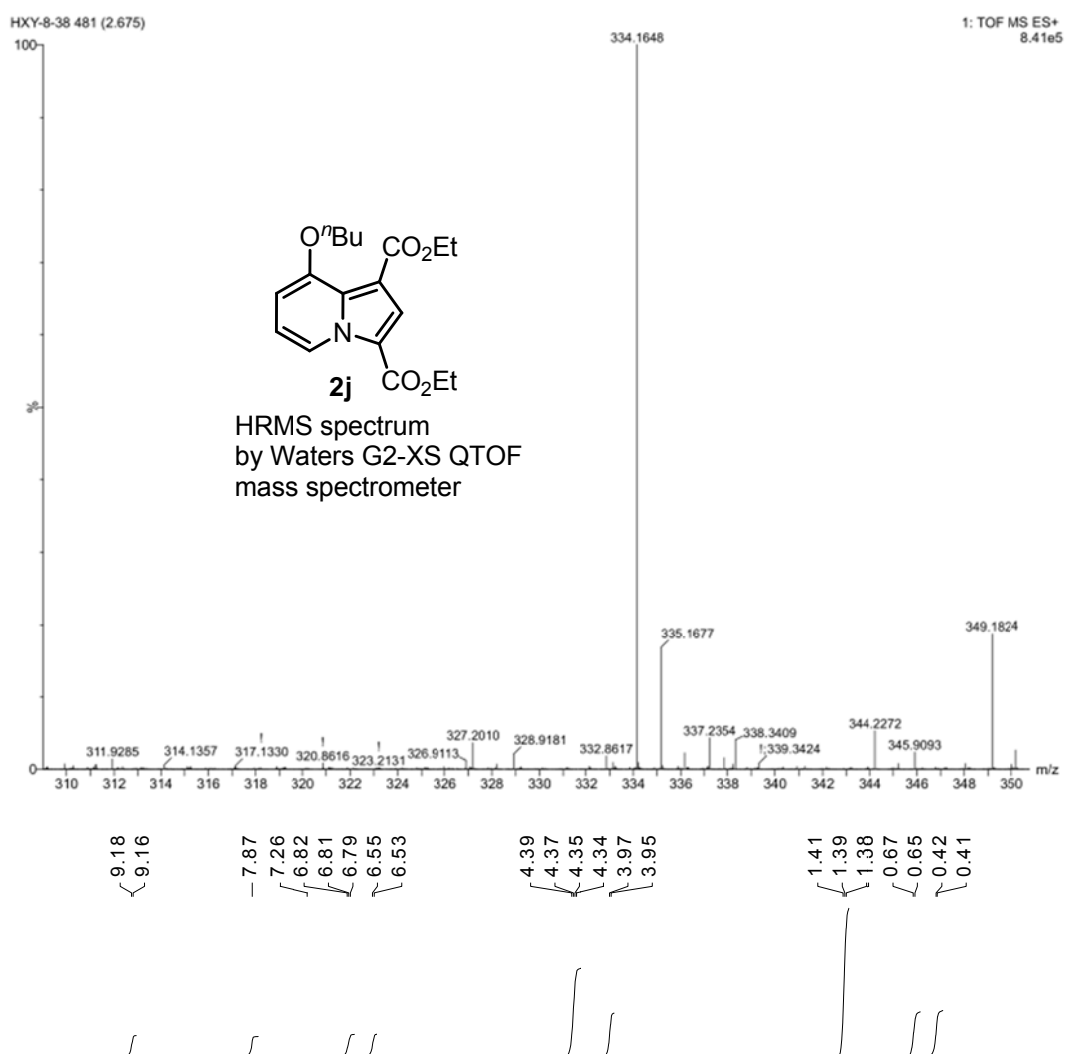


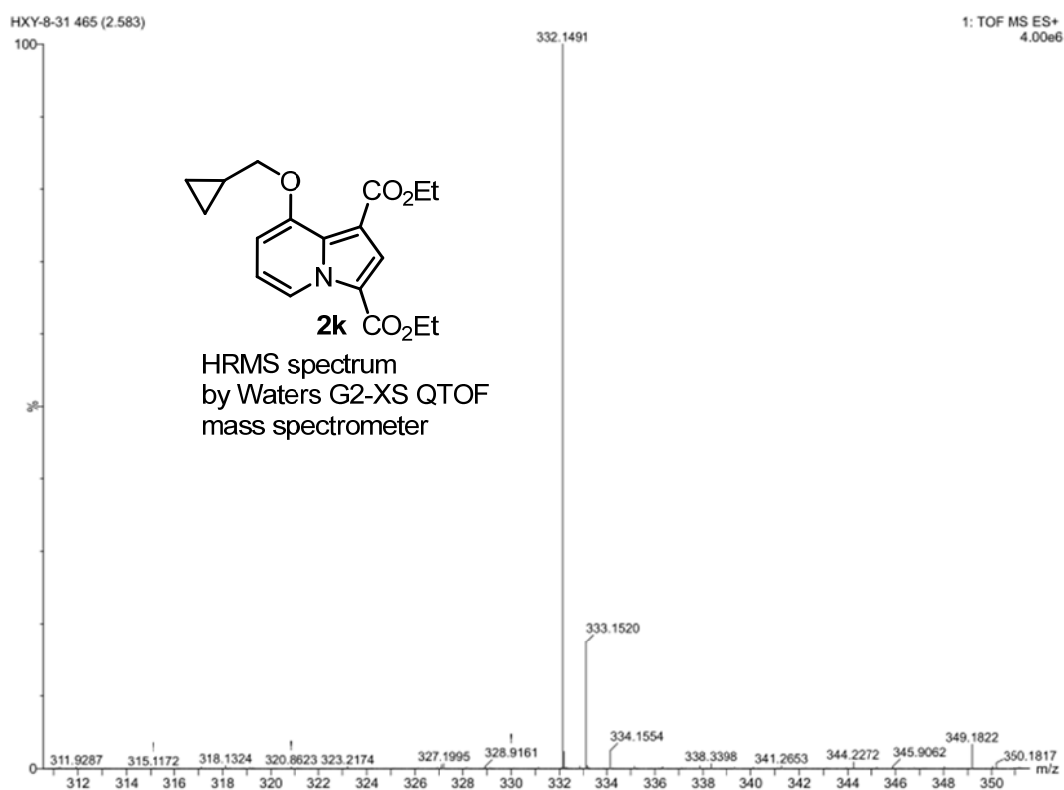
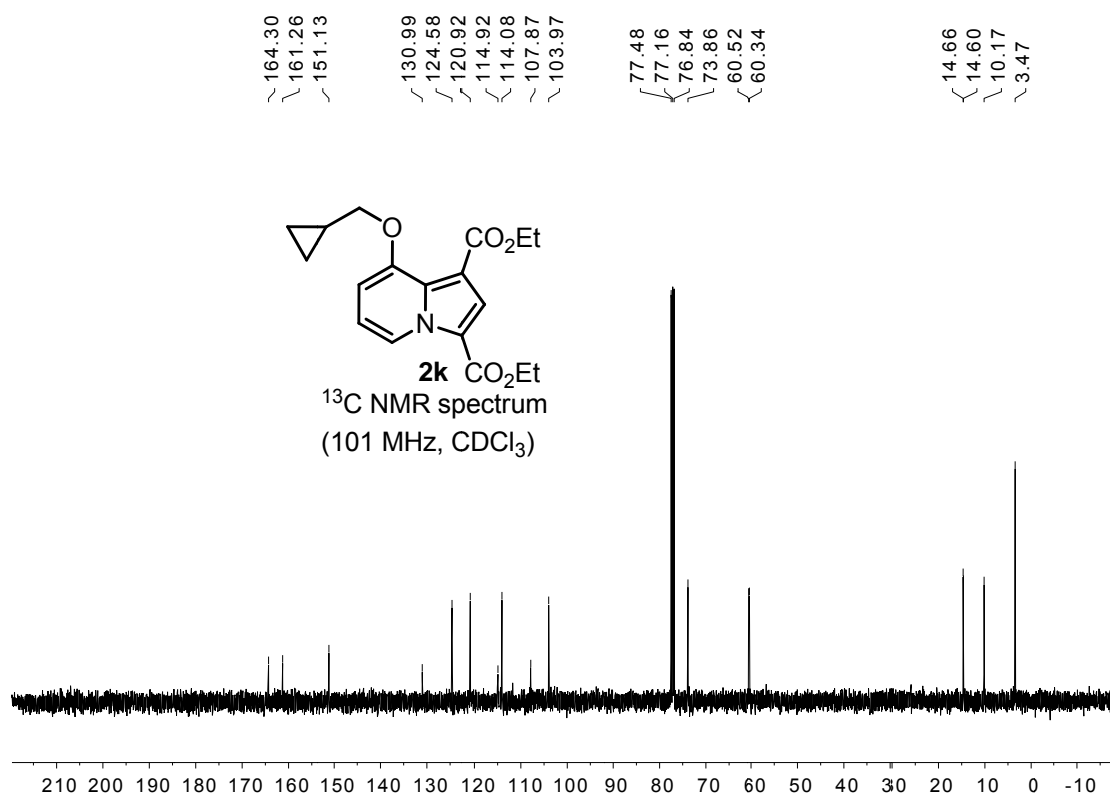


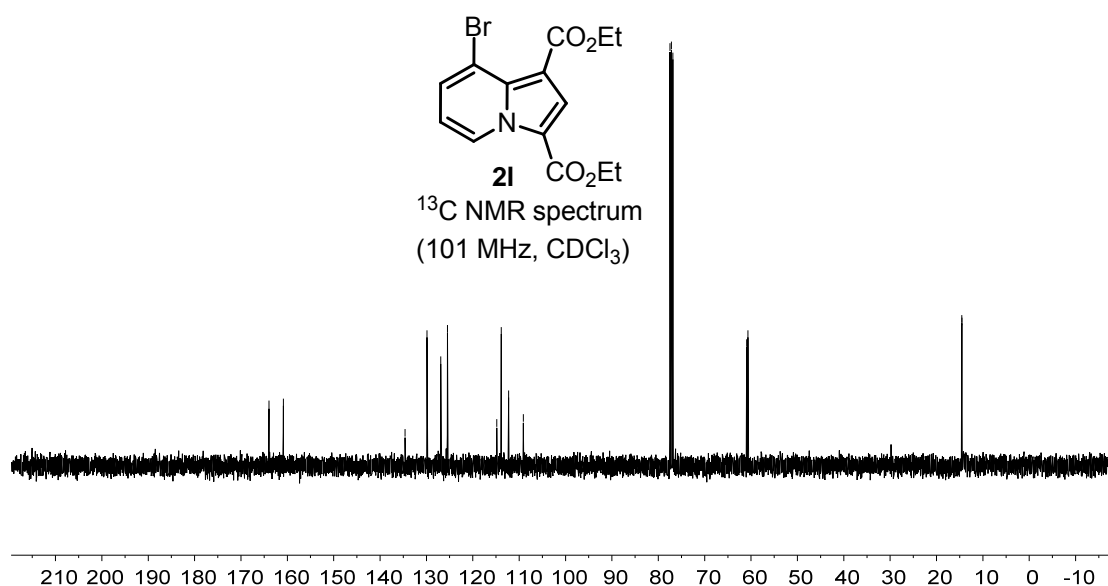
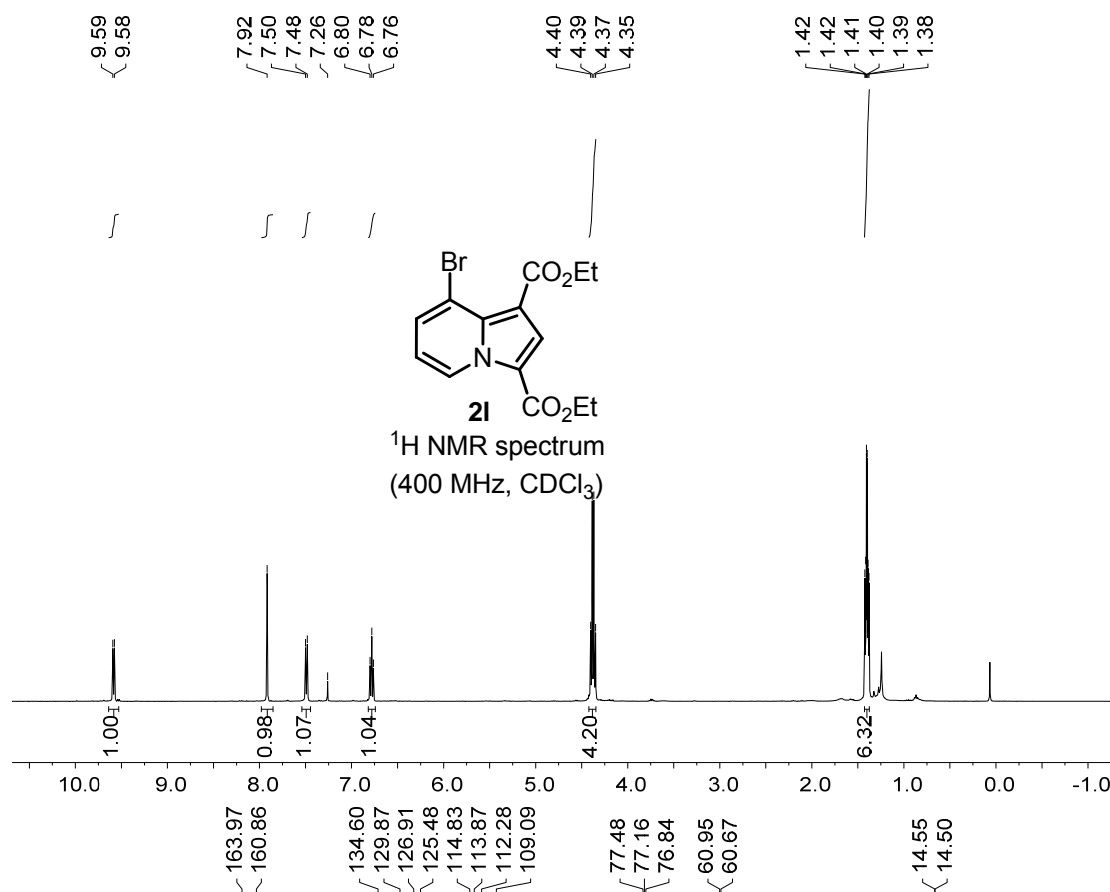


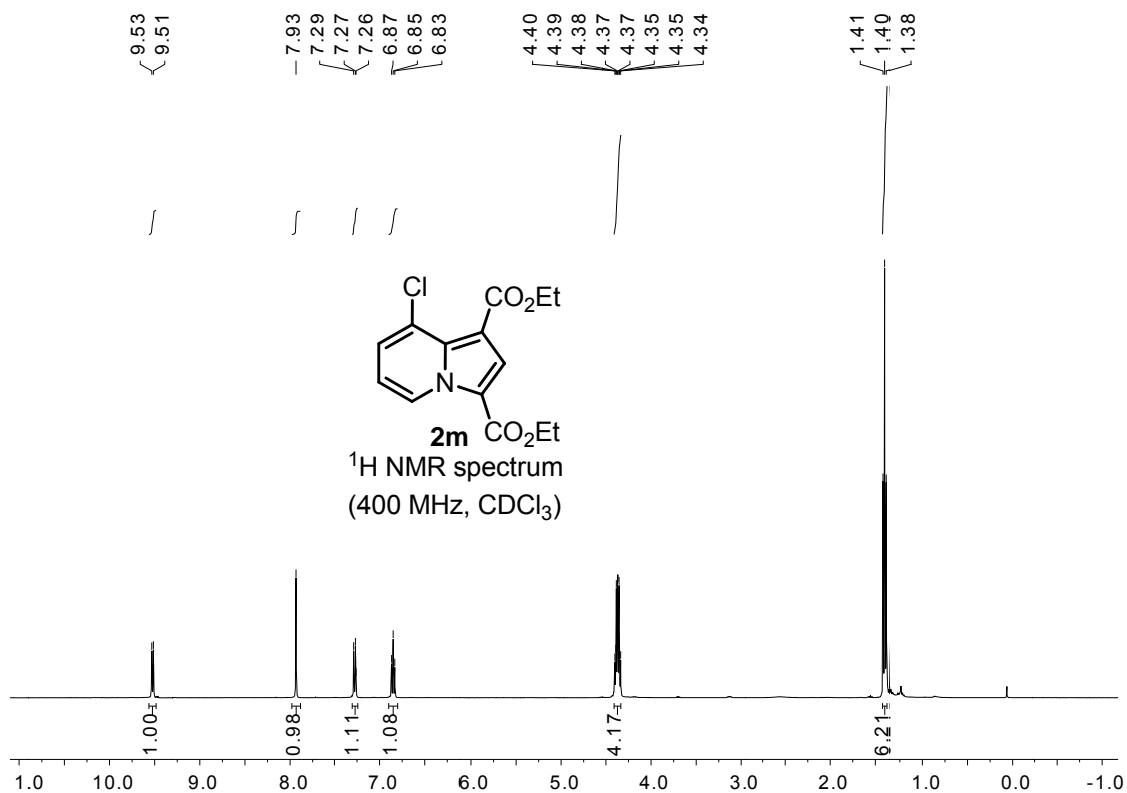
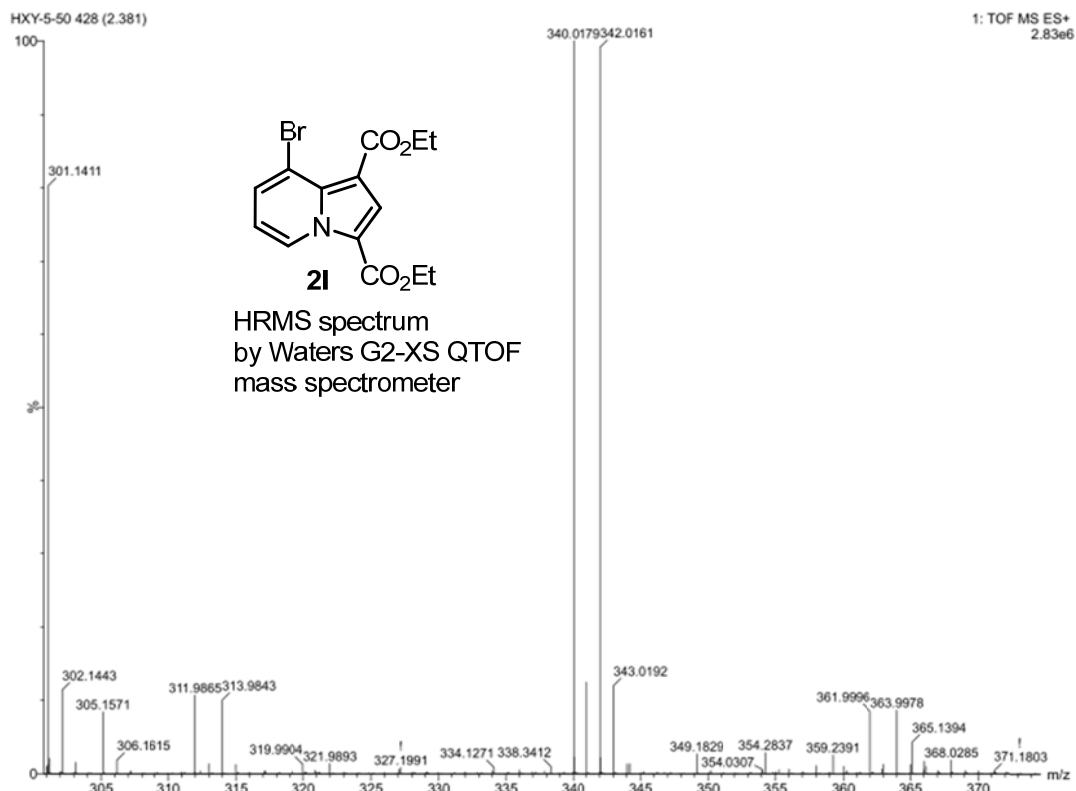


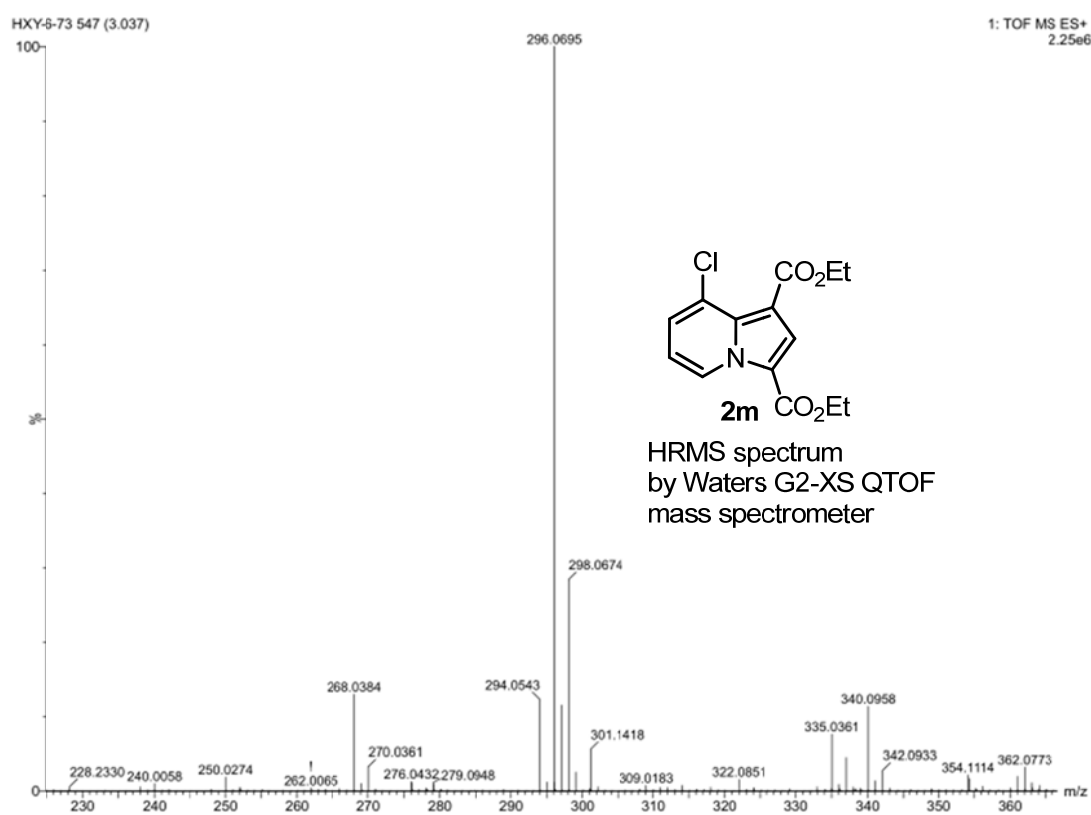
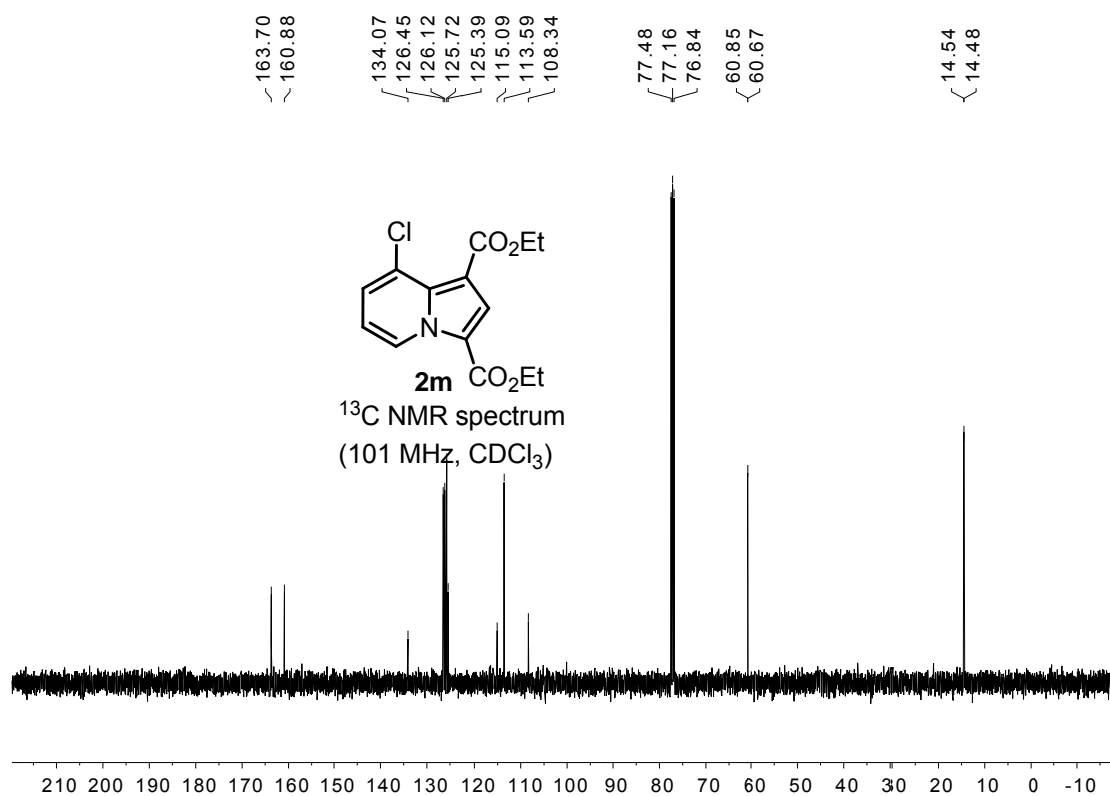


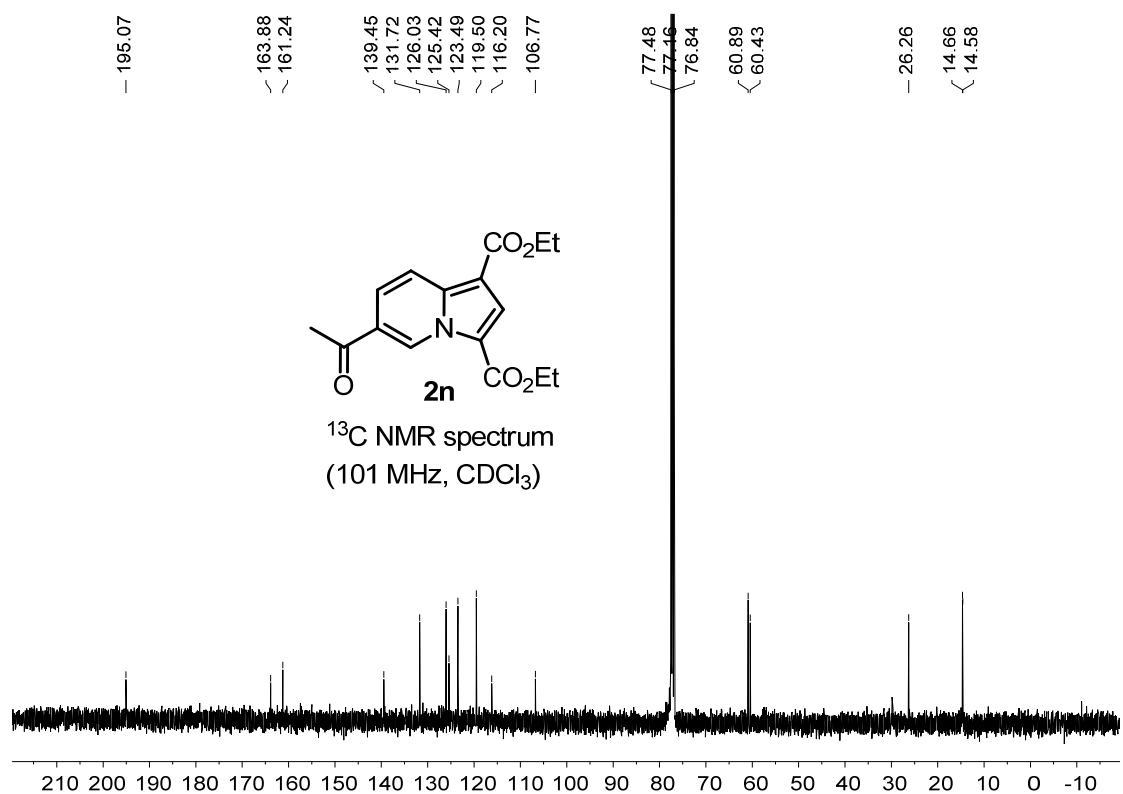
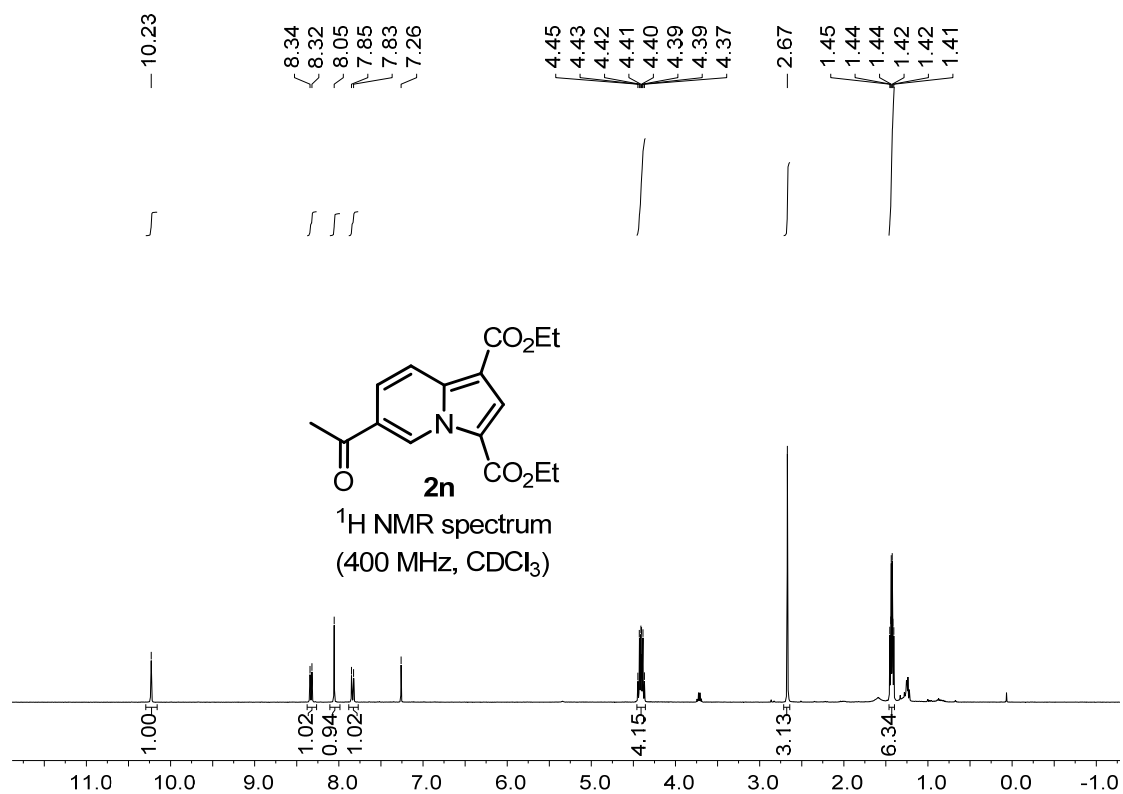


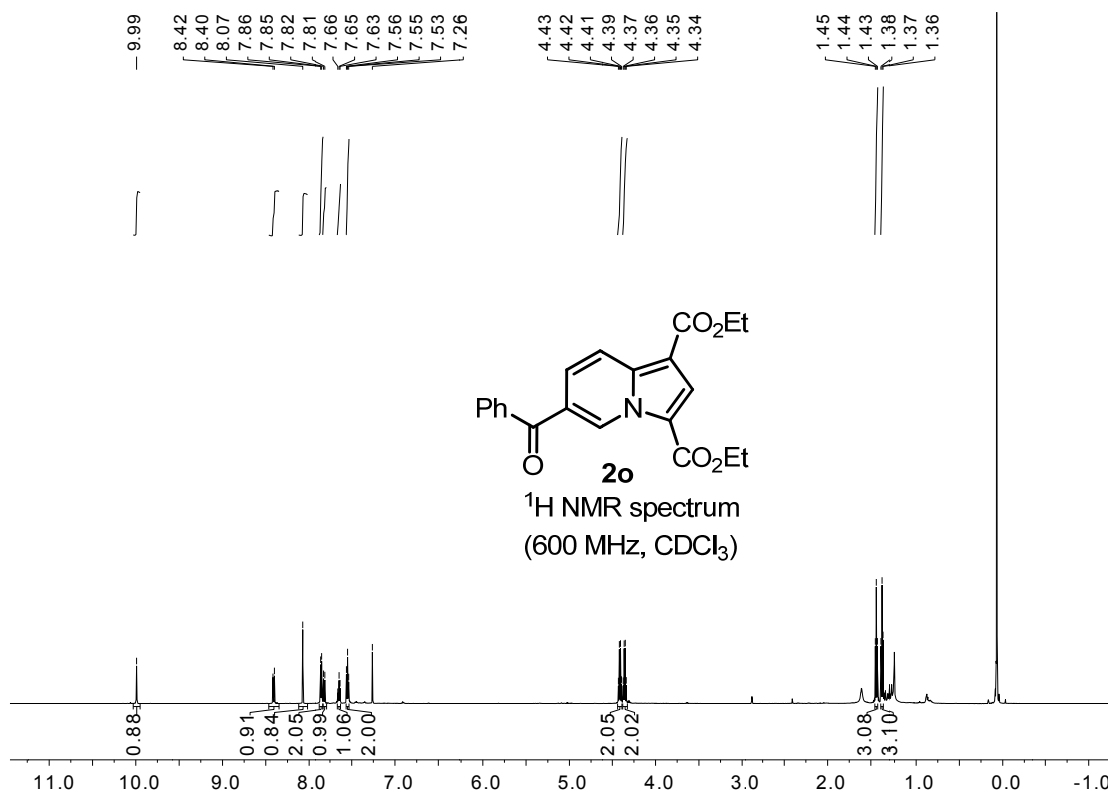
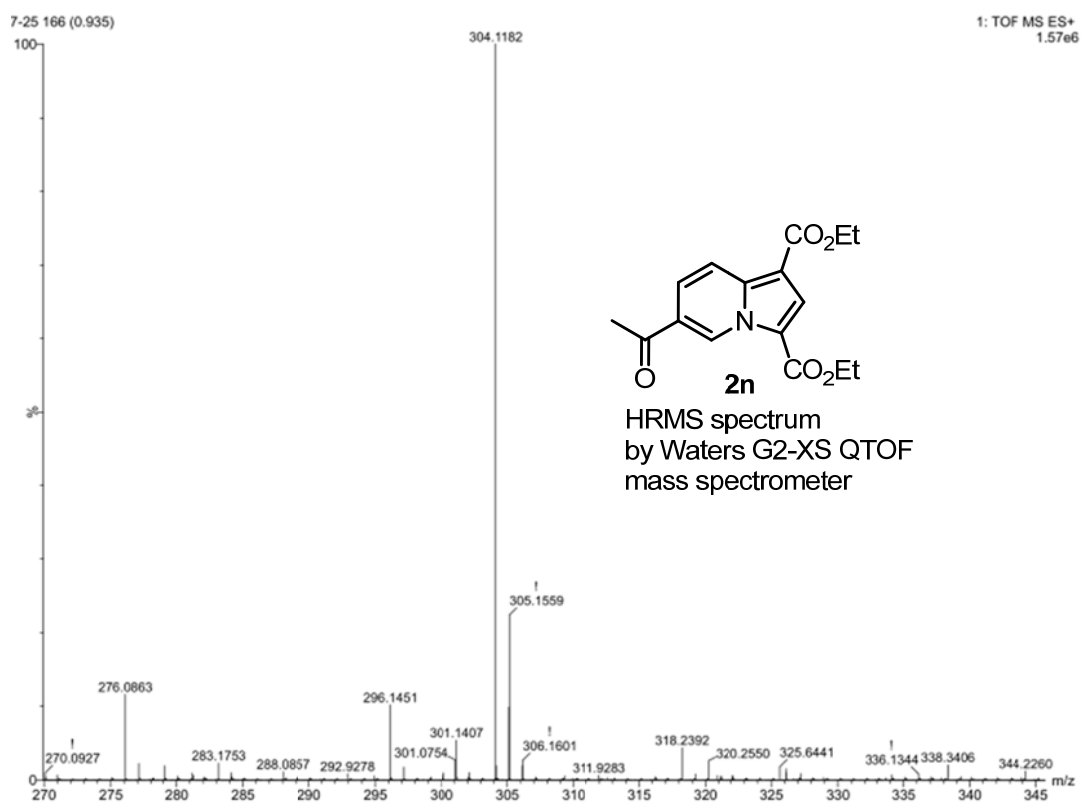


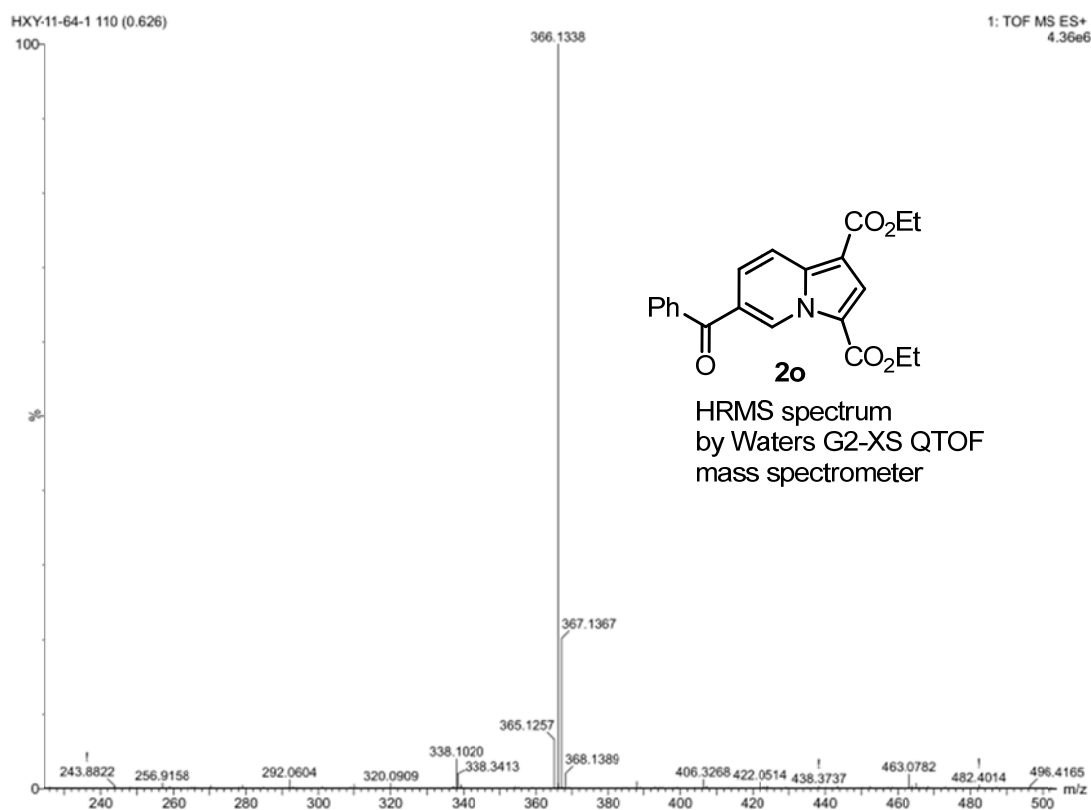
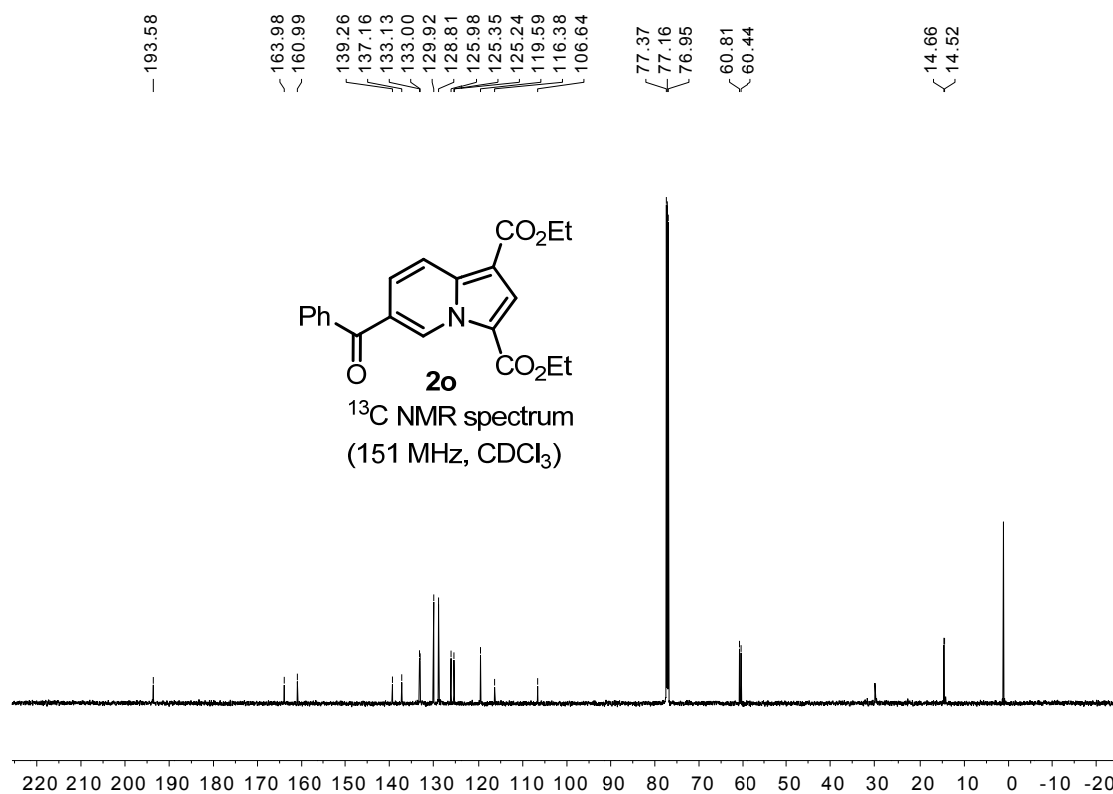


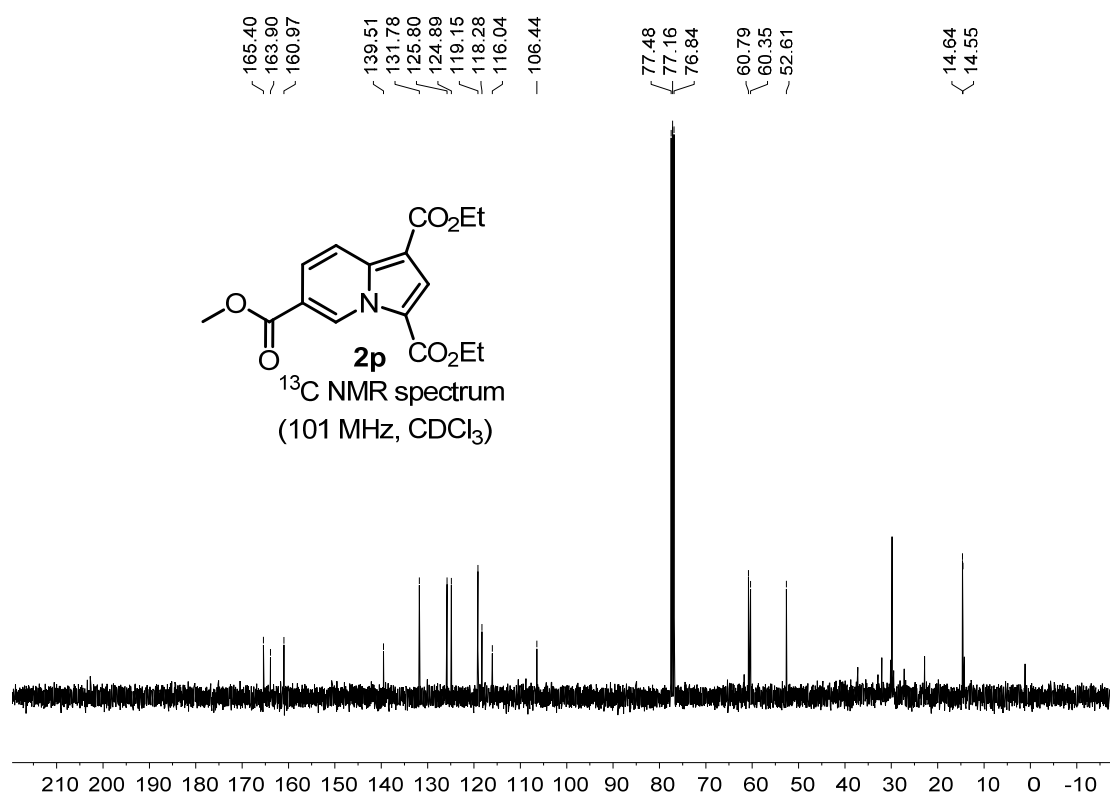
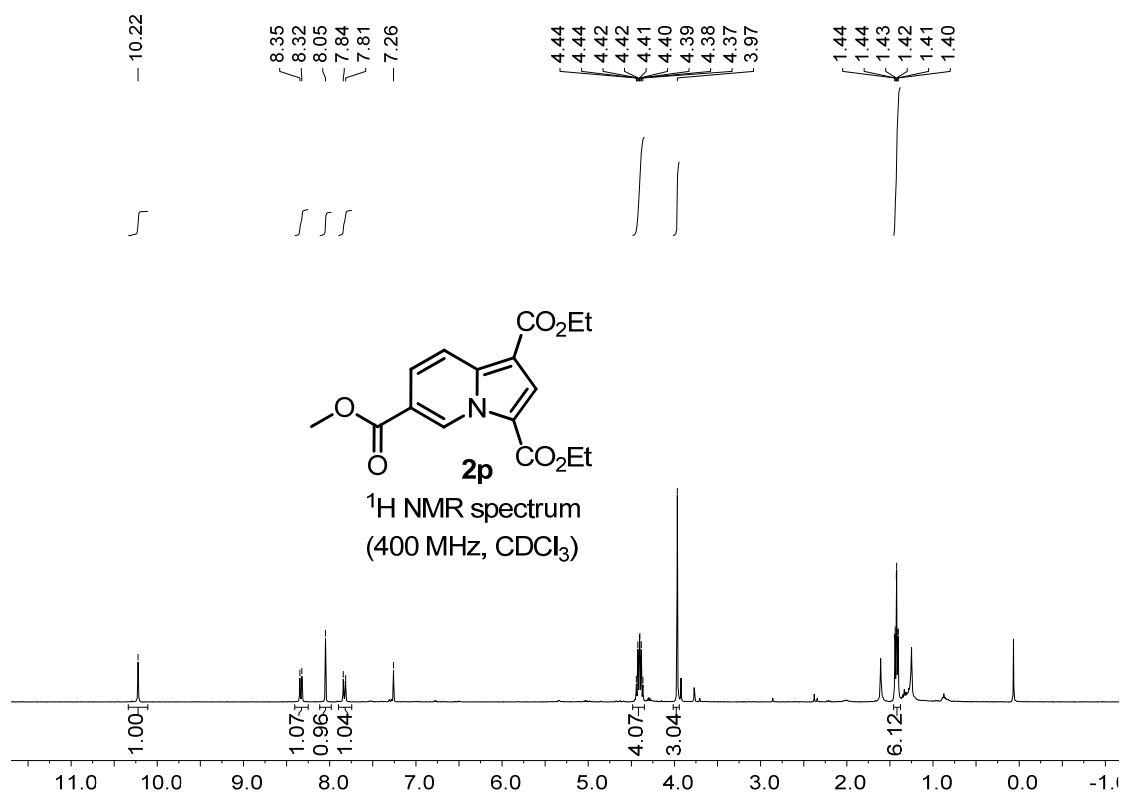


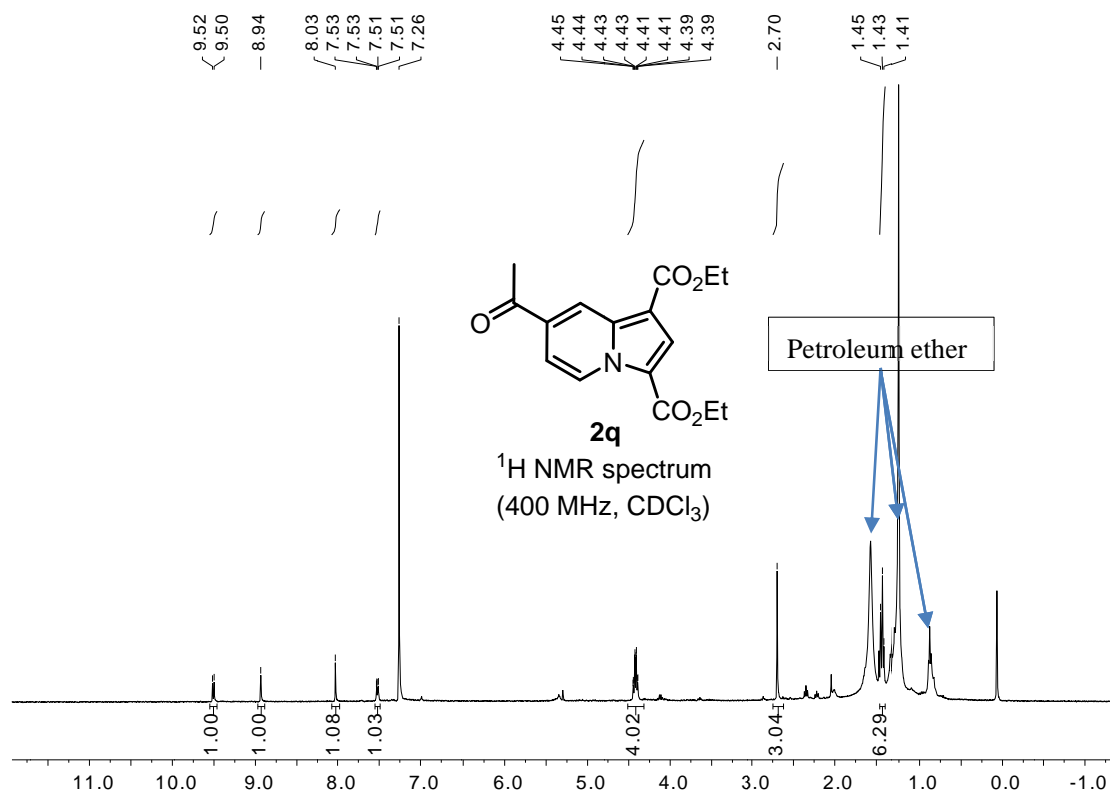
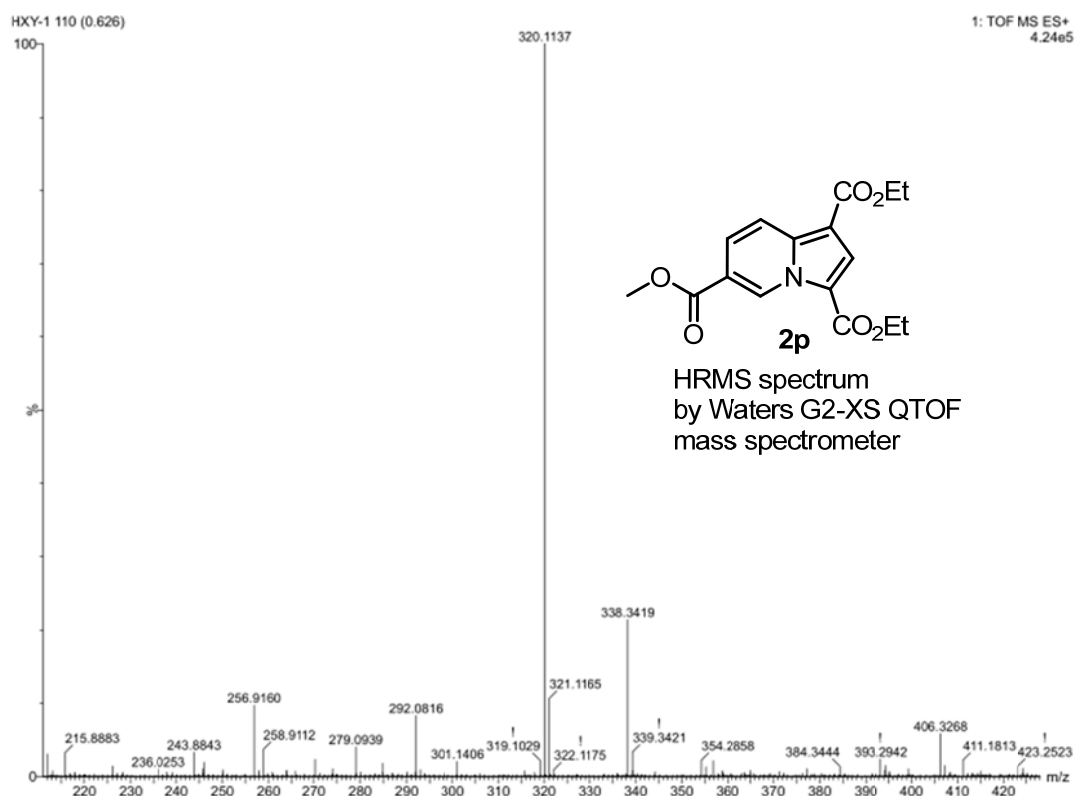




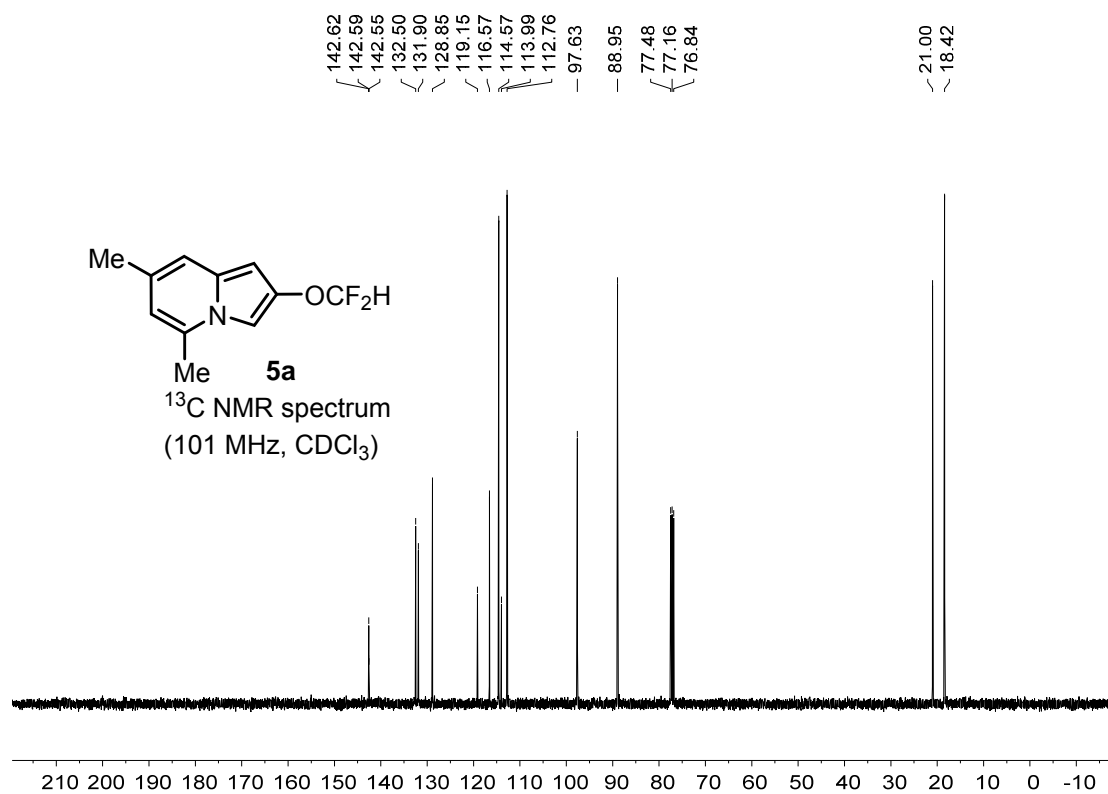
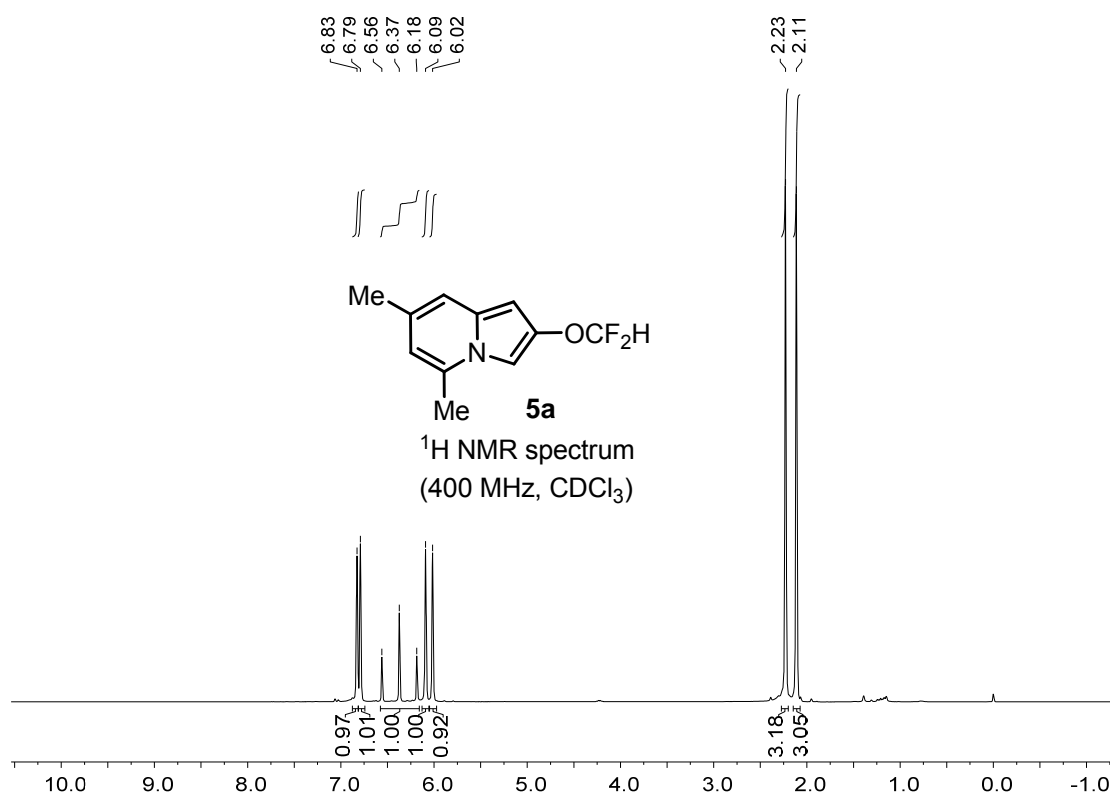


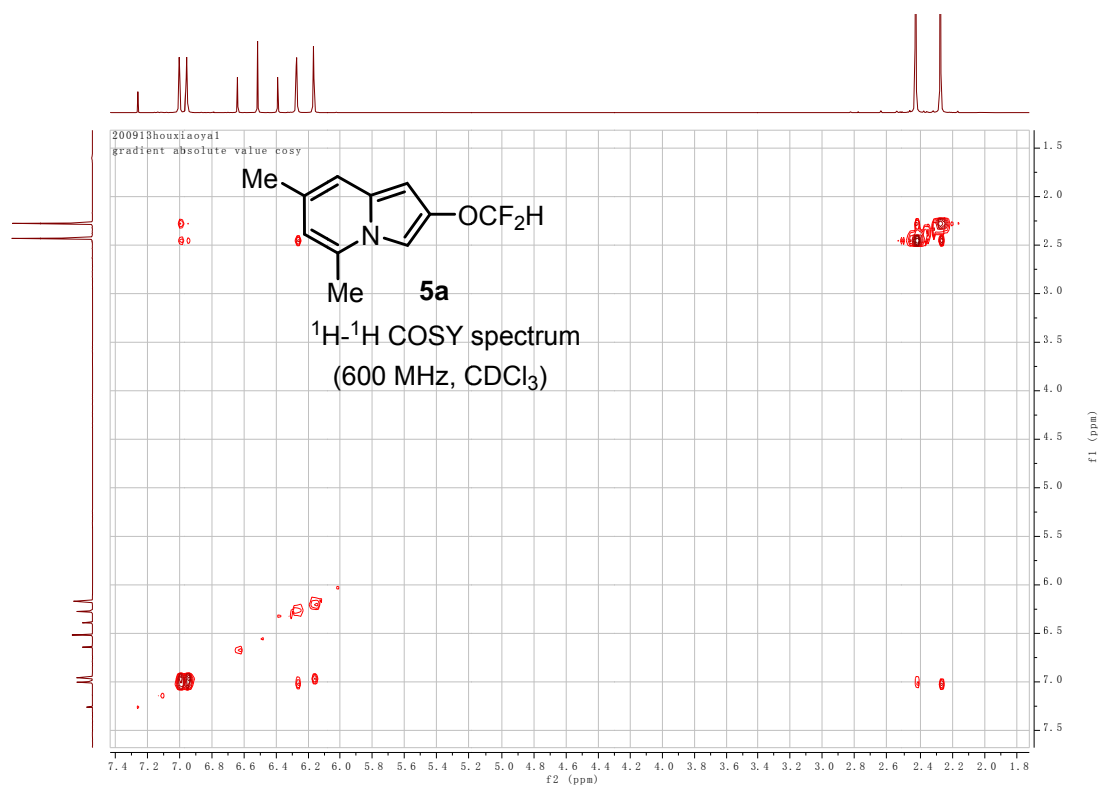
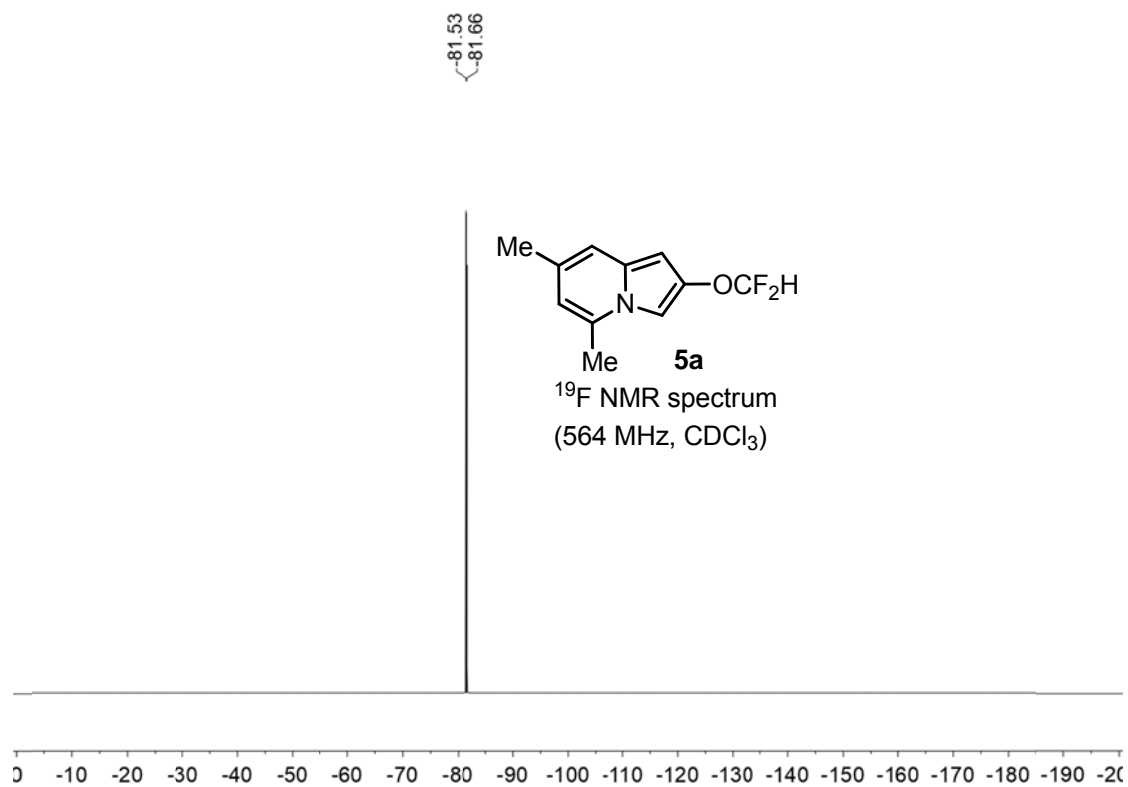


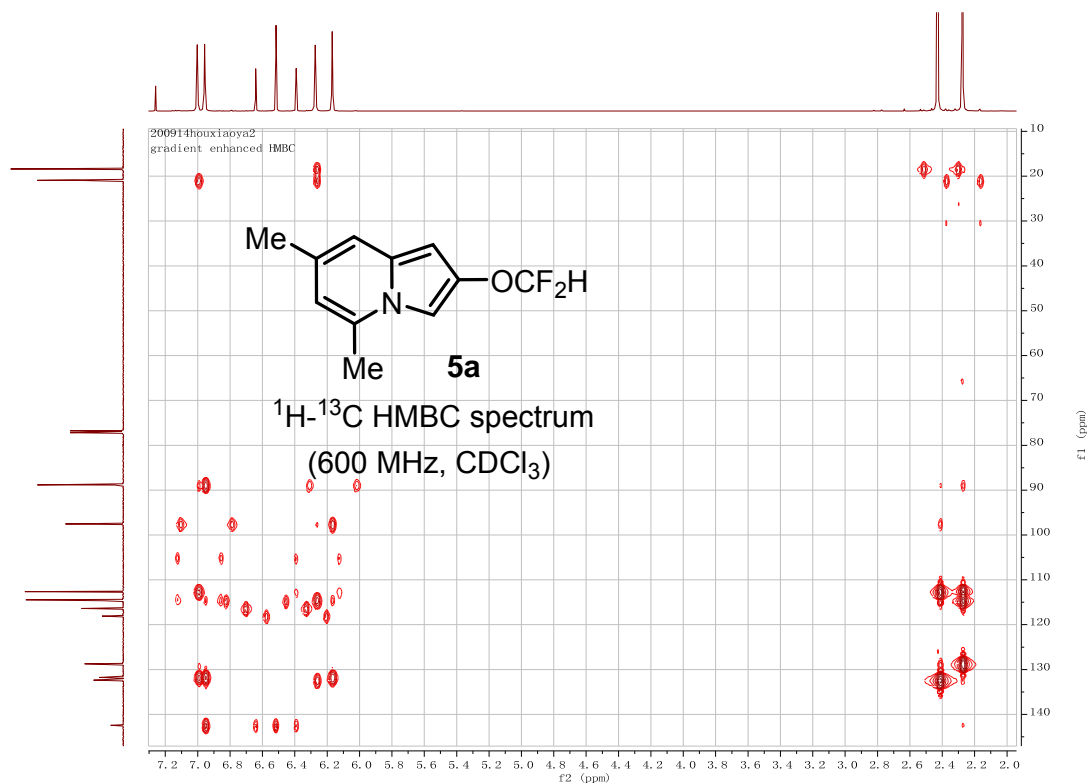
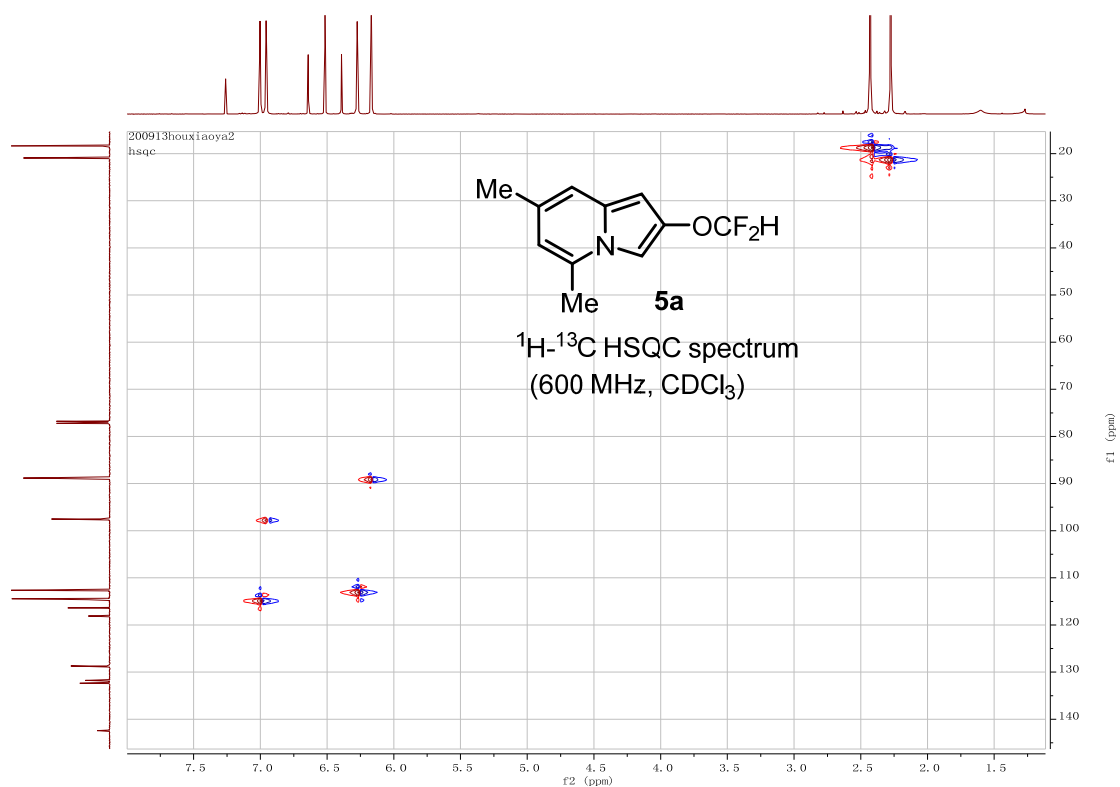


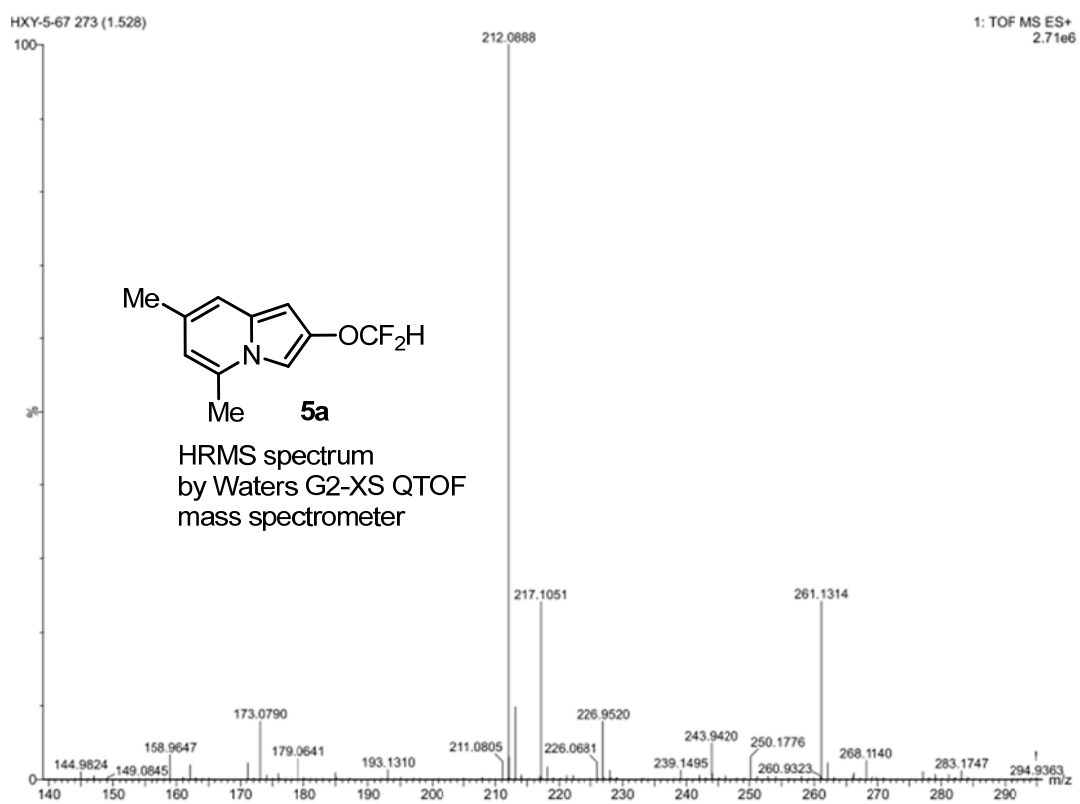
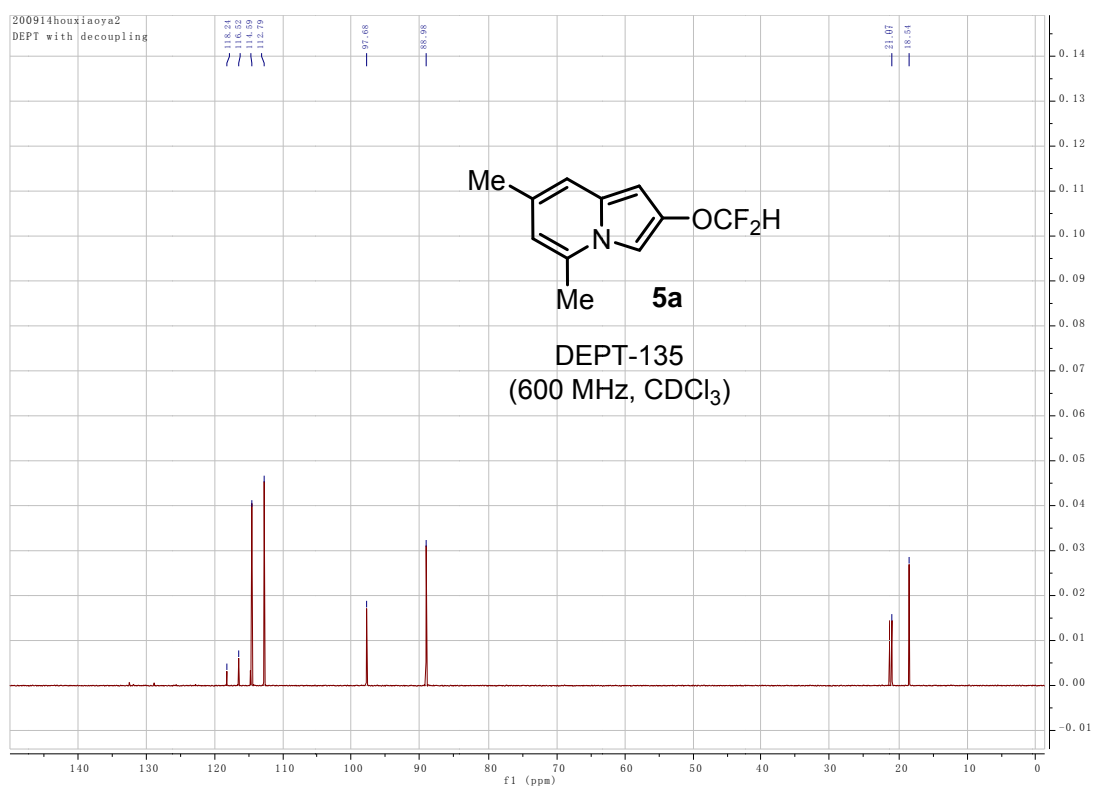


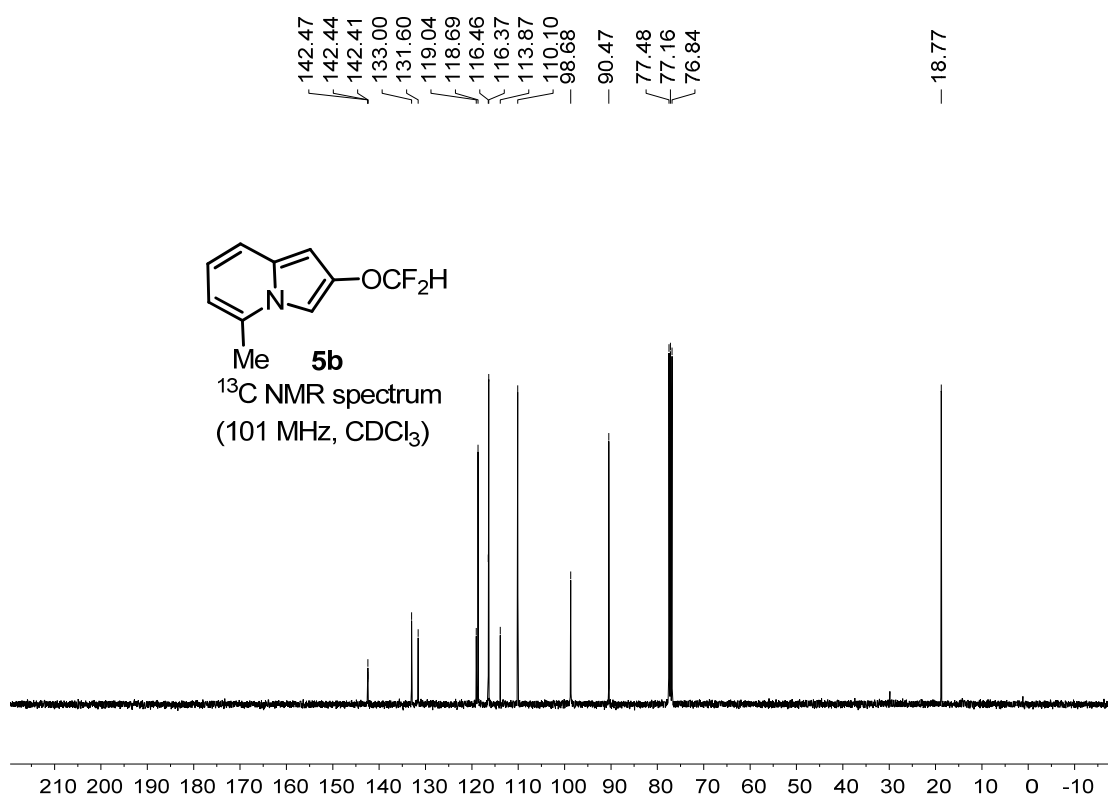
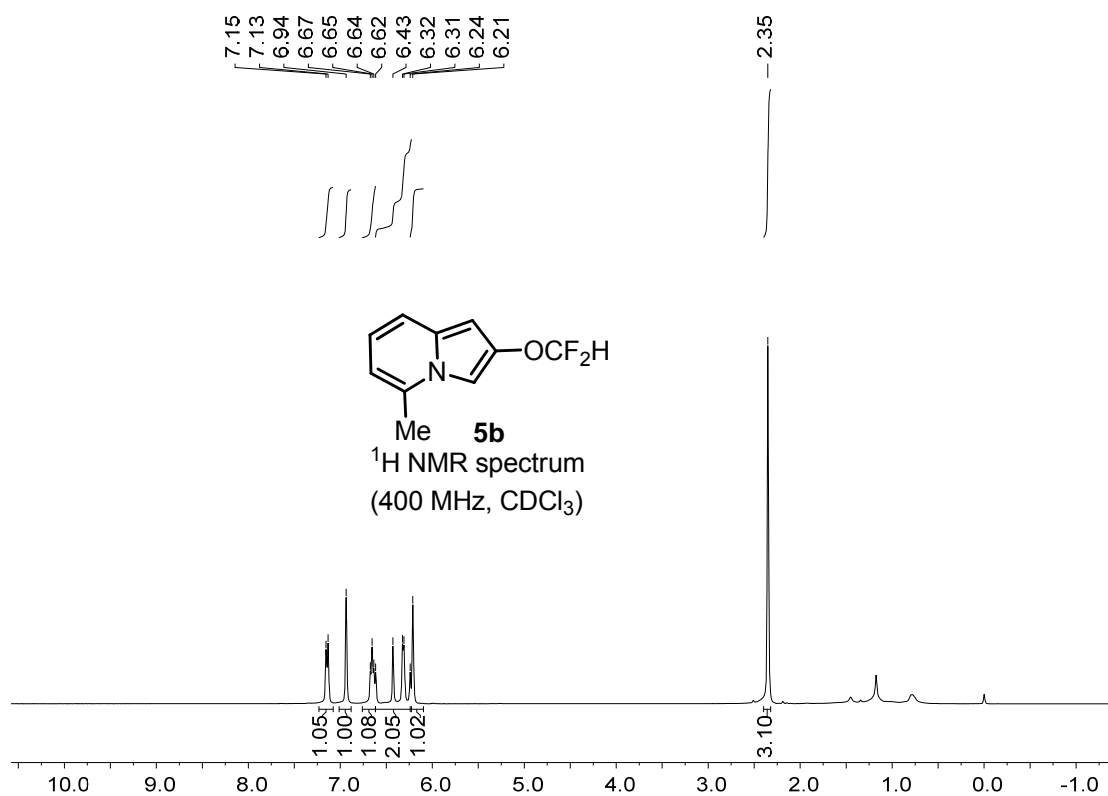
(e) ^1H NMR, ^{13}C NMR, and HRMS spectra of **5**.

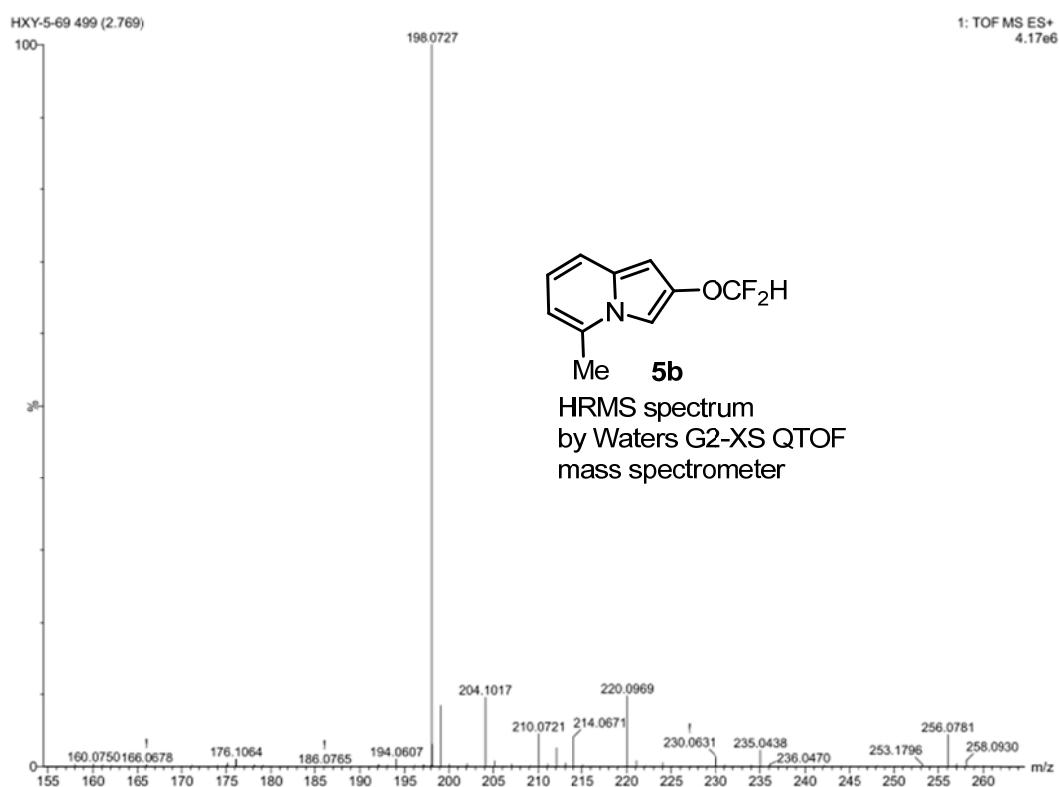
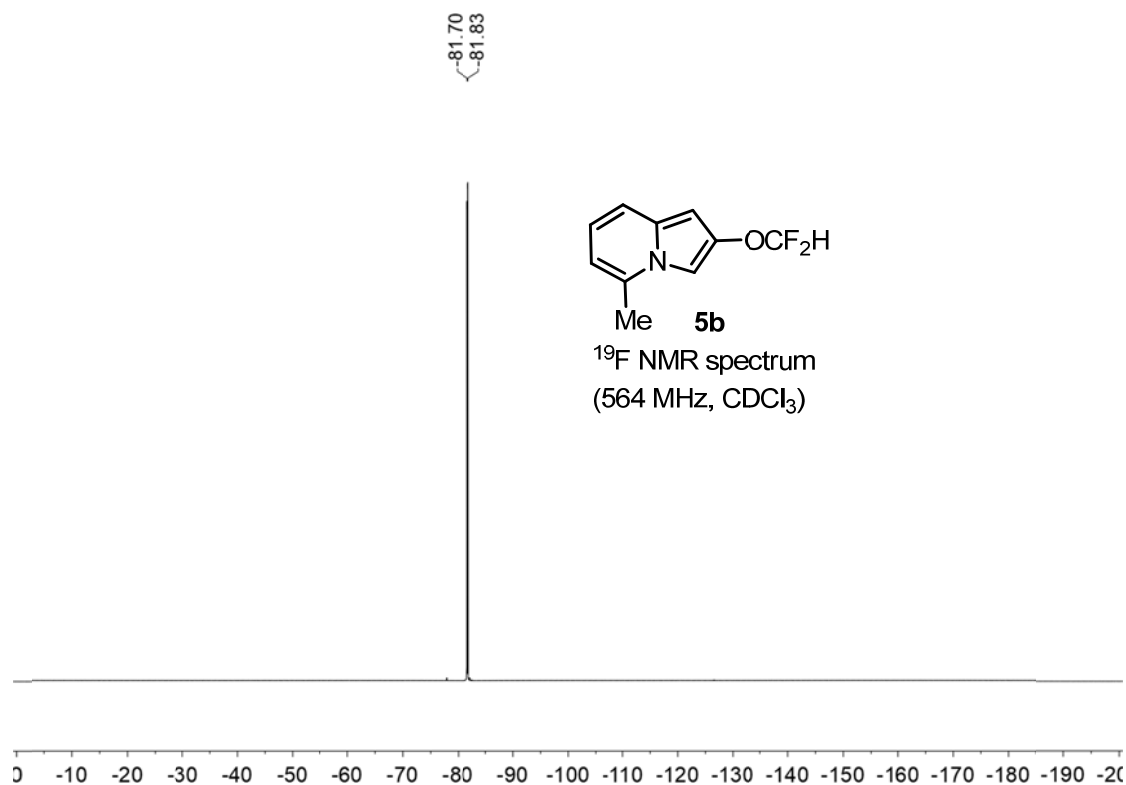


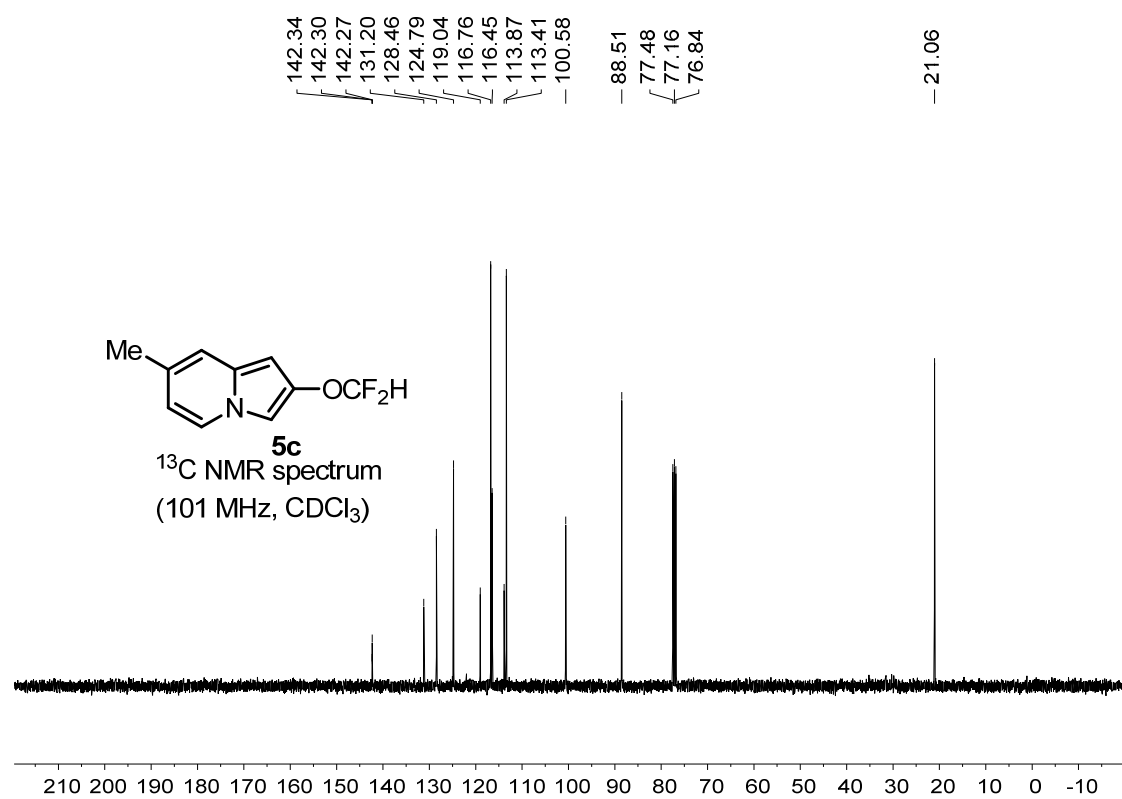
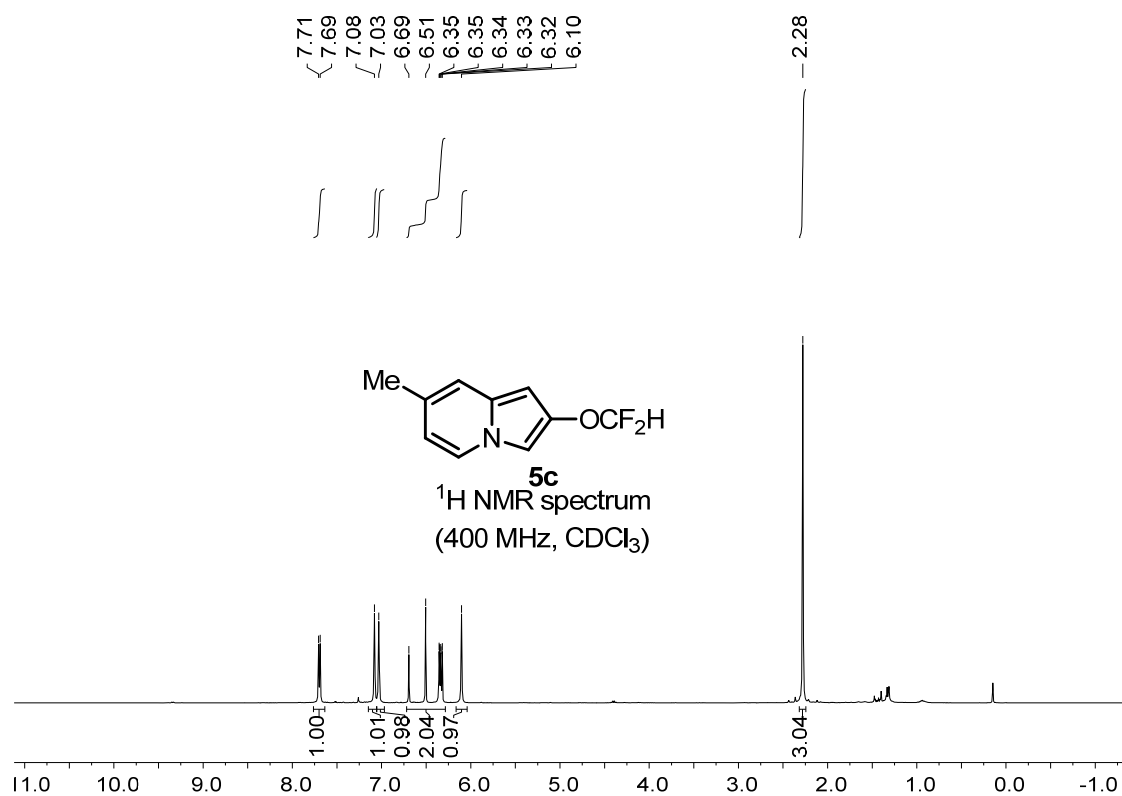


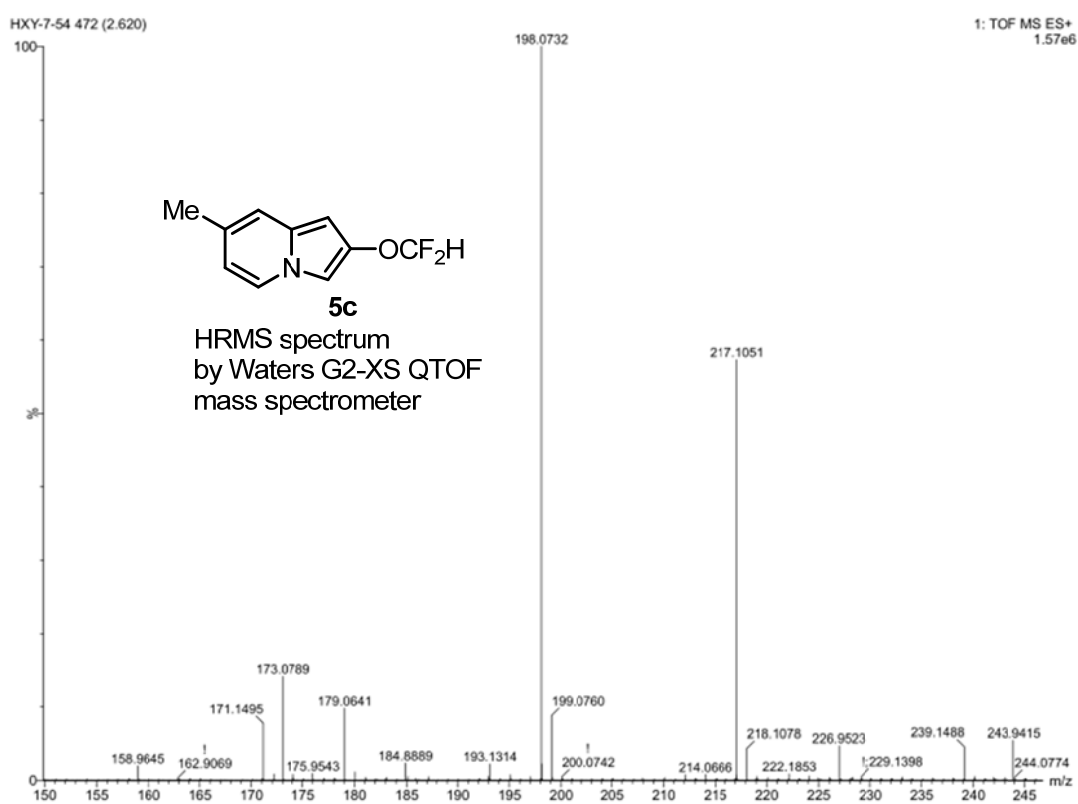
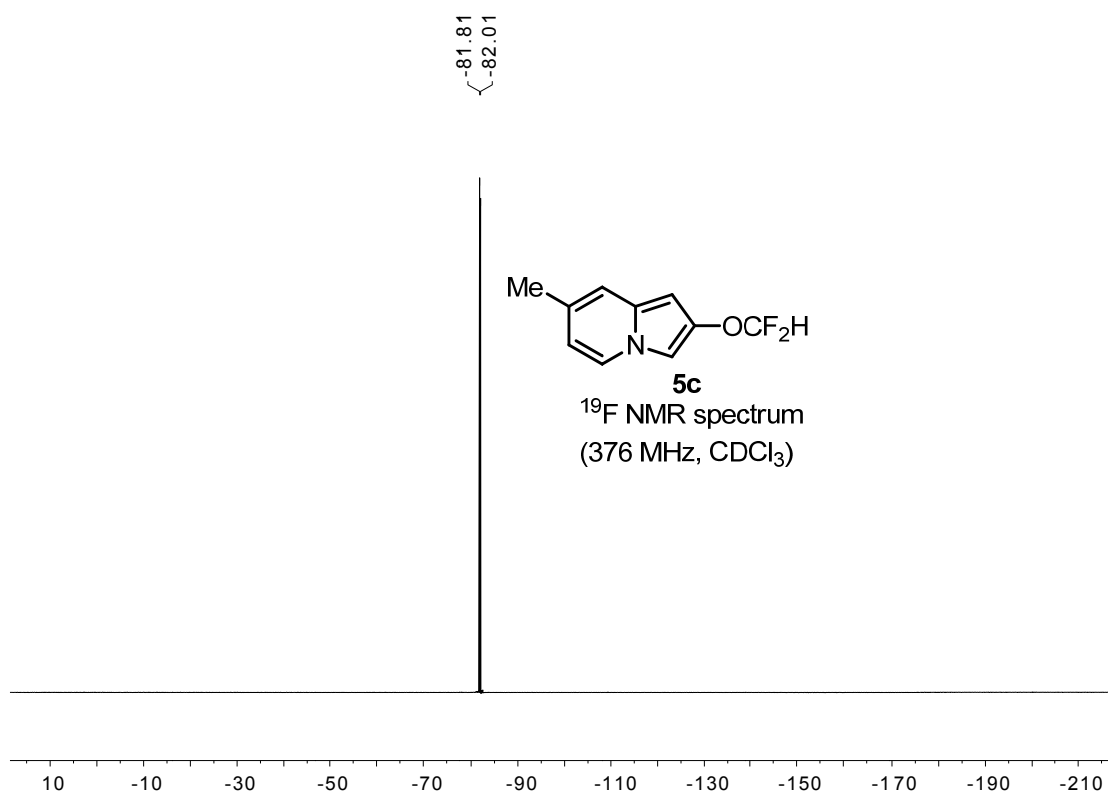


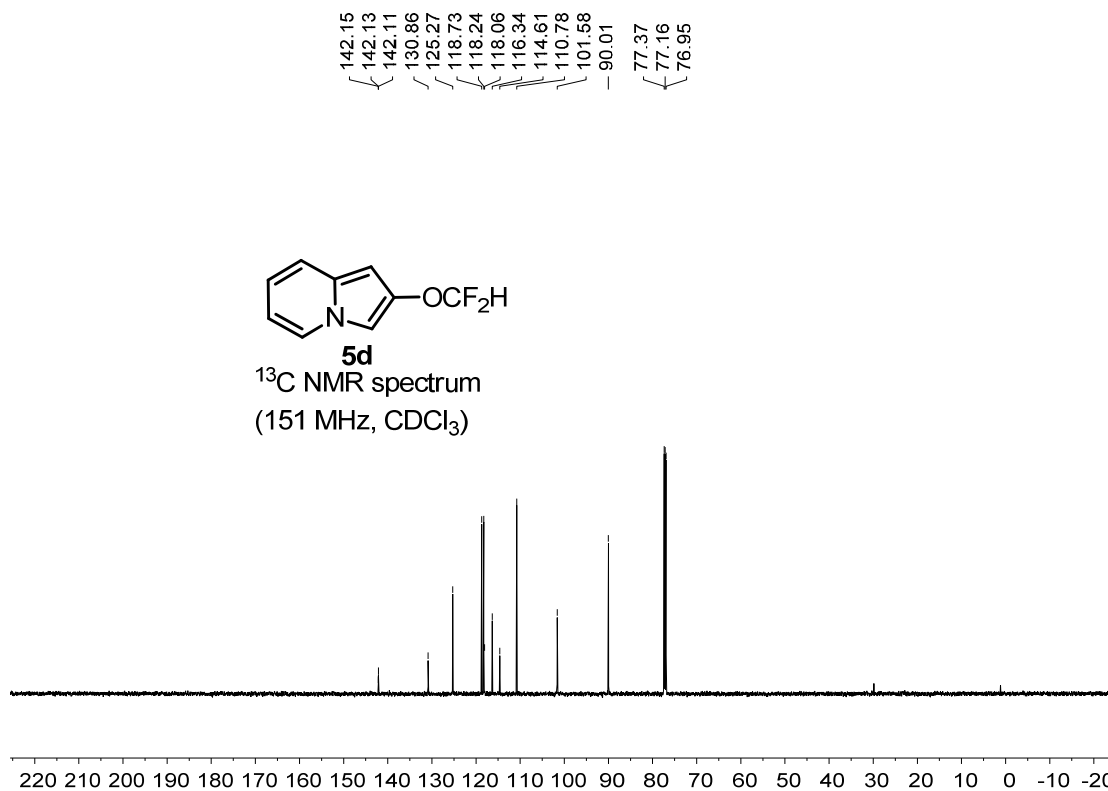
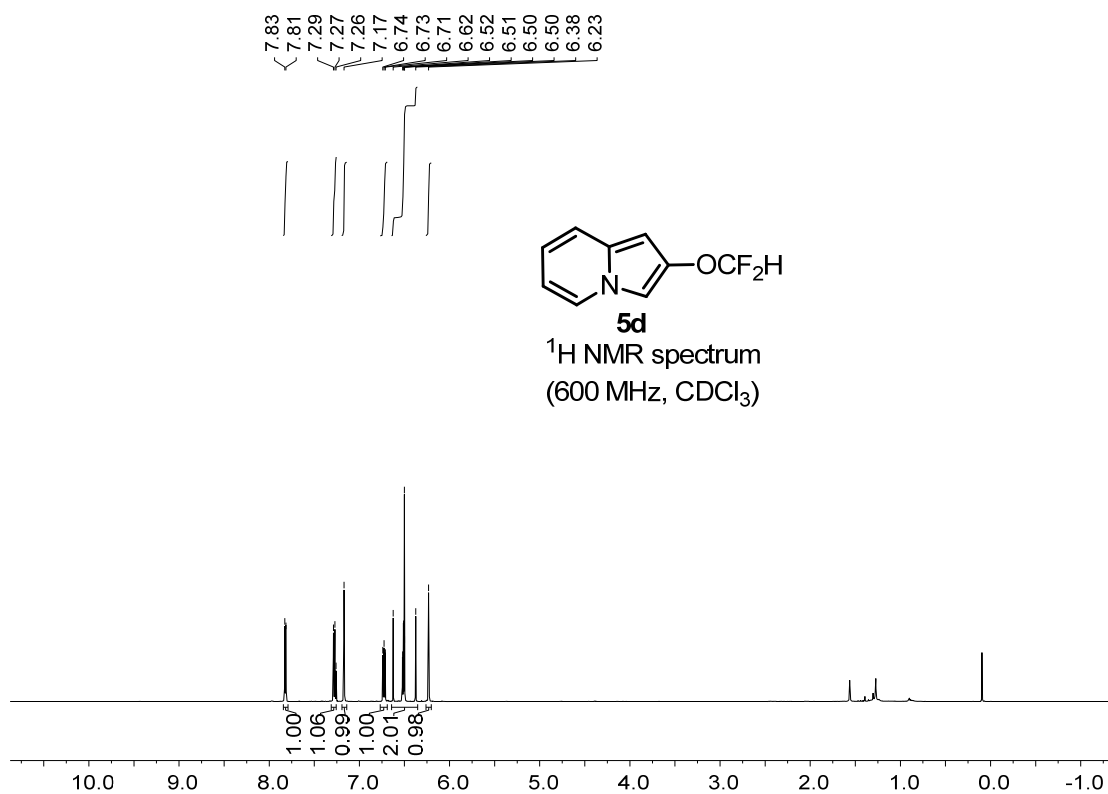


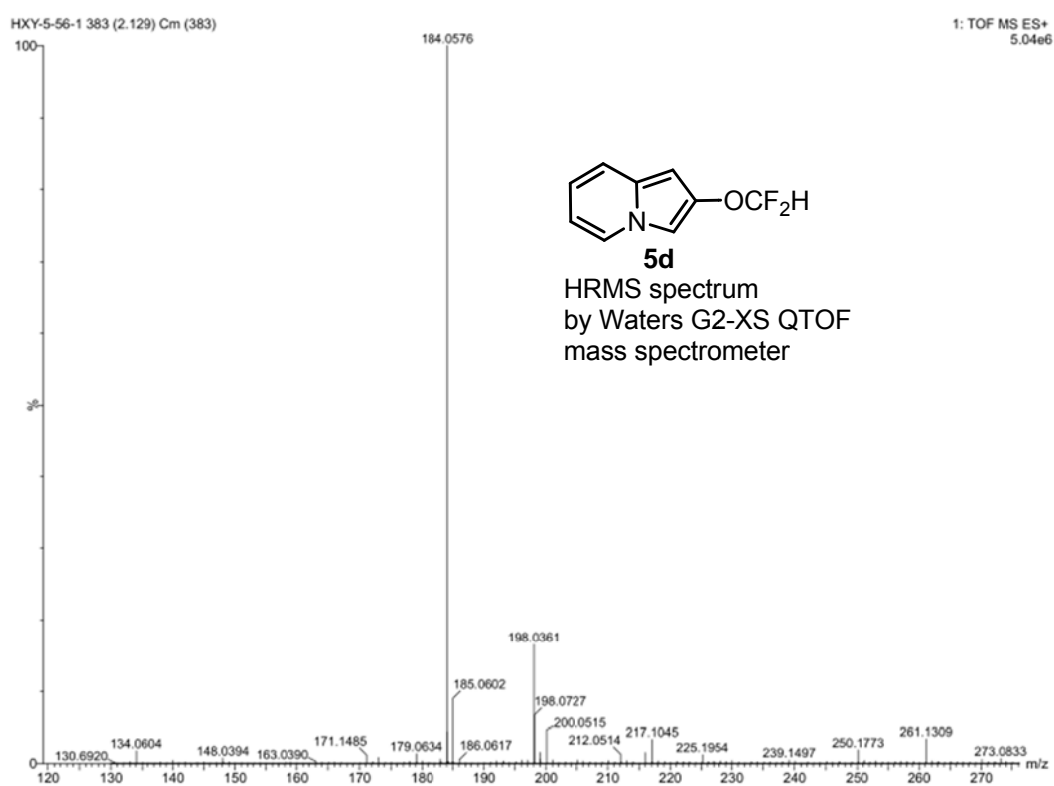
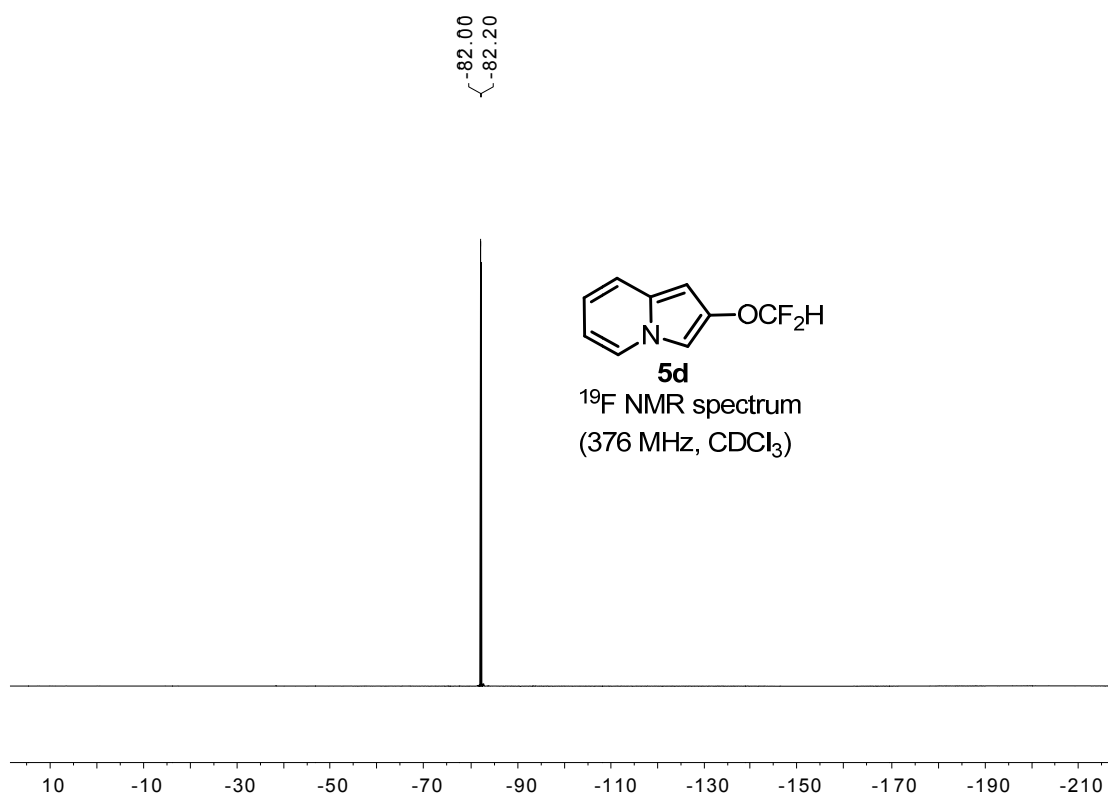


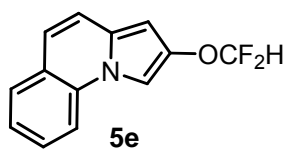
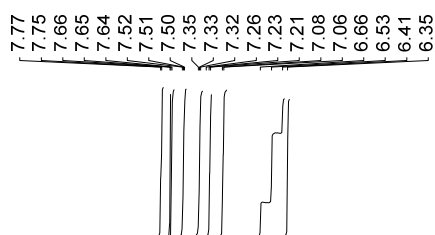




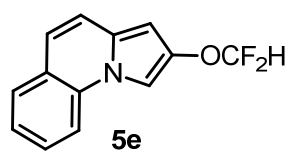
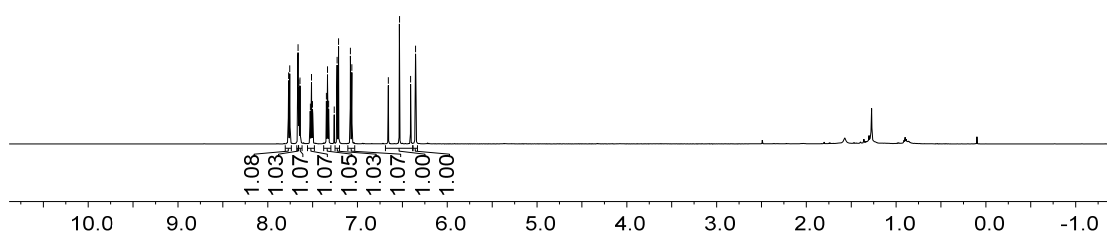








¹H NMR spectrum
(600 MHz, CDCl₃)



¹³C NMR spectrum
(101 MHz, CDCl₃)

