EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Four-Component Reaction for the Synthesis of Indolizines via a Copper-Catalyzed Aerobic Oxidative Dehydrogenative Aromatization

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To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201601272

Link to VoR: https://doi.org/10.1002/ejoc.201601272

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Supporting Information

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General Methods and materials:

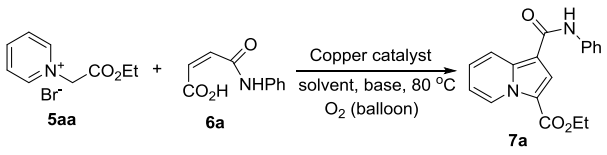
Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane or $CDCl_3$ for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR. Flash column chromatography was performed on 300-400 mesh silica gels. Analytical thin layer chromatography was performed with pre-coated glass baked plates (250μ) and visualized by fluorescence. HRMS were recorded on Bruker micrOTOF-Q spectrometer. IR spectra were recorded by Nicolet iS50 FT-IR spectrometer.

General procedures for synthesizing indolizines Characteristic data of new compounds:

Amine (0.20 mmol, 1.0 equiv.) and maleic anhydride (0.30 mmol, 1.5 equiv.) and 0.20 mL of ethyl acetate were added to a reaction vial and the mixture was heated at 60 ^{o}C for 4 h. Then pyridine (0.40 mmol, 2.0 equiv.) and α-halide carbonyl compound were added to the mixture and heated at 60 ^{o}C for another 5 h. Then cuprous bromide (0.06 mmol, 30%), potassium carbonate (0.50 mmol, 2.5 equiv.) and 1.8 mL of DMSO (dimethylsulfoxide) were added to the vial. Then the mixture was heated at 80 ^{o}C under oxygen atmosphere (balloon). The reaction was monitored by TLC. After the reaction was completed, the mixture was poured into water and extracted by ethyl acetate (10 mL ×3). The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate and filtered. The organic solvent was removed under vacuum and the residue was purified by flash chromatography (silica gel, eluted by petroleum ether/ ethyl acetate).

Optimization of reaction conditions

Table 1. Optimization of reaction conditions.



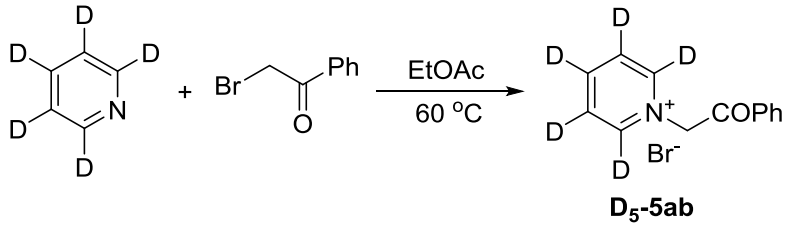
entry	Catalyst [a]	Base	solvent	yield of **7a** (%) [b]
1	$Cu(OAc)_2$	NaOAc	DMF	83
2	CuI	NaOAc	DMF	69
3	CuCl	NaOAc	DMF	59
4	$CuBr_2$	NaOAc	DMF	78
5	$CuCl_2$	NaOAc	DMF	61
6	$CuSO_4$	NaOAc	DMF	68
7	$Cu(AcAc)_2$	NaOAc	DMF	73

8	CuBr	NaOAc	DMF	87
9	CuBr	NaOAc	DMSO	91
10	CuBr	NaOAc	DMSO	91
11	CuBr	NaOAc	DMSO	91
12	CuBr	NaOAc	DMA	91
13	CuBr	NaOAc	1,4-dioxane	66
14	CuBr	NaOAc	MeCN	50
15	CuBr	NaOAc	toluene	32
16	CuBr	NaOAc	NMP	40
17	CuBr	NaOAc	water	trace
18	CuBr	KOAc	DMSO	83
19	CuBr	$KHCO_3$	DMSO	80
20	CuBr	$NaHCO_3$	DMSO	74
21	CuBr	Na_2CO_3	DMSO	69
22	CuBr	NEt_3	DMSO	71
23	CuBr	pyridine	DMSO	21
24	CuBr	K_2CO_3	DMSO	96
25	CuBr	NaOAc	DMSO	68 [d]
26	CuBr	-	DMSO	10
27	CuBr	NaOAc	DMSO	69 [e]
28	-	NaOAc	DMSO	38
29	CuBr	K_2CO_3	**DMSO**	100 [f]
30	CuBr	NaOAc	DMSO	64 [g]
31	CuBr	NaOAc	DMSO	61 [h]
32	CuBr	K_2CO_3	**DMSO**	86 [i]

[a] Reaction conditions: **5a** (0.40 mmol, 2.0 equiv.), **6a** (0.20 mmol, 1.0 equiv.), base (0.80 mmol, 4.0 equiv.) with catalyst (30%), in solvent (2.0 mL) under O_2 (balloon) heated at 80 ℃ for 8 h. [b] Isolated yield. [c] See SI. [d] 20% CuBr was used. [e] 1.0 mL DMSO was used. [f] 0.50 mmol K_2CO_3 was used. [g] Under air. [h] 0.30 mmol of **5a** was used. [i] **Four-component reaction conditions**: maleic anhydride (0.30 mmol, 1.5 equiv.) and aniline (0.20 mmol, 1.0 equiv.) were heated in 0.20 mL ethyl acetate at 60 ^oC for 4 h, then pyridine (0.40 mmol, 2.0 equiv.) and ethyl 2-bromoacetate (0.40 mmol, 2.0 equiv.) were added and heated at 60 ^oC for another 5 h, then copper bromide (0.06 mmol, 0.30 equiv.), K_2CO_3 (0.50 mmol, 2.5 equiv.) and 1.8 mL DMSO were added, the mixture was heated at 80 ^oC for 12 h under oxygen atmosphere (balloon).

Procedures for isotope experiments and control experiments:

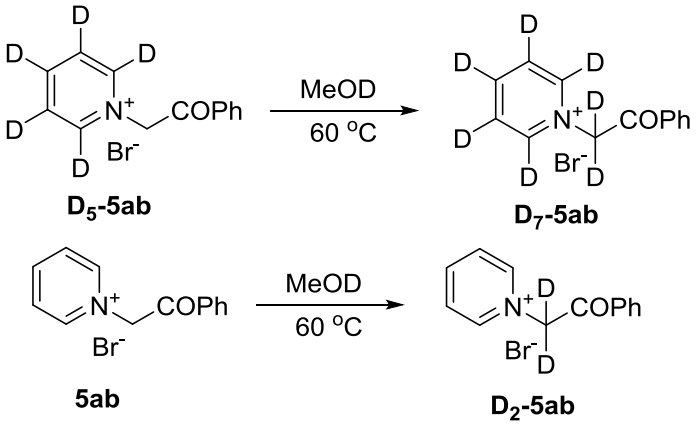
Procedure for prepared **D_5-5ab**:



D_5-5ab

D_5-pyridine (10 mmol) and 2-bromo-1-phenylethan-1-one (10 mmol) and 10 mL ethyl acetate was heated at 60 °C for 4 h in a round bottom flask. Then the mixture was cooled to room temperature and filtered. The solid was washed with cold ethyl acetate and dried to give **D_5-5ab** in 81% yield (2.29 g).

Procedure for prepared **D_7-5ab** and **D_2-5ab**:



D_5-5ab

D_7-5ab

5ab

D_2-5ab

D_5-5ab or **5ab** (2.0 mmol) and 1.0 mL MeOD was added to a sealed flask and heated at 60 °C for 4 h, then the solvent was removed under vacuum. The ratios of deuterium were monitored by ^{1}H NMR. The procedures were repeated to confirm the ratios of deuterium were more than 95%.

Procedure for prepared **6a**:
Aniline (10 mmol) and maleic anhydride (10 mmol) and ethyl acetate 10 mL was heated at 60 °C for 4 h. Then the mixture was cooled to room temperature and filtered. The solid was washed with cold ethyl acetate and dried to give **6a** in 90% yield (1.74 g).

Procedures for isotope experiments:
D_7-5ab, **D_7-5ab**, **D_2-5ab** and **5ab** (0.40 mmol) were added to different vials, then **6a** (0.20 mmol), CuBr (0.06 mmol), K_2CO_3 (0.50 mmol) and 2.0 mL DMSO were added to vials. Then all vials were heated and stirred at 80 °C under O_2 (balloon) for 15 min. Then all reaction mixture were poured into water and extracted by ethyl acetate (10 mL *3). The organic layers were combined, washed with brine, dried with anhydrous sodium sulfate and filtered. The organic solvent was removed under vacuum and the residue was purified by flash chromatography (silica gel, eluted by petroleum ether/

ethyl acetate). The relative reaction speed was calculated based on the yields of **D_4-9a** or **9a**.

Characteristic data of new compounds

Ethyl 1-(phenylcarbamoyl)indolizine-3-carboxylate (**7a**): 53.0 mg (52 %, PE/ EA = 3/1); yellow solid; m. p. 141.7-143.9 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.55 (d, *J* = 7.1 Hz, 1H), 8.61 (d, *J* = 9.0 Hz, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.39 – 7.32 (m, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 6.8 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.51 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.4, 161.0, 139.0, 138.3, 129.0, 127.5, 125.3, 124.0, 120.1, 120.1, 119.7, 114.6, 114.1, 108.2, 60.4, 14.5; IR (KBr): 3302, 3117, 2984, 1689, 1635, 1594, 1560, 1522, 1481, 1442, 1372, 1347, 1305; HRMS (ESI): m/z calcd for $C_{18}H_{16}N_2O_3$: 331.1059 $[M+Na]^+$; found: 331.1055.

Ethyl 1-((4-methoxyphenyl)carbamoyl)indolizine-3-carboxylate (**7b**): 54.4 mg (80 %, PE/ EA = 5/1); yellow solid; m. p. 152.8-153.9 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.45 (d, *J* = 7.1 Hz, 1H), 8.51 (d, *J* = 8.9 Hz, 1H), 7.80 (s, 1H), 7.78 (s, 1H), 7.54 (d, *J* = 7.1 Hz, 2H), 7.29 – 7.21 (m, 1H), 6.95 (t, *J* = 6.9 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 2H), 4.38 (q, *J* = 7.3 Hz, 2H), 3.80 (d, *J* = 1.6 Hz, 3H), 1.40 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.4, 161.0, 156.3, 138.9, 131.3, 127.5, 125.1, 122.1, 120.2, 119.7, 114.6, 114.2, 114.0, 108.2, 60.3, 55.5, 14.5; IR (KBr): 3276, 3123, 2972, 2928, 2835, 1687, 1631, 1597, 1537, 1511, 1481, 1425, 1373, 1349, 1302; HRMS (ESI): m/z calcd for $C_{19}H_{18}N_2O_4$: 361.1164 $[M+Na]^+$; found: 361.1160.

Ethyl 1-((4-nitrophenyl)carbamoyl)indolizine-3-carboxylate (**7c**): 32.9 mg (45 %, PE/ EA = 4/1); yellow solid; m. p. 217.4-218.8 ^{o}C; ^{1}H NMR (DMSO-D_6, 400 MHz): 10.43 (s, 1H), 9.42 (d, *J* = 7.0 Hz, 1H), 8.47 (d, *J* = 8.9 Hz, 1H), 8.42 (s, 1H), 8.20 (d, *J* = 9.2 Hz, 2H), 8.05 (d, *J* = 9.2 Hz, 2H), 7.46 (t, *J* = 7.8 Hz 1H), 7.19 (t, *J* = 6.6 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (DMSO-D_6, 100 MHz): 162.9, 160.8, 146.4, 142.3, 139.3, 127.9, 126.8, 125.2, 122.0, 120.0, 119.7, 115.8, 114.1, 107.7, 60.6, 14.9; IR (KBr): 3735, 3725, 3649, 3420, 1673, 1541, 1527, 1497, 1426, 1375, 1331, 1301; HRMS (ESI): m/z calcd for $C_{18}H_{15}N_3O_5$: 376.0909 $[M+Na]^+$; found: 376.0909.

Ethyl 1-(*o*-tolylcarbamoyl)indolizine-3-carboxylate (**7d**): 38.0 mg (59 %, PE/ EA = 5/1); yellow solid; m. p. 140.9-141.8 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.50 (d, *J* = 7.0 Hz, 1H), 8.54 (d, *J* = 8.9 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.81 (s, 1H), 7.62 (s, 1H), 7.33 – 7.21 (m, 3H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 6.9 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.5, 161.0, 139.0, 135.9, 130.5, 129.5, 127.6, 126.8, 125.3, 125.0, 123.5, 120.2, 119.6, 114.7, 114.1, 108.1, 60.4, 18.0, 14.6; IR (KBr): 3299, 2979, 1694, 1654, 1637, 1523, 1487, 1444, 1376, 1302; HRMS (ESI): m/z calcd for $C_{19}H_{18}N_2O_3$: 345.1215 $[M+Na]^+$; found: 345.1219.

Ethyl 1-(*m*-tolylcarbamoyl)indolizine-3-carboxylate (**7e**): 28.9 mg (45 %, PE/ EA = 5/1); yellow solid; m. p. 159.1-160.0 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.46 (d, *J* = 7.1 Hz, 1H), 8.53 (d, *J* = 9.0 Hz, 1H), 7.84 (s, 1H), 7.82 (s, 1H), 7.56 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.31 – 7.21 (m, 2H),

6.93 – 6.99 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.4, 161.0, 139.0, 138.9, 138.2, 128.8, 127.5, 125.3, 124.8, 120.7, 120.1, 119.7, 117.1, 114.7, 114.0, 108.2, 60.4, 21.6, 14.6; IR (KBr): 3300, 3109, 3048, 2980, 1692, 1632, 1540, 1525, 1486, 1443, 1374, 13051; HRMS (ESI): m/z calcd for $C_{19}H_{18}N_2O_3$: 345.1215 $[M+Na]^+$; found: 345.1212.

Ethyl 1-(*p*-tolylcarbamoyl)indolizine-3-carboxylate (**7f**): 55.5 mg (80 %, PE/ EA = 3/1); yellow solid; m. p. 170.2-172.4 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.45 (d, *J* = 7.0 Hz, 1H), 8.51 (d, *J* = 8.9 Hz, 1H), 7.78 (d, *J* = 7.4 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.22 (m, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 6.8 Hz, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR ($CDCl_3$, 100 MHz): 162.4, 161.0, 138.9, 135.7, 133.6, 129.5, 127.5, 125.2, 120.2, 120.1, 119.6, 114.6, 114.0, 108.3, 60.3, 20.9, 14.5; IR (KBr): 3282, 3112, 2984, 2919, 1689, 1636, 1517, 1483, 1422, 1373, 1302; HRMS (ESI): m/z calcd for $C_{19}H_{18}N_2O_3$: 345.1215 $[M+Na]^+$; found: 345.1210.

Ethyl 1-((4-methoxybenzyl)carbamoyl)indolizine-3-carboxylate (**7g**): 45.9 mg (65 %, PE/ EA = 5/1); yellow solid; m. p. 152.8-154.2 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.44 (d, *J* = 7.0 Hz, 1H), 8.53 (d, *J* = 8.9 Hz, 1H), 7.68 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.24 (t, *J* = 7.9 Hz, 1H), 6.93 (t, *J* = 6.8 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.34 (s, 1H), 4.58 (d, *J* = 5.3 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 164.1, 161.0, 159.0, 138.7, 130.8, 129.2, 127.4, 124.8, 120.2, 119.7, 114.4, 114.1, 113.9, 108.0, 60.2, 55.3, 42.9, 14.5; IR (KBr): 3268, 3115, 2982, 2932, 2837, 1686, 1624, 1548, 1513, 1485, 1375, 1348; HRMS (ESI): m/z calcd for $C_{20}H_{20}N_2O_4$: 375.1321 $[M+Na]^+$; found: 375.1318.

Ethyl 1-(benzylcarbamoyl)indolizine-3-carboxylate (**7h**): 46.4 mg (72 %, PE/ EA = 7/1); yellow solid; m. p. 159.9.3-161.9 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.45 (d, *J* = 7.0 Hz, 1H), 8.54 (d, *J* = 9.0 Hz, 1H), 7.70 (s, 1H), 7.40 – 7.32 (m, 4H), 7.31 – 7.22 (m, 2H), 6.94 (t, *J* = 6.9 Hz, 1H), 6.37 (s, 1H), 4.65 (d, *J* = 5.6 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 164.1, 161.0, 138.7, 138.7, 128.7, 127.9, 127.5, 127.4, 125.0, 120.2, 119.6, 114.5, 113.9, 107.8, 60.3, 43.5, 14.5; IR (KBr):3263, 3034, 2983, 2926, 1686, 1616, 1542, 1478, 1376, 1349; HRMS (ESI): m/z calcd for $C_{19}H_{18}N_2O_3$: 345.1215 $[M+Na]^+$; found: 345.1216.

Ethyl 1-(butylcarbamoyl)indolizine-3-carboxylate (**7i**): 31.7 mg (55 %, PE/ EA = 7/1); yellow solid; m. p. 121.9-123.7 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.45 (d, *J* = 7.0 Hz, 1H), 8.51 (d, *J* = 9.0 Hz, 1H), 7.67 (s, 1H), 7.27 – 7.20 (m, 1H), 6.94 (t, *J* = 7.0 Hz, 1H), 6.02 - 5.94 (m, 1H), 4.39 (qd, *J* = 7.1, 1.6 Hz, 2H), 3.47 (q, *J* = 6.8 Hz, 2H), 1.68 – 1.55 (m, 2H), 1.49 – 1.38 (m, 5H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 164.3, 161.0, 138.6, 127.4, 124.7, 120.2, 119.4, 114.3, 113.8, 108.3, 60.2, 39.2, 32.1, 20.2, 14.5, 13.8; IR (KBr): 3275, 2961, 2930, 2862, 1690, 1624, 1549, 1519, 1479, 1374; HRMS (ESI): m/z calcd for $C_{16}H_{20}N_2O_3$: 311.1366 $[M+Na]^+$; found: 311.1369.

Ethyl 1-(phenethylcarbamoyl)indolizine-3-carboxylate (**7j**): 44.9 mg (67 %, PE/ EA = 5/1); yellow solid; m. p. 130.5-131.7 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.44 (d, *J* = 7.0 Hz, 1H), 8.48 (d, *J* = 8.9 Hz, 1H), 7.60 (s, 1H), 7.36 – 7.29 (m, 2H), 7.25 (d, *J* = 7.5 Hz, 4H), 6.93 (t, *J* = 6.9 Hz, 1H), 6.14 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.72 (q, *J* = 6.7 Hz, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 1.38 (t, *J* = 7.1

Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 164.3, 161.0, 139.2, 138.5, 128.9, 128.6, 127.4, 126.5, 124.8, 120.1, 119.6, 114.3, 113.9, 108.2, 60.2, 40.7, 36.1, 14.5; IR (KBr): 3276, 3025, 2976, 2957, 2926, 2854, 1689, 1618, 1550, 1523, 1481, 1373; HRMS (ESI): m/z calcd for $C_{20}H_{20}N_2O_3$: 359.1372 $[M+Na]^+$; found: 359.1369.

Ethyl 1-(*tert*-butylcarbamoyl)indolizine-3-carboxylate (**7k**): 12.0 mg (21 %, PE/ EA = 5/1); yellow solid; m. p. 208.0-210.1 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.44 (d, *J* = 7.1 Hz, 1H), 8.50 (d, *J* = 9.0 Hz, 1H), 7.60 (s, 1H), 7.26 – 7.18 (m, 1H), 6.93 (t, *J* = 6.5 Hz, 1H), 5.81 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.51 (s, 9H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 164.0, 161.1, 138.5, 127.3, 124.6, 120.2, 119.5, 114.3, 113.5, 109.3, 60.2, 51.4, 29.2, 14.6; IR (KBr): 3300, 3120, 2976, 2934, 1687, 1620, 1546, 1519, 1483, 1455, 1444, 1373; HRMS (ESI): m/z calcd for $C_{16}H_{20}N_2O_3$: 311.1372 $[M+Na]^+$; found: 311.1371.

Ethyl 1-(phenylcarbamoyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**8b**): 64.4 mg (90 %, PE/ EA = 7/1); yellow solid; m. p. 218.3-220.4 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.32 (d, *J* = 7.4 Hz, 1H), 9.12 – 9.04 (m, 1H), 7.86 (s, 1H), 7.76 (s, 1H), 7.71 – 7.67 (m, 3H), 7.61 – 7.52 (m, 2H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.20 (d, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 4.42 (q, *J* = 7.0 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 164.5, 161.0, 138.4, 133.5, 129.1, 129.0, 128.4, 127.9, 126.8, 126.2, 124.5, 124.4 123.9, 120.9, 120.1, 115.5, 114.6, 114.0, 60.5, 14.5.; IR (KBr): 3294, 3129, 3059, 2979, 2927, 2854, 1694, 1645, 1596, 1541, 1521, 1467, 1455, 1439, 1379, 1341; HRMS (ESI): m/z calcd for $C_{22}H_{18}N_2O_3$: 381.1215 $[M+Na]^+$; found: 381.1214.

Ethyl 7-methyl-1-(phenylcarbamoyl)indolizine-3-carboxylate (**8c**): 33.5 mg (52 %, PE/ EA = 5/1); yellow solid; m. p. 193.1-194.6 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.28 (d, *J* = 7.2 Hz, 1H), 8.25 (s, 1H), 7.88 (s, 1H), 7.73 (s, 1H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 7.1 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.36 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.7, 161.0, 139.4, 138.4, 136.7, 129.0, 126.8, 123.8, 120.0, 119.9, 118.7, 117.1, 113.5, 106.9, 60.2, 21.3, 14.5; IR (KBr): 3332, 3117, 3058, 2979, 1694, 1641, 1596, 1537, 1499, 1487, 1441, 1372, 1352, 1313; HRMS (ESI): m/z calcd for $C_{19}H_{18}N_2O_3$: 345.1215 $[M+Na]^+$; found: 345.1212.

Ethyl 8-chloro-1-(phenylcarbamoyl)indolizine-3-carboxylate (**8e**): 20.7 mg (30 %, PE/ EA = 5/1); yellow solid; m. p. 88.8-91.2 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.35 (d, *J* = 7.0 Hz, 1H), 8.18 (s, 1H), 7.77 – 7.66 (m, 3H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.17 (m, 2H), 6.78 (t, *J* = 7.2 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.9, 160.8, 138.3, 131.8, 129.1, 125.9, 124.6, 124.3, 124.3, 122.8, 119.8, 114.6, 113.2, 113.0, 60.6, 14.4; IR (KBr): 3423, 3267, 3134, 2985, 1695, 1686, 1652, 1597, 1535, 1500, 1473, 1443, 1377, 1315; HRMS (ESI): m/z calcd for $C_{18}H_{15}ClN_2O_3$: 365.0669 $[M+Na]^+$; found: 365.0669.

Ethyl 6-chloro-1-(phenylcarbamoyl)indolizine-3-carboxylate (**8e'**): 11.6 mg (17 %, PE/ EA = 5/1); yellow solid; m. p. 156.6-158.2 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): 9.56 (s, 1H), 8.49 (d, *J* = 9.5 Hz, 1H), 7.76 (s, 1H), 7.68 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.26 – 7.22 (m, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 161.9, 160.7, 138.0, 137.0, 129.1, 126.4, 125.5, 124.2, 123.3, 120.5, 120.1, 119.4,

114.5, 109.0, 60.7, 14.5; IR (KBr): 3289, 3127, 2983, 1694, 1640, 1597, 1537, 1499, 1482, 1443, 1375, 1315; HRMS (ESI): m/z calcd for $C_{18}H_{15}ClN_2O_3$: $C_{18}H_{15}ClN_2O_3$: 365.0668 $[M+Na]^+$; found: 365.0669.

Ethyl 8-phenyl-1-(phenylcarbamoyl)indolizine-3-carboxylate (**8f**): 45.3 mg (59 %, PE/ EA = 5/1); yellow solid; m. p. 185.1-186.3 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): 9.67 (s, 1H), 8.49 (d, *J* = 9.4 Hz, 1H), 8.09 (d, *J* = 7.0 Hz, 1H), 7.81 (s, 1H), 7.72 (d, *J* = 7.9 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.47 (m, 3H), 7.39 (m, 3H), 7.14 (t, *J* = 7.4 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.5, 161.0, 138.3, 137.8, 136.9, 129.1, 129.0, 128.7, 128.1, 127.0, 125.4, 124.9, 124.0, 120.1, 120.1, 119.8, 114.2, 108.2, 60.5, 14.5; IR (KBr): 3302, 3124, 3058, 2982, 1690, 1640, 1596, 1544, 1522, 1499, 1483, 1443, 1376, 1311; HRMS (ESI): m/z calcd for $C_{24}H_{20}N_2O_3$: 407.1372 $[M+Na]^+$; found: 407.1370.

Ethyl 6-phenyl-1-(phenylcarbamoyl)indolizine-3-carboxylate (**8f'**): 30.7 mg (40 %, PE/ EA = 5/1); yellow solid; m. p. 196.0-198.0 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): 9.60 (d, *J* = 7.0 Hz, 1H), 7.96 (s, 1H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.15 (m, 4H), 7.08 (d, *J* = 7.8 Hz, 2H), 7.04 – 6.96 (m, 2H), 6.76 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.5, 161.2, 138.3, 137.8, 133.2, 132.8, 129.0, 128.5, 128.4, 127.9, 126.7, 125.8, 124.4, 123.8, 119.2, 114.5, 113.7, 112.8, 60.3, 14.5; IR (KBr): 3351, 3123, 3057, 2981, 1685, 1655, 1599, 1538, 1499, 1467, 1445, 1431, 1378, 1313; HRMS (ESI): m/z calcd for $C_{24}H_{20}N_2O_3$: 407.1372 $[M+Na]^+$; found: 407.1374.

3-(4-Methoxybenzoyl)-*N*-phenylindolizine-1-carboxamide (**9c**): 53.6 mg (72 %, PE/ EA = 3/1); yellow solid; m. p. 106.2-108.4 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): 9.77 (d, *J* = 7.0 Hz, 1H), 8.46 (d, *J* = 8.9 Hz, 1H), 8.22 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 3H), 7.36 – 7.26 (m, 3H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.98 (t, *J* = 6.9 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 184.2, 162.6, 162.4, 139.6, 138.3, 132.2, 131.1, 129.0, 128.6 127.1, 124.2, 124.0, 122.0, 120.3, 119.8, 115.3, 113.6, 109.2, 55.4; IR (KBr): 3315, 3126, 2933, 2838, 1603, 1526, 1498, 1480, 1441, 1346, 1312; HRMS (ESI): m/z calcd for $C_{23}H_{18}N_2O_3$: 393.1215 $[M+Na]^+$; found: 393.1218.

3-(4-Nitrobenzoyl)-*N*-phenylindolizine-1-carboxamide (**9d**): 23.7 mg (31 %, PE/ EA = 3/1); yellow solid; m. p. 229.6-231.7 ^oC; ^1H NMR (DMSO-D_6, 400 MHz): 9.96 – 9.88 (m, 2H), 8.62 (d, *J* = 8.9 Hz, 1H), 8.43 (d, *J* = 8.5 Hz, 2H), 8.25 (s, 1H), 8.09 (d, *J* = 8.7 Hz, 2H), 7.71 (d, *J* = 7.9 Hz, 2H), 7.66 (t, *J* = 7.9 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.07 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (DMSO-D_6, 100 MHz): 182.8, 162.2, 149.4, 145.7, 140.4, 139.5, 130.6, 129.02, 128.98, 126.7, 124.1, 123.8, 121.4, 120.8, 120.2, 116.8, 110.3; IR (KBr): 3393, 2925, 1652, 1616, 1596, 1527, 1497, 1479, 1442, 1342, 1311, 1227, 1207, 1078; HRMS (ESI): m/z calcd for $C_{22}H_{15}N_3O_4$: 408.0960 $[M+Na]^+$; found: 408.0957.

3-(4-Chlorobenzoyl)-*N*-phenylindolizine-1-carboxamide (**9e**): 62.5 mg (84 %, PE/ EA = 5/1); yellow solid; m. p. 89.3-91.3 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): 9.84 (d, *J* = 7.0 Hz, 1H), 8.50 (d, *J* = 9.0 Hz, 1H), 8.28 (s, 1H), 7.70 – 7.63 (m, 3H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.37 (m, 1H), 7.36 – 7.27 (m, 4H), 7.08 (q, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 183.7, 162.3, 140.0,

138.1, 138.0, 137.7, 130.2, 129.0, 128.8, 128.6, 127.8, 124.7, 124.2, 121.6, 120.4, 119.9, 115.8, 109.7; IR (KBr): 3347, 3125, 1596, 1527, 1498, 1480, 1442, 1345, 1313; HRMS (ESI): m/z calcd for $C_{22}H_{15}ClN_2O_2$: 397.0720 $[M+Na]^+$; found: 398.0718.

3-(4-Bromobenzoyl)-*N*-phenylindolizine-1-carboxamide (**9f**): 62.5 mg (75 %, PE/ EA = 5/1); yellow solid; m. p. 80.2-81.7 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): 9.85 (d, *J* = 7.0 Hz, 1H), 8.51 (d, *J* = 8.9 Hz, 1H), 8.24 (s, 1H), 7.65 (s, 1H), 7.60 (t, *J* = 8.1 Hz, 4H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.09 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 183.8, 162.3, 140.0, 138.5, 138.0, 131.6, 130.4, 129.0, 128.078, 127.9, 126.2, 124.7, 124.2, 121.6, 120.4, 120.0, 115.9, 109.7; IR (KBr): 3423, 3126, 1596, 1528, 1497, 1478, 1442, 1345, 1313,; HRMS (ESI): m/z calcd for $C_{22}H_{15}BrN_2O_2$: 441.0215 $[M+Na]^+$; found: 441.0218.

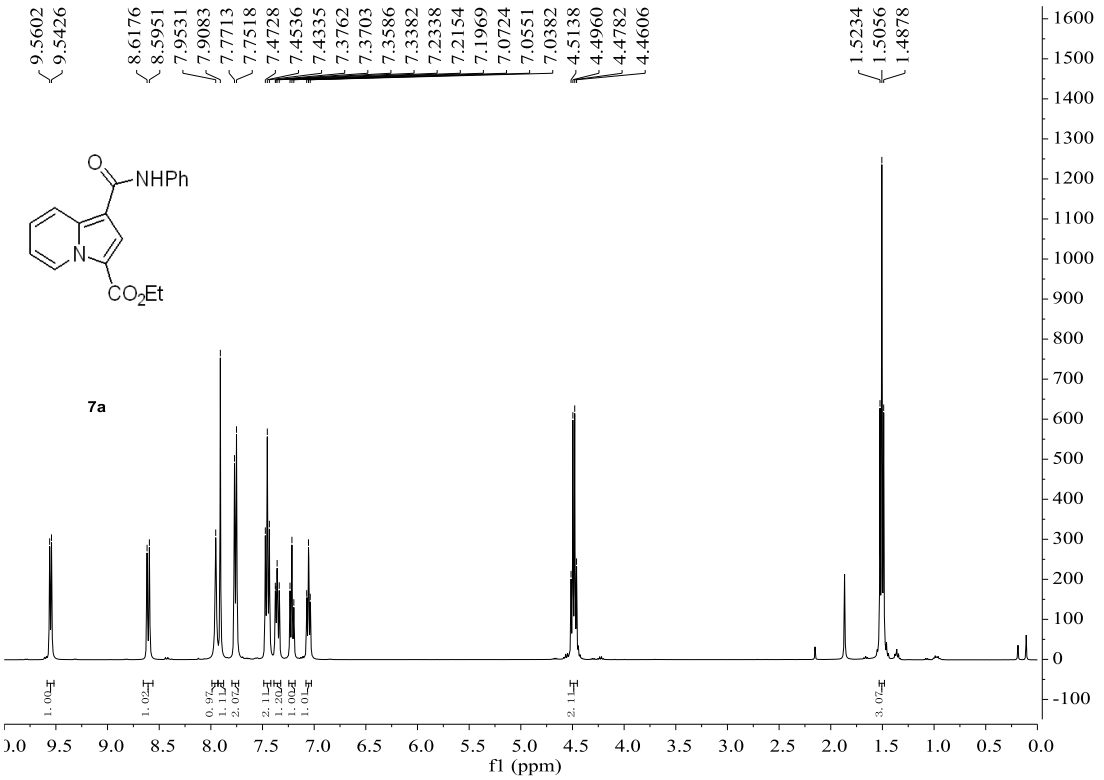
3-(4-Nitrophenyl)-*N*-phenylindolizine-1-carboxamide (**9g**): 41.6 mg (58 %, PE/ EA = 5/1); yellow solid; m. p. 232.2-233.6 ^oC; ^1H NMR (DMSO-D_6, 400 MHz): 9.79 (s, 1H), 8.69 (d, *J* = 6.7 Hz, 1H), 8.45 (d, *J* = 9.0 Hz, 1H), 8.40 (d, *J* = 8.6 Hz, 2H), 8.02 – 7.94 (m, 3H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.34 (t, *J* = 7.1 Hz, 2H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 6.9 Hz, 1H), 6.98 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (DMSO-D_6, 100 MHz): 162.9, 146.3, 140.1, 138.0, 137.3, 129.0, 128.4, 125.0, 124.6, 123.7, 123.5, 123.3, 120.5, 120.4, 116.6, 114.4, 108.8; IR (KBr): 3277, 3112, 2924, 1623, 1593, 1541, 1512, 1498, 1442, 1343, 1319, 1308; HRMS (ESI): m/z calcd for $C_{21}H_{15}N_3O_3$: 380.1011 $[M+Na]^+$; found: 380.1008.

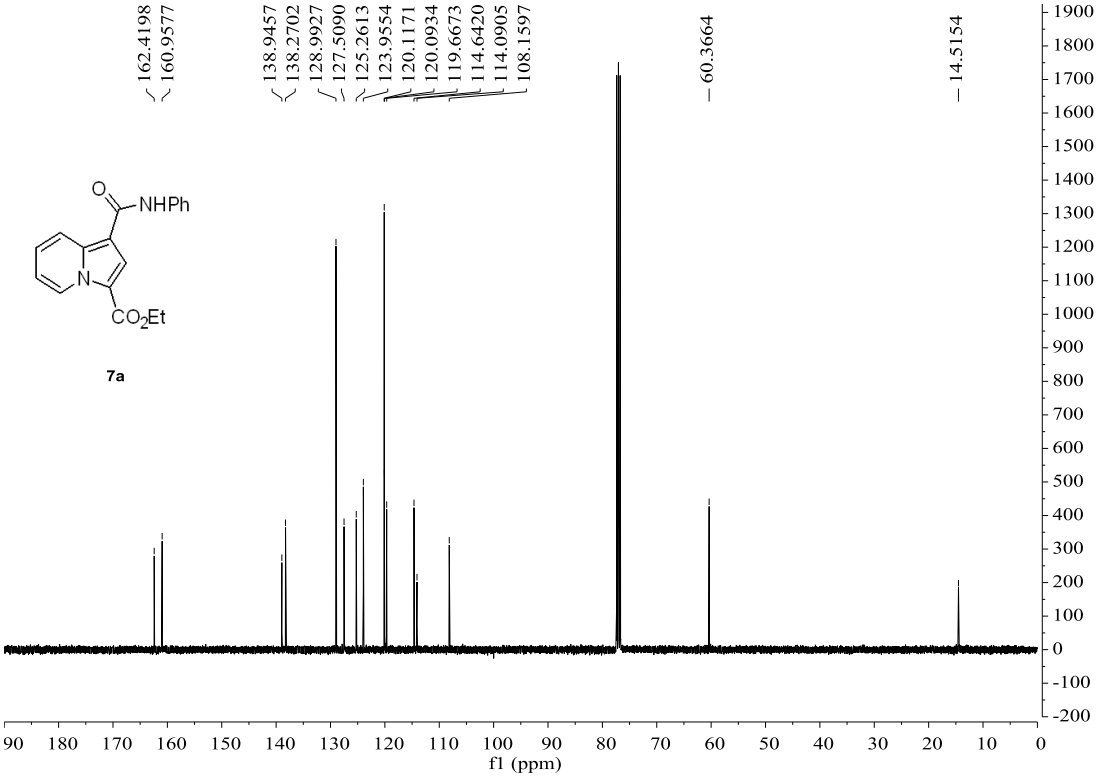
tert-Butyl 1-(phenylcarbamoyl)indolizine-3-carboxylate (**9h**): 63.2 mg (94 %, PE/ EA = 5/1); yellow solid; m. p. 174.7-175.7 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): 9.46 (d, *J* = 6.5 Hz, 1H), 8.50 (d, *J* = 9.5 Hz, 1H), 7.85 (s, 1H), 7.74 (s, 1H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.35 (t, *J* = 5.8 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 6.9 Hz, 1H), 6.93 (t, *J* = 6.7 Hz, 1H), 1.64 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 162.6, 160.6, 138.7, 138.3, 129.0, 127.6, 125.0, 123.9, 120.2, 120.0, 119.6, 115.4, 114.4, 107.8, 81.4, 28.6; IR (KBr): 3293, 3135, 3058, 2975, 2930, 1682, 1644, 1596, 1540, 1524, 1487, 1442, 1368, 1304; HRMS (ESI): m/z calcd for $C_{20}H_{20}N_2O_3$: 359.1372 $[M+Na]^+$; found: 359.1371.

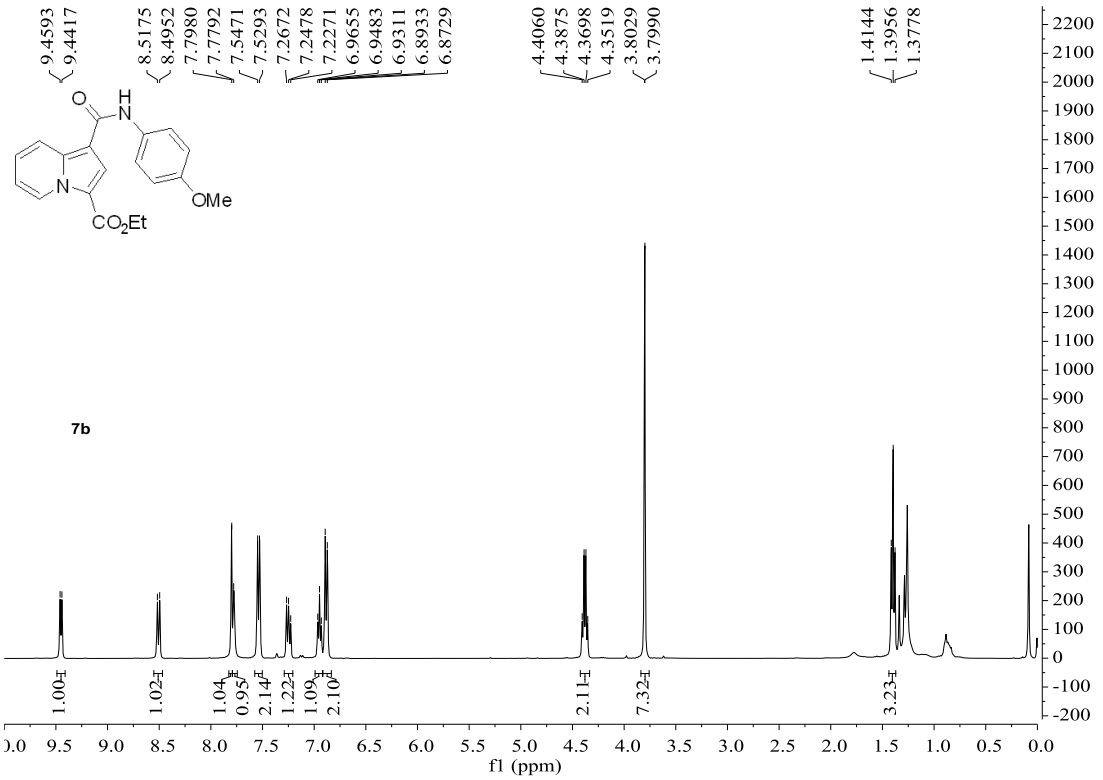
3-Cyano-*N*-phenylindolizine-1-carboxamide (**9i**):19.0 mg (36 %, PE/ EA = 5/1); yellow solid; m. p. 194.9-196.8 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): 8.54 (d, *J* = 9.1 Hz, 1H), 8.34 (d, *J* = 6.8 Hz, 1H), 7.76 (s, 1H), 7.69 – 7.61 (m, 3H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 161.4, 137.8, 137.8, 129.1, 125.7, 125.5, 124.4, 121.0, 120.6, 120.3, 115.3, 112.7, 108.9, 96.1; IR (KBr): 3402, 3123, 2210, 1655, 1632, 1596, 1541, 1524, 1500, 1486, 1442, 1365, 1314; HRMS (ESI): m/z calcd for $C_{16}H_{11}N_3O$: 284.0800 $[M+H]^+$; found: 284.0896.

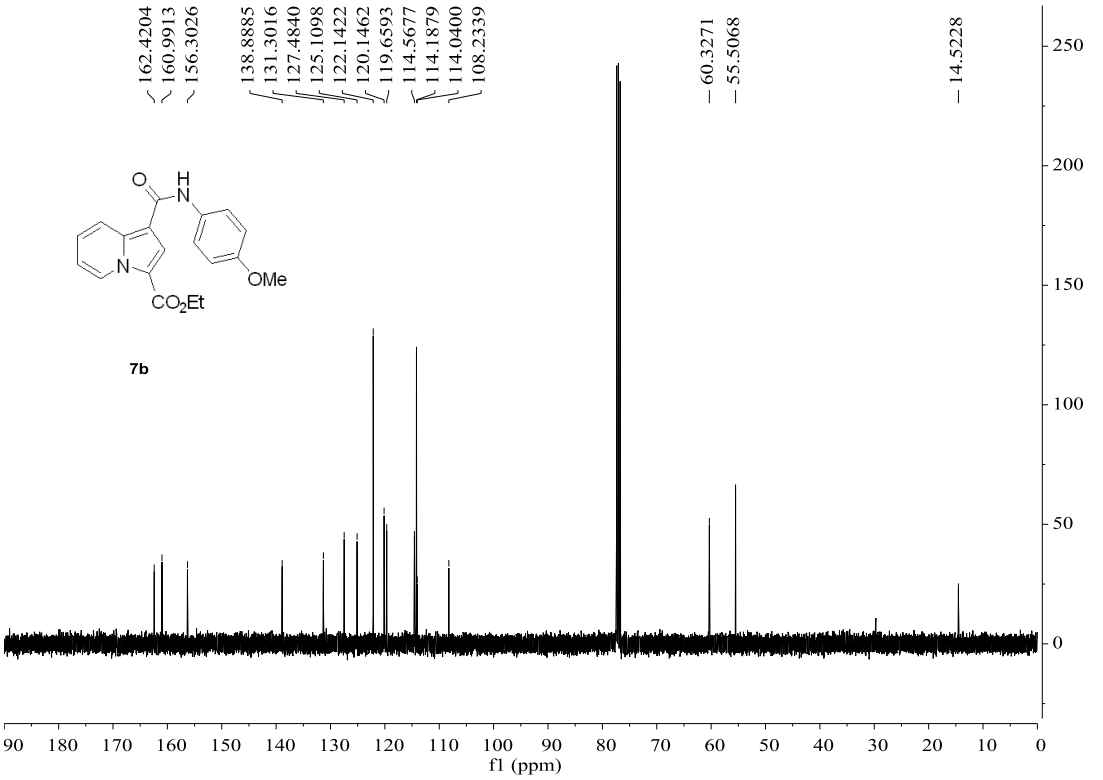
3-Benzoyl-*N*-phenylindolizine-5,6,7,8-d_4-1-carboxamide (**D_4-9a**): ^1H NMR ($CDCl_3$, 400 MHz): 7.84 (s, 1H), 7.76 (d, *J* = 7.0 Hz, 2H), 7.61 – 7.55 (m, 3H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.09 (t, *J* = 6.3 Hz, 1H).

Copies of New Compounds' NMR spectra









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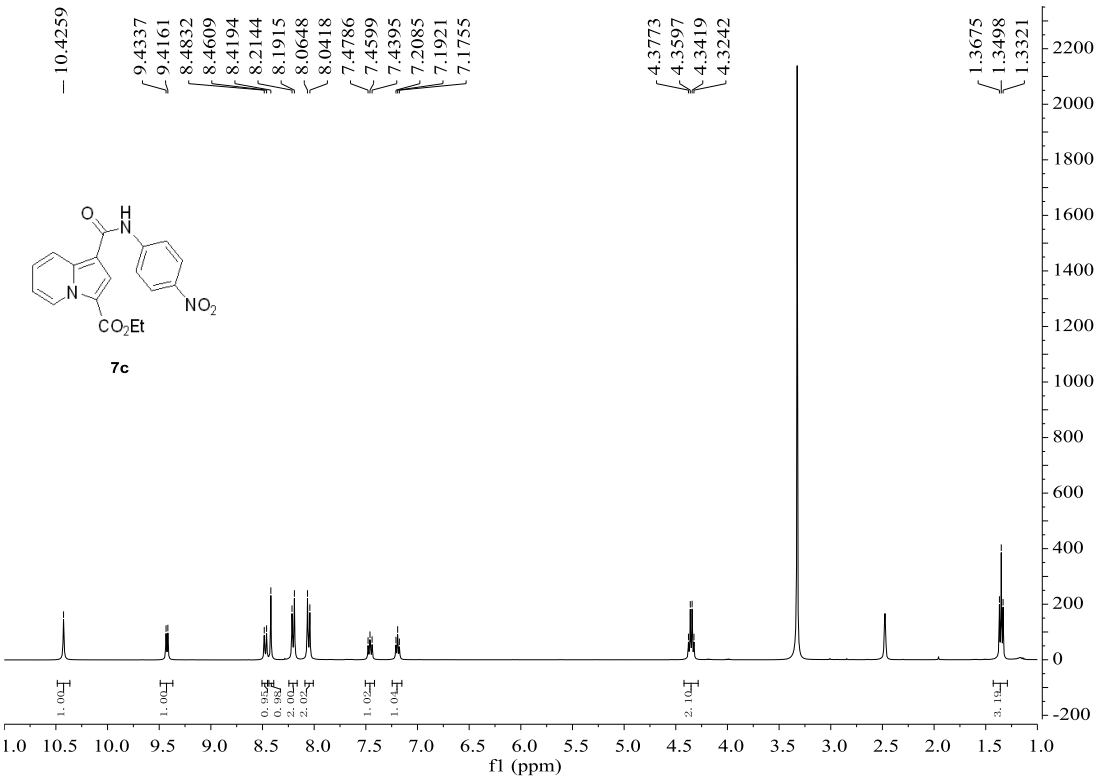

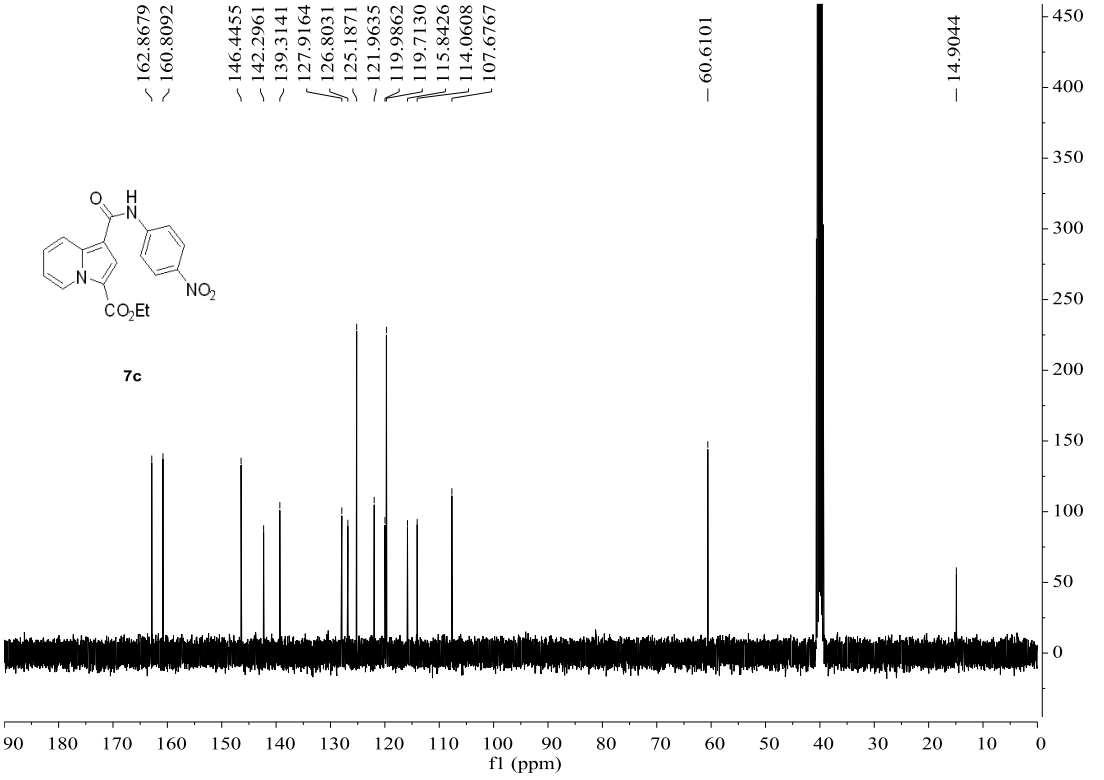

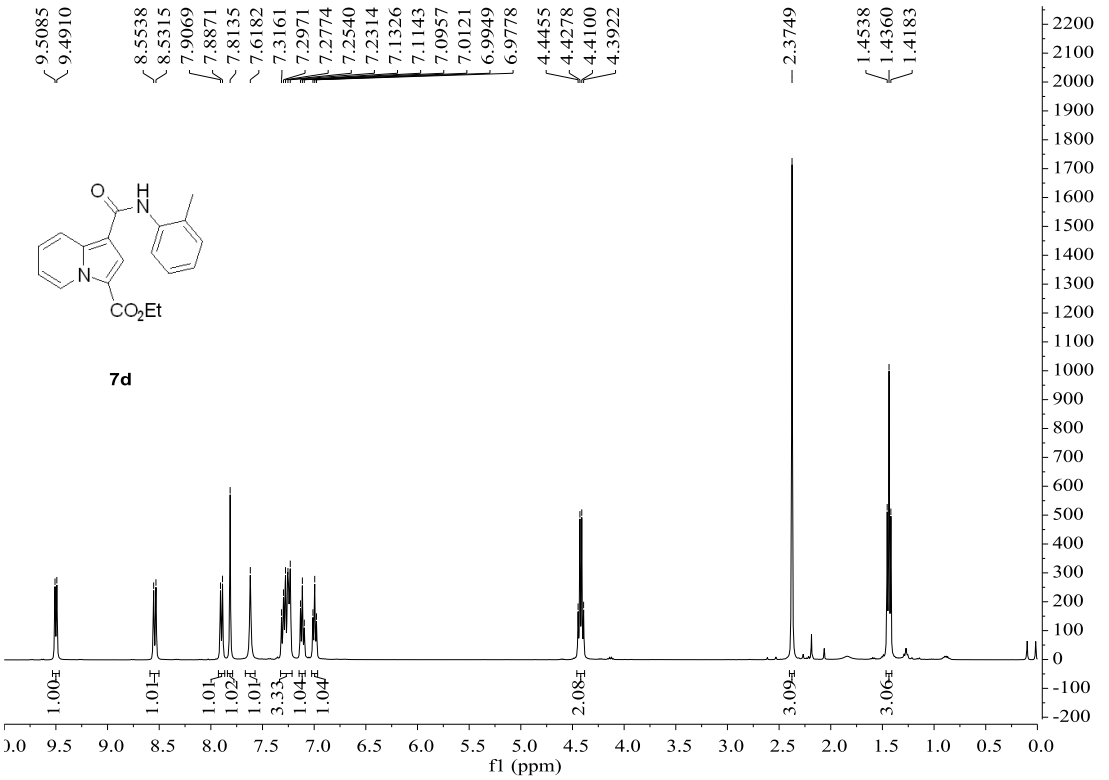

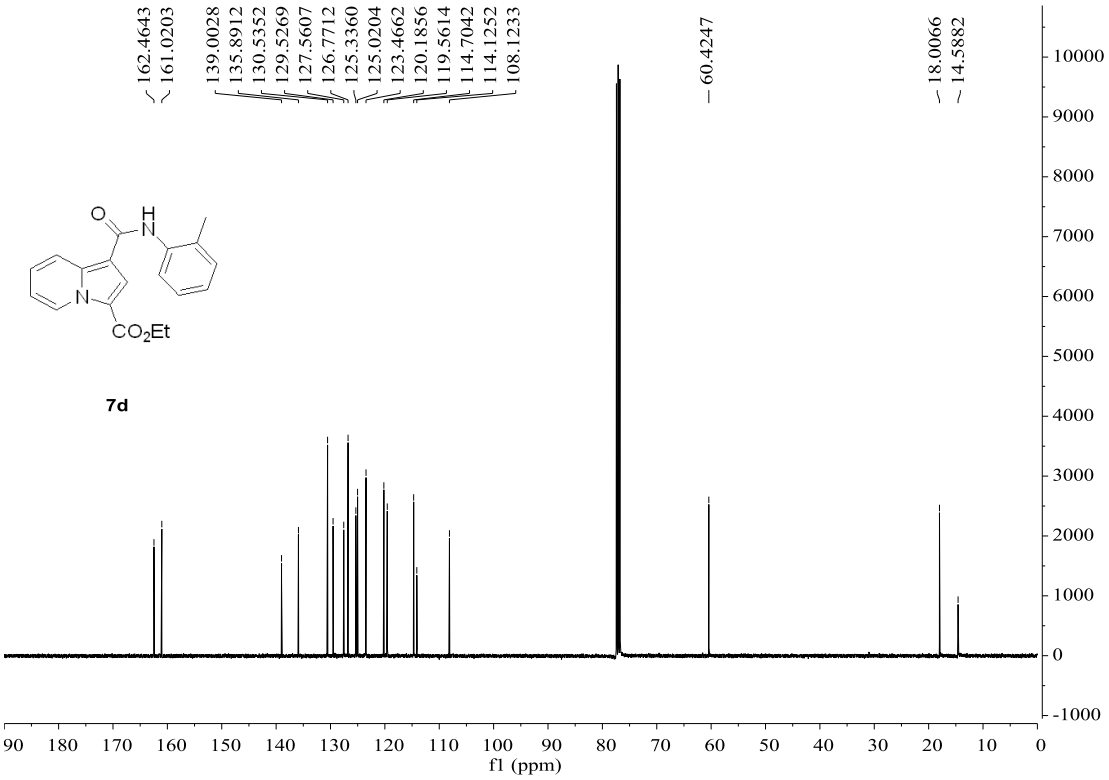

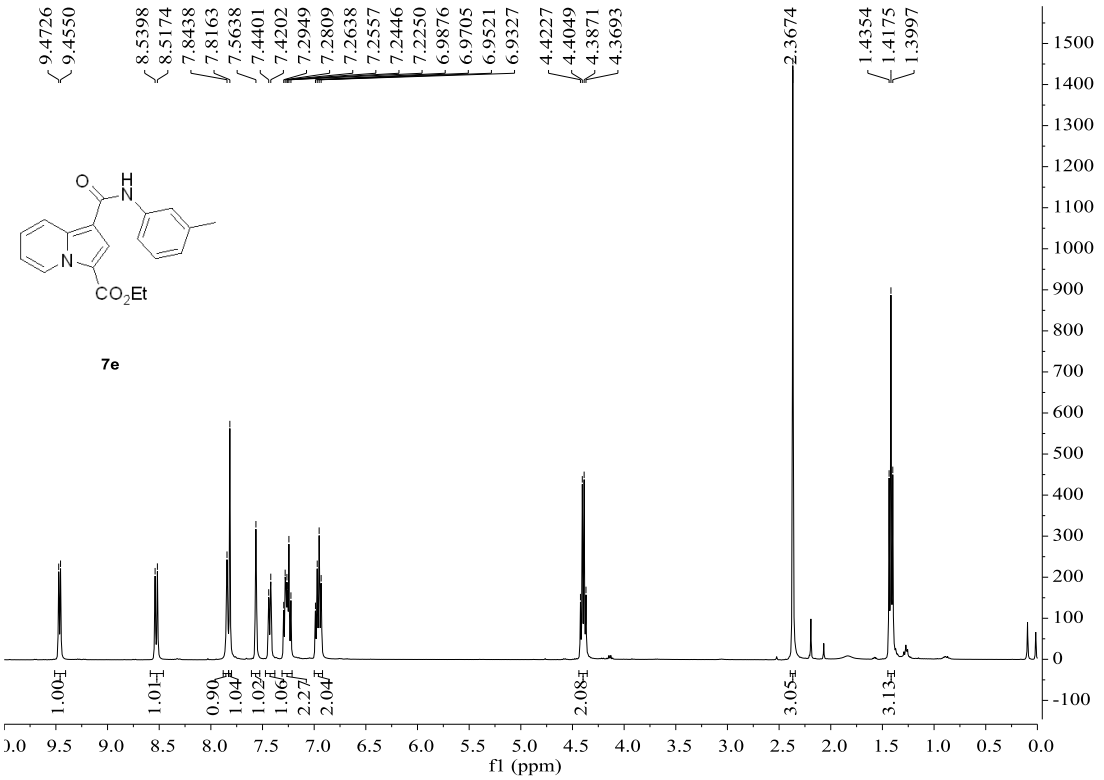

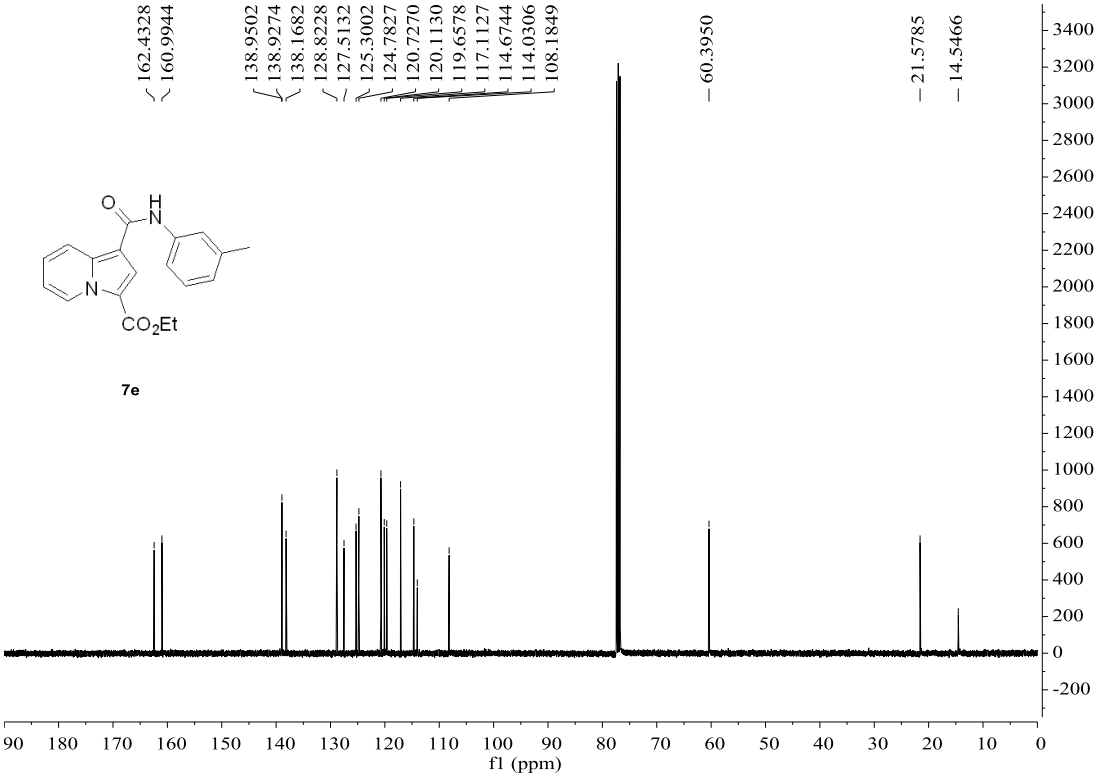

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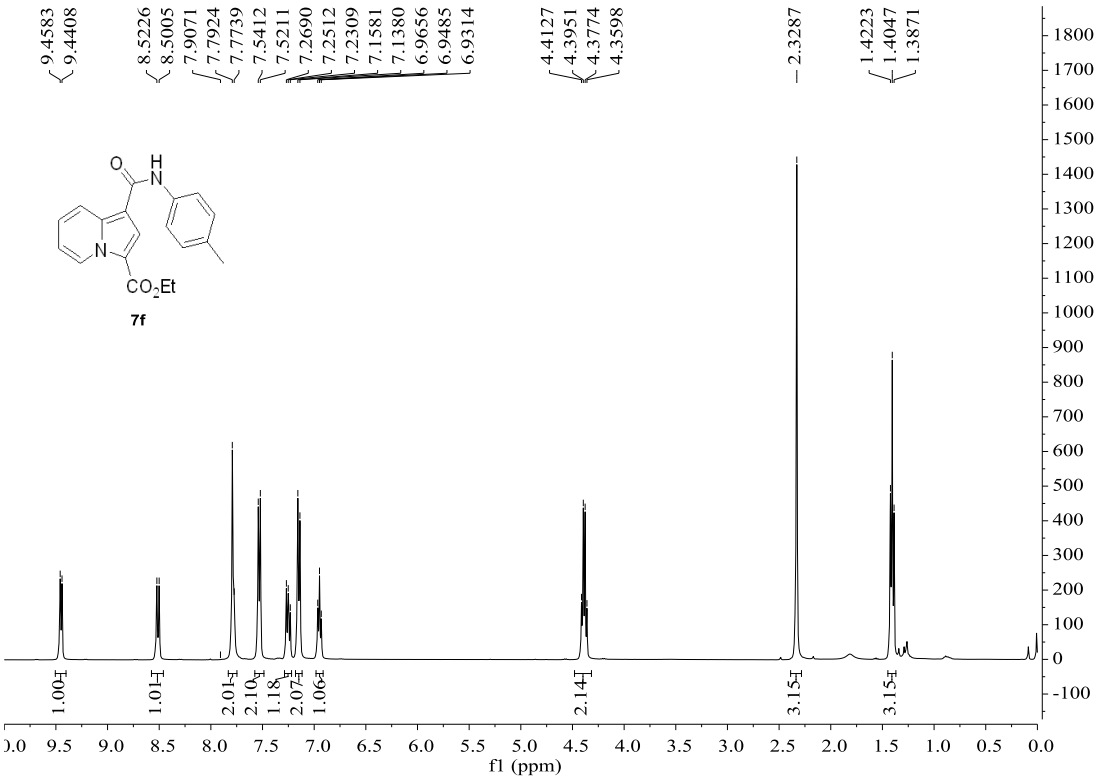

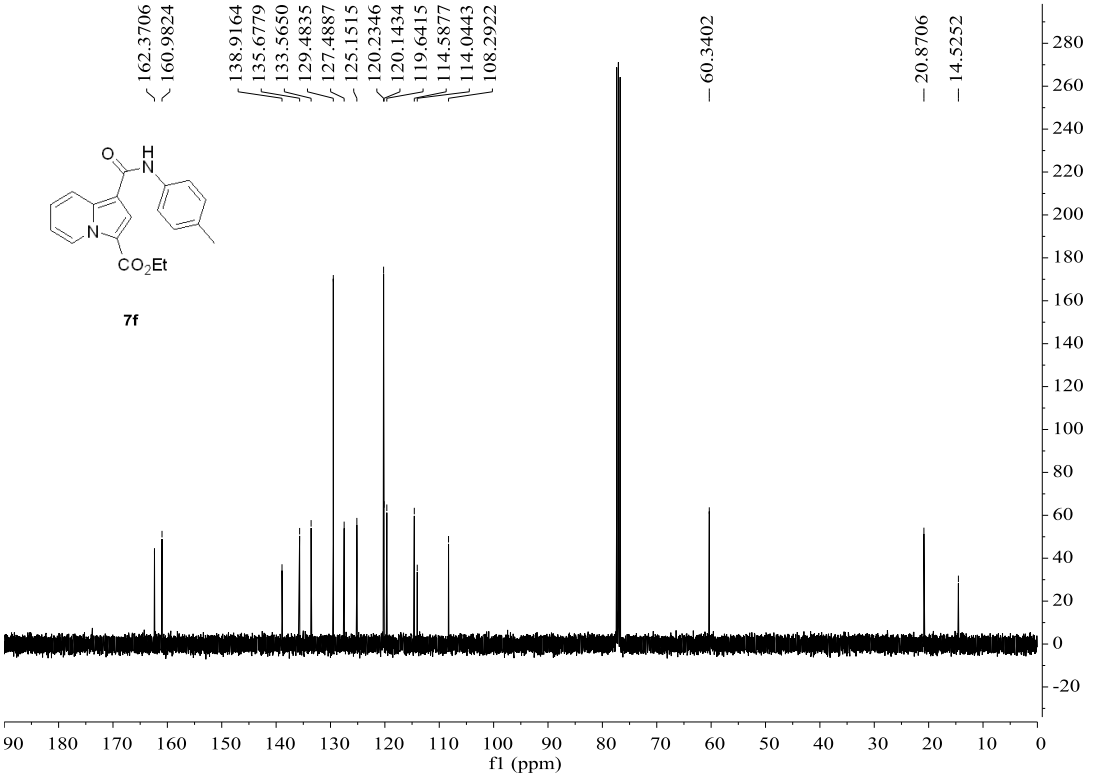

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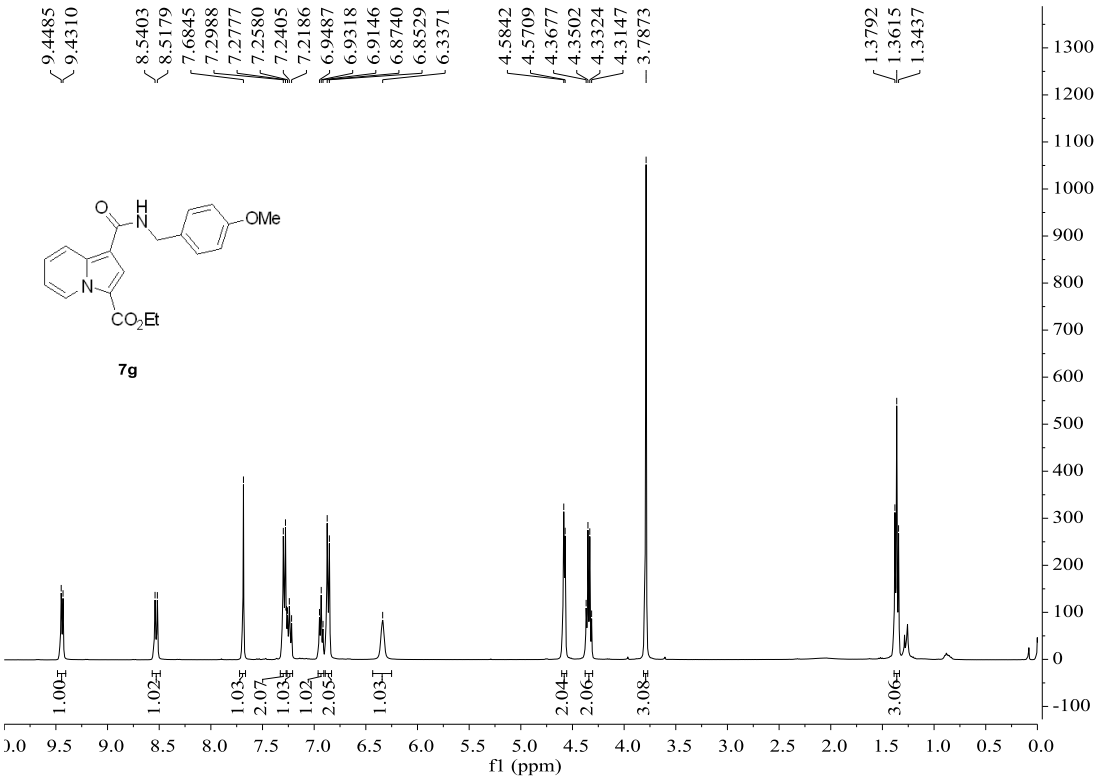

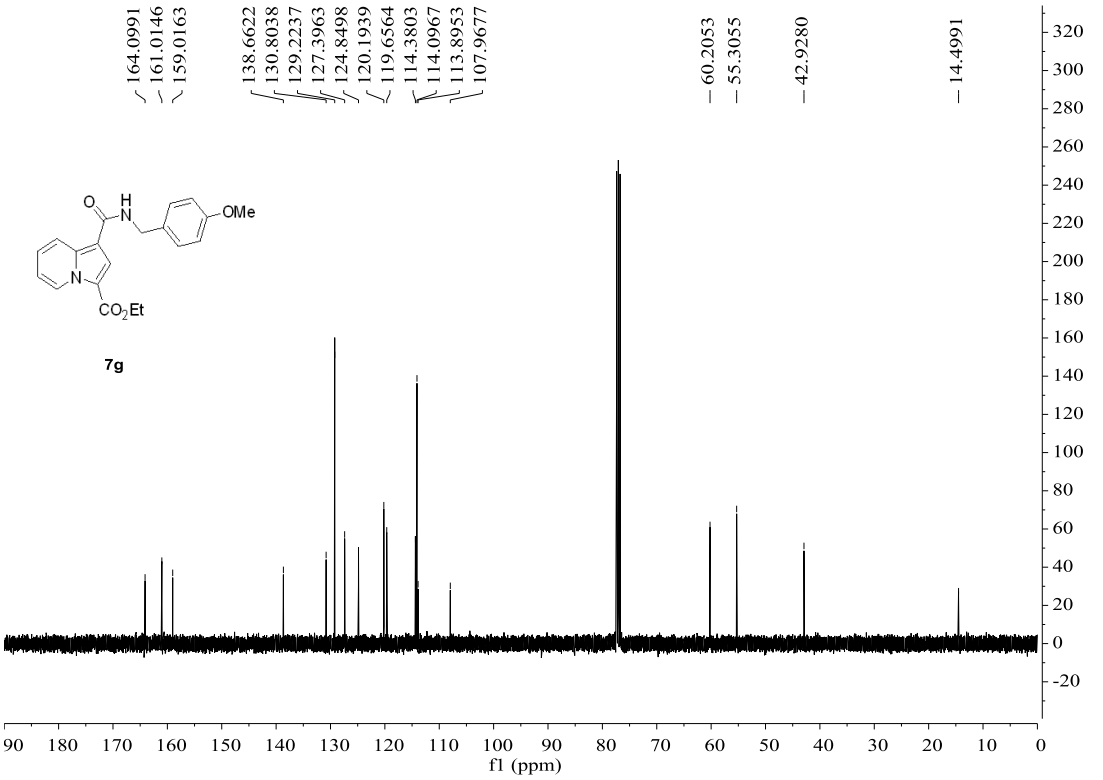

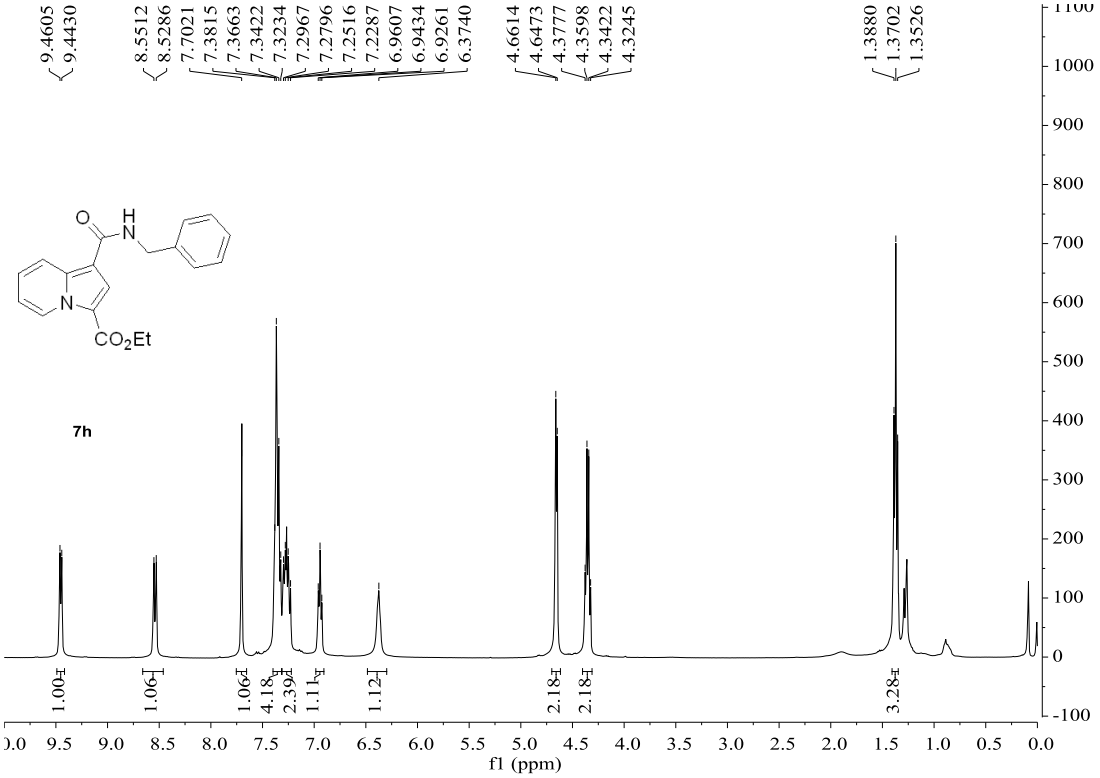

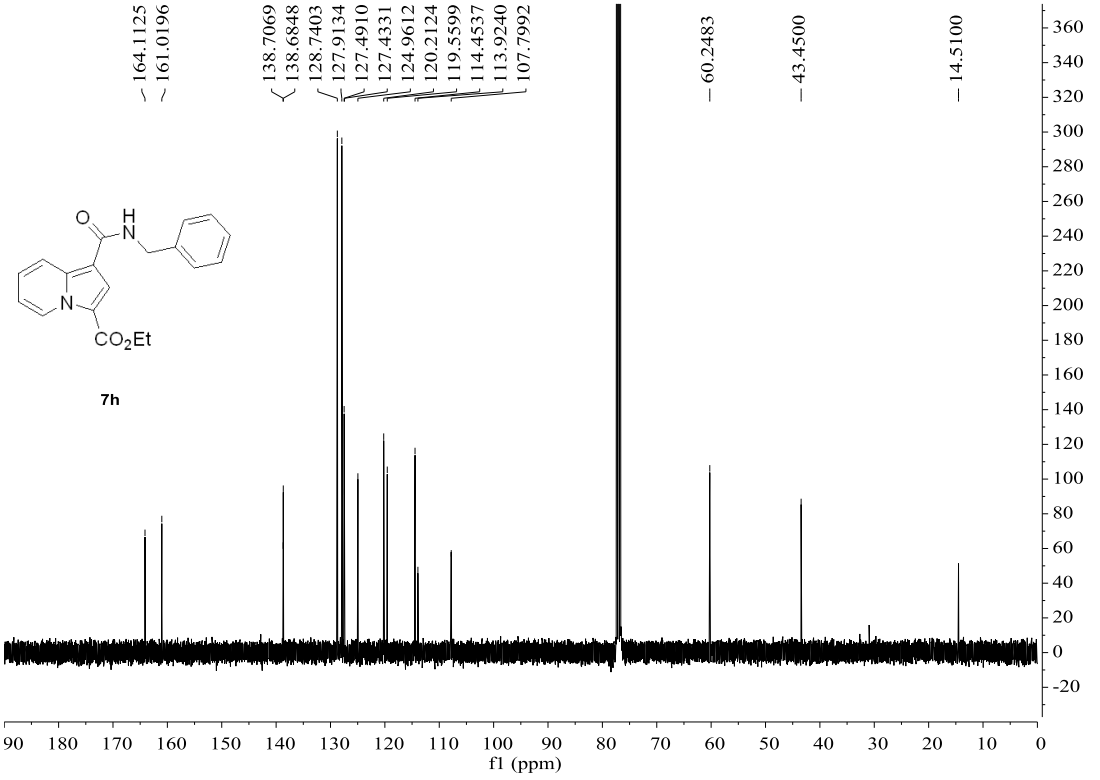

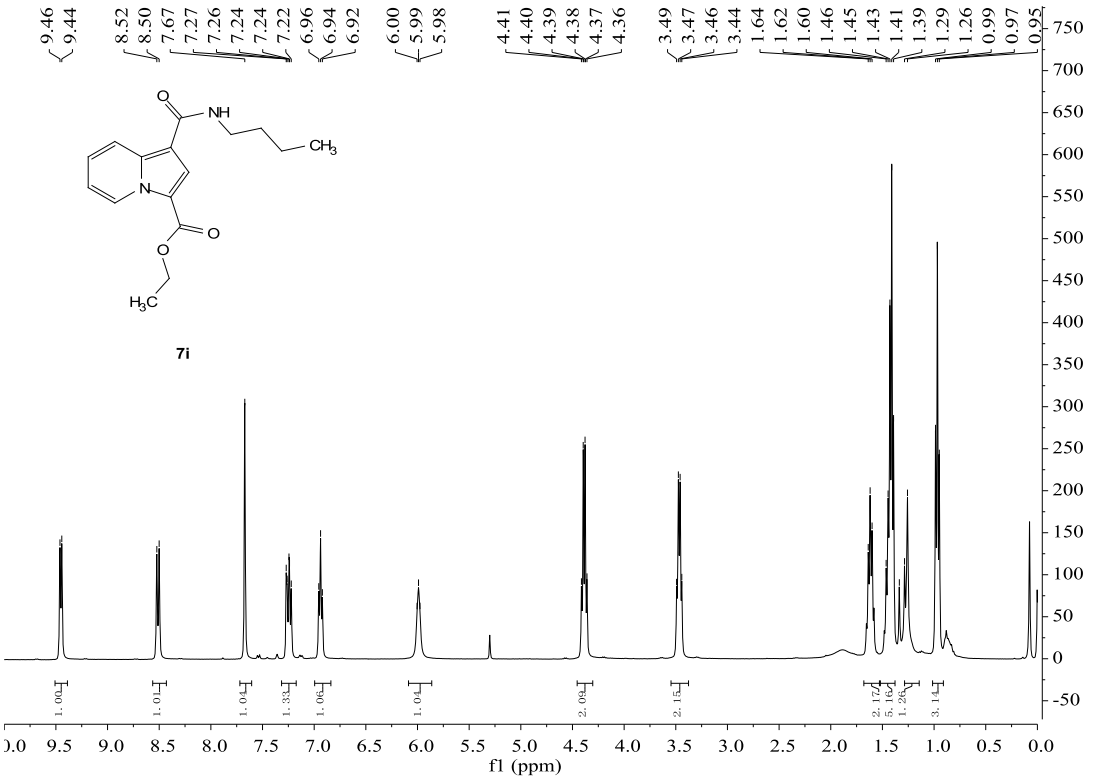

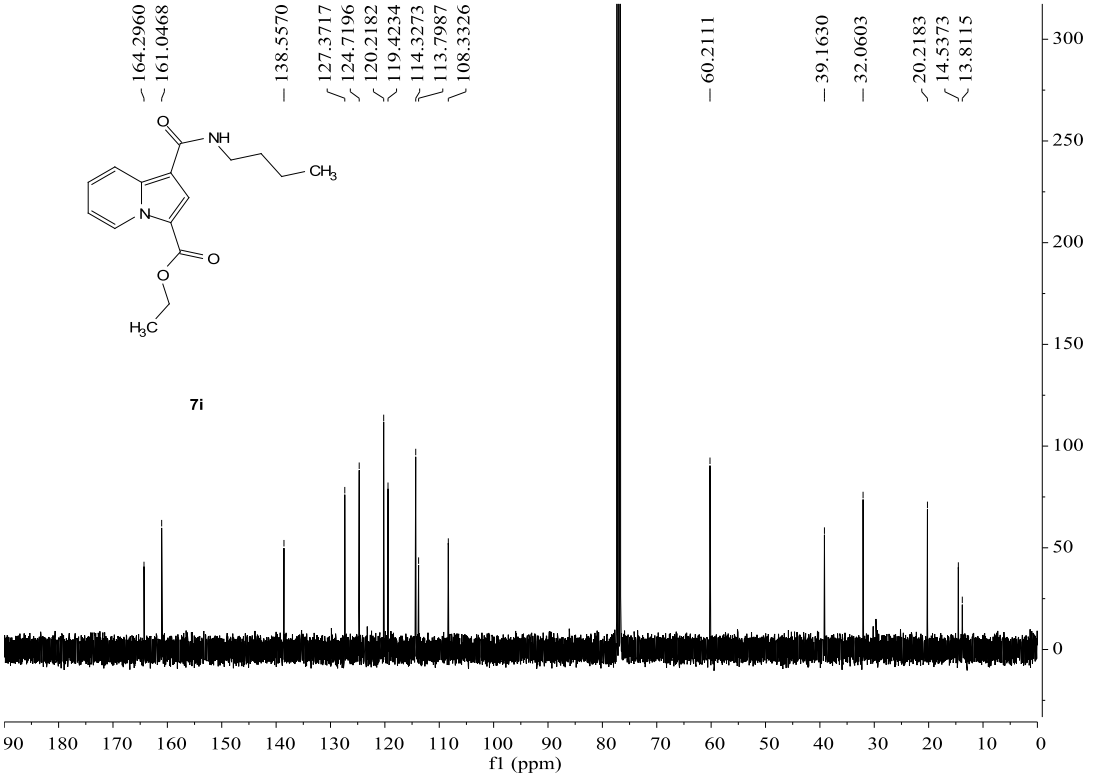

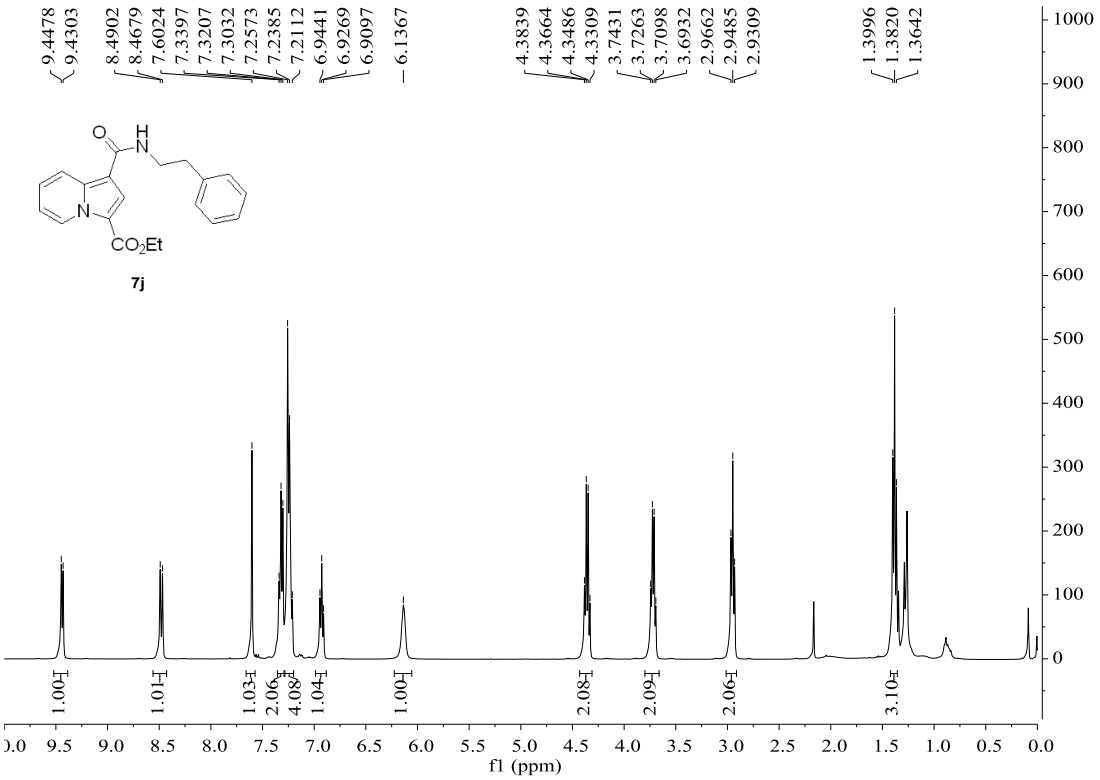

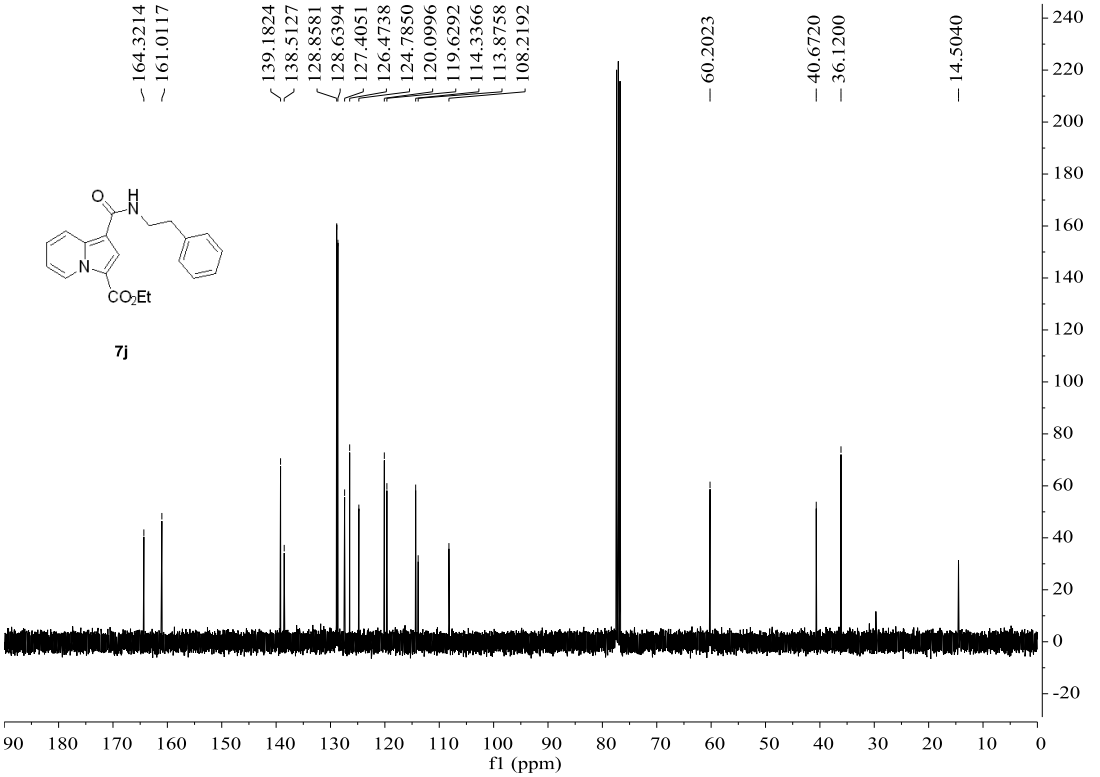

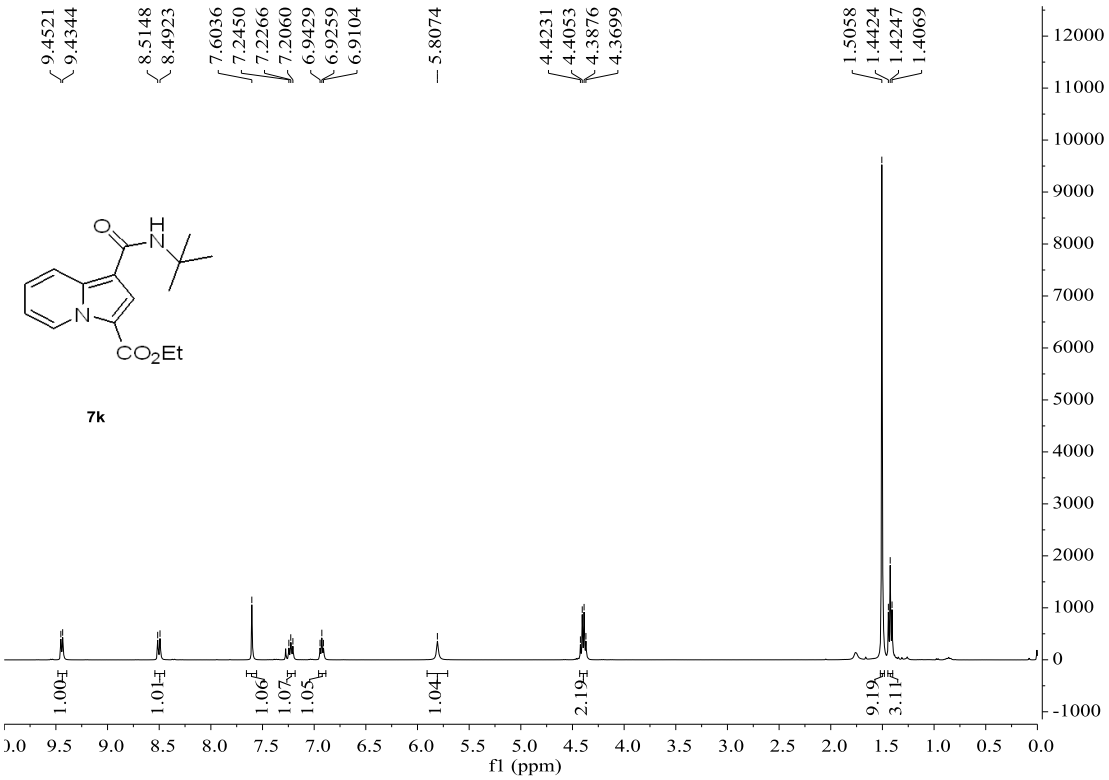

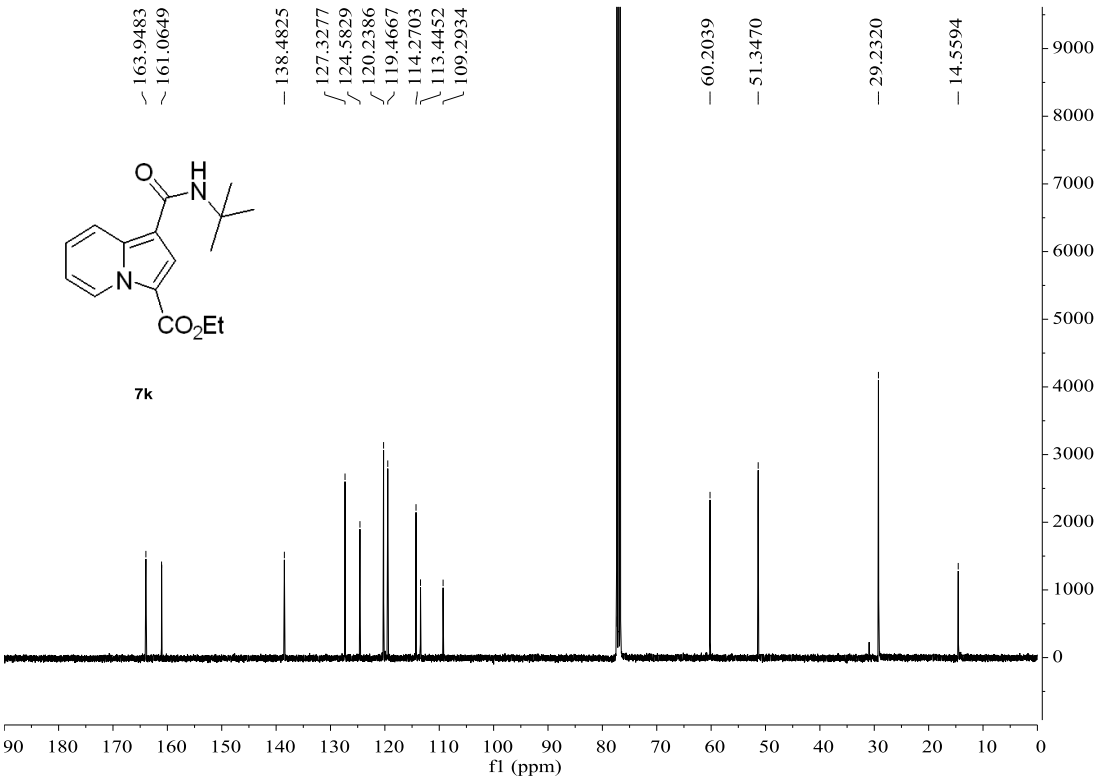

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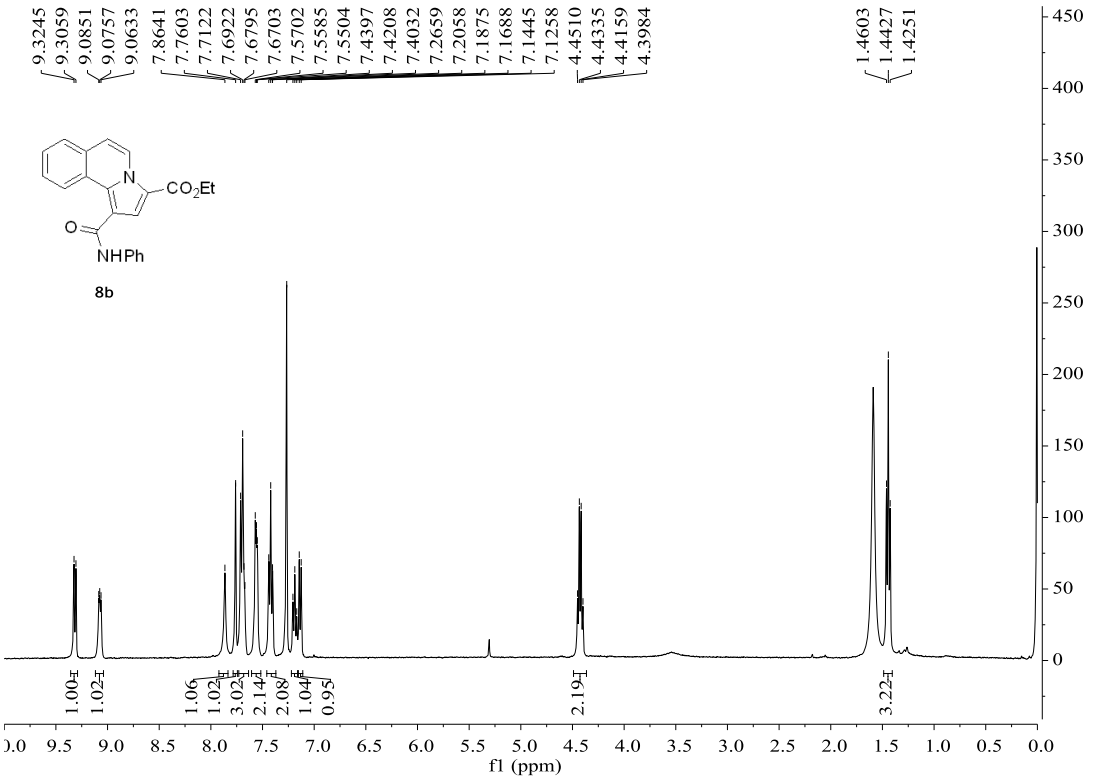

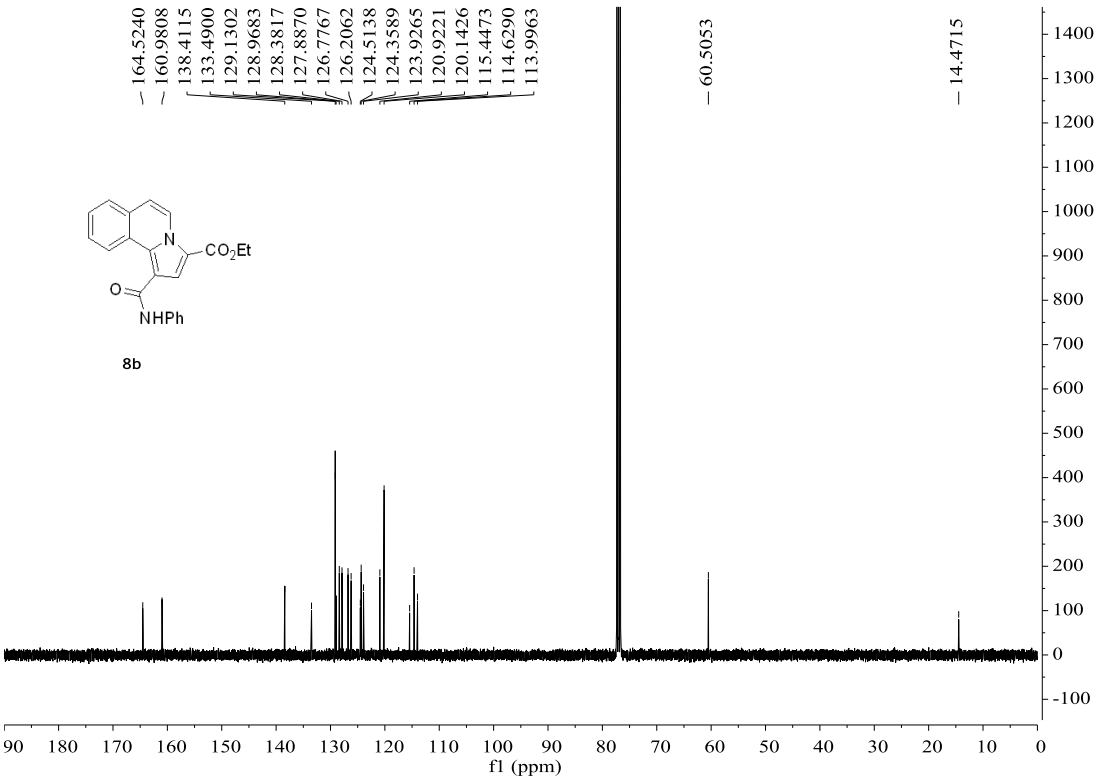

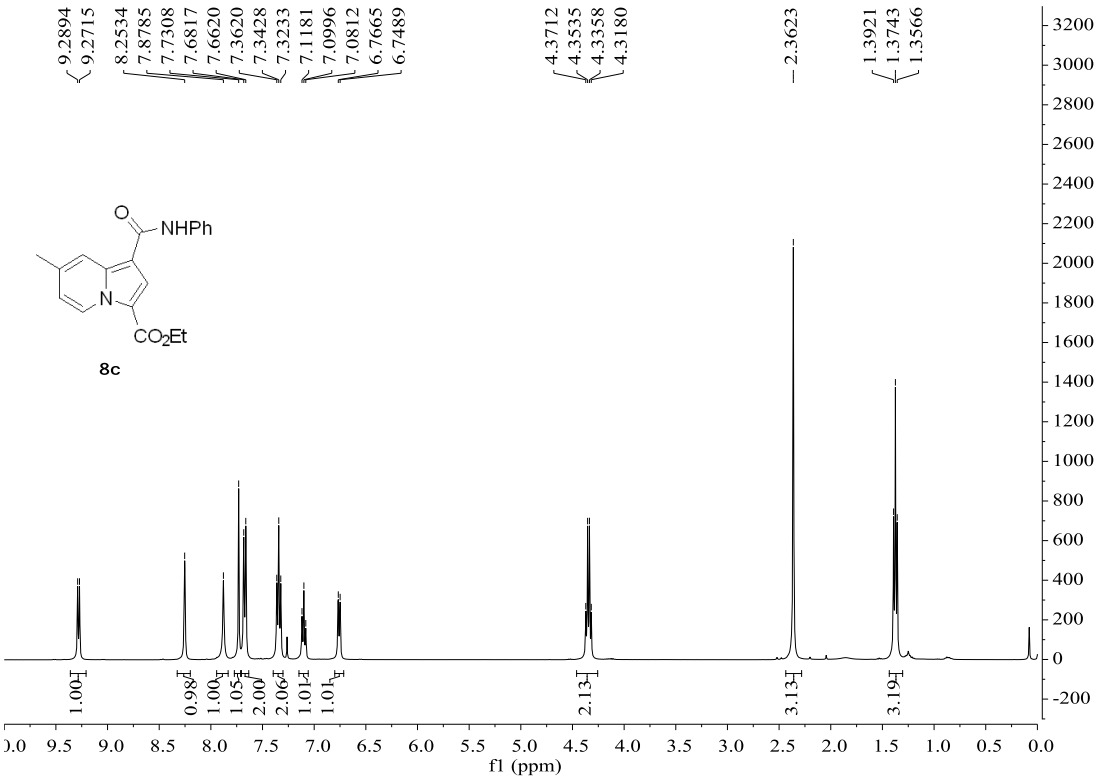

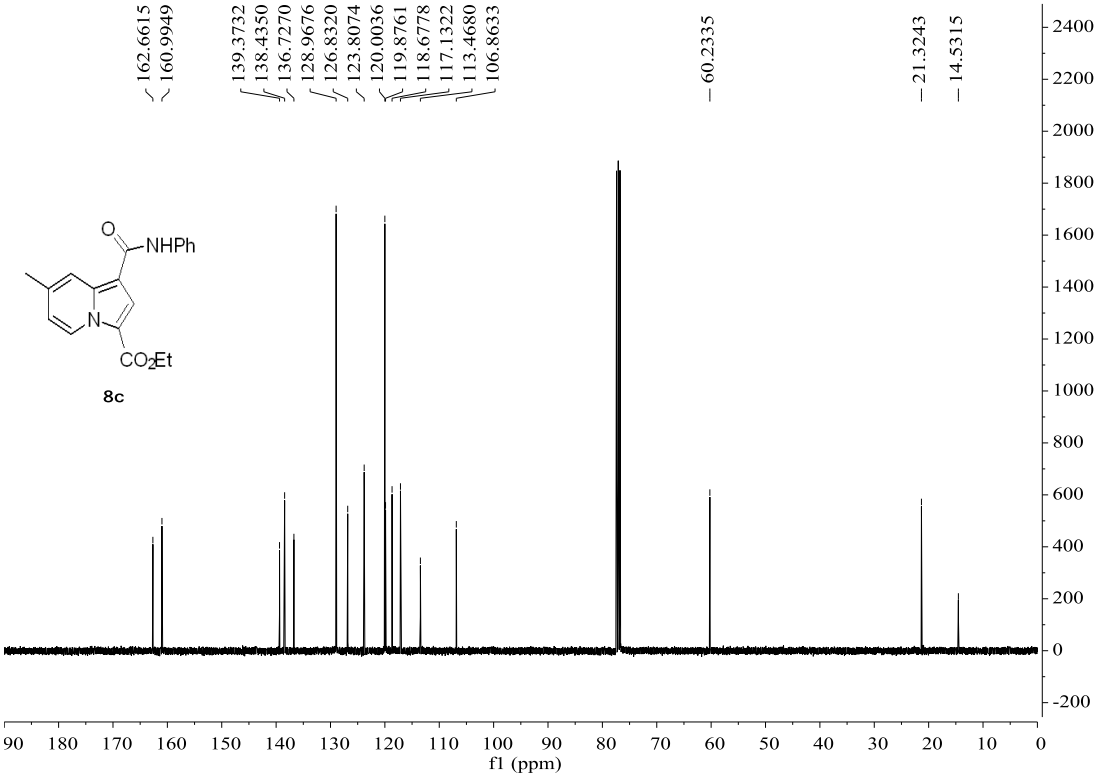

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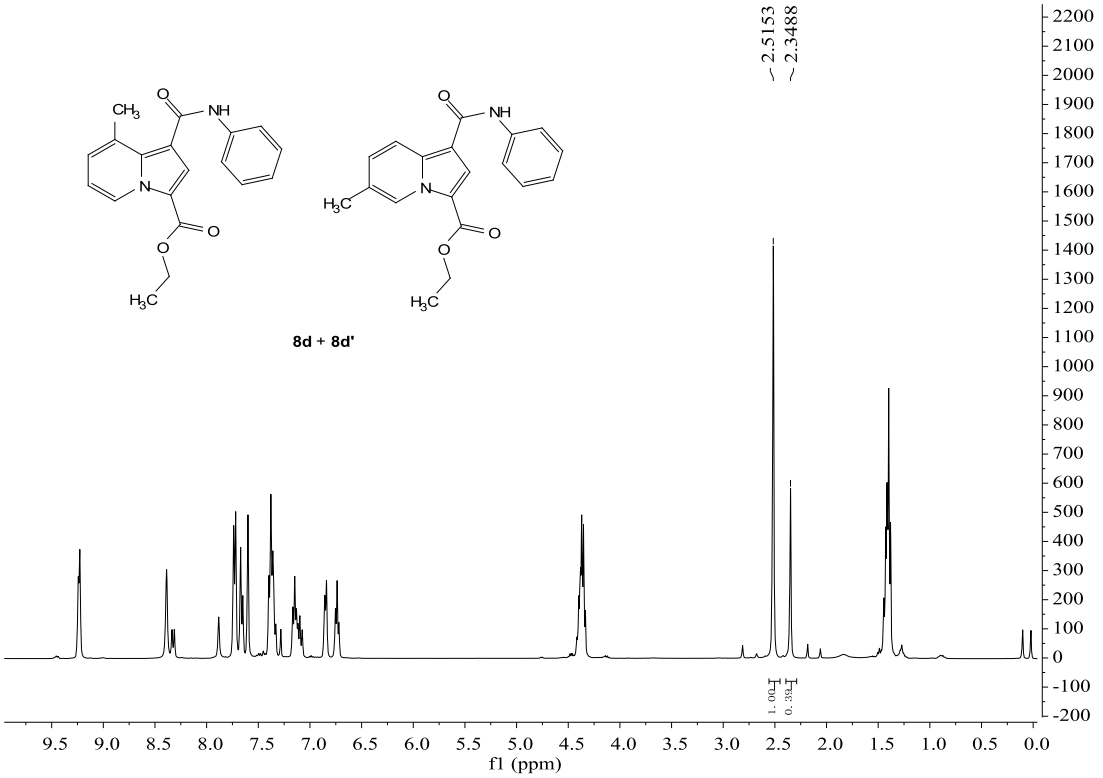

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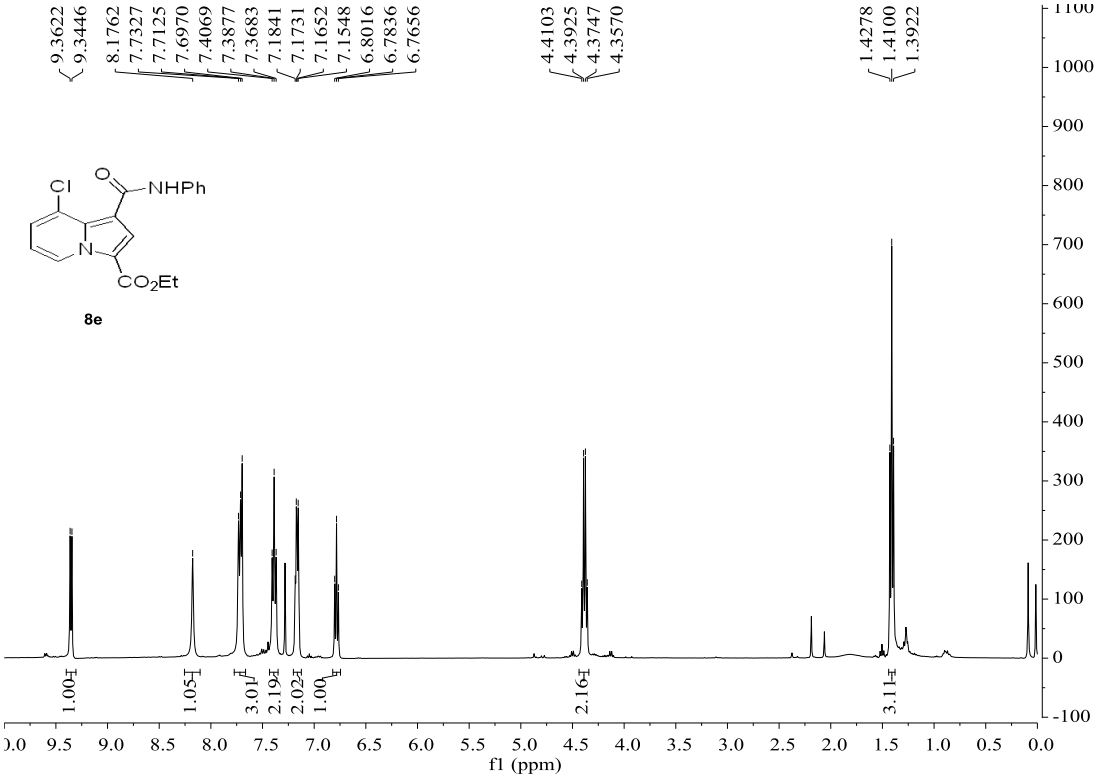

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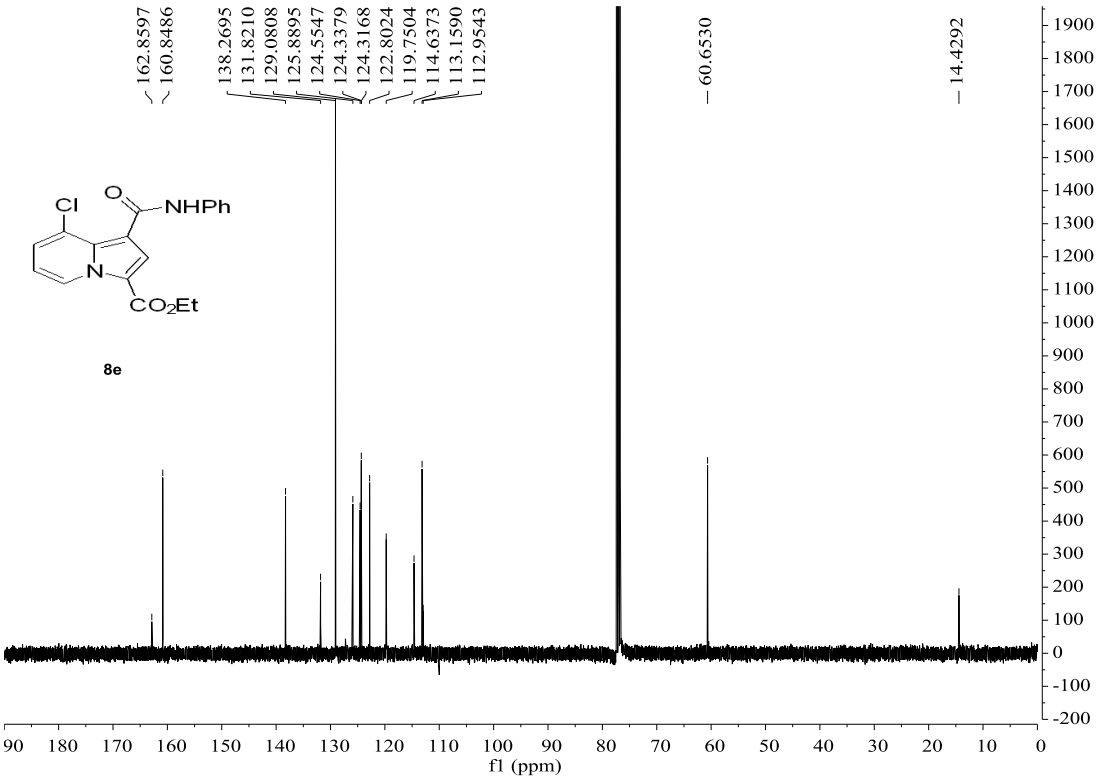

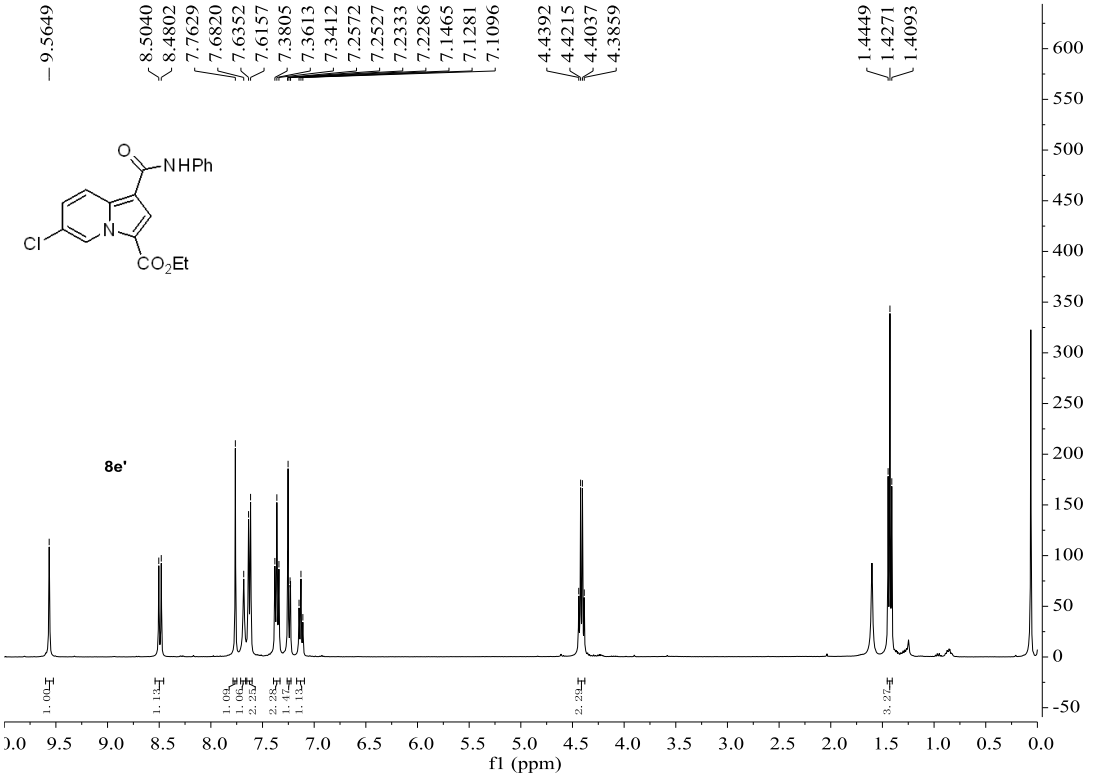

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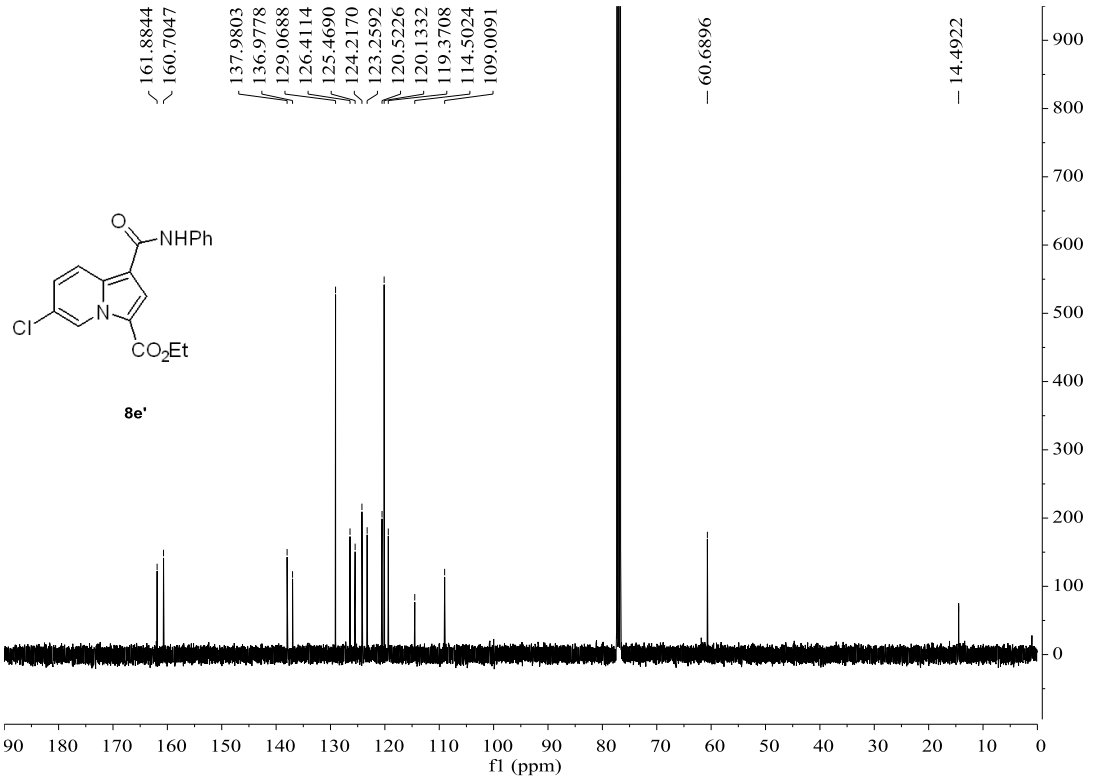

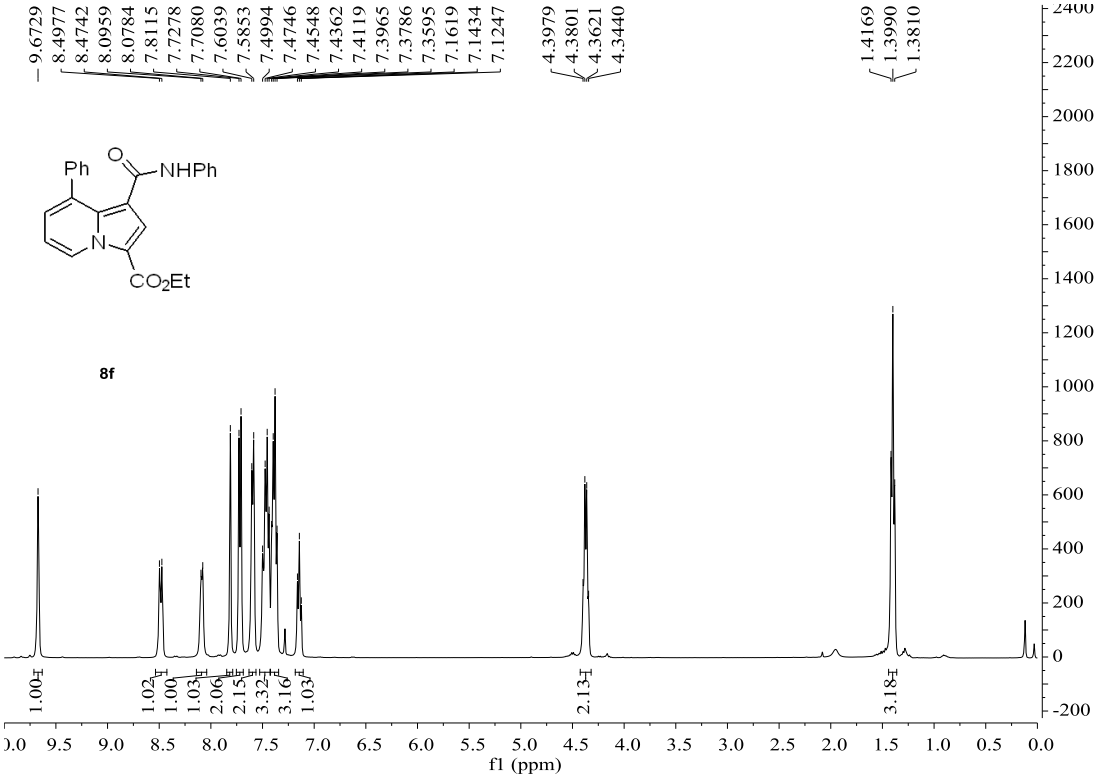

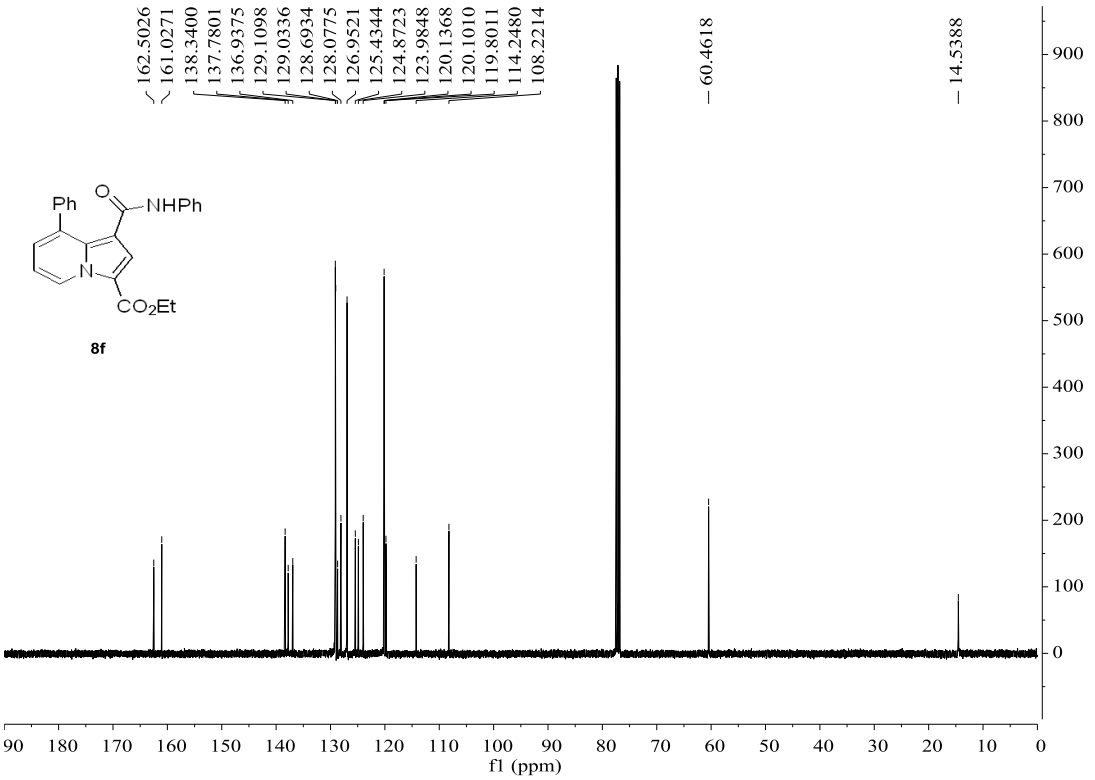

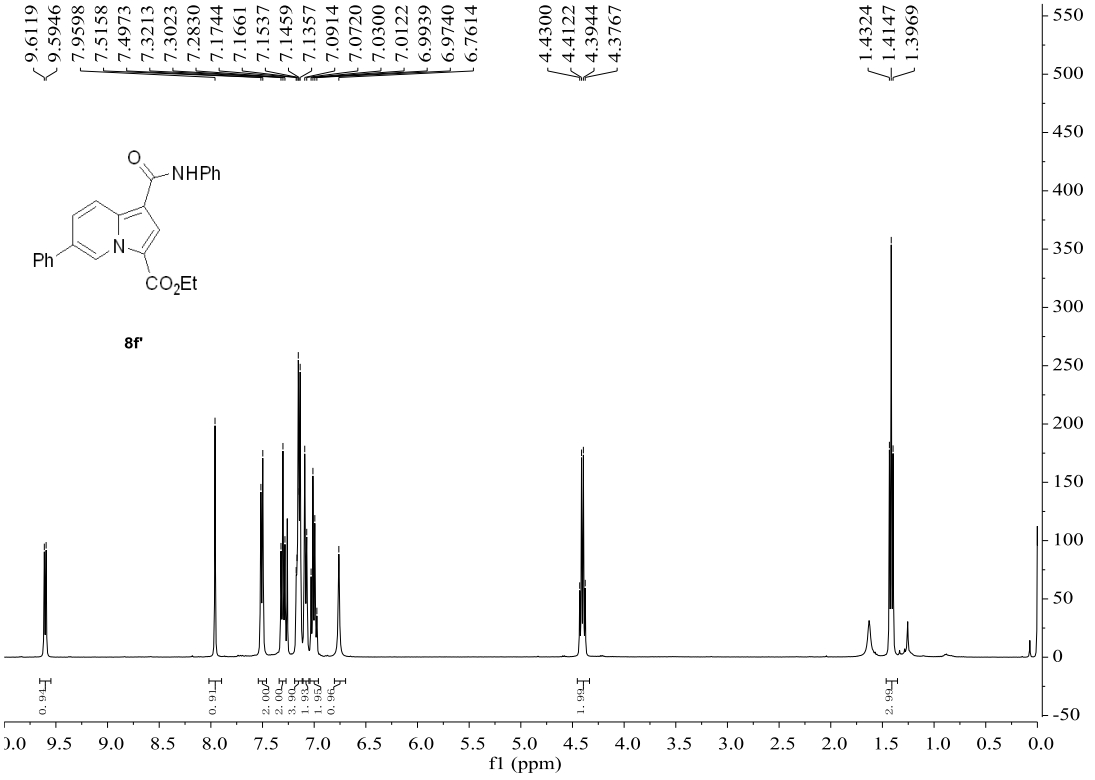

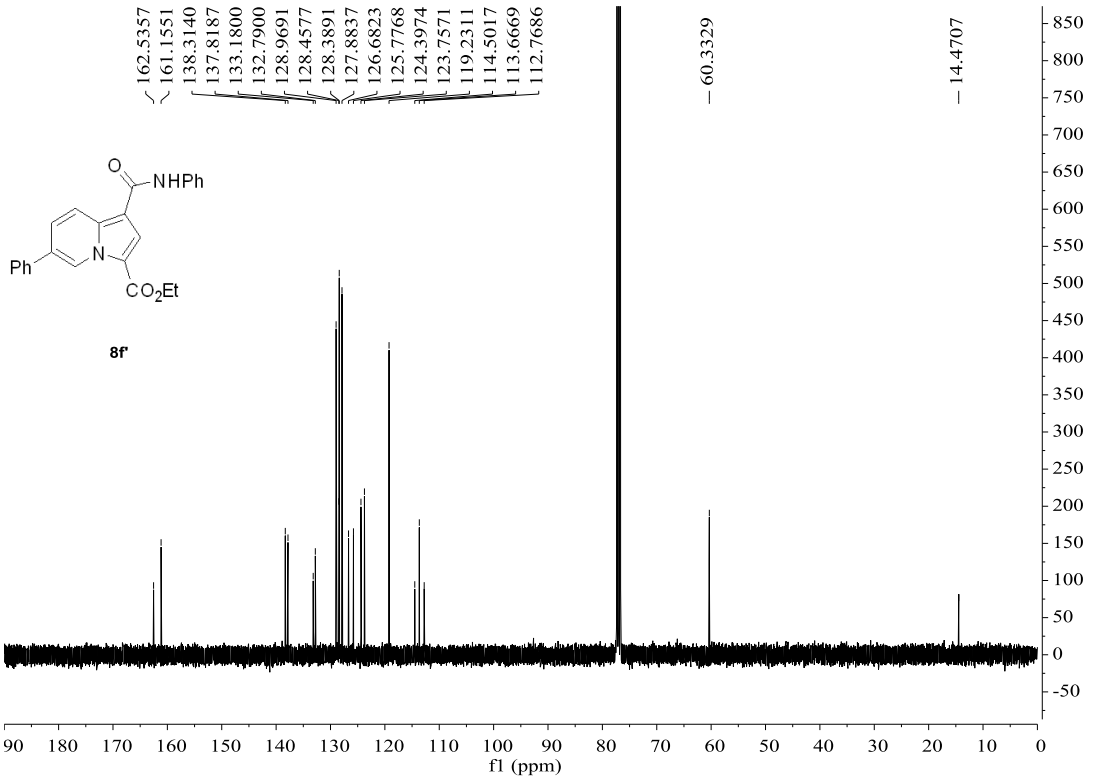

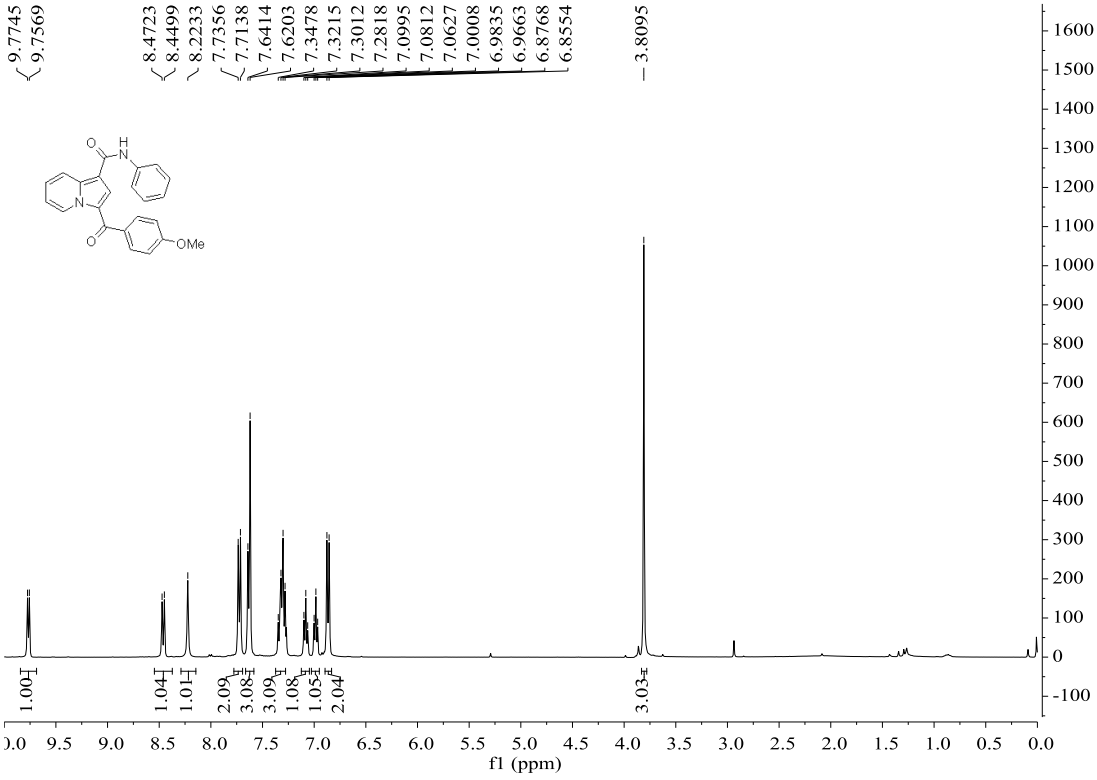

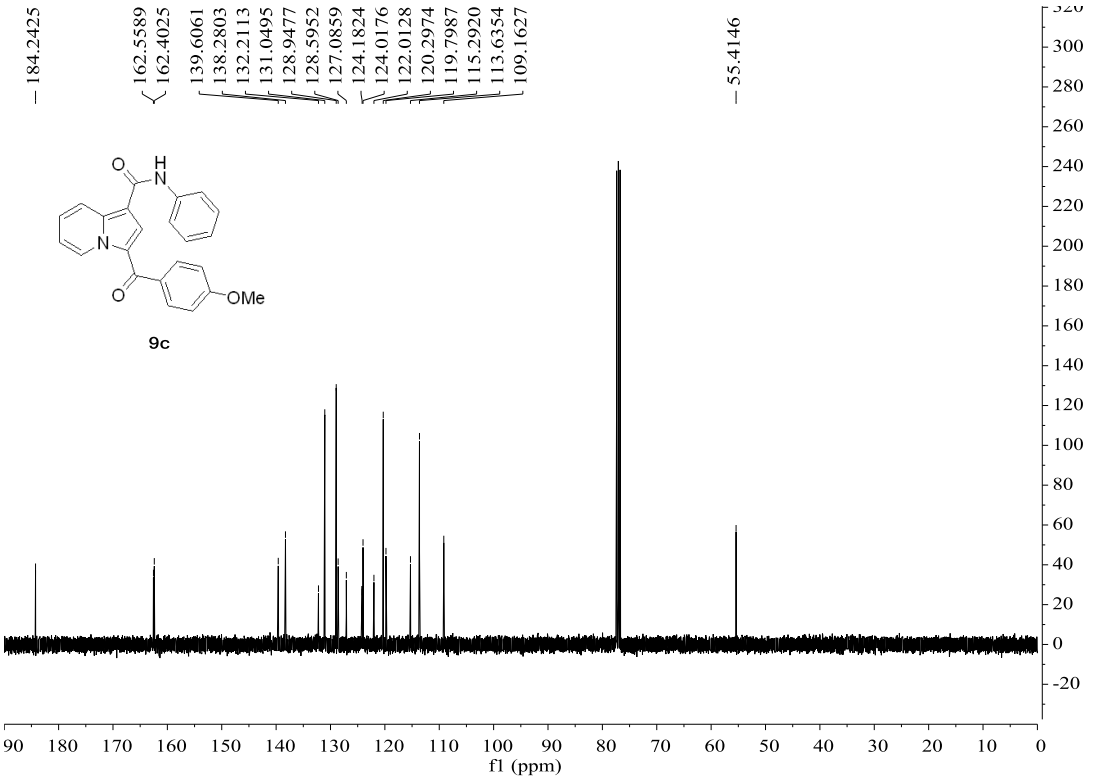

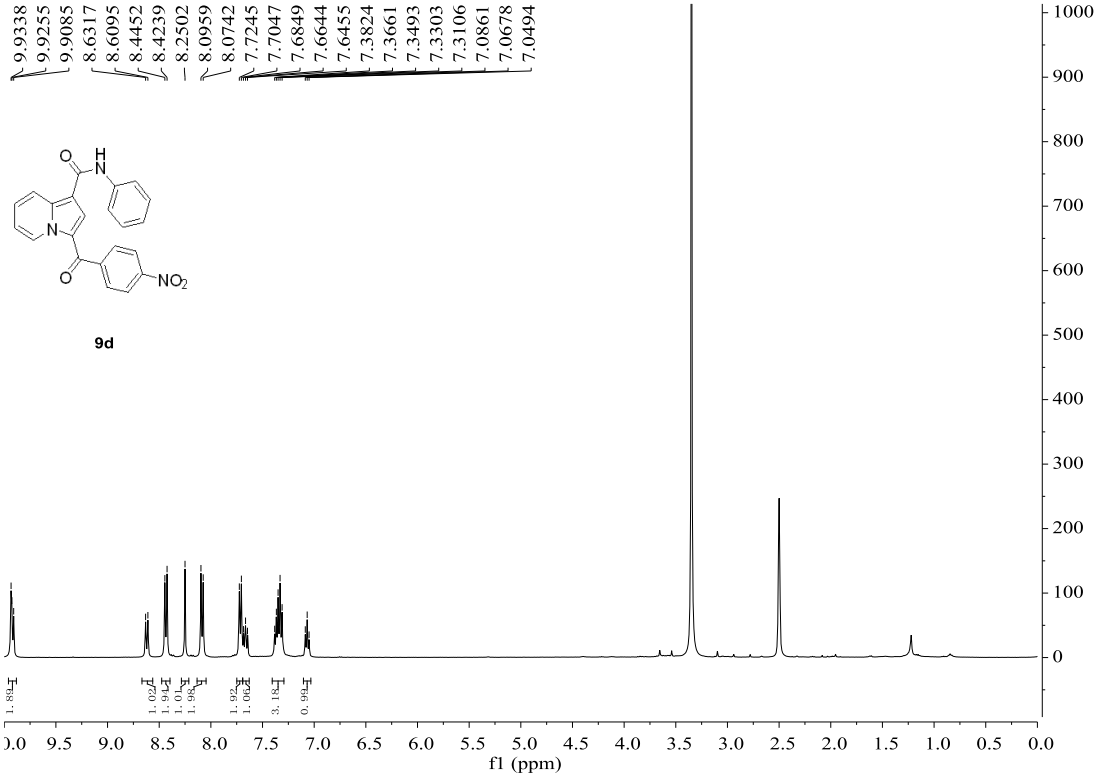

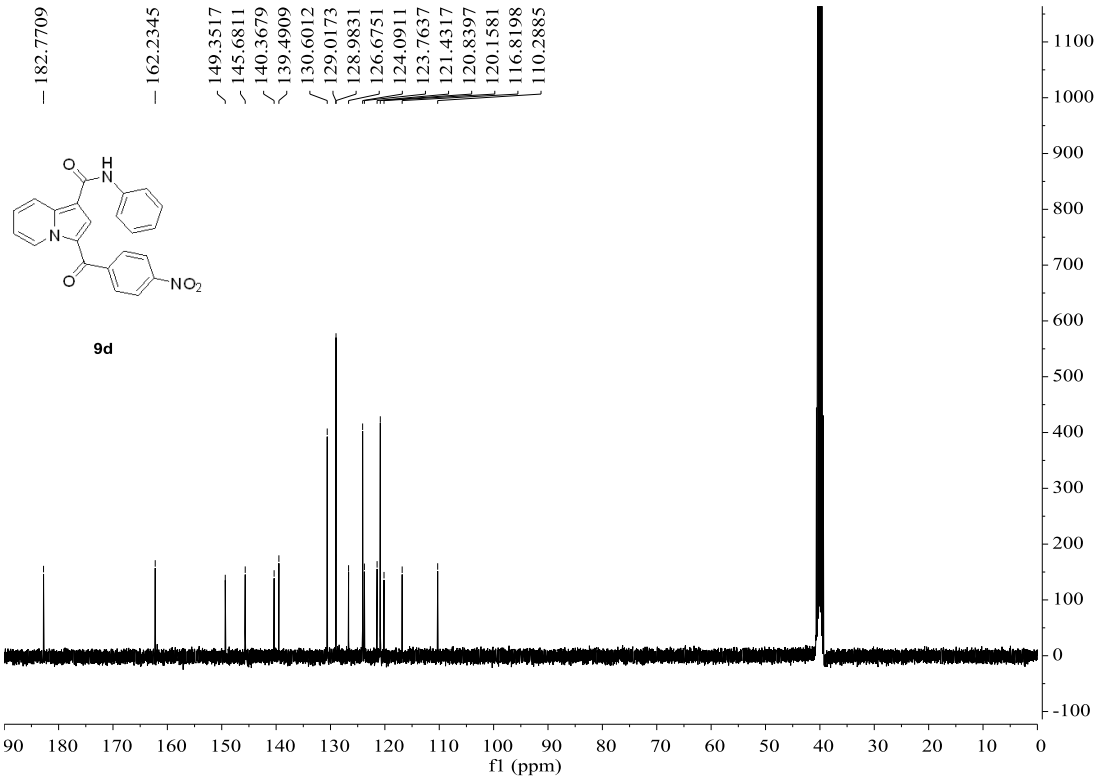

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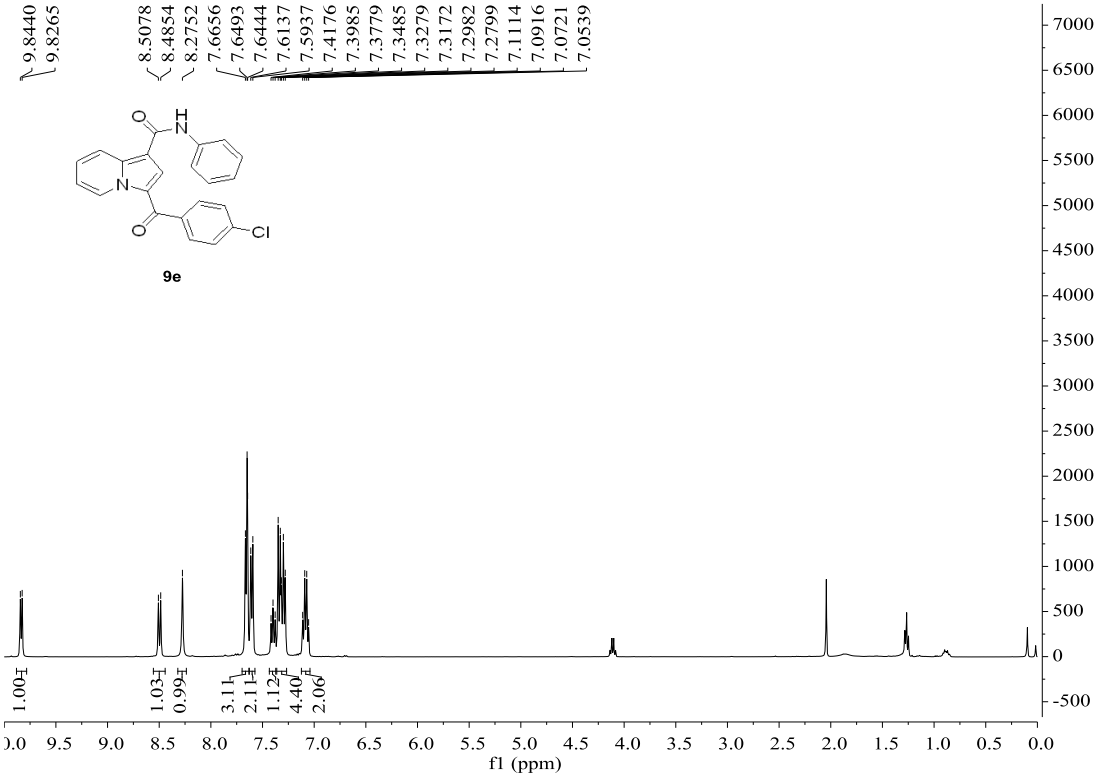

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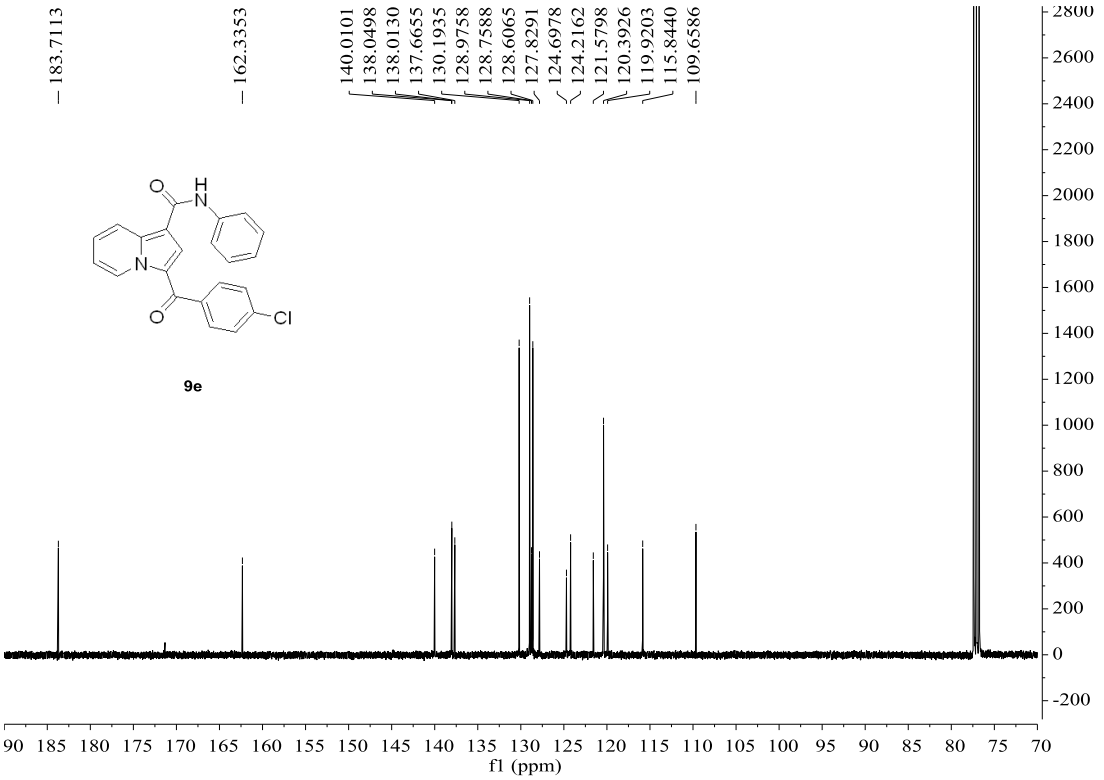

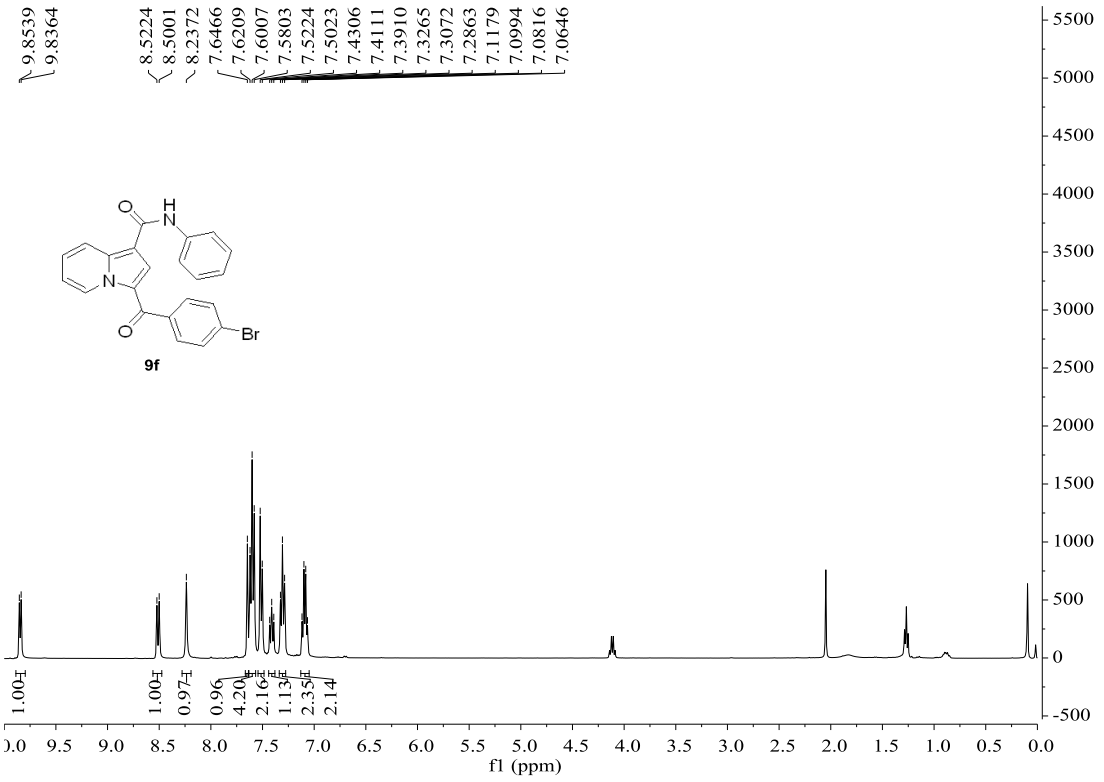

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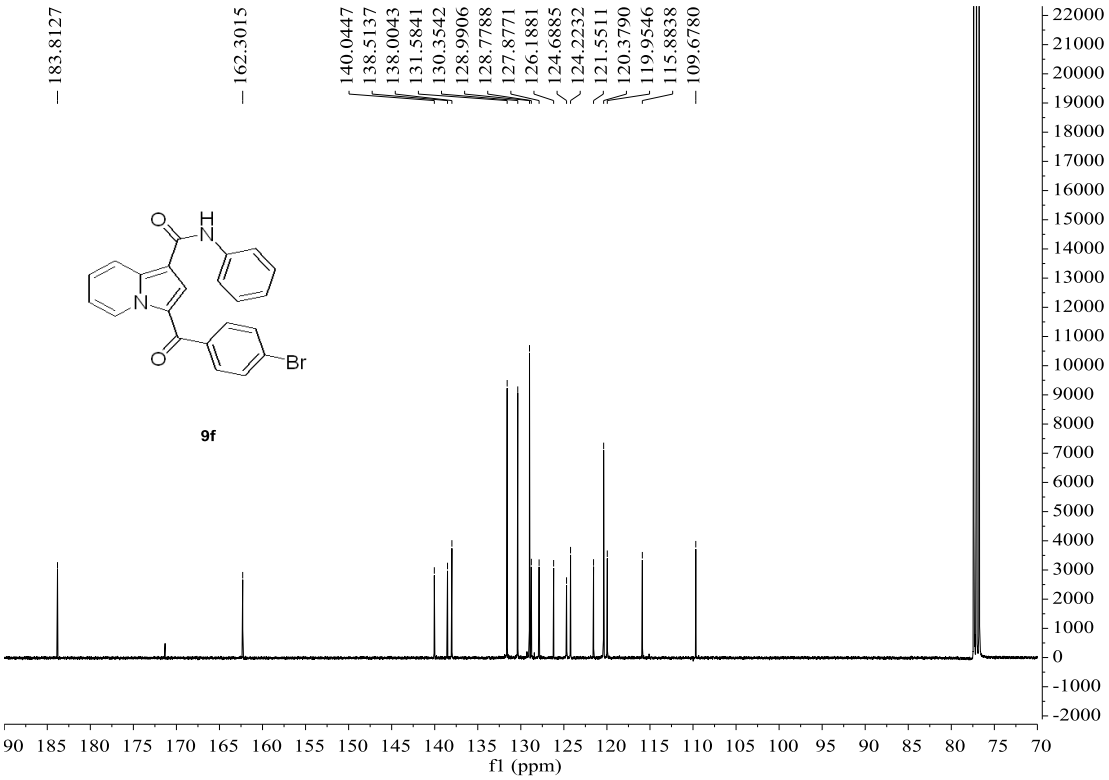

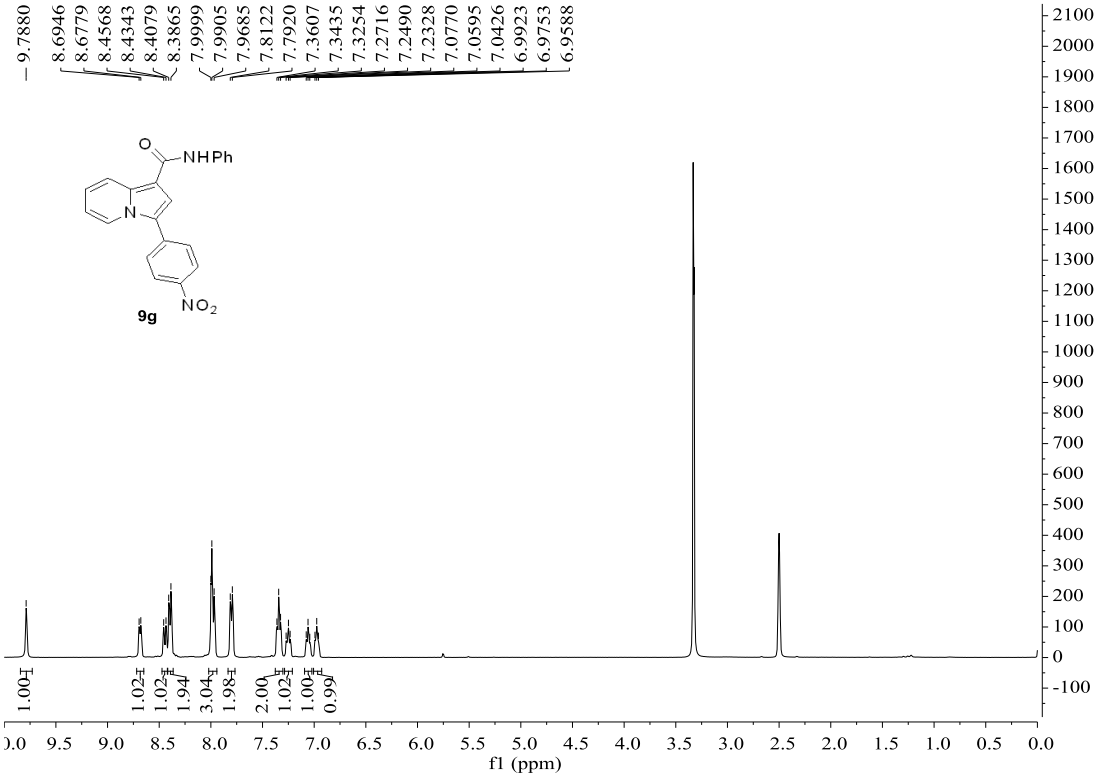

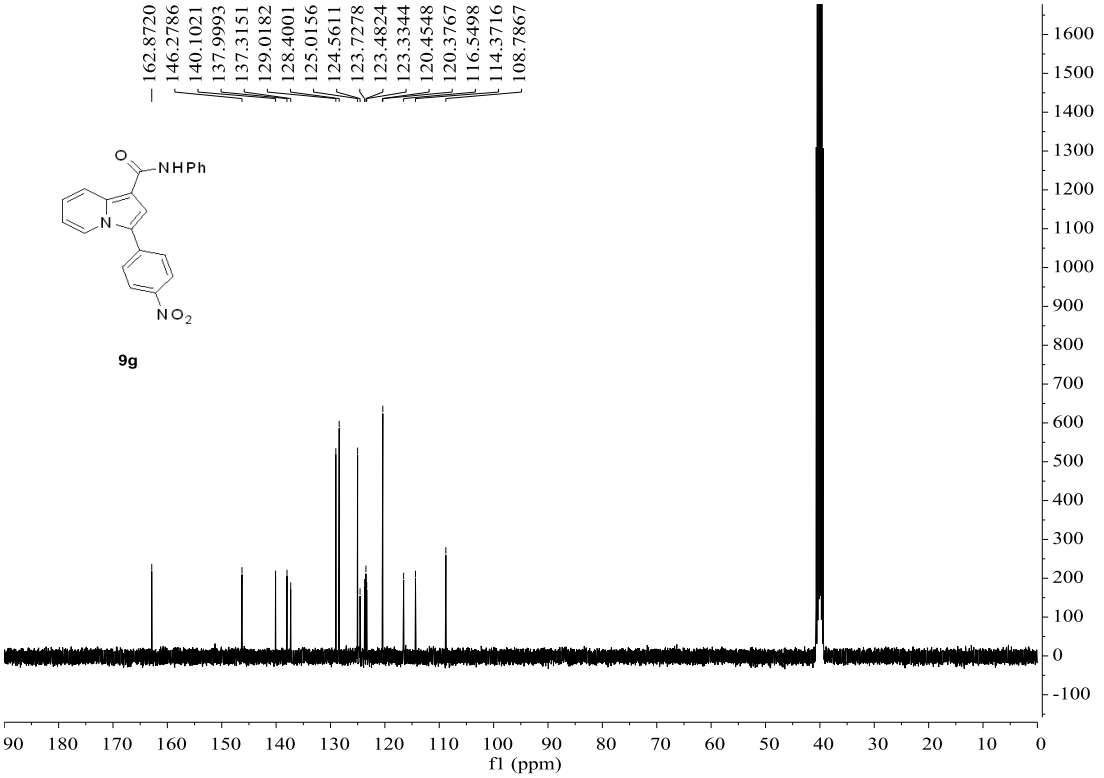

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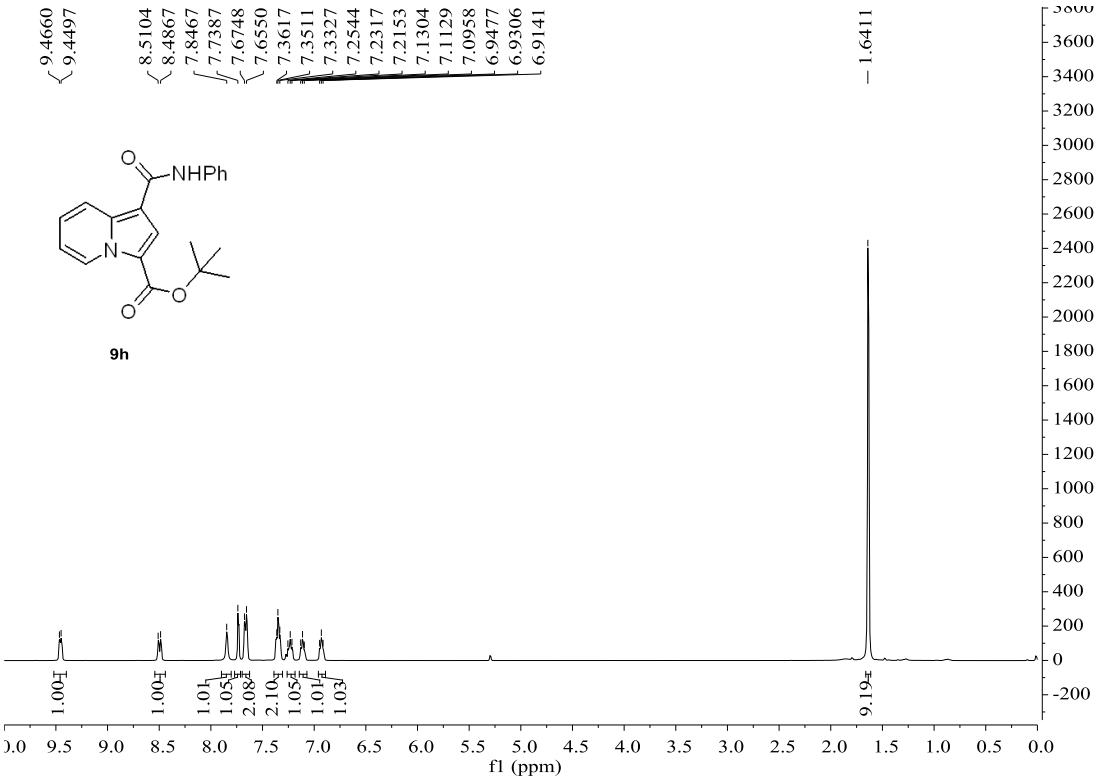

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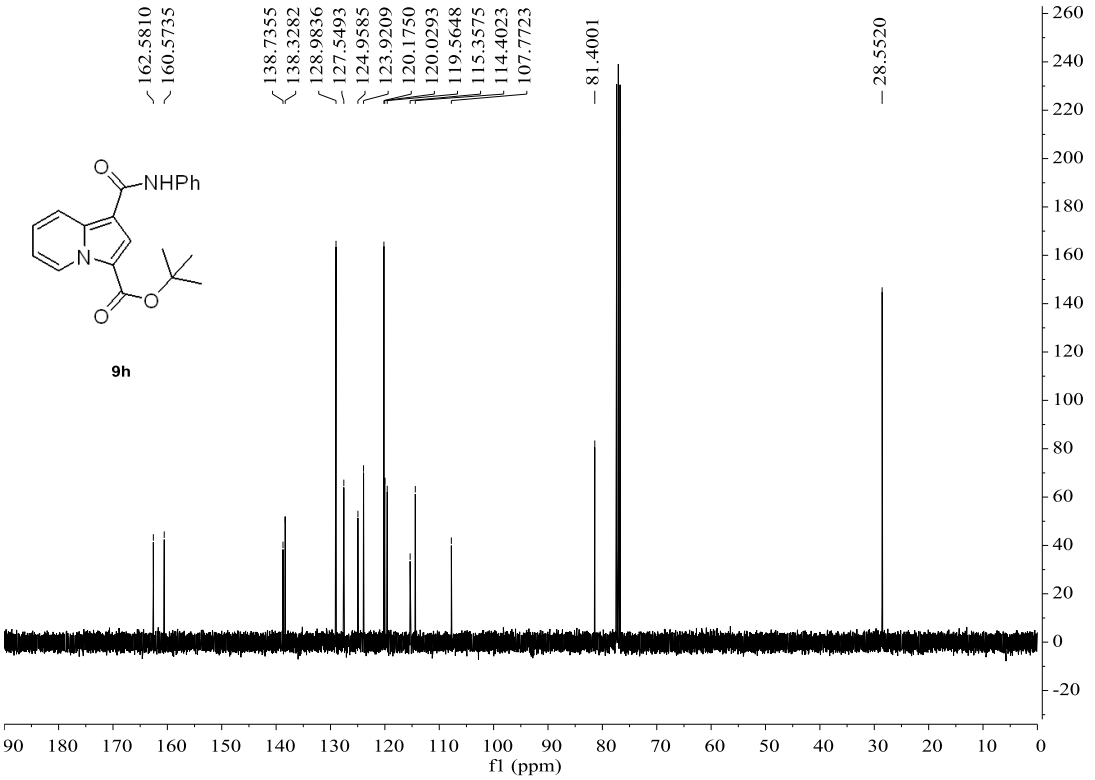

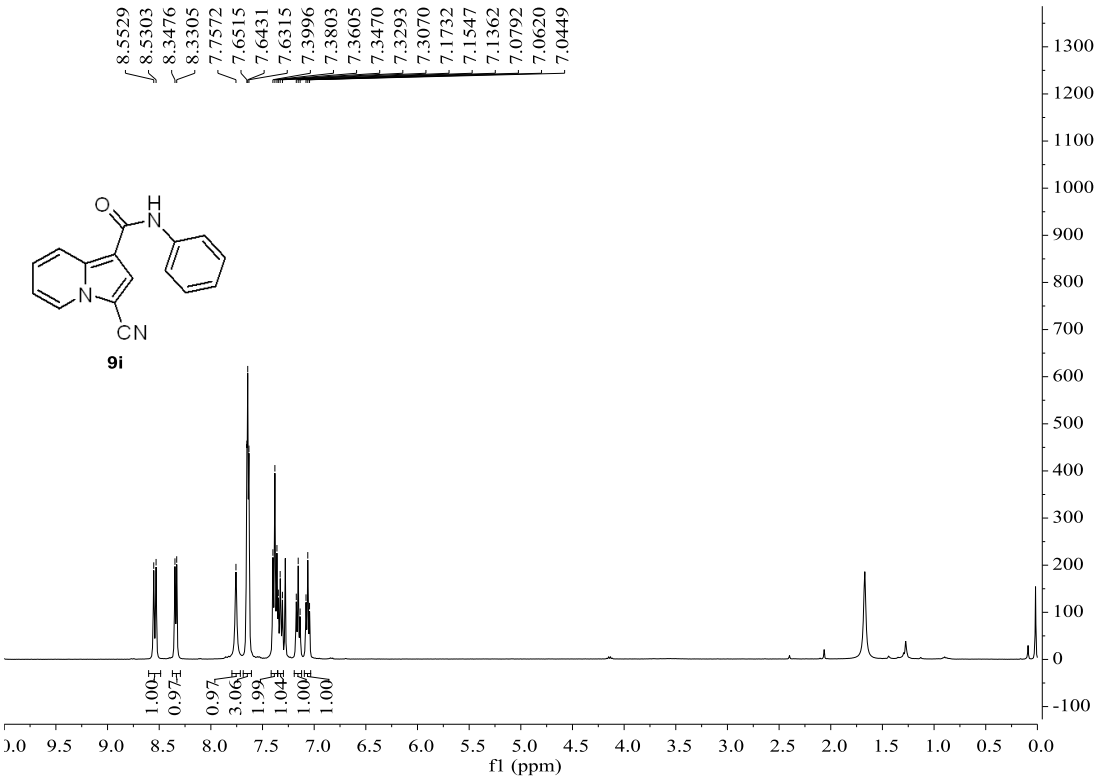

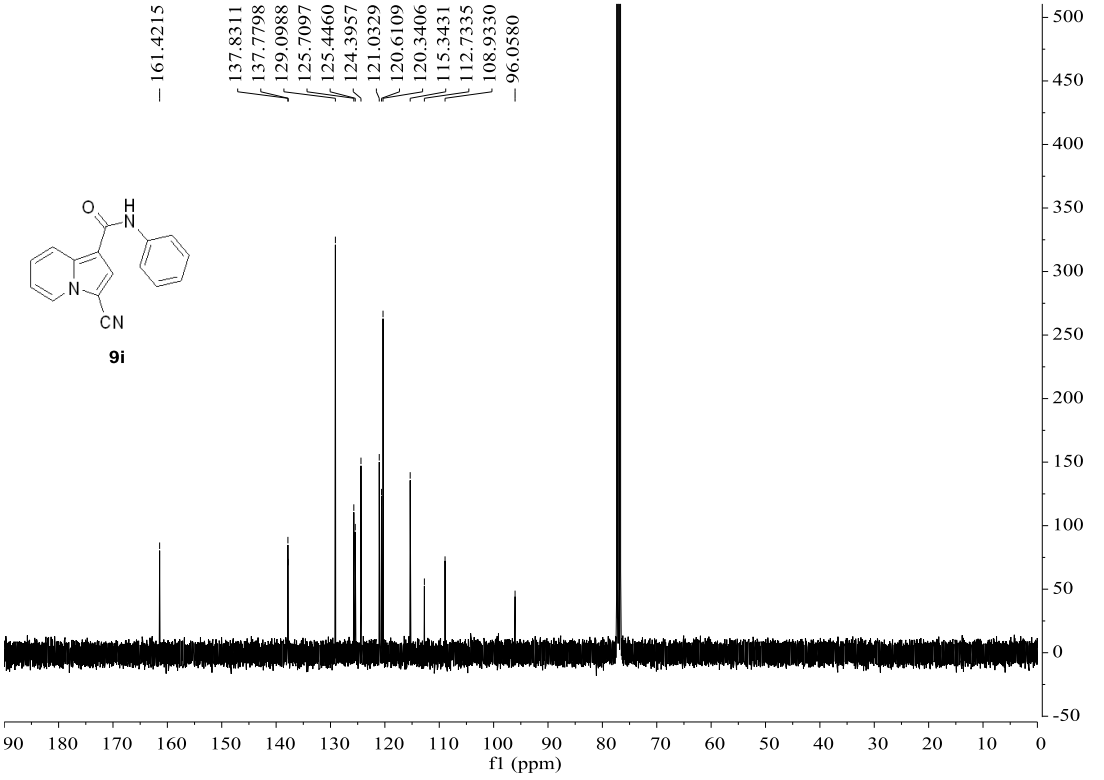

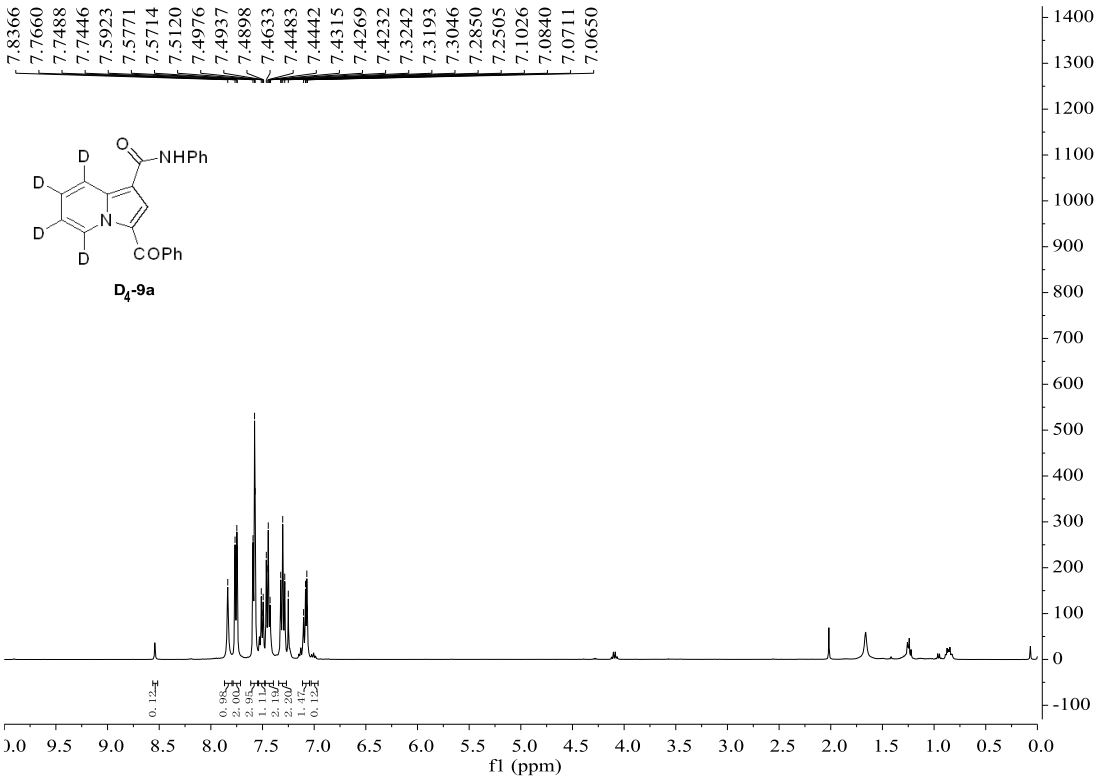

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