Supporting Information

Copper-Mediated Oxidative Coupling of Benzamides with Maleimides via Directed C–H Cleavage

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Contents

Instrumentation and Chemicals

^{1}H, ^{13}C{^{1}H}, and ^{19}F NMR spectra were recorded at 400, 100, and 376 MHz, respectively, for $CDCl_3$ solutions. HRMS data were obtained by APCI using TOF. GC analysis was carried out using a silicon OV-17 column (2.6 mm i.d. x 1.5 m) or a CBP-1 capillary column (0.5 mm i.d. x 25 m). TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck silica gel $60F_{254}$. Silica gel was used for column chromatography. Gel permeation chromatography (GPC) was performed with a $CHCl_3$ eluent (3.5 mL/min, UV detector). Unless otherwise noted, materials obtained from commercial suppliers were used as received. DMF was dried on a Glass Contour Solvent dispending system (Nikko Hansen & Co., Ltd.) prior to use. The starting amides **1a–n**, **1a-*d*$_5$**, and **1a'** were prepared from the corresponding benzoyl chlorides or benzoic acids and 8-aminoquinoline or 8-amino-5-methoxyquinoline according to the literature.[1]

[1] Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4457.

Experimental Procedures

Typical Procedure for Synthesis of Isoindolone-Incorporated Spirosuccinimides 3.

The synthesis of **3aa** is representative. $Cu(OAc)_2$ (182 mg, 1.0 mmol), *N*-(quinolin-8-yl)benzamide (**1a**; 62 mg, 0.25 mmol), and *N*-methylmaleimide (**2a**; 111 mg, 1.0 mmol) were placed in a 20 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. *N*,*N*-Dimethylformamide (DMF, 0.50 mL) was sequentially injected via a syringe. The suspension was stirred for 15 min at room temperature. A solution of PivOH (26 mg, 0.25 mmol) in DMF (1.0 mL) and *N*,*N*-dicyclohexylmethylamine (0.21 mL, 1.0 mmol) were added to the suspension. The mixture was stirred for 24 h at 80 ºC. The resulting mixture was allowed to cool to room temperature and then quenched with water. The mixture was extracted with ethyl acetate three times. The combined organic layer was then washed with saturated aqueous NH_4Cl and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with dichloromethane/ethyl acetate (1/1, v/v) afforded 1'-methyl-2-(quinolin-8-yl)spiro-[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (**3aa**; 79 mg, 0.22 mmol) in 89% yield. X-ray quality crystals were grown from CH_2Cl_2/heptane.

Procedure for Synthesis of 4aa.

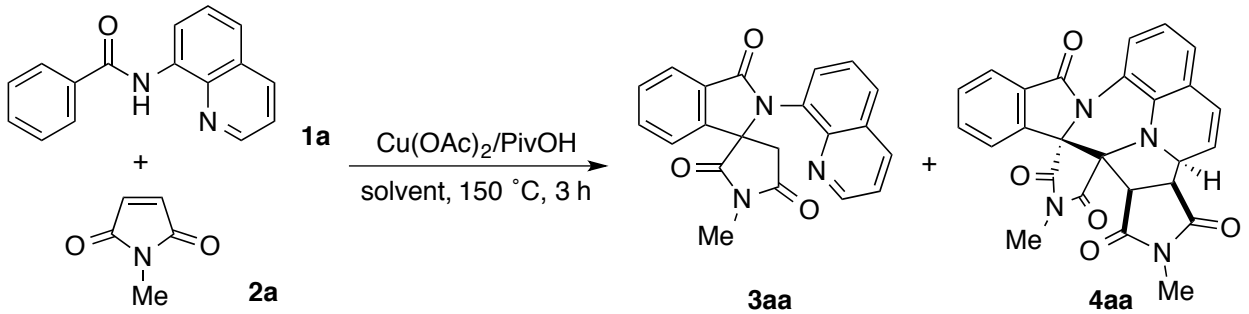
1'-Methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (**3aa**; 33 mg, 0.093 mmol), $Cu(OAc)_2$ (68 mg, 0.37 mmol), and *N*-methylmaleimide (**2a**; 41 mg, 0.37 mmol) were placed in a 20 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. *N*,*N*-Dimethylformamide (DMF, 0.50 mL) was sequentially injected via a syringe. The suspension was stirred for 15 min at room temperature. A solution of PivOH (10 mg, 0.093 mmol) in DMF (1.0 mL) was added to the suspension. The mixture was stirred for 4 h at 150 ºC. The resulting mixture was allowed to cool to room temperature and then quenched with water. The mixture was extracted with ethyl acetate three times. The combined organic layer was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/ethyl acetate (1/1, v/v) afforded (3a*S**,3b*S**,14b*R**,17a*R**,17b*R**)-2,16-dimethyl-3a,17b-dihydro-10*H*,15*H*-isoindolo[2,1-*a*]pyrrolo[3,4-*b*]pyrrolo[3',4':1,2]indolizino[3,4,5,6-cde]quinoxaline-1,3,10,15,17(2*H*,3b*H*,16*H*)-pentaone (**4aa**; 22 mg, 0.047 mmol, major diastereomer) in 52% yield. X-ray quality crystals were grown from acetone/heptane.

Procedure for Removal of Directing Group.

1'-Benzyl-2-(5-methoxyquinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (**3ab'**; 47 mg, 0.10 mmol) was placed in a 20 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. CH_2Cl_2 (1.0 mL) was sequentially injected via a syringe. To the suspension was added BBr_3 (0.60 mL, 1.0 M in CH_2Cl_2, 0.60 mmol) at 0 ºC. The mixture was stirred at 0 ºC for 5 min and then allowed to warm to room temperature for 18 h. The resulting mixture was quenched with water at 0 ºC and extracted with ethyl acetate three times. The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. After evaporation, the residue was dissolved in $CH_3CN/THF/H_2O$ (4/1.2/3.5, v/v, 8.7 mL total volume), and the suspension was cooled to 0 ºC. [Bis(trifluoroacetoxy)iodo]benzene ($PhI(TFA)_2$, 65 mg, 0.15 mmol) was added to the solution. The mixture was stirred for 4 h at 0 ºC. The resulting mixture was quenched with water and extracted with $CHCl_3$/*i*-PrOH (3/1, v/v) three times. The combined organic layer was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the residue was purified by GPC to afford 1'-benzylspiro(isoindoline-1,3'-pyrrolidine)-2',3,5'-trione (**3ab-H**; 16 mg, 0.052 mmol) in 53% yield.

Detailed Optimization Studies

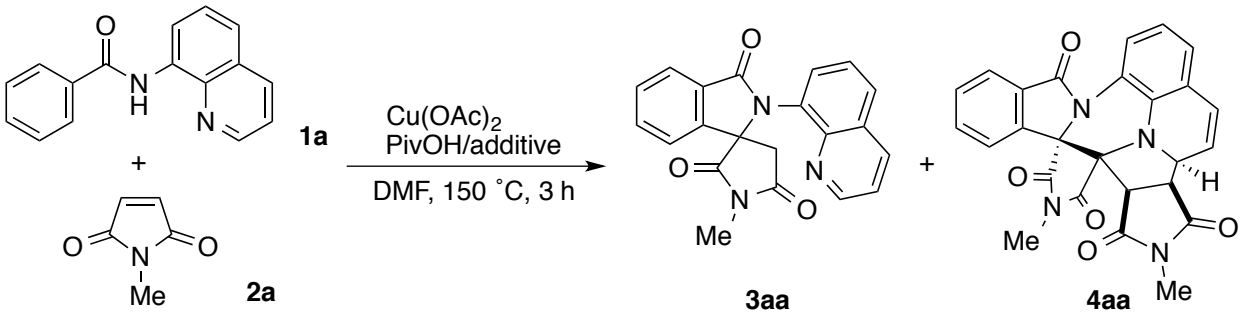
Table S1. Solvent Screening[a]



entry	solvent	NMR yield (%)	
		3aa	**4aa**
1	***DMF***	***49***	***33***
2	DMSO	14	8
3	diglyme	0	10
4	DMAc	3	5
5	NMP	0	1
6	*o*-xylene	11	22
7	CH_3CN (reflux)	0	0
8	$ClCH_2CH_2Cl$ (reflux)	0	0

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), $Cu(OAc)_2$ (0.50 mmol), PivOH (0.25 mmol), solvent (1.5 mL), N_2.

Table S2. Additive Screening[a]



entry	additive	NMR yield (%)	
		3aa	**4aa**
1	pyridine	32	trace
2	2,6-lutidine	16	1
3	Et_3N	46	5
4	Bu_3N	50	4
3	*i*-$PrNEt_2$	41	5
4	***Cy_2NMe***	***43***	***trace***
5	DABCO	28	trace
6	DBU	0	0
7	urotropine	0	0
8	Me-TBD	0	0
9	Ph_3N	32	25
10	Na_2CO_3	0	0
11[b]	***Cy_2NMe***	***78***	***trace***

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), $Cu(OAc)_2$ (0.50 mmol), PivOH (0.25 mmol), additive (1.0 mmol), DMF (1.5 mL), N_2. [b] With **2a** (1.0 mmol) and $Cu(OAc)_2$ (1.0 mmol).

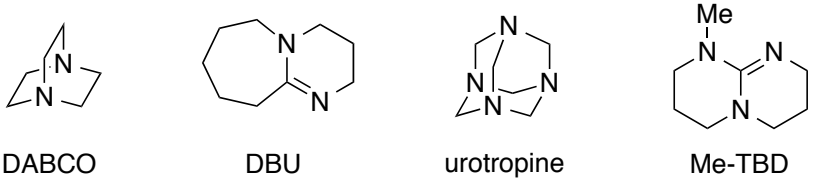
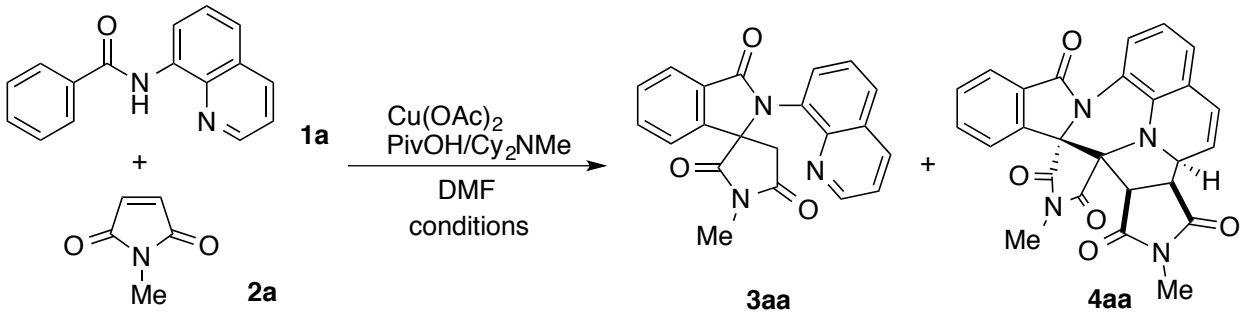


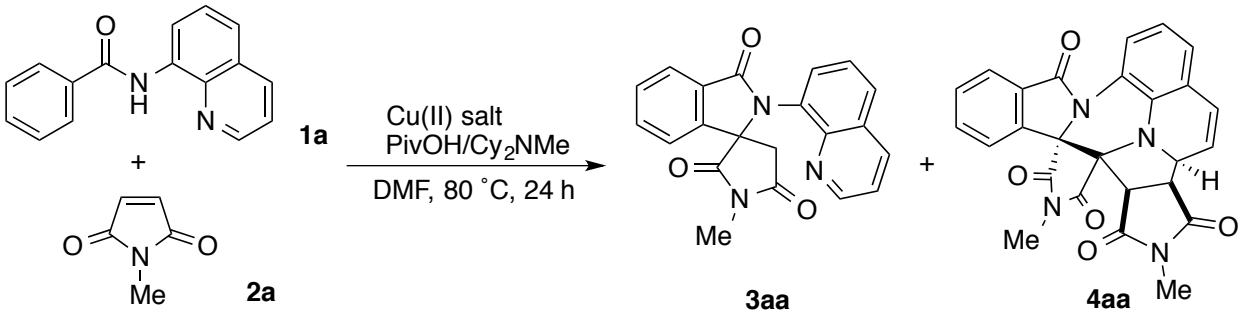
Table S3. Temperature and Time Screening[a]



entry	conditions	NMR yield (%)	
		3aa	**4aa**
1	150 ˚C, 3 h	78	trace
2	120 ˚C, 4 h	90	trace
3	100 ˚C, 4 h	88	0
4	***80 ˚C, 24 h***	***quant (89)***[b]	***0***

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (1.0 mmol), $Cu(OAc)_2$ (1.0 mmol), PivOH (0.25 mmol), Cy_2NMe (1.0 mmol), DMF (1.5 mL), N_2. [b] Isolated yield in parentheses.

Table S4. Cu(II) Salt Screening[a]

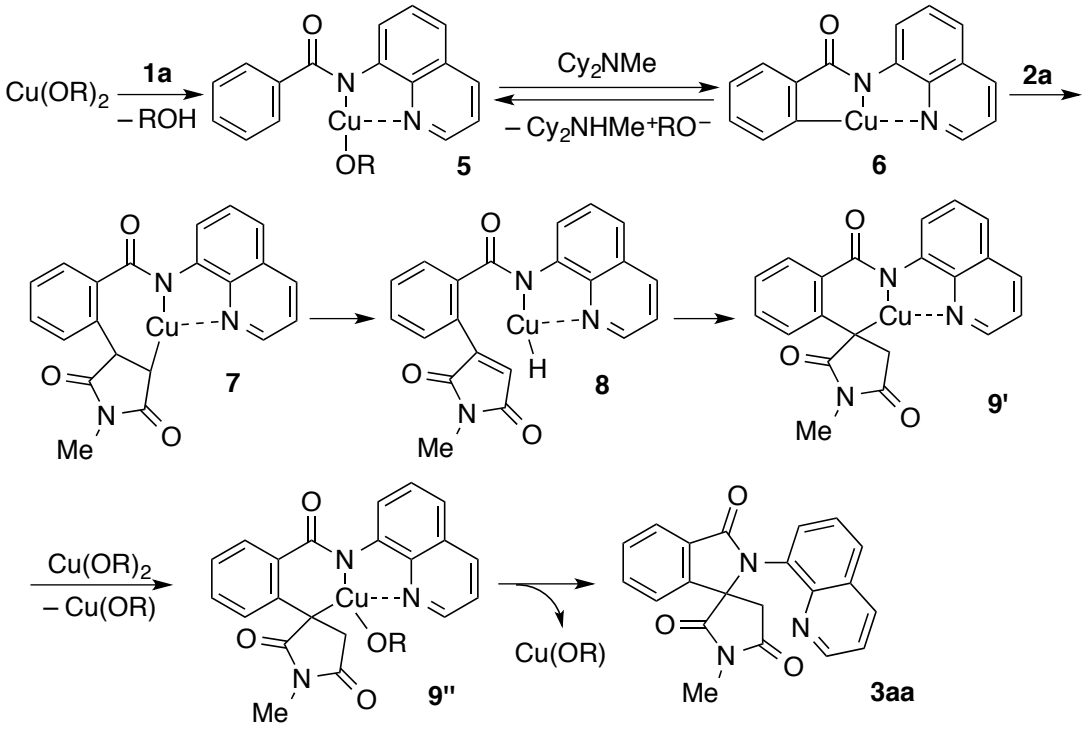


entry	Cu(II) salt	NMR yield (%)	
		3aa	**4aa**
1	***Cu(OAc)$_2$***	***quant (89)[b]***	***0***
2	Cu(eh)$_2$[c]	53	~16
3	Cu(OTf)$_2$	0	0
4	CuCl$_2$	0	0

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (1.0 mmol), Cu(II) salt (1.0 mmol), PivOH (0.25 mmol), Cy_2NMe (1.0 mmol), DMF (1.5 mL), N_2. [b] Isolated yield in parentheses. [c] eh = 2-ethylhexanoate.

Another Mechanism Involving Cu(III)

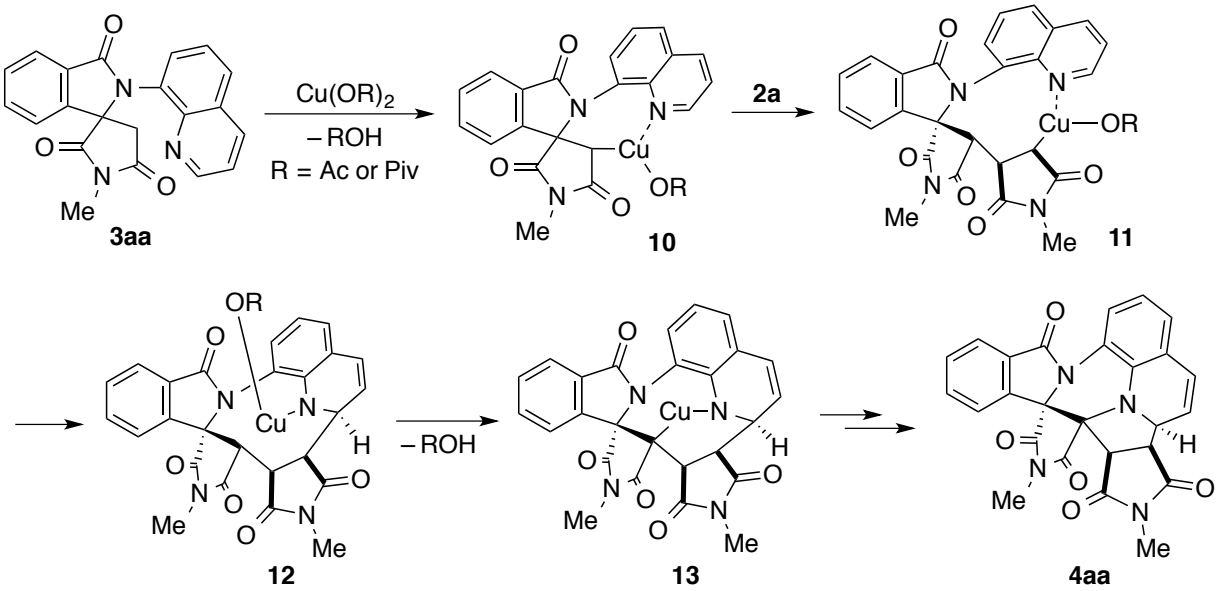
An alternative mechanism involving a Cu(III) intermediate is shown in Scheme S1. The copper hydride **8** undergoes the reinsertion to form the (alkyl)(amido)copper **9'**. Subsequent disproportionation-induced C–N forming reductive elimination occurs through a Cu(III) species **9''** to produce the final product **3aa**.



Scheme S1

Plausible Mechanism for Formation of 4aa

As shown in Scheme S2, under more harsh conditions (150 ˚C, without Cy_2NMe), the initially formed **3aa** is remetalated by $Cu(OR)_2$, and successive insertion of the second maleimide **2a** and C–N double bond of the quinoline ring affords the copper amide intermediate **12**. The formation of **4aa** then follows from the cupration at the relatively acidic, proximal proximal C–H α to the carbonyl (**12** → **13**) and reductive elimination (**13** → **4aa**).



Scheme S2

X-Ray Analysis

Crystal structure of 3aa

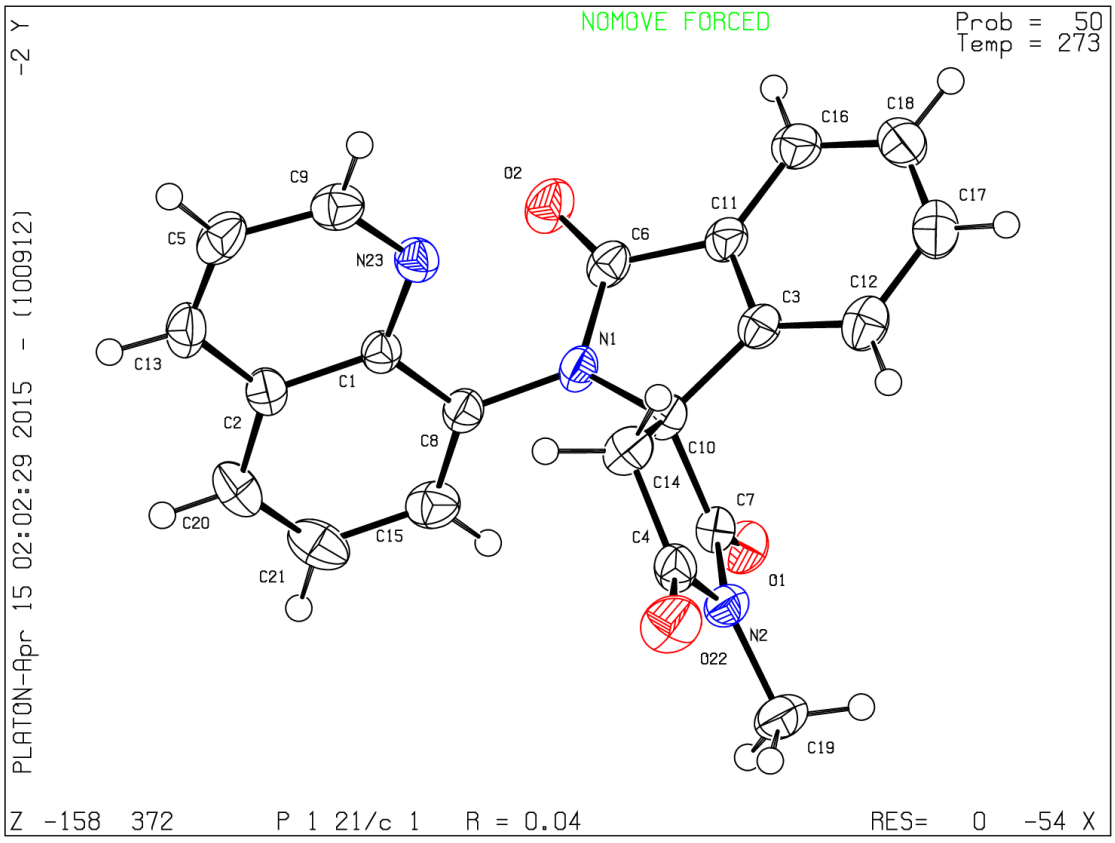


Figure S1. ORTEP Drawing of **3aa** (CCDC 1408682)

Crystal structure of 4aa

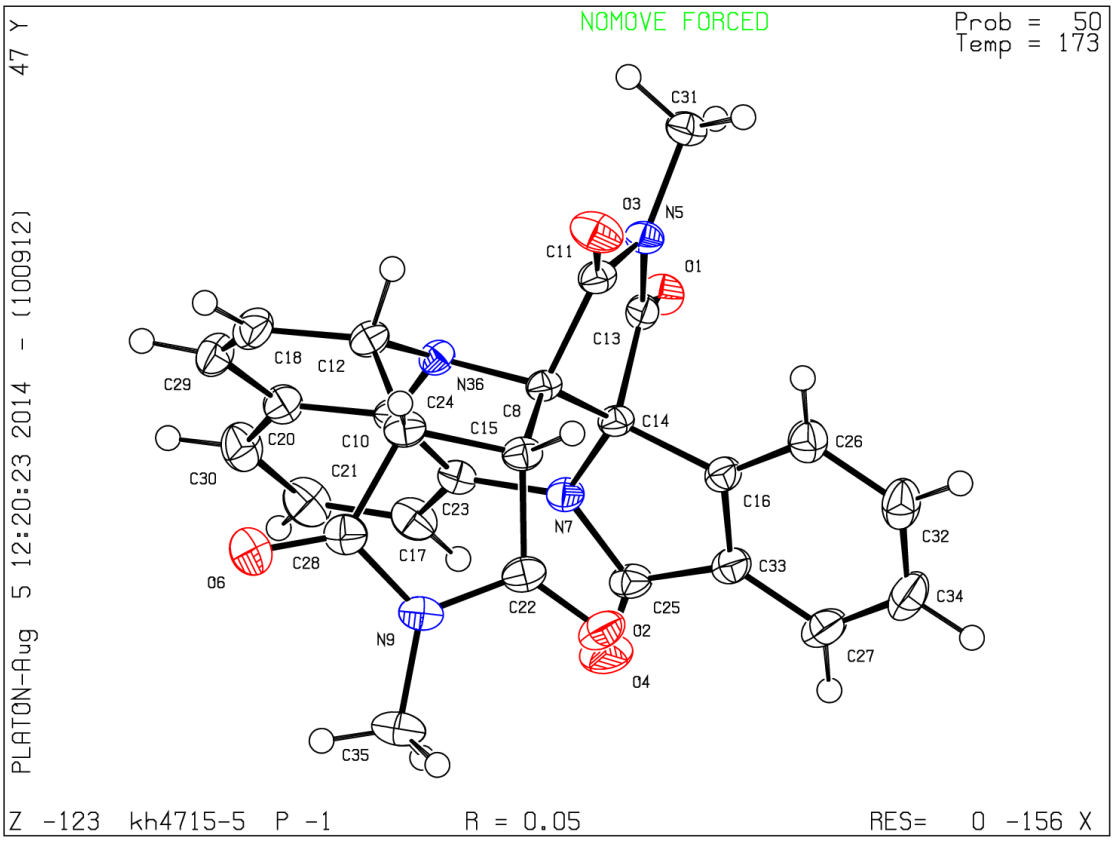


Figure S2. ORTEP Drawing of **4aa** (CCDC 1408683)

Characterization Data for Products

^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR spectra for all compounds are attached in the last part.

1'-Methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3aa). White solid. Purified by column chromatography on silica gel with CH_2Cl_2/ethyl acetate (1/1, v/v) as an eluent; 79 mg (89%). m.p. 272.3-273.3 ºC (from $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.07 (s, 3H), 3.14 (d, *J* = 18.9 Hz, 1H), 3.36 (d, *J* = 18.9 Hz, 1H), 7.34 (dd, *J* = 1.3, 7.4 Hz, 1H), 7.43 (dd, *J* = 4.2, 8.3 Hz 1H), 7.59 -7.68(m, 3H), 7.38 (dd, *J* = 1.3, 7.4 Hz, 1H), 7.91 (dd, *J* = 1.3, 8.2 Hz, 1H), 8.01 (dd, *J* = 1.3, 8.2 Hz, 1H), 8.21, (dd, *J* = 1.7, 8.3 Hz, 1H), 8.84 (dd, *J* = 1.7, 4.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 25.8, 37.7, 71.4, 120.3, 122.1, 125.2, 126.9, 129.8, 129.9, 130.0, 131.4, 131.7, 132.7, 133.2, 136.7, 144.7, 145.4, 151.2, 168.8, 174.0, 175.1. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{21}H_{16}N_3O_3$ 358.1186, found 358.1183.

1'-Benzyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ab). Brown solid. Purified by column chromatography on silica gel with CH_2Cl_2/ethyl acetate (1/1, v/v) as an eluent; 90 mg (83%). m.p. 113.0-115.0 ºC (from $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.11 (d, *J* = 19.0 Hz, 1H), 3.32 (d, *J* = 19.0 Hz, 1H), 4.67 (d, *J* = 13.9 Hz, 1H), 4.74 (d, *J* = 13.9 Hz, 1H), 7.13-7.16 (m, 1H), 7.27-7.31 (m, 5H), 7.40-7.45 (m, 2H), 7.55-7.62 (m, 2H), 7.68 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.86 (dd, *J* = 1.4, 8.3 Hz, 1H), 8.00-8.02 (m, 1H), 8.19 (dd, *J* = 1.7, 8.4 Hz, 1H), 8.75, (dd, *J* = 1.7, 4.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 37.7, 43.3, 71.1, 120.3, 122.1, 125.2, 126.8, 128.4, 128.85, 128.91, 129.7, 129.8, 130.0, 131.46, 131.49, 132.5, 133.1, 135.3, 136.7, 144.7, 145.3, 151.2, 168.8, 173.5, 174.8. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{27}H_{20}N_3O_3$ 434.1499, found 434.1500.

1'-Phenyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ac). Ivory solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (1/2, v/v) as an eluent; 75 mg (72%). m.p. 137.6-139.6 ºC (from hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30 (d, *J* = 18.9 Hz, 1H), 3.52 (d, *J* = 18.9 Hz, 1H), 7.22-7.24 (m, 2H), 7.39-7.43 (m, 1H), 7.45-7.53 (m, 4H), 7.63-7.68 (m, 2H), 7.70 (dt, *J* = 1.3, 7.5 Hz, 1H), 7.94-7.98 (m, 2H), 8.06 (d, *J* = 7.4 Hz, 1H), 8.25 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.87 (dd, *J* = 1.7, 4.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 37.9, 71.3, 120.2, 122.2, 125.4, 126.2, 127.0, 129.2, 129.5, 129.8, 129.9, 130.2, 131.5, 131.57, 131.64, 132.7, 133.3, 136.8, 144.7, 145.2, 151.2, 168.9, 172.9, 174.02. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{26}H_{18}N_3O_3$ 420.1343, found 420.1359.

6-(*tert*-Butyl)-1'-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ba). Brown solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (1/2, v/v) as an eluent; 88 mg (85%). m.p. 277.9-279.3 ºC (from hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9H), 3.08 (s, 3H), 3.16 (d, *J* = 19.0 Hz, 1H), 3.38 (d, *J* = 19.0 Hz, 1H), 7.27 (d, *J* = 1.4 Hz, 1H), 7.43 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.58 (t, *J* = 8.1 Hz, 1H), 7.65 (dd, *J* = 1.6, 8.1 Hz, 1H), 7.81 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.91 (dt, *J* = 1.3, 8.3 Hz, 2H), 8.21 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.84 (dd, *J* = 1.7, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.8, 31.5, 35.7, 37.8, 71.4, 116.7, 122.1, 124.8, 126.9, 127.7, 128.9, 129.8, 129.9, 131.6, 132.8, 136.7, 144.8, 145.5, 151.2, 157.6, 168.9, 174.3, 175.4. HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{25}H_{24}N_3O_3$ 414.1812, found 414.1824.

1'-Benzyl-6-methoxy-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3cb). Brown solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (1/2, v/v) to ethyl acetate as an eluent; 67 mg (58%). m.p. 96.2-98.2 ºC (from hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.09 (d, *J* = 19.0 Hz, 1H), 3.29 (d, *J* = 19.0 Hz, 1H), 3.71 (s, 3H), 4.68 (d, *J* = 13.9 Hz, 1H), 4.74 (d, *J* = 13.9 Hz, 1H), 6.50 (d, *J* = 2.1 Hz, 1H), 7.06 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.30 (s, 5H), 7.40-7.46 (m, 2H), 7.71 (dd, *J* = 1.2, 7.4 Hz, 1H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 8.18 (dd, *J* = 1.5, 8.3 Hz, 1H), 8.75 (dd, *J* = 1.6, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 37.8, 43.2, 55.9, 70.8, 104.6, 116.8, 122.0, 123.8, 126.6, 126.8, 128.4, 128.9 (two signals were overlapped.), 129.5, 129.6, 131.5, 132.7, 135.4, 136.7, 145.3, 146.9, 151.1, 164.0, 168.7, 173.6, 174.7. HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{28}H_{22}N_3O_4$ 464.1605, found 464.1582.

1'-Benzyl-6-chloro-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3db). Brown solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) to ethyl acetate as an eluent; 65 mg (56%). m.p.121.2-123.2 ºC (from hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.09 (d, *J* = 19.0 Hz, 1H), 3.29 (d, *J* = 19.0 Hz, 1H), 4.68 (d, *J* = 13.9 Hz, 1H), 4.74 (d, *J* = 13.9 Hz, 1H), 7.09 (d, *J* = 1.6 Hz, 1H), 7.26-7.34 (m, 5H), 7.39-7.44 (m, 2H), 7.55 (dd, *J* = 1.7, 8.1 Hz, 1H), 7.64 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.86 (dd, *J* = 1.2, 8.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 8.19 (dd, *J* = 1.6, 8.3 Hz, 1H), 8.75 (dd, *J* = 1.7, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 37.5, 43.4, 70.7, 121.0, 122.2, 126.4, 126.8, 128.5, 128.8, 129.0, 129.7, 129.91, 129.94, 130.6, 131.4, 132.1, 135.1, 136.7, 139.4, 145.1, 146.1, 151.3, 167.7, 173.0, 174.2. HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{27}H_{19}ClN_3O_3$ 468.1109, found 468.1111.

1'-Benzyl-2-(quinolin-8-yl)-6-(trifluoromethyl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3eb). White solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) to ethyl acetate as an eluent followed by GPC; 46 mg (37%). m.p. 124.6-126.6 ºC (from $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.19 (d, *J* = 19.1 Hz, 1H), 3.31 (d, *J* = 19.1 Hz, 1H), 4.70 (d, *J* = 13.9 Hz, 1H), 4.79 (d, *J* = 13.9 Hz, 1H), 7.27-7.36 (m, 6H), 7.41-7.47 (m, 2H), 7.65 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.87-7.91 (m, 2H), 8.12 (d, *J* = 7.9 Hz, 1H), 8.21 (dd, *J* = 1.7, 8.4 Hz, 1H), 8.77 (dd, *J* = 1.7, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 37.2, 43.3, 70.9, 117.6 (q, *J* = 3.6 Hz), 119.2 (q, *J* = 273.8 Hz), 122.1, 125.7, 126.7, 127.2 (q, *J* = 3.4 Hz), 128.5, 128.6, 129.0, 129.6, 130.0, 131.2, 131.8, 134.4 (q, *J* = 32.7 Hz), 134.6, 134.9, 136.6, 144.8, 144.9, 151.2, 167.1, 172.8, 173.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.42. HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{28}H_{19}F_3N_3O_3$ 502.1373, found 502.1385.

1',4-Dimethyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3fa). Brown solid. Purified by column chromatography on silica gel with CH_2Cl_2/ethyl acetate (1/1, v/v) as an eluent; 95 mg (>99%). m.p. 133.6-135.2 ºC (from CH_2Cl_2/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78 (s, 3H), 3.06 (s, 3H), 3.13 (d, *J* = 19.0 Hz, 1H), 3.38 (d, *J* = 19.0 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.43 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.83 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.91 (dd, *J* = 1.4, 8.2 Hz, 1H), 8.22 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.86 (dd, *J* = 1.7, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 17.5, 25.8, 38.1, 70.8, 117.6, 122,1, 126.9, 128.4, 129.8, 129.9, 132.0, 132.1, 132.6, 132.9, 136.8, 139.5, 145.2, 145.6, 151.3, 169.6, 174.2, 175.4. HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{22}H_{18}N_3O_3$ 372.1343, found 372.1355.

1'-Benzyl-2-(quinolin-8-yl)-4-(trifluoromethyl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3hb). Brown solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent followed by GPC; 40 mg (32%). m.p. 239.6-241.6 ºC (from $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.15 (d, *J* = 19.1 Hz, 1H), 3.46 (d, *J* = 19.1 Hz, 1H), 4.68 (d, *J* = 13.9 Hz, 1H), 4.73 (d, *J* = 13.9 Hz, 1H), 7.27-7.34 (m, 6H), 7.42-7.46 (m, 2H), 7.66-7.72 (m, 2H), 7.87-7.90 (m, 2H), 8.19 (dd, *J* = 1.6, 8.3 Hz, 1H), 8.76 (dd, *J* = 1.7, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 37.6, 43.4, 70.6, 118.4 (q, *J* = 272.3 Hz), 122.2, 124.02, 126.79, 127.52 (q, *J* = 5.6 Hz), 127.9 (q, *J* = 35.0 Hz), 128.49, 128.6 (q, *J* = 2.9 Hz), 128.9, 129.0, 129.6, 123.0, 131.8, 132.0, 132.9, 135.1, 136.7, 145.2, 146.7, 151.3, 165.2, 173.1, 174.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ -60.06. HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{28}H_{19}F_3N_3O_3$ 502.1373, found 502.1383.

1',5-Dimethyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ia). Brown solid. Purified by column chromatography on silica gel with CH_2Cl_2/ethyl acetate (1/1, v/v) as an eluent; 78 mg (84%). m.p. 243.3-245.3 ºC (from CH_2Cl_2/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 3.06 (s, 3H), 3.11 (d, *J* = 19.0 Hz, 1H), 3.32 (d, *J* = 19.0 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.43-7.48 (m, 2H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.82-7.84 (m, 2H), 7.91 (dd, *J* = 1.1, 8.2 Hz, 1H), 8.21 (dd, *J* = 1.6, 8.3 Hz, 1H), 8.84 (dd, *J* = 1.7, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.6, 25.7, 37.8, 71.2, 120.0, 122.1, 125.4, 126.9, 129.8, 129.9, 131.5, 131.6, 132.8, 134.1, 136.7, 140.4, 142.0, 145.4, 151.2, 169.0, 174.1, 175.3. HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{22}H_{18}N_3O_3$ 372.1343, found 372.1355.

5-Methoxy-1'-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ja). Brown solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (2/3, v/v) as an eluent; 62 mg (64%). m.p. 245.8-247.2 ºC (from hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (s, 3H), 3.10 (d, *J* = 18.9 Hz, 1H), 3.31 (d, *J* = 18.9 Hz, 1H), 3.91 (s, 3H), 7.18 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.50 (d, *J* = 2.2 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.81 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.92 (dd, *J* = 1.3, 8.2 Hz, 1H), 8.21 (dd, *J* = 1.7, 8.3 Hz, 1H), 8,85 (dd, *J* = 1.7, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 25.8, 37.7, 56.1, 71.0, 107.9, 121.3, 121.5, 122.1, 126.9, 129.8, 130.0, 131.6, 132.8, 133.0, 136.7, 136.8, 145.4, 151.3, 161.4, 168.9, 174.1, 175.3. HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{22}H_{18}N_3O_4$ 388.1292, found 388.1288.

1'-Methyl-2-(quinolin-8-yl)-5-(trifluoromethyl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ka). Gray solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent followed by GPC; 54 mg (50%). m.p. 129.5-131.5 ºC (from $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.09 (s, 3H), 3.16 (d, *J* = 19.0 Hz, 1H), 3.39 (d, *J* = 19.0 Hz, 1H), 7.47-7.52 (m, 2H), 7.61 (t, *J* = 7.4 Hz ,1H), 7.81 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.93-7.98 (m, 2H), 8.24 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.32 (s, 1H), 8.85 (dd, *J* = 1.7, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 26.0, 37.4, 71.4, 119.5 (q, *J* = 271.2 Hz), 121.2, 122.3, 122.6 (q, *J* = 3.8 Hz), 127.0, 129.8, 130.0 (q, *J* = 3.3 Hz), 130.3, 131.5, 132.1, 132.38 (q, *J* = 33.4 Hz), 132.44, 136.9, 145.2, 147.7, 151.4, 167.3, 173.5, 174.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.49. HRMS (APCI) m/z ([M+H]$^+$) calcd for $C_{22}H_{15}F_3N_3O_3$ 426.1060, found 426.1063.

1'-Benzyl-5-chloro-2-(quinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3lb). White solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (1/2, v/v) as an eluent followed by GPC; 66 mg (57%). m.p. 132.3-134.3 ºC (from $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 3.08 (d, *J* = 19.0 Hz, 1H), 3.29 (d, *J* = 19.0 Hz, 1H), 4.66 (d, *J* = 13.9 Hz, 1H), 4.73 (d, *J* = 13.9 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 7.27-7.34 (m, 5H), 7.39-7.45 (m, 2H), 7.52 (dd, *J* = 2.0, 8.2 Hz, 1H), 7.64 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.86 (dd, *J* = 1.3, 8.3 Hz, 1H), 7.98 (d, *J* = 2.0 Hz, 1H), 8.19 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.76 (dd, *J* = 1.7, 4.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 37.5, 43.4, 70.8, 121.6, 122.2, 125.4, 126.8, 127.6, 128.5, 128.7, 128.9, 129.0, 129.7, 123.0, 131.4, 132.1, 133.2, 133.3, 135.2, 136.5, 136.7, 142.7, 145.1, 151.3, 167.4, 173.1, 174.3. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{27}H_{19}ClN_3O_3$ 468.1109, found 468.1119.

1'-Methyl-2-(quinolin-8-yl)spiro[benzo[*e*]isoindole-3,3'-pyrrolidine]-1,2',5'(2*H*)-trione (3ma). Light-yellow solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (1/2, v/v) as an eluent; 87 mg (85%). m.p. 233.9-235.9 ºC (from hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 3.11 (s, 3H), 3.23 (d, *J* = 19.0 Hz, 1H), 3.46 (d, *J* = 19.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.63 (t, *J* = 7.9 Hz, 2H), 7.70-7.75 (m, 1H), 7.89 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.95-7.99 (m, 2H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.24 (dd, *J* = 1.6, 8.3 Hz, 1H), 8.85 (dd, *J* = 1.7, 4.2 Hz, 1H), 9.25 (d, *J* = 7.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 25.9, 37.3, 71.1, 116.8, 122.1, 124.6, 125.8, 127.0, 127.6, 128.4, 129.0, 129.7, 129.8, 129.9, 131.9, 132.9, 134.0, 134.5, 136.8, 144.4, 145.6, 151.3, 169.9, 174.2, 175.1. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{25}H_{18}N_3O_3$. 408.1343, found 408.1349.

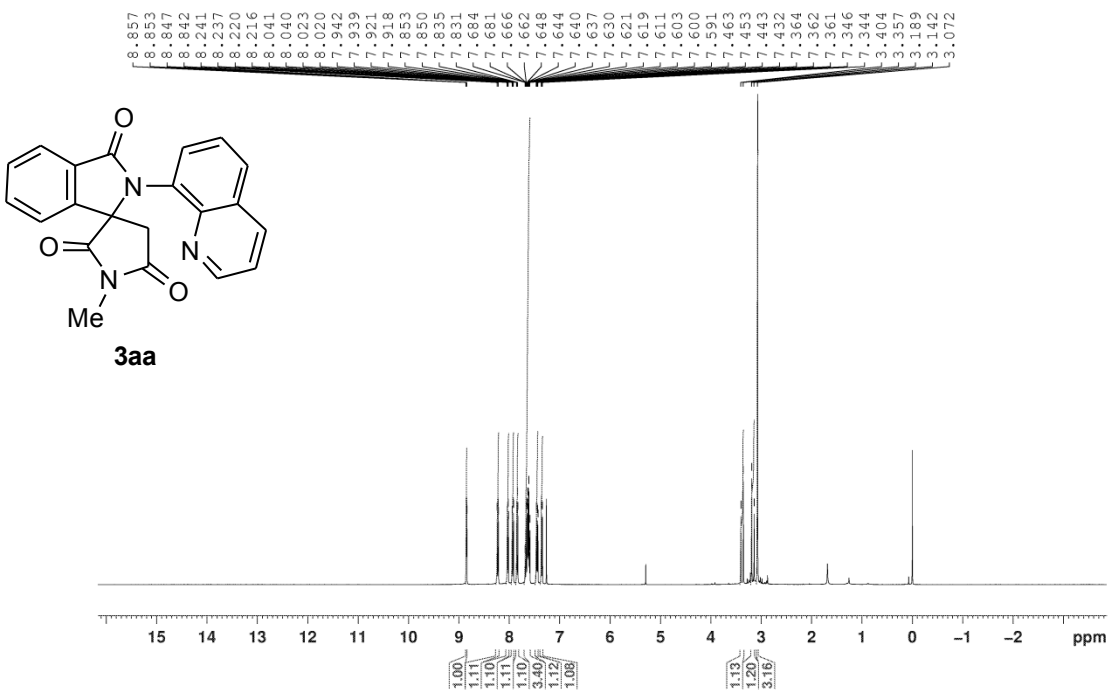
1'-Methyl-2-(quinolin-8-yl)spiro[benzo[*f*]isoindole-1,3'-pyrrolidine]-2',3,5'(2*H*)-trione (3na). White solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (1/2, v/v) as an eluent; 89 mg (88%). m.p. 166.0-168.0 ºC (from hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 3.13 (s, 3H), 3.24 (d, *J* = 19.0 Hz, 1H), 3.39 (d, *J* = 19.0 Hz, 1H), 7.45 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.60-7.67 (m, 3H), 7.79 (s, 1H), 7.88 (dd, *J* = 1.1, 7.4 Hz, 1H), 7.92-7.97 (m, 2H), 8.08 (d, *J* = 7.5 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 8.57 (s, 1H), 8.85 (d, *J* = 2.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 25.8, 38.7, 71.3, 119.6, 122.2, 125.9, 127.0, 127.5, 128.4, 128.5, 128.6, 129.8, 129.98, 130.04, 131.7, 132.8, 133.9, 135.7, 136.8, 140.2, 145.4, 151.3, 168.7, 174.2, 175.5. HRMS (APCI) m/z ($[M+H]^+$) calcd for: $C_{25}H_{18}N_3O_3$ 408.1343, found 408.1347.

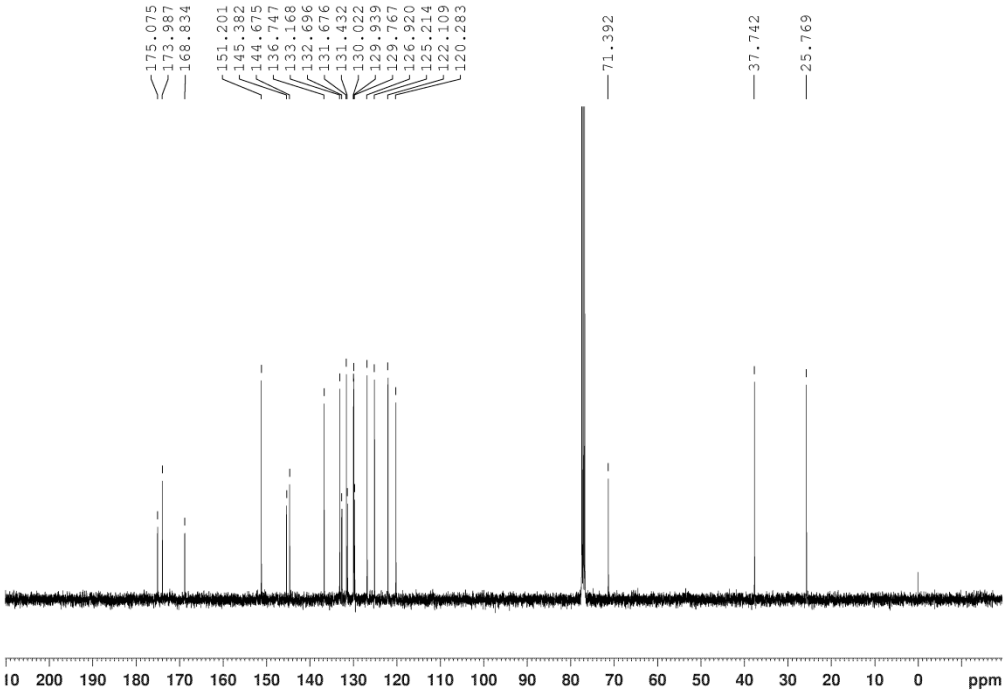
1'-Benzyl-2-(5-methoxyquinolin-8-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (3ab'). Reddish brown solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (1/2, v/v) to ethyl acetate as an eluent; 82 mg (71%). m.p. 95.9-97.9 ºC (from hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.12 (d, *J* = 19.0 Hz, 1H), 3.43 (d, *J* = 19.0 Hz, 1H), 4.01 (s, 3H), 4.65 (d, *J* = 14.0 Hz, 1H), 4.72 (d, *J* = 14.0 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 7.13-7.15 (m, 1H), 7.24 (d, *J* = 3.1 Hz, 1H), 7.27-7.31 (m, 4H), 7.38 (dd, *J* = 4.2, 8.5 Hz, 1H), 7.56-7.59 (m, 3H), 7.99-8.01 (m, 1H), 8.58 (dd, *J* = 1.8, 8.5 Hz, 1H), 8.79 (dd, *J* = 1.8, 4.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.8, 43.2, 56.1, 71.1, 104.3, 120.4, 121.1, 121.9, 124.4, 125.1, 128.3, 128.8, 128.9, 129.9, 131.6, 131.7, 132.1, 133.0, 135.3, 144.5, 146.0, 151.5, 156.3, 168.9, 173.7, 174.9. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{28}H_{22}N_3O_4$ 464.1605, found 464.1621.

1'-Benzylspiro(isoindoline-1,3'-pyrrolidine)-2',3,5'-trione (3ab-H). Brown solid. Purified by GPC; 16 mg (53%). m.p. 182.9-184.9 ºC (from $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, at -40 ºC): δ 3.19 (d, *J* = 18.3 Hz, 1H), 3.32 (d, *J* = 18.3 Hz, 1H), 4.76-4.84 (m, 2H), 7.05 (s, 1H), 7.34-7.44 (m, 5H), 7.55-7.60 (m, 2H), 7.83 (s, 1H), 8.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.2, 43.5, 64.5, 120.3, 124.7, 128.5, 128.8, 128.99, 129.03, 130.1, 133.4, 135.3, 145.5, 170.8 (broad), 172.9, 174.5. HRMS (APCI) m/z ($[M+H]^+$) called for $C_{18}H_{15}N_2O_3$ 307.1077, found 307.1067.

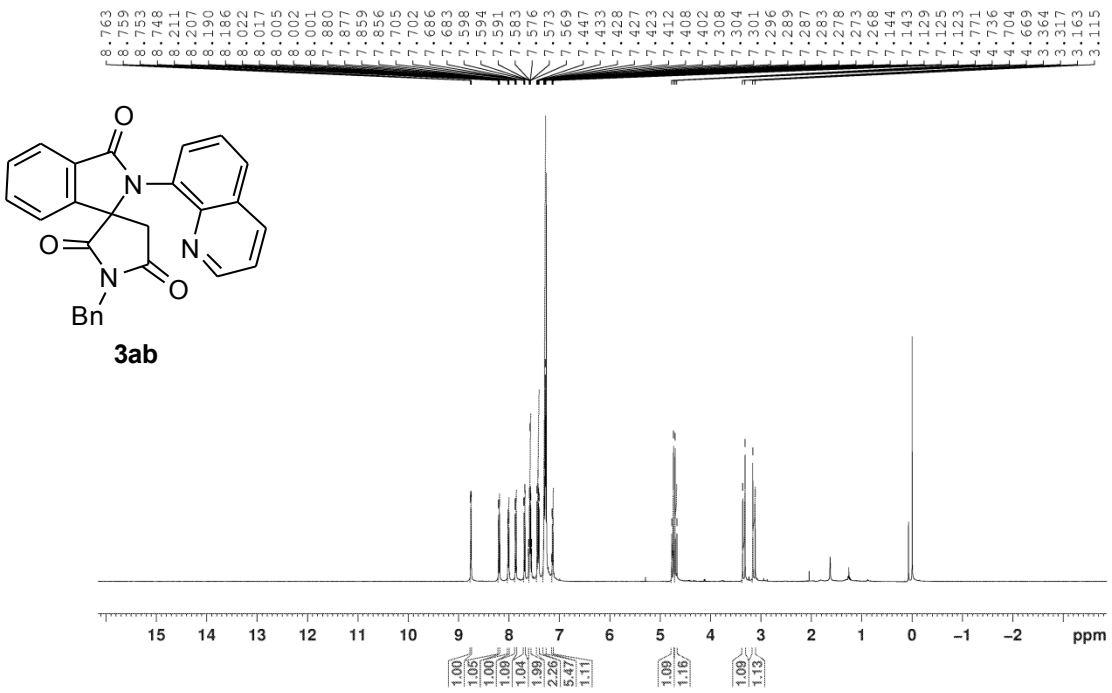
(3a*S,3b*S**,14b*R**,17a*R**,17b*R**)-2,16-Dimethyl-3a,17b-dihydro-10*H*,15*H*-isoindolo[2,1-*a*]pyrrolo[3,4-*b*]pyrrolo[3',4':1,2]indolizino[3,4,5,6-cde]quinoxaline-1,3,10,15,17(2*H*,3b*H*,16*H*)-pentaone (4aa)**. Brown solid. Purified by column chromatography on silica gel with hexane/ethyl acetate (1/1, v/v) as an eluent; 22 mg (52%). m.p. 271.2-273.2 ºC (from hexane/ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.19 (s, 3H), 3.70 (t, *J* = 7.4 Hz, 1H), 3.76 (d, *J* = 7.4 Hz, 1H), 4.80-4.84 (m, 1H), 5.93 (dd, *J* = 5.0, 10.0 Hz, 1H), 6.49 (dd, *J* = 1.3, 10.0 Hz, 1H), 6.74 (dd, *J* = 1.2, 7.5 Hz, 1H), 6.82 (dd, *J* = 7.5, 8.2 Hz, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.64-7.72 (m, 2H), 8.09 (dt, *J* = 0.6, 1.8, 6.8 Hz, 1H), 8.37 (dd, *J* = 1.2, 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 26.3, 43.8, 52.8, 58.3, 68.9, 69.5, 119.3, 119.4, 120.0, 120.9, 121.1, 121.4, 123.8, 125.5, 126.2, 126.6, 130.9, 132.6, 133.1, 138.5, 167.1, 171.6, 172.0, 172.3, 174.2. HRMS (APCI) m/z ($[M+H]^+$) called for $C_{26}H_{19}N_4O_5$ 467.1350, found 467.1370.

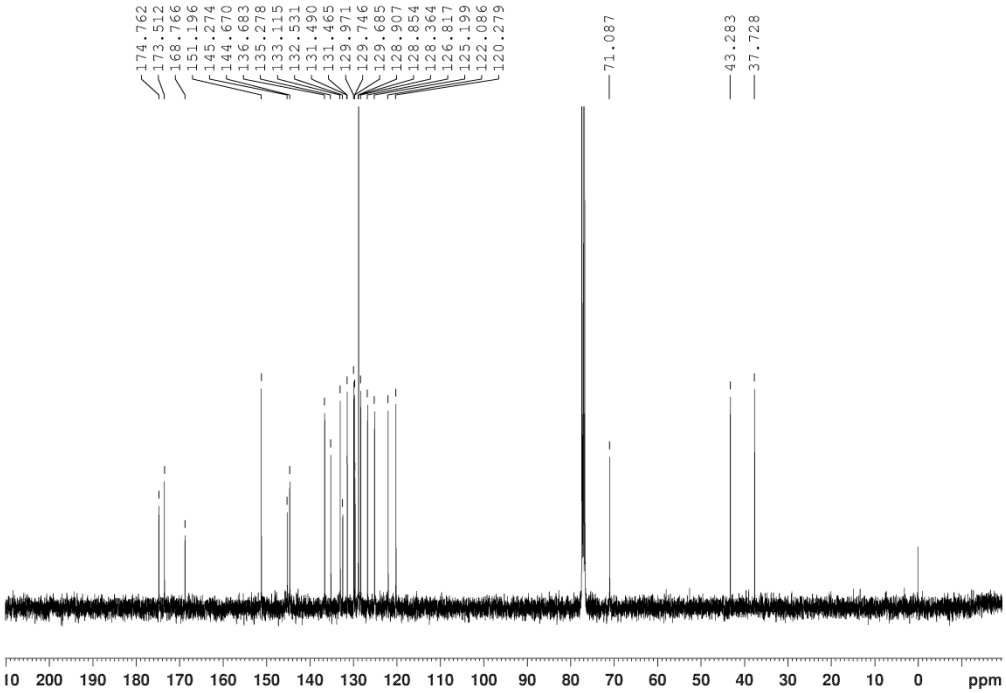
[^{1}H and ^{13}C NMR Spectra of **3aa**]



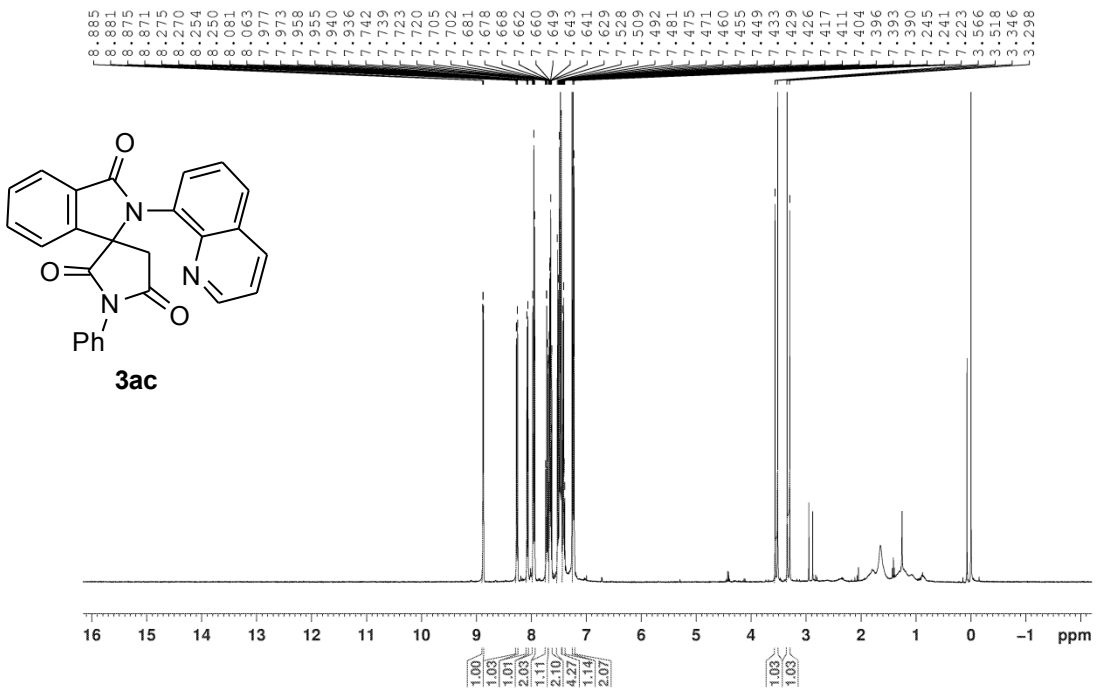


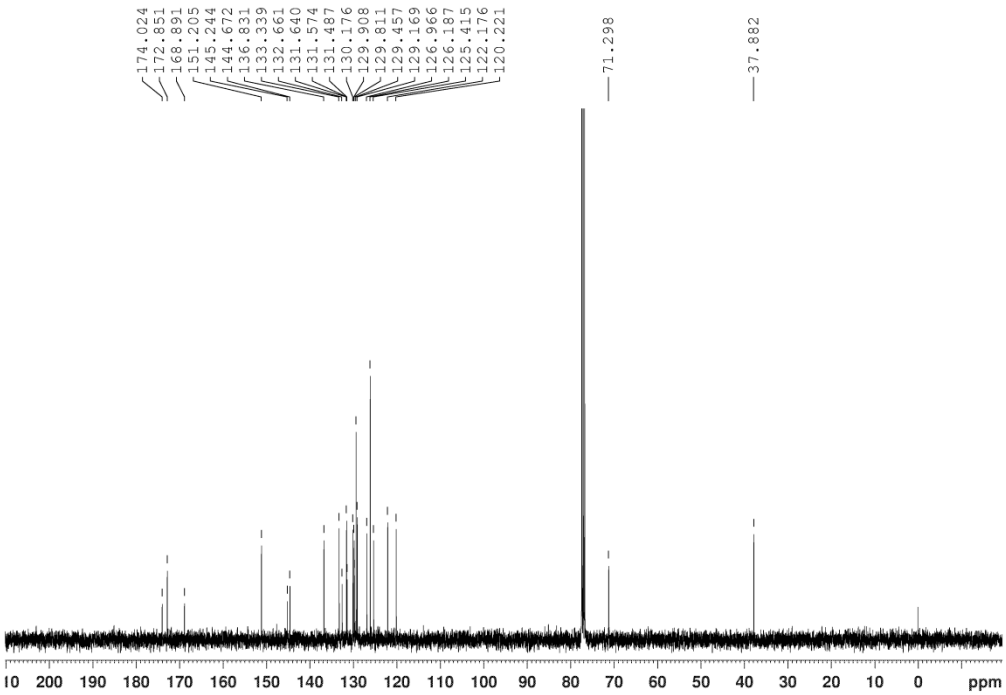
[^{1}H and ^{13}C NMR Spectra of **3ab**]



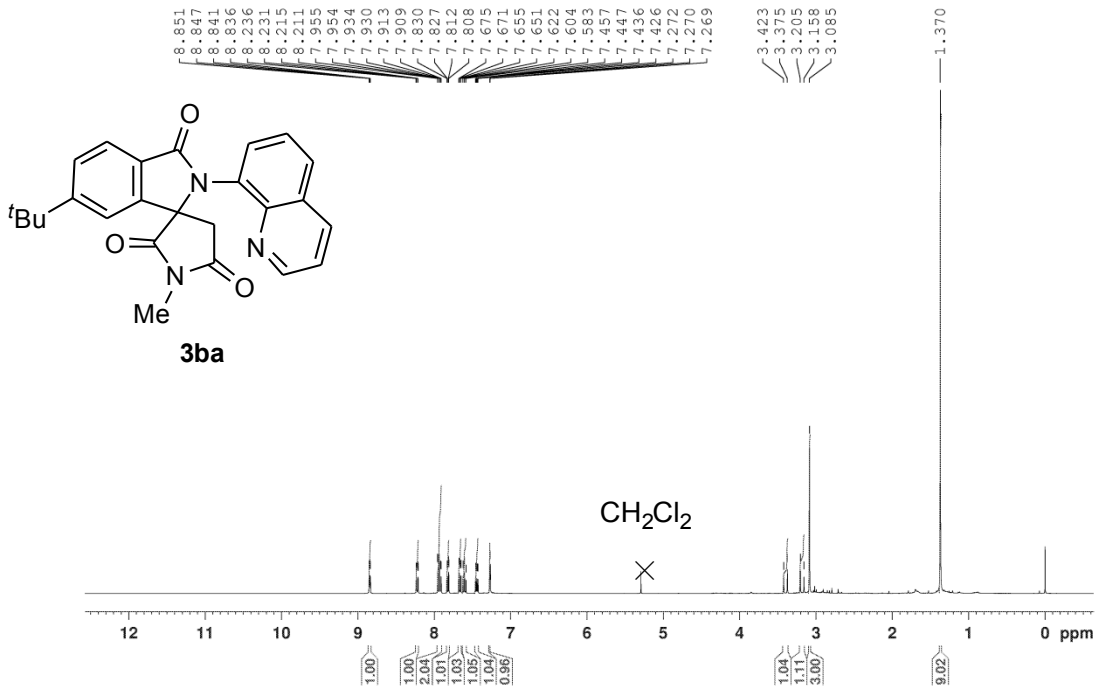


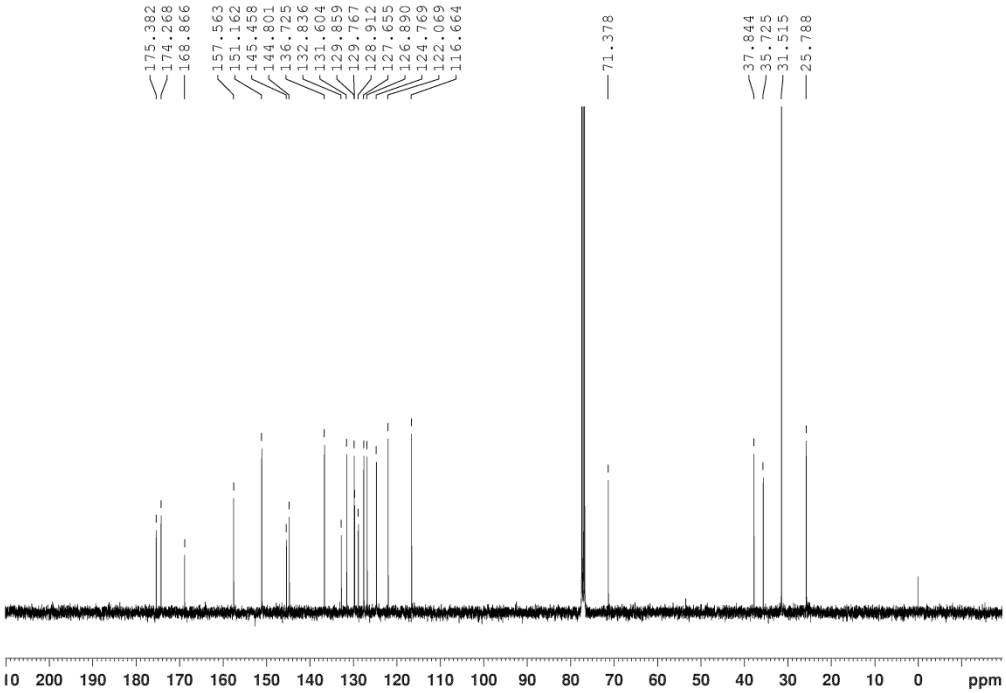
[^{1}H and ^{13}C NMR Spectra of **3ac**]



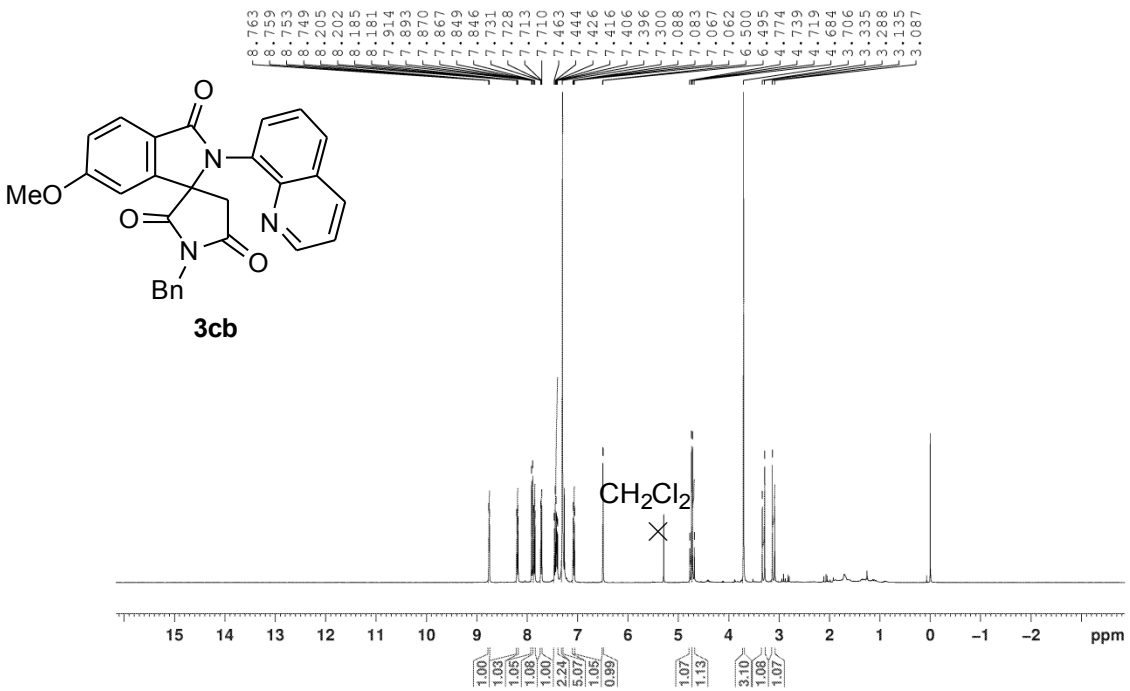


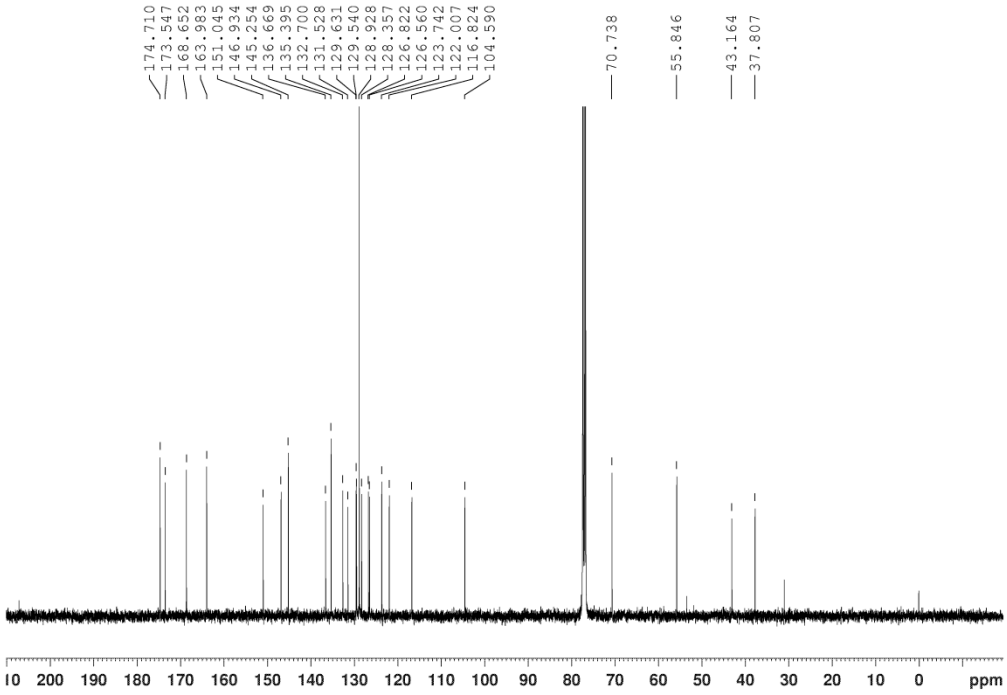
[^{1}H and ^{13}C Spectra of **3ba**]



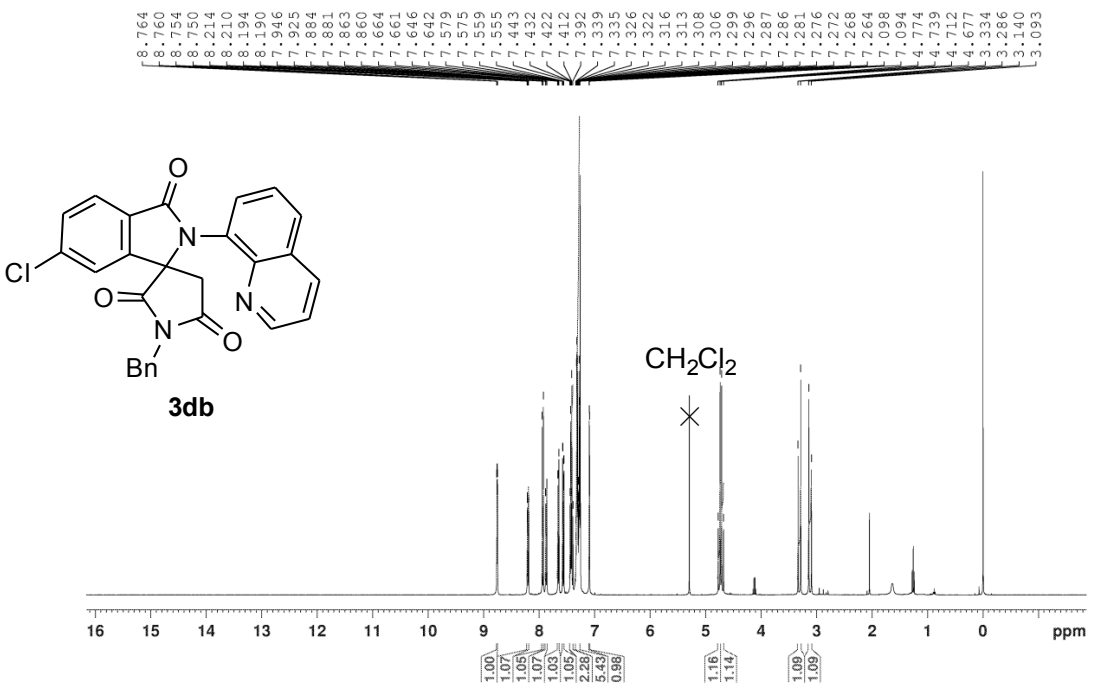


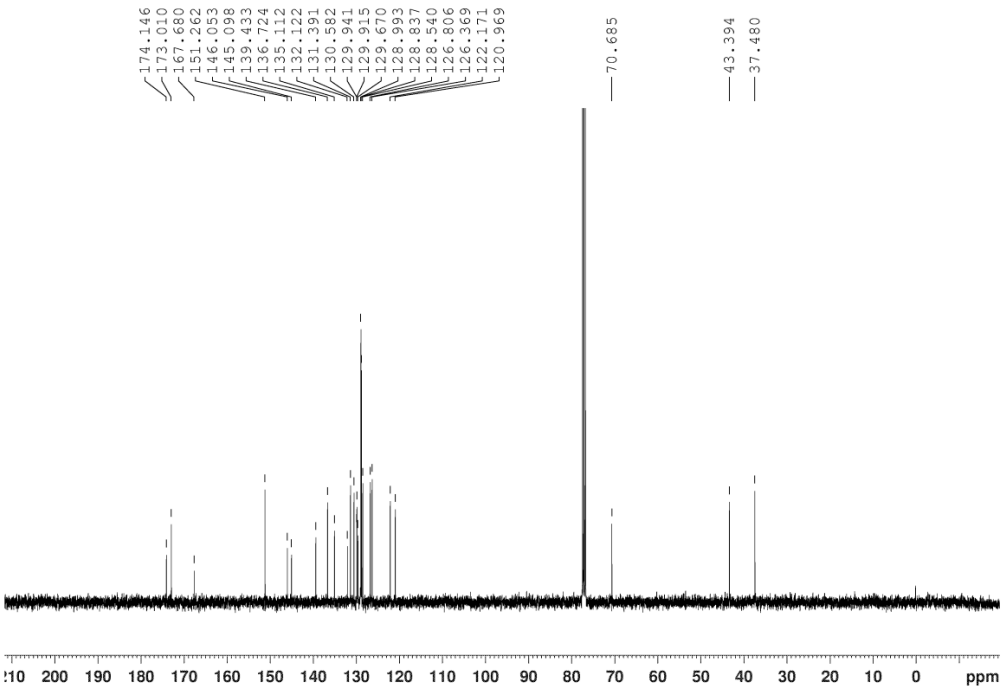
[^{1}H and ^{13}C NMR Spectra of **3cb**]



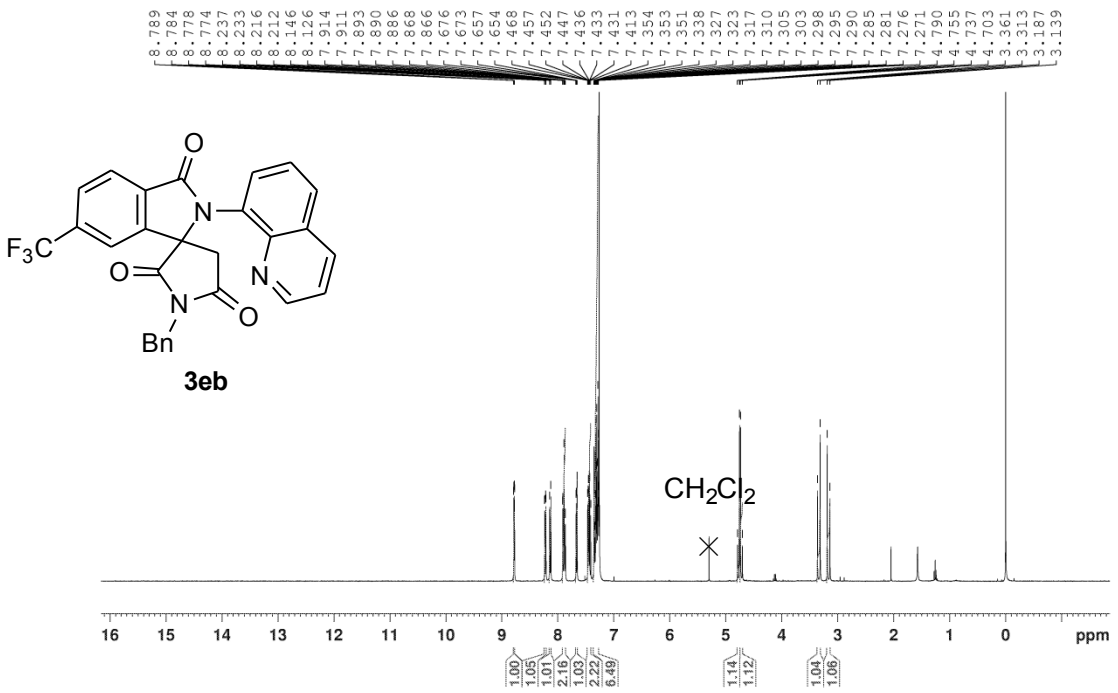


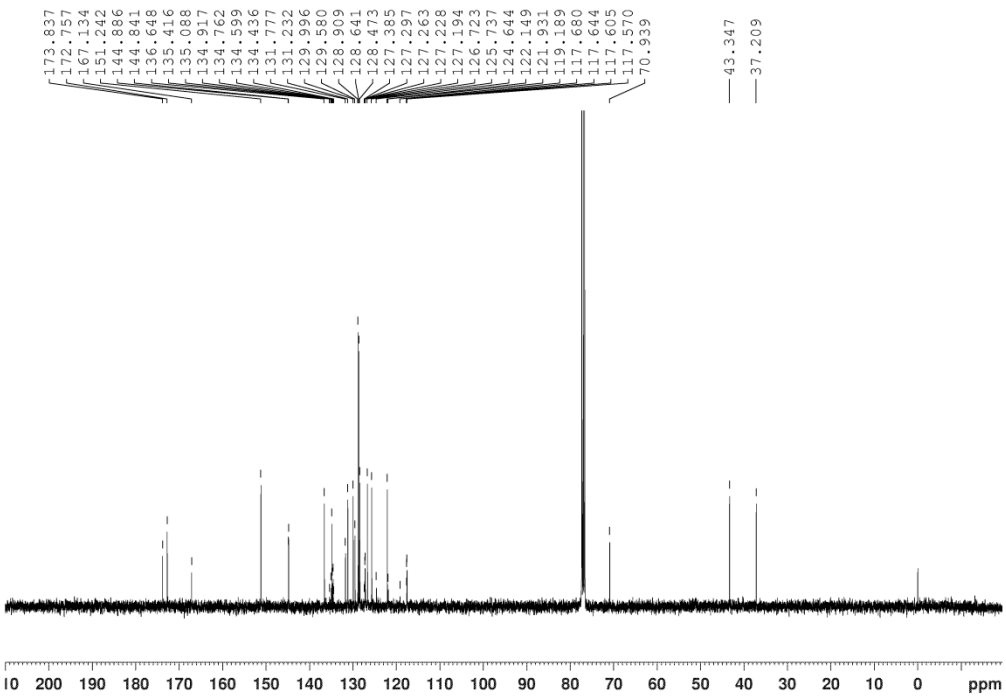
[^{1}H and ^{13}C NMR Spectra of **3db**]

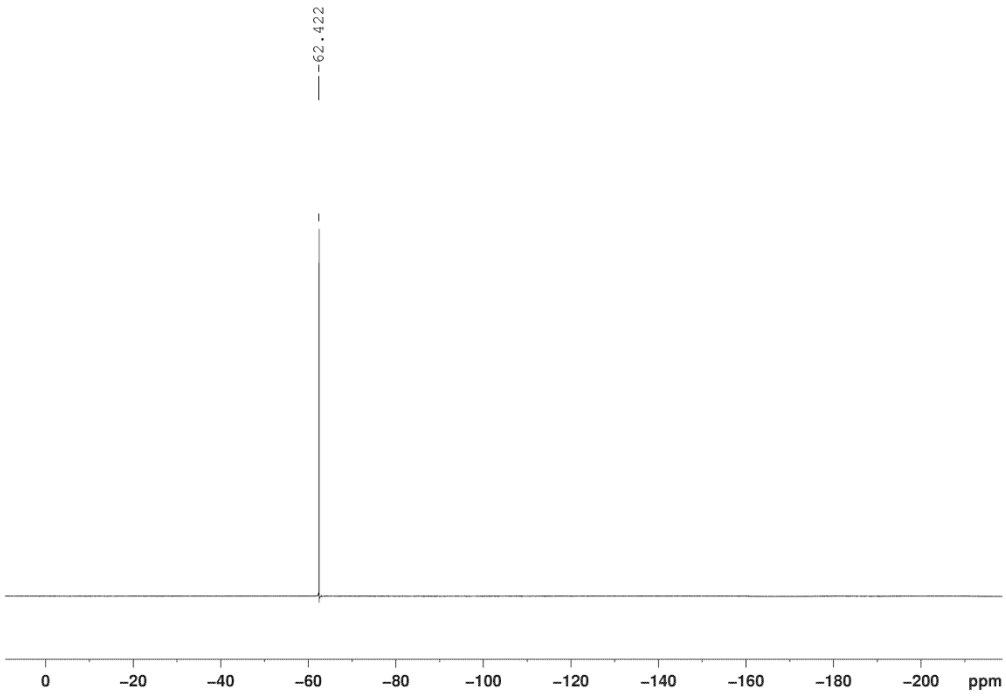




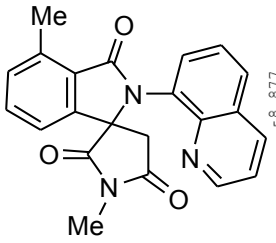
[^{1}H, ^{13}C, and ^{19}F NMR Spectra of **3eb**]



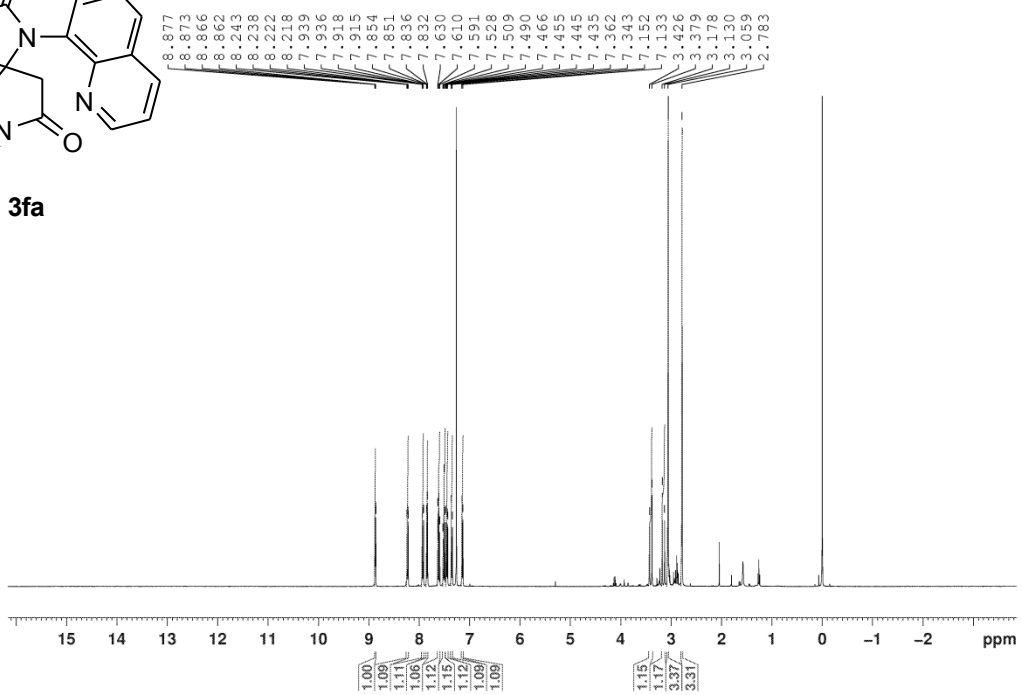


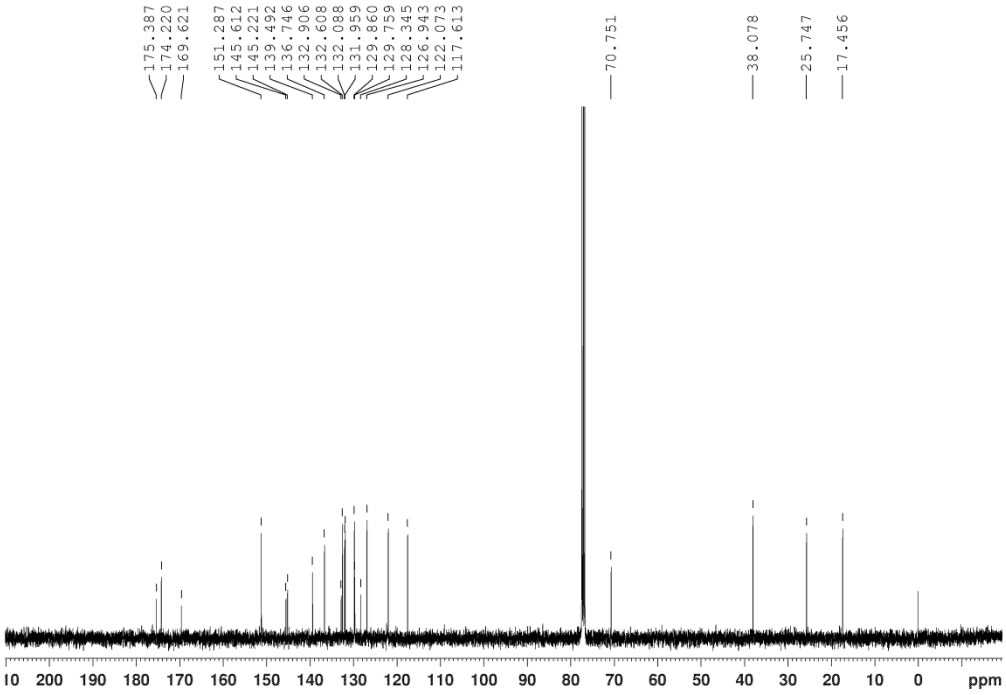

-62.422
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

[^{1}H and ^{13}C and NMR Spectra of **3fa**]

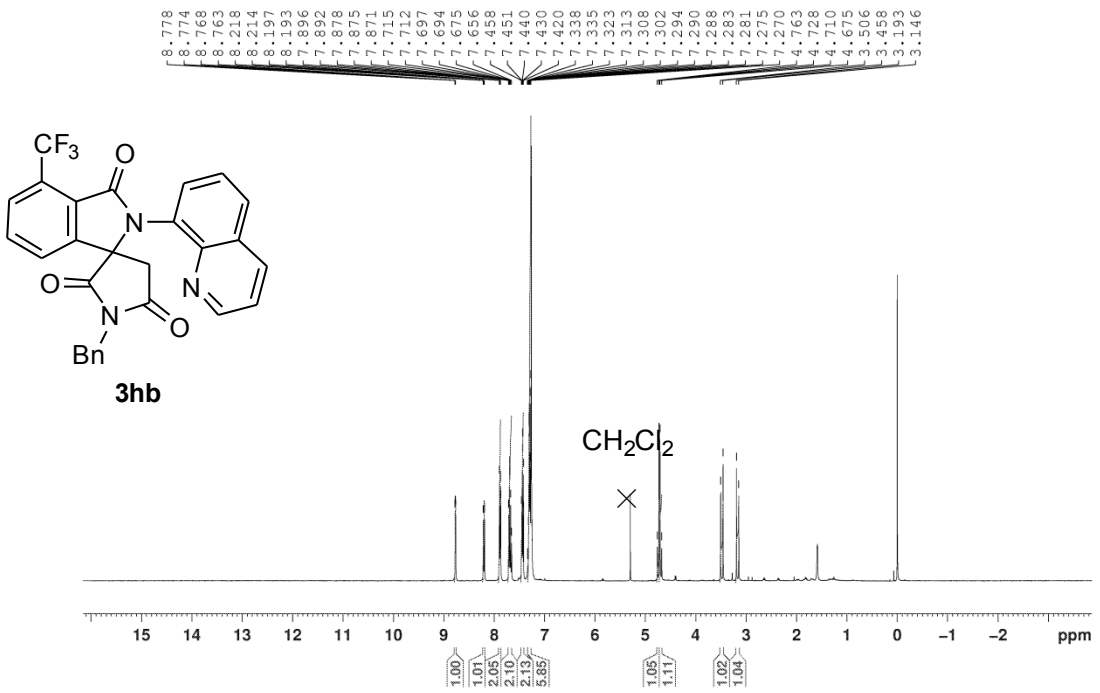


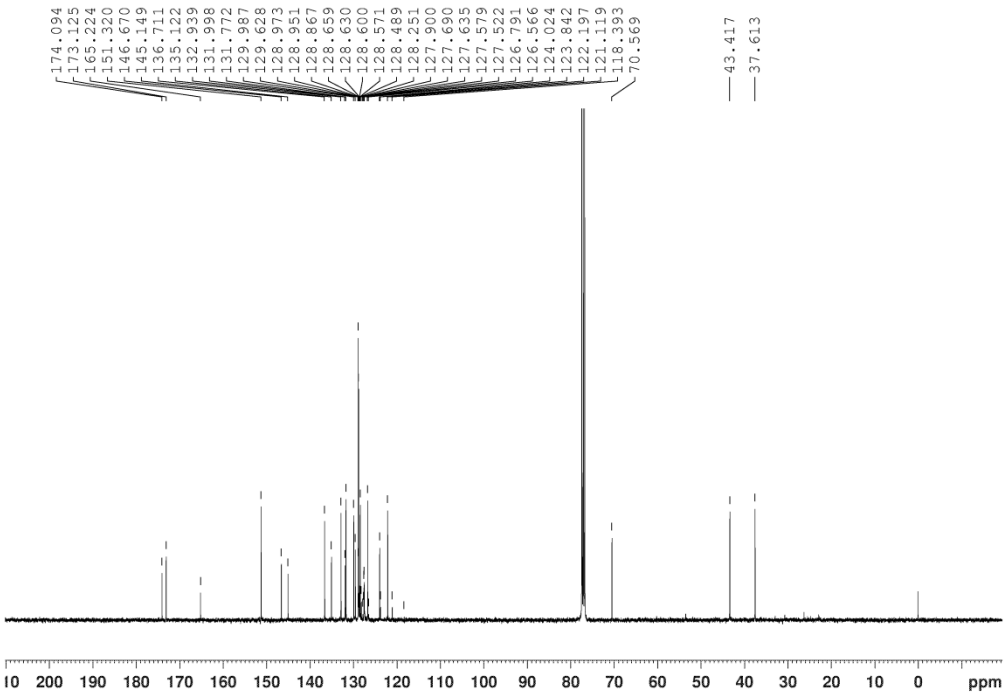
3fa

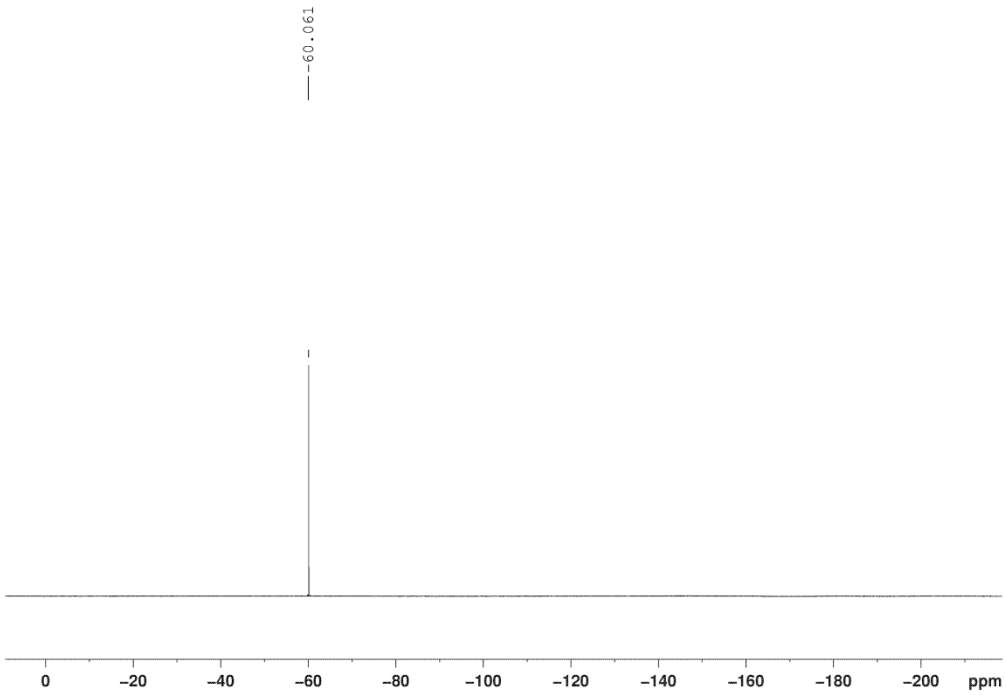




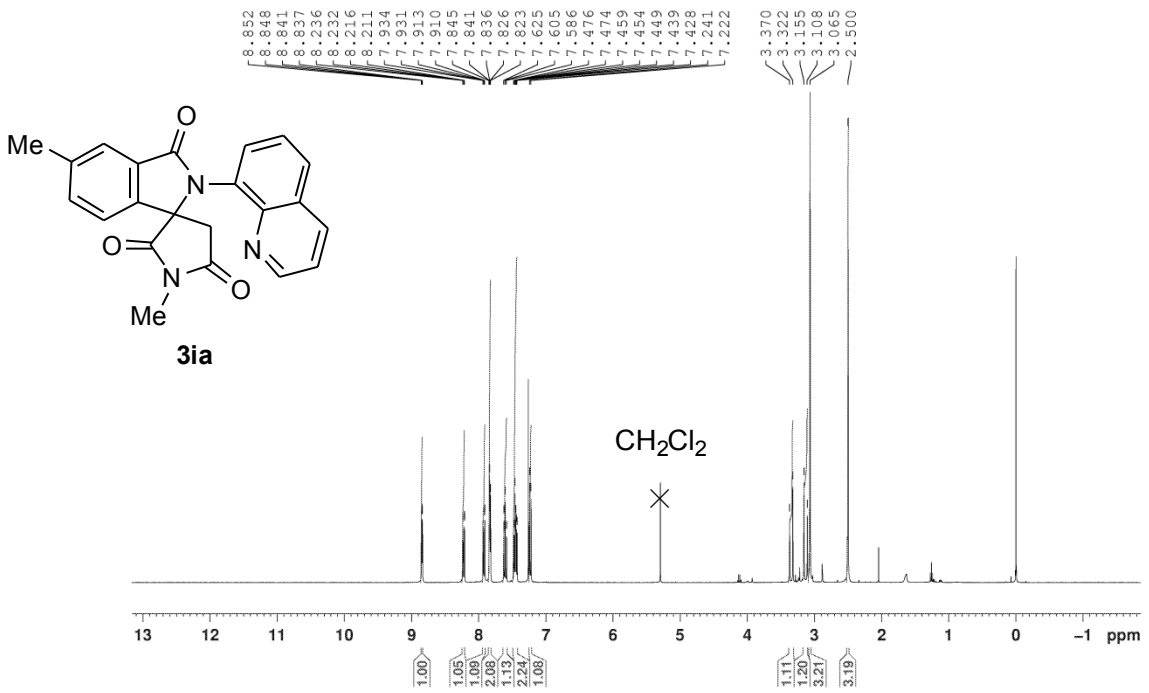
[^{1}H, ^{13}C, and ^{19}F NMR Spectra of **3hb**]

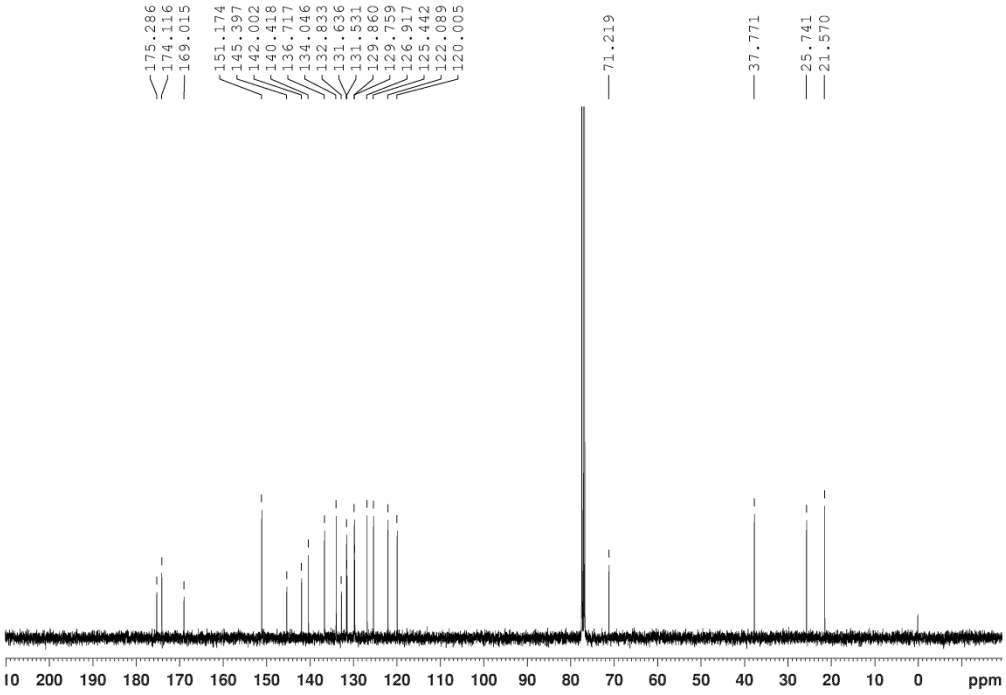




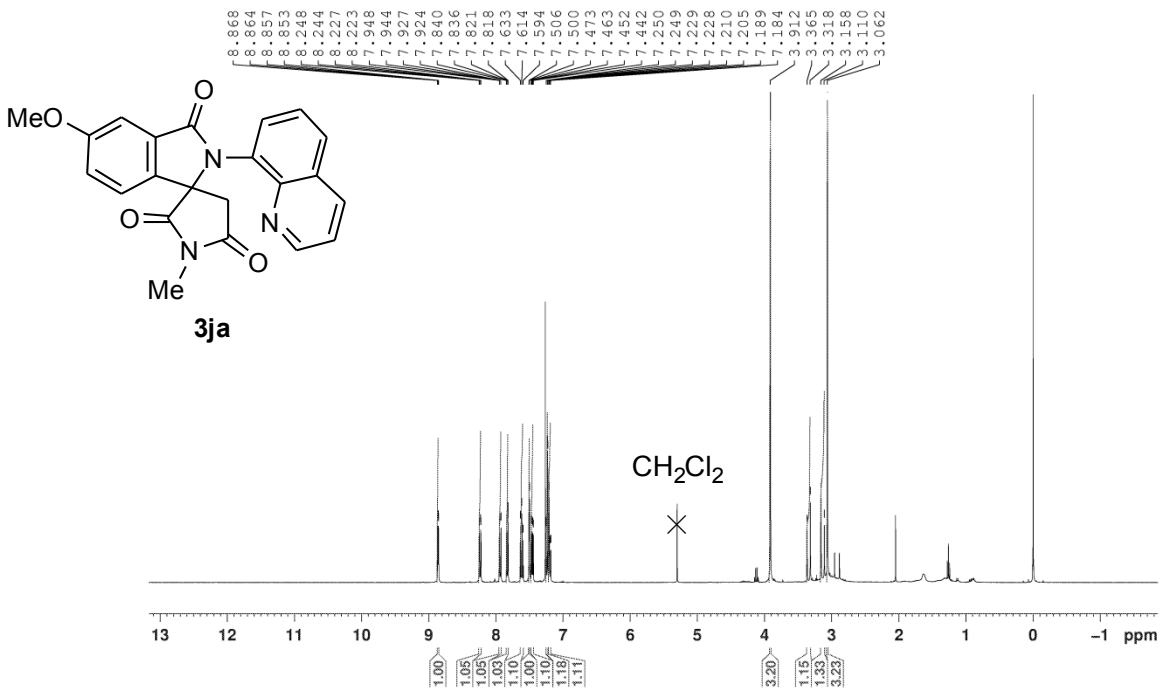

-60.061
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

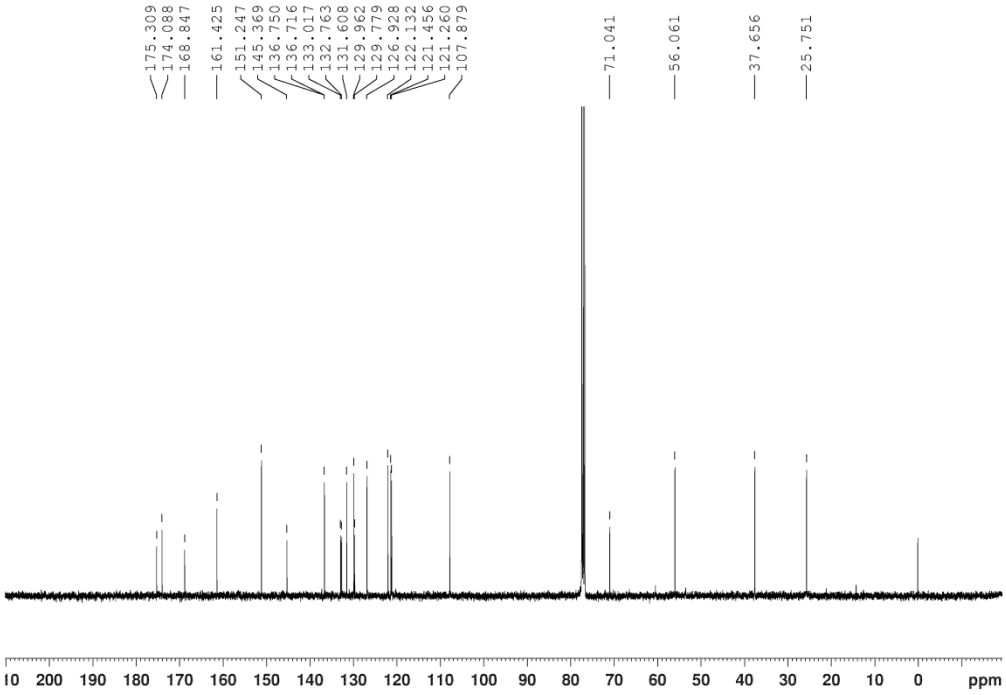
[^{1}H and ^{13}C NMR Spectra of **3ia**]



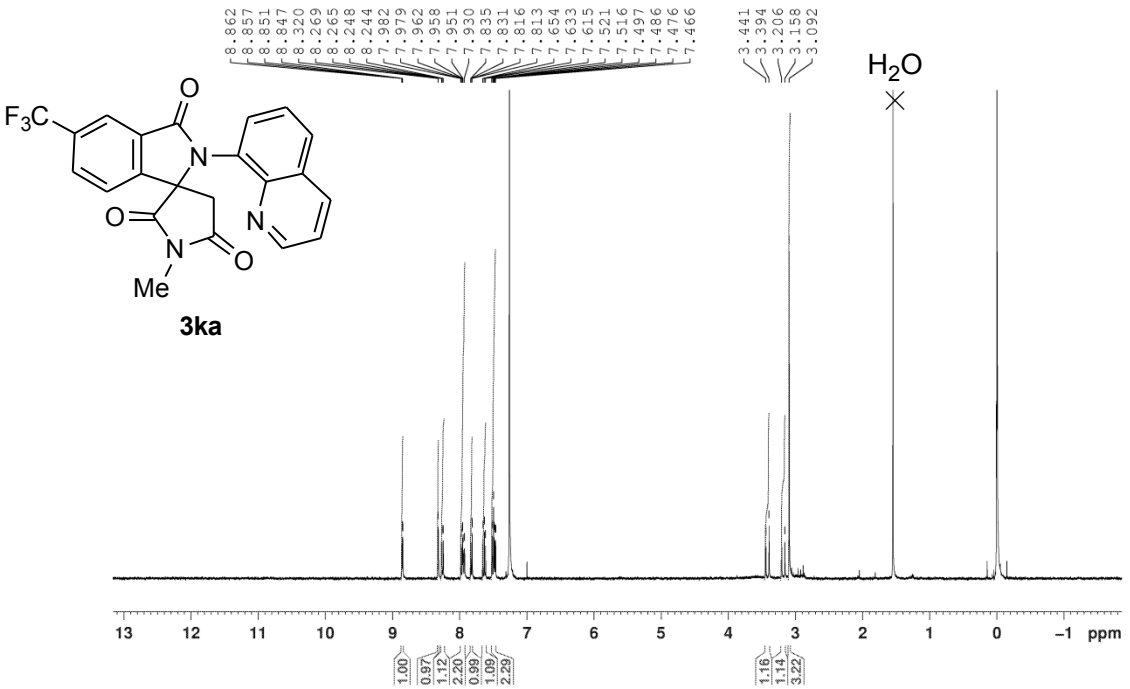


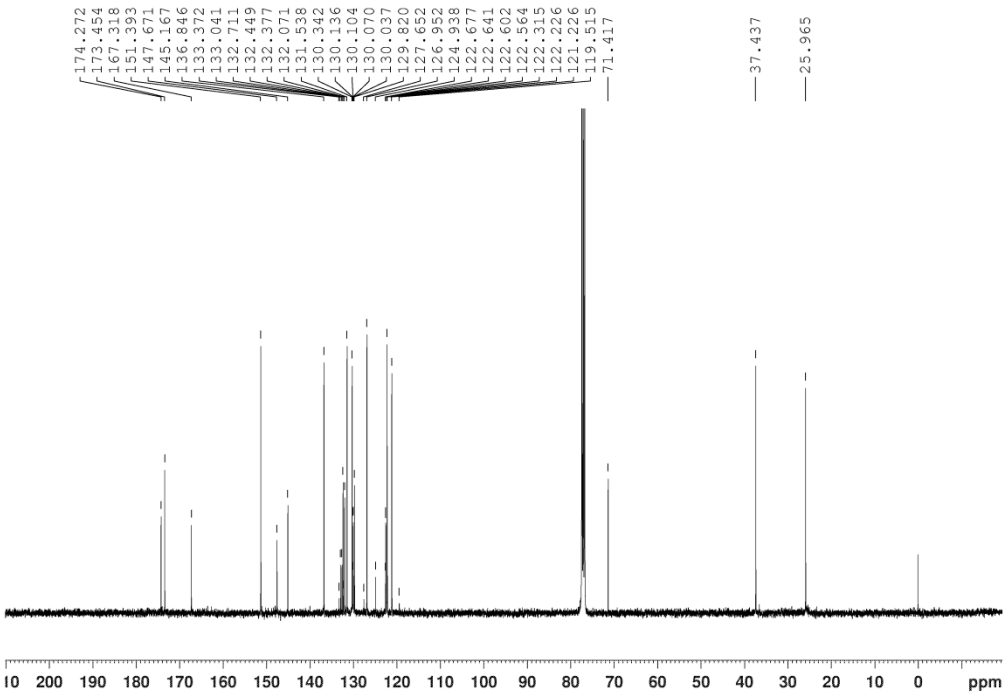
[^{1}H and ^{13}C NMR Spectra of **3ja**]

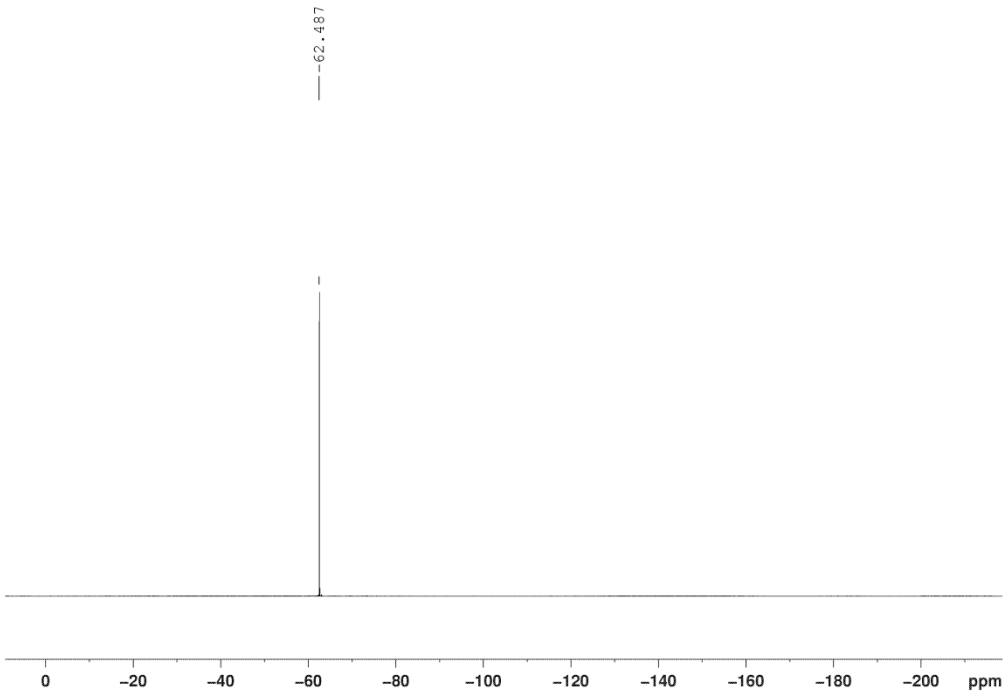




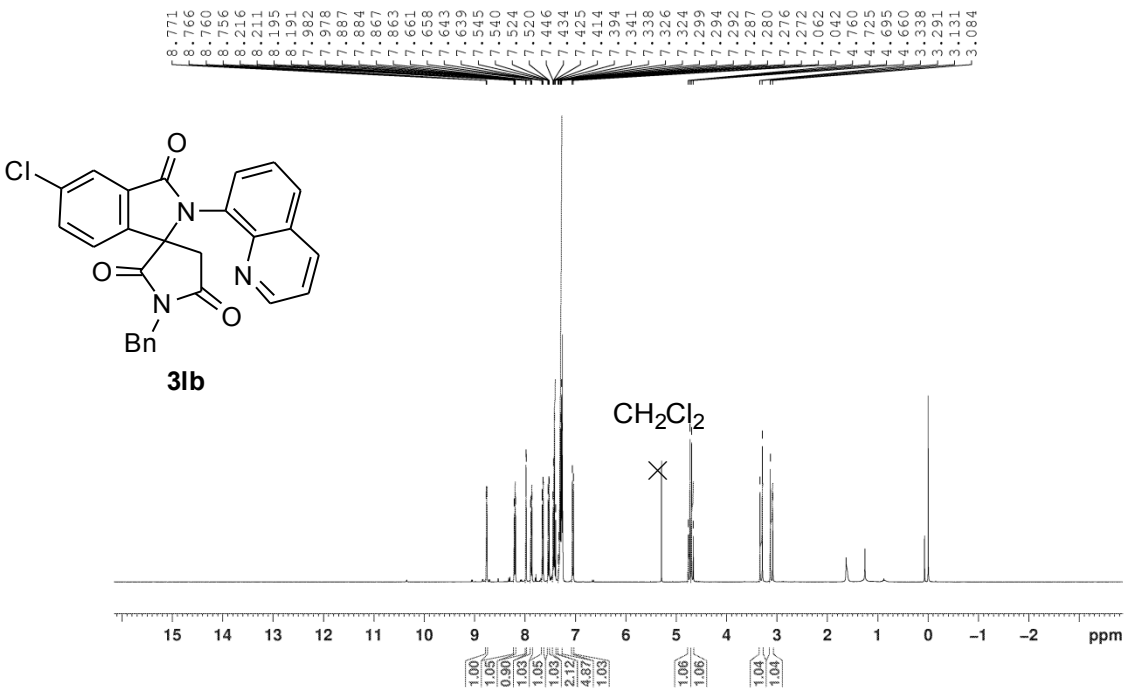
[^{1}H, ^{13}C, and ^{19}F NMR Spectra of **3ka**]

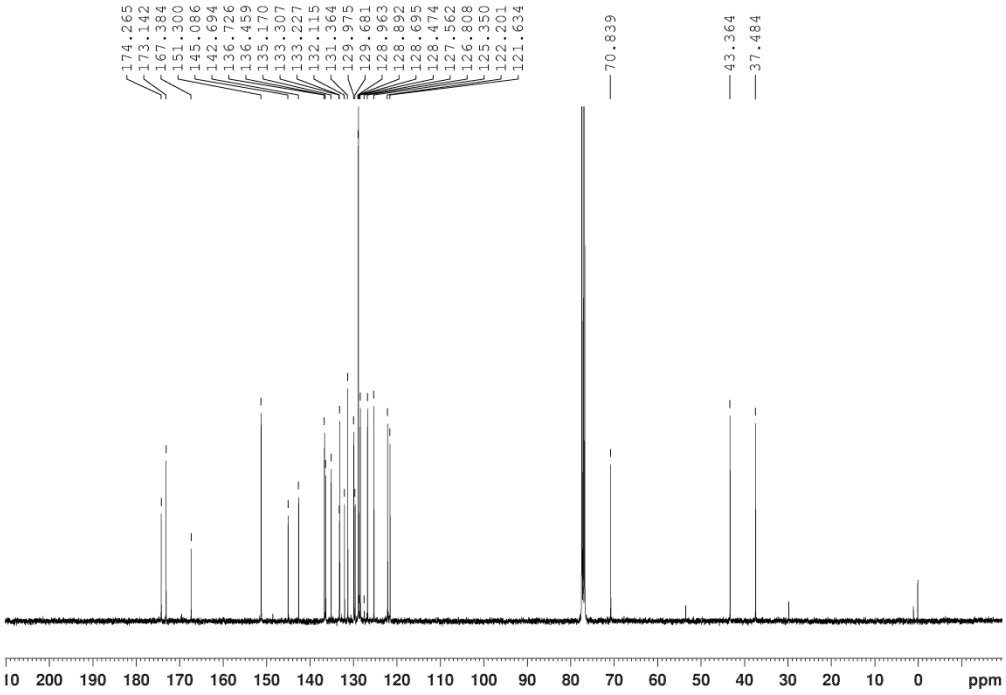




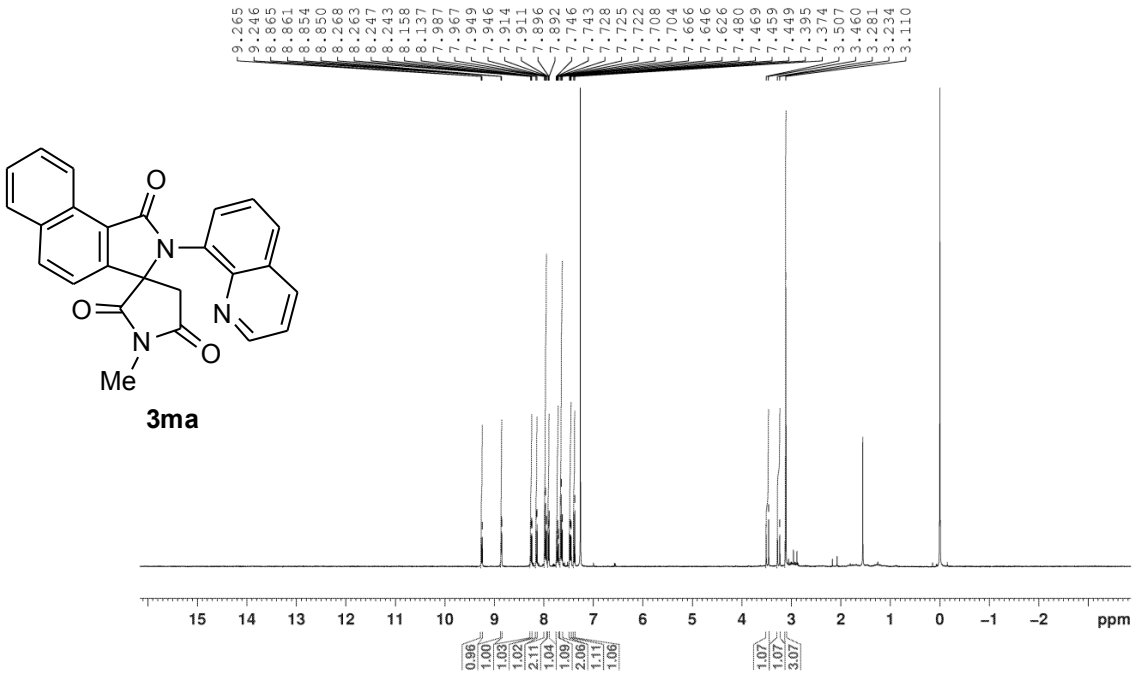

-62.487
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

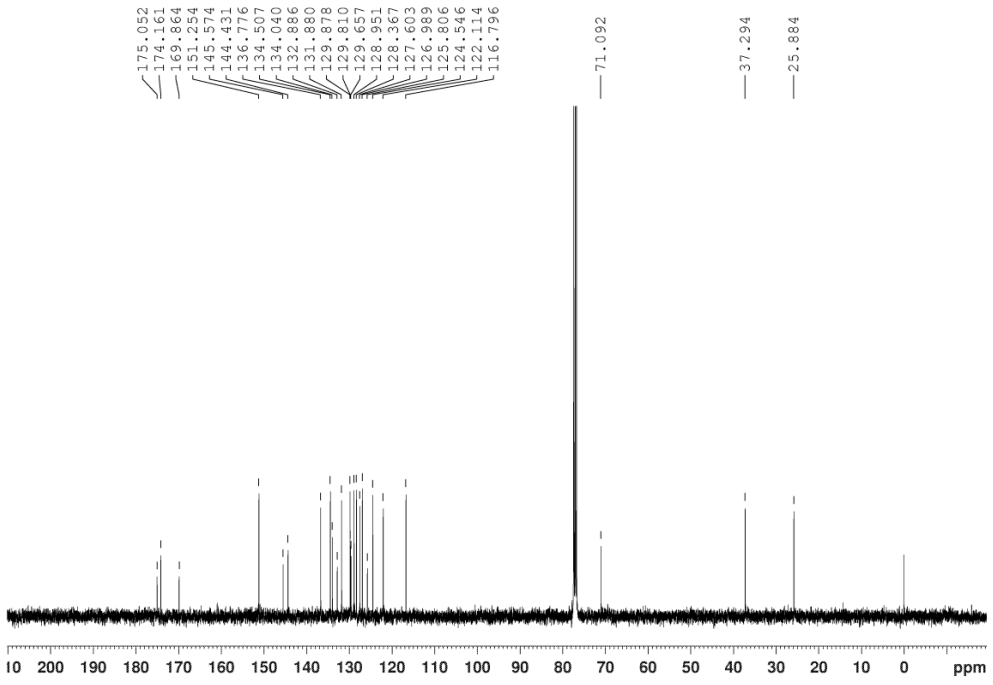
[^{1}H and ^{13}C NMR Spectra of **3lb**]



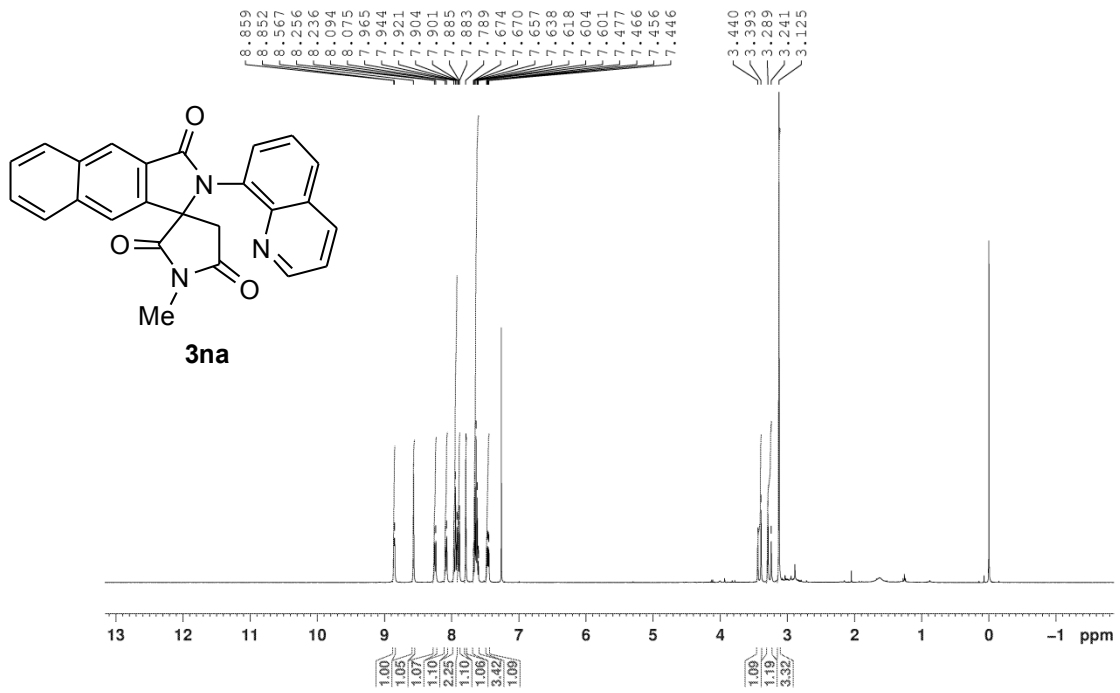


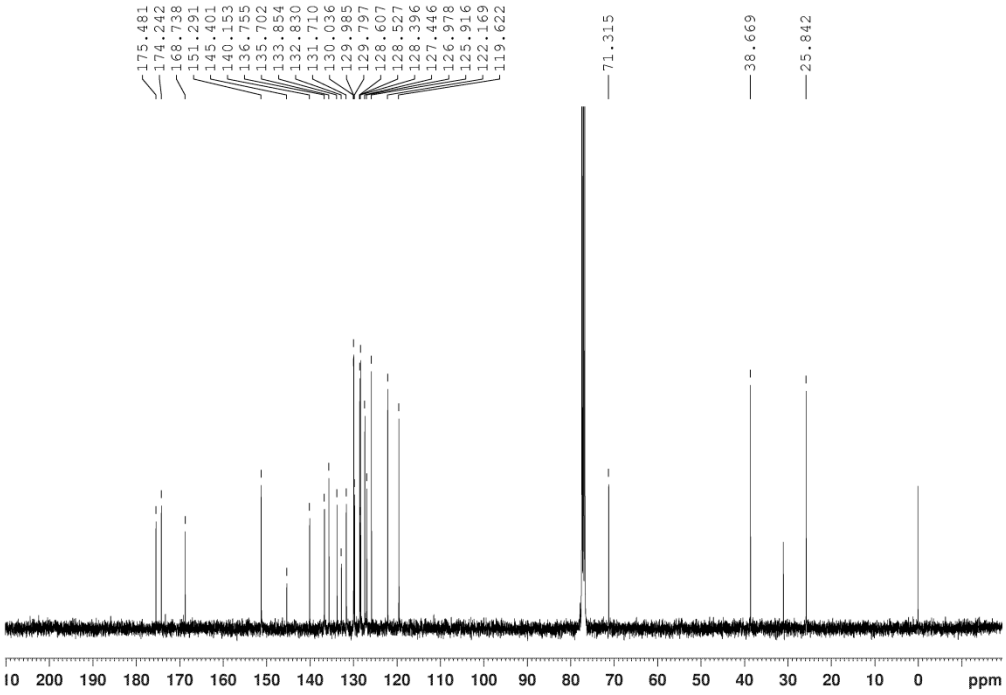
[^{1}H and ^{13}C NMR Spectra of **3ma**]



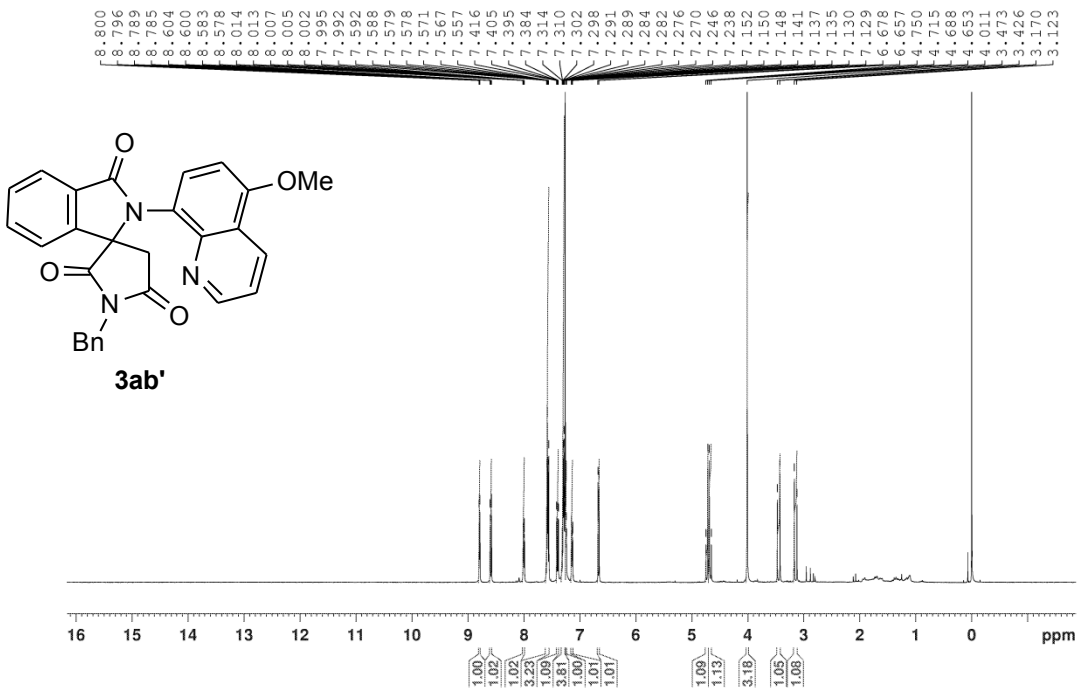


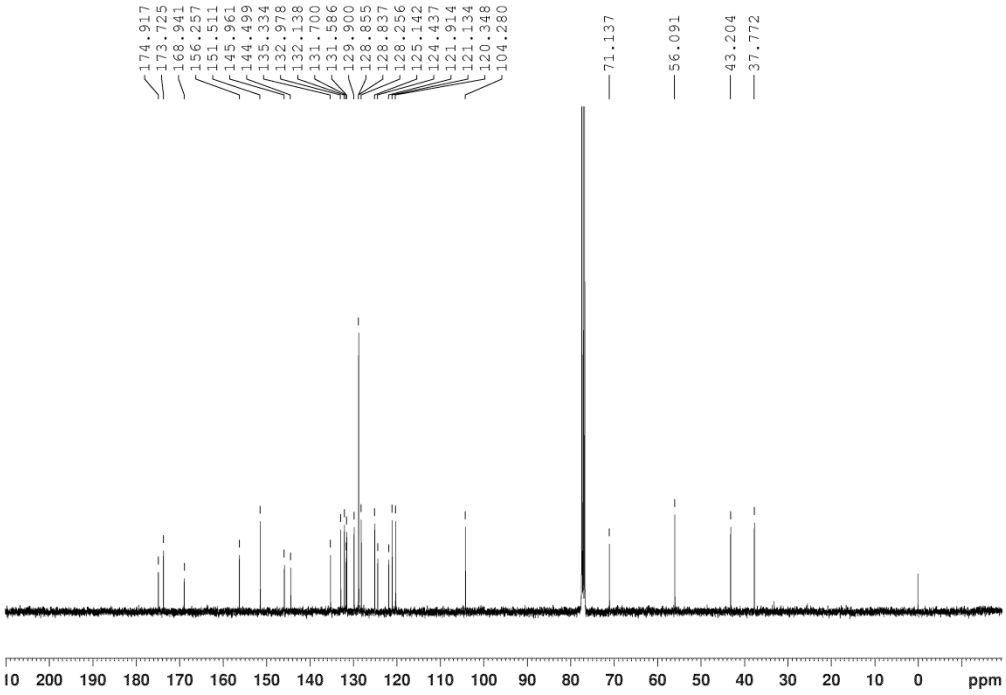
[^{1}H and ^{13}C NMR Spectra of **3na**]



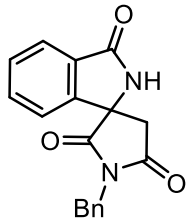


[^{1}H and ^{13}C NMR Spectra of **3ab'**]

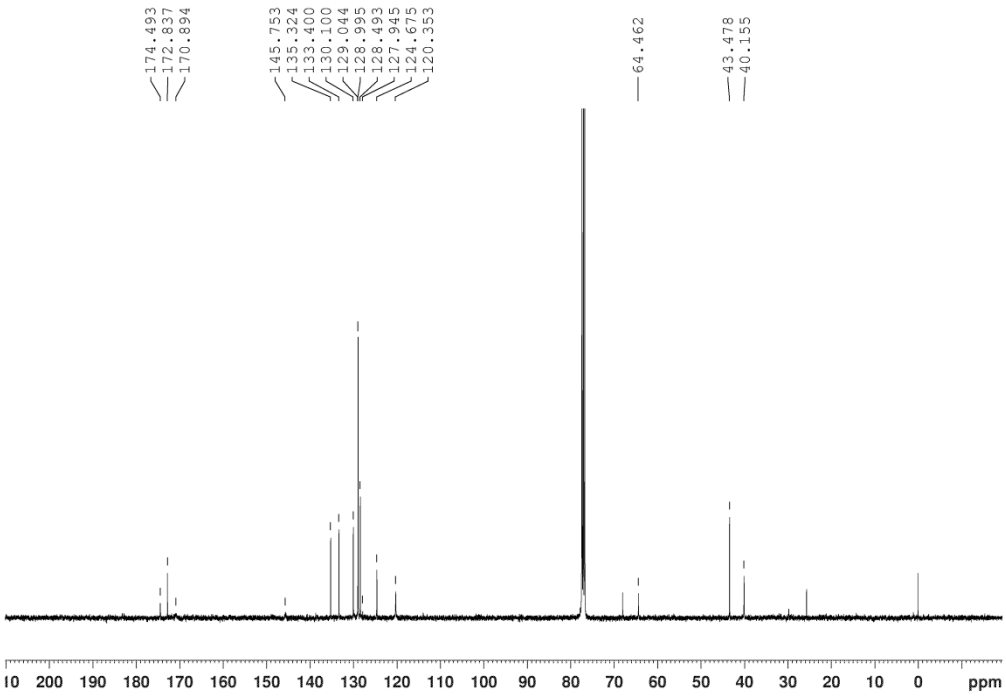




[^{1}H (at –40 ˚C) and ^{13}C (at 25 ˚C) NMR Spectra of **3ab-H**]



3ab-H



[^{1}H and ^{13}C NMR Spectra of **4aa**]