Electronic Supplementary Information (ESI)

Total Mechano-synthesis of 2-Cyclopropyl-4-(4-Fluorophenyl) Quinoline-3-Acrylaldehyde—A Pivotal intermediate of Pitavastatin

Jingbo Yu,*[ab] Yanhua Zhang,[a] Zehao Zheng [a] and Weike Su*[ab]

[a] *National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Huzhou Key Laboratory of mechanochemistry, Zhejiang University of Technology. Hangzhou, 310014, P.R. China. E-mail: yjb@zjut.edu.cn*

[b] *Huzhou Key Laboratory of mechanochemistry, Zhejiang Yangtze River Delta Biomedical Industry Technology Research Park, Deqing, 313200*

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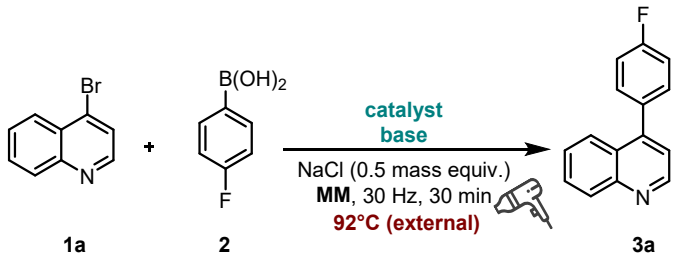
1. General Information

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All of the ball milling reactions were conducted in a mixer mill (MM 400 RetschGmbh, Hann, Germany) with 15 or 50 mL stainless steel grinding vessels with stainless steel balls, if not mentioned otherwise. All of the extrusion reactions were conducted in a twin-screw extruder (SJZS-7A, China). Reactions were monitored by Thin Layer Chromatography (TLC) using UV light (254/365 nm) for detection. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker 400 or 600 MHz spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. The following abbreviations were used to explain multiplicities: s = singlet, brs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet and the *J* coupling constants were reported in Hertz unit (Hz). The melting points were recorded on melting point apparatus (Büchi B-540). The synthesis of substrates **3m**, **3n**, **3o** and were according to literature method[1] and the synthesis of **3p** was referred to literature 2[2].

2. Reactions optimization & typical procedures

2.1 Optimization of Reaction Conditions

Table S1. Optimization of chemical conditions for Suzuki-Miyaura coupling[a]



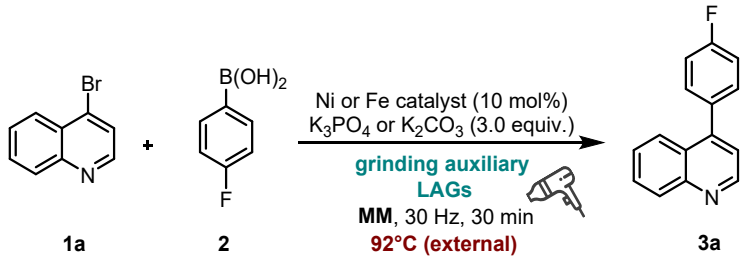
1a 2 3a

Entry	Catalyst (mol %)	Base (equiv.)	Yield (%)[b]
1	$Pd(OAc)_2$ (10)	K_3PO_4 (3.0)	81
2	$PdCl_2(PPh_3)_2$ (10)	K_3PO_4 (3.0)	75
3	$NiCl_2(PPh_3)_2$ (10)	K_3PO_4 (3.0)	75
4	$NiCl_2$(dppp) (10)	K_3PO_4 (3.0)	83
5	$NiCl_2(PCy_3)_2$ (10)	K_3PO_4 (3.0)	82
6	$FeCl_3(PPh_3)_3$ (10)	K_3PO_4 (3.0)	29
7	$FeCl_3$(dppe)$_3$ (10)	K_3PO_4 (3.0)	32
8	$FeCl_3$ (10)	K_3PO_4 (3.0)	50
9	$FeCl_2$ (10)	K_3PO_4 (3.0)	33
13	$NiCl_2$(dppp) (10)/**$FeCl_3$ (10)**	**K_2CO_3 (3.0)**	43/**53**
14	$NiCl_2$(dppp) (10)/$FeCl_3$ (10)	Na_2CO_3 (3.0)	56/25
15	$NiCl_2$(dppp) (10)/$FeCl_3$ (10)	$NaHCO_3$ (3.0)	65/38

16	$NiCl_2$(dppp) (10)/$FeCl_3$ (10)	Cs_2CO_3 (3.0)	39/n.d.
17	$NiCl_2$(dppp) (10)/$FeCl_3$ (10)	KF (3.0)	43/30
18	$NiCl_2$(dppp) (10)/$FeCl_3$ (10)	CsF (3.0)	70/trace
19	**$NiCl_2$(dppp) (10)**	**K_3PO_4 (3.0)**	76[c]/**86**[c]/80[d]
20	$NiCl_2$(dppp) (8/6)	K_3PO_4 (3.0)	71/56
21	$NiCl_2$(dppp) (10)	K_3PO_4 (2.0/4.0)	76/65
22	$FeCl_3$ (10)	K_2CO_3 (3.0)	43[c]/48[d]/42[e]
23	$FeCl_3$ (10)	K_2CO_3 (2.0/3.5/4.0)	33/40/37
24[f]	$FeCl_3$ (8)	K_2CO_3 (3.0)	65
25[f]	$FeCl_3$ (6)	K_2CO_3 (3.0)	48

[a] Reaction conditions unless specified otherwise: **1a** (0.4 mmol), **2** (0.6 mmol), catalyst, base and NaCl (0.5 mass equiv.) were placed in a 15 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 10 mm), heated by heat-gun, milling in a mixer mill (RETSCH MM 400) for 30 min at 30 Hz. [b] Isolated yields. [c] **2** (0.48 mmol). [d] **2** (0.56 mmol). [e] **2** (0.64 mmol). [f] LAGs (H_2O: 0.08 μL/mg). **MM** = mixer mill. n.d. = not detected.

Table S2. Optimization of grinding auxiliary and LAGs for Suzuki-Miyaura coupling[a]

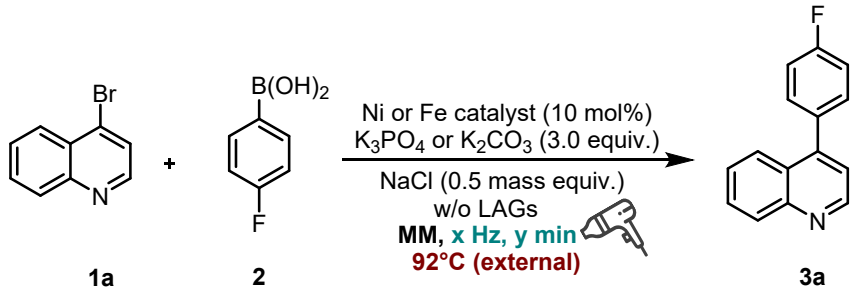


Entry	Grinding auxiliary（mass equiv.）	LAGs (μL/mg)	Yield (%)[b] $NiCl_2$(dppp)/K_3PO	Yield (%)[b] $FeCl_3/K_2CO_3$
1	–	–	62	trace
2	**NaCl (0.5)**	–	**86**	53
3	Na_2SO_4 (0.5)	–	58	trace
4	Silica gel (0.5)	–	34	trace
5	neutral-Al_2O_3 (0.5)	–	79	trace
6	PEG-4000 (0.5)	–	63	trace
7	NaCl (1.0)	–	41	25
8	NaCl (0.3)	–	74	30
9	NaCl (0.5)	H_2O (0.10)	/	60
10	**NaCl (0.5)**	**H_2O (0.08)**	62	80
11	NaCl (0.5)	H_2O (0.07)	/	63
12	NaCl (0.5)	H_2O (0.06)	/	55

13	NaCl (0.5)	MeOH (0.08)	n.d.	31
14	NaCl (0.5)	Dioxane (0.08)	n.d.	28
15	NaCl (0.5)	THF (0.08)	59	trace
16	NaCl (0.5)	*n*-Hexane (0.08)	73	trace
17	NaCl (0.5)	EtOAc (0.08)	47	trace

[a] Reaction conditions unless specified otherwise: **1a** (0.4 mmol), **2** (0.6 mmol), Ni or Fe catalyst (10 mol%), K_3PO_4 or K_2CO_3 (3.0 equiv.), grinding auxiliary and LAGs were placed in a 15 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 10 mm), heated by heat-gun, milling in a mixer mill (RETSCH MM 400) for 30 min at 30 Hz. [b] Isolated yields. **MM** = mixer mill; n.d. = not detected.

Table S3. Optimization of ball-milling parameters for Suzuki-Miyaura coupling

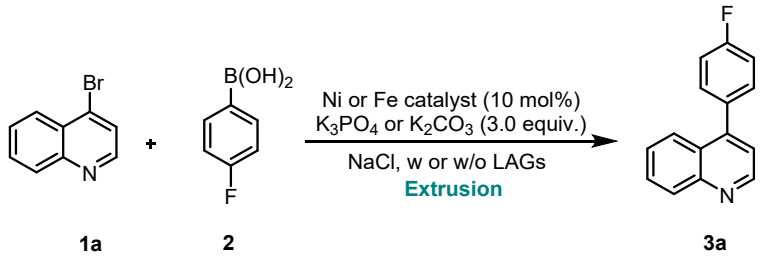


1a **2** **3a**

Entry	Time (min)	Ball size (mm)	Frequency (Hz)	Yield (%)	
				$NiCl_2(dppp)/K_3PO_4$[a]	$FeCl_3/K_2CO_3$[b]
1	**30**	**10**	**30**	86	**80**
2	30	12	30	83	70
3	30	8	30	75	43
4	20	10	30	72	60
5	45	10	30	85	71
6	**60**	**10**	**30**	**93**	58
7	60	10	25	76	/
8	60	10	20	68	/
9	30	10	25	/	64
10	30	10	20	/	32

[a] Reaction conditions: **1a** (0.4 mmol), **2** (0.56 mmol), $NiCl_2(dppp)$ (10 mol%), K_3PO_4(3.0 equiv.) and NaCl (0.5 mass equiv.) were placed in a 15 mL stainless-steel vessel with a stainless-steel ball, heated by heat-gun, milling in a mixer mill (RETSCH MM 400) for y time at x Hz. Isolated yields. [b] Reaction conditions: **1a** (0.4 mmol), **2** (0.6 mmol), $FeCl_3$ (10 mol%), K_2CO_3 (3.0 equiv.), LAGs (H_2O: 0.08 μL/mg) and NaCl (0.5 mass equiv.) were placed in a 15 mL stainless-steel vessel with a stainless-steel ball, heated by heat-gun, milling in a mixer mill (RETSCH MM 400) for x time at y Hz. Isolated yields. **MM** = mixer mill. Isolated yields.

Table S4. Optimization of extrusion conditions for Suzuki-Miyaura coupling

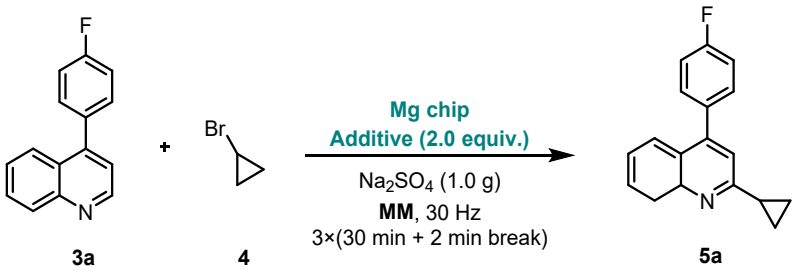


1a **2** **3a**

Entry	T (°C)			Screw speed (rpm)	STY[c] (kg/m³·day)	
	I	II	III		$NiCl_2$(dppp) /K_3PO_4[a]	$FeCl_3$ /K_2CO_3[b]
1	50	65	50	25	1.80×10^3	/
2	60	65	60	25	2.10×10^3	/
3	65	75	80	25	2.43×10^3	/
4	70	80	85	25	2.33×10^3	/
5	**65**	**75**	**80**	**18**	**2.78×10^3**	**/**
6	65	75	80	15	2.63×10^3	/
7	100	105	100	25	/	1.84×10^3
8	80	90	80	25	/	1.68×10^3
9	75	85	75	25	/	1.72×10^3
10	**80**	**90**	**80**	**18**	**/**	**2.13×10^3**
11	80	90	80	15	/	2.05×10^3

[a] TSE reaction conditions **A**: **1a** (36 mmol), **2** (50.4 mmol), $NiCl_2$(dppp) (10 mol%) and K_3PO_4 (3.0 equiv.) were reacted in a twin-screw extruder (SJZS-7A). Feed rate: 2.63 g/min, temperature as specified, x rpm. [b] TSE reaction conditions **B**: **1a** (36 mmol), **2** (50.4 mmol), $FeCl_3$ (10 mol%), K_2CO_3 (3.0 equiv.), LAGs (H_2O: 0.08 μL/mg) and NaCl (10 g) reacted in a twin-screw extruder (SJZS-7A). Feed rate: 2.63 g/min, temperature as specified, x rpm.[c] STY = total product mass (kg) / (reactant volume (m^3) × time (day).

Table S5. Optimization of chemical conditions for Minisci C–H alkylation[a]



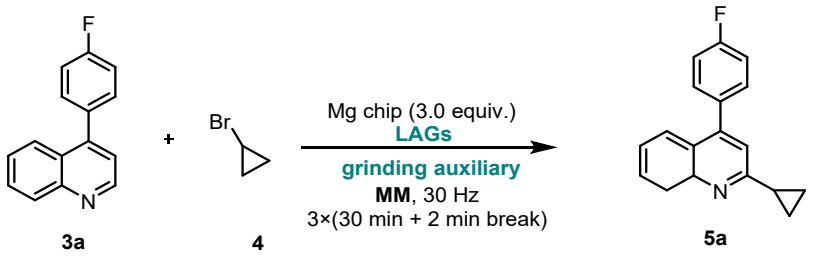
3a **4** **5a**

Entry	Mg (equiv.)	Additive (2.0 equiv.)	4 (equiv.)	Yield (%)[b]
1	–	–	5.0	n.d.
2	2.0	–	5.0	18

3	3.0	–	5.0	43
4	4.0	–	5.0	37
5	4.5	–	5.0	25
6	3.0	TMEDA	5.0	30
7	3.0	TMPDA	5.0	trace
8	3.0	DBEDA	5.0	5
9[c]	3.0	–	3.0	43
10[c]	**3.0**	**–**	**4.0**	**53**
11[c]	3.0	–	4.5	50
12[c]	3.0	–	5.0	48
13[c]	3.0	–	5.5	40
14[c]	3.0	–	6.0	36

[a] Reaction conditions: **3a** (0.2 mmol), **4**, Mg chip, additive (2.0 equiv.) and Na_2SO_4 (1.0 g) were placed in a 15 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 12 mm), milling in a mixer mill (RETSCH MM 400) for [3 × (30 min + 2 min break)] at 30 Hz. [b] Isolated yields. [c] Na_2SO_4 (0.9 g). **MM** = mixer mill; n.d.= not detected. TMEDA = *N*, *N*, *N*', *N*'-tetramethylethylenediamine; TMPDA = tetramethyl-1,3-diaminopropane; DBEDA = *N*, *N*'-dibenzylethylenediamine.

Table S6. Optimization of grinding auxiliary and LAGs for Minisci C–H alkylation[a]

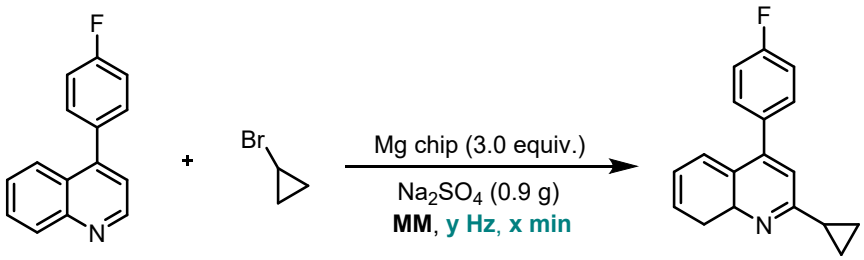


Entry	LAGs (η = 0.02)	Grinding auxiliary (g)	Yield (%)[b]
1	–	Na_2SO_4 (1.0)	43
2	MeCN	Na_2SO_4 (1.0)	20
3	EtOAc	Na_2SO_4 (1.0)	trace
4	DMSO	Na_2SO_4 (1.0)	trace
5	DMF	Na_2SO_4 (1.0)	27
6	DCE	Na_2SO_4 (1.0)	7
7	Hexane	Na_2SO_4 (1.0)	7
8	–	NaCl (1.0)	n.d.
9	–	Silica gel (1.0)	n.d.
10	–	KF (1.0)	15
11	–	KF/Na_2SO_4 = 2/3 (1.0)	trace

12	–	KF/Na_2SO_4= 3/7 (1.0)	28
13	–	KF/Na_2SO_4= 1/4 (1.0)	32
14	–	KF/Na_2SO_4= 1/9 (1.0)	41
15	–	Na_2SO_4 (0.6)	42
16	–	Na_2SO_4 (0.8)	45
17	–	**Na_2SO_4 (0.9)**	**53**

[a] Reaction conditions: **3a** (0.2 mmol), **4** (0.8 mmol), Mg chip (3.0 equiv.) LAGs (η = 0.02) and grinding auxiliary (1.0 g) were placed in a 15 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 12 mm), milling in a mixer mill (RETSCH MM 400) for [3 × (30 min + 2 min break)] at 30 Hz. [b] Isolated yields. n.d. = not detected. DMSO = dimethyl sulfoxide; DMF = dimethylformamide; DCE = dichloroethane. **MM** = mixer mill.

Table S7. Optimization of ball-milling parameters for Minisci C-H alkylation[a]

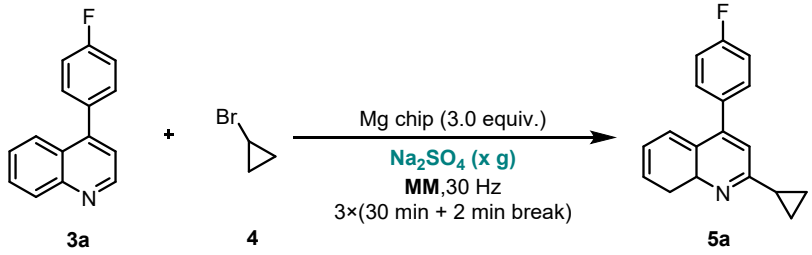


3a **4** **5a**

Entry	Frequency (Hz)	Time (min)	Mill balls (n×mm)	Yield (%)[b]
1	30	30×3	1×12	53
2	25	30×3	1×12	38
3	20	30×3	1×12	25
4	30	30×3	2×8	trace
5	30	30×3	1×10	23
6	**30**	**30×3**	**1×14**	**64**
7	30	30×3	1×15	50
8	30	30×4	1×14	43
9	30	30×5	1×14	40

[a] Reaction conditions: **3a** (0.2 mmol), **4** (0.8 mmol), Mg chip (3.0 equiv.) and Na_2SO_4 (0.9 g) were placed in a 15 mL stainless-steel vessel, milling in a mixer mill (RETSCH MM 400) for x time at y Hz. [b] Isolated yields. **MM** = mixer mill.

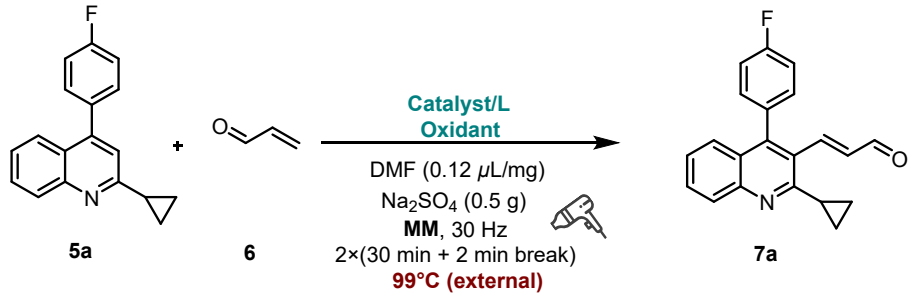
Table S8. Optimization of gram-scale reaction conditions[a]



Entry	4:3a (mmol)	Na_2SO_4 (g)	Mill balls (n×mm)	Yield (%)[b]
1	32:8	10	2×14	trace
2	24:8	10	2×14	28
3	16:8	10	2×14	35
4	16:8	12	2×14	42
5	16:8	13	2×14	45
6	**16:8**	**14**	**2×14**	**51**
7	16:8	15	2×14	50
8	16:8	17	2×14	40
9	16:8	19	2×12	38

[a] Reaction conditions: **3a**, **4**, Mg chip (3.0 equiv.) and Na_2SO_4 were placed in a 50 mL stainless-steel vessel, milling in a mixer mill (RETSCH MM 400) for [3 × (30 min + 2 min break)] at 30 Hz. **MM** = mixer mill. [b] Isolated yields.

Table S9. Chemical conditions optimization for Oxidative Heck reaction[a]

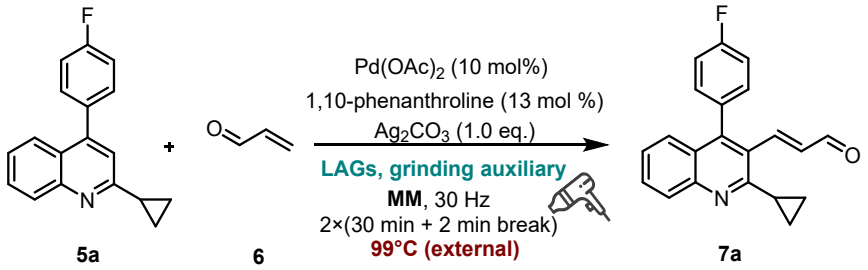


Entry	Catalyst (mol %)	L (mol %)	Oxidant (equiv.)	Yield (%)[b]
1	$Pd(OAc)_2$ (10)	$\mathbf{L_1}$ (13)	Ag_2CO_3 (0.5)	23
2	$Pd(OAc)_2$ (10)	$\mathbf{L_1}$ (13)	Ag_2O (0.5)	12
3	$Pd(OAc)_2$ (10)	$\mathbf{L_1}$ (13)	CF_3SO_2OAg (0.5)	18
4	$Pd(OAc)_2$ (10)	$\mathbf{L_1}$ (13)	$AgBF_4$ (0.5)	n.d.
5	$Pd(OAc)_2$ (10)	$\mathbf{L_1}$ (13)	AgOAc (0.5)	n.d.
6	$Pd(OAc)_2$ (10)	$\mathbf{L_1}$ (13)	$Ag_2CO_3/Cu(OAc)_2$ = 1/1 (0.5)	18

7	$Pd(OAc)_2$ (10)	**L_1** (13)	$Ag_2CO_3/CuCO_3$ = 1/1 (0.5)	trace
8	$Pd(OAc)_2$ (10)	**L_1** (13)	$Ag_2CO_3/Cu(OAc)_2$ = 1/1 (1.0)	27
9	**$Pd(OAc)_2$ (10)**	**L_1 (13)**	**Ag_2CO_3 (1.0)**	**43 (28[c]/34[d])**
10	$Pd(OAc)_2$ (10)	**L_1** (13)	Ag_2CO_3 (1.5/2.0)	34/31
11	$Pd[O_2C(CH_3)_3]_2$ (10)	**L_1** (13)	Ag_2CO_3 (1.0)	24
12	$Pd(acac)_2$ (10)	**L_1** (13)	Ag_2CO_3 (1.0)	27
13	$PdCl_2(PPh_3)_2$ (10)	**L_1** (13)	Ag_2CO_3 (1.0)	30
14	$Pd[O_2C(CH_3)_3]_2$ (10)	**L_1** (13)	Ag_2CO_3 (1.0)	24
15	$Pd(OAc)_2$ (8)	**L_1** (10.4)	Ag_2CO_3 (1.0)	35
16	$Pd(OAc)_2$ (6)	**L_1** (7.8)	Ag_2CO_3 (1.0)	31
17	$Pd(OAc)_2$ (10)	**L_2** (13)	Ag_2CO_3 (1.0)	32
18	$Pd(OAc)_2$ (10)	**L_3** (13)	Ag_2CO_3 (1.0)	31

[a] Reaction conditions: **5a** (0.4 mmol), **6** (0.6 mmol), catalyst (x mol %), 1,10-phenanthroline (**L_1**, 1.3x mol%), oxidant, DMF (0.12 μL/mg) and Na_2SO_4 (0.5 g) were placed in a 15 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 10 mm), heated by heat-gun, and milling in a mixer mill (RETSCH MM 400) for [2 × (30 min + 2 min break)] at 30 Hz. [b] Isolated yields. [c] **6** (0.4 mmol). [d] **6** (0.8 mmol). **L_2**= CEMTPP (ethyl (triphenylphosphoranylidene)acetate). **L_3**=DPPE (1,2-bis(diphenylphosphino)ethane). **MM** = mixer mill; n.d. = not detected.

Table S10. Optimization of grinding auxiliary and LAGs for oxidative Heck coupling[a]

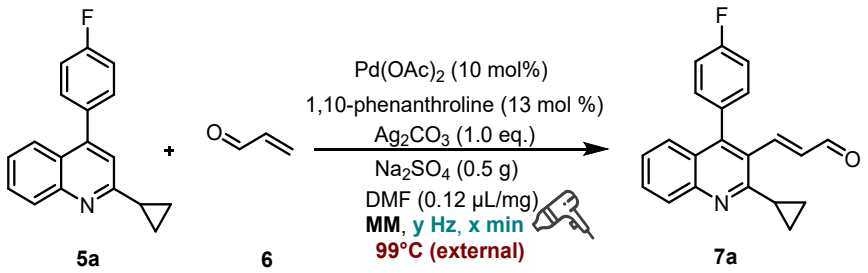


Entry	LAGs (μL/mg)	Grinding auxiliary (g)	Yield (%)[b]
1	**DMF (0.12)**	**Na_2SO_4 (0.5)**	**43**
2	DMF (0.12)	–	trace
3	–	Na_2SO_4 (0.5)	trace
4	MeCN (0.12)	Na_2SO_4 (0.5)	23
5	EtOAc (0.12)	Na_2SO_4 (0.5)	18
6	DMSO (0.12)	Na_2SO_4 (0.5)	25
7	Hexane (0.12)	Na_2SO_4 (0.5)	22
8	DMF (0.10)	Na_2SO_4 (0.5)	34
9	DMF (0.80)	Na_2SO_4 (0.5)	28
10	DMF (0.60)	Na_2SO_4 (0.5)	23

11	DMF (0.12)	silica gel (0.5)	32
12	DMF (0.12)	$NaHCO_3$ (0.5)	n.d.
13	DMF (0.12)	Na_2CO_3 (0.5)	trace
14	DMF (0.12)	Na_2SO_4 (0.25)	39
15	DMF (0.12)	Na_2SO_4 (0.75)	35

[a] Reaction conditions: **5a** (0.4 mmol), **6** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), 1,10-phenanthroline (13 mol %), Ag_2CO_3 (1.0 eq.), LAGs and grinding auxiliary were placed in a 15 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 10 mm), heated by heat-gun, milling in a mixer mill (RETSCH MM 400) for [2 × (30 min + 2 min break)] at 30 Hz. [b] Isolated yields. DMSO = dimethyl sulfoxide. DMF = dimethylformamide. **MM** = mixer mill. n.d. = not detected.

Table S11. Optimization of ball-milling parameters for oxidative Heck coupling[a]

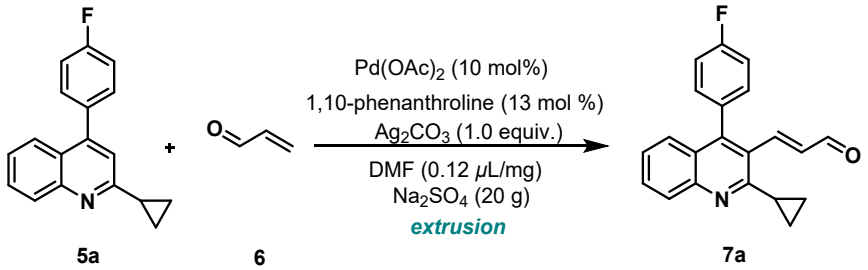


5a **6** **7a**

Entry	Time (min)	Frequency (Hz)	Mill ball (1×mm)	Yield (%)[b]
1	**30×2**	**30**	**10**	**43**
2	30×2+15	30	10	30
3	30×2+30	30	10	31
4	30×2	25	10	33
5	30×2	20	10	24
6	30×2	30	8	28
7	30×2	30	12	37

[a] Reaction conditions: **5a** (0.4 mmol), **6** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), 1,10-phenanthroline (13 mol %), Ag_2CO_3 (1.0 eq.), DMF (0.12 μL/mg) and Na_2SO_4 (0.5 g) were placed in a 15 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 10 mm), heated by heat-gun, milling in a mixer mill (RETSCH MM 400) for x time at y Hz. [b] Isolated yields. **MM** = mixer mill; n.d. = not detected.

Table S12. Optimization of extrusion conditions for Oxidative Heck coupling[a]



5a 6 7a

Entry	T (°C)			Screw speed (rpm)	STY (kg/m^3·day)
	Ⅰ	Ⅱ	Ⅲ		
1	105	115	105	25	/
2	100	110	85	25	1.07×10^3
3	90	105	80	25	1.10×10^3
4	85	100	75	25	1.03×10^3
5	**90**	**105**	**80**	**18**	**1.32×10^3**
6	90	105	80	15	1.23×103

[a] TSE reaction conditions: **5a** (32 mmol), **6** (64 mmol), $Pd(OAc)_2$ (10 mol%), 1,10-phenanthroline (13 mol%), Ag_2CO_3 (1.0 equiv.), DMF (0.12 μL/mg) and Na_2SO_4 (20 g) were reacted in a twin-screw extruder (SJZS-7A). Feed rate: 2.63 g/min, temperature as specified, x rpm. STY = total product mass (kg) / (reactant volume (m^3) × time (day)

3 General Procedures

3.1 General procedure for the synthesis of 4-(4-fluorophenyl) quinoline (3a)

a) Ni catalytic procedure

4-bromoquinoline (**1a**) (83 mg, 0.4 mmol, 1.0 equiv.), *p*-fluorophenylboronic acid (**2**) (78 mg, 0.56 mmol, 1.4 equiv.), $NiCl_2$(dppp) (22 mg, 0.04 mmol, 10 mol%), K_3PO_4 (255 mg, 1.2 mmol, 3.0 equiv.), and NaCl (220 mg, 0.5 mass equiv.) were successively added to a 15 mL stainless-steel grinding jar containing one stainless-steel ball with a diameter of 10 mm. The jar was sealed and placed on a mixer mill (RETSCH MM 400), with a high-temperature heat gun installed 3 cm away from the jar (keep external temperature at 92 ℃). The mixture was milled at a frequency of 30 Hz for 60 minutes (every 30-minute milling with a 2-minute break). Upon completion of grinding, the heat gun was switched off, and the resulting material was carefully transferred to a beaker. It was then dissolved in 15 mL of water, followed by exhaustive extraction with ethyl acetate (20 mL × 3). The combined organic layers were subsequently washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The crude residue was then purified by low temperature crystallization with petroleum ether to afford the target product (**3a**) as yellow solid (83 mg, 93% yield).

*The synthesis of substrates **3a~3f** adhered to the described procedure.*

b) Fe catalytic procedure

4-bromoquinoline (**1a**) (83 mg, 0.4 mmol, 1.0 equiv.), *p*-fluorobenzeneboronic acid (**2**) (84 mg, 0.6 mmol, 1.5 equiv.), $FeCl_3$ (7 mg, 0.04 mmol, 10 mol%), K_2CO_3 (166 mg, 1.2 mmol, 3.0 equiv.) NaCl (170 mg, 0.5 mass equiv.) and H_2O (40 μL, 0.08 μL/mg) were successively added into a 15 mL stainless-steel grinding jar containing one stainless-steel ball with a diameter of 10 mm. The jar was sealed and placed on a mixer mill (RETSCH MM 400), with a high-temperature heat gun installed 3 cm away from the jar (keep external temperature at 92 ℃). The mixture was milled at a frequency of 30 Hz for 30 minutes. Upon completion of grinding, the heat gun was switched off, and the resulting material was carefully transferred to a beaker. It was then dissolved in 15 mL of water, followed by exhaustive extraction with ethyl acetate (20 mL × 3). The combined organic layers were subsequently washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The crude residue was then purified by recrystallization with cold petroleum ether to afford the target product (**3a**) as yellow solid (71 mg, 80% yield).

3.2 Extrusion procedure for the synthesis of 4-(4-fluorophenyl) quinoline (3a)

a) Ni catalytic procedure

A mixture of 4-bromoquinoline (**1a**) (7.50 g, 36 mmol, 1.0 equiv.), *p*-fluorobenzeneboronic acid (**2**) (7.56 g, 54 mmol, 1.4 equiv.), $NiCl_2$(dppp) (1.95 g, 3.6 mmol, 10 mol%), and K_3PO_4 (23 g, 108 mmol, 3.0 equiv.) was prepared in a 50 mL beaker by manual stirring with a spatula until homogeneous. The resultant blend was then carefully transferred into a twin-screw extruder, set to operate at a feed rate of 2.63 g/min. During extrusion, the screws rotated at a speed of 18 rpm, while the temperature within the extruder was maintained at 65°C, 75°C, and 80°C in the respective zones. A yellow, viscous solid will emerge from the extruder outlet, with the reactants experiencing an approximate residence time of 15 minutes within the extruder. Once extrusion ceases, recover approximately 18 g of the solid product in the beaker. Stirring the solid with water (150 mL), followed by extracting the aqueous phase with ethyl acetate (150 mL × 3). The combined organic layers were subsequently washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The crude residue was then purified by rinsing with cold petroleum ether to yield the target product (**3a**). The space-time yield for this process is calculated as 2.78×10^3 (STY = total product mass (kg) / (reactant volume (m^3) × time (day)).

b) Fe catalytic procedure

A mixture of 4-bromoquinoline (**1a**) (7.50 g, 36 mmol, 1.0 equiv.), *p*-fluorobenzeneboronic acid (**2**) (7.56 g, 54 mmol, 1.4 equiv.), $FeCl_3$ (584 mg, 3.6 mmol, 10 mol%), K_2CO_3 (15.00 g, 108 mmol, 3.0 equiv.), NaCl (10.00 g) and H_2O (3.65 mL, 0.08 μL/mg) was prepared in a 50 mL beaker by manual stirring with a spatula until homogeneous. The resultant blend was then carefully transferred into a twin-screw extruder, set to operate at a feed rate of 2.63 g/min. During extrusion, the screws rotated at a speed of 18 rpm, while the temperature within the extruder was maintained at 80°C, 90°C, and 80°C in the respective zones. A gray, viscous solid will emerge from the extruder outlet, with the reactants experiencing an approximate residence time of 15 minutes within the extruder. Once extrusion ceases, recover approximately 17 g of the solid product in the beaker. Stirring the solid with water (150 mL), followed by extracting the aqueous phase with ethyl acetate (150 mL × 3). The combined organic layers were subsequently washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent

was evaporated under reduced pressure. The crude residue was then purified by recrystallization with cold petroleum ether to yield the target product (**3a**). The space-time yield for this process is calculated as 2.13×10^3 (STY = total product mass (kg) / (reactant volume (m^3) × time (day)).

3.3 General procedure for the synthesis of 2-cyclopropyl-4-(4-fluorophenyl)quinoline (5a)

a) 0.2 mmol scale

4-(4-fluorophenyl)quinoline (**3a**) (45 mg, 0.2 mmol, 1.0 equiv.), magnesium (14 mg, 0.6 mmol, 3.0 equiv.), Na_2SO_4 (0.9 g) and bromocyclopropane (**4**) (64 μL, 0.8 mmol, 4.0 equiv.) were added successively into a 15 mL ball milling jar containing one stainless-steel ball with a diameter of 14 mm. The jar was sealed and placed on a mixer mill (RETSCH MM 400), milling at 30 Hz for 90 minutes (every 30-minute milling with a 2-minute break). Upon completion of grinding, the resulting material was quenched with saturation NH_4Cl solution (10 mL) before transferred into a beaker, followed by exhaustive extraction with ethyl acetate (10 mL × 3). The combined organic layers were subsequently washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was then purified by flash chromatography (petroleum ether/ethyl acetate = 40/1) to give the target product **5a** as a yellow oil (34 mg, 64 % yield).

b) gram scale

4-(4-fluorophenyl)quinoline (**3a**) (1.8 g, 8 mmol, 1.0 equiv.), magnesium (576 mg, 24 mmol, 3.0 equiv.), Na_2SO_4 (14 g) and bromocyclopropane (**4**) (1.3 mL, 16 mmol, 2.0 equiv.) were added successively into a 50 mL ball milling jar containing two stainless-steel balls with a diameter of 14 mm. The jar was sealed and placed on a mixer mill (RETSCH MM 400), milling at 30 Hz for 90 minutes (every 30-minute milling with a 2-minute break). Upon completion of grinding, the resulting material was quenched with saturation NH_4Cl solution (30 mL) before transferred into a beaker, followed by exhaustive extraction with ethyl acetate (30 mL × 3). The combined organic layers were subsequently washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was then purified by flash chromatography (petroleum ether/ethyl acetate = 40/1) to give the target product **5a** as a yellow oil (1.1 g, 51 % yield).

3.4 General procedure for the synthesis of 3-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolin-2-yl]-2-propenal (7a)

2-cyclopropyl-4-(4-fluorophenyl)quinoline (**5a**) (105 mg, 0.4 mmol, 1.0 equiv.), cinnamaldehyde (**6**) (34 mg, 0.6 mmol, 1.5 equiv.), $Pd(OAc)_2$ (9 mg, 0.04 mmol, 10 mol%), 1,10-phenanthroline (9 mg, 0.052 mmol, 13 mol%), Ag_2CO_3 (110 mg, 0.4 mmol, 1.0 equiv.), Na_2SO_4 (500 mg) and DMF (10 μL, 0.12 μL/mg) were added successively into a 15 mL ball milling jar containing one stainless-steel ball with a diameter of 10 mm. The jar was sealed and placed on a mixer mill (RETSCH MM 400), with a high-temperature heat gun installed 3 cm away from the jar (keep external temperature at 99 ℃). The mixture was milled at a frequency of 30 Hz for 60 minutes (every 30-minute milling with a 2-minute break). Upon completion of grinding, the heat gun was switched off, and the resulting material was carefully transferred to

a beaker. It was then dissolved in 15 mL of water, followed by exhaustive extraction with ethyl acetate (20 mL × 3). The combined organic layers were subsequently washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The crude residue was then purified by flash chromatography (*n*-hexane/ethyl acetate = 40/1) to afford the target product (**7a**) as a yellow solid (54 mg, 39% yield).

3.5 Extrusion procedure for the synthesis of 3-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolin-2-yl]-2-propenal (7a)

A mixture of 2-cyclopropyl-4-(4-fluorophenyl)quinoline (**5a**) (7.56 g, 36 mmol, 1.0 equiv.), $Pd(OAc)_2$ (808 mg, 3.6 mmol, 10 mol%), 1,10-phenanthroline (842 mg, 4.68 mmol, 13 mol%), Ag_2CO_3 (9.00 g, 36 mmol, 1.0 equiv.), propenyl aldehyde (**6**) (4.27 mL, 64 mmol, 2.0 equiv.) and Na_2SO_4 (20.00 g) was prepared in a 50 mL beaker by manual stirring with a spatula until homogeneous. The resultant blend was then carefully transferred into a twin-screw extruder, set to operate at a feed rate of 2.63 g/min. During extrusion, the screws rotated at a speed of 18 rpm, while the temperature within the extruder was maintained at 90°C, 105°C, and 80°C in the respective zones. A gray, viscous solid will emerge from the extruder outlet, with the reactants experiencing an approximate residence time of 18 minutes within the extruder. Once extrusion ceases, recover approximately 15 g of the solid product in the beaker. Stirring the solid with water (200 mL), followed by extracting the aqueous phase with ethyl acetate (150 mL × 3). The combined organic layers were subsequently washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The crude residue was then purified by recrystallization with petroleum ether/ethyl acetate to yield the target product (**7a**). The space-time yield for this process is calculated as 1.32×10^3 (STY = total product mass (kg) / (reactant volume (m^3) × time (day)).

Quantitative nuclear magnetic resonance (NMR) analysis was utilized to confirm the purity of **7a** by using 1,3,5-trimethylbenzene (97% purity) as an internal standard. The product **7a** (15.8 mg) and 1,3,5-trimethylbenzene (6.3 mg) were added into the NMR tube. $CDCl_3$ was then added, and the mixture was thoroughly homogenized. The NMR analysis was performed using a 400 MHz spectrometer, resulting in a determination of the content of crude product **7a** as 95.7%.

The measurement time was ~10 min. 16 FID repetitions (number of scans) resulted in a suitable signal-to-noise ratio. Phasing and integration of the spectrum was performed manually, and the start and end points of each integral region were forced to zero amplitude using a fifth order polynomial baseline correction algorithm. The area of the signals appearing on a ^1H spectrum is directly proportional to the number of protons present in the active volume of the sample.

Hence, using Eq. (1), all the determinations in this study were performed on ^1H NMR spectra through the proportional comparison of the peak areas integrated for both the selected signal from the internal standard and from the substance in question:

$$m_{(7a)} = P_{(std)} \cdot \frac{MW_{(7a)}}{MW_{(std)}} \cdot \frac{nH_{(std)}}{nH_{(7a)}} \cdot \frac{m_{(std)}}{P_{(7a)}} \cdot \frac{A_{(7a)}}{A_{(std)}} \qquad (1)$$

where $m_{(\mathbf{7a})}$ and $m_{(std)}$ are the masses (weights) in mg, $MW_{(\mathbf{7a})}$ and $MW_{(std)}$ are the molecular weights in mg/mmol, $P_{(\mathbf{7a})}$ and $P_{(std)}$ are the purities, $nH_{(\mathbf{7a})}$ and $nH_{(std)}$ are the number of protons generating the selected signals for integration, $A_{(\mathbf{7a})}$ and $A_{(std)}$ are the areas for the selected peaks of the product **7a** and the internal standard, all respectively.

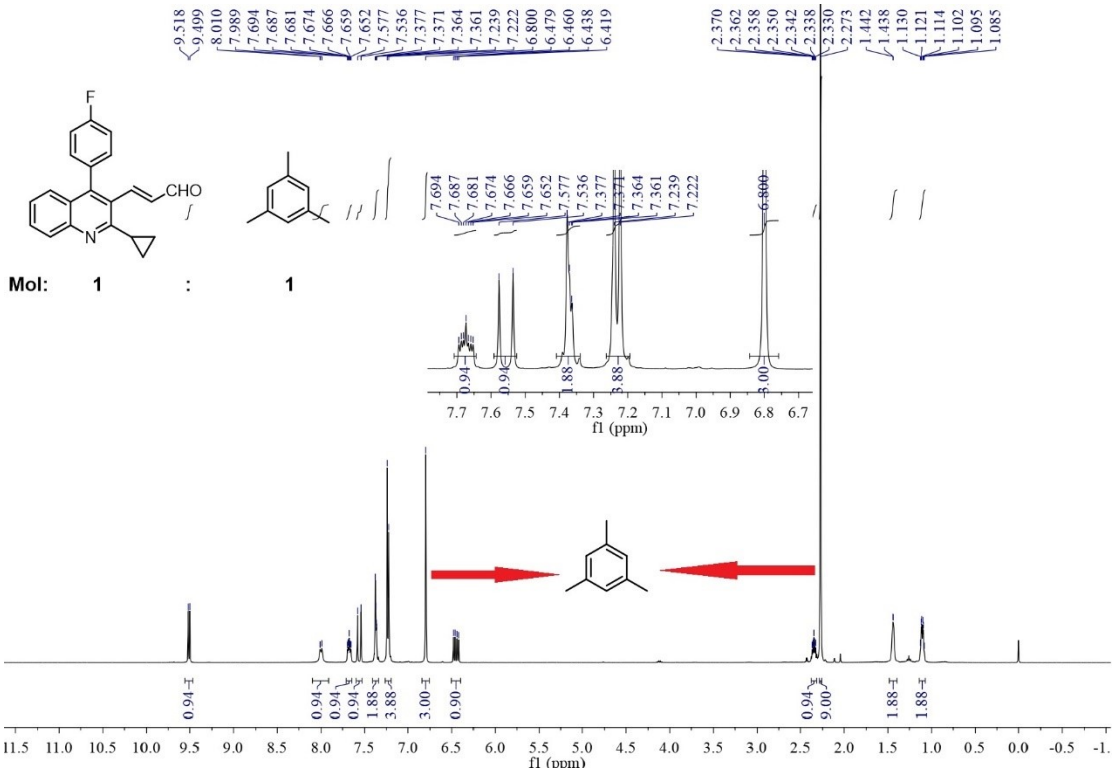


Figure S1. ^{1}H (400 MHz, $CDCl_3$) NMR spectra of compound **7a** and internal standard (trimethylbenzene)

4. Comparison of the synthetic routes of 3-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolin-2-yl]-2-propenal (7a)

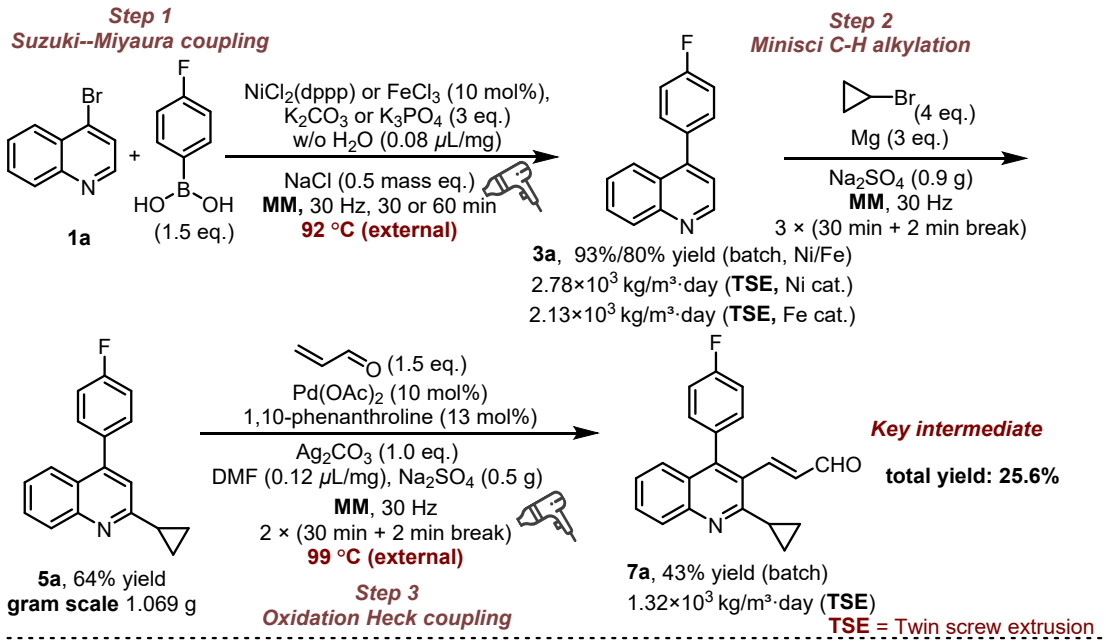


Figure S2. Total mechano-synthesis of pivastatin intermediate 7a

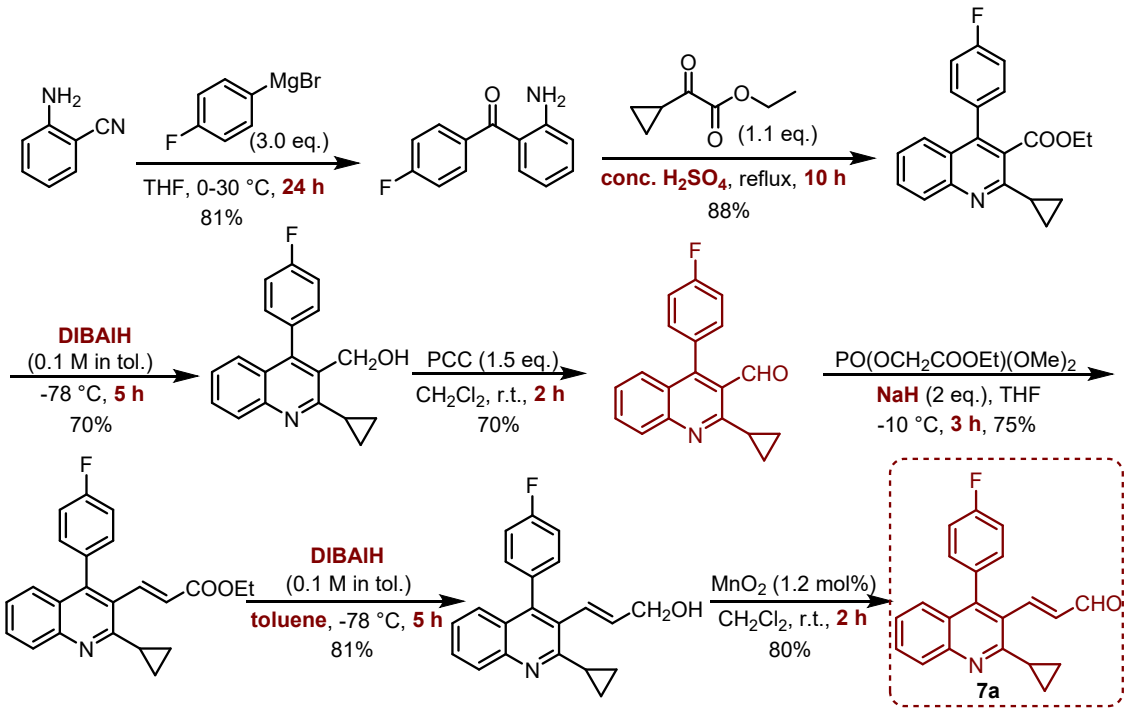


Figure S3. Traditional synthesis method of pitavastatin intermediate 7a (1)[3-5]

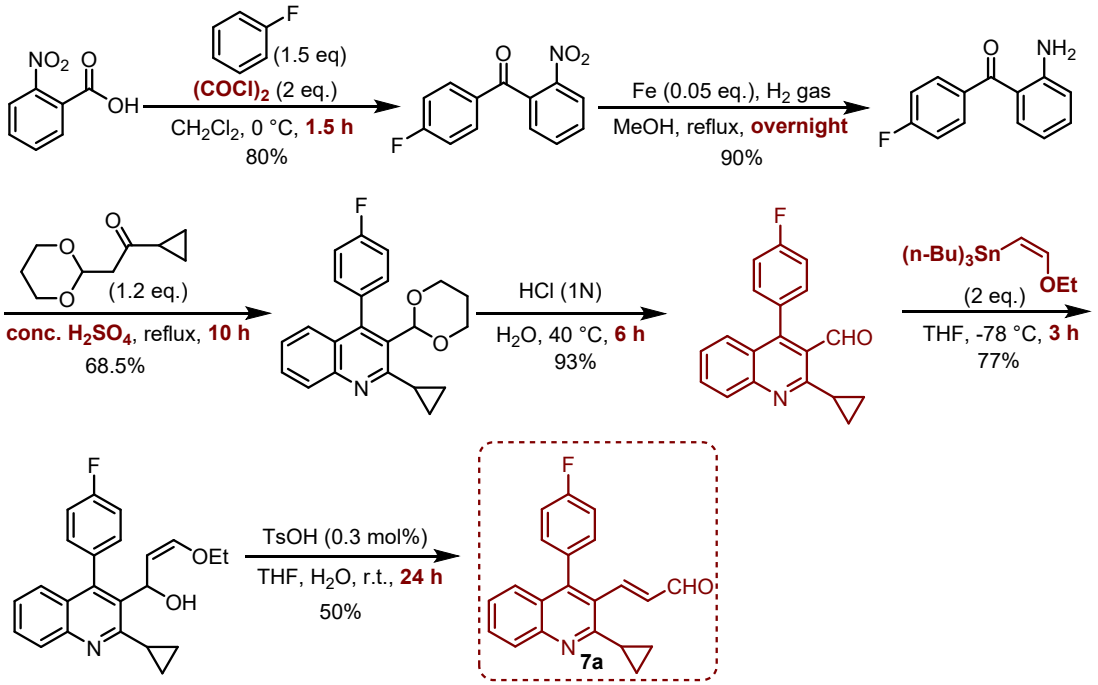


Figure S4. Traditional synthesis method of pitavastatin intermediate 7a (2)[6-8]

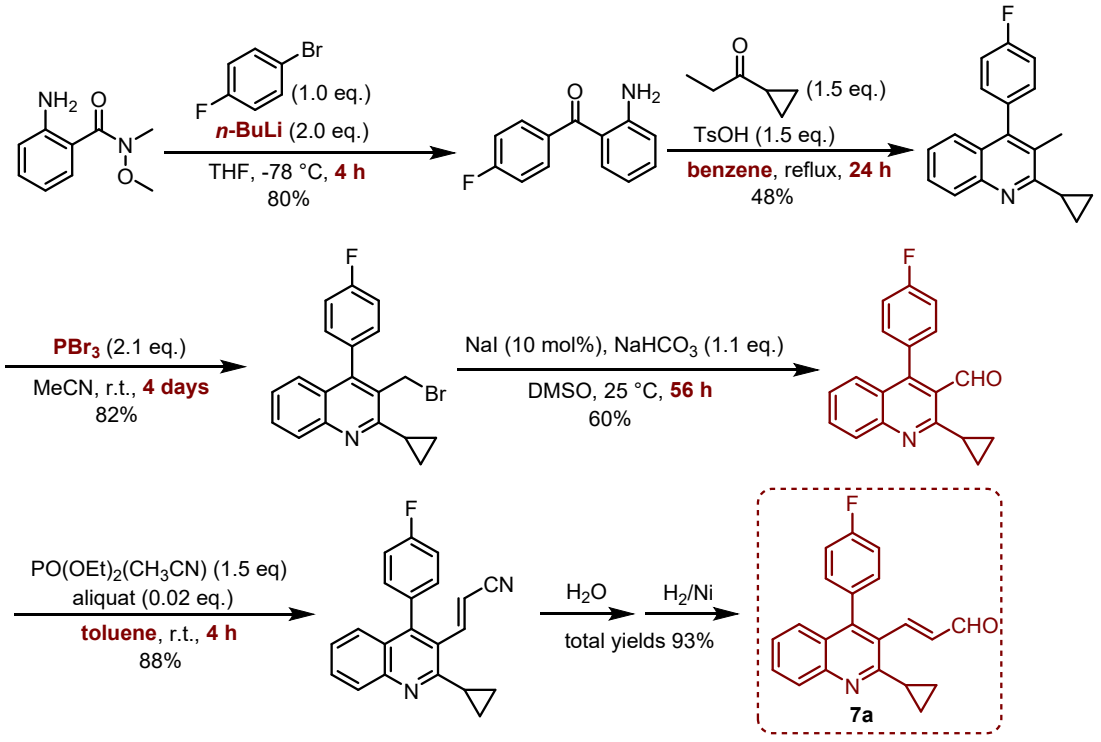


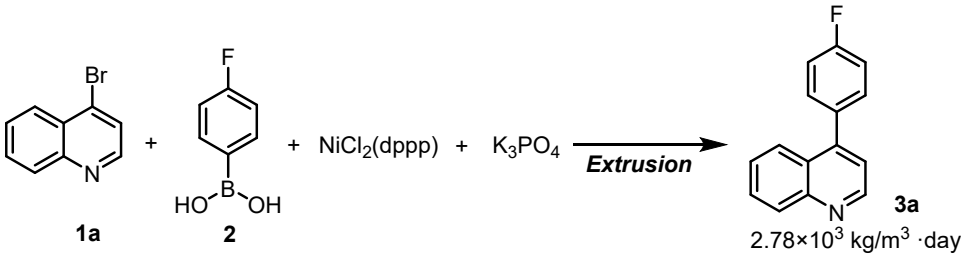
Figure S5. Traditional synthesis method of pitavastatin intermediate 7a (3)[9-11]

5. Calculations of *E*-factor for the mechanochemical method

The *E*-factor calculation[12] was derived utilizing upscaled reactions.

$$E-factor=\frac{Total\ mass\ of\ waste}{Mass\ of\ products}$$

Step 1 (Ni catalysis)

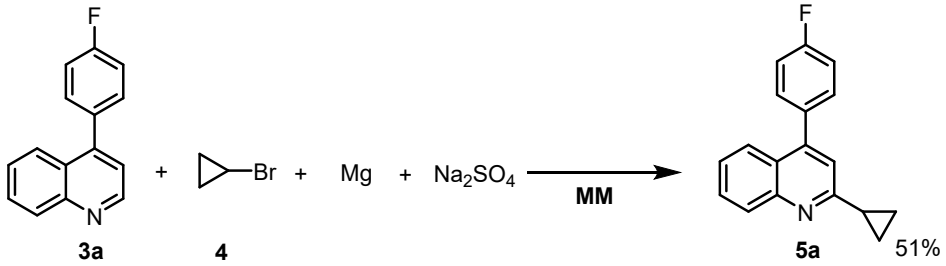


1a **2**

MW	208.06	139.92	542.05	212.27	223.35
n/mmol	36.00	54.00	3.60	108.00	
m/mg	7500	7560	1950	2300	6100

$$E-factor=\frac{(7500+7560+1950+2300-6110)\ mg}{6100\ mg}=5.55$$

Step 2



3a **4** **5a**

MW	223.35	120.98	24.00		263.32
n/mmol	8	16	24		
m/mg	1800	1936	576	1400	1100

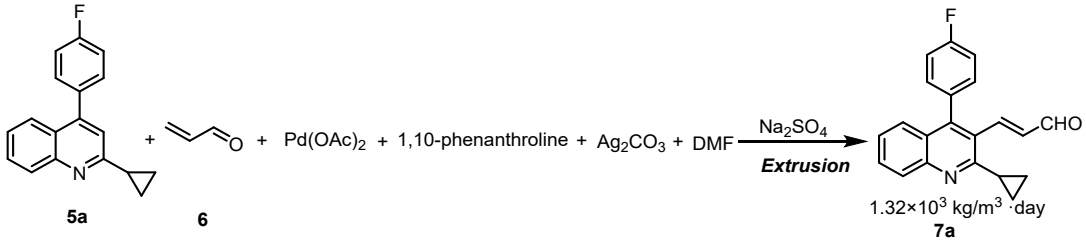
a) without grinding auxiliary

$$E-factor=\frac{(1800+1936+576-1100)\ mg}{1100\ mg}=2.92$$

b) with grinding auxiliary

$$E-factor=\frac{(1800+1936+576+14000-1100)\ mg}{1100\ mg}=15.65$$

Step 3



5a **6** **7a**

MW	263.32	56.03	224.51	180.21	275.75			317.36
n/mmol	36.00	64.00	3.60	4.68	36.00			
m/mg	7560	3586	808	842	9000	4356	20000	3760

a) without grinding auxiliary

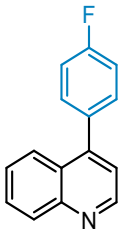
$$E-factor=\frac{(7560+3586+808+842+9000+4356-3760)\,mg}{3760\,mg}=5.96$$

b) with grinding auxiliary

$$E-factor=\frac{(7560+3586+808+842+9000+4356+20000-3760)\,mg}{3760\,mg}=11.27$$

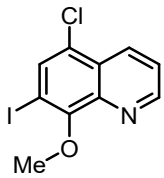
6. Characterization Data for Products

4-(4-fluorophenyl)quinoline (3a)[13]



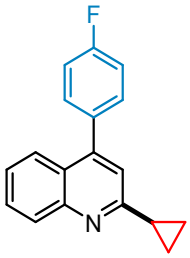
Yellow solid (Ni catalysis: 83 mg, 93% yield; Fe catalysis: 71 mg, 80% yield); mp 42.7~43.2 °C; **^{1}H NMR** (400 MHz, chloroform-*d*) δ 8.94 (d, *J* = 4.4 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.89 – 7.86 (m, 1H), 7.74 (m, 1H), 7.54 – 7.45 (m, 3H), 7.31 (d, *J* = 4.4 Hz, 1H), 7.25 – 7.20 (m, 2H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 162.9 (d, $J_{C\text{-}F}$ = 248.3 Hz), 149.8, 148.5, 147.7, 133.9 (d, $J_{C\text{-}F}$ = 3.3 Hz), 131.3 (d, $J_{C\text{-}F}$ = 8.2 Hz), 129.8, 129.6, 126.9, 126.8, 125.6, 115.7 (d, $J_{C\text{-}F}$ = 21.7 Hz). **^{19}F NMR** (377 MHz, chloroform-*d*) δ -113.13.

5-chloro-7-iodo-8-methoxyquinoline (3p)



Yellow solid (281 mg, 88 % yield); mp 76.9~77.5 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.02 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.54 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.13 (s, 1H), 7.76 (dd, *J* = 8.4, 4.0 Hz, 1H), 4.05 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 155.7, 151.1, 141.7, 134.6, 133.2, 126.7, 125.60, 123.2, 91.2, 61.8. **HR-MS** (ESI) *m/z:* calculated for $C_{10}H_8{}^{35}ClINO$ 319.9339 $[M+H]^+$, found 319.9334.

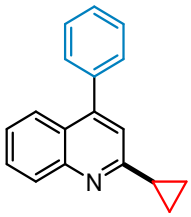
2-cyclopropyl-4-(4-fluorophenyl)quinoline (5a)



Yellow oil (34 mg, 64% yield); **^{1}H NMR** (400 MHz, chloroform-*d*) δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.61 (m, 1H), 7.51 – 7.43 (m, 2H), 7.44 – 7.35 (m, 2H), 7.26 – 7.17 (m, 2H), 2.33 – 2.22 (m, 1H), 1.25 – 1.16 (m, 2H), 1.11 (m, 2H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 162.9, 162.8 (d, $J_{C\text{-}F}$ = 246 Hz), 148.4, 147.3, 134.3 (d, $J_{C\text{-}F}$ = 3.3 Hz), 131.2 (d, $J_{C\text{-}F}$ = 8.1 Hz), 129.4, 129.0, 126.5 (2C), 125.5, 125.3, 119.7, 115.7 (2C), 18.0, 10.4 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{18}H_{14}N^{19}F$ 264.1189 $[M+H]^+$, found 264.1183. **^{19}F NMR**

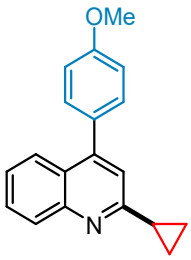
(377 MHz, chloroform-*d*) δ -113.53.

2-cyclopropyl-4-phenylquinoline (5b)



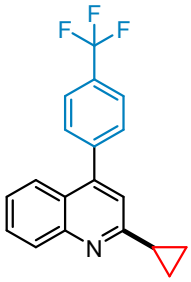
Yellow oil (24 mg, 48% yield); **^{1}H NMR** (400 MHz, chloroform-*d*) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.55 – 7.45 (m, 7H), 7.39 (m, *J* = 1H), 2.36 – 2.23 (m, 1H), 1.24 – 1.17 (m, 2H), 1.17 – 1.09 (m, 2H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 162.9, 148.4, 148.3, 138.4, 129.5, 129.3, 128.9 (2C), 128.5 (2C), 128.3, 125.7, 125.3 (2C), 119.5, 18.1, 10.3 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{18}H_{15}N$ 246.1283 $[M+H]^+$, found 246.1277.

2-cyclopropyl-4-(4-methoxyphenyl)quinoline (5c)



Yellow oil (28 mg, 50% yield), **^{1}H NMR** (400 MHz, chloroform-*d*) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.61 (m, 1H), 7.49 – 7.41 (m, 2H), 7.43 – 7.34 (m, 1H), 7.07 (d, *J* = 2.9 Hz, 2H), 7.04 (s, 1H), 3.90 (s, 3H), 2.30 (m, 1H), 1.19 (m, 2H), 1.12 (m, 2H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 162.9, 160, 130.8 (2C), 130.6, 129.3, 128.7 (2C), 125.7, 125.5, 125.3, 119.3 (2C), 114.0 (2C), 55.4, 17.9, 10.4 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{19}H_{17}NO$ 276.1388 $[M+H]^+$, found 276.1383.

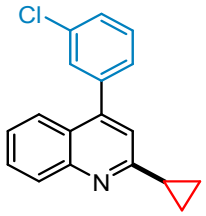
2-cyclopropyl-4-(4-(trifluoromethyl)phenyl)quinoline (5d)



Yellow oil (30 mg, 48% yield); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.43 – 7.37 (m, 1H), 7.12 (s, 1H), 2.34 – 2.22 (m, 1H), 1.25 – 1.18 (m, 2H), 1.16 – 1.08 (m, 2H). **^{13}C NMR** (150 MHz, Chloroform-*d*) δ 162.9, 148.5, 146.6, 142.1, 130.5 (q, $J_{C\text{-}F}$ = 30 Hz),

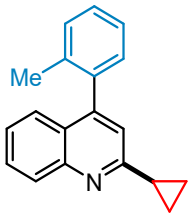
129.9 (2C), 129.4, 129.3, 125.6 (2C), 125.5 (d, $J_{C\text{-}F}$ = 8 Hz), 125.1, 124.9, 121.4 (d, $J_{C\text{-}F}$ = 270 Hz), 119.8, 18.1, 10.4 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{19}H_{14}{}^{19}F_3N$ 314.1157 $[M+H]^+$, found 314.1151. **^{19}F NMR** (377 MHz, chloroform-*d*) δ -62.54.

4-(3-chlorophenyl)-2-cyclopropylquinoline (5e)



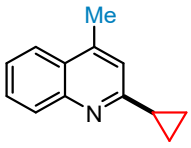
Yellow oil (28 mg, 50% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.66 (m, 1H), 7.68 – 7.63 (m, 1H), 7.49 (d, *J* = 1.9 Hz, 2H), 7.46 – 7.43 (m, 2H), 7.42 – 7.35 (m, 2H), 7.10 (s, 1H), 2.30 – 2.22 (m, 1H), 1.24 – 1.19 (m, 2H), 1.14 – 1.09 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 162.9, 148.4, 146.7, 140.2, 134.5, 129.8, 129.5 (2C), 129.1, 128.4, 127.8, 125.6, 125.2, 124.9, 119.7, 18.1, 10.4 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{18}H_{14}{}^{35}ClN$ 280.0893 $[M+H]^+$, found 280.0888.

2-cyclopropyl-4-(*o*-tolyl)quinoline (5f)



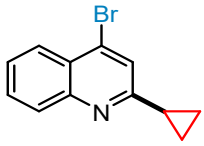
Yellow oil (26 mg, 51% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.60 (m, 1H), 7.39 – 7.31 (m, 5H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 2.04 (s, 3H), 2.33 – 2.26 (m, 1H), 1.24 – 1.18 (m, 2H), 1.16 – 1.10 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 163.0, 137.8, 136.1, 130.1, 129.6, 129.4 (2C), 128.7 (2C), 128.3, 125.9, 125.8 (2C), 125.4, 119.5, 19.9, 18.0, 10.5 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{19}H_{17}N$ 260.1439 $[M+H]^+$, found 260.1433.

2-cyclopropyl-4-methylquinoline (5g)



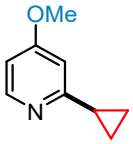
Yellow oil (17 mg, 47% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.68 – 7.59 (m, 1H), 7.48 – 7.42 (m, 1H), 6.99 (s, 1H), 2.64 (s, 3H), 2.24 – 2.16 (m, 1H), 1.17 – 1.11 (m, 2H), 1.12 – 1.02 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 163.02, 147.81, 143.80, 129.08 (2C), 126.84, 124.96, 123.58, 119.86, 18.70, 17.95, 9.95 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{13}H_{13}N$ 184.1126 $[M+H]^+$, found 184.1121.

4-bromo-2-cyclopropylquinoline (5h)



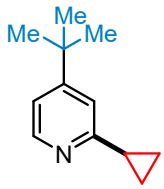
Yellow oil (18 mg, 36% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.55 – 7.47 (m, 2H), 2.22 – 2.14 (m, 1H), 1.22 – 1.13 (m, 2H), 1.13 – 1.08 (m, 2H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 163.5, 148.5, 133.8, 130.3, 129.0, 126.6, 126.4, 126.2, 123.5, 17.8, 10.6 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{12}H_{10}{}^{79}BrN$ 248.0075 $[M+H]^+$, found 248.0069.

2-cyclopropyl-4-methoxypyridine (5i)



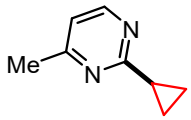
Yellow oil (8 mg, 28% yield); **^{1}H NMR** (400 MHz, chloroform-*d*) δ 8.25 (d, *J* = 6 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.58 (dd, *J* = 6, 2.4 Hz, 1H), 3.82 (s, 3H), 2.03 – 1.93 (m, 1H), 1.05 – 0.96 (m, 2H), 0.98 – 0.92 (m, 2H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 165.79, 164.55, 150.31, 106.93 (2C), 54.97, 17.28, 9.55 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{19}H_{11}NO$, 150.0919 $[M+H]^+$, found 150.0913.

4-(*tert*-butyl)-2-cyclopropylpyridine (5j)



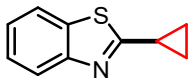
Yellow oil (18 mg, 53% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.33 (d, *J* = 5.2 Hz, 1H), 7.13 (d, *J* = 1.2 Hz, 1H), 7.02 (dd, *J* = 5.6, 2 Hz, 1H), 2.06 – 1.95 (m, 2H), 1.30 (s, 10H), 1.05 – 0.99 (m, 2H), 0.99 – 0.93 (m, 2H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 162.4, 159.8, 149.0, 118.0 (2C), 34.5, 30.5, 17.2, 9.6(2C). **HR-MS** (ESI) *m/z:* calculated for $C_{12}H_{17}N$ 176.1439 $[M+H]^+$, found 176.1434.

2-cyclopropyl-4-methylpyrimidine (5k)



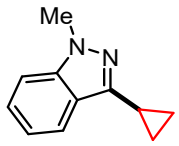
Yellow oil (9 mg, 33% yield); **^{1}H NMR** (400 MHz, chloroform-*d*) δ 8.81 (s, 1H), 6.98 (s, 1H), 1.92 – 1.82 (m, 1H), 1.10 – 1.06 (m, 2H), 1.06 – 0.97 (m, 2H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 171.49, 165.53, 158.23, 118.37, 23.85, 16.69, 10.90 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_8H_{10}N_2$ 135.0922 $[M+H]^+$, found 135.0917.

2-cyclopropylbenzo[*d*]thiazole (5i)



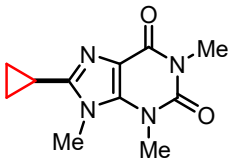
Yellow oil (15 mg, 42% yield); **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.37 (m, 1H), 7.35 – 7.26 (m, 1H), 2.44 – 2.35 (m, 1H), 1.23 (m, 4H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 174.6, 153.2, 134.1, 125.9, 124.4, 122.0, 121.4, 15.3, 11.8 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{10}H_9NS$ 176.0534 $[M+H]^+$, found 176.0529.

3-cyclopropyl-1-methyl-1*H*-indazole (5m)



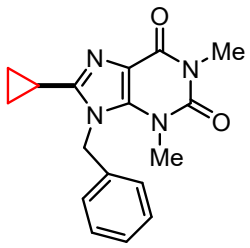
Yellow oil (12 mg, 36% yield); **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.39 – 7.29 (m, 3H), 7.13 – 7.07 (m, 2H), 3.97 (s, 3H), 2.27 – 2.16 (m, 1H), 1.07 – 1.03 (m, 4H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 146.5, 141.0, 126.2, 122.8, 120.4, 119.5, 108.9, 35.1, 8.1, 7.0 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{11}H_{12}N_2$ 173.1079 $[M+H]^+$, found 173.1073.

8-cyclopropyl-1,3,9-trimethyl-3,9-dihydro-1*H*-purine-2,6-dione (5n)



Yellow oil (21 mg, 45% yield); **^{1}H NMR** (400 MHz, chloroform-*d*) δ 3.99 (s, 3H), 3.50 (s, 3H), 3.38 (s, 3H), 1.92 – 1.79 (m, 1H), 1.14 – 1.07 (m, 4H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 155.7, 155.0, 151.8, 147.9, 107.3, 31.5, 29.7, 27.8, 8.4, 7.2 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{11}H_{14}N_4O_2$ 235.1195 $[M+H]^+$, found 235.1190.

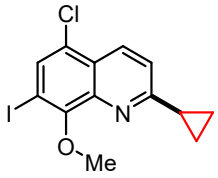
9-benzyl-8-cyclopropyl-1,3-dimethyl-3,9-dihydro-1*H*-purine-2,6-dione(5o)



Yellow oil (27 mg, 43% yield); **^{1}H NMR** (400 MHz, chloroform-*d*) δ 7.37 – 7.27 (m, 5H), 7.27 – 7.20 (m, 3H), 3.52 (s, 3H), 3.38 (s, 3H), 1.90 – 1.79 (m, 1H), 1.15 – 1.08 (m, 2H), 1.07 – 0.99 (m, 2H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 156.0, 154.8, 151.8, 148.2, 136.3, 128.9 (2C), 127.9 (3C), 127.0, 47.9, 29.7, 27.9, 8.8, 7.8 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{17}H_{18}N_4O_2$

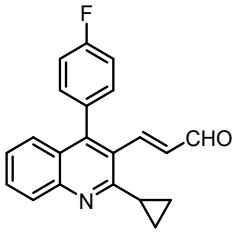
311.1508 $[M+H]^+$, found 311.1503.

5-chloro-2-cyclopropyl-7-iodo-8-methoxyquinoline (5p)



Yellow oil (27 mg, 38% yield); **^{1}H NMR** (600 MHz, chloroform-*d*) δ 8.32 (d, *J* = 8.7 Hz, 1H), 7.81 (s, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 4.15 (s, 3H), 2.30 – 2.22 (m, 1H), 1.30 – 1.21 (m, 2H), 1.17 – 1.09 (m, 2H). **^{13}C NMR** (150 MHz, chloroform-*d*) δ 164.3, 155.1, 133.5, 133.3, 126.4, 125.9, 121.5, 89.8, 62.1, 17.9, 11.6 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{13}H_{11}{}^{35}ClINO$ 359.9652 $[M+H]^+$, found 359.9647.

3-[2-Cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-2-propenal (7a)



Yellow solid (38 mg, 43% yield); mp 132.8~133.7 °C; **^{1}H NMR** (400 MHz, chloroform-*d*) δ 9.51 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.66 (s, 1H), 7.56 (d, *J* = 16.4 Hz, 1H), 7.42 – 7.29 (m, 2H), 7.29 – 7.16 (m, 4H), 6.45 (dd, *J* = 16.4, 7.6 Hz, 1H), 2.35 (s, 1H), 1.43 (m, 2H), 1.10 (m, 2H). **^{13}C NMR** (100 MHz, chloroform-*d*) δ 193.4, 162.6 (d, $J_{C\text{-}F}$ = 148 Hz), 159.4, 149.9, 147.5, 146.4, 135.6, 131.9 (d, $J_{C\text{-}F}$ = 4 Hz), 131.5 (2C), 130.2, 129.0, 126.4 (2C), 126.1, 126.0 (d, $J_{C\text{-}F}$ = 68 Hz) 115.6 (2C), 16.5, 10.6 (2C). **HR-MS** (ESI) *m/z:* calculated for $C_{21}H_{16}{}^{19}FNO$ 318.1294 $[M+H]^+$, found 318.1289. **^{19}F NMR** (377 MHz, chloroform-*d*) δ -113.53.

7. References

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8. Spectra for All Compounds

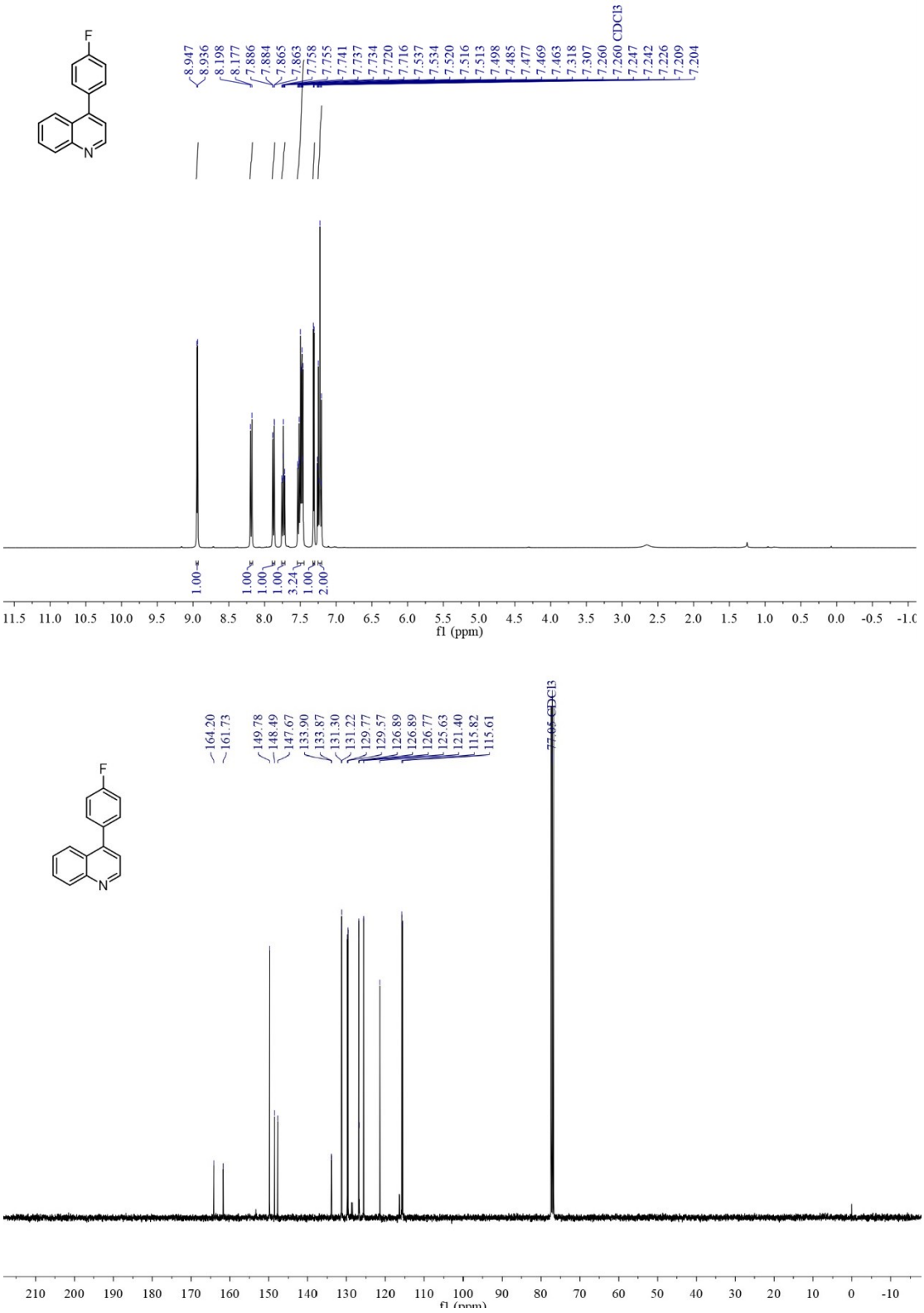

Figure S6. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **3a**

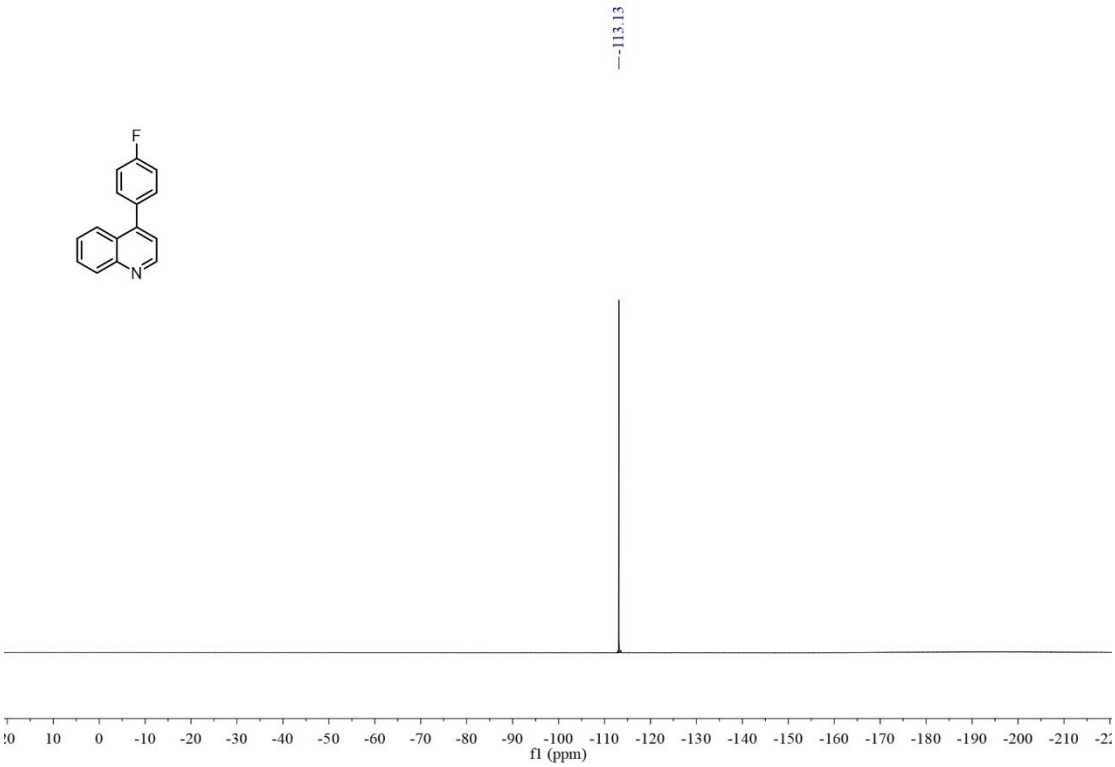

Figure S7. ^{19}F (377 MHz, $CDCl_3$) NMR spectra of compound **3a**

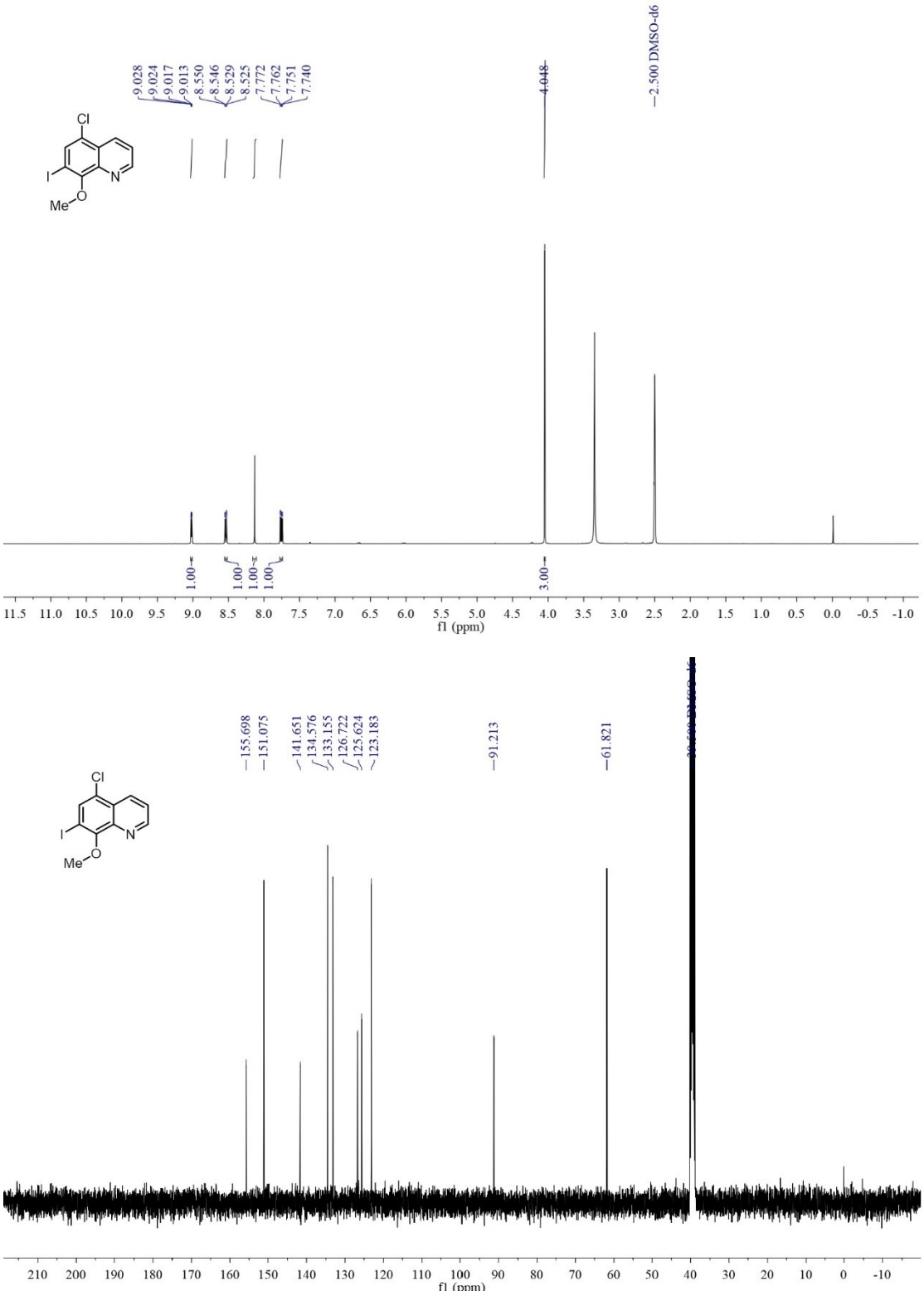

Figure S8. ^{1}H (400 MHz, DMSO-d_6) and ^{13}C (100 MHz) NMR spectra of compound **3a**

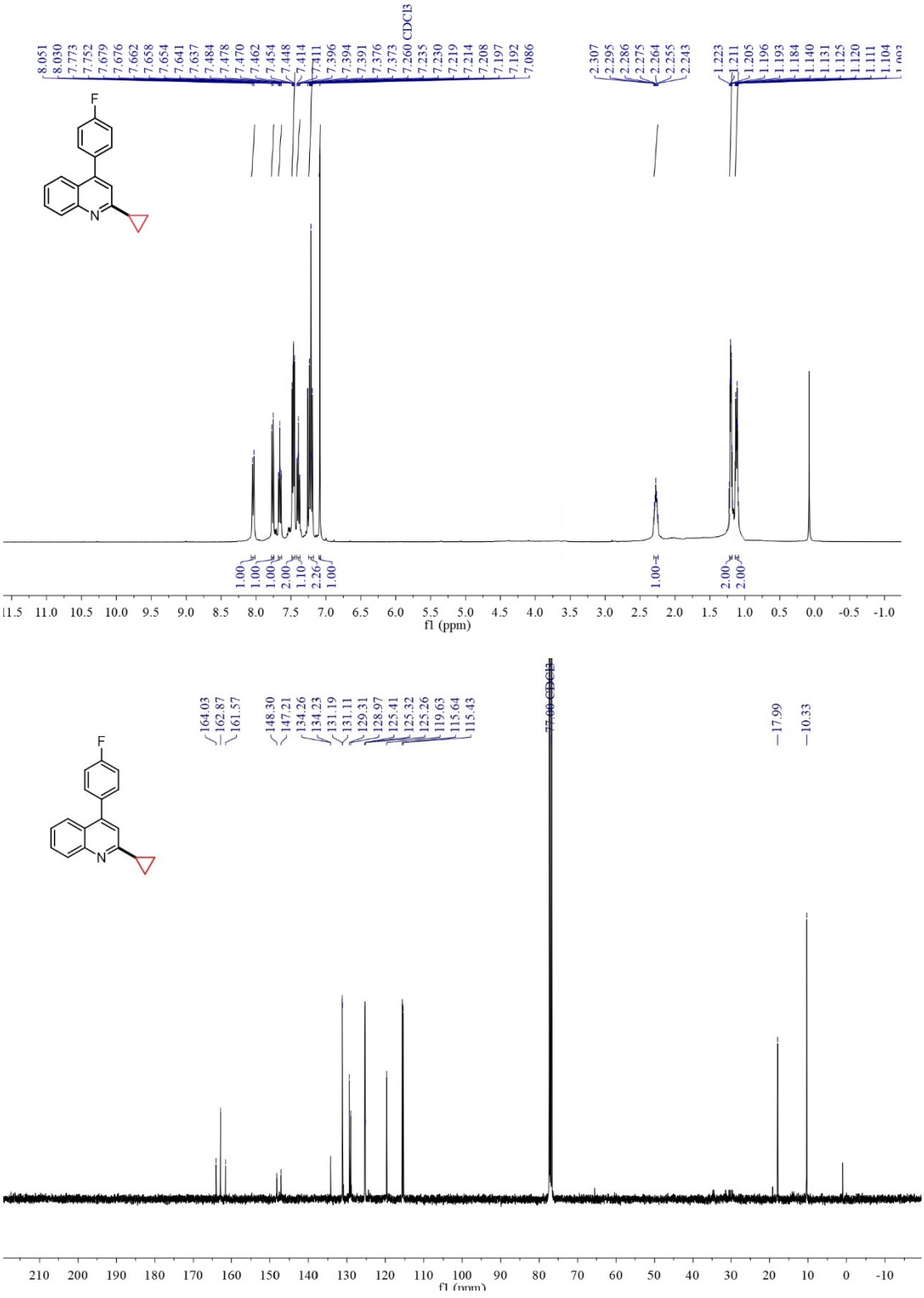

Figure S9. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5a**

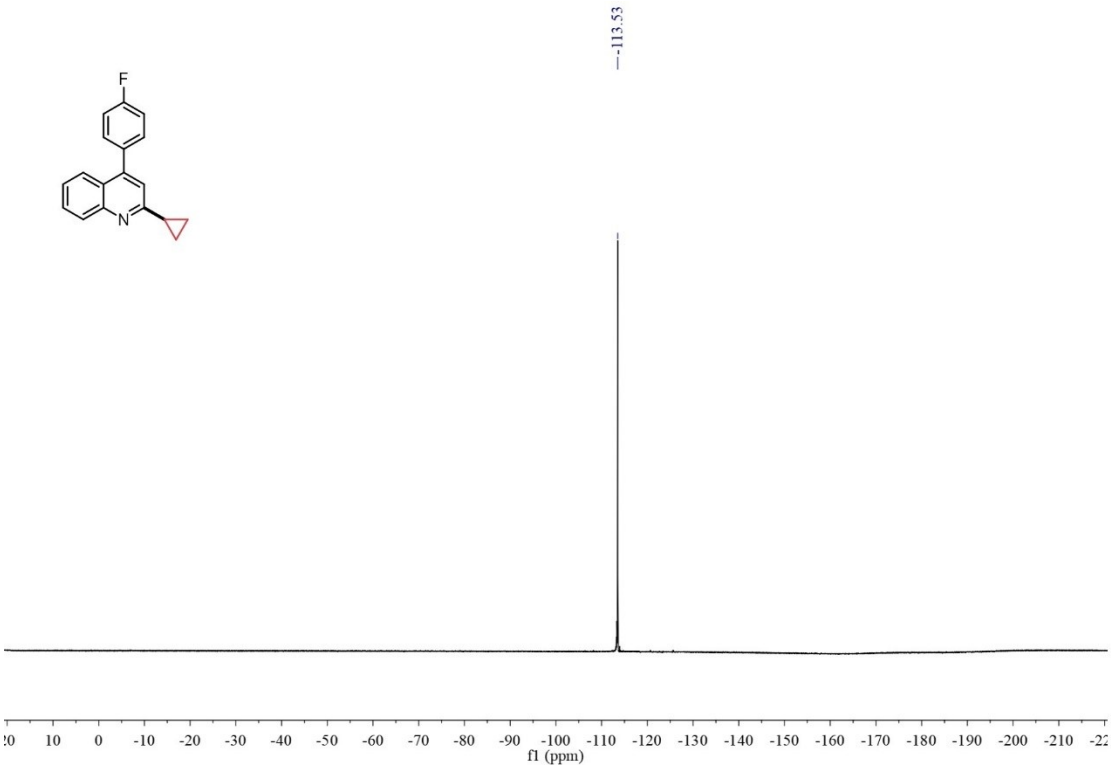

Figure S10. ^{19}F (377 MHz, $CDCl_3$) NMR spectra of compound **5a**

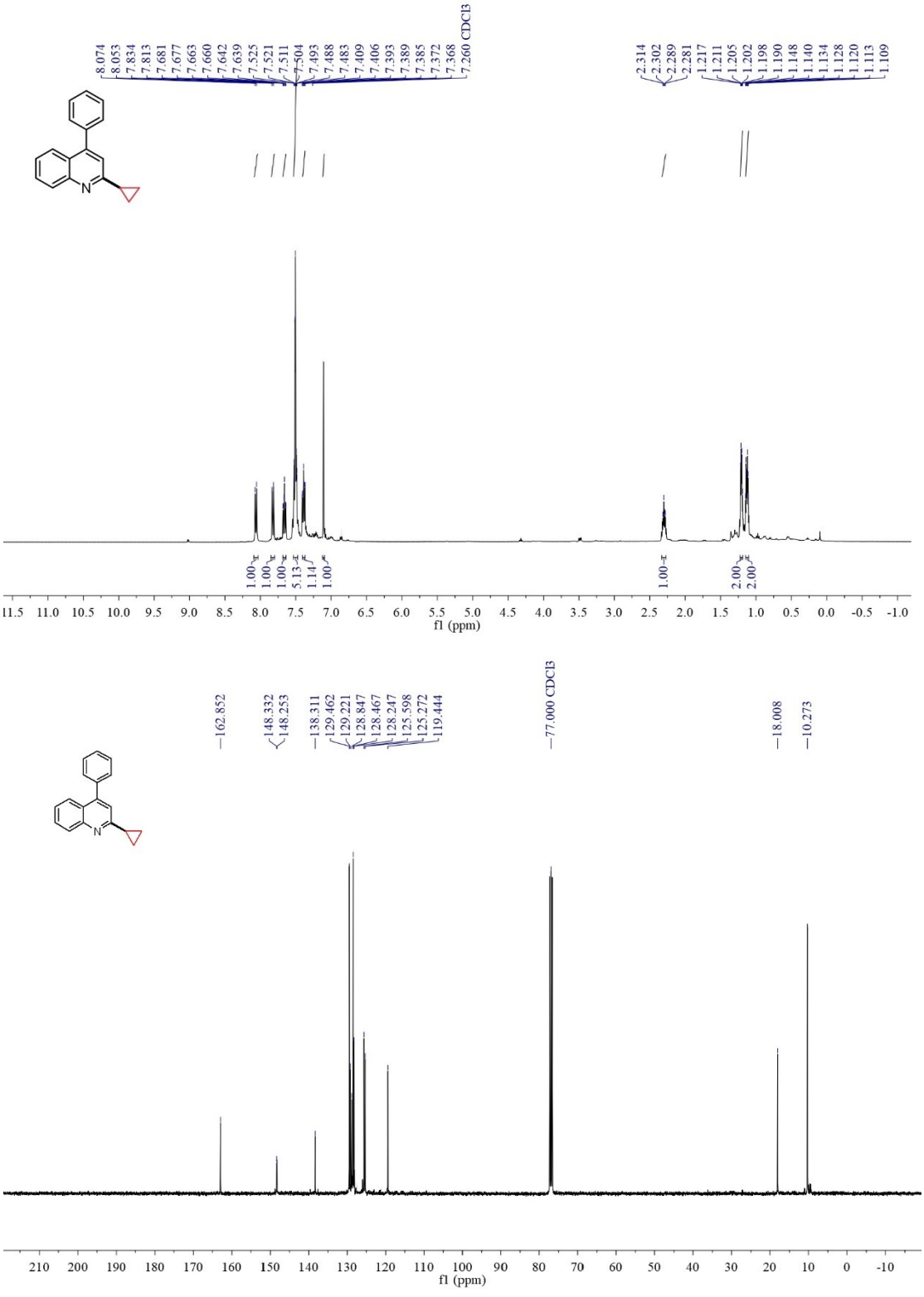

Figure S11. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5b**

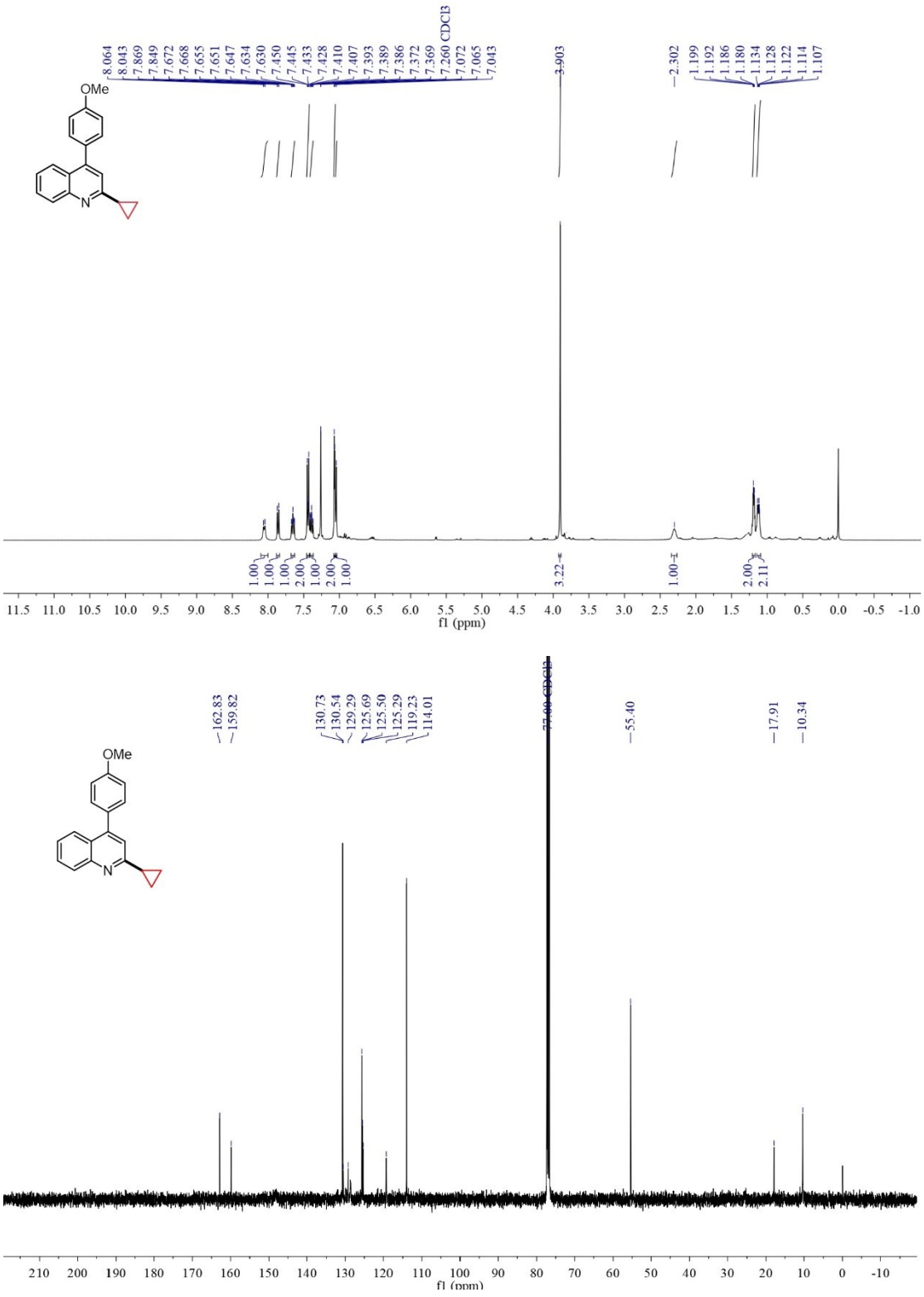

Figure S12. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5c**

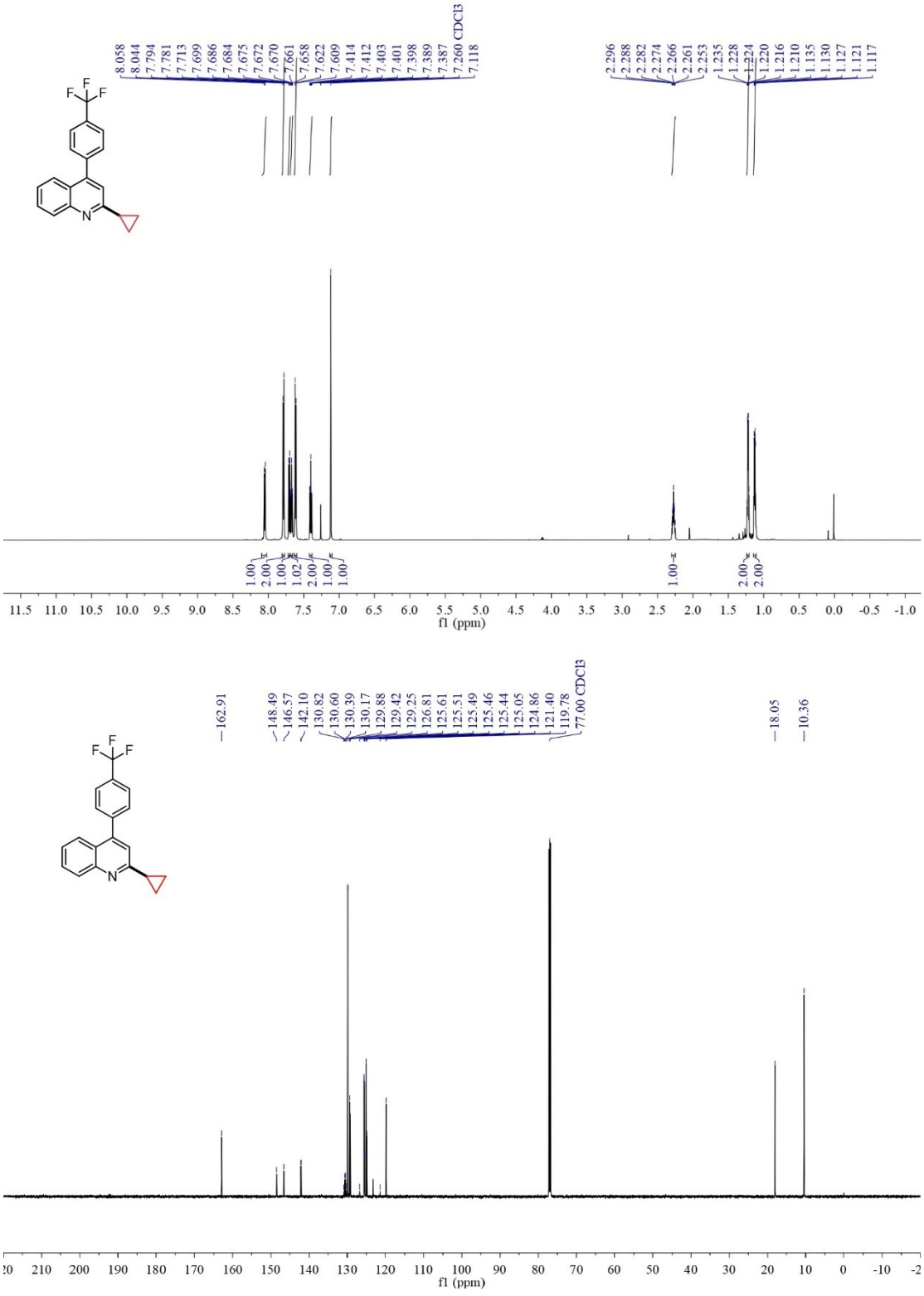

Figure S13. ^{1}H (600 MHz, $CDCl_3$) and ^{13}C (150 MHz) NMR spectra of compound **5d**

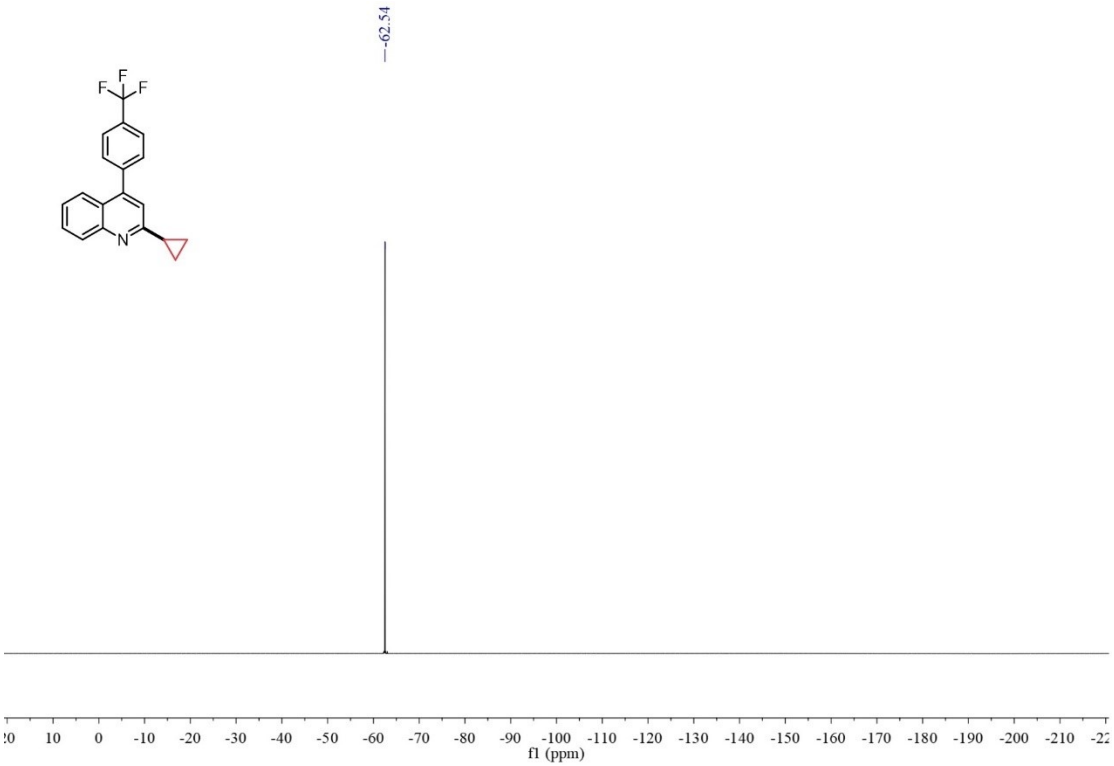

Figure S14. ^{19}F (377 MHz, $CDCl_3$) NMR spectra of compound **5d**

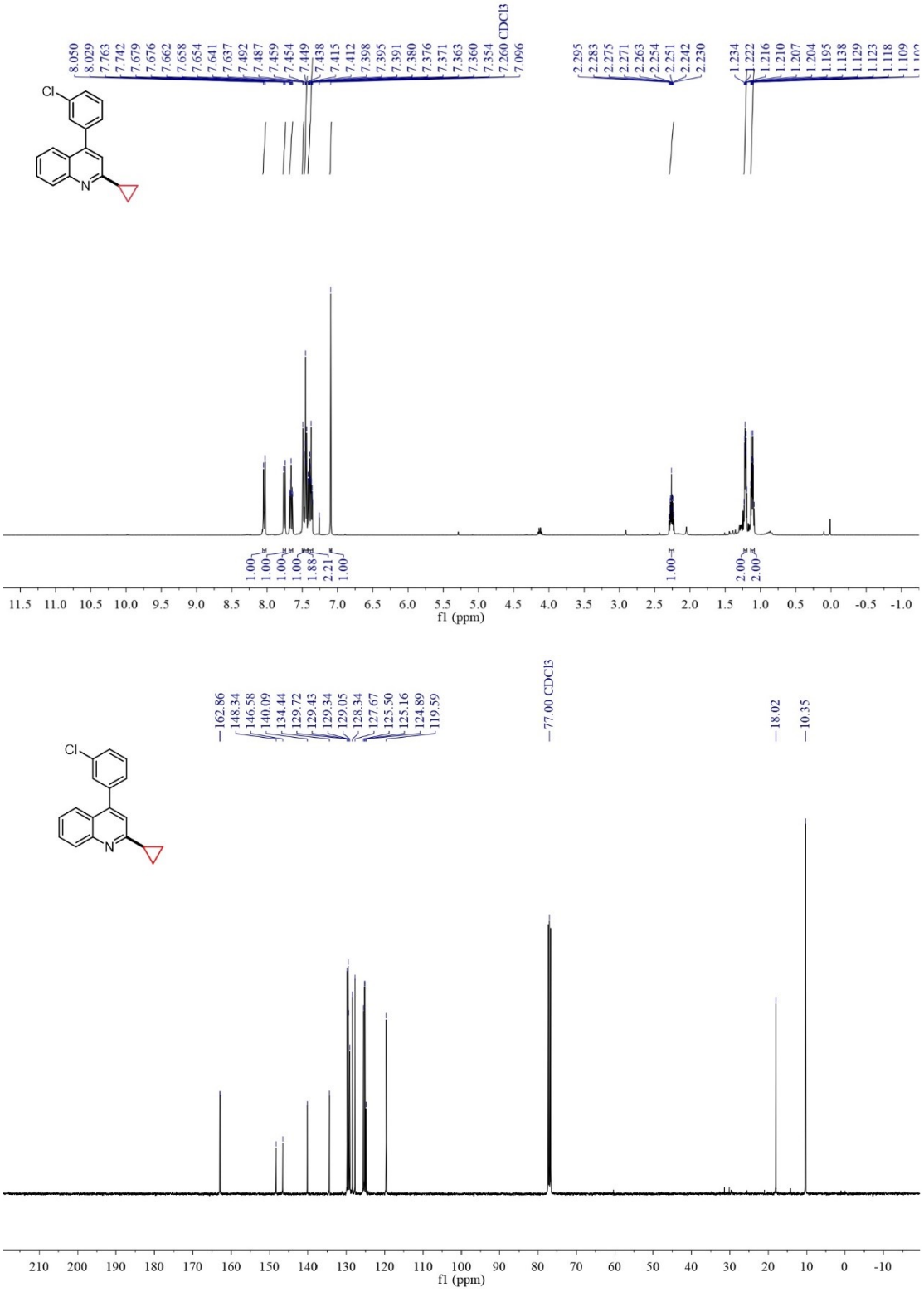

Figure S15. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5e**

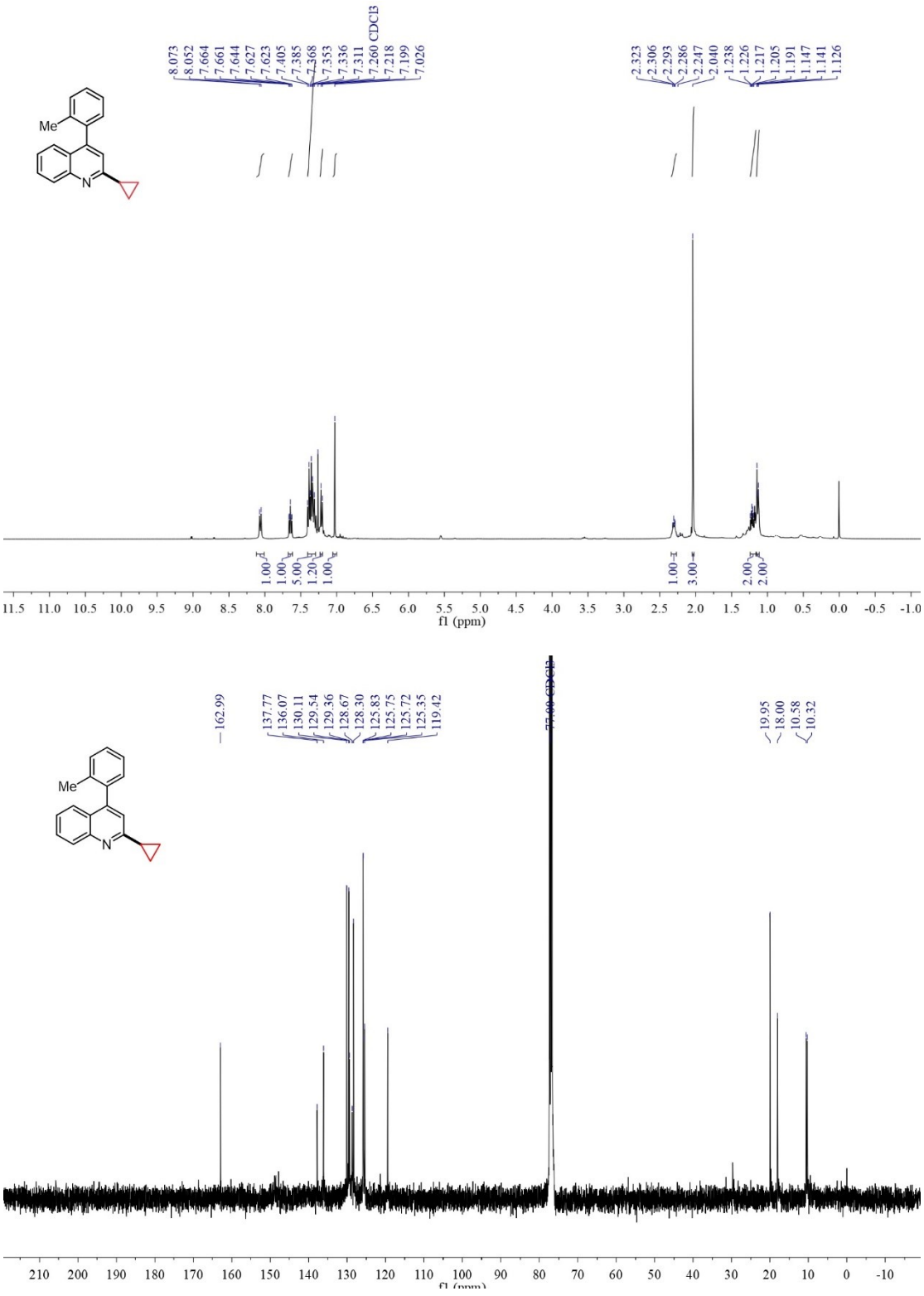

Figure S16. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5f**

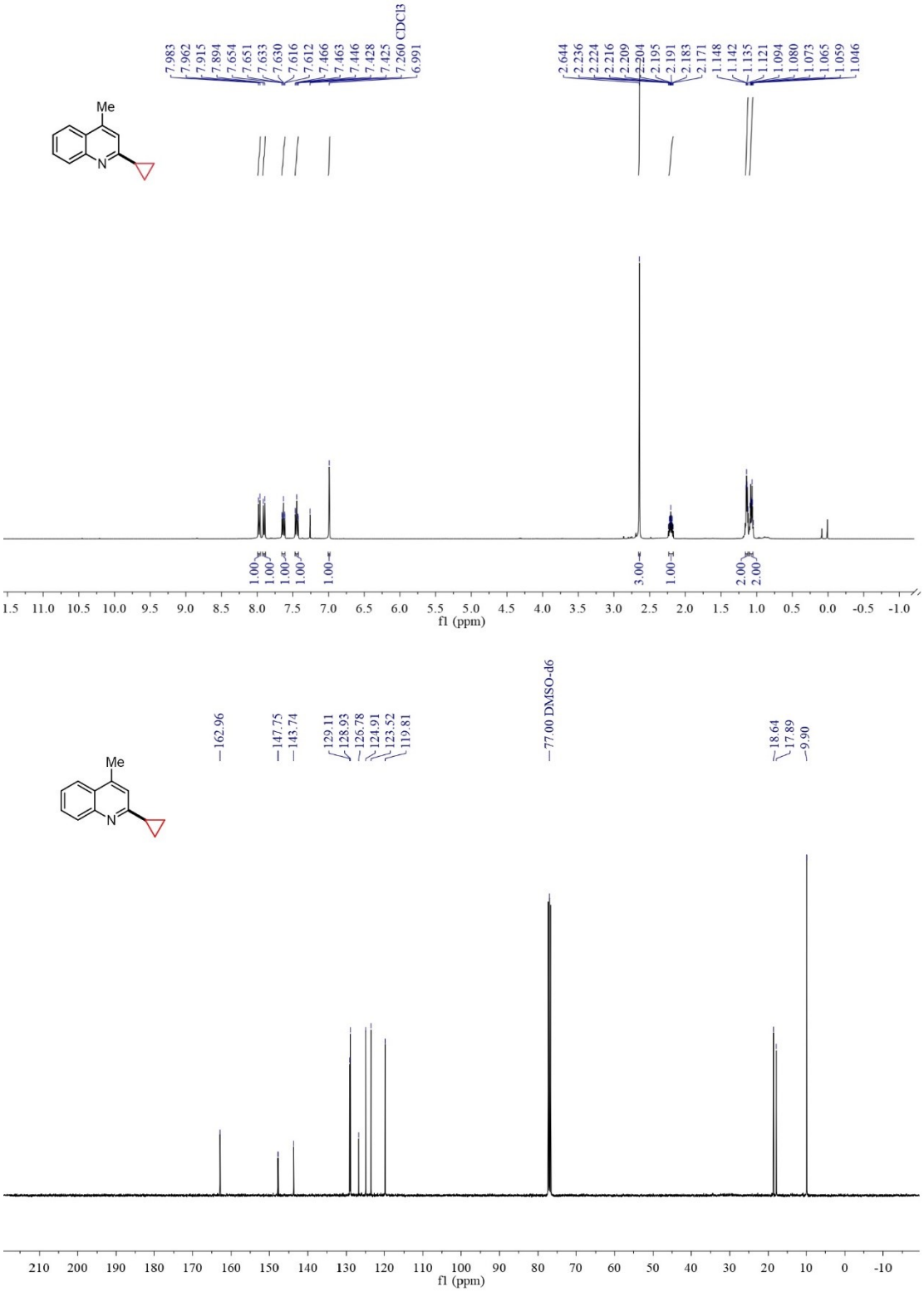

Figure S17. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5g**

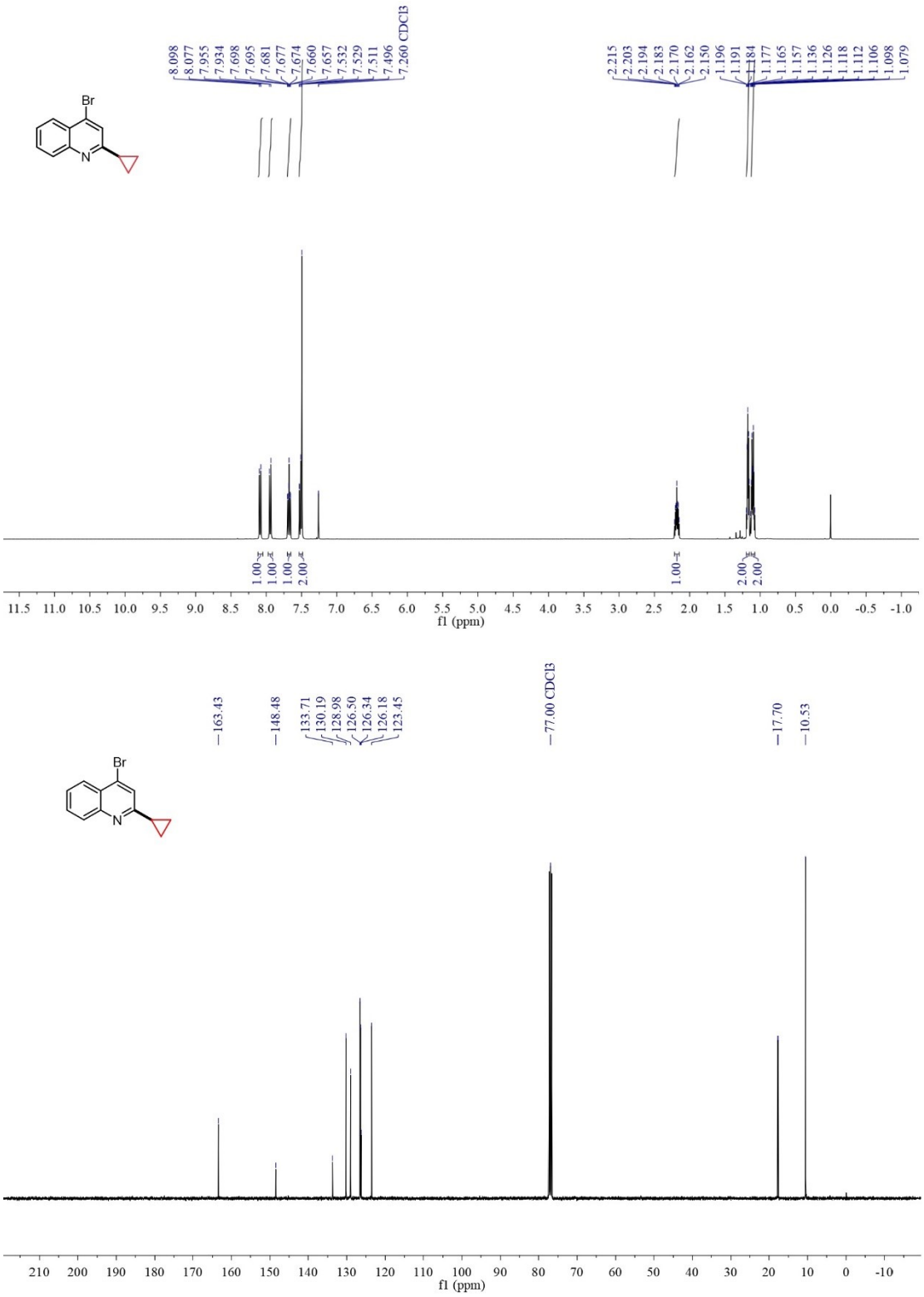

Figure S18. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5h**

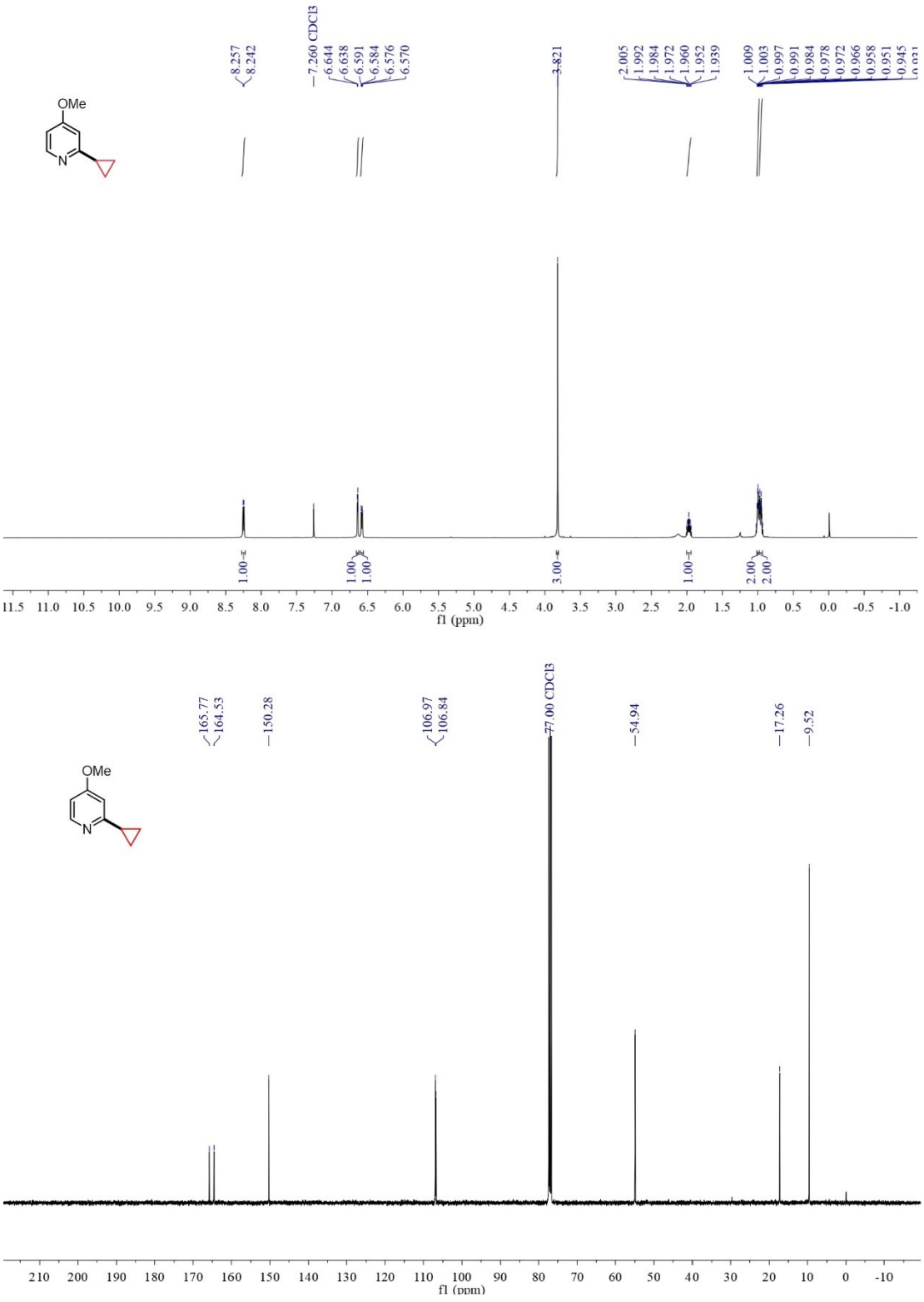

Figure S19. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5i**

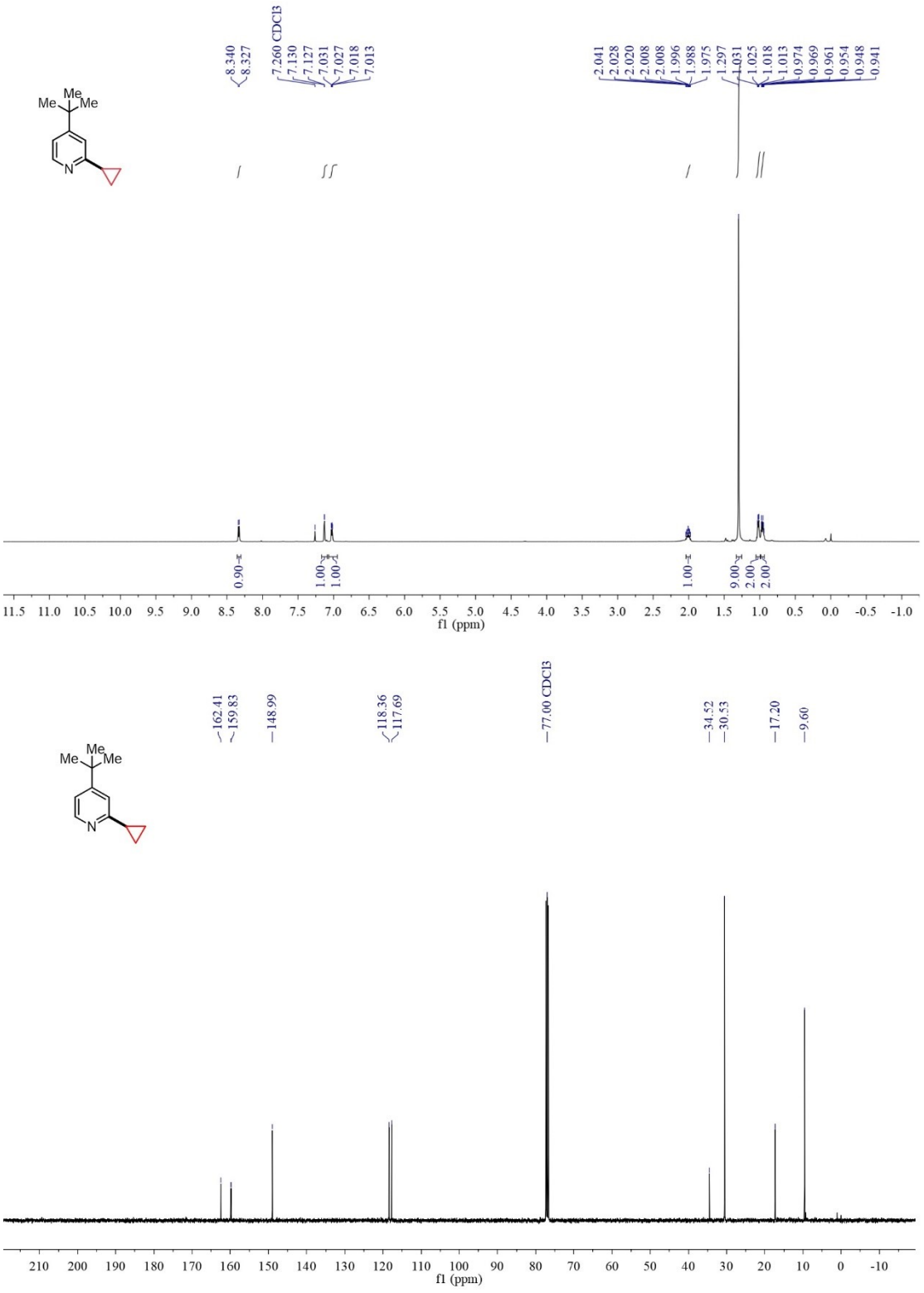

Figure S20. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5j**

Figure S21. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5k**

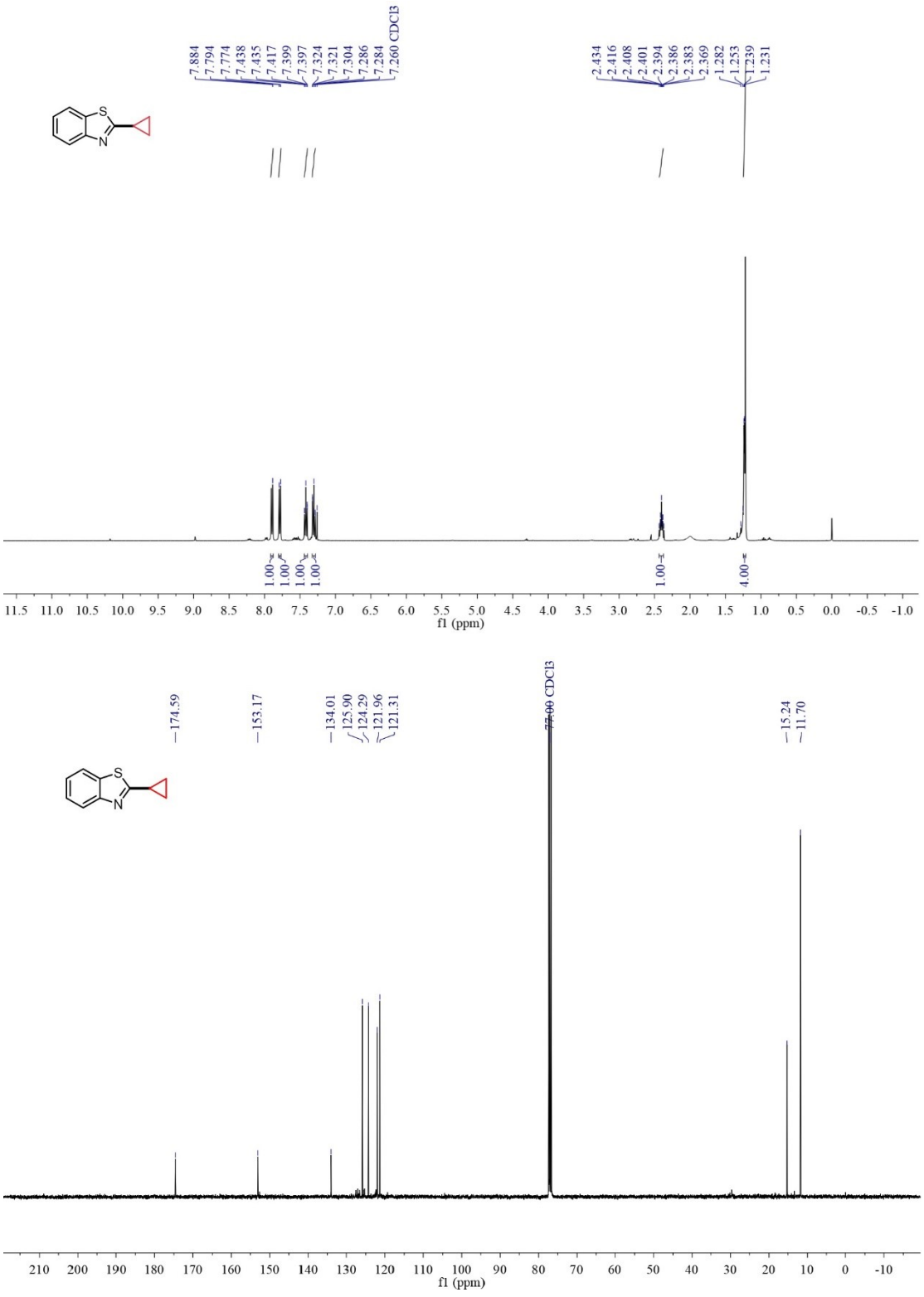

Figure S22. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5l**

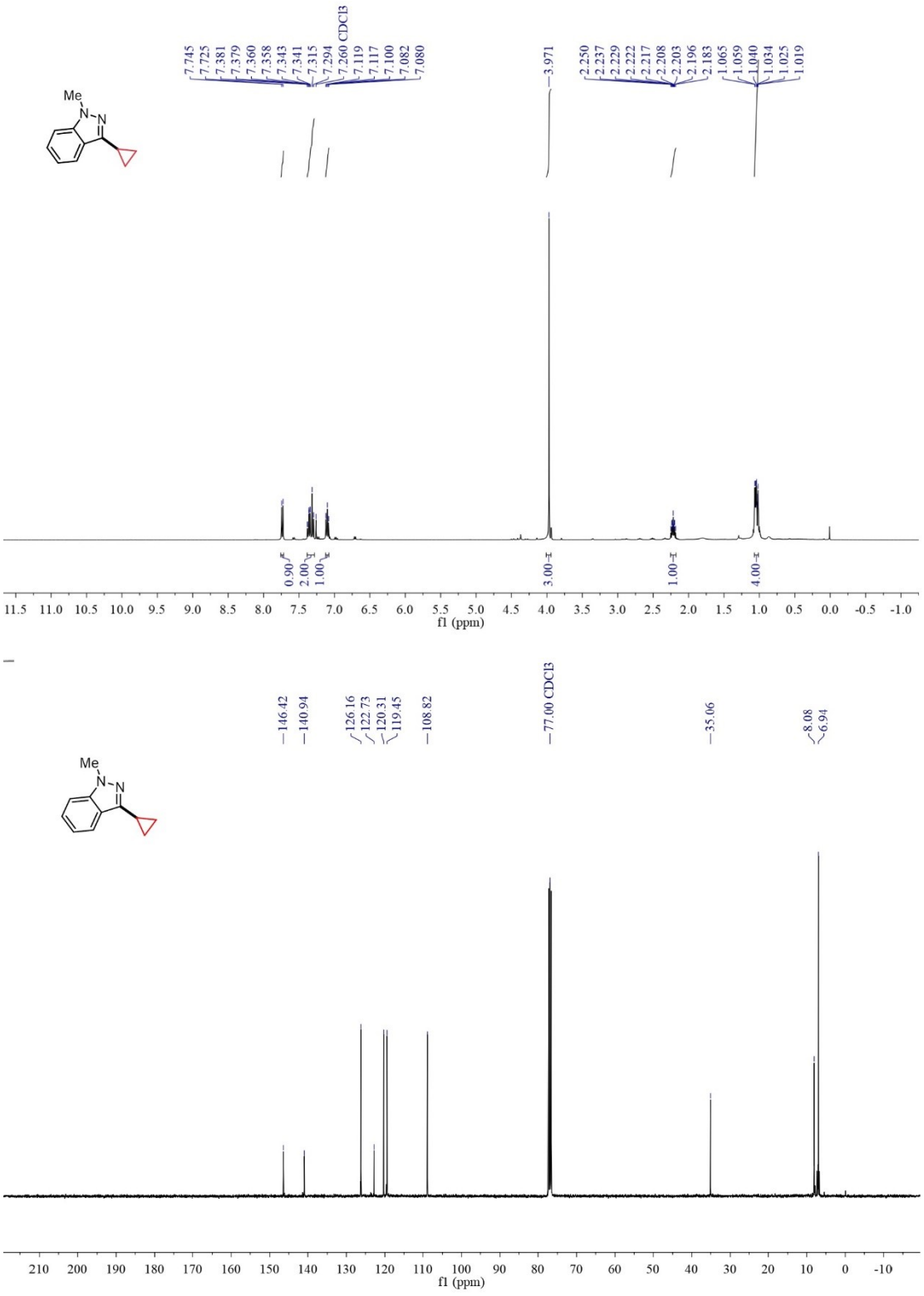

Figure S23. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5m**

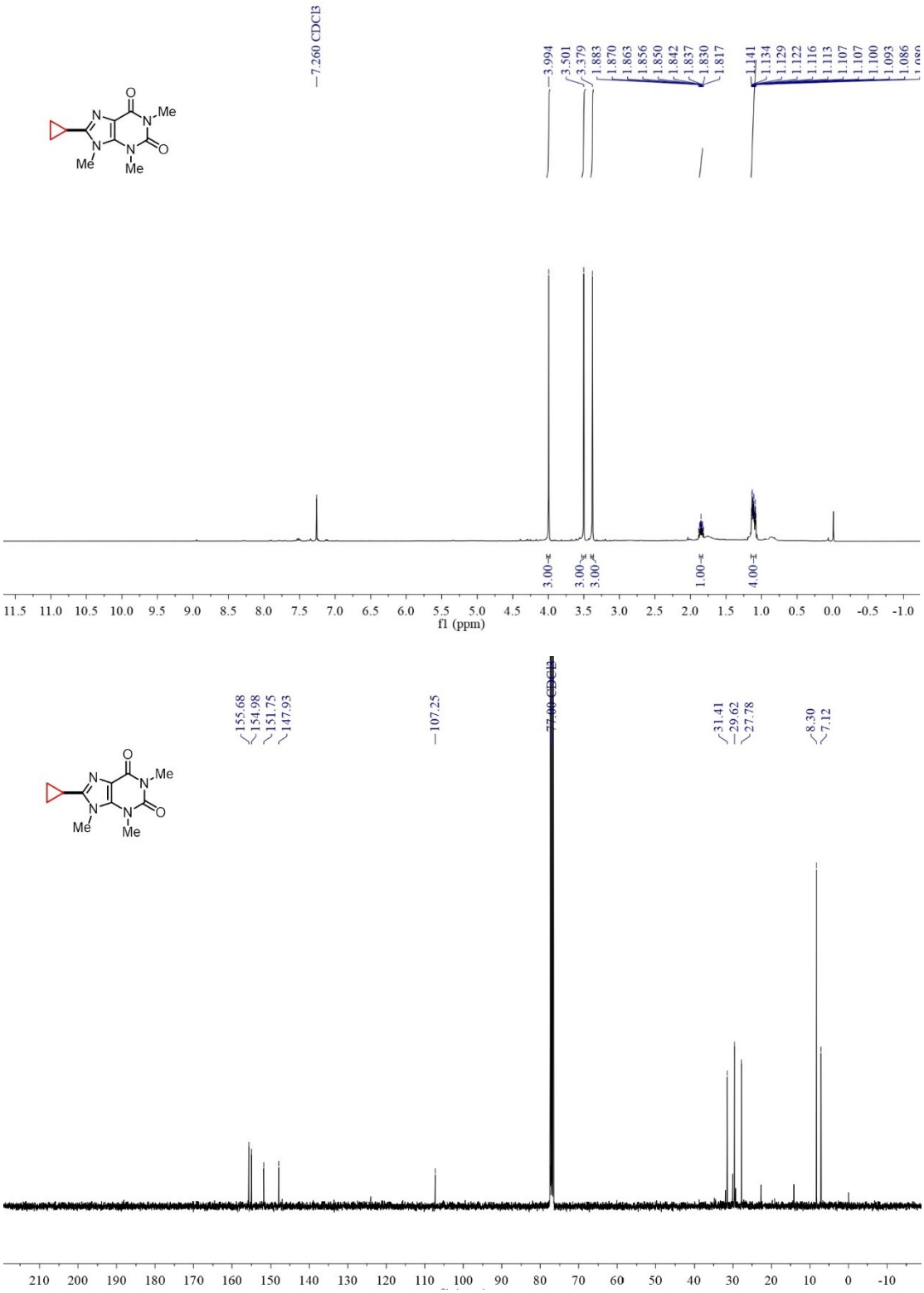

Figure S24. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5n**

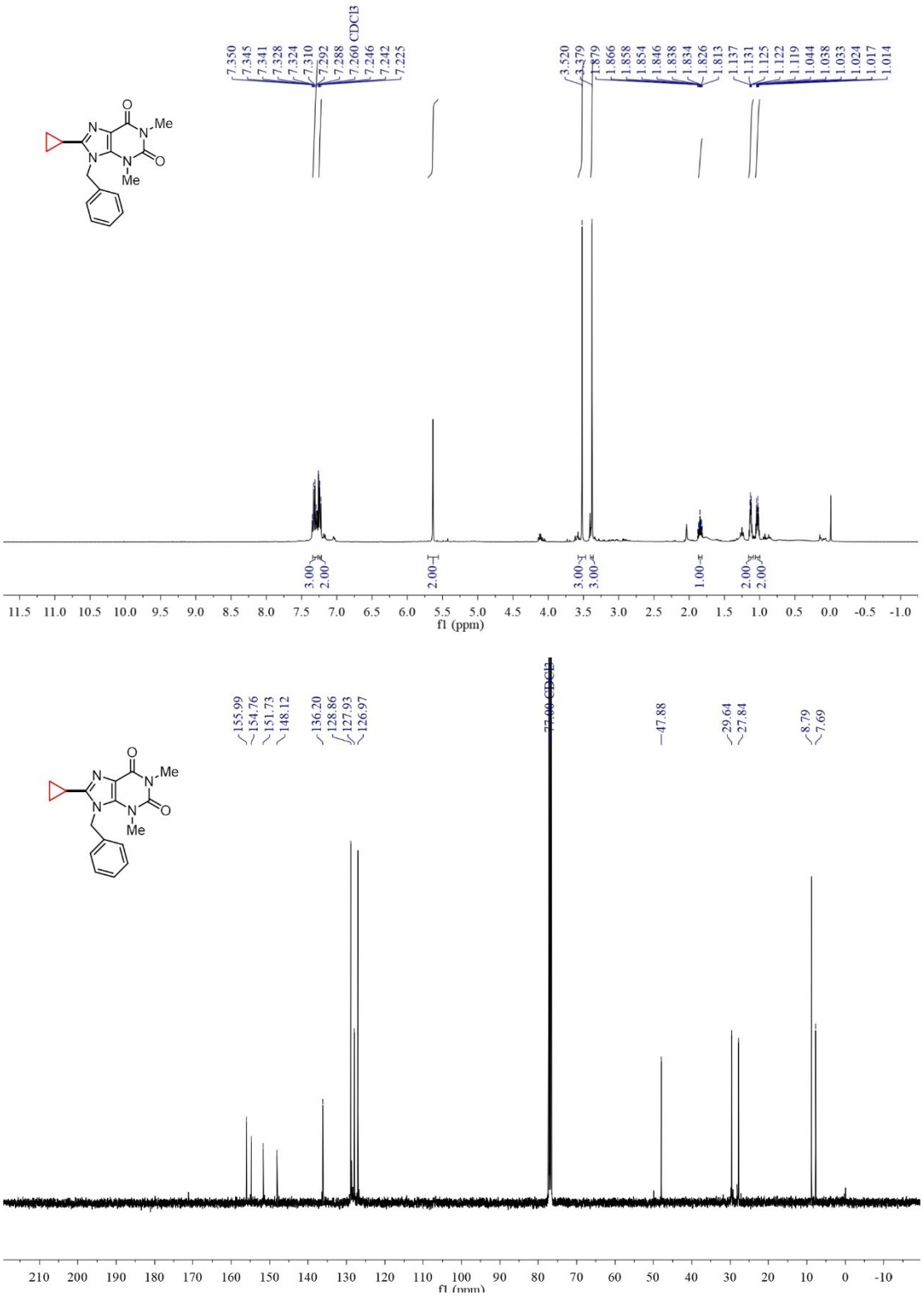

Figure S25. ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100 MHz) NMR spectra of compound **5o**

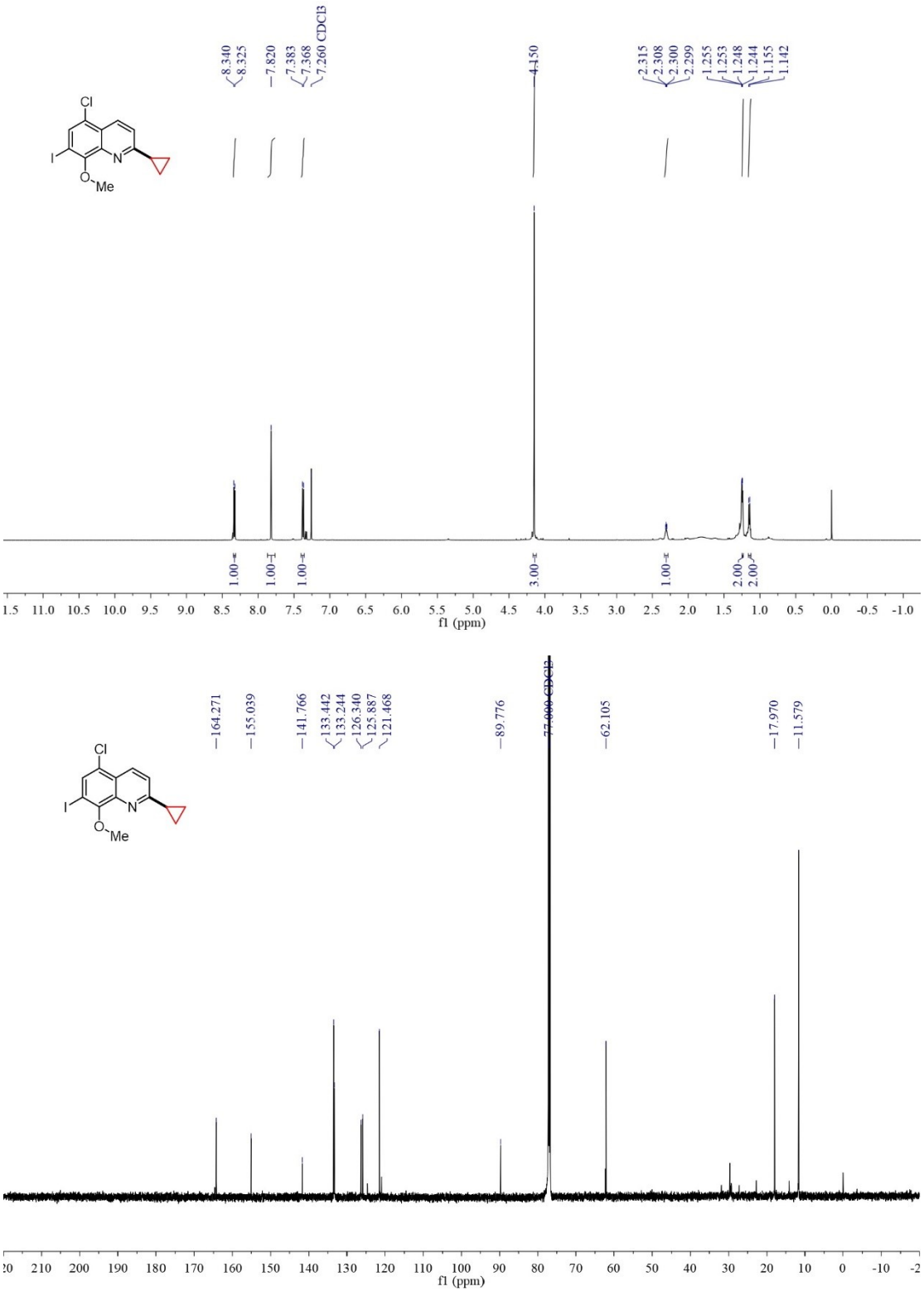

Figure S26. ^{1}H (600 MHz, $CDCl_3$) and ^{13}C (150 MHz) NMR spectra of compound **5p**

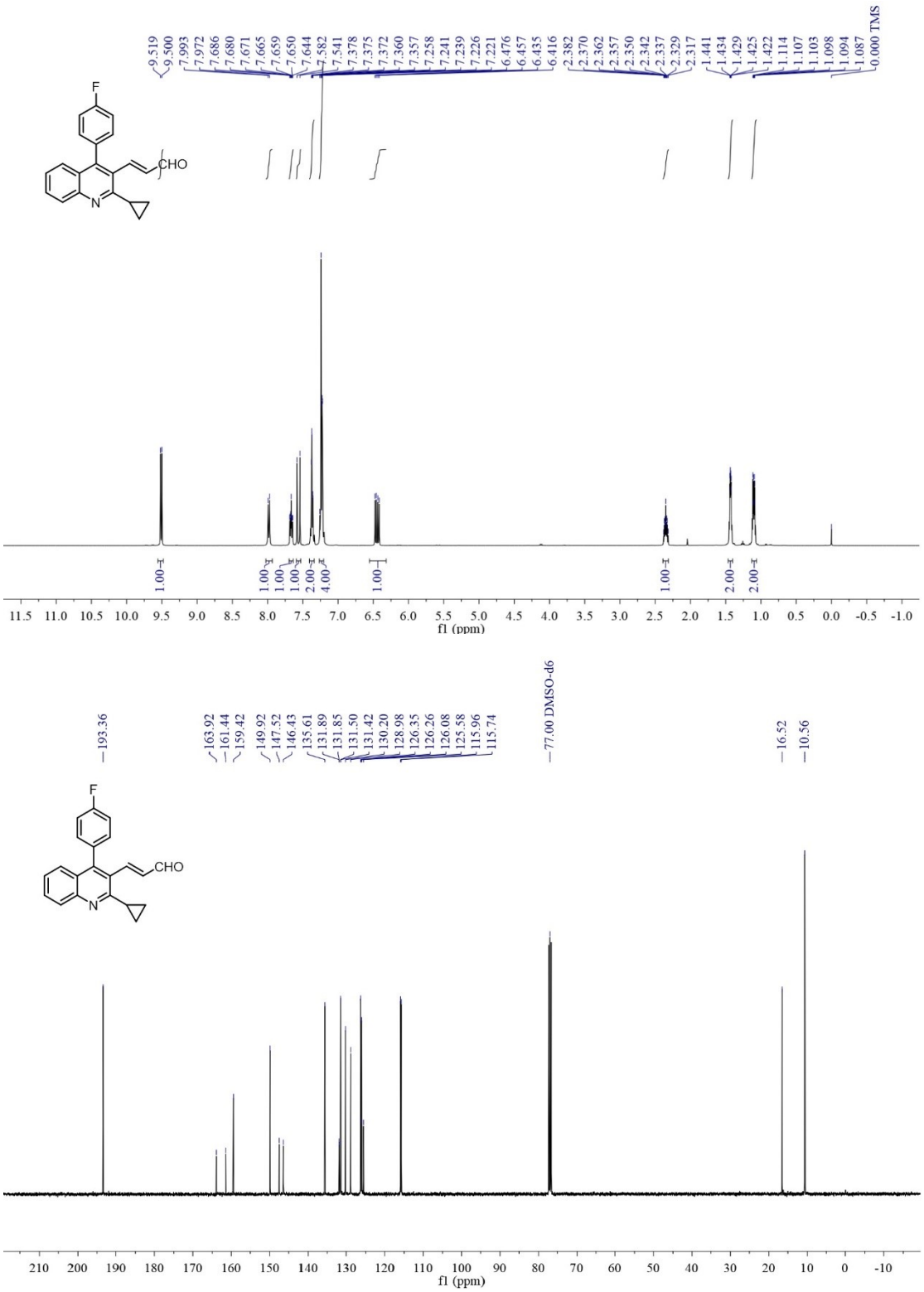

Figure S27. ^{1}H (600 MHz, $CDCl_3$) and ^{13}C (150 MHz) NMR spectra of compound **7a**

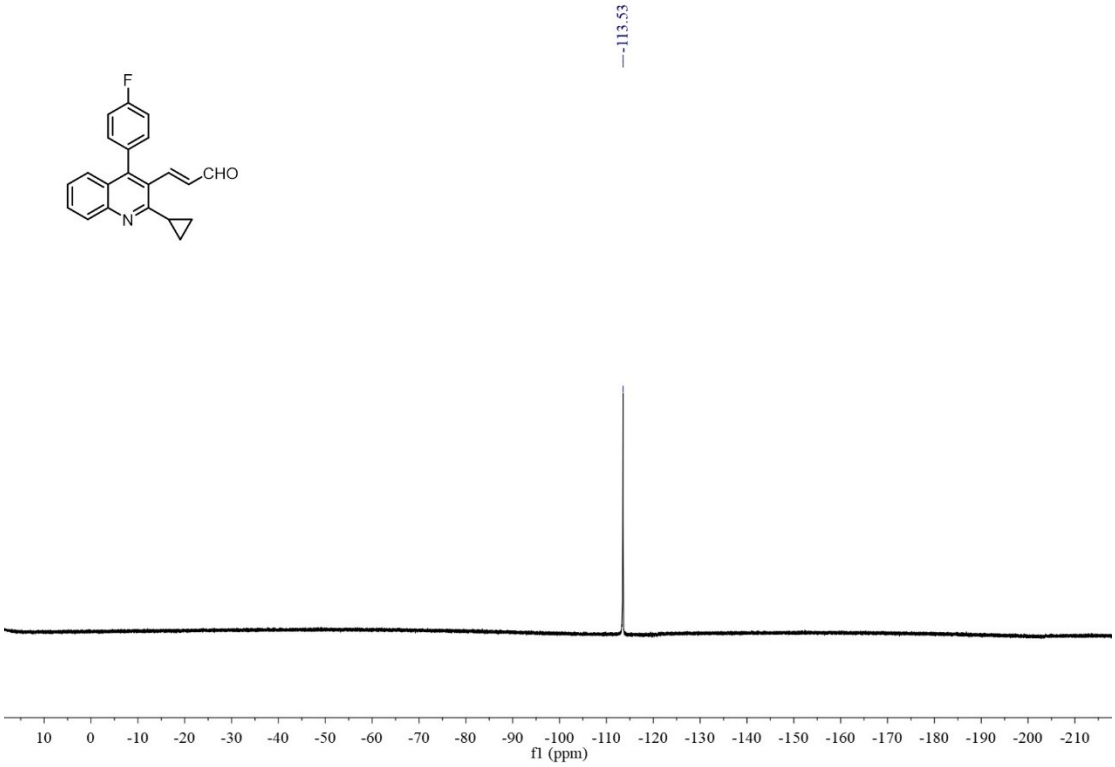

Figure S28. ^{19}F (377 MHz, $CDCl_3$) NMR spectra of compound **7a**