Supporting Information

Total Synthesis of (+)-Spiroindimicin A via Asymmetric Palladium-Catalyzed Spirocyclization

Zhen Zhang, Sneha Ray, Leah Imlay, Lauren T. Callaghan, Hanspeter Niederstrasser, Prema Latha Mallipeddi, Bruce A. Posner, Dawn M. Wetzel, Margaret A. Phillips, Myles W. Smith*

Department of Biochemistry and Department of Pediatrics, UT Southwestern

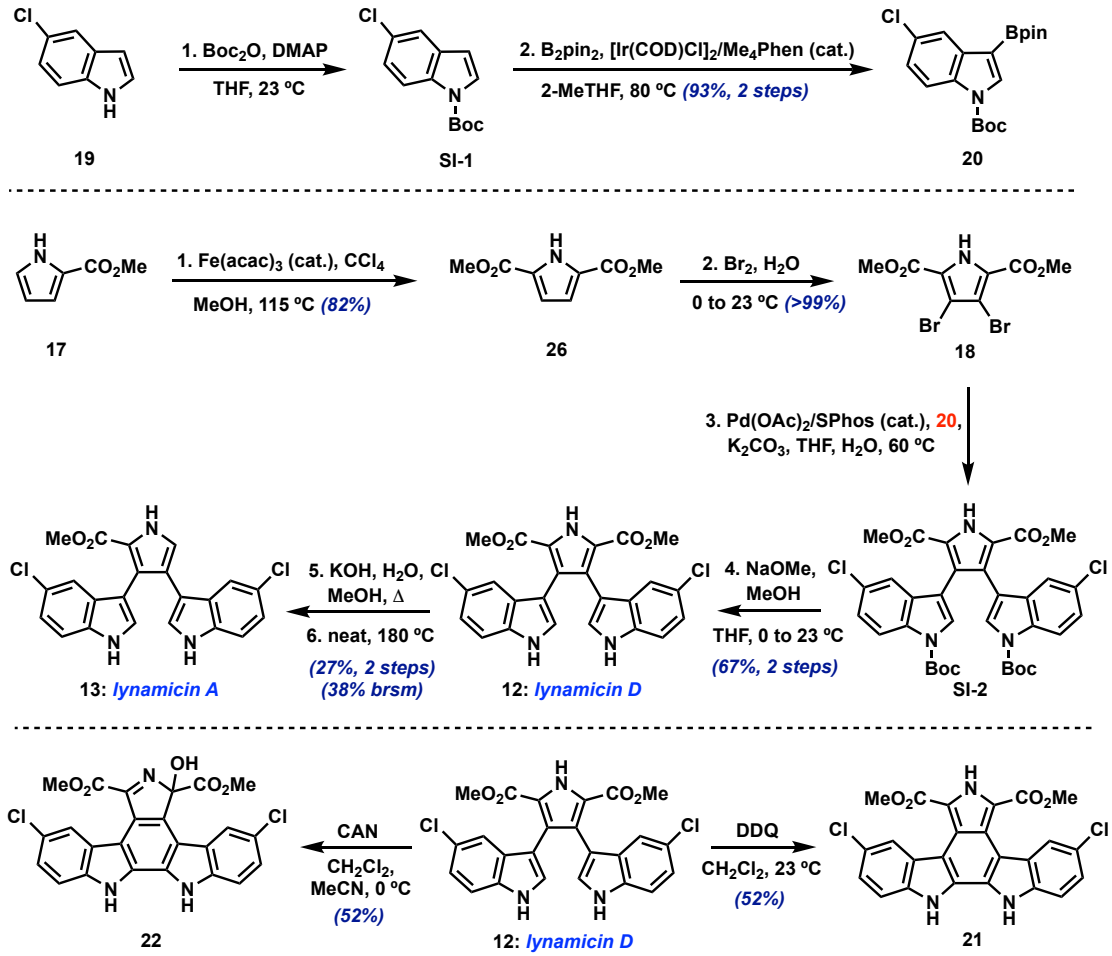
*myles.smith@utsouthwestern.edu

1. General Information

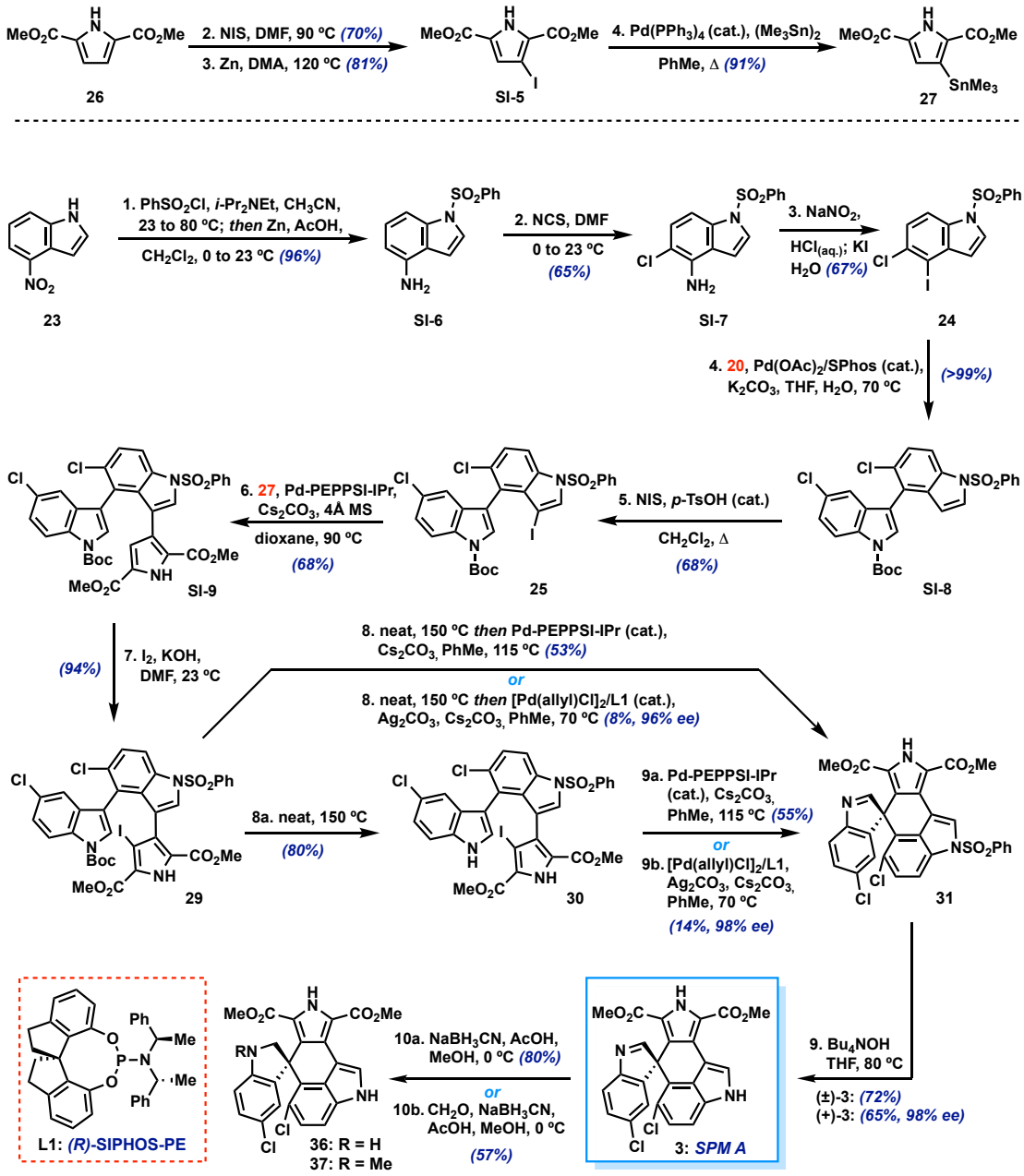
All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. Dry methylene chloride (CH_2Cl_2), tetrahydrofuran (THF), and toluene (PhMe) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns; 2-methyltetrahydrofuran (2-MeTHF), acetonitrile (MeCN), *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), and methanol (MeOH) were purchased in anhydrous form from Sigma–Aldrich or Acros and used as received; carbon tetrachloride (CCl_4) and acetic acid (AcOH) were purchased from Acros and Oakwood, respectively, and used as received. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60 F_{254}) using UV light and an aqueous solution of cerium ammonium sulfate and ammonium molybdate and heat as visualizing agents. Preparative TLC was carried out on 0.25 mm E. Merck silica gel plates (60 F_{254}). SiliCycle silica gel (60 Å, academic grade, particle size 40–63 μm) was used for flash column chromatography. NMR spectra were recorded on Varian MR400, Bruker AN400 and AN600 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations are used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. Mass spectra were acquired on an Agilent technologies 1200 series LC/MS using indicated ionization methods. HPLC analyses were performed on an Agilent 1200 Series system using CHIRALCEL AD-H and OD-H columns. Optical rotation data were recorded on a Rudolph Research Analytical Autopol® IV Polarimeter.

2. Chemical Synthesis Schemes

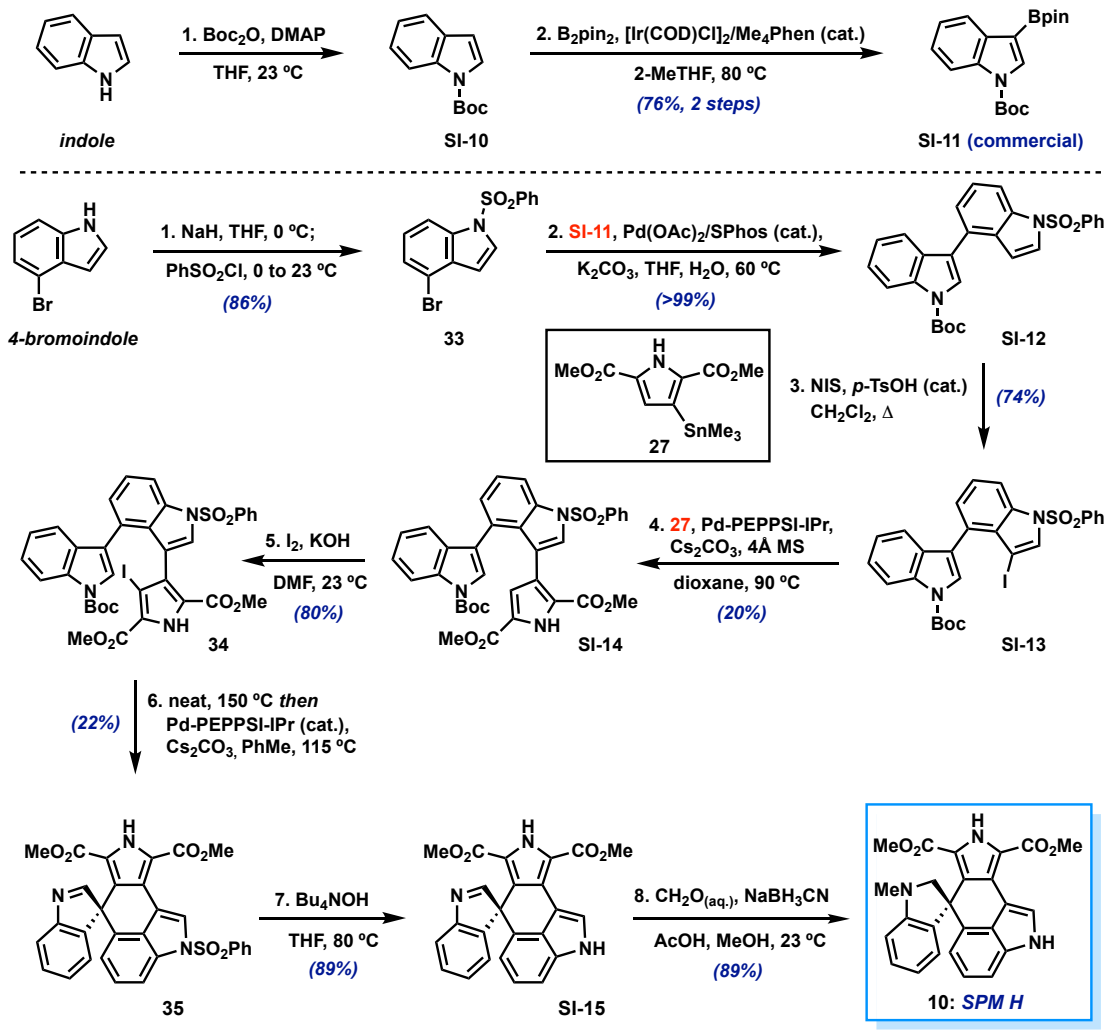
Scheme S1. Synthesis of Lynamicins A (**13**) and D (**12**).



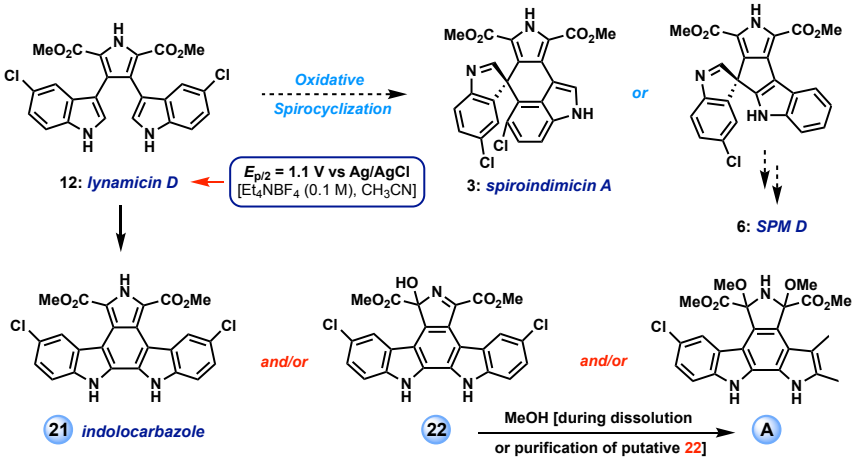
Scheme S2. Synthesis of Spiroindimicin A (**3**) and Dihydro Analogues **36** and **37**.



Scheme S3. Synthesis of (±)-Spiroindimicin H (**10**)



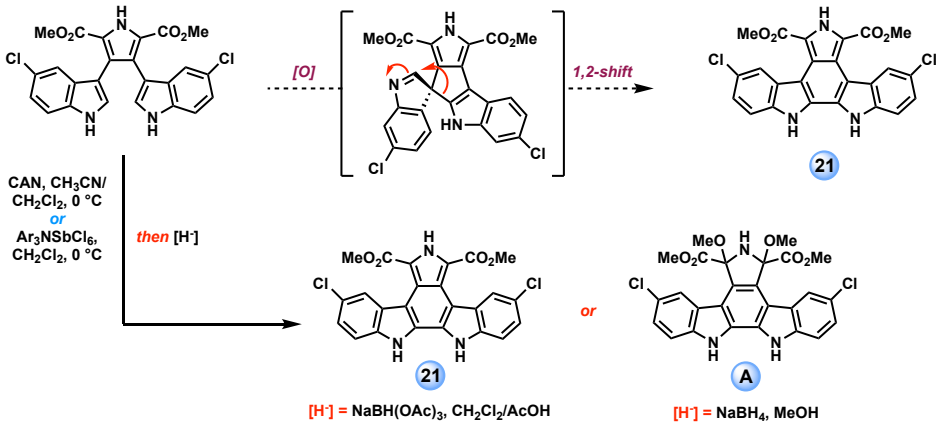
3. Biomimetic Oxidative Spirocyclization Attempts



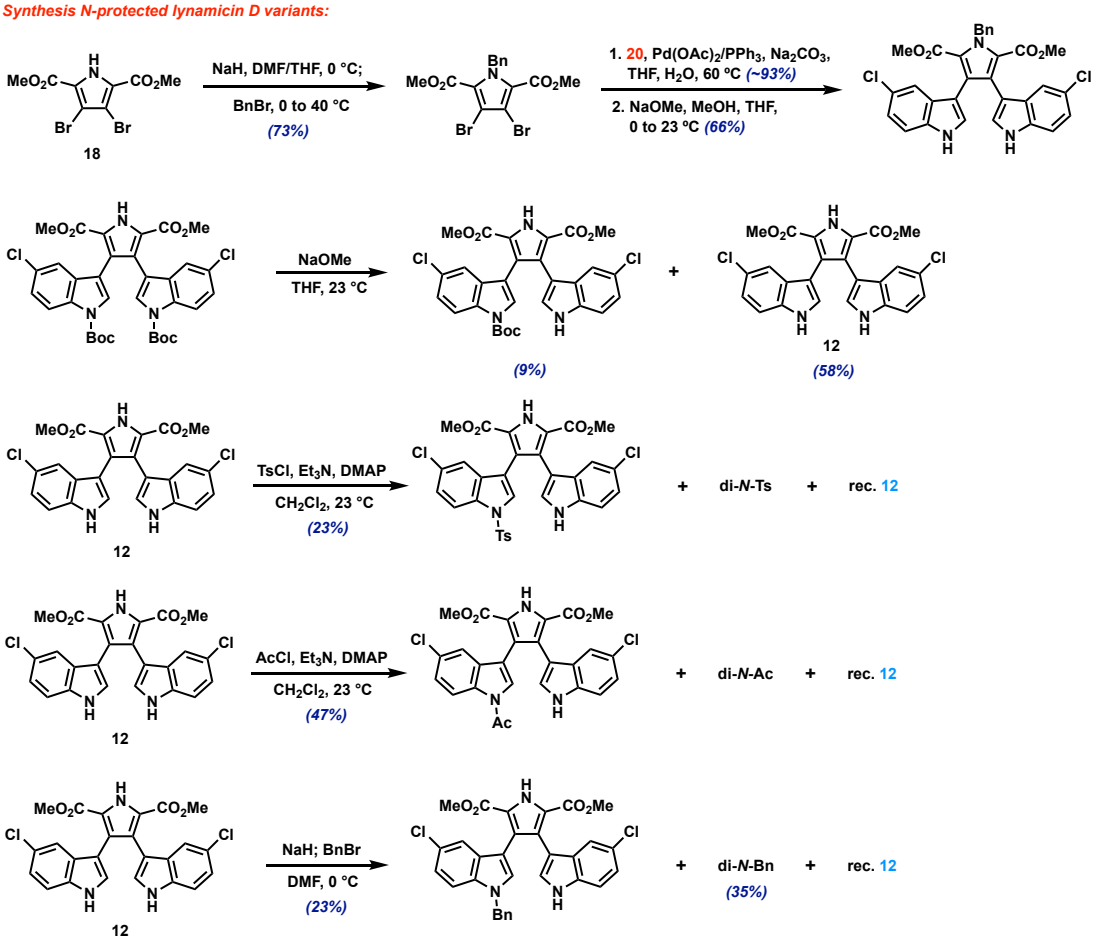
	CONDITIONS	RESULT
1	$PhI(OAc)_2$, CH_2Cl_2/TFE (10:1), 23 °C	decomposition
2	$PhI(OAc)_2$, CH_2Cl_2, 0 °C	decomposition
3	$PhI(OAc)_2$, CH_2Cl_2/TFE (2:1), –30 °C	decomposition
4	$PhI(TFA)_2$, CH_2Cl_2, 0 °C	21
5	$PhI(TFA)_2$, CH_2Cl_2, –20 to 0 °C	21 + other product(s)
6	$Cu(OAc)_2•H_2O$, $Mn(OAc)_3•2H_2O$, CH_3CN, 0 to 23 °C	No reaction
7	$Mn(OAc)_3•2H_2O$, AcOH, 23 to 75 °C	12 + some decomp.
8	DDQ, CH_2Cl_2, 0 to 23 °C	Clean formation of 21
9	$FeCl_3$, CH_3CN, 0 °C	Some 21 and A
10	$FeCl_3$, CH_3CN/CH_2Cl_2, 0 °C	Some 21 and A
11	CAN, CH_3CN/CH_2Cl_2, 0 °C	Clean formation of 22
12	Ar_3NSbCl_6, CH_2Cl_2, 0 °C[b]	21, 22 formed but messy
13	Ar_3NSbCl_6, CH_2Cl_2/TFE, –30 to –8 °C[b]	22 formed but messy
14	Ar_3NSbCl_6, CH_2Cl_2, –30 to –3 °C[b]	22 formed but messy
15	NBS, CH_2Cl_2, 0 °C	21 + other products
16	Br_2, CH_2Cl_2, –78 to –40 °C	22 + trace 21
17	*t*-BuOCl, CH_2Cl_2, 0 to 23 °C	A formed
18	*t*-BuOCl, TMEDA, CH_2Cl_2, 23 °C; 1 M H_2SO_4	chlorination + 2′,2″-bond
19	AgOAc, CH_3CN, CH_2Cl_2, 0 to 40 °C	12, 22 + other major
20	$Pd(TFA)_2$ (cat.), Ag_2CO_3, K_2CO_3, dioxane, Δ	decomposition
21	$Pd(OAc)_2$ (1.1 equiv), AcOH, 70 °C	Fairly clean 21
22	$Pd(TFA)_2$ (cat.), $Cu(OAc)_2•H_2O$, DMSO, 23 °C	No reaction
23	CuBr, $(NH_4)_2S_2O_8$; MeCN, H_2O, 50 °C	No reaction
24	$Pb(OAc)_4$, CH_2Cl_2, –20 to 0 °C	12 + minor product(s)
25	TPP, air, hood light, CH_2Cl_2, 23 °C	No reaction
26	$Tl(TFA)_3$, TFA, 23 °C; KI, H_2O, 23 °C	A
27	$Ir(ppy)_3$, $PhI(OAc)_2$, THF *or* CH_3CN, Blue LED, 23 °C	No reaction
28	$Ir(ppy)_3$, $PhI(OAc)_2$, B, THF, Blue LED, 23 °C	12 + decomp.
29	$Ir(ppy)_3$, $PhI(OAc)_2$, TEMPO, B, THF, Blue LED, 23 °C	No reaction
30	V = 1.2 V, Ar_3NSbCl_6 (cat.), Et_4NBF_4, CH_3CN, 23 °C	No reaction
31	V = 1.2 V, Ar_3NSbCl_6 (cat.), Et_4NBF_4, CH_3CN, HFIP, 23 °C	No reaction

[a]Typical reaction screening scale: 5–15 mg of 12; [b]Ar = 4-BrC_6H_4; B = Bu_4N^+(3,3′-ArBINOL)PO_2^-

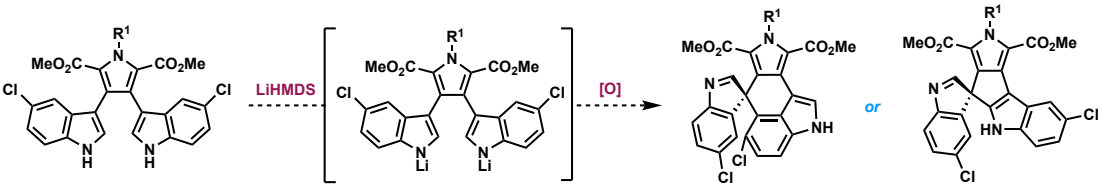
Possible transient spiroindolenine formation:



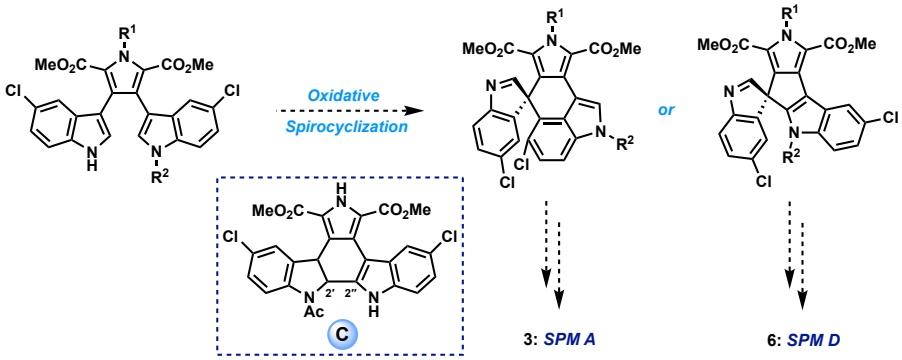
Synthesis N-protected lynamicin D variants:



Attempted spircocylization of protected variants:



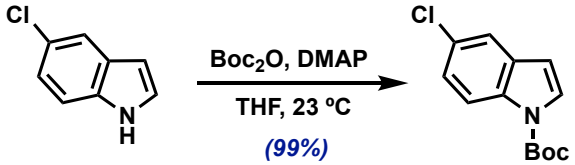
R^1 = H: LiHMDS (3.3 equiv), THF, –78 °C; I_2, –78 to 0 °C	few products; inseparable
R^1 = Bn: LiHMDS (2.3 equiv), THF, –78 °C; $Cu(OTf)_2$ *or* I_2, –78 to 0 °C	$Cu(OTf)_2$: no reaction; I_2: mostly SM



	SUBSTRATE	CONDITIONS	RESULT
1	R^1 = Bn, R^2 = H	CAN, CH_3CN/CH_2Cl_2, 0 °C	2′,2″-bond + [O]
2	R^1 = Bn, R^2 = H	Ar_3NSbCl_6, CH_2Cl_2, 0 °C[b]	messy
3	R^1 = Bn, R^2 = H	*t*-BuOCl, TMEDA, CH_2Cl_2, 23 °C; 1 M H_2SO_4	chlorination + 2′,2″-bond
4	R^1 = H, R^2 = Boc	CAN, CH_3CN/CH_2Cl_2, 0 °C	messy
5	R^1 = H, R^2 = Boc	$FeCl_3$, CH_3CN/CH_2Cl_2, 0 °C	deBoc to 12
6	R^1 = H, R^2 = Boc	NBS, PPTS, CH_2Cl_2, 0 °C	2 bromination products
7	R^1 = H, R^2 = Ts	CAN, CH_3CN/CH_2Cl_2, 0 °C	*N*-Ts-22 (major)
8	R^1 = H, R^2 = Ts	$FeCl_3$ (cat.), air, CH_2Cl_2, 0 °C	almost no reaction
9	R^1 = H, R^2 = Ts	Ar_3NSbCl_6, CH_2Cl_2, –30 °C[b]	messy
10	R^1 = H, R^2 = Ts	$Pd(OAc)_2$, DMSO, 50 °C	no reaction
11	R^1 = H, R^2 = Ts	Pd(TFA)2, $Cu(OAc)_2 \cdot H_2O$, DMSO, 23 to 110 °C	no reaction
12	R^1 = H, R^2 = Ts	Pd(TFA)2, DMSO, 23 to 50 °C	no reaction
13	R^1 = H, R^2 = Ac	$FeCl_3$, CH_2Cl_2, 23 °C	C + minor products
14	R^1 = H, R^2 = Bn	CAN, CH_3CN/CH_2Cl_2, 0 °C	likely 2′,2″-bond
15	R^1 = H, R^2 = Bn	$FeCl_3$, CH_2Cl_2, 23 °C	messy
16	R^1 = H, R^2 = Bn	Pd(TFA)2, $Cu(OAc)_2 \cdot H_2O$, DMSO, 23 to 110 °C	no reaction
17	R^1 = H, R^2 = Boc	V = 1.1 V, Et_4NBF_4 (0.1 M), CH_3CN	no reaction[c]

[a]Typical reaction scale: 4–10 mg; [b]Ar = 4-BrC_6H_4; [c]decomp. with H_2O (15% v/v) and further reaction.

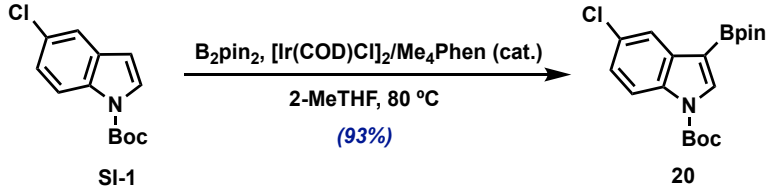
4. Experimental Procedures



N-Boc-5-chloroindole **(SI-1):** To a solution of 5-chloroindole (**19**, 9.09 g, 60 mmol, 1.0 equiv) in THF (50 mL) was added $(Boc)_2O$ (14.4 g, 66 mmol, 1.1 equiv) and 4-(dimethylamino)pyridine (64 mg, 0.60 mmol, 0.01 equiv), and the reaction was stirred overnight (16 h) at room temperature. Silica gel was directly added to the reaction mixture, which was concentrated under vacuum and chromatographed on silica gel (10–15%

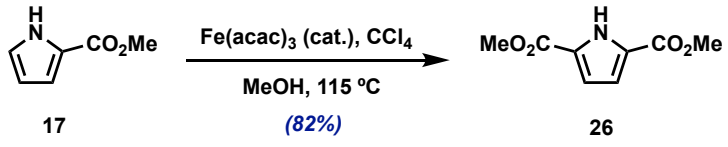
EtOAc/hexanes gradient) to give pure Boc-protected indole **SI-1** (15.2 g, 99%). ^{1}H NMR spectral data are in agreement with the literature.[1]

Physical properties: colorless oil;
R_f = 0.73 (silica gel, 17% EtOAc/hexanes);
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (br d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 3.7 Hz, 1H), 7.52 (d, *J* = 2.1 Hz, 1H), 7.26 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.50 (d, *J* = 3.7 Hz, 1H), 1.68 (s, 9H).



***N-Boc-3-(pinacolatoboryl)-5-chloroindole* (20):** To a solution of compound **SI-1** (15.0 g, 59.7 mmol, 1.0 equiv) in 2-methyltetrahydrofuran (60 mL, degassed by argon sparge for 20 min) was added $[Ir(COD)Cl]_2$ (403 mg, 0.6 mmol, 0.01 equiv) and 3,4,7,8-tetramethyl-1,10-phenanthroline (284 mg, 1.2 mmol, 0.02 equiv), followed by bis(pinacolato)diboron (16.7 g, 65.7 mmol, 1.1 equiv). The reaction mixture was heated to 80 °C and soon became dark red. After 24 h at this temperature, the reaction mixture was allowed to cool to room temperature and subsequently passed through a silica gel plug to remove iridium catalyst residue, rinsing with EtOAc (2 × 120 mL). The organics were then transferred to a separatory funnel and diluted with H_2O (200 mL). The layers were separated and the aqueous layer was reextracted with EtOAc (100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude product was chromatographed on silica gel (5–15% EtOAc/hexanes gradient) to give pure 3-borylated indole **20** (21.1 g, 93%). ^{1}H NMR spectral data are in agreement with the literature.[2]

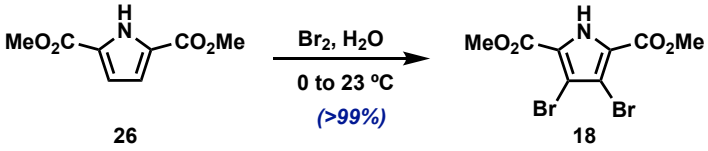
Physical properties: white solid;
R_f = 0.55 (silica gel, 9% EtOAc/hexanes);
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.8 Hz, 1H), 8.01 (s, 1H), 7.95 (d, *J* = 2.2 Hz, 1H), 7.26 (dd, *J* = 8.8, 2.2 Hz, 1H), 1.65 (s, 9H), 1.37 (s, 12H).



***Dimethyl pyrrole-2,5-dicarboxylate* (26):** A reaction flask was charged under argon with methyl 2-pyrrolecarboxylate (**17**, 5.45 g, 43.6 mmol, 1.0 equiv) and $Fe(acac)_3$ (927 mg, 2.62 mmol, 0.06 equiv), and CCl_4 (12 mL) and MeOH (66 mL) were added. The flask was sealed and heated for 40 h at 115 °C with continuous stirring. When the reaction was complete, the reaction was cooled to room temperature, and the flask was carefully opened (**CAUTION:**

some pressure build-up is seen on large scale). The reaction mixture was filtered through a short pad of silica gel, rinsing with EtOAc (2 × 100 mL). The eluent was concentrated, and the residue chromatographed on silica gel (20–35% EtOAc/hexanes gradient) to give pure dimethyl pyrrole-2,5-dicarboxylate (**26**) (6.55 g, 82%). ^{1}H NMR spectral data are in agreement with the literature.[3]

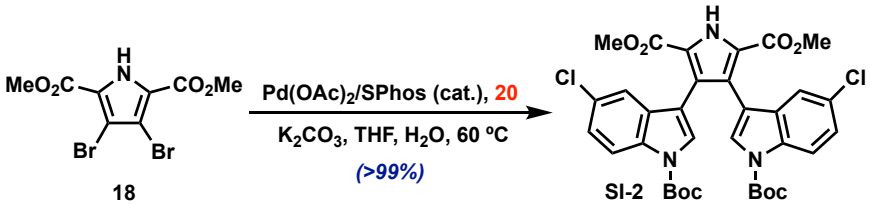
Physical properties: white solid;
R_f = 0.34 (silica gel, 25% EtOAc/hexanes);
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (br s, 1H), 6.87 (d, *J* = 2.6 Hz, 2H), 3.89 (s, 6H).



26 18

Dimethyl 3,4-dibromopyrrole-2,5-dicarboxylate **(18):** Bromine (1.0 mL, 19.6 mmol, 9.0 equiv) was added dropwise to a suspension of compound **26** (399 mg, 2.18 mmol, 1.0 equiv) in water (20 mL) at 0 °C. The reaction mixture is then allowed to warm to room temperature and stirred for 20 min. Saturated aqueous Na_2SO_3 was added and stirring was continued until complete reduction of excess bromine was achieved. The product was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated. The residue was recrystallized from DCM/hexane (47 mL/7.5 mL) to afford pure dimethyl 3,4-dibromopyrrole-2,5-dicarboxylate **18** (371 mg, 50%) as colorless needles. The mother liquor was then concentrated to afford another 386 mg of pure **18** as an amorphous solid (757 mg in total, >99% in total). ^{1}H NMR spectral data are in agreement with the literature.[2]

Physical properties: white solid;
R_f = 0.22 (silica gel, 25% EtOAc/hexanes);
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (br s, 1H), 3.95 (s, 6H).

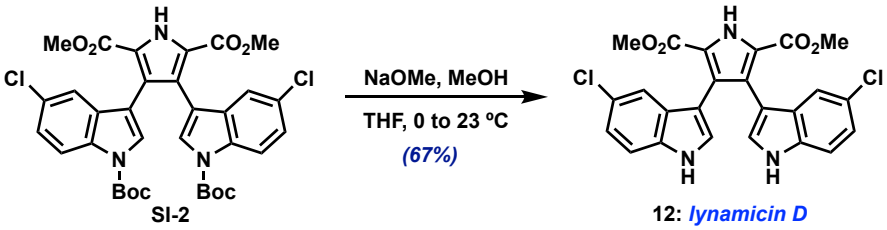


18 SI-2

DiBoc lynamicin D **(SI-2):** A mixture of boronate **20** (1.21 g, 3.54 mmol, 5.0 equiv) and dibromide **18** (267 mg, 0.71 mmol, 1.0 equiv) were dissolved in THF (14 mL) and degassed by argon sparge for 30 min. SPhos (116 mg, 0.28 mmol, 0.4 equiv) and $Pd(OAc)_2$ (32 mg, 0.14 mmol, 0.2 equiv) were then added, followed by K_2CO_3 (977 mg, 7.1 mmol, 10.0 equiv) in degassed H_2O (2.8 mL). The mixture was heated at 75 °C overnight (10 h). After cooling to room temperature, the contents were transferred to a separatory funnel and diluted with H_2O/EtOAc (40 mL/20 mL). The layers were separated and the aqueous layer was reextracted with EtOAc (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel

(20–35% EtOAc/hexanes gradient) to afford pure diBoc-lynamicin D (**SI-2**) (664 mg, >99%). ^{1}H NMR spectral data are in agreement with the literature.[2]

Physical properties: white solid;
R_f = 0.24 (silica gel, 25% EtOAc/hexanes);
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 7.99 (br s, 2H), 7.34 (br s, 2H), 7.21 – 7.11 (m, 4H), 3.74 (s, 6H), 1.57 (s, 18H).



***Lynamicin D* (12):** To a solution of compound **SI-2** (513 mg, 0.75 mmol, 1.0 equiv) in THF (25 mL) at 0 °C under argon was added NaOMe (1.8 M in MeOH, 4.18 mL, 15.0 equiv) dropwise. After the addition was complete, the ice bath was removed and the reaction mixture was stirred for 6 h at room temperature. The reaction was slowly quenched with 1 N HCl to adjust the pH to ~7 and extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (40–60% EtOAc/hexanes gradient) to afford pure lynamicin D (**12**) (242 mg, 67%). ^{1}H and ^{13}C NMR spectral data are in agreement with the literature.[2,4]

Physical properties: white solid;
R_f = 0.35 (silica gel, 50% EtOAc/hexanes);
MS (ESI): calcd for $C_{24}H_{16}Cl_2N_3O_4$ $[M - H]^-$ 480.1, found 479.8;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 7.96 (s, 2H), 7.15 (s, 2H), 7.01 (d, J = 8.6 Hz, 2H), 6.97 (dd, J = 8.6, 1.9 Hz, 2H), 6.81 (d, J = 2.4 Hz, 2H), 3.74 (s, 6H);
^{13}C NMR (100 MHz, $CDCl_3$): δ 51.8, 108.2, 112.0, 119.4, 121.9, 122.4, 124.4, 125.2, 125.8, 128.5, 133.8, 160.6.

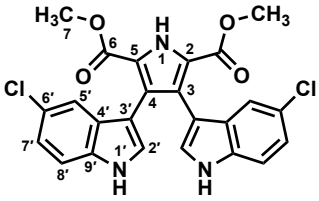


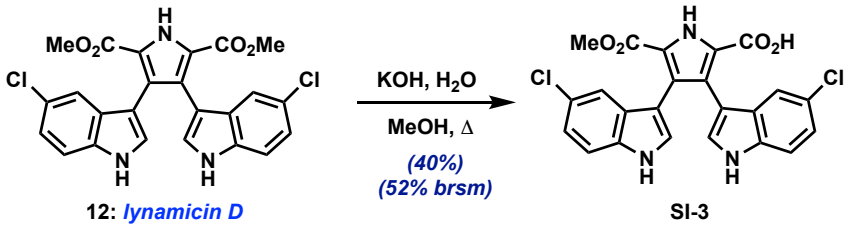
Table S1: Comparison of ^{1}H NMR shifts (δ) of natural[4] lynamicin D (**12**), Nikolakaki[2] and co-workers' synthetic **12**, and our own synthetic **12** in $CDCl_3$.

Position	Natural **12** (500 MHz)	Synthetic **12** *(Nikolakaki)* (500 MHz)	Synthetic **12** *(Smith)* (400 MHz)
1	9.98 (s, 1H)	9.98 (s, 1H)	9.97 (s, 1H)
2			
3			

4			
5			
6			
7	3.74 (s, 6H)	3.75 (s, 6H)	3.74 (s, 6H)
1’	8.01 (s, 2H)	8.01 (s, 2H)	7.96 (s, 2H)
2’	6.85 (d, *J* = 2.5 Hz, 2H)	6.85 (d, *J* = 2.5 Hz, 2H)	6.81 (d, *J* = 2.4 Hz, 2H)
3’			
4’			
5’	7.14 (d, *J* = 1.0 Hz, 2H)	7.14 (d, *J* = 1.0 Hz, 2H)	7.15 (s, 2H)
6’			
7’	6.98 (dd, *J* = 8.5 Hz; 2.0 Hz, 2H)	6.98 (dd, *J* = 8.5 Hz; 2.0 Hz, 2H)	6.97 (dd, *J* = 8.6 Hz; 1.9 Hz, 2H)
8’	7.05 (d, *J* = 8.5 Hz, 2H)	7.05 (d, *J* = 8.5 Hz, 2H)	7.01 (d, *J* = 8.6 Hz, 2H)
9’			

Table S2: Comparison of ^{13}C NMR shifts (δ) of natural[4] lynamicin D (**12**), Nikolakaki[2] and co-workers’ synthetic **12**, and our own synthetic **12** in $CDCl_3$.

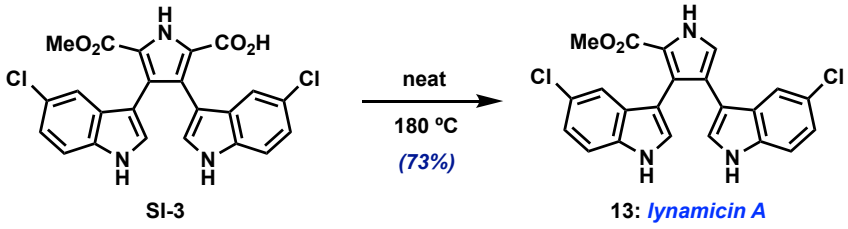
Position	Natural **12** (500 MHz)	Synthetic **12** *(Nikolakaki)* (500 MHz)	Synthetic **12** *(Smith)* (400 MHz)
1			
2	122.4	122.4	122.4
3	124.4	124.4	124.4
4	124.4	124.4	124.4
5	122.4	122.4	122.4
6	160.7	160.7	160.6
7	51.8	51.8	51.8
1’			
2’	125.8	125.8	125.8
3’	108.3	108.3	108.2
4’	128.5	128.5	128.5
5’	119.4	119.4	119.4
6’	125.2	125.2	125.2
7’	121.9	121.9	121.9
8’	111.9	111.9	112.0
9’	133.8	133.8	133.8



12: *lynamicin D* **SI-3**

***Demethyl lynamicin D* (SI-3):** To a solution of lynamicin D (**12**) (220 mg, 0.46 mmol, 1.0 equiv) in MeOH/H_2O (8 mL/2 mL) at room temperature under argon was added KOH (56 mg, 0.46 mmol, 1.0 equiv). The mixture was heated to reflux and stirred for 12 h at this temperature. After cooling to room temperature, the reaction was quenched with 1 N HCl to pH = 6 and the product was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed on silica gel (5–10% MeOH/DCM gradient) to afford pure demethyl lynamicin D (**SI-3**) (85 mg, 40%, 52% brsm) and recovered lynamicin D (**12**) (51 mg, 23%).

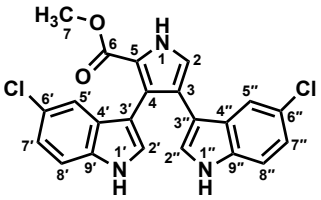
Physical properties: white solid;
R_f = 0.46 (silica gel, 9% MeOH/DCM);
MS (ESI): calcd for $C_{23}H_{16}Cl_2N_3O_4$ $[M + H]^+$ 468.0, found 467.9;
^{1}H NMR (600 MHz, DMSO-d_6): δ 12.66 (br s, 1H), 12.09 (s, 1H), 11.12 (s, 1H), 11.08 (s, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.15 (s, 1H), 7.12 (s, 1H), 7.03 – 6.88 (m, 4H), 3.62 (s, 3H);
^{13}C NMR (150 MHz, DMSO-d_6): δ 51.2, 107.5, 107.8, 112.7, 118.4, 118.5, 120.40, 120.44, 122.2, 123.1, 123.2, 123.9, 124.0, 127.0, 127.1, 128.5, 128.7, 134.0, 160.5, 161.6. [**Note**: three carbon signals missing due to signal overlap]



SI-3 **13:** *lynamicin A*

***Lynamicin A* (13)**: Compound **SI-3** (117 mg, 0.25 mmol, 1.0 equiv) was heated neat at 180 °C under argon for 2 h. After cooling to room temperature, the residue was chromatographed on silica gel (1–5% MeOH/DCM gradient) to afford pure lynamicin A (**13**) (77.5 mg, 73%). ^{1}H and ^{13}C NMR spectral data are in agreement with the literature.[4]

Physical properties: yellow powder;
R_f = 0.65 (silica gel, 5% MeOH/DCM);
MS (ESI): calcd for $C_{22}H_{16}Cl_2N_3O_2$ $[M + H]^+$ 424.1, found 423.9;
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.34 (s, 1H), 8.09 (s, 1H), 7.86 (s, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.21 (d, *J* = 3.0 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 7.06 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.99 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.55 (d, *J* = 2.5 Hz, 1H), 3.69 (s, 3H);
^{13}C NMR (150 MHz, $CDCl_3$): δ 51.3, 109.2, 109.7, 112.0, 112.1, 119.0, 119.7, 120.1, 120.2, 120.7, 121.7, 121.9, 122.1, 123.7, 125.1, 125.4, 125.6, 127.7, 128.5, 134.0, 134.1, 161.3.



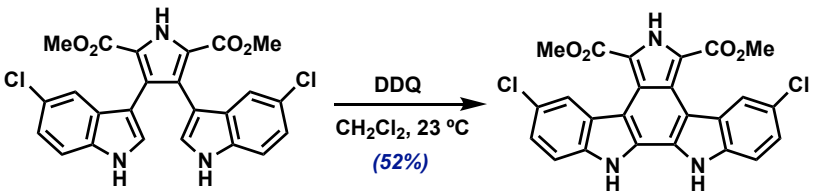
13: ***lynamicin A***

Table S3: Comparison of ^{1}H NMR shifts (δ) of natural[4] lynamicin A (**13**) and our own synthetic **13** in $CDCl_3$.

Position	Natural **13** (500 MHz)	Synthetic **13** *(Smith)* (600 MHz)
1	9.37 (br s, 1H)	9.34 (s, 1H)
2	7.23 (d, *J* = 2.0 Hz, 1H)	7.22 (d, *J* = 2.0 Hz, 2H)
3		
4		
5		
6		
7	3.68 (s, 3H)	3.69 (s, 3H)
1’	7.92 (br s, 1H)	7.86 (s, 1H)
2’	6.59 (d, *J* = 2.5 Hz, 1H)	6.55 (d, *J* = 2.5 Hz, 1H)
3’		
4’		
5’	7.50 (d, *J* = 2.0 Hz, 1H)	7.50 (d, *J* = 1.8 Hz, 1H)
6’		
7’	7.00 (dd, *J* = 8.5 Hz; 2.0 Hz, 1H)	6.99 (dd, *J* = 8.6, 2.0 Hz, 1H)
8’	7.08 (d, *J* = 8.5 Hz, 1H)	7.04 (d, *J* = 8.6 Hz, 1H)
9’		
1’’	8.14 (br s, 1H)	8.09 (s, 1H)
2’’	6.96 (d, *J* = 2.5 Hz, 1H)	6.92 (d, *J* = 2.4 Hz, 1H)
3’’		
4’’		
5’’	7.22 (d, *J* = 2.0 Hz, 1H)	7.21 (d, *J* = 3.0 Hz, 1H)
6’’		
7’’	7.06 (dd, *J* = 8.5 Hz; 2.0 Hz, 1H)	7.06 (dd, *J* = 8.5 Hz; 1.9 Hz, 1H)
8’’	7.11 (d, *J* = 8.5 Hz, 1H)	7.09 (d, *J* = 8.6 Hz, 1H)
9’’		

Table S4: Comparison of ^{13}C NMR shifts (δ) of natural[4] lynamicin A (**13**) and our own synthetic **13** in $CDCl_3$.

Position	Natural **13** (500 MHz)	Synthetic **13** *(Smith)* (600 MHz)
1		
2	121.7	121.7
3	120.2	120.2
4	120.1	120.1
5	120.7	120.7
6	161.3	161.3
7	51.3	51.3
1’		
2’	123.7	123.7
3’	109.8	109.7
4’	127.8	127.7
5’	119.0	119.0
6’	125.1	125.1
7’	121.9	121.9
8’	112.03	112.07
9’	134.07	134.08
1”		
2”	125.6	125.6
3”	109.3	109.2
4”	128.6	128.5
5”	119.7	119.7
6”	125.4	125.4
7”	122.1	122.1
8”	112.0	112.03
9”	134.1	134.1

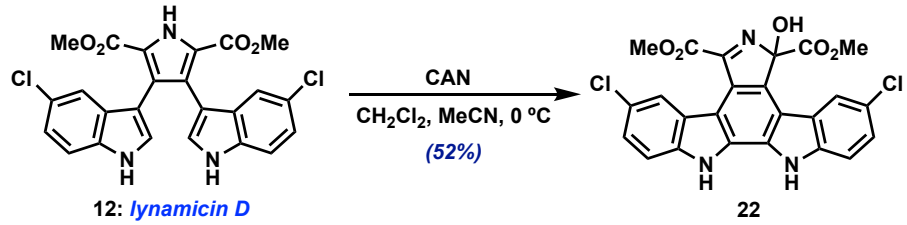


12: *lynamicin D* 21

***2′,2′′-Dehydrolynamicin D* (21):** To a solution of lynamicin D (**12**, 53 mg, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) was added DDQ (249 mg, 1.1 mmol, 10.0 equiv) under nitrogen at room temperature. After stirring for 4 h (monitored by TLC), the reaction mixture was filtered through Celite, rinsing with ethyl acetate. The filtrate was washed with saturated aqueous $NaHCO_3$ solution, and the aqueous layer reextracted with ethyl acetate. The combined organic

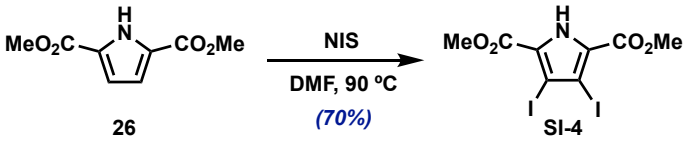
extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (60–90% EtOAc/hexanes gradient) to afford pure dehydrolynamicin D (**21**) (27.6 mg, 52%).

Physical properties: yellow solid;
R_f = 0.39 (silica gel, 50% EtOAc/hexanes);
MS (ESI): calcd for $C_{24}H_{14}Cl_2N_3O_4$ $[M - H]^-$ 478.0; Found 477.9;
^{1}H NMR (600 MHz, DMSO-d_6): δ 13.02 (s, 1H), 11.82 (s, 2H), 8.23 (d, J = 2.2 Hz, 2H), 7.78 (d, J = 8.6 Hz, 2H), 7.39 (dd, J = 8.6, 2.1 Hz, 2H), 4.04 (s, 6H).
^{13}C NMR (150 MHz, DMSO-d_6): δ 52.1, 108.5, 113.0, 116.5, 117.8, 123.2, 123.3, 123.6, 124.5, 128.2, 136.7, 162.0.



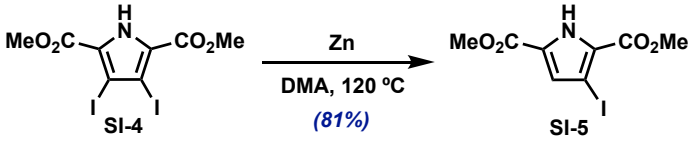
***2-Hydroxy-2′,2′′-dehydrolynamicin D* (22):** To a solution of lynamicin D (**12**, 11.2 mg, 0.023 mmol, 1.0 equiv) in CH_3CN/CH_2Cl_2 (4:1; 2.5 mL) was added ceric ammonium nitrate (25.5 mg, 0.046 mmol, 2.0 equiv) under nitrogen at 0 ºC with stirring. After 45 min, the initially green reaction mixture had turned dark orange and TLC indicated full consumption of starting material. The reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3 (1:1, 4 mL) and transferred to a separatory funnel, diluting with ethyl acetate (10 mL) and water (4 mL). The layers were separated and the aqueous layer reextracted with EtOAc (8 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum to give crude hydroxydehydrolynamicin D (**22**) (12.8 mg) of ~90% purity (6.0 mg, 52% by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard) [**Note**: attempted purification of **22** on silica gel resulted in decomposition].

Physical properties: yellow solid;
R_f = 0.42 (silica gel, EtOAc);
MS (ESI): calcd for $C_{26}H_{20}Cl_2N_3O_6$ $[M - H_2O + 2MeOH - H]^-$ 541.1, found 540.0. [**Note**: A dimethoxy adduct (formed via MeOH substitution of the C-2 OH and attack at the C-5 imine) was found to form readily upon dissolution in MeOH for LC-MS]
^{1}H NMR (600 MHz, DMSO-d_6): δ 11.85 (s, 1H), 11.82 (s, 1H), 8.50 (d, J = 2.1 Hz, 1H), 7.89 (s, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.55 – 7.50 (m, 2H), 4.17 (s, 3H), 3.48 (s, 3H).
^{13}C NMR (150 MHz, DMSO-d_6): δ 52.9, 53.4, 100.8, 112.1, 113.7, 114.1, 115.0, 121.0, 121.6, 122.3, 122.5, 122.8, 123.9, 124.4, 125.5, 125.9, 127.4, 127.9, 138.0, 138.3, 140.8, 166.4, 166.7, 169.6.



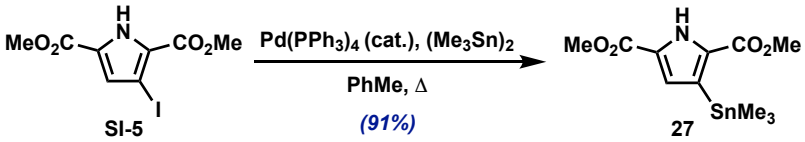
Dimethyl 3,4-diiodo-pyrrole-2,5-dicarboxylate **(SI-4):** To a solution of compound **26** (5.55 g, 30.3 mmol, 1.0 equiv) in DMF (61 mL) at room temperature was added NIS (15.1 g, 67 mmol, 2.2 equiv). The ensuing mixture was heated to 80 °C and stirred at this temperature for 4 h. The reaction was then cooled and concentrated to dryness (50 °C bath temperature on rotary evaporator). The residue was recrystallized from CH_2Cl_2/hexanes to afford a solid, which is a mixture of **SI-4** and the byproduct of the reaction, succinimide, (13.5 g in total, **SI-4**: succinimide = 1:2.5), which was carried into the next step without further purification. The mother liquor could be concentrated and purified by column chromatography (15–30% EtOAc/hexanes gradient) to afford another 700 mg pure **SI-4** (9.3 g in total, 70%). ^{1}H NMR spectral data are in agreement with the literature.[5]

Physical properties: white solid;
R_f = 0.23 (silica gel, 25% EtOAc/hexanes);
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (br s, 1H), 3.95 (s, 6H).



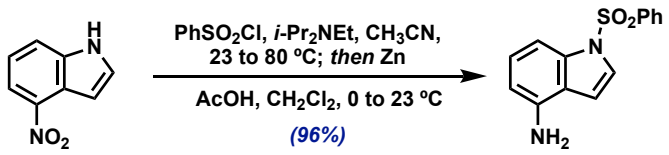
Dimethyl 3-iodopyrrole-2,5-dicarboxylate **(SI-5):** Iodine (493 mg, 1.94 mmol, 0.1 equiv) was added to zinc powder (1.46 g, 22.3 mmol, 1.15 equiv) under an argon atmosphere and the ensuing mixture was stirred at room temperature for 2 min before being treated with DMA (13.6 mL). The resulting suspension was stirred for a further 2 min before a mixture of compound **SI-4** and succinimide, (13.5 g in total, **SI-4**: succinimide = 1:2.5, 1.0 equiv) was added and the reaction heated at 120 °C for 2.5 h. After cooling to room temperature, the reaction mixture was treated with silica gel (20 g) and concentrated under reduced pressure. The free flowing solid thus obtained was chromatographed on silica gel (15–30% EtOAc/hexanes gradient) to give pure dimethyl 3-iodopyrrole-2,5-dicarboxylate (**SI-5**) (4.94 g, 81%). ^{1}H NMR spectral data are in agreement with the literature.[5]

Physical properties: white solid;
R_f = 0.24 (silica gel, 25% EtOAc/hexanes);
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (br s, 1H), 7.06 (d, J = 2.8 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H).



***Dimethyl 3-(trimethylstannyl)pyrrole-2,5-dicarboxylate* (27):** To a solution of compound **SI-5** (982 mg, 2.5 mmol, 1.0 equiv) in toluene (11 ml) was added hexamethyldistannane (1.23 g, 3.75 mmol, 1.5 equiv) and the mixture was degassed by argon sparge for 20 min. $Pd(PPh_3)_4$ (115 mg, 0.1 mmol, 0.04 equiv) was added and the reaction was heated to 115 °C and stirred at this temperature for 12 h. After cooling to room temperature, the reaction mixture was concentrated and the crude product purified by flash chromatography (5–20% EtOAc/hexanes gradient) to afford pure pyrrolestannane **27** (790 mg, 91%).

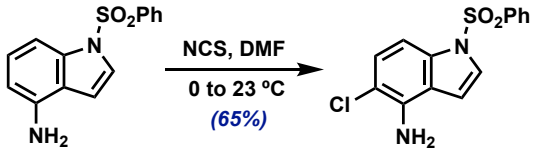
Physical properties: white solid;
R_f = 0.48 (silica gel, 25% EtOAc/hexanes);
MS (ESI): calcd for $C_{11}H_{16}NO_4Sn$ $[M - H]^-$ 346.0, found 345.9.
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (br s, 1H), 6.95 (d, J = 2.4 Hz, 1H, $^3J_{SnH}$ = 9.2 Hz), 3.88 (s, 3H), 3.88 (s, 3H), 0.28 (s, 9H, $^2J_{SnH}$ = 28.2 Hz);
^{13}C NMR (150 MHz, $CDCl_3$): δ -8.9 ($^1J_{SnC}$ = 184.8 Hz), 51.7, 51.8, 122.7, 126.8, 127.1, 130.9, 160.8, 161.2.



23 **SI-6**

***1-(Benzenesulfonyl)-4-aminoindole* (SI-6):** To a solution of 4-nitroindole (**23**, 5.0 g, 30.8 mmol, 1.0 equiv) in MeCN (50 mL) at room temperature was added DIPEA (5.9 mL, 36 mmol, 1.17 equiv) followed by benzenesulfonyl chloride (4.6 mL, 36 mmol, 1.17 equiv), and the reaction was heated at 80 °C for 5 h. After completion, the volatiles were removed under vacuum to afford crude 1-(benzenesulfonyl)-4-nitroindole, which was redissolved in CH_2Cl_2 (113 mL) and cooled to 0 °C. Zinc (15.1 g, 0.23 mol, 7.5 equiv) was added followed by dropwise addition of AcOH (11.26 mL). The reaction mixture was allowed to warm slowly to room temperature over 2 h and then filtered through a Celite pad, rinsing with CH_2Cl_2 (100 mL). The filtrate was carefully treated with saturated aqueous $NaHCO_3$ (200 mL) and the layers separated. The aqueous layer was reextracted with CH_2Cl_2 (100 mL) and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (25–40% EtOAc/hexanes gradient) to afford pure protected 4-aminoindole **SI-6** (8.1 g, 96%). ^{1}H NMR spectral data are in agreement with the literature.[6]

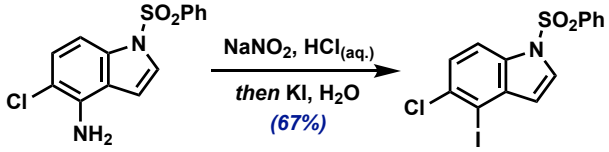
Physical properties: orange solid;
R_f = 0.10 (silica gel, 25% EtOAc/hexanes);
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 – 7.86 (m, 2H), 7.69 – 7.64 (m, 1H), 7.60 – 7.55 (m, 2H), 7.54 (d, J = 3.7 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 3.7 Hz, 1H), 6.36 (d, J = 7.3 Hz, 1H), 5.56 (s, 2H).



SI-6 **SI-7**

1-(Benzenesulfonyl)-5-chloroindol-4-amine **(SI-7):** To a solution of compound **SI-6** (4.85 g, 17.8 mmol, 1.0 equiv) in DMF (60 mL) at 0 °C was added *N*-chlorosuccinimide (2.38 g, 17.8 mmol, 1.0 equiv) in one portion. The mixture was stirred at this temperature for 1 h, then at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with H_2O (150 mL), and extracted with EtOAc (2 × 50 mL). The organic layers were washed with H_2O (3 × 50 mL), brine (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (10–30% EtOAc/hexanes gradient) to afford pure chloroindole **SI-7** (3.54 g, 65%). ^{1}H spectral data are in agreement with the literature.[6]

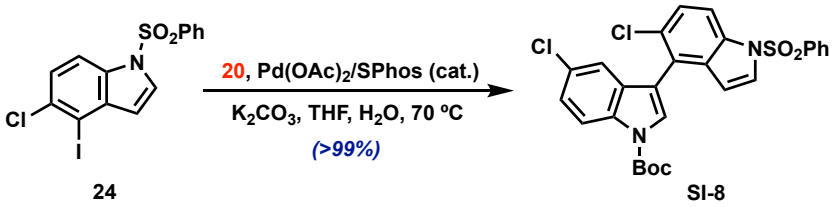
Physical properties: yellow solid;
R_f = 0.32 (silica gel, 25% EtOAc/hexanes);
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 – 7.88 (m, 2H), 7.71 – 7.66 (m, 1H), 7.63 (d, J = 3.7 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.13 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 8.9 Hz, 1H), 7.08 (d, J = 3.8 Hz, 1H), 5.81 (s, 2H).



SI-7 **24**

1-(Benzenesulfonyl)-5-chloro-4-iodoindole **(24):** To a suspension of compound **SI-7** (3.91 g, 12.75 mmol, 1.0 equiv) in 5% aqueous solution of HCl (127 mL) at 0 °C was added a solution of $NaNO_2$ (1.94 g, 28.12 mmol, 2.2 equiv) in water (63 mL) dropwise via addition funnel. After the addition was complete, the mixture was stirred for 2 h at the same temperature. A solution of KI (53 g, 0.32 mol, 25.0 equiv) in water (126 mL) was then added dropwise via addition funnel at 0 °C. After completion of the addition, the reaction mixture was stirred at the same temperature for a further 2 h. The reaction mixture was then transferred to a separatory funnel and extracted with EtOAc (3 × 150 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was chromatographed on silica gel (10–20% EtOAc/hexanes gradient) to afford pure 5-chloro-4-iodoindole **24** (3.59 g, 67%, 84% brsm) and recovered amine **SI-7** (768 mg, 20%). ^{1}H NMR spectral data are in agreement with the literature.[6]

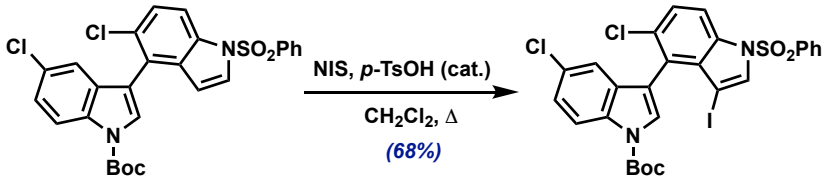
Physical properties: yellow solid;
R_f = 0.54 (silica gel, 25% EtOAc/hexanes);
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 – 7.99 (m, 3H), 7.97 (d, J = 8.8 Hz, 1H), 7.75 – 7.69 (m, 1H), 7.64 – 7.58 (m, 2H), 7.50 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 3.7 Hz, 1H).



24 SI-8

***3,4′-bisindole* SI-8:** A mixture of boronate **20** (5.22 g, 15.5 mmol, 1.8 equiv) and iodide **24** (3.59 g, 8.6 mmol, 1.0 equiv) were dissolved in THF (60 mL) and degassed by argon sparge for 30 min. SPhos (705 mg, 1.7 mmol, 0.2 equiv) and $Pd(OAc)_2$ (193 mg, 0.86 mmol, 0.1 equiv) were then added to the mixture followed by K_2CO_3 (5.93 g, 49.2 mmol, 5.0 equiv) in degassed H_2O (12 mL). The mixture was heated at 75 °C for 6 h. After cooling to room temperature, the contents were transferred to a separatory funnel and diluted with H_2O/EtOAc (60 mL/40 mL). The layers were separated and the aqueous layer was reextracted with EtOAc (40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (10–25% EtOAc/hexanes gradient) to afford pure 3,4′-bisindole **SI-8** (4.72 g, >99%).

Physical properties: white solid;
R_f = 0.52 (silica gel, 25% EtOAc/hexanes);
MS (ESI): calcd for $C_{27}H_{21}Cl_2N_2O_4S$ $[M - H]^-$ 539.1, found 538.9;
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14 (br s, 1H), 7.98 (d, *J* = 8.9 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.70 (s, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 3.8 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.30 (d, *J* = 8.9 Hz, 1H), 7.17 (s, 1H), 6.41 (d, *J* = 3.7 Hz, 1H), 1.68 (s, 9H);
^{13}C NMR (150 MHz, $CDCl_3$): δ 28.1, 84.6, 108.7, 114.0, 115.9, 116.4, 120.2, 124.4, 124.8, 126.1, 126.5, 126.8, 127.4, 128.5, 129.0, 129.5, 130.6, 132.4, 133.1, 133.5, 134.2, 137.9, 149.2.

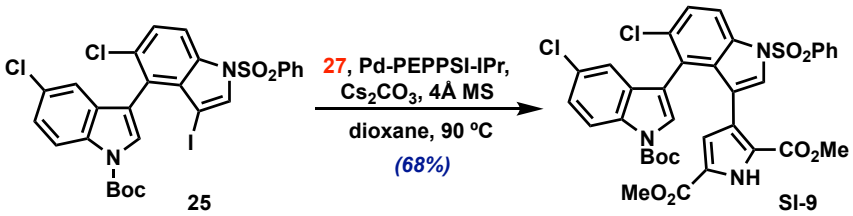


SI-8 25

***3′-iodobisindole* 25:** To a solution of compound **SI-8** (282 mg, 0.52 mmol, 1.0 equiv) in CH_2Cl_2 (5.2 mL) at room temperature was added *p*-TsOH•H_2O (9.9 mg, 0.052 mmol, 0.1 equiv) and *N*-iodosuccinimide (129 mg, 0.57 mmol, 1.1 equiv). The reaction was heated to 40 °C and stirred at this temperature for 6 h. After completion (monitored by aliquot ^{1}H NMR, the C3′–H peak at 6.4 ppm disappeared), the reaction mixture was quenched with 10 mL water and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were washed with saturated aqueous Na_2SO_3 solution, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (10–25% EtOAc/hexanes gradient) to afford pure 3′-iodobisindole **25** (237 mg, 68%). [**Note:** Upon scale-up with 2.71 g **SI-8**, 2.02 g of **25** was obtained; yield: 60%].

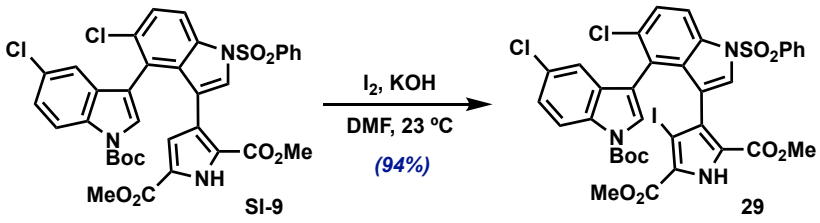
Physical properties: white solid;
R_f = 0.52 (silica gel, 25% EtOAc/hexanes);
MS (ESI): calcd for $C_{27}H_{20}Cl_2IN_2O_4S$ $[M - H]^-$ 665.0, found 664.8;

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (br s, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 2H), 7.74 (s, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.57 (s, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.30 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.01 (d, *J* = 2.2 Hz, 1H), 1.67 (s, 9H);
^{13}C NMR (150 MHz, $CDCl_3$): δ 28.2, 62.8, 84.4, 112.9, 114.0, 116.4, 119.8, 124.8, 125.1, 126.4, 127.0, 128.2, 128.6, 129.7, 129.8, 131.5, 132.4, 132.8, 133.0, 133.1, 134.5, 137.5, 149.4.



***Triaryl* SI-9:** A mixture of pyrrolestannane **27** (842 mg, 2.43 mmol, 2.0 equiv) and compound **25** (810 mg, 1.21 mmol, 1.0 equiv) were dissolved in dioxane (50 mL) and degassed by argon sparge for 30 min. Pd-PEPPSI-IPr (65 mg, 0.095 mmol, 0.08 equiv), Cs_2CO_3 (753 mg, 2.31 mmol, 1.9 equiv) and activated, powdered 4Å molecular sieves (324 mg) were then added and the reaction was heated at 90 °C overnight (14 h). After cooling to room temperature, silica gel was directly added to the reaction mixture, which was then concentrated to remove all volatiles. The adsorbed crude material was chromatographed on silica gel (10–20% EtOAc/hexanes gradient) to afford pure triaryl **SI-9** (594 mg, 68%).

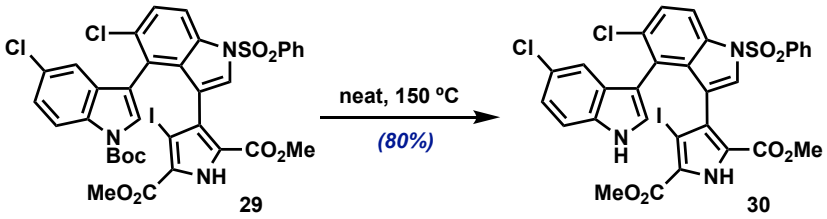
Physical properties: white solid;
R_f = 0.12 (silica gel, 25% EtOAc/hexanes);
MS (ESI): calcd for $C_{35}H_{28}Cl_2N_3O_8S$ $[M - H]^-$ 720.1, found 720.0;
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.18 (br s, 1H), 8.05 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 2H), 7.90 (br s, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.56 (s, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.07 (br s, 1H), 6.97 (s, 1H), 6.27 (br s, 1H), 3.80 (s, 3H), 3.46 (s, 3H), 1.61 (s, 9H);
^{13}C NMR (150 MHz, $CDCl_3$): δ 28.0, 51.6, 51.9, 84.1, 114.4, 114.8, 115.7, 116.4, 117.3, 120.0, 121.6, 123.0, 123.5, 124.3, 124.5, 125.8, 126.7, 126.86, 126.92, 128.1, 129.4, 130.3, 130.97, 131.01, 132.7, 133.4, 134.1, 138.0, 148.7, 159.3, 160.1.



***N-Boc triaryl iodide* 29:** KOH (7 mg, 0.13 mmol, 3.0 equiv) was added to a solution of compound **SI-9** (30 mg, 0.042 mmol, 1.0 equiv) in DMF (3 mL) at room temperature. After stirring for 20 min, iodine (15.8 mg, 0.062 mmol, 1.5 equiv) was added. After a further 6 h, the reaction was quenched with water (15 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were washed with water (3 × 10 mL), brine (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (25–40%

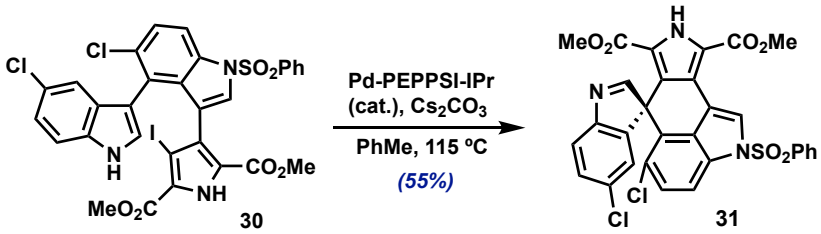
EtOAc/hexanes gradient) to afford pure *N*-Boc triaryl iodide **29** (33 mg, 94%). [**Note:** Upon scale-up with 201 mg **SI-9**, 200 mg of **29** was obtained; yield: 85%. The corresponding bromide could be prepared by substituting NBS for I_2 under analogous conditions; yield: 99%].

Physical properties: yellow powder;
R_f = 0.12 (silica gel, 25% EtOAc/hexanes);
MS (ESI): calcd for $C_{35}H_{27}Cl_2IN_3O_8S$ $[M - H]^-$ 846.0, found 845.8;
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.33 (br s, 1H), 8.07 (d, *J* = 9.0 Hz, 1H), 7.99 – 7.92 (m, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.52 – 7.47 (m, 4H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.14 (s, 1H), 6.96 (s, 1H), 3.88 (s, 3H), 3.34 (s, 3H), 1.59 (s, 9H);
^{13}C NMR (150 MHz, $CDCl_3$): δ 28.0, 52.0, 52.1, 84.2, 114.4, 114.6, 115.9, 116.8, 119.8, 123.9, 124.4, 124.5, 125.9, 126.7, 126.8, 126.88, 126.93, 128.1, 128.2, 129.4, 129.5, 130.5, 130.6, 131.3, 132.9, 133.5, 134.1, 137.9, 148.5, 158.0, 158.9.



***N-H triaryl iodide* 30:** Compound **29** (388 mg, 0.457 mmol) was heated neat at 150 °C under argon for 3 h. After cooling to room temperature, the residue was chromatographed on silica gel (30–60% EtOAc/hexanes gradient) to afford pure *N*-H triaryl iodide **30** as a mixture of separable but interconverting atropisomers (major:minor = 2:1, 273 mg, 80%) [**Note:** crude dr (major:minor) = ~3:1].

Physical properties: white solid;
R_f = 0.14 (minor), 0.47 (major) (silica gel, 50% EtOAc/hexanes);
MS (ESI): calcd for $C_{30}H_{19}Cl_2IN_3O_6S$ $[M - H]^-$ 746.0, found 745.7;
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.37 (br s, $1H_{minor}$), 9.34 (br s, $1H_{major}$), 8.17 (br s, $1H_{minor}$), 8.04 (d, J = 9.0 Hz, $1H_{minor}$), 8.04 (d, J = 9.0 Hz, $1H_{major}$), 8.00 – 7.97 (m, $2H_{minor}$), 7.95 – 7.92 (m, $3H_{major}$), 7.63 – 7.58 (m, $1H_{major}$ + $1H_{minor}$), 7.54 (s, $1H_{minor}$), 7.53 – 7.46 (m, $4H_{major}$ + $3H_{minor}$), 7.13 (d, J = 8.6 Hz, $1H_{major}$), 7.07 (dd, J = 8.7, 2.1 Hz, $1H_{major}$), 7.05 (d, J = 8.5 Hz, $1H_{minor}$), 7.00 (d, J = 1.9 Hz, $1H_{major}$), 6.92 (dd, *J* = 8.6, 2.0 Hz, $1H_{minor}$), 6.90 (d, *J* = 1.9 Hz, $1H_{minor}$), 6.80 (d, J = 2.5 Hz, $1H_{major}$), 6.77 (d, J = 2.4 Hz, $1H_{minor}$), 3.92 (s, $3H_{major}$), 3.83 (s, $3H_{minor}$), 3.50 (s, $3H_{minor}$), 3.37 (s, $3H_{major}$). [**Note:** where possible, individual signals for the major and minor atropisomers are indicated]
^{13}C NMR (100 MHz, $CDCl_3$): δ 51.8, 52.1, 52.2, 77.6, 78.6, 110.7, 111.2, 111.5, 111.7, 114.06, 114.12, 117.1, 117.3, 119.4, 120.0, 122.3, 122.4, 123.4, 123.92, 123.94, 124.3, 124.4, 125.5, 125.6, 125.84, 125.89, 125.92, 125.99, 126.1, 126.87, 126.91, 127.0, 127.77, 127.82, 128.2, 129.4, 130.94, 130.95, 131.2, 131.4, 133.3, 133.4, 133.47, 133.50, 134.1, 134.2, 137.8, 137.9, 158.2, 159.3, 159.4, 159.7. [**Note**: four carbon signals missing due to signal overlap]



***Protected* (±)-*SPM A* (31)**: Compound **30** (18 mg, 0.024 mmol) was dissolved in toluene (2 mL) and degassed by argon sparge for 30 min. Pd-PEPPSI-IPr (0.8 mg, 0.0012 mmol, 0.05 equiv) and Cs_2CO_3 (11.8 mg, 0.036 mmol, 1.5 equiv) were then added. The mixture was heated at 115 °C for 4 h. After cooling to room temperature, the reaction mixture was quenched by 10 mL water and extracted with EtOAc (3 × 5 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was chromatographed by PTLC (Et_2O) to afford pure protected SPM A (**31**) (8.2 mg, 55%).

***Spirocycle* 31:**

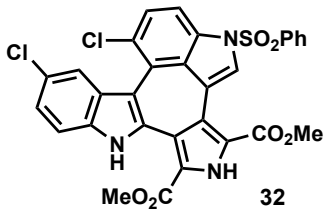
Physical properties: yellow solid;

R_f = 0.24 (silica gel, Et_2O);

MS (ESI): calcd for $C_{30}H_{18}Cl_2N_3O_6S$ $[M - H]^-$ 618.0, found 617.9.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.90 (br s, 1H), 8.54 (s, 1H), 7.99 (d, *J* = 7.9 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.76 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 6.88 (s, 1H), 4.05 (s, 3H), 3.52 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 51.9, 52.3, 61.2, 111.3, 114.3, 118.4, 119.9, 120.6, 121.2, 122.1, 123.2, 123.5, 126.9, 126.96, 127.00, 128.6, 129.5, 129.6, 129.7, 132.3, 132.5, 134.2, 138.0, 145.4, 157.9, 158.7, 159.5, 167.0.



***Byproduct* 32:**

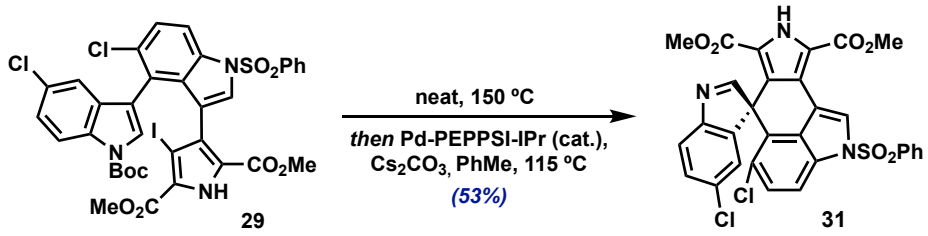
Physical properties: yellow solid;

R_f = 0.15 (silica gel, Et_2O);

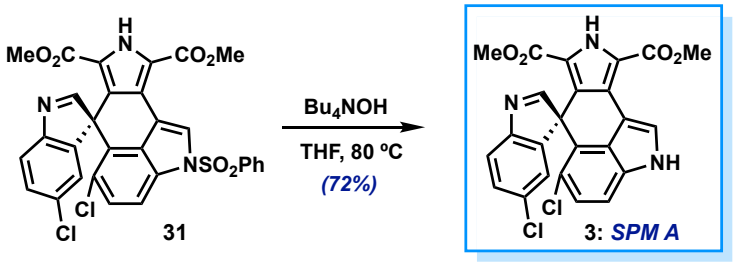
MS (ESI): calcd for $C_{30}H_{18}Cl_2N_3O_6S$ $[M - H]^-$ 618.0, found 618.0.

^{1}H NMR (600 MHz, $CDCl_3$): δ 11.43 (br s, 1H), 9.87 (br s, 1H), 9.04 (s, 1H), 7.99 – 7.96 (m, 2H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 1.9 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.15 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 52.6, 53.1, 111.3, 111.9, 112.2, 114.3, 119.3, 120.5, 122.50, 122.54, 123.3, 124.8, 125.1, 125.2, 126.0, 127.0, 127.7, 128.2, 129.3, 129.6, 133.0, 134.0, 134.1, 134.9, 137.7, 159.1, 161.0. [**Note**: one carbon signal missing due to signal overlap]



***One-pot synthesis of protected* (±)-*SPM A* (31):** Compound **29** (42 mg, 0.05 mmol, 1.0 equiv) was heated neat at 150 °C under argon for 3 h. After cooling to room temperature, the residue was dissolved in toluene (4 mL) and degassed by argon sparge for 30 min. Pd-PEPPSI-IPr (1.7 mg, 0.0025 mmol, 0.05 equiv) and Cs_2CO_3 (24.4 mg, 0.075 mmol, 1.5 equiv) were then added. The reaction mixture was heated at 115 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched with water (20 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by PTLC (Et_2O) to afford pure protected SPM A (**31**) (14.3 mg, 46%). [**Note:** When the reaction was scaled up to 120 mg of **29**, 65 mg of an 8:1 mixture of **31**:**32** was obtained by column chromatography; yield of **31**: 53%. The small amount of **32** present could be more easily removed after the next step]

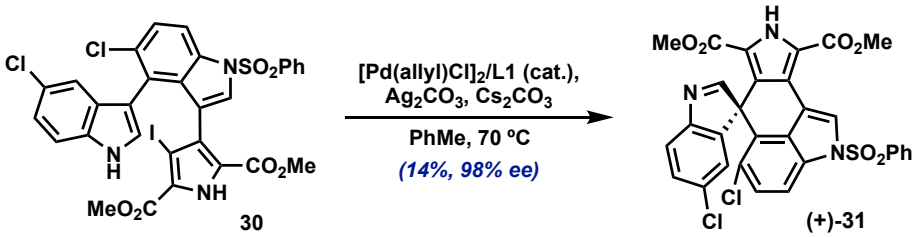


(±)-*Spiroindimicin A* [(±)-3]: Tetrabutylammonium hydroxide solution (685 mg, 10 wt% in MeOH, 6.0 equiv) was added dropwise to a solution of compound **31** (27 mg, 0.044 mmol, 1.0 equiv) in dry THF (3 mL) at room temperature. The reaction vial was then sealed and the mixture heated at 80 °C for 8 h. After cooling to room temperature, the reaction was quenched with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (60–90% EtOAc/hexanes gradient) to afford pure racemic SPM A (**(±)-3**) (15 mg, 72%). ^{1}H and ^{13}C NMR spectral data are in agreement with the literature.[4]

Physical properties: yellow solid;
R_f = 0.63 (silica gel, 83% EtOAc/hexanes);
MS (ESI): calcd for $C_{24}H_{14}Cl_2N_3O_4$ $[M - H]^-$ 478.0, found 478.0.
^{1}H NMR (400 MHz, DMSO-d_6): δ 12.20 (s, 1H), 11.48 (d, J = 2.6 Hz, 1H), 8.08 (d, J = 2.5 Hz, 1H), 8.04 (s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.40 (dd, J = 8.3, 2.2 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 2.1 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 3.92 (s, 3H), 3.36 (s, 3H).

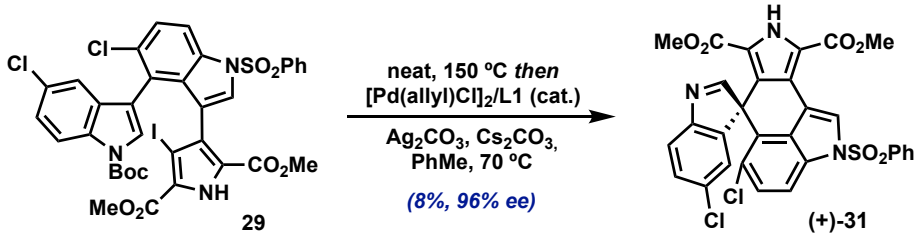
^{13}C NMR (150 MHz, DMSO-d_6): δ 51.5, 51.6, 61.3, 105.6, 112.6, 116.2, 116.3, 120.7, 120.8, 121.5, 122.3, 122.7, 123.6, 123.7, 125.8, 127.3, 128.0, 130.6, 133.5, 147.3, 157.6, 159.7, 160.4, 169.3.

[**Note:** The enantiomers of **3** could be separated via preparative HPLC on a CHIRALCEL AD column using a 10–20% *i*-propanol/hexanes gradient, with (+)-(*S*)-**3** eluting first, followed by (–)-(*R*)-**3**]



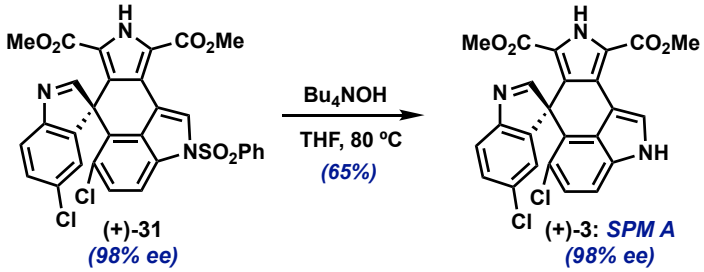
***Protected* (+)-*SPM A* (31):** A vial was charged with toluene (2.0 mL) and degassed by argon sparge for 30 min, then [Pd(allyl)Cl]$_2$ (2.0 mg, 0.0055 mmol, 0.2 equiv) and **L1** (8.4 mg, 0.016 mmol, 0.6 equiv) were added and stirred for 1 h at room temperature. In a separate vial, **30** (20.4 mg, 0.027 mmol, 1.0 equiv) was dissolved in toluene (2.0 mL) and degassed by argon sparge for 30 min. Ag_2CO_3 (18.8 mg, 0.068 mmol, 2.5 equiv) and Cs_2CO_3 (22.3 mg, 0.068 mmol, 2.5 equiv) were then added to this solution, followed by the catalyst solution. The reaction was then heated at 70 °C and monitored by TLC. After completion (12 h), the reaction mixture was allowed to cool to room temperature, filtered through a pad of Celite, and washed with MeOH/EtOAc (v/v = 1/4) (2 × 5 mL). The filtrate was concentrated and the residue was purified by PTLC (Et_2O) to afford pure spirocycle **31** (2.4 mg, 14%). The enantiopurity was determined to be 98% ee by HPLC (OD-H, hexane/*i*-PrOH = 60/40, 0.8 mL/min, t_R (major) = 15.80 min, t_R (minor) = 37.34 min). ^{1}H and ^{13}C NMR data matched that of our racemic sample. [**Note:** Attempted aqueous work-up (e.g., H_2O/EtOAc) and purification of the crude material on silica gel often led to a significant drop in enantiopurity, for reasons we currently do not fully understand. Pure **31** is stable to silica gel (column chromatography or PTLC)].

Optical rotation: $[\alpha]^{26}_D$ = +4 (c = 0.05, MeOH; 97% ee). [**Note:** optical rotation was measured on a different sample of 97% ee]



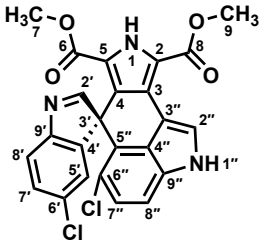
***One-pot synthesis of protected* (+)-*SPM A* (31):** Compound **29** (92.6 mg, 0.11 mmol, 1.0 equiv) was heated neat at 150 °C under argon for 3 h. After cooling to room temperature, the residue was dissolved in toluene (4 mL) and degassed by argon sparge for 30 min. Cs_2CO_3 (88.9 mg, 0.27 mmol, 2.5 equiv) and Ag_2CO_3 (74.5 mg, 0.27 mmol, 2.5 equiv) were added to the solution followed by a solution of [Pd(allyl)Cl]$_2$ (8.0 mg, 0.022 mmol, 0.2 equiv) and (*R*)-SIPHOS-PE (**L1**, 33.1 mg, 0.065 mmol, 0.6 equiv) in degassed toluene (2 mL) that had

been prestirred for 1 h. The reaction mixture was heated at 70 °C for 12 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite and washed with MeOH/EtOAc (v/v = 1/4) (3 × 5 mL). The filtrate was concentrated under vacuum and the residue was purified by PTLC (Et_2O) to afford pure protected SPM A (**31**) (5.6 mg, 8%). The enantiopurity was determined to be 96% ee by HPLC (OD-H, hexane/*i*-PrOH = 60/40, 0.8 mL/min, t_R (major) = 15.80 min, t_R (minor) = 37.34 min).



(+)-*Spiroindimicin A* [(+)-3]: Tetrabutylammonium hydroxide solution (67 mg, 10 wt% in MeOH, 0.0258 mmol, 5.7 equiv) was added dropwise to a solution of compound **31** (2.8 mg, 0.0045 mmol, 1.0 equiv) in dry THF (2 mL) at room temperature. The reaction vial was then sealed and the mixture heated at 80 °C for 8 h. After cooling to room temperature, the reaction was quenched with water (6 mL) and extracted with EtOAc (2 × 6 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by PTLC (Et_2O) to afford pure SPM A (**(+)-3**) (1.4 mg, 65%). The enantiopurity was determined to be 98% ee by HPLC (AD-H, hexane/*i*-PrOH = 75/25, 0.8 mL/min, t_R (major) = 10.43 min, t_R (minor) =11.54 min). ^{1}H and ^{13}C NMR data matched that of our racemic sample.

Optical rotation: $[\alpha]^{26}_D$ = +64.0 (c = 0.05, MeOH; 98% ee). [Lit:[4] $[\alpha]^{20}_D$ = +46.49 (c = 0.15, MeOH)]



3: ***spiroindimicin A***

Table S5: Comparison of ^{1}H NMR shifts (δ) of natural[4] spiroindimicin A (**3**) and our own synthetic **3** in DMSO-d_6.

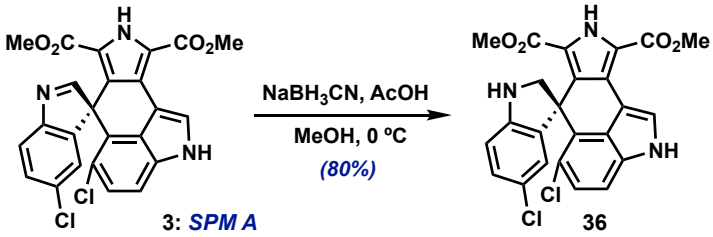
Position	Natural **3** (500 MHz)	Synthetic **3** *(Smith)* (600 MHz)
1	12.20 (br s, 1H)	12.20 (br s, 1H)
2		
3		
4		
5		

6		
7	3.36 (s, 3H)	3.36 (s, 3H)
8		
9	3.92 (s, 3H)	3.92 (s, 3H)
1’		
2’	8.04 (s, 1H)	8.04 (s, 1H)
3’		
4’		
5’	6.97 (d, *J* = 2.0 Hz, 1H)	6.97 (d, *J* = 2.1 Hz, 2H)
6’		
7’	7.41 (dd, *J* = 8.0 Hz; 2.0 Hz, 1H)	7.40 (dd, *J* = 8.3, 2.2 Hz, 1H)
8’	7.62 (d, *J* = 8.0 Hz, 1H)	7.61 (d, *J* = 8.3 Hz, 1H)
9’		
1’’	11.47 (s, 1H)	11.48 (d, *J* = 2.6 Hz, 1H)
2’’	8.08 (d, *J* = 2.0 Hz, 1H)	8.08 (d, *J* = 2.5 Hz, 1H)
3’’		
4’’		
5’’		
6’’		
7’’	7.35 (d, *J* = 8.5 Hz, 1H)	7.35 (d, *J* = 8.4 Hz, 1H)
8’’	6.98 (d, *J* = 8.5 Hz, 1H)	6.97 (d, *J* = 8.4 Hz, 2H)
9’’		

Table S6: Comparison of ^{13}C NMR shifts (δ) of natural[4] spiroindimicin A (**3**) and our own synthetic **3** in DMSO-d_6.

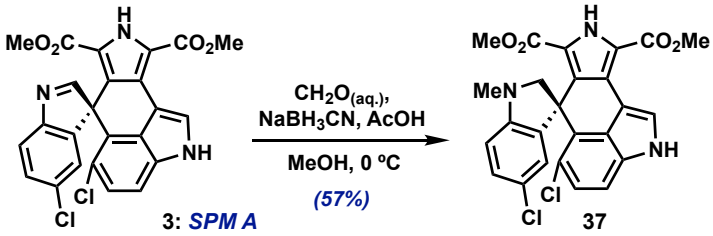
Position	Natural **3** (500 MHz)	Synthetic **3** *(Smith)* (600 MHz)
1		
2	116.1	116.2
3	122.2	122.2
4	116.2	116.3
5	123.6	123.7
6	159.6	159.7
7	51.4	51.5
8	160.3	160.4
9	51.5	51.6
1’		
2’	169.2	169.3
3’	61.2	61.3
4’	147.2	147.3
5’	122.6	122.7

6’	130.5	130.6
7’	127.9	128.0
8’	121.4	121.5
9’	157.5	157.6
1”		
2”	123.5	123.6
3”	105.5	105.6
4”	133.4	133.5
5”	120.7	120.7
6”	120.7	120.8
7”	112.5	112.6
8”	125.7	125.8
9”	127.2	127.2



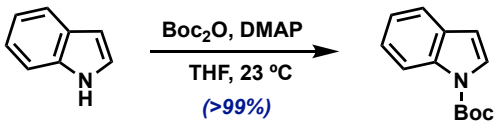
***Dihydrospiroindimicin A* (36):** $NaBH_3CN$ (2.3 mg, 0.037 mmol, 5.0 equiv) was added in one portion to a solution of SPM A (**3**, 3.5 mg, 0.0073 mmol, 1.0 equiv) in MeOH/acetic acid (1.0 mL/10 μL) at 0 °C. The reaction was kept at this temperature for 20 min then quenched with saturated aqueous $NaHCO_3$ (3 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by PTLC (50% EtOAc/hexane) to afford pure dihydrospiroindimicin A (**36**) (2.8 mg, 80%).

Physical properties: yellow solid;
R_f = 0.27 (silica gel, 50% EtOAc/hexanes);
MS (ESI): Calcd for $C_{24}H_{18}Cl_2N_3O_4$ $[M + H]^+$ 482.1; Found 482.0.
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.66 (br s, 1H), 8.24 (br s, 1H), 8.11 (d, *J* = 2.3 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.98 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 4.43 (br s, 1H), 4.28 (d, *J* = 11.1 Hz, 1H), 4.12 (d, *J* = 11.0 Hz, 1H), 4.01 (s, 3H), 3.74 (s, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 51.7, 51.79, 51.85, 64.7, 106.7, 110.4, 110.9, 115.7, 121.5, 122.2, 123.6, 124.5, 124.7, 125.6, 127.6, 127.8, 132.5, 133.1, 134.4, 137.2, 152.6, 159.4, 160.6. [**Note**: one carbon signal missing due to signal overlap]



***N-methyl dihydrospiroindimicin A* (37):** Aqueous formaldehyde (37 wt%, 3.5 mg, 5.0 equiv) was added to a solution of SPM A (**3**, 4.1 mg, 0.0085 mmol, 1.0 equiv) in MeOH/CH_3COOH (1.0 mL/10 µL) at 0 °C, followed by $NaBH_3CN$ (4.6 mg, 0.085 mmol, 10.0 equiv). The reaction was allowed to warm to room temperature and stir for 20 min, then quenched with saturated aqueous $NaHCO_3$ (3 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by PTLC (50% EtOAc/hexane) to afford pure *N*-methyl dihydrospiroindimicin A (**37**) (2.4 mg, 57%).

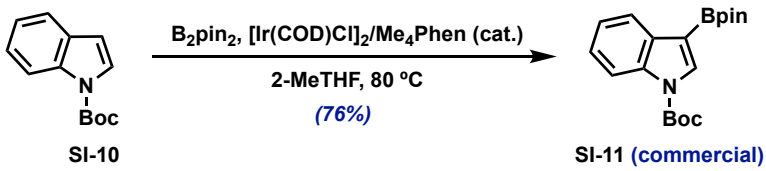
Physical properties: yellow solid;
R_f = 0.40 (silica gel, 50% EtOAc/hexanes);
MS (ESI): Calcd for $C_{25}H_{18}Cl_2N_3O_4$ $[M - H]^-$ 494.1; Found 494.0.
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.69 (br s, 1H), 8.20 (br s, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 6.23 (d, *J* = 8.4 Hz, 1H), 4.16 (d, *J* = 9.9 Hz, 1H), 4.03 (d, *J* = 9.9 Hz, 1H), 4.00 (s, 3H), 3.67 (s, 3H), 3.02 (s, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 33.0, 49.2, 51.6, 51.8, 71.6, 103.2, 106.8, 110.3, 115.7, 118.8, 121.7, 122.1, 122.7, 124.2, 124.5, 125.4, 127.69, 127.74, 132.4, 133.0, 133.4, 135.6, 152.5, 159.8, 160.6.



indole **SI-10**

***N-Boc-indole* (SI-10):** To a solution of indole (2.34 g, 20 mmol, 1.0 equiv) in THF (20 mL) was added $(Boc)_2O$ (4.8 g, 22 mmol, 1.1 equiv) and 4-(dimethylamino)pyridine (21.4 mg, 0.20 mmol, 0.01 equiv), and the reaction was stirred overnight (16 h) at room temperature. Silica gel was directly added to the reaction mixture, which was concentrated under vacuum and chromatographed on silica gel (5–10% EtOAc/hexanes gradient) to give pure Boc-protected indole **SI-10** (4.4 g, >99%). ^{1}H NMR spectral data are in agreement with the literature.[7]

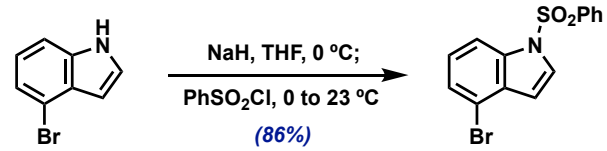
Physical properties: colorless oil;
R_f = 0.81 (silica gel, 17% EtOAc/hexanes);
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 3.7 Hz, 1H), 7.58 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.33 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.28 – 7.21 (m, 1H), 6.59 (d, *J* = 3.7 Hz, 1H), 1.69 (s, 9H).



SI-10 **SI-11 (commercial)**

***N-Boc-3-(pinacolatoboryl)indole* (SI-11):** To a solution of compound **SI-10** (1.09 g, 5.02 mmol, 1.0 equiv) in 2-methyltetrahydrofuran (22 mL, degassed by argon sparge for ~20 min) was added $[Ir(COD)Cl]_2$ (85 mg, 0.126 mmol, 0.025 equiv) and 3,4,7,8-tetramethyl-1,10-phenanthroline (60 mg, 0.254 mmol, 0.051 equiv), followed by bis(pinacolato)diboron (1.29 g, 5.08 mmol, 1.0 equiv). The reaction mixture was heated to 80 °C and soon became dark red. After 23 h at this temperature, the reaction mixture was allowed to cool to room temperature and subsequently passed through a silica gel plug to remove iridium catalyst residue, rinsing with 40% EtOAc/hexanes. The eluent was concentrated and the resulting crude product was chromatographed on silica gel (0–12% EtOAc/hexanes gradient) to give pure 3-borylated indole **SI-11** (1.30 g, 76%). ^{1}H NMR spectral data are in agreement with the literature.[8]

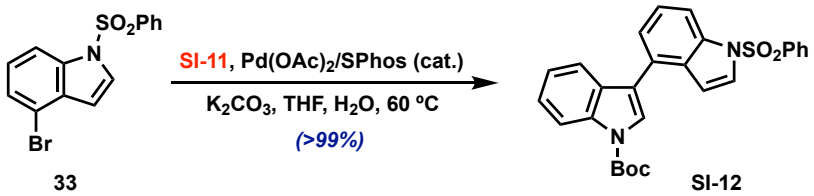
Physical properties: white solid;
R_f = 0.39 (silica gel, 9% EtOAc/hexanes);
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 8.00 – 7.97 (m, 1H), 7.31 (td, *J* = 8.2, 7.7, 1.6 Hz, 1H), 7.28 – 7.24 (m, 1H), 1.66 (s, 9H), 1.38 (s, 12H).



4-bromoindole **33**

***N-benzenesulfonyl-4-bromoindole* (33):** To a solution of 4-bromoindole (96%, 1.047 g, 5.13 mmol, 1.0 equiv) in THF (21 mL) at 0 °C was added sodium hydride (60% in mineral oil, 0.256 g, 6.41 mmol, 1.25 equiv). After stirring for 1 h at this temperature, benzenesulfonyl chloride (0.82 mL, 6.41 mmol, 1.25 equiv) was added dropwise and the reaction was allowed to warm slowly to room temperature. After 1.5 h, TLC indicated full conversion of starting material so the reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and transferred to a separatory funnel, diluting with EtOAc (30 mL) and H_2O (20 mL). The layers were separated and the aqueous layer reextracted with EtOAc (30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed on silica gel (5–15% EtOAc/hexanes gradient) to give pure protected indole **33** (1.482 g, 86%). ^{1}H NMR spectral data are in agreement with the literature.[9]

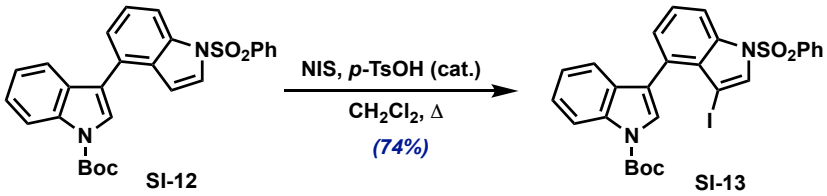
Physical properties: light yellow solid;
R_f = 0.55 (silica gel, 15% EtOAc/hexanes);
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.3 Hz, 1H), 7.92 – 7.84 (m, 2H), 7.64 (d, *J* = 3.7 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.47 – 7.42 (m, 2H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 3.7 Hz, 1H).



33 SI-12

***3,4′-bisindole* SI-12:** Bromide **33** (0.766 g, 2.278 mmol, 1.0 equiv) and boronate **SI-11** (1.302 g, 3.792 mmol, 1.67 equiv) were dissolved in THF (16 mL) and degassed by argon sparge for 15 min. SPhos (187 mg, 0.456 mmol, 0.2 equiv) and $Pd(OAc)_2$ (51 mg, 0.228 mmol, 0.1 equiv) were then added, followed by K_2CO_3 (1.51 g, 10.92 mmol, 4.8 equiv) in degassed H_2O (4 mL). The reaction mixture was heated at 60 °C for 3.75 h, at which point TLC showed full consumption of starting material. After cooling to room temperature, the contents were transferred to a separatory funnel and diluted with H_2O/EtOAc (35 mL/35 mL). The layers were separated and the aqueous layer was reextracted with EtOAc (35 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (5–25% EtOAc/hexanes gradient) to afford pure 3,4′-bisindole **SI-12** (1.069 g, >99%).

Physical properties: light brown foam;
R_f = 0.40 (silica gel, 17% EtOAc/hexanes);
MS (ESI): calcd for $C_{23}H_{20}N_2NaO_3S$ $[M - Boc + MeOH + Na]^+$ 427.1, found 427.2;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (br d, *J* = 8.4 Hz, 1H), 8.04 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.97 – 7.91 (m, 2H), 7.74 (s, 1H), 7.62 (d, *J* = 3.7 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.50 – 7.45 (m, 2H), 7.45 – 7.41 (m, 2H), 7.41 – 7.35 (m, 1H), 7.25 (td, *J* = 7.6, 7.2, 1.0 Hz, 1H), 6.77 (d, *J* = 3.7 Hz, 1H), 1.70 (s, 9H);
^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 84.0, 108.8, 112.5, 115.4, 120.0, 120.3, 122.8, 123.8, 123.9, 124.7, 124.8, 126.2, 126.8, 127.0, 129.3, 129.4, 129.7, 133.8, 135.2, 135.6, 138.3, 149.7.

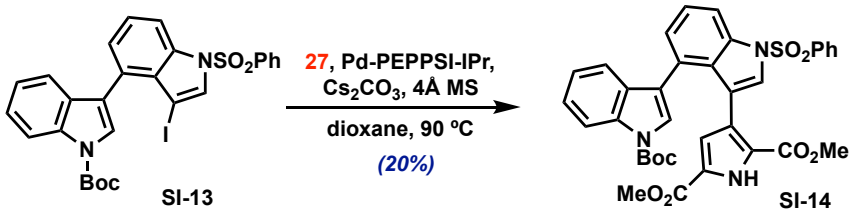


SI-12 SI-13

***3′-iodobisindole* SI-13:** To a solution of compound **SI-12** (934 mg, 1.98 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at room temperature were added *p*-TsOH•H_2O (38 mg, 0.20 mmol, 0.1 equiv) and NIS (490 mg, 2.18 mmol, 1.1 equiv). The reaction was heated to 40 °C and stirred at this temperature for 6 h. After completion (monitored by aliquot ^{1}H NMR, the C3′–H peak at 6.7 ppm disappeared), the reaction mixture was quenched with 10 mL water and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with saturated aqueous Na_2SO_3 solution, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was chromatographed on silica gel (10–25% EtOAc/hexanes gradient) to afford pure 3′-iodobisindole **SI-13** (875 mg, 74%).

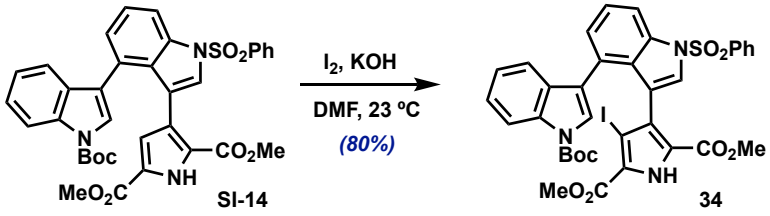
Physical properties: white solid;

R_f = 0.40 (silica gel, 17% EtOAc/hexanes);
MS (ESI): calcd for $C_{27}H_{23}N_2O_4S$ [M - I]$^-$ 471.1, found 471.1;
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.76 (s, 1H), 7.64 – 7.59 (m, 2H), 7.52 (t, *J* = 7.9 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.34 (ddd, *J* = 8.4, 6.7, 1.7 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.21 – 7.15 (m, 2H), 1.68 (s, 9H);
^{13}C NMR (150 MHz, $CDCl_3$): δ 28.2, 63.2, 83.8, 112.9, 115.1, 116.9, 120.4, 122.8, 124.5, 125.0, 126.0, 126.96, 127.01, 127.7, 128.2, 129.5, 131.8, 132.5, 134.2, 134.4, 134.6, 137.8, 149.8.



***Triaryl* SI-14:** Pyrrolestannane **27** (424 mg, 1.23 mmol, 2.0 equiv) and iodide **SI-13** (367 mg, 0.61 mmol, 1.0 equiv) were dissolved in dioxane (20 mL) and degassed by argon sparge for 30 min. Pd-PEPPSI-IPr (33 mg, 0.049 mmol, 0.08 equiv), Cs_2CO_3 (399 mg, 1.23 mmol, 2.0 equiv) and activated, powdered 4Å molecular sieves (367 mg) were then added and the reaction was heated at 90 °C overnight (14 h). After cooling to room temperature, silica gel was directly added to the reaction mixture, which was then concentrated to remove all volatiles. The adsorbed crude material was chromatographed on silica gel (25–40% EtOAc/hexanes gradient) to afford pure triaryl **SI-14** (82 mg, 20%).

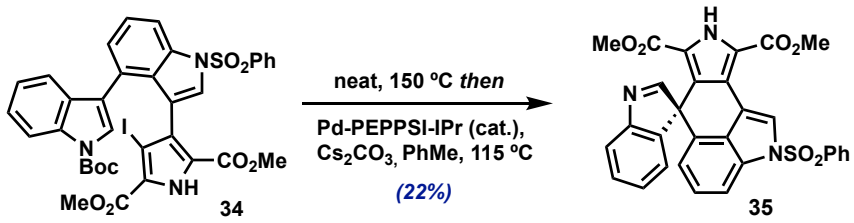
Physical properties: white solid;
R_f = 0.18 (silica gel, 25% EtOAc/hexanes);
MS (ESI): calcd for $C_{35}H_{30}N_3O_8S$ [M - H]$^-$ 652.2, found 652.0;
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.24 (br s, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 8.04 (br s, 1H), 7.97 (d, J =7.7 Hz, 2H), 7.63 (s, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.93 (br s, 1H), 6.48 (br s, 1H), 3.82 (s, 3H), 3.26 (s, 3H), 1.59 (s, 9H);
^{13}C NMR (150 MHz, $CDCl_3$): δ 28.0, 51.3, 51.8, 83.3, 112.8, 114.7, 116.7, 117.3, 118.6, 119.8, 122.3, 122.6, 123.4, 123.5, 124.2, 124.55, 124.60, 125.66, 125.68, 126.9, 127.2, 128.2, 129.3, 130.2, 133.9, 134.6, 135.4, 138.2, 149.2, 159.4, 160.2.



***N-Boc triaryl iodide* 34:** KOH (27.4 mg, 0.49 mmol, 3.0 equiv) was added to a solution of compound **SI-14** (106 mg, 0.163 mmol, 1.0 equiv) in DMF (3 mL). After stirring for 20 minutes at room temperature, iodine (62 mg, 0.21 mmol, 1.5 equiv) was added. After a further 6 h, the reaction mixture was quenched with water (15 mL) and extracted with EtOAc (3 × 10

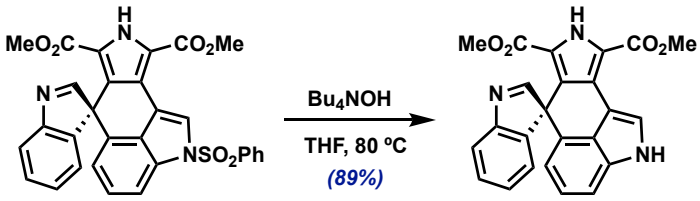
mL). The combined organic layers were washed with water (3 × 10 mL), brine (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel (25–40% EtOAc/hexanes gradient) to afford pure *N*-Boc triaryl iodide **34** (102 mg, 80%).

Physical properties: yellow powder;
R_f = 0.18 (silica gel, 25% EtOAc/hexanes);
MS (ESI): calcd for $C_{35}H_{29}IN_3O_8S$ [M - H]$^-$ 778.1, found 777.9;
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.40 (br s, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.03 (br s, 1H), 8.00 – 7.97 (m, 2H), 7.60 (s, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.29 – 7.16 (m, 3H), 7.08 (br t, *J* = 7.4 Hz, 1H), 6.95 (br s, 1H), 3.88 (s, 3H), 3.20 (br s, 3H), 1.60 (s, 9H);
^{13}C NMR (150 MHz, $CDCl_3$): δ 28.1, 51.6, 51.9, 83.5, 113.1, 114.7, 116.6, 119.8, 122.3, 124.0, 124.2, 124.3, 124.6, 125.8, 126.98, 127.01, 127.3, 128.6, 129.3, 130.0, 133.9, 134.5, 135.4, 138.1, 149.2, 158.4, 159.0. [**Note**: four carbon signals missing due to signal overlap]



***N-Benzenesulfonyl Spiroindolenine* 35:** Compound **34** (45 mg, 0.058 mmol, 1.0 equiv) was heated neat at 150 °C under argon for 3 h. After cooling to room temperature, the residue was dissolved in toluene (4 mL) and degassed by argon sparge for 30 min. Pd-PEPPSI-IPr (4 mg, 0.0058 mmol, 0.1 equiv), and Cs_2CO_3 (28 mg, 0.087 mmol, 1.5 equiv) were then added. The reaction mixture was heated at 115 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched with water (20 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by PTLC (Et_2O) to afford pure spirocycle **35** (6.9 mg, 22%).

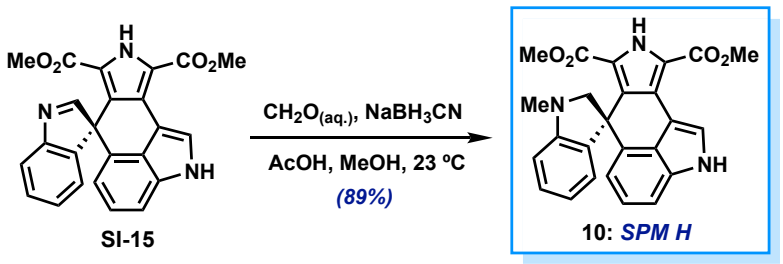
Physical properties: yellow solid;
R_f = 0.30 (silica gel, 75% EtOAc/hexanes);
MS (ESI): calcd for $C_{30}H_{19}ClN_3O_6S$ [M - H]$^-$ 584.1, found 584.0.
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (br s, 1H), 8.41 (s, 1H), 8.01 – 7.98 (m, 2H), 7.94 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 2H), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H), 7.14 (t, *J* = 7.9 Hz, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 7.3 Hz, 1H), 6.34 (d, *J* = 7.7 Hz, 1H), 4.07 (s, 3H), 3.40 (s, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 51.5, 52.2, 61.5, 111.3, 112.2, 119.2, 119.8, 120.8, 121.1, 121.3, 122.2, 122.6, 122.8, 125.6, 126.5, 126.9, 127.1, 127.8, 128.0, 129.4, 133.9, 134.2, 138.3, 148.1, 155.9, 159.4, 159.9, 173.3.



35 **SI-15**

***N-H Spiroindolenine* SI-15:** Tetrabutylammonium hydroxide solution (268 mg, 10 wt% in MeOH, 6.0 equiv) was added dropwise to a solution of compound **35** (9.5 mg, 0.017 mmol) in dry THF (3 mL) at room temperature. The reaction vial was then sealed and the mixture heated at 80 °C for 8 h. After cooling to room temperature, the reaction was quenched with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by PTLC (83% EtOAc/hexanes) to afford pure *N*-H spirocycle **SI-15** (6.3 mg, 89%).

Physical properties: yellow solid;
R_f = 0.31 (silica gel, 75% EtOAc/hexanes);
MS (ESI): Calcd for $C_{24}H_{16}N_3O_4$ [M - H]$^-$ 410.1; Found 410.1.
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.67 (br s, 1H), 8.25 (br s, 1H), 8.09 (d, *J* = 2.3 Hz, 1H), 8.04 (s, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.34 (td, *J* = 7.6, 1.2 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 7.3 Hz, 1H), 6.24 (d, *J* = 7.5 Hz, 1H), 4.03 (s, 3H), 3.41 (s, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 51.3, 51.9, 62.0, 106.1, 109.3, 116.1, 117.7, 120.6, 121.9, 122.2, 123.0, 124.2, 124.3, 124.7, 125.6, 126.9, 127.6, 134.9, 149.3, 155.8, 159.8, 160.5, 173.9. [**Note**: one carbon signal missing due to signal overlap]

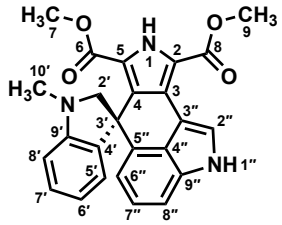


SI-15 **10: *SPM H***

***Spiroindimicin H* (10):** Aqueous formaldehyde (37 wt%, 6.2 mg, 0.076 mmol, 5.0 equiv) was added to a solution of compound **SI-15** (6.3 mg, 0.015 mmol, 1.0 equiv) in MeOH/CH_3COOH (1.0 mL/10 μL) at 0 °C, followed by $NaBH_3CN$ (9.6 mg, 0.15 mmol, 10.0 equiv). The reaction was allowed to warm to room temperature and stir for 20 min, then quenched with saturated aqueous $NaHCO_3$ (3 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by PTLC (50% EtOAc/hexane) to afford SPM H (**10**) (5.8 mg, 89%).

Physical properties: yellow solid;
R_f = 0.44 (silica gel, 50% EtOAc/hexanes);
MS (ESI): calcd for $C_{25}H_{20}N_3O_4$ [M - H]$^-$ 426.2, found 426.0.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.65 (br s, 1H), 8.15 (br s, 1H), 7.98 (d, *J* = 2.3 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.10 – 7.06 (m, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 6.52 (d, *J* = 7.1 Hz, 1H), 6.47 (t, *J* = 7.3 Hz, 1H), 4.02 (s, 3H), 3.93 (d, *J* = 8.5 Hz, 1H), 3.82 (d, *J* = 8.5 Hz, 1H), 3.49 (s, 3H), 2.94 (s, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 35.6, 49.2, 51.6, 51.9, 74.6, 106.2, 106.6, 108.4, 116.7, 116.8, 117.7, 121.3, 123.0, 123.25, 123.34, 123.9, 125.1, 127.5, 132.0, 134.1, 137.3, 141.0, 152.8, 160.4, 161.0. [**Note**: carbon spectrum referenced to $CDCl_3$ at δ 77.16]



10: ***spiroindimicin H***

Table S7: Comparison of ^{1}H NMR shifts (δ) of natural[10] spiroindimicin H (**10**) and our own synthetic **10** in $CDCl_3$.

Position	Natural **10** (500 MHz)	Synthetic **10** *(Smith)* (600 MHz)
1 (NH)	9.66 (s, 1H)	9.65 (br s, 1H)
2		
3		
4		
5		
6		
7	3.49 (s, 3H)	3.49 (s, 3H)
8		
9	4.02 (s, 3H)	4.02 (s, 3H)
1’		
2’	(a) 3.93 (d, *J* = 8.6 Hz, 1H) (b) 3.83 (d, *J* = 8.6 Hz, 1H)	(a) 3.93 (d, *J* = 8.5 Hz, 1H) (b) 3.82 (d, *J* = 8.5 Hz, 1H)
3’		
4’		
5’	6.52 (d, *J* = 7.3 Hz, 1H)	6.52 (d, *J* = 7.3, 1H)
6’	6.47 (dd, *J* = 7.3 Hz; 7.3 Hz, 1H)	6.47 (t, *J* = 7.3 Hz, 1H)
7’	7.09 (dd, *J* = 7.3 Hz; 7.3 Hz, 1H)	7.10 – 7.06 (m, 1H)
8’	6.64 (d, *J* = 7.3 Hz, 1H)	6.64 (d, *J* = 7.7 Hz, 1H)
9’		
10’	2.95 (s, 3H)	2.94 (s, 3H)
1’’ (NH)	8.15 (br s, 1H)	8.15 (br s, 1H)
2’’	7.97 (d, *J* = 2.2 Hz, 1H)	7.98 (d, *J* = 2.3 Hz, 1H)

3”		
4”		
5”		
6”	7.05 (d, *J* = 7.6 Hz, 1H)	7.06 (d, *J* = 7.2 Hz, 1H)
7”	7.14 (dd, *J* = 7.6 Hz; 7.6 Hz, 1H)	7.14 (t, *J* = 7.5 Hz, 1H)
8”	7.17 (d, *J* = 7.6 Hz, 1H)	7.17 (d, *J* = 7.5 Hz, 1H)
9”		

Table S8: Comparison of ^{13}C NMR shifts (δ) of natural[10] spiroindimicin H (**10**) and our own synthetic **10** in $CDCl_3$.

Position	Natural **10** (125 MHz)	Synthetic **10** *(Smith)* (600 MHz)
1		
2	116.7	116.7
3	123.9	123.9
4	132.0	132.0
5	123.0	123.0
6	161.0	161.0
7	51.9	51.9
8	160.4	160.4
9	51.6	51.6
1’		
2’	74.6	74.6
3’	49.2	49.2
4’	141.1	141.0
5’	123.4	123.34
6’	117.7	117.7
7’	127.5	127.5
8’	106.3	106.2
9’	152.7	152.8
10’	35.6	35.6
1”		
2”	121.3	121.3
3”	106.6	106.6
4”	123.3	123.25
5”	137.3	137.3
6”	116.8	116.8
7”	125.1	125.1
8”	108.4	108.4
9”	134.1	134.1

5. Asymmetric Spirocyclization Studies.

General Procedure A for Pd-catalyzed Spirocylization (entries 2–53)

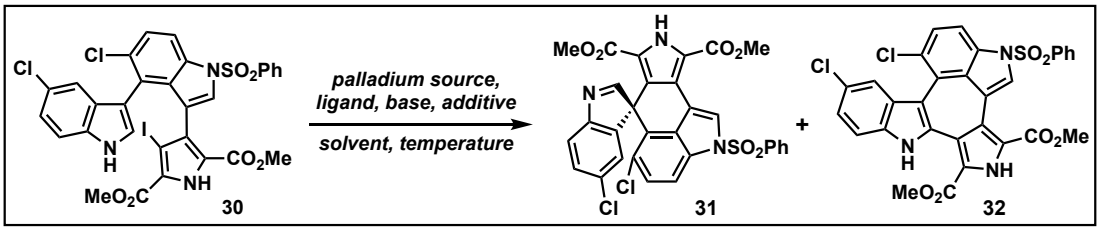
N-H iodide **30** was dissolved in toluene and degassed by argon sparge for 30 min. A Pd source (0.1 equiv), ligand (0.15 equiv), and Cs_2CO_3 (2.5 equiv) were then added. The reaction mixture was heated at the indicated temperature and monitored by TLC. After completion, the reaction mixture was allowed to cool to room temperature and quenched with water and extracted with EtOAc (× 2). The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by PTLC (Et_2O) to afford pure spirocycle **31**.

General Procedure B for Pd-catalyzed Spirocylization (entries 54–89)

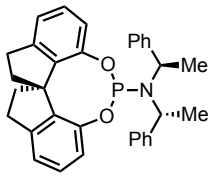
A vial was charged with toluene and degassed by argon sparge for 30 min, then a Pd source and ligand were added and stirred for one hour at room temperature. In a separate vial, **30** was dissolved in toluene and degassed by argon sparge for 30 min. Ag_2CO_3 and Cs_2CO_3 were then added to the solution of **30** in toluene, followed by the catalyst solution. The reaction was then heated at the indicated temperature and monitored by TLC. After completion, the reaction mixture was allowed to cool to room temperature and quenched with water and extracted with EtOAc (× 2). The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by PTLC (Et_2O) to afford pure spirocycle **31**.

Discussion of the Stability of the Enantiopurity of 31:

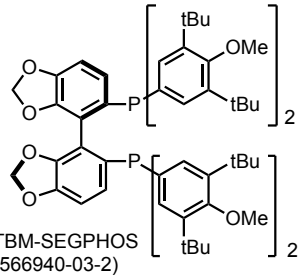
As noted above in the procedure for the preparation of enantioenriched **31**, we found that work-up conditions dramatically affected the enantiomeric excess of isolated **31**. As can be seen in Table S9 we were able to obtain higher yields and ee than our final result (29%, 98% ee, entry 72) but these results proved challenging to consistently reproduce. Ultimately, we determined through a series of control experiments that **31** was isolated with lower ee depending on how the crude reaction mixture was processed. Aqueous work-up (either with H_2O/EtOAc or saturated aq. Rochelle's salt/EtOAc), followed by CH_2Cl_2 loading of the crude mixture onto silica gel often resulted in 40–50% drop in ee; similar loading onto a PTLC plate caused a smaller but still significant drop. Ultimately, a reproducible solution was found, at the expense of some yield, where the crude reaction mixture was filtered through Celite, rinsing with 20% MeOH/EtOAc, concentrated, and directly purified by PTLC. This protocol allowed the ee to be maintained at 95–99%. The cause of this issue is unclear to us at this time but may involve some component of the post-work-up crude material partially racemizing the product upon concentration or contact with silica gel. The mechanism for such a racemization is unknown. Another possibility could be a process that converts the major enantiomer of **31** to achiral **32** via a kinetic resolution, lowering the overall ee. We do note that the enantiomeric excess of pure **31** is stable when this material is subjected to column chromatography or PTLC on silica gel.



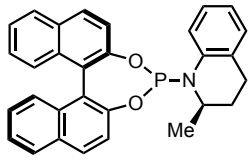
ligand structures:



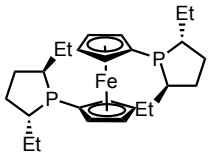
(R)-SIPHOS-PE
L1 (500997-69-3)



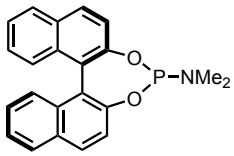
(R)-DTBM-SEGPHOS
L2 (566940-03-2)



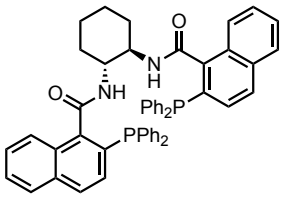
L3
(1186392-43-7)



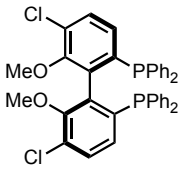
(R,R)-Et-Ferrocelane
L4 (147762-89-8)



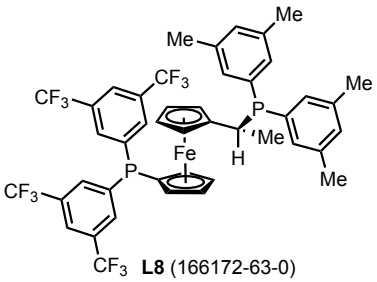
(R)-MonoPhos
L5 (157488-65-8)



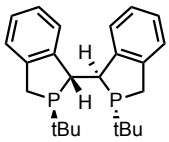
L6 (174810-09-4)



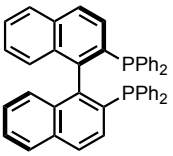
(R)-Cl-MeO-BIPHEP
L7 (185913-97-7)



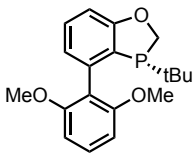
L8 (166172-63-0)



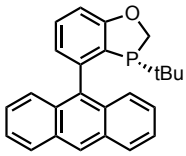
(1R,1'R,2S,2'S)-DuanPhos
L9 (528814-26-8)



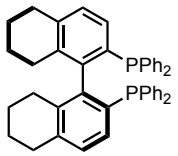
(R)-BINAP
L10 (76189-55-4)



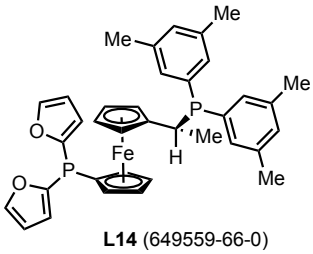
(R)-BI-DIME
L11 (1338454-03-7)



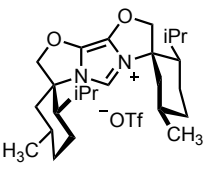
(R)-AntPhos
L12 (1456816-37-7)



(S)-H8-BINAP
L13 (139139-93-8)

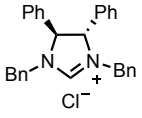


L14 (649559-66-0)

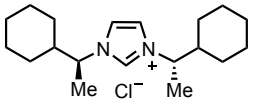


IBiox[(−)-menthyl] HOTf
L15 (1164334-36-4)

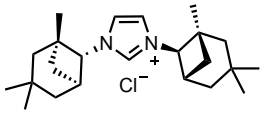
ligand structures:



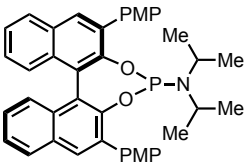
L16



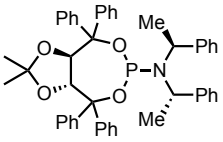
L17



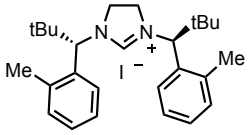
L18



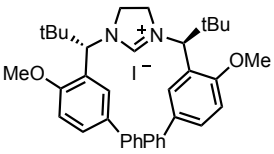
L19



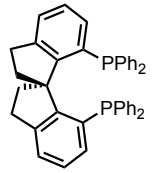
L20



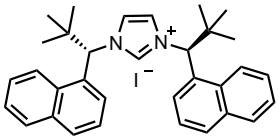
L21



L22



L23 (917377-74-3)



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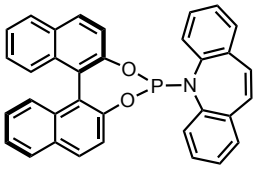
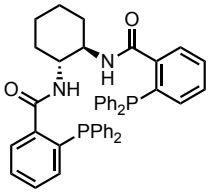
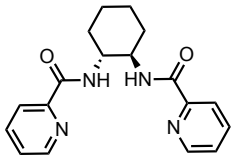


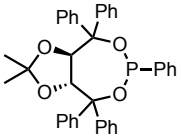
L25



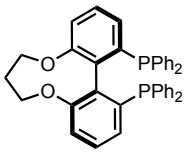
L26 (169689-05-8)



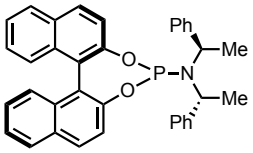
L27 (218290-24-5)



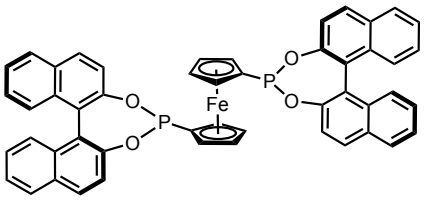
L28



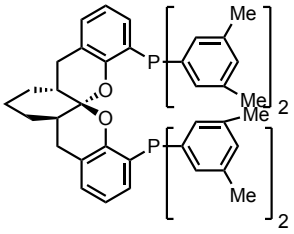
(R)-C3-TUNEPHOS
L29 (301847-89-2)



L30 (415918-91-1)

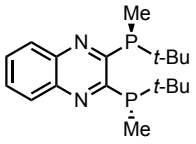


L31 (260395-56-0)

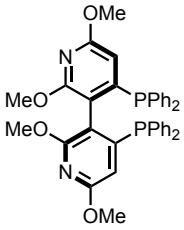


L32 (1429939-35-4)

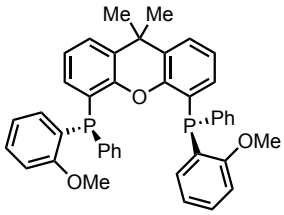
ligand structures:



(R,R)-QuinoxP*
L33 (866081-62-1)



CTH-*(R)*-P-Phos
L34 (221012-82-4)



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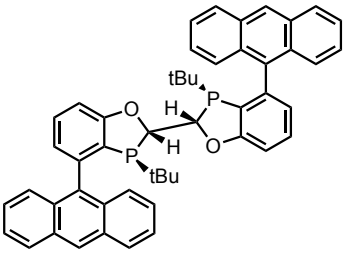
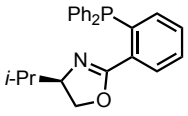
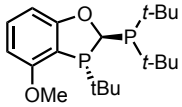


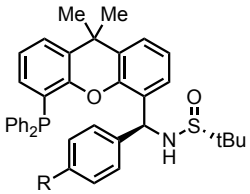
(2S,2"S,3S,3"S)-WingPhos
L36 (1435940-19-4)



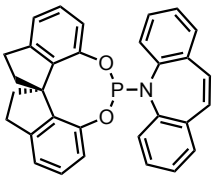
(R)-iPr-PHOX
L37 (164858-78-0)



(2S,3R)-MeO-POP
L38 (1215081-28-9)



L39 (R = H)
L40 (R = OMe)



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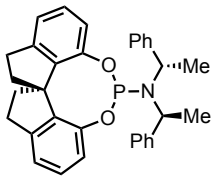

L42

Table S9. Screen of Pd-Catalyzed Spirocyclization

Entry	Pd source	Ligand	Base (equiv)	Solvent	Temp. (°C)	**31**:**32**[b]	yield (%)[c]	ee (%)
1		Pd-PEPPSI-IPr	Cs_2CO_3 (1.5)	toluene	115	1.8:1	55	n/a
2	$[Pd(C_3H_5)Cl]_2$	PPh_3	Cs_2CO_3 (1.5)	toluene	90		**32** only	
3	$[Pd(C_3H_5)Cl]_2$	SPhos	Cs_2CO_3 (1.5)	toluene	85		**32** only	
4	$[Pd(C_3H_5)Cl]_2$	PAr_3[d]	Cs_2CO_3 (1.5)	toluene	85		**32** only	
5	$[Pd(C_3H_5)Cl]_2$	**L1**	Cs_2CO_3 (1.5)	toluene	115			23
6	$[Pd(C_3H_5)Cl]_2$	**L1**	Cs_2CO_3 (1.5)	toluene	90			24
7	$[Pd(C_3H_5)Cl]_2$	**L2**	Cs_2CO_3 (1.5)	toluene	90			30
8	$[Pd(C_3H_5)Cl]_2$	**L3**	Cs_2CO_3 (1.5)	toluene	90			-5
9	$[Pd(C_3H_5)Cl]_2$	**L4**	Cs_2CO_3 (1.5)	toluene	90			-38
10	$[Pd(C_3H_5)Cl]_2$	**L5**	Cs_2CO_3 (1.5)	toluene	90			0
11	$[Pd(C_3H_5)Cl]_2$	**L6**	Cs_2CO_3 (1.5)	toluene	90			46
12	$[Pd(C_3H_5)Cl]_2$	**L7**	Cs_2CO_3 (1.5)	toluene	90			20
13	$[Pd(C_3H_5)Cl]_2$	**L8**	Cs_2CO_3 (1.5)	toluene	90			9
14	$[Pd(C_3H_5)Cl]_2$	**L9**	Cs_2CO_3 (1.5)	toluene	90			30
15	$[Pd(C_3H_5)Cl]_2$	**L10**	Cs_2CO_3 (1.5)	toluene	90			-18
16	$[Pd(C_3H_5)Cl]_2$	**L11**	Cs_2CO_3 (1.5)	toluene	90			20
17	$[Pd(C_3H_5)Cl]_2$	**L12**	Cs_2CO_3 (1.5)	toluene	90			15
18	$[Pd(C_3H_5)Cl]_2$	**L13**	Cs_2CO_3 (1.5)	toluene	90			20

19	$[Pd(C_3H_5)Cl]_2$	**L14**	Cs_2CO_3 (1.5)	toluene	90			-9
22	$[Pd(C_3H_5)Cl]_2$	**L15**	Cs_2CO_3 (1.5)	toluene	90			-18
23	$[Pd(C_3H_5)Cl]_2$	**L16**	Cs_2CO_3 (1.5)	toluene	90			1
24	$[Pd(C_3H_5)Cl]_2$	**L17**	Cs_2CO_3 (1.5)	toluene	90			0
25	$[Pd(C_3H_5)Cl]_2$	**L18**	Cs_2CO_3 (1.5)	toluene	90			-20
26	$[Pd(C_3H_5)Cl]_2$	**L19**	Cs_2CO_3 (1.5)	toluene	90			-6
27	$[Pd(C_3H_5)Cl]_2$	**L20**	Cs_2CO_3 (1.5)	toluene	90			-4
28	$[Pd(C_3H_5)Cl]_2$	**L21**	Cs_2CO_3 (1.5)	toluene	90			0
29	$[Pd(C_3H_5)Cl]_2$	**L22**	Cs_2CO_3 (1.5)	toluene	90			6
30	$[Pd(C_3H_5)Cl]_2$	**L23**	Cs_2CO_3 (1.5)	toluene	90		**32** only	
31	$[Pd(C_3H_5)Cl]_2$	**L24**	Cs_2CO_3 (1.5)	toluene	90			6
32	$[Pd(C_3H_5)Cl]_2$	**L25**	Cs_2CO_3 (1.5)	toluene	90			7
33	$[Pd(C_3H_5)Cl]_2$	**L26**	Cs_2CO_3 (1.5)	toluene	90			0
34	$[Pd(C_3H_5)Cl]_2$	**L27**	Cs_2CO_3 (1.5)	toluene	90			12
35	$[Pd(C_3H_5)Cl]_2$	**L28**	Cs_2CO_3 (1.5)	toluene	90			-20
36	$[Pd(C_3H_5)Cl]_2$	**L29**	Cs_2CO_3 (1.5)	toluene	90			21
37	$[Pd(C_3H_5)Cl]_2$	**L30**	Cs_2CO_3 (1.5)	toluene	90			14
38	$[Pd(C_3H_5)Cl]_2$	**L30**	Ag_2CO_3 (1.5)	toluene	90	1.2:1		15
39	$[Pd(C_3H_5)Cl]_2$	**L30**	1.5Cs+1.5Ag	dioxane	90	1.2:1		20
40	$[Pd(C_3H_5)Cl]_2$	**L30**	Cs_2CO_3 (1.0)	dioxane	90	1:1.7		4
41	$[Pd(C_3H_5)Cl]_2$	**L30**	Cs_2CO_3 (2.5)	dioxane	90	2.2:1		-10
42	$[Pd(C_3H_5)Cl]_2$	**L30** (0.1)	Cs_2CO_3 (1.5)	dioxane	90	1:1.5		-10
43	$[Pd(C_3H_5)Cl]_2$	**L30** (0.25)	Cs_2CO_3 (1.5)	dioxane	90	2.1:1		-10
44	$[Pd(C_3H_5)Cl]_2$	**none**	Cs_2CO_3 (1.5)	dioxane	90	6:1		
45	$[Pd(C_3H_5)Cl]_2$	**L30**	none	dioxane	90			NR
46	$[Pd(C_3H_5)Cl]_2$	**L30**	Cs_2CO_3 (5.0)	dioxane	90	8.5:1		-12
47	$Pd(OAc)_2$	**L30**	Cs_2CO_3 (5.0)	dioxane	90			mix
48	$Pd_2(dba)_3$	**L30**	Cs_2CO_3 (5.0)	dioxane	90		**32** only	
49	$[Pd(C_3H_5)Cl]_2$	**L31**	Cs_2CO_3 (1.5)	toluene	90	2:1		30
50	$[Pd(C_3H_5)Cl]_2$	**L32**	Cs_2CO_3 (1.5)	toluene	90	1:1.2		-10
51	$[Pd(C_3H_5)Cl]_2$	**L33**	Cs_2CO_3 (1.5)	toluene	90	1:6.2		20
52	$[Pd(C_3H_5)Cl]_2$	**L34**	Cs_2CO_3 (1.5)	toluene	90	1:2.8		15
53	$[Pd(C_3H_5)Cl]_2$	**L35**	Cs_2CO_3 (1.5)	toluene	90	1:1.2		-17
			With Pd/L Prestirring for 1 h (General Procedure B)					
54	$[Pd(C_3H_5)Cl]_2$	**L36**	Cs_2CO_3 (1.5)	toluene	90	7:1		3
55	$[Pd(C_3H_5)Cl]_2$	**L37**	Cs_2CO_3 (1.5)	toluene	90	1:1		-3
56	$[Pd(C_3H_5)Cl]_2$	**L38**	Cs_2CO_3 (1.5)	toluene	90	1:8		19
57	$0.5[Pd(C_3H_5)Cl]_2$	**L39** (1.5)	Cs_2CO_3 (1.5)	toluene	70		**32** only	
58	$0.5[Pd(C_3H_5)Cl]_2$	**L40** (1.5)	Cs_2CO_3 (1.5)	toluene	70		**32** only	
59	$0.5[Pd(C_3H_5)Cl]_2$	**L41** (1.5)	Cs_2CO_3 (1.5)	toluene	50		**32** only	
60	$[Pd(C_3H_5)Cl]_2$	**L1**	Cs_2CO_3 (5.0)	toluene	90	2:1		20
61	$[Pd(C_3H_5)Cl]_2$	**L1**	2.5Cs+2.5Ag	dioxane	90	1:1.4		43

62	$[Pd(C_3H_5)Cl]_2$	**L1**	Cs_2CO_3 (5.0)	DMF	90	2.1:1		18
63	$[Pd(C_3H_5)Cl]_2$	**L1**	*t*-BuOK (5.0)	toluene	90		decomp.	
64	0.5$[Pd(C_3H_5)Cl]_2$	**L1** (1.5)	2.5Cs+2.5Ag	dioxane	75	1:1.3		28
65	0.5$[Pd(C_3H_5)Cl]_2$	**L1** (1.5)	2.5Cs+2.5Ag	toluene	75	1:2.5		50
66	0.5$[Pd(C_3H_5)Cl]_2$	**L1** (1.5)	2.5Cs+2.5Ag	dioxane	65	1:1		43
67	0.2$[Pd(C_3H_5)Cl]_2$	**L1** (0.6)	2.5Cs+2.5Ag	toluene	65	1:1.6		46
68	0.5$[Pd(C_3H_5)Cl]_2$	**L1** (1.5)	2.5Cs+2.5Ag	toluene	50 (3.5 h)	1:1.3		72
69	0.5$[Pd(C_3H_5)Cl]_2$	**L1** (1.5)	2.5Cs+2.5Ag	toluene	50 (20 h)	1:1.1		77
70	0.2$[Pd(C_3H_5)Cl]_2$	**L1** (0.6)	2.5Cs+2.5Ag	toluene	50	1:1		95
71	0.5$[Pd(C_3H_5)Cl]_2$	**L1** (1.5)	2.5Cs+2.5Ag	toluene	40	1.5:1		81
72	0.15 x 2 $[Pd(C_3H_5)Cl]_2$	**L1** (0.45 x 2)	2.5Cs+2.5Ag	toluene	50	1:1	29	97
73	0.15 $[Pd(C_3H_5)Cl]_2$	**L1** (0.45)	2.5Cs+2.5Ag	toluene	105	1:2	33	73
74	0.15 x 2 $[Pd(C_3H_5)Cl]_2$	**L1** (0.45 x 2)	2.5Cs+2.5Ag	toluene	80	1:2.2	21	86
75	0.3 $[Pd(C_3H_5)Cl]_2$	**L1** (0.9)	2.5Cs+2.5Ag	toluene	80	1:1.4	23	78
76	0.15 x 2 $[Pd(C_3H_5)Cl]_2$	**L1** (0.45 x 2)	2.5Cs+2.5Ag	toluene	70	1:0.8	18	96
77	0.3 $[Pd(C_3H_5)Cl]_2$	**L1** (0.9)	2.5Cs+2.5Ag	toluene	70	1:1	15	95
78	0.2 $[Pd(C_3H_5)Cl]_2$	**L1** (0.6)	2.5Cs+2.5Ag	toluene	70	1:1	8.5	98
79	0.3 $[Pd(C_3H_5)Cl]_2$	**L1** (0.9)	2.5Cs+2.5Ag	toluene	60	1:1	10	98
80	0.15 $[Pd(C_3H_5)Cl]_2$	**L42** (0.45)	2.5Cs+2.5Ag	toluene	105	1:1.2	21	20
81	0.15 $[Pd(C_3H_5)Cl]_2$	**L42** (0.45)	2.5Cs+2.5Ag	toluene	80	1:1.2	17	24
82	0.15 $[Pd(C_3H_5)Cl]_2$	**L42** (0.45)	2.5Cs+2.5Ag	toluene	70	1:2.2	13	20
83[e]	0.2 $[Pd(C_3H_5)Cl]_2$	**L1** (0.6)	2.5Cs+2.5Ag	toluene	70	1:2.2	14	98
84[f]	0.15 $[Pd(C_3H_5)Cl]_2$	**L1** (0.45)	2.5Cs+2.5Ag	toluene	80	1:1	7	25
85[f]	0.15 $[Pd(C_3H_5)Cl]_2$	**L1** (0.45)	2.5Cs+2.5Ag	toluene	110	2:1	34	13
86[f]	0.15 $[Pd(C_3H_5)Cl]_2$	**L29** (0.45)	2.5Cs+2.5Ag	toluene	90	**32** only		
87[f]	0.15 $[Pd(C_3H_5)Cl]_2$	**L29** (0.45)	2.5Cs+2.5Ag	toluene	120	1:3	6	5
88[f]	0.15 $[Pd(C_3H_5)Cl]_2$	**L31** (0.45)	2.5Cs+2.5Ag	toluene	90	**32** only		
89[f]	0.15 $[Pd(C_3H_5)Cl]_2$	**L31** (0.45)	2.5Cs+2.5Ag	toluene	120	1:3	14	0

[a]Unless otherwise noted, reactions were conducted with 10 mol% Pd and 15 mol% ligand; [b]From NMR integration of crude NMR; [c]Isolated yield; [d]Ar = 3,5-$(CF_3)_2C_6H_3$-; [e]Reaction mixture directly filtered through Celite and concentrated, prior to purification; [f]Performed using bromo-**30** instead of iodide **30**.

6. Experimental Details for Biological Assays

T. brucei cell viability assay

T. brucei brucei Lister 427 (ATCC® PRA-377™) bloodstream-form parasites were cultured in HMI-19 medium supplemented with 10% fetal bovine serum (Atlanta Biologicals, Flowery Branch, GA, USA) in 96-well plates for the cell viability assay.[11] A Tecan HP D300e Digital Dispenser was used for non-contact dispensing of test compounds (0.0045–30 μM) and a fixed concentration of vehicle (0.3% DMSO). Cell densities in the cell viability assay were analyzed using ATP–bioluminescence assay with CellTiter-Glo reagent (Promega, Madison, WI, USA) after 48 h culturing in the presence of the compounds.[11] The data were fitted to the normalized response versus log (inhibitor concentration) equation in Prism constraining bottom to 0. The EC_{50} value was obtained based on the best-fit value of a four-parameter fit in Graphpad Prism software (Graphpad Software Inc.).

Hep G2 cytotoxicity assay

Hep G2 cells (ATCC® HB-8065™) were cultured in ATCC complete Eagle's Minimum Essential Medium supplemented with 10 % fetal bovine serum (Atlanta Biologicals, Flowery Branch, GA, USA) and 2 mM L-glutamine. The cells were maintained until ≈ 90 % confluency at 37 °C under a humidified atmosphere and 5% CO_2 before resuspending or plating. For cytotoxicity assay, 60 μl of the cells were dispensed at 10^4 cells/ml in a white 384 well plates (Corning) using BioTek MultiFlo FX Washer Dispenser. A Tecan HP D300e Digital Dispenser was used for non-contact dispensing of test compounds (0.009–10 μM) and a fixed concentration of vehicle (0.3% DMSO). The plates were shaken on a plate shaker for 5 min, centrifuged at 300 g for 3 min, and incubated for 72 h at 37 °C in a humidified 5% CO_2 incubator. After 72 h the plates were equilibrated at room temperature for 40 min before addition of 30 μL Cell Titer Glo (Promega) to each well using BioTek MultiFlo FX Washer Dispenser. Luminescence was read with 1 sec integration time, 1 mm read height, gain of 200 using Synergy H1 at 27 °C.

P. falciparum growth inhibition assays

P. falciparum parasites were cultured in human red blood cells[12] (RBCs) at 2% hematocrit in RPMI (HEPES modification, Sigma R4130), supplemented with 0.5% Albumax I, 23 mM sodium bicarbonate, 10 μg/mL gentamicin sulfate, and 12.5 μg/mL hypoxanthine (92 μM). Parasites were cultured at 37 °C, with 5% CO_2. Assays were performed in 200 μL volumes in the inner wells of 96-well plates. Each biological replicate ($n \geq 3$ at each concentration) represents three technical replicates. Each assay was started with ring-stage parasites, at 0.5% parasitemia, and with a final DMSO concentration of 0.5%. Parasites were allowed to grow for 72 hours. Plates were frozen at -80 °C, thawed, and lysed by addition of 100 μL lysis buffer: 20 mM Tris-HCl pH 7.5, 5 mM EDTA, 0.008% saponin, 0.2% Triton X-100, 0.02% SYBR Green (ThermoFisher S7563). Parasite growth was assessed using SYBR Green fluorescence to measure DNA, using 485 nm excitation and 528 nm emission wavelengths.[13]

Compounds were initially screened at 30 μM, 10 μM, and 3 μM, against *P. falciparum* strain 3D7, at 0.5% DMSO. Parasite growth was normalized against no-compound (100% growth)

and no-parasite (only uninfected RBCs; 0% growth) controls. For compounds that caused substantial growth reduction at 10 μM, EC_{50} assays were performed against *P. falciparum* strains 3D7 and Dd2. EC_{50} assays were performed in 200 μL volumes in the inner wells of 96-well plates. Technical replicates were performed in triplicate rows. Each row included a 2X dilution series of the compound, plus no-compound and no-parasite controls. To calculate EC_{50} values, nonlinear regression analyses were performed using GraphPad Prism.

Concentration−Response Assays in *Leishmania amazonensis* and RAW 264.7 cells

Stocks of compounds and the reference drug paclitaxel (Sigma) were made in DMSO at 10 mM and stored at -20 °C. Maximum DMSO concentration in assays was 0.2% v/v.

L. amazonensis promastigotes (strain IFLA/BR/67/PH8, from Norma W. Andrews, University of Maryland, College Park, MD) were maintained as described previously.[14] They were converted to *L. amazonensis* amastigotes by growing them axenically at 32 °C and pH 4.5 in M199 media (Invitrogen) supplemented with 20% heat-inactivated FBS (Invitrogen), 0.25% glucose, 0.1% hemin (25 mg/mL in 50% triethanolamine), 10 mM adenine, 5 mM L glutamine, 1% penicillin−streptomycin, 0.5% trypticase, and 40 mM sodium succinate.[15,16] For compound testing, 6–9 day old axenic amastigotes were used. Compounds were dry spotted onto 96-well plates using an Echo 655 acoustic liquid dispenser (Beckman-Coulter). Axenic amastigotes were then added (200 μL, 1×10^6 cells/mL) and plates incubated at 32 °C for 72 h.[14] DMSO at 0.1% (no drug) served as a neutral control (100% survival), and 10 μM paclitaxel was a inhibitory control (0% survival). Antiparasitic activity was measured using a CellTiter-Glo® Luminescent Cell Viability Assay (Promega)[14] on a Perkin Elmer EnVision plate reader, and EC_{50} values were determined using Genedata Screener v16.

RAW 264.7 cells (ATCC TIB-71) were maintained in Dulbecco's modified Eagle's medium (DMEM) plus 10% FBS. Compounds were added as described for *L. amazonensis*. After compound addition to the plates, RAW 264.7 cells (7.5×10^4 cells/mL) were added to the plate and incubated for 72 h at 37 °C.[14] Cytotoxicity was measured via alamarBlue® (10%, Thermo Fisher Scientific) on a Synergy H1 plate reader (530 nm excitation, 570 nm emission; BioTek Instruments).[14] Percent growth was normalized to the positive control (100%), plotted against compound concentration, and $\log_{10}$ transformed.[14,17,18] EC_{50} values were determined using nonlinear regression for each biological repeat in GraphPad Prism v5.0 (GraphPad Software, Inc.).[14,17,18]

All experiments were performed as 3 technical replicates, using only internal wells to decrease evaporation-related edge effects; at least 3 biological repeats were independently conducted.[14] The mean EC_{50} values ± SE shown were calculated from each biological replicate.[14]

7. References

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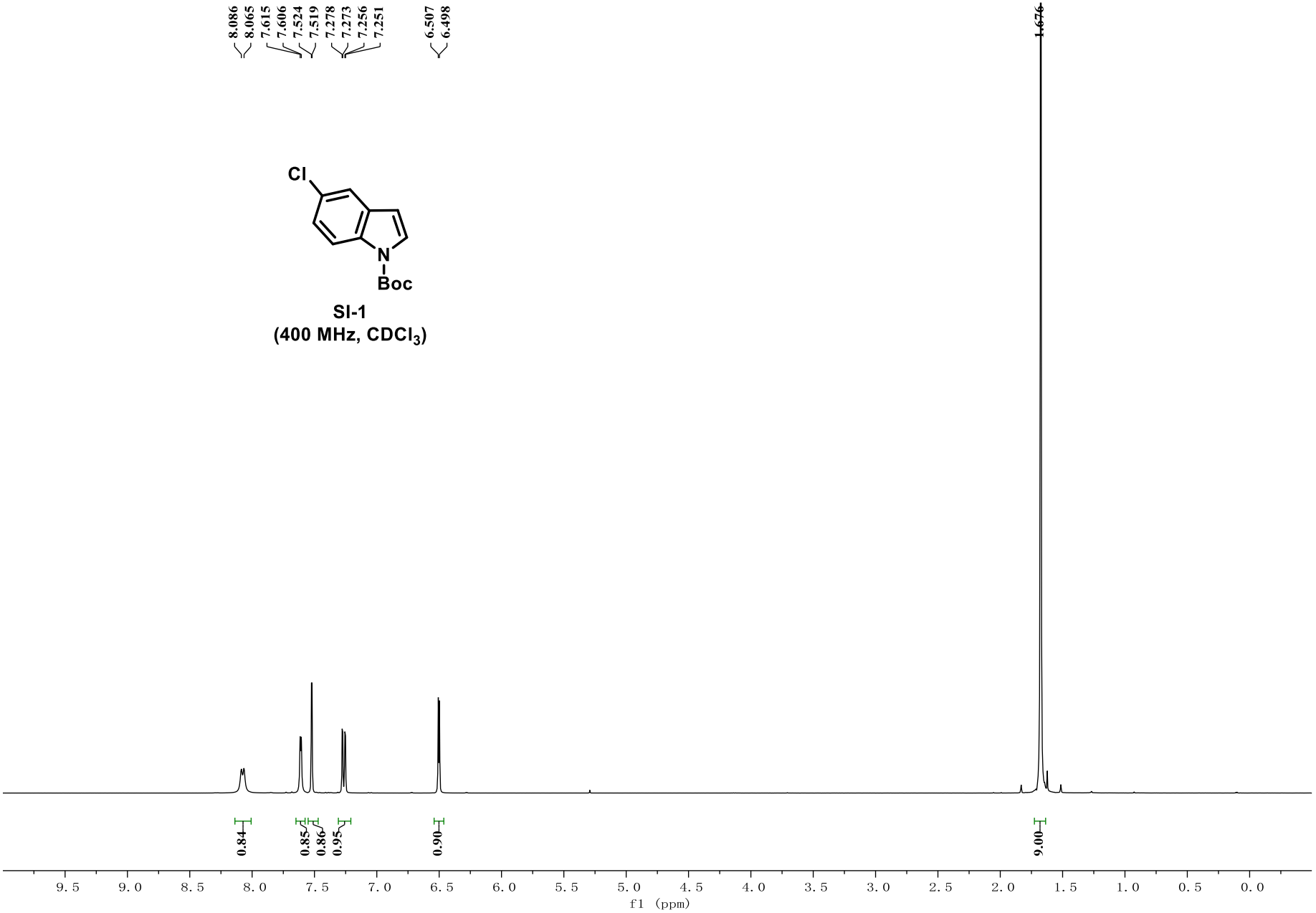
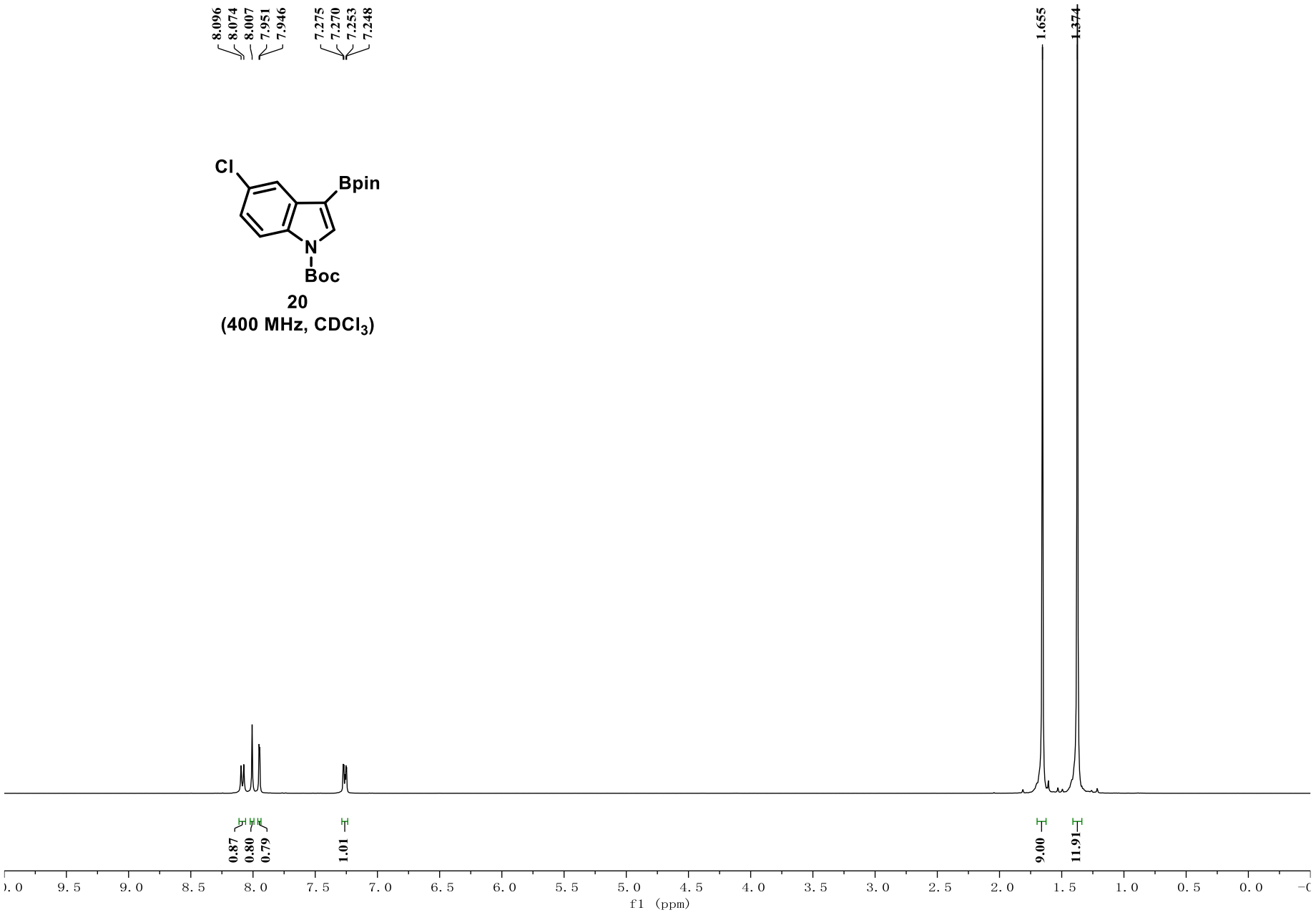
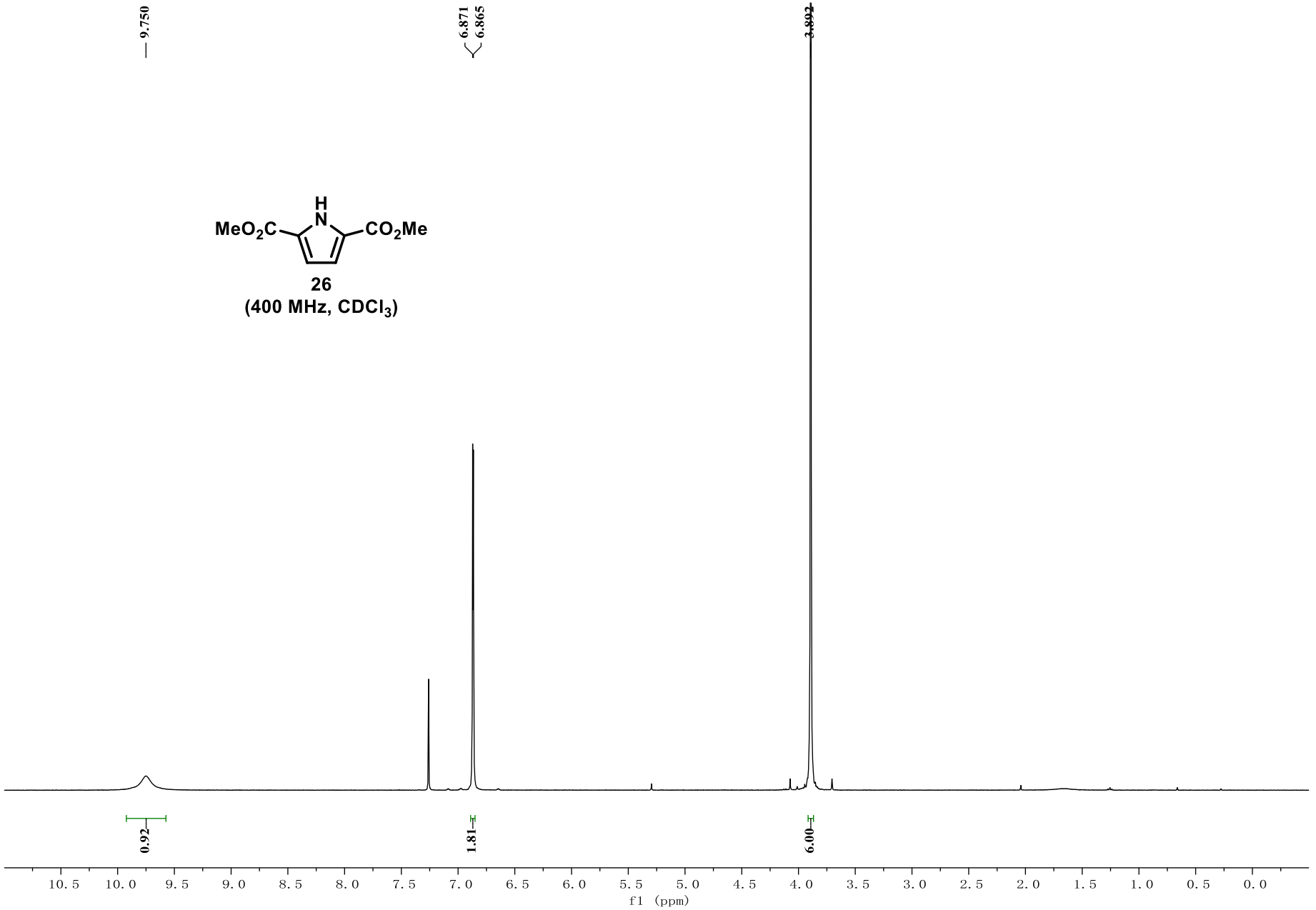
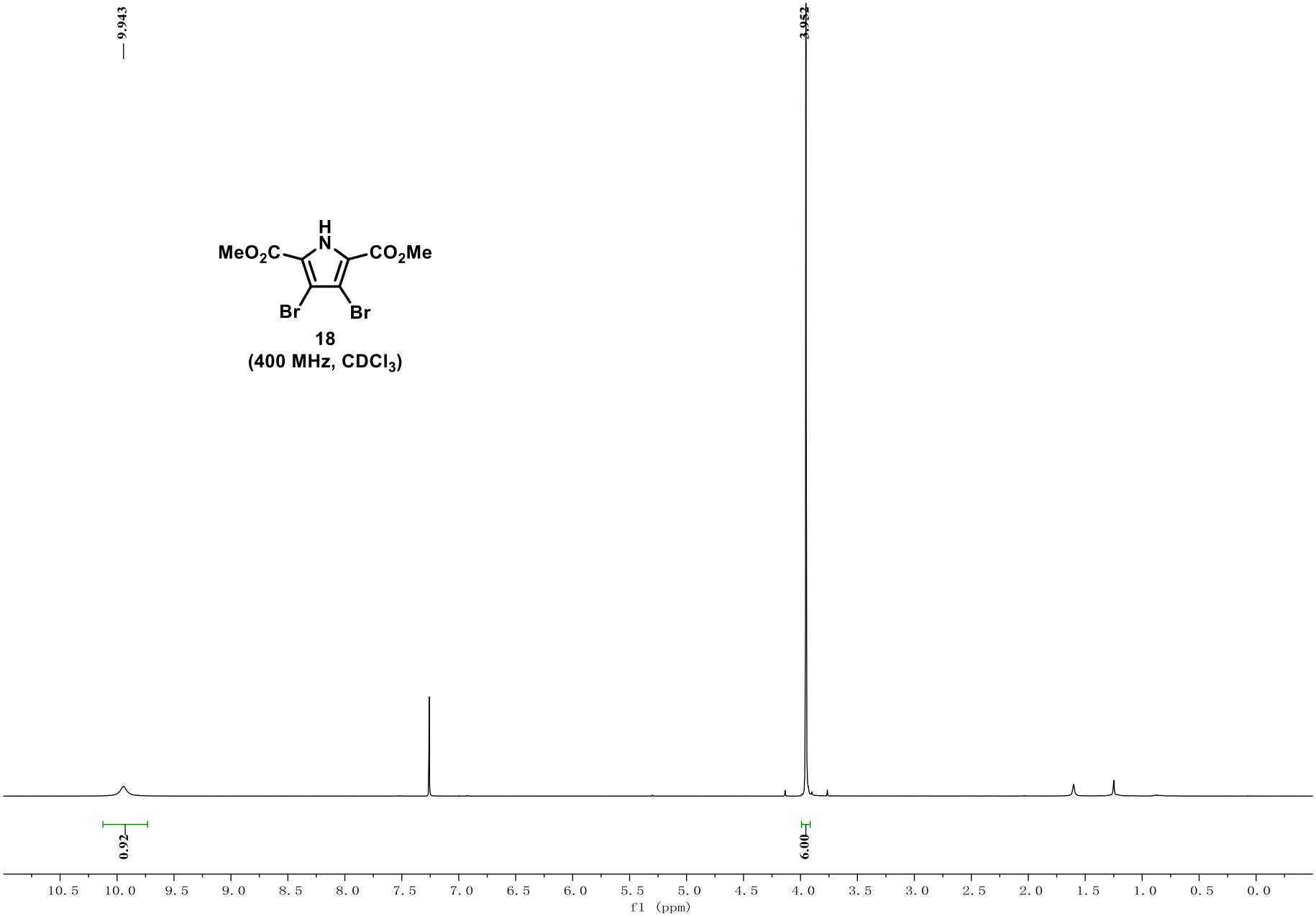
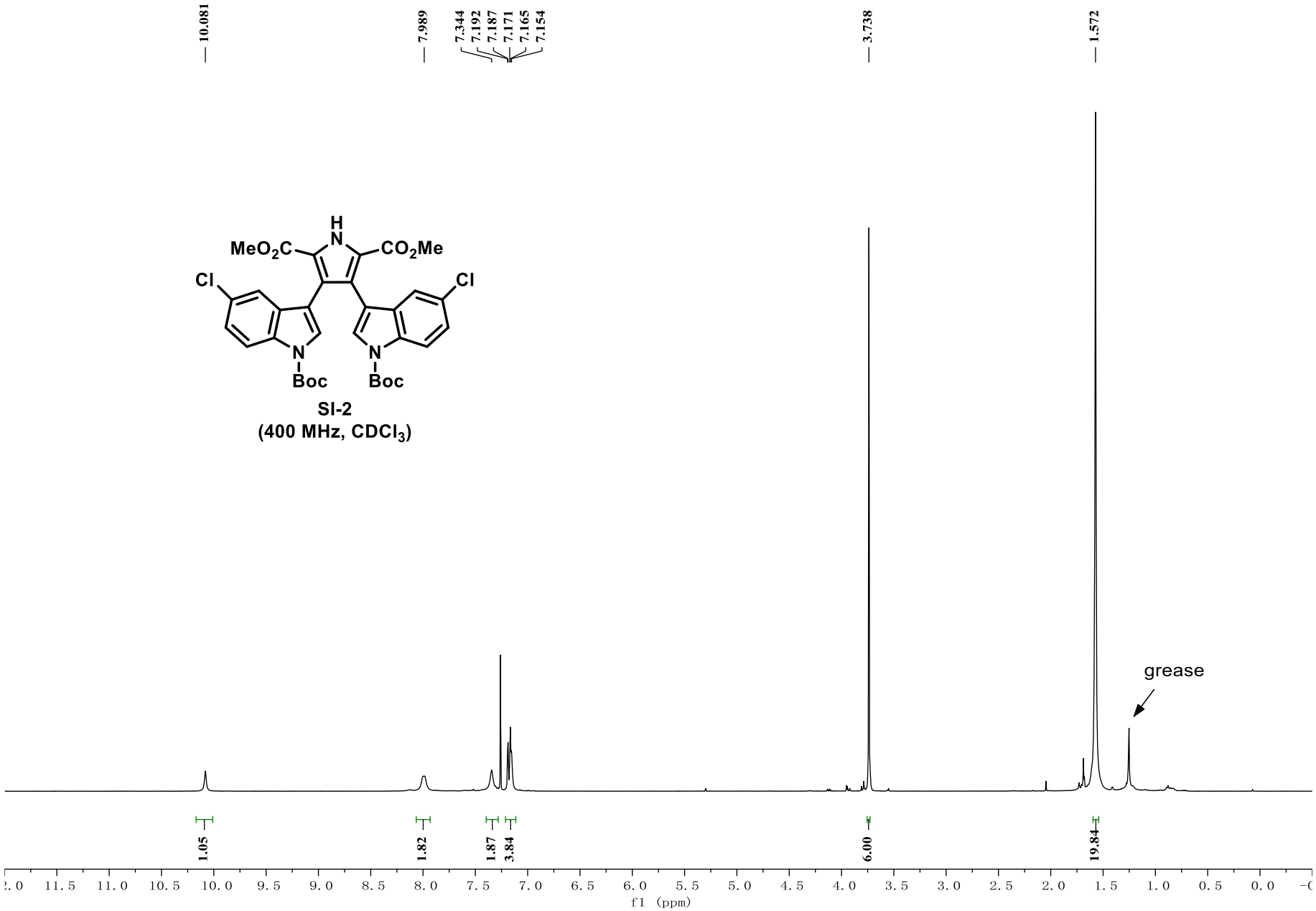
8. [1] H and [13]C NMR Spectra



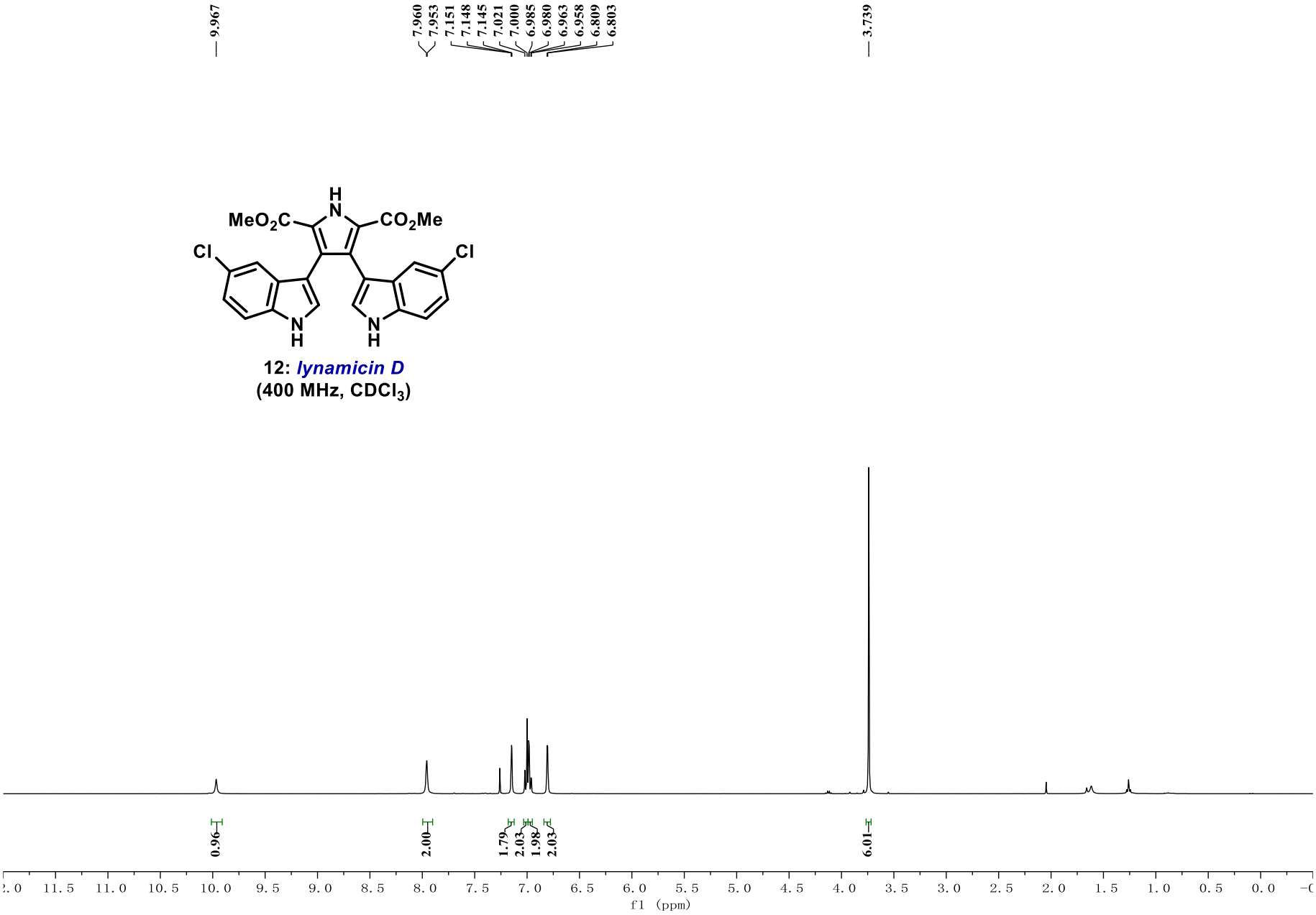

8.096
8.074
8.007
7.951
7.946
7.275
7.270
7.253
7.248
1.655
1.374
Cl
Bpin
N
Boc
20
(400 MHz, CDCl3)
0.87
0.80
0.79
1.01
9.00
11.91
f1 (ppm)

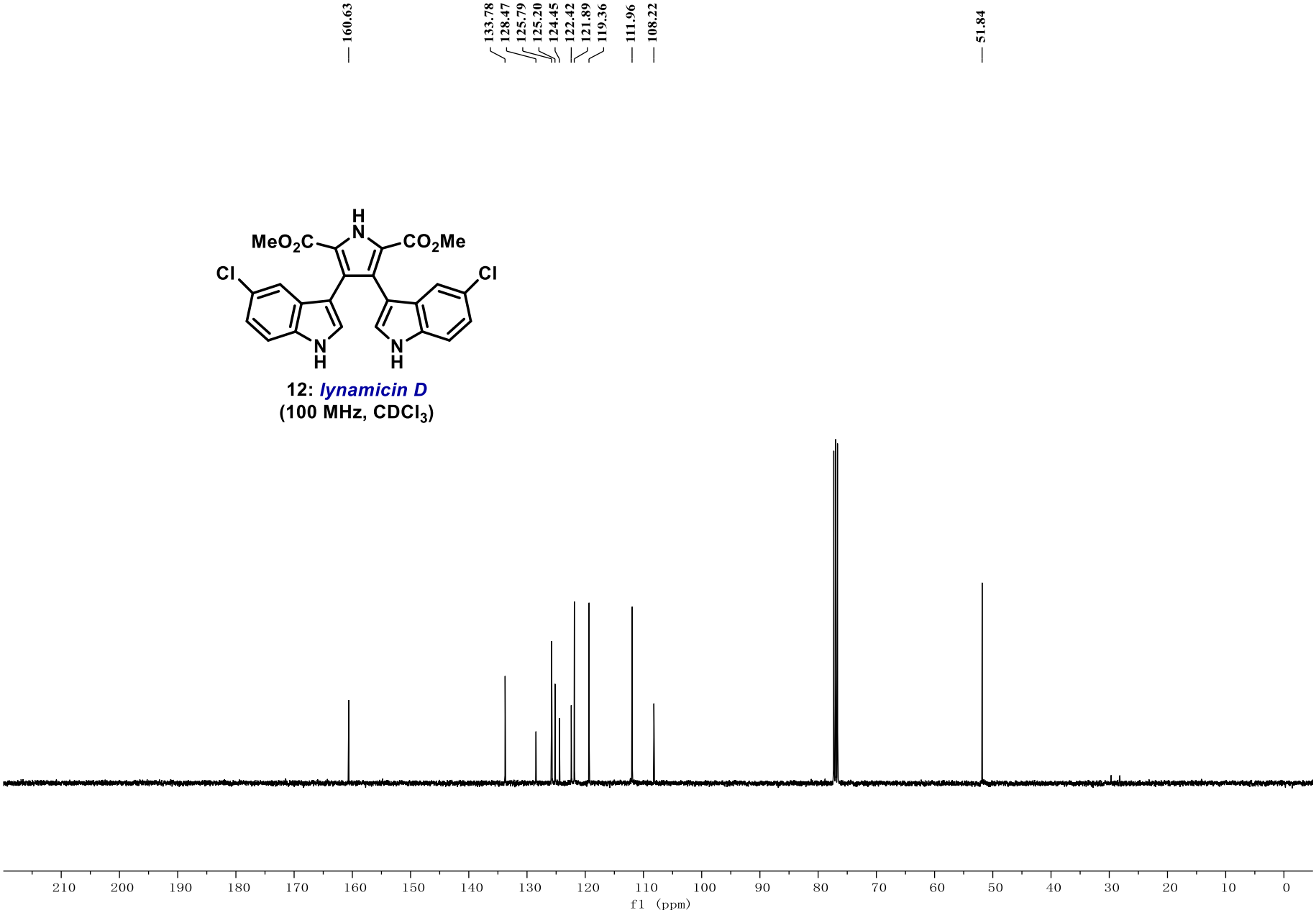

9.750
6.871
6.865
3.892
MeO2C
H
N
CO2Me
26
(400 MHz, CDCl3)
0.92
1.81
6.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


9.943
3.952
MeO2C
CO2Me
H
N
Br
Br
18
(400 MHz, CDCl3)
0.92
6.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

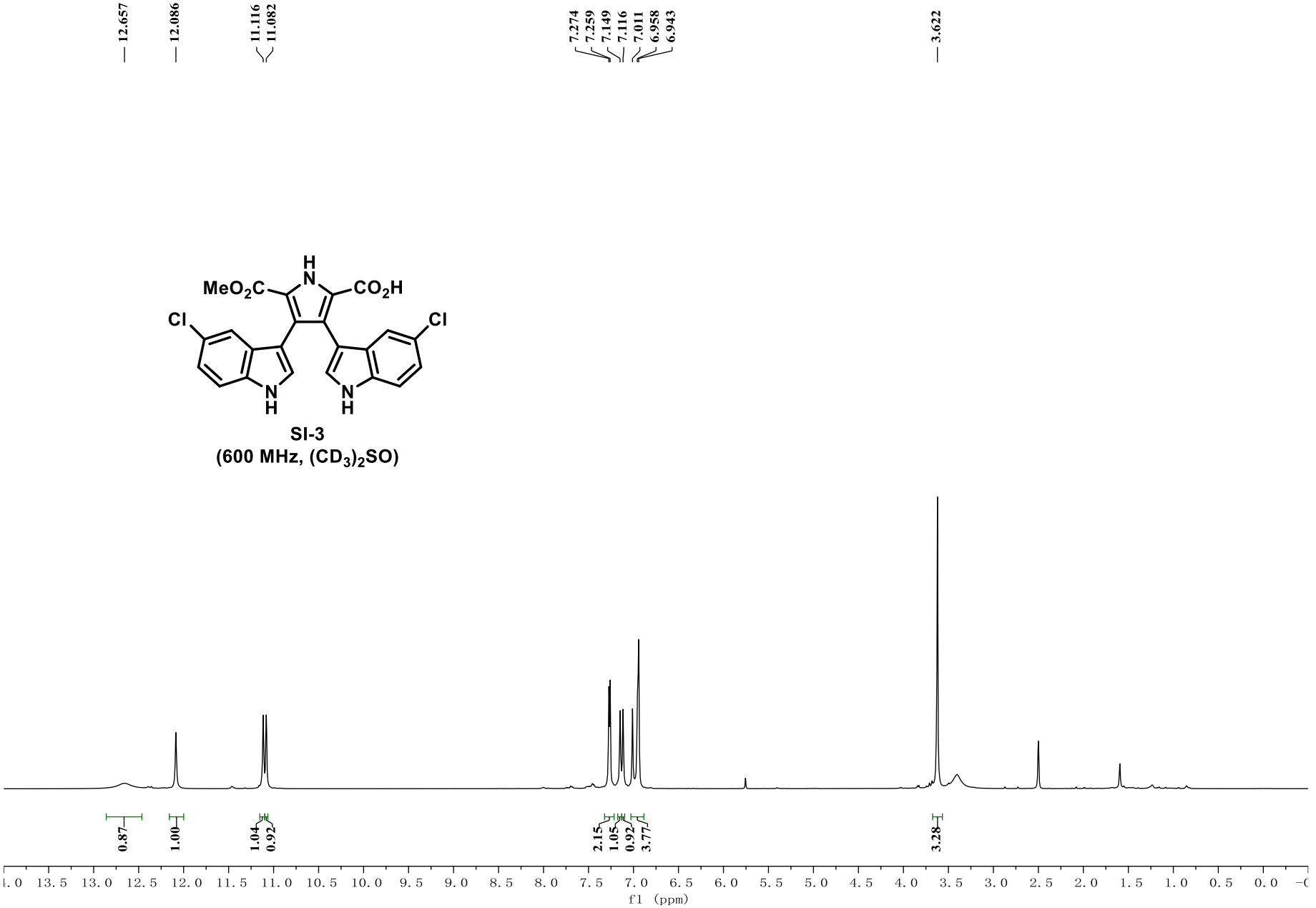


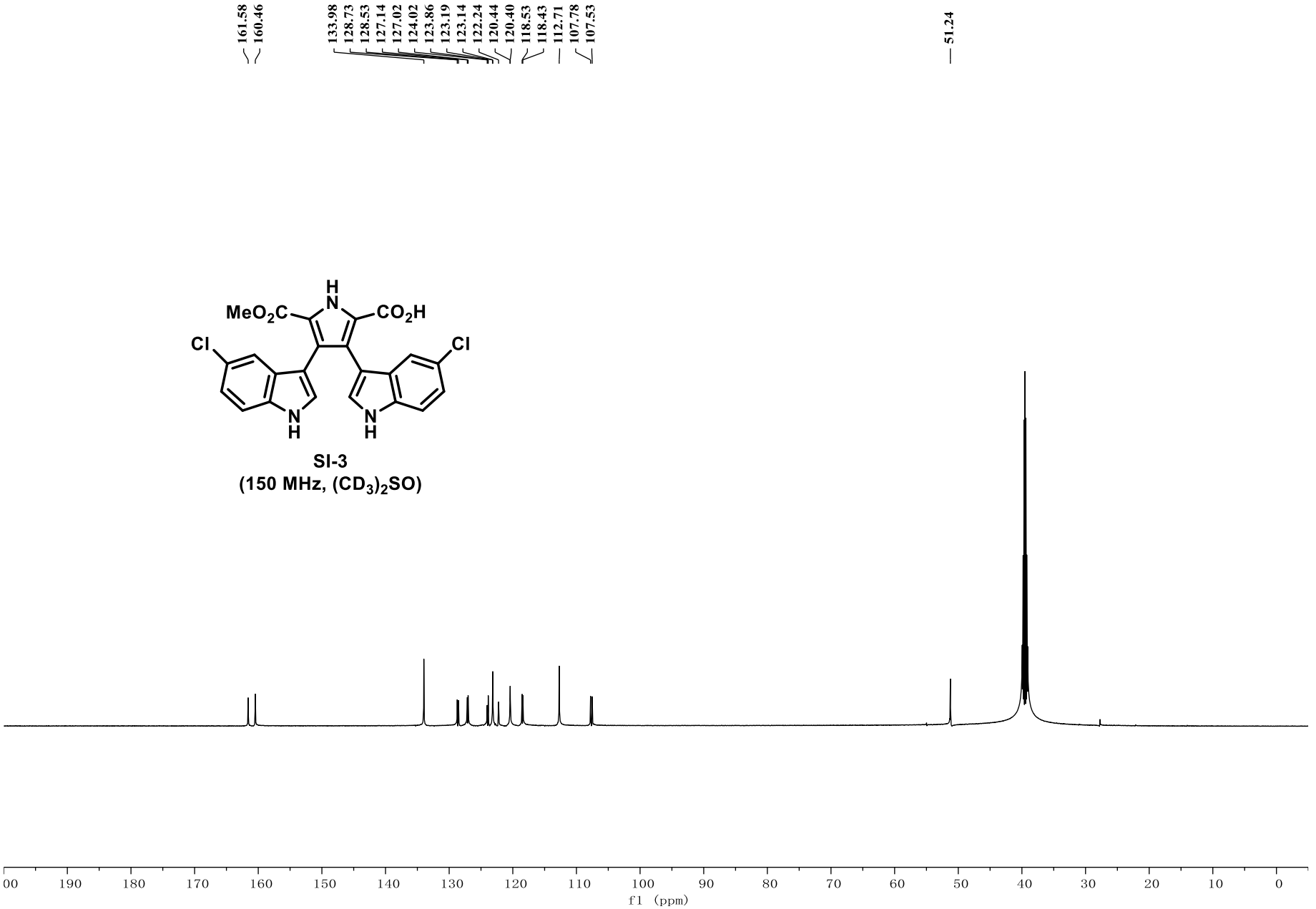
SI-2
(400 MHz, $CDCl_3$)

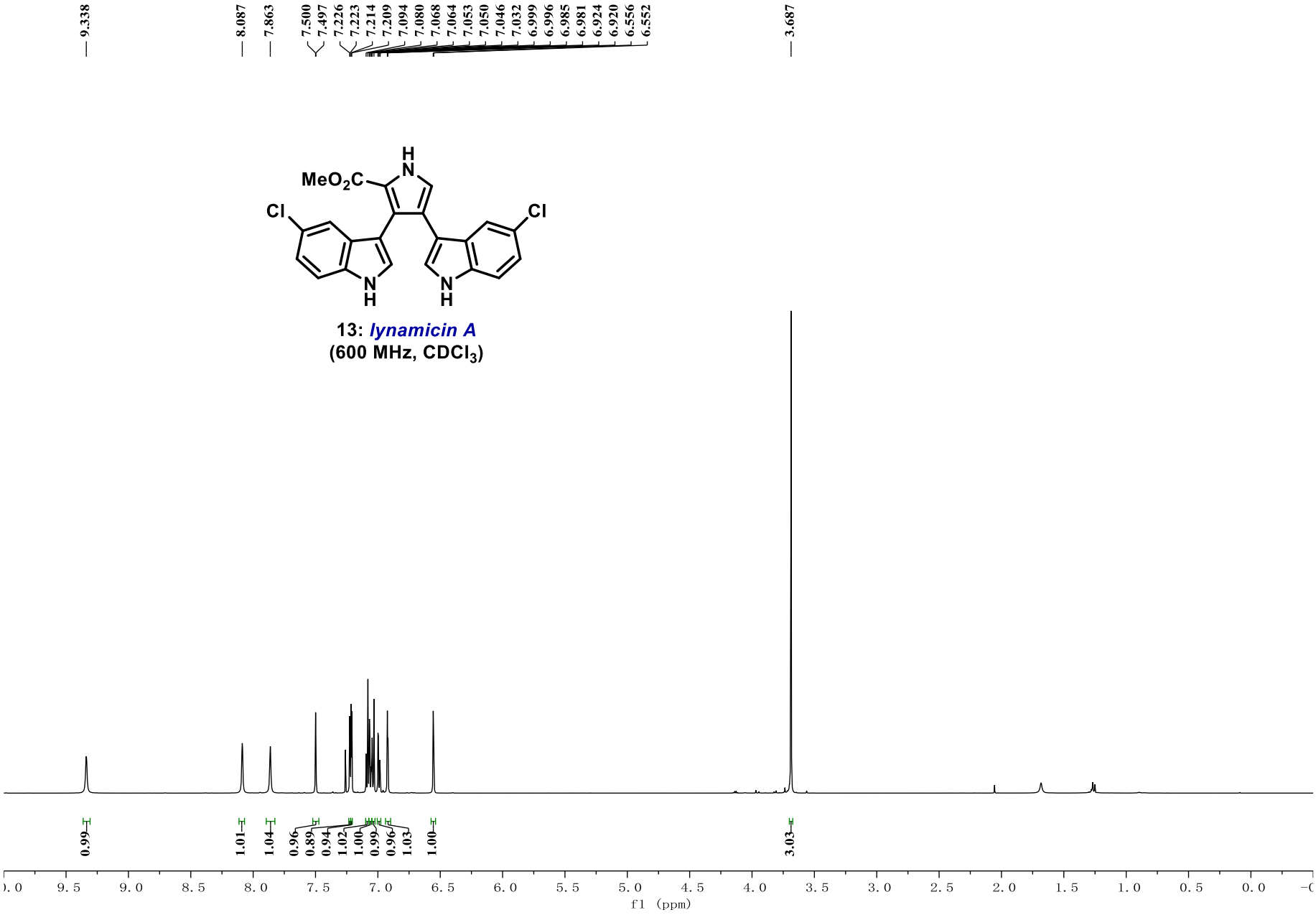

9.967
7.960
7.953
7.151
7.148
7.145
7.021
7.000
6.985
6.980
6.963
6.958
6.809
6.803
3.739
MeO2C
CO2Me
Cl
Cl
H
N
N
H
H
12: lynamicin D
(400 MHz, CDCl3)
0.96
2.00
1.79
2.03
1.98
2.03
6.01
f1 (ppm)



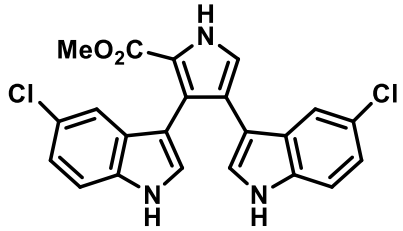
12: *lynamicin D*
(100 MHz, $CDCl_3$)


12.657
12.086
11.116
11.082
7.274
7.259
7.149
7.116
7.011
6.958
6.943
3.622
MeO2C
CO2H
Cl
Cl
H
N
N
H
N
H
SI-3
(600 MHz, (CD3)2SO)
0.87
1.00
1.04
0.92
2.15
1.05
0.92
3.77
3.28
f1 (ppm)

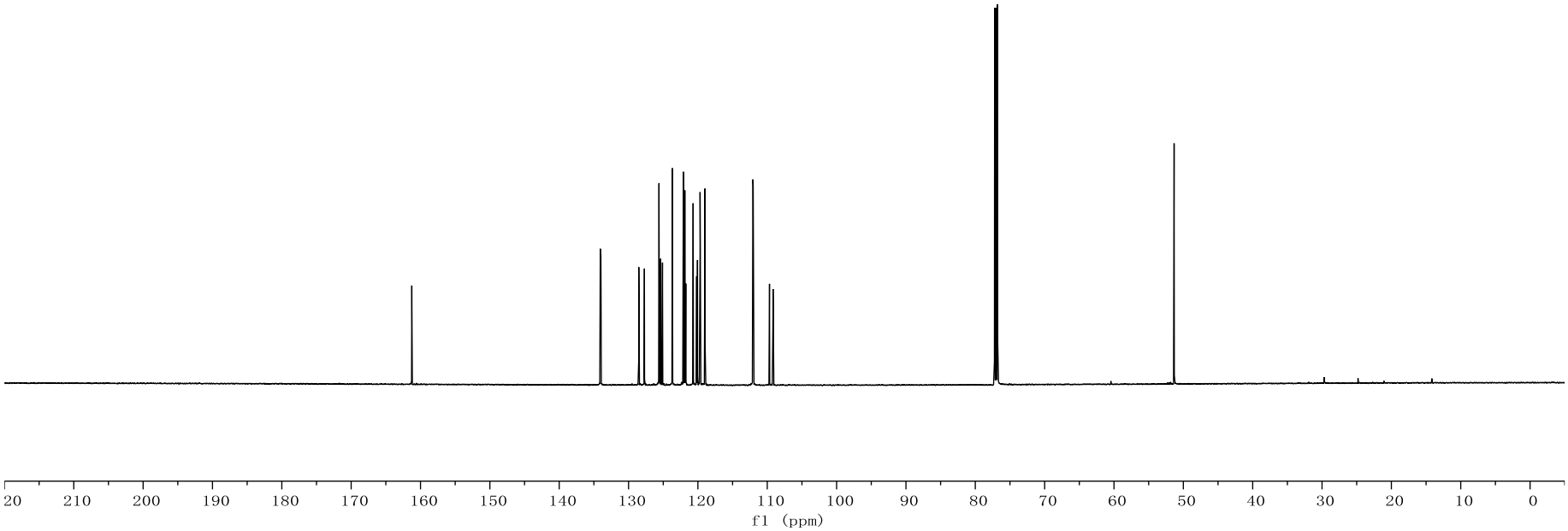

161.58
160.46
133.98
128.73
128.53
127.14
127.02
124.02
123.86
123.19
123.14
122.24
120.44
120.40
118.53
118.43
112.71
107.78
107.53
51.24
MeO2C
CO2H
Cl
Cl
H
N
N
H
N
H
SI-3
(150 MHz, (CD3)2SO)
f1 (ppm)

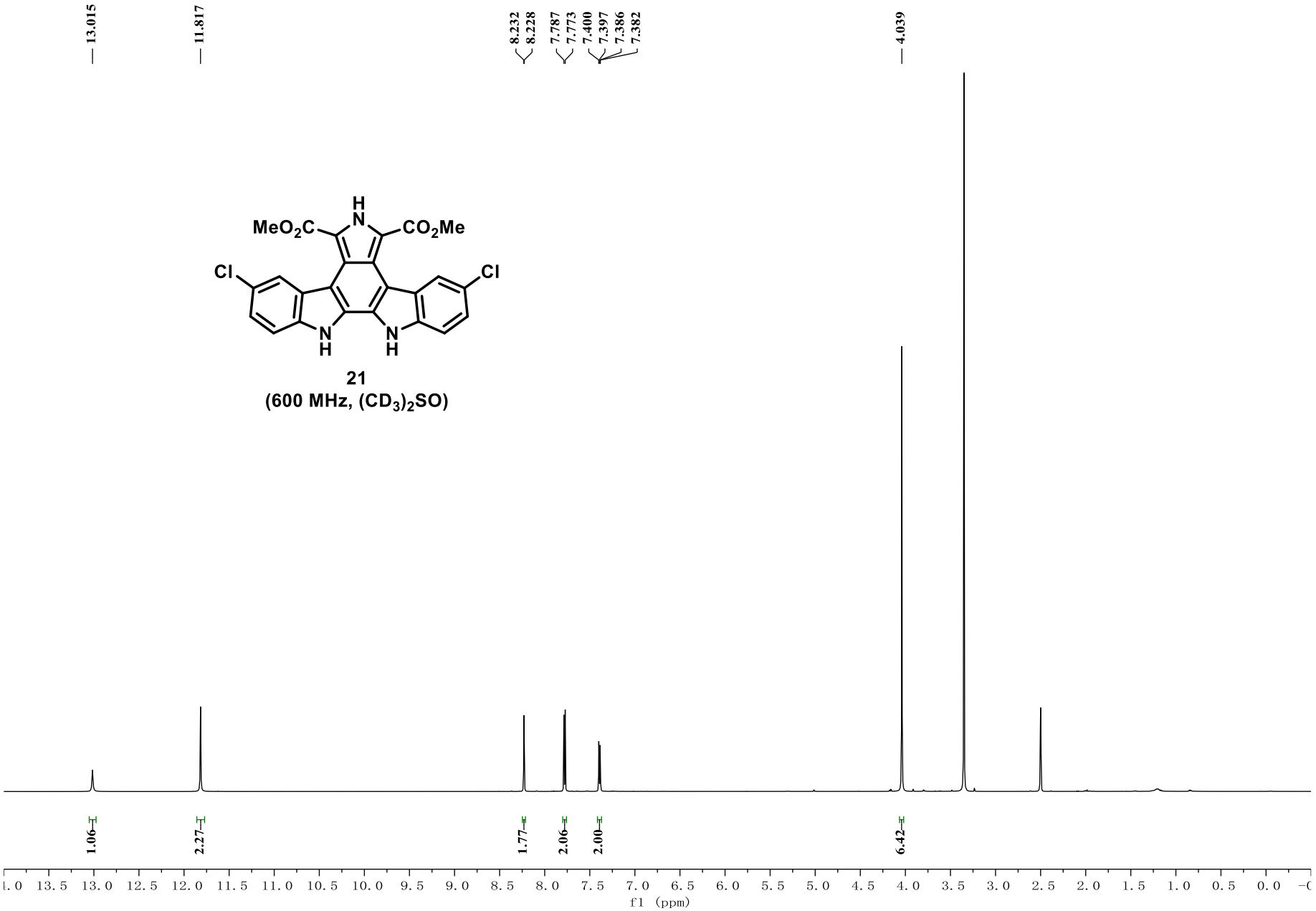


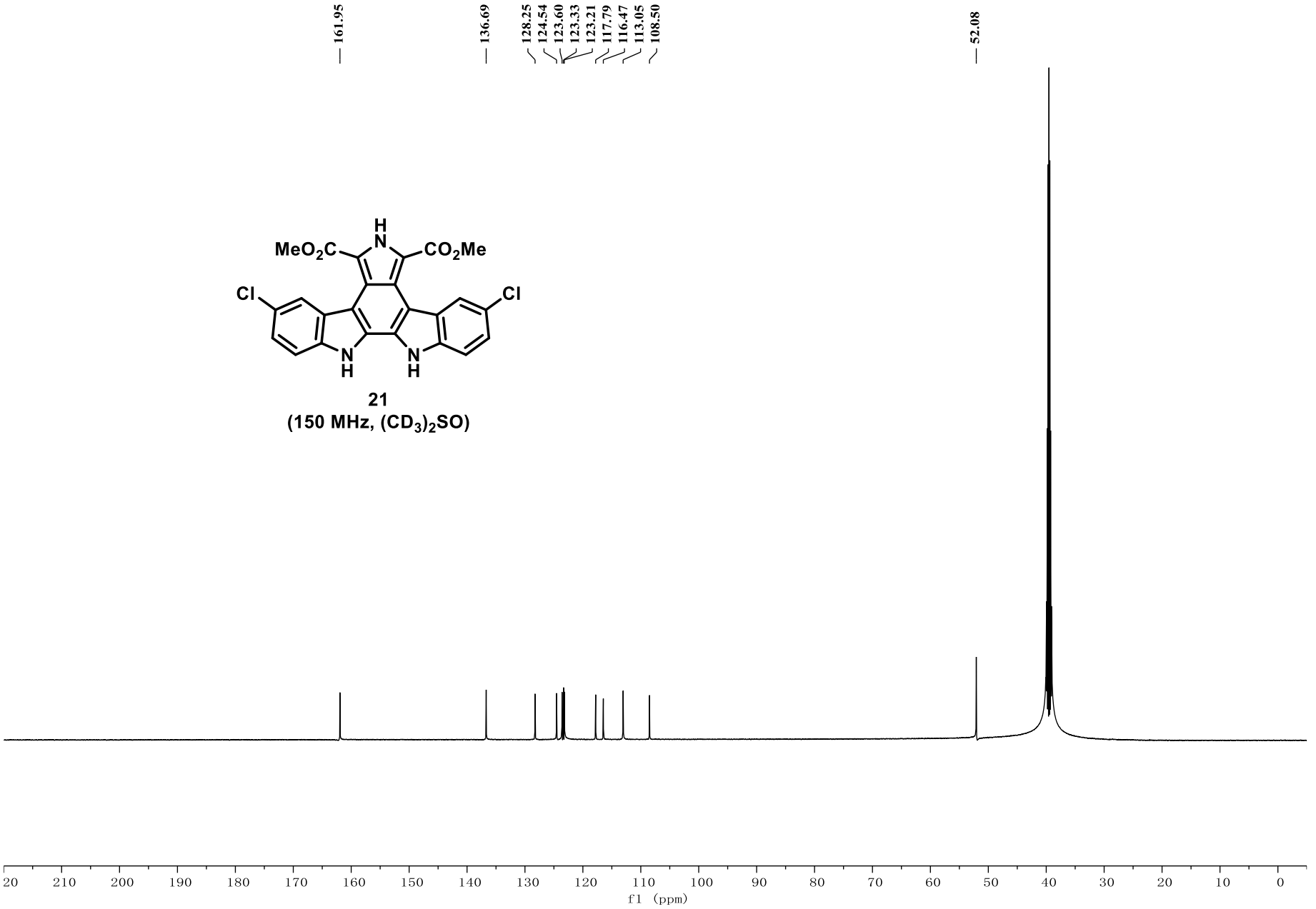
13: *lynamicin A*
(600 MHz, $CDCl_3$)

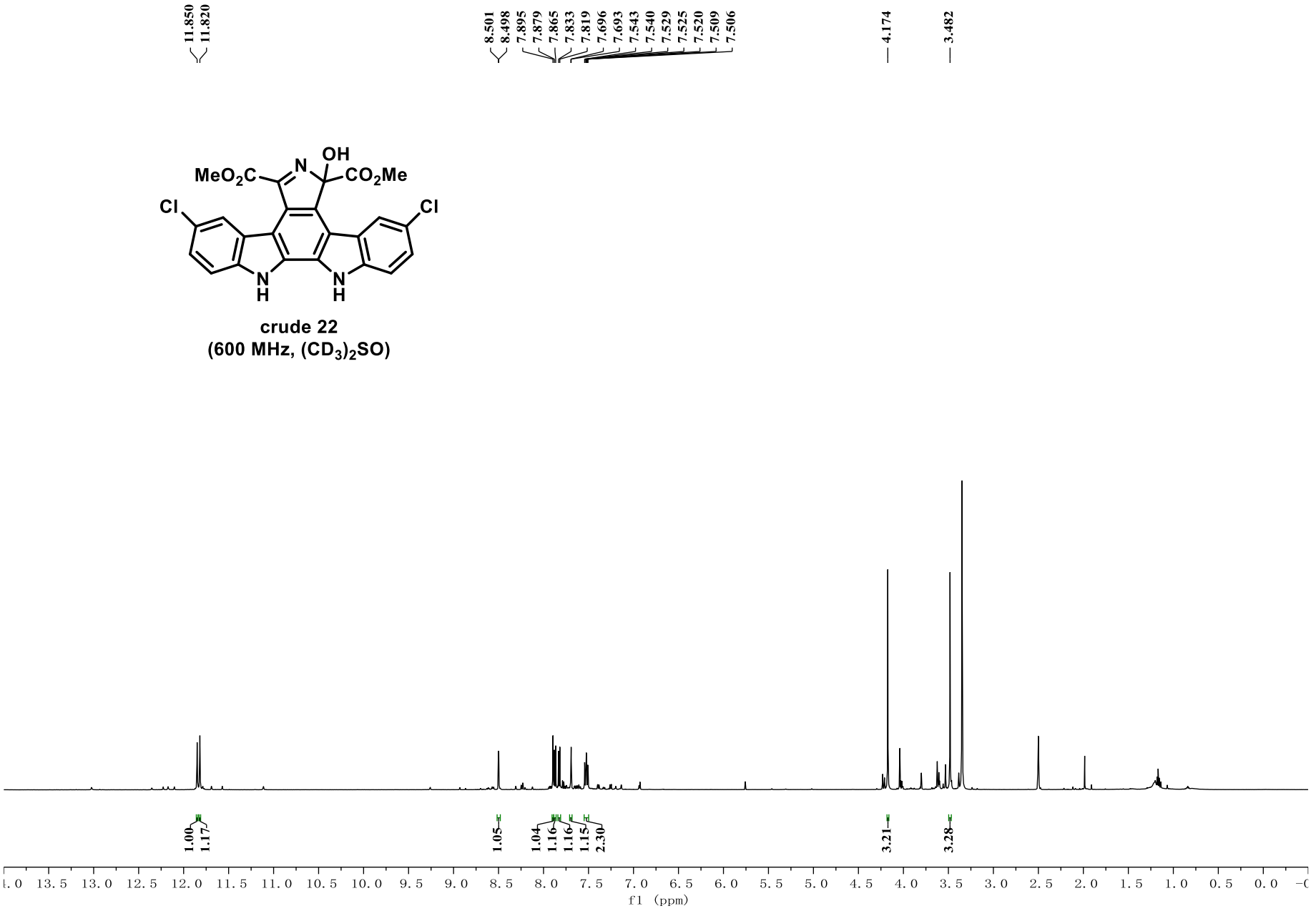


13: *lynamicin A*
(150 MHz, $CDCl_3$)

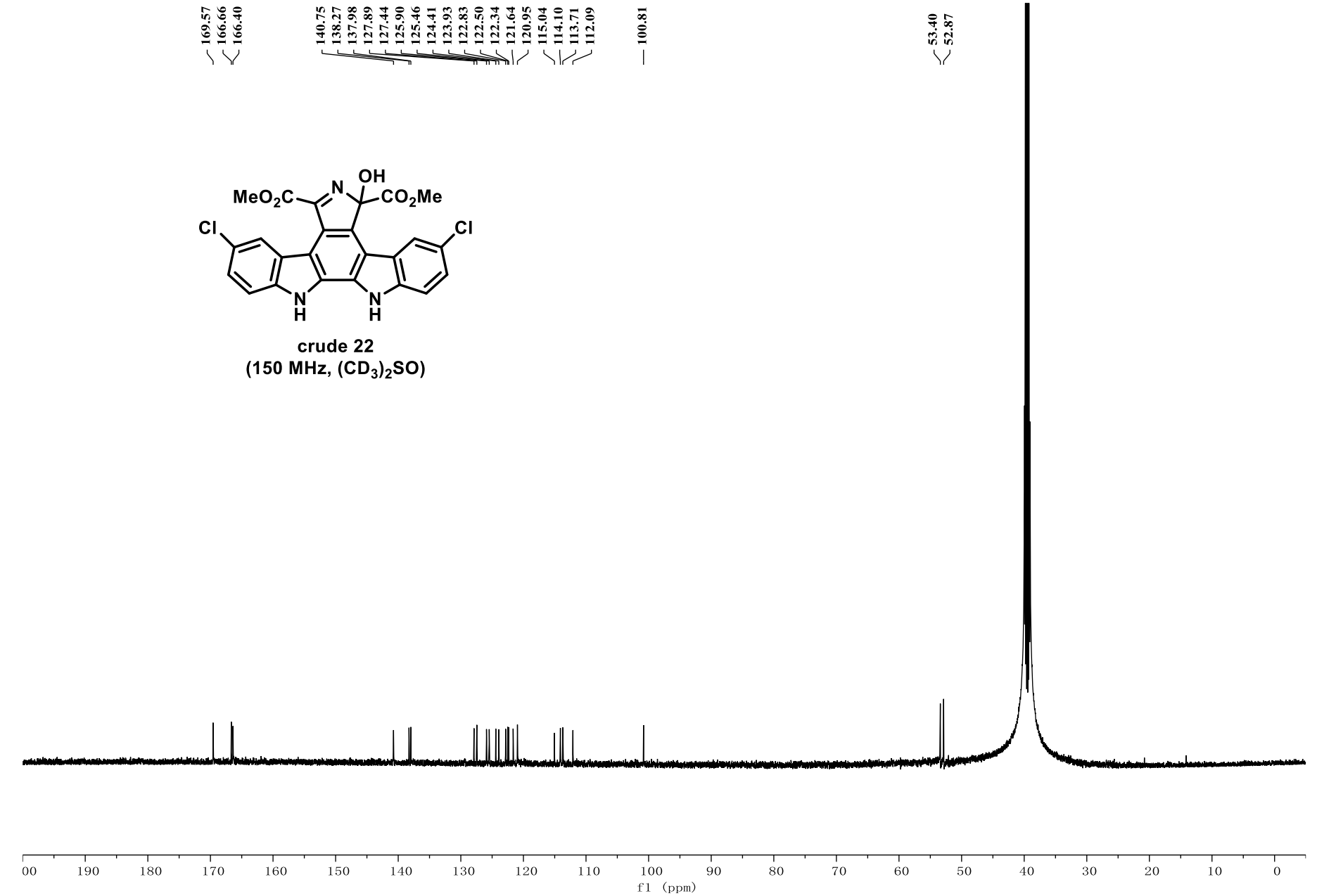



13.015
11.817
8.232
8.228
7.787
7.773
7.400
7.397
7.386
7.382
4.039
MeO2C
CO2Me
Cl
Cl
H
N
N
H
N
H
21
(600 MHz, (CD3)2SO)
1.06
2.27
1.77
2.06
2.00
6.42
f1 (ppm)

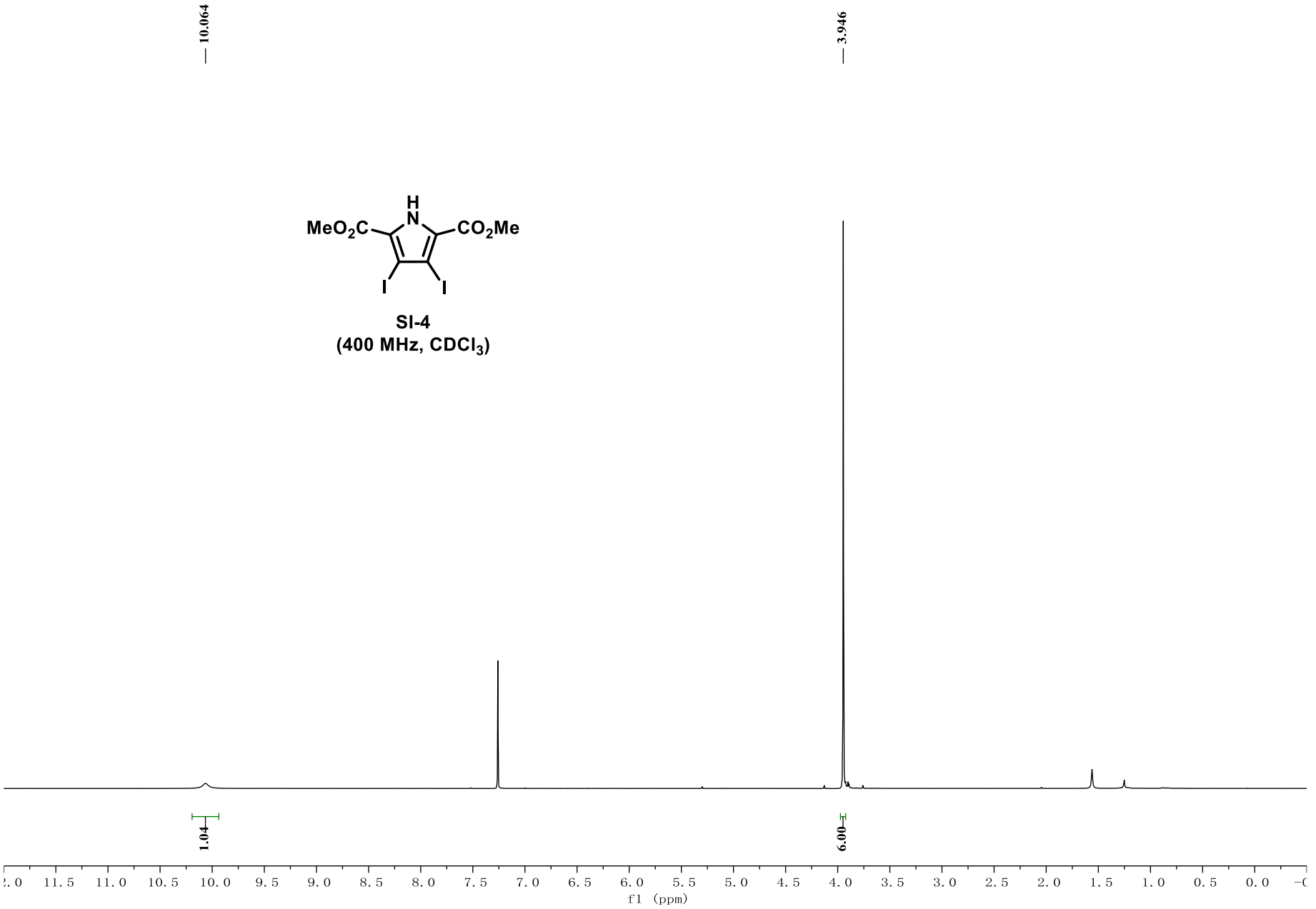

161.95
136.69
128.25
124.54
123.60
123.33
123.21
117.79
116.47
113.05
108.50
52.08
H
N
MeO2C
CO2Me
Cl
Cl
N
H
N
H
21
(150 MHz, (CD3)2SO)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



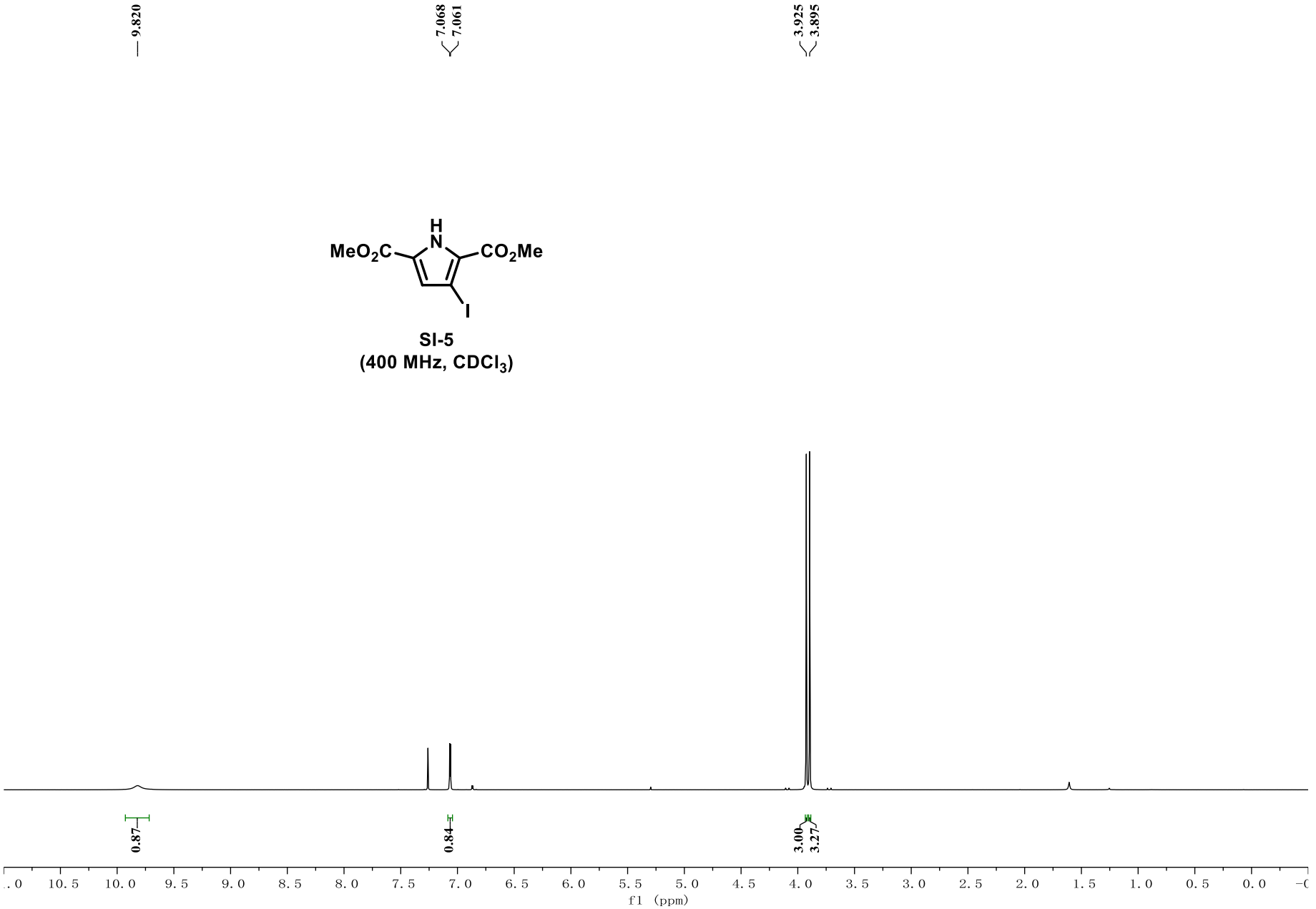
crude 22
(600 MHz, $(CD_3)_2SO$)



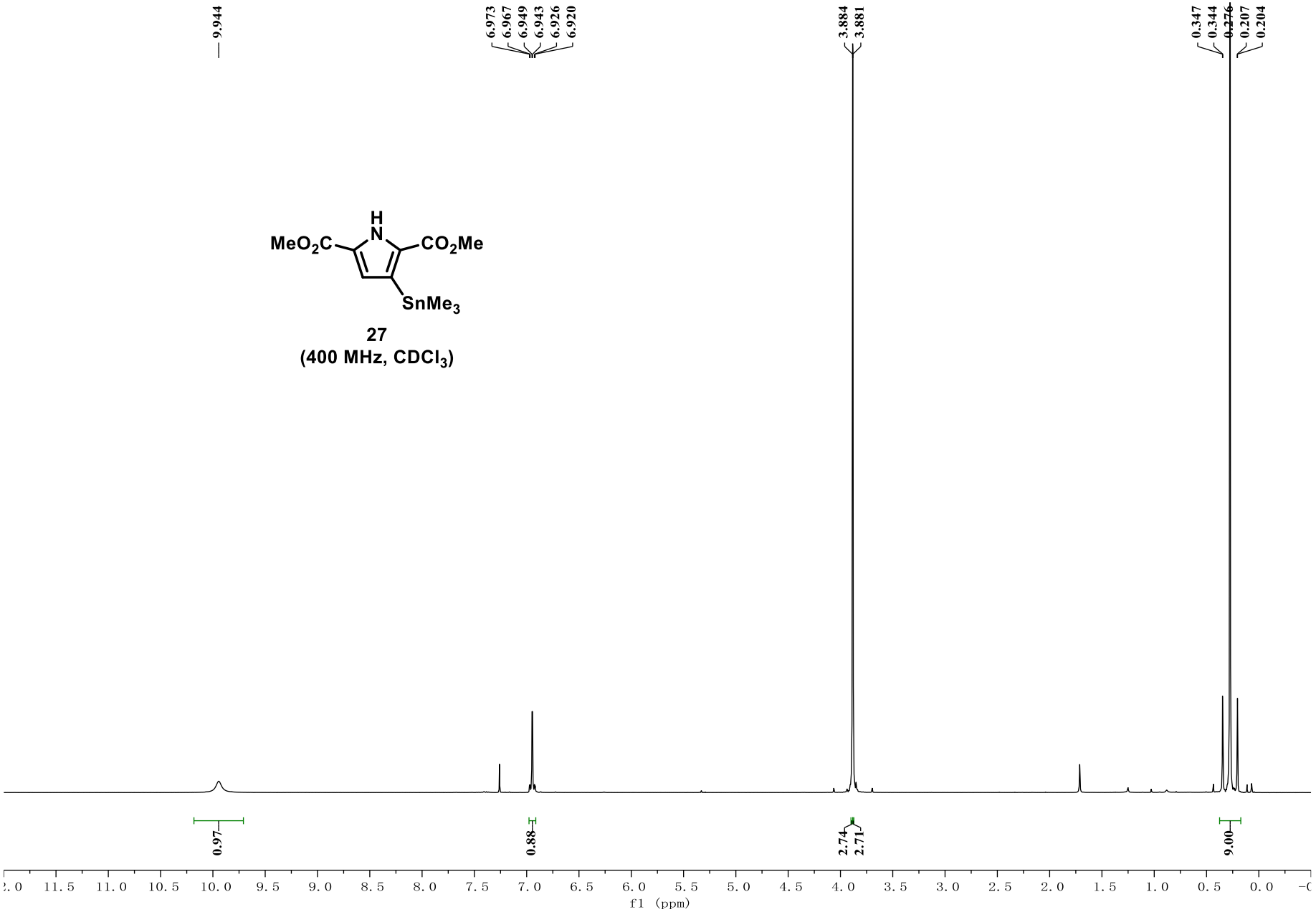
crude 22
(150 MHz, $(CD_3)_2SO$)

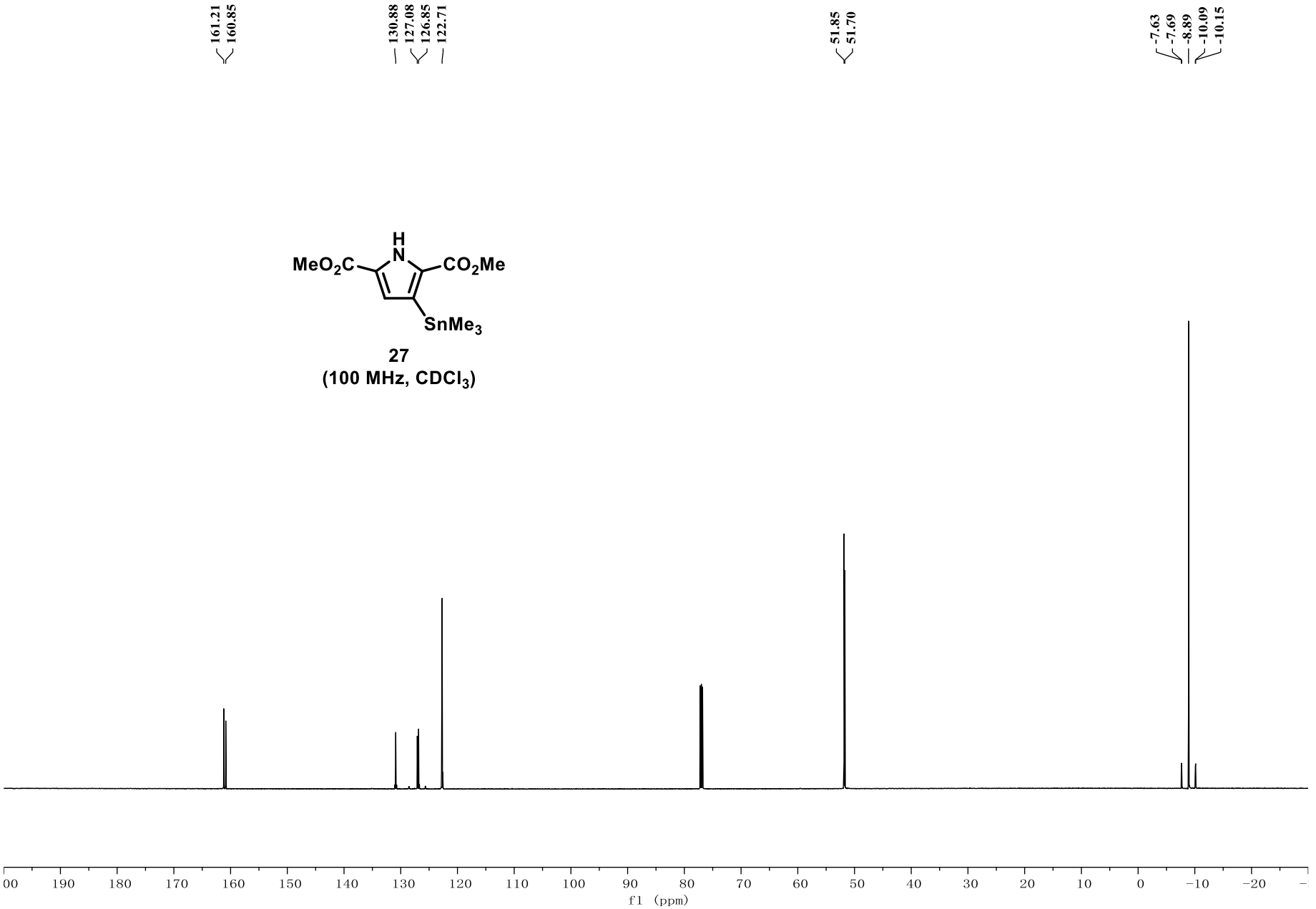


SI-4
(400 MHz, $CDCl_3$)

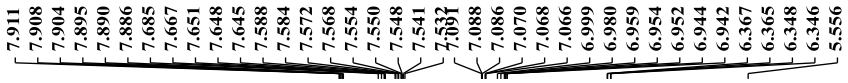


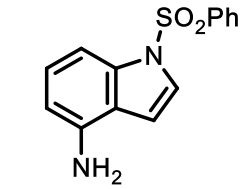
SI-5
(400 MHz, $CDCl_3$)


9.944
6.973
6.967
6.949
6.943
6.926
6.920
3.884
3.881
0.347
0.344
0.276
0.207
0.204
MeO2C
CO2Me
H
N
SnMe3
27
(400 MHz, CDCl3)
0.97
0.88
2.74
2.71
9.00
f1 (ppm)

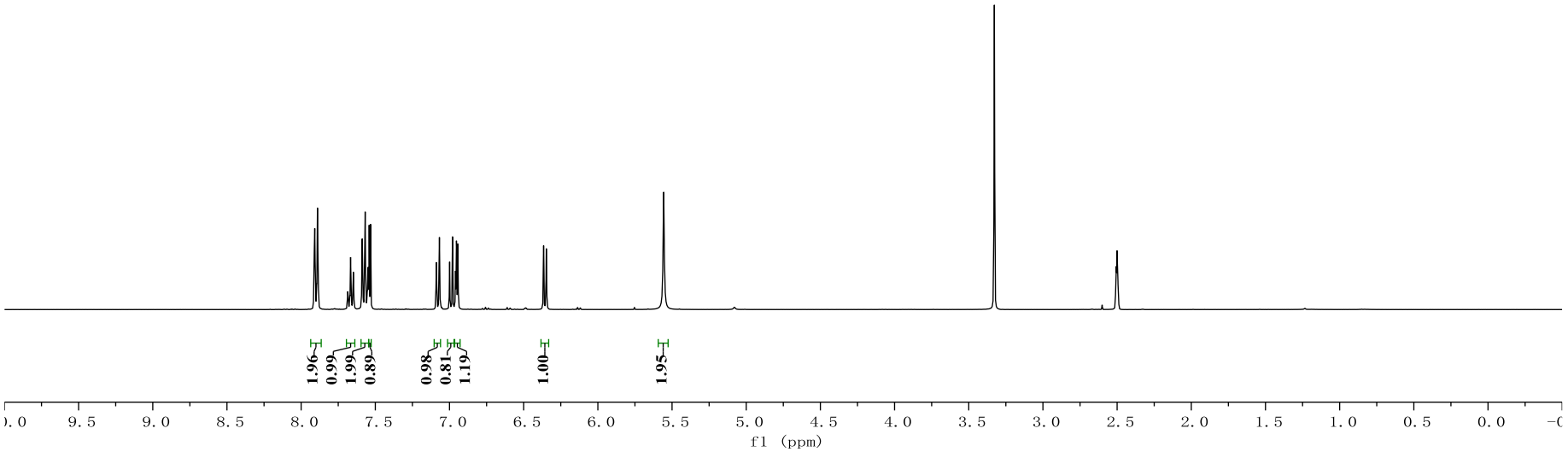


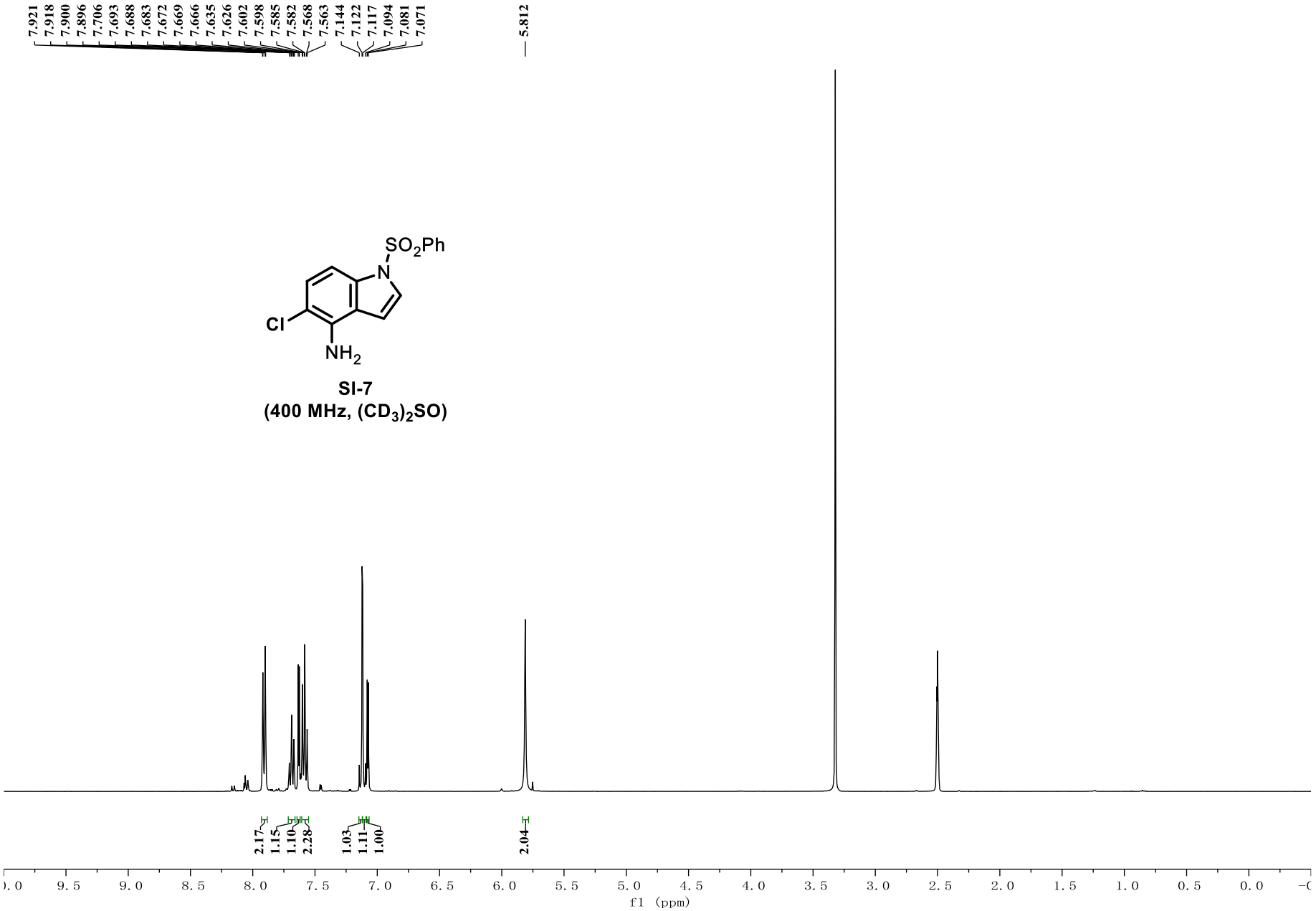
27
(100 MHz, $CDCl_3$)



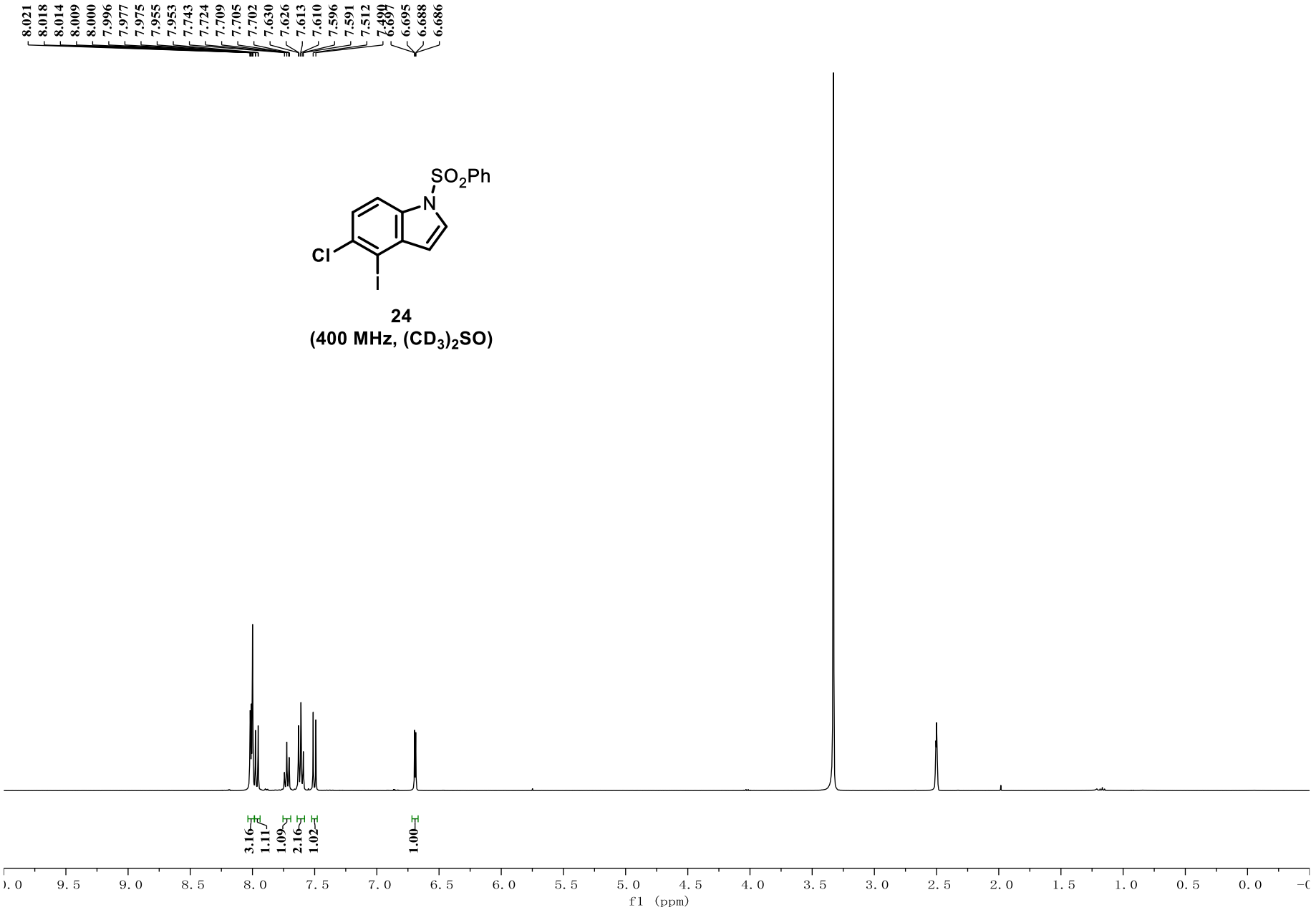


SI-6
(400 MHz, $(CD_3)_2SO$)

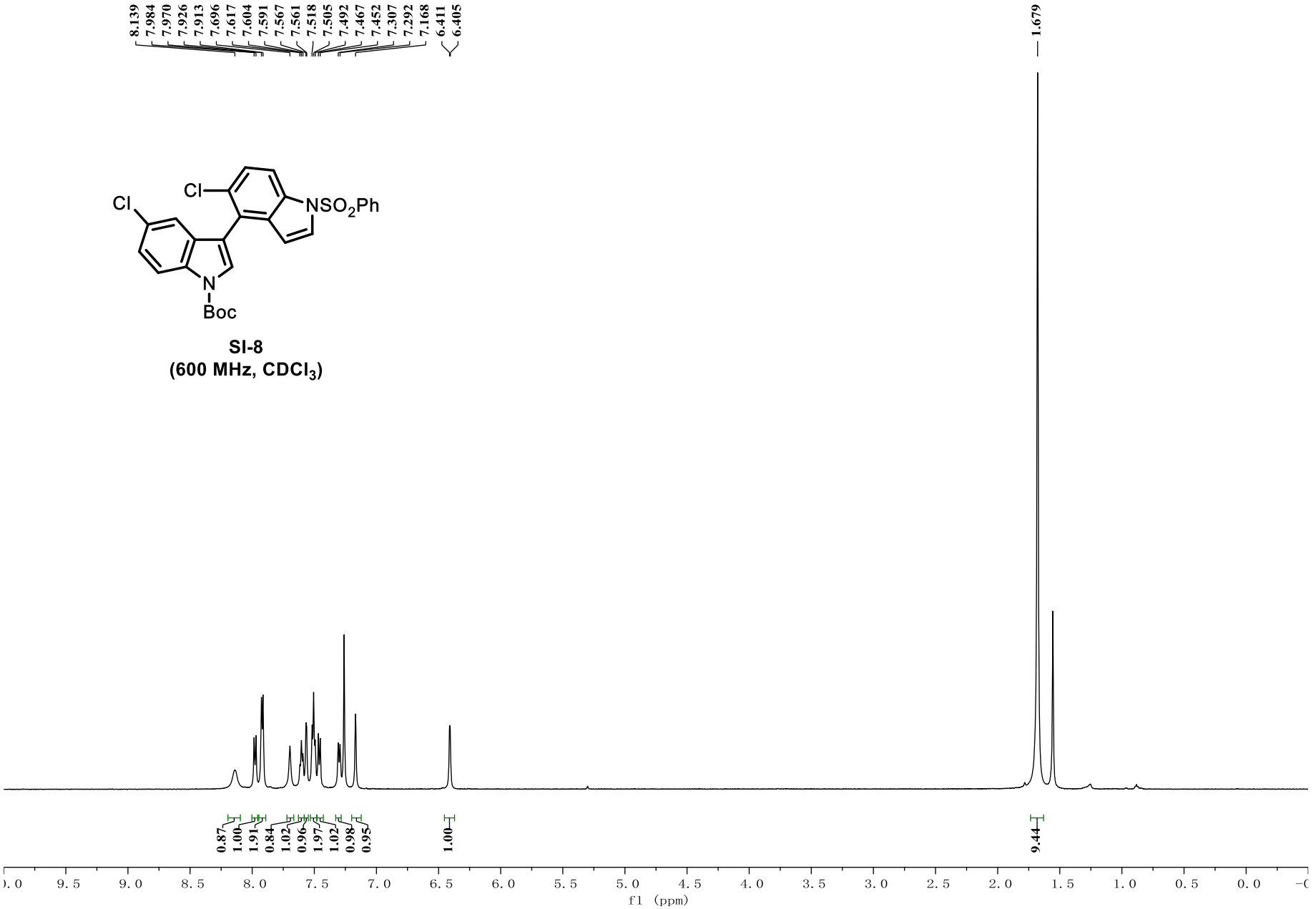




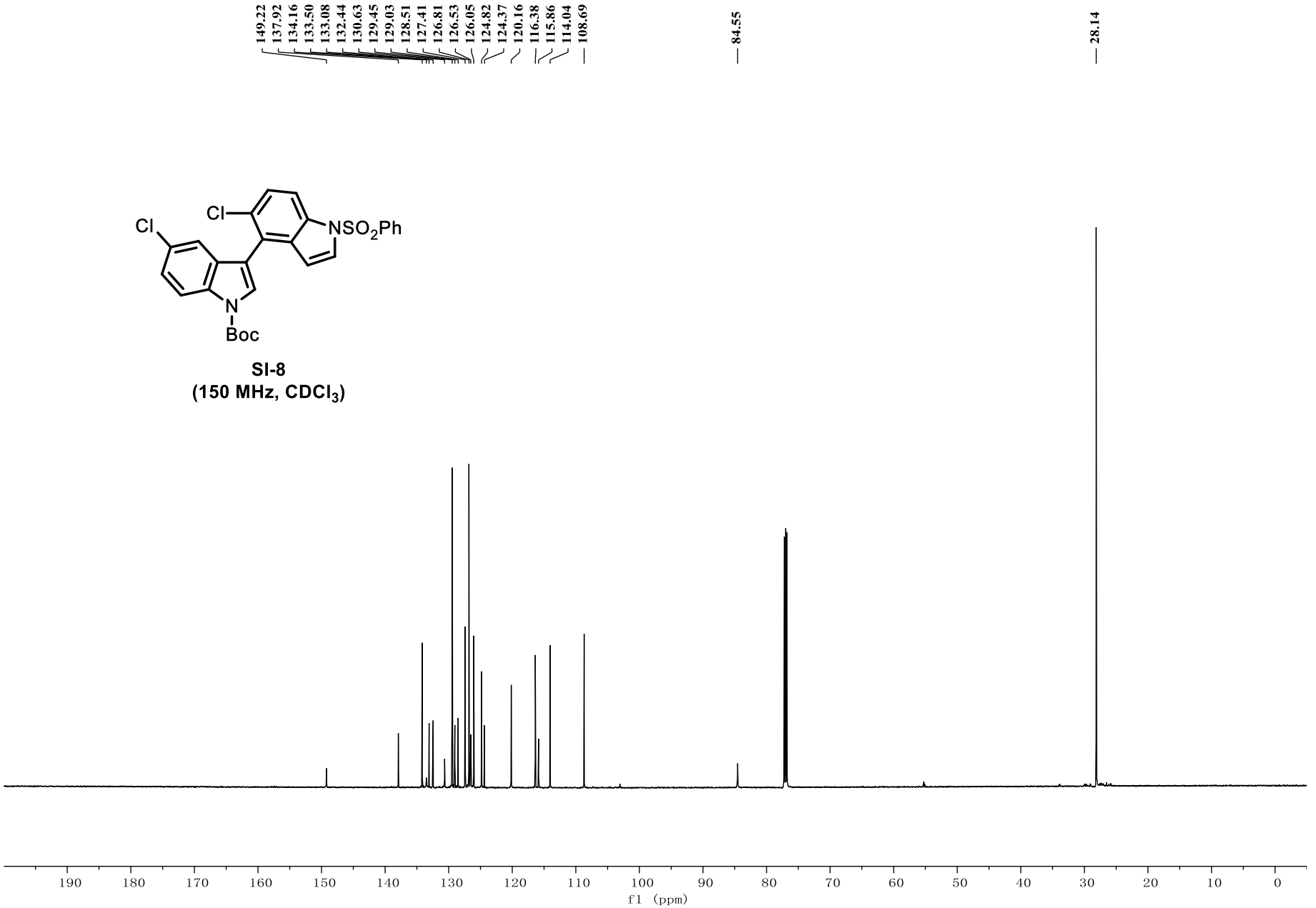
SI-7
(400 MHz, $(CD_3)_2SO$)



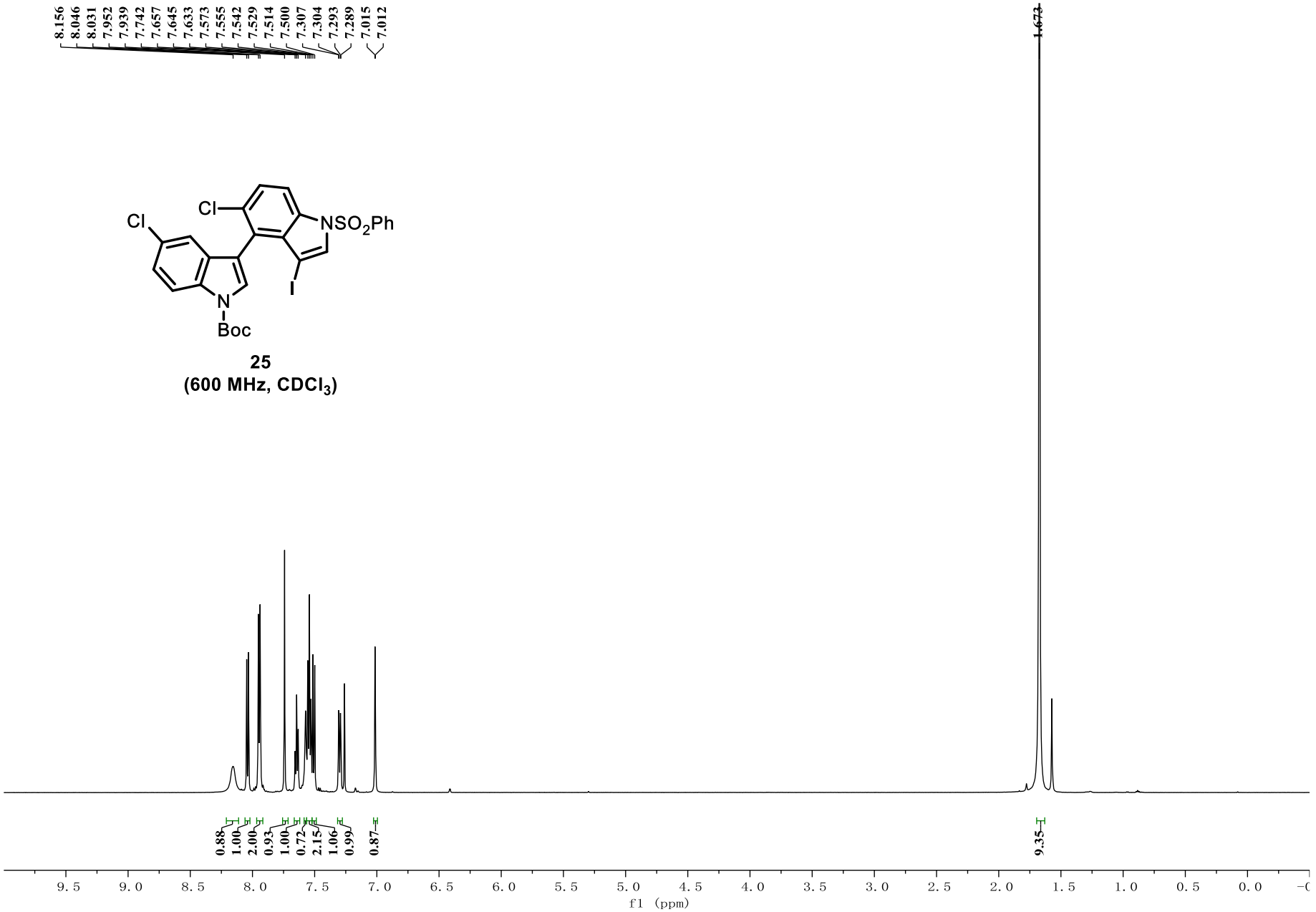
24
(400 MHz, $(CD_3)_2SO$)



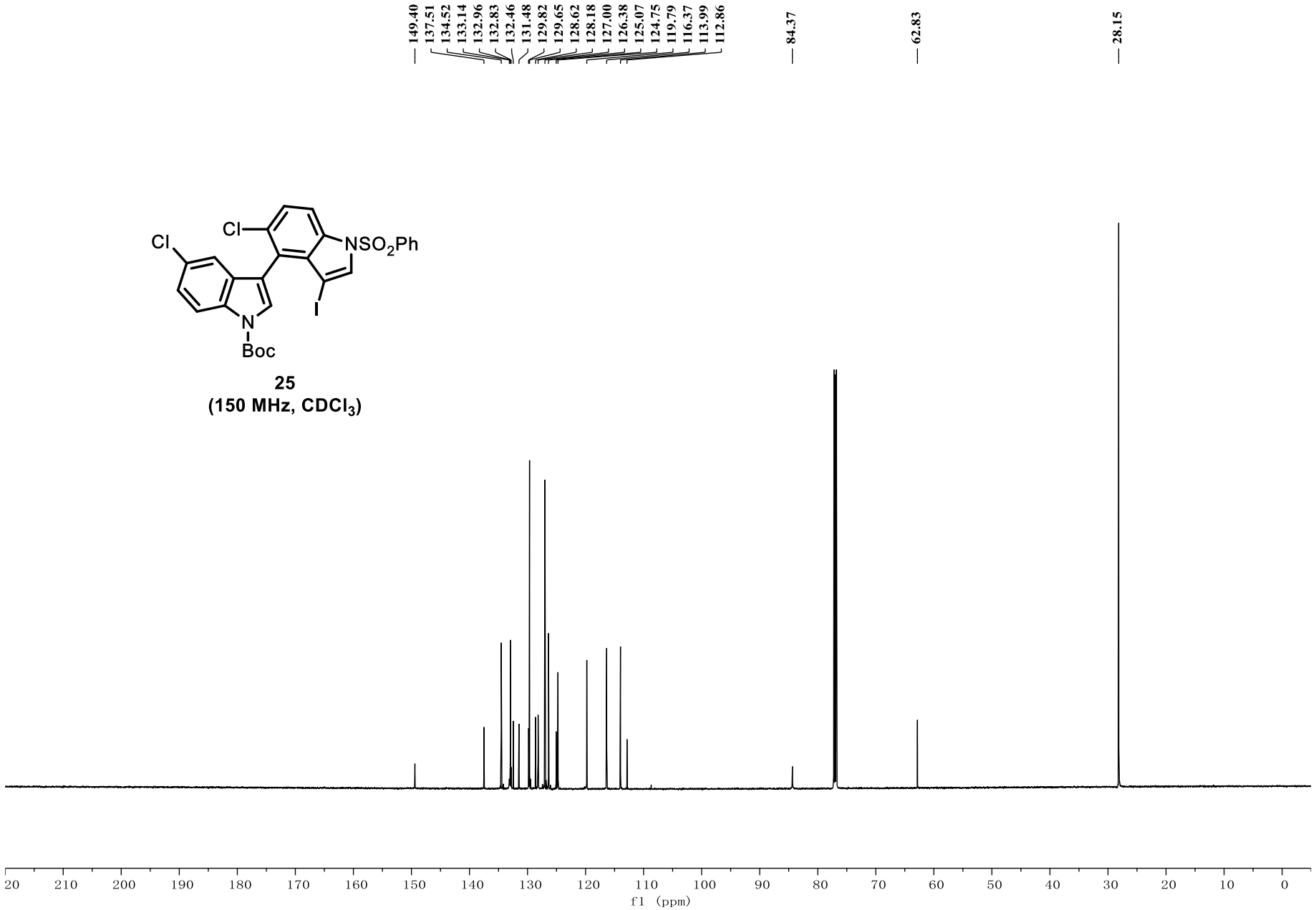
SI-8
(600 MHz, $CDCl_3$)

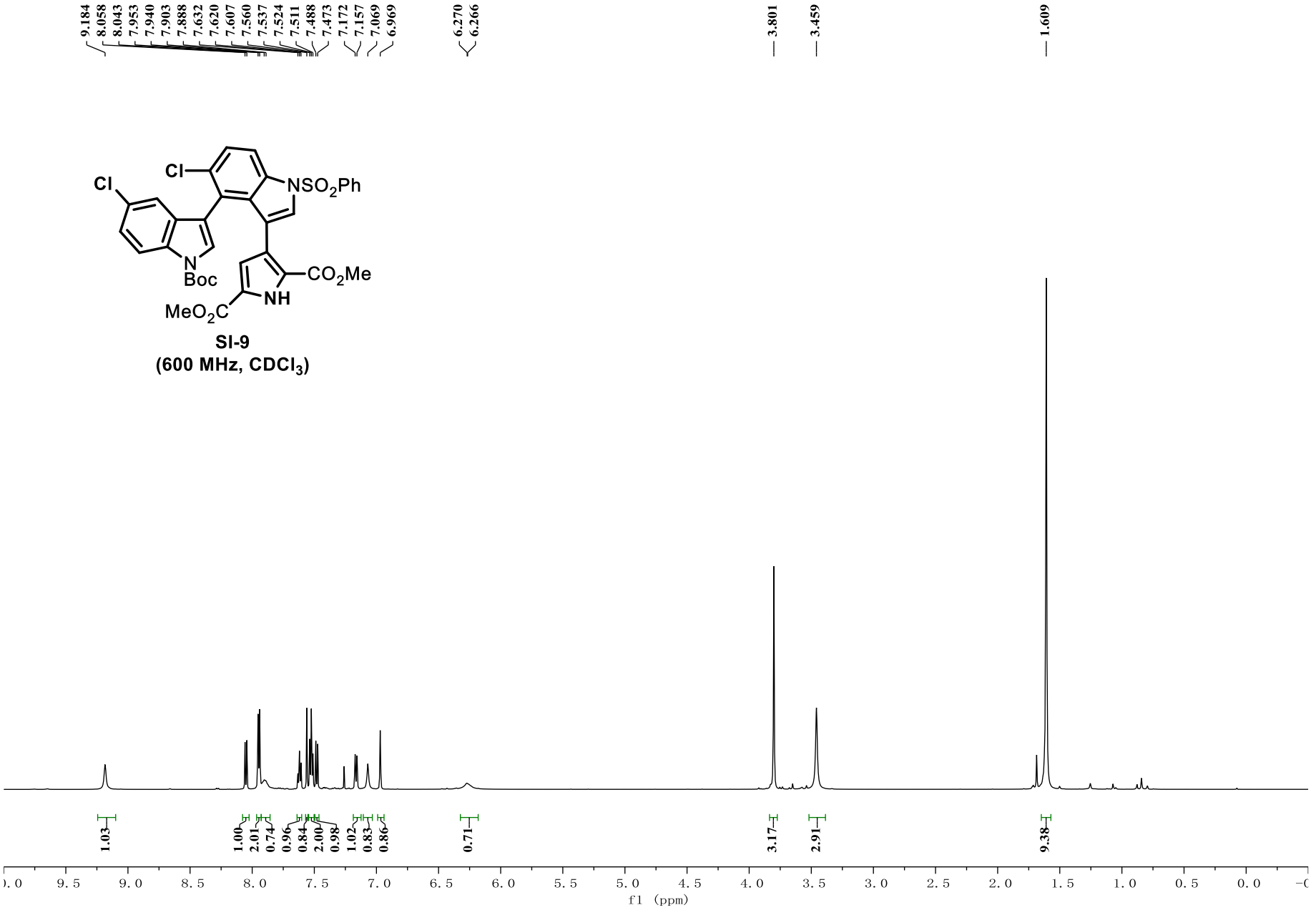


SI-8
(150 MHz, $CDCl_3$)

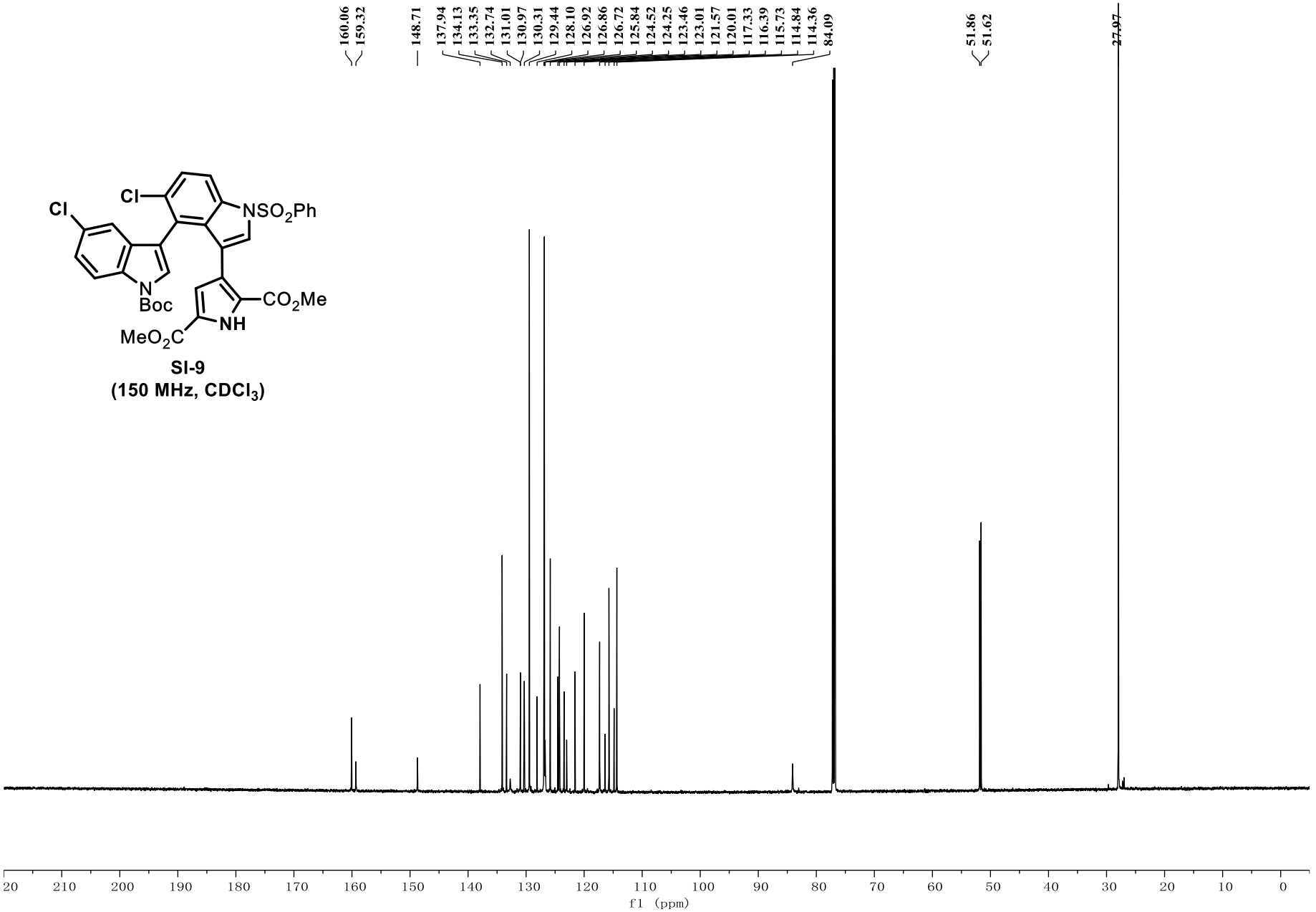


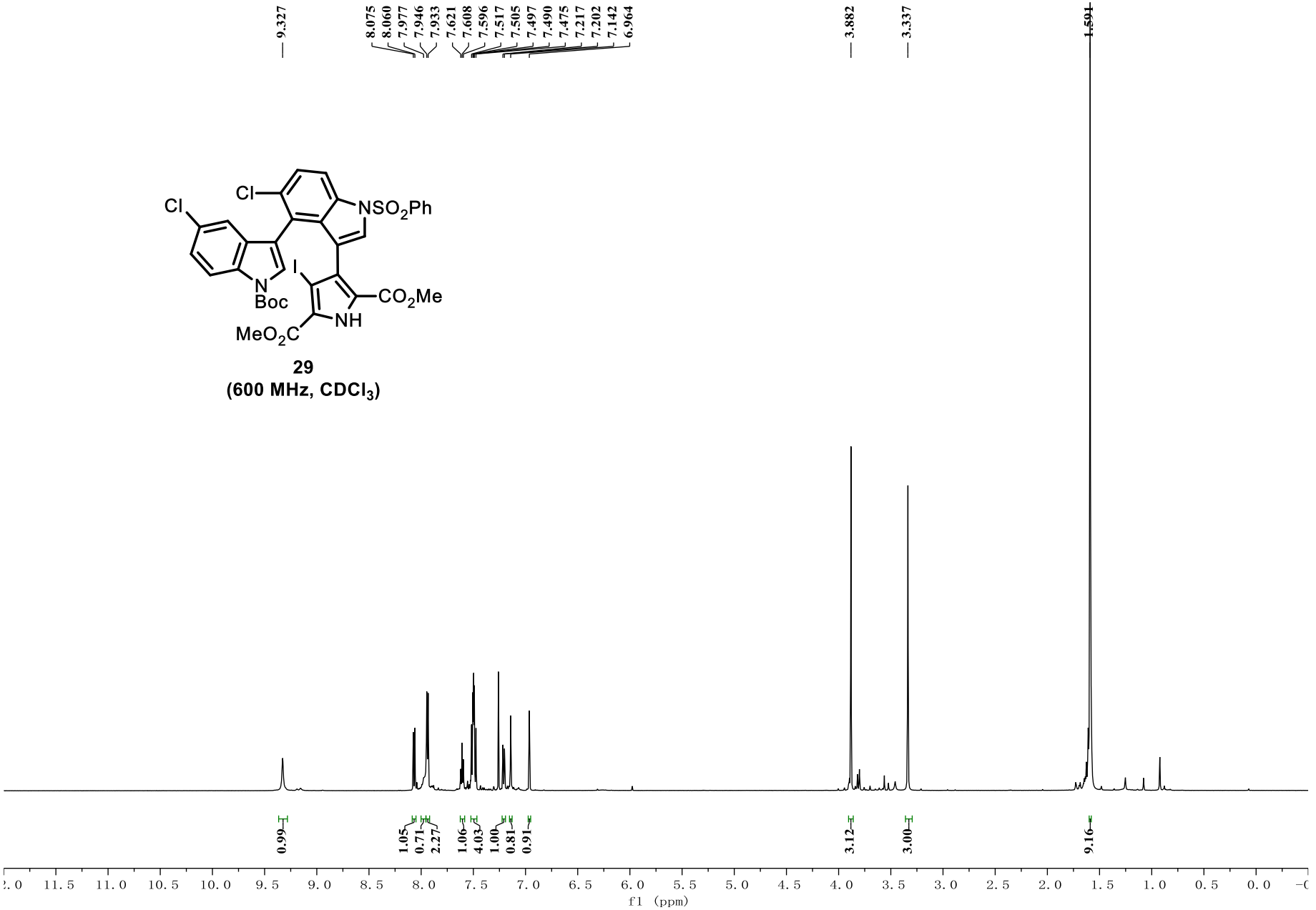
25
(600 MHz, $CDCl_3$)


149.40
137.51
134.52
133.14
132.96
132.83
132.46
131.48
129.82
129.65
128.62
128.18
127.00
126.38
125.07
124.75
119.79
116.37
113.99
112.86
84.37
62.83
28.15
Cl
Cl
NSO2Ph
I
N
Boc
25
(150 MHz, CDCl3)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

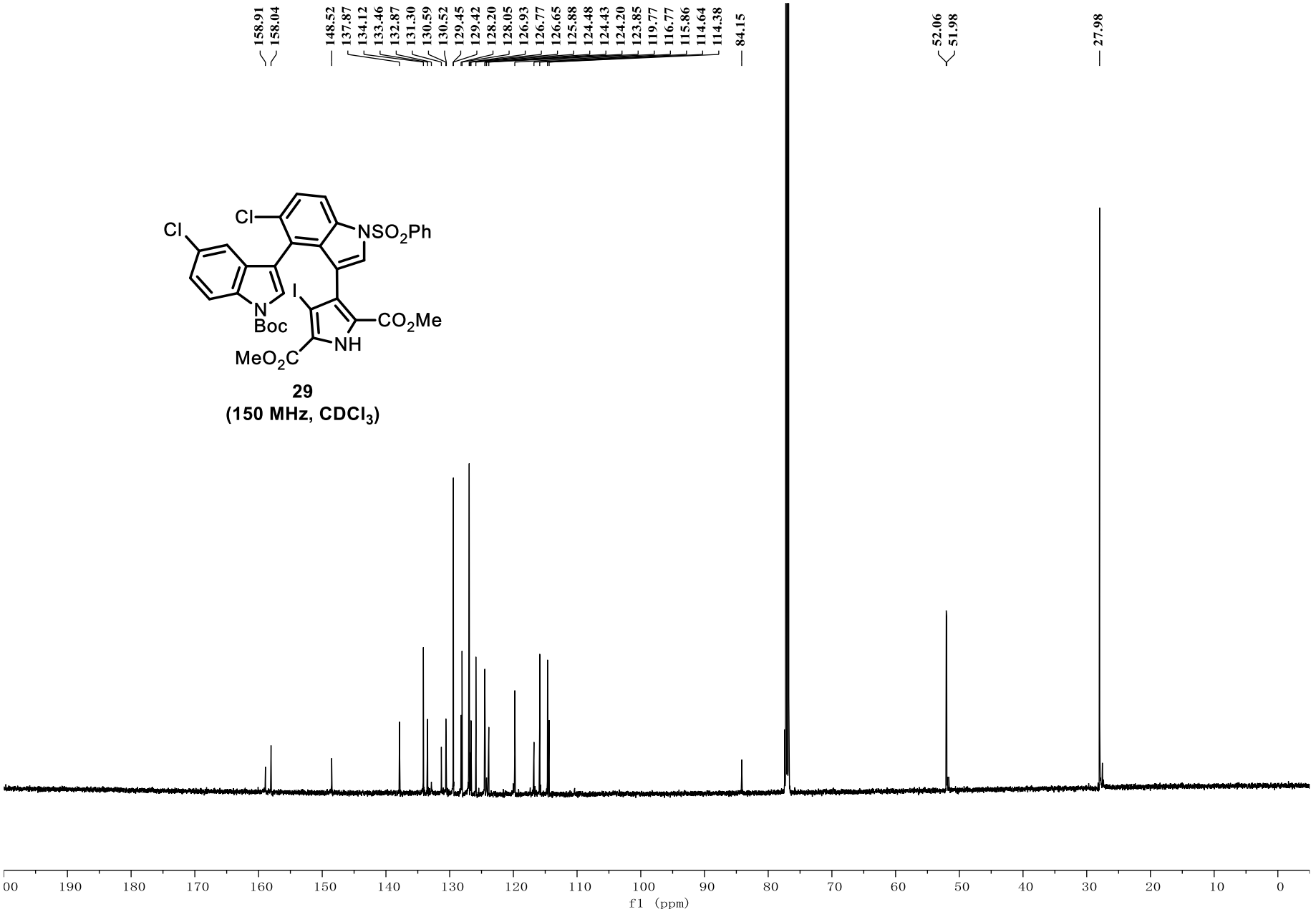


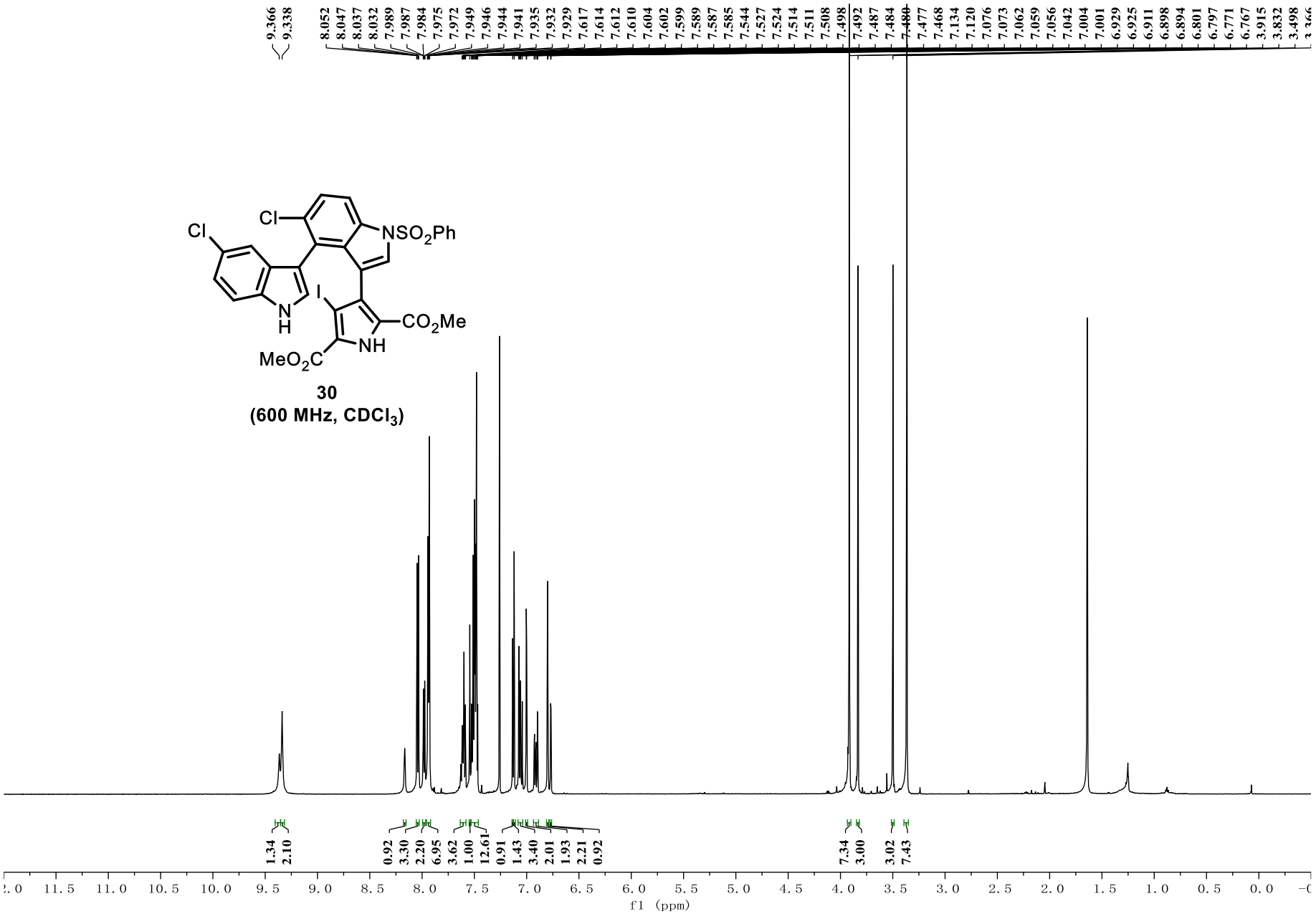
SI-9
(600 MHz, $CDCl_3$)

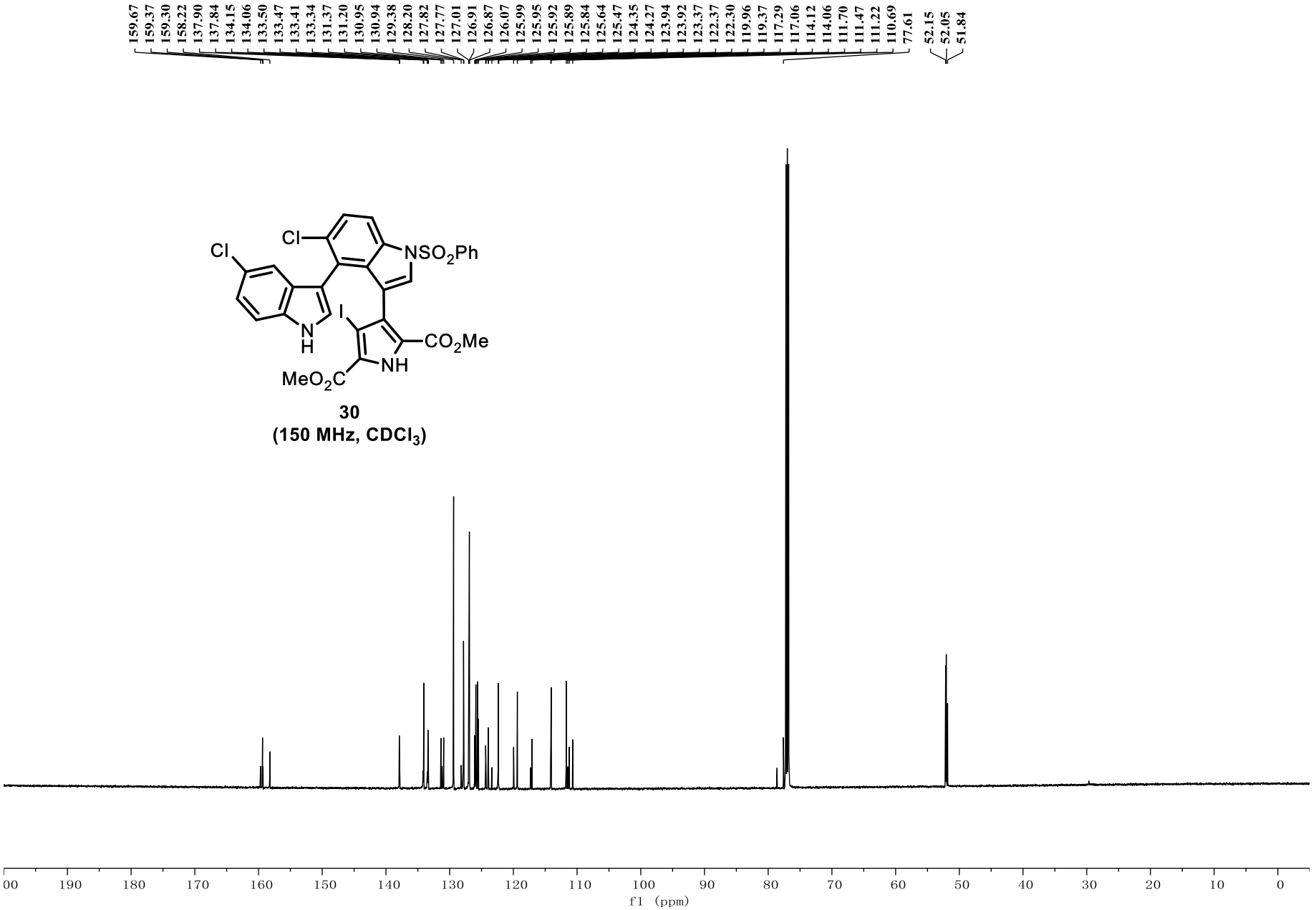

160.06
159.32
148.71
137.94
134.13
133.35
132.74
131.01
130.97
130.31
129.44
128.10
126.92
126.86
126.72
125.84
124.52
124.25
123.46
123.01
121.57
120.01
117.33
116.39
115.73
114.84
114.36
84.09
51.86
51.62
27.97
Cl
Cl
NSO2Ph
N
Boc
CO2Me
NH
MeO2C
SI-9
(150 MHz, CDCl3)
f1 (ppm)

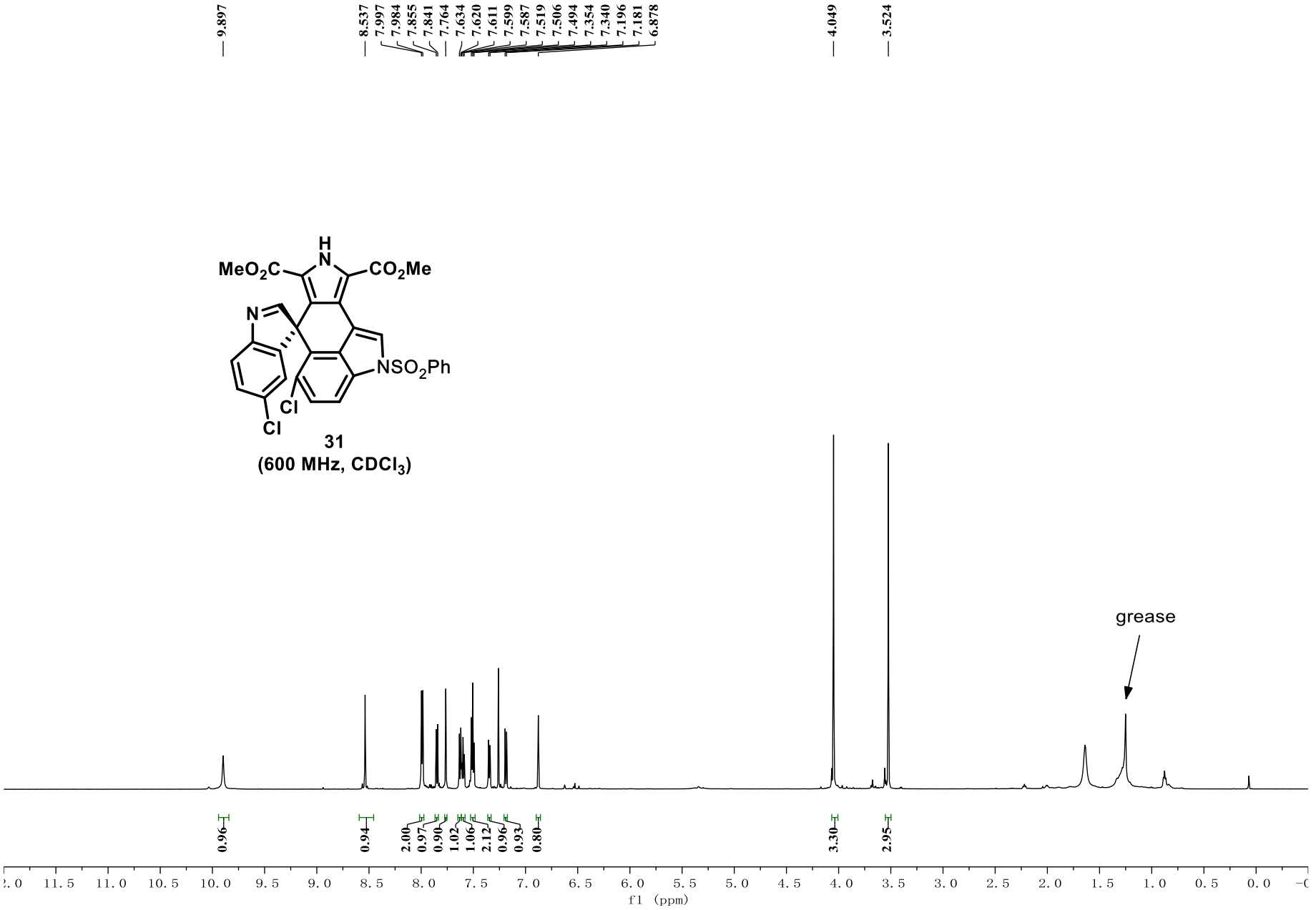


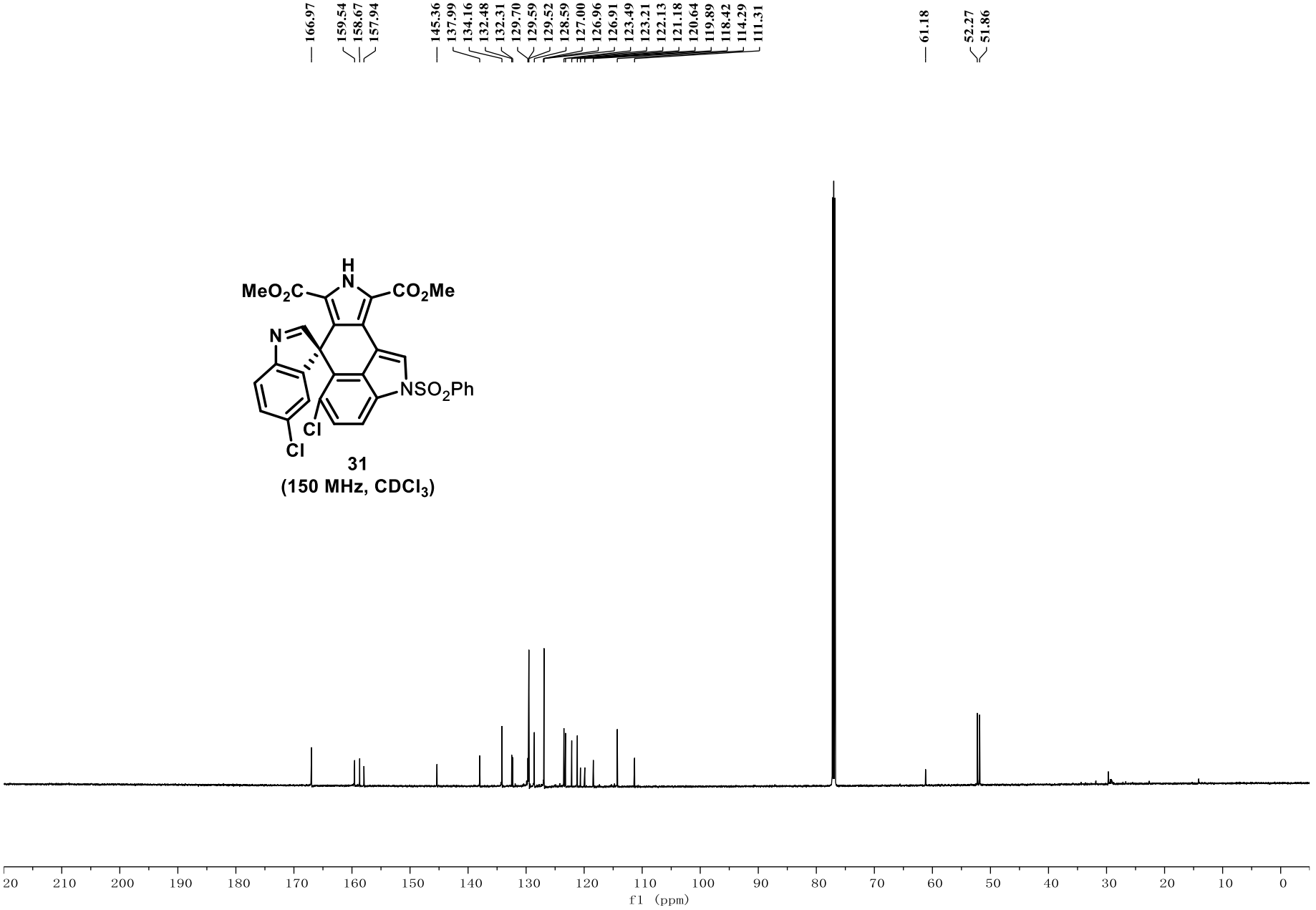
29
(600 MHz, $CDCl_3$)

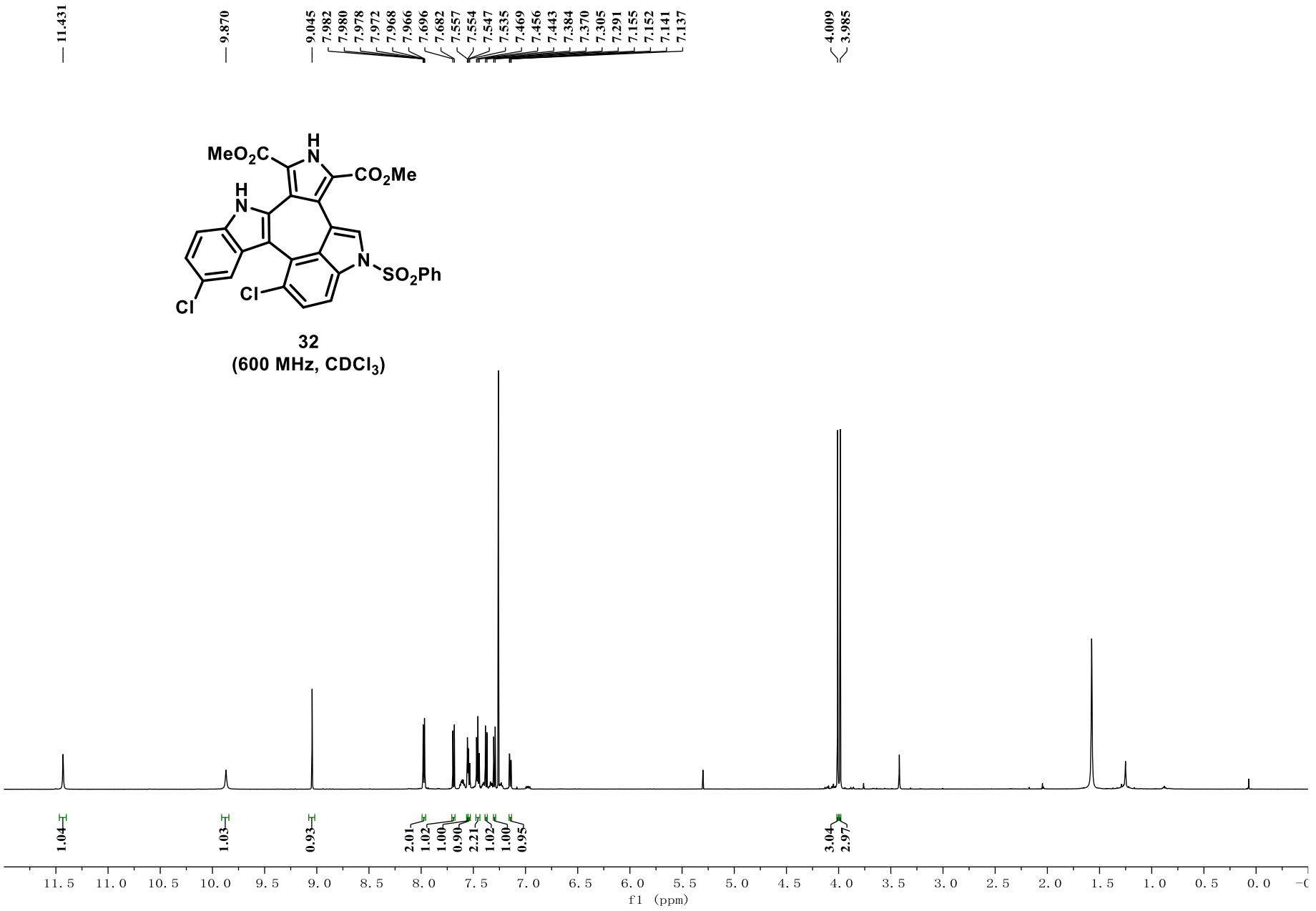

158.91
158.04
148.52
137.87
134.12
133.46
132.87
131.30
130.59
130.52
129.45
129.42
128.20
128.05
126.93
126.77
126.65
125.88
124.48
124.43
124.20
123.85
119.77
116.77
115.86
114.64
114.38
84.15
52.06
51.98
27.98
Cl
Cl
NSO2Ph
I
N
Boc
CO2Me
NH
MeO2C
29
(150 MHz, CDCl3)
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

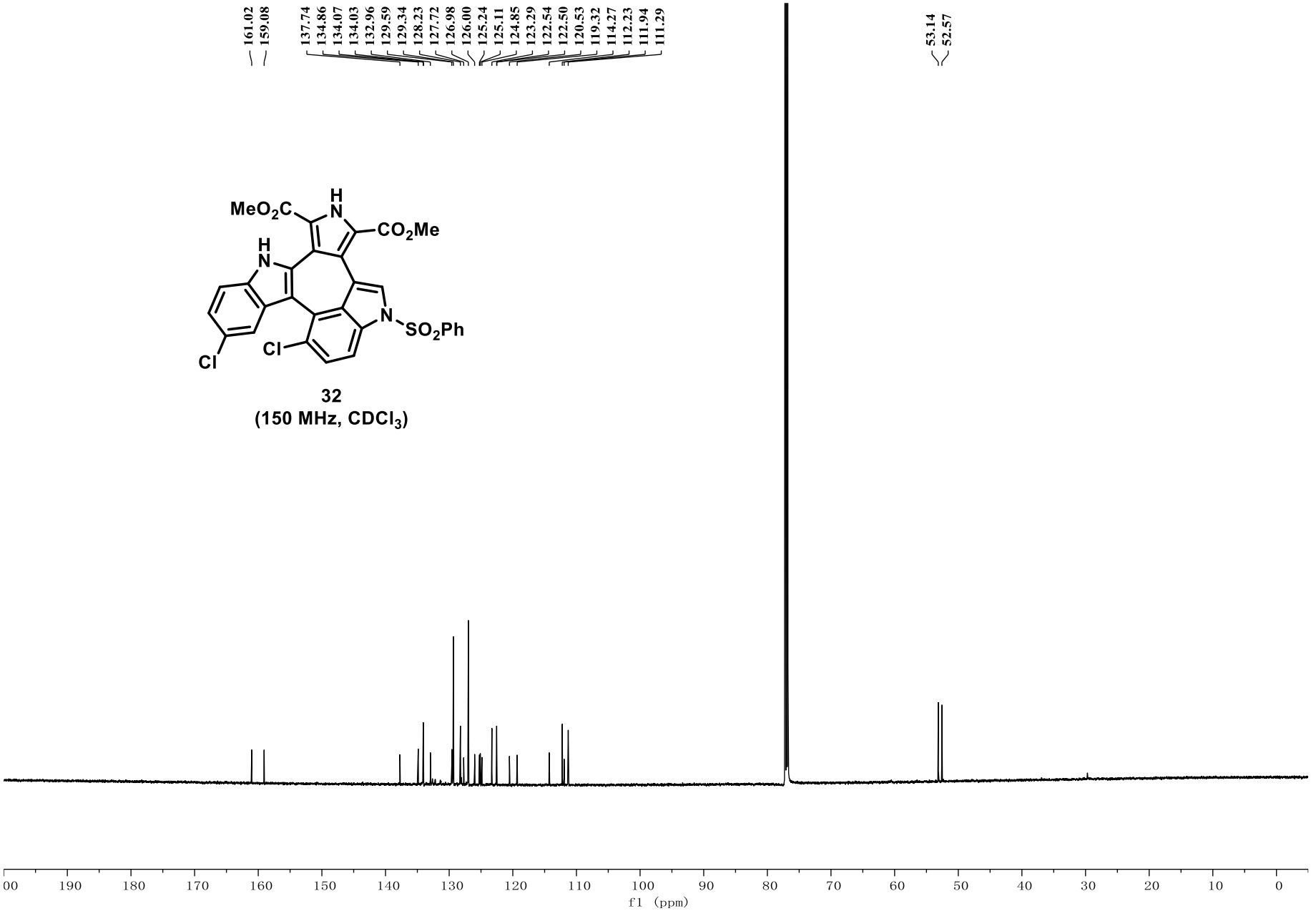

9.366
9.338
8.052
8.047
8.037
8.032
7.989
7.987
7.984
7.975
7.972
7.949
7.946
7.944
7.941
7.935
7.932
7.929
7.617
7.614
7.612
7.610
7.604
7.602
7.599
7.589
7.587
7.585
7.544
7.527
7.524
7.514
7.511
7.508
7.498
7.492
7.487
7.484
7.480
7.477
7.468
7.134
7.120
7.076
7.073
7.062
7.059
7.056
7.042
7.004
7.001
6.929
6.925
6.911
6.898
6.894
6.801
6.797
6.771
6.767
3.915
3.832
3.498
Cl
Cl
NSO2Ph
I
N
H
CO2Me
NH
MeO2C
30
(600 MHz, CDCl3)
1.34
2.10
0.92
3.30
2.20
6.95
3.62
1.00
12.61
0.91
1.43
3.40
2.01
1.93
2.21
0.92
7.34
3.00
3.02
7.43
f1 (ppm)

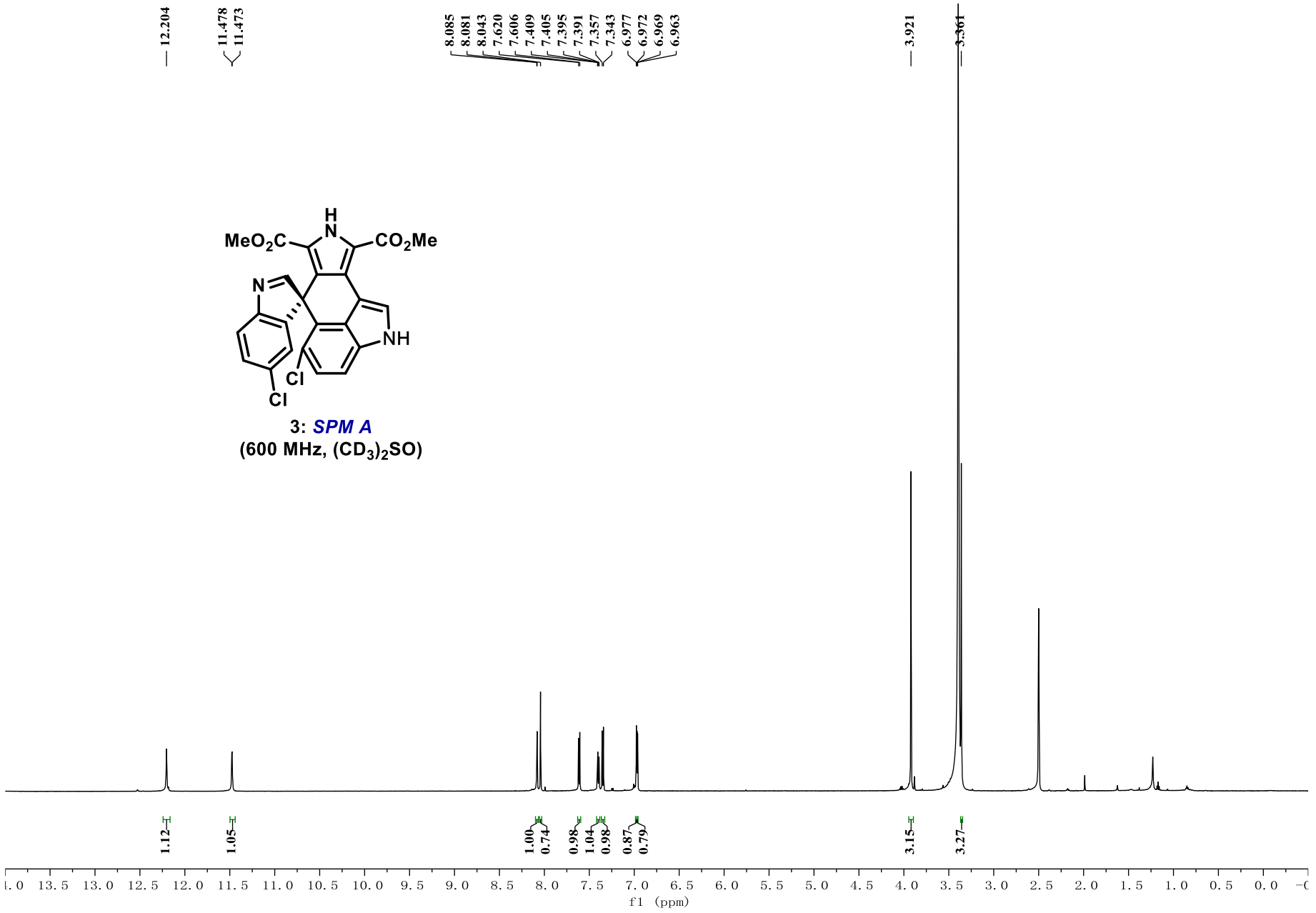

159.67
159.37
159.30
158.22
137.90
137.84
134.15
134.06
133.50
133.47
133.41
133.34
131.37
131.20
130.95
130.94
129.38
128.20
127.82
127.77
127.01
126.91
126.87
126.07
125.99
125.95
125.92
125.89
125.84
125.64
125.47
124.35
124.27
123.94
123.92
123.37
122.37
122.30
119.96
119.37
117.29
117.06
114.12
114.06
111.70
111.47
111.22
110.69
77.61
52.15
52.05
51.84
Cl
Cl
NSO2Ph
I
N
H
CO2Me
NH
MeO2C
30
(150 MHz, CDCl3)
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


9.897
8.537
7.997
7.984
7.855
7.841
7.764
7.634
7.620
7.611
7.599
7.587
7.519
7.506
7.494
7.354
7.340
7.196
7.181
6.878
4.049
3.524
MeO2C
CO2Me
H
N
N
NSO2Ph
Cl
Cl
31
(600 MHz, CDCl3)
grease
0.96
0.94
2.00
0.97
0.90
1.02
1.06
2.12
0.96
0.93
0.80
3.30
2.95
f1 (ppm)

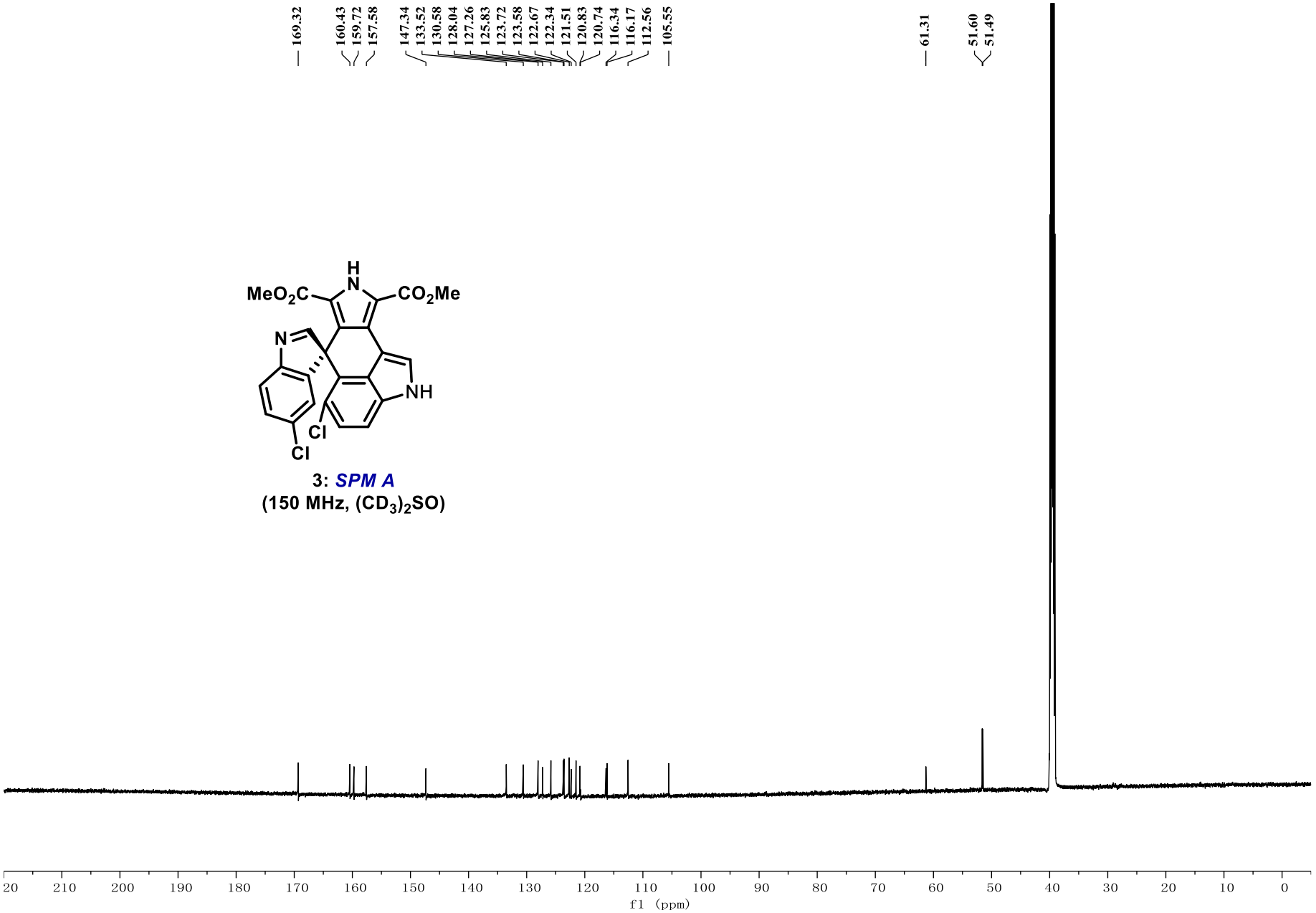

166.97
159.54
158.67
157.94
145.36
137.99
134.16
132.48
132.31
129.70
129.59
129.52
128.59
127.00
126.96
126.91
123.49
123.21
122.13
121.18
120.64
119.89
118.42
114.29
111.31
61.18
52.27
51.86
H
N
MeO2C
CO2Me
N
NSO2Ph
Cl
Cl
31
(150 MHz, CDCl3)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


11.431
9.870
9.045
7.982
7.980
7.978
7.972
7.968
7.966
7.696
7.682
7.557
7.554
7.547
7.535
7.469
7.456
7.443
7.384
7.370
7.305
7.291
7.155
7.152
7.141
7.137
4.009
3.985
MeO2C
CO2Me
H
N
H
N
N
SO2Ph
Cl
Cl
32
(600 MHz, CDCl3)
1.04
1.03
0.93
2.01
1.02
1.00
0.90
2.21
1.02
1.00
0.95
3.04
2.97
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

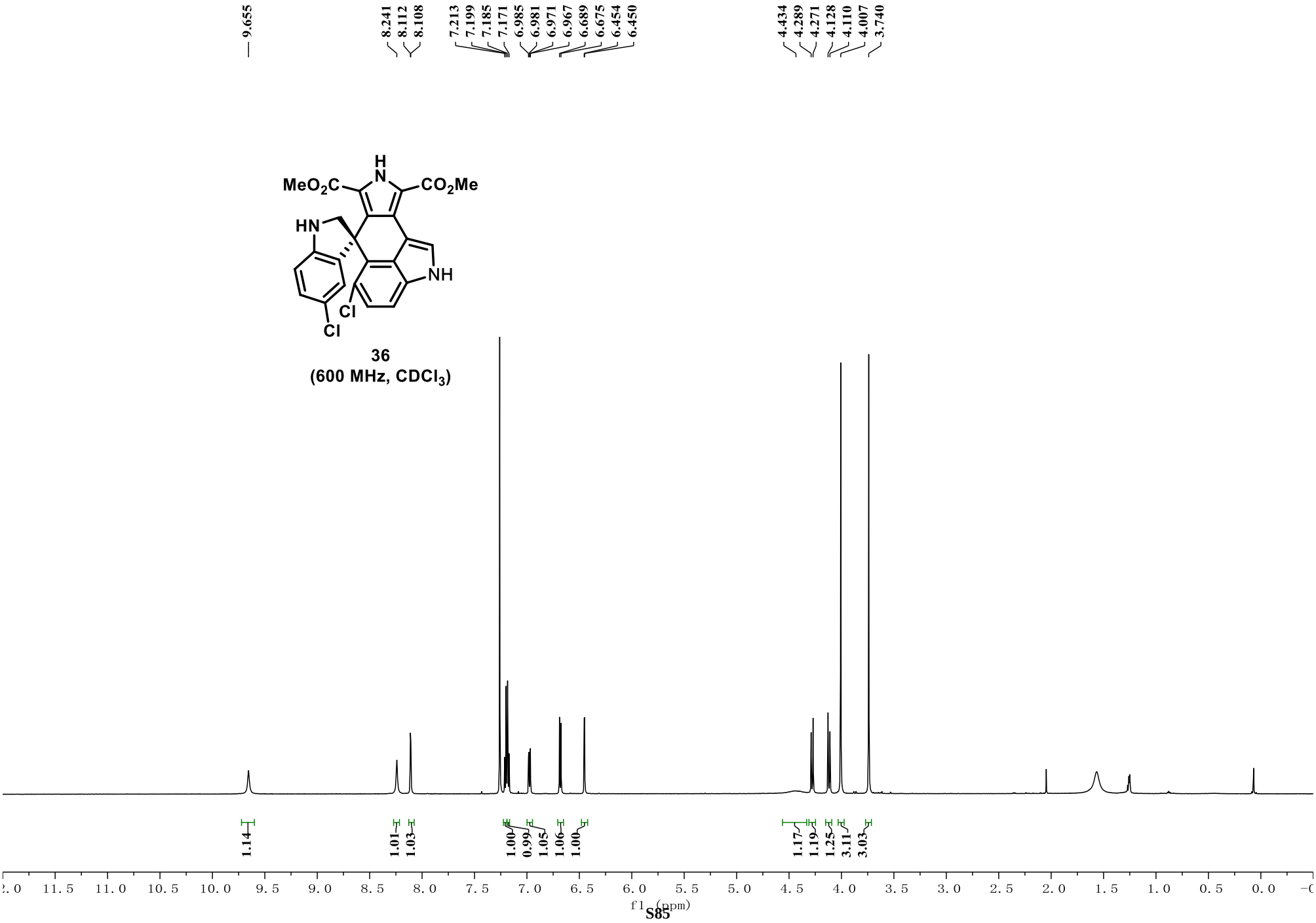

161.02
159.08
137.74
134.86
134.07
134.03
132.96
129.59
129.34
128.23
127.72
126.98
126.00
125.24
125.11
124.85
123.29
122.54
122.50
120.53
119.32
114.27
112.23
111.94
111.29
53.14
52.57
MeO2C
H
N
CO2Me
H
N
N
SO2Ph
Cl
Cl
32
(150 MHz, CDCl3)
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

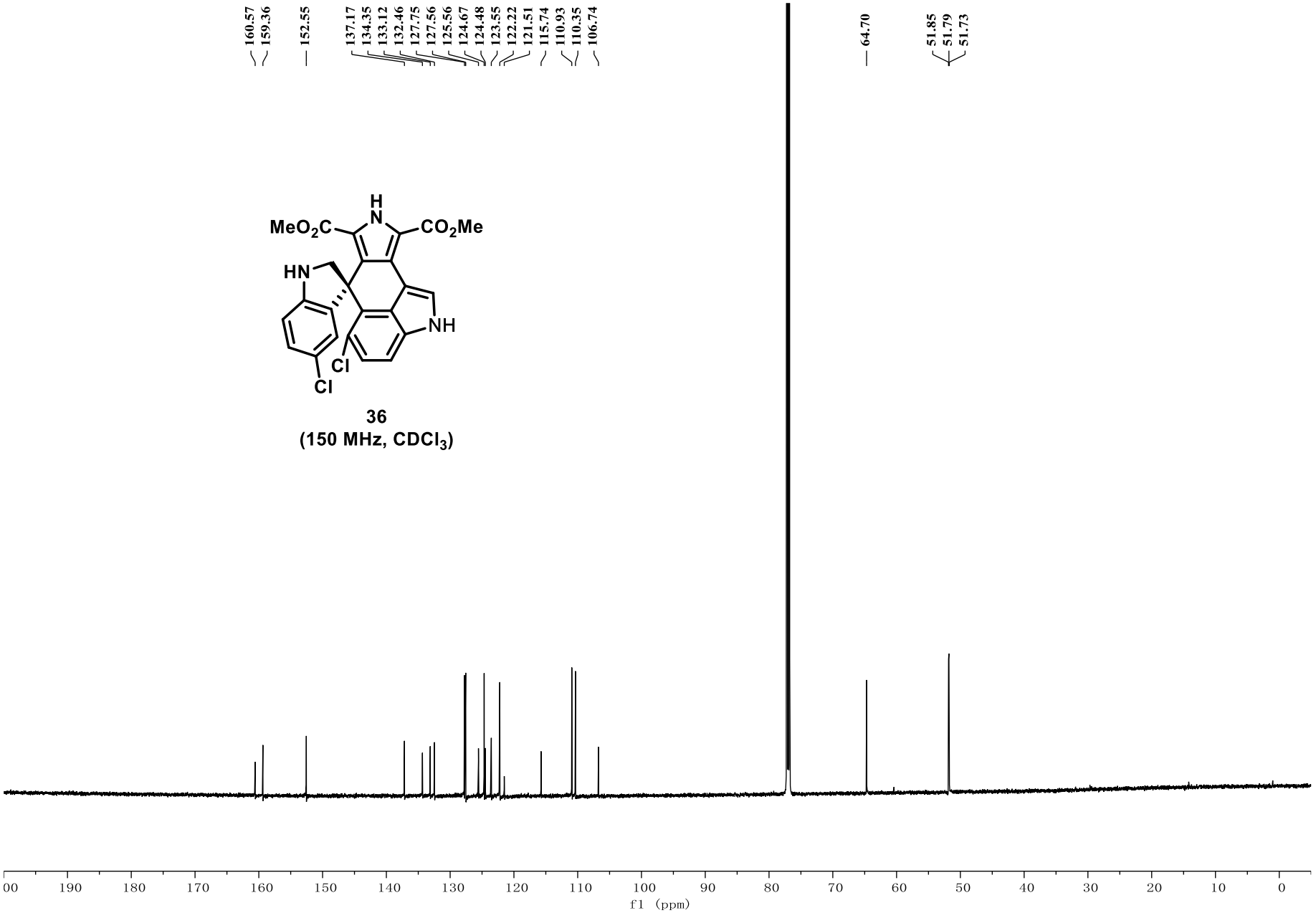


3: *SPM A*
(600 MHz, $(CD_3)_2SO$)

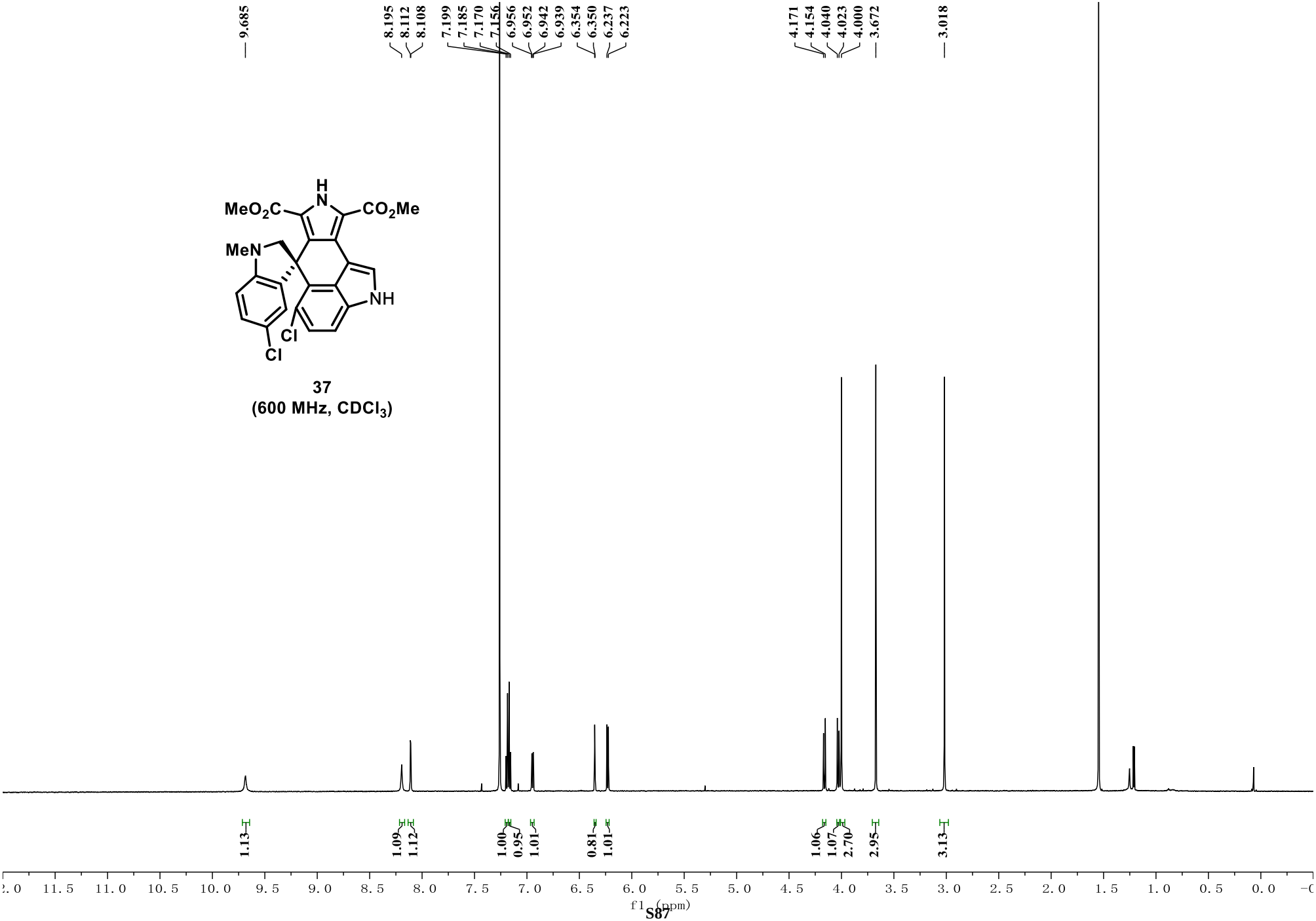


3: *SPM A*
(150 MHz, $(CD_3)_2SO$)

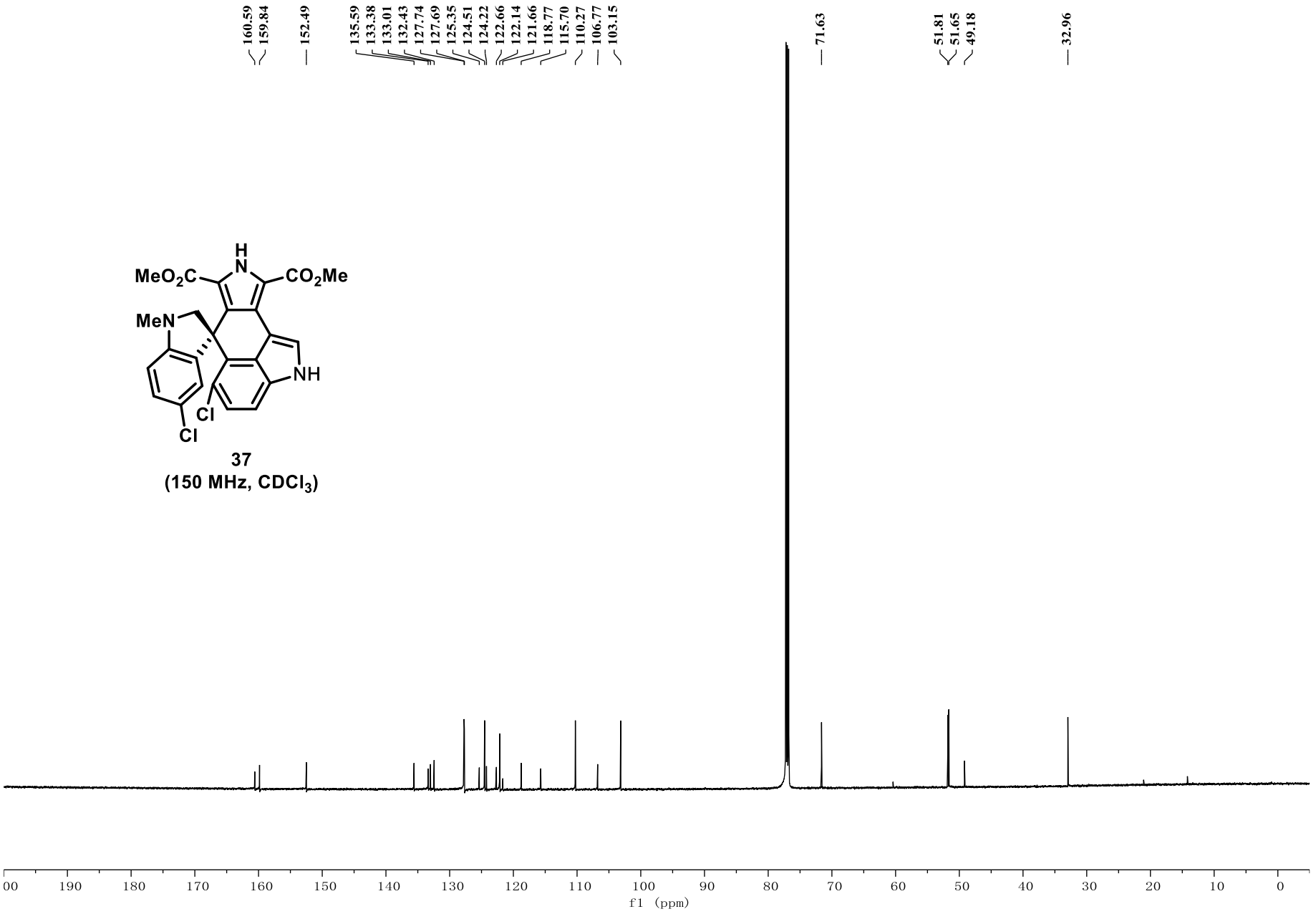

9.655
8.241
8.112
8.108
7.213
7.199
7.185
7.171
6.985
6.981
6.971
6.967
6.689
6.675
6.454
6.450
4.434
4.289
4.271
4.128
4.110
4.007
3.740
MeO2C
CO2Me
HN
NH
Cl
Cl
36
(600 MHz, CDCl3)
1.14
1.01
1.03
1.00
0.99
1.05
1.06
1.00
1.17
1.19
1.25
3.11
3.03
f1 (ppm)

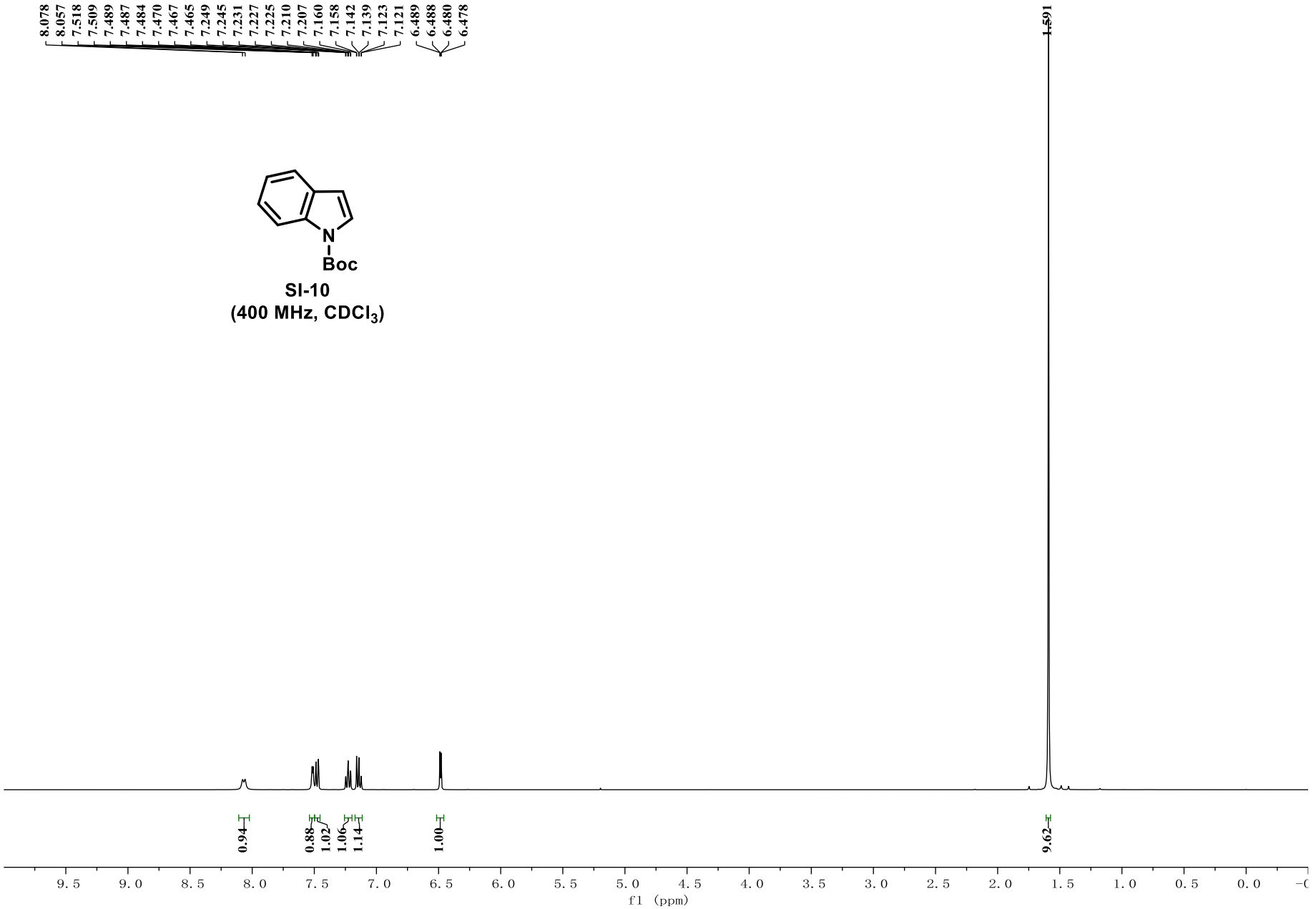


36
(150 MHz, $CDCl_3$)

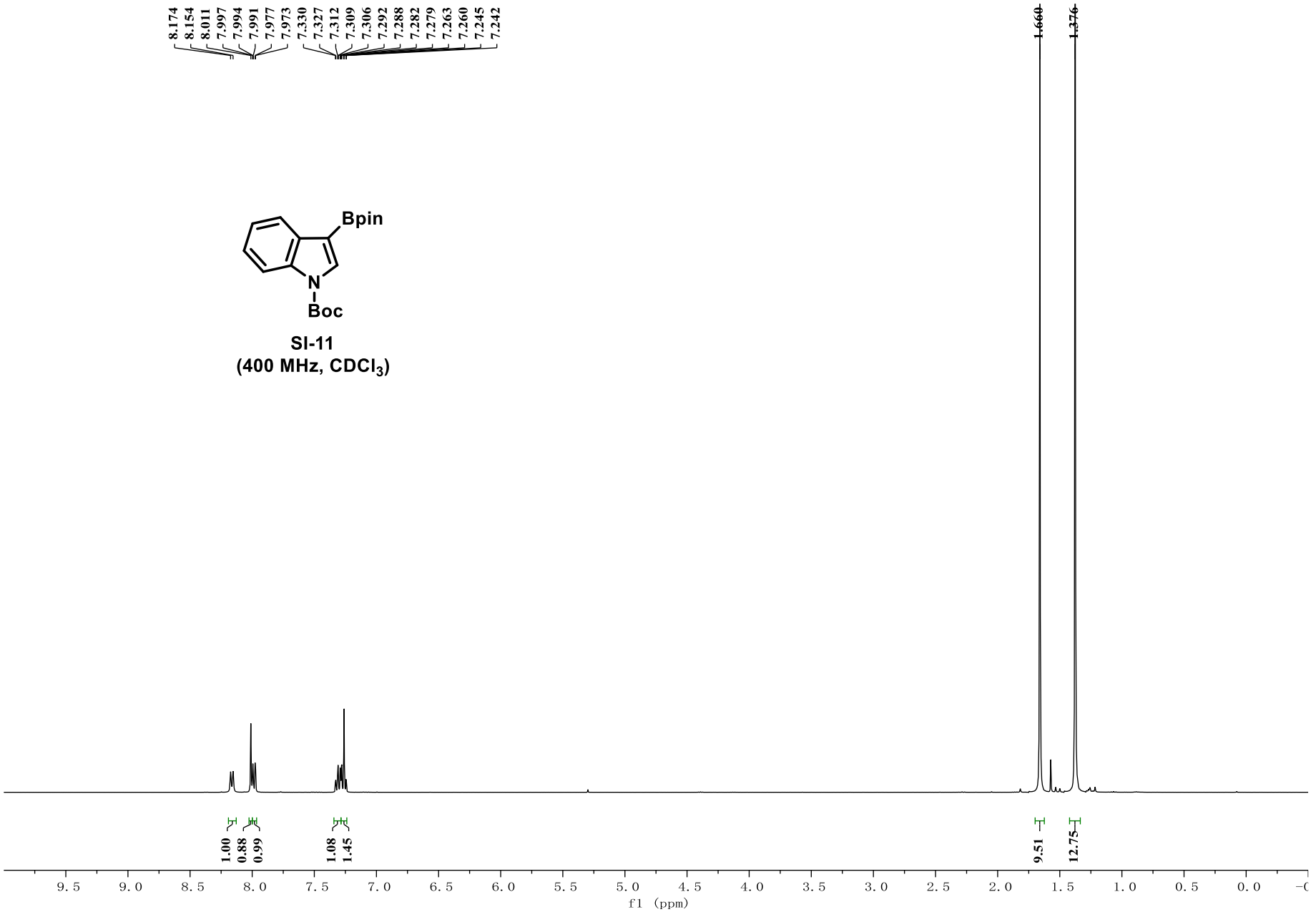


37
(600 MHz, $CDCl_3$)

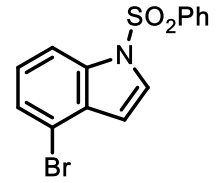

160.59
159.84
152.49
135.59
133.38
133.01
132.43
127.74
127.69
125.35
124.51
124.22
122.66
122.14
121.66
118.77
115.70
110.27
106.77
103.15
71.63
51.81
51.65
49.18
32.96
MeO2C
CO2Me
MeN
H
N
NH
Cl
Cl
37
(150 MHz, CDCl3)
f1 (ppm)



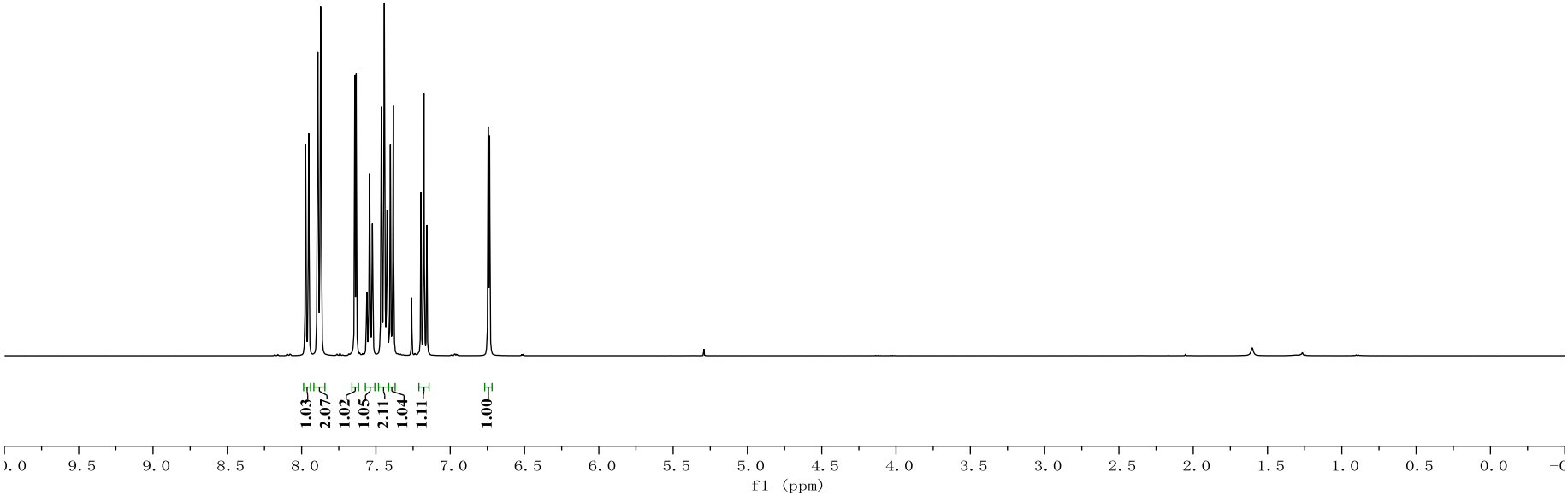
SI-10
(400 MHz, $CDCl_3$)

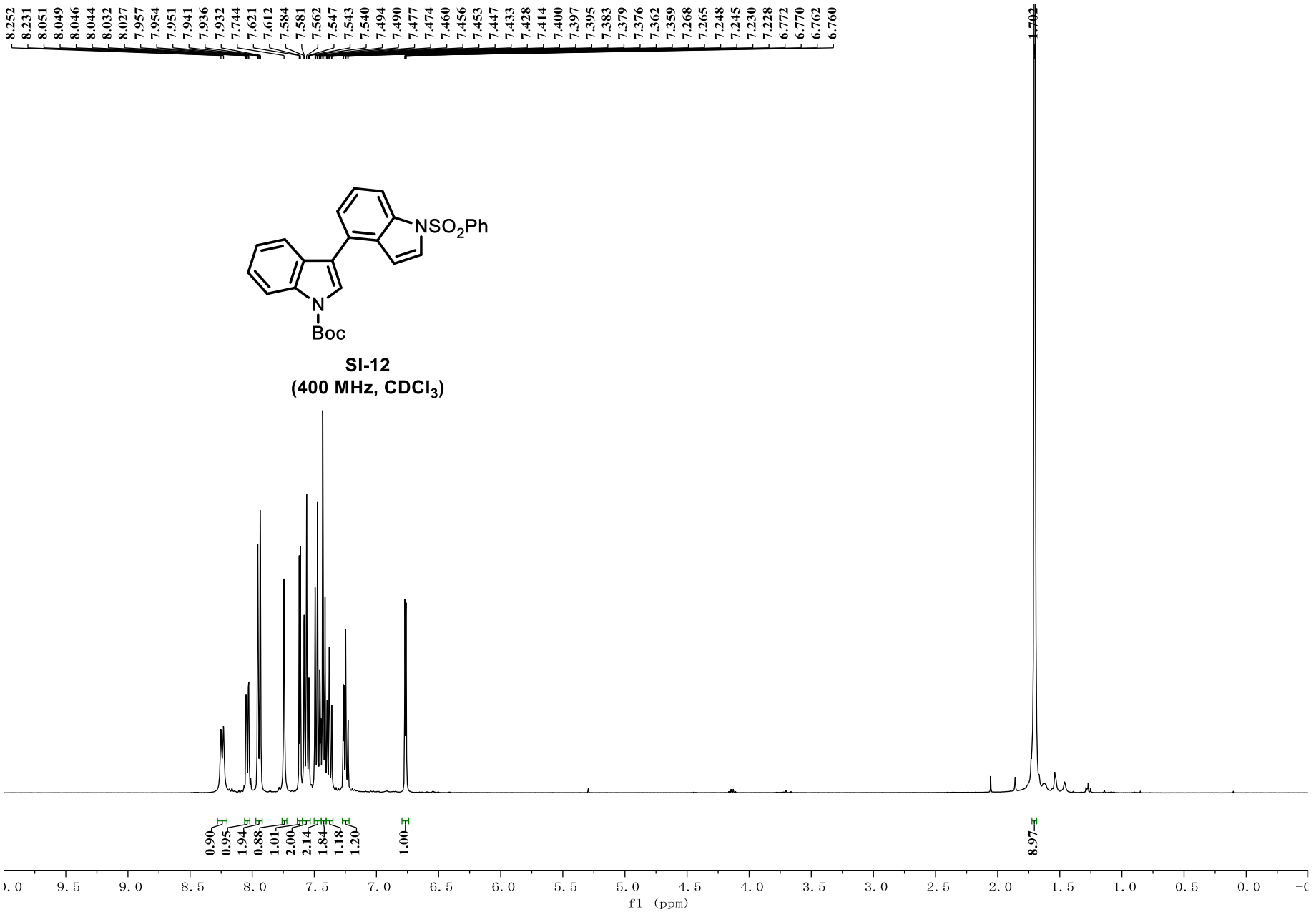


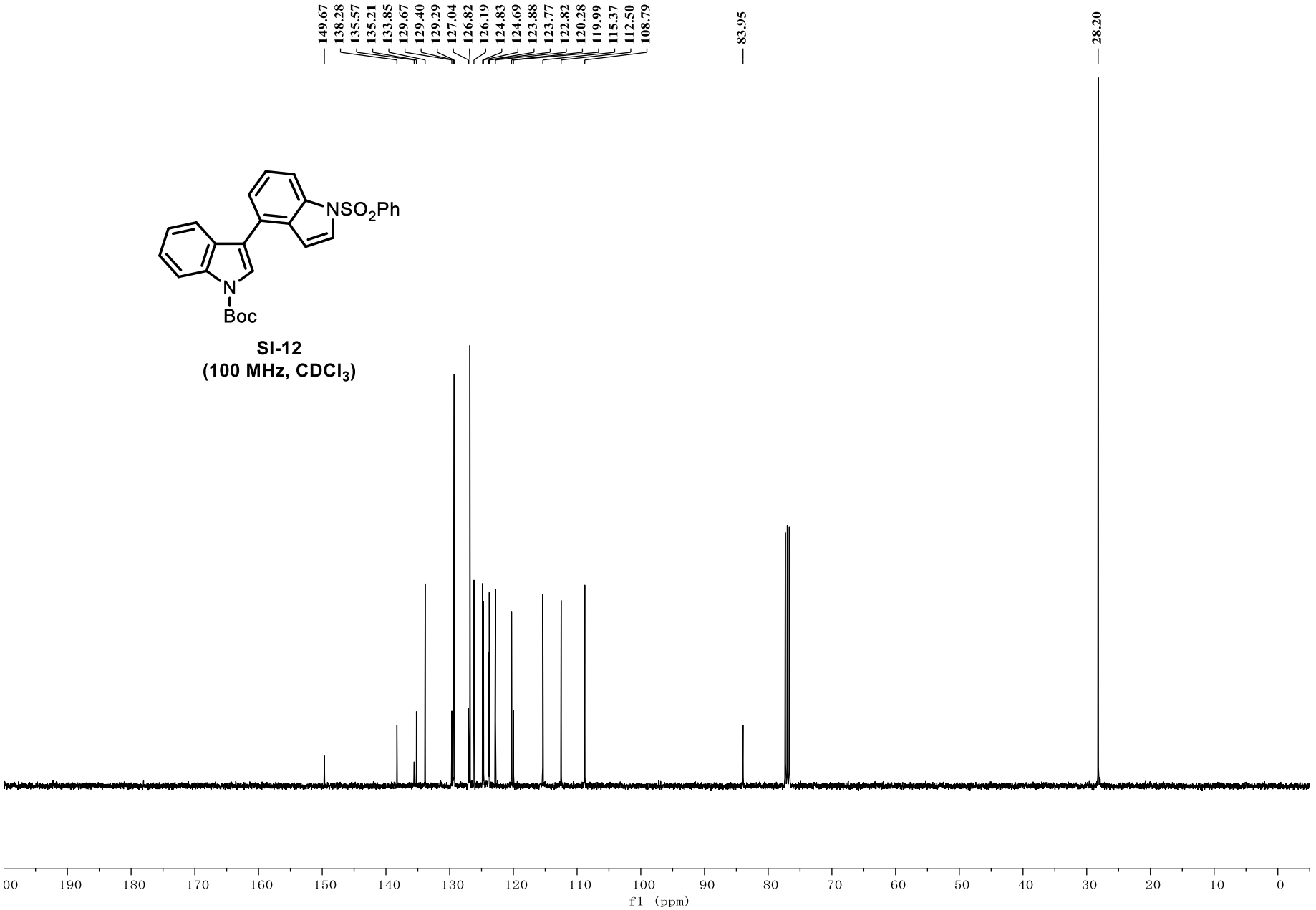
SI-11
(400 MHz, $CDCl_3$)

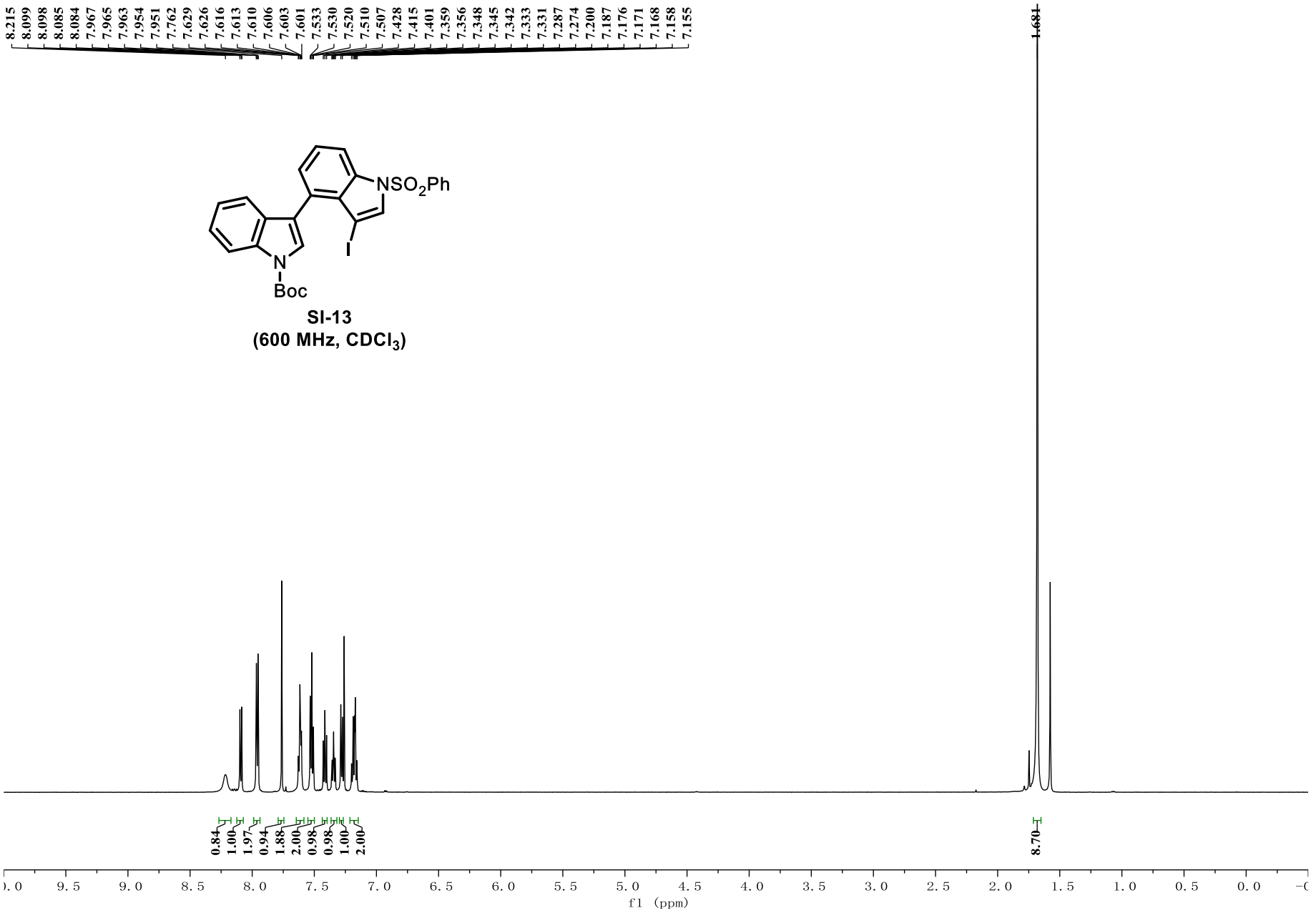


33
(400 MHz, $CDCl_3$)

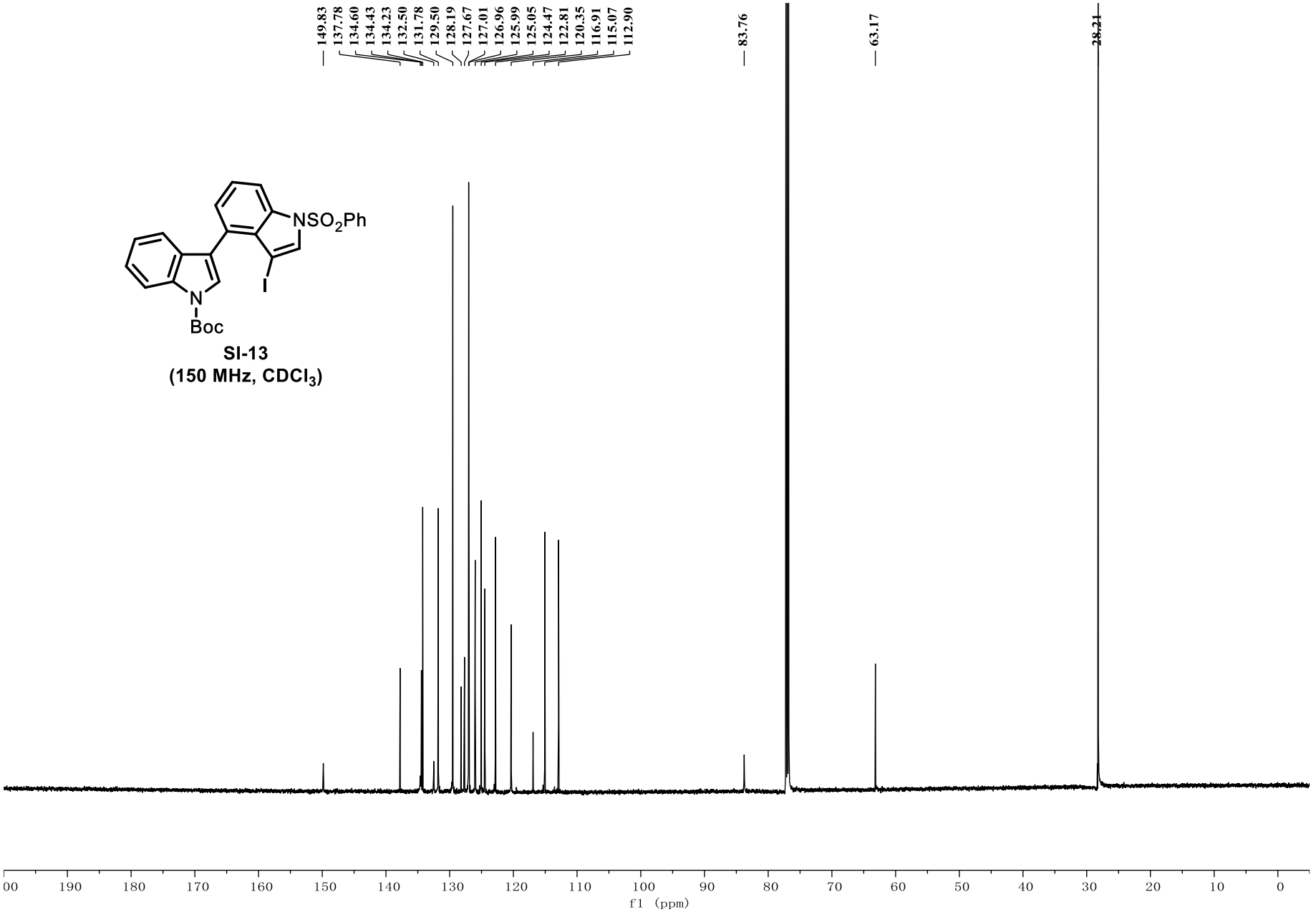


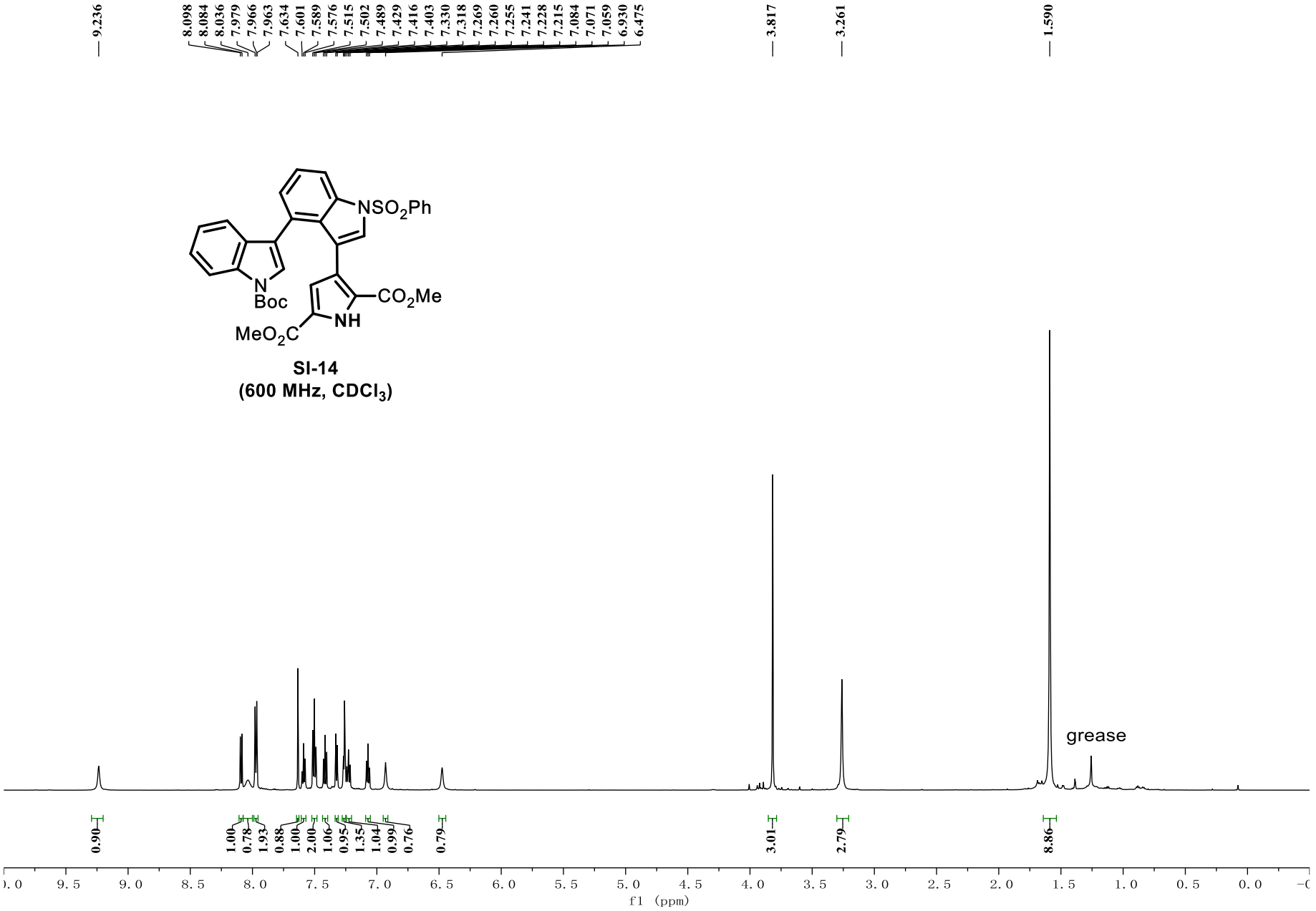

8.252
8.231
8.051
8.049
8.046
8.044
8.032
8.027
7.957
7.954
7.951
7.941
7.936
7.932
7.744
7.621
7.612
7.584
7.581
7.562
7.547
7.543
7.540
7.494
7.490
7.477
7.474
7.460
7.456
7.453
7.447
7.433
7.428
7.414
7.400
7.397
7.395
7.383
7.379
7.376
7.362
7.359
7.268
7.265
7.248
7.245
7.230
7.228
6.772
6.770
6.762
6.760
1.702
NSO2Ph
N
Boc
SI-12
(400 MHz, CDCl3)
0.90
0.95
1.94
0.88
1.01
2.00
2.14
1.84
1.18
1.20
1.00
8.97
f1 (ppm)


149.67
138.28
135.57
135.21
133.85
129.67
129.40
129.29
127.04
126.82
126.19
124.83
124.69
123.88
123.77
122.82
120.28
119.99
115.37
112.50
108.79
83.95
28.20
NSO2Ph
N
Boc
SI-12
(100 MHz, CDCl3)
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

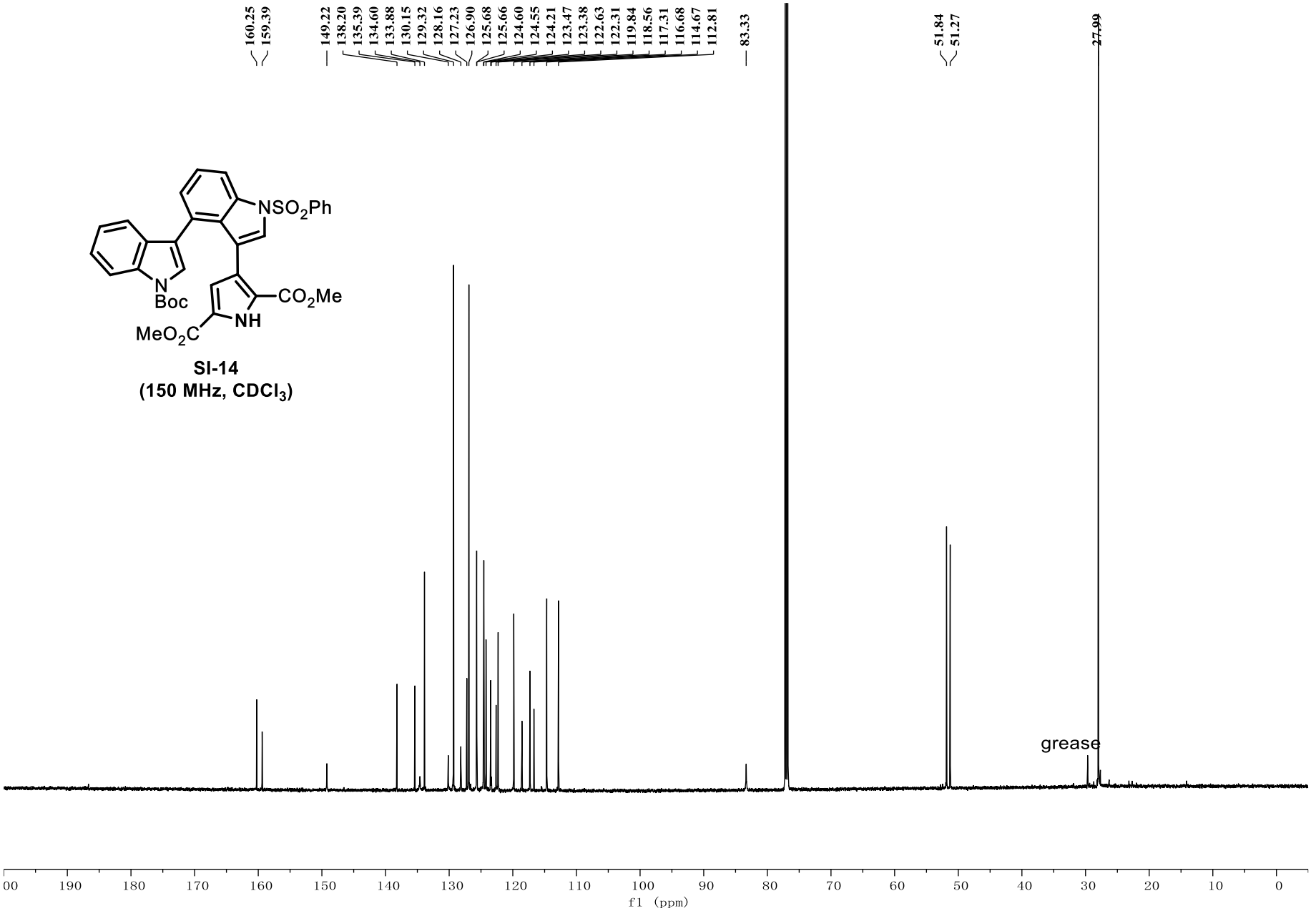


SI-13
(600 MHz, $CDCl_3$)

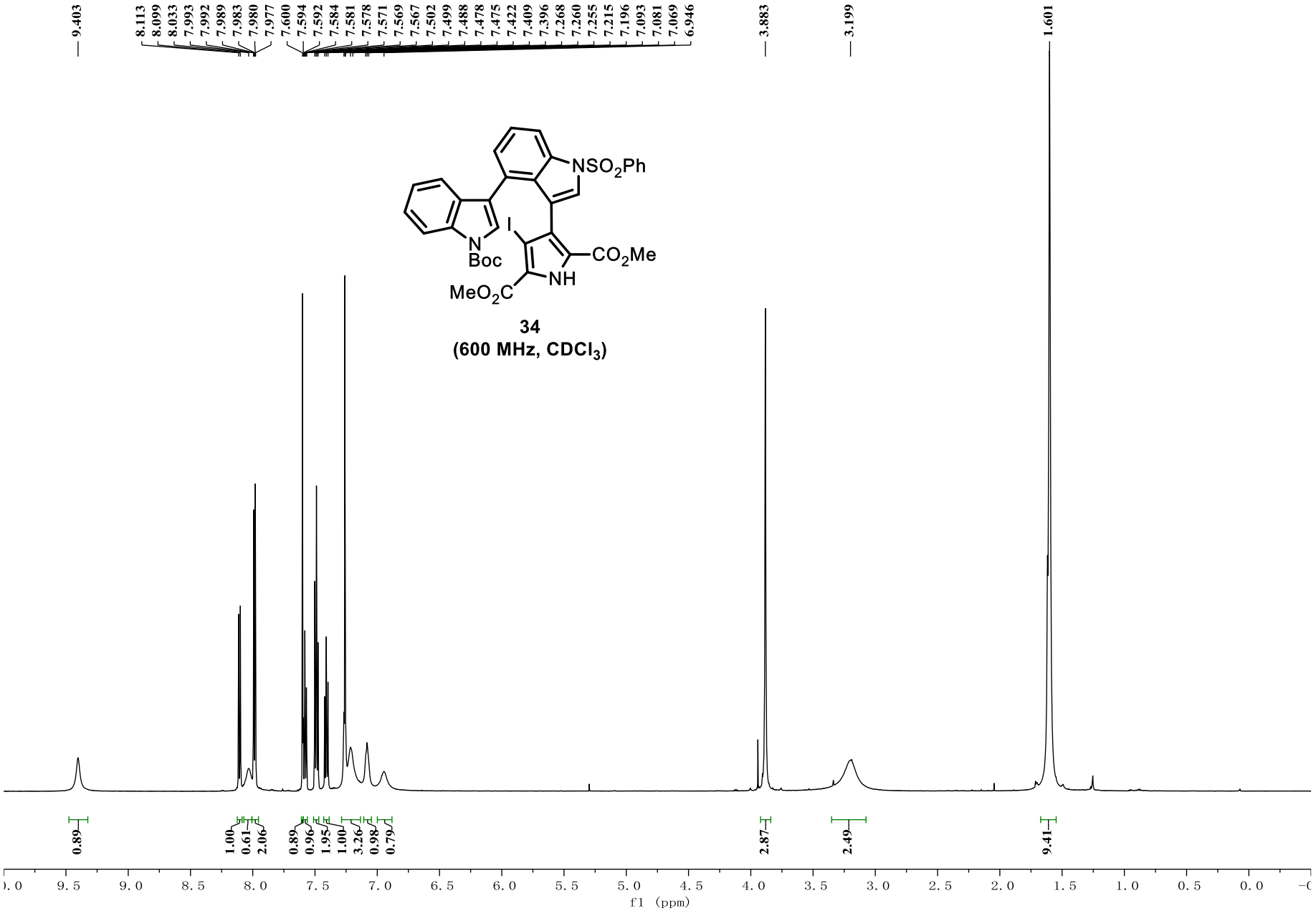

149.83
137.78
134.60
134.43
134.23
132.50
131.78
129.50
128.19
127.67
127.01
126.96
125.99
125.05
124.47
122.81
120.35
116.91
115.07
112.90
83.76
63.17
28.21
NSO2Ph
I
N
Boc
SI-13
(150 MHz, CDCl3)
f1 (ppm)

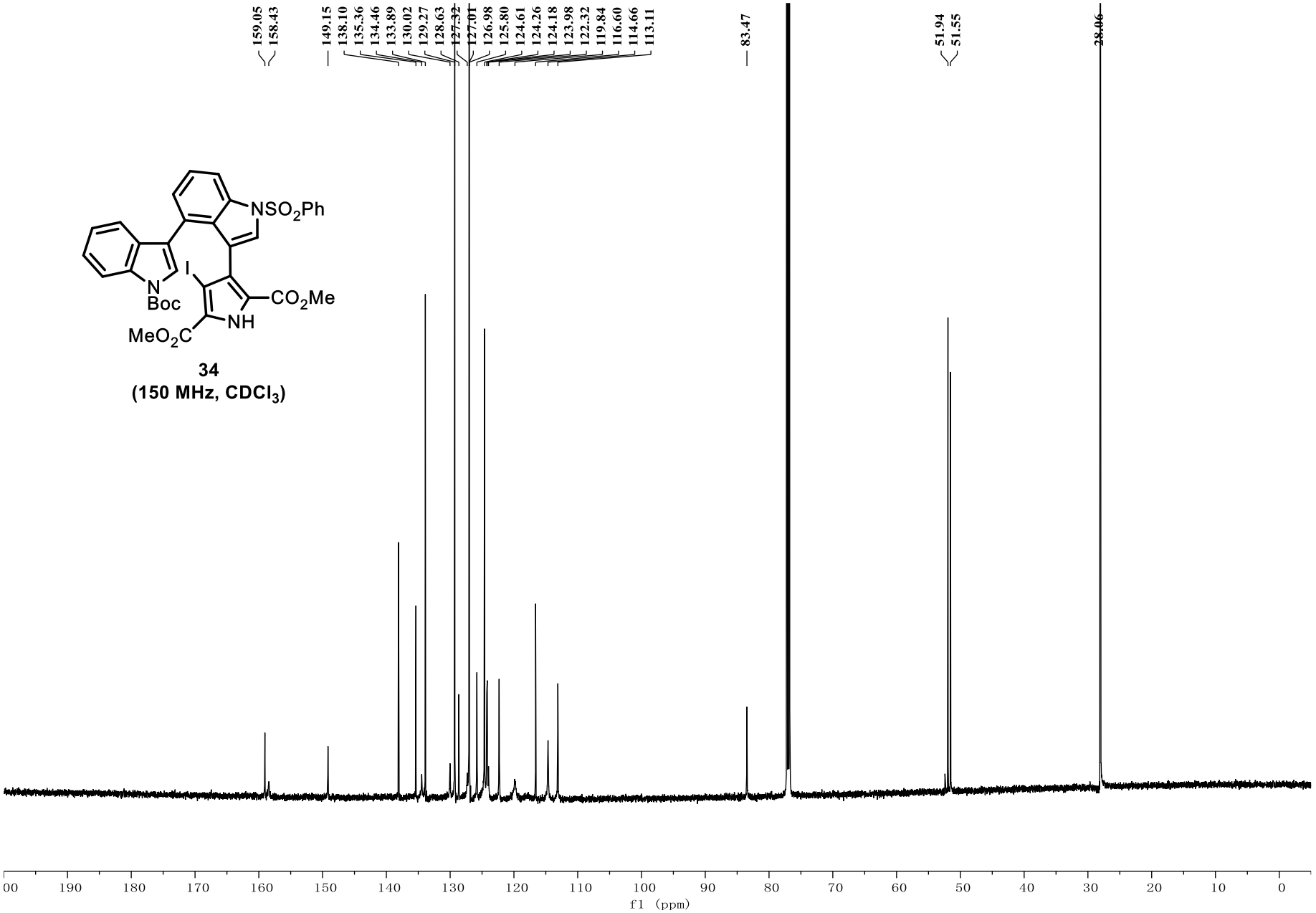


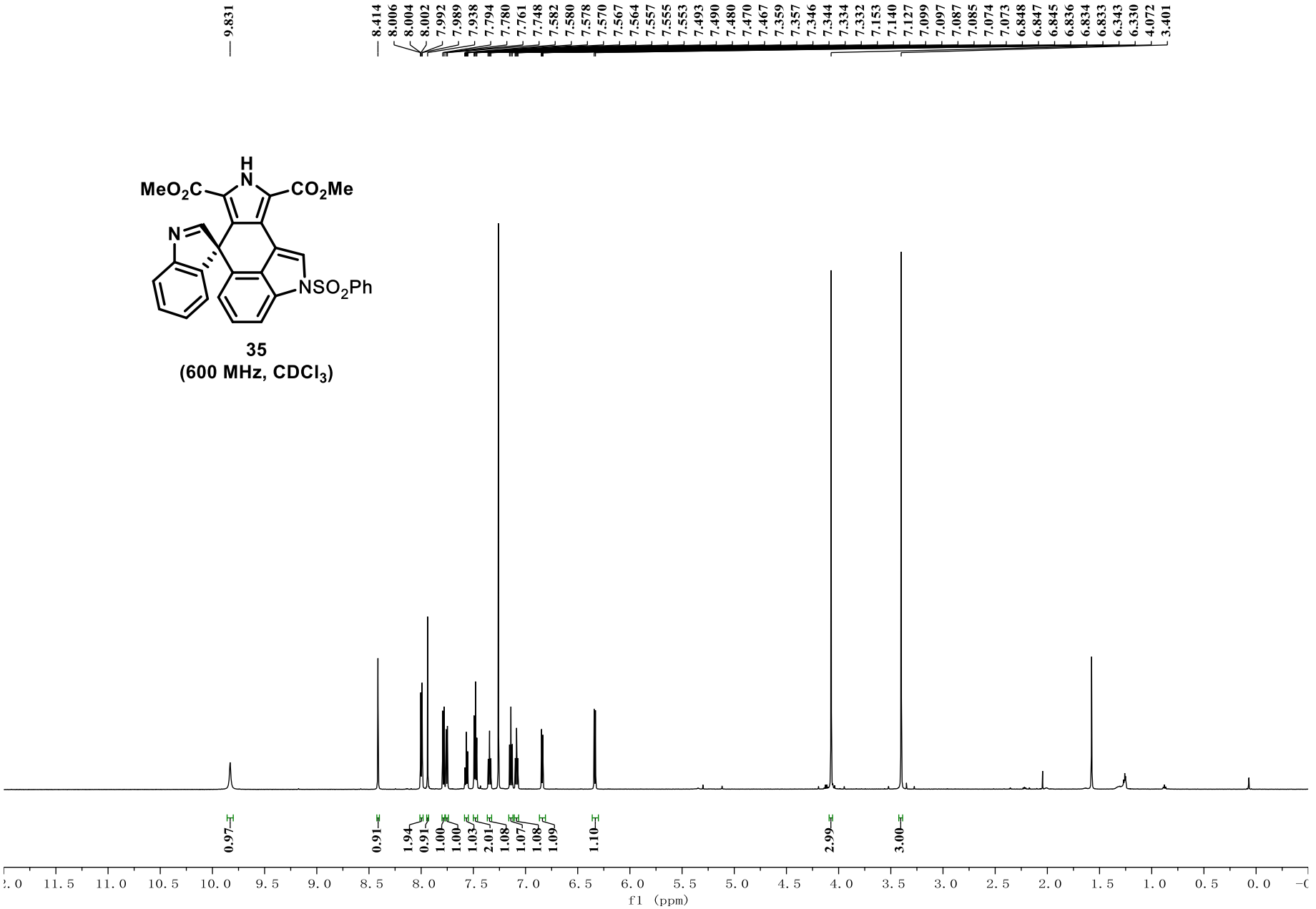
SI-14
(600 MHz, $CDCl_3$)

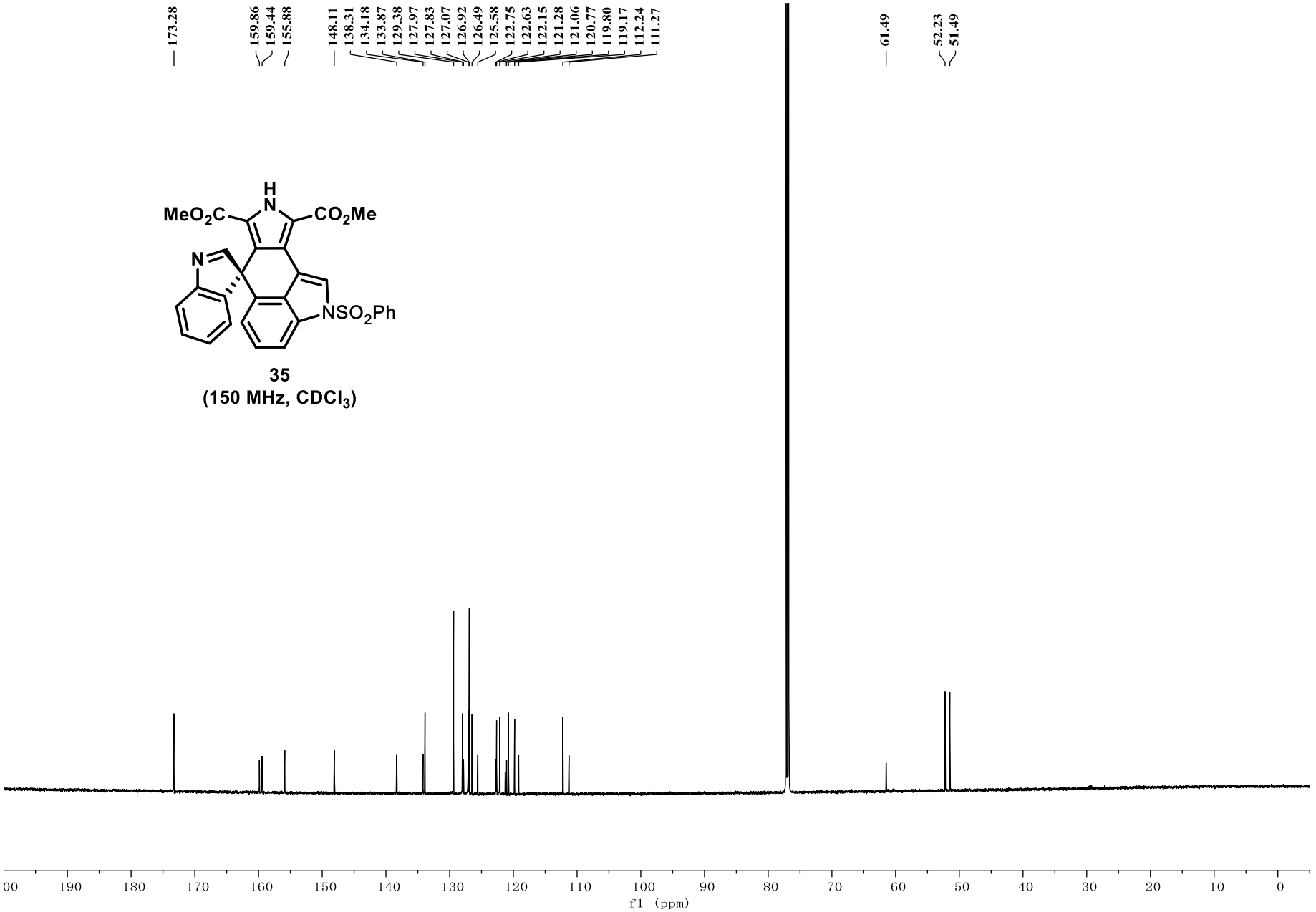


SI-14
(150 MHz, $CDCl_3$)

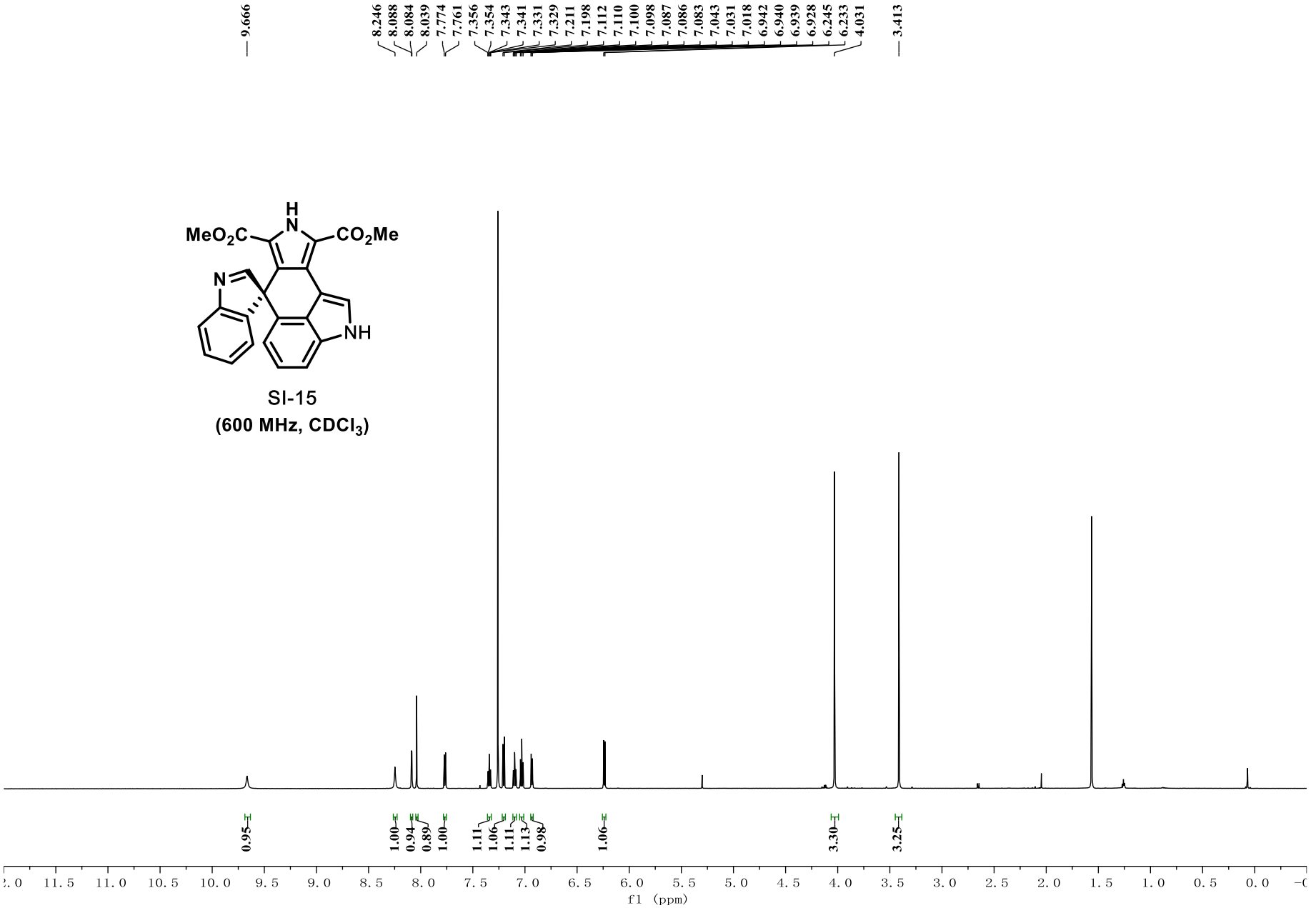

9.403
8.113
8.099
8.033
7.993
7.992
7.989
7.983
7.980
7.977
7.600
7.594
7.592
7.584
7.581
7.578
7.571
7.569
7.567
7.502
7.499
7.488
7.478
7.475
7.422
7.409
7.396
7.268
7.260
7.255
7.215
7.196
7.093
7.081
7.069
6.946
3.883
3.199
1.601
NSO2Ph
I
N
Boc
CO2Me
NH
MeO2C
34
(600 MHz, CDCl3)
0.89
1.00
0.61
2.06
0.89
0.96
1.95
1.00
3.26
0.98
0.79
2.87
2.49
9.41
f1 (ppm)

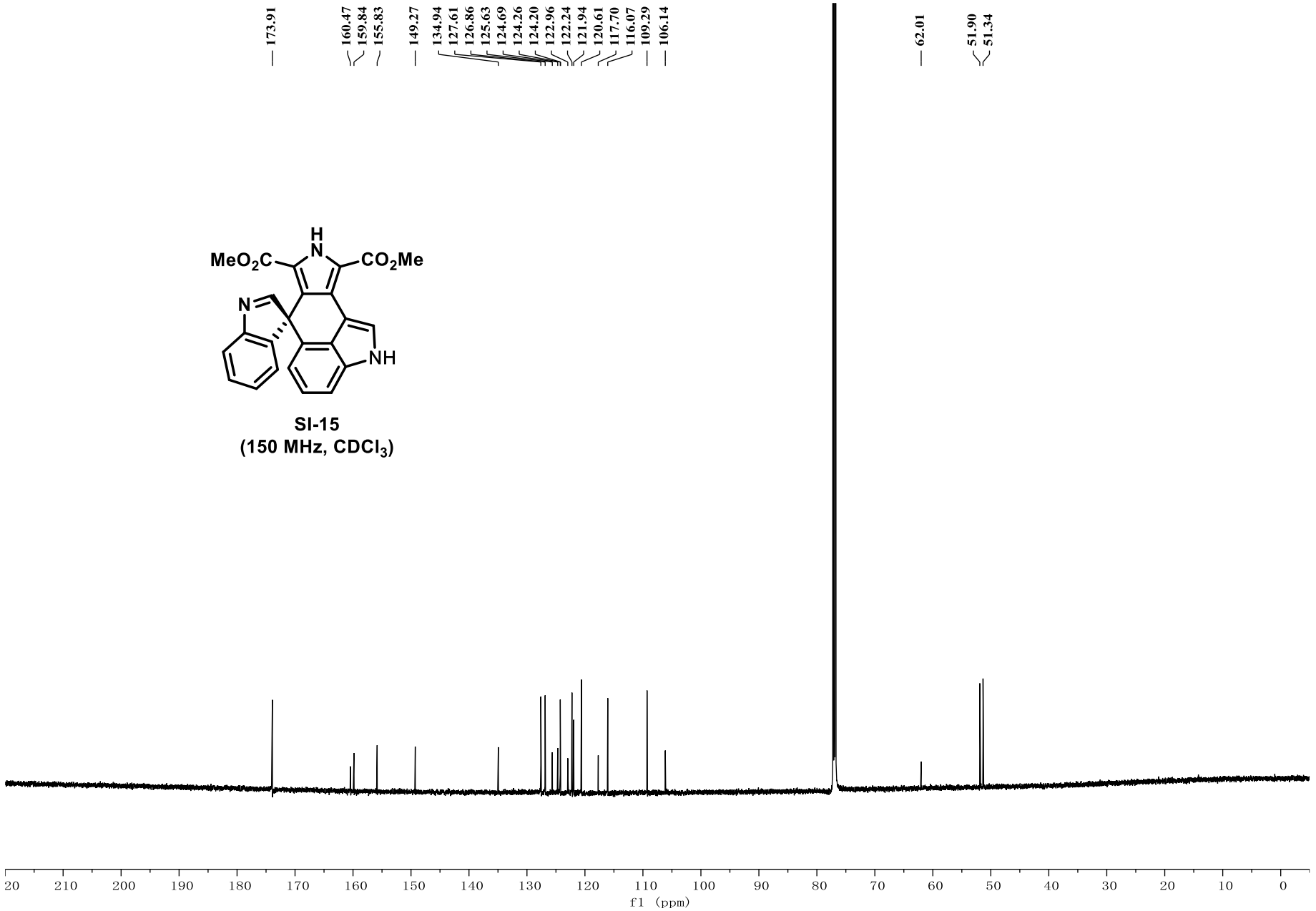

159.05
158.43
149.15
138.10
135.36
134.46
133.89
130.02
129.27
128.63
127.32
127.01
126.98
125.80
124.61
124.26
124.18
123.98
122.32
119.84
116.60
114.66
113.11
83.47
51.94
51.55
28.06
NSO2Ph
I
N
Boc
CO2Me
NH
MeO2C
34
(150 MHz, CDCl3)
f1 (ppm)

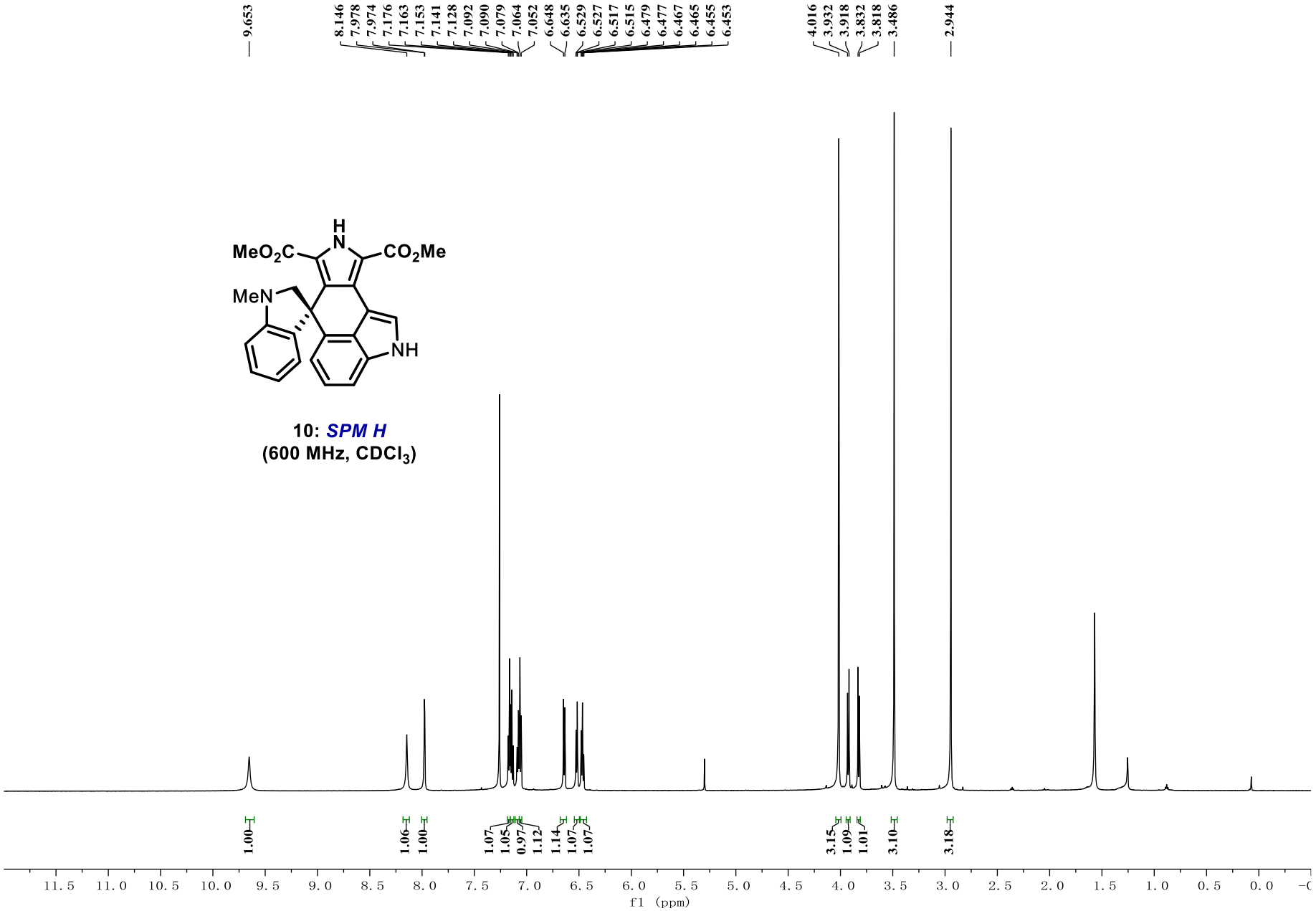

9.831
8.414
8.006
8.004
8.002
7.992
7.989
7.938
7.794
7.780
7.761
7.748
7.582
7.580
7.578
7.570
7.567
7.564
7.557
7.555
7.553
7.493
7.490
7.480
7.470
7.467
7.359
7.357
7.346
7.344
7.334
7.332
7.153
7.140
7.127
7.099
7.097
7.087
7.085
7.074
7.073
6.848
6.847
6.845
6.836
6.834
6.833
6.343
6.330
4.072
3.401
MeO2C
CO2Me
H
N
N
NSO2Ph
35
(600 MHz, CDCl3)
0.97
0.91
1.94
0.91
1.00
1.00
1.03
2.01
1.08
1.07
1.08
1.09
1.10
2.99
3.00
f1 (ppm)

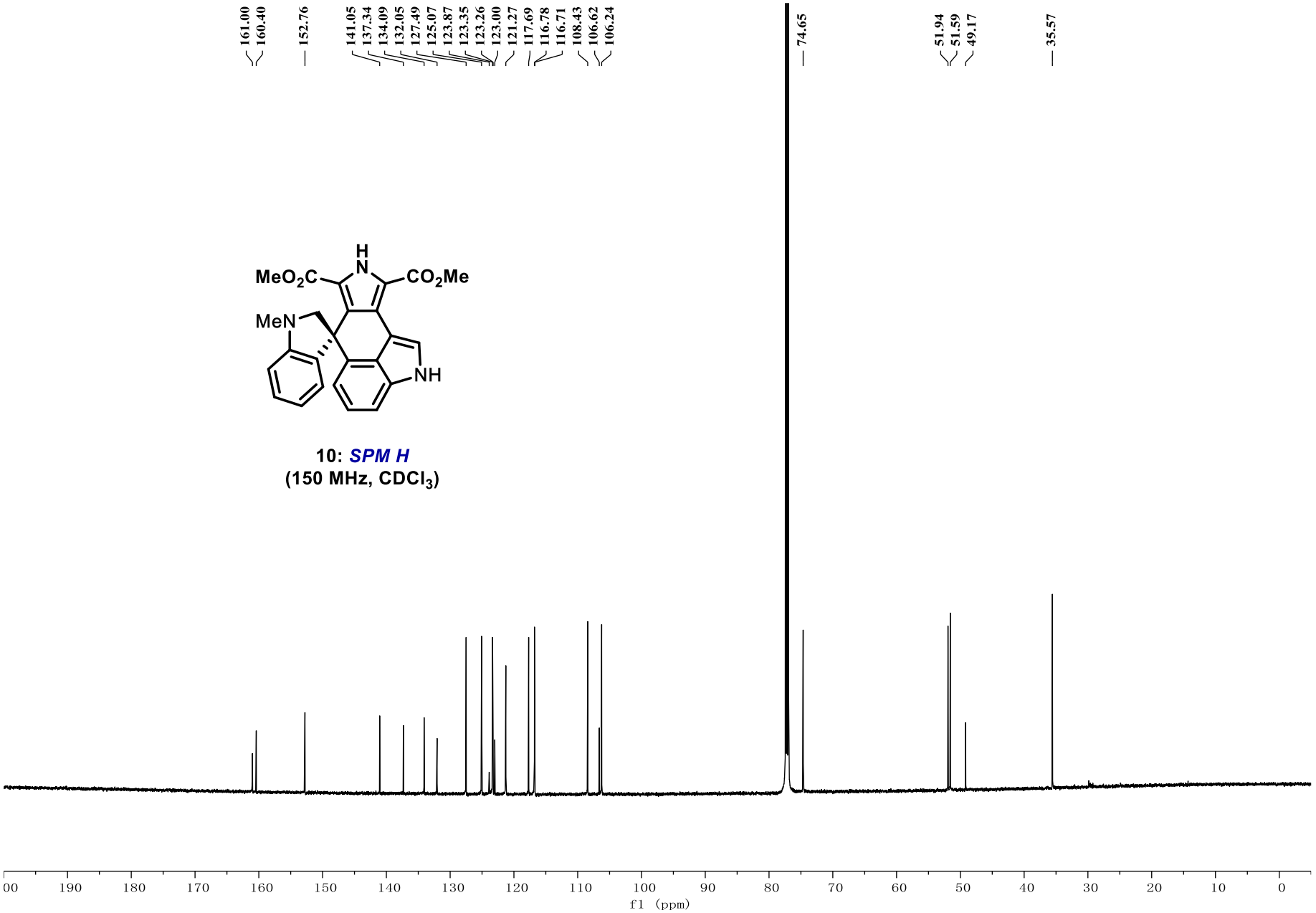


35
(150 MHz, $CDCl_3$)


9.666
8.246
8.088
8.084
8.039
7.774
7.761
7.356
7.354
7.343
7.341
7.331
7.329
7.211
7.198
7.112
7.110
7.100
7.098
7.087
7.086
7.083
7.043
7.031
7.018
6.942
6.940
6.939
6.928
6.245
6.233
4.031
3.413
MeO2C
CO2Me
H
N
N
NH
SI-15
(600 MHz, CDCl3)
0.95
1.00
0.94
0.89
1.00
1.11
1.06
1.11
1.13
0.98
1.06
3.30
3.25
f1 (ppm)


173.91
160.47
159.84
155.83
149.27
134.94
127.61
126.86
125.63
124.69
124.26
124.20
122.96
122.24
121.94
120.61
117.70
116.07
109.29
106.14
62.01
51.90
51.34
MeO2C
CO2Me
H
N
N
NH
SI-15
(150 MHz, CDCl3)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

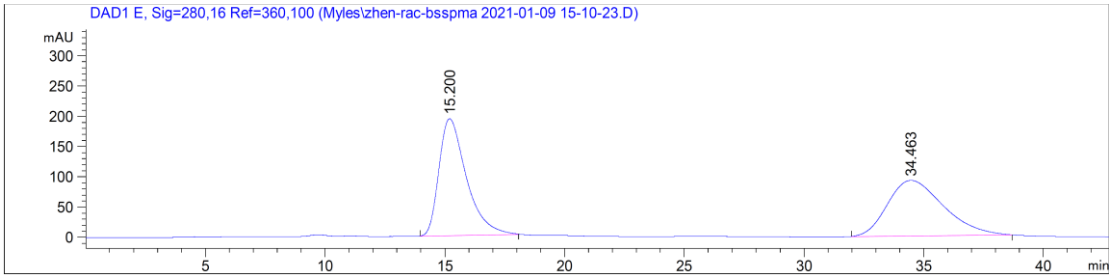

9.653
8.146
7.978
7.974
7.176
7.163
7.153
7.141
7.128
7.092
7.090
7.079
7.064
7.052
6.648
6.635
6.529
6.527
6.517
6.515
6.479
6.477
6.467
6.465
6.455
6.453
4.016
3.932
3.918
3.832
3.818
3.486
2.944
MeO2C
CO2Me
MeN
NH
H
N
10: SPM H
(600 MHz, CDCl3)
1.00
1.06
1.00
1.07
1.05
0.97
1.12
1.14
1.07
1.07
3.15
1.09
1.01
3.10
3.18
f1 (ppm)


161.00
160.40
152.76
141.05
137.34
134.09
132.05
127.49
125.07
123.87
123.35
123.26
123.00
121.27
117.69
116.78
116.71
108.43
106.62
106.24
74.65
51.94
51.59
49.17
35.57
MeO2C
CO2Me
MeN
H
N
NH
10: SPM H
(150 MHz, CDCl3)
f1 (ppm)

9. HPLC Traces

Rac-**31** (OD-H, hexane/*i*−PrOH = 60/40, 0.8 mL/min)

Sample Info : OD Hex/IPA: 60:40, 0.8 mL/min



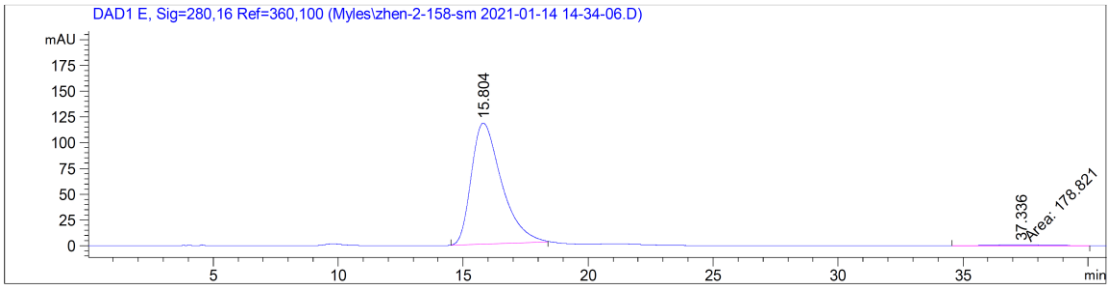
Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %	Name
1	15.200	BB	1.1542	1.53993e4	50.7442	?
2	34.463	BB	1.9036	1.49476e4	49.2558	?

Totals : 3.03469e4

Enantioenriched-**31** (OD-H, hexane/*i*-PrOH = 60/40, 0.8 mL/min)

Sample Info : OD Hex/IPA: 60:40, 0.8 mL/min



Signal 5: DAD1 E, Sig=280,16 Ref=360,100

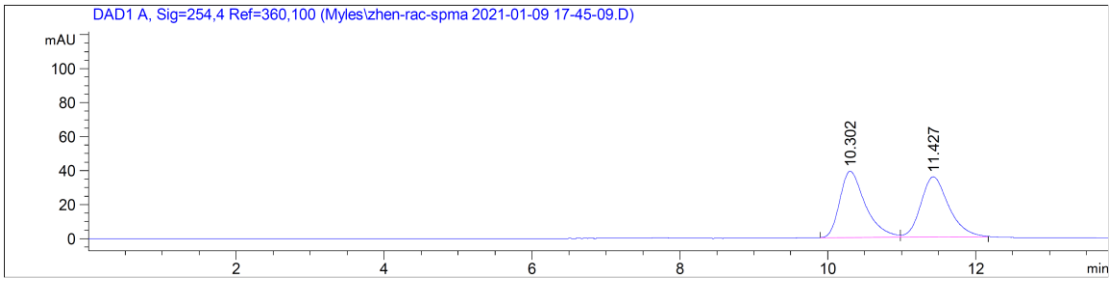
Uncalibrated Peaks:

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %	Name
1	15.804	BB	1.1793	9899.94141	98.2258	?
2	37.336	MM	3.0218	178.82091	1.7742	?

Uncalib. totals : 1.00788e4 100.0000

Rac-**SPM A** (AD-H, hexane/*i*-PrOH = 75/25, 0.8 mL/min)

Sample Info : AD Hex/IPA: 75:25, 0.8 mL/min



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

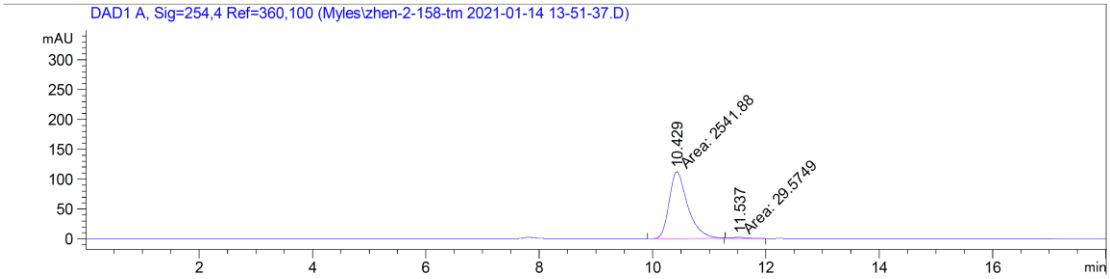
Uncalibrated Peaks:

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %	Name
1	10.302	BB	0.3521	936.14691	49.9765	?
2	11.427	BB	0.3950	937.02759	50.0235	?

Uncalib. totals : 1873.17450 100.0000

Enantioenriched-**SPM A** (AD-H, hexane/*i*PrOH = 75/25, 0.8 mL/min)

Sample Info : AD Hex/IPA: 75:25, 0.8 mL/min



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Uncalibrated Peaks:

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %	Name
1	10.429	MM	0.3794	2541.88037	98.8499	?
2	11.537	MM	0.3619	29.57494	1.1501	?

Uncalib. totals : 2571.45531 100.0000