Supporting Information

New One-Pot Synthesis of N-Fused Isoquinoline Derivatives by Palladium-Catalyzed C-H Arylation: Potent Inhibitors of Nucleotide Pyrophosphatase-1 and -3

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Contents

General information

All reactions were carried out under argon atmosphere. Solvents and reagents were commercially purchased and used without further purification. Column chromatography was performed using Merck Silicagel 60 (particle size 0.063-0.200 mm). Precoated silica gel 60 F254 aluminium sheets from Fluka were used for TLC analyses.

If not otherwise stated NMR data were recorded at room temperature on a Bruker AVANCE 250 MHz, 300 MHz or 500 MHz. Chemical shifts in ppm of ^{1}H and ^{13}C NMR spectra were referenced to residual solvent peaks of deuterated solvents $CDCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.16 ppm) or DMSO-*d*6 (^{1}H, 2,50 ppm; ^{13}C, 39.52 ppm). Peak characterization: s = singlet, brs = broad singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets.

Infrared spectra were recorded on a Nicolet 550 FT-IR spectrometer with ATR sampling technique. Signal characterization: w = weak, m = medium, s = strong.

Gas-chromatography-mass-analysis was carried out on an Agilent HP-5890 instrument with an Agilent HP-5973 Mass Selective Detector (EI) and HP-5 capillary column using helium carrier gas. ESI HRMS measurements were performed on an Agilent 1969A TOF mass spectrometer. For High Resolution MS (HRMS) Finnigan MAT 95 XP was used.
Melting points were determined on a Micro-Hot-Stage GalenTM III Cambridge Instruments. The melting points are not corrected.

X-Ray single crystal structure analysis was performed on a Bruker-Nonius Apex X8 CCD-diffractometer.

General synthesis procedures

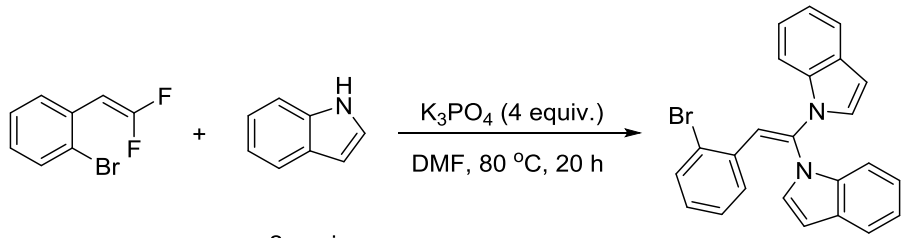
Starting materials **1** and **5** were synthesized according to the method described in literature.[1]

1,1'-(2-(2-Bromophenyl)ethene-1,1-diyl)bis(1*H*-indole) **3a** was obtained following a procedure reported in literature:[2]

To 0.5 mmol (109.5 mg, 1 equiv.) of 1-bromo-2-(2,2-difluorovinyl)benzene **1a** were added 1 mmol (117.1 mg, 2 equiv.) of 1*H*-indole **2a**, 2 mmol (424.5 mg, 4 equiv.) of K_3PO_4 and DMF (10 mL). Reaction was stirred at 80 °C for 20 h. After cooling to room temperature reaction was quenched with H_2O, aqueous phase was extracted with EtOAc (3 times). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and

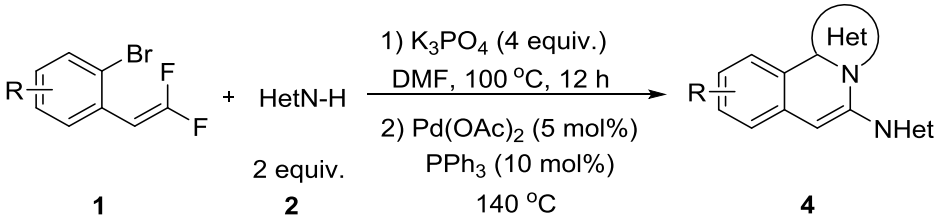
[1] C. S. Thomoson, H. Martinez, W. R. Dolbier, *J. Fluorine Chem.*, 2013, **150**, 53–59.
[2] Y. Xiong, X. Zhang, T. Huang,; S. Cao, *J. Org. Chem.*, 2014, **79**, 6395– 6402.

concentrated under reduced pressure. The synthesized compound was purified by column chromatography using heptane as eluent.



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

Synthesis of products **4a-s** and **6**:



1 **2** **4**

In a glass pressure tube to 0.05 g (1 equiv.) of (2,2-difluorovinyl)arene **1** were added 2 equiv. of N-H azole **2,** 4 equiv. of K_3PO_4, and 5 mL of DMF. The reaction mixture was stirred at 100 °C for 12 h. After cooling to room temperature $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) were added to the reaction mixture. The pressure tube was flushed with Ar and stirred at 140 °C (reaction times various, see compound characterization). After being cooled to room temperature reaction mixture was quenched with H_2O. The aqueous phase was extracted with EtOAc (3 times). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The synthesized compounds were purified by column chromatography using Hept/EtOAc or Hept/DCM mixture as eluent.

Synthesis of naphthyridine derivative **6** was carried out following the above mentioned reaction procedure starting from 2-bromo-3-(2,2-difluorovinyl)pyridine **5** and 3-methyl-1*H*-indole.

Biological protocols

Cell Transfection with human NPPs. The plasmids expressing human NPPs (h-NPP-1[3] or h-NPP-3[4]) were transfected with COS-7 in 10 cm plates. Transfection was carried out using Lipofectamine: the confluent cells were incubated for 5 h at 37 °C in DMEM/F-12 (without fetal bovine serum) containing 6 µg of plasmid DNA and 24 µL of Lipofectamine reagent, the

transfection was stopped by adding the same volume of DMEM/F-12 containing 20% FBS and cells were harvested 48–72 h later as described before.[5]

Preparation of membrane fractions. Tris-saline buffer (4 °C) was used for washing transfected cells. Cells were collected by scraping in the harvesting buffer – 95 mM NaCl, 0.1 mM PMSF and 45 mM Tris (pH 7.5). The cells where washed twice by centrifugation at 300×*g* for 5 min at 4 °C.[5] The obtained cells were resuspended in the harvesting buffer containing 10 µg/mL aprotinin and sonicated. Nuclear and cellular debris were separated out by a 10 min centrifugation (300×*g* at 4 °C). The supernatant was collected and glycerol was added at the final concentration of 7.5%. All the samples were kept at -80 °C until used. Protein estimation was done using Bradford microplate assay.[6] Bovine serum albumin was used as a reference standard.

Nucleotide pyrophosphatase inhibition assays. The inhibitory effects of all the tested compounds on nucleotide pyrophosphatase (h-NPP-1 and h-NPP-3) were performed using slightly modified previously reported spectrophotometric method.[7] The assay was carried out in reaction buffer containing 5 mM $MgCl_2$, 0.1 mM $ZnCl_2$, 25% glycerol and 50 mM tris-HCl (pH 9.5), and 0.1 mM concentrations of the tested compounds. To the reaction mixture, 10 µl of h-NPP-1 (final conc. of 27 ng) or h-NPP-3 (final conc. of 25 ng) was added and incubated at 37 °C for 10 min. The absorbance was measured at 405 nm using microplate reader (BioTek ELx800, Instruments, Inc. USA). The reaction was initiated by adding 10 µL of *p*-nitrophenyl-5'-thymidine monophosphate (p-Nph-5'-TMP, 0.5 mM) substrate, incubated again at 37 °C and the change in absorbance was measured after 30 min. The compounds, which exhibited over 50% inhibition of either the h-NPP-1 activity or h-NPP-3 activity, were further evaluated for determination of IC_{50} values. All experiments were carried out in triplicate. The IC_{50} values were determined using non-linear curve fitting program PRISM 5.0 (GraphPad, San Diego, California, USA).

Mechanism of Inhibition. In order to characterize the interaction of most potent inhibitors of h-NPP-1 and h-NPP-3, the type of inhibition was determined by Michaelis-Menten kinetics. For this purpose, the initial rates of the enzyme inhibition at four different substrate concentrations

[3] S. I. Belli and J. W. Goding, *Eur. J. Biochem.*, 1994, **226**, 433-443.

[4] P. Jinhua, J. W. Goding, H. Nakamura and K. Sano. *Genomics*, 1997, **45**, 412-415.

[5] F. Kukulski, S. A. Lévesque, E. G. Lavoie, J. Lecka, F. Bigonnesse, A. F. Knowles, S. C. Robson, T. L. Kirley and J. Sévigny, *Purinergic Signalling*, 2005, **1** 193-204.

[6] M. M. Bradford, *Anal. Biochem.*, 1976, **72**, 248-254.

[7] A. Tashfeen, H. Shahid, A. A. M. Najim, L. Roberta and L. Paolo, *Acta Pharm.*, 2008, **58**, 135-149.

(125 µM, 250 µM, 500 µM and 750 µM) in the absence and in the presence of four different concentrations (0 µM, 0.50 µM, 1.00 µM and 2.00 µM) of the selected representative inhibitor **4i** against h-NPP1 and **4d** against h-NPP3 were measured. The results are depicted as double reciprocal Lineweaver-Burk plots.

Homology modelling of human NPP-1 and NPP-3. Homology modelling of target proteins h-NPP-1 and h-NPP-3 was carried out using MOE (2014.0901) suit. Amino acid sequence of h-NPP-1and h-NPP-3 was downloaded from NCBI protein database. UniprotKB/Swiss-prot ID P22413 of h-NPP-1 and accession code O14638 for h-NPP-3 were retrieved from NCBI protein data bank and then loaded to MOE suit.[8] MOE built-in BLOSUM62 search utility was used for identification of suitable template protein structure. X-ray crystallographic structure of mouse Enpp1 (PDB ID 4B56)[9] was retrieved from protein data bank and used as a template structure for homology modelling of our target proteins. The template and the modelled target proteins were aligned using MOE utility - align sequence and structural alignment. In total ten homology models of target protein were generated, among which one final model was refined using Amber12:EHT[10] force field and protonation of the model proteins was carried out using built-in Protonate-3D. Then these homology models were compared with the template X-ray crystal structure, used by realigning and superimposing it. The root mean square deviation values were noted down and Ramachandran graph was plotted for both modelled target proteins.

Molecular docking studies. Molecular docking of the most potent inhibitors of h-NPP-1 and h-NPP-3, **4i** and **4d** respectively, was carried out to investigate the putative binding interaction in active site of modelled proteins. First of all chemical structure of potent compounds was drawn using builder tool of MOE suit and then 3D optimized. Prior to molecular docking studies protonation and energy minimization of all target proteins structures was carried out using Molecular Operating Environment (MOE) 2014, 09 software.[8] After prerequisite preparation of inhibitors and target protein, AutoDock4 and AutoDock Tools were used for performing molecular docking calculation.

Grid box of 60 x 60 x 60 was built in XYZ dimension for both, modelled proteins and centred on the active site of target protein. Lamarckian genetic algorithm (LGA) was used for docking

[8] Molecular Operating Environment (MOE), 2013.08; Chemical Computing Group Inc., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, **2016**.

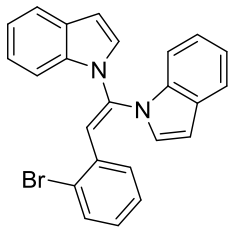
[9] S. Jansen, A. Perrakis, C. Ulens, C. Winkler, M. Andries, R. P. Joosten, M. Van Acker, F. P. Luyten, W. H. Moolenaar and M. Bollen, *Structure*, 2012, **20**, 1948-1959.

[10] (a) J. Wang, R. M. Wolf, J. W. Caldwell, P. A. Kollman and D. A. Case, *J. Comput. Chem.*, 2004, **25**, 1157-1174; (b) R. Hoffmann, *J. Chem. Phys.*, 1963, **39**, 1397-1412.

search parameter and the number of GA runs was set to 100, number of maximum evaluation was 5 x 10^6. After successful completion of docking, pdbqt files were converted into pdb files using Open Babel.[11] Best pose having lowest free binding energy was selected for visual inspection of putative binding mode. For visualization of putative binding interactions Discovery Studio Visualizer v4.0 was used.[12]

Experimental data

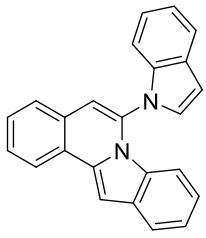
1,1'-(2-(2-Bromophenyl)ethene-1,1-diyl)bis(1*H*-indole) (3a).



Yield 82% (170.8 mg), light pink solid, R_f 0.16 (Hept), mp 139-140 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.55 (dd, *J* = 7.8, 1.7 Hz, 1H, CH), 6.62 (dd, *J* = 3.4, 0.7 Hz, 1H, CH), 6.68 (dd, *J* = 3.4, 0.6 Hz, 1H, CH), 6.71-6.74 (m, 2H, CH), 6.86-6.92 (m, 1H, CH), 6.95-7.02 (m, 4H, CH), 7.06-7.19 (m, 3H, CH), 7.21 (d, *J* = 3.4 Hz, 1H, CH), 7.56-7.61 (m, 2H, CH), 7.65 ppm (d, *J* = 7.5 Hz, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 105.7, 106.2, 111.6, 111.6, 112.1, 121.1, 121.5, 121.5, 121.6, 123.4, 123.4 (CH), 124.3 (C_q), 127.3, 127.4, 127.6, 128.7, 129.0 (CH), 129.4, 130.1 (C_q), 132.9 (CH), 133.0, 134.6, 135.2, 136.1 ppm (C_q). **IR** (ATR): $\tilde{\nu}$ =

3136 (w), 3103 (w), 3057 (w), 1637 (m), 1447 (s), 1411 (m), 1327 (m), 1208 (m), 1021 (m), 763 (m), 737 cm^{-1} (s). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 414 ($[M]^{+2}$, ^{81}Br, 44), 412 ($[M]^+$, ^{79}Br, 42), 333 (100), 298 (30), 217 (77), 189 (12), 166 (38), 89 (9). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{24}H_{17}N_2{}^{81}Br_1$ $[M]^+$: 414.05492; found: 414.05499, *m/z* calcd. for $C_{24}H_{17}N_2{}^{79}Br_1$ $[M]^+$: 412.05696; found: 412.05684.

6-(1*H*-Indol-1-yl)indolo[2,1-*a*]isoquinoline (4a).



Reaction time for C-H arylation step 2 h, yield 80% (61.2 mg), dark yellow solid, R_f 0.29 (Hept/DCM 10:1), mp 68-69 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 5.75 (d, *J* = 8.6 Hz, 1H, CH), 6.78 (s, 1H, CH), 6.83-6.95 (m, 2H, CH), 7.12-7.28 (m, 4H, CH), 7.32 (d, *J* = 3.3 Hz, 1H, CH), 7.38-7.55 (m, 2H, CH), 7.56-7.64 (m, 2H, CH), 7.75-7.85 (m, 2H, CH), 8.29 ppm (d, *J* = 7.3 Hz, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 95.8, 105.1, 109.4, 110.9, 113.5, 120.4, 121.4, 121.4, 121.8, 122.4, 123.5, 123.6 (CH), 125.9 (C_q), 127.1, 128.0, 128.2, 128.2 (CH), 128.6, 128.9, 129.3, 130.7, 132.2, 136.6, 137.3 ppm (C_q). **IR** (ATR): $\tilde{\nu}$ =

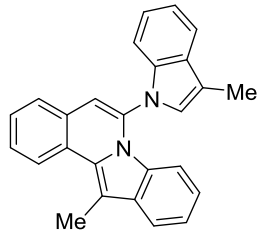
3102 (w), 3055 (w), 2919 (w), 2849 (w), 1646 (m), 1446 (m), 1401 (m), 1325 (m), 757 (m), 735 cm^{-1} (s). **MS** (EI,

[11] N. M. O'Boyle, M. Banck, C. A. James, C. Morley, T. Vandermeersch and G. R. Hutchison, *J. Cheminform.*, 2011, **3**:33.

[12] Discovery StudioVisualizer. 4.0 ed: Accelrys Software Inc; 2005.

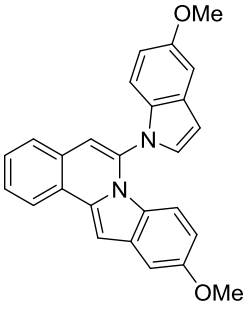
70 eV): *m/z* (relative intensity, %) = 332 ($[M]^+$, 100), 302 (2), 214 (6), 165 (29), 151 (5). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{24}H_{16}N_2$ $[M]^+$: 332.13080; found: 332.13032.

12-Methyl-6-(3-methyl-1*H*-indol-1-yl)indolo[2,1-*a*]isoquinoline (4b).



Reaction time for C-H arylation step 4 h, yield 71% (58.1 mg), yellow solid, R_f 0.50 (Hept/DCM 5:1), mp 134-135 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.50 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 5.84 (d, *J* = 8.6 Hz, 1H, CH), 6.65 (s, 1H, CH), 6.87-6.92 (m, 1H, CH), 7.07-7.28 (m, 5H, CH), 7.45-7.62 (m, 3H, CH), 7.73-7.81 (m, 2H, CH), 8.50 ppm (d, *J* = 8.1 Hz, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 9.9, 11.9 (CH_3), 106.9 (C_q), 108.8, 110.9, 113.6 (CH), 114.3 (C_q), 118.1, 119.4, 120.6, 121.7, 122.0, 123.3, 124.6, 125.4, 126.8, 127.0, 127.6 (CH), 129.2, 129.4, 129.9, 130.0, 131.6, 132.7, 137.5 ppm (C_q) (one C_q signal could not be detected). **IR** (ATR): $\tilde{\nu}$ = 3046 (w), 2915 (w), 2861 (w), 1646 (m), 1448 (m), 1113 (m), 732 cm^{-1} (s). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 360 ($[M]^+$, 100), 343 (16), 228 (6), 180 (7), 172 (23). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{26}H_{20}N_2$ $[M]^+$: 360.16210; found: 360.16140.

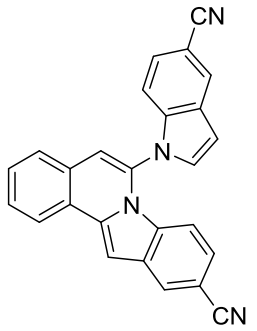
10-Methoxy-6-(5-methoxy-1*H*-indol-1-yl)indolo[2,1-*a*]isoquinoline (4c).



Reaction time for C-H arylation step 4 h, yield 79% (71.3 mg), pale yellow solid, mp 155-156 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 3.82 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.66 (d, *J* = 9.3 Hz, 1H, CH), 6.52 (dd, *J* = 9.3, 2.6 Hz, 1H, CH), 6.75 (s, 1H, CH), 6.78-6.82 (m, 2H, CH), 6.99 (d, *J* = 8.9 Hz, 1H, CH), 7.17-7.28 (m, 3H, CH), 7.33 (s, 1H, CH), 7.46-7.60 (m, 3H, CH), 8.24 (d, *J* = 7.7 Hz, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 55.7, 55.9 (OCH_3), 95.4, 101.2, 103.1, 104.8, 108.8, 111.6, 112.1, 113.6, 114.4, 123.6 (CH), 125.6, 125.9 (C_q), 127.0, 127.8, 128.0, 128.6 (CH), 128.8, 129.1, 130.2, 132.2, 132.3, 137.1, 155.3, 155.7 (C_q). **IR** (ATR): $\tilde{\nu}$ = 3106 (w), 3069 (w), 2995 (w), 2929 (w), 2829 (w), 1612 (m), 1477 (m), 1443 (m), 1434 (m), 1220 (m), 1127 (m), 1018 (m), 753 (m), 727 cm^{-1} (m). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 392 ($[M]^+$, 100), 377 (5), 349 (8), 305 (10), 279 (3), 196

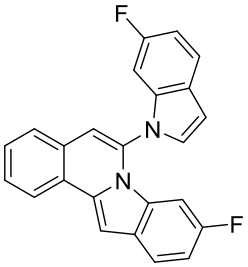
(9), 153 (13). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{26}H_{20}O_2N_2$ $[M]^+$: 392.15193; found: 392.15181.

6-(5-Cyano-1*H*-indol-1-yl)indolo[2,1-*a*]isoquinoline-10-carbonitrile (4d).



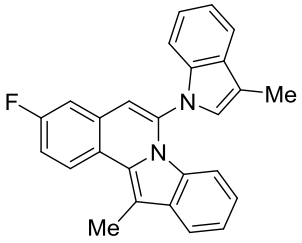
Reaction time for C-H arylation step 8 h, yield 71% (61.9 mg), light brown solid, mp 260-261 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 5.57 (d, *J* = 8.9 Hz, 1H, CH), 6.93 (s, 1H, CH), 7.01-7.07 (m, 2H, CH), 7.16 (d, *J* = 8.6 Hz, 1H, CH), 7.41 (dd, *J* = 8.6, 1.4 Hz, 1H, CH), 7.46 (d, *J* = 3.3 Hz, 1H, CH), 7.48 (s, 1H, CH), 7.57-7.71 (m, 3H, CH), 8.15 (dd, *J* = 14.5, 0.9 Hz, 2H, CH), 8.30 ppm (d, *J* = 7.9 Hz, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 96.4 (CH), 105.4, 105.9 (C_q), 106.2, 111.7, 111.8, 113.5 (CH), 119.9, 120.0 (C_q), 124.1, 124.2 (CH), 125.5 (C_q), 126.0, 126.8, 127.3, 127.6 (CH), 128.4 ($2C_q$), 128.9 (C_q), 129.2, 129.4, 130.3 (CH), 131.5, 138.4, 138.6 ppm (C_q) (one C_q signal could not be detected). **IR** (ATR): $\tilde{\nu}$ = 3141 (w), 3113 (w), 3081 (w), 2222 (m), 1455 (m), 1447 (m), 1404 (m), 1331 (m), 799 (m), 760 (m), 738 cm^{-1} (m). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 382 ($[M]^+$, 100), 354 (4), 239 (4), 214 (4), 177 (14). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{26}H_{14}N_4$ $[M]^+$: 382.12130; found: 382.12064.

9-Fluoro-6-(6-fluoro-1*H*-indol-1-yl)indolo[2,1-*a*]isoquinoline (4e).



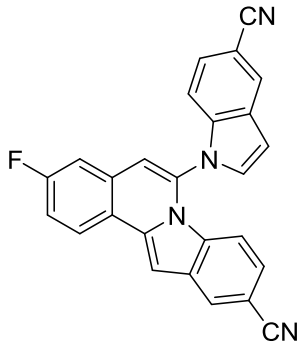
Reaction time for C-H arylation step 4 h, yield 84% (70.8 mg), white solid, mp 140-141 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 5.36 (dd, *J* = 11.0, 2.2 Hz, 1H, CH), 6.78 (s, 1H, CH), 6.81 (dd, *J* = 9.6, 2.6 Hz, 1H, CH), 6.89 (dd, *J* = 3.3, 0.7 Hz, 1H, CH), 6.97-7.04 (m, 2H, CH), 7.28 (d, *J* = 3.3 Hz, 1H, CH), 7.38 (s, 1H, CH), 7.48-7.53 (m, 1H, CH), 7.57-7.62 (m, 2H, CH), 7.67-7.74 (m, 2H, CH), 8.23 ppm (d, *J* = 7.4 Hz, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 95.8 (CH), 97.3 (d, J_{CF} = 26.8 Hz, CH), 99.9 (d, J_{CF} = 28.9 Hz, CH), 105.4, 110.0 (CH), 110.5 (d, J_{CF} = 24.6 Hz, CH), 111.6 (d, J_{CF} = 25.0 Hz, CH), 121.1 (d, J_{CF} = 9.9 Hz, CH), 122.6 (d, J_{CF} = 9.9 Hz, CH), 123.4 (CH), 124.9, 125.7, 126.1 (C_q), 127.3, 128.1 (CH), 128.4 (C_q), 128.5, 128.6 (CH), 130.0 (d, J_{CF} = 12.7 Hz, C_q), 131.3 (C_q), 137.0 (d, J_{CF} = 3.6 Hz, C_q), 137.3 (d, J_{CF} = 12.2 Hz, C_q), 159.0 (d, J_{CF} = 238.1 Hz, C_q), 160.7 ppm (d, J_{CF} = 240.6 Hz, C_q). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = - 118.3, -119.1 ppm (CF). **IR** (ATR): $\tilde{\nu}$ = 3109 (w), 1616 (m), 1484 (m), 1474 (m), 1435 (m), 1401 (m), 1212 (m), 1171 (m), 1145 (m), 949 (m), 805 (m), 754 cm^{-1} (m). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 368 ($[M]^+$, 100), 348 (7), 232 (5), 184 (5), 107 (3). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{24}H_{14}N_2F_2$ $[M]^+$: 368.11196; found: 368.11149.

3-Fluoro-12-methyl-6-(3-methyl-1*H*-indol-1-yl)indolo[2,1-*a*]isoquinoline (4f).



Reaction time for C-H arylation step 4 h, yield 72 % (57.2 mg), yellow solid, mp 187-188 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.49 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 5.86 (d, *J* = 8.6 Hz, 1H, CH), 6.57 (s, 1H, CH), 6.86-6.92 (m, 1H, CH), 7.06 (d, *J* = 8.8 Hz, 2H, CH), 7.12-7.33 (m, 5H, CH), 7.72-7.79 (m, 2H, CH), 8.41-8.46 ppm (m, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 9.9, 11.8 (CH_3), 106.4 (d, J_{CF} = 1.6 Hz, C_q), 107.8 (d, J_{CF} = 2.9 Hz, CH), 110.8 (CH), 112.2 (d, J_{CF} = 22.0 Hz, CH), 113.6 (CH), 114.6 (C_q), 115.3 (d, J_{CF} = 22.7 Hz, CH), 118.0, 119.5, 120.8, 122.0, 122.1, 123.4 (CH), 124.0 (d, J_{CF} = 2.6 Hz, C_q), 125.2 (CH), 126.6 (d, J_{CF} = 8.5 Hz, CH), 129.3, 129.3, 130.1, 131.1 (C_q), 131.9 (d, J_{CF} = 8.8 Hz, C_q), 133.9, 137.4 (C_q), 161.5 ppm (d, J_{CF}= 247.4 Hz, C_q). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -114.0 ppm (CF). **IR** (ATR): $\tilde{\nu}$ = 3098 (w), 3067 (w), 2919 (w), 2860 (w), 1647 (w), 1448 (m), 1227 (m), 1214 (m), 881 (m), 806 (m), 729 cm^{-1} (m). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 378 ($[M]^+$, 100), 361 (15), 246 (4), 220 (3), 181 (12), 77 (3). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{26}H_{19}N_2F_1$ $[M]^+$: 378.15268; found: 378.15178.

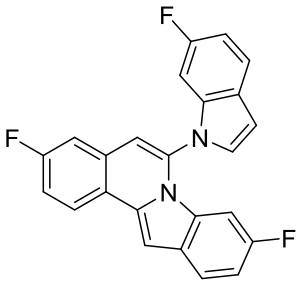
6-(5-Cyano-1*H*-indol-1-yl)-3-fluoroindolo[2,1-*a*]isoquinoline-10-carbonitrile (4g).



Reaction time for C-H arylation step 9 h, yield 78% (66.3 mg), yellow solid, R_f 0.30 (Hept/EtOAc 1:1), mp 296-297 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 5.58 (d, *J* = 8.9 Hz, 1H), 6.86 (s, 1H, CH), 7.03 (dd, *J* = 3.3, 0.8 Hz, 1H, CH), 7.06 (dd, *J* = 8.9, 1.7 Hz, 1H, CH), 7.16 (d, *J* = 8.5 Hz, 1H, CH), 7.32 (dd, *J* = 8.8, 2.5 Hz, 1H, CH), 7.37-7.45 (m, 4H, CH), 8.15 (dd, *J* = 17.0, 0.9 Hz, 2H, CH), 8.29 ppm (dd, *J* = 8.8, 5.2 Hz, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 96.2 (CH), 105.6, 106.2 (C_q), 106.5 (CH), 110.9 (d, *J* = 3.1 Hz, CH), 111.6, 112.9 (CH), 113.0 (d, J_{CF} = 22.4 Hz, CH), 117.6 (d, J_{CF} = 23.4 Hz, CH), 119.8, 119.9 (C_q), 122.0 (d, J_{CF} = 2.5 Hz, C_q), 124.4, 126.0 (CH), 126.4 (d, J_{CF} = 8.9 Hz, CH), 126.9, 127.3 (CH), 128.4, 129.0 (C_q), 130.1 (CH), 130.3 (d, J_{CF} = 9.0 Hz, C_q), 131.5 131.6, 137.9, 138.5 (C_q), 162.8 ppm (d, J_{CF} = 250.4 Hz, C_q). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -110.3 ppm (CF). **IR** (ATR): $\tilde{\nu}$ = 3116 (w), 3072 (w), 2923 (w), 2218 (m), 1731 (w), 1609 (m), 1562 (m), 1459 (m), 1402 (m), 1327 (m),

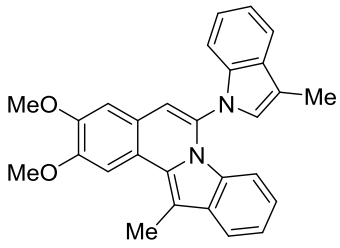
1216 (m), 794 (m), 725 cm^{-1} (m). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 400 ($[M]^+$, 100), 371 93), 200 (8), 84 (2). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{26}H_{13}N_4F_1$ $[M]^+$: 400.11188; found: 400.11142.

3,9-Difluoro-6-(6-fluoro-1*H*-indol-1-yl)indolo[2,1-*a*]isoquinoline (4h).



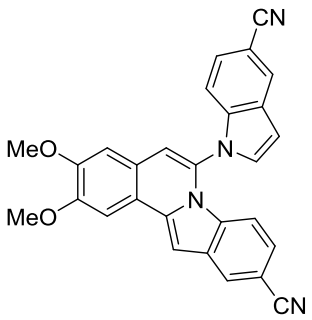
Reaction time for C-H arylation step 4 h, yield 83% (68.0 mg), light yellow solid, mp 54-55 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 5.37 (dd, *J* = 11.0, 2.2 Hz, 1H, CH), 6.68 (s, 1H, CH), 6.78 (dd, *J* = 9.2, 2.2 Hz, 1H, CH), 6.88 (dd, *J* = 3.3, 0.8 Hz, 1H, CH), 6.96-7.03 (m, 2H, CH), 7.21-7.32 (m, 4H, CH), 7.63-7.73 (m, 2H, CH), 8.16 ppm (dd, *J* = 8.8, 5.3 Hz, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 95.5 (CH), 97.3 (d, J_{CF} = 26.9 Hz, CH), 100.0 (d, J_{CF} = 28.9 Hz, CH), 105.6 (CH), 109.0 (d, J_{CF} = 3.0 Hz, CH), 110.6 (d, J_{CF} = 24.6 Hz, CH), 111.8 (d, J_{CF} = 24.9 Hz, CH), 112.6 (d, J_{CF} = 22.2 Hz, CH), 116.7 (d, J_{CF} = 23.4 Hz, CH), 121.1 (d, J_{CF} = 9.9 Hz, CH), 122.5 (d, J_{CF} = 2.6 Hz, C_q), 122.6 (d, J_{CF} = 9.9 Hz, CH), 124.9 (d, J_{CF} = 1.0 Hz, C_q), 125.5 (d, J_{CF} = 8.7 Hz, CH), 125.8 (C_q), 128.2 (d, J_{CF} = 3.9 Hz, CH), 129.9 (d, J_{CF} = 12.6 Hz, C_q), 130.2 (d, J_{CF} = 9.0 Hz, C_q), 132.5 (C_q), 136.4 (d, J_{CF} = 3.2 Hz, C_q), 137.2 (d, J_{CF} = 12.2 Hz, C_q), 159.0 (d, J_{CF} = 239.6 Hz, C_q), 160.8 (d, J_{CF} = 240.8 Hz, C_q), 162.2 ppm (d, J_{CF} = 249.4 Hz, C_q). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -112.4, -118.1, -118.9 ppm (CF). **IR** (ATR): $\tilde{\nu}$ = 3109 (w), 3078 (w), 2921 (w), 2850 (w), 1613 (m), 1483 (m), 1444 (m), 1210 (m), 1171 (m), 1143 (m), 947 (m), 802 cm^{-1} (m). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 386 ($[M]^+$, 100), 366 (9), 250 (7), 225 (5), 192 (28), 107 (6). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{24}H_{13}N_2F_3$ $[M]^+$: 386.10253; found: 386.10217.

2,3-Dimethoxy-12-methyl-6-(3-methyl-1H-indol-1-yl)indolo[2,1-*a*]isoquinoline (4i).



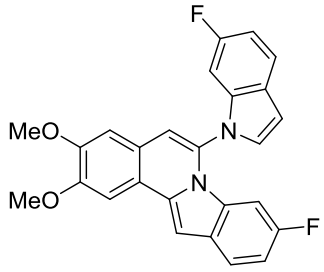
Reaction time for C-H arylation step 4 h, yield 55% (41.8 mg), yellow solid, mp 158-159 °C. **^{1}H NMR** (250 MHz, $CDCl_3$): δ = 2.49 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 5.79 (d, *J* = 8.6 Hz, 1H, CH), 6.60 (s, 1H, CH), 6.81-6.87 (m, 1H, CH), 7.00 (s, 1H, CH), 7.04-7.23 (m, 5H, CH), 7.72-7.77 (m, 2H, CH), 8.02 ppm (s, 1H, CH). **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 9.9, 11.7 (CH_3), 56.1, 56.2 (OCH_3), 104.0 (C_q), 106.8, 108.2, 108.5, 110.8, 113.5 (CH), 114.2 (C_q), 117.7, 119.4, 120.6, 121.3 (CH), 121.5 (C_q), 121.6, 123.3 (CH), 124.0 (C_q), 125.6 (CH), 129.1, 129.1, 130.1, 131.3, 131.8, 137.6, 148.9, 149.3 ppm (C_q). **IR** (ATR): $\tilde{\nu}$ = 3062 (w),

3002 (w), 2923 (w), 2834 (w), 1610 (w), 1507 (m), 1451 (m), 1438 (m), 21250 (m), 1214 (m), 733 cm^{-1} (m). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 420 ($[M]^+$, 100), 405 (13), 376 (6), 317 (4), 210 (18), 159 (14). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{28}H_{24}O_2N_2$ $[M]^+$: 420.18323; found: 420.18323.



6-(5-Cyano-1*H*-indol-1-yl)-2,3-dimethoxyindolo[2,1-*a*]isoquinoline-10-carbonitrile (4j).

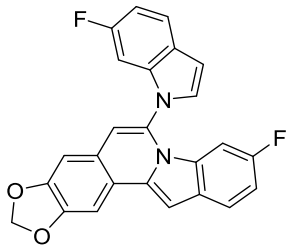
Reaction time for C-H arylation step 4 h, yield 87%, (69.2 mg), yellow solid, R_f 0.36 (EtOAc), mp 300 °C (decomp.). **^{1}H NMR** 30 °C (500 MHz, DMSO-d_6): δ = 3.90 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 5.45 (d, *J* = 8.9 Hz, 1H, CH), 7.12-7.14 (m, 2H, CH), 7.24 (s, 1H, CH), 7.29 (d, *J* = 8.6 Hz, 1H, CH), 7.41 (s, 1H, CH), 7.48 (dd, *J* = 8.5, 1.4 Hz, 1H, CH), 7.75 (s, 1H, CH), 7.98 (s, 1H, CH), 8.00 (d, *J* = 3.3 Hz, 1H, CH), 8.33 (d, *J* = 1.1 Hz, 1H, CH), 8.39 (d, *J* = 0.7 Hz, 1H, CH). **^{13}C NMR** 30 °C (126 MHz, DMSO-d_6) δ = 55.7, 56.1 (OCH_3), 94.7 (CH), 103.7, 104.2 (C_q), 105.6, 105.8, 109.0, 111.6, 111.8, 112.9 (CH), 118.8, 119.8, 119.9 (C_q), 122.5 (CH), 122.5 (C_q), 125.6, 126.1, 127.0 (CH), 128.0 ($2C_q$), 128.6, 130.6 (C_q), 132.0 (CH), 138.3, 138.4, 150.4, 150.5 ppm (C_q). **IR** (ATR): $\tilde{\nu}$ = 3114 (w), 2923 (w), 2849 (w), 2219 (m), 1611 (m), 1507 (m), 1450 (m), 1253 (s), 862 (m), 730 (m), 698 cm^{-1} (m). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 442 ($[M]^+$, 100), 398 (9), 258 (16), 221 (8), 184 (6). **HRMS** (ESI-TOF): *m/z* calcd. for $C_{28}H_{18}N_4O_2$ $[M+H]^+$: 443.15025; found: 443.15037, *m/z* calcd. for $C_{28}H_{18}N_4O_2$ $[M+Na]^+$: 465.13220; found: 465.13211.



9-Fluoro-6-(6-fluoro-1*H*-indol-1-yl)-2,3-dimethoxyindolo[2,1-*a*]isoquinoline (4k).

Reaction time for C-H arylation step 4 h, yield 73% (55.7 mg), light brown solid, mp 251-252 °C. **^{1}H NMR** (250 MHz, $CDCl_3$): δ = 4.00 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 5.34 (dd, *J* = 11.1, 2.2 Hz, 1H, CH), 6.73 (s, 1H, CH), 6.80 (dd, *J* = 9.3, 2.3 Hz, 1H, CH), 6.88 (dd, *J* = 3.3, 0.8 Hz, 1H, CH), 6.94-7.04 (m, 3H, CH), 7.27 (d, *J* = 3.5 Hz, 1H, CH), 7.59 (s, 1H, CH), 7.63-7.74 ppm (m, 2H, CH) (one H signal could not be detected). **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 56.2, 56.4 (OCH_3), 93.6 (CH), 97.3 (d, J_{CF} = 26.9 Hz, CH), 99.9 (d, J_{CF} = 28.8 Hz, CH), 104.8, 105.3, 108.3, 109.6 (CH), 110.4 (d, J_{CF} = 24.6 Hz, CH), 111.4 (d, J_{CF} = 25.0 Hz, CH), 120.0 (C_q), 120.6 (d, J_{CF} = 9.9 Hz, CH), 122.5 (d, J_{CF} = 10.0 Hz, CH), 122.5,

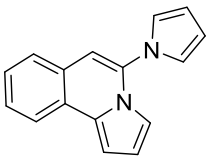
124.9, 125.9 (C_q), 128.6 (d, J_{CF} = 3.9 Hz, CH), 129.7 (d, J_{CF} = 12.7 Hz, C_q), 129.8 (C_q), 137.0 (d, J_{CF} = 3.5 Hz, C_q), 137.4 (d, J_{CF} = 12.2 Hz, C_q), 150.0, 150.4 (C_q), 158.6 (d, J_{CF} = 237.3 Hz, C_q), 160.7 ppm (d, J_{CF} = 240.5 Hz, C_q). **^{19}F NMR** (235 MHz, $CDCl_3$): δ = -118.5, -120.1 ppm (CF). **IR** (ATR): $\tilde{\nu}$ = 3080 (w), 2926 (w), 2830 (w), 1611 (m), 1506 (m), 1481 (m), 1447 (m), 1254 (m), 1212 (m), 1169 (m), 861 (m), 799 cm^{-1} (m). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 428 ($[M]^+$, 100), 384 (20), 341 (7), 251 (20), 214 (22), 177 (14). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{26}H_{18}O_2N_2F_2$ $[M]^+$: 428.13309; found: 428.13318.



9-Fluoro-6-(6-fluoro-1*H*-indol-1-yl)-[1,3]dioxolo[4,5-g]indolo[2,1-a]isoquinoline (4l).

Reaction time for C-H arylation step 12 h, yield 84% (78.4 mg), yellow solid, R_f 0.30 (Hept/EtOAc 5:1), mp 256-257 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 5.34 (dd, *J* = 11.0, 2.2 Hz, 1H, CH), 6.11 (s, 2H, CH_2), 6.69 (s, 1H, CH), 6.78 (dd, *J* = 9.3, 2.3 Hz, 1H, CH), 6.88 (dd, *J* = 3.3, 0.8 Hz, 1H, CH), 6.95-7.03 (m, 3H, CH), 7.17 (s, 1H, CH), 7.26 (d, *J* = 3.2 Hz, 1H, CH), 7.60 (s, 1H, CH), 7.63-7.73 ppm (m, 2H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 93.9 (CH), 97.3 (d, J_{CF} = 26.8 Hz, CH), 99.9 (d, J_{CF} = 28.8 Hz, CH), 101.9 (CH_2), 102.6, 105.3, 105.8, 109.9 (CH), 110.5 (d, J_{CF} = 24.6 Hz, CH), 111.6 (d, J_{CF} = 24.9 Hz, CH), 120.8 (d, J_{CF} = 9.8 Hz, CH), 121.5 (C_q), 122.5 (d, J_{CF} = 10.0 Hz, CH), 123.8, 124.9, 125.8 (C_q), 128.6 (d, J_{CF} = 3.9 Hz, CH), 129.5 (d, J_{CF} = 12.6 Hz, C_q), 130.0 (C_q), 137.1 (d, J_{CF} = 3.5 Hz, C_q), 137.4 (d, J_{CF} = 12.1 Hz, C_q), 148.5, 149.0 (C_q), 158.7 (d, J_{CF} = 237.3 Hz, C_q), 160.7 ppm (d, J_{CF} = 240.4 Hz, C_q). **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -118.4, -119.9 ppm (CF). **IR** (ATR): $\tilde{\nu}$ = 3010 (w), 2905 (w), 2852 (w), 2780 (w), 1653 (m), 1483 (s), 1445 (s), 1386 (m), 1174 (s), 938 (s), 802 cm^{-1} (s). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 412 ($[M]^+$, 100), 353 (13), 206 (8), 176 (6). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{25}H_{14}F_2N_2O_2$ $[M]^+$: 412.10179; found: 412.10163.

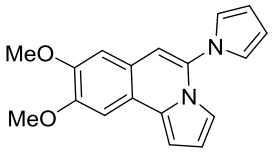
5-(1*H*-Pyrrol-1-yl)pyrrolo[2,1-*a*]isoquinoline (4m).



Reaction time for C-H arylation step 4 h, yield 67% (71.4 mg) starting from 0.10 g (1 equiv.) of **1a**, dark yellow solid, R_f 0.42 (Hept), mp 60-61 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.43-6.45 (m, 2H, CH), 6.73 (dd, *J* = 3.6, 3.0 Hz, 1H, CH), 6.78 (s, 1H, CH), 7.05-7.10 (m, 4H, CH), 7.36-7.41 (m, 1H, CH), 7.48-7.53 (m, 1H, CH), 7.58 (d, *J* = 7.9 Hz, 1H, CH), 8.08 ppm (d, *J* = 8.02 Hz, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 101.5, 107.1 (CH), 110.5, 112.4, 122.0 (2CH), 122.2 (CH), 125.6 (C_q),

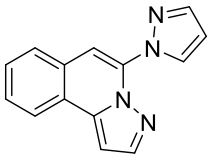
126.0 (CH), 127.0 (C_q), 127.2, 127.8 (CH), 131.6, 132.8 ppm (C_q). **IR** (ATR): $\tilde{\nu}$ = 3100 (w), 3054 (w), 2990 (w), 2926 (w), 2853 (w), 1732 (w), 1655 (m), 1541 (m), 1478 (m), 1069 (m), 996 (m), 846 (m), 757 cm^{-1} (m). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 232 ($[M]^+$, 100), 204 (54), 176 (5), 139 (9), 116 (8), 102 (9), 89 (4). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{16}H_{12}N_2$ $[M]^+$: 232.09950; found: 232.09937.

8,9-Dimethoxy-5-(1*H*-pyrrol-1-yl)pyrrolo[2,1-*a*]isoquinoline (4n).

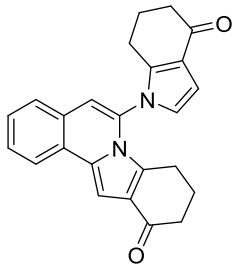


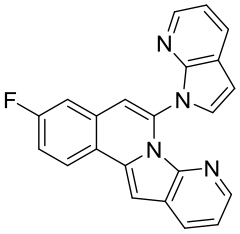
Reaction time for C-H arylation step 16 h, yield 59% (30.9 mg), light yellow solid, R_f 0.27 (Hept/EtOAc 5:1), mp 199-200 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 3.98 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 6.41-6.43 (m, 2H, CH), 6.71 (brs, 2H, CH), 6.89 (d, *J* = 3.6 Hz, 1H, CH), 6.99 (s, 1H, CH), 7.01 (d, *J* = 2.1 Hz, 1H, CH), 7.02-7.04 (m, 2H, CH), 7.43 ppm (s, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 56.1, 56.2 (OCH_3), 99.5, 103.5, 106.7, 108.1 (CH), 110.3 (2CH), 111.5, 112.3 (CH), 120.0, 120.9 (C_q), 122.1 (2CH), 131.5 ($2C_q$), 148.7, 150.0 ppm (C_q). **IR** (ATR): $\tilde{\nu}$ = 3126 (w), 2918 (w), 2848 (w), 1657 (m), 1617 (m), 1508 (m), 1465 (m), 1248 (s), 1012 (s), 694 (s), 689 cm^{-1} (s). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 294 ($[M]^+$, 100), 277 (6), 249 (21), 206 (14), 183 (9), 115 (4), 89 (3). **HRMS** (ESI-TOF): *m/z* calcd. for $C_{18}H_{16}N_2O_2$ $[M+H]^+$: 293.12845; found: 293.12848.

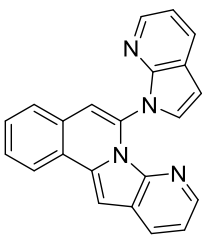
5-(1*H*-Pyrazol-1-yl)pyrazolo[5,1-*a*]isoquinoline (4o).



Reaction time for C-H arylation step 20 h, yield 23% (12.1 mg), white solid, R_f 0.18 (Hept/EtOAc 2:1), mp 100-101 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.58-6.60 (m, 1H, CH), 7.14 (d, *J* = 2.2 Hz, 1H, CH), 7.49 (s, 1H, CH), 7.55-7.62 (m, 2H, CH), 7.78-7.81 (m, 1H, CH), 7.86 (d, *J* = 1.5 Hz, 1H, CH), 8.06 (d, *J* = 2.1 Hz, 1H, CH), 8.12-8.15 (m, 1H, CH), 8.81 ppm (d, *J* = 2.6 Hz, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 98.7, 105.5, 107.5 (CH), 123.3 (C_q), 123.7, 127.7, 127.7, 128.6 (CH), 129.1 (C_q), 132.7 (CH), 133.9, 140.5 (C_q), 141.5, 141.9 (CH). **IR** (ATR): $\tilde{\nu}$ = 3152 (w), 3110 (w), 3099 (w), 2918 (w), 2850 (w), 1643 (m), 1546 (m), 1444 (m), 1390 (m), 1326 (m), 1095 (m), 741 cm^{-1} (s). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 234 ($[M]^+$, 100), 206 (22), 194 (6), 179 (16), 140 (13), 103 (9), 76 (2). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{14}H_{10}N_4$ $[M]^+$: 234.09000; found: 234.09026.

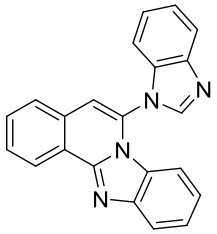
6-(4-Oxo-4,5,6,7-tetrahydro-1*H*-indol-1-yl)-9,10-dihydroindolo[2,1-*a*]isoquinolin-11(8*H*)-one (4p).  Reaction time for C-H arylation step 4 h, yield 34% (28.5 mg), white solid, R_f 0.24 (EtOAc), mp 269-270 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.94-2.05 (m, 2H, CH_2), 2.10-2.22 (m, 4H, CH_2), 2.39-2.46 (m, 1H, CH_2), 2.48-2.56 (m, 4H, CH_2), 2.66-2.76 (m, 1H, CH_2), 6.77 (d, *J* = 3.1 Hz, 1H, CH), 6.85 (s, 1H, CH), 6.86 (d, *J* = 3.2 Hz, 1H, CH), 7.40-7.59 (m, 4H, CH), 8.05 ppm (d, *J* = 7.8 Hz, 1H, CH). **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 21.1, 21.8, 23.6, 24.2, 37.9, 38.1 (CH_2), 98.7, 107.5, 114.4 (CH), 121.9 (C_q), 122.6 (CH), 124.1 (C_q), 125.3 (CH), 125.9, 126.7 (C_q), 127.2, 127.5 (CH), 129.3 (C_q), 129.6 (CH), 132.8, 135.5, 146.2 (C_q), 194.4, 195.6 ppm (CO). **IR** (ATR): $\tilde{\nu}$ = 3103 (w), 2924 (w), 2850 (w), 1734 (w), 1651 (s), 1455 (m), 1414 (m), 1237 (m), 759 cm^{-1} (m). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 368 ([M]$^+$, 100), 339 (12), 312 (24), 255 (13), 204 (9), 128 (6). **HRMS** (ESI-TOF): *m/z* calcd. for $C_{24}H_{20}N_2O_2$ [M+H]$^+$: 369.15975; found: 369.15981, *m/z* calcd. for [M+Na]$^+$: 391.14170; found: 391.14180.

3-Fluoro-6-(1H-pyrrolo[2,3-b]pyridin-1-yl)pyrido[3',2':4,5]pyrrolo[2,1-a]isoquinoline (4q).  Reaction time for C-H arylation step 20 h, yield 64% (47.6 mg), yellow solid, R_f 0.40 (Hept/EtOAc 1:1), mp 232-233 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.80 (d, *J* = 3.6 Hz, 1H, CH), 6.86 (s, 1H, CH), 7.04-7.08 (m, 1H, CH), 7.12-7.16 (s, 1H, CH), 7.18 (s, 1H, CH), 7.25-7.31 (m, 2H, CH), 7.45 (d, *J* = 3.6 Hz, 1H, CH), 7.78 (dd, *J* = 4.6, 1.6 Hz, 1H, CH), 7.97 (dd, *J* = 8.0, 1.6 Hz, 1H, CH), 8.08 (dd, *J* = 7.8, 1.5 Hz, 1H, CH), 8.19-8.24 ppm (m, 2H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 92.4, 102.5 (CH), 110.0 (d, J_{CF} = 3.0 Hz, CH), 112.8 (d, J_{CF} = 22.2 Hz, CH), 116.5 (d, J_{CF} = 23.4 Hz, CH), 116.8, 118.3 (CH), 121.5, 121.7 (C_q), 122.2 (d, J_{CF} = 2.6 Hz, C_q), 125.7 (d, J_{CF} = 8.8 Hz, CH), 127.8 (CH), 129.8 (2CH), 131.2 (d, J_{CF} = 9.2 Hz, C_q), 131.8, 135.9 (C_q), 142.2, 143.2 (CH), 143.7, 149.5 (C_q), 162.5 ppm (d, J_{CF} = 248.3 Hz, C_q). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -112.0 ppm (CF). **IR** (ATR): $\tilde{\nu}$ = 3100 (w), 3053 (w), 1648 (m), 1545 (m), 1428 (m), 1317 (m), 1229 (m), 1146 (m), 1121 (m), 790 (s), 758 (s), 718 (s), 706 cm^{-1} (s). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 352 ([M]$^+$, 100), 324 (7), 234 (4), 208 (3), 176 (31), 162 (7). **HRMS** (ESI-TOF): *m/z* calcd. for $C_{22}H_{13}FN_4$ [M+H]$^+$: 353.11970; found: 353.12027.

6-(1*H*-Pyrrolo[2,3-*b*]pyridin-1-yl)pyrido[3',2':4,5]pyrrolo[2,1-*a*]isoquinoline (4r). 

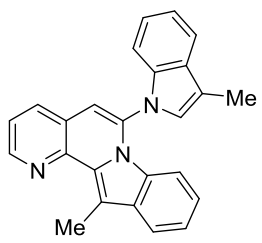
Reaction time for C-H arylation step 20 h, yield 52% (39.9 mg), light yellow solid, mp 212-213 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.81 (d, *J* = 3.6 Hz, 1H, CH), 6.94 (s, 1H, CH), 7.05 (dd, *J* = 8.0, 4.6 Hz, 1H, CH), 7.15 (dd, *J* = 7.8, 4.8 Hz, 1H, CH), 7.26 (s, 1H, CH), 7.46 (d, *J* = 3.6 Hz, 1H, CH), 7.49-7.65 (m, 3H, CH), 7.77 (dd, *J* = 4.5, 1.6 Hz, 1H, CH), 7.99 (dd, *J* = 8.0, 1.6 Hz, 1H, CH), 8.10 (dd, *J* = 7.8, 1.3 Hz, 1H, CH), 8.21 (dd, *J* = 4.8, 1.3 Hz, 1H, CH), 8.25 ppm (d, *J* = 7.6 Hz, 1H, CH). **^{13}C NMR** (63 MHz, $CDCl_3$): δ = 92.7, 102.3, 110.9, 116.7, 118.1 (CH), 121.5, 121.8 (C_q), 123.5 (CH), 125.7 (C_q), 127.5, 127.9, 128.4, 128.4 (CH), 129.3 (C_q), 129.8, 130.1 (CH), 130.6, 136.5 (C_q), 142.2, 143.0 (CH), 143.8 ppm (C_q) (one C_q signal could not be detected). **IR** (ATR): $\tilde{\nu}$ = 3046 (w), 2919 (w), 2850 (w), 1924 (w), 1828 (w), 1732 (w), 1647 (m), 1540 (m), 1430 (m), 1406 (m), 1319 (m), 1279 (m), 751 (s), 707 cm^{-1} (s). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 334 ($[M]^+$, 100), 306 (7), 216 (5), 167 (28), 153 (8). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{22}H_{14}N_4$ $[M]^+$: 334.12130; found: 334.12042.

6-(1*H*-Benzo[*d*]imidazol-1-yl)benzo[4,5]imidazo[2,1-*a*]isoquinoline (4s).



Reaction time for C-H arylation step 20 h, yield 53% (40.1 mg), white solid, R_f 0.29 (Hept/EtOAc 1:1), mp >300 °C. **^{1}H NMR** 30 °C (500 MHz, DMSO-d_6): δ = 5.66 (d, *J* = 8.3 Hz, 1H, CH), 6.98-7.01 (m, 1H, CH), 7.27-7.30 (m, 1H, CH), 7.37-7.43 (m, 3H, CH), 7.71 (s, 1H, CH), 7.88 (dd, *J* = 5.7, 3.5 Hz, 2H, CH), 7.95 (dd, *J* = 10.7, 8.4 Hz, 2H, CH), 8.02-8.05 (m, 1H, CH), 8.78 (s, 1H, CH), 8.81-8.84 ppm (m, 1H, CH). **^{13}C NMR** 30 °C (126 MHz, DMSO-d_6) δ = 110.9, 111.7, 112.0, 119.6, 120.3, 122.3 (CH), 122.9 (C_q), 123.5 (CH), 124.5 (2CH), 124.61 (CH), 127.7 (C_q), 127.8 (CH), 128.63 (C_q), 129.3, 130.7 (CH), 131.0, 134.4, 142.7, 143.4, 143.9 ppm (C_q) (one CH signal could not be detected). **IR** (ATR): $\tilde{\nu}$ = 3060 (w), 3029 (w), 1658 (m), 1527 (m), 1449 (m), 1228 (m), 748 (s), 727 cm^{-1} (s). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 334 ($[M]^+$, 100), 306 (2), 206 (15), 153 (10), 89 (6). **HRMS** (ESI-TOF): *m/z* calcd. for $C_{22}H_{14}N_4$ $[M+H]^+$: 335.12912; found: 335.12928.

12-Methyl-6(3-methyl-1*H*-indol-1-yl)indolo[1,2-h][1,7]naphthyridine (6).

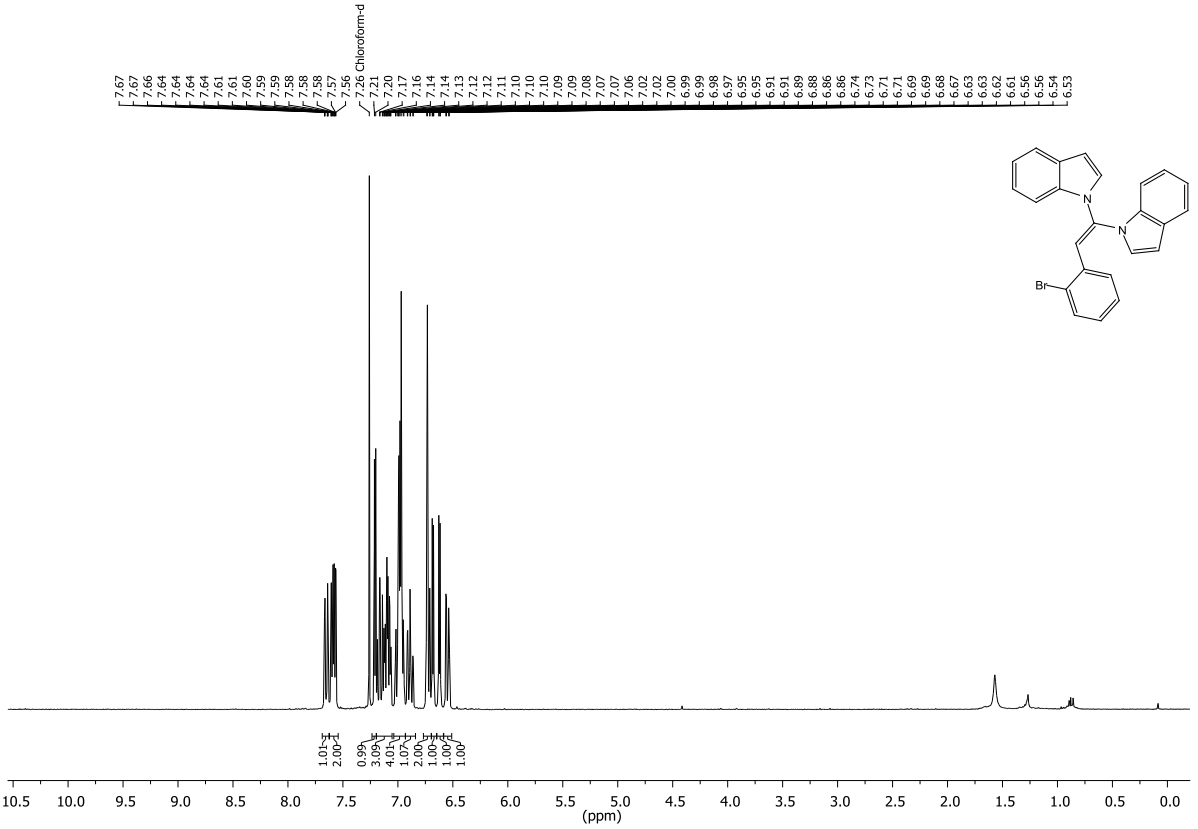


Reaction time for C-H arylation step 9 h, yield 85% (69.6 mg), light yellow solid, R_f 0.42 (Hept/EtOAc 5:1), mp 201-202 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.49 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 5.89 (d, *J* = 8.6 Hz, 1H, CH), 6.52 (s, 1H, CH), 6.92-6.98 (m, 1H, CH), 7.06-7.09 (m, 2H, CH), 7.12-7.18 (m, 1H, CH), 7.21-7.25 (m, 1H, CH),

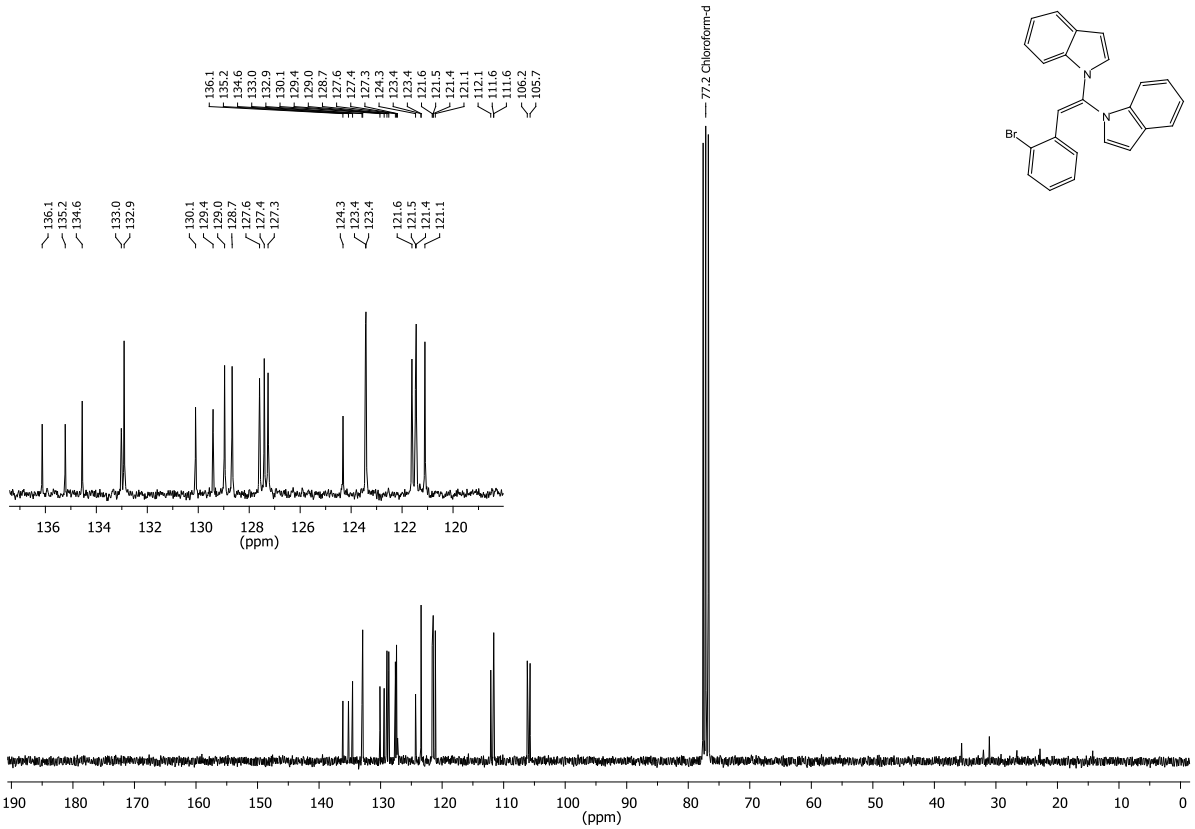
7.27-7.35 (m, 2H, CH), 7.72-7.75 (m, 1H, CH), 7.77 (dd, *J* = 7.9, 1.6 Hz, 1H, CH), 7.83-7.86 (m, 1H, CH), 8.86 ppm (dd, *J* = 4.7, 1.7 Hz, 1H, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 9.9, 11.1 (CH_3), 106.4, 110.8 (CH), 112.0 (C_q), 113.6 (CH), 114.7 (C_q), 119.2, 119.5, 120.9, 121.5, 122.1, 123.1, 123.5, 125.2 (CH), 125.6, 129.3, 130.0, 130.0, 130.7 (C_q), 133.5 (CH), 133.8, 137.3, 146.0 (C_q), 148.4 ppm (CH). **IR** (ATR): $\tilde{\nu}$ = 3050 (w), 2915 (w), 2851 (w), 1927 (w), 1886 (w), 1644 (m), 1564 (m), 1454 (s), 1402 (s), 1225 (m), 1113 (m), 833 (s), 734 cm^{-1} (s). **MS** (EI, 70 eV): *m/z* (relative intensity, %) = 361 ($[M]^+$, 100), 344 (32), 231 (10), 173 (20), 115 (3), 69 (2). **HRMS** (EI, 70 eV): *m/z* calcd. for $C_{25}H_{19}N_3$ $[M]^+$: 361.15735; found: 361.15686.

^{1}H, ^{13}C, ^{19}F NMR spectra copies of synthesized compounds

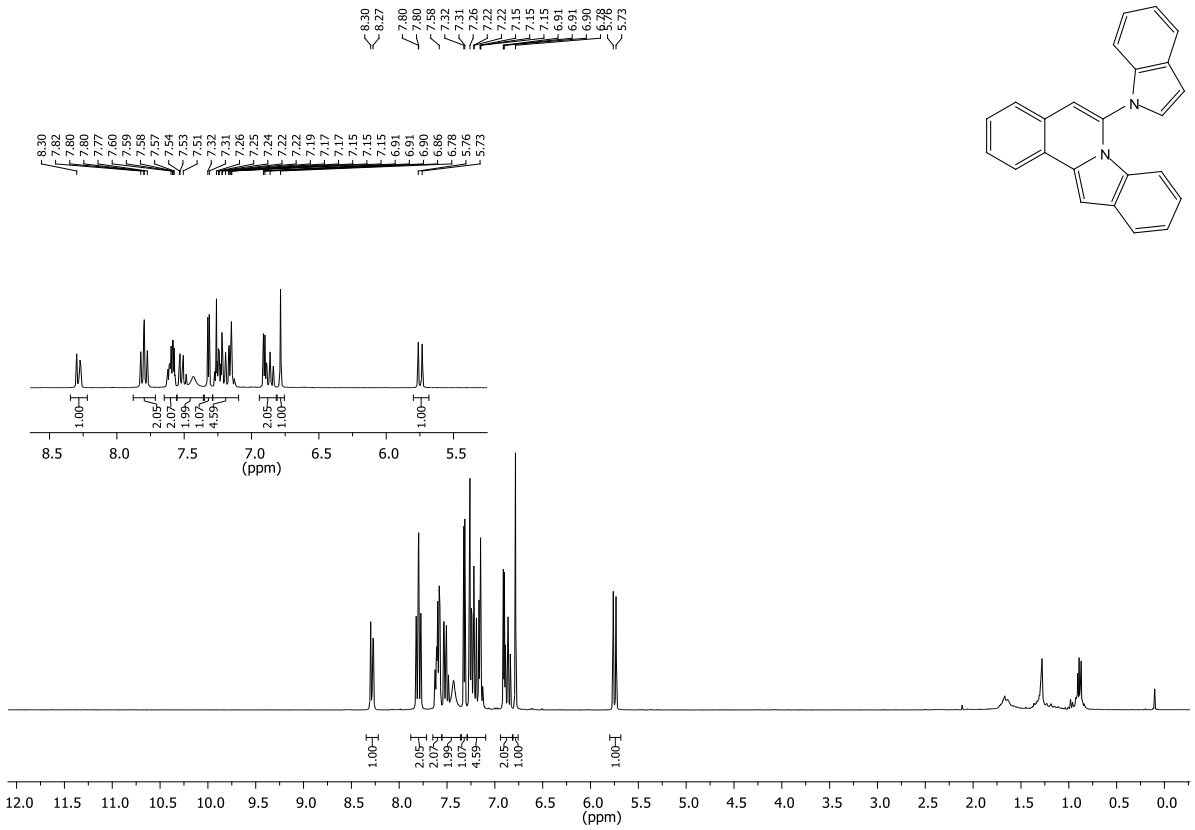
^{1}H NMR (300 MHz, $CDCl_3$) of **3a**.



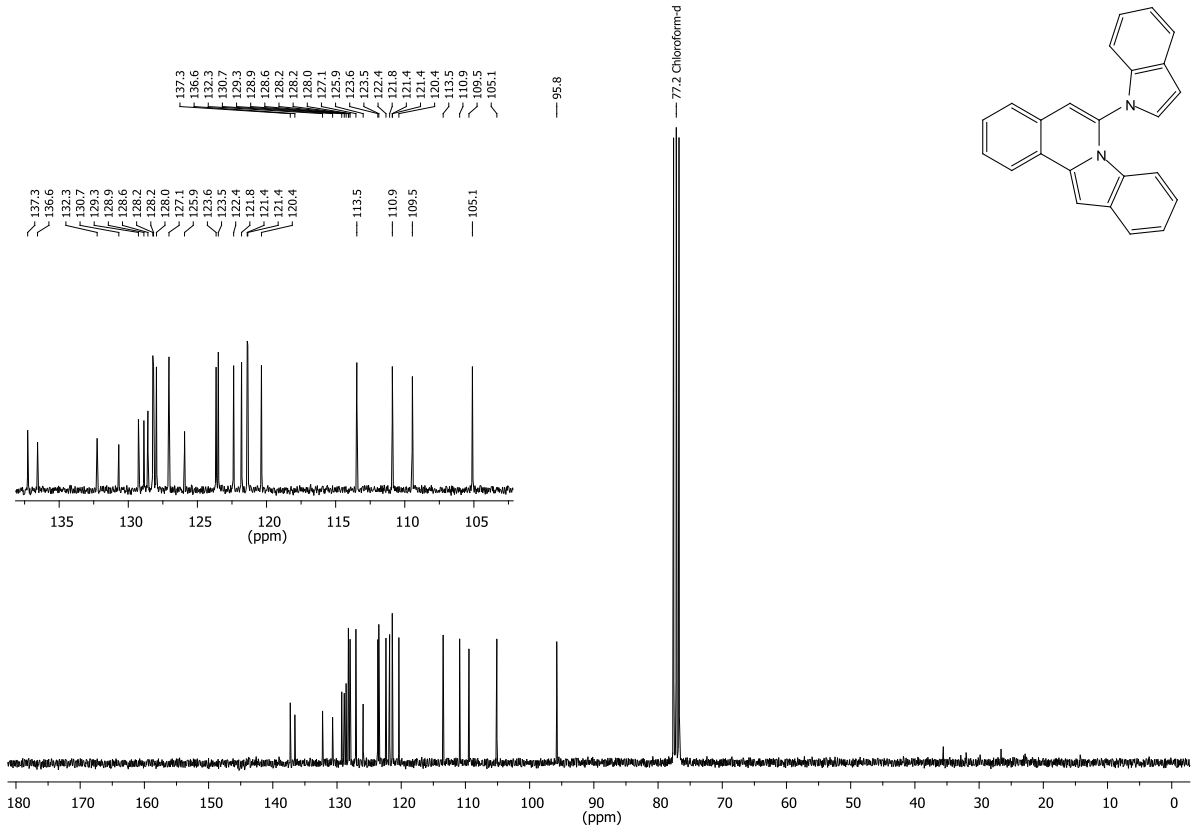
^{13}C NMR (75 MHz, $CDCl_3$) of **3a**.



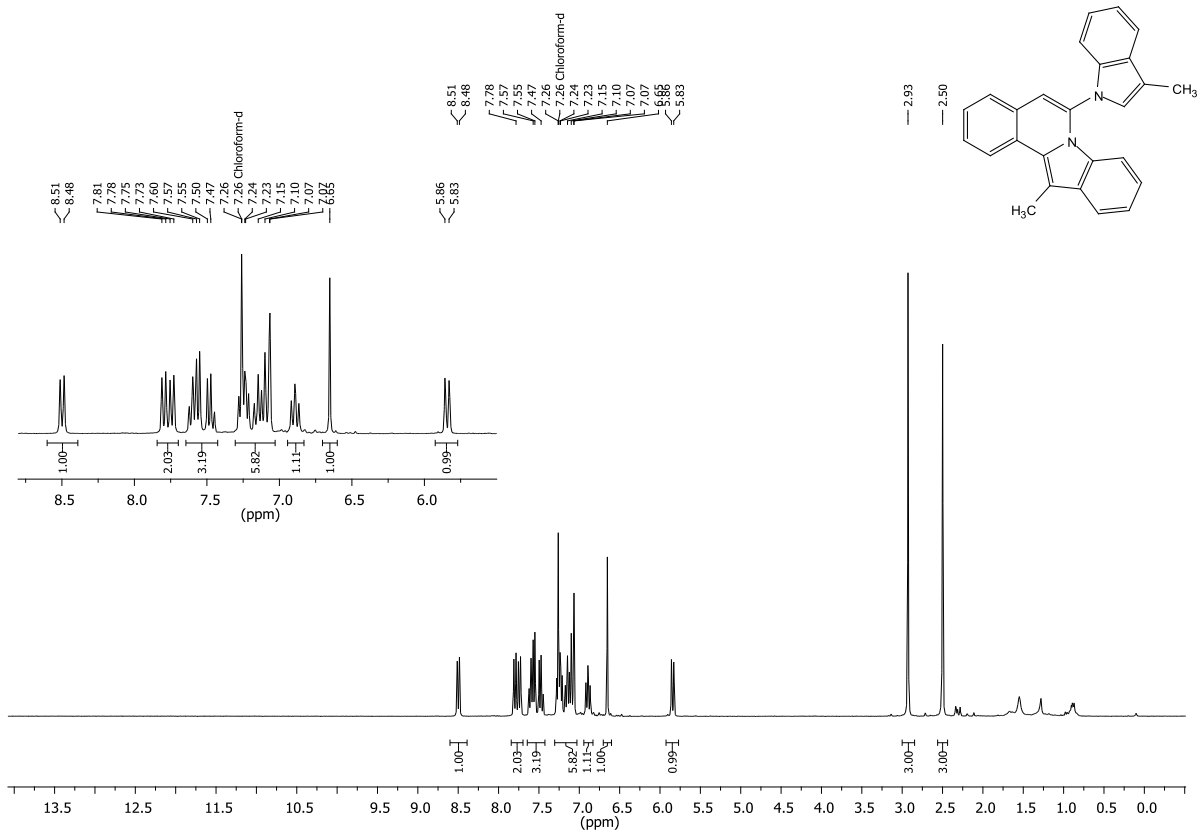
^{1}H NMR (300 MHz, $CDCl_3$) of **4a**.



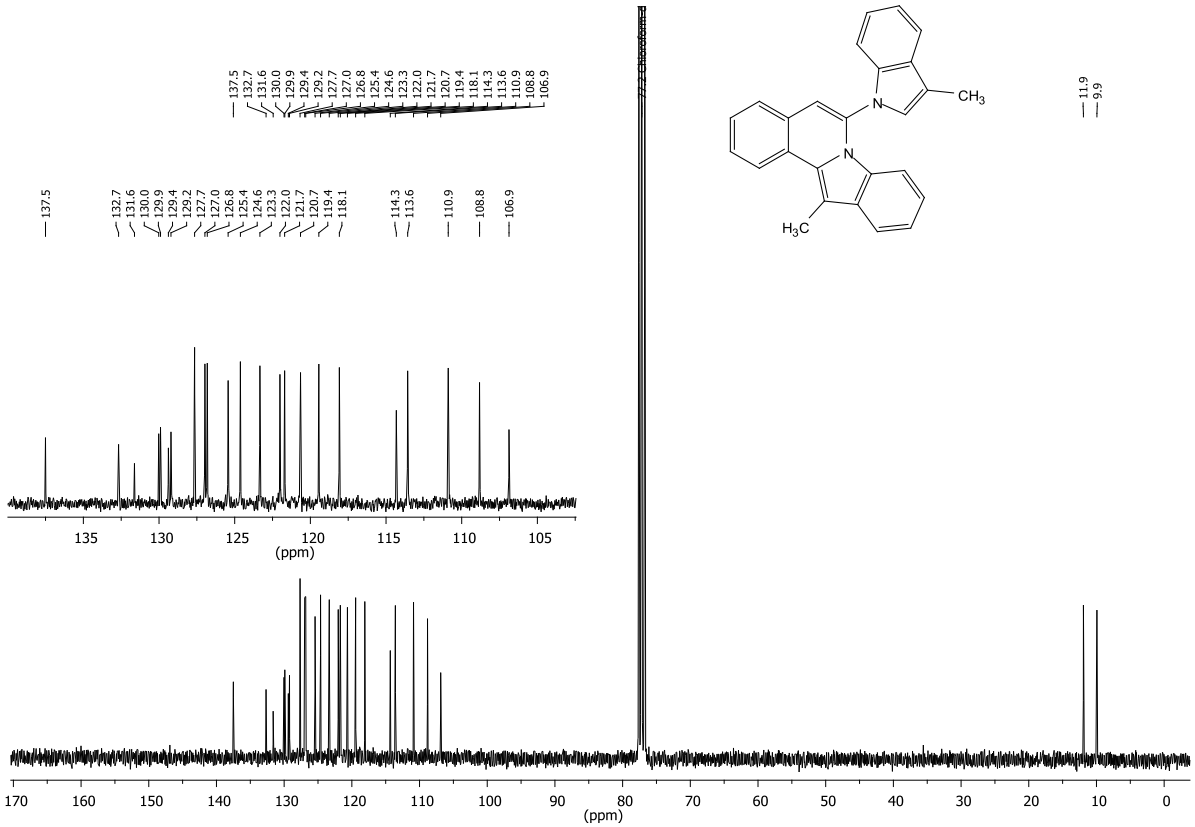
^{13}C NMR (75 MHz, $CDCl_3$) of **4a**.



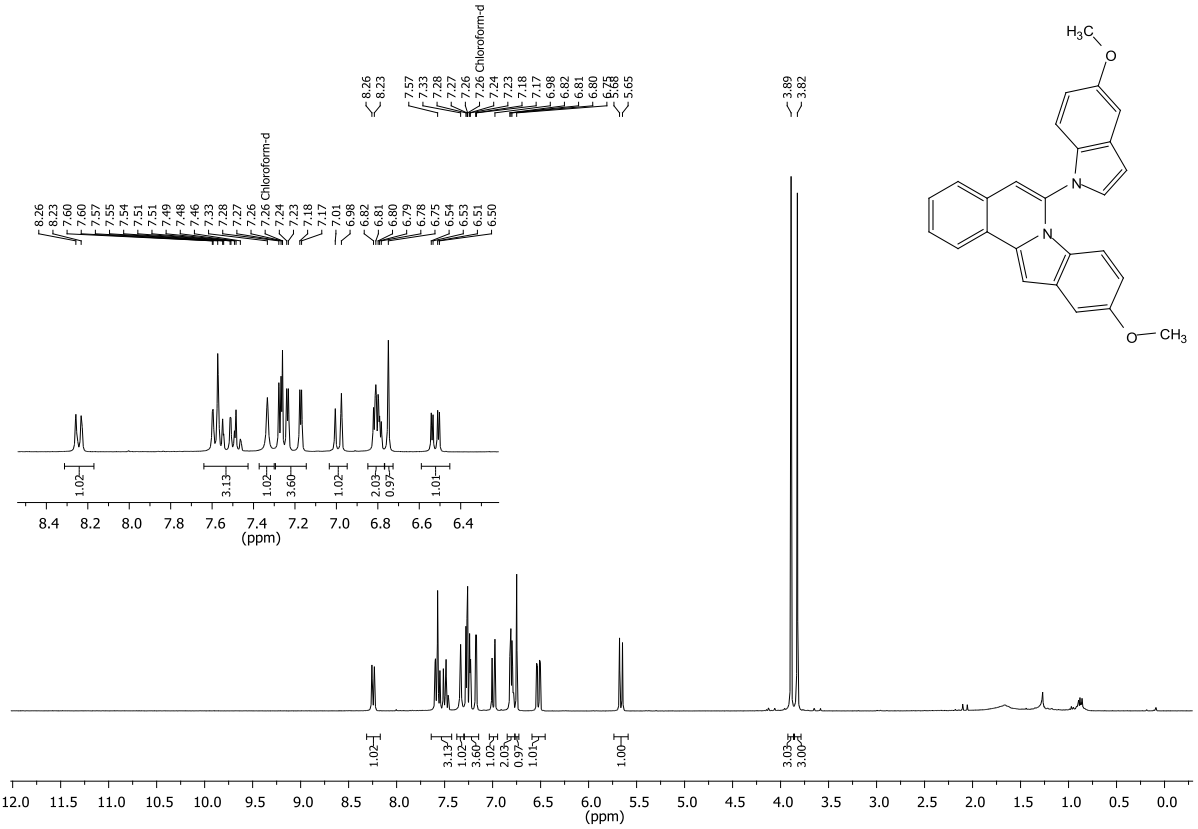
^{1}H NMR (300 MHz, $CDCl_3$) of **4b**.



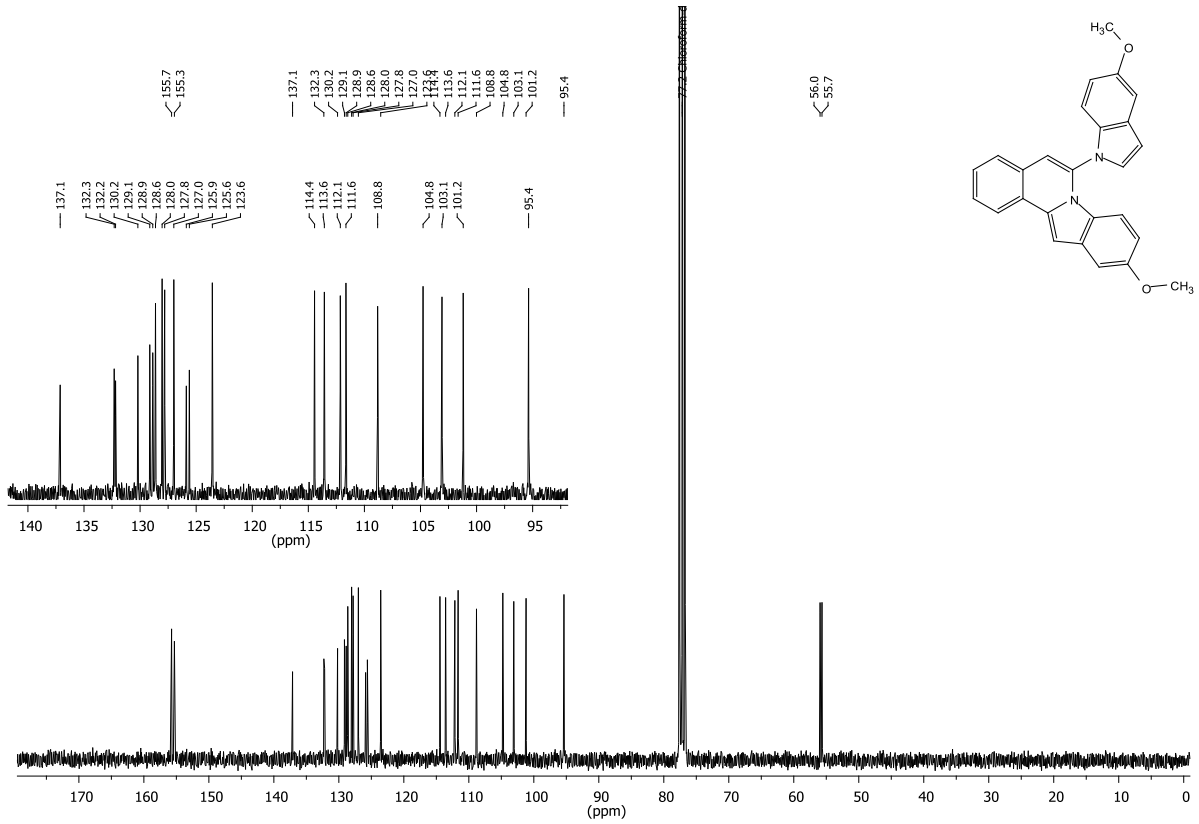
^{13}C NMR (75 MHz, $CDCl_3$) of **4b**.



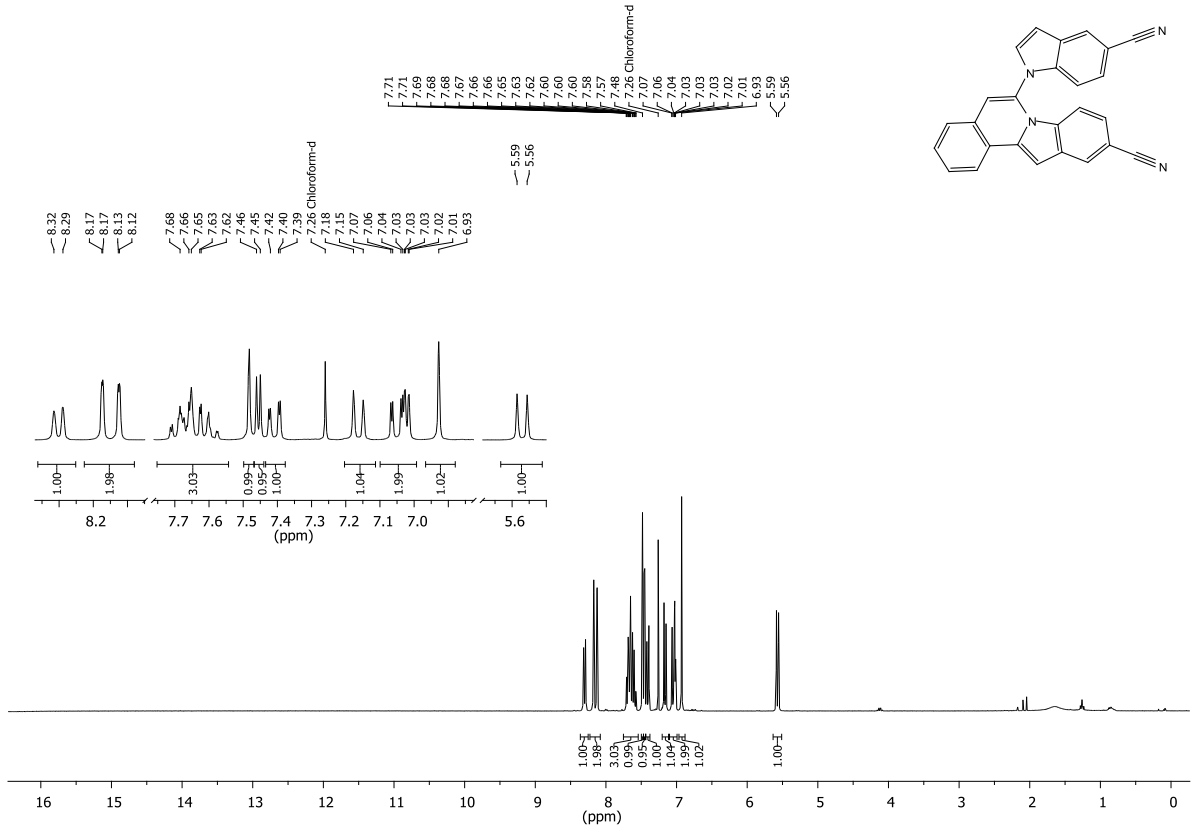
^{1}H NMR (300 MHz, $CDCl_3$) of **4c**.



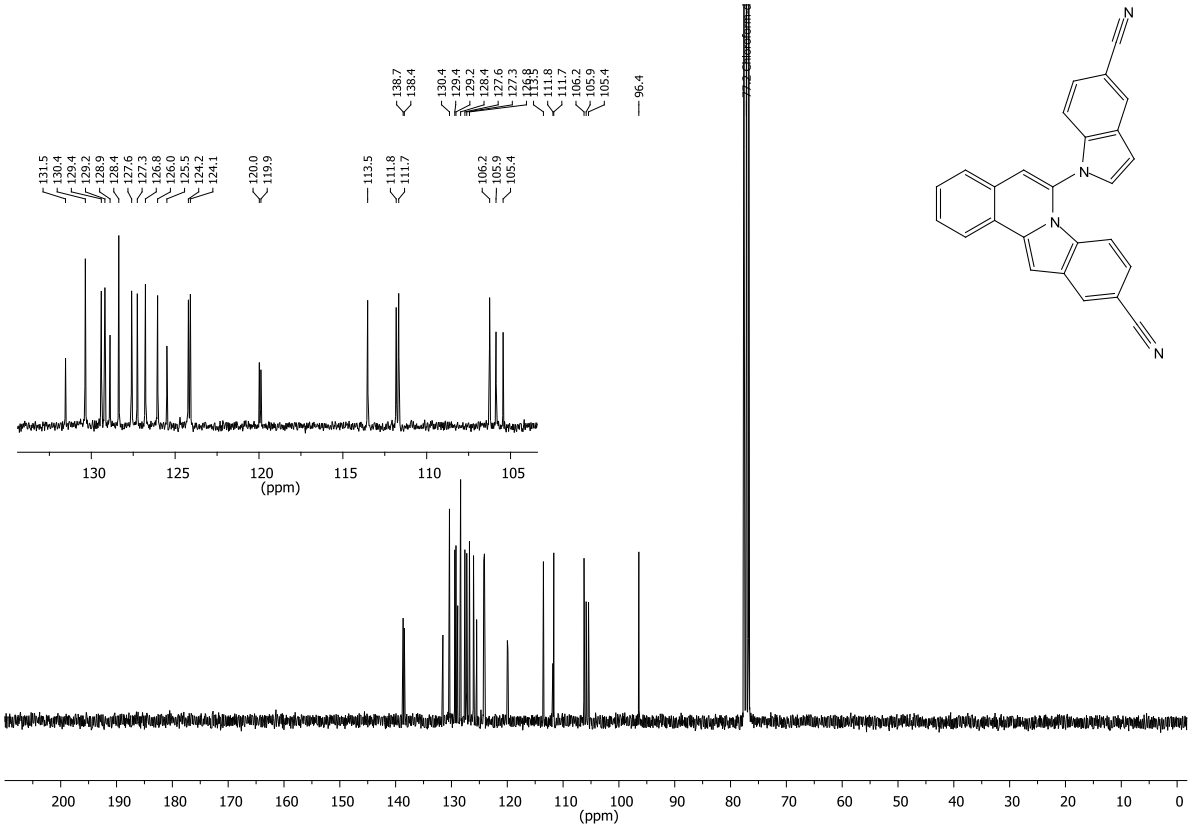
^{13}C NMR (75 MHz, $CDCl_3$) of **4c**.



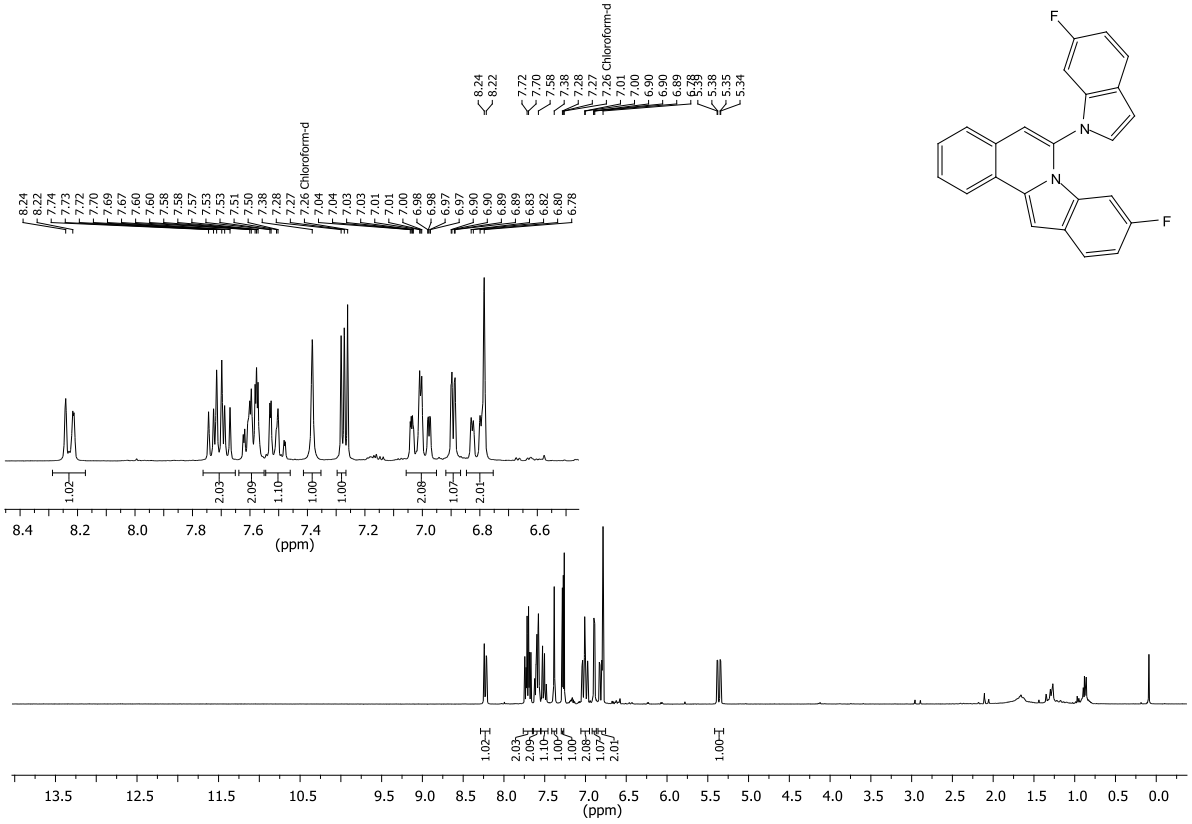
^{1}H NMR (300 MHz, $CDCl_3$) of **4d**.



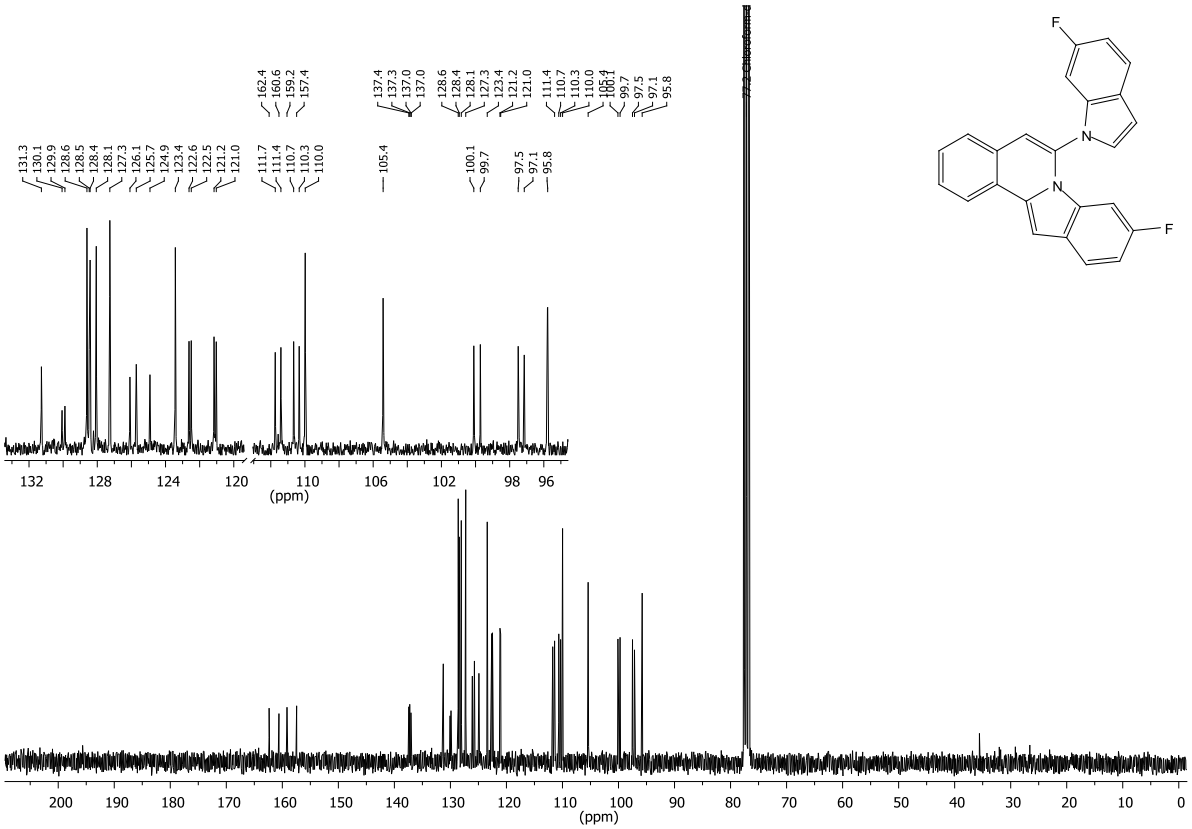
^{13}C NMR (75 MHz, $CDCl_3$) of **4d**.



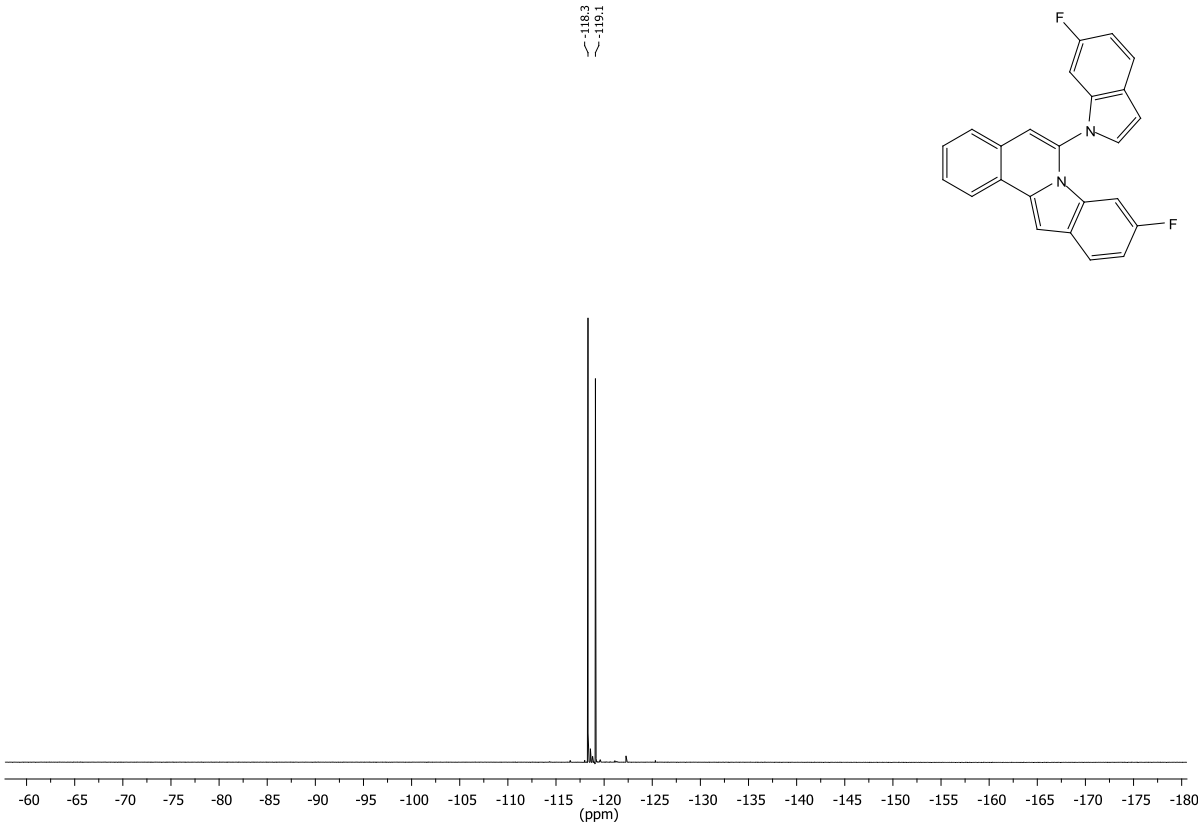
^{1}H NMR (300 MHz, $CDCl_3$) of **4e**



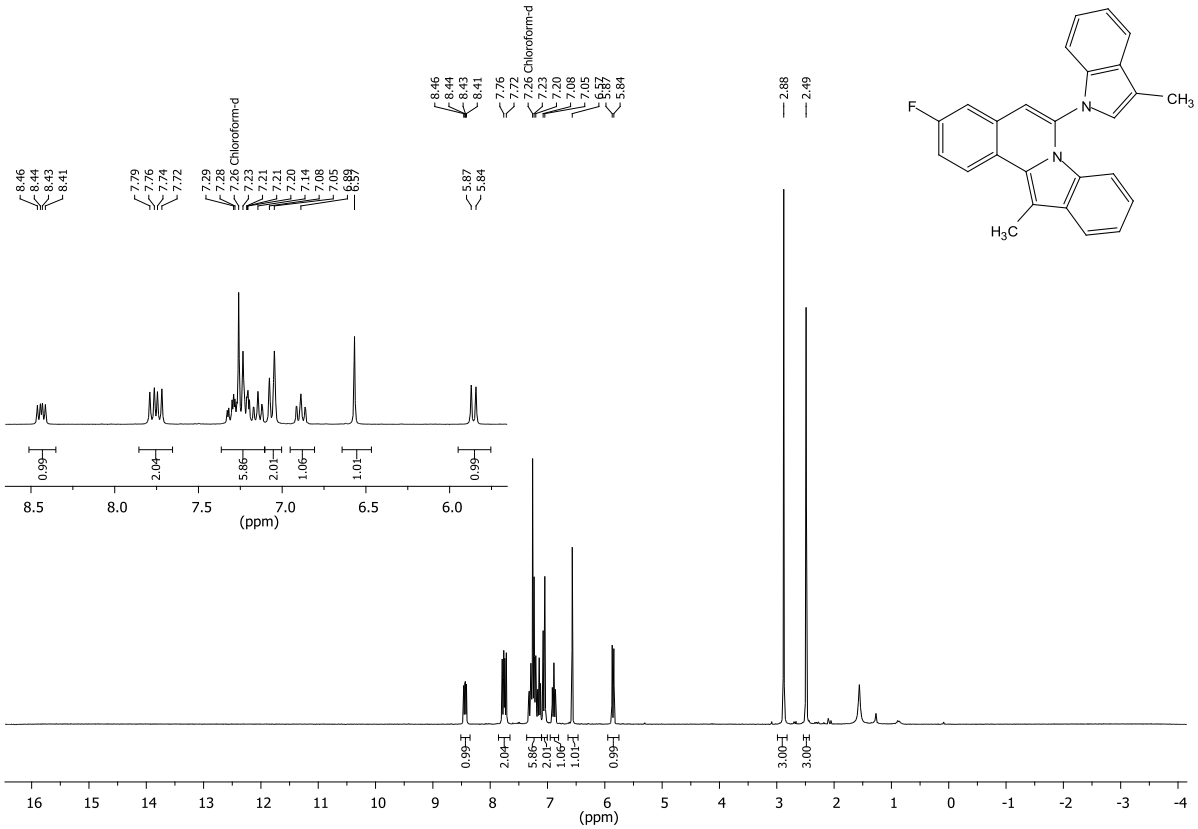
^{13}C NMR (75 MHz, $CDCl_3$) of **4e**.



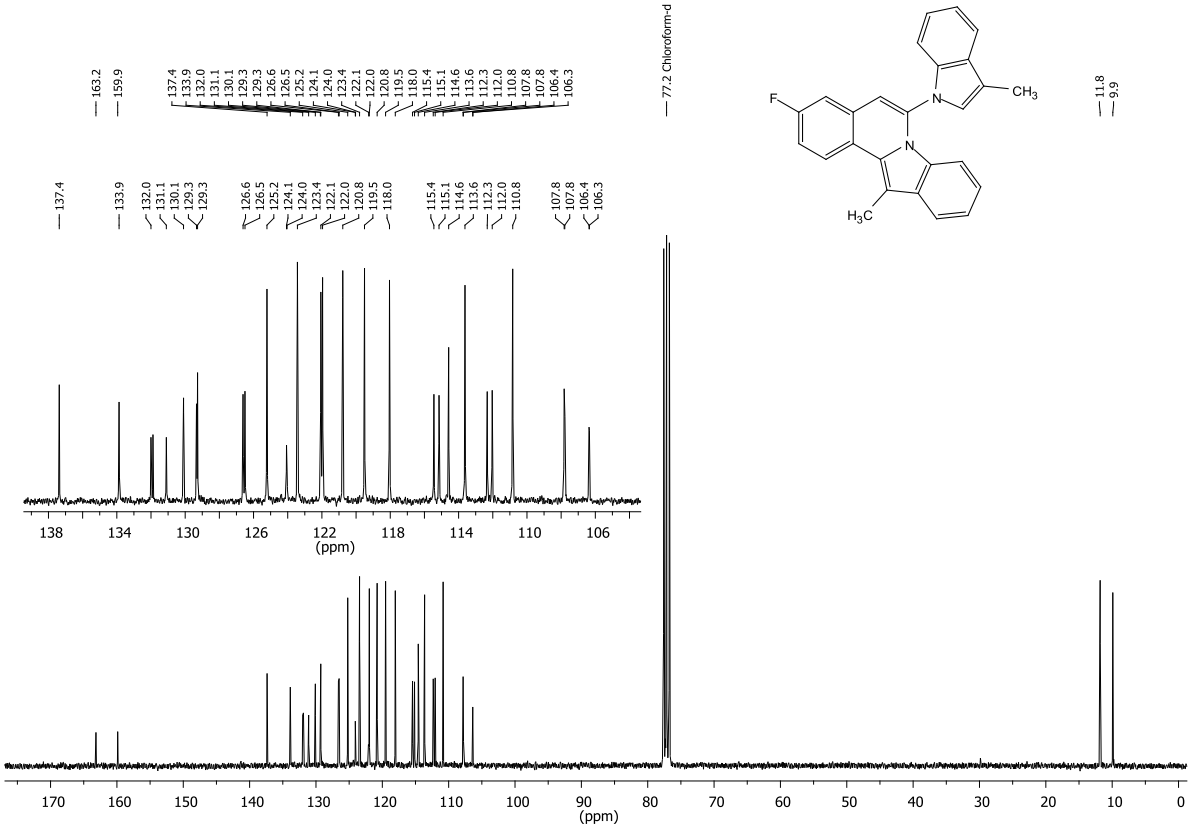
^{19}F NMR (282 MHz, $CDCl_3$) of **4e**.



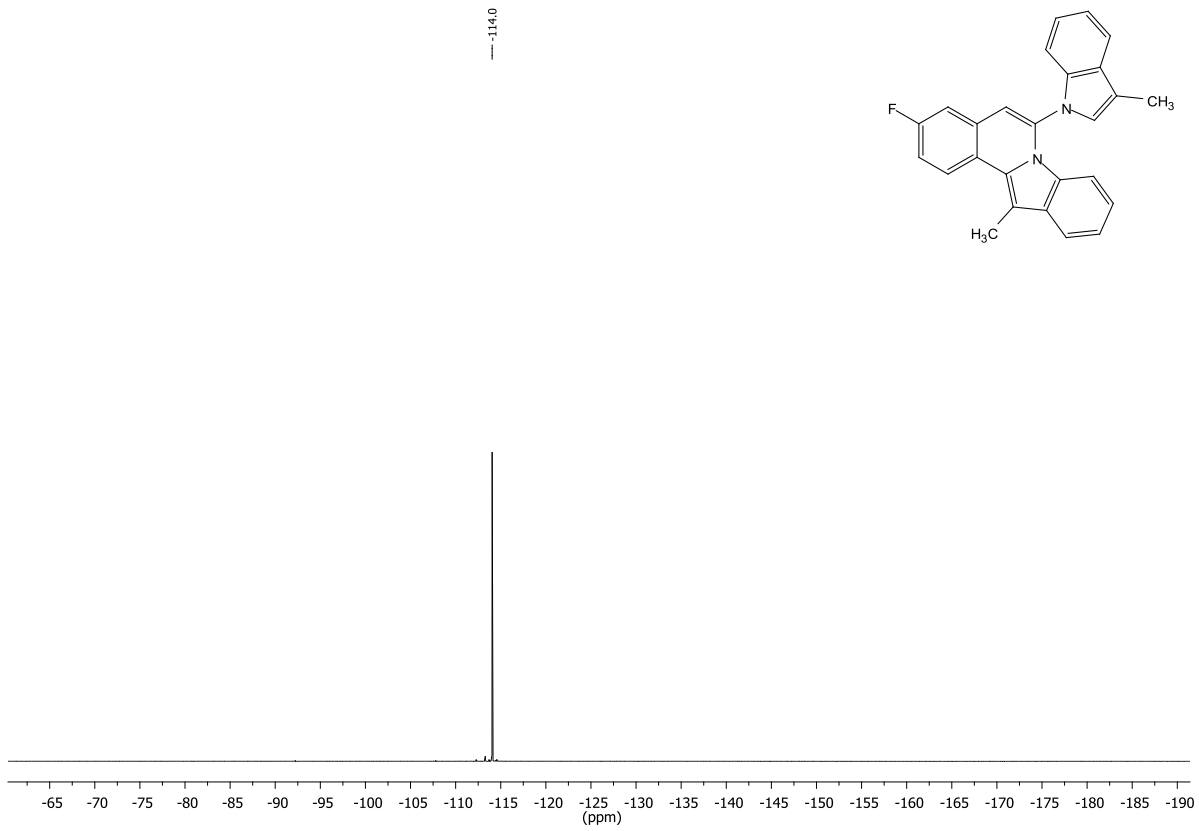
^{1}H NMR (300 MHz, $CDCl_3$) of **4f**.



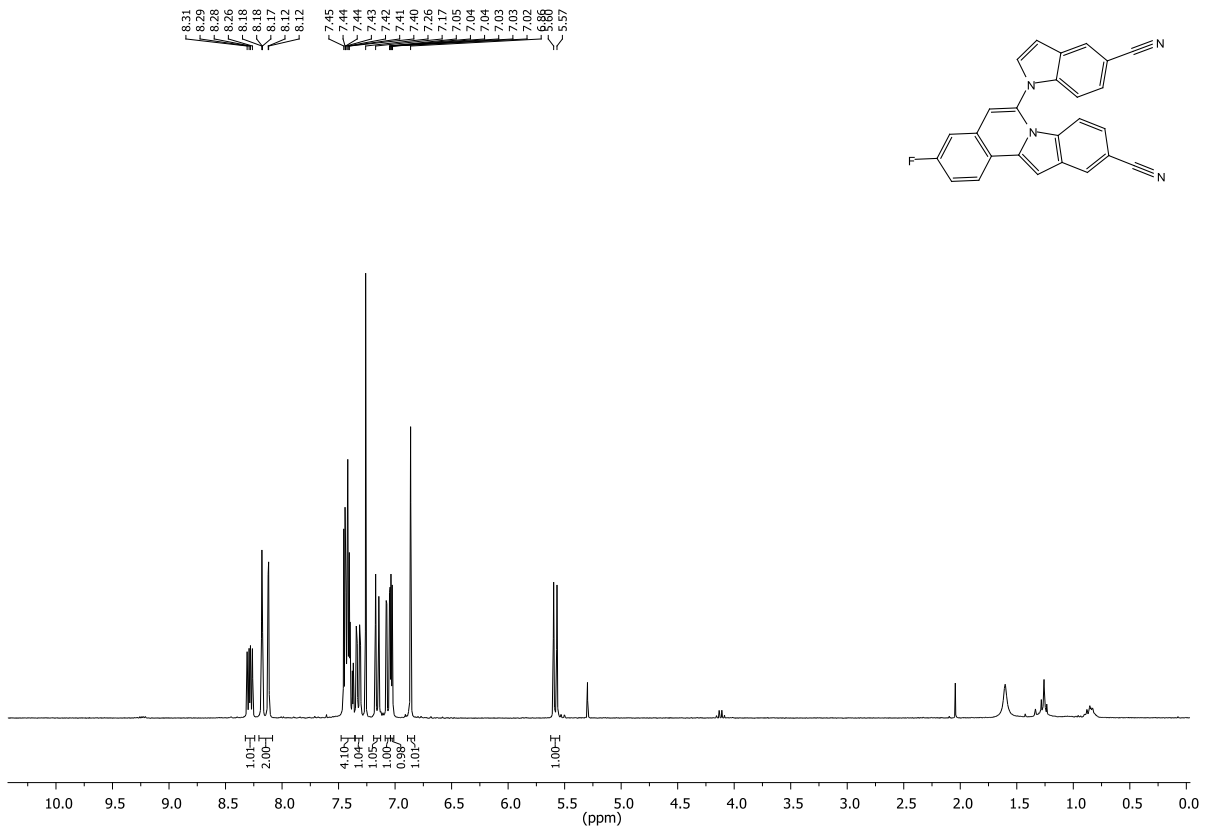
^{13}C NMR (75 MHz, $CDCl_3$) of **4f**.



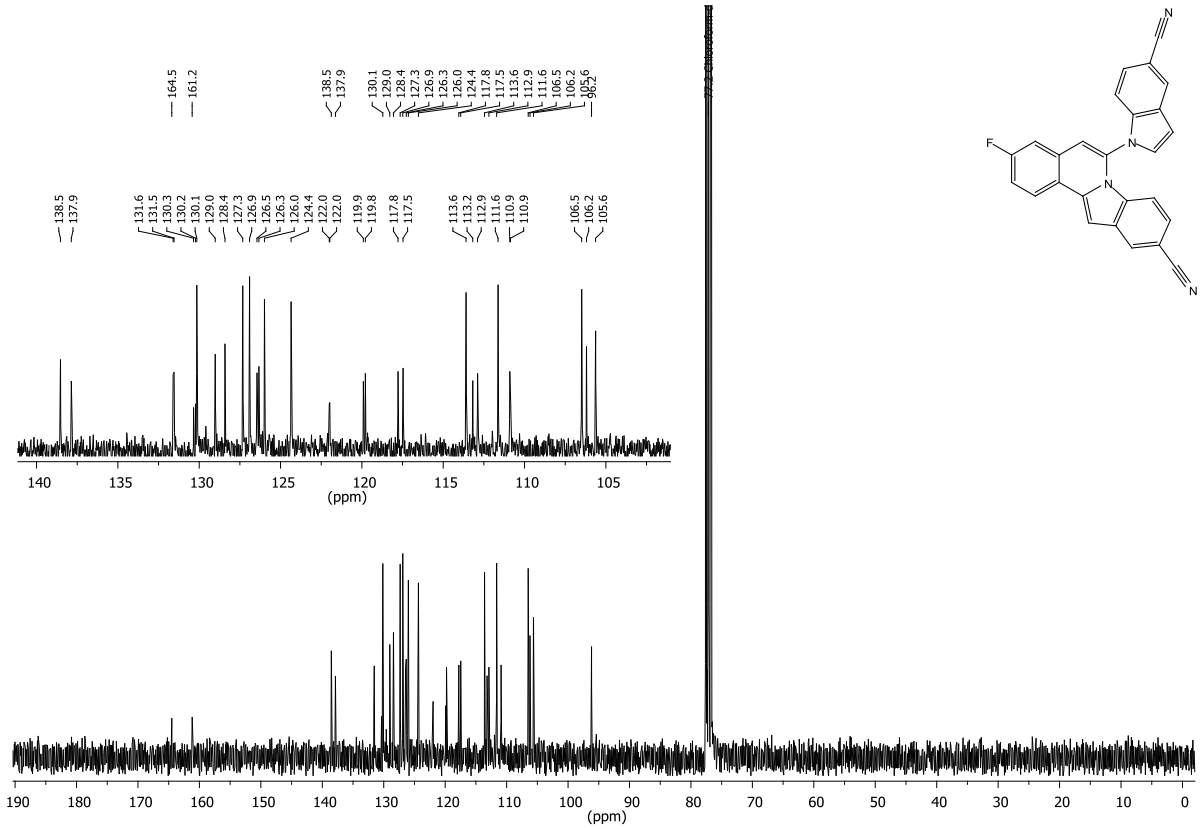
^{19}F NMR (282 MHz, $CDCl_3$) of **4f**.



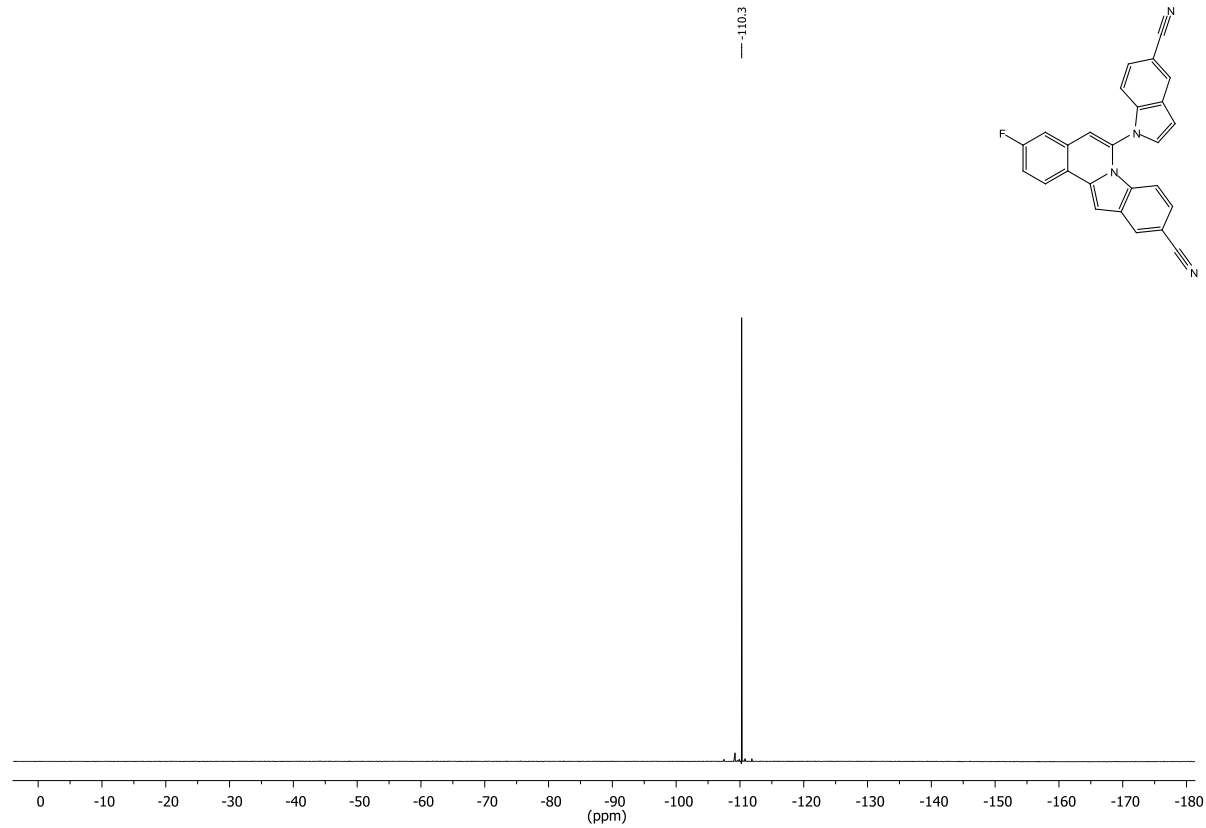
[1]H NMR (300 MHz, $CDCl_3$) of **4g**.



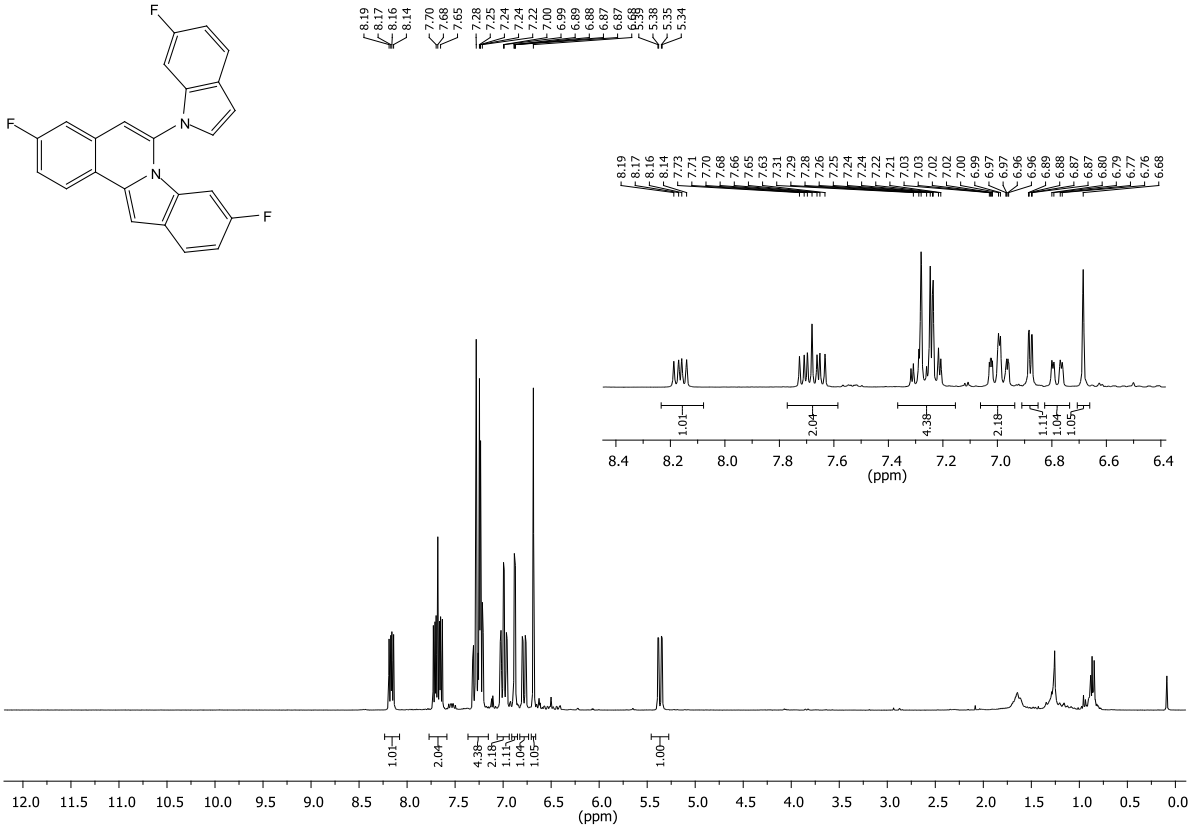
^{13}C NMR (75 MHz, $CDCl_3$) of **4g**.



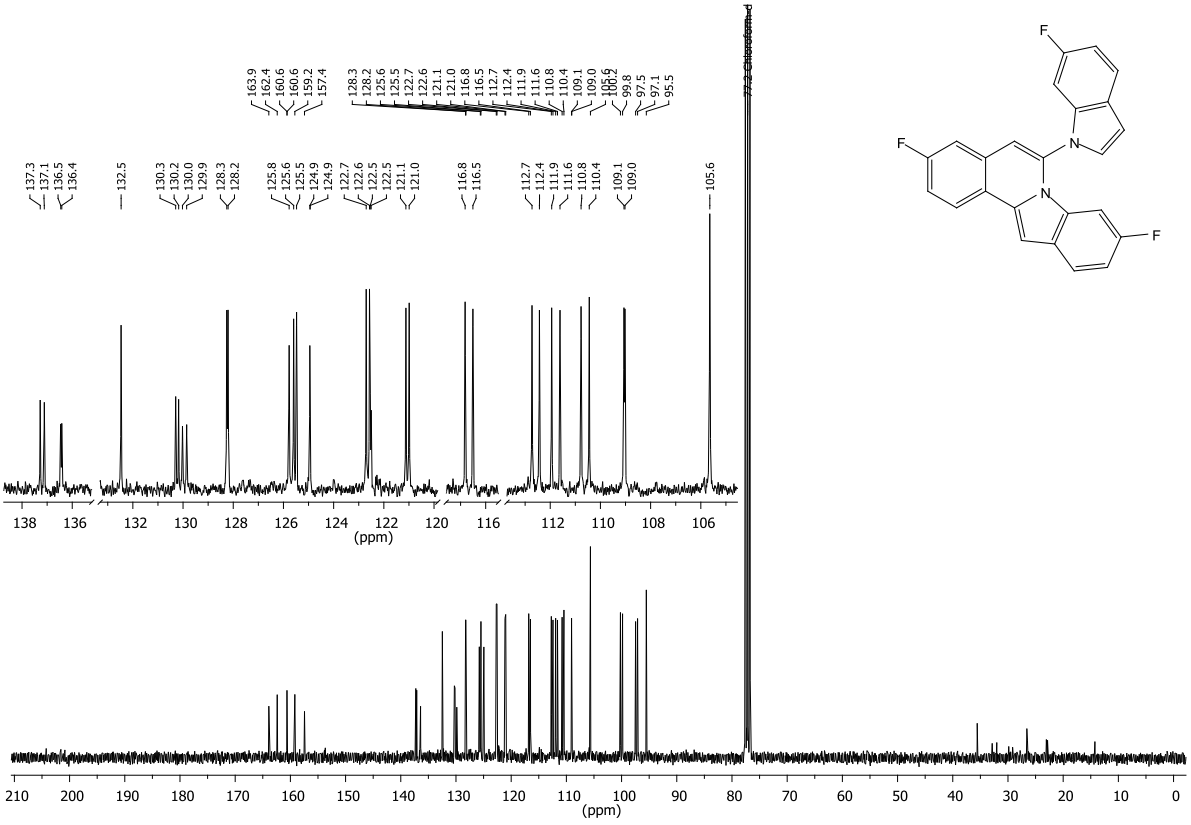
^{19}F NMR (282 MHz, $CDCl_3$) of **4g**.



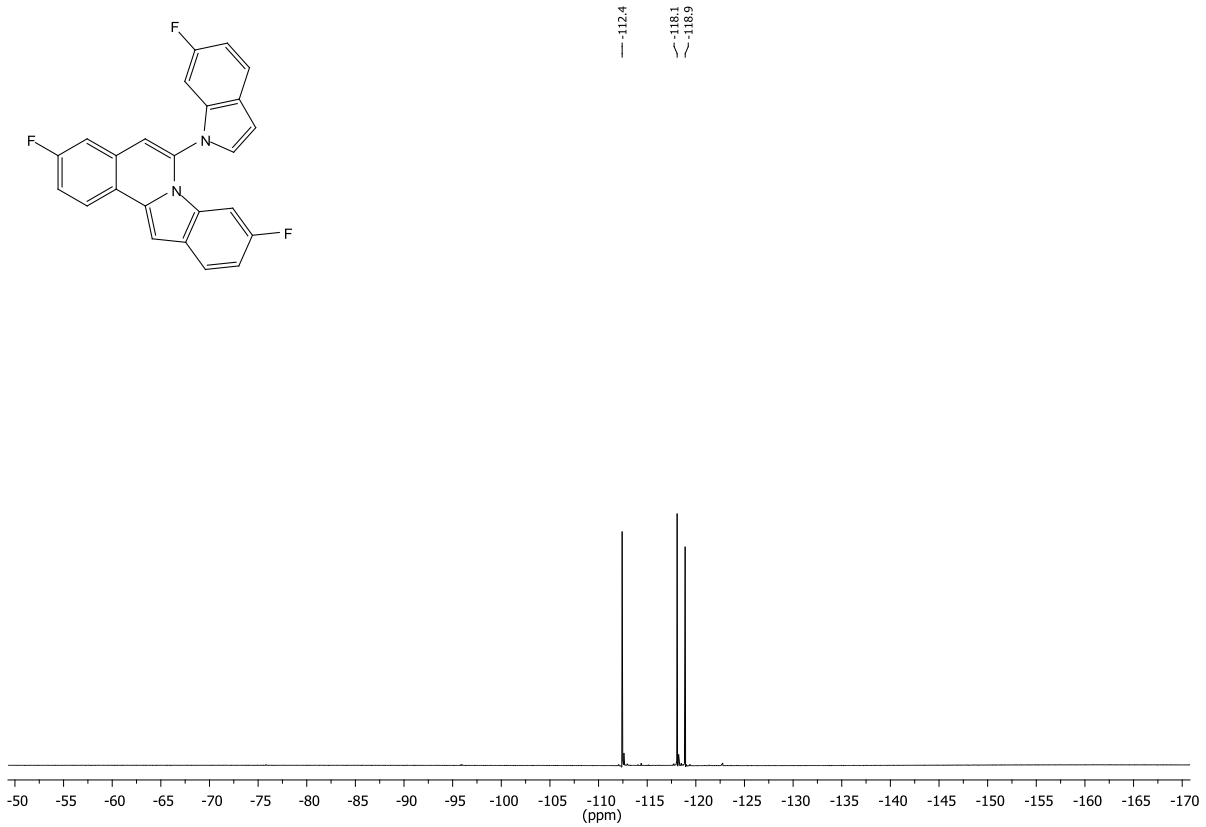
^{1}H NMR (300 MHz, $CDCl_3$) of **4h**.



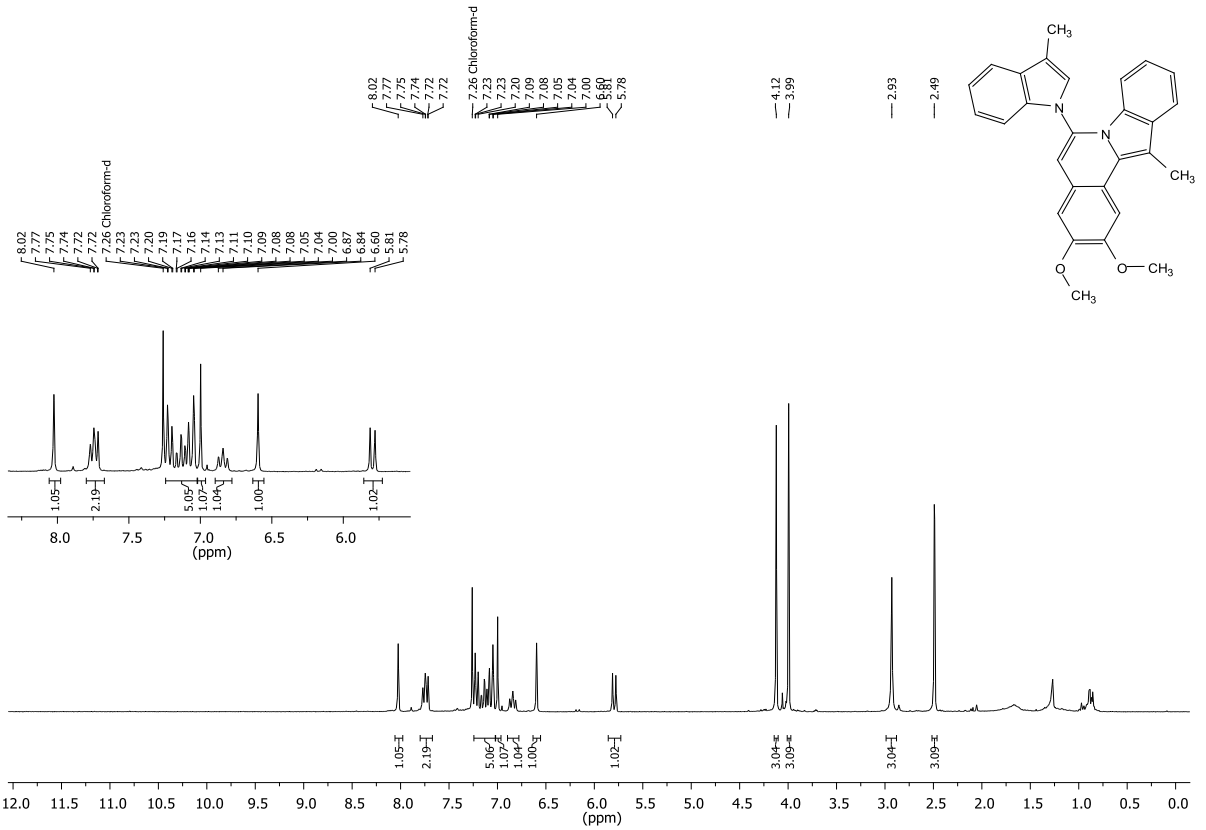
^{13}C NMR (75 MHz, $CDCl_3$) of **4h**.



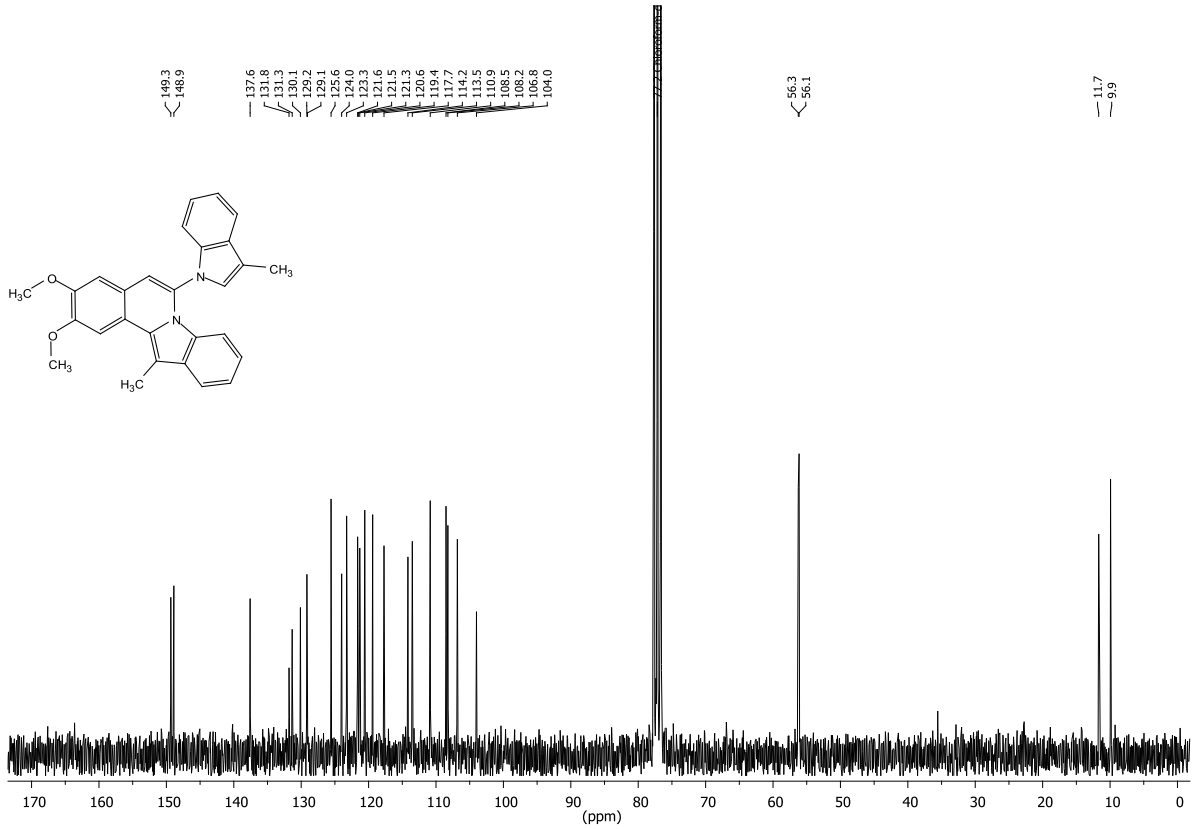
^{19}F NMR (282 MHz, $CDCl_3$) of **4h**.



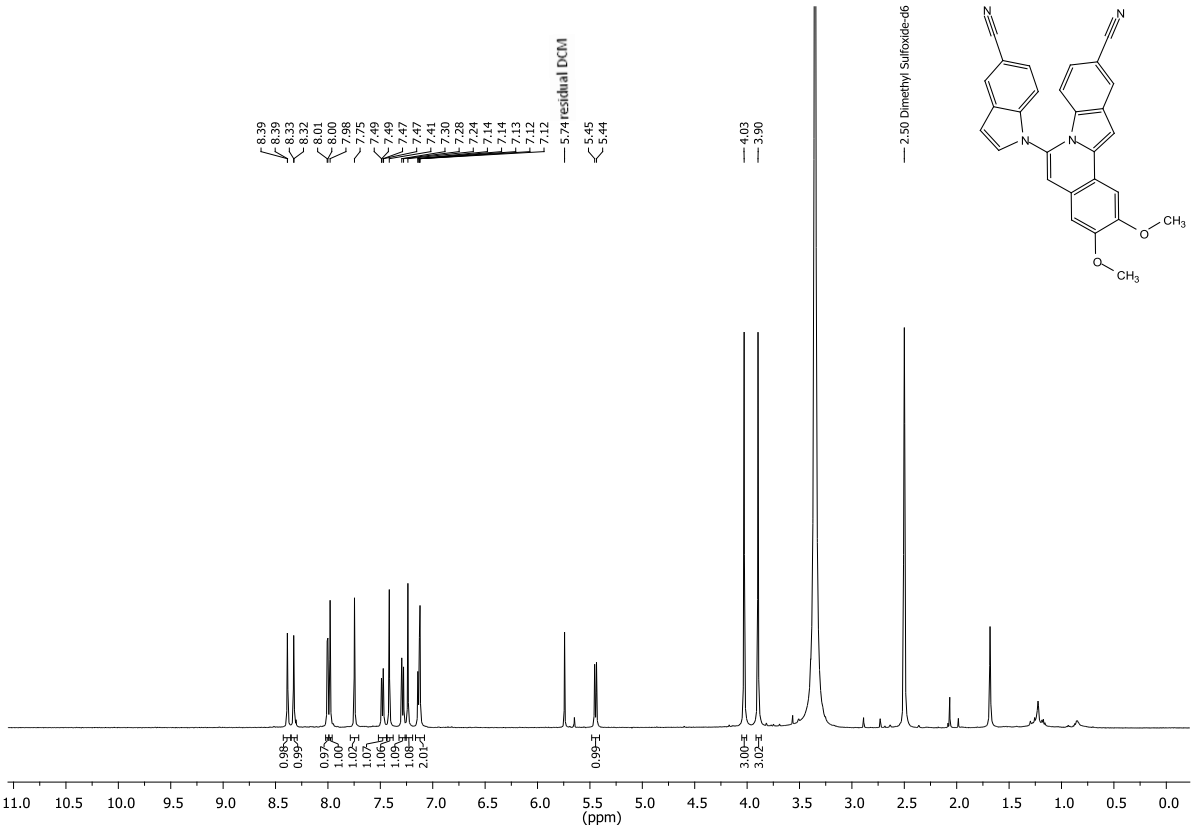
^{1}H NMR (250 MHz, $CDCl_3$) of **4i**.



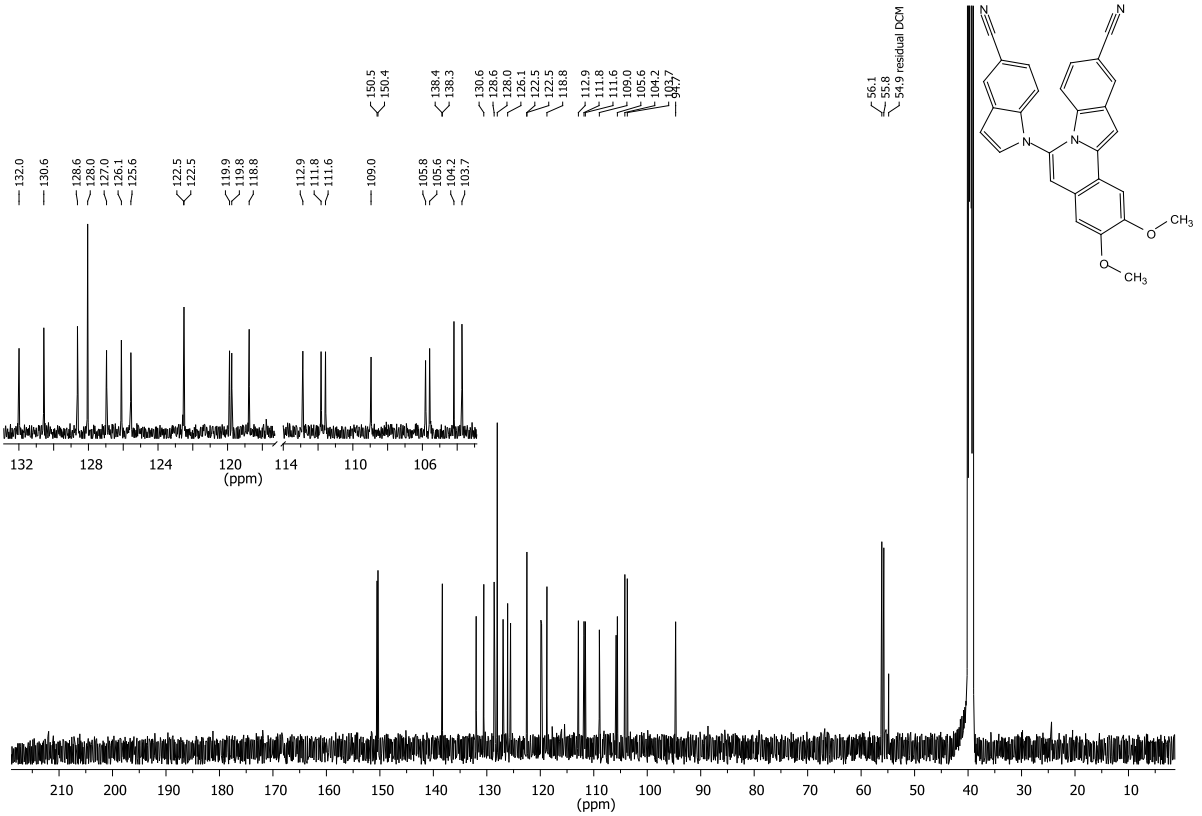
^{13}C NMR (63 MHz, $CDCl_3$) of **4i**.



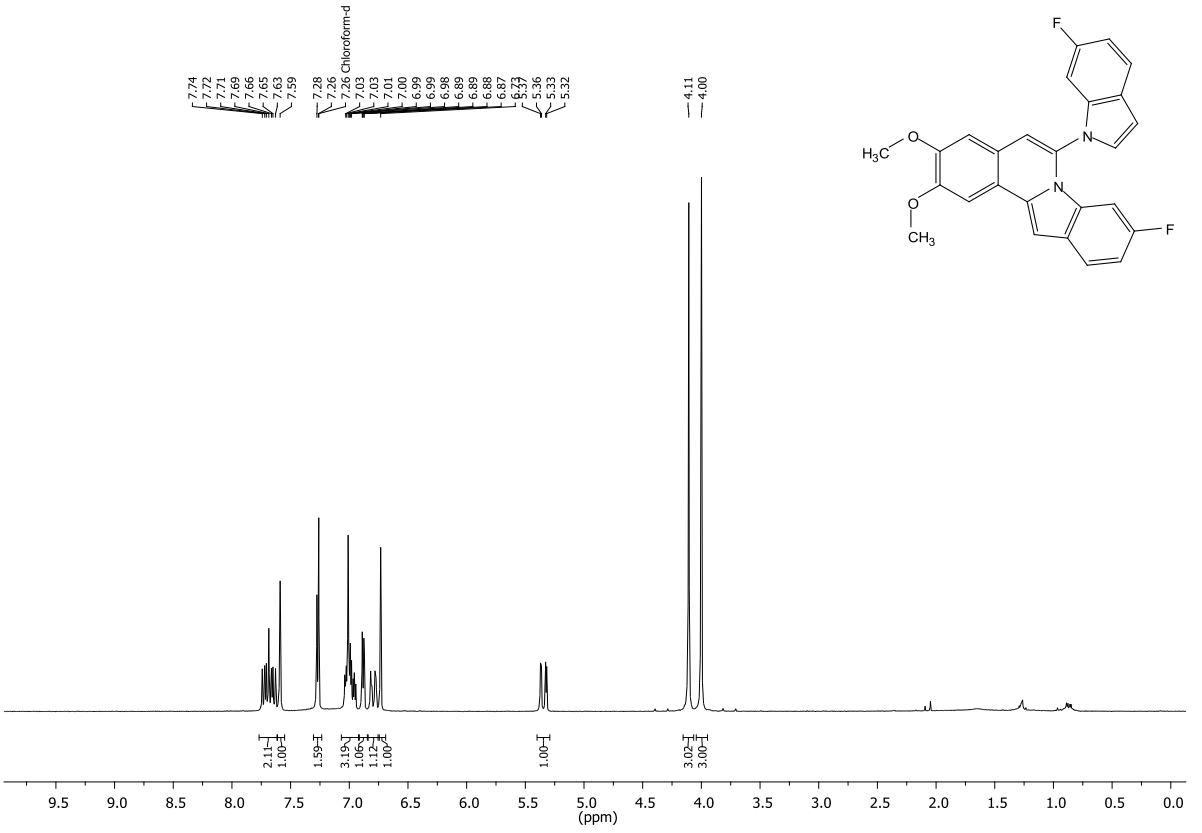
^{1}H NMR (500 MHz, DMSO-d_6, 30 °C) of **4j**.



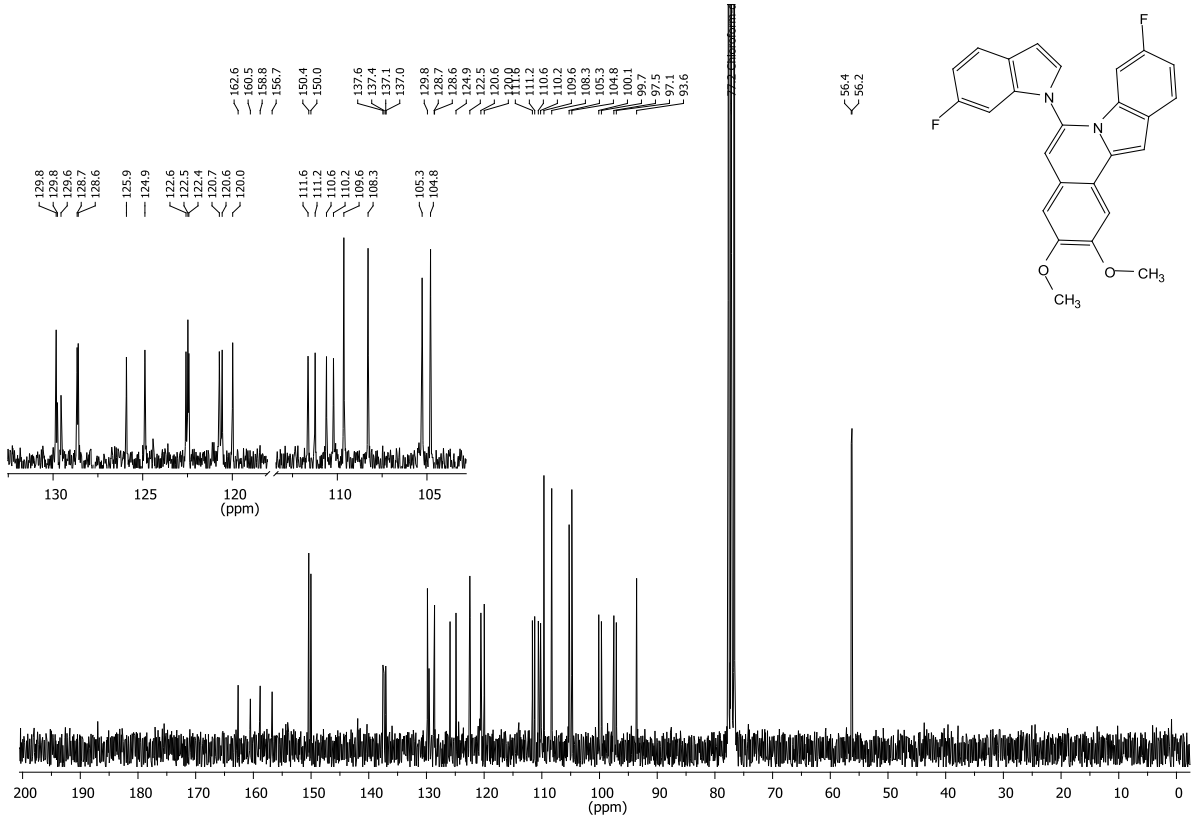
^{13}C NMR (126 MHz, DMSO-d_6, 30 °C) of **4j**.



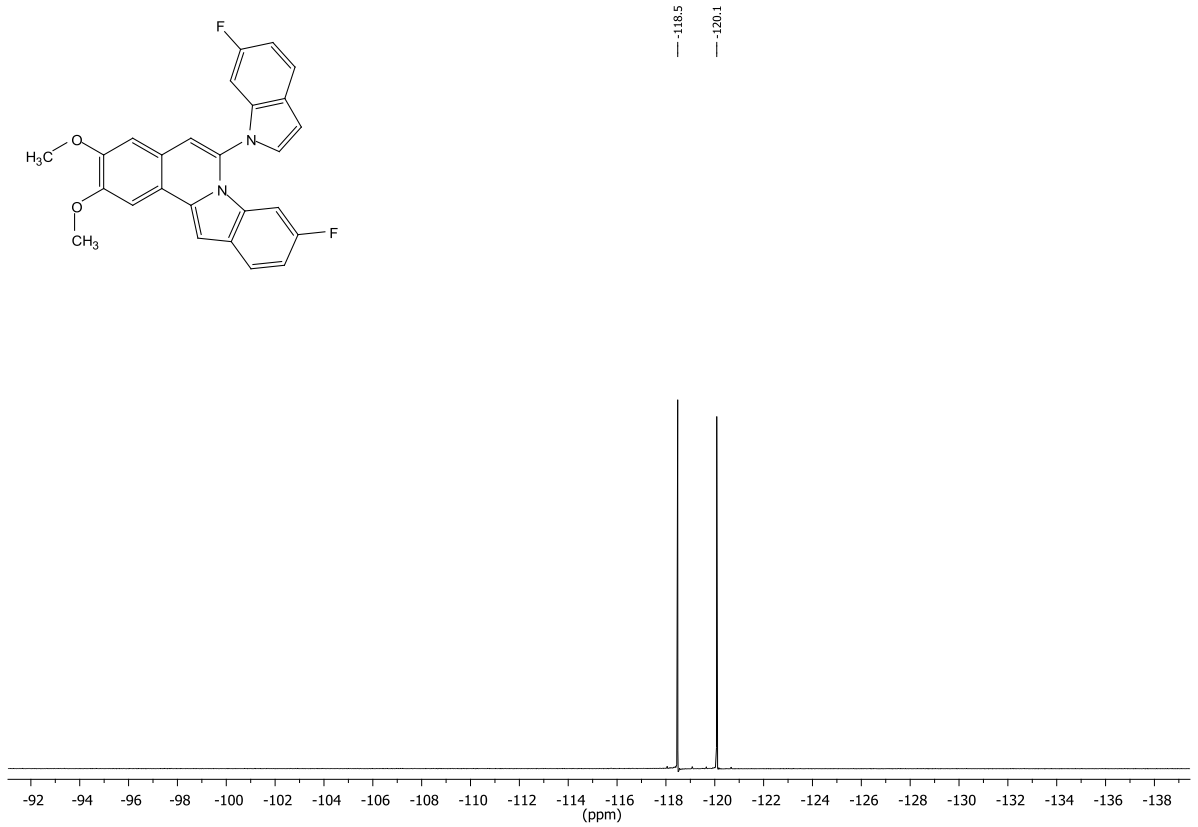
^{1}H NMR (250 MHz, $CDCl_3$) of **4k**.



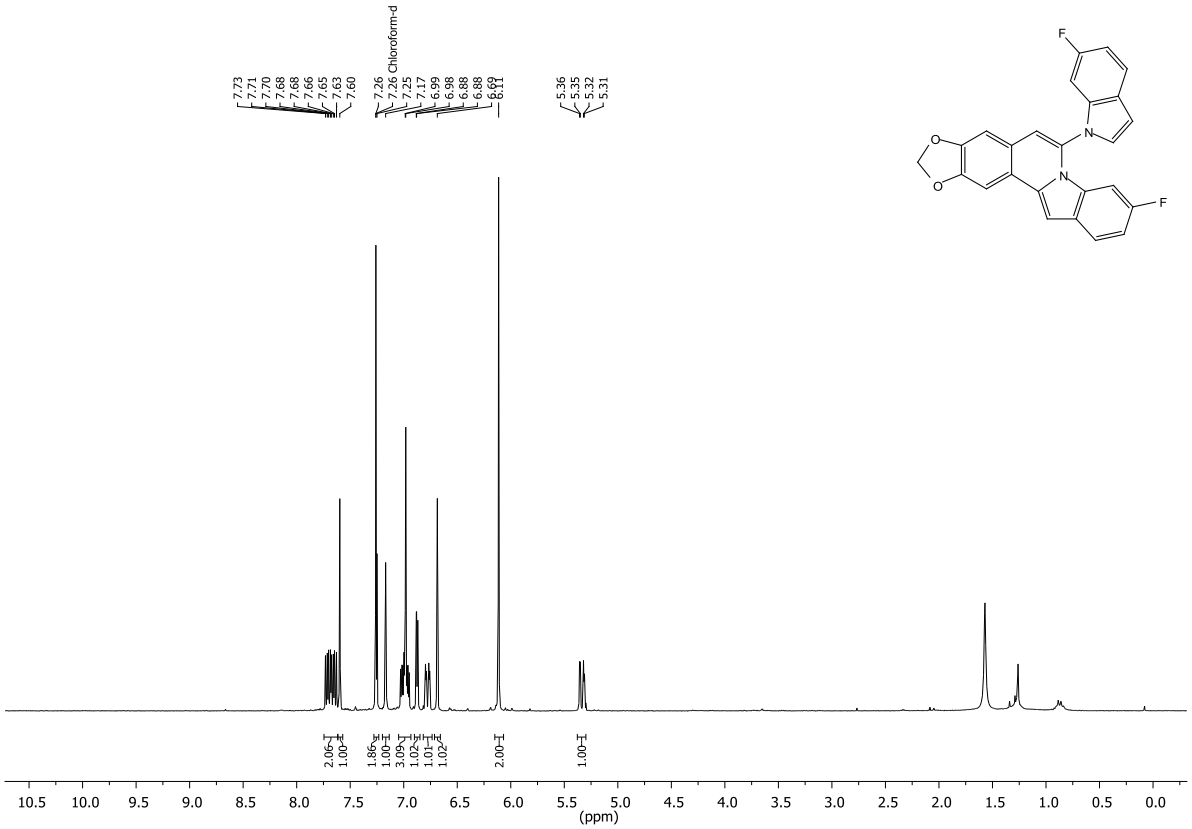
^{13}C NMR (63 MHz, $CDCl_3$) of **4k**.



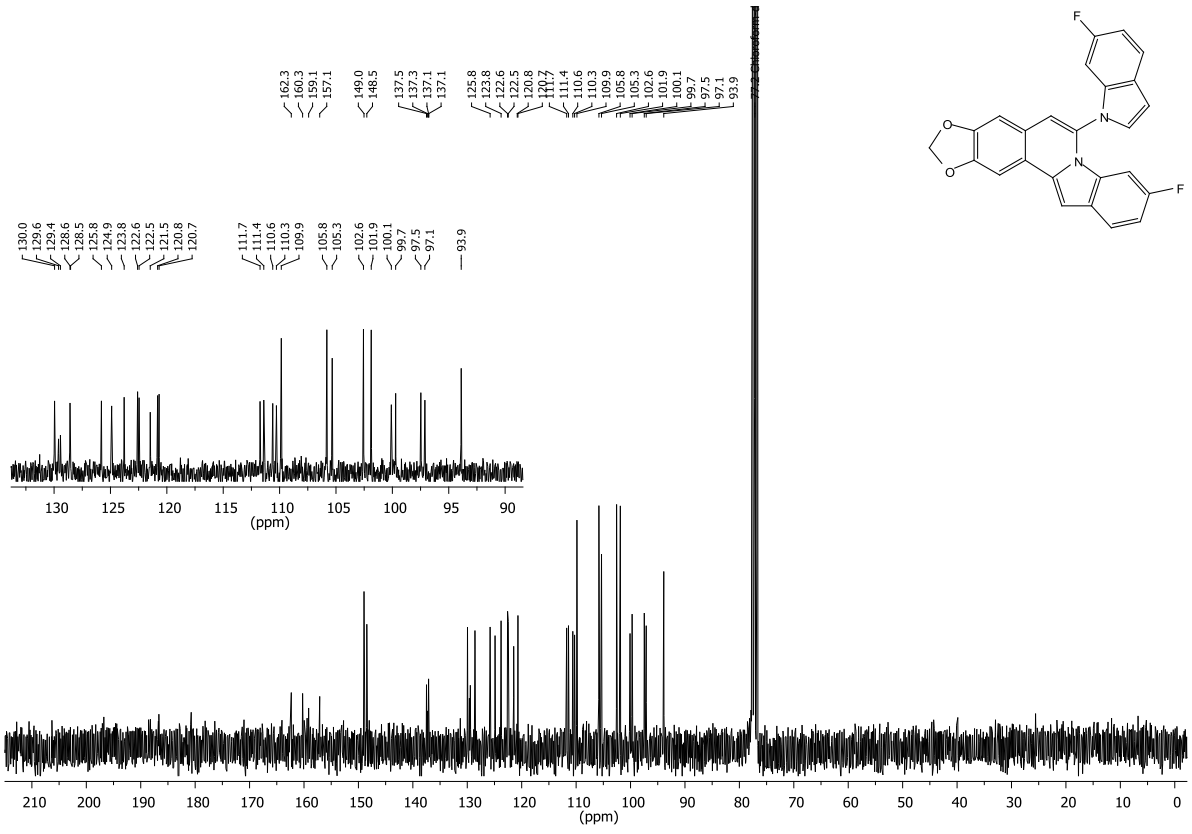
^{19}F NMR (235 MHz, $CDCl_3$) of **4k**.



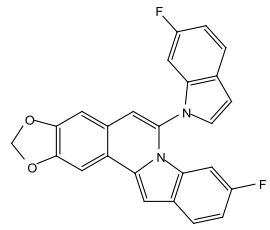
^{1}H NMR (300 MHz, $CDCl_3$) of **4l**.



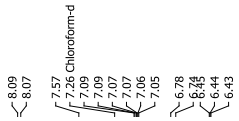
^{13}C NMR (75 MHz, $CDCl_3$) of **4l**.

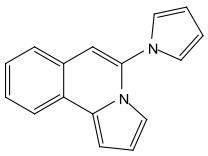


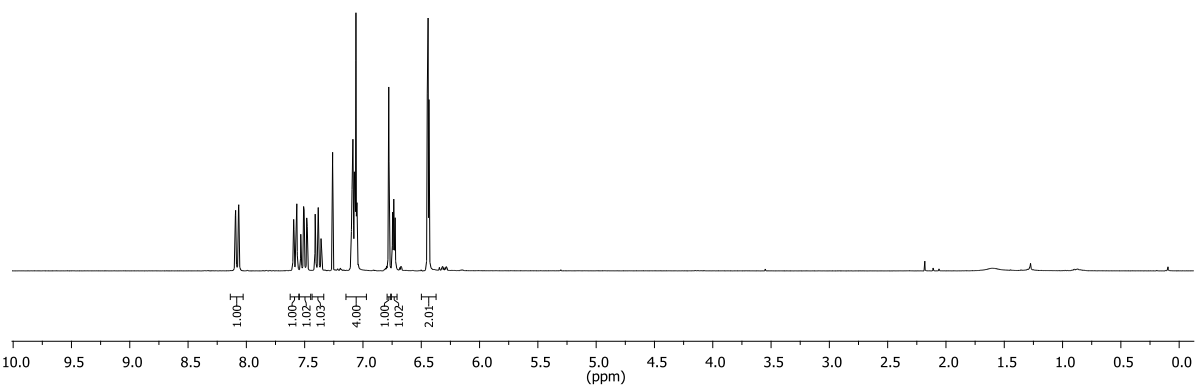
^{19}F NMR (282 MHz, $CDCl_3$) of **4l**.



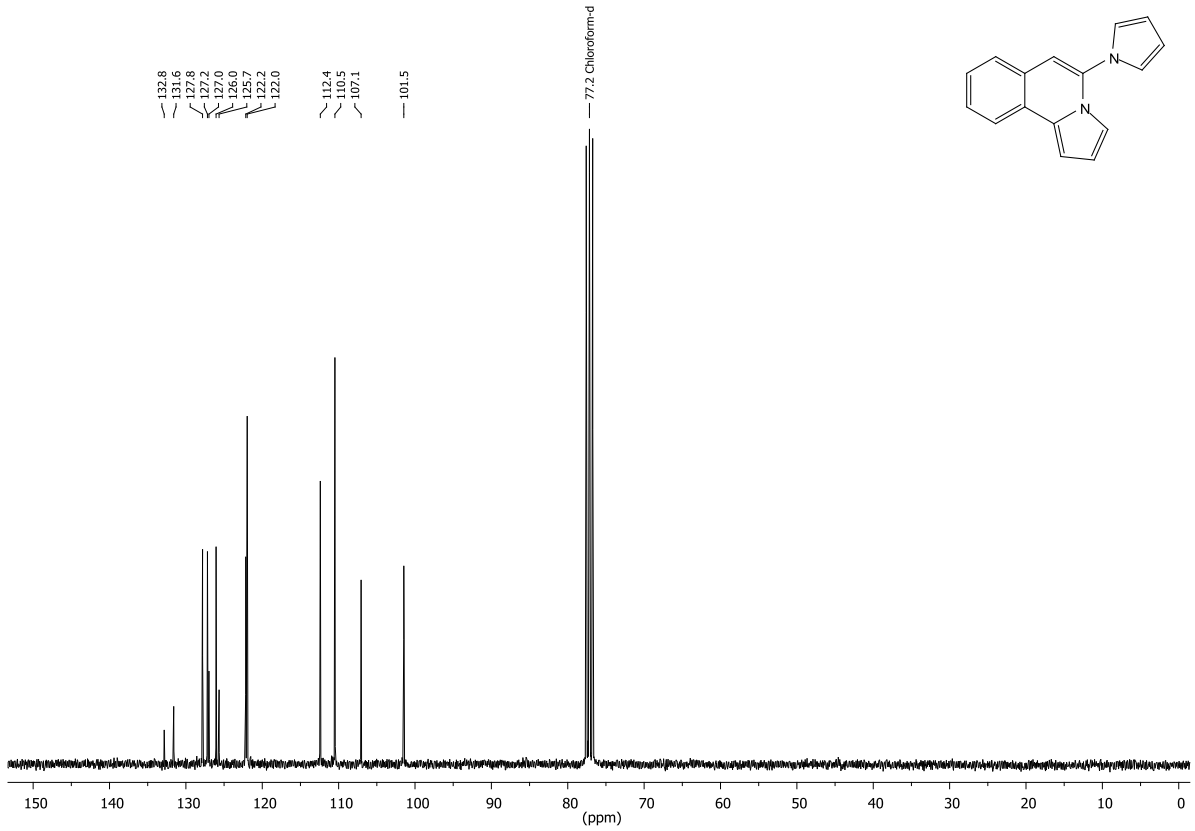
^{1}H NMR (300 MHz, $CDCl_3$) of **4m**.



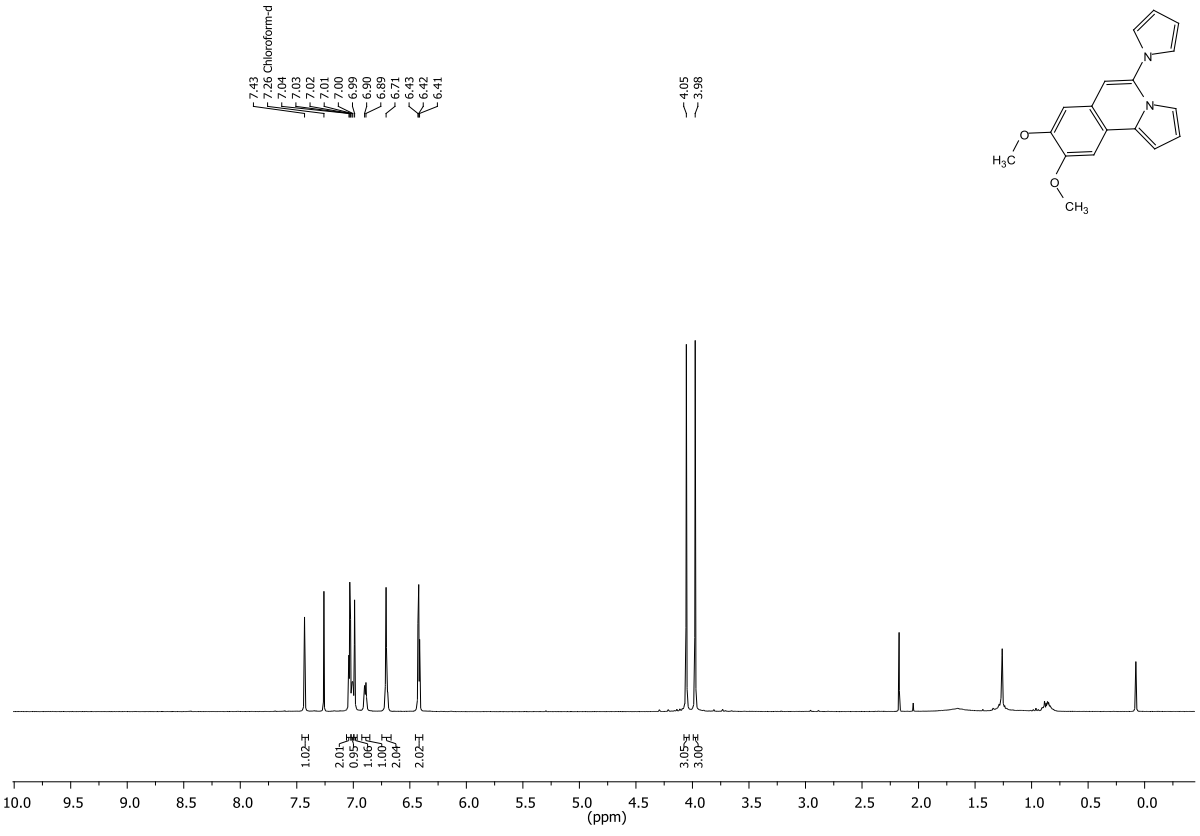




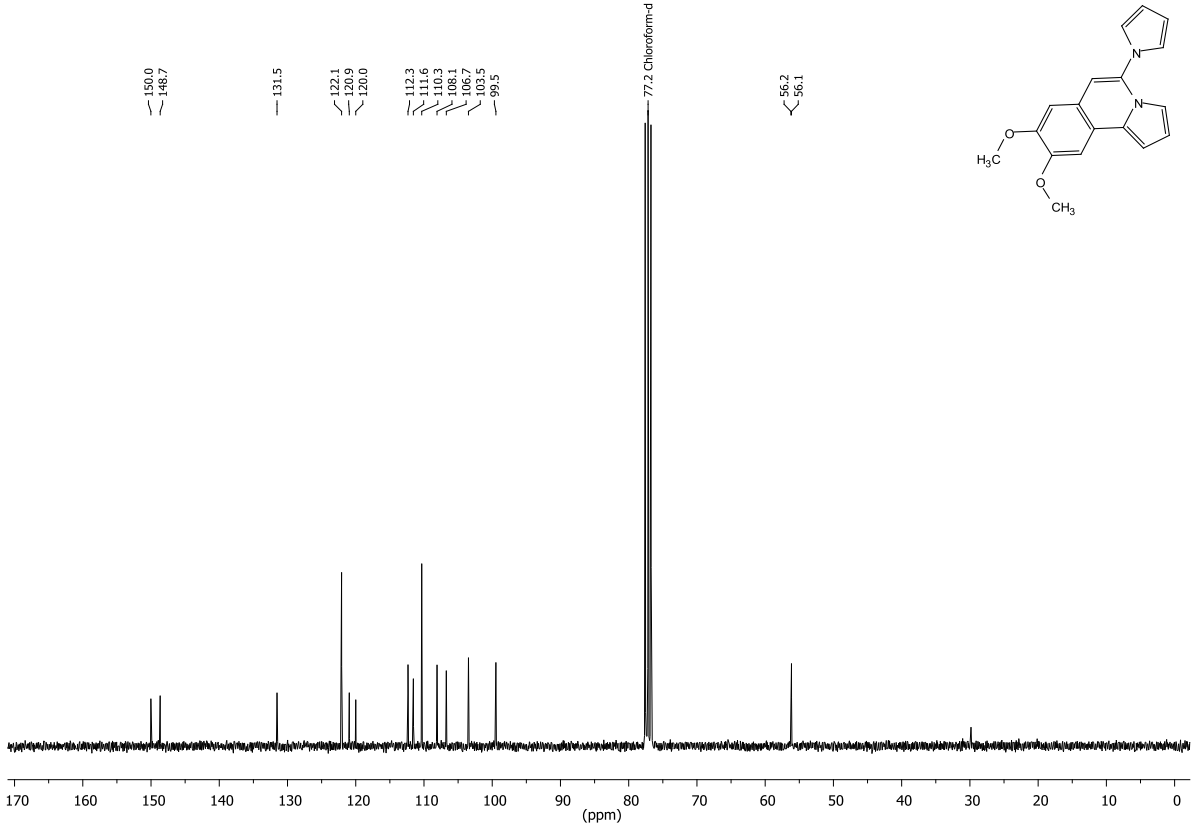
^{13}C NMR (75 MHz, $CDCl_3$) of **4m**.



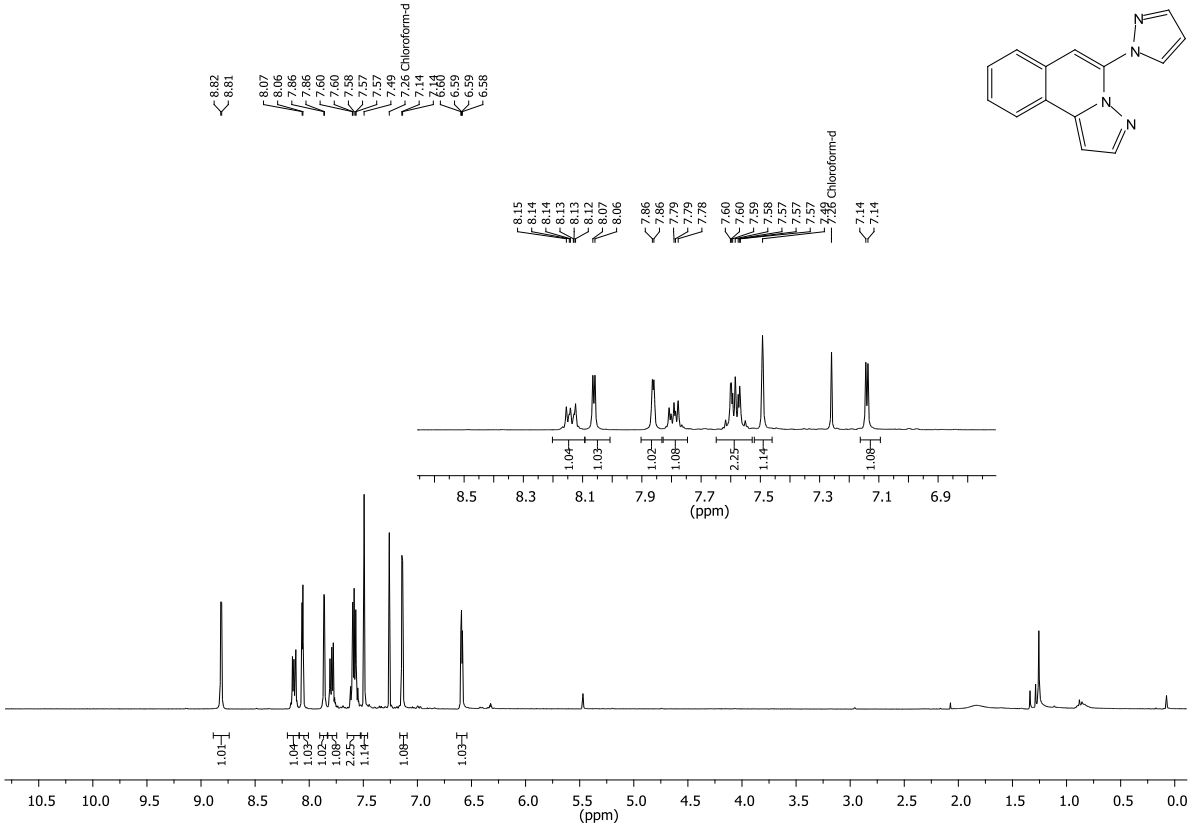
^{1}H NMR (300 MHz, $CDCl_3$) of **4n**.



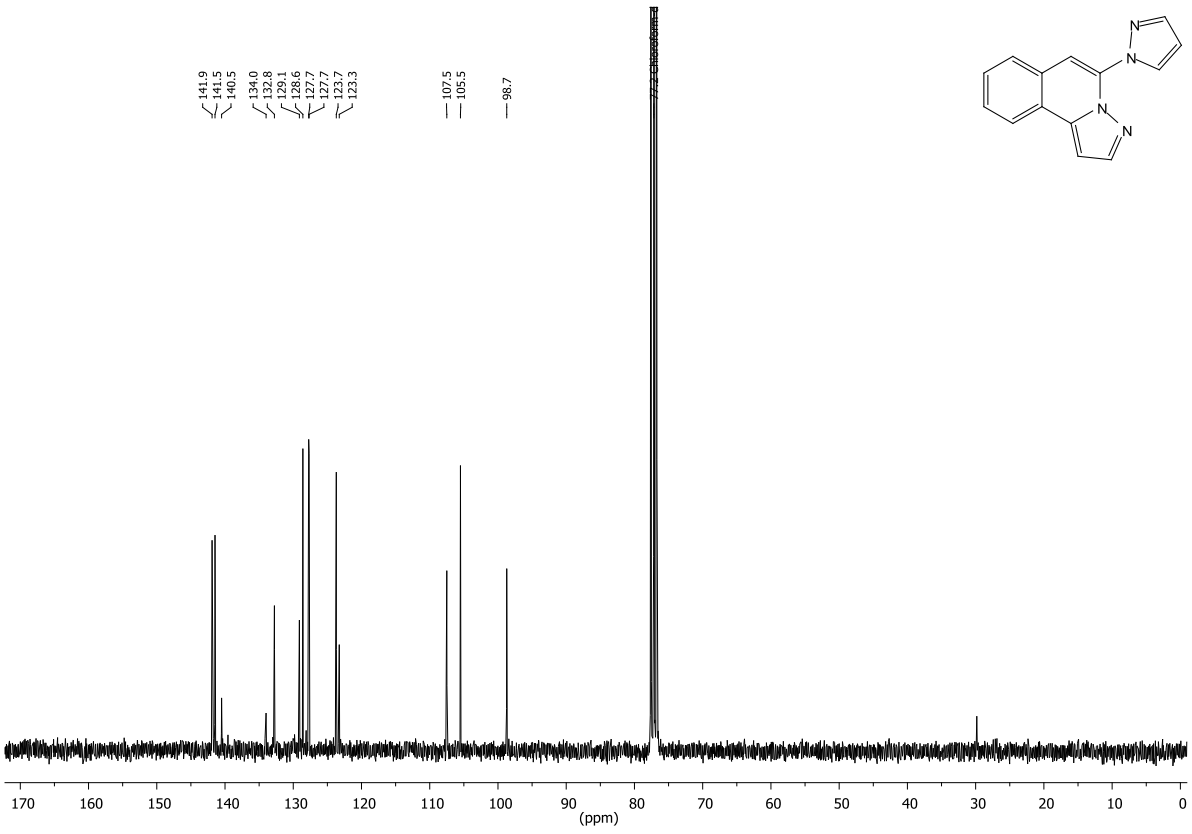
^{13}C NMR (75 MHz, $CDCl_3$) of **4n**.



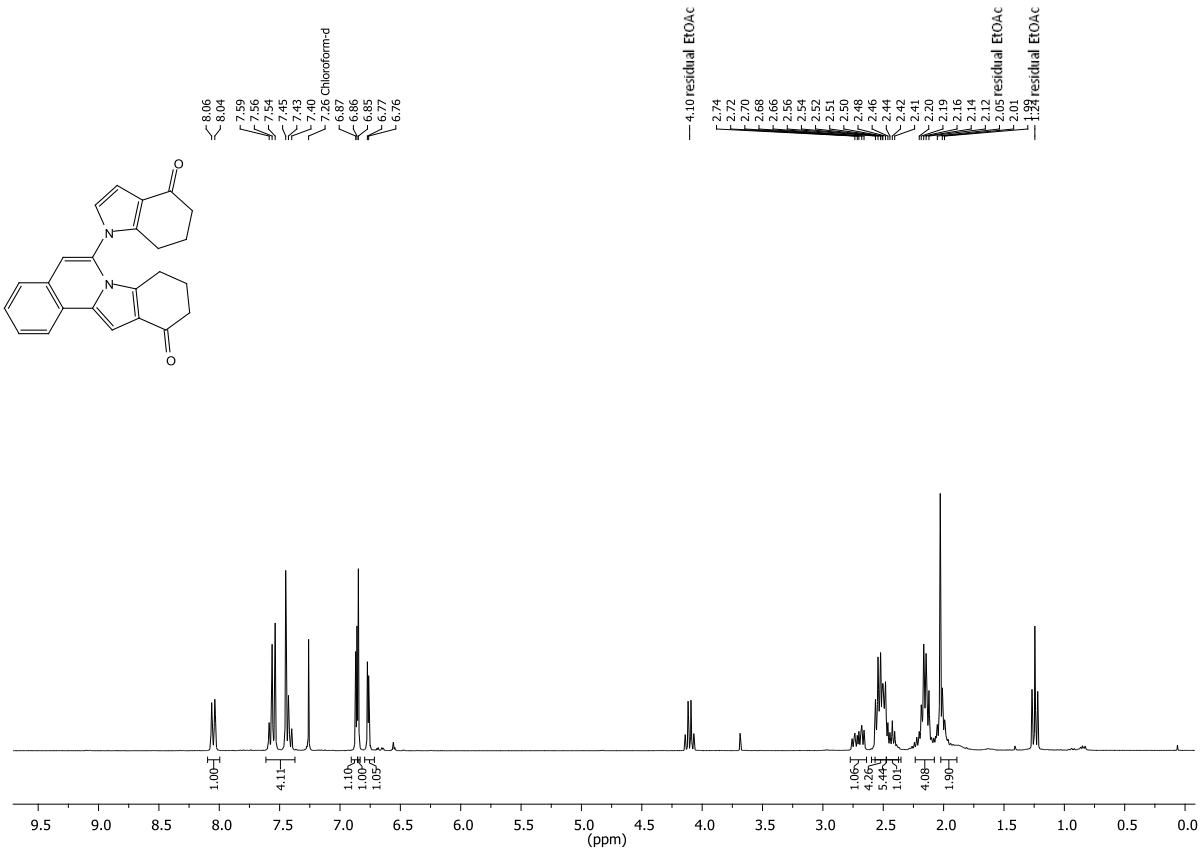
^{1}H NMR (300 MHz, $CDCl_3$) of **4o**.



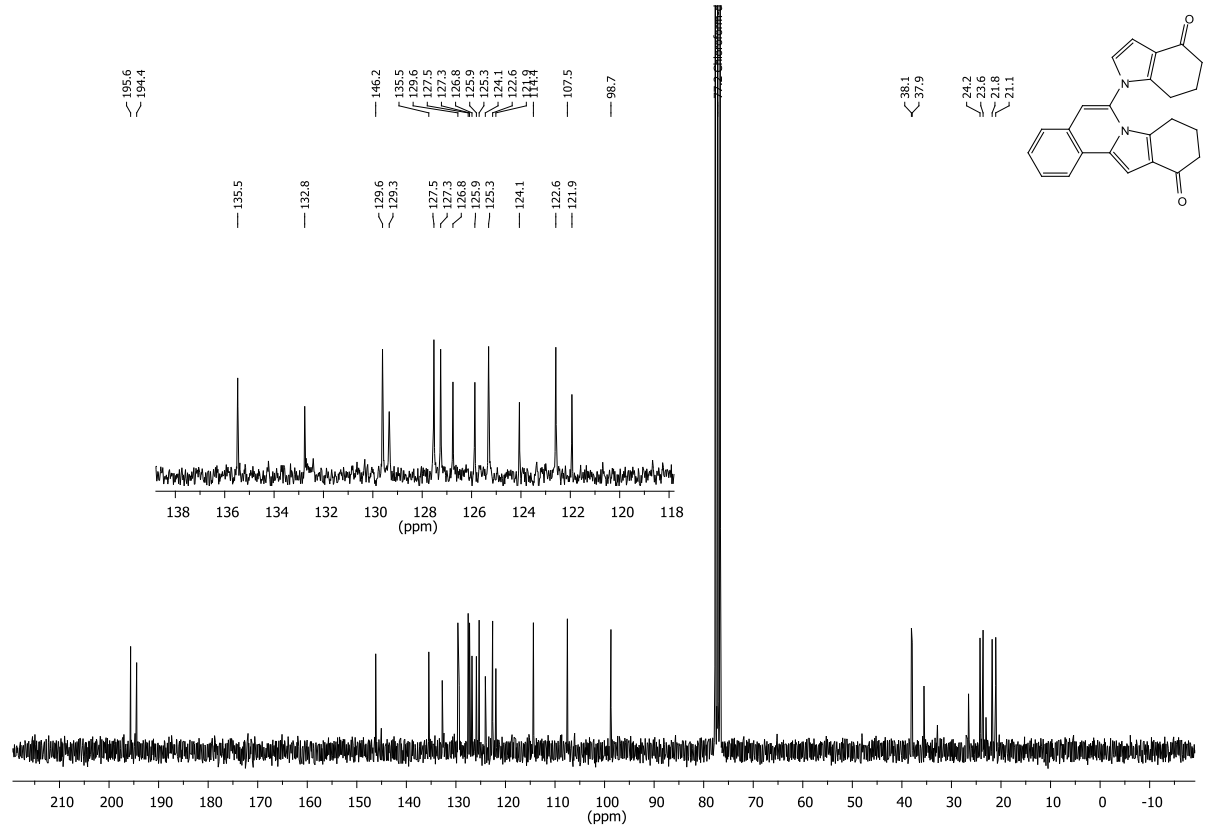
^{13}C NMR (75 MHz, $CDCl_3$) of **4o**.



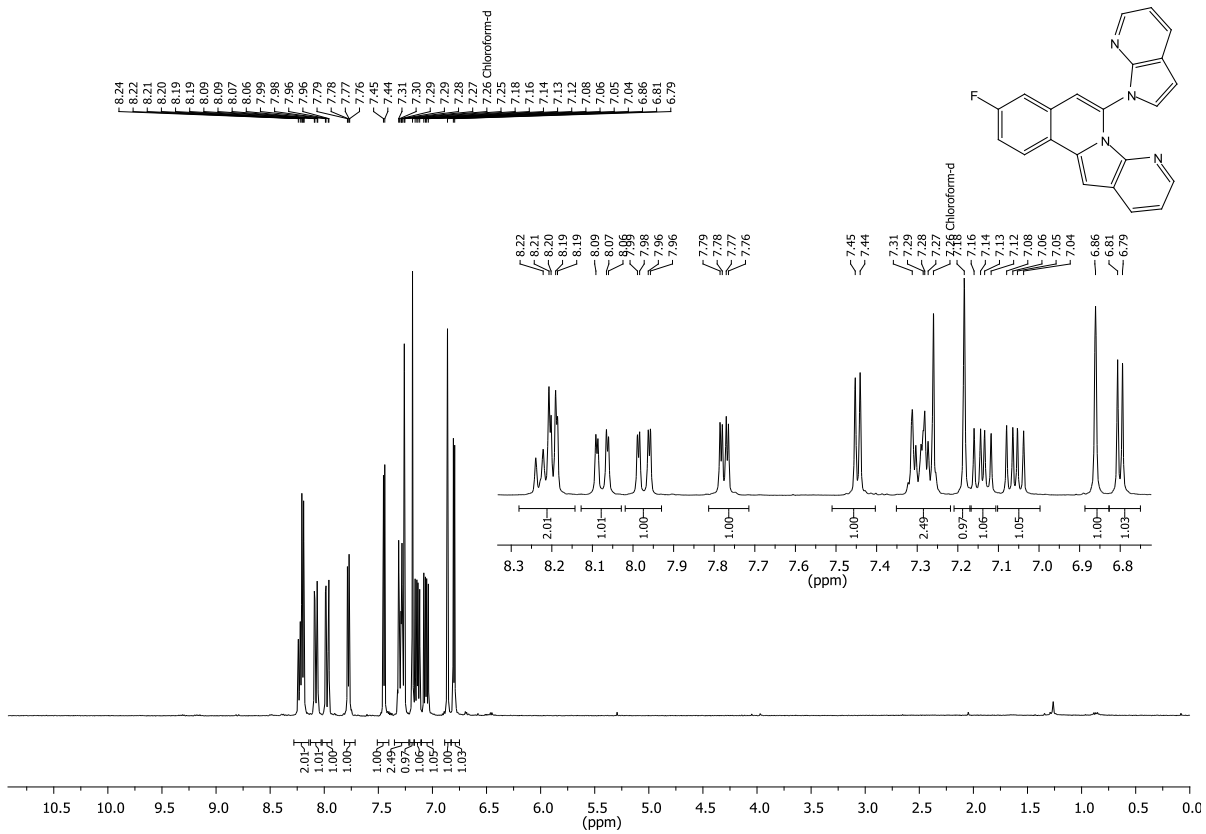
^{1}H NMR (300 MHz, $CDCl_3$) **4p**.



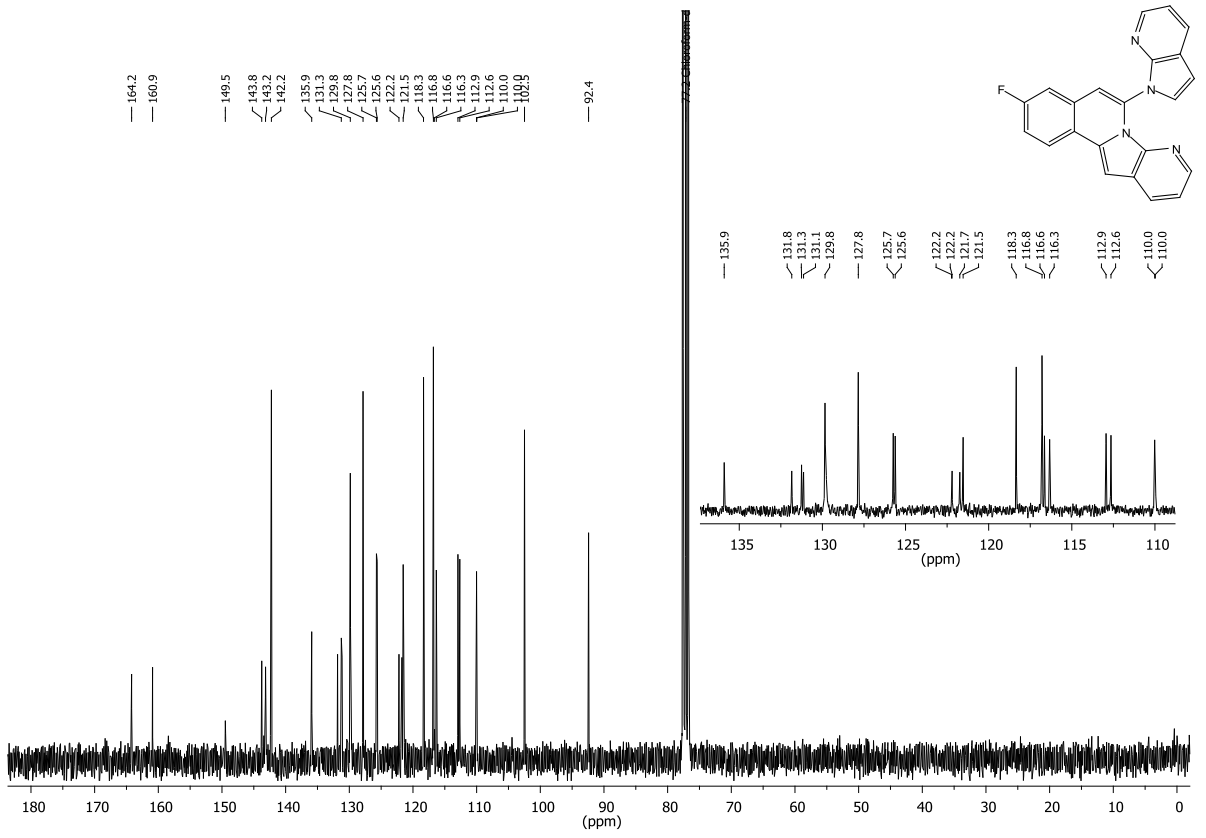
^{13}C NMR (63 MHz, $CDCl_3$) of **4p**.



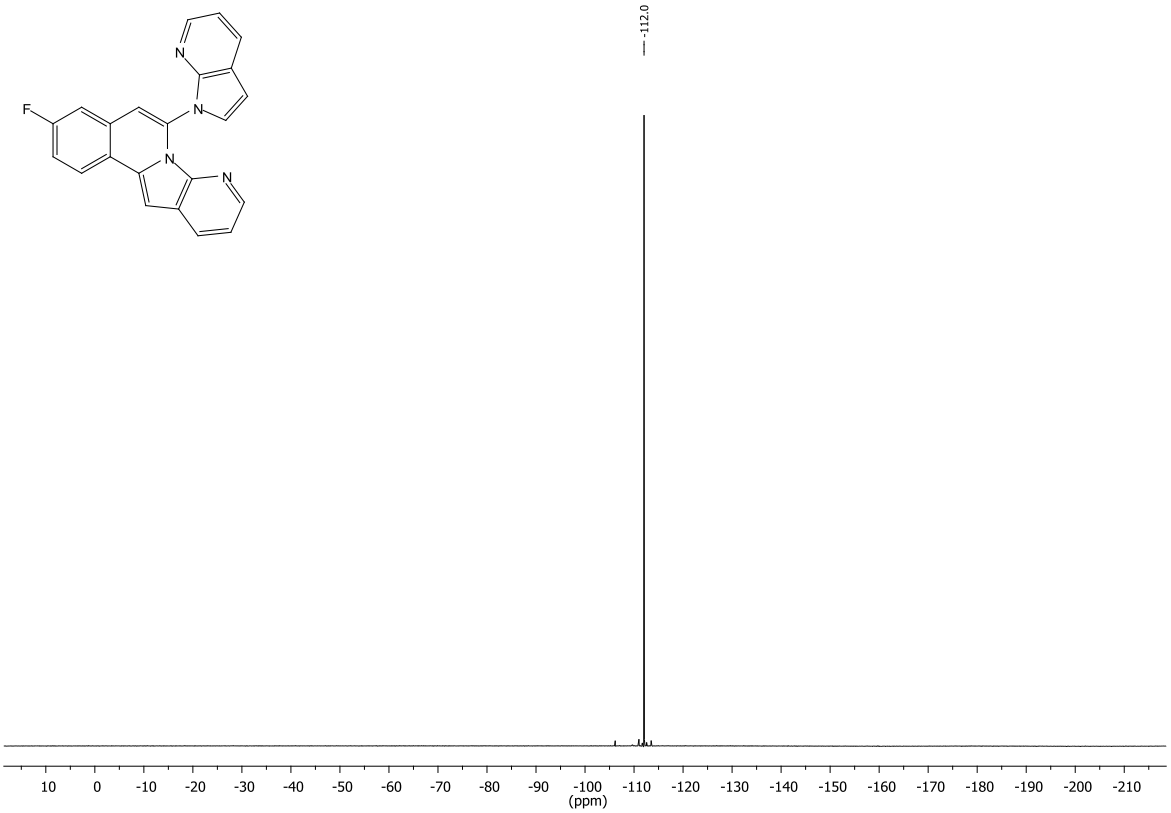
^{1}H NMR (300 MHz, $CDCl_3$) **4q**.



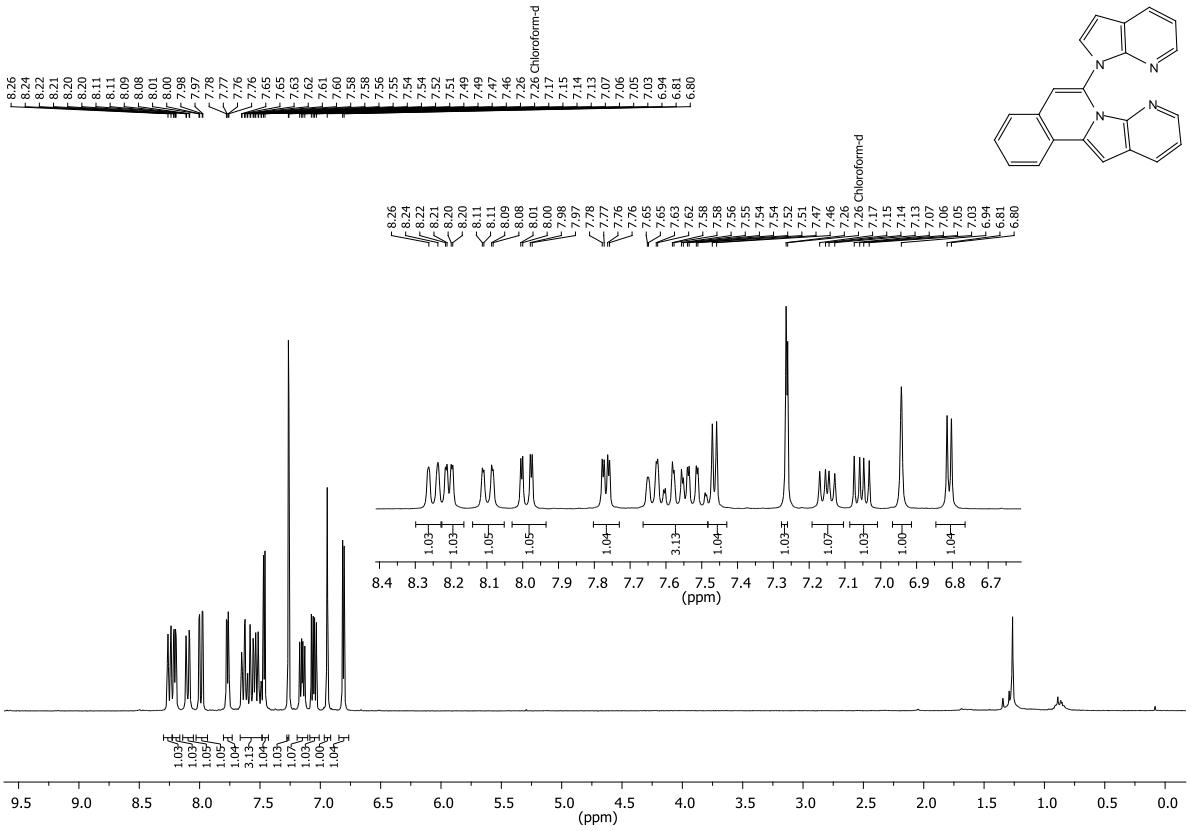
^{13}C NMR (75 MHz, $CDCl_3$) of **4q**.



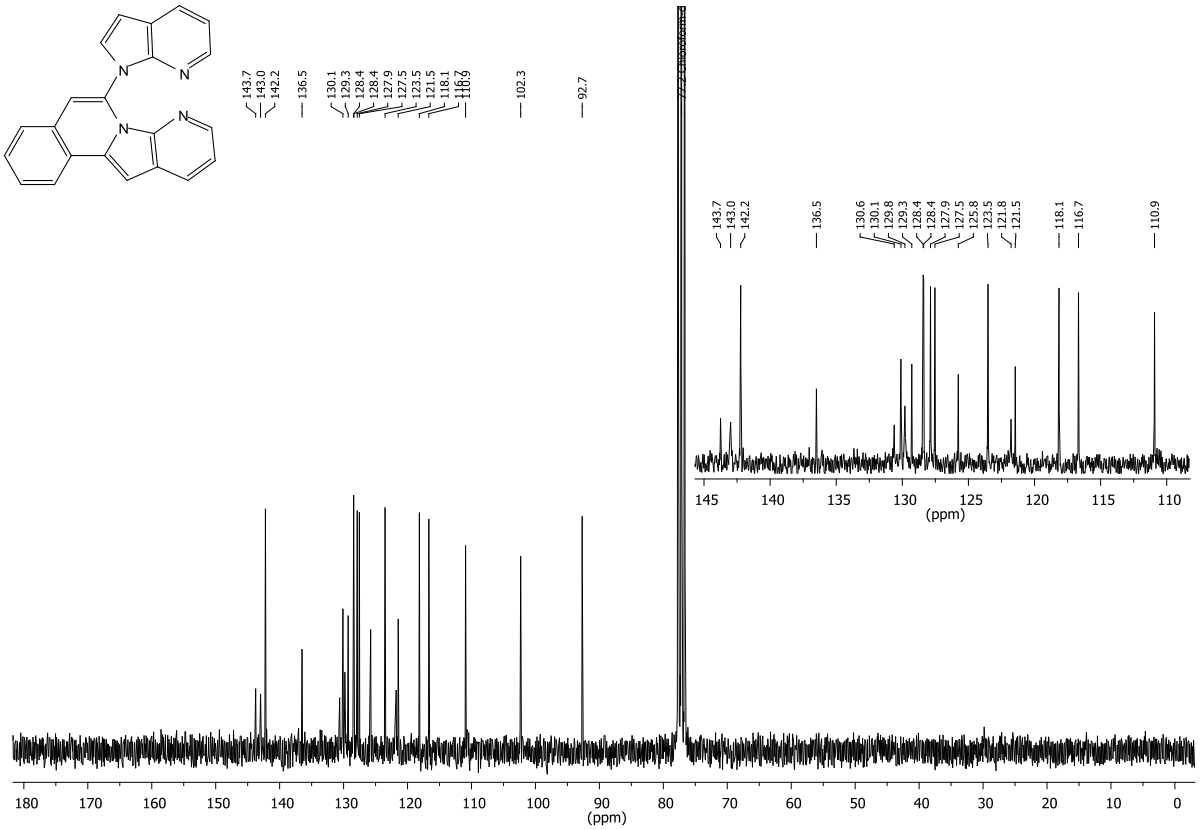
^{19}F NMR (282 MHz, $CDCl_3$) of **4q**.



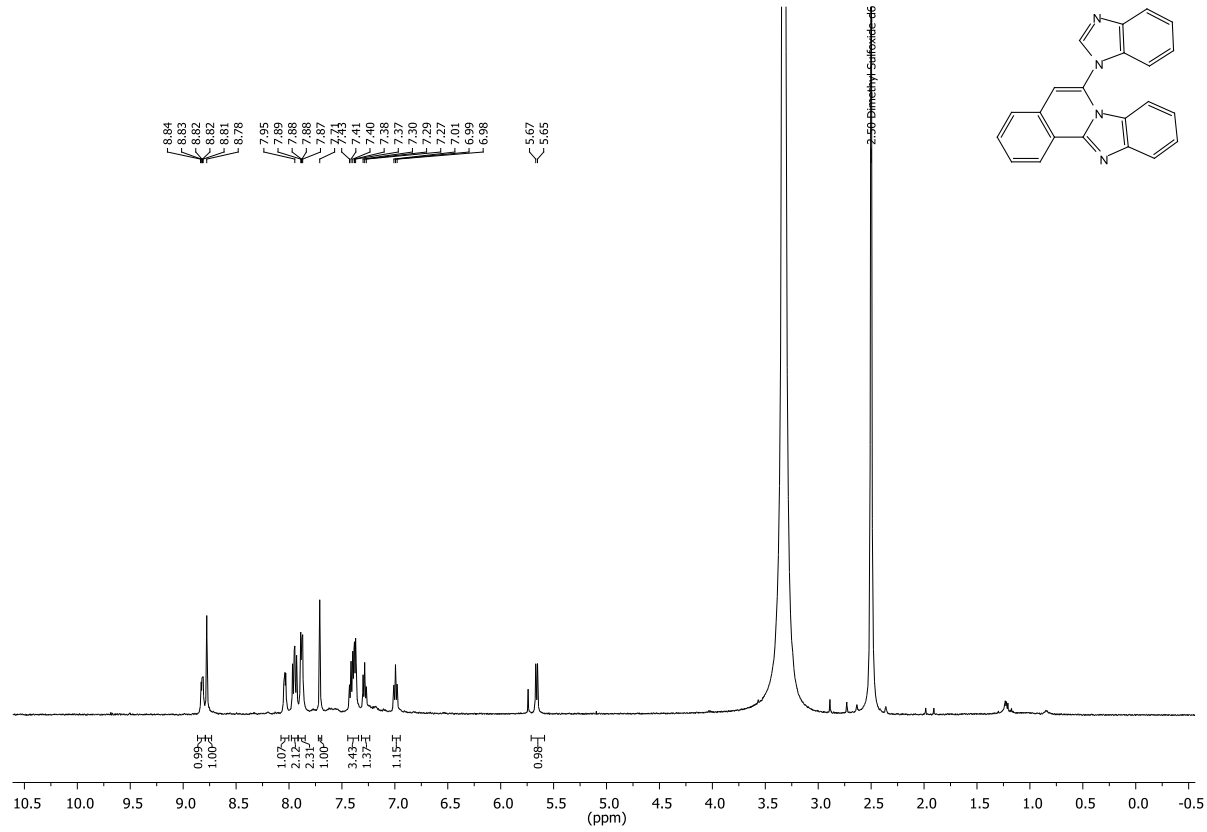
^{1}H NMR (300 MHz, $CDCl_3$) of **4r**.



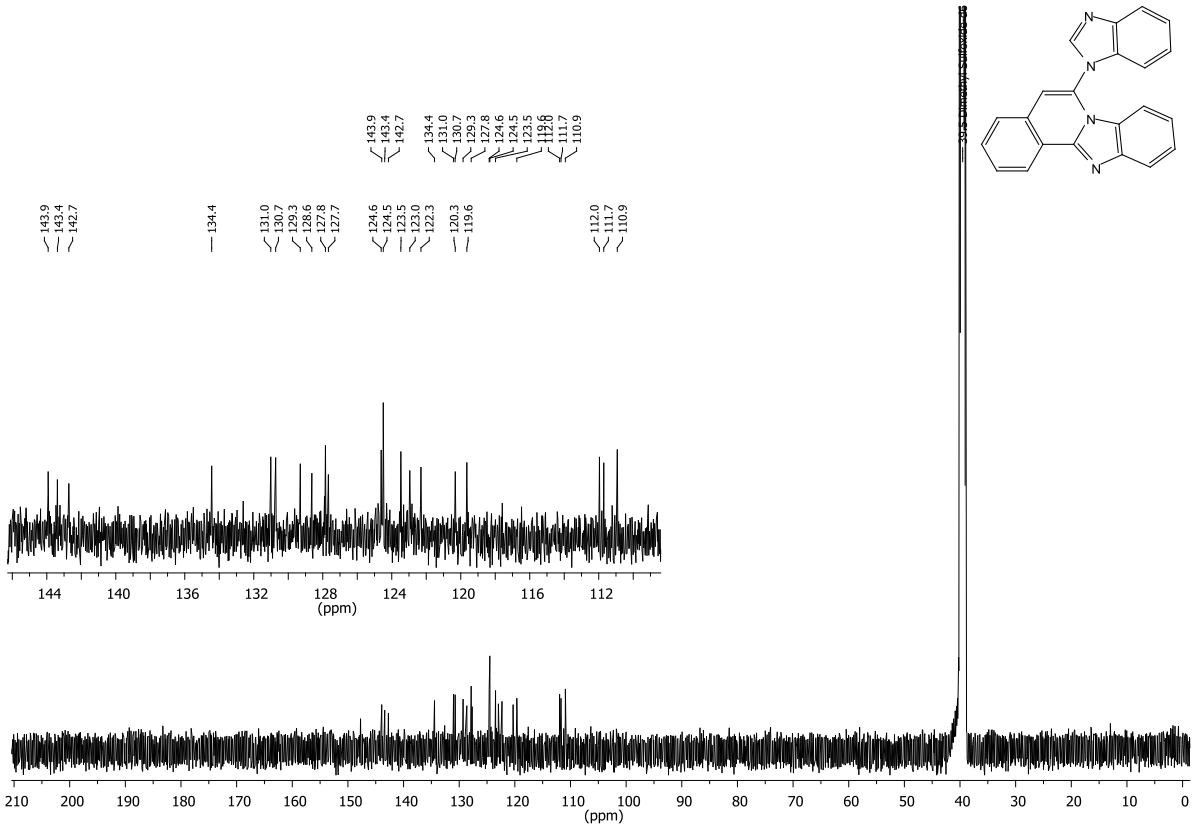
^{13}C NMR (63 MHz, $CDCl_3$) **4r**.



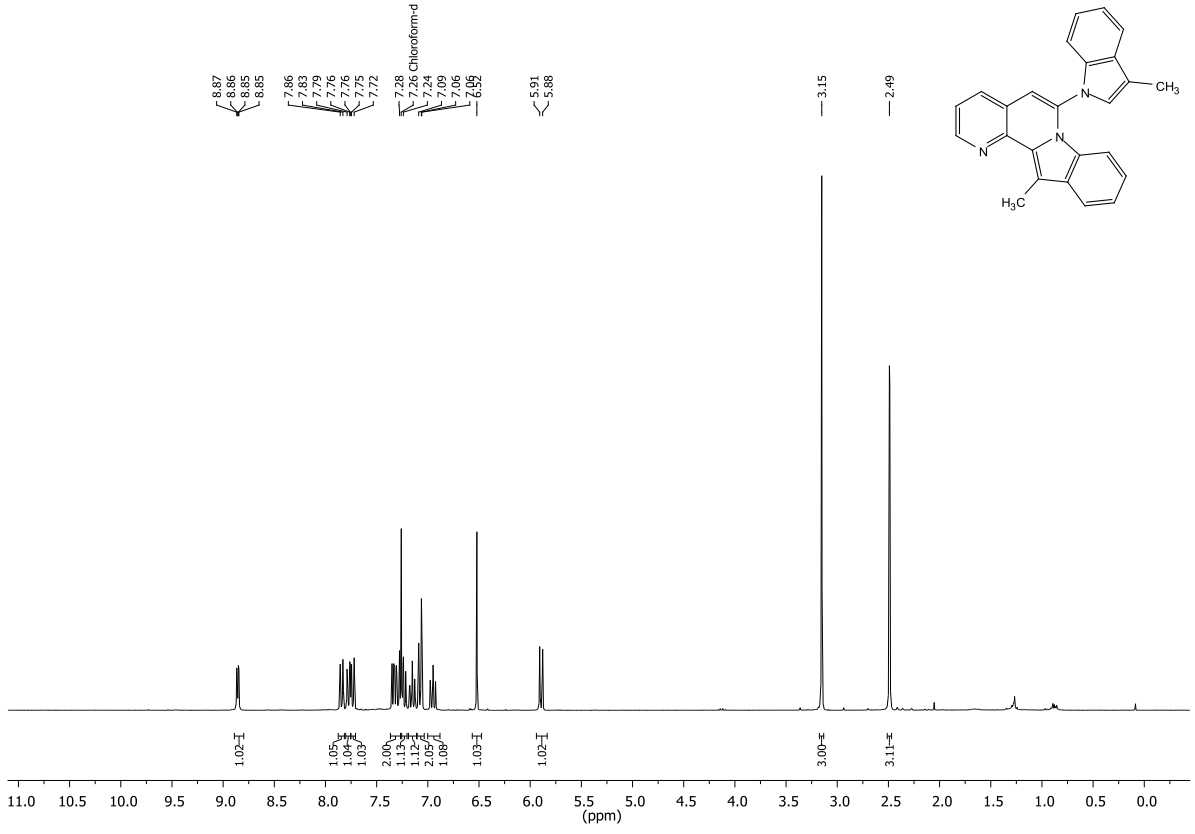
^{1}H NMR 30 °C (500 MHz, DMSO-d_6) of **4s**.



^{13}C NMR 30 °C (126 MHz, DMSO-d_6) of **4s**.



^{1}H NMR (300 MHz, $CDCl_3$) of **6**.



^{13}C NMR (75 MHz, $CDCl_3$) of **6**.