Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

One-pot access to 11-methyl-6*H*-indolo[2,3-*b*]quinolines via iodine-mediated cyclisation of indoles with 2-vinylanilines and evaluation of their biological activities

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Supplementary Information

Contents

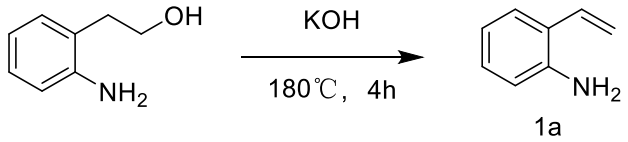
Experimental Section

Instrumentation and chemicals.

^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR (376 MHz) were recorded on a Bruker NMR apparatus with $CDCl_3$ and DMSO-d_6 as the solvent. The chemical shifts are reported in δ (ppm) values. ^{1}H NMR chemical shifts were determined relative to internal tetramethylsilane signal at δ 0.0. ^{19}F NMR chemical shifts were determined relative to external $CFCl_3$ at δ 0.0. Data for ^{1}H, ^{13}C, and ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, br = broad). Coupling constants (J) are reported in Hertz unit (Hz). Melting points were measured by SGW X-4A microscopic apparatus. HRMS was measured by Q Exactive Hybrid Quadrupole-Orbitrap LC/MS spectrometer.

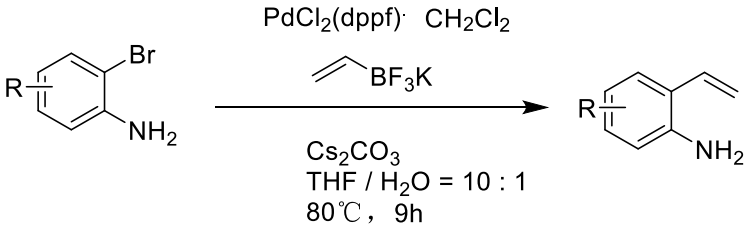
The starting materials, including the 2 - (2-aminophenyl) ethanol, potassium hydroxidewere obtained from commercial sources such as Aladdin, Macklin, Alfa Aesar, Ourchem and used as received unless otherwise noted. The ethyl acetate and petroleum ether were used for column chromatography without further purification.

Preparation of Substrates:



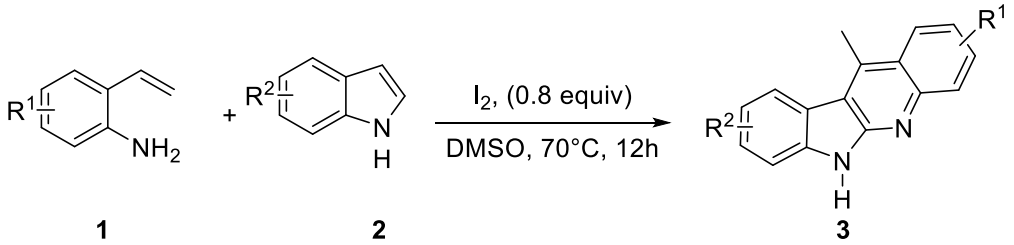
1a

2-vinylanilines 1a was synthesized by following a slightly modified procedure reported in literautre. [1] A mixture of 2-(2-aminophenyl)ethanol (20 mmol, 1 equiv.) and KOH (20 mmol, 1 equiv.) was refluxed at a temperature of 180 ℃ for 4 hours. The reaction completion was monitored by TLC. After completion of reaction, reaction mixture was cooled to around 50 ℃. (Note: Cooling to room temperature was avoided as further dissolution of solidified crude material becomes difficult during workup). DI water was added to the crude reaction mixture (20 mL) to dissolve excess of KOH, followed by the addition of ethyl acetate (60 mL). The organic layer was separated and compounds from the aqueous layer was extracted with ethyl acetate (10 mL × 3). Combined organic layer was washed with 10 mL of brine solution, dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude product was purified by chromatography (Combiflash) using ethyl acetate/ petroleum ether (1:100) mixture as mobile phase.



To a suspension of potassium vinyltrifluoroborate (0.59 g, 4.4 mmol), Cs_2CO_3 (3.9 g, 12.0 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (0.29 g, 0.36 mmol) and the corresponding 2-bromoaniline (4.0 mmol) in THF (60 mL) was added water (6.0 mL). The reaction mixture was stirred under reflux for 16 h, then cooled to room temperature and diluted with water (30 mL) followed by extraction with ethyl acetate (50 mL x 3). The ethyl acetate solution was washed with brine (50 mL), and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (petroleum ether / ethyl acetate =100 : 1) to give the desired products.[2,3]

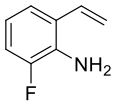
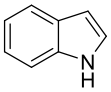
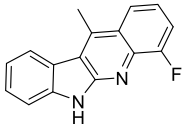
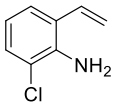
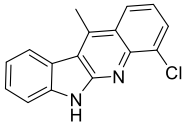
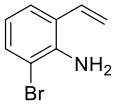
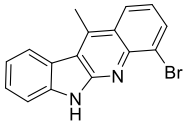
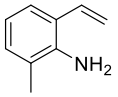
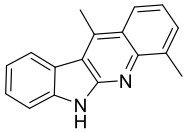
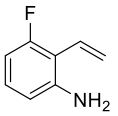
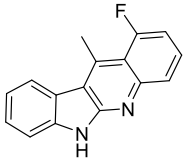
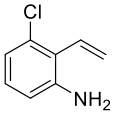
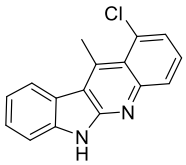
Experimental procedures

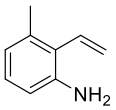
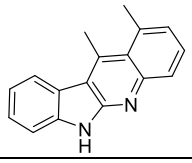


1 **2** **3**

General procedure for the iodine-mediated annulation of indoles with 2-vinylanilines: To a 4 mL round-bottomed flask was charged with indole **2** (0.4 mmol), I_2 (80 mol%), DMSO (2 mL), add 2-vinylaniline **1** (0.2 mmol) in 5 batches within 1 hour. The resulting mixture was stirred at 80 ℃ for 12 h. After the completion of the reaction, 30 mL of $Na_2S_2O_3$ (aq) was then added to the mixture, which was then extracted with EtOAc three times (3 × 30 mL). The product was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel (petroleum ether/ EtOAc = 8:1) to afford the desired product **3**.

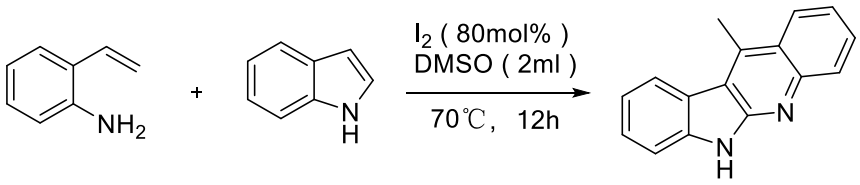
NR and poor effect Reactions

Entry	1	2	Product	Yield (%)[a,b]
1				15%
2				10%
3				11%
4				NR
5				NR
6				NR

7			**NR**

[a] Reaction conditions: **1** (0.2mmol), **2** (2 equiv), I_2 (80 mol%) in DMSO (2.0 mL) stirring under air for 12 h.

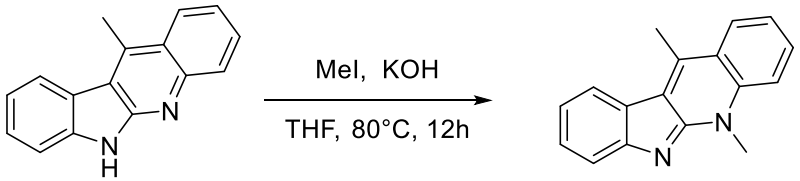
Large scale experiments



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

To a mixture of indole (**2**, 13.4 mmol), I_2 (5.3 mmol), DMSO (60 mL), add 2-vinylaniline (**1**, 6.7 mmol) in 5 batches within 1 hour. The resulting mixture was stirred at 80 ℃ for 12 h. After reaction, 50 mL of $Na_2S_2O_3$ (aq) was then added to the mixture, which was then extracted with EtOAc three times (3 × 50 mL). The product was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel (petroleum ether/ EtOAc = 2:1) to afford the desired product (1.07 g). The isolated yield is 69%.

Transformations experiments



3a DIMIQ

A solution of norneocryptolepine 3a (46.5 mg, 0.2 mmol,1.0 equiv), CH_3I (31 μl, 0.5 mmol, 2.5 equiv), and 5% aqueous KOH solution (2 mL) in THF (4 mL) was kept stirring at 80 ℃ for 12 h and then cooled to room temperature. The product was extracted by washing with ethyl acetate. The combined organic phases were dried over the Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography with silica gel using a mixture of petroleum ether and ethyl acetate as an eluent to give product DIMIQ (yield 65%). The characterization data of product DIMIQ match those reported in the literature.[4]

Biological evaluation methods

Biological evaluation

The synthesized compounds were initially dissolved in DMSO at stock concentration of 10 mg/mL. The resulting solutions were diluted with cell culture medium to achieve a final DMSO content (v/v) of less than 1% in the cell culture fluid. This DMSO content was nontoxic to cells.

Cytotoxicity assays

The cytotoxicities of the synthesized compounds were evaluated in rhabdomyosarcoma (RD) and human laryngeal epithelial cancer (Hep-2) cells with the 3-(4,5-dimethylthiazol-2-yl)-2,5 -diphenyl tetrazolium bromide

(MTT) assay as previously described [5]. Briefly, the cells were seeded into a 96-well plate. After 24 h, the medium was replaced with fresh medium (2% fetal calf serum [FCS]) and a two-fold serial dilution of the compounds. After 72 h of exposure, the medium was removed and MTT was added and incubated for 4 h at 37°C. DMSO (50 mL/well) was added to dissolve the MTT formazan and the optical density of the cells was measured at 420 nm (OD_{420}) with a microplate reader (Thermo Scientifific, MK3). The 50% cell cytotoxic concentration (CC50) of compounds was calculated using statistical package for the social sciences (SPSS) software.

Antiviral assays & selectivity index

The antiviral activity of compounds against EV71 and CVB3 was determined by measuring its inhibition of virus-induced cytopathic effects (CPEs) in acutely infected RD or Hep-2 cells, respectively. Generally, confluent cell monolayers in 96-well dishes were infected with 100 TCID50 of EV71 for 1.5 h at 37°C. Inocula were aspirated and the cells then were incubated with various concentrations of compounds at 37 ℃, 5% CO_2, for 48 h. CPEs were observed microscopically and the viability of the cells determined using MTT assays. The concentrations of test compounds required to achieve 50% protection from virus-induced cytopathogenicity (EC50) were determined. The selectivity index (SI) was calculated as the ratio of CC50/EC50. Each experiment was performed in triplicate and at least three independent experiments.

Progeny viral yield

The RD or Hep-2 cells in 24-well plates infected with 100 TCID50 of EV71 or CVB3 were left untreated or treated with specific concentrations of compounds for 48 h, the culture media and cell lysates were collected following freeze-thaw cycles and then subjected to virus titration.

Virus titration

Viral suspensions, serially diluted ten-fold with dulbecco's modifified Eagle medium (DMEM) containing 2% fetal bovine serum (FBS), were used to inoculate RD or Hep-2 cells in a 96-well plate. After 1.5 h incubation at 37 ℃ in 5% CO_2, unbound virus was washed out and DMEM maintenance medium (MM) supplemented with 2% FBS added to the cells. After 2 days, the infected cells were monitored for CPEs. Virus titers were calculated by the Reed–Muench method [6].

Reference:

[1] Li, L.; Gao, H.; Sun, M.; Zhou, Z.; Yi, W. Experimental and computational studies on Cp*CyRh(III)/KOPiv-catalyzed intramolecular dehydrogenative cross-couplings for building eight-membered sultam/lactam Frameworks. *Org. Lett.* **2020**, *22*, 5473–5478.

[2] Li, Y.-M, Sun, M, Wang, H.-L, Tian, Q.-P, Yang, S.-D. Direct annulations toward phosphorylated oxindoles: silver-catalyzed carbon-phosphorus functionalization of alkenes. *Angew. Chem., Int. Ed*. **2013**, *52*, 3972−3976.

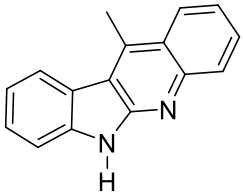
[3] B. Majhi, A. Parwez, S. Palit, S. Dutta. One-pot cascade annulation-triggered synthesis of N-6-substituted norcryptotackieine alkaloids and evaluation of their antileishmanial activities. *J. Org. Chem*. **2022**, 87, 14695–14705.

[4] S. Ali, Y.-X. Li, S. Anwar, F. Yang, Z.-S. Chen, Y.-M. Liang, One-pot access to indolo[2,3-b]quinolines by electrophile-triggered cross-amination/friedel−crafts alkylation of indoles with 1-(2-tosylaminophenyl)ketones. *J. Org. Chem.* **2012**, 77, 424−431.

[5] P. Kumar, A. Nagarajan, P.D. Uchil, 2018. Analysis of cell viability by the MTT assay. Cold Spring Harb Protoc 2018.
[6] L.J. Reed, 1938. A simple method of estimating fifty percent endpoints. Am J Hyg 27.

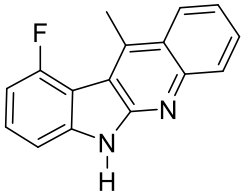
Characterization Data

11-methyl-6*H*-indolo[*2,3-b*]quinoline (3a)



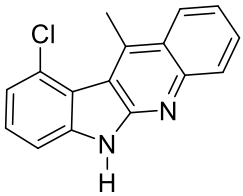
Yellow solid, 38.5 mg, 82.8% yield; mp 250.5 – 251.0 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): 11.66 (s, 1H), 8.32–8.36 (t, *J* = 7.2 Hz, 2H), 7.95–7.98 (d, *J* = 8.3 Hz, 1H), 7.69–7.74 (t, *J* = 8.0 Hz, 1H), 7.48-7.56 (m, 3H), 7.26-7.30 (t, *J* = 6.8 Hz, 1H), 3.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.8, 146.6, 141.8, 139.1, 128.9, 127.9, 124.9, 124.2, 123.9, 122.9, 121.5, 120.1, 116.4, 111.2, 15.3. HRMS-ESI(m/z): calcd for $C_{16}H_{13}N_2$ $(M+H)^+$: 233.1073, found 233.1077.

10-fluoro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3b)



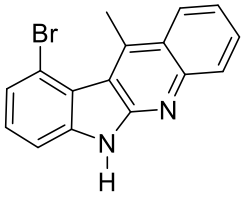
Yellow solid, 25.0 mg, 51% yield; mp 259.1 – 261.3 ℃ ; 1H NMR (400 MHz, DMSO-d_6): δ 11.68 (s, 1H), 8.32-8.37 (t, *J* = 7.5 Hz, 2H), 7.95-7.98 (d, *J* = 8.0 Hz, 1H), 7.69-7.75 (m, 1H), 7.48-7.54 (m, 2H), 7.26-7.31 (m, 1H), 3.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.6 (d, *J* = 241.0 Hz), 145.8, 131.1 (d, *J* = 5.9 Hz), 130.0, 127.5, 126.7, 124.8 (d, *J* = 12.9 Hz), 123.7, 120.8, 118.7 (d, *J* = 6.1 Hz), 116.8, 115.9 (d, *J* = 2.9 Hz), 115.5, 106.2 (d, *J* = 15.8 Hz), 20.8. ^{19}F NMR (376 MHz, DMSO-d_6): δ -133.8 ~ -133.9 (m). HRMS-ESI(m/z): calcd for $C_{16}H_{12}FN_2$ $(M+H)^+$: 251.0979, found 251.0977.

10-chloro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3c)



Yellow solid, 29.7 mg, 56% yield; mp 234.7 – 235.0 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.67 (s, 1H), 8.32-8.38 (m, 2H), 7.95-7.98 (d, *J* = 8.3 Hz, 1H), 7.69-7.74 (m, 1H), 7.48-7.54 (m, 2H), 7.25-7.33 (m, 1H), 3.19(s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.8, 146.7, 141.8, 139.1, 128.9, 128.0, 124.9, 124.2, 123.9, 122.9, 121.5, 120.1, 116.4, 111.2, 15.3. HRMS-ESI(m/z): calcd for $C_{16}H_{12}ClN_2$ $(M+H)^+$: 267.0684, found 267.0688.

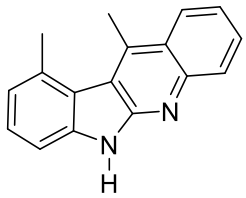
10-bromo-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3d)



Yellow solid, 26.3 mg, 42% yield; mp 247.9 – 248.4 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.67 (s, 1H),8.32-

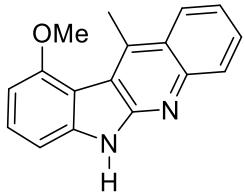
8.36 (m, 2H), 7.97 (d, *J* =8.4 Hz, 1H), 7.70-7.77 (m, 1H), 7.48-7.53 (m, 3H), 7.26-7.30 (m, 1H), 3.19 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 152.8, 146.7, 141.8, 139.2, 128.9, 128.0, 124.9, 123.9, 122.9, 121.5, 120.1, 116.4, 111.2, 15.3. HRMS-ESI(m/z): calcd for $C_{16}H_{12}BrN_2$ $(M+H)^+$: 311.0178, found 311.0175.

10,11-dimethyl-6*H*-indolo[*2,3-b*]quinoline (3e)



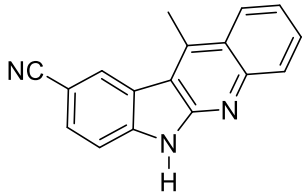
Yellow solid, 39.2 mg, 79% yield; mp 285.1 – 285.6 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.67 (s, 1H), 8.30-8.33 (d, *J* = 8.4 Hz, 1H), 7.89–7.92 (d, *J* =7.8 Hz, 1H),7.67-7.72 (m, 1H), 7.45-7.52 (m, 1H), 7.37-7.42 (d, *J* = 7.72 Hz, 1H), 7.28-7.31 (d, *J* =7.9 Hz, 1H), 7.02-7.05 (d, *J* = 7.3 Hz, 1H), 3.27 (s, 3H), 2.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.8, 146.2, 142.7, 138.5, 133.6, 128.9, 128.3, 127.4, 125.3, 124.3, 123.4, 122.8, 120.5, 108.9, 25.9, 19.7. HRMS-ESI(m/z): calcd for $C_{17}H_{15}N_2$ $(M+H)^+$: 247.1230, found 247.1233.

10-methoxy-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3f)



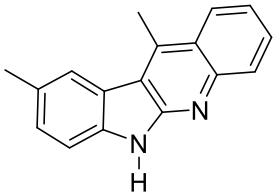
Yellow solid, 32.4 mg, 62% yield; mp 282.5 – 283.0 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.73 (s, 1H), 8.30-8.33 (d, *J* = 8.2 Hz, 1H), 7.89-793 (d, *J* = 8.2 Hz, 1H), 7.67-7.71 (t, *J* =7.1 Hz, 1H), 7.45-7.50 (t, *J* = 7.8 Hz, 2H), 7.07-7.10 (d, *J* = 7.9 Hz, 1H), 6.82-6.85 (d, *J* = 8.2 Hz, 1H), 4.04 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.4, 152.5, 146.0, 143.5, 139.1, 129.7, 128.7, 127.6, 125.3, 124.5, 122.8, 116.9, 109.9, 104.4, 102.5, 79.6, 55.9, 17.7. HRMS-ESI(m/z): calcd for $C_{17}H_{15}N_2O$ $(M+H)^+$: 263.1179, found 263.1180.

11-methyl-6*H*-indolo[*2,3-b*]quinoline-9-carbonitrile (3g)



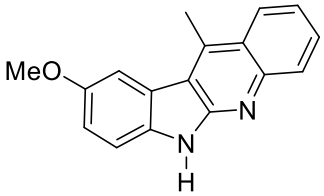
Yellow solid, 26.8 mg, 52% yield; mp 162.0 – 162.4 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.77 (s, 1H), 8.32-8.37 (t, *J* = 8.0 Hz, 2H), 7.96-7.99 (d, *J* = 8.4 Hz, 1H), 7.71-7.76 (t, *J* = 7.9 Hz, 1H), 7.49-7.56 (m, 2H), 7.27-7.31 (t, *J* = 7.7 Hz, 1H), 3.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.1, 153.2, 145.9, 143,5, 136.8, 128.3, 127.9, 125.0, 124.6, 124.1, 122.9, 114.8, 108.2, 95.5, 55.8, 15.2. HRMS-ESI(m/z): calcd for $C_{17}H_{12}N_3$ $(M+H)^+$: 258.1026, found 258.1024.

9,11-dimethyl-6*H*-indolo[*2,3-b*]quinoline (3h)



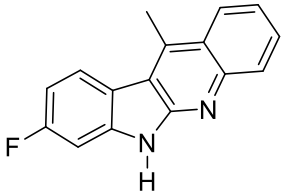
Yellow solid, 26.2 mg, 54% yield; mp 287.0 – 287.5 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.52 (s, 1H), 8.32-8.35 (d, J = 7.7 Hz, 1H), 8.14 (s, 1H), 7.92-7.95 (d, J = 8.9 Hz, 1H), 7.68-7.72 (t, J = 6.9 Hz, 1H), 7.46-7.51 (t, J = 7.1 Hz, 1H), 7.33-7.40 (m, 2H), 3.18 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 148.4, 141.8, 138.3, 134.1, 129.2, 124.5, 123.9, 123.0, 120.9, 119.9, 119.0, 118.4, 116.1, 113.6,104.5, 21.5, 15.3. HRMS-ESI(m/z): calcd for $C_{17}H_{15}N_2$ $(M+H)^+$: 247.1230, found 247.1233.

9-methoxy-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3i)



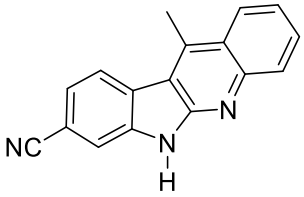
Yellow solid, 45.5 mg, 86% yield; mp 260.3 – 260.7 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.61 (s, 1H), 8.28-8.31 (d, J = 8.2 Hz, 1H), 8.17-8.20 (d, J = 8.7 Hz, 1H), 7.92-7.95 (d, J = 8.2 Hz, 1H), 7.65-7.70 (t, J = 7.1 Hz, 1H), 7.46-7.50 (t, J = 7.3 Hz, 1H), 6.98-6.99 (d, J = 2.2 Hz, 1H), 6.84-6.87 (dd, J = 8.6 Hz, 1H), 3.88 (s, 3H), 3.11 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.0, 153.2, 145.9, 143.5, 136.8, 128.3, 127.9, 125.0, 124.6, 124.1, 122.9, 116.6, 114.8, 108.2, 95.5, 55.8, 15.2. HRMS-ESI(m/z): calcd for $C_{17}H_{15}N_2O$ $(M+H)^+$: 263.1179, found 263.1177.

8-fluoro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3j)



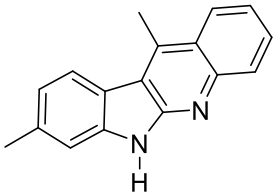
Yellow solid, 19.7 mg, 41% yield; mp 267.1 – 267.6 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.80 (s, 1H), 8.31-8.36 (t, J = 7.8 Hz, 2H), 7.95-7.98 (d, J = 8.3 Hz, 1H), 7.70-7.75 (t, J = 7.2 Hz, 1H), 7.49-7.54 (t, J = 7.6 Hz, 1H), 7.24-7.27 (d, J = 9.6 Hz, 1H), 7.07-7.13 (t, J = 9.3 Hz, 1H), 3.16 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.4 (d, J = 241.0 Hz), 153.2, 146.4, 142.9, 138.8, 129.0, 128.0, 125.7 (d, J = 10.4 Hz), 124.8, 124.1, 123.2, 118.2, 115.9, 107.5 (d, J =23.2 Hz), 98.1 (d, J = 26.1 Hz) , 15.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ -112.5 ~ -112.7 (m). HRMS-ESI(m/z): calcd for $C_{16}H_{12}FN_2$ $(M+H)^+$: 251.0979, found 251.0981.

11-methyl-6*H*-indolo[*2,3-b*]quinoline-8-carbonitrile (3k)



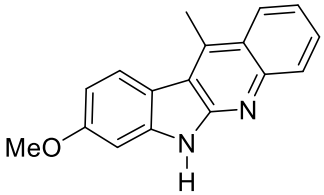
Yellow solid, 27 mg, 55% yield; mp 270.3 – 270.7 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.72 (s, 1H), 8.38-8.42 (t, J = 6.4 Hz, 2H), 8.00-8.03 (d, J = 8.0 Hz, 1H), 7.75-7.80 (t, J = 6.5 Hz, 1H), 7.54-7.65 (m, 2H), 7.34 (s, 1H), 3.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.8, 146.7, 141.8, 139.1, 128.9, 128.0, 124.9, 124.2, 122.9, 121.5, 120.1, 116.4, 111.2, 79.6, 15.3. HRMS-ESI(m/z): calcd for $C_{17}H_{12}N_3$ $(M+H)^+$: 258.1026, found 258.1029.

8,11-dimethyl-6*H*-indolo[*2,3-b*]quinoline (3l)



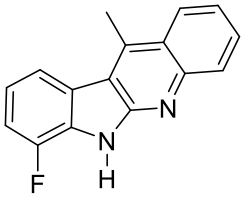
Yellow solid, 38.6 mg, 78% yield; mp 260.7 – 261.2 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.55 (s, 1H), 8.18-8.21 (d, J = 8.6 Hz, 1H), 8.14-8.17 (d, J = 8 Hz, 1H), 7.72 (s, 1H), 7.32-7.34 (dd, J = 8.6 Hz, 1H), 7.26 (s, 1H), 7.06-7.09 (d, J = 8.0 Hz, 1H), 3.11 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.0, 146.4, 142.2, 138.2, 137.8, 128.6, 127.9, 124.8, 123.9, 122.8, 121.4, 119.1, 111.4, 22.2, 15.3. HRMS-ESI(m/z): calcd for $C_{17}H_{15}N_2$ $(M+H)^+$: 247.1230, found 247.1232.

8-methoxy-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3m)



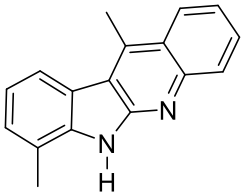
Yellow solid, 31.4 mg, 60% yield; mp 255.2 – 255.7 ℃; ^{1}H NMR (400 MHz, DMSO-d_6)): δ 11.61 (s, 1H), 8.28-8.31 (t, J = 8.2 Hz, 1H), 8.17-8.20 (d, J = 8.7 Hz, 1H), 7.92-7.95 (d, J = 8.2 Hz, 1H), 7.65-7.70 (t, J = 7.1 Hz, 1H), 7.46-7.50 (t, J = 7.3 Hz, 1H), 6.98-6.99 (d, J = 2.2 Hz, 1H), 6.84-6.87 (dd, J = 8.6 Hz, 1H), 3.88 (s, 3H), 3.11 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6)): δ 160.0, 153.2, 145.9, 143.5, 136.8, 128.3, 127.9, 125.0, 124.6, 124.1, 122.9, 116.6, 114.8, 108.2, 95.5, 55.8, 15.2. HRMS-ESI(m/z): calcd for $C_{17}H_{15}N_2O$ $(M+H)^+$: 263.1179, found 263.1176.

7-fluoro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3n)



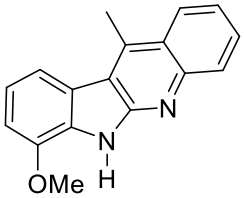
Yellow solid, 15.1 mg, 40% yield; mp 257.3 – 257.8 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.22 (s, 1H), 8.41-8.45 (d, J = 8.3 Hz, 1H), 8.22-8.24 (d, J = 7.8 Hz, 1H), 8.03-8.06 (d, J = 8.4 Hz, 1H), 7.79-7.83 (t, J = 7.1 Hz, 1H), 7.57-7.61 (t, J= 7.3 Hz, 1H), 7.45-7.51(m, 1H), 7.29-7.35 (m, 1H), 3.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.9, 148.5 (d, J = 240.6 Hz), 147.0, 140.1, 129.4, 129.2, 128.1, 125.1, 124.0, 123.3, 120.5 (d, J = 5.9 Hz), 120.2 (d, J = 3.3 Hz), 116.2 (d, J = 3.0 Hz), 113.6 (d, J = 16.2 Hz) , 15.3. ^{19}F NMR (376 MHz, DMSO-d_6): δ -132.7 ~ -132.9 (m). HRMS-ESI(m/z): calcd for $C_{16}H_{12}FN_2$ $(M+H)^+$: 251.0979, found 251.0982.

7,11-dimethyl-6*H*-indolo[*2,3-b*]quinoline (3o)



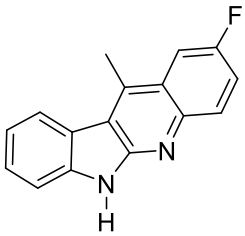
Yellow solid, 35 mg, 71% yield; mp 246.3 – 246.7 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.72 (s, 1H), 8.37-8.41 (t, J = 7.2 Hz, 2H), 8.00-8.03 (d, J = 8.3 Hz, 1H), 7.74-7.79 (t, J = 7.2 Hz, 1H), 7.53-7.60 (m, 2H), 7.31-7.35 (t, J = 7.1 Hz, 1H), 3.24 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.5, 146.1, 139.9, 139.5, 128.6, 128.3, 127.5, 124.2, 124.1, 122.8,, 121.5, 121.1, 120.2, 120.0, 117.3, 16.9, 15.1. HRMS-ESI(m/z): calcd for $C_{17}H_{15}N_2$ $(M+H)^+$: 247.1230, found 247.1233.

7-methoxy-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3p).



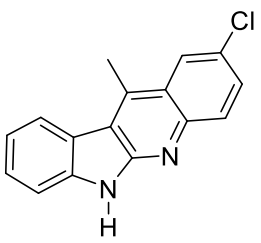
Yellow solid, 36.2 mg, 70% yield; mp 234.3 – 234.8 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.75 (s, 1H), 8.32-8.36 (d, J = 8.5 Hz, 1H), 7.92-7.98 (m, 2H), 7.69-7.74 (m, 1H), 7.47-7.52 (m, 1H), 7.16-7.25 (m, 2H), 3.99 (s, 3H), 3.17 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.7, 146.7, 145.6, 139.1, 131.4, 128.9, 127.9, 124.9, 123.9, 122.4, 120.7, 116.8, 116.5, 109.4, 56.1, 15.2. HRMS-ESI(m/z): calcd for $C_{17}H_{15}N_2O$ $(M+H)^+$: 263.1179, found 263.1177.

2-fluoro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3q).



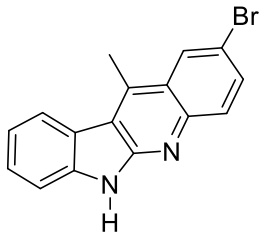
Yellow solid, 26.1 mg, 52% yield; mp 276.1 – 276.6 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.74 (s, 1H), 8.36-8.41 (m, 1H), 8.28-8.31 (d, J = 7.8 Hz, 1H), 7.61-7.66 (dd, J = 10.9 Hz, 1H),7.47-7.54 (m, 2H), 7.34-7.40 (m, 1H), 7.25-7.29 (t, J = 7.0 Hz, 1H), 3.16 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.6 (d, J = 244.3 Hz), 153.6, 147.8 (d, J = 12.8 Hz), 141.3, 139.7, 128.0, 127.6 (d, J = 10.3 Hz), 124.1, 121.3 (d, J = 28.7 Hz), 120.3, 116.1, 112.7 (d, J = 24.5 Hz), 111.3, 111.0 (d, J = 19.9 Hz), 15.5. ^{19}F NMR (376 MHz, DMSO-d_6): -123.6 ~ -123.7. HRMS-ESI(m/z): calcd for $C_{16}H_{12}FN_2$ $(M+H)^+$: 251.0979, found 251.0980.

2-chloro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3r)



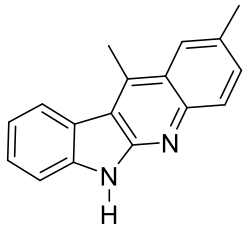
Yellow solid, 24 mg, 45% yield; mp 289.2 – 290.3 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.78 (s, 1H), 8.36-8.38 (m, 2H), 7.95-7.99 (d, *J*=9.0 Hz, 1H), 7.70-7.73 (dd, *J* = 8.9 Hz, 1H), 7.40-7.58 (m, 2H), 7.27-7.32 (t, *J* = 7.5 Hz, 1H), 3.17 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.0, 145.0, 142.0, 138.7, 129.9, 129.2, 128.4, 127.3, 124.7, 124.4, 123.8, 121.2, 120.3, 117.1, 111.3, 15.4. HRMS-ESI(m/z): calcd for $C_{16}H_{12}ClN_2$ $(M+H)^+$: 267.0684, found 267.0686.

2-bromo-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3s).



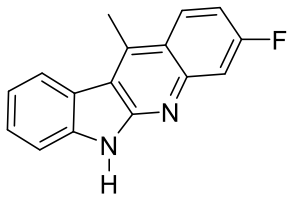
Yellow solid, 29.7 mg, 48% yield; mp 272.3 – 272.7 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 11.7 (s, 1H), 8.34-8.38 (d, *J* = 8.4 Hz, 1H), 8.12-8.15 (d, *J* = 8.8 Hz, 1H), 7.95-7.98 (d, *J* = 8.4 Hz, 1H), 7.71-7.76 (t, *J* = 7.1 Hz, 1H), 7.47-7.53 (m, 2H), 7.37-7.42 (t, *J* = 9.0 Hz, 1H), 3.17 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 153.0, 145.1, 142.0, 138.7, 129.9, 129.2, 128.4, 127.3, 124.7, 124.4, 123.8, 121.2, 120.3, 111.3, 15.4. HRMS-ESI(m/z): calcd for $C_{16}H_{12}BrN_2$ $(M+H)^+$: 311.0178, found 311.0178.

2,11-dimethyl-6*H*-indolo[*2,3-b*]quinoline (3t)



Yellow solid, 21.4 mg, 44% yield; mp 265.6 – 265.0 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 11.59 (s, 1H), 8.30-8.33 (d, *J* = 7.8 Hz, 1H), 8.10 (s, 1H), 7.85-7.88 (d, *J* = 8.5 Hz, 1H), 7.49-7.57 (m, 3H), 7.24-7.28 (d, *J* = 7.9 Hz, 1H), 3.15 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 152.4, 145.1, 141.8, 138.4, 131.9, 131.0, 127.8, 124.1, 123.8, 123.7, 121.6, 119.9, 116.3, 111.1, 21.8, 15.3. HRMS-ESI(m/z): calcd for $C_{17}H_{15}N_2$ $(M+H)^+$: 247.1230, found 247.1232.

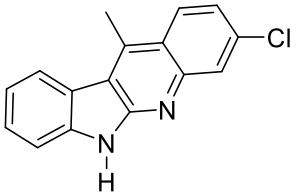
3-fluoro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3u).



Yellow solid, 23.5 mg, 47% yield; mp 262.5 – 263.0 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 11.74 (s, 1H), 8.40-8.45 (m, 1H), 8.31-8.34 (d, *J* = 7.8 Hz, 1H), 7.63-7.67 (dd, *J* = 10.9 Hz, 1H), 7.48-7.56 (m, 2H), 7.37-7.42 (m, 1H), 7.27-7.31 (t, *J* = 7.6 Hz, 1H), 3.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 162.6 (d, *J* = 244.3 Hz), 153.6, 147.8 (d, J = 12.8 Hz), 141.5, 139.7, 128.0, 127.6 (d, *J* = 10.3 Hz), 124.1, 121.3 (d, *J* = 28.7 Hz), 120.3, 116.1,

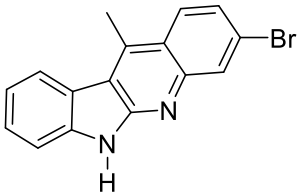
112.7 (d, *J* = 24.5 Hz), 111.3, 111.0 (d, *J* = 19.9 Hz), 15.5. ^{19}F NMR (376 MHz, DMSO-d_6): δ –123.5 ~ –123.7(m). HRMS-ESI(m/z): calcd for $C_{16}H_{12}FN_2$ $(M+H)^+$: 251.0979, found 251.0976.

3-chloro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3v)



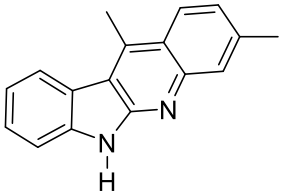
Yellow solid, 27.3 mg, 55% yield; mp 279.0 – 279.5 ℃; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.81 (s, 1H), 8.37-8.40 (d, *J* = 8.9 Hz, 1H), 8.32-8.35 (d, *J* = 7.6 Hz ,1H), 7.97 (s, 1H), 7.49-7.55 (m, 3H), 7.27-7.32 (t, *J* = 6.8Hz, 1H), 3.18 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.4, 147.2, 141.8, 139.6, 133.5, 128.3, 127.1, 126.3, 124.3, 120.4, 123.3, 122.6, 121.3, 116.8, 111.4, 15.4. HRMS-ESI(m/z): calcd for $C_{16}H_{12}ClN_2$ $(M+H)^+$: 267.0684, found 267.0686.

3-bromo-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3w).



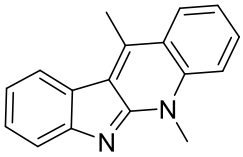
Yellow solid, 33.6 mg, 54% yield; mp 266.3 – 255.7 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.82 (s, 1H), 8.37-8.40 (d, *J* = 9.0 Hz, 1H), 8.32-8.35 (d, *J* = 7.9 Hz, 1H), 7.97-7.98 (d, *J* = 2.2 Hz, 1H), 7.48-7.57 (m, 3H), 7.27-7.32 (m, 1H), 3.18 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.5, 147.2, 139.6, 133.5, 128.3, 126.4, 123.3, 122.6, 121.4, 120.4, 116.9, 111.4, 15.5. HRMS-ESI(m/z): calcd for $C_{16}H_{12}BrN_2$ $(M+H)^+$: 311.0178, found 311.0180.

3,11-dimethyl-6*H*-indolo[*2,3-b*]quinoline (3x).



Yellow solid, 19.7 mg, 40% yield; mp 258.1 – 258.6 ℃; 1H NMR (400 MHz, DMSO-d6): δ 11.61 (s, 1H), 8.28-8.31 (d, *J* = 7.8 Hz, 1H), 8.21-8.24 (d, *J* = 8.6 Hz, 1H), 7.74 (s, 1H), 7.45-7.51 (m, 2H), 7.32-7.35 (d, *J* = 8.0 Hz, 1H), 7.23-7.28 (t, *J* = 7.5 Hz, 1H), 3.15 (s, 3H), 2.55 (s, 3H). 13C NMR (100 MHz, DMSO-d6): δ 152.9, 147.0, 141.6, 139.0, 138.6, 127.6, 127.0, 125.1, 124.6, 123.9, 122.0, 121.7, 120.0, 115.7, 111.1, 21.8, 15.3. HRMS-ESI(m/z): calcd for $C_{17}H_{15}N_2$ $(M+H)^+$: 247.1230, found 247.1228.

5,11-dimethyl-5*H*-indolo[*2,3-b*]quinoline



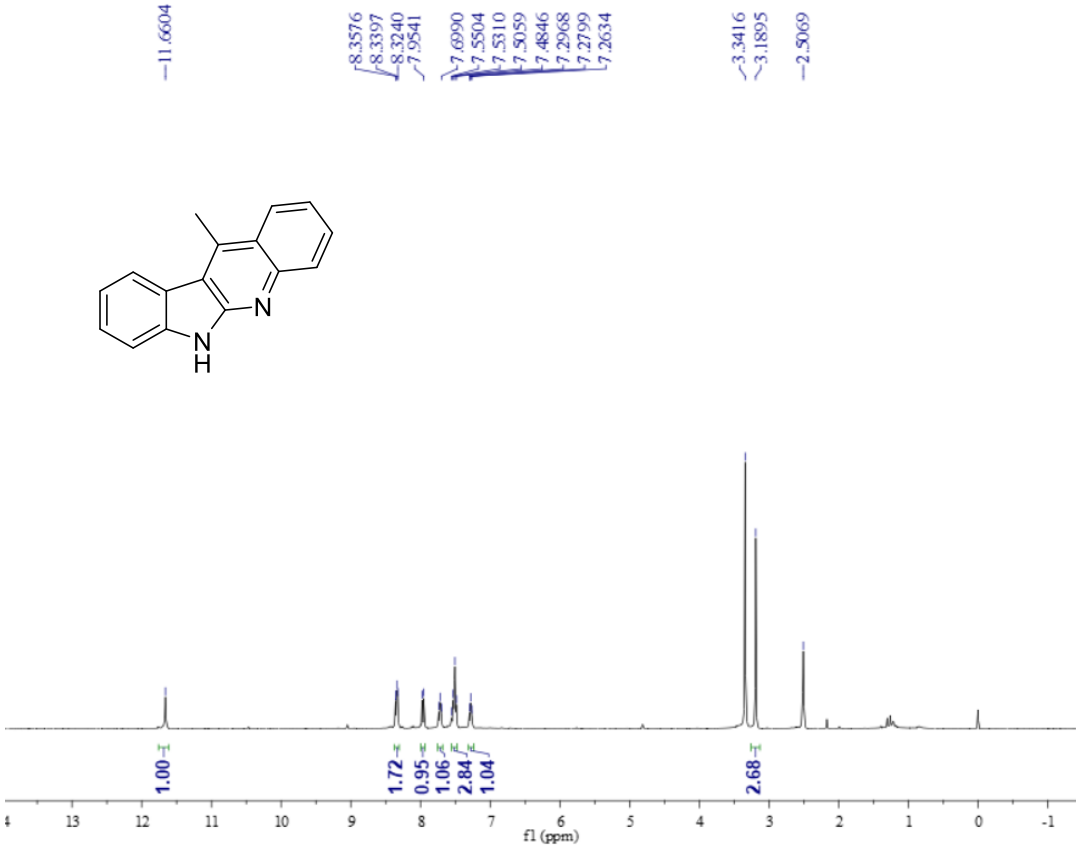
White solid, 32.0 mg, 65% yield; mp 119.5 – 120.0 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27-8.30 (d, *J* = 7.8 Hz,

1H), 8.23-8.26 (d, J = 8.4 Hz, 1H), 8.12-8.15 (d, J = 8.4 Hz, 1H), 7.69-7.74 (m, 1H), 7.56-7.60 (t, J = 7.9 Hz, 1H), 7.46-7.51 (t, J = 8.0 Hz, 1H), 7.41-7.44 (d, J = 8.0 Hz, 1H), 7.30-7.35 (t, J = 7.7 Hz, 1H), 3.98 (s, 3H), 3.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 145.4, 141.7, 138.0, 127.6, 126.9, 126.3, 123.0, 122.5, 121.6, 120.4, 118.9, 115.4, 107.5, 28.7, 14.1. HRMS-ESI(m/z): calcd for $C_{17}H_{15}N_2$ $(M+H)^+$: 247.1230, found 247.1234. These data are in good agreement with the literature data.[4]

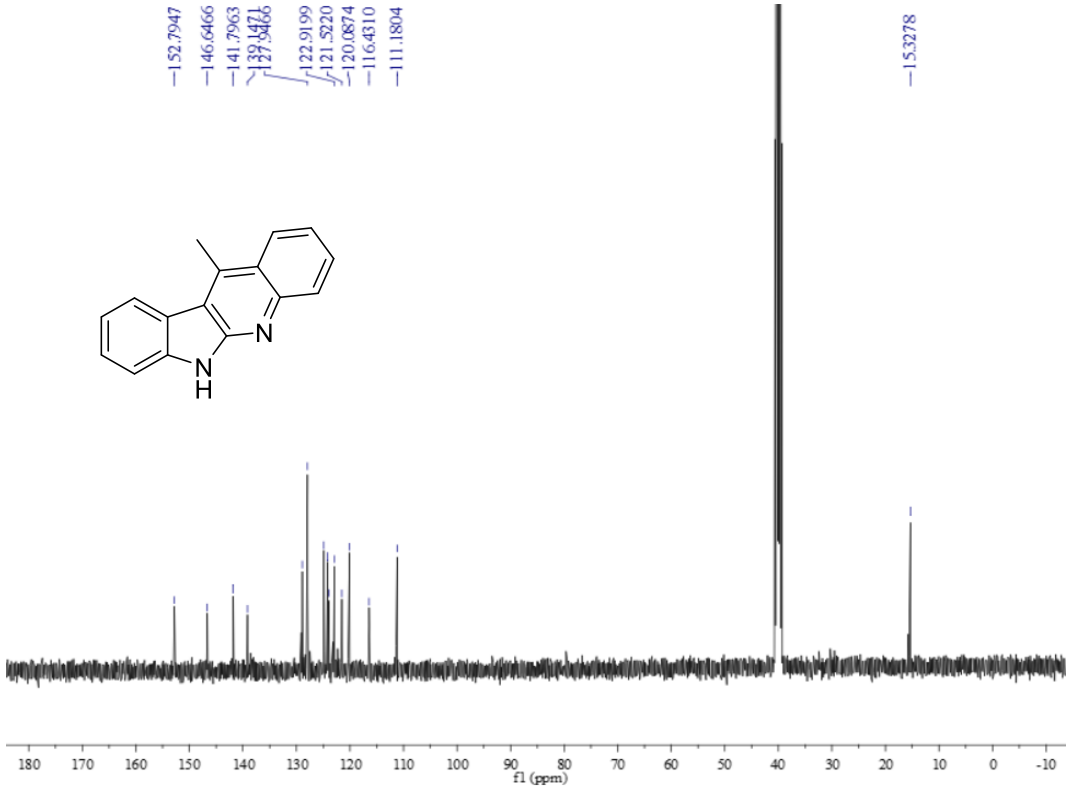
Copies of ^{1}H and ^{13}C NMR spectra

11-methyl-6*H*-indolo[*2,3-b*]quinoline (3a)

^{1}H NMR (400 MHz, DMSO-d_6)

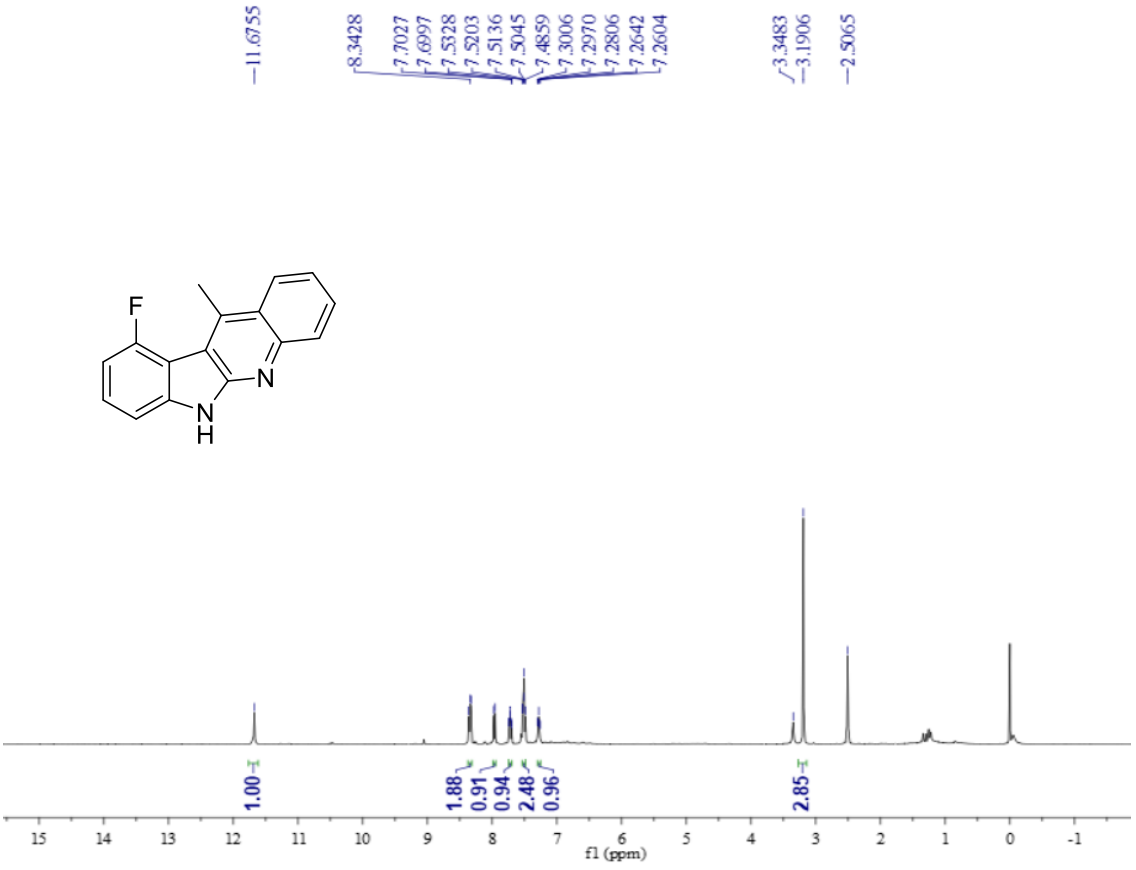


^{13}C NMR (100 MHz, DMSO-d_6)

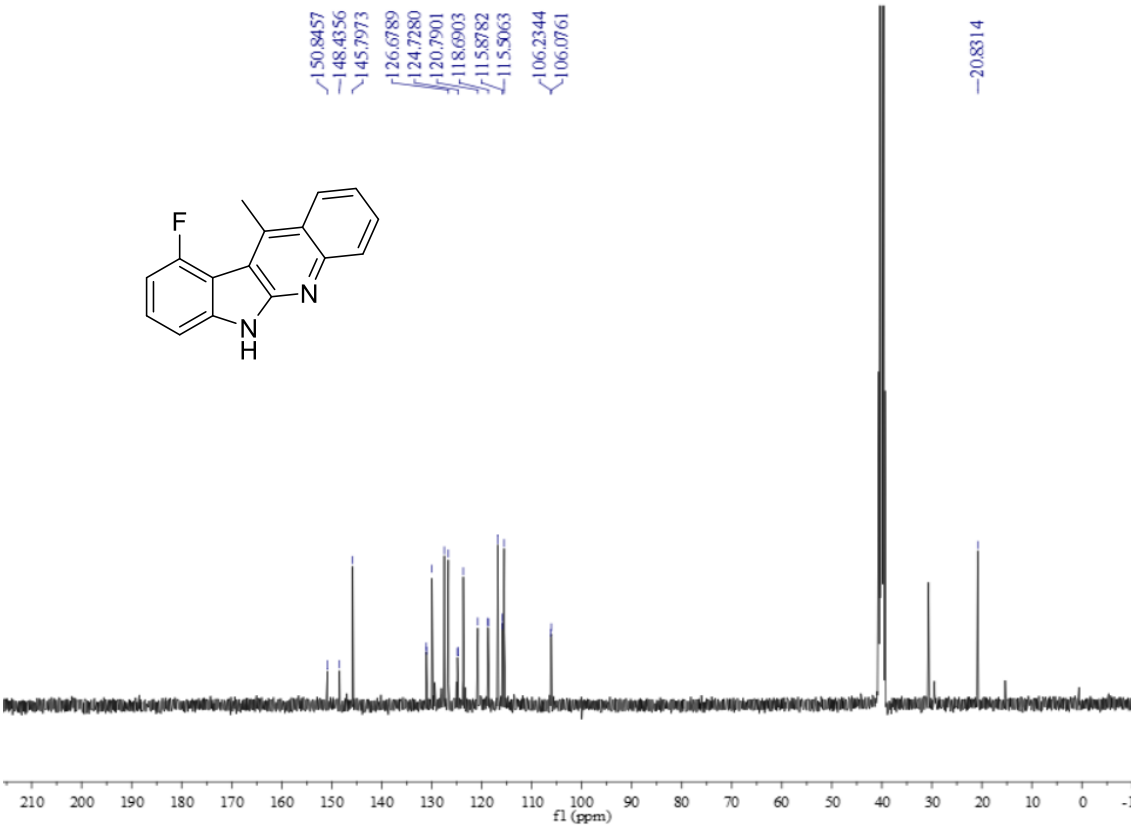


10-fluoro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3b)

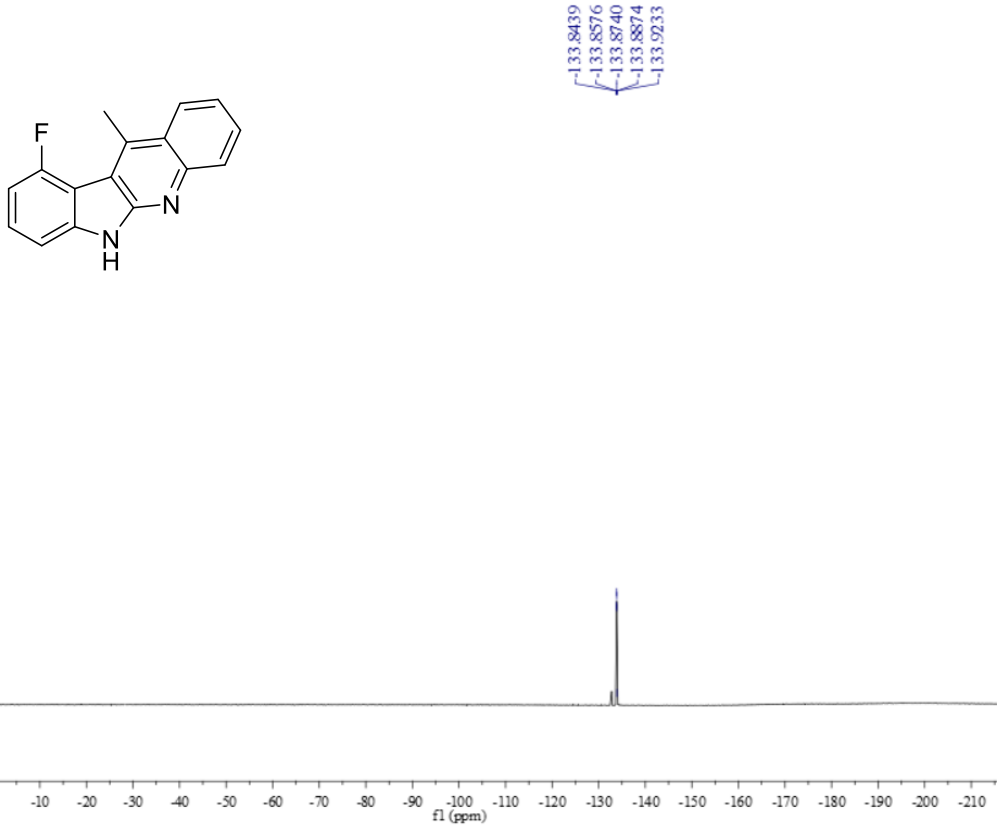
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (100 MHz, DMSO-d_6)

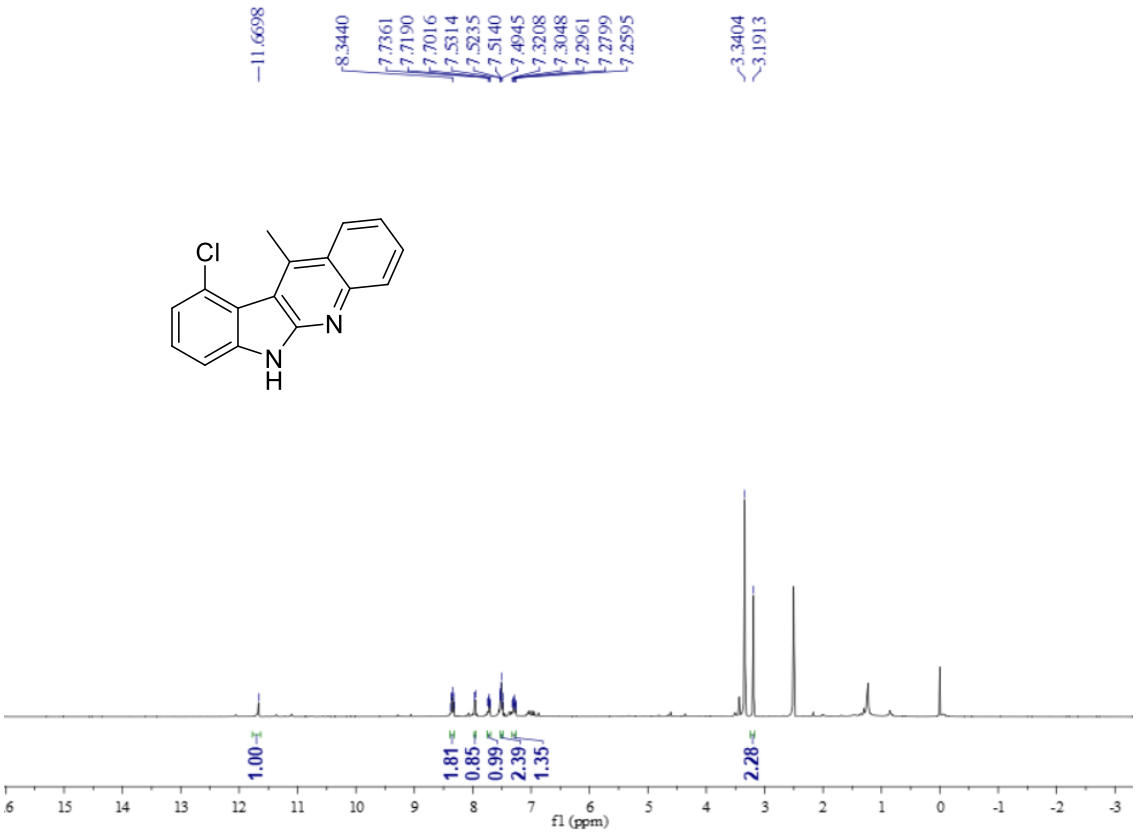


^{19}F NMR (376 MHz, DMSO-d_6)

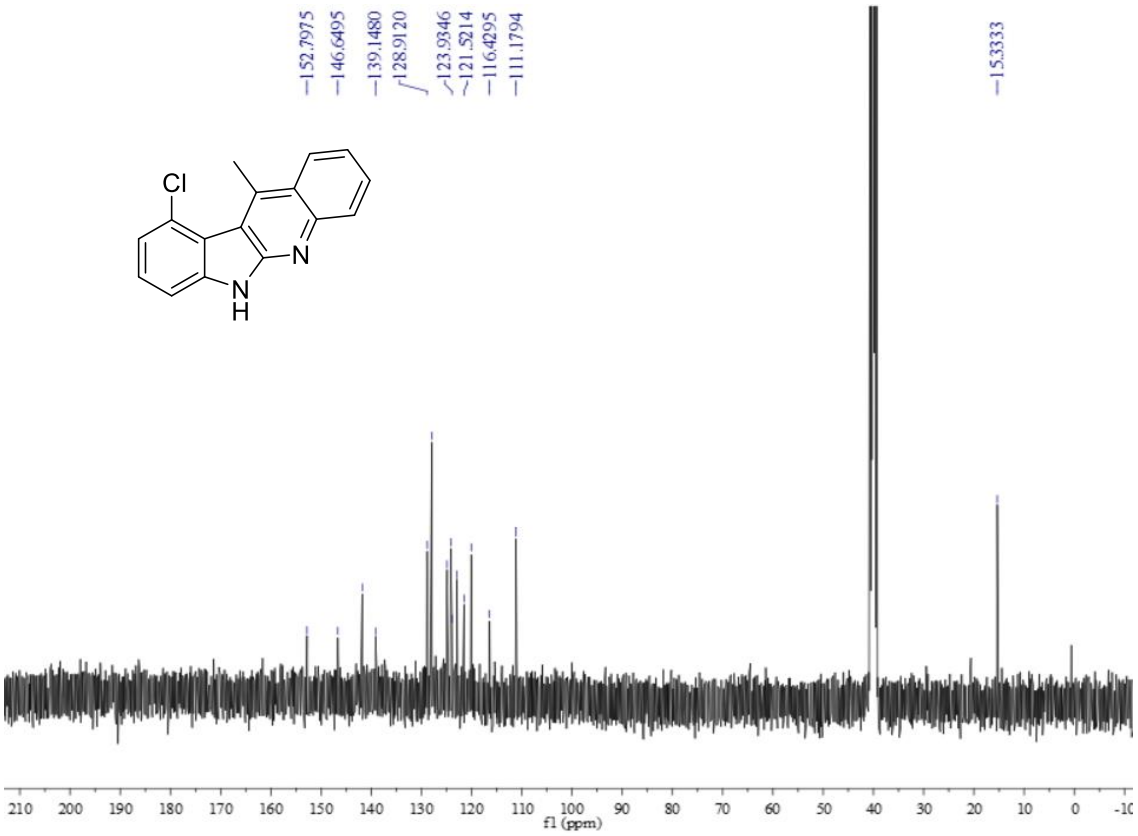


10-chloro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3c)

^{1}H NMR (400 MHz, DMSO-d_6)

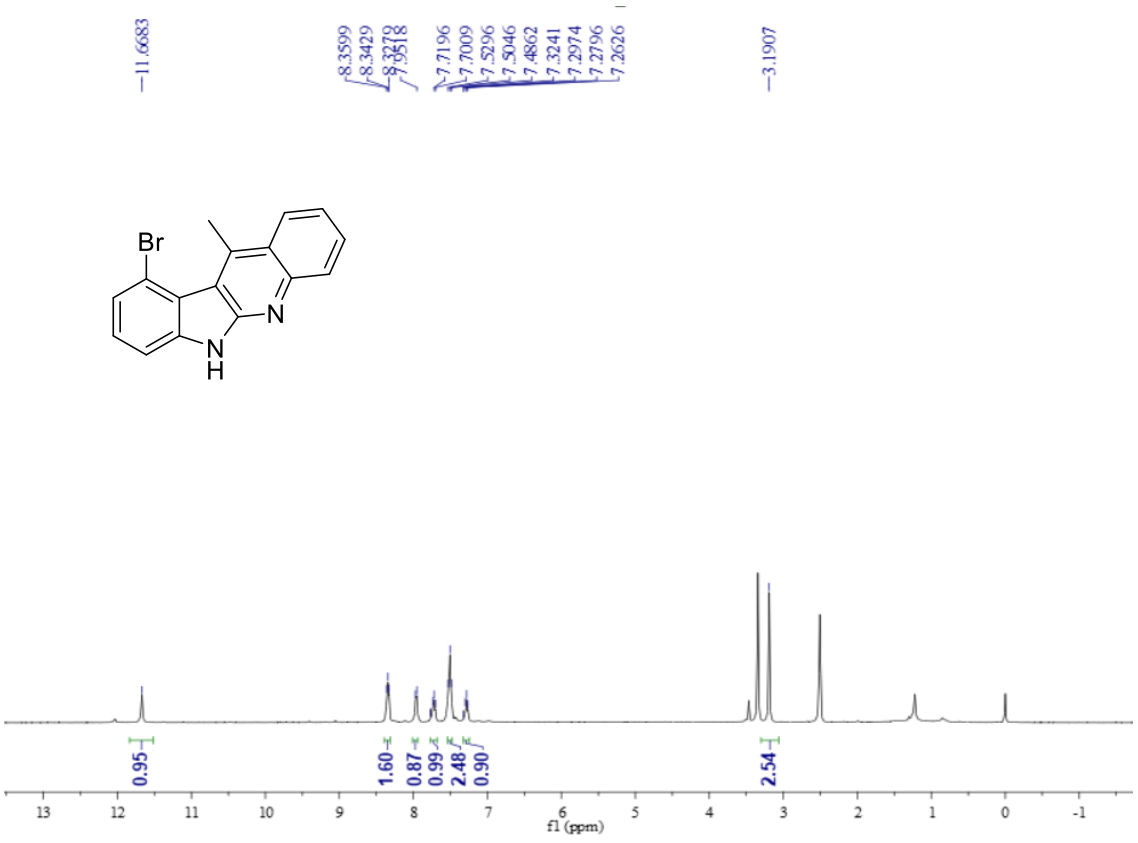


^{13}C NMR (100 MHz, DMSO-d_6)

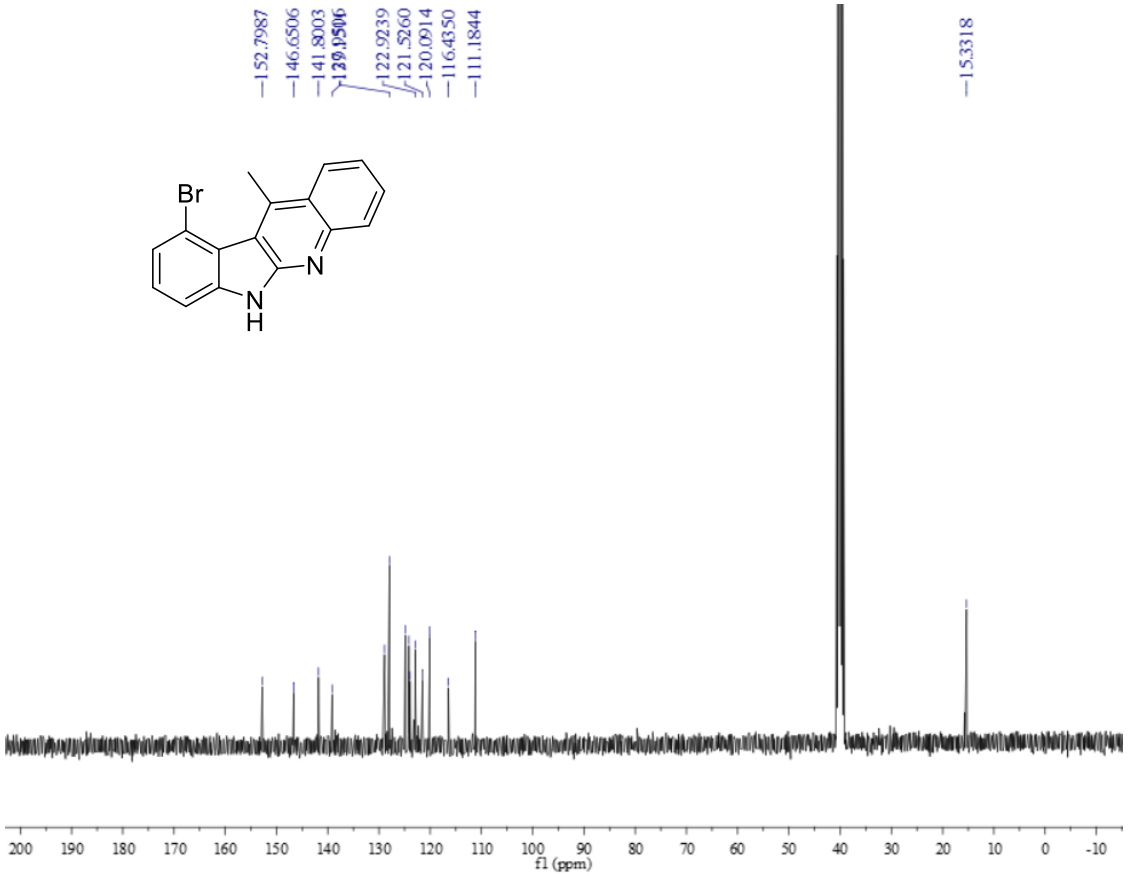


10-bromo-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3d)

^{1}H NMR (400 MHz, DMSO-d_6)

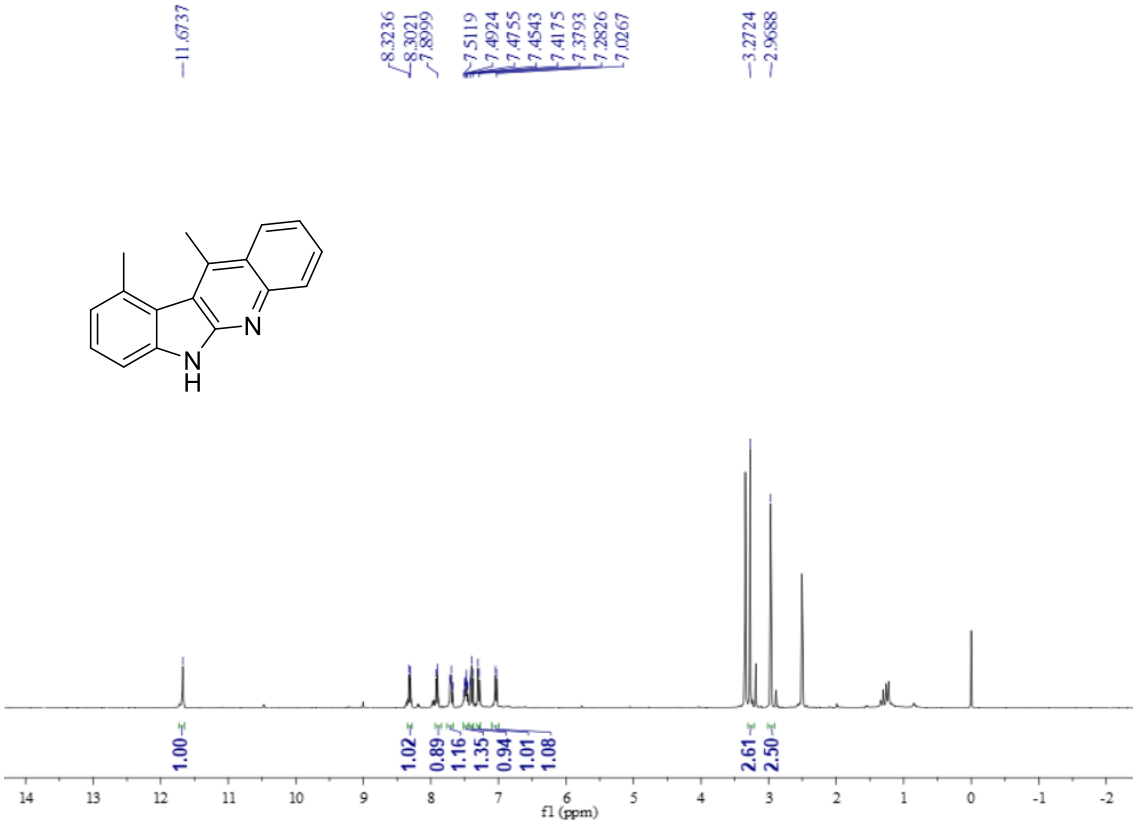


^{13}C NMR (100 MHz, DMSO-d_6)

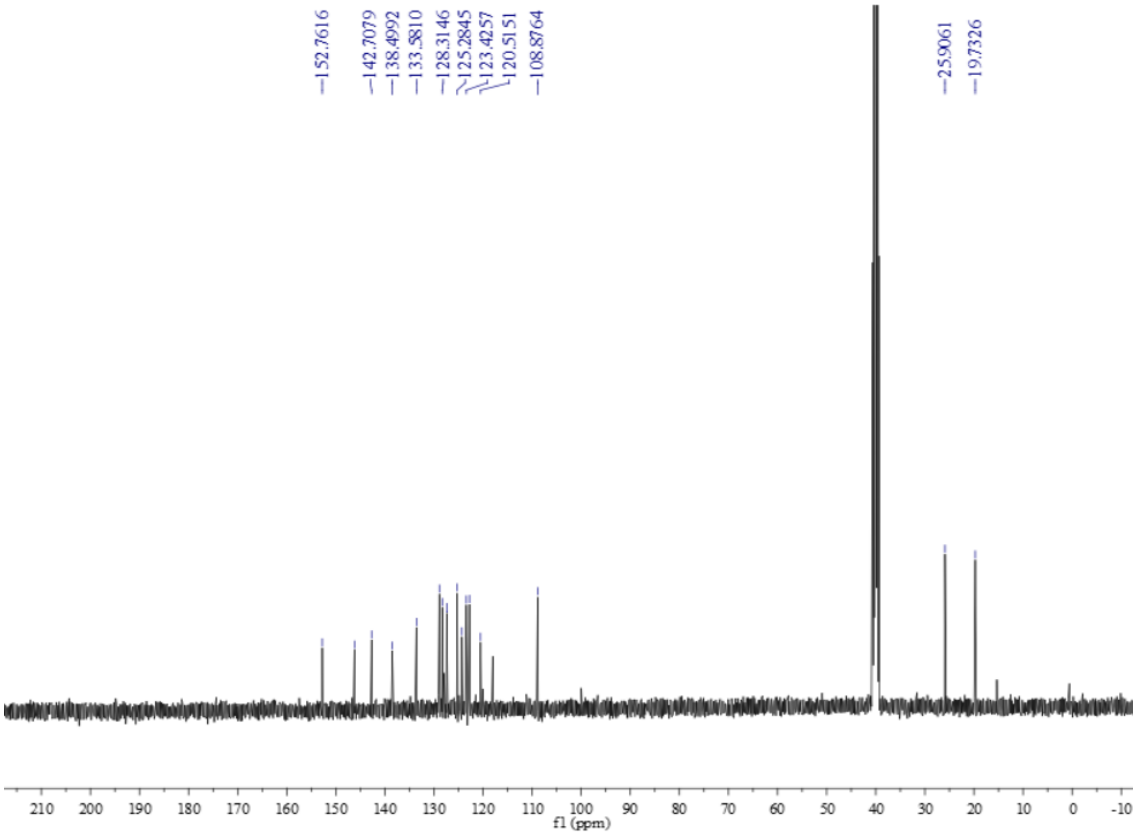


10,11-*dimethyl*-6*H*-indolo[*2,3-b*]quinoline (3e)

^{1}H NMR (400 MHz, DMSO-d_6)

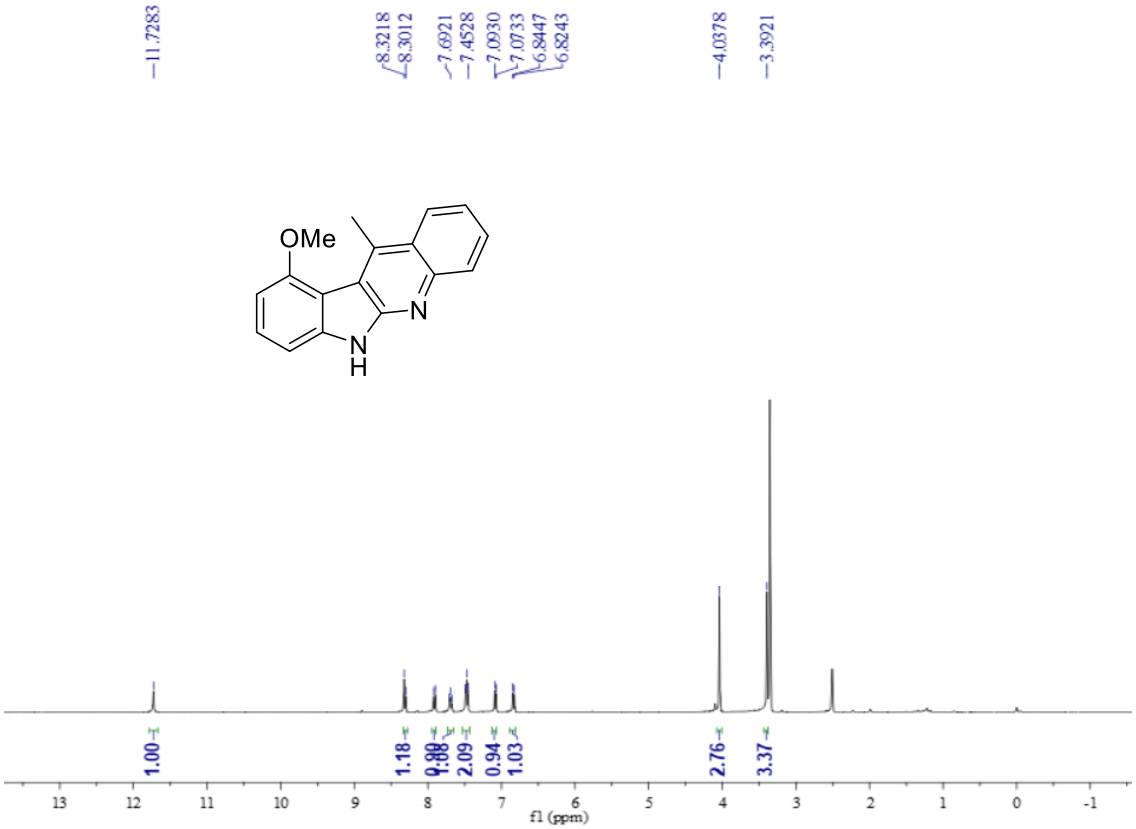


^{13}C NMR (100 MHz, DMSO-d_6)

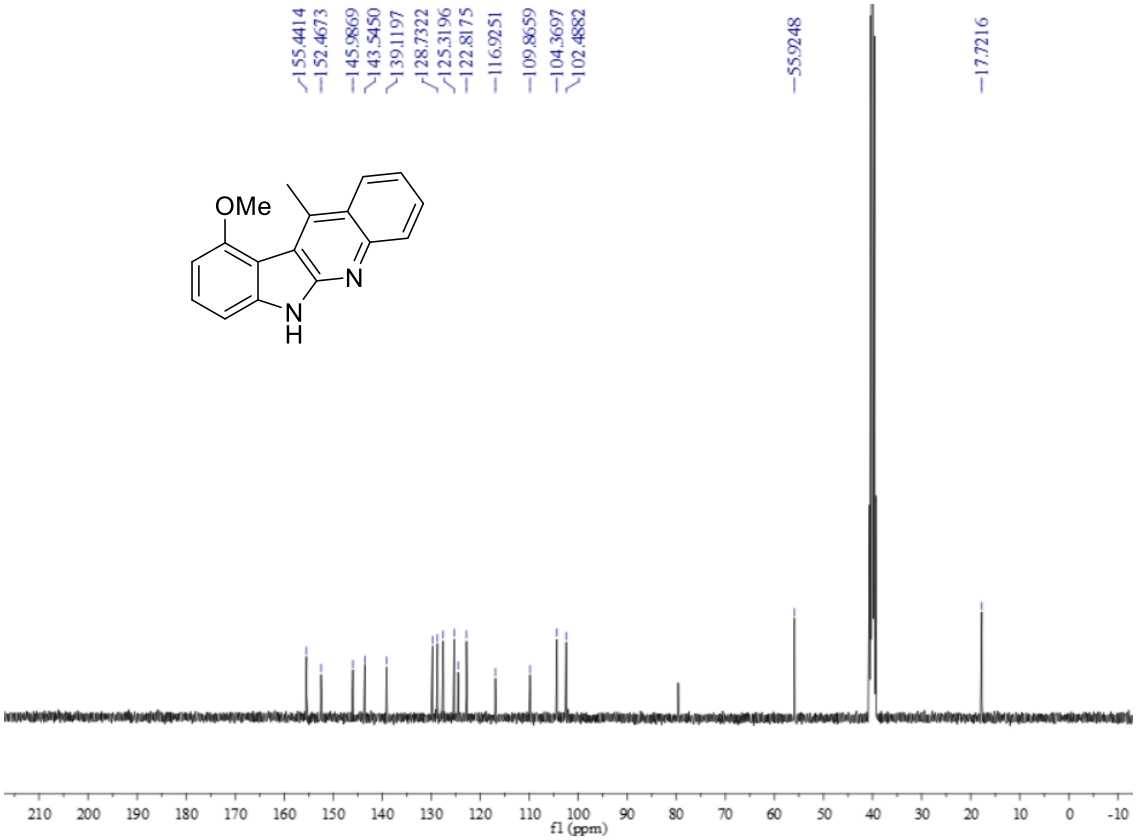


10-methoxy-11-methyl-6H-indolo[2,3-b]quinoline (3f)

^{1}H NMR (400 MHz, DMSO-d_6)

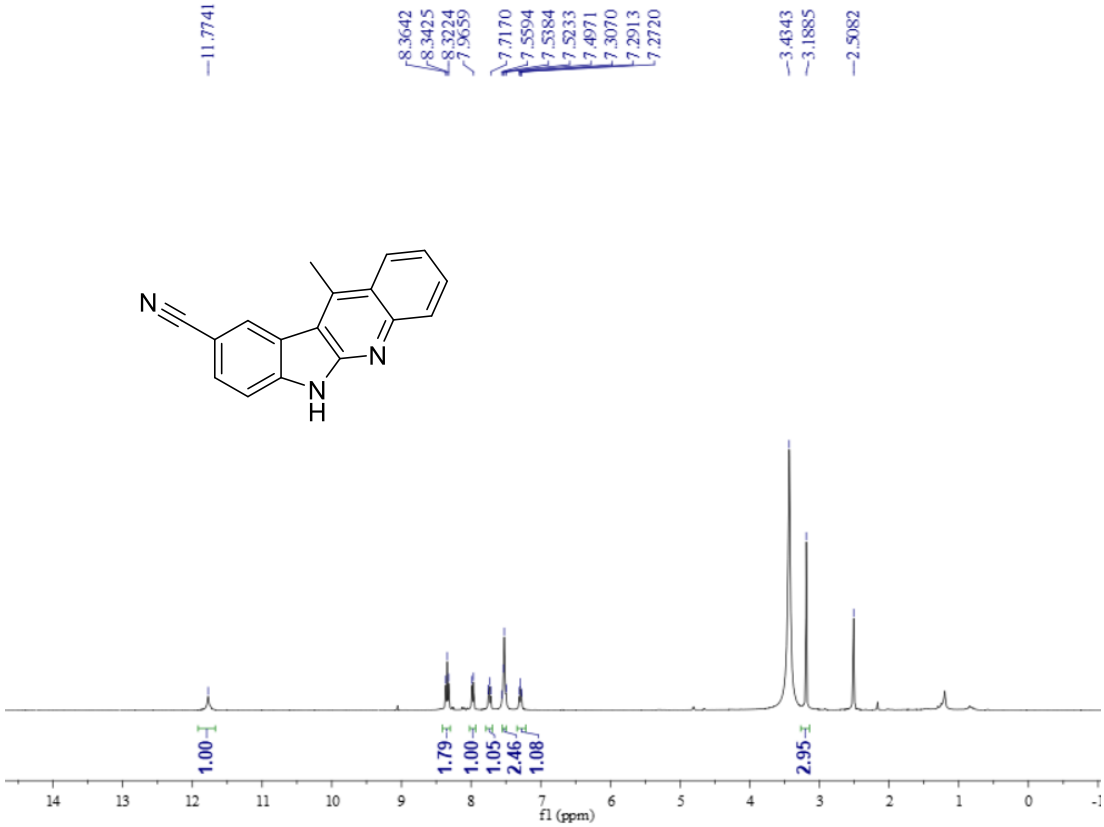


^{13}C NMR (100 MHz, DMSO-d_6)

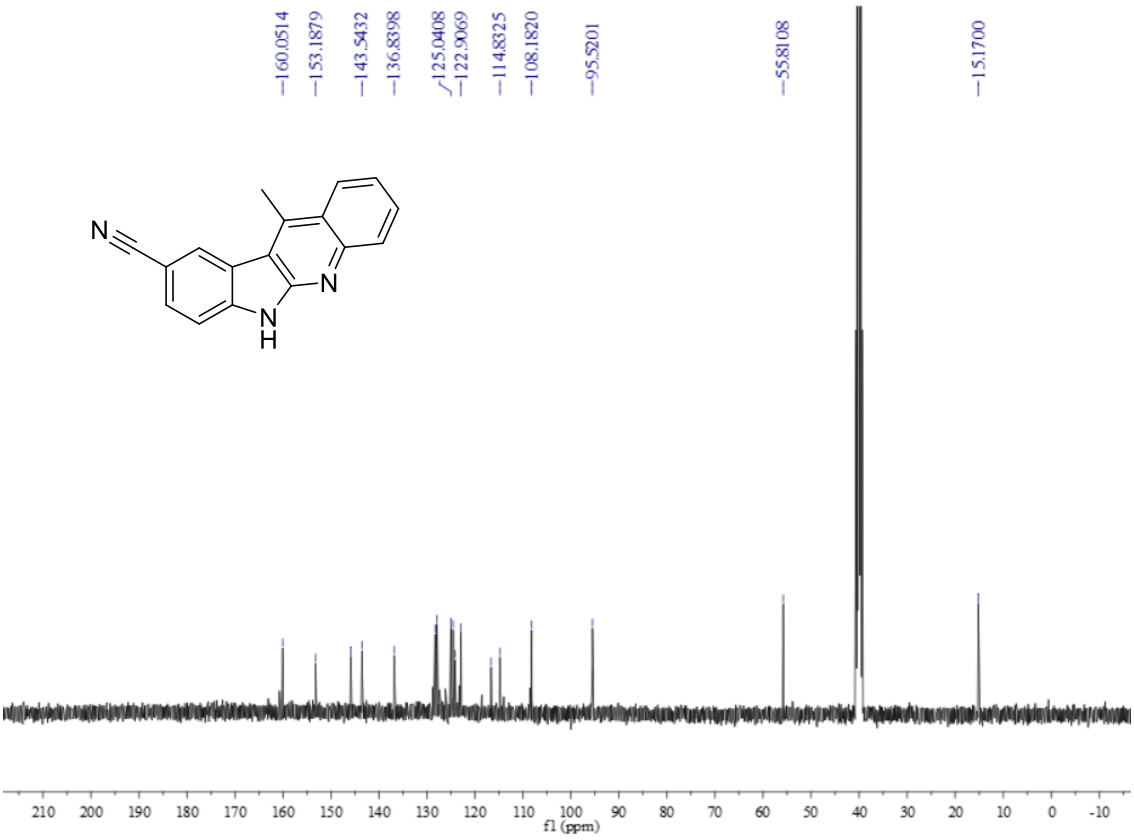


11-methyl-6*H*-indolo[*2,3-b*]quinoline-9-carbonitrile (3g)

^{1}H NMR (400 MHz, DMSO-d_6)

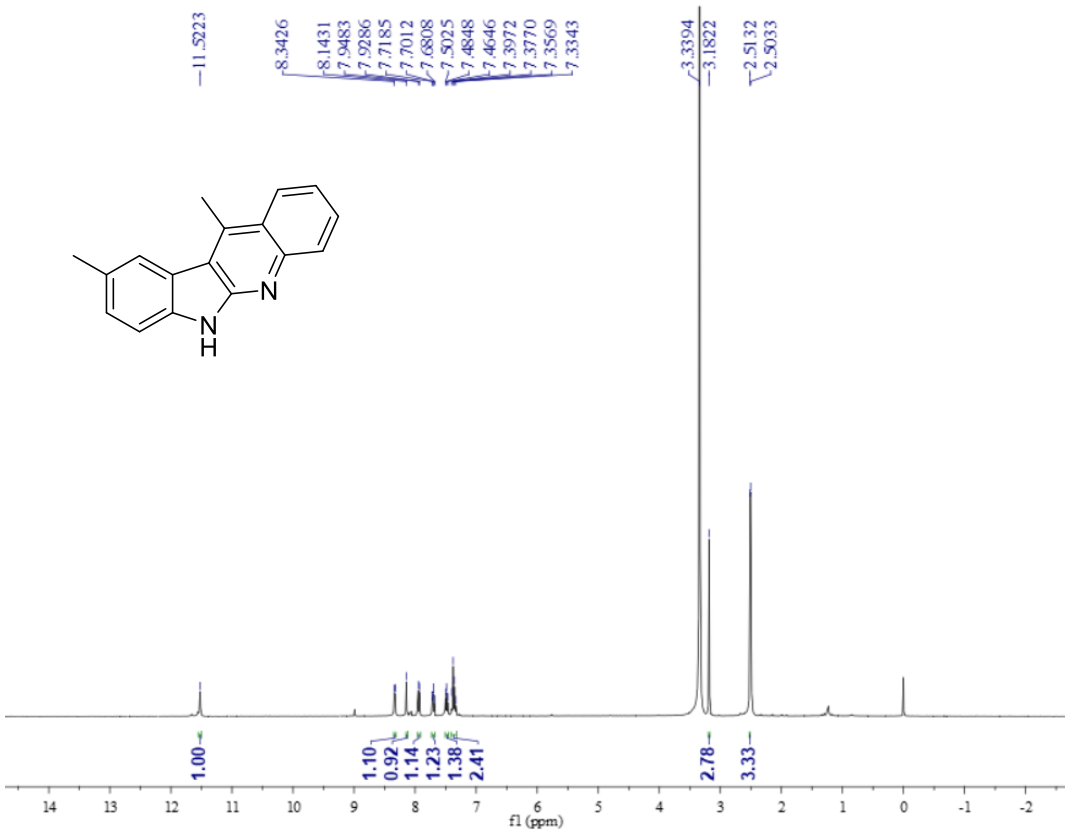


^{13}C NMR (100 MHz, DMSO-d_6)

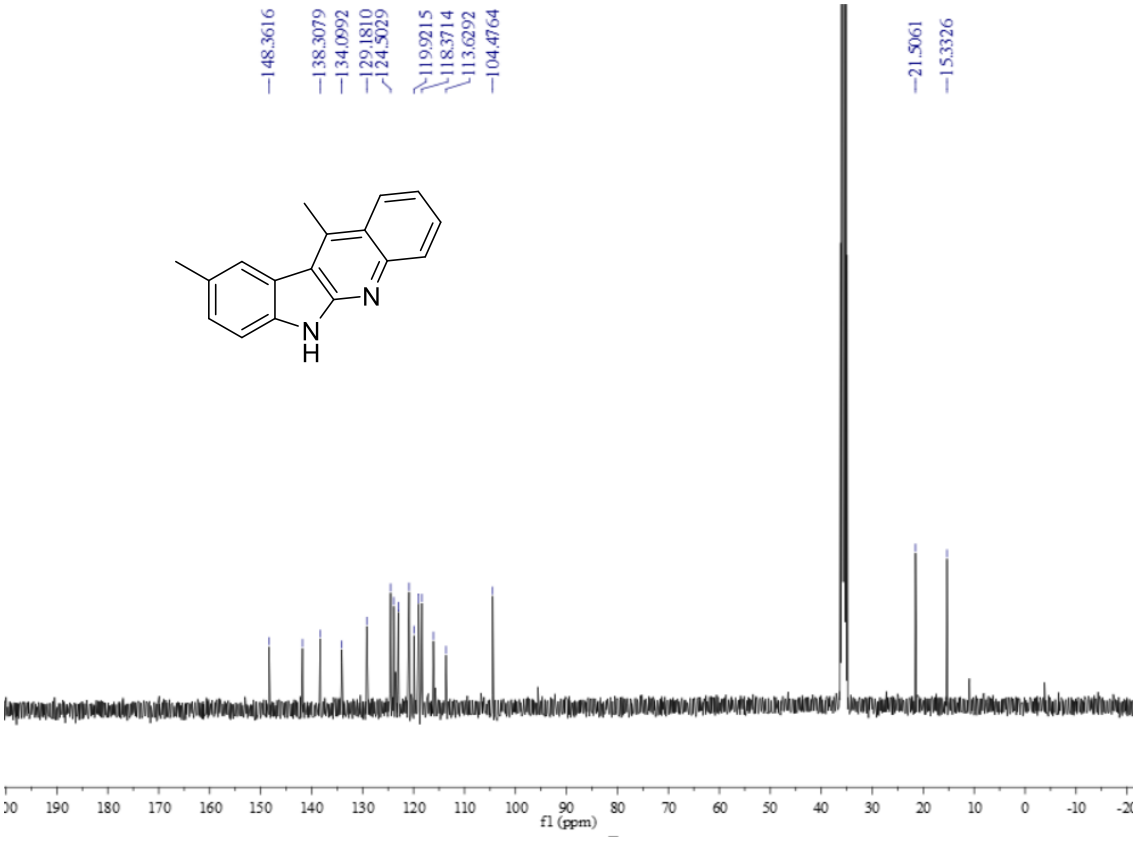


9,11-dimethyl-6*H*-indolo[*2,3-b*]quinoline (3h)

^{1}H NMR (400 MHz, DMSO-d_6)

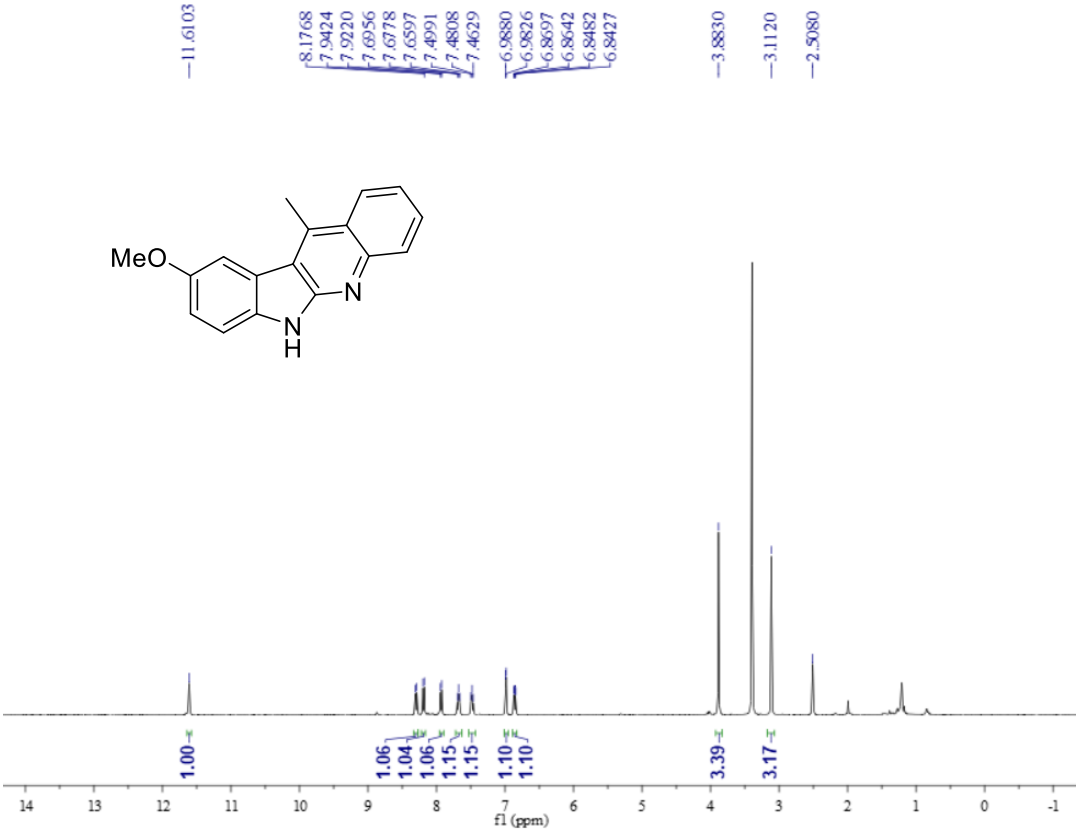


^{13}C NMR (100 MHz, DMSO-d_6)

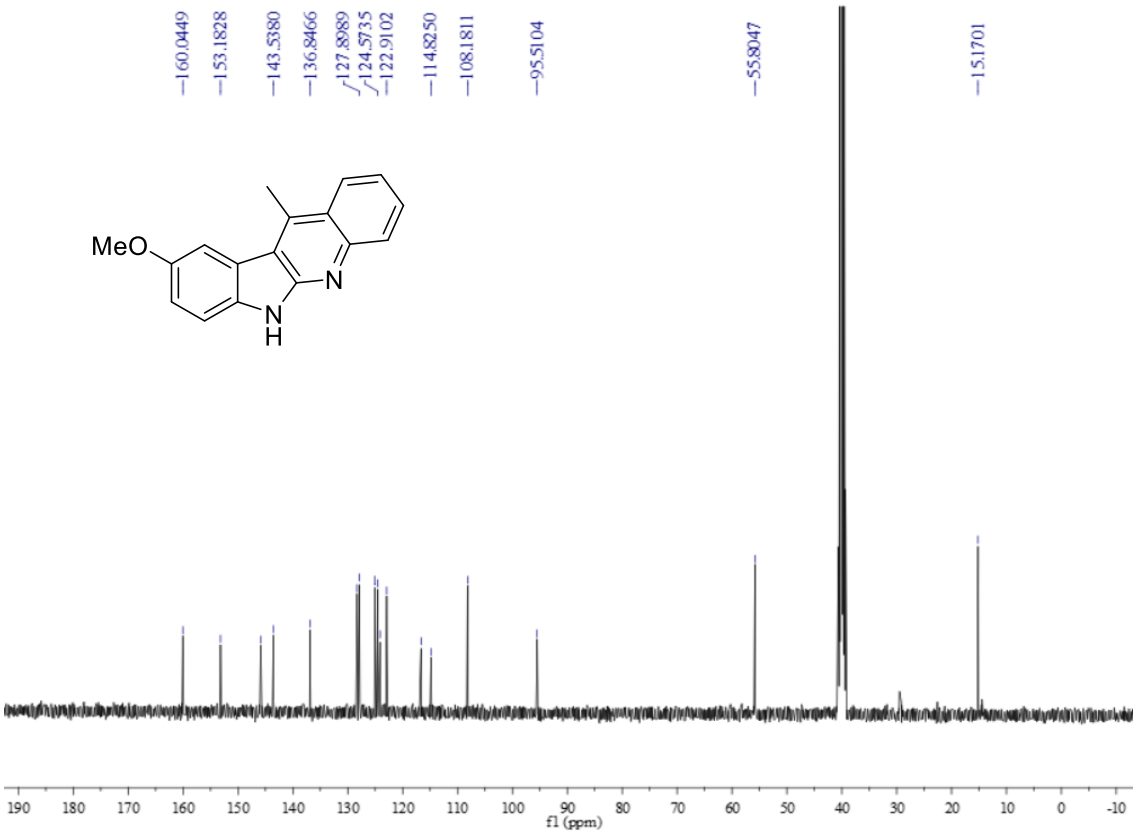


9-methoxy-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3i)

^{1}H NMR (400 MHz, DMSO-d_6)

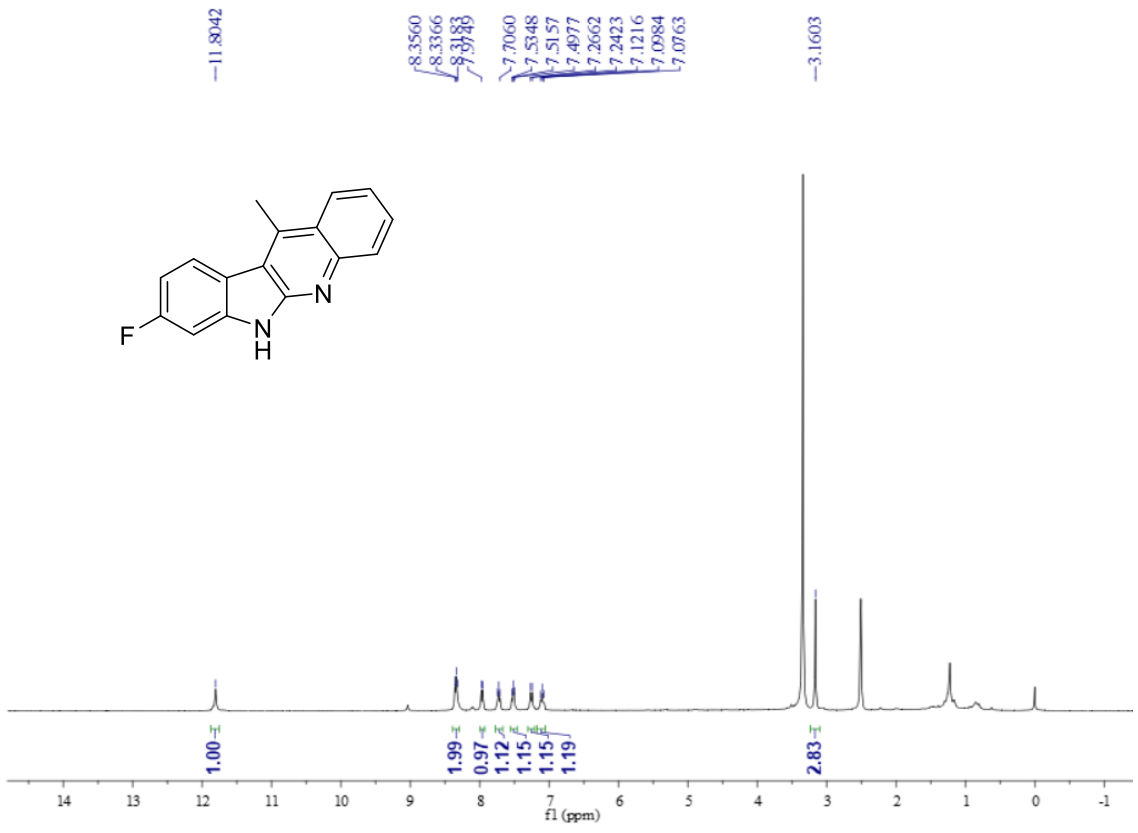


^{13}C NMR (100 MHz, DMSO-d_6)

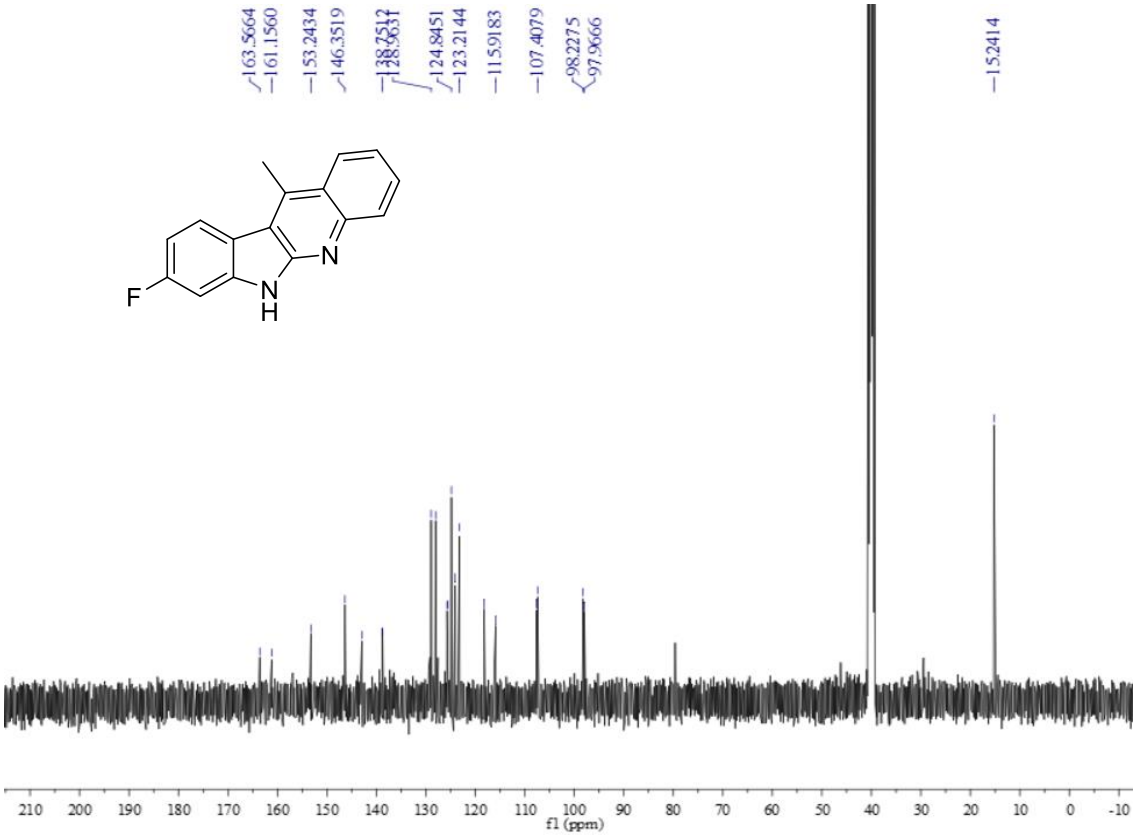


8-fluoro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3j)

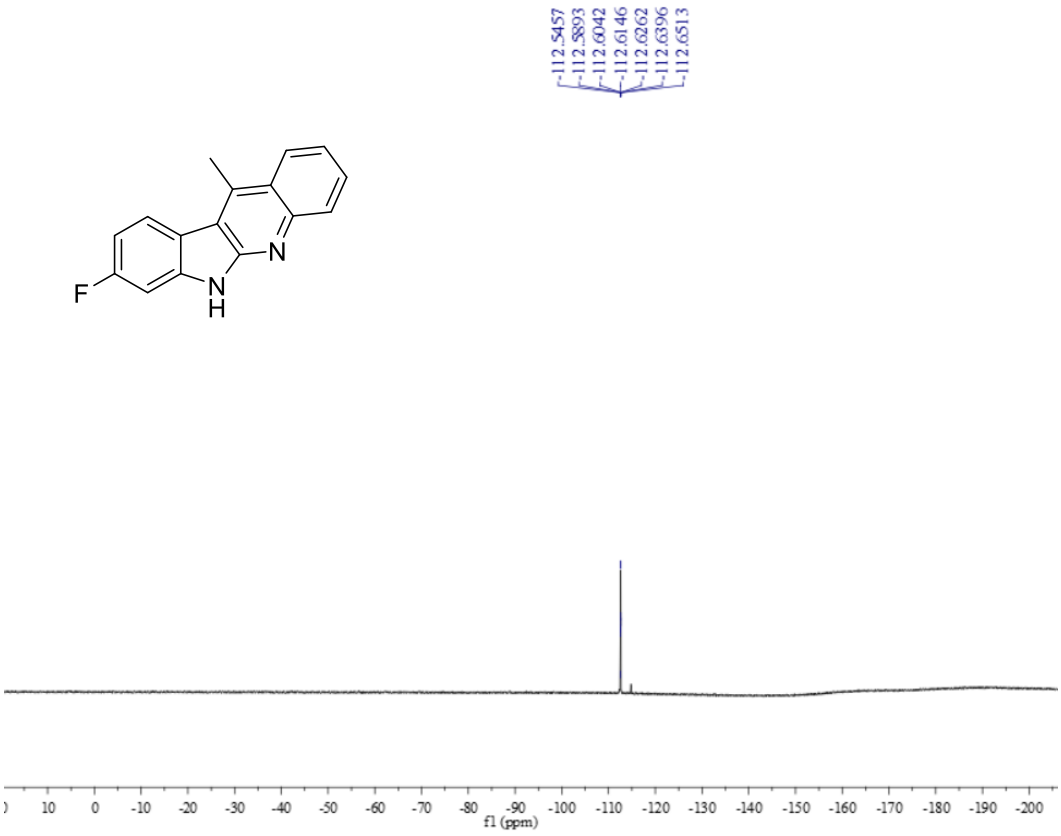
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (100 MHz, DMSO-d_6)

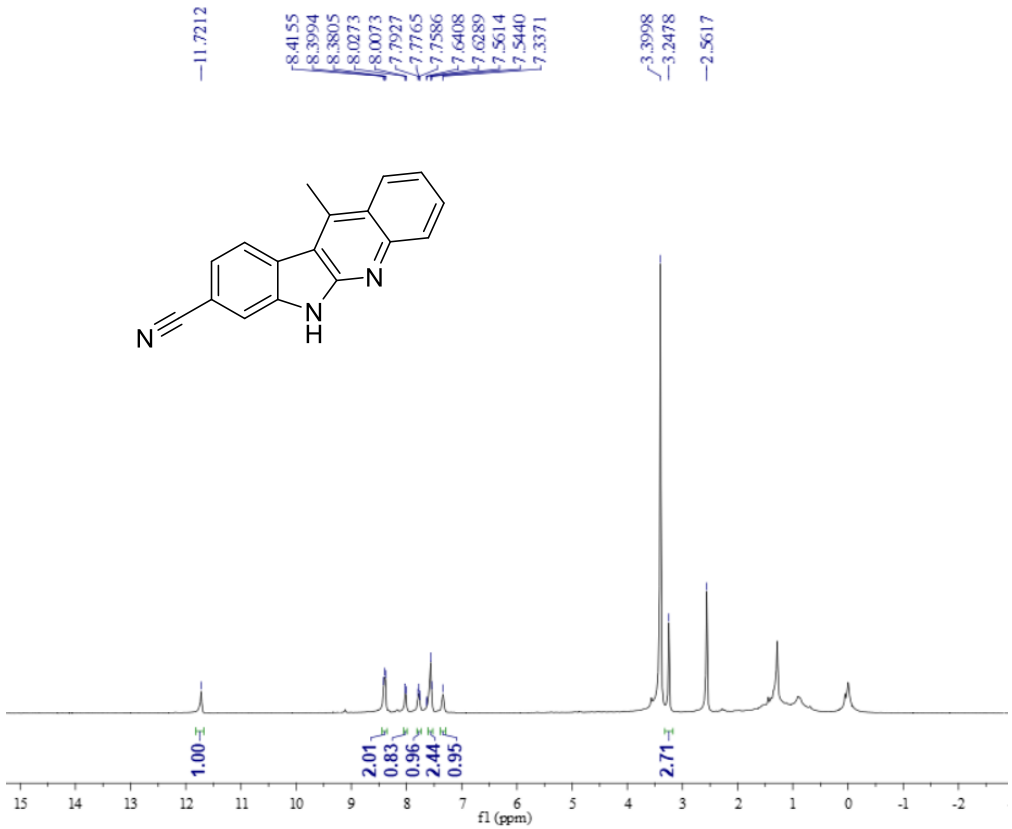


^{19}F NMR (376 MHz, DMSO-d_6)

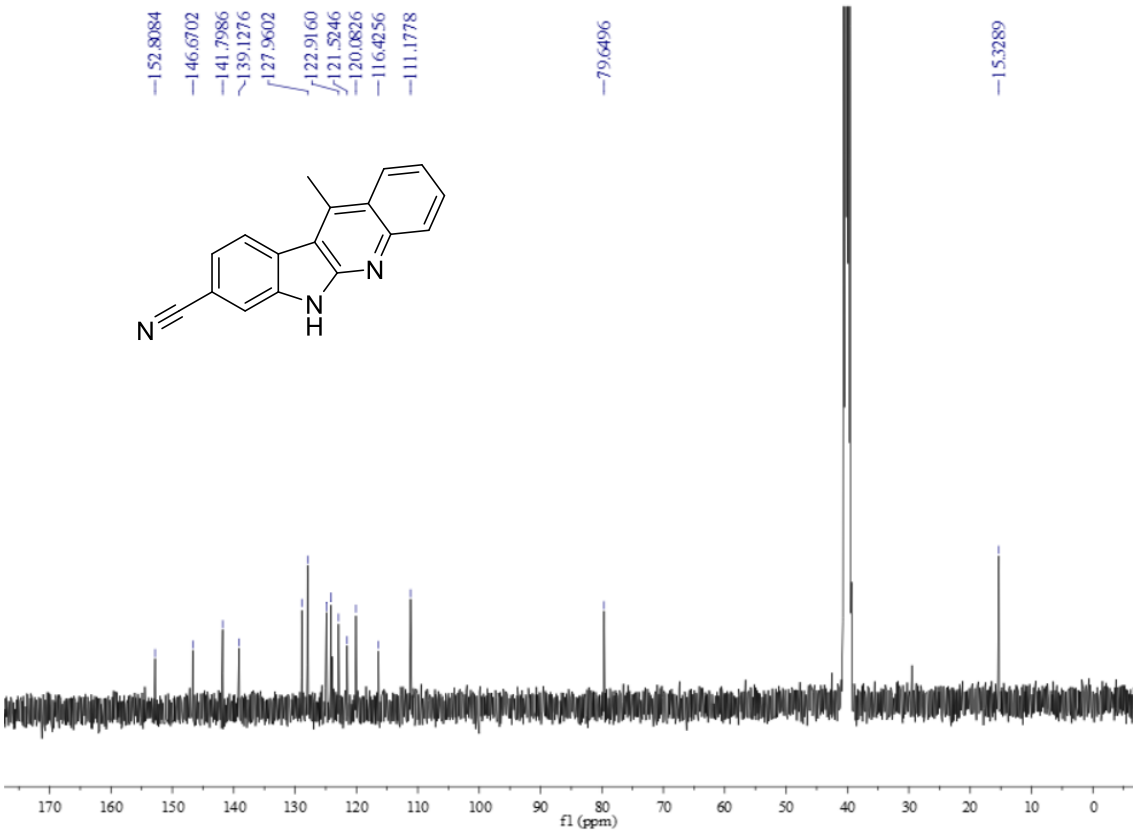


11-methyl-6*H*-indolo[*2,3-b*]quinoline-8-carbonitrile (3k)

^{1}H NMR (400 MHz, DMSO-d_6)

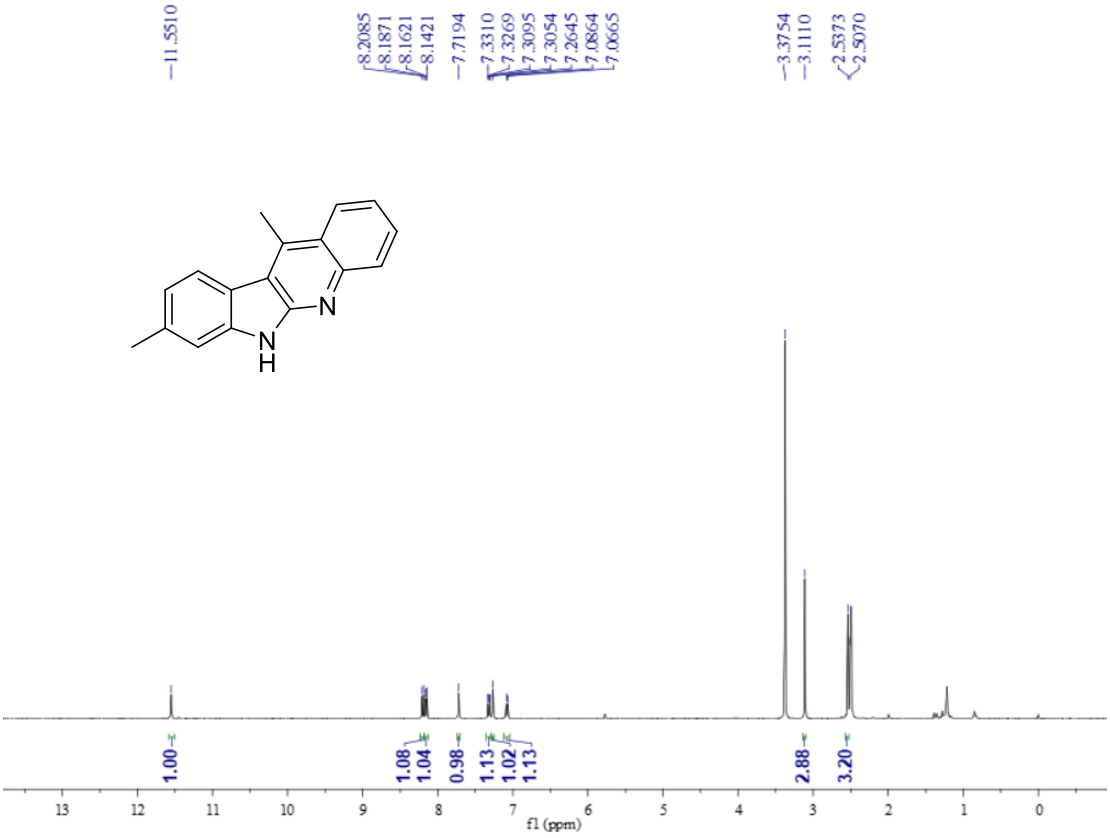


^{13}C NMR (100 MHz, DMSO-d_6)

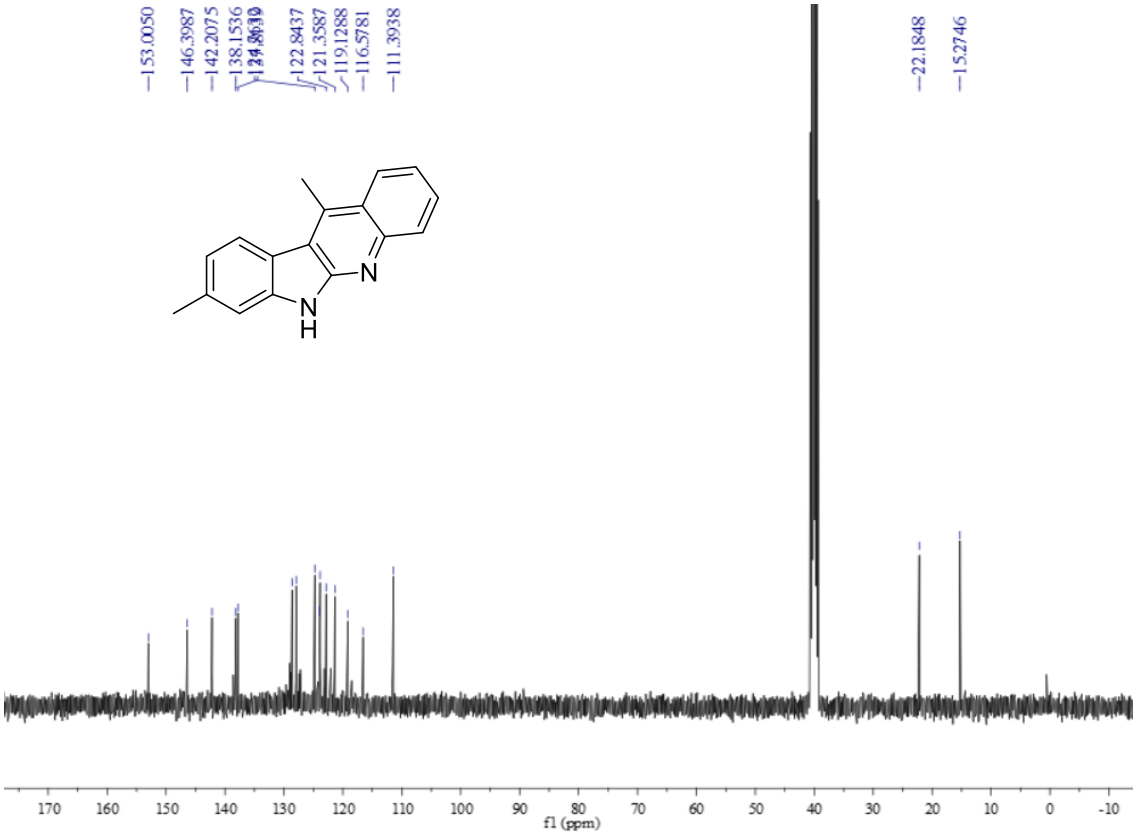


8,11-dimethyl-6*H*-indolo[*2,3-b*]quinoline (3l)

^{1}H NMR (400 MHz, DMSO-d_6)

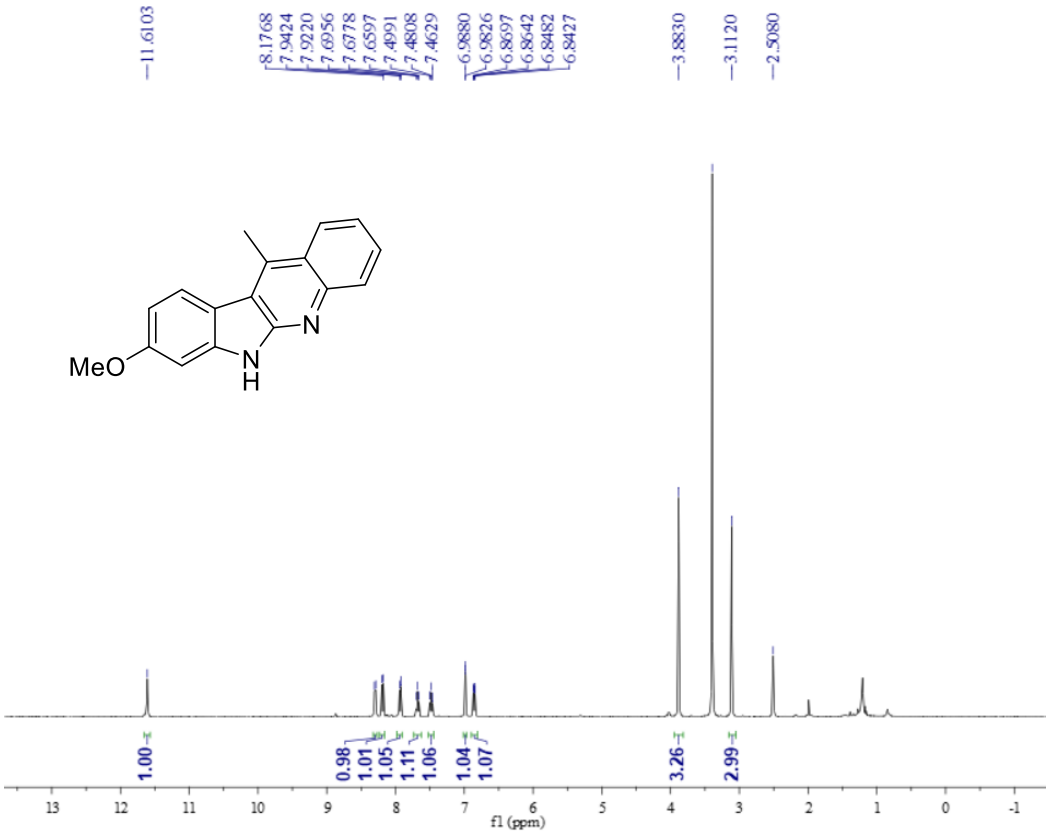


^{13}C NMR (100 MHz, DMSO-d_6)

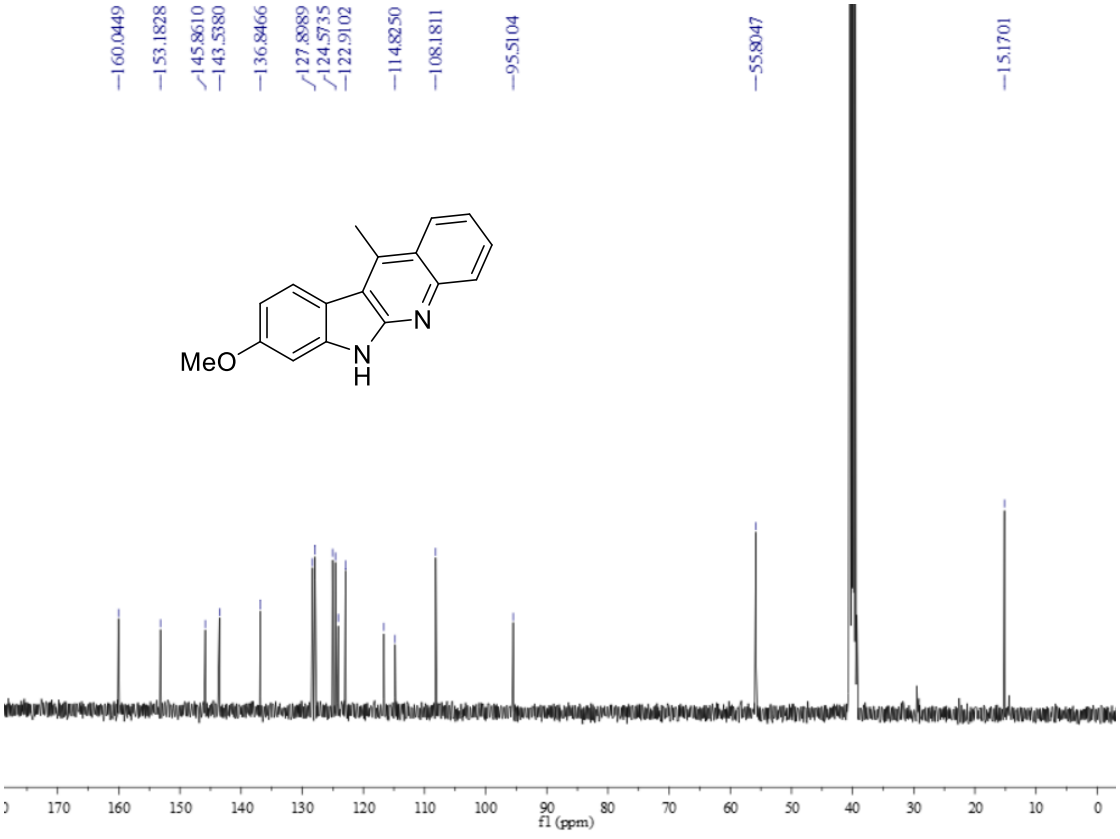


8-methoxy-11-methyl-6H-indolo[2,3-b]quinoline (3m)

^{1}H NMR (400 MHz, DMSO-d_6)

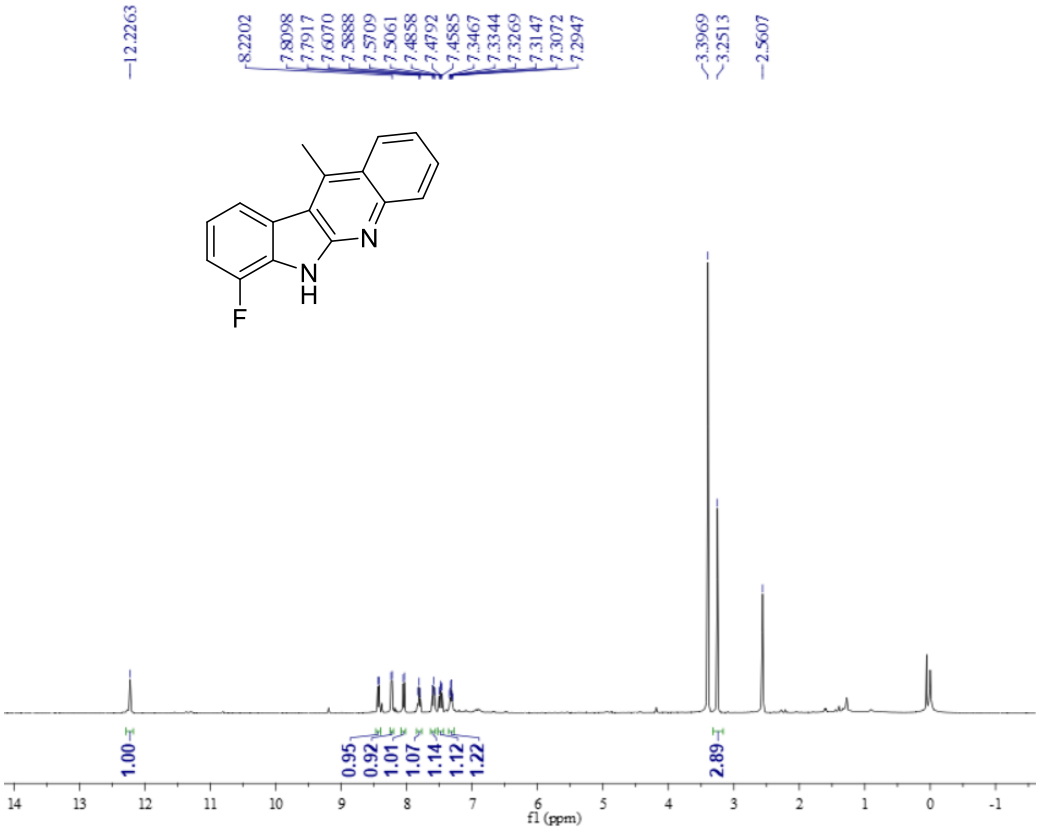


^{13}C NMR (100 MHz, DMSO-d_6)

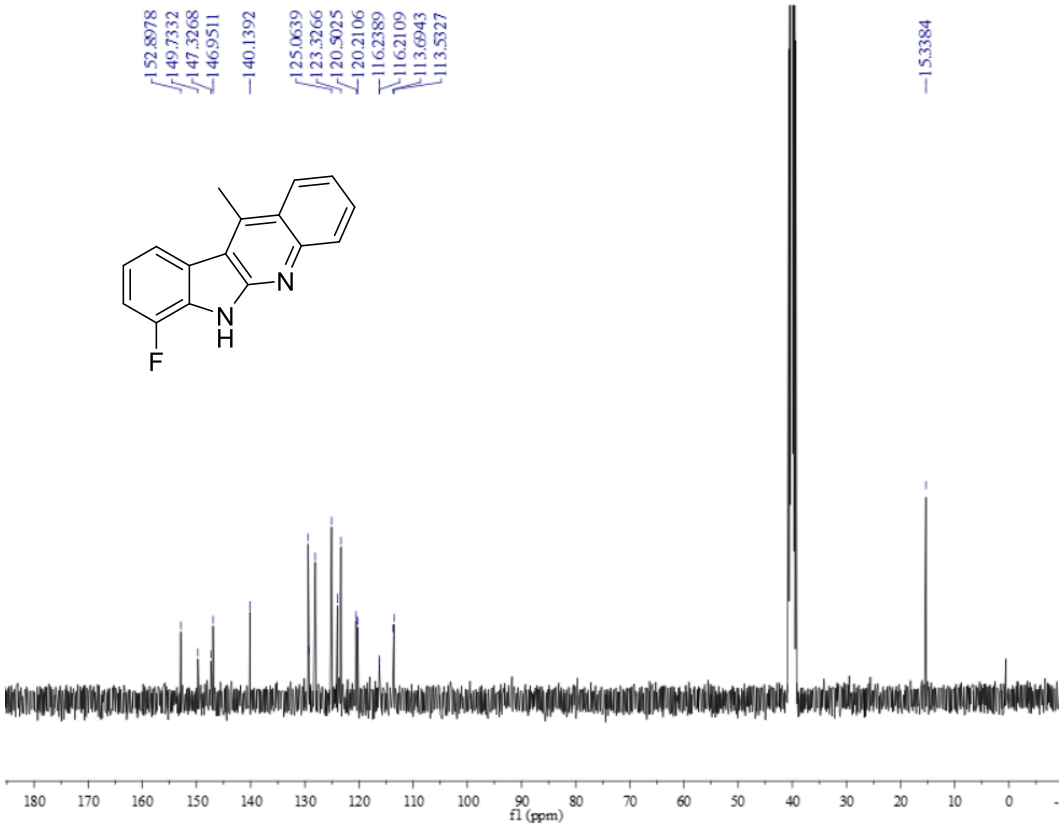


7-fluoro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3n)

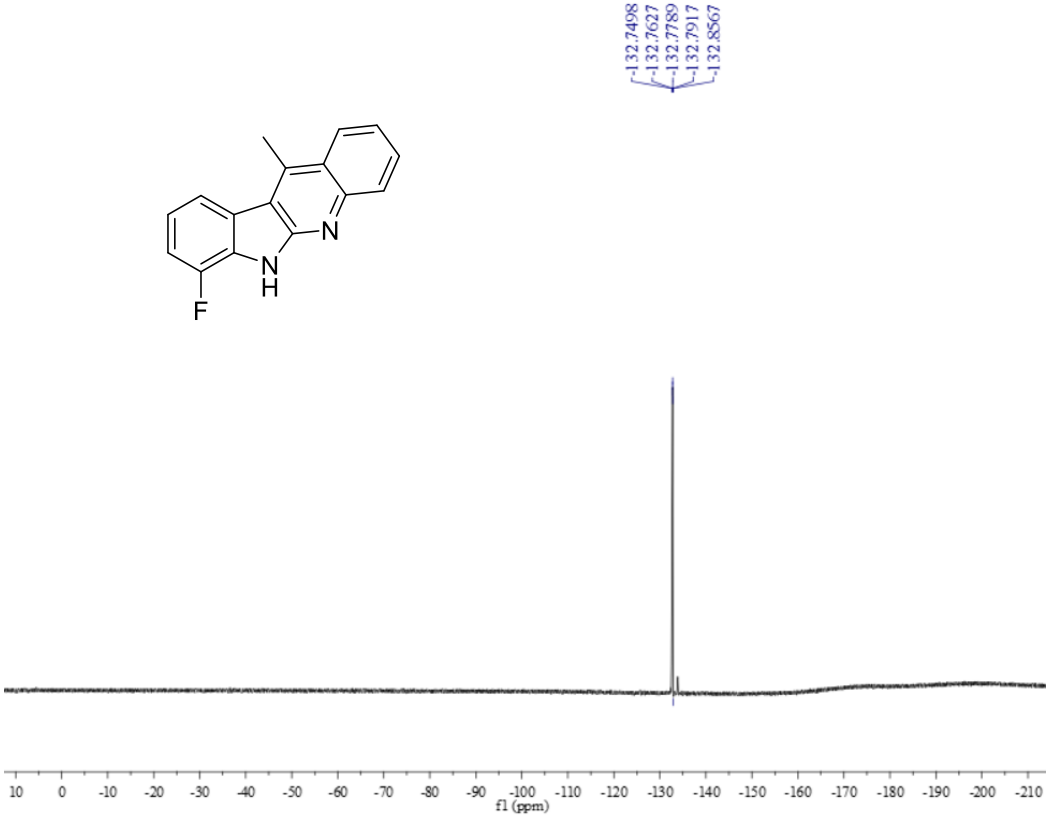
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (100 MHz, DMSO-d_6)

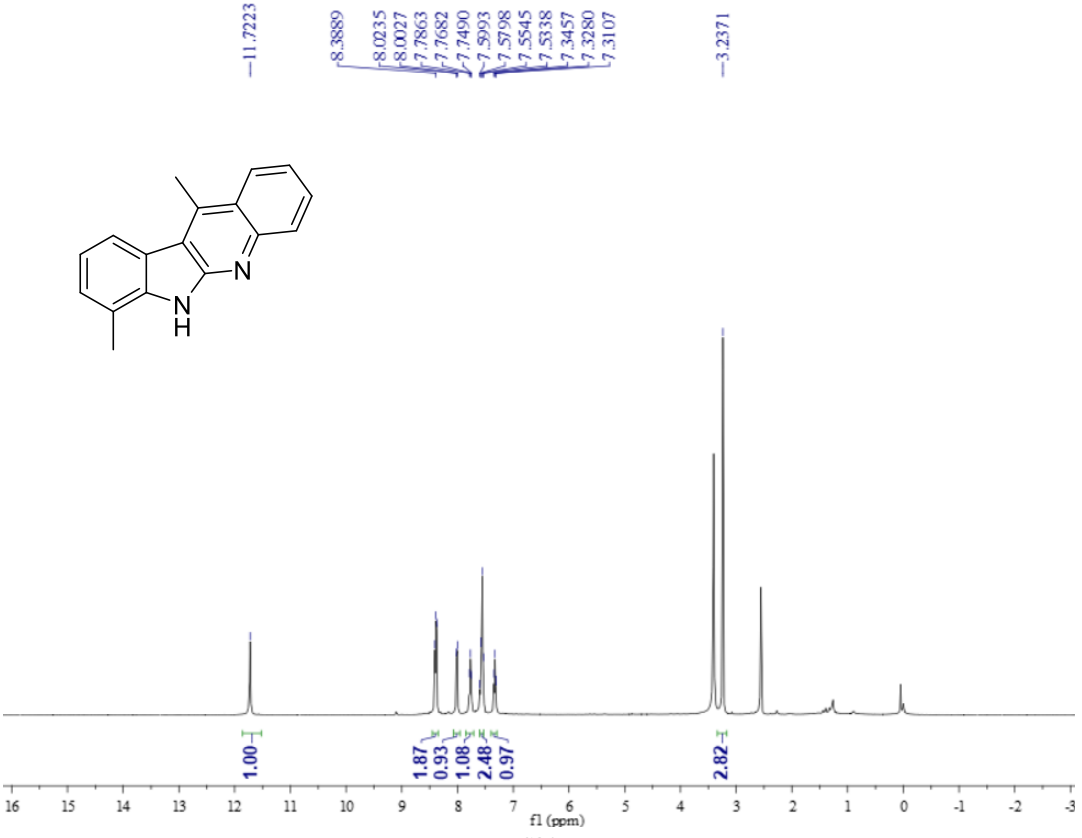


^{19}F NMR (376 MHz, DMSO-d_6)

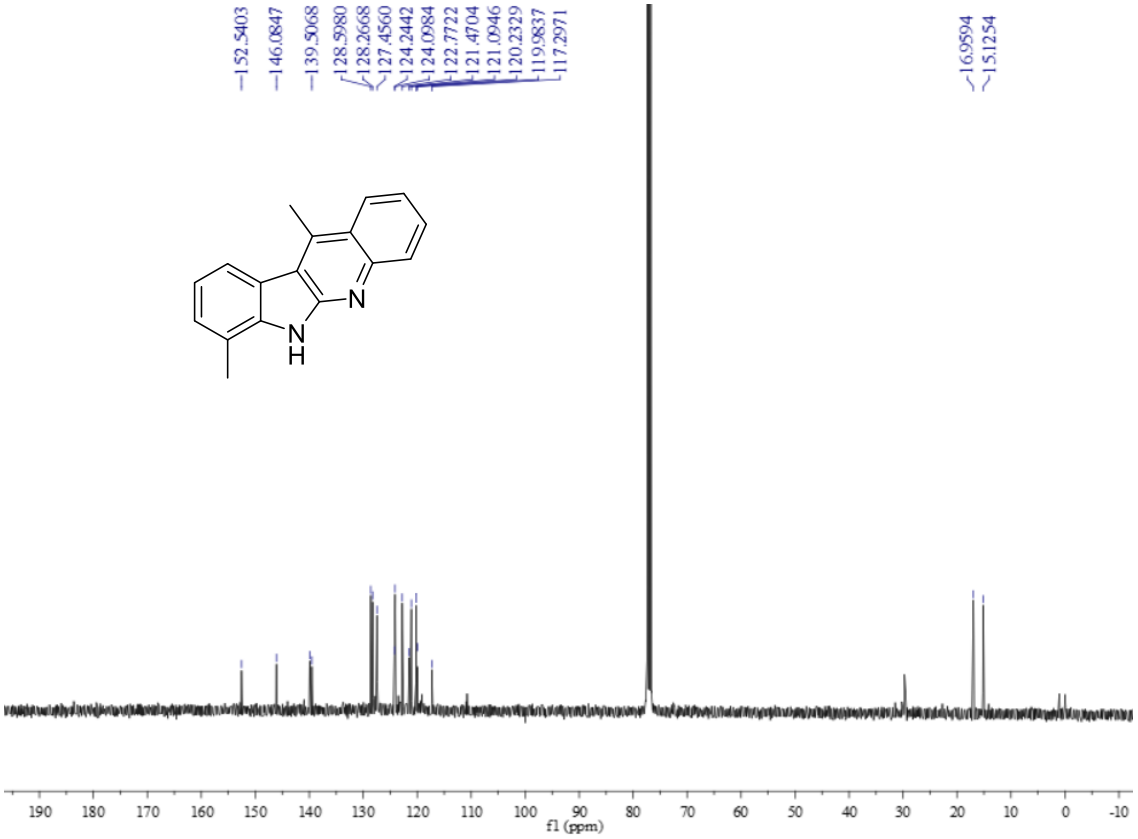


7,11-dimethyl-6*H*-indolo[*2,3-b*]quinoline (3o)

^{1}H NMR (400 MHz, DMSO-d_6)

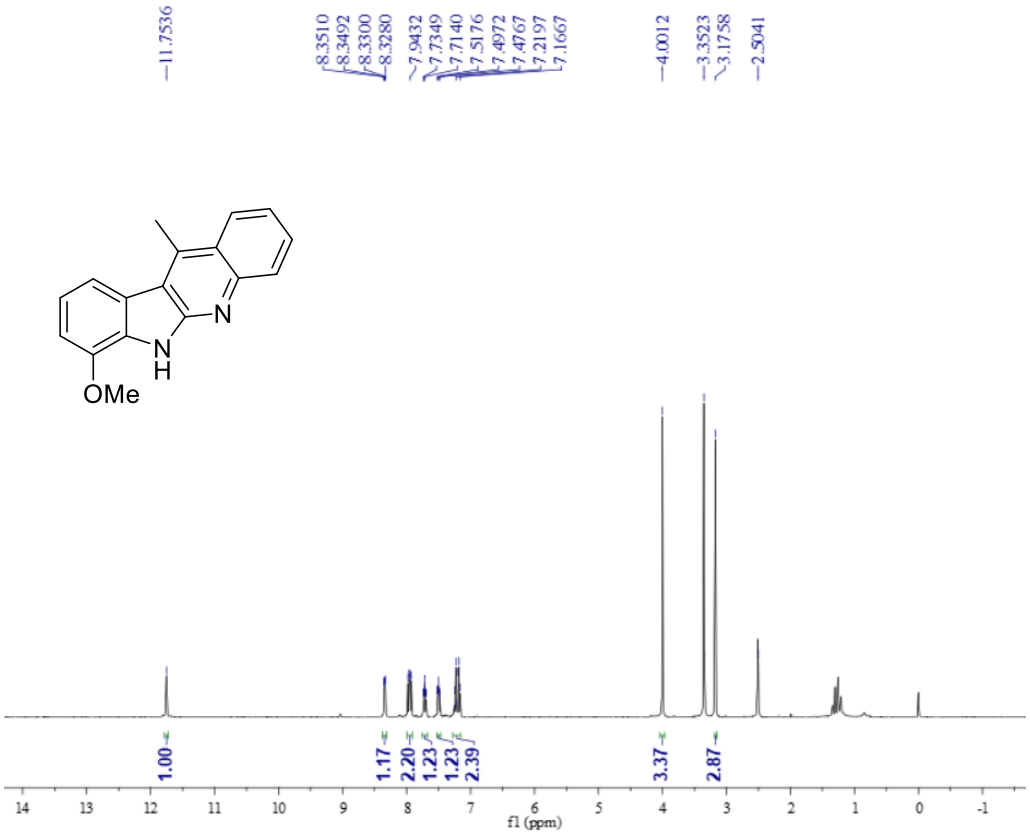


^{13}C NMR (100 MHz, DMSO-d_6)

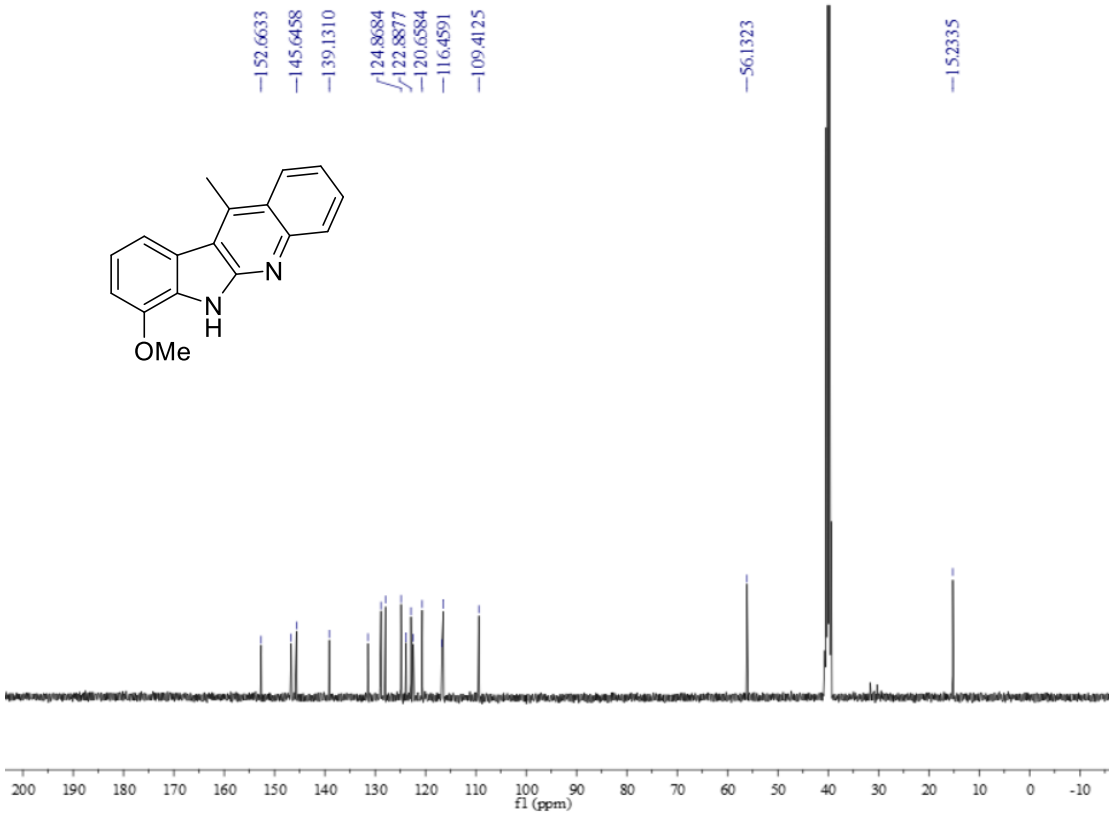


7-methoxy-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3p)

^{1}H NMR (400 MHz, DMSO-d_6)

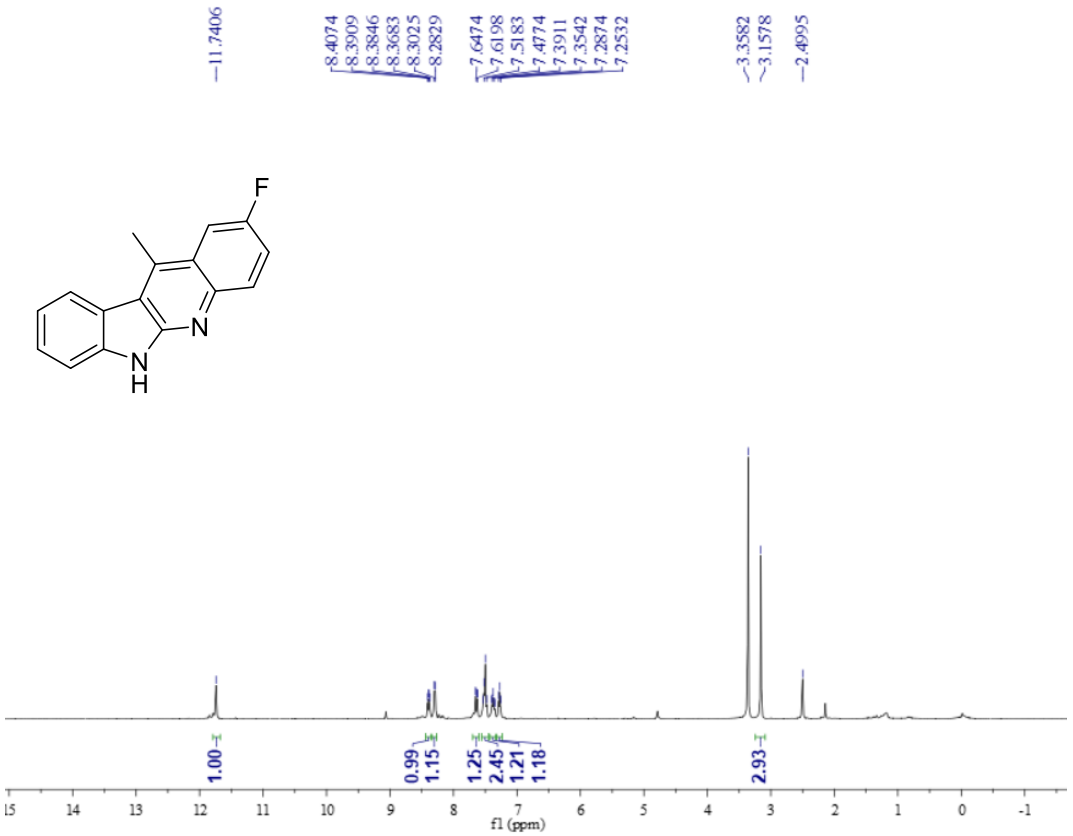


^{13}C NMR (100 MHz, DMSO-d_6)

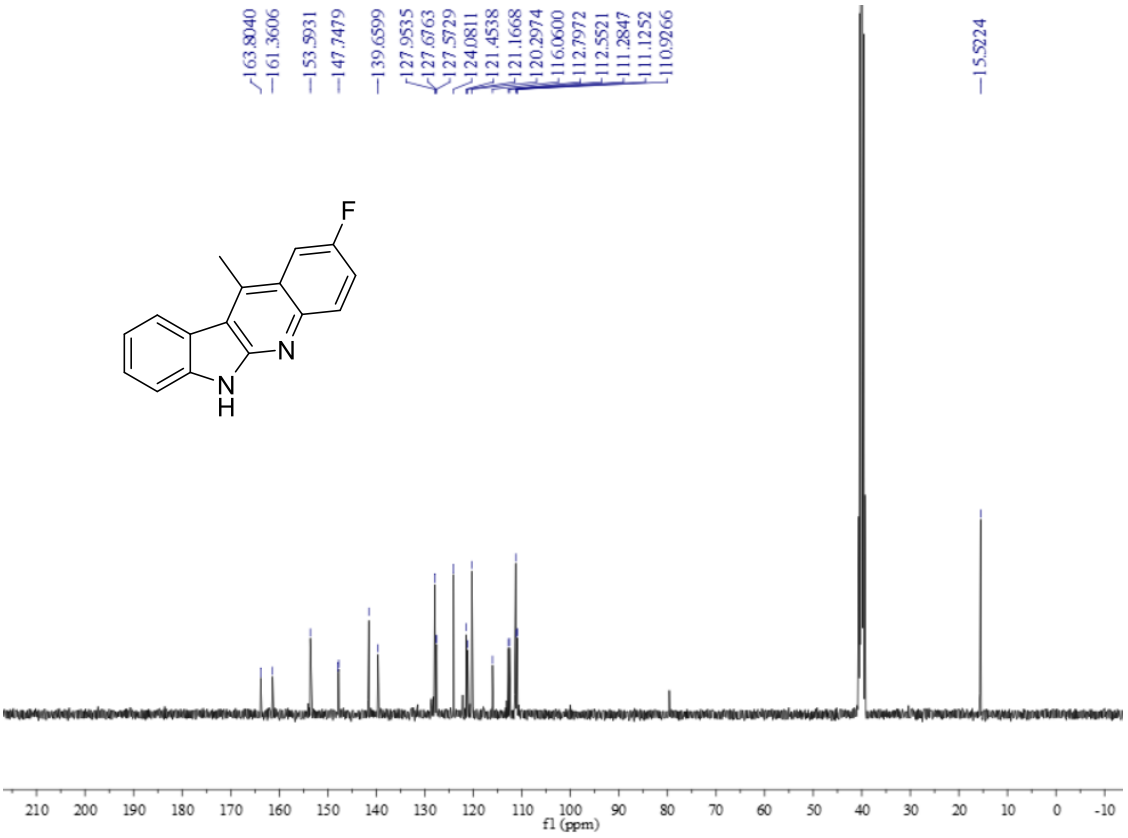


2-fluoro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3q)

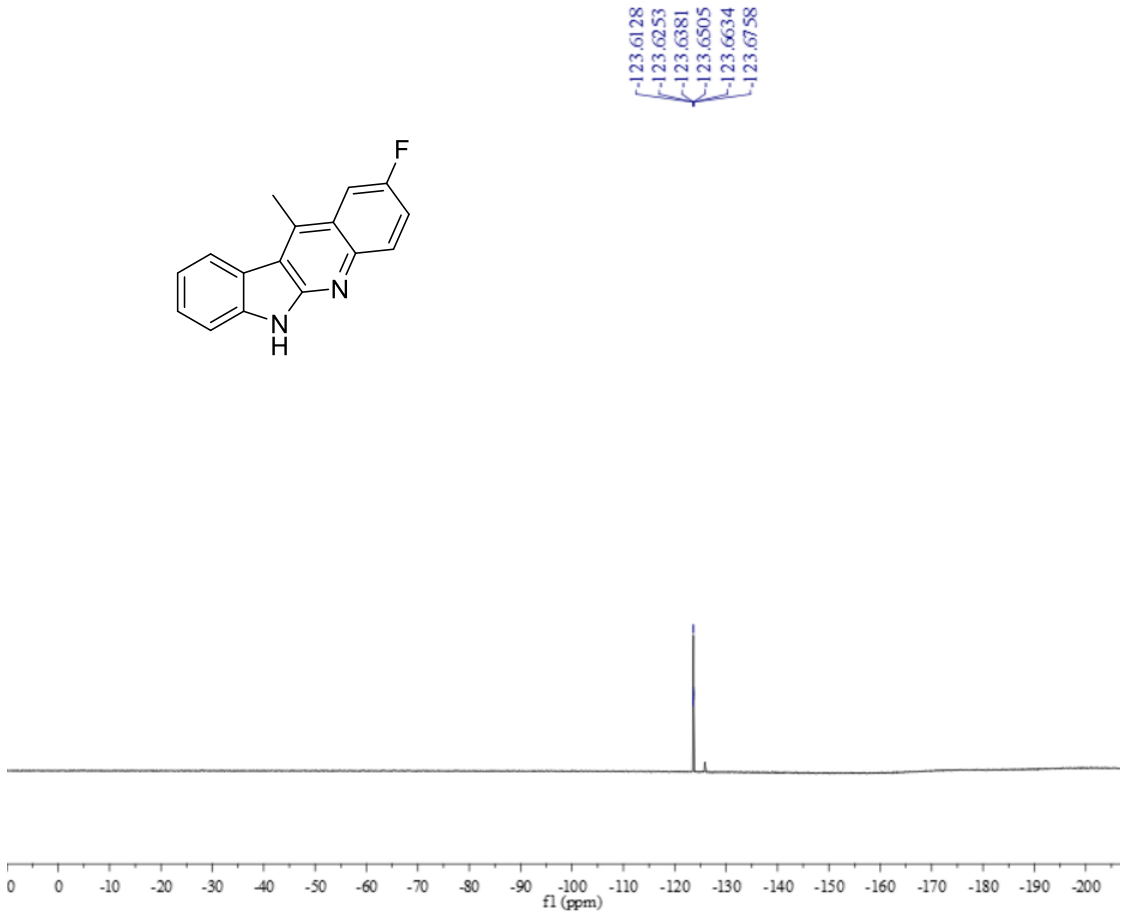
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (100 MHz, DMSO-d_6)

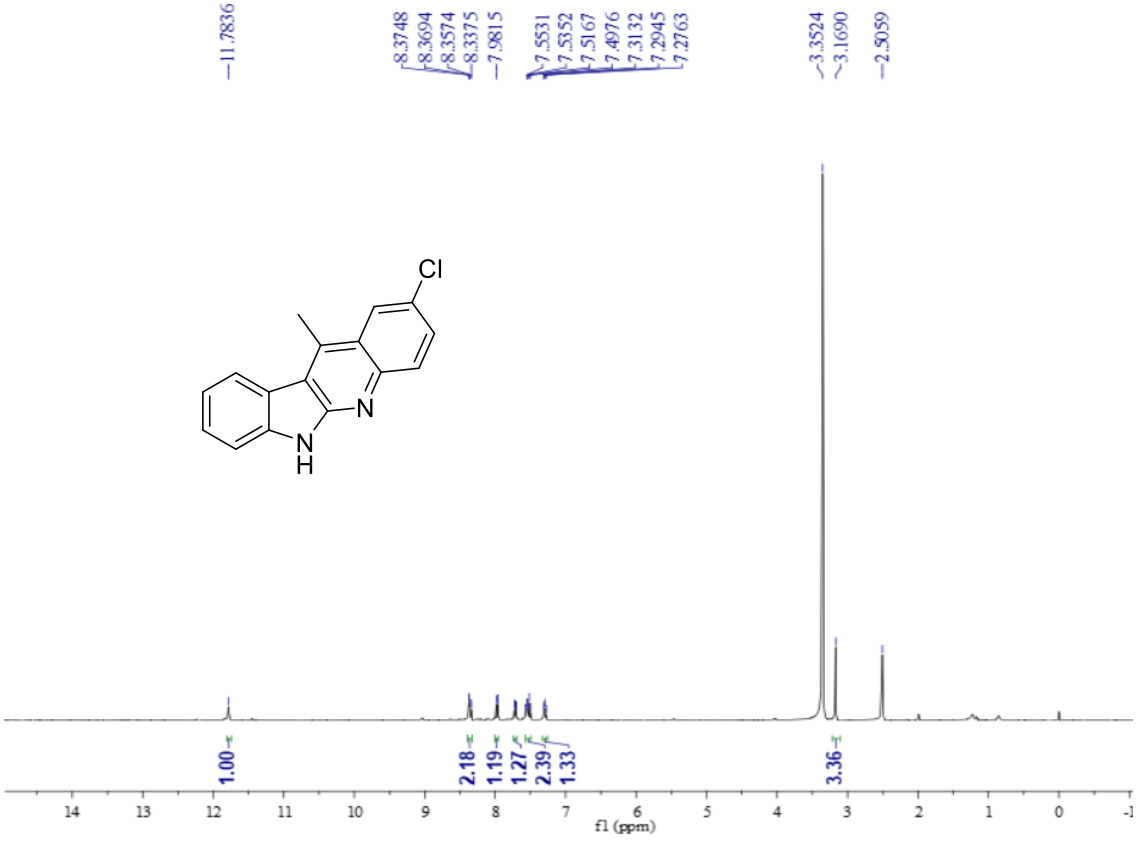


^{19}F NMR (376 MHz, DMSO-d_6)

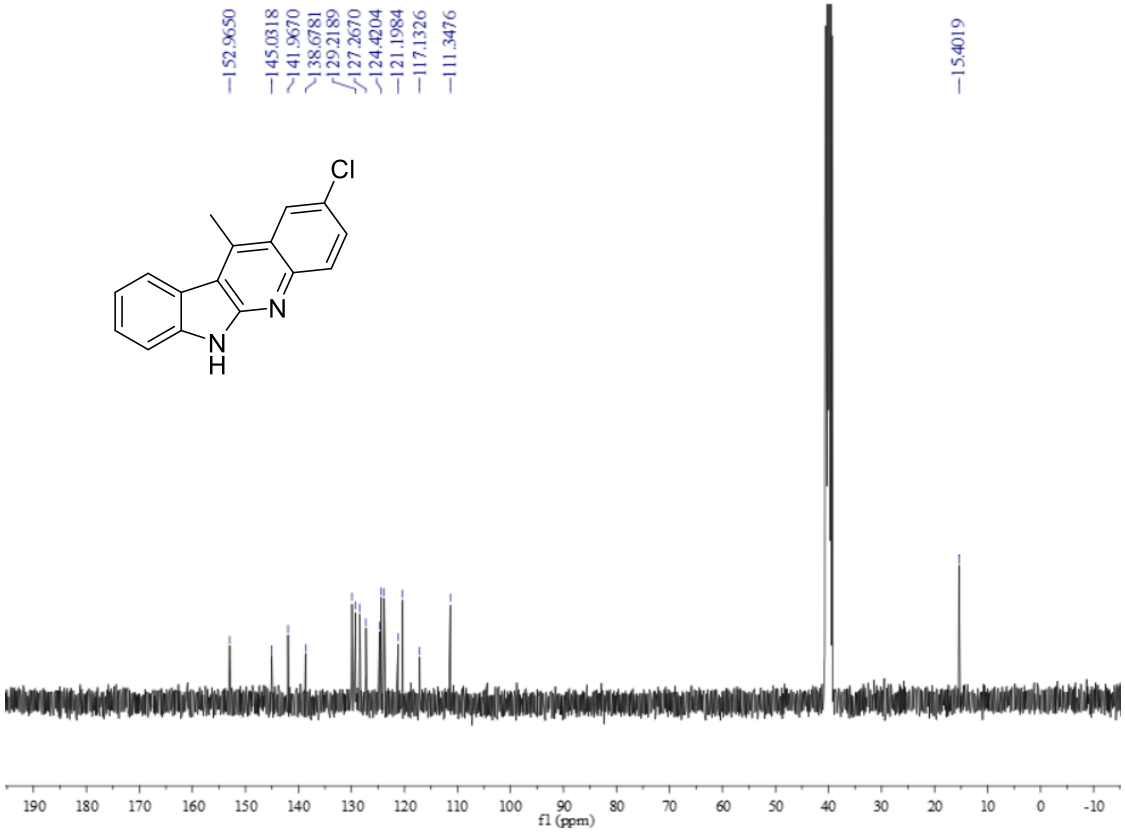


2-chloro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3r)

^{1}H NMR (400 MHz, DMSO-d_6)

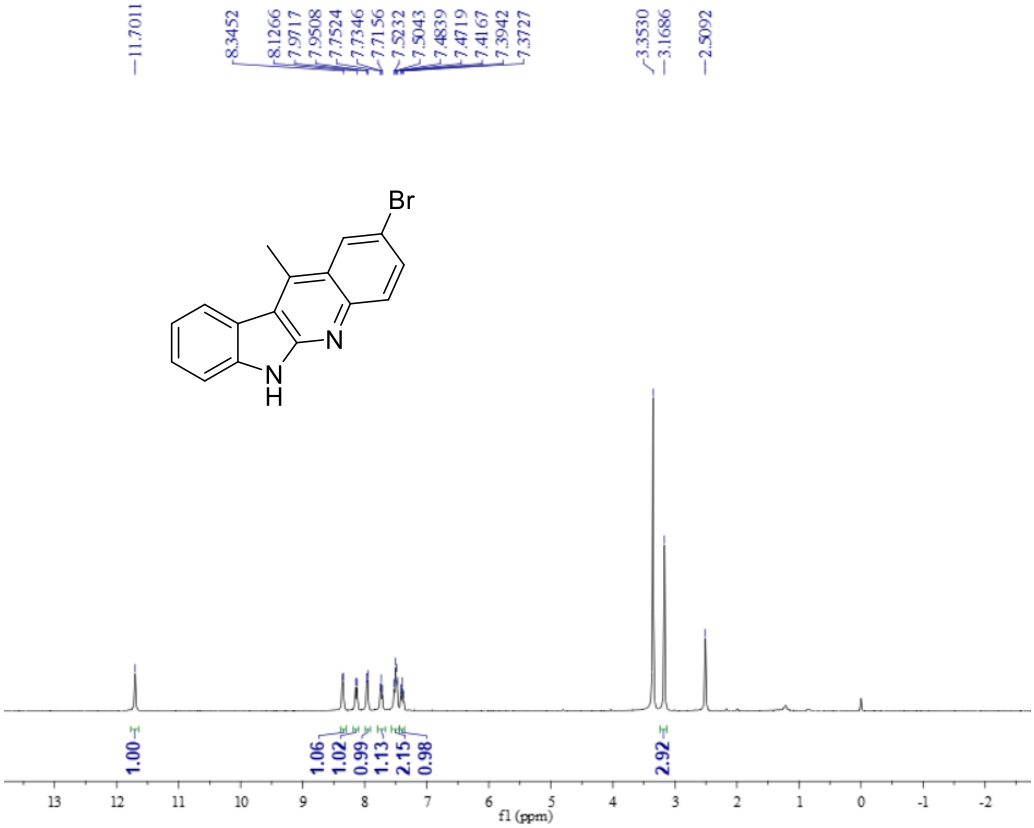


^{13}C NMR (100 MHz, DMSO-d_6)

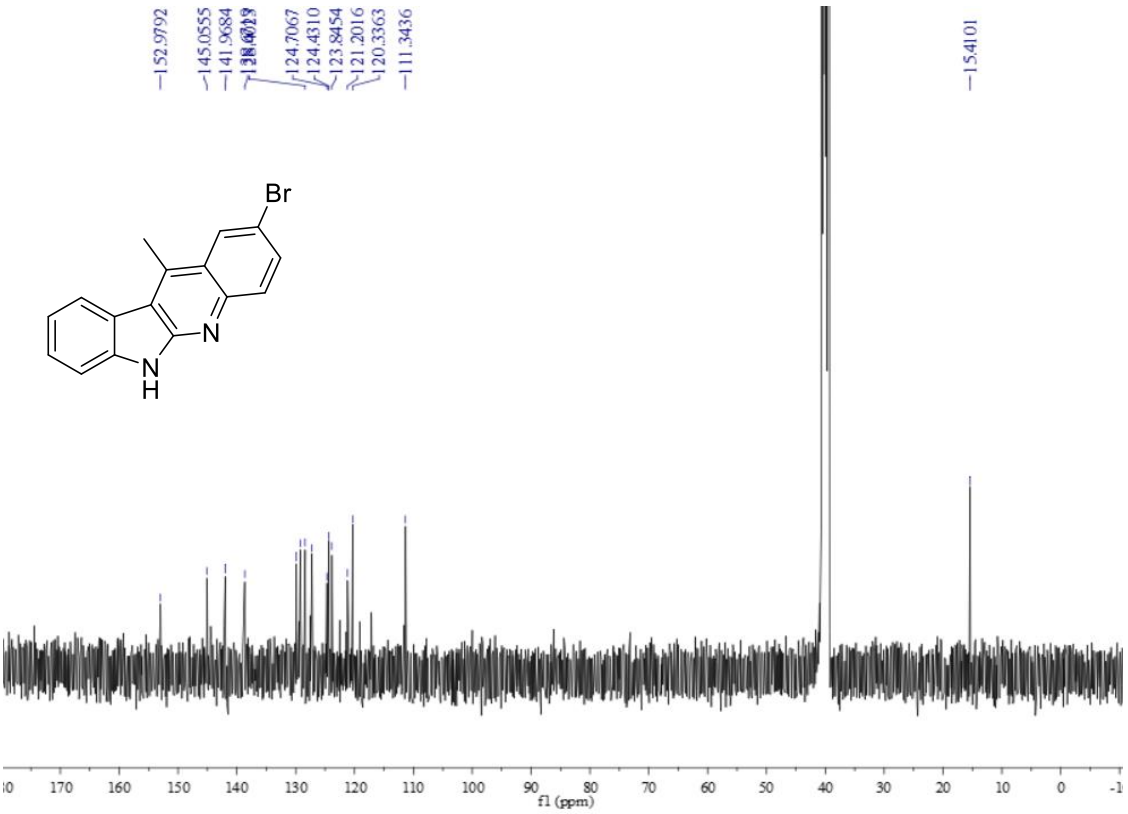


2-bromo-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3s)

^{1}H NMR (400 MHz, DMSO-d_6)

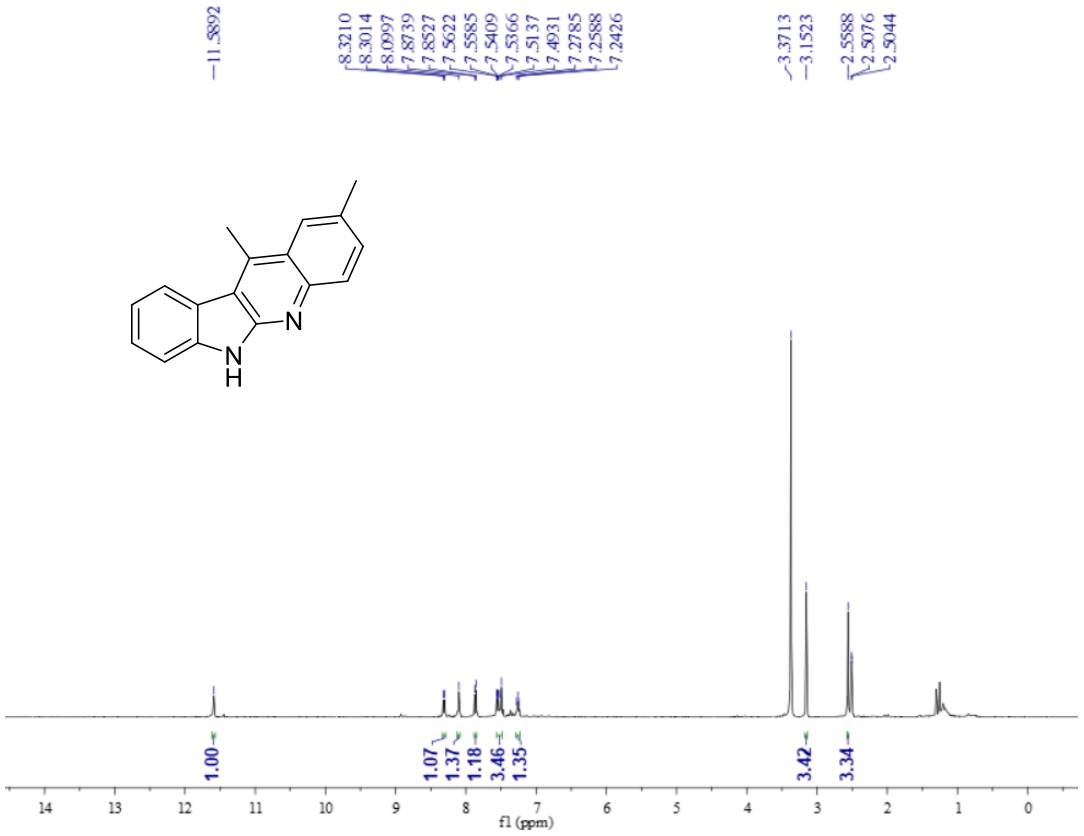


^{13}C NMR (100 MHz, DMSO-d_6)

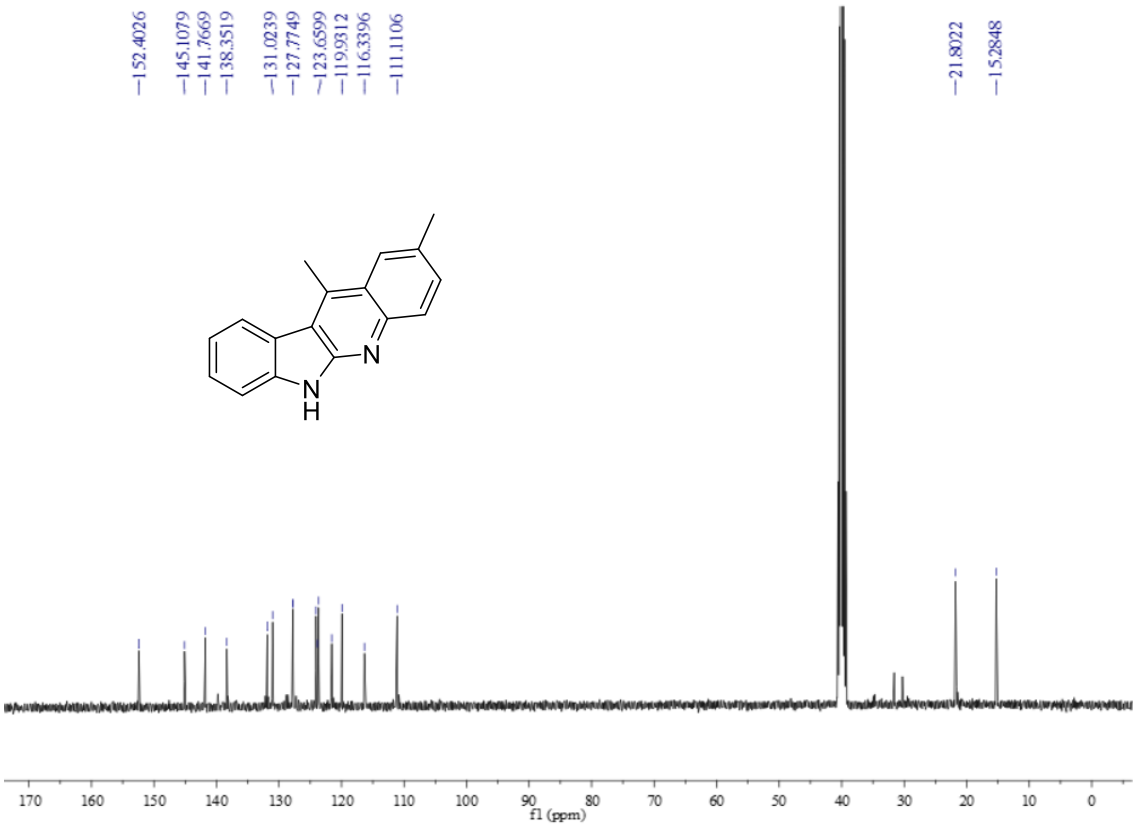


2,11-dimethyl-6*H*-indolo[*2,3-b*]quinoline (3t)

^{1}H NMR (400 MHz, DMSO-d_6)

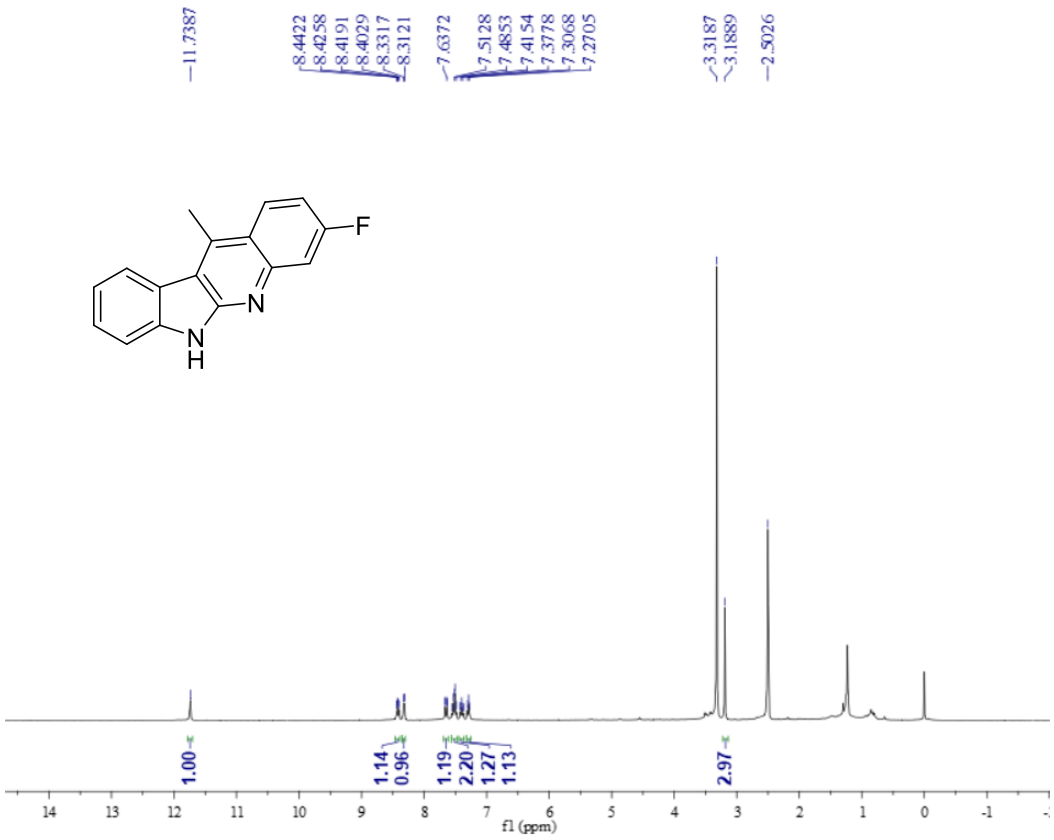


^{13}C NMR (100 MHz, DMSO-d_6)

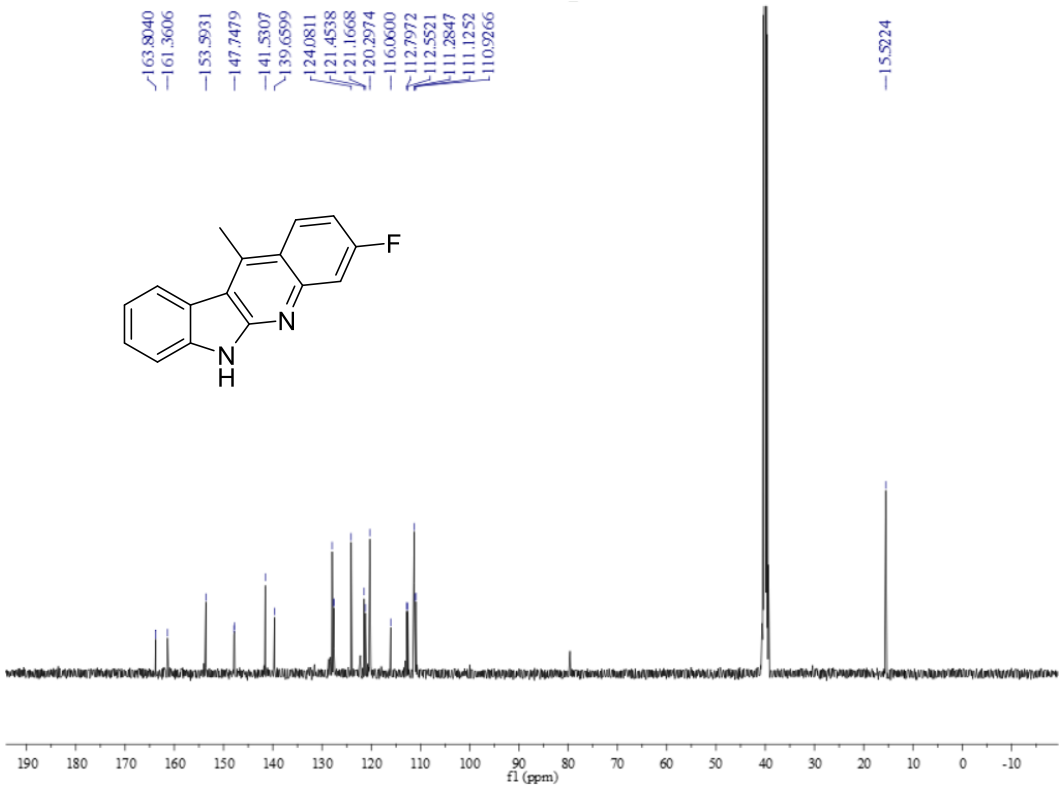


3-fluoro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3u)

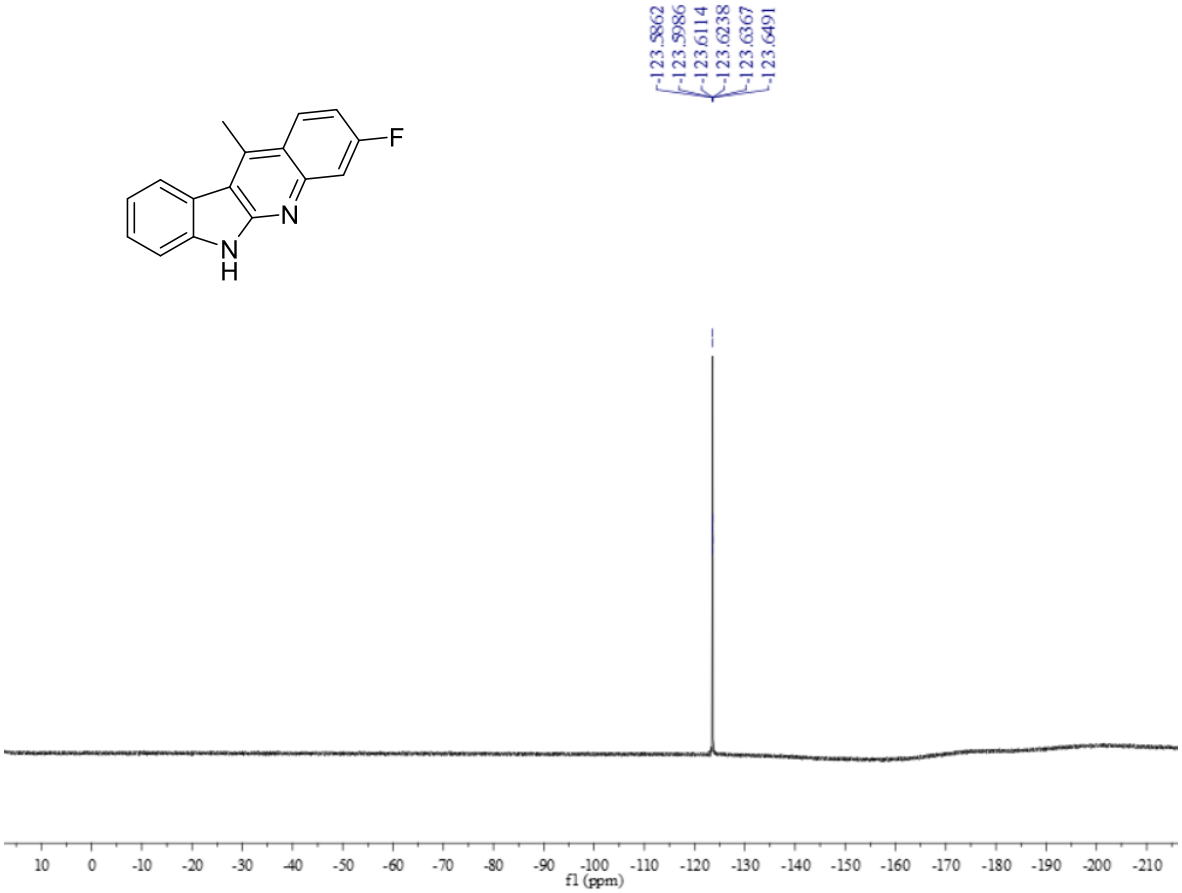
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (100 MHz, DMSO-d_6)

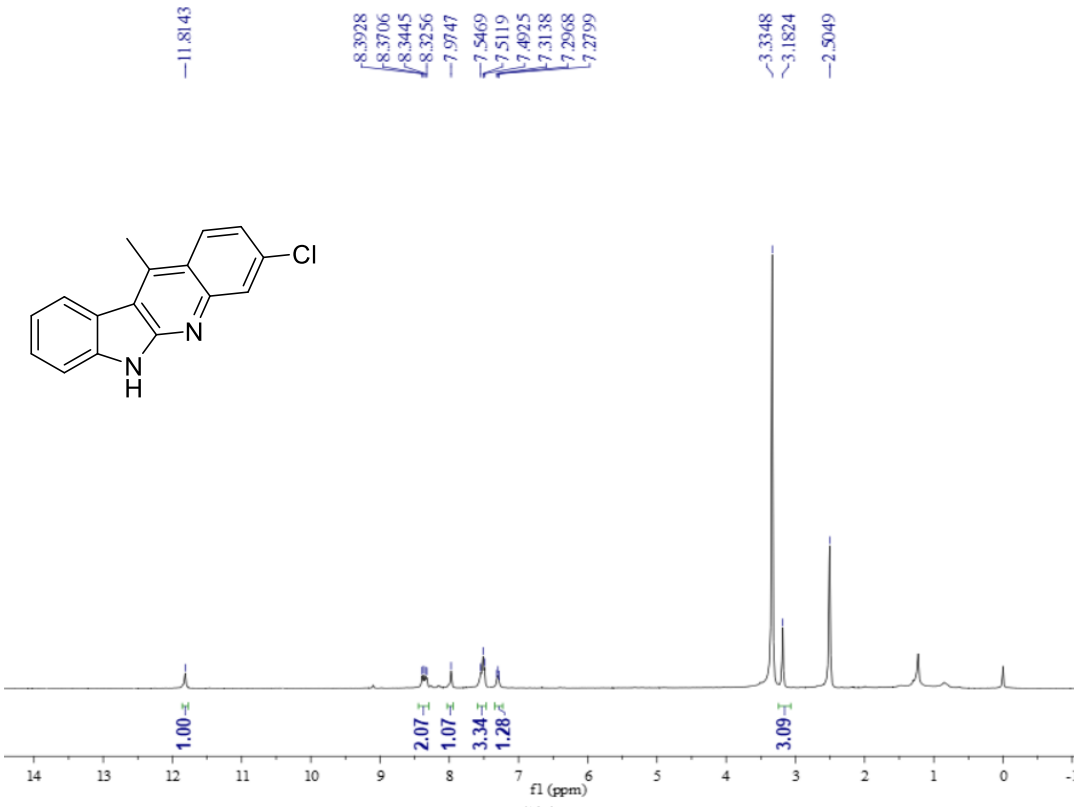


^{19}F NMR (376 MHz, DMSO-d_6)

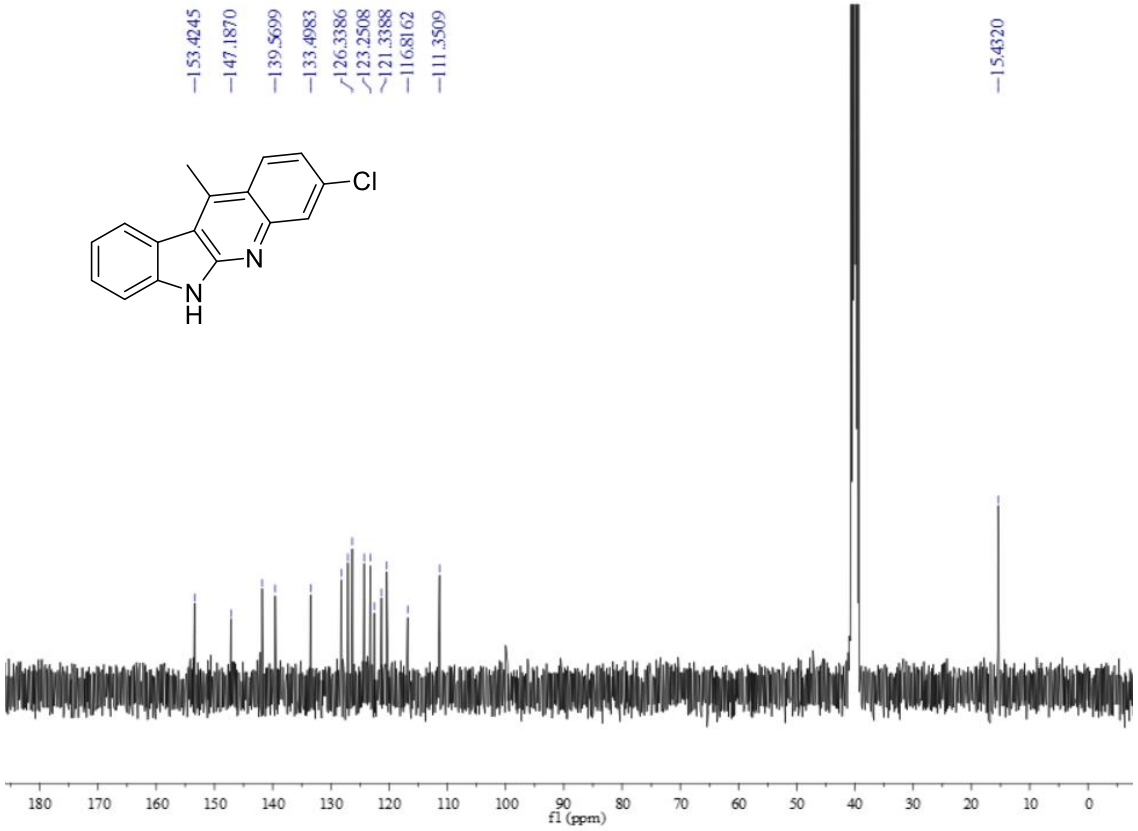


3-chloro-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3v)

^{1}H NMR (400 MHz, DMSO-d_6)

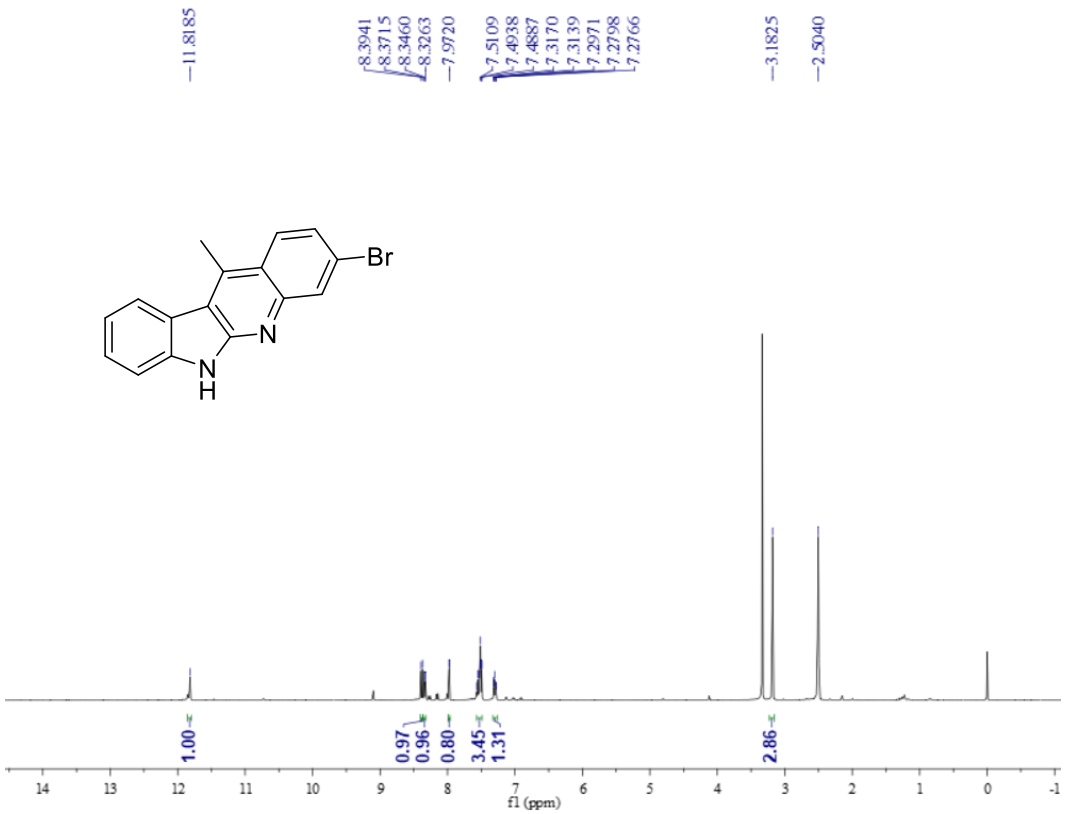


^{13}C NMR (100 MHz, DMSO-d_6)

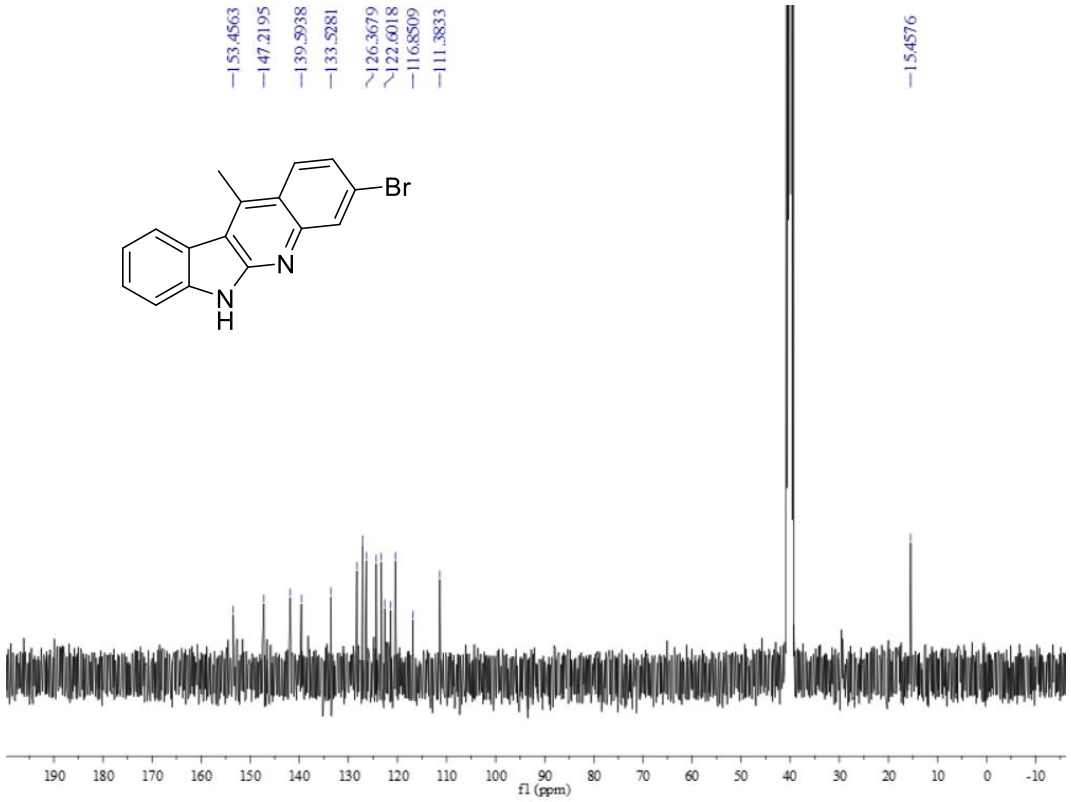


3-bromo-11-methyl-6*H*-indolo[*2,3-b*]quinoline (3w)

^{1}H NMR (400 MHz, DMSO-d_6)

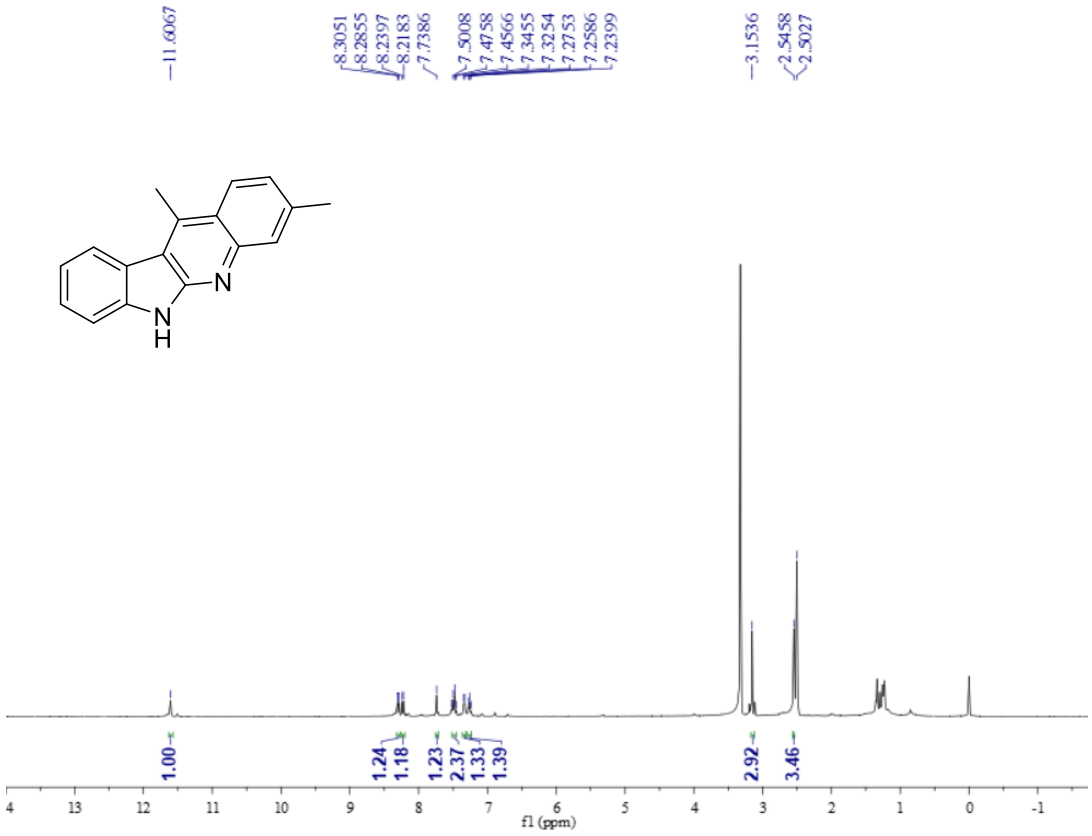


^{13}C NMR (100 MHz, DMSO-d_6)



3,11-dimethyl-6*H*-indolo[*2,3-b*]quinoline (3x)

^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (100 MHz, DMSO-d_6)