

# Synthesis and Structure-Activity Relationships of 1-Aryl- $\beta$ -carbolines as Affinity Probes for the 5-Hydroxytryptamine Receptor

Caroline A. Foley, Yazan A. Al-Issa, Kathryn P. Hiller, and Seann P. Mulcahy\*

*Department of Chemistry and Biochemistry, Providence College  
1 Cunningham Square, Providence, RI 02918*

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## Supporting Information

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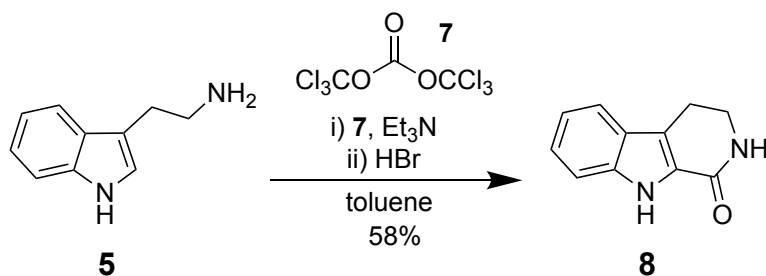
**General Experimental Procedures.** All reactions were performed in single-neck, oven-dried, round-bottomed flask unless otherwise noted. Each reaction flask was fitted with a rubber septum under a positive pressure of nitrogen and charged with a magnetic stir bar. Air- and moisture-sensitive liquids were transferred via syringe. Organic solutions were concentrated by rotary evaporation at 30–33 °C. Flash-column chromatography was performed as described by Still *et al.*,<sup>1</sup> employing silica gel (60 Å, 40–63 µm particle size) purchased from BDH. Automated flash chromatography was performed on a Biotage Isolera One with accompanying Dalton compact mass spectrometer using Biotage SNAP Ultra cartridges pre-packed with 25 µm Biosphere silica gel or KP-Sil silica gel. Analytical thin-layered chromatography (TLC) was performed using plastic plates pre-coated with silica gel (0.25 mm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous potassium permanganate solution (KMnO<sub>4</sub>), followed by brief heating with a heat gun (120 °C, 10–15 s).

**Materials.** Chromatography solvents were used as received from Pharmco-AAPER. All other commercial reagents, including anhydrous dioxane, pyridine, toluene, and triethylamine, were used as received from Sigma-Aldrich, Strem Chemicals, or Acros Organics. Dry tetrahydrofuran was obtained using the method of Pangborn *et al.*<sup>2</sup>

**Instrumentation.** Proton nuclear magnetic resonance spectra (<sup>1</sup>H NMR) were recorded on a Bruker Avance DRX 400 MHz spectrometer at 24 °C. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (*d*<sub>6</sub>-DMSO, δ 2.51; CDCl<sub>3</sub>, δ 7.26). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad), integration, and coupling constant in Hertz. Proton-decoupled carbon nuclear magnetic resonance spectra (<sup>13</sup>C NMR) were recorded at 100 MHz at 24 °C. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (*d*<sub>6</sub>-DMSO, δ 39.52; CDCl<sub>3</sub>, δ 77.16). All IR spectra were measured with a PerkinElmer Spectrum One FTIR spectrometer using a thin film on NaCl plates. Data are represented as follows: frequency of absorption (cm<sup>-1</sup>), intensity of absorption (s = strong, m = medium, w = weak, br = broad). High-resolution mass spectrometry (HRMS) data were acquired on an Agilent 6530 Q-TOF mass spectrometer in positive ESI and processed with Agilent MassHunter software at Brown University.

## Synthetic Procedures:

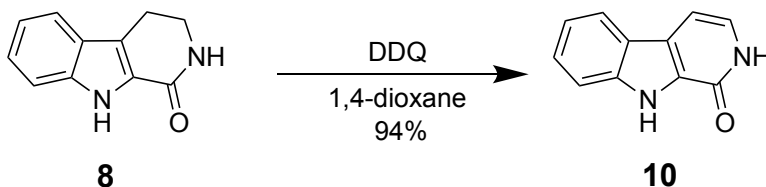
### Scheme S1. Bischler-Napieralski cyclization of tryptamine 5



Tryptamine **1** (3.0 g, 18.7 mmol, 1.0 equiv.) was dissolved in toluene (267 mL) and warmed to 60 °C to increase solubility. Once completely dissolved, the solution was cooled to room temperature and sparged with a stream of nitrogen for 5 minutes. Triethylamine (6.3 mL, 45.2 mmol, 2.4 equiv.) was then added to the reaction mixture. In an addition funnel, triphosgene **7** (2.2 g, 7.50 mmol, 0.40 equiv.) was dissolved in toluene (11.8 mL) and added dropwise to the reaction mixture over 5 minutes. The yellowish brown solution was left to stir at room temperature for 1 hour. A solution of 48% aqueous HBr (4.3 mL) was added to the reaction mixture in a steady stream over 30 seconds. The resulting greenish yellow solution was heated at reflux for 1 hour. The solution was then cooled to roughly 4 °C and water (150 mL) was added to the product mixture dropwise. The diluted mixture was then poured into a separatory funnel and extracted with ethyl acetate (4 x 60 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was recrystallized using ethyl acetate (15 mL) to yield the solid, pale-yellow cyclized product. The filtrate was concentrated and two additional crops of purified product were collected via recrystallization with ethyl acetate to obtain **8** (1.99 g, 58%) as a yellow solid whose spectra were consistent with a literature procedure.<sup>3</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 7.60 (d, J = 8.4 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.32 (dd, J = 7.6 Hz, 1 H), 7.16 (dd, J = 7.6 Hz, 1 H), 3.73 (t, J = 6.8 Hz, 2 H), 3.07 (t, J = 7.2 Hz, 2 H).

### Scheme S2. Oxidation of lactam 8

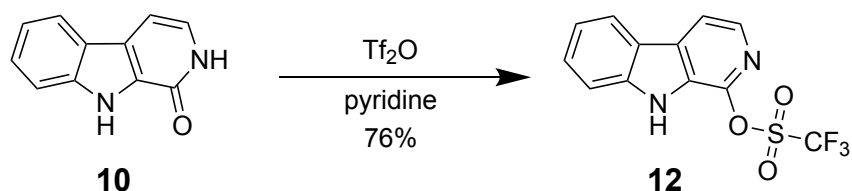


Lactam **8** (750 mg, 4.0 mmol, 1.0 equiv.) was dissolved in anhydrous 1,4-dioxane (57.3 mL), cooled to 15 °C, and sparged with a stream of nitrogen for 5 minutes. In a separate flask, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.1 g, 4.8 mmol, 1.2 equiv.) was dissolved in anhydrous dioxane, sparged with a stream of nitrogen for 5 minutes, and then

added to the reaction flask containing **8**. The reddish brown solution was warmed to room temperature and stirred for 25 minutes. The product mixture was then poured into a separatory funnel containing 120 mL water. The diluted mixture was extracted with ethyl acetate (3 x 40 mL). The organic layer obtained was washed with 0.1 M sodium hydroxide (4 x 40 mL). The combined organic layers obtained were then dried over magnesium sulfate, filtered, and concentrated to provide an orange-brown solid **10** (707 mg, 94%), whose spectra were consistent with a literature procedure.<sup>4</sup> Pyridone **10** was taken onto the next step without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 11.92 (br s, 1 H), 11.38 (br s, 1 H), 8.01 (d, J = 7.6 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.39 (dd, J = 6.8 Hz, 1 H), 7.16 (dd, J = 7.6 Hz, 1 H), 7.07 (dd, J = 6.8 Hz, 1 H), 6.97 (d, J = 6.8 Hz, 1 H).

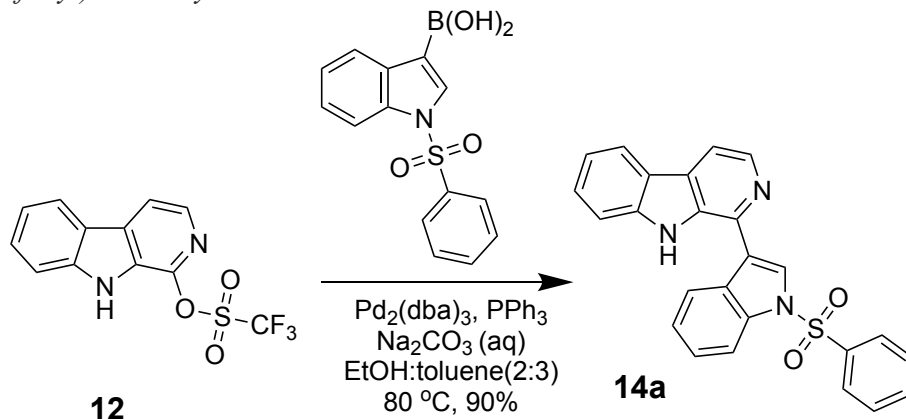
*Scheme S3. Triflation of pyridone 10*



Pyridone **10** (300 mg, 1.6 mmol, 1.0 equiv.) was dissolved in pyridine (16.3 mL), cooled to 4 °C, and sparged with a stream of nitrogen for 5 minutes. Trifluoromethanesulfonic anhydride (0.55 mL, 3.3 mmol, 2.0 equiv.) was then added to the solution dropwise over 30 minutes. The resulting orange solution was warmed to room temperature and stirred for 30 minutes. The product mixture was then poured into a separatory funnel containing 250 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 125 mL). The organic layer obtained was washed with 1.0 M hydrochloric acid (3 x 40 mL). The combined organic layers were then dried over magnesium sulfate, filtered, and concentrated to provide triflate **12** as a brown film (396 mg, 76%) whose spectra were consistent with a literature procedure.<sup>5</sup> Triflate **12** was taken onto the next step without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.48 (br s, 1 H), 8.16 (d, J = 5.1 Hz, 1 H), 8.14 (d, J = 7.9 Hz, 1 H), 8.01 (d, J = 5.1 Hz, 1 H), 7.67-7.58 (m, 2 H), 7.37 (dd, J = 7.4 Hz, 1 H).

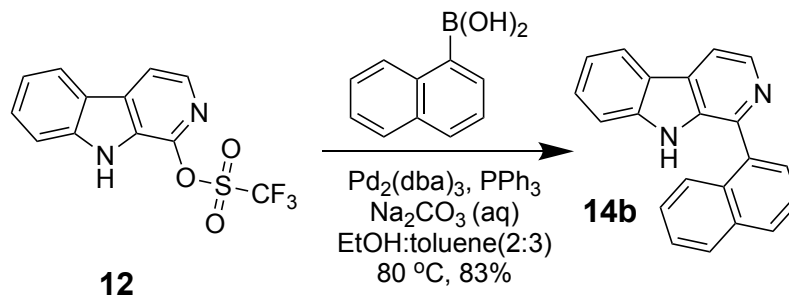
Scheme S4. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 1-(phenylsulfonyl)-3-indolylboronic acid



Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, 1-(phenylsulfonyl)-3-indolylboronic acid (67.1 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.24 mg, 0.00791 mmol, 0.0500 equiv.) and triphenylphosphine (4.15 mg, 0.00158 mmol, 0.100 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to  $80\text{ }^\circ\text{C}$  for 4 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide **14a**, as a bluish-green foam (60.0 mg, 90%) whose spectra were consistent with the literature.<sup>6</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.96 (s, 1 H), 8.55 (d,  $J = 5.2$  Hz, 1 H), 8.21 (s, 1 H), 8.15 (d,  $J = 7.6$  Hz, 1 H), 8.11 (t,  $J = 12.8$  Hz, 2 H), 7.93 (m, 3 H), 7.55 (d,  $J = 4.0$  Hz, 2 H), 7.51 (t,  $J = 7.6$  Hz, 1 H), 7.40 (t,  $J = 7.6$  Hz, 3 H), 7.32 (m, 2 H).

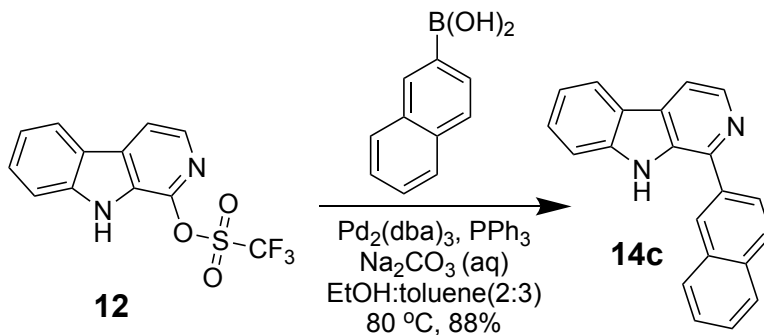
Scheme S5. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 1-naphthaleneboronic acid



Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, 1-naphthaleneboronic acid (38.1 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 2.5 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14b** as an amorphous beige solid (38.8 mg, 83%) whose spectra were consistent with the literature.<sup>7</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.64 (d,  $J$  = 5.3 Hz, 1H), 8.21 (d,  $J$  = 7.9 Hz, 1H), 8.07 (s, 1H), 8.05 (d,  $J$  = 5.3 Hz, 1H), 8.01 (d,  $J$  = 8.1 Hz, 1H), 7.98 (d,  $J$  = 8.8 Hz, 1H), 7.78 (d,  $J$  = 6.9 Hz, 1H), 7.74 (d,  $J$  = 8.6 Hz, 1H), 7.64 (t,  $J$  = 7.6 Hz, 1H), 7.55 (dd, 1H), 7.51 (dd,  $J$  = 6.9 Hz, 1H), 7.42 (dd, 1H), 7.36 (d,  $J$  = 8.3 Hz, 1H), 7.32 (t,  $J$  = 7.6 Hz, 1H).

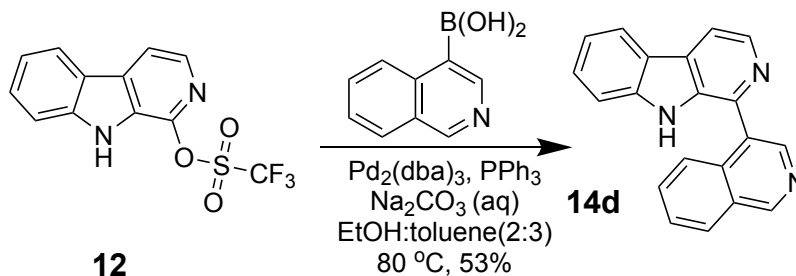
Scheme S6. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 2-naphthylboronic acid



Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, 2-naphthylboronic acid (38.1 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to  $80^\circ\text{C}$  for 4 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14c** as an orange solid (41.0 mg, 88%) whose spectra were consistent with the literature.<sup>8</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.70 (s, 1H), 8.63 (d,  $J = 5.2$  Hz, 1H), 8.41 (s, 1H), 8.19 (d,  $J = 7.8$  Hz, 1H), 8.09 (dd,  $J = 8.5, 1.7$  Hz, 1H), 8.04 (d,  $J = 8.5$  Hz, 1H), 7.98 (d,  $J = 5.3$  Hz, 1H), 7.94 (ddd,  $J = 9.3, 4.8, 1.7$  Hz, 2H), 7.60 – 7.52 (m, 4H), 7.34 (ddd,  $J = 8.0, 6.8, 1.3$  Hz, 1H).

Scheme S7. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 4-isoquinolineboronic acid

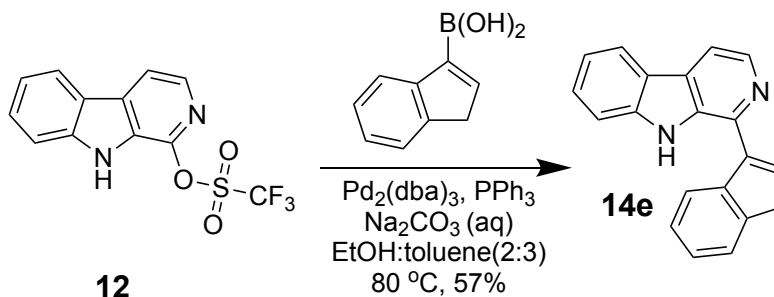


Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, 4-isoquinolineboronic acid (38.3 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to  $80\text{ }^\circ\text{C}$  for 4 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14d** as an amorphous tan solid (24.9 mg, 53%).

Characterization of **14d**:

$R_f = 0.17$  (30% ethyl acetate–70% hexanes; UV), MP =  $121.4\text{ }^\circ\text{C}$  (decomp.).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.14 (s, 1H), 8.82 (s, 1H), 8.68 (s, 1H), 8.64 (d,  $J = 5.3\text{ Hz}$ , 1H), 8.22 (d,  $J = 7.9\text{ Hz}$ , 1H), 8.09 (d,  $J = 5.3\text{ Hz}$ , 1H), 7.99 (d,  $J = 8.4\text{ Hz}$ , 1H), 7.76 – 7.67 (m, 2H), 7.65 – 7.59 (t, 1H), 7.56 – 7.44 (m, 2H), 7.34 – 7.28 (t, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 152.5, 142.9, 141.6, 139.9, 139.2, 136.3, 134.7, 131.7, 130.3, 130.0, 129.0, 128.9, 128.2, 128.0, 125.3, 122.1, 121.8, 120.3, 114.8, 112.3. IR (FT-IR)  $\text{cm}^{-1}$ : 3118 (m), 3052 (m), 2962 (m), 2849 (m), 2765 (m), 1623 (s), 1563 (s), 1500 (s), 1423 (s), 1382 (s), 1320 (s), 1236 (s), 741 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{14}\text{N}_3$ , 296.1179; found, 296.1185.

Scheme S8. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 1H-inden-3-ylboronic acid

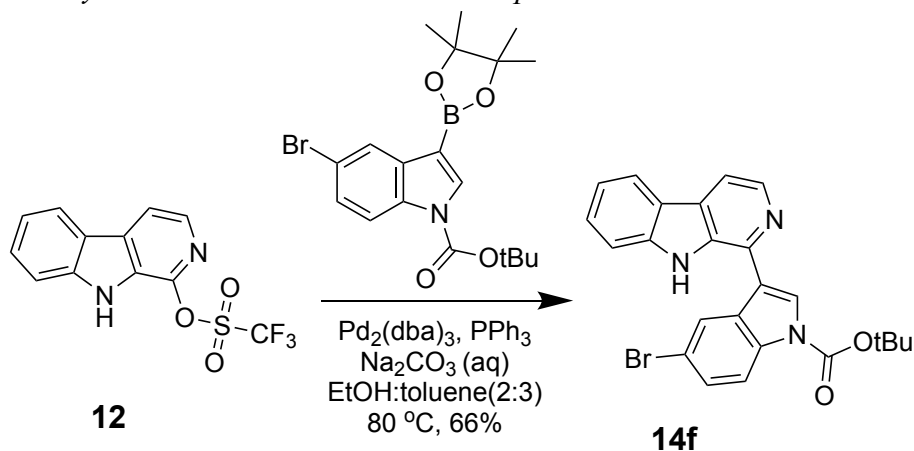


Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, 1H-inden-3-ylboronic acid (35.4 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 3.5 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14e** as a dark brown solid (25.5 mg, 57%).

Characterization of **14e**:

$R_f$  = 0.22 (60% ethyl acetate–40% hexanes; UV), MP = 170 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.59 (d,  $J$  = 5.2 Hz, 1H), 8.50 (br s, 1H), 8.17 (d,  $J$  = 7.9 Hz, 1H), 7.96 (d,  $J$  = 5.2 Hz, 1H), 7.84 (d,  $J$  = 7.2 Hz, 1H), 7.58 (d,  $J$  = 7.1 Hz, 1H), 7.54 (d,  $J$  = 7.0 Hz, 1H), 7.48 (d,  $J$  = 8.1 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.06 (t,  $J$  = 2.2 Hz, 1H), 3.67 (d,  $J$  = 2.1 Hz, 2H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  144.6, 143.6, 142.5, 140.4, 139.5, 139.4, 134.4, 134.1, 129.7, 128.8, 126.8, 125.8, 124.3, 122.2, 122.1, 120.5, 114.2, 111.9, 39.2. IR (FT-IR) cm<sup>-1</sup>: 3060 (br), 1699 (s), 1625 (m), 1559 (m), 1492 (m), 1453 (s), 1422 (s), 1318 (s), 1233 (s), 741 (s). HR-MS ( $m/z$ ): [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>15</sub>N<sub>2</sub>, 283.1227; found, 283.1234.

Scheme S9. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 1-*tert*-butyloxycarbonyl-5-bromoindole-2-boronic acid pinacol ester

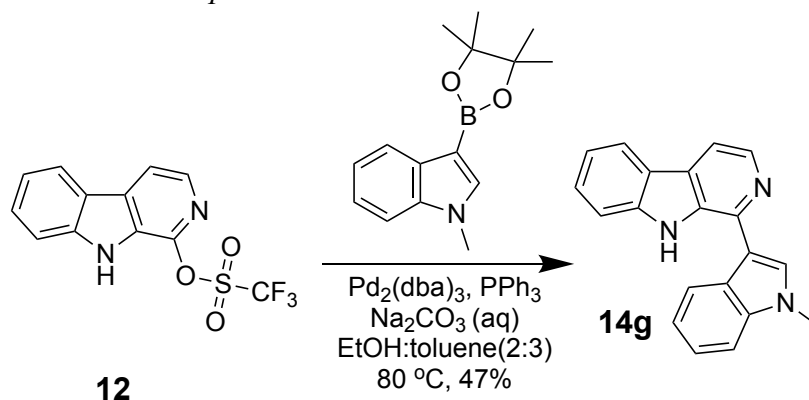


Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, 1-*tert*-butyloxycarbonyl-5-bromoindole-2-boronic acid pinacol ester (93.4 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 2.5 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14f** as an amorphous yellow solid (48.4 mg, 66%).

Characterization of **14f**:

$R_f$  = 0.44 (25% ethyl acetate–75% petroleum ether; UV), MP = 186 °C (decomp.).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.74 (br s, 2H), 8.57 (d,  $J$  = 5.2 Hz, 1H), 8.17 (d,  $J$  = 7.9 Hz, 1H), 8.04 (s, 1H), 7.94 (d,  $J$  = 5.3 Hz, 1H), 7.72 (d,  $J$  = 3.8 Hz, 1H), 7.55 (m,  $J$  = 4.2 Hz, 2H), 7.32 (ddd,  $J$  = 8.1, 6.2, 1.8 Hz, 1H), 6.70 (d,  $J$  = 3.8 Hz, 1H), 1.68 (s, 9H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 149.6, 142.4, 140.7, 139.9, 133.8, 131.7, 130.3, 128.8, 127.8, 126.0, 122.2, 122.1, 120.6, 115.9, 114.2, 114.2, 112.0, 107.5, 84.9, 31.3, 30.1, 28.5. IR (FT-IR)  $\text{cm}^{-1}$ : 3116 (m), 3032 (m), 2971 (m), 2931 (m), 2848 (m), 2770 (m), 1742 (s), 1626 (s), 1519 (s), 1408 (s), 1339 (s), 1321 (s), 1242 (s), 1155 (s), 1146 (s), 1132 (s), 846 (s), 807 (s), 767 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{21}\text{BrN}_3\text{O}_2$ , 462.0809; found, 462.0819.

Scheme S10. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with *N*-methylindole-3-boronic acid pinacol ester

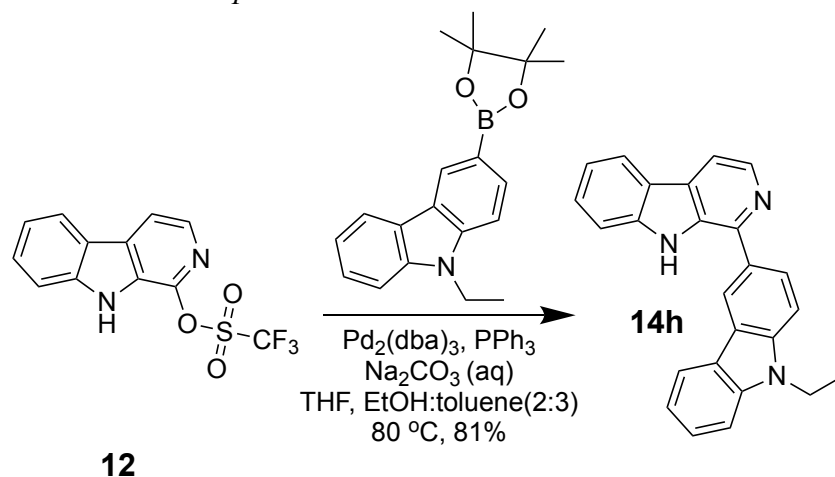


Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, *N*-methylindole-3-boronic acid pinacol ester (56.9 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 24 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14g** as an amorphous yellow solid (22.3 mg, 47%).

Characterization of **14g**:

$R_f = 0.35$  (75% ethyl acetate–25% hexanes; UV), MP 190 °C (decomp.).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.57 (br s, 1H), 8.53 (d,  $J = 5.4$  Hz, 1H), 8.17 (d,  $J = 7.9$  Hz, 1H), 7.94 (d,  $J = 7.9$  Hz, 1H), 7.89 (d,  $J = 5.4$  Hz, 1H), 7.73 (s, 1H), 7.58 – 7.49 (m, 2H), 7.44 (d,  $J = 8.2$  Hz, 1H), 7.38 – 7.30 (m, 2H), 7.24 (d,  $J = 7.5$  Hz, 1H), 3.90 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 140.5, 139.7, 139.4, 137.7, 133.9, 129.4, 128.5, 126.6, 122.7, 122.4, 122.1, 121.0, 120.9, 120.4, 113.8, 112.8, 111.9, 110.2, 33.4, 30.1. IR (FT-IR)  $\text{cm}^{-1}$ : 3047 (m), 2923 (m), 2848 (m), 1624 (s), 1563 (s), 1544 (s), 1464 (s), 1456 (s), 1327 (s), 1233 (s), 736 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{25}\text{H}_{16}\text{N}_3$ , 298.1336; found, 298.1340.

Scheme S11. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 9-ethyl-9H-carbazole-3-boronic acid pinacol ester

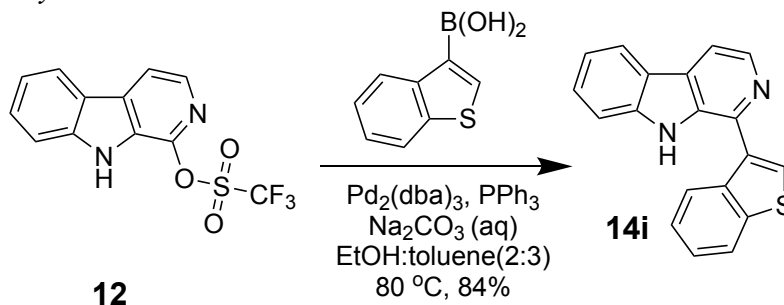


Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158  $\mu\text{mol}$ , 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, 9-ethyl-9H-carbazole-3-boronic acid pinacol ester (71.1 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 4 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14h** as a yellow solid (46.5 mg, 81%).

Characterization of **14h**:

$R_f$  = 0.17 (40% ethyl acetate– 60% petroleum ether; UV), MP 226–231 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 9.05 (br s, 1H), 8.58 (dd,  $J$  = 5.6, 3.4 Hz, 2H), 8.16 (d,  $J$  = 7.9 Hz, 1H), 8.06 (d,  $J$  = 7.7 Hz, 1H), 8.02 (dd,  $J$  = 8.4, 1.7 Hz, 1H), 7.89 (d,  $J$  = 5.3 Hz, 1H), 7.53 – 7.39 (m, 5H), 7.31 (ddd,  $J$  = 8.1, 6.3, 1.7 Hz, 1H), 7.21 (t,  $J$  = 7.4 Hz, 1H), 4.31 (q,  $J$  = 7.2 Hz, 2H), 1.41 (t,  $J$  = 7.2 Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  140.8, 140.5, 128.7, 126.4, 126.2, 124.0, 123.3, 122.2, 121.1, 120.6, 120.5, 119.6, 113.4, 111.9, 109.4, 109.1, 38.1, 14.2. IR (FT-IR)  $\text{cm}^{-1}$ : 3048 (m), 2974 (m), 1625 (s), 1600 (s), 1562 (s), 1492 (s), 1468 (s), 1456 (s), 1322 (s), 1227 (s), 743 (s), 727.41 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{25}\text{H}_{20}\text{N}_3$ , 362.1649; found, 362.1656.

Scheme S12. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with benzo[*b*]thien-3-ylboronic acid

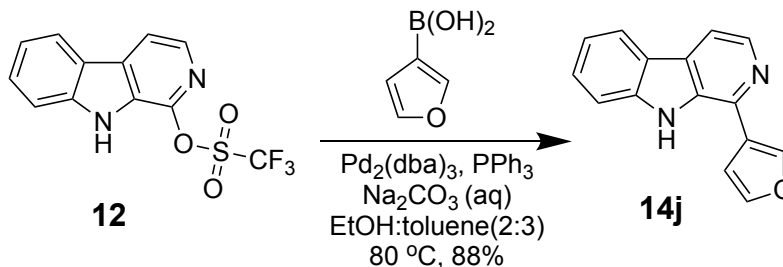


Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, benzo[*b*]thien-3-ylboronic acid (39.4 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 4 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14i** as a yellow solid (40.1 mg, 84%).

Characterization of **14i**:

R<sub>f</sub> = 0.21 (40% ethyl acetate–60% petroleum ether; UV), MP 135–140 °C (decomp.). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.61 (d, *J* = 5.3 Hz, 1H), 8.44 (br s, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 8.06 (dd, *J* = 6.6, 2.5 Hz, 1H), 8.00 – 7.97 (m, 2H), 7.90 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.33 (t, *J* = 7.5 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  141.0, 140.5, 139.7, 139.0, 138.0, 134.6, 130.0, 128.9, 126.8, 125.3, 125.1, 124.1, 123.2, 122.2, 122.2, 120.7, 114.3, 111.9. IR (FT-IR) cm<sup>-1</sup>: 3053 (m), 2915 (m), 2849 (m), 1625 (s), 1566 (s), 1495 (s), 1454 (s), 1422 (s), 1320 (s), 1244 (s), 1231 (s), 760 (s), 735 (s). HR-MS (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>13</sub>N<sub>2</sub>S, 301.0791; found, 301.0796.

Scheme S13. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 3-furanylboronic acid

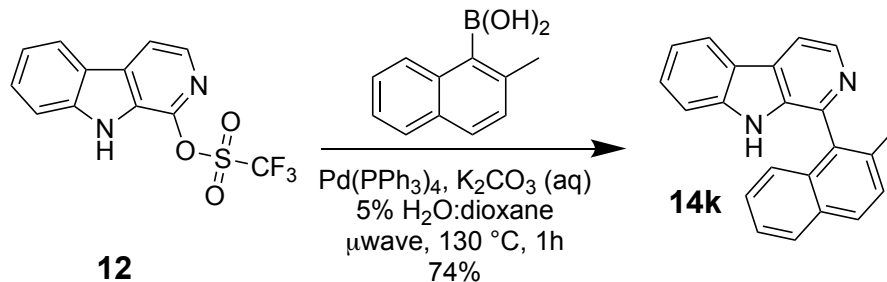


Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, 3-furanylboronic acid (27.0 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 3 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14j** as a yellow solid (32.6 mg, 88%).

Characterization of **14j**:

R<sub>f</sub> = 0.30 (40% ethyl acetate–60% hexanes; UV). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.55 – 8.48 (m, 2H), 8.17 – 8.11 (m, 2H), 7.89 (d, *J* = 5.3 Hz, 1H), 7.62 (t, *J* = 1.6 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.32 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 1H), 7.10 (d, *J* = 1.8 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 144.9, 144.5, 141.7, 141.2, 138.4, 135.9, 133.4, 130.7, 129.3, 122.2, 122.1, 121.0, 113.9, 112.4, 109.9. IR (FT-IR) cm<sup>-1</sup>: 3115 (m), 3030 (m), 2919 (s), 2849 (s), 2759 (m), 2664 (m), 1625 (s), 1605 (s), 1559 (s), 1500 (s), 1453 (s), 1425 (s), 1239 (s), 1070 (s), 1009 (s), 872 (s), 792 (s), 734 (s), 631 (s). HR-MS (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>11</sub>N<sub>2</sub>O, 235.0863; found, 235.0866.

Scheme S14. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 2-methylnaphthalene-1-boronic acid

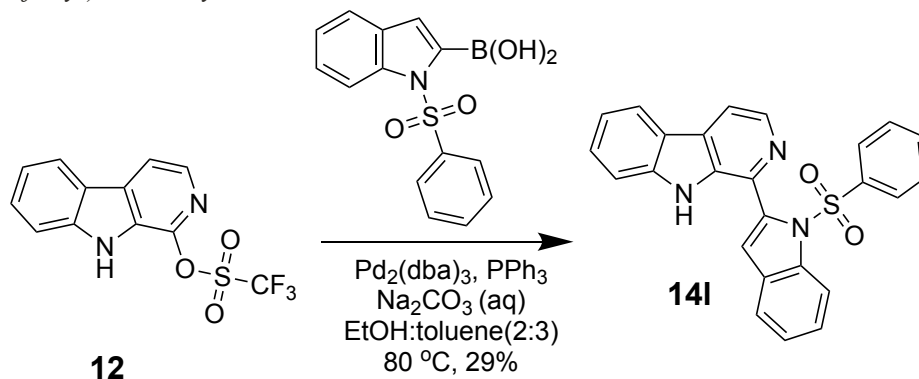


Triflate-substituted  $\beta$ -carboline **12** (100.0 mg, 0.333 mmol, 1.00 equiv.), 2-methylnaphthalene-1-boronic acid (134.5 mg, 0.833 mmol, 2.00 equiv.), potassium carbonate (92.0 mg, 0.667 mmol, 2.00 equiv.), and tetrakis(triphenylphosphine) palladium (38.5 mg, 0.033 mmol, 0.10 equiv.) were dissolved in 5% H<sub>2</sub>O: 95% dioxane (3.33 mL) in a microwave tube equipped with a magnetic stirbar. The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then irradiated at 300 W and 130 °C for 1 h. The product-mixture was then poured into a separatory funnel containing 30 mL ethyl acetate. The diluted mixture was then extracted with water (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14k** as a beige solid (76 mg, 74%).

Characterization of **14k**:

R<sub>f</sub> = 0.23 (25% ethyl acetate–75% hexanes; UV), MP = 178 °C (decomp.). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  11.05 (br s, 1H), 8.56 (d, *J* = 5.3 Hz, 1H), 8.34 (d, *J* = 7.9 Hz, 1H), 8.26 (d, *J* = 5.3 Hz, 1H), 8.05 (dd, *J* = 11.3, 8.3 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.45 (m, 3H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 2.17 (s, 3H). <sup>13</sup>C NMR (101 MHz, DMSO)  $\delta$  143.3, 141.8, 139.2, 135.8, 135.1, 134.5, 133.1, 132.8, 129.8, 129.2, 129.1, 128.9, 128.9, 127.2, 126.1, 126.0, 122.8, 121.8, 120.3, 115.0, 113.1, 20.6. IR (FT-IR) cm<sup>-1</sup>: 3047 (w), 2850 (w), 1625 (m), 1498 (m), 1421 (m), 1320 (m), 1236 (s), 811 (s), 738 (s). HR-MS (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>17</sub>N<sub>2</sub>, 309.1383; found, 309.1390.

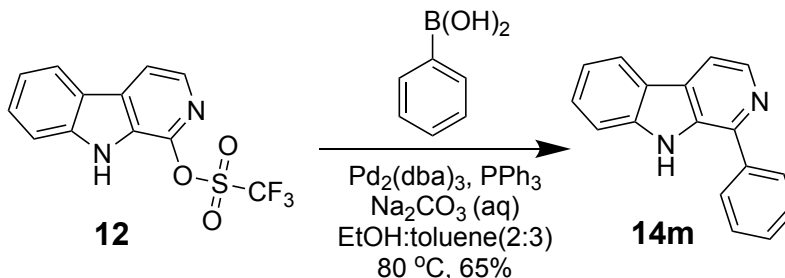
Scheme S15. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 1-(phenylsulfonyl)-2-indolylboronic acid



Triflate-substituted  $\beta$ -carboline **12** (48.0 mg, 0.152 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, 1-(phenylsulfonyl)-2-indolylboronic acid (64.0 mg, 0.213 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (6.9 mg, 0.00760 mmol, 0.0500 equiv.) and triphenylphosphine (4.0 mg, 0.00152 mmol, 0.100 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 5.5 h under inert atmosphere. At 5.5 h, another 1.0 equiv. (45.7 mg) of 1-(phenylsulfonyl)-2-indolylboronic acid was added to the reaction mixture. The reaction was heated to 80 °C for another 1 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ether to provide the analog **14I**, as a yellow solid (18.7 mg, 29%) whose spectra were consistent with the literature.<sup>6</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.58 (d,  $J$  = 5.2 Hz, 1H), 8.55 (s, 1H), 8.29 (d,  $J$  = 8.4 Hz, 1H), 8.17 (d,  $J$  = 7.9 Hz, 1H), 8.06 (d,  $J$  = 5.2 Hz, 1H), 7.74 – 7.69 (m, 2H), 7.60 – 7.49 (m, 3H), 7.49 – 7.40 (m, 2H), 7.37 – 7.27 (m, 4H), 7.00 (s, 1H).

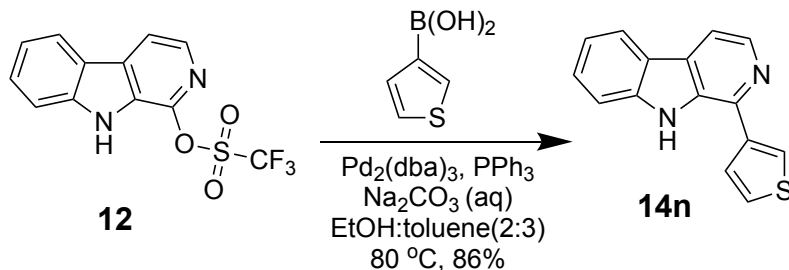
Scheme S16. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with phenylboronic acid



Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, phenylboronic acid (27.0 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 24 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14m** as a tan solid (25.0 mg, 65%) whose spectra were consistent with the literature.<sup>9</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.58 (d,  $J$  = 5.3 Hz, 1H), 8.56 (s, 1H), 8.17 (d,  $J$  = 7.9 Hz, 1H), 7.99 – 7.94 (m, 3H), 7.62 – 7.57 (m, 2H), 7.56 (dd,  $J$  = 7.0, 1.2 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.32 (ddd,  $J$  = 8.0, 6.9, 1.1 Hz, 1H).

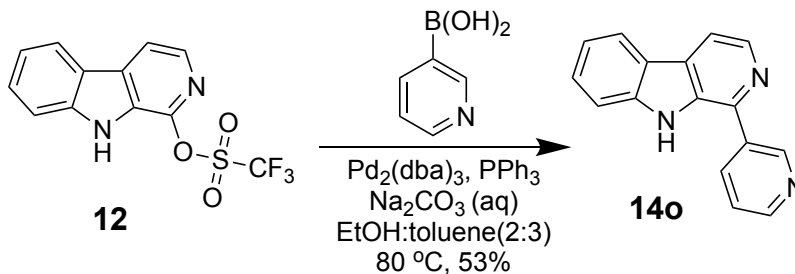
Scheme S17. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 3-thienylboronic acid



Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, 3-thienylboronic acid (28.3 mg, 0.221 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to  $80\text{ }^\circ\text{C}$  for 4 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14n** as a yellow solid (33.9 mg, 86%) whose spectra were consistent with the literature.<sup>10</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.61 (s, 1H), 8.52 (d,  $J = 5.3$  Hz, 1H), 8.15 (d,  $J = 7.9$  Hz, 1H), 7.92 (d,  $J = 5.3$  Hz, 2H), 7.77 (d,  $J = 5.0$  Hz, 1H), 7.60 – 7.50 (m, 3H), 7.32 (t,  $J = 7.3$  Hz, 1H).

Scheme S18. Suzuki Cross Coupling of triflate-substituted  $\beta$ -carboline **12** with 3-pyridinylboronic acid

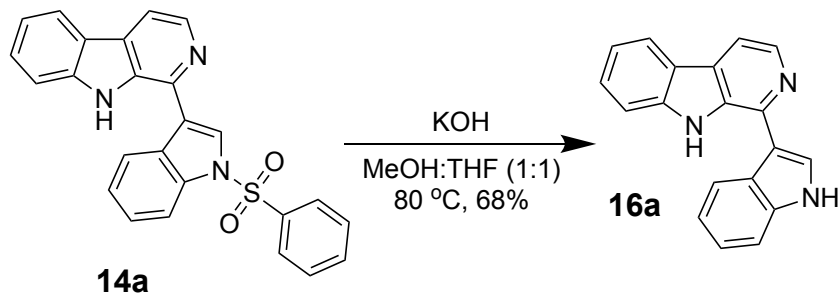


Triflate-substituted  $\beta$ -carboline **12** (50.0 mg, 0.158 mmol, 1.00 equiv.) was dissolved in toluene (1.58 mL). In a separate flask, 3-pyridinylboronic acid (36.9 mg, 0.300 mmol, 1.90 equiv.) was dissolved in ethanol (1.05 mL). The resulting solution was added to the reaction mixture containing **12**. Saturated sodium carbonate (0.53 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (7.2 mg, 0.008 mmol, 0.05 equiv.) and triphenylphosphine (4.1 mg, 0.016 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to  $80\text{ }^\circ\text{C}$  for 4 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **14o** as a tan solid (39.0 mg, 53%) whose spectra were consistent with the literature.<sup>10</sup>

Characterization of **14o**:

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.53 (s, 1H), 9.46 (d,  $J = 2.2$  Hz, 1H), 8.63 (dd,  $J = 4.8$ , 1.6 Hz, 1H), 8.61 (d,  $J = 5.2$  Hz, 1H), 8.38 (dt,  $J = 8.0$ , 2.0 Hz, 1H), 8.19 (d,  $J = 7.8$  Hz, 1H), 8.03 (d,  $J = 5.2$  Hz, 1H), 7.60 – 7.49 (m, 3H), 7.33 (ddd,  $J = 8.1$ , 5.7, 2.5 Hz, 1H).

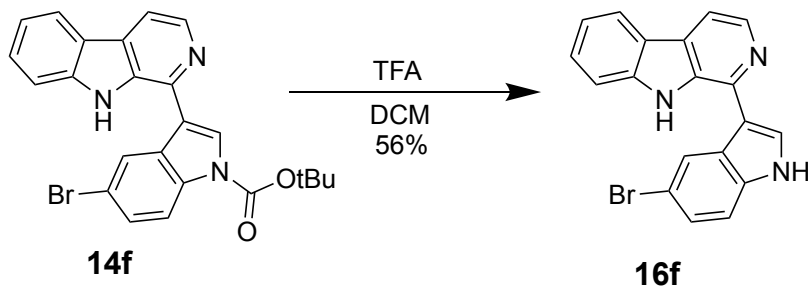
Scheme S19. Deprotection of **14a**



Compound **14a** (60.0 mg, 0.142 mmol, 1.00 equiv.) was dissolved in a 1:1 mixture of MeOH (1.84 mL) and dry THF (1.84 mL). Solid KOH (39.8 mg, 0.710 mmol, 5.00 equiv.) was then added to the solution. The yellow reaction mixture was sparged with a stream of nitrogen for 5 minutes, refluxed at 80 °C, and stirred for 1 h under inert atmosphere. The product mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the  $\beta$ -carboline **16a** as a yellow solid (27.2 mg, 68%) whose spectra were consistent with the literature.<sup>6,11</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  11.70 (s, 1 H), 11.29 (s, 1 H), 8.56 (d, J = 7.6 Hz, 1 H), 8.45 (d, J = 5.2 Hz, 1 H), 8.29 (d, J = 2.8 Hz, 1 H), 8.24 (d, J = 8.0 Hz, 1 H), 7.96 (d, J = 4.8 Hz, 1 H), 7.69 (d, J = 8.4 Hz, 1 H), 7.56-7.51 (m, 2 H), 7.27-7.20 (m, 2 H), 7.14 (dd, J = 7.2 Hz, 1 H).

Scheme S20. Boc-deprotection of analog **14f**

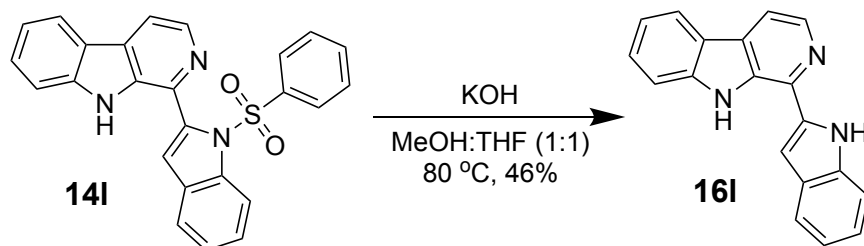


Analog **14f** was dissolved in anhydrous dichloromethane (0.99 mL). Trifluoroacetic acid (0.05 mL) was then added dropwise at 0 °C. The yellow reaction mixture was stirred at 0 °C for one hour and then stirred at room temperature for another 5 h. The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **16f** as a red solid (21.1 mg, 56%).

Characterization of **16f**:

$R_f$  = 0.16 (50% ethyl acetate–50% hexanes; UV), MP = 248–250 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.52 (br s, 1H), 12.30 (br s, 1H), 8.53 (s, 2H), 8.49 (d,  $J$  = 8.0 Hz, 1H), 8.43 (d,  $J$  = 2.8 Hz, 1H), 8.22 (br s, 1H), 7.80 – 7.71 (m, 2H), 7.63 (d,  $J$  = 8.6 Hz, 1H), 7.48 – 7.41 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  159.0, 158.7, 144.0, 136.3, 133.4, 131.6, 131.4, 127.8, 126.4, 123.8, 123.5, 121.9, 121.3, 115.4, 115.0, 114.5, 113.9. IR (FT-IR)  $\text{cm}^{-1}$ : 3107 (w), 3021 (w), 2911 (w), 2851 (w), 1686 (s), 1674 (s), 1629 (s), 1619 (s), 1196 (s), 1172 (s), 1128 (s), 1020 (s), 1004 (s), 831 (s), 794 (s), 749 (s), 741 (s), 720 (s).

Scheme S21. Deprotection of analog **14I**

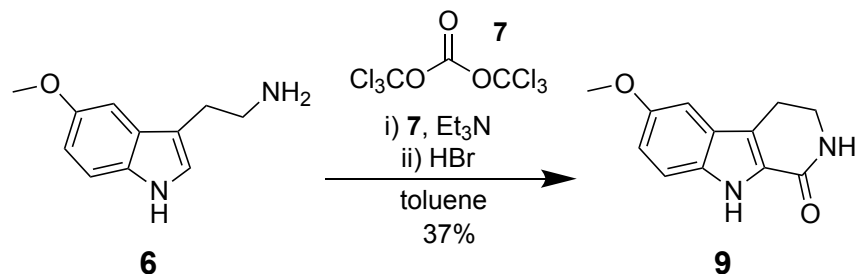


Analog **14I** (18.7 mg, 0.0442 mmol, 1.00 equiv.) was dissolved in a 1:1 mixture of MeOH (0.37 mL) and dry THF (0.37 mL). Solid KOH (12.4 mg, 0.221 mmol, 5.00 equiv.) was then added to the solution. The yellow reaction mixture was sparged with a stream of nitrogen for 5 minutes, refluxed 80 °C, and stirred for 4 h under inert atmosphere. The product mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide analog **16I** as a yellow solid (5.7 mg, 46%).

Characterization of **16I**:

$R_f$  = 0.61 (100% ethyl acetate; UV).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.85 (br s, 1H), 11.55 (br s, 1H), 8.52 (d,  $J$  = 5.1 Hz, 1H), 8.32 (d,  $J$  = 7.8 Hz, 1H), 8.17 (d,  $J$  = 5.1 Hz, 1H), 7.82 (d,  $J$  = 8.2 Hz, 1H), 7.73 (d,  $J$  = 7.9 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.59 (d,  $J$  = 8.1 Hz, 1H), 7.34 (t,  $J$  = 7.5 Hz, 1H), 7.21 (t,  $J$  = 7.5 Hz, 1H), 7.10 (t,  $J$  = 7.4 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  142.1, 138.7, 137.6, 136.1, 135.8, 132.7, 130.5, 130.4, 129.7, 129.3, 123.4, 122.5, 121.8, 121.5, 120.8, 120.3, 114.8, 113.6, 113.0, 102.7. IR (FT-IR)  $\text{cm}^{-1}$ : 3059 (m), 2922 (m), 2851 (m), 1624 (m), 1566 (m), 1494 (m), 1450 (m), 1433 (m), 1450 (m), 1306 (m), 1232 (s), 1110 (m), 1047 (m), 1022 (s), 1004 (s), 793 (m), 741 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{14}\text{N}_3$ , 284.1179; found, 284.1186.

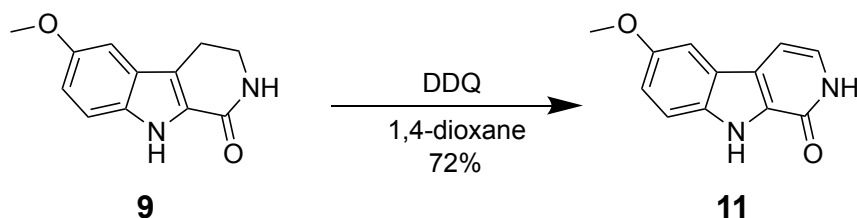
Scheme S22. Bischler-Napieralski cyclization of 5-methoxytryptamine **6**



5-methoxytryptamine **6** (3.0 g, 15.7 mmol, 1.0 equiv.) was dissolved in toluene (228 mL) and warmed to 80 °C to increase solubility. Once completely dissolved, the solution was cooled to 50 °C and sparged with a stream of nitrogen for 5 minutes. Triethylamine (5.3 mL, 37.7 mmol, 2.4 equiv.) was then added to the reaction mixture. In an addition funnel, triphosgene **7** (1.9 g, 6.3 mmol, 0.40 equiv.) was dissolved in toluene (13 mL) and added dropwise to the reaction mixture over 5 minutes. The solution was left to stir at 60 °C - 70 °C for 20 minutes. A solution of 48% aqueous HBr/AcOH (3.6 mL) was added to the reaction mixture in a steady stream over 30 seconds. The resulting solution was heated at reflux for 30 minutes. The solution was then cooled and water (100 mL) was added to the product mixture dropwise. The diluted mixture was then poured into a separatory funnel and extracted with ethyl acetate (2 x 200 mL) and with dichloromethane (1 x 200 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was recrystallized using ethyl acetate (20 mL) to yield the solid, pale-yellow cyclized product. The filtrate was concentrated and two additional crops of purified product were collected via recrystallization with ethyl acetate to obtain **9** (1.28 g, 37%) as a yellow solid whose spectra were consistent with a literature procedure.<sup>12</sup>

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.44 (s, 1H), 7.53 (s, 1H), 7.28 (d, *J* = 8.9 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.87 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.77 (s, 3H), 3.50 (td, *J* = 6.9, 2.5 Hz, 2H), 2.89 (t, *J* = 6.9 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 2H).

Scheme S23. Oxidation of lactam **9**

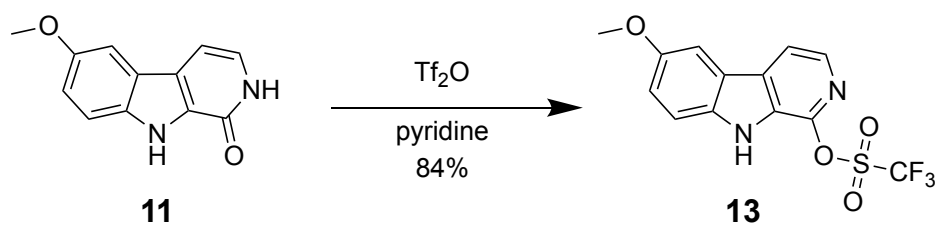


Lactam **9** (704 mg, 3.3 mmol, 1.0 equiv.) was dissolved in anhydrous 1,4-dioxane (44.0 mL), cooled to 15 °C, and sparged with a stream of nitrogen for 5 minutes. In a separate flask, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.5 g, 6.5 mmol, 2.0 equiv.) was dissolved in anhydrous 1,4-dioxane (21 mL), sparged with a stream of nitrogen for 5 minutes, and then added to the reaction flask containing **9**. The greenish black solution was

warmed to room temperature and stirred for 3 hours. The product mixture was then poured into a separatory funnel containing 200 mL water. The diluted mixture was extracted with ethyl acetate (3 x 200 mL). The organic layer obtained was washed with 0.1 M sodium hydroxide (4 x 120 mL). The combined organic layers obtained were then dried over magnesium sulfate, filtered, and concentrated to provide a dark brown solid **11** (503 mg, 72%).<sup>12</sup> Pyridone **11** was taken onto the next step without further purification.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.77 (s, 1H), 11.31 (d, *J* = 5.1 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 1H), 7.10 – 7.01 (m, 2H), 6.97 (d, *J* = 6.7 Hz, 1H), 3.83 (s, 3H).

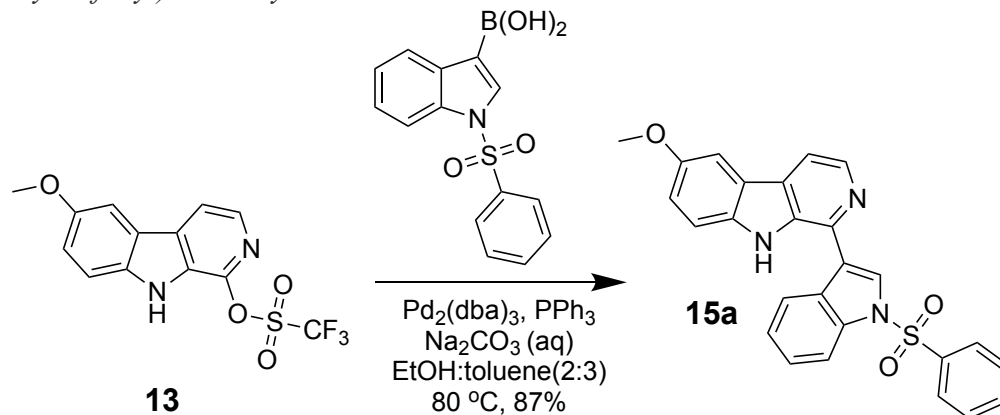
*Scheme S24. Triflation of pyridone 11*



Pyridone **11** (440 mg, 2.1 mmol, 1.0 equiv.) was dissolved in pyridine (20.5 mL), cooled to 4° C, and sparged with a stream of nitrogen for 5 minutes. The solution was left to stir at room temperature for 30 minutes. Trifluoromethanesulfonic anhydride (0.69 mL, 4.1 mmol, 2.0 equiv.) was then added dropwise to the solution over 30 minutes. The resulting solution was warmed to room temperature and stirred for 30 minutes. The product mixture was then poured into a separatory funnel containing 100 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 100 mL). The organic layer obtained was washed with 1.0 M hydrochloric acid (3 x 150 mL). The combined organic layers were then dried over magnesium sulfate, filtered, and concentrated to provide triflate **13** as a brown film (597 mg, 84%).<sup>12</sup> Triflate **13** was taken onto the next step without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.62 (s, 1H), 8.08 (d, *J* = 5.2 Hz, 1H), 7.91 (d, *J* = 5.3 Hz, 1H), 7.53 – 7.42 (m, 2H), 7.24 (dd, *J* = 9.2, 2.2 Hz, 1H), 3.92 (s, 3H).

Scheme S25. Suzuki Cross Coupling of triflate-substituted 6-methoxy- $\beta$ -carboline **13** with 1-(phenylsulfonyl)-3-indolylboronic acid

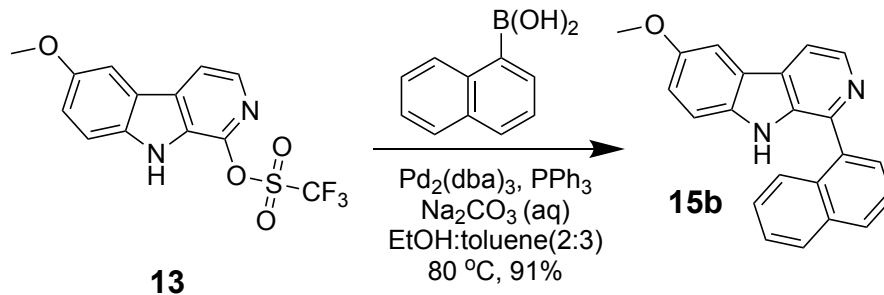


Triflate-substituted 6-methoxy- $\beta$ -carboline **13** (50.0 mg, 0.144 mmol, 1.00 equiv.) was dissolved in toluene (0.86 mL). In a separate flask, 1-(phenylsulfonyl)-3-indolylboronic acid (60.1 mg, 0.202 mmol, 1.40 equiv.) was dissolved in ethanol (0.58 mL). The resulting solution was added to the reaction mixture containing **13**. Saturated sodium carbonate (0.29 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 0.008 mmol, 0.050 equiv.) and triphenylphosphine (3.8 mg, 0.014 mmol, 0.100 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 3 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ether to provide analog **15a** as a yellow solid (57.0 mg, 87%).

Characterization of **15a**:

$R_f$  = 0.24 (25% ethyl acetate–75% petroleum ether; UV), MP = 173.6–174.6 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.50 (br s, 1H), 8.66 (s, 1H), 8.51 (t,  $J$  = 6.4 Hz, 2H), 8.22 – 8.13 (m, 3H), 8.08 (d,  $J$  = 8.2 Hz, 1H), 7.89 (d,  $J$  = 2.5 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.64 (t,  $J$  = 7.6 Hz, 2H), 7.53 – 7.44 (t,  $J$  = 7.2 Hz, 1H), 7.40 (t,  $J$  = 7.7 Hz, 1H), 7.30 (dd,  $J$  = 8.9, 2.5 Hz, 1H), 3.93 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}$ )  $\delta$  154.6, 138.4, 137.8, 137.7, 136.8, 135.7, 135.4, 134.5, 130.8, 130.4, 130.0, 128.0, 126.7, 126.4, 124.9, 124.4, 122.4, 120.8, 119.3, 114.7, 114.3, 114.0, 104.3, 56.6. IR (FT-IR)  $\text{cm}^{-1}$ : 1567 (m), 1492 (m), 1446 (m), 1369 (m), 1285 (m), 1207 (m), 1168 (s), 1132 (s), 1095 (s), 1017 (s), 966 (m), 820 (m), 749 (s), 727 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{26}\text{H}_{20}\text{N}_3\text{O}_3\text{S}$ , 454.1217; found, 454.1227.

Scheme S26. Suzuki Cross Coupling of triflate-substituted 6-methoxy- $\beta$ -carboline **13** with 1-naphthaleneboronic acid

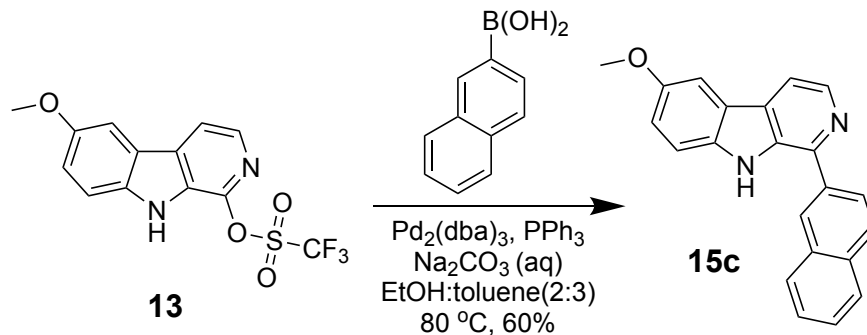


Triflate-substituted 6-methoxy- $\beta$ -carboline **13** (50.0 mg, 0.144 mmol, 1.00 equiv.) was dissolved in toluene (0.86 mL). In a separate flask, 1-naphthaleneboronic acid (34.7 mg, 0.202 mmol, 1.40 equiv.) was dissolved in ethanol (0.58 mL). The resulting solution was added to the reaction mixture containing **13**. Saturated sodium carbonate (0.29 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 0.007 mmol, 0.05 equiv.) and triphenylphosphine (3.8 mg, 0.014 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to  $80\text{ }^\circ\text{C}$  for 1 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ether to provide the 6-methoxy- $\beta$ -carboline analog **15b** as an amorphous yellow solid (42.5 mg, 91%).

Characterization of **15b**:

$R_f = 0.20$  (25% ethyl acetate–75% petroleum ether; UV), MP =  $185\text{ }^\circ\text{C}$  (decomp.).  $^1\text{H}$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  11.02 (br s, 1H), 8.51 (d,  $J = 5.3$  Hz, 1H), 8.23 (d,  $J = 5.3$  Hz, 1H), 8.14 (d,  $J = 8.0$  Hz, 1H), 8.11 (d,  $J = 8.2$  Hz, 1H), 7.90 (d,  $J = 2.6$  Hz, 1H), 7.82 – 7.71 (m, 3H), 7.60 (t,  $J = 7.4$  Hz, 1H), 7.49 (d,  $J = 7.7$  Hz, 1H), 7.45 (d,  $J = 8.8$  Hz, 1H), 7.21 (dd,  $J = 8.9, 2.6$  Hz, 1H), 3.92 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $DMSO$ )  $\delta$  154.4, 143.7, 138.3, 136.7, 136.6, 136.1, 134.6, 132.1, 129.6, 129.3, 129.2, 128.4, 127.3, 127.0, 126.6, 126.5, 122.1, 119.2, 115.0, 114.0, 104.4, 56.6. IR (FT-IR)  $\text{cm}^{-1}$ : 1559 (w), 1492 (m), 1464 (m), 1436 (w), 1288 (m), 1206 (m), 1175 (m), 1023 (m), 1006 (m), 821 (s), 803 (s), 777 (s), 761 (m), 736 (m). HR-MS ( $m/z$ ):  $[M + H]^+$  calcd for  $C_{22}H_{17}N_2O$ , 325.1333; found, 325.1340.

Scheme S27. Suzuki Cross Coupling of triflate-substituted 6-methoxy- $\beta$ -carboline **13** with 2-naphthylboronic acid

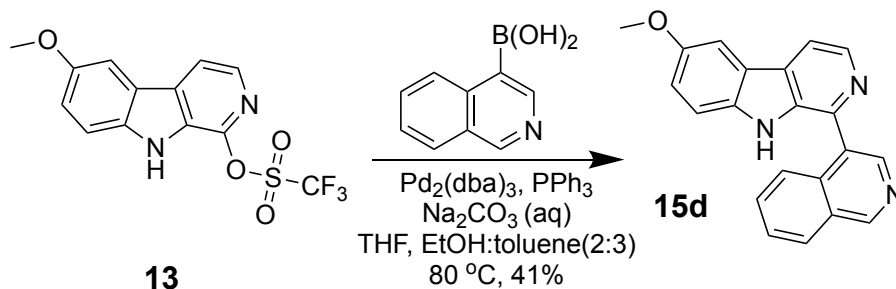


Triflate-substituted 6-methoxy- $\beta$ -carboline **13** (40.0 mg, 0.115 mmol, 1.00 equiv.) was dissolved in toluene (0.69 mL). In a separate flask, 2-naphthylboronic acid (27.7 mg, 0.161 mmol, 1.40 equiv.) was dissolved in ethanol (0.46 mL). The resulting solution was added to the reaction mixture containing **13**. Saturated sodium carbonate (0.23 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (5.3 mg, 0.007 mmol, 0.05 equiv.) and triphenylphosphine (3.0 mg, 0.014 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to  $80\text{ }^\circ\text{C}$  for 1.5 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ether to provide the 6-methoxy- $\beta$ -carboline analog **15c** as an orange solid (22.3 mg, 60%).

Characterization of **15c**:

$R_f = 0.28$  (25% ethyl acetate–75% petroleum ether; UV), MP  $187\text{--}190\text{ }^\circ\text{C}$ .  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.58 (br s, 1H), 8.63 (d,  $J = 1.7\text{ Hz}$ , 1H), 8.51 (d,  $J = 5.2\text{ Hz}$ , 1H), 8.23 (dd,  $J = 8.5, 1.7\text{ Hz}$ , 1H), 8.20 – 8.13 (m, 3H), 8.08 – 8.04 (m, 1H), 7.89 (d,  $J = 2.5\text{ Hz}$ , 1H), 7.65 (d,  $J = 3.9\text{ Hz}$ , 1H), 7.64 – 7.59 (m, 2H), 7.26 (dd,  $J = 8.9, 2.5\text{ Hz}$ , 1H), 3.93 (s, 3H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{DMSO}$ )  $\delta$  154.5, 143.0, 138.9, 137.0, 136.8, 134.8, 133.9, 133.8, 130.1, 129.7, 129.2, 128.6, 128.4, 127.6, 127.3, 127.3, 122.2, 119.3, 115.0, 114.2, 104.3, 56.6. IR (FT-IR)  $\text{cm}^{-1}$ : 1583 (w), 1563 (m), 1492 (m), 1466 (m), 1436 (m), 1283 (m), 1215 (s), 1181 (m), 1134 (m), 1122 (m), 1040 (m), 822 (m), 812 (m), 783 (m), 767 (m), 746 (s), 738 (m). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{22}\text{H}_{17}\text{N}_2\text{O}$ , 325.1333; found, 325.1337.

Scheme S28. Suzuki Cross Coupling of triflate-substituted 6-methoxy- $\beta$ -carboline **13** with 4-isoquinolineboronic acid

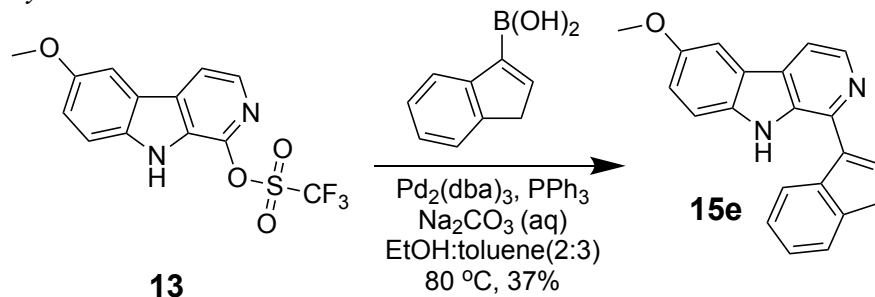


Triflate-substituted 6-methoxy- $\beta$ -carboline **13** (50.0 mg, 0.144 mmol, 1.00 equiv.) was dissolved in toluene (0.86 mL). In a separate flask, 4-isoquinolineboronic acid (34.9 mg, 0.202 mmol, 1.40 equiv.) was dissolved in ethanol (0.58 mL) and THF (0.58 mL). The resulting solution was added to the reaction mixture containing **13**. Saturated sodium carbonate (0.29 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 0.007 mmol, 0.05 equiv.) and triphenylphosphine (3.8 mg, 0.014 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 3 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ether to provide the 6-methoxy- $\beta$ -carboline analog **15d** as an off-white solid (19.2 mg, 41%).

Characterization of **15d**:

$R_f$  = 0.22 (75% ethyl acetate–25% petroleum ether; UV), MP > 250 °C (decomp.).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.24 (br s, 1H), 9.54 (s, 1H), 8.80 (s, 1H), 8.55 (d,  $J$  = 5.3 Hz, 1H), 8.35 – 8.30 (m, 1H), 8.27 (d,  $J$  = 5.3 Hz, 1H), 7.91 (d,  $J$  = 2.5 Hz, 1H), 7.85 – 7.75 (m, 3H), 7.45 (d,  $J$  = 8.8 Hz, 1H), 7.22 (dd,  $J$  = 9.1, 2.5 Hz, 1H), 3.92 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}$ )  $\delta$  154.4, 153.9, 144.2, 140.7, 138.6, 136.8, 136.4, 134.6, 132.0, 129.9, 129.6, 129.3, 129.0, 128.6, 125.5, 122.0, 119.4, 115.4, 114.0, 104.4, 56.6. IR (FT-IR)  $\text{cm}^{-1}$ : 1581 (w), 1563 (w), 1498 (m), 1471 (m), 1386 (m), 1290 (m), 1277 (m), 1210 (m), 1200 (m), 1175 (m), 1101 (m), 1060 (m), 1033 (m), 816 (s), 756 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{16}\text{N}_3\text{O}$ , 326.1285; found, 326.1291.

Scheme S29. Suzuki Cross Coupling of triflate-substituted 6-methoxy- $\beta$ -carboline **13** with 1H-inden-3-ylboronic acid

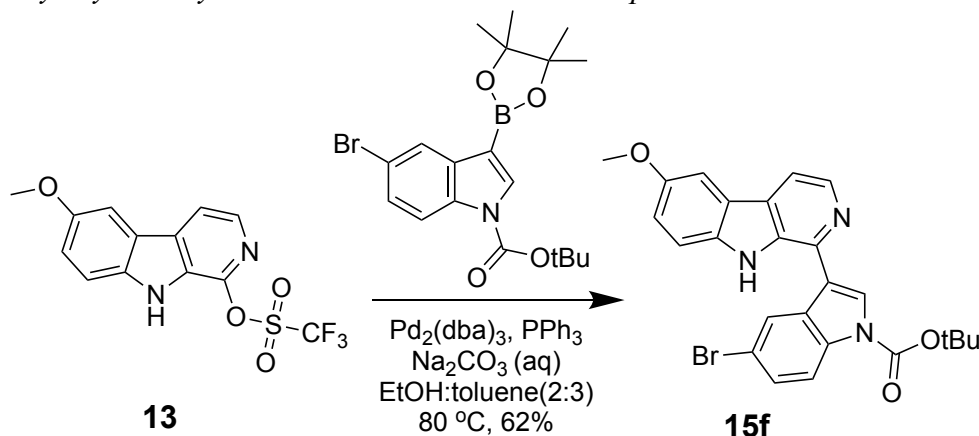


Triflate-substituted 6-methoxy- $\beta$ -carboline **13** (50.0 mg, 0.144 mmol, 1.00 equiv.) was dissolved in toluene (0.86 mL). In a separate flask, 1H-inden-3-ylboronic acid (32.3 mg, 0.202 mmol, 1.40 equiv.) was dissolved in ethanol (0.58 mL). The resulting solution was added to the reaction mixture containing **13**. Saturated sodium carbonate (0.29 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 0.007 mmol, 0.05 equiv.) and triphenylphosphine (3.8 mg, 0.014 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 1.5 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ether to provide the 6-methoxy- $\beta$ -carboline analog **15e** as a red solid (16.6 mg, 37%).

Characterization of **15e**:

$R_f = 0.27$  (25% ethyl acetate–75% petroleum ether; UV), MP 133–137 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.30 (br s, 1H), 8.50 (d,  $J = 5.3$  Hz, 1H), 8.19 (d,  $J = 7.0$  Hz, 1H), 8.15 (d,  $J = 5.3$  Hz, 1H), 7.87 (d,  $J = 2.5$  Hz, 1H), 7.65 (d,  $J = 7.2$  Hz, 1H), 7.62 (d,  $J = 8.7$  Hz, 1H), 7.42 – 7.28 (m, 3H), 7.25 (dd,  $J = 8.8, 2.6$  Hz, 1H), 3.92 (s, 3H), 3.80 (d,  $J = 2.2$  Hz, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}$ )  $\delta$  154.5, 144.8, 144.5, 141.2, 140.0, 138.0, 136.6, 135.7, 135.1, 129.5, 126.9, 125.9, 124.7, 123.6, 122.2, 119.1, 114.8, 114.2, 104.2, 56.5, 39.4. IR (FT-IR)  $\text{cm}^{-1}$ : 1767 (w), 1683 (w), 1602 (w), 1582 (w), 1559 (w), 1492 (m), 1464 (m), 1456 (m), 1436 (w), 1414 (w), 1287 (m), 1204 (s), 1174 (m), 1023 (m), 1004 (m), 820 (m), 752 (m). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}$ , 313.1333; found, 313.1344.

Scheme S30. Suzuki Cross Coupling of triflate-substituted 6-methoxy- $\beta$ -carboline **13** with 1-*tert*-butyloxycarbonyl-5-bromoindole-2-boronic acid pinacol ester

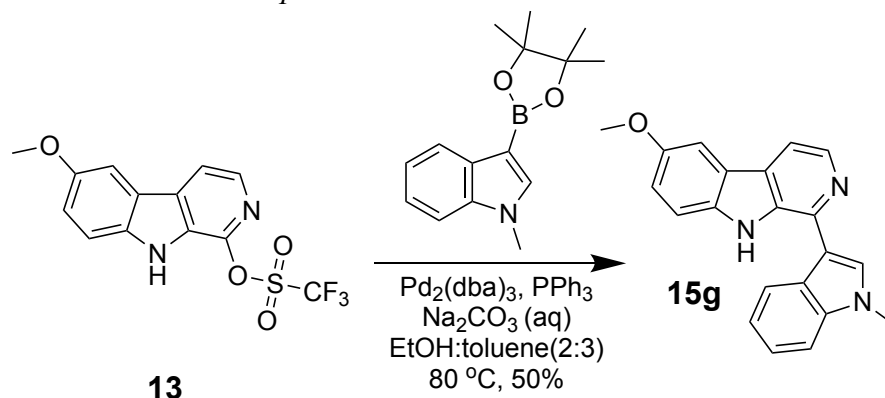


Triflate-substituted 6-methoxy- $\beta$ -carboline **13** (50.0 mg, 0.144 mmol, 1.00 equiv.) was dissolved in toluene (1.08 mL). In a separate flask, 1-*tert*-butyloxycarbonyl-5-bromoindole-2-boronic acid pinacol ester (101.2 mg, 0.240 mmol, 1.70 equiv.) was dissolved in ethanol (0.72 mL). The resulting solution was added to the reaction mixture containing **13**. Saturated sodium carbonate (0.36 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 0.007 mmol, 0.05 equiv.) and triphenylphosphine (3.8 mg, 0.014 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 2 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ether to provide the 6-methoxy- $\beta$ -carboline analog **15f** as a yellow solid (44.1 mg, 62%).

Characterization of **15f**:

$R_f$  = 0.33 (25% ethyl acetate–75% petroleum ether; UV), MP = 159.8–166.8 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.50 (br s, 1H), 8.73 (d,  $J$  = 2.2 Hz, 1H), 8.56 (s, 1H), 8.53 (d,  $J$  = 5.2 Hz, 1H), 8.12 (t,  $J$  = 8.0 Hz, 2H), 7.86 (d,  $J$  = 2.5 Hz, 1H), 7.68 – 7.57 (m, 2H), 7.26 (dd,  $J$  = 9.0, 2.5 Hz, 1H), 3.92 (s, 3H), 1.74 (s, 9H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}$ )  $\delta$  154.6, 149.8, 138.5, 137.8, 136.8, 134.6, 134.5, 131.8, 129.9, 128.5, 127.7, 126.0, 122.4, 119.2, 118.1, 117.6, 116.7, 114.6, 114.3, 104.3, 86.0, 56.5, 28.6. IR (FT-IR)  $\text{cm}^{-1}$ : 1733 (m), 1492 (m), 1438 (m), 1365 (s), 1289 (m), 1270 (m), 1256 (m), 1233 (m), 1199 (s), 1149 (s), 1095 (m), 1047 (s), 1027 (s), 800 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{25}\text{H}_{23}\text{BrN}_3\text{O}_3$ , 492.0915; found, 492.0934.

Scheme S31. Suzuki Cross Coupling of triflate-substituted 6-methoxy- $\beta$ -carboline **13** with *N*-methylindole-3-boronic acid pinacol ester

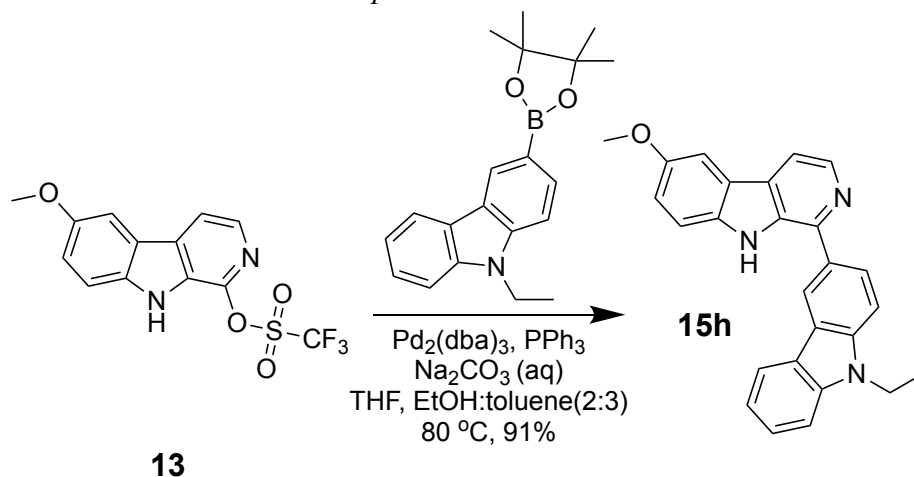


Triflate-substituted 6-methoxy- $\beta$ -carboline **13** (50.0 mg, 0.144 mmol, 1.00 equiv.) was dissolved in toluene (1.08 mL). In a separate flask, *N*-methylindole-3-boronic acid pinacol ester (70.0 mg, 0.272 mmol, 1.90 equiv.) was dissolved in ethanol (0.72 mL). The resulting solution was added to the reaction mixture containing **13**. Saturated sodium carbonate (0.36 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 0.007 mmol, 0.05 equiv.) and triphenylphosphine (3.8 mg, 0.014 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to 80 °C for 5 h under inert atmosphere. At 5 h, another 1.0 equiv. (37.1 mg) of *N*-methylindole-3-boronic acid pinacol ester was added to the reaction mixture. The reaction was heated to 80 °C for another 1 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ether to provide the 6-methoxy- $\beta$ -carboline analog **15g** as an amorphous green solid (23.5 mg, 50%).

Characterization of **15g**:

$R_f$  = 0.39 (80% ethyl acetate–20% petroleum ether; UV), MP = 115 °C (decomp.).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.14 (br s, 1H), 8.61 (d,  $J$  = 8.0 Hz, 1H), 8.45 (d,  $J$  = 5.2 Hz, 1H), 8.31 (s, 1H), 7.98 (d,  $J$  = 5.2 Hz, 1H), 7.83 (d,  $J$  = 2.5 Hz, 1H), 7.64 (d,  $J$  = 8.8 Hz, 1H), 7.60 (d,  $J$  = 8.2 Hz, 1H), 7.32 (t,  $J$  = 7.6 Hz, 1H), 7.29 – 7.18 (m, 2H), 4.01 (s, 3H), 3.92 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}$ )  $\delta$  154.4, 141.1, 138.4, 137.9, 136.5, 133.6, 131.0, 129.0, 127.5, 123.4, 123.1, 122.6, 120.9, 118.7, 114.1, 113.3, 112.6, 110.8, 104.2, 56.5, 33.9. IR (FT-IR)  $\text{cm}^{-1}$ : 3041 (w), 2829 (w), 1561 (m), 1559 (m), 1492 (m), 1464 (m), 1288 (m), 1207 (s), 1112 (m), 1023 (s), 815 (s), 784 (m), 735 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{18}\text{N}_3\text{O}$ , 328.1442; found, 328.1453.

Scheme S32. Suzuki Cross Coupling of triflate-substituted 6-methoxy- $\beta$ -carboline **13** with 9-ethyl-9H-carbazole-3-boronic acid pinacol ester

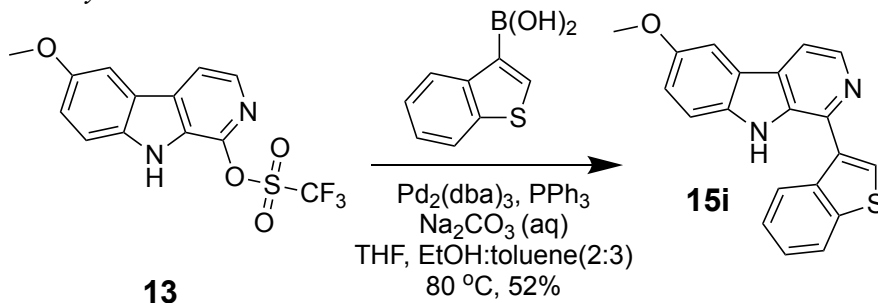


Triflate-substituted 6-methoxy- $\beta$ -carboline **13** (50.0 mg, 0.144 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, 9-ethyl-9H-carbazole-3-boronic acid pinacol ester (64.8 mg, 0.202 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL) and THF (0.63 mL). The resulting solution was added to the reaction mixture containing **13**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 0.007 mmol, 0.05 equiv.) and triphenylphosphine (3.8 mg, 0.014 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to  $80\text{ }^\circ\text{C}$  for 1.5 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ether to provide the 6-methoxy- $\beta$ -carboline analog **15h** as a yellow solid (51.5 mg, 91%).

Characterization of **15h**:

$R_f = 0.15$  (33% ethyl acetate–67% petroleum ether; UV), MP  $106\text{--}110\text{ }^\circ\text{C}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.48 (br s, 1H), 8.83 (s, 1H), 8.48 (d,  $J = 5.2$  Hz, 1H), 8.34 (d,  $J = 7.7$  Hz, 1H), 8.20 (dd,  $J = 8.6, 1.7$  Hz, 1H), 8.11 (d,  $J = 5.2$  Hz, 1H), 7.89–7.82 (m, 2H), 7.70 (d,  $J = 8.2$  Hz, 1H), 7.62 (d,  $J = 8.9$  Hz, 1H), 7.54 (t,  $J = 7.7$  Hz, 1H), 7.29 (t,  $J = 7.5$  Hz, 1H), 7.24 (dd,  $J = 8.8, 2.5$  Hz, 1H), 4.57 (q,  $J = 7.1$  Hz, 2H), 3.92 (s, 3H), 1.41 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}$ )  $\delta$  154.4, 144.4, 141.0, 140.6, 138.7, 136.9, 134.5, 130.3, 129.7, 127.3, 126.9, 123.4, 123.4, 122.2, 121.9, 121.4, 119.9, 119.0, 114.2, 114.1, 110.2, 110.2, 104.2, 56.6, 38.1, 14.8. IR (FT-IR)  $\text{cm}^{-1}$ : 1599 (w), 1598 (w), 1492 (m), 1464 (m), 1434 (w), 1384 (w), 1287 (m), 1206 (s), 1147 (w), 1133 (w), 1022 (s), 1005 (m), 814 (s), 748 (s), 732 (m). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}$ , 392.1755; found, 392.1768.

Scheme S33. Suzuki Cross Coupling of triflate-substituted 6-methoxy- $\beta$ -carboline **13** with benzo[*b*]thien-3-ylboronic acid

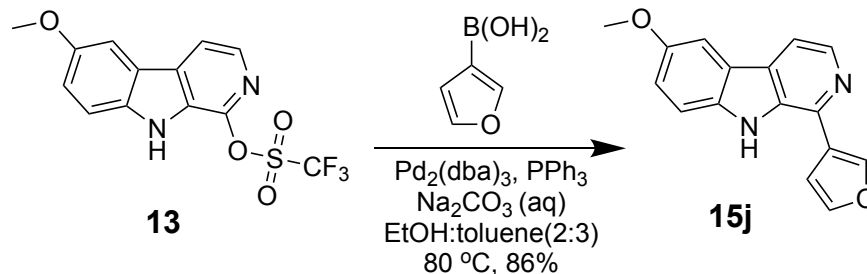


Triflate-substituted 6-methoxy- $\beta$ -carboline **13** (50.0 mg, 0.144 mmol, 1.00 equiv.) was dissolved in toluene (0.95 mL). In a separate flask, benzo[*b*]thien-3-ylboronic acid (35.9 mg, 0.202 mmol, 1.40 equiv.) was dissolved in ethanol (0.63 mL) and THF (0.63 mL). The resulting solution was added to the reaction mixture containing **13**. Saturated sodium carbonate (0.32 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 0.007 mmol, 0.05 equiv.) and triphenylphosphine (3.8 mg, 0.014 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to  $80^\circ\text{C}$  for 2 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ether to provide the 6-methoxy- $\beta$ -carboline analog **15i** as a yellow solid (24.9 mg, 52%).

Characterization of **15i**:

$R_f = 0.31$  (25% ethyl acetate–75% petroleum ether; UV), MP =  $185^\circ\text{C}$  (decomp.).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.38 (br s, 1H), 8.52 (d,  $J = 5.3$  Hz, 1H), 8.36 (d,  $J = 5.9$  Hz, 2H), 8.19 (d,  $J = 5.2$  Hz, 1H), 8.18 – 8.14 (m, 1H), 7.88 (d,  $J = 2.5$  Hz, 1H), 7.59 (d,  $J = 8.8$  Hz, 1H), 7.53 – 7.45 (m, 2H), 7.25 (dd,  $J = 8.9, 2.5$  Hz, 1H), 3.93 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}$ )  $\delta$  154.5, 140.6, 139.6, 138.9, 138.2, 136.7, 135.4, 134.2, 129.7, 128.5, 125.8, 125.4, 125.4, 123.7, 122.2, 119.2, 114.9, 114.2, 104.3, 56.6. IR (FT-IR)  $\text{cm}^{-1}$ : 1562 (w), 1490 (m), 1460 (m), 1456 (m), 1286 (m), 1205 (s), 1174 (m), 1022 (m), 820 (m), 760 (s), 734 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{15}\text{N}_2\text{OS}$ , 331.0897; found, 331.0903.

Scheme S34. Suzuki Cross Coupling of triflate-substituted 6-methoxy- $\beta$ -carboline **13** with 3-furanylboronic acid

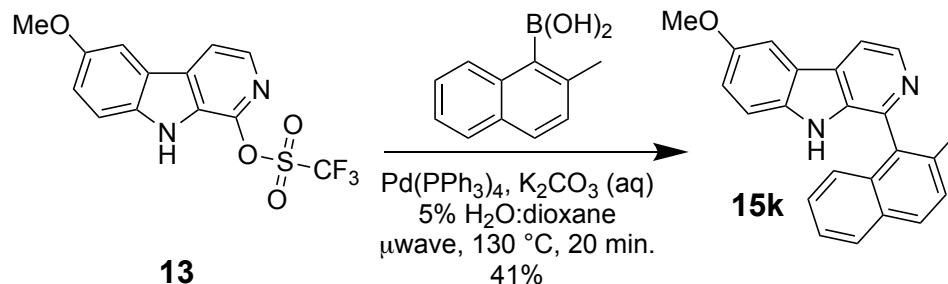


Triflate-substituted 6-methoxy- $\beta$ -carboline **13** (50.0 mg, 0.144 mmol, 1.00 equiv.) was dissolved in toluene (0.86 mL). In a separate flask, 3-furanylboronic acid (22.6 mg, 0.202 mmol, 1.40 equiv.) was dissolved in ethanol (0.58 mL). The resulting solution was added to the reaction mixture containing **13**. Saturated sodium carbonate (0.29 mL) was next added to the reaction mixture, followed by addition of tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 0.007 mmol, 0.05 equiv.) and triphenylphosphine (3.8 mg, 0.014 mmol, 0.10 equiv.). The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then heated to  $80^\circ\text{C}$  for 2 h under inert atmosphere. The product-mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ether to provide the 6-methoxy- $\beta$ -carboline analog **15j** as an amorphous yellow solid (32.8 mg, 86%).

Characterization of **15j**:

$R_f$  = 0.22 (25% ethyl acetate–75% petroleum ether; UV), MP  $121^\circ\text{C}$  (decomp.).  $147\text{--}151^\circ\text{C}$  (decomp.).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.10 (br s, 1H), 8.69 (s, 1H), 8.40 (d,  $J$  = 5.2 Hz, 1H), 8.08 (d,  $J$  = 5.2 Hz, 1H), 7.94 (d,  $J$  = 1.6 Hz, 1H), 7.84 (d,  $J$  = 2.5 Hz, 1H), 7.64 (d,  $J$  = 8.8 Hz, 1H), 7.31 (d,  $J$  = 1.8 Hz, 1H), 7.26 (dd,  $J$  = 8.9, 2.5 Hz, 1H), 3.91 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}$ )  $\delta$  154.6, 144.8, 142.6, 138.5, 136.7, 136.4, 133.6, 129.8, 125.8, 122.2, 119.2, 114.5, 114.2, 110.8, 104.3, 56.5. IR (FT-IR)  $\text{cm}^{-1}$ : 1587 (w), 1559 (w), 1492 (m), 1471 (m), 1436 (m), 1288 (m), 1212 (s), 1156 (s), 1069 (m), 1026 (m), 874 (m), 818 (m), 805 (s), 777 (m), 770 (m), 741 (m). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}_2$ , 265.0969; found, 265.0975.

Scheme S35. Suzuki Cross Coupling of triflate-substituted 6-methoxy- $\beta$ -carboline **13** with 2-methylnaphthalene-1-boronic acid

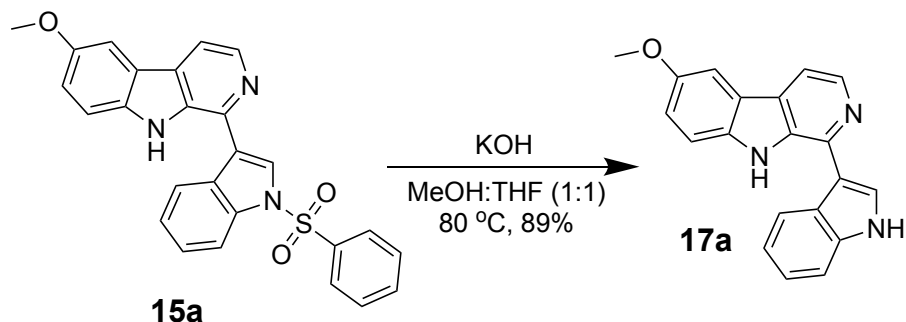


Triflate-substituted 6-methoxy- $\beta$ -carboline **13** (30.0 mg, 0.087 mmol, 1.00 equiv.), 2-methylnaphthalene-1-boronic acid (40.5 mg, 0.218 mmol, 2.50 equiv.), potassium carbonate (24.0 mg, 0.174 mmol, 2.00 equiv.), and tetrakis(triphenylphosphine) palladium (10.1 mg, 0.009 mmol, 0.10 equiv.) were dissolved in 5%  $\text{H}_2\text{O}$ : 95% dioxane (0.87 mL) in a microwave tube equipped with a magnetic stirbar. The yellowish brown reaction mixture was stirred at room temperature and sparged with a stream of nitrogen for 5 min. The solution was then irradiated at 300 W and 130 °C for 20 minutes. The product-mixture was then poured into a separatory funnel containing 30 mL ethyl acetate. The diluted mixture was then extracted with water (3 x 30 mL). The organic layer was then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the analog **15k** as a beige solid (11.5 mg, 41%).

Characterization of **15k**:

$R_f = 0.26$  (33% ethyl acetate–67% hexanes; UV), MP = 220.6–221.5 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.81 (br s, 1H), 8.48 (dd,  $J = 5.3, 1.5$  Hz, 1H), 8.20 (dd,  $J = 5.4, 1.5$  Hz, 1H), 8.01 (t,  $J = 9.2$  Hz, 2H), 7.86 (t,  $J = 2.0$  Hz, 1H), 7.60 (dd,  $J = 8.5, 1.5$  Hz, 1H), 7.49–7.42 (m, 1H), 7.34 (dd,  $J = 8.9, 1.5$  Hz, 1H), 7.30 (dt,  $J = 6.8, 1.6$  Hz, 1H), 7.15 (dt,  $J = 8.9, 2.1$  Hz, 1H), 7.06 (d,  $J = 8.5$  Hz, 1H), 3.88 (d,  $J = 1.5$  Hz, 3H), 2.14 (d,  $J = 1.5$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  153.4, 142.5, 137.7, 135.8, 135.4, 134.1, 133.6, 132.1, 131.8, 128.9, 128.2, 128.0, 127.8, 126.2, 125.1, 125.0, 121.2, 118.2, 114.0, 113.0, 103.6, 55.7, 40.1, 19.7. IR (FT-IR)  $\text{cm}^{-1}$ : 2923 (w), 1562 (m), 1492 (s), 1413 (m), 1273 (s), 1206 (s), 1175 (m), 1141 (m), 1025 (m), 812 (s), 743 (s), 621 (s).

Scheme S36. Benzenesulfonyl deprotection of **15a**

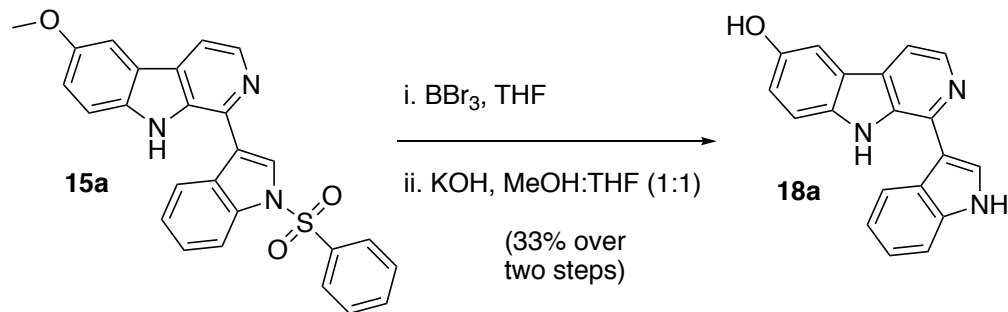


Analog **15a** (57.0 mg, 0.126 mmol, 1.00 equiv.) was dissolved in a 1:1 mixture of MeOH (1.05 mL) and dry THF (1.05 mL). Solid KOH (35.3 mg, 0.629 mmol, 5.00 equiv.) was then added to the solution. The yellow reaction mixture was sparged with a stream of nitrogen for 5 minutes, refluxed at 80 °C, and stirred for 1 h under inert atmosphere. The product mixture was then poured into a separatory funnel containing 30 mL water. The diluted mixture was then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were then dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and petroleum ethers to provide the 6-methoxy-β-carboline analog **17a** as an amorphous yellow solid (35.1 mg, 89%).

Characterization of **17a**:

$R_f$  = 0.35 (100% ethyl acetate; UV), MP = 155 °C (decomp.).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.88 (br s, 1H), 8.54 (d,  $J$  = 5.4 Hz, 1H), 8.31 (br s, 1H), 7.97 (d,  $J$  = 7.9 Hz, 1H), 7.87 (d,  $J$  = 5.3 Hz, 1H), 7.75 (d,  $J$  = 2.4 Hz, 1H), 7.60 (d,  $J$  = 2.5 Hz, 1H), 7.50 (d,  $J$  = 8.1 Hz, 1H), 7.39 (d,  $J$  = 8.9 Hz, 1H), 7.31 (t,  $J$  = 7.5 Hz, 1H), 7.23 (d,  $J$  = 7.6 Hz, 1H), 7.20 (dd,  $J$  = 8.8, 2.5 Hz, 1H), 3.96 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.3, 139.4, 138.5, 136.5, 135.1, 134.4, 129.1, 125.8, 124.5, 122.9, 122.4, 120.9, 120.6, 118.4, 112.6, 112.5, 111.8, 103.5, 56.0, 29.7. IR (FT-IR)  $\text{cm}^{-1}$ : 3416 (m), 3394 (m), 2958 (m), 2917 (m), 2848 (m), 1572 (s), 1492 (s), 1456 (s), 1435 (s), 1288 (s), 1216 (s), 1169 (s), 1027 (s), 811 (s), 753 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}$ , 314.1285; found, 314.1289.

Scheme S37. Global deprotection of **15a**



Analog **15a** (200 mg, 0.44 mmol, 1.0 equiv.) was dissolved in dry dichloromethane under a nitrogen atmosphere. Boron tribromide was added dropwise and the resulting solution was stirred for 40 minutes. The product mixture was diluted with EtOAc (30 mL) and washed with water (3 x 20 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo to give a crude solid that was used without further purification. The crude residue was dissolved in a 1:1 mixture of MeOH (3.8 mL) and dry THF (3.8 mL). Solid KOH (128 mg, 2.23 mmol, 5.00 equiv.) was then added to the solution. The reaction mixture was sparged with a stream of nitrogen for 5 minutes, heated to 60 °C, and stirred for 1 h under inert atmosphere. The product mixture was then poured into a separatory funnel containing 30 mL ethyl acetate. The diluted mixture was then washed with sat. aq. Ammonium chloride (3 x 20 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated. The residue obtained was purified by automated flash-column chromatography using ethyl acetate and hexanes to provide the 6-methoxy- $\beta$ -carboline analog **18a** as a yellow film (45.8 mg, 33% over two steps).

Characterization of **18a**:

$R_f$  = 0.10 (100% ethyl acetate; UV), MP = .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.67 (br s, 1H), 10.96 (br s, 1H), 9.13 (s, 1H), 8.56 (d,  $J$  = 8.0 Hz, 1H), 8.36 (d,  $J$  = 5.2 Hz, 1H), 8.26 (d,  $J$  = 2.4 Hz, 1H), 7.82 (d,  $J$  = 5.2 Hz, 1H), 7.50 (m, 2H), 7.20 (t,  $J$  = 3.2 Hz, 1H), 7.12 (t,  $J$  = 3.2 Hz, 1H), 7.05 (dd,  $J$  = 8.8, 2.4 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  151.0, 140.3, 137.2, 136.5, 134.9, 132.7, 127.8, 126.2, 125.8, 122.4, 122.0, 121.9, 119.7, 117.7, 113.4, 113.0, 111.5, 105.3. IR (FT-IR)  $\text{cm}^{-1}$ : 3388 (s), 3293 (m), 2960 (br), 1705 (s), 1602 (m), 1498 (m), 1469 (s), 1418 (s), 1391 (m), 1242 (s), 1219 (s), 1197 (s), 1177 (s), 1124 (m), 1094 (m), 1041 (m), 826 (s), 815 (s), 750 (s), 642 (s). HR-MS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}$ , 300.1139; found, 300.1129.

## Biological assays:

Radioligand binding assays were performed by the Psychoactive Drug Screening Program of the National Institutes of Mental Health, according to a published procedure.<sup>12</sup> All compounds submitted for screening at the PDSP were taken from the same synthetic samples that gave the NMR spectra provided (vide infra).

**Primary binding:** Data represent mean % inhibition (N = 4 determinations) for compound tested at receptor subtypes. Significant inhibition is considered > 50%. In cases where negative inhibition (-) is seen, this represents a stimulation of binding. Occasionally, compounds at high concentrations will non-specifically increase binding. The default concentration for primary binding experiments is 10  $\mu$ M. A few compounds against a few receptors were not tested (N/A).

Table S1. Primary Binding Assay

CMPD	5-HT1A	5-HT1B	5-HT1D	5-HT1e	5-HT2A	5-HT2B	5-HT2C	5-HT3	5-HT5a	5-HT6	5-HT7	Alpha1A	Alpha1B	Alpha1D	Alpha2A	Alpha2B	Alpha2C	Beta1	Beta2	Beta3
16a	58.9	1.2	8.3	-12.2	72.1	94	95.1	32.5	20.9	29.6	27.3	52.1	69.7	42.2	63.5	59.7	62.3	14.7	-7.2	28.2
14b	67.9	4.1	24.3	-12.7	60.6	78.9	59.8	1	1.5	9.2	12.4	19.3	29	1.8	29.1	64.1	26.4	3.6	-10.7	30.8
14c	22.8	N/A	4.5	-12.5	75	72.9	62.9	-11.2	36.5	24.2	16.2	20.5	48.4	18.7	21.9	34.4	39	60.9	-4.3	33
14d	47.3	N/A	9	-11.4	41.2	66.7	51.8	12.9	11.4	25.9	-6.1	18.4	36.9	7.2	16.3	28.2	30.8	3.5	-3.7	27.5
14e	36.8	N/A	22	-9	38.1	69.2	59.6	-13	12.4	8.5	-6.3	11.8	21.1	7.6	3.8	32.9	23.2	-0.5	-8.4	18.3
16f	15.6	-2.5	8.8	3	32.9	74	80.6	13.7	2	2.1	15.5	5.8	46.7	3.3	35.3	40.3	53.6	25.5	3.7	34.4
14g	63.2	N/A	53.3	8.5	67.5	85.2	75.5	25.3	37.6	-1	24	48.7	55.8	43.8	81.5	74.6	70.6	12.8	2.4	31.3
14h	29.4	-8.9	16.1	-26.6	30.1	86.1	68.4	34.9	28.5	-2.2	11.7	12.2	18.8	17.3	41	42	30.6	3.6	-13.9	-7.2
14i	46.9	-10.3	13.3	-16	52.5	82.3	73.2	-18.3	-1.2	4.5	-12.7	9.1	23.1	1	26.4	51.7	44	11.4	-4.1	36.6
14j	10.9	-11.8	9.4	-12.4	12.2	81.2	62.8	-11.2	-3.6	-4.3	0.4	15.5	39.4	5.3	15.3	27.8	13.2	10	-3.4	26.5
14k	35.7	0.8	9	0.3	27.1	48.1	50	-11.3	8.1	2.1	-9	5.9	21	-1.1	18.3	45.6	40.1	12.8	3.4	27.5
16i	-0.5	0.7	4.9	-1.3	30.7	40.5	41.8	-7.9	7.2	-2.6	-19	1.3	31.3	-6.3	5.6	13.7	6.2	36.9	-17	18.8
14m	19.6	N/A	3.7	-18.3	66.6	73.2	56.2	-11.5	18.3	6.6	17	19.2	54.6	-3.6	4.9	18.7	7.9	6.2	-7.1	17
14n	18.2	N/A	3.5	-17.7	13.5	84.9	71.8	-3.1	12	25	-3.3	27.7	40.2	8.8	26.2	30	15	11.1	-7.7	20.2
14o	13.5	N/A	22.2	-2.3	-3.7	60.2	43.6	-7.5	11.4	30.6	-0.4	-1	35.3	2.5	42.6	36.4	15.9	16.8	1.6	23.5
17a	25.2	12.9	12.8	-6.8	74.6	87.8	92	0.6	14	16.3	14.3	31.3	56.5	21.2	59.1	31.5	49.8	42.5	-0.8	23.2
15b	9	-2.2	6.8	-6.6	74.4	81.5	88.8	65	-10.2	21.6	-9.5	10.8	30.4	-0.6	42.4	47.2	27.1	24.7	1.3	21.9
15c	23.5	N/A	-6.5	11.7	24	86.3	55.8	-14.8	38.8	9.2	28.7	40.6	46.9	22	42	37.1	40.9	25.5	-10.7	23.4
15d	18.9	33.2	5	-14.3	64.1	80.6	86.7	-15	-3.2	-8.7	-10.7	22.4	51.7	10.1	32.6	45.1	21.5	43.6	-9.3	16.2
15e	6.7	-2.9	30.8	-9.4	54.7	50.7	65.5	-19.1	-19.4	-6.5	-16.6	11.1	28.8	0.5	16.7	30.8	13.2	30.3	2.4	5.4
15f	-3.4	5.5	7.4	9	19.4	9.5	27.4	-8	-2.9	-16.7	-9.2	9.1	41.9	-5.9	7.6	-7.8	10.1			
15g	25.8	49.4	33.1	8.3	81.7	84	93.8	18.2	66	N/A	N/A	56.9	56.4	34.8	85.1	66.6	77.7	49	4.7	33
15h	6.7	17.6	22.4	-5.3	28.7	75.6	53.4	20.7	36.7	2	59.7	16.9	39.3	-13.7	14.3	32.3	25.3	36	-7.4	-12.5
15i	13.4	-5.5	11	8.3	66.1	69.9	92.3	34.6	23.1	20.6	32.4	12.4	34.6	-12.1	39.3	40.1	34.8	18.9	-10.5	13.8
15j	-3.4	-7.7	19.3	-12.9	-16.3	84.6	49.2	-19.6	15.7	-14.7	-12.5	20.2	35.6	17	51.7	24	12.3	31.7	3.1	14.2
15k	-6.5	N/A	-14.2	26.4	-8.9	74.9	47.9	2.4	13.9	44.7	-3.6	7.8	39.1	-1.3	7.7	11.3	28.8	-4.6	-10.7	-2.1
18a	49.6	32	46	N/A	64.8	93.7	91.1	-14	53.2	26.3	75.3	54.6	82.7	34.7	N/A	N/A	40.4	15.4	N/A	19.1
1	14.6	N/A	-9	27.2	20.7	89.7	81.2	-3.8	41.5	47.7	58.5	0.9	43	-0.3	32.1	33.9	9	-18.4	-13.1	-6
2	14.5	N/A	-1.1	30.2	15.2	63.4	69.1	8.9	46	0.6	54	-1.5	40.8	2.8	33.3	33.2	15.2	1.4	-10.8	45.8

CMPD	BZP	Rat Brain Site	D1	D2	D3	D4	D5	DAT	DOR	GABAA	H1	H2	H3	H4	KOR	MOR	NET	PBR	SERT	Sigma 1 GP	Sigma 2
16a	14.9	86.3	18.2	40.8	18.9	33.4	24.2	9.1	4.7	17.1	63.4	21	36.3	28.8	33.6	71	40.6	25.6	8.4	71.1	
14b	16.8	28.7	24.5	-8.9	1.3	10.4	25.5	34	-5.4	12.7	57.9	14.4	32.3	51.4	46.9	20.4	60.9	2.1	29.2	63.8	
14c	57.4	50	-11.2	-3.4	9.2	27.7	-1	84	-6.5	26.4	73.1	25.4	22.8	49.8	48.2	27.8	24	2.9	-6.1	50.9	
14d	28.2	2.1	-5.5	0.8	-7.7	3.9	11.5	18.1	4	30.5	73.4	24	33.4	-9	31.3	33.3	52.1	5.1	-1.8	22.3	
14e	35.7	15.3	5.1	20.7	-15.9	6.6	-7	17.8	13.2	-39.3	77.1	-40.2	17.2	-12.9	61.3	37.7	20.7	19.2	12.4	48.5	
16f	32.7	37.4	8.2	-2.9	4.7	39.5	-7.1	11.2	N/A	75.3	72.3	13.3	37.1	17.3	50	21.6	53.1	-18.1	41.3	83.4	
14g	47.1	52.8	22.8	17.2	34.5	28.8	3.5	7.7	-2.9	-7.8	52.5	-10.1	41.2	61.8	55	38.6	53.6	37	15	72.3	
14h	31.5	16	15.5	-15.7	10.4	13.8	-0.5	5.8	13	7.2	51	-11.4	13.1	20.8	27.1	9.5	45.2	9.5	-1.7	34.7	
14i	8.3	34.8	24.2	-12	4	29.3	12.5	12.7	9.3	2.8	54	-5.2	-8.2	46.9	36.2	65.7	81	-10.2	43.3	70.2	
14j	45.6	22.3	19.8	-4.2	12.1	-6.6	34.7	-15.9	4.6	21.1	60.5	5.1	3.6	22.3	34.8	69.6	23	2	28.4	-31.8	
14k	-8.8	30.2	-10.2	-0.8	18.6	3.5	54.1	31.8	1.1	31.1	67.6	8.2	-0.1	-2.5	42.6	14.9	38.2	-6.8	30.3	60.5	
16i	46.1	5	-10.3	4.1	-2.6	18.8	4.2	9.2	N/A	7.2	73.9	2.5	44.2	17.9	58.1	70.6	4.9	-8.7	50.7	64.9	
14m	26.7	18.8	5.4	-1.2	-6.3	-4.1	3.7	-6.5	-3.8	19.8	52.8	17.1	30.1	35.8	32.3	58	31.2	3.5	14.5	-5.4	
14n	27.1	28.6	-0.3	-13.7	0	3.3	26	0.4	-5.8	17.9	63	31.7	27.4	24.4	25.4	70.1	36.4	-6	7.3	-29.6	
14o	31.3	14.1	1.3	6	11.9	-5.7	-13.4	15.5	6.9	15	19.3	-34.1	16.8	27.3	51.5	55.4	39.6	20.3	7.1	-32.4	
17a	45.7	83.9	22.1	29.1	-10.3	37.4	21.2	7.8	N/A	10.8	83.4	-11.1	48.8	35.7	59.5	50.2	49.9	13.9	43.8	64.1	
15b	-7.1	31	0.9	9.1	0	38.3	21.6	21.4	-10.1	-0.9	50.1	25.6	54.3	11.9	49.1	56.9	74	-11.3	39.9	59	
15c	23.6	45.2	-10.2	4.3	35.1	42.5	36.3	6.4	-14.6	25.5	70	35.9	27.9	36.4	60	72.4	34.4	22.6	13.5	38.1	
15d	9.3	39	5.7	15.6	9.3	6.7	12.9	0.1	-9.9	8.1	57.1	12.6	19.3	7.9	41.3	31.1	41.9	-15.6	21.3	27.9	
15e	23.1	21.7	-3.3	-7.8	-11.2	22.5	19.3	-6.8	8.1	-6.1	46.9	11.5	-13.1	4.1	46.2	31	28.7	-9.8	48.6	32.1	
15f	27.9	2.2	-16.9	-5.5	-6.4	-0.6	-13.9	2.3		-15	17.7	-16.7	35.1	3	35.4	56.7	1.5	11	28.3	22.1	
15g	34.9	49.2	18.4	20.7	24.9	40.4	10.5	31.5	N/A	-11.2	62.5	10.1	-8	67.7	81.9	41.1	71.8	-5.4	N/A	66.2	
15h	39.1	11.6	-5.3	7.2	0	18.9	13.2	-14.6	6.2	26.2	41.3	-7.8	24.2	3.3	39.7	58.1	72.5	-16	30.6	19.4	
15i	10.3	41.5	-0.6	6.6	-8.4	31.9	19.2	15.7	0.9	2.7	45.8	13.4	54.6	18	44.8	79	81	-17.7	35.3	68.8	
15j	33.3	28.8	2.4	-17.6	17	2.9	80.1	1.3	6.3	6.7	56.3	15.3	-12.6	28.6	62.1	70.1	19.1	0.7	52.2	-49.9	
15k	1.8	-8	1.7	3.6	5	9.8	-9.1	-0.6	-9.5	12.9	69	5.9	28.9	-1.3	31.2	85.4	-12	20.1	40.5	40.5	
18a	70.8	N/A	N/A	N/A	N/A	N/A	53.5	6.7	N/A	44.9	21.4	7.5	8.2	27.3	49.1	74.2	15.6	37.7	N/A	21.6	
1	41.3	16.5	2.9	2	12.6	35.6	-2.8	-2.4	16.8	4.4	29.3	-16.8	33.4	20.3	24.6	85.8	-6.3	19.3	49.5	-41.3	
2	62.8	-2	5	6.6	13.3	22.1	14.4	5.3	18.9	18.2	18.1	-10.5	-15.8	8.5	12.2	61.7	-2.4	16.2	28.9	-80.1	

**Secondary binding:** Unless otherwise indicated (see Note), data represent  $K_i$  (nM) values obtained from non-linear regression of radioligand competition binding isotherms.  $K_i$  values are calculated from best fit  $IC_{50}$  values using the Cheng-Prusoff equation. Note: When the Hill coefficient (nH) is significantly different from -1 (assessed by F test), the  $IC_{50}$  and nH are reported instead of the  $K_i$ . A \* next to a value denotes  $IC_{50}$ . Entries without a value denote a primary binding less than 50% inhibition, or a compound that was not tested.

Table S2. Secondary Binding Assay

CMPD	5-HT1A	5-HT1B	5-HT1D	5-HT1e	5-HT2A	5-HT2B	5-HT2C	5-HT3	5-HT5a	5-HT6	5-HT7	Alpha1A	Alpha1B	Alpha1D	Alpha2A	Alpha2B	Alpha2C	Beta1	Beta2	Beta3
16a	1,229.00				897	231	251					3,151.00	1,816.00		2,761.00	1,959.00	2,354.00			
14b	717				2,265.00	1,135.00	4,786.00									2,951.00				
14c					558	1,467.00	4,977.00											3,087.00		
14d						1,802.00	8,815.00													
14e						1,658.00	5,618.00													
16f						1,497.00	2,463.00										1,174.00			
14g	1,018.00		1,112.00		2,117.00	2,073.00	3,263.00					4,011.00			2,463.00	2,350.00	3,689.00			
14h				10,000.0(AVE)		364	1,311.00													
14i					1,535.00	1,131.00	3,938.00									5,189.00				
14j							818	5,229.00												
14k																				
16i																				
14m					685	1,442.00	8,614.00						7,015.00							
14n						701	4,925.00													
14o						2,169.00														
17a					523	380	195						2,149.00		3,697.00					
15b					675	800	1,407.00	4,729.00												
15c						261	3,752.00													
15d					1,137.00	653	1,478.00						6,941.00							
15e					>10,000	1,503.00	2,905.00													
15f																				
15g					807	100	201		1,410.00			2,925.00	1,807.00		1,496.00	2,019.00	1,160.00			
15h						234	>10,000			294										
15i					654	528	743													
15j						743										>10,000				
15k						814														
18a						172	204					1,247.00	2,816.00							
1						267	1,135.00					779								
2						738	2,522.00					1,304.00								

CMPD	BZP Rat Brain Site	D1	D2	D3	D4	D5	DAT	DOR	GABAA	H1	H2	H3	H4	KOR	MOR	NET	PBR	SERT	Sigma 1 GP	Sigma 2
16a		639									3,966.00					3,497.00				1,012.00
14b											3,524.00			2,848.00			1,143.00			1,377.00
14c	2,656.00	4,275.00									2,073.00									1,126.00
14d											8,610.00						971			
14e											6,852.00				1,529.00					
16f										>10,000	>10,000				2,328.00		832			517
14g		3,870.00									4,957.00			4,257.00	4,220.00		3,049.00			1,419.00
14h											2,957.00									
14i											4,889.00						1,886.00	689		1,296.00
14j											5,169.00						1,245.00			>10,000
14k							1,376.00				4,657.00									1,173.00
16i											4,490.00				3,208.00	1,031.00				930
14m											8,644.00					3,049.00				
14n											6,968.00					1,944.00				2576
14o															3,256.00	2,285.00				1879
17a		536									4,425.00				2,800.00	952				1,627.00
15b											7,921.00		>10,000			3,140.00	1,408.00			997
15c											4,951.00				494	1,830.00				
15d											6,605.00									
15e																				
15f																				
15g											2,334.00			2,632.00	1,757.00		582			926.5(AVE)
15h																>10,000	1,153.00			
15i													1,754.00			2,003.00	312			728
15j											6,926.00				2,166.00	1,036.00				1189
15k											7,349.00					1,823.00				
18a	1,640.00						1,114.00													
1																1,581.00				5284
2	1,386.00															2,782.00				2561

# Catalog of Nuclear Magnetic Resonance and Infrared Spectra:

Figure S1.  $^1\text{H}$  NMR of **14d**:

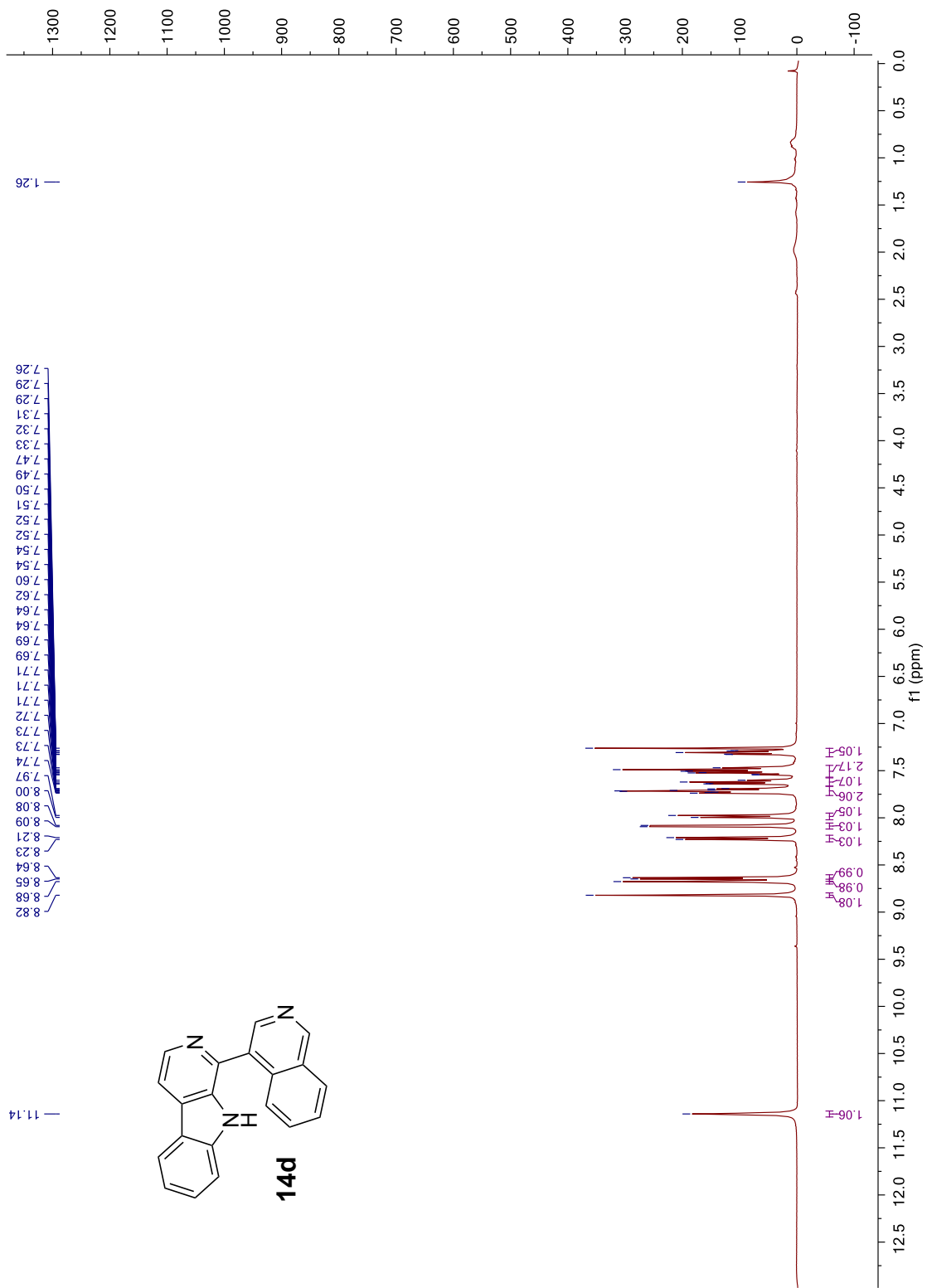


Figure S2.  $^{13}\text{C}$  NMR of **14d**:

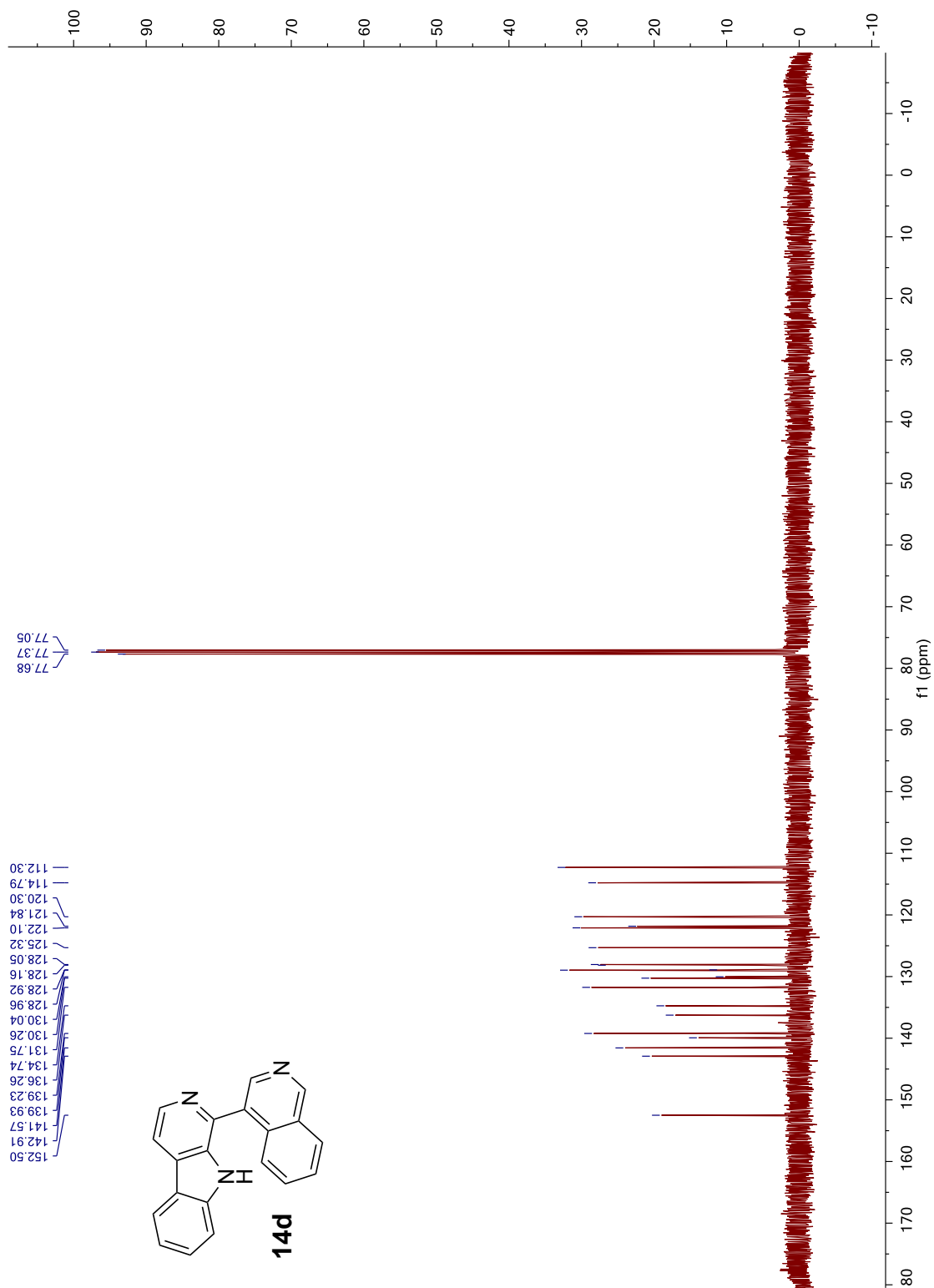


Figure S3. IR of **14d**:

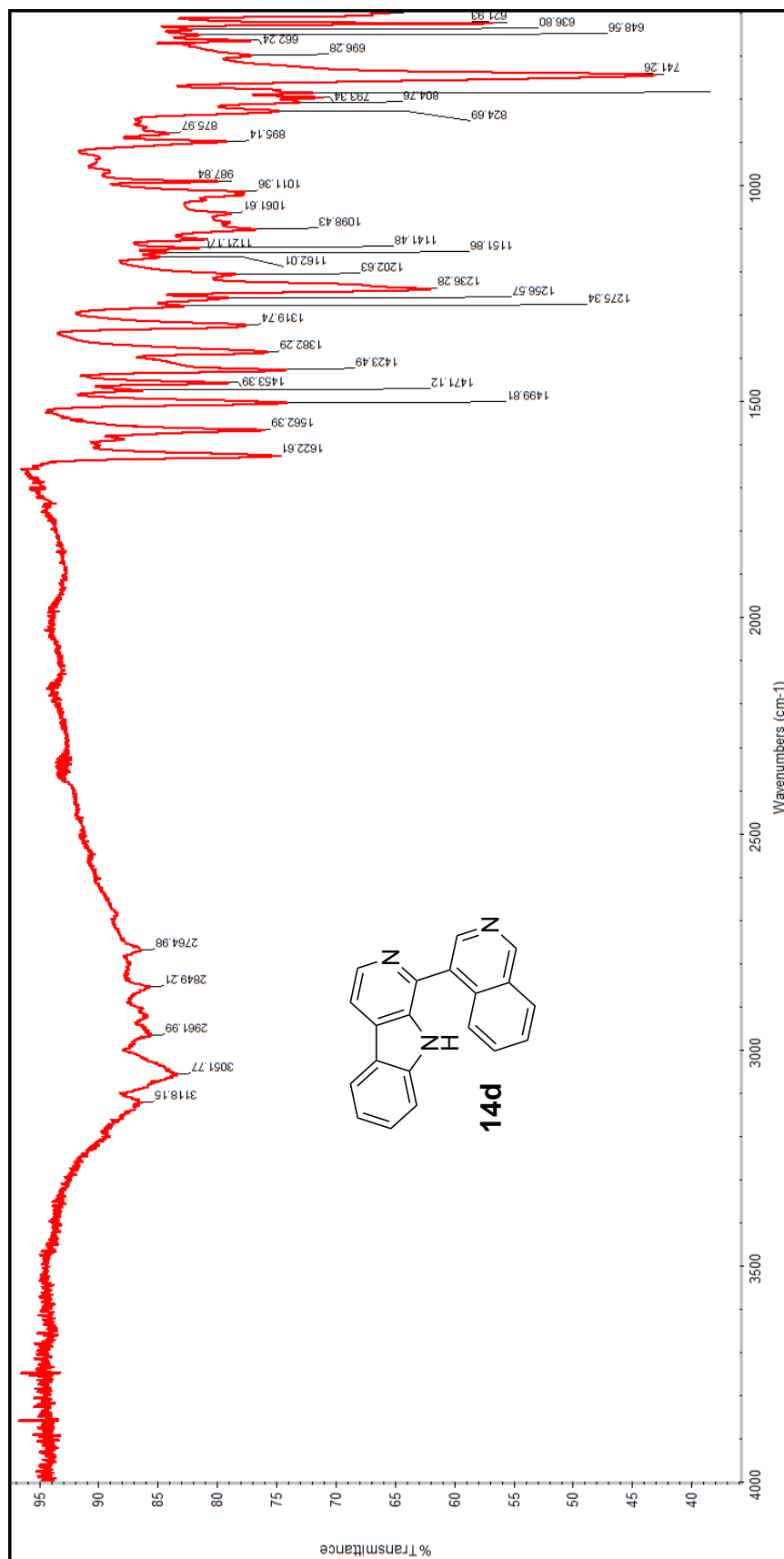


Figure S4.  $^1\text{H}$  NMR of **14e**:

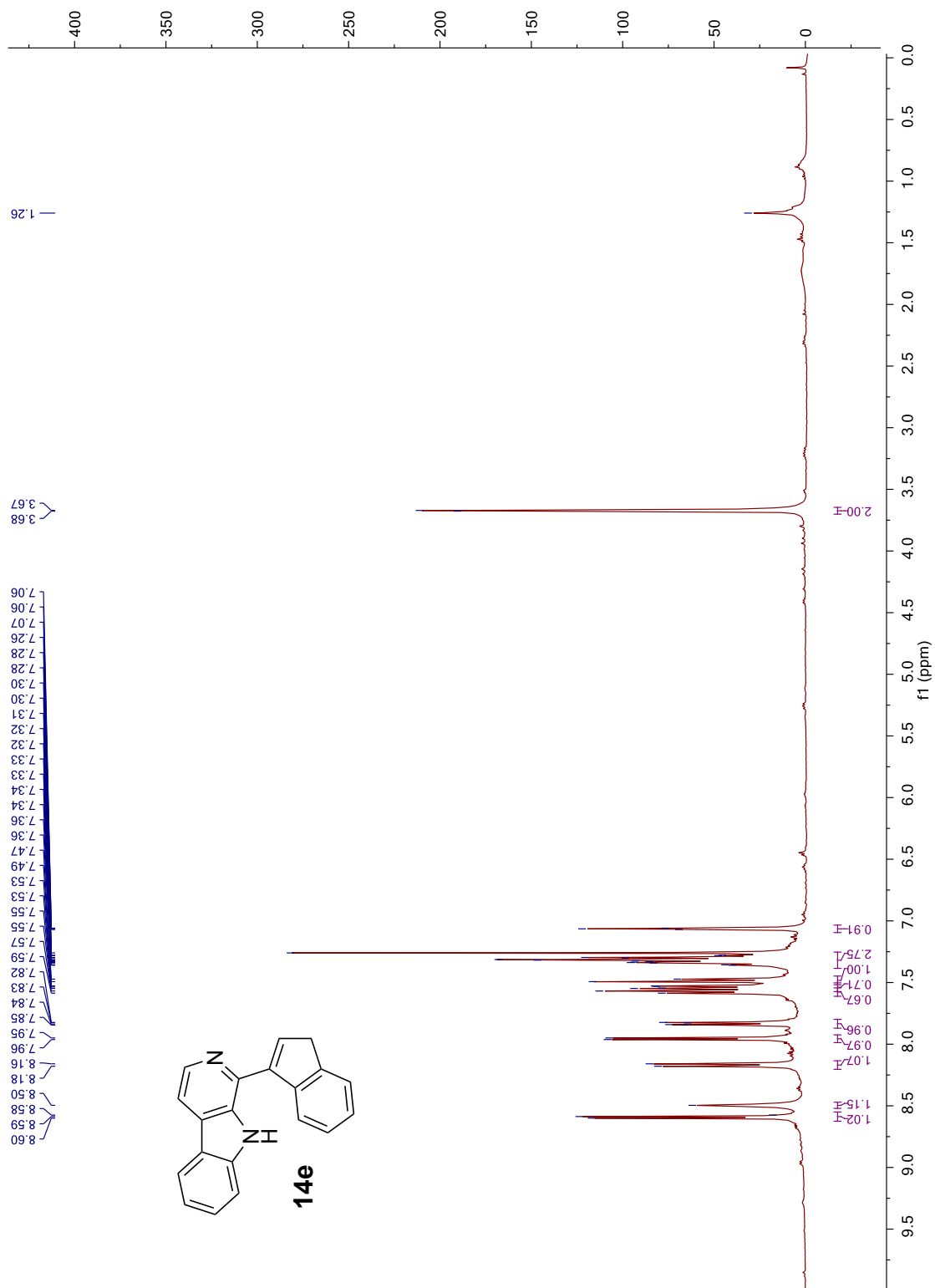


Figure S5.  $^{13}\text{C}$  NMR of **14e**:

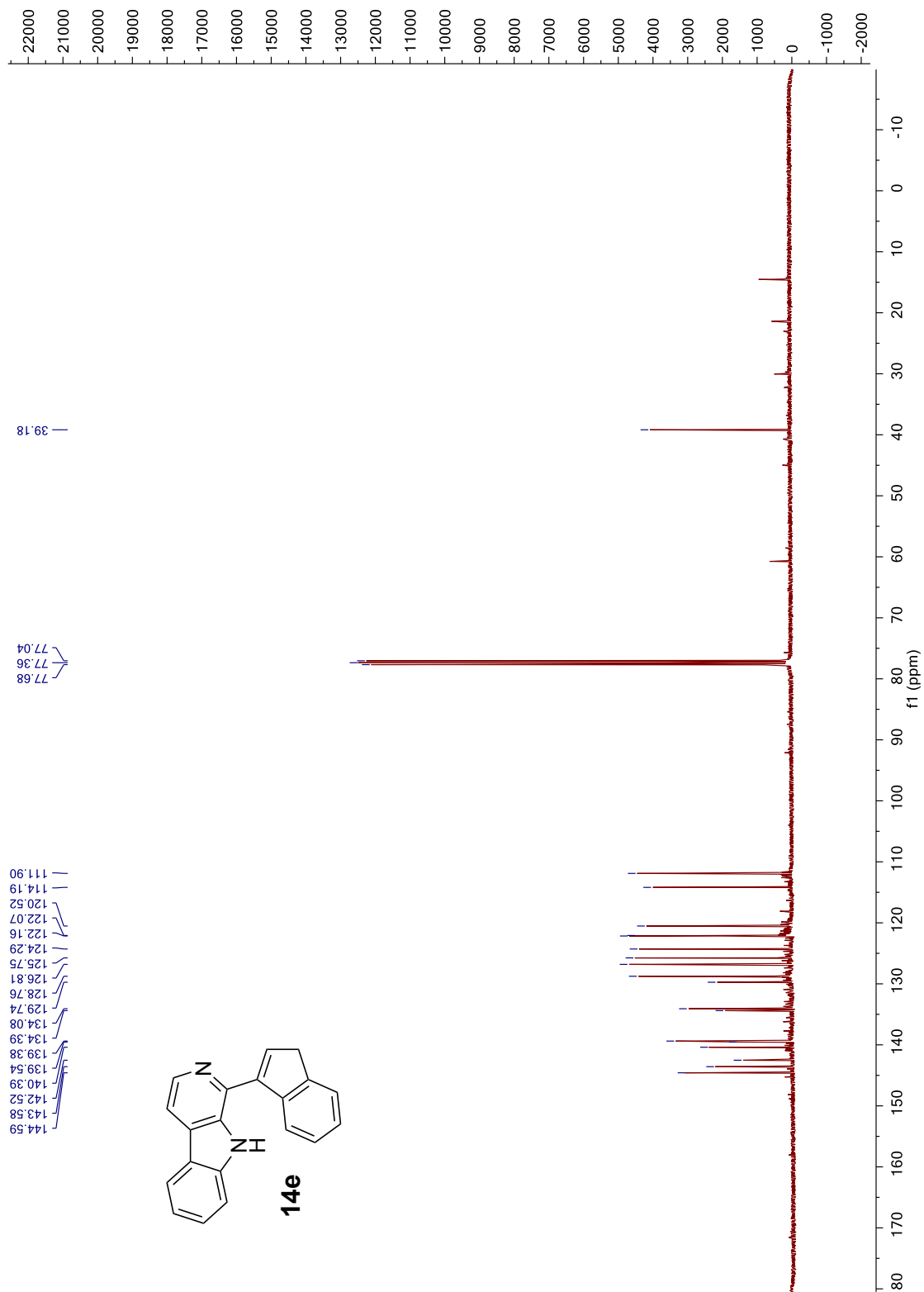


Figure S6. IR of **14e**:

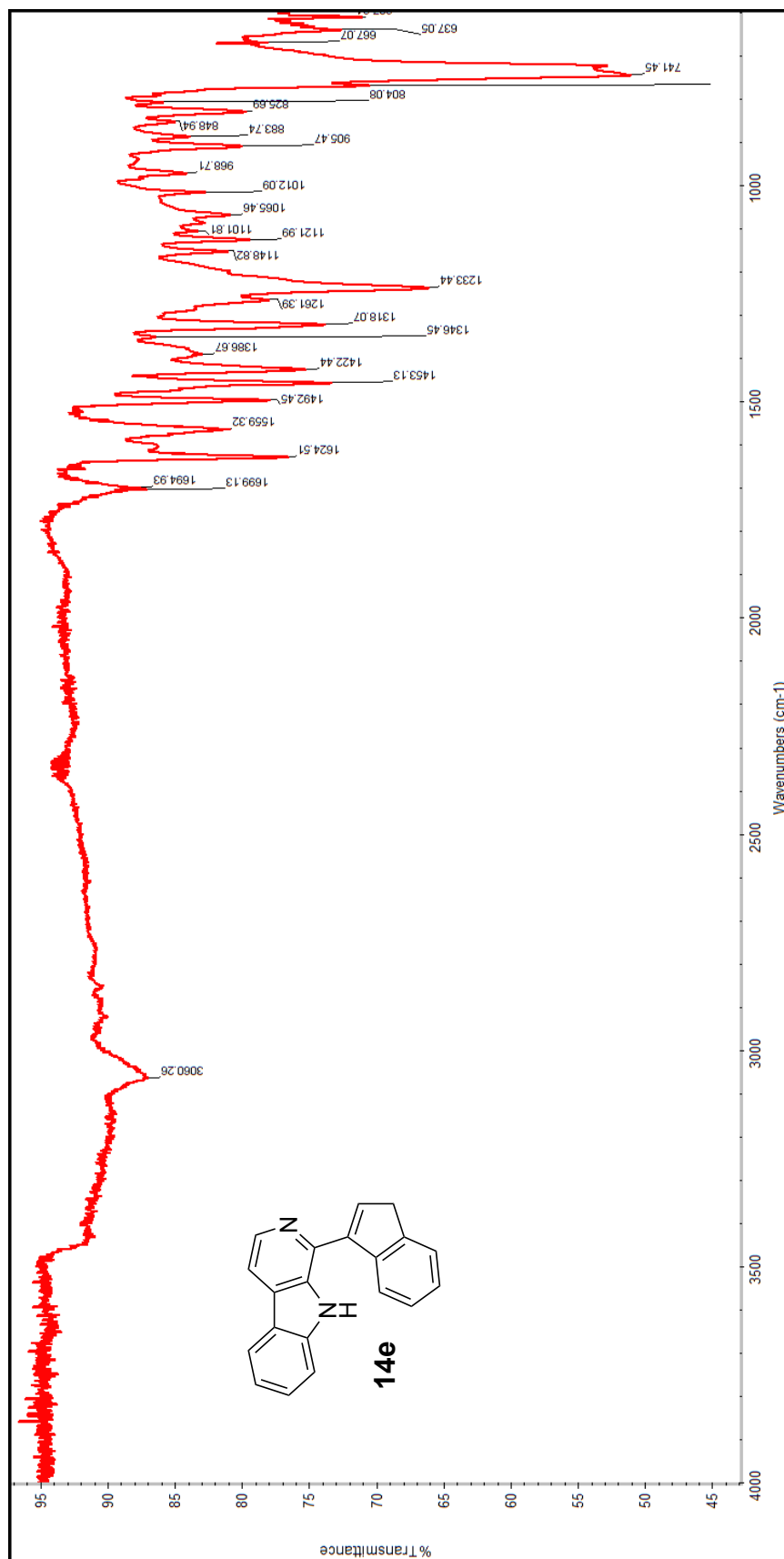




Figure S8.  $^{13}\text{C}$  NMR of **14f**:

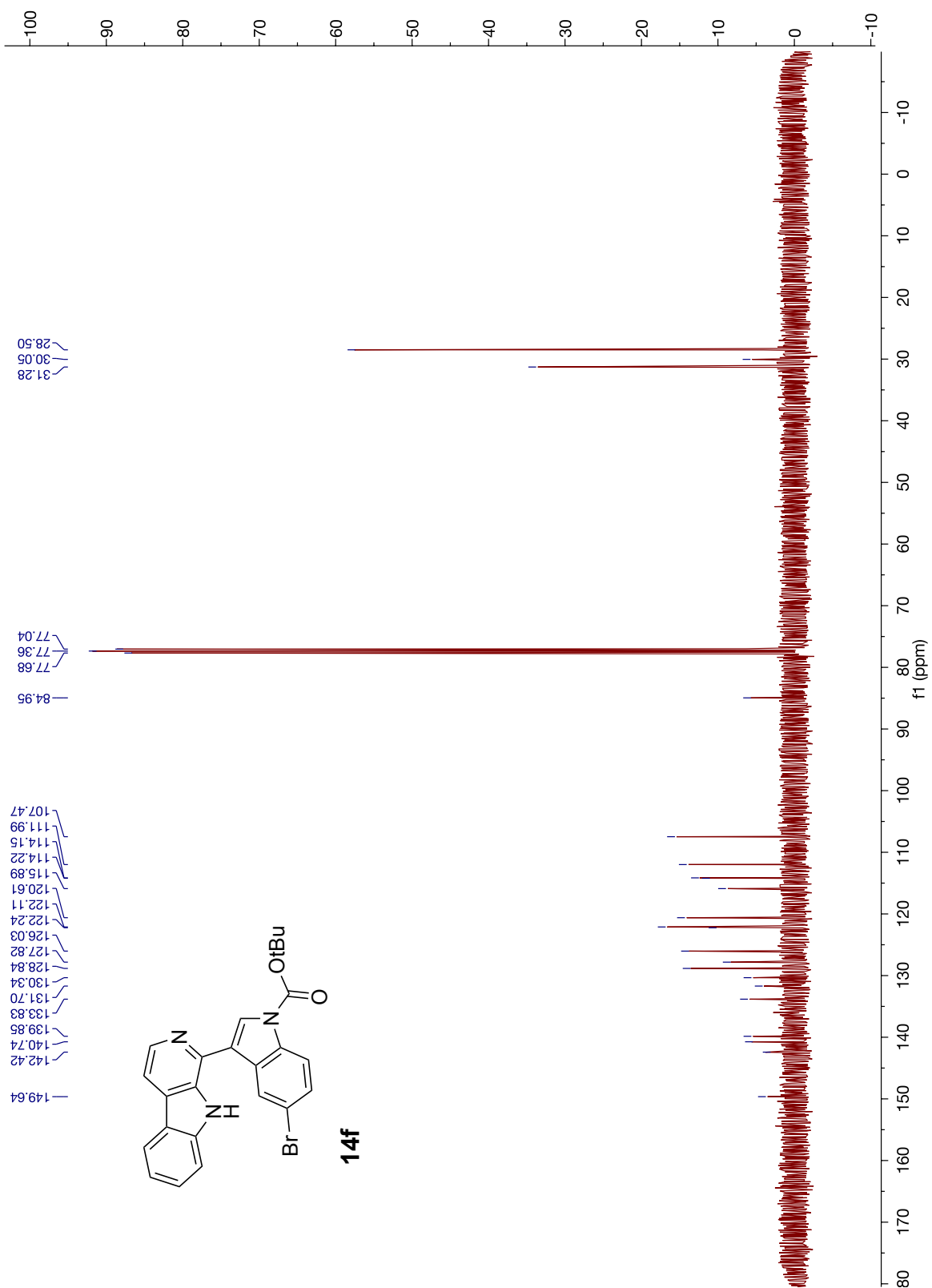


Figure S9. IR of **14f**:

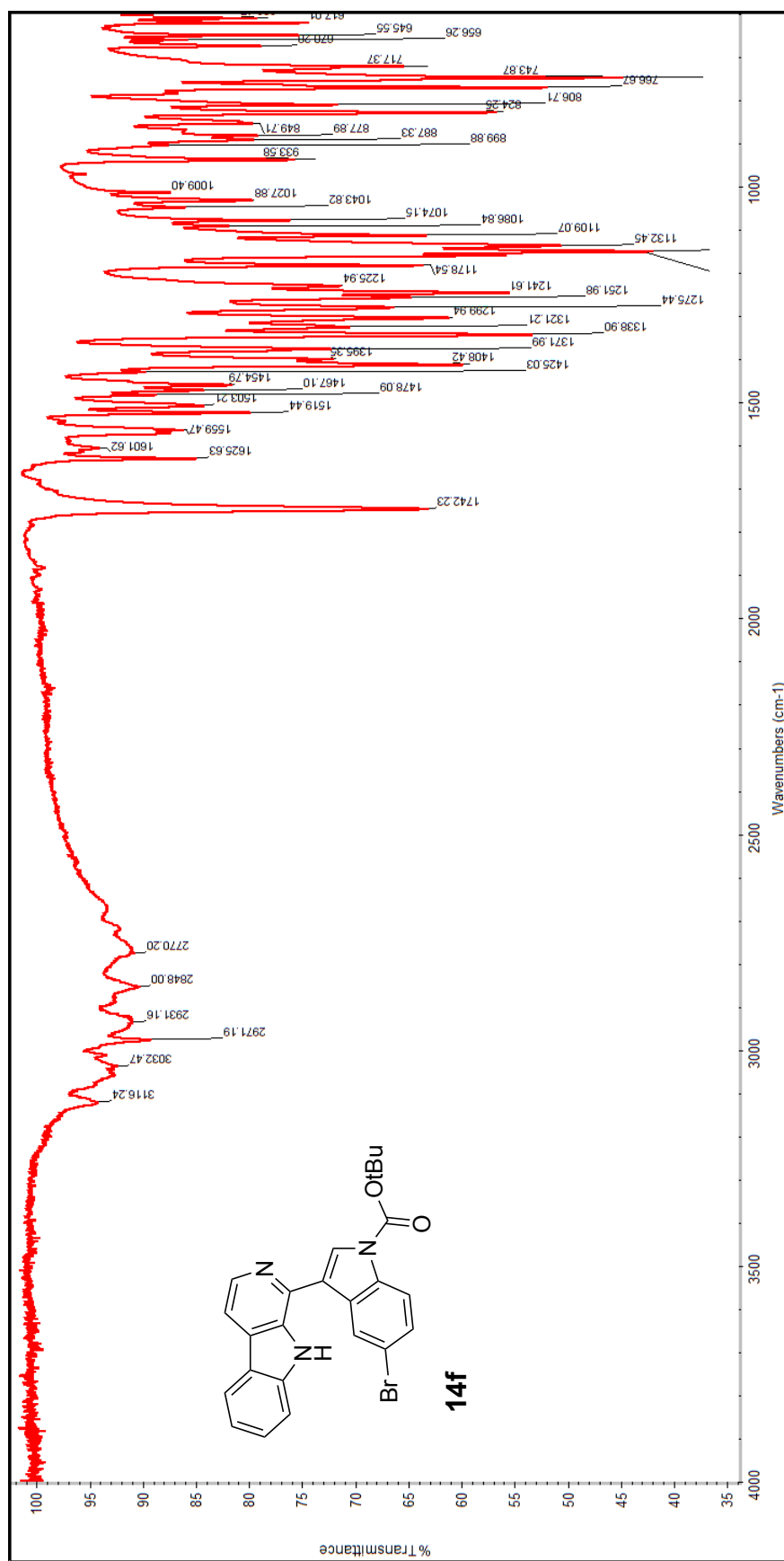


Figure S10.  $^1\text{H}$  NMR of **14g**:

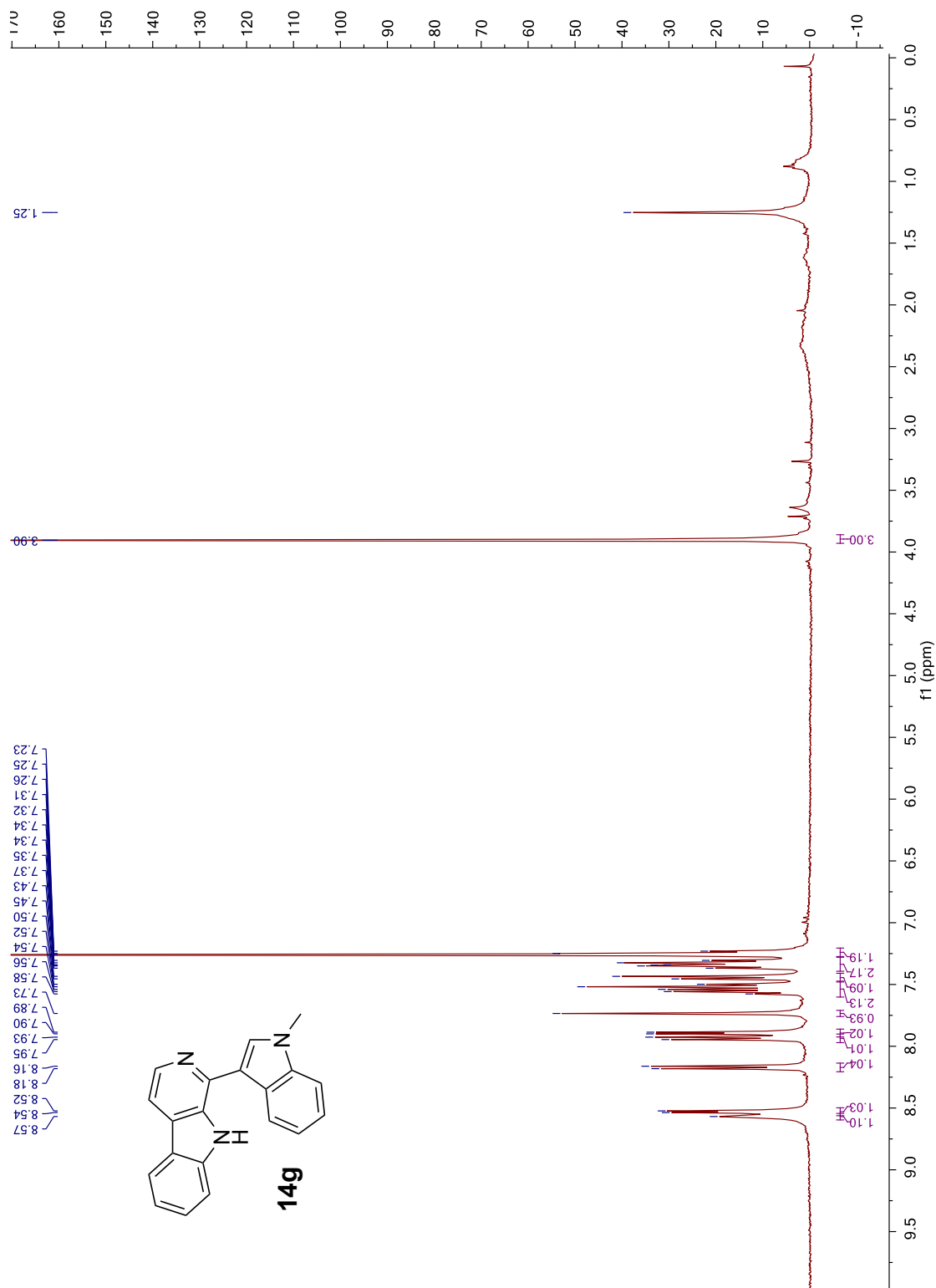


Figure S11.  $^{13}\text{C}$  NMR of **14g**:

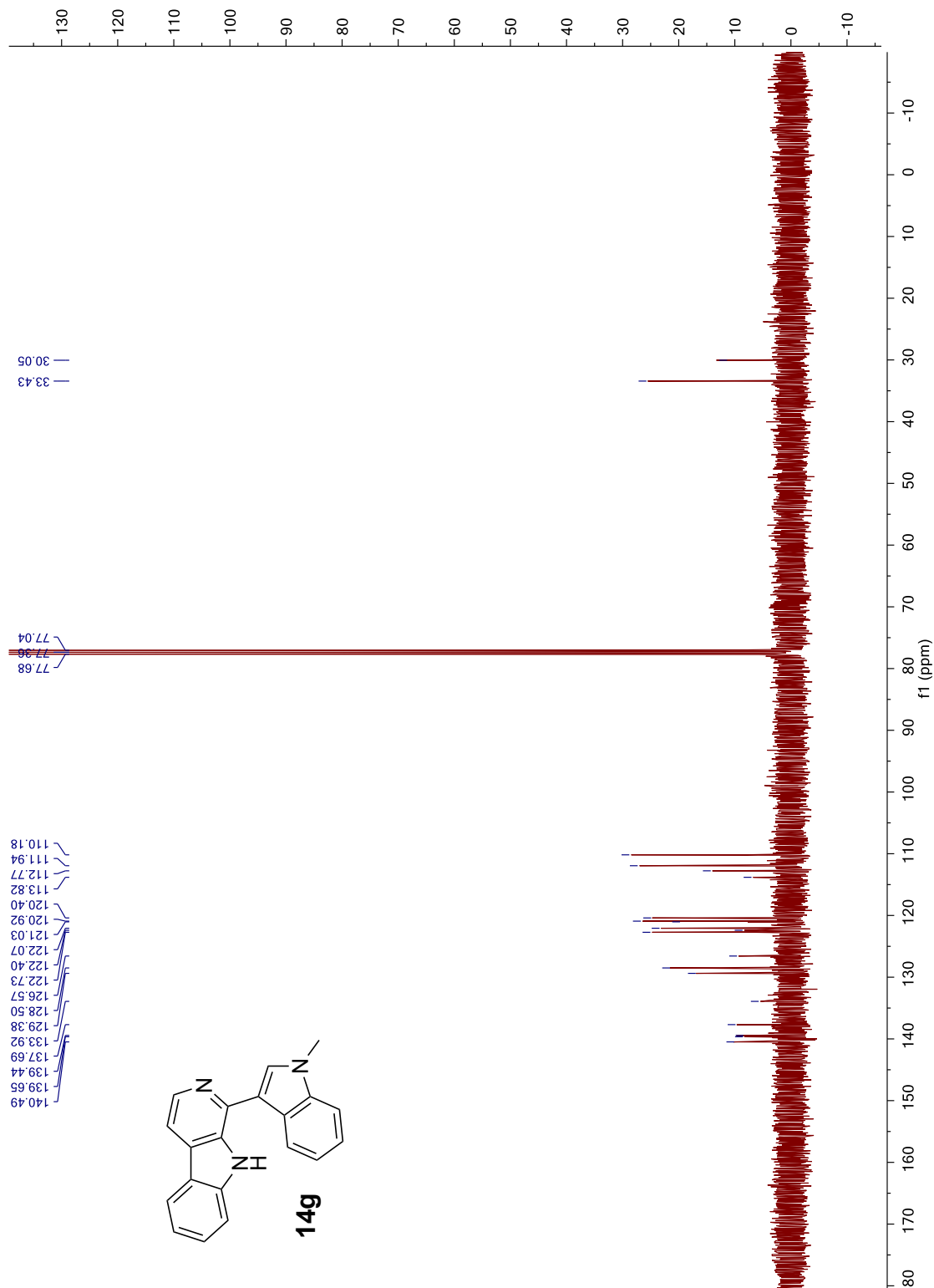


Figure S12. IR of **14g**:

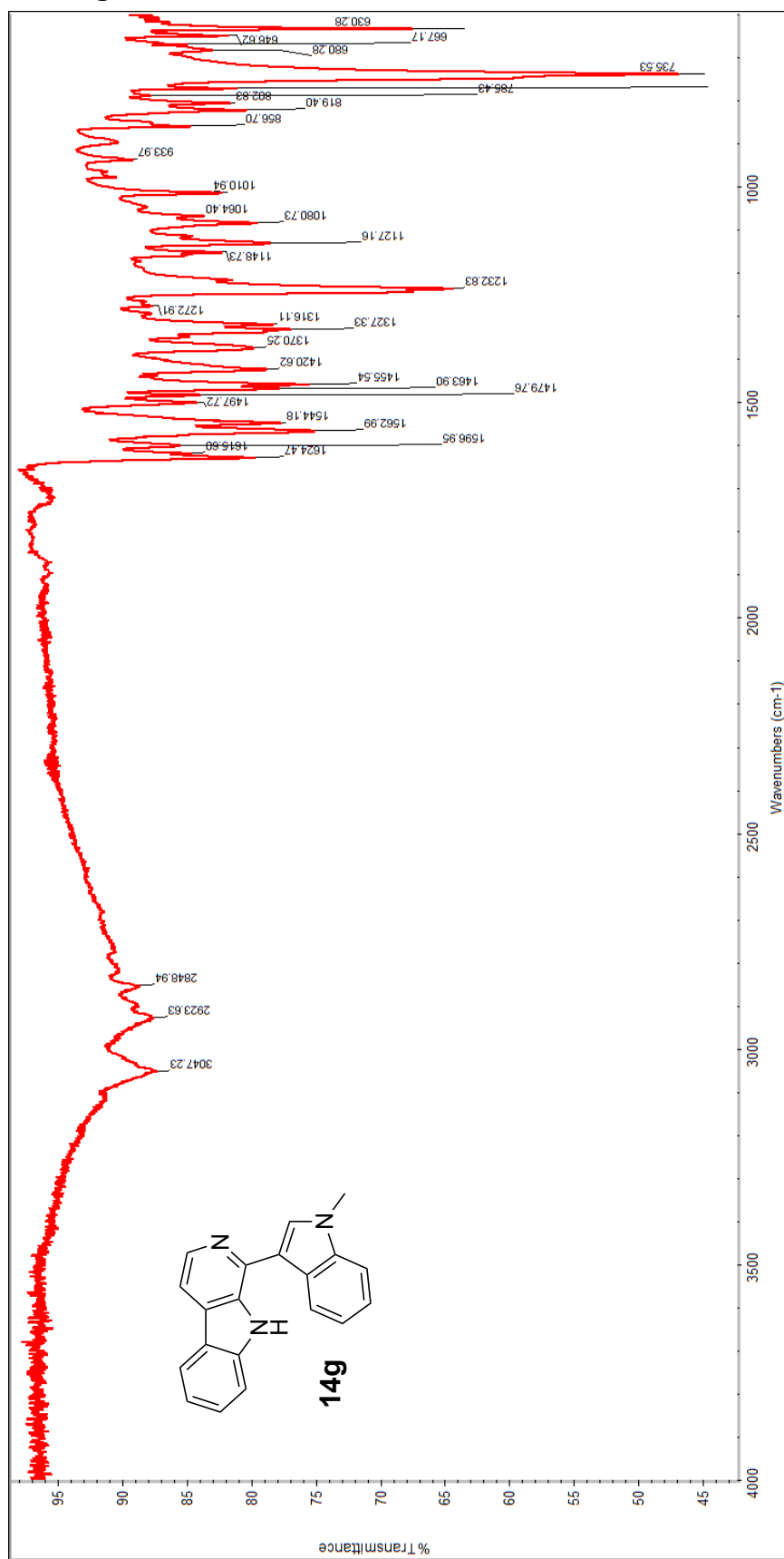


Figure S13.  $^1\text{H}$  NMR of **14h**:

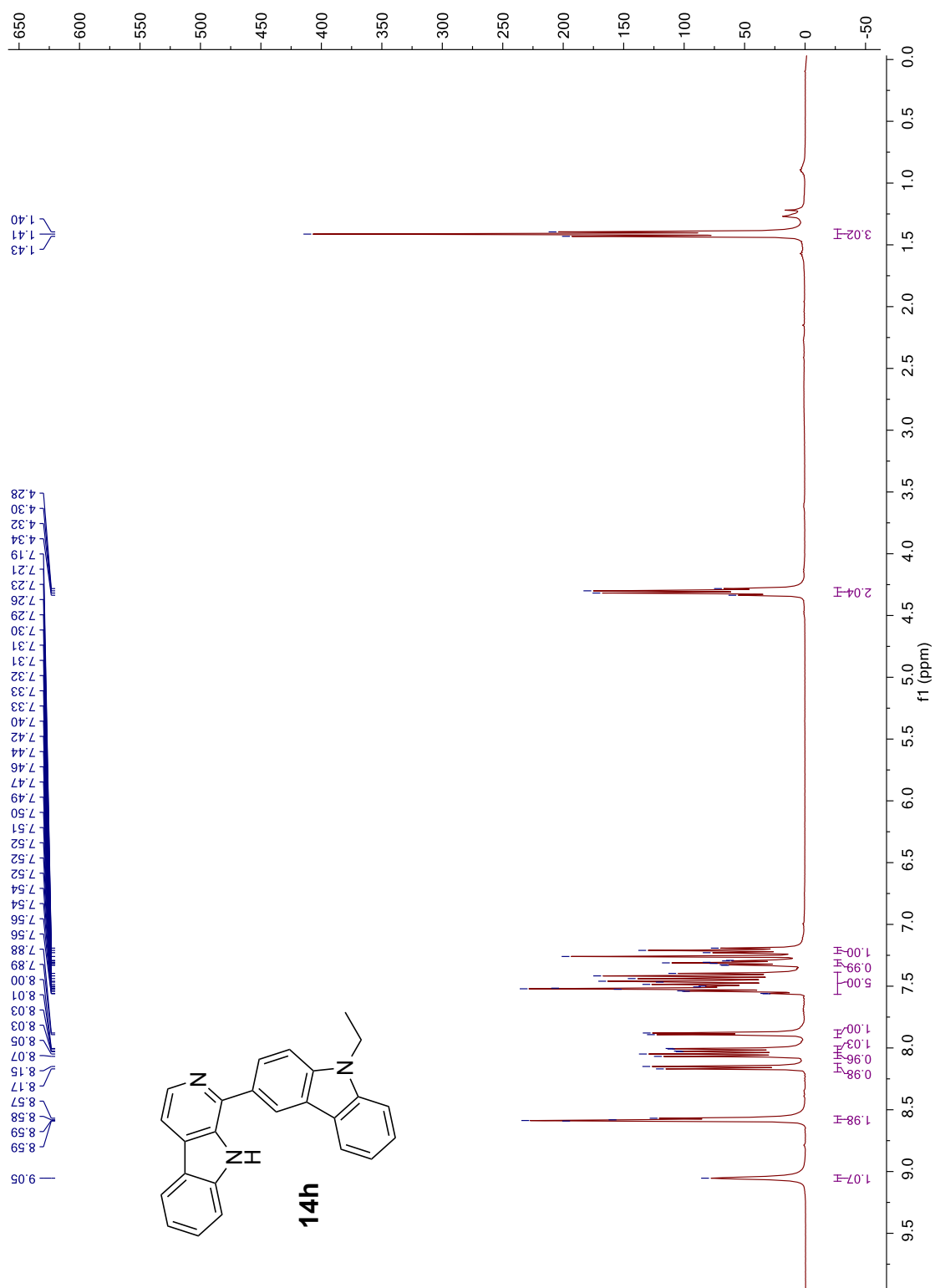


Figure S14.  $^{13}\text{C}$  NMR of **14h**:

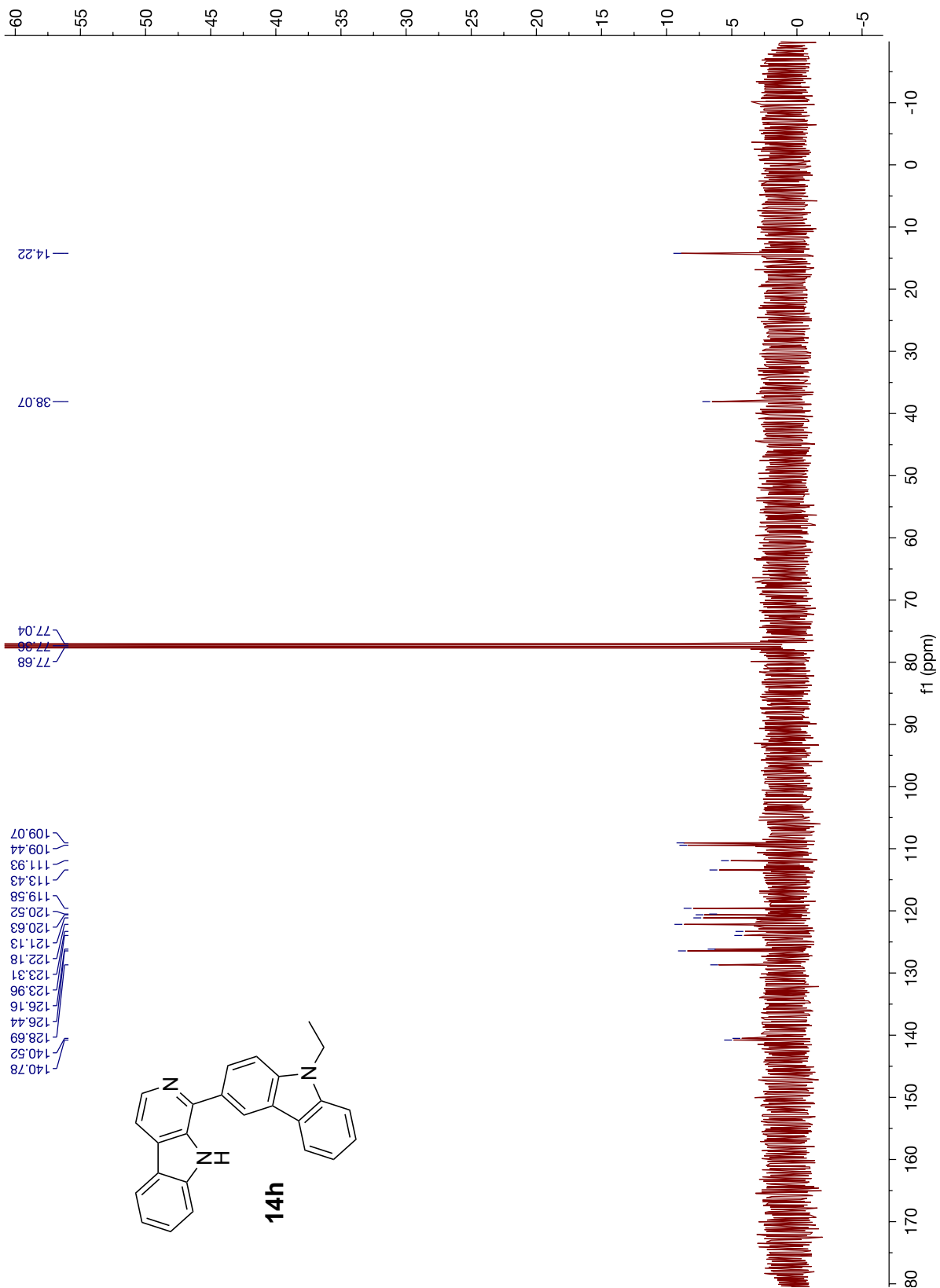


Figure S15. IR of **14h**:

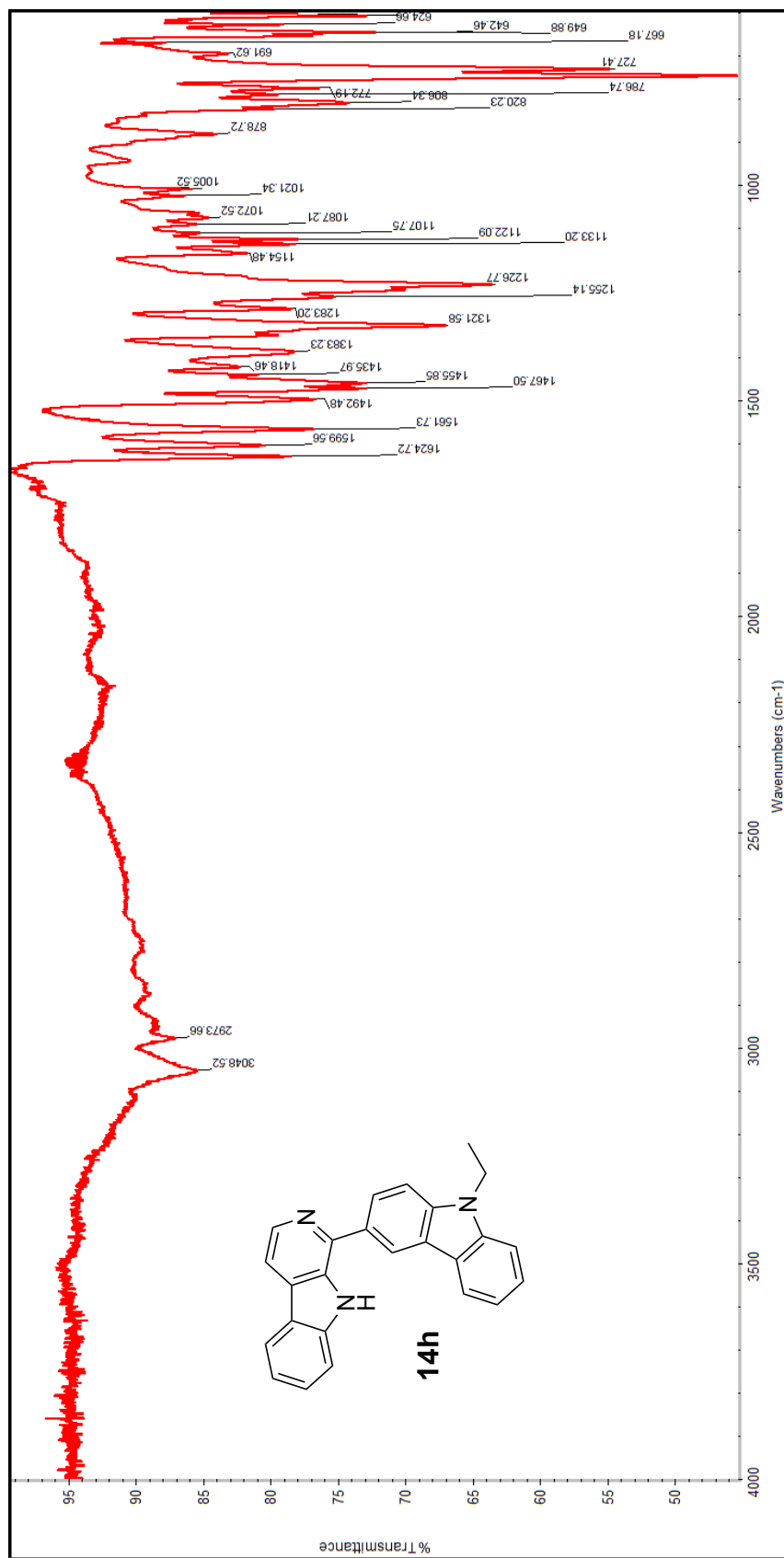


Figure S16.  $^1\text{H}$  NMR of **14i**:

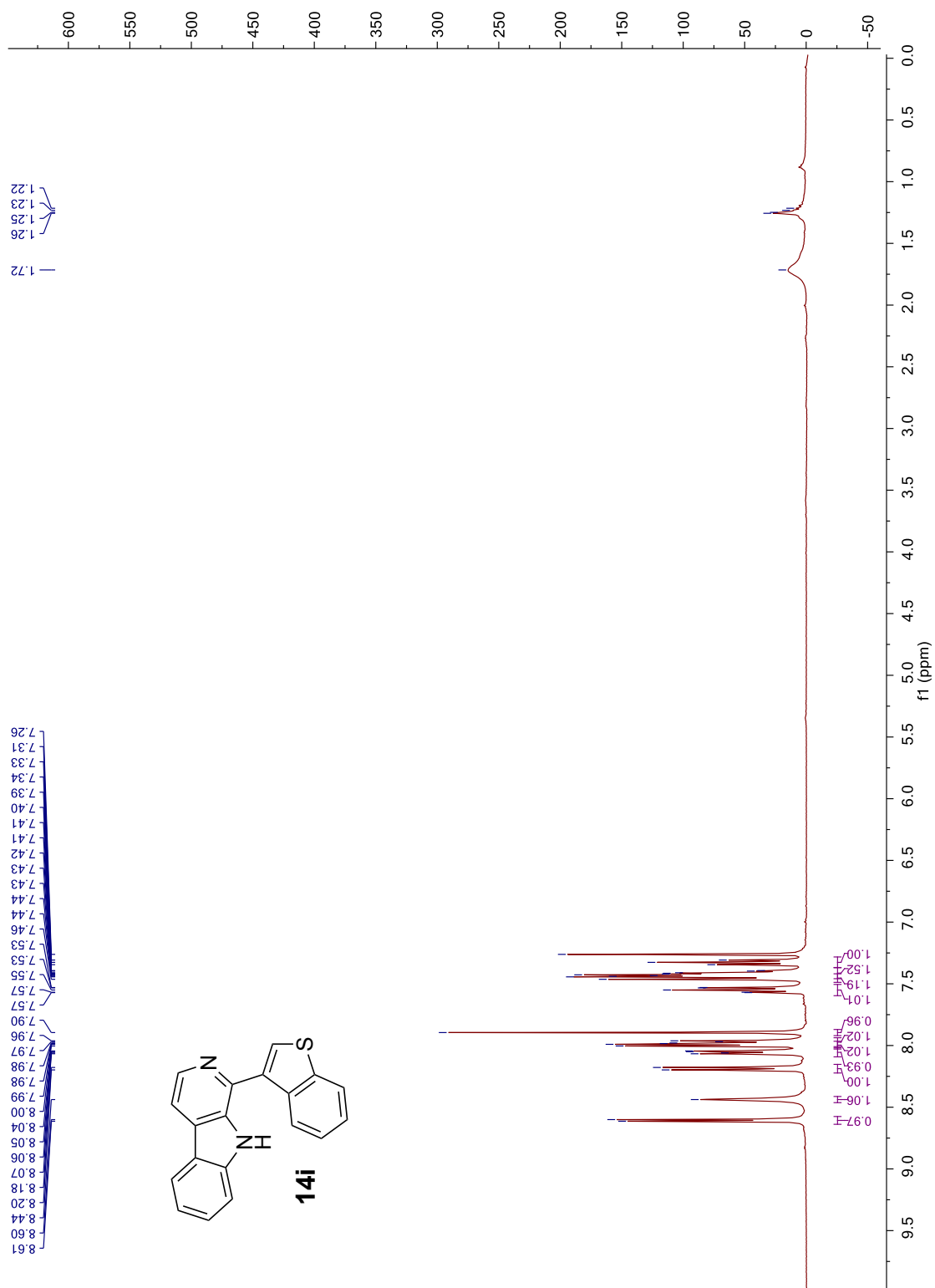


Figure S17.  $^{13}\text{C}$  NMR of **14i**:

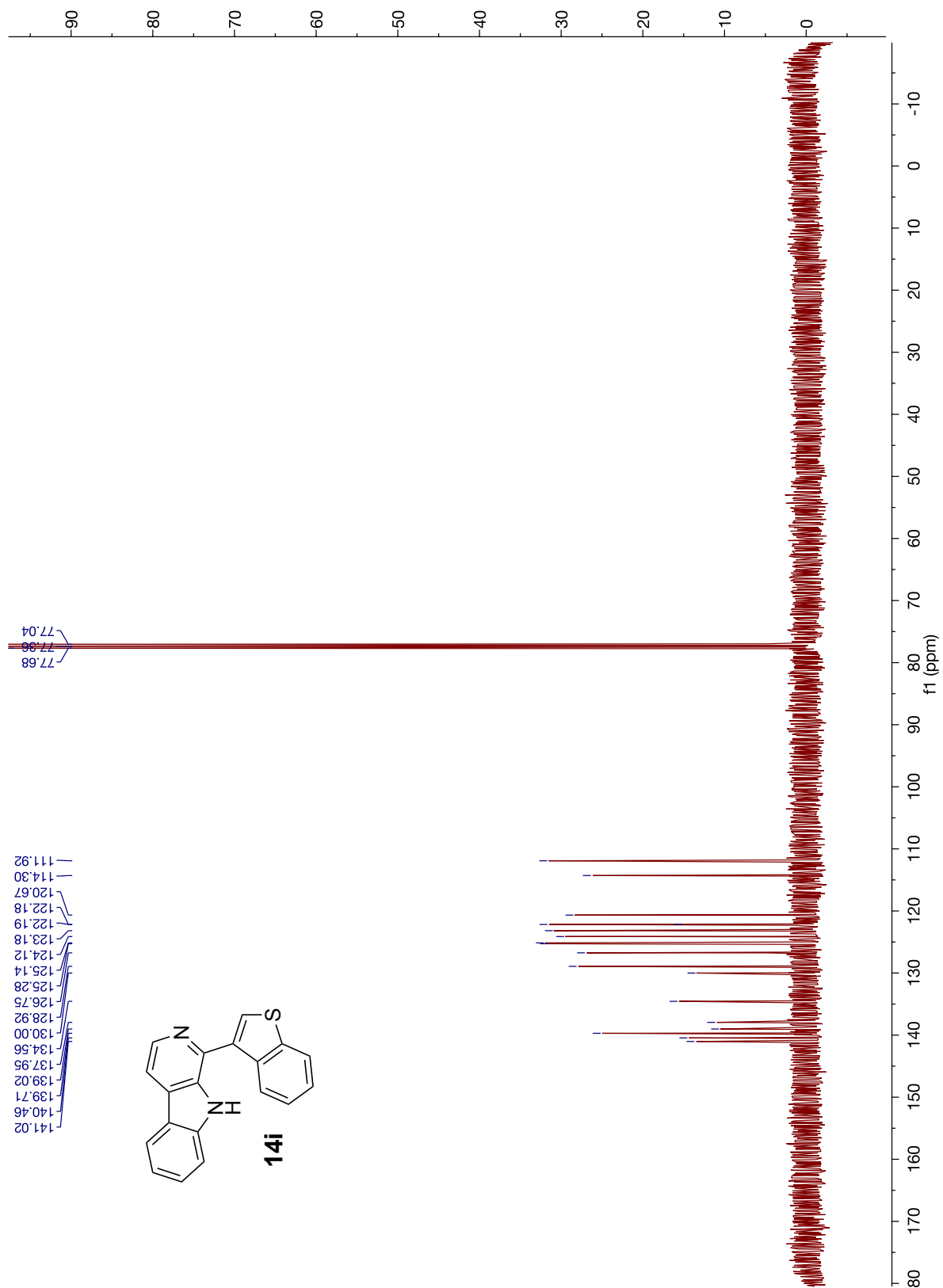


Figure S18. IR of **14i**:

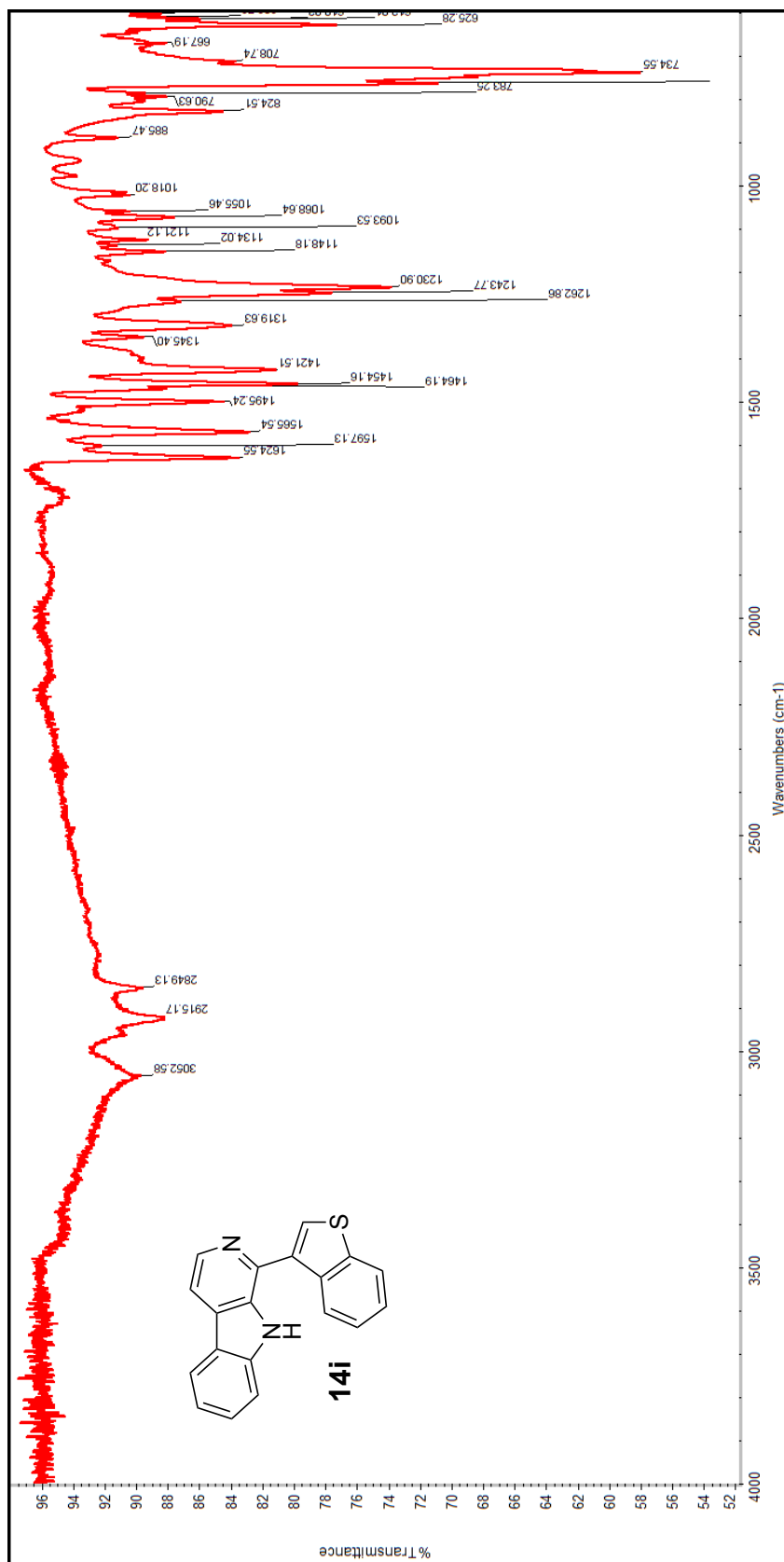


Figure S19.  $^1\text{H}$  NMR of **14j**:

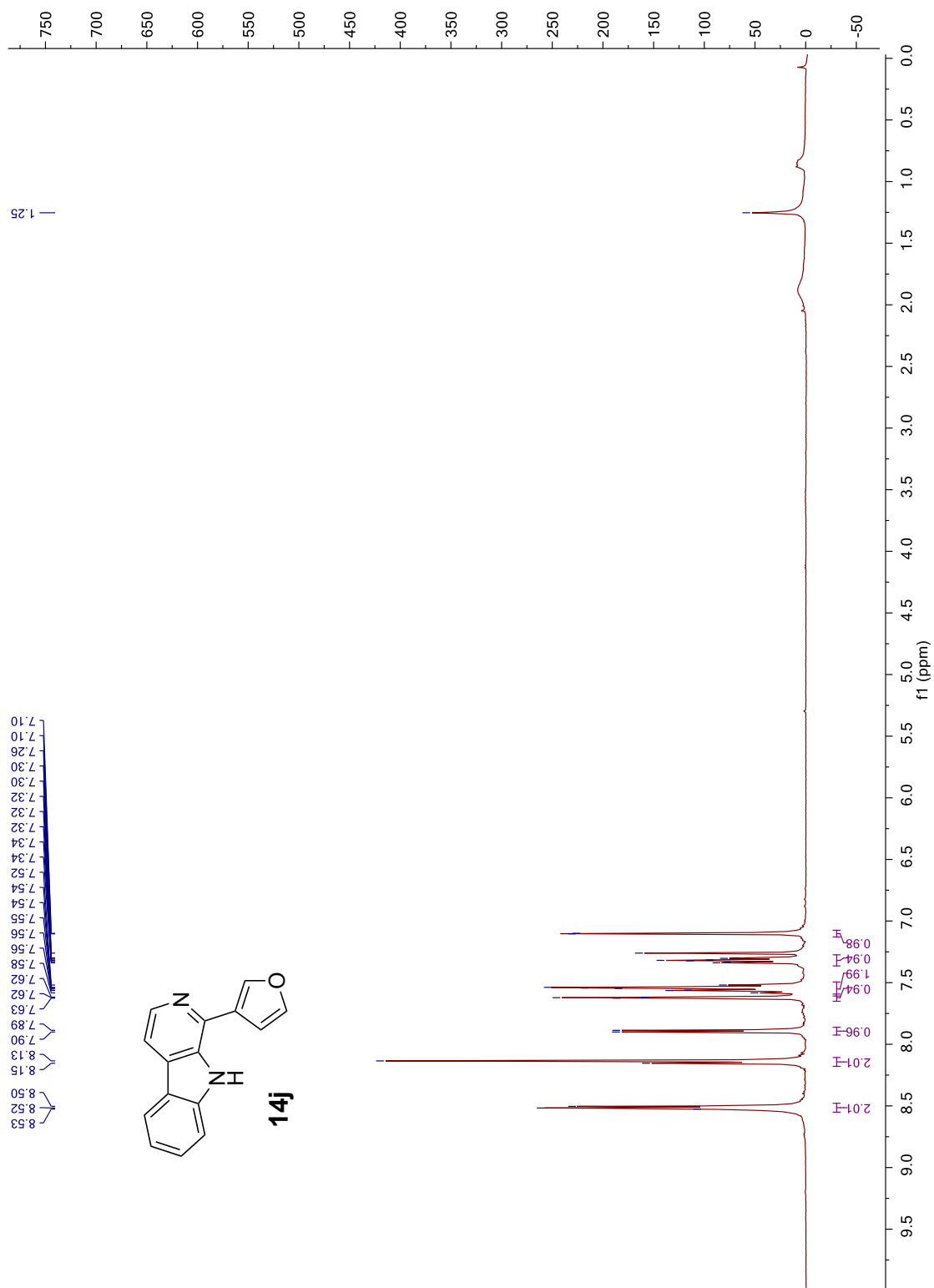


Figure S20.  $^{13}\text{C}$  NMR of **14j**:

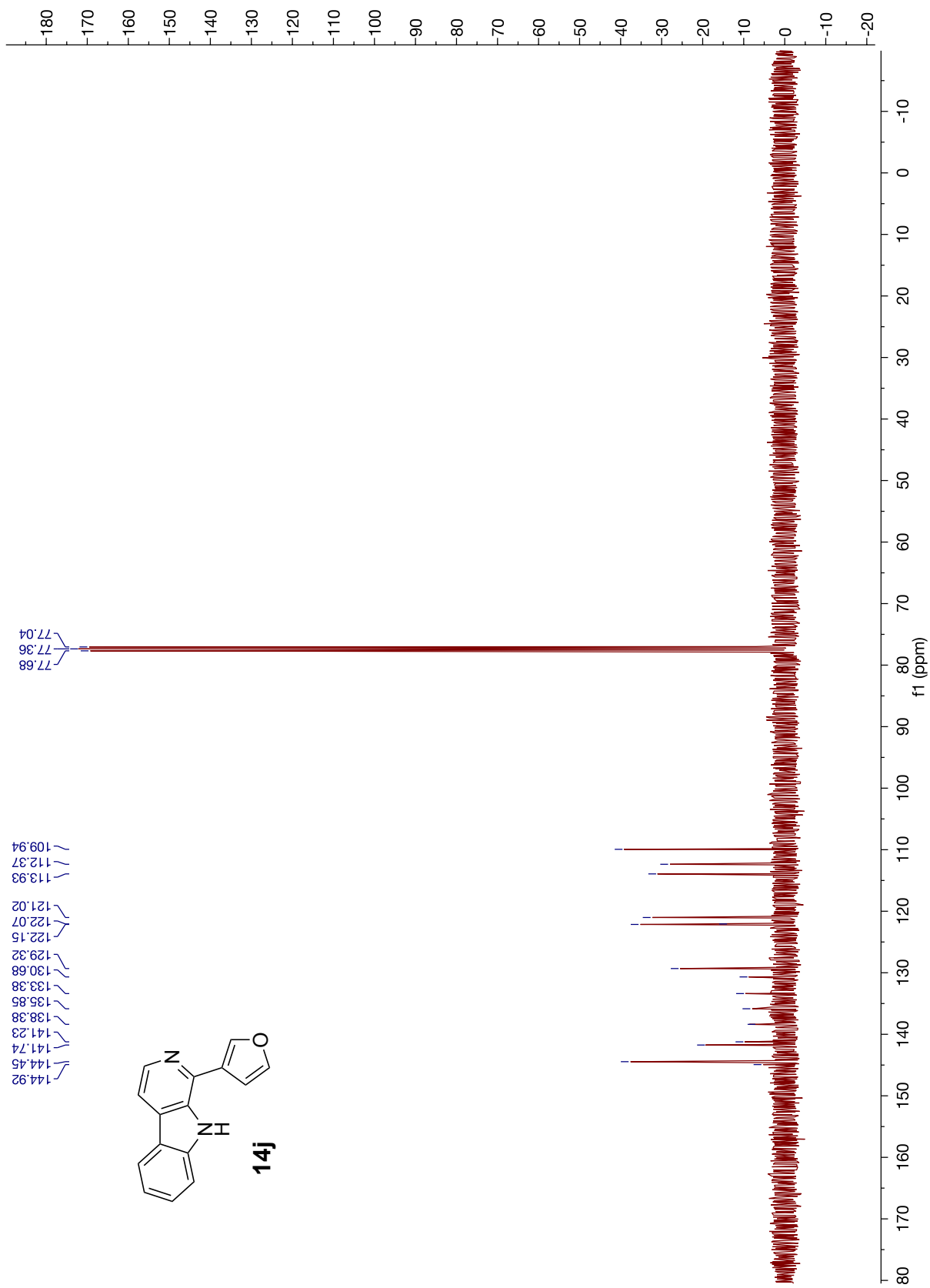


Figure S21. IR of 14j:

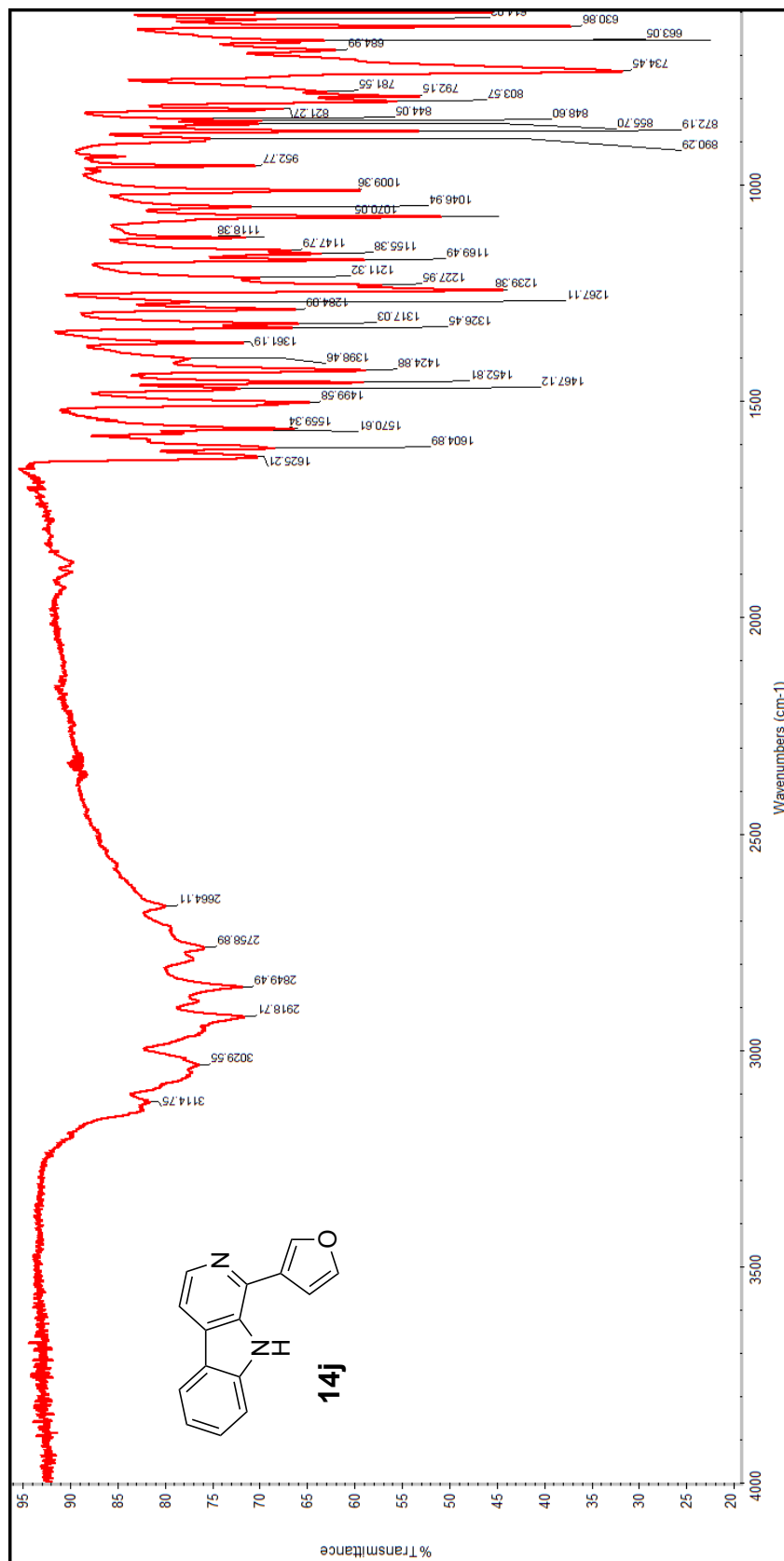


Figure S22.  $^1\text{H}$  NMR of **14k**:

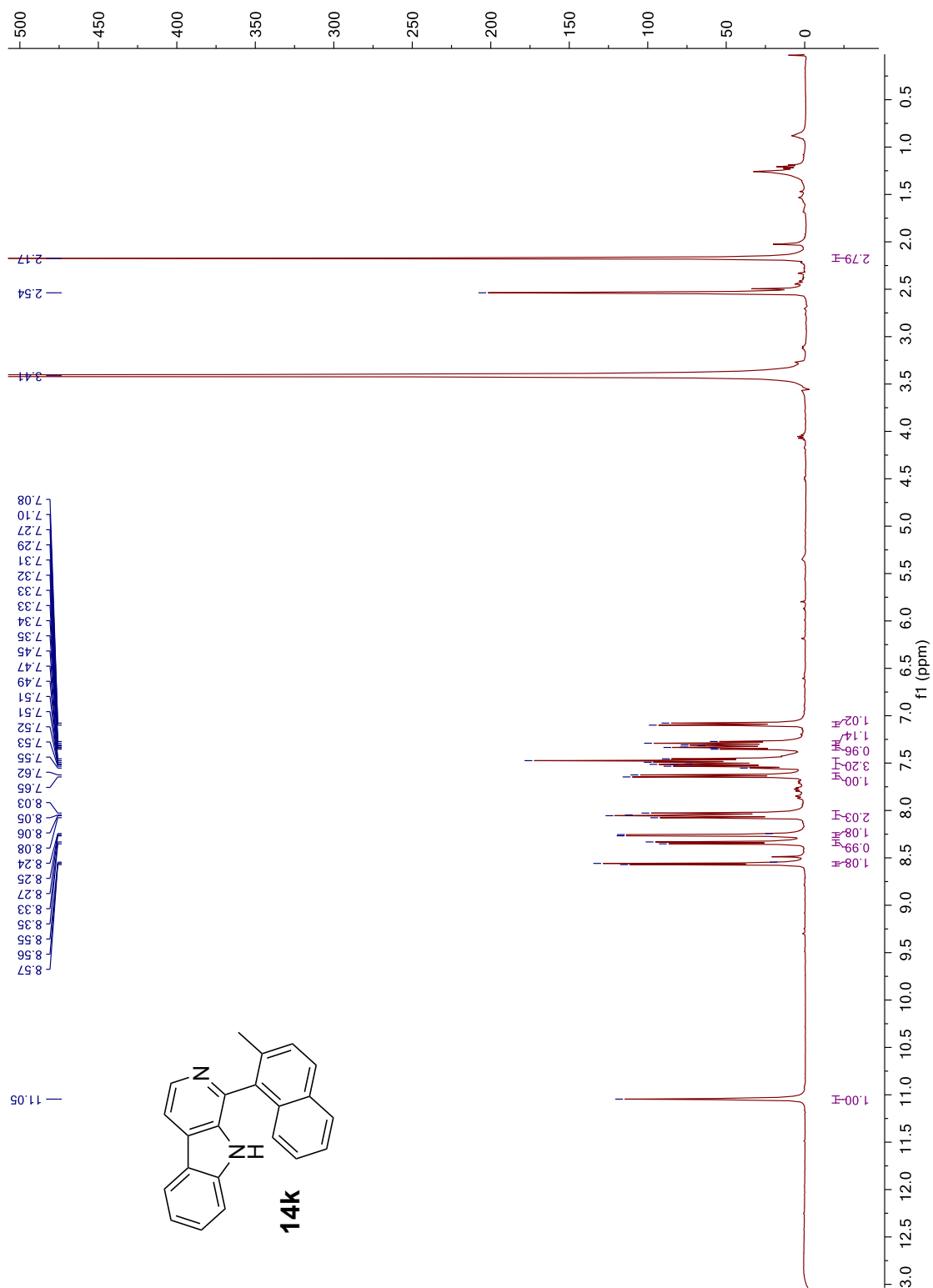


Figure S23.  $^{13}\text{C}$  NMR of **14k**:

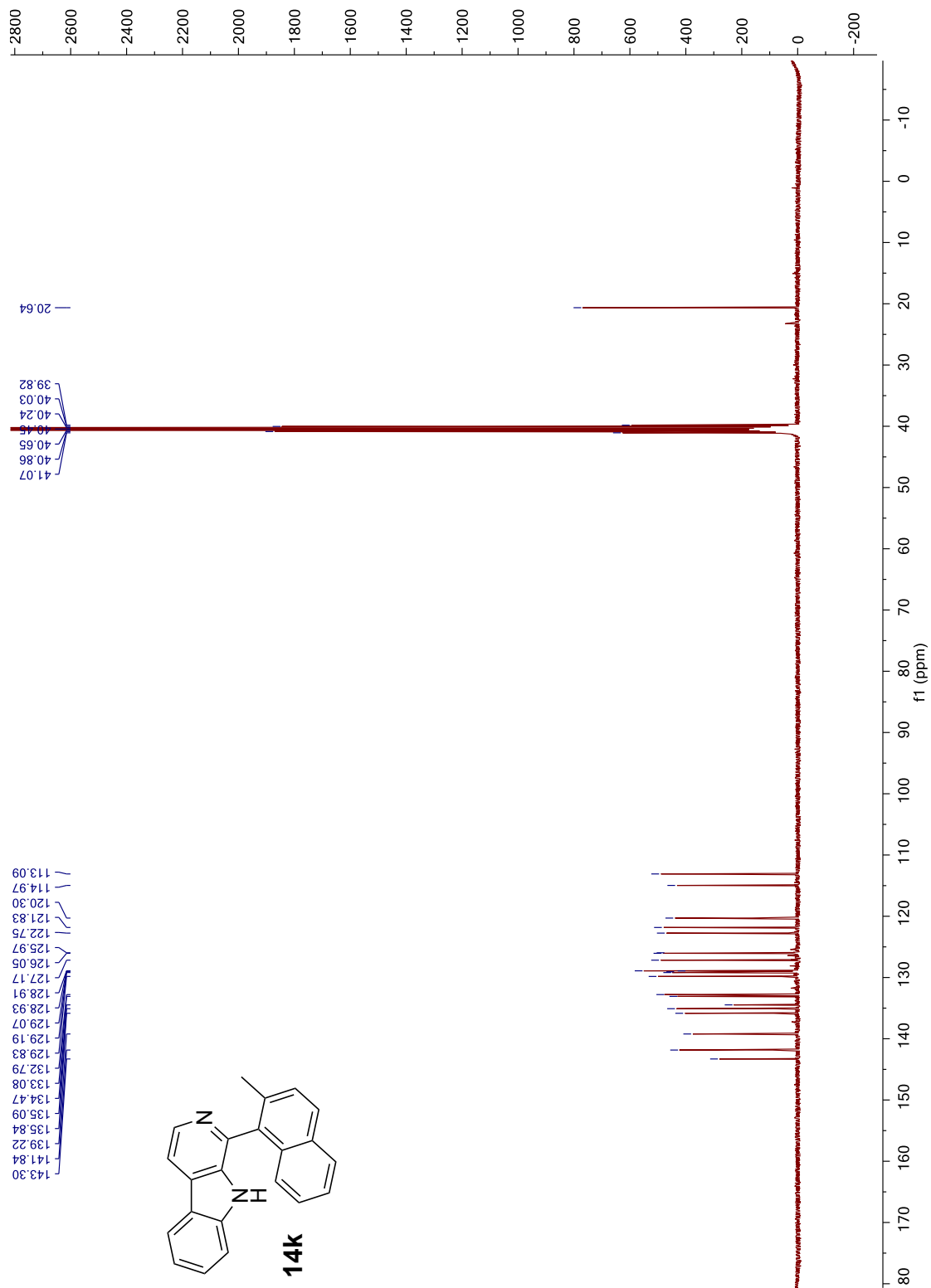


Figure S24. IR of **14k**:

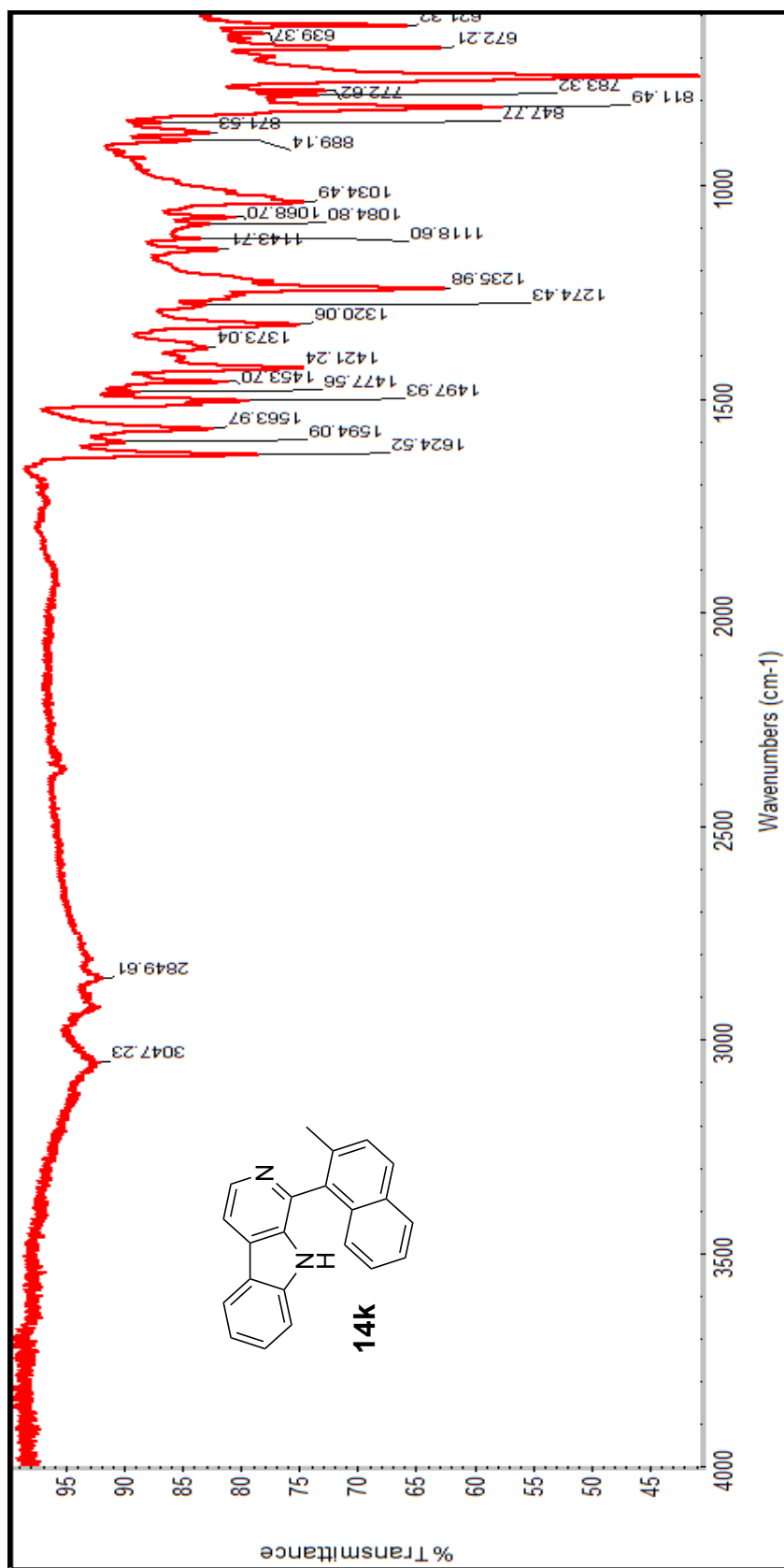


Figure S25.  $^1\text{H}$  NMR of **15a**:

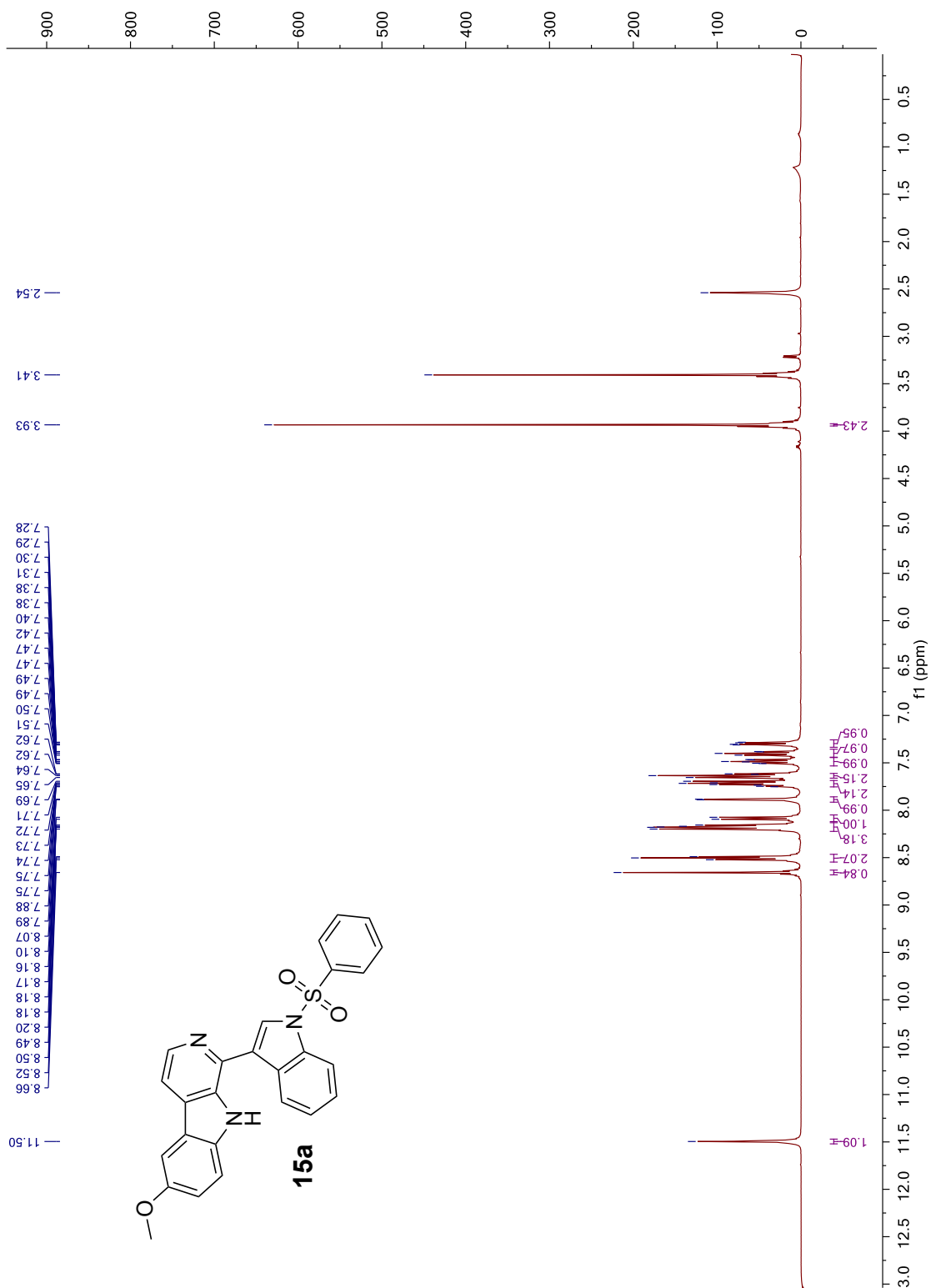


Figure S26.  $^{13}\text{C}$  NMR of **15a**:

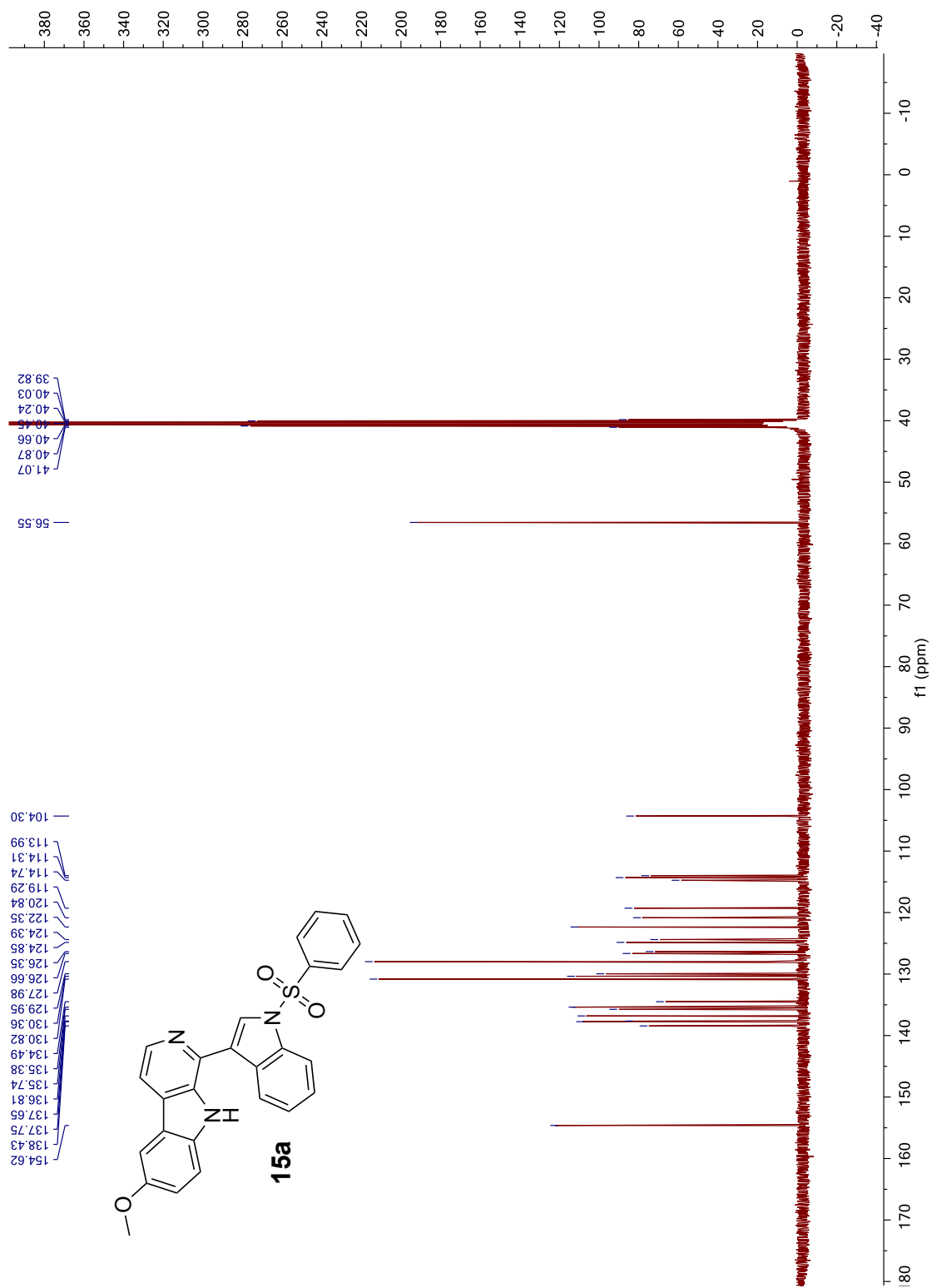


Figure S27. IR of **15a**:

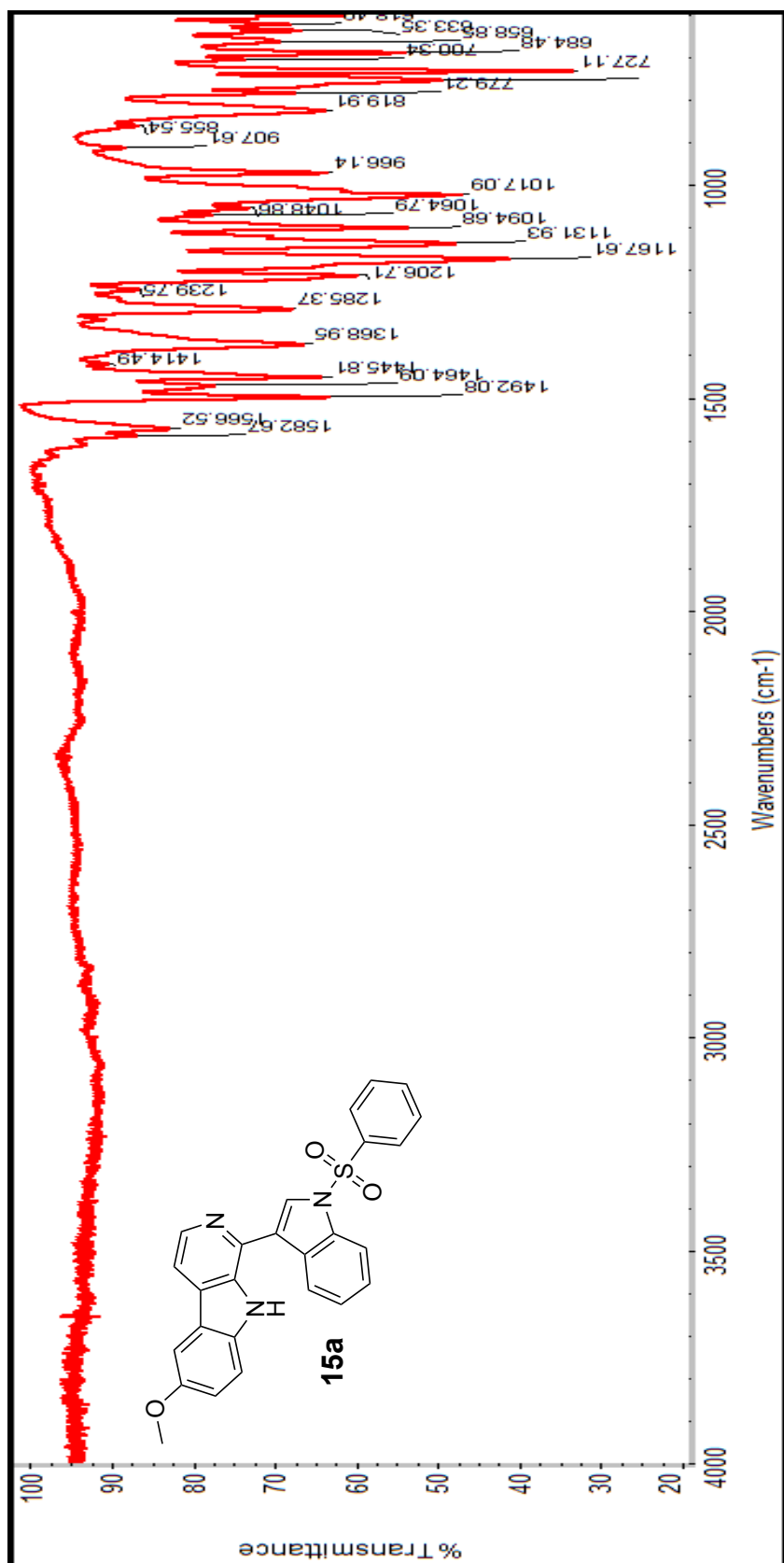




Figure S29.  $^{13}\text{C}$  NMR of **15b**:

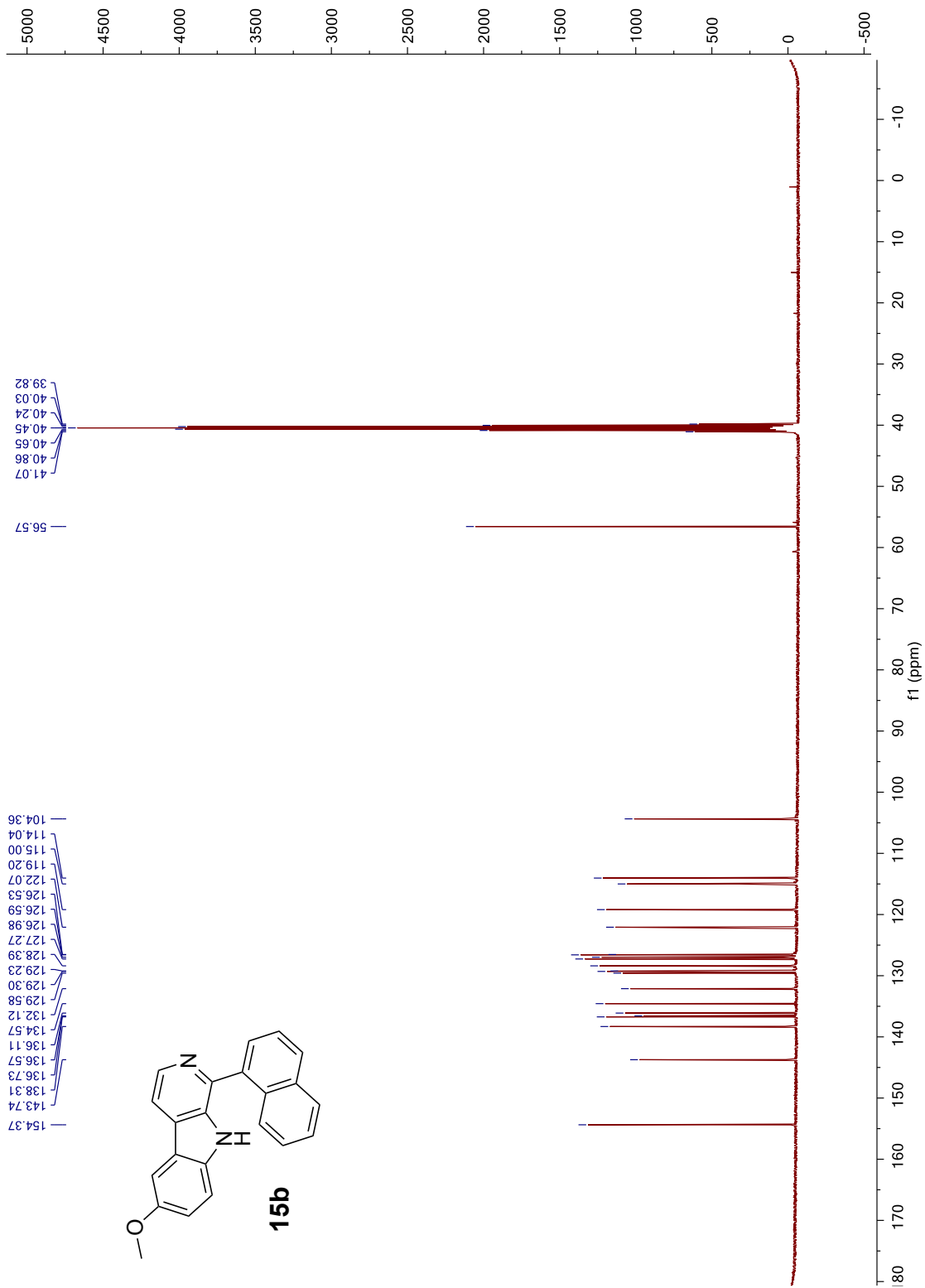


Figure S30. IR of **15b**:

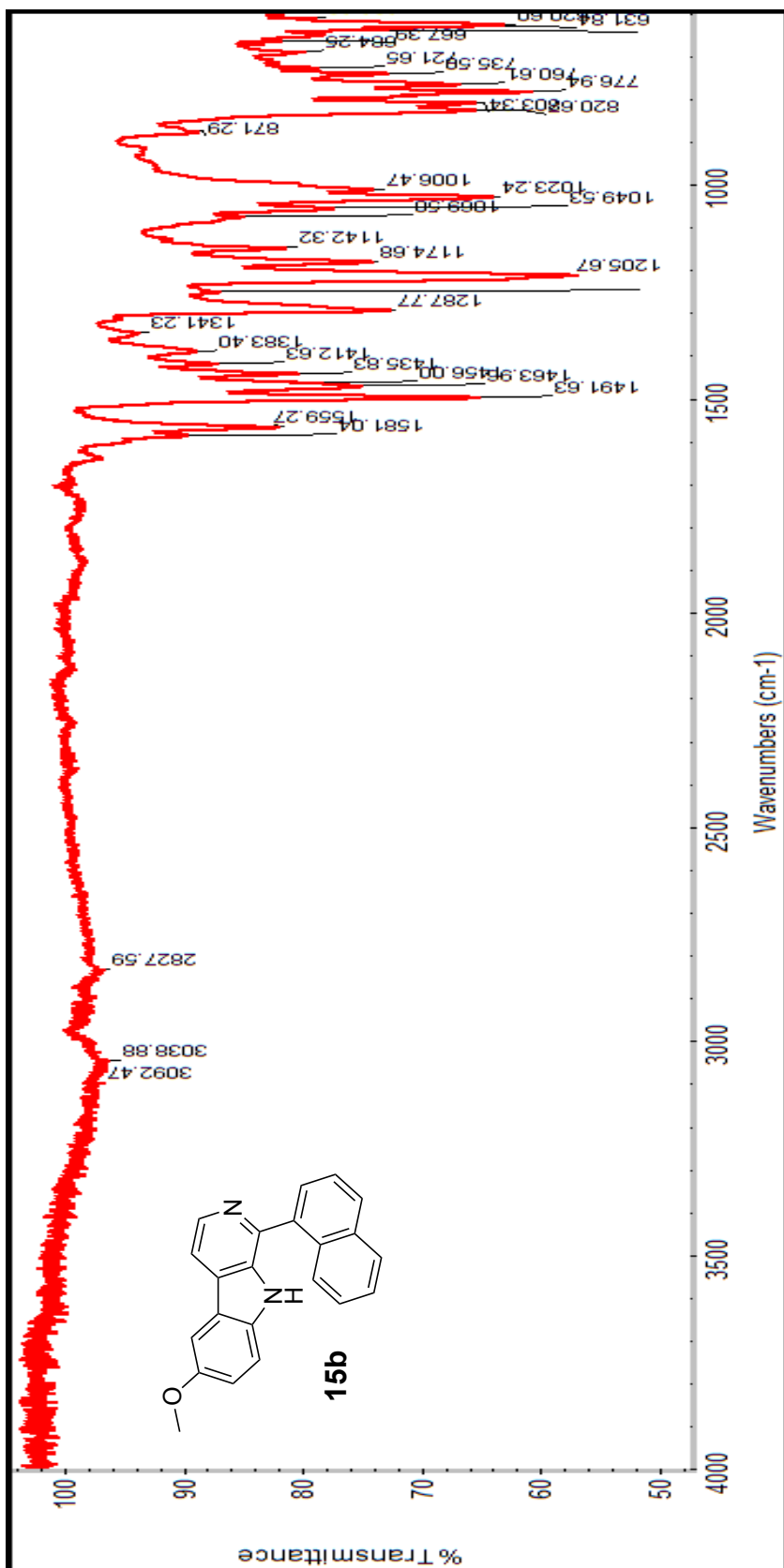


Figure S31.  $^1\text{H}$  NMR of **15c**:

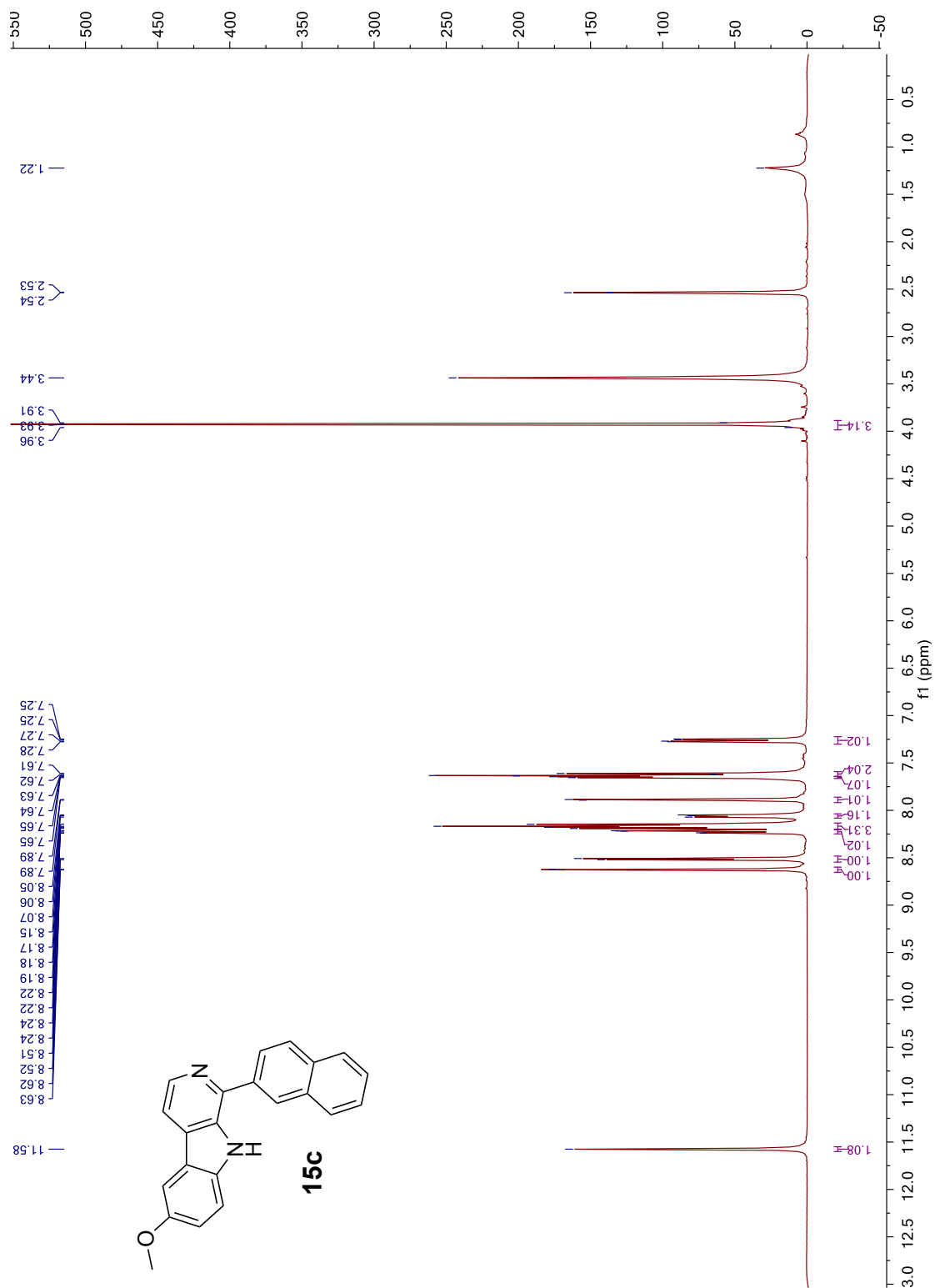


Figure S32.  $^{13}\text{C}$  NMR of **15c**:

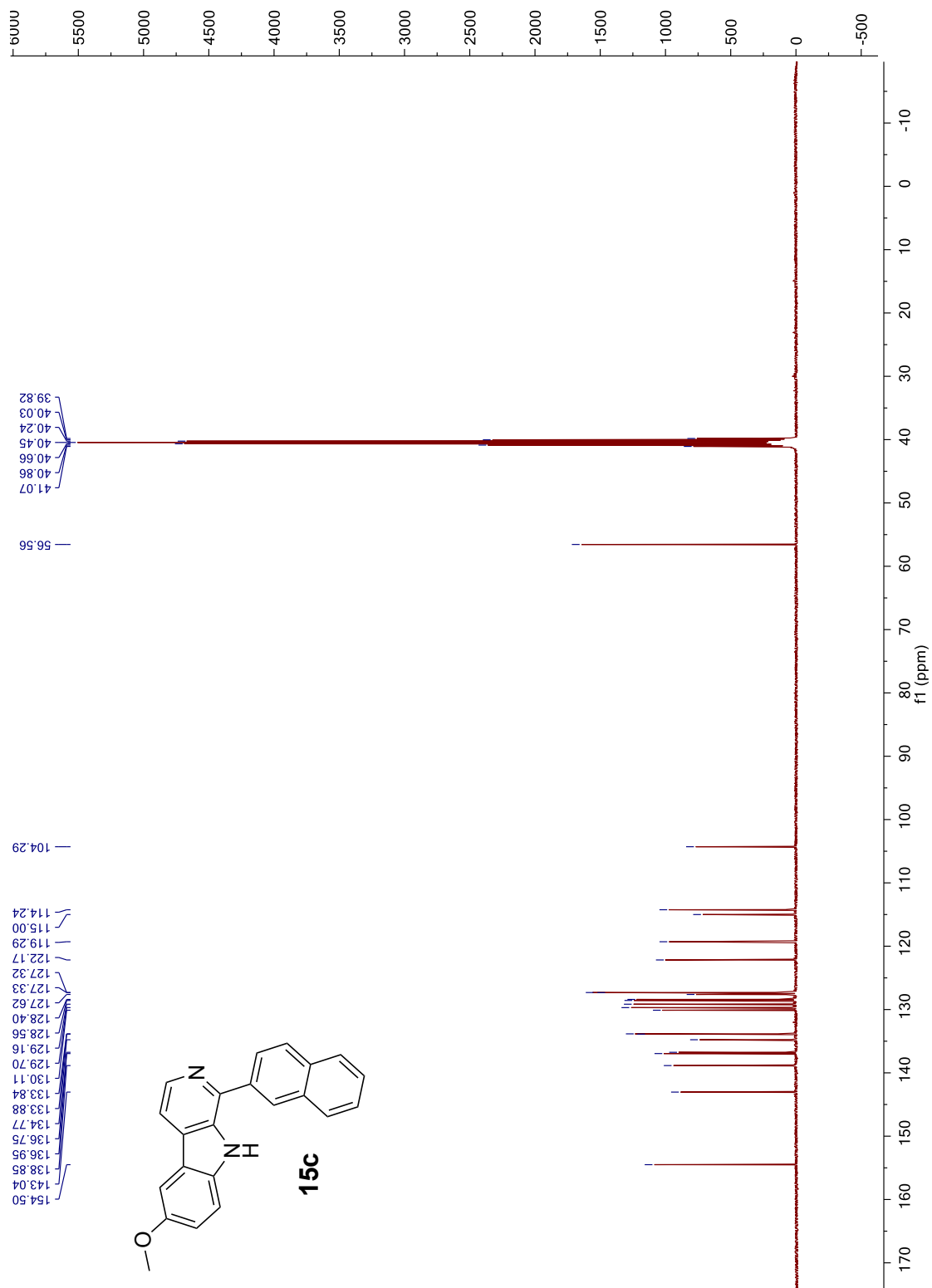


Figure S33. IR of **15c**:

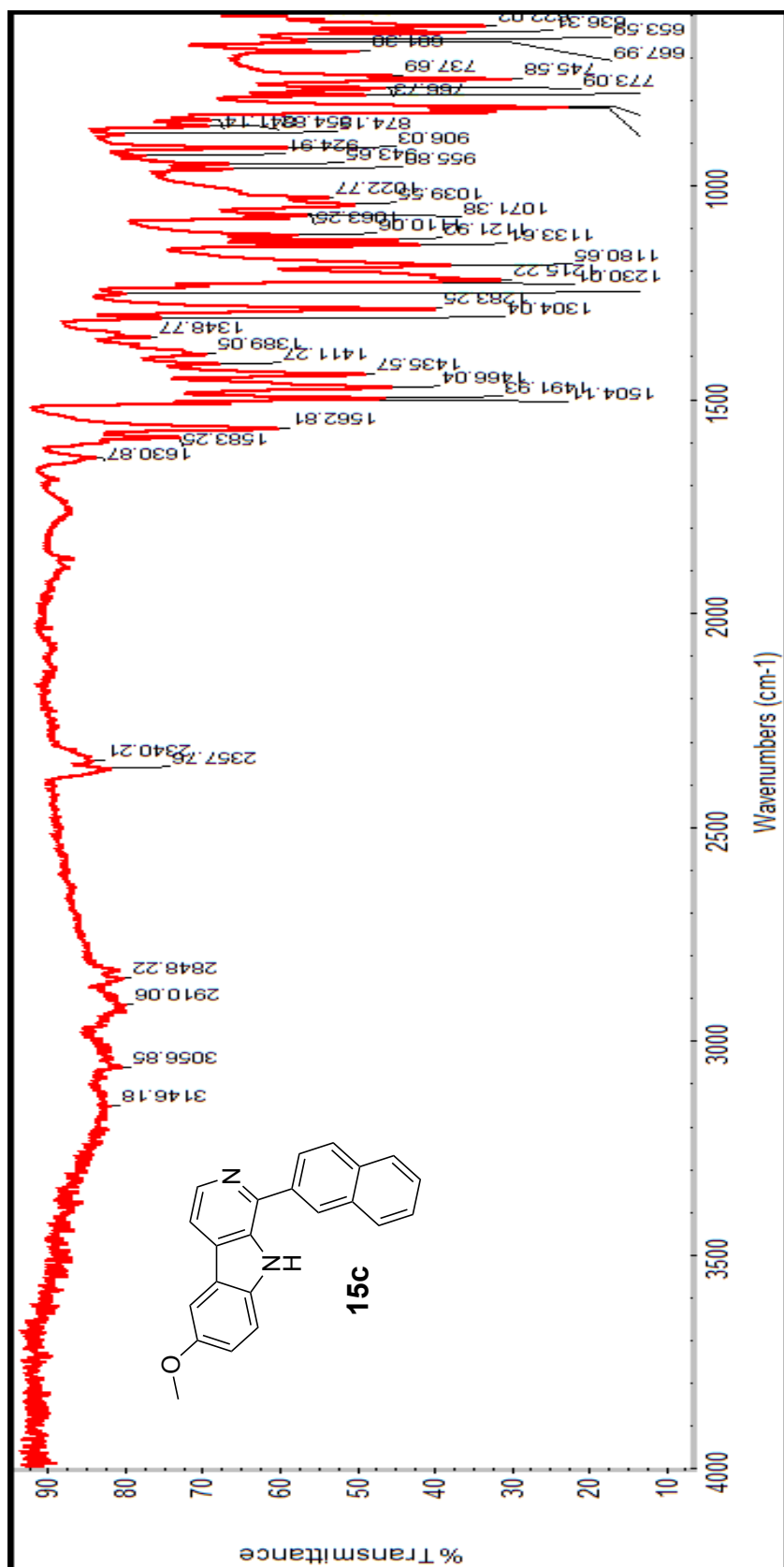


Figure S34.  $^1\text{H}$  NMR of **15d**:

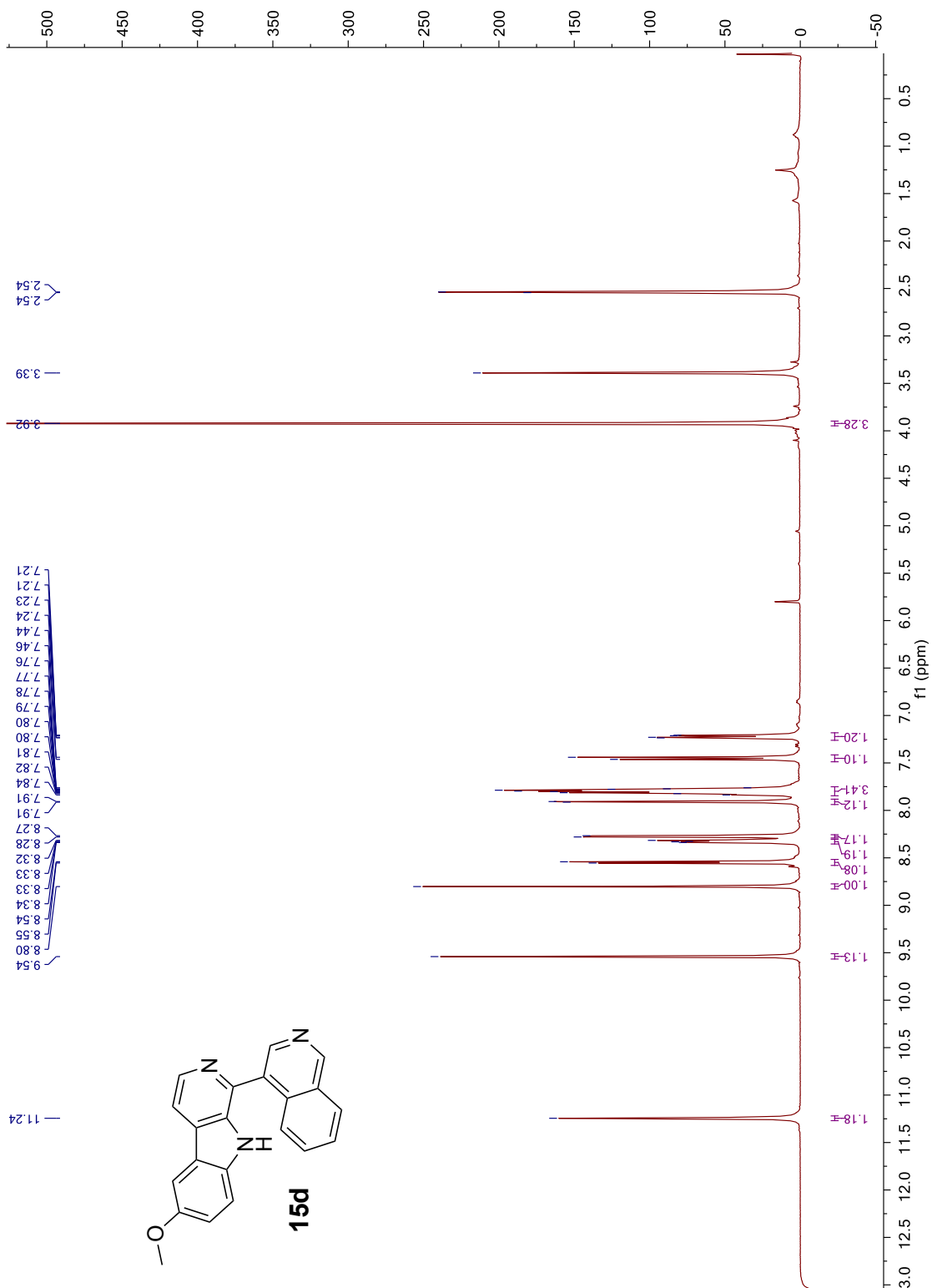


Figure S35.  $^{13}\text{C}$  NMR of **15d**:

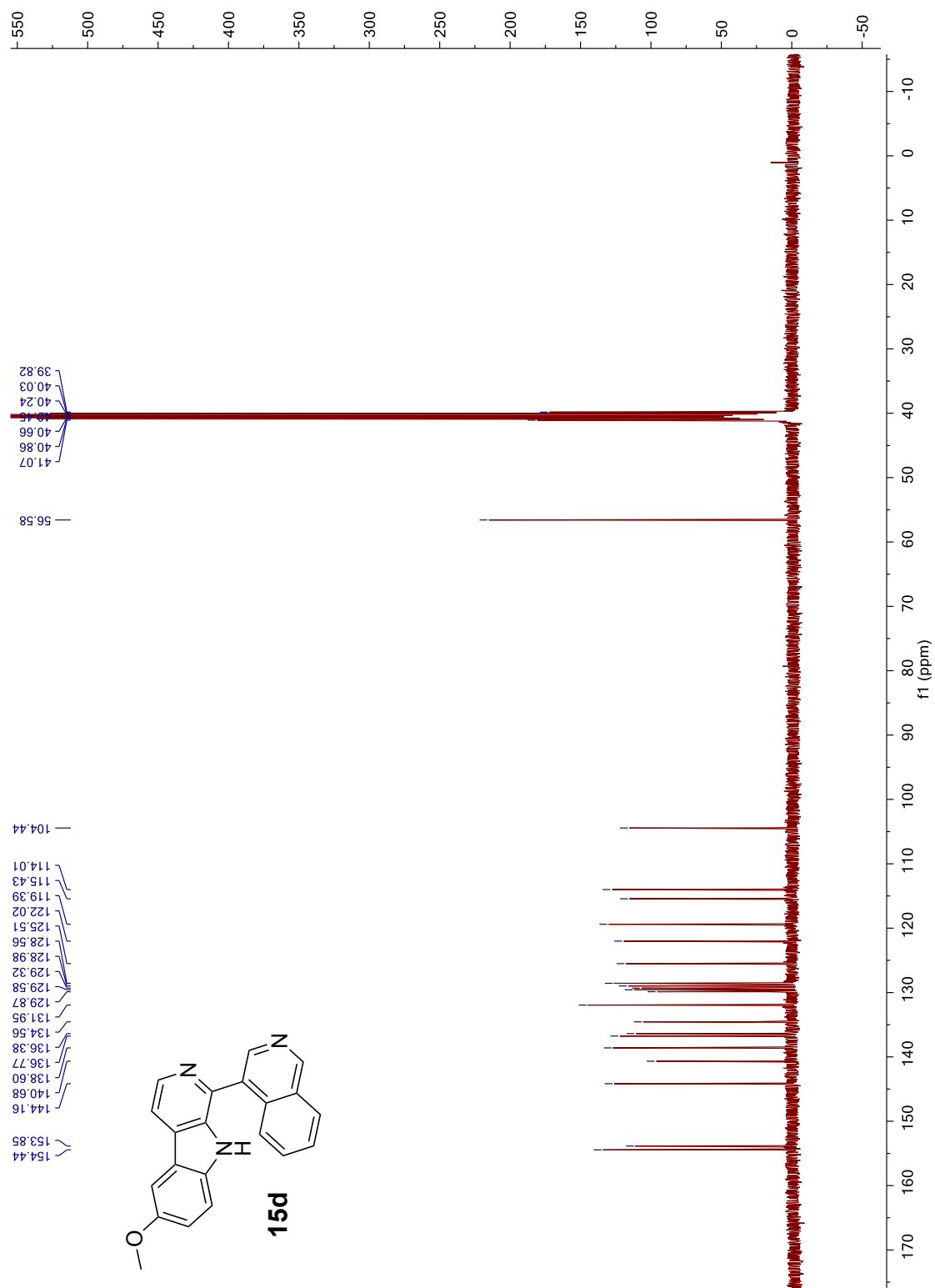


Figure S36. IR of **15d**:

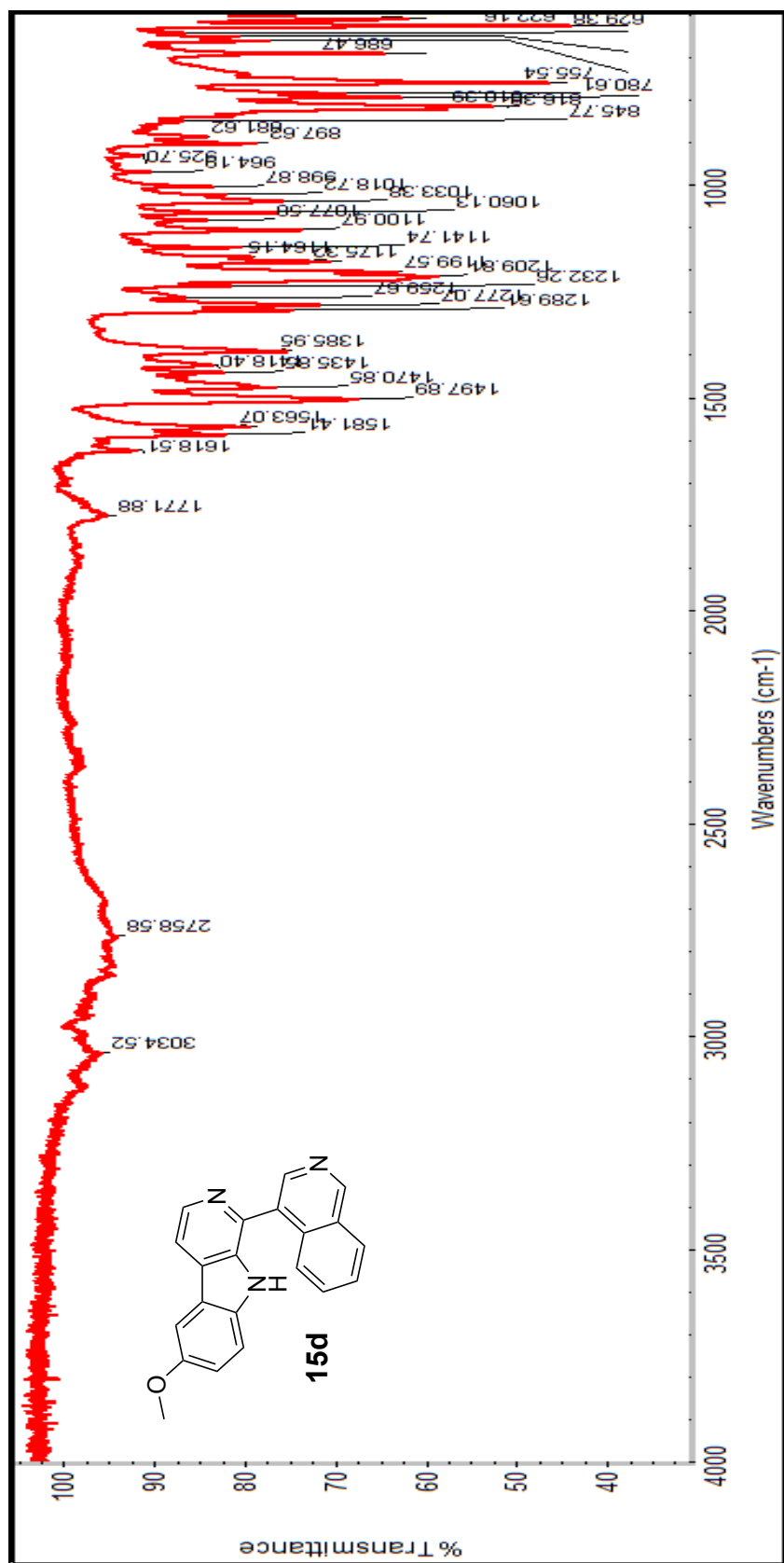


Figure S37.  $^1\text{H}$  NMR of **15e**:

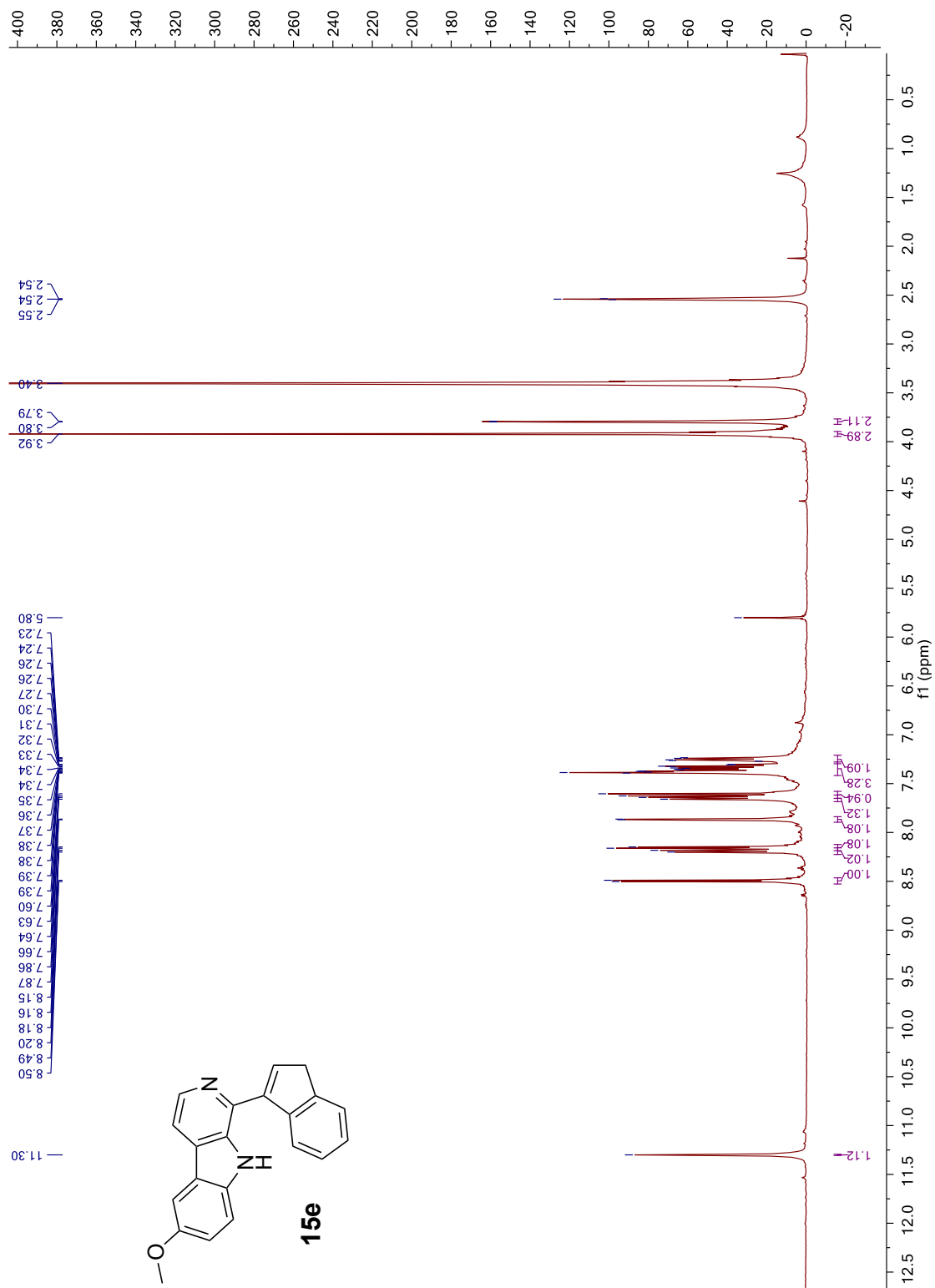


Figure S38.  $^{13}\text{C}$  NMR of **15e**:

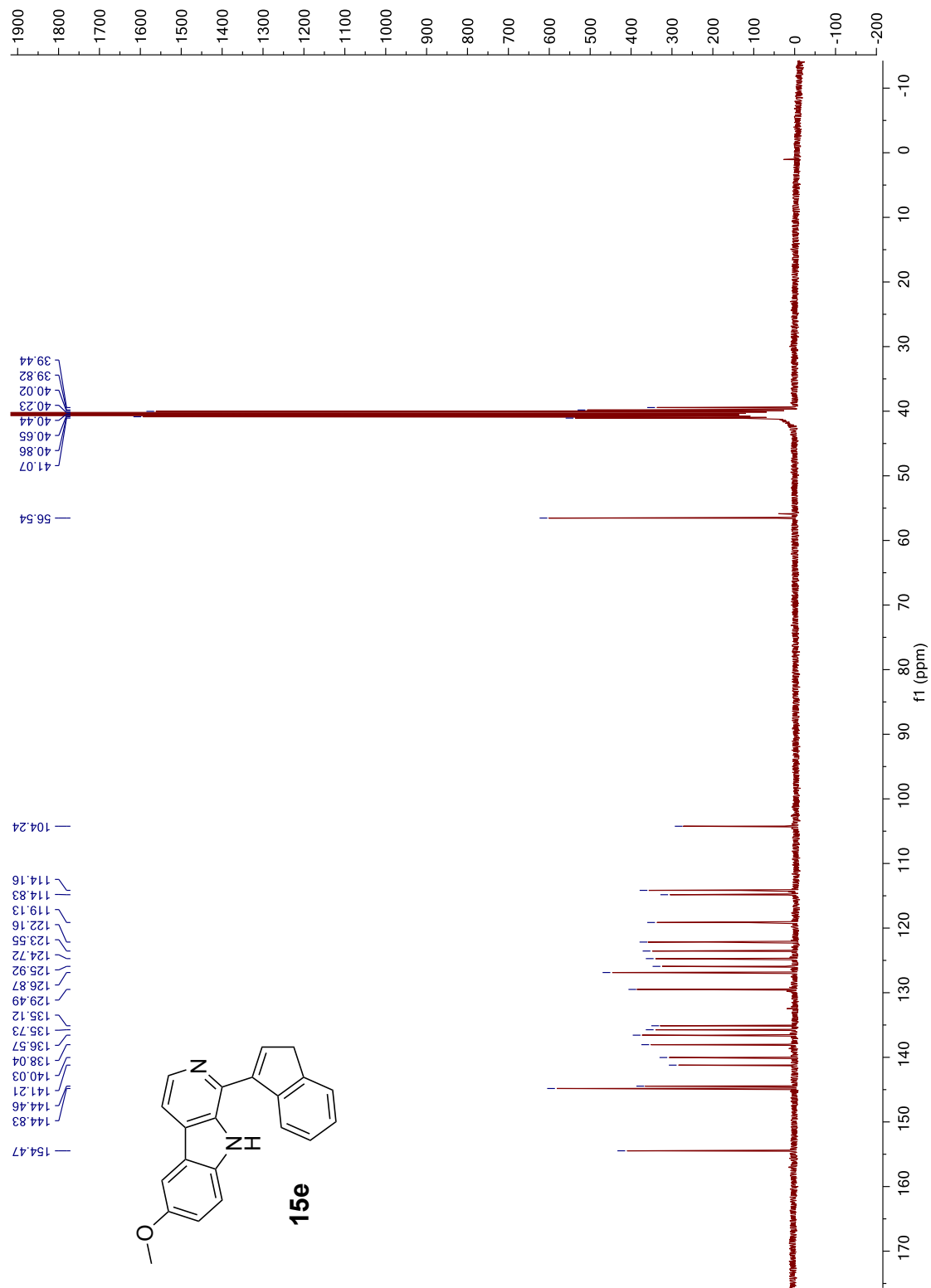


Figure S39. IR of **15e**:

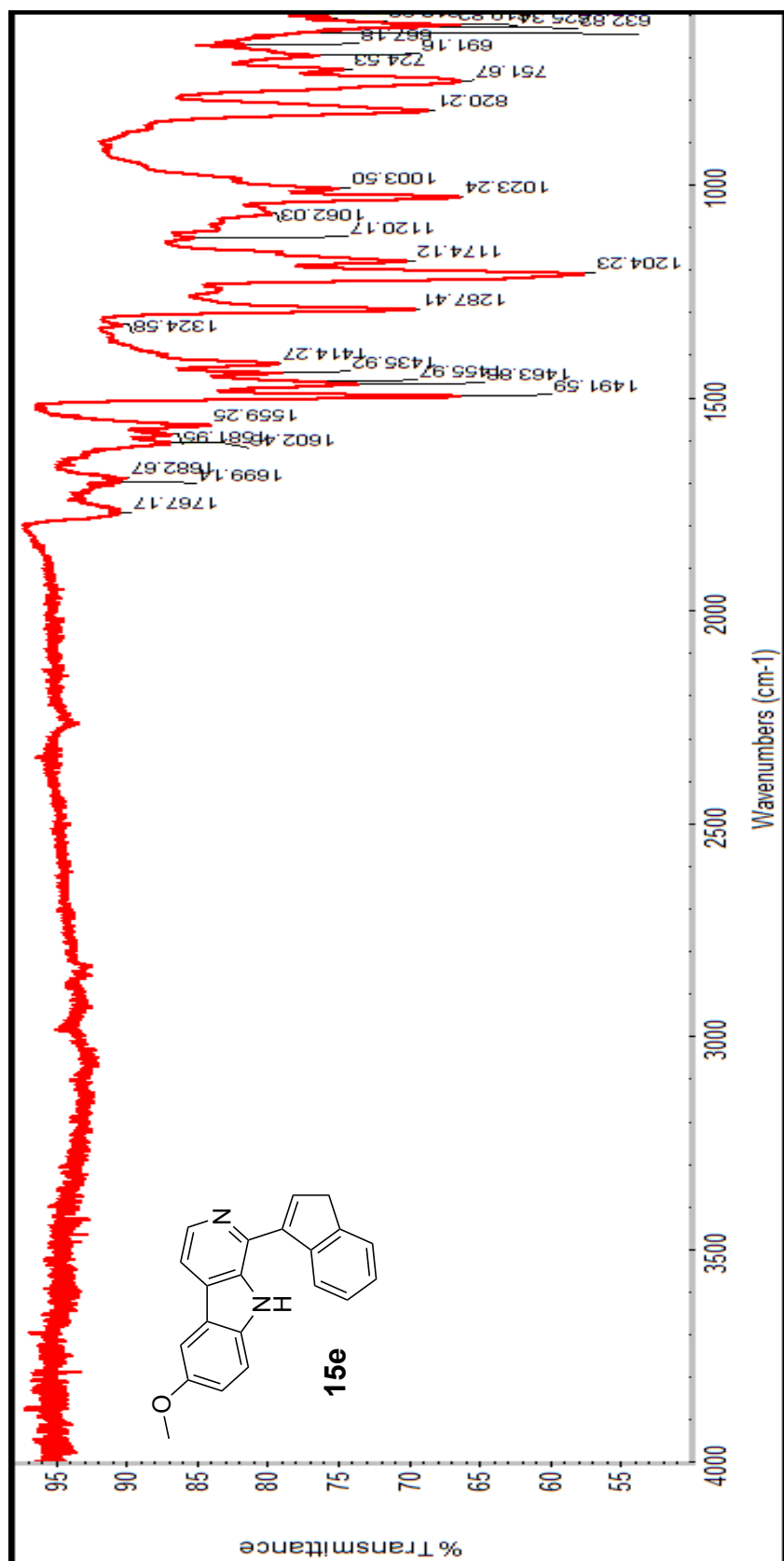


Figure S40.  $^1\text{H}$  NMR of **15f**:

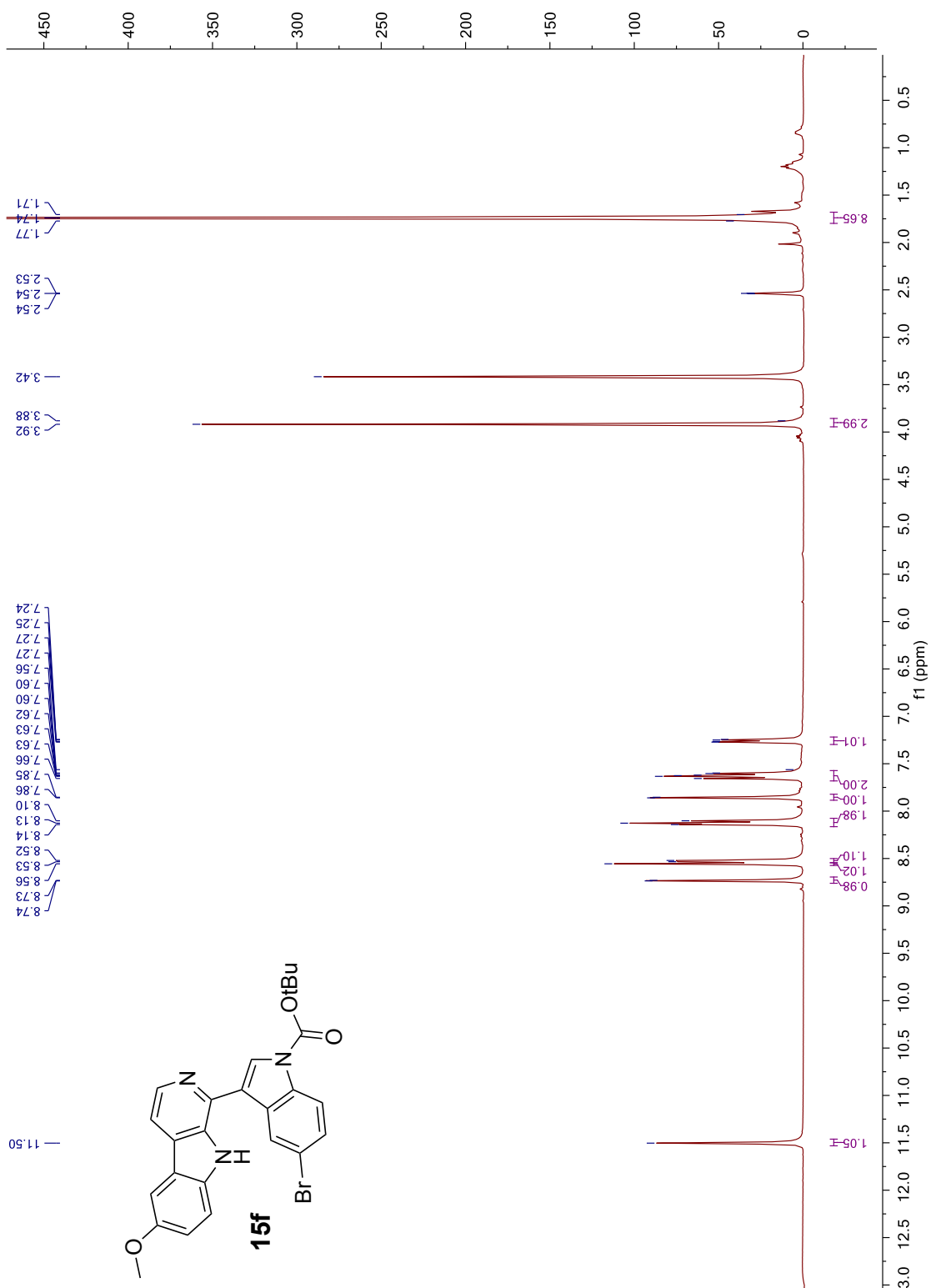


Figure S41.  $^{13}\text{C}$  NMR of **15f**:

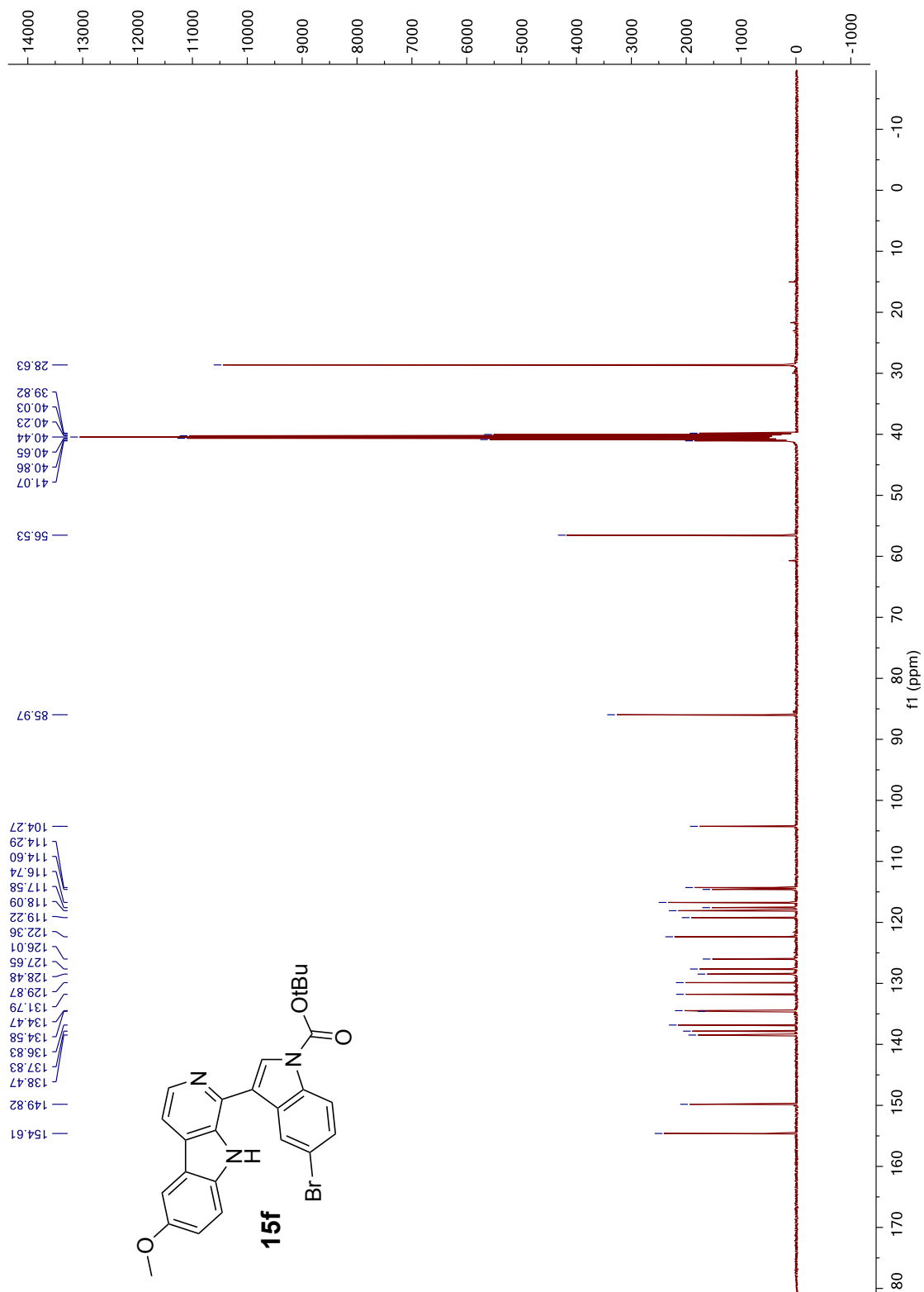


Figure S42. IR of **15f**:

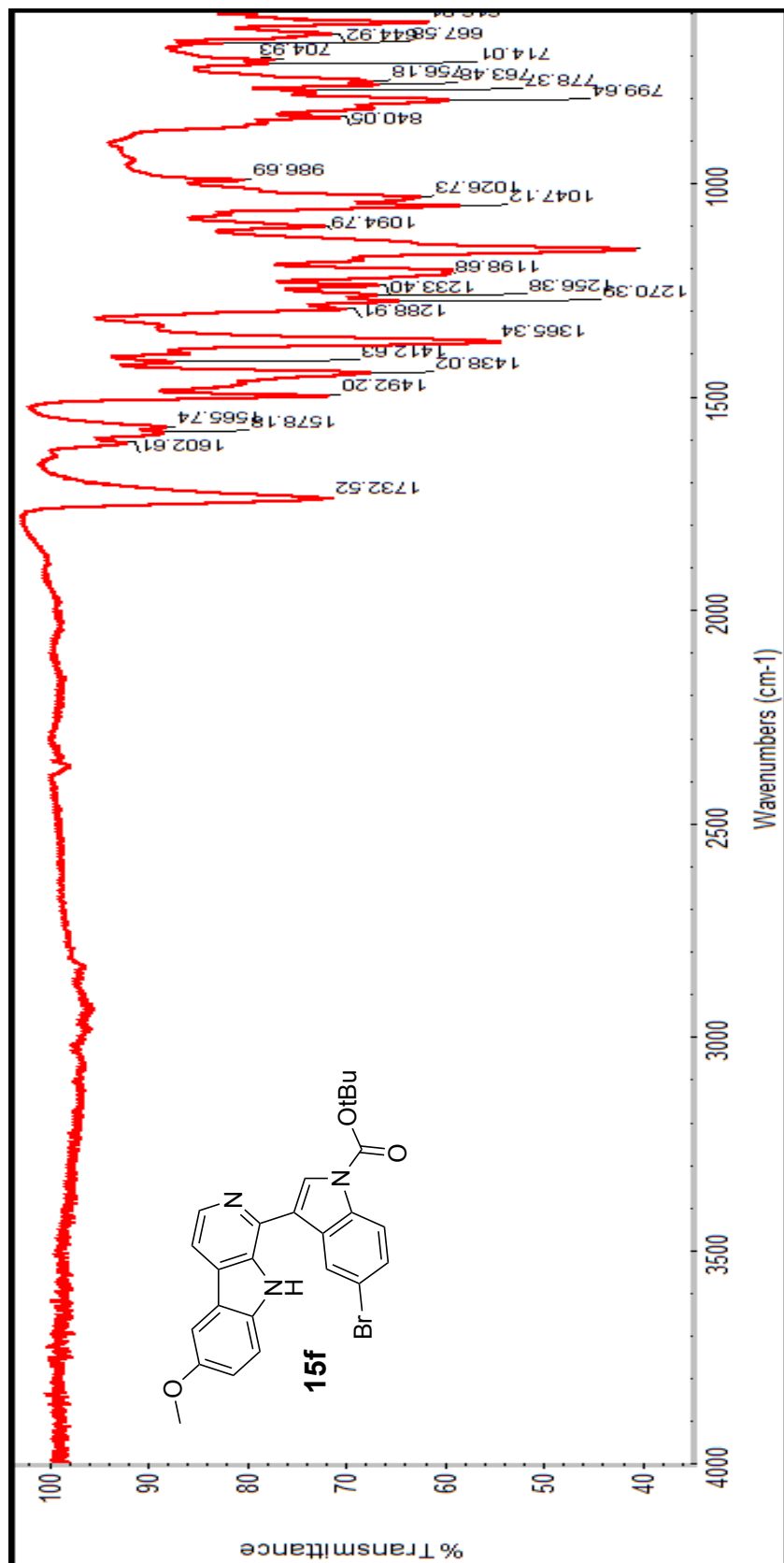


Figure S43.  $^1\text{H}$  NMR of **15g**:

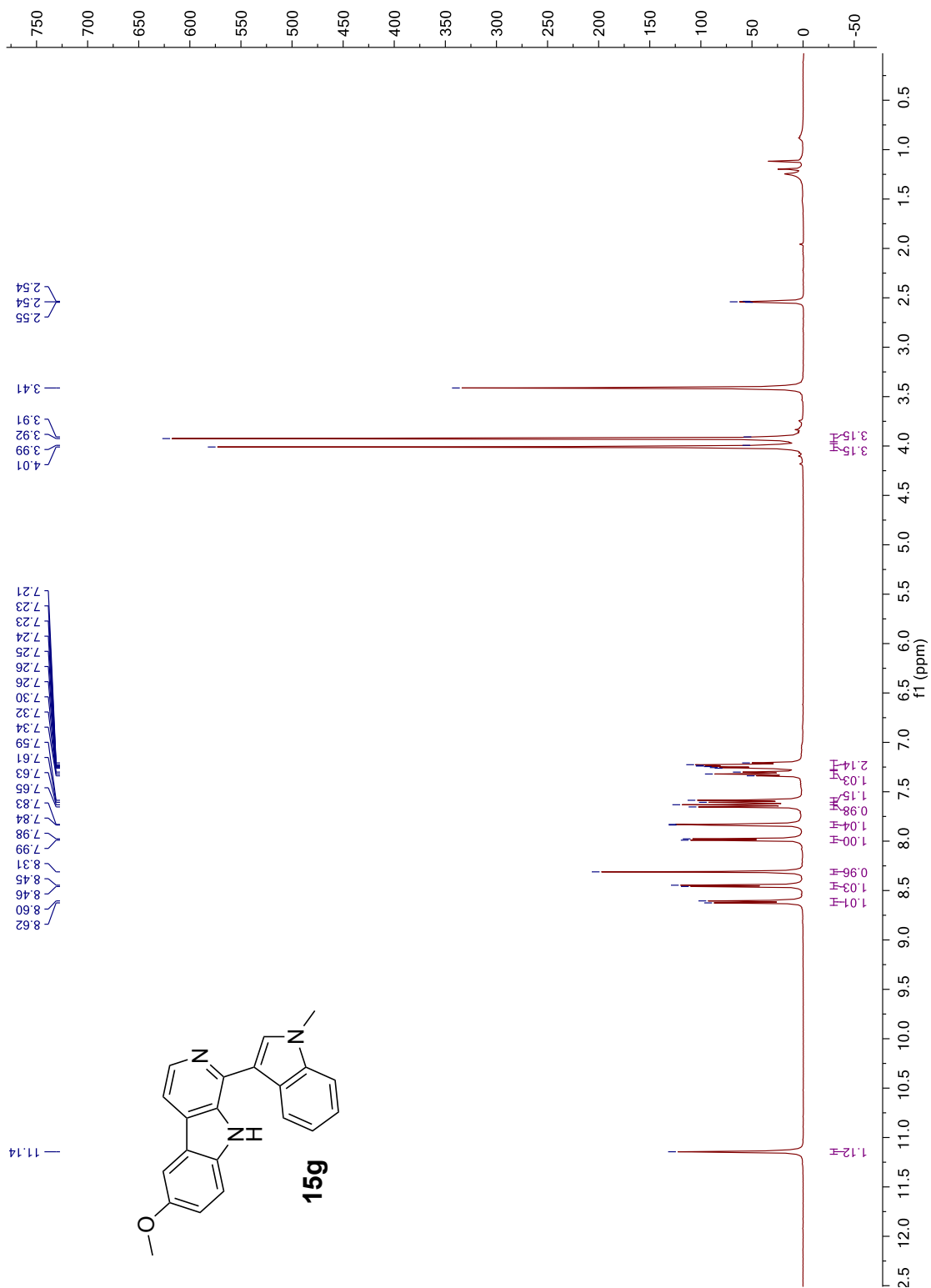


Figure S44.  $^{13}\text{C}$  NMR of **15g**:

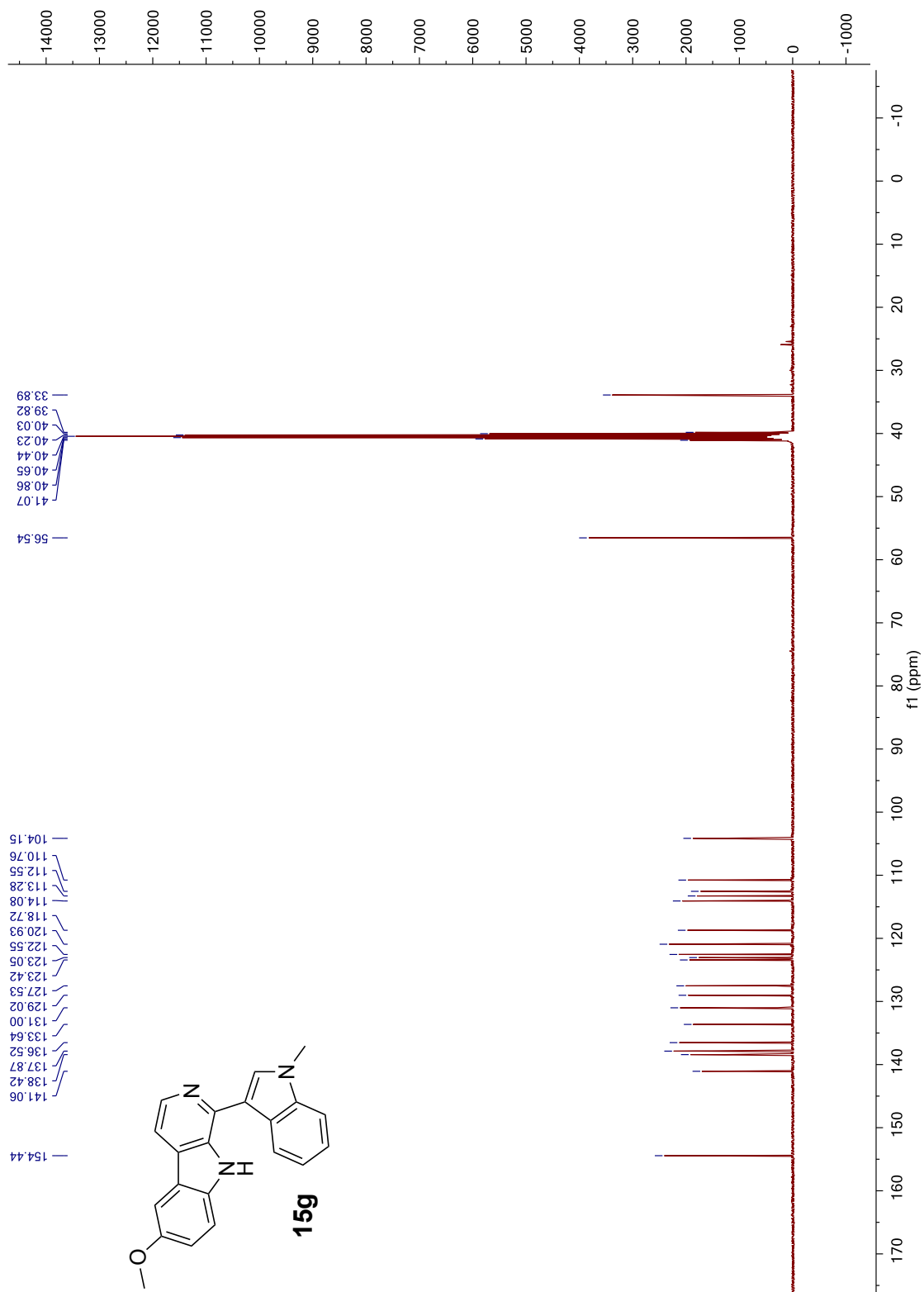


Figure S45. IR of **15g**:

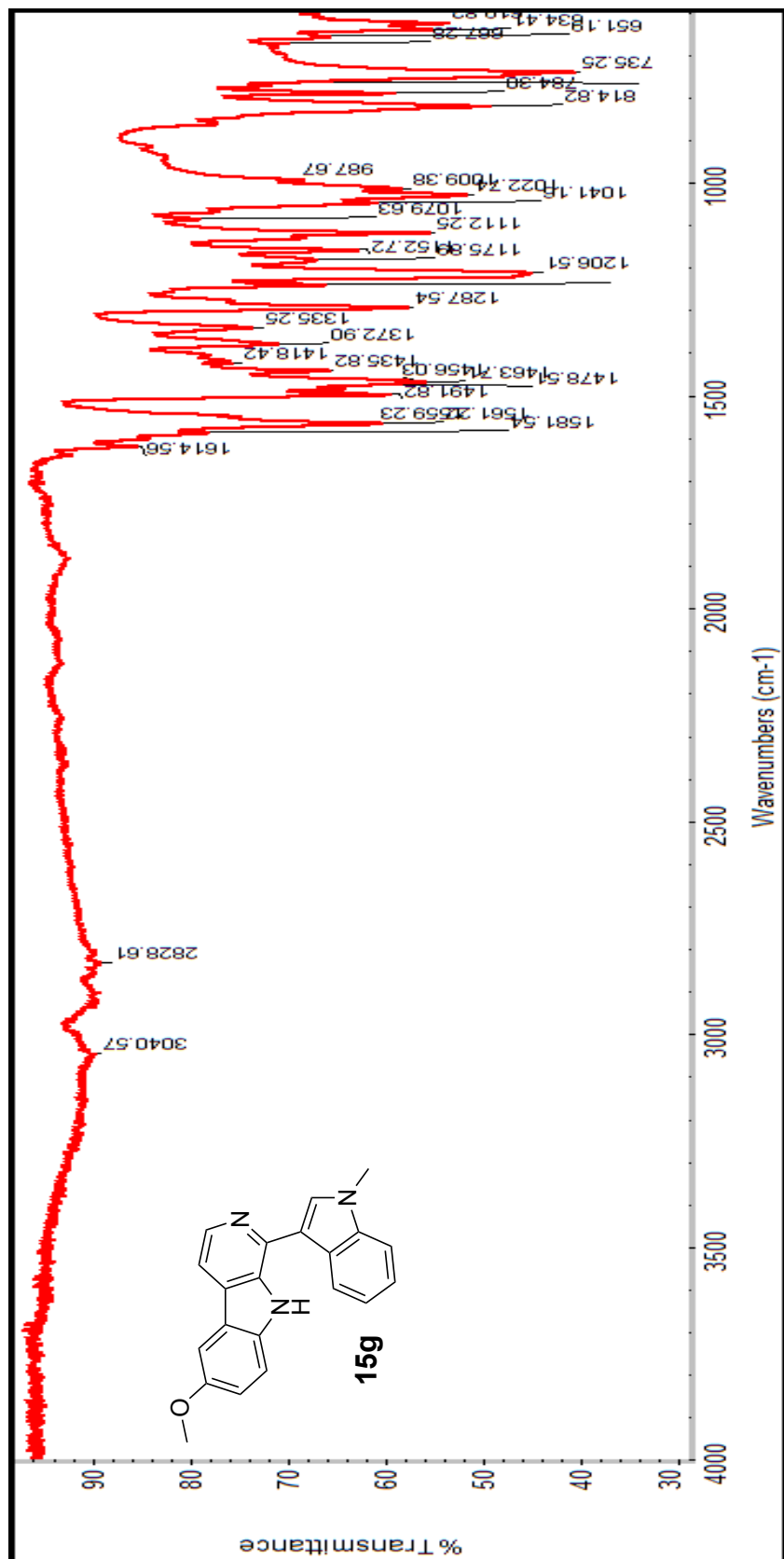




Figure S47.  $^{13}\text{C}$  NMR of **15h**:

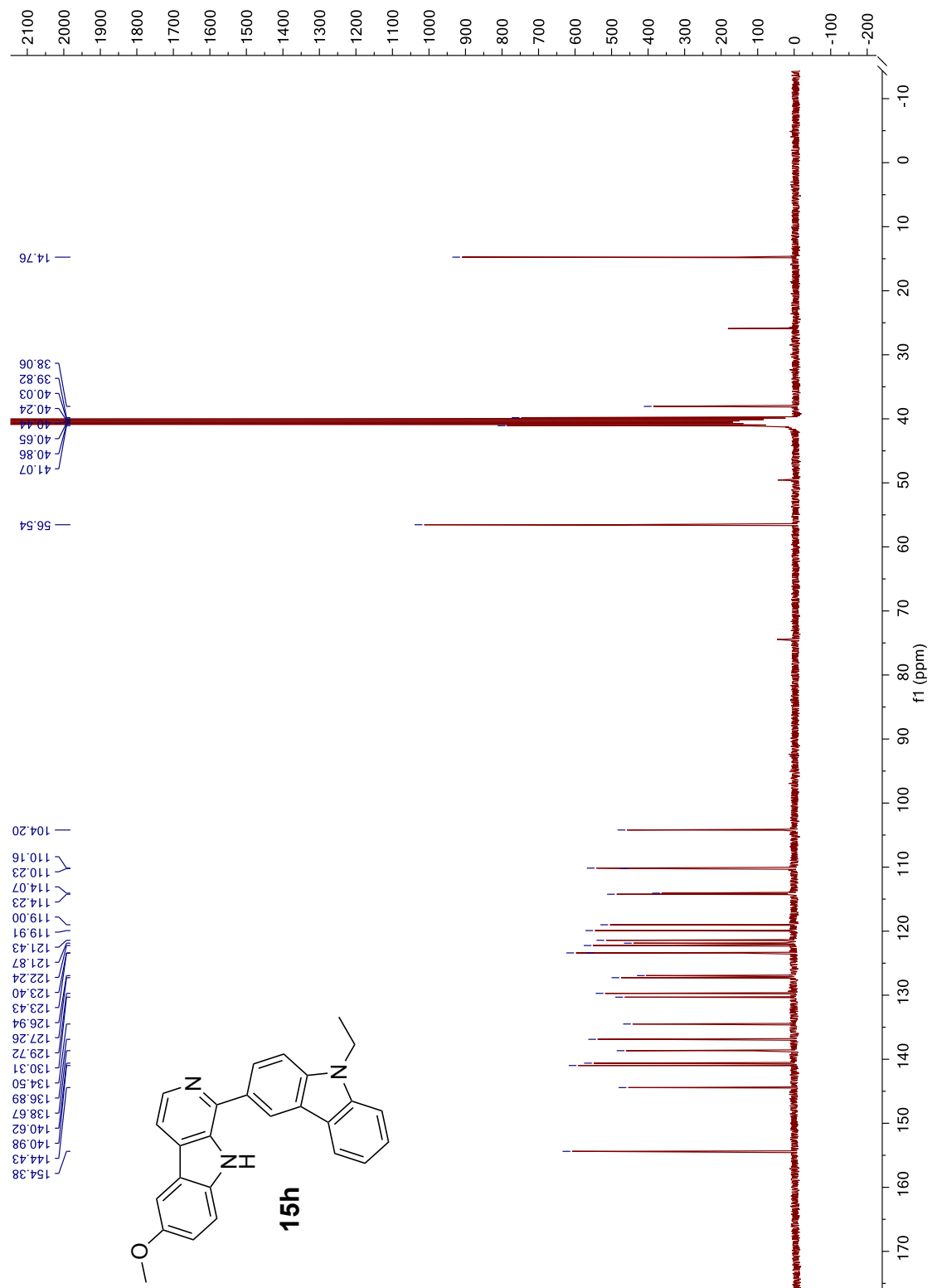


Figure S48. IR of **15h**:

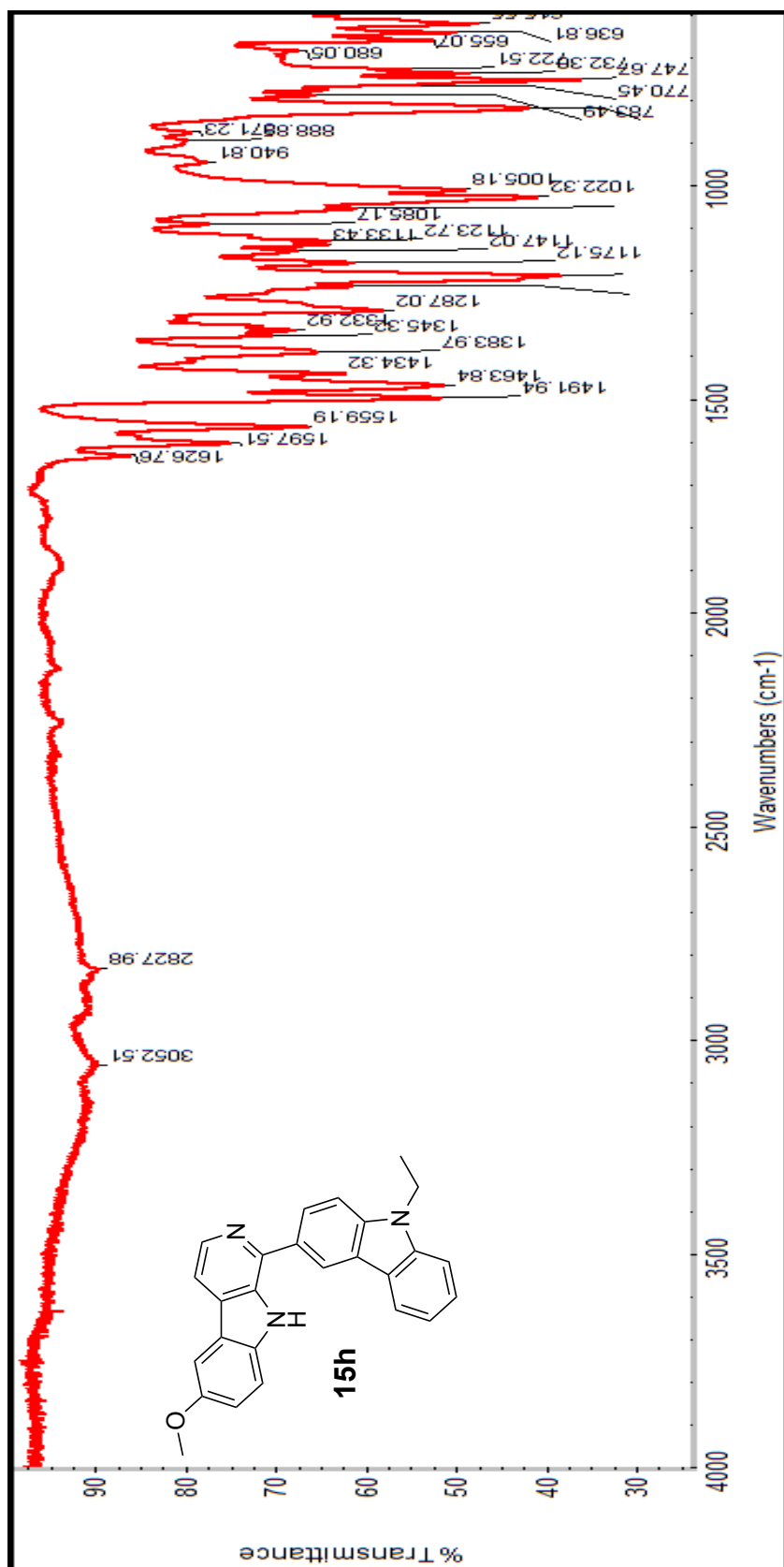




Figure S50.  $^{13}\text{C}$  NMR of **15i**:

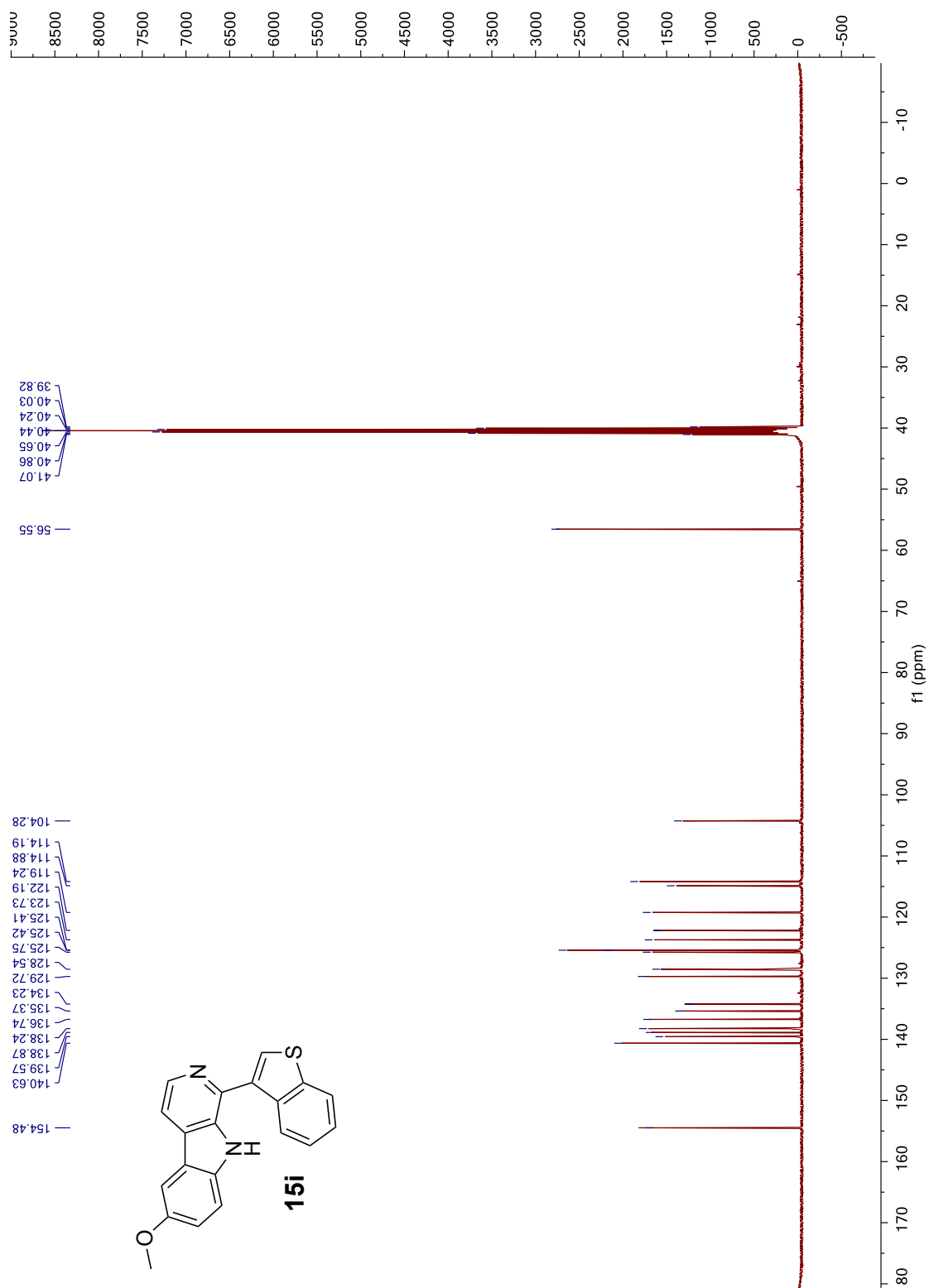


Figure S51. IR of **15i**:

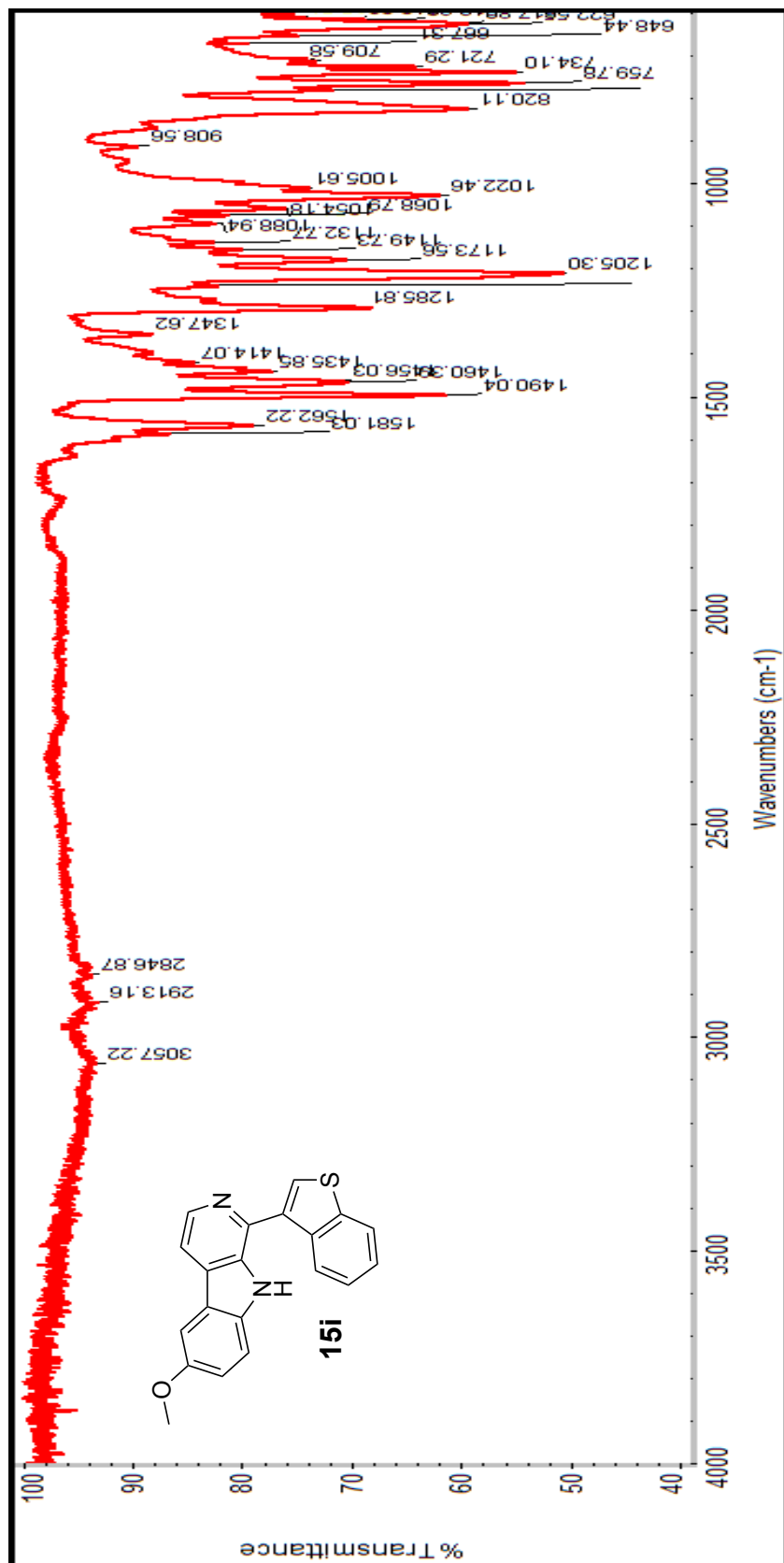




Figure S53.  $^{13}\text{C}$  NMR of **15j**:

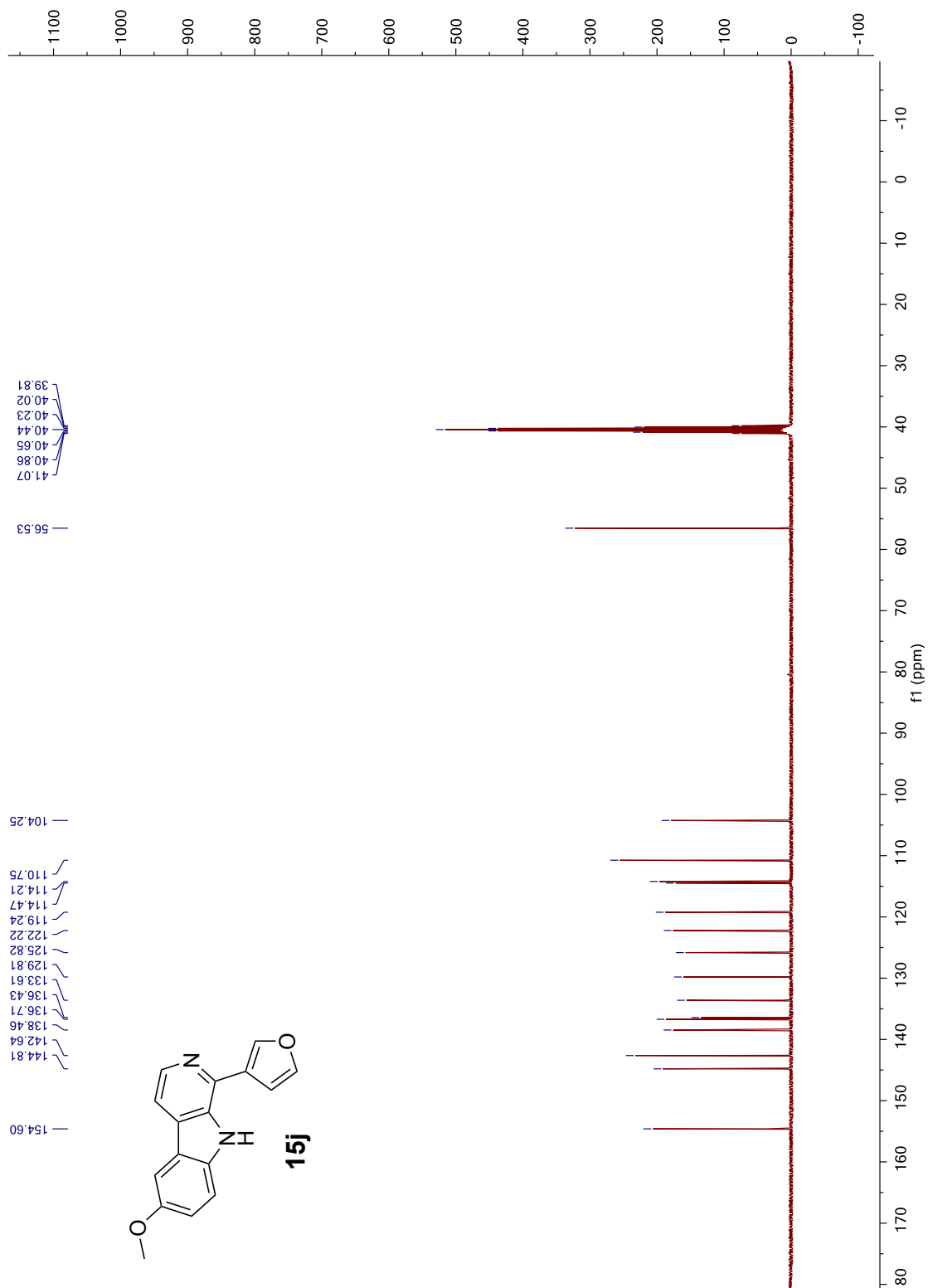


Figure S54. IR of **15j**:

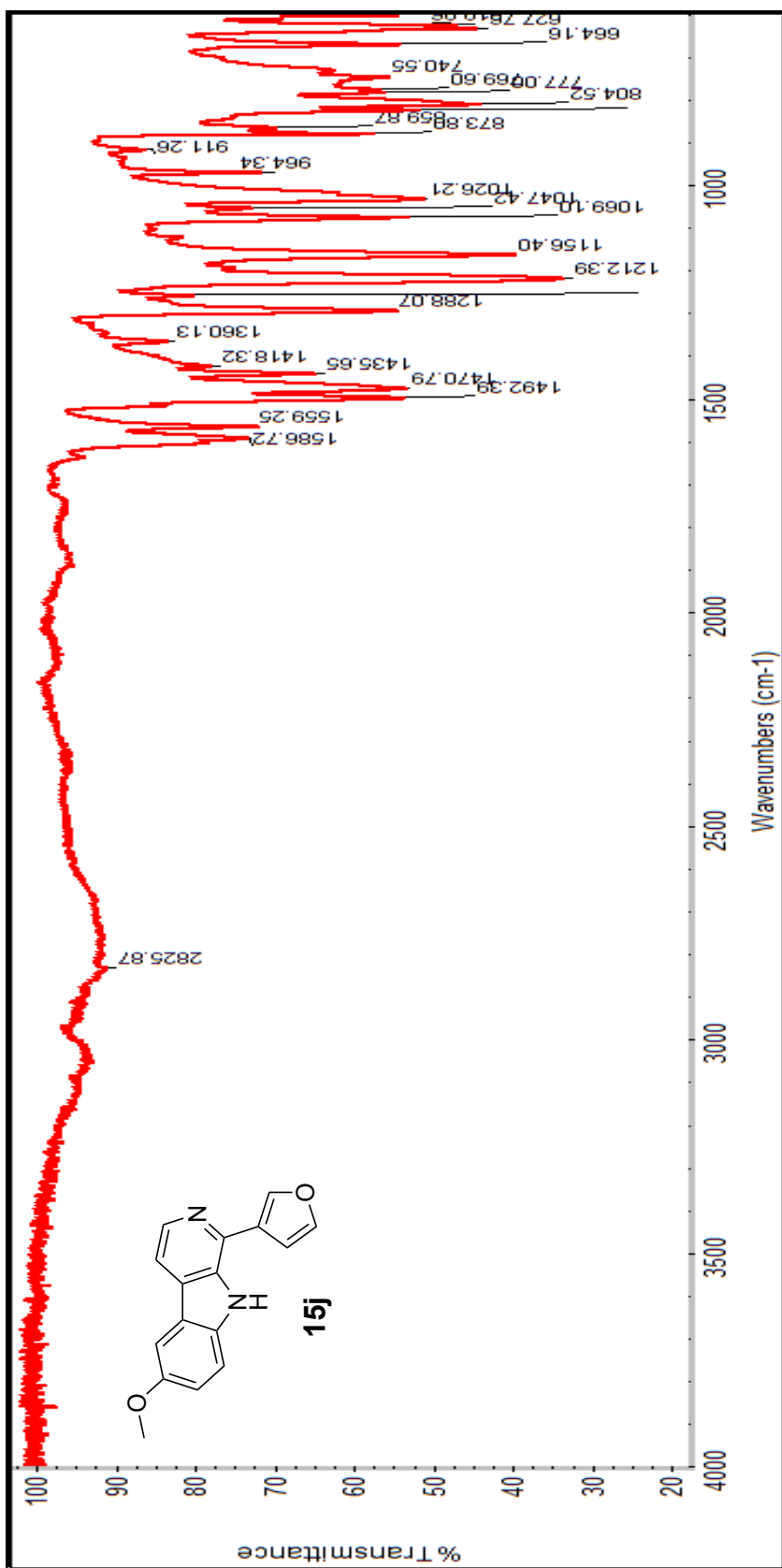


Figure S55.  $^1\text{H}$  NMR of **15k**:

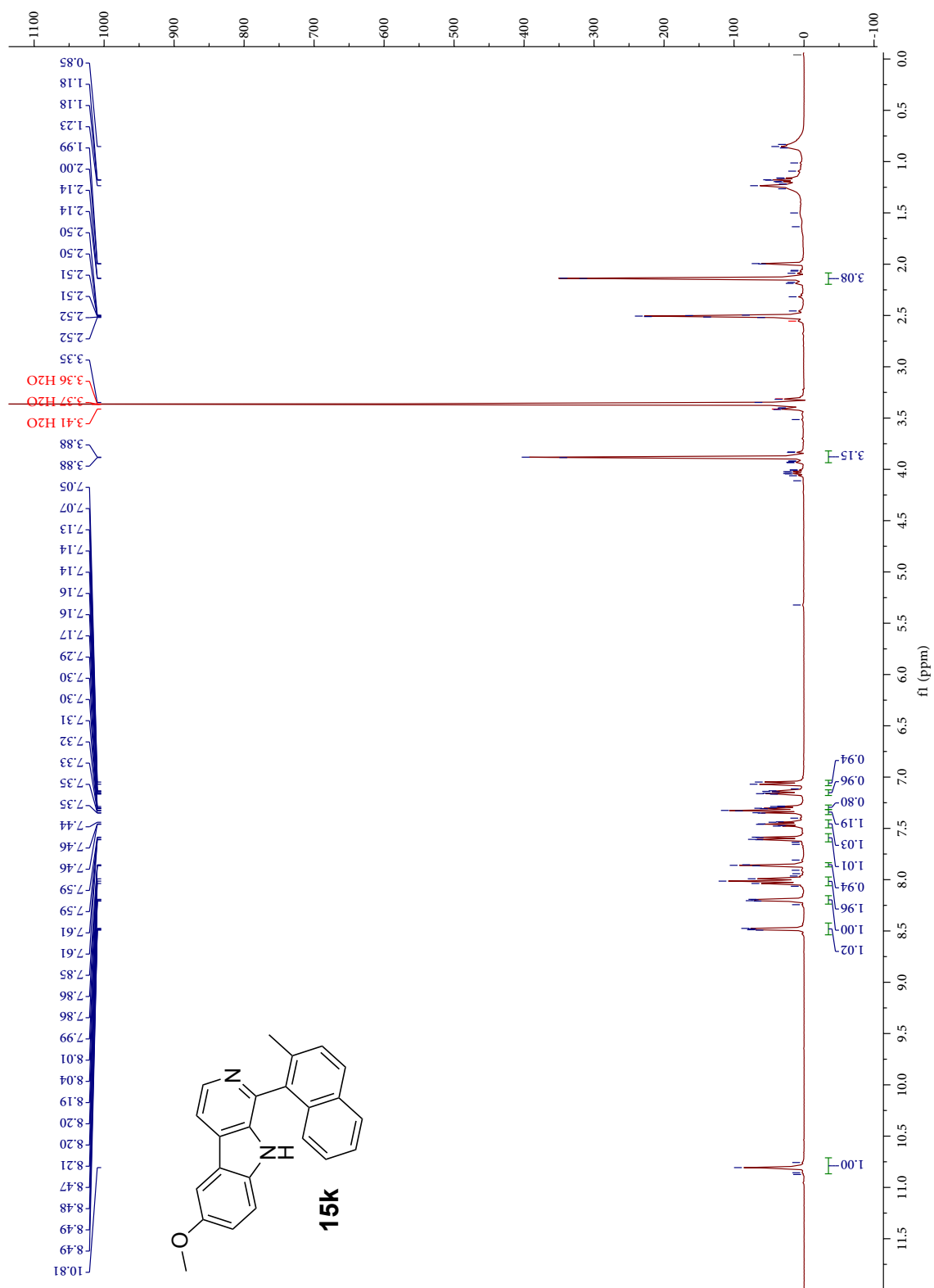


Figure S56.  $^{13}\text{C}$  NMR of **15k**:

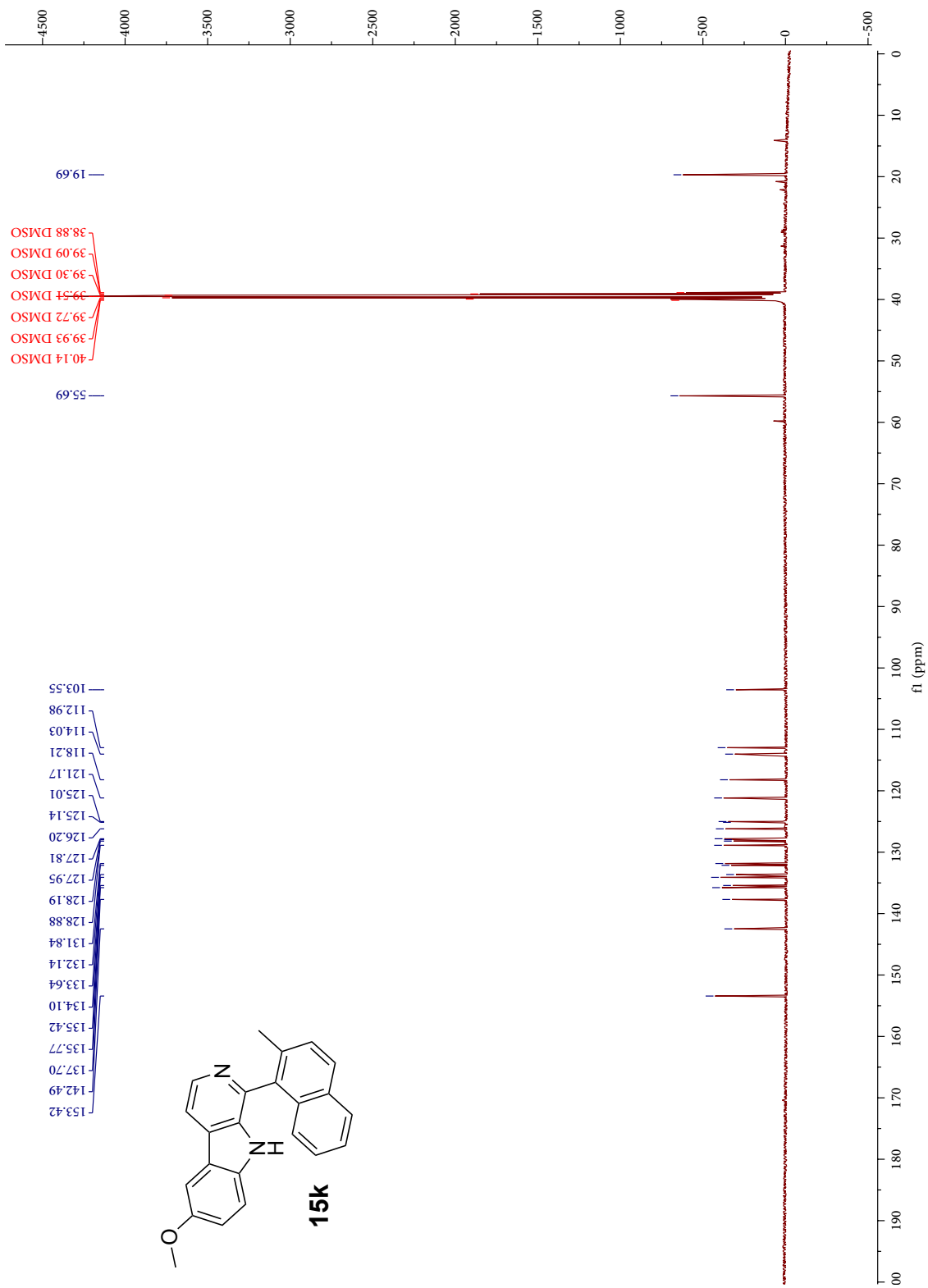


Figure S57. IR of **15k**:

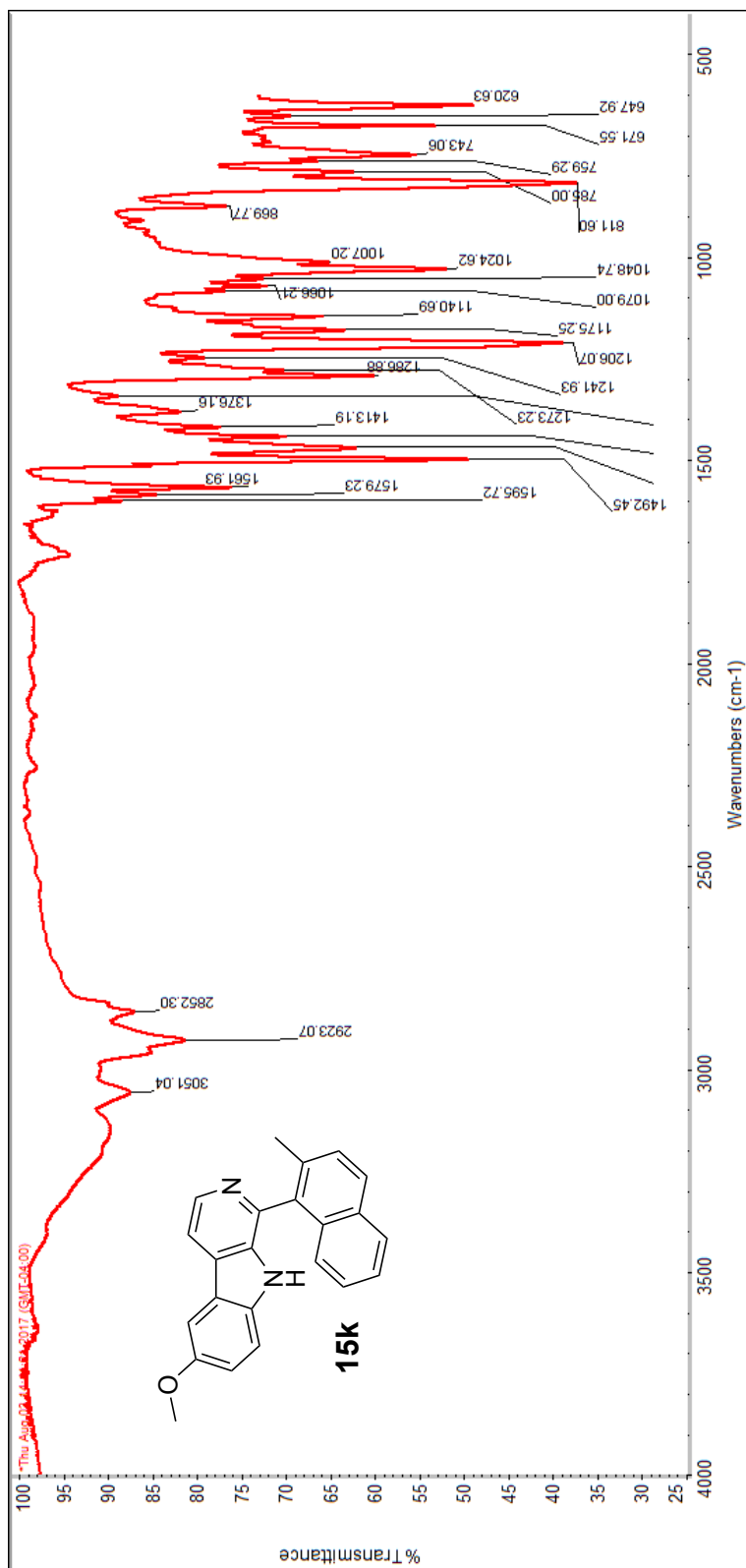


Figure S58.  $^1\text{H}$  NMR of **16f**:

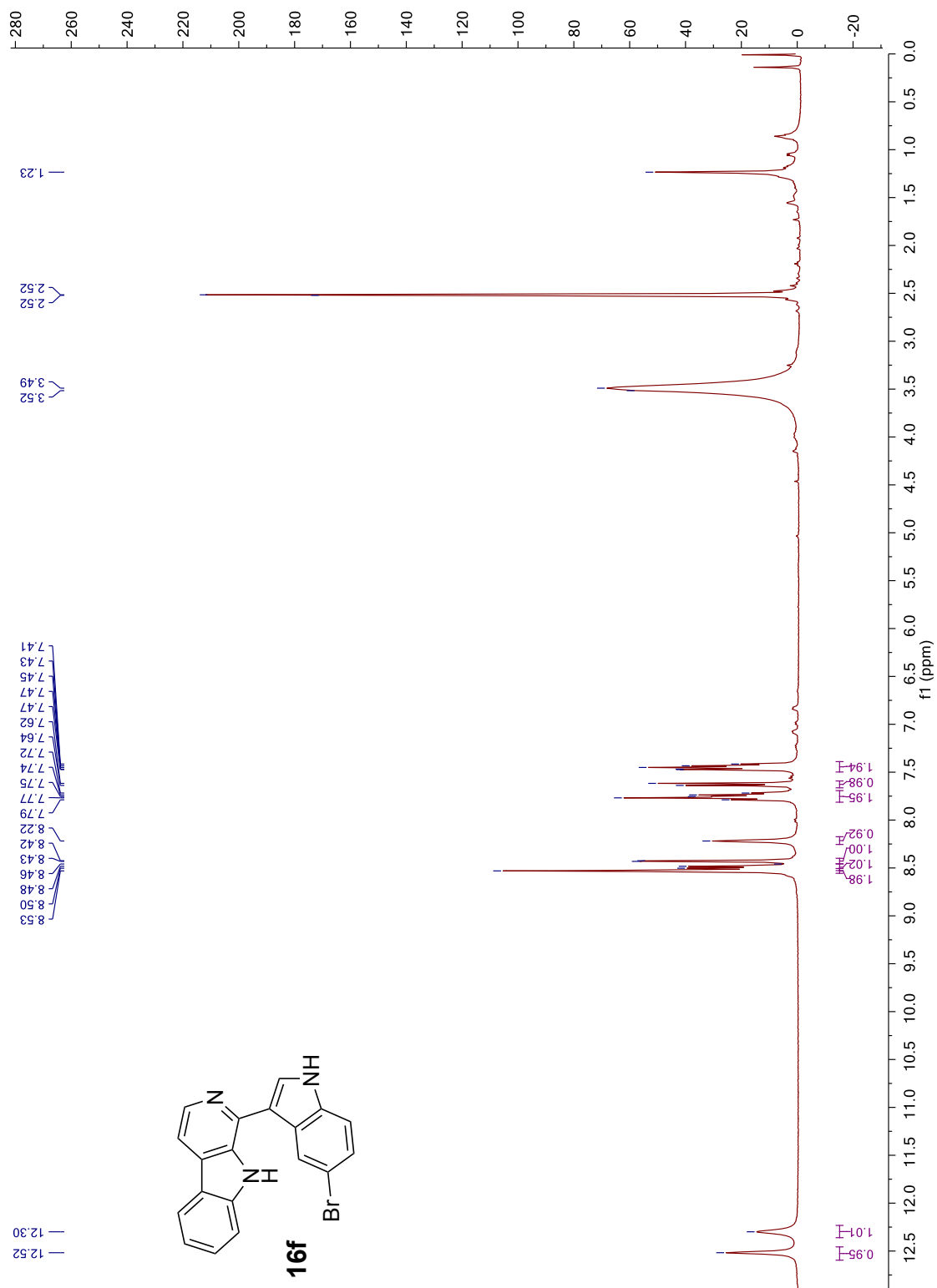


Figure S59.  $^{13}\text{C}$  NMR of **16f**:

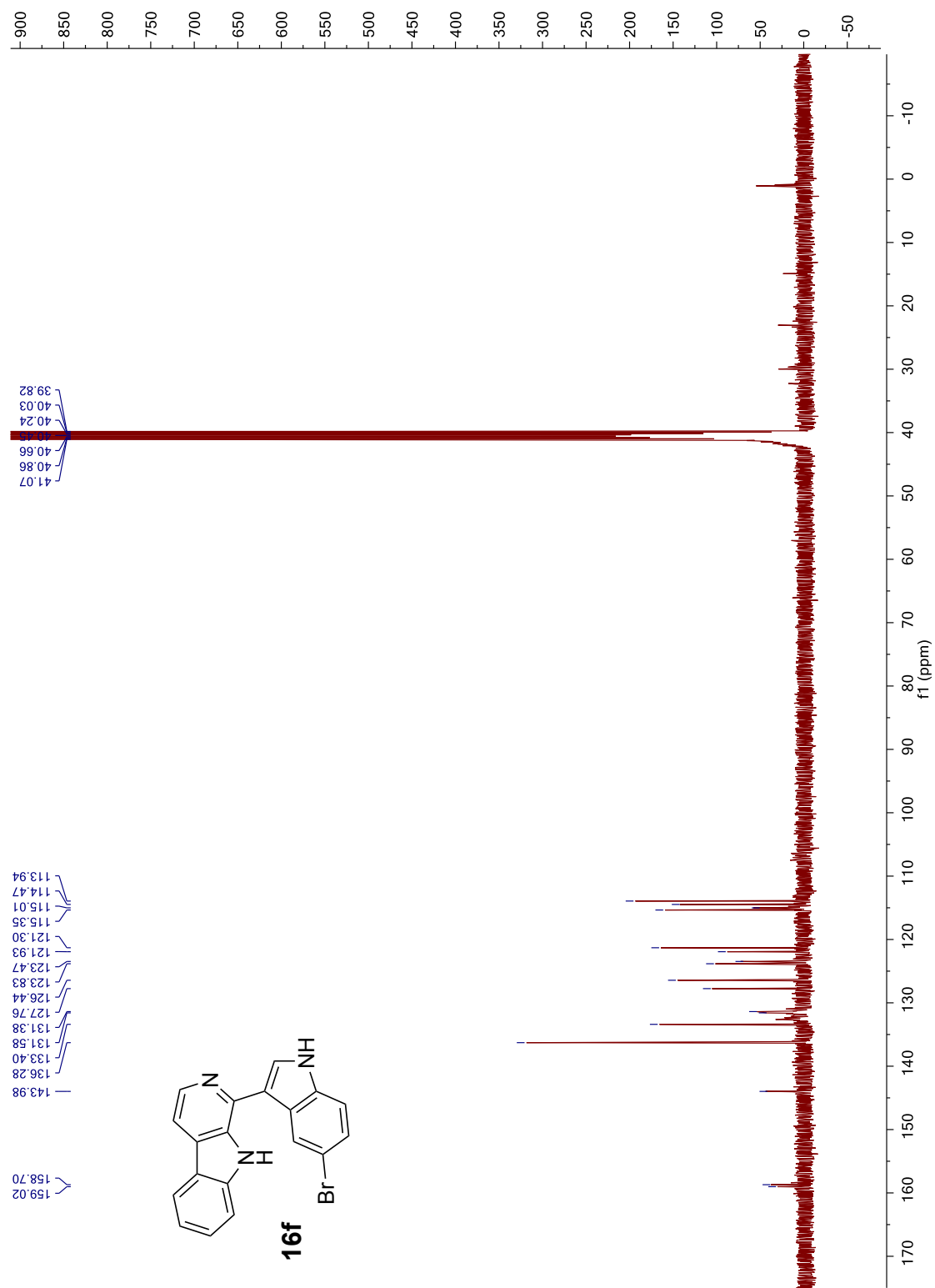


Figure S60. IR of **16f**:

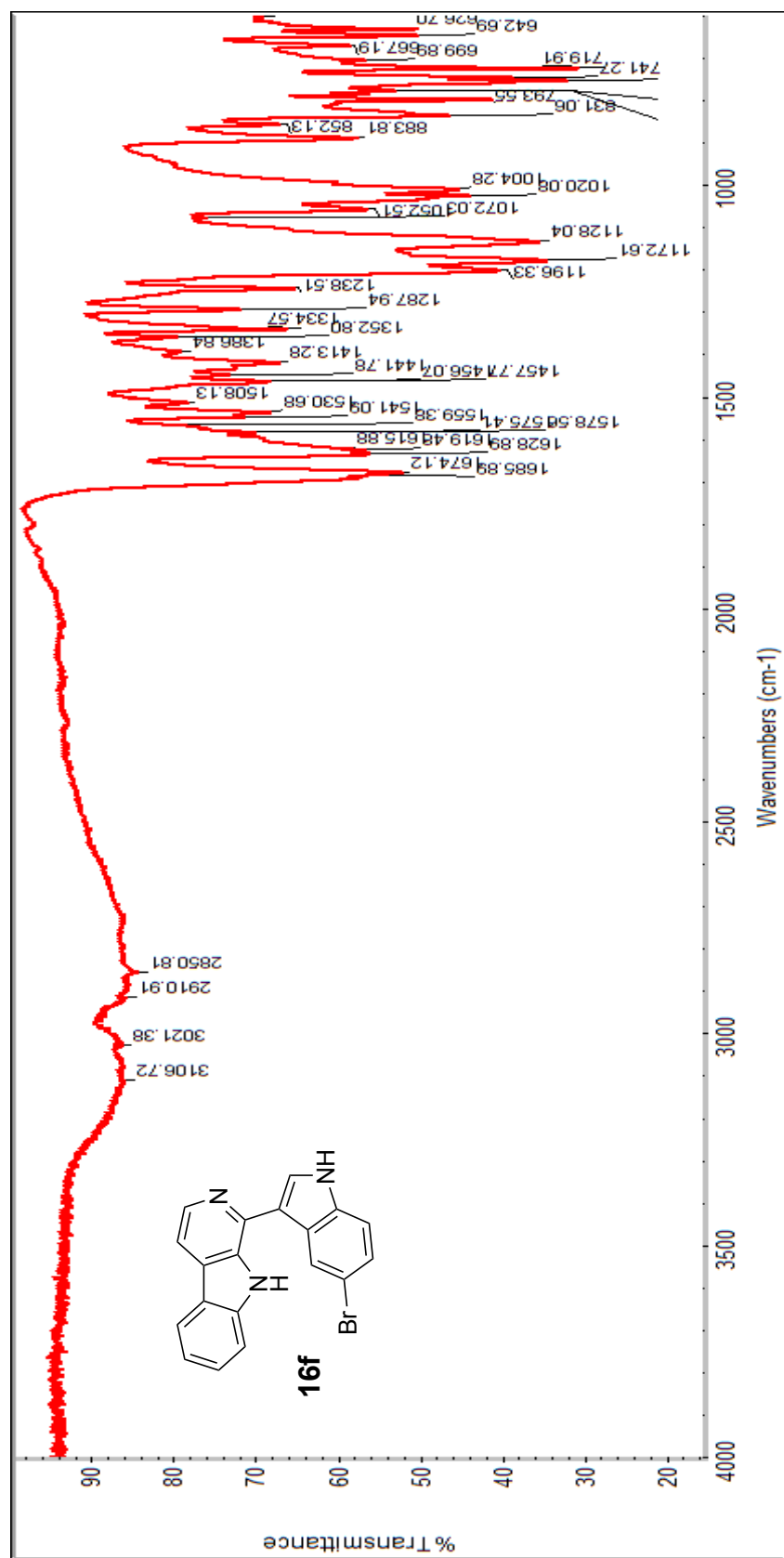


Figure S61. <sup>1</sup>H NMR of 16l:

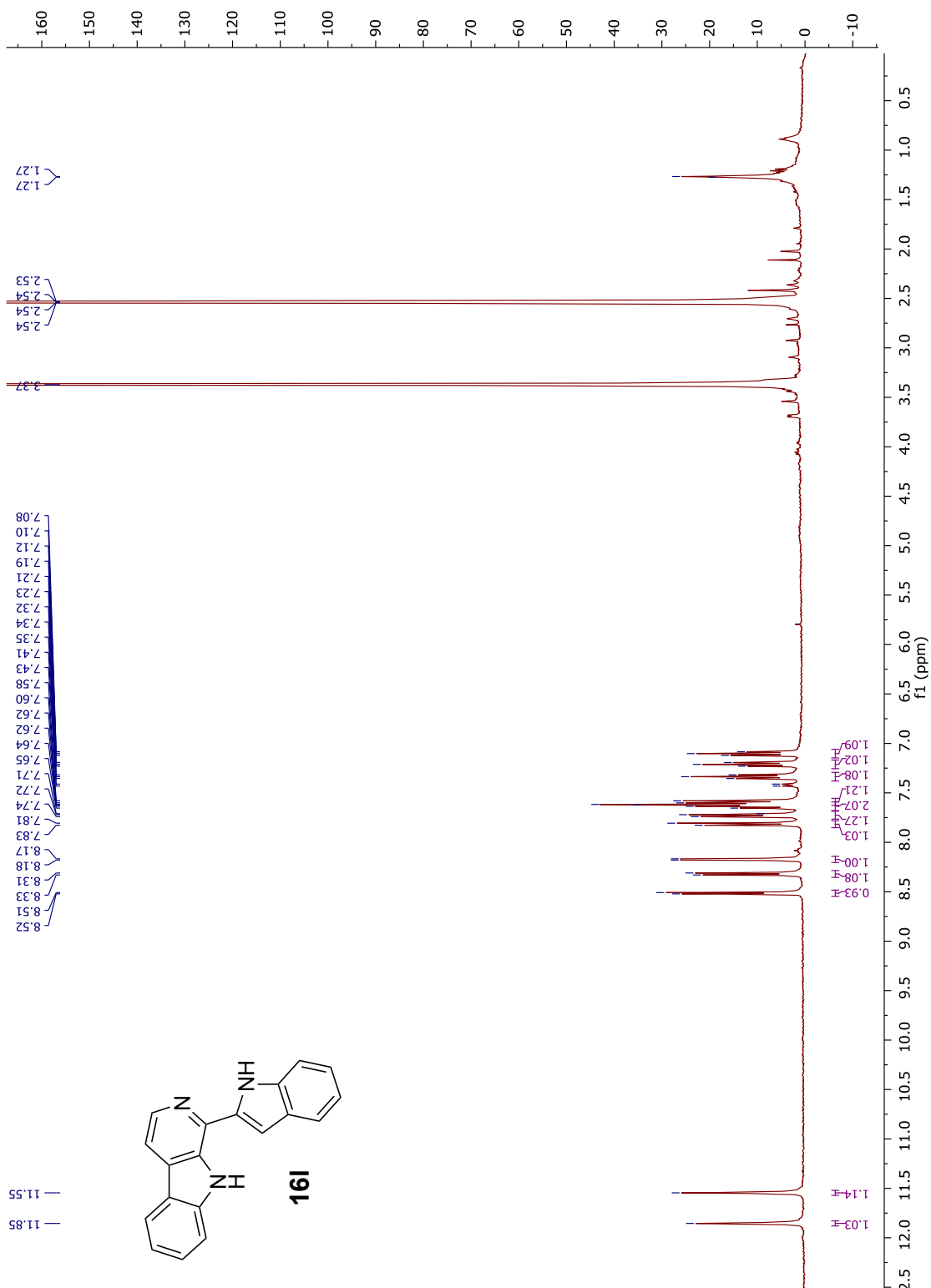


Figure S62.  $^{13}\text{C}$  NMR of **16l**:

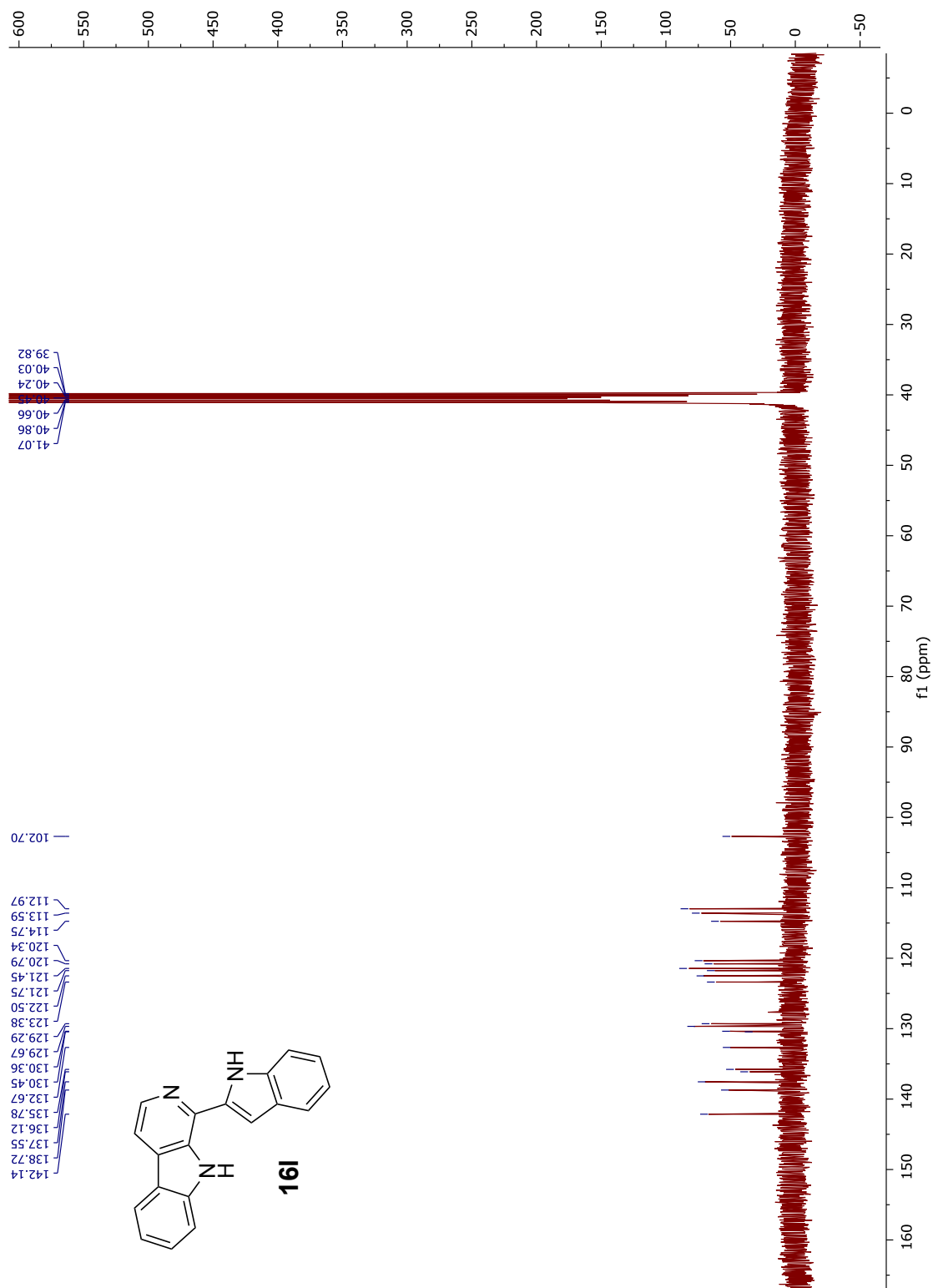


Figure S63. IR of **16l**:

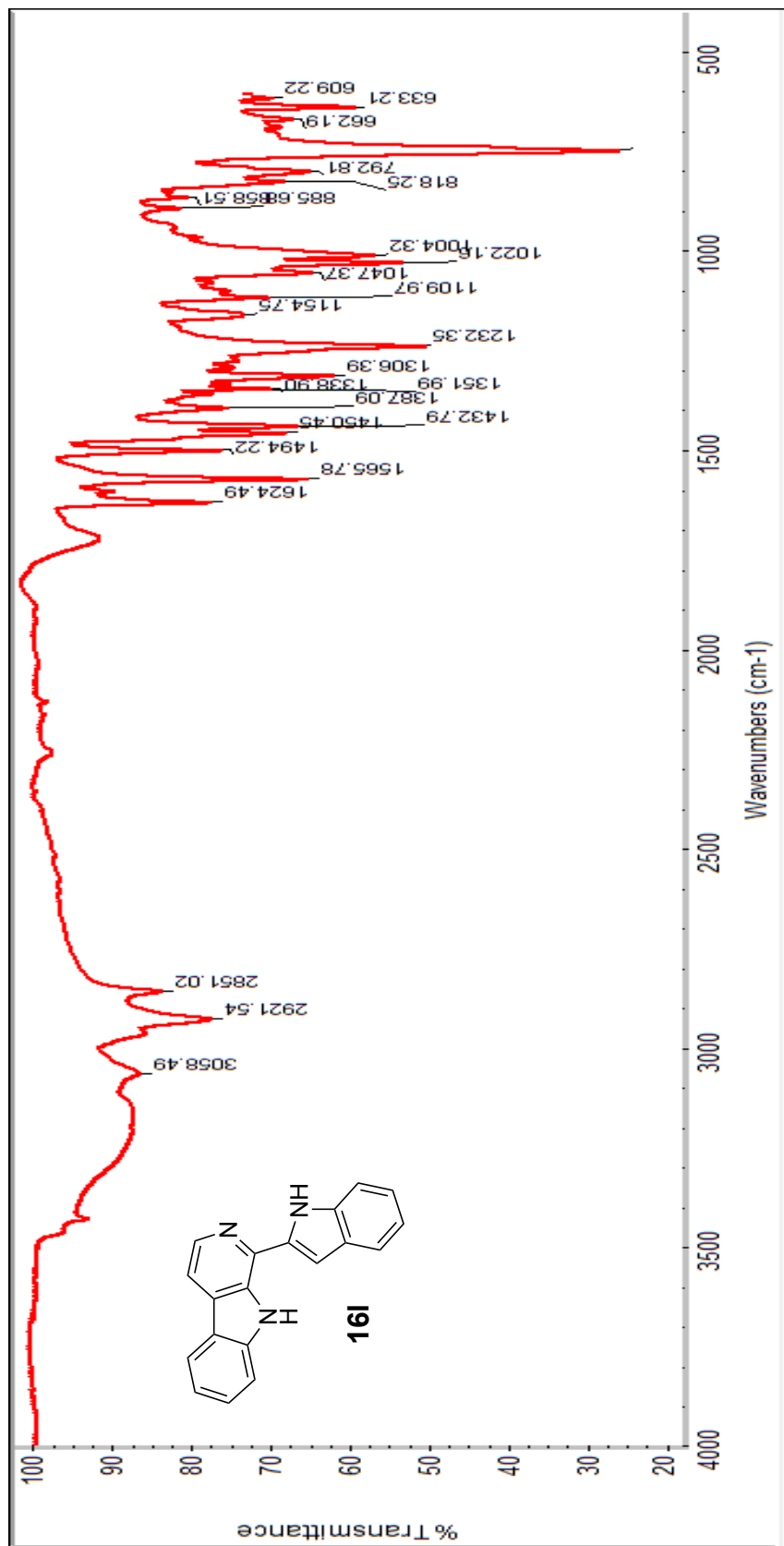


Figure S64.  $^1\text{H}$  NMR of **17a**:

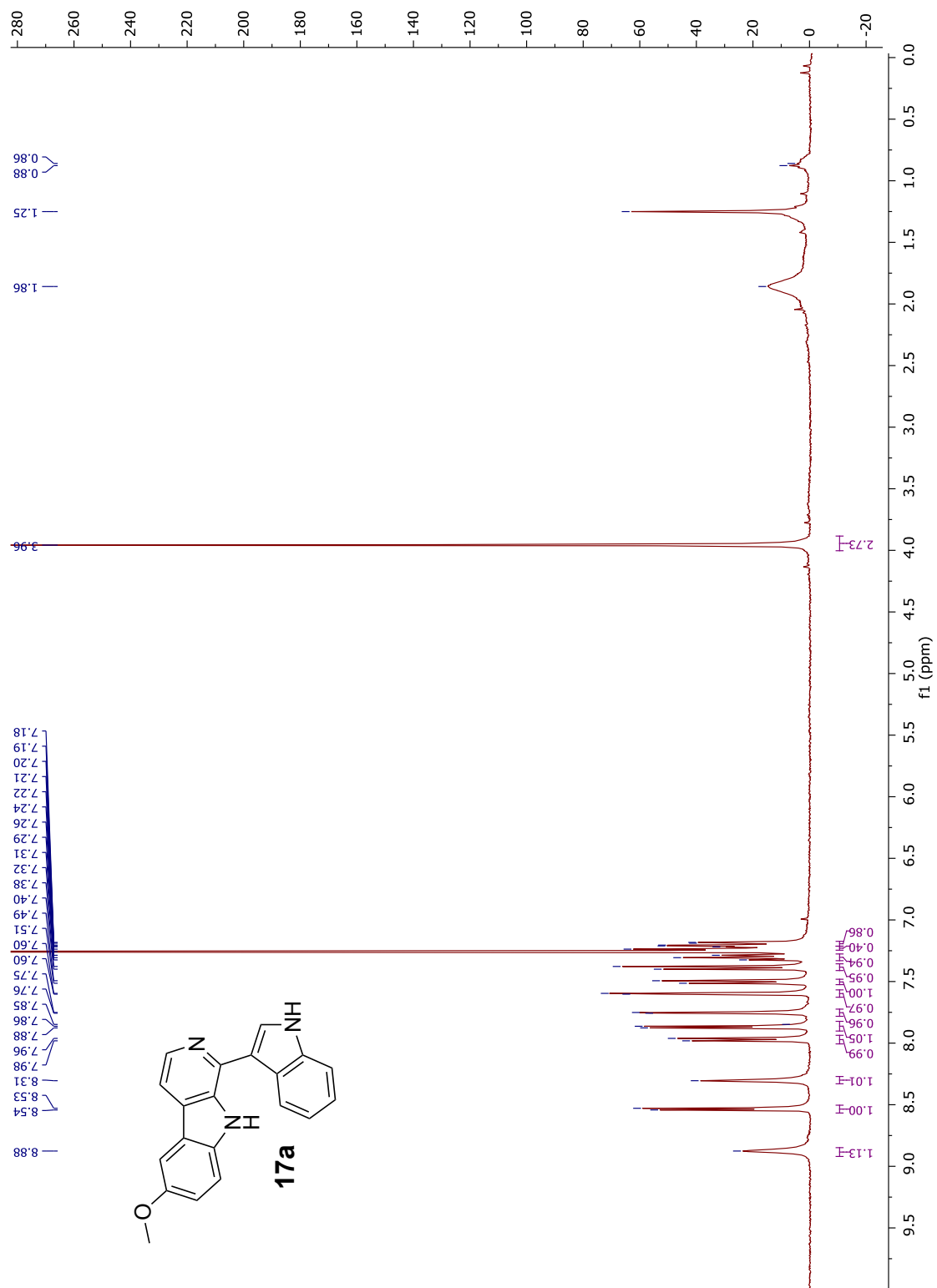


Figure S65.  $^{13}\text{C}$  NMR of **17a**:

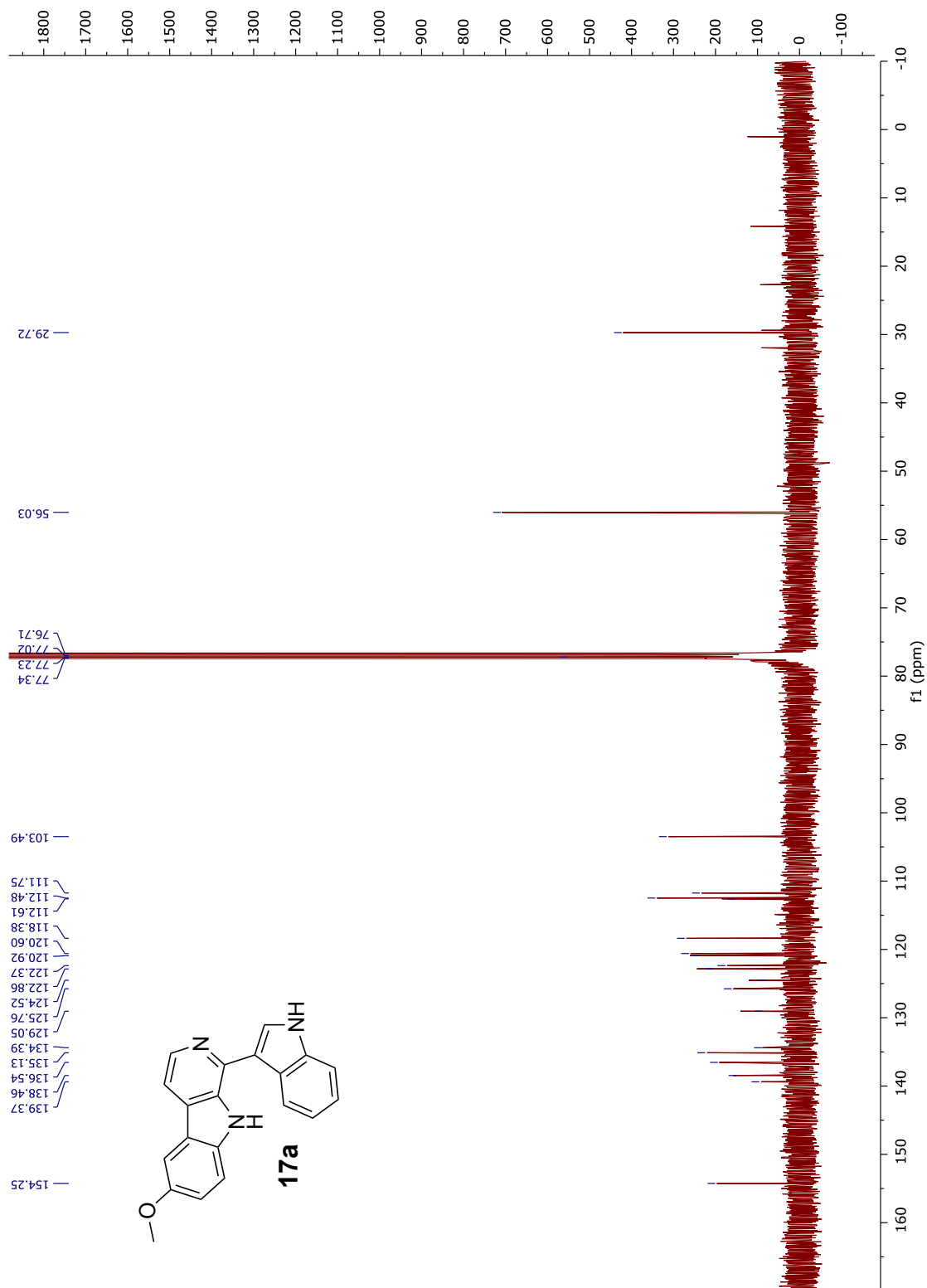


Figure S66. IR of **17a**:

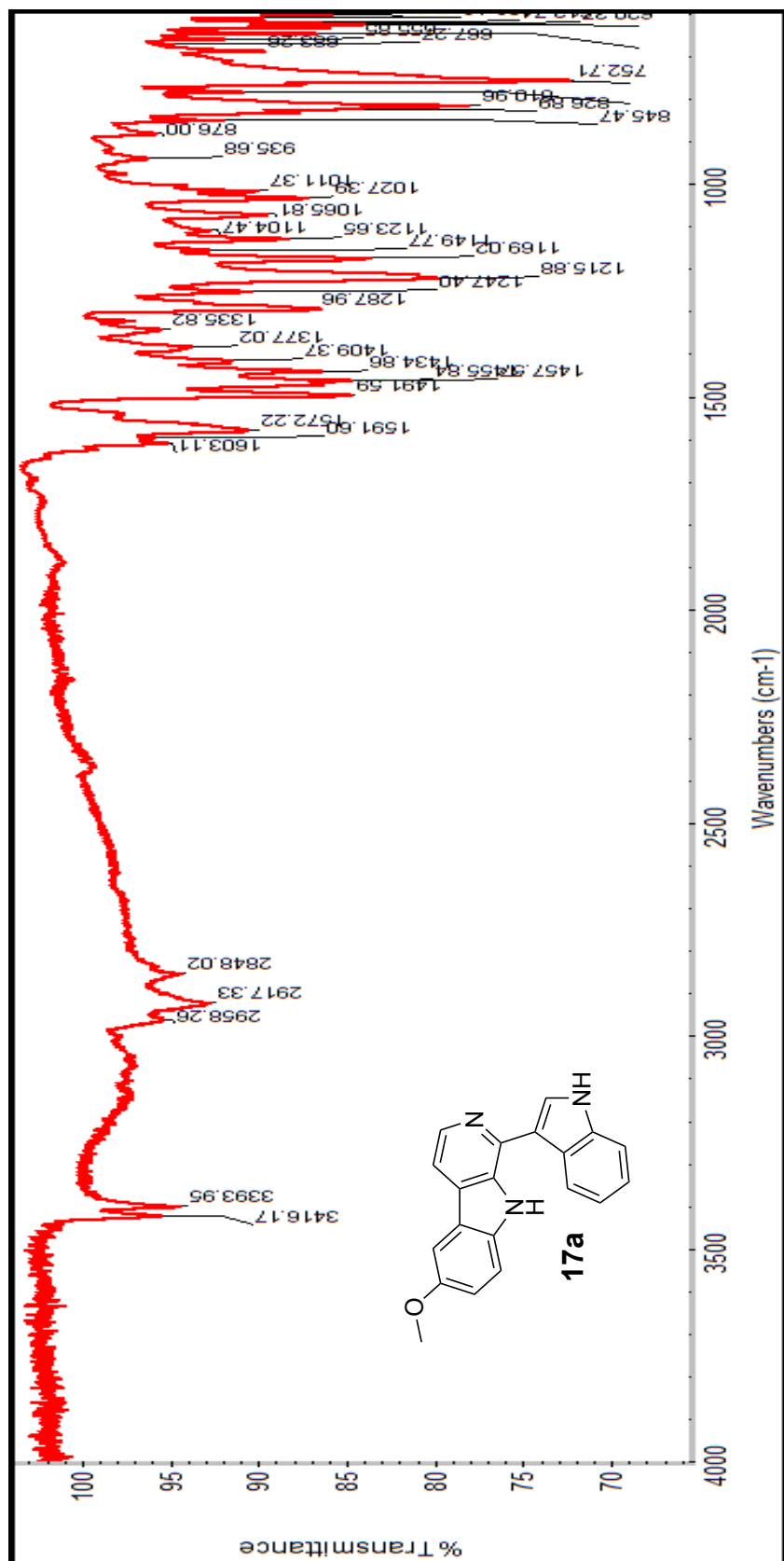


Figure S67.  $^1\text{H}$  NMR of **18a**:

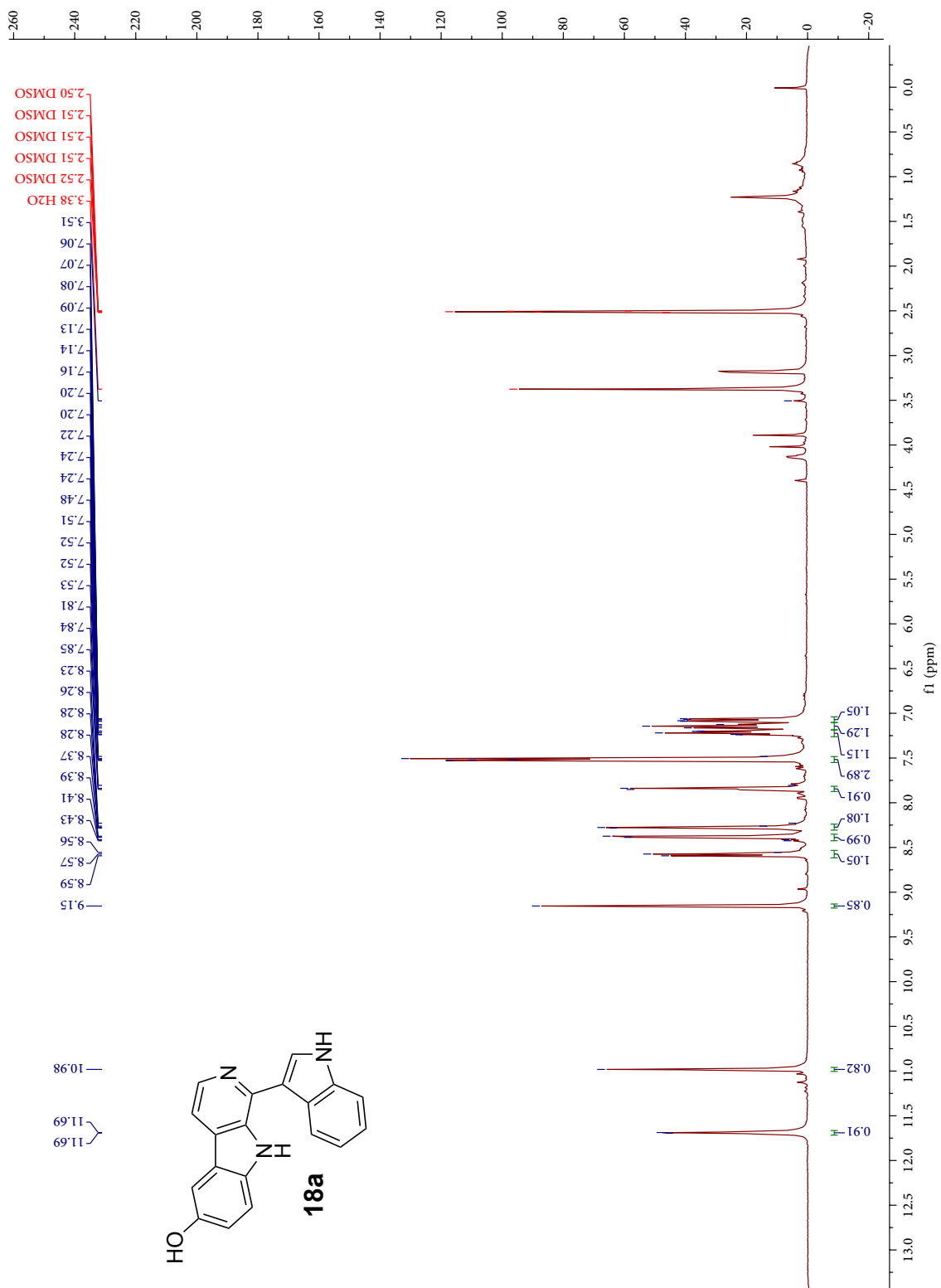


Figure S68.  $^{13}\text{C}$  NMR of **18a**:

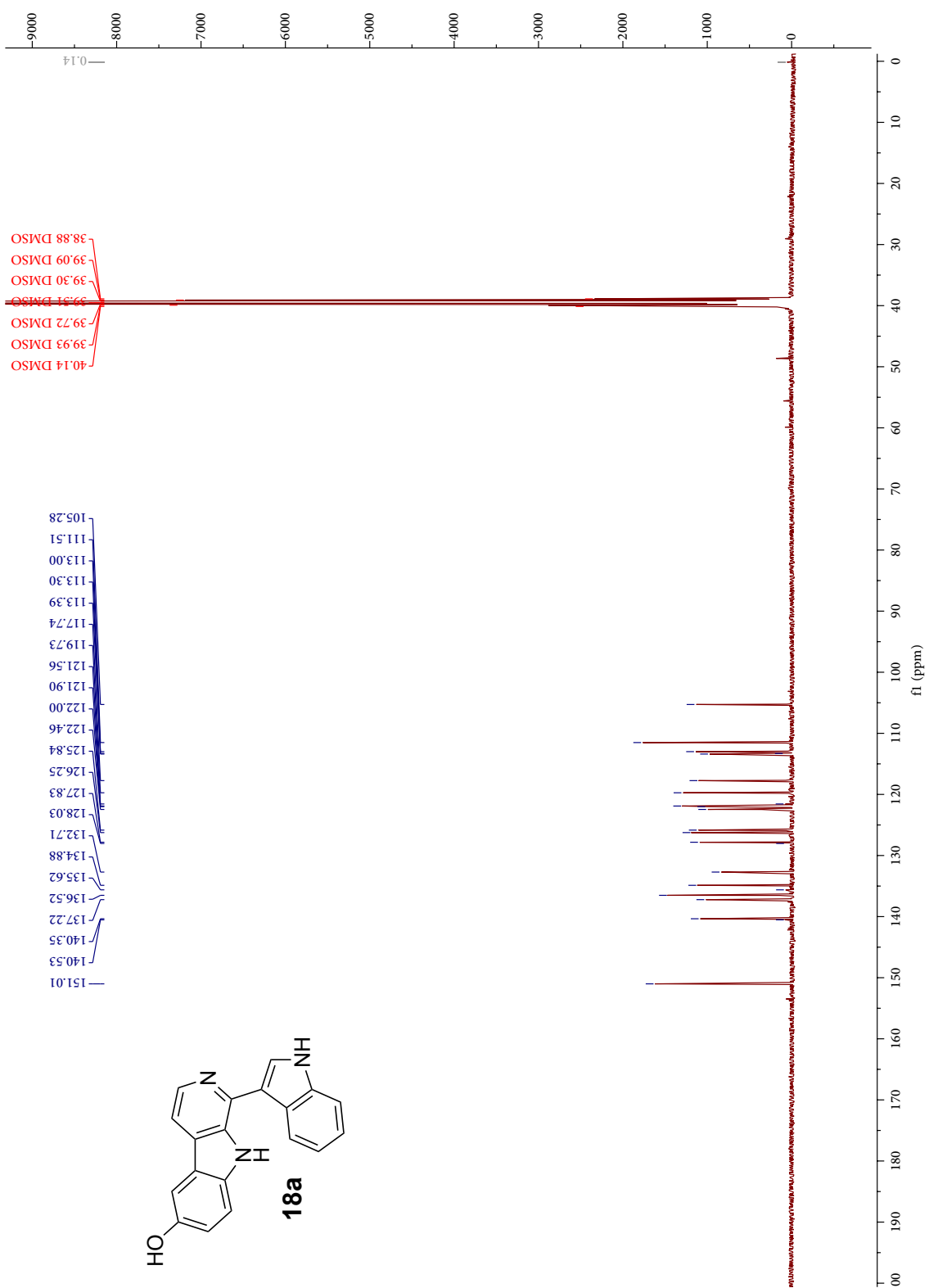
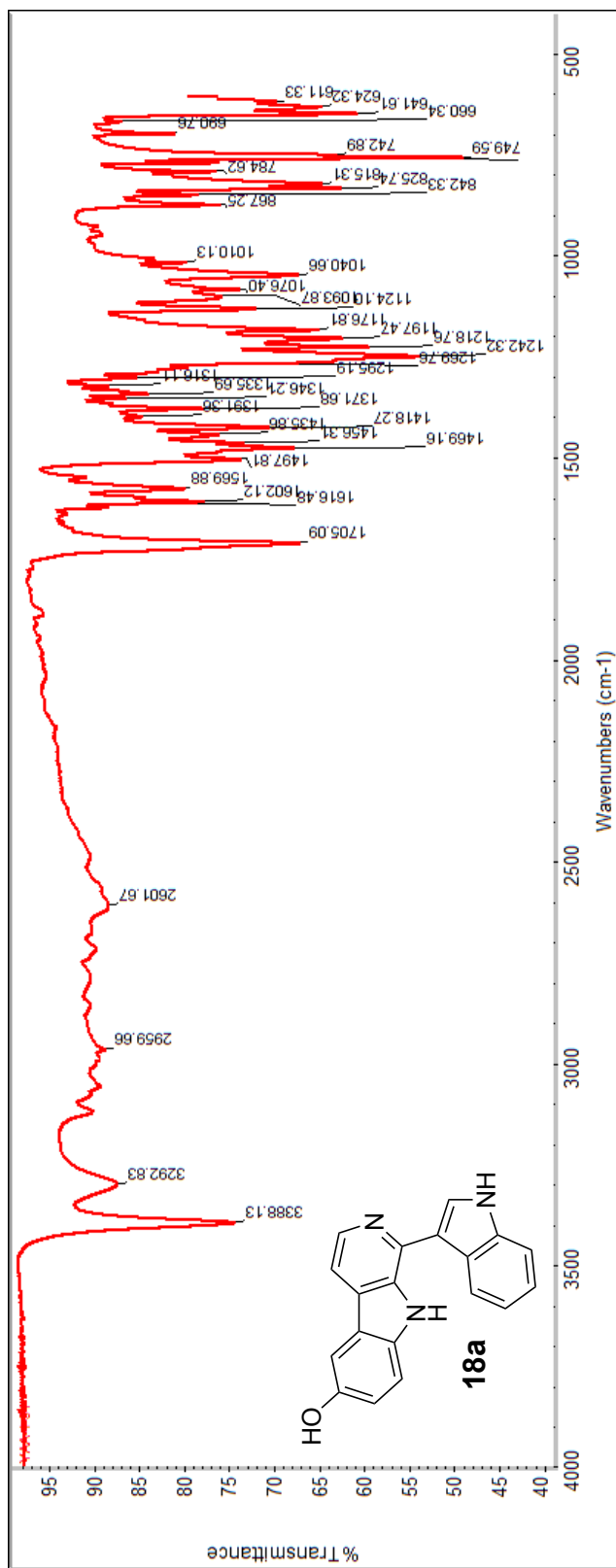


Figure S69. IR of **18a**:



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