Supporting Information

Enzymatic Synthesis of Health-beneficial Oligoindoles by Peroxidase

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1. General and materials

1.1 Solvents and Reagents

Solvents for HPLC (high performance liquid chromatography) and LC-HR/MS (liquid chromatography coupled with high-resolution mass spectrometry) analysis, such as acetonitrile and methanol, were purchased from Merck in a purity of over 99% (HPLC or LC-MS-grade). Water was purified and deionized using a Milli-Q water treatment system. Horseradish peroxidase (HRP) was purchased from Aladdin (product no. H597642, ≥240 units/mg dry weight) and used for all experiments presented. Other chemicals, solvents and reagents were purchased from commercial suppliers (Aladdin, Bide Pharmatech, Yuanye Bio-Technology, Sigma Aldrich) and used as received unless otherwise indicated.

1.2 Chromatography

Thin-layer chromatography (TLC) was performed on precoated plates of silica gel F254 (Kangyexin Medicinal) with UV detection at 254 and 365 nm. Column chromatography was performed on 200-300 mesh silica gel (Ding kang). HPLC analysis was performed on an Agilent 1260 Infinity II system consisting of a 1260 Vialsampler, a 1260 Quat Pump VL and a 1260 DAD WR detector. The system was controlled by Agilent Lab software. A reversed-phase column (XBridge C18 column, 4.6 × 250 mm, 5 μm) was used with the following solvents: A = H_2O + 0.1% formic acid, B = acetonitrile. The separation method consisted of the following gradient system: 30-60% (B) in 5 minutes, 60% (B) from 5→10 min, 60-95% (B) from 10→15 min, 95% (B) from 15→20 min, and then re-equilibration at 30% (B), with a flow rate of 0.8 mL/min. Eluting compounds were monitored at 254 nm or 280 nm with additional detection of UV-VIS (190–600 nm) by a diode array detector (DAD).

1.3 LC-HR/MS

For high resolution mass spectrometry (HR/MS) after HPLC separation, an Agilent HPLC consisting of a 1290 Vialsampler and a 1290 High Speed Pump was used. This was coupled to a 6546 Accurate-Mass spectrometer with ESI source and Q-TOF mass analyzer manufactured by Agilent. Experiments were carried out in positive ionization mode. The electrospray source was set to 3.5 kV and 350 °C. The following parameters were used: solvents: A = H_2O + 0.1% formic acid, B = acetonitrile; separation method I (for Figs 3A, 3B, S1, S3, and S4A): 0–13 min: 10–100% (B), 13–20 min: 100% (B), 20–20.5 min: 100–10% (B), 20.5–23 min: 10% (B); flow rate: 0.3 mL/min;

separation method II (for Figs 4A, 4B, 4C, S6, S7, and S8) : 0–5 min: 10% (B), 5–25 min: 10–95% (B), 25–30 min: 95% (B), 30–31 min: 95–10% (B), 31–33 min: 10% (B) column: Agilent InfinityLab Poroshell 120 SB-C8, 4.6 × 100 mm, 2.7 μm (in column oven: 35 °C). The MS data were acquired and processed using Agilent MassHunter Workstation.

1.4 NMR Spectroscopy

All NMR spectra were acquired in acetone-d_6 (unless stated otherwise) on a Bruker AV-500 spectrometer using TMS as an internal standard with ^{1}H and ^{13}C nuclei observed at 500 and 125 MHz, respectively. The chemical shift was recorded relative to the solvent acetone-d_6 (δ_H 2.05 and δ_C 29.8). The coupling constants J are given in Hertz [Hz] and determined assuming first-order spin-spin coupling. The following abbreviations were used for the allocation of signal multiplicities: s – singlet, br – broad singlet, d – doublet, dd – double doublet, dt – double triplet, t – triplet, q – quartet, m – multiplet, or a combination thereof.

1.5 Preparation of HPLC calibration curves[1]

The compounds synthesized in the work were used to prepare standard solutions for HPLC calibration curves in this study. Above standards were resolved in MeCN-H_2O (v:v = 1:1) to provide a series samples in 1, 0.5, 0.25, 0.1, 0.05, 0.02, and 0.01 mM. Each solution was then analyzed by HPLC as described above. A calibration curve was prepared by taking the average peak area at each concentration plotted against the concentration value. Standard linear-regression fitting was applied with the y-intercept set to 0.

2. HRP-facilitated coupling reaction for generating diindoles

General method: In a glass vial (5 mL) equipped with a magnetic stirring bar, IAA (14.0 mg, 0.08 mmol, 1 equiv), indole (12.2 mg, 0.094 mmol, 1.3 equiv), and H_2O_2 (30%, w/v, 2.0 equiv) were suspended in the mixture solvent of MeCN (300 μL) and PBS (pH = 5.5, 0.1 M, 3000 μL). The vessel was purged with N_2 for 3 times. Thereafter, 150 μL HRP solution (240 U/mg, 4 mg dissolved in 1 mL PBS prior to use) was added slowly while stirring. The reaction mixture was stirred for 2 h at room temperature. Then ethyl acetate (3 mL) was added and centrifuged at 3500 x g for 10 minutes. The organic layer was evaporated on a rotary evaporator under reduced pressure. On the one hand, the crude product was diluted with 50% MeCN-H_2O solution and subjected to

HPLC analysis, and the yield was calculated by referencing the peak area to an HPLC calibration curve. On the other hand, the crude product was purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 8:1) to give DIM (**1**) in 80% (15.7 mg). ^{1}H NMR δ 9.90 (br, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.14-7.04 (m, 4H), 6.98 (dt, J = 7.8, 1.1 Hz, 2H) and 4.24 (s, 2H). ^{13}C NMR δ 137.9, 128.6, 123.5, 121.9, 119.7, 119.2, 115.9, 112.0 and 21.9. HR-MS (ESI, positive mode) exact mass calculated for $C_{17}H_{14}N_2$ $[M+H]^+$: 247.1230; found: 247.1235.

3-((1H-Indole-3-yl)methyl)-4-methyl-1H-indole (**1a**) was obtained in 69% (17.9 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 8:1). ^{1}H NMR δ 9.89 (br, 2H), 7.60 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.14-7.04 (m, 1H), 7.04-6.92 (m, 3H), 6.86 (s, 1H), 6.71 (d, J = 7.0 Hz, 1H), 4.38 (s, 2H) and 2.58 (s, 3H). ^{13}C NMR δ 138.4, 138.0, 131.3, 128.4, 127.2, 124.1, 123.8, 122.1, 122.0, 120.9, 119.6, 119.3, 117.3, 116.2, 112.1, 110.1, 24.1 and 20.3. HR-MS (ESI, positive mode) exact mass calculated for $C_{18}H_{17}N_2$ $[M+H]^+$: 261.1386; found: 261.1390.

3-((1H-Indole-3-yl)methyl)-5-methyl-1H-indole (**1b**) was obtained in 76% (19.8 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 8:1). ^{1}H NMR δ 9.89 (br, 1H), 9.76 (br, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.41-7.34 (m, 2H), 7.26 (d, J = 8.2 Hz, 1H), 7.13-7.01 (m, 3H), 6.98 (dt, J = 7.0, 1.0 Hz, 1H), 6.92 (dd, J = 8.2, 1.6 Hz, 1H), 4.20 (s, 2H) and 2.37 (s, 3H). ^{13}C NMR δ 137.9, 136.3, 128.9, 128.7, 127.9, 123.6, 123.6, 123.5, 121.9, 119.7, 119.4, 119.2, 116.0, 115.3, 112.0, 111.8, 21.9 and 21.7. HR-MS (ESI, positive mode) exact mass calculated for $C_{18}H_{17}N_2$ $[M+H]^+$: 261.1386; found: 261.1390.

3-((1H-Indole-3-yl)methyl)-6-methyl-1H-indole (**1c**) was obtained in 63% (16.4 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 8:1). ^{1}H NMR δ 9.89 (br, 1H), 9.73 (br, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.17 (s, 1H), 7.13-7.04 (m, 2H), 7.02 (s, 1H), 7.00-6.93 (m, 1H), 6.82 (d, J = 6.4 Hz, 1H), 4.20 (s, 2H) and 2.39 (s, 3H). ^{13}C NMR δ 138.3, 137.9, 131.2, 128.7, 126.7, 123.4, 122.8, 121.9, 121.0, 119.7, 119.5, 119.2, 116.0, 115.7, 112.0, 112.0, 22.0 and 21.8. HR-MS (ESI, positive mode) exact mass calculated for $C_{18}H_{17}N_2$ $[M+H]^+$: 261.1386; found: 261.1387.

3-((1H-Indole-3-yl)methyl)-7-methyl-1H-indole (**1d**) was obtained in 78% (20.3 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 8:1). ^{1}H NMR

δ 9.90 (br, 1H), 9.86 (br, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.47-7.40 (m, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.22-7.04 (m, 3H), 6.97 (t, J = 7.5 Hz, 1H), 6.93-6.86 (m, 2H), 4.22 (s, 2H) and 2.47 (s, 3H). ^{13}C NMR δ 137.9, 137.3, 128.7, 128.3, 123.5, 123.2, 122.6, 121.9, 121.1, 119.7, 119.5, 119.2, 117.5, 116.3, 115.9, 112.0, 22.0 and 16.9. HR-MS (ESI, positive mode) exact mass calculated for $C_{18}H_{17}N_2$ $[M+H]^+$: 261.1386; found: 261.1384.

3-((1H-Indole-3-yl)methyl)-2-methyl-1H-indole (**1e**) was obtained in 69% (17.9 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 8:1). ^{1}H NMR δ 9.85 (br, 2H), 7.59 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.00-6.85 (m, 4H), 4.15 (s, 2H) and 2.44 (s, 3H). ^{13}C NMR δ 137.9, 136.7, 132.2, 130.0, 128.5, 123.3, 121.9, 120.9, 119.5, 119.2, 119.1, 119.0, 116.3, 112.0, 111.0, 110.8, 20.6 and 11.7. HR-MS (ESI, positive mode) exact mass calculated for $C_{18}H_{17}N_2$ $[M+H]^+$: 261.1386; found: 261.1390.

2-((1H-Indole-3-yl)methyl)-3-methyl-1H-indole (**1f**) was obtained in 42% (10.9 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 8:1). ^{1}H NMR δ 10.02 (br, 1H), 9.62 (br, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.3 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.13 (s, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.01-6.93 (m, 3H), 4.23 (s, 2H) and 2.35 (s, 3H). ^{13}C NMR δ 137.8, 136.7, 135.3, 130.4, 128.3, 123.9, 122.2, 121.1, 119.5, 119.4, 119.1, 118.5, 113.6, 112.1, 111.2, 106.4, 22.8 and 8.8. HR-MS (ESI, positive mode) exact mass calculated for $C_{18}H_{17}N_2$ $[M+H]^+$: 261.1386; found: 261.1391.

3-((1H-Indole-3-yl)methyl)-5-nitro-1H-indole (**1g**) was obtained in 15% (4.4 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 3:1). ^{1}H NMR δ 10.66 (br, 1H), 10.00 (br, 1H), 8.57 (s, 1H), 8.01 (dd, J = 9.0, 2.3 Hz, 1H), 7.60-7.52 (m, 2H), 7.42-7.35 (m, 2H), 7.21 (s, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.97 (t, J = 7.9 Hz, 1H) and 4.33 (s, 2H).^{13}C NMR δ 141.9, 140.9, 138.0, 128.5, 127.9, 127.3, 123.6, 122.1, 119.6, 119.4, 118.9, 117.4, 116.9, 115.0, 112.4, 112.2, 21.7. HR-MS (ESI, positive mode) exact mass calculated for $C_{17}H_{14}N_3O_2$ $[M+H]^+$: 292.1081; found: 292.1083.

3-((1H-Indole-3-yl)methyl)-4-fluoro-1H-indole (**1h**) was obtained in 53% (14.0 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 6:1). ^{1}H NMR δ 10.16 (br, 1H), 9.93 (br, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H), 7.13 (s, 1H), 7.10-6.93 (m, 4H), 6.72-6.64 (m, 1H) and 4.33 (s, 2H). ^{13}C NMR δ 158.3 (d,

J = 244.3 Hz), 140.7 (d, *J* = 12.3 Hz), 137.9, 128.5, 124.0, 123.5, 122.5 (d, *J* = 7.7 Hz), 121.9, 119.6, 119.3, 117.0 (d, *J* = 20.0 Hz), 116.1, 114.9 (d, *J* = 3.6 Hz), 112.1, 108.6 (d, *J* = 3.5 Hz), 104.3 (d, *J* = 19.5 Hz) and 23.0 (d, *J* = 2.1 Hz). HR-MS (ESI, positive mode) exact mass calculated for $C_{17}H_{14}FN_2$ $[M+H]^+$: 265.1136; found: 265.1139.

3-((1H-Indole-3-yl)methyl)-5-fluoro-1H-indole (**1i**) was obtained in 49% (12.9 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 6:1). ^{1}H NMR δ 10.02 (br, 1H), 9.94 (br, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.41-7.32 (m, 2H), 7.31-7.19 (m, 2H), 7.15 (s, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.86 (dt, *J* = 9.2, 2.4 Hz, 1H) and 4.21 (s, 2H). ^{13}C NMR δ 158.2 (d, *J* = 231.3 Hz), 137.9, 134.5, 128.9 (d, *J* = 9.6 Hz), 128.6, 125.6, 123.5, 122.0, 119.7, 119.3, 116.1 (d, *J* = 4.8 Hz), 115.5, 112.9 (d, *J* = 9.9 Hz), 112.1, 109.9 (d, *J* = 26.4 Hz), 104.3 (d, *J* = 23.3 Hz) and 21.9. HR-MS (ESI, positive mode) exact mass calculated for $C_{17}H_{14}FN_2$ $[M+H]^+$: 265.1136; found: 265.1140.

3-((1H-Indole-3-yl)methyl)-5-methoxy-1H-indole (**1j**) was obtained in 44% (12.1 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 3:1). ^{1}H NMR δ 9.90 (br, 1H), 9.75 (br, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 8.9 Hz, 1H), 7.14-7.04 (m, 4H), 6.98 (dt, *J* = 7.0, 0.9 Hz, 1H), 6.74 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.20 (s, 2H) and 3.74 (s, 3H). ^{13}C NMR δ 154.5, 137.9, 133.0, 129.0, 128.7, 124.2, 123.5, 121.9, 119.7, 119.2, 115.9, 115.6, 112.6, 112.1, 112.0, 101.7, 55.8 and 21.9. HR-MS (ESI, positive mode) exact mass calculated for $C_{18}H_{17}N_2O$ $[M+H]^+$: 277.1335; found: 277.1340.

3-((1H-Indole-3-yl)methyl)-1-methyl-1H-indole (**1k**) was obtained in 65% (16.9 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 8:1). ^{1}H NMR δ 9.92 (br, 1H), 7.62-7.55 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.17-7.04 (m, 3H), 7.03-6.92 (m, 3H), 4.21 (s, 2H) and 3.72 (s, 3H). ^{13}C NMR δ 138.3, 137.9, 129.0, 128.6, 127.9, 123.5, 122.0, 121.9, 119.9, 119.7, 119.2, 119.1, 115.8, 115.1, 112.1, 110.0, 32.6 and 21.7. HR-MS (ESI, positive mode) exact mass calculated for $C_{18}H_{17}N_2$ $[M+H]^+$: 261.1392; found: 261.1395.

3-((1H-Indole-3-yl)methyl)-1-ethyl-1H-indole (**1l**) was obtained in 69% (18.9 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 20:1 to 10:1). ^{1}H NMR δ 9.94 (br, 1H), 7.57 (dd, *J* = 8.0, 3.4 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.14-7.03 (m, 4H), 6.96 (dt, *J* = 7.5, 4.2 Hz, 2H), 4.21 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H) and 1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR δ 137.9, 137.2, 129.2, 128.6, 126.2, 123.5, 122.0, 121.8, 120.0, 119.7, 119.2, 119.1, 115.8, 115.2,

112.1, 110.1, 41.1, 21.8 and 15.9. HR-MS (ESI, positive mode) exact mass calculated for $C_{19}H_{19}N_2$ $[M+H]^+$: 275.1543; found: 275.1542.

3-((1H-Indole-3-yl)methyl)-1-benzyl-1H-indole (**1m**) was obtained in 70% (23.5 mg) being purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 20:1 to 10:1). ^{1}H NMR δ 9.92 (s, 1H), 7.61 (dd, J = 13.3, 8.0 Hz, 2H), 7.39 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.30-7.20 (m, 3H), 7.17-7.07 (m, 6H), 7.00 (dt, J = 7.5, 3.0 Hz, 2H), 5.31 (s, 2H) and 4.26 (s, 2H). ^{13}C NMR δ 139.5, 137.9, 137.7, 129.3, 129.3, 128.6, 128.0, 127.6, 127.5, 123.5, 122.1, 122.0, 120.1, 119.8, 119.4, 119.2, 115.6, 115.6, 112.1, 110.6, 50.1 and 21.9. HR-MS (ESI, positive mode) exact mass calculated for $C_{24}H_{21}N_2$ $[M+H]^+$: 337.1699; found: 337.1701.

3. HRP-catalyzed reaction paradigm for constructing complex oligoindoles

3.1 The biocatalytic procedure for LTr1

To a 50 mL round bottom flask containing anhydrous dichloromethane (12 mL) was added indole (**6**, 234.3 mg, 2 mmol, 2 equiv.) and $Sc(OTf)_3$ (49.2 mg, 0.1 mmol, 0.1 equiv). Indole-2-carbinol (**9**, 147.2 mg, 1 mmol, 1 equiv.) was added slowly under ice bath. The resulting mixture was stirred for 6 h and then poured into ice-water. Then the reaction mixture was diluted with dichloromethane and filtered. After extracted with dichloromethane twice, the combined organic portions were washed with brine and then dried with Na_2SO_4. The organic portion was evaporated on a rotary evaporator under reduced pressure and the crude product was purified by flash column chromatography (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 6:1) to afford 2,3'-diindolylmethane (**8**, 155.2 mg, 63%). ^{1}H NMR ($CDCl_3$) δ 7.99 (br, 1H), 7.85 (br, 1H), 7.61-7.49 (m, 2H), 7.39 (d, J = 8.1 Hz, 1H), 7.30-7.17 (m, 2H), 7.13-7.01 (m, 4H), 6.42 (s, 1H) and 4.29 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 138.4, 136.5, 136.0, 129.0, 127.4, 122.8, 122.5, 121.1, 120.0, 119.9, 119.7, 119.2, 112.9, 111.3, 110.6, 100.2 and 24.6. HR-MS (ESI, positive mode) exact mass calculated for $C_{17}H_{14}N_2$ $[M+H]^+$: 247.1230; found: 247.1228.

The method for the LTr1 (**2**) synthesis was described in **section 2**, but with the reaction time prolonged to 4 hours. Under the HRP catalysis, IAA (**5**, 14.0 mg, 0.08 mmol, 1 equiv.) and **8** (23.1 mg, 0.094 mmol, 1.3 equiv.) coupled into LTr1 in 74% (22.2 mg). ^{1}H NMR δ 10.03 (br, 1H), 9.88 (br, 1H), 9.68 (br, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.1 Hz, 1H), 7.13 (s, 1H), 7.10-7.04 (m, 2H), 7.00-6.93 (m,

3H), 6.93-6.87 (m, 2H) and 4.34 (d, J = 7.3 Hz, 4H). ^{13}C NMR δ 137.9, 137.8, 136.8, 135.7, 130.0, 128.6, 128.4, 124.1, 123.5, 122.2, 121.9, 121.1, 119.7, 119.6, 119.5, 119.2, 119.2, 119.1, 116.4, 113.5, 112.0, 112.0, 111.4, 110.6, 23.0 and 20.8. HR-MS (ESI, positive mode) exact mass calculated for $C_{26}H_{21}N_3$ $[M+H]^+$: 376.1808; found: 376.1805.

3.2 The biocatalytic procedure for LTe2

Following the synthesis procedure of **8** (vide supra), compound **10** was prepared from **8** (123.2 mg, 0.5 mmol, 2 equiv) and indole-2-carbinol (**9**, 36.8 mg, 0.25 mmol, 1 equiv). And 52% (48.8 mg) of **10** was obtained by purified with flash column chromatography (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 4:1). ^{1}H NMR δ 10.10 (br, 1H), 9.88 (br, 1H), 9.56 (br, 1H), 7.44 (dd, J = 8.0, 4.8 Hz, 2H), 7.43-7.37 (m, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.19-7.15 (m, 2H), 7.09 (t, J = 7.6 Hz, 1H), 7.01-6.95 (m, 2H), 6.95-6.88 (m, 3H), 6.24 (s, 1H) and 4.35 (d, J = 13.5 Hz, 4H). ^{13}C NMR δ 140.5, 137.8, 137.4, 136.7, 136.5, 129.9, 129.8, 128.2, 124.2, 122.3, 121.3, 121.0, 120.1, 119.6, 119.6, 119.5, 119.4, 119.0, 113.4, 112.2, 111.4, 111.4, 108.4, 100.1, 23.9 and 23.0. HR-MS (ESI, positive mode) exact mass calculated for $C_{26}H_{21}N_3$ $[M+H]^+$: 376.1808; found: 376.1807.

In the enzymatic step, IAA (**5**, 14.0 mg, 0.08 mmol, 1 equiv), **10** (39.0 mg, 0.094 mmol, 1.3 equiv), and H_2O_2 (30%, w/v, 2 equiv) were suspended in the mixture solvent of MeCN (600 μL) and PBS (pH = 5.5, 0.1 M, 3000 μL). The vessel was purged with N_2 for 3 times. Thereafter, 150 μL HRP solution (240 U/mg, 4 mg dissolved in 1 mL PBS prior to use) was added slowly while stirring. The reaction mixture was stirred for 8 h at room temperature. And then, ethyl acetate (3 mL) was added and centrifuged at 3500 x g for 10 minutes. The organic layer was evaporated on a rotary evaporator under reduced pressure. On the one hand, the crude product was diluted with 50% MeCN-H_2O solution and subjected to HPLC analysis. The conversion of product was calculated by referencing the peak area to an HPLC calibration curve. On the other hand, the crude product was purified by column (200~300 mesh silica gel, petroleum ether/ethyl acetate = 10:1 to 4:1) to give LTe2 (**4**) in 42% (16.9 mg). ^{1}H NMR δ 10.05 (br, 1H), 9.84 (br, 2H), 9.07 (br, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.39-7.33 (m, 3H), 7.23 (d, J = 8.7 Hz, 2H), 7.14 (s, 1H), 7.11-7.04 (m, 3H), 7.01-6.84 (m, 6H), 6.79 (t, J = 7.3 Hz, 1H), 4.39 (s, 2H), 4.35 (s, 2H) and 4.27 (s, 2H). ^{13}C NMR δ 137.9, 137.8, 136.7, 136.7, 135.9, 130.1, 129.8, 128.7, 128.2, 124.2, 123.5, 122.3,

121.9, 121.3, 120.9, 119.7, 119.7, 119.5, 119.4, 119.2, 119.1, 119.0, 116.4, 113.5, 112.2, 112.0, 111.4, 110.3, 108.3, 23.1, 22.0 and 20.8. HR-MS (ESI, positive mode) exact mass calculated for $C_{35}H_{29}N_4$ $[M+H]^+$: 505.2387; found: 505.2390.

3.3 The biocatalytic procedure for LTr3

To a 15 mL Schlenk pressure tube equipped with a magnetic stir bar was added the indole-3-methanol (I3C, **7**, 588 mg, 4 mmol, 1 equiv), indole (**6**, 936 mg, 8 mmol, 2 equiv), and 1-ethyl-3-methylimidazolium chloride ([EMIm][Cl], 470 mg, 3.2 mmol, 0.8 eq). The mixture was heated to 80 °C for 10 min. After that, the tube was sealed and heated to 120 °C for other 1.5 h. The reaction mixture was cooled to room temperature, extracted with ethyl acetate twice. The combined organic portions were washed with brine and then dried with Na_2SO_4.The organic portion was evaporated on a rotary evaporator under reduced pressure and the crude product was purified by flash column chromatography (200~300 mesh silica gel, petroleum ether/EtOAc/dichloromethane = 15/1/1) to afford the desired product **11** in 63% (620.7 mg). ^{1}H NMR δ 10.23 (br, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.43-7.38 (m, 2H), 7.35 (d, J = 3.1 Hz, 1H), 7.11 (dt, J = 14.6, 7.7 Hz, 2H), 6.99 (dt, J = 15.2, 7.5 Hz, 2H), 6.42 (d, J = 3.2 Hz, 1H) and 5.56 (s, 2H). ^{13}C NMR δ 137.8, 137.2, 129.8, 129.0, 127.6, 125.1, 122.5, 121.8, 121.4, 120.0, 119.8, 119.5, 112.6, 112.4, 110.7, 101.4 and 42.3. HR-MS (ESI, positive mode) exact mass calculated for $C_{17}H_{14}N_2$ $[M+H]^+$: 247.1230; found: 247.1232.

The biocatalytic synthesis procedure of LTr3 was identical with LTr1, and 72% (21.5 mg) yield of target product was obtained by the coupling of compound **11** (25.5 mg, 0.094 mmol, 1.3 equiv) and IAA (**5**, 14.0 mg, 0.068 mmol, 1 equiv). ^{1}H NMR δ 10.17 (br, 1H), 9.89 (br, 1H), 7.60-7.51 (m, 3H), 7.47 (d, J = 8.0 Hz, 1H), 7.41-7.32 (m, 3H), 7.19 (s, 1H), 7.12-7.02 (m, 4H), 7.00-6.91 (m, 3H), 5.49 (s, 2H) and 4.19 (s, 2H). ^{13}C NMR δ 137.9, 137.8, 137.7, 129.3, 128.6, 127.6, 127.2, 124.8, 123.4, 122.4, 121.9, 121.8, 120.0, 119.9, 119.8, 119.6, 119.2, 119.1, 115.8, 114.9, 112.9, 112.3, 112.0, 110.6, 42.3 and 21.9. HR-MS (ESI, positive mode) exact mass calculated for $C_{26}H_{21}N_3$ $[M+H]^+$: 376.1808; found: 376.1805.

4. Control experiments

IAA (**5**, 0.6 mmol, 1 equiv) was suspended in the mixture solvent of MeCN (2 mL) and PBS (pH = 5.5, 0.1 M, 20 mL). After the injection of H_2O_2 (1.2 mmol, 2 equiv), the vessel was purged with N_2 for 3 times. Thereafter, HRP (12 mg, 240 U/mg) was added slowly while stirring. The

reaction mixture was stirred for 8 h at room temperature. The workup process was identical with the general method described in **section 2**, and the crude product was purified with preparative reverse phase-HPLC. The IAA-contained transformation provided **15** (5.2 mg) and **16** (7.3 mg) in 6% and 8% yield. Similarly, indole (**6**, 1.2 mmol, 1 equiv), being suspended in the mixture solvent of MeCN (4 mL) and PBS (pH = 5.5, 0.1 M, 40 mL), was catalyzed by HRP (24 mg, 240 U/mg) and H_2O_2 (2.4 mmol, 2 equiv) to provide isatin (**17**, 3.5 mg, 2%), indole-3-one (**18**, 8.0 mg, 5%), compound **19** (16.0 mg, 11%) and **20** (4.4 mg, 3%).

Indole-3-carboxaldehyde (IAld, **15**): ^{1}H NMR δ 11.16 (br, 1H), 10.04 (s, 1H), 8.24 (d, J = 6.7 Hz, 1H), 8.20 (d, J = 3.2 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H) and 7.44-7.20 (m, 2H). ^{13}C NMR δ 185.5, 138.4, 138.2, 125.7, 124.7, 123.2, 122.4, 120.3 and 113.1. HR-MS (ESI, positive mode) exact mass calculated for C_9H_7NO $[M+H]^+$: 146.0601; found: 146.0600.

2-(Indol-3-ylmethyl)-1H-indole-3-acetic acid (**16**): ^{1}H NMR δ 10.59 (br, 1H), 10.03 (br, 1H), 9.76 (br, 1H), 7.59-7.49 (m, 2H), 7.38 (d, J = 8.2 Hz, 1H), 7.25-7.21 (m, 1H), 7.18 (s, 1H), 7.08 (t, J = 7.0 Hz, 1H), 7.03-6.90 (m, 3H), 4.31 (s, 2H) and 3.84 (s, 2H). ^{13}C NMR δ 173.5, 137.8, 137.2, 136.7, 129.8, 128.4, 124.3, 122.2, 121.4, 119.6, 119.5, 118.9, 113.0, 112.1, 111.5, 105.0, 30.5 and 22.9. HR-MS (ESI, positive mode) exact mass calculated for $C_{19}H_{16}N_2O_2$ $[M+H]^+$: 305.1285; found: 305.1288.

Isatin (**17**): ^{1}H NMR δ 9.97 (br, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H) and 7.03 (d, J = 7.9 Hz, 1H). ^{13}C NMR δ 184.8, 159.9, 151.6, 139.2, 125.5, 123.9, 119.1 and 113.2. HR-MS (ESI, positive mode) exact mass calculated for $C_8H_5NO_2$ $[M+H]^+$: 148.0394; found: 148.0399.

Indole-3-one (**18**, ca. 90%): ^{1}H NMR (DMSO-d_6) δ 7.42 (t, J = 9.0 Hz, 2H), 7.03 (s, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.70 (t, J = 7.4 Hz, 1H), 3.79 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 200.3, 163.2, 136.7, 123.4, 120.7, 117.2, 112.9, 53.8. Indol-3-ol (ca. 10%): ^{1}H NMR (DMSO-d_6, 10%) δ 10.15 (br, 1H), 8.33 (s, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.70 (t, J = 7.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 135.9, 133.7, 120.9, 119.9, 117.4, 111.3, 107.1. HR-MS (ESI, positive mode) exact mass calculated for C_8H_8NO $[M+H]^+$: 134.0600; found: 134.0602.

2,2-Bis(indol-3-yl)indoline-3-ones (**19**): ^{1}H NMR δ 10.17 (br, 2H), 7.56 (d, J = 7.7 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 2.6 Hz, 2H),

7.15 (s, 1H), 7.05 (t, J = 8.0 Hz, 3H), 6.85 (t, J = 7.6 Hz, 2H) and 6.80 (t, J = 7.4 Hz, 1H). ^{13}C NMR δ 201.4, 161.6, 138.4, 137.9, 127.1, 125.4, 124.9, 122.2, 121.8, 120.1, 119.5, 118.6, 116.0, 113.1, 112.3 and 69.0. HR-MS (ESI, positive mode) exact mass calculated for $C_{24}H_{17}N_3O$ $[M+H]^+$: 364.1445; found: 364.1440.

2,3'-Bisindole-3-one (**20**): ^{1}H NMR δ 12.17 (br, 1H), 8.52 (d, J = 2.8 Hz, 1H), 8.41 (dd, J = 6.7, 1.4 Hz, 1H), 7.60-7.52 (m, 3H), 7.36 (d, J = 7.6 Hz, 1H), 7.30-7.25 (m, 2H), and 7.19 (t, J = 7.4 Hz, 1H). ^{13}C NMR δ 195.7, 163.4, 158.5, 137.8, 137.3, 133.8, 126.8, 126.4, 124.9, 123.9, 123.0, 122.2, 121.1, 113.0, and 106.9. HR-MS (ESI, positive mode) exact mass calculated for $C_{16}H_{11}N_2O$ $[M+H]^+$: 247.0866; found: 247.0870.

5. Molecular docking[2]

The 2D structure of HRP was downloaded on the RCSB protein date bank using the HRP-C1A (PDB: 1H5A) structure. Ligand was downloaded on the pubchem molecule database. The docking was implemented using AutoDock Vina (version 1.1.2) with the center coordinates of the docking area set to (2.065, 3, 11.706). The number of grid points in each direction of X, Y and Z set to 28, 24 and 30, respectively. Docking processes was set to 32 and grid step size to 0.375. The rest of the parameters were used as the default values. The results with the highest binding energy were selected and visualized in PyMOL.

6. Indole- and IAA-coupling cascade reactions in gut bacteria

6.1 Strains and culture condition

As mentioned in our proceeding communication[3], all strains used in this work were available in our laboratory and stored at −80 ℃ as glycerol tubes prior to use. *Lactobacillus fermentum*, *L. murinus*, *L. acidophilus*, and *L. reuteri* were isolated from healthy individuals. *Escherichia coli* DH5α and BL21(DE3) strains were purchased from Vazyme (Nanjing, China) for plasmid construction and heterologous expression, respectively. Cultured at 37 ℃ for 24–48 h were *Lactobacillus* strains in de Man Rogosa Sharpe (MRS) medium (1 g/L peptone, 1 g/L beef extract, 4 g/L yeast extract, 20 g/L glucose, 5 g/L sodium acetate trihydrate, 1 g/L Tween 80, 2 g/L $K_2HPO_4{\cdot}3H_2O$, 2 g/L tribasic ammonium citric acid, 0.2 g/L $MgSO_4{\cdot}7H_2O$, and 0.05 g/L $MnSO_4{\cdot}7H_2O$; pH= 6.2 ± 0.2), and *E. coli* DH5α and BL21(DE3) were cultured in the Luria Bertani

(LB) medium (10.0g/L tryptone, 5.0 g/L yeast extract, and 10.0 g/L NaCl).

6.2 Gut bacterial generation of oligoindoles

Lactobacillus species were cultured in the medium pre-supplemented with indole and tryptophan (both at 0.5 mM) for 3 days. The supernatants collected by centrifugation were extracted twice with ethyl acetate. The extracts were combined and concentrated under reduced pressure, and dry residue was suspended in HPLC-grade methanol. The insoluble material was removed by centrifugation at 13,000 rpm for 10 min to prepare supernatants for assessing the oligoindole production. Formic acid-containing (0.1%) aqueous acetonitrile (0→5 min, 10% acetonitrile; 5→25 min, 10%→95%; 25→30 min, 95%; 30→31 min, 95%→10%; and 31→33 min, 10%) was used for LC-HR/MS analysis. For DIM biosynthesis via *E. coli* equipped with *Plem416-IdhL-LfDyp* plasmid, activation of seed solution was carried out in shaking tubes containing 3 mL of LB medium, which cultured overnight at 37 °C and 220 rpm. The resulting seed solution was inoculated in 250 mL flasks in using fermentation medium (containing 0.5 mM Trp and 0.5 mM IAA). After incubation at 37 °C for 3 h, isopropyl-beta-D-thiogalactopyranoside (IPTG) was added at a final concentration of 0.1 mM, the temperature was adjusted to 30 °C while being shaken at 220 rpm. Samples were collected at 48 h to evaluate the production of DIM, LTr1, and LTe2.

6.3 Amino acid sequences of *Lactobacillus* peroxidases used in this work.

Protein names	**Amino acid sequences**
*La*DyP	MPINPNRAQDVWKDVGEHVQFTVLQLNRQDQQHDREVFQEFADRSQAIIR SLRIRDAKPETGTQLKVSIGISSAAWDYLFPGAPKPKELETYTTLSGPKYTMP ATPGDLFFHIRASNEAVVYECQTQFQRVLAPITTVLDETKGFRYFEGRAIIGF IDGTEAPAVEDAADYALVGDEDPQFINGSYAFAQKWQHDMPVWEHMHTE DQEKAVGREKFSDFELEDEDKFKNAHNVASKLEIDGVEQKIVRMNVPYSNP AAGNTGMYFIGYARHWTVTKGMLQNMIDQSDFLLTFSTLLSGQAFFIPSRD LFAQIADNDF
*Lf*DyP	MSVNPQRSQDVYRDAGKNVLFLMLSLNRQDQTNEKAAVEETADRLQAIKR SLNVRYPDSHLRIACGISSKAWDYLFPQAPKPKELEDFTGIKGDKYDAPGTP ADLFFHVRADDQSLTYEVIDEIMTFLRPVTKVVDETHGFRYFEGRAIIGFVD GTENPVDADAVEWGIIHEEDPEFENGSYAFAQKYLHQMDAWKSLSTEQQE QVIGRRKFTDLEQGDEDKNQRAHNVVSQDNRNDVEHKIIRMNVPFSDPGEN VTGTYFIGYGRYWDVTKTMLTNMFTKNDLLLDYSTPVNGQVFFIPSIDTLD KIADDEY
*Lr*DyP	MVMNPNKAQDVWKDAGEHVQFTVLELKRQDRAKEQEAIKEFVDRFQAIT RSLRIRDNKGNLKVALGFSSDAWDYLFPNAPKPKELEAYQTLTGPKYKMPA

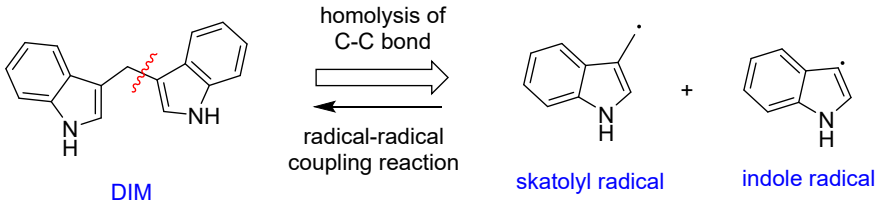
	AKGDIFLHIRANDEAAVYEFMAQVMLFIRDITTVIDETKGFRYFEGRAIIGFI DGTENPEPQDAAEYAIIGDEDPTFENGSYAFAQKWRHNMDIWNKLTTETQE KAVGRKKFSDLELSEKEKFKNAHNVASQAEIDGVEQKIVRMNVPYSDPAA NNTGTFFIGYSRHWTVTKKMLENMLEQNDYLLTFSDILGGQLFFIPSRPMLD QIAEGELN
*Lm*DyP	MTVEPKLAQDVWKDAGKHVQFTVLELKRQDQKHEQEVITAFADRYQAILR SLHIRDNECCLRATFGFSSDAWDYLFPNAPKPKELASYQTLRGDKYEMPAT KGDLFFHIRANDEAVVYEAMSQFMLFLRDITNVVDETKGFRYFEGRAIVGFI DGTEAPEMELASQYALVGDEDPEFVNGSYAFAQKWLHNMDFWNKLKTED QEKAIGRQKFNDLELDDDEKFKNAHNVVSKVELNGEEQKIIRMNVPYSDPA SGKTGTYFMGYSRYWQVTKLMLLSMLKGHDFLLSFSKILSGQLFFIPSKTVL DEIADGEFTK

6.4 *Lf*DyP catalyzed oligomerization of IAA and indole

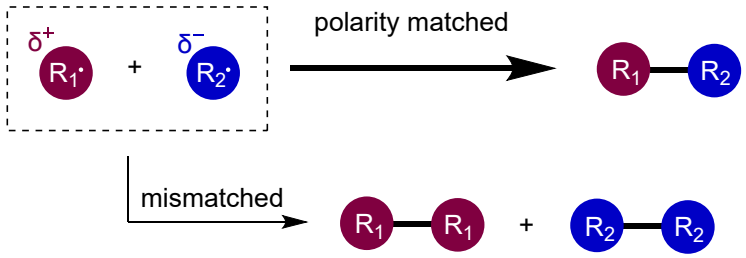
*Lf*DyP (8 μM) and H_2O_2 (500 μM) were added to the mixture (200 μL) of IAA (**5**, 250 μM) and indole (**6**, 325 μM) in 100 mM citrate buffer. After incubation at room temperature for 2 h, the reaction was quenched by the addition of methanol, followed by the centrifugation at 13,000 rpm for 10 min. The reaction products were analyzed by LC-HR/MS.

Supplemental Schemes, Tables, and Figures

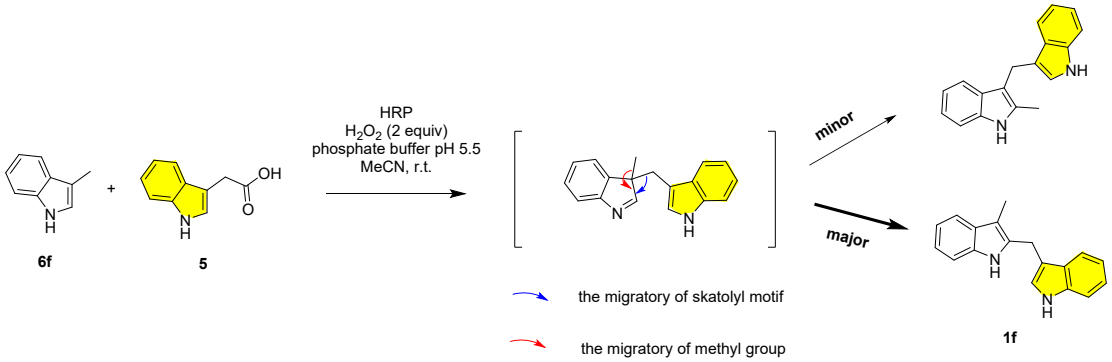
Scheme S1. Retrosynthetic analysis for the DIM formation.



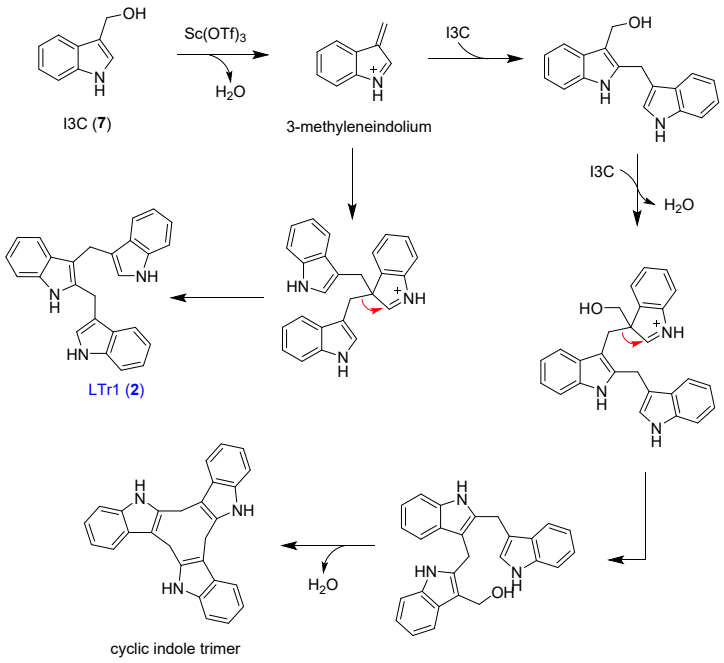
Scheme S2. Polar effect in controlling the selectivity of radical-radical coupling reactions.[4]



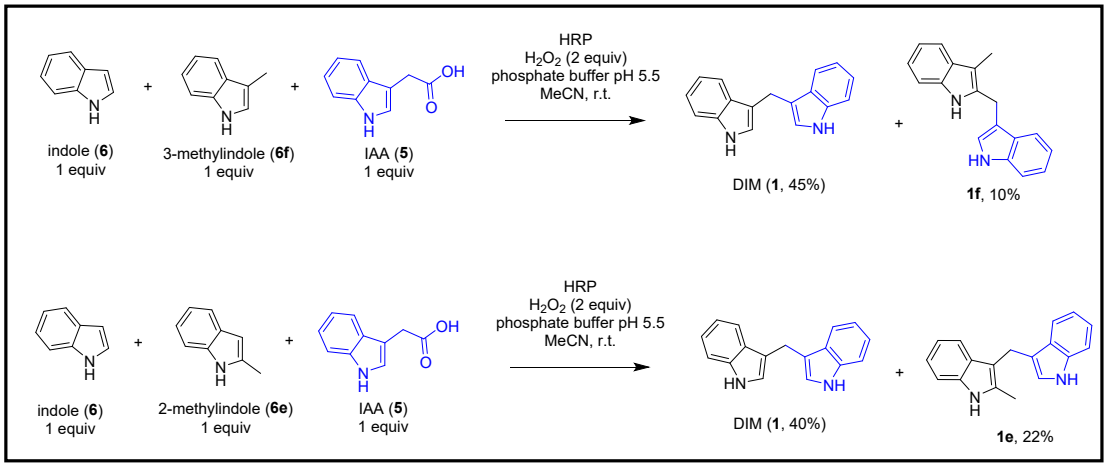
Scheme S3. The synthesis of **1f** by coupling reaction of **6f** and **5**.



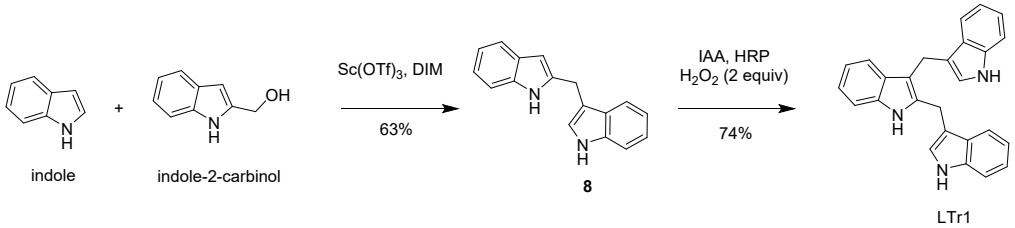
Scheme S4. $Sc(OTf)_3$-facilitated synthesis of LTr1.



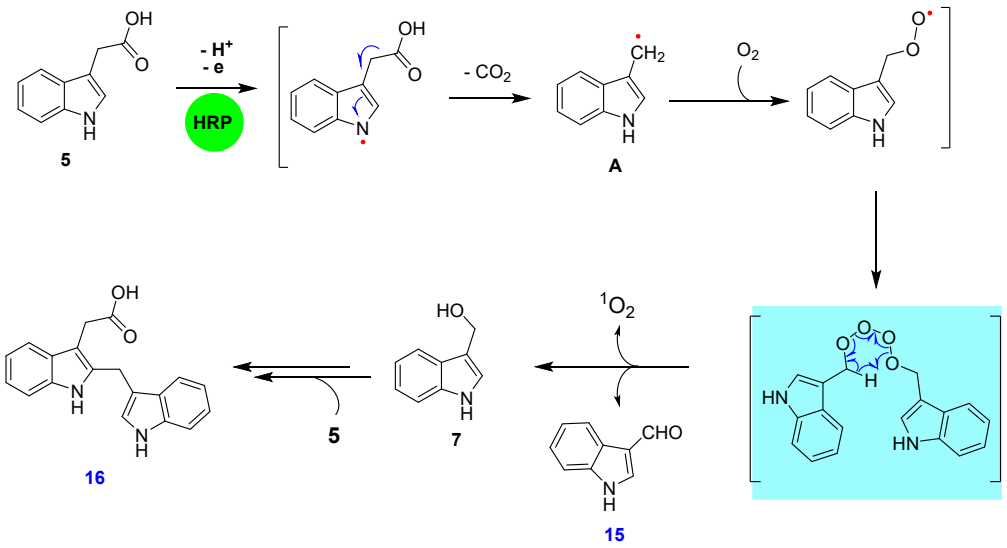
Scheme S5. Kinetic experiments



Scheme S6. Chemo-enzymatic synthesis of LTr1.



Scheme S7. The generation of **15** and **16** via Russell mechanism.



Scheme S8. The generation of **17**, **18**, **19**, and **20** from via Russell mechanism

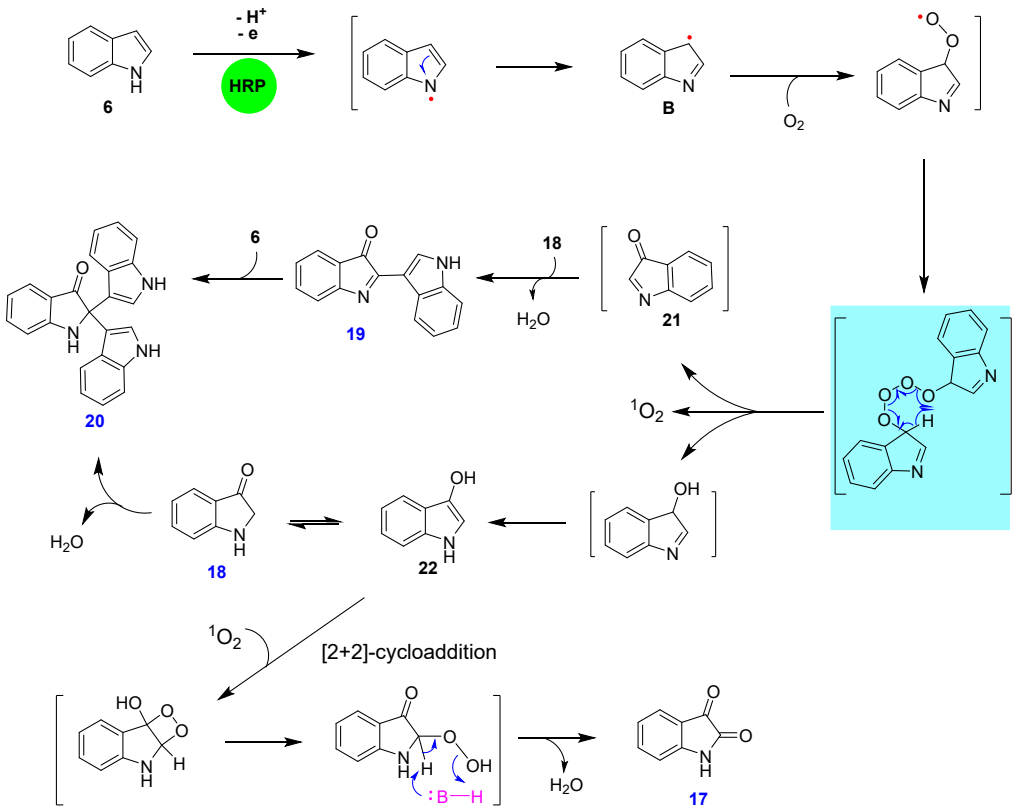
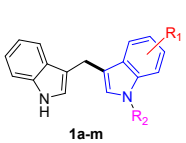
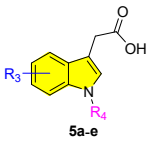


Table S1. Chemical structures of **1a-m**, **5a-e**, and **6a-m**.



1a-m

number	R_1	R_2
1a	4-CH3	H
1b	5-CH3	H
1c	6-CH3	H
1d	7-CH3	H
1e	2-CH3	H
1f	3-CH3	H
1g	5-NO2	H
1h	4-F	H
1i	5-F	H
1j	5-MeO	H
1k	H	Me
1l	H	Et
1m	H	Bn



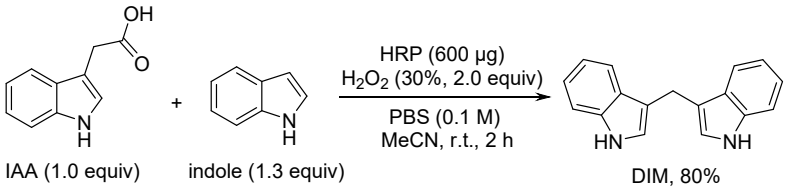
5a-e

number	R_3	R_4
5a	5-CH3	H
5b	5-NO2	H
5c	5-F	H
5d	5-MeO	H
5e	H	Me

6a-m

number	R_1	R_2
6a	4-CH3	H
6b	5-CH3	H
6c	6-CH3	H
6d	7-CH3	H
6e	2-CH3	H
6f	3-CH3	H
6g	5-NO2	H
6h	4-F	H
6i	5-F	H
6j	5-MeO	H
6k	H	Me
6l	H	Et
6m	H	Bn

Table S2. Evaluation of green chemistry metrics and EcoScale for the synthesis of **1** via our method.



IAA (1.0 equiv) indole (1.3 equiv) DIM, 80%

Reactant IAA:	14.02 mg	0.08 mmol	175.19
Reactant indole:	12.18 mg	0.104 mmol	117.15
Catalyst HRP:	0.6 mg		
Reagent H_2O_2:	1.63 mg	0.048 mmol	34.01
Solvent MeCN:	235.8 mg		
Product DIM:	15.7 mg	0.064 mmol	246.31
Waste (byproducts):	248.53 mg		

$$\text{Atom Economy (\%)} = \frac{\text{Mol.wt. of product}}{\text{Mol.wt. of all reactants}} \times 100 = \frac{246.31}{175.19 + 117.15} \times 100 = 84.3\%$$

$$\text{Atom Efficiency (\%)} = (\%\text{yield of product} \times \%\text{atom economy}) \times 100 = (80\% \times 84.3\%) \times 100 = 67.4\%$$

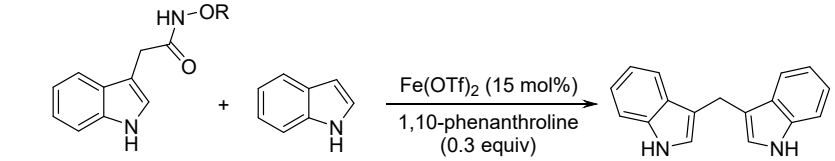
$$\text{Carbon Efficiency (\%)} = \frac{\text{amount of carbon in product}}{\text{amount of carbon in reactants}} \times 100 = \frac{17}{10 + 8} \times 100 = 94.4\%$$

$$\text{Reaction Mass Efficiency (\%)} = \frac{\text{mass of isolated product}}{\text{mass of all reactants}} \times 100 = \frac{15.7}{14.02 + 12.18} \times 100 = 60.0\%$$

$$E\text{-factor} = \frac{\text{total waste (mg)}}{\text{total product (mg)}} = \frac{248.53}{15.7} = 15.8 \text{ mg waste/mg product}$$

Parameter	Penalty points
1. Yield (100 − %yield)/2 = (100 − 80)/2	10
2. Price of reaction components (to obtain 10 mmol of the end product), (< $50) =	0
3. Safety (solvent: MeCN, highly flammable) =	5
4. Technical setup (simple setup) =	0
5. Temperature/time (room temperature, < 24 h) =	1
6. Workup and purification (classical chromatography) =	10
Total of individual penalties =	26
EcoScale calculation = 100 − sum of individual penalties = 100 − 26 = 74	
Following scores: > 75, excellent; > 50, **acceptable**; and < 50, inadequate.	

Table S3. Evaluation of green chemistry metrics and EcoScale for the synthesis of **1** via Xia's method[5].



R = 3,5-$(CF_3)_2$-benzoyl A (1.0 equiv) indole (2.0 equiv) DIM, 72%

Reactant A:	43.03 mg	0.1 mmol	430.31
Reactant indole:	23.43 mg	0.2 mmol	117.15
Catalyst $Fe(OTf)_2$:	5.31 mg	0.015 mmol	353.97
Reagent 1,10-phenanthroline:	5.41 mg	0.03 mmol	180.21
Solvent CH_2Cl_2:	5300 mg		
Product DIM:	17.8 mg	0.072 mmol	246.31
Waste (byproducts):	5359.38 mg		

$$\text{Atom Economy (\%)} = \frac{\text{Mol.wt. of product}}{\text{Mol.wt. of all reactants}} \times 100 = \frac{246.31}{430.31 + 117.15} \times 100 = 45.0\%$$

$$\text{Atom Efficiency (\%)} = (\%\text{yield of product} \times \%\text{atom economy}) \times 100 = (72\% \times 45.0\%) \times 100 = 32.4\%$$

$$\text{Carbon Efficiency (\%)} = \frac{\text{amount of carbon in product}}{\text{amount of carbon in reactants}} \times 100 = \frac{17}{19 + 8} \times 100 = 63.0\%$$

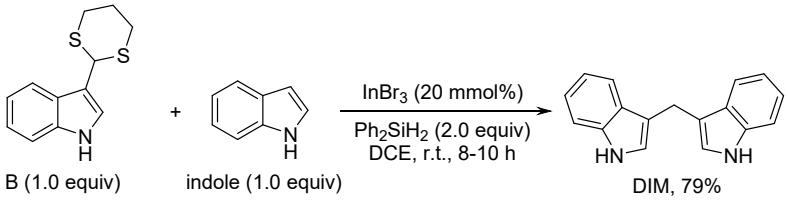
$$\text{Reaction Mass Efficiency (\%)} = \frac{\text{mass of isolated product}}{\text{mass of all reactants}} \times 100 = \frac{17.8}{43.03 + 23.43} \times 100 = 26.8\%$$

$$E\text{-factor} = \frac{\text{total waste (mg)}}{\text{total product (mg)}} = \frac{5359.38}{17.8} = 301.1 \text{ mg waste/mg product}$$

Parameter	Penalty points
1. Yield (100 − %yield)/2 = (100 − 72)/2	14
2. Price of reaction components (to obtain 10 mmol of the end product), (< $50) =	0
3. Safety (reagent: 1,10-phenanthroline, toxic)=	5
(solvent: CH_2Cl_2, harmful) =	5
4. Technical setup (amide ester construction, more complex) =	2
5. Temperature/time (room temperature, < 24 h) =	1
6. Workup and purification (classical chromatography) =	10
Total of individual penalties =	37
EcoScale calculation = 100 − sum of individual penalties = 100 − 37 = 63	

Following scores: > 75, excellent; > 50, **acceptable**; and < 50, inadequate.

Table S4. Evaluation of green chemistry metrics and EcoScale for the synthesis of **1** via Tang's method[6].



B (1.0 equiv) indole (1.0 equiv) DIM, 79%

Reactant B:	23.54 mg	0.1 mmol	235.36
Reactant indole:	11.72 mg	0.1 mmol	117.15
Catalyst $InBr_3$:	7.09 mg	0.02 mmol	354.53
Reagent Ph_2SiH_2:	36.86 mg	0.2 mmol	184.31
Solvent DCE:	6280 mg		
Product DIM:	20.2 mg	0.082 mmol	246.31
Waste (byproducts):	6339.01 mg		

$$\text{Atom Economy (\%)} = \frac{\text{Mol.wt. of product}}{\text{Mol.wt. of all reactants}} \times 100 = \frac{246.31}{235.36 + 117.15} \times 100 = 69.9\%$$

$$\text{Atom Efficiency (\%)} = (\%\text{yield of product} \times \%\text{atom economy}) \times 100 = (79\% \times 69.9\%) \times 100 = 55.2\%$$

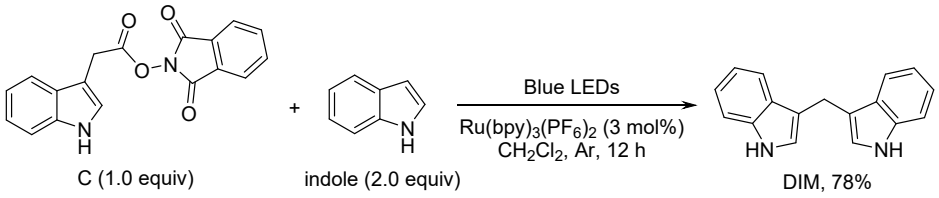
$$\text{Carbon Efficiency (\%)} = \frac{\text{amount of carbon in product}}{\text{amount of carbon in reactants}} \times 100 = \frac{17}{12 + 8} \times 100 = 85.0\%$$

$$\text{Reaction Mass Efficiency (\%)} = \frac{\text{mass of isolated product}}{\text{mass of all reactants}} \times 100 = \frac{20.2}{23.54 + 11.72} \times 100 = 57.3\%$$

$$E\text{-factor} = \frac{\text{total waste (mg)}}{\text{total product (mg)}} = \frac{6339.01}{20.2} = 313.8 \text{ mg waste/mg product}$$

Parameter	Penalty points
1. Yield (100 − %yield)/2 = (100 − 79)/2	11
2. Price of reaction components (to obtain 10 mmol of the end product), (< $50) =	0
3. Safety (catalyst: $InBr_3$, irritant)=	5
(reagent: Ph_2SiH_2, irritant) =	5
(solvent: DCE, highly flammable; toxic) =	10
4. Technical setup (simple setup) =	0
5. Temperature/time (room temperature, < 24 h) =	1
6. Workup and purification (classical chromatography) =	10
Total of individual penalties =	42
EcoScale calculation = 100 − sum of individual penalties = 100 − 42 = 58	
Following scores: > 75, excellent; > 50, **acceptable**; and < 50, inadequate.	

Table S5. Evaluation of green chemistry metrics and EcoScale for the synthesis of **1** via Huo's method[7].



C (1.0 equiv) indole (2.0 equiv) DIM, 78%

Reactant C:	64.06 mg	0.2 mmol	320.30
Reactant indole:	46.86 mg	0.4 mmol	117.15
Catalyst $Ru(bpy)_3(PF_6)_2$:	5.16 mg	0.006 mmol	859.56
Solvent CH_2Cl_2:	2650 mg		
Product DIM:	38.5 mg	0.156 mmol	246.31
Waste (byproducts):	2727.58 mg		

$$\text{Atom Economy (\%)} = \frac{\text{Mol.wt. of product}}{\text{Mol.wt. of all reactants}} \times 100 = \frac{246.31}{320.30 + 117.15} \times 100 = 56.3\%$$

$$\text{Atom Efficiency (\%)} = (\%\text{yield of product} \times \%\text{atom economy}) \times 100 = (78\% \times 56.3\%) \times 100 = 43.9\%$$

$$\text{Carbon Efficiency (\%)} = \frac{\text{amount of carbon in product}}{\text{amount of carbon in reactants}} \times 100 = \frac{17}{18 + 8} \times 100 = 65.4\%$$

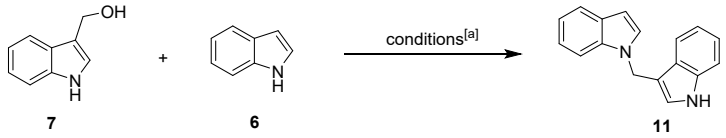
$$\text{Reaction Mass Efficiency (\%)} = \frac{\text{mass of isolated product}}{\text{mass of all reactants}} \times 100 = \frac{38.5}{64.06 + 46.86} \times 100 = 34.7\%$$

$$E\text{-factor} = \frac{\text{total waste (mg)}}{\text{total product (mg)}} = \frac{2727.58}{38.5} = 70.8 \text{ mg waste/mg product}$$

Parameter	Penalty points
1. Yield (100 − %yield)/2 = (100 − 78)/2	11
2. Price of reaction components (to obtain 10 mmol of the end product), (< $50) =	0
3. Safety (catalyst: $Ru(bpy)_3(PF_6)_2$, irritant)=	5
(solvent: CH_2Cl_2, harmful) =	5
4. Technical setup (Inconventional activation technique: Photochemical activation) =	2
5. Temperature/time (room temperature, < 24 h) =	1
6. Workup and purification (classical chromatography) =	10
Total of individual penalties =	34
EcoScale calculation = 100 − sum of individual penalties = 100 − 34 = 66	

Following scores: > 75, excellent; > 50, **acceptable**; and < 50, inadequate.

Table S6. Parameter optimization for the ILs-facilitated synthesis of **11**.



7 **6** **11**

entry	ionic liquids	temperature (°C)	yield (%)
1	[EMIm][Cl]	140	62
2	[EMIm][Cl]	120	63
3	[EMIm][Cl]	100	20
4	[EMIm][Cl]	80	0
5	[EMIm][Cl]	60	0
6	[EMIm][Cl]	40	0
7	[EMIm][Cl]	25	0
8	[EMIm][AcO]	120	38
9	[EMIm][TsO]	120	0
10	[EMIm][$N(CN)_2$]	120	0

[a]Standard conditions: **7** (0.25 mmol, 1 equiv.), indole (0.5 mmol, 2 equiv.), ILs (0.2 mmol), 1.5 h. [EMIm][Cl], 1-ethyl-3-methylimidazolium chloride; [EMIm][AcO], 1-ethyl-3-methylimidazolium acetate; [EMIm][TsO], 1-ethyl-3-methylimidazolium -*p*-toluene sulfonate; [BMIm][$N(CN)_2$], 1-butyl-3-methylimidazolium dicyanamide.

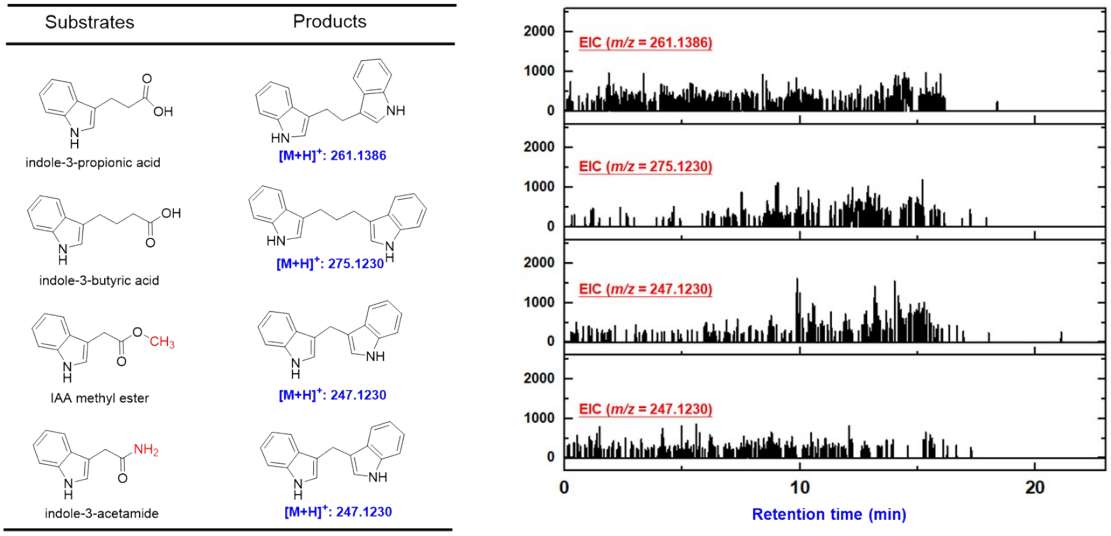


Figure S1. HRP failed to catalyze transformation of indole-3-carboxylic acid, indole-3-propionic acid, indole-3-butyric acid, IAA methyl ester, and indole-3-acetamide. EIC, extracted ion chromatogram

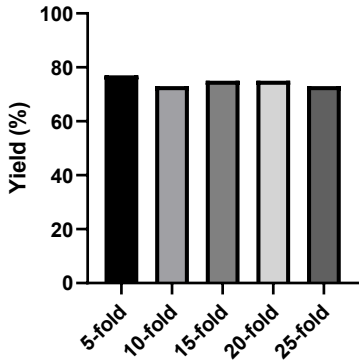


Figure S2. Upscaling studies for the HRP-catalyzed synthesis of compound **1**.

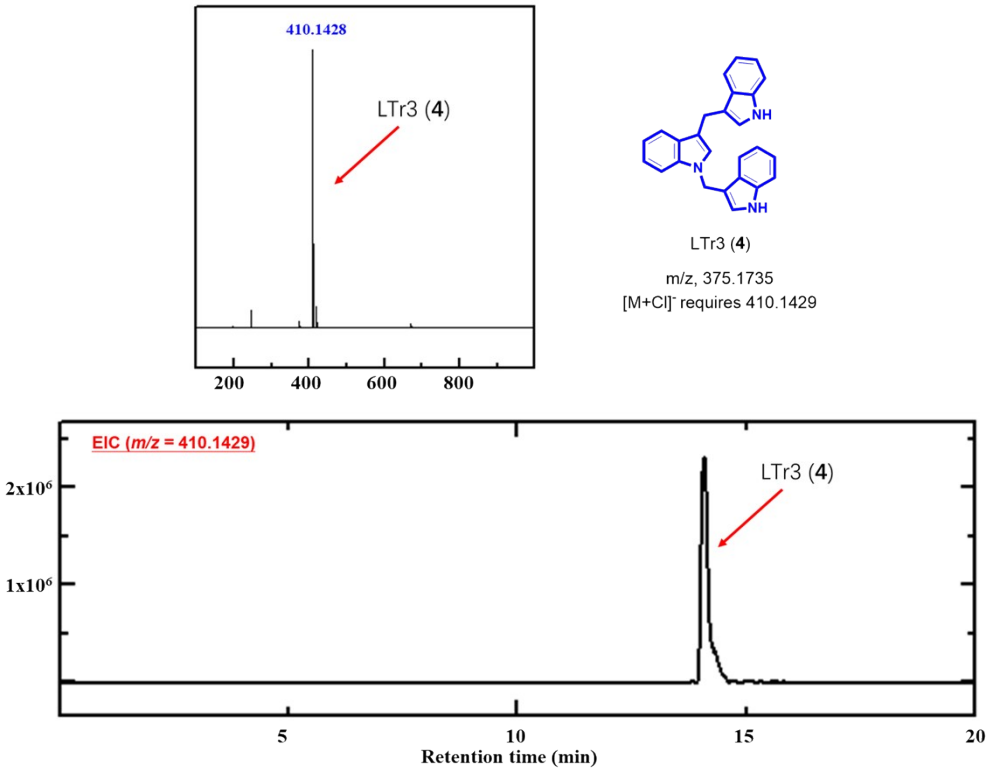


Figure S3. LC-MS detection of LTr3 (**4**).

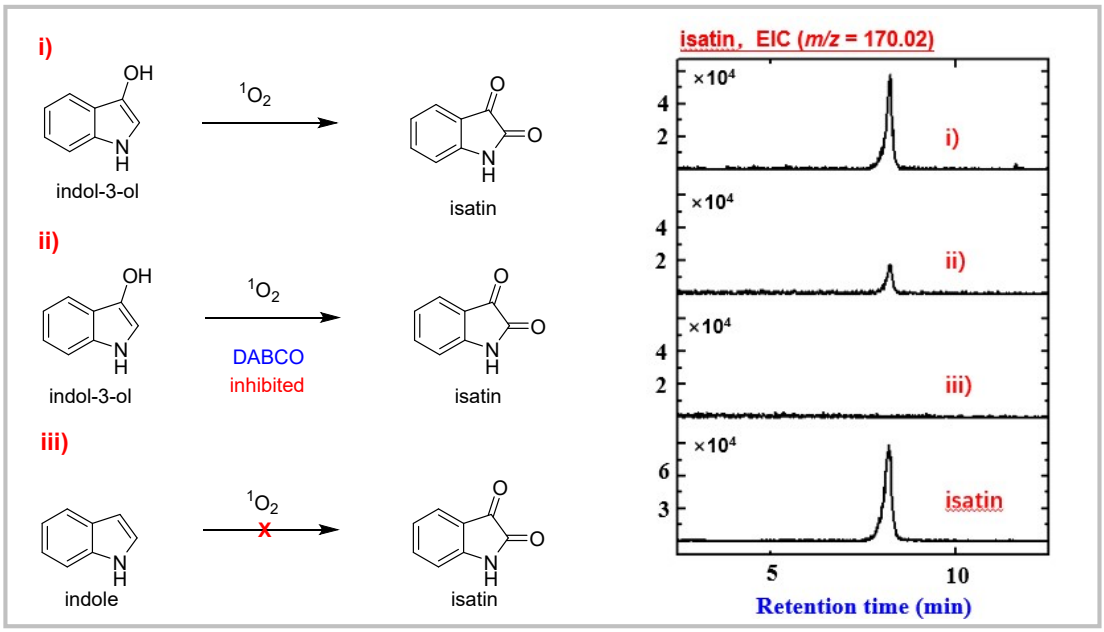


Figure S4. The synthesis of isatin from indol-3-ol in the presence of $^1O_2$.

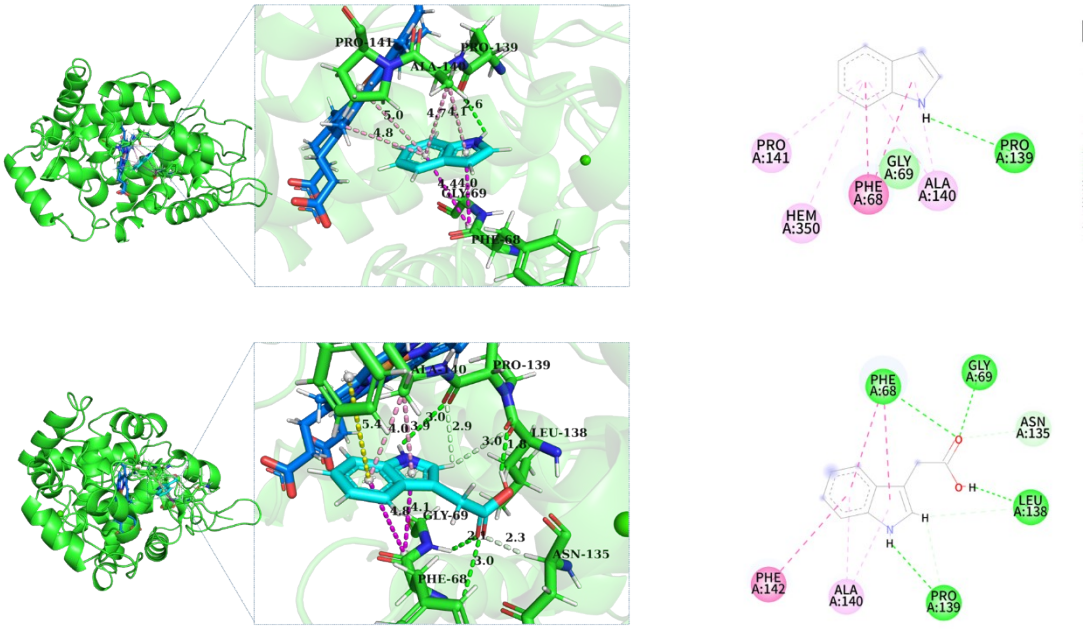


Figure S5. Docking experiments between HRP with indole and IAA.

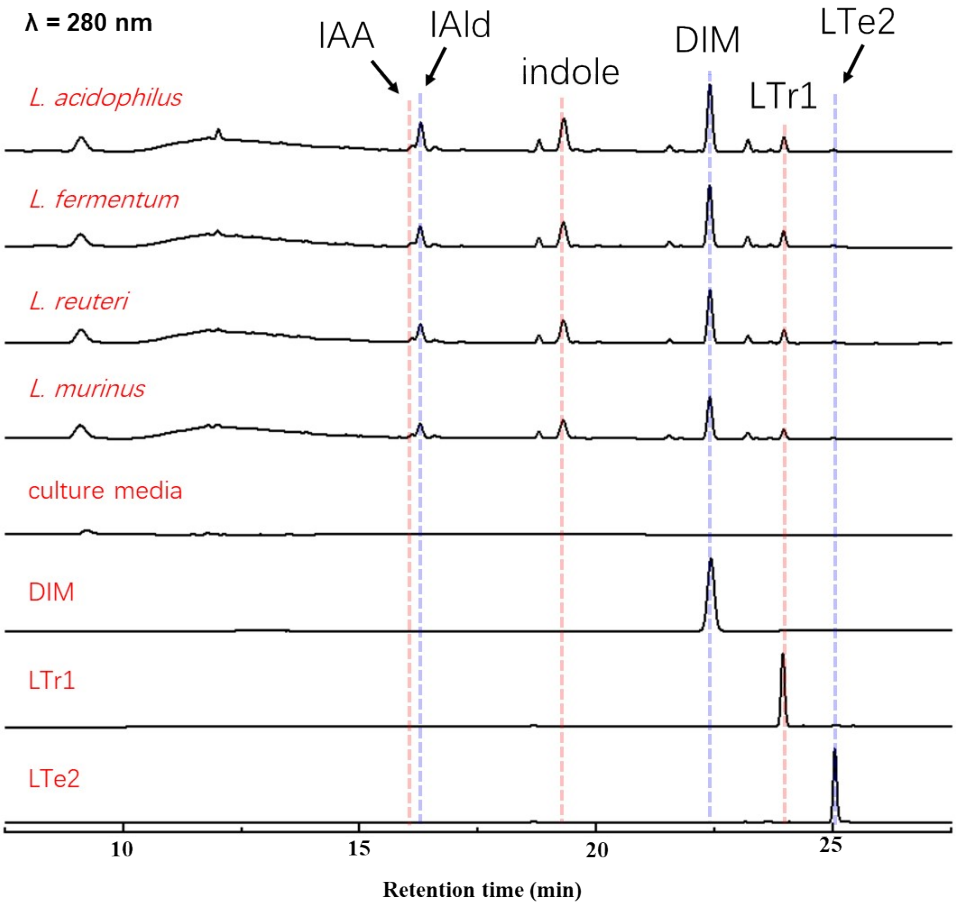


Figure S6. The production of DIM, LTr1, and IAld in the tryptophan- and indole-supplemented fermentation of human gut-derived *Lactobacillus* strains. Indole was added for the test because *Lactobacillus* strains can catabolize tryptophan into IAA, but not indole (a co-substrate in this work).

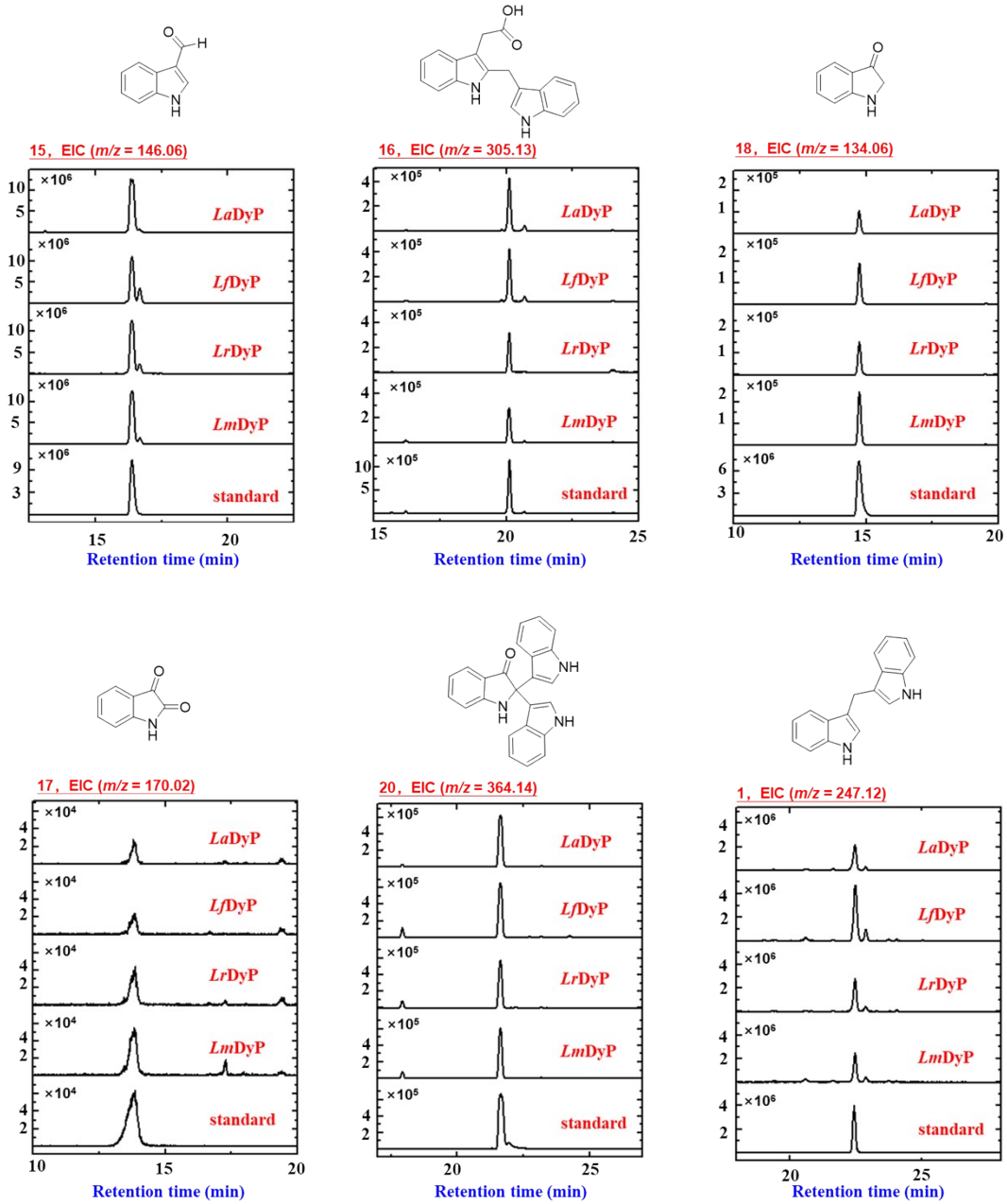


Figure S7. EICs for *Lactobacillus* DyP-facilitated reaction of IAA with indole. EIC, extracted ion chromatogram.

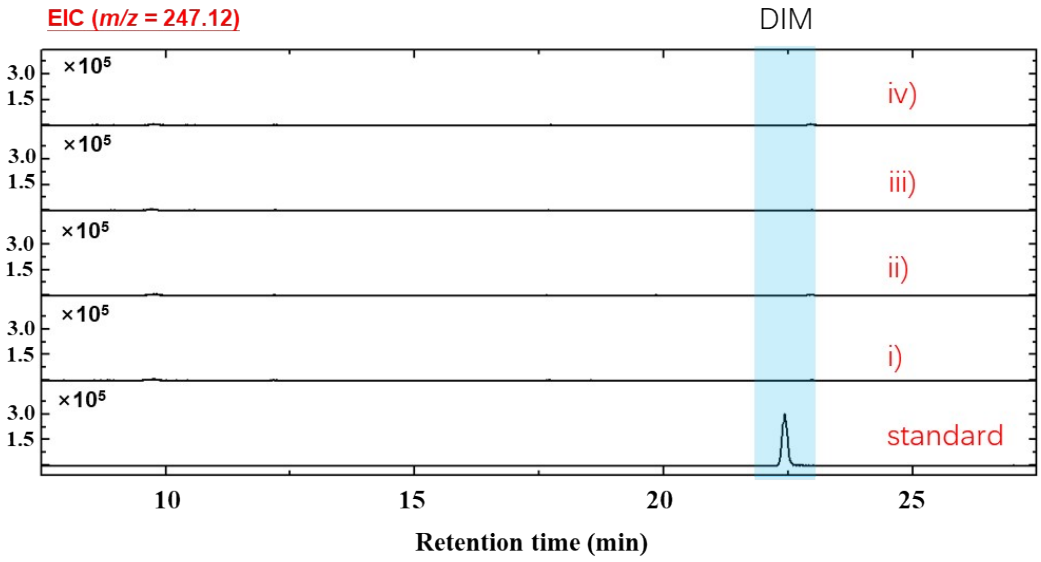


Figure S8. DIM was undetectable in the *E. coli* culture in different media. i) Luria-Bertani (LB) medium; ii) LB medium supplemented with 0.5 mM tryptophan; iii) LB medium supplemented with 0.5 mM IAA; iv) LB medium supplemented with 0.5 mM tryptophan and 0.5 mM IAA.

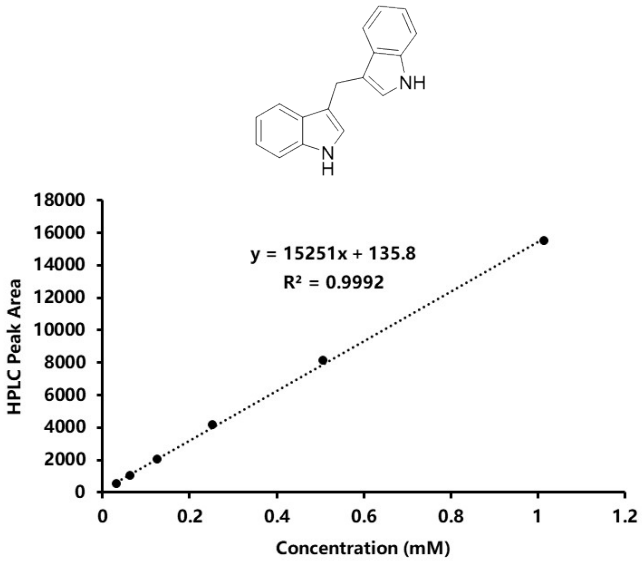


Fig. S9. Calibration curve for **1** based on absorbance at 280 nm.

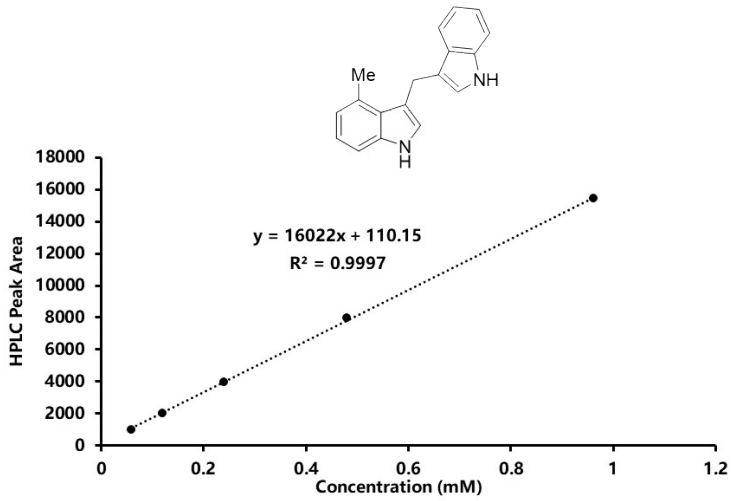


Fig. S10. Calibration curve for **1a** based on absorbance at 280 nm.

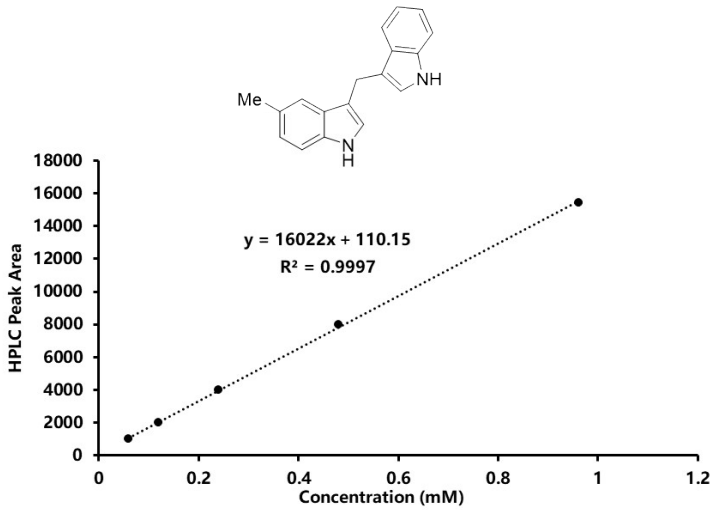


Fig. S11. Calibration curve for **1b** based on absorbance at 280 nm.

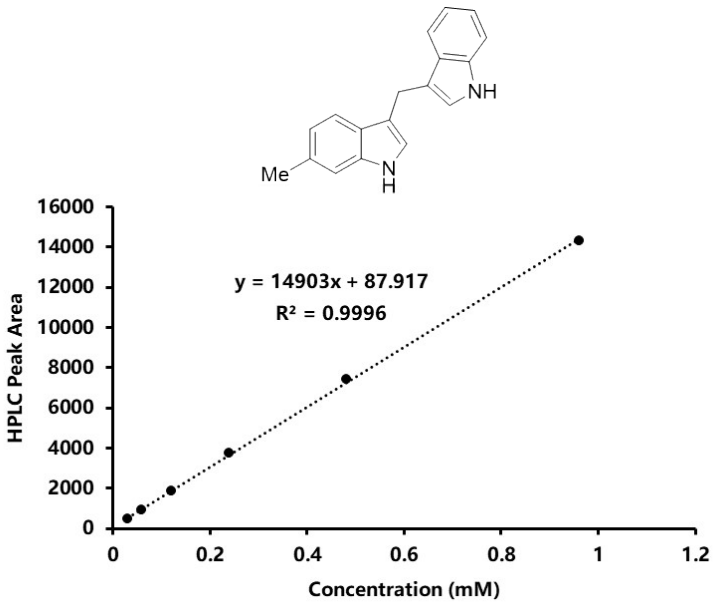


Fig. S12. Calibration curve for **1c** based on absorbance at 280 nm.

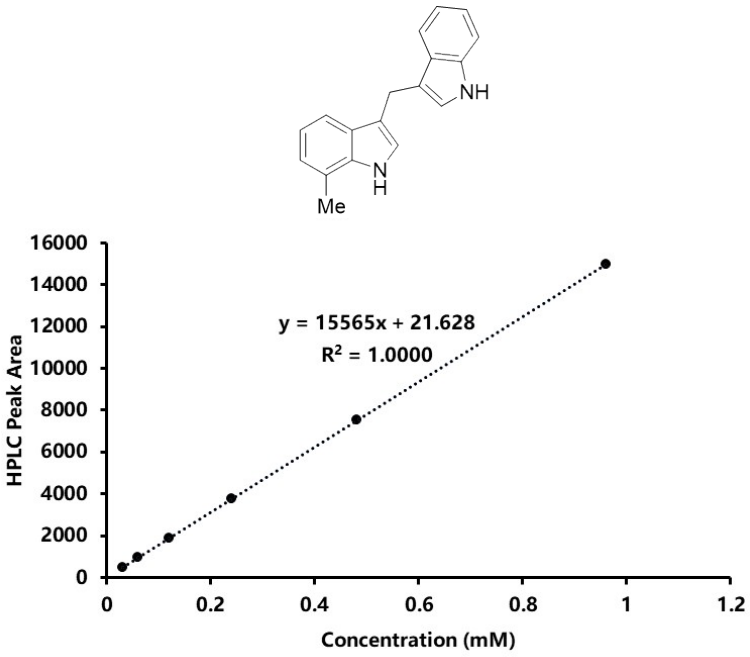


Fig. S13. Calibration curve for **1d** based on absorbance at 280 nm.

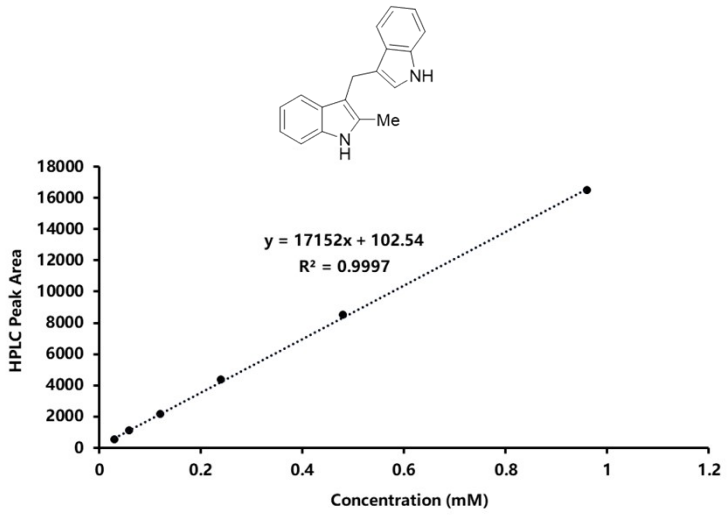


Fig. S14. Calibration curve for **1e** based on absorbance at 280 nm.

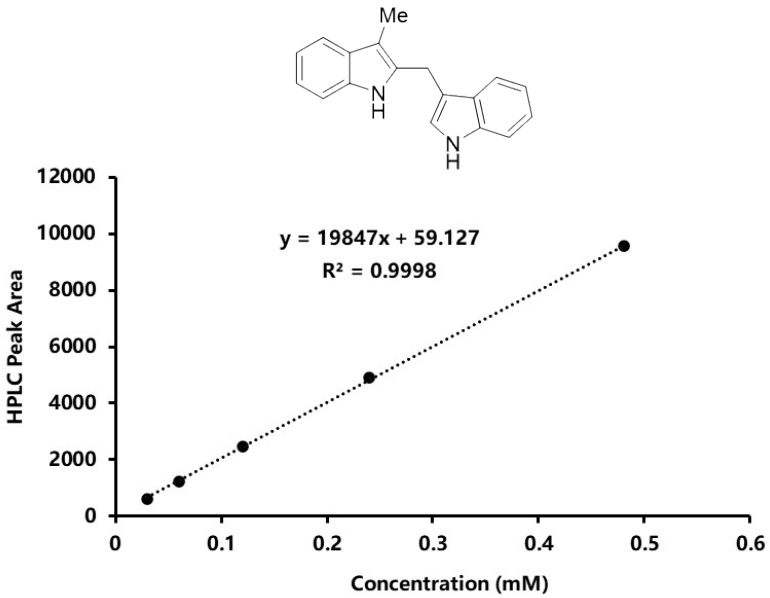


Fig. S15. Calibration curve for **1f** based on absorbance at 280 nm.

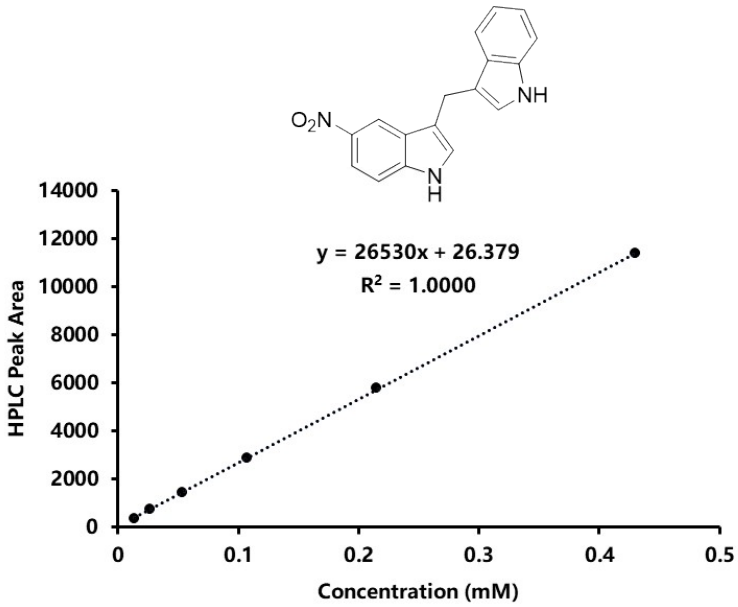


Fig. S16. Calibration curve for **1g** based on absorbance at 280 nm.

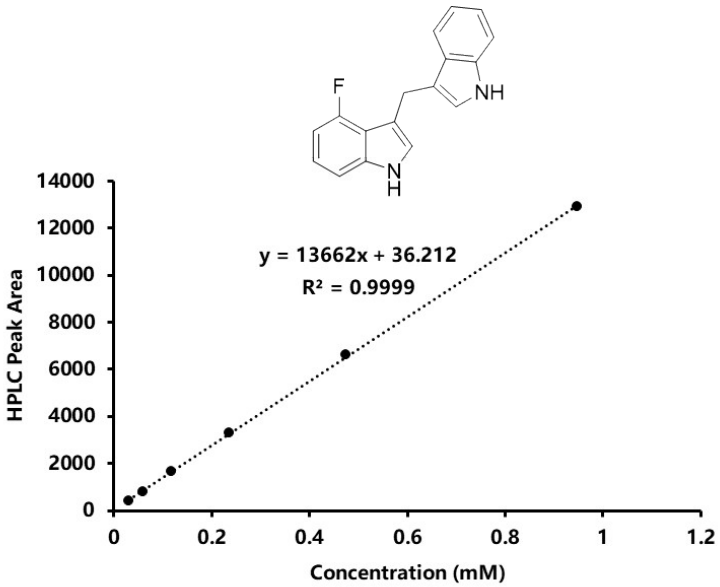


Fig. S17. Calibration curve for **1h** based on absorbance at 280 nm.

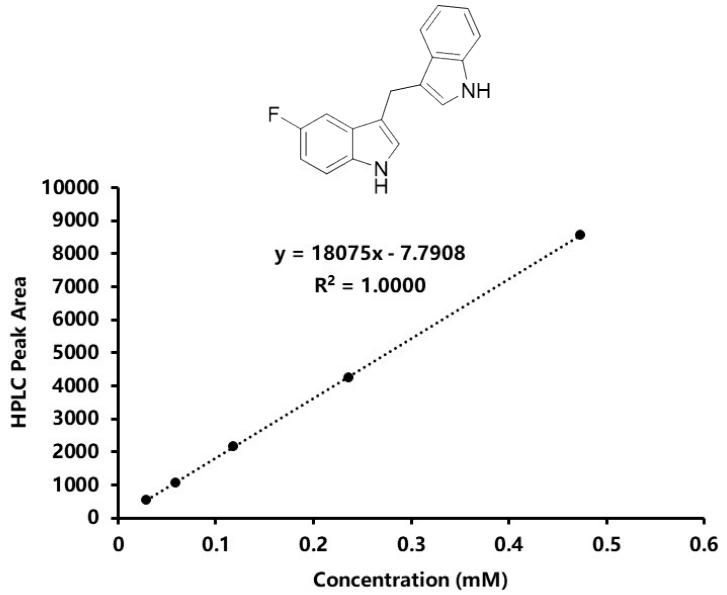


Fig. S18. Calibration curve for **1i** based on absorbance at 280 nm.

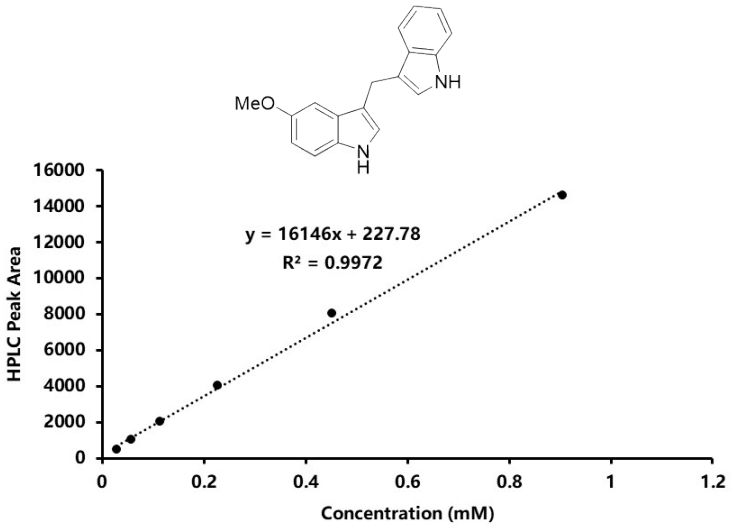


Fig. S19. Calibration curve for **1j** based on absorbance at 280 nm.

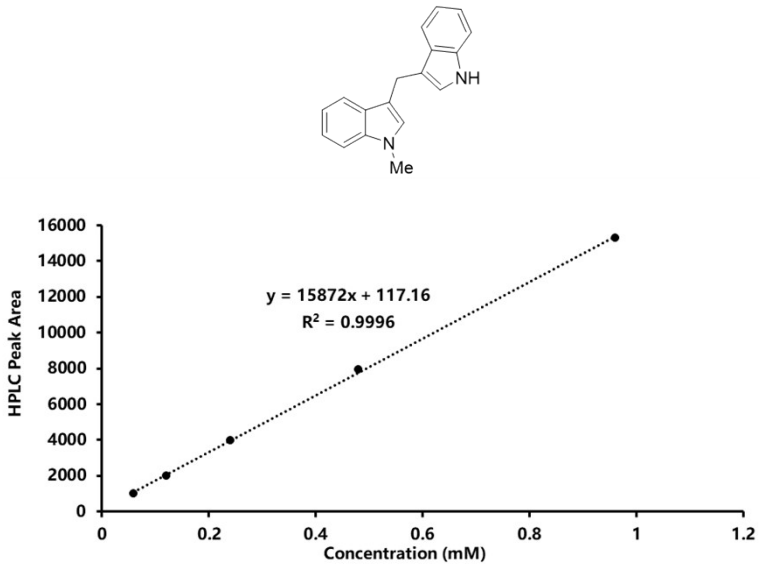


Fig. S20. Calibration curve for **1k** based on absorbance at 280 nm.

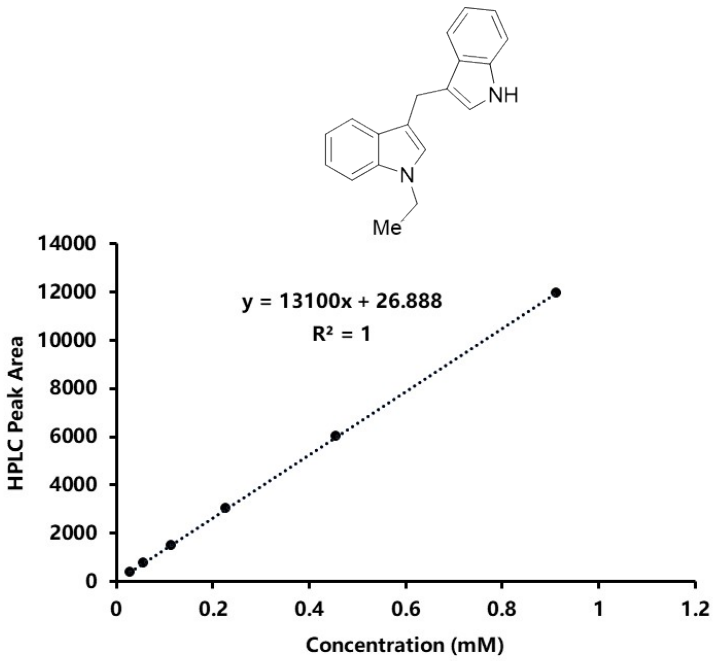


Fig. S21. Calibration curve for **1l** based on absorbance at 280 nm.

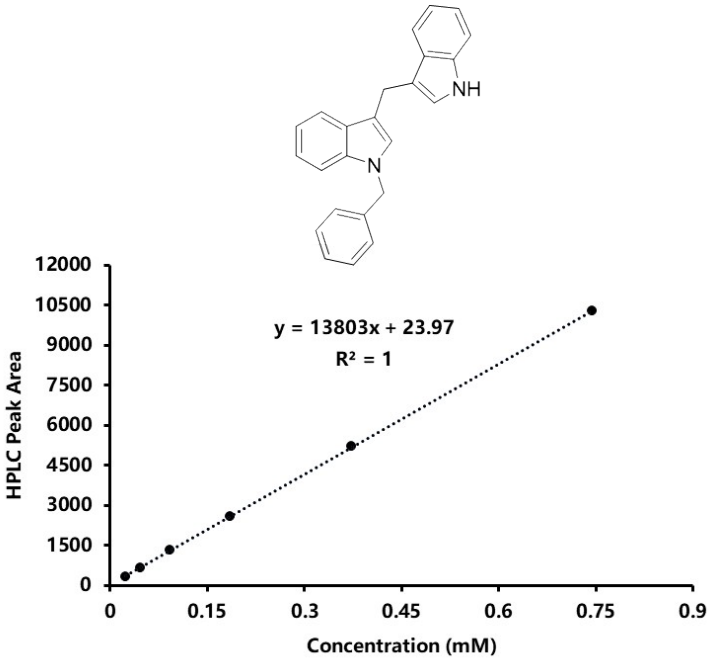


Fig. S22. Calibration curve for **1m** based on absorbance at 280 nm.

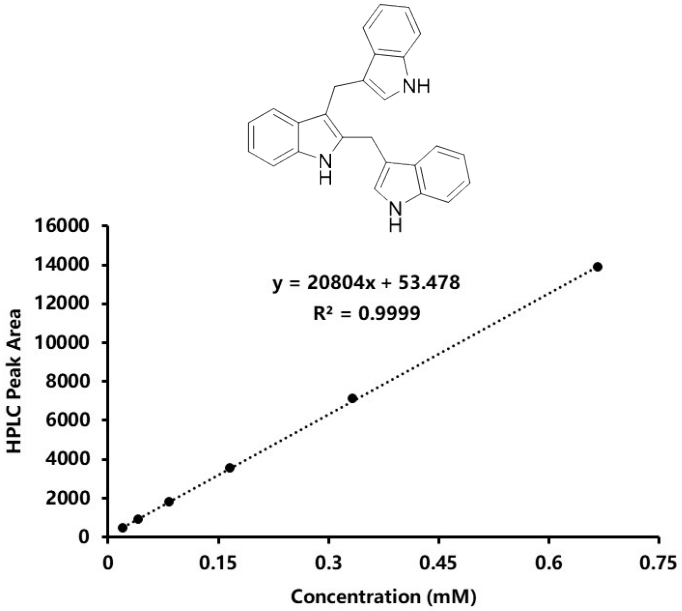


Fig. S23. Calibration curve for LTr1 based on absorbance at 280 nm.

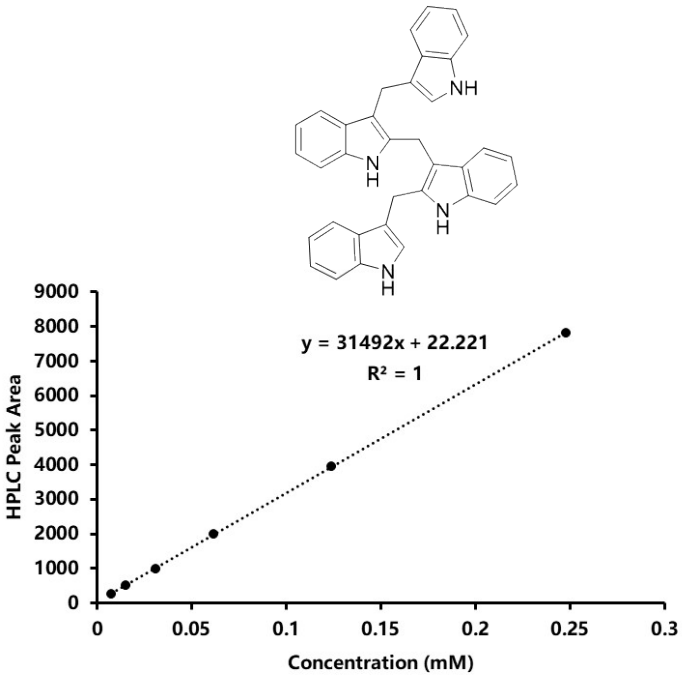


Fig. S24. Calibration curve for LTe2 based on absorbance at 280 nm.

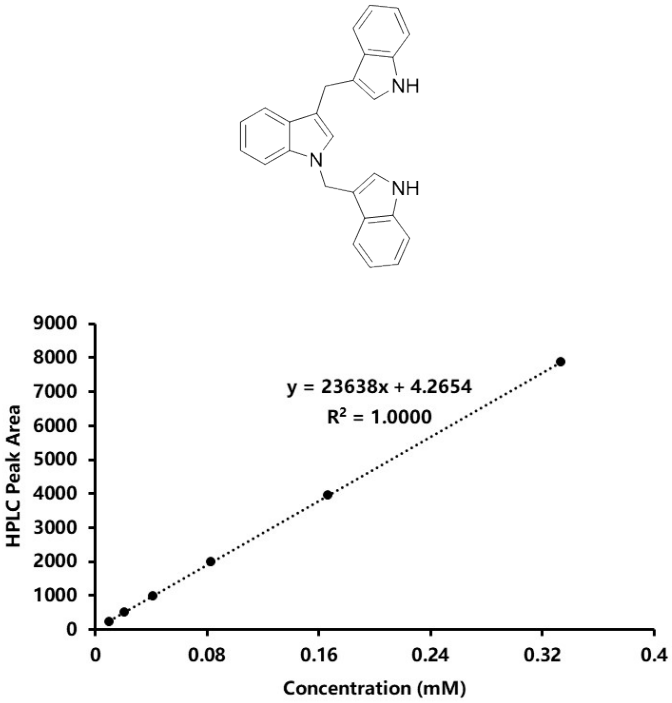


Fig. S25. Calibration curve for LTr3 based on absorbance at 280 nm.

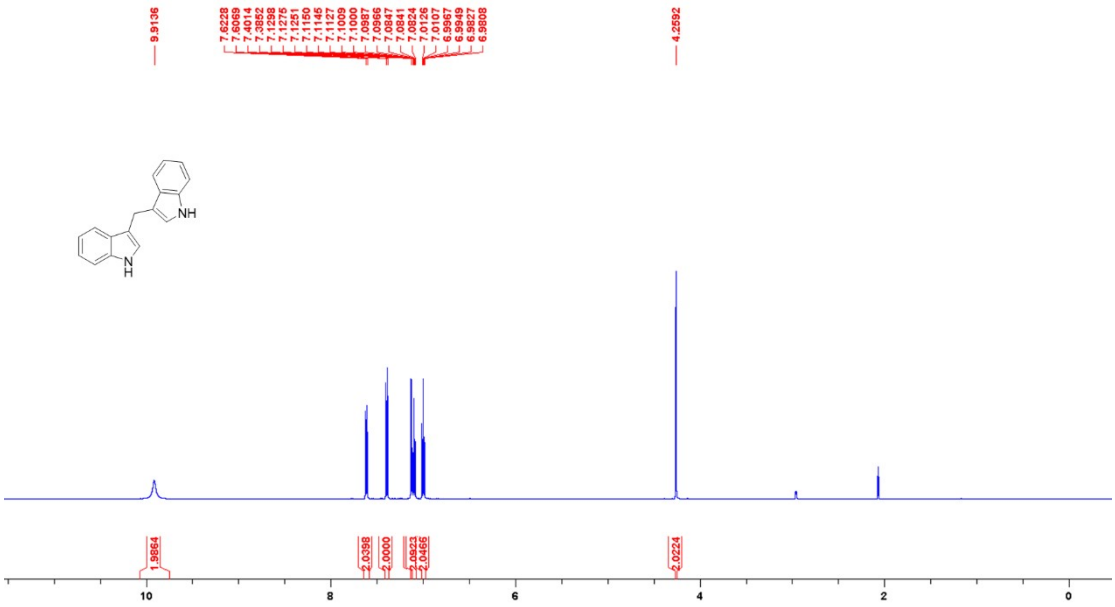


Figure S26. ^{1}H NMR spectrum of DIM.

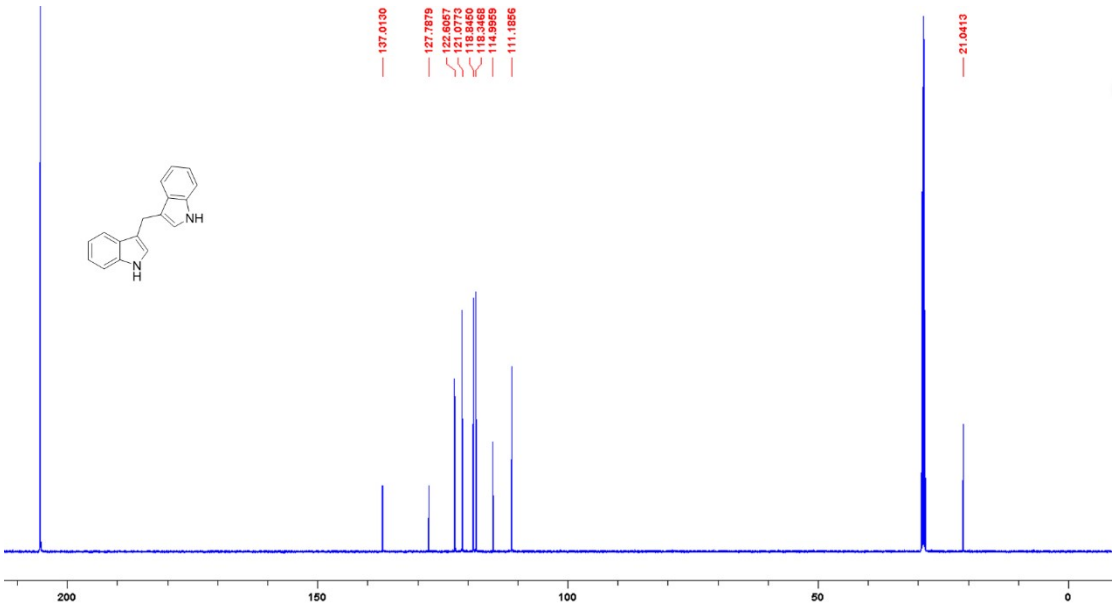


Figure S27. ^{13}C NMR spectrum of DIM.

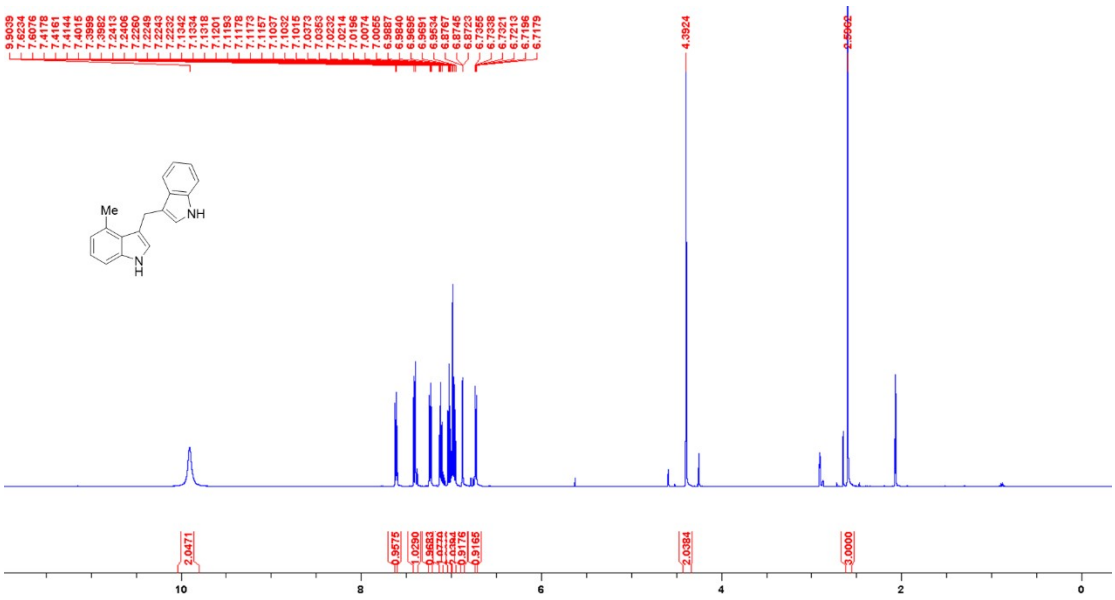


Figure S28. [1]H NMR spectrum of **1a**.

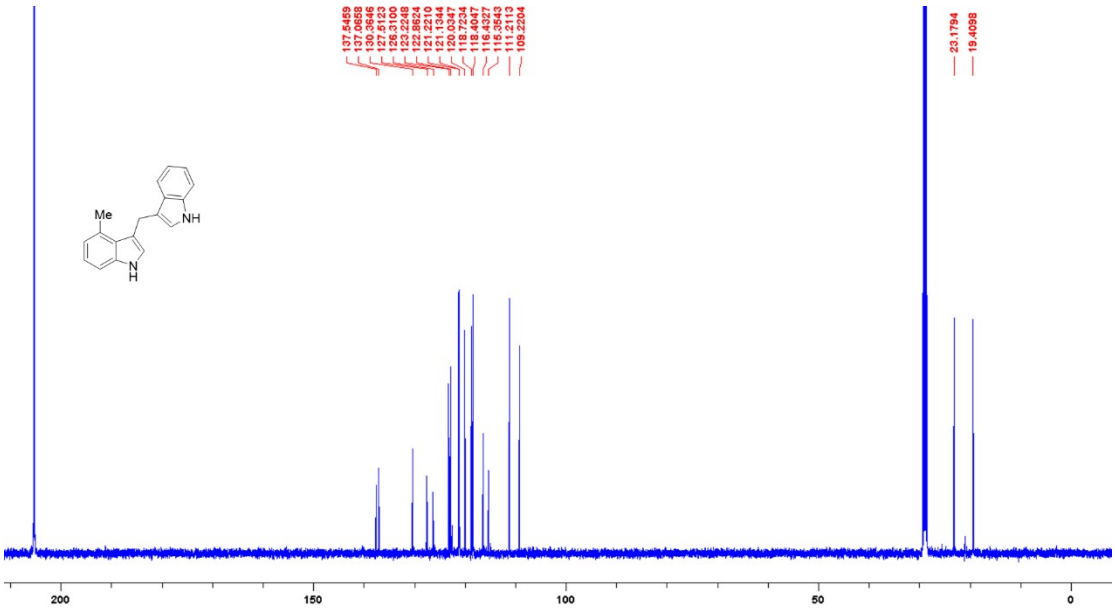


Figure S29. [13]C NMR spectrum of **1a**.

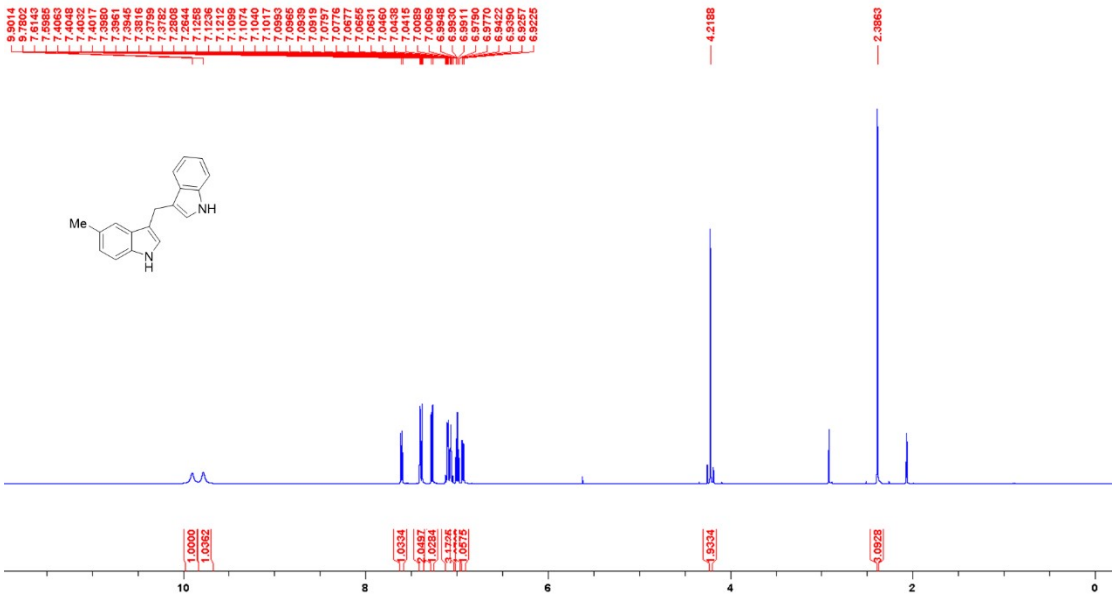


Figure S30. ^{1}H NMR spectrum of **1b**.

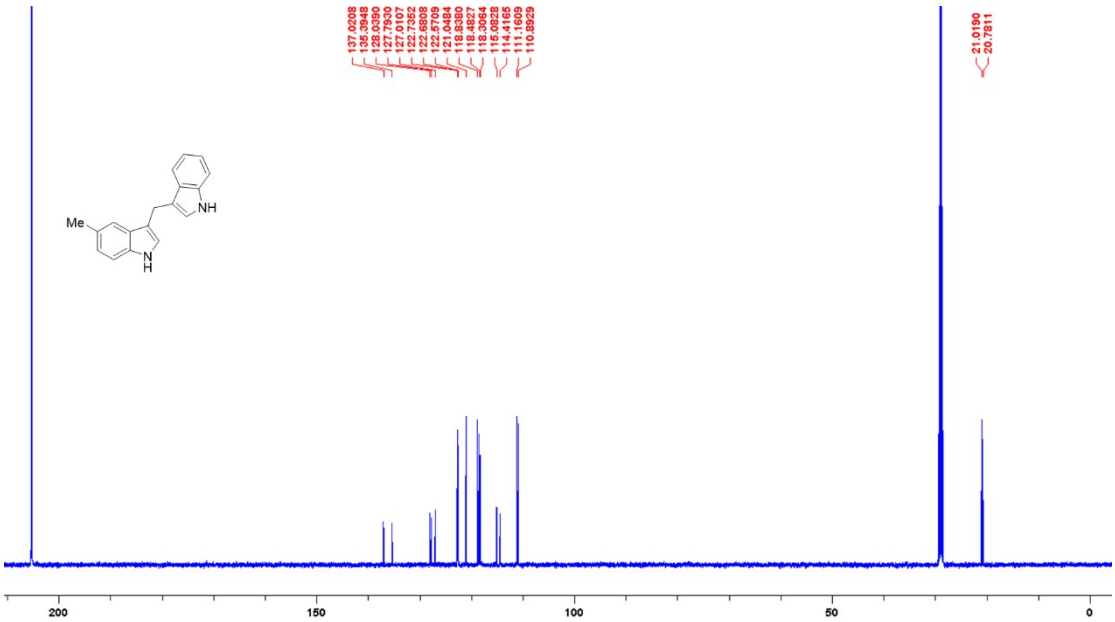


Figure S31. ^{13}C NMR spectrum of **1b**.

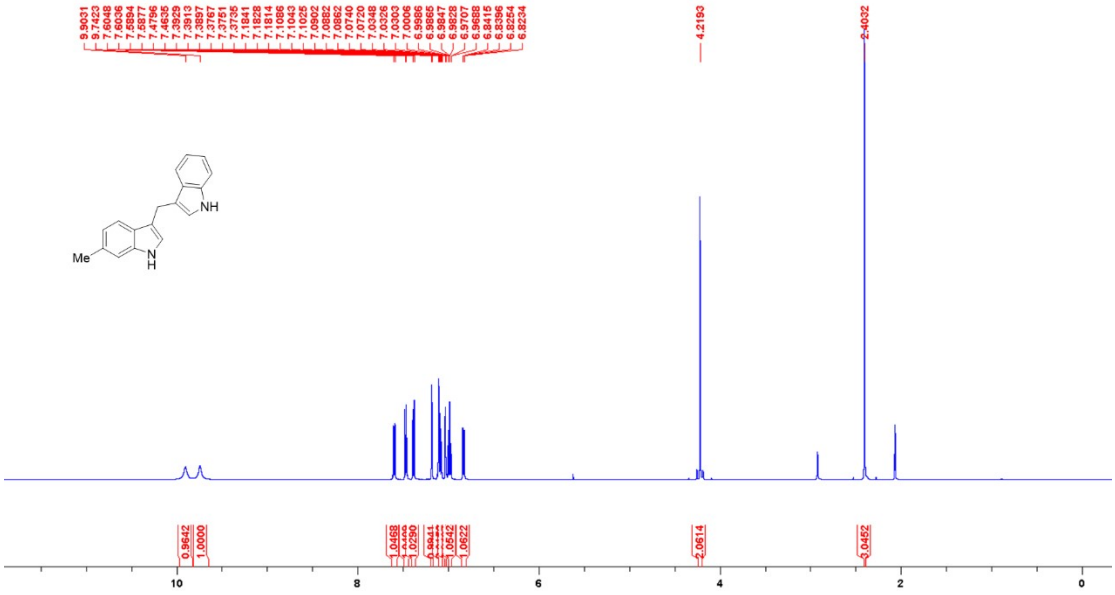


Figure S32. ^{1}H NMR spectrum of **1c**.

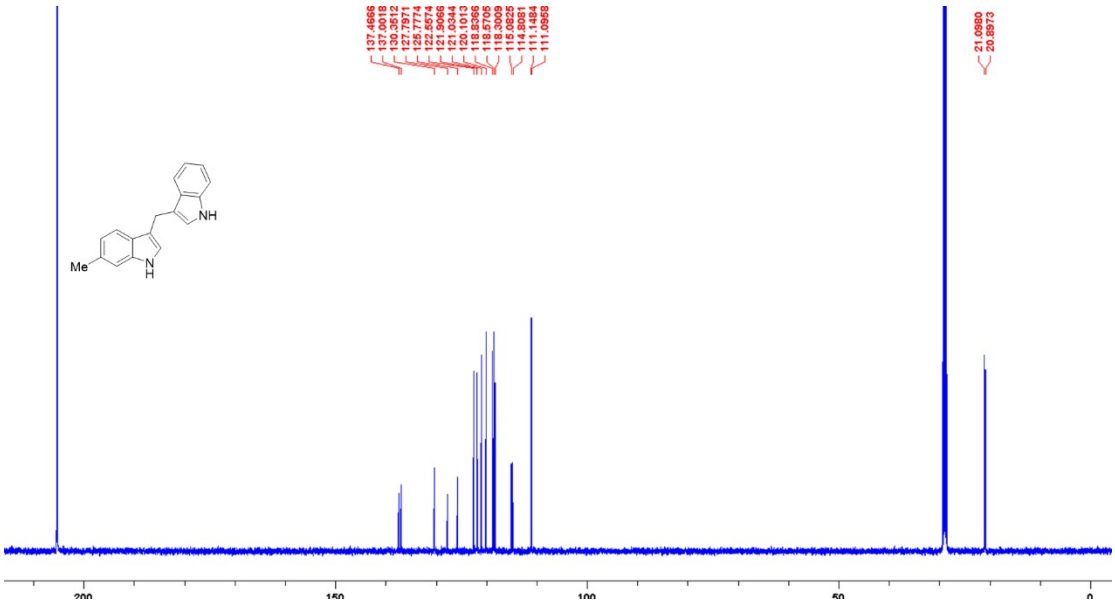


Figure S33. ^{13}C NMR spectrum of **1c**.

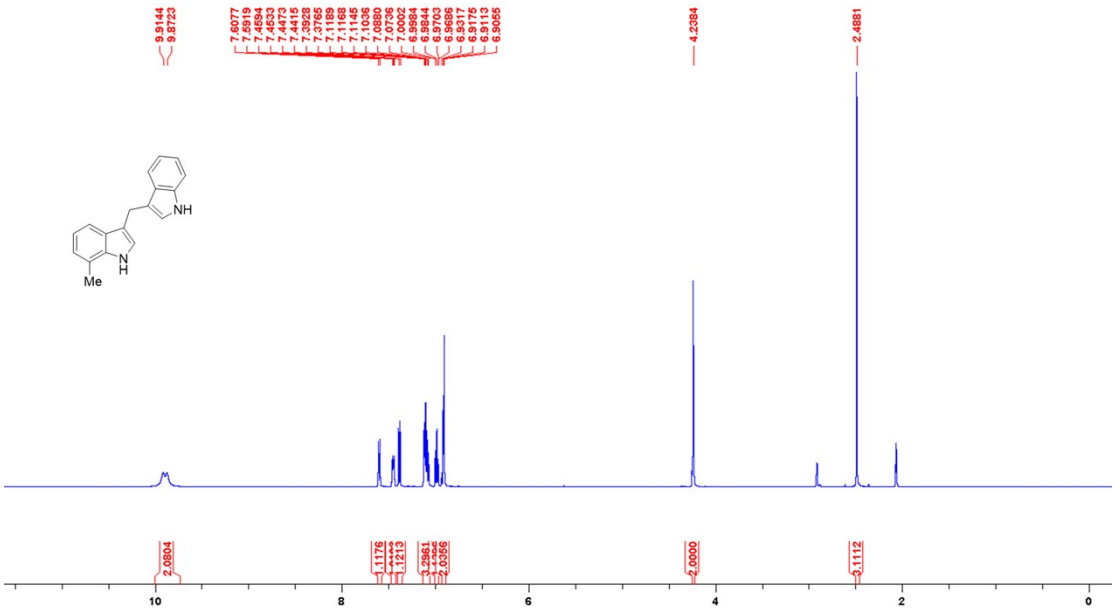


Figure S34. [1]H NMR spectrum of **1d**.

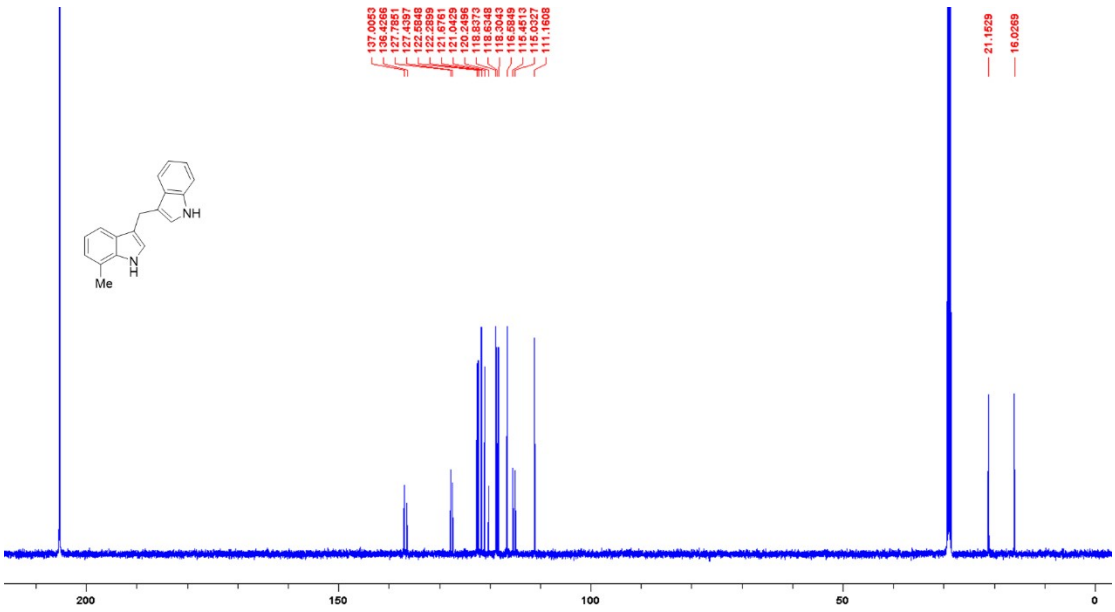


Figure S35. [13]C NMR spectrum of **1d**.

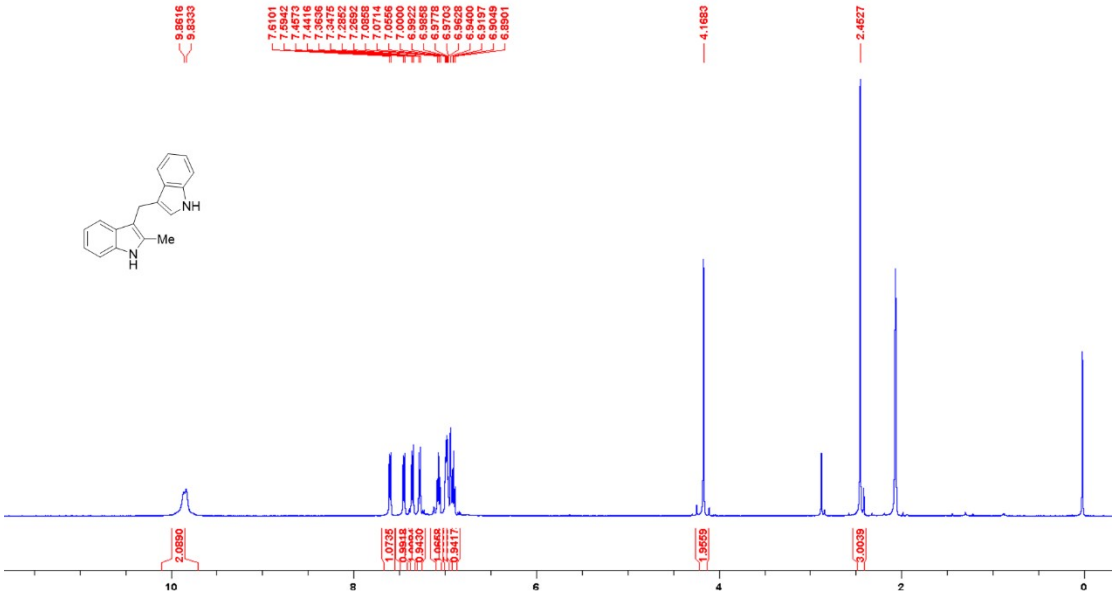


Figure S36. [1]H NMR spectrum of **1e**.

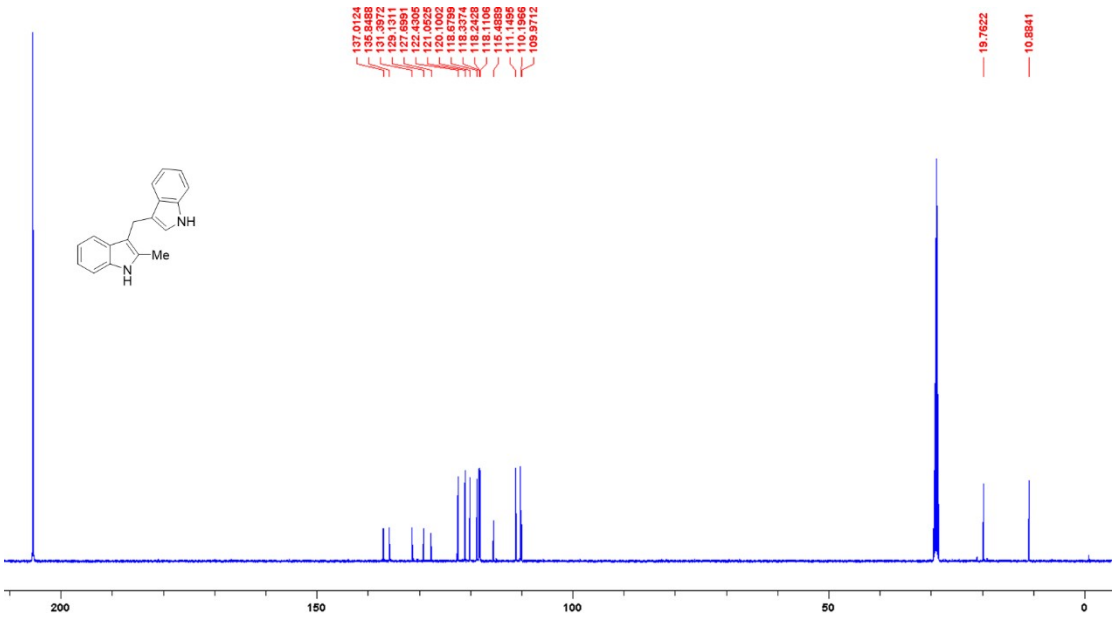


Figure S37. [13]C NMR spectrum of **1e**.

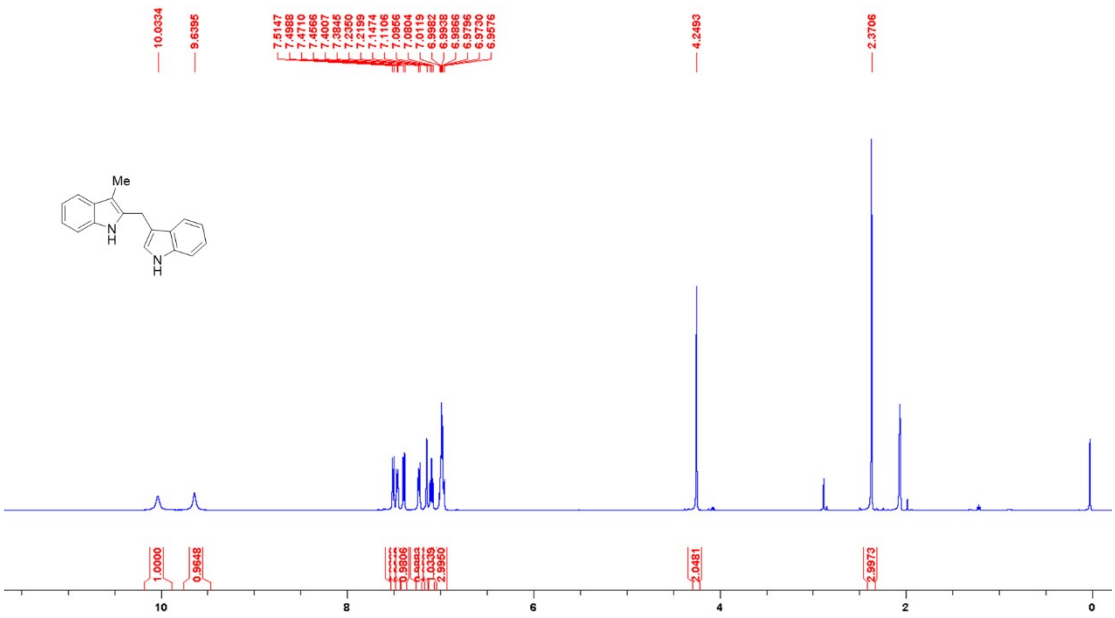


Figure S38. [1]H NMR spectrum of **1f**.

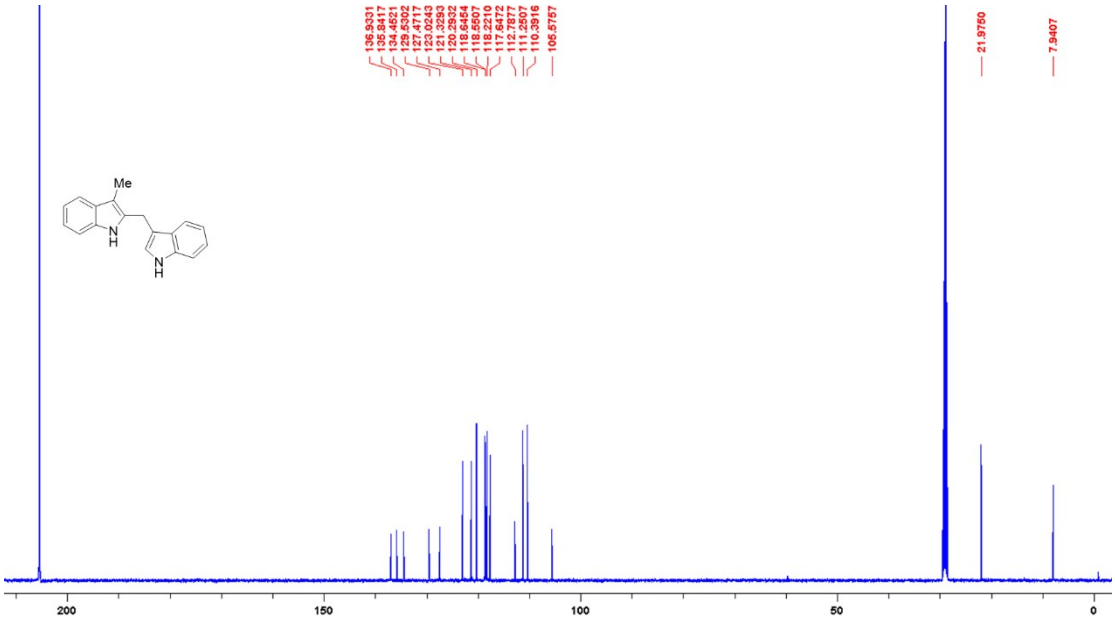


Figure S39. [13]C NMR spectrum of **1f**.

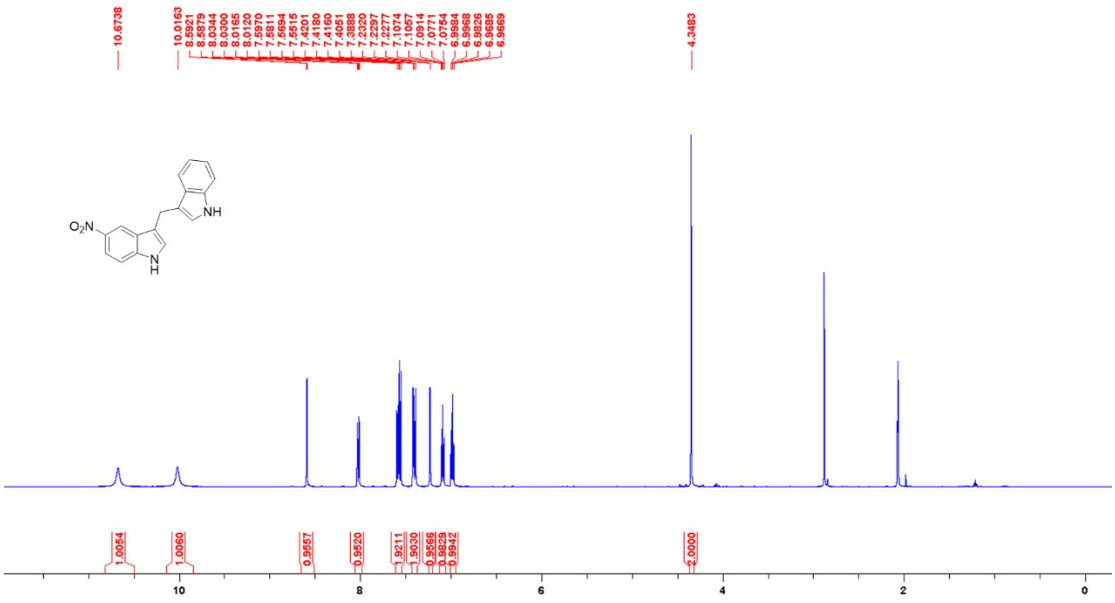


Figure S40. [1]H NMR spectrum of **1g**.

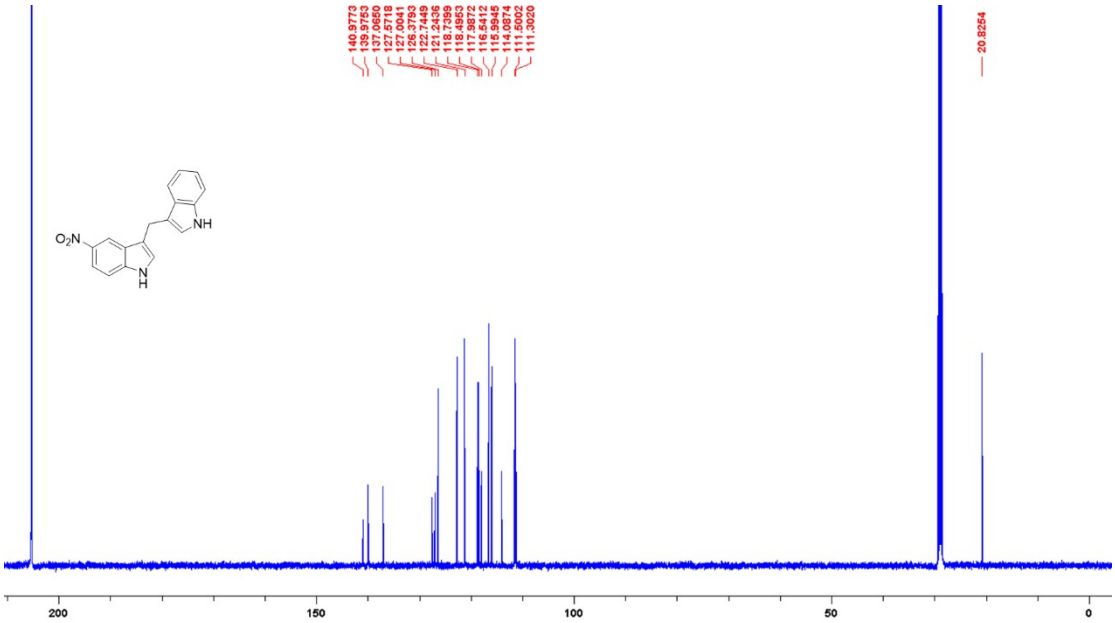


Figure S41. [13]C NMR spectrum of **1g**.

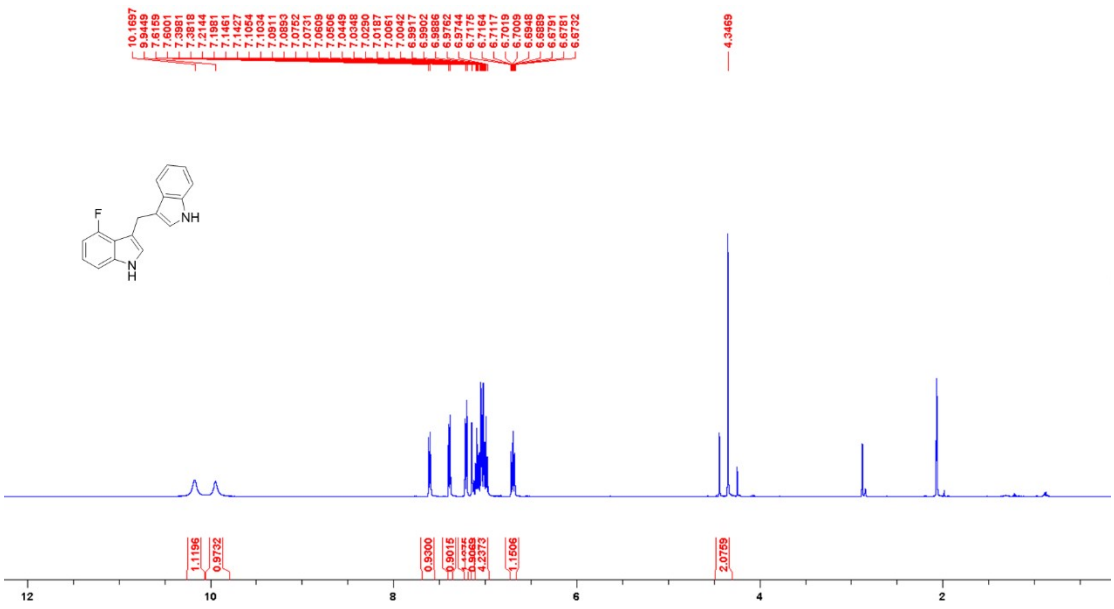


Figure S42. [1]H NMR spectrum of **1h**.

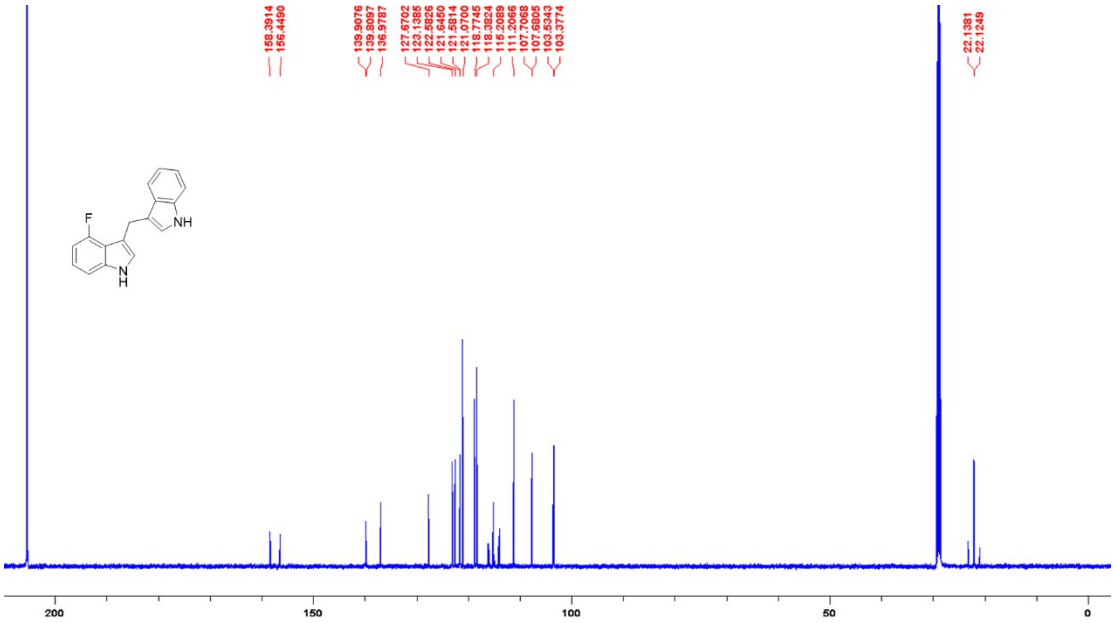


Figure S43. [13]C NMR spectrum of **1h**.

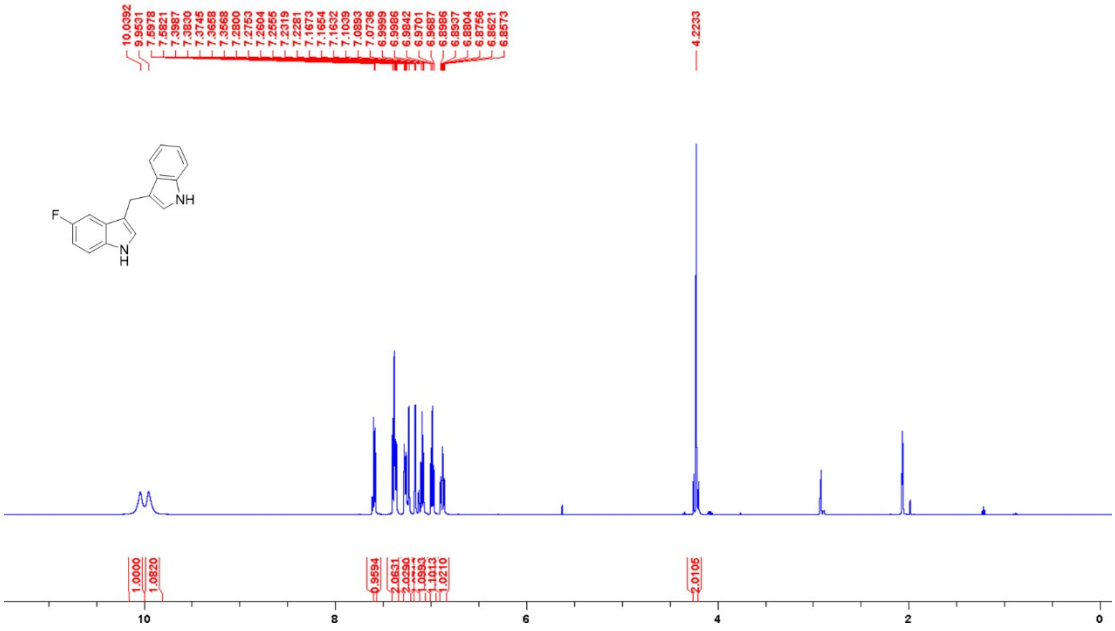


Figure S44. [1]H NMR spectrum of **1i**.

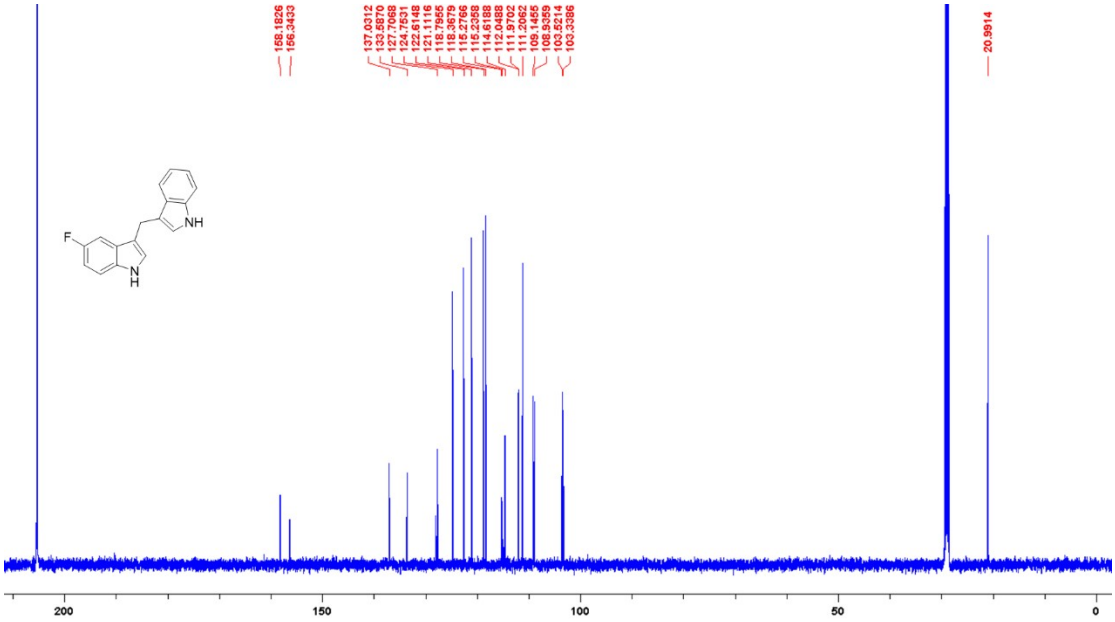


Figure S45. [13]C NMR spectrum of **1i**.

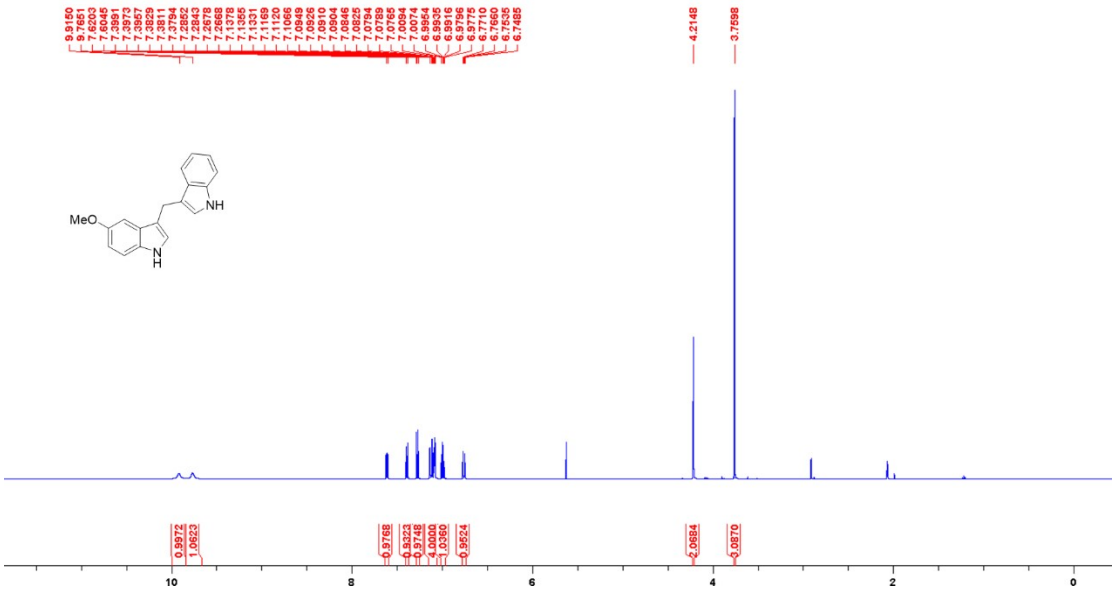


Figure S46. ^{1}H NMR spectrum of **1j**.

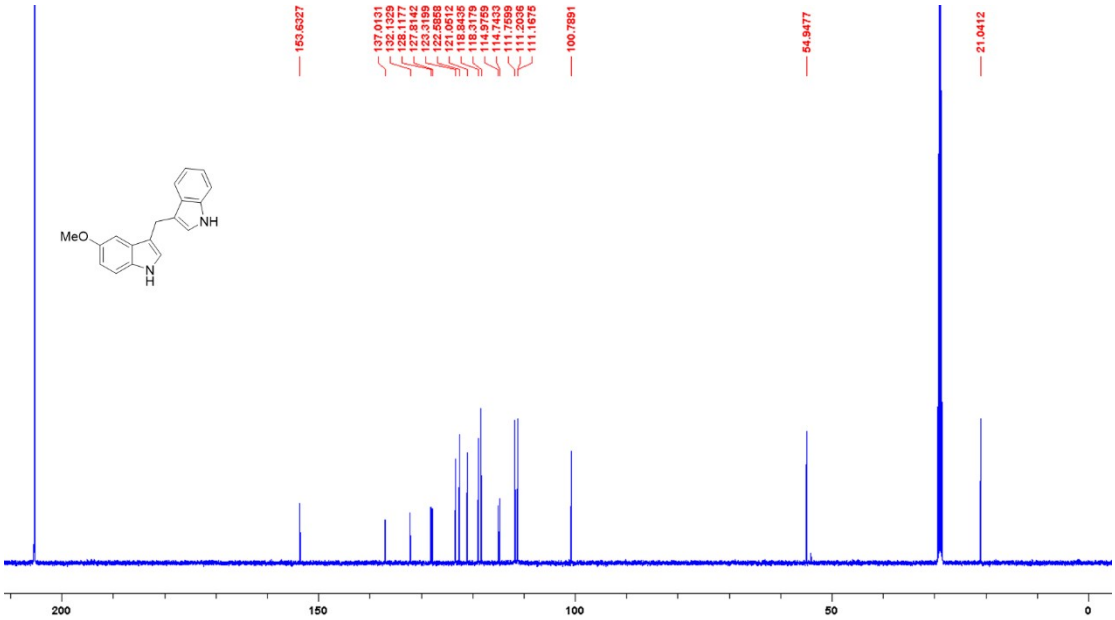


Figure S47. ^{13}C NMR spectrum of **1j**.

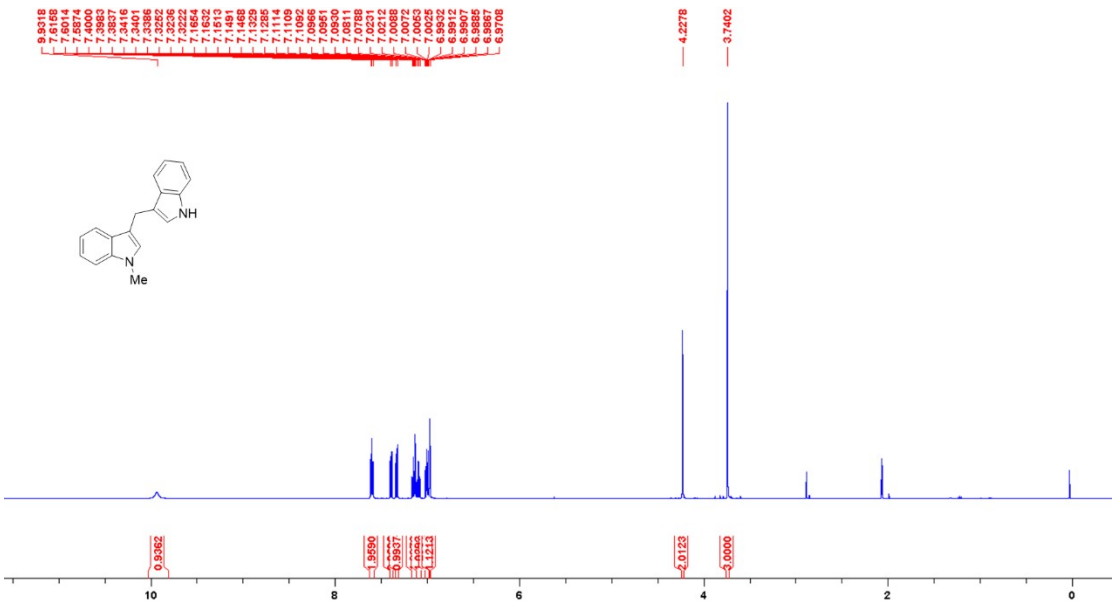


Figure S48. [1]H NMR spectrum of **1k**.

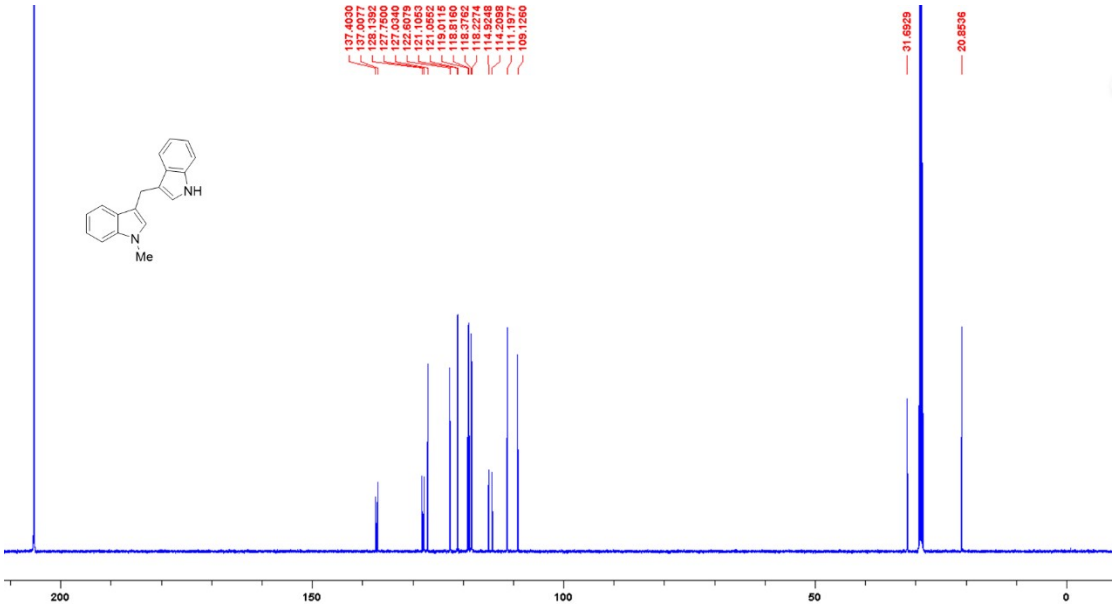


Figure S49. [13]C NMR spectrum of **1k**.

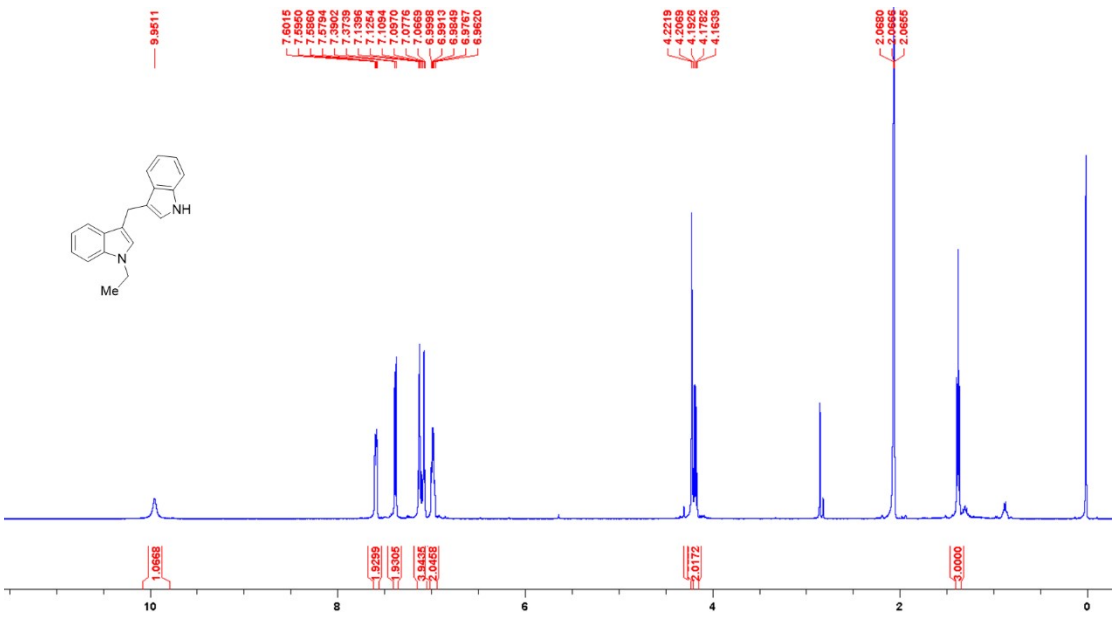


Figure S50. [1]H NMR spectrum of **1l**.

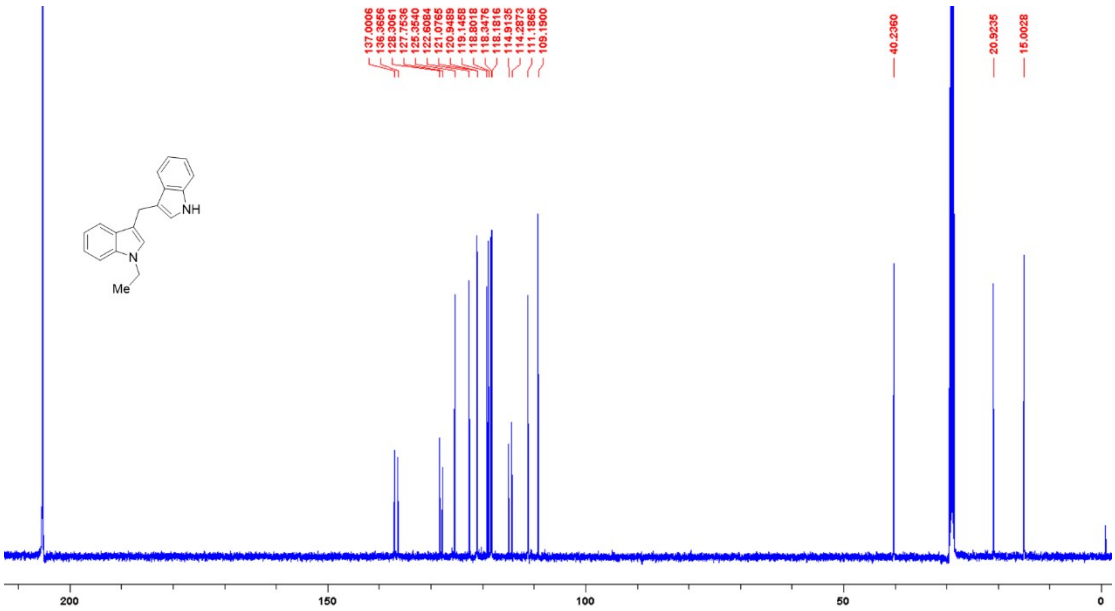


Figure S51. [13]C NMR spectrum of **1l**.

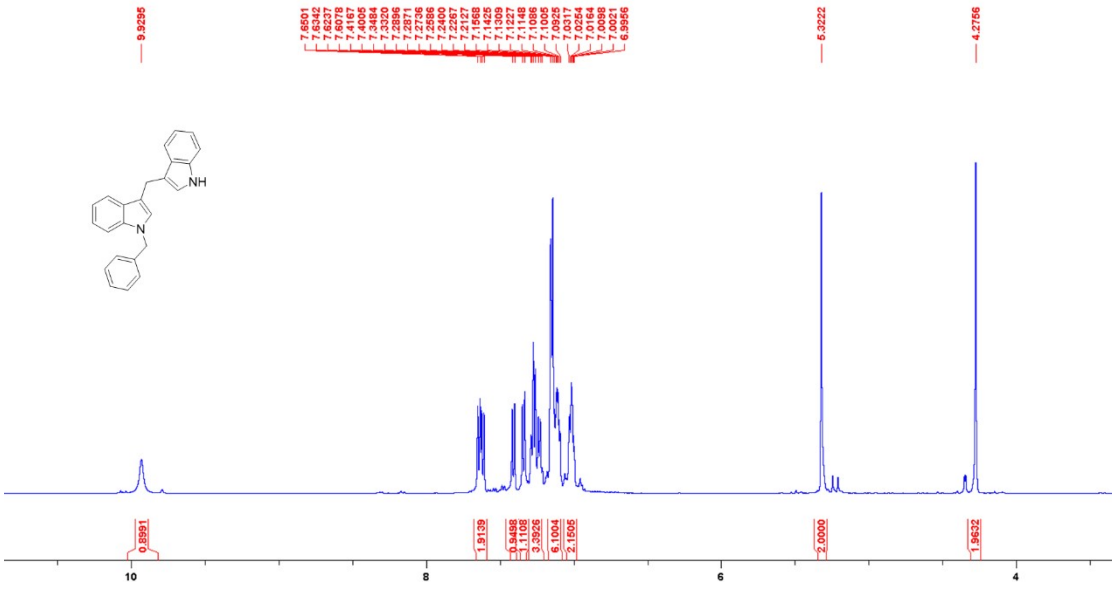


Figure S52. [1]H NMR spectrum of **1m**.

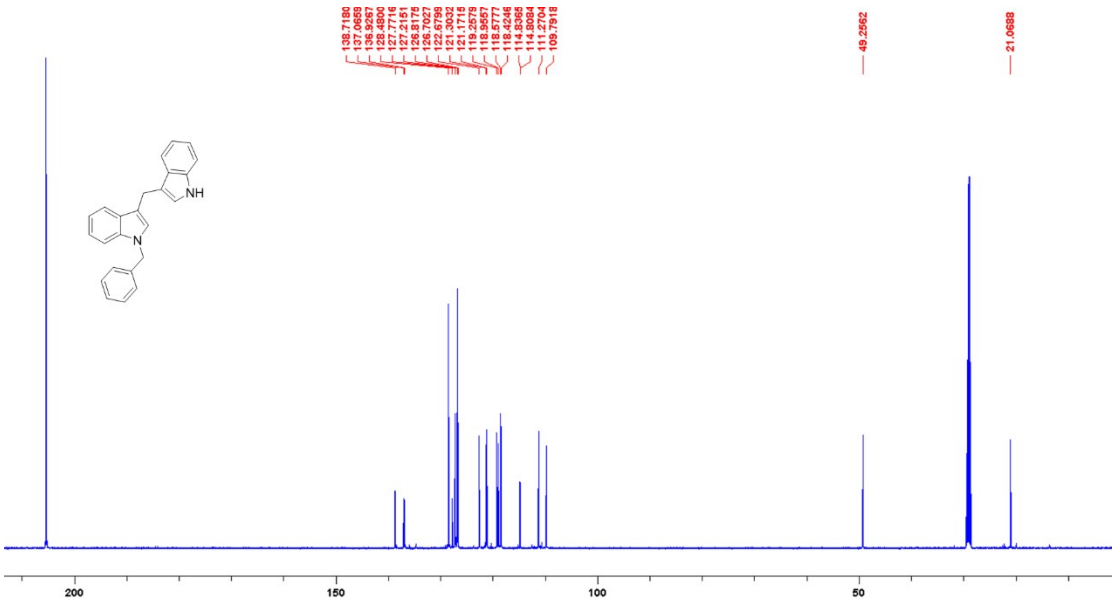


Figure S53. [13]C NMR spectrum of **1m**.

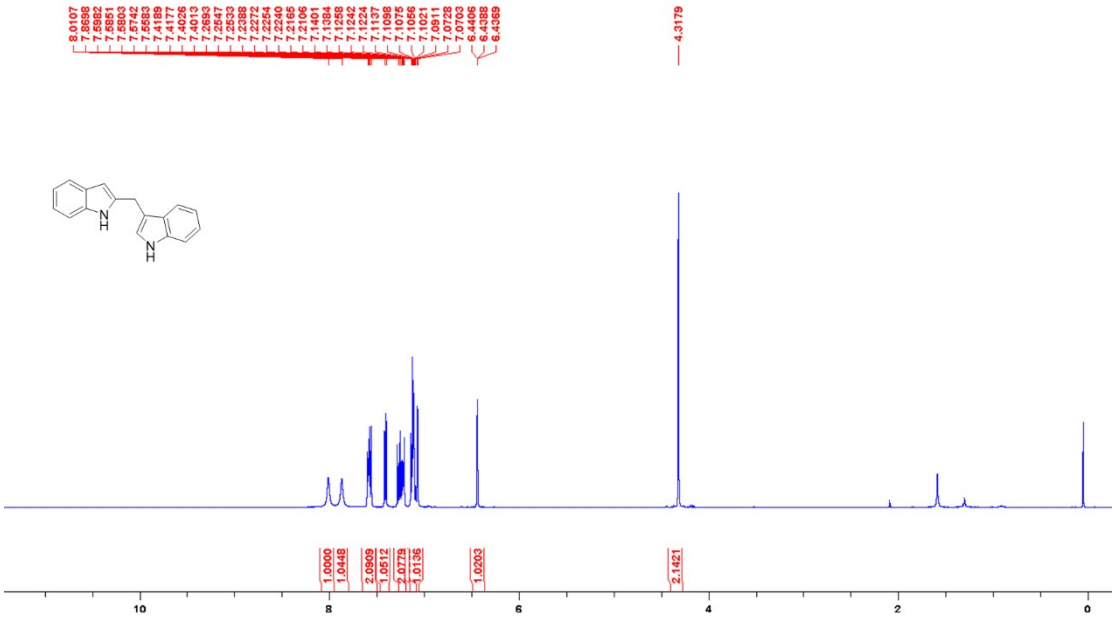


Figure S54. [1]H NMR spectrum of **8**.

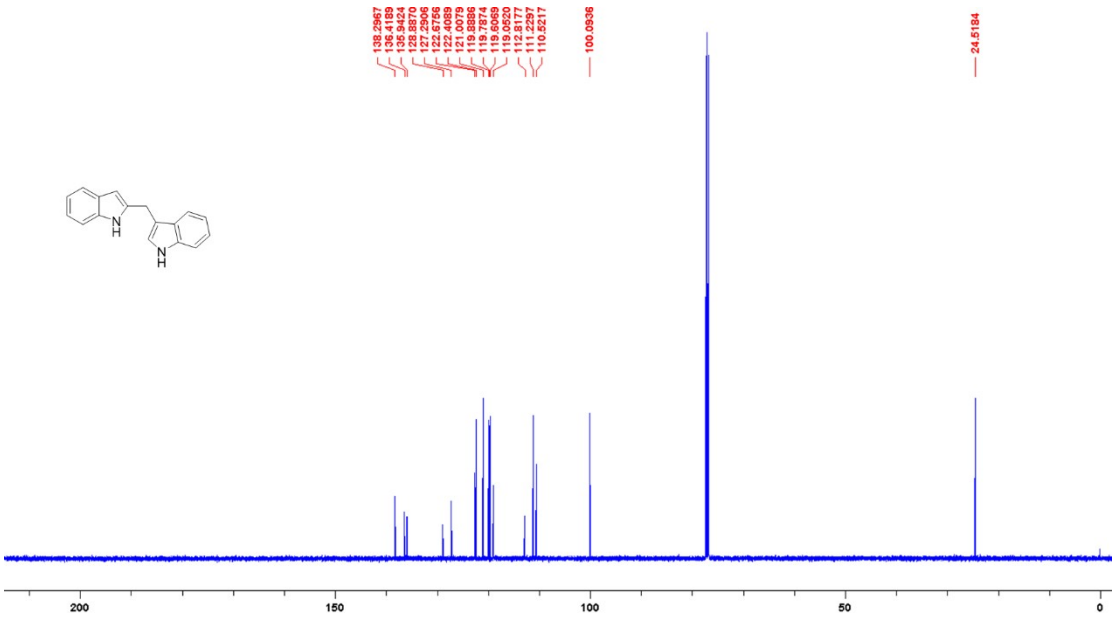


Figure S55. [13]C NMR spectrum of **8**.

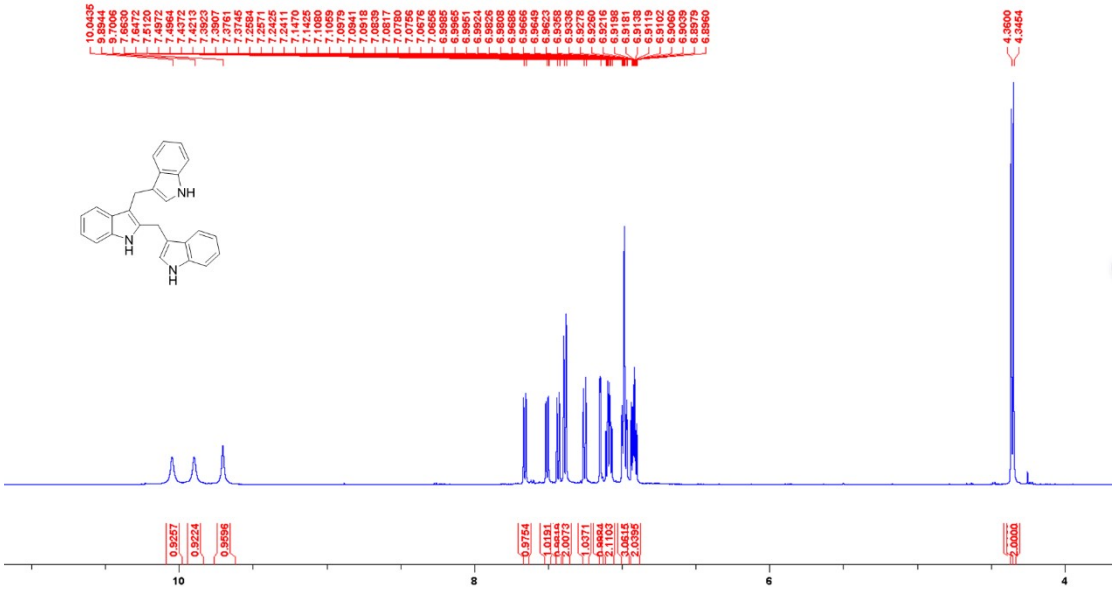


Figure S56. [1]H NMR spectrum of LTr1.

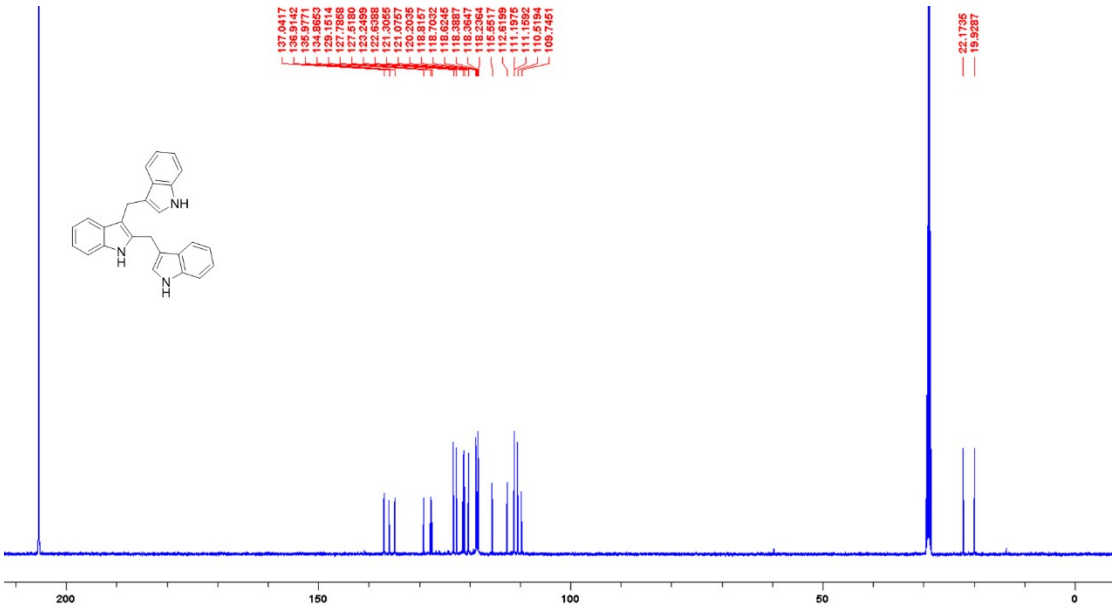


Figure S57. [13]C NMR spectrum of LTr1.

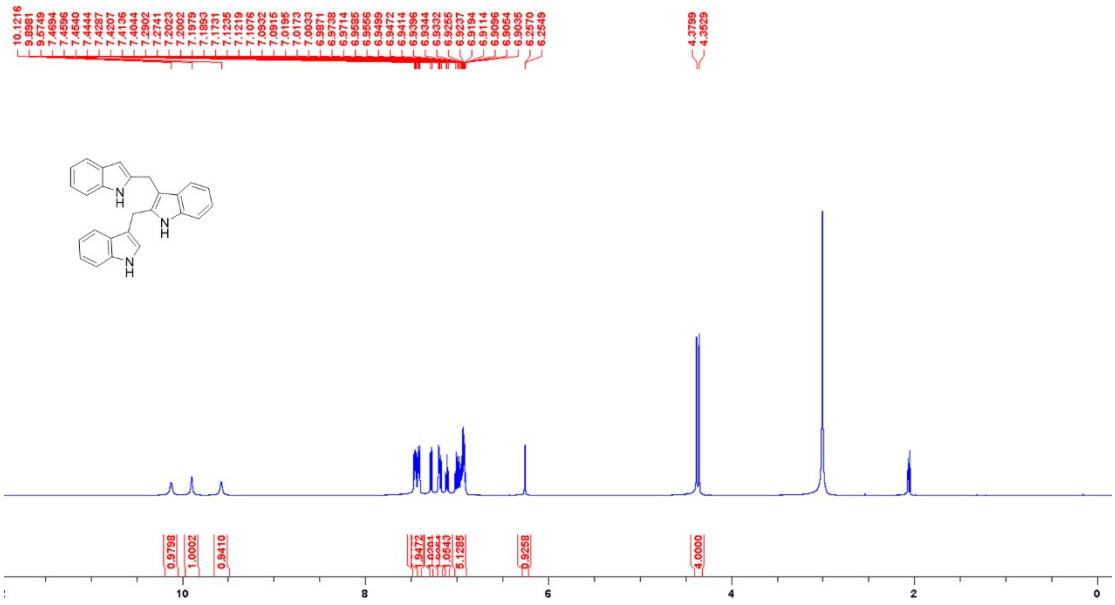


Figure S58. [1]H NMR spectrum of **10**.

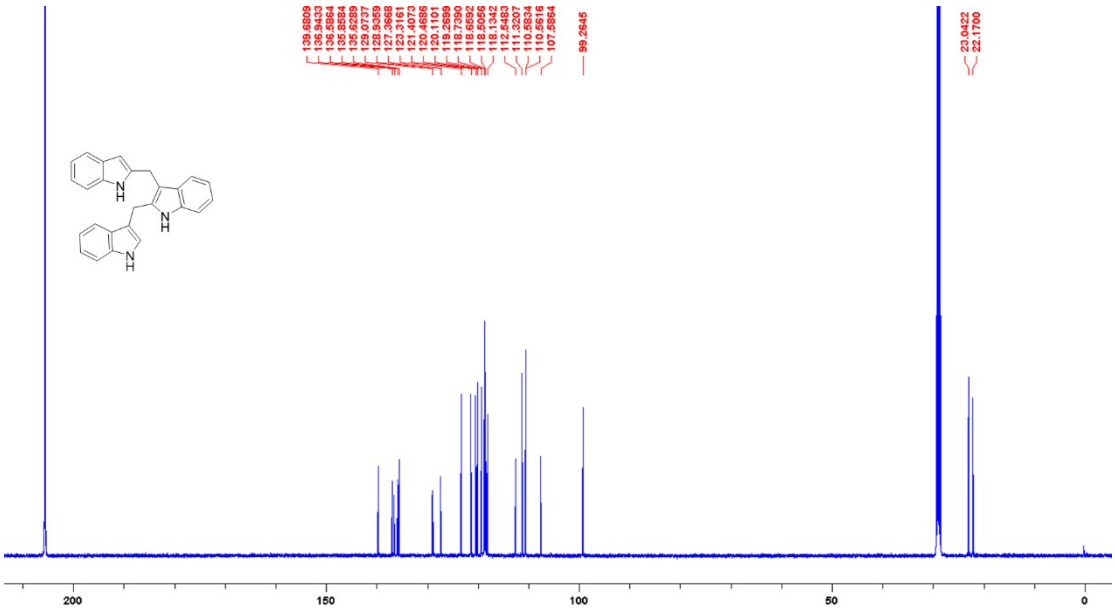


Figure S59. [13]C NMR spectrum of **10**.

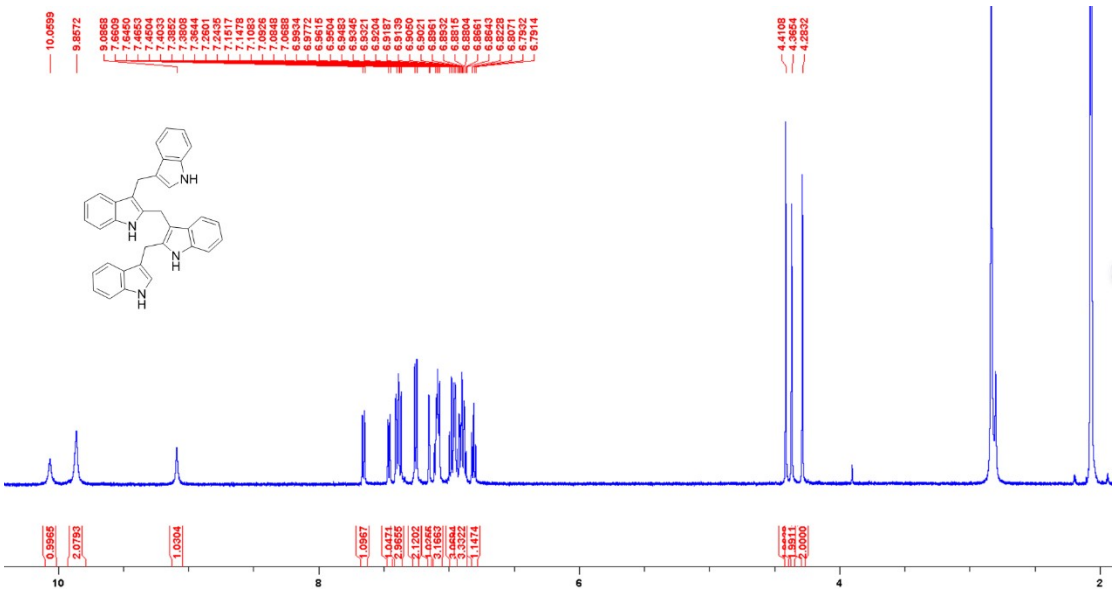


Figure S60. [1]H NMR spectrum of LTe2.

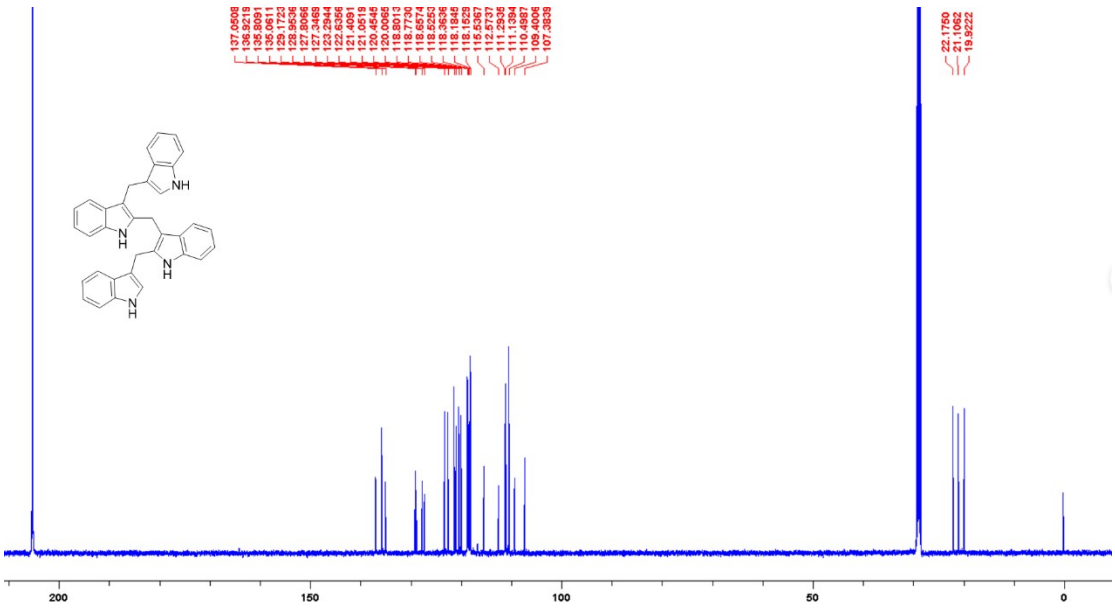


Figure S61. [13]C NMR spectrum of LTe2.

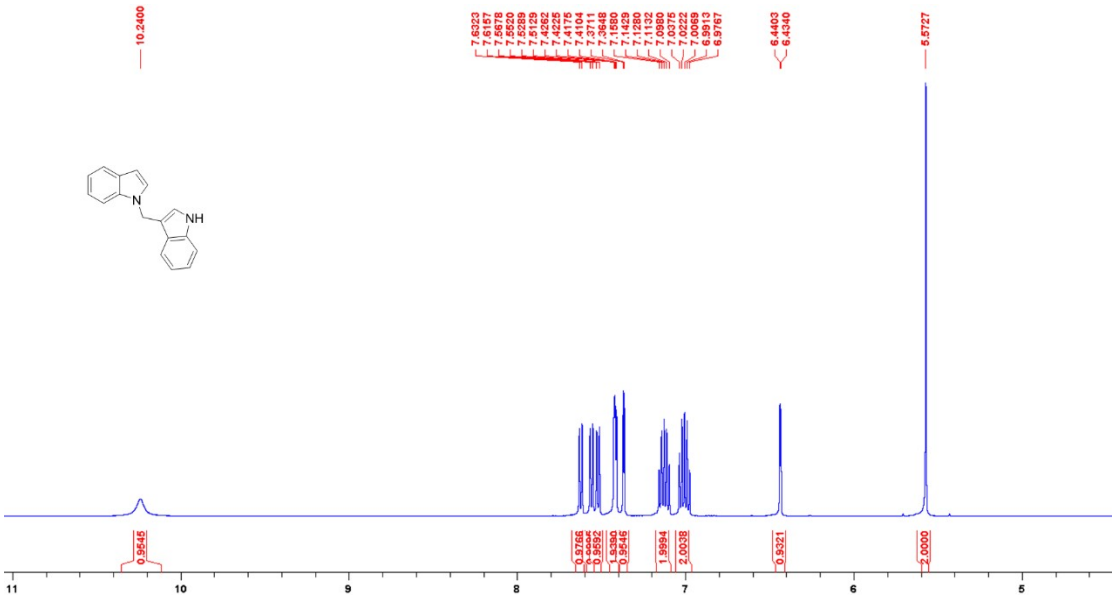


Figure S62. [1]H NMR spectrum of **11**.

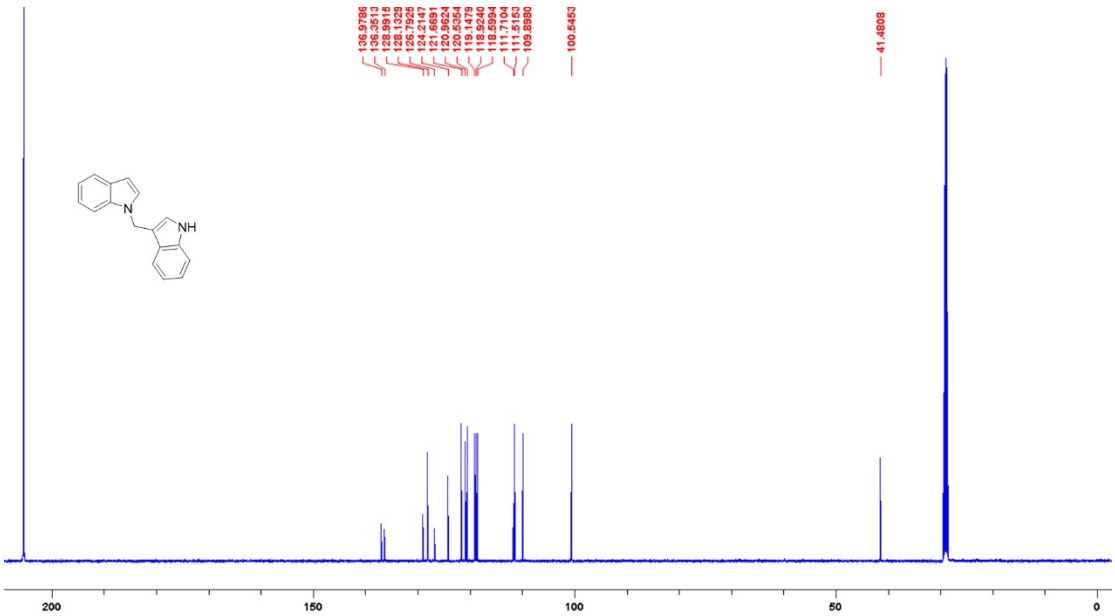


Figure S63. [13]C NMR spectrum of **11**.

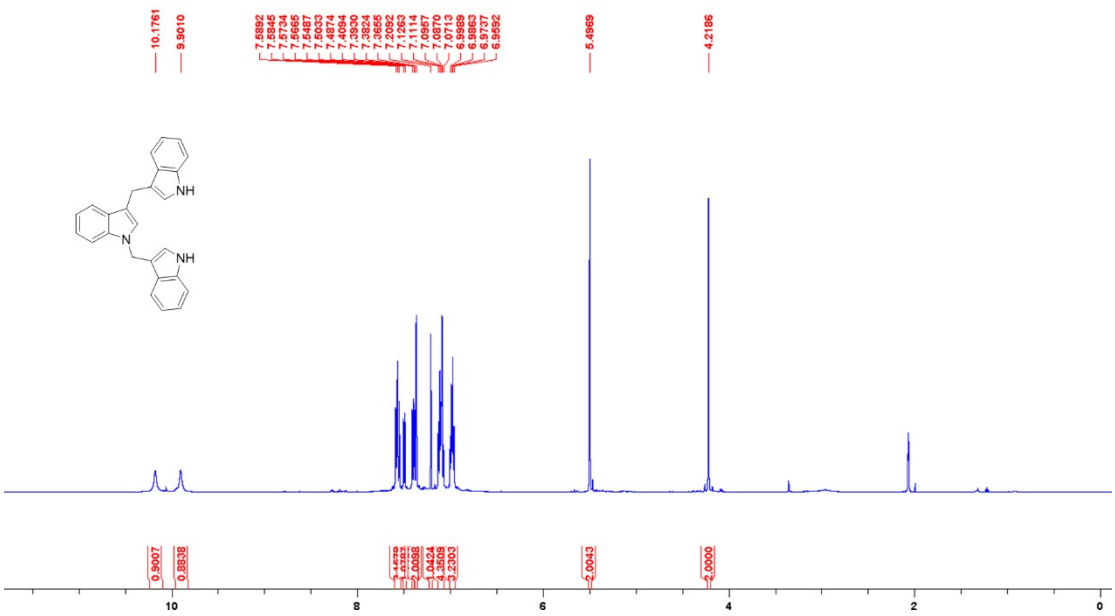


Figure S64. [1]H NMR spectrum of LTr3.

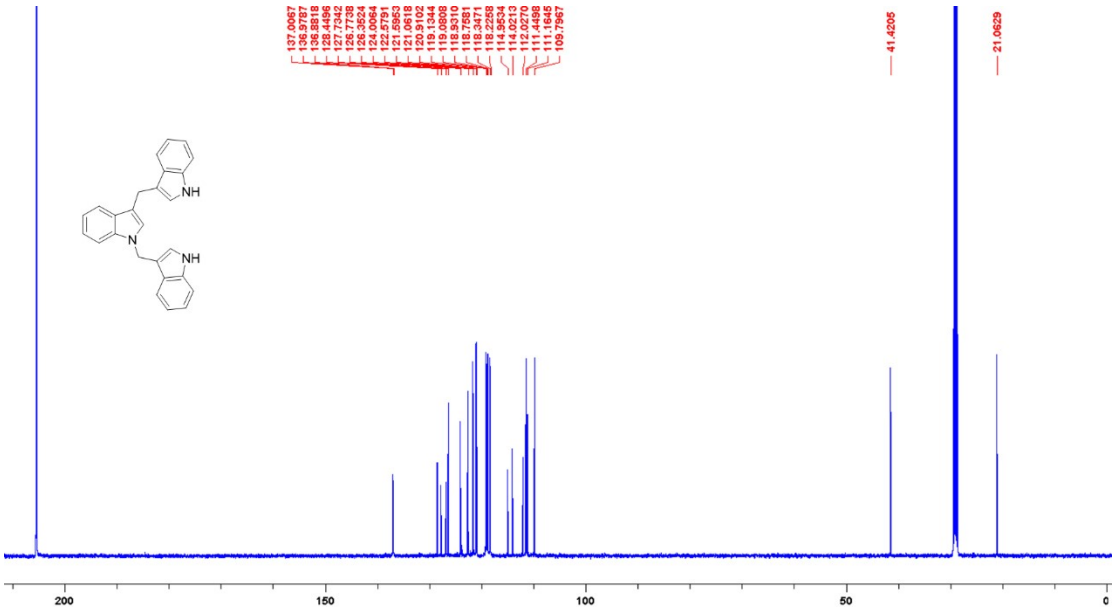


Figure S65. [13]C NMR spectrum of LTr3.

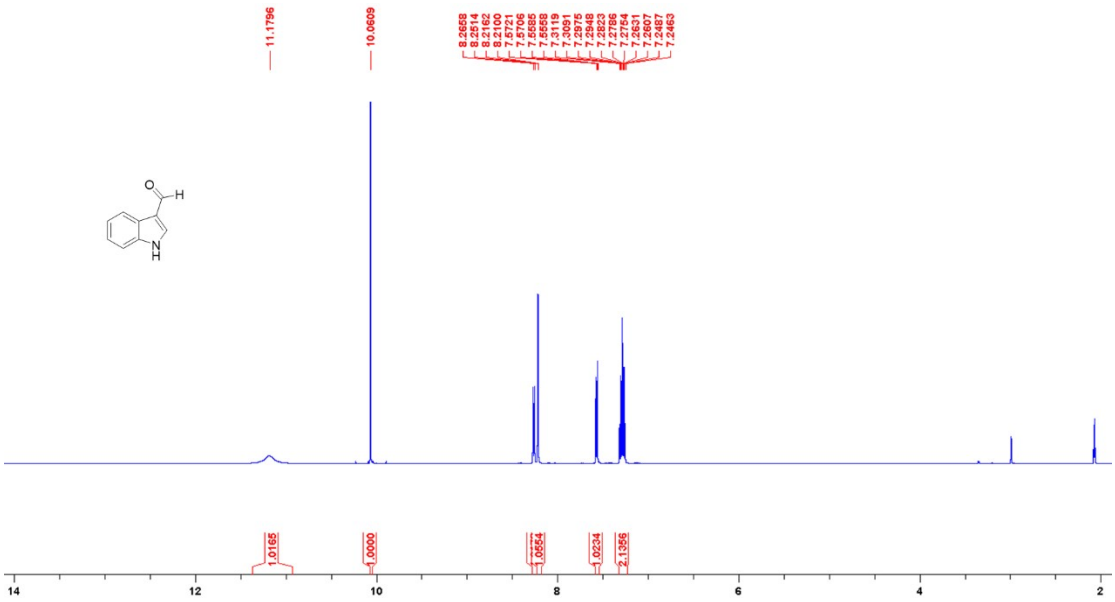


Figure S66. ^{1}H NMR spectrum of **15**.

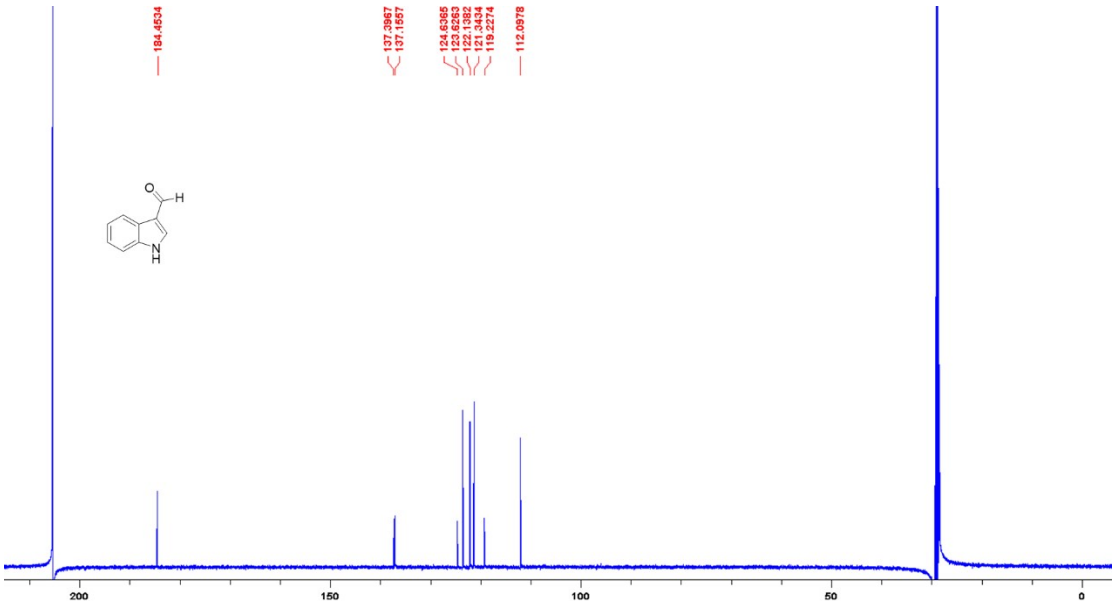


Figure S67. ^{13}C NMR spectrum of **15**.

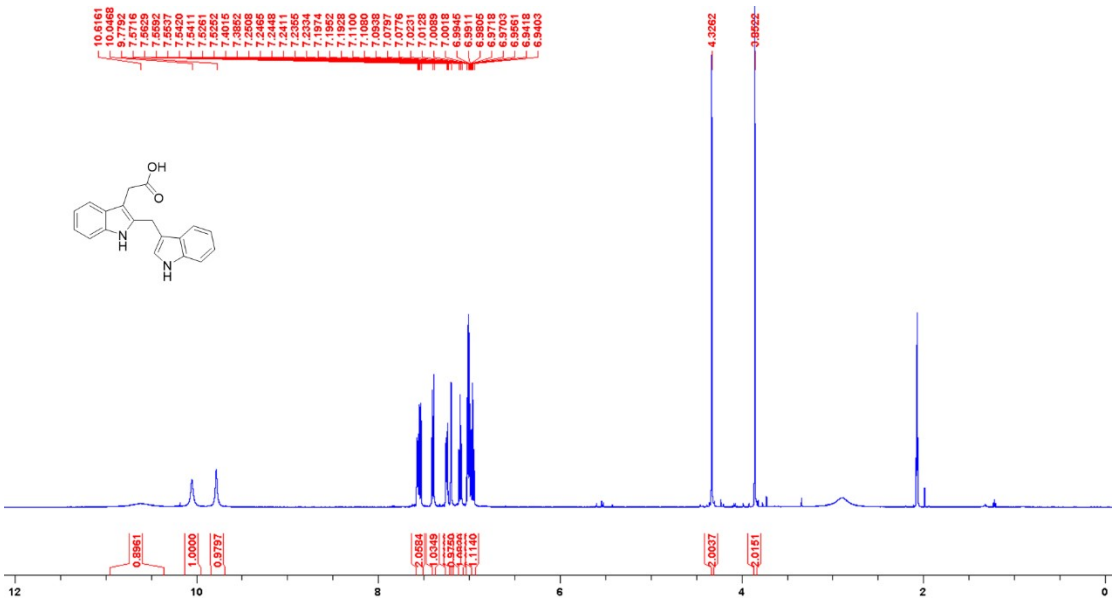


Figure S68. [1]H NMR spectrum of **16**.

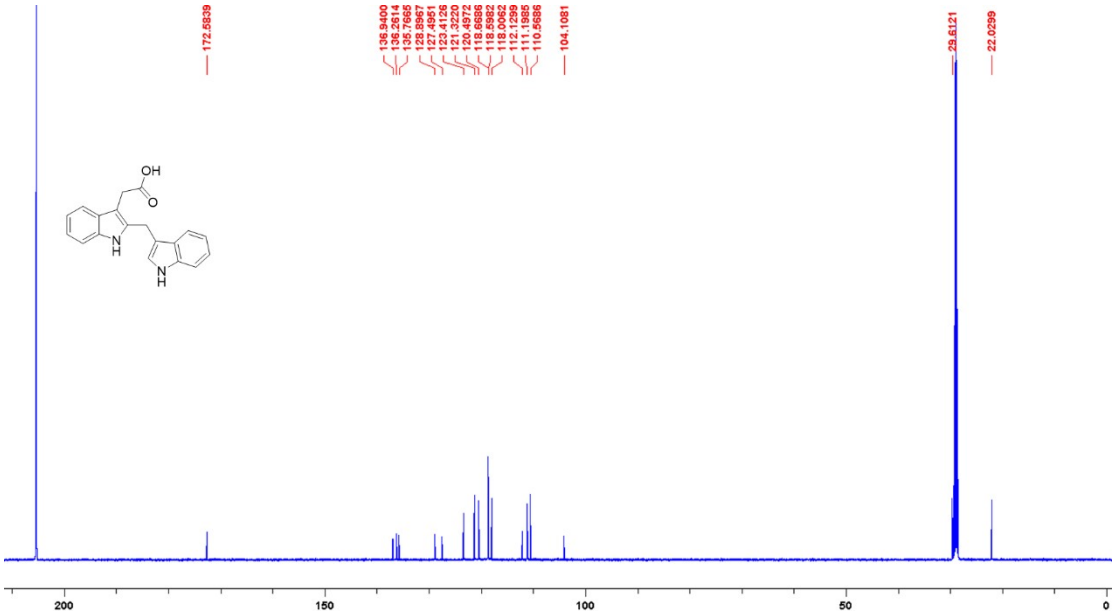


Figure S69. [13]C NMR spectrum of **16**.

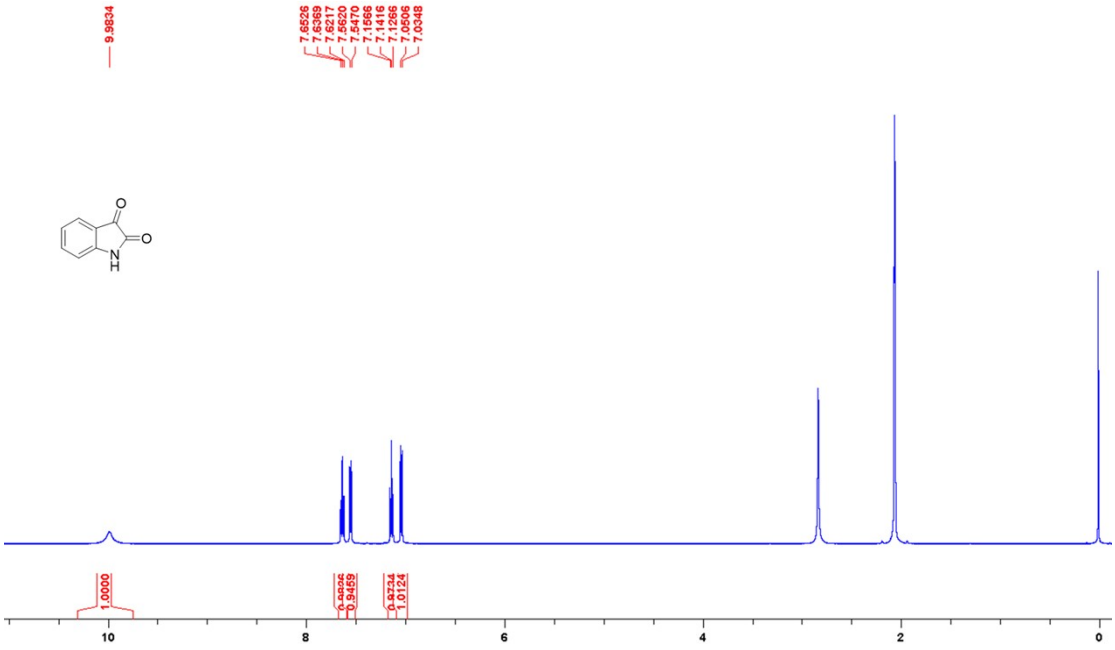


Figure S70. ^{1}H NMR spectrum of **17**.

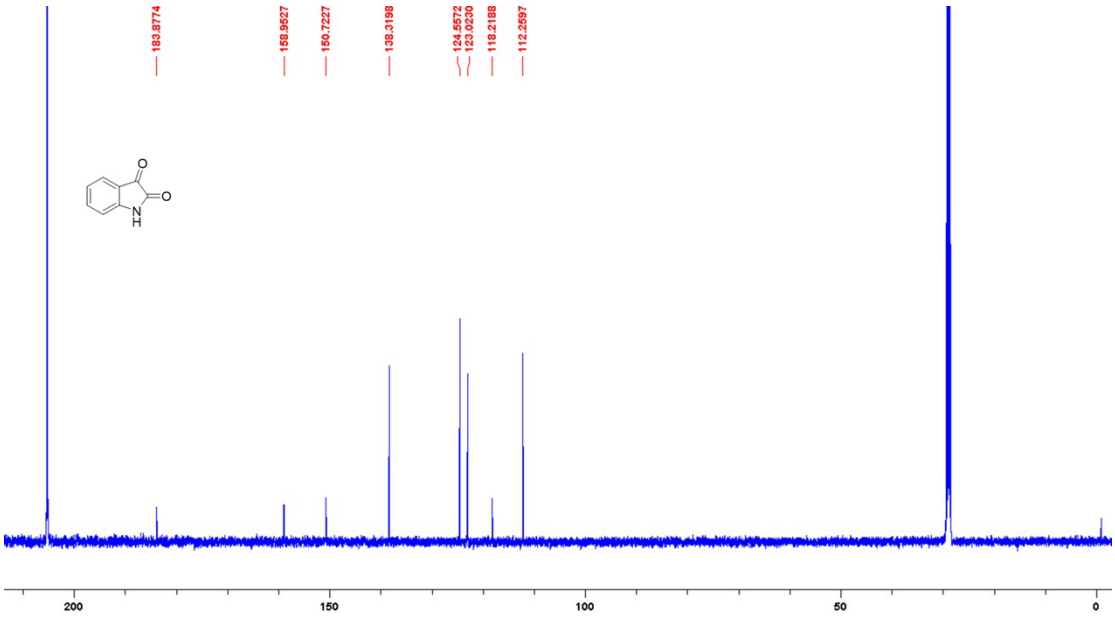


Figure S71. ^{13}C NMR spectrum of **17**.

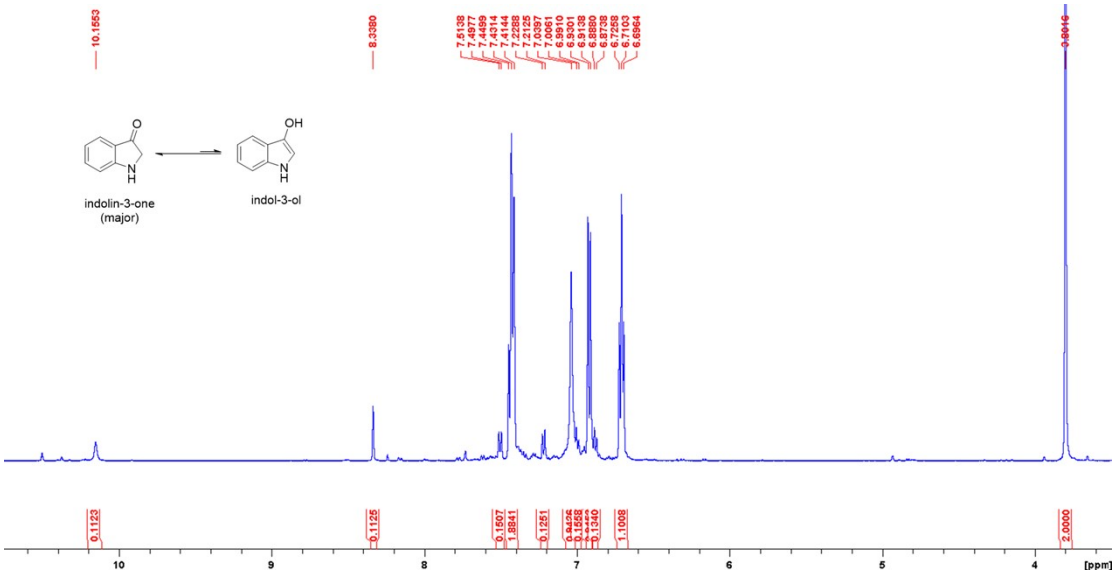


Figure S72. ^{1}H NMR spectrum of indolin-3-one and indol-3-ol.

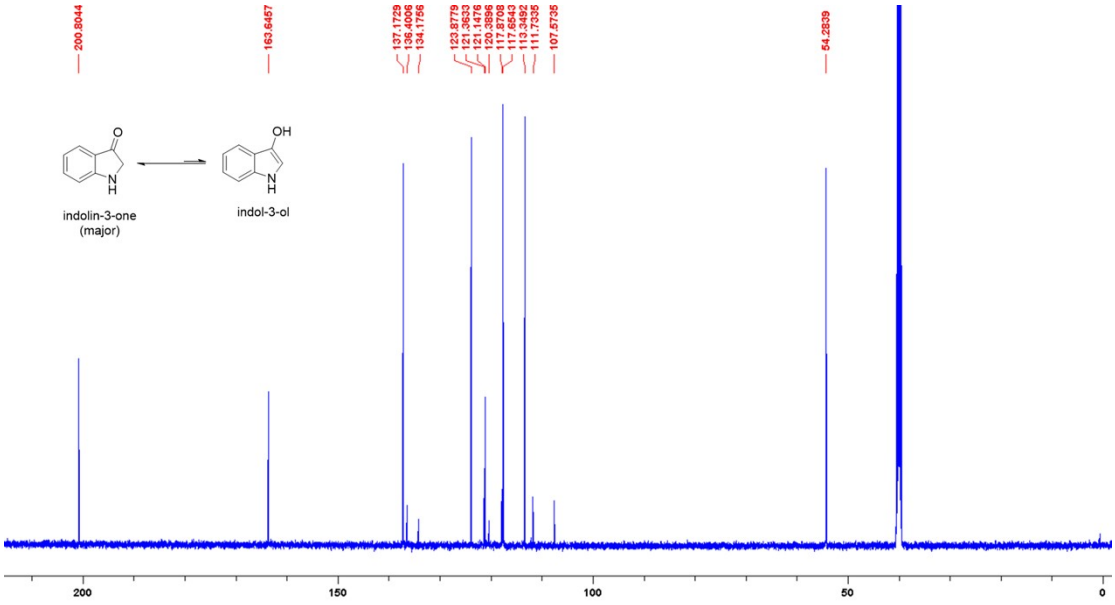


Figure S73. ^{13}C NMR spectrum of indolin-3-one and indol-3-ol.

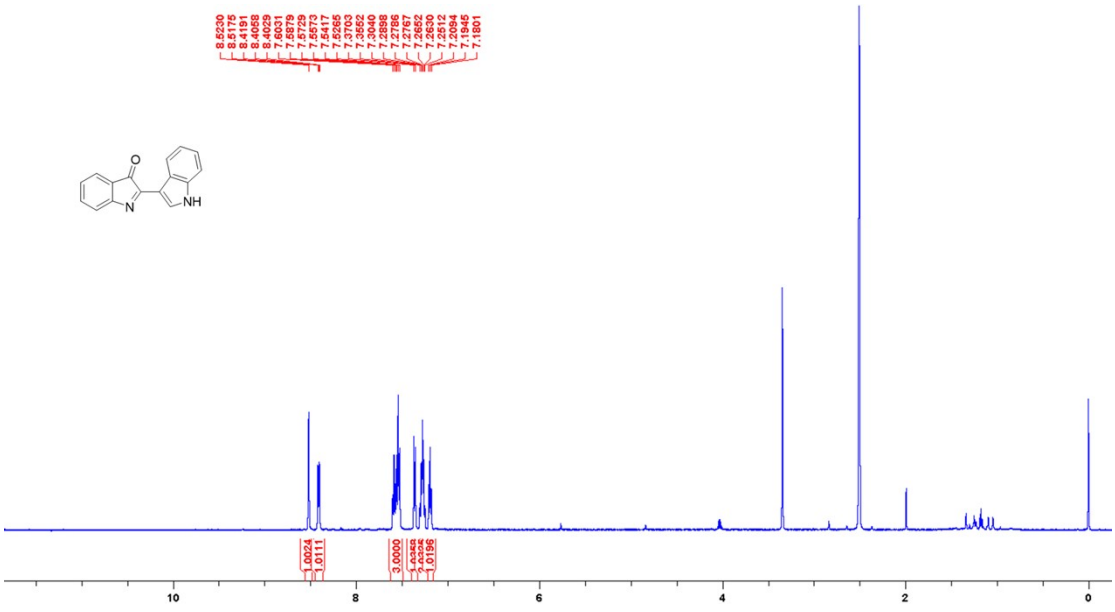


Figure S74. [1]H NMR spectrum of **19**.

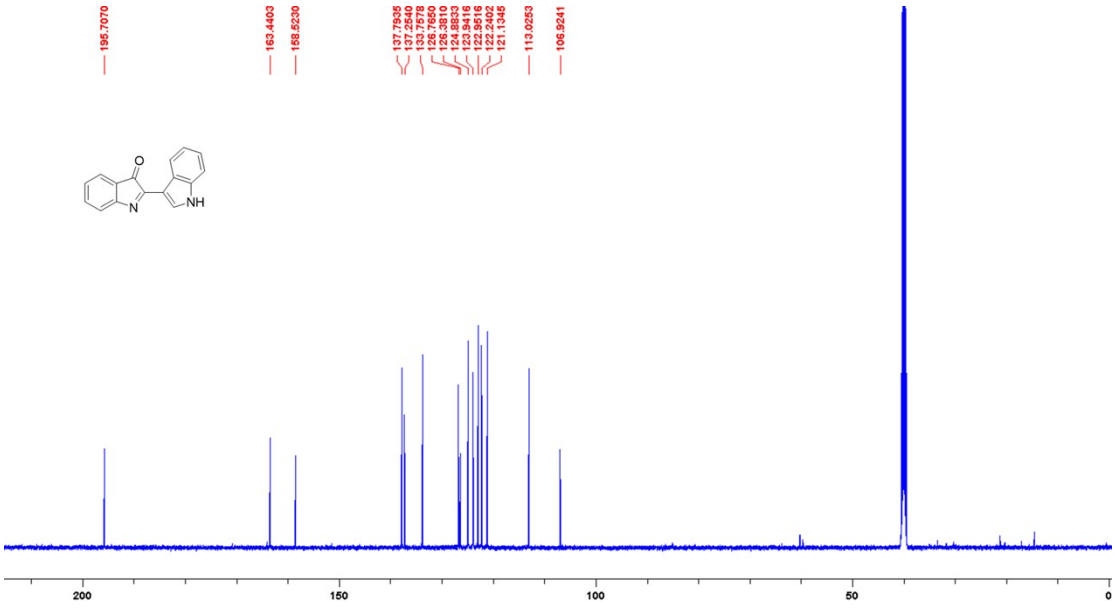


Figure S75. [13]C NMR spectrum of **19**.

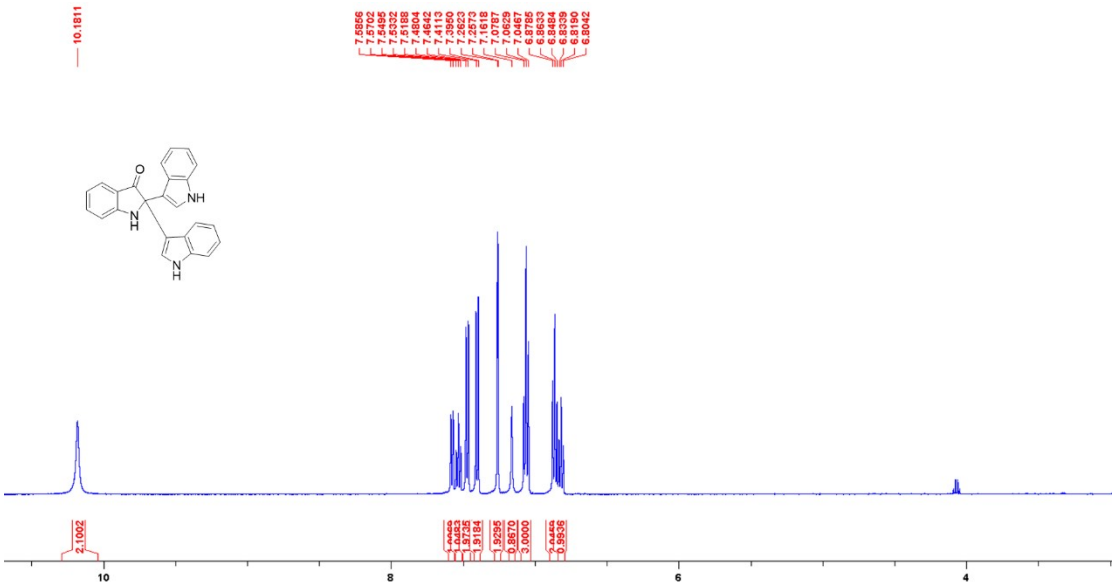


Figure S76. [1]H NMR spectrum of **20**.

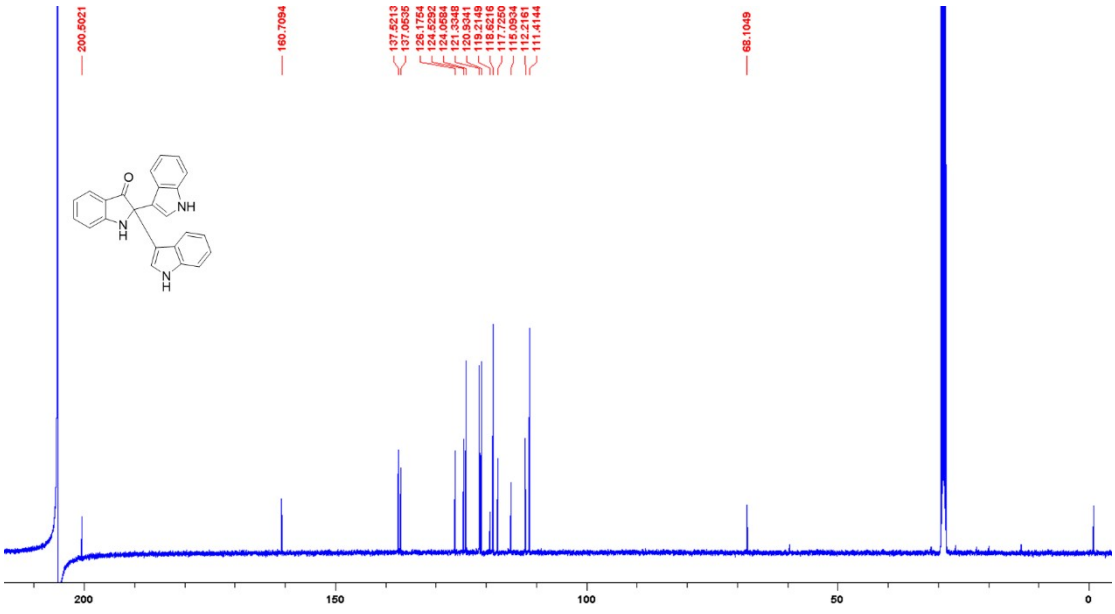


Figure S77. [13]C NMR spectrum of **20**.

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