Supporting Information

for

CF_3SO_2Na-Mediated, UV-Light-Induced Friedel-Crafts Alkylation of Indoles with Ketones/Aldehydes and Bioactivities of Products

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1. General Information

All reactions were carried out under air/oxygen atmosphere using standard Schlenk techniques unless stated otherwise. The glassware was dried in an oven (110 °C) and heated under reduced pressure before use. Thin layer chromatography (TLC) and column chromatography analyses were performed using Anhui Liangchen silica gel (200–300) with distilled solvents. NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) in $CDCl_3$. All ^{1}H and ^{13}C NMR chemical shifts were reported in ppm relative to internal references of $CDCl_3$ at 7.26 ppm and carbon resonance in chloroform-d_1 at 77.00 ppm, respectively. The following abbreviations are used to describe peak patterns where appropriate: singlet, doublet (d), triplet (t), multiplet (m), broad resonances (br).

Chemicals

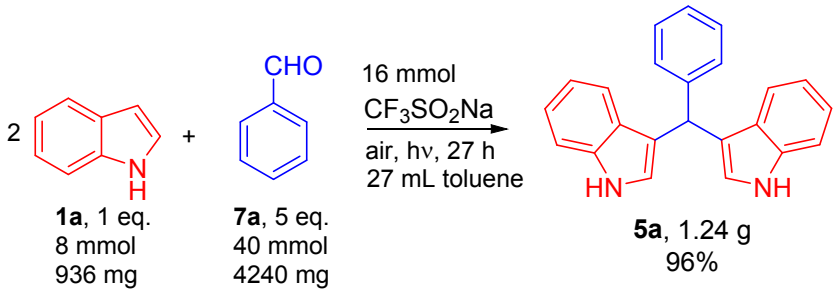
Unless noted otherwise, the materials obtained from commercial suppliers were used without further purification. All solvents were general grade.

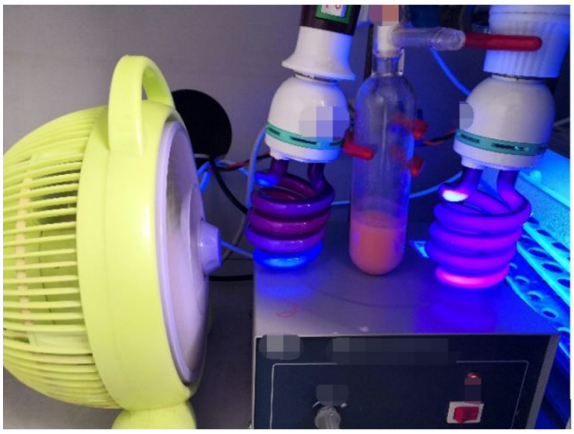
General Procedure for the 3,3′-diindolylmethanes

To a 10.0 mL screw capped vial equipped with a magnetic stirring bar was added indole derivatives (**1**, 0.3 mmol), aldehyde or acetone derivatives (**2**, 1.5 mmol), CF_3SO_2Na (0.6 mmol, 93.6 mg), and general toluene (1.0 mL) under air/oxygen atmosphere and UV light. The reaction mixture was vigorously stirred at room temperature for 24 h. Afterward the solvents were removed under reduced pressure, and the crude mixture was purified by chromatography on silica gel (petroleum ether/ethyl acetate=10/1 as eluent) to obtain the desired product. The other representative methods for the synthesis of bis(indolyl) methanes are available in references.[1-3]

Procedure for the synthesis of 3,3′-(phenylmethylene)bis(1H-indole) in 1 Gram Scale

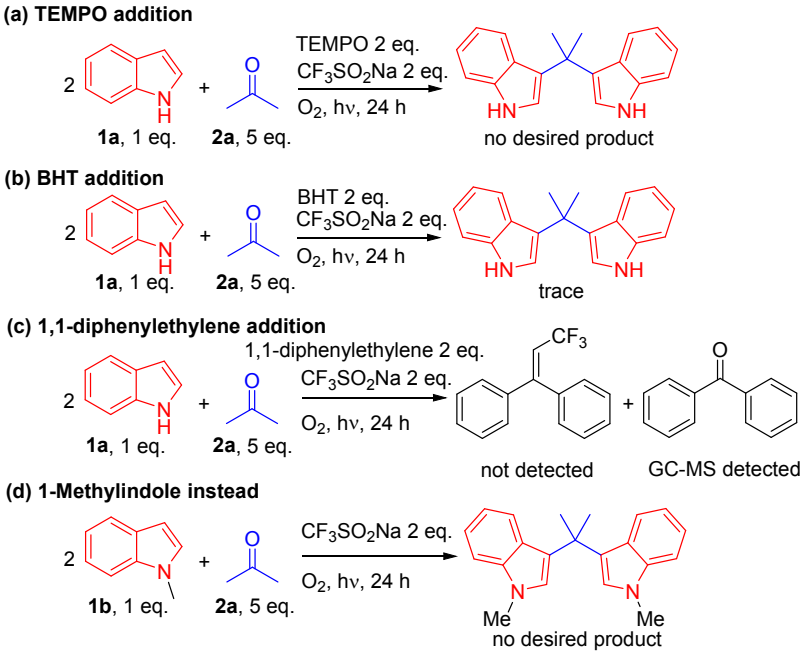
To a 100.0 mL screw capped vial equipped with a magnetic stirring bar was added indole (**1a**, 8.0 mmol, 936 mg), aldehyde (**7a**, 40 mmol, 4240 mg), CF_3SO_2Na (16 mmol, 2496 mg), and toluene (27.0 mL) under air atmosphere and two UV bulbs. The reaction mixture was vigorously stirred at room temperature for 27 h. Afterward the solvents were removed under reduced pressure, and the crude mixture was purified by chromatography on silica gel (petroleum ether/ethyl acetate=10/1 as eluent) to obtain the desired product (**5a**, 1.24 g, 96%).





2. Control Experiments

2.1 Experiments



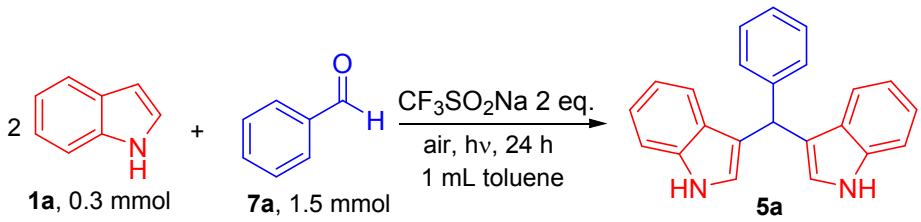
Control experiment (a): A mixture of indole (**1a**, 0.3 mmol, 1.0 equiv., 35.1 mg), acetone (**2a**, 1.5 mmol, 3.0 equiv., 87.0 mg), CF_3SO_2Na (0.6 mmol, 2.0 equiv., 93.6 mg), **TEMPO** (0.6 mmol, 2.0 equiv., 93.6 mg) and toluene (1.0 mL) in a 10.0 mL oven-dried Schlenk tube (equipped with a magnetic stirring bar) was vigorously stirred at room temperature for 24 h under UV irradiation and O_2 atmosphere. It has no desired product according to the result of TLC analysis.

Control experiment (b): A mixture of indole (**1a**, 0.3 mmol, 1.0 equiv., 35.1 mg), acetone (**2a**, 1.5 mmol, 3.0 equiv., 87.0 mg), CF_3SO_2Na (0.6 mmol, 2.0 equiv., 93.6 mg), **BHT** (0.6 mmol, 2.0 equiv., 132.0 mg) and toluene (1.0 mL) in a 10.0 mL oven-dried Schlenk tube (equipped with a magnetic stirring bar) was vigorously stirred at room temperature for 24 h under UV irradiation and O_2 atmosphere. It gives trace amount of product as revealed in TLC analysis.

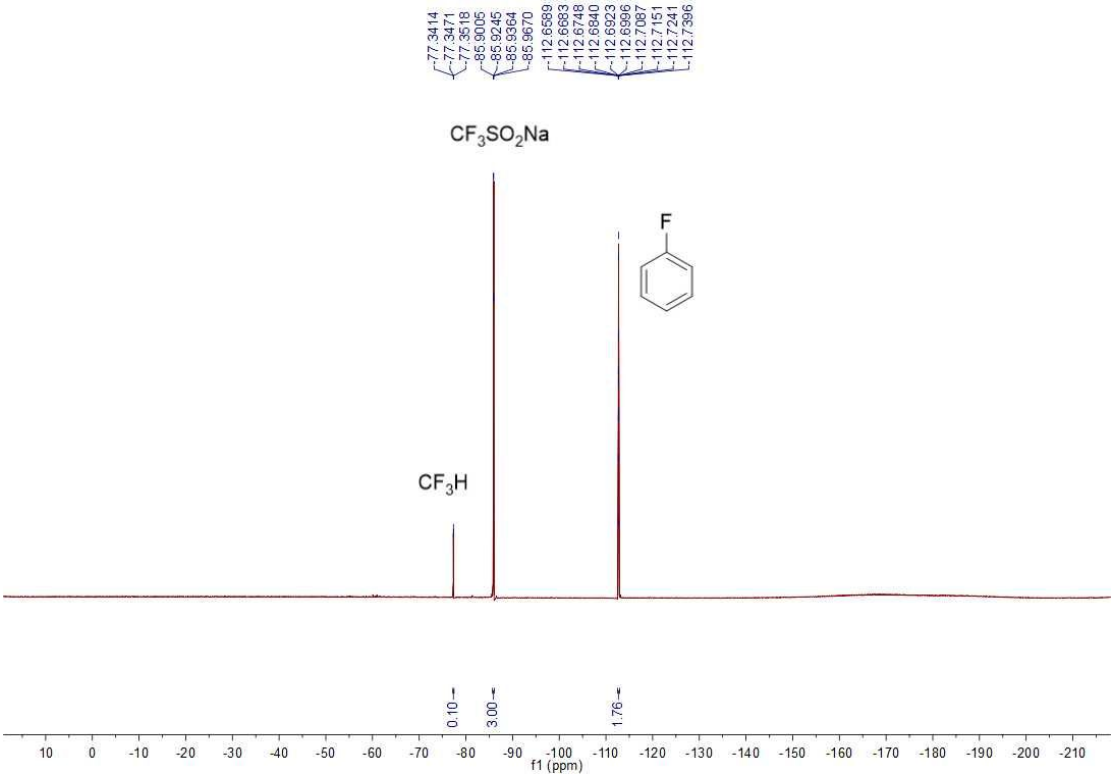
Control experiment (c): A mixture of indole (**1a**, 0.3 mmol, 1.0 equiv., 35.1 mg), acetone (**2a**, 1.5 mmol, 3.0 equiv., 87.0 mg), CF_3SO_2Na (0.6 mmol, 2.0 equiv., 93.6 mg), **1,1-diphenylethylene** (0.6 mmol, 2.0 equiv., 108.0 mg) and toluene (1.0 mL) in a 10.0 mL oven-dried Schlenk tube (equipped with a magnetic stirring bar) was vigorously stirred at room temperature for 24 h under UV irradiation and O_2 atmosphere. **No trifluoromethyl radicals were captured and only benzophenone was detected through TLC and GC-MS analyses**.

Control experiment (d): A mixture of **1-methylindole** (**1b**, 0.3 mmol, 1.0 equiv., 35.1 mg), acetone (**2a**, 1.5 mmol, 3.0 equiv., 87.0 mg), CF_3SO_2Na (0.6 mmol, 2.0 equiv., 93.6 mg), and toluene (1.0 mL) in a 10.0 mL oven-dried Schlenk tube (equipped with a magnetic stirring bar) was vigorously stirred at room temperature for 24 h under UV irradiation and O_2 atmosphere. According to the results of TLC and GC-MS analyses, without **N–H bond**, there is no generation of the expected product.

2.2 Intermediate CF_3H detection by ^{19}F NMR



A mixture of indole (**1a,** 0.3 mmol, 1.0 equiv., 35.1 mg), aldehyde (**7a**, 1.5 mmol, 3.0 equiv., 159.0 mg), CF_3SO_2Na (0.6 mmol, 2.0 equiv., 93.6 mg), and toluene (1.0 mL) in a 10.0 mL oven-dried Schlenk tube (equipped with a magnetic stirring bar) was vigorously stirred at room temperature for 24 h under air atmosphere. Then fluorobenzene (217.0 mg) was added to the mixture for ^{19}F NMR detection of CF_3H.



^{19}F NMR (376 MHz, DMSO) δ -77.34–-77.36 (m), -85.90–-85.97 (m), -112.66–-112.74 (m).[4]

3. X-Ray Information of Complex 3a (CCDC 1965538)

Table S1 Crystal data and structure refinement for 3a.	
Identification code	3a
Empirical formula	$C_{19}H_{18}N_2$
Formula weight	274.35
Temperature/K	100.01(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	10.5165(9)
b/Å	20.4356(18)
c/Å	13.7548(10)
α/°	90
β/°	99.033(8)
γ/°	90
Volume/Å^3	2919.4(4)
Z	8
ρ_{calc}g/cm^3	1.248
μ/mm^{-1}	0.074
F(000)	1168.0
Crystal size/mm^3	0.13×0.12×0.11
Radiation	MoKα (λ=0.71073)
2Θ range for data collection/°	4.4 to 49.998
Index ranges	$-8 \le h \le 12$, $-20 \le k \le 24$, $-16 \le l \le 16$
Reflections collected	13403
Independent reflections	5141 [R_{int}=0.0385, R_{sigma}=0.0532]
Data/restraints/parameters	5141/0/383
Goodness-of-fit on F^2	1.052

Final R indexes [I≥2σ (I)]	R_1=0.0520, wR_2=0.1148
Final R indexes [all data]	R_1=0.0724, wR_2=0.1276
Largest diff. peak/hole/e $Å^{-3}$	0.18/-0.21

4. Bioactivity Experiments

Materials and Methods

Cell culture and chemical compounds

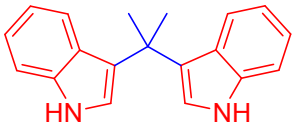
Human bladder cancer cell lines T24 and EJ were obtained from the American Type Culture Collection (Manassas, VA, USA). These two cell lines were cultured in Minimum Essential Medium (MEM, Hyclone) supplemented with 10% Fetal Bovine Serum (FBS) (Every green, China). Cell lines were maintained at 37 °C in a humidified 5% CO_2 incubator. Chemical compounds in this study were dissolved in dimethyl sulfoxide (DMSO, Sigma) and stored at -20 °C.

Cell viability assay

To determine cell viability, the cells were seeded in 96-well plates (100 μL per well) and incubated overnight, then they were treated with a designated chemical compound for 24 h. Following the treatment, cell viability was evaluated using the Cell Counting Kit-8 (CCK-8) (Yeasen, Shanghai, China) according to the manufacturer's protocol. Briefly, the cells were exposed to 10 μL of the CCK-8 reagent for 1 h at 37 °C in a humidified 5% CO_2 incubator. The optical density of viable cells was measured at 450 nm using a microplate reader.

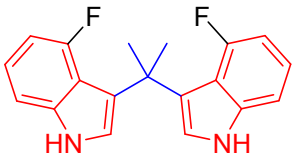
5. Analytical Data of Products

3,3'-(propane-2,2-diyl)bis(1H-indole) (3a)



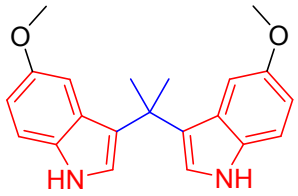
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **3a** (81%, 33.3 mg) as a brown solid; mp: 132.4–133.9 °C; Rf=0.38 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (s, 2H), 7.45 (d, *J*=8.1 Hz, 2H), 7.32 (d, *J*=8.1 Hz, 2H), 7.11 (t, *J*=7.6 Hz, 2H), 7.04 (s, 2H), 6.92 (t, *J*=7.5 Hz, 2H), 1.95 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.0, 126.3, 125.4, 121.3, 121.2, 120.5, 118.6, 111.0, 34.9, 29.9. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{19}H_{19}N_2^+$ 275.1543, Found 275.1548.

3,3'-(propane-2,2-diyl)bis(4-fluoro-1H-indole) (3b)



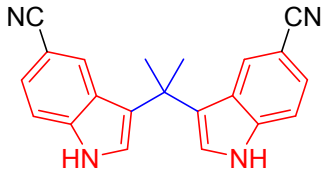
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **3b** (in 17%, 7.9 mg) as a brown solid; mp: 129.6–131.2 °C; Rf=0.36 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (s, 2H), 7.11 (d, *J*=8.0 Hz, 2H), 7.03 (dd, *J*=14.2, 9.2 Hz, 4H), 6.65 (dd, *J*=11.6, 7.8 Hz, 2H), 1.93 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.2 (d, $J_{C\text{-}F}$=247.8 Hz), 140.0 (d, $J_{C\text{-}F}$=12.2 Hz), 125.3 (dd, $J_{C\text{-}F}$=4.3, 2.8 Hz), 122.0 (d, $J_{C\text{-}F}$=8.3 Hz), 121.5, 115.0 (d, $J_{C\text{-}F}$=20.8 Hz), 107.1 (d, $J_{C\text{-}F}$=3.6 Hz), 104.9 (d, $J_{C\text{-}F}$=22.7 Hz), 34.5, 30.4. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.91 (s, 2F). HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{19}H_{17}F_2N_2^+$ 311.1354, Found 311.1361.

3,3'-(propane-2,2-diyl)bis(5-methoxy-1H-indole) (3c)



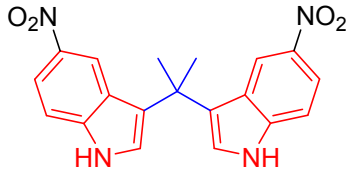
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **3c** (49%, 24.5 mg) as a brown solid; mp: 50.1–52.3 °C; Rf=0.35 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.19 (d, *J*=8.7 Hz, 2H), 7.05 (s, 2H), 6.87 (s, 2H), 6.77 (d, *J*=8.7 Hz, 2H), 3.66 (s, 6H), 1.91 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.0, 132.5, 126.8, 124.9, 121.4, 111.5, 111.0, 103.9, 55.8, 34.7, 29.7. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{21}H_{23}N_2O_2^+$ 335.1754, Found 335.1761.

3,3'-(propane-2,2-diyl)bis(1H-indole-5-carbonitrile) (3d)



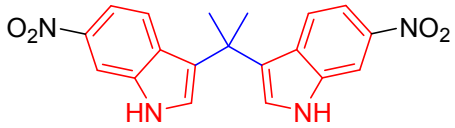
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **3d** (84%, 41.0 mg) as a brown solid; mp: 256.4–257.8 °C; Rf=0.31 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.56 (s, 2H), 7.38 (s, 2H), 7.29 (d, *J*=9.7 Hz, 4H), 7.18 (d, *J*=8.4 Hz, 2H), 1.76 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.8, 126.1, 125.8, 125.5, 124.5, 122.2, 121.0, 112.2, 101.6, 34.3, 30.0. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{21}H_{17}N_4^+$ 325.1448, Found 325.1451.

3,3'-(propane-2,2-diyl)bis(5-nitro-1H-indole) (3e) in d_6-DMSO



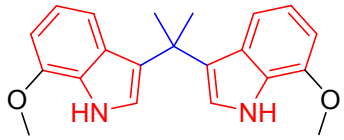
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **3e** (70%, 38.3 mg) as a yellow solid; mp: 69.9–71.1 °C; Rf=0.34 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, DMSO) δ 11.74 (s, 2H), 7.92 (s, 2H), 7.83 (d, *J*=8.9 Hz, 2H), 7.77 (s, 2H), 7.47 (d, *J*=9.0 Hz, 2H), 1.85 (s, 6H). **^{13}C NMR** (100 MHz, DMSO) δ 140.7, 140.0, 126.4, 125.5, 125.3, 116.8, 116.6, 112.4, 34.4, 30.7. HRMS (EI) m/z: $[M+Na]^+$ calcd for $C_{19}H_{16}N_4NaO_4^+$ 387.1064, Found 387.1067.

3,3'-(propane-2,2-diyl)bis(6-nitro-1H-indole) (3f) in d_6-DMSO



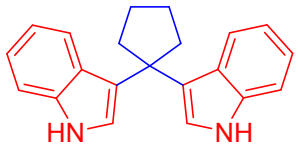
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **3f** (38%, 20.8 mg) as a yellow solid; mp: 205.5–207.4 °C; Rf=0.35 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, DMSO) δ 11.72 (s, 2H), 8.27 (d, *J*=2.0 Hz, 2H), 7.84 (d, *J*=2.4 Hz, 2H), 7.59 (dd, *J*=8.9, 2.0 Hz, 2H), 7.16 (d, *J*=8.9 Hz, 2H), 1.86 (s, 6H). **^{13}C NMR** (100 MHz, DMSO) δ 141.4, 135.4, 130.3, 128.4, 124.6, 119.7, 113.0, 108.3, 34.0, 30.0. HRMS (EI) m/z: $[M+Na]^+$ calcd for $C_{19}H_{16}N_4NaO_4^+$ 387.1064, Found 387.1072.

3,3'-(propane-2,2-diyl)bis(7-methoxy-1H-indole) (3g)



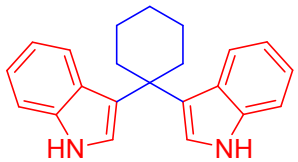
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **3g** (55%, 27.6 mg) as a brown solid; mp: 51.3–53.7 °C; Rf=0.35 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (s, 2H), 7.13–6.92 (m, 4H), 6.84 (t, *J*=7.8 Hz, 2H), 6.56 (d, *J*=7.6 Hz, 2H), 3.94 (s, 6H), 1.93 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.0, 127.6, 127.6, 126.0, 120.09, 118.9, 114.1, 101.2, 55.2, 34.9, 30.0. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{21}H_{23}N_2O_2^+$ 335.1754, Found 335.1751.

3,3'-(cyclopentane-1,1-diyl)bis(1H-indole) (3h)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **3h** (40%, 18.0 mg) as a brown solid; mp: 137.7–139.4 °C; Rf=0.37 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (s, 2H), 7.52 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.1 Hz, 2H), 7.08 (d, *J*=10.7 Hz, 4H), 6.92 (t, *J*=7.5 Hz, 2H), 2.52 (s, 4H), 1.84 (s, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.2, 126.5, 123.4, 121.3, 121.1, 121.0, 118.6, 111.0, 46.1, 38.6, 24.0. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{21}H_{21}N_2^+$ 301.1699, Found 301.1703.

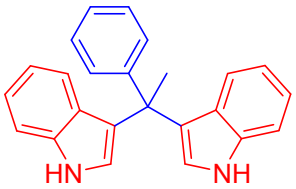
3,3'-(cyclohexane-1,1-diyl)bis(1H-indole) (3i)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **3i** (30%, 14.2 mg) as a brown solid; mp: 74.8–76.5 °C; Rf=0.35 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (s, 2H),

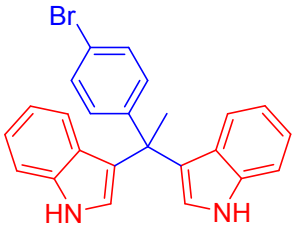
7.57 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.1 Hz, 2H), 7.07 (d, *J*=12.4 Hz, 4H), 6.91 (t, *J*=7.4 Hz, 2H), 2.56 (s, 4H), 1.80–1.42 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.0, 126.3, 123.7, 122.0, 121.4, 121.2, 118.5, 111.0, 39.5, 36.8, 26.8, 23.0. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{22}H_{23}N_2^+$ 315.1856, Found 315.1862.

3,3'-(1-phenylethane-1,1-diyl)bis(1H-indole) (4a)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **4a** (58%, 29.3 mg) as a brown solid; mp: 166.7–168.3 °C; Rf=0.39 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (s, 2H), 7.47 (d, *J*=7.4 Hz, 2H), 7.39 (d, *J*=8.1 Hz, 4H), 7.30 (dd, *J*=14.5, 7.4 Hz, 3H), 7.20 (t, *J*=7.5 Hz, 2H), 7.00 (t, *J*=7.5 Hz, 2H), 6.65 (s, 2H), 2.43 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.0, 137.1, 128.0, 127.8, 126.4, 125.8, 124.7, 123.3, 122.04, 121.5, 118.9, 111.1, 43.7, 28.7. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{24}H_{21}N_2^+$ 337.1699, Found 337.1695.

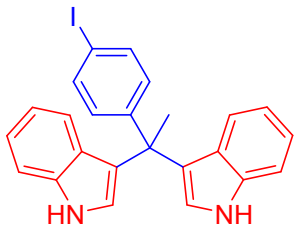
3,3'-(1-(4-bromophenyl)ethane-1,1-diyl)bis(1H-indole) (4b)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **4b** (59%, 36.6 mg) as a brown solid; mp: 106.2–107.8 °C; Rf=0.35 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.32 (dt, *J*=27.5, 8.5 Hz, 8H), 7.16 (t, *J*=7.5 Hz, 2H), 6.97 (t, *J*=7.5 Hz, 2H), 6.60 (d, *J*=2.2 Hz, 2H), 2.34 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.1, 137.0, 130.8,

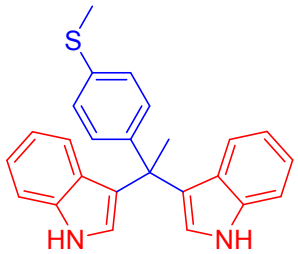
130.0, 126.1, 124.0, 123.3, 121.9, 121.7, 119.7, 119.0, 111.2, 43.4, 28.6. HRMS (EI) m/z: $[M+Na]^+$ calcd for $C_{24}H_{19}BrN_2Na^+$ 437.0624, Found 437.0629.

3,3'-(1-(4-iodophenyl)ethane-1,1-diyl)bis(1H-indole) (4c)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **4c** (62%, 43.0 mg) as a brown solid; mp: 201.5–203.2 °C; Rf=0.35 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.56 (d, *J*=7.9 Hz, 2H), 7.33 (t, *J*=7.7 Hz, 4H), 7.16 (t, *J*=7.9 Hz, 4H), 6.97 (t, *J*=7.4 Hz, 2H), 6.59 (s, 2H), 2.33 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.8, 136.8, 130.3, 126.1, 123.9, 123.3, 121.9, 121.6, 119.0, 111.2, 99.9, 91.4, 43.5, 28.6. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{24}H_{20}IN_2^+$ 463.0666, Found 463.0673.

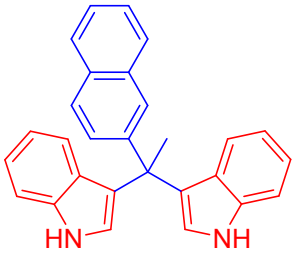
3,3'-(1-(4-(methylthio)phenyl)ethane-1,1-diyl)bis(1H-indole) (4d)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **4d** (31%, 17.8 mg) as a brown solid; mp: 73.4–75.6 °C; Rf=0.36 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.33 (t, *J*=8.0 Hz, 6H), 7.15 (t, *J*=7.8 Hz, 4H), 6.95 (t, *J*=7.4 Hz, 2H), 6.60 (s, 2H),

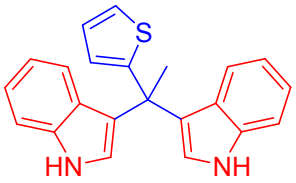
2.45 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.1, 137.0, 135.2, 128.6, 126.3, 126.0, 124.5, 123.3, 122.0, 121.5, 118.9, 111.1, 43.3, 28.6, 15.8. HRMS (EI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{22}N_2SNa^+$ 405.1396, Found 405.1391.

3,3'-(1-(naphthalen-2-yl)ethane-1,1-diyl)bis(1H-indole) (4e)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **4e** (26%, 15.1 mg) as a brown solid; mp: 93.5–96.2 °C; Rf=0.34 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J*=17.7 Hz, 3H), 7.79 (d, *J*=7.5 Hz, 1H), 7.69 (d, *J*=8.0 Hz, 2H), 7.52 (d, *J*=8.6 Hz, 1H), 7.42 (d, *J*=3.5 Hz, 6H), 7.36 (t, *J*=7.1 Hz, 2H), 7.14 (t, *J*=7.5 Hz, 2H), 6.92 (t, *J*=7.5 Hz, 2H), 6.63 (s, 1H), 2.47 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.5, 137.1, 133.2, 132.0, 128.3, 127.4, 127.3, 127.2, 126.4, 125.9, 125.5, 125.4, 124.5, 123.5, 122.1, 121.5, 119.0, 111.1, 43.9, 28.6. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{28}H_{23}N_2^+$ 387.1856, Found 387.1859.

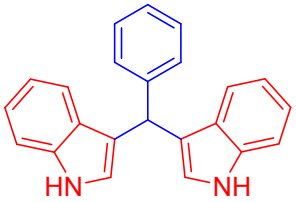
3,3'-(1-(thiophen-2-yl)ethane-1,1-diyl)bis(1H-indole) (4f)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **4f** (36%, 18.5 mg) as a brown solid; mp: 67.7–69.2 °C; Rf=0.35

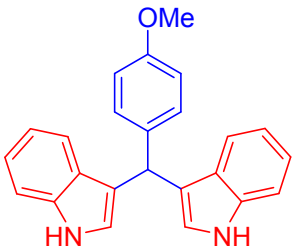
(petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (s, 2H), 7.40 (d, *J*=8.1 Hz, 2H), 7.34 (d, *J*=8.1 Hz, 2H), 7.21–7.10 (m, 3H), 6.95 (dd, *J*=18.2, 10.8 Hz, 4H), 6.74 (s, 2H), 2.43 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.4, 137.0, 126.1, 126.0, 124.9, 124.5, 123.5, 123.0, 121.8, 121.6, 119.0, 111.2, 77.3, 77.0, 76.7, 41.8, 30.3. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{22}H_{19}N_2S^+$ 343.1263, Found 343.1269.

3,3'-(phenylmethylene)bis(1H-indole) (5a)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **5a** (89%, 43.0 mg) as a brown solid; mp: 141.6–142.7 °C; Rf=0.31 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (s, 2H), 7.30 (d, *J*=7.8 Hz, 2H), 7.15 (ddd, *J*=29.0, 18.6, 10.9 Hz, 9H), 6.92 (t, *J*=7.2 Hz, 2H), 6.45 (s, 2H), 5.79 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.0, 136.6, 128.7, 128.2, 127.0, 126.1, 123.6, 121.9, 119.9, 119.6, 119.2, 111.0, 40.1. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{23}H_{19}N_2^+$ 323.1543, Found 323.1547.

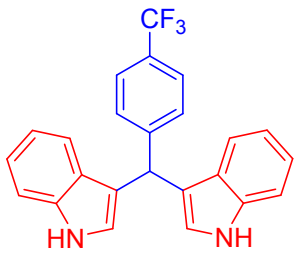
3,3'-((4-methoxyphenyl)methylene)bis(1H-indole) (5b)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **5b** (77%, 40.7 mg) as a brown solid; mp: 188.9–190.2 °C;

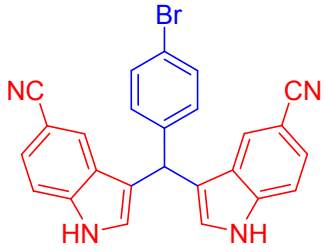
Rf=0.32 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.40 (d, *J*=7.9 Hz, 2H), 7.31 (d, *J*=8.1 Hz, 2H), 7.25 (d, *J*=7.5 Hz, 2H), 7.17 (t, *J*=7.5 Hz, 2H), 7.02 (t, *J*=7.4 Hz, 2H), 6.82 (d, *J*=8.1 Hz, 2H), 6.57 (s, 2H), 5.84 (s, 1H), 3.78 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.8, 136.6, 136.2, 129.6, 127.0, 123.5, 121.8, 119.9, 119.1, 113.5, 111.0, 55.2, 39.3. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{24}H_{21}N_2O^+$ 353.1648, Found 353.1654.

3,3'-((4-(trifluoromethyl)phenyl)methylene)bis(1H-indole) (5c)



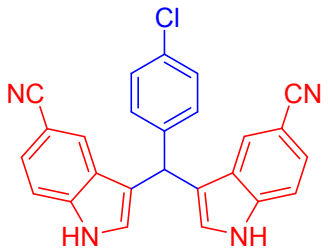
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **5c** (76%, 44.5 mg) as a brown solid; mp: 68.6–69.4 °C; Rf=0.32 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (s, 2H), 7.55 (d, *J*=7.8 Hz, 2H), 7.46 (d, *J*=7.8 Hz, 2H), 7.38 (t, *J*=8.5 Hz, 4H), 7.22 (t, *J*=7.4 Hz, 2H), 7.05 (t, *J*=7.3 Hz, 2H), 6.62 (s, 2H), 5.96 (s, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.11 (s, 3F). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.1, 136.6, 129.0, 128.4 (d, $J_{C\text{-}F}$=32.0 Hz), 126.8, 125.2 (q, $J_{C\text{-}F}$=3.7 Hz), 124.4 (d, $J_{C\text{-}F}$=270.2), 123.0, 122.1, 119.7, 119.4, 118.7, 111.2, 40.1. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{24}H_{18}F_3N_2^+$ 391.1417, Found 391.1422.

3,3'-((4-bromophenyl)methylene)bis(1H-indole-5-carbonitrile) (5d)



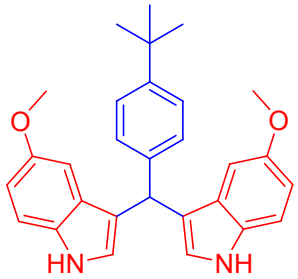
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **5d** (85%, 57.4 mg) as a brown solid; mp: 72.6–74.5 °C; Rf=0.30 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, DMSO) δ 11.54 (s, 2H), 7.83 (s, 2H), 7.55 (d, *J*=8.4 Hz, 2H), 7.49 (d, *J*=8.3 Hz, 2H), 7.42 (d, *J*=8.4 Hz, 2H), 7.32 (d, *J*=8.2 Hz, 2H), 7.15 (s, 2H), 6.05 (s, 1H). **^{13}C NMR** (100 MHz, DMSO) δ 143.5, 138.3, 131.3, 130.4, 126.4, 126.2, 124.5, 123.9, 120.8, 119.3, 118.4, 113.0, 100.5, 37.9. HRMS (EI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{15}BrN_4Na^+$ 473.0372, Found 473.0377.

3,3'-((4-chlorophenyl)methylene)bis(1H-indole-5-carbonitrile) (5e)



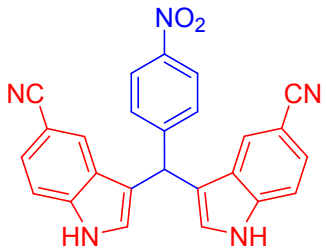
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **5e** (83%, 50.5 mg) as a brown solid; mp: 95.4–96.7 °C; Rf=0.30 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, DMSO) δ 11.56 (s, 2H), 7.85 (s, 2H), 7.57 (d, *J*=8.4 Hz, 2H), 7.44–7.36 (m, 6H), 7.18 (s, 2H), 6.09 (s, 1H). **^{13}C NMR** (100 MHz, DMSO) δ 143.4, 138.7, 131.2, 130.4, 128.7, 126.8, 126.6, 124.9, 124.3, 121.2, 118.8, 113.4, 100.9, 38.2. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{15}ClN_4Na^+$ 429.0877, Found 429.0876.

3,3'-((4-(tert-butyl)phenyl)methylene)bis(5-methoxy-1H-indole) (5f)



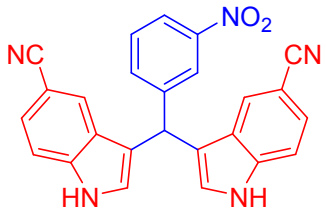
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **5f** (49%, 32.2 mg) as a brown solid; mp: 209.2–210.8 °C; Rf=0.30 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.37–7.18 (m, 6H), 6.96–6.81 (m, 4H), 6.71 (d, *J*=1.9 Hz, 2H), 5.80 (s, 1H), 3.74 (s, 6H), 1.36 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.6, 148.7, 140.8, 131.8, 128.3, 127.5, 125.0, 124.3, 119.5, 111.8, 111.6, 102.0, 55.8, 39.8, 34.3, 31.4. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{29}H_{30}N_2O_2Na^+$ 461.2199, Found 461.2195.

3,3'-((4-nitrophenyl)methylene)bis(1H-indole-5-carbonitrile) (5g)



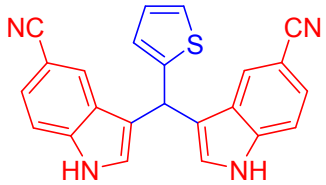
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **5g** (80%, 50.0 mg) as a brown solid; mp: 51.6–53.4 °C; Rf=0.34 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, DMSO) δ 11.62 (s, 2H), 8.18 (d, *J*=8.6 Hz, 2H), 7.89 (s, 2H), 7.64 (d, *J*=8.6 Hz, 2H), 7.56 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=8.4 Hz, 2H), 7.22 (s, 2H), 6.26 (s, 1H). **^{13}C NMR** (100 MHz, DMSO) δ 152.0, 146.1, 138.3, 129.4, 126.7, 126.2, 124.5, 124.0, 123.8, 120.8, 117.6, 113.1, 100.7, 38.2. HRMS (EI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{15}N_5O_2Na^+$ 440.1118, Found 440.1121.

3,3'-((3-nitrophenyl)methylene)bis(1H-indole-5-carbonitrile) (5h)



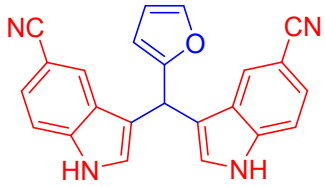
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **5h** (87%, 54.4 mg) as a brown solid; mp: 63.8–65.9 °C; Rf=0.34 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, DMSO) δ 11.61 (s, 2H), 8.21 (s, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.91 (s, 2H), 7.86 (d, *J*=7.5 Hz, 1H), 7.59 (dd, *J*=18.7, 8.3 Hz, 3H), 7.43 (d, *J*=8.4 Hz, 2H), 7.24 (s, 2H), 6.29 (s, 1H). **^{13}C NMR** (100 MHz, DMSO) δ 148.0, 146.3, 138.3, 134.9, 129.9, 126.7, 126.2, 124.5, 124.0, 122.7, 121.5, 120.8, 117.9, 113.1, 100.7, 40.2, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 37.9. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{25}H_{16}N_5O_2^+$ 418.1299, Found 418.1305.

3,3'-(thiophen-2-ylmethylene)bis(1H-indole-5-carbonitrile) (5i)



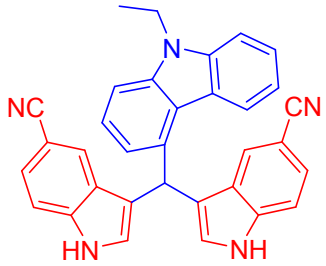
The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **5i** (87%, 49.3 mg) as a brown solid; mp: 252.9–253.5 °C; Rf=0.34 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, DMSO) δ 11.55 (s, 2H), 7.91 (s, 2H), 7.55 (d, *J*=8.3 Hz, 2H), 7.41 (d, *J*=8.4 Hz, 2H), 7.35 (s, 3H), 6.95 (s, 2H), 6.35 (s, 1H). **^{13}C NMR** (100 MHz, DMSO) δ 148.2, 138.2, 126.7, 126.2, 126.0, 125.1, 124.6, 124.4, 123.8, 120.8, 118.8, 113.0, 100.5, 33.9. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{23}H_{15}N_4S^+$ 379.1012, Found 379.1019.

3,3'-(furan-2-ylmethylene)bis(1H-indole-5-carbonitrile) (5j)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **5j** (43%, 23.3 mg) as a brown solid; mp: 242.6–243.9 °C; Rf=0.32 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, DMSO) δ 11.58 (s, 2H), 7.95 (s, 2H), 7.64–7.50 (m, 3H), 7.41 (dd, *J*=15.1, 4.8 Hz, 4H), 6.42 (s, 1H), 6.21 (d, *J*=2.8 Hz, 1H), 6.14 (s, 1H). **^{13}C NMR** (100 MHz, DMSO) δ 156.7, 142.3, 138.6, 126.6, 126.5, 125.0, 124.2, 121.2, 116.9, 113.4, 110.8, 106.8, 101.0, 33.2. HRMS (EI) m/z: $[M+Na]^+$ calcd for $C_{23}H_{14}N_4ONa^+$ 385.1060, Found 385.1062.

3,3'-((9-ethyl-9H-carbazol-4-yl)methylene)bis(1H-indole-5-carbonitrile) (5k)



The representative general procedure mentioned above was followed. Purification by chromatographic column on silica gel (petroleum ether/ethyl acetate=10/1) yielded the title compound **5k** (87%, 63.8 mg) as a brown solid; mp: 177.5–179.2 °C; Rf=0.32 (petroleum ether/ethyl acetate=10/1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.52 (s, 2H), 7.97 (d, *J*=7.3 Hz, 2H), 7.72 (s, 2H), 7.49–7.29 (m, 8H), 7.17 (s, 1H), 6.78 (s, 2H), 6.02 (s, 1H), 4.35 (d, *J*=6.9 Hz, 2H), 1.43 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.2, 139.0, 138.5, 132.9, 126.6, 126.2, 125.7, 125.7, 125.4, 124.9, 123.0, 122.6, 120.8, 120.6, 120.4, 119.9, 118.7, 112.2, 108.5, 102.1, 39.9, 37.6, 13.8. HRMS (EI) m/z: $[M+H]^+$ calcd for $C_{33}H_{24}N_5^+$ 490.2026, Found 490.2031.

6. References

[1] Pillaiyar, T.; Gorska, E.; Schnakenburg, G.; Müller, C. E. General Synthesis of Unsymmetrical 3,3′-(Aza)diindolylmethane Derivatives. *J. Org. Chem.* **2018**, *83*, 9902.

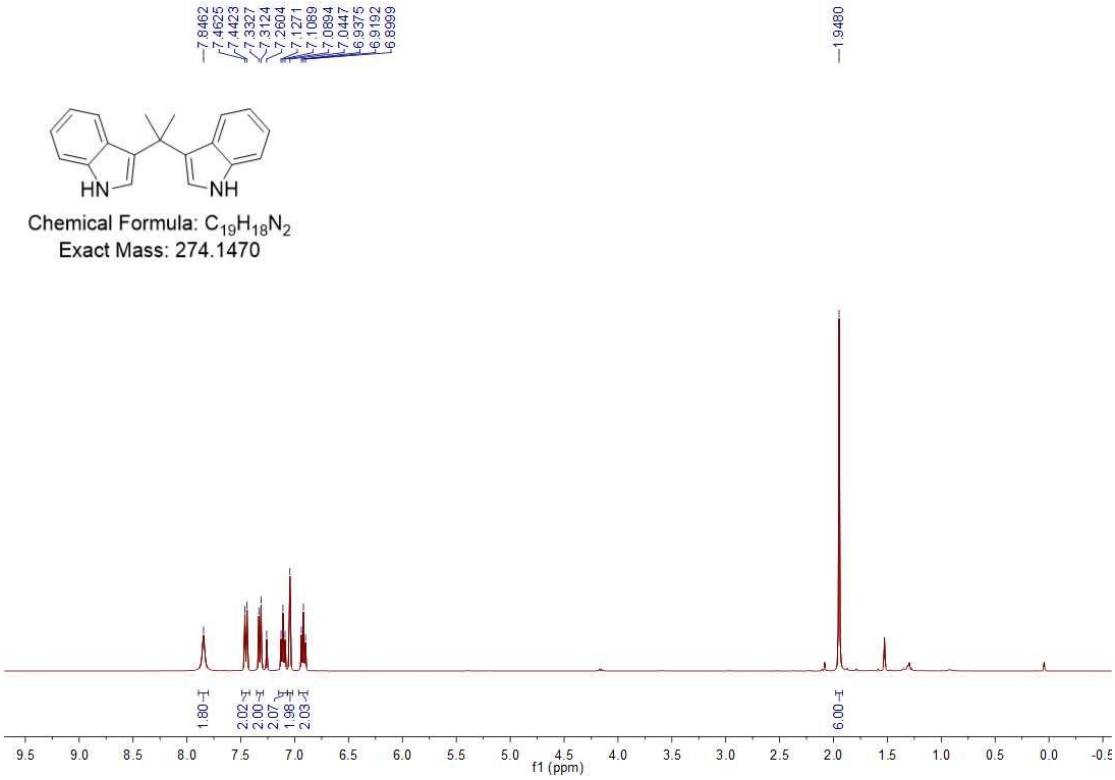
[2] Xiao, J.; Wen, H.; Wang, L.; Xu, L. B.; Hao, Z. H.; Shao, C.-L.; Wang, C.-Y. Catalyst-free dehydrative SN1-type reaction of indolyl alcohols with diverse nucleophiles "on water". *Green Chem.* **2016**, *18*, 1032.

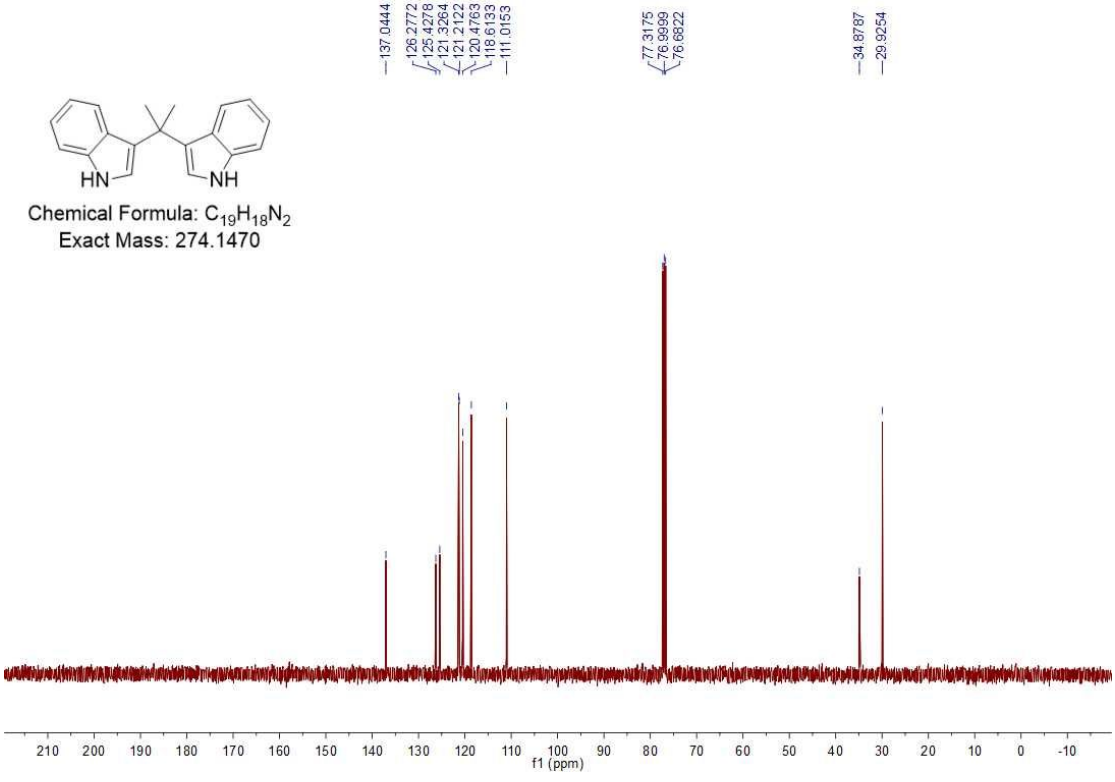
[3] Ishikura, M.; Abe, T.; Ikeda, T.; Itoh, T.; Hatae, N.; Toyota, E. One-Pot Access to 3,3′-Bisindolylmethanes through the Intermolecular Pummerer Reaction. *Heterocycles* **2014**, *88*, 187.

[4] Sartori, P.; Habel, W. Die elektrofluorierung von chlormethylsulfochlorid. *J. Fluorine Chem.* **1980**, *16*, 265.

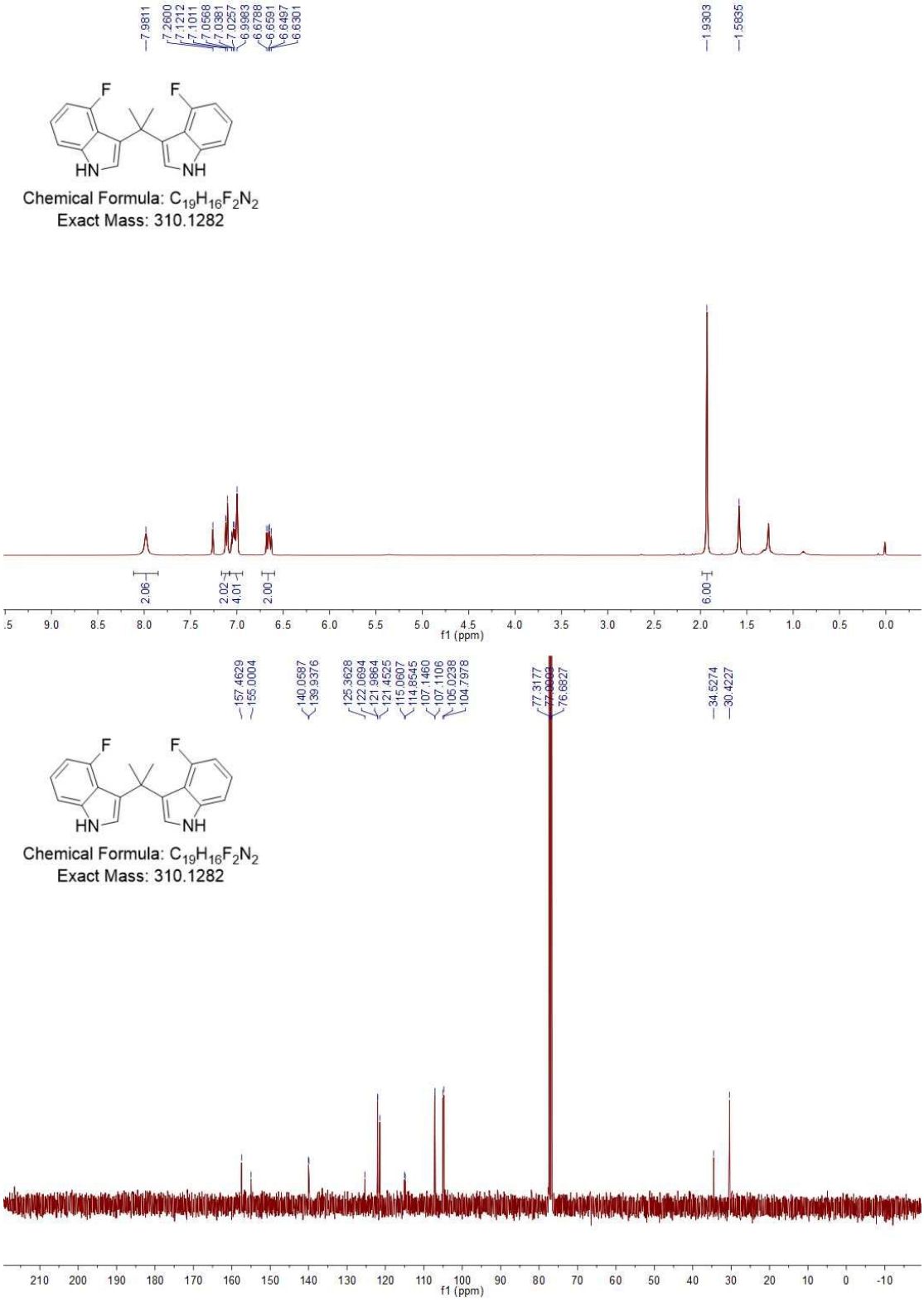
7. Copies of ^{1}H, ^{13}C, ^{19}F NMR Charts for the Compounds

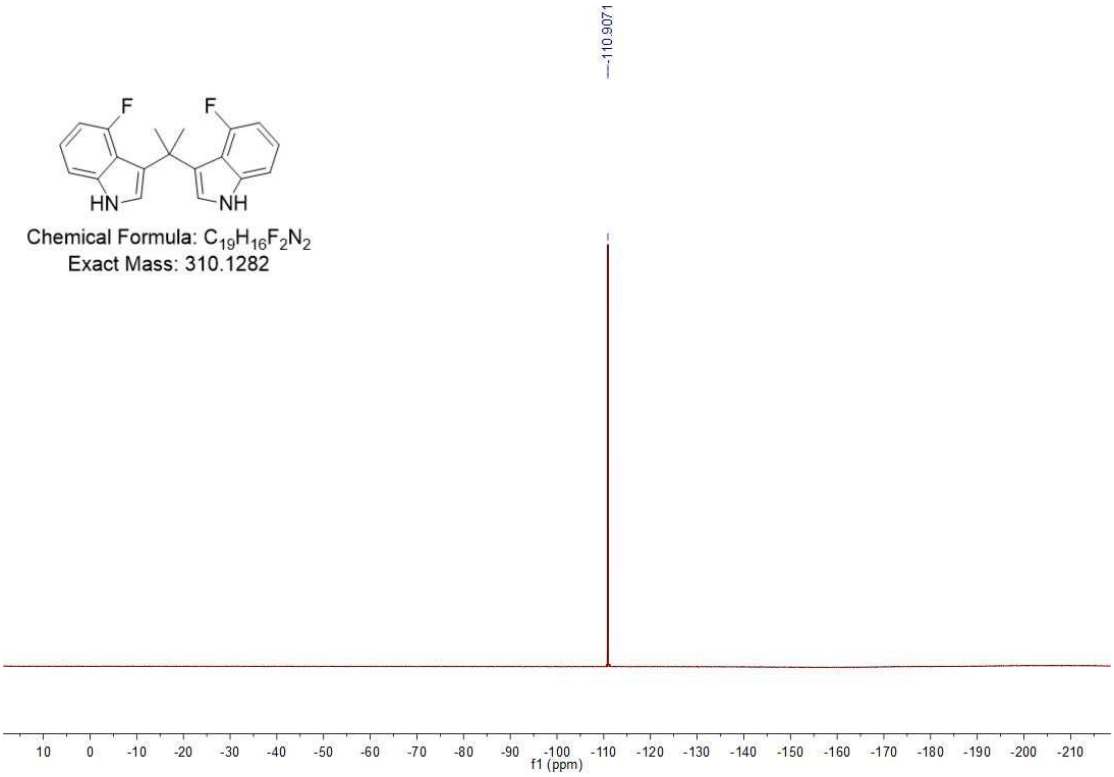
3,3'-(propane-2,2-diyl)bis(1H-indole) (**3a**)



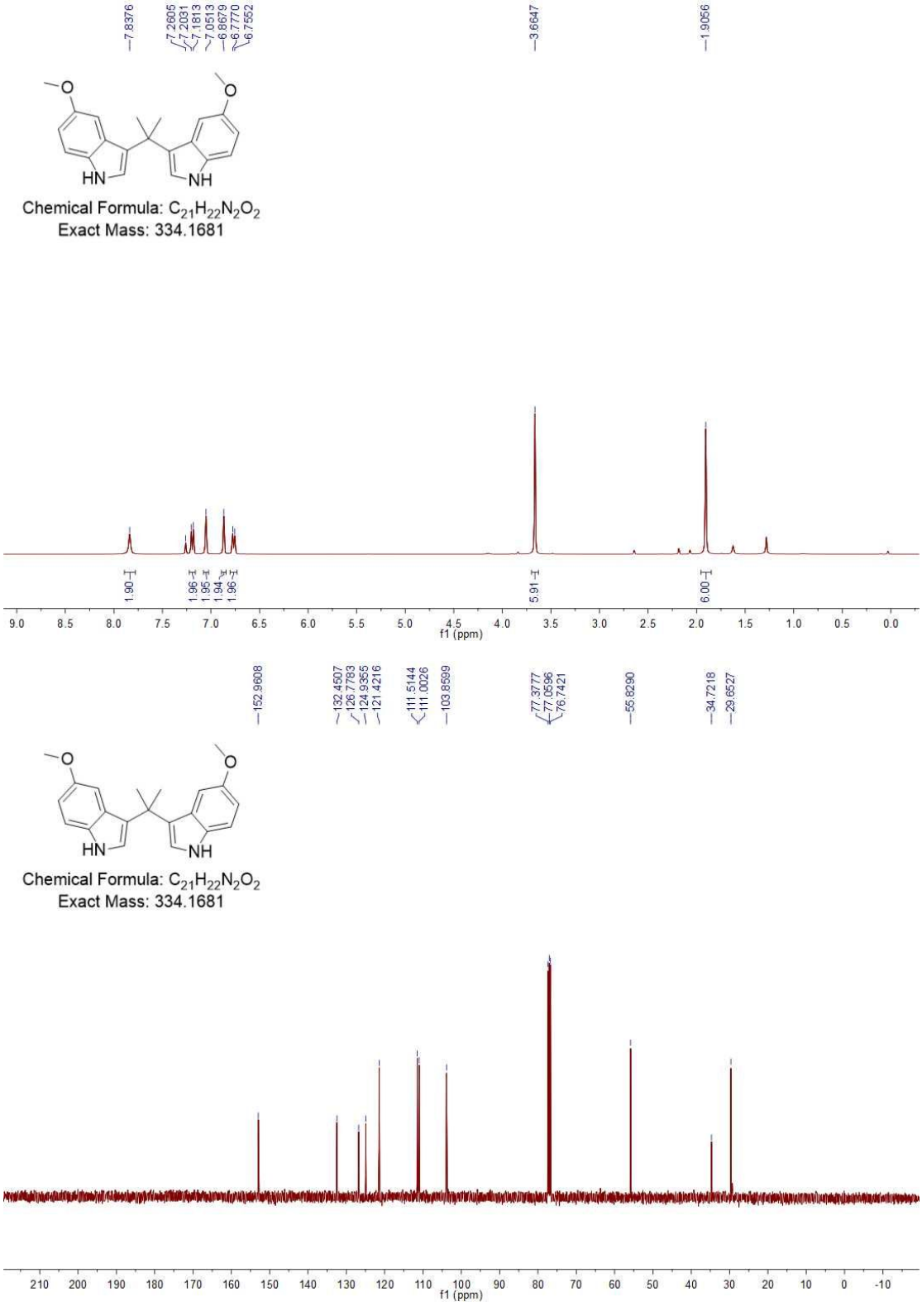


3,3'-(propane-2,2-diyl)bis(4-fluoro-1H-indole) (**3b**)

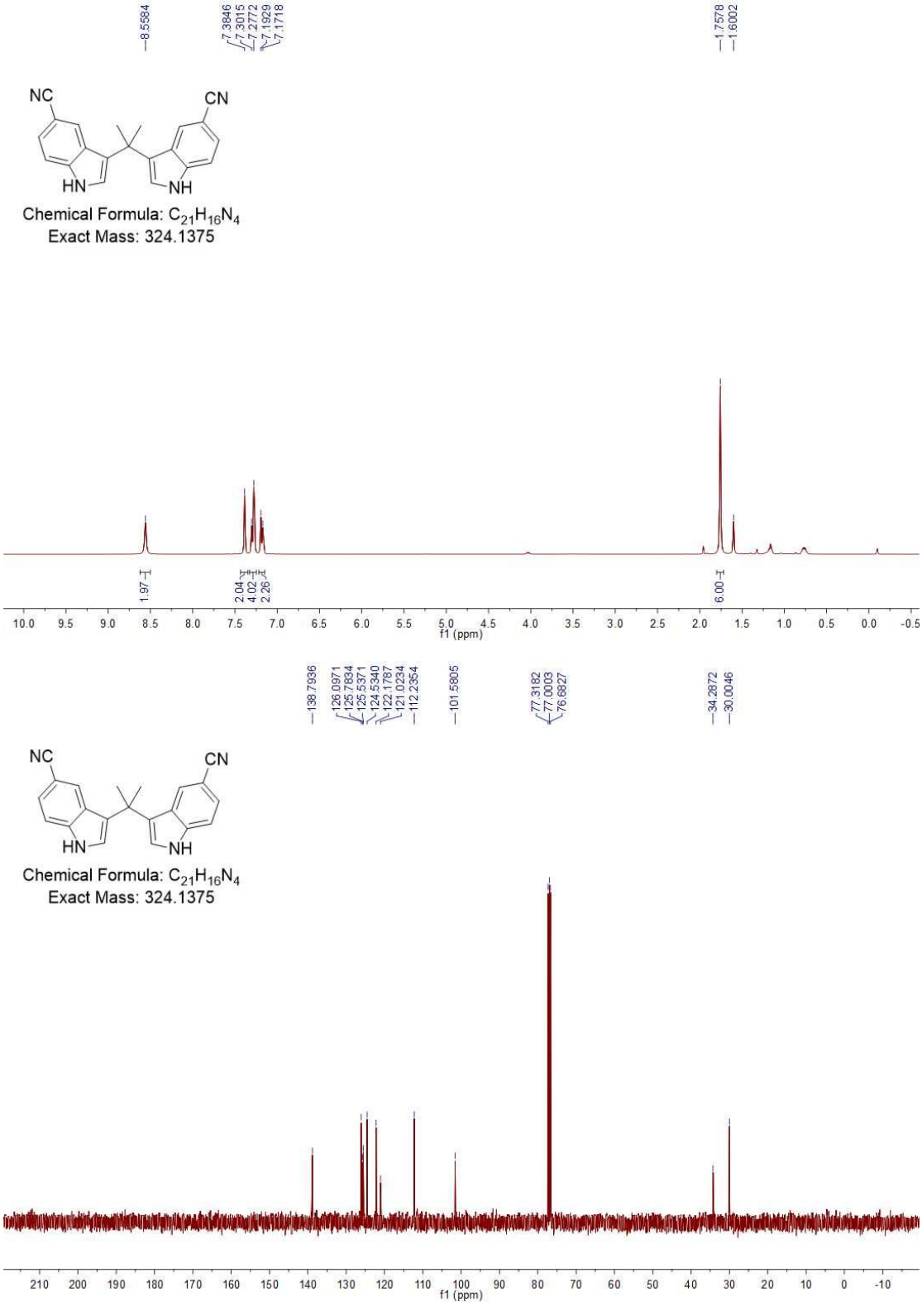



-110.9071
F
F
HN
NH
Chemical Formula: $C_{19}H_{16}F_2N_2$
Exact Mass: 310.1282
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

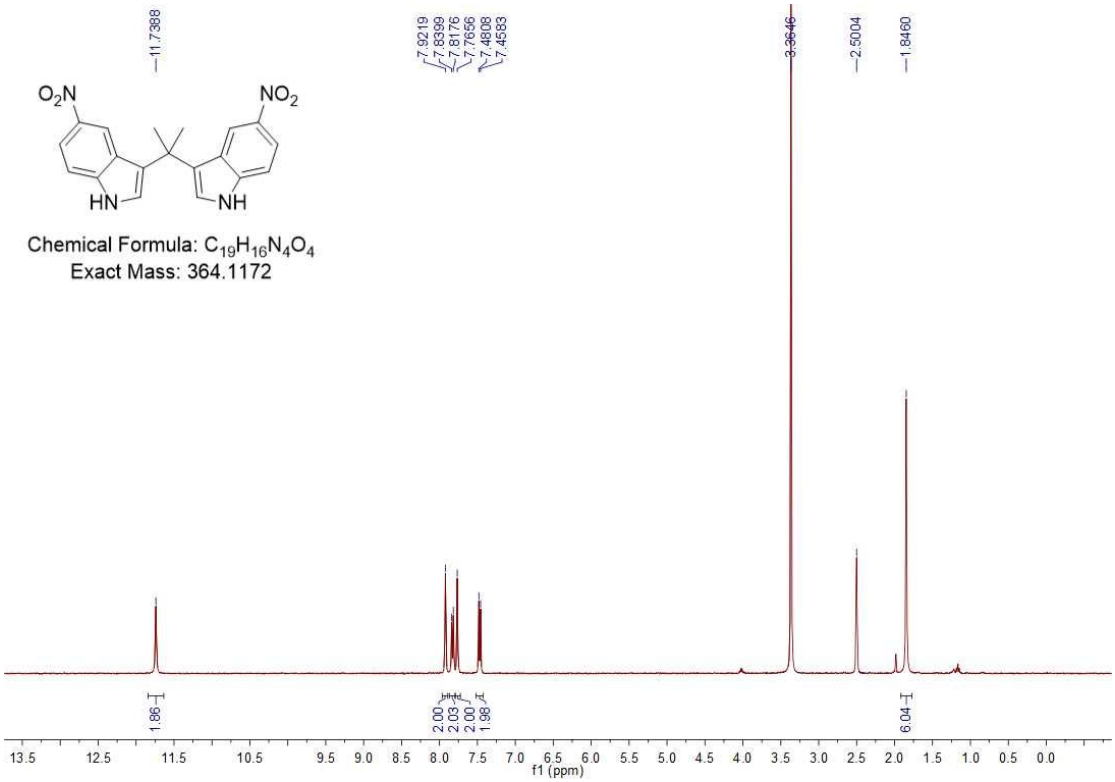
3,3'-(propane-2,2-diyl)bis(5-methoxy-1H-indole) (**3c**)

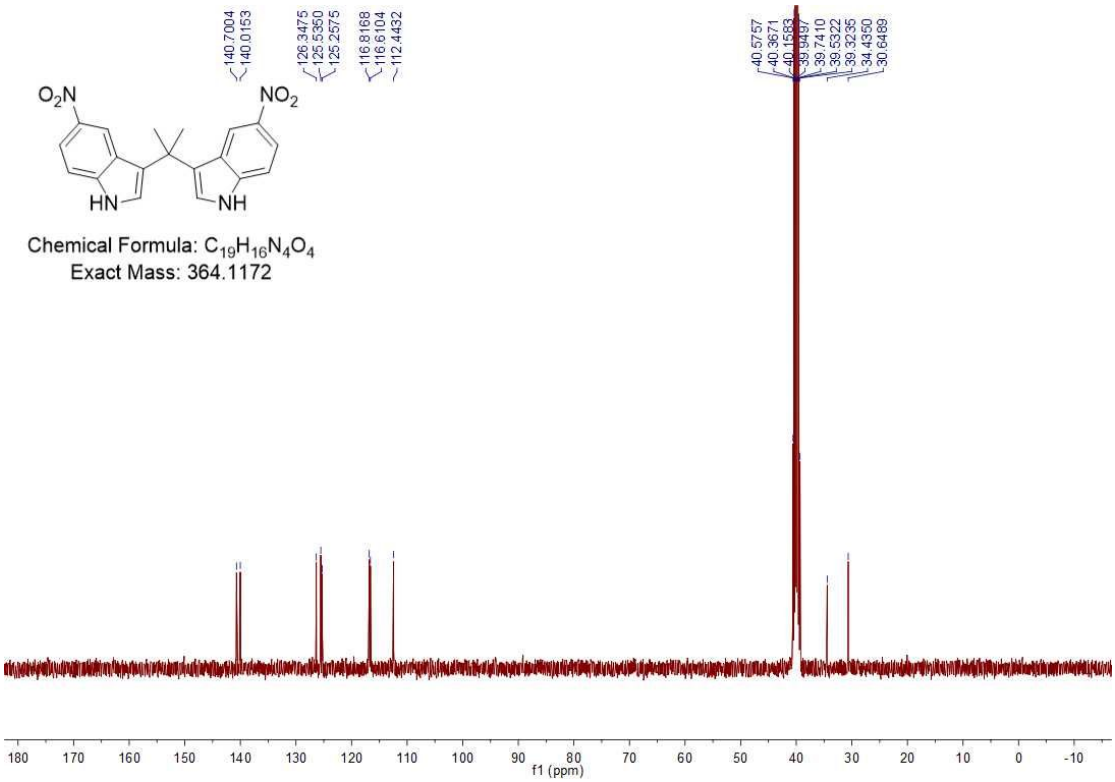


3,3'-(propane-2,2-diyl)bis(1H-indole-5-carbonitrile) (**3d**)

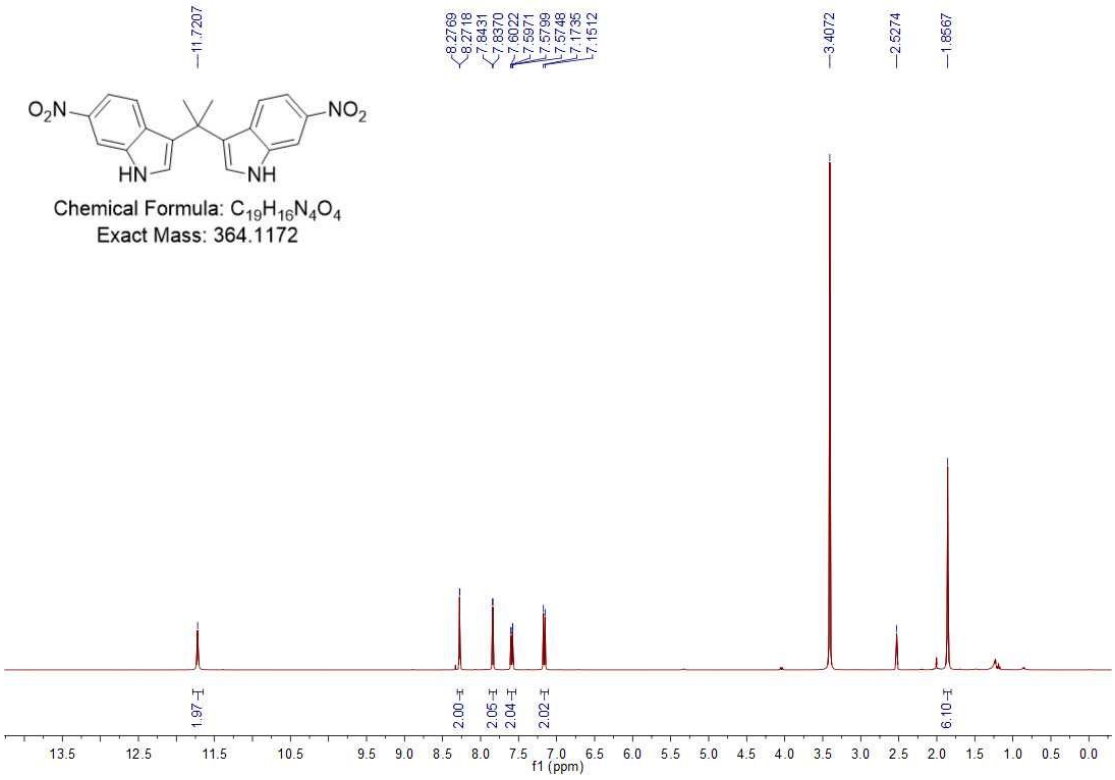


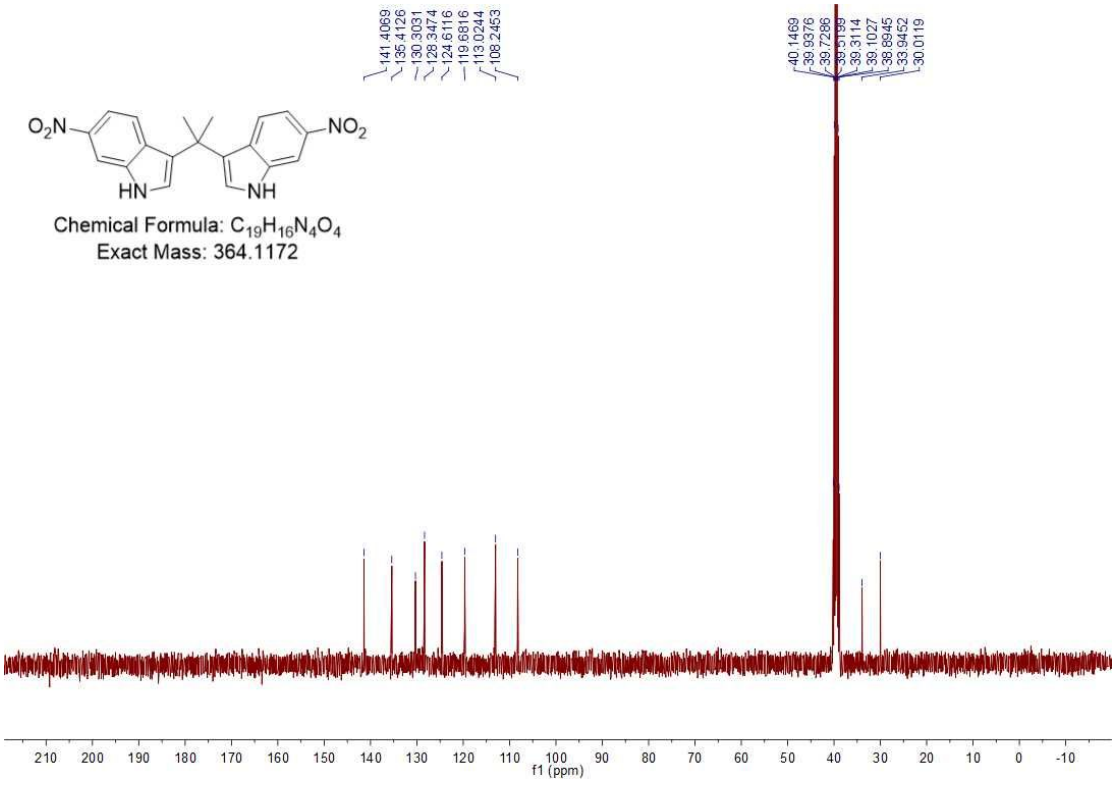
3,3'-(propane-2,2-diyl)bis(5-nitro-1H-indole) (**3e**) in d_6-DMSO



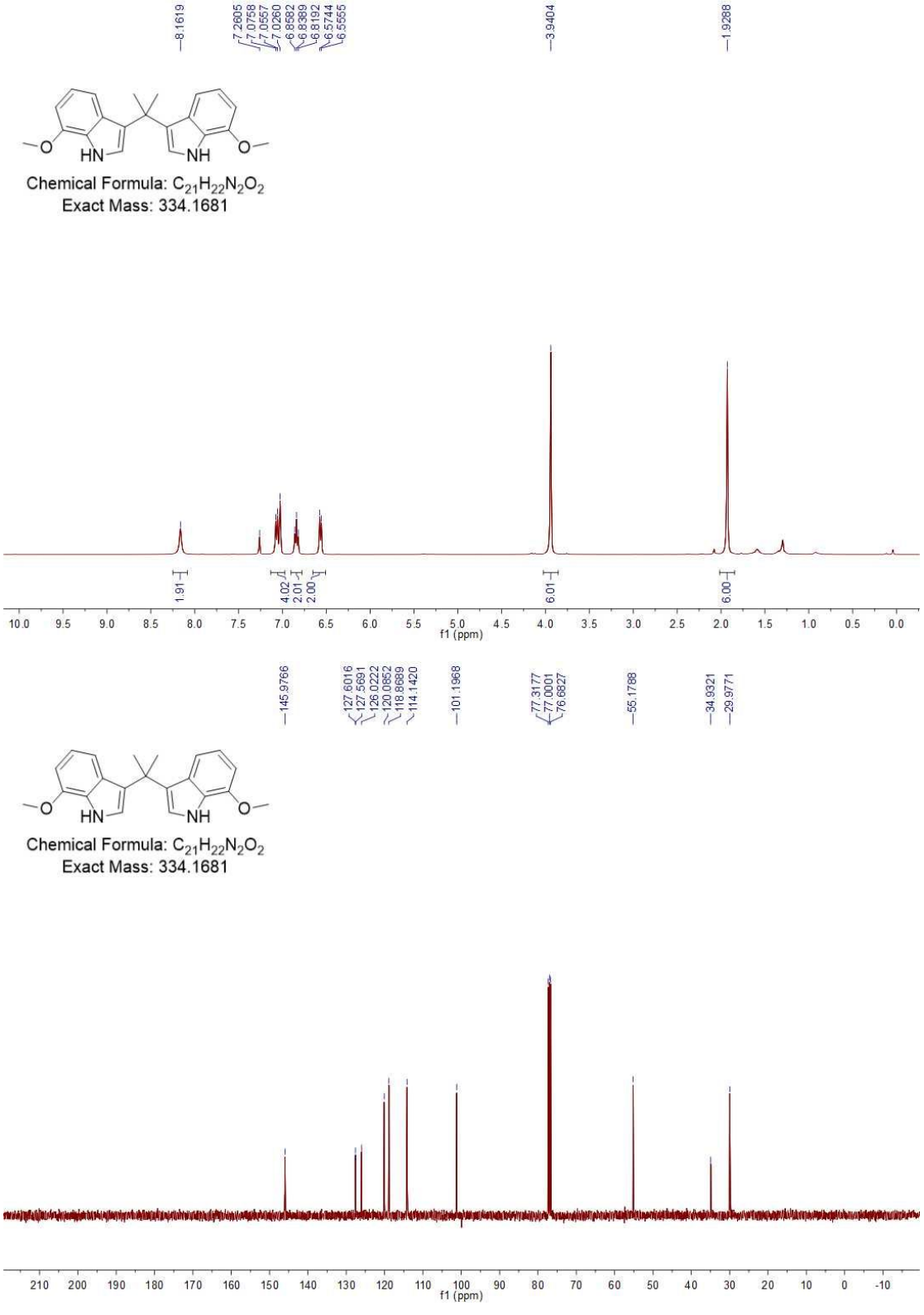


3,3'-(propane-2,2-diyl)bis(6-nitro-1H-indole) (**3f**) in d_6-DMSO

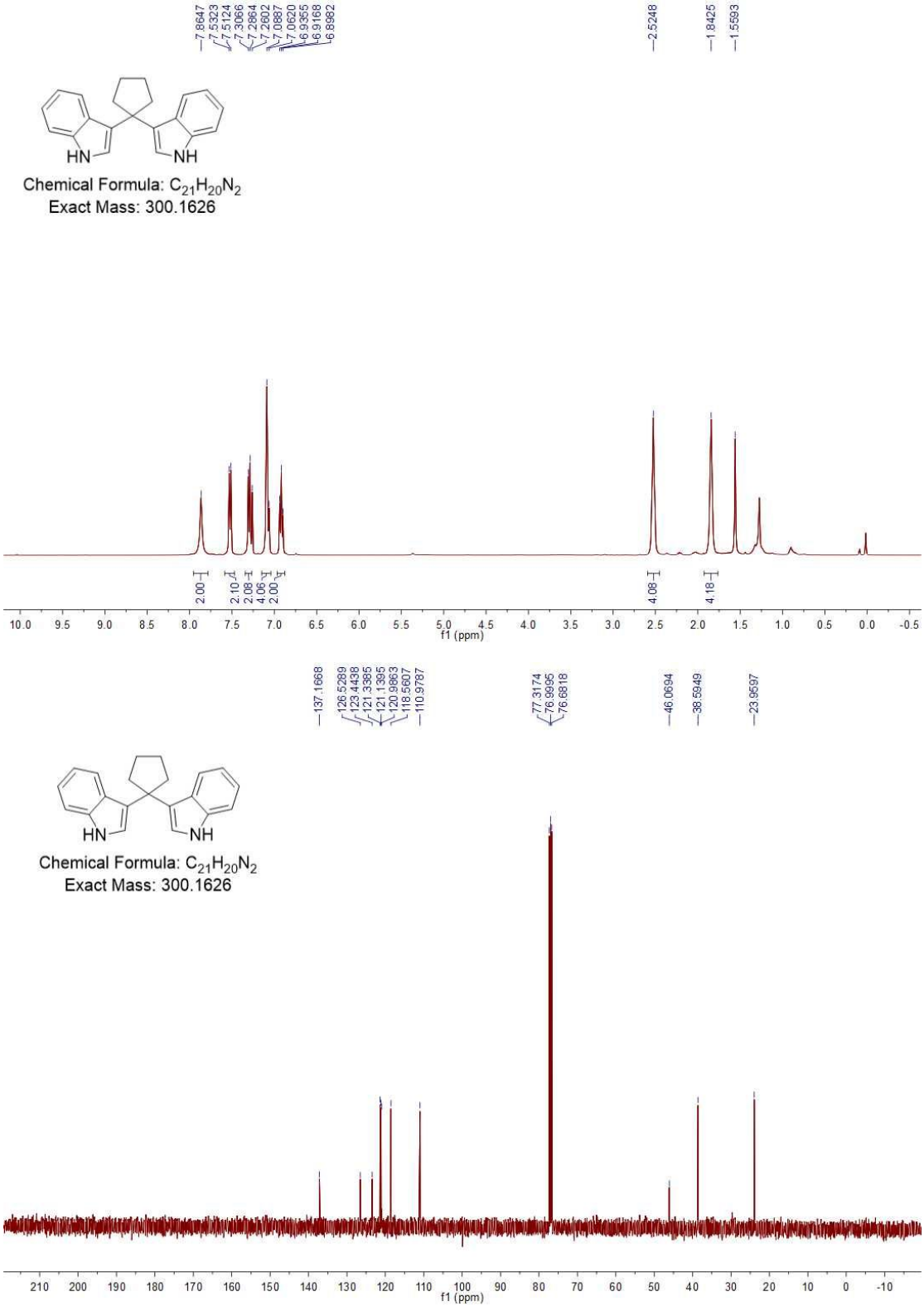




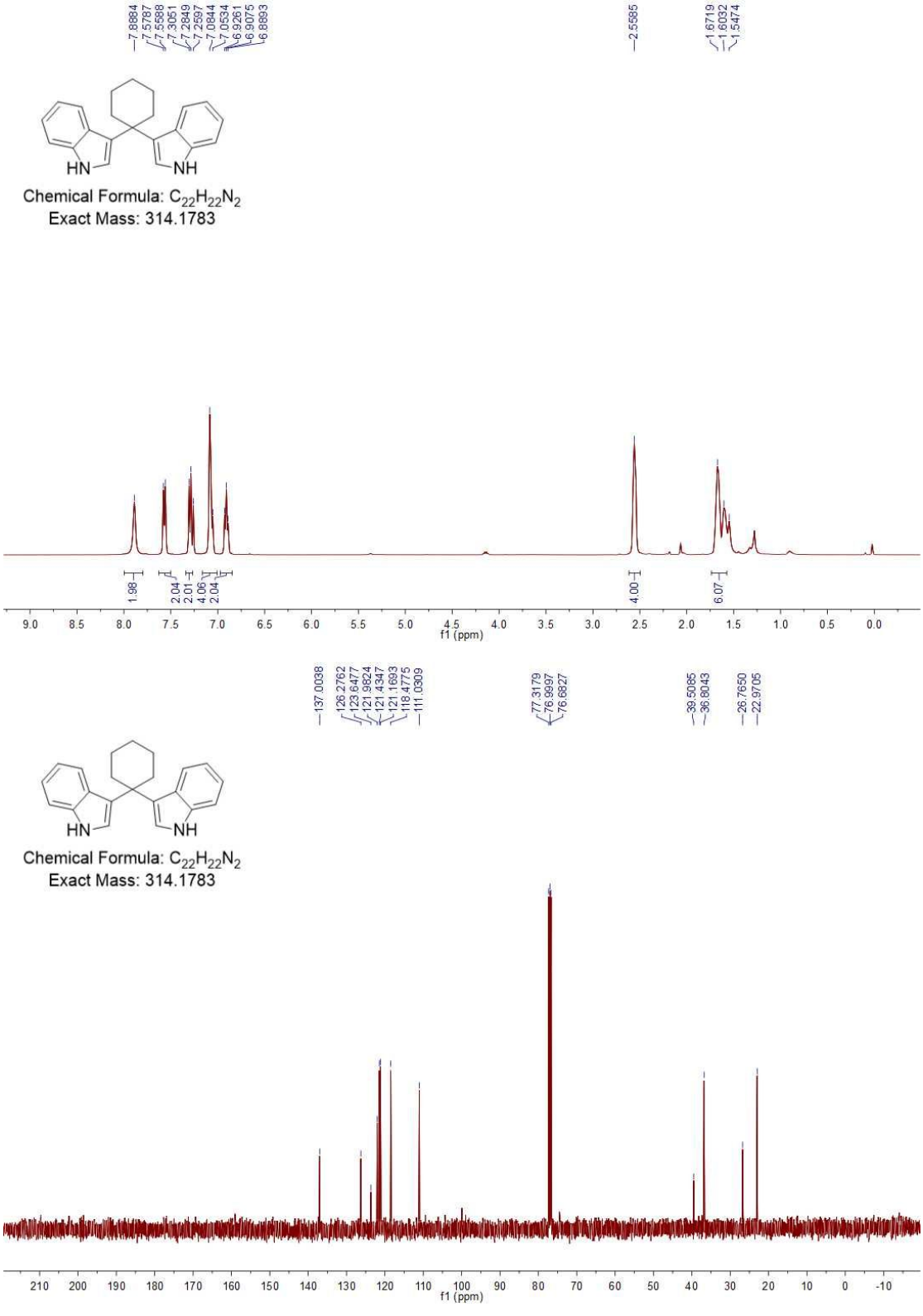
3,3'-(propane-2,2-diyl)bis(7-methoxy-1H-indole) (**3g**)



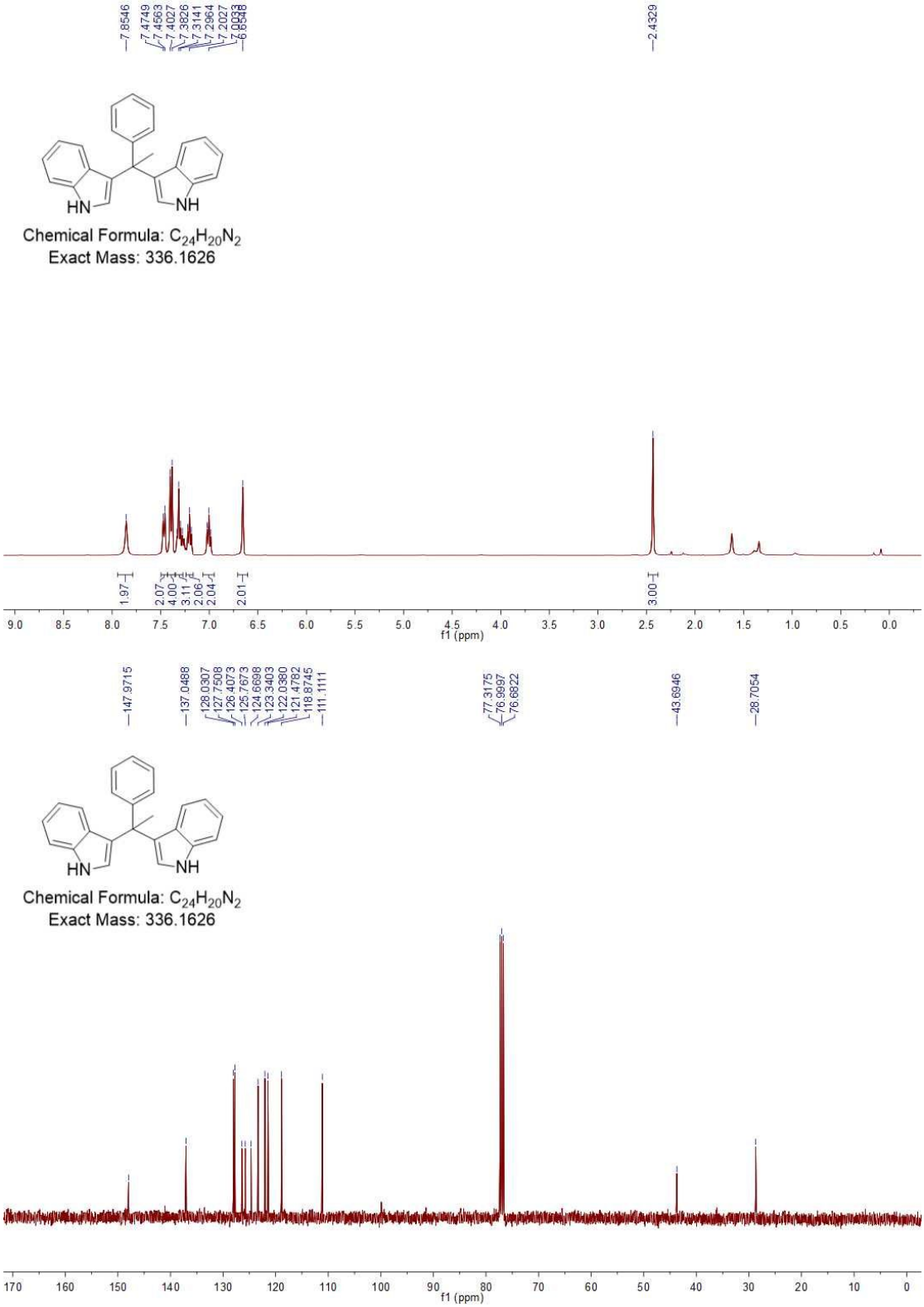
3,3'-(cyclopentane-1,1-diyl)bis(1H-indole) (**3h**)



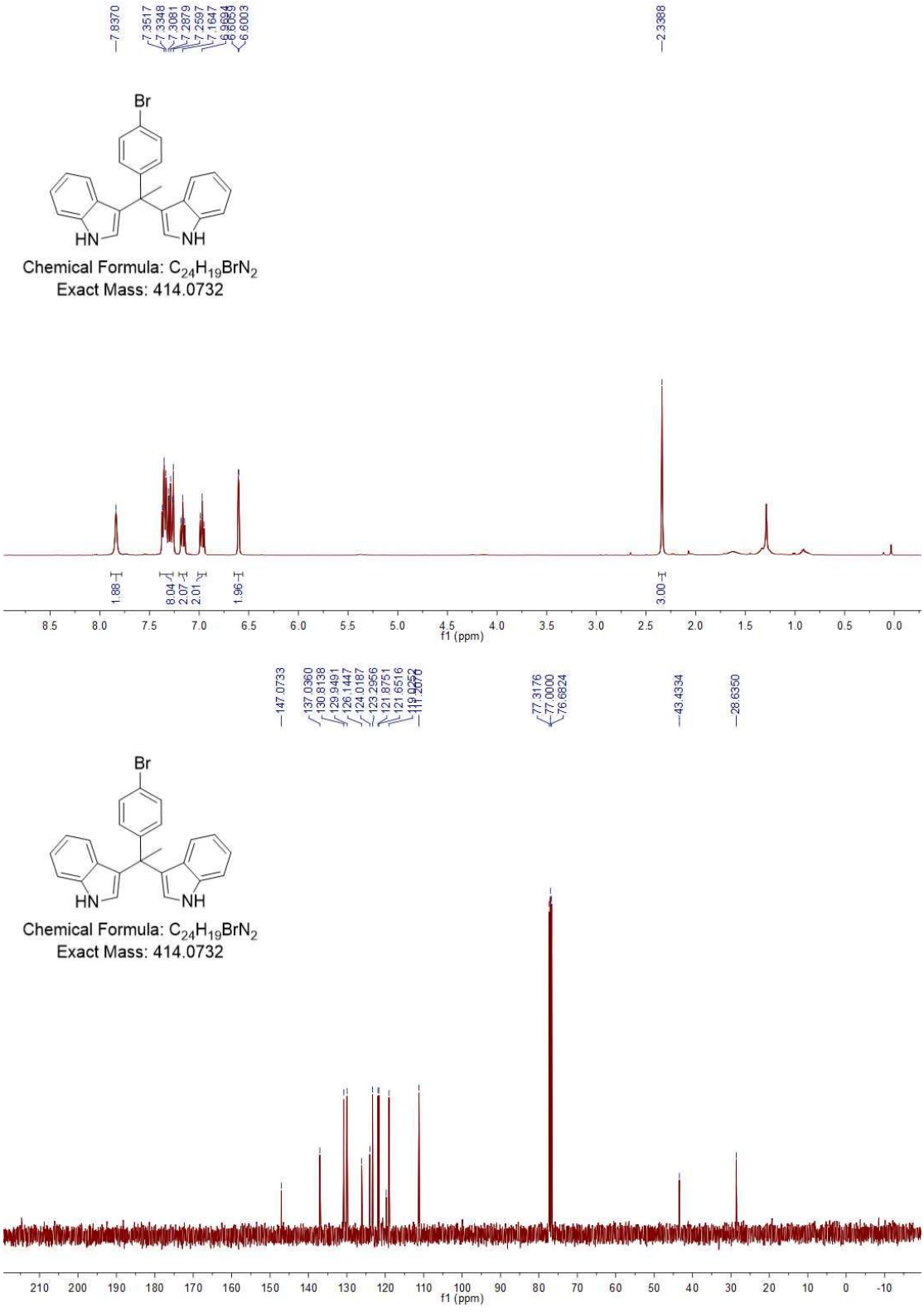
3,3'-(cyclohexane-1,1-diyl)bis(1H-indole) (**3i**)



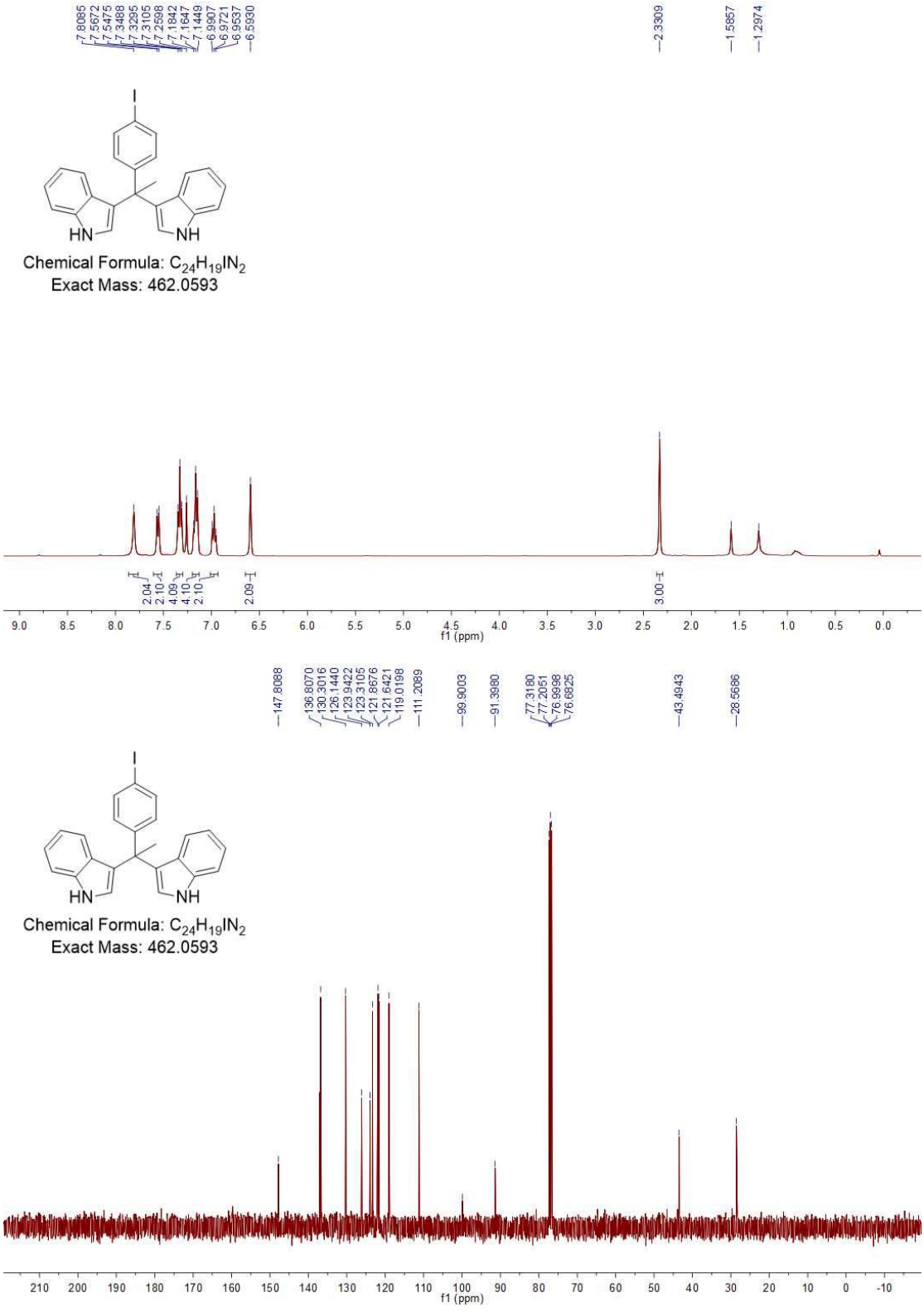
3,3'-(1-phenylethane-1,1-diyl)bis(1H-indole) (**4a**)



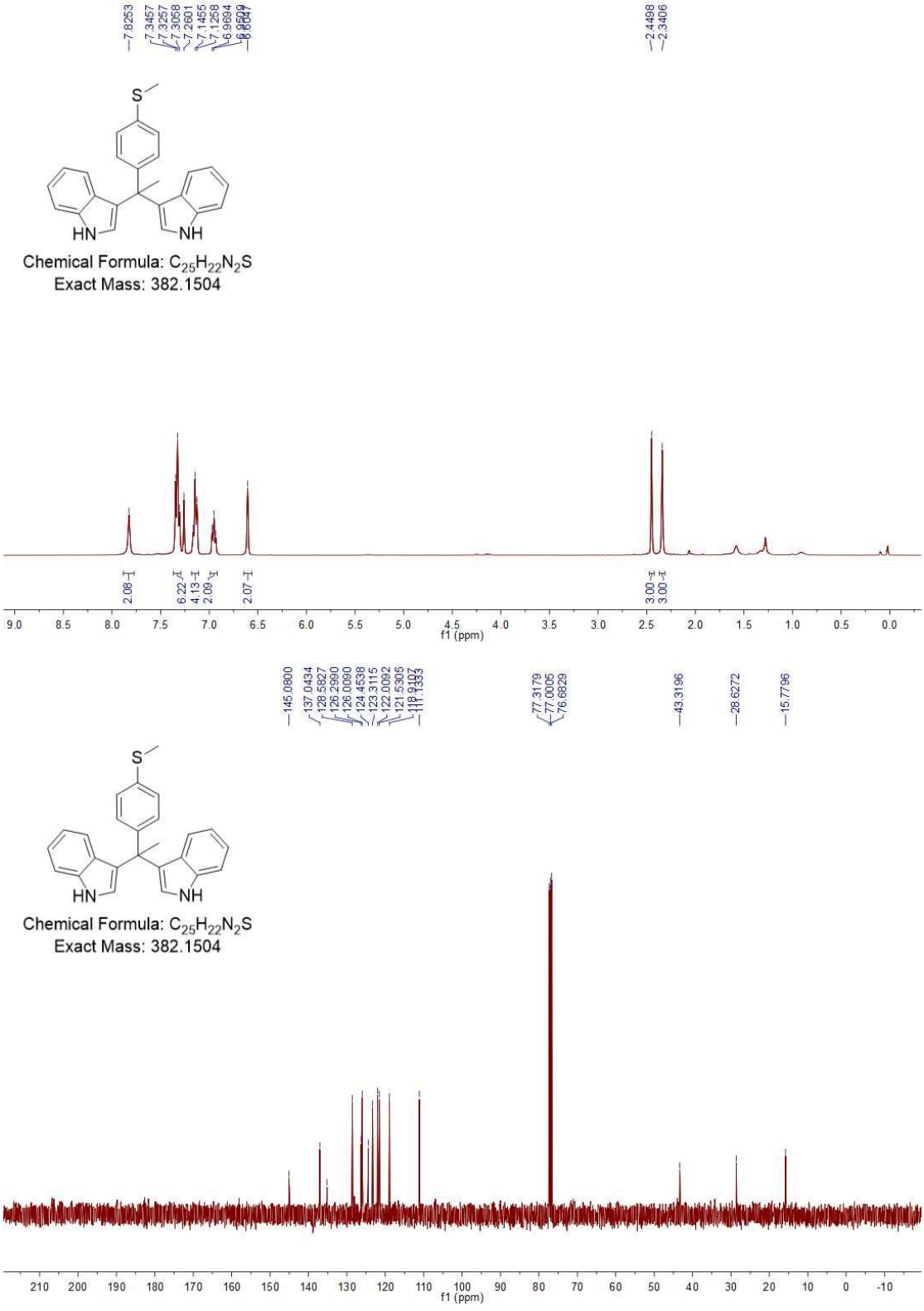
3,3'-(1-(4-bromophenyl)ethane-1,1-diyl)bis(1H-indole) (**4b**)



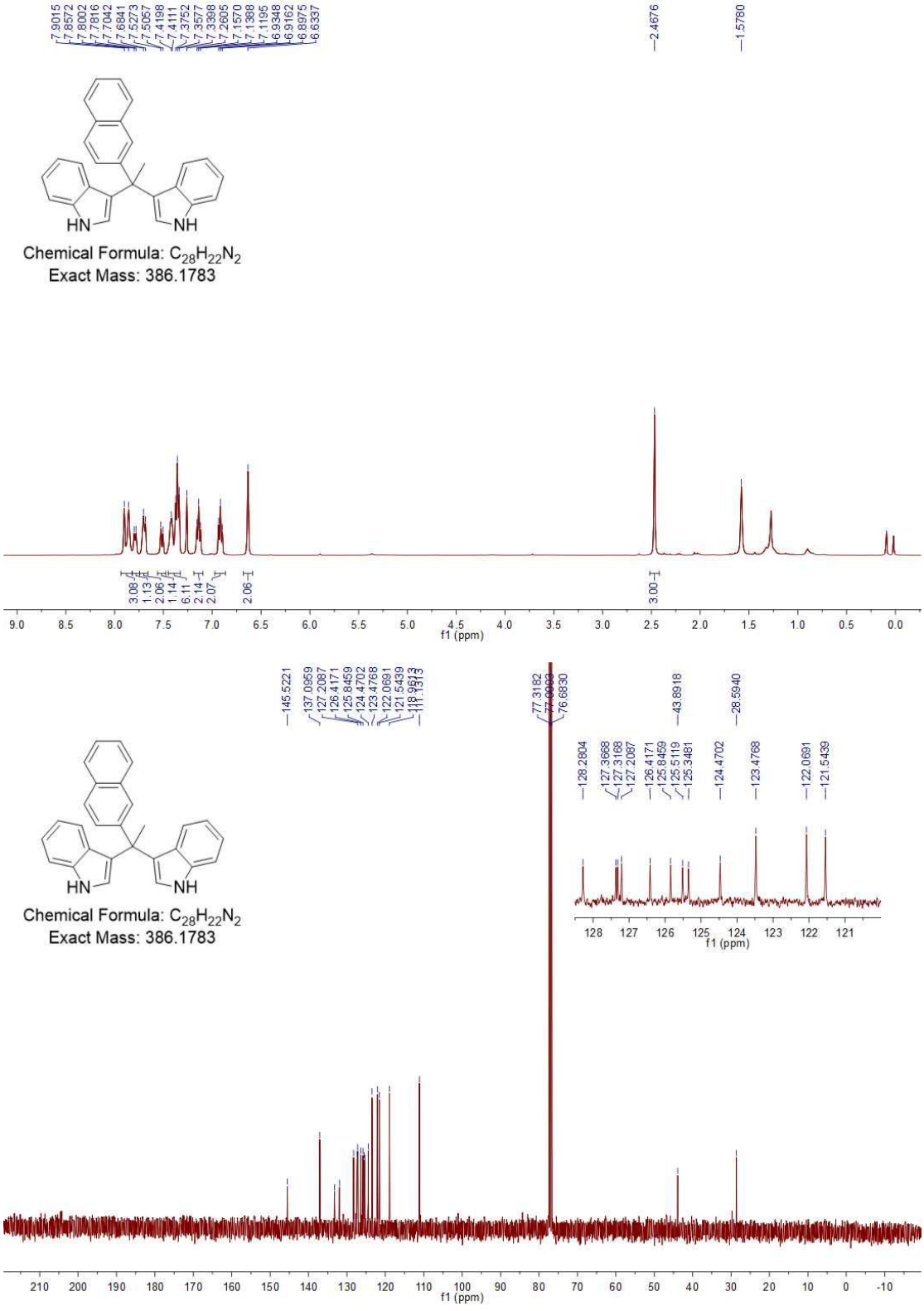
3,3'-(1-(4-iodophenyl)ethane-1,1-diyl)bis(1H-indole) (**4c**)



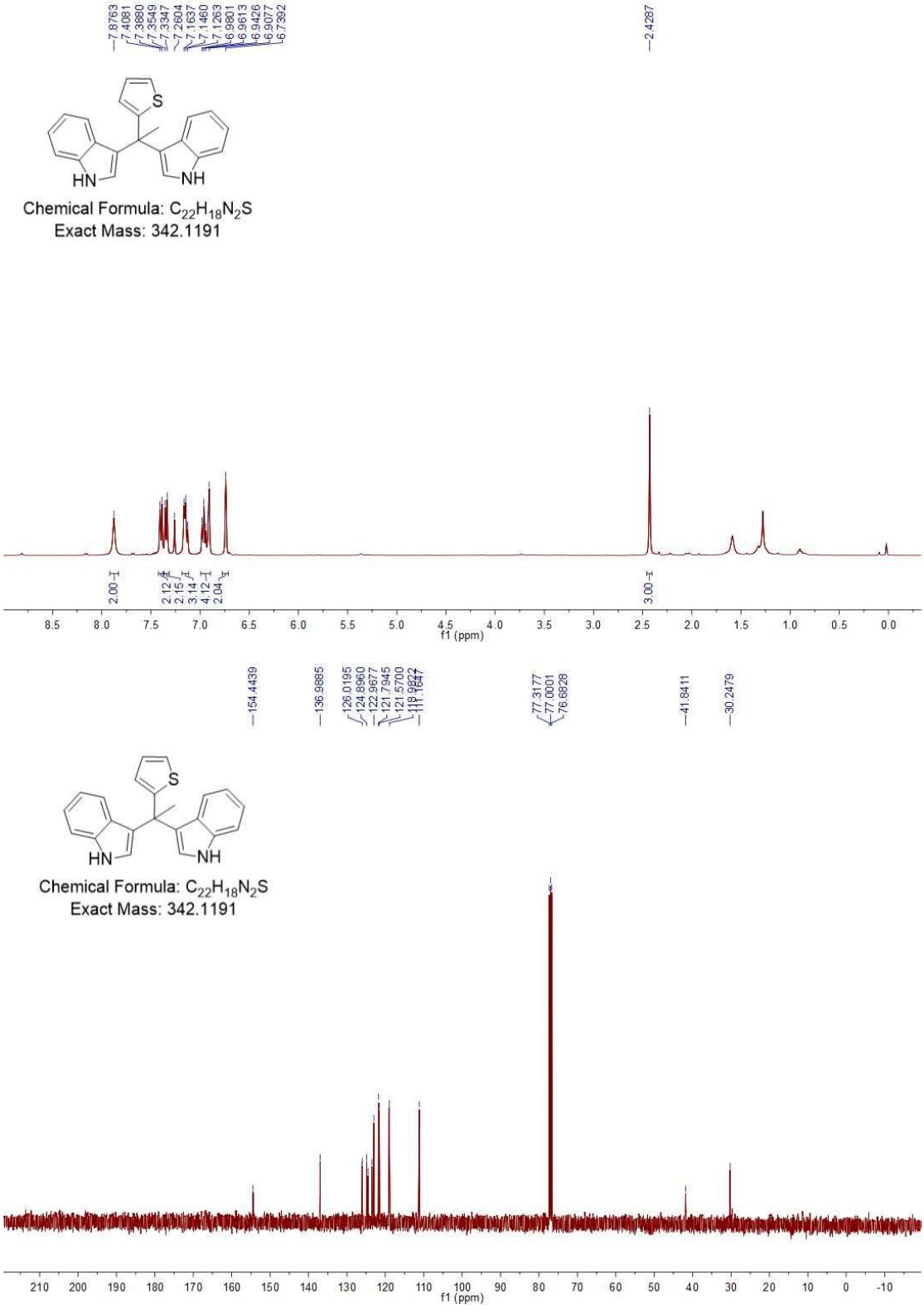
3,3'-(1-(4-(methylthio)phenyl)ethane-1,1-diyl)bis(1H-indole) (**4d**)



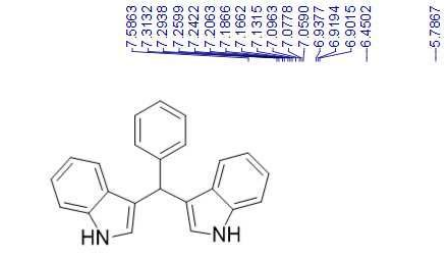
3,3'-(1-(naphthalen-2-yl)ethane-1,1-diyl)bis(1H-indole) (**4e**)



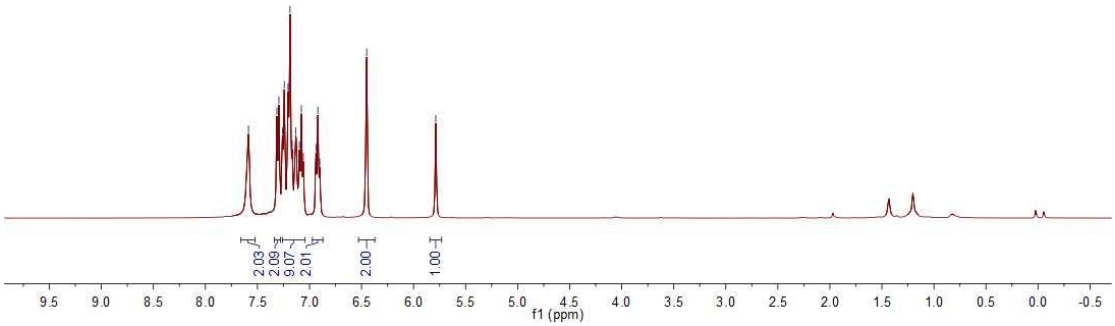
3,3'-(1-(thiophen-2-yl)ethane-1,1-diyl)bis(1H-indole) (**4f**)

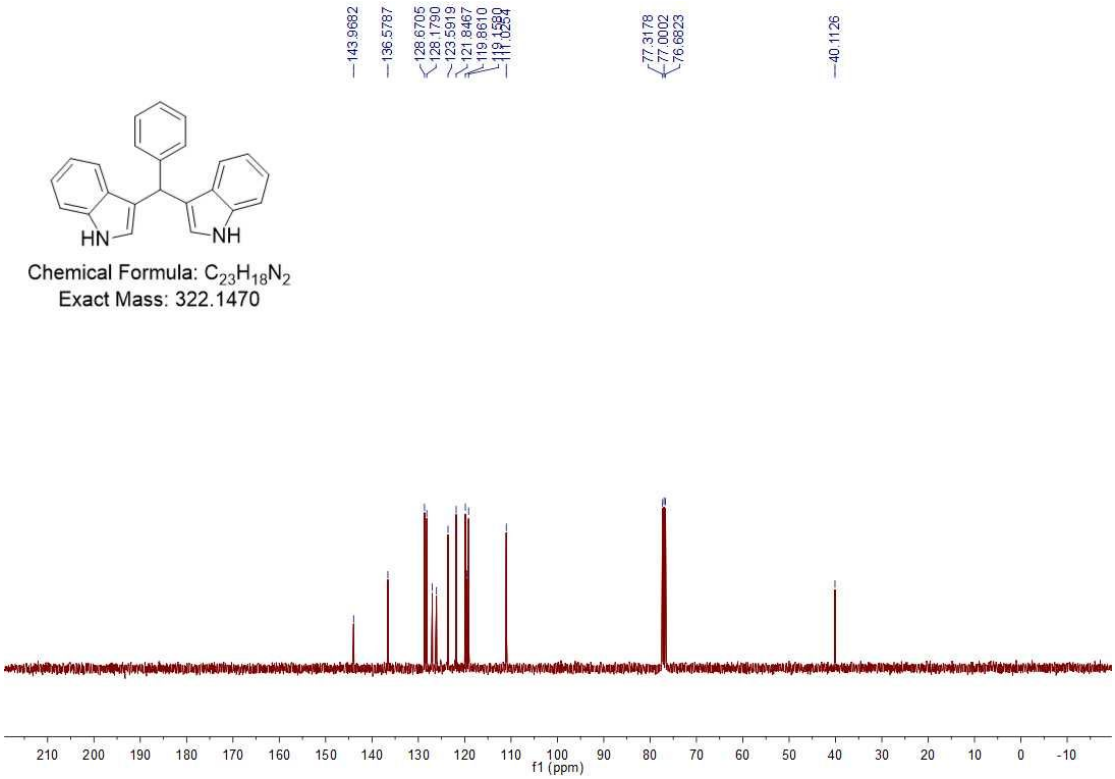


3,3'-(phenylmethylene)bis(1H-indole) (**5a**)



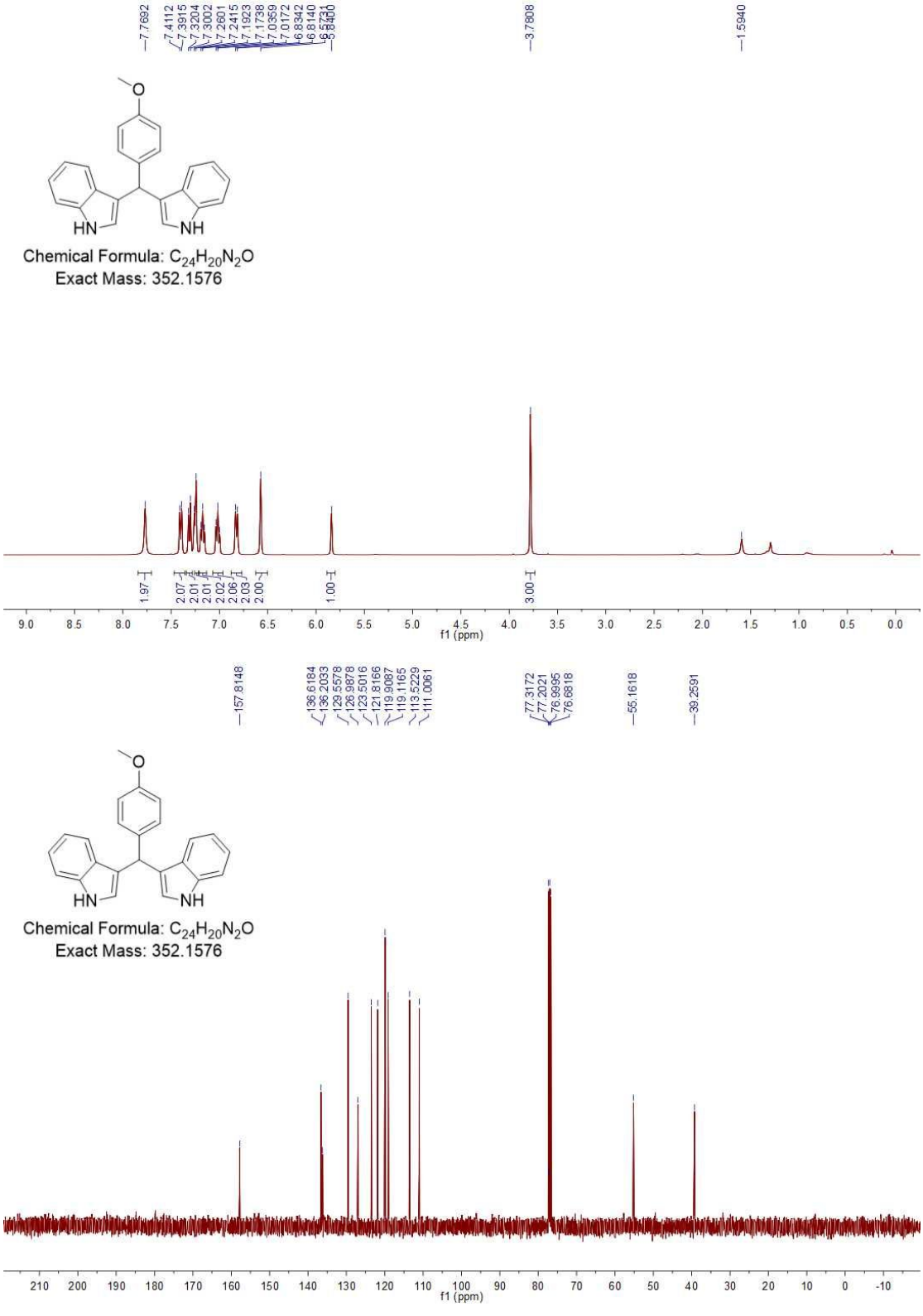
Chemical Formula: $C_{23}H_{18}N_2$
Exact Mass: 322.1470



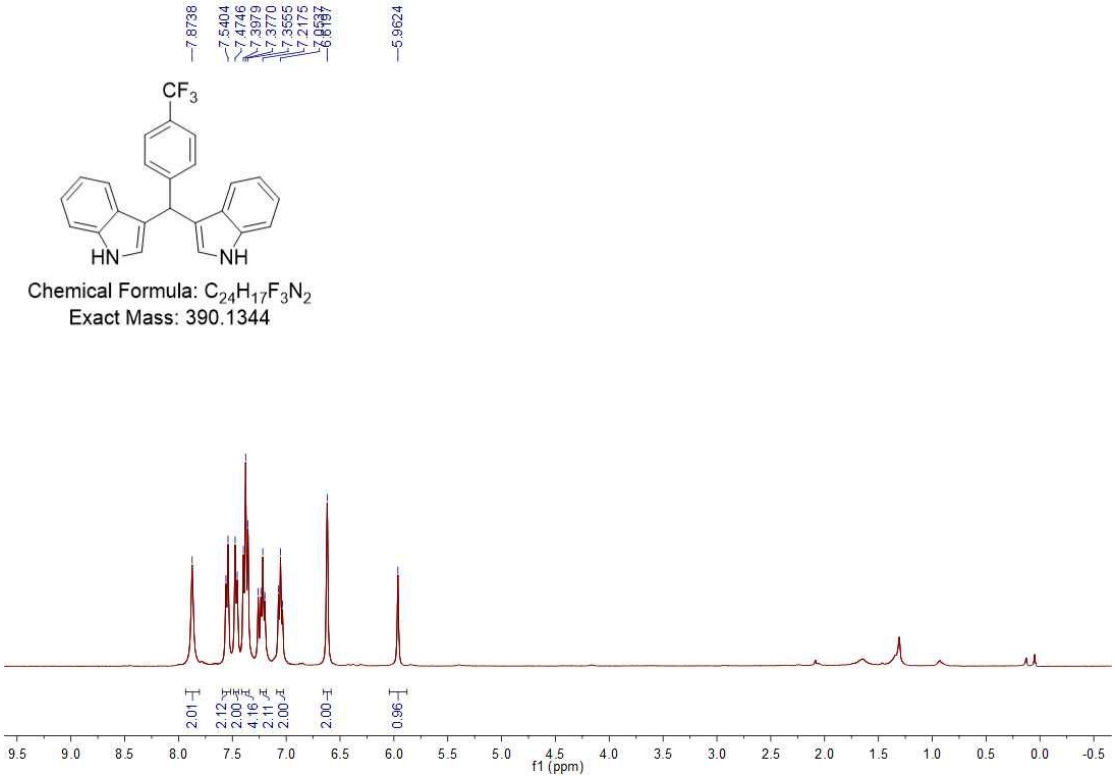


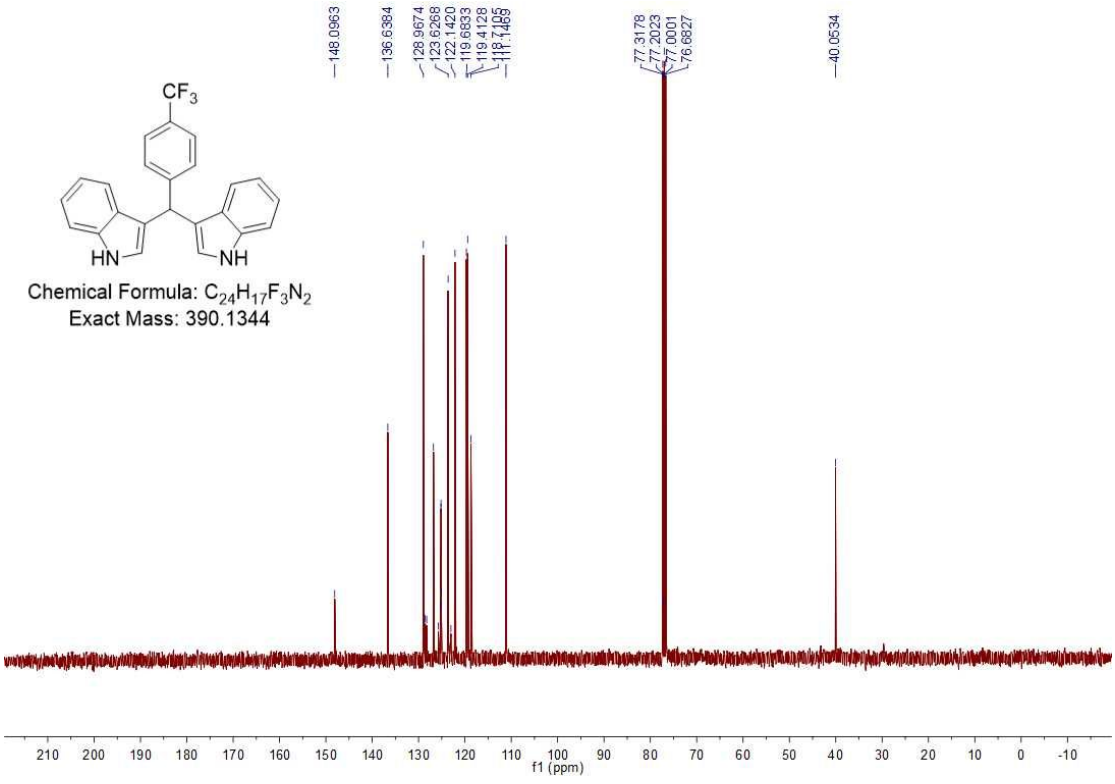
Chemical Formula: $C_{23}H_{18}N_2$
Exact Mass: 322.1470

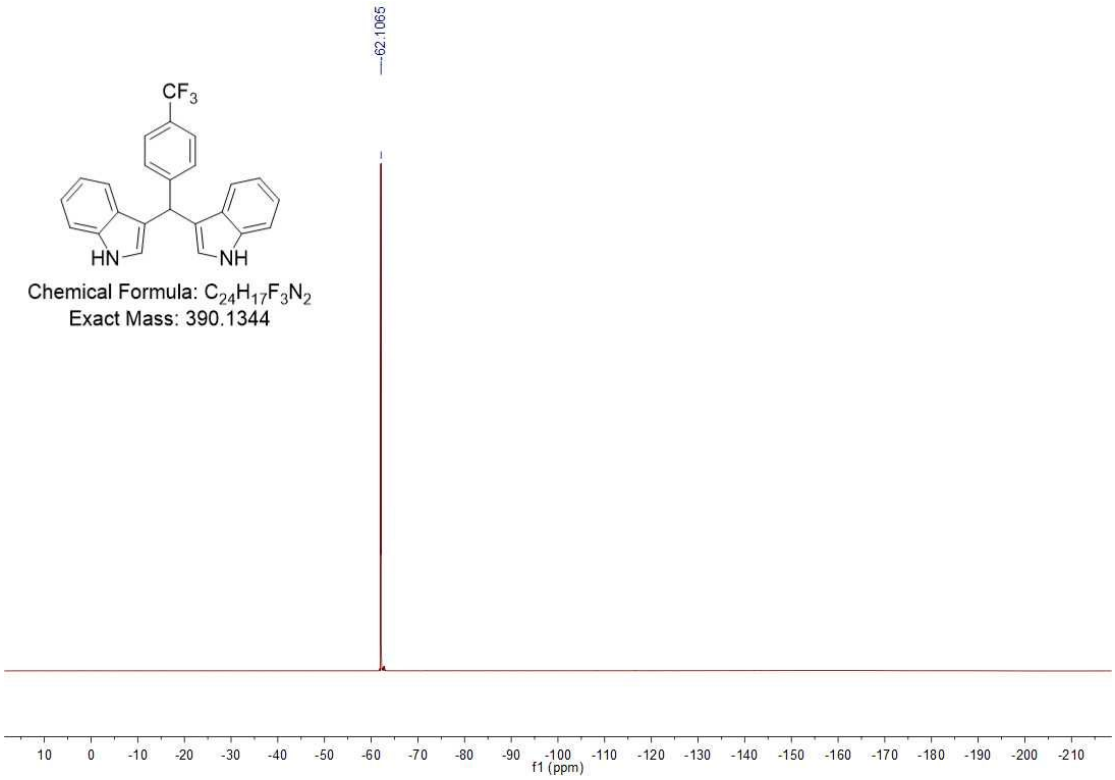
3,3'-((4-methoxyphenyl)methylene)bis(1H-indole) (**5b**)



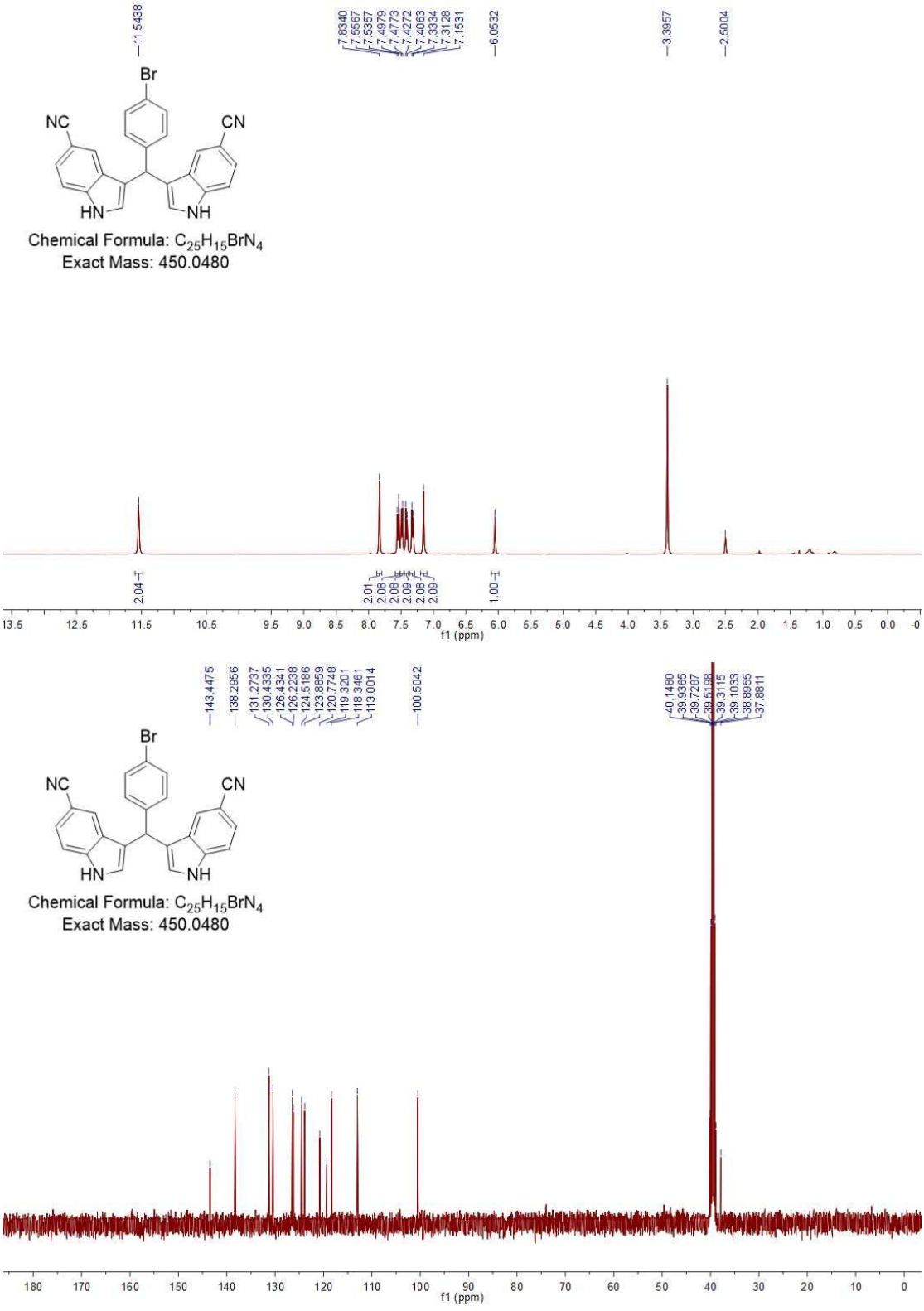
3,3'-((4-(trifluoromethyl)phenyl)methylene)bis(1H-indole) (**5c**)



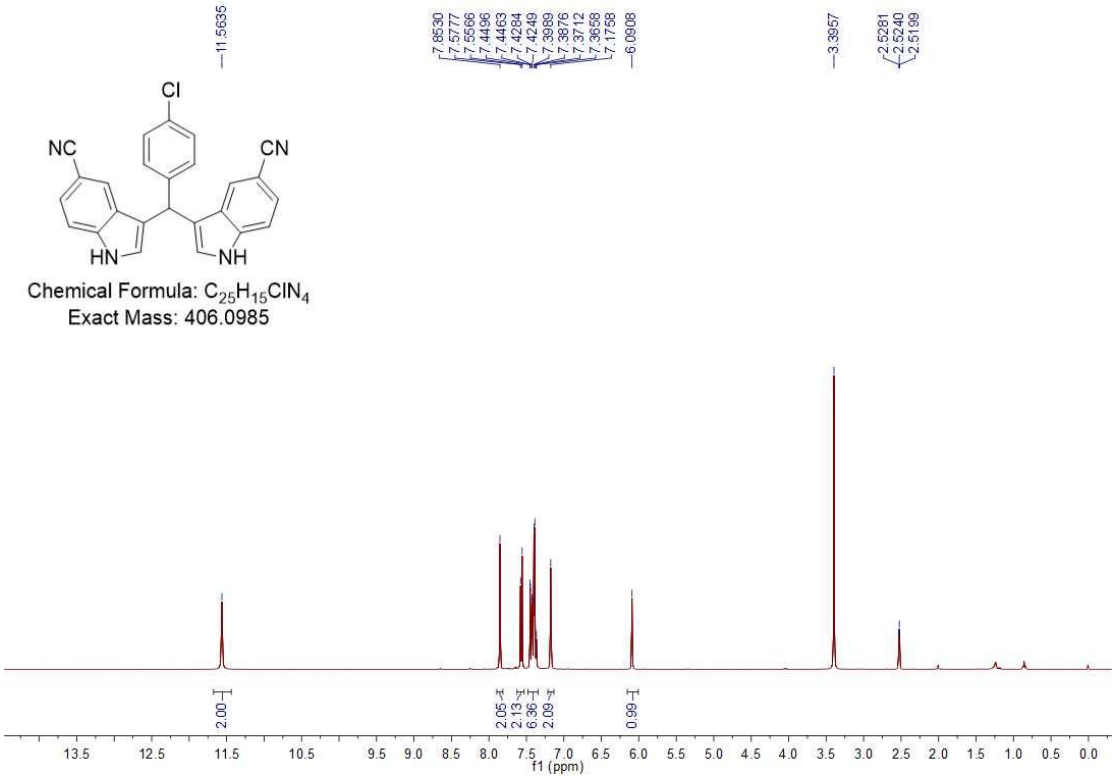


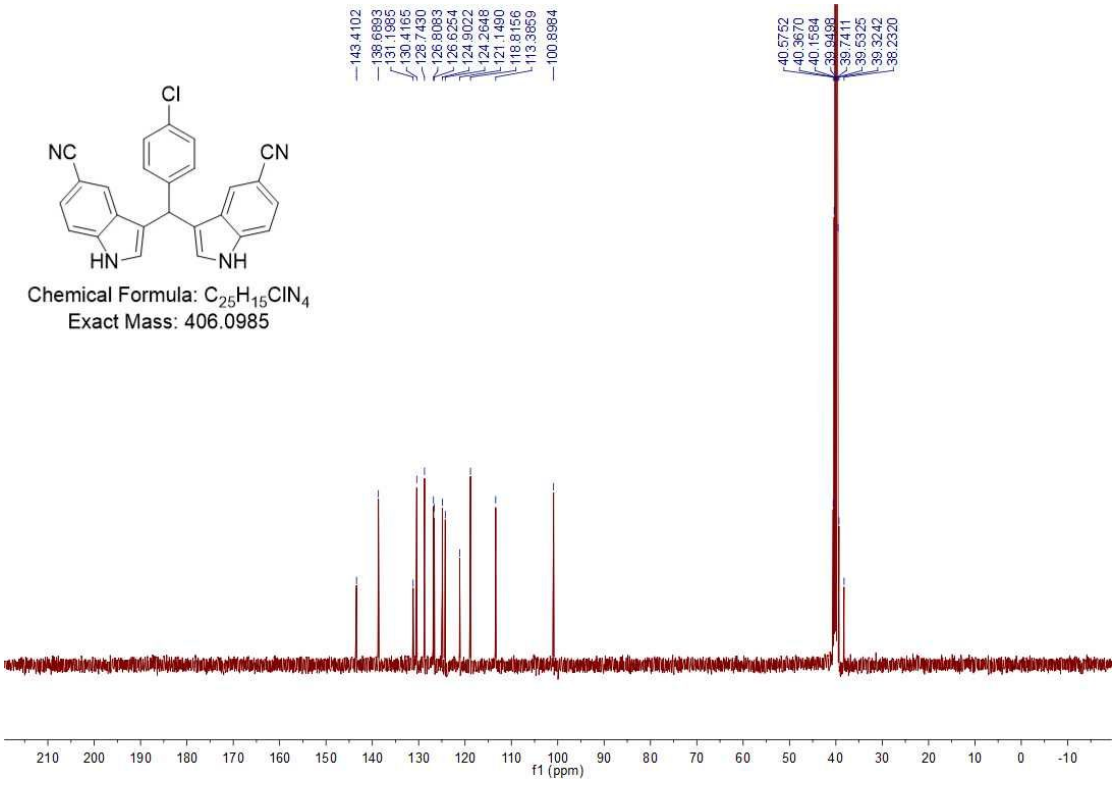

CF3
HN
NH
Chemical Formula: C24H17F3N2
Exact Mass: 390.1344
-62.1065
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

3,3'-((4-bromophenyl)methylene)bis(1H-indole-5-carbonitrile) (**5d**) in d_6-DMSO

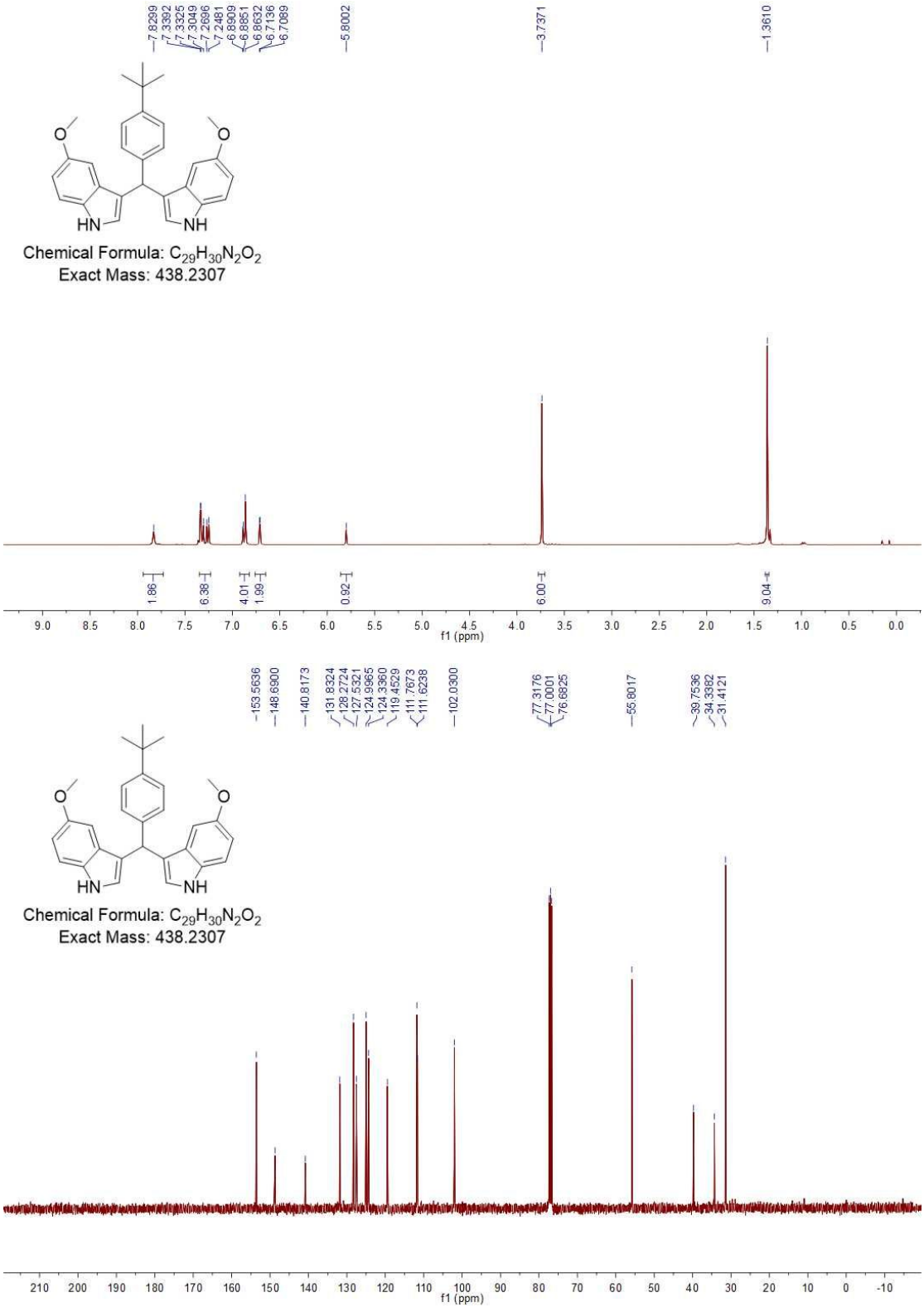


3,3'-((4-chlorophenyl)methylene)bis(1H-indole-5-carbonitrile) (**5e**) in d_6-DMSO

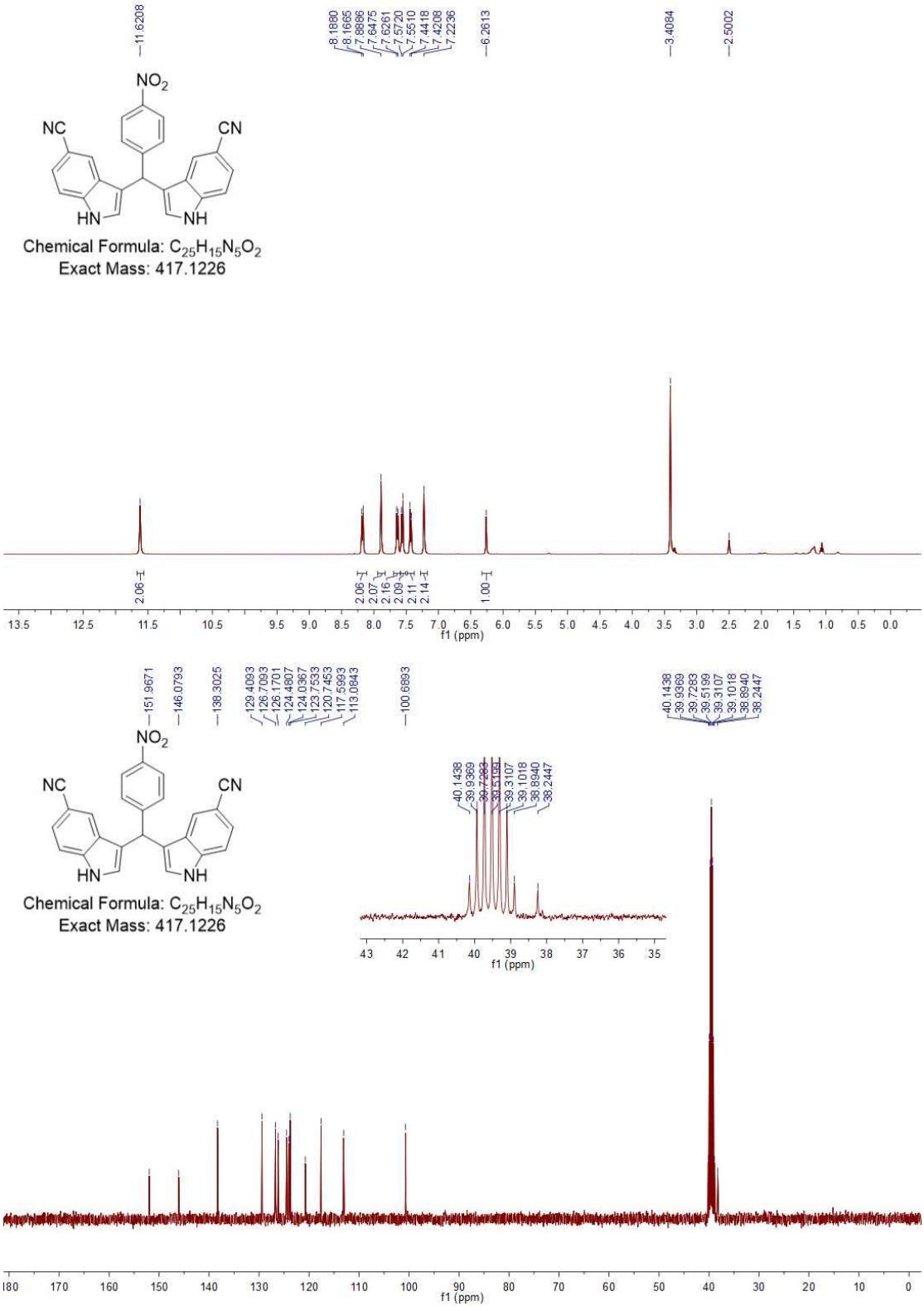




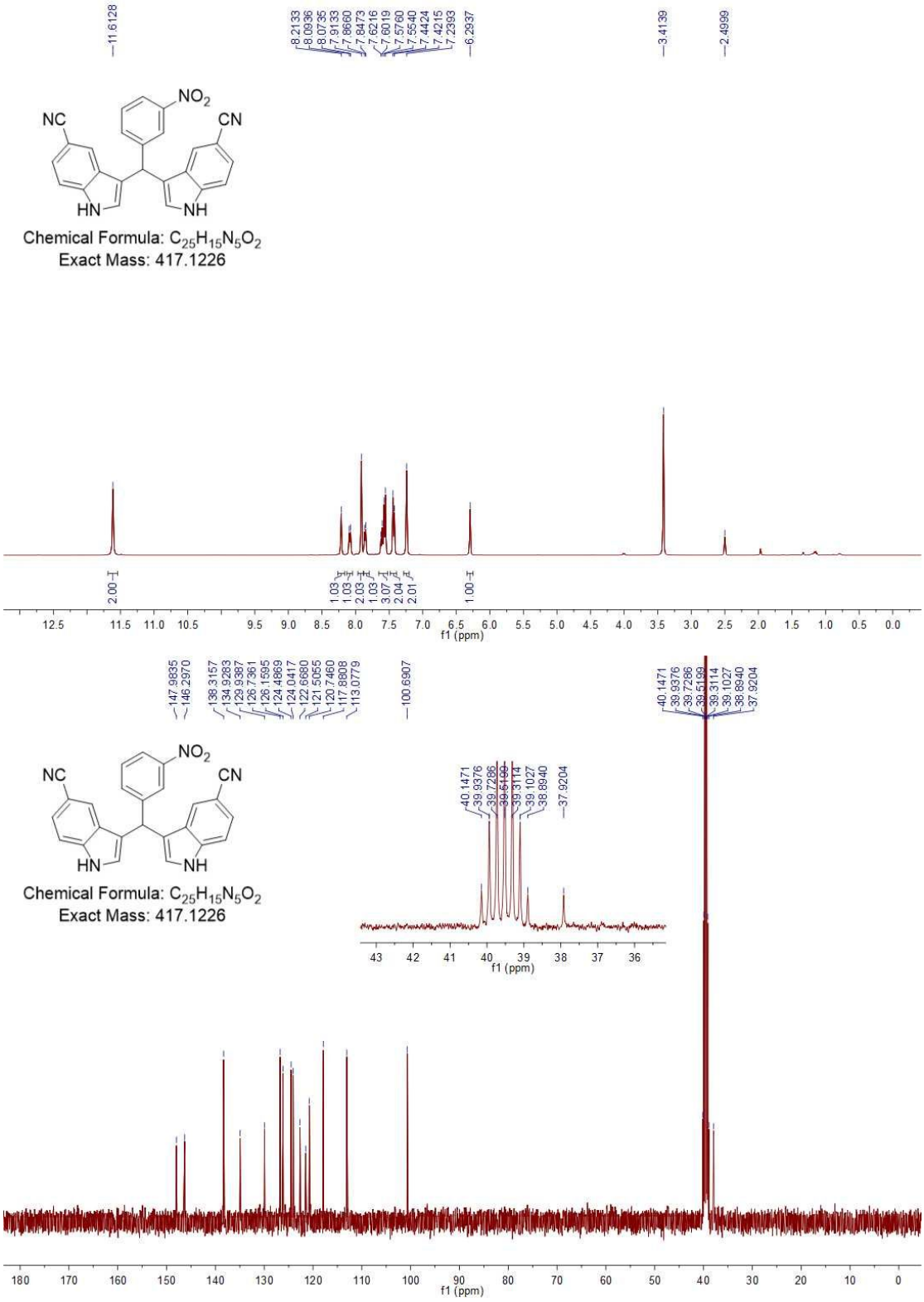
3,3'-((4-(tert-butyl)phenyl)methylene)bis(5-methoxy-1H-indole) (**5f**)



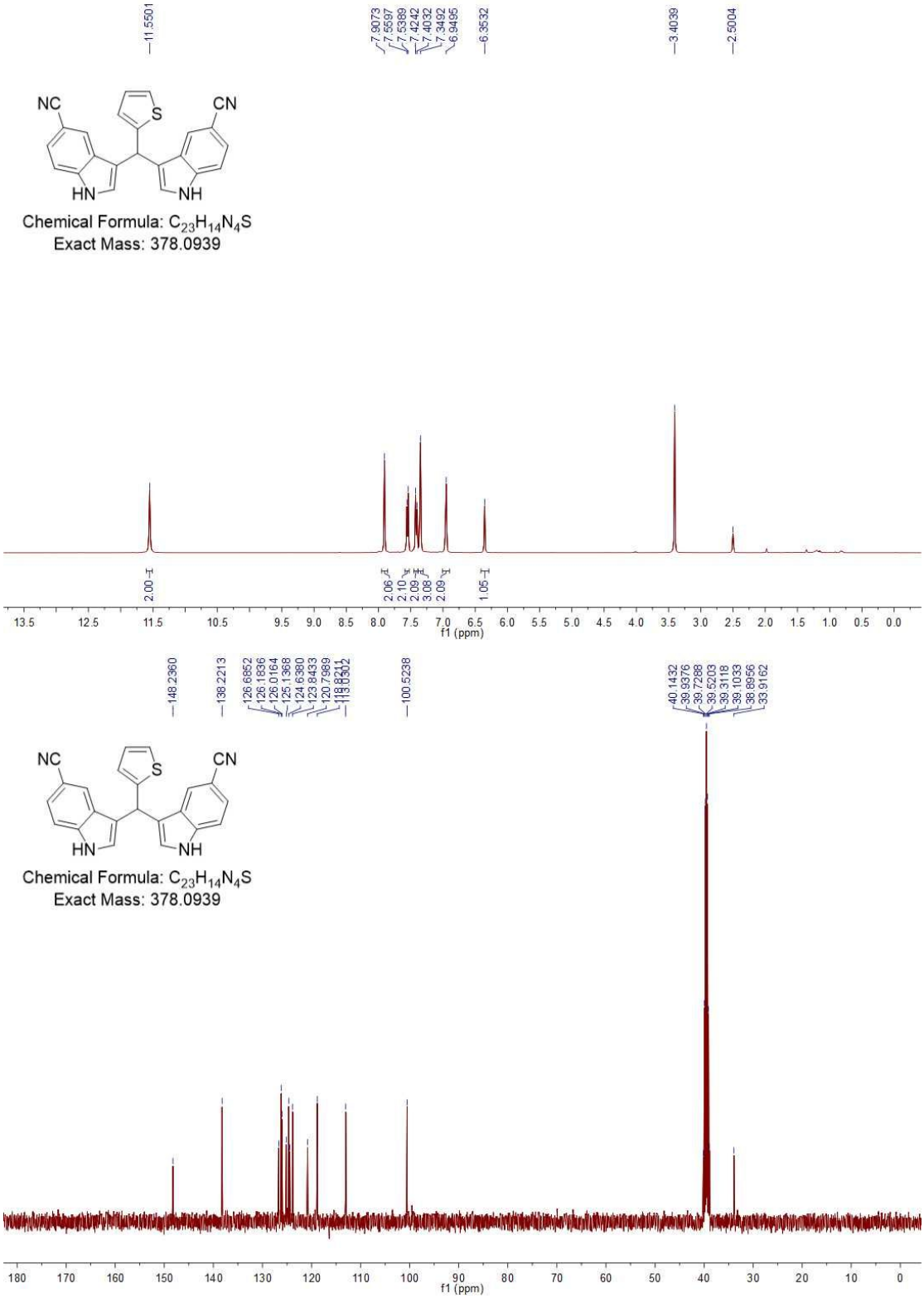
3,3'-((4-nitrophenyl)methylene)bis(1H-indole-5-carbonitrile) (**5g**) in d_6-DMSO



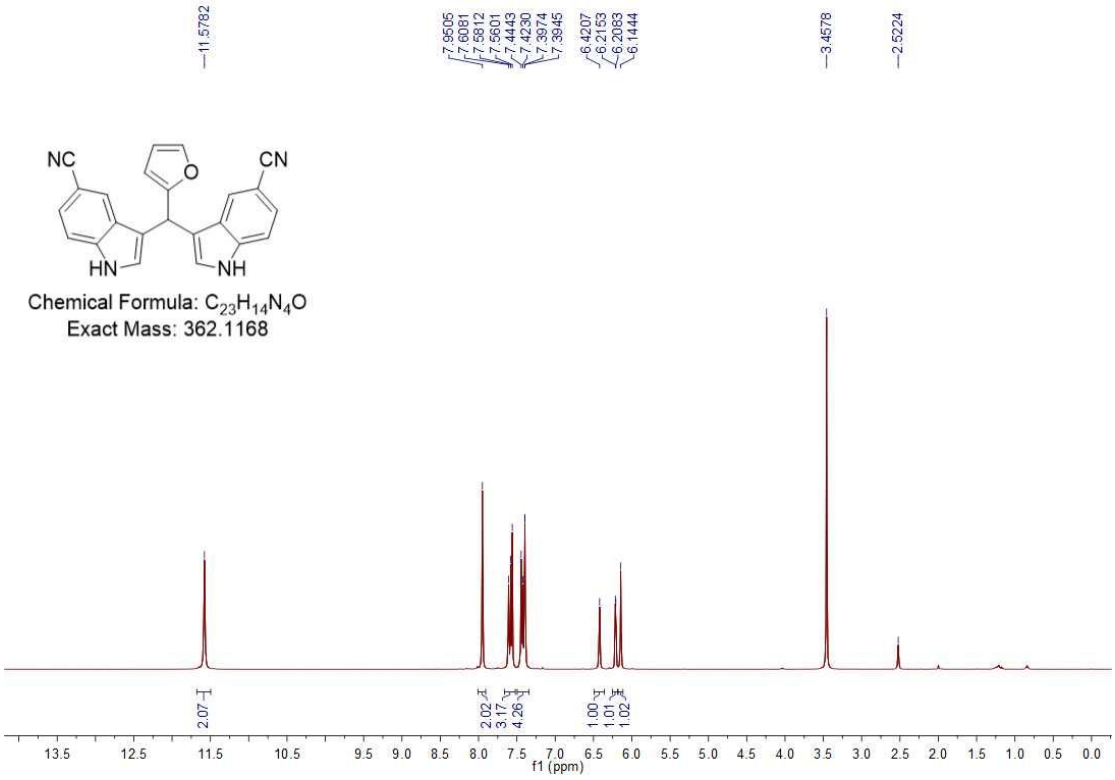
3,3'-((3-nitrophenyl)methylene)bis(1H-indole-5-carbonitrile) (**5h**) in d_6-DMSO

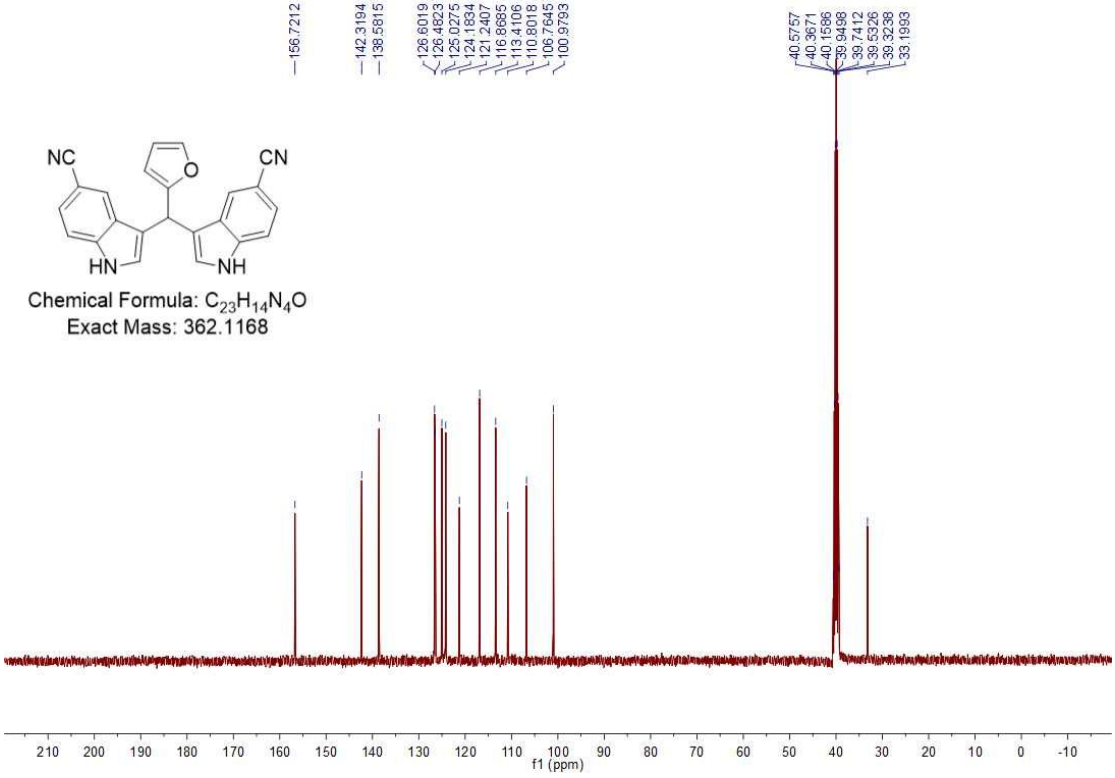


3,3'-(thiophen-2-ylmethylene)bis(1H-indole-5-carbonitrile) (**5i**) in d_6-DMSO



3,3'-(furan-2-ylmethylene)bis(1H-indole-5-carbonitrile) (**5j**) in d_6-DMSO





3,3'-((9-ethyl-9H-carbazol-4-yl)methylene)bis(1H-indole-5-carbonitrile) (**5k**)