Second-generation aryl isonitrile compounds targeting multidrug-resistant *Staphylococcus aureus*

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Part I. Supplementary Biological table

Supplementary Table 1: Bacterial isolates used in this study.

Bacterial Species	Strain Name/Designation	Year Isolated	Location	Resistance Profile
A. baumannii	ATCC BAA-1605	2006	From sputum (Canada)	Resistant to ceftazidime, gentamicin, ticarcillin, piperacillin, aztreonam, cefepime, ciprofloxacin, imipenem, and meropemem
E. cloacae	ATCC BAA-1134	1982	-	-
E. coli	BW25113	-	-	Lab strain
E. coli	JW25113 (Δ*tolC*)	-	-	Lab strain
E. faecium	ATCC 700221	-	From feces (Connecticut)	Resistant to vancomycin
K. pneumoniae	ATCC BAA-1705	-	From urine	Resistant to Imipenem and Ertapenem
P. aeruginosa	ATCC 15442	-	From animal room bottle	-
S. aureus	NRS107	-	-	Resistant to mupirocin, rifampicin and novobiocin
S. aureus	NRS119	2001	From peritoneal fluid (Massachusetts)	Resistant to methicillin, linezolid, and tedizolid
S. aureus	NRS123 (USA400)	1999	From pleural fluid (Minnesota)	Resistant to methicillin
S. aureus	NRS384 (USA300)	-	From wound (Mississippi)	Resistant to erythromycin, methicillin, and tetracycline
S. aureus	NRS385 (USA500)	-	From bloodstream (Connecticut)	Resistant to methicillin, erythromycin, clindamycin, trimethoprim/sulfamethoxazole, levofloxacin, gentamicin and tetracycline
S. aureus	VRS10	2009	From wound (Michigan)	Resistant to methicillin and vancomycin
S. aureus	VRS11a	2010	From prosthetic joint infection (Delaware)	Resistant to methicillin and vancomycin
S. epidermidis	NRS101	-	-	Resistant to methicillin and gentamicin

S. pneumoniae	ATCC 700677	1987	Human patient (Czechoslovakia)	Resistant to penicillin, tetracycline, and erythromycin

Part II. Chemistry Experimental Procedures and Spectral Data

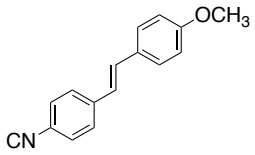
General Chemistry: All chemical reactions were performed using standard syringe techniques under argon unless otherwise stated. Starting materials and reagents were used as received from commercial suppliers. Acetonitrile (CH_3CN), methanol (MeOH), and toluene were purified by passing the previously degassed solvents through activated alumina columns. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were distilled prior to use.

All compounds were purified using flash chromatography with silica gel (230-400 mesh). Thin layer chromatography (TLC) was performed using glass-backed silica plates (Silicycle). NMR spectra were recorded on a Bruker ARX-400 spectrometer or AV-500 spectrometer at room temperature. Chemical shifts δ (in ppm) are given in reference to the solvent signal [^{1}H NMR: $CDCl_3$ (7.26); ^{13}C NMR: $CDCl_3$ (77.2)]. ^{1}H NMR data are reported as follows: chemical shifts (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, m = multiplet, br = broad), coupling constant (Hz), and integration. ^{13}C NMR data are reported in terms of chemical shift and multiplicity. IR data were recorded on a Thermo Nicolet Nexus 470 FTIR. High-resolution mass measurements for compound characterization were determined using a FinniganMAT XL95 double focusing mass spectrometer system.

All compounds for biological testing were confirmed to be of >95% purity based on HPLC.

General procedure for the synthesis of stilbene aryl isonitriles 6-14 from 5.

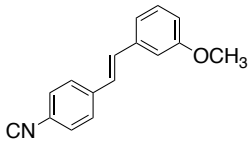
A solution of *n*-BuLi (2.5 M in hexane, 0.2 ml, 0.46 mmol, 1.15 equiv) was added dropwise to a stirring solution of diisopropyl amine (53 mg, 0.52 mmol, 1.3 equiv) in THF (1.5 ml) at -78 °C. After stirring for 5 mins at -78 °C, a solution of diethyl (4-isocyanobenzyl)phosphonate **5** (100 mg, 0.40 mmol, 1 equiv) in THF (1 ml) was added dropwise, after which the solution was allowed to sit and stir for 30-60 mins. Still at -78 °C, the respective aldehyde (0.36 mmol, 0.9 equiv) dissolved in THF (1 ml) was added dropwise and then allowed to sit and stir for an additional 30-40 mins. The resulting mixture was then allowed to warm to room temperature and stirred for 2 h. Water, saturated aqueous ammonium chloride and Et_2O were added. The aqueous layer was then extracted with Et_2O (3x) followed by the washing of the combined organic fractions with brine. The organic layer was then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to obtain the required stilbene aryl isonitrile.



6

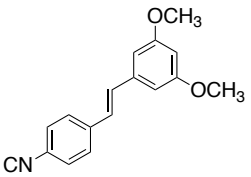
(E)-1-isocyano-4-(4-methoxystyryl)benzene (6). Analogue **6** was synthesized from intermediate **5** and 4-methoxybenzaldehyde according to the general procedure (70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 11.6, 8.6 Hz, 4H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 16.3 Hz, 1H), 6.96 – 6.88 (m, 3H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.27, 159.85, 138.96, 130.66, 129.34, 128.06 (2C), 126.90 (2C), 126.71 (2C), 124.85, 124.64, 114.27 (2C), 55.37; IR (neat, cm^{-1}): ν = 3054, 3021, 2963, 2935, 2840, 2122, 1603, 1596, 1573, 1512, 1458, 1424, 1307,

1297, 1267, 1253, 1175, 1031, 972, 835. HRMS (ESI): m/z = 236.1070 calculated for $C_{16}H_{14}NO$ $[M+H]^+$, found 236.1072.



7

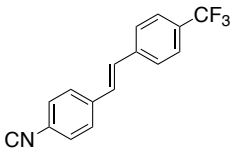
(E)-1-(4-isocyanostyryl)-3-methoxybenzene *(7)*. Analogue **7** was synthesized from intermediate **5** and 3-methoxybenzaldehyde according to the general procedure (53% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.13 – 7.02 (m, 4H), 6.86 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 3.85 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.56, 159.97, 138.50, 137.99, 131.02, 129.81, 127.26 (2C), 127.09 (2C), 126.75, 125.30, 119.47, 113.95, 112.06, 55.31. IR (neat, cm^{-1}): ν = 3088, 3060, 3019, 2964, 2943, 2840, 2125, 2089, 1600, 1576, 1568, 1506, 1432, 1274, 1257, 1173, 1050, 973, 862, 781. HRMS (ESI): m/z = 236.1070 calculated for $C_{16}H_{14}NO$ $[M+H]^+$, found 236.1071.



8

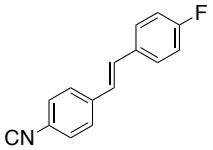
(E)-1-(4-isocyanostyryl)-3,5-dimethoxybenzene (8). Analogue **8** was synthesized from intermediate **5** and 3,5-dimethoxybenzaldehyde according to the general procedure (79% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 2.6 Hz, 2H), 6.66 (d, *J* = 2.2 Hz, 2H), 6.43 (t, *J* = 2.2 Hz, 1H), 3.84 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.58, 161.07 (2C), 138.53, 138.41, 131.11 (2C), 127.29 (2C), 126.75 (2C), 125.35,

104.86 (2C), 100.55, 55.42 (2C); IR (neat, cm^{-1}): ν = 3093, 3064, 3051, 3001, 2940, 2842, 2121, 1608, 1582, 1458, 1429, 1339, 1320, 1311, 1207, 1167, 1151, 1070, 1059, 959, 946. HRMS (ESI): m/z = 266.1176 calculated for $C_{16}H_{16}NO_2$ $[M+H]^+$, found 266.1174.



9

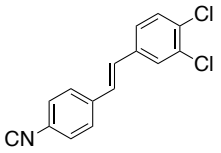
(E)-1-isocyano-4-(4-(trifluoromethyl)styryl)benzene (9). Analogue **9** was synthesized from intermediate **5** and 4-trifluoromethylbenzaldehyde according to the general procedure (50% yield) ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.58 (m, 4H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.15 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.00, 139.99, 137.85, 130.07, 129.81, 129.49, 129.24, 127.54, 127.34, 126.86, 126.82, 125.79, 125.76, 125.18, 123.02; IR (neat, cm^{-1}): ν = 3052, 2926, 2854, 2127, 1614, 1504, 1421, 1322, 1265, 1222, 1162, 1124, 1107, 1066, 1016, 961. HRMS (ESI): m/z = 274.0838 calculated for $C_{16}H_{11}F_3N$ $[M+H]^+$, found 273.8538.



10

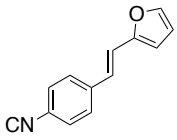
(E)-1-fluoro-4-(4-isocyanostyryl)benzene (10). Analogue **10** was synthesized from intermediate **5** and 4-fluorobenzaldehyde according to the general procedure (47% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 4H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.12 – 7.04 (m, 3H), 6.98 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.58, 163.71, 161.74, 138.43, 132.75, 129.88, 128.35, 128.29, 127.16, 126.78 (2C), 126.58, 115.92, 115.75; IR (neat, cm^{-1}): ν = 3408, 3032, 2925, 2854,

2121, 2043, 1595, 1509, 1233, 1159, 968, 838. HRMS (ESI): m/z = 224.0870 calculated for $C_{15}H_{11}FN$ $[M+H]^+$, found 224.0866.



11

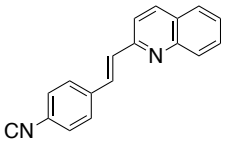
(E)-1,2-dichloro-4-(4-isocyanostyryl)benzene (11). Analogue **11** was synthesized from intermediate **5** and 1,2-dichlorobenzaldehyde according to the general procedure (80% yield).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.33 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.10 – 6.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.98, 137.78, 136.68, 133.03, 131.96, 130.73 (2C), 128.63, 128.52, 128.31, 127.44 (2C), 126.87 (2C), 125.86; IR (neat, cm^{-1}): ν = 3408, 3038, 2924, 2853, 2123, 1505, 1475, 1131, 961, 857, 823. HRMS (ESI): m/z = 274.0185 calculated for $C_{16}H_{10}Cl_2N$ $[M+H]^+$, found 274.0188.



12

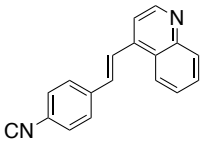
(E)-2-(4-isocyanostyryl)furan (12). Analogue **12** was synthesized from intermediate **5** and furan 2-carbaldehyde according to the general procedure (97% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 3H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.02 – 6.85 (m, 2H), 6.47 – 6.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.52, 152.58, 142.83, 138.32, 126.98 (2C), 126.75 (2C), 125.23, 125.05, 118.59, 111.89, 110.07; IR (neat, cm^{-1}): ν = 3337, 3146, 2970, 2931, 2883, 2125, 1635, 1507,

1476, 1378, 1305, 1146, 1128, 1108, 969, 952, 926, 828, 738. HRMS (ESI): m/z = 196.0757 calculated for $C_{13}H_{10}NO$ $[M+H]^+$, found 196.0759.



13

(E)-2-(4-isocyanostyryl)quinolone (13). Analogue **13** was synthesized from intermediate **5** and quinoline-2-carbaldehyde according to the general procedure (36% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.80 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.73 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.67 (d, *J* = 16.3 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 3H), 7.52 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.43 – 7.38 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.00, 155.10, 148.29, 137.80, 136.60, 132.27, 131.20, 129.98, 129.33, 128.00, 127.93, 127.57, 127.55, 126.87, 126.81, 126.58, 126.51, 119.49; IR (neat, cm^{-1}): ν = 3048, 3035, 2924, 2854, 2120, 1614, 1593, 1556, 1507, 1432, 1418, 1317, 1300, 1206, 1111, 969, 953. HRMS (ESI): m/z = 257.1073 calculated for $C_{18}H_{13}N_2$ $[M+H]^+$, found 257.1076.



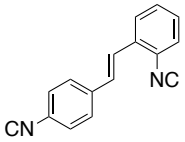
14

(E)-4-(4-isocyanostyryl)quinolone (14). Analogue **14** was synthesized from intermediate **5** and quinoline-4-carbaldehyde according to the general procedure (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, *J* = 4.6 Hz, 1H), 8.17 (dd, *J* = 14.9, 8.4 Hz, 2H), 7.84 (d, *J* = 16.1 Hz, 1H), 7.75 (t, *J* = 7.1 Hz, 1H), 7.65 – 7.55 (m, 4H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 16.1 Hz, 1H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 165.34, 150.24, 148.74, 142.13, 137.70, 133.12, 130.30, 129.53, 127.93 (3C), 126.97 (2C), 126.82, 126.26, 125.42, 123.28, 117.29; IR (neat, cm^{-1}): ν = 3059, 3031, 2922, 2853, 2121, 1630, 1600, 1578, 1572, 1563, 1507, 1463, 1423, 1389, 1301, 1253, 976, 964, 863. HRMS (ESI): m/z = 257.1073 calculated for $C_{18}H_{13}N_2$ $[M+H]^+$, found 257.1069.

General procedure for the synthesis of stilbene aryl bisisonitriles 17-18 from 16.

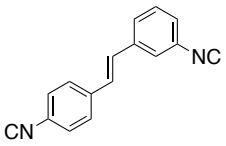
$CHCl_3$ (0.50 mL, 6.21 mmol, 15 equiv) was added to a stirring solution of requisite diamine (120 mg, 0.57 mmol, 1 equiv) in CH_2Cl_2 (0.8 mL). Triethylbenzylammonium chloride (11.40 mg, 0.012 mmol, 0.12 equiv) was added to the mixture followed by 50 % aqueous KOH (0.8 mL). The resulting mixture was stirred vigorously at room temperature. Solvent began to reflux, and the mixture allowed to stir until the reaction was confirmed complete via TLC. Water, saturated aqueous ammonium chloride and Et_2O were added. The organic layer was separated, and the aqueous layer extracted with large amounts of Et_2O (4x). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography to obtain the desired isonitrile.



17

(E)-1-isocyano-2-(4-isocyanostyryl)benzene (17). Analogue **17** was synthesized from intermediate **16** according to the general procedure (19% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.38 (m, 5H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.53, 165.14, 137.62, 132.95, 130.71,

129.57, 128.76 (2C), 127.81 (2C), 127.45 (2C), 126.90 (2C), 125.64, 124.59; IR (neat, cm^{-1}): ν = 3063, 3039, 2924, 2853, 2119, 1648, 1596, 1505, 1480, 1449, 1417, 1379, 1293, 1263, 1225, 1198, 1090, 963. HRMS (ESI): m/z = 231.0917 calculated for $C_{16}H_{11}N_2$ $[M+H]^+$, found 230.0839.



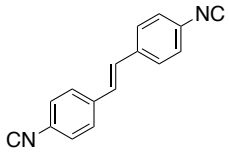
18

(E)-1-isocyano-3-(4-isocyanostyryl)benzene (18). Analogue **18** was synthesized from intermediate **16** according to the general procedure (24% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 4H), 7.42 – 7.37 (m, 3H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.12 – 7.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.05, 164.50, 138.25, 137.66, 129.88, 129.12, 128.78 (2C), 127.60 (2C), 127.53 (2C), 126.89 (2C), 125.76, 124.23; IR (neat, cm^{-1}): ν = 3033, 2925, 2122, 1599, 1580, 1505, 1443, 1228, 1167, 1107, 962, 863, 820, 787, 679. HRMS (ESI): m/z = 231.0917 calculated for $C_{16}H_{11}N_2$ $[M+H]^+$, found 231.0918.

General procedure for the synthesis of stilbene aryl bis-isonitriles 19 from 16.

A mixture of diamine (200 mg, 0.95 mmol, 1 equiv), formic acid (0.14 mL, 3.8 mmol, 4 equiv) and toluene (2 mL) was refluxed for eight hours. After allowing to cool to room temperature, the mixture was evaporated to complete dryness. Toluene (2 mL) was added and evaporated to dryness to give diformamide. Triethylamine (0.95 ml, 6.84 mmol, 7.2 equiv) and dichloromethane (4 mL) was added to a flask containing crude diformamide. The resulting mixture was cooled to 0 °C and $POCl_3$ (0.26 mL, 2.28 mmol, 2.4 equiv) was added dropwise over 30 minutes. The mixture was stirred for one hour at 0 °C and for an additional two hours at room temperature. The resultant

mixture was cooled to 0 °C and a solution of 0.5 g Na_2CO_3 in 2 mL of water was added dropwise for over 20 minutes. The mixture was then stirred for one hour. The organic layer was separated, and the aqueous layer extracted with dichloromethane (3×), The combined organics were washed with brine, dried over sodium sulfate, concentrated in vacuo and recrystallized to yield **19**.



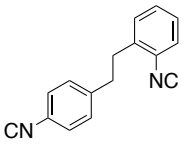
19

(E)-1,2-bis(4-isocyanophenyl)ethane (19). Analogue **19** was synthesized from intermediate **16** according to the general procedure (70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, J = 8.6, 2.0 Hz, 4H), 7.42 – 7.35 (m, 2H), 7.09 (s, 2H); ^{13}C NMR (125 MHz, C) δ 165.04 (2C), 137.76 (2C), 129.13 (4C), 127.51 (4C), 127.51 (2 C). 126.8 (2C); IR (neat, cm^{-1}): ν = 3036, 2604, 2499, 2157, 2124, 2022, 2013, 1997, 1971, 1696, 1603, 1507, 1422, 1305, 962, 942, 862, 834. HRMS (ESI): m/z = 231.0917 calculated for $C_{16}H_{11}N_2$ $[M+H]^+$, found 231.0920.

General procedure for the synthesis of saturated isonitriles 21-28 from intermediate 20 (scheme 3).

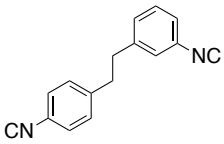
$CHCl_3$ (0.12 mL, 1.51 mmol) was added to a stirring solution of 4-(2-(pyridin-2-yl)ethyl)aniline (120 mg, 0.61 mmol) in CH_2Cl_2 (1.2 mL). Triethylbenzylammonium chloride (2.73 mg, 0.012 mmol) was added to the mixture followed by 50 % aqueous KOH (1.2 mL). The resulting mixture was stirred vigorously at room temperature. Solvent began to reflux, and the mixture allowed to stir until the reaction was confirmed complete via TLC. Water, saturated aqueous ammonium chloride and Et_2O were added. The organic layer was separated, and the aqueous layer extracted

with large amounts of Et_2O (4×). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography to obtain the desired isonitrile.



21

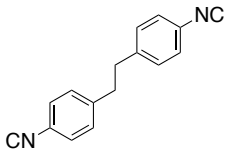
1-isocyano-2-(4-isocyanophenethyl)benzene (21). Analogue **21** was synthesized from corresponding dinitro intermediate **20** (10 yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.36 (m, 1H), 7.33 – 7.28 (m, 3H), 7.17 (dd, *J* = 17.6, 7.8 Hz, 4H), 3.04 (dd, *J* = 9.6, 6.4 Hz, 2H), 2.96 (dd, *J* = 9.0, 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.31, 163.56, 142.40 (2C), 137.36, 129.95, 129.58 (2C), 129.51 (2C), 127.43, 127.02, 126.49 (2C), 35.65, 34.24; IR (neat, cm^{-1}): ν = 2956, 2921, 2851, 2121, 1739, 1659, 1633, 1520, 1487, 1463, 1347, 1250, 1092, 1053, 1026, 967. HRMS (ESI): m/z = 233.1073 calculated for $C_{16}H_{13}N_2$ $[M+H]^+$, found 233.1074.



22

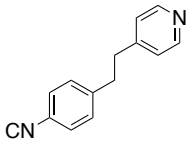
1-isocyano-3-(4-isocyanophenethyl)benzene (22). Analogue **22** was synthesized from corresponding dinitro intermediate **20** (15% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dt, *J* = 7.8, 3.6 Hz, 3H), 7.24 – 7.20 (m, 1H), 7.15 – 7.11 (m, 4H), 2.94 – 2.91 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.91, 163.79, 142.61, 142.41, 129.60, 129.47 (2C), 129.45 (2C), 126.72, 126.47, 126.30, 124.81, 124.30, 37.00, 36.87; IR (neat, cm^{-1}): ν = 2954, 2923, 2852, 2177, 2162, 2144,

2124, 2041, 2025, 1601, 1554, 1520, 1505, 1485, 1464, 1379, 1346, 1247, 1102, 1053, 1042. HRMS (ESI): m/z = 233.1073 calculated for $C_{16}H_{13}N_2$ $[M+H]^+$, found 233.1077.



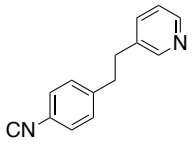
23

1,2-bis(4-isocyanophenyl)ethane (23). Analogue **23** was synthesized from corresponding dinitro intermediate **20** (18% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.3 Hz, 4H), 7.11 (d, *J* = 8.2 Hz, 4H), 2.93 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.78 (2C), 142.46 (2C), 129.46 (4C), 126.45 (4C), 124.77 (2C), 37.07 (2C); IR (neat, cm^{-1}): ν = 3062, 3047, 2948, 2925, 2854, 2160, 2130, 2038, 1990, 1733, 1534, 1505, 1457, 1295, 1294, 1167, 1092, 1022. HRMS (ESI): m/z = 233.1073 calculated for $C_{16}H_{13}N_2$ $[M+H]^+$, found 233.1077.



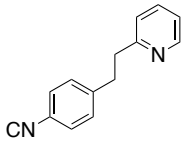
24

4-(4-isocyanophenethyl)pyridine (24). Analogue **24** was synthesized from corresponding intermediate **20** (45% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 – 8.47 (m, 2H), 7.28 (d, *J* = 1.9 Hz, 2H), 7.15 – 7.13 (m, 2H), 7.05 – 7.03 (m, 2H), 2.95 – 2.90 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.81, 149.86 (2C), 149.59 (2C), 142.31, 129.44 (2C), 126.47 (2C), 123.86 (2C), 36.59, 36.18; IR (neat, cm^{-1}): ν = 3060, 2951, 2936, 2899, 2854, 2128, 1690, 1607, 1558, 1507, 1431, 1414, 992, 868. HRMS (ESI): m/z = 209.1073 calculated for $C_{14}H_{13}N_2$ $[M+H]^+$, found 209.1075.



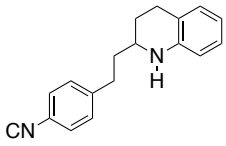
25

3-(4-isocyanophenethyl)pyridine (25). Analogue **25** was synthesized from corresponding intermediate **20** (36% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.39 (d, *J* = 2.3 Hz, 1H), 7.39 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.19 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.15 – 7.13 (m, 2H), 2.97 – 2.88 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.73, 149.96, 147.82, 142.45, 135.95, 135.90 (2C), 129.50 (2C), 126.46, 123.32 (2C), 37.07, 34.50; IR (neat, cm^{-1}): ν = 3030, 2995, 2926, 2859, 2123, 1592, 1575, 1506, 1478, 1443, 1423, 1192, 1099, 1027. HRMS (ESI): m/z = 209.1073 calculated for $C_{14}H_{13}N_2$ $[M+H]^+$, found 209.1075.



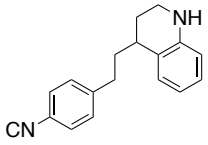
26

2-(4-isocyanophenethyl)pyridine (26). Analogue **26** was synthesized from corresponding intermediate **20** (43% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.56 (td, *J* = 7.6, 1.9 Hz, 1H), 7.27 (d, *J* = 4.5 Hz, 2H), 7.20 – 7.16 (m, 2H), 7.12 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 7.03 (dd, *J* = 7.8, 1.0 Hz, 1H), 3.07 – 3.09 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.41, 160.36, 149.47, 143.33, 136.40, 129.46, 126.34 (2C), 124.54 (2C), 123.03, 121.41, 39.67, 35.49; IR (neat, cm^{-1}): ν = 3062, 3009, 2925, 2855, 2124, 1591, 1569, 1506, 1474, 1435, 1197, 1147, 1089, 1051, 1020, 993, 869. HRMS (ESI): m/z = 209.1073 calculated for $C_{14}H_{13}N_2$ $[M+H]^+$, found 209.1072.



27

2-(4-isocyanophenethyl)-1,2,3,4-tetrahydroquinoline (27). Analogue **27** was synthesized from corresponding intermediate **20** (8% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.97 (t, *J* = 8.2 Hz, 2H), 6.63 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 1H), 3.75 (s, 1H), 3.34 – 3.28 (m, 1H), 2.78 (ddd, *J* = 21.3, 10.9, 6.7 Hz, 4H), 2.03 – 1.96 (m, 1H), 1.82 (ddd, *J* = 13.7, 7.9, 6.0 Hz, 2H), 1.73 – 1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.55, 144.30, 143.69, 129.31 (2C), 126.84 (2C), 126.48 (2C), 121.23, 117.29, 114.21 (2C), 50.98, 37.97, 31.81, 27.82, 26.10; IR (neat, cm^{-1}): ν = 3386, 3016, 2923, 2853, 2122, 1622, 1605, 1597, 1579, 1494, 1455, 1417, 1355, 1310, 1276, 1254, 1202, 1155, 1117, 1019, 965. HRMS (ESI): m/z = 263.1546 calculated for $C_{18}H_{19}N_2$ $[M+H]^+$, found 263.1543.

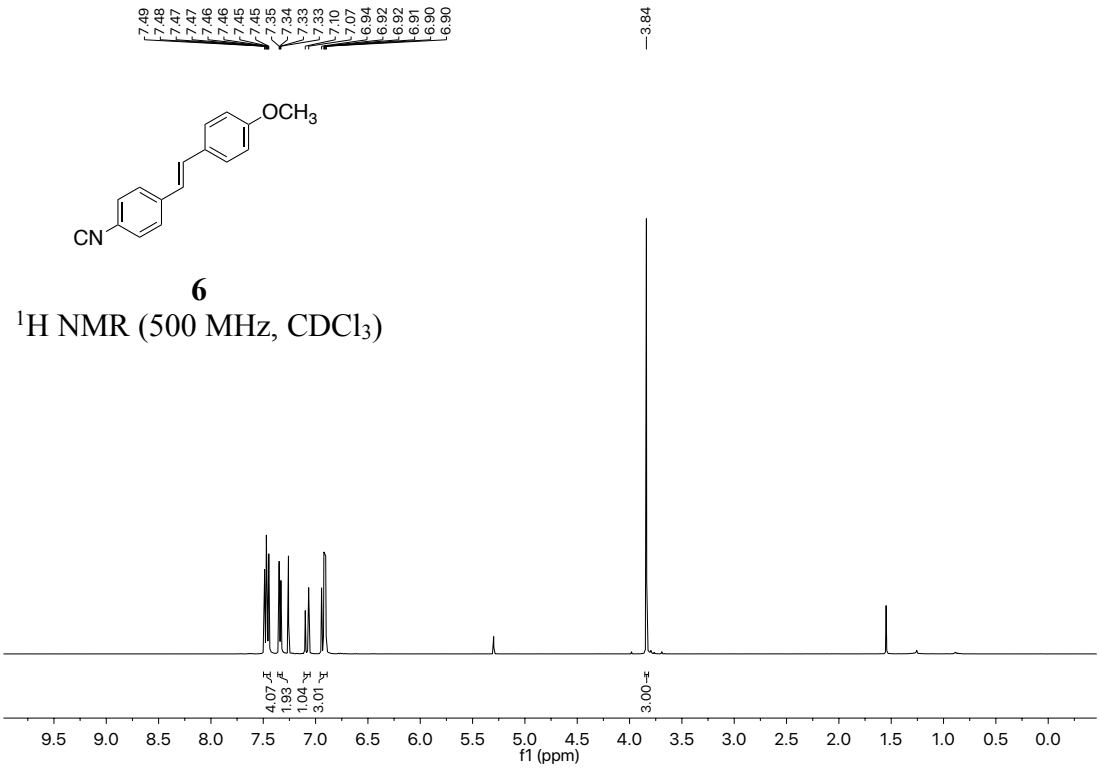


28

4-(4-isocyanophenethyl)-1,2,3,4-tetrahydroquinoline (28). Analogue **28** was synthesized from corresponding intermediate **20** (5.3% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 2H), 6.61 (t, *J* = 7.0 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 3.88 (s, 1H), 3.38 – 3.27 (m, 2H), 2.83 – 2.66 (m, 3H), 2.03-1.94 (m, 2H), 1.89 – 1.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.35, 144.31, 144.22, 129.33 (2C), 129.01, 127.09, 126.37 (2C), 124.45, 124.37, 116.71, 114.25, 38.36, 37.89, 35.17, 33.04, 26.22; IR (neat, cm^{-1}): ν = 3405, 3049, 3018, 2923, 2854, 2122, 1605, 1582, 1501, 1473, 1443, 1359, 1313, 1270, 1193, 1155, 1121,

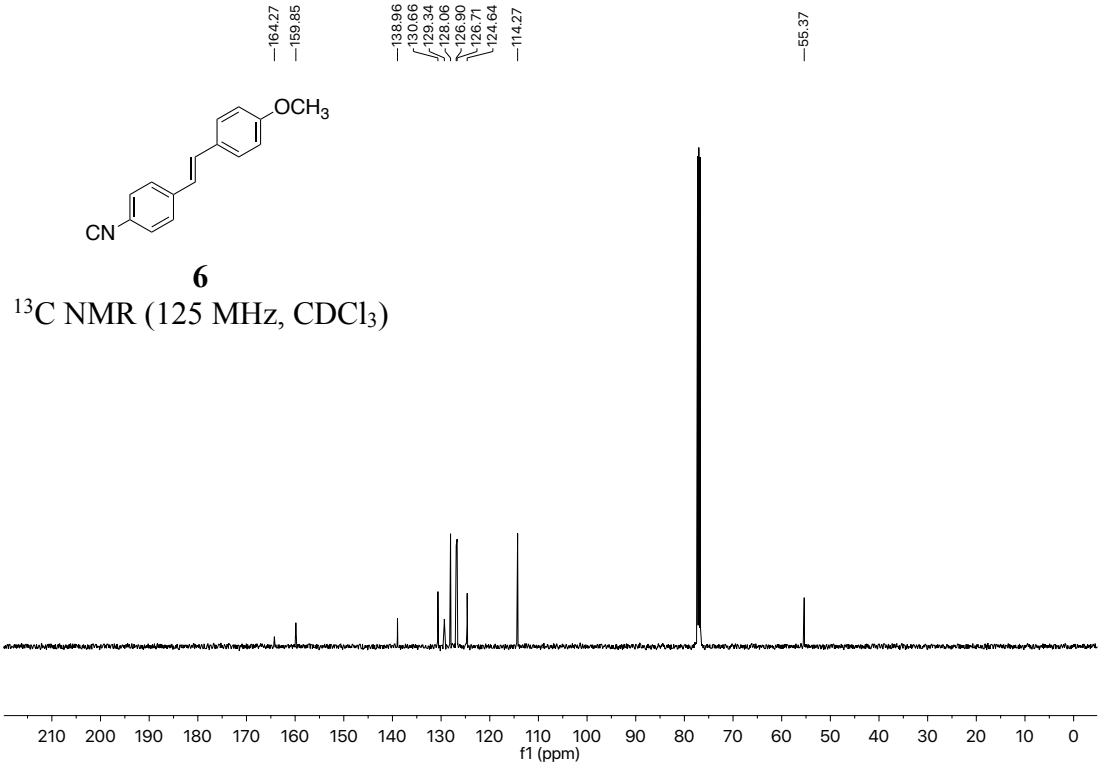
1107, 1048, 1019. HRMS (ESI): m/z = 263.1543 calculated for $C_{18}H_{19}N_2$ $[M+H]^+$, found 263.1540.

Part III. ^{1}H and ^{13}C NMR Spectra



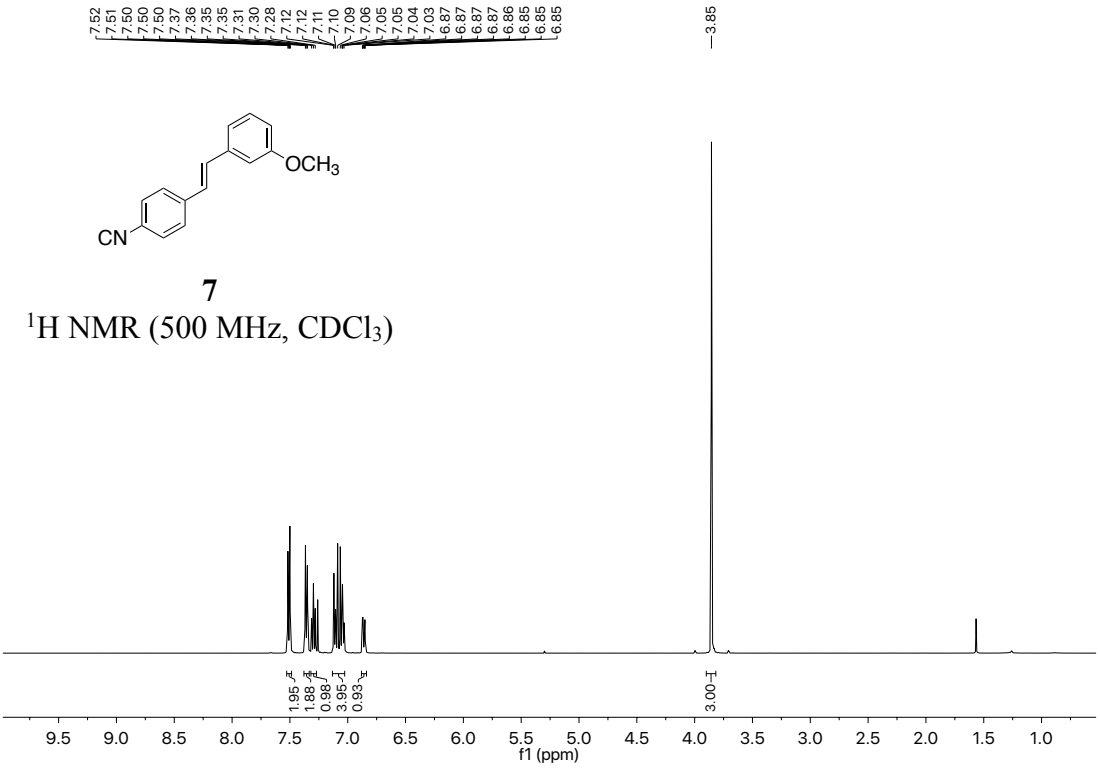
6

^{1}H NMR (500 MHz, $CDCl_3$)



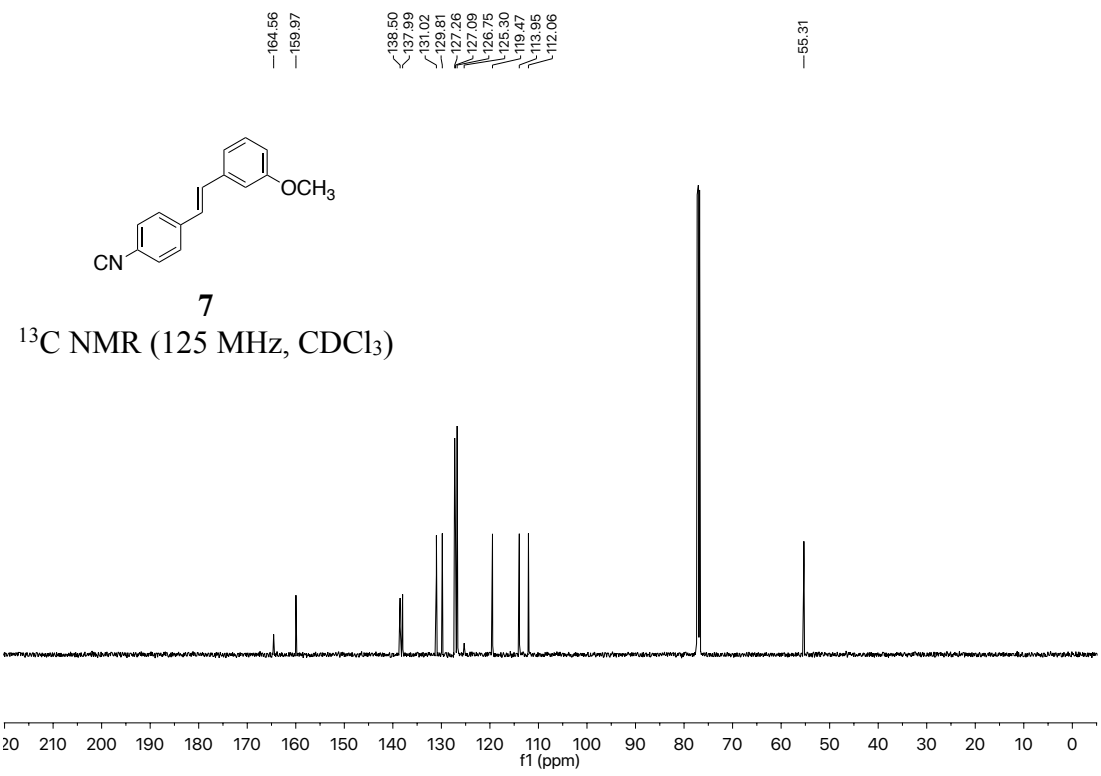
6

^{13}C NMR (125 MHz, $CDCl_3$)



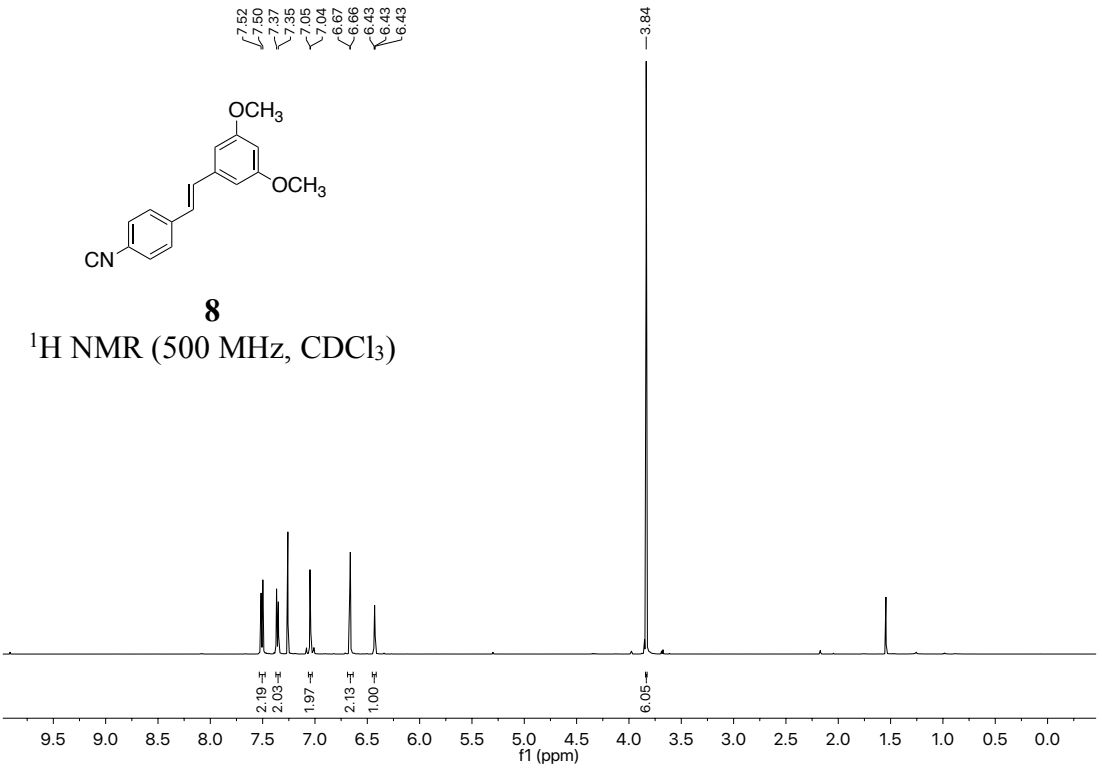
7

^{1}H NMR (500 MHz, $CDCl_3$)



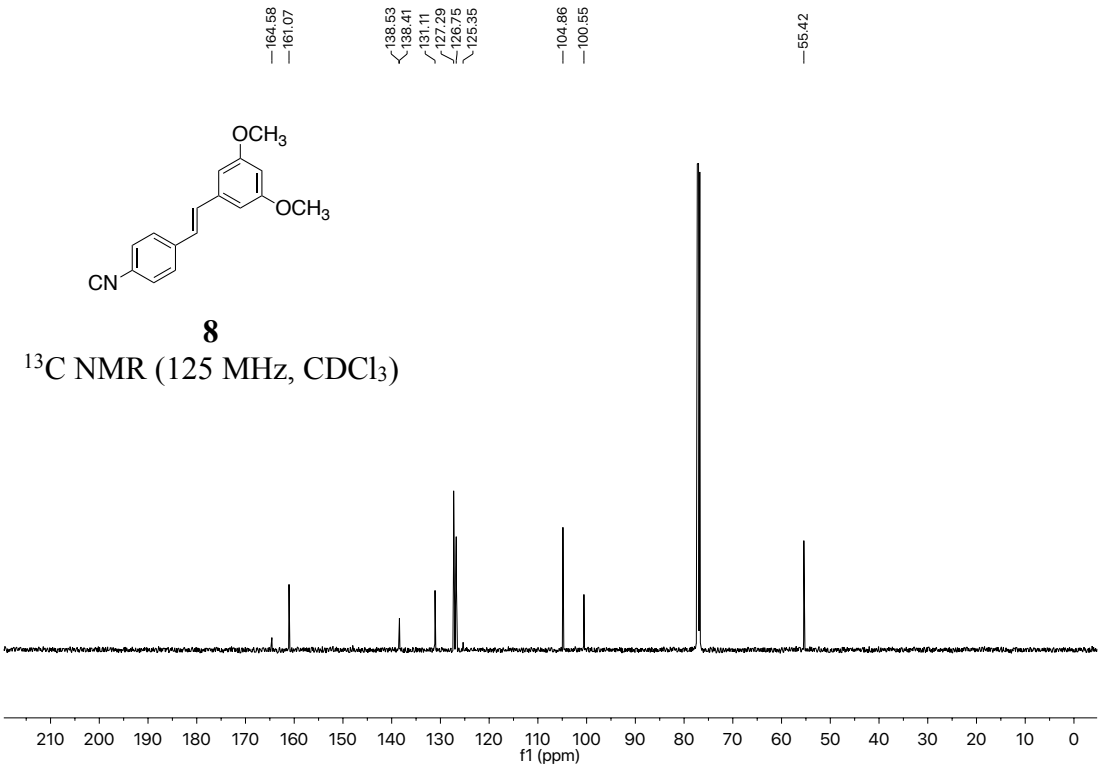
7

^{13}C NMR (125 MHz, $CDCl_3$)



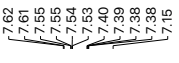
8

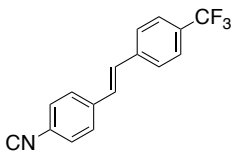
^{1}H NMR (500 MHz, $CDCl_3$)



8

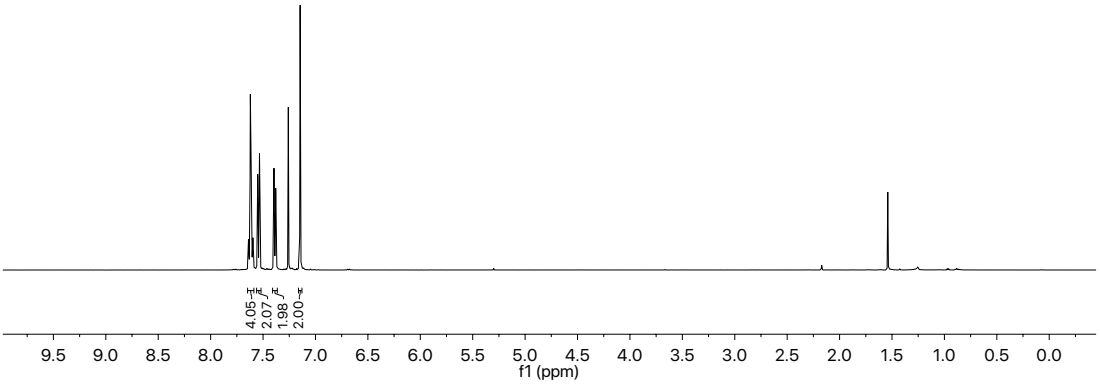
^{13}C NMR (125 MHz, $CDCl_3$)

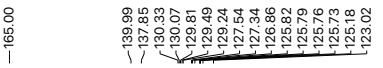


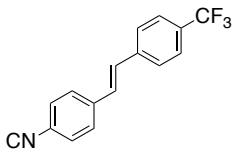


9

^{1}H NMR (500 MHz, $CDCl_3$)

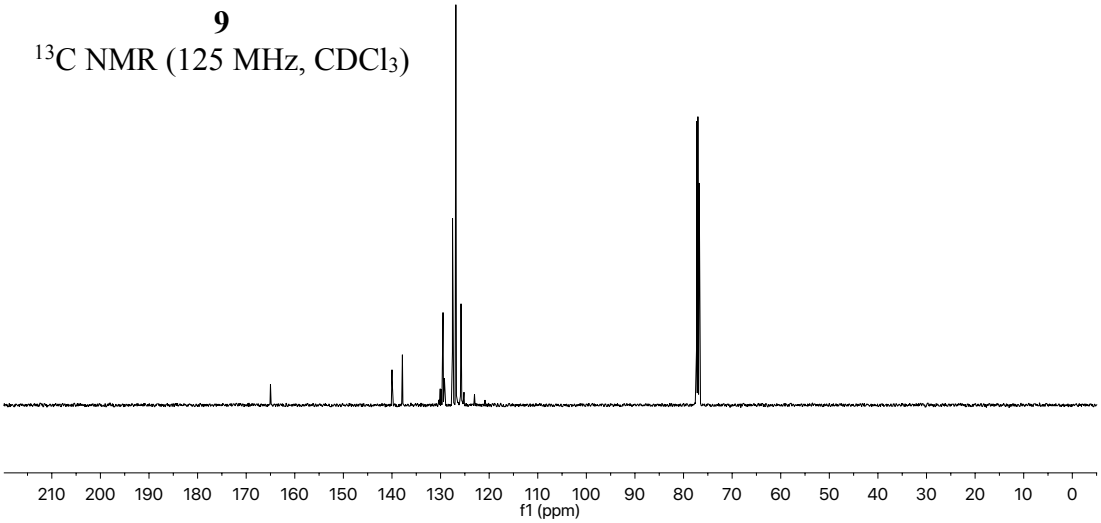


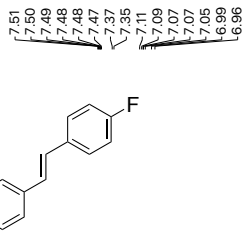




9

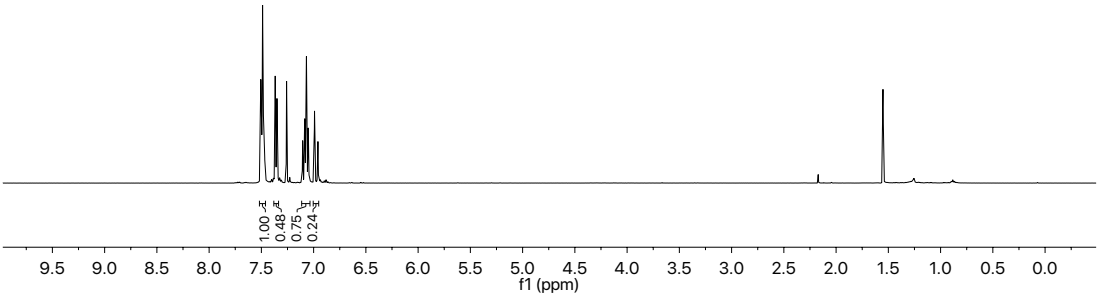
^{13}C NMR (125 MHz, $CDCl_3$)

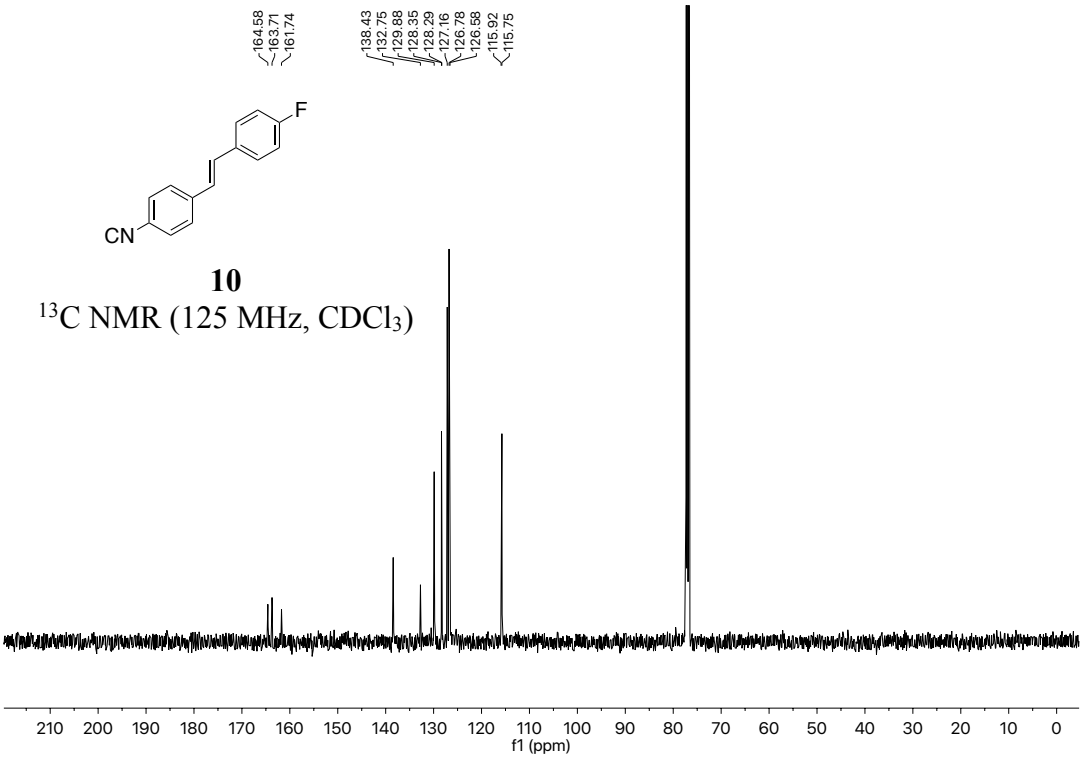




10

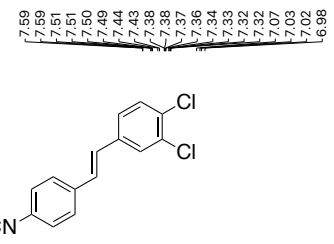
^{1}H NMR (500 MHz, $CDCl_3$)





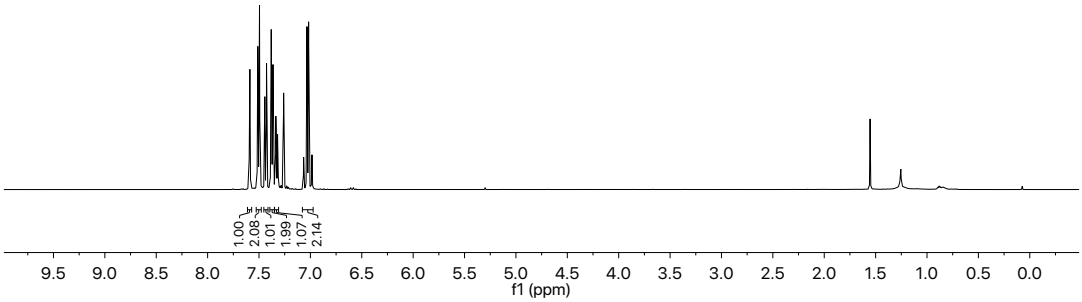
10

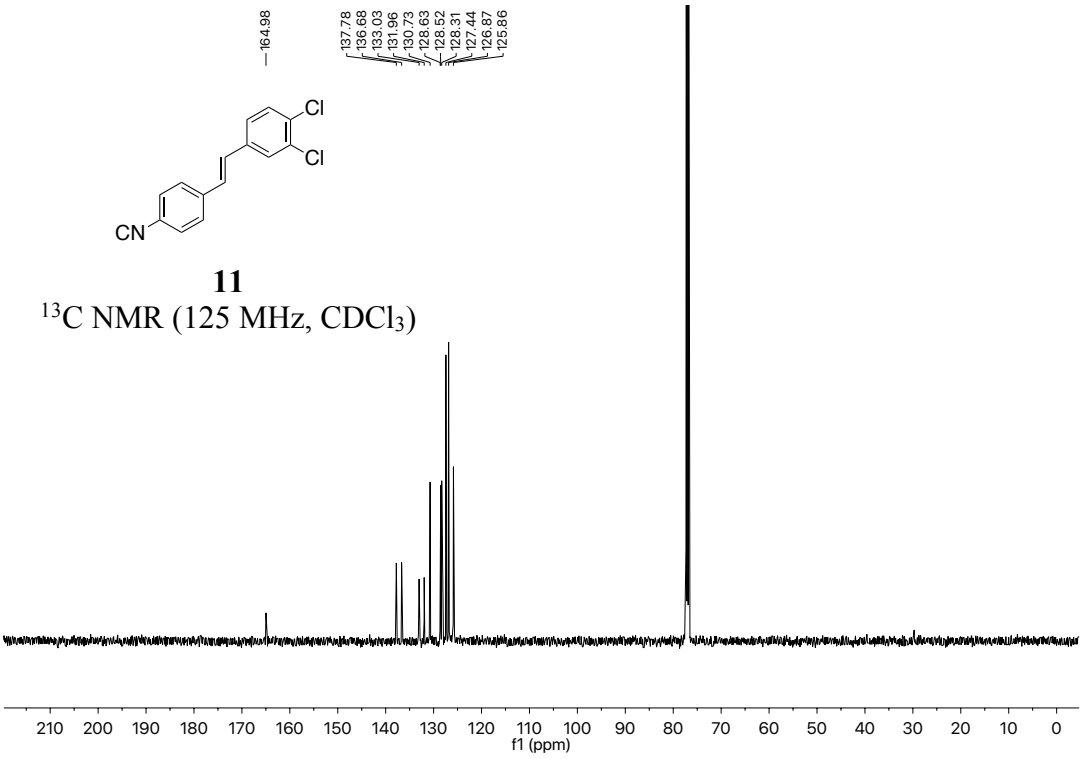
^{13}C NMR (125 MHz, $CDCl_3$)



11

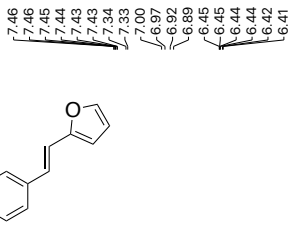
^{1}H NMR (500 MHz, $CDCl_3$)





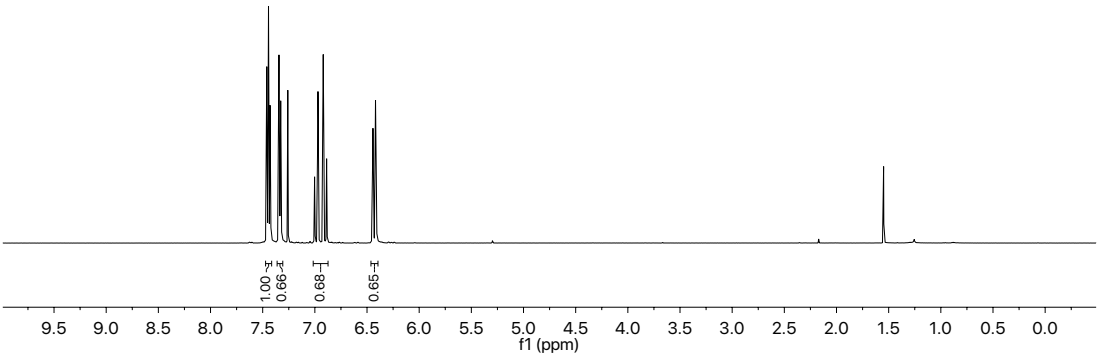
11

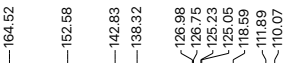
^{13}C NMR (125 MHz, $CDCl_3$)

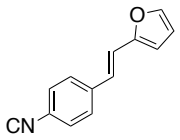


12

^{1}H NMR (500 MHz, $CDCl_3$)

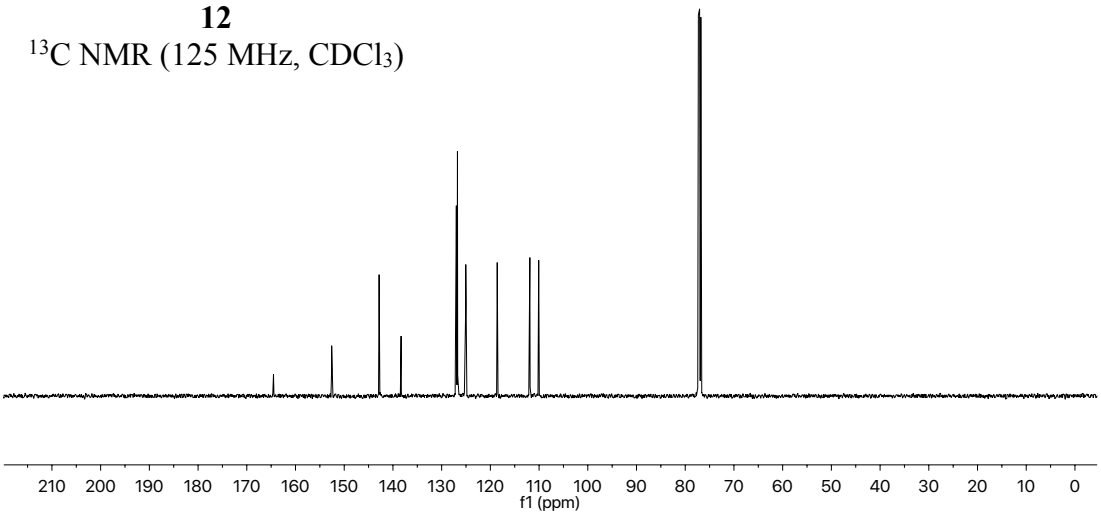


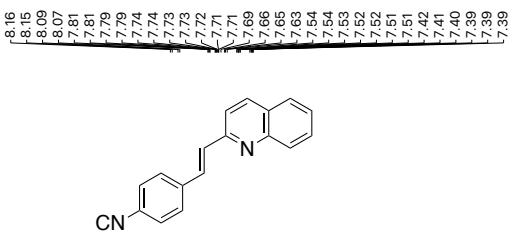




12

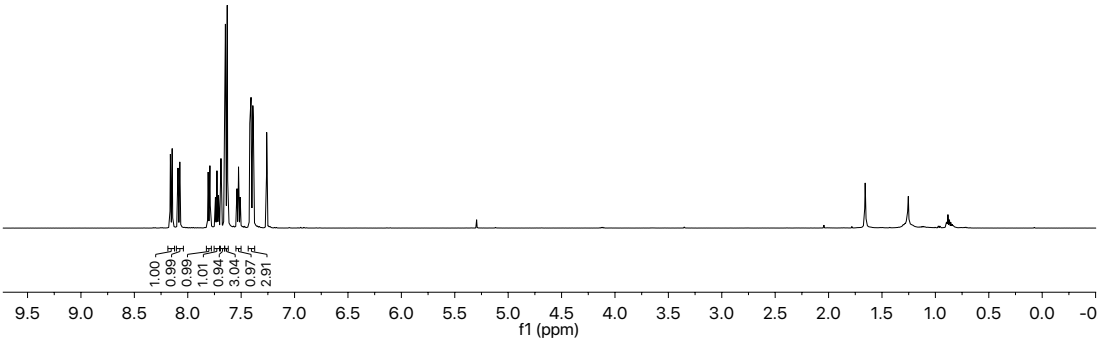
^{13}C NMR (125 MHz, $CDCl_3$)

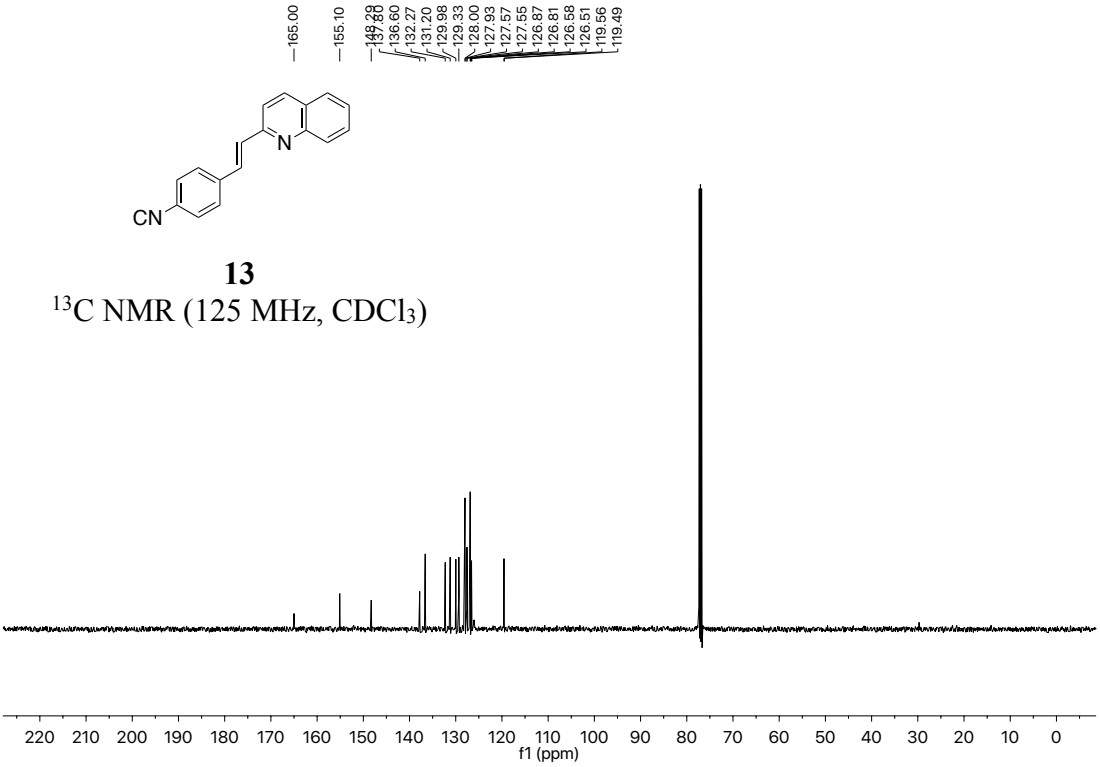




13

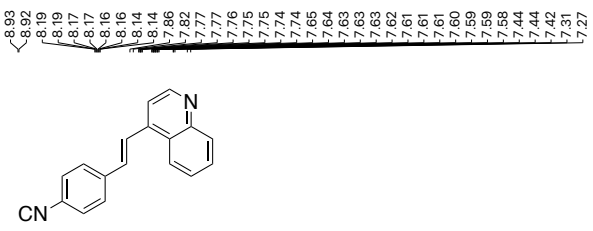
^{1}H NMR (500 MHz, $CDCl_3$)





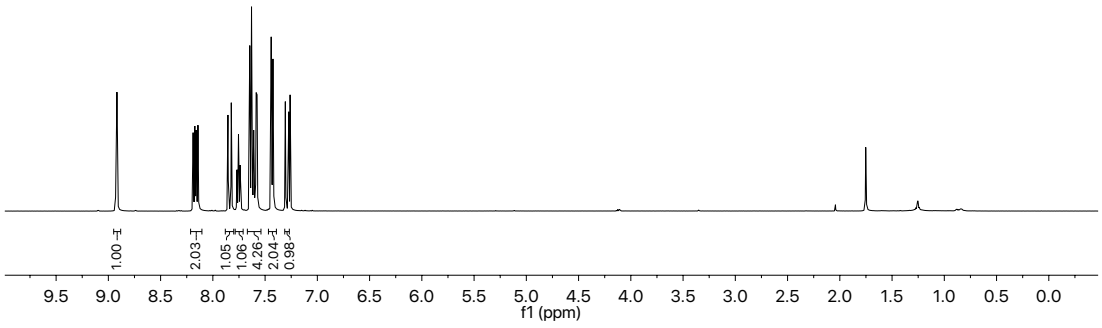
13

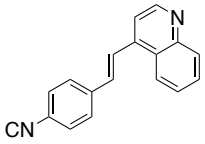
^{13}C NMR (125 MHz, $CDCl_3$)



14

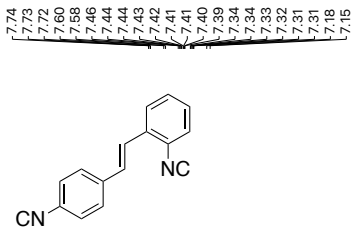
^{1}H NMR (500 MHz, $CDCl_3$)





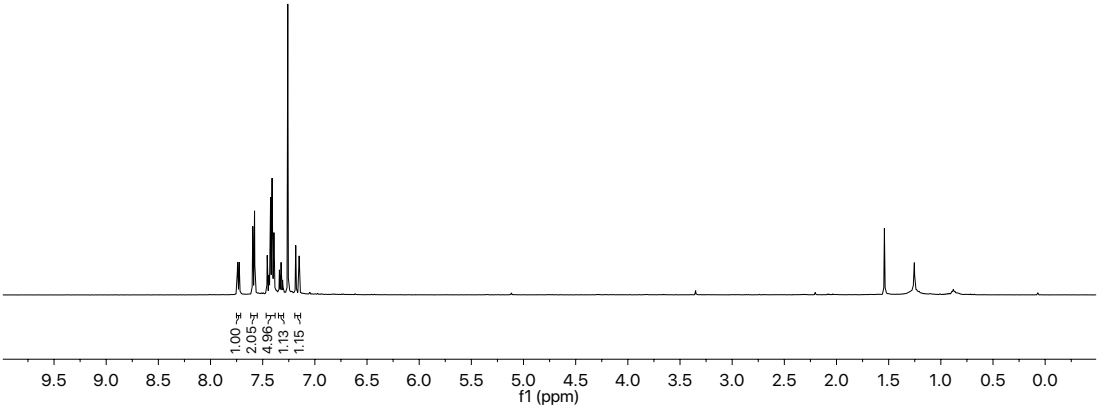
14

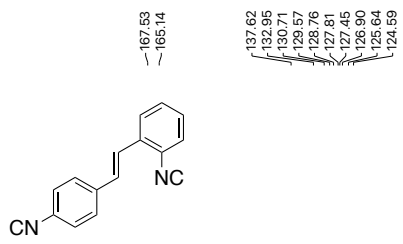
^{13}C NMR (125 MHz, $CDCl_3$)



17

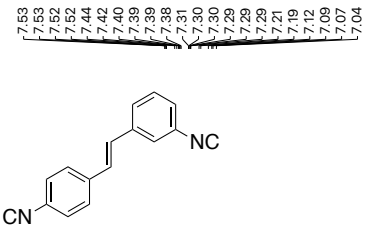
^{1}H NMR (500 MHz, $CDCl_3$)





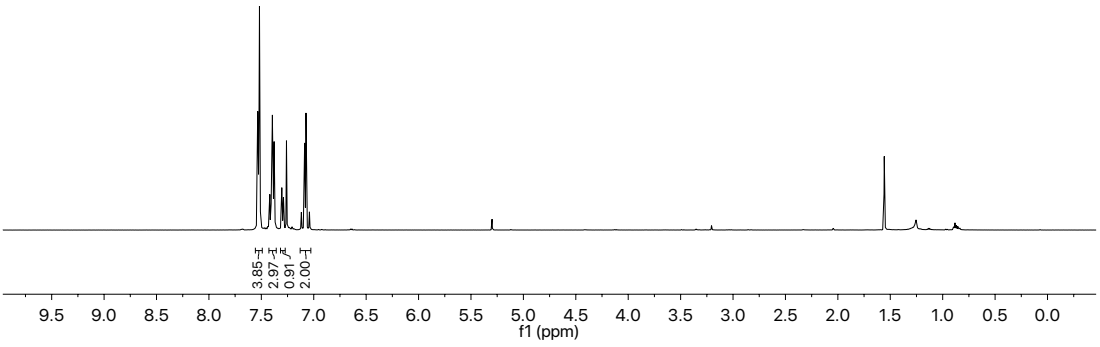
17

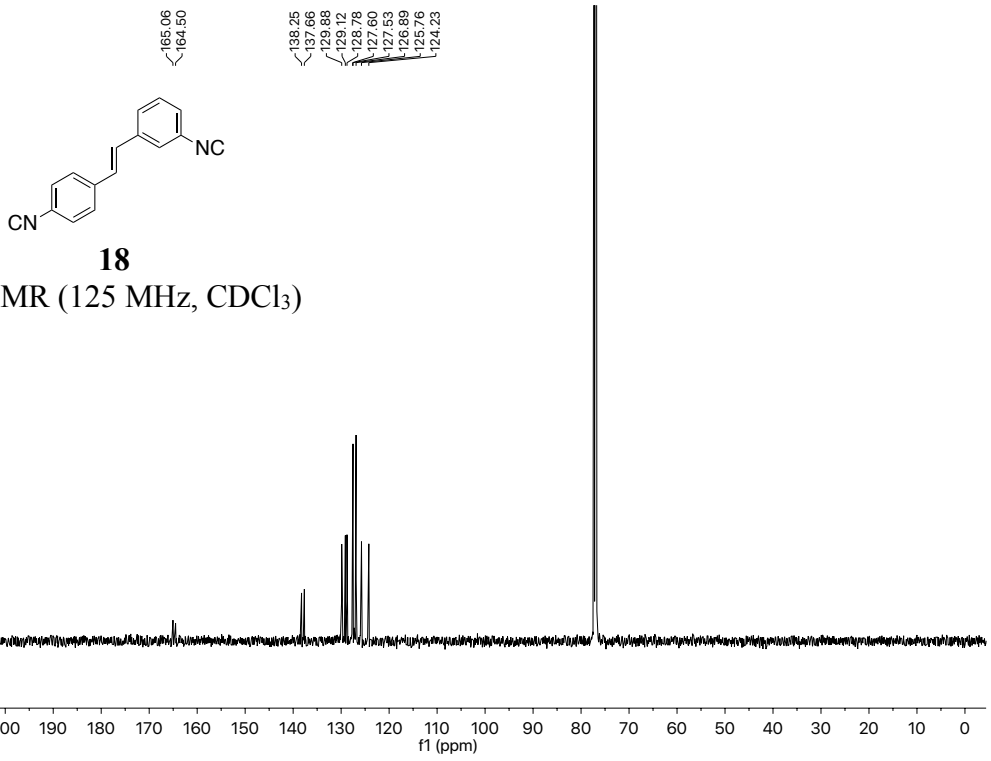
^{13}C NMR (125 MHz, $CDCl_3$)



18

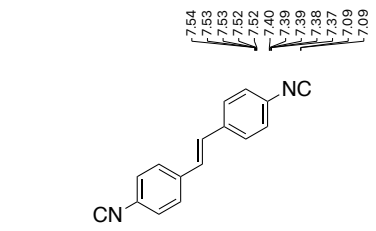
^{1}H NMR (500 MHz, $CDCl_3$)





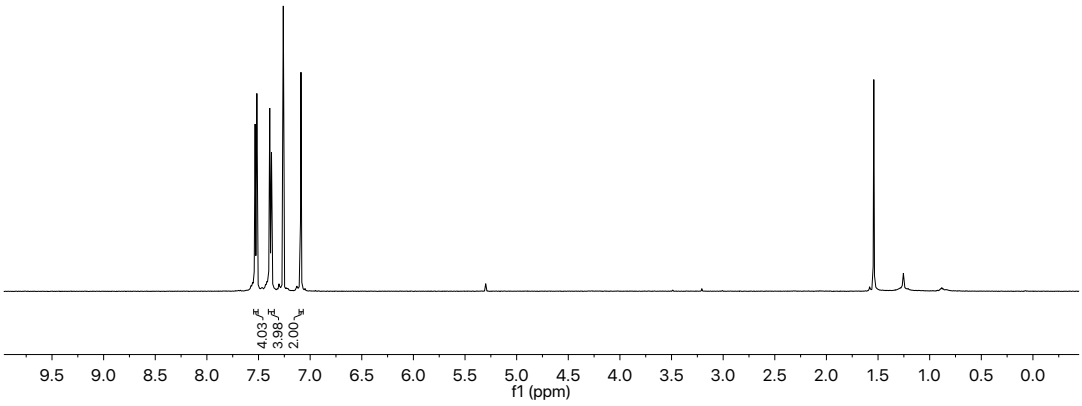
18

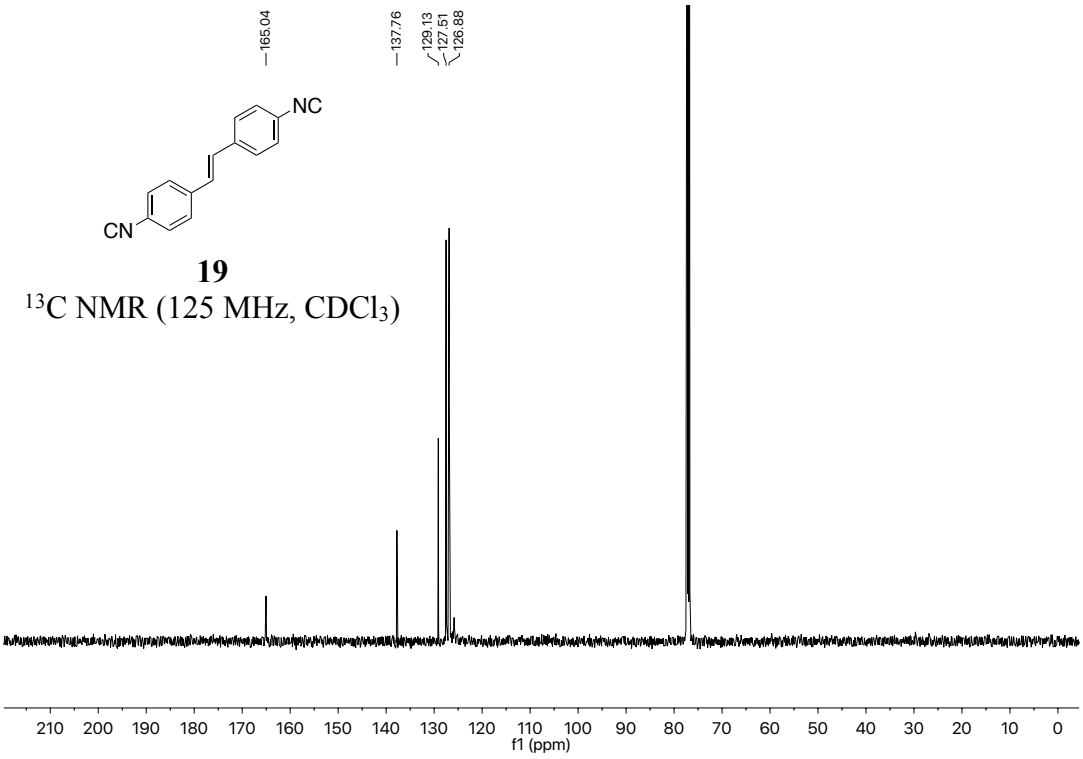
^{13}C NMR (125 MHz, $CDCl_3$)



19

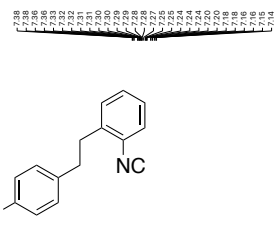
^{1}H NMR (500 MHz, $CDCl_3$)





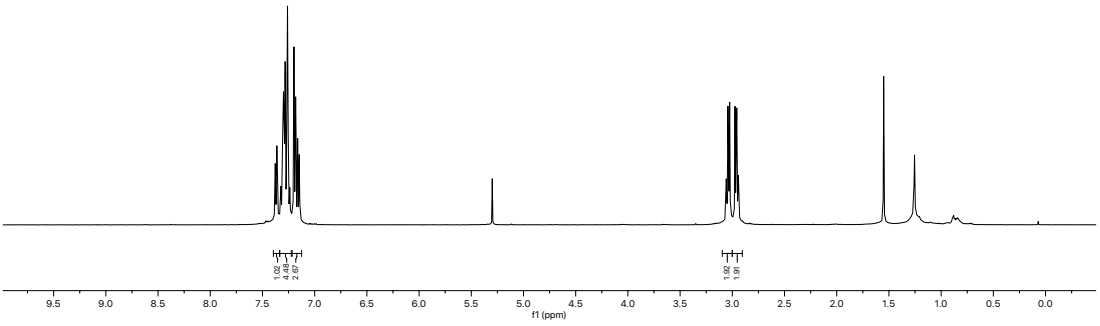
19

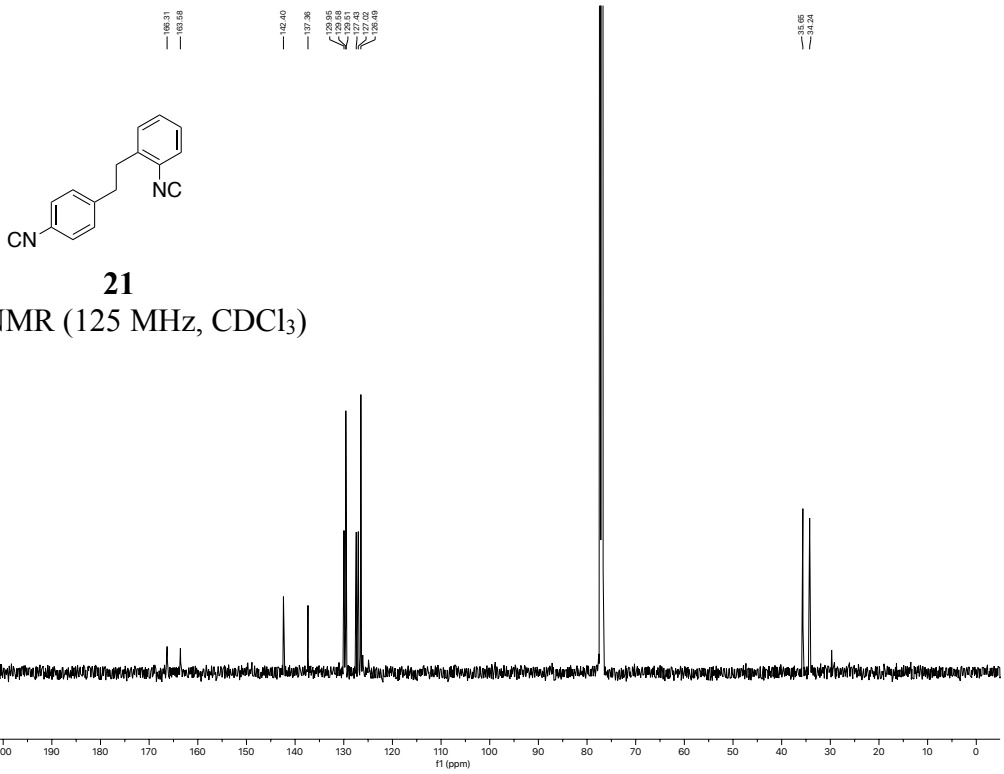
^{13}C NMR (125 MHz, $CDCl_3$)



21

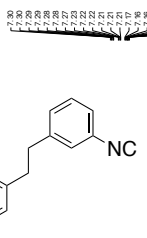
^{1}H NMR (500 MHz, $CDCl_3$)





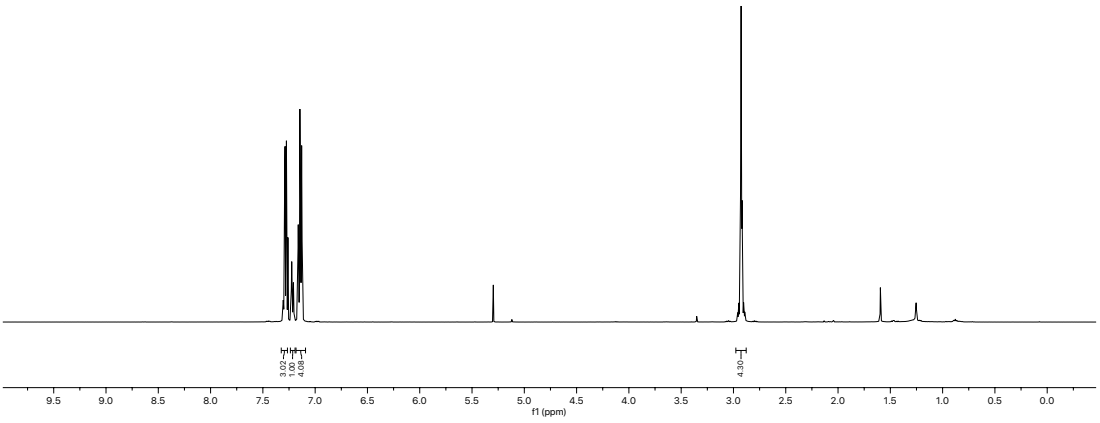
21

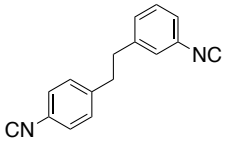
^{13}C NMR (125 MHz, $CDCl_3$)



22

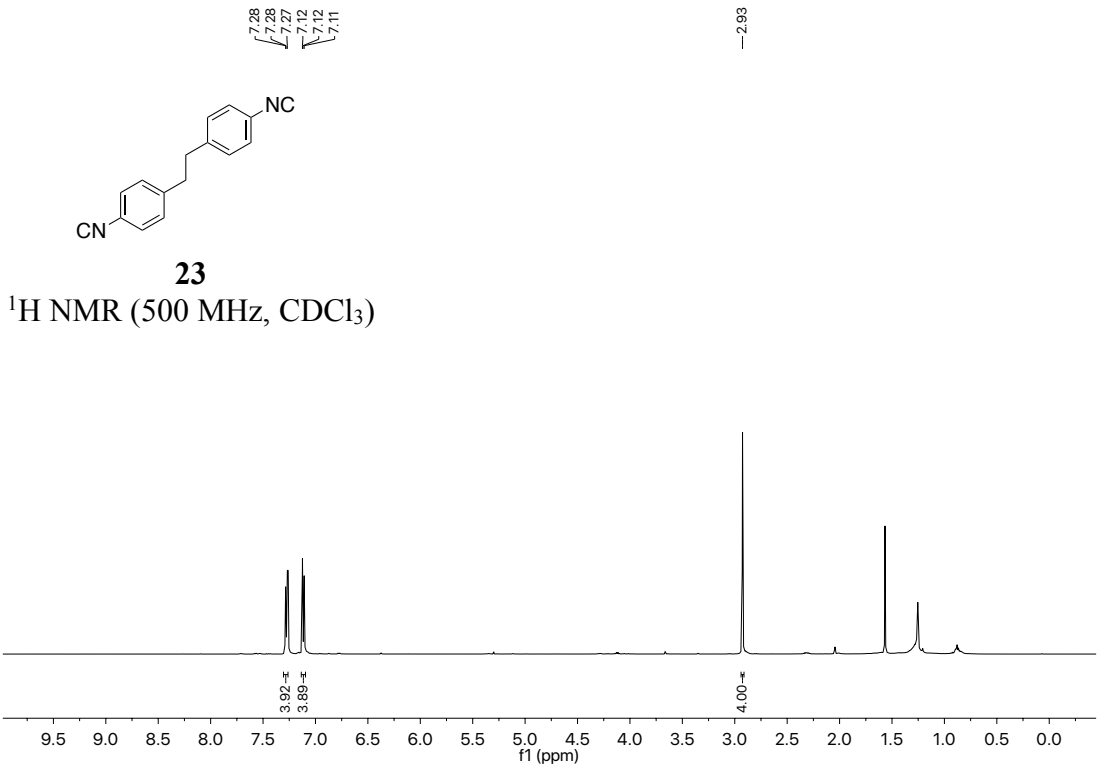
^{1}H NMR (500 MHz, $CDCl_3$)





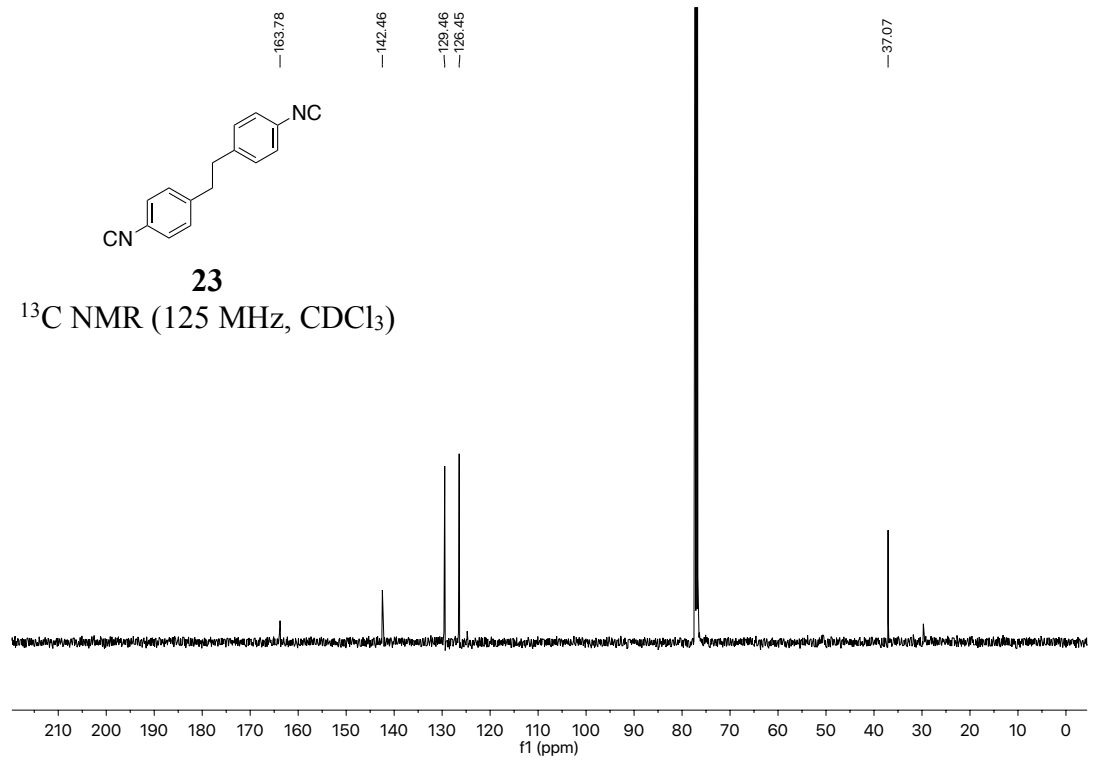
22

^{13}C NMR (125 MHz, $CDCl_3$)



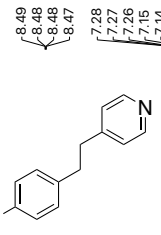
23

^{1}H NMR (500 MHz, $CDCl_3$)



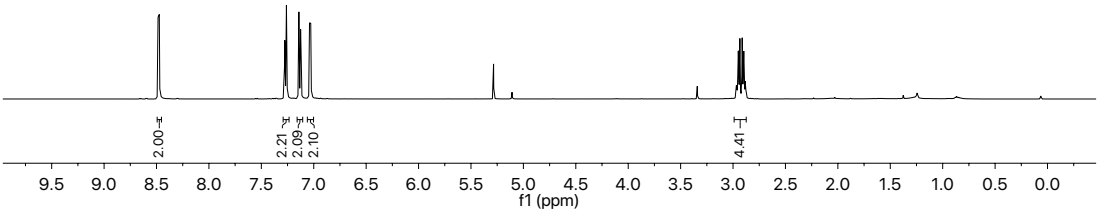
23

^{13}C NMR (125 MHz, $CDCl_3$)



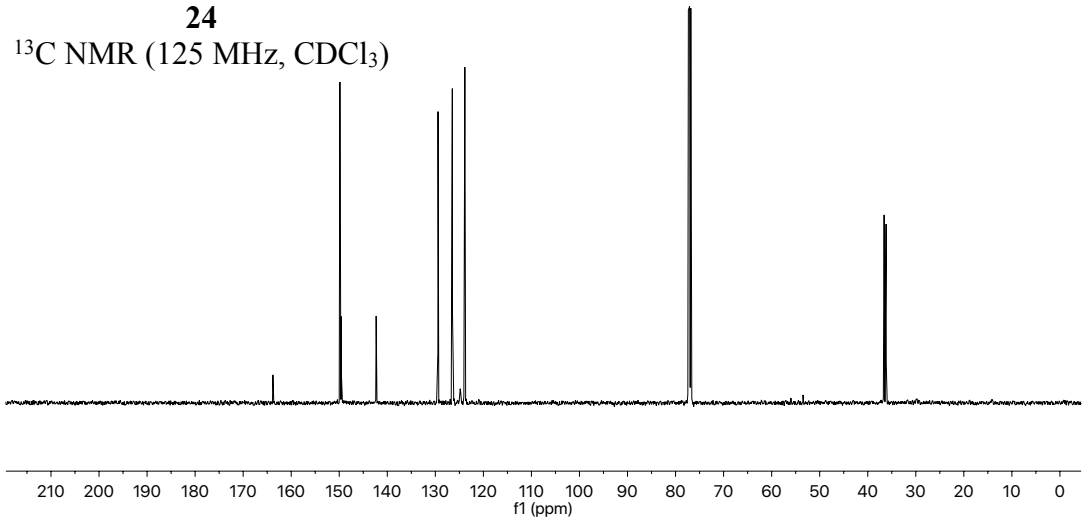
24

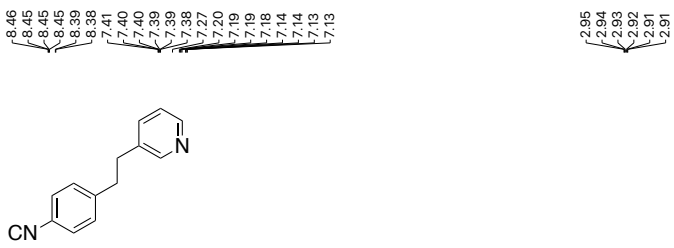
^{1}H NMR (500 MHz, $CDCl_3$)



24

^{13}C NMR (125 MHz, $CDCl_3$)





25

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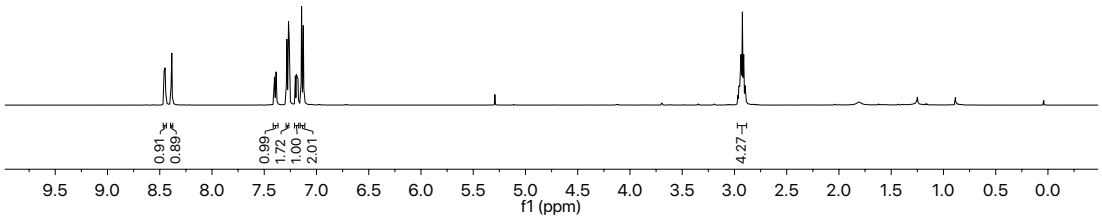
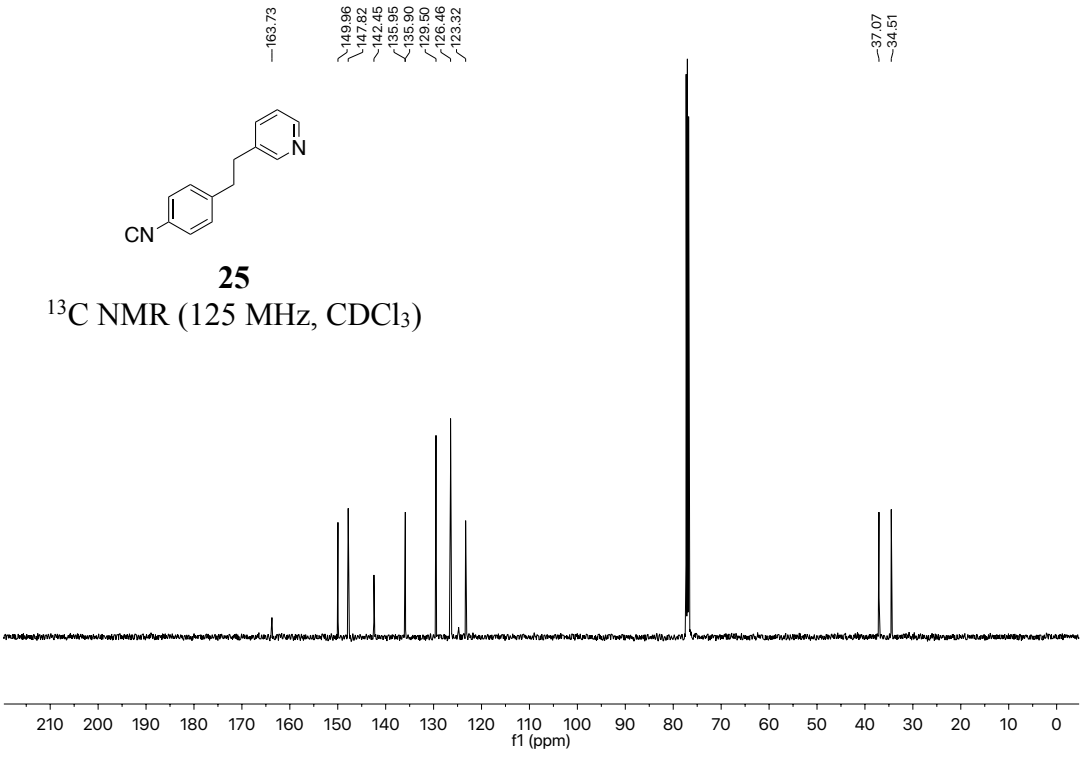
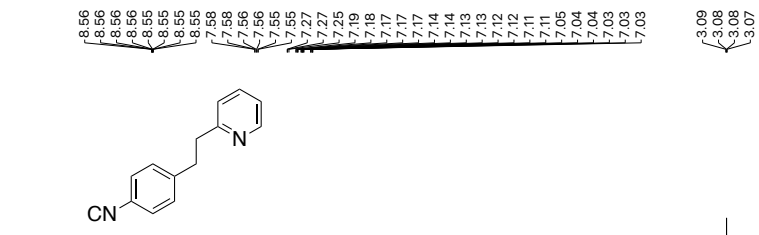




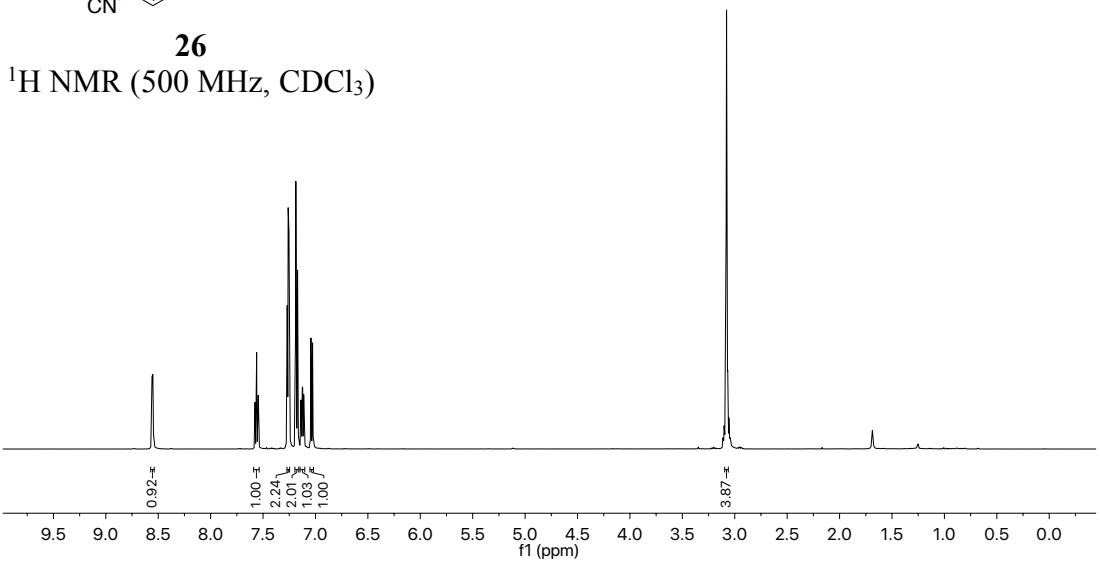
25

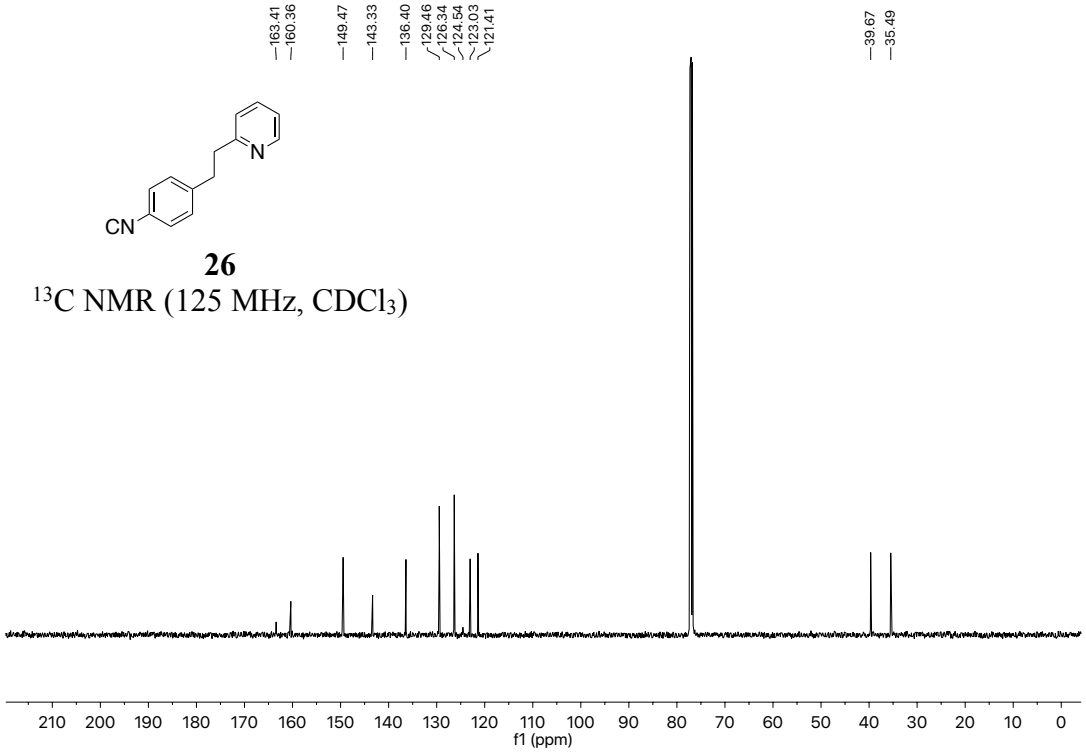
^{13}C NMR (125 MHz, $CDCl_3$)



26

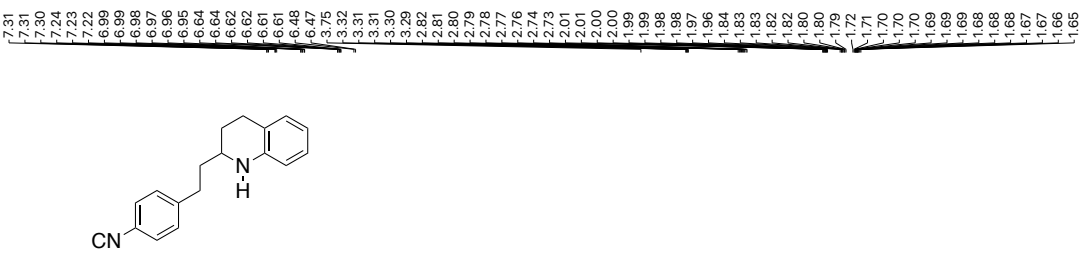
^{1}H NMR (500 MHz, $CDCl_3$)





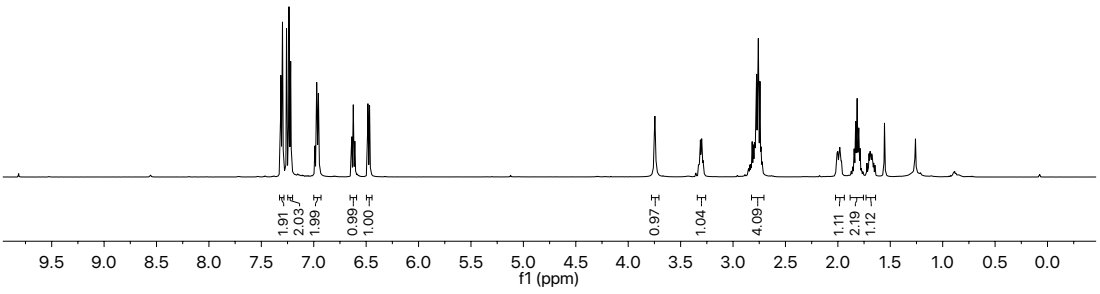
26

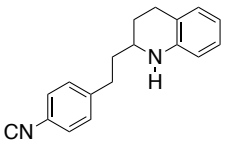
^{13}C NMR (125 MHz, $CDCl_3$)



27

^{1}H NMR (500 MHz, $CDCl_3$)





27

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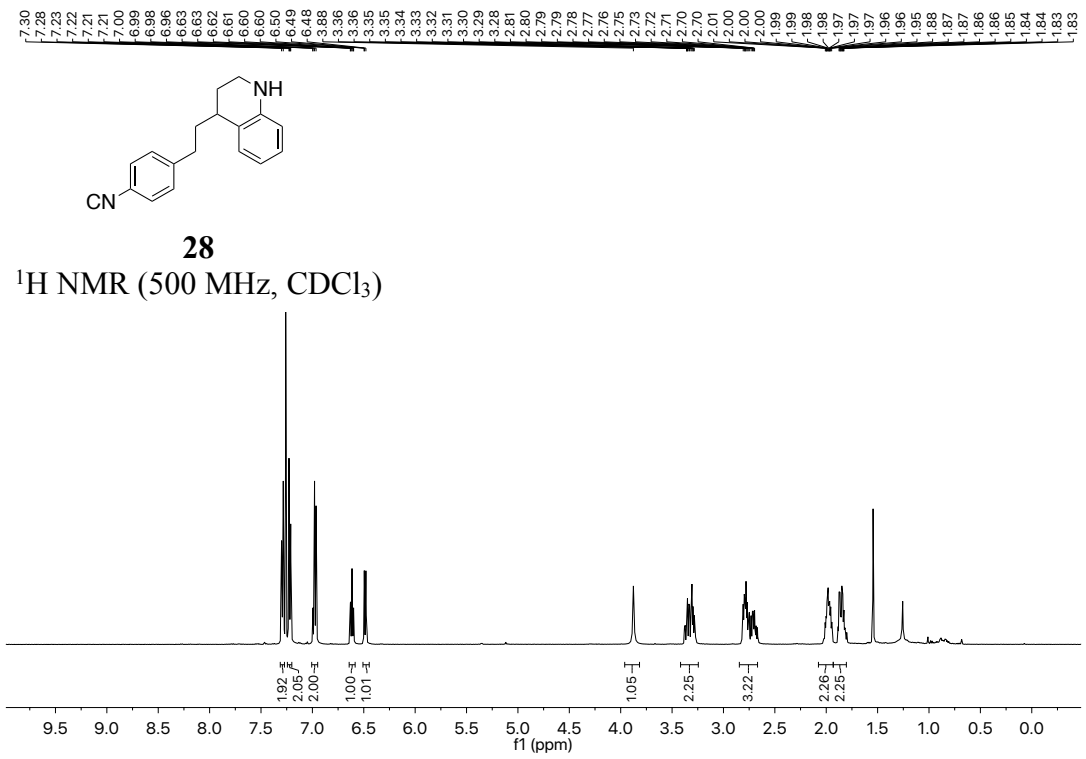
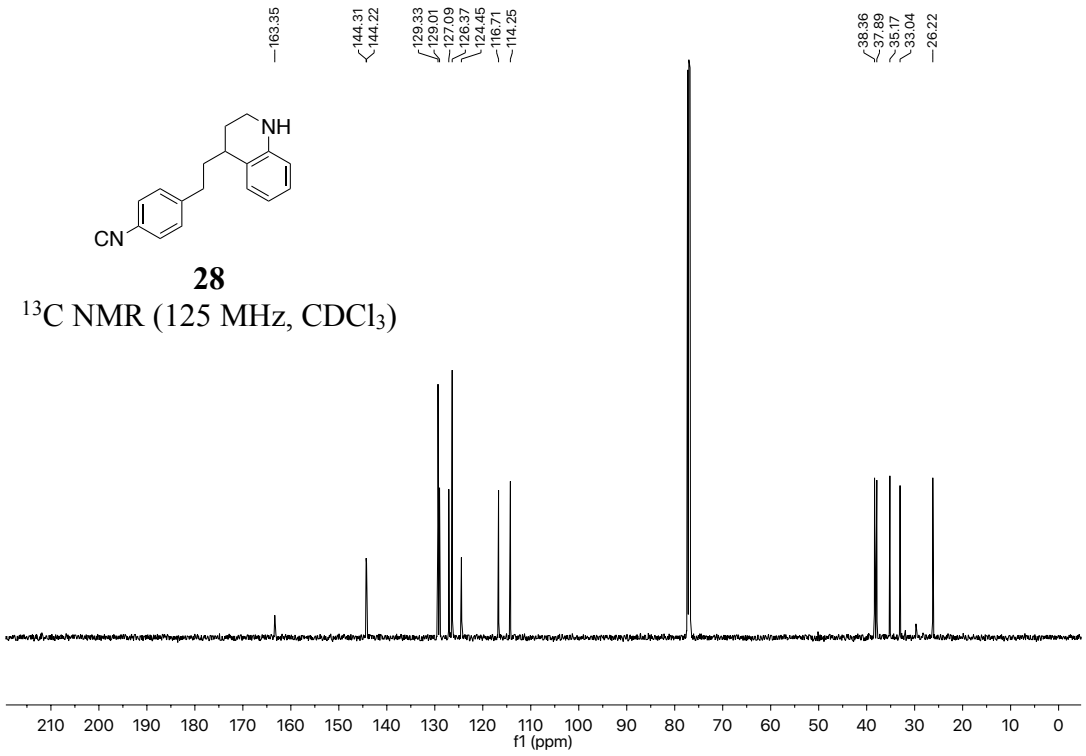


28

^{1}H NMR (500 MHz, $CDCl_3$)



28

^{13}C NMR (125 MHz, $CDCl_3$)