Mild and General Palladium-Catalyzed Synthesis of Methyl Aryl Ethers Enabled by the Use of a Palladacycle Precatalyst

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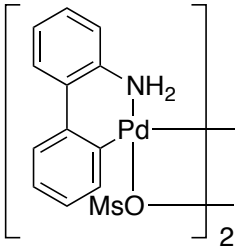
Supporting Information

General Analytical Information

Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instruments at ambient temperature. All ^{1}H NMR spectra were measured in part per million (ppm) relative to the signals for tetramethylsilane (TMS) added into the deuterated chloroform ($CDCl_3$) (0 ppm) unless otherwise stated. Data for ^{1}H NMR were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, sex = sextet, sep = septet, m = multiplet, ovrlp = overlap, br = broad), coupling constants, and integration. All ^{13}C NMR spectra were reported in ppm relative to $CDCl_3$ (77.16 ppm) unless otherwise stated, and were obtained with complete ^{1}H decoupling. All GC analyses were performed on an Agilent 6890 gas chromatograph with a FID detector using a J&W DB-1 column (10 m, 0.1 mm I.D.). All GC-MS analyses were performed on an Agilent 6850 gas chromatograph with a 5975 inert mass selective detector. IR spectra were reported on a Nicolet iS5 FT-IR Spectrometer. Melting points (uncorrected) were obtained on a Mel-Temp II capillary melting point apparatus. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. ESI-MS spectra were recorded on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS).

General Reagent Information

Unless otherwise noted, all chemicals used in the preparations of (hetero)aryl halides, and all the (hetero)aryl halides used in the coupling reactions with alcohols, were commercially available and were used as received without further purification. THF and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent-delivery kegs and vigorously purged with argon for 1 h. The solvents were further purified by passing it under argon pressure through two packed columns of neutral alumina (for THF) or through neutral alumina and copper(II) oxide (for toluene). Anhydrous 1,4-dioxane (99.8%) and methanol (99.8%) were purchased from Aldrich Chemical Co. in Seal-Seal® bottles and stored under argon. Ethanol (200 proof, 100%) was purchased from KOPTEC and a small of it was kept in a capped glass vial containing anhydrous Na_2SO_4 as a drying agent. Sodium *tert*-butoxide and cesium carbonate were purchased from Aldrich Chemical Co. and Alfa Aesar, respectively, and the bulks were stored in a glove-box; small quantities (~5 g) of bases were periodically transferred into capped glass vials in the glove-box, taken out of the glove-box for use, and stored in the air in a desiccator cabinet (with anhydrous calcium sulfate). Degassed deionized water was prepared by bubbling argon gas into the deionized water in a 100 mL round-bottom flask capped with a rubber septum for 15 min, and the bulk was stored under an argon atmosphere. Ligands **L4**, **L5**, and **L6** were purchased from Aldrich Chemical Co. and Strem Chemicals. Inc.. Pd_2dba_3 was purchased from Strem Chemicals. Inc.. Ligands **L1**,[1] **L2**,[1] and **L3**,[2] the palladacycle precatalyst precursor Pd μ-OMs dimer (**S1**)[3] (used for the synthesis of palladacycle precatalyst **3**), the palladacycle precatalyst **3**,[4] 1-benzyl-6-chloroindole (**S2**),[5] and (*E*)-1-(2-bromovinyl)-4-methylbenzene (**S3**)[6] were prepared according to the literature procedures.



S1

General Considerations

All reactions for the palladium-catalyzed arylation of alcohols (methanol, methanol-d_4, ethanol) were set up on bench-top in the open air and carried out in re-sealable test tubes with Teflon septa under an argon atmosphere. Unless otherwise noted, the reaction test tubes were cooled to room temperature (if they were previously heated at elevated temperatures), prior to the transfers of compounds into the tubes or the purifications by column chromatography. Unless otherwise noted, the solutions of reagents / reactants were transferred via plastic syringe (fitted with metal needle) into the reaction test tubes under a positive argon pressure. Flash column chromatography was performed using silica gel (Silicycle, ultra pure grade). The solvent system as an eluent for column chromatography is presented as a ratio of solvent volumes. Yields reported in the publication are of isolated materials. The yields of ether products represent an average of two independent runs unless otherwise noted. All ether products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopies and elemental analyses / high-resolution mass spectrometry. All unknown products and most known products were further characterized by IR spectroscopy and melting point determination (for solids). Unless otherwise noted, the formation of (hetero)arene side-product in the crude product was determined by GC-MS analysis, and the ratio of ether product to (hetero)arene of the crude product was determined by ^{1}H NMR spectroscopy based on 0.25 mmol (hetero)aryl halide. In case the ether product and the (hetero)arene were inseparable by column chromatography, the ratio of ether to (hetero)arene was determined by ^{1}H NMR spectroscopy of the inseparable isolated product mixture. In case no (hetero)arene was detected by GC-MS analysis in the crude product, the ratio of ether to (hetero)arene was assumed to be > 50 : 1.

Supplementary Experimental Results

(A) Additional data for the optimization of the palladium-catalyzed arylation of methanol

The optimal loading of methanol was found to be 5 equivalents at both high and ambient temperatures, since the use of a higher loading (10 equiv) gave similar yield of ether product, and the use of a lower loading (3 equiv) resulted in incomplete conversion of substrate (Table S1, entries 1-3, 13, 14). NaO^{t}Bu was found to be the optimal base at both high and ambient temperatures; in contrast, the use of weaker bases (Cs_2CO_3, K_3PO_4) and other alkali metal *tert*-butoxides led to incomplete conversions of substrate (entries 1, 4-7, 10, 11, 13, 15). Although the use of NaOMe led to complete conversion of substrate at 50 ^oC, it was not efficient to promote complete conversion at room temperature (entries 12 and 16); moreover, NaOMe is a hydroscopic base and the use of it should be avoided. 1,4-Dioxane was selected as the optimal solvent as it is a cheaper solvent compared with THF, while the use of toluene gave more arene side-product (entries 1, 8, and 9).

(B) Optimization of reaction conditions for the palladium-catalyzed arylation of ethanol

By using 2-(4-chlorophenyl)benzothiazole as a test substrate, the reaction conditions for coupling with ethanol was optimized. At 50 ^oC, a considerable amount of arene side-product was generated (Table S2, entry 1). At room temperature, only the desired ether product was formed in excellent yield without the formation of arene (entry 2). The optimal loading of ethanol was found to be 2 equivalents as similar yield of ether product was generated (entries 3 and 4).

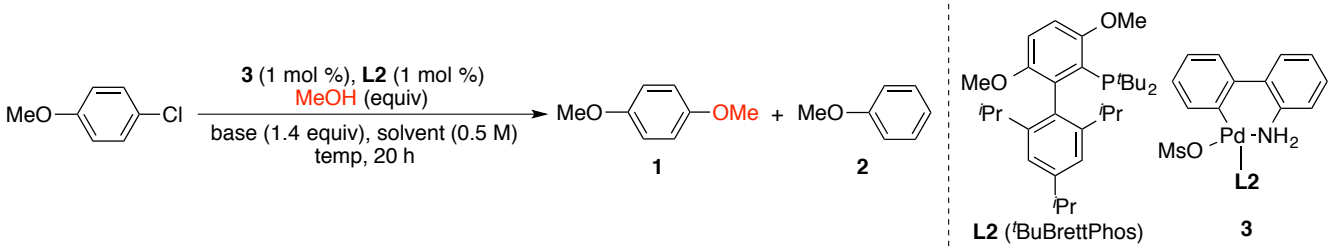
(C) Additional results for the palladium-catalyzed arylation of alcohols

The reaction protocols were also applicable for the coupling of alcohols (methanol / ethanol) with other (hetero)aryl halides (Scheme S1). The yields of the alkyl aryl ether products were determined by ^{1}H NMR spectroscopy. The products were characterized by ^{1}H NMR spectroscopy and most of them were further characterized by GC-MS analysis. However, some of the (hetero)aryl halides remained difficult coupling partners, including 3-chlorobenzamide, 4-chlorobenzaldehyde, 6-bromo-4*H*-chromen-4-one, and some five-membered heteroaryl halides (e.g.: 3-chloroindazole, 4-bromo-1-methyl-1*H*-pyrazole, 4-bromo-1-(*p*-tolyl)-1*H*-pyrazole, 4-bromo-1-trityl-1*H*-pyrazole, 4-bromo-3-methyl-1-trityl-1*H*-pyrazole, 4-bromo-3,5-dimethyl-1-trityl-1*H*-pyrazole, and 4-bromo-1-trityl-1*H*-imidazole). Even the use of bulky AdBrettPhos (**L3**) and the corresponding Pd precatalyst could not promote the coupling of five-membered heteroaryl halides with methanol and only heteroarenes were generated.

(D) Control experiments for the palladium-catalyzed arylation of alcohols

To ensure that the coupling of alcohols (methanol/ethanol) with electron-poor and activated (hetero)aryl halides is mediated by palladium rather than nucleophilic aromatic substitution, control experiments without the addition of Pd precatalyst **3** were carried out (Scheme S2). In the presence of **3**, all (hetero)aryl halides were completely converted to the ether products. In contrast, when no **3** was added, no or only traces of ether products were detected (as shown in the parentheses in Scheme S2). The control experiments suggest that palladium-catalyzed arylation of alcohols does operate.

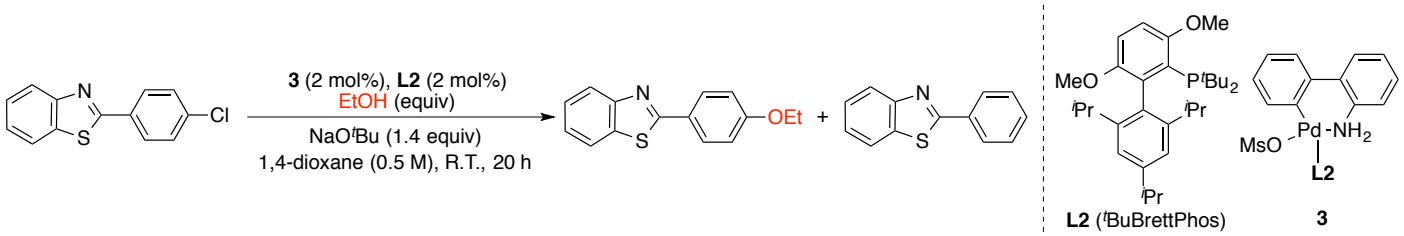
Table S1. Additional Data for the Optimization of the Palladium-catalyzed Arylation of Methanol[a]



entry	MeOH (equiv)	base	solvent	temp (°C)	conv (%)[b]	yield of **1** (%)[b]	yield of **2** (%)[b]
1	5	NaO^{t}Bu	1,4-dioxane	80	100	92	7
2	10	NaO^{t}Bu	1,4-dioxane	80	100	94	6
3	3	NaO^{t}Bu	1,4-dioxane	80	59	42	12
4	5	Cs_2CO_3	1,4-dioxane	80	94	92	2
5	5	K_3PO_4	1,4-dioxane	80	53	51	2
6	5	LiO^{t}Bu	1,4-dioxane	80	4	2	2
7	5	KO^{t}Bu	1,4-dioxane	80	12	7	5
8	5	NaO^{t}Bu	THF	80	100	92	6
9	5	NaO^{t}Bu	Toluene	80	100	91	9
10	5	NaO^{t}Bu	1,4-dioxane	50	100	94	6
11	5	Cs_2CO_3	1,4-dioxane	50	62	60	2
12	5	NaOMe	1,4-dioxane	50	100	95	5
13[c]	5	NaO^{t}Bu	1,4-dioxane	rt	100	95	5
14[c]	3	NaO^{t}Bu	1,4-dioxane	rt	98	95	3
15[c]	5	Cs_2CO_3	1,4-dioxane	rt	29	27	2
16[c]	5	NaOMe	1,4-dioxane	rt	87	77	10

[a] Reaction conditions: 4-Chloroanisole (0.25 mmol), MeOH (3-10 equiv), base (0.35 mmol), **3** (1 mol %), **L2** (1 mol %), solvent (0.5 mL, 0.50 M), 20 h. [b] Determined by GC using 1,3,5-trimethoxybenzne as internal standard. [c] **3** (2 mol %), **L2** (2 mol %).

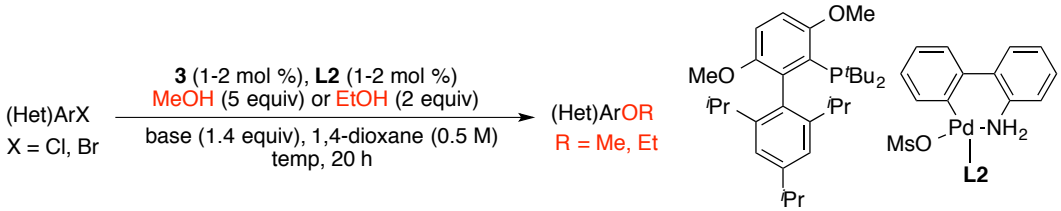
Table S2. Optimization of Reaction Conditions for the Palladium-catalyzed Arylation of Ethanol[a]



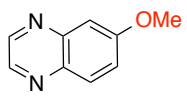
entry	EtOH (equiv)	temp. (°C)	conv. (%)[b]	yield of **1** (%)[b]	yield of **2** (%)[b]
1[c]	5	50	100	~60[d]	~40[d]
2	5	rt	100	98	0
3	3	rt	100	45	0
4	2	rt	100	99	0

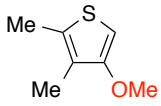
[a] Reaction conditions: 2-(4-Chlorophenyl)benzothiazole (0.25 mmol), EtOH (2-5 equiv), base (0.35 mmol), **3** (2 mol %), **L2** (2 mol %), solvent (0.5 mL, 0.50 M), 20 h. [b] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] **3** (1 mol %), **L2** (1 mol %). [d] Estimated by GC without using internal standard.

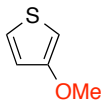
Scheme S1. Additional results for the palladium-catalyzed arylation of methanol

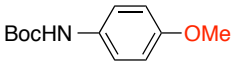


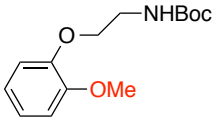
(A) **3** (1 mol %), **L2** (1 mol %), MeOH (5 equiv), 50 °C:[a]

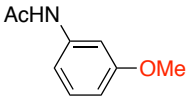

X = Br, 96%[b]


X = Br, 68% (~50%)[c]

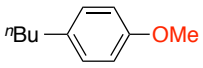

X = Br, 37%

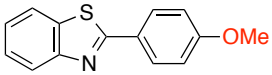

X = Br, 100%[d]

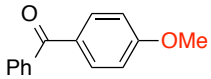

X = Cl, 90%[e]

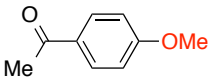

X = Cl, 87%[f]

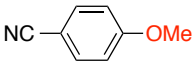
(B) **3** (2 mol %), **L2** (2 mol %), MeOH (5 equiv), rt:[g]

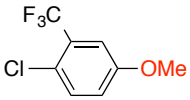

X = Cl, 91%

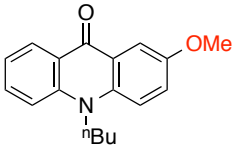

X = Cl, 99%

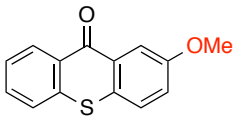

X = Cl, 88%

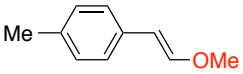

X = Cl, 92%


X = Cl, 69%

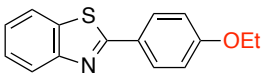

X = Br, 84%[h]

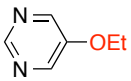

X = Cl, 98%

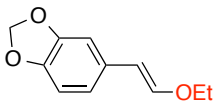

X = Cl, 96%

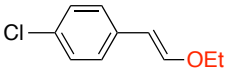

X = Br, 89%

(C) **3** (2 mol %), **L2** (2 mol %), EtOH (2 equiv), rt:[i]


X = Cl, 99%


X = Br, 61%[j]

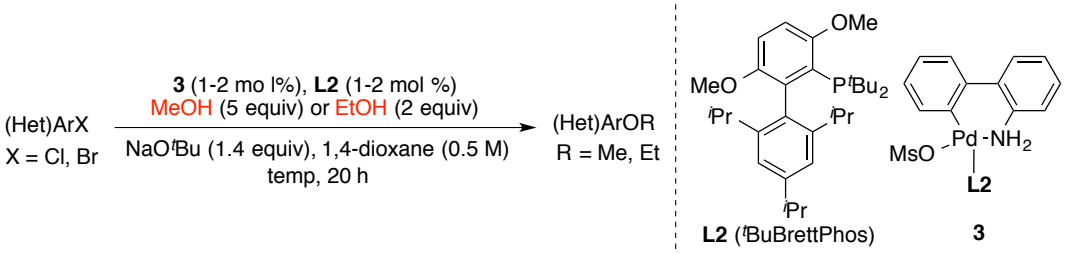

X = Br, 85% (~80%)[c]


X = Br, 85%

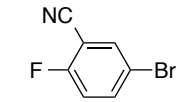
[a] Reaction conditions **(A)**: (Het)ArX (0.25 mmol, 1 equiv), MeOH (1.25 mmol, 5 equiv), NaO^{t}Bu (0.35 mmol, 1.4 equiv), **3** (1 mol %), **L2** (1 mol %), 1,4-dioxane (0.5 mL, 0.50 M), 50 °C, 20 h; ^{1}H NMR yield reported using 1,3,5-trimethoxybenzene as internal standard. [b] 12 h. [c] An inseparable mixture of product and a small amount of unknown

compound were isolated; the estimated yield of product was reported based on 1 mmol (Het)ArX. [d] Cs_2CO_3 (1.5 equiv), **3** (2 mol %), **L2** (2 mol %). [e] Cs_2CO_3 (1.5 equiv), 80 °C. [f] NaO^{t}Bu (2.4 equiv). [g] Reaction conditions **(B)**: (Het)ArX (0.25 mmol, 1 equiv), MeOH (1.25 mmol, 5 equiv), NaO^{t}Bu (0.35 mmol, 1.4 equiv), **3** (2 mol %), **L2** (2 mol %), 1,4-dioxane (0.5 mL, 0.50 M), RT, 20 h; ^{1}H NMR yield reported using 1,3,5-trimethoxybenzene as internal standard. [h] **3** (1.5 mol %), **L2** (1.5 mol %), NaO^{t}Bu (1.2 equiv); ratio of product from C-Br cleavage to C-Cl cleavage = 23 : 1. [i] Reaction conditions **(C)**: (Het)ArX (0.25 mmol, 1 equiv), EtOH (0.5 mmol, 2 equiv), NaO^{t}Bu (0.35 mmol, 1.4 equiv), **3** (2 mol %), **L2** (2 mol %), 1,4-dioxane (0.5 mL, 0.50 M), rt, 20 h; ^{1}H NMR yield reported using 1,3,5-trimethoxybenzene as internal standard. [j] **3** (3 mol %), **L2** (3 mol %), EtOH (5 equiv).

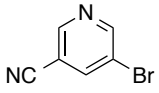
Scheme S2. Control experiments for the palladium-catalyzed arylation of methanol



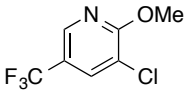
(A) 3 (1 mol %), **L2** (1 mol %), MeOH (5 equiv):[a]



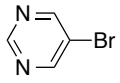
80 °C, 67%[b] (0%)[b,c]



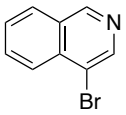
50 °C, 69%[b] (0%)[b]



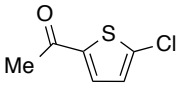
50 °C, 87% (0%)



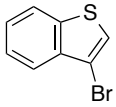
50 °C, 58% (0%)



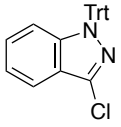
50 °C, 91% (0%)



50 °C, 94%[b] (8%, 32% conv.)[b,d]

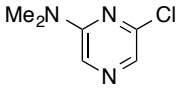


50 °C, 78% (0%)

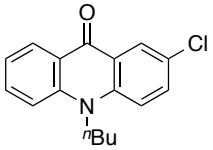


80 °C, 91% (0%)[d]

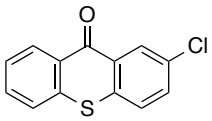
(B) 3 (2 mol %), **L2** (2 mol %), MeOH (5 equiv), rt:[e]



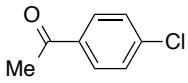
97% (2%, 7% conv.)[d]



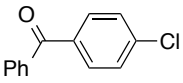
98%[f] (0%)



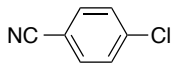
96%[f] (0%)



92%[f] (0%)

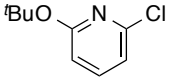


88%[f] (0%)

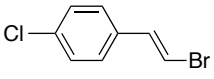


69%[f] (0%)

(C) 3 (2 mol %), **L2** (2 mol %), EtOH (2 equiv), rt:[g]



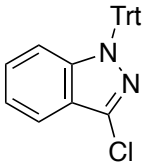
77% (0%)



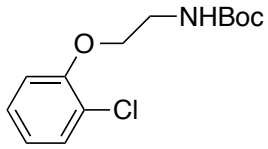
85%[f] (0%)

[a] Reaction conditions **(A)**: **(i) with Pd:** (Het)ArX (1 mmol, 1 equiv), MeOH (5 mmol, 5 equiv), NaO^{t}Bu (1.4 mmol, 1.4 equiv), **3** (1 mol %), **L2** (1 mol %), 1,4-dioxane (2 mL, 0.50 M), 50 or 80 ^{o}C, 20 h; isolated yields, average of two runs. **(ii) without Pd:** (Het)ArX (0.25 mmol, 1 equiv), MeOH (1.25 mmol, 5 equiv), NaO^{t}Bu (0.35 mmol, 1.4 equiv), **L2** (2 mol %), 1,4-dioxane (0.5 mL, 0.50 M), 50 or 80 ^{o}C, 20 h; yields (in parentheses) determined by GC-MS. [b] Cs_2CO_3 (1.5 equiv). [c] 100% conversion to 5-bromo-2-methoxybenzonitrile via S_NAr of Ar-F. [d] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [e] Reaction conditions **(B)**: **(i) with Pd:** (Het)ArX (1 mmol, 1 equiv), MeOH (5 mmol, 5 equiv), NaO^{t}Bu (1.4 mmol, 1.4 equiv), **3** (2 mol %), **L2** (2 mol %), 1,4-dioxane (2 mL, 0.50 M), rt, 20 h; isolated yields, average of two runs. **(ii) without Pd:** (Het)ArX (0.25 mmol, 1 equiv), MeOH (1.25 mmol, 5 equiv), NaO^{t}Bu (0.35 mmol, 1.4 equiv), **L2** (4 mol %), 1,4-dioxane (0.5 mL, 0.50 M), rt, 20 h; yields (in parentheses) determined by GC-MS. [f] ^{1}H NMR yield based on 0.25 mmol ArX using 1,3,5-trimethoxybenzene as internal standard. [g] Reaction conditions **(C)**: **(i) with Pd:** (Het)ArX (1 mmol, 1 equiv), EtOH (2 mmol, 2 equiv), NaO^{t}Bu (1.4 mmol, 1.4 equiv), **3** (2 mol %), **L2** (2 mol %), 1,4-dioxane (2 mL, 0.50 M), rt, 20 h; isolated yields, average of two runs. **(ii) without Pd:** (Het)ArX (0.25 mmol, 1 equiv), EtOH (0.5 mmol, 2 equiv), NaO^{t}Bu (0.35 mmol, 1.4 equiv), **L2** (4 mol %), 1,4-dioxane (0.5 mL, 0.50 M), rt, 20 h; yields (in parentheses) determined by GC-MS.

Preparation of Starting Materials ((Hetero)aryl Halides)



3-Chloro-1-trityl-1*H*-indazole (S4). The title compound was prepared according to the reported procedure.[7] An oven-dried 100 mL round-bottom flask tube equipped with a Teflon-coated magnetic stir bar was charged with 3-chloroindazole (763 mg, 5.0 mmol, 1 equiv), trityl chloride (1.81 g, 6.5 mmol, 1.3 equiv), potassium *tert*-butoxide (673 mg, 6.0 mmol, 1.2 equiv), and DMF (20 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was then washed with deionized water (~200 mL) and dichloromethane (~50 mL). The aqueous layer was further extracted with dichloromethane (2 x ~20 mL). The combined organic fractions were concentrated *in vacuo* with the aid of a rotary evaporator. The residue was dissolved with dichloromethane (~10 mL) and then triturated with methanol (~50 mL) to give an off-white solid. The solid was filtered, washed with methanol, and dried *in vacuo* to afford 3-chloro-1-trityl-1*H*-indazole (**S4**) (1.21 g, 3.05 mmol, 61%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 8.0 Hz, 1 H), 7.28-7.17 (ovrlp, 15 H), 7.08 (t, *J* = 8.0 Hz, 1 H), 7.00 (t, *J* = 8.0 Hz, 1 H), 6.39 (d, *J* = 8.8 Hz, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 142.65, 142.55, 133.3, 130.2, 127.8, 127.6, 126.7, 122.9, 121.4, 119.7, 114.5, 79.1.



***tert*-Butyl (2-(2-chlorophenoxy)ethyl)carbamate (S5).** The title compound was prepared according to the reported procedure.[8] An oven-dried 25 mL re-sealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with *tert*-butyl (2-bromoethyl)carbamate[9] (1.57 g, 7.0 mmol, 1.0 equiv), 2-chlorophenol (1.08 g, 8.4 mmol, 1.2 equiv), K_2CO_3 (1.93 g, 14.0 mmol, 2.0 equiv), and

acetone (10 mL). The sealed tube was then stirred at 80 ^{o}C in an oil bath overnight. After cooling to room temperature, the reaction mixture was washed with water (200 mL) and EtOAc (50 mL). The aqueous layer was further extracted with EtOAc (2 x 50 mL). The combined organic fractions were dried over Na_2SO_4 and then concentrated *in vacuo* with the aid of a rotary evaporator. The residue was purified by flash chromatography with silica gel using CH_2Cl_2 as an eluent to give *tert*-butyl (2-(2-chlorophenoxy)ethyl)carbamate (**S5**) as a viscous, pale-yellow oil (1.33 g, 4.90 mmol, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.36 (dd, J = 8.4 Hz, J = 1.6 Hz, 1 H), 7.20 (td, J = 8.4 Hz, J = 1.6 Hz, 1 H), 6.93-6.89 (ovrlp, 2 H), 5.11 (br s, 1 H), 4.07 (t, J = 5.2 Hz, 2 H), 3.57 (q, J = 5.2 Hz, 2 H), 1.45 (s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.0, 154.2, 130.4, 127.9, 123.2, 122.0, 113.9, 79.7, 68.7, 40.1, 28.5.

Optimization of Reaction Conditions for the Palladium-Catalyzed Arylation of Alcohols (Methanol and Ethanol) (Tables 1, S1, and S2).

(i) Use of Pd_2dba_3 as the Pd Source. An oven-dried 10 mL re-sealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with Pd_2dba_3 (1.2 mg, 0.00125 mmol, 0.005 equiv, or 2.3 mg, 0.0025 mmol, 0.01 equiv), ligand (**L1-L6**; 0.005 mmol, 0.02 equiv, or 0.010 mmol, 0.04 equiv), and sodium *tert*-butoxide (33.6 mg, 0.35 mmol, 1.4 equiv). The tube was then evacuated and backfilled with argon (this sequence was repeated a total of three times). 4-Chloroanisole (31 μL, 0.25 mmol, 1.0 equiv), methanol (31-101 μL, 0.75-2.5 mmol, 3-10 equiv), and 1,4-dioxane (0.50 mL) were added into the tube via syringe. The reaction mixture was then stirred in an oil bath at the elevated temperatures for 20-24 h. After cooling to room temperature, ethyl acetate (~4 mL) and 1,3,5-trimethoxybenzene (42.1 mg, 0.25 mmol, 1.0 equiv) were added into the reaction mixture. A small fraction of reaction mixture was filtered through a plug of silica gel and then subjected to GC analysis to determine the reaction conversion and the GC yields of product, 1,4-dimethoxybenzene (**1**), and side-product, anisole (**2**), using 1,3,5-trimethoxybenzene (42.1 mg, 0.25 mmol. 1.0 equiv) as internal standard.

(ii) Use of Pd precatalyst 3 as the Pd Source. An oven-dried 10 mL re-sealable screw-cap test tube (**A**) equipped with a Teflon-coated magnetic stir bar was charged with *t*BuBrettPhos **(L2**) (1.2-2.4 mg, 0.0025-0.005 mmol, 0.01-0.02 equiv), base (MO^{t}Bu (M = Li, Na, K), Cs_2CO_3, K_3PO_4, NaOMe; 0.35 mmol, 1.4 equiv), (and 2-(4-chlorophenyl)benzothiazole (61.4 mg, 0.25 mmol, 1.0 equiv)). Tube **A** was evacuated and backfilled with argon (this sequence was repeated a total of three times), and alcohols (methanol: 51 μL, 1.25 mmol, 5 equiv; ethanol: 29 μL, 0.50 mmol, 2 equiv) (and 4-chloroanisole (31 μL, 0.25 mmol, 1.0 equiv)) were then added into tube **A** via syringe. Simultaneously, an oven-dried 10 mL re-sealable screw-cap test tube (**B**) equipped with a Teflon-coated magnetic stir bar was charged with Pd precatalyst **3** (2.1-4.2 mg, 0.0025-0.005 mmol, 0.01-0.02 equiv), and the tube was evacuated and backfilled with argon (this sequence was repeated a total of three times). Solvent (1,4-dioxane, THF, or toluene; 0.50 mL) was added into tube **B** via syringe, and the reaction mixture was then stirred at room temperature for ~1 min to form a homogeneous solution (or sonicated with the aid of a ultrasonic water-bath to facilitate the dissolution). The solution of **3** from tube **B** was then transferred into tube **A** via syringe. The resulting reaction mixture in tube **A** was then stirred at elevated temperatures in an oil bath or at room temperature for 20 h. After cooling to room temperature, ethyl acetate (~4 mL) and 1,3,5-trimethoxybenzene were added into the reaction mixture. A small fraction of reaction mixture was (i) filtered through a plug of silica gel and then subjected to GC analysis, or (ii) concentrated *in vacuo* and then analyzed by ^{1}H NMR spectroscopy, to determine the reaction conversions and the GC yields of ether products and arene side-products using 1,3,5-trimethoxybenzene as internal standard (amount of 1,3,5-trimethoxybenzene for GC: 42.1 mg, 0.25 mmol, 1.0 equiv; for ^{1}H NMR: 14.0 mg, 0.083 mmol, 0.33 equiv).

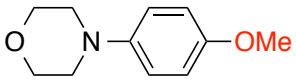
Substrate Scope for the Palladium-Catalyzed Arylation of Alcohols (Methanol, Methanol-d_4, and Ethanol) (Schemes 1-3).

General Procedure A (Synthesis of Methyl Aryl Ethers, Scheme 1): An oven-dried 20 mL re-sealable screw-cap test tube (**A**) equipped with a Teflon-coated magnetic stir bar was charged with ^{t}BuBrettPhos (**L2**) (4.8 mg, 0.010 mmol, 1 mol %), sodium *tert*-butoxide (134.5 mg, 1.4 mmol, 1.4 equiv), and (hetero)aryl halide (if solid) (1.0 mmol, 1 equiv). Tube **A** was evacuated and backfilled with argon (this sequence was repeated a total of three times), and methanol (203 μL, 5.0 mmol, 5 equiv) and (hetero)aryl halide (if liquid) (1.0 mmol, 1 equiv) were then added into tube **A** via syringe. Simultaneously, an oven-dried 10 mL re-sealable screw-cap test tube (**B**) equipped with a Teflon-coated magnetic stir bar was charged with Pd precatalyst **3** (8.5 mg, 0.010 mmol, 1 mol %). Tube **B** was then evacuated and backfilled with argon (this sequence was repeated a total of three times), and 1,4-dioxane (2.0 mL) was added into tube **B** via syringe. The reaction mixture in tube **B** was stirred at room temperature for ~1 min to form a homogeneous solution. The precatalyst solution from tube **B** was transferred into tube **A** via syringe. The resulting reaction mixture in tube **A** was stirred at 50 ^{o}C for 20 h. After cooling to room temperature, the crude product was diluted with ethyl acetate and concentrated *in vacuo* with the aid of a rotary evaporator. The crude product residue was purified by flash column chromatography with silica gel using a solvent mixture (ethyl acetate (EtOAc) / hexanes) as an eluent to afford the isolated product. The reported yields are of isolated products and average of two runs.

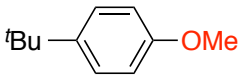
General Procedure B (Synthesis of Trideuteriomethyl Aryl Ethers, Scheme 2): An oven-dried 20 mL re-sealable screw-cap test tube (**A**) equipped with a Teflon-coated magnetic stir bar was charged with ^{t}BuBrettPhos (**L2**) (9.7 mg, 0.020 mmol, 2 mol %), sodium *tert*-butoxide (134.5 mg, 1.4 mmol, 1.4 equiv), and (hetero)aryl halide (if solid) (1.0 mmol, 1 equiv). Tube **A** was evacuated and backfilled with argon (this sequence was repeated a total of three times), and methanol-d_4 (203 μL, 5.0 mmol, 5 equiv) and (hetero)aryl halide (if liquid) (1.0 mmol, 1 equiv) were then added into tube **A** via syringe. Simultaneously, an oven-dried 10 mL re-sealable screw-cap test tube (**B**) equipped with a Teflon-coated magnetic stir bar was charged with Pd precatalyst **3** (17.1 mg, 0.020 mmol, 2 mol %). Tube **B** was then evacuated and backfilled with argon (this sequence was repeated a total of three times), and 1,4-dioxane (2.0 mL) was added into tube **B** via syringe. The reaction mixture in tube **B** was stirred at room temperature for ~1 min to form a homogeneous solution. The precatalyst solution from tube **B** was transferred into tube **A** via syringe. The resulting reaction mixture in tube **A** was stirred at room temperature for 20 h. The crude product was diluted with ethyl acetate and concentrated *in vacuo* with the aid of a rotary evaporator. The crude product residue was purified by flash column chromatography with silica gel using a solvent mixture (ethyl acetate (EtOAc)/hexanes) as an eluent to afford the isolated product. The reported yields are of isolated products and average of two runs.

General Procedure C (Synthesis of Ethyl Aryl Ethers, Scheme 3): An oven-dried 20 mL re-sealable screw-cap test tube (**A**) equipped with a Teflon-coated magnetic stir bar was charged with ^{t}BuBrettPhos (**L2**) (9.7 mg, 0.020 mmol, 2 mol %), sodium *tert*-butoxide (134.5 mg, 1.4 mmol, 1.4 equiv), and (hetero)aryl halide (if solid) (1.0 mmol, 1.4 equiv). Tube **A** was evacuated and backfilled with argon (this sequence was repeated a total of three times), and ethanol (117 μL, 2.0 mmol, 2 equiv) and (hetero)aryl halide (if liquid) (1.0 mmol, 1 equiv) were then added into tube **A** via syringe. Simultaneously, an oven-dried 10 mL re-sealable screw-cap test tube (**B**) equipped with a Teflon-coated magnetic stir bar was charged with Pd precatalyst **3** (17.1 mg, 0.020 mmol, 2 mol %). Tube **B** was then evacuated and backfilled with argon (this sequence was repeated a total of three times), and 1,4-dioxane

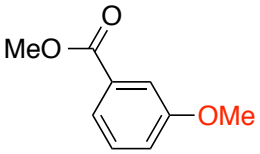
(2.0 mL) was added into tube **B** via syringe. The reaction mixture in tube **B** was stirred at room temperature for ~1 min to form a homogeneous solution. The precatalyst solution from tube **B** was transferred into tube **A** via syringe. The resulting reaction mixture in tube **A** was stirred at room temperature for 20 h. The crude product was diluted with ethyl acetate and concentrated *in vacuo* with the aid of a rotary evaporator. The crude product residue was purified by flash column chromatography with silica gel using a solvent mixture (ethyl acetate (EtOAc)/hexanes) as an eluent to afford the isolated product. The reported yields are of isolated products and average of two runs.



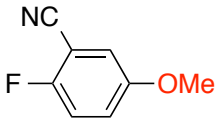
4-(4-Methoxyphenyl)morpholine (4a).[10] Following the general procedure A, the title compound was prepared using 4-(4-chlorophenyl)morpholine (197.7 mg, 1.0 mmol), Pd precatalyst **3** (17.1 mg, 0.02 mmol), and **L2** (9.7 mg, 0.02 mmol) at room temperature. After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:6) and then EtOAc/hexanes (1:3) as eluents to afford 4-(4-methoxyphenyl)morpholine (**4a**) (170.4 mg, 0.88 mmol, 88%) as a pale-brown solid. **m.p.:** 71-72 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87-6.82 (ovrlp, 4 H), 3.82 (t, J = 4.8 Hz, 4 H), 3.74 (s, 3 H), 3.02 (t, J = 4.8 Hz, 4 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.9, 145.6, 117.7, 114.5, 67.0, 55.5, 50.7. **IR** (neat cm^{-1}) 2970, 2853, 2816, 1512, 1452, 1265, 1246, 1229, 1184, 1121, 1030, 927. **Anal.** Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; Found: C, 68.63; H, 7.75.



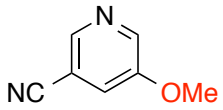
1-(*tert*-Butyl)-4-methoxybenzene (4b).[11] Following the general procedure A, the title compound was prepared using 1-(*tert*-butyl)-4-chlorobenzene (167 μL, 1.0 mmol), Pd precatalyst **3** (17.1 mg, 0.02 mmol), and **L2** (9.7 mg, 0.02 mmol) at room temperature. After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:10) as an eluent to afford 1-(*tert*-butyl)-4-methoxybenzene (**4b**) (153.6 mg, 0.93 mmol, 93%) as a pale-yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.29 (d, J = 8.8 Hz, 2 H), 6.83 (d, J = 9.2 Hz, 2 H), 3.76 (s, 3 H), 1.29 (s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.5, 143.4, 126.3, 113.5, 55.3, 34.2, 31.7. **IR** (neat cm^{-1}) 2956, 1612, 1513, 1464, 1363, 1298, 1246, 1183, 1037, 827, 793, 656. **Anal.** Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82; Found: C, 80.54; H, 9.77.



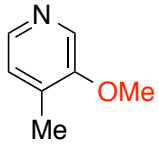
Methyl 3-methoxybenzoate (4c).[12] Following the general procedure A, the title compound was prepared using methyl 3-chlorobenzoate (139 μL, 1.0 mmol) and cesium carbonate (489 mg, 1.5 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:4) as an eluent to afford methyl 3-methoxybenzoate (**4c**) (135.2 mg, 0.81 mmol, 81%) as a pale-yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.62 (ddd, J = 8.0 Hz, J = 1.2 Hz, J = 0.8 Hz, 1 H), 7.55 (dd, J = 2.4 Hz, J = 1.2 Hz, 1 H), 7.32 (t, J = 8.0 Hz, 1 H), 7.08 (ddd, J = 8.0 Hz, J = 2.4 Hz, J = 0.8 Hz, 1 H), 3.89 (s, 3 H), 3.82 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.9, 159.6, 131.5, 129.4, 122.0, 119.4, 114.0, 55.4, 52.1. **IR** (neat cm^{-1}) 1718, 1587, 1487, 1456, 1434, 1276, 1221, 1098, 1043, 988, 874, 784, 753, 682. **Anal.** Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07; Found: C, 65.04; H, 6.08.



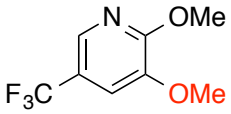
2-Fluoro-5-methoxybenzonitrile (**4d**).[13] Following the general procedure A, the title compound was prepared using 5-bromo-2-fluorobenzonitrile (200.0 mg, 1.0 mmol) and cesium carbonate (489 mg, 1.5 mmol) at 80 °C. After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:10) as an eluent to afford 2-fluoro-5-methoxybenzonitrile (**4d**) (101.7 mg, 0.67 mmol, 67%) as an off-white solid. The ^{1}H NMR yield of product was 88% based on 0.25 mmol aryl halides using 1,3,5-trimethoxybenzene as internal standard. **m.p.:** 82-83 °C (lit: 82-84 °C).[13] **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.14-7.11 (ovrlp, 2 H), 7.07-7.05 (m, 1 H), 3.83 (3, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.6 (d, $^1J_{CF}$ = 250.1 Hz), 155.8 ($^3J_{CF}$ = 2.2 Hz), 121.3 (d, $^3J_{CF}$ = 7.6 Hz), 117.3 (d, $^2J_{CF}$ = 21.2 Hz), 116.8, 114.0, 101.4 (d, $^2J_{CF}$ = 17.2 Hz), 56.1. **IR** (neat cm^{-1}) 2232, 1500, 1413, 1332, 1219, 1152, 1026, 925, 864, 826, 776, 701. **Anal.** Calcd. for C_8H_6FNO: C, 63.57; H, 4.00; Found: C, 63.76; H, 3.98.



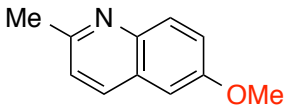
3-Cyano-5-methoxypyridine (4e).[14] Following the general procedure A, the title compound was prepared using 3-bromo-5-cyanopyridine (183.0 mg, 1.0 mmol) and cesium carbonate (489 mg, 1.5 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:4) as an eluent to afford 3-cyano-5-methoxypyridine (**4e**) (89.7 mg, 0.69 mmol, 69%) as an off-white solid. The ^{1}H NMR yield of product was 90% based on 0.25 mmol heteroaryl halides using 1,3,5-trimethoxybenzene as internal standard. **m.p.:** 112-113 °C (lit: 98-100 °C).[15] **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.52 (d, J = 2.8 Hz, 1 H), 8.49 (d, J = 1.2 Hz, 1 H), 7.43 (dd, J = 2.8 Hz, J = 1.6 Hz, 1 H), 3.93 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 155.1, 144.4, 142.2, 122.2, 116.5, 109.9, 56.0. **IR** (neat cm^{-1}) 3032, 2235, 1586, 1421, 1294, 1240, 1183, 1034, 1014, 938, 891, 699, 589. **Anal.** Calcd. for $C_7H_6N_2O$: C, 62.68; H, 4.51; Found: C, 62.60; H, 4.58.



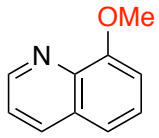
3-Methoxy-4-methylpyridine (4f). Following the general procedure A, the title compound was prepared using 3-bromo-4-methylpyridine (111 μL, 1.0 mmol). After work up, the crude product was purified by flash chromatography with silica gel (initially eluted with hexanes/triethylamine (50:1)) using EtOAc/hexanes (1:2) as an eluent to afford 3-methoxy-4-methylpyridine (**4f**) (62.9 mg, 0.51 mmol, 51%) as a pale-yellow oil. The ^{1}H NMR yield of product was 85% based on 0.25 mmol aryl halides using 1,3,5-trimethoxybenzene as internal standard. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.17 (s, 1 H), 8.13 (d, J = 4.0 Hz, 1 H), 7.05 (d, J = 4.4 Hz, 1 H), 3.91 (s, 3 H), 2.22 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 154.4, 142.4, 135.5, 132.4, 125.4, 55.8, 15.6. **IR** (neat cm^{-1}) 2924, 1598, 1500, 1415, 1305, 1268, 1211, 1185, 1072, 1025, 825, 760, 730. **HRMS** (ESI) Calcd for C_7H_9NO [M+H]: 124.0757; Found: 124.0756.



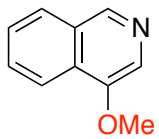
2,3-Dimethoxy-5-(trifluoromethyl)pyridine (4g). Following the general procedure A, the title compound was prepared using 3-chloro-2-methoxy-5-(trifluoromethyl)pyridine (152 μL, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:10) as an eluent to afford 2,3-dimethoxy-5-(trifluoromethyl)pyridine (**4g**) (180.0 mg, 0.87 mmol, 87%) as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.03 (s, 1 H), 7.16 (s, 1 H), 4.07 (s, 3 H), 3.93 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.7, 144.1, 134.8 (q, $^3J_{CF}$ = 4.9 Hz), 123.9 (q, $^1J_{CF}$ = 269.8 Hz), 120.2 (q, $^2J_{CF}$ = 32.6 Hz), 113.3 (q, $^3J_{CF}$ = 3.1 Hz), 55.9, 54.3. **IR** (neat cm^{-1}) 1609, 1497, 1409, 1326, 1263, 1207, 1113, 1011, 913, 766, 736, 619. **Anal.** Calcd. for : C, 46.38; H, 3.89; Found: C, 46.22; H, 4.00.



6-Methoxy-2-methylquinoline (4h).[16] Following the general procedure A, the title compound was prepared using 6-chloro-2-methylquinoline (177.6 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc as an eluent to afford an inseparable brown oily mixture of product, 6-methoxy-2-methylquinoline (**4h**) (128.2 mg, 0.74 mmol, 74%), and side-product, 2-methylquinoline (2.9 mg, 0.02 mmol, 2%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.91 (d, J = 9.2 Hz, 1 H), 7.84 (d, J = 8.4 Hz, 1 H), 7.30 (dd, J = 9.2 Hz, J = 2.8 Hz, 1 H), 7.15 (d, J = 8.4 Hz, 1 H), 6.95 (d, J = 2.8 Hz, 1 H), 3.82 (s, 3 H), 2.67 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.0, 156.1, 143.7, 134.9, 129.8, 127.2, 122.0, 121.7, 105.0, 55.2, 24.8. **IR** (neat cm^{-1}) 1625, 1602, 1498, 1483, 1374, 1345, 1307, 1232, 1160, 1111, 1030, 831, 730, 596. **HRMS** (ESI) Calcd. for $C_{11}H_{11}NO$ [M+H]: 174.0913; Found: 174.0903.

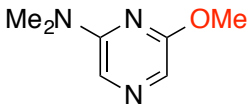


8-Methoxyquinoline (4i).[17] Following the general procedure A, the title compound was prepared using 8-chloroquinoline (163.6 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/MeOH (12:1) as an eluent to afford an inseparable brown oily mixture of product, 8-methoxyquinoline (**4i**) (136.9 mg, 0.86 mmol, 86%), and side-product, quinoline (5.2 mg, 0.04 mmol, 4%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.90 (dd, J = 4.0 Hz, J = 2.0 Hz, 1 H), 8.03 (dd, J = 8.4 Hz, J = 2.0 Hz, 1 H), 7.38 (t, J = 8.4 Hz, 1 H), 7.35-7.29 (ovrlp, 2 H), 6.97 (dd, J = 7.6 Hz, J = 0.8 Hz, 1 H), 4.03 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 155.0, 148.8, 139.8, 135.5, 128.9, 126.3, 121.3, 119.2, 107.2, 55.5. **HRMS** (ESI) Calcd. for $C_{10}H_9NO$ [M+H]: 160.0757; found: 160.0749.

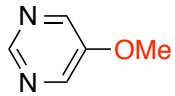


4-Methoxyisoquinoline (4j).[18] Following the general procedure A, the title compound was prepared using 4-bromoisoquinoline (208.1 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (5:1) as an eluent to afford 4-methoxyisoquinoline (**4j**) (145.6 mg, 0.91 mmol, 91%) as a brown solid. **m.p.:** 71-72 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.88 (s,

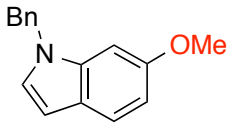
1 H), 8.16 (d, J = 8.4 Hz, 1 H), 8.06 (s, 1 H), 7.87 (d, J = 8.0 Hz, 1 H), 7.63 (ddd, J = 8.4 Hz, J = 6.8 Hz, J = 1.2 Hz, 1 H), 7.55 (ddd, J = 8.0 Hz, J = 6.8 Hz, J = 1.2 Hz, 1 H), 4.01 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 150.4, 145.2, 129.4, 129.0, 128.0, 127.5, 126.7, 123.0, 121.0, 55.9. **IR** (neat cm^{-1}) 1580, 1461, 1395, 1265, 1122, 1094, 993, 852, 780, 732, 589. **Anal.** Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; Found: C, 75.25; H, 5.77.



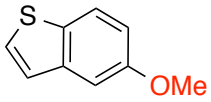
2-Methoxy-6-dimethylaminopyrazine (4k). Following the general procedure A, the title compound was prepared using 2-chloro-6-dimethylaminopyrazine (157.6 mg, 1.0 mmol), Pd precatalyst **3** (17.1 mg, 0.02 mmol), and **L2** (9.7 mg, 0.02 mmol) at room temperature. After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:2) as an eluent to afford 2-methoxy-6-dimethylaminopyrazine (**4k**) (149.3 mg, 0.97 mmol, 97%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.50 (s, 1 H), 7.45 (s, 1 H), 3.88 (s, 3 H), 3.06 (s, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.7, 153.4, 119.8, 119.3, 52.7, 37.3. **IR** (neat cm^{-1}) 2943, 1575, 1531, 1402, 1373, 1279, 1191, 1147, 1046, 997, 814, 689. **Anal.** Calcd. for $C_7H_{11}N_3O$: C, 54.89; H, 7.24; Found: 55.05; H, 7.17.



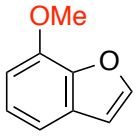
5-Methoxypyrimidine (4l).[19] Following the general procedure A, the title compound was prepared using 5-bromopyrimidine (159.0 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (4:1) as an eluent to afford 5-methoxypyrimidine (**4l**) (64.2 mg, 0.58 mmol, 58%) as a low-melting brown solid. The ^{1}H NMR yield of product was 93% based on 0.25 mmol heteroaryl halides using 1,3,5-trimethoxybenzene as internal standard. **m.p.:** 44-45 °C (lit: 46-47 °C).[20] **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.86 (s, 1 H), 8.42 (s, 2 H), 3.93 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 153.6, 151.7, 143.3, 55.9. **IR** (neat cm^{-1}) 1563, 1448, 1411, 1277, 1200, 1184, 1110, 1041, 1013, 899, 725, 620, 581. **HRMS** (ESI) Calcd. for $C_5H_6N_2O$ [M+H]: 111.0553; found: 111.0555.



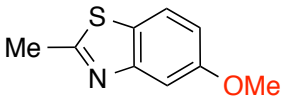
1-Benzyl-6-methoxy-1*H*-indole (4m).[21] Following the general procedure A, the title compound was prepared using 1-benzyl-6-chloro-1*H*-indole (**S2**) (241.7 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:20) as an eluent to afford 1-benzyl-6-methoxy-1*H*-indole (**4m**) (209.4 mg, 0.88 mmol, 88%) as a viscous brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.48 (d, J = 8.8 Hz, 1 H), 7.24-7.16 (ovrlp, 3 H), 7.03 (d, J = 6.4 Hz, 2 H), 6.93 (d, J = 3.2 Hz, 1 H), 6.77 (dd, J = 8.8 Hz, J = 2.4 Hz, 1 H), 6.69 (d, J = 2.0 Hz, 1 H), 6.44 (d, J = 3.2 Hz, 1 H), 5.13 (s, 2 H), 3.71 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.3, 137.6, 137.1, 128.8, 127.6, 127.3, 127.0, 123.1, 121.6, 109.4, 101.6, 93.5, 55.6, 50.0. **IR** (neat cm^{-1}) 1621, 1491, 1453, 1316, 1262, 1217, 1170, 1028, 935, 810, 733, 703, 631. **HRMS** (ESI) Calcd. for $C_{16}H_{15}NO$ [M+H]: 238.1226; found: 238.1216.



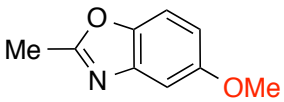
5-Methoxybenzothiophene (4n).[22] Following the general procedure A, the title compound was prepared using 5-chlorobenzothiophene (168.6 mg, 1.0 mmol), Pd precatalyst **3** (17.1 mg, 0.02 mmol), and **L2** (9.7 mg, 0.02 mmol) at 80 °C. After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:12) as an eluent to afford 5-methoxybenzothiophene (**4n**) (156.9 mg, 0.96 mmol, 96%) as a pale-brown solid. The ratio of **4n** to benzothiophene was determined to be 30 : 1 based on 0.25 mmol heteroaryl halide. **m.p.:** 42-43 °C (lit: 43-44 °C).[23] **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 8.8 Hz, 1 H), 7.37 (d, *J* = 5.6 Hz, 1 H), 7.22 (d, *J* = 2.4 Hz, 1 H), 7.19 (d, *J* = 5.2 Hz, 1 H), 6.97 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1 H), 3.79 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.5, 140.8, 132.2, 127.5, 123.7, 123.1, 114.7, 105.7, 55.5. **IR** (neat cm^{-1}) 1602, 1501, 1446, 1412, 1334, 1259, 1237, 1154, 1024, 832, 747, 690, 633. **Anal.** Calcd. for C_9H_8OS: C, 65.82; H, 4.91; Found: 65.97; H, 4.96.



7-Methoxybenzofuran (4o).[24] Following the general procedure A, the title compound was prepared using 7-chlorobenzofuran (152.6 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:25) as an eluent to afford 7-methoxybenzofuran (**4o**) (119.8 mg, 0.81 mmol, 81%) as a pale-yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 2.0 Hz, 1 H), 7.21-7.11 (ovrlp, 2 H), 6.76 (d, *J* = 7.6 Hz, 1 H), 6.72 (dd, *J* = 2.0 Hz, *J* = 1.2 Hz, 1 H), 3.97 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 145.6, 145.0, 144.4, 129.2, 123.5, 113.5, 106.9, 106.3, 56.0. **IR** (neat cm^{-1}) 1590, 1484, 1434, 1340, 1280, 1254, 1202, 1181, 1124, 1092, 1028, 971, 875, 783, 725, 684. **Anal.** Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44; Found: C, 73.09; H, 5.50.

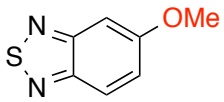


5-Methoxy-2-methylbenzothiazole (4p).[25] Following the general procedure A, the title compound was prepared using 5-chloro-2-methylbenzoxazole (183.7 mg, 1.0 mmol), Pd precatalyst **3** (17.1 mg, 0.02 mmol), and **L2** (9.7 mg, 0.02 mmol) at 80 °C. After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:6) as an eluent to afford 5-methoxy-2-methylbenzothiazole (**4p**) (158.8 mg, 0.89 mmol, 89%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 8.8 Hz, 1 H), 7.44 (d, *J* = 2.4 Hz, 1 H), 6.96 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1 H), 3.84 (s, 3 H), 2.77 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 168.0, 158.7, 154.5, 127.3, 121.5, 114.4, 105.1, 55.4, 20.0. **IR** (neat cm^{-1}) 2927, 1600, 1558, 1520, 1465, 1433, 1321, 1275, 1200, 1157, 1137, 1070, 1024, 937, 839, 802, 702, 642. **Anal.** Calcd for C_9H_9NOS: C, 60.31; H, 5.06; Found: C, 60.24; H, 5.18.

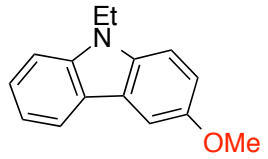


5-Methoxy-2-methylbenzoxazole (4q).[26] Following the general procedure A, the title compound was prepared using 5-chloro-2-methylbenzothiazole (167.6 mg, 1.0 mmol) at 80 °C. After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:3) as an eluent to afford 5-

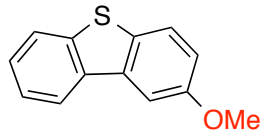
methoxy-2-methylbenzothiazole (**4q**) (143.3 mg, 0.88 mmol, 88%) as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.31 (d, *J* = 8.8 Hz, 1 H), 7.13 (d, *J* = 2.8 Hz, 1 H), 6.86 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1 H), 3.82 (s, 3 H), 2.58 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 164.6, 157.0, 145.6, 142.3, 112.6, 110.2, 102.7, 55.8, 14.5. **IR** (neat cm^{-1}) 2937, 1575, 1481, 1438, 1271, 1195, 1171, 1148, 1026, 925, 845, 802, 663. **Anal.** Calcd. for $C_9H_9NO_2$: C, 66.25; H 5.56, ; Found: C, 65.96; H, 5.77.



5-Methoxybenzo-2,1,3-thiadiazole (4r).[27] Following the general procedure A, the title compound was prepared using 5-chlorobenzo-2,1,3-thiadiazole (170.6 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:8) as an eluent to afford 5-methoxybenzo-2,1,3-thiadiazole (**4r**) (149.9 mg, 0.90 mmol, 90%) as an off-white solid. **m.p.:** 81-82 °C (lit: 79-80 °C).[27] **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 9.6 Hz, 1 H), 7.25 (dd, *J* = 9.2 Hz, *J* = 2.4 Hz, 1 H), 7.16 (d, *J* = 2.4 Hz, 1 H), 3.90 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 161.3, 156.1, 151.2, 125.3, 121.5, 97.8, 55.7. **IR** (neat cm^{-1}) 1618, 1495, 1457, 1439, 1282, 1220, 1181, 1138, 1024, 841, 817. **Anal.** Calcd. for $C_7H_6N_2OS$: C, 50.59; H, 3.64; Found: C, 50.86; H, 3.65.

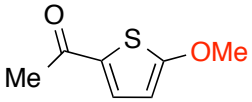


9-Ethyl-3-methoxy-9*H*-carbazole (4s). Following the general procedure A, the title compound was prepared using 3-bromo-9-ethyl-9*H*-carbazole (274.2 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:30) as an eluent to afford 9-ethyl-3-methoxy-9*H*-carbazole (**4s**) (212.4 mg, 0.94 mmol, 94%) as a pale-brown solid. **m.p.:** 62-63 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 2.4 Hz, 1 H), 7.39 (ddd, *J* = 8.4 Hz, *J* = 7.2 Hz, *J* = 1.2 Hz, 1 H), 7.27 (d, *J* = 8.4 Hz, 1 H), 7.19 (d, *J* = 8.8 Hz, 1 H), 7.15 (ddd, *J* = 7.6 Hz, *J* = 6.8 Hz, *J* = 0.8 Hz, 1 H), 7.06 (dd, *J* = 8.8 Hz, *J* = 2.8 Hz, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 3.86 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 153.6, 140.5, 135.0, 125.6, 123.3, 122.8, 120.4, 118.3, 114.8, 109.2, 108.6, 103.5, 56.1, 37.5, 13.9. **IR** (neat cm^{-1}) 1489, 1473, 1292, 1264, 1205, 1173, 1154, 733, 703. **HRMS** (ESI) Calcd for $C_{15}H_{15}NO$ [M+H]: 226.1226; found: 226.1220.

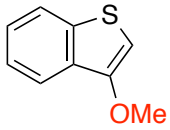


2-Methoxydibenzothiophene (4t).[28] Following the general procedure A, the title compound was prepared using 2-bromodibenzothiophene (263.2 mg, 1.0 mmol), Pd precatalyst **3** (17.1 mg, 0.02 mmol), and **L2** (9.7 mg, 0.02 mmol) at room temperature. After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:15) as an eluent to afford 2-methoxydibenzothiophene (**4t**) (205.3 mg, 0.96 mmol, 96%) as a pale-yellow solid. **m.p.:** 55-56 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.02-7.96 (m, 1 H), 7.78-7.72 (m, 1 H), 7.61 (d, *J* = 8.8 Hz, 1 H), 7.52 (d, *J* = 2.4 Hz, 1 H), 7.37-7.31 (ovrlp, 2 H), 7.00 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1 H), 3.80 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.6, 140.6, 136.6, 135.5, 131.3, 126.7, 124.1, 123.4, 122.9, 121.6, 115.8, 104.9, 55.6. **IR** (neat cm^{-1}) 1605,

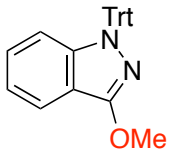
1474, 1431, 1264, 1214, 1175, 1031, 843, 803, 761, 727, 660. **Anal.** Calcd. for $C_{13}H_{10}OS$: C, 72.87; H, 4.70; Found: C, 73.03; H, 4.85.



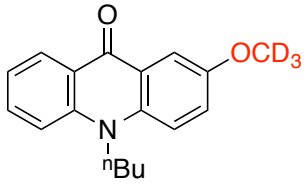
2-Acetyl-5-methoxythiophene (4u).[29] Following the general procedure A, the title compound was prepared using 2-acetyl-5-chlorothiophene (160.6 mg, 1.0 mmol) and cesium carbonate (489 mg, 1.5 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:4) as an eluent to afford 2-acetyl-5-methoxythiophene (**4u**) (147.5 mg, 0.94 mmol, 94%) as a brown solid. **m.p.:** 35-36 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.44 (d, J = 4.4 Hz, 1 H), 6.24 (d, J = 4.4 Hz, 1 H), 3.95 (s, 3 H), 2.44 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 189.9, 174.5, 133.0, 130.7, 105.8, 60.3, 25.2. **IR** (neat cm^{-1}) 1643, 1472, 1414, 1345, 1247, 1214, 1074, 1026, 926, 778, 732, 604. **Anal.** Calcd. for $C_7H_8O_2S$: C, 53.82; H, 5.16; Found: C, 54.17; H, 5.35.



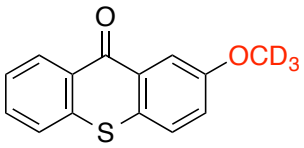
3-Methoxybenzothiophene (4v).[30] Following the general procedure A, the title compound was prepared using 3-bromobenzothiophene (131 μL, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:25) as an eluent to afford an inseparable pale-yellow oily mixture of product, 3-methoxybenzothiophene (**4v**) (128.1 mg, 0.78 mmol, 78%), and side-product, benzothiophene (2.7 mg, 0.02 mmol, 2%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.79-7.77 (m, 1 H), 7.73-7.69 (m, 1 H), 7.34-7.29 (ovrlp, 2 H), 6.21 (s, 1 H), 3.89 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.0, 137.9, 132.1, 125.3, 123.8, 122.9, 121.0, 95.6, 57.2. **IR** (neat cm^{-1}) 1572, 1532, 1439, 1364, 1205, 1155, 1118, 987, 858, 759, 714. **HRMS** (ESI) Calcd. for C_9H_8OS [M+H]: 165.0369; Found: 165.0372.



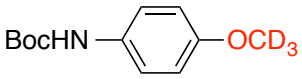
3-Methoxy-1-trityl-1*H*-indazole (4w). Following the general procedure A, the title compound was prepared using 3-chloro-1-trityl-1*H*-indazole (**S4**) (394.9 mg, 1.0 mmol) at 80 °C. After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:20) as an eluent to afford 3-methoxy-1-trityl-1*H*-indazole (**4w**) (353.9 mg, 0.91 mmol, 91%) as an off-white solid. **m.p.:** 148-150 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.56-7.53 (m, 1 H), 7.33-7.31 (m, 6 H), 7.22-7.14 (m, 9 H), 6.91-6.86 (ovrlp, 2 H), 6.28-6.24 (m, 1 H), 3.88 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.0, 143,9, 143.3, 130.2, 127.5, 127.1, 126.5, 119.7, 119.6, 115.1, 113.9, 78.0, 56.1. **IR** (neat cm^{-1}) 1538, 1492, 1445, 1395, 1265, 1204, 1031, 736, 700. **HRMS** (ESI) Calcd for $C_{27}H_{22}N_2O$ [M+H]: 391.1805; found: 391.1818.



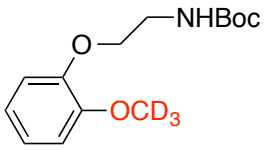
10-*n*-Butyl-2-trideuteriomethoxyacridin-9(10*H*)-one (5a). Following the general procedure B, the title compound was prepared using 10-*n*-butyl-2-chloroacridin-9(10*H*)-one (285.8 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:3) and then EtOAc/hexanes (1:2) as eluents to afford 10-*n*-butyl-2-trideuteriomethoxyacridin-9(10*H*)-one (**5a**) (282.6 mg, 0.99 mmol, 99%) as a yellow solid. **m.p.:** 101-102 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.51 (dd, J = 8.4 Hz, J = 1.2 Hz, 1 H), 7.88 (d, J = 3.2 Hz, 1 H), 7.60 (t, J = 8.0 Hz, 1 H), 7.35-7.31 (ovrlp, 2 H), 7.27 (dd, J = 9.6 Hz, J = 3.2 Hz, 1 H), 7.18 (t, J = 7.6 Hz, 1 H), 4.14 (t, J = 8.0 Hz, 2 H), 1.77 (qu, J = 8.0 Hz, 2 H), 1.49 (sex, J = 7.2 Hz, 2 H), 1.01 (t, J = 7.6 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 176.8, 154.0, 140.8, 136.1, 133.2, 127.4, 124.0, 122.7, 121.3, 120.4, 116.2, 114.2, 106.4, 54.6 (sep, $^1J_{CD}$ = 22.0 Hz), 45.6, 29.1, 19.9, 13.6. **IR** (neat cm^{-1}) 2956, 1594, 1489, 1464, 1360, 1269, 1173, 1107, 1014, 809, 754. **Anal.** Calcd. for $C_{18}H_{16}D_3NO_2$: C, 76.03; (H+D as H), 6.81; Found: C, 75.68; H, 6.72.



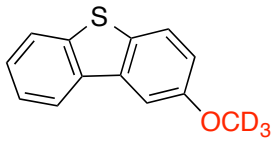
2-Trideuteriomethoxy-9*H*-thioxanthen-9-one (5b). Following the general procedure B, the title compound was prepared using 2-chloro-9*H*-thioxanthen-9-one (246.7 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:4) as an eluent to afford 2-trideuteriomethoxy-9*H*-thioxanthen-9-one (**5b**) (280.2 mg, 0.94 mmol, 94%) as a yellow solid. **m.p.:** 127-128 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.59 (ddd, J = 8.0 Hz, J = 1.2 Hz, J = 0.4 Hz, 1 H), 8.02 (d, J = 2.8 Hz, 1 H), 7.57-7.49 (ovrlp, 2 H), 7.45-7.40 (ovrlp, 2 H), 7.19 (dd, J = 9.2 Hz, J = 3.2 Hz, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 179.3, 158.2, 137.4, 131.8, 130.1, 129.7, 128.9, 128.5, 127.1, 125.9, 125.8, 122.4, 110.3, 54.7, (sep, $^1J_{CD}$ = 21.3 Hz). **IR** (neat cm^{-1}) 1637, 1591, 1471, 1438, 1343, 1293, 1101, 741. **HRMS** (ESI) Calcd for $C_{14}H_7D_3O_2S$ [M+H]: 246.0663; Found: 246.0645.



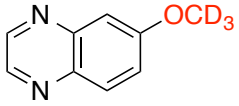
***tert*-Butyl (4-trideuteriomethoxyphenyl)carbamate (5c).** Following the general procedure B, the title compound was prepared using *tert*-butyl (4-bromophenyl)carbamate (272.1 mg, 1.0 mmol) and cesium carbonate (489 mg, 1.5 mmol) at 50 °C. After cooling to room temperature, degassed water (1.80 mL, 100 equiv) was added into the reaction mixture via syringe under a positive argon pressure, and the resulting reaction mixture was heated at 50 °C for 20 min. After cooling to room temperature, the crude product was purified by flash chromatography using EtOAc/hexanes (1:6) as an eluent to afford *tert*-butyl (4-trideuteriomethoxyphenyl)carbamate (**5c**) (201.6 mg, 0.89 mmol, 89%) as an off-white solid. **m.p.:** 94-95 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.26 (d, J = 8.4 Hz, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 6.39 (br s, 1 H), 1.51 (s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 155.6, 153.3, 131.6, 120.7, 114.1, 80.1, 54.6 (sep, $^1J_{CD}$ = 22.2 Hz), 28.4. **IR** (neat cm^{-1}) 3365, 1695, 1513, 1413, 1367, 1232, 1157, 1109, 1055, 993, 823, 737, 714, 624. **Anal.** Calcd for $C_{12}H_{14}D_3NO_3$: C, 63.69; (H+D as H), 7.67; Found: C, 63.90, H, 7.46.



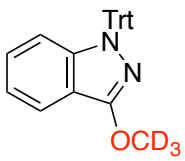
***tert*-Butyl (2-(2-trideuteriomethoxyphenoxy)ethyl)carbamate (5d).** Following the general procedure B, the title compound was prepared using *tert*-butyl (2-(2-chlorophenoxy)ethyl)carbamate (**S5**) (271.7 mg, 1.0 mmol), Pd precatalyst **3** (8.5 mg, 0.01 mmol), **L2** (4.8 mg, 0.01 mmol), and cesium carbonate (489 mg, 1.5 mmol) at 80 °C. After cooling to room temperature, degassed water (1.80 mL, 100 equiv) was added into the reaction mixture via syringe under a positive argon pressure, and the resulting reaction mixture was heated at 80 °C for 20 min. After cooling to room temperature, the crude product was purified by flash chromatography using EtOAc/hexanes (1:4) as an eluent to afford *tert*-butyl (2-(2-trideuteriomethoxyphenoxy)ethyl)carbamate (**5d**) (234.4 mg, 0.87 mmol, 87%) as an viscous yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.90-6.82 (ovrlp, 4 H), 5.26 (s, 1 H), 4.07 (t, J = 5.2 Hz, 2 H), 3.53 (q, J = 5.2 Hz, 2 H), 1.45 (s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 155.9, 149.7, 148.0, 121.8, 120.9, 114.6, 111.8, 79.1, 68.9, 54.8 (sep, $^1J_{CD}$ = 21.9 Hz), 40.1, 28.3. **IR** (neat cm^{-1}) 3368, 2976, 1699, 1500, 1453, 1365, 1257, 1221, 1167, 1127, 1108, 1053, 993, 739. **HRMS** (ESI) Calcd for $C_{14}H_{18}D_3NO_4$ [M+H]: 271.1732; found: 271.1722.



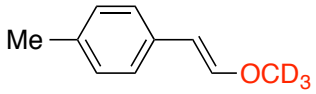
2-Trideuteriomethoxydibenzothiophene (5e). Following the general procedure B, the title compound was prepared using 2-bromodibenzothiophene (263.2 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:15) as an eluent to afford 2-trideuteriomethoxydibenzothiophene (**5e**) (200.8 mg, 0.92 mmol, 92%) as an off-white solid. **m.p.:** 58-59 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.00-7.96 (m, 1 H), 7.76-7.72 (m, 1 H), 7.61 (d, J = 8.4 Hz, 1 H), 7.50 (d, J = 2.4 Hz, 1 H), 7.36-7.30 (overlp, 2 H), 6.99 (dd, J = 8.4 Hz, J = 2.4 Hz, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.6, 140.6, 136.6, 135.5, 131.3, 126.7, 124.1, 123.4, 122.9, 121.5, 115.7, 104.9, 54.8 (sep, $^1J_{CD}$ = 21.9 Hz). **IR** (neat cm^{-1}) 1604, 1470, 1433, 1264, 1213, 1109, 992, 761, 730, 649. **Anal.** Calcd. for $C_{13}H_7D_3OS$: C, 71.85; (H+D as H), 4.70; Found: C, 71.55, H, 4.81.



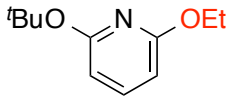
6-Trideuteriomethoxyquinoxaline (5f). Following the general procedure B, the title compound was prepared using 6-bromoquinoxaline (209.0 mg, 1.0 mmol), Pd precatalyst **3** (8.5 mg, 0.01 mmol), and **L2** (4.8 mg, 0.01 mmol) at 50 °C. After cooling to room temperature, the crude product was purified by flash chromatography using EtOAc/hexanes (1:1) as an eluent to afford 6-trideuteriomethoxyquinoxaline (**5f**) (142.2 mg, 0.87 mmol, 87%) as a brown solid. **m.p.:** 60-61 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.74 (d, J = 1.6 Hz, 1 H), 8.68 (d, J = 2.0 Hz, 1 H), 7.96 (d, J = 9.2 Hz, 1 H), 7.40 (dd, J = 9.2 Hz, J = 2.8 Hz, 1 H), 7.34 (d, J = 2.8 Hz, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 160.6, 144.8, 144.5, 142.3, 139.1, 130.3, 123.3, 106.5, 54.8 (sep, $^1J_{CD}$ = 21.8 Hz). **IR** (neat cm^{-1}) 1614, 1495, 1438, 1305, 1229, 1203, 1105, 1029, 951, 867, 825, 734. **Anal.** Calcd. for $C_9H_5D_3N_2O$: C, 66.24; (H+D as H), 5.43; Found: C, 46.22; H, 5.20.



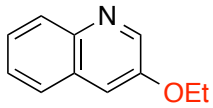
3-Trideuteriomethoxy-1-trityl-1*H*-indazole (5g). Following the general procedure B, the title compound was prepared using 3-chloro-1-trityl-1*H*-indazole (**S4**) (394.9 mg, 1.0 mmol), Pd precatalyst **3** (8.5 mg, 0.01 mmol), and **L2** (4.8 mg, 0.01 mmol) at 80 °C. After cooling to room temperature, the crude product was purified by flash chromatography using EtOAc/hexanes (1:20) as an eluent to afford 3-trideuteriomethoxy-1-trityl-1*H*-indazole (**5g**) (313.6 mg, 0.80 mmol, 80%) as an off-white solid. **m.p.:** 146-147 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.56-7.53 (m, 1 H), 7.33-7.31 (m, 6 H), 7.23-7.14 (m, 9 H), 7.92-6.87 (ovrlp, 2 H), 6.28-6.23 (m, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.0, 143.9, 143.3, 130.2, 127.5, 127.1, 126.5, 119.7, 119.6, 115.1, 114.0, 78.0, 55.3 (sep, $^1J_{CD}$ = 21.8 Hz). **IR** (neat cm^{-1}) 1528, 1491, 1437, 1408, 1264, 1183, 1091, 1031, 899, 866, 729, 698, 630. **HRMS** (ESI) Calcd. for $C_{27}H_{19}D_3N_2O$ [M+H]: 394.1993; Found: 394.1999.



(*E*)-1-Methyl-4-(2-trideuteriomethoxyvinyl)benzene (5h). Following the general procedure B, the title compound was prepared using (*E*)-1-(2-bromovinyl)-4-methylbenzene (**S3**) (197.1 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:30) as an eluent to afford (*E*)-1-methyl-4-(2-trideuteriomethoxyvinyl)benzene (**5h**) (118.5 mg, 0.88 mmol, 88%) as a pale-yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.11 (d, *J* = 8.0 Hz, 2 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 6.99 (d, *J* = 12.8 Hz, 1 H), 5.77 (d, *J* = 13.2 Hz, 1 H), 2.29 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 148.3, 135.3, 133.5, 129.4, 125.1, 105.0, 55.6 (sep, $^1J_{CD}$ = 21.8 Hz), 21.1. **IR** (neat cm^{-1}) 2920, 1703, 1639, 1515, 1208, 1168, 1083, 1004, 970, 812, 750. **HRMS** (ESI) Calcd. for $C_{10}H_9D_3O$ [M+H]: 152.1149; Found: 152.1158.

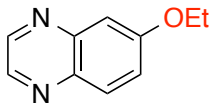


2-(*tert*-Butoxy)-6-ethoxypyridine (6a). Following the general procedure C, the title compound was prepared using 2-(*tert*-butoxy)-6-chloropyridine (173 μL, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:20) as an eluent to afford 2-(*tert*-butoxy)-6-ethoxypyridine (**6a**) (149.5 mg, 0.77 mmol, 77%) as a pale-yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38 (t, *J* = 8.0 Hz, 1 H), 6.24 (d, *J* = 8.0 Hz, 1 H), 6.20 (d, *J* = 7.6 Hz, 1 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 1.58 (s, 9 H), 1.37 (t, *J* = 7.2 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 162.7, 162.2, 140.5, 104.0, 101.4, 79.1, 61.6, 29.0, 14.8. **IR** (neat cm^{-1}) 2977, 1583, 1436, 1387, 1361, 1317, 1236, 1173, 1047, 909, 788, 729. **Anal.** Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; Found: C, 67.89; H, 8.75.

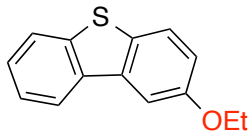


3-Ethoxyquinoline (6b).[31] Following the general procedure C, the title compound was prepared using 3-bromoquinoline (208.1 mg, 1.0 mmol) and ethanol (292 μL, 5.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:4) as an eluent to afford 3-ethoxyquinoline (**6b**) (161.0 mg, 0.93 mmol, 93%) as a pale-yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.65 (d, *J* = 2.8 Hz, 1 H), 8.03 (d, *J* = 8.4 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 6.8 Hz, 1 H), 7.44 (t, *J* = 6.8 Hz, 1 H), 7.24 (d, *J* = 2.8 Hz, 1 H), 4.03 (q, *J* = 6.8 Hz 2 H), 1.43 (t, *J* = 6.8 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 152.3, 144.7, 143.3, 129.0, 128.8, 126.9, 126.6, 126.4, 112.7, 63.7, 14.5. **IR**

(neat cm^{-1}) 2980, 1603, 1495, 1427, 1380, 1345, 1274, 1210, 1183, 1140, 1112, 1040, 986, 874, 780, 748, 723, 614. **HRMS** (ESI) Calcd. for $C_{11}H_{11}NO$ [M+H]: 174.0913; Found: 174.0904.



6-Ethoxyquinoxaline (6c).[32] Following the general procedure C, the title compound was prepared using 6-bromoquinoxaline (209.0 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:1) as an eluent to afford 6-ethoxyquinoxaline (**6c**) (144.0 mg, 0.83 mmol, 83%) as a brown solid. **m.p.:** 80-81 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.74 (d, J = 2.0 Hz, 1 H), 8.67 (d, J = 2.0 Hz, 1 H), 7.96 (d, J = 9.2 Hz, 1 H), 7.40 (dd, J = 9.2 Hz, J = 2.8 Hz, 1 H), 7.33 (d, J = 2.4 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 1.50 (t, J = 7.2 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 160.0, 144.8, 144.6, 142.2, 139.1, 130.3, 123.6, 107.1, 64.0, 14.5. **IR** (neat cm^{-1}) 1616, 1501, 1303, 1265, 1221, 1200, 1120, 1029, 948, 868, 821, 732. **Anal.** Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; Found: C, 68.66; H, 5.96.



2-Ethoxydibenzothiophene (6d). Following the general procedure C, the title compound was prepared using 2-bromodibenzothiophene (263.2 mg, 1.0 mmol). After work up, the crude product was purified by flash chromatography using EtOAc/hexanes (1:30) as an eluent to afford 2-ethoxydibenzothiophene (**6d**) (201.3 mg, 0.88 mmol, 88%) as a viscous, pale-yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.01-7.96 (m, 1 H), 7.77-7.72 (m, 1 H), 7.61 (d, J = 8.8 Hz, 1 H), 7.52 (d, J = 2.4 Hz, 1 H), 7.37-7.31 (ovrlp, 2 H), 6.99 (dd, J = 8.8 Hz, J = 2.4 Hz, 1 H), 4.01 (q, J = 6.8 Hz, 2 H), 1.39 (t, J = 6.8 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.0, 140.6, 136.6, 135.5, 131.2, 126.6, 124.1, 123.4, 122.9, 121.5, 116.2, 105.8, 63.9, 15.0. **IR** (neat cm^{-1}) 1604, 1466, 1428, 1393, 1265, 1203, 1113, 1044, 933, 808, 760, 730, 680, 612. **Anal.** Calcd. for $C_{14}H_{12}OS$: C, 73.65; H, 5.30; Found: C, 73.39; H, 5.45.

Additional Results for the Palladium-Catalyzed Arylation of Alcohols (Scheme S1). An oven-dried 10 mL re-sealable screw-cap test tube (**A**) equipped with a Teflon-coated magnetic stir bar was charged with ^{t}BuBrettPhos (**L2**) (1.2 mg, 0.0025 mmol, 1.0 mol %, or 2.4 mg, 0.0050 mmol, 2.0 mol %), sodium *tert*-butoxide (33.6 mg, 0.35 mmol, 1.4 equiv) (or cesium carbonate (122.2 mg, 0.375 mmol, 1.5 equiv)), and (hetero)aryl halides (if solid) (0.25 mmol, 1.0 equiv). Tube **A** was evacuated and backfilled with argon (this sequence was repeated a total of three times), and alcohols (methanol: 51 μL, 1.25 mmol, 5.0 equiv; ethanol: 29 μL, 0.5 mmol, 2.0 equiv) and (hetero)aryl halides (if liquid) (0.25 mmol, 1.0 equiv) were then added into tube **A** via syringe. Simultaneously, an oven-dried 10 mL re-sealable screw-cap test tube (**B**) equipped with a Teflon-coated magnetic stir bar was charged with Pd precatalyst **3** (2.1 mg, 0.0025 mmol, 1.0 mol %, or 4.3 mg, 0.0050 mmol, 2.0 mol %). Tube **B** was then evacuated and backfilled with argon (this sequence was repeated a total of three times), and 1,4-dioxane (0.50 mL) was added into tube **B** via syringe. The reaction mixture in tube **B** was stirred at room temperature for ~1 min to form a homogeneous solution. The precatalyst solution from tube **B** was transferred into tube **A** via syringe. The reaction mixture in tube **A** was stirred at 50 °C in an oil bath or at room temperature for

20 h. After cooling to room temperature, ethyl acetate (~4 mL) and 1,3,5-trimethoxybenzene (14.0 mg, 0.0083 mmol) were added into the resulting reaction mixture. A fraction of reaction mixture was concentrated *in vacuo* with the aid of a rotary evaporator to give a crude product. The yield of ether product was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene (14.0 mg, 0.083 mmol, 0.33 equiv) as internal standard.

Control Experiments for Palladium-Catalyzed Arylation of Alcohols (Scheme S2).
An oven-dried 10 mL re-sealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with ^{t}BuBrettPhos (**L2**) (2.4 mg, 0.0050 mmol, 2.0 mol %, or 4.8 mg, 0.010 mmol, 4.0 mol %), sodium *tert*-butoxide (33.6 mg, 0.35 mmol, 1.4 equiv) (or cesium carbonate (122.2 mg, 0.375 mmol, 1.5 equiv)), and (hetero)aryl halides (if solid) (0.25 mmol, 1.0 equiv). The tube was evacuated and backfilled with argon (this sequence was repeated a total of three times), and alcohols (methanol: 51 μL, 1.25 mmol, 5.0 equiv; ethanol: 29 μL, 0.5 mmol, 2.0 equiv), 1,4-dioxane (0.50 mL), and (hetero)aryl halides (if liquid) (0.25 mmol, 1.0 equiv) were then added into the tube via syringe. The reaction mixture was stirred at elevated temperatures in an oil bath or at room temperature for 20 h. After cooling to room temperature, ethyl acetate (~4 mL) was added into the reaction mixture, and a portion of the reaction mixture was analyzed for the existence of the ether product by (i) GC-MS analysis, or (ii) ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene (14.0 mg, 0.083 mmol, 0.33 equiv) as internal standard.

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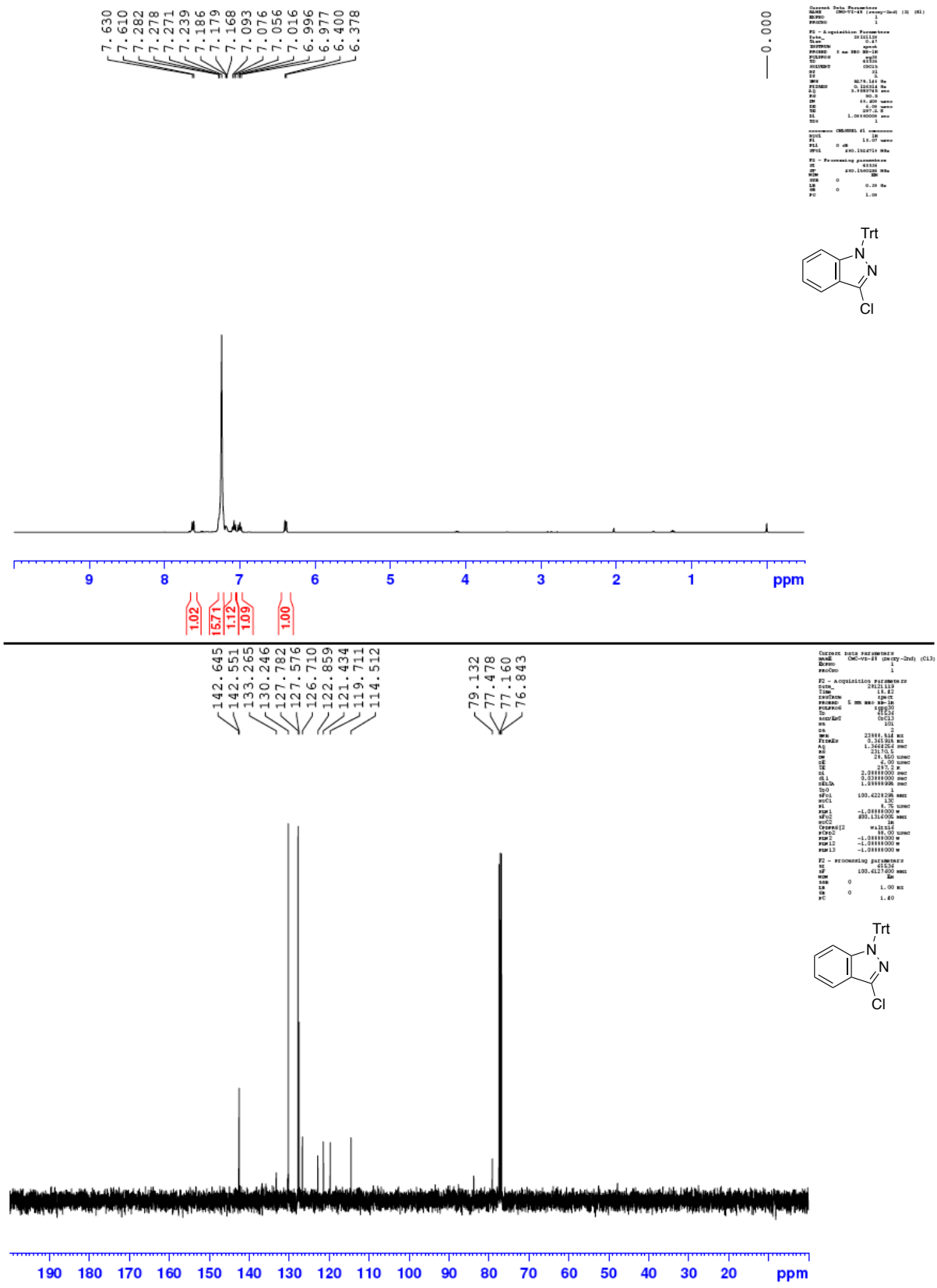
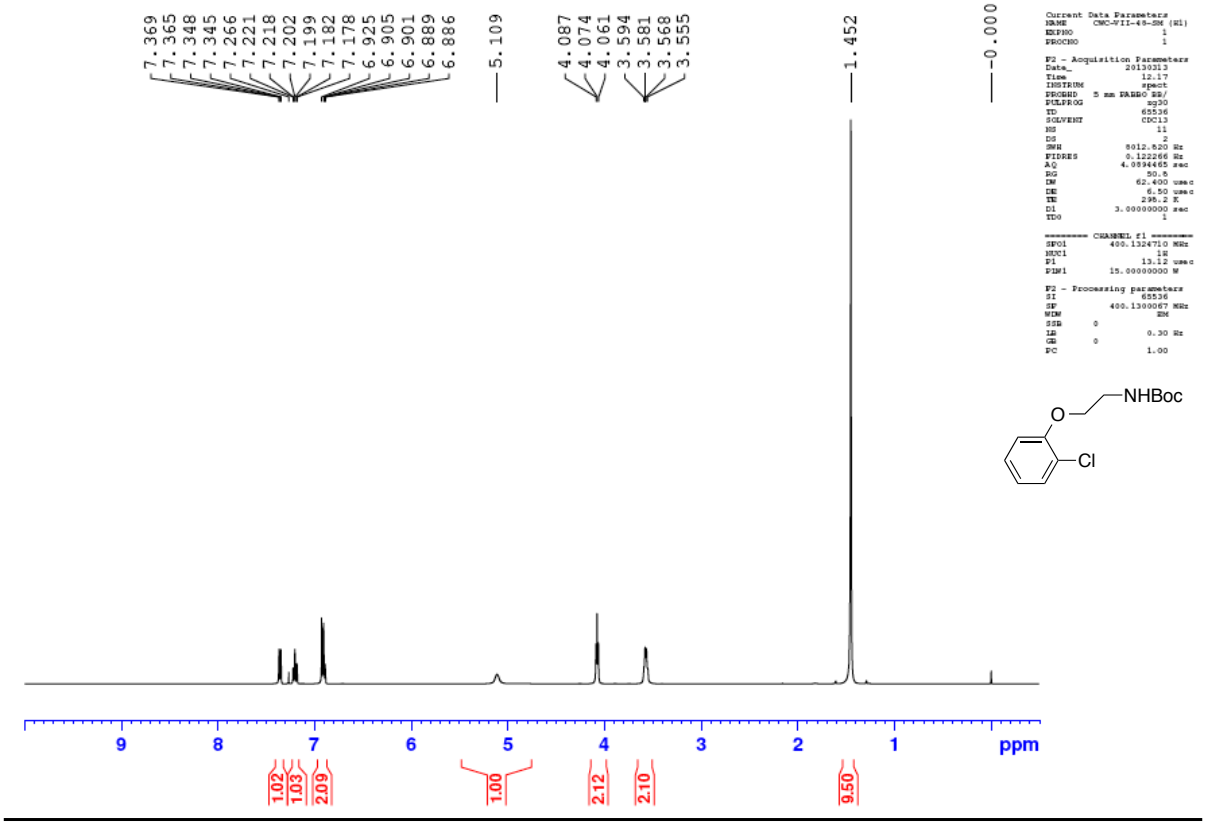
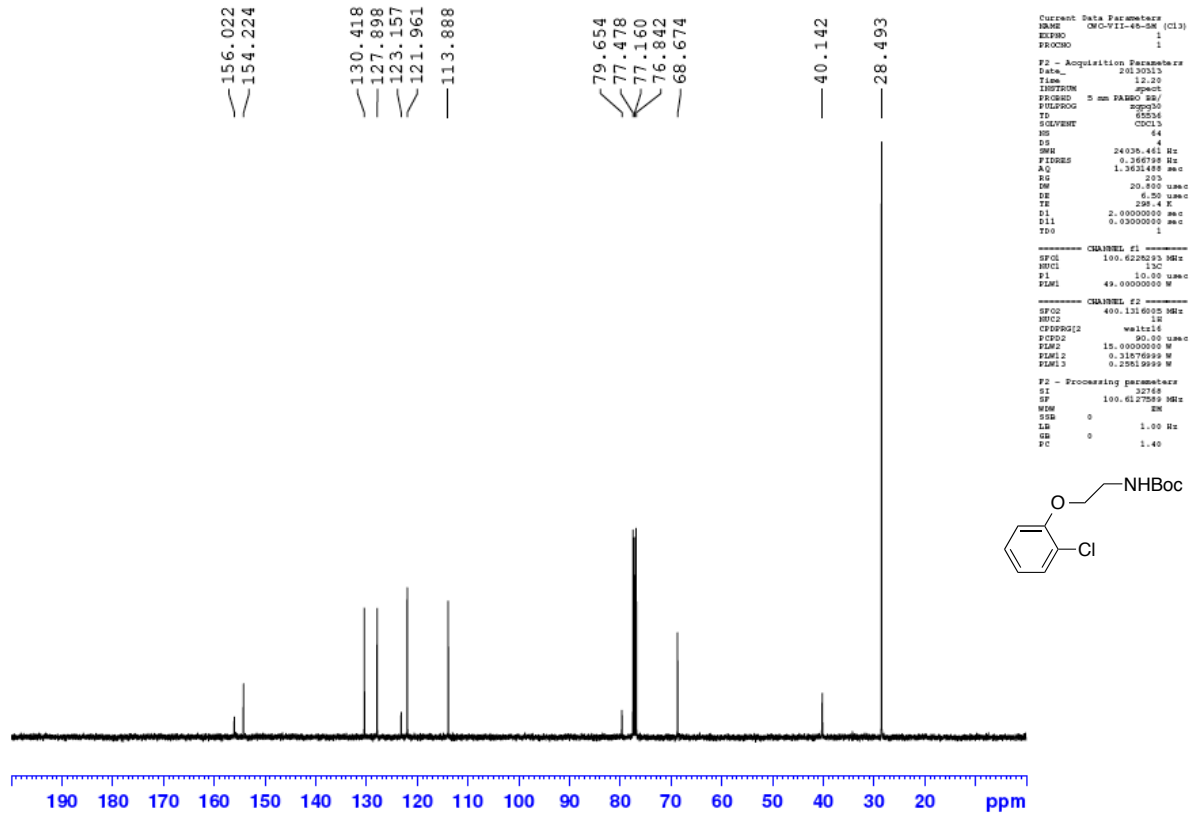
List of Spectra of Compounds

^{1}H and ^{13}C NMR of 3-chloro-1-trityl-1*H*-indazole (S4)

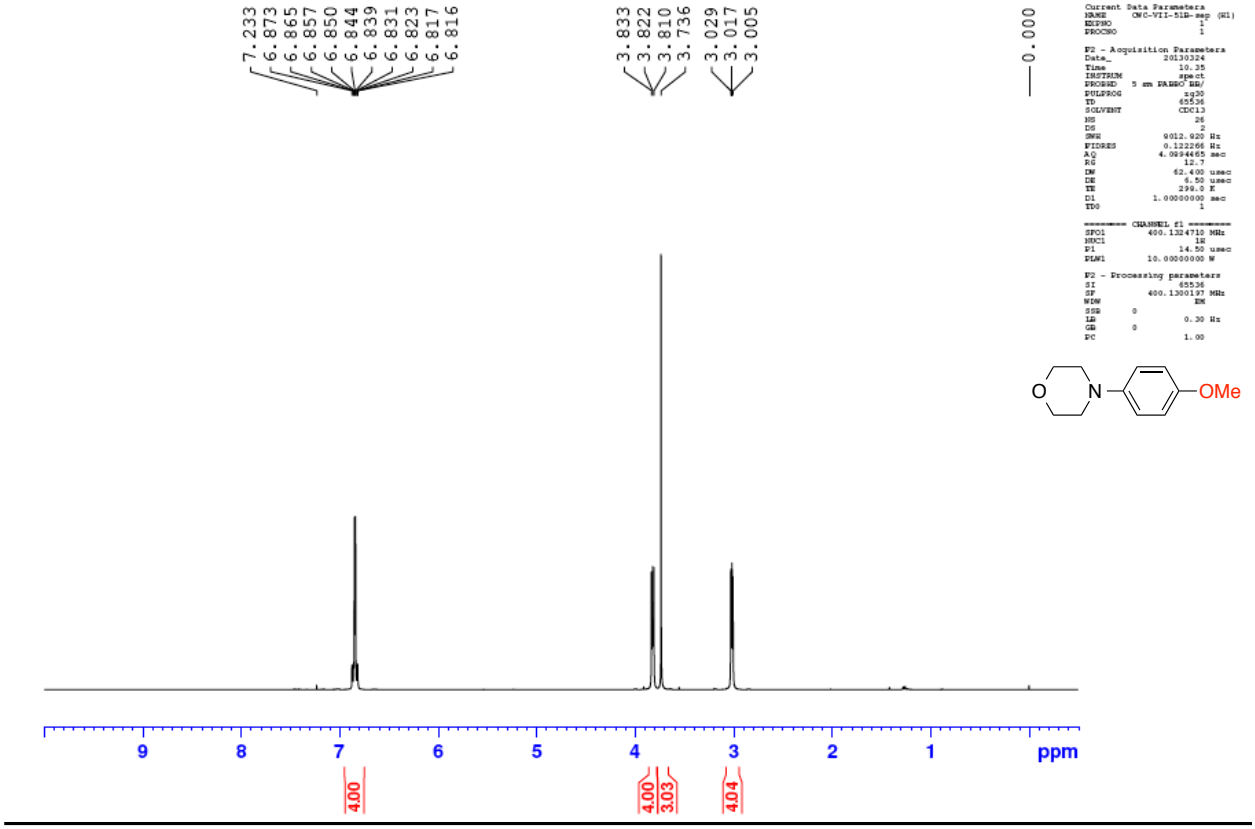


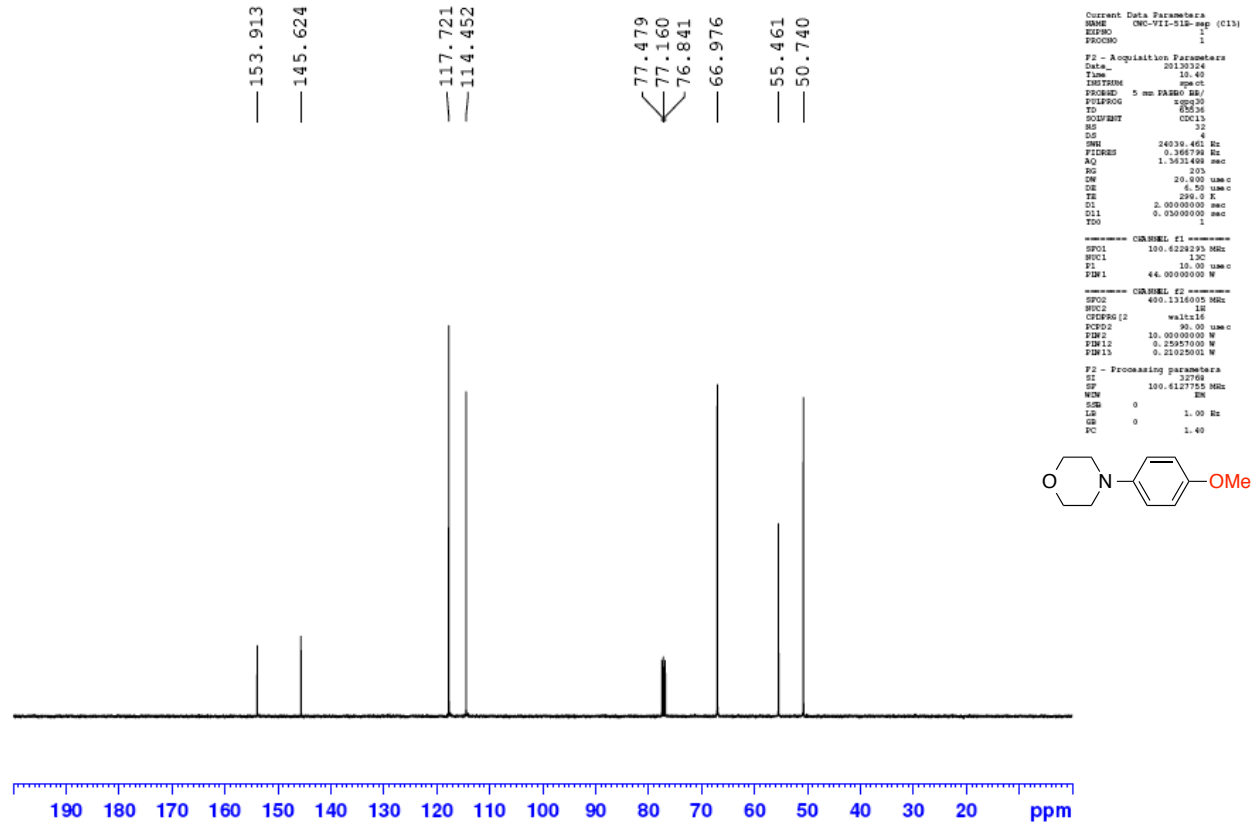
^{1}H and ^{13}C NMR of *tert*-butyl (2-(2-chlorophenoxy)ethyl)carbamate (S5)





^{1}H and ^{13}C NMR of 4-(4-methoxyphenyl)morpholine (4a)





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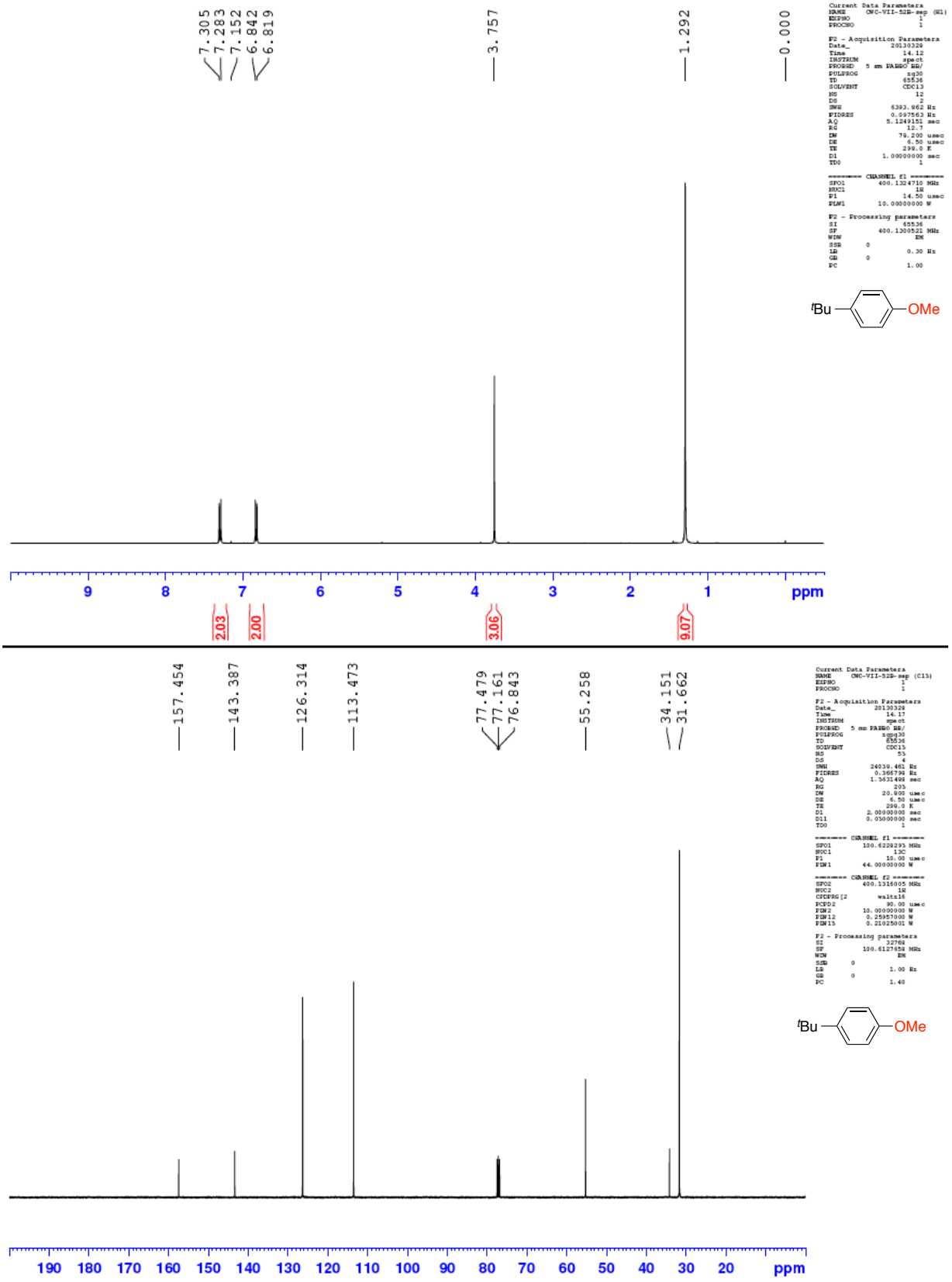
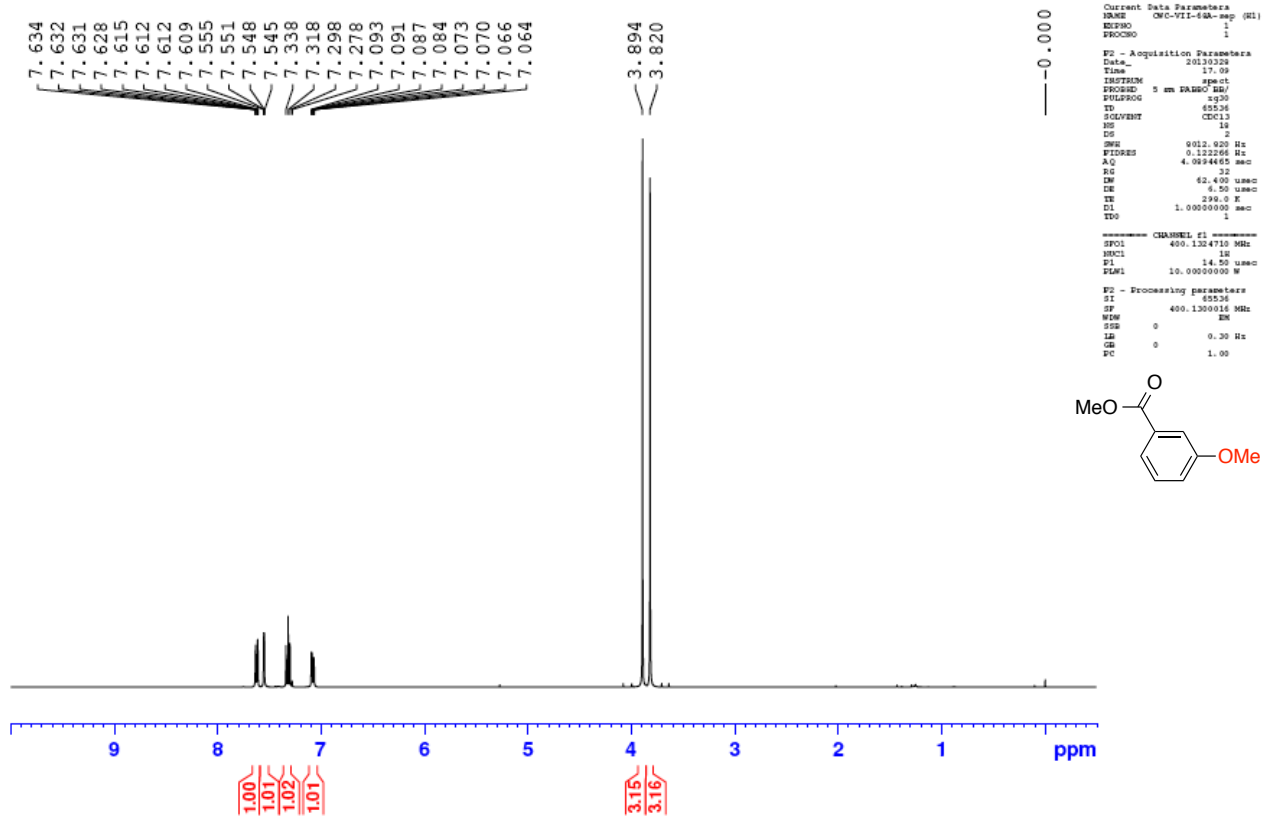
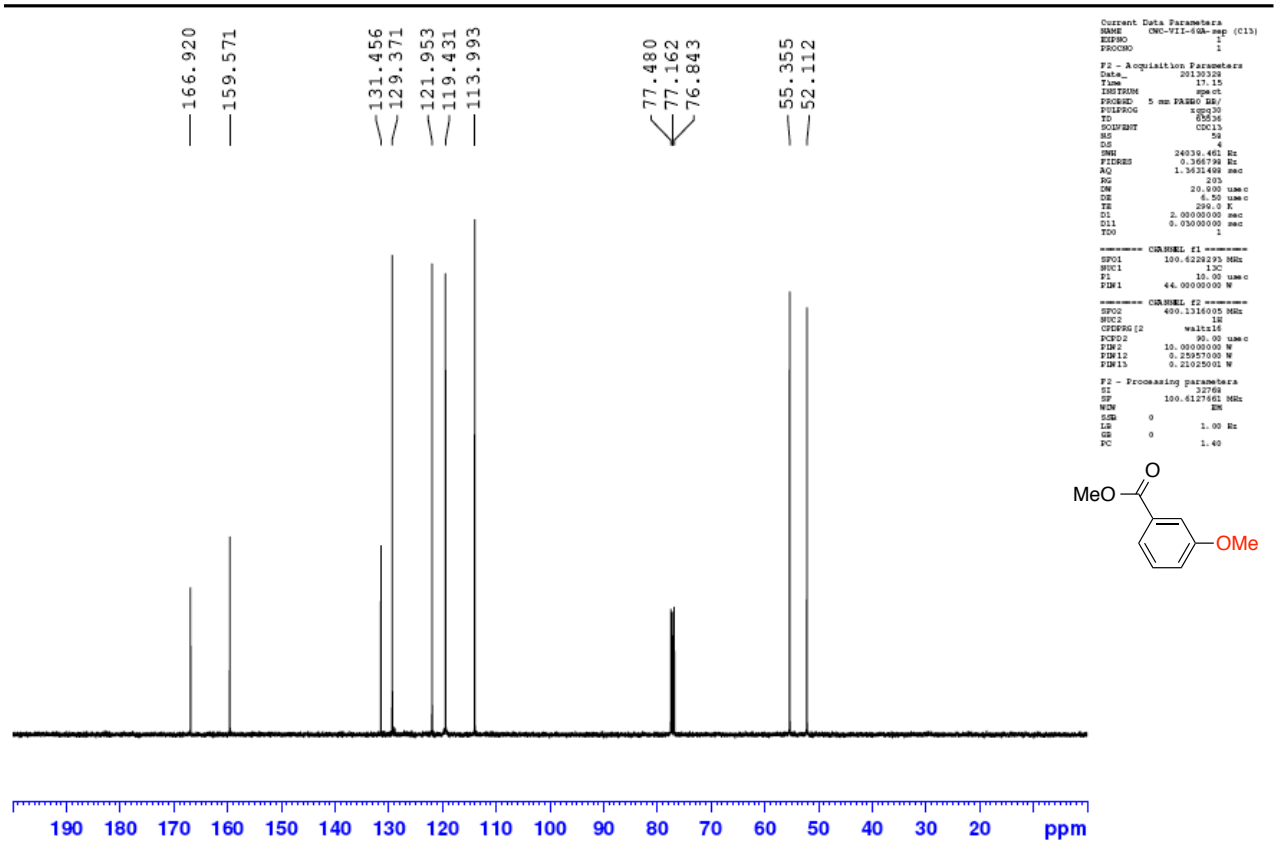
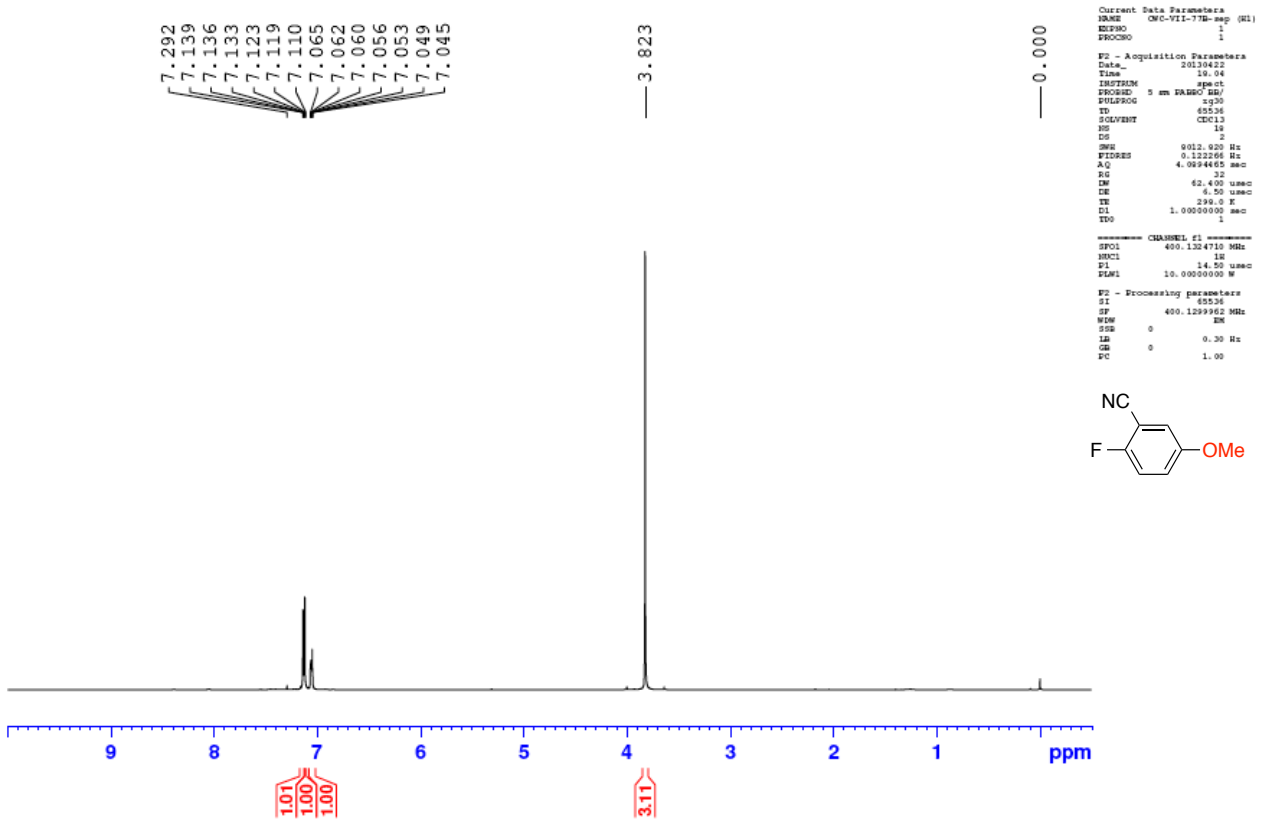


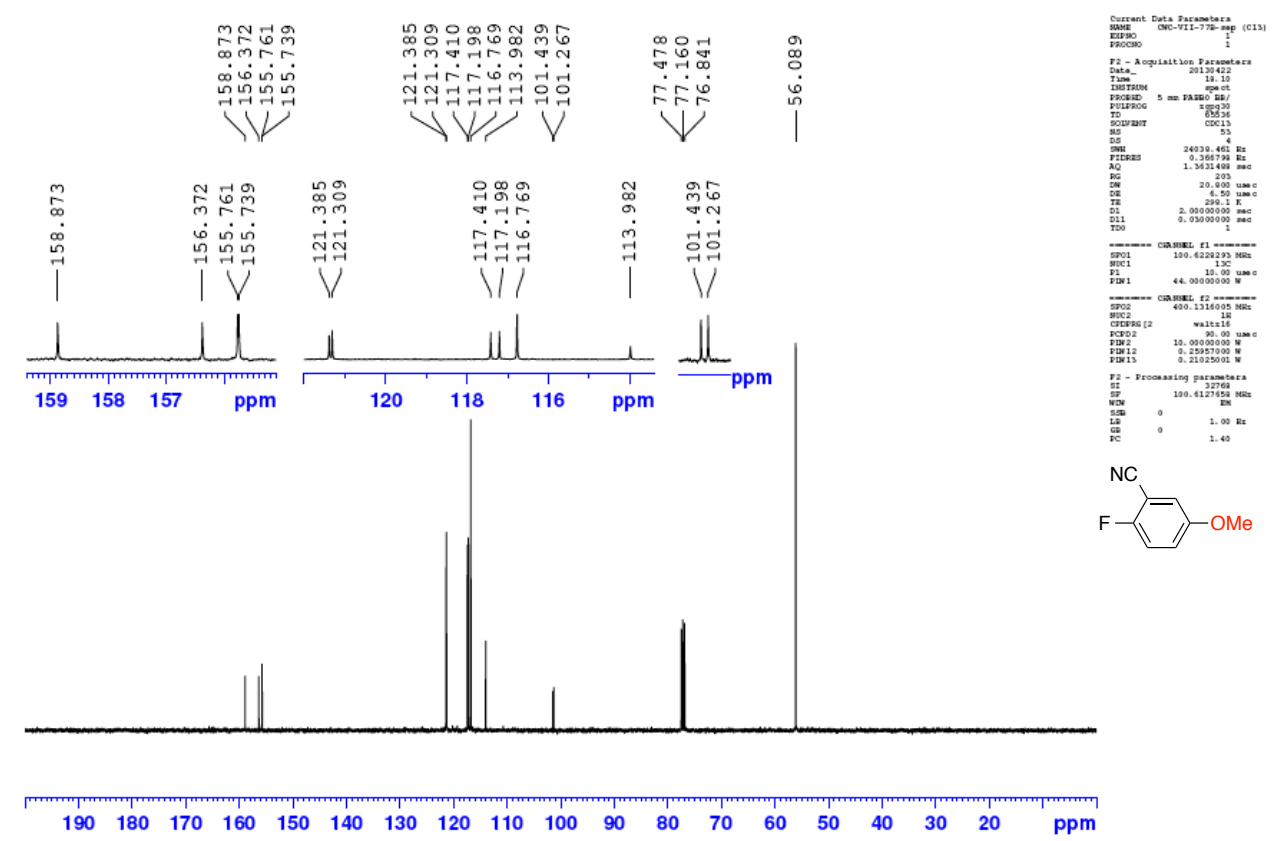
^{1}H and ^{13}C NMR of methyl 3-methoxybenzoate (4c)





^{1}H and ^{13}C NMR of 2-fluoro-5-methoxybenzonitrile (4d)





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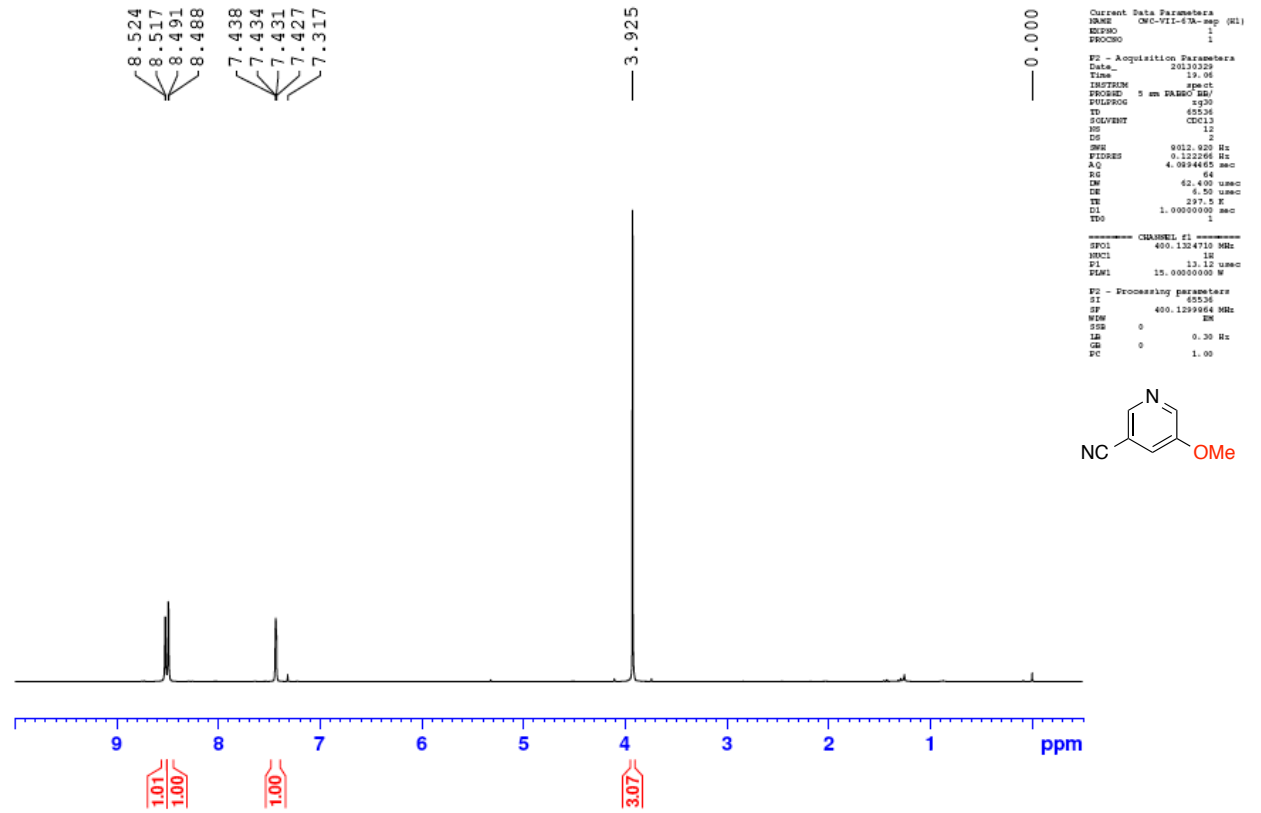

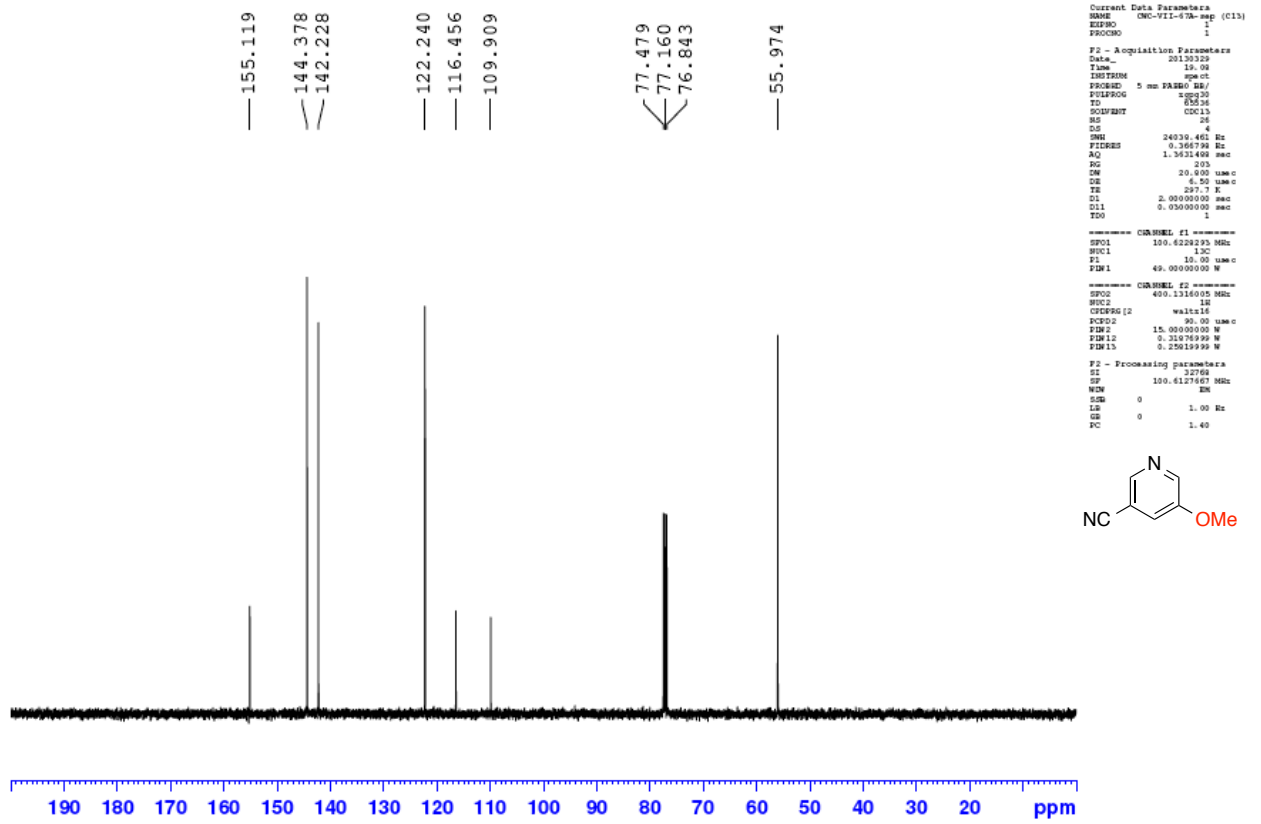

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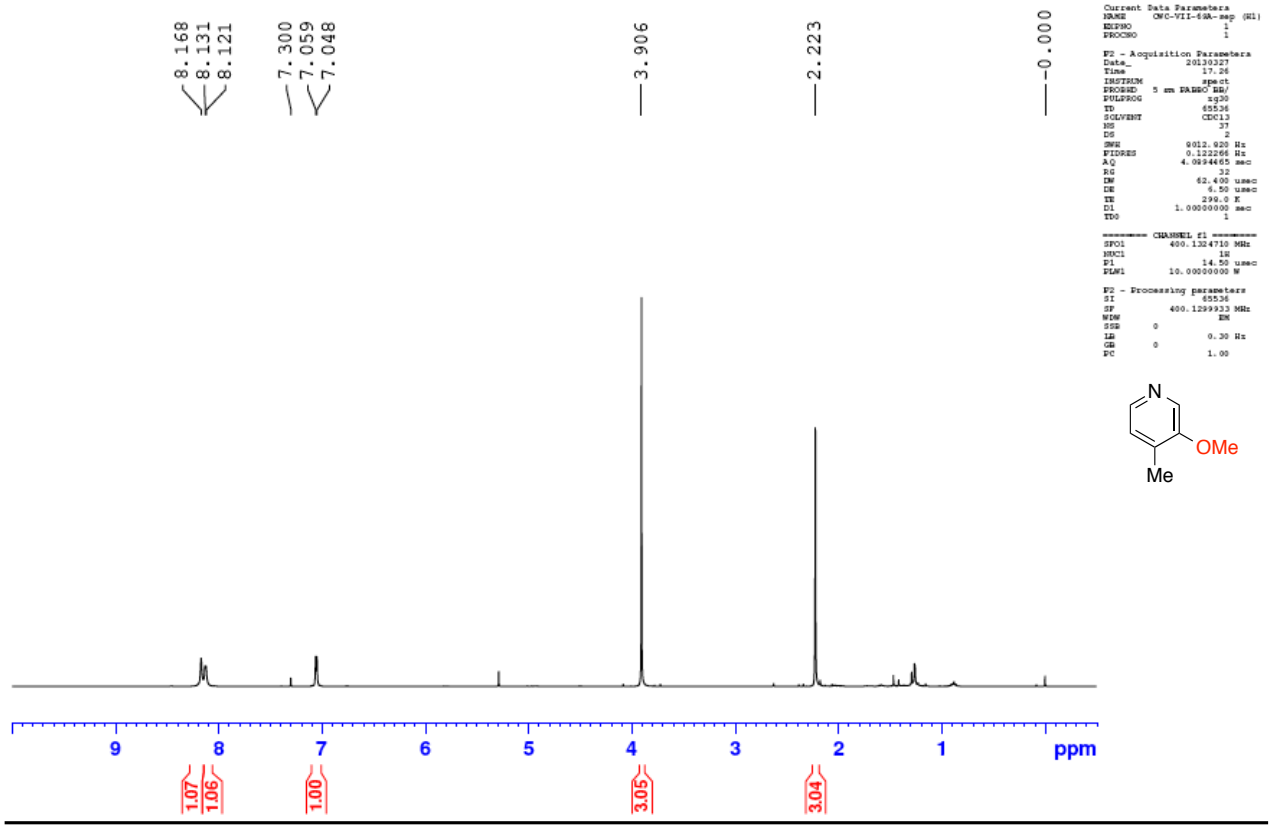

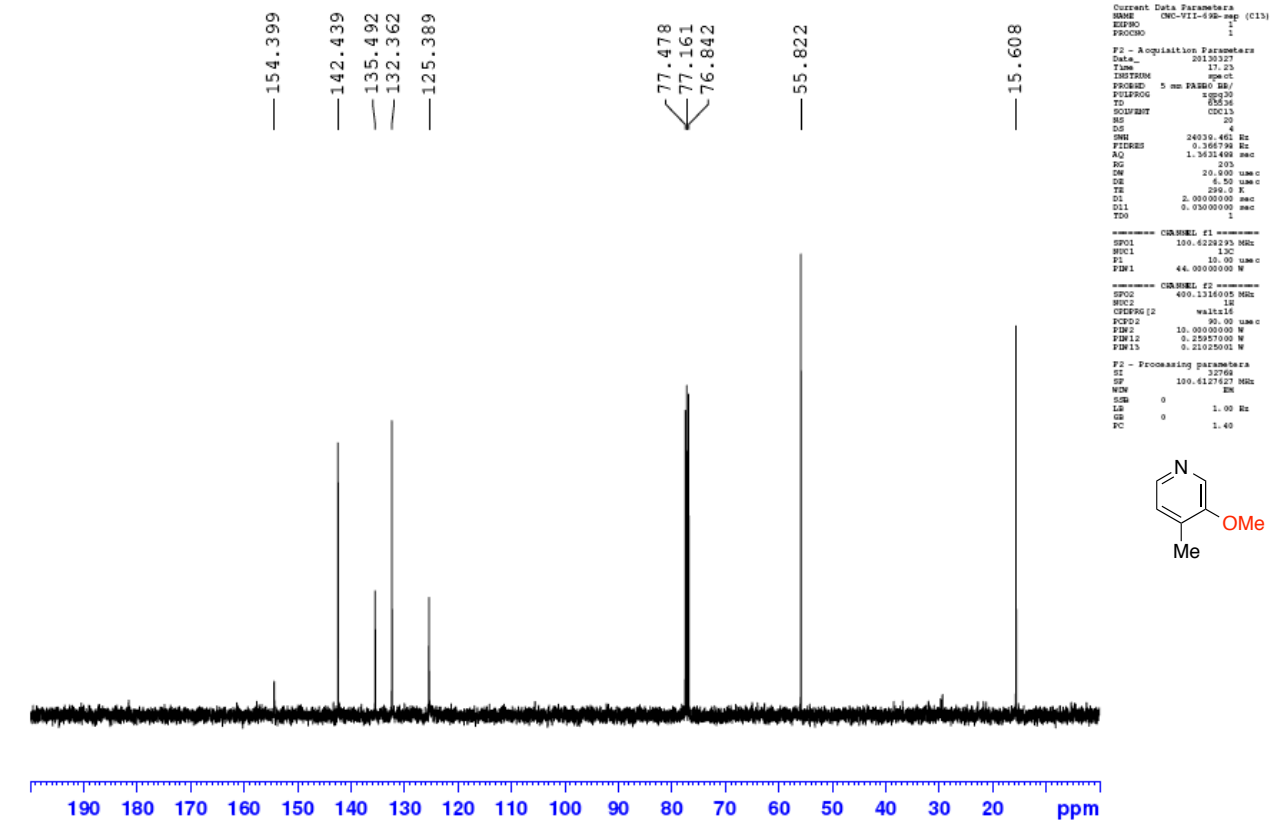

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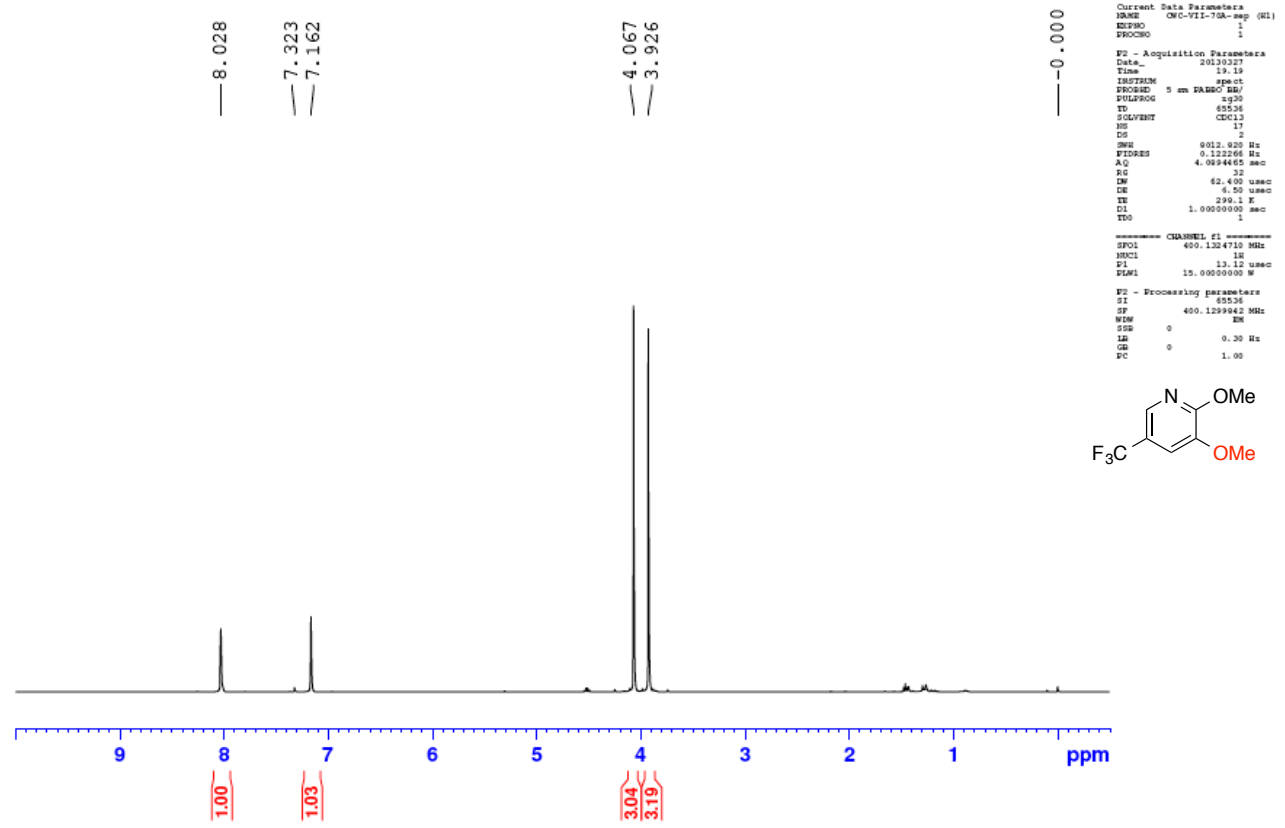
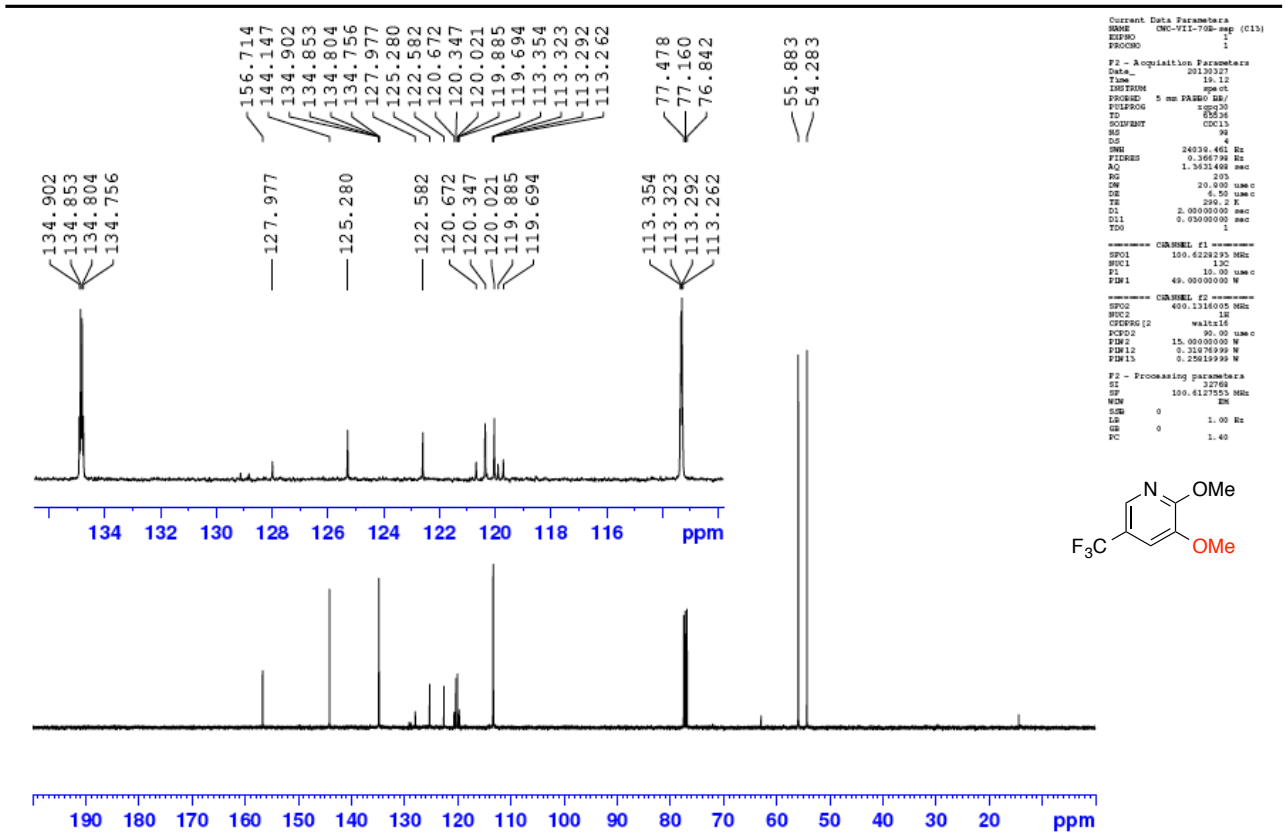
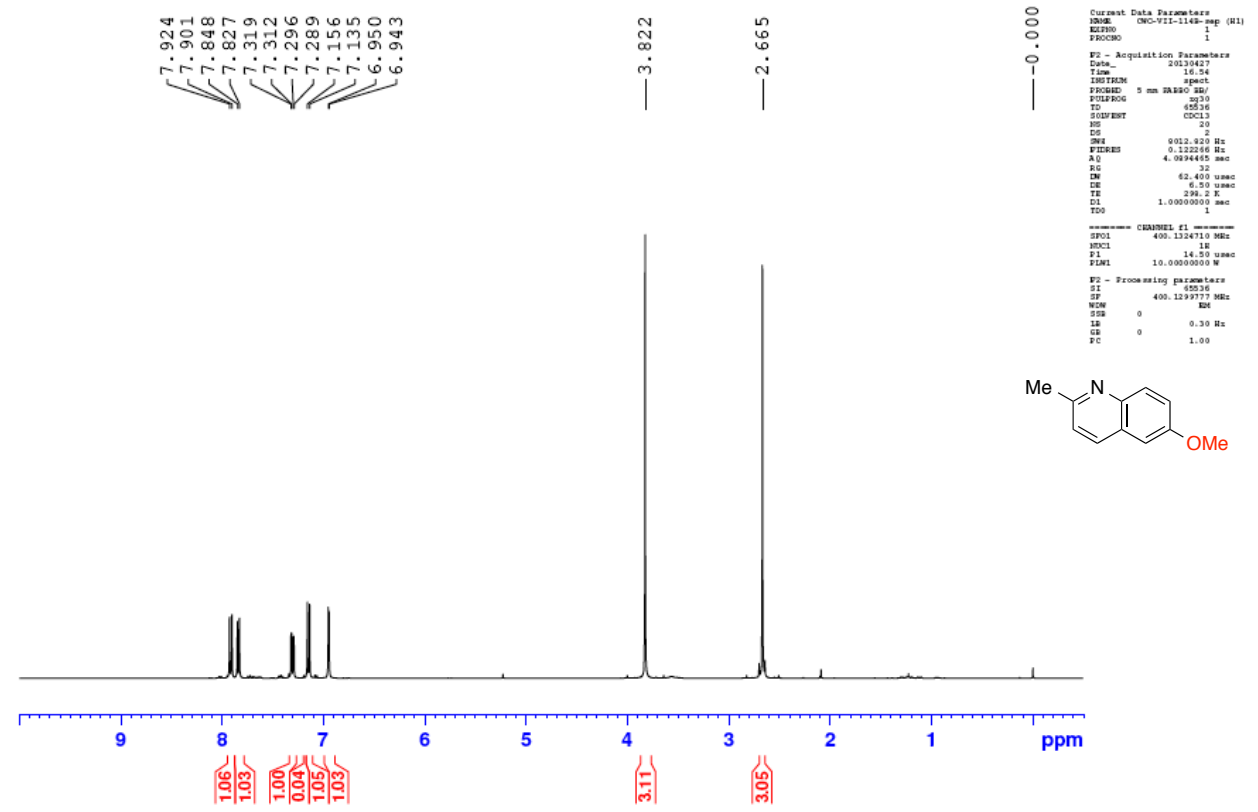
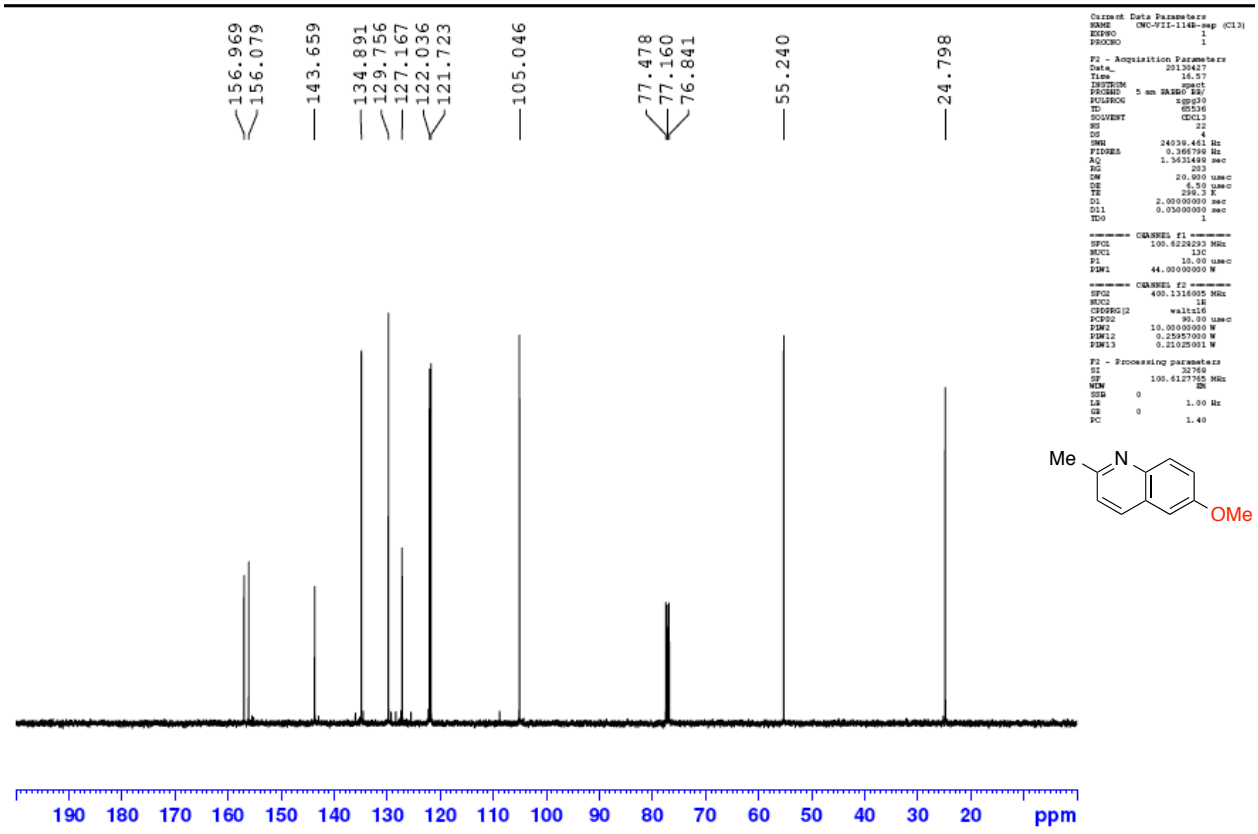


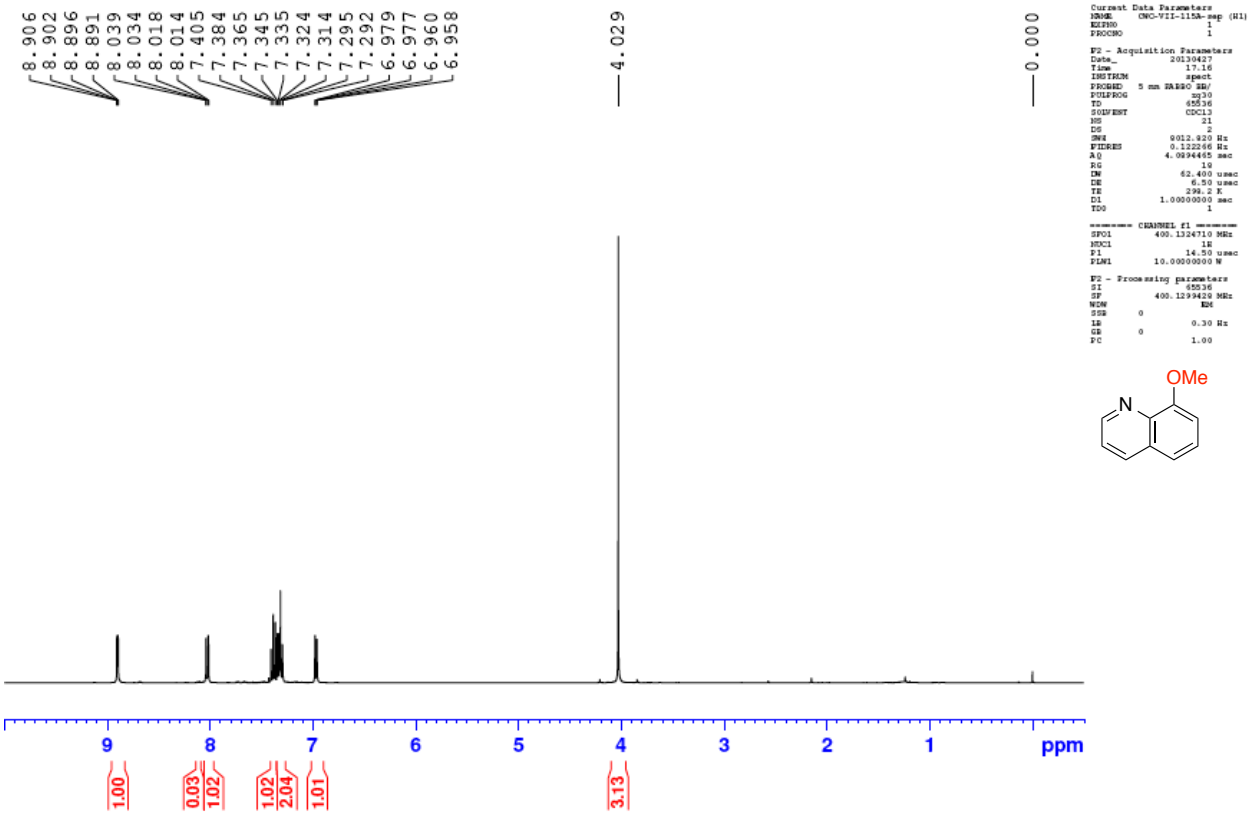


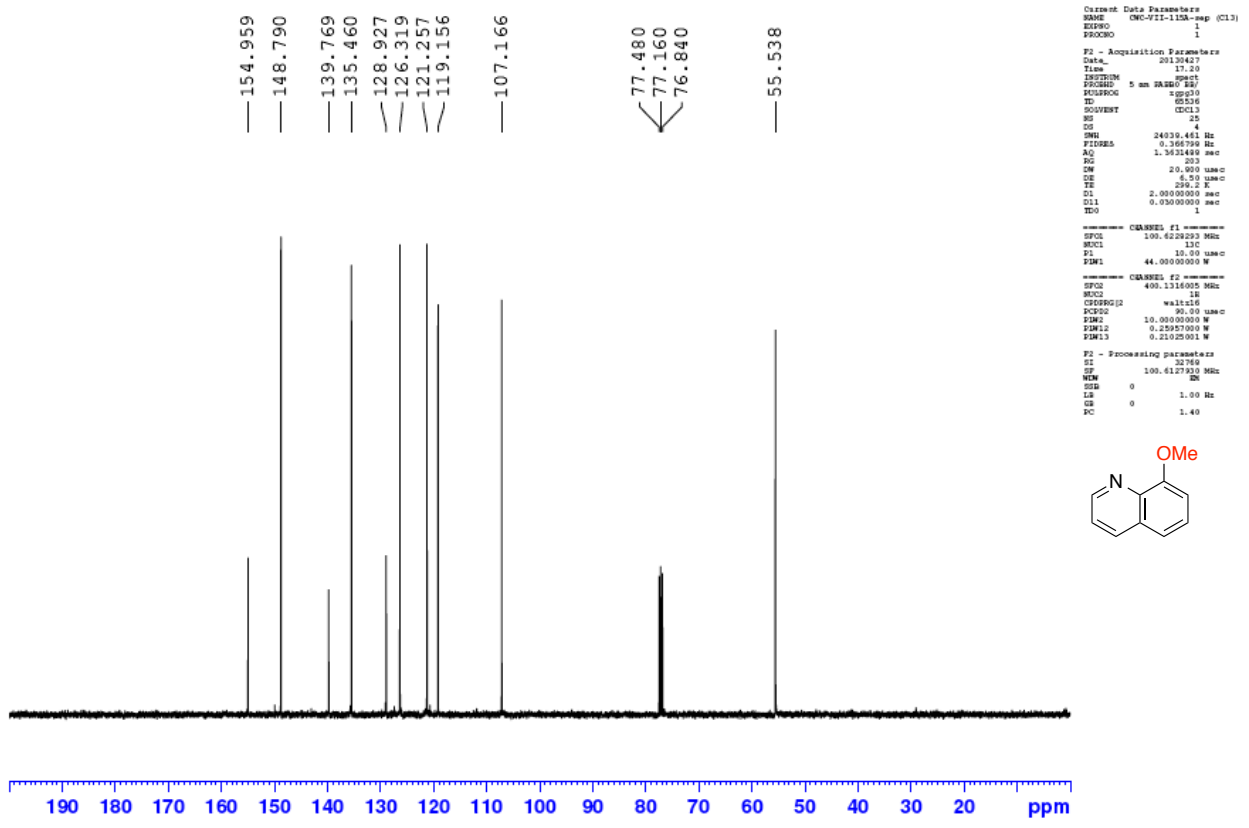
^{1}H and ^{13}C NMR of 6-methoxy-2-methylquinoline (4h)



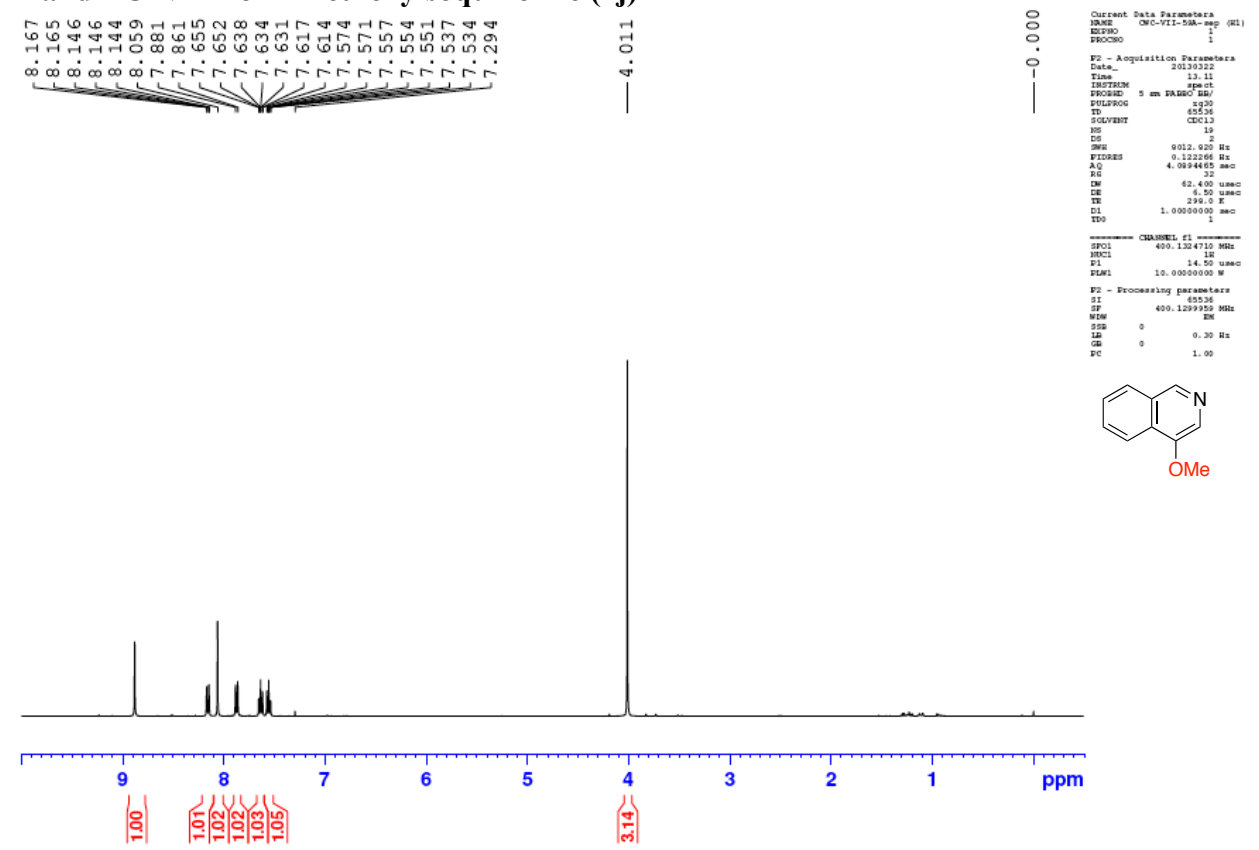


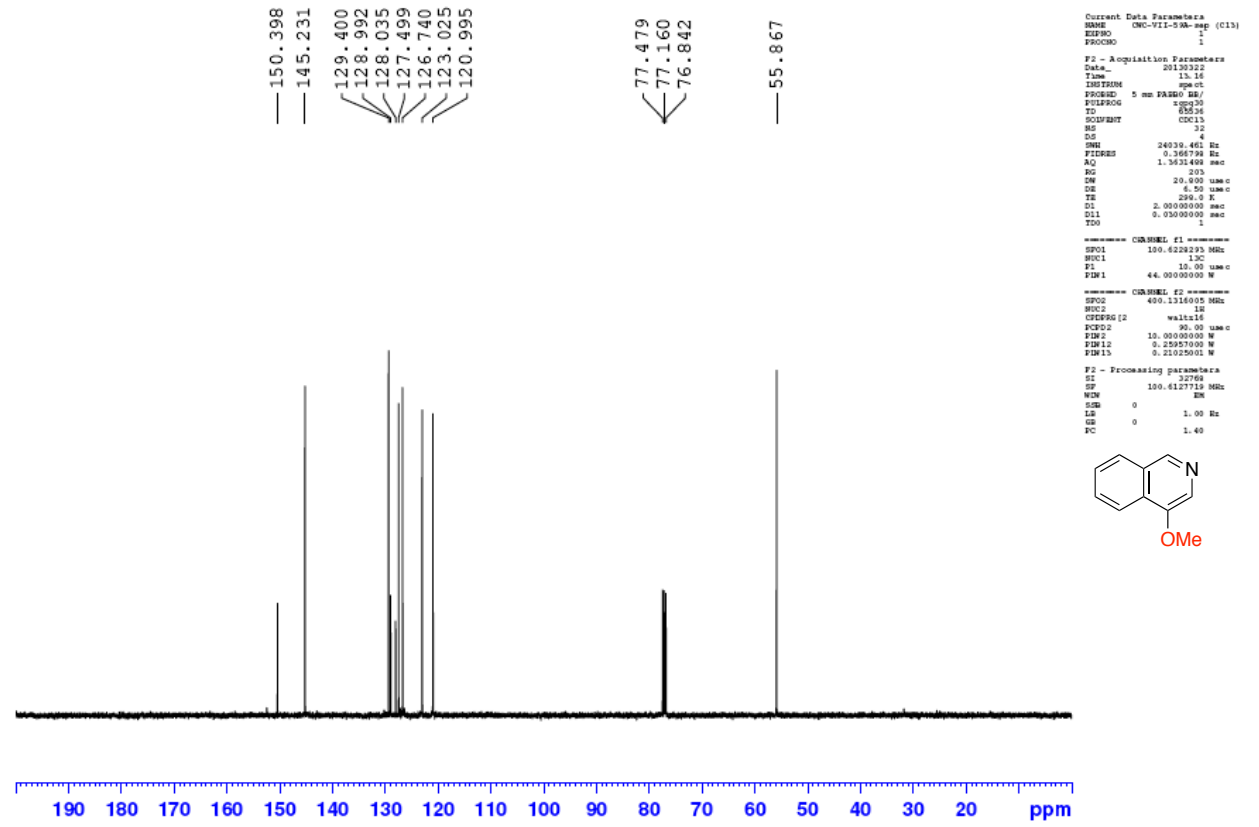
^{1}H and ^{13}C NMR of 8-methoxyquinoline (4i)



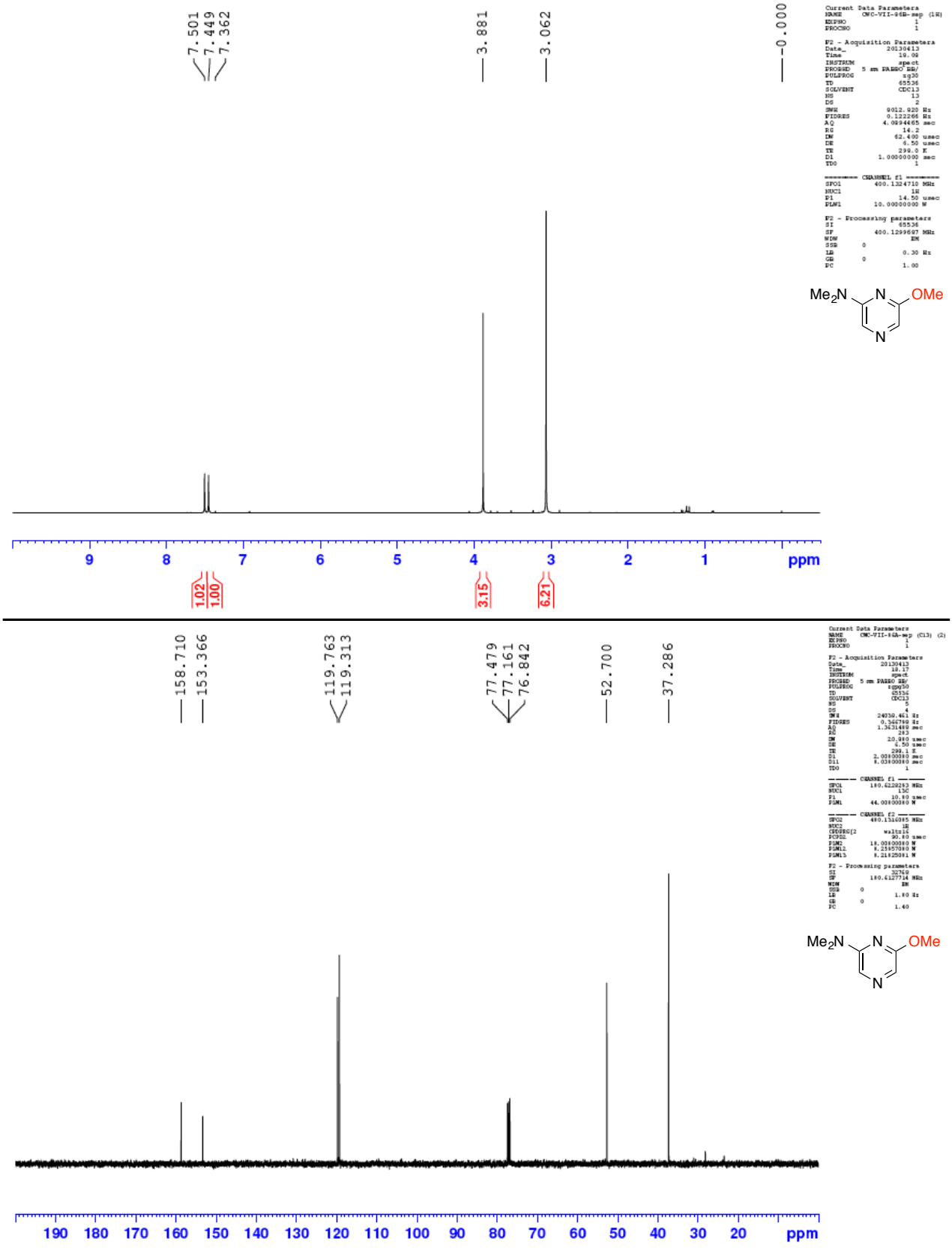


^{1}H and ^{13}C NMR of 4-methoxyisoquinoline (4j)

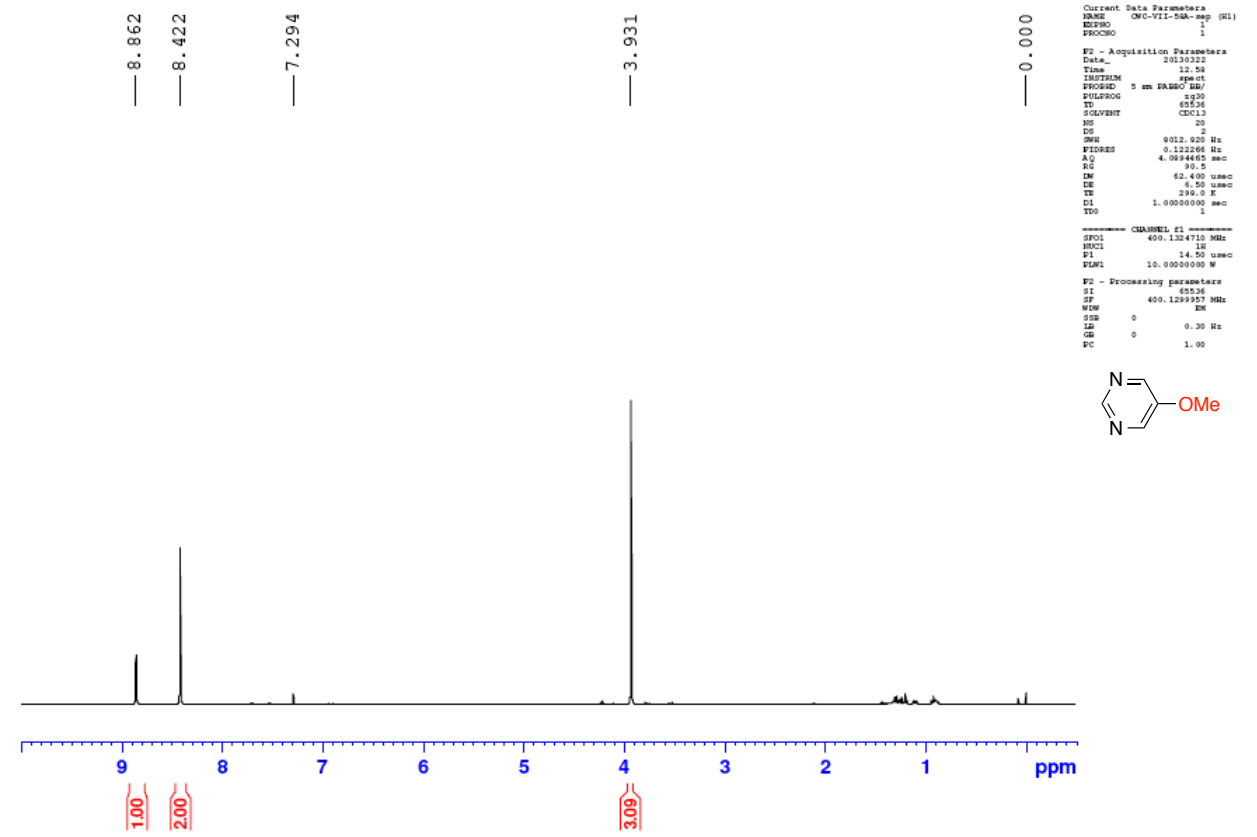


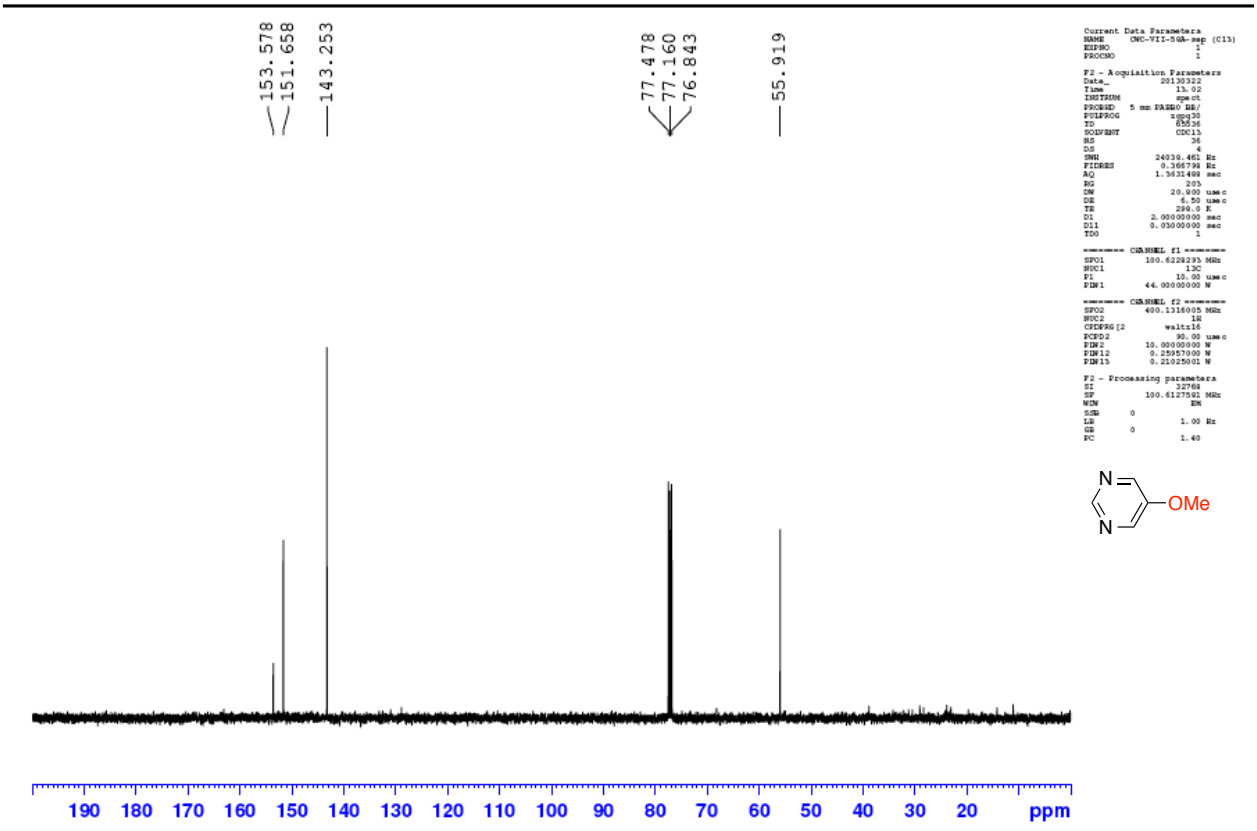


^{1}H and ^{13}C NMR of 2-methoxy-6-dimethylaminopyrazine (4k)

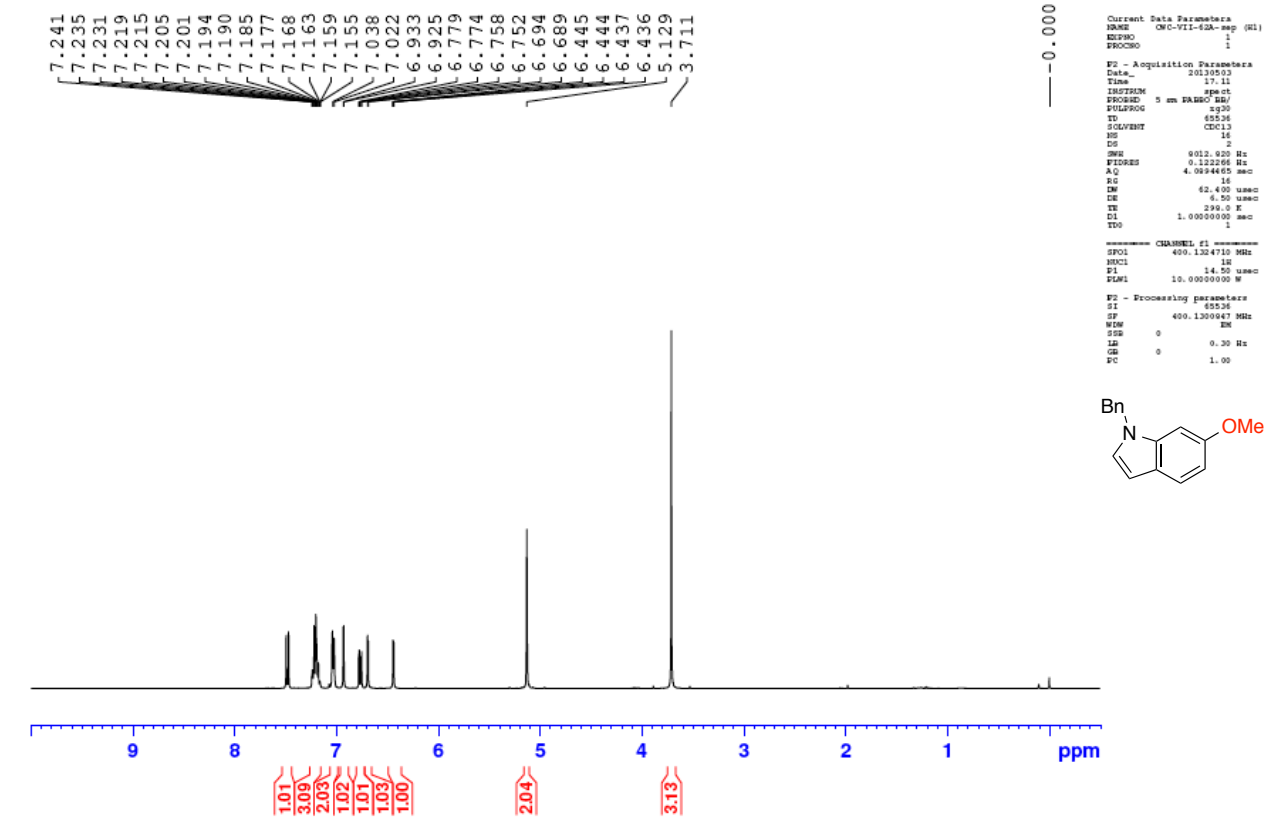


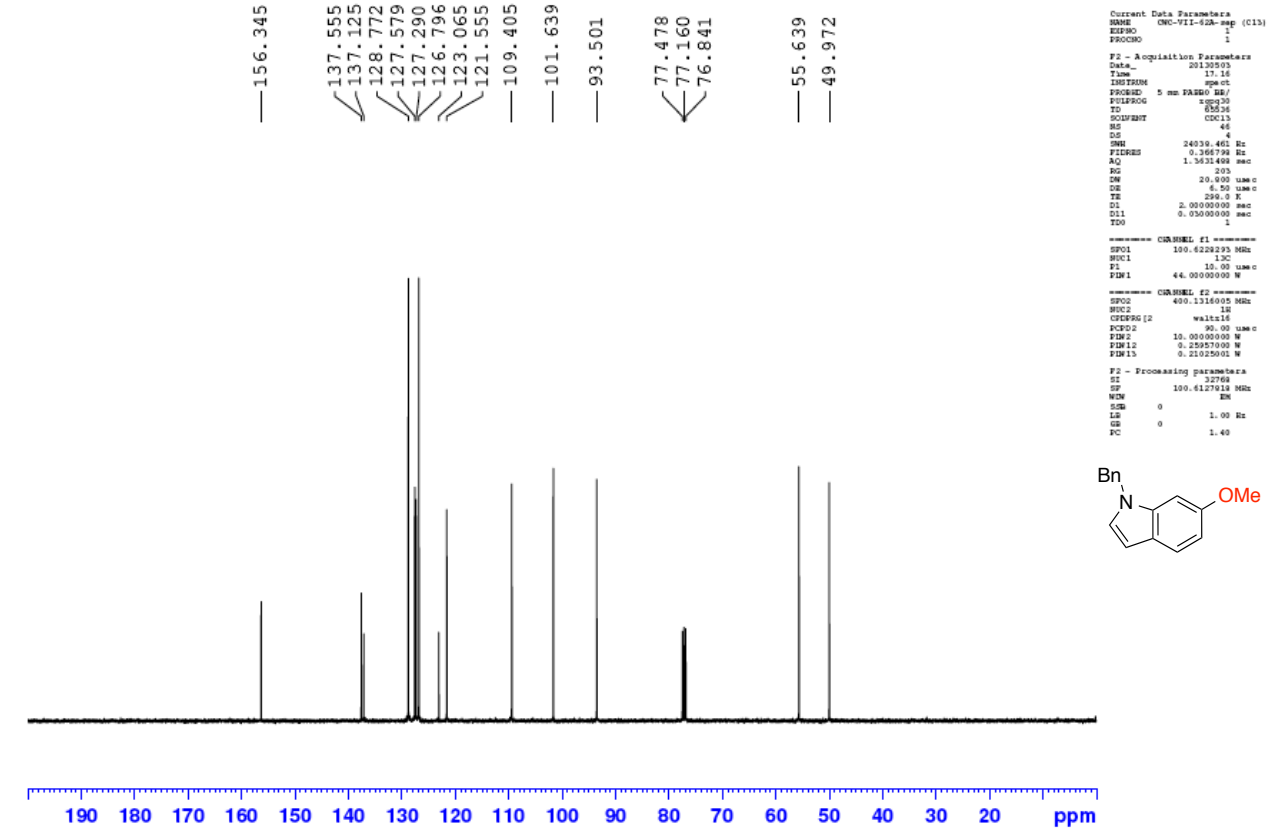
^{1}H and ^{13}C NMR of 5-methoxypyrimidine (4l)



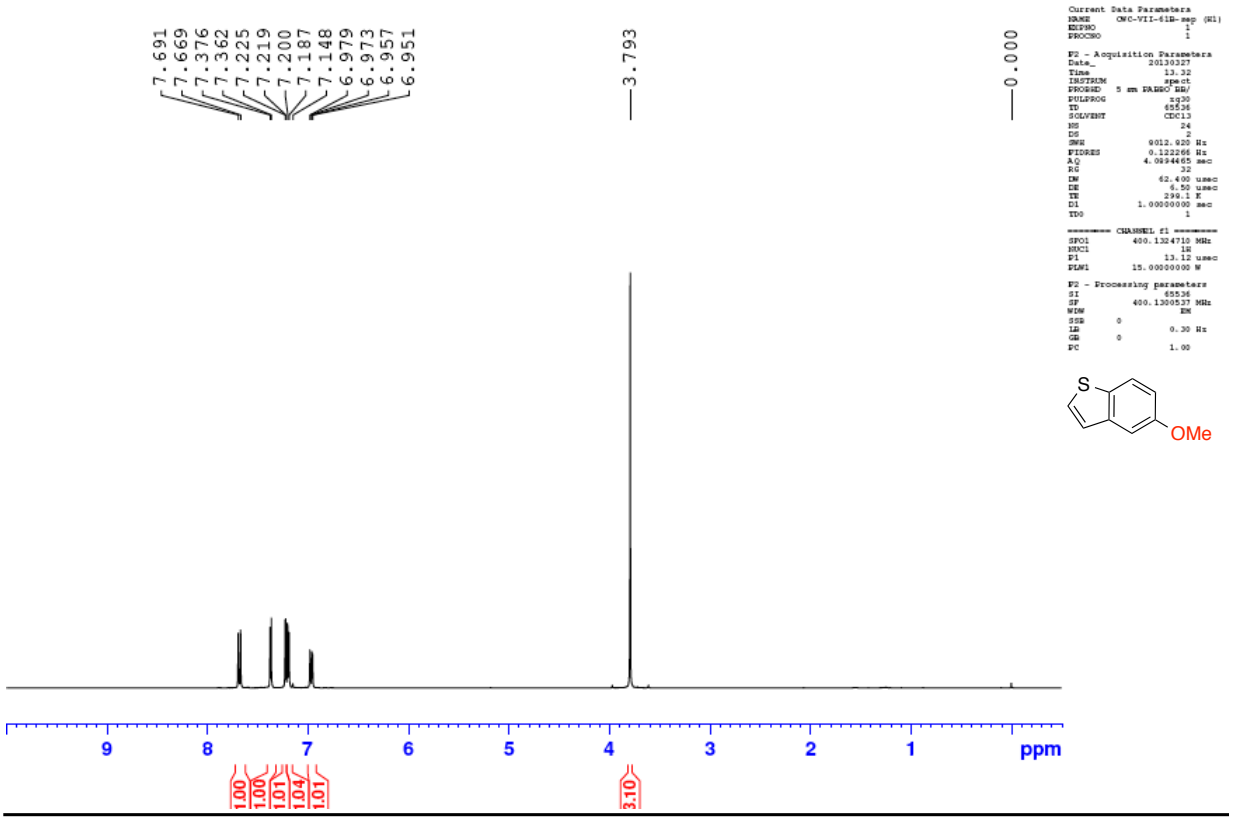


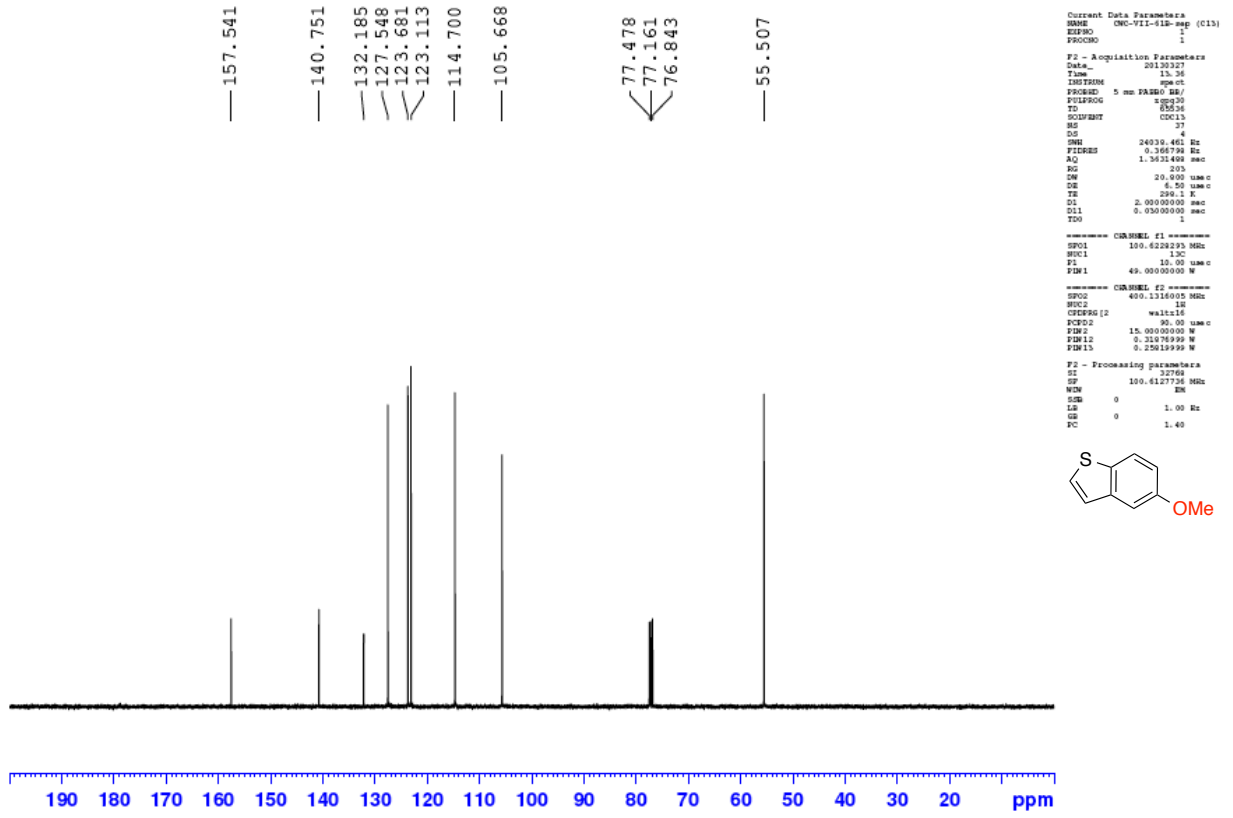
^{1}H and ^{13}C NMR of 1-benzyl-6-methoxy-1*H*-indole (4m)



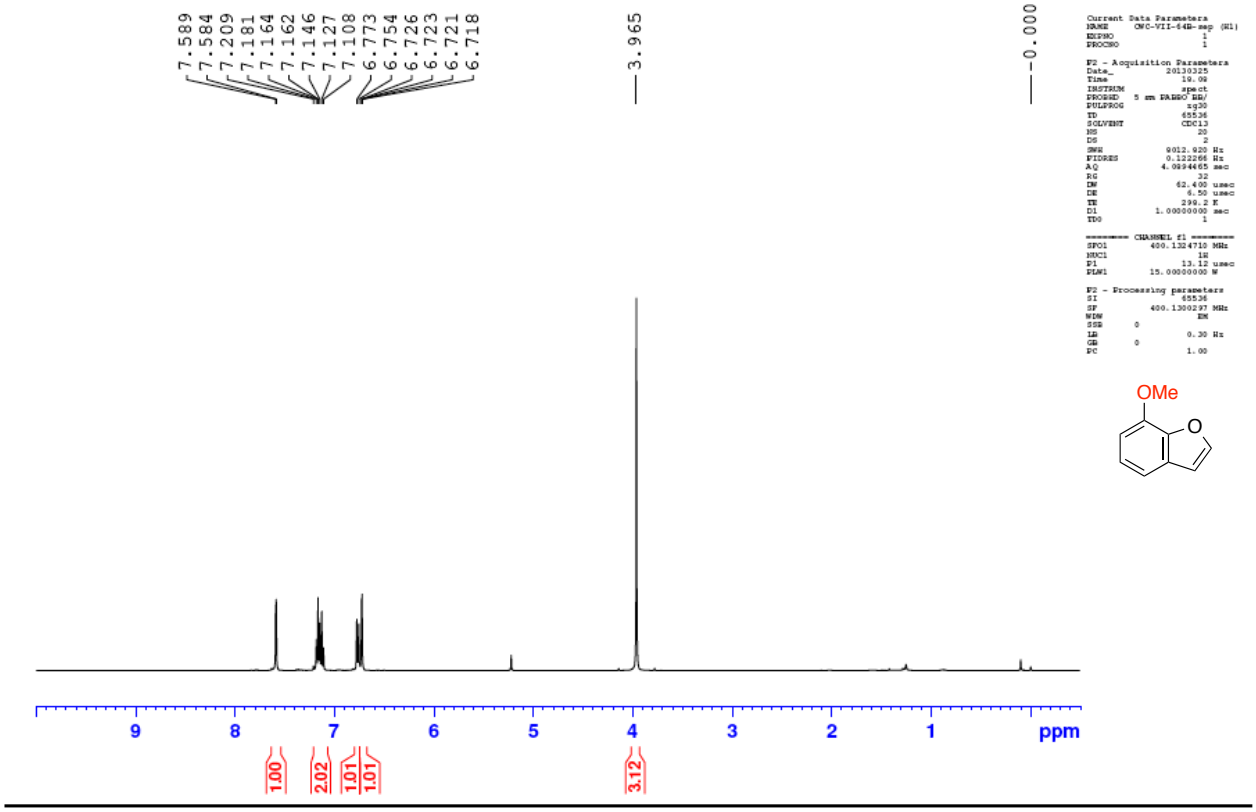


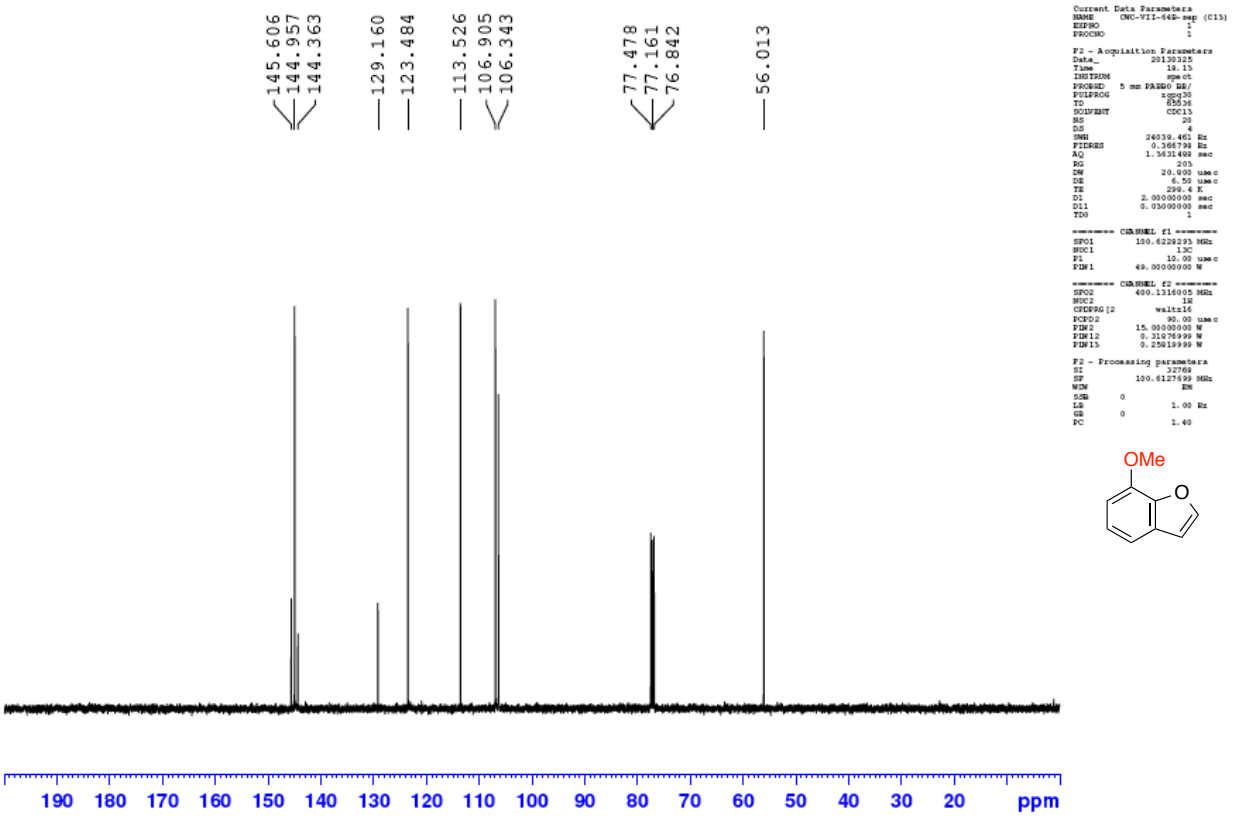
^{1}H and ^{13}C NMR of 5-methoxybenzothiophene (4n)



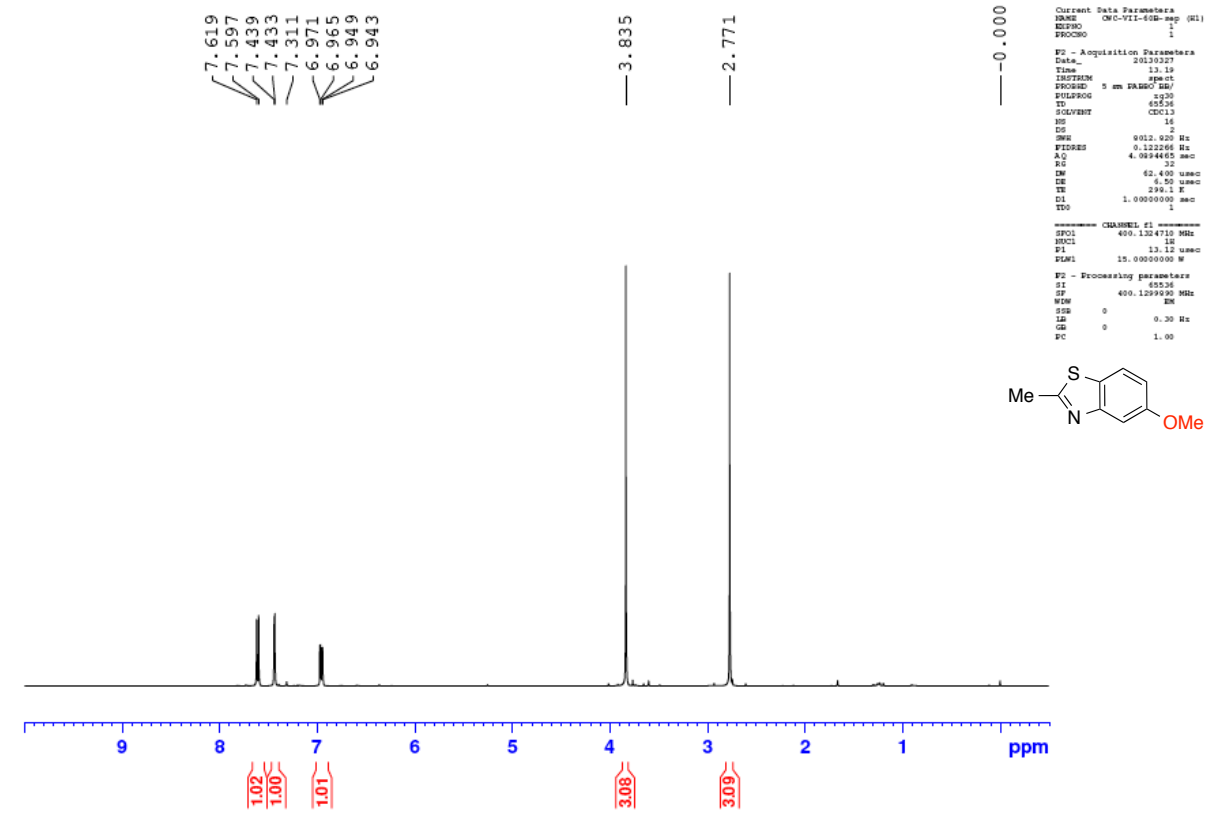


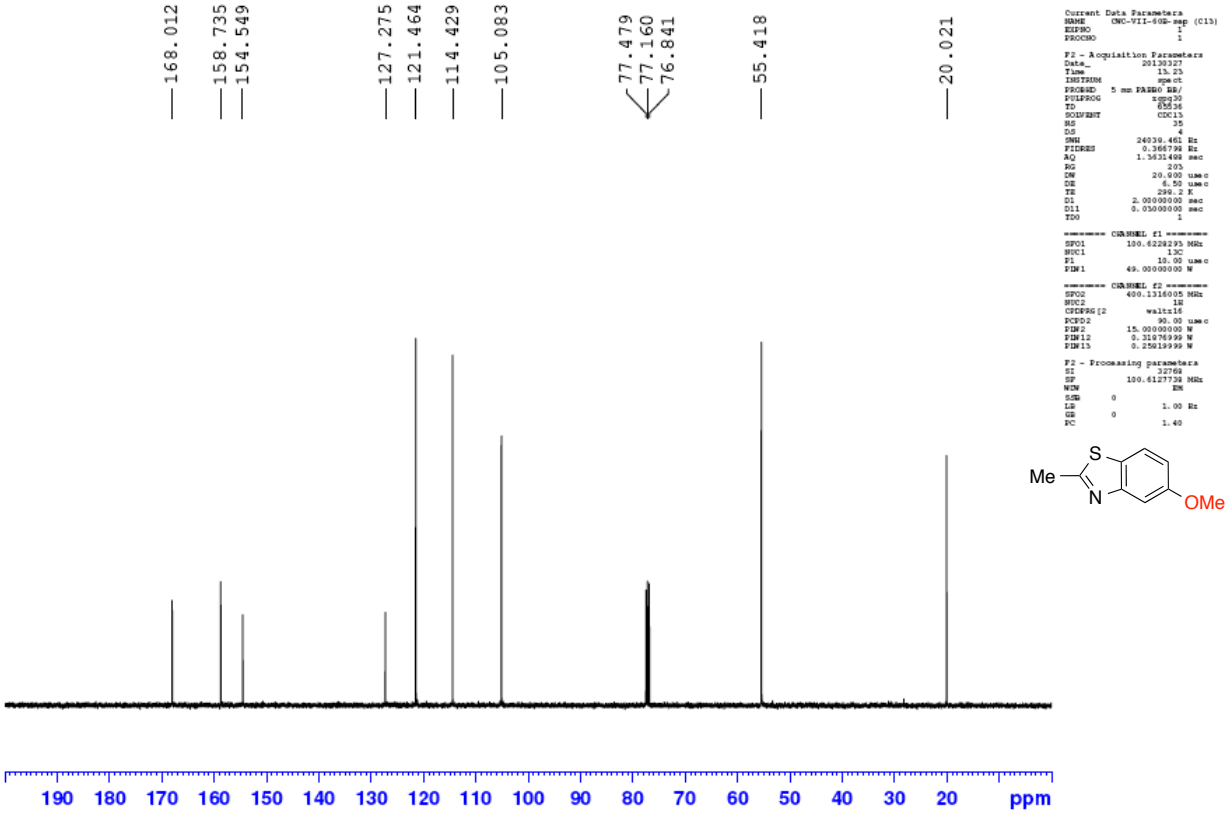
^{1}H and ^{13}C NMR of 7-methoxybenzofuran (4o)



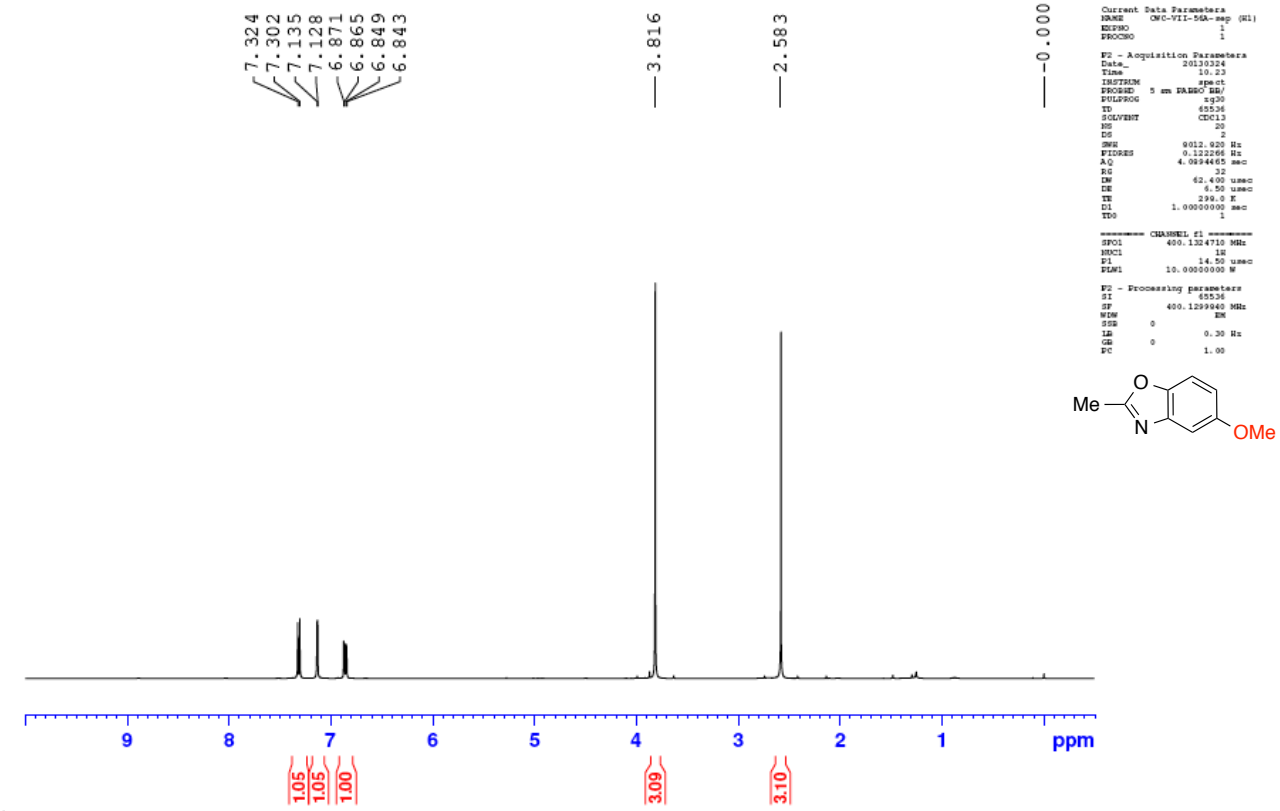


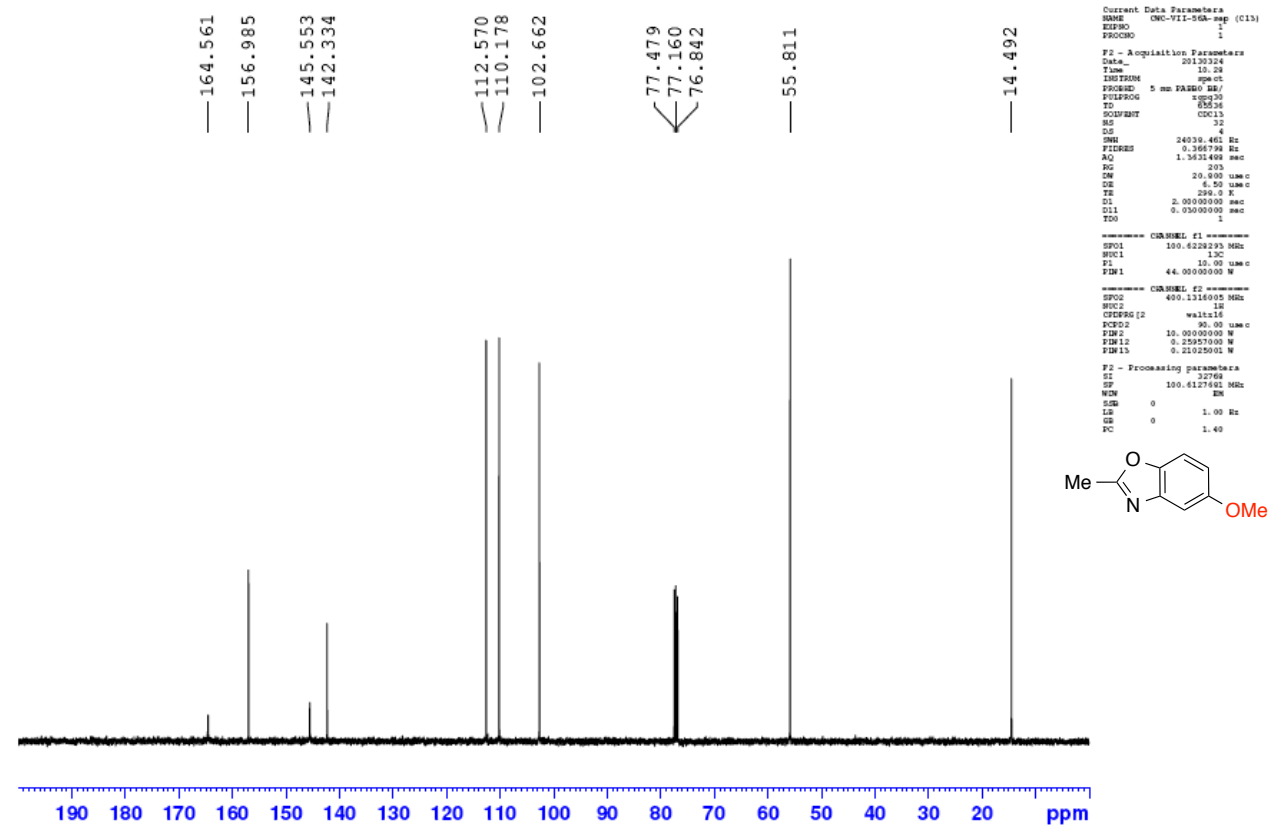
^{1}H and ^{13}C NMR of 5-methoxy-2-methylbenzothiazole (4p)



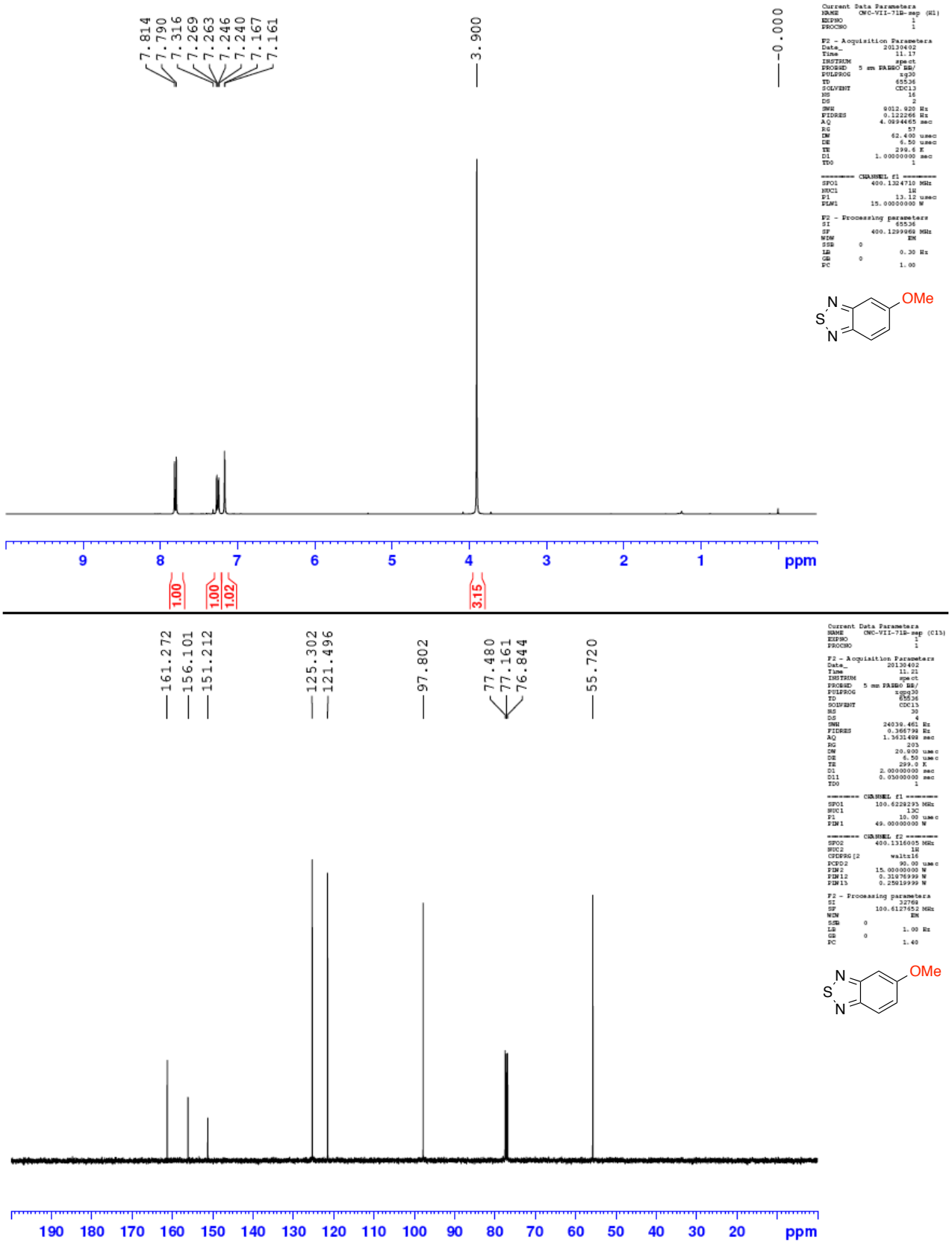


^{1}H and ^{13}C NMR of 5-methoxy-2-methylbenzoxazole (4q)

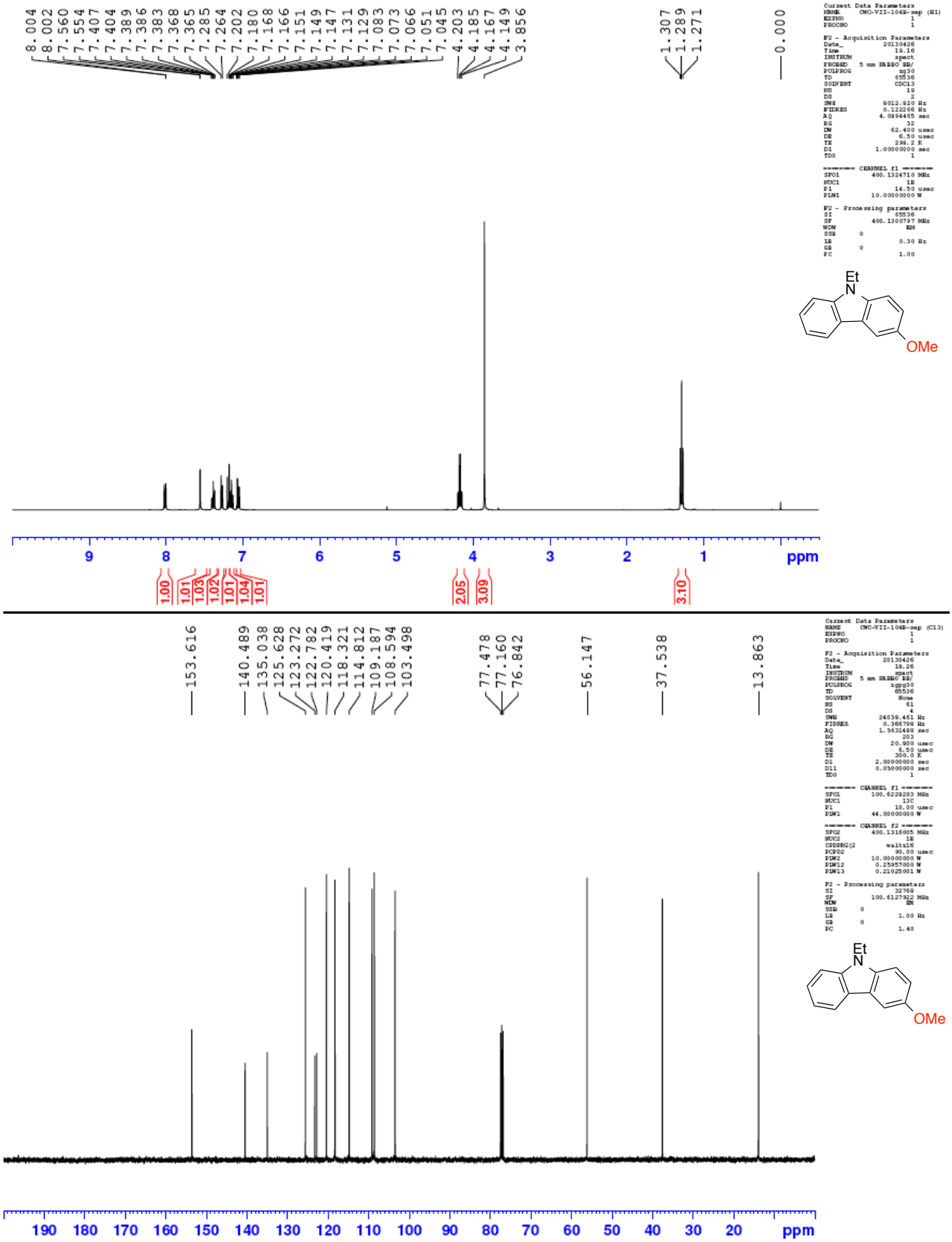




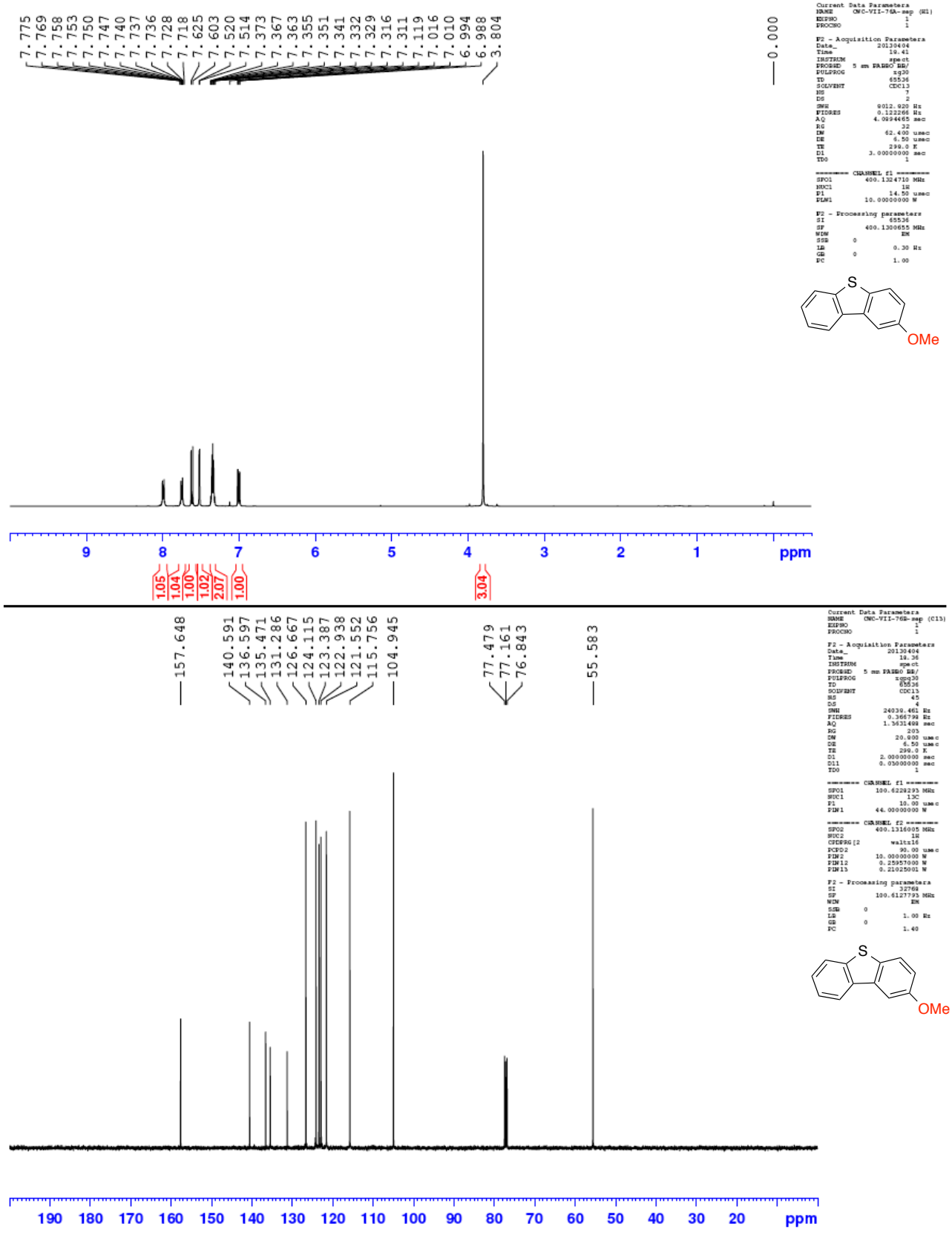
^{1}H and ^{13}C NMR of 5-methoxybenzo-2,1,3-thiadiazole (4r)



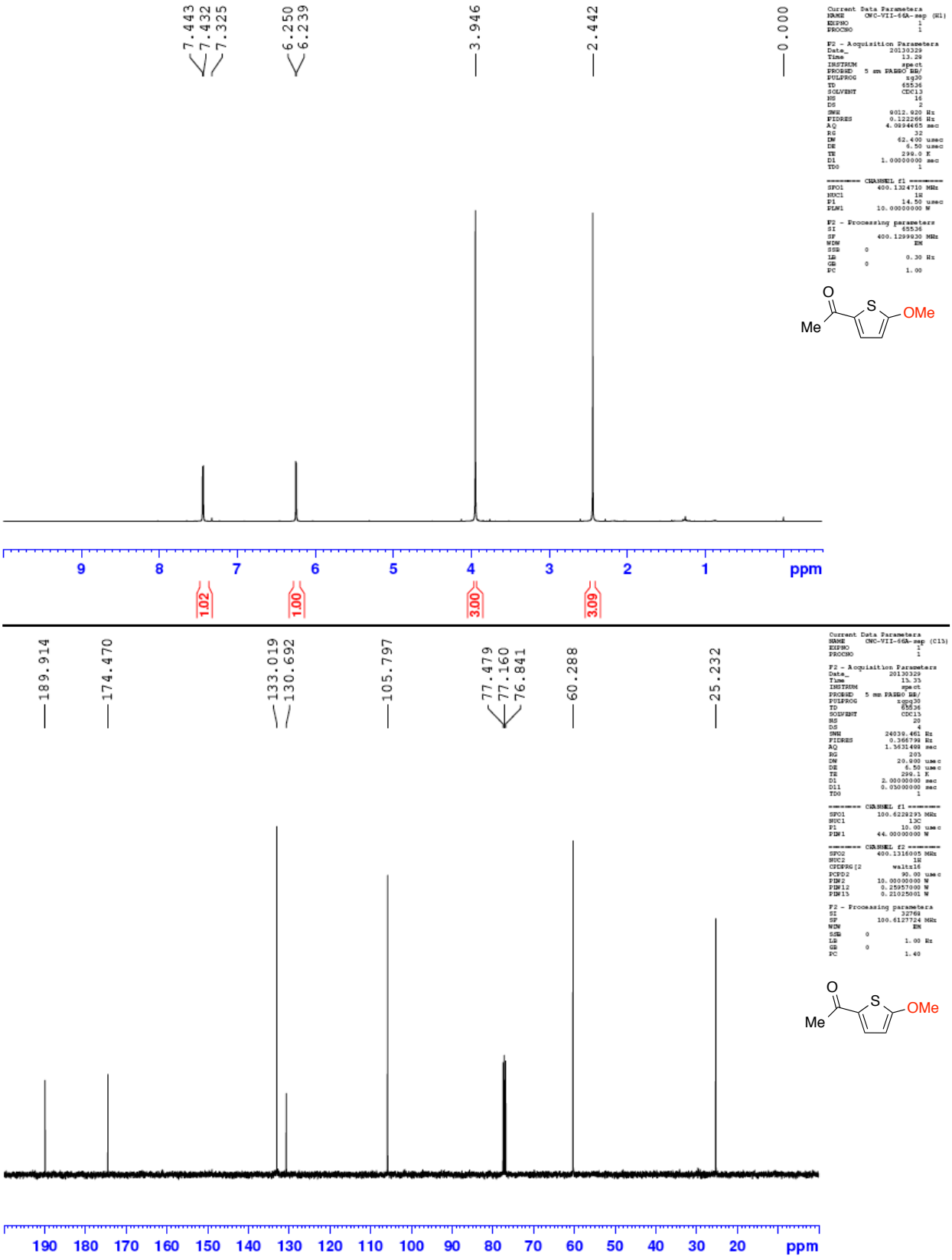
^{1}H and ^{13}C NMR of 9-ethyl-3-methoxy-9*H*-carbazole (4s)



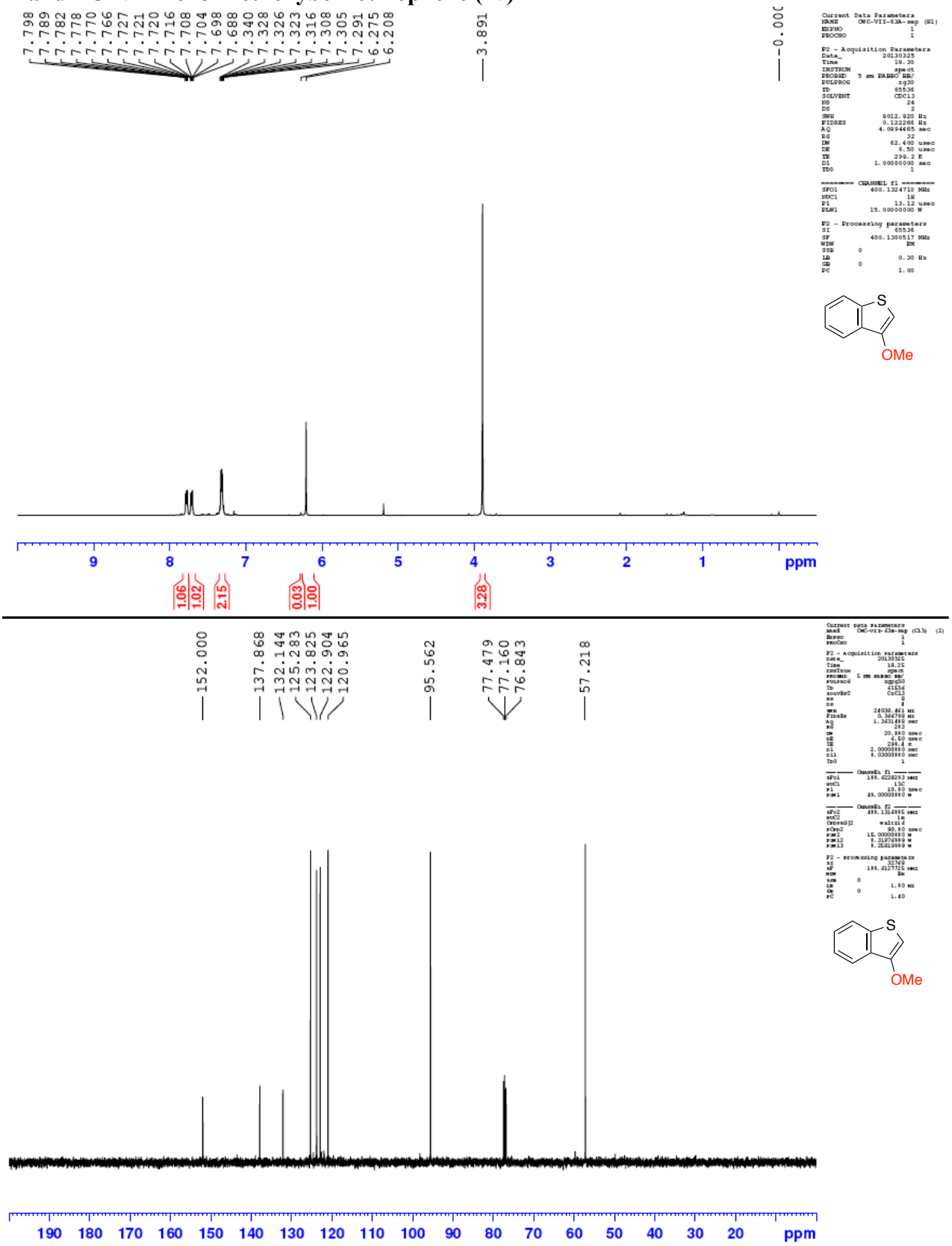
^{1}H and ^{13}C NMR of 2-methoxydibenzothiophene (4t)



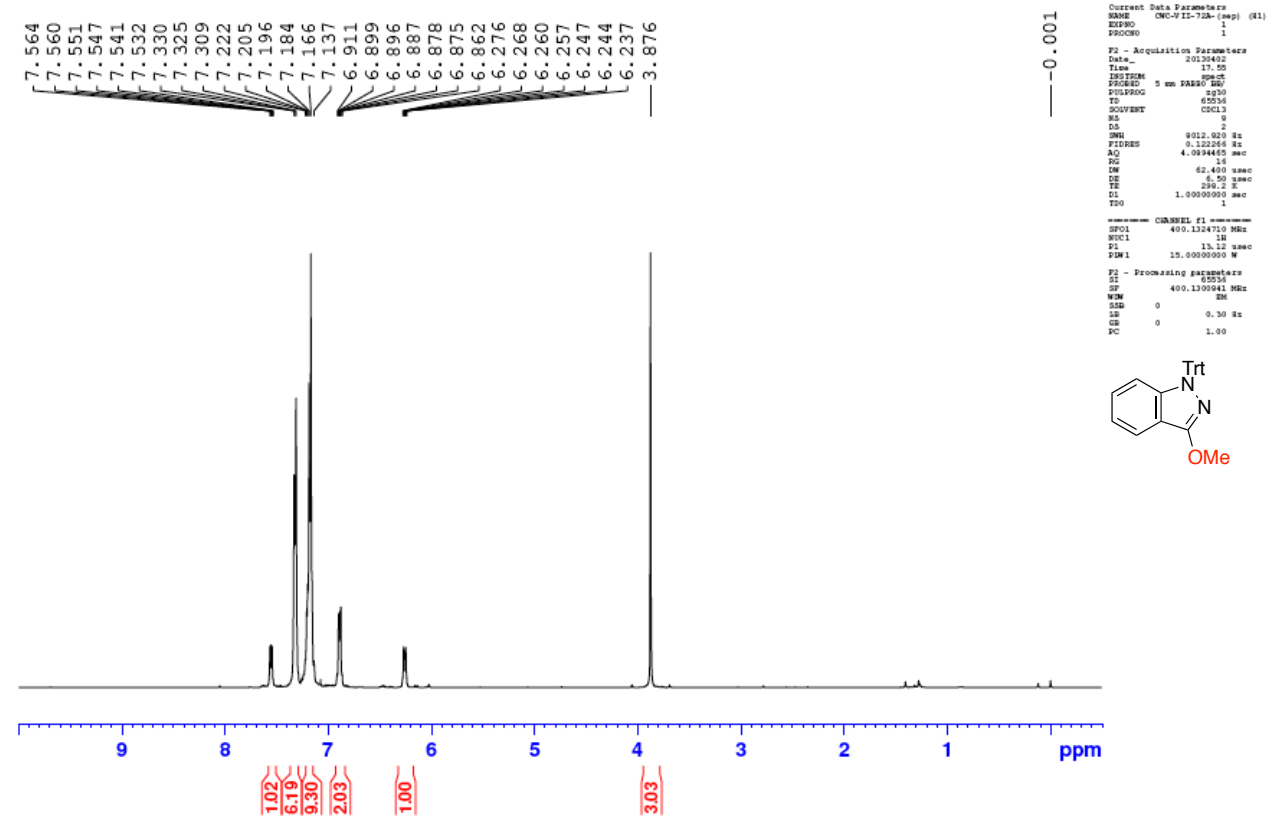
^{1}H and ^{13}C NMR of 1-acetyl-5-methoxythiophene (4u)

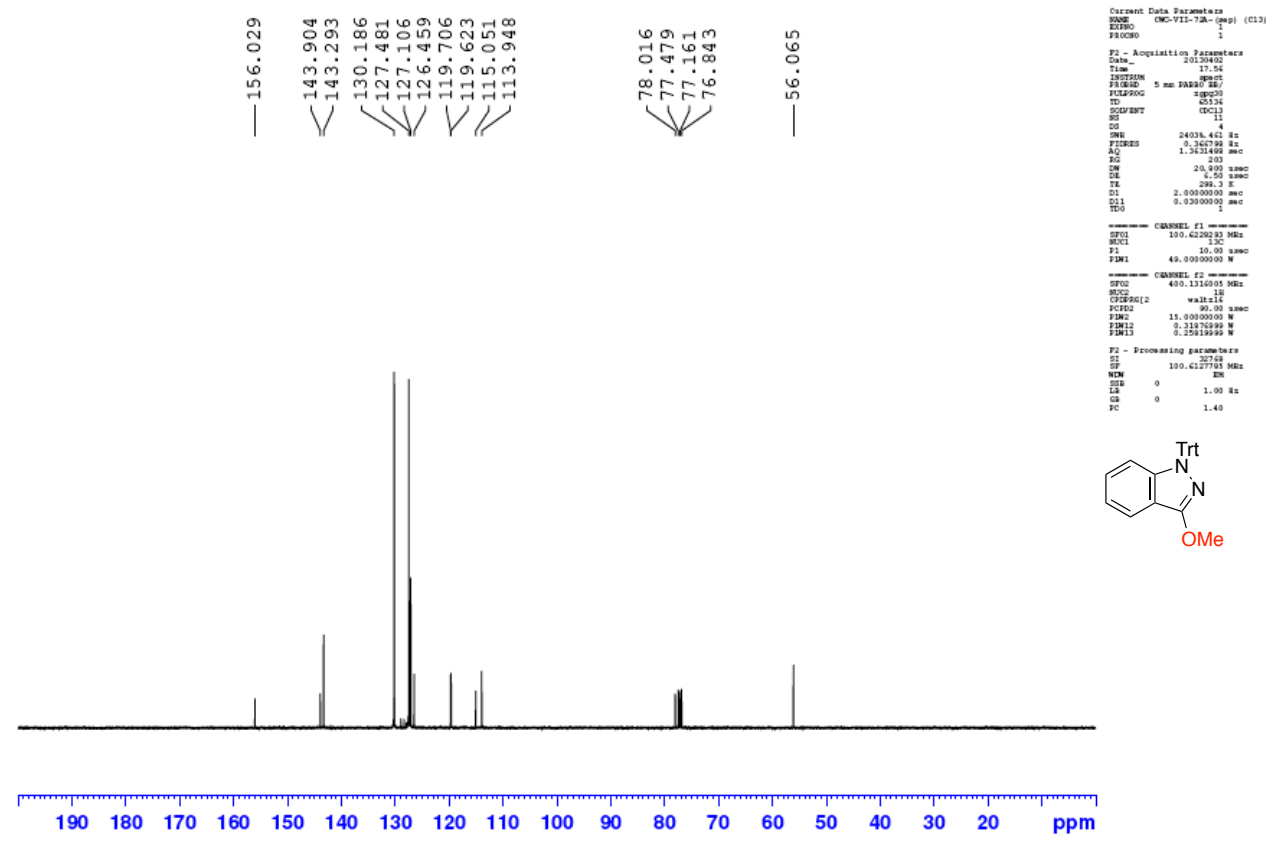


^{1}H and ^{13}C NMR of 3-methoxybenzothiophene (4v)

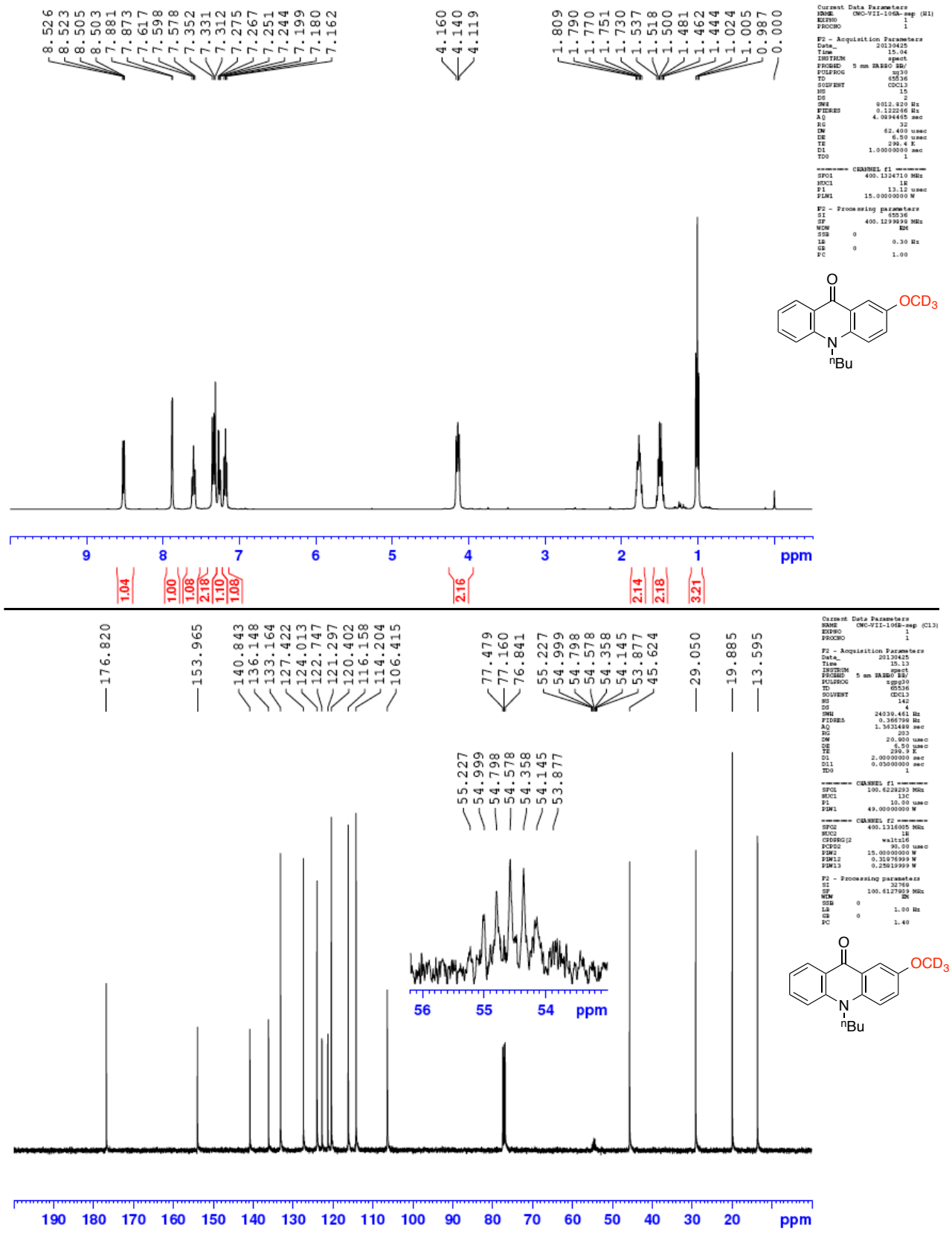


^{1}H and ^{13}C NMR of 3-methoxy-1-trityl-1*H*-indazole (4w)

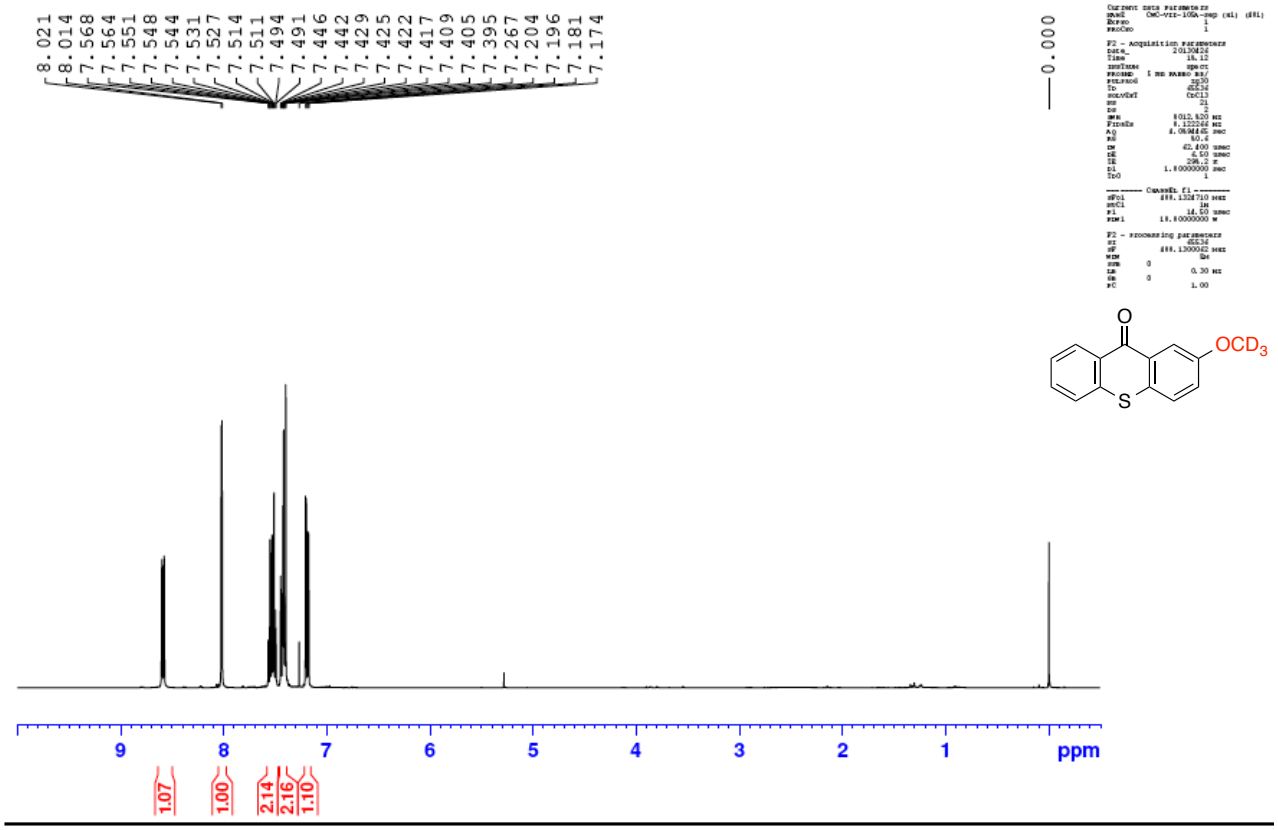


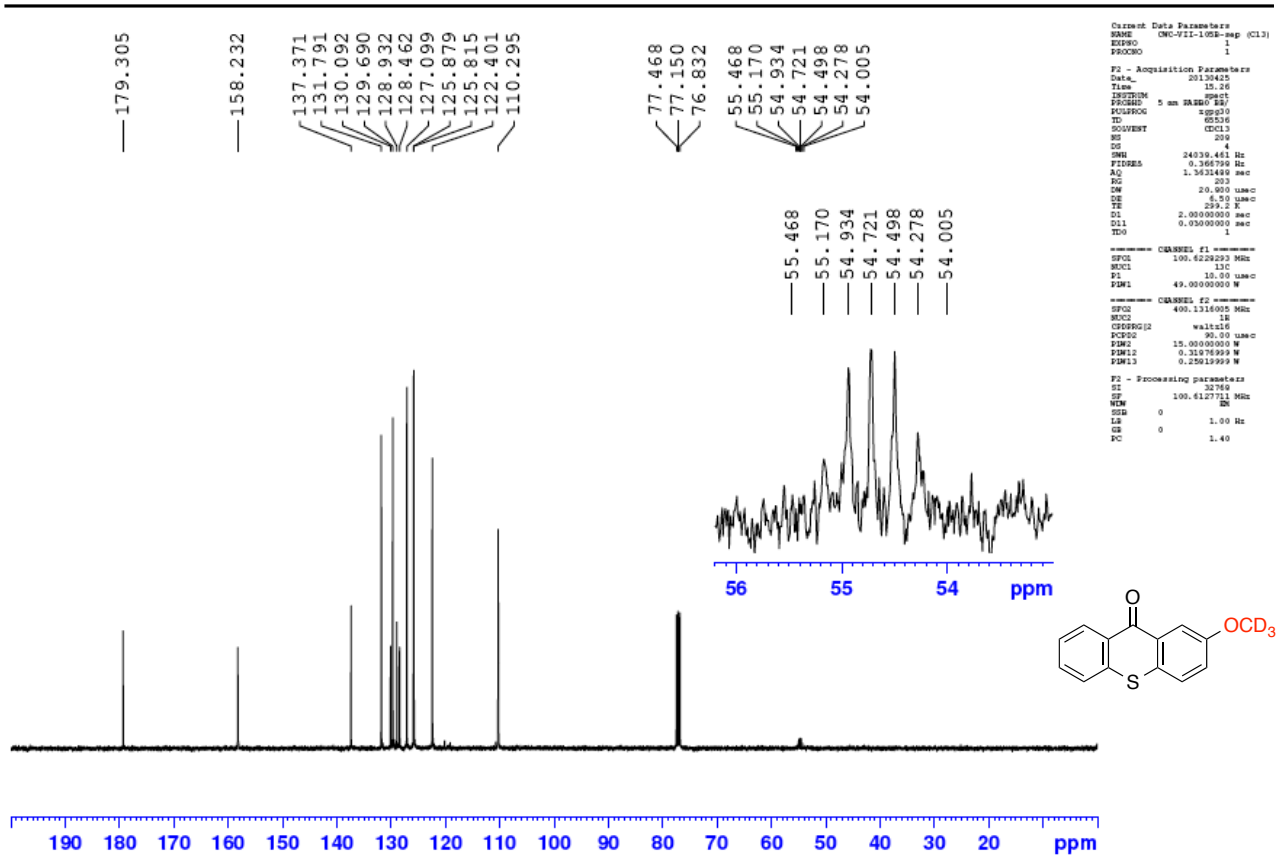


^{1}H and ^{13}C NMR of 10-*n*-butyl-2-trideuteriomethoxyacridin-9(10*H*)-one (5a)

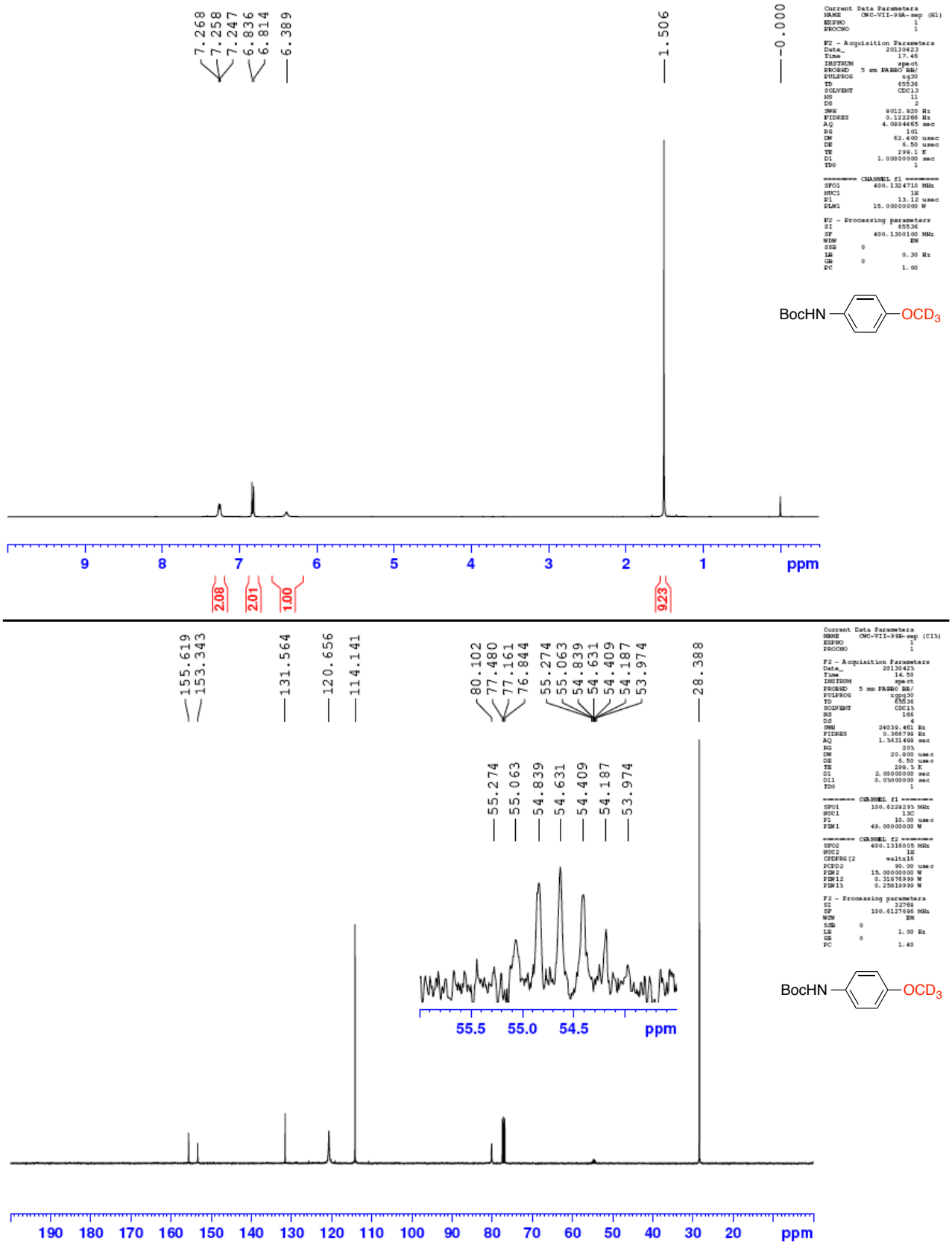


^{1}H and ^{13}C NMR of 2-trideuteriomethoxy-9*H*-thioxanthen-9-one (5b)

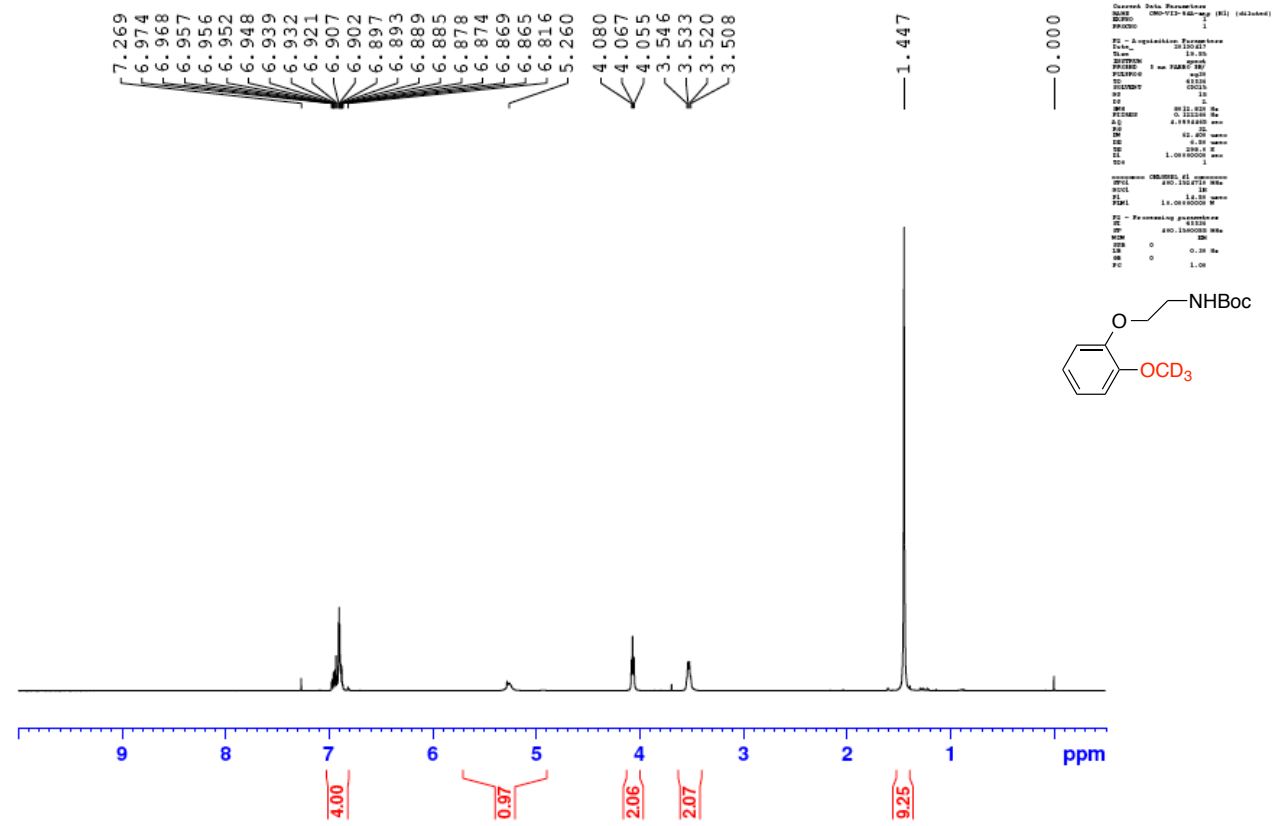


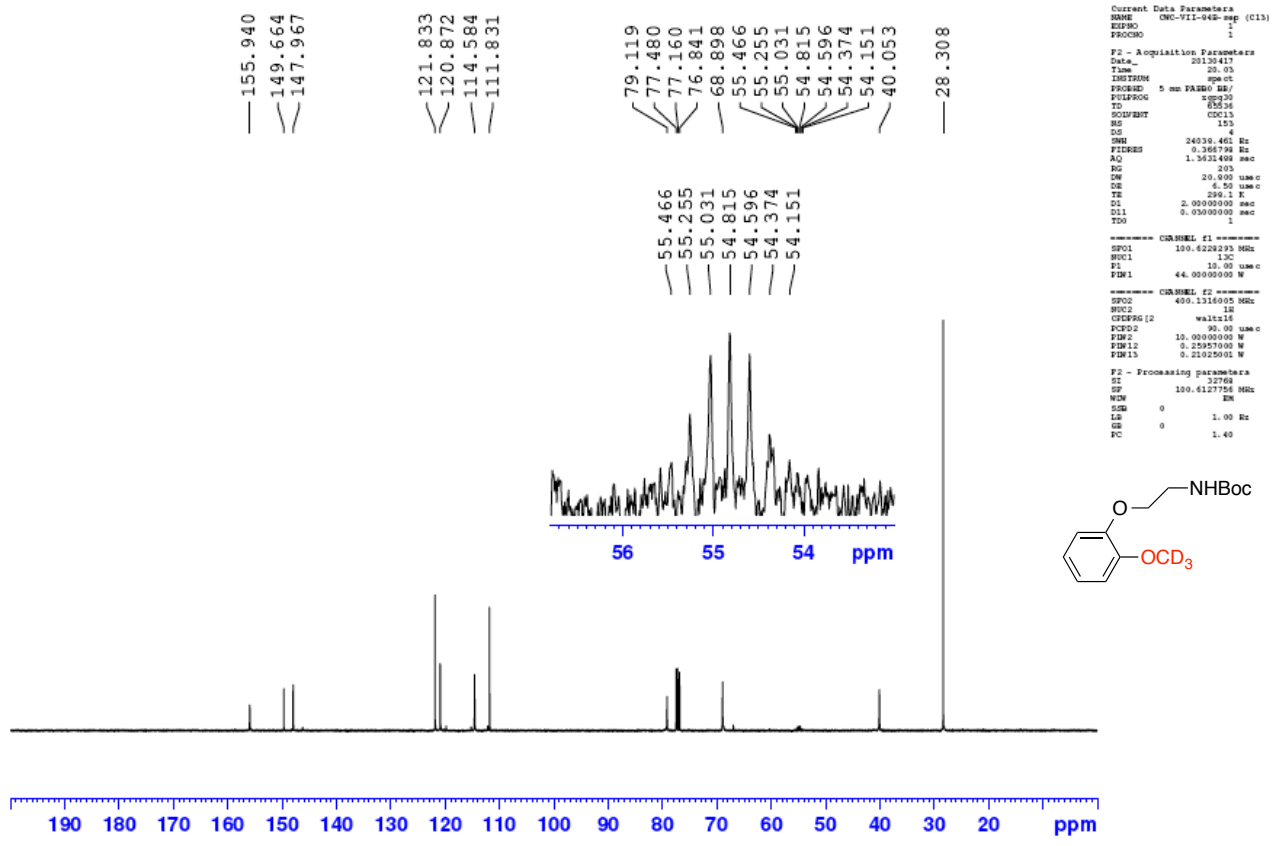


^{1}H and ^{13}C NMR of *tert*-butyl (4-trideuteriomethoxyphenyl)carbamate (5c)

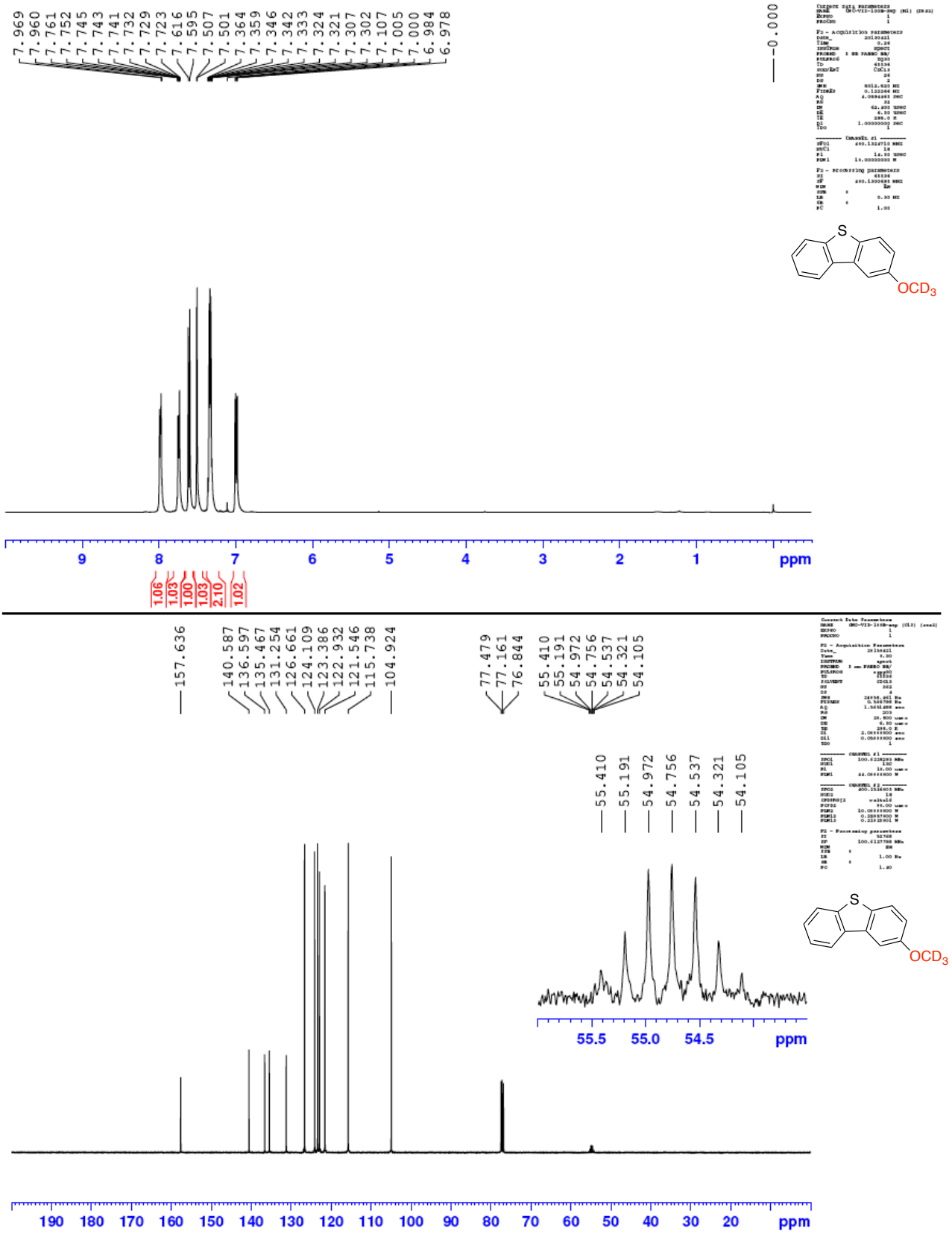


^{1}H and ^{13}C NMR of *tert*-butyl (2-(2-trideuteriomethoxyphenoxy)ethyl)carbamate (5d)

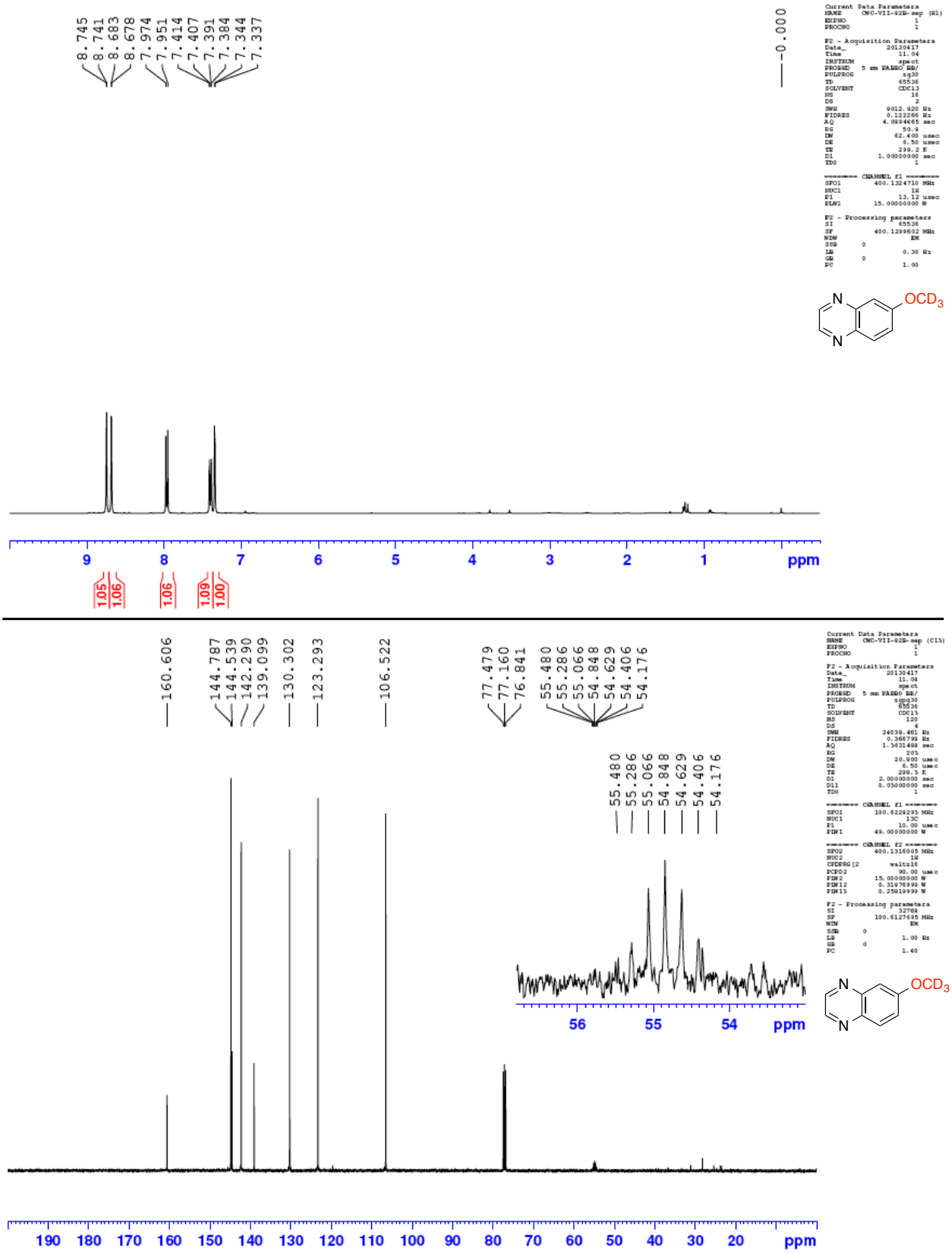




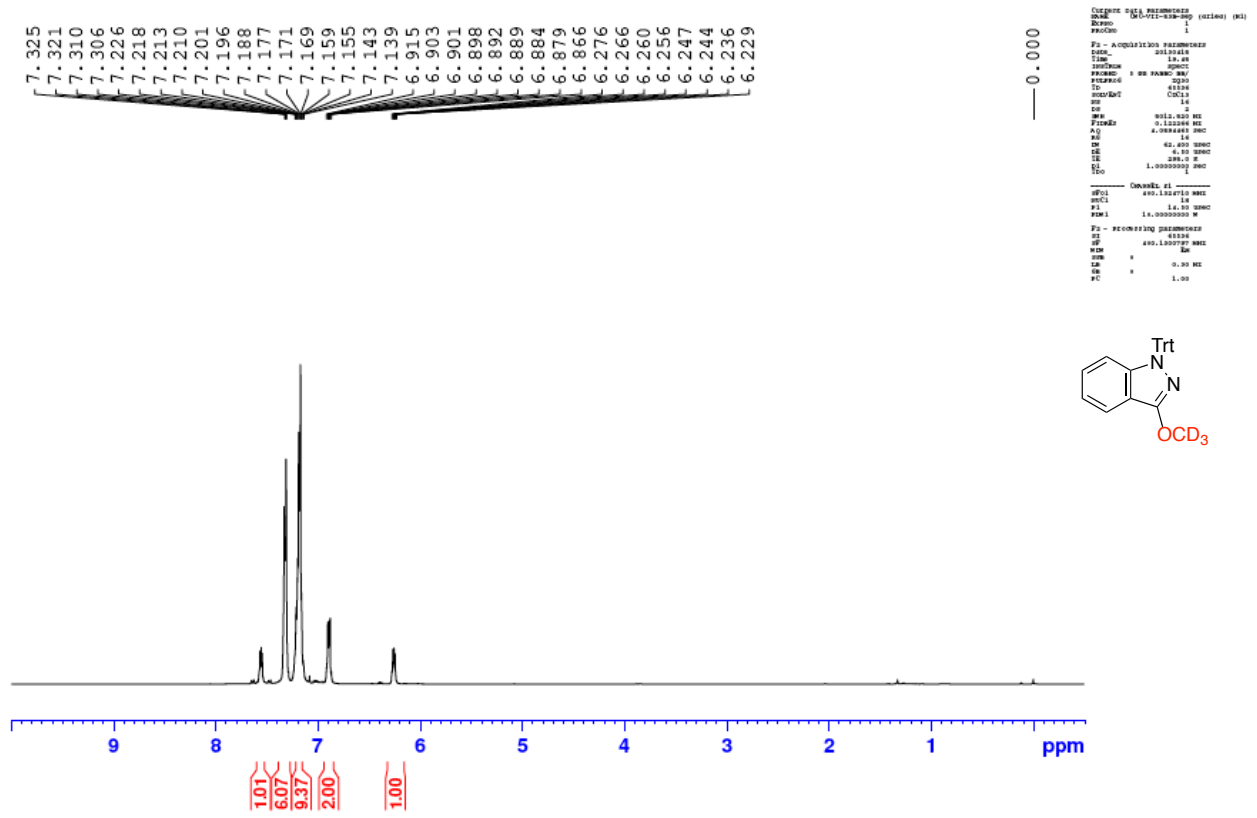
^{1}H and ^{13}C NMR of 2-trideuteriomethoxydibenzothiophene (5e)

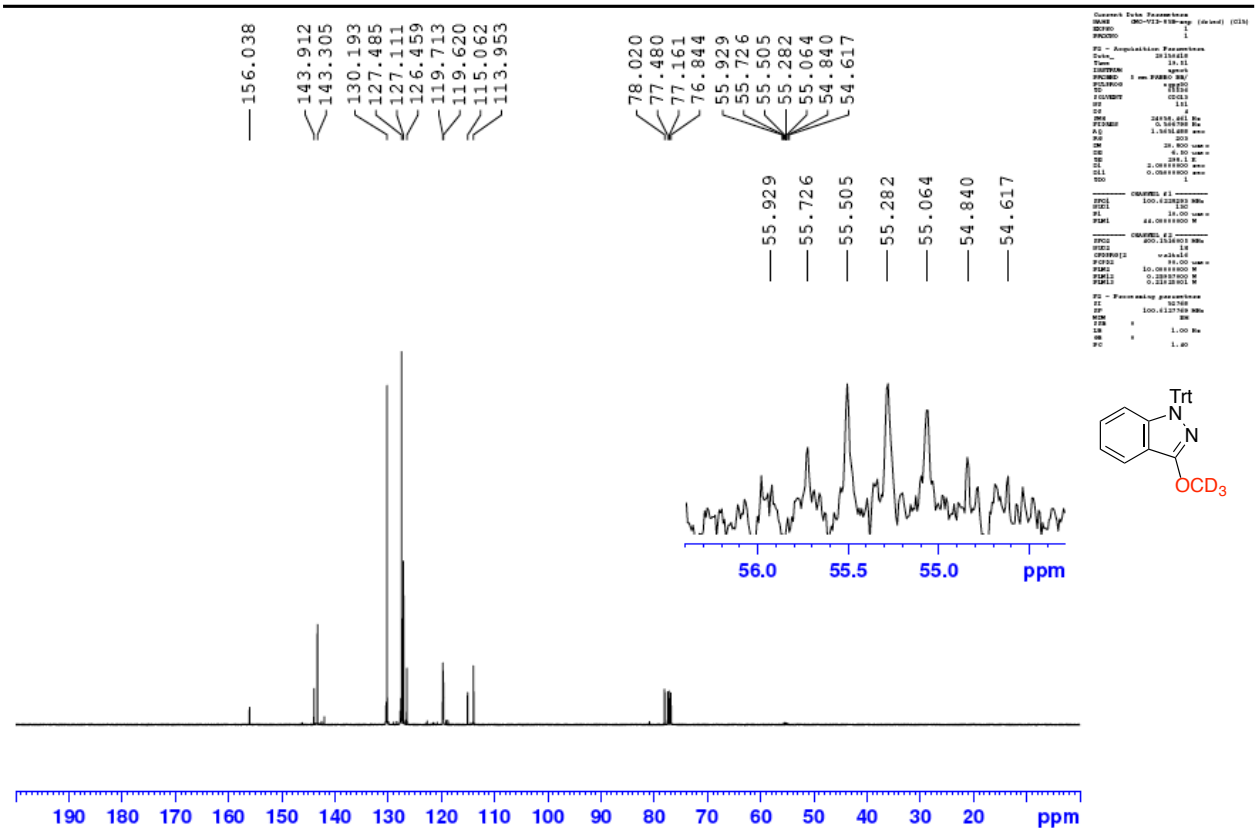


^{1}H and ^{13}C NMR of 6-trideuteriomethoxyquinoxaline (5f)

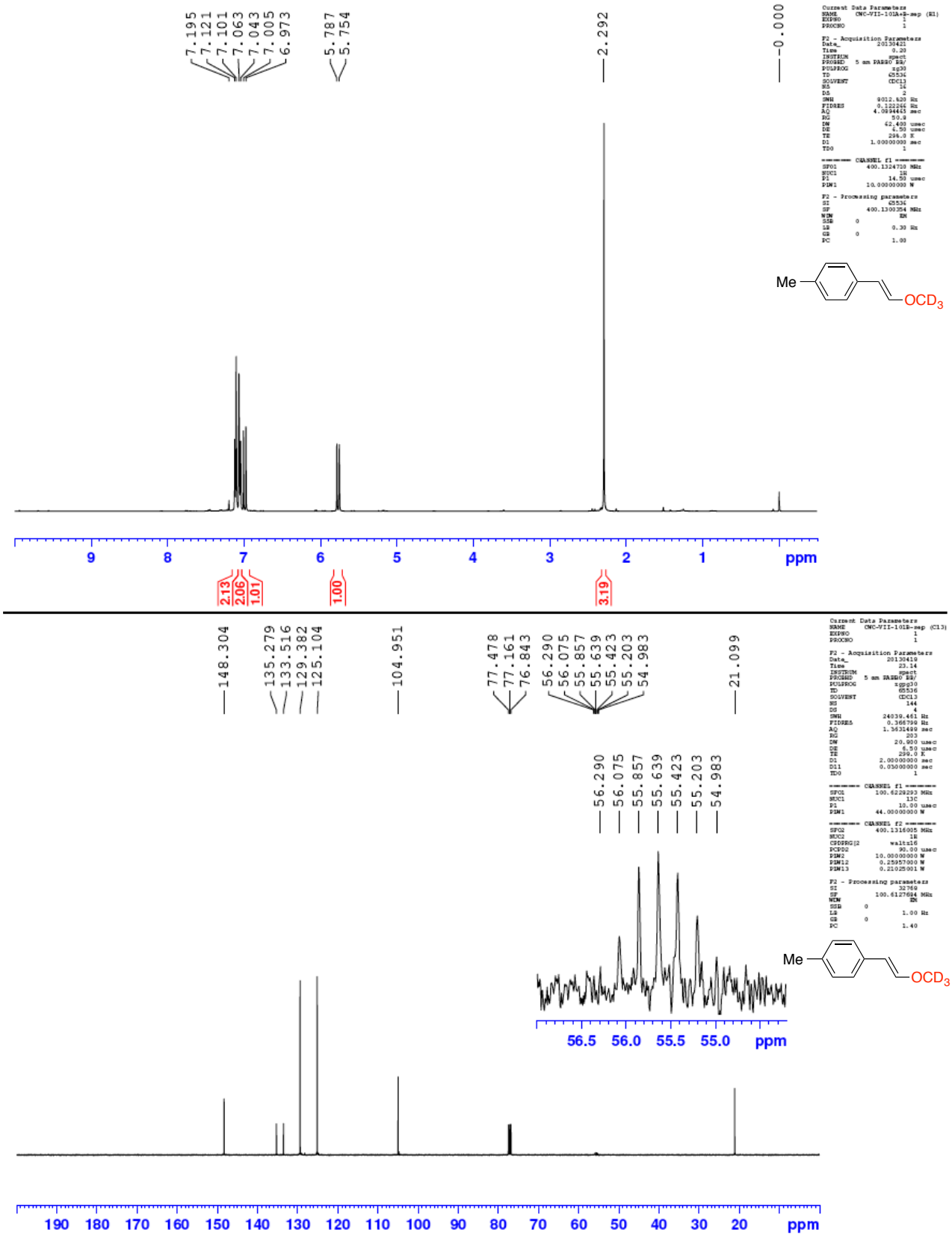


^{1}H and ^{13}C NMR of 3-trideuteriomethoxy-1-trityl-1*H*-indazole (5g)

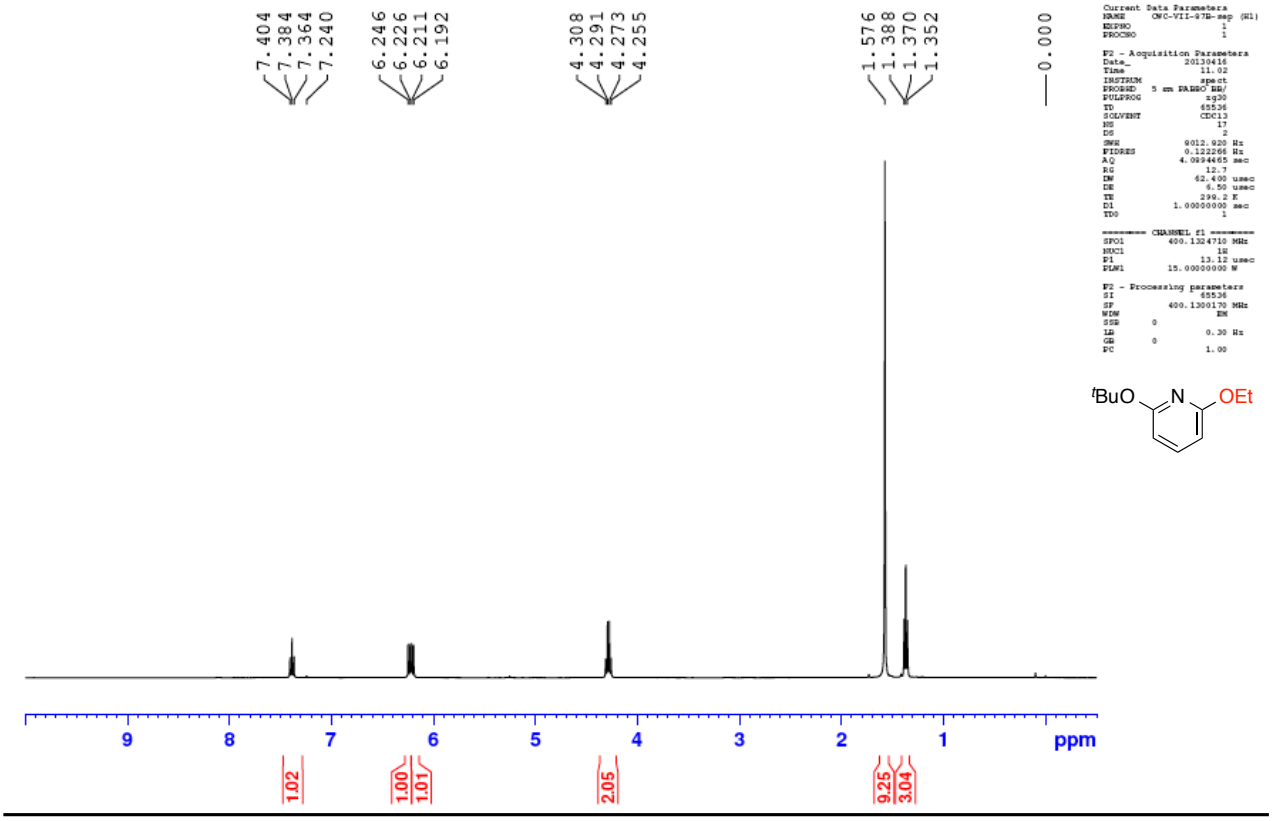


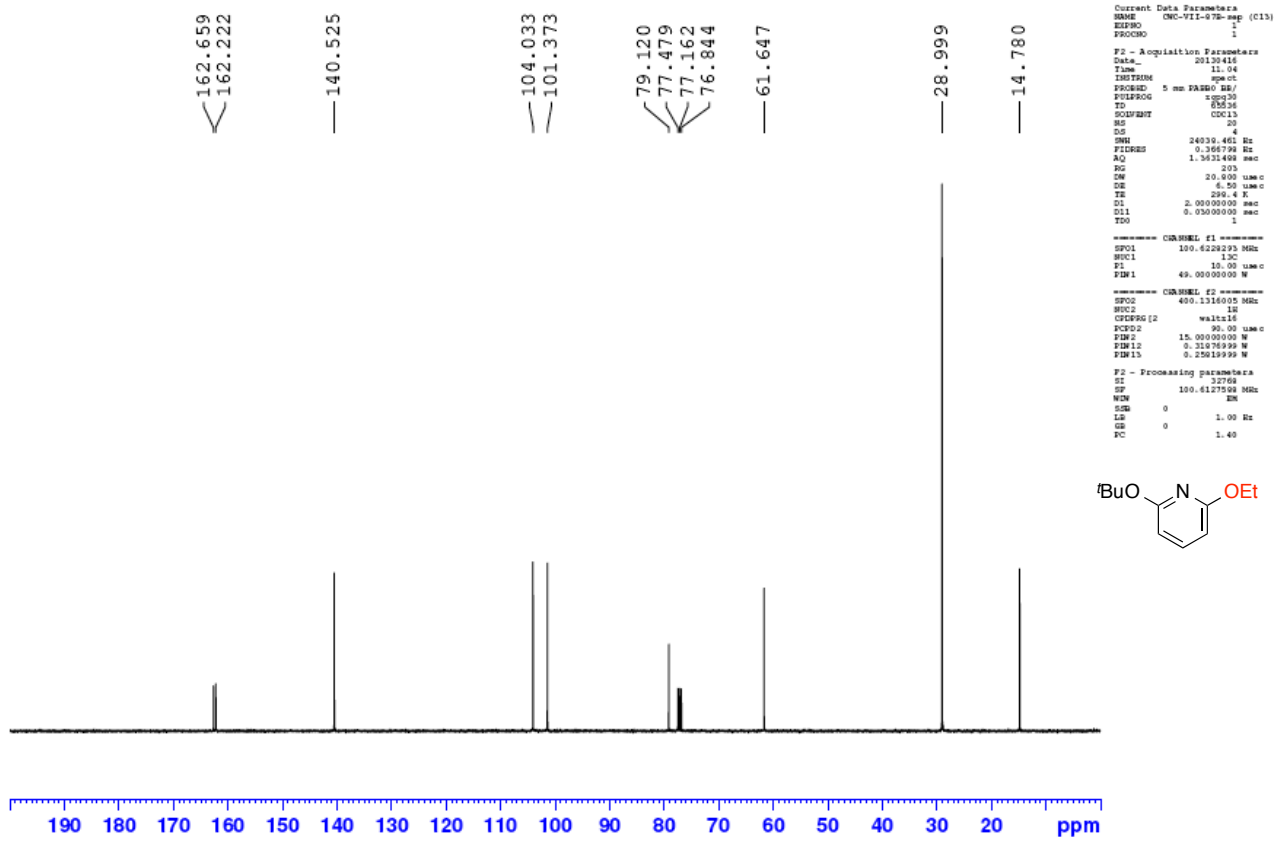


^{1}H and ^{13}C NMR of (*E*)-1-methyl-4-(2-trideuteriomethoxyvinyl)benzene (5h)

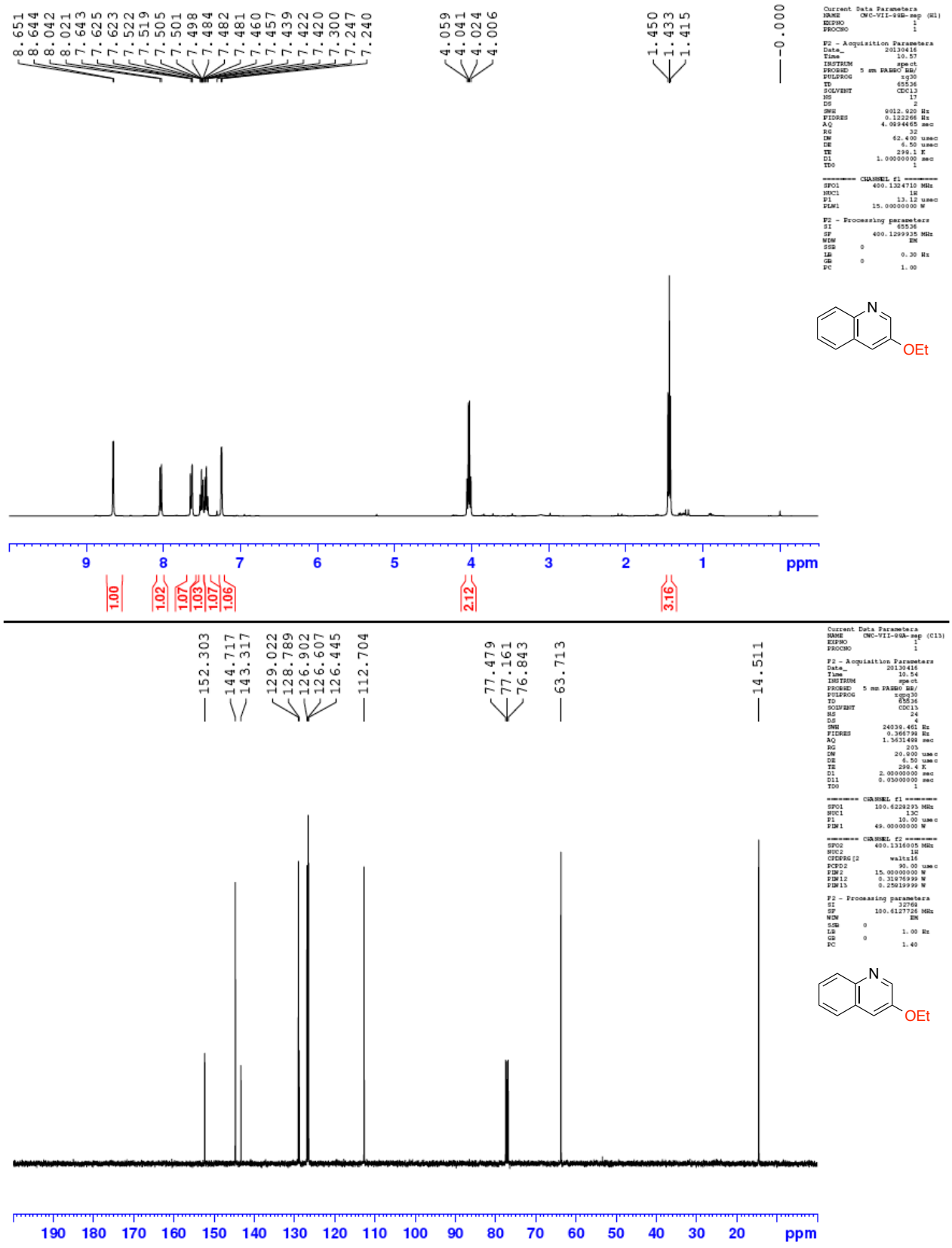


^{1}H and ^{13}C NMR of 2-(*tert*-butoxy)-6-ethoxypyridine (6a)

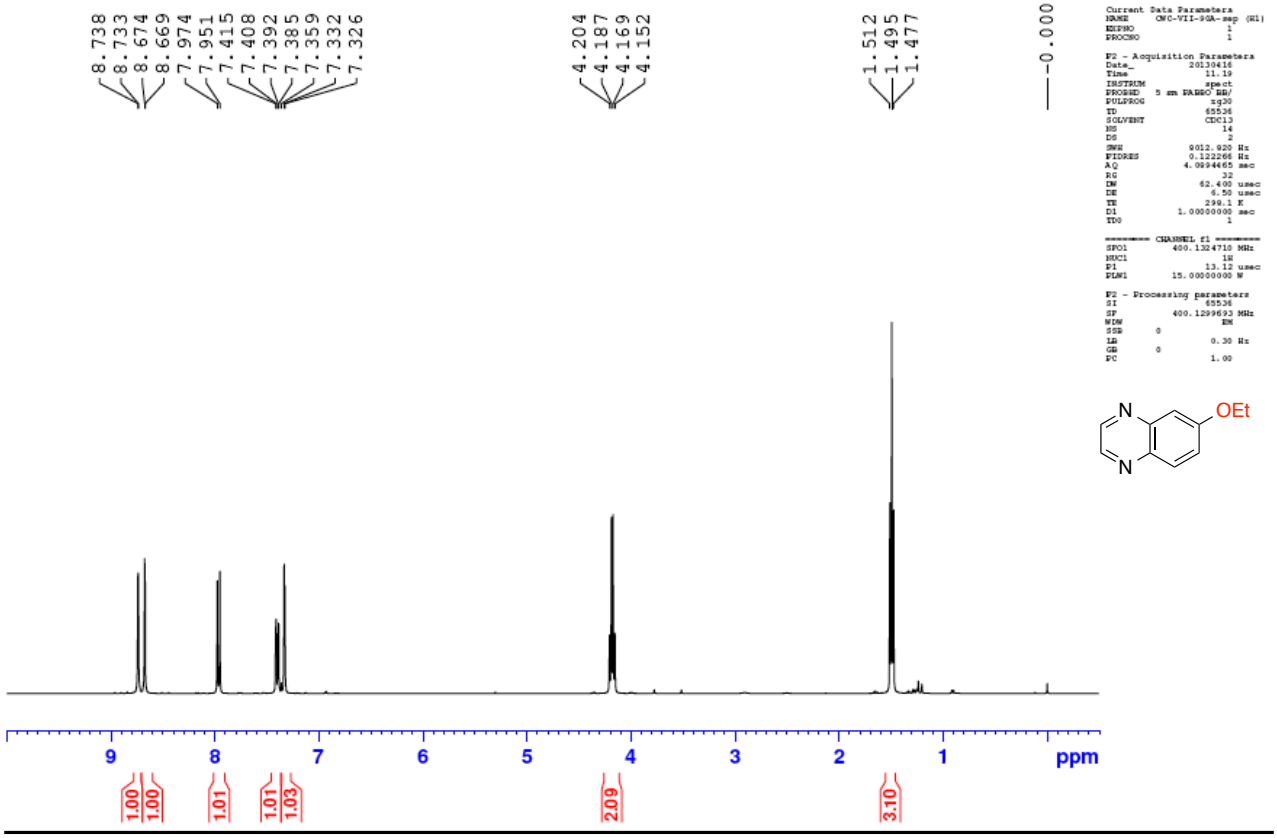


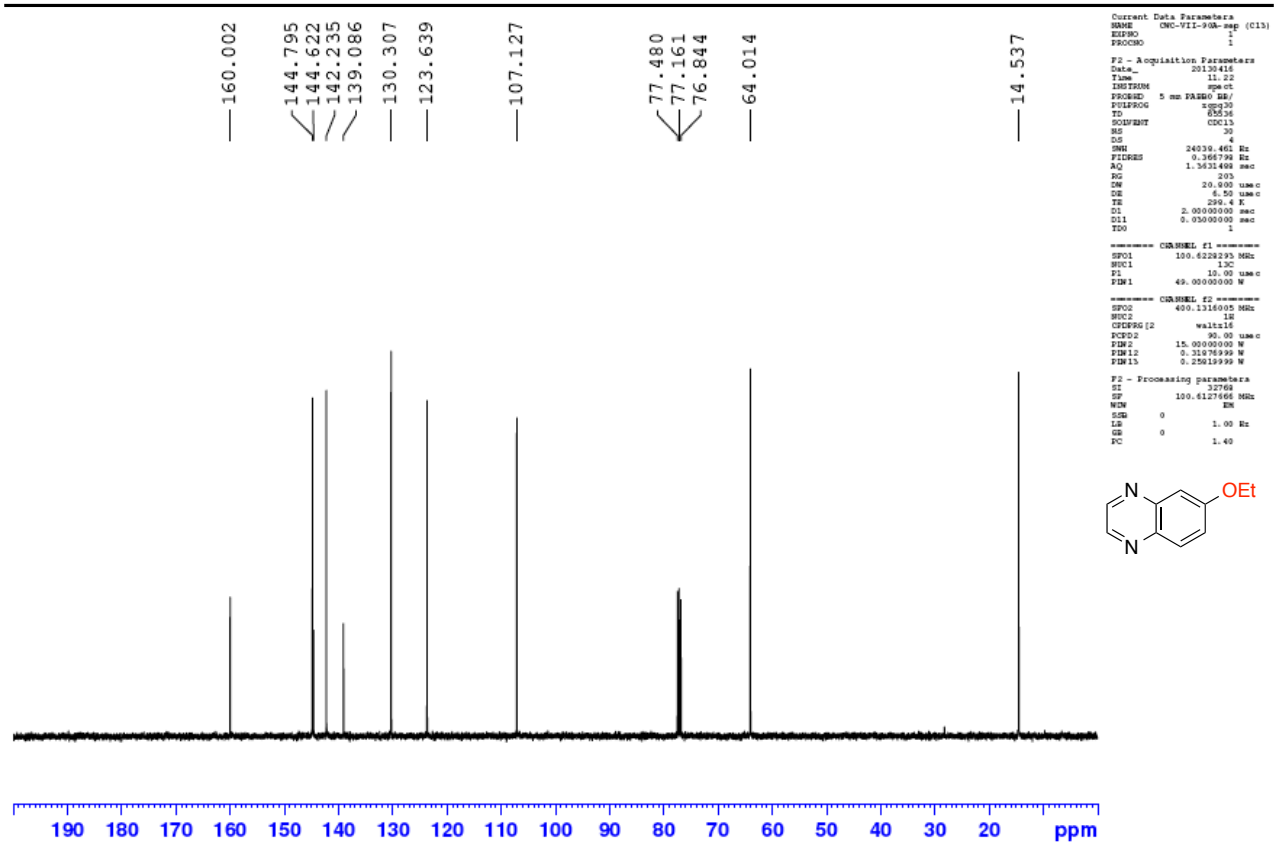


^{1}H and ^{13}C NMR of 3-ethoxyquinoline (6b)



^{1}H and ^{13}C NMR of 6-ethoxyquinoxaline (6c)





^{1}H and ^{13}C NMR of 2-ethoxydibenzothiophene (6d)