Synthesis of Quinolinone Alkaloids via Aryne Insertions into Unsymmetric Imides in Flow

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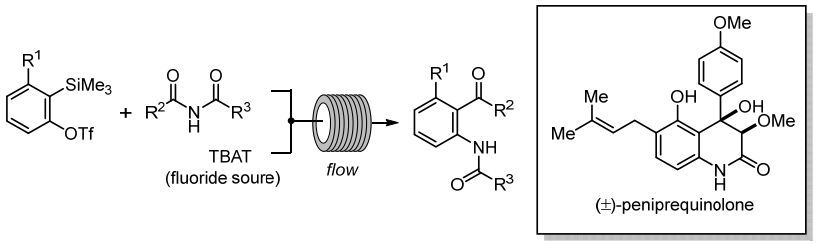
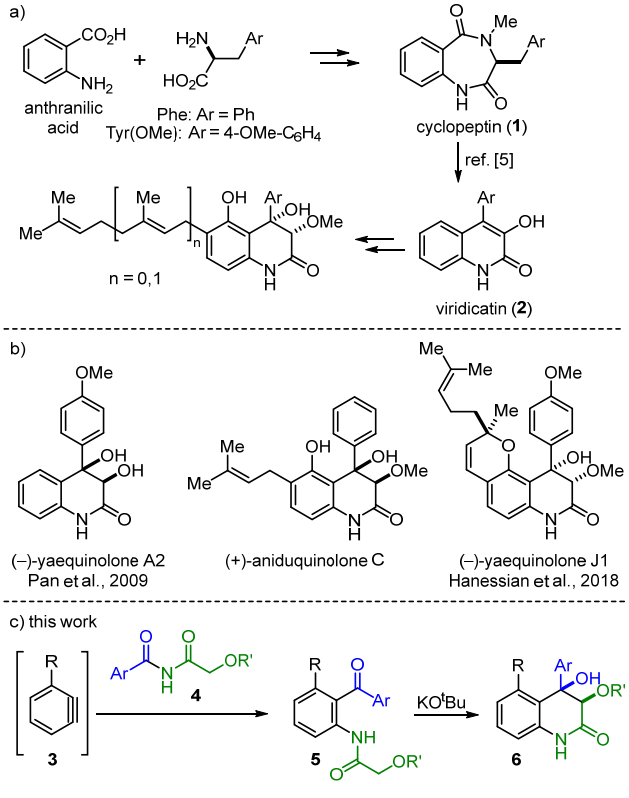
Supporting Information Placeholder



ABSTRACT: A general strategy for the synthesis of 3,4-dioxygenated quinolin-2-one natural products is reported. The key step is a regioselective insertion of arynes into unsymmetric imides. When performed in continuous flow, the reaction proceeded within minutes. The resulting *N*-acylated 2-aminobenzophenones were transformed to (±)-peniprequinolone, (±)-aflaquinolones E and F, (±)-6-deoxyaflaquinolone E, (±)-quinolinones A and B, and (±)-aniduquinolone C in 1–3 steps.

The growing family of 3,4-dioxygenated quinolin-2-ones constitutes a valuable source of molecules with cytotoxic, nematicidal and antiviral activities.[1,2] Biosynthetically, these fungal secondary metabolites are derived from the nonribosomal peptide synthetase (NRPS) product cyclopeptin (**1**), an adduct of anthranilic acid and either *O*-methyl-L-tyrosine[3] or phenylalanine[4] (Scheme 1a). Groll and Hintermann demonstrated that a single enzyme, AsqJ, catalyzes a multistep transformation of the benzodiazepine core of **1** into the parent quinolone **2**.[5] Downstream processing into the final natural products may involve prenylation (n=0), double prenylation (n=1) as well as additional oxidation steps.[6] Following this synthetic blueprint, Nature has evolved a "library" of bioactive secondary metabolites[3,7] from which only yaequinolone J1, J2, and A_2 have been synthesized to date (Scheme 1b).[8] Since these natural products share a common heterocyclic core, we decided to develop a step-efficient,[9] modular approach to access the entire group of these alkaloids (Scheme 1c). Synthetically, the 3,4-dioxygenated quinolin-2-one core (**6**) can be obtained by intramolecular glycolate aldolizations.[10] We speculated that aryne chemistry[11] could provide a straightforward access to *N*-glycolated 2-aminobenzophenones (**5**) and thus enable the synthesis of this natural product family. Based on the contributions of Greaney[11a] (acyclated carbamates), Stoltz[11b] (symmetric imides), and Xu[11d] (acrylamides), we speculated that a selective σ-C–N insertion of in-situ generate arynes (**3**) into unsymmetric imides **4** could deliver **5** in a one-pot operation[12] (Scheme 2). With these substrates, the challenge lies in the differentiation of two similar *N*-acyl groups.

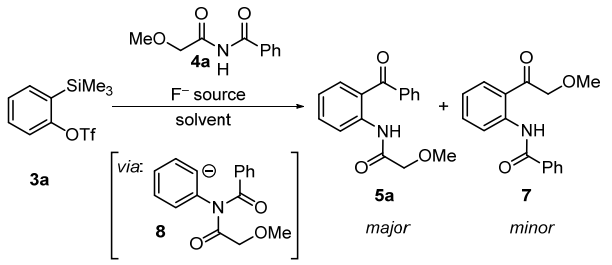
Scheme 1. Outline of the Work



As a starting point, we investigated the insertion of benzyne precursor **3a**[13] into the unsymmetric imide **4a**. Under the conditions reported by Stoltz et al.,[11b] benzophenone **5a** was formed in 16% yield with only a slight preference for the **5a** over its constitutional isomer **7** (Table 1, entry 1). A screening of solvents revealed that acetonitrile gave the best selectivity of 5.7:1 (entry 3). Among different fluoride sources, cesium fluoride gave the highest yield of **5a** with 33% and an isomeric ration of 3.7:1 (entry 4). Upon extended reaction time, **7** undergoes slow thermal decomposition leading to a slightly increased isomer in favor of **5a**. Furthermore, it turned out that also imide **4a** slowly decomposes to benzamide at elevated temperatures and under basic conditions.

Due to superior heat and mass transfer, reactions performed in flow can significantly be accelerated. Therefore, intermediates such as **8** often react with higher selectivity and yield, enabling reactions that are otherwise impossible.[14] Surprisingly, only few examples are reported, where arynes are generated and used in a flow reactor.[15]

Table 1. Reaction Development in Batch[a]



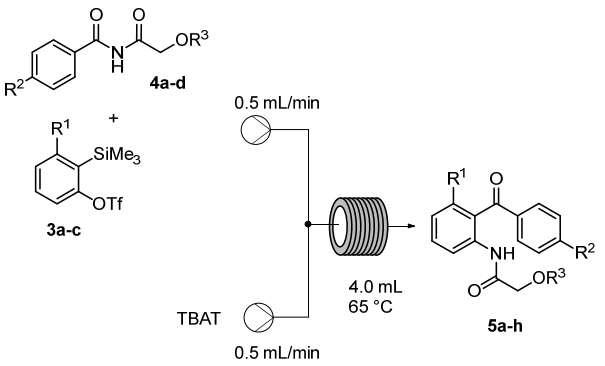
Entry	Solvent	F⁻ Source	5a:7[b]	5a (%)[c]
1	PhMe	TBAT	1.3:1	16
2	THF	TBAT	2.0:1	18
3	MeCN	TBAT	5.7:1	25
4[d]	MeCN	CsF	3.7:1	33
5[d,e]	MeCN	KF	4.0:1	20

[a]Reaction conditions: **4a** (0.26 mmol, 1 equiv.), **3a** (0.39 mmol, 1.5 equiv.), F⁻ source (0.52 mmol, 2 equiv.), solvent (2.0 mL), 60 °C, 16 h; [b]ratios were determined by ^{1}H NMR integration; [c]isolated yield; [d]conducted at 80 °C for 4 h; [e]18-crown-6 (1 equiv.) and 4 Å mol sieves were used as additives.

In order to suppress thermal imide decomposition by shortening the reaction time, a flow protocol seemed promising. Due to its high solubility, tetrabutylammonium difluorotriphenylsilicate (TBAT) is a better fluoride source for flow reactions than cesium fluoride. An optimization of reaction time, temperature and stoichiometry (see SI, for details), increased the yield of **5a** from 25% in batch (Table 1, entry 3), to 52% when conducted at 65 °C with 1.5 equiv. of **3a** at a flow rate of 1 mL/min (Table 2, entry 1). Under these conditions, a regioselectivity of 2.9:1 (**5a**:**7**) was observed, while the residence time was reduced to 4 minutes.

Using the optimized conditions, a collection of substituted arynes and imides were reacted. According to the proposed mechanism, the aryne insertion proceeds *via* intermediacy of **8**.[11a,b,16] Greaney et al.[11a] showed that a major byproduct results from premature protonation of **8.** Remarkably, under flow conditions even the use of wet acetonitrile did not increase the amount of byproduct**,** thus rendering the flow process more sustainable. As arynes bearing a 3-alkoxy substituent have been reported undergo regioselective nucleophilic attack in the *meta*-position,[17] we expected the resulting benzophenones to provide us with an access to the 5-hydroxyquinolinone cores present in aflaquinolone E (**9**)[18] and quinolinone B (**10**).[19c] In agreement with the literature reports,[11a,b,20] we too observed significantly lower yields with those substrates. Thus, when using 3-*O*-benzyl and 3-*O*-allyl substituted aryne precursors **3b** and **3c**, the yield dropped to 18% to 30% (Table 2, entry 3-6). The insertion was also performed with 4-bromo substituted imide **4c** to access an unnatural quinolinone derivative with a handle for cross coupling chemistry as well as *O*-benzyl substituted imide **4d** to access aflaquinolone F (**11**).[18] In all cases, benzophenones **5a**–**h** were obtained as the major product along with unreacted imide **4a**–**d**.

Table 2. Aryne Insertion in Flow[a]



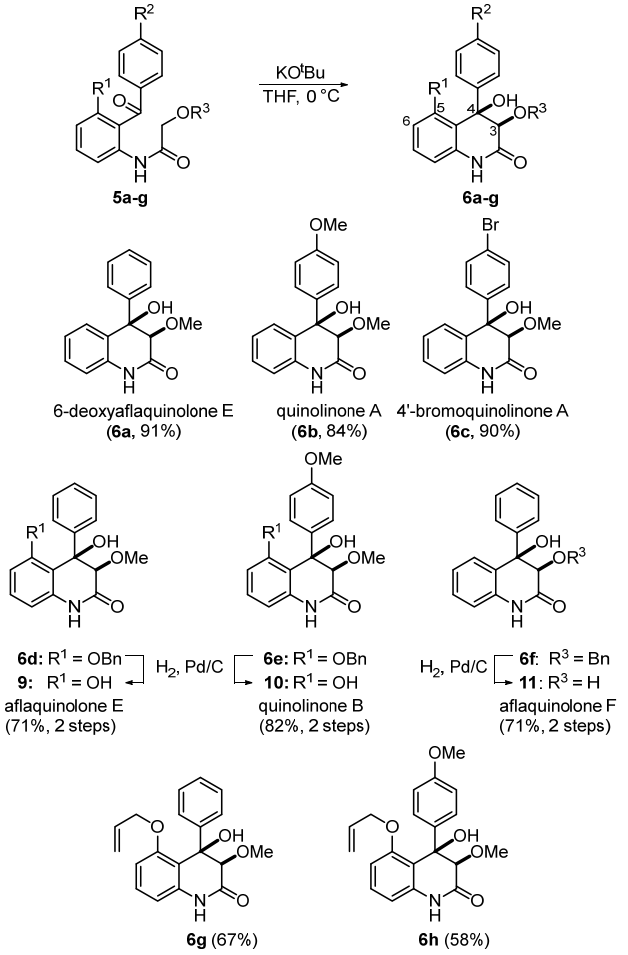
Entry	Compound 5	R¹	R²	R³	5 (%)[b]
1	**a**	H	H	Me	52
2[c]	**b**	H	OMe	Me	60
3	**c**	H	Br	Me	23
4	**d**	OBn	H	Me	35
5[c]	**e**	OBn	OMe	Me	24
6	**f**	H	H	Bn	40
7	**g**	OAllyl	H	Me	18
8[c]	**h**	OAllyl	OMe	Me	30

[a]Reaction conditions: **4** (0.20 mmol, 1 equiv., 0.1 M in MeCN), **3** (0.30 mmol, 1.5 equiv., 0.15 M in MeCN), TBAT (0.36 mmol, 1.8 equiv., 0.18 M in MeCN), 4 mL reactor volume, 65 °C; [b]isolated yield; [c]**4b** (c = 0.01 M in MeCN), **3a**–**c** (c = 0.015 M in MeCN), TBAT (c = 0.018 M in MeCN).

With the benzophenones **5a**–**h** in hand, we next investigated an intramolecular reaction[10] to forge the 3,4-dioxygenated quinoline-2-one core. Using an excess of potassium *tert*-butoxide in tetrahydrofuran at 0 °C, the quinolinones **6a**–**g** were obtained as single diastereomers (Scheme 2).

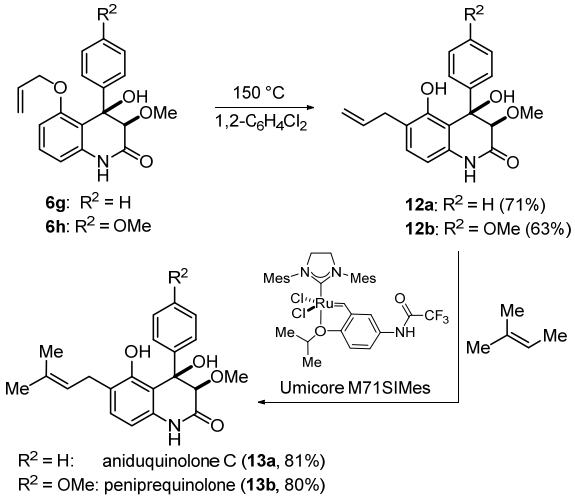
Following this procedure, the natural products (±)-6-deoxyaflaquinolone E (**6a**)[21] and (±)-quinolinone A (**6b**)[20c] were prepared in 91% and 84% yield, respectively.

Scheme 2. Intramolecular Aldolization



Cyclization of **5d**, **5e**, and **5f** delivered the benzyl protected quinolinones **6d**, **6e**, and **6f** which were subjected to hydrogenolysis to afford the natural products (±)-aflaquinolone E (**9**), F (**11**),[18] and (±)-quinolinone B (**10**)[20c] in up to 82% yield over two steps. Quinolinones **6g** and **6h** underwent Claisen rearrangement at 150 °C in 1,2-dichlorobenzene for 10 hours to give **12a** and **12b** in 71% and 63% yield, respectively (Scheme 3).[22] At higher temperature and prolonged reaction time, elimination of the tertiary alcohol was observed. Olefin metathesis of **12a** using Umicore M71SIMes as catalyst and an excess of 2-methylbut-2-ene gave (±)-aniduquinolone C (**13a**)[21] in 81% yield, whereas (±)-peniprequinolone (**13b**)[20] was obtained in 80% yield starting from **12b**.

Scheme 3. Synthesis of Aniduquinolone C and Peniprequinolone



In conclusion, we have devised a general approach for the synthesis of 3,4-dioxygenated quinolin-2-one natural products. The sequence proceeds through an insertion of arynes into unsymmetric imides followed by a diastereoselective intramolecular aldolization. A flow protocol for the aryne insertion was developed giving access to *N*-glycolated 2-aminobenzophenones within minutes. By this not immediately evident, yet powerful disconnection, the quinolinone natural products peniprequinolone, aflaquinolone E, F, quinolone A, B, and aniduquinolone C were synthesized in three to six steps.[23] Future work will focus on the synthesis of quinolinone natural products with other side chains and higher oxidation levels.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Florian Bartels and Reinhold Zimmer (FU Berlin) for helpful discussions. We also thank Umicore for the generous donation of metathesis catalysts.

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(23) All spectra of prepared natural products are in agreement with those reported in ref. (18), (19) and (21).

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Supporting Information

General working methods

The analytical data was obtained with the help of the following equipment.

NMR spectroscopy

^{1}H and ^{13}C NMR spectra were acquired on a JEOL ECX 400 (400 MHz), JEOL ECP 500 (500 MHz) and a Bruker Avance 700 (700 MHZ) in $CDCl_3$ as a solvent. The chemical shifts were reported relative to $CDCl_3$ (δ = ^{1}H: 7.26 ppm, ^{13}C: 77.16 ppm). The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = quintuplet, br = broad and combinations thereof.

The spectra were evaluated with the software MestRec.

Mass spectra were obtained on a ESI-FTICR-MS: Ionspec QFT-7 (Agilent/Varian), or a HR-EI-MS: Autospec Premier (Waters).

GC-MS: were recorded on a GC system Agilent Technologies 7890-A series/Mass selective detector, Agilent Technologies 5975 C (column: HP-5MS (J&W Scientific, Agilent); 30 m, 0.250 mm i.D., Film 0.25 µm).

IR: spectra were measured on a JASCO FT/IR-4100 Spectrometer. Characteristic absorption bands are displayed in wavelengths $\tilde{\nu}$ in cm^{-1} and were analyzed with the software Spectral Manager from JASCO.

Melting points were measured on a Thermovar from the company Reichert and are not corrected.

Chromatography Reaction progress was monitored by thin layer chromatography on aluminum backed silica gel plates (silica gel 60 F 254 from E. Merck), visualizing with UV light (λ = 254 nm). The plates were developed using vanillin dip solution (170 mL methanol, 20.0 ml conc. acetic acid, 10.0 mL conc. sulfuric acid with 1.0 g vanillin), $KMnO_4$ dip solution (3.0 g potassium permanganate, 5.0 mL NaOH-solution (5 w/w), 300 mL dest. water) or an anisaldehyde solution (450 mL ethanol, 25.0 mL anisaldehyde, 25.0 mL conc. sulfuric acid, 8.0 mL acetic acid).

Flash chromatography was performed using silica gel M60 from Macherey & Nagel (particle size: 40–63 µm).

HPLC: were conducted on a modular Knauer HPLC system with a UV detector at 254 nm and differential refractometer on a 4 x 250 mm column packed with Nucleosil 50-5 from Machery-Nagel.

Flow Reactions: Flow reactions were performed in 1/16 inch PTFE tubing with an inner diameter of 1.0 mm. The tubing was embedded in an aluminum block from ThalesNano and heated with an Ika stirring plate. A stainless-steel T-piece from Vici or static mixer (Upchurch Scientific) was used to mix the reagents. Fittings were either coned 10/32 stainless steel fittings from Upchurch scientific or flat bottom 1/4-28 gripper fittings from Dibafit. A kdScientific syringe pump (model no. KDS 200CE) was used to pump the reagents through the reactor.

Microwave Reactions: Reactions in a microwave were performed in a sealed tube using a Biotage Initiator Microwave with a maximum power of 400 W.

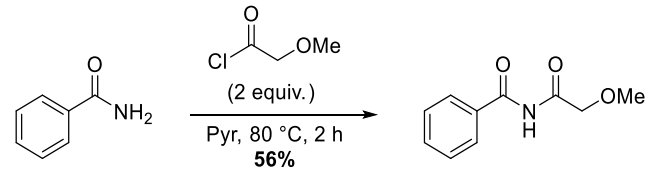
Reagents and Solvents Reactions with air or moisture-sensitive substances were, if not otherwise indicated, carried out under an argon atmosphere with the help of the Schlenk technique. All other reagents and solvents were used as purchased from commercial suppliers unless otherwise noted. Anhydrous solvents were purified with the solvent purification system MB-SPS-800 (Braun). Water free Acetonitrile was purchased from Acros Organics in AcroSeal©-bottles under Argon atmosphere with molecular sieves (3 Å) or HPLC-grade acetonitrile from Fischer Scientific was used. The solvents (ethyl acetate, pentane) used for column chromatography and work up were purified from commercially available technical grade solvents by distillation under reduced pressure with the help of rotatory evaporators (Heidolph or IKA) at 40 °C water bath temperature.

Benzamides,[1] benzyloxy acetic acid,[2] benzyloxyacetyl chloride[3] and 3-hydroxy-2-(trimethylsilyl)phenyl triflate[4] were prepared according to literature procedures.

Compound names are derived from Chemdraw and are not necessarily identical with the IUPAC nomenclature.

Synthesis of Compounds

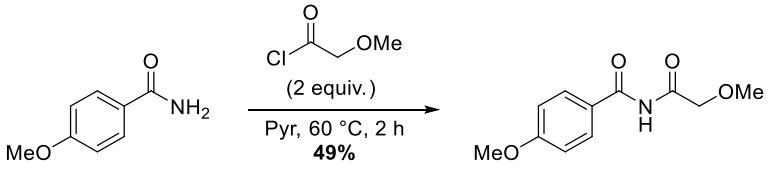
N-(2-Methoxyacetyl)-benzamide (4a)



Benzamide (2.00 g, 16.5 mmol, 1 equiv.) was dissolved in anhydrous pyridine (26 mL) and 2-methoxyacetyl chloride (3.01 mL, 33.0 mmol, 2 equiv.) was added in one portion at room temperature. The yellow mixture was stirred in a sealed tube at 80 °C for 2 hours. After cooling to room temperature, the mixture was concentrated under reduced pressure to 1/4 of its volume and diluted with NH_4Cl (sat. aq., 50 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with NH_4Cl (sat. aq., 3 × 150 mL) and NaCl (sat. aq., 100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, *n*-pentane/EtOAc = 1:1) affording the title compound (**Ia**, 1.77 g, 9.17 mmol, 56%) as a colorless solid.

R_f = 0.41 (*n*-pentane/EtOAc = 1:1); **m.p.:** 105 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 9.44 (s, 1H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 4.38 (s, 2H), 3.49 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 171.1, 165.2, 133.4, 132.5, 129.0, 127.9, 73.1, 59.5 ppm; **IR** (neat): $\tilde{\nu}$ = 3378, 3280, 3168, 3071, 2990, 2963, 2938, 2920, 2825, 2748, 2600, 1909, 1771, 1709, 1685, 1636, 1602, 1584, 1555, 1508, 1465, 1448, 1396, 1384, 1346, 1327, 1310, 1287, 1250, 1239, 1196, 1169, 1120, 1090, 1069, 1031, 1012, 1002, 973, 933, 907, 842, 818, 805, 751, 701 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{10}H_{11}NNaO_3^+$ ($[M+Na]^+$): 216.0631; found: 216.0641.

4-methoxy-*N*-(2-methoxyacetyl)-benzamide (4b)

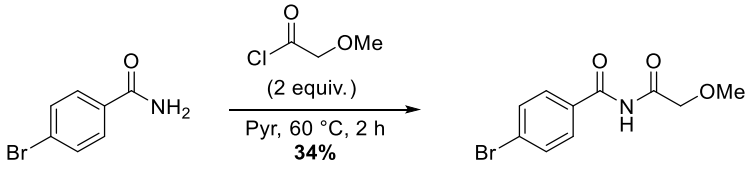


4-Methoxybenzamide (2.00 g, 13.2 mmol, 1 equiv.) was dissolved in anhydrous pyridine (20 mL) and 2-methoxyacetyl chloride (1.50 mL, 16.5 mmol, 2 equiv.) was added at room temperature. The orange mixture was stirred in a sealed tube at 60 °C for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was suspended in $NaHCO_3$ (sat. aq., 250 mL) and EtOAc (250 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with NaCl (sat. aq., 2 × 400 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was recrystallized from hot EtOAc affording the title compound (**Ib**, 1.45 g, 6.48 mmol, 49%) as a colorless solid.

R_f = 0.42 (*n*-pentane/EtOAc = 1:2); **m.p.:** 156 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 11.00 (s, 1H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.9 Hz, 2H), 4.44 (s, 2H), 3.83 (s, 3H), 3.34 (s, 3H) ppm; **^{13}C NMR** (101

MHz, DMSO-d_6): δ = 172.9, 165.7, 163.0, 130.7, 124.6, 113.8, 72.8, 58.5, 55.6 ppm; **IR** (neat): $\tilde{\nu}$ = 3390, 3291, 3169, 3094, 3080, 3014, 2970, 2942, 2843, 1769, 1710, 1685, 1645, 1618, 1607, 1574, 1517, 1458, 1422, 1394, 1311, 1254, 1182, 1146, 1124, 1025, 849, 809, 764 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{11}H_{13}NNaO_4^+$ ([M+Na]$^+$): 246.0737; found 246.0738.

4-bromo-*N*-(2-methoxyacetyl)-benzamide (4c)

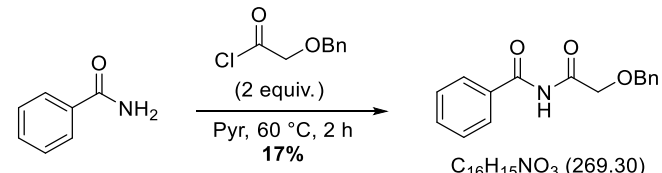


C_7H_6BrNO (200.04) $C_{10}H_{10}BrNO_3$ (272.10)

4-Bromobenzamide (150 mg, 0.992 mmol, 1 equiv.) was dissolved in anhydrous pyridine (1.6 mL) and 2-methoxyacetyl chloride (0.181 mL, 1.99 mmol, 2 equiv.) was added at room temperature. The orange mixture was stirred in a sealed tube at 60 °C for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was suspended in $NaHCO_3$ (sat. aq., 20 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with NaCl (sat. aq., 2 × 50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, *n*-pentane/EtOAc 2:1) to afford the title compound (**Ic**, 74.0 mg, 0.332 mmol, 34%) as a colorless solid.

$\mathbf{R_f}$ = 0.30 (*n*-pentane/EtOAc = 1:2); **m.p.:** 141 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.37 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 4.35 (s, 2H), 3.51 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 170.7, 164.5, 132.4, 131.5, 129.5, 128.6, 73.0, 59.6 ppm; **IR** (neat): $\tilde{\nu}$ = 3240, 3196, 3160, 2970, 2952, 2926, 2823, 1731, 16696, 1591, 1524, 1502, 1479, 1400, 1386, 1257, 1232, 1202, 1136, 1110, 1069, 1012, 939, 907, 840, 818, 772, 763, 744, 717, 684, 661 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{10}H_{10}BrNO_3Na^+$ ([M+Na]$^+$): 293.9736; found: 293.9745.

***N*-(2-(benzyloxy)acetyl)benzamide (4d)**

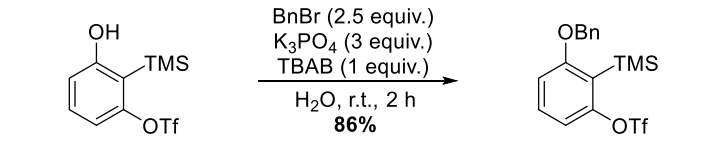


C_7H_7NO (121.14) $C_{16}H_{15}NO_3$ (269.30)

Benzamide (800 mg, 6.60 mmol, 1 equiv.) was dissolved in anhydrous pyridine (11 mL). Benzyloxyacetyl chloride (2.44 g, 13.2 mmol, 2 equiv.) was added and the mixture was stirred in a sealed tube at 60 °C for 2 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL) and $NaHCO_3$ (sat. aq., 10 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with NaCl (sat. aq., 2 x 10 mL) and dried ($MgSO_4$). The solvents were removed under reduced pressure. The crude product was recrystallized from hot EtOAc affording the title compound (**Id**, 300 mg, 1.10 mmol, 17%) as a colorless solid.

m.p.: 113 °C; **^{1}H NMR** (700 MHz, $CDCl_3$) δ = 9.32 (s, 1H), 7.82 – 7.80 (m, 2H), 7.60 (td, *J* = 7.3, 1.3 Hz, 1H), 7.50 – 7.47 (m, 2H), 7.39 (s, 2H), 7.38 (d, *J* = 1.6 Hz, 2H), 7.36 – 7.33 (m, 1H), 4.70 (s, 2H), 4.43 (s, 2H) ppm; **^{13}C NMR** (176 MHz, $CDCl_3$) δ = 170.5, 165.0, 136.8, 133.5, 132.6, 129.2, 128.8, 128.5, 128.2, 127.8, 73.9, 70.5 ppm; **IR** (neat): $\tilde{\nu}$ = 3284, 2951, 2922, 2868, 1712, 1688, 1599, 1582, 1500, 1469, 1406, 1390, 1373, 1324, 1304, 1244, 1216, 1115, 1102, 1072, 1028, 1001, 975, 949, 933, 908, 872, 862, 841, 822, 800, 785, 757, 702, 657 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{16}H_{15}NNaO_3^+$ ([M+Na]$^+$): 292.0944; found: 292.0951.

3-(benzyloxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (3b)

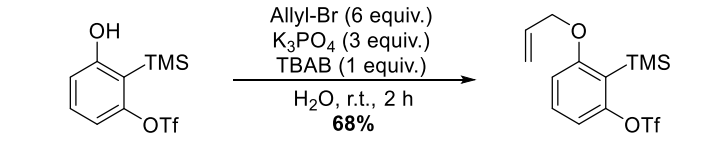


$C_{10}H_{13}F_3O_4SSi$ (314.35) $C_{17}H_{19}F_3O_4SSi$ (404.48)

3-Hydroxy-2-trimethylsilyl-phenyl trifluoromethanesulfonate (500 mg, 1.59 mmol, 1 equiv.) was suspended in water (15 mL) and BnBr (0.472 mL, 3.98 mmol, 2.5 equiv.), TBAB (513 mg, 1.59 mmol, 1 equiv.) and K_3PO_4 (1.01 g, 4.77 mmol, 3 equiv.) were added at room temperature. The suspension was stirred vigorously at room temperature for two hours, diluted with water and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, *n*-pentane/EtOAc = 20:1) to afford the title compound (**IVb**, 555 mg, 1.37 mmol, 86%) as a colorless oil.

R_f = 0.83 (*n*-pentane/EtOAc = 10:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.41 (s, 4H), 7.39 – 7.32 (m, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.09 (s, 2H), 0.34 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 164.8, 154.9, 136.2, 131.7, 128.8, 128.4, 127.9, 121.2, 120.1, 117.5, 113.1, 110.6, 71.1, 1.1 ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -73.98 ppm; **IR** (neat): $\tilde{\nu}$ = 3067, 3036, 2954, 2901, 2876, 1594, 1565, 1434, 1417, 1247, 1207, 1160, 1137, 1116, 1024, 934, 842, 826, 785, 735 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{17}H_{19}F_3SSiNa$ ([M+Na]$^+$): 427.0617, found 427.0667.

3-(allyloxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (3c)

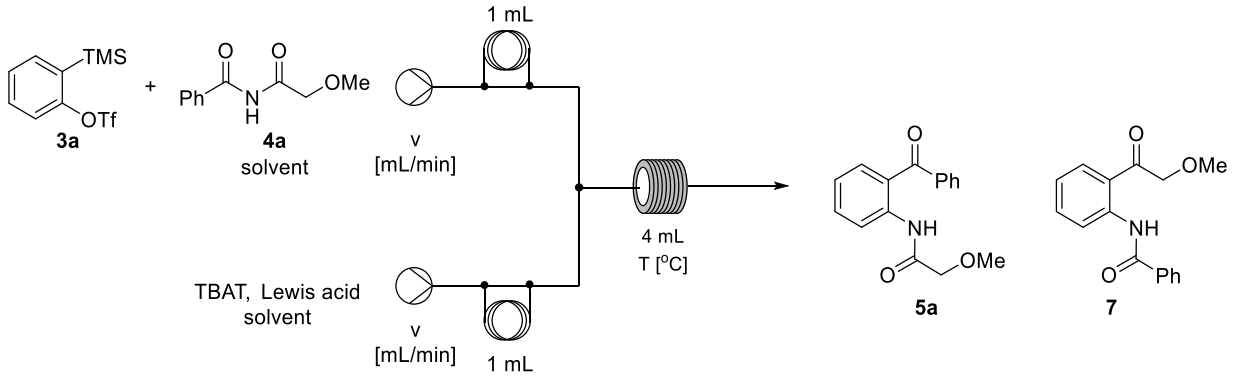


$C_{10}H_{13}F_3O_4SSi$ (314.35) $C_{13}H_{17}F_3O_4SSi$ (354.42)

3-Hydroxy-2-trimethylsilyl-phenyl trifluoromethanesulfonate (1.47 g, 4.66 mmol, 1 equiv.) was suspended in water (150 mL). Allyl bromide (2.42 mL, 28.0 mmol, 6.0 equiv.), TBAB (1.50 g, 4.66 mmol, 1.0 equiv.) and K_3PO_4 (2.97 g, 14.0 mmol, 3 equiv.) were added at room temperature. The suspension was stirred vigorously at room temperature for one hour, diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, *n*-pentane) to afford the title compound (**IVc**, 1.12 g, 3.16 mmol, 68%) as a colorless oil.

R_f = 0.65 (*n*-pentane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.34 (t, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.09 – 5.98 (m, 1H), 5.45 – 5.35 (m, 1H), 5.34 – 5.30 (m, 1H), 4.56 (d, *J* = 5.4 Hz, 2H), 0.38 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 164.6, 154.8, 132.7, 131.7, 121.2, 118.5, 117.5, 113.0, 110.6, 69.7, 1.1 ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -72.77 ppm; **IR** (neat): $\tilde{\nu}$ = 3089, 2988, 2955, 2901, 2865, 1595, 1565, 1436, 1420, 1362, 1247, 1206, 1160, 1140, 1117, 1057, 1034, 996, 939, 924, 894, 837, 787, 769, 738, 712, 693, 668 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{13}H_{17}F_3O_4SSiNa^+$ ([M+Na]$^+$): 377.0461, found: 377.0461.

Table S1. Analysis of main parameters for the synthesis of benzophenone **5a** and acetophenone **7**

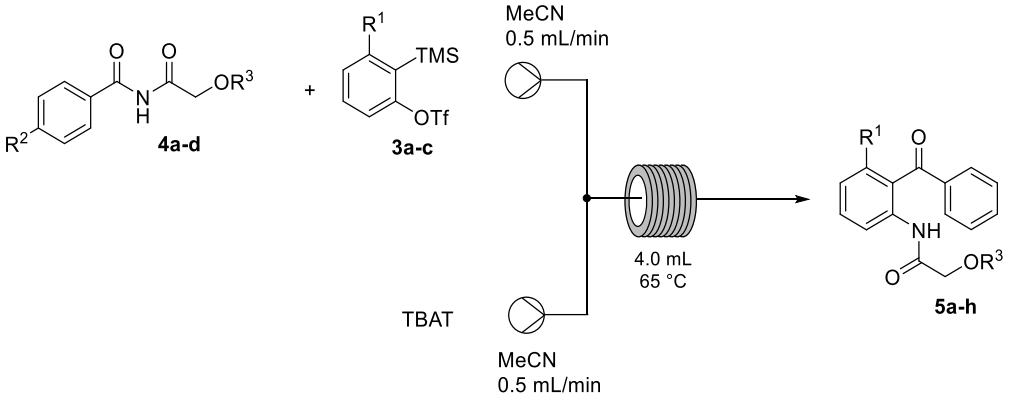


Entry	v [ml/min]	Residence time [min]	Lewis acid	C_{Imid} [mol/L]	C_{Arin} [mol/L]	C_{TBAT} [mol/L]	T [°C]	**IIa : III**[a]	Solvent/cond.	**5a**[a] [%]
1	0.5	4	none	0.05	0.06	0.10	55	-	no workup	32
2	0.5	4	none	0.05	0.06	0.10	55	-	aqueous workup	42
3	0.5	4	none	0.05	0.06	0.10	55	-	wet MeCN, no workup, static mixer	31
4	0.5	4	none	0.05	0.06	0.10	55	-	static mixer, dry MeCN	36
5	0.2	10	none	0.05	0.06	0.10	55	-	wet MeCN, no workup, static mixer	32
6	0.2	10	none	0.05	0.06	0.10	65	-	wet MeCN, no workup, static mixer	32
7	0.2	10	none	0.05	0.08	0.10	55	-	wet MeCN, no workup, static mixer	26
8	0.2	10	none	0.09	0.05	0.10	55	-	wet MeCN, no workup, static mixer	24
9	0.5	4	none	0.05	0.08	0.10	80	-	wet MeCN, no workup, static mixer	42
10	0.5	4	none	0.025	0.04	0.05	55	2.7 : 1	PhMe/MeCN (1:1)	31
11	0.5	4	none	0.025	0.04	0.05	80	4.2 : 1	PhMe/MeCN (1:1); 40 psi BPR	42

12	0.2	10	none	0.025	0.04	0.05	65	3.1 : 1	PhMe/MeCN (1:1), static mixer	32
13	0.5	4	none	0.05	0.08	0.1	55	2.5 : 1	THF	20
14	0.5	4	none	0.04	0.08	0.1	80	4.1 : 1	wet MeCN; 40 psi BPR	36
15	0.5	4	none	0.04	0.08	0.1	90	4.2 : 1	wet MeCN; 40 psi BPR	35
16	0.5	4	none	0.04	0.08	0.1	100	4.0 : 1	wet MeCN; 40 psi BPR	40
17	0.5	4	$Sc(OTf)_3$	0.1	0.15	0.18	65	-	dry MeCN	<5[b]
18	0.5	4	$MgCl_2$	0.1	0.15	0.18	65	-	dry MeCN	<5[b]
19	0.5	4	$BF_3{\cdot}OEt_2$	0.1	0.15	0.18	65	-	dry MeCN	<5[b]
20	0.5	4	$AlCl_3$	0.1	0.15	0.18	65	-	dry MeCN	<5[b]
21	0.5	4	$Ti(OiPr)_4$	0.1	0.15	0.18	65	-	dry MeCN	<5[b]
22	0.5	4	$Ti(OiPr)_4$	0.1	0.15	0.18	65	-	dry MeCN	<5[b]
23	0.5	4	none	0.1	0.15	0.18	65	2.9 : 1[c]	wet MeCN	52[c]
24	0.2	10	none	0.05	0.06	0.075	65	3.3 : 1[b]	dry MeCn	42[c]
25	0.2	10	none	0.05	0.06	0.075	80	3.8 : 1[b]	dry MeCN	39[c]

[a]The ratio of **5a**:**7** as well as the yield of IIa were determined via GC-MS acetanilid as standard. An aliquot of the reactor output (100 µL or 500 µL) was taken, diluted to yield a volume of 900 µL and treated with a solution of acetanilide (100 µL, 0.05 M). [b]Determined by ^{1}H NMR integration. [c]isolated yield.

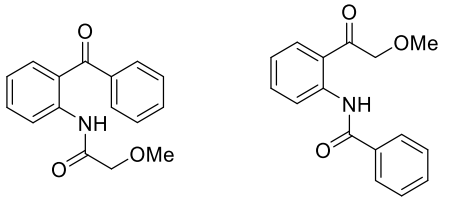
General Procedure for the Aryne Insertion in Flow (GP1)



Prior use, the flow reactor was washed with three reactor volumes of acetonitrile using a syringe pumps. A stock solution of aryne precursor (**3a-c**, 0.150 M in MeCN, 1.5 equiv.) and imide (**4a-d**, 0.100 M in

MeCN, 1.0 equiv.) was loaded on a sample loop with a volume of 1 mL. Then, a stock solution of TBAT (0.180 M in acetonitrile, 1.8 equiv.) was loaded on a sample loop with a volume of 1 mL. Both solutions were pumped simultaneously at a rate of 0.5 mL/min, driven by MeCN. The stock solutions were combined at a T-piece to react in a 4.0 mL PTFE coil, preheated to 65 °C using an aluminum block. The reaction mixture was collected, concentrated under reduced pressure and purified by column chromatography to afford the *ortho*-aminobenzophenones **5a-h**.

_N_-(2-benzoylphenyl)-2-methoxyacetamide (5a)



5a $C_{16}H_{15}NO_3$ (269.30) **7** $C_{16}H_{15}NO_3$ (269.30)

Compound **5a** was prepared according to **GP1** starting from **3a** (127 mg, 0.427 mmol, 1.5 equiv.) and **4a** (55.0 mg, 0.285 mmol, 1 equiv.). Column chromatography (silica gel, *n*-pentane/EtOAc = 4:1) afforded the title compound (**5a**, 40.0 mg, 0.148 mmol, 52%) as a colorless oil that solidified in the fridge and compound **7** (14.5 mg, 0.054 mmol, 19%) as a colorless solid.

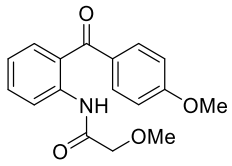
5a:

R_f = 0.40 (*n*-pentane/EtOAc = 3:1); **^{1}H NMR** (700 MHz, $CDCl_3$): δ = 11.39 (s, 1H), 8.69 (d, *J* = 8.3 Hz, 1H), 7.73 – 7.70 (m, 2H), 7.60 – 7.54 (m, 3H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 4.04 (s, 2H), 3.55 (s, 3H) ppm; **^{13}C NMR** (176 MHz, $CDCl_3$): δ 199.1, 169.2, 139.4, 138.7, 134.1, 133.5, 132.5, 130.0, 128.4, 124.3, 122.6, 121.7, 72.7, 59.8 ppm; **IR** (neat): $\tilde{\nu}$ = 3286, 3060, 3033, 2996, 2934, 2828, 2756, 2249, 1832, 1692, 1639, 1598, 1577, 1515, 1446, 1432, 1362, 1317, 1293, 1263, 1196, 1180, 1158, 1114, 1076, 1048, 1028, 987, 959, 935, 917, 880, 852, 805, 752, 728 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{15}NNaO_3^+$ ([M+Na]$^+$): 292.0944; found: 292.0959.

7:

R_f = 0.35 (*n*-pentane/EtOAc = 3:1); **m.p.:** 138–139 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 12.57 (s, 1H), 9.02 (dd, J = 8.6, 1.1 Hz, 1H), 8.12 – 8.08 (m, 2H), 7.82 (dd, J = 8.0, 1.4 Hz, 1H), 7.64 (ddd, J = 8.7, 7.3, 1.5 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.53 – 7.49 (m, 2H), 7.14 (t, J = 8.2 Hz, 1H), 4.81 (s, 2H), 3.55 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 200.2, 166.2, 141.8, 135.9, 134.6, 132.2, 129.6, 129.0, 127.7, 122.6, 121.3, 119.7, 75.5, 59.7 ppm; **IR** (neat): $\tilde{\nu}$ = 3268, 3236, 3130, 3062, 2995, 2942, 2829, 1672, 1653, 1610, 1585, 1559, 1537, 1507, 1496, 1448, 1368, 1322, 1311, 1258, 1216, 1196, 1139, 1120, 1029, 978, 925, 699, 661 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{15}NNaO_3^+$ ([M+Na]$^+$): 292.0944; found: 292.0944.

2-methoxy-*N*-(2-(4-methoxybenzoyl)phenyl)acetamide (5b)

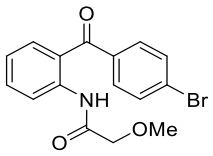


$C_{17}H_{17}NO_4$ (299.33)

Compound **5b** was prepared according to **GP1** starting from **3a** (90.4 mg, 0.303 mmol, 1.5 equiv., 0.015 M) and and **4b** (45.0 mg, 0.202 mmol, 1 equiv., 0.010 M). Column chromatography (silica gel, *n*-pentane/EtOAc = 3:1) afforded the title compound (**5b**, 32.8 mg, 0.122 mmol, 60%) as a slightly yellow oil.

R_f = 0.49 (*n*-pentane/EtOAc = 2:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 11.09 (s, 1H), 8.62 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.58 – 7.52 (m, 2H), 7.16 – 7.09 (m, 1H), 6.99 – 6.93 (m, 2H), 4.03 (s, 2H), 3.89 (s, 3H), 3.53 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 197.3, 169.1, 163.5, 138.8, 133.4, 132.8, 132.7, 131.1, 125.3, 122.7, 121.9, 113.7, 72.7, 59.8, 55.7 ppm; **IR** (neat): $\tilde{\nu}$ = 3310, 3006, 2931, 2840, 1687, 1633, 1597, 1578, 1510, 1447, 1419, 1315, 1306, 1293, 1253, 1196, 1172, 1154, 1110, 1026, 986, 925, 844, 788, 760, 739, 696 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{15}NNaO_3^+$ ($[M+Na]^+$): 322.1050; found: 322.1062.

***N*-(2-(4-bromobenzoyl)phenyl)-2-methoxyacetamide (5c)**

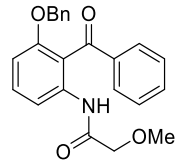


$C_{16}H_{14}BrNO_3$ (348.20)

Compound **5c** was prepared according to **GP1** starting from **3a** (44.8 mg, 0.150 mmol, 1.5 equiv.) **4c** (27.2 mg, 0.100 mmol, 1 equiv.). Column chromatography (silica gel, *n*-pentane/EtOAc 3:1) afforded the title compound (**5c**, 8.10 mg, 0.023 mmol, 23%) as a slightly yellow oil.

R_f = 0.33 (*n*-pentane/EtOAc = 3:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 11.31 (s, 1H), 8.68 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.67 – 7.54 (m, 5H), 7.52 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.15 – 7.11 (m, 1H), 4.05 (s, 2H), 3.56 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 197.9, 169.2, 139.5, 137.5, 134.4, 133.2, 131.8, 131.6, 127.7, 124.0, 122.8, 121.9, 72.7, 59.9 ppm; **IR** (neat): $\tilde{\nu}$ = 3298, 3081, 3033, 2995, 2932, 2827, 1692, 1641, 1601, 1577, 1515, 1483, 1446, 1432, 1394, 1361, 1314, 1293, 1262, 1196, 1178, 1167, 1157, 1114, 1068, 1051, 1010, 987, 959, 921, 880, 841, 783, 758, 725, 675, 654 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{14}BrNNaO_3^+$ ($[M+Na]^+$): 370.0049; found: 370.0063.

N-(2-benzoyl-3-(benzyloxy)phenyl)-2-methoxyacetamide (5d)

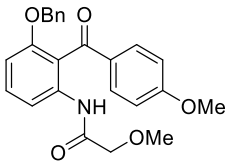


$C_{23}H_{21}NO_4$ (375.42)

Compound **5d** was prepared according to **GP1** starting from **3b** (62.0 mg, 0.153 mmol, 1.5 equiv.) and **4a** (44.6 mg, 0.230 mmol, 1 equiv.). Column chromatography (silica gel, *n*-pentane/EtOAc = 3:1) afforded the title compound (**5d**, 30.6 mg, 0.082 mmol, 35%) as a slightly yellow oil.

R_f = 0.25 (*n*-pentane/EtOAc = 4:1); **^{1}H NMR** (700 MHz, $CDCl_3$): δ = 9.51 (s, 1H), 8.03 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.80 – 7.77 (m, 2H), 7.55 (tt, *J* = 8.7, 1.3 Hz, 1H), 7.47 – 7.41 (m, 3H), 7.21 – 7.17 (m, 1H), 7.16 – 7.13 (m, 2H), 6.81 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 2H), 4.90 (s, 2H), 3.93 (s, 2H), 3.41 (s, 3H) ppm; **^{13}C NMR** (176 MHz, $CDCl_3$): δ = 197.1, 168.6, 157.4, 139.4, 137.1, 136.1, 133.1, 132.5, 129.4, 128.5, 128.4, 127.8, 126.8, 118.8, 115.2, 108.5, 72.4, 70.4, 59.6 ppm; **IR** (neat): $\tilde{\nu}$ = 3359, 3061, 3031, 3003, 2929, 2829, 1802, 1693, 1646, 1597, 1581, 1523, 1497, 1466, 1460, 1450, 1428, 1381, 1313, 1275, 1256, 1196, 1178, 1146, 1112, 1087, 1071, 1028, 986, 925, 875, 865, 846, 807, 782, 739 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{23}H_{21}NNaO4^+$ ([M+Na]$^+$): 398.1363; found: 398.1367.

N-(3-(benzyloxy)-2-(4-methoxybenzoyl)phenyl)-2-methoxyacetamide (5e)

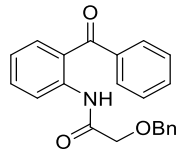


$C_{24}H_{23}NO_5$ (405.45)

Compound **5e** was prepared according to **GP1** starting from **3b** (571 mg, 1.41 mmol, 1.5 equiv., 0.015 M) and **4b** (210 mg, 0.941 mmol, 1 equiv., 0.010 M). Column chromatography (silica gel, *n*-pentane/EtOAc = 3:1) afforded the title compound (**5e**, 90.6 mg, 0.122 mmol, 24%) as a slightly yellow oil.

R_f = 0.18 (*n*-pentane/EtOAc = 3:1); **^{1}H NMR** (700 MHz, CD_3CN): δ = 8.96 (s, 1H), 7.87 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.76 – 7.73 (m, 2H), 7.47 (t, *J* = 8.3 Hz, 1H), 7.24 – 7.18 (m, 3H), 6.99 – 6.96 (m, 3H), 6.95 – 6.93 (m, 2H), 4.98 (s, 2H), 3.85 (s, 3H), 3.84 (s, 2H), 3.30 (s, 3H) ppm; **^{13}C NMR** (176 MHz, CD_3CN): δ = 195.8, 169.1, 165.2, 157.6, 137.4, 137.3, 132.6, 132.2, 129.2, 128.7, 128.1, 120.7, 115.9, 114.9, 109.8, 72.7, 71.1, 59.7, 56.4 ppm; **IR** (neat): $\tilde{\nu}$ = 3360, 3062, 3034, 3009, 2935, 2840, 1691, 1645, 1593, 1509, 1461, 1382, 1280, 1254, 1173, 1145, 1111, 1070, 1028, 986, 927, 844, 793, 735, 696, 668 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{24}H_{23}NNaO_5^+$ ([M+Na]$^+$): 428.1468; found: 428.1461.

N-(2-benzoylphenyl)-2-(benzyloxy)acetamide (5f)

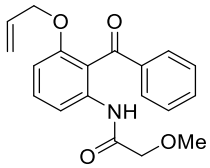


$C_{22}H_{19}NO_3$ (345.40)

Compound **5f** was prepared according to **GP1** starting from **3a** (44.8 mg, 0.150 mmol, 1.5 equiv.) and **4d** (29.0 mg, 0.100 mmol, 1 equiv.). Column chromatography (silica gel, *n*-pentane/EtOAc 6:1) afforded the title compound (**5f**, 14.1 mg, 0.0404 mmol, 40%) as a colorless oil.

R_f = 0.60 (*n*-pentane/EtOAc = 4:1); **^{1}H NMR** (700 MHz, $CDCl_3$): δ = 11.46 (s, 1H), 8.67 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.77 – 7.74 (m, 2H), 7.62 – 7.55 (m, 3H), 7.52 – 7.45 (m, 4H), 7.37 – 7.33 (m, 2H), 7.32 – 7.28 (m, 1H), 7.15 – 7.10 (m, 1H), 4.73 (s, 2H), 4.10 (s, 2H) ppm; **^{13}C NMR** (176 MHz, $CDCl_3$): δ = 198.8, 169.2, 139.3, 138.7, 136.9, 134.0, 133.3, 132.6, 130.2, 128.7, 128.4, 128.2, 128.1, 124.6, 122.7, 121.8, 73.8, 69.8 ppm; **IR** (neat): $\tilde{\nu}$ = 3300, 3061, 3029, 2955, 2924, 2867, 1694, 1641, 1599, 1578, 1519, 1447, 1397, 1373, 1317, 1293, 1265, 1207, 1163, 1099, 1027, 1000, 974, 936, 921, 852, 805, 75 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{22}H_{19}NNaO_3^+$ ($[M+Na]^+$): 368.1257; found: 368.1263.

N-(3-(allyloxy)-2-benzoylphenyl)-2-methoxyacetamide (5g)

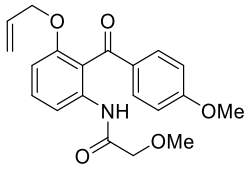


$C_{19}H_{19}NO_4$ (325.36)

Compound 5**g** was prepared according to **GP1** starting from **3c** (107 mg, 0.303 mmol, 1.5 equiv.) and **4a** (45.0 mg, 0.202 mmol, 1 equiv.). Column chromatography (silica gel, *n*-pentane/EtOAc = 3:1) afforded the title compound (**5g**, 12.0 mg, 0.0371 mmol, 18%) as a slightly yellow oil.

R_f = 0.29 (*n*-pentane/EtOAc = 3:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 8.01 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.56 – 7.51 (m, 1H), 7.47 – 7.38 (m, 3H), 6.73 (dd, *J* = 8.4, 0.9 Hz, 1H), 5.53 (ddt, *J* = 17.2, 10.7, 4.9 Hz, 1H), 4.97 (dq, *J* = 10.7, 1.5 Hz, 1H), 4.87 (dq, *J* = 17.3, 1.7 Hz, 1H), 4.35 (dt, *J* = 5.0, 1.7 Hz, 2H), 3.93 (s, 2H), 3.40 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 197.1, 168.6, 157.4, 139.3, 137.1, 133.1, 132.5, 132.1, 129.3, 128.4, 118.6, 117.1, 115.1, 108.6, 72.4, 69.3, 59.6 ppm; **IR** (neat): $\tilde{\nu}$ = 3356, 3066, 2951, 2922, 2850, 1696, 1648, 1597, 1584, 1522, 1468, 1422, 1370, 1362, 1314, 1277, 1197, 1178, 1145, 1114, 1076, 986, 926, 853, 808, 782, 746, 718, 702, 671, 661 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{19}H_{19}NNaO_4^+$ ($[M+Na]^+$): 348.1206; found: 348.1207.

_N_-(3-(allyloxy)-2-(4-methoxybenzoyl)phenyl)-2-methoxyacetamide (5h)

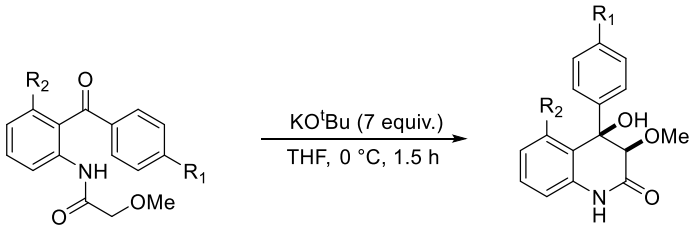


$C_{20}H_{21}NO_5$ (355.39)

Compound **5h** was prepared according to **GP1** starting from **3c** (198 mg, 0.555 mmol, 1.5 equiv., 0.015 M) and **4b** (83.0 mg, 0.370 mmol, 1 equiv., 0.010 M). Column chromatography (silica gel, *n*-pentane/EtOAc = 2:1) afforded the title compound (**5h**, 39.3 mg, 0.111 mmol, 30%) as a slightly yellow oil.

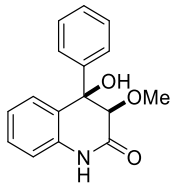
R_f = 0.32 (*n*-pentane/EtOAc = 2:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 9.25 (s, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.40 (t, *J* = 8.3 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.74 (d, *J* = 9.1 Hz, 1H), 5.65 (ddt, *J* = 17.2, 10.6, 4.9 Hz, 1H), 5.02 (dq, *J* = 10.7, 1.5 Hz, 1H), 4.96 (dq, *J* = 17.3, 1.7 Hz, 1H), 4.40 (dt, *J* = 4.8, 1.7 Hz, 2H), 3.90 (s, 2H), 3.86 (s, 3H), 3.37 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 195.1, 168.5, 164.0, 156.8, 136.5, 132.4, 132.0, 131.8, 131.6, 119.5, 117.1, 115.2, 113.7, 108.7, 72.3, 69.3, 59.6, 55.7 ppm; **IR** (neat): $\tilde{\nu}$ = 3359, 3075, 2931, 2840, 1810, 1693, 1646, 1594, 1522, 1509, 1467, 1421, 1382, 1362, 1315, 1281, 1256, 1196, 1173, 1146, 1113, 1073, 1026, 986, 929, 880, 846, 817, 792, 768, 734, 709, 693, 672, 663 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{20}H_{21}NNaO_5^+$ ($[M+Na]^+$): 378.1312; found: 378.1331.

General Procedure for the Aldol Reaction (GP2)



The *ortho*-aminobenzophenone (**5a-h**, 1 equiv.) was dissolved in anhydrous THF (50 mL/mmol substrate) and a solution of KO^{t}Bu (7 equiv., 1 M in THF) was added dropwise at 0 °C. Upon addition of KO^{t}Bu the solution turned bright yellow. After stirring at 0 °C for 1.5 h, water (50 mL/mmol substrate) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL/mmol substrate). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography to afford the quinolinones **6a-g**.

(±)–6-Deoxyaflaquinolone E (6a)

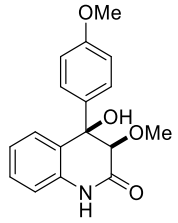


$C_{16}H_{15}NO_3$ (269.30)

6-Deoxyaflaquinolone E was prepared according to **GP2** starting from **5a** (20 mg, 0.075 mmol, 1 equiv.) and KO^{t}Bu (59 mg, 0.53 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 100:3) to afford the title compound (**6a**, 18 mg, 0.068 mmol, 92%) as a colorless solid.

R_f = 0.21 (*n*-pentane/EtOAc = 1:1); **m.p.:** 160 °C – 165 °C; **^{1}H NMR** (700 MHz, DMSO-d_6): δ = 10.21 (s, 1H), 7.33 (d, *J* = 4.4 Hz, 4H), 7.28 (dt, *J* = 8.5, 4.2 Hz, 1H), 7.24 – 7.20 (m, 1H), 6.93 – 6.90 (m, 2H), 6.88 (dd, *J* = 7.5, 1.6 Hz, 1H), 5.81 (s, 1H), 4.18 (s, 1H), 3.34 (s, 3H) ppm; **^{13}C NMR** (176 MHz, DMSO-d_6): δ = 168.4, 142.3, 136.8, 129.2, 128.7, 127.8, 127.5, 127.3, 126.7, 122.1, 115.1, 83.9, 76.7, 59.1 ppm; **IR** (neat): $\tilde{\nu}$ = 3446, 3361, 3211, 3085, 3022, 2993, 2931, 2845, 2831, 1681, 1609, 1593, 1559, 1486, 1446, 1433, 1397, 1318, 1285, 1263, 1246, 1226, 1203, 1181, 1157, 1142, 1119, 1097, 1069, 1048, 1020, 1001, 953, 940, 910, 871, 858, 824, 791, 762, 752, 704, 674, 658 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{15}NNaO_3^+$ ([M+Na]$^+$): 292.0944; found: 292.0945. The NMR data match those reported for 6-deoxyaflaquinolone E.[5]

(±)–Quinolinone A (6b)

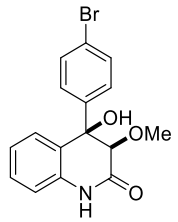


$C_{17}H_{17}NO_4$ (299.33)

Quinolinone A was prepared according to **GP2** starting from **5b** (20 mg, 0.067 mmol, 1 equiv.) and KO*t*Bu (53 mg, 0.47 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 100:3) to afford the title compound (**6b**, 16.7 mg, 0.056 mmol, 84%) as a colorless solid.

R_f = 0.22 (*n*-pentane/EtOAc = 1:1); **m.p.:** 172 °C – 175 °C; **^{1}H NMR** (500 MHz, acetone-d_6): δ = 9.29 (s, 1H), 7.35 – 7.20 (m, 4H), 7.07 – 6.97 (m, 2H), 6.91 – 6.81 (m, 2H), 4.61 (s, 1H), 3.93 (s, 1H), 3.76 (s, 3H), 3.45 (s, 3H) ppm; **^{13}C NMR** (126 MHz, acetone-d_6): δ = 168.2, 160.3, 137.6, 134.5, 129.6, 129.0, 128.4, 123.6, 115.9, 115.9, 114.2, 85.7, 77.3, 59.4, 55.5 ppm; **IR** (neat): $\tilde{\nu}$ = 3249, 3081, 3002, 2931, 2836, 1687, 1611, 1595, 1512, 1483, 1463, 1379, 1306, 1252, 1173, 1146, 1106, 1081, 1033, 991, 942, 903, 860, 833, 812, 757 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{17}H_{17}NNaO_4^+$ ([M+Na]$^+$): 322.1050; found: 322.1047. The NMR data match those reported for Quinolinone A.[6]

***cis*-4-(4-bromophenyl)-4-hydroxy-3-methoxy-3,4-dihydroquinolin-2(1*H*)-one (6c)**

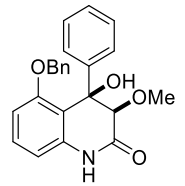


$C_{16}H_{14}BrNO_3$ (348.20)

Compound **6c** was prepared according to **GP2** starting from **5c** (8.0 mg, 0.021 mmol, 1 equiv.) and KO*t*Bu (16 mg, 0.15 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 100:3) to afford the title compound (**6c**, 7.2 mg, 0.019 mmol, 90%) as a colorless oil.

R_f = 0.21 (*n*-pentane/EtOAc = 1:1); **^{1}H NMR** (700 MHz, CD_3OD): δ = 7.51 (d, *J* = 8.8 Hz, 2H), 7.36 – 7.33 (m, 2H), 7.28 (ddd, *J* = 8.0, 5.8, 3.0 Hz, 1H), 7.00 – 6.98 (m, 2H), 6.95 (dt, *J* = 7.9, 0.8 Hz, 1H), 4.23 (s, 1H), 3.40 (s, 3H) ppm; **^{13}C NMR** (176 MHz, $CDCl_3$): δ = 170.9, 142.4, 138.0, 132.2, 130.5, 130.2, 129.7, 129.1, 124.3, 122.7, 116.8, 85.4, 78.4, 60.6 ppm; **IR** (neat): $\tilde{\nu}$ = 3241, 3069, 2954, 2927, 2853, 2358, 1685, 1607, 1592, 1488, 1467, 1394, 1309, 1205, 1173, 1143, 989, 802, 759 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{14}BrNO_3Na^+$ ([M+Na]$^+$): 370.0049; found: 370.0051.

***cis*-5-(benzyloxy)-4-hydroxy-3-methoxy-4-phenyl-3,4-dihydroquinolin-2(1*H*)-one (6d)**

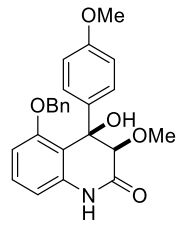


$C_{23}H_{21}NO_4$ (375.42)

Compound **6d** was prepared according to **GP2** starting from **5d** (28 mg, 0.075 mmol, 1 equiv.) and KO*t*Bu (59 mg, 0.53 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 100:2) to afford the title compound (**6d**, 23 mg, 0.062 mmol, 84%) as a colorless oil.

R_f = 0.25 (*n*-pentane/EtOAc = 1:1); **^{1}H NMR** (700 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 7.28 – 7.21 (m, 5H), 7.07 (dd, *J* = 7.6, 1.9 Hz, 2H), 6.73 (dd, *J* = 8.5, 0.9 Hz, 1H), 6.57 (dd, *J* = 8.0, 0.9 Hz, 1H), 5.29 (s, 1H), 5.05 (d, *J* = 11.5 Hz, 1H), 4.96 (d, *J* = 11.6 Hz, 1H), 3.85 (d, *J* = 1.4 Hz, 1H), 3.61 (s, 3H) ppm; **^{13}C NMR** (176 MHz, $CDCl_3$): δ = 168.0, 158.0, 142.0, 137.2, 135.7, 130.1, 128.7, 128.7, 128.4, 128.3, 127.5, 126.2, 115.2, 109.6, 108.8, 85.0, 78.4, 71.1, 59.8 ppm; **IR** (neat): $\tilde{\nu}$ = 3503, 3232, 3062, 3031, 2930, 2829, 2248, 1691, 1595, 1498, 1471, 1448, 1383, 1315, 1277, 1259, 1222, 1176, 1138, 1102, 1059, 1028, 993, 910, 846, 783, 730, 697, 654 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{23}H_{21}NNaO_4^+$ ($[M+Na]^+$): 398.1363; found: 398.1368.

***cis*-5-(benzyloxy)-4-hydroxy-3-methoxy-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1*H*)-one (6e)**

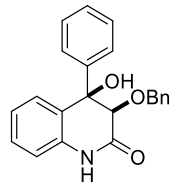


$C_{24}H_{23}NO_5$ (405.45)

Compound **6e** was prepared according to **GP2** starting from **5e** (30 mg, 0.080 mmol, 1 equiv.) and KO*t*Bu (63 mg, 0.56 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 100:3) to afford the title compound (**6e**, 25 mg, 0.067 mmol, 84%) as a colorless oil.

R_f = 0.25 (*n*-pentane/EtOAc = 1:1); **^{1}H NMR** (700 MHz, $CDCl_3$): δ = 8.33 (s, 1H), 7.29 – 7.23 (m, 3H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.11 – 7.08 (m, 2H), 6.79 (d, *J* = 7.5 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 5.28 (s, 1H), 5.05 (d, *J* = 11.5 Hz, 1H), 4.97 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 1H), 3.76 (s, 3H), 3.59 (s, 3H) ppm; **^{13}C NMR** (176 MHz, $CDCl_3$): δ = 168.0, 159.7, 158.1, 137.1, 135.7, 133.6, 129.9, 128.8, 128.4, 127.6, 127.5, 115.4, 114.1, 109.5, 108.8, 85.2, 78.2, 71.1, 59.7, 55.4 ppm; **IR** (neat): $\tilde{\nu}$ = 3502, 3237, 3066, 3034, 2999, 2930, 2834, 1693, 1596, 1508, 1471, 1388, 1302, 1280, 1253, 1231, 1172, 1103, 1061, 1031, 993, 913, 895, 834, 778, 734, 698, 656 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{24}H_{23}NNaO_5^+$ ($[M+Na]^+$): 428.1468; found: 428.1467.

cis-3-(benzyloxy)-4-hydroxy-4-phenyl-3,4-dihydroquinolin-2(1_H_)-one (6f)

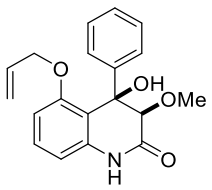


$C_{22}H_{19}NO_3$ (345.40)

Compound **6f** was prepared according to **GP2** starting from **5f** (14 mg, 0.043 mmol, 1 equiv.) and KO*t*Bu (34 mg, 0.30 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 100:3) to afford the title compound (**6f**, 12 mg, 0.031 mmol, 72%) as a colorless oil.

R_f = 0.23 (Pentane/EtOAc = 1:1); **^{1}H NMR** (500 MHz, CD_3OD): δ = 7.40 – 7.32 (m, 5H), 7.27 (ddd, *J* = 7.9, 6.3, 2.6 Hz, 1H), 7.20 – 7.15 (m, 3H), 7.03 – 6.99 (m, 2H), 6.99 – 6.93 (m, 3H), 4.81 (d, *J* = 11.5 Hz, 1H), 4.50 (s, 1H), 4.45 (d, *J* = 11.5 Hz, 1H) ppm; **^{13}C NMR** (176 MHz, $CDCl_3$): δ = 168.5, 140.7, 136.7, 135.7, 129.7, 128.8, 128.6, 128.6, 128.5, 128.5, 128.2, 128.1, 126.8, 124.1, 115.5, 81.1, 73.8 ppm; **IR** (neat): $\tilde{\nu}$ = 3263, 3087, 3060, 3029, 2923, 2854, 1692, 1610, 1595, 1485, 1448, 1375, 1296, 1265, 1241, 1211, 1174, 1143, 1125, 1096, 1070, 1044, 1028, 989, 936, 907, 853, 811, 753 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{22}H_{19}NO_3K^+$ ([M+K]$^+$): 384.0997; found: 384.1002.

cis-5-(allyloxy)-4-hydroxy-3-methoxy-4-phenyl-3,4-dihydroquinolin-2(1_H_)-one (6g)

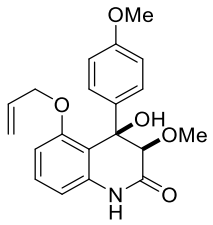


$C_{19}H_{19}NO_4$ (325.36)

Compound **6g** was prepared according to **GP2** starting from **5g** (35 mg, 0.11 mmol, 1 equiv.) and KO*t*Bu (86 mg, 0.77 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 100:2) to afford the title compound (**6g**, 27 mg, 0.072 mmol, 67%) as a colorless oil.

R_f = 0.23 (*n*-pentane/EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 8.07 (s, 1H), 7.29 – 7.26 (m, 5H), 7.22 (t, *J* = 8.2 Hz, 1H), 6.65 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.52 (dd, *J* = 8.0, 0.9 Hz, 1H), 5.78 (ddt, *J* = 17.2, 10.6, 5.4 Hz, 1H), 5.34 (s, 1H), 5.21 – 5.15 (m, 2H), 4.52 – 4.41 (m, 2H), 3.84 (d, *J* = 1.4 Hz, 1H), 3.58 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 167.7, 158.0, 141.9, 137.2, 132.1, 130.0, 128.7, 128.5, 126.1, 118.8, 115.0, 109.4, 108.7, 85.1, 78.4, 69.8, 59.8 ppm; **IR** (neat): $\tilde{\nu}$ = 3494, 3249, 3235, 3083, 3002, 2928, 2829, 1692, 1596, 1502, 1473, 1447, 1421, 1391, 1324, 1313, 1278, 1259, 1224, 1179, 1103, 1059, 1028, 992, 930, 887, 824, 784, 750, 731, 699, 674, 665, 654 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{19}H_{19}NO_4Na^+$ ([M+Na]$^+$): 348.1206; found: 348.1195.

***cis*-5-(allyloxy)-4-hydroxy-3-methoxy-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1*H*)-one (6h)**

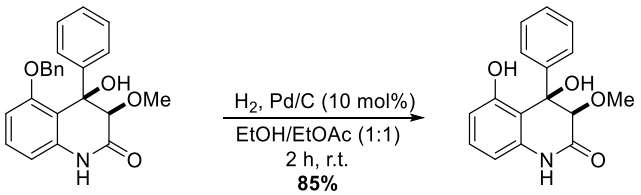


$C_{20}H_{21}NO_5$ (355.39)

Compound **6h** was prepared according to **GP2** starting from **5h** (43 mg, 0.12 mmol, 1 equiv.) and KO^{t}Bu (94 mg, 0.84 mmol, 7 equiv.). The crude product was purified by column chromatography (silica gel CH_2Cl_2/MeOH = 100:3) to afford the title compound (**6h**, 25 mg, 0.070 mmol, 58%) as a colorless oil.

R_f = 0.23 (*n*-pentane/EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 8.34 (s, 1H), 7.21 (t, *J* = 8.2 Hz, 1H), 7.18 – 7.15 (m, 2H), 6.81 – 6.77 (m, 2H), 6.65 (d, *J* = 8.5 Hz, 1H), 6.51 (dd, *J* = 8.0, 0.8 Hz, 1H), 5.83 (ddt, *J* = 17.0, 10.4, 5.3 Hz, 1H), 5.40 (s, 1H), 5.25 – 5.16 (m, 2H), 4.54 – 4.44 (m, 2H), 3.81 (d, *J* = 1.5 Hz, 1H), 3.74 (s, 3H), 3.59 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 167.9, 159.7, 158.0, 137.0, 133.6, 132.1, 129.8, 127.5, 118.8, 115.2, 114.1, 109.5, 108.7, 85.2, 78.2, 69.8, 59.6, 55.3 ppm; **IR** (neat): $\tilde{\nu}$ = 3697, 3251, 3237, 3196, 3101, 3087 3039, 2997, 2932, 2833, 2246, 1691, 1595, 1508, 1471, 1442, 1417, 1392, 1303, 1280, 1251, 1224, 1172, 1101, 993, 928, 912, 893, 833, 809, 779, 729, 693, 670, 661cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{20}H_{21}NNaO_5^+$ ([M+Na]$^+$): 378.1312; found: 378.1317.

(±)–Aflaquinolone E (9)



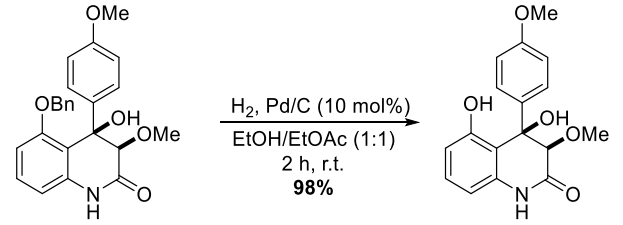
6d
$C_{23}H_{21}NO_4$ (375.42)

9
$C_{16}H_{15}NO_4$ (285.30)

To a solution of **6d** (23 mg, 0.060 mmol, 1 equiv.) EtOH/EtOAc (1:1, 1 mL) was added Pd/C (6.4 mg, 0.0061 mmol, 10 w% Pd, 10 mol%) and the atmosphere was changed from Ar to H_2 by short evacuation and backfilling with H_2. The reaction mixture was then stirred vigorously at room temperature for 2 h under an atmosphere of H_2. Then the reaction mixture was then filtered over a short pad of Celite® and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 50:1) to afford the title compound (**9**, 15 mg, 0.051 mmol, 85%) as a colorless solid.

R_f = 0.21 (*n*-pentane/EtOAc = 3:1); **m.p.:** 143 °C – 148 °C; **^{1}H NMR** (700 MHz, CD_3OD): δ = 7.32 – 7.29 (m, 3H), 7.29 – 7.26 (m, 2H), 7.15 (t, *J* = 8.1 Hz, 1H), 6.54 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.46 (dd, *J* = 8.0, 1.1 Hz, 1H), 3.66 (s, 1H), 3.53 (s, 3H) ppm; **^{13}C NMR** (176 MHz, CD_3OD): δ = 169.1, 159.1, 140.9, 138.1, 131.0, 129.8, 129.6, 127.5, 113.2, 113.0, 108.2, 86.3, 79.9, 59.2 ppm; **IR** (neat): $\tilde{\nu}$ = 3281, 3061, 2998, 2935, 2832, 1681, 1620, 1595, 1475, 1448, 1387, 1243, 1207, 1169, 1099, 1021, 879, 791, 745, 725, 698, 659 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{15}NNaO_4^+$ ([M+Na]$^+$): 308.0893; found: 308.0900. The NMR data match those reported for Aflaquinolone E.[7]

(±)–Quinolinone B (10)



6e
$C_{24}H_{23}NO_5$ (405.45)

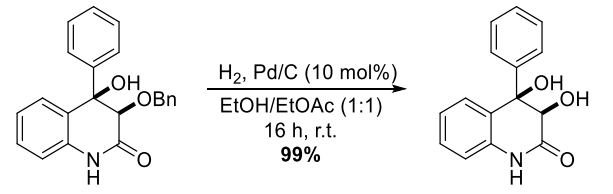
10
$C_{17}H_{17}NO_5$ (315.33)

To a solution of **6e** (12 mg, 0.028 mmol, 1 equiv.) in EtOH/EtOAc (1:1, 1 mL) was added Pd/C (3.0 mg, 0.0029 mmol, 10 w% Pd, 10 mol%) and the atmosphere was changed from Ar to H_2 by short evacuation and backfilling with H_2. The reaction mixture was then stirred vigorously at room temperature for 2 h under an atmosphere of H_2. The reaction mixture was then filtered over a short pad of Celite® and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel CH_2Cl_2/MeOH = 50:1) to afford the title compound (**10**, 8.8 mg, 0.028 mmol, 98%) as a colorless oil.

R_f = 0.60 (CH_2Cl_2/MeOH = 50:1); **^{1}H NMR** (700 MHz, acetone-d_6): δ = 9.28 (s, 1H), 9.16 (s, 1H), 7.22 (d, *J* = 8.9 Hz, 1H), 7.16 (t, *J* = 8.1 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 6.55 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.49 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.14 (s, 1H), 3.77 (s, 3H), 3.67 (d, *J* = 1.6 Hz, 1H), 3.50 (s, 3H) ppm; **^{13}C NMR**

(176 MHz, acetone-d_6): δ = 166.5, 161.0, 159.2, 138.1, 131.9, 130.7, 128.8, 114.7, 112.5, 112.4, 107.4, 85.8, 79.6, 58.9, 55.5. ppm; **IR** (neat): $\tilde{\nu}$ = 3294, 3066, 2993, 2932, 2837, 1685, 1626, 1595, 1510, 1439, 1379, 1305, 1253, 1207, 1170, 1103, 1076, 1051, 1025, 989, 936, 884, 834, 783, 756, 716 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{17}H_{17}NNaO_5^+$ ([M+Na]$^+$): 338.0999; found: 338.1006. The NMR data match those reported for Quinolinone B.[6]

(±)–Aflaquinolone F (11)



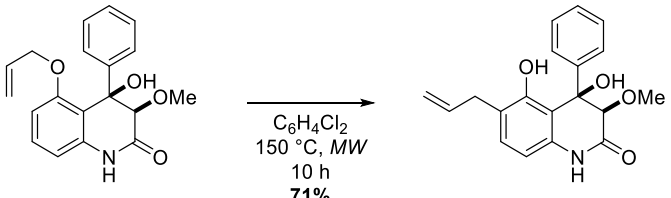
6f
$C_{22}H_{19}NO_3$ (345.40)

11
$C_{15}H_{13}NO_3$ (255.27)

To a solution of **6f** (12 mg, 0.034 mmol, 1 equiv.) in EtOH/EtOAc (1:1, 1 mL) was added Pd/C (3.6 mg, 0.0031 mmol, 10 w% Pd, 10 mol%) and the atmosphere was changed from Ar to H_2 by short evacuation and backfilling with H_2. The reaction mixture was then stirred vigorously at room temperature for 16 h under an atmosphere of H_2. The reaction mixture was then filtered over a short pad of Celite® and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 100:3) to afford the title compound (**11**, 8.7 mg, 0.034 mmol, 99%) as a colorless oil.

R_f = 0.30 (CH_2Cl_2/MeOH = 50:1); **^{1}H NMR** (600 MHz, CD_3OD): δ = 7.50 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.36 (m, 2H), 7.34 – 7.30 (m, 1H), 7.29 – 7.20 (m, 1H), 6.96 (s, 1H), 6.98 – 6.85 (m, 1H), 6.73 – 6.70 (m, 1H), 5.48 (s, 1H), 4.75 (s, 1H) ppm; **^{13}C NMR** (151 MHz, CD_3OD): δ = 172.7, 143.2, 138.4, 130.6, 130.1, 129.0, 128.4, 128.3, 124.0, 117.0, 78.7, 75.8, 49.4 ppm; **IR** (neat): $\tilde{\nu}$ = 3294, 2954, 2922, 2853, 1727, 1707, 1606, 1464, 1376, 1282, 1248, 1116, 1031, 824, 762, 722 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{15}H_{13}NNaO_3^+$ ([M+Na]$^+$): 278.0787; found: 278.0795. The NMR data match those reported for Aflaquinolone F.[7]

***cis*-6-allyl-4,5-dihydroxy-3-methoxy-4-phenyl-3,4-dihydroquinolin-2(1*H*)-one (12a)**



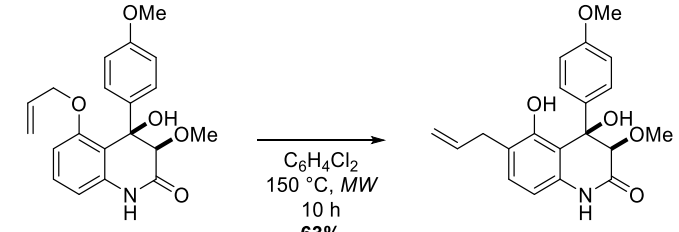
6g
$C_{19}H_{19}NO_4$ (325.36)

12a
$C_{19}H_{19}NO_4$ (325.36)

6g (14 mg, 0.040 mmol, 1 equiv.) was dissolved in 1,2-dichlorobenzene (1 mL) and heated in a microwave at 150 °C for 10 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, *n*-pentane/EtOAc = 1:2) to afford the title compound (**12a**, 9.9 mg, 0.030 mmol, 71%) as a colorless oil.

R_f = 0.32 (CH_2Cl_2/MeOH = 50:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 8.90 (d, *J* = 0.5 Hz, 1H), 7.85 (s, 1H), 7.33 – 7.29 (m, 3H), 7.28 – 7.25 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.32 (d, *J* = 8.0 Hz, 1H), 5.97 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.07 – 5.02 (m, 2H), 4.60 (s, 1H), 3.69 (d, *J* = 1.5 Hz, 1H), 3.62 (s, 3H), 3.31 (qdt, *J* = 15.7, 6.7, 1.7 Hz, 2H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 165.7, 155.7, 137.7, 136.9, 133.8, 130.8, 129.3, 129.0, 126.5, 124.4, 115.7, 110.5, 106.5, 84.3, 79.1, 59.1, 33.7 ppm; **IR** (neat): $\tilde{\nu}$ = 3465, 3290, 3074, 2954, 2924, 2869, 1683, 1638, 1622, 1602, 1505, 1493, 1463, 1449, 1421, 1378, 1346, 1272, 1223, 1174, 1102, 1077, 1036, 1027, 992, 947, 916, 892, 856, 846, 815, 754, 697, 673, 666 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{19}H_{19}NNaO_4^+$ ($[M+Na]^+$): 348.1206; found: 348.1216.

cis-6-allyl-4,5-dihydroxy-3-methoxy-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1*H*)-one (12b)



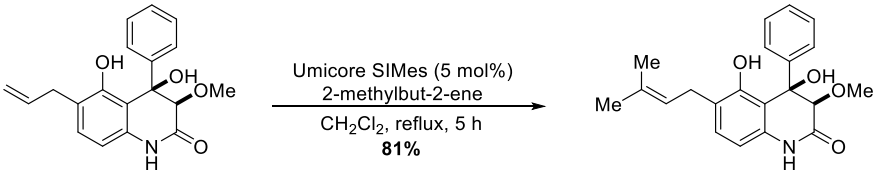
6h
$C_{20}H_{21}NO_5$ (355.39)

12b
$C_{20}H_{21}NO_5$ (355.39)

6h (39 mg, 0.11 mmol, 1 equiv.) was dissolved in 1,2-dichlorobenzene (1 mL) and heated in a microwave at 150 °C for 10 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, *n*-pentane/EtOAc = 1:2) to afford the title compound (**12b**, 25 mg, 0.070 mmol, 63%) as a colorless oil.

R_f = 0.32 (*n*-Pentane/EtOAc = 1:1); **^{1}H NMR** (400 MHz, acetone-d_6): δ= 9.45 (s, 1H), 9.25 (s, 1H), 7.28 – 7.15 (m, 2H), 7.04 (dt, *J* = 8.1, 0.7 Hz, 1H), 6.93 – 6.82 (m, 2H), 6.51 (d, *J* = 8.5 Hz, 1H), 6.23 (s, 1H), 6.01 – 5.89 (m, 1H), 5.08 – 5.00 (m, 1H), 4.96 (ddtd, *J* = 10.1, 2.0, 1.4, 0.5 Hz, 1H), 3.76 (s, 2H), 3.65 (dd, *J* = 1.5, 0.5 Hz, 1H), 3.50 (s, 1H), 3.33 – 3.20 (m, 2H) ppm; **^{13}C NMR** (126 MHz, acetone-d_6): δ = 166.4, 161.0, 156.6, 138.1, 136.3, 131.9, 130.8, 128.8, 123.2, 115.4, 114.7, 112.0, 107.1, 85.8, 79.7, 58.8, 55.5, 34.2. ppm; **IR** (neat): $\tilde{\nu}$ = 3280, 3069, 2955, 2924, 2853, 1683, 1638, 1623, 1603, 1509, 1463, 1418, 1379, 1306, 1253, 1224, 1172, 1103, 1077, 1028, 993, 944, 909, 891, 860, 830, 812, 798, 765, 754, 730, 709, 701, 687, 681, 666 cm^{-1}; **HMRS** (ESI): *m/z* calculated for $C_{20}H_{21}NNaO_5^+$ ($[M+Na]^+$): 378.1312; found: 378.1328.

(±)–Aniduquinolone C (13a)



$C_{19}H_{19}NO_4$ (325.36)

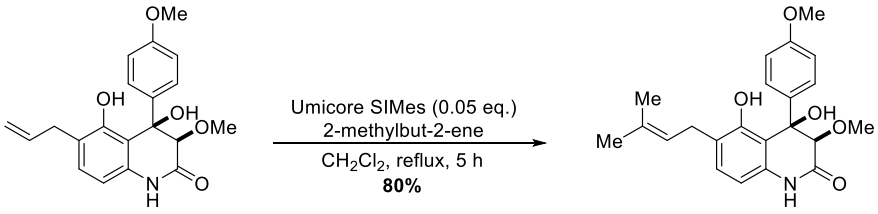
$C_{21}H_{23}NO_4$ (353.42)

12a (9.9 mg, 0.030 mmol, 1 equiv.) and Umicore M71 SIMes (1.1 mg, 0.0015 mmol, 5 mol%) were dissolved in CH_2Cl_2 (0.5 mL). 2-methylbut-2-ene (0.030 mL, 0.30 mmol, 10 equiv.) was added and the reaction mixture was heated to reflux for 5 h in a sealed tube. After cooling to room temperature, the

reaction mixture was filtered through a short pad of silica gel. All volatiles were removed under reduced pressure, and the crude product was purified by HPLC (EtOH/*n*-pentane = 1:10, 1 mL/min, t_r = 7.00 min) to afford the title compound (**13a**, 8.0 mg, 0.024 mmol, 81%) as a colorless oil.

R_f = 0.35 (CH_2Cl_2/MeOH 50:1); **^{1}H NMR** (700 MHz, DMSO-d_6): δ = 10.15 (s, 1H), 7.37 – 7.28 (m, 3H), 7.19 (dd, *J* = 5.8, 3.6 Hz, 2H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.37 (d, *J* = 7.9 Hz, 1H), 5.24 (t, *J* = 7.4 Hz, 1H), 3.58 (s, 1H), 3.43 (s, 3H), 3.19 (dd, *J* = 15.4, 7.4 Hz, 1H), 3.08 (dd, *J* = 15.4, 7.3 Hz, 1H), 1.68 (s, 3H), 1.65 (s, 3H) ppm; **^{13}C NMR** (176 MHz, DMSO-d_6): δ = 166.1, 155.0, 140.0, 135.0, 131.3, 129.2, 128.6, 126.2, 123.0, 122.8, 110.9, 106.3, 84.4, 78.7, 58.3, 27.5, 25.6, 17.7 ppm; **IR** (neat): $\tilde{\nu}$ = 3218, 3142, 3062, 2912, 2832, 2255, 1685, 1623, 1602, 1506, 1493, 1447, 1422, 1375, 1274, 1224, 1174, 1105, 1076, 1024, 1003, 943, 902, 867, 818, 767, 734 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{21}H_{23}NNaO_4^+$ ($[M+Na]^+$): 376.1519; found: 376.1513. The NMR data match those reported for Aniduquinolone C.[5]

(±)–Peniprequinolone (**13b**)



$C_{20}H_{21}NO_5$ (355.39) → $C_{22}H_{25}NO_5$ (383.44)

12b (11 mg, 0.030 mmol, 1 equiv.) and Umicore M71 SIMes (1.1 mg, 0.0015 mmol, 5 mol%) were dissolved in CH_2Cl_2 (0.5 mL). 2-methylbut-2-ene (0.030 mL, 0.30 mmol, 10 equiv.) was added and the reaction mixture was heated to reflux for 5 h in a sealed tube. After cooling to room temperature, the reaction mixture was filtered through a short pad of silica gel. All volatiles were removed under reduced pressure, and the crude product was purified by HPLC (EtOH/*n*-pentane = 1:10, 1 mL/min, t_r = 8.60 min) to afford the title compound (**13b**, 9.0 mg, 0.024 mmol, 80%) as a colorless solid.

R_f = 0.40 (CH_2Cl_2/MeOH 50:1); **m.p.:** 59°C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 8.91 (s, 1H), 7.91 (s, 1H), 7.19 – 7.14 (m, 2H), 7.03 (d, J = 8.0 Hz, 1H), 6.84 – 6.78 (m, 2H), 6.28 (d, J = 8.0 Hz, 1H), 5.30 – 5.26 (m, 1H), 4.54 (s, 1H), 3.76 (s, 3H), 3.68 (d, J = 1.5 Hz, 1H), 3.60 (s, 3H), 3.29 (dd, J = 16.0, 7.5 Hz, 1H), 3.20 (dd, J = 16.0, 7.2 Hz, 1H), 1.74 (s, 3H), 1.68 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 166.0, 160.3, 155.7, 133.3, 132.8, 130.1, 129.5, 128.0, 125.8, 122.4, 114.4, 110.5, 106.4, 84.5, 84.5, 78.9, 59.0, 55.4, 27.8, 25.9, 17.9 ppm; **IR** (neat): $\tilde{\nu}$ = 3277, 3059, 2954, 2923, 2869, 2853, 1684, 1621, 1603, 1510, 1462, 1419, 1377, 1306, 1254, 1221, 1188, 1172, 1105, 1079, 1032, 989, 974, 940, 929, 903, 867, 829, 810, 767, 755, 734, 707, 698, 974, 661, 652 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{22}H_{25}NNaO_5^+$ ($[M+Na]^+$): 406.1625; found: 406.1627. The NMR data match those reported for Peniprequinolone.[6]

References

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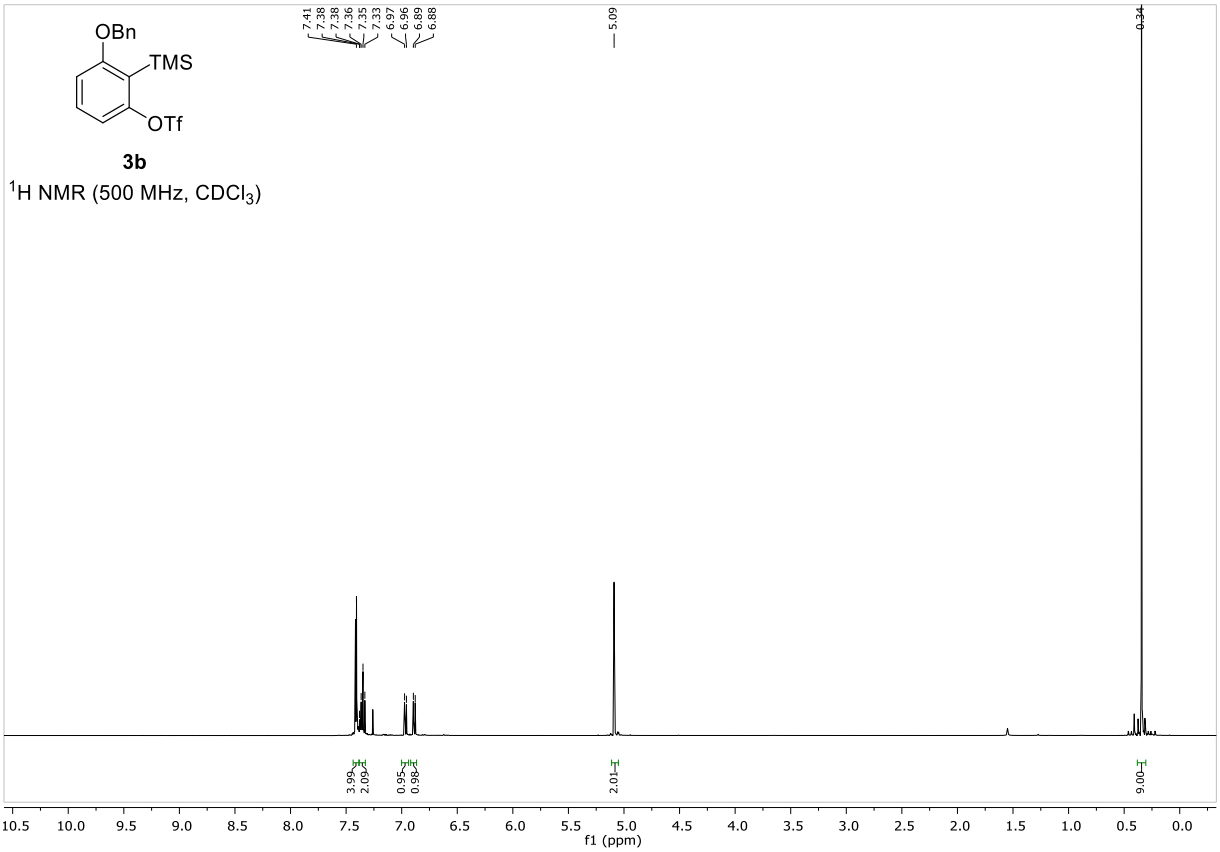
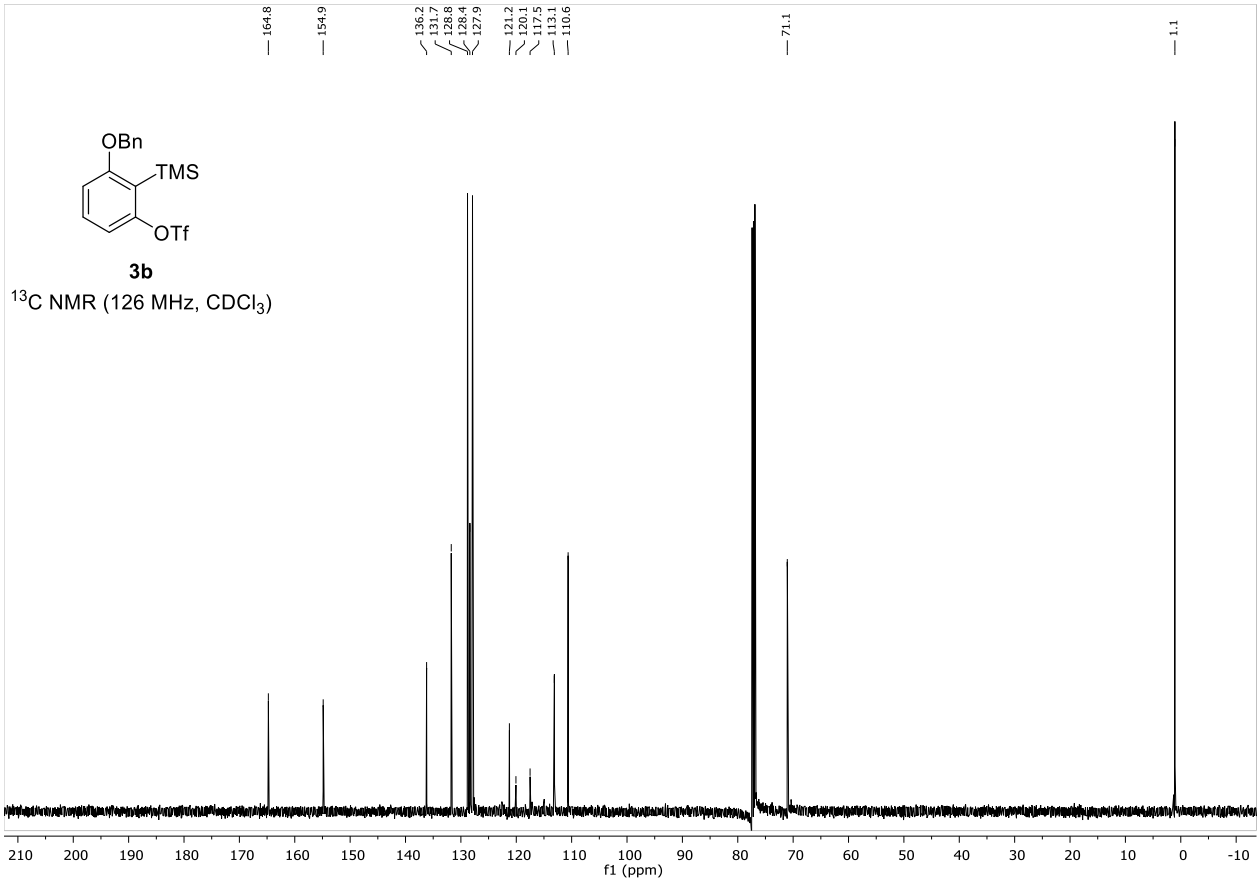
Appendix



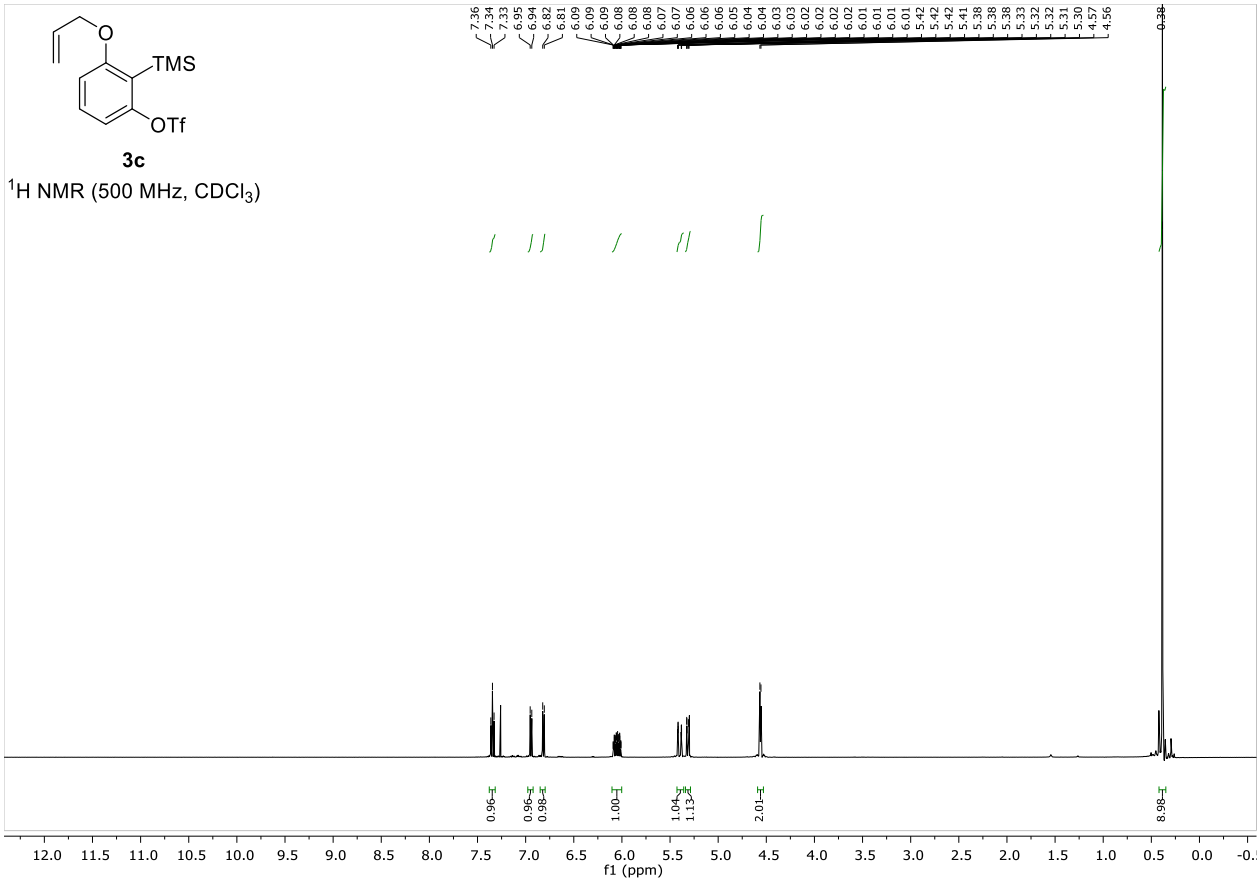
3b

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



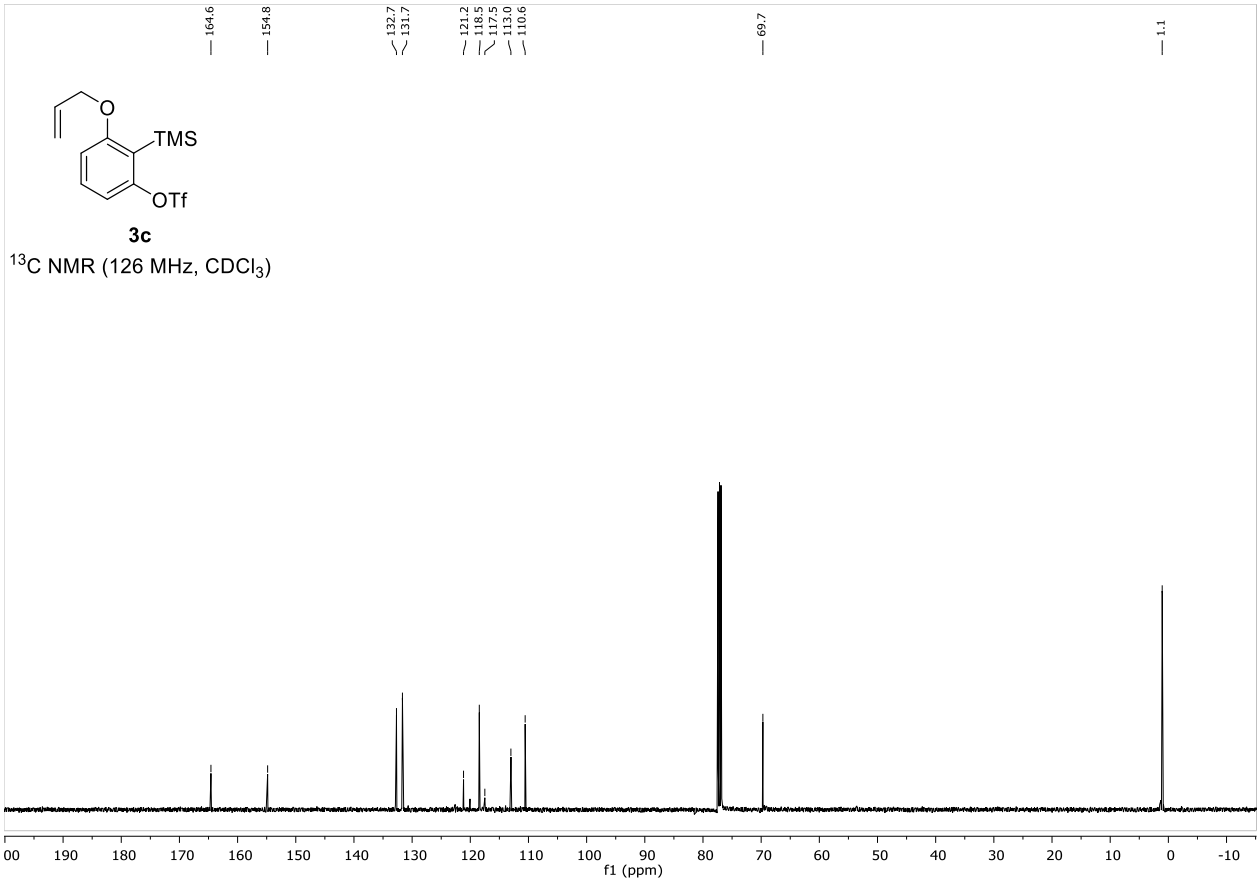
3b

^{13}C NMR (126 MHz, $CDCl_3$)



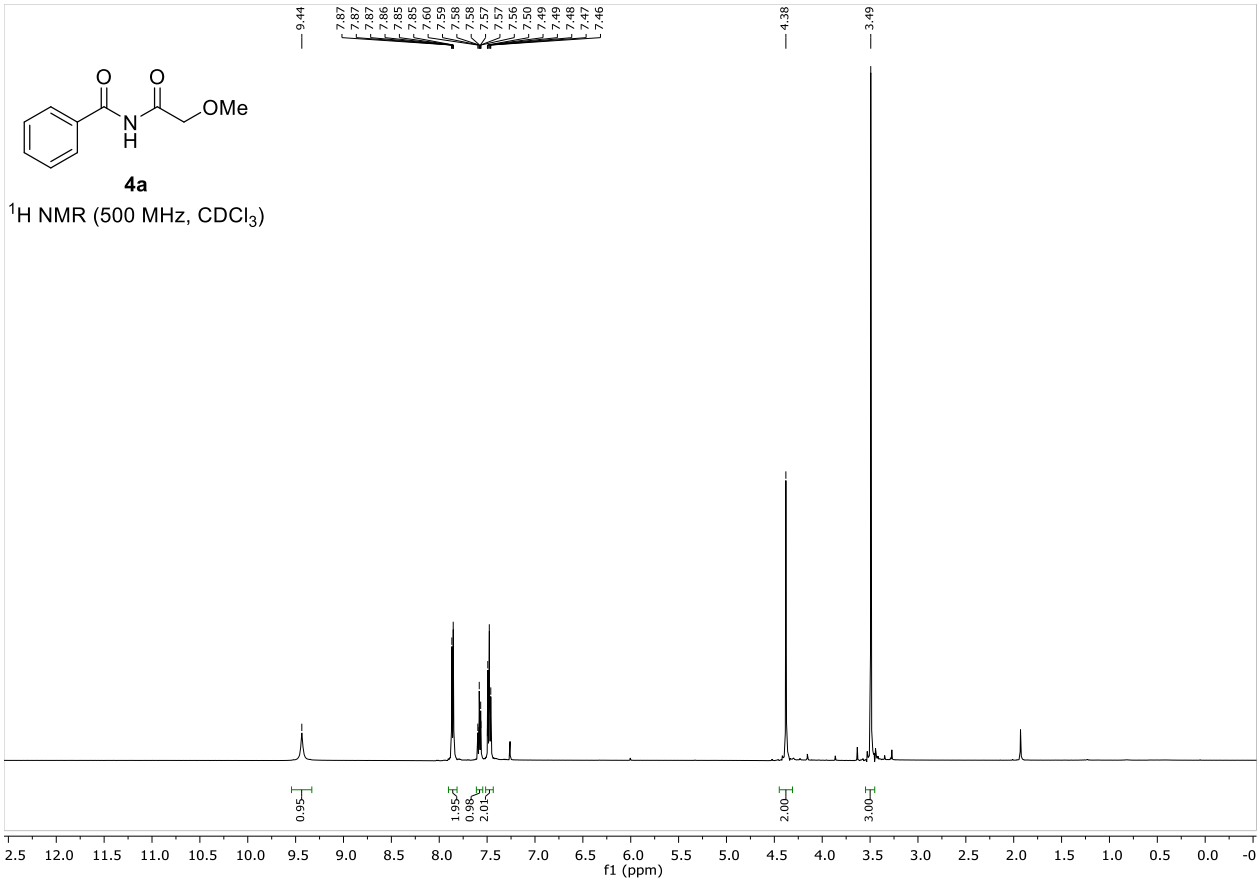
3c

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



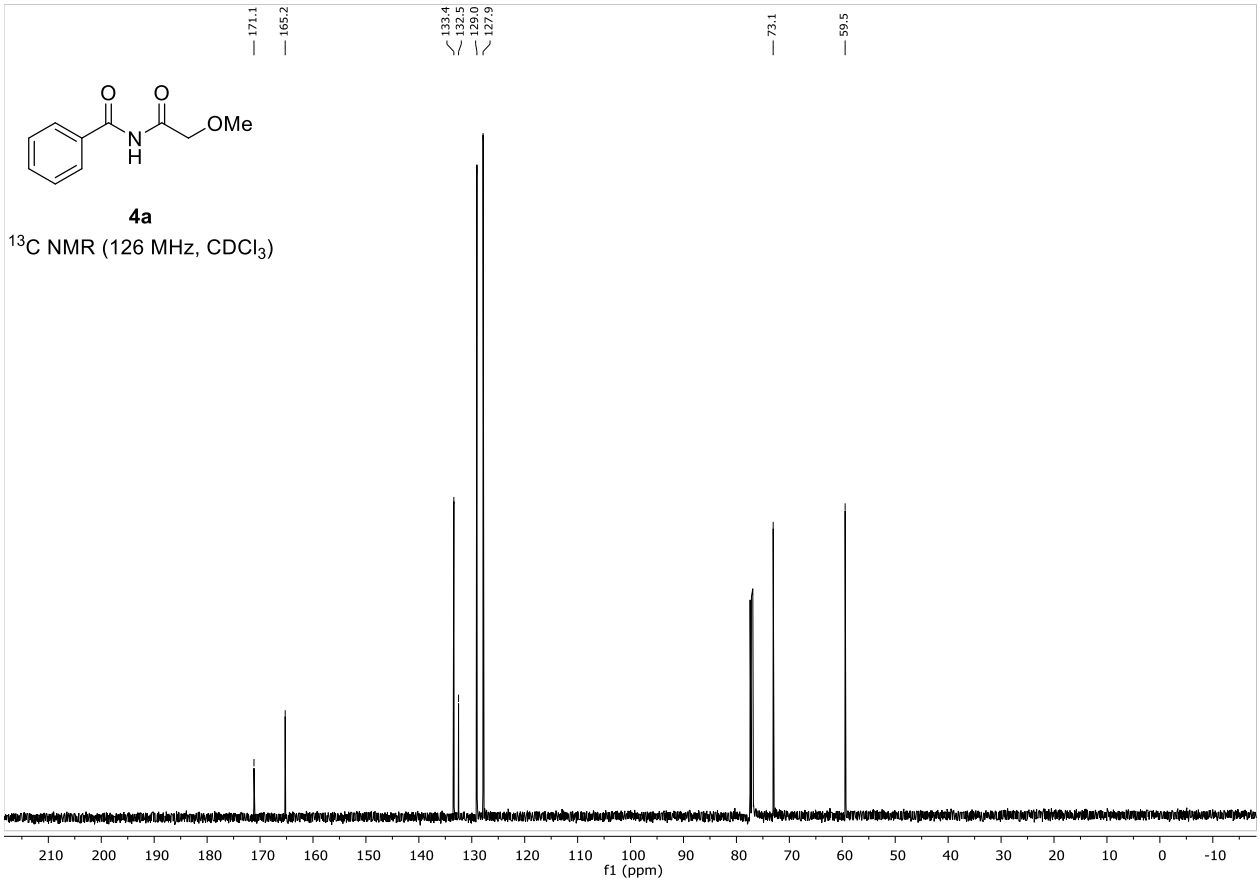
3c

^{13}C NMR (126 MHz, $CDCl_3$)



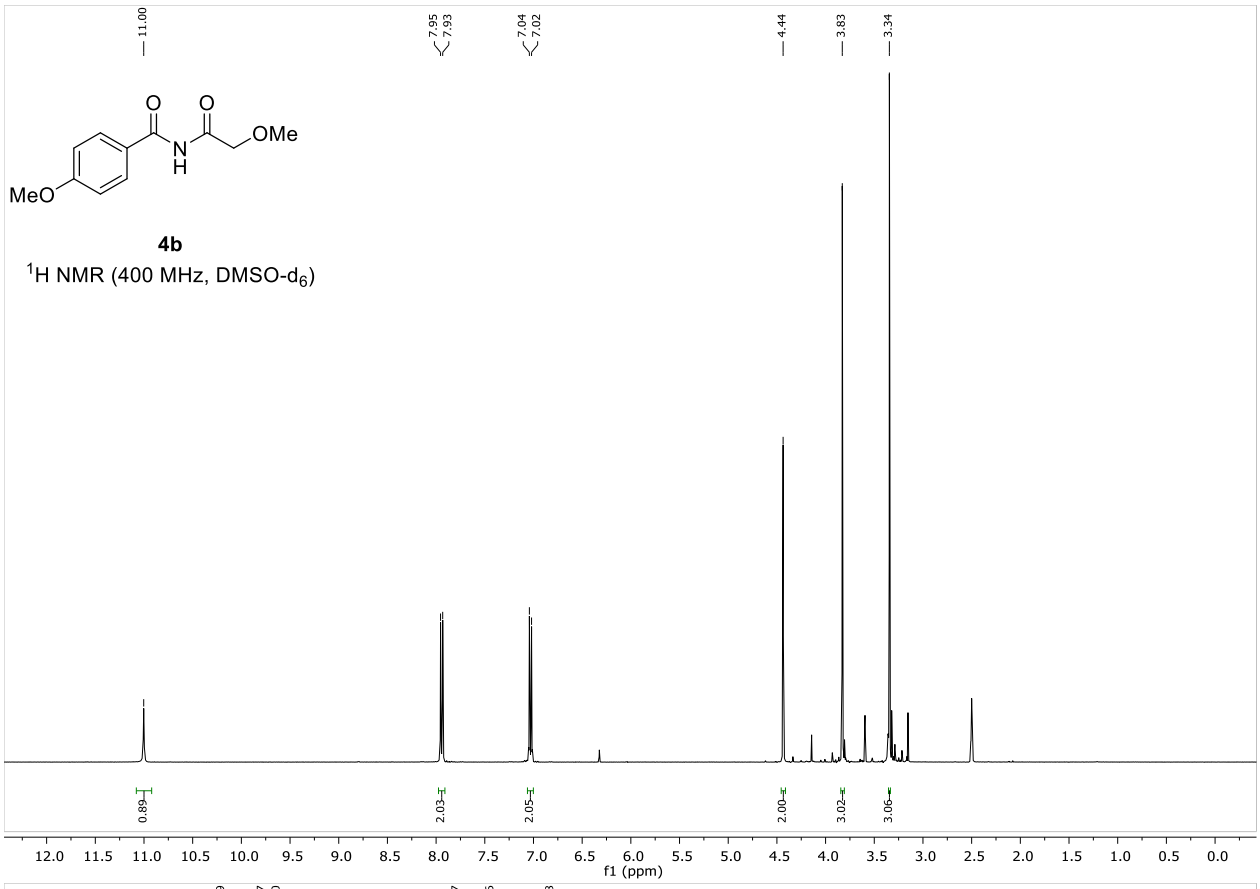
4a

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



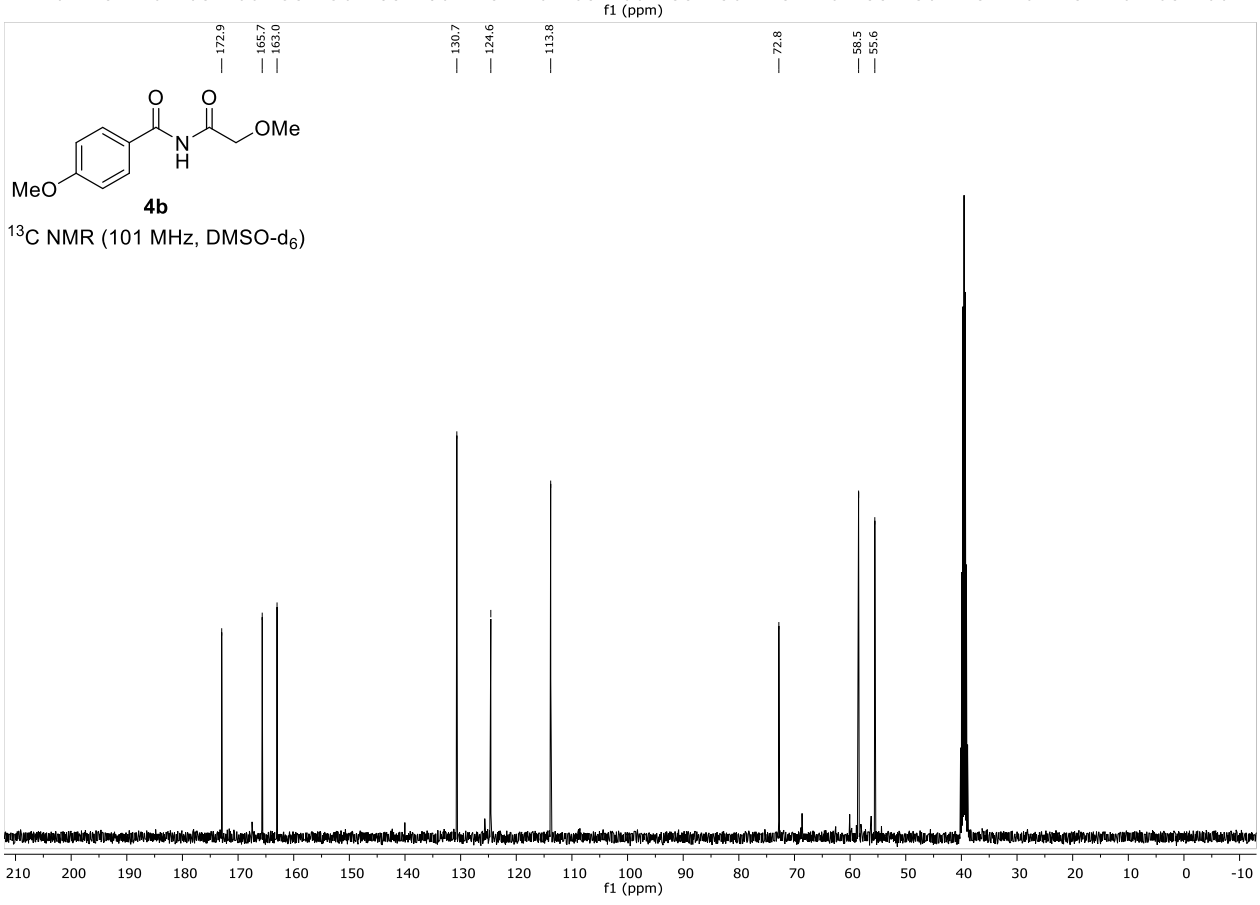
4a

^{13}C NMR (126 MHz, $CDCl_3$)



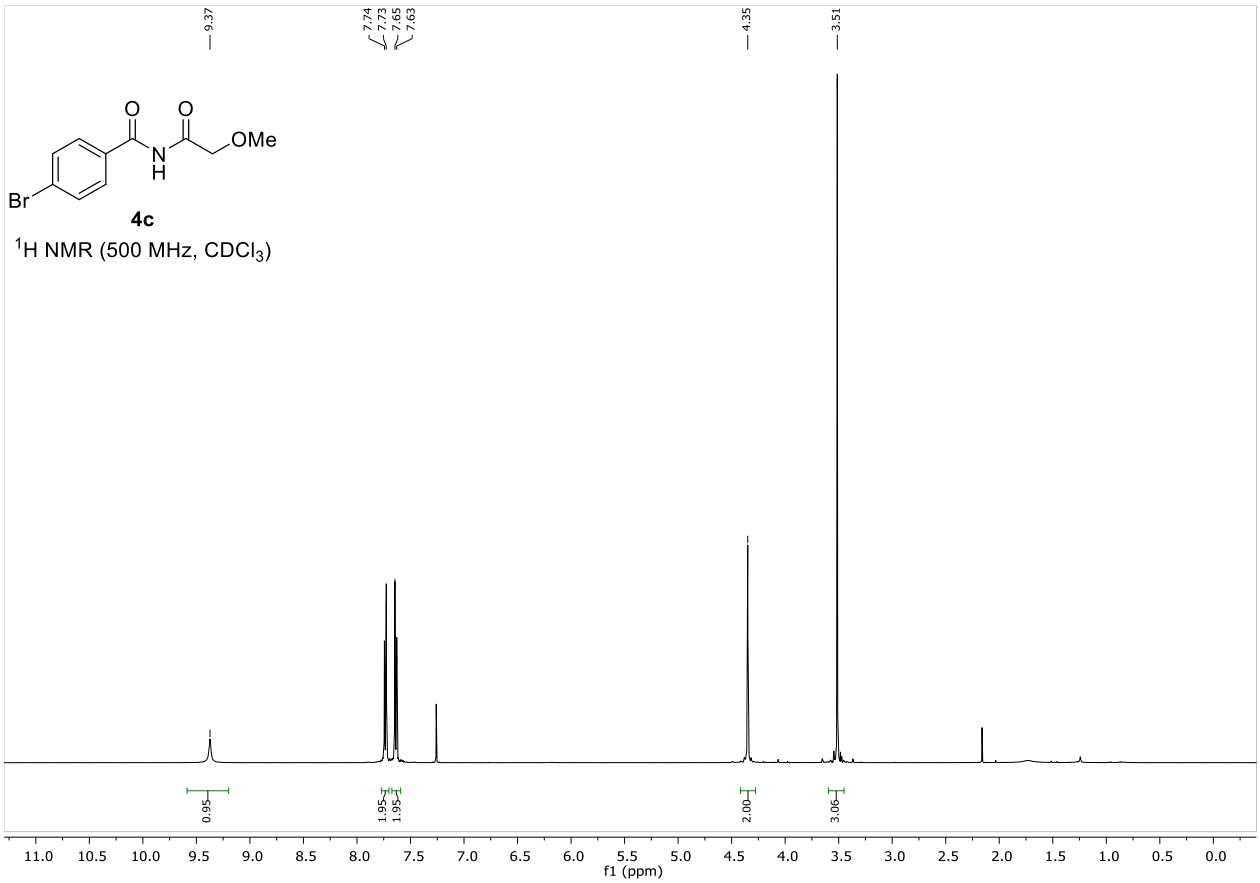
4b

^{1}H NMR (400 MHz, DMSO-d_6)



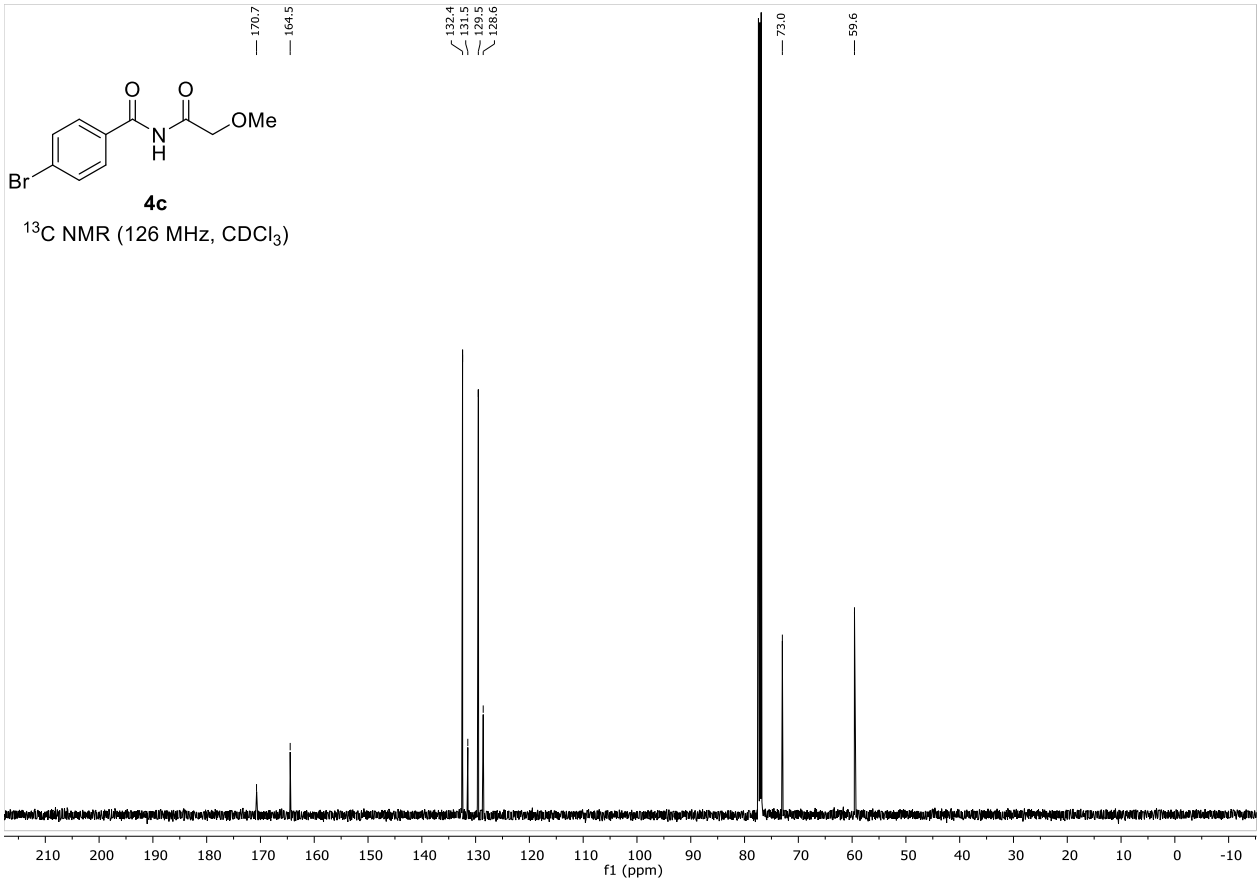
4b

^{13}C NMR (101 MHz, DMSO-d_6)



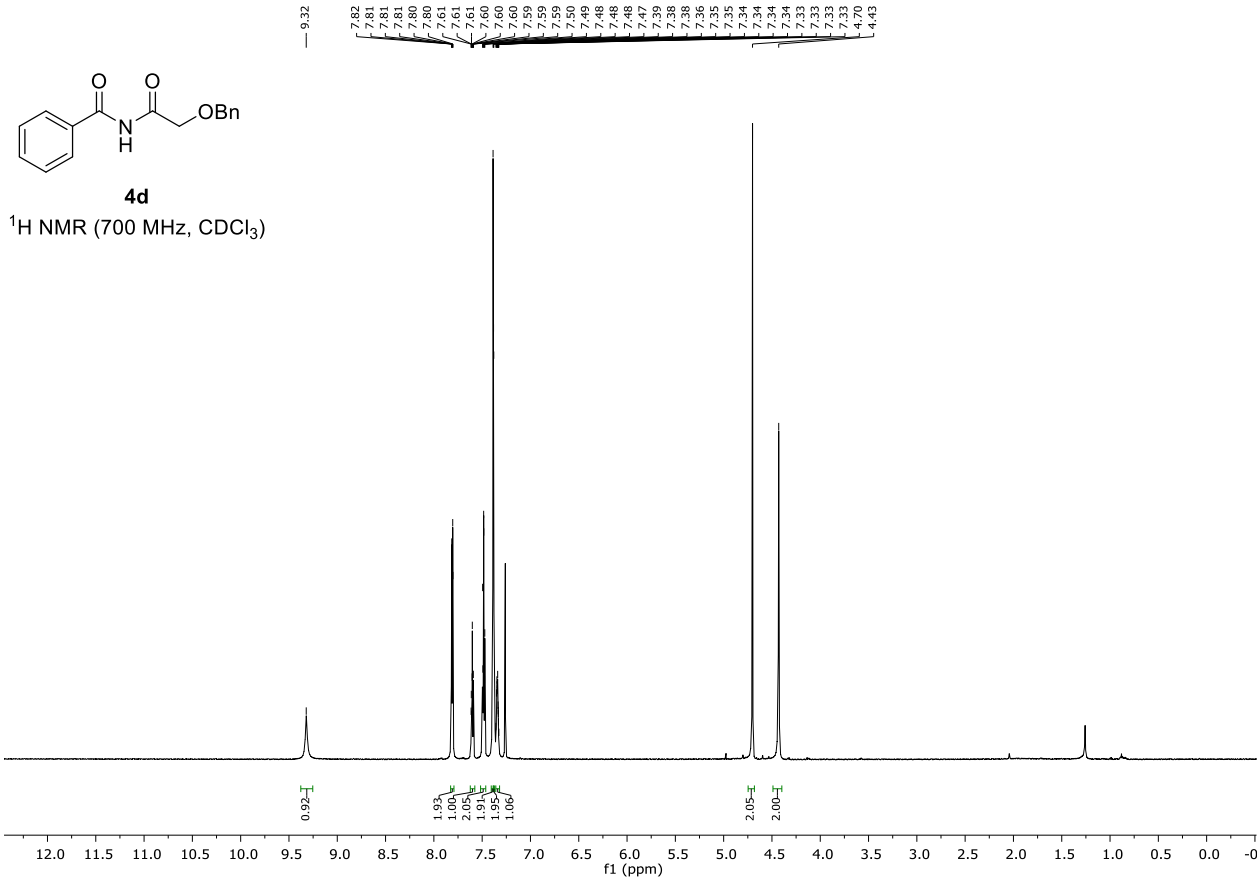
4c

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



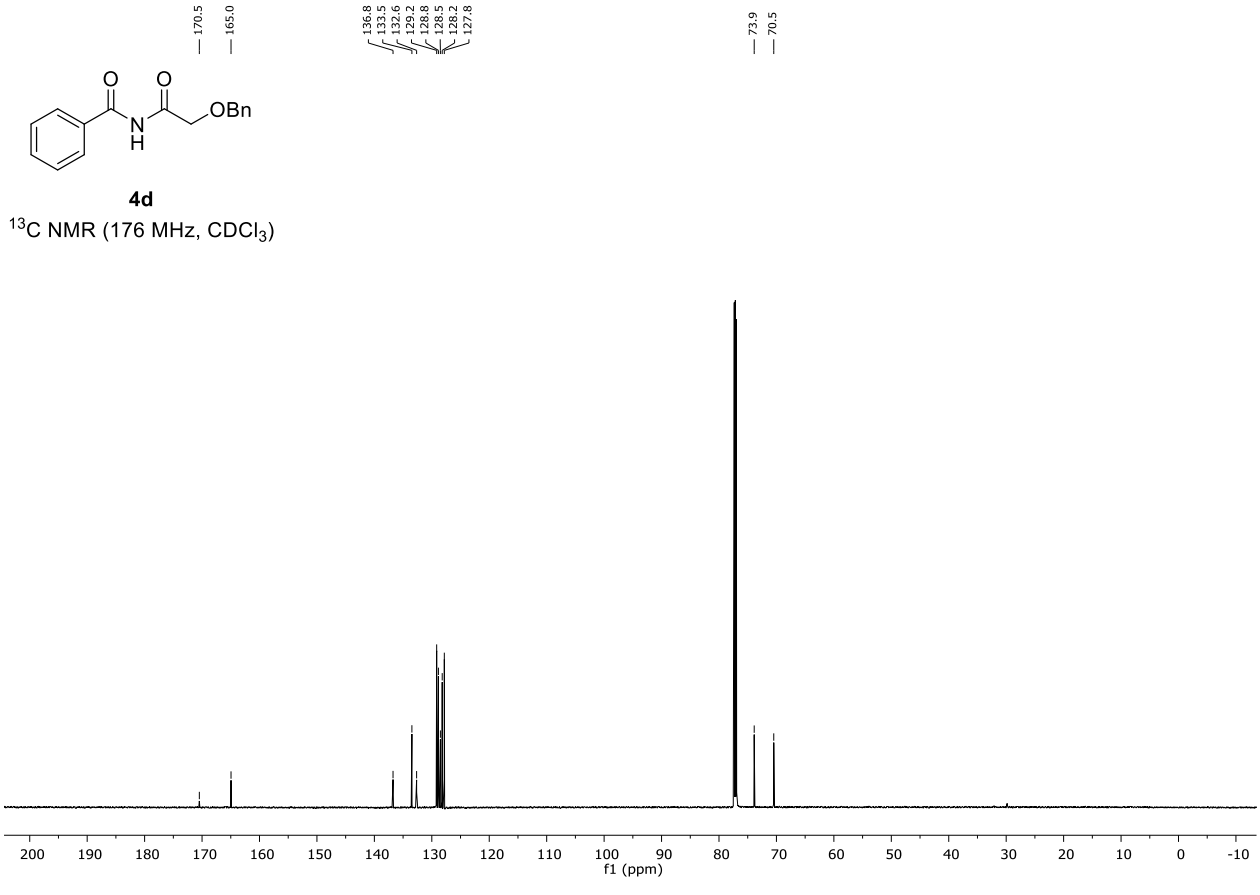
4c

^{13}C NMR (126 MHz, $CDCl_3$)



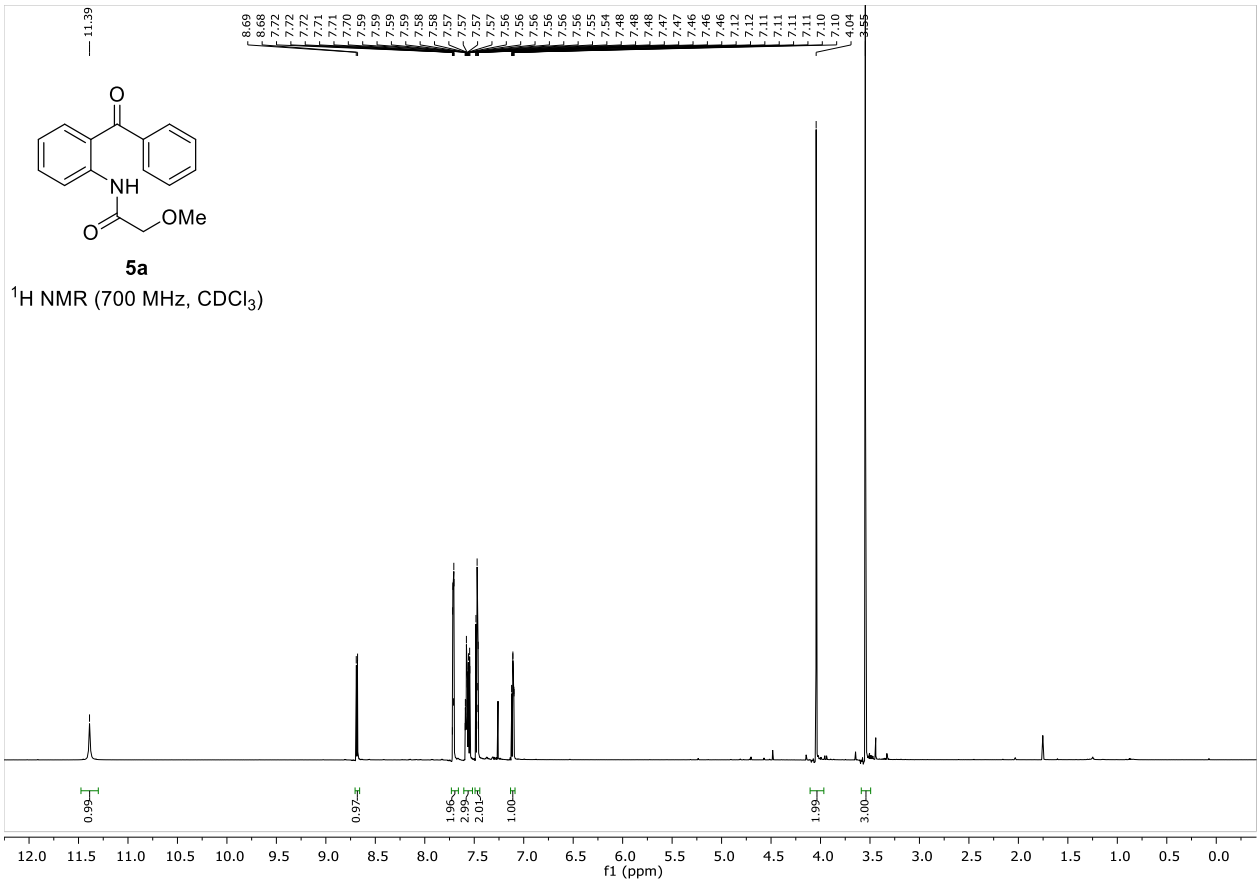
4d

^{1}H NMR (700 MHz, $CDCl_3$)



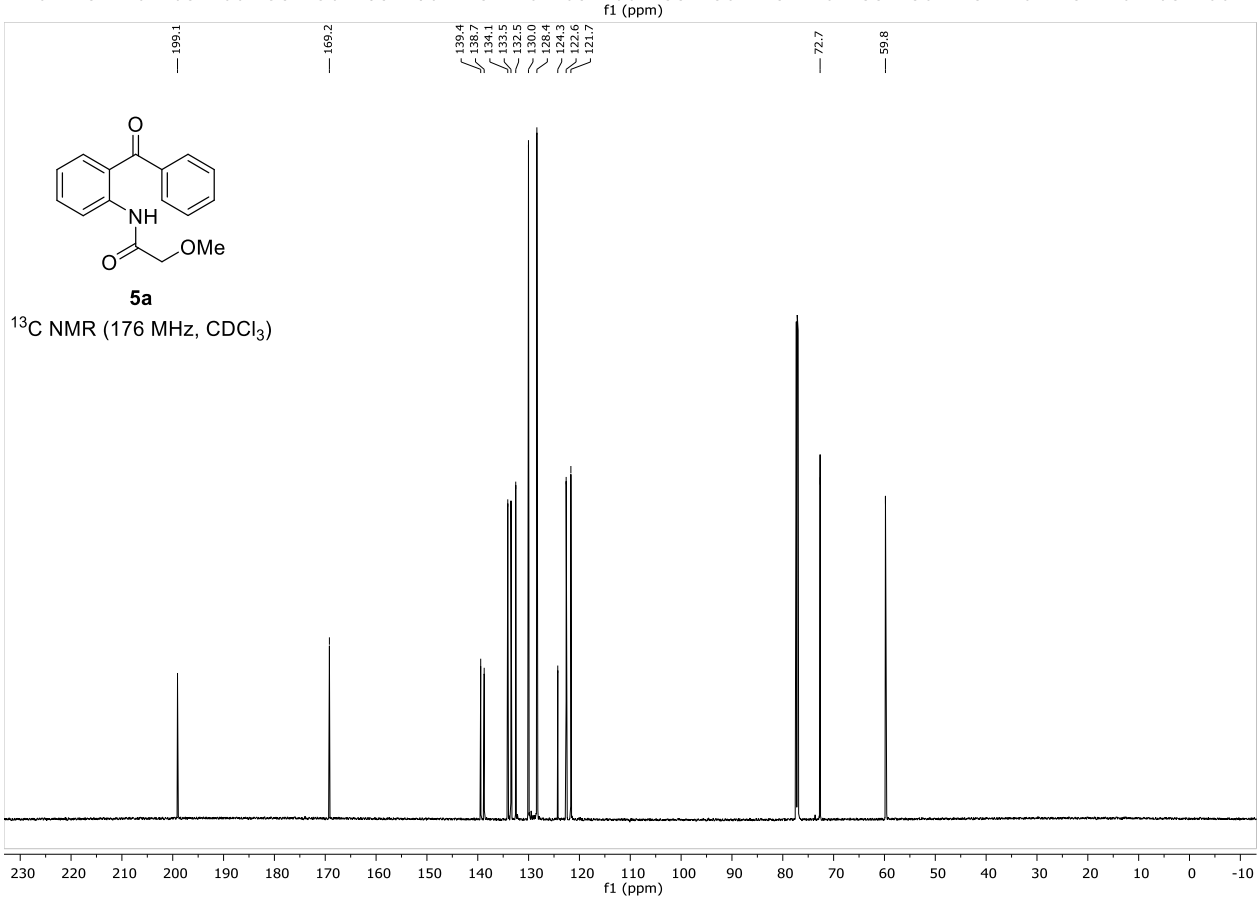
4d

^{13}C NMR (176 MHz, $CDCl_3$)



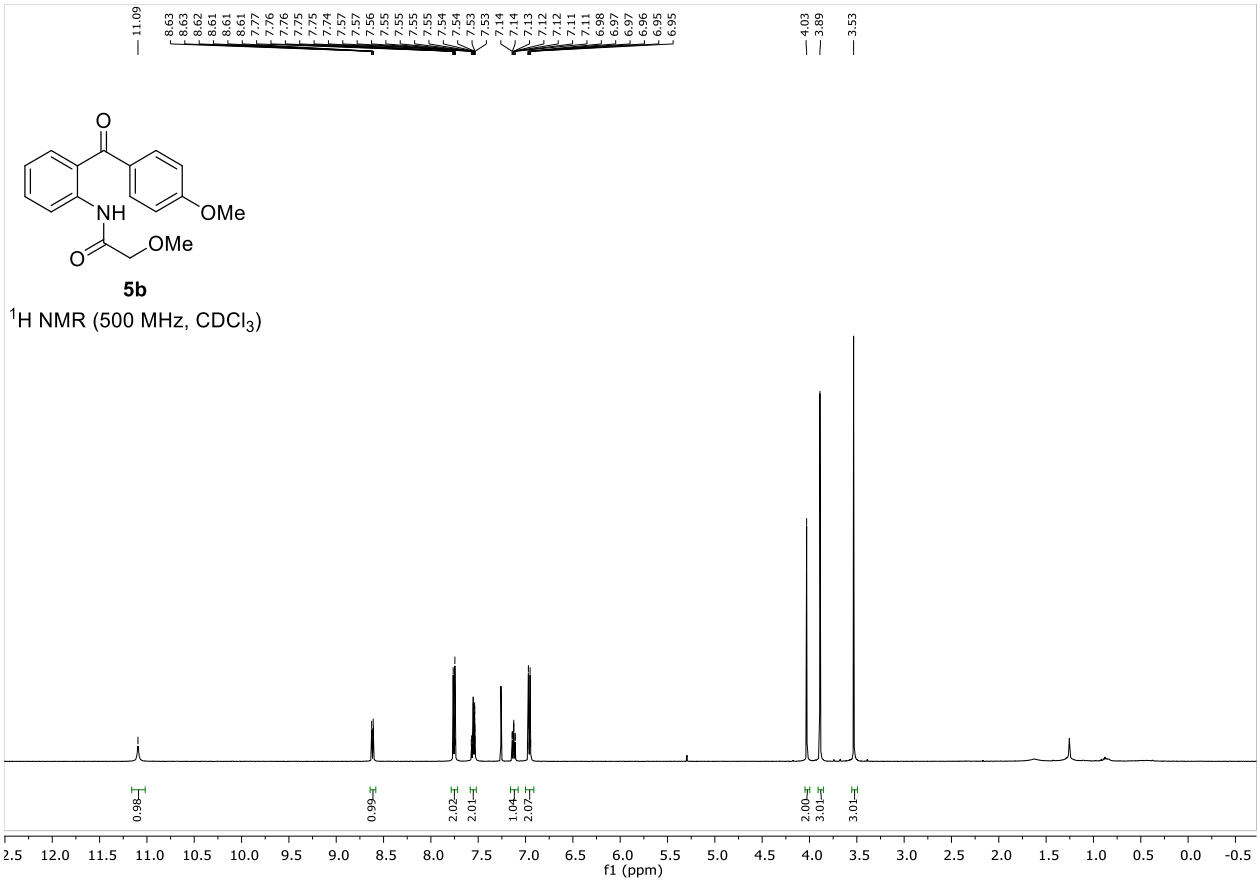
5a

^{1}H NMR (700 MHz, $CDCl_3$)



5a

^{13}C NMR (176 MHz, $CDCl_3$)



5b

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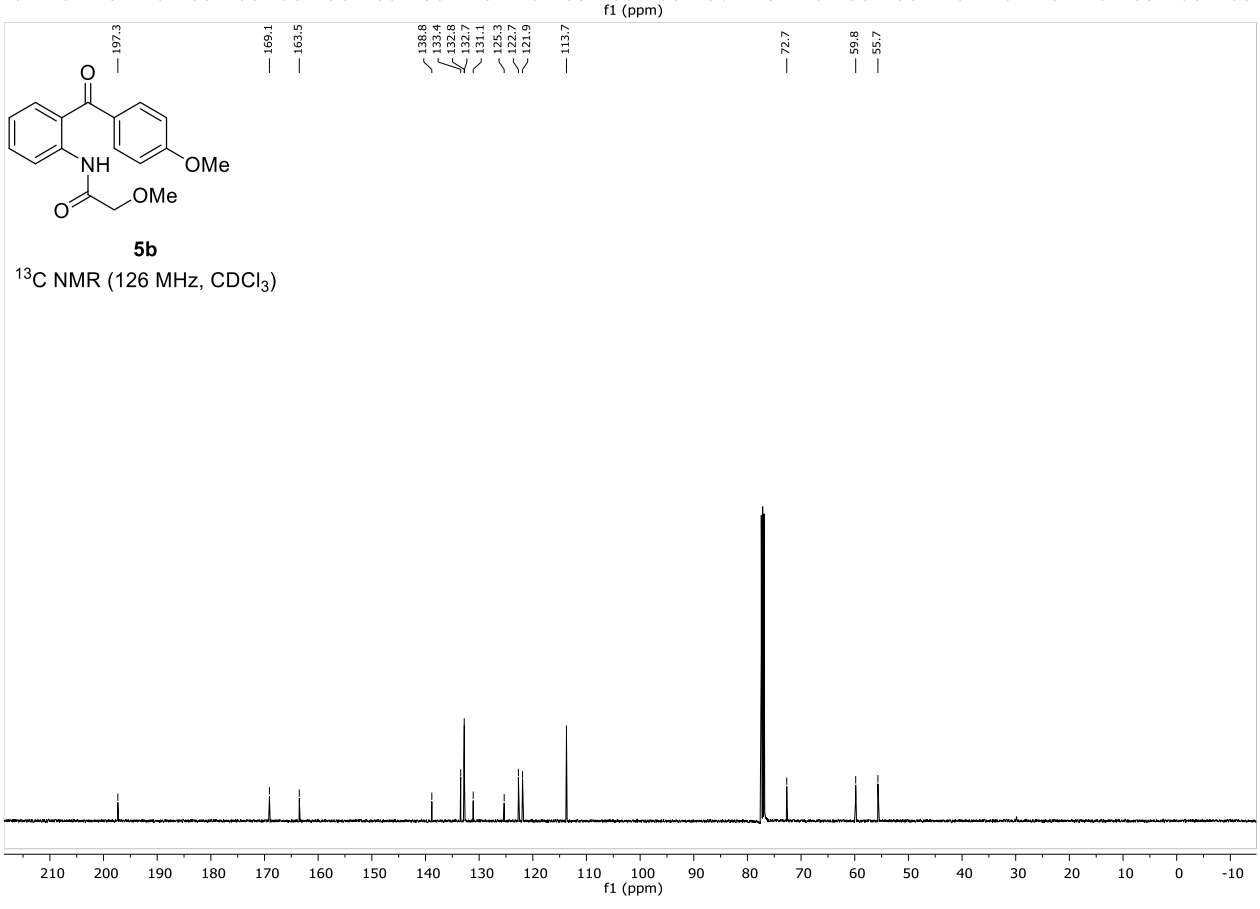
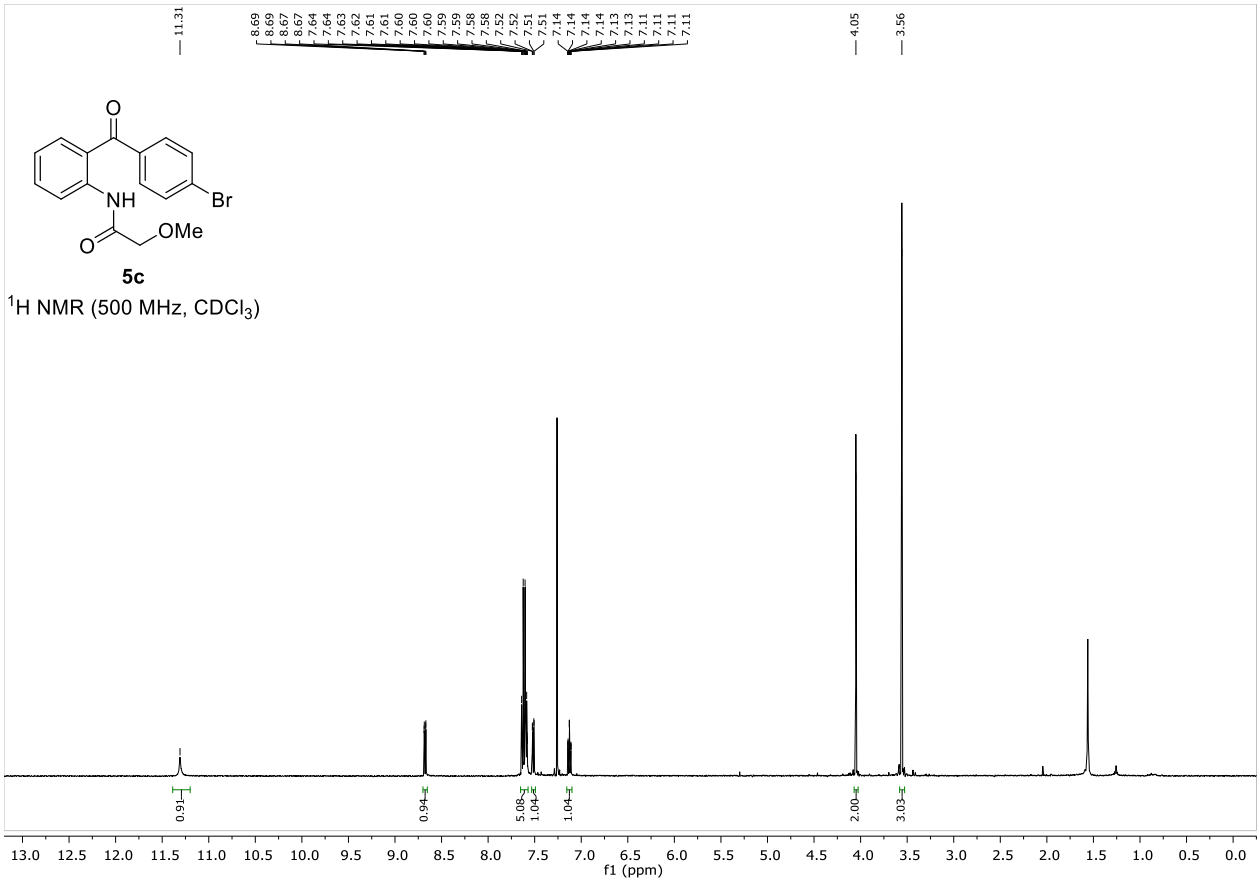


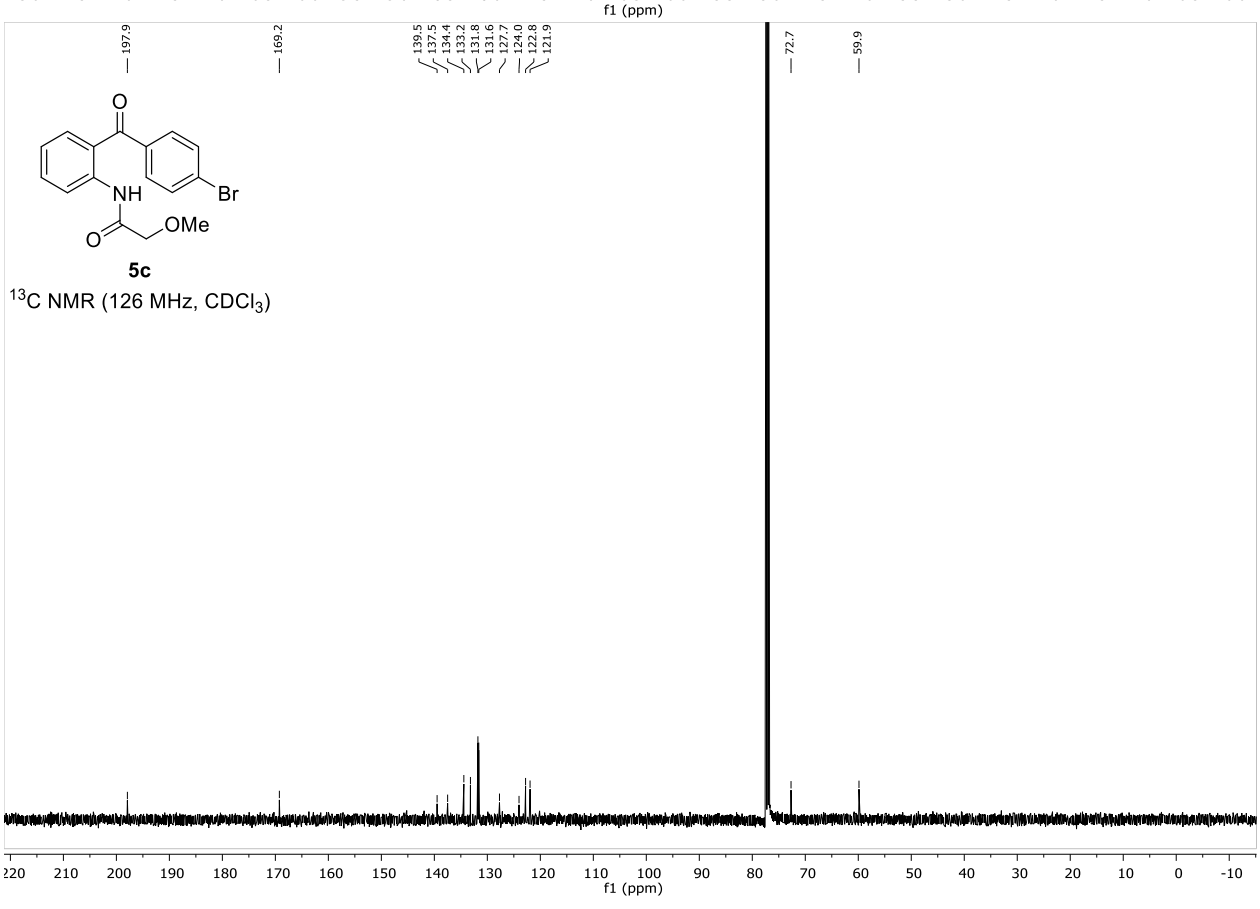
5b

^{13}C NMR (126 MHz, $CDCl_3$)



5c

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



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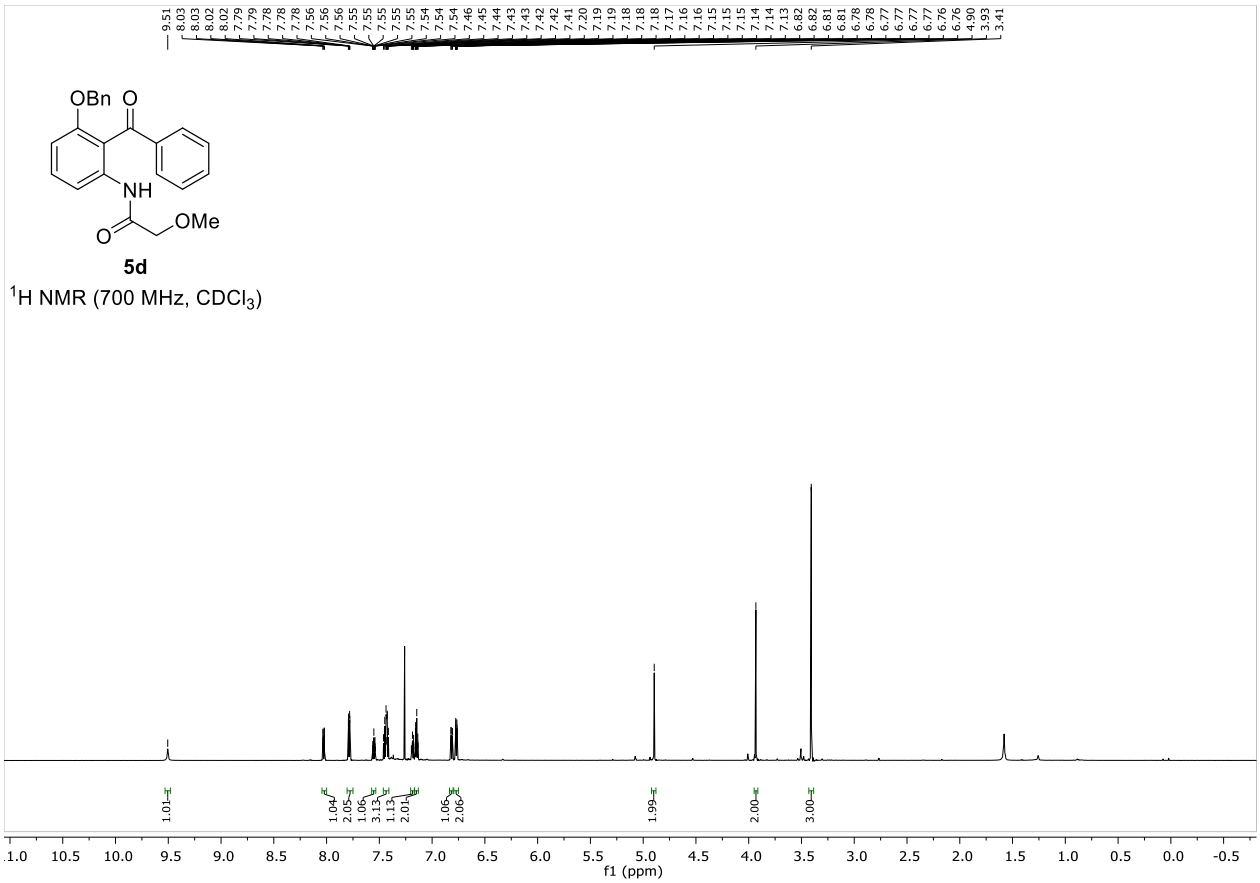
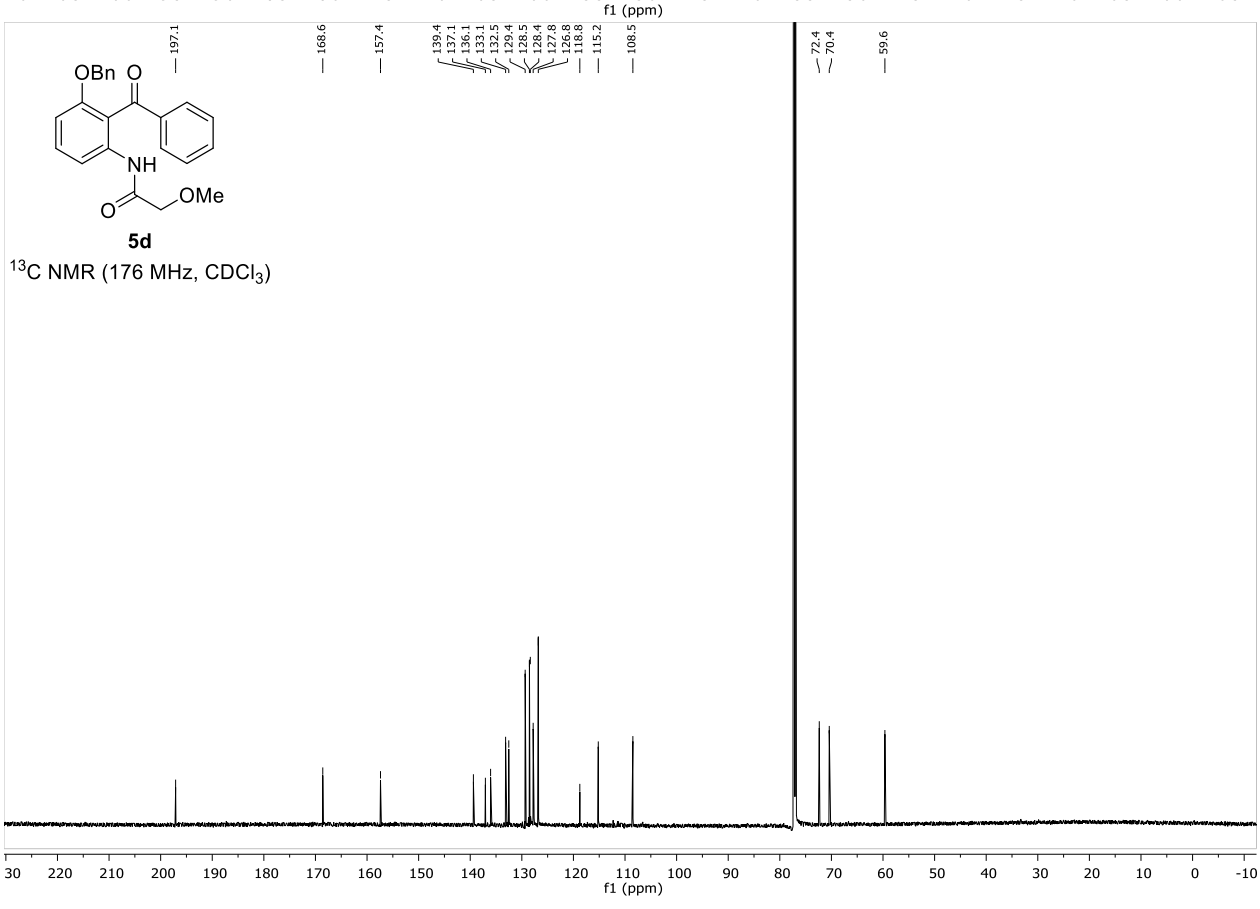


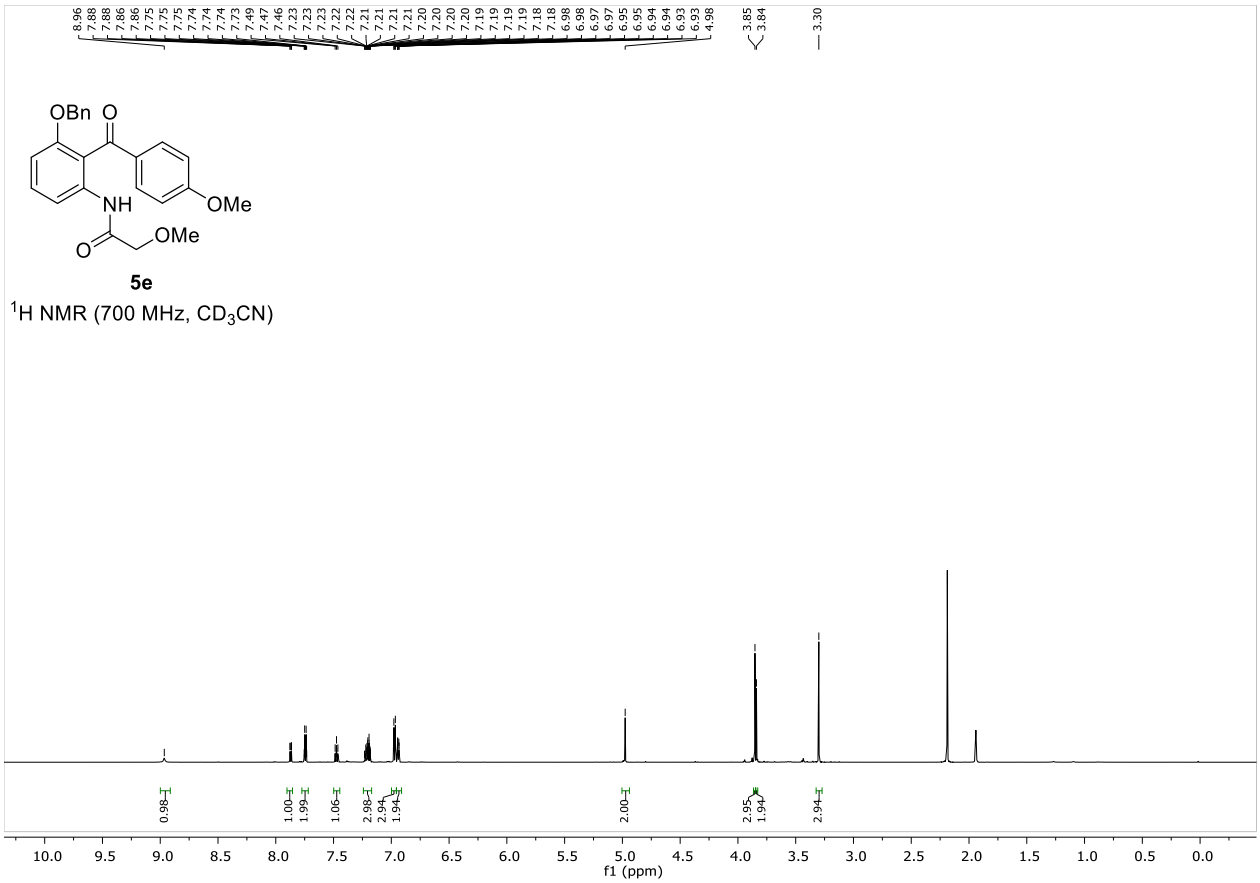
5d

^{1}H NMR (700 MHz, $CDCl_3$)



5d

^{13}C NMR (176 MHz, $CDCl_3$)



5e

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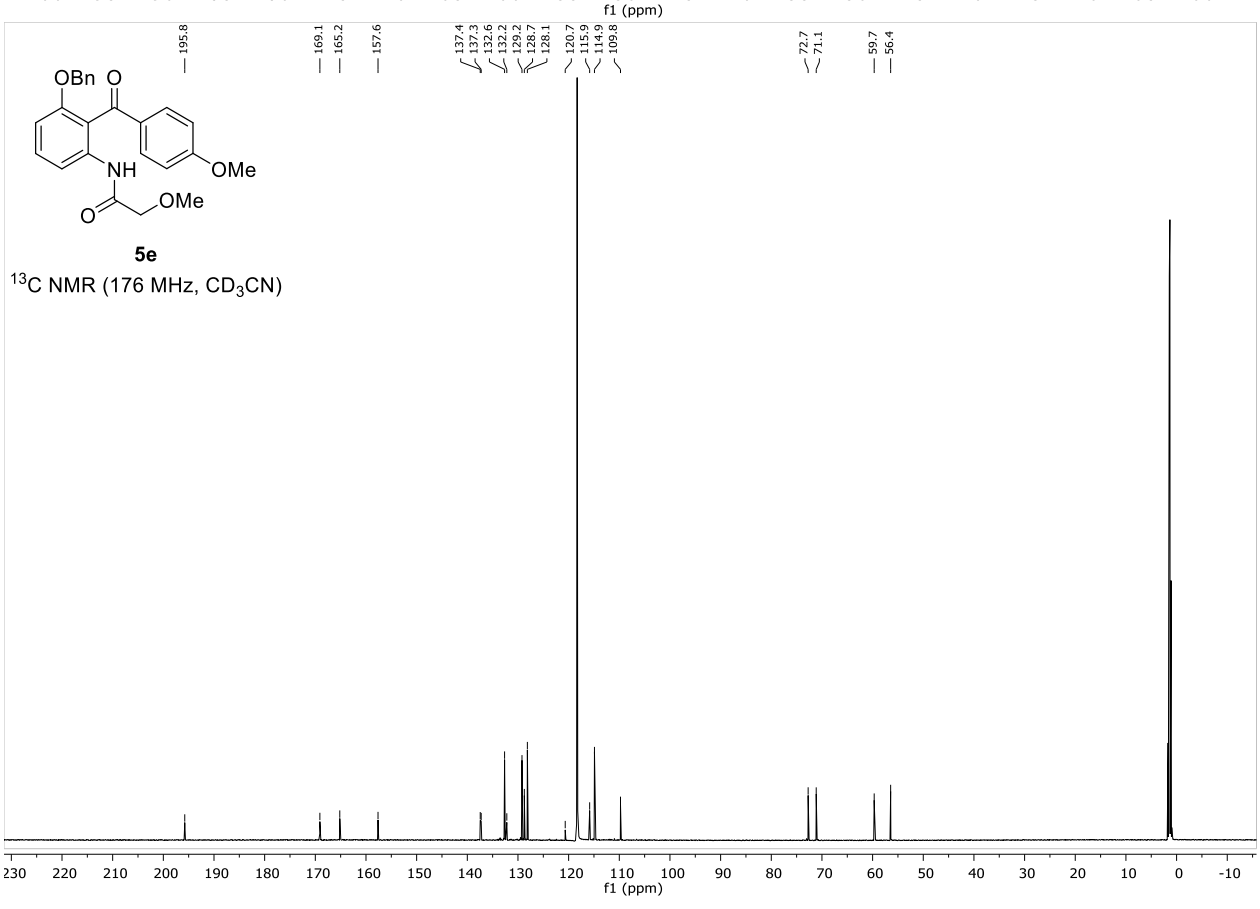
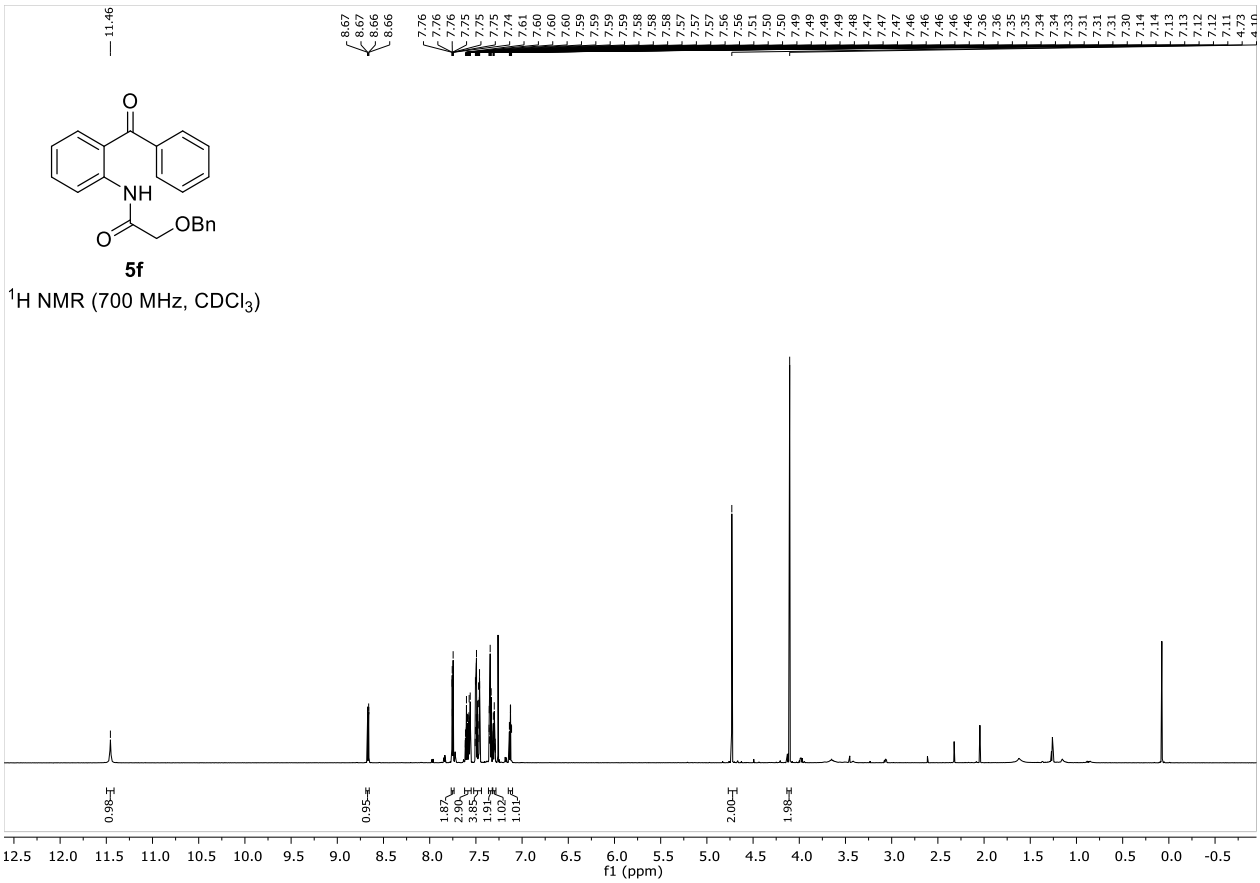


5e

^{13}C NMR (176 MHz, CD_3CN)



5f

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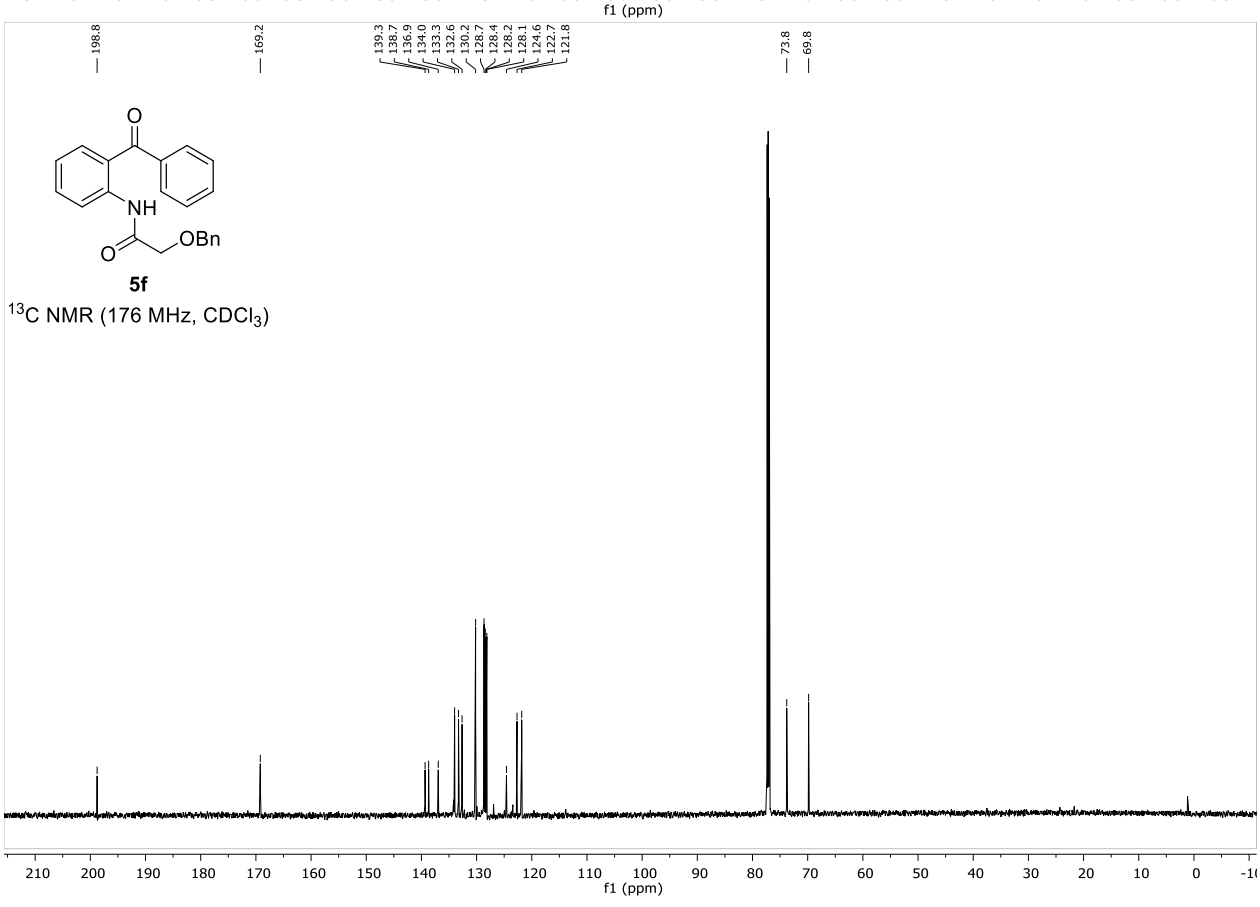

5f

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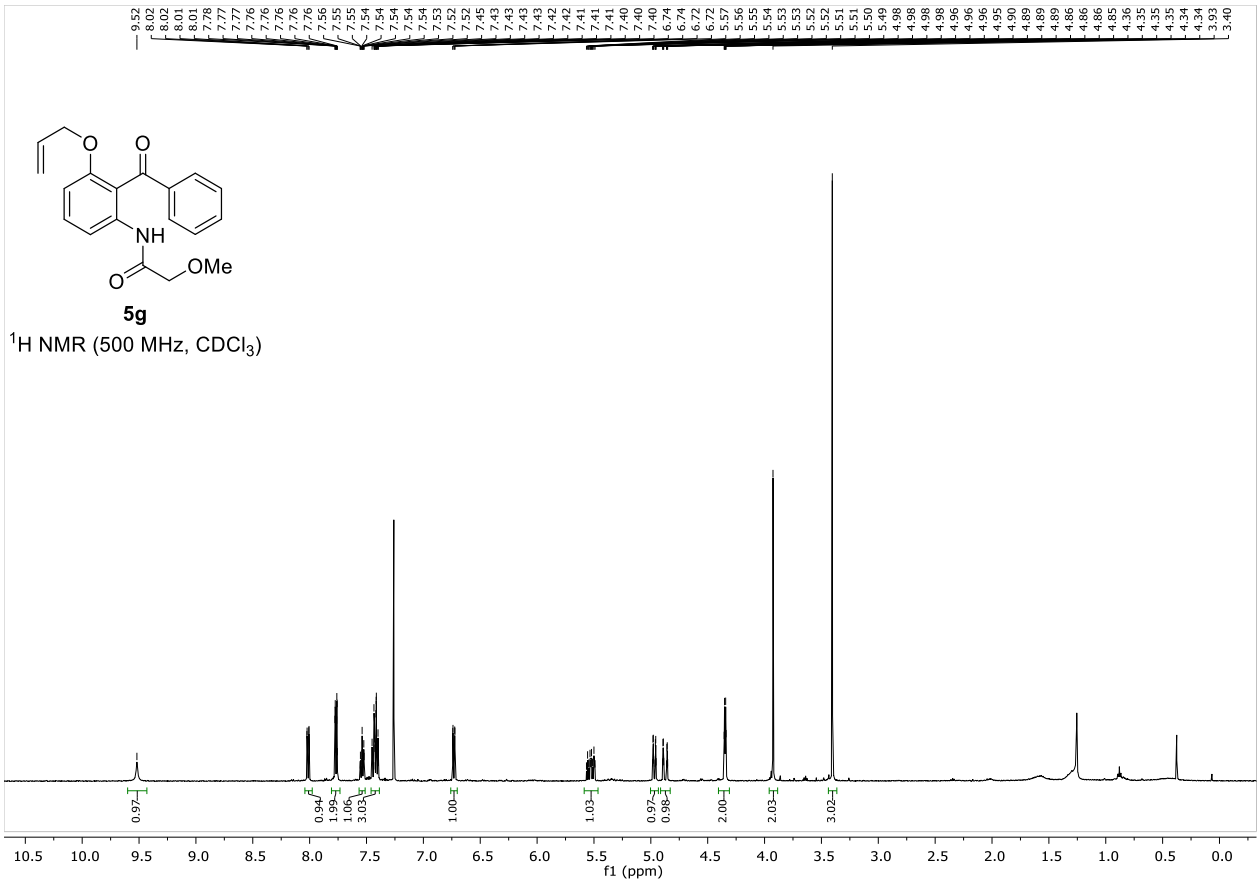

5g

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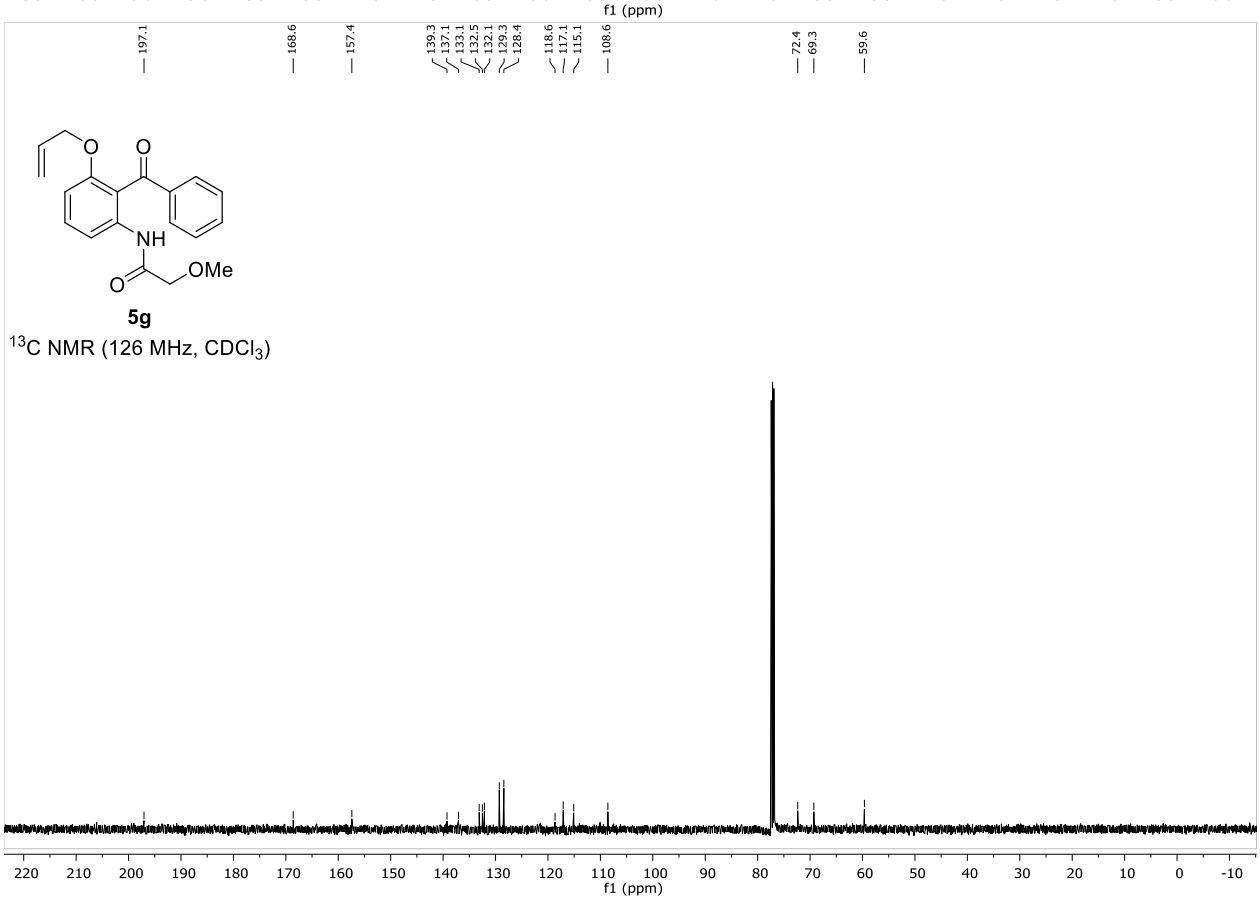
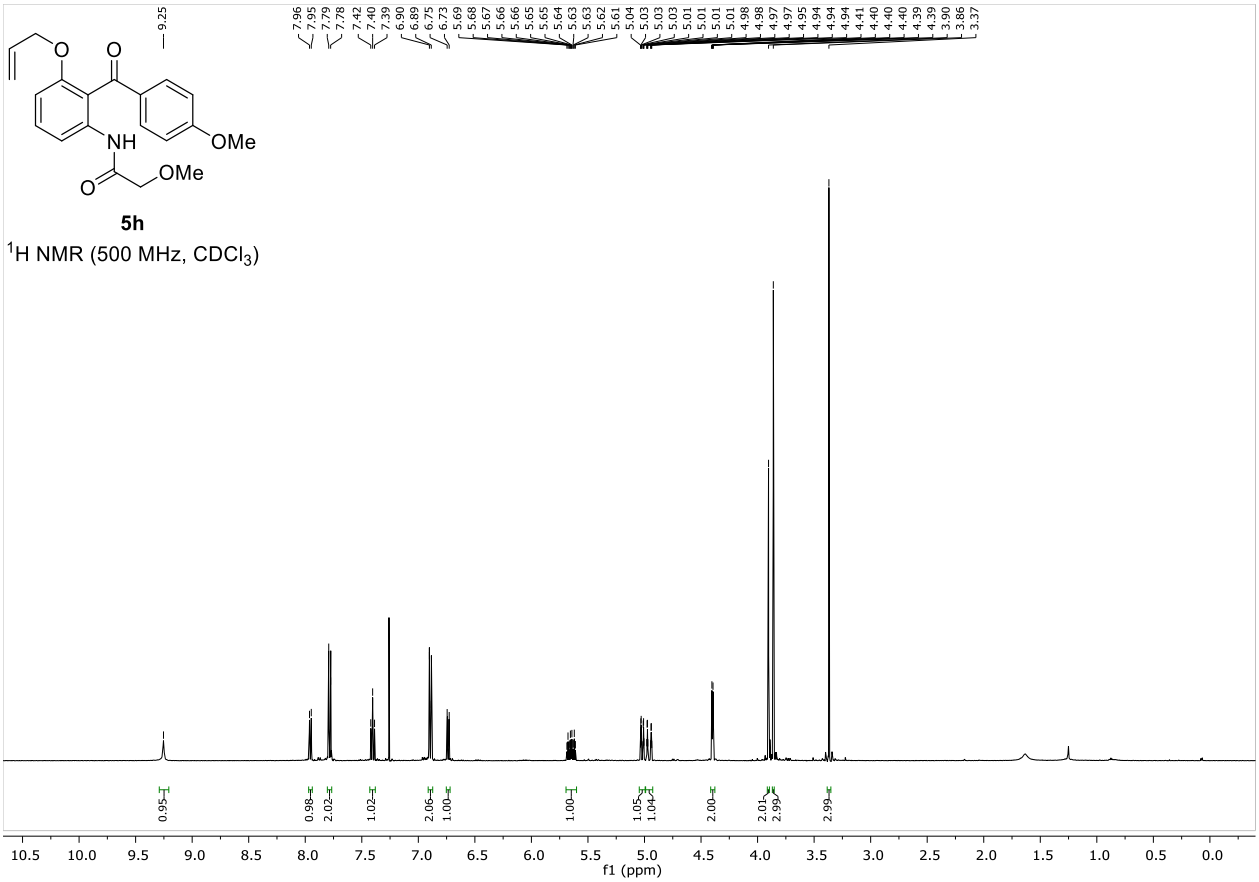


5g

^{13}C NMR (126 MHz, $CDCl_3$)



5h

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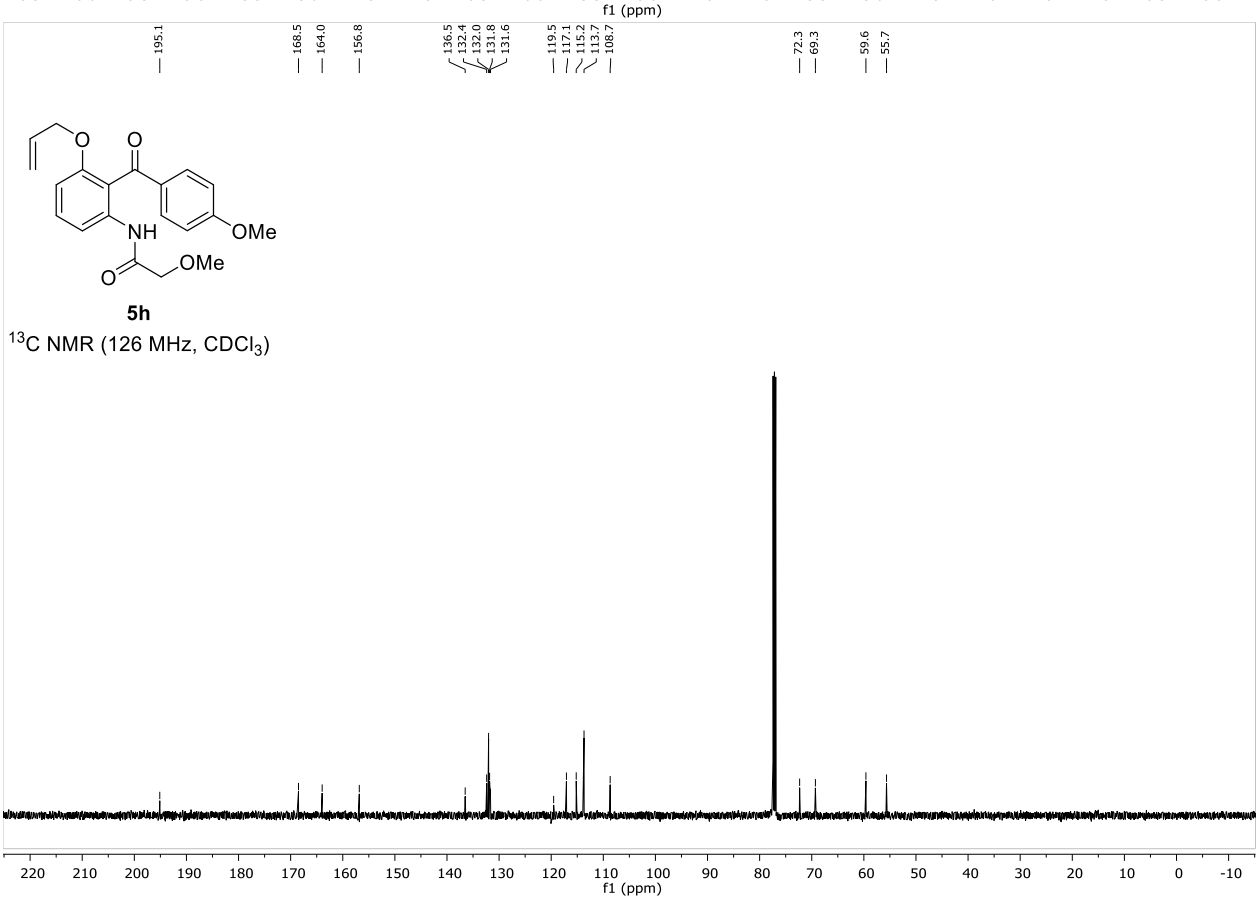

5h

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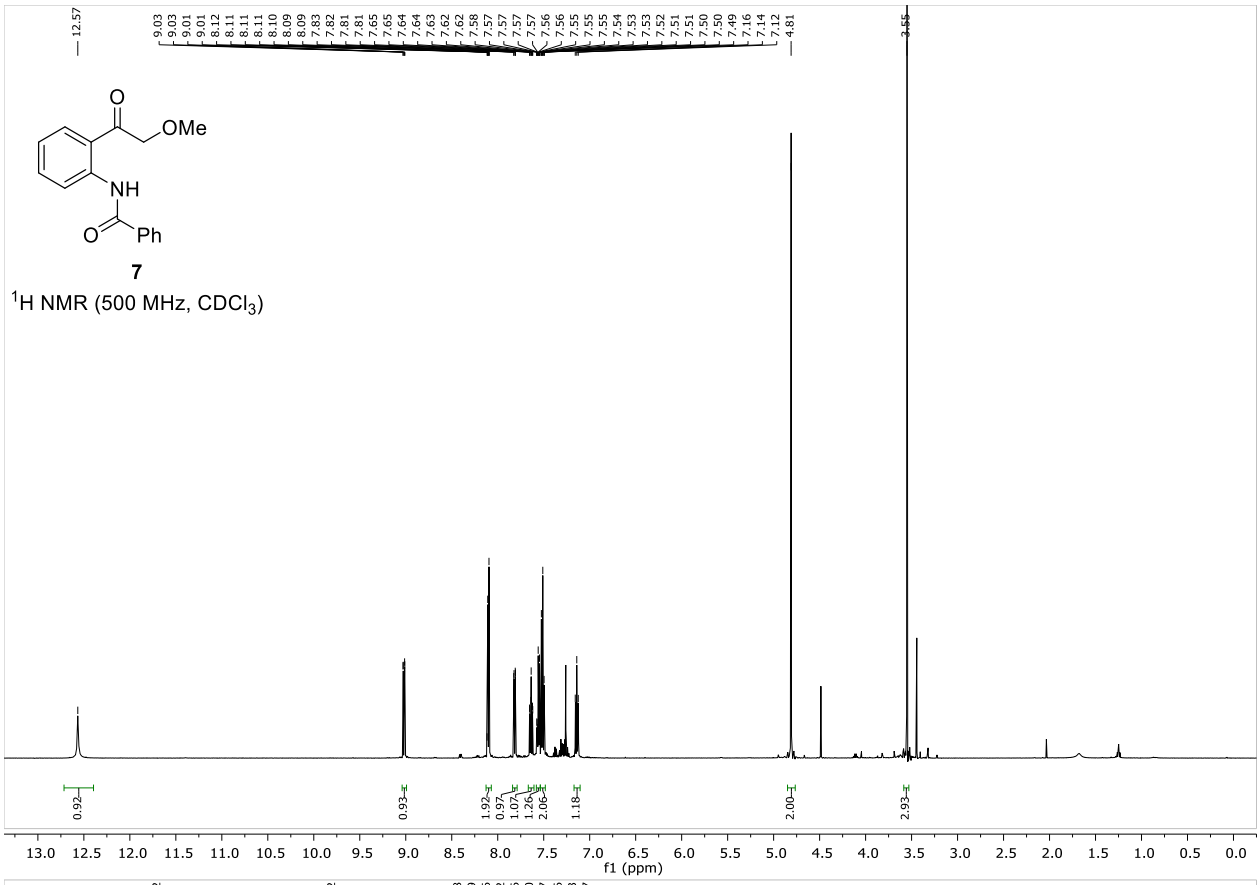

7

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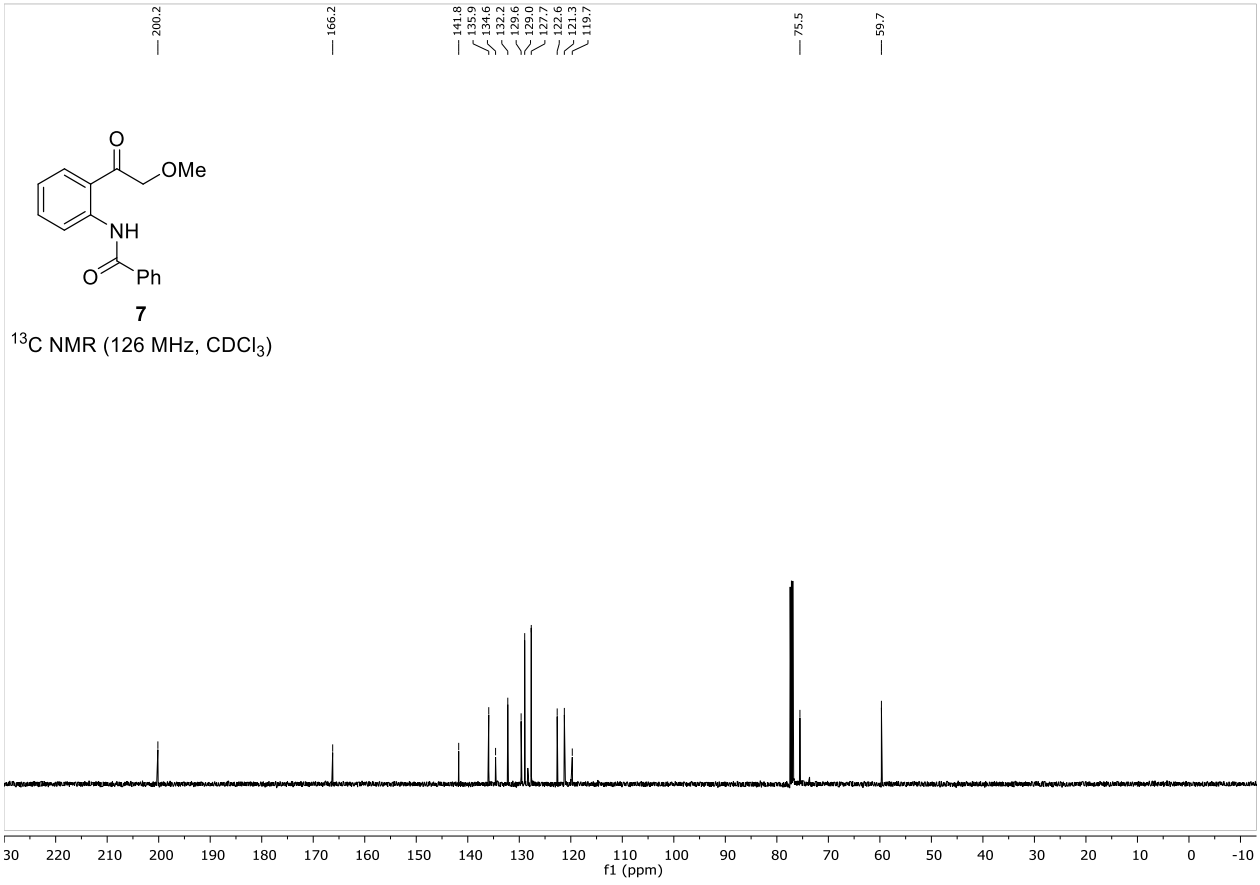

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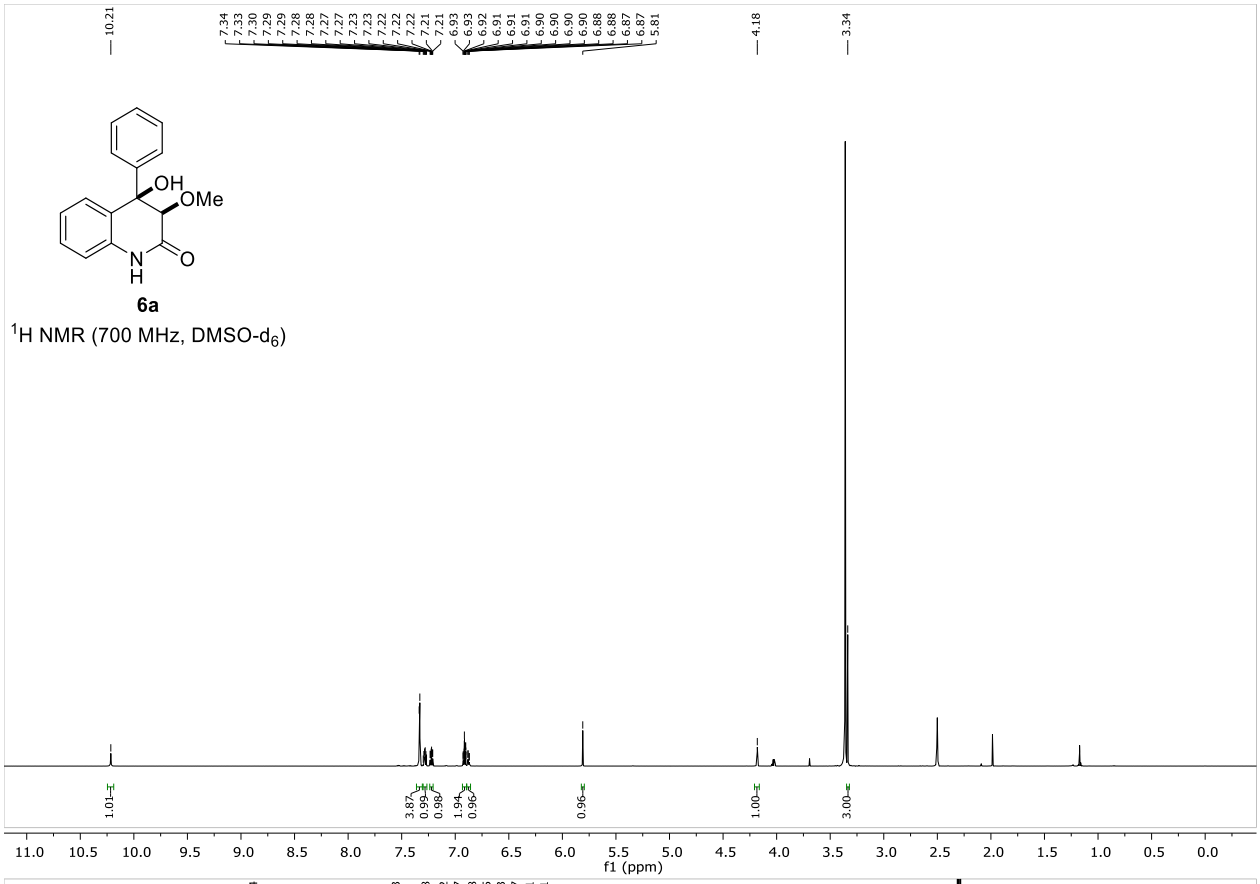
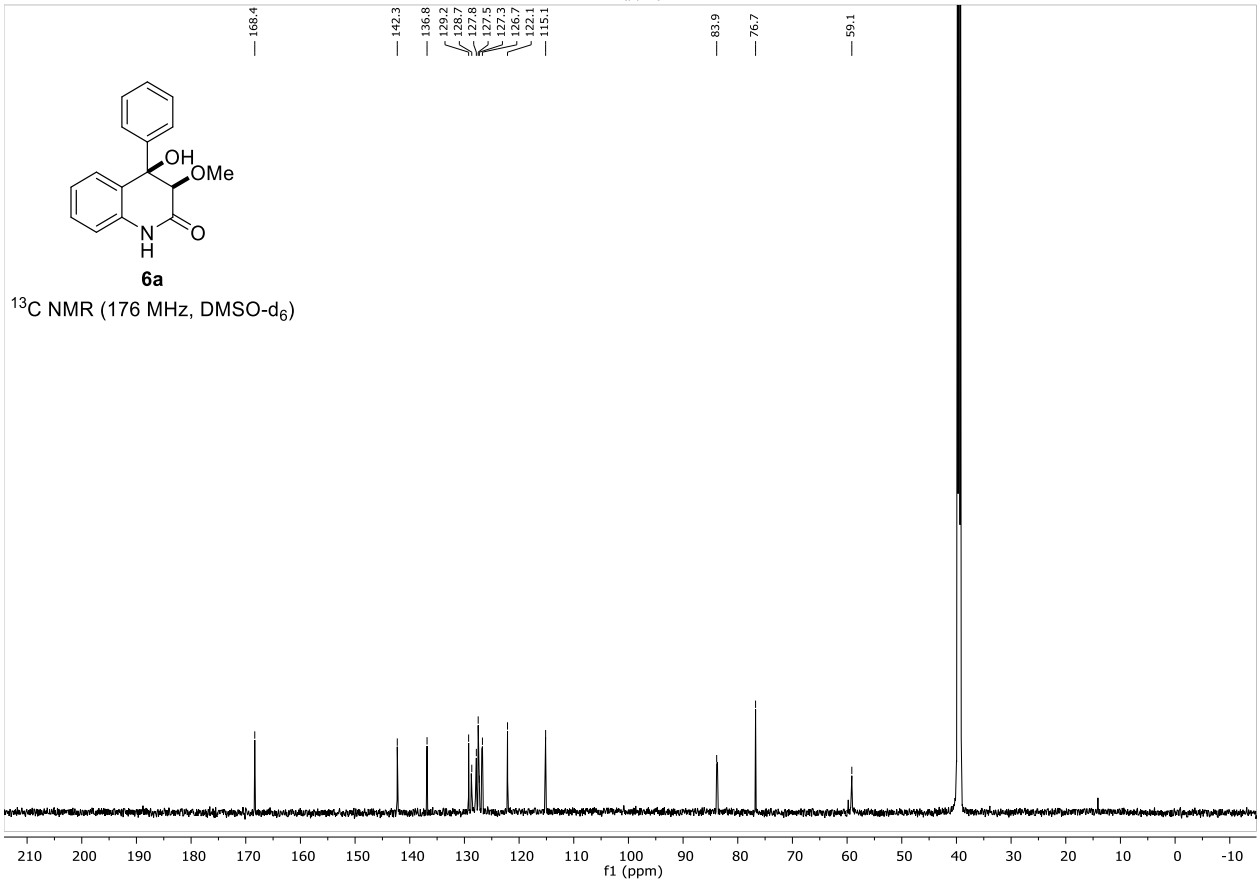


6a

^{1}H NMR (700 MHz, DMSO-d_6)



6a

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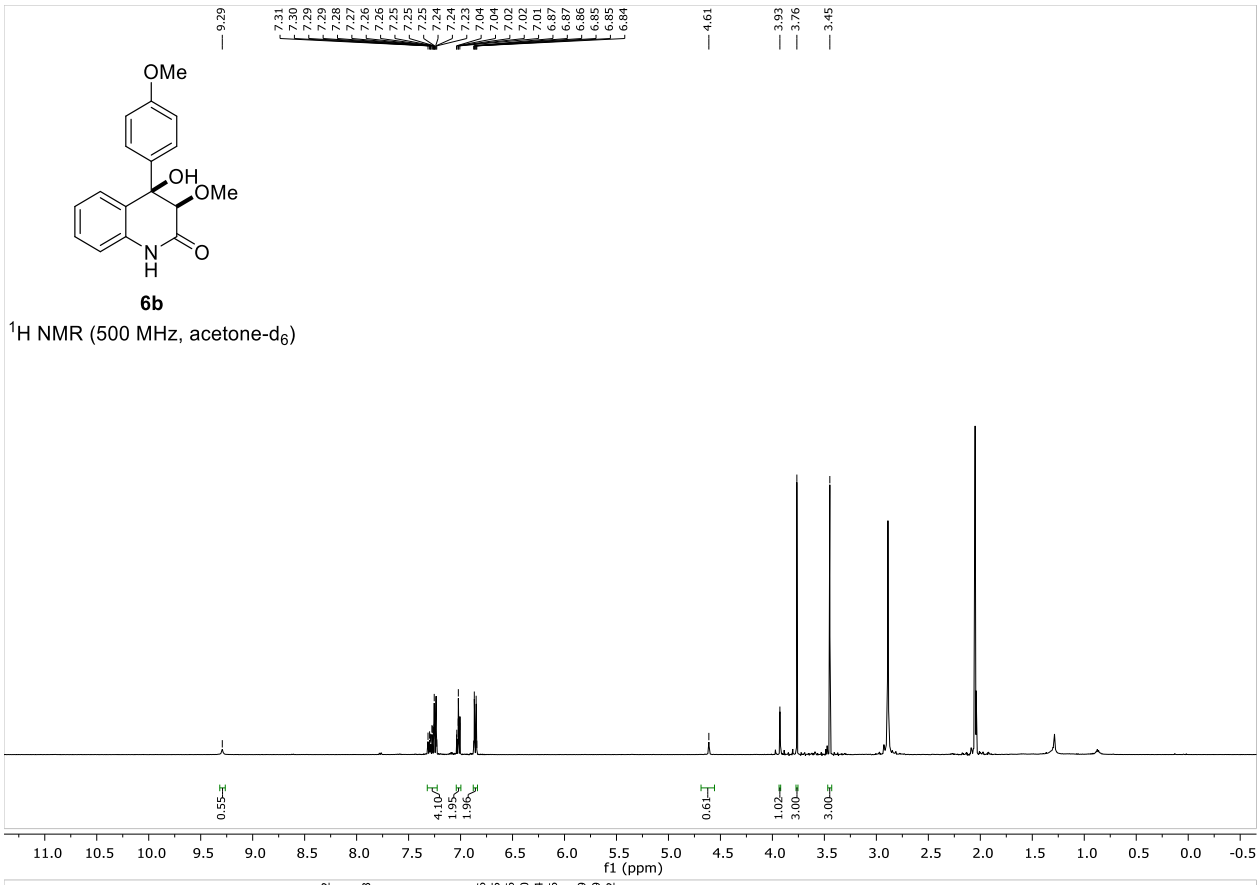

6b

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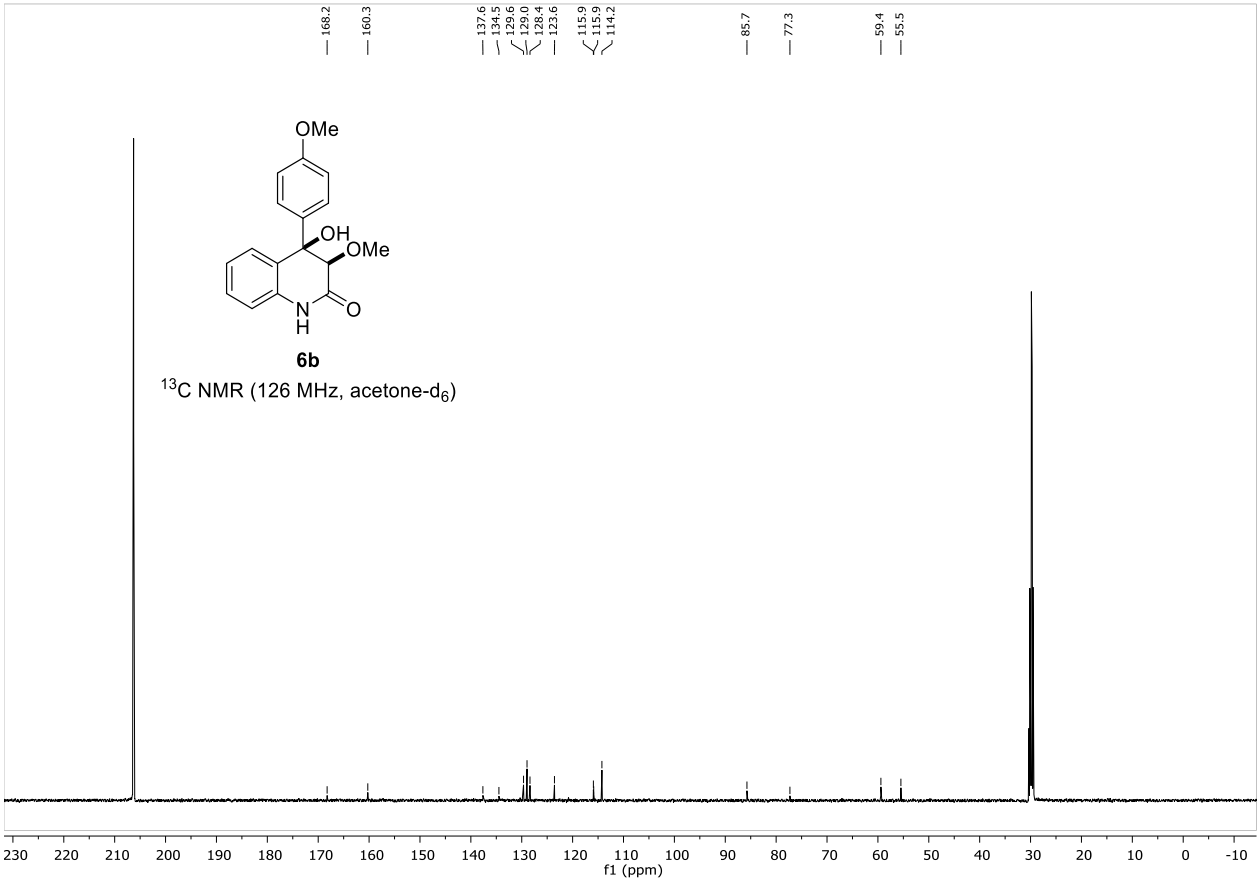

6b

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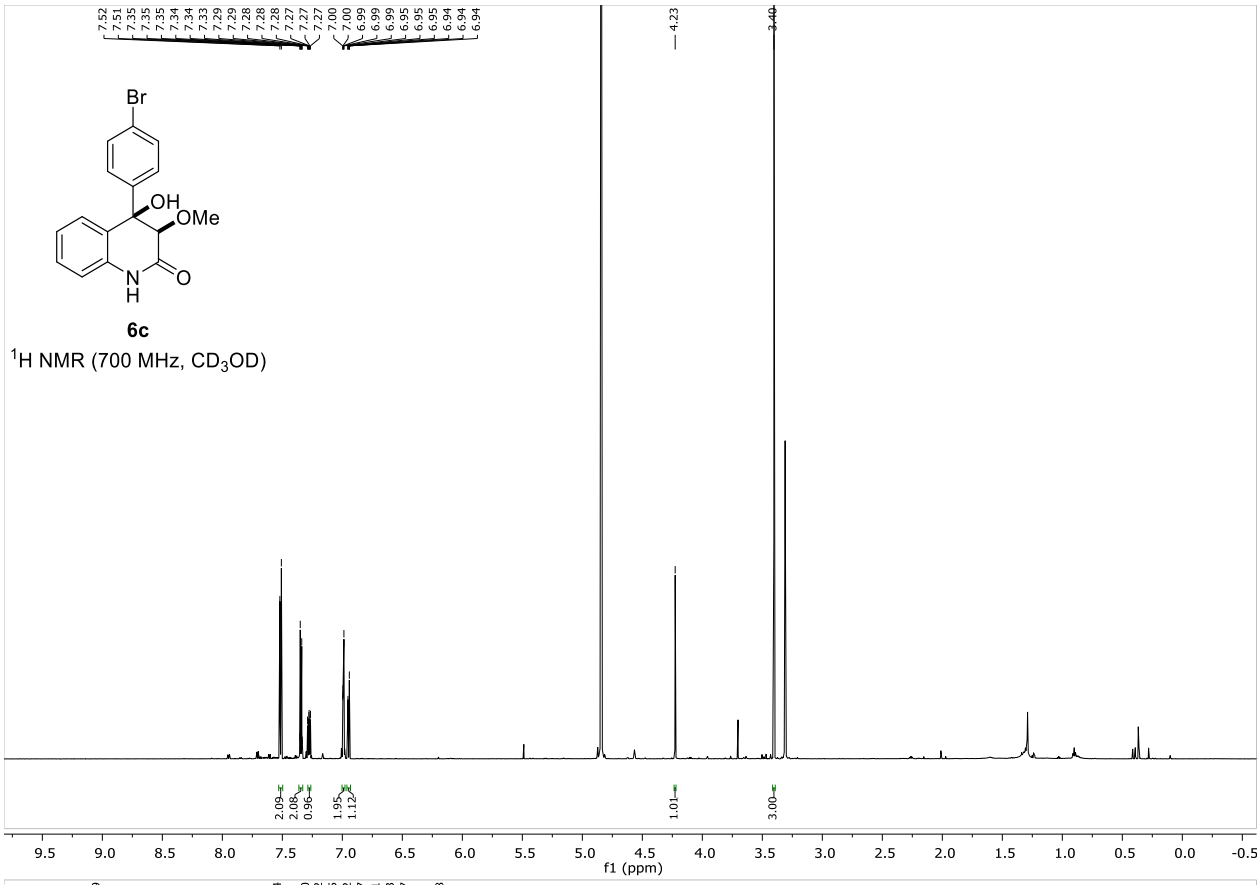

6c

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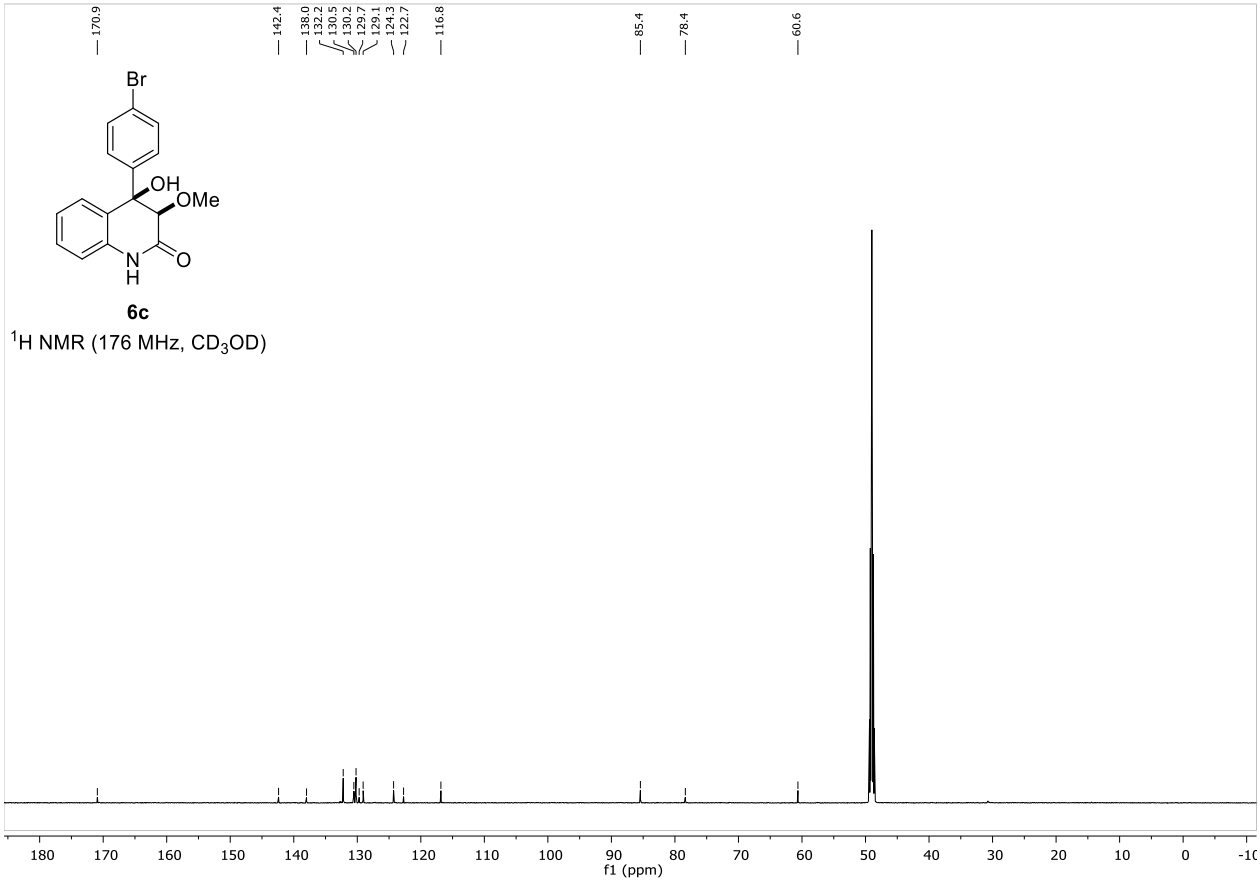

6c

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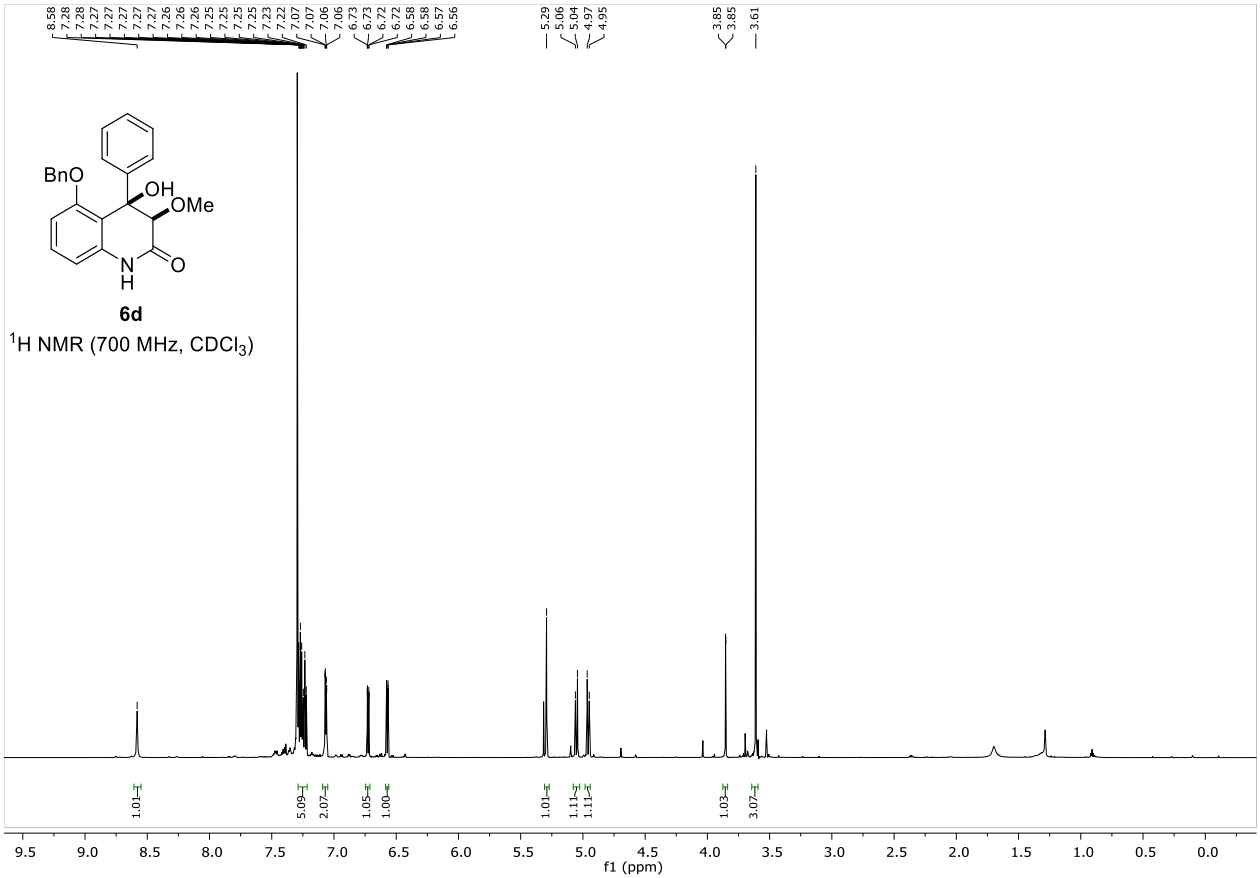
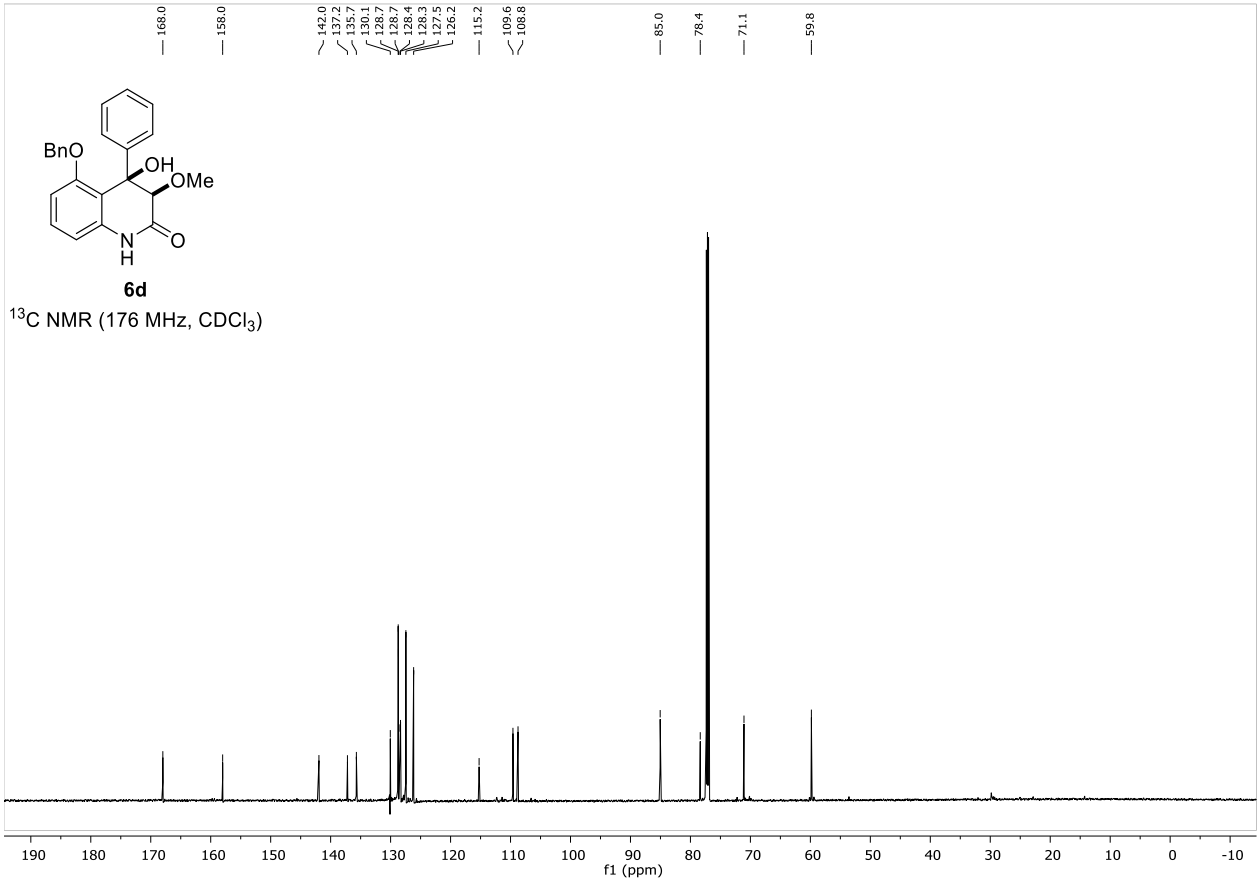


6d

^{1}H NMR (700 MHz, $CDCl_3$)



6d

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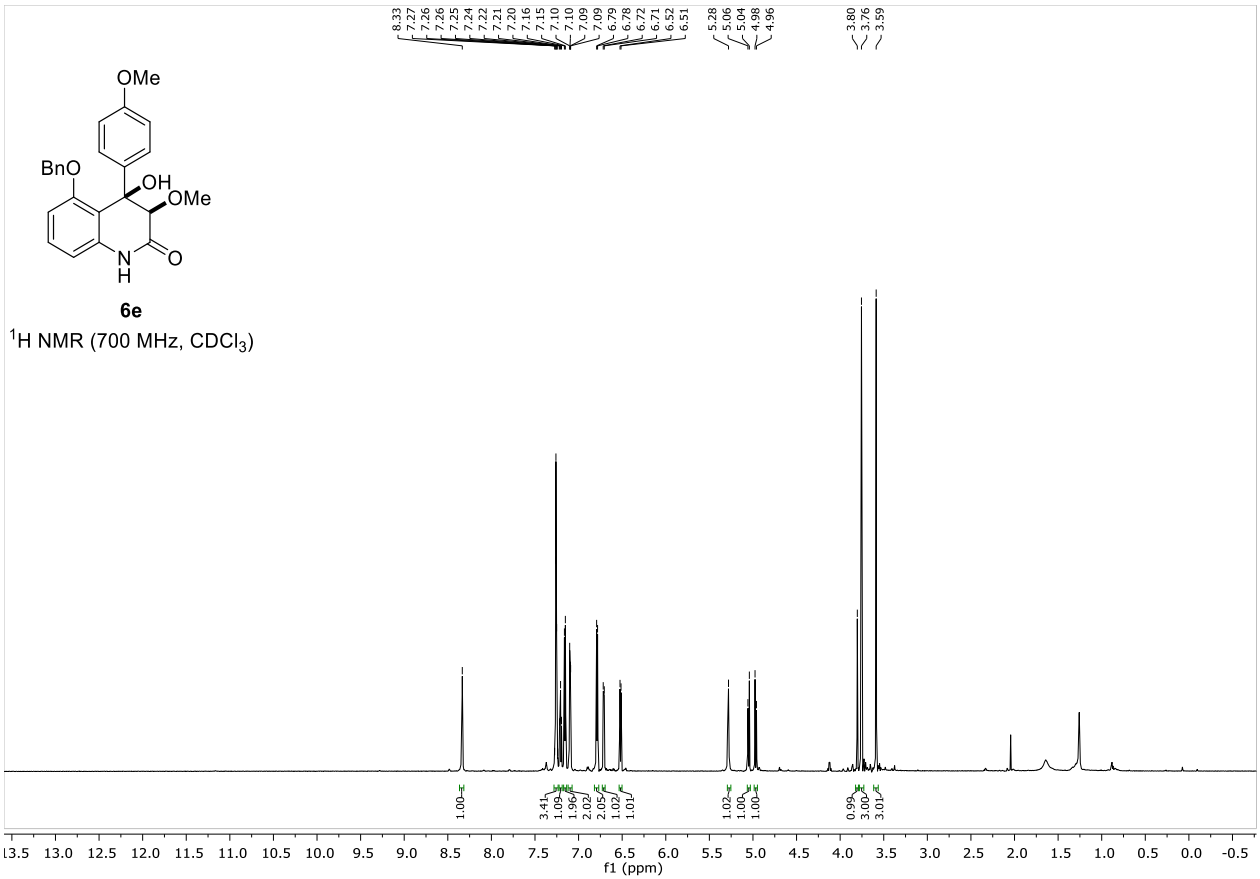
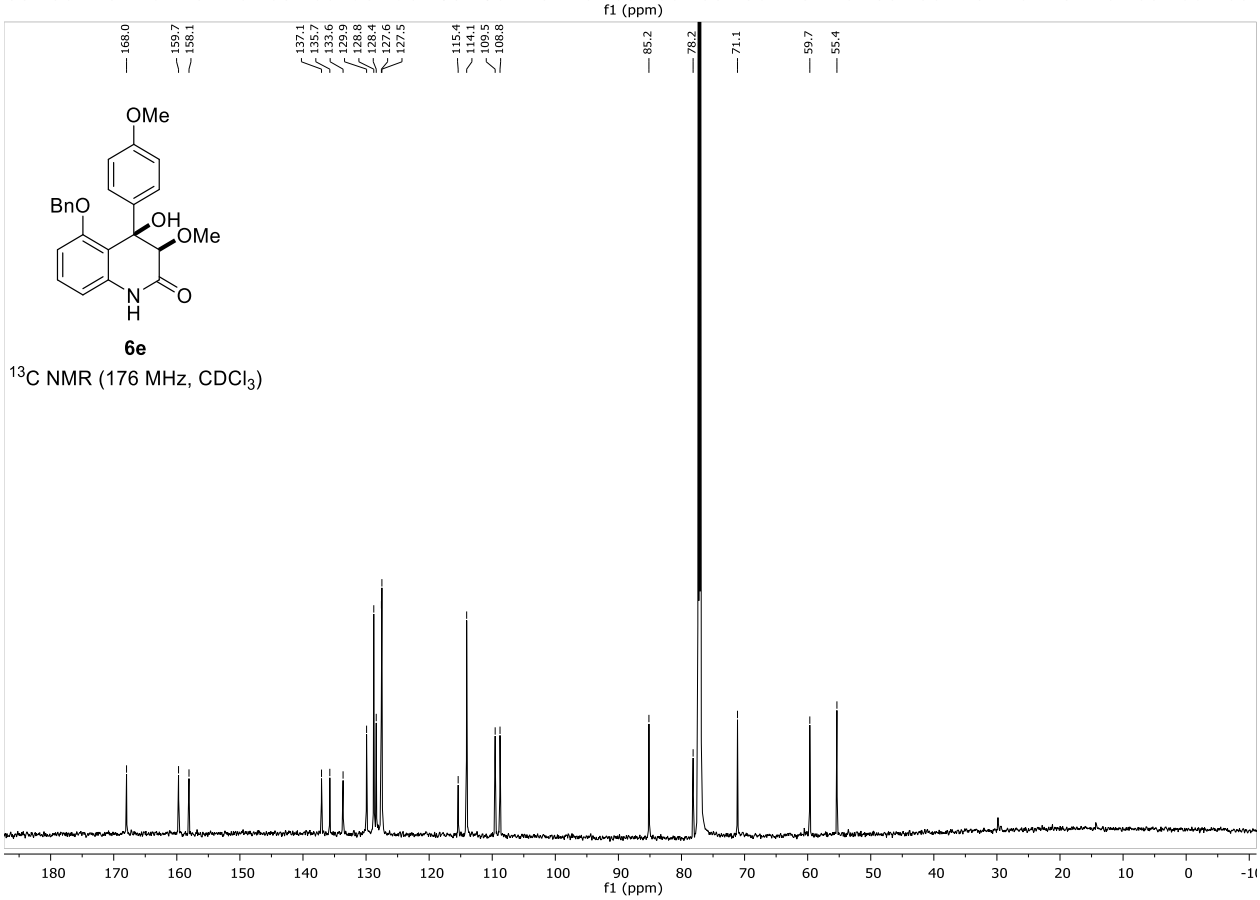


6e

^{1}H NMR (700 MHz, $CDCl_3$)



6e

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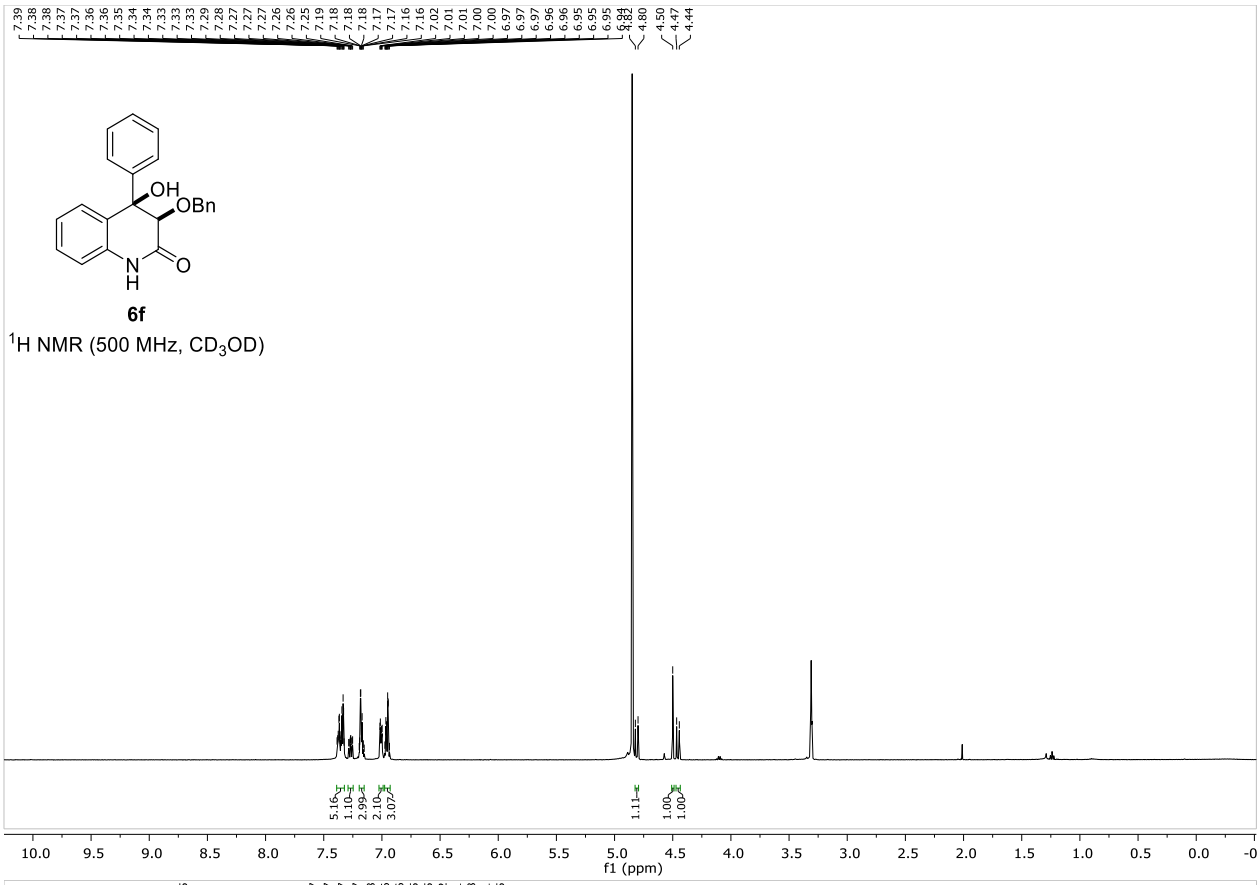
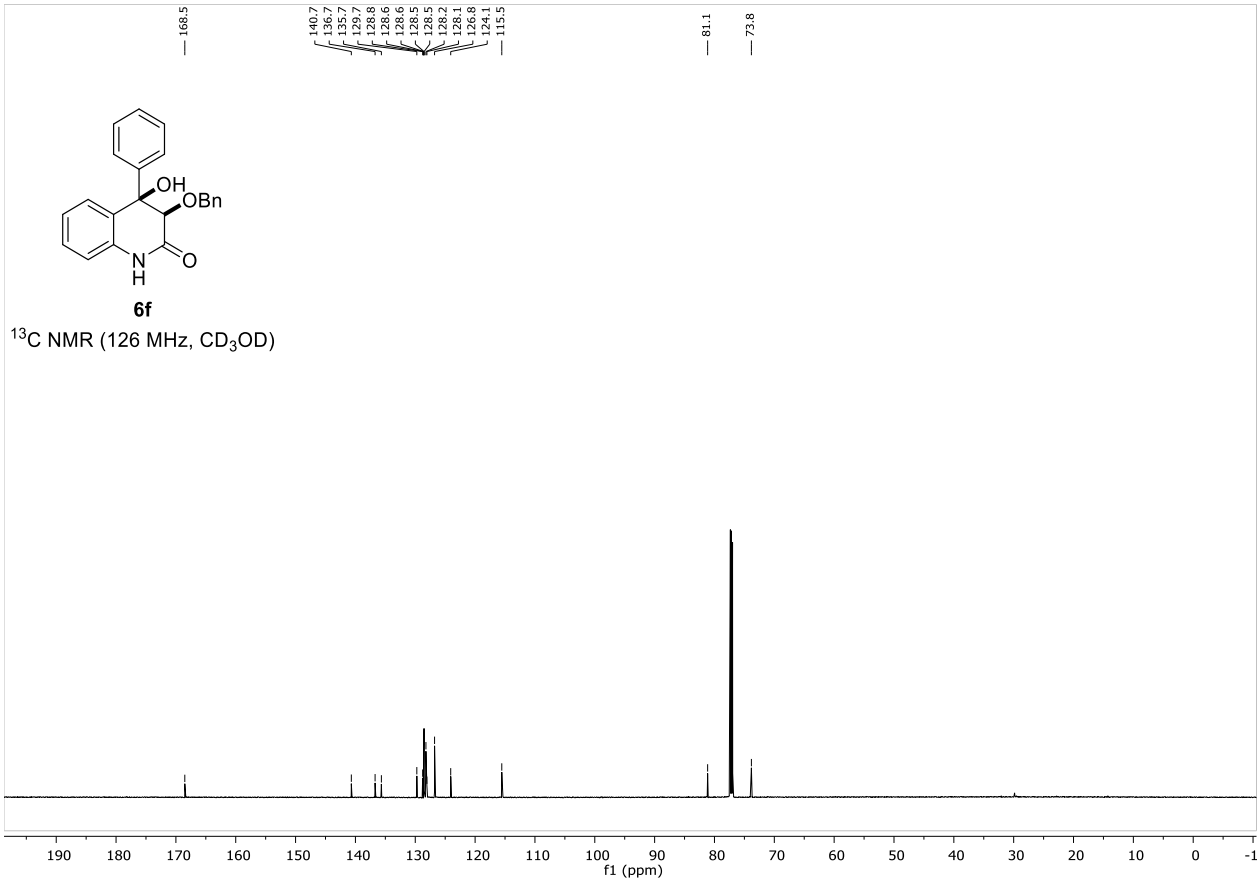
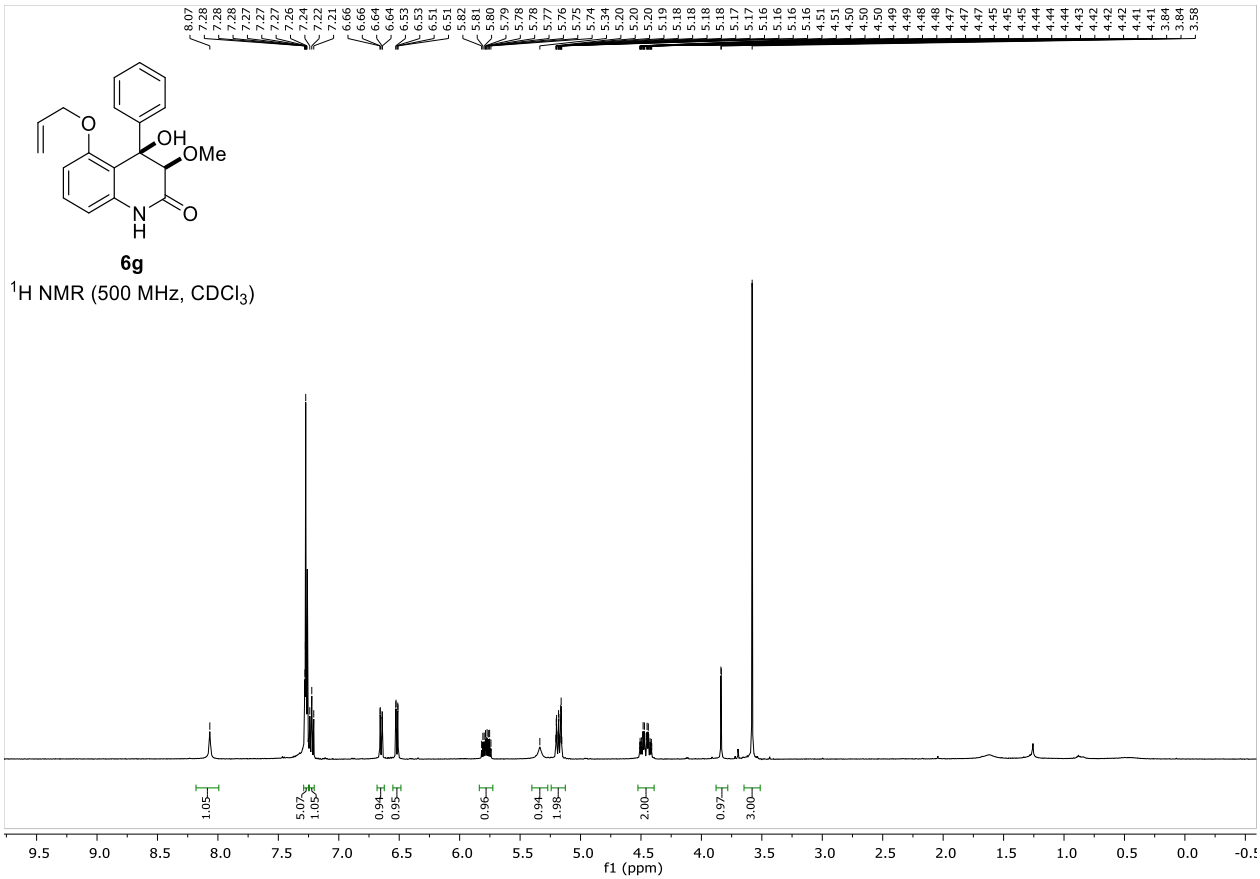
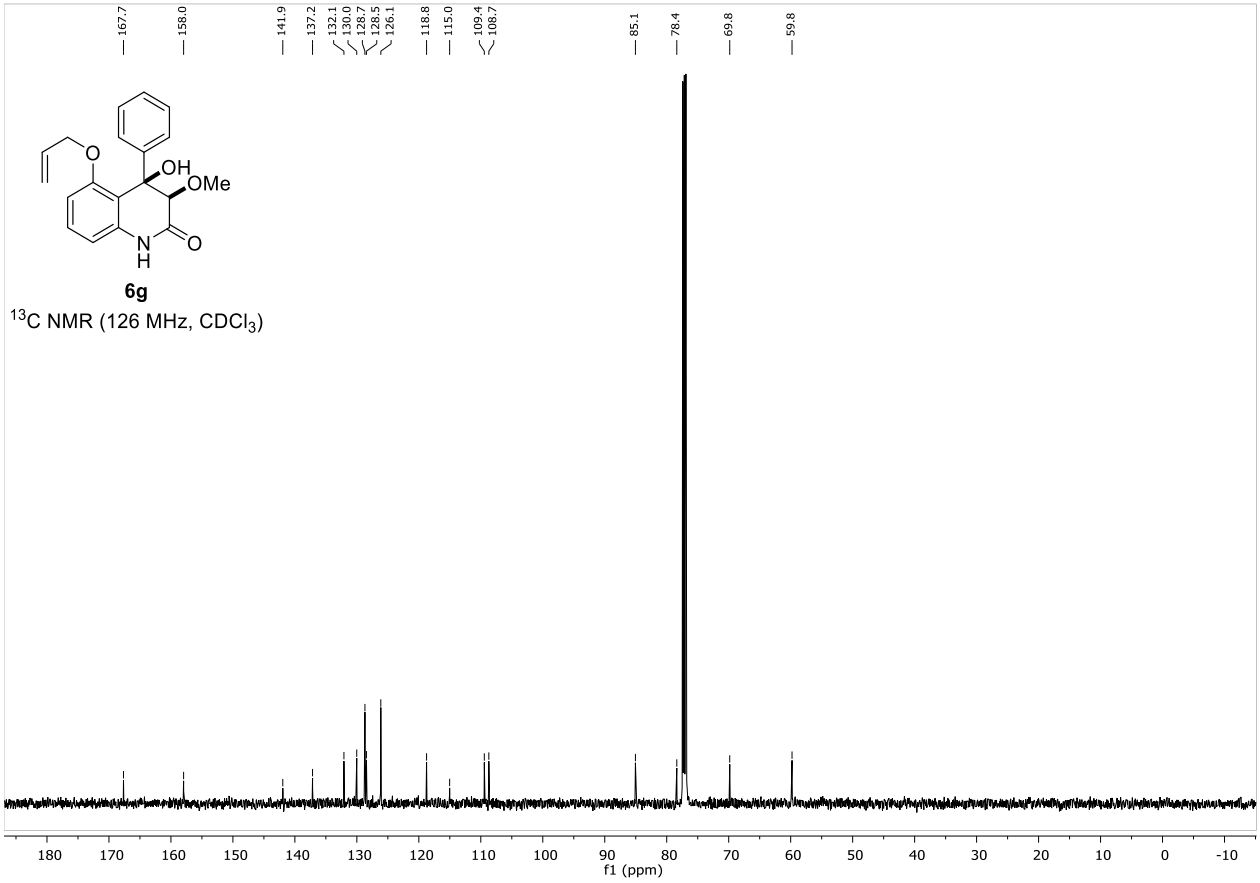

OH
OBn
N
H
O
6f
1H NMR (500 MHz, CD3OD)
f1 (ppm)


OH
OBn
N
H
O
6f
13C NMR (126 MHz, CD3OD)
f1 (ppm)



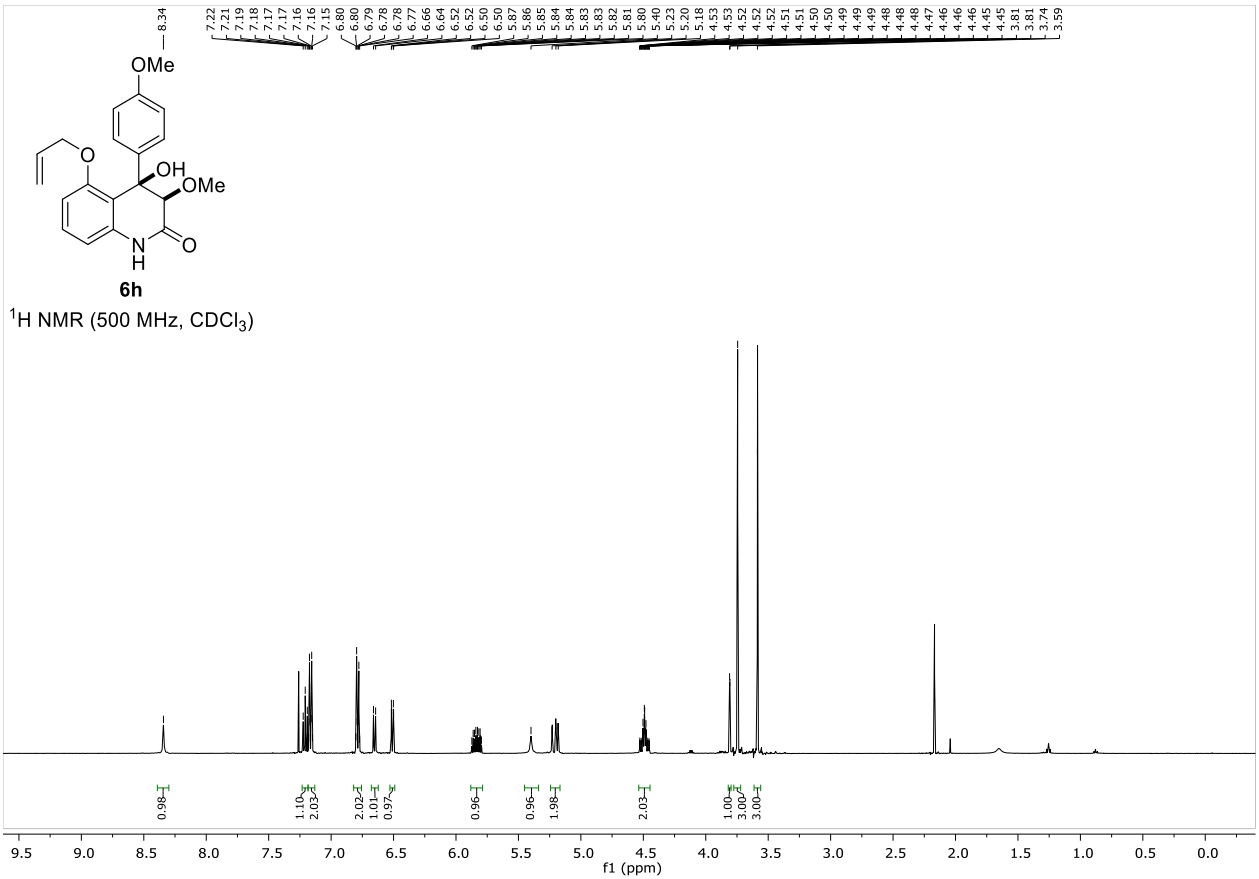
6g

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



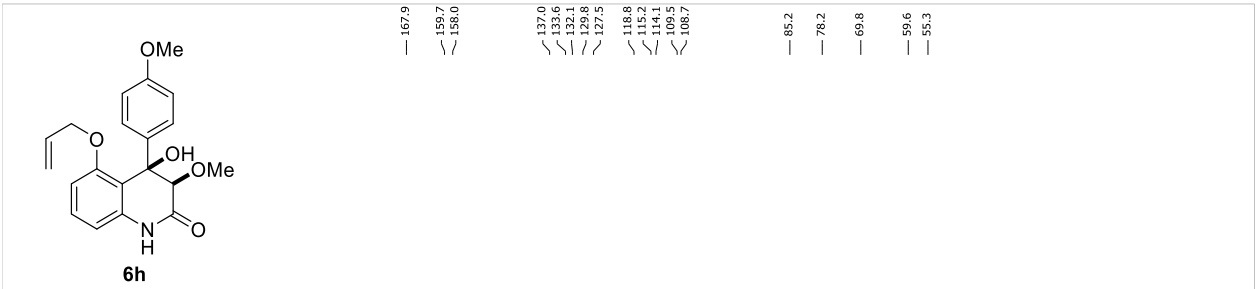
6g

^{13}C NMR (126 MHz, $CDCl_3$)



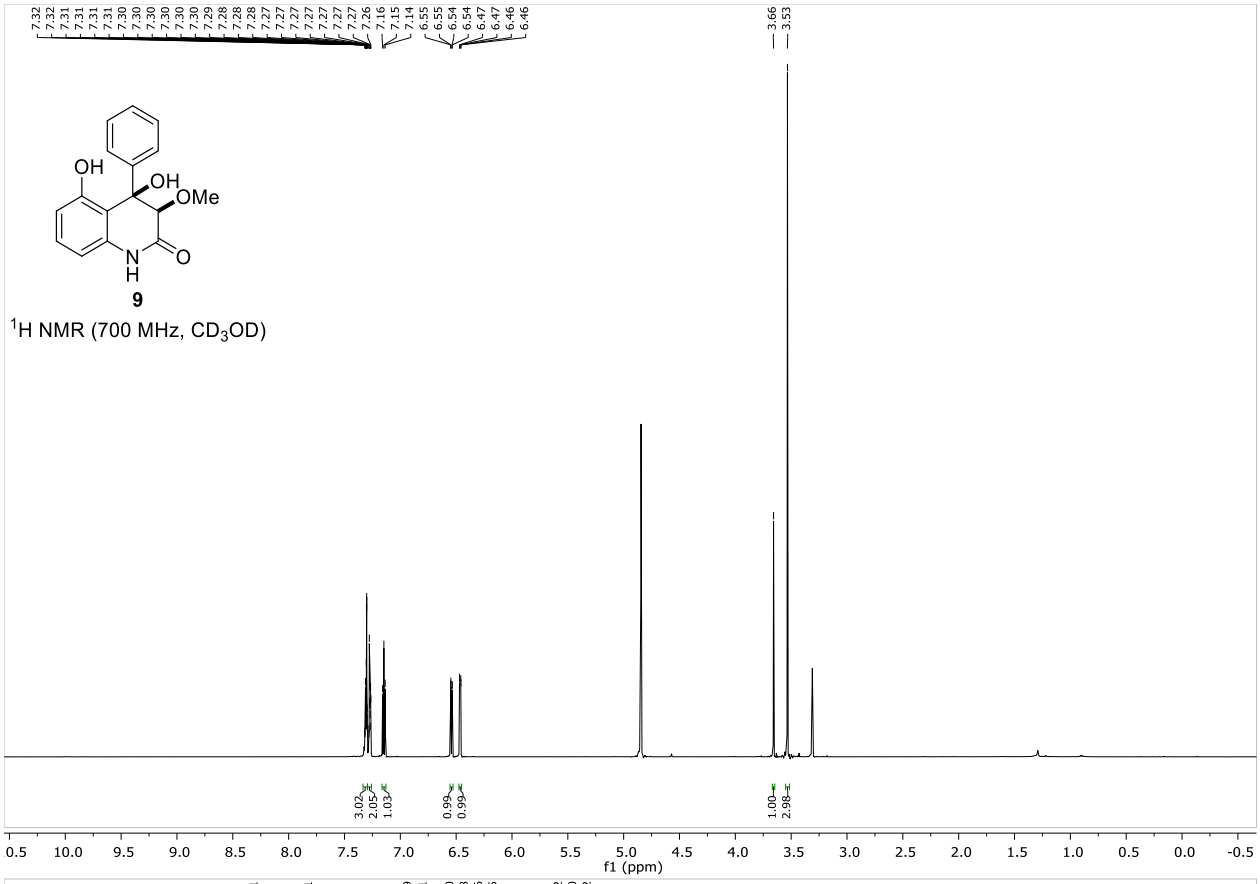
6h

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



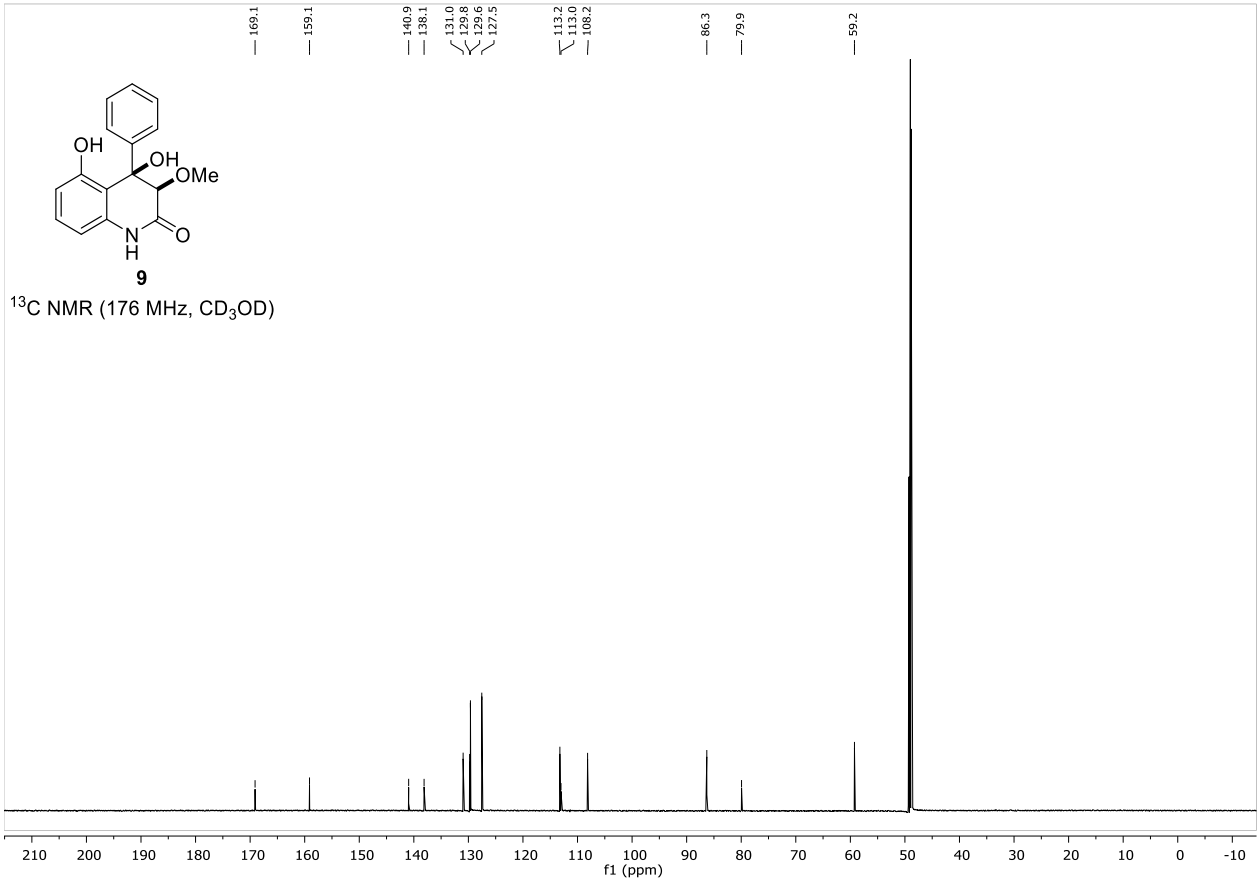
6h

^{13}C NMR (126 MHz, $CDCl_3$)



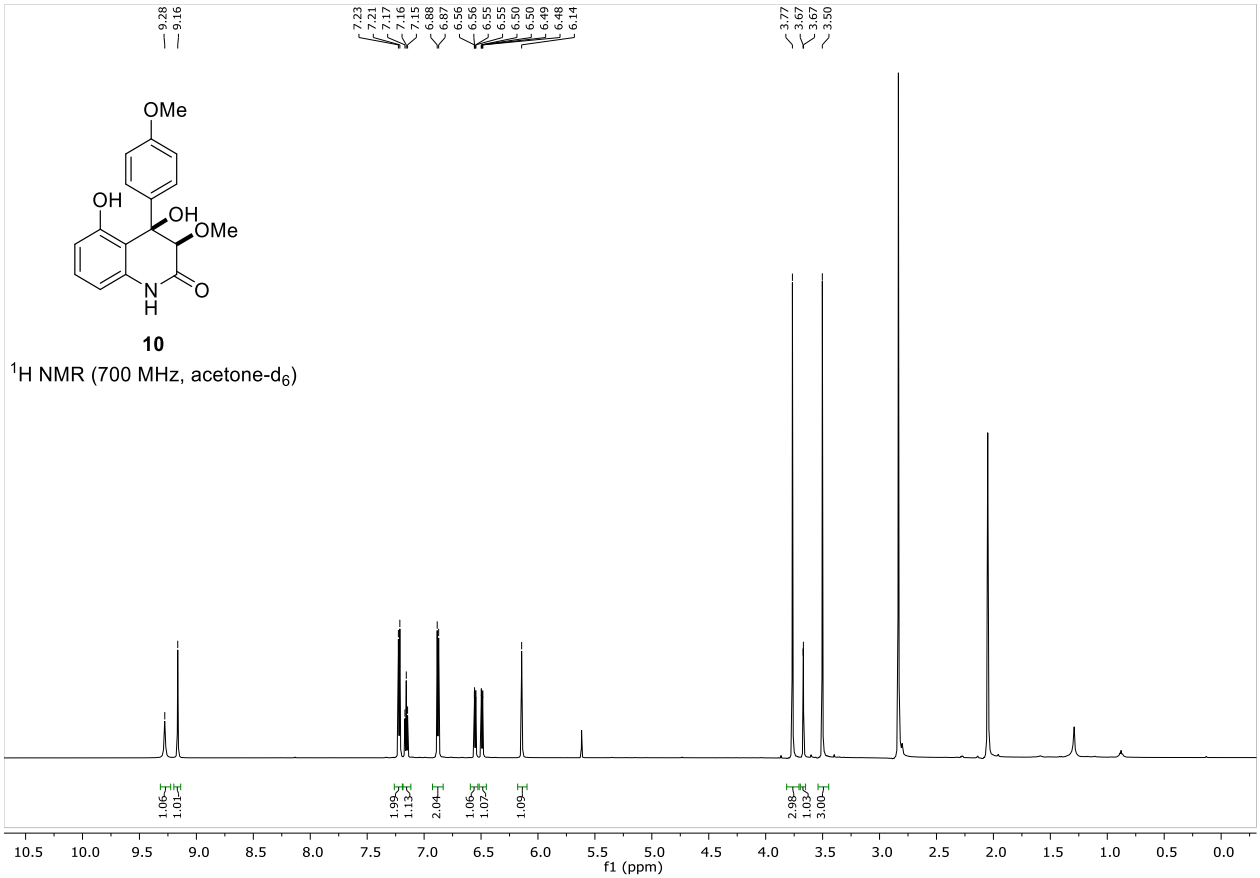
9

^{1}H NMR (700 MHz, CD_3OD)



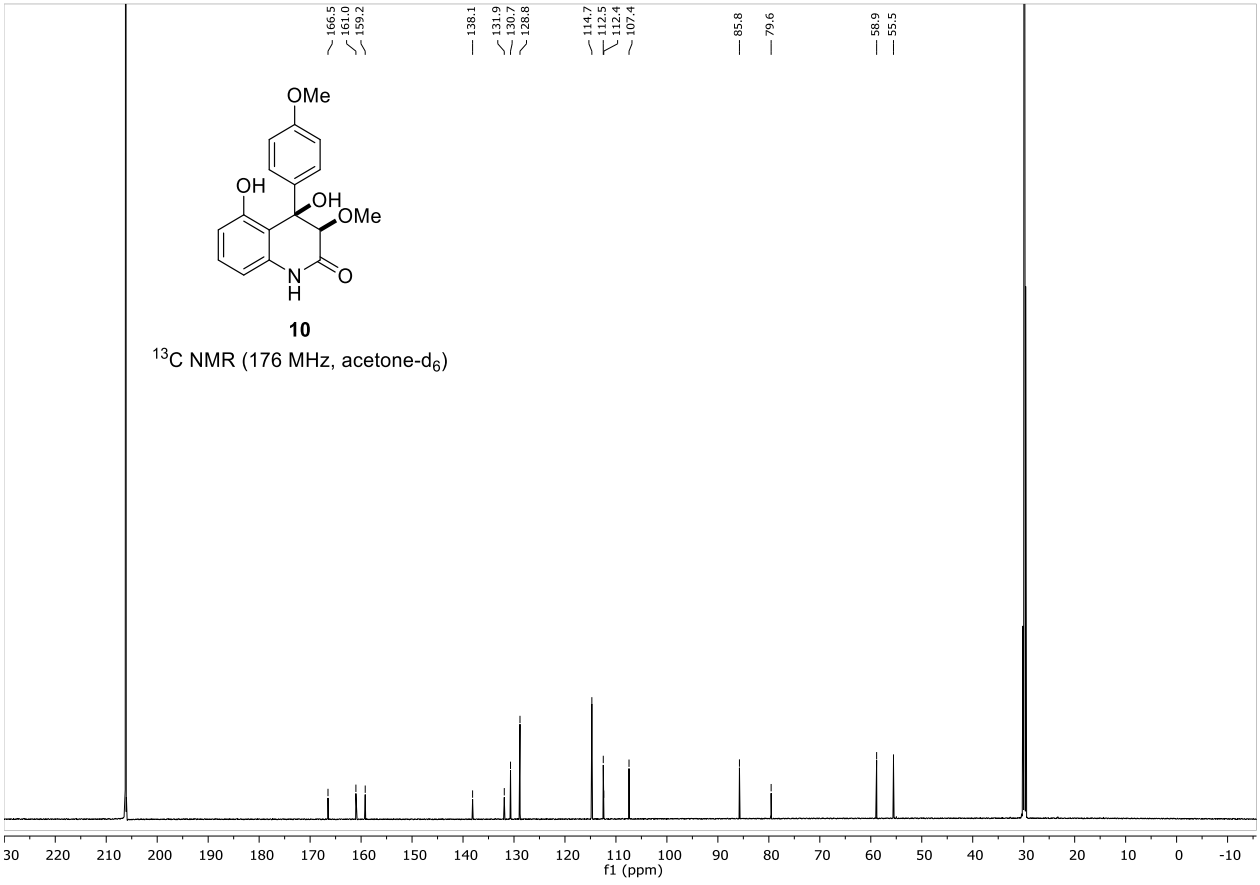
9

^{13}C NMR (176 MHz, CD_3OD)



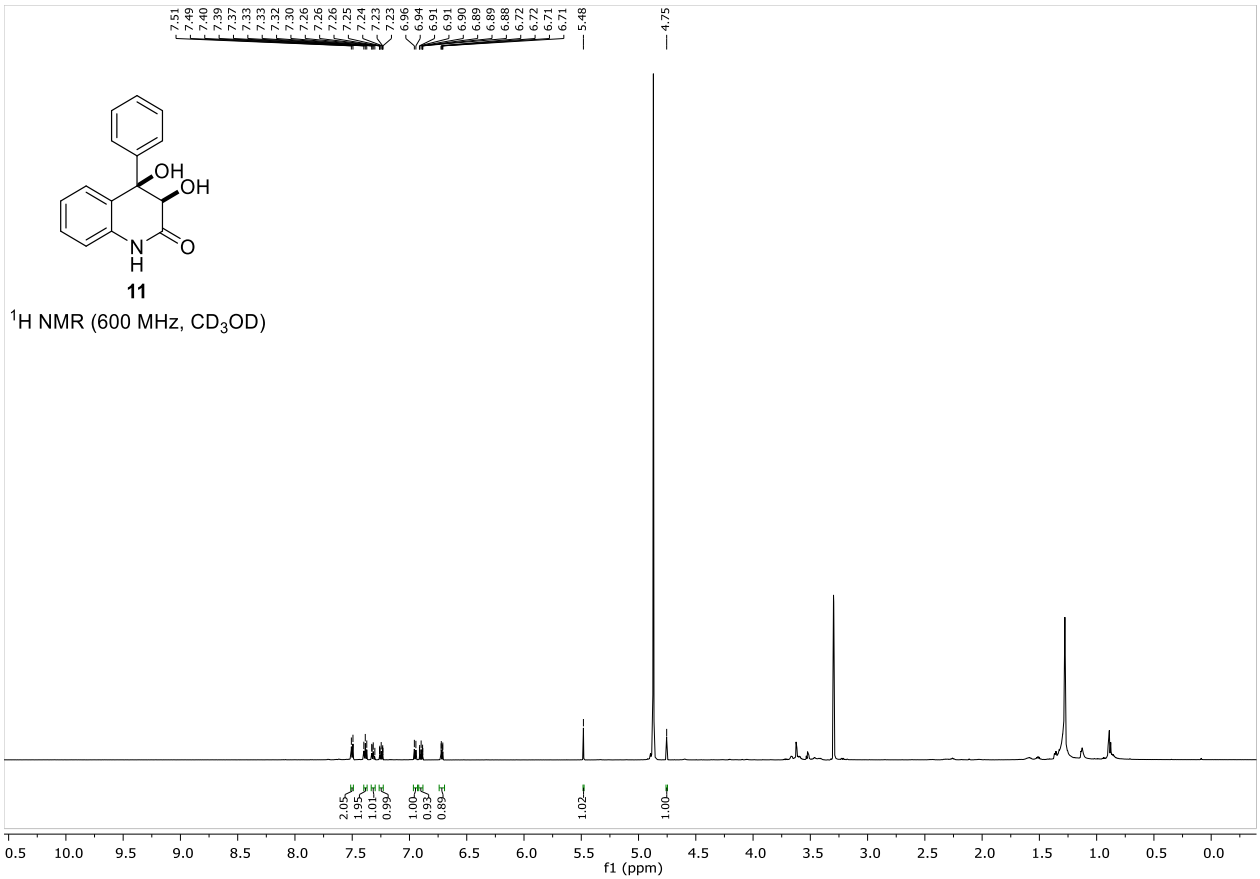
10

^{1}H NMR (700 MHz, acetone-d_6)



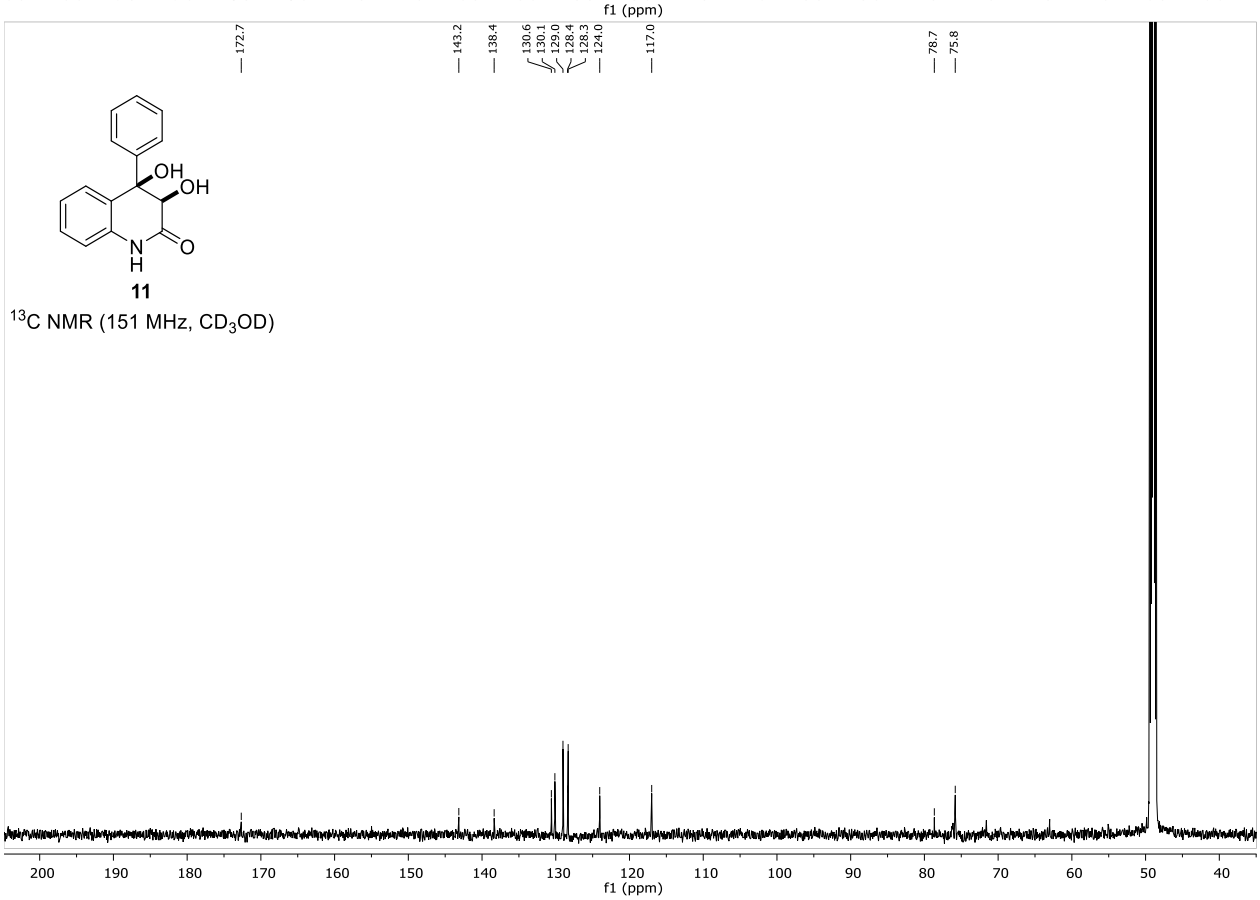
10

^{13}C NMR (176 MHz, acetone-d_6)



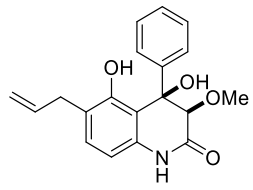
11

^{1}H NMR (600 MHz, CD_3OD)



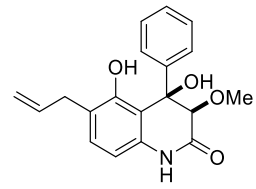
11

^{13}C NMR (151 MHz, CD_3OD)



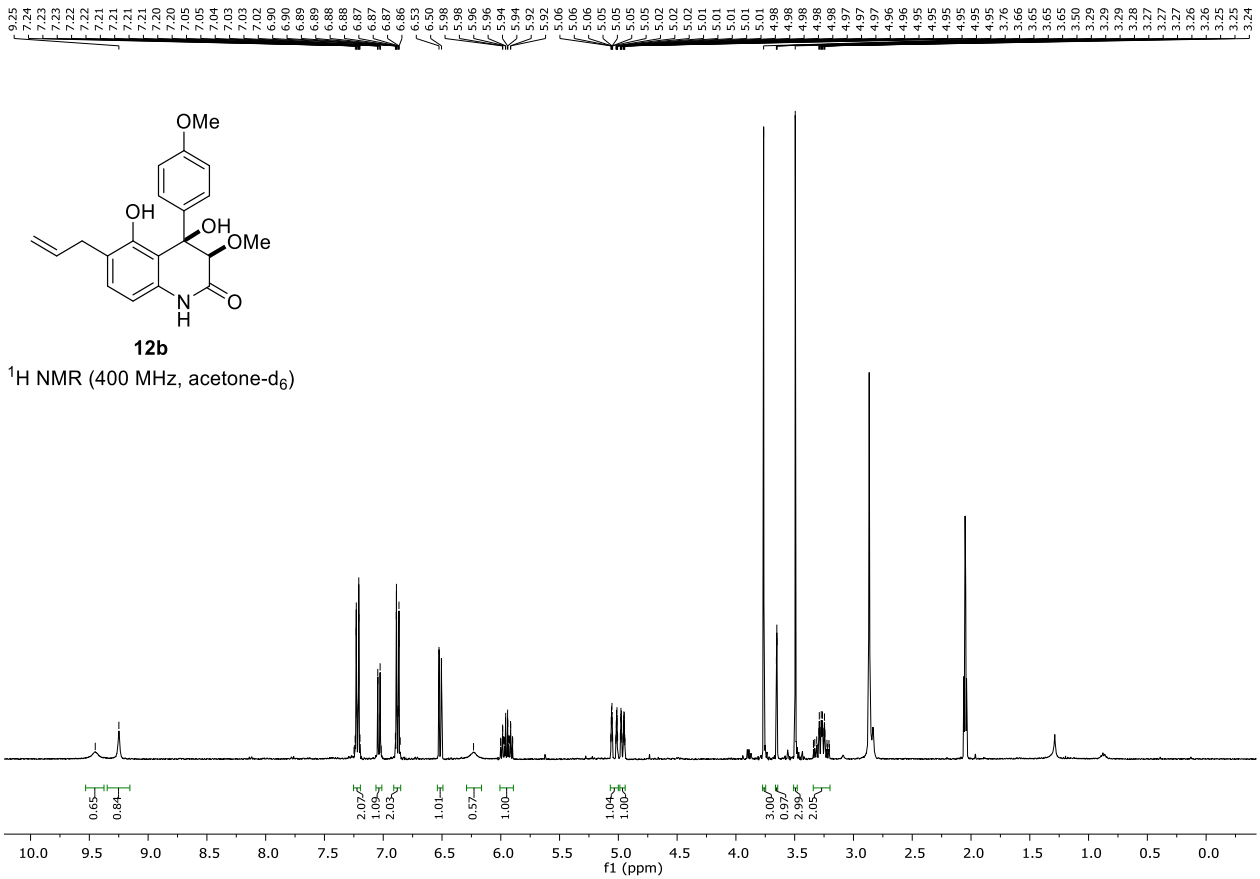
12a

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



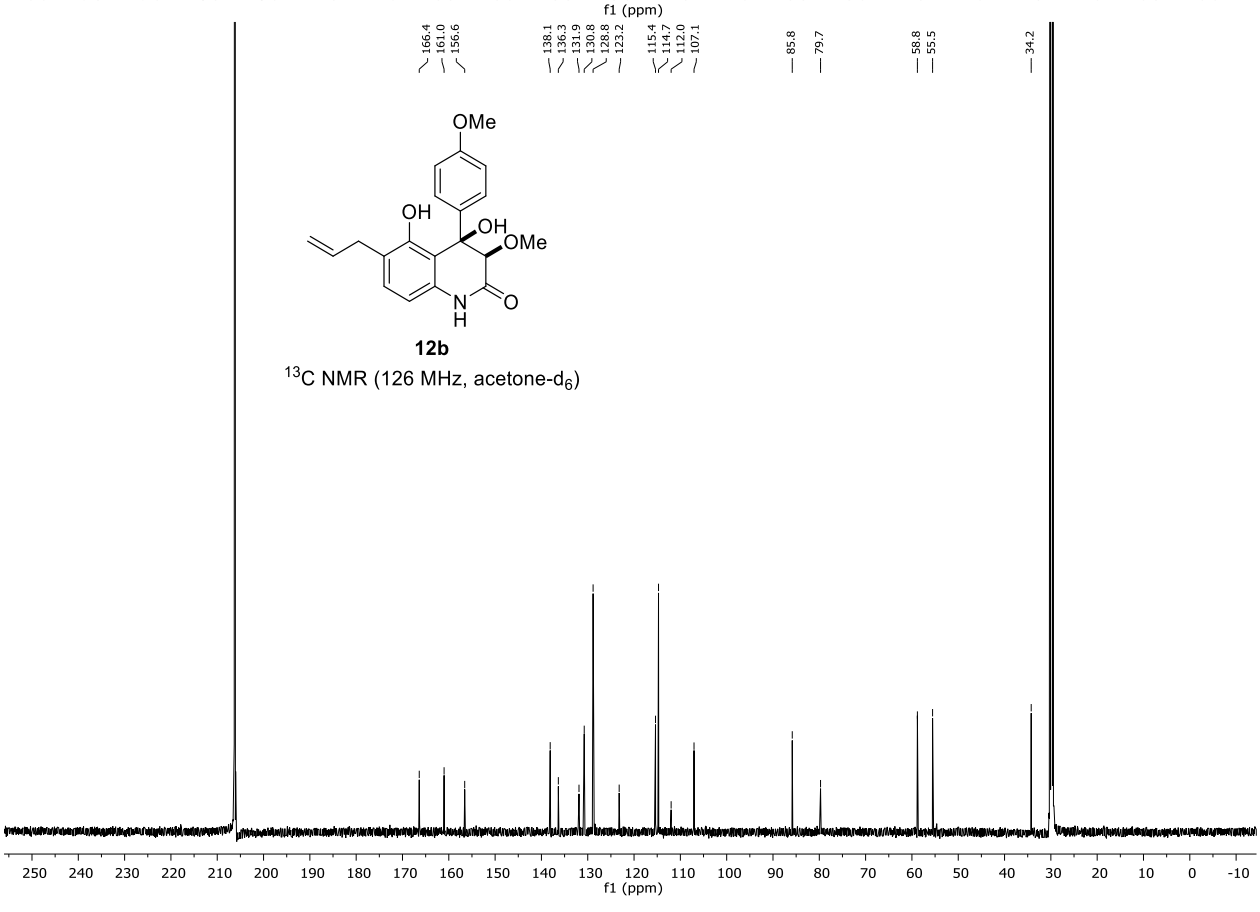
12a

^{13}C NMR (126 MHz, $CDCl_3$)



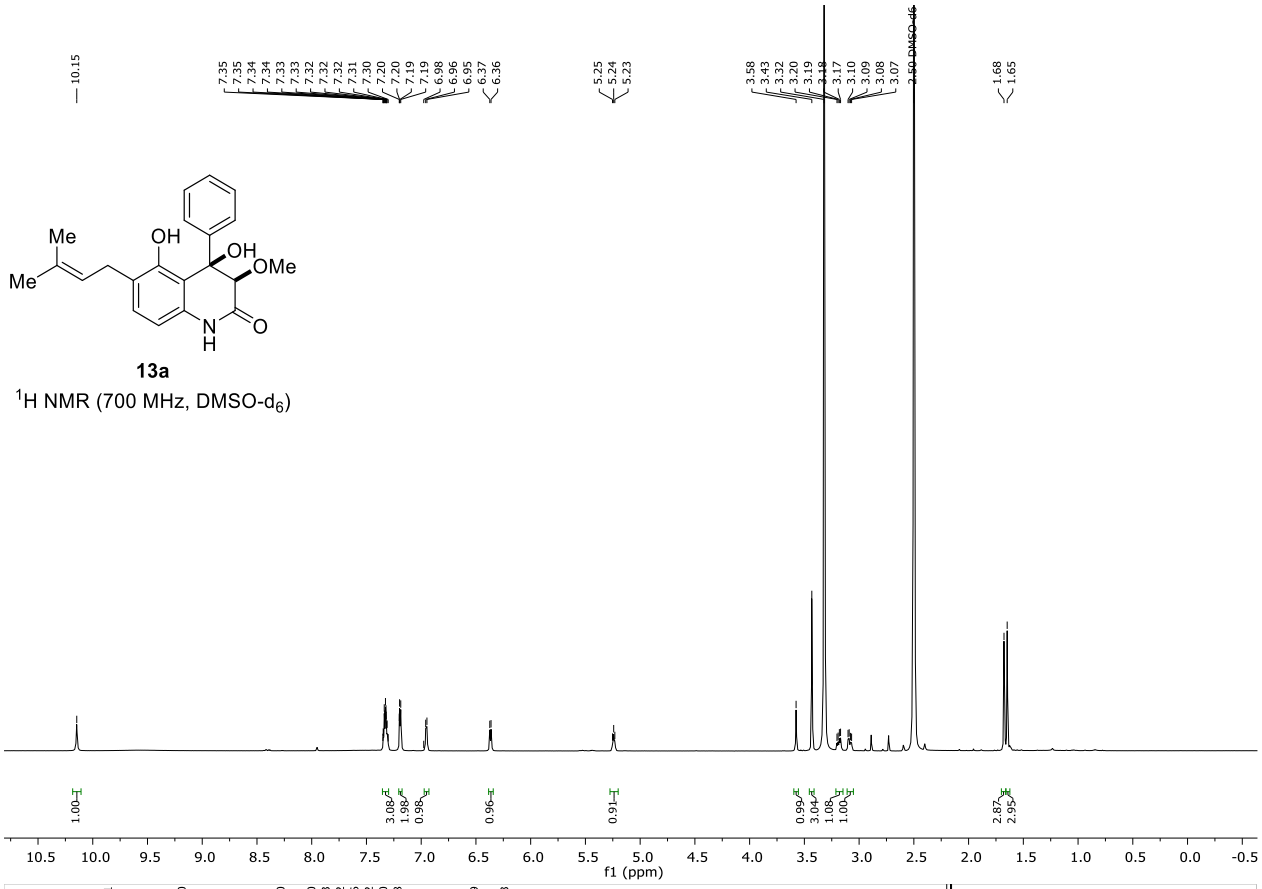
12b

^{1}H NMR (400 MHz, acetone-d_6)



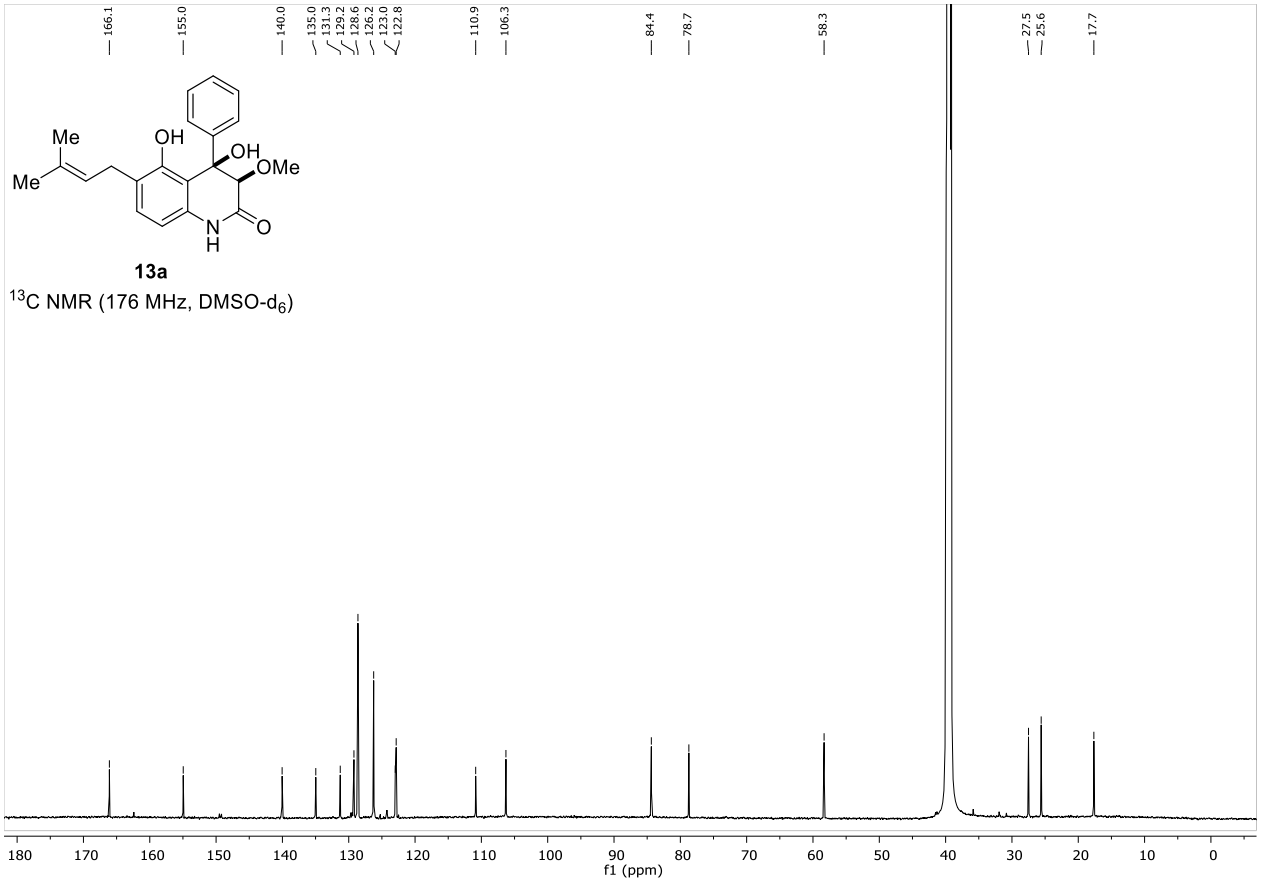
12b

^{13}C NMR (126 MHz, acetone-d_6)



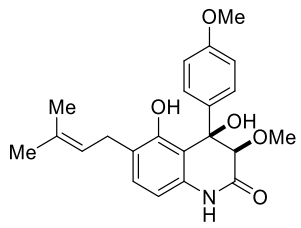
13a

^{1}H NMR (700 MHz, DMSO-d_6)



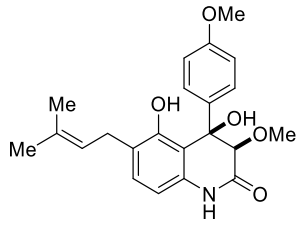
13a

^{13}C NMR (176 MHz, DMSO-d_6)



13b

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



13b

^{13}C NMR (126 MHz, $CDCl_3$)