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Supporting Information to Accompany:

Intermolecular Cyclotrimerization of Haloketoalkynes and Internal Alkynes: Facile Access to Arenes and Phthalides

Xx and xx

Department of Chemistry, xx

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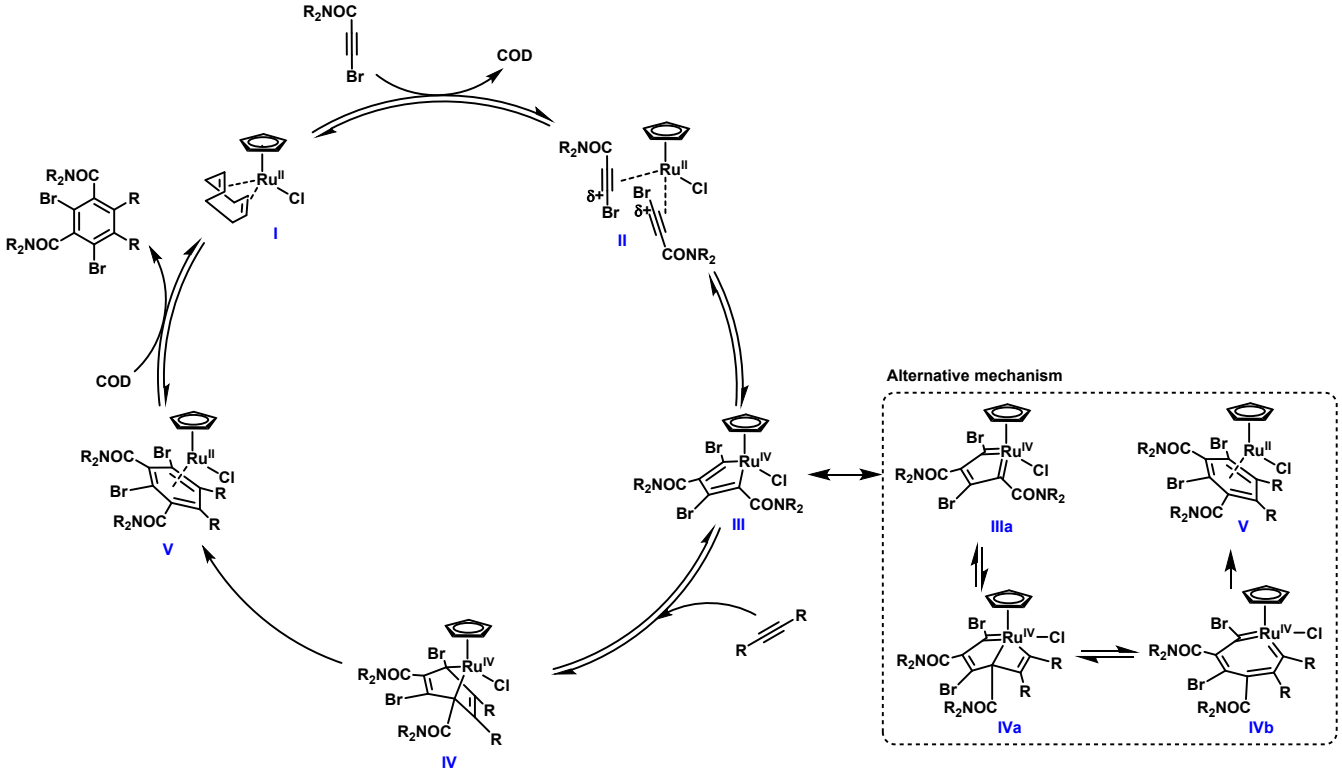
General Experimental Procedures:

^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX-400 and Varian Inova-400 instruments at 295 K. Chemical shifts (δ) are expressed in parts per million relative to residual $CHCl_3$, acetone or DMSO as internal standards. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz. Carbon magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz. Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; sex, sextet; sept, septet; app, apparent. When possible, NMR signals belonging to the major and minor isomers of inseparable mixtures or regioisomers were identified with a superscript major or minor, respectively. Infrared spectra were recorded on a ThermoNicolet Avatar 370 Fourier transform infrared spectrometer and are expressed in wavenumbers (cm^{-1}). Melting points (mp) were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Melting points were not obtained for compounds with regioisomeric purity less than 95:05. GCMS data were recorded on an Agilent 7890A GC system with an Agilent 5975C Inert MSD system operating in electron impact (EI+) mode. HPLC was preformed on an Agilent 1100 LC/MSD with an Agilent 1100 SL mass spectrometer (electrospray ionization, ES) eluting with 0.1% trifluoroacetic acid in H_2) and 0.05% trifluoroacetic acid in CH_3CN. Percoated Merck F-254 silica gel plates were used for thin layer analytical chromography (TLC) and visualized with short wave UV light or by potassium permanganate stain. Column chromatography was carried out employing EMD (Merck) Silica Gel 60 (40-63 μm).

We provide thin-layer chromatographic, infrared resonance tabulations, LRMS (ESI+ or EI+) data, as well as 1H and 13C-NMR tabulations and spectra for all new and synthesized compounds. These data, in combination with X-ray crystallographic information for select compounds, confirm the structure, regiochemistry, and homogeneity of all compounds detailed in this manuscript.

Unless otherwise noted, all starting materials were purchased from Aldrich, Acros Organics, Fisher, TCI, Alfa Aesar or Strem Chemicals and used as received. All solvents were purchased from Fisher and used as received. Dichloromethane and tetrahydrofuran were dried by passage through alumina. 1,4-Dioxane was obtained from Acros Organics as 99.5% extra dry over molecular sieves. Ethanol was purchased as 200 proof 1 pint quantities from Pharmco-AAPER and used as received. Chloro(cyclopentadienyl)-(cyclooctadiene)ruthenium [CpRuCl(cod)] was prepared in four steps from $RuCl_3 \cdot xH_2O$ according to literature procedures.[1,2] Alternatively, a detailed procedure can be found in supporting information of the following reference: Oakdale, J. S.; Sit, R. K.; Fokin, V. V. *Chem. Eur. J.* **2014**, *20*, 11101-11110. Cp*RuCl(cod) was purchased from Strem Chemicals and used as received.

Mechanistic Hypothesis

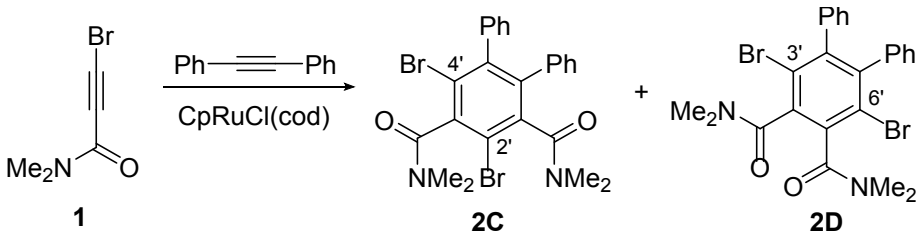


The mechanistic hypothesis and origins of observed diasteroselectivity and chemoselectivity are discussed.

The reaction mechanism begins with COD ligand dissociation from **I** and ligand association of two equivalents of halopropiolamide to generate intermediate **II**. Oxidative cyclization of organized and polarity-matched haloalkynes on the Ru-center generates Ru-cyclopentadiene intermediate **III**. The polarity-matching on the Ru-center of these ligands prior to cyclization is crucial and thought to be the origin of the observed regioselectivity. Importantly, that Cp ligand is preferred over Cp* (in terms of yield) for these cyclizations indicates that a less sterically occluded Ru-center is required for this preorganization of bulky halopropiolamide ligands. Direct cyclization of internal alkyne onto diene **III** then generates intermediate **IV**, which subsequently undergoes reductive cyclization to furnish the product arene and regenerate Ru(II) catalyst, after coordination of COD ligand. The preference for reaction between **III** and internal alkyne is due to the fact that **III** is very electron poor and the internal alkyne is electron rich. This predisposes intermediate **III** to reaction with internal alkyne, and not an additional equivalent of halopropiolamide, giving rise to the observed chemoselectivity of this cycloaddition.

A plausible alternative mechanism beginning from the resonance structure **IIIa** could be operative but less likely due to the excess coordinative saturation at the Ru-center of intermediate **IVa**, as well as the non-optimal bond angles present in **IVa** and **IVb**.

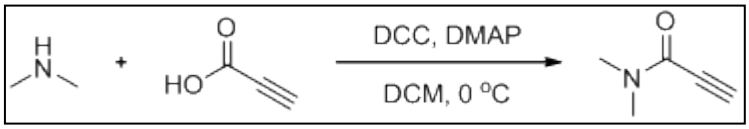
Table S1. Reaction Optimization and Solvent Screen



Entry	Eq. **1a**	Eq. **3**	Mol% [Ru]	Solvent	Temp	Atmos-phere	Yield[a]	LC/MS Ratio	NMR Ratio **C:D** (crude)[isolated]
1	1	2	8%	Dioxane	r.t.	Ar	87%	N/A	(N/A) [90:10]
2	2	1.9	4%	Dioxane	r.t.	N_2	69%	87:13	(88:12) [N/A]
3	1	20	4%	Dioxane	r.t.	N_2	92%	87:13	(86:14) [N/A]
4	1	1.8	4%	Dioxane	r.t.	N_2	85%	87:13	(89:11) [90:10]
5	1	1.8	4%	DCE	r.t.	N_2	77%	82:18	(85:15) [93:07]
6	1	1.8	4%	DMF	r.t.	N_2	~70%	85:15	(91:9) [N/A]
7	1	1.8	4%	PhMe	r.t.	N_2	92%	N/A	(89:11) [95:05]
8	1	1.8	4%	EtOH	r.t.	N_2	87%	94:06	(96:04) [97:03]
9	1	1.8	4%	ACN	r.t.	N_2	<40%	87:13	(N/A) [N/A]
10	1	1.8	4%	EtOAc	r.t.	N_2	76%	88:12	(87:13) [88:12]
11	1	1.8	4%	*t*-BuOH: H_2O:THF	r.t.	N_2	90%	94:06	(93:07) [95:05]
12	1	1.8	4%	$CHCl_3$	r.t.	N_2	88%	88:12	(91:09) [91:09]
13	1	1.8	4%	THF	r.t.	N_2	94%	88:12	(85:15) [86:14]
14	1	1.8	4%	DIEPA /DCM	r.t.	N_2	<40%	N/A	(N/A) [N/A]
15	1	1.8	4%	Acetone	r.t.	N_2	80%	85:15	(86:14) [N/A]
16	1	1.5	4%	EtOH	0°C	Ar	N/A	96:04	(N/A) [N/A]
17	1	1.6	1%	EtOH	r.t.	Ar	81%	96:04	(N/A) [98:02]
18	1	1.6	1.8%	EtOH	r.t.	Air	86%	96:04	(N/A) [97:03]
19	1	1.5	0.4%	EtOH	r.t.	Air	59%[b]	96:04	[97:03]
20	1	1.5	1%	EtOH	r.t.	Air	82%	96:04	[96:04]
21[c]	1	1.5	0.2% 0.2%	EtOH	r.t.	Air	70%[d]	96:04	[96:04]
				[Ru] = Cp*RuCl(cod)					
22	1	1.5	2%	EtOH	r.t.	N_2	7%	-	[98:02]
23	1	1.5	20%	EtOH	r.t.	N_2	47%	-	[98:02]

General Notes: The equivalents of **3** vs **1a** impacts the reaction by suppressing the formation of **2aA/B**, the result of the direct trimerization of **1a** (see S16). **9aC** and **9aD** can be separated by column chromatography but the separation is tedious. However the isolated NMR ratio of **C:D** was often better than the crude ratio indicating that some separation had occurred during purification which involved column chromatography. [a]Isolated yield after silica gel chromatography. [b]70% conversion or 82% yield based on recovered starting material. [c]Batch-wise addition of catalyst 0.2 mol% followed by 0.2 mol% after 1 hour. [d]85% conversion based on recovered starting material.

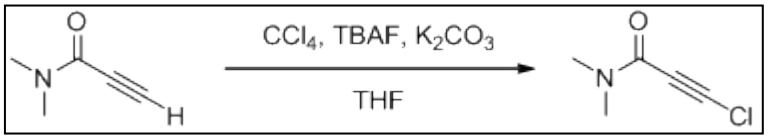
Preparation and Characterization of Starting Materials



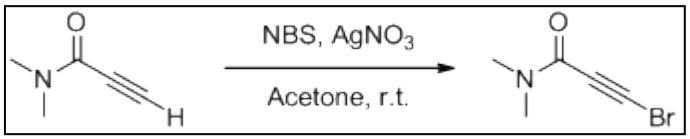
Dimethylpropiolamide (7). A 1 L 3-neck round bottom flask equipped with a rubber septum, a glass stopper, a vacuum adaptor and a stirring bar was charged with 4-dimethylaminopyridine (DMAP; 1.71 g, 14.0 mmol). The reaction vessel was subsequently placed under argon, filled with 250 mL of dry DCM and cooled to 0 °C with an ice bath. 100 mL dimethylamine (9.00g, 200 mmol) as a 2M solution in THF was added directly to the reaction vessel, followed by *N,N*-dicyclohexylcarbodiimide (DCC; 42.4g, 204 mmol). Finally, propiolic acid (12.6 mL, 14.3g, 204 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight with stirring (note 1). The crude reaction mixture was filtered to remove urea and the filtrate was concentrated onto silica gel and subjected to flash chromatography (note 2) (SiO_2, 40% EtOAc-hexanes; R_f = 0.15 at 40% EtOAc-hexanes) to afford **7** as an off-white crystalline solid (15.0g, 77%): mp 68-70 °C; IR (neat) υ_{max} 3176, 2926, 2855, 2094, 1627, 1615, 1573, 1484, 1442, 1395, 1367, 1257, 1203 1163, 760, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 3H), 3.11 (s, 1H), 2.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 79.0, 75.8, 38.3, 34.1; LRMS (ESI) m/z = 98.3 $[M + H]^+$. See S26 for NMR spectra.

Note 1: Upon addition of the propiolic acid the reaction mixture immediately became cloudy with beige precipitate (1,3-dicyclohexylurea). The crude reaction varied between heterogeneous yellow and heterogeneous dark red/brown after stirring overnight.

Note 2: While column chromatography was effective at removing trace colored impurities, complete removal of dicyclohexyl urea was not always achieved. Propargyl-amides contaminated with urea were carried forward to the halogenation reaction where subsequent purification was often effective for removing remaining trace urea.

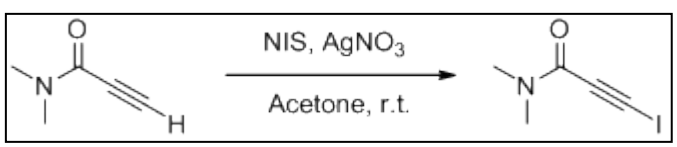


3-Chloro-dimethylpropiolamide (5). A 50 mL round bottom flask equipped with a stirring bar was charged with dimethylpropiolamide (**7**; 970 mg, 10.0 mmol), and K_2CO_3 (1.38 g, 10 mmol) and placed under argon. Carbon tetrachloride (6mL) was added to the reaction vessel and the resulting heterogeneous solution was allowed to stir for 1 min. 1 mL of 1M Bu_4NF in THF (TBAF; 1 mmol) and an additional 3 mL of dry THF were then added to the reaction mixture. Upon stirring at room temperature over 4 hr, the reaction mixture turned from clear to orange to dark red. The crude reaction mixture was placed on silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 40% EtOAc-hexanes; R_f = 0.15 at 40% EtOAc-hexanes) to afford **5** as a low melting, colorless crystalline solid (825 mg, 63%): IR (neat) υ_{max} 2932, 2220, 1631, 1494, 1446, 1396, 1264, 1172, 1061, 1009, 844, 725, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.14 (s, 3H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 79.0, 75.8, 38.3, 34.1; LRMS (ESI) m/z = 132.2 $[M + H]^+$. See S27 for NMR spectra.



3-Bromo-dimethylpropiolamide (1).

Dimethylpropiolamide (**7**; 6.00 g, 61.9 mmol), and a stirring bar were added to a 500 mL round bottom flask under argon and the reaction vessel was subsequently filled with 200 mL of acetone. $AgNO_3$ (1.01 g, 6.19 mmol) and *n*-bromosuccinimide (NBS; 12.1 g, 68.0 mmol) were then added to the reaction flask by partial removal of the septum. As a precaution, the reaction vessel was wrapped in aluminum foil to protect the silver catalyst from light. The reaction mixture was stirred overnight and the resulting heterogeneous solution was then placed directly onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 30% EtOAc-hexanes; R_f = 0.29 at 40% EtOAc-hexanes) to afford **1** as a colorless crystalline solid (9.68 g, 89%): mp 85-88 °C; IR (neat) υ_{max} 2930, 2200, 1757, 1620, 1489, 1436, 1395, 1264, 1235, 1172, 1049, 1017, 719, 649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 73.7, 55.3, 38.2, 34.2; LRMS (ESI) m/z = 176.3 $[M + H]^+$. See S28 for NMR spectra.

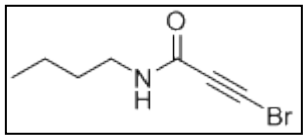


3-Iodo-dimethylpropiolamide (6).

Dimethylpropiolamide (**1**; 1.00 g, 10.3 mmol), and a stirring bar were added to a 100 mL round bottom flask

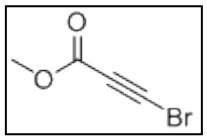
and the reaction vessel was placed under argon. 36 mL of acetone was added followed by the addition of $AgNO_3$ (202 mg, 1.24 mmol) and *n*-iodosuccinimide (NIS; 2.78 g, 12.4 mmol) to the reaction flask by partial removal of the septum. As a precaution, the reaction vessel was wrapped in aluminum foil to protect the silver catalyst from light. The reaction mixture was stirred overnight and the resulting heterogeneous solution was then placed directly onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 1% MeOH-DCM; R_f = 0.24 at 40% EtOAc-hexanes) to afford **1** as a beige powder (note 1) (2.07 g, we will just say 65%): mp 155-156 °C; IR (neat) υ_{max} 2931, 2169, 1618, 1479, 1441, 1393, 1265, 1168, 1055, 779, 719, 628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 3H), 2.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 88.0, 38.3, 34.3, 16.1; LRMS (ESI) m/z = 224.1 $[M + H]^+$. See S29 for NMR spectra.

Note 1: On occasion the iodoalkyne would be contaminated by succinimide after column chromatography. The succinimide contamination can be removed by washing an ethyl acetate solution of the iodoalkyne with a 1M solution of NaOH.



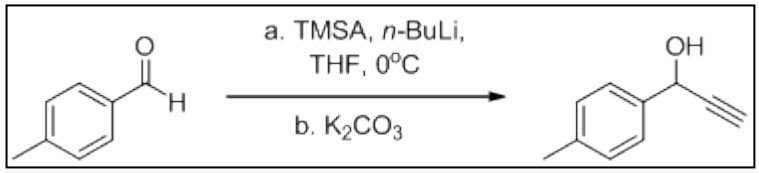
3-Bromo-butylpropiolamide (8). The general procedure for the synthesis of propiolamides (see **7**, dimethylpropiolamide, page S3) was employed using 6.1 mL butylamine (4.50 g, 61.5 mmol), 3.98 mL propiolic acid (4.5 g, 64.6 mmol), DCC (13.9 g, 67.7 mmol) and DMAP (525 mg, 4.31 mmol). The crude material was purified via flash chromatography (SiO_2, 30% EtOAc-hexanes; R_f = 0.29 at 40% EtOAc-hexanes) to deliver butylpropiolamide.

The general procedure for the synthesis of bromoalkynes (see **1**, 3-bromo-dimethylpropiolamide, page S3) was employed using butylpropiolamide (1.08 g, 8.64 mmol), $AgNO_3$ (141 mg, 0.864 mmol) and NBS (1.69 g, 9.50 mmol). The crude material was purified via flash chromatography (SiO_2, 20% EtOAc-hexanes; R_f = 0.43 at 40% EtOAc-hexanes) to afford **8** as a slightly yellow crystalline solid (1.14 g, 65%) as a 92:08 ratio of rotamers: mp 69-71 °C; IR (neat) υ_{max} 3300, 2950, 2926, 2861, 2199, 1638, 1621, 1528, 1441, 1362, 1273, 697, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (s, 1H), 3.26 (app q, J = 6.8 Hz, 2H), 1.48 (p, J = 7.3 Hz, 2H), 1.33 (sex, J = 7.8 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 75.3, 50.0, 39.8, 31.2, 20.1, 13.7; LRMS (ESI) m/z = 204.2 $[M + H]^+$. See S30 for NMR spectra.



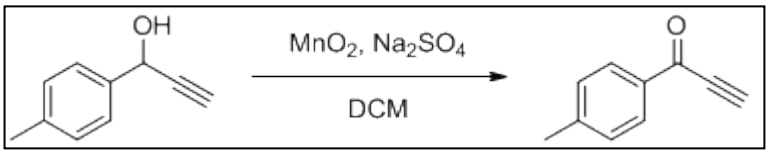
Methyl 3-bromopropiolate (3). The general procedure for the synthesis of bromo-alkynes (see **1**, 3-bromo-dimethylpropiolamide, page S3) was employed using 1.06 mL methylpropiolate (1.00 g, 11.9 mmol), $AgNO_3$ (194 mg, 1.19 mmol) and NBS (2.33 g, 13.09 mmol). The crude material was purified via flash chromatography (SiO_2, 5% EtOAc-hexanes; R_f = 0.38 at 5% EtOAc-hexanes) to afford **7** as a low melting, colorless, crystalline solid (note 1) (1.07 g, 55%): IR (neat) υ_{max} 2957, 2202, 1709, 1631, 1434, 1238, 1013, 889, 745, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 72.5, 53.0, 52.9. See S31 for NMR spectra.

Note 1: Methyl 3-bromopropiolate is a lachrymator.

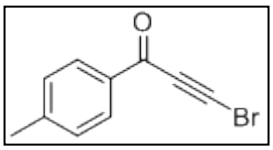


1-*p*-Tolylprop-2-yn-1-ol (si_1). 8.47 mL of trimethylsilylacetylene (TMSA; 5.89g, 59.9 mmol) and 120 mL dry THF were added to a 250 mL round bottom flask under argon and the resulting solution was cooled to 0 °C. The reaction mixture was treated with 27.2 mL of 2.2 M *n*-BuLi in hexanes (59.9 mmol) and allowed to stir at 0 °C for 30 min. *p*-Tolylaldehyde (5.91 mL, 6.00 g, 49.9 mmol) was added dropwise and the solution was allowed to come to room temperature over 3 hr with stirring. The reaction mixture was diluted with 60 mL water and 40 mL MeOH and further treated with K_2CO_3 (13.8 g, 100 mmol). The removal of TMS was deemed complete by TLC analysis after 30 min, at which point MeOH and THF were removed by rotary evaporation. The aqueous solution was further diluted by water and extracted with EtOAc (2x). The organic extract was then washed with brine, dried over Na_2SO_4 and concentrated to deliver an orange oil (6.30 g). The crude material was carried forward without further purification. A small amount of material was purified by flash chromatography (SiO_2, 10% EtOAc-hexanes; R_f = 0.1 at 10% EtOAc-hexanes): IR (neat) υ_{max} 3290, 2097, 1647, 1603, 1513, 1416, 1260, 1178, 1010, 946, 816, 760, 638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 5.41 (app s, 1H), 2.75 (d, J = 5.1 Hz, 1H), 2.66 (d, J = 2.3 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.3, 129.4,

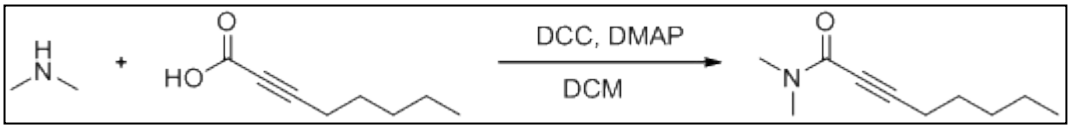
129.7, 83.8, 74.7, 64.2, 21.2; LRMS (ESI) m/z = 129.3 $[M - OH]^+$. See S32 for NMR spectra; note NMR spectra contains EtOAc.



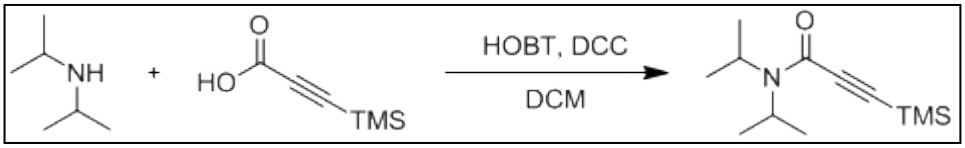
1-*p*-Tolylprop-2-yn-1-one (si_2). To a 250 mL round bottom flask was charged with 1-*p*-tolylprop-2-yn-1-ol (**si_1**; 6.30, 43 mmol), Na_2SO_4 (61.1 g, 430 mmol), 180 mL DCM and a stirring bar. MnO_2 (26.0 g, 302 mmol) was then added and the resulting slurry was stirred overnight and filtered to arrive at a yellow/brown filtrate. The crude material was placed on silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 5→10% EtOAc-hexanes; R_f = 0.26 at 10% EtOAc-hexanes) to afford the desired ketone as a yellow solid that slowly turned orange over several weeks at refrigerated temperatures (2.37 g, 44%): mp 36-38 °C; IR (neat) υ_{max} 3263, 2094, 1638, 1601, 1569, 1408, 1308, 1257, 1174, 1115, 1106, 831, 741, 682, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 7.3 Hz, 2H), 3.42 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 145.8, 133.9, 129.9, 129.5, 80.5, 80.4, 21.9; LRMS (ESI) m/z = 145.3 $[M + H]^+$. See S33 for NMR spectra.



3-Bromo-1-p-tolylprop-2-yn-1-one (4). The general procedure for the synthesis of bromoalkynes (see **1**, 3-bromo-dimethylpropiolamide, page S3) was employed using 1-*p*-tolylprop-2-yn-1-one (**si_2**; 780 mg, 5.42 mmol), $AgNO_3$ (88 mg, 0.542 mmol) and NBS (1.06 g, 5.96 mmol). The crude material was purified via flash chromatography (SiO_2, 1→2% EtOAc-hexanes; R_f = 0.25 at 2% EtOAc-hexanes) to afford **4** as a white powder (1.05 g, 87%): mp 80-83 °C; IR (neat) υ_{max} 2176, 1632, 1602, 1570, 1309, 1261, 1177, 1120, 1047, 1017, 841, 821, 746, 731, 678, 602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (app s, 2H), 7.25 (app s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 145.9, 134.1, 130.0, 129.5, 79.2, 58.4, 22.0; LRMS (ESI) m/z = 223.1 $[M + H]^+$. See S34 for NMR spectra.

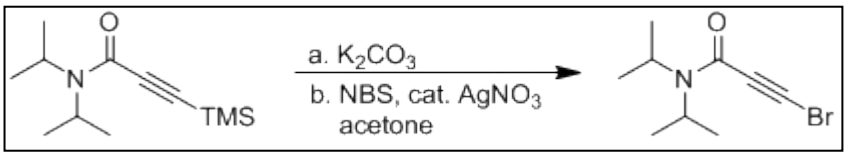


***N,N*-Dimethyloct-2-ynamide (10).** The general procedure for the synthesis of propiolamides (see **7**, dimethylpropiolamide, page S2) was employed using 3.57 mL of a 2M THF solution of dimethylamine (321 mg, 7.14 mmol), 1.04 mL oct-2-ynoic acid (1.00 g, 7.14 mmol), DCC dissolved in dry DCM (1.52 g, 7.35 mmol) and DMAP (65 mg, 0.536 mmol). The crude material was purified via flash chromatography (SiO_2, 20→30% EtOAc-hexanes; R_f = 0.25 at 20% EtOAc-hexanes) to afford **10** as a light yellow oil (770 mg, 65%): IR (neat) υ_{max} 2933, 2865, 2245, 2223, 1626, 1494, 1466, 1393, 1268, 1187, 1051, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.12 (s, 3H), 2.88 (s, 3H), 2.28 (t, J = 7.0 Hz, 2H), 1.51 (p, J = 7.4 Hz, 2H), 1.35-1.23 (m, 4H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 93.1, 74.1, 38.3, 33.9, 31.0, 27.5, 22.1, 18.8, 13.8; LRMS (ESI) m/z = 168.3 $[M + H]^+$. See S35 for NMR spectra.



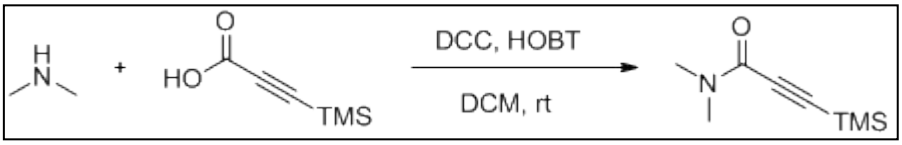
***N,N*-diisopropyl-3-(trimethylsilyl)propiolamide (si_3).** A 100 mL round bottom flask equipped with a stirring bar and rubber septum was charged with 3-(trimethylsilyl)propiolic acid (1.00 g, 7.04 mmol) and placed under argon. 80 mL dry DCM was added followed by hydroxybenzotriazole (HOBT; 1.05 g, 7.74 mmol) and dicyclohexyl-carbodiimide (DCC; 1.60 g, 7.74 mmol) in that order by partial removal of the septum. The resulting slurry was stirred at room temperature for 1 h. 1.39 mL Diisopropylamine (997 mg, 9.88 mmol) was then added dropwise and the resulting reaction mixture was stirred overnight. The resulting heterogeneous solution was filtered over a büchner funnel and the filtrate was placed on silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 5→10% EtOAc-hexanes; R_f = 0.30 at 10% EtOAc-hexanes) to afford the desired compound

si_3 as a white crystalline solid (1.21 g, 77%): mp 67-69 °C; IR (neat) υ_{max} 2969, 2943, 2175, 2120, 2088, 1681, 1617, 1443, 1369, 1328, 1252, 1207, 1133, 1043, 963, 898, 866, 839, 759, 740, 700, 638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (sept, J = 5.9 Hz, 1H), 3.54 (app br s, 1H), 1.24 (d, J = 6.9 Hz, 6H), 1.14 (d, J = 6.8 Hz, 6H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 97.7, 94.7, 50.1, 45.5, 20.8, 19.2, -0.8; LRMS (ESI) m/z = 226.3 $[M + H]^+$. See S36 for NMR spectra.

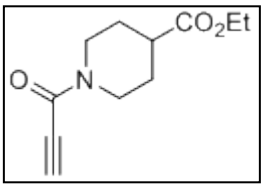


3-Bromo- diisopropyl-propiolamide (si_4). Diisopropyl-3-(trimethylsilyl)-propiolamide (**si_3**; 989 mg, 4.4 mmol) was dissolved in 60 mL of a 3:2:2 THF:MeOH:water solution, treated with K_2CO_3 (1.2 g, 8.8 mmol) and stirred for 1 h. The reaction mixture was then concentrated via rotary evaporation to remove the THF and MeOH before being further diluted with water and extracted with EtOAc (2x). The organic layer was washed with brine, dried over Na_2SO_4, concentrated to deliver the terminal alkyne as a white crystalline solid (397 mg, 59%).

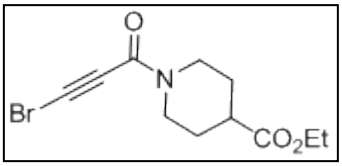
The general procedure for the synthesis of bromoalkynes (see **1**, 3-bromo-dimethylpropiolamide, page S3) was employed using diisopropylpropiolamide (341 mg, 2.23 mmol), $AgNO_3$ (36 mg, 0.223 mmol) and NBS (436 mg, 2.45 mmol). The crude material was purified via flash chromatography (SiO_2, 20% EtOAc-hexanes; R_f = 0.39 at 20% EtOAc-hexanes) to afford the desired compound **si_4** as a white powder (491 mg, 95%): mp 129-131 °C; IR (neat) υ_{max} 2967, 2935, 2188, 2091, 1714, 1680, 1611, 1439, 1375, 1330, 1206, 1136, 1045, 764, 731, 699, 618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.47 (sept, J = 6.4 Hz, 1H), 3.57 (sept, J = 6.4 Hz, 1H), 1.33 (d, J = 6.8 Hz, 6H), 1.22 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 75.0, 53.5, 50.6, 45.9, 21.1, 20.0; LRMS (ESI) m/z = 232.2 $[M + H]^+$. See S37 for NMR spectra.



Dimethyl-3-(trimethyl-silyl)propiolamide (9). The general procedure for the synthesis of propiolamides (see **si_3**, page S6) was employed using 5.00 mL of a 2M THF solution of dimethylamine (450 mg, 10.0 mmol), 3-(trimethylsilyl)propiolic acid (1.02 g, 7.14 mmol), DCC (1.62 g, 7.85 mmol) and HOBT (1.06 mg, 7.85 mmol). The crude material was purified via flash chromatography (SiO_2, 20→30% EtOAc-hexanes; R_f = 0.30 at 20% EtOAc-hexanes) to afford **9** as a white crystalline solid (905 g, 75%): mp 50-52 °C; IR (neat) υ_{max} 2933, 2119, 1618, 1501, 1439, 1394, 1252, 1154, 981, 862, 841, 764, 734, 707, 656, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.14 (s, 3H), 2.88 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 96.9, 96.1, 38.3, 33.9, -0.7; LRMS (ESI) m/z = 170.3 $[M + H]^+$. See S38 for NMR spectra.

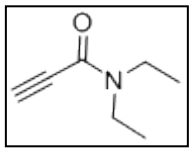


Ethyl 1-propioloylpiperidine-4-carboxylate (si_5). The general procedure for the synthesis of propiolamides (see **7**, dimethylpropiolamide, page S2) was employed using 3.92 mL ethyl isonipecotate (4.00 g, 25.5 mmol), 1.65 mL propiolic acid (1.88 g, 26.8 mmol), DCC dissolved in dry DCM (5.52 g, 26.8 mmol) and DMAP (311 mg, 2.25 mmol). The crude material was purified via flash chromatography (SiO_2, 30% EtOAc-hexanes; R_f = 0.15 at 30% EtOAc-hexanes) to afford the desired alkyne as a light orange solid (3.04 g, 57%): mp 64-66 °C; IR (neat) υ_{max} 3202, 2934, 2099, 1752, 1618, 1446, 1368, 1310, 1275, 1231, 1203, 1174, 1105, 1041, 925, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.28-4.17 (m, 3H), 4.08 (q, J = 7.2 Hz, 2H), 3.23 (ddd, J =12.4, 11.1, 3.1 Hz, 1H), 3.13 (s, 1H), 2.87 (ddd, J =12.3, 11.3, 3.1 Hz, 1H), 2.54-2.46 (m, 1H), 1.94-1.86 (m, 2H), 1.71-1.63 (m, 1H), 1.62-1.53 (m, 1H), 1.19 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 151,7, 79.4, 75.3, 60.7, 46.2, 40.7, 40.5, 28.3, 27.4, 14.1; LRMS (ESI) m/z = 210.3 $[M + H]^+$. See S39 for NMR spectra.

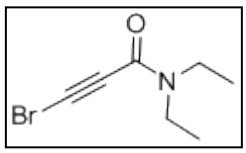


Ethyl 1-(3-bromopropioloyl)piperidine-4-carboxylate (si_6). The general procedure for the synthesis of bromoalkynes (see **1**, 3-bromo-dimethylpropiolamide, page S3) was employed using ethyl 1-propioloylpiperidine-4-carboxylate (**si_5**; 836 mg, 4.00 mmol), $AgNO_3$ (65.2 mg, 0.400 mmol) and NBS (783 mg, 4.40 mmol). The crude material was purified via flash chromatography (SiO_2, 20→30% EtOAc-

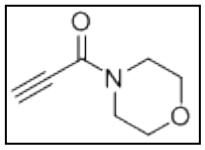
hexanes; R_f = 0.22 at 30% EtOAc-hexanes) to afford the desired compound, **si_6**, as a white crystalline solid (1.03 g, 89%): mp 75-76 °C; IR (neat) υ_{max} 2985, 2862, 2187, 1730, 1606, 1440, 1380, 1320, 1193, 1171, 1113, 1043, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.28 (dtd, J = 13.5, 4.3, 1.3 Hz, 1H), 4.19 (dtd, J = 13.6, 4.3, 1.3 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.25 (ddd, J = 11.3, 11.0, 3.2 Hz, 1H), 2.91 (ddd, J = 14.3, 11.1, 3.4 Hz, 1H), 2.53 (tt, J = 10.5, 4.3 Hz, 1H), 1.99-1.89 (m, 2), 1.76-1.66 (m, 1), 1.67-1.57 (m, 1), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 151.6, 73.3, 70.8, 55.8, 46.3, 40.9, 40.8, 28.5, 27.6, 14.3; LRMS (ESI) m/z = 288.3 $[M + H]^+$. See S40 for NMR spectra; note NMR spectrum contains DCM.



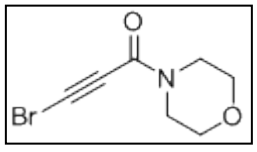
***N,N*-Diethylpropiolamide (si_7).** The general procedure for the synthesis of propiolamides (see **7**, dimethylpropiolamide, page S2) was employed using 7.00 mL diethylamine (5.00 g, 68.0 mmol), 4.40 mL propiolic acid (5.00 g, 71.4 mmol), DCC dissolved in dry DCM (14.8 g, 71.8 mmol) and DMAP (830 mg, 6.8 mmol). The crude material was purified via flash chromatography (SiO_2, 20→40% EtOAc-hexanes; R_f = 0.33 at 30% EtOAc-hexanes) to afford the desired alkyne as a yellow semi-solid that was contaminated with 1,3-dicyclohexylurea (6.6 g, 78%): IR (neat) υ_{max} 3200, 2973, 2933, 2856, 2102, 1681, 1624, 1572, 1430, 1381, 1364, 1274, 1219, 1150, 1081, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.38 (q, J = 7.1 Hz, 2H), 3.18 (q, J = 7.1 Hz, 2H), 3.05 (s, 1H), 1.00 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 77.8, 75.7, 43.1, 38.8, 13.9, 12.3; LRMS (ESI) m/z = 126.3 $[M + H]^+$. See S41 for NMR spectra.



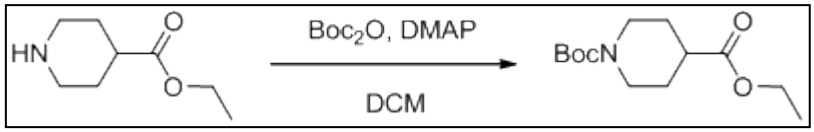
3-Bromo-*N,N*-diethylpropiolamide (si_8). The general procedure for the synthesis of bromo-alkynes (see **1**, 3-bromo-dimethylpropiolamide, page S3) was employed using *N,N*-diethylpropiolamide (925 mg, 7.4 mmol), $AgNO_3$ (121 mg, 0.74 mmol) and NBS (1.45 g, 8.14 mmol). The crude material was purified via flash chromatography (SiO_2, 30% EtOAc-hexanes; R_f = 0.36 at 40% EtOAc-hexanes) to afford the desired compound, **si_8**, as a colorless crystalline solid (1.61 g, 77%): mp 40-43 °C; IR (neat) υ_{max} 2973, 2935, 2196, 1617, 1475, 1454, 1427, 1361, 1280, 1218, 1157, 1089, 956, 796, 726, 633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.47 (q, J = 7.2 Hz, 2H), 3.31 (q, J = 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 73.8, 54.0, 43.3, 39.3, 14.3, 12.6; LRMS (ESI) m/z = 204.2 $[M + H]^+$. See S42 for NMR spectra.



1-Morpholinoprop-2-yn-1-one (si_9). The general procedure for the synthesis of propiolamides (see **7**, dimethylpropiolamide, page S2) was employed using 3.00 mL morpholine (3.00 g, 34.4 mmol), 2.23 mL propiolic acid (2.53 g, 36.1 mmol), DCC dissolved in dry DCM (7.44 g, 36.1 mmol) and DMAP (420 mg, 3.44 mmol). The crude material was purified via flash chromatography (SiO_2, 20→40% EtOAc-hexanes; R_f = 0.25 at 40% EtOAc-hexanes) to afford the desired alkyne, **si_9**, as a white powder (3.59 g, 75%): mp 72-74 °C; IR (neat) υ_{max} 3175, 2980, 2927, 2867, 2102, 1612, 1440, 1430, 1359, 1272, 1111, 1038, 959, 844, 771, 745, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76-3.73 (m, 2H), 3.69-3.67 (m, 2H), 3.65-3.59 (m, 4H), 3.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 79.9, 75.1, 66.8, 66.4, 47.3, 41.9; LRMS (ESI) m/z = 140.3 $[M + H]^+$. See S43 for NMR spectra.

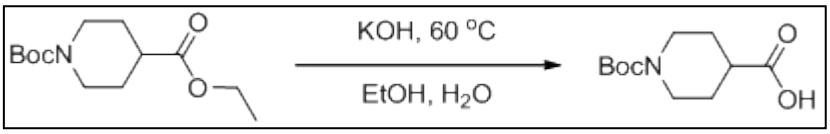


3-Bromo-1-morpholinoprop-2-yn-1-one (si_10). The general procedure for the synthesis of bromoalkynes (see **1**, 3-bromo-dimethylpropiolamide, page S3) was employed using 1-morpholinoprop-2-yn-1-one (**si_9**; 760 mg, 5.50 mmol), $AgNO_3$ (89 mg, 0.55 mmol) and NBS (1.08 g, 6.05 mmol). The crude material was purified via flash chromatography (SiO_2, 40% EtOAc-hexanes; R_f = 0.3 at 40% EtOAc-hexanes) to afford the desired compound as a white crystalline solid (1.02 g, 85%): mp 73-75 °C; IR (neat) υ_{max} 2968, 2929, 2861, 2196, 1615, 1428, 1273, 1242, 1222, 1109, 1069, 1055, 978, 850, 721, 655, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.67-3.61 (m, 4H), 3.59-3.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 72.8, 66.7, 66.2, 56.4, 47.0, 41.9; LRMS (ESI) m/z = 218.1 $[M + H]^+$. See S44 for NMR spectra.

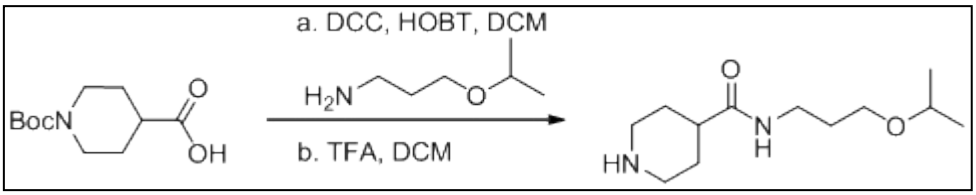


1-*tert*-Butyl 4-ethyl piperidine-1,4-dicarboxylate (si_11). Boc anhydride (16.7 g, 76.0 mmol) and a stirring bar was placed in a 250 mL round bottom flask, dissolved in 150 mL of dry DCM and cooled to 0 °C. 4-Dimethylaminopyridine (DMAP; 233 mg, 1.91 mmol) was added to

the reaction vessel followed by the dropwise addition of piperidine (9.8 mL, 10.0 g, 63.7 mmol). The orange reaction mixture was stirred for several hours before being diluted with water and extracted with DCM (2x). The organic layer was washed with water, dried over Na_2SO_4 and concentrated to deliver a crude orange oil which was subsequently purified via flash chromatography (SiO_2, 40% EtOAc-hexanes; R_f = 0.3 at 40% EtOAc-hexanes) to afford the desired ester as a colorless oil (12.6 g, 77%): IR (neat) υ_{max} 2973, 1731, 1691, 1422, 1366, 1313, 1240, 1158, 1123, 1041, 944, 868, 768, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.04 (q, J = 7.1 Hz, 2H), 3.91 (app br d, J = 9.3 Hz, 2H), 2.74 (app t, J = 11.8 Hz, 2H), 2.34 (tt, J = 11.0, 3.9 Hz, 1H), 1.79-1.75 (m, 2H), 1.57-1.47 (m, 2H), 1.36 (s, 9H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 154.6, 79.4, 60.4, 43.0 (br), 41.1, 28.4, 27.9, 14.1; LRMS (ESI) m/z = 280.3 $[M + Na]^+$. See S45 for NMR spectra.



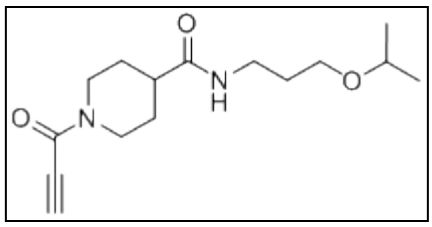
1-(*tert*-Butoxycarbonyl)-piperidine-4-carboxylic acid (si_12). 1-*tert*-butyl 4-ethyl piperidine-1,4-dicarboxylate (**si_11**; 10.0g, 38.9 mmol) was dissolved in 15 mL ethanol and 200 mL water. The resulting solution was warmed to 60 °C and treated with crushed potassium hydroxide (32.7 g, 584 mmol). The reaction mixture was stirred for 4 hours, cooled to room temperature and acidified to pH ~1-2 with the addition of 1N HCl. A white precipitate formed and was subsequently filtered and dried under reduced pressure to deliver the desired acid as a white powder (6.53, 74%): mp 149-152 °C; IR (neat) υ_{max} 3193, 2972, 2930, 1732, 1656, 1470, 1450, 1430, 1391, 1366, 1280, 1240, 1206, 1154, 1130, 1080, 1032, 923, 860, 816, 765, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.86 (br s, 1H), 3.99 (app br d, J = 9.6 Hz, 2H), 2.83 (app t, J = 11.6 Hz, 2H), 2.45 (tt, J = 10.9, 3.8 Hz, 1H), 1.89-1.86 (m, 2H), 1.66-1.56 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 154.9, 80.0, 43.2 (br), 40.9, 28.5, 27.8; LRMS (ESI) m/z = 252.3 $[M + Na]^+$. See S46 for NMR spectra.



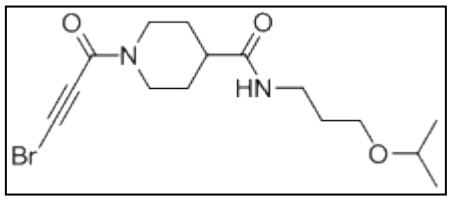
***N*-(3-Isopropoxypropyl)-piperidine-4-carboxamide (si_13).** A 100 mL round bottom flask equipped with a stirring bar and rubber septum was charged with 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (2.00 g, 8.73 mmol) and placed under argon. 65 mL dry DCM was added followed by the addition of hydroxybenzotriazole (HOBT; 1.30 g, 9.60 mmol) and *N,N'*-dicyclohexylcarbodiimide (DCC; 1.99 g, 9.60 mmol) in that order by partial removal of the septum. The resulting slurry was stirred at room temperature for 30 min. 1.82 mL 3-isopropoxypropan-1-amine (1.53 g, 13.1 mmol) was then added dropwise and the reaction mixture was stirred overnight. The resulting heterogeneous solution was then filtered over a büchner funnel and the filtrate was placed on silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 60→80% EtOAc-hexanes) to afford *tert*-butyl 4-(3-isopropoxypropyl-carbamoyl)piperidine-1-carboxylate as a crude oil.

Tert-butyl 4-(3-isopropoxypropylcarbamoyl)piperidine-1-carboxylate (~2.86, 8.73 mmol) was dissolved in 100 DCM and treated with trifluoroacetic acid (TFA, 6.53 mL, 9.95 g, 80.7). the reaction mixture was stirred overnight, concentrated by rotary evaporation and made alkaline with saturated Na_2CO_3. (Note 1) The aqueous solution was then concentrated via rotary evaporation to deliver a white solid, which was subsequently stirred with DCM for 1 hour and filtered. The DCM filtrate was dried with Na_2SO_4 and concentrated to deliver a clear oil, **si_13**, that slowly solidified (1.32 g, 66% over two steps): IR (neat) υ_{max} 3288, 2973, 2938, 2866, 1642, 1534, 1470, 1428, 1368, 1334, 1284, 1230, 1147, 1129, 1080, 941, 813, 683, 645, 619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (app br s, 1H), 3.50 (sept, J = 6.1 Hz, 1H), 3.46 (t, J = 5.6 Hz, 2H), 3.29 (app dd, J = 6.9, 5.4 Hz, 2H), 3.08 (app dt, J = 12.4, 3.4 Hz, 2H), 2.64-2.54 (m, 3H), 2.14 (tt, J = 11.7, 3.9 Hz, 1H), 1.80-1.76 (m, 2H), 1.68 (p, J = 5.8 Hz, 2H) 1.58-1.48 (m, 2H), 1.10 (d, J = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 71.8, 67.6, 45.9, 43.5, 38.6, 29.7, 29.2, 22.2; LRMS (ESI) m/z = 229.5 $[M + H]^+$. See S47 for NMR spectra; note NMR spectrum contains DCM.

Note 1. The aqueous solution was extracted by both EtOAc and DCM, however both extractions yielded very little organic material upon concentration.

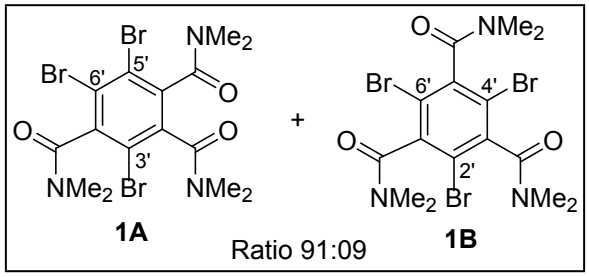


***N*-(3-Isopropoxypropyl)-1-propioloylpiperidine-4-carboxamide (si_14).** The general procedure for the synthesis of propiolamides (see **7**, dimethylpropiolamide, page S2) was employed using *N*-(3-isopropoxypropyl)piperidine-4-carboxamide (1.20 g, 5.25 mmol), 0.356 mL propiolic acid (404 mg, 5.77 mmol), DCC dissolved in dry DCM (1.19 g, 5.77 mmol) and DMAP (64 mg, 0.525 mmol). The crude material was purified via flash chromatography (SiO_2, 90→100% EtOAc-hexanes; R_f = 0.15 at 90% EtOAc-hexanes) to afford the desired alkyne as a beige solid (1.22 g, 83%): mp 76-78 ^oC; IR (neat) υ_{max} 3257, 3200, 2972, 2945, 2929, 2863, 2106, 1654, 1628, 1608, 1561, 1449, 1366, 1333, 1282, 1209, 1144, 1095, 1013, 984, 939, 765, 727, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (br t, J = 4.5 Hz, 1H), 4.46 (dt, J = 13.4, 3.0 Hz, 1H), 4.28 (dt, J = 13.4, 3.0 Hz, 1H), 3.45 (sept, J = 6.1 Hz, 1H), 3.40 (t, J = 5.8 Hz, 2H), 3.23 (app q, J = 6.0 Hz, 2H), 3.16 (s, 1H), 3.10 (app ddd, J = 16.3, 11.9, 3.0 Hz, 1H), 2.73-2.66 (m, 1H), 2.14 (tt, J = 11.2, 3.8 Hz, 1H), 1.84-1.75 (m, 2H), 1.60 (p, J = 6.3 Hz, 2H) 1.60-1.46 (m, 2H), 1.04 (d, J = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 151.6, 79.5, 75.2, 71.6, 67.1, 46.5, 42.6, 40.7, 38.3, 29.2, 28.9, 28.1, 22.0; LRMS (ESI) m/z = 281.3 $[M + H]^+$. See S48 for NMR spectra.



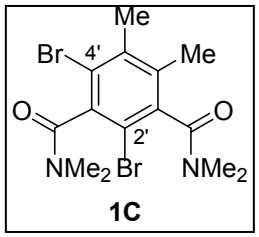
1-(3-Bromopropioloyl)-*N*-(3-isopropoxypropyl)piperidine-4-carboxamide (si_15). The general procedure for the synthesis of bromoalkynes (see **1**, 3-bromo-dimethylpropiolamide, page S3) was employed using *N*-(3-isopropoxypropyl)-1-propioloylpiperidine-4-carboxamide (961 mg, 3.40 mmol), $AgNO_3$ (55 mg, 0.34 mmol) and NBS (666 mg, 3.74 mmol). The crude material was purified via flash chromatography (SiO_2, 4% MeOH-DCM; R_f = 0.15 at 4% MeOH-DCM) to afford the desired compound as a white powder that was still contaminated by *n*-hydrosuccinimide. The solids were redissolved in EtOAc, washed5with 1M NaOH (2x) and brine (1x), dried with Na_2SO_4 and concentrated to deliver a white powder (1.02 g, 85%): mp 113-115 ^oC; IR (neat) υ_{max} 3277, 3093, 2946, 2870, 2184, 1663, 1632, 1614, 1561, 1462, 1438, 1371, 1343, 1279, 1217, 1150, 1125, 1077, 1041, 953, 723, 668, 642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.56 (br s, 1H), 4.41 (dt, J = 13.4, 3.0 Hz, 1H), 4.28 (dt, J = 13.4, 3.0 Hz, 1H), 3.52 (sept, J = 6.1 Hz, 1H), 3.48 (t, J = 5.8 Hz, 2H), 3.31 (app q, J = 6.0 Hz, 2H), 3.18-3.11 (m, 1H), 2.79-2.72 (m, 1H), 2.28 (tt, J = 11.2, 3.8 Hz, 1H), 1.91-1.81 (m, 2H), 1.70 (p, J = 6.3 Hz, 2H) 1.65-1.51 (m, 2H), 1.11 (d, J = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 151.5, 73.3, 71.9, 67.7, 55.8, 46.5, 42.9, 41.0, 38.9, 29.2, 29.1, 28.2, 22.2; LRMS (ESI) m/z = 359.3 $[M + H]^+$. See S49 for NMR spectra.

Cyclo(co)trimerization Product Characterization

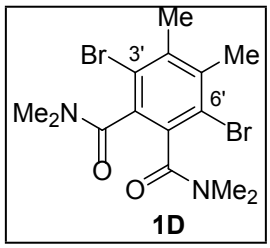


3,5,6-Tribromo-hexamethylbenzene-1,2,4-tricarboxamide (1A). A 15 mL round bottom flask was charged with 3-bromo-dimethylpropiolamide, [**1**] (88 mg, 0.5 mmol) and 3 mL DCE. 1.5 mol% CpRuCl(cod) was added as 0.5 mol% (CpRuCl(cod); 0.8 mg, 0.0025 mmol) additions of catalyst every 2 h to complete the reaction. The crude reaction mixture was concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 4% MeOH-DCM; R_f = 0.14 at 4% MeOH-DCM) to afford **1A/B** as a beige solid (81 mg, 92%) favoring the 3,5,6-tribromo isomer in 91:09 ratio (Note 1) (Note 2): IR (neat) υ_{max} 2926, 1657, 1649, 1640, 1632, 1613, 1402, 1336, 1263, 1189, 1148, 1074, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.13 (s, 1H), 3.01 (s, 1H), 3.00 (s, 1H), 2.86 (s, 1H), 2.84 (s, 1H), 2.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.9, 165.4, 141.3, 138.8, 136.8, 123.8, 123.0, 116.3, 38.2, 37.9, 37.3, 34.7, 34.6, 34.6; LRMS (ESI) m/z = 292.3 $[M + H]^+$. See S50 for NMR spectra.

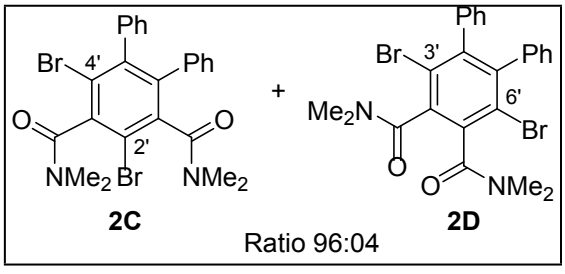
Note 1: The regioisomeric ratio of **1A**:**B** (91:09) was determined by NMR and GC/MS analysis.



2,4-Dibromo-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-5,6-hexamethylisophthalamide (1C). 3-bromo-dimethylpropiolamide (**1**; 264 mg, 1.50 mmol) and 2-butyne (88 µL, 61 mg, 1.13 mmol) were dissolved in 15 mL EtOH and 3 mol% CpRuCl(cod) was added as 2 mol% (CpRuCl(cod); 4.6 mg, 0.015 mmol) additions of catalyst every 2 h to complete the reaction as determined by thin layer chromatography. The crude reaction mixture was concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 50→90% EtOAc-Hexanes; R_f = 0.12 at 80% EtOAc-hexanes) to afford **1C** as a white solid (256 mg, 84 %): mp 175-178 ^oC; IR (neat) υ_{max} 1644, 1501, 1408, 1384, 1259, 1145, 1128, 1051, 675, 662, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.00 (s, 6H), 2.72 (s, 3H), 2.69 (s, 3H) 2.25 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 167.1, 137.9, 137.6, 137.5, 135.7, 122.4, 113.3, 37.3, 37.1, 34.2, 34.1, 19.8, 18.3; LRMS (ESI) m/z = 407.1 $[M + H]^+$. See S51 for NMR spectra.

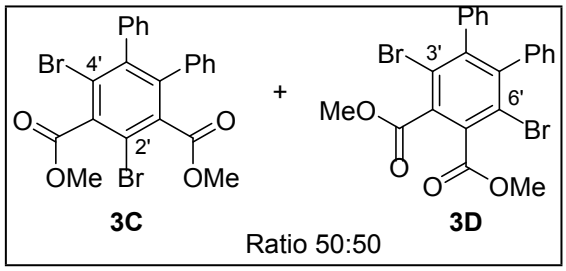


3,6-Dibromo-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-4,5-hexamethylisophthalamide (1D). A 50 mL round bottom flask was charged with 3-bromo-dimethylpropiolamide (**1**; 352 mg, 2.00 mmol) and 2-butyne (156 µL, 108 mg, 2.00 mmol) were dissolved in 20 mL 1,2-dichloroethane (DCE gives an 82:18 mixture of regio-isomers, as opposed to EtOH, which gives a 96:04 ratio of isomers) followed by the addition of 4.0 mol% CpRuCl(cod) (12.3 mg, 0.04 mmol). The reaction was allowed to stir at room temperature overnight before being placed on silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 60→80% EtOAc-hexanes) to afford pure minor isomer **1D** as a white crystalline solid (45 mg, 11%, re-running this reaction and collecting both isomers, **1C/D**, in 87% combined yield): mp 170-173 ^oC; IR (neat) υ_{max} 2925, 1635, 1494, 1398, 1380, 1263, 1198, 1130, 1057, 1034, 1004, 797, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 6H), 2.86 (s, 6H), 2.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 138.7, 135.1, 121.7, 38.2, 34.6, 21.5; LRMS (ESI) m/z = 407.1 $[M + H]^+$. See S52 for NMR spectra.

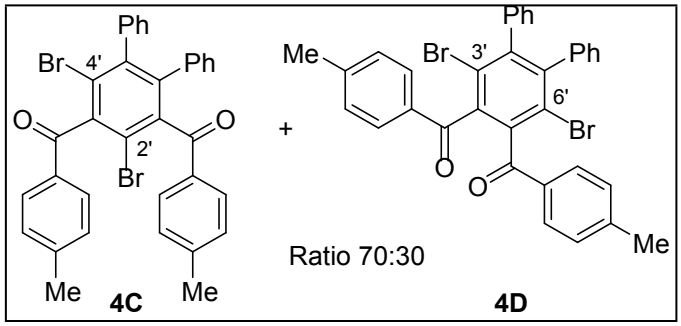


2,4-Dibromo-5,6-diphenyl-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylisophthalamide (2C/D). A 250 mL round bottom flask was charged with 3-bromo-dimethylpropiolamide (**1**, 1.76 g, 10.0 mmol) and diphenylacetylene (1.34 g, 7.50 mmol). 100 mL EtOH was added followed by addition of 1 mol% chloro(1,5-cyclooctadiene)cyclopentadienyl)-ruthenium(II) (CpRuCl(cod); 15.0 mg, 0.05 mmol). The reaction was allowed to stir at room, during which time a portion of the desired product (**2C/D**) precipitated out of solution as a white powder. The reaction was confirmed complete by thin layer chromatography

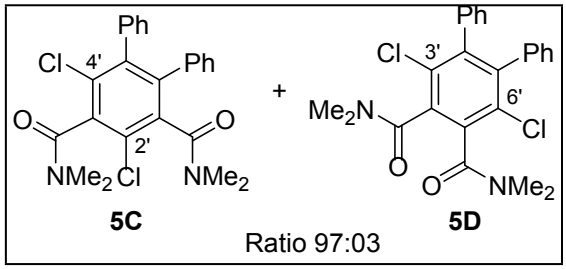
after several hours. The crude reaction mixture was filtered to deliver (1.43 g) of pure **2C/D** as a white powder. The filtrate was then placed on silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 80% EtOAc-hexanes; R_f = 0.20 at 80% EtOAc-hexanes) to afford the remaining **2C/D** as a beige solid (744mg + 1.43 g, 82%). The samples isolated by filtration and column were combined and characterized: mp 284-287 °C; IR (neat) υ_{max} 1639, 1555, 1531, 1404, 1157, 1076, 761, 717, 703, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.20 (m, 2H), 7.16-7.12 (m, 3H), 7.09-7.05 (m, 2H), 7.00-6.97 (m, 1H), 6.80-6.78 (m, 1H), 6.76-6.75 (m, 1H), 3.17 (s, 3H), 3.07 (s, 3H), 2.71 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.8, 143.0, 141.3, 139.7, 138.7, 138.6, 136.8, 130.5, 130.3, 130.0, 128.7, 128.1, 127.9, 127.6, 127.5, 127.4, 127.0, 121.8, 116.1, 37.7, 37.5, 34.6, 34.1; LRMS (ESI) m/z = 531.1 $[M + H]^+$. See S53 for NMR spectra.



Dimethyl 2,4-dibromo-5,6-diphenylisophthalate and **Dimethyl 3,6-dibromo-4,5-diphenylisophthalate (3C/D)**. A 50 mL round bottom flask was charged with methyl 3-bromopropiolate (**7** see page S4, 285 mg, 1.75 mmol) and diphenylacetylene (250 mg, 1.40 mmol). 17 mL EtOH was added followed by addition of 2.0 mol% chloro(1,5-cyclooctadiene)cyclopentadienyl-ruthenium(II) (CpRuCl(cod); 5.4 mg, 0.018 mmol) and allowed to stir at room temperature overnight. The reaction was confirmed complete by thin layer chromatography and the crude mixture was then placed on silica gel via rotary evaporation and subsequently subjected to flash chromatography (SiO_2, 5→20% EtOAc-hexanes; R_f = 0.12 at 5% EtOAc-hexanes) to afford **3C/D** as a beige solid (388 mg, 88%): IR (neat) υ_{max}1731, 1630, 1441, 1258, 1215, 1179, 1074, 993, 886, 756, 700, 655, 604 cm^{-1}; (major/minor isomer) ^1H NMR (400 MHz, $CDCl_3$) δ 7.19-6.15 (m, 8H), 7.12-7.10 (m, 4), 6.98-6.93 (m, 8H), 4.02 (s, 3H), 3.96 (s, 4.6H), 3.52 (s, 3H); (major/minor isomer) ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 166.5, 166.2, 146.3, 142.8, 142.5, 139.4, 138.3, 138.1, 136.9, 136.7, 134.9, 129.9, 129.5, 129.5, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 122.5, 121.2, 115.2, 53.4, 53.4, 52.6; LRMS (ESI) m/z = 505.0 $[M + H]^+$. See S54 for NMR spectra.

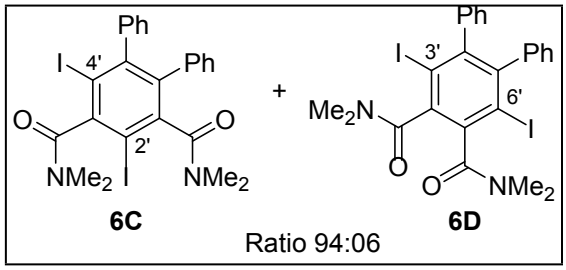


(2,4-Dibromo-5,6-diphenyl-1,3-phenylene)bis(p-tolylmethanone) (4C/D). A 50 mL round bottom flask was charged with 3-bromo-1-p-tolylprop-2-yn-1-one (**4** see page S5, 268 mg, 1.2 mmol) and diphenylacetylene (161 mg, 0.90 mmol). 12 mL EtOH was added followed by addition of 2 mol% chloro(1,5-cyclooctadiene)cyclopentadienyl)ruthenium(II) (CpRuCl(cod); 3.7 mg, 0.012 mmol) and the reaction was allowed to stir at room temperature overnight. The crude reaction mixture was then placed on silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 5→20% EtOAc-hexanes; R_f = 0.05 at 5% EtOAc-hexanes) to afford **4C/D** as a tan solid (368 mg, 96%): IR (neat) υ_{max} 1665, 1062, 1442, 1312, 1258, 1221, 1175, 1028, 1010, 934, 828, 752, 701, 604 cm^{-1}; (major/minor isomer) ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.9 Hz, 1.7H), 7.69 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.1 Hz, 1.7H), 7.23 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 3H), 7.09-7.01 (m, 9H), 6.97- 6.95 (m, 3H), 6.84-6.78 (m, 2H), 6.61 (t, J = 7.1 Hz, 1H), 6.48 (d, J = 7.3 Hz, 0.7H), 2.34 (s, 3H), 2.29 (s, 3H), 2.23 (s, 3H); (major/minor isomer) ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 193.8, 193.6, 145.8, 145.3, 145.1, 145.1, 143.1, 142.4, 141.9, 141.2, 140.6, 139.2, 138.2, 136.4, 133.5, 132.2, 130.9, 130.5, 130.1, 130.4, 130.3, 130.0, 129.9, 129.8, 129.6, 129.4, 127.9, 127.8, 127.7, 127.6, 127.6, 127.6, 127.5, 127.2, 122.1, 120.7, 115.1, 22.1, 22.0, 21.9; LRMS (ESI) m/z = 625.2 $[M + H]^+$. See S55 for NMR spectra.

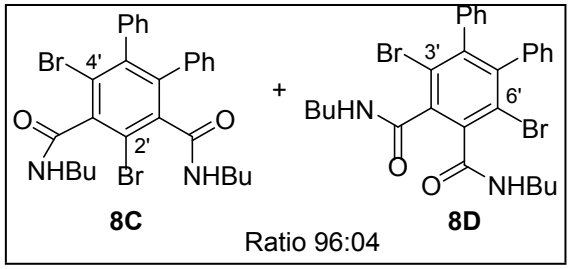


2,4-Dichloro-5,6-diphenyl-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylisophthalamide (5C/D). A 100 mL round bottom flask was charged with 3-chloro-dimethylpropiolamide [**5**] (393 mg, 3.0 mmol) and diphenylacetylene (401 mg, 2.25 mmol). 30 mL EtOH was added followed by addition of 2 mol% chloro(1,5-cyclooctadiene)cyclopentadienyl)-ruthenium(II) (CpRuCl(cod); 9.3 mg, 0.03 mmol) and the reaction was allowed to stir at room temperature overnight. The reaction was confirmed complete by

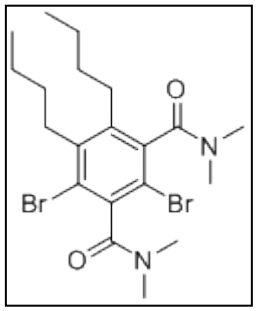
thin layer chromatography and was then placed on silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 4% MeOH-DCM; R_f = 0.33 at 4% MeOH-DCM) to afford **5C/D** as a beige solid (449 mg, 69%): mp 263-265 °C; IR (neat) υ_{max} 1648, 1638, 1502, 1400, 1368, 1262, 1152, 1086, 1064, 759, 726, 699, 608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (m, 2H), 7.21-7.18 (m, 2H), 7.16-7.14 (m, 1H), 7.13-7.08 (m, 2H), 7.03 (app br s, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.79 (app br s, 1H), 3.21 (s, 3H), 3.04 (s, 3H), 2.75 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.2, 141.4, 140.4, 136.4, 136.4, 135.8, 135.5, 131.2, 130.4, 130.4, 130.2, 128.7, 128.1, 127.9, 127.7, 127.5, 127.4, 127.1, 126.8, 37.6, 37.5, 34.6, 34.1; LRMS (ESI) m/z = 441.2 $[M + H]^+$. See S56 for NMR spectra.



2,4-Diiodo-5,6-diphenyl-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylisophthalamide (6C/D). A 100 mL round bottom flask was charged with 3-iodo-dimethylpropiolamide (**6**; 892 mg, 4.0 mmol) and diphenylacetylene (534 mg, 3.00 mmol). 40 mL EtOH was added followed by addition of 1.0 mol% chloro(1,5-cyclooctadiene)cyclopentadienyl)-ruthenium(II) (CpRuCl(cod); 15.0 mg, 0.05 mmol) and the reaction was allowed to stir at room temperature overnight. During the course of the reaction, the desired product (**6C/D**) precipitated out of solution as a white powder and was subsequently filtered to deliver (432 g) of pure **6C/D** as a white powder. The filtrate was then placed on silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 80→100% EtOAc-hexanes; R_f = 0.25 at 80% EtOAc-hexanes) to afford the remaining **6C/D** as a beige solid (432 mg + 609 mg, 84%). The samples isolated by filtration and column were combined and characterized: mp 254-256 °C; IR (neat) υ_{max} 2980, 1639, 1623, 1518, 1496, 1400, 1377, 1344, 1263, 1153, 1075, 767, 737, 715, 698, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22-7.17 (m, 2H), 7.14-7.07 (m, 3H), 7.07-7.01 (m, 2H), 6.98-6.94 (m, 1H), 6.76-6.72 (m, 2H), 3.16 (s, 3H), 2.99 (s, 3H), 2.71 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 168.6, 147.8, 147.8, 143.7, 142.6, 139.3, 137.4, 130.3, 130.2, 129.6, 128.6, 128.0, 127.7, 127.5, 127.5, 127.3, 126.8, 99.0, 90.0, 37.8, 37.8, 34.7, 34.1; LRMS (ESI) m/z = 525.1 $[M + H]^+$. See S57 for NMR spectra.

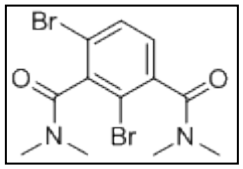


2,4-Dibromo-*N*^{1},*N*^{3}-dibutyl-5,6-diphenylisophthalamide (8C/D). 3-Bromo-butylpropiolamide (**8**; 102mg, 0.5 mmol) and diphenylyacetylene (68 mg, 0.4 mmol) were dissolved in 5 mL EtOH. CpRuCl(cod) (15 mg, 0.05 mmol) was added to the solution and the reaction mixture was stirred overnight. The dark brown reaction mixture was concentrated onto silica gel and subjected to flash chromatography (SiO_2, 30→40% EtOAc-hexanes; R_f = 0.15 at 20% EtOAc-hexanes) to yield a brown solid that was then resubjected to chromatography (SiO_2, 5→30% EtOAc-hexanes) to finally deliver **8C/D** as a beige solid (73 mg, 49%): mp 234-236 °C; IR (neat) υ_{max} 3230, 2956, 1639, 1561, 1442, 1360, 1287, 1225, 1148, 753, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14-6.79 (m, 10H), 6.16 (t, J = 5.5 Hz, 1H), 6.10 (t, J = 5.0 Hz, 1H), 3.47 (q, J = 6.8 Hz, 2H), 3.07 (app br s, 1H), 2.99 (app br s, 1H), 1.67-1.57 (m, 2H), 1.49-1.40 (m, 2H), 1.05-0.98 (m, 4H), 0.94 (t, J = 7.4 Hz, 3H), 0.72 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 166.6, 142.9, 142.0, 140.4, 139.6, 139.0, 137.3, 129.9, 127.8, 127.6, 127.5, 122.5, 116.6, 39.9, 39.4, 31.2, 31.0, 20.3, 19.9, 13.8, 13.8; LRMS (ESI) m/z = 587.2 $[M + H]^+$. See S58 for NMR spectra.

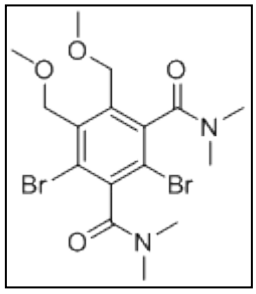


2,4-Dibromo-5,6-dibutyl-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylisophthalamide (11C). 3-bromo-dimethylpropiolamide (**1**, 528 mg, 3.00 mmol) and 5-decyne (400 µL, 310 mg, 2.25 mmol) were dissolved in 30 mL EtOH and treated with a total of 4 mol% CpRuCl(cod). The catalyst was added as 2 mol% (CpRuCl(cod); 9.3 mg, 0.03 mmol) additions every 2 h to complete the reaction as determined by thin layer chromatography. The crude reaction mixture was concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 50→80% EtOAc-Hexanes; R_f = 0.25 at 60% EtOAc-hexanes) to afford **11C** as a tan solid (478 mg, 65%): mp 100-103 °C; IR (neat) υ_{max} 2925, 2929, 1633, 1546, 1495, 1460, 1396, 1364, 1263, 1145, 1130, 1091, 672 cm^{-1}; ^1H NMR (400 MHz,

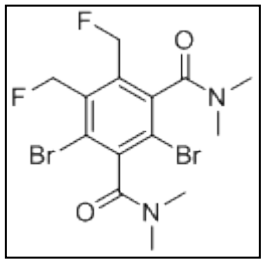
$CDCl_3$) δ 2.96 (s, 3H), 2.94 (s, 3H), 2.68 (s, 3H), 2.63 (s, 3H), 2.61-2.57 (m, 2H), 2.55-2.51 (m, 2H), 2.30-2.22 (m, 1H), 1.52-1.48 (m, 1H), 1.37-1.28 (m, 4H), 1.27-1.19 (m, 3H), 0.80 (t, J = 6.9 Hz, 3H), 0.76 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.1, 141.4, 140.3, 137.9, 137.8, 122.3, 113.8, 37.5, 37.0, 34.1, 34.0, 32.5, 32.2, 31.4, 31.2, 22.9, 22.7, 13.5, 13.4; LRMS (ESI) m/z = 491.1 $[M + H]^+$. See S59 for NMR spectra.



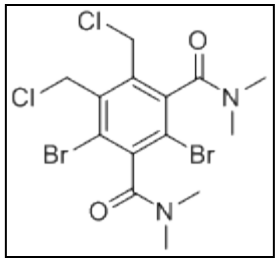
2,4-Dibromo-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylisophthalamide (12C). 3-Bromo-dimethyl propiolamide (**1a**; 176 mg, 1.0 mmol) was dissolved in 9 mL EtOH in a 25 mL round bottom flask equipped with a rubber septum. Acetylene gas was then bubbled through the solution via a syringe connected to a balloon and a syringe outlet. After several minutes, CpRuCl(cod) (3.0 mg, 0.1 mmol), dissolved in 0.5 mL EtOH, was added to the reaction mixture and the syringe outlet was removed. Additional CpRuCl(cod) was added every 1.5 hr as necessary to completely consume **1a**. Once 10 mol% catalyst had been added the reaction was deemed complete by TLC analysis and was subsequently concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 80% EtOAc-Hexanes; R_f = 0.08 at 80% EtOAc-hexanes) to afford **12C** as a brown solid (116 mg, 61%): mp 173-176 (decomp) ^{o}C; IR (neat) υ_{max} 1638, 1626, 1577, 1509, 1435, 1396, 1366, 1265, 1157, 1126, 1058, 862, 769, 754, 731, 686, 652 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 3.11 (s, 3H), 3.08 (s, 3H), 2.83 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 166.7, 140.4, 138.8, 132.3, 128.4, 120.2, 116.9, 38.3, 37.5, 34.8, 34.6; LRMS (ESI) m/z = 379.2 $[M + H]^+$. See S60 for NMR spectra.



2,4-Dibromo-5,6-bis(methoxymethyl)-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylisophthalamide (13C). 3-Bromo-dimethylpropiolamide (**1a**; 440 mg, 2.50 mmol) and 1,4-dimethoxybut-2-yne (214 mg, 1.88 mmol) were dissolved in 25 mL EtOH and 4 mol% CpRuCl(cod) was added as 2 mol% (CpRuCl(cod); 7.7 mg, 0.025 mmol) additions of catalyst every 2 h to complete the reaction as determined by thin layer chromatography. The crude reaction mixture was concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 60→100% EtOAc-Hexanes; R_f = 0.05 at 80% EtOAc-hexanes) to afford **13C** as a brown sticky semi-solid (425 mg, 73%): IR (neat) υ_{max} 2930, 2816, 1638, 1547, 1498, 1458, 1401, 1360, 1263, 1190, 1143, 1126, 1091, 950, 673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (app d, J = 1.6 Hz, 2H), 4.56 (d, J = 11.0 Hz, 1H), 4.46 (d, J = 11.0 Hz, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 3.15 (s, 3H), 3.14 (s, 3H), 2.84 (s, 3H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.7, 140.3, 139.5, 137.3, 137.3, 123.8, 116.8, 69.9, 69.2, 59.0, 58.4, 37.8, 37.1, 34.3, 34.3; LRMS (ESI) m/z = 467.1 $[M + H]^+$. See S61 for NMR spectra.

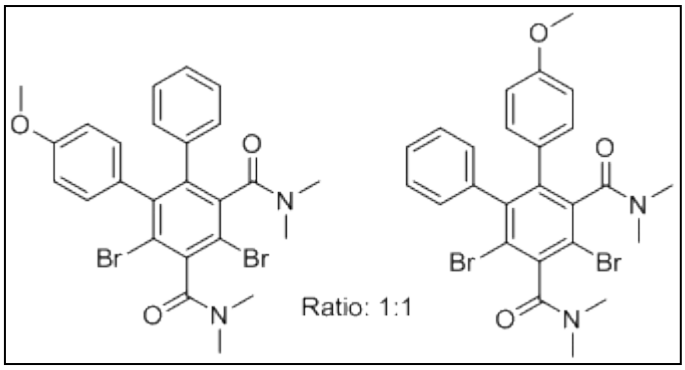


2,4-Dibromo-5,6-bis(fluoromethyl)-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethyl-isophthalamide (14C). 3-bromo-dimethylpropiolamide (**1a**; 176 mg, 1.00 mmol) and 1,4-difluorobut-2-yne[2] (90 mg, 1.00 mmol; ~80% pure by NMR) were dissolved in 5 mL EtOH and treated with 4 mol% CpRuCl(cod). The catalyst was added as 2 mol% (CpRuCl(cod); 3.1 mg, 0.03 mmol) additions of catalyst every 2 h to complete the reaction. The crude reaction mixture was concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 80% EtOAc-Hexanes; R_f = 0.12 at 80% EtOAc-hexanes) to afford **14C** as a beige solid (162 mg, 69 %): mp 152-155 ^{o}C; IR (neat) υ_{max} 2924, 1638, 1548, 1498, 1402, 1362, 1260, 1147, 1126, 1044, 1005, 983, 862, 699, 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (s, 1H), 5.60 (d, J = 12.1 Hz, 0.5H), 5.59 (s, 1H), 5.48 (d, J = 12.2 Hz, 0.5H), 5.42 (d, J = 11.3 Hz, 0.5H), 5.30 (d, J = 11.3 Hz, 0.5H), 3.12 (s, 3H), 3.11 (s, 3H), 2.83 (s, 3H), 2.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.2, 142.3, 142.3, 142.3, 140.4, 140.4, 140.4, 135.7, 135.7, 134.9, 134.8, 134.7, 134.7, 124.1, 124.0, 124.0, 124.0, 118.8, 118.8, 118.7, 118.7, 80.9, 80.2, 80.2, 79.2, 78.5, 78.5, 37.9, 37.2, 34.6, 34.5; F^{19} NMR (400 MHz, CDCl3) δ -205.1, -205.1, -208.7, -208.7; LRMS (ESI) m/z = 443.1 $[M + H]^+$. See S62 for NMR spectra.

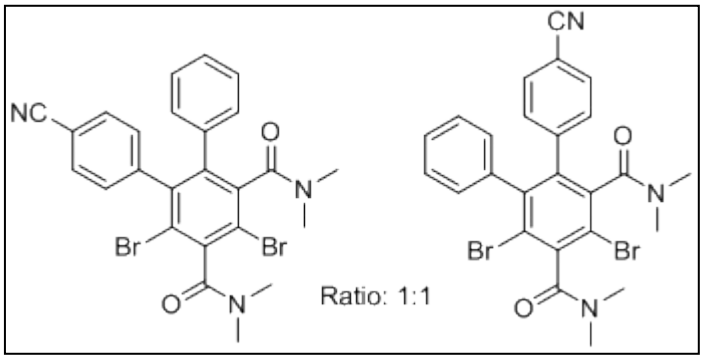


2,4-Dibromo-5,6-bis(chloromethyl)-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethyl-isophthalamide (15C). 3-bromo-dimethylpropiolamide (**1a**; 352 mg, 2.00 mmol) and 1,4-dichlorobut-2-yne (195 µL, 246 mg, 2.00 mmol) were dissolved in 20 mL EtOH and 5 mol% CpRuCl(cod) was added as 2 mol% (CpRuCl(cod); 6.2 mg, 0.02 mmol) additions of catalyst every 2h to

complete the reaction as determined by thin layer chromatography. The crude reaction mixture was concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 50→80% EtOAc-Hexanes; R_f = 0.18 at 70% EtOAc-hexanes) to afford **15C** as a yellow solid (295 mg, 62 %): mp 150-152 ^oC; IR (neat) υ_{max} 1633, 1547, 1501, 1443, 1402, 1364, 1260, 1134, 1112, 1057, 937, 854, 723, 709, 671, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (app dd, J = 20.1,12.0 Hz, 2H), 4.73 (d, J = 1.6 Hz, 2H), 3.15 (s, 6H), 2.87 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.2, 141.6, 140.1, 137.4, 136.1, 124.0, 117.9, 41.5, 40.1, 38.2, 37.4, 34.7, 34.6; LRMS (ESI) m/z = 475.1 $[M + H]^+$. See S63 for NMR spectra.

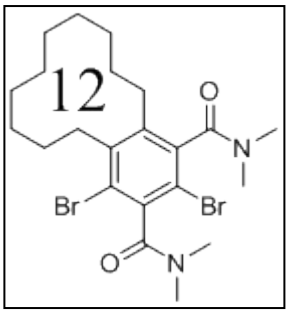


2,4-dibromo-5-(4'-methoxy)phenyl-6-phenyl-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethyl-isophthalamide (16C). 3-Bromo-dimethylpropiolamide (**1a**; 616 mg, 3.50 mmol) and 1-methoxy-4-(phenylethynyl)benzene[4] (546 mg, 2.63 mmol) were dissolved in 35 mL EtOH followed by the addition of 2 mol% CpRuCl(cod) (10.8 mg, 0.035 mmol). After stirring overnight, the crude reaction mixture was filtered to deliver 238 mg of **16C** as a white powder and the filtrate was then concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 50→80% EtOAc-Hexanes; R_f = 0.2 at 80% EtOAc-hexanes) to afford the remaining **16** as a beige solid (587 mg + 238 mg, 84 %) The products isolated by filtration and column were combined and characterized: IR (neat) υ_{max} 2987, 1637, 1609, 1513, 1403, 1395, 1247, 1177, 1147, 1078, 1046, 1021, 840, 702, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.23 (m, 4H), 7.19-7.07 (m, 7H), 6.82-6.80 (m, 3H), 6.74-6.73 (m , 3H), 6.63-6.58 (m, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 3.21 (s, 6H), 3.06 (s, 6H), 2.79 (s, 3H), 2.76 (s, 6H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.8, 166.6, 158.4, 158.4, 142.9, 142.4, 141.2, 140.8, 139.4, 139.2, 138.6, 138.5, 138.3, 136.7, 131.4, 131.2, 130.8, 130.7, 130.6, 130.1, 130.0, 129.5, 128.7, 128.5, 127.8, 127.5, 127.3, 127.2, 127.2, 126.9, 122.1, 121.5, 115.7, 115.5, 113.0, 112.7, 54.8, 54.8, 37.5, 37.4, 37.3, 34.3, 33.8, 33.8; LRMS (ESI) m/z = 561.1 $[M + H]^+$. See S64 for NMR spectra.

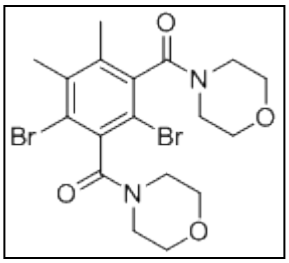


2,4-dibromo-5-(4'-cyano)phenyl-6-phenyl-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethyl-isophthalamide (17C). 3-Bromo-dimethylpropiolamide (**1a**; 50 mg, 0.284 mmol) and 1-cyano-4-(phenylethynyl)benzene[4] (57 mg, 0.284 mmol) were dissolved in 4 mL EtOH followed by the addition of 4 mol% CpRuCl(cod) (1.7 mg, 0.0057 mmol) and the reaction was stirred overnight. The crude reaction mixture was then concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 50→80% EtOAc-Hexanes; R_f = 0.23 at 80% EtOAc-hexanes) to afford the remaining **17C** as a slightly yellow solid (69 mg, 88 %): IR (neat) υ_{max} 1641, 1610, 1532, 1502, 1402, 1386, 1358, 1263, 1149, 1080, 851, 808, 731, 702, 610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 8.0, 1.2 Hz, 0.5H), 7.46 (d, J = 8.0 Hz, 0.5H), 7.37 (app dd, J = 8.1, 1.2 Hz, 1H), 7.30 (app dd, J = 7.9 1.3 Hz, 1H), 7.2-7.15 (m, 2H), 7.11-7.09 (m, 1.5H), 7.01 (app t, J = 7.5 Hz, 0.5H), 6.92 (dd, J = 8.0 1.2 Hz, 0.5H), 6.88 (d, J = 8.0 Hz, 0.5H), 6.76 (d, J = 7.7 Hz, 0.5H), 6.70 (d, J = 7.4 Hz, 0.5H), 3.17 (s, 3H), 3.00 (s, 3H), 2.74 (s, 1.5H), 2.73 (s, 1.5H), 2.70 (s, 3.0H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 166.7, 166.4, 166.3, 143.4, 142.7, 141.7, 141.0, 140.9, 140.6, 140.1, 139.1, 138.9, 138.2, 137.9, 136.0, 131.9, 131.7 (br), 131.6 (br), 131.3, 131.2, 130.9, 130.9 (br), 130.4, 130.0, 129.8, 129.4 (br), 128.4, 128.3 (br), 128.2, 128.1, 127.7, 127.4, 122.2, 120.9, 118.5, 118.3, 117.2,

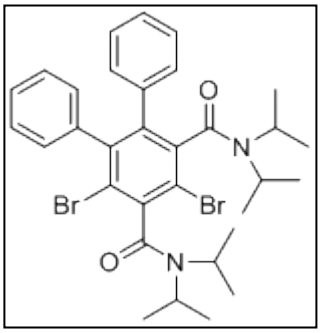
116.3, 111.6, 111.5, 37.6, 37.6, 37.5, 37.5, 34.6, 34.2, 34.1; LRMS (ESI) m/z = 556.1 $[M + H]^+$. See S65 for NMR spectra.



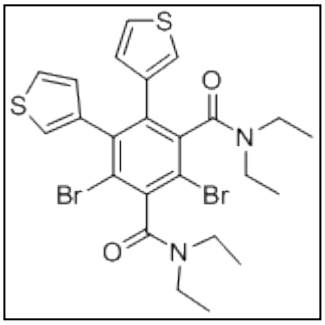
2,4-Dibromo-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethyl-5,6,7,8,9,10,11,12,13,14-decahydrobenzo-[12]annulene-1,3-dicarboxamide (18C). 3-Bromo-dimethylpropiolamide (**1a**; 40 mg, 0.227 mmol) and cyclododecyne[4] (74 mg, 0.45 mmol) [excess internal alkyne was used as GC/MS analysis of the laboratory sample of this alkyne indicated purity to be ~60%] were dissolved in 4 mL EtOH and 4 mol% CpRuCl(cod) was added as 2 mol% (CpRuCl(cod); 1.7 mg, 0.0045 mmol) additions of catalyst every 2 h to complete the reaction. The crude reaction mixture was concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 50→80% EtOAc-Hexanes; R_f = 0.35 at 80% EtOAc-hexanes) to afford **18C** as a white (65 mg, 90%): mp 201-203 °C; IR (neat) υ_{max} 2924, 2858, 1641, 1479, 1443, 1402, 1362, 1265, 1120, 1089, 729, 676cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (s, 3H), 3.10 (s, 3H), 2.92-2.80 (m, 2H), 2.83 (s, 3H), 2.76 (s, 3H), 2.41-2.35 (m, 1H), 1..87-1.75 (m, 2H), 1.55-1.47 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.5, 141.9, 141.0, 138.6, 138.2, 123.4, 114.2, 37.7, 37.4, 34.5, 34.5, 31.4, 31.3, 29.0, 28.7, 28.2, 28.1, 27.5, 26.5, 22.6, 22.3; LRMS (ESI) m/z = 517.2 $[M + H]^+$. See S66 for NMR spectra.



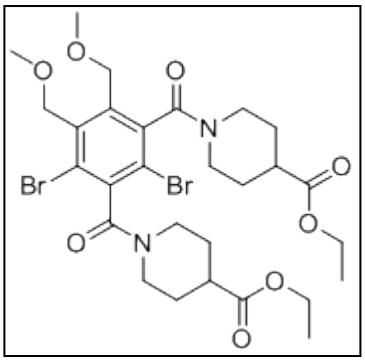
(2,4-Dibromo-5,6-dimethyl-1,3-phenylene)bis(morpholine-methanone) (19C). 3-Bromo-1-morpholinoprop-2-yn-1-one (410 mg, 1.64 mmol) and 2-butyne (118 µL, 81 mg, 1.5 mmol) were dissolved in 18 mL EtOH and 2 mol% CpRuCl(cod) (5.0 mg, 0.016 mmol) was added. The crude reaction mixture was determined complete by thin layer chromatography and subsequently filtered to deliver 125 mg of **19C** as a white powder. The filtrate was then concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 60→80% EtOAc-Hexanes; R_f = 0.19 at 80% EtOAc-hexanes) to afford the remaining **19C** as a beige solid (125 mg + 301 mg, 93 %). The samples isolated by filtration and column were combined and characterized: mp 205-207 °C; IR (neat) υ_{max} 2981, 2859, 1642, 1626, 1547, 1462, 1441, 1305, 1274, 1238, 1213, 1112, 1069, 1043, 1024, 954, 855, 613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90-3.80 (m, 3H), 3.80-3.74 (m, 3H), 3.72-3.66 (m, 5H), 3.55-3.48 (m, 1H), 3.22-3.11 (m, 4H), 2.28 (s, 3), 2.21 (s, 3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 165.6, 138.1, 137.1, 137.0, 136.4, 123.2, 113.7, 66.6, 66.6, 66.5, 66.5, 46.5, 46.5, 41.8, 41.7, 20.1, 18.7; LRMS (ESI) m/z = 491.1 $[M + H]^+$. See S67 for NMR spectra.



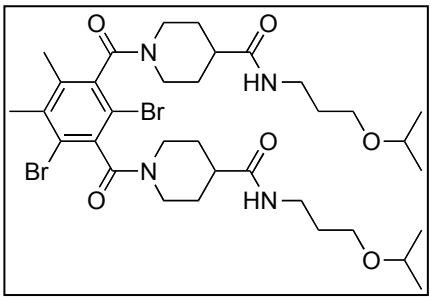
2,4-dibromo-5,6-diphenyl-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetraisopropylisophthalamide (20C). 3-Bromo-*N,N*-diisopropylpropiolamide (209 mg, 0.90 mmol) and diphenylacetylene (121 mg, 0.68 mmol) were dissolved in 9 mL EtOH and 4 mol% CpRuCl(cod) was added as 2 mol% (2.8 mg, 0.009 mmol) additions of catalyst every 2 h to complete the reaction. The crude reaction mixture was concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 15→20% EtOAc-Hexanes; R_f = 0.12 at 20% EtOAc-hexanes) to afford **20C** as a yellow solid (272 mg, 94%): mp 119-123 °C; IR (neat) υ_{max} 2975, 1641, 1629, 1469, 1442, 1369, 1334, 1317, 1265, 1210, 1156, 1139, 1037, 708, 697, 615 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 3.77 (sept, *J* = 6.6 Hz, 1H), 3.57 (sept, *J* = 6.8 Hz, 1H), 3.50 (sept, *J* = 6.6 Hz, 1H), 3.16 (sept, *J* = 6.9 Hz, 1H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.56 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.8, 142.6, 140.6, 139.8, 139.5, 139.2, 136.7, 131.7, 131.1, 130.7, 130.0, 128.2, 127.8, 127.4, 127.4, 127.0, 126.7, 121.4, 116.8, 52.0, 51.0, 46.6, 46.0, 21.3, 20.8, 20.7, 20.6, 20.2, 20.2, 20.0, 19.8; LRMS (ESI) m/z = 643.2 $[M + H]^+$. See S68 for NMR spectra.



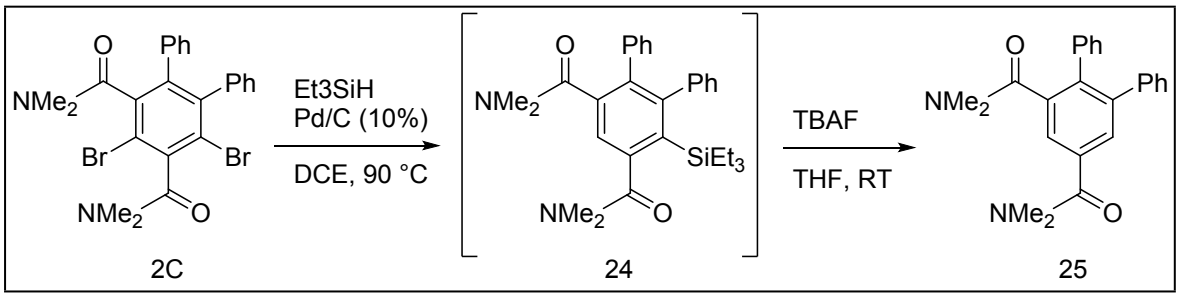
2,4-dibromo-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetraethyl-5,6-di(thiophen-3-yl)isophthalamide (21C). 3-Bromo-*N,N*-diethylpropiolamide (203 mg, 1.00 mmol) and 1,2-di(thiophen-3-yl)ethyne[5] (143 mg, 0.75 mmol) were dissolved in 8 mL EtOH and 2 mol% CpRuCl(cod) (3.0 mg, 0.01 mmol) was added. After 2 hours, the crude reaction mixture was concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 40% EtOAc-Hexanes; R_f = 0.24 at 50% EtOAc-hexanes) to afford **21C** as a beige solid (274 mg, 92%): mp 154-156 ^oC; IR (neat) υ_{max} 2980, 2935, 1645, 1629, 1459, 1438, 1378, 1304, 1270, 1217, 1143, 1078, 856, 784, 771, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, J = 3.0, 1.2 Hz, 2H), 7.02 (dd, J = 5.0, 3.0 Hz, 1H), 6.94 (br app s, 1H), 6.82 (br app s, 1H), 6.64 (dd, J = 5.0, 0.9 Hz, 1H), 3.72-3.55 (m, 3H), 3.38-3.23 (m, 2H), 3.10-2.97 (m, 2H), 2.81-2.72 (m, 1H), 1.30 (t, J = 6.7 Hz, 3H), 1.27 (t, J = 6.7 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 166.0, 139.9, 138.8, 138.1, 138.2, 136.4, 136.3, 129.0, 128.7, 125.7, 125.3, 124.6, 124.3, 121.9, 116.7, 42.7, 42.3, 38.8, 38.2, 13.6, 13.2, 12.1, 11.7; LRMS (ESI) m/z = 599.1 $[M + H]^+$. See S69 for NMR spectra.



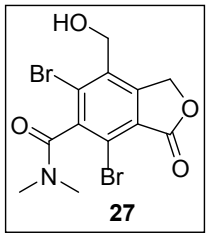
Diethyl-1,5-(4,6-dibromo-2,3-bis(methoxymethyl)benzoyl)-bispiperidine-4-carboxylate (22C). Ethyl 1-(3-bromopropioloyl)piperidine-4-carboxylate (471 mg, 1.64 mmol) and 1,4-dimethoxybut-2-yne (187 mg, 1.64 mmol) were dissolved in 16 mL EtOH and 4 mol% CpRuCl(cod) was added as 2 mol% (5.0 mg, 0.016 mmol) additions of catalyst every 2 h to complete the reaction. The crude reaction mixture was concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 80% EtOAc-Hexanes; R_f = 0.16 at 80% EtOAc-hexanes) to afford **22C** as a tan solid (407 mg, 72%) and as a mixture of atropisomers: mp 59-62 ^oC; IR (neat) υ_{max} 2988, 2933, 1726, 1640, 1548, 1444, 1377, 1318, 1272, 1175, 1093, 1039, 945, 862, 666, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.56 (app s, 2H), 4.49-4.40 (m, 2H), 4.38-4.28 (m, 2H), 4.07-4.01 (m, 4H), 3.32 (s, 1.5H), 3.30 (s, 1.5H), 3.30 (s, 1.5H), 3.28 (s, 1.5H), 3.25-3.22 (m, 2H), 3.10-2.93 (m, 3H), 2.92-2.81 (m, 1H), 2.51-2.42 (m, 2H), 1.96-1.89 (m, 2H), 1.79-1.54 (m, 6H), 1.17-1.12 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 173.9, 173.8, 173.8, 173.7, 173.7, 173.6, 173.6, 165.4, 165.4, 165.3, 165.3, 164.8, 164.8, 164.8, 164.8, 140.0, 139.9, 139.9, 139.3, 139.2, 139.1, 139.0, 137.5, 137.4, 137.4, 137.2, 124.0, 123.9, 123.9, 123.9, 116.9, 116.9, 116.9, 116.9, 69.9, 69.9, 69.2, 69.1, 69.9, 69.9, 69.2, 69.1, 60.6, 60.5, 60.5, 60.5, 60.5, 59.0, 58.9, 58.4, 46.3, 46.2, 45.3, 45.3, 45.2, 45.1, 40.8, 40.6, 40.6, 40.5, 40.4, 40.4, 40.3, 27.9, 27.7, 27.7, 27.6, 27.5, 27.4, 27.3, 27.3, 27.2, 27.2, 14.0; LRMS (ESI) m/z = 691.2 $[M + H]^+$. See S70 for NMR spectra.



1,2-(4,6-Dibromo-2,3-dimethylbenzoyl)-*N*,*N*-(di-3-isopropoxypropyl)bispiperidine-4-carboxamide (23C). 1-(3-Bromopropioloyl)-*N*-(3-isopropoxypropyl)piperidine-4-carboxamide (539 mg, 1.5 mmol) and 2-butyne (94 µL, 65 mg, 1.2 mmol) were dissolved in 25 mL EtOH followed by the addition of 2 mol% CpRuCl(cod) (9.3 mg, 0.03 mmol). After stirring for 2 hr, the crude reaction mixture was concentrated onto silica gel via rotary evaporation and subjected to flash chromatography (SiO_2, 4% MeOH-DCM; R_f = 0.19 at 5% MeOH-DCM) to afford **23C** as a light brown solid (387 mg, 67%) and as a mixture of atropisomers: mp N/A ^oC; IR (neat) υ_{max} 3325, 1628, 1542, 1446, 1369, 1327, 1274, 1202, 1148, 1127, 1083, 1010, 938, 753, 668, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.84 (m, 1H), 6.77-6.71 (m, 1H), 4.52-4.42 (m, 2H), 3.39 (sept, J = 5.1 Hz, 2H), 3.33-3.31 (m, 4H), 3.26-3.23 (m, 2H), 3.15-3.09 (m, 4H), 2.89-2.81 (m, 2H), 2.78-2.66 (m, 2H), 2.22 (app s, 3H), 2.15 (app s, 3H), 2.10 (app s, 2H), 1.78-1.71 (m, 2H), 1.64-1.42 (m, 10H), 0.98-0.97 (m, 12H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 173.5, 173.5, 173.4, 173.4, 173.4, 173.2, 173.2, 166.1, 166.1, 166.0, 165.9, 165.3, 165.3, 165.2, 165.1, 137.8, 137.7, 137.6, 137.6, 137.5, 137.4, 137.4, 137.4, 137.3, 137.2, 135.9, 135.9, 135.7, 122.5, 122.4, 122.4, 122.4, 113.3, 113.3, 113.3, 113.2, 71.4, 71.4, 71.3, 71.3, 66.8, 66.8, 66.7, 66.6, 66.5, 66.5, 45.7, 45.7, 45.6, 45.5, 45.5, 45.3, 45.3, 45.2, 45.2, 42.4, 42.4, 42.2, 42.2, 42.1, 40.5, 40.57, 50.5, 50.5, 40.4, 40.4, 38.0, 37.9, 37.8, 37.8, 37.8, 37.7, 29.3, 29.2, 29.2, 29.1, 28.8, 28.8, 28.6, 28.5, 28.2, 28.2, 28.0, 27.9, 27.9, 21.9, 19.8, 19.8, 19.8, 19.7, 18.6, 18.5, 18.3; LRMS (ESI) m/z = 773.4 $[M + H]^+$. See S71 for NMR spectra.

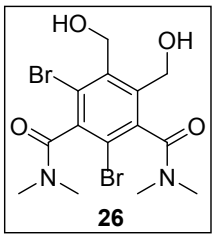


5,6-diphenyl-N^1,N^1,N^3,N^3-tetramethylisophthalamide (25). To a microwave vial equipped with a stir bar there was added 53 mg (0.10 mmol, 1.0 equiv.) aryl bromide **2C** and 43 mg (0.040 mmol Pd, 0.40 equiv. by Pd content) 10% palladium on carbon. Anhydrous DCE (1.0 mL) was added, followed by 320 µL (233 mg, 2.00 mmol, 20 equiv.) triethylsilane. Hydrogen evolution was observed and the vial was immediately capped. A needle was introduced for approximately 15 seconds and upon shaking, the residual air in the reaction headspace was displaced. The needle was removed and the vial placed in an oil bath at 90 °C for 72 hours. The reaction mixture was then cooled, concentrated, dissolved in EtOAc, and passed through a plug of celite. The resulting yellow residue was analyzed by LC/MS and was observed to consist almost entirely of a species with mass corresponding to aryl silane **24**; m/z 457.2 [M – Et]+; m/z 487.3 $[M + H]^+$. This product was not purified further, but subjected to 2.0 mL (2.0 mmol, 20 equiv.) of a 1M THF solution of tetrabutylammonium fluoride directly. After 24 hours at RT under air, 623 mg $CaCO_3$, MeOH (4.5 mL), and 1.87 g DOWEX 50WX8-400 resin were added. This mixture was stirred for 2 hours at RT under air and filtered through celite using MeOH as eluent thereby removing excess TBAF.[6] This residue was concentrated and purified by flash column chromatography (100% DCM to remove excess silane, then switching to 1% MeOH in DCM to elute product) to afford 38 mg (0.10 mmol, quantitative yield) of the title compound as a white solid, **25**; (38 mg, 0.10 mmol, quantitative yield, white solid). Rf = 0.49 (1% MeOH in DCM). 1H NMR (500 MHz, CDCl3) δ 7.60 (d, J = 1.8 Hz, 1H), 7.49 (d, J = 1.7 Hz, 1H), 7.34 (s, 1H), 7.25 (dd, J = 6.1, 2.6 Hz, 6H), 7.18 – 7.13 (m, 3H), 3.21 (s, 3H), 3.15 (s, 3H), 2.82 (s, 3H), 2.52 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 170.67, 170.43, 141.99, 140.36, 138.20, 138.16, 137.65, 136.18, 130.36, 129.93, 129.67, 129.15, 128.34, 128.03, 127.45, 127.01, 124.50, 39.92, 38.39, 35.54, 34.46. LRMS (ESI): m/z 373.2 $[M + H]^+$. See S72 for NMR spectra.



4,6-dibromo-7-(hydroxymethyl)-dimethyl-3-oxo-1,3-dihydro-isobenzofuran-5-carboxamide (27). A 50 mL round bottom flask was charged with 5.1 (1.5 g, 8.5 mmol), commercially available 1,4-diol-but-2-yne (1.1 g, 12.8 mmol) and 25 mL ethanol. The reaction vessel was placed into a 50 °C oil bath and treated with CpRuCl(cod) (50 mg, 0.17 mmol). After 1 h, the reaction was analyzed by TLC, deemed incomplete and treated with an additional portion of CpRuCl(cod) (50 mg, 0.17 mmol). The reaction was stirred for 3 more hours at which point TLC analysis indicated the reaction was complete. The crude mixture was concentrated directly onto silica gel and subjected to column chromatography (SiO_2, 80 → 100% EtOAc-Hexanes). The only fraction that eluted (R_f = 0.28 at 100% EtOAc-hexanes) was determined by ^{1}H NMR to be **27** (~600 mg). At this point, the solvent phase was changed from EtOAc to 2 → 15% MeOH/DCM. Several additional fractions eluted: The first was determined to be **1A/B** (~50 mg), next impure **27** eluted (~400-500 mg) and finally **26** (~450 mg).

Isolated **27** was found to have margin solubility in EtOAc and better solubility in DCM. After a period of one week, all of the fractions eluted with DCM would collected, re-concentrated on silica gel and subjected to a second round of column chromatography (SiO_2, 2 → 3% MeOH-DCM) to arrive again at **27** (~700 mg). Combined isolated yield of **27** was ~1.3 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (d, J = 17.0 Hz, 1H), 5.48 (d, J = 17.1 Hz, 1H), 4.89 (s, 1H), 4.57 (q, J = 16.8 Hz, 2H), 3.18 (s, 3H), 2.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 167.1, 148.1, 141.0, 137.7, 124.7, 123.1, 115.9, 69.2, 64.7, 37.8, 35.0. See S73 for NMR spectra.

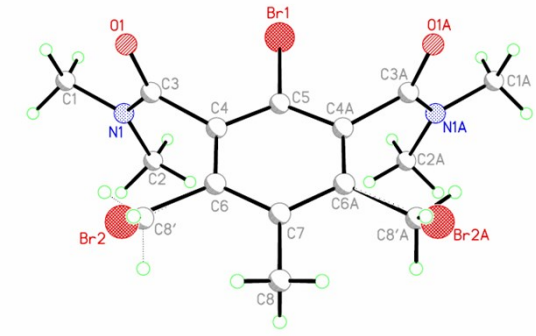


2,4-dibromo-5,6-bis(hydroxymethyl)-tetramethylisophthalamide (26). **26** was isolated from the above reaction mixture as a slightly yellow foam-solid. An ^{1}H NMR spectra was obtained shortly after isolation and the remaining material was allowed to rest at room temperature, as a solid, in a 100 mL round bottom flask. After 1 week, the cap on the flask was removed and a strong amine smell was apparent. Subsequent ^{1}H NMR analysis revealed **26** has a completely converted to **27**. ^{1}H NMR characterization of crude **26** is as follows: ^{1}H NMR

(400 MHz, $CDCl_3$) δ 4.96-4.88 (m, 2H), 4.64-5.57 (m, 2H), 3.16 (s, 3H), 3.14 (s, 3H), 2.87 (s, 3H), 2.85 (s, 3H). See S74 for NMR spectra.

X-ray Crystal Structures

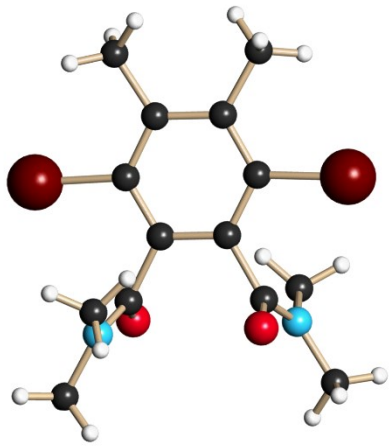
Atomic coordinates for compounds **1C**, **1D**, **2C** and 27 were obtained by Curtis Moore and Arnie Rheingold of the UCSD Crystallography Facility, University of California, San Diego.



Crystal data and structure refinement for xx (**1C**).

Identification code	xx
Empirical formula	C14 H18 Br2 N2 O2
Formula weight	406.12
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pnma

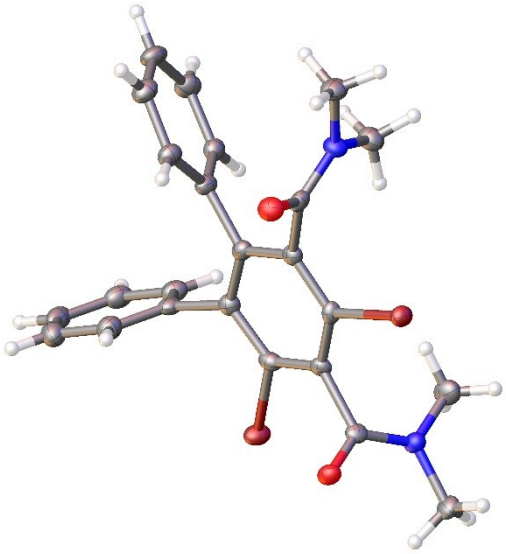
Unit cell dimensions	a = 10.6272(8) Å	α= 90°
	b = 19.9580(15) Å	β= 90°
	c = 7.6673(5) Å	γ = 90°
Volume	1626.2(2) $Å^3$	
Z	4	
Density (calculated)	1.659 g/cm^3	
Absorption coefficient	4.987 mm^{-1}	
F(000)	808	
Crystal size	0.42 x 0.38 x 0.32 mm^3	
Theta range for data collection	2.85 to 26.45°	
Index ranges	-13<=h<=13, -24<=k<=24, -9<=l<=9	
Reflections collected	12400	
Independent reflections	1727 [R(int) = 0.0209]	
Completeness to theta = 25.00°	99.5 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.2983 and 0.2285	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1727 / 1 / 110	
Goodness-of-fit on F^2	1.191	
Final R indices [I>2sigma(I)]	R1 = 0.0182, wR2 = 0.0417	
R indices (all data)	R1 = 0.0197, wR2 = 0.0421	
Largest diff. peak and hole	0.357 and -0.267 e $Å^{-3}$	
Disorder	50/50 Me/Br mirror-plane disorder	



Crystal data and structure refinement for xx1 (**1D**)

Identification code	xx1
Empirical formula	C14 H18 Br2 N2 O2
Formula weight	406.12
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c

Unit cell dimensions	a = 16.1663(14) Å	α= 90°
	b = 14.2630(12) Å	β= 99.5080(10)°
	c = 6.9159(6) Å	γ = 90°
Volume	1572.8(2) $Å^3$	
Z	4	
Density (calculated)	1.715 g/cm^3	
Absorption coefficient	5.157 mm^{-1}	
F(000)	808	
Crystal size	0.30 x 0.26 x 0.16 mm^3	
Theta range for data collection	1.92 to 25.39°	
Index ranges	-15<=h<=19, -17<=k<=16, -8<=l<=7	
Reflections collected	6982	
Independent reflections	1457 [R(int) = 0.0261]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.4925 and 0.3068	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	1457 / 0 / 94	
Goodness-of-fit on F2	1.074	
Final R indices [I>2sigma(I)]	R1 = 0.0214, wR2 = 0.0553	
R indices (all data)	R1 = 0.0219, wR2 = 0.0556	
Largest diff. peak and hole	0.375 and -0.527 e $Å^{-3}$	



Crystal data and structure refinement for xx2 (**2C**).

Identification code	xx2
Empirical formula	C24 H22 Br2 N2 O2
Formula weight	530.25
Temperature	100.0 K
Wavelength	0.71073 Å

Crystal system	Monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 6.0728(8) Å	□= 90°.
	b = 24.305(2) Å	□= 98.929(4)°.
	c = 15.0006(14) Å	□ = 90°.
Volume	2187.2(4) $Å^3$	
Z	4	
Density (calculated)	1.610 Mg/m^3	
Absorption coefficient	3.730 mm^{-1}	
F(000)	1064	
Crystal size	0.24 x 0.1 x 0.07 mm^3	
Theta range for data collection	2.167 to 25.390°.	
Index ranges	-7<=h<=7, -29<=k<=23, -15<=l<=18	
Reflections collected	9162	
Independent reflections	4022 [R(int) = 0.0393]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.0570 and 0.0297	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4022 / 0 / 275	
Goodness-of-fit on F^2	1.013	
Final R indices [I>2sigma(I)]	R1 = 0.0346, wR2 = 0.0701	
R indices (all data)	R1 = 0.0496, wR2 = 0.0745	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.616 and -0.380 $e.Å^{-3}$	

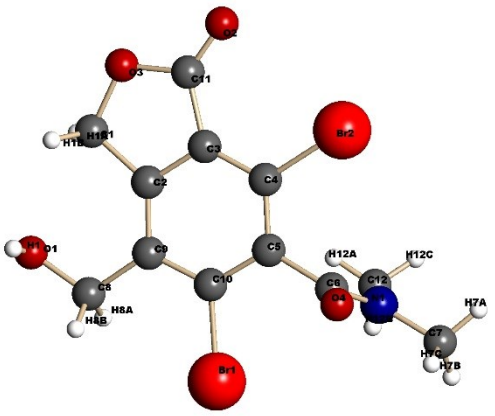


Table 1. Crystal data and structure refinement for xx3 (**27**).

Identification code	xx3
Empirical formula	C12 H11 Br2 N O4
Formula weight	393.04

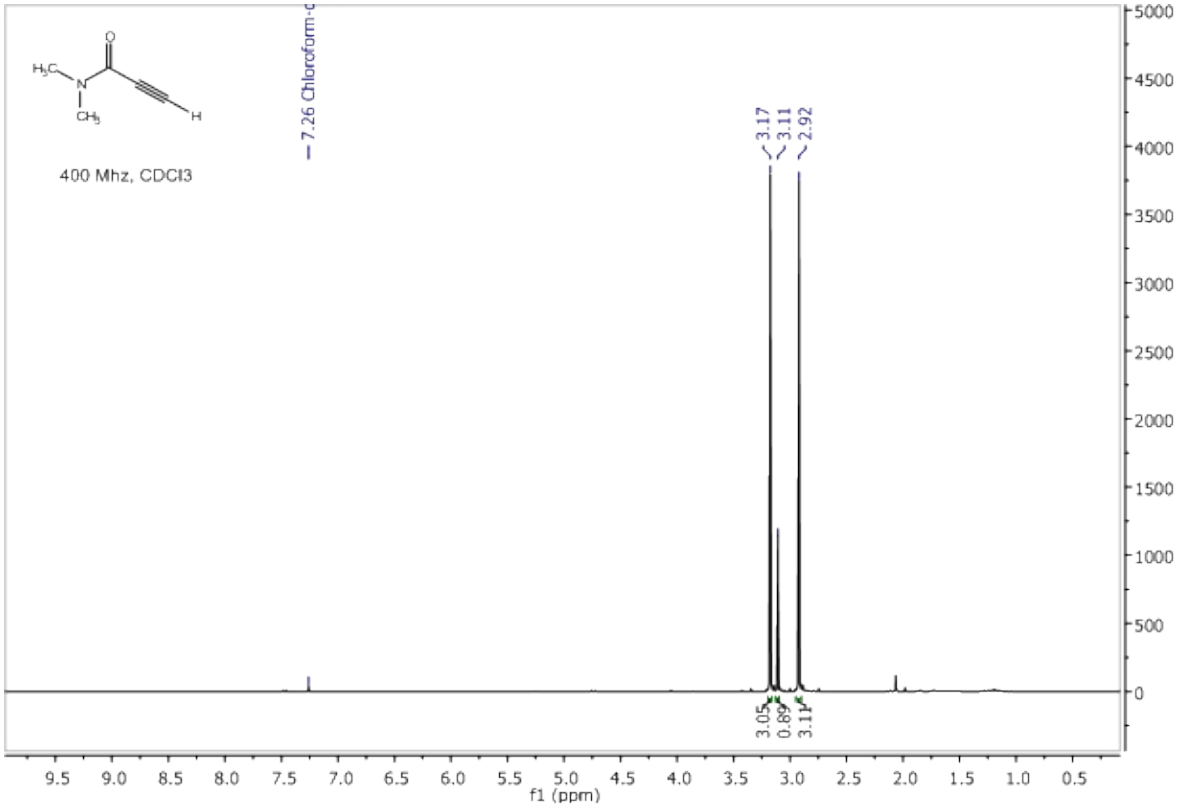
Temperature	100.0 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 8.5662(6) Å □= 96.065(2)°. b = 8.5847(6) Å □= 102.093(2)°. c = 9.5341(6) Å □ = 95.978(2)°.
Volume	675.95(8) $Å^3$
Z	2
Density (calculated)	1.931 Mg/m^3
Absorption coefficient	6.005 mm^{-1}
F(000)	384
Crystal size	0.3 x 0.3 x 0.22 mm^3
Theta range for data collection	2.406 to 31.281°.
Index ranges	-12<=h<=12, -12<=k<=12, -13<=l<=9
Reflections collected	11041
Independent reflections	3881 [R(int) = 0.0406]
Completeness to theta = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.1011 and 0.0535
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3881 / 0 / 177
Goodness-of-fit on F^2	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0302, wR2 = 0.0625
R indices (all data)	R1 = 0.0490, wR2 = 0.0684
Extinction coefficient	n/a
Largest diff. peak and hole	0.653 and -0.517 $e.Å^{-3}$

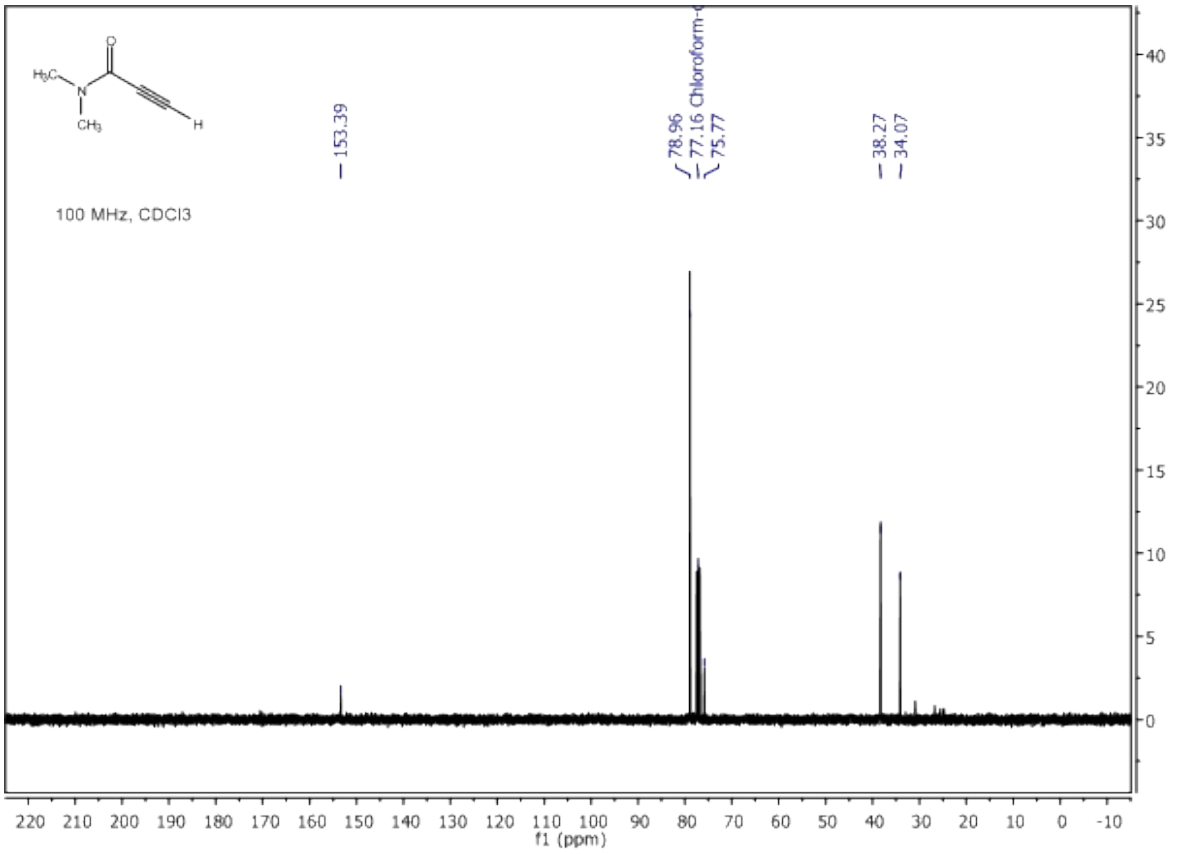
References

(1) Ashworth, T.V.; Singleton, E.; Hough, J. J. *J. Chem. Soc., Dalton Trans.* **1977**, 1809.
(2) Albers, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199.
(3) (a) Pattison, F. L. M.; Norman, J. J. *J. Am. Chem. Soc.* **1957**, 79, 2311
(4) Cyclododecyne, 1-methoxy-4-(phenylethynyl)benzene, and 1-cyano-4-(phenylethynyl)benzene were from the laboratory of Professor Barry K. Sharpless, The Scripps Research Institute. The purity of cyclododecyne by GC/MS analysis was approximately 65%.
(5) Park, K.; Bae, G.; Moon, J.; Choe, J.; Song, K. H.; Lee, S. *J. Org. Chem.* **2010**, *75*, 6244.
(6) As addapted from: Org. Lett. 2007, 9, 723.

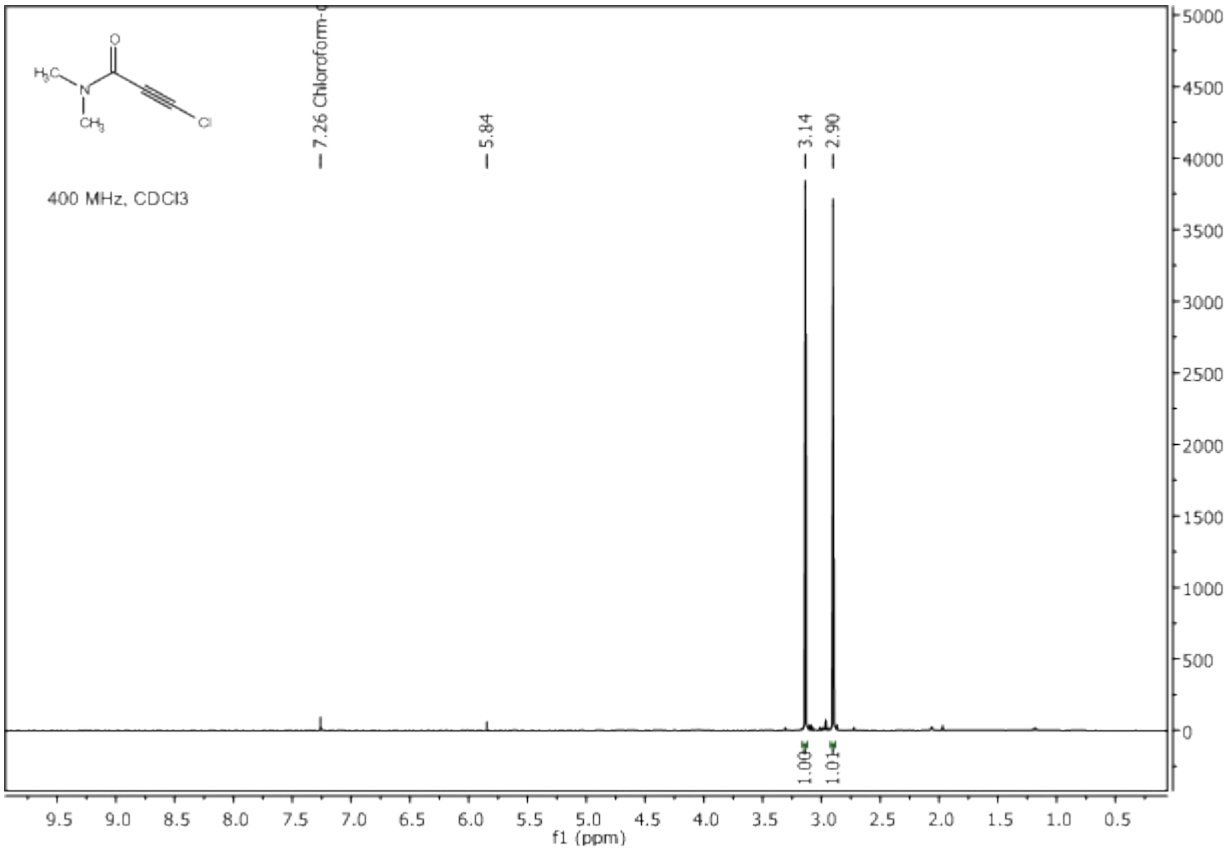
[1]H and [13]C NMR

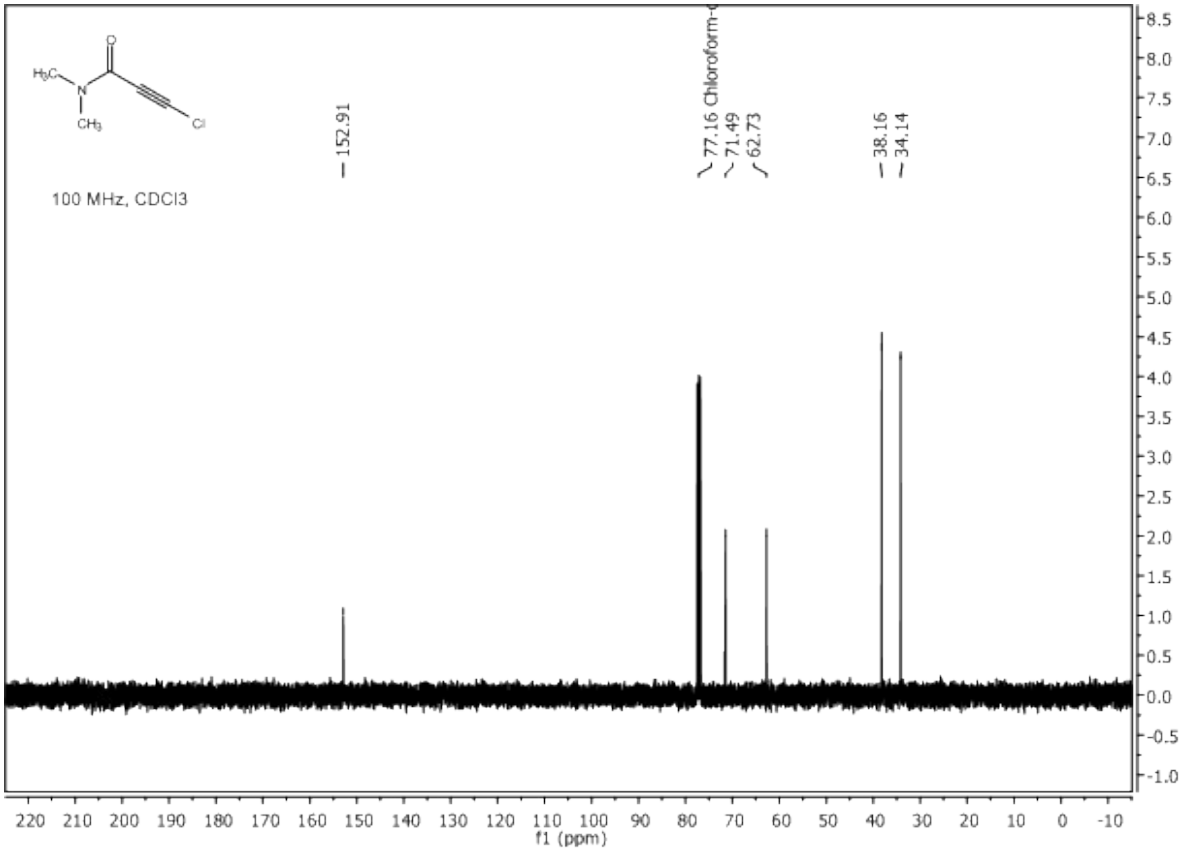
Dimethylpropiolamide (**7**)



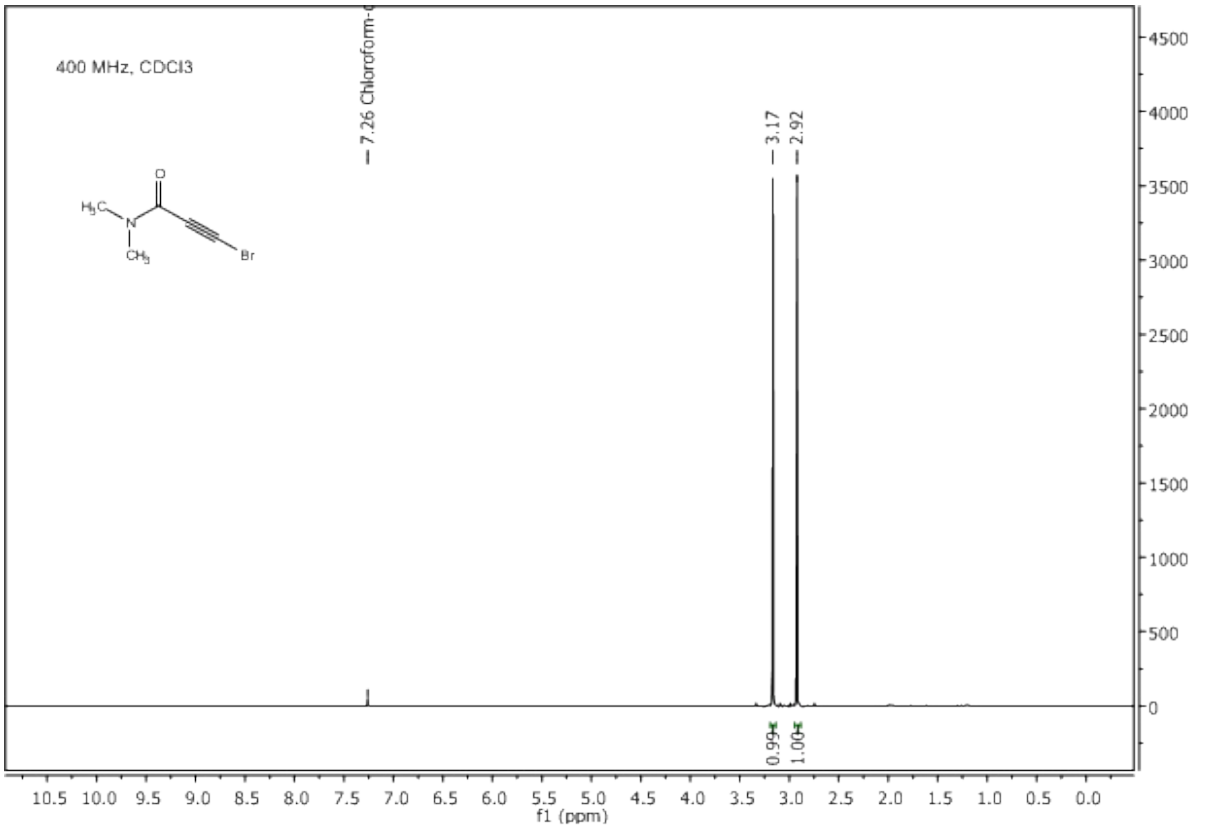


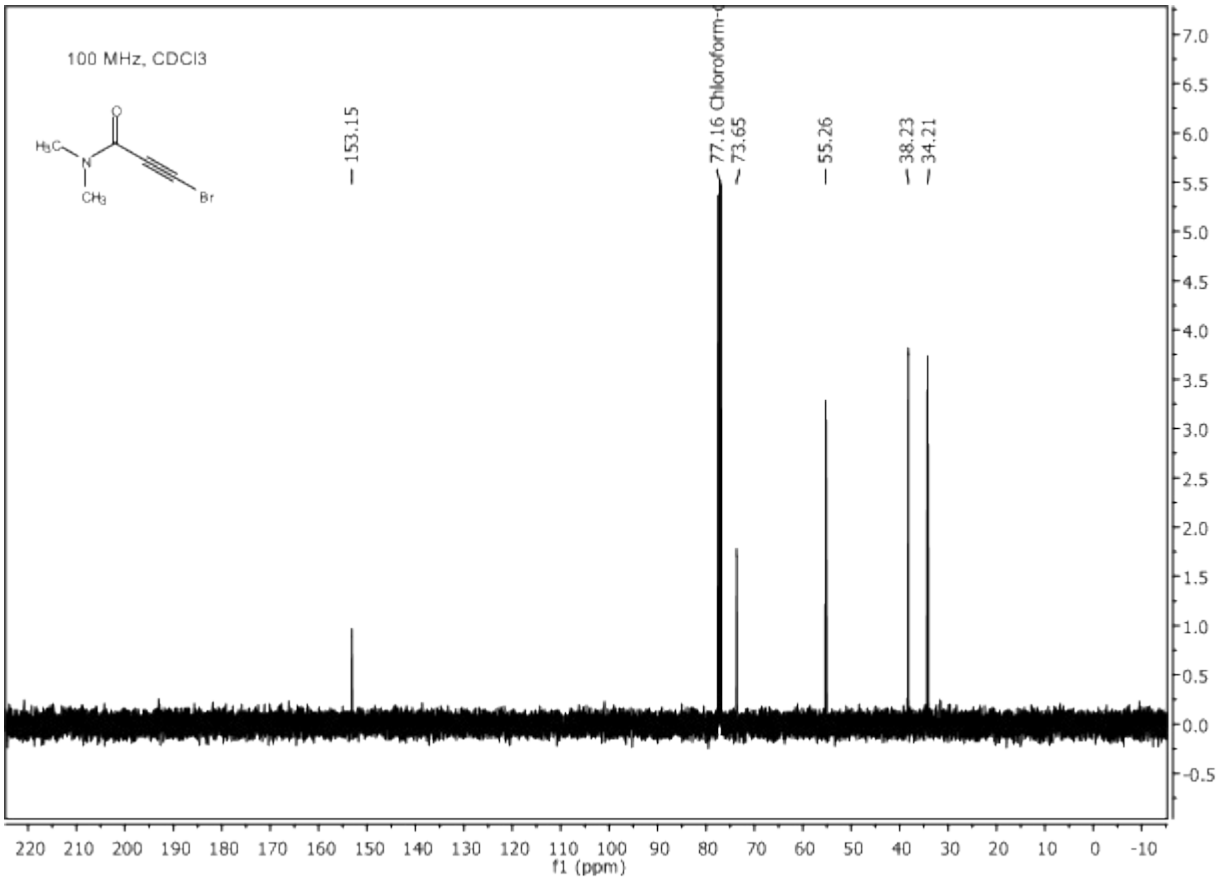
3-Chloro-dimethylpropiolamide (**5**)



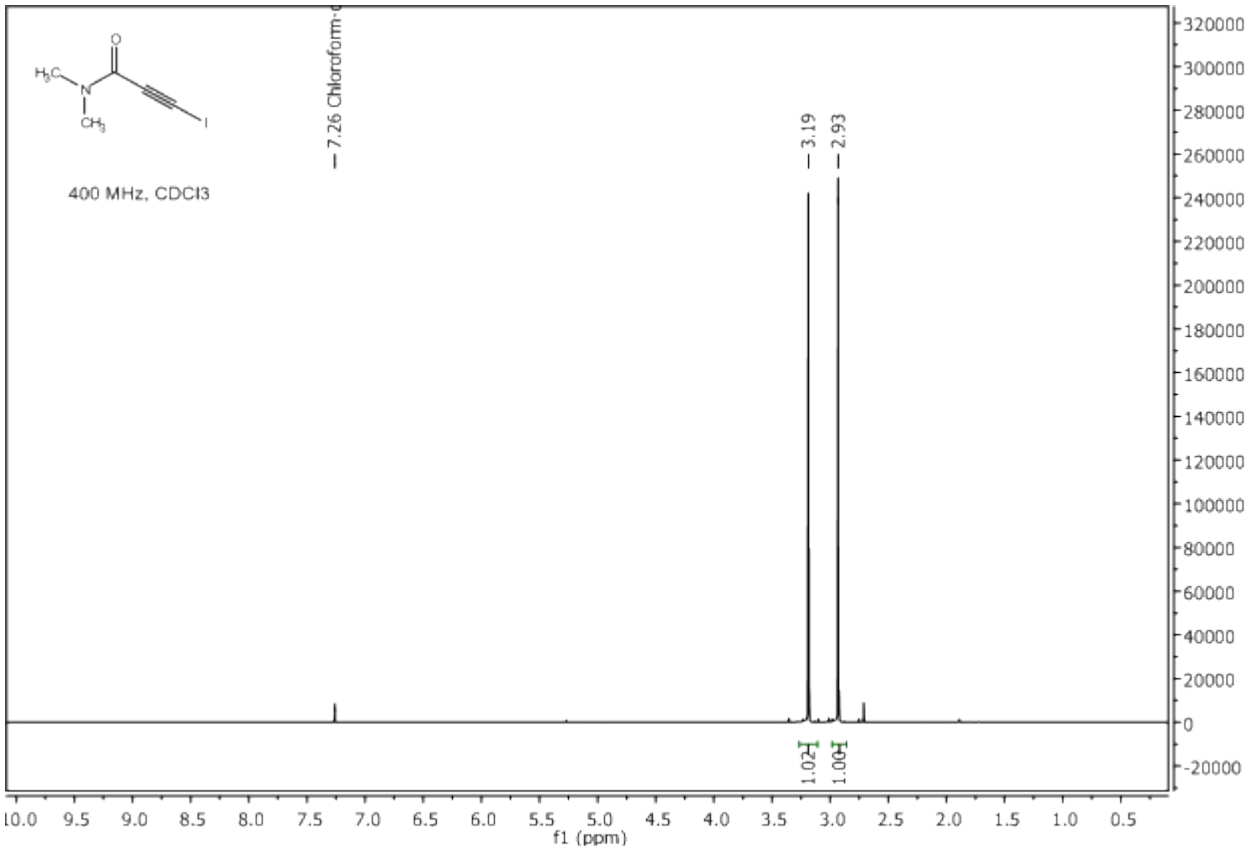


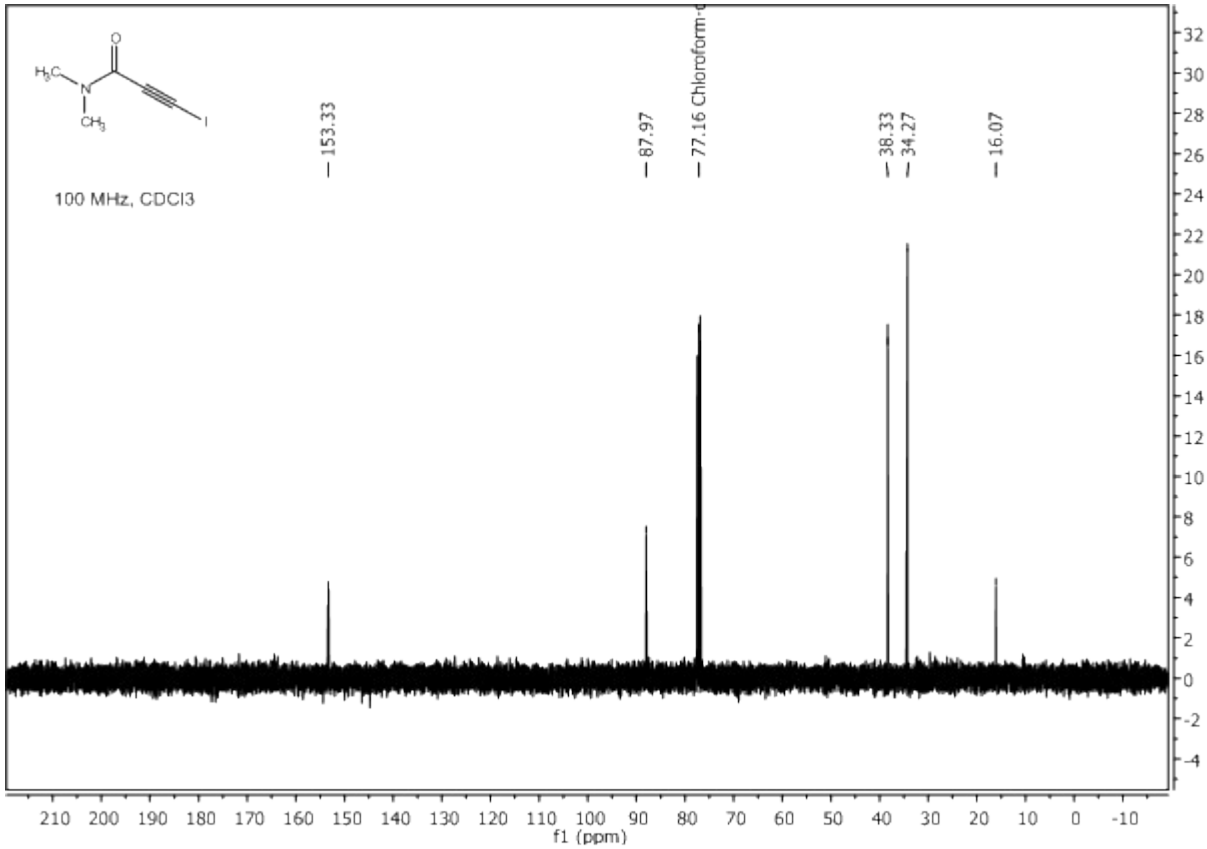
3-Bromo-dimethylpropiolamide (**1**)



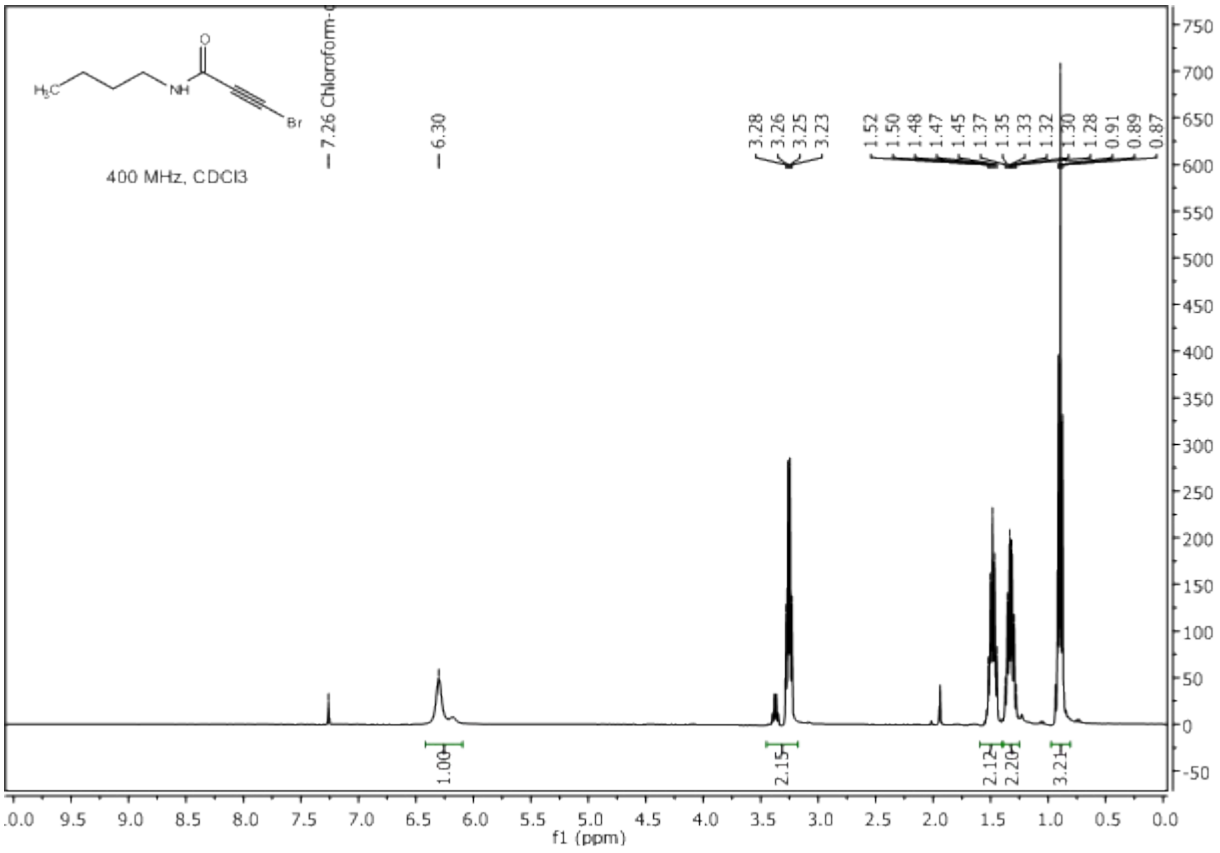


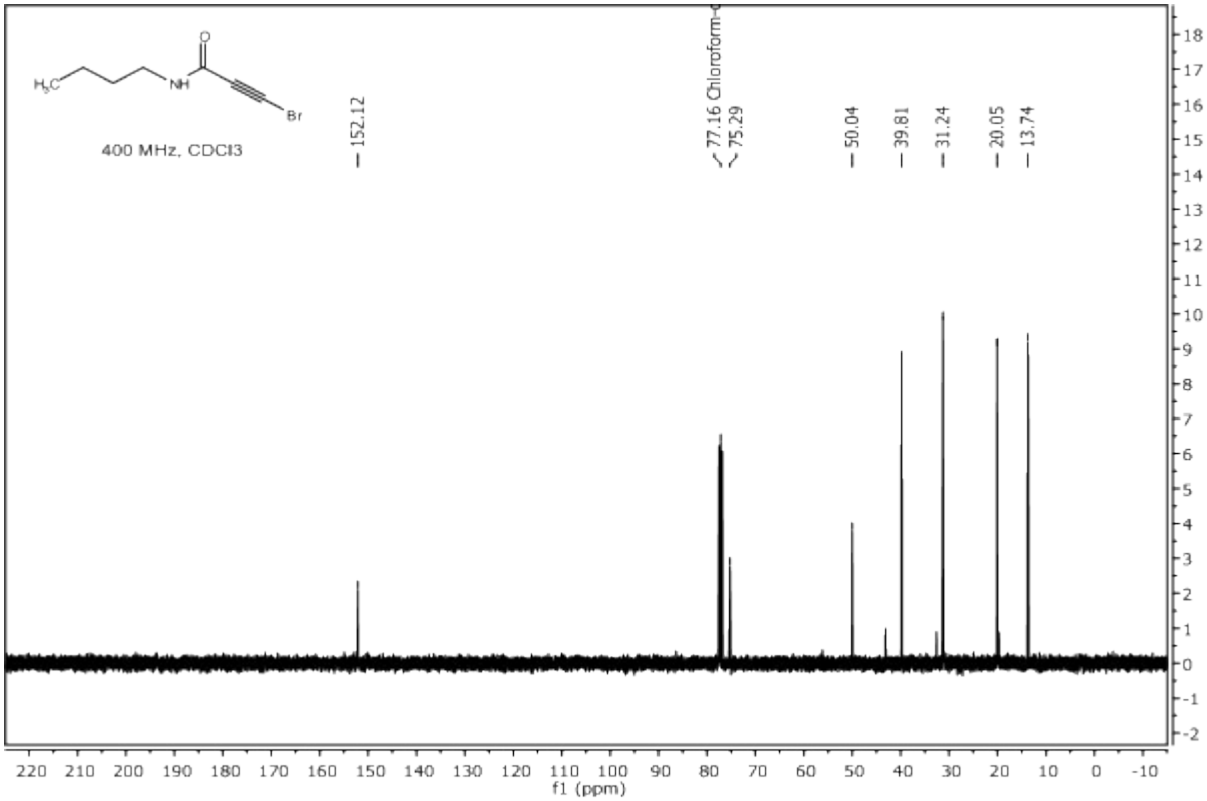
3-Iodo-dimethylpropiolamide (**6**)



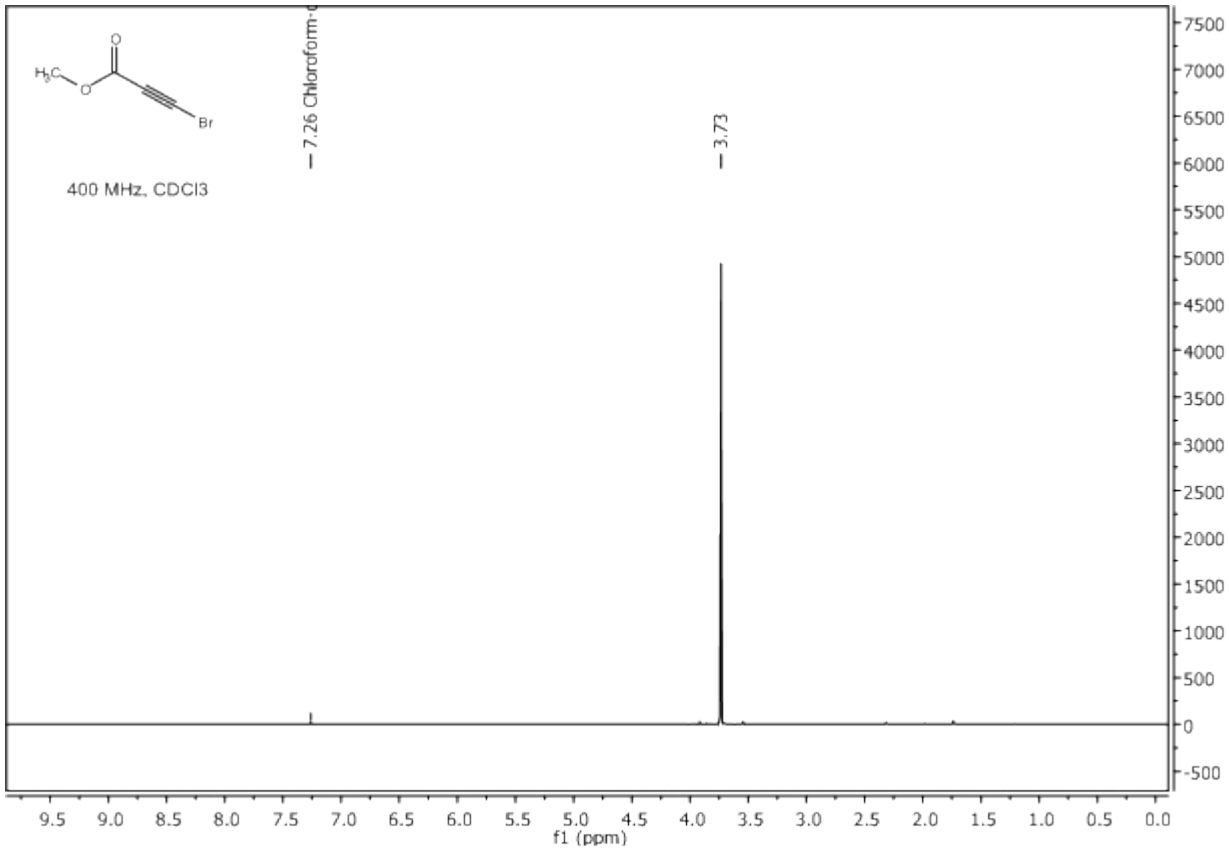


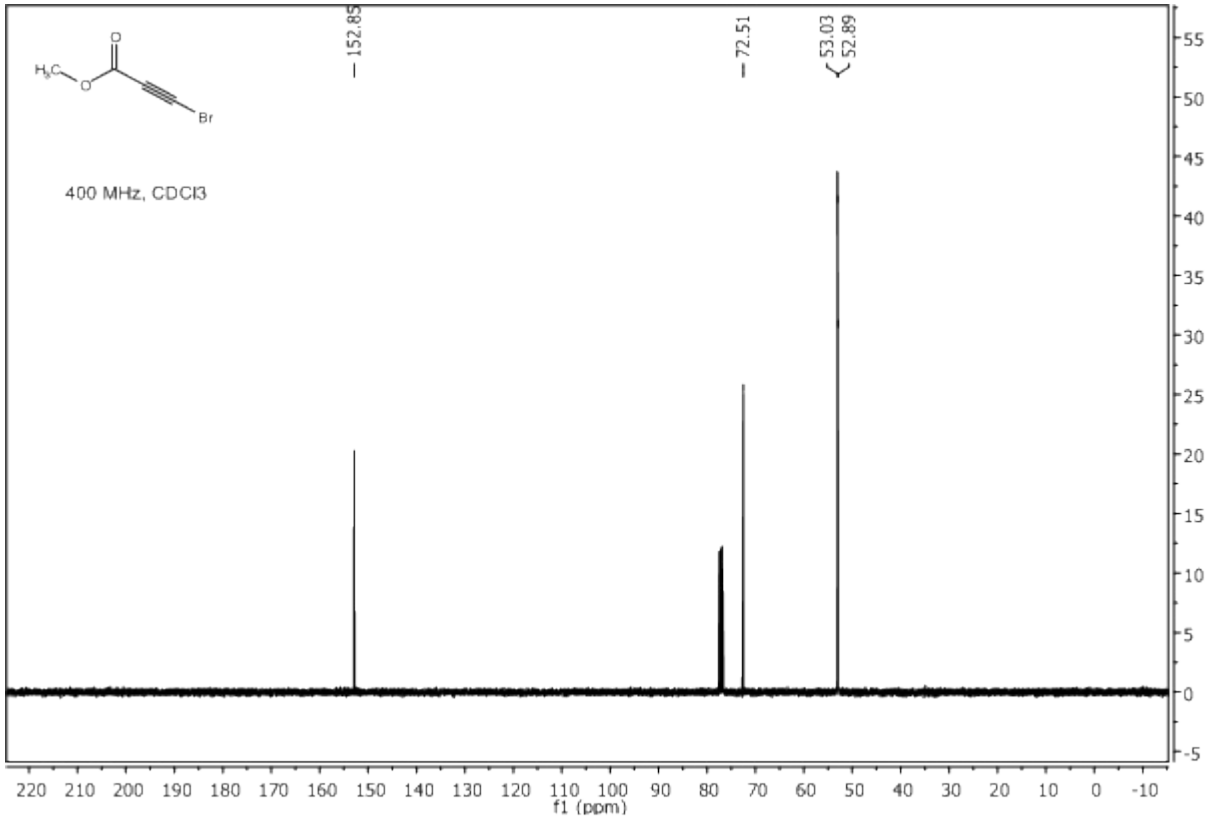
3-Bromo-butylpropiolamide (**8**)



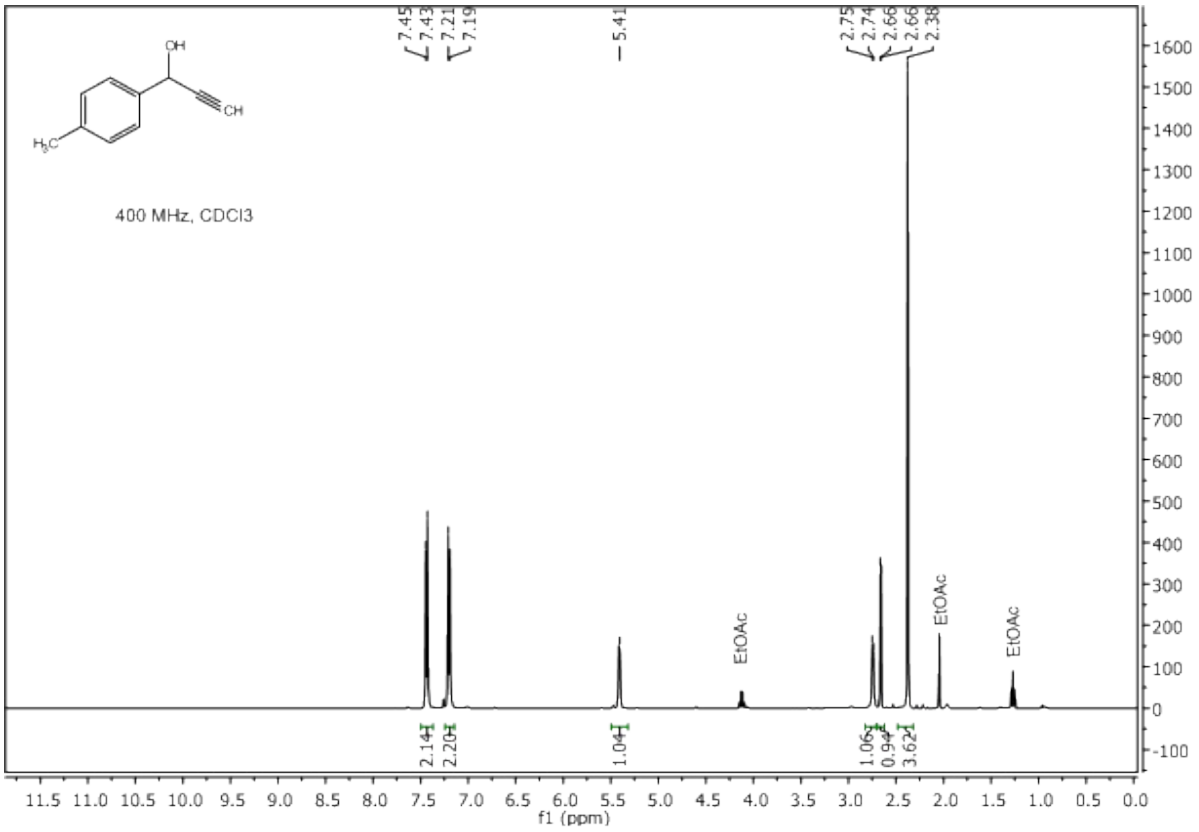


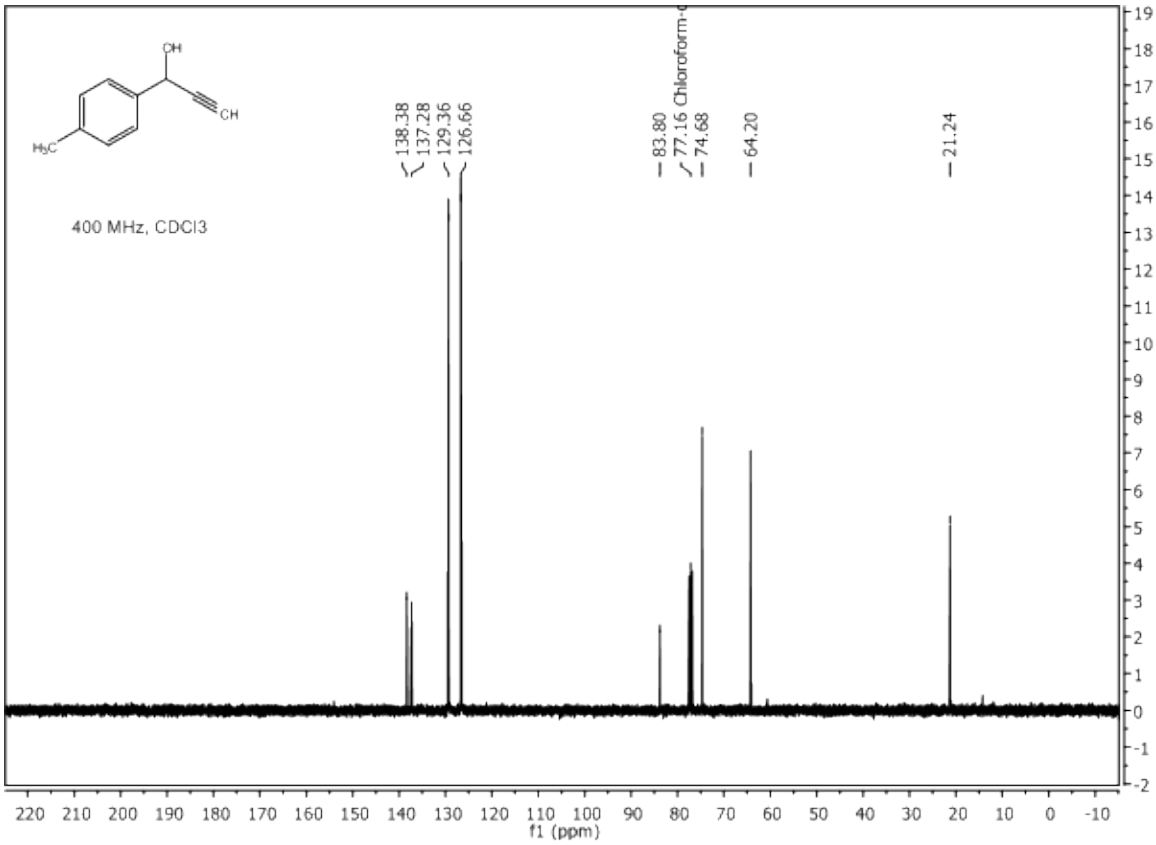
Methyl 3-bromopropiolate (**3**)



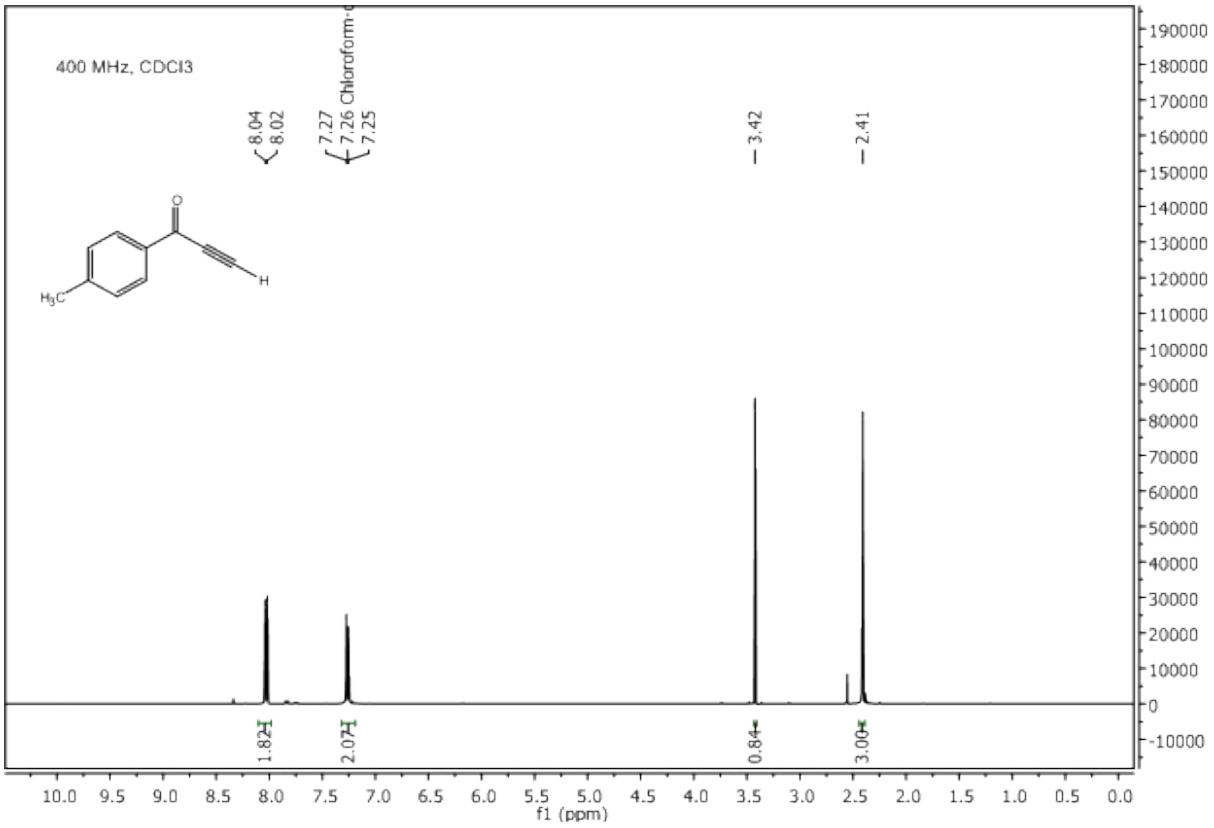


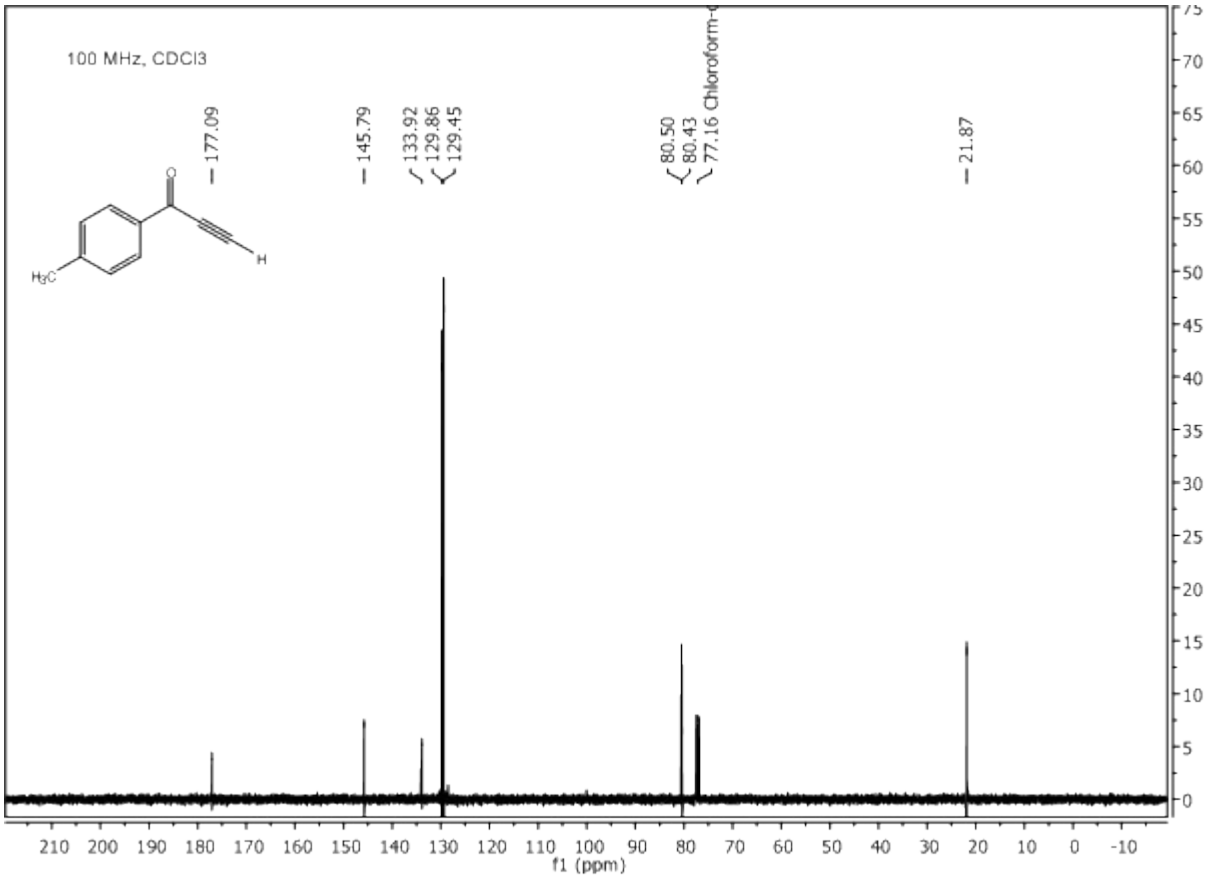
1-*p*-Tolylprop-2-yn-1-ol (**si_1**)



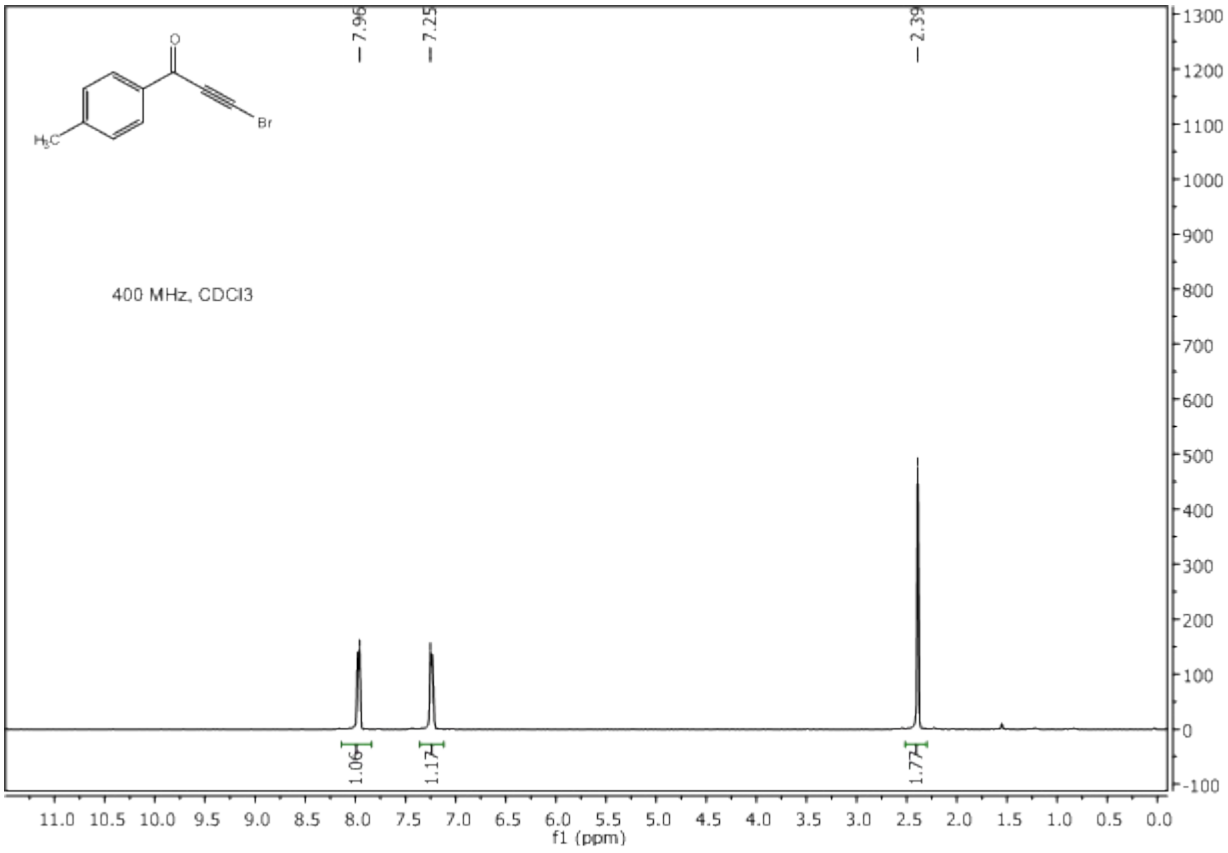


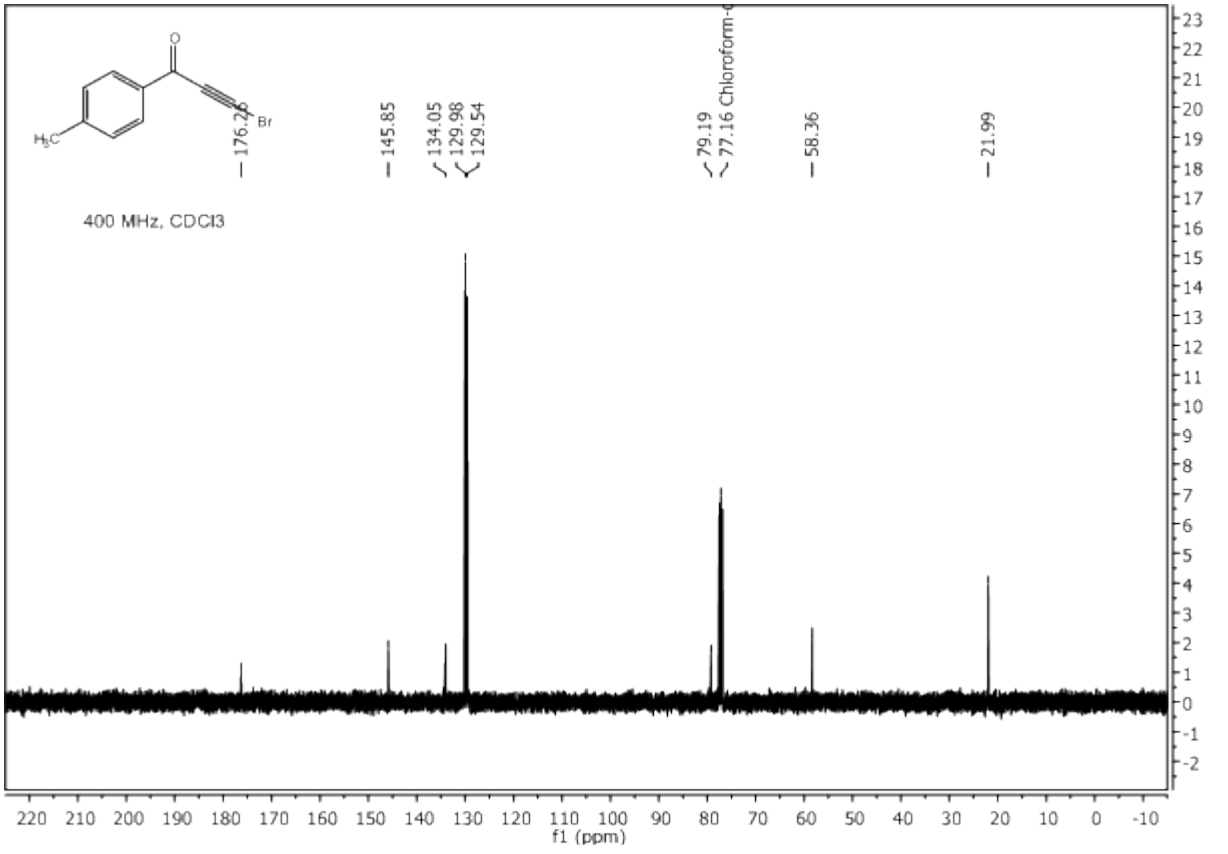
1-*p*-Tolylprop-2-yn-1-one (**si_2**)



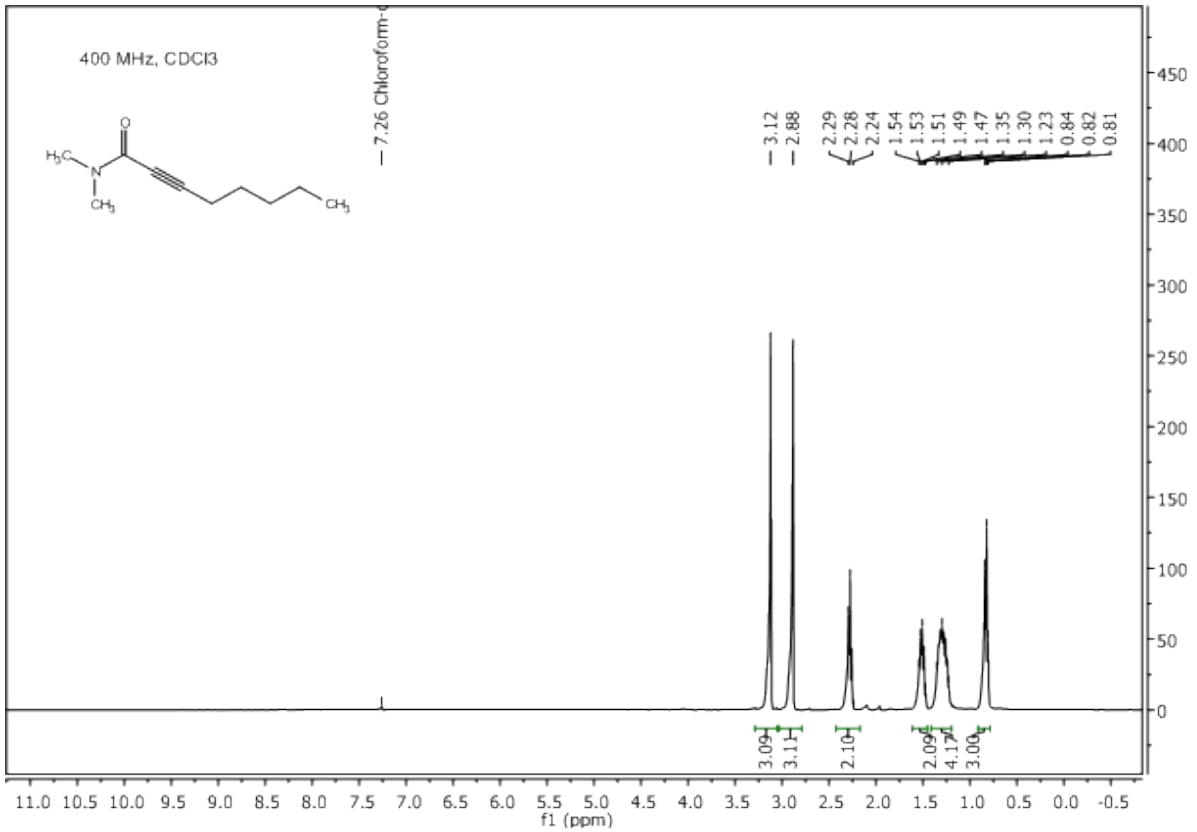


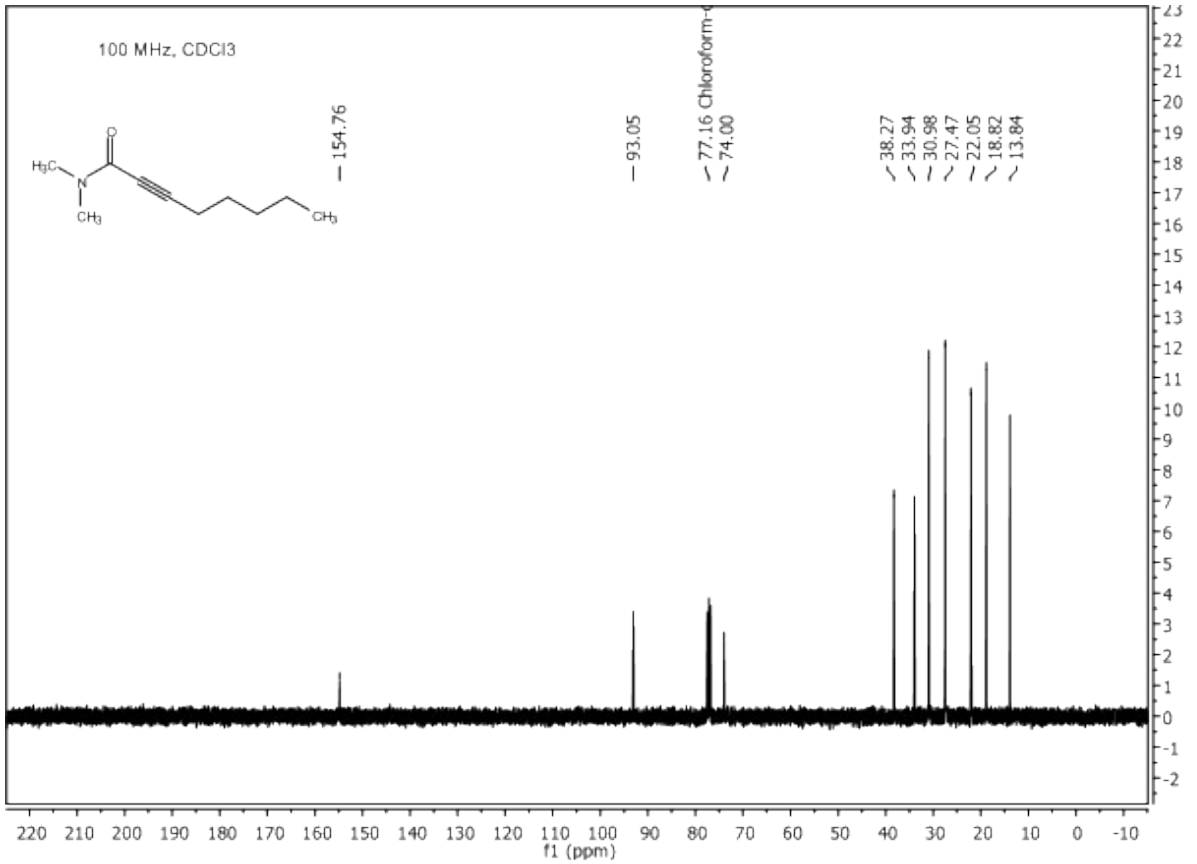
3-Bromo-1-*p*-tolylprop-2-yn-1-one (**4**)



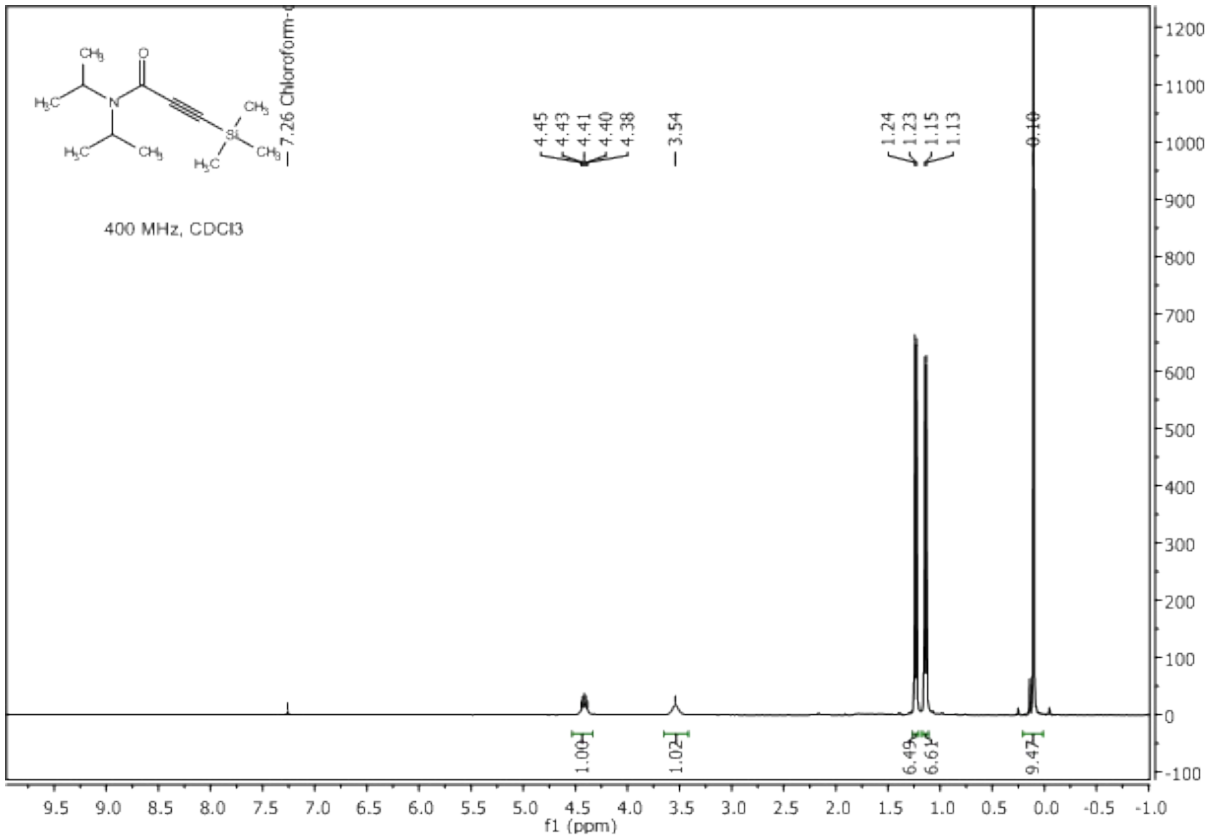


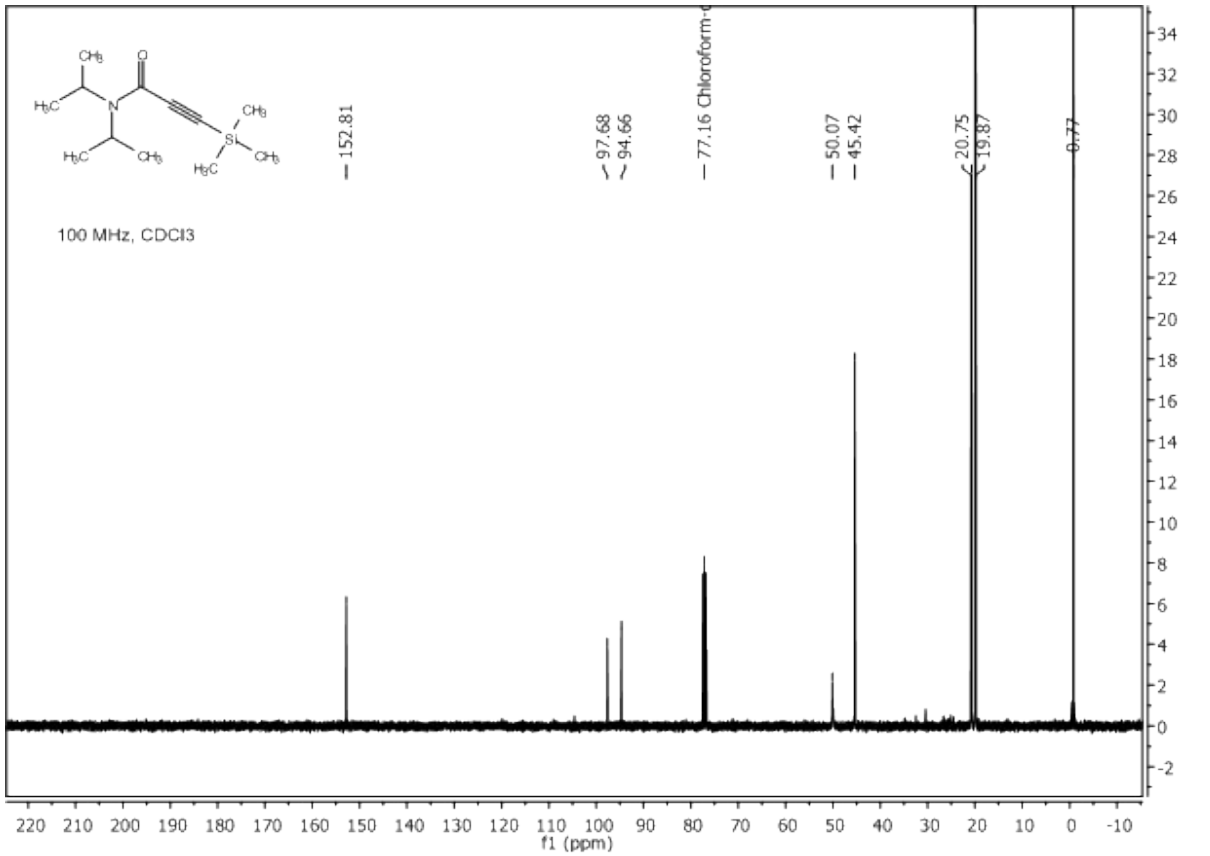
N,N-Dimethyloct-2-ynamide (**10**)



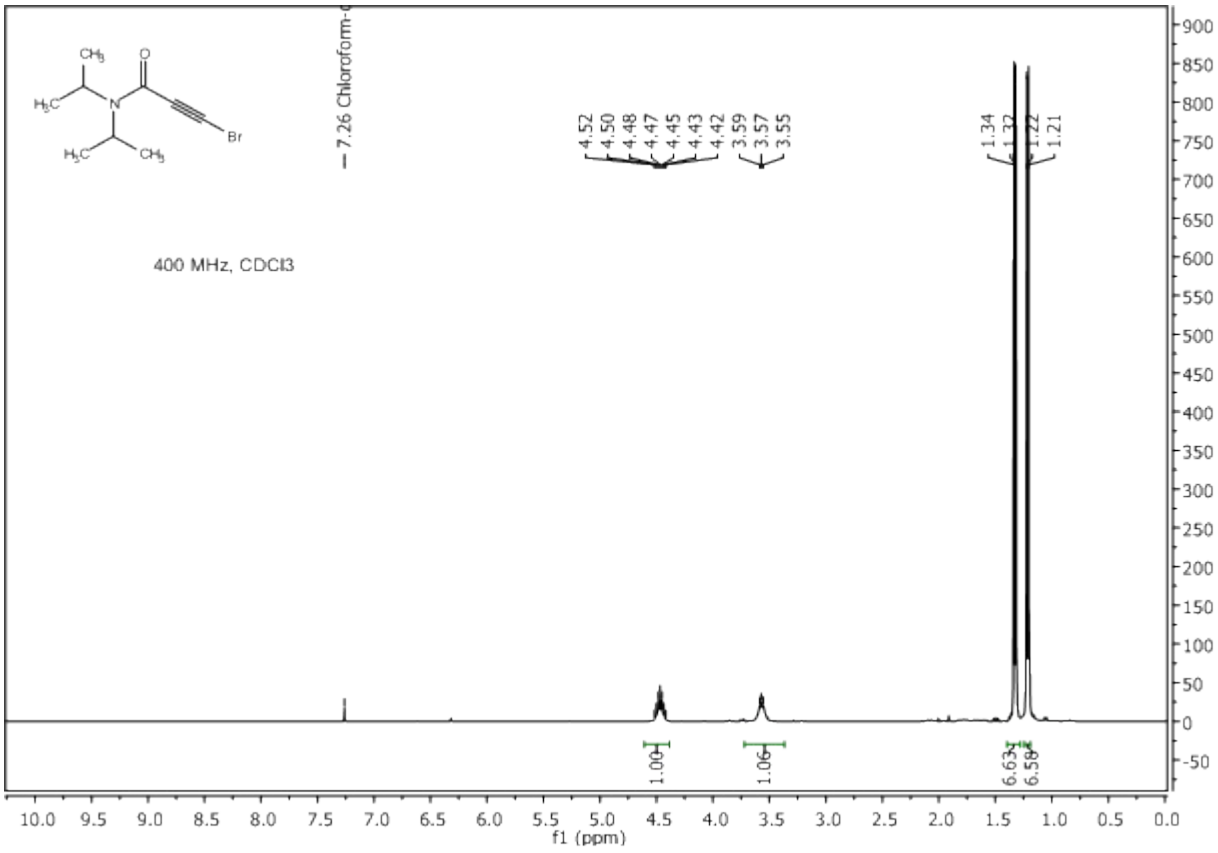


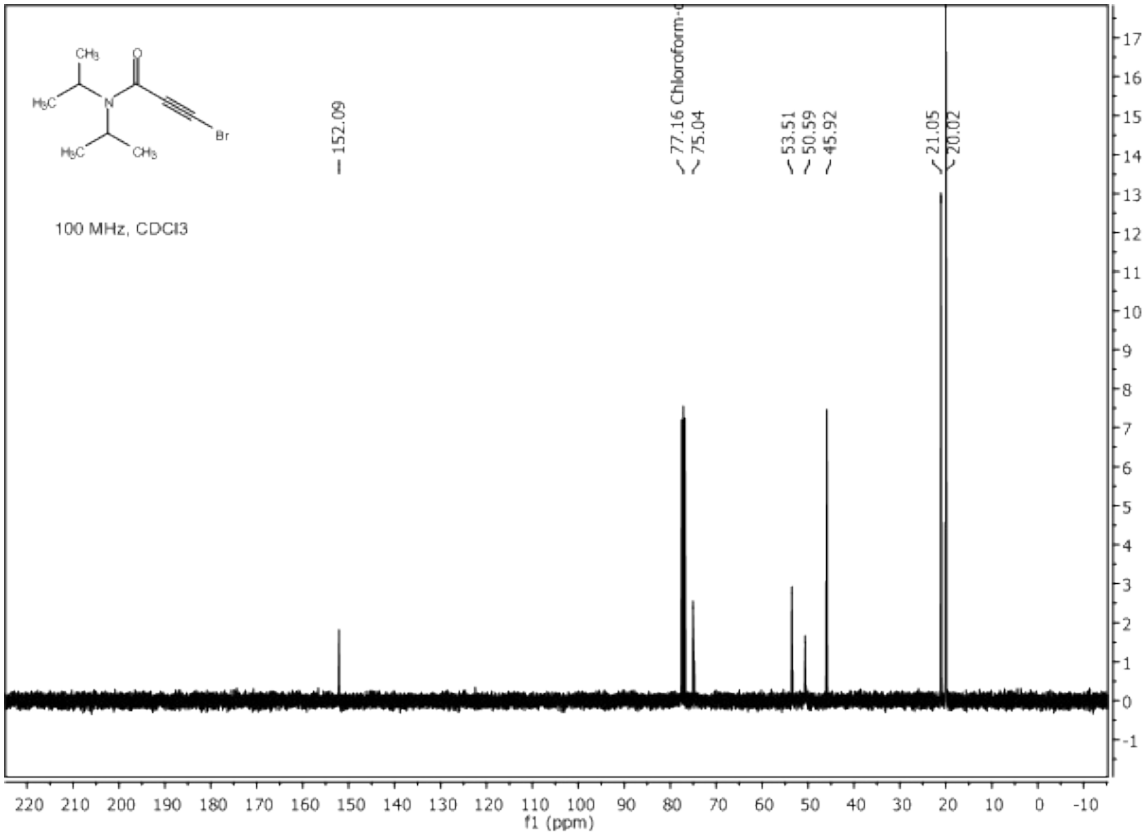
N,N-Diisopropyl-3-(trimethylsilyl)propiolamide (**si_3**)



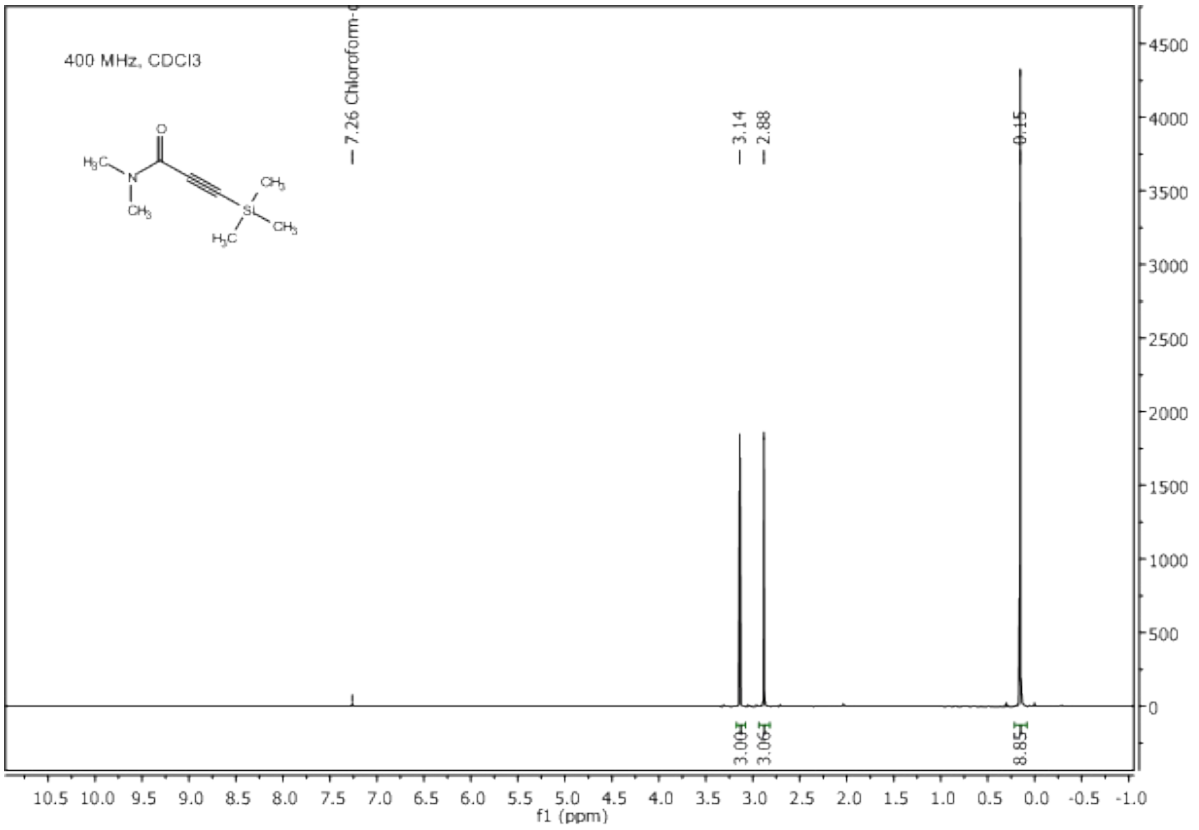


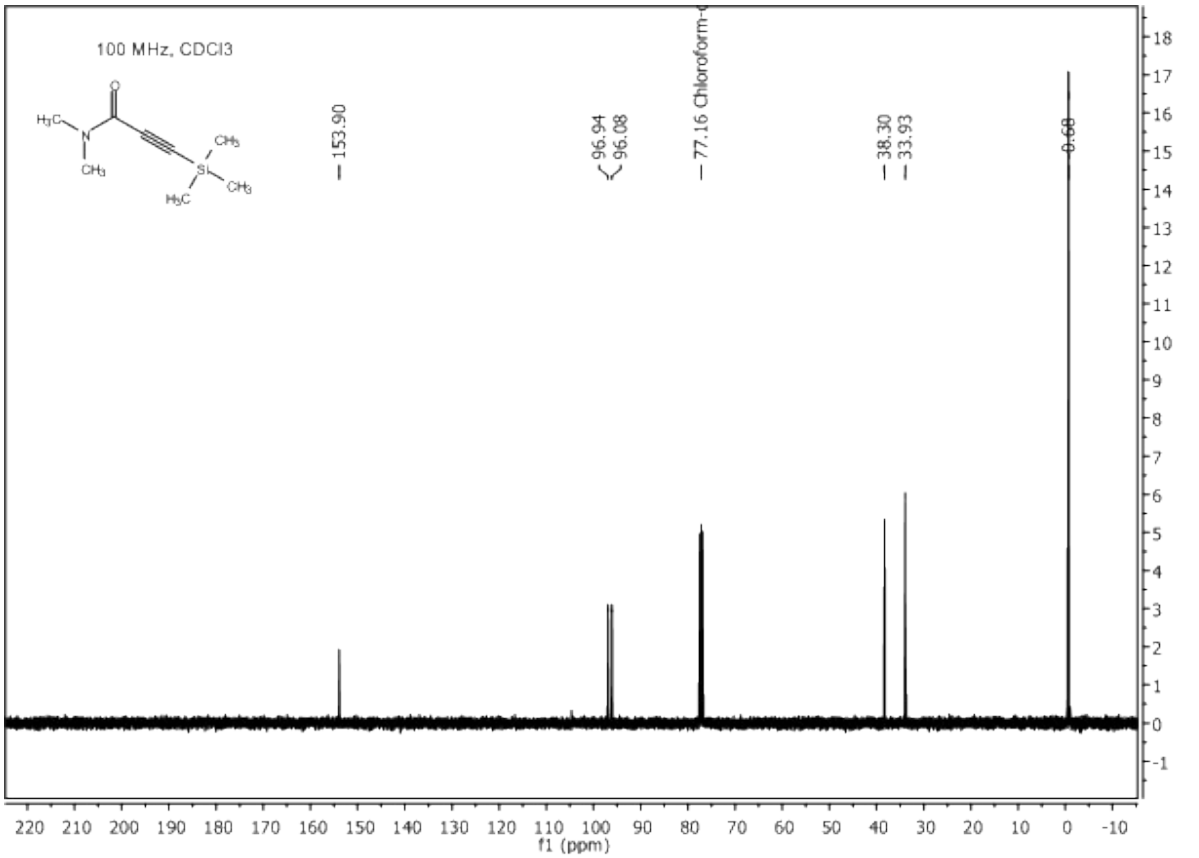
3-Bromo-N,N-diisopropiolamide (**si_4**)



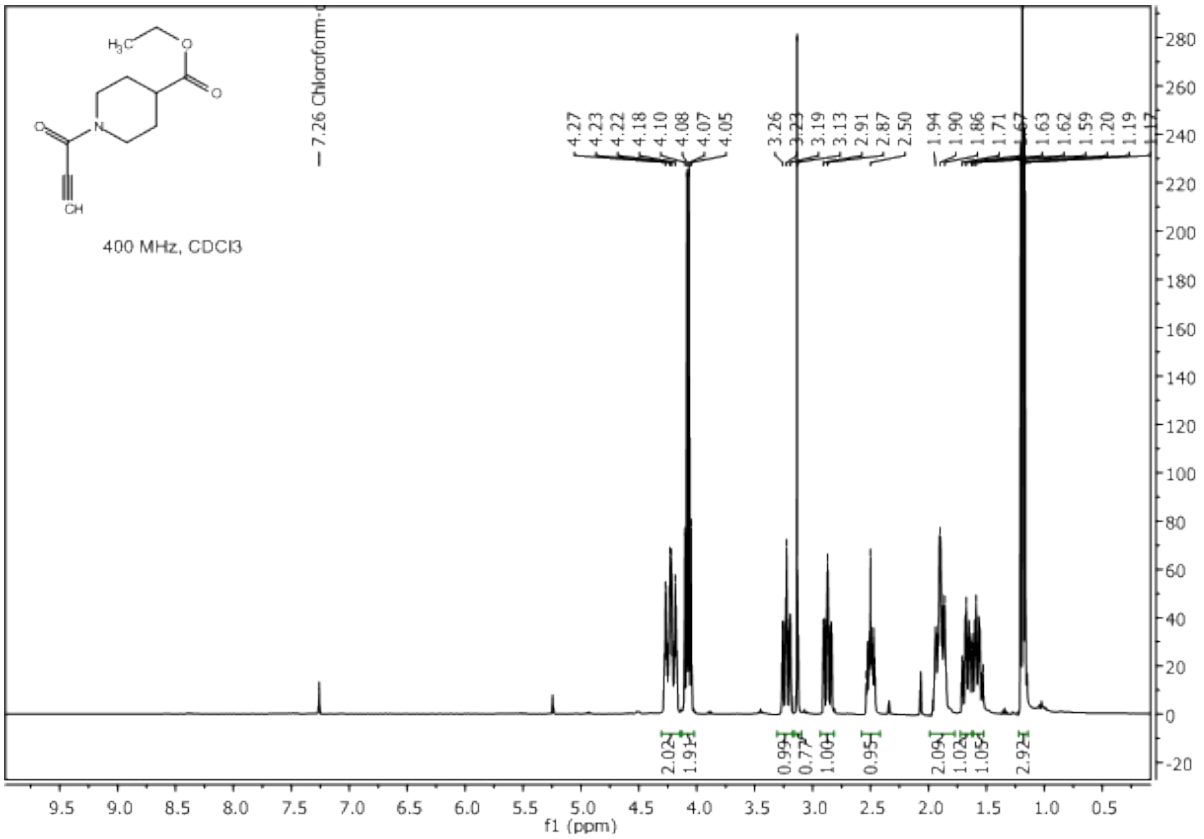


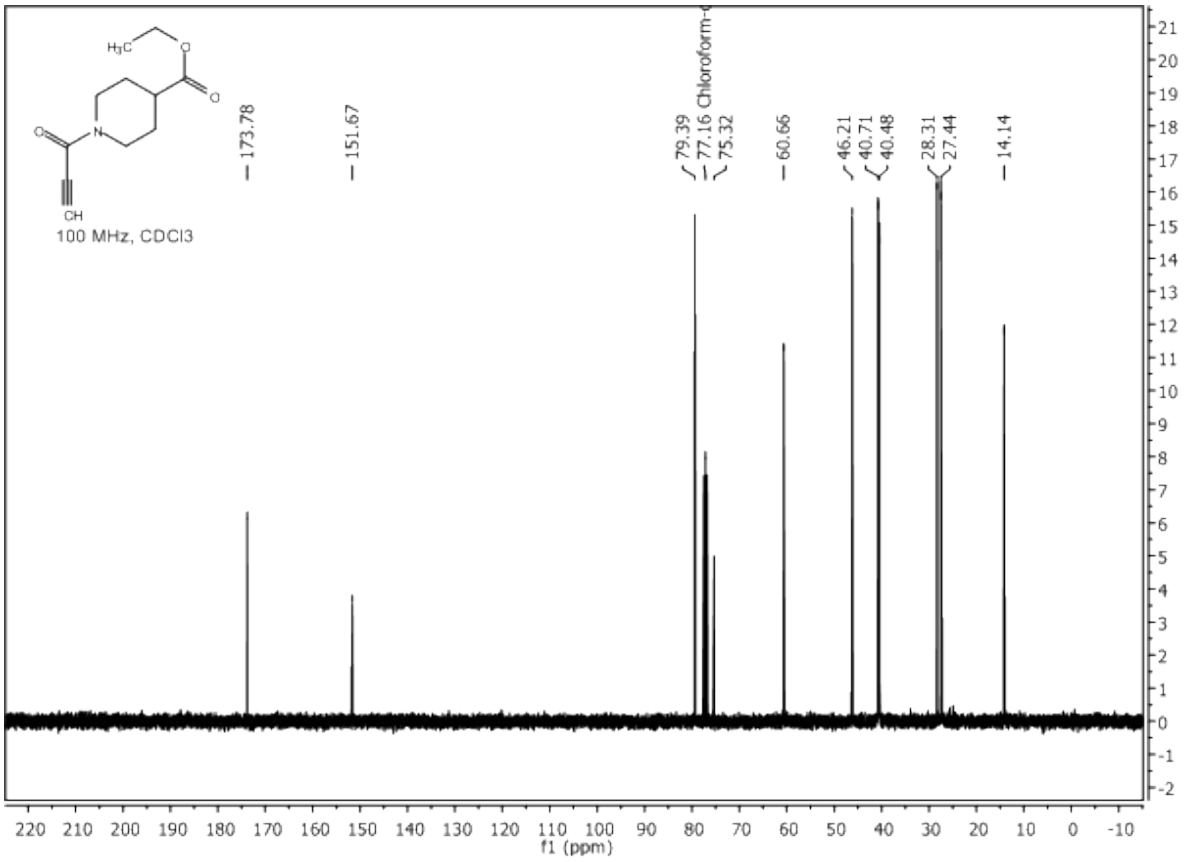
N,N-Dimethyl-3-(trimethylsilyl)propiolamide (**9**)



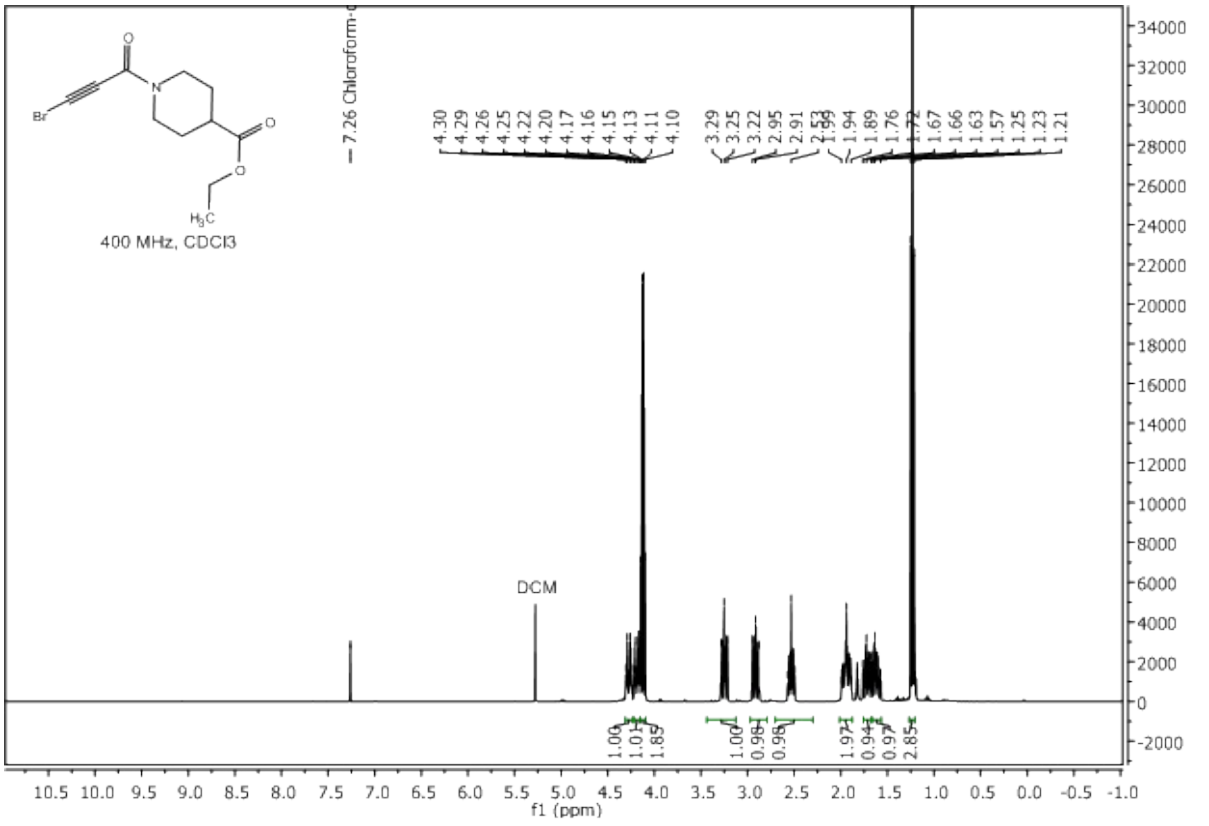


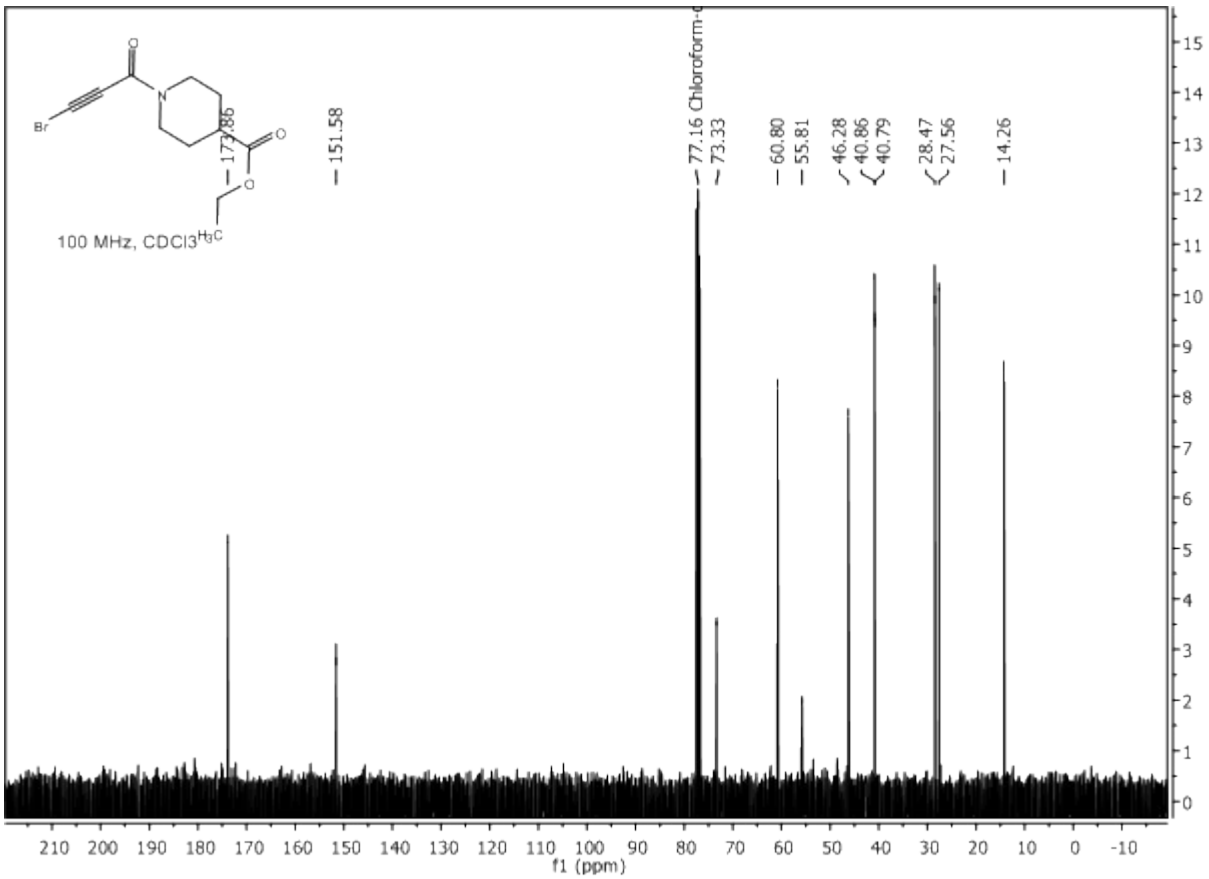
Ethyl 1-propioloylpiperidine-4-carboxylate (**si_5**)



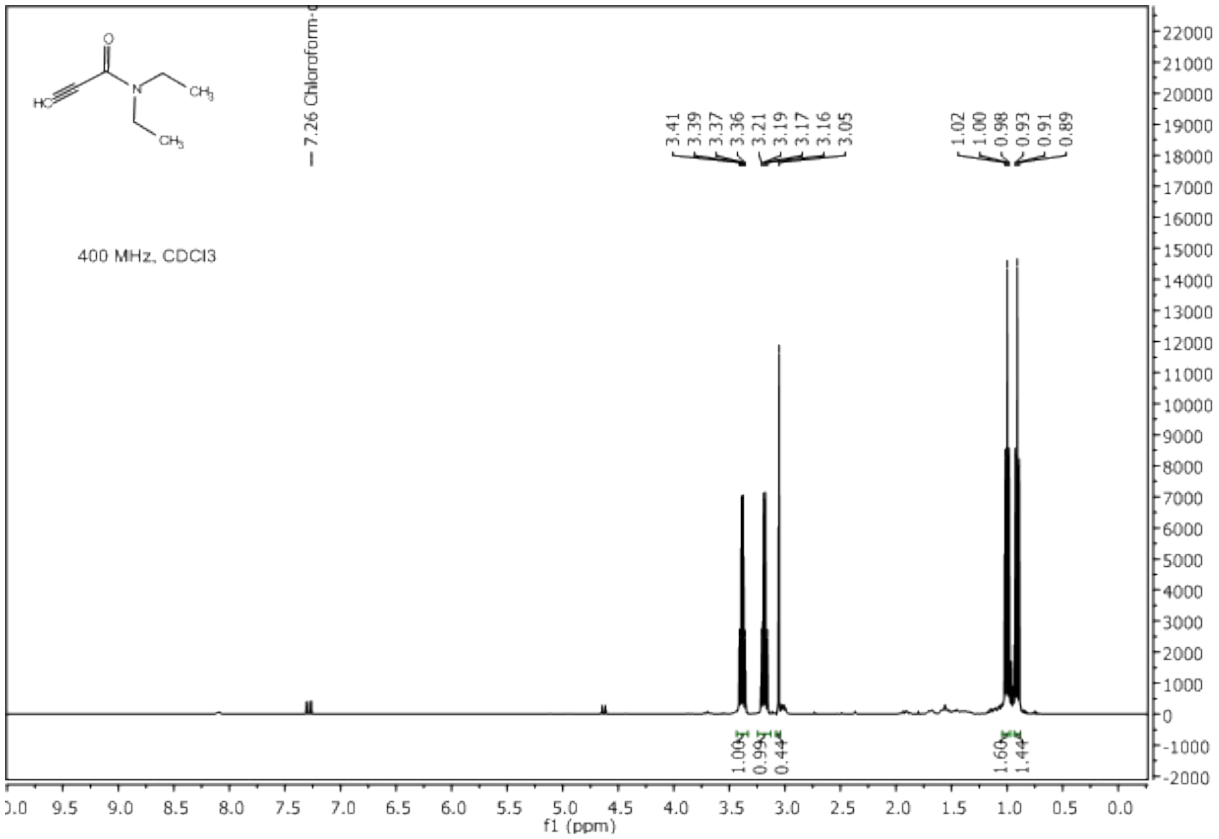


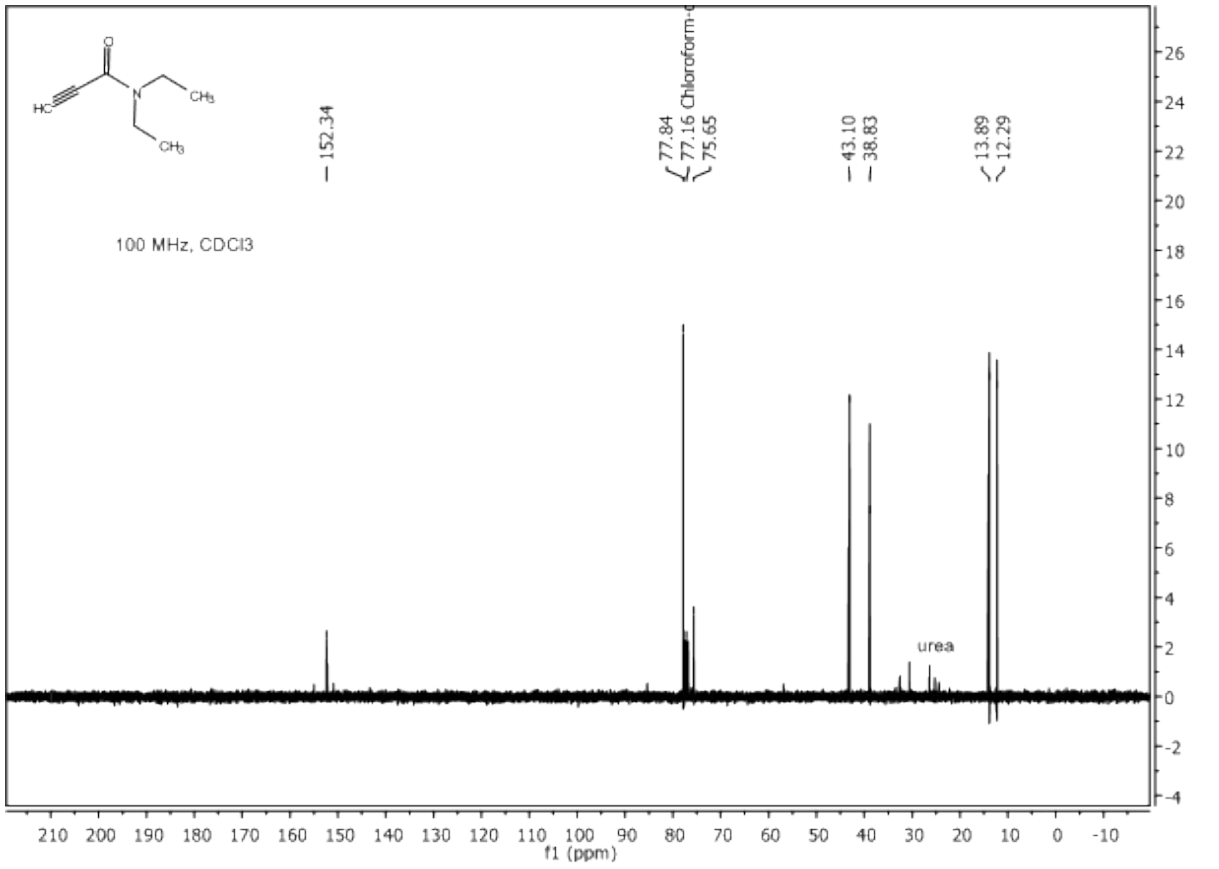
Ethyl 1-(3-bromopropioloyl)piperidine-4-carboxylate (**si_6**)



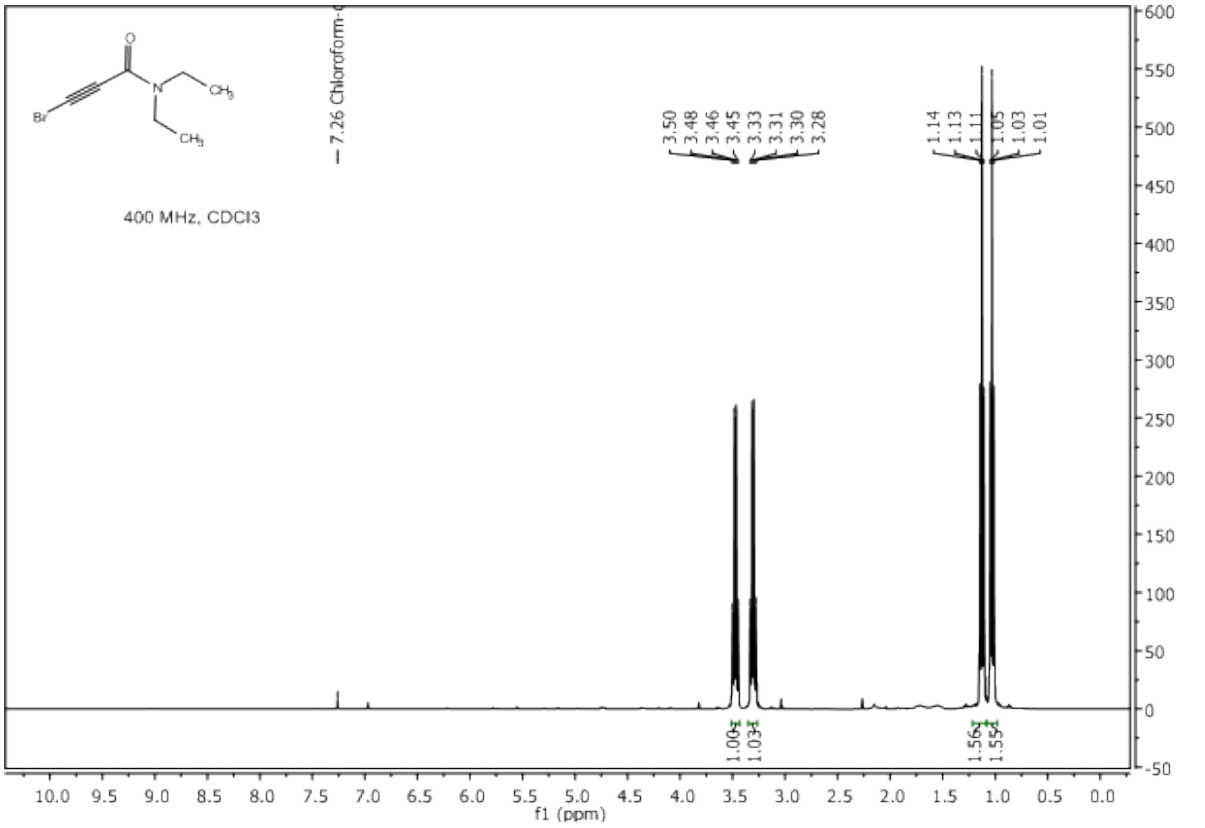


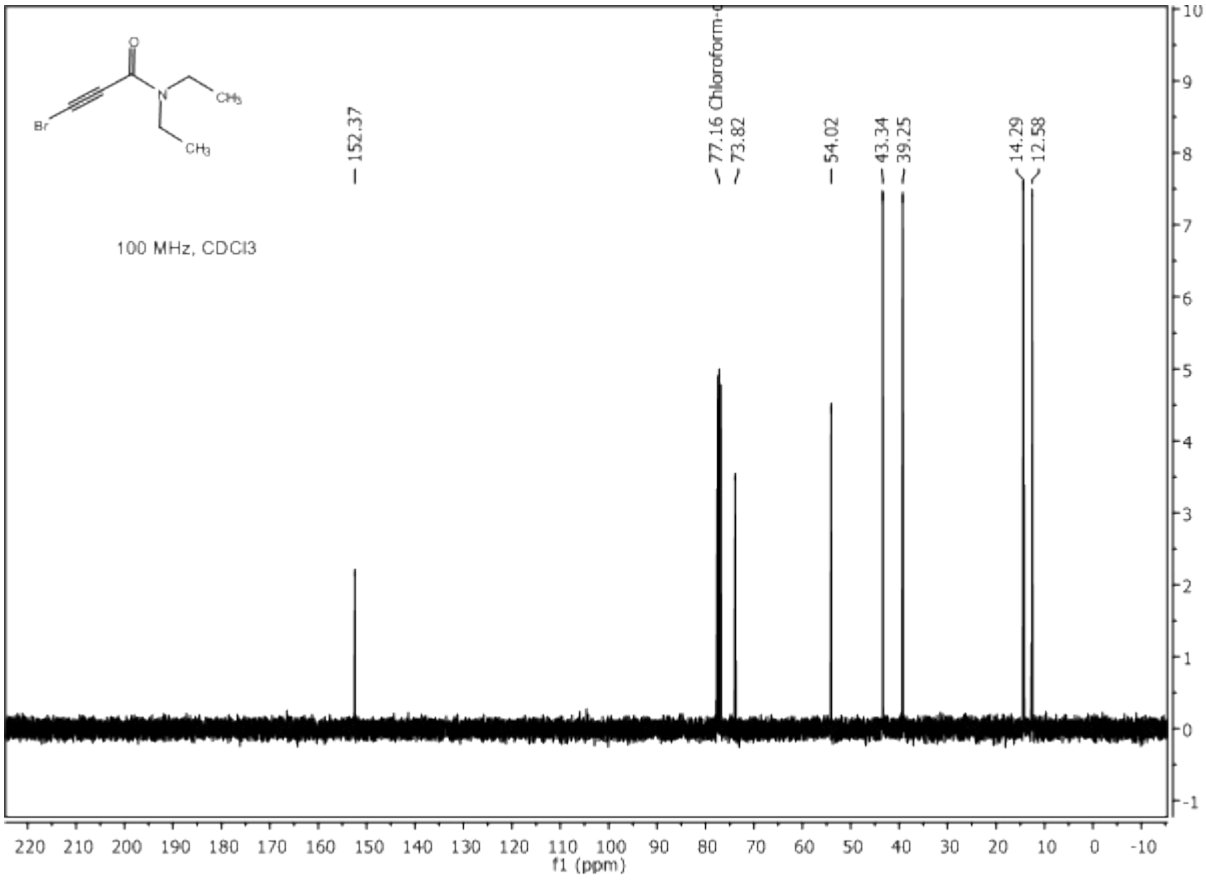
N,N-Diethylpropiolamide (**si_7**)



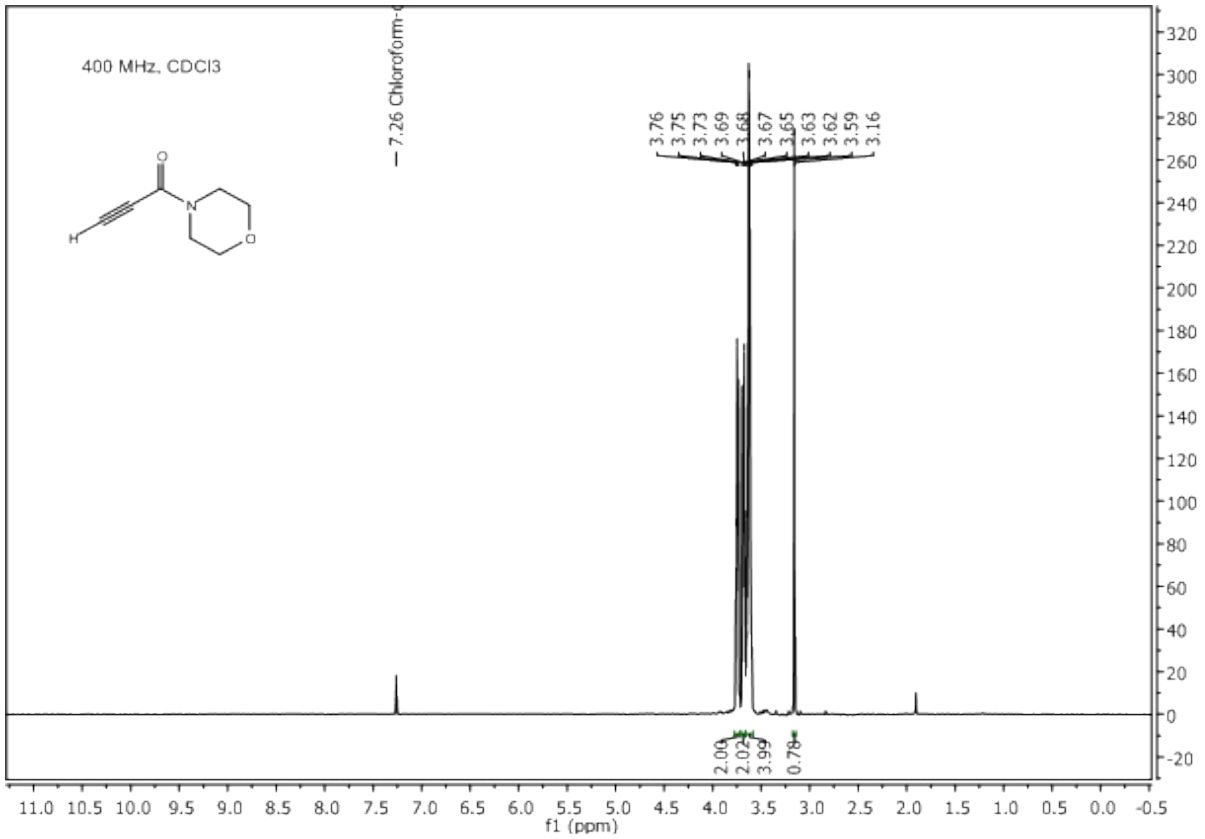


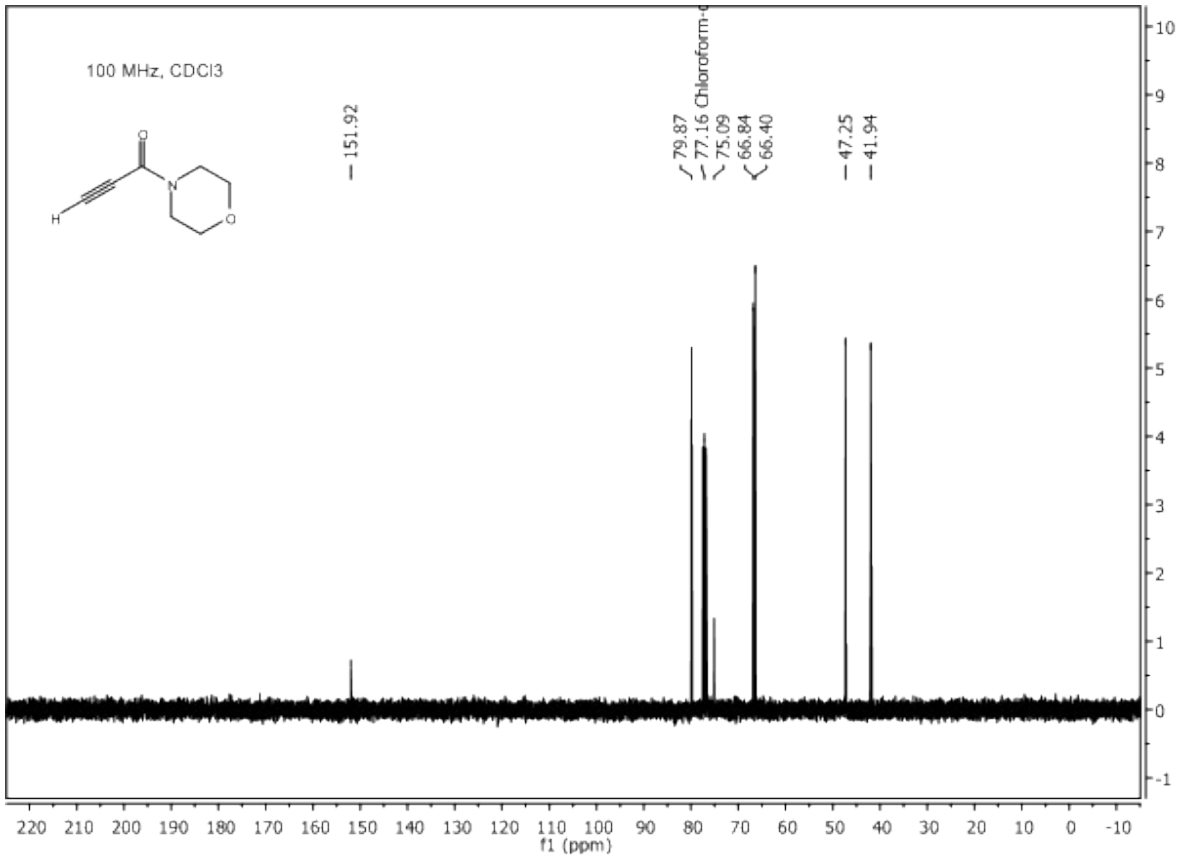
3-Bromo-*N,N*-diethylpropiolamiden (**si_8**)



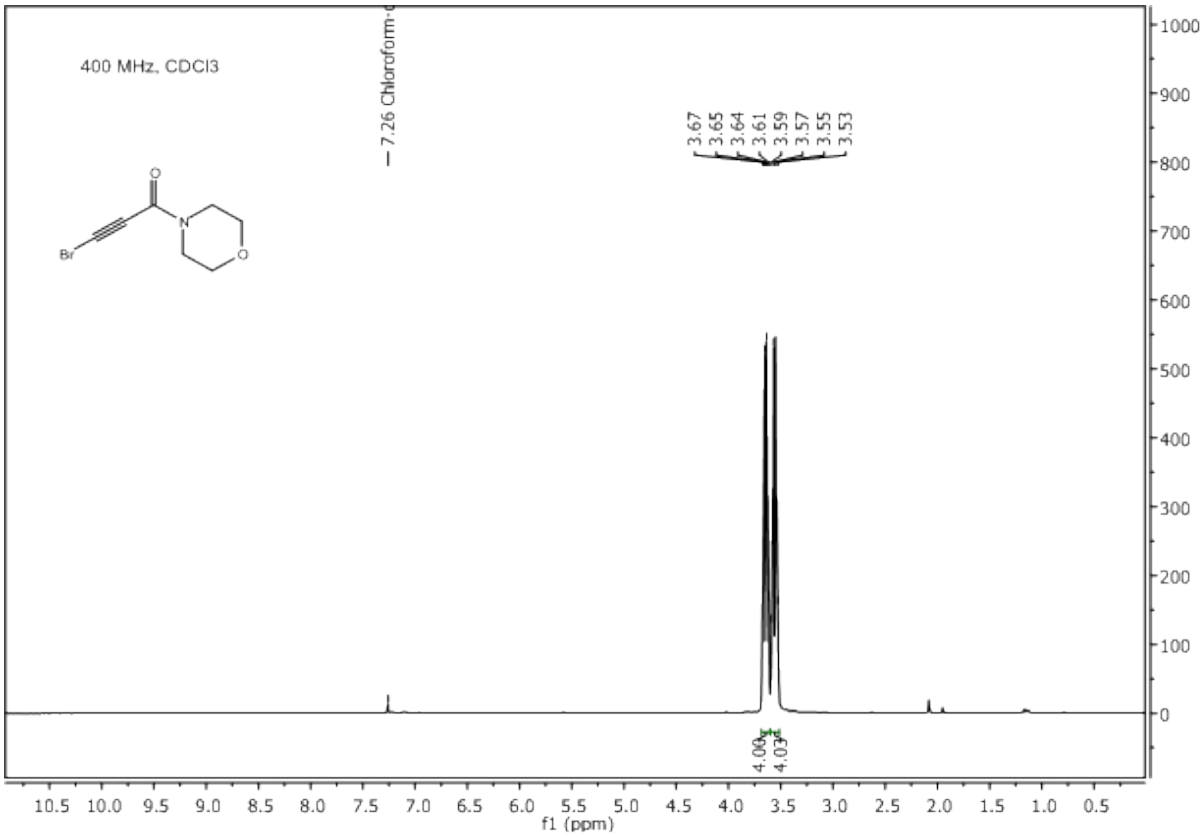


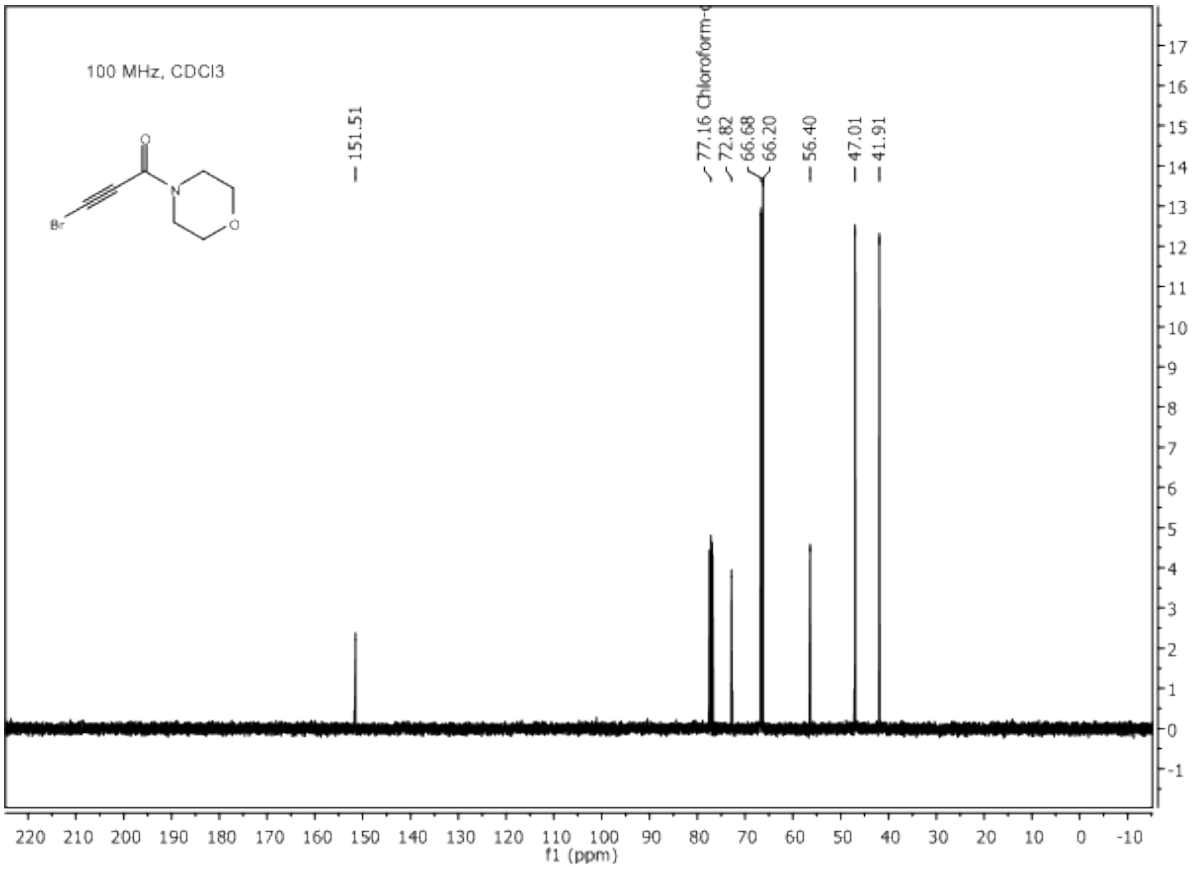
1-Morpholinoprop-2-yn-1-one (**si_9**)



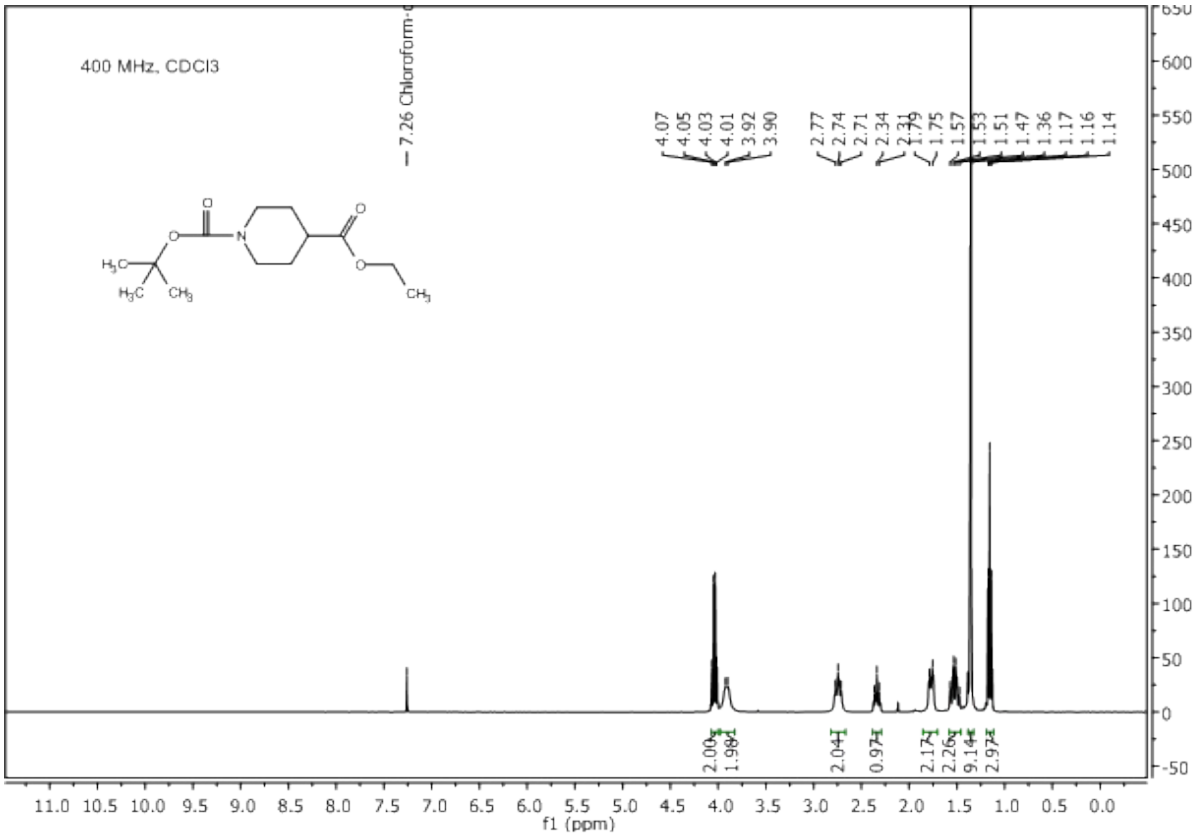


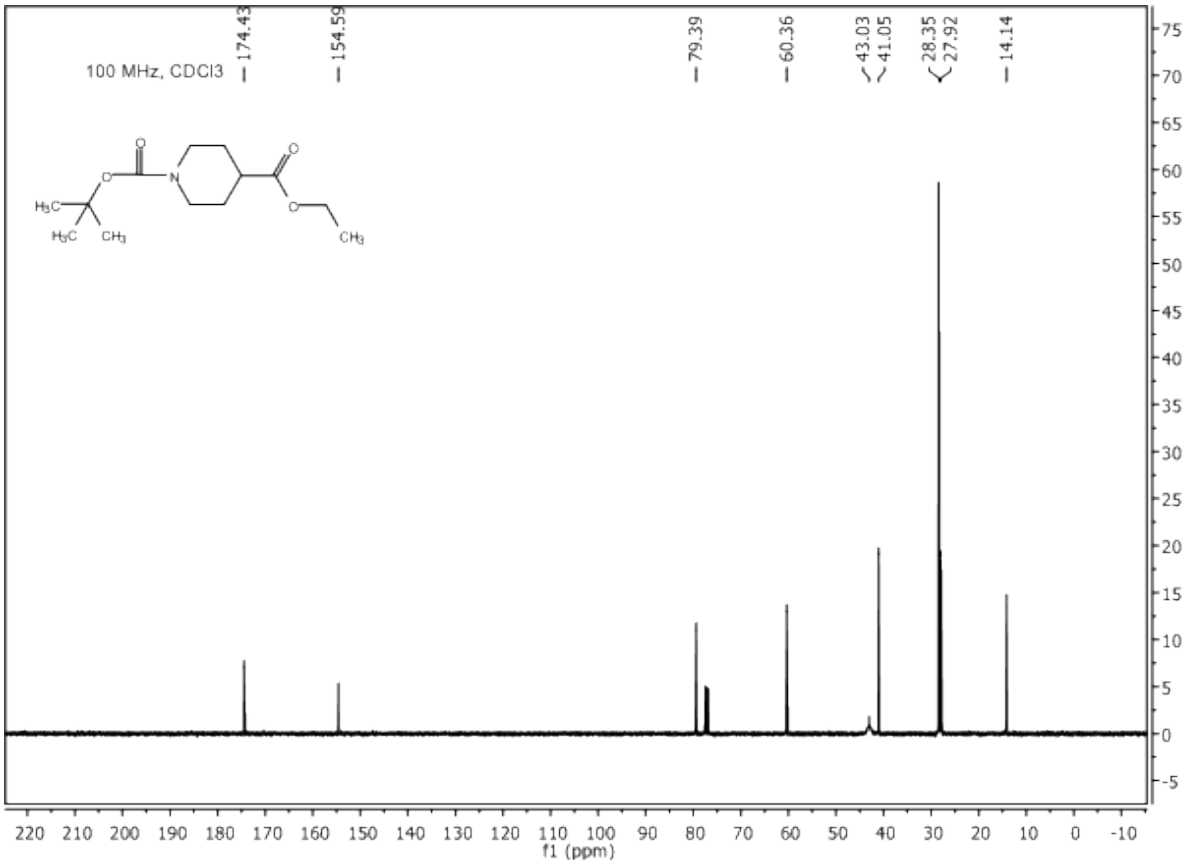
3-Bromo-1-morpholinoprop-2-yn-1-one (**si_10**)



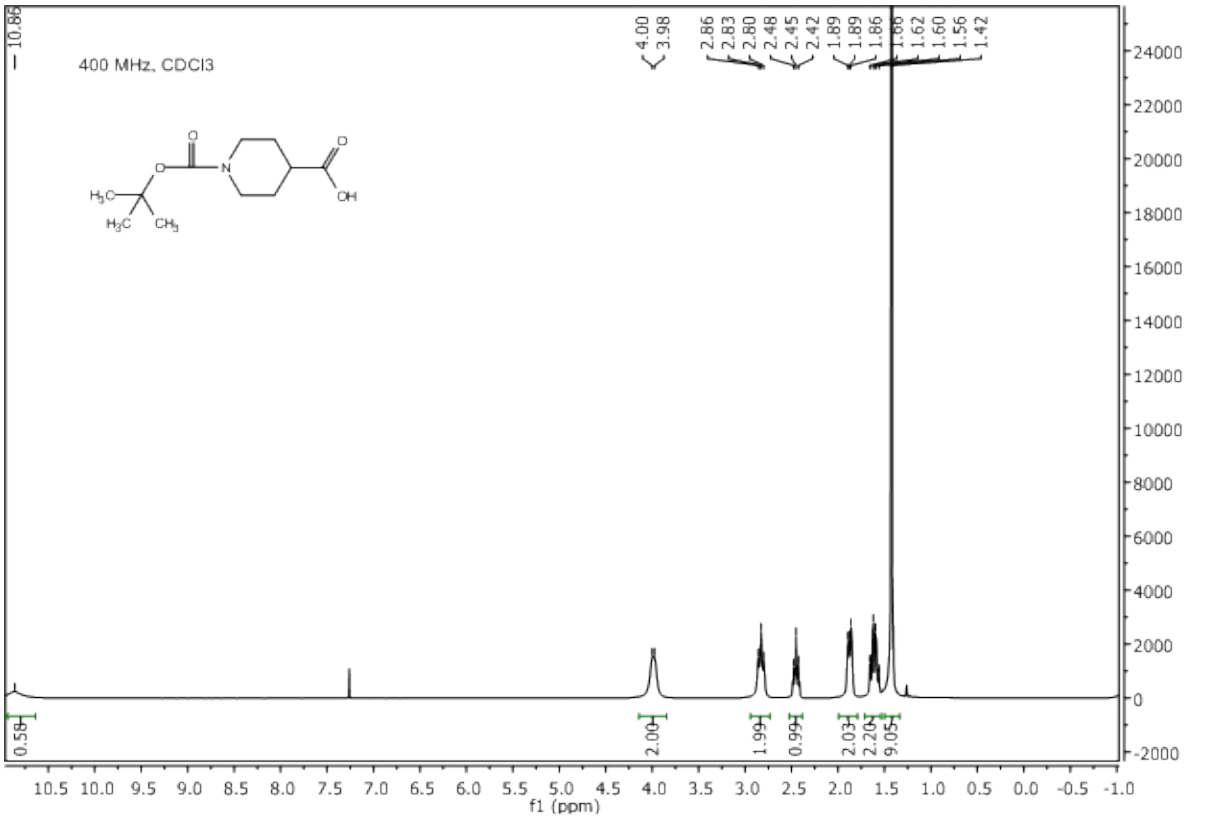


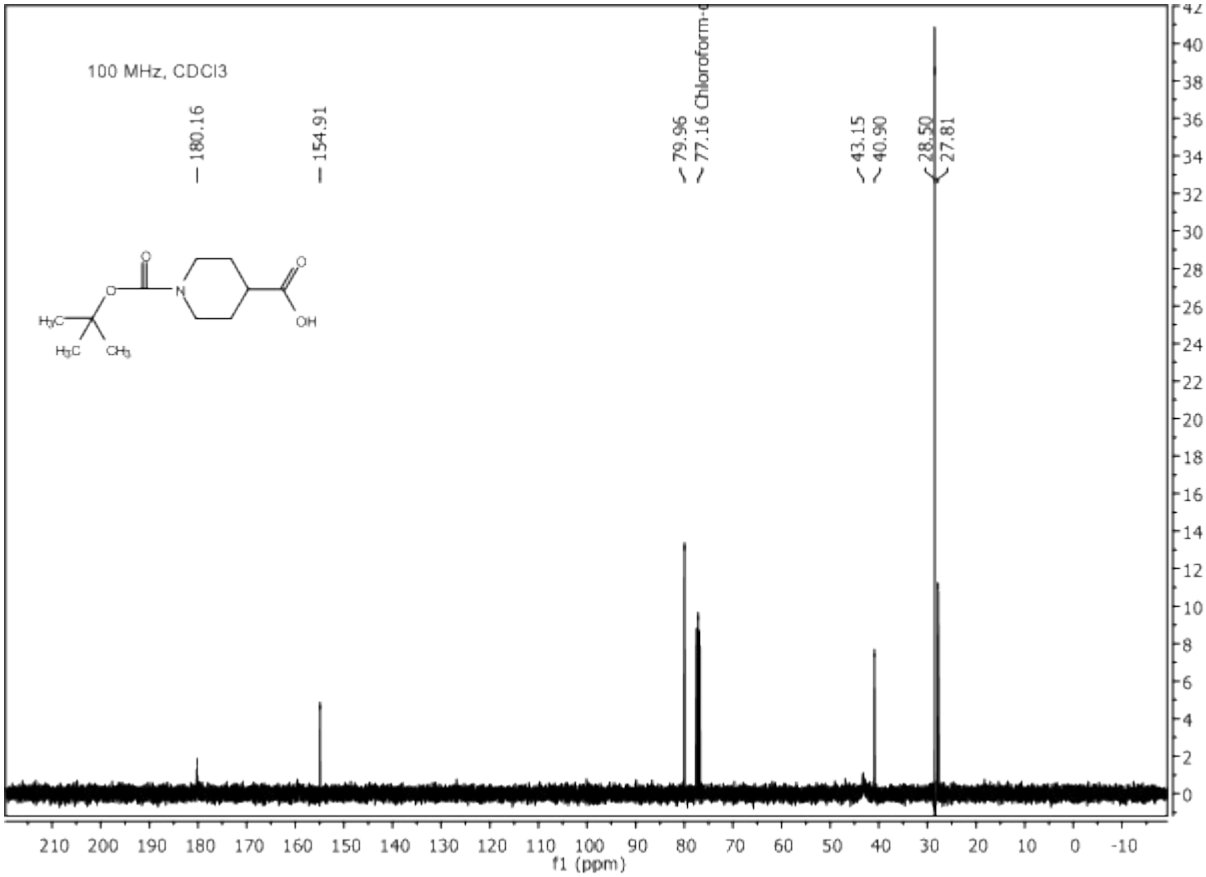
1-*tert*-Butyl 4-ethyl piperidine-1,4-dicarboxylate (**si_11**)



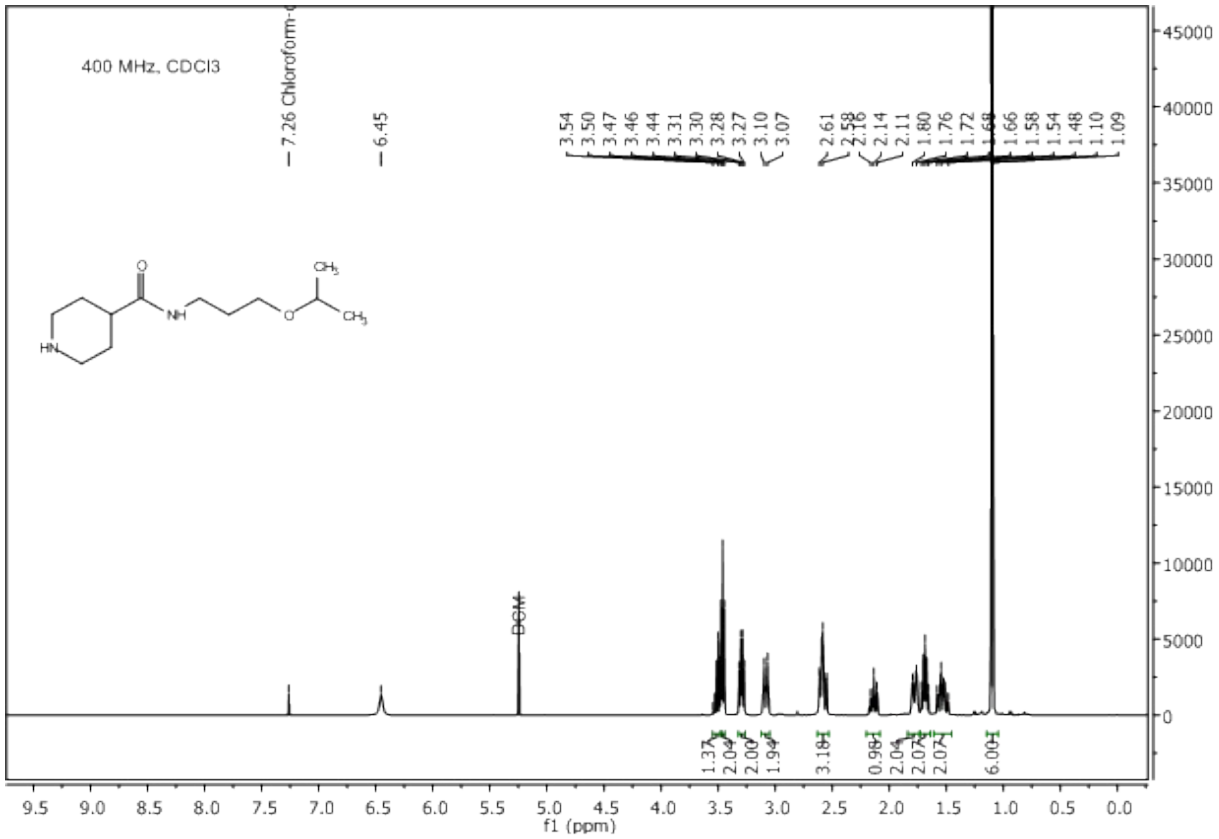


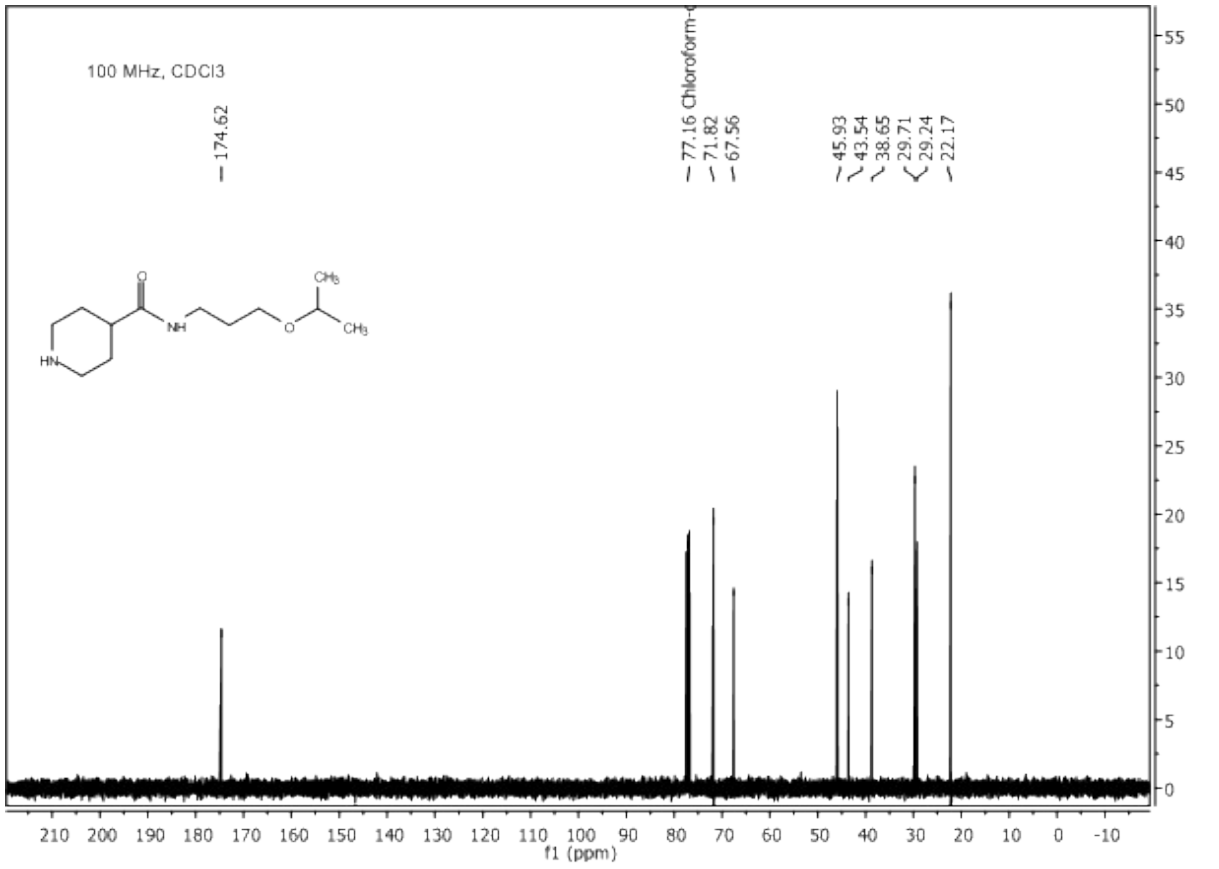
1-(*tert*-Butoxycarbonyl)piperidine-4-carboxylic acid (**si_12**)



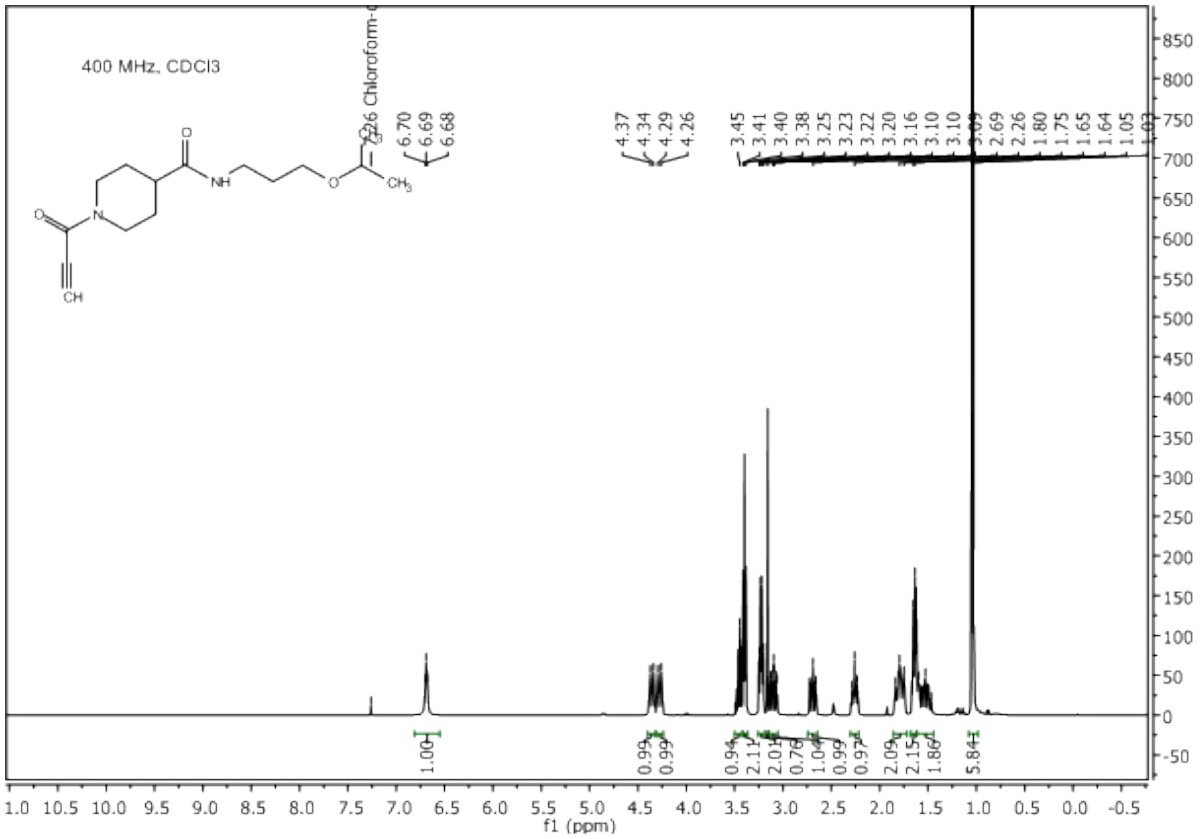


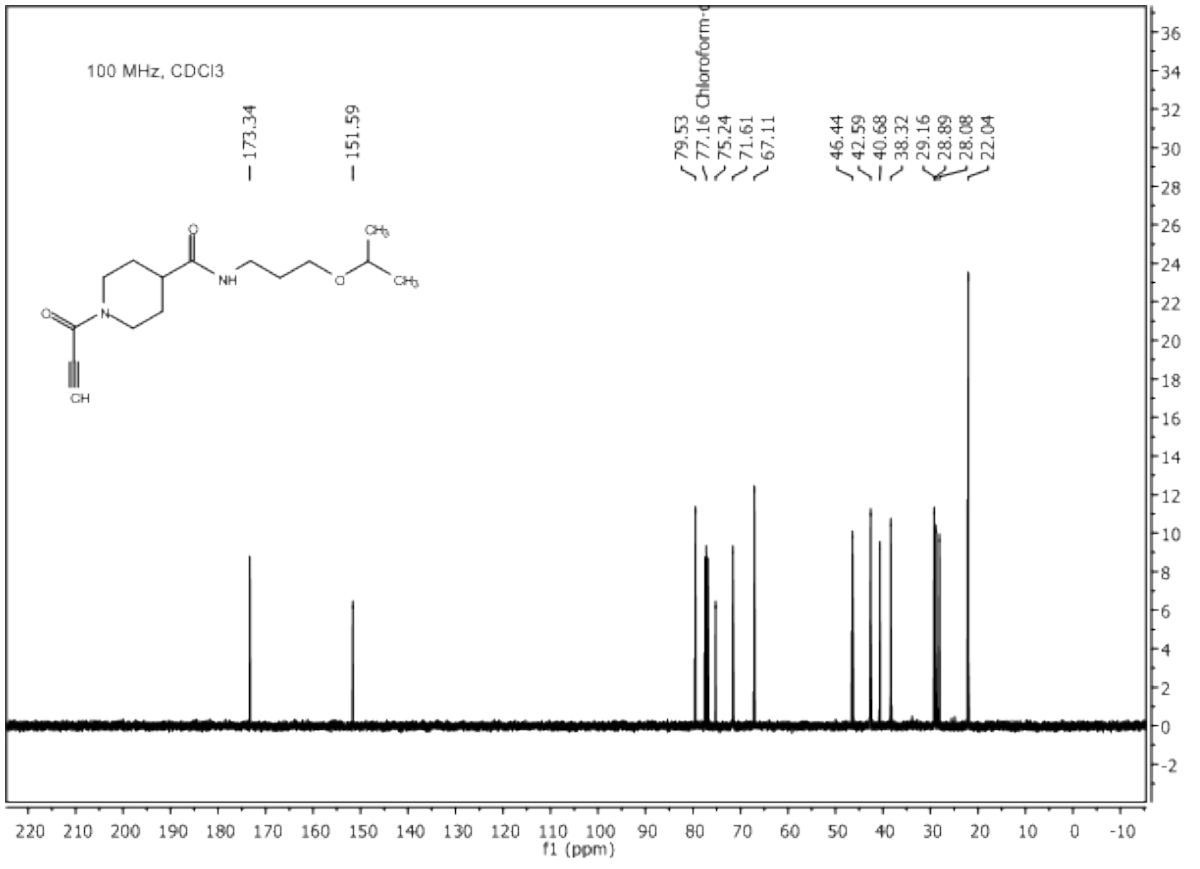
N-(3-Isopropoxypropyl)piperidine-4-carboxamide (**si_13**)



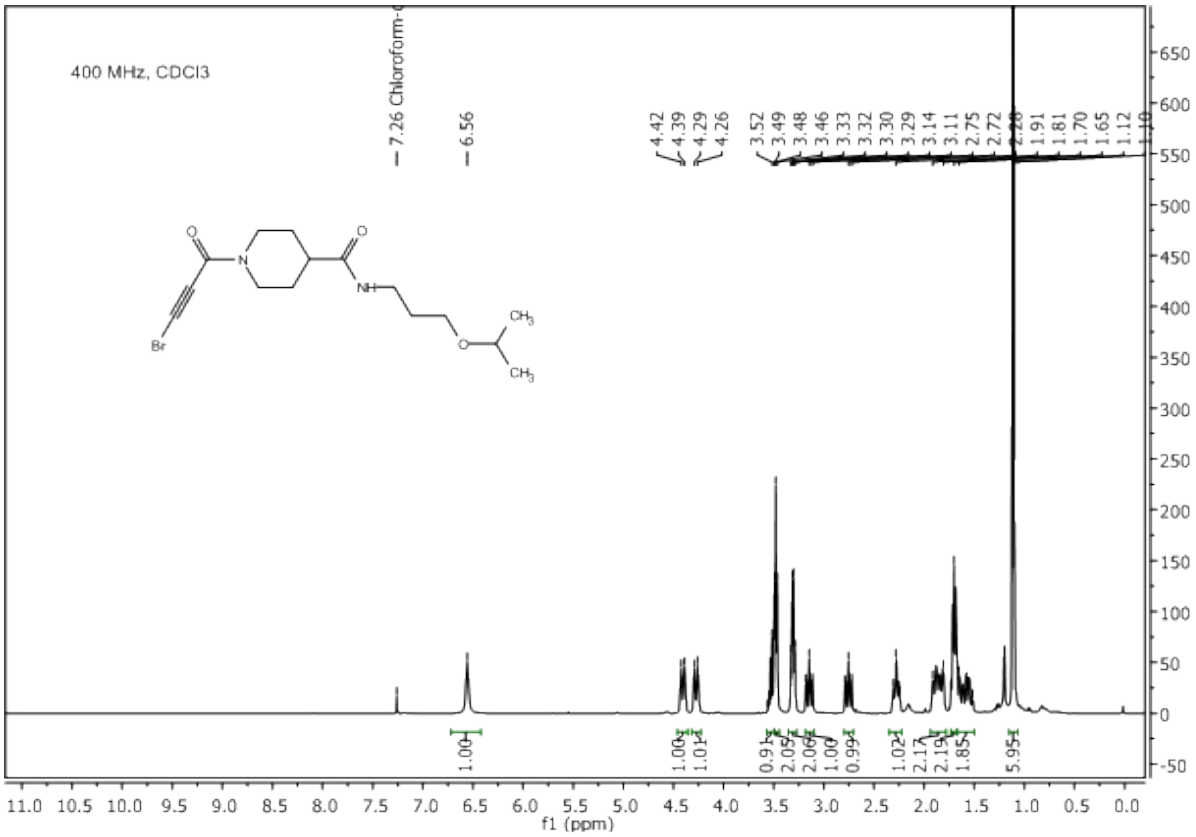


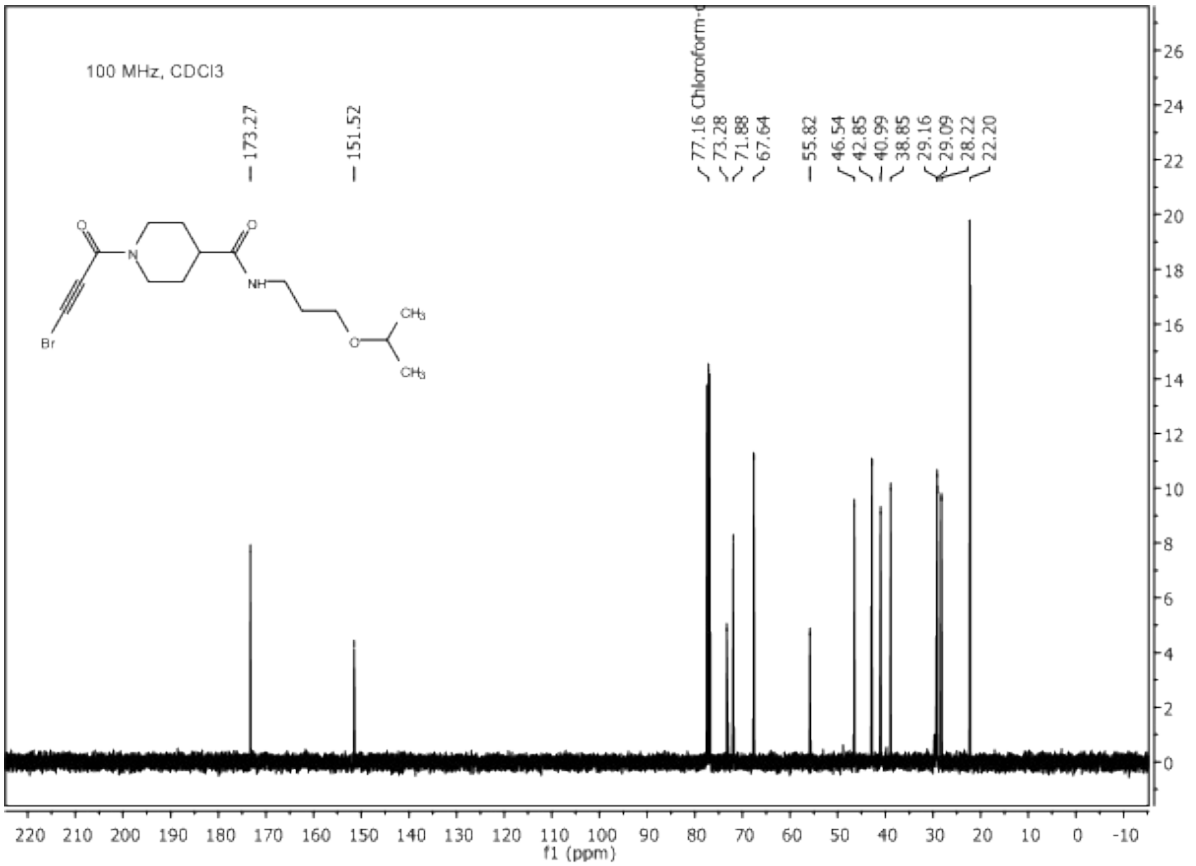
N-(3-isopropoxypropyl)-1-propioloylpiperidine-4-carboxamide (**si_14**)



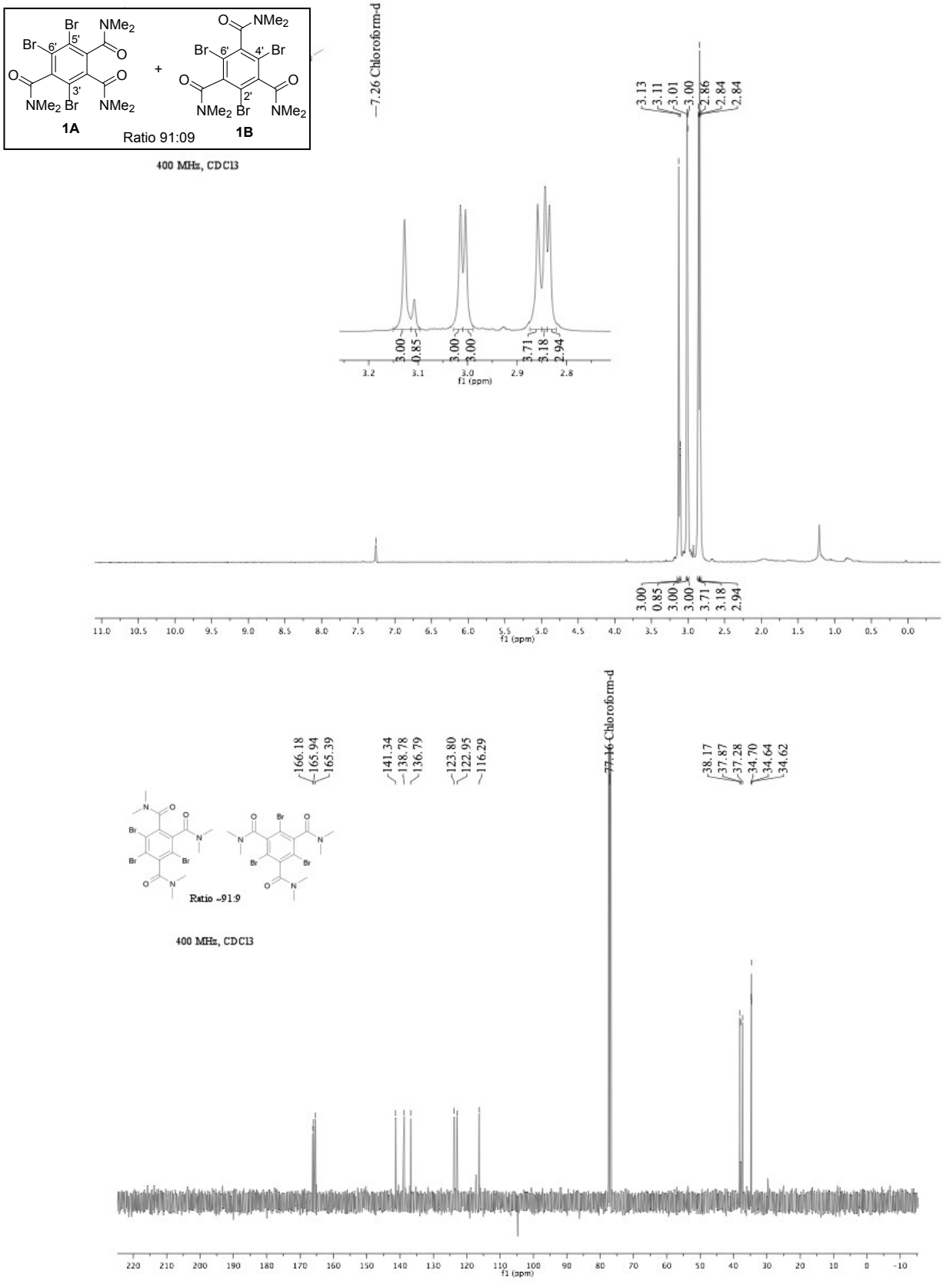


1-(3-Bromopropioloyl)-*N*-(3-isopropxypropyl)piperidine-4-carboxamide (**si_15**)

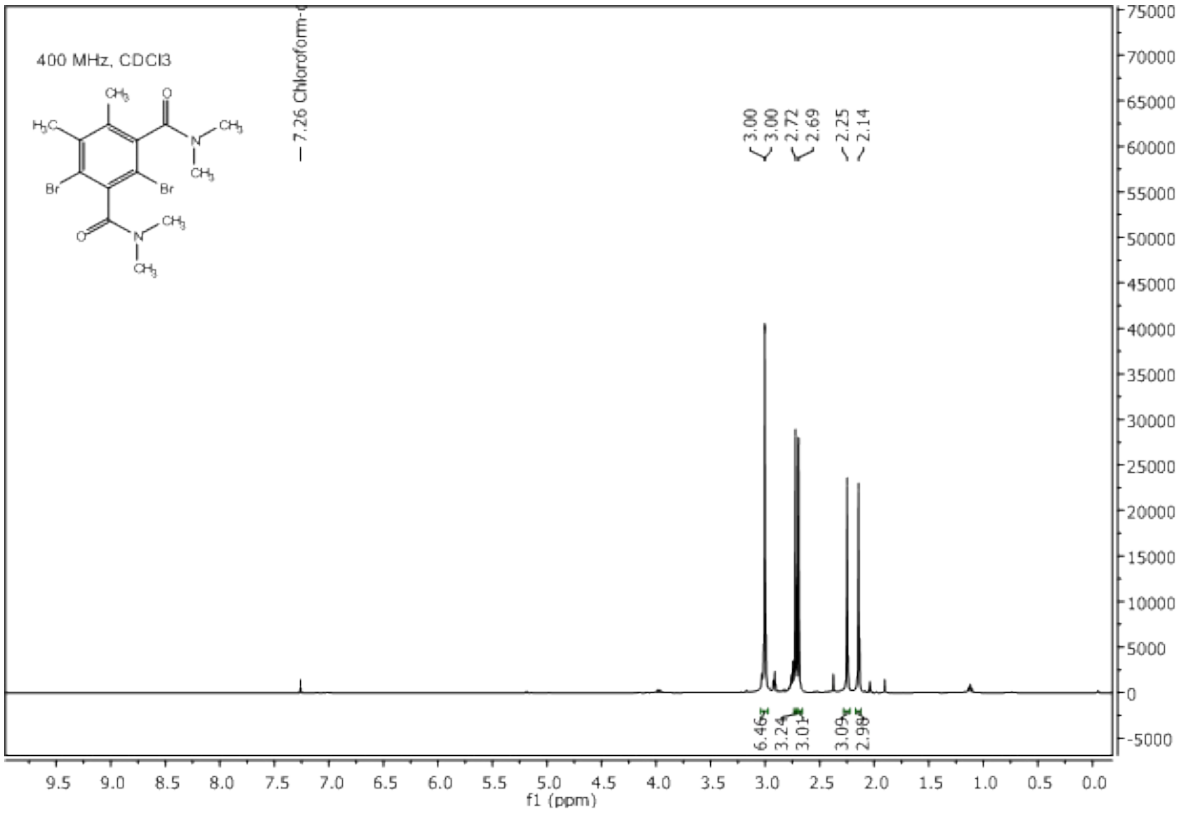


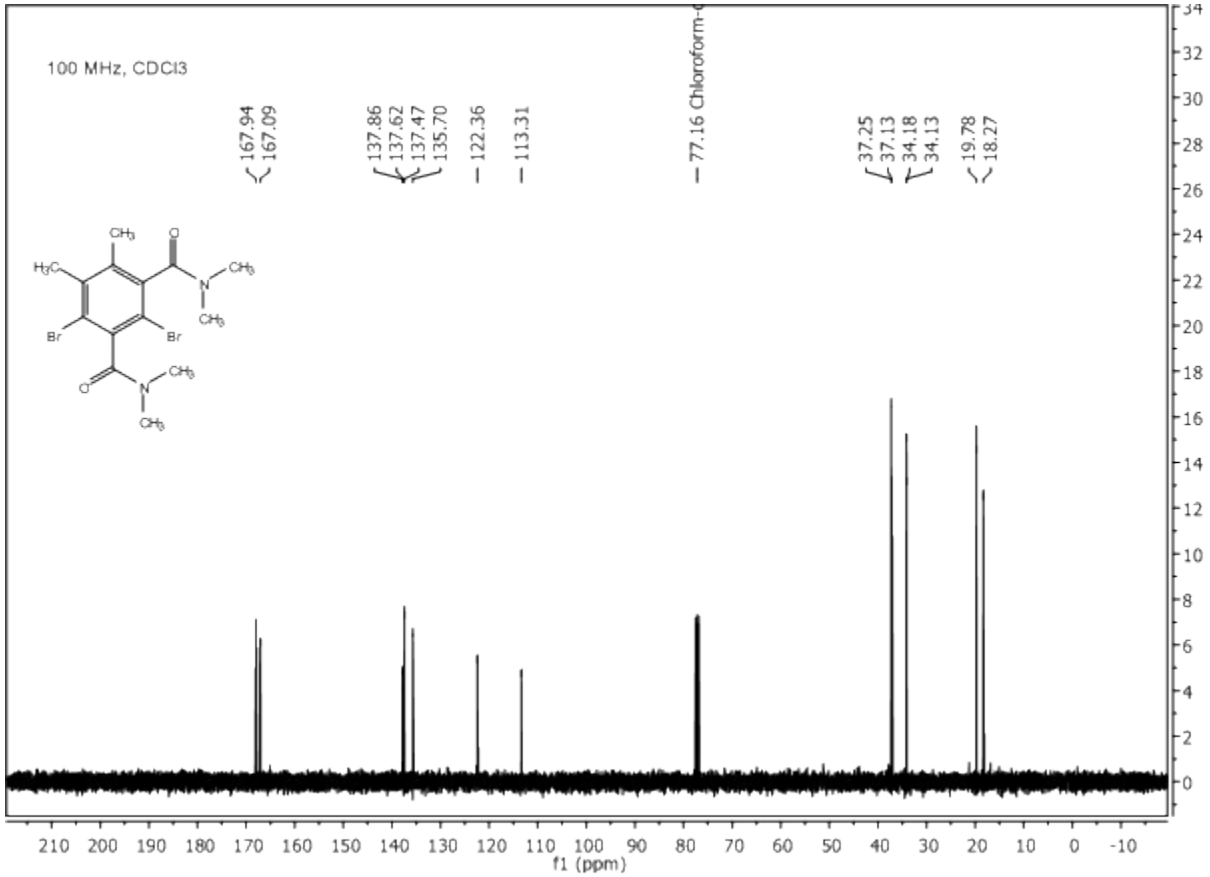


3,5,6-Tibromo-hexamethylbenzene-1,2,4-tricarboxamide (**1A/B**)

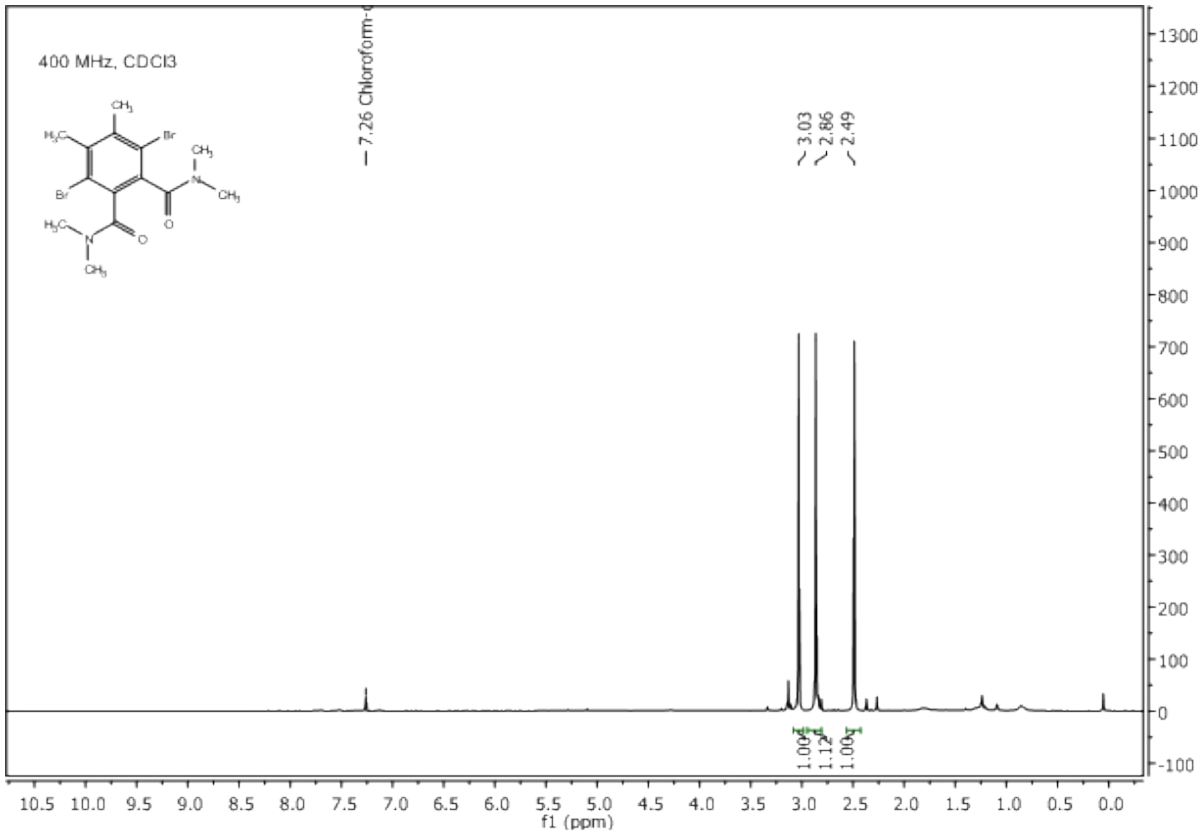


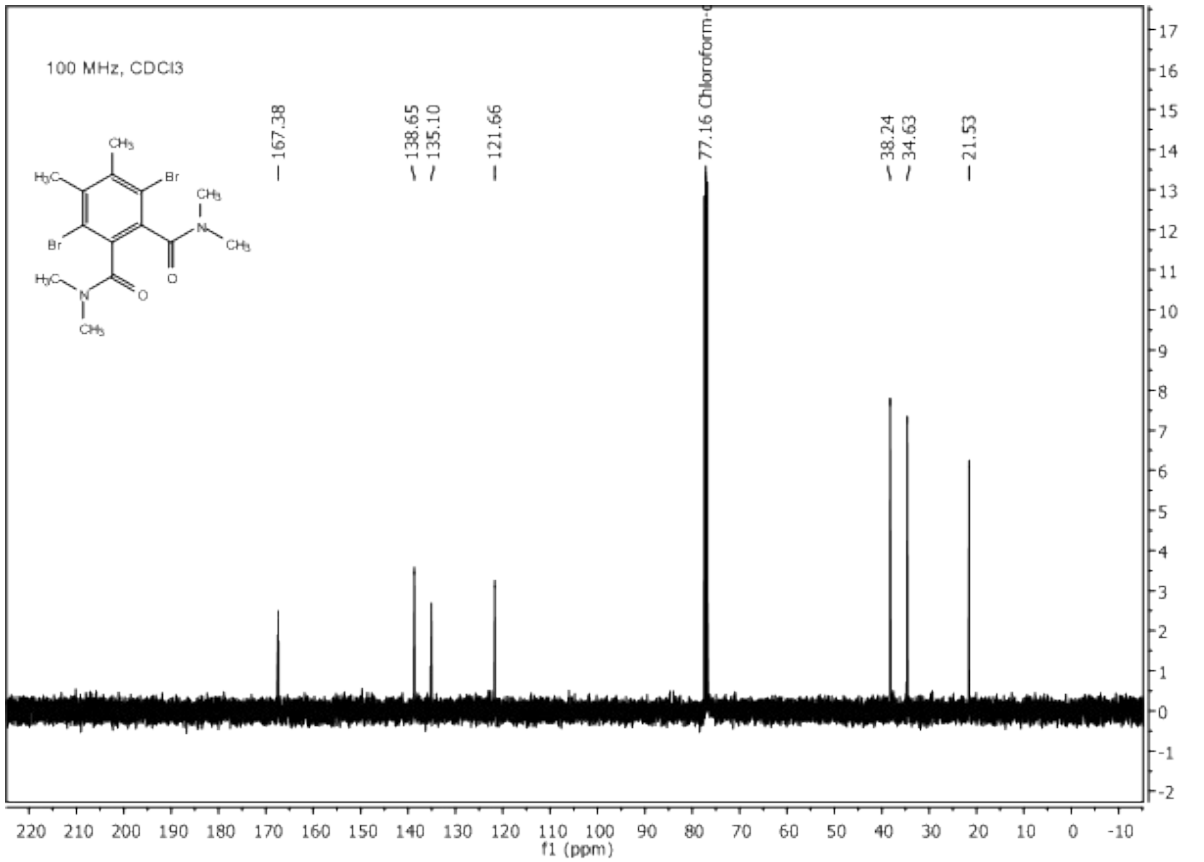
2,4-Dibromo-*N,N,N,N*-5,6-hexamethylisophthalamide (**1C**)



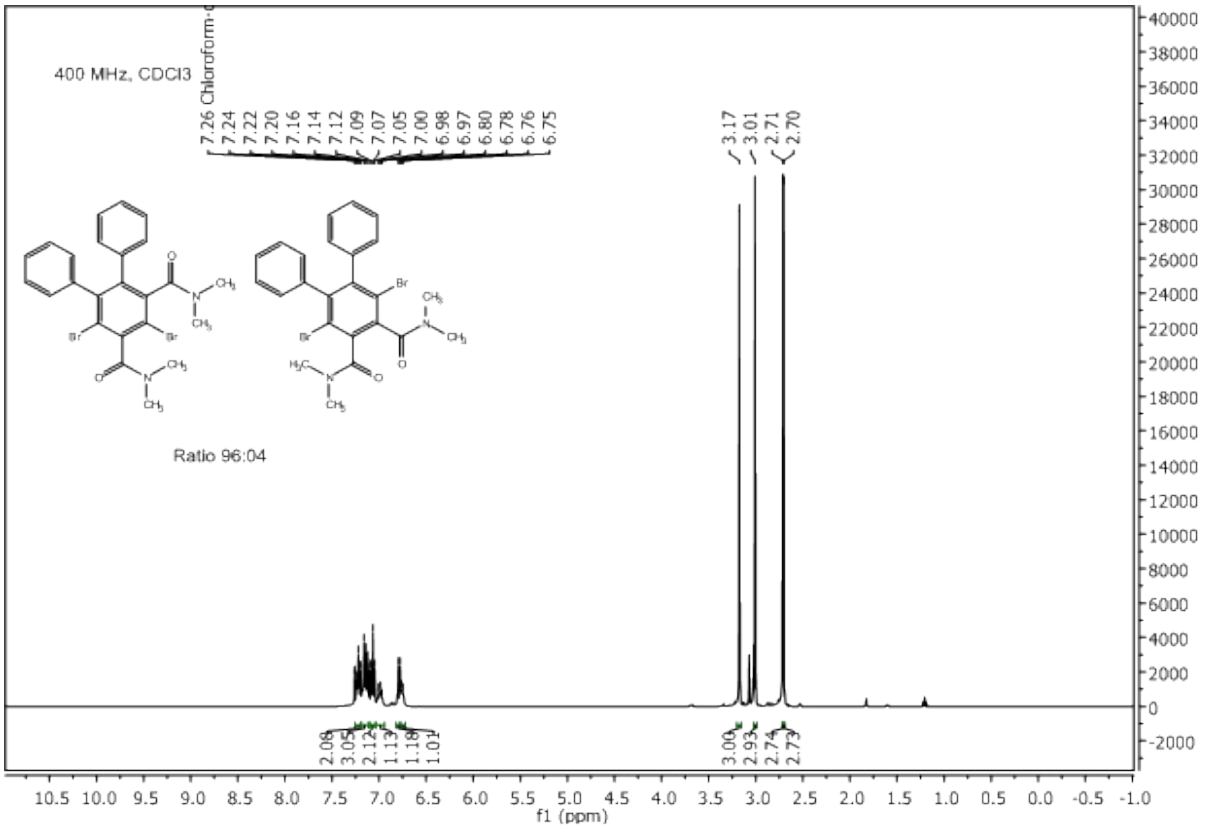


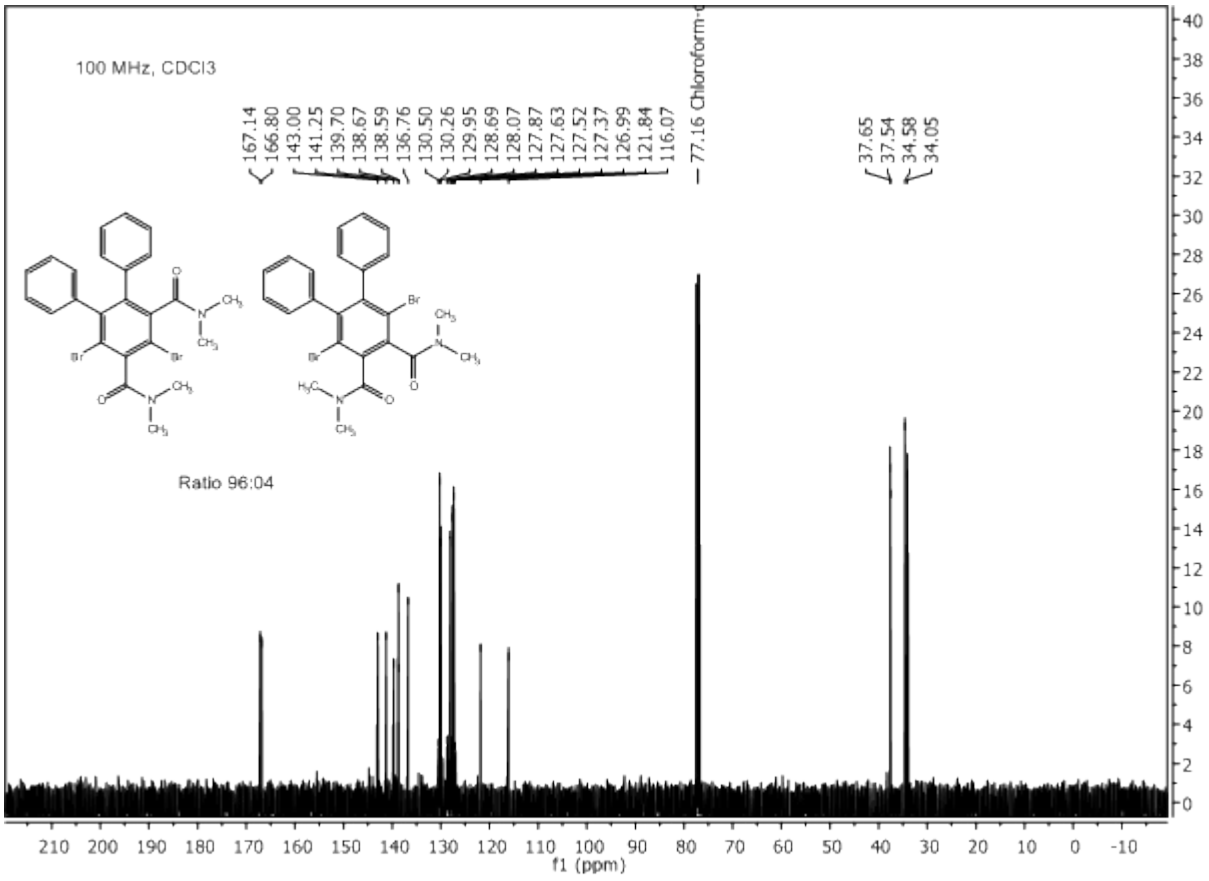
3,6-Dibromo-*N,N,N,N*-4,5-hexamethylphthalamide (**1D**)



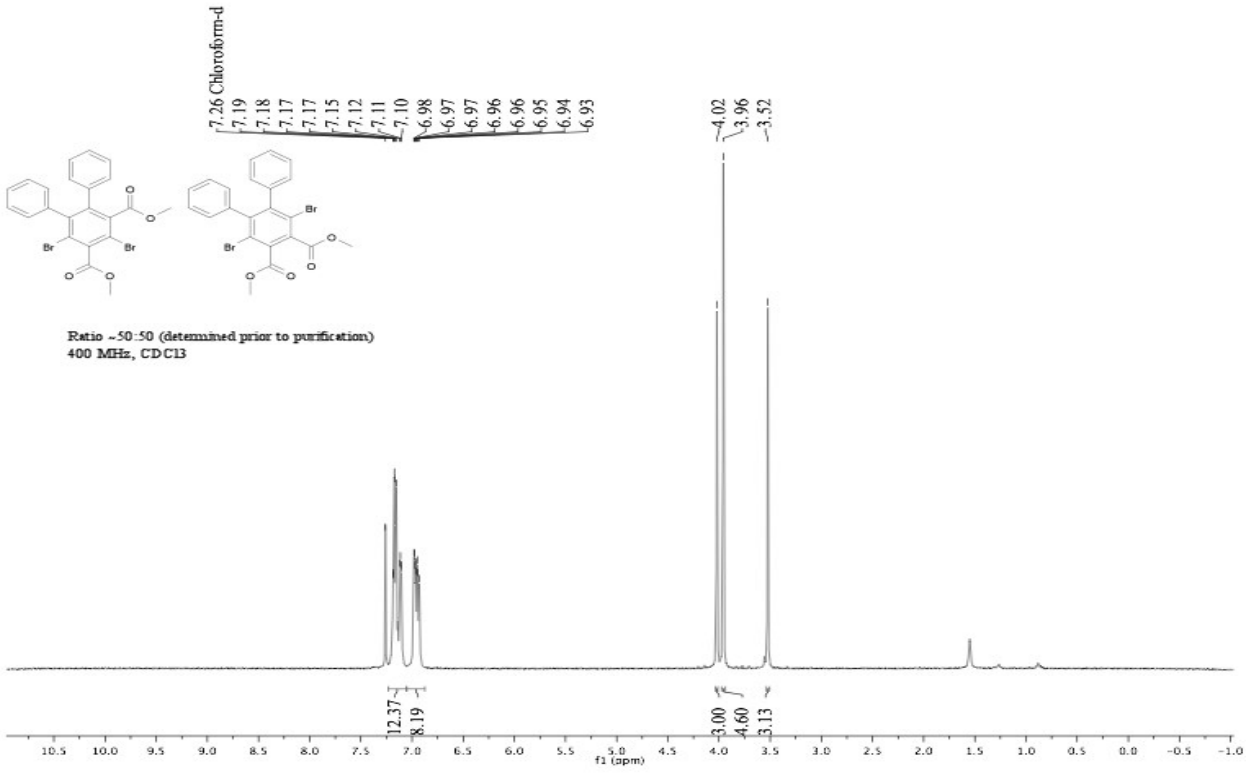


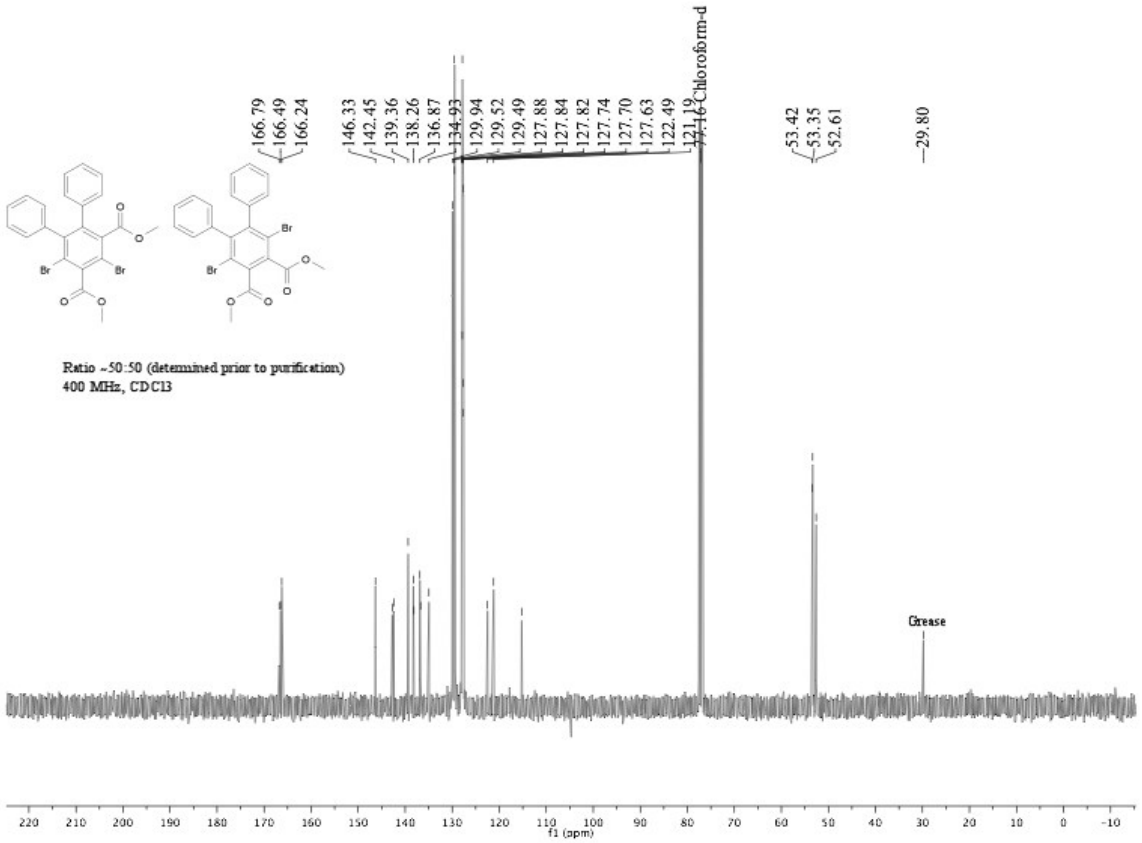
2,4-Dibromo-5,6-diphenyl-*N,N,N,N*-tetramethylisophtalamide (**2C**/**D**)



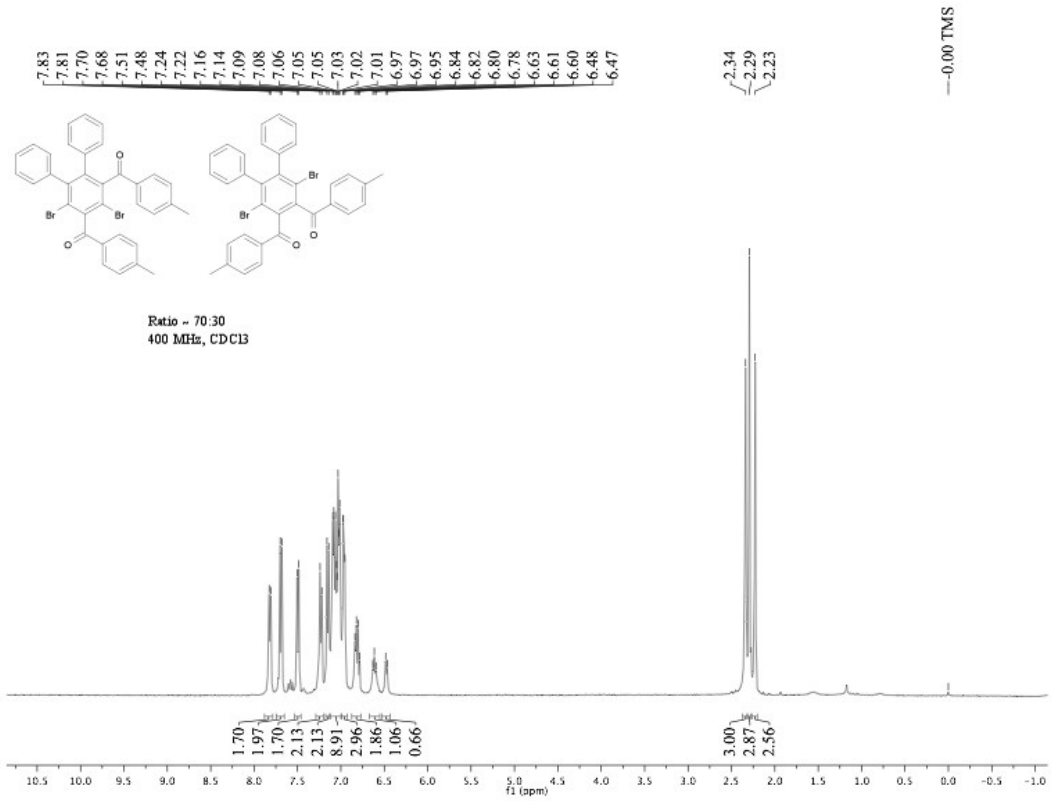


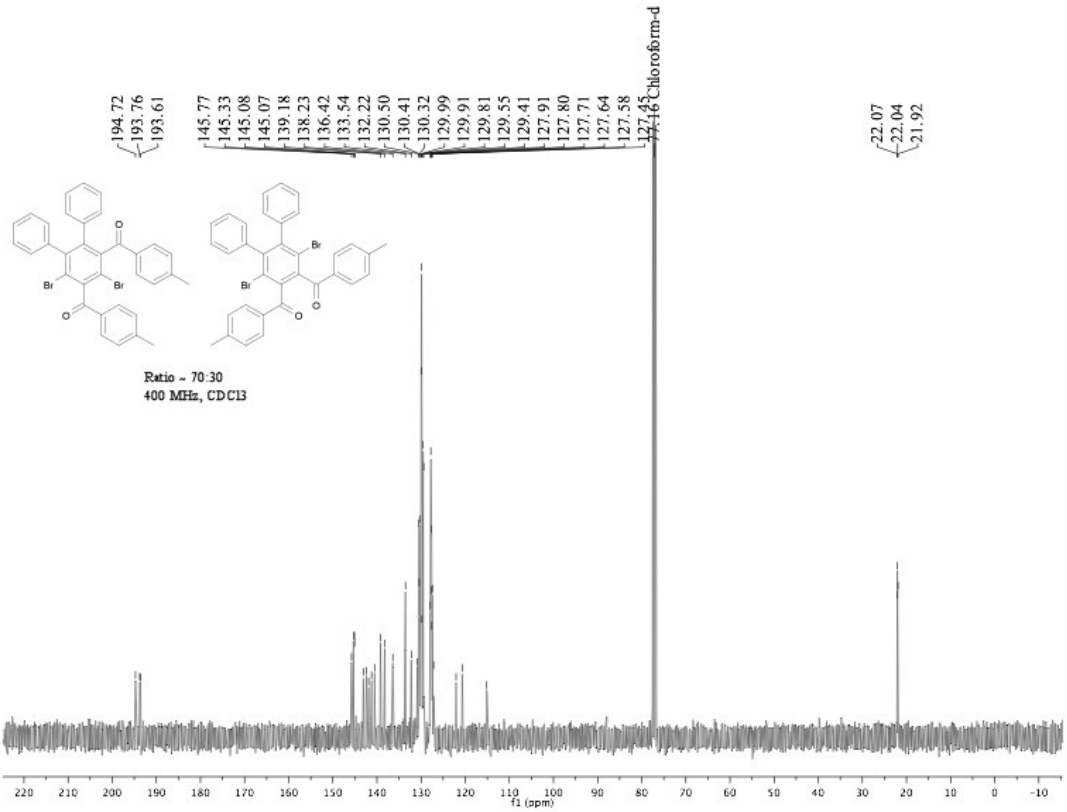
Dimethyl 2,4-dibromo-5,6-diphenylisophthalate and Dimethyl 3,6-dibromo-4,5-diphenylisophthalate (**3C/D**)



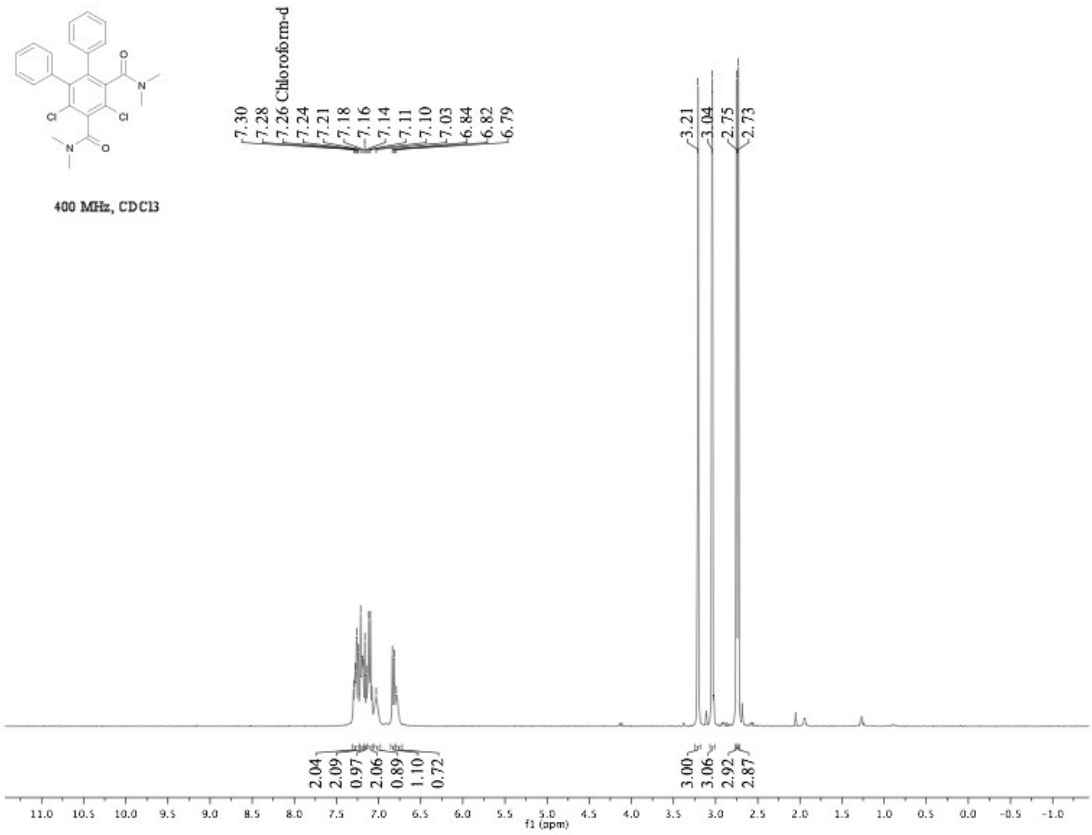


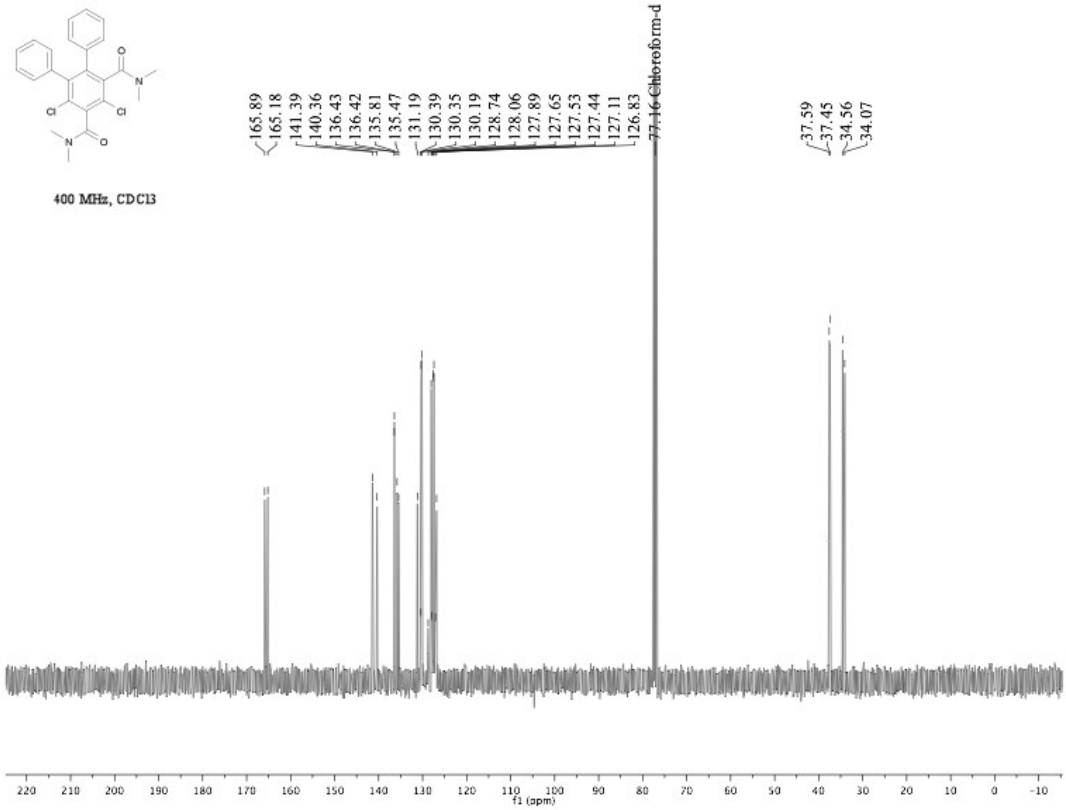
(2,4-Dibromo-5,6-diphenyl-1,3-phenylene)bis(p-tolylmethanone) (**4C/D**)



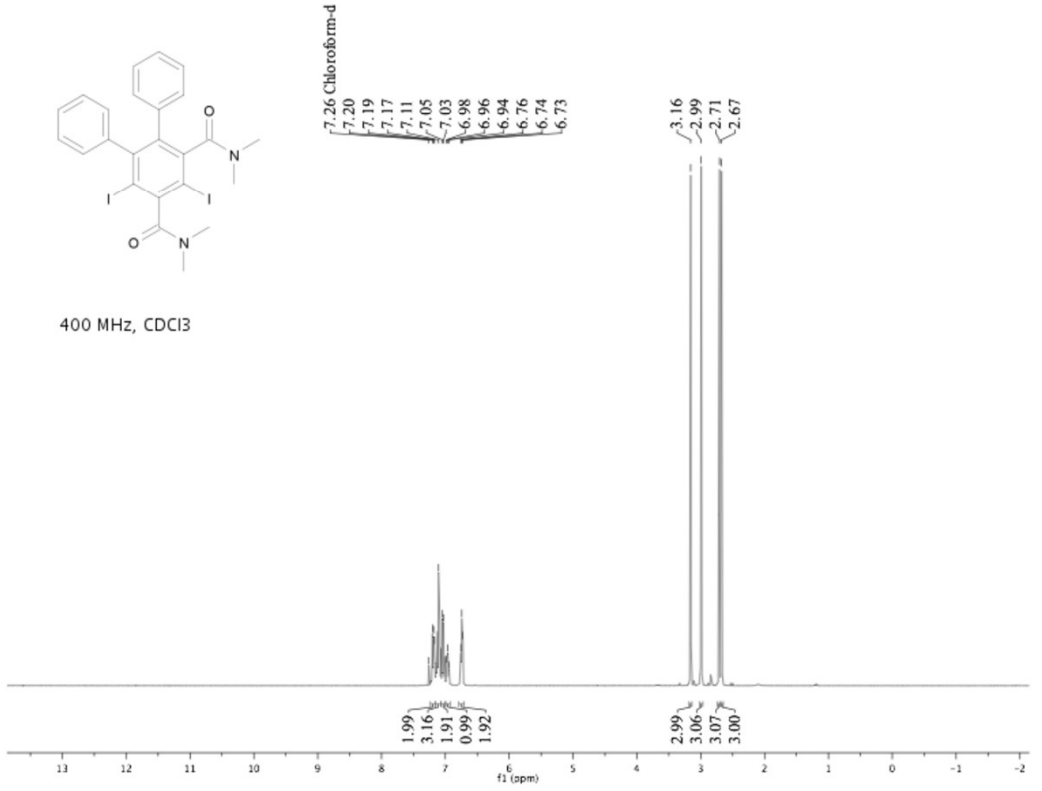


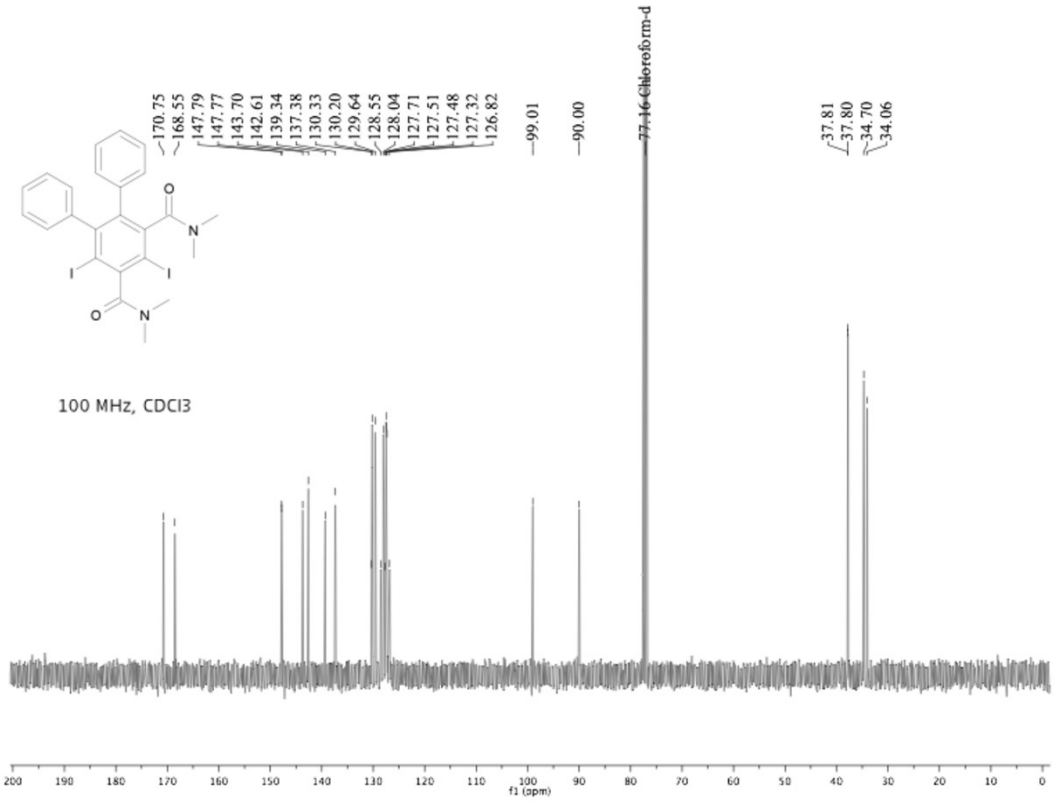
2,4-Dichloro-5,6-diphenyl-*N,N,N,N*-tetramethylisophtalamide (**5C/D**)



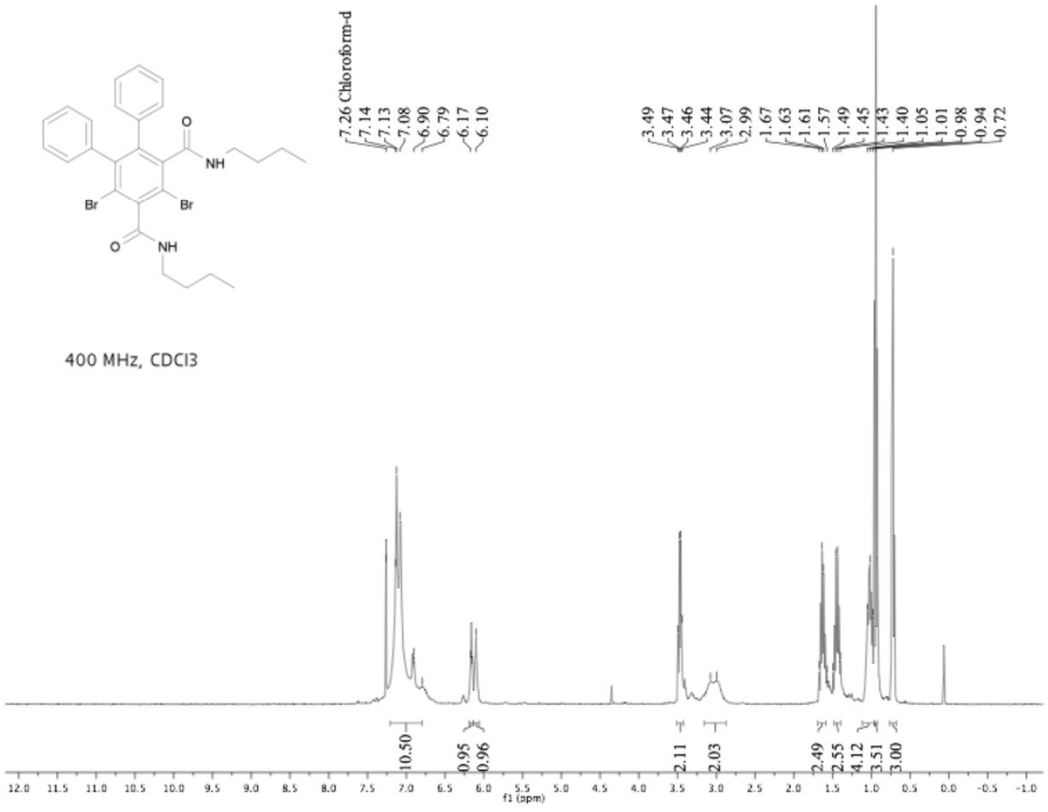


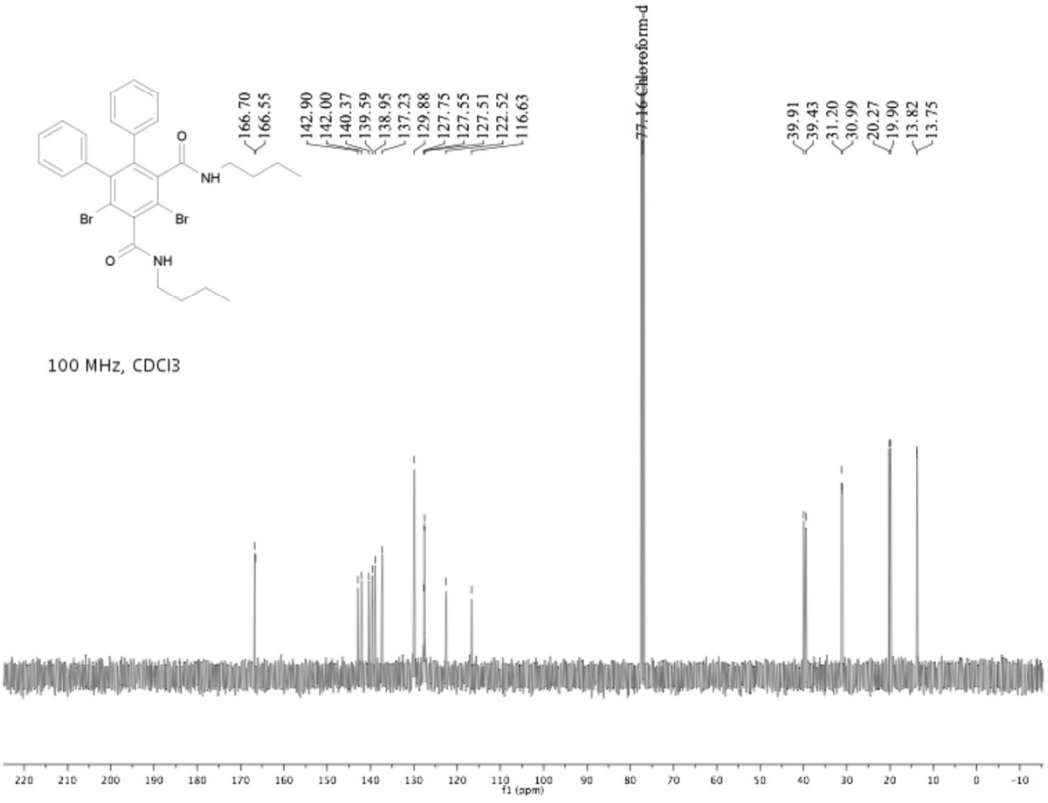
2,4-Diiodo-5,6-diphenyl-*N,N,N,N*-tetramethylisophtalamide (**6C/D**)



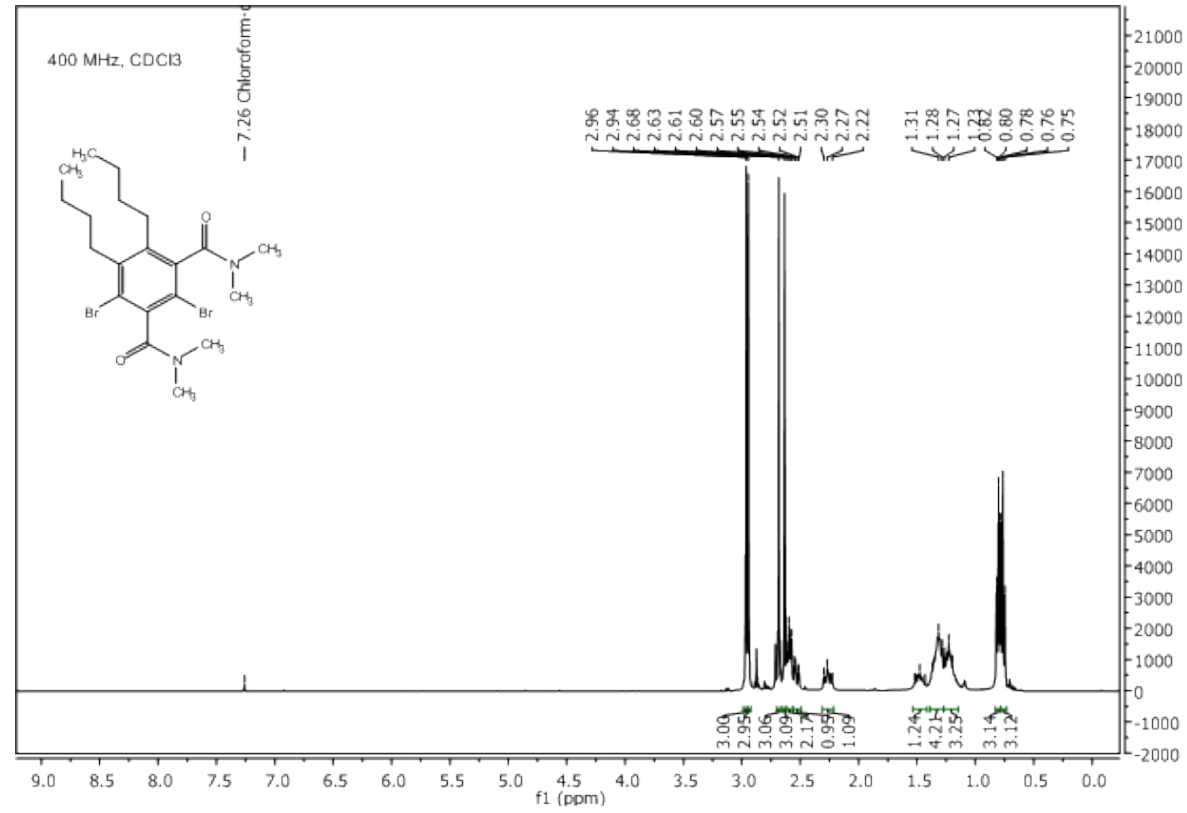


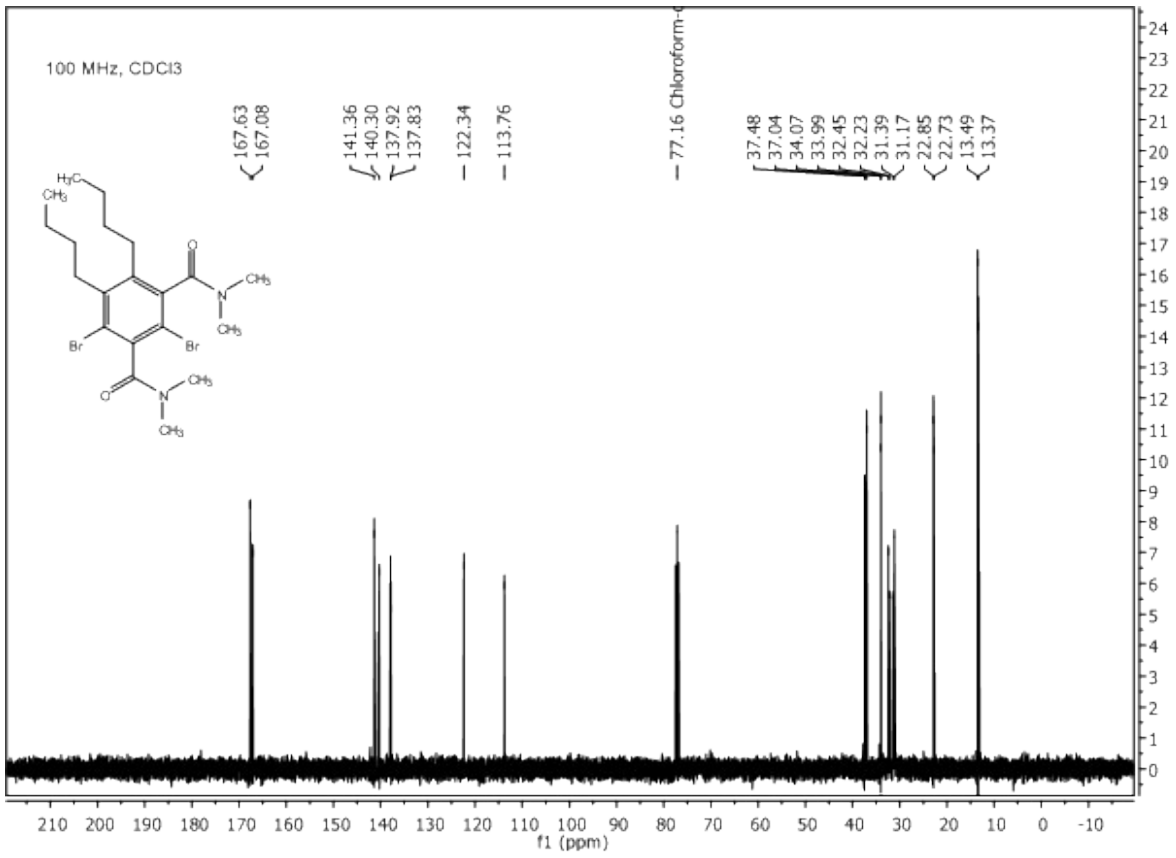
2,4-Dibromo-*N,N*-dibutyl-5,6-diphenylisophthalamide (**8C/D**)



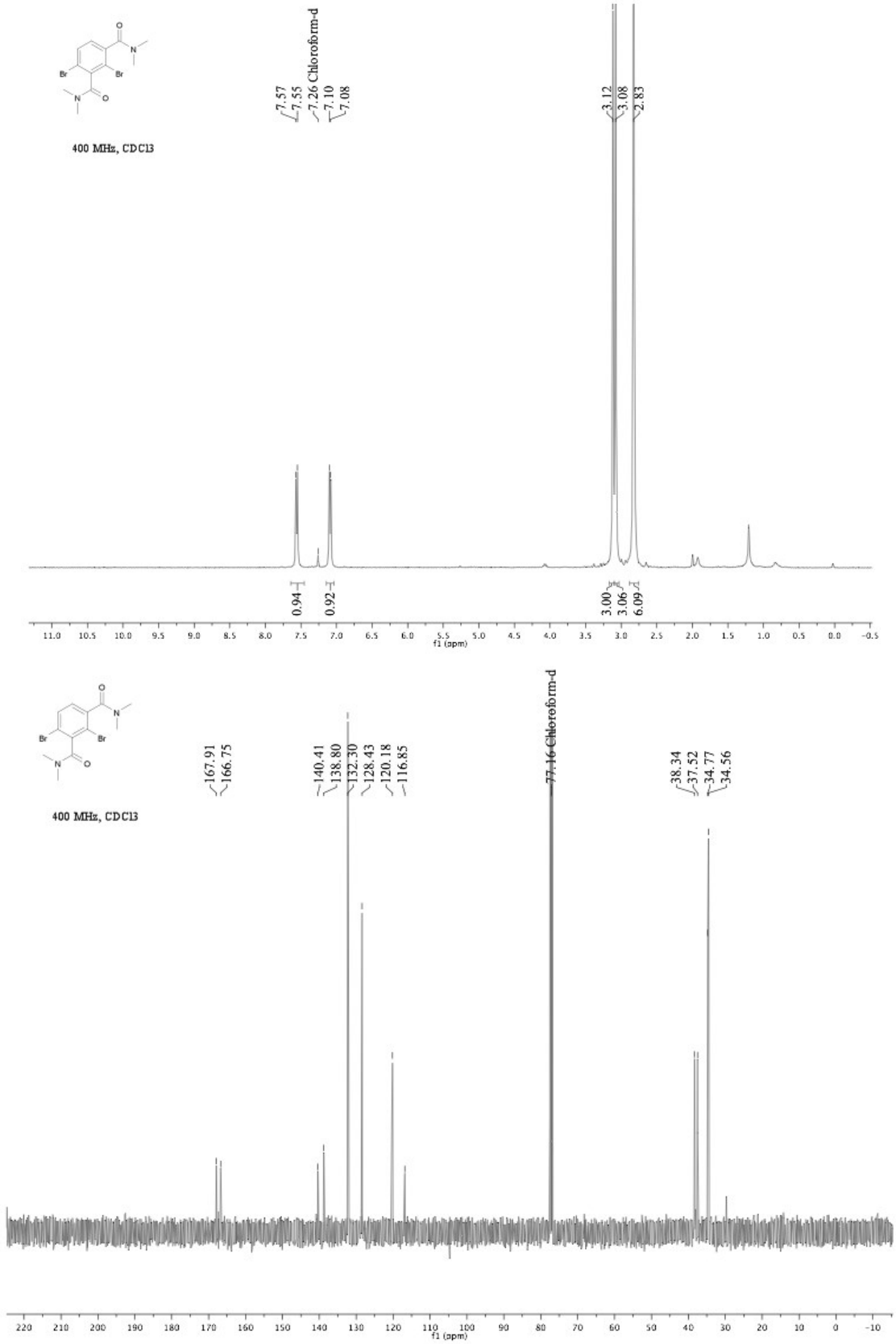


2,4-Dibromo-5,6-dibutyl-*N,N,N,N*-tetramethylisophthalamide (**11**)

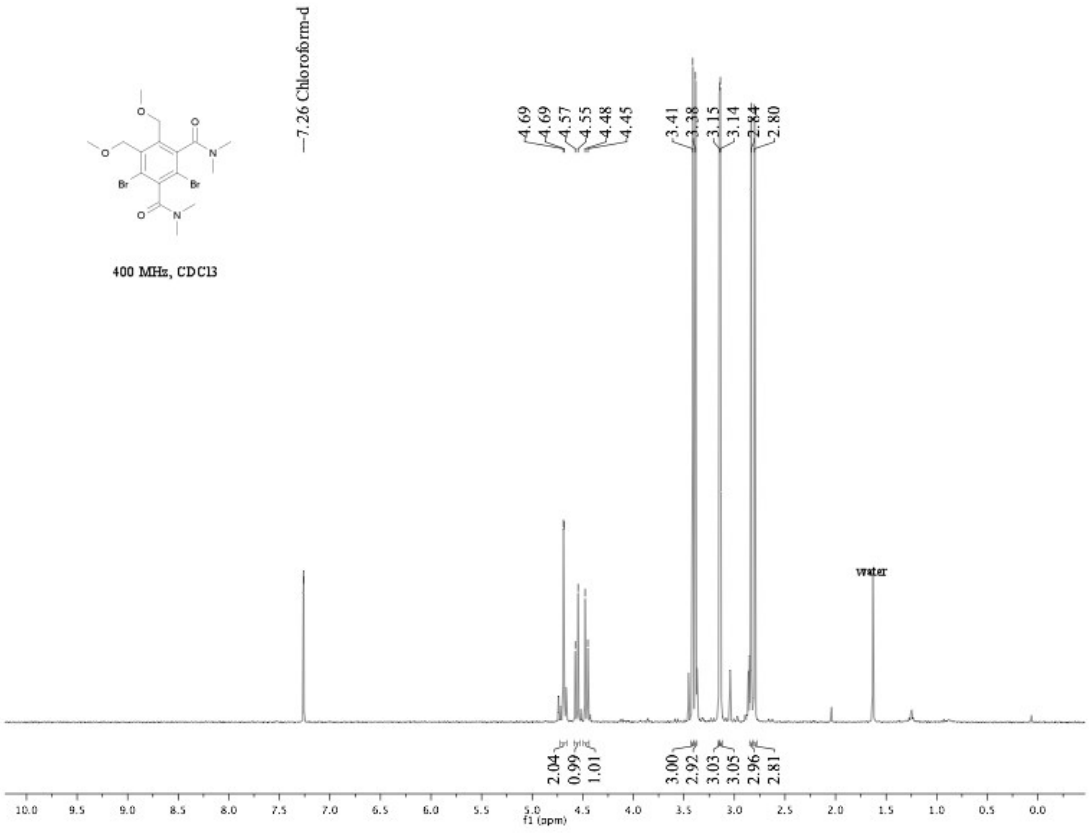


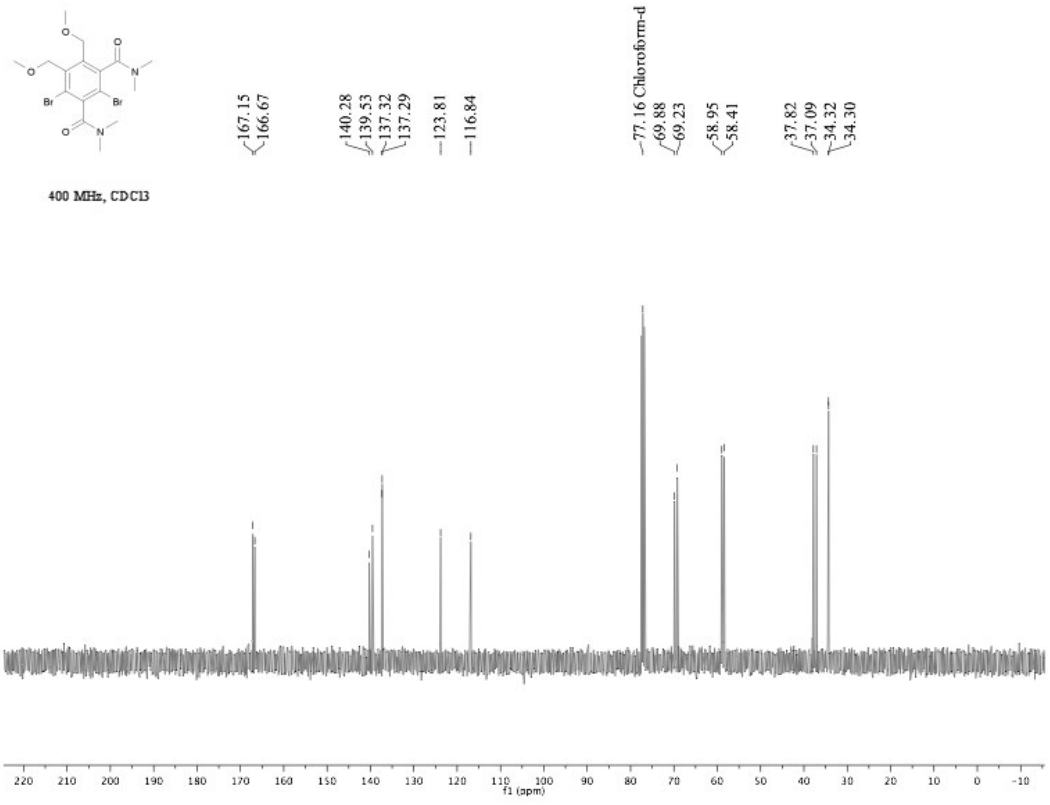


2,4-Dibromo-*N,N,N,N*-tetramethylisophthalamide (**12**)

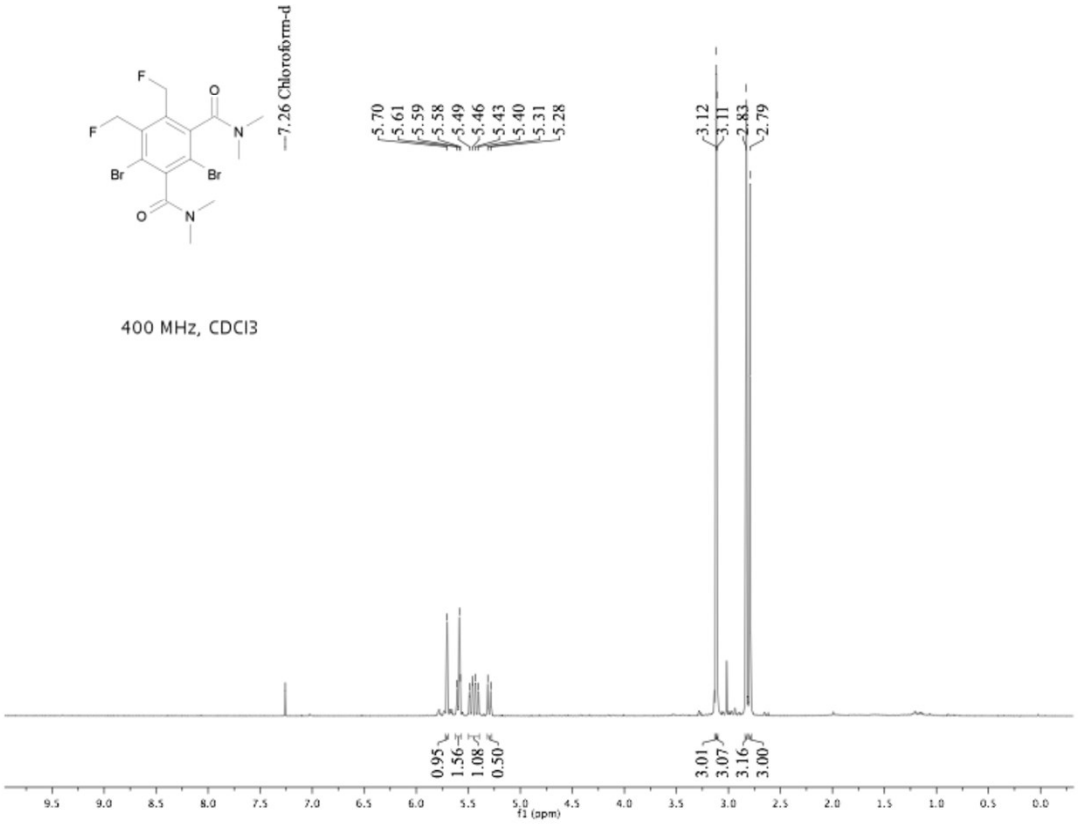


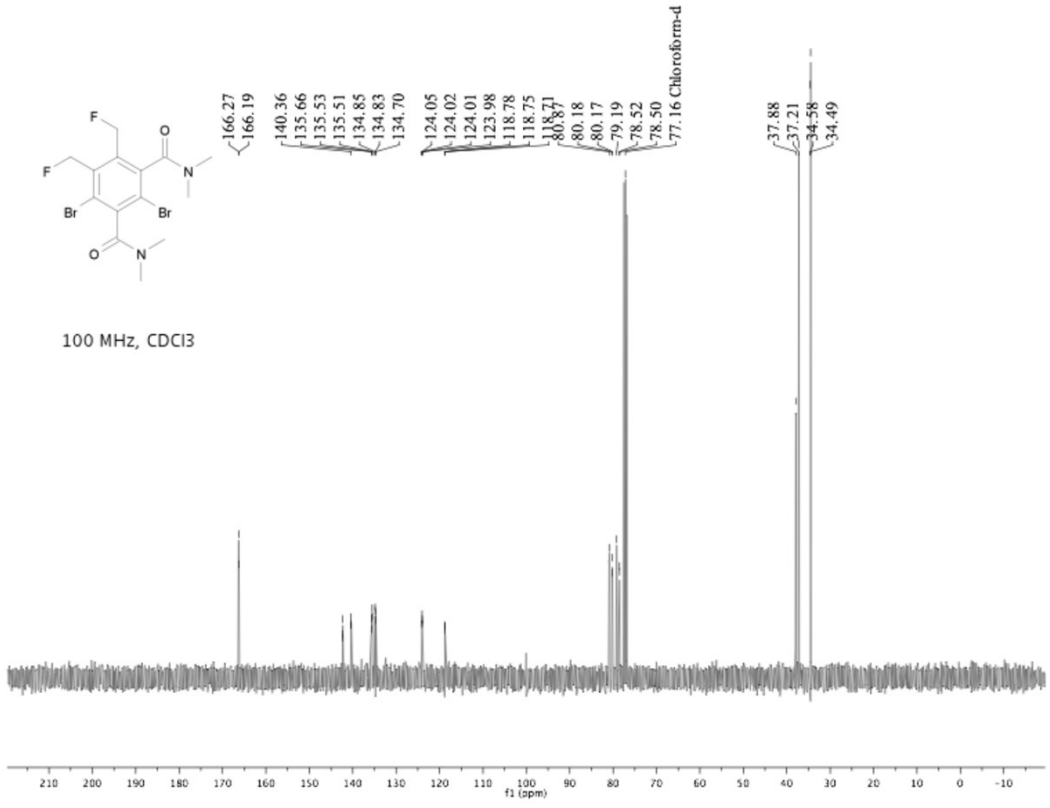
2,4-Dibromo-5,6-bis(methoxymethyl)-*N,N,N,N*-tetramethylisophthalamide (**13**)



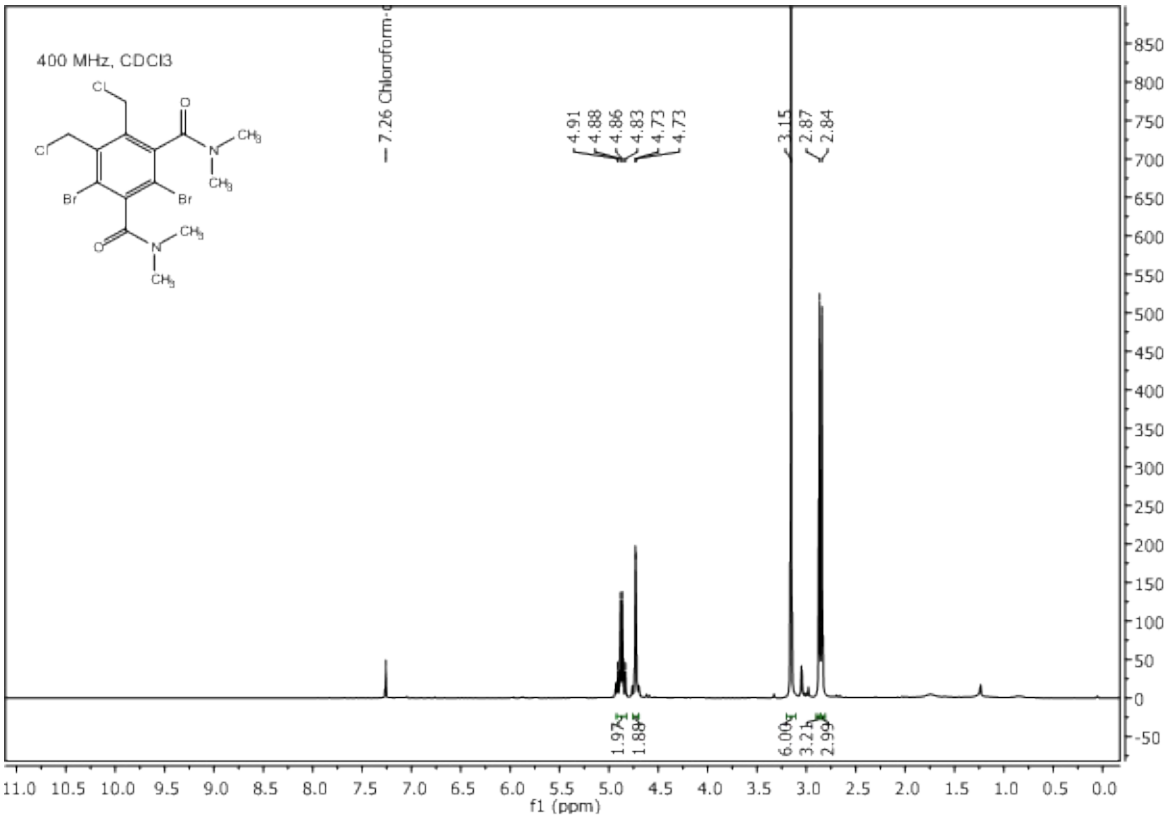


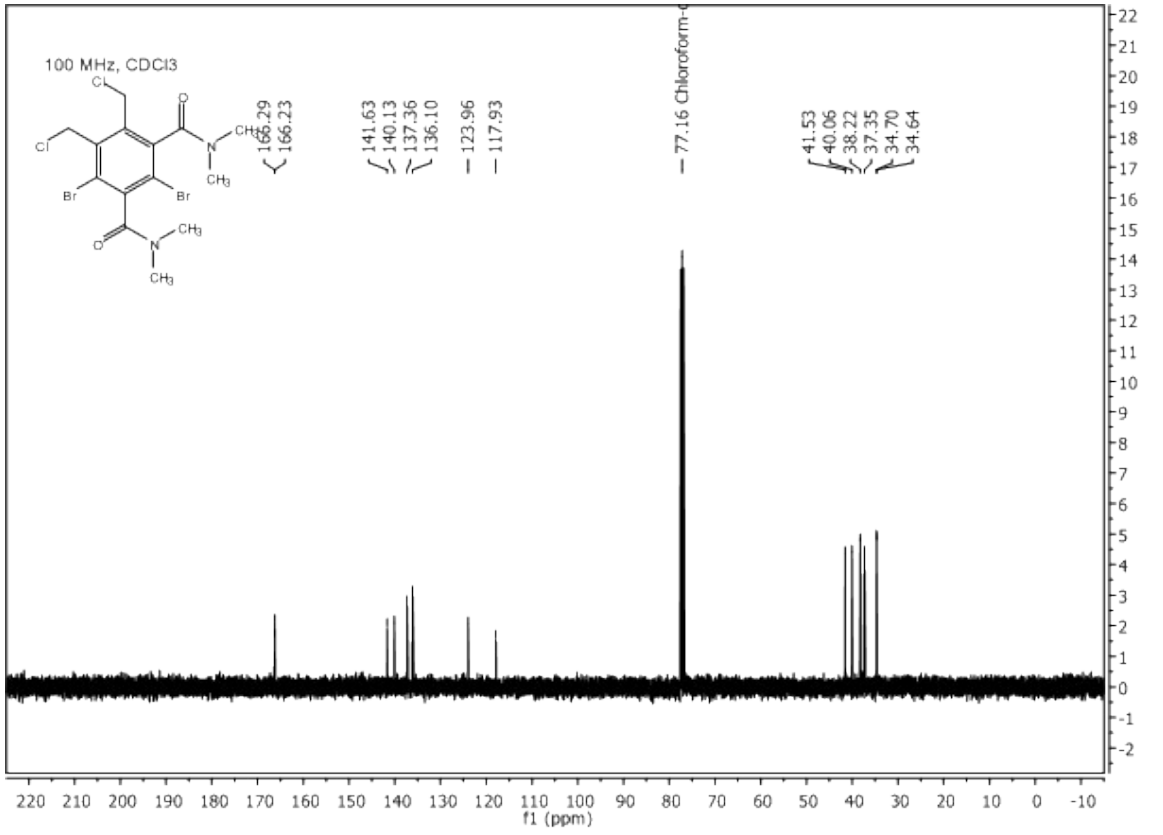
2,4-Dibromo-5,6-bis(fluoromethyl)-*N,N,N,N*-tetramethylisophthalamide (**14**)



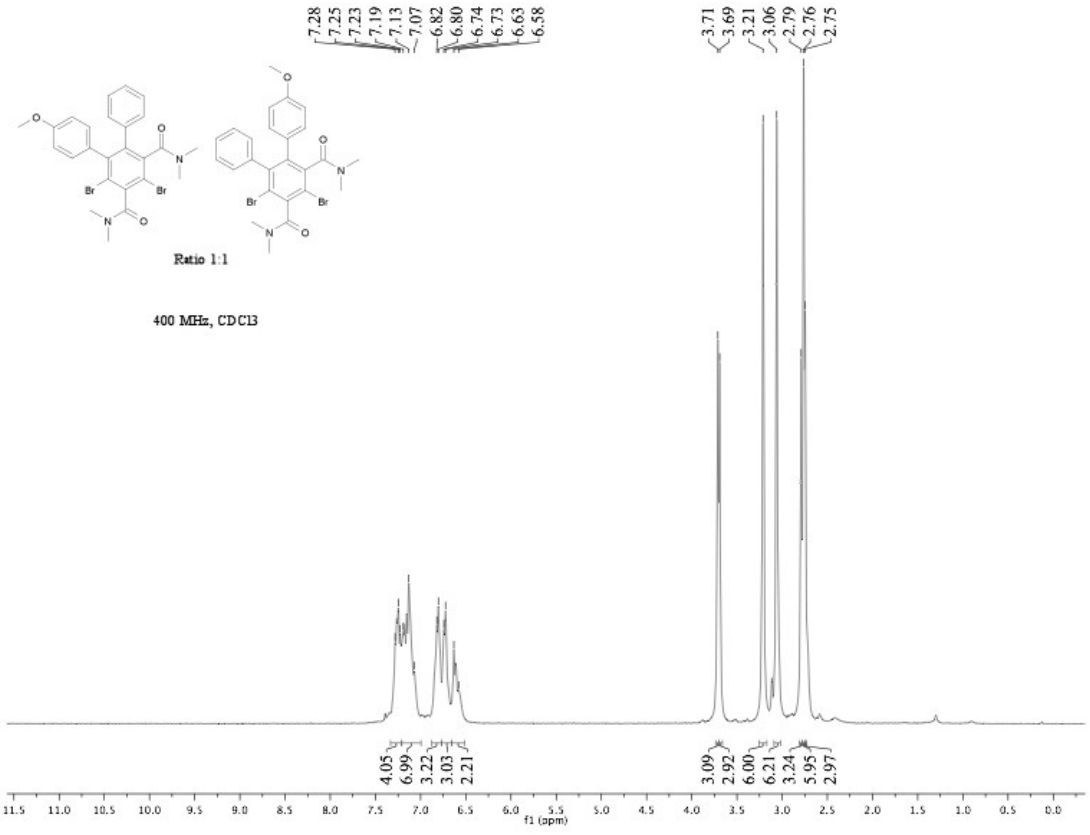


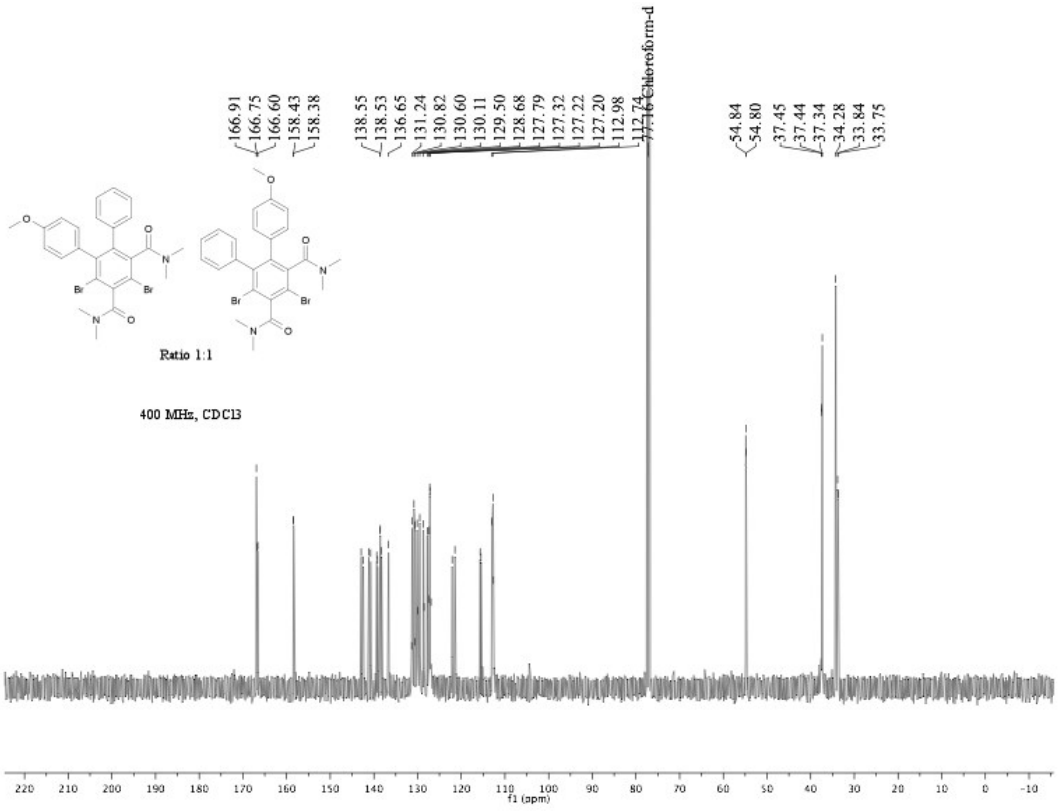
2,4-Dibromo-5,6-bis(chloromethyl)-*N,N,N,N*-tetramethylisophthalamide (**15**)



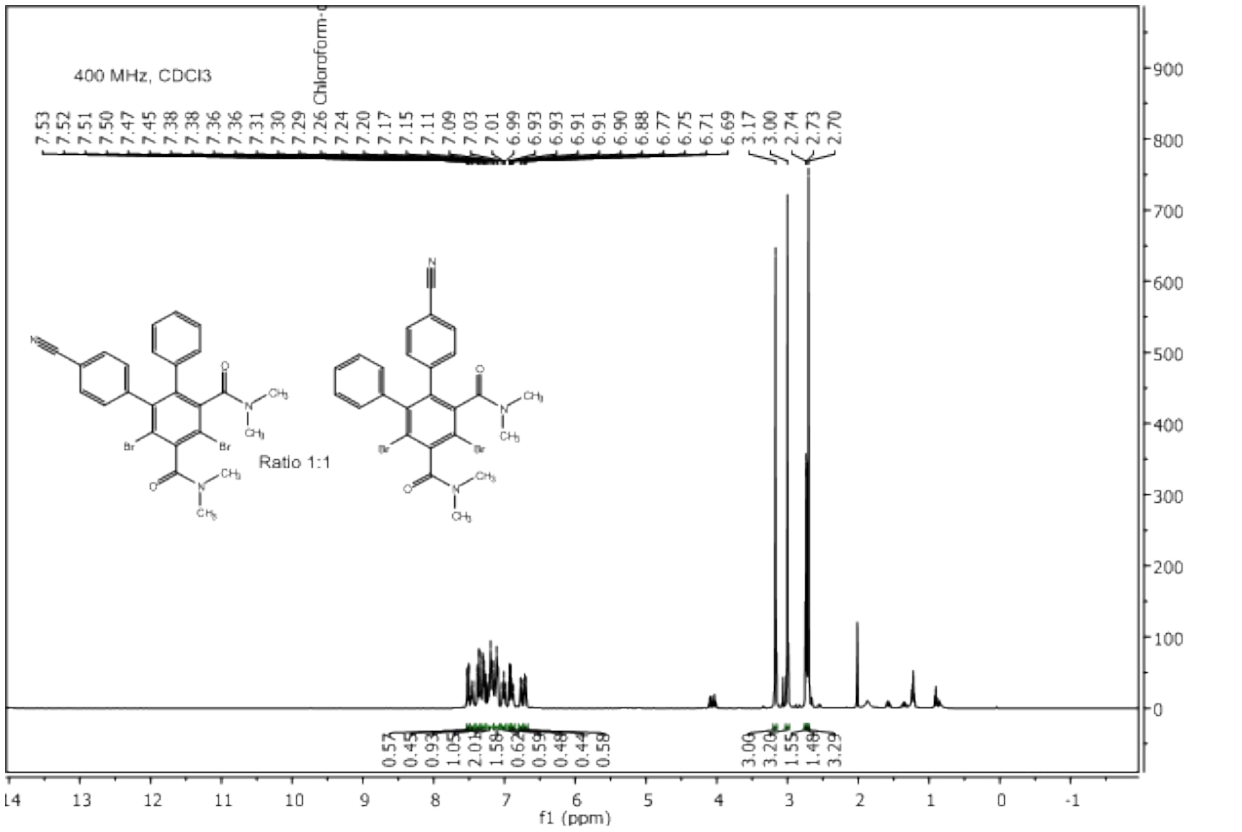


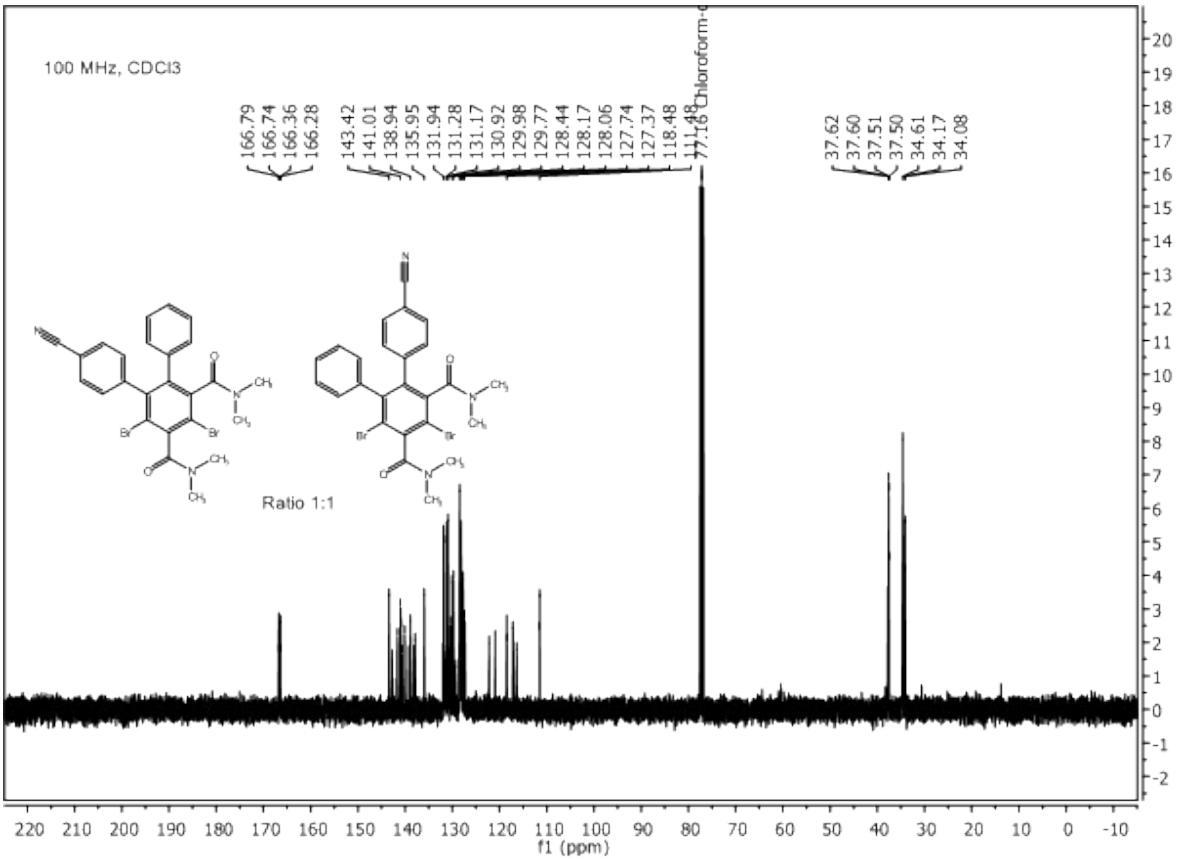
2,4-Dibromo-5-(4’-methoxy)phenyl-6-phenyl-*N,N,N,N*-tetramethylisophtalamide (**16**)



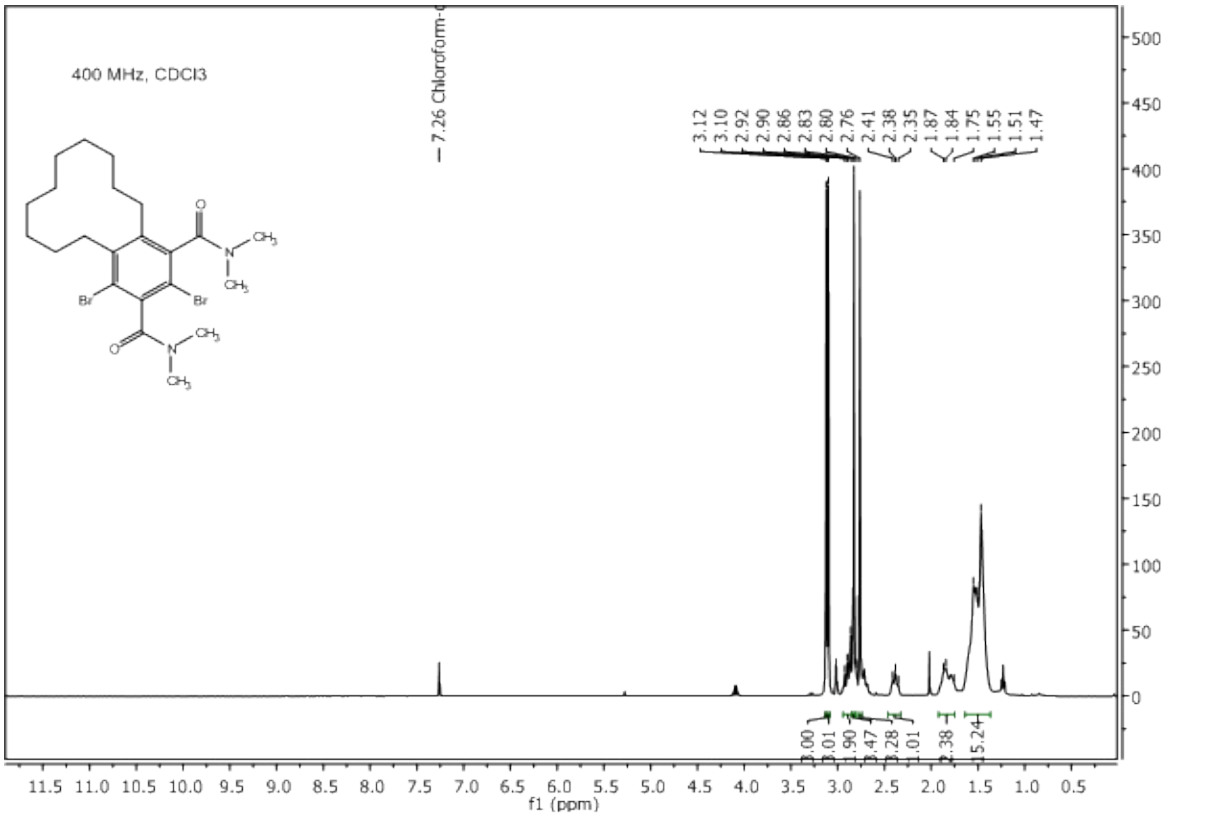


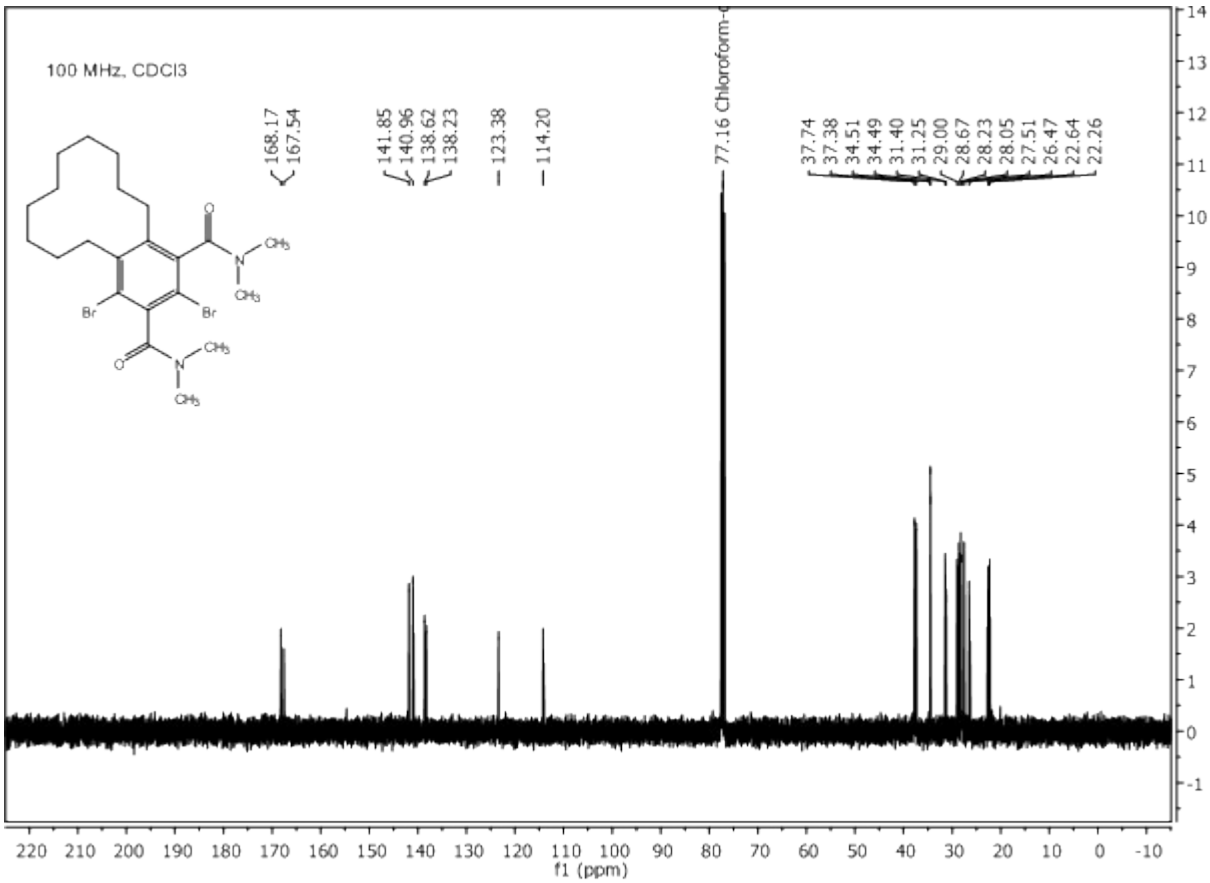
2,4-Dibromo-5-(4’-cyano)phenyl-6-phenyl-*N,N,N,N*-tetramethylisophtalamide (**17**)



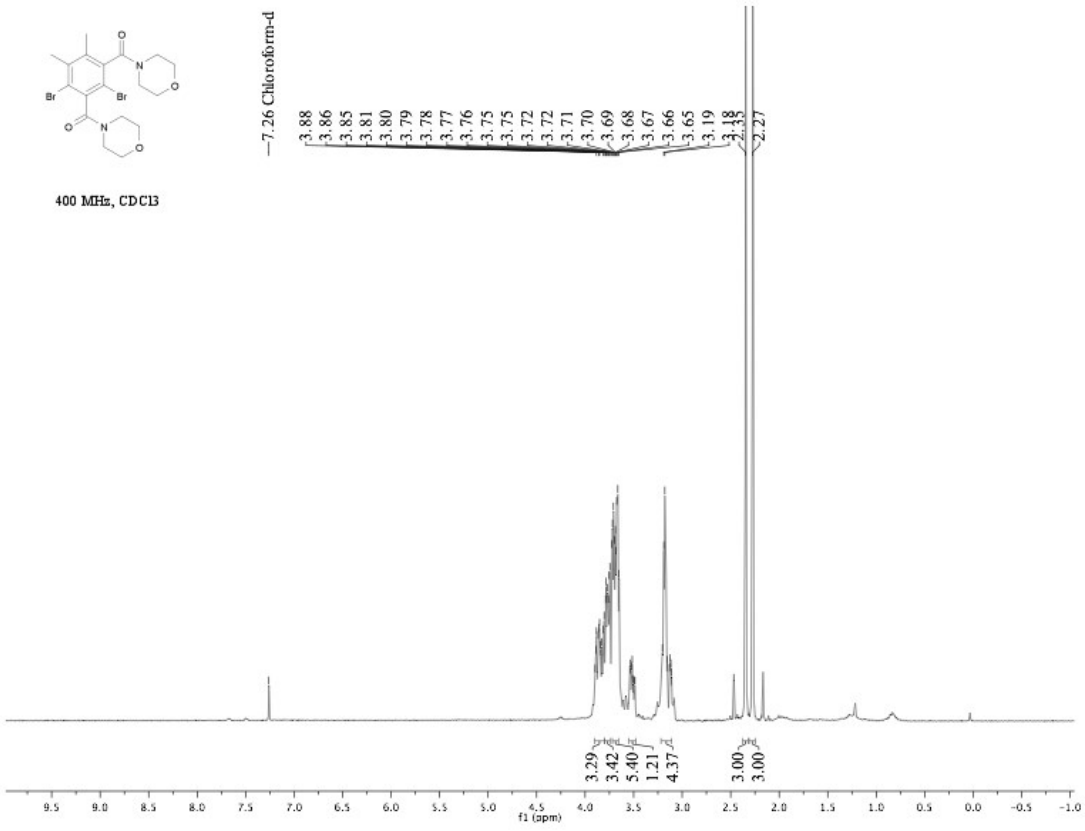


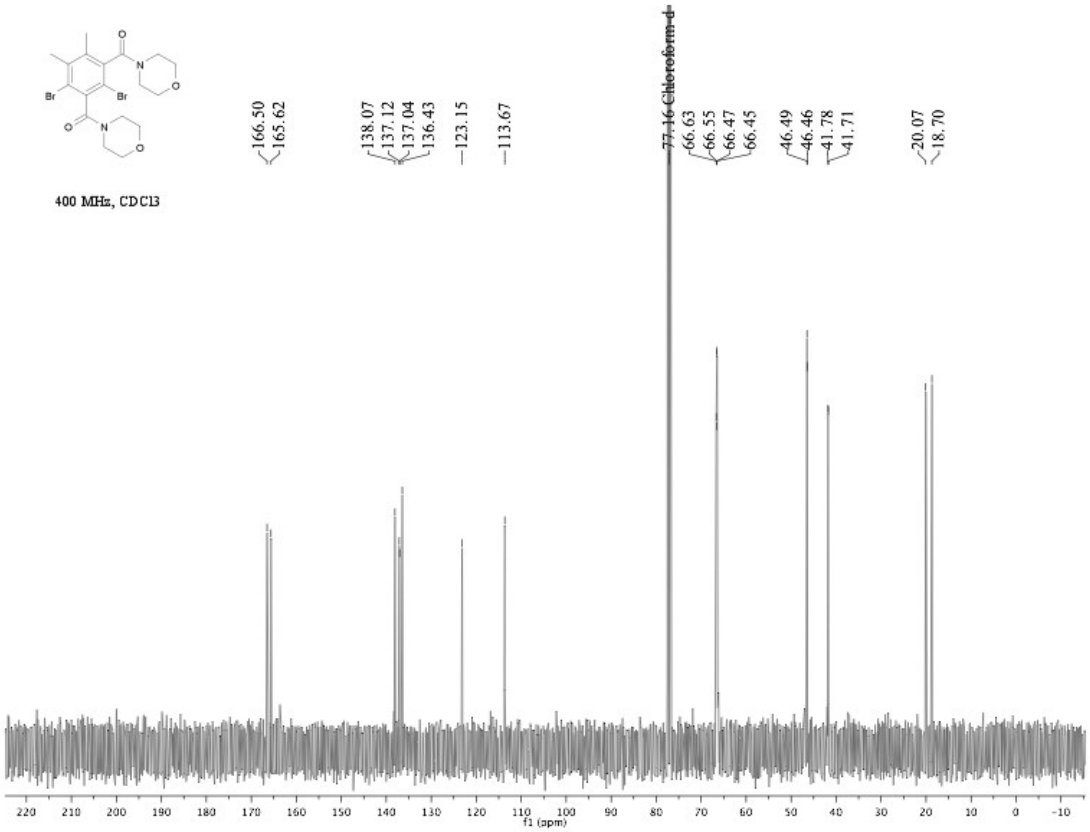
2,4-Dibromo-tetramethyl-decahydrobenzo[12]annulene-1,3-dicarboxamide (**18**)



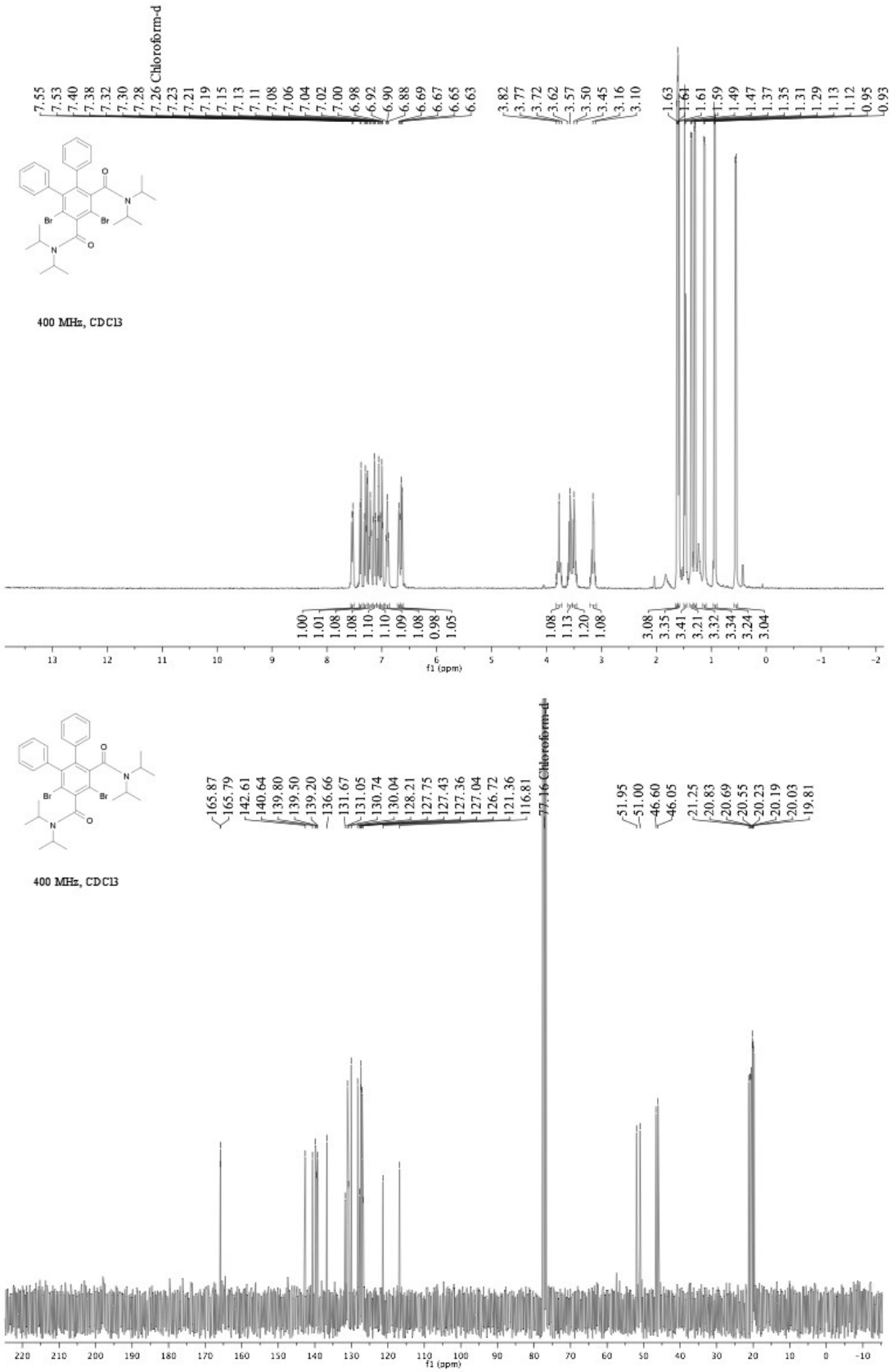


(2,4-Dibromo-5,6-dimethyl-1,3-phenylene)bis(morpholine-methanone) **(19)**

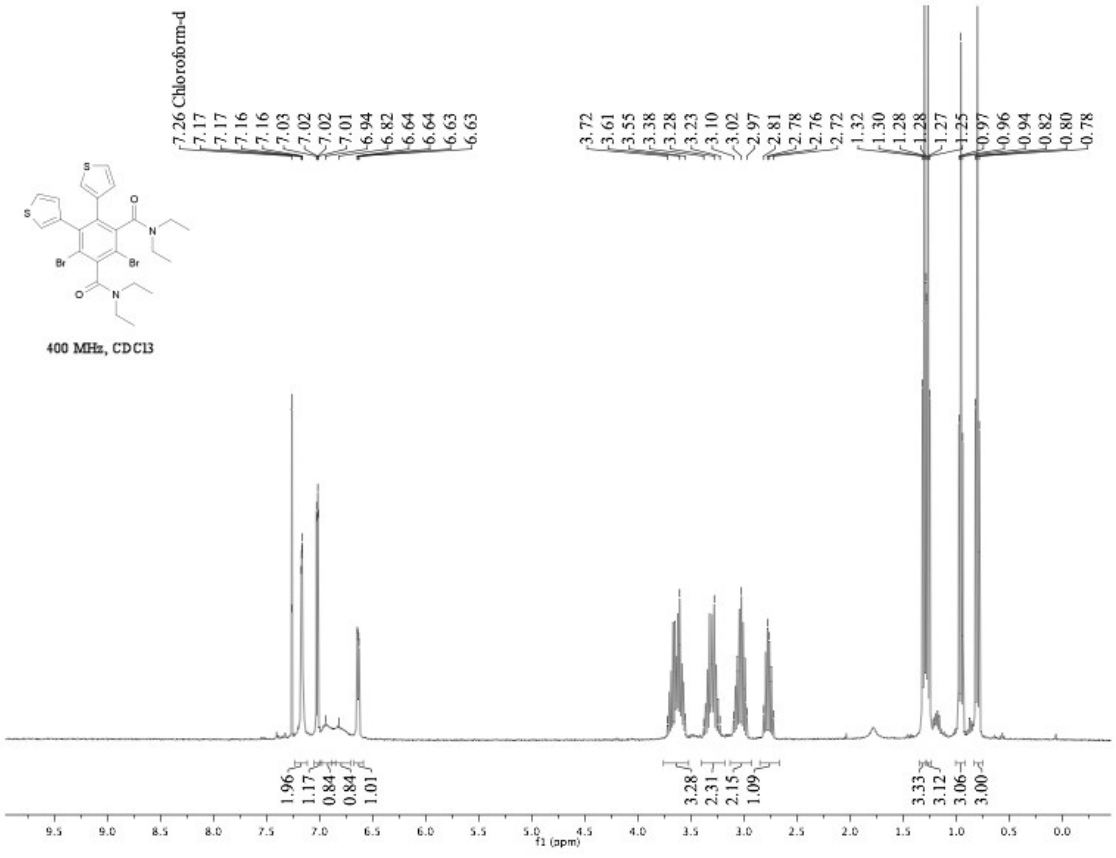


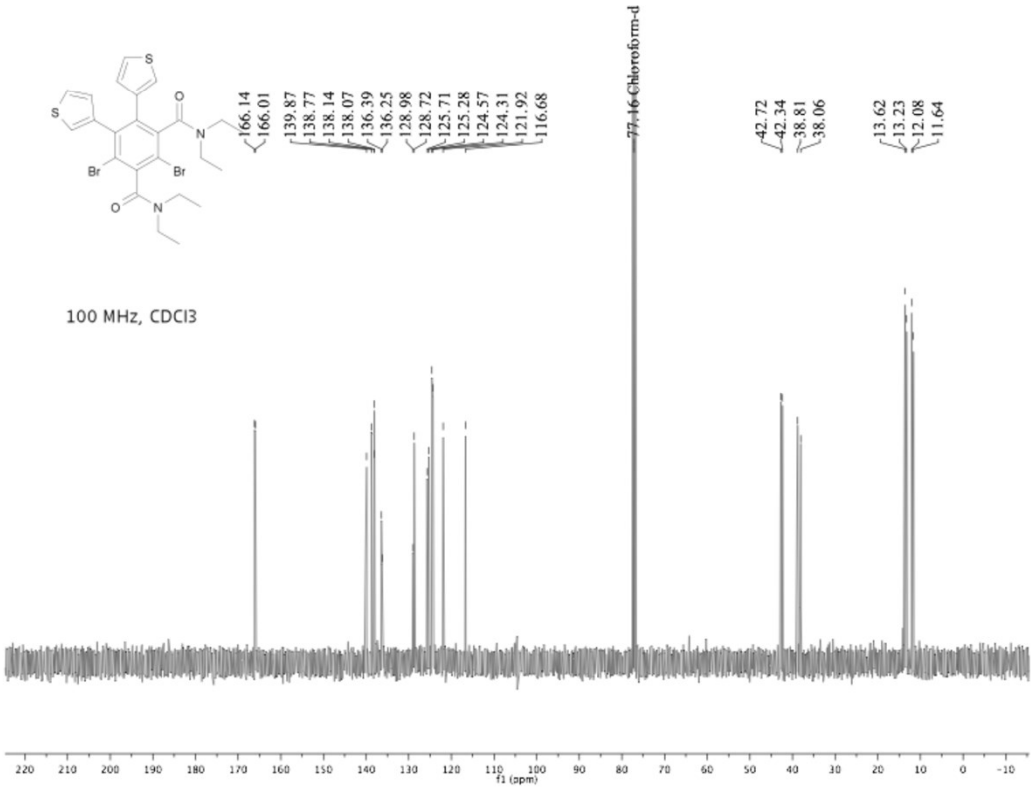


2,4-Dibromo-5,6-phenyl-*N,N,N,N*-tetraisopropylisophtalamide (**20**)

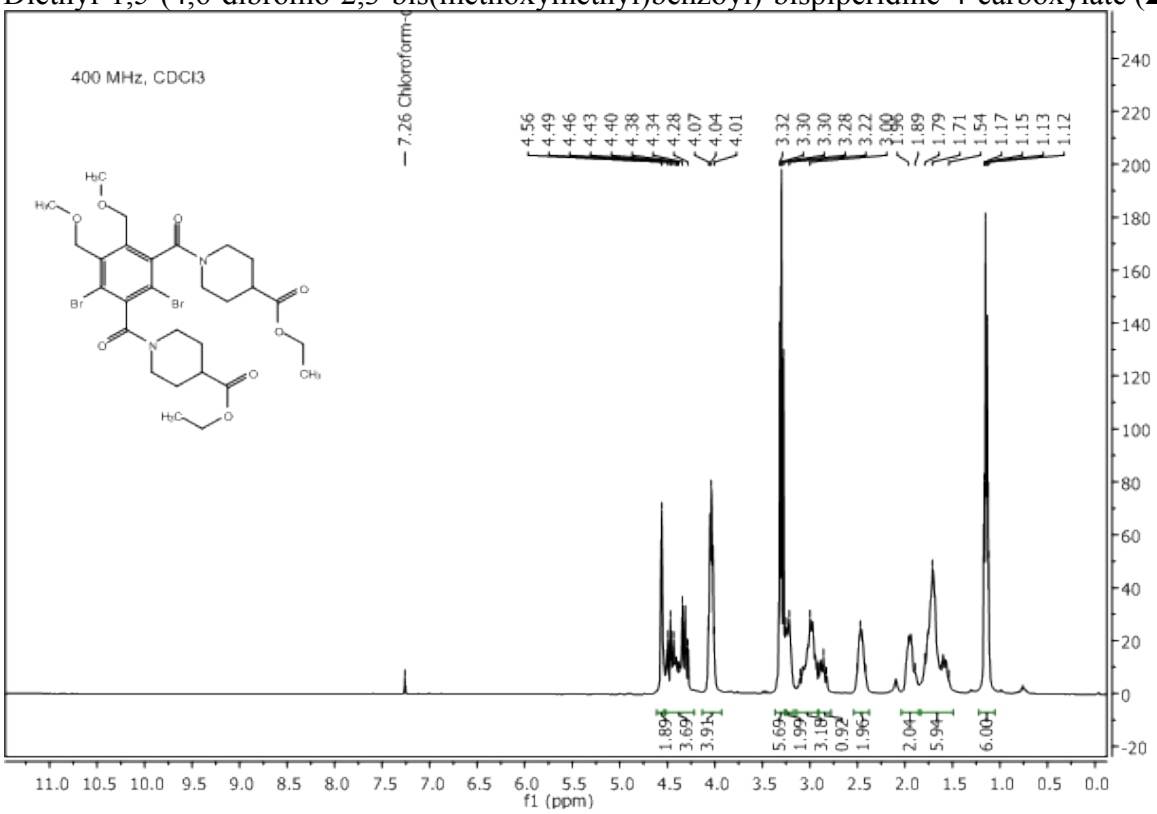


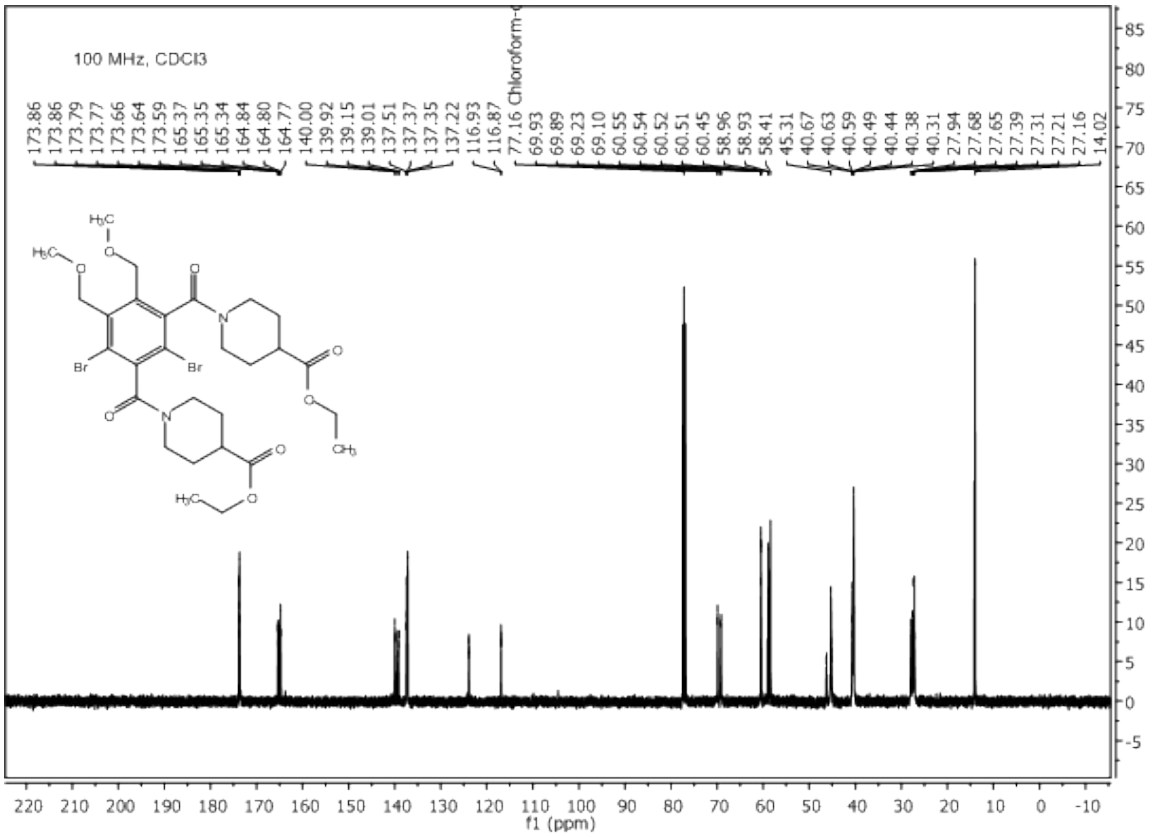
2,4-Dibromo-*N,N,N,N*-tetraethyl-5,6-di(thiophen-3-yl)isophtalamide (**21**)



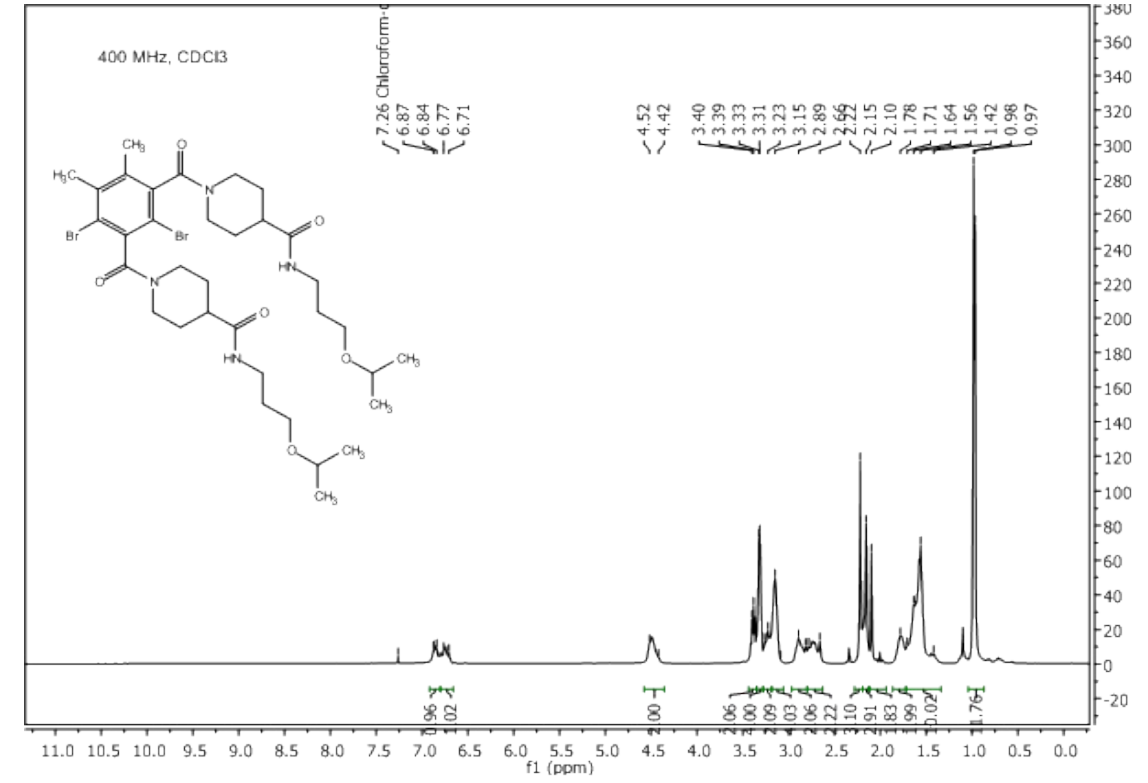


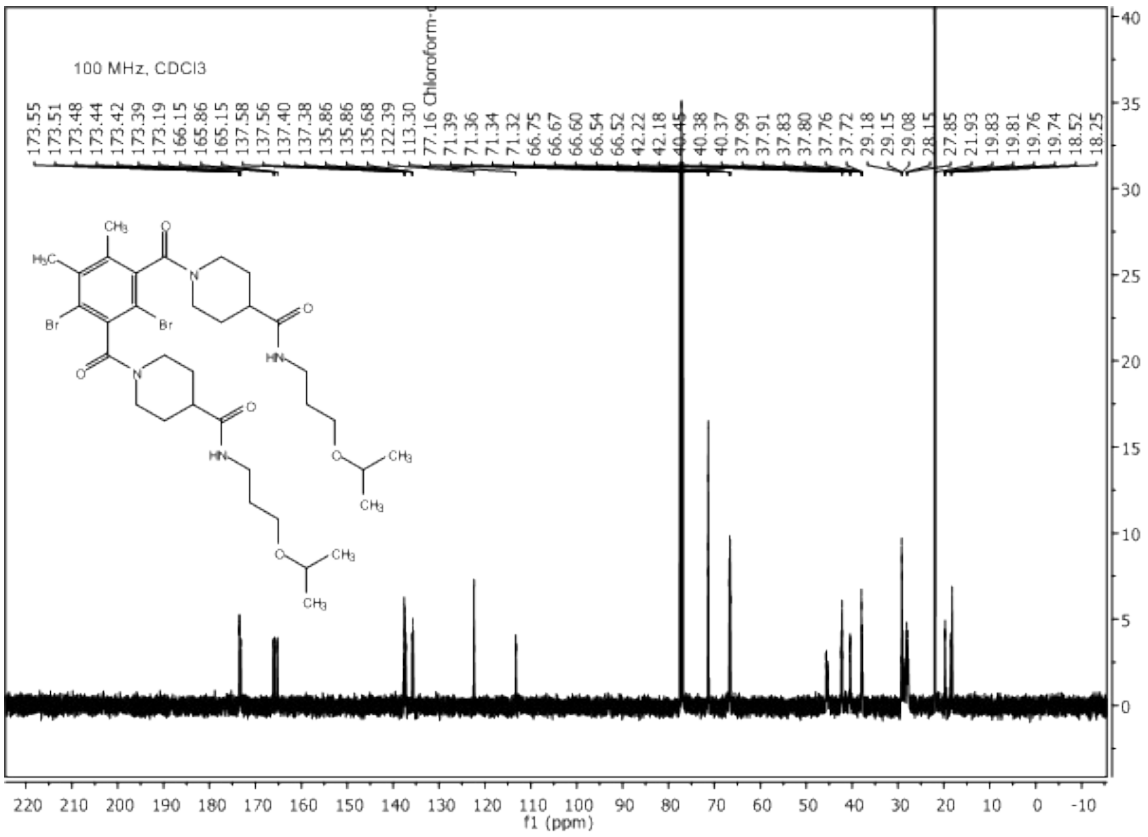
Diethyl-1,5-(4,6-dibromo-2,3-bis(methoxymethyl)benzoyl)-bispiperidine-4-carboxylate (**22**)



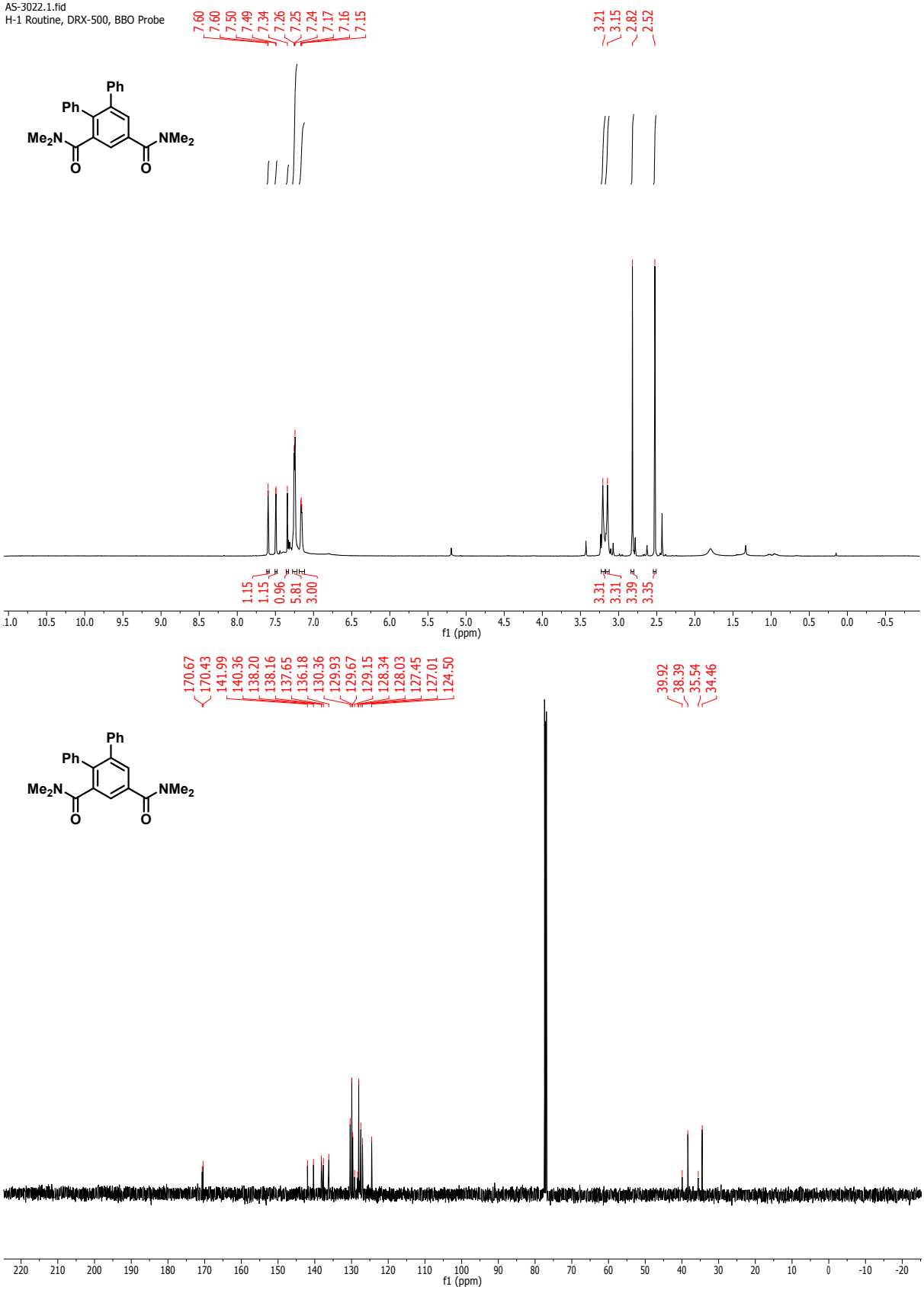


1,2-(4,6-dibromo-2,3-dimethylbenzoyl)-N,N-(di-3-isopropoxypropyl)bispiperidine-4-carboxamide (**23**)

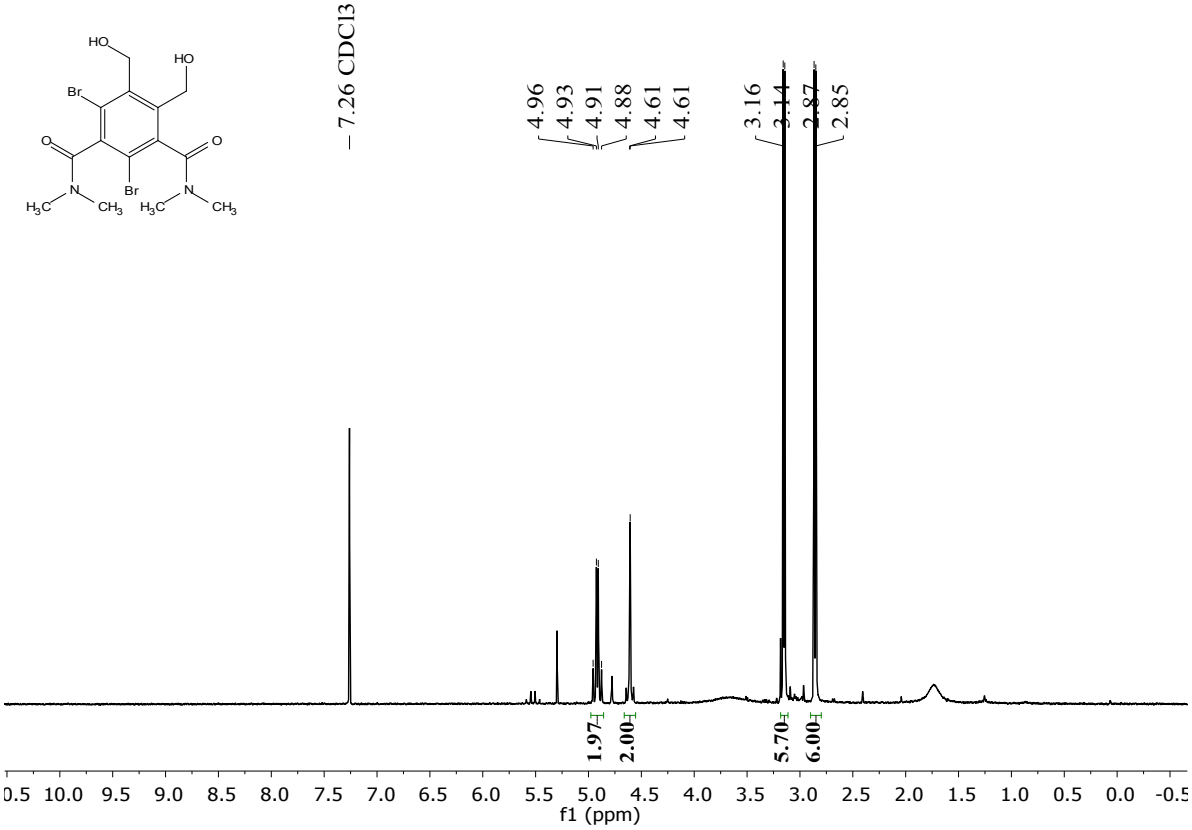




5,6-diphenyl-N^1,N^1,N^3,N^3-tetramethylisophthalamide **(25)**



2,4-dibromo-5,6-bis(hydroxymethyl)-tetramethylisophthalamide **(26)**



4,6-dibromo-7-(hydroxymethyl)-dimethyl-3-oxo-1,3-dihydro-isobenzofuran-5-carboxamide **(27)**