Synthesis of Substituted Pyrazines from N-Allyl Malonamides

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Supplementary Information

1. General remarks

The commercial reagents and solvents were used as purchased. TLC was conducted with precoated glass-backed plates (silica gel 60 F_{254}) and visualized by exposure to UV light (254 nm) or stained with ceric ammonium molybdate (CAM), basic potassium permanganate ($KMnO_4$) and subsequent heating. Flash column chromatography was performed on silica gel (40-60 μm), the eluent used is reported in the respective experiments. Abbreviations of solvents are as followed: PE: petroleum ether, EA: ethyl acetate, DCM: dichloromethane, MeOH: methanol, *i*PrOH: isopropanol. IR spectra were measured using ATR-technique in the range of 400-4000 cm^{-1}. ^1H NMR spectra were recorded with 400 MHz or 600 MHz instruments, ^{13}C NMR spectra at 101 MHz or 151 MHz. Chemical shifts are reported in ppm relative to the solvent signal, coupling constants *J* in Hz. Multiplicities were defined by standard abbreviations. Low-resolution mass spectra (LRMS) were recorded using a LC/MS-combination (ESI). High-resolution mass spectra (HRMS) were obtained using ESI ionization (positive) on a Bruker micrOTOF.

Caution! *Geminal diazides are potentially hazardous and should be handled with care.*

2. General procedures

General procedure A for the synthesis of *N*-allyl malonamides 5

The reaction was carried out under argon atmosphere. Potassium 3-ethoxy-3-oxopropanoate (**3**) (1 eq.) and HOBt (2 eq.) were dissolved in dry dichloromethane (0.3M), and molecular sieve 3A (0.6 g/mmol substrate) were added. The mixture was cooled to 0 °C. Allylic amine (**4**) (2.5 eq.) or (1.6 eq.) and EDC (1.5 eq.) were added at 0 °C, and the mixture was stirred for 30 minutes at this temperature. The reaction was warmed to room temperature over night. The mixture was poured into 10% HCl (aq.) (14 mL/mmol substrate), and the phases were separated. The organic phase was washed with saturated $NaHCO_3$ solution once and dried with $MgSO_4$. The solvent was evaporated under reduced pressure to yield the crude product, which was used without further purification.

General procedure B for the synthesis of *N*-allyl malonamides 5

The reaction was carried out under argon atmosphere. Potassium 3-ethoxy-3-oxopropanoate (**3**)(1.6 eq.), HOBt (2 eq.) and molecular sieve 3A (0.6 g/mmol substrate) are suspended in dry dichloromethane

(0.3M), and the suspension was cooled to 0 °C. Allylic amine (**4**) (1 eq.) and EDC (1.5 eq.) were added at 0 °C, and the mixture was stirred for 30 minutes at this temperature. The reaction was warmed to roomtemperature over night. The mixture was poured into 10% HCl (aq.) (14 mL/mmol substrate), and the phases were separated. The organic phase was washed with saturated $NaHCO_3$ solution twice and dried with $MgSO_4$. The solvent was evaporated under reduced pressure to yield the crude product, which was used without further purification.

General procedure C for the synthesis of *gem*-diazido *N*-allyl malonamides 1

N-Allyl malonamides **5** (1 eq.) were dissolved in DMSO/water (2/1) (0.1 M), and NaN_3 (4 eq.) and $NaHCO_3$ (3 eq.) were added under heavy stirring. The suspension was cooled to 0 °C, and iodine (2.05 eq.) wwas slowly added. The reaction maintained at this temperature for 10 min before warming to room temperature. The mixture was stirred at room temperature until complete consumption of the starting material (monitored via TLC) (~ 2 h). The reaction mixture was quenched with aqueous saturated solution of $Na_2S_2O_3$ until complete discoloration appeared. The mixture was extracted with EtOAc, and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash-chromatography on silica gel furnished the corresponding *gem*-diazido *N*-allyl malonamides **1**.

General procedure D for the synthesis of pyrazines 2

The reaction was carried out under argon atmosphere. *Gem*-diazido *N*-allyl malonamide **1** (1 eq.) was dissolved in xylenes (0.05 M) and stirred at 140 °C for 24 h. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. Purification by flash-chromatography on silica gel furnished the corresponding pyrazines **2**.

General procedure E for the synthesis of pyrazines 2

The reaction was carried out under argon atmosphere. *Gem*-diazido *N*-allyl malonamide **1** (1 eq.) was dissolved in glacial acetic acid (0.05 M). Copper(I)iodide (1.5 eq.) was added, and the reaction was stirred at 120 °C for 24 h. The reaction mixture was cooled to room temperature and filtered through a short pad of celite. The filtrate was evaporated under reduced pressure. Purification by flash-chromatography on silica gel furnished the corresponding pyrazines **2**.

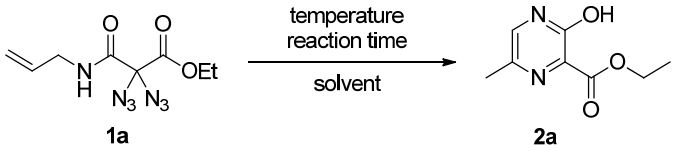
General procedure F for the Suzuki coupling

The reaction was carried out under argon atmosphere in degassed solvents. Ethyl 6-methyl-3-(((trifluoromethyl)sulfonyl)oxy)pyrazine-2-carboxylate **9c** (1 eq.), Cs_2CO_3 (3 eq.) and the arylboronic acid were dissolved in dioxane/water (4/1) (0.1 M). $Pd(PPh_3)_4$ (5 mol%) were added at once, and the reaction was stirred at 85 °C over night. The reaction mixture was filtered through a short pad of celite, and the filtrate was evaporated. Purification by flash-chromatography on silica gel furnished the corresponding 3-arylpyrazines **10**.

3. Optimization of reaction conditions

The formation of pyrazine **2a** through conversion of diazide **1a** was optimized as summarized in the following tables.

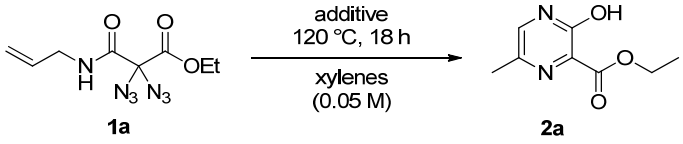
Table 1: Thermolysis conditions.



entry	temperature [°C]	solvent	time [h]	yield [%][a]
1	140 (mw)	xylenes (0.025M)	4	38
2	130	xylenes (0.05M)	18	39
3	120	xylenes (0.05M)	18	39
4	110	toluene (0.05M)	18	43
5	140	xylenes (0.05M)	18	43
6	140	xylenes (0.025M)	18	34
7	140	xylenes (0.1M)	18	25
8	160	1,2-dichlorobenzene (0.05M)	1	27
9	160	1,2-dichlorobenzene (0.025M)	1	25
10	140	DMSO (0.05M)	4	---[b]
11	120	DMF (0.05M)	18	---[b]
12	120	pyridine (0.05M)	18	21[c]
13	120	acetic acid (0.05M)	18	52[c]

[a] = isolated yield after column chromatography; [b] = decomposition; [c] = yield according to ^{1}H-NMR with tetrachloroethane as internal standard (0.3M in $CDCl_3$).

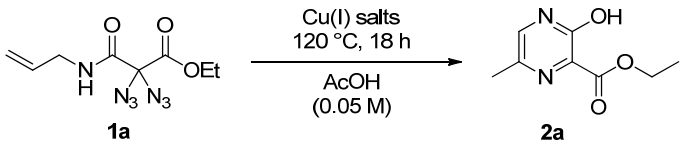
Table 2: Screening of additives.



entry	additive	yield [%][a]
1	*p*TsOH	14
2	TFA	45
3	NBu_4HSO_4	43
4	Benzoic acid	23
5	Acetic acid	21
6	Pivaloic acid	20
7	morpholine	28
8	NEt_3	34
9	DBU	---[b]
10	H_2O	35
11	CuI	40
12	$CuSO_4$	33
13	$FeCl_3$	---[b]
14	$PdOAc_2$	---[b]

[a] = yield according to ^{1}H-NMR with tetrachloroethane as internal standard (0.3M in $CDCl_3$); [b] = no product formation.

Table 3: Screening with copper salts.

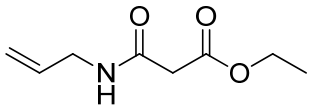


entry	Cu(I) salt	equivalents	yield [%][a]
1	CuOTf	1.00	---
2	CuCN	1.00	45
3	CuCl	1.00	---
4	CuBr	1.00	44
5	CuI	1.00	53
6	CuI	0.25	33
7	CuI	0.50	30
8	CuI	0.75	43
9	CuI	1.50	57
10	CuI	2.00	57
11	CuI	1.50	68[c]

[a] = yield according to ^{1}H-NMR with tetrachloroethane as internal standard (0.3M in $CDCl_3$); [b] = no product formation; [c] = isolated yield (2 g scale).

4. Experimental details

Ethyl 3-(allylamino)-3-oxopropanoate (5a)

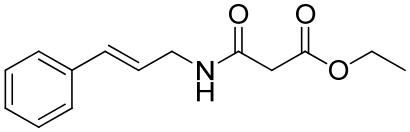


$C_8H_{13}NO_3$

171.1937

According to the general procedure A using potassium 3-ethoxy-3-oxopropanoate (**3)** (6.00 g, 35.2 mmol, 1.0 eq.) and allyl amine (6.61 mL, 88 mmol, 2.5 eq.), ethyl 3-(allylamino)-3-oxopropanoate (4.79 g, 28.0 mmol, 79%) (**5a**) was obtained without further purification as yellow solid. TLC: R_f = 0.1 (CH:EE 80:20)[UV, $KMnO_4$]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 7.20 (s, 1H), 5.85 (ddt, *J* = 17.2, 10.3, 5.5 Hz, 1H), 5.21 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.15 (dq, *J* = 10.3, 1.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.92 (tt, *J* = 5.7, 1.6 Hz, 2H), 3.33 (s, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 169.8, 164.9, 133.9, 116.5, 61.7, 42.0, 41.2, 14.2. The analytical data are in agreement with previously reported ones.[1]

Ethyl 3-(cinnamylamino)-3-oxopropanoate (5b)



$C_{14}H_{17}NO_3$

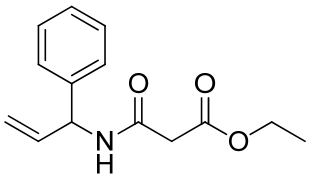
247.2897

According to the general procedure A using potassium 3-ethoxy-3-oxopropanoate (**3**) (200 mg, 1.18 mmol, 1.0 eq.) and cinnamyl amine (250 mg, 1.88 mmol, 1.6 eq.), Ethyl 3-(cinnamylamino)-3-oxopropanoate (**5b**) (290 mg, 1.14 mmol, 99%) was obtained without further purification as yellow oil. TLC: R_f = 0.33 (CH:EE 50:50)[UV, $KMnO_4$].^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 7.38 – 7.33 (m, 2H), 7.34 – 7.28 (m, 2H), 7.27 – 7.20 (m, 1H), 6.54 (dt, *J* = 15.8, 1.6 Hz, 1H), 6.20 (dt, *J* = 15.8, 6.3 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.08 (td, *J* = 6.2, 1.6 Hz, 2H), 3.35 (s, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 169.6, 164.8, 136.5, 132.3, 128.5, 127.7, 126.4, 125.1, 61.6, 41.5,

[1] T.A. Alanine, Galloway, R. J. D. Warren, T.M. McGuire and D. R. Spring, *Eur. J. Org. Chem.*, 2014, 5767.

41.1, 14.0. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3294, 3083, 2996, 2873, 1739, 1634, 1556, 1152, 961, 688. LRMS (ESI) = 248.1 (100%)$[M+H]^+$, 270.1 (35%). HRMS (ESI): [m/z] 270.1103 (calc'd for $C_{14}H_{17}NNaO_3$: 270.1101).

Ethyl 3-oxo-3-((1-phenylallyl)amino)propanoate (5c)

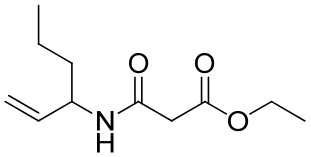


$C_{14}H_{17}NO_3$

247.2897

According to the general procedure B using potassium 3-ethoxy-3-oxopropanoate (**3**) (711 mg, 4.18 mmol, 1.6 eq.) and 1-phenylprop-2-en-1-amine (348 mg, 2.61 mmol, 1.0 eq.), ethyl 3-oxo-3-((1-phenylallyl)amino)propanoate (**5c**) (670 mg, 2.57 mmol, 98%) was obtained without further purification as yellow oil. TLC: R_f = 0.2 (CH:EE 50:50)[UV, $KMnO_4$]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 7.57 (d, *J* = 6.7 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.32 – 7.26 (m, 3H), 6.02 (ddd, *J* = 17.3, 10.2, 5.3 Hz, 1H), 5.70 – 5.64 (m, 1H), 5.27 – 5.25 (m, 1H), 5.24 – 5.22 (m, 1H), 4.20 (q, *J* = 7.2, 2H), 3.37 (d, *J* = 17.6 Hz, 1H), 3.33 (d, *J* = 17.6 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 4H).^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 169.8, 164.1, 140.5, 137.4, 128.9, 127.8, 127.3, 115.9, 61.8, 55.3, 41.2, 14.2. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3292, 3063, 3031, 2982, 2938, 2907, 1735, 1649, 1536, 1031, 699. MS (ESI) = 248.1 (100%)$[M+H]^+$, 270.1 (15%). HRMS (ESI): [m/z] 270.1100 (calc'd for $C_{14}H_{17}NNaO_3$: 270.1001).

Ethyl 3-(hex-1-en-3-ylamino)-3-oxopropanoate (5d)



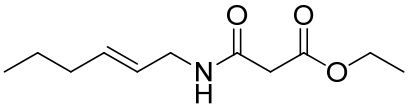
$C_{11}H_{19}NO_3$

213.2735

According to the general procedure B using potassium 3-ethoxy-3-oxopropanoate (**3**) (994 mg, 5.84 mmol, 1.6 eq.) and hex-1-en-3-amine (362 mg, 3.65 mmol, 1.0 eq.), Ethyl 3-(hex-1-en-3-ylamino)-3-oxopropanoate (**5d**) (605 mg, 2.84 mmol, 77%) was obtained without further purification as yellow

oil. TLC: R_f = 0.3 (CH:EE 50:50)[UV, $KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.05 (s, 1H), 5.77 (ddd, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.16 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.09 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.55 – 4.45 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.32 (s, 2H), 1.60 – 1.32 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 169.9, 164.3, 138.3, 114.8, 61.7, 51.4, 41.3, 37.1, 19.0, 14.2, 14.0. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3290, 3081, 2960, 2935, 2873, 1739, 1640, 1544, 1153, 1035, 920. LRMS (ESI) = 214.1 (100%)$[M+H]^+$, 236.1 (9%). HRMS (ESI): [m/z] 236.1255 (calc'd for $C_{11}H_{19}NNaO_3$: 236.1257)

(*E*)-Ethyl 3-(hex-2-en-1-ylamino)-3-oxopropanoate (5e)

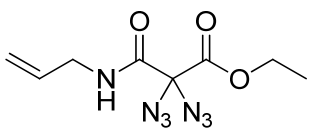


$C_{11}H_{19}NO_3$

213.2735

According to the general procedure A using potassium 3-ethoxy-3-oxopropanoate (**3**) (600 mg, 3.53 mmol, 1.0 eq.) and (E)-hex-2-en-1-amine (559 mg, 5.64 mmol, 1.6 eq.), (E)-ethyl 3-(hex-2-en-1-ylamino)-3-oxopropanoate (**5e**) (712 mg, 3.34 mmol, 94%) was obtained without further purification as yellow oil. TLC: R_f = 0.3 (CH:EE 50:50)[UV, $KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.07 (s, 1H), 5.68 – 5.56 (m, 1H), 5.51 – 5.37 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.90 – 3.81 (m, 2H), 3.30 (s, 2H), 2.03 – 1.96 (m, 2H), 1.39 (h, *J* = 7.4 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 169.6, 164.6, 133.7, 125.3, 61.5, 41.5, 41.1, 34.3, 22.2, 14.0, 13.6. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3293, 3078, 2959, 2873, 1739, 1648, 1544, 1152, 1030, 968, 542. LRMS (ESI) = 214.1 (100%)$[M+H]^+$, 236.1 (10%). HRMS (ESI): [m/z] 236.1250 (calc'd for $C_{11}H_{19}NNaO_3$: 236.1257).

Ethyl 3-(allylamino)-2,2-diazido-3-oxopropanoate (1a)



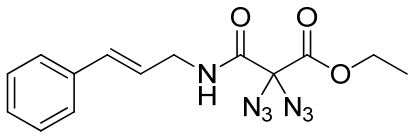
$C_8H_{11}N_7O_3$

253.2180

According to the general procedure C using Ethyl 3-(allylamino)-3-oxopropanoate (**5a**) (4.00 g, 23.4 mmol, 1.0 eq.), ethyl 3-(allylamino)-2,2-diazido-3-oxopropanoate (**1a**). (4.61 g, 18.2 mmol, 78%)

was obtained after flash chromatography (CH:EE 90:10 → 80/20) as slightly yellow oil. TLC: R_f = 0.4 (CH:EE 80:20)[UV, $KMnO_4$]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.57 (s, 1H), 5.83 (ddt, *J* = 17.2, 10.3, 5.5 Hz, 1H), 5.30 – 5.20 (m, 1H), 5.20 (dq, *J* = 10.3, 1.3 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.93 (tt, *J* = 5.8, 1.6 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 164.6, 163.3, 132.8, 117.4, 79.6, 64.3, 42.4, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3339, 2987, 2939, 2124, 1751, 1684, 1518, 1028, 545. HRMS (ESI): [m/z] 276.0815 (calc'd for $C_8H_{11}N_7NaO_3$ 276.0816).

Ethyl 2,2-diazido-3-(cinnamylamino)-3-oxopropanoate (1b)

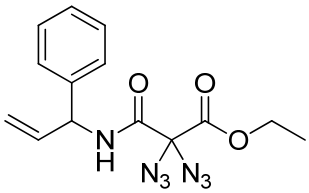


$C_{14}H_{15}N_7O_3$

329.3140

According to the general procedure C using ethyl 3-(cinnamylamino)-3-oxopropanoate (**5b**) (290 mg, 1.17 mmol, 1.0 eq.), ethyl 2,2-diazido-3-(cinnamylamino)-3-oxopropanoate (**1b**) (202 mg, 0.61 mmol, 52%) was obtained after flash chromatography (CH:EE 90:10 → 80:20) as white solid. TLC: R_f = 0.3 (CH:EE 80:20)[UV, $KMnO_4$]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 7.38 – 7.31 (m, 4H), 7.28 – 7.26 (m, 1H), 6.63 (s, 1H), 6.57 (dt, *J* = 15.8, 1.5 Hz, 1H), 6.16 (dt, *J* = 15.8, 6.3 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.09 (td, *J* = 6.3, 1.5 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 164.6, 163.3, 136.3, 133.5, 128.8, 128.2, 126.6, 123.8, 79.6, 64.3, 42.2, 14.2. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3339, 3059, 3027, 2983, 2934, 2856, 2124, 1749, 1684, 1518, 1225, 1026, 747, 692. LRMS (ESI) = 330.1 (100%)$[M+H]^+$, 352.1 (28%). HRMS (ESI): 352.1130 [m/z] (calc'd for $C_{14}H_{15}N_7NaO_3$: 352.1129).

Ethyl 2,2-diazido-3-oxo-3-((1-phenylallyl)amino)propanoate (1c)

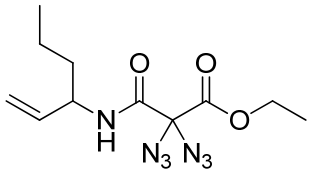


$C_{14}H_{15}N_7O_3$

329.3140

According to the general procedure C using ethyl 3-oxo-3-((1-phenylallyl)amino)propanoate (**5c**) (670 mg, 2.57 mmol, 1.0 eq.), ethyl 2,2-diazido-3-oxo-3-((1-phenylallyl)amino)propanoate (**1c**) (637 mg, 1.93 mmol, 75%) was obtained after flash chromatography (CH:EE 90:10 → 80:20) as white solid. TLC: R_f = 0.5 (CH:EE 75:25)[UV, $KMnO_4$]. ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.39 – 7.35 (m, 2H), 7.34 – 7.27 (m, 3H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.02 (ddd, *J* = 17.2, 10.4, 5.3 Hz, 1H), 5.61 – 5.57 (m, 1H), 5.31 (ddd, *J* = 10.4, 1.7, 0.9 Hz, 1H), 5.27 (ddd, *J* = 17.2, 1.7, 0.9 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 164.5, 162.6, 139.3, 136.1, 129.1, 128.3, 127.2, 116.9, 79.5, 64.3, 55.9, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3299, 3033, 2994, 2933, 2127, 1755, 1634, 1522, 1225, 1028, 703. LRMS (ESI) = 330.1 (100%)$[M+H]^+$. HRMS (ESI): [m/z] 352.1131 (calc'd for $C_{14}H_{15}N_7NaO_3$: 352.1129).

Ethyl 2,2-diazido-3-(hex-1-en-3-ylamino)-3-oxopropanoate (1d)

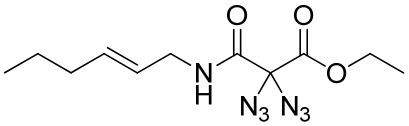


$C_{11}H_{17}N_7O_3$

295.2978

According to the general procedure C using ethyl 3-(hex-1-en-3-ylamino)-3-oxopropanoate (**5d**) (593 mg, 2.78 mmol, 1.0 eq.), ethyl 2,2-diazido-3-(hex-1-en-3-ylamino)-3-oxopropanoate (**1d**) (749 mg, 2.31 mmol, 83%) was obtained after flash chromatography (CH:EE 90:10 → 70:30) as colorless oil. TLC: R_f = 0.7 (CH:EE 50:50)[UV, $KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.34 (d, *J* = 8.8 Hz, 1H), 5.76 (ddd, *J* = 17.2, 10.4, 5.5 Hz, 1H), 5.27 – 5.06 (m, 2H), 4.50 – 4.40 (m, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.63 – 1.30 (m, 8H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 164.7, 162.8, 137.3, 115.7, 79.6, 64.2, 52.1, 36.8, 19.0, 14.1, 13.9. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3329, 2961, 2936, 2875, 2125, 1752, 1686, 1517, 1228, 1044. LRMS (ESI) = 296.1 (100%)$[M+H]^+$, 318.1 (19%). HRMS (ESI): [m/z] 318.1283 (calc'd for $C_{11}H_{17}N_7NaO_3$: 318.1285).

(*E*)-Ethyl 2,2-diazido-3-(hex-2-en-1-ylamino)-3-oxopropanoate (1e)

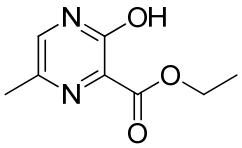


$C_{11}H_{17}N_7O_3$

295.2978

According to the general procedure C using (*E*)-ethyl 3-(hex-2-en-1-ylamino)-3-oxopropanoate (**5e**) (780 mg, 3.66 mmol, 1.0 eq.), (E)-ethyl 2,2-diazido-3-(hex-2-en-1-ylamino)-3-oxopropanoate (**1e**) (724 mg, 2.45 mmol, 67%) was obtained after flash chromatography (CH:EE 90:10 → 80:20) as yellow oil. TLC: R_f = 0.4 (CH:EE 80:20)[UV, $KMnO_4$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.47 (s, 1H), 5.71 – 5.61 (m, 1H), 5.48 – 5.38 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.86 (tq, *J* = 6.0, 1.0 Hz, 2H), 2.01 (m, 2H), 1.45 – 1.32 (m, 5H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 164.5, 162.8, 134.9, 124.1, 79.4, 64.1, 42.0, 34.2, 22.1, 14.0, 13.6. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3339, 2961, 2931, 2873, 2125, 1751, 1685, 1518, 1226, 1028, 968, 755, 546; LRMS (ESI) = 296.1 (100%)$[M+H]^+$, 318.1 (66%). HRMS (ESI): [m/z] 318.1291 (calc'd for $C_{11}H_{17}N_7NaO_3$: 318.1285).

Ethyl 3-hydroxy-6-methylpyrazine-2-carboxylate (2a)

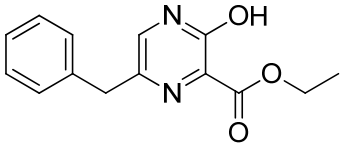


$C_8H_{10}N_2O_3$

182.1766

According to general procedure E using ethyl 3-(allylamino)-2,2-diazido-3-oxopropanoate (**1a**) (2.00 g, 7.79 mmol, 1 eq.), ethyl 3-hydroxy-6-methylpyrazine-2-carboxylate (**2a**) (963 mg, 5.29 mmol, 68%) was obtained after flash chromatography (DCM:MeOH 100:0 → 95:5) as yellow solid. TLC: R_f = 0.25 (DCM:MeOH 97:3)[UV, $KMnO_4$]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 11.17 (s, 1H), 8.29 (s, 1H), 4.57 (q, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 168.6, 160.9, 147.7, 146.1, 125.4, 63.3, 20.5, 14.2. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3035, 2983, 2929, 2128, 1736, 1668, 1526, 1136, 736. LRMS (ESI) = 205.0 (100%), 183.1 (61%)$[M+H]^+$. HRMS (ESI): [m/z] 205.0583 (calc'd for $C_8H_{10}N_2NaO_3$: 205.0584).

Ethyl 6-benzyl-3-hydroxypyrazine-2-carboxylate (2b)

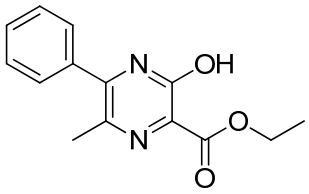


$C_{14}H_{14}N_2O_3$

258.2726

According to general procedure E using ethyl 2,2-diazido-3-(cinnamylamino)-3-oxopropanoate (**1b**) (100 mg, 0.30 mmol, 1 eq.), ethyl 6-benzyl-3-hydroxypyrazine-2-carboxylate (**2b**) (25.7 mg, 0.1 mmol, 32%) was obtained after flash chromatography (DCM:MeOH 100:0 → 95:5) as yellow oil. TLC: R_f = 0.5 (DCM:MeOH 97:3)[UV, $KMnO_4$]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 10.91 (s, 1H), 8.18 (s, 1H), 7.34 – 7.30 (m, 2H), 7.25 (dd, *J* = 7.7, 5.8 Hz, 3H), 4.57 (q, *J* = 7.1 Hz, 2H), 4.20 (s, 2H), 1.49 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 168.5, 160.9, 148.5, 147.4, 138.0, 128.9, 128.8, 126.9, 125.8, 63.3, 40.9, 14.2. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3063, 3029, 2983, 2930, 2130, 1727, 1651, 1451, 1135. LRMS (ESI) = 259.1 (100%)$[M+H]^+$, 281.1 (10%). HRMS (ESI): [m/z] 281.0896 (calc'd for $C_{14}H_{14}N_2NaO_3$: 281.0897).

Ethyl 3-hydroxy-6-methyl-5-phenylpyrazine-2-carboxylate (2c)



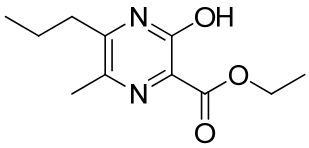
$C_{14}H_{14}N_2O_3$

258.2726

According to general procedure E using ethyl 2,2-diazido-3-oxo-3-((1-phenylallyl)amino)propanoate (**1c**) (50 mg, 0.15 mmol, 1 eq.) and a reaction time of 60 h, ethyl 3-hydroxy-6-methyl-5-phenylpyrazine-2-carboxylate (**2c**) (22.2 mg, 0.08 mmol, 50%) was obtained after flash chromatography (CH:EA 60:40) as white-yellow solid. TLC: R_f = 0.3 (CH:EA 60:40)[UV, $KMnO_4$]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 10.35 (s, 1H), 7.68 – 7.63 (m, 2H), 7.50 – 7.46 (m, 3H), 4.58 (q, *J* = 7.1 Hz, 2H), 2.65 (s, 3H), 1.50 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 168.7, 160.4, 157.2, 144.1, 137.3, 129.8, 129.3, 128.5, 123.9, 63.3, 22.6, 14.4. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3062, 2983, 2932, 1732, 1671, 1396,

1126, 726, 698. LRMS (ESI) = 259.1 (100%)$[M+H]^+$, 281.1 (11%). HRMS (ESI): [m/z] 281.0895 (calc'd for $C_{14}H_{14}N_2NaO_3$: 281.0897).

Ethyl 3-hydroxy-6-methyl-5-propylpyrazine-2-carboxylate (2d)

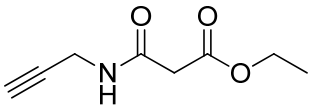


$C_{11}H_{16}N_2O_3$

224.2563

According to general procedure D using ethyl 2,2-diazido-3-(hex-1-en-3-ylamino)-3-oxopropanoate (**1d**) (50 mg, 0.15 mmol, 1 eq.), ethyl 3-hydroxy-6-methyl-5-propylpyrazine-2-carboxylate (**2d**) (11 mg, 0.05 mmol, 32%) was obtained after flash chromatography (CH:EA 60:40 → 50:50) as yellow oil. TLC: R_f = 0.3 (CH:EA 50:50)[UV, $KMnO_4$]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 4.54 (q, *J* = 7.1 Hz, 2H), 2.79 – 2.75 (m, 2H), 2.55 (s, 3H), 1.78 (h, *J* = 7.4 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 169.0, 161.3, 160.9, 144.7, 122.7, 63.1, 37.2, 21.3, 20.9, 14.4, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2963, 2933, 2873, 1732, 1667, 1408, 1154, 730 LRMS (ESI) = 179.1 (100%), 225.1 (93%)$[M+H]^+$, 247.1 (13%). HRMS (ESI): [m/z] 247.1068 (calc'd for $C_{11}H_{16}N_2NaO_3$: 247.1053).

Ethyl 3-oxo-3-(prop-2-yn-1-ylamino)propanoate (13)



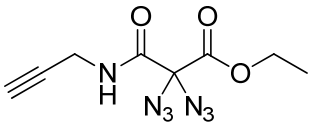
$C_8H_{11}NO_3$

169.1778

According to general procedure A using potassium 3-ethoxy-3-oxopropanoate (**3**) (2.00 g, 11.7 mmol, 1.0 eq.) and propargyl amine (1.88 mL, 29.4 mmol, 2.5 eq.), ethyl 3-oxo-3-(prop-2-yn-1-ylamino)propanoate (**13**) (1.22 g, 7.21 mmol, 61%) was obtained without further purification as yellow oil. TLC: R_f = 0.22 (CH.EA 50:50). ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 7.42 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.07 (dd, *J* = 5.3, 2.6 Hz, 2H), 3.32 (s, 2H), 2.23 (t, *J* = 2.6 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 169.5, 164.9, 79.3, 71.8, 61.8, 40.9, 29.3, 14.2. IR (ATR):

$\tilde{\nu}$ [cm^{-1}] = 3286, 3077, 2984, 2939, 2122, 1732, 1651, 1536, 1155, 1021, 663. LRMS (ESI) = 170.1 (100%)$[M+H]^+$. HRMS (ESI): [m/z] 192.0631 (calc'd for $C_8H_{11}NNaO_3$: 192.0631).

Ethyl 2,2-diazido-3-oxo-3-(prop-2-yn-1-ylamino)propanoate (6)

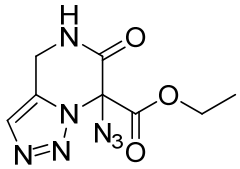


$C_8H_9N_7O_3$

251.2022

According to general procedure C using ethyl 3-oxo-3-(prop-2-yn-1-ylamino)propanoate (**13**) (1.2 g, 7.09 mmol, 1 eq.), ethyl 2,2-diazido-3-oxo-3-(prop-2-yn-1-ylamino)propanoate (**6**) (1.32 g, 4.99 mmol, 70%) was obtained after flash-chromatography (CH:EA 90:10 → 50:50) as yellow oil. TLC: R_f = 0.5 (CH/EE : 50/50). ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 6.68 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.09 (dd, *J* = 5.4, 2.6 Hz, 2H), 2.29 (t, *J* = 2.6 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 164.3, 163.1, 79.3, 78.0, 72.9, 64.4, 30.0, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3300, 2986, 2941, 2124, 1750, 1686, 1512, 1225, 1031, 853, 545. HRMS (ESI): [m/z] calc'd for $[C_8H_9N_7NaO_3][M+Na]^+$: 274.0659, found 274.0657.

Ethyl 7-azido-6-oxo-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine-7-carboxylate (7)



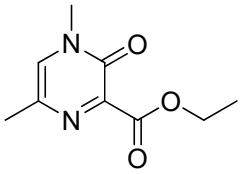
$C_8H_9N_7O_3$

251.2022

According to general procedure E using ethyl 2,2-diazido-3-oxo-3-(prop-2-yn-1-ylamino)propanoate (**6**) (25 mg, 0.1 mmol, 1 eq.) stirred at 100 °C, ethyl 7-azido-6-oxo-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine-7-carboxylate (**7**) (18.6 mg, 44.7 µmol, 37%) was obtained after flash-chromatography (DCM:MeOH 100:0 → 97:3) as yellow oil. (contains 50% DCM, determined via ^{1}H-NMR). TLC: R_f = 0.3 (DCM:MeOH 97:3). ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 7.70 (t, *J* = 0.8 Hz, 1H), 7.68 (s, 1H), 4.85 – 4.74 (m, 2H), 4.48 – 4.28 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 162.5, 162.0, 129.3, 127.7, 75.4, 64.9, 37.1, 13.8. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3223,

3151, 2986, 2940, 2253, 2133, 1765, 1702, 1227, 1042, 908, 725, 647, 527. LRMS (ESI) = 252.1 (20%)$[M+H]^+$, 274.1 (100%)$[M+Na]^+$. HRMS (ESI): [m/z] 274.0660 (calc'd for $C_8H_9N_7NaO_3$: 274.0659).

Ethyl 4,6-dimethyl-3-oxo-3,4-dihydropyrazine-2-carboxylate (8)

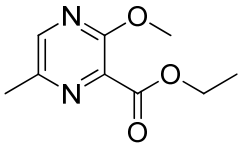


$C_9H_{12}N_2O_3$

196.2032

Ethyl 3-hydroxy-6-methylpyrazine-2-carboxylate (**2a**) (100 mg, 0.55 mmol, 1 eq.) was dissolved in MeCN (4 mL, 0.1 M). Cs_2CO_3 (214 mg, 0.66 mmol, 1.2 eq.) and MeI (41 µL, 0.66 mmol, 1.2 eq.) were added. The mixture was stirred at room temperature over night. Water and dichloromethane were added and the organic phase was separated. The aqueous phase was washed with dichloromethane, and the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash-chromatography (DCM:MeOH 100/0 → 95/5) on silica gel gave ethyl 4,6-dimethyl-3-oxo-3,4-dihydropyrazine-2-carboxylate (**8**) (93 mg, 0.48 mmol, 86%) as yellow solid. TLC**:** R_f = 0.3 (DCM/MeOH: 97/3) [UV, CAM]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 7.14 (s, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.55 (s, 3H), 2.31 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 164.0, 153.4, 145.9, 131.3, 130.2, 62.3, 37.7, 19.5, 14.3. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3053, 2988, 2930, 2856, 1725, 1641, 1591, 1146, 1020; LRMS (ESI) = 169.1 (100%), 197.1 (75%)$[M+H]^+$. HRMS (ESI): [m/z] 219.0741 (calc'd for $C_9H_{12}N_2NaO_3$: 219.0740)

Ethyl 3-methoxy-6-methylpyrazine-2-carboxylate (9a)



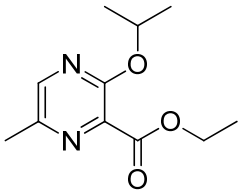
$C_9H_{12}N_2O_3$

196.2032

The reaction was carried out under argon atmosphere. Ethyl 3-hydroxy-6-methylpyrazine-2-carboxylate (**2a**) (400 mg, 2.2 mmol, 1 eq.) was dissolved in a 1:1 mixture of benzene/heptane (11 mL, 0.2 M).

Ag_2CO_3 (726.5 mg, 2.63 mmol, 1.2 eq.) and MeI (273 µL, 4.39 mmol, 2 eq.) were added in the dark. The reaction was protected from light and stirred at 90 °C for 18 h. The resulting suspension was filtered through a short pad of celite, and the filtrate was evaporated under reduced pressure. Purification by flash-chromatography (CH:EA 80:20 → 60:40) afforded ethyl 3-methoxy-6-methylpyrazine-2-carboxylate (**9a**) (289 mg, 1.47 mmol, 67%) as yellow oil. TLC: R_f = 0.4 (CH:EA 50:50)[UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.11 (d, *J* = 0.6 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 4.02 (s, 3H), 2.53 (d, *J* = 0.6 Hz, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 164.4, 157.5, 144.9, 143.1, 133.1, 62.2, 54.3, 20.4, 14.4. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2986, 2955, 2931, 2861, 1730, 1469, 1101. LRMS (ESI) = 169.1 (100%), 197.1 (80%)$[M+H]^+$, 219.1 (46%). HRMS (ESI): [m/z] 219.0739 (calc'd for $C_9H_{12}N_2NaO_3$: 219.0740).

Ethyl 3-isopropoxy-6-methylpyrazine-2-carboxylate (9b)

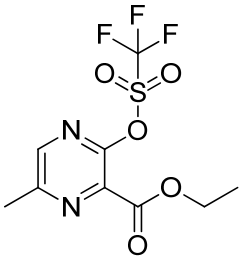


$C_{11}H_{16}N_2O_3$

224.2563

The reaction was carried out under argon atmosphere. Ethyl 3-hydroxy-6-methylpyrazine-2-carboxylate (**2a**) (200 mg, 1.1 mmol, 1 eq.) was dissolved in a 1:1 mixture of benzene/heptane (5.5 mL, 0.2 M). Ag_2CO_3 (363 mg, 1.32 mmol, 1.2 eq.) and *i*PrI (219 µL, 4.39 mmol, 2 eq.) were added in the dark. The reaction was protected from light and stirred at 90 °C for 18 h. The resulting suspension was filtered through a short pad of celite, and the filtrate was evaporated under reduced pressure. Purification by flash-chromatography (CH:EA 90:10 → 80/20) gave ethyl 3-isopropoxy-6-methylpyrazine-2-carboxylate (**9b**) (221 mg, 0.99 mmol, 89%) as pale yellow oil. TLC: R_f = 0.6 (CH:EE 50:50)[UV]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 8.07 – 8.05 (m, 1H), 5.31 (hept, *J* = 6.2 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.51 – 2.49 (m, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.37 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 164.7, 156.7, 144.3, 142.8, 133.9, 70.1, 61.9, 22.0, 20.3, 14.3. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2980, 2935, 2873, 1732, 1441, 1307, 1098. LRMS (ESI) = 183.1 (100%), 225.1 (41%)$[M+H]^+$, 247.1 (12%). HRMS (ESI): [m/z] 247.1058 (calc'd for $C_{11}H_{16}N_2NaO_3$: 247.1053).

Ethyl 6-methyl-3-(((trifluoromethyl)sulfonyl)oxy)pyrazine-2-carboxylate (9c)



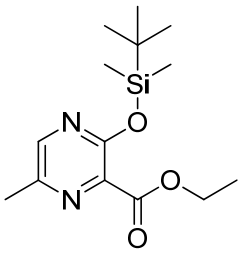
$C_9H_9F_3N_2O_5S$

314.2384

The reaction was carried out under argon atmosphere. Ethyl 3-hydroxy-6-methylpyrazine-2-carboxylate (**2a**) (250 mg, 1.37 mmol, 1 eq.) was dissolved in dichloromethane (5 mL, 0.27 M). NEt_3 (570 µL, 4.12 mmol, 3 eq.) and Tf_2O (300 µL, 1.78 mmol, 1.3 eq.) were added at -20 °C, and the reaction was stirred

at this temperature for 10 min, before it was warmed up to 0 °C and stirred for another 1.5 h. Diethylether and aqueous saturated $NaHCO_3$ solution was added. The aqueous phase was extracted with diethylether. The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash-chromatography (CH:EA 70:30) gave ethyl 6-methyl-3-(((trifluoromethyl)sulfonyl)oxy)pyrazine-2-carboxylate (**9c**) (295 mg, 0.94 mmol, 68%) as white solid. TLC: R_f = 0.4 (CH/EE : 50/50)[UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.37 (d, *J* = 0.7 Hz, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 2.72 (d, *J* = 0.7 Hz, 3H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 161.9 , 154.9 , 149.9 , 144.9 , 136.2 , 118.6 (q, *J* = 320.8 Hz), 63.4 , 21.2 , 14.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ [ppm] = -73.6. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2986, 2941, 1736, 1610, 1425, 1206, 1087, 872, 602. LRMS (ESI) = 315.0 (100%)$[M+H]^+$, 287.0 (26%). HRMS (ESI): [m/z] 337.0076 (calc'd for $C_9H_9F_3N_2NaO_5S$: 337.0076).

Ethyl 3-((tert-butyldimethylsilyl)oxy)-6-methylpyrazine-2-carboxylate (9d)



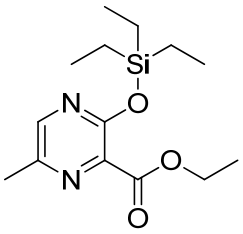
$C_{14}H_{24}N_2O_3Si$

296.4375

The reaction was carried out under argon atmosphere. Ethyl 3-hydroxy-6-methylpyrazine-2-carboxylate (**2a**) (100 mg, 0.55 mmol, 1 eq.) was dissolved in pyridine (1.8 mL, 0.3 M). Imidazole (112 mg, 1.65 mmol, 3 eq.) and TBSCl (248 mL, 1.65 mmol, 3 eq.) were added and stirred at ambient temperature over night. The reaction was quenched with water and extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash-chromatography (CH:EA 90:10 → 80:20) afforded ethyl 3-((*tert*-butyldimethylsilyl)oxy)-6-methylpyrazine-2-carboxylate (**9d**) (136 mg, 0.46 mmol, 83%) as yellow oil. TLC: R_f = 0.6 (CH:EA 50:50)[UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.04 (d, *J* = 0.7 Hz, 1H),

4.43 (q, J = 7.1 Hz, 2H), 2.51 (d, J = 0.7 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H), 1.00 (s, 9H), 0.33 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 165.0, 155.7, 145.4, 143.3, 134.8, 62.0, 25.7, 20.4, 18.1, 14.4, -4.3. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2956, 2931, 2897, 2859, 1734, 1450, 1101, 785. LRMS (ESI) = 297.2 (100%)$[M+H]^+$. HRMS (ESI): [m/z] 319.1449 (calc'd for $C_{14}H_{24}N_2NaO_3Si$: 319.1448).

Ethyl 6-methyl-3-((triethylsilyl)oxy)pyrazine-2-carboxylate (9e)

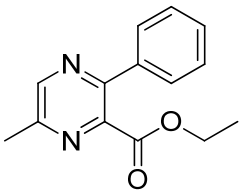


$C_{14}H_{24}N_2O_3Si$

296.4375

The reaction was carried out under argon atmosphere. Ethyl 3-hydroxy-6-methylpyrazine-2-carboxylate (**2a**) (50 mg, 0.27 mmol, 1 eq.) was dissolved in dichloromethane (2.7 mL, 0.1 M). At 0 °C, 2,6-lutidine (97 µL, 0.82 mmol, 3 eq.) and TESOTf (186 µL, 0.82 mmol, 3 eq.) were added and stirred at 0 °C for another hour. The reaction was warmed up to ambient temperature over night and quenched with aqueous saturated $NaHCO_3$ solution and extracted with dichloromethane. The combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash-chromatography (CH:EA 90:10 → 80:20) afforded ethyl 6-methyl-3-((triethylsilyl)oxy)pyrazine-2-carboxylate (**9e**) (54 mg, 0.18 mmol, 66%) as yellow oil. TLC: R_f = 0.4 (CH:EE 80:20)[UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.04 (s, 1H), 4.43 (q, J = 7.1 Hz, 2H), 2.51 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H), 1.03 – 0.97 (m, 9H), 0.88 – 0.81 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 165.0, 155.6, 145.4, 143.5, 134.4, 61.9, 20.5, 14.4, 6.7, 5.2. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2956, 2938, 2913, 2877, 1734, 1448, 1101, 722. LRMS (ESI) = 251.1 (37%), 269.1 (23%), 297.2 (100%)$[M+H]^+$. HRMS (ESI): [m/z] 319.1486 (calc'd for $C_{14}H_{24}N_2NaO_3Si$: 319.1448).

Ethyl 6-methyl-3-phenylpyrazine-2-carboxylate (10a)

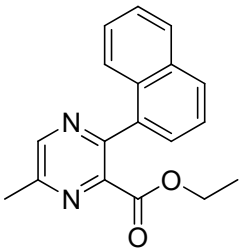


$C_{14}H_{14}N_2O_2$

242.2732

According to general procedure F using ethyl 6-methyl-3-(((trifluoromethyl)sulfonyl)oxy)pyrazine-2-carboxylate (**9c**) (30 mg, 95.4 µmol, 1 eq.) and phenylboronic acid (17.5 mg, 0.14 mmol, 1.5 eq.), ethyl 6-methyl-3-phenylpyrazine-2-carboxylate (**10a**) (19.8 mg, 81.7 µmol, 85%) was obtained after flash chromatography (CH:EA 80:20 → 60:40) as yellow oil. TLC: R_f = 0.4 (CH:EE 50:50)[UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.61 (s, 1H), 7.63 – 7.56 (m, 2H), 7.48 – 7.42 (m, 3H), 4.26 (q, J = 7.2 Hz, 2H), 2.67 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 166.8, 151.3, 150.3, 145.0, 143.9, 137.3, 129.3, 128.5, 62.1, 21.2, 13.7. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3061, 3032, 2982, 2932, 2857, 1732, 1442, 1217, 1118, 697. LRMS (ESI) = 243.1 (100%)$[M+H]^+$, 265.1 (39%). HRMS (ESI): [m/z] 265.0947 (calc'd for $C_{14}H_{14}N_2NaO_2$ 265.0947).

Ethyl 6-methyl-3-(naphthalen-1-yl)pyrazine-2-carboxylate (10b)



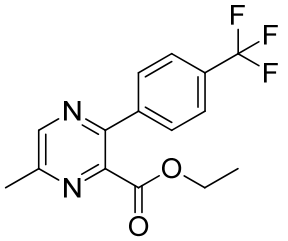
$C_{18}H_{16}N_2O_2$

292.3318

According to general procedure F using ethyl 6-methyl-3-(((trifluoromethyl)sulfonyl)oxy)pyrazine-2-carboxylate (**9c**) (30 mg, 95.4 µmol, 1 eq.) and naphthalen-1-ylboronic acid (24.6 mg, 0.14 mmol, 1.5 eq.), ethyl 6-methyl-3-(naphthalen-1-yl)pyrazine-2-carboxylate (**10b**) (22.4 mg, 76.6 µmol, 80%) was obtained after flash chromatography (CH:EA 70:30 → 50:50) as yellow oil. TLC: R_f = 0.4 (CH:EE 50:50)[UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.73 (s, 1H), 7.96 – 7.88 (m, 2H), 7.63 – 7.40 (m, 5H), 3.94 (q, *J* = 7.1 Hz, 2H), 2.76 (s, 3H), 0.68 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

[ppm] = 165.7, 152.2, 150.9, 145.5, 144.9, 135.4, 133.5, 131.5, 129.3, 128.4, 127.0, 126.7, 126.0, 125.0, 124.8, 61.7, 21.4, 13.2. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3048, 2981, 2931, 2856, 1732, 1446, 1093, 778. LRMS (ESI) = 293.1 (100%)$[M+H]^+$, 315.1 (10%). HRMS (ESI): [m/z] 315.1102 (calc'd for $C_{18}H_{16}N_2NaO_2$: 315.1104).

Ethyl 6-methyl-3-(4-(trifluoromethyl)phenyl)pyrazine-2-carboxylate (10c)

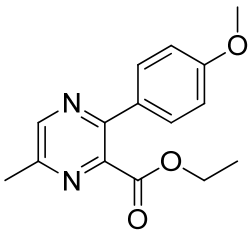


$C_{15}H_{13}F_3N_2O_2$

310.2711

According to general procedure F using ethyl 6-methyl-3-(((trifluoromethyl)sulfonyl)oxy)pyrazine-2-carboxylate (**9c**) (30 mg, 95.4 µmol, 1 eq.) and (4-(trifluoromethyl)phenyl)boronic acid (27.2 mg, 0.14 mmol, 1.5 eq.), ethyl 6-methyl-3-(4-(trifluoromethyl)phenyl)pyrazine-2-carboxylate (**10c**) (18.1 mg, 58.3 µmol, 61%) was obtained after flash chromatography (CH:EA 70:30 → 50:50) as pale yellow solid. TLC: R_f = 0.39 (CH:EE 50:50)[UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.64 (d, *J* = 0.6 Hz, 1H), 7.72 (s, 4H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.70 (d, *J* = 0.6 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 166.4 , 152.5 , 149.2 , 145.4 , 144.0 , 141.0 , 131.6 , 131.3 , 129.1 , 125.5 (q, *J* = 3.9 Hz), 62.5 , 21.4 , 13.9 .^{19}F NMR (376 MHz, $CDCl_3$) δ [ppm] = -63.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2982, 2933, 2856, 1734, 1618, 1445, 1323, 1108, 731. LRMS (ESI) = 311.1 (100%)$[M+H]^+$, 333.1 (20%). HRMS (ESI): [m/z] 311.1003 (calc'd for $C_{15}H_{14}F_3N_2O_2$: 311.1002).

Ethyl 3-(4-methoxyphenyl)-6-methylpyrazine-2-carboxylate (10d)

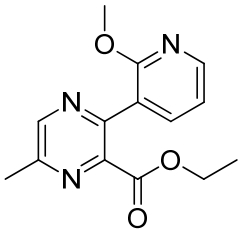


$C_{15}H_{16}N_2O_3$

272.2991

According to general procedure F using ethyl 6-methyl-3-(((trifluoromethyl)sulfonyl)oxy)pyrazine-2-carboxylate (**9c**) (30 mg, 95.4 µmol, 1 eq.) and (4-methoxyphenyl)boronic acid (21.8 mg, 0.14 mmol, 1.5 eq.), ethyl 3-(4-methoxyphenyl)-6-methylpyrazine-2-carboxylate (**10d**) (23.3 mg, 83.0 µmol, 87%) was obtained after flash chromatography (CH:EA 70:30 → 50:50) as yellow solid. TLC: R_f = 0.33 (CH:EE 50:50)[UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.57 (s, 1H), 7.60 – 7.54 (m, 2H), 7.01 – 6.95 (m, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 2.65 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 167.2, 160.8, 150.8, 149.9, 145.1, 143.7, 130.0, 129.7, 114.2, 62.3, 55.5, 21.3, 14.0. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3034 2932, 2856, 1732, 1610, 1517, 1437, 1217, 1109, 838. MS (ESI) = 273.1 (100%)$[M+H]^+$, 295.1 (9%). HRMS (ESI): [m/z] 295.1052 (calc'd for $C_{15}H_{16}N_2NaO_3$: 295.1053).

Ethyl 3-(2-methoxypyridin-3-yl)-6-methylpyrazine-2-carboxylate (10e)

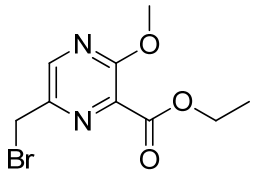


$C_{14}H_{15}N_3O_3$

273.2872

According to general procedure F using ethyl 6-methyl-3-(((trifluoromethyl)sulfonyl)oxy)pyrazine-2-carboxylate (**9c**) (30 mg, 95.4 µmol, 1 eq.) and (2-methoxypyridin-3-yl)boronic acid (21.9 mg, 0.14 mmol, 1.5 eq.), ethyl 3-(2-methoxypyridin-3-yl)-6-methylpyrazine-2-carboxylate (**10e**) (17.4 mg, 63.7 µmol, 67%) was obtained after flash chromatography (CH:EA 70:30 → 50:50) as pale yellow solid. TLC: R_f = 0.3 (CH:EE 50:50)[UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.65 (d, J = 0.6 Hz, 1H), 8.26 (dd, J = 5.0, 1.9 Hz, 1H), 7.93 (dd, J = 7.3, 1.9 Hz, 1H), 7.08 (dd, J = 7.3, 5.0 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H), 2.71 (d, J = 0.6 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 165.9, 160.6, 151.8, 147.8, 147.3, 145.6, 144.5, 139.1, 122.1, 117.4, 62.0, 53.4, 21.4, 14.0. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2982, 2951, 2933, 2856, 1727, 1582, 1463, 1405, 1100, 1013, 775. LRMS (ESI) = 274.1 (100%)$[M+H]^+$. HRMS (ESI): [m/z] 296.1005 (calc'd for $C_{14}H_{15}N_3NaO_3$: 296.1006).

Ethyl 6-(bromomethyl)-3-methoxypyrazine-2-carboxylate (11a)

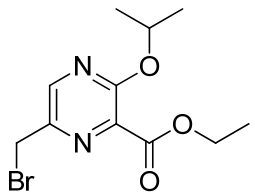


$C_9H_{11}BrN_2O_3$

275.0992

The reaction was carried out under argon atmosphere. Ethyl 3-methoxy-6-methylpyrazine-2-carboxylate (**9a**) (108 mg, 0.55 mmol, 1 eq.) was dissolved in CCl_4 (2.7 mL, 0.2 M). NBS (97.9 mg, 0.55 mmol, 1 eq.). AIBN (9 mg, 0.05 mmol, 10 mol%) was added, and the reaction was stirred at 75 °C over night. After completion of the reaction (monitored via TLC), the mixture was filtered through a short pad of celite, and the filtrate was evaporated under reduced pressure. Purification by flash-chromatography (PE:EA 90:10 → 80:20) on silica gel gave ethyl 6-(bromomethyl)-3-methoxypyrazine-2-carboxylate (**11a**) (77.5 mg, 0.28 mmol, 51%) as pale yellow oil. TLC: R_f = 0.5 (PE:EA 50:50)[UV]. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.39 (s, 1H), 4.58 (s, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 4.06 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 163.6, 158.1, 143.7, 143.6, 133.7, 62.2, 54.6, 29.7, 14.2. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2982, 2957, 2929, 1729, 1541, 1099, 1000. LRMS (ESI) = 274.98 (100%), 276.98 (97%); HRMS (ESI): [m/z] 296.9846 (calc'd for $C_9H_{11}BrN_2NaO_3$: 296.9845).

Ethyl 6-(bromomethyl)-3-isopropoxypyrazine-2-carboxylate (11b)



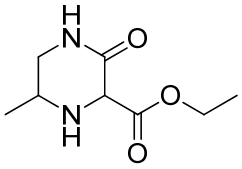
$C_{11}H_{15}BrN_2O_3$

303.1524

The reaction was carried out under argon atmosphere. Ethyl 3-isopropoxy-6-methyl-pyrazine-2-carboxylate (**9b**) (100 mg, 0.45 mmol, 1 eq.) was dissolved in CCl_4 (2.2 mL, 0.2 M). NBS (87.3 mg, 0.49 mmol, 1.1 eq.). AIBN (10.9 mg, 0.07 mL, 15 mol%) was added, and the reaction was stirred at 75 °C over night. After completion of the reaction (monitored via TLC), the mixture was filtered through a short pad of celite, and the filtrate was evaporated under reduced pressure. Purification by flash-

chromatography (CH:EA 80:20 → 60:40) on silica gel gave Ethyl 6-(bromomethyl)-3-isopropoxypyrazine-2-carboxylate (**11b**) (80 mg, 0.26 mmol, 59%) as yellow oil. TLC: R_f = 0.65 (CH:EE 50:50)[UV]. ^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 8.33 (s, 1H), 5.37 (hept, *J* = 6.2 Hz, 1H), 4.57 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.39 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 163.9, 157.3, 143.5, 143.0, 134.5, 70.8, 61.9, 29.9, 21.8, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2981, 2935, 2858, 1732, 1537, 1448, 1315, 1097, 933. LRMS (ESI) = 261.0(97%), 263.0 (100%), 303.0(49%), 305.0 (49%). HRMS (ESI): [m/z] 325.0141 (calc'd for $C_{11}H_{15}BrN_2NaO_3$: 325.0158).

Ethyl 6-methyl-3-oxopiperazine-2-carboxylate (12)

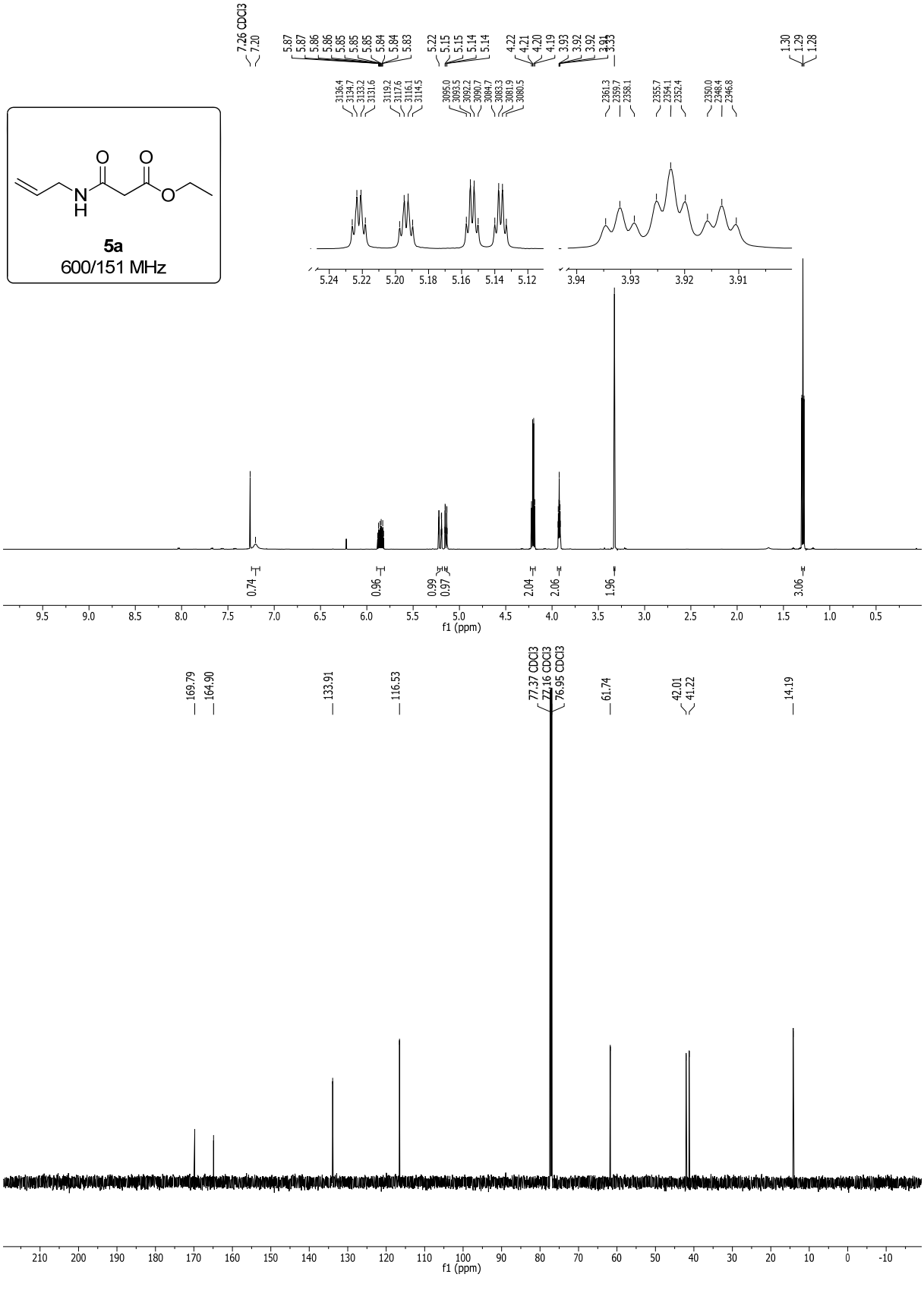


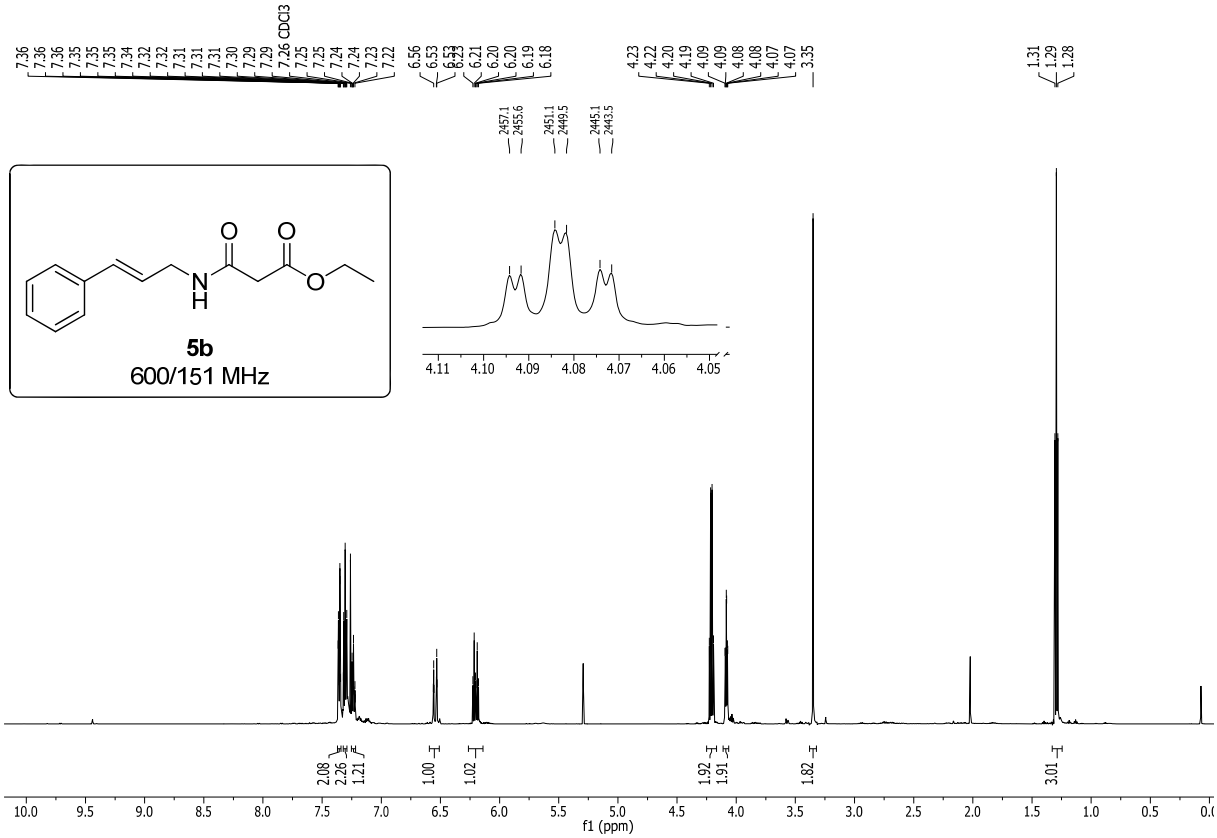
$C_8H_{14}N_2O_3$

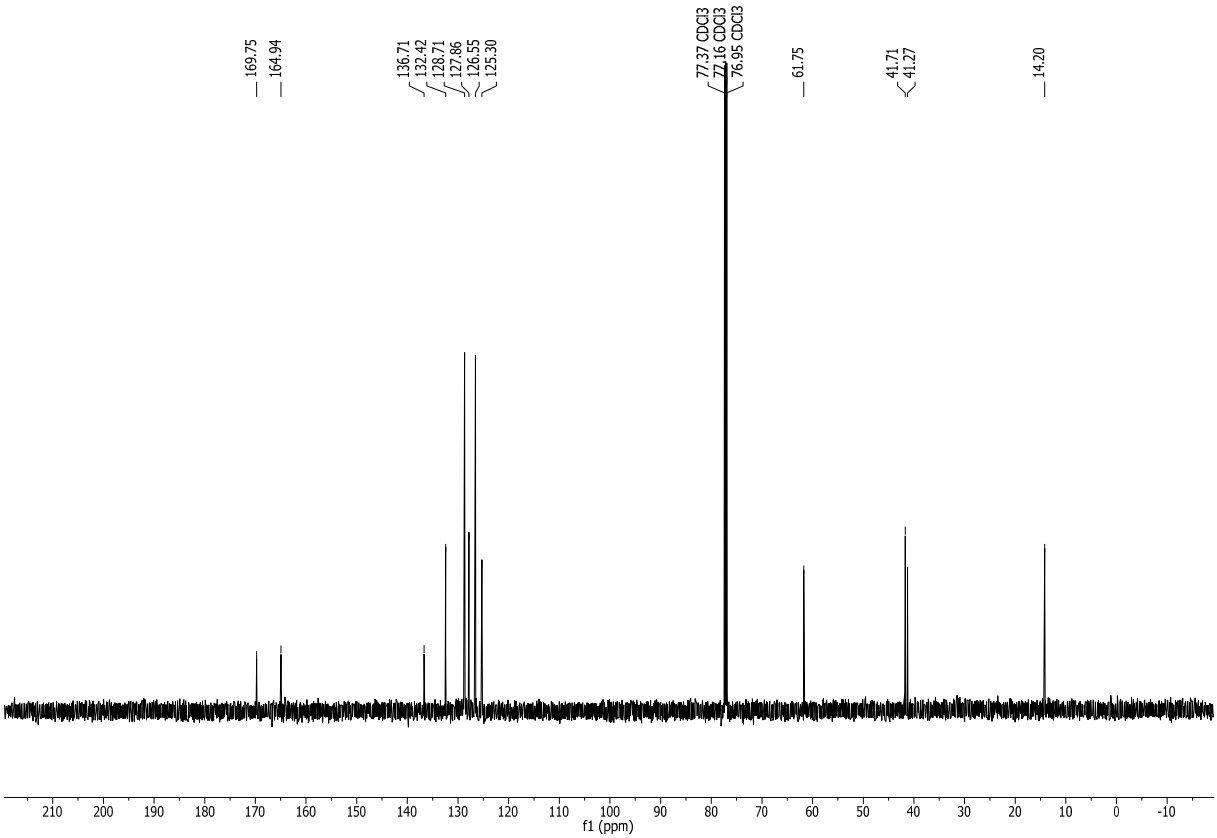
186.2084

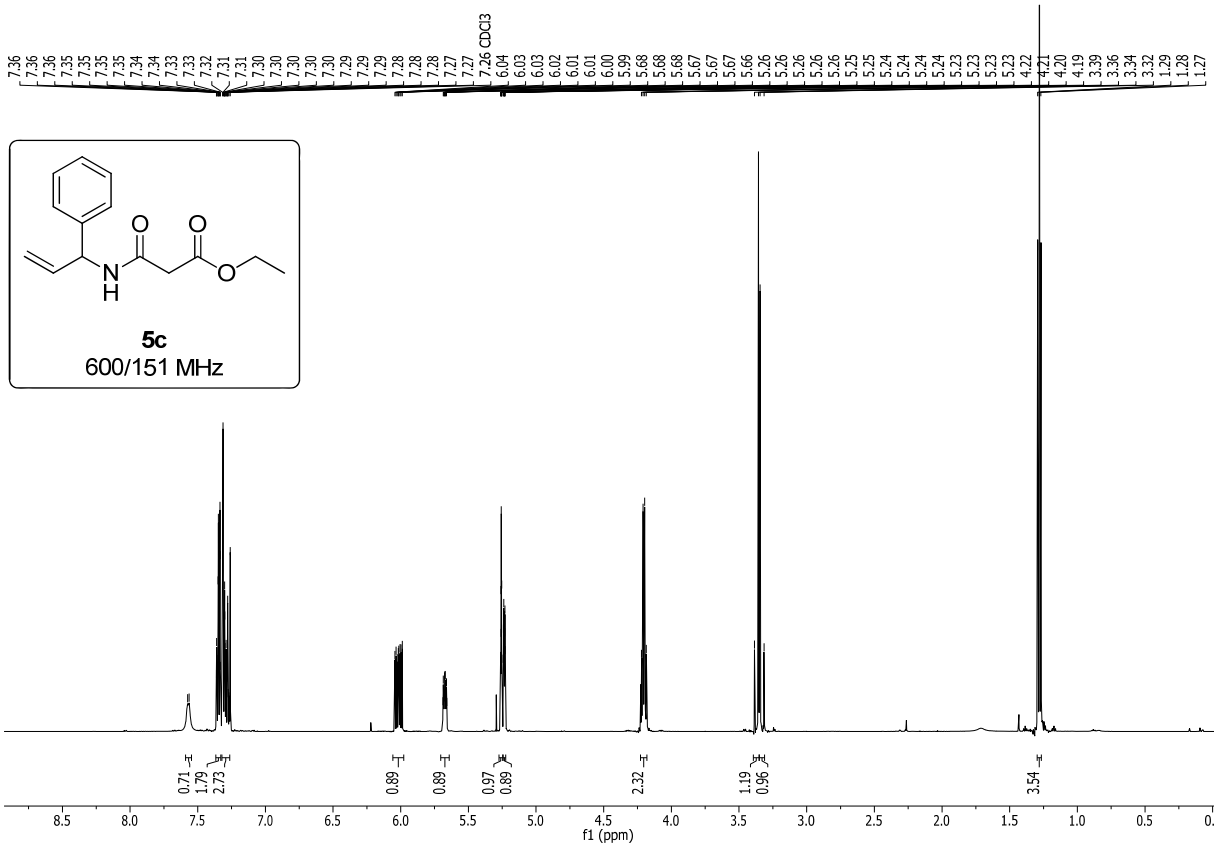
Ethyl 3-hydroxy-6-methylpyrazine-2-carboxylate (**2**) (30 mg, 0.16 mmol, 1 eq.) was dissolved in EtOH (0.5 mL, 0.3 M). Rhodium on alumina (34 mg, 0.05 w/w%, 0.02 mmol, 10 mol%) was added and the autoclave was sealed. The vessel was purged with hydrogen for 5 min. The pressure was raised to 30 bar, and the reaction was stirred for 18 h. Filtration over celite and evaporation of the filtrate gave the crude product, which was purified by flash-chromatography (DCM:MeOH 95:5 → 80:20) to afford ethyl 6-methyl-3-oxopiperazine-2-carboxylate (**12**) (26.9 mg, 0.14 mmol, 87%) (mixture of two diastereomers). TLC: R_f = 0.3 (DCM:MeOH 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.00 (s, 1H), 6.90 (s, 1H), 4.28 – 4.23 (m, 4H), 4.23 – 4.17 (m, 2H), 3.38 – 3.26 (m, 2H), 3.25 – 2.99 (m, 4H), 2.22 (s, 2H), 1.33 – 1.27 (m, 6H), 1.17 (m , 3H), 1.14 (m , 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 170.0, 168.7, 166.3, 165.8, 62.7, 62.3, 62.0, 61.4, 49.6, 48.9, 46.9, 44.4, 18.8, 18.7, 18.3, 14.1, 14.0, 14.0. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3233, 2980, 2934, 2873, 1734, 1673, 1300, 1023, 908, 724, 645. LRMS (ESI) = 187.1 (100%)$[M+H]^+$. HRMS (ESI): [m/z] 209.0904 (calc'd for $C_8H_{14}N_2NaO_3$: 209.0897).

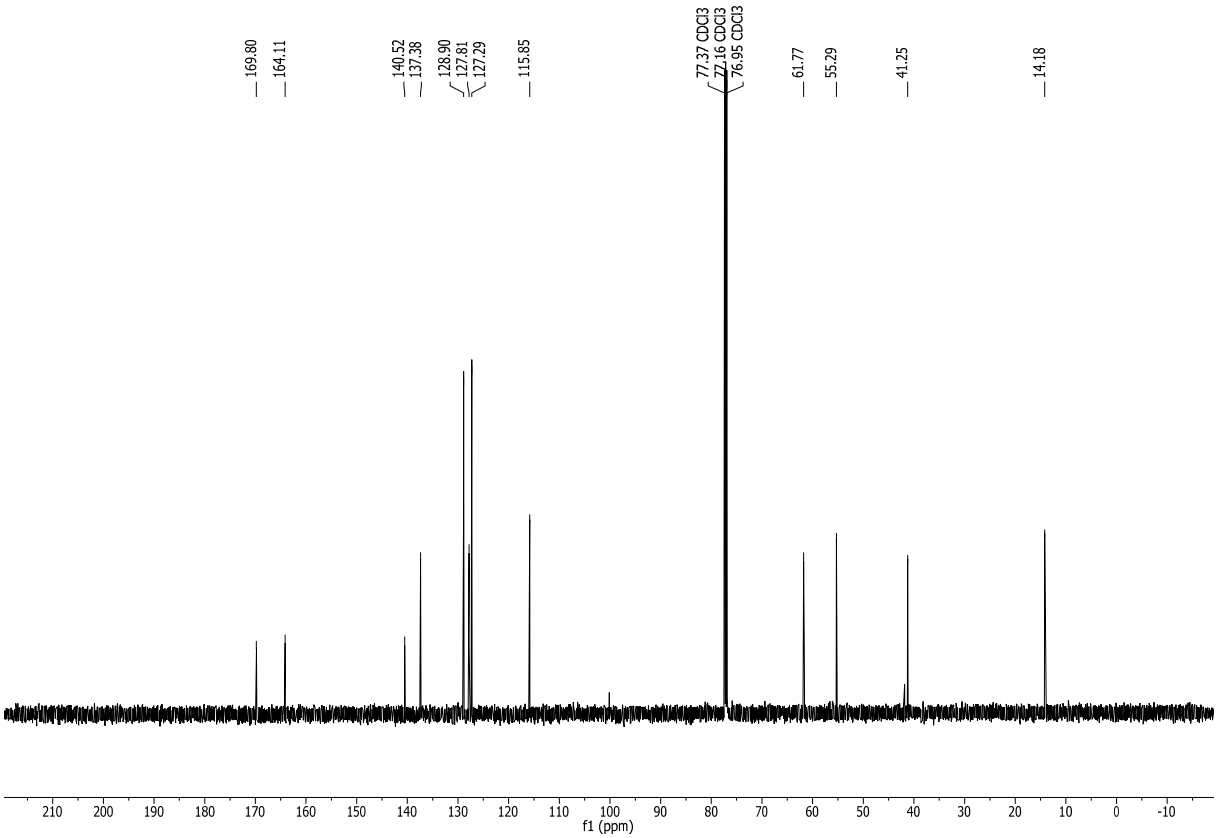
5. Spectra



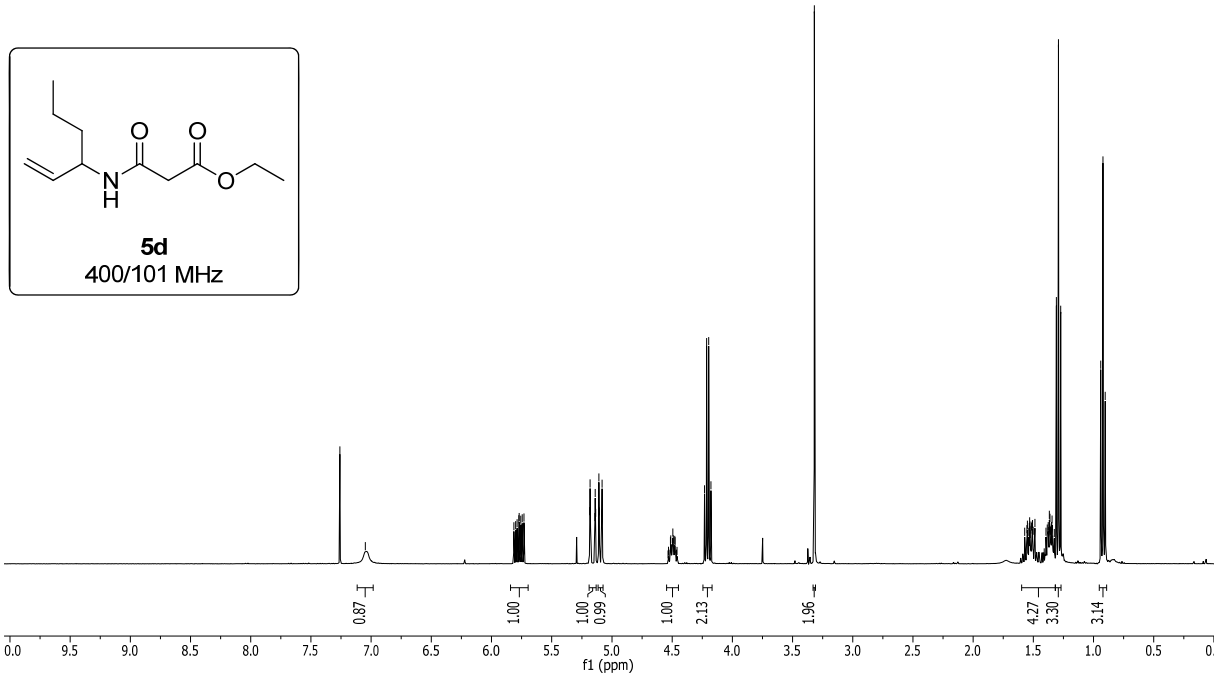

7.36 7.36 7.36 7.35 7.35 7.35 7.34 7.32 7.32 7.31 7.31 7.31 7.30 7.29 7.29 7.26 CDCl3 7.25 7.25 7.24 7.24 7.23 7.22
6.56 6.53 6.53 6.23 6.21 6.20 6.20 6.19 6.18
4.23 4.22 4.20 4.19 4.09 4.09 4.08 4.08 4.07 4.07 3.35
1.31 1.29 1.28
2457.1 2455.6 2451.1 2449.5 2445.1 2443.5
O O N H O
5b
600/151 MHz
4.11 4.10 4.09 4.08 4.07 4.06 4.05
2.08 2.26 1.21 1.00 1.02 1.92 1.91 1.82 3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

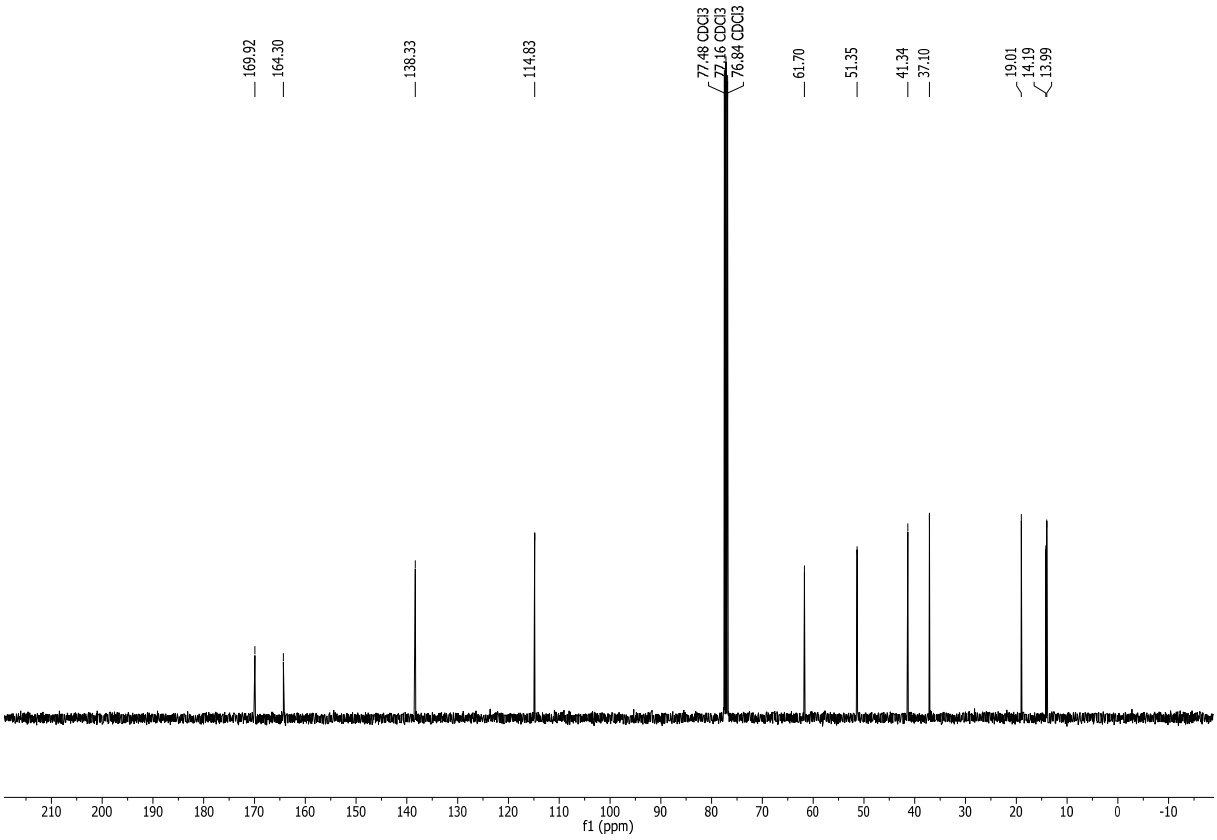

169.75 164.94 136.71 132.42 128.71 127.86 126.55 125.30 77.37 CDCl3 77.16 CDCl3 76.95 CDCl3 61.75 41.71 41.27 14.20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

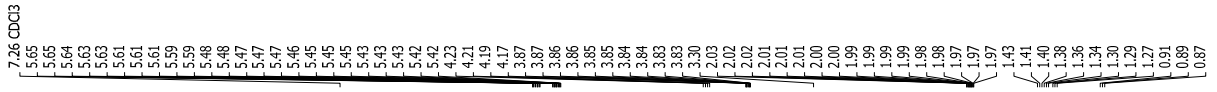

7.36 7.36 7.36 7.35 7.35 7.35 7.34 7.34 7.33 7.33 7.32 7.31 7.31 7.30 7.30 7.30 7.30 7.29 7.29 7.29 7.28 7.28 7.28 7.27 7.27 7.26 CDCl3 6.04 6.03 6.03 6.02 6.01 6.01 6.00 5.99 5.68 5.68 5.68 5.67 5.67 5.67 5.66 5.26 5.26 5.26 5.26 5.25 5.25 5.24 5.24 5.24 5.23 5.23 5.23 4.22 4.21 4.20 4.19 3.39 3.36 3.34 3.32 1.29 1.28 1.27
O
O
N
H
O
5c
600/151 MHz
0.71
1.79
2.73
0.89
0.89
0.97
0.89
2.32
1.19
0.96
3.54
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

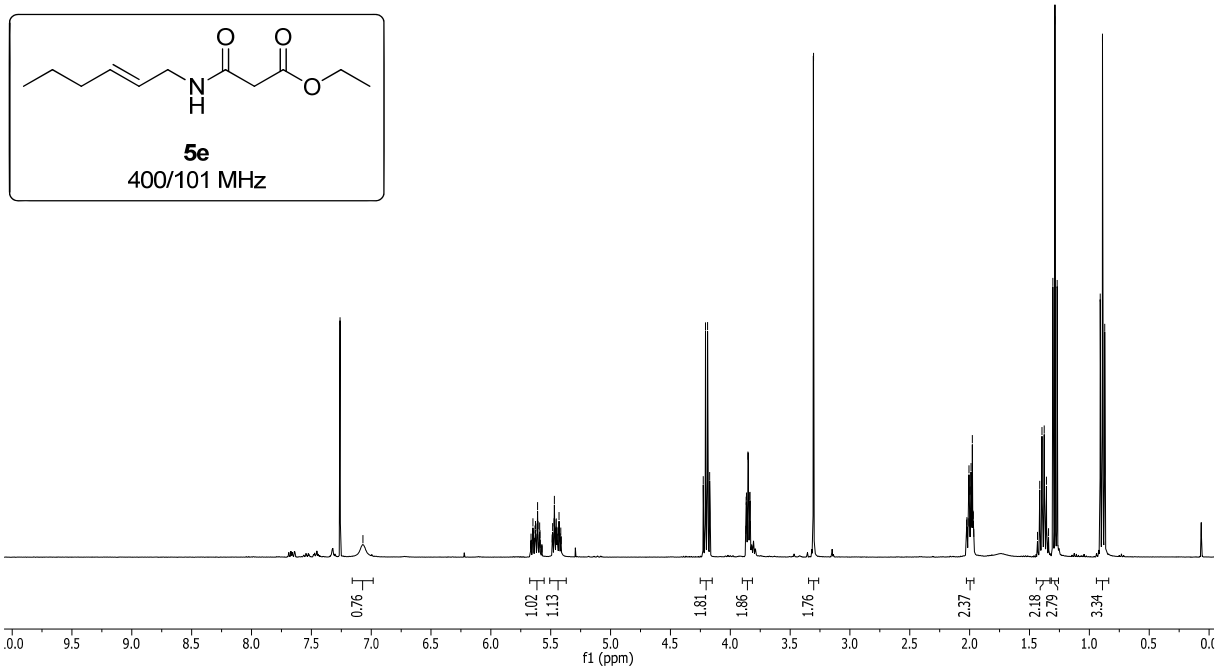

169.80
164.11
140.52
137.38
128.90
127.81
127.29
115.85
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
61.77
55.29
41.25
14.18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

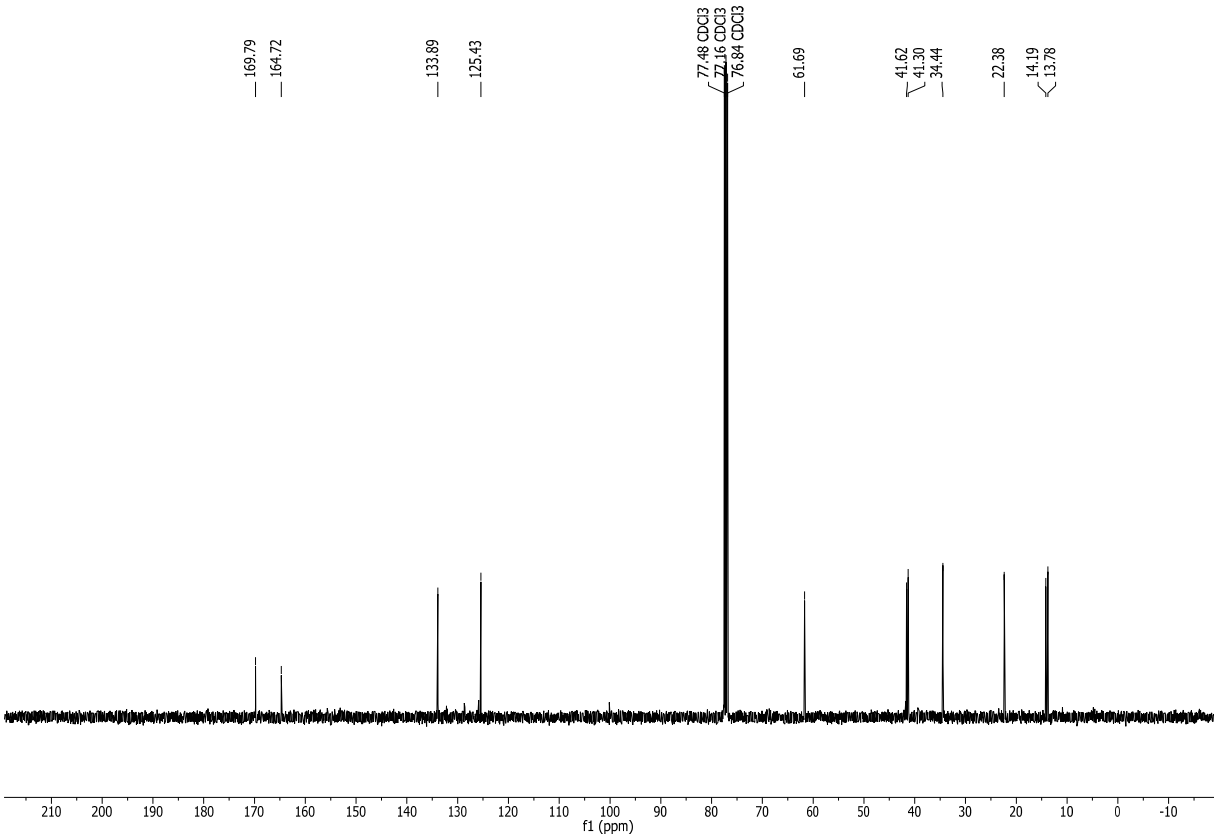

7.26 CDCl3
7.05
5.81
5.80
5.79
5.77
5.77
5.76
5.74
5.73
5.19
5.18
5.18
5.14
5.14
5.14
5.11
5.11
5.10
5.09
5.08
5.08
4.53
4.51
4.51
4.50
4.49
4.49
4.49
4.48
4.48
4.46
4.23
4.21
4.20
4.18
3.32
1.57
1.55
1.55
1.54
1.53
1.53
1.53
1.52
1.52
1.51
1.51
1.51
1.50
1.49
1.39
1.38
1.38
1.37
1.37
1.36
1.36
1.35
1.35
1.34
1.34
1.33
1.31
1.29
1.27
0.94
0.92
0.90

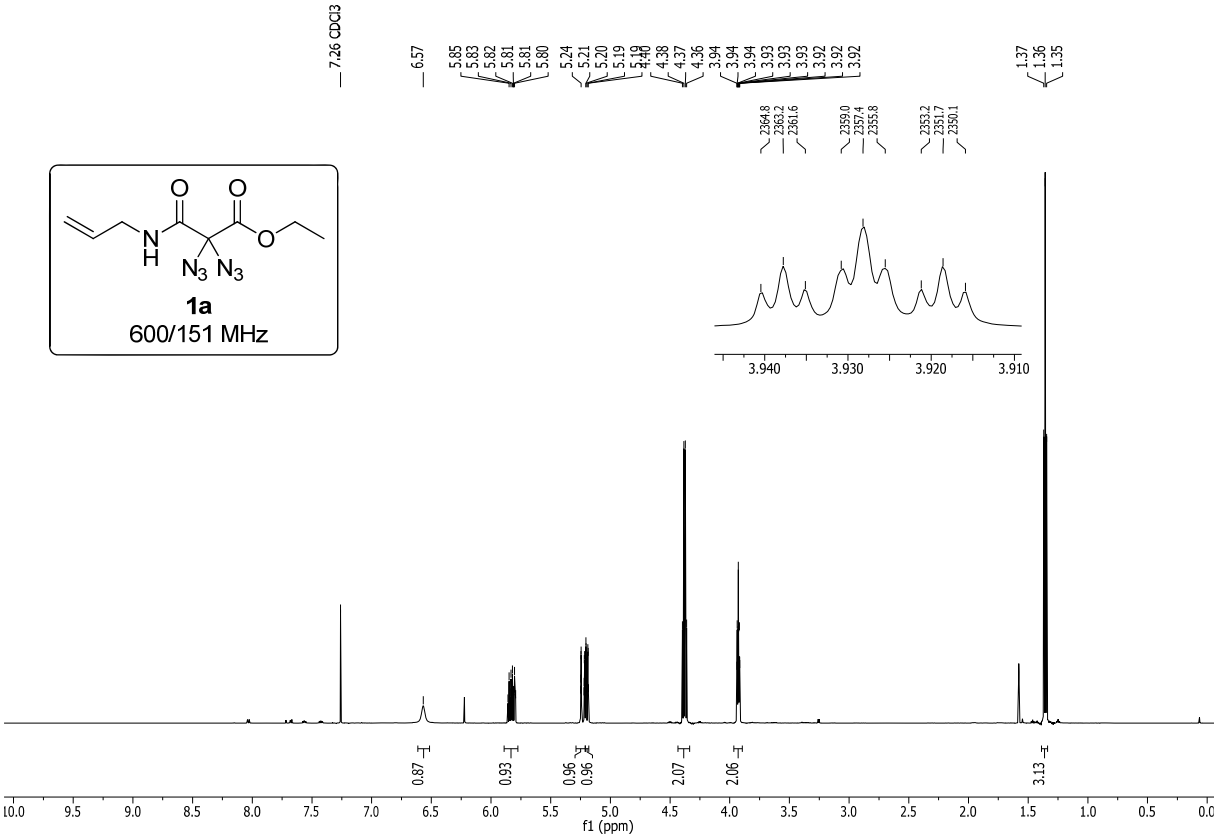

O
O
N
H
O
5d
400/101 MHz
0.87
1.00
1.00
0.99
1.00
2.13
1.96
4.27
3.30
3.14
f1 (ppm)

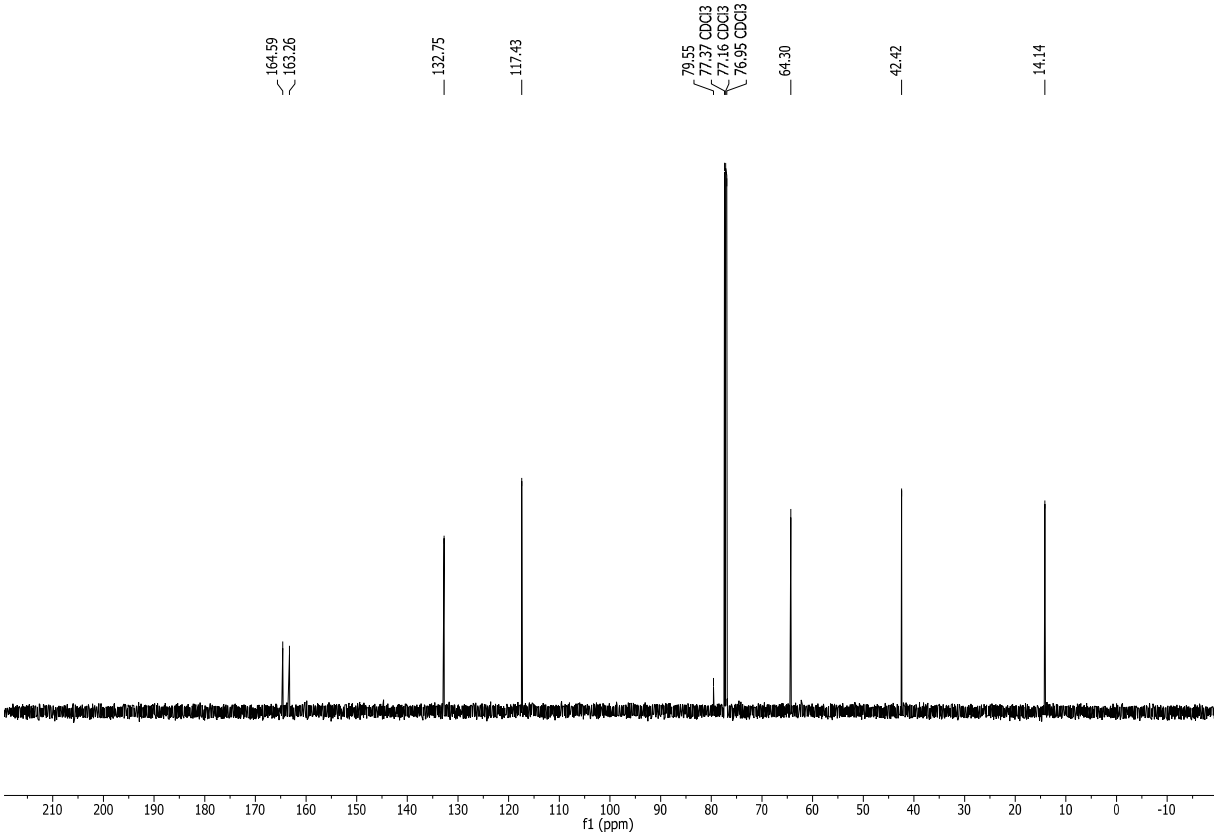

169.92
164.30
138.33
114.83
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.70
51.35
41.34
37.10
19.01
14.19
13.99
f1 (ppm)

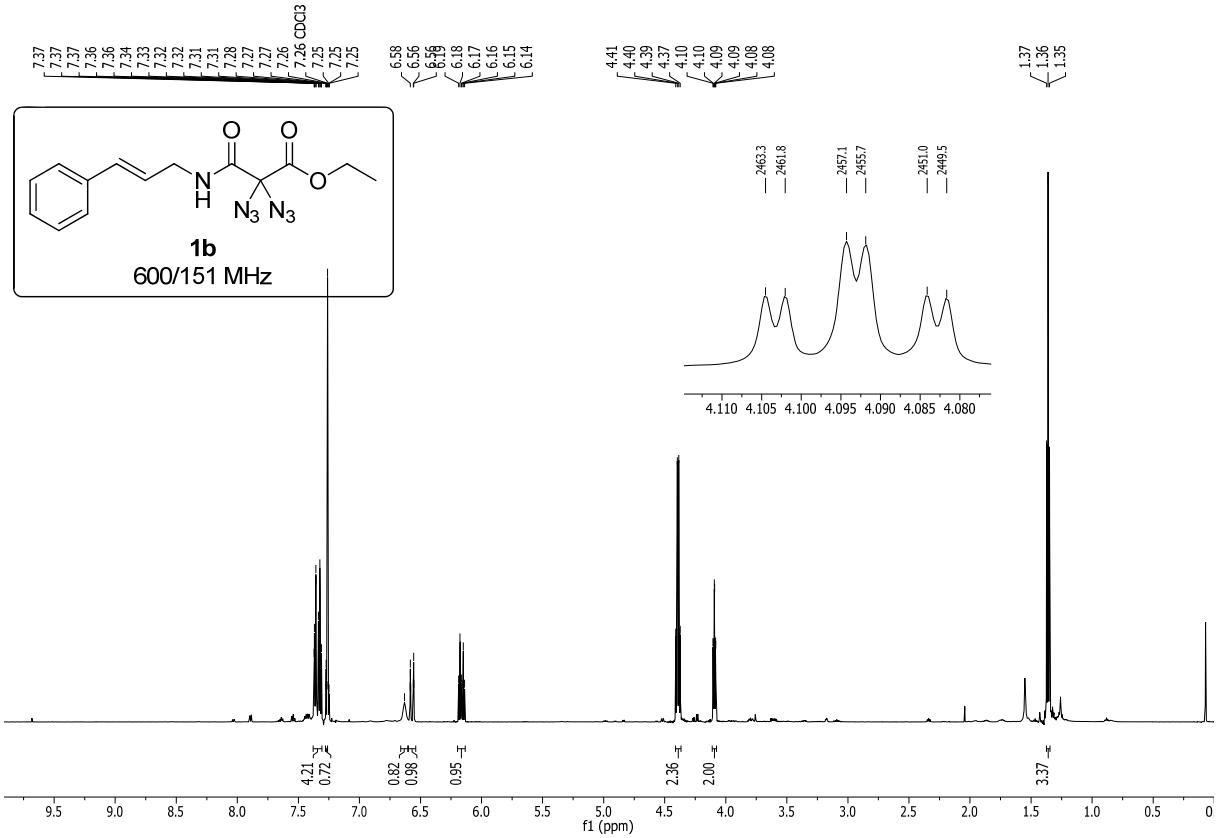

7.26 CDCl3
5.65 5.65 5.64 5.63 5.63 5.61 5.61 5.61 5.59 5.59 5.48 5.48 5.47 5.47 5.47 5.46 5.45 5.45 5.45 5.43 5.43 5.43 5.42 5.42 4.23 4.21 4.19 4.17 3.87 3.87 3.86 3.86 3.85 3.85 3.84 3.84 3.83 3.83 3.30 2.03 2.02 2.02 2.01 2.01 2.01 2.00 2.00 1.99 1.99 1.99 1.99 1.98 1.98 1.97 1.97 1.97 1.43 1.41 1.40 1.38 1.36 1.34 1.30 1.29 1.27 0.91 0.89 0.87

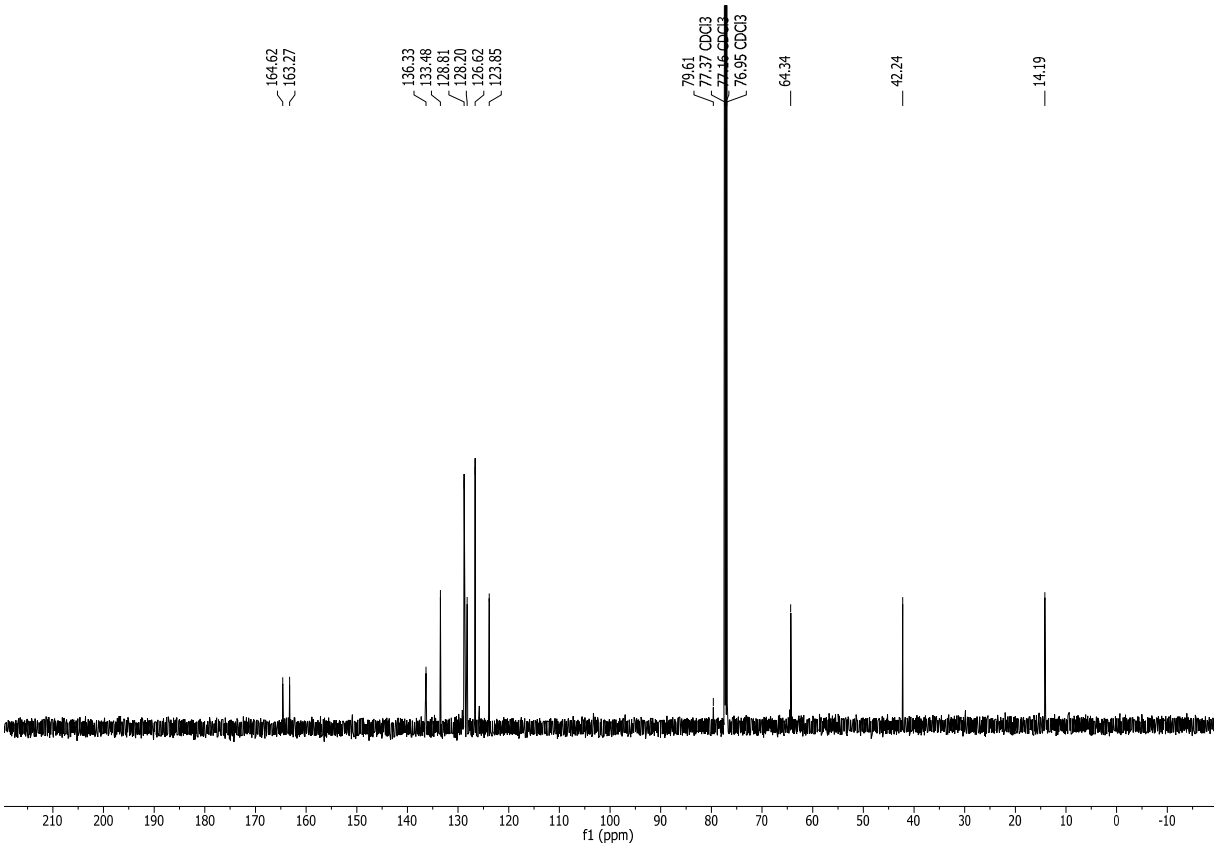

O
O
N
H
O
5e
400/101 MHz
0.76
1.02
1.13
1.81
1.86
1.76
2.37
2.18
2.79
3.34
f1 (ppm)

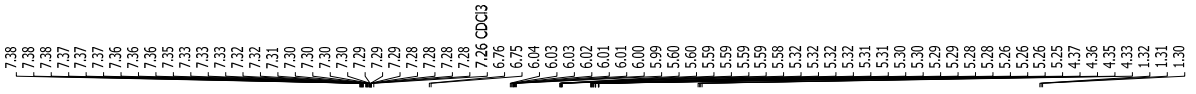

169.79
164.72
133.89
125.43
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.69
41.62
41.30
34.44
22.38
14.19
13.78
f1 (ppm)

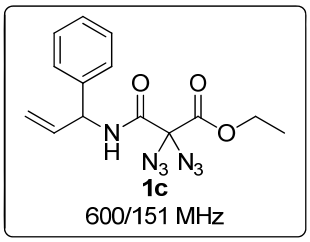

7.26 CDCl3
6.57
5.85
5.83
5.82
5.81
5.81
5.80
5.24
5.21
5.20
5.19
5.19
4.40
4.38
4.37
4.36
3.94
3.94
3.94
3.93
3.93
3.93
3.92
3.92
3.92
1.37
1.36
1.35
2364.8
2363.2
2361.6
2339.0
2357.4
2355.8
2353.2
2351.7
2350.1
O
O
O
N
H
N3 N3
1a
600/151 MHz
3.940
3.930
3.920
3.910
0.87
0.93
0.96
0.96
2.07
2.06
3.13
f1 (ppm)


164.59
163.26
132.75
117.43
79.55
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
64.30
42.42
14.14
f1 (ppm)


7.37 7.37 7.37 7.36 7.36 7.34 7.33 7.32 7.32 7.31 7.31 7.28 7.27 7.27 7.26 7.26 CDCl3 7.25 7.25 7.25
6.58 6.56 6.56 6.18 6.17 6.16 6.15 6.14
4.41 4.40 4.39 4.37 4.10 4.10 4.09 4.09 4.08 4.08
1.37 1.36 1.35
1b
600/151 MHz
2463.3 2461.8 2457.1 2455.7 2451.0 2449.5
4.110 4.105 4.100 4.095 4.090 4.085 4.080
4.21 0.72 0.82 0.98 0.95 2.36 2.00 3.37
f1 (ppm)

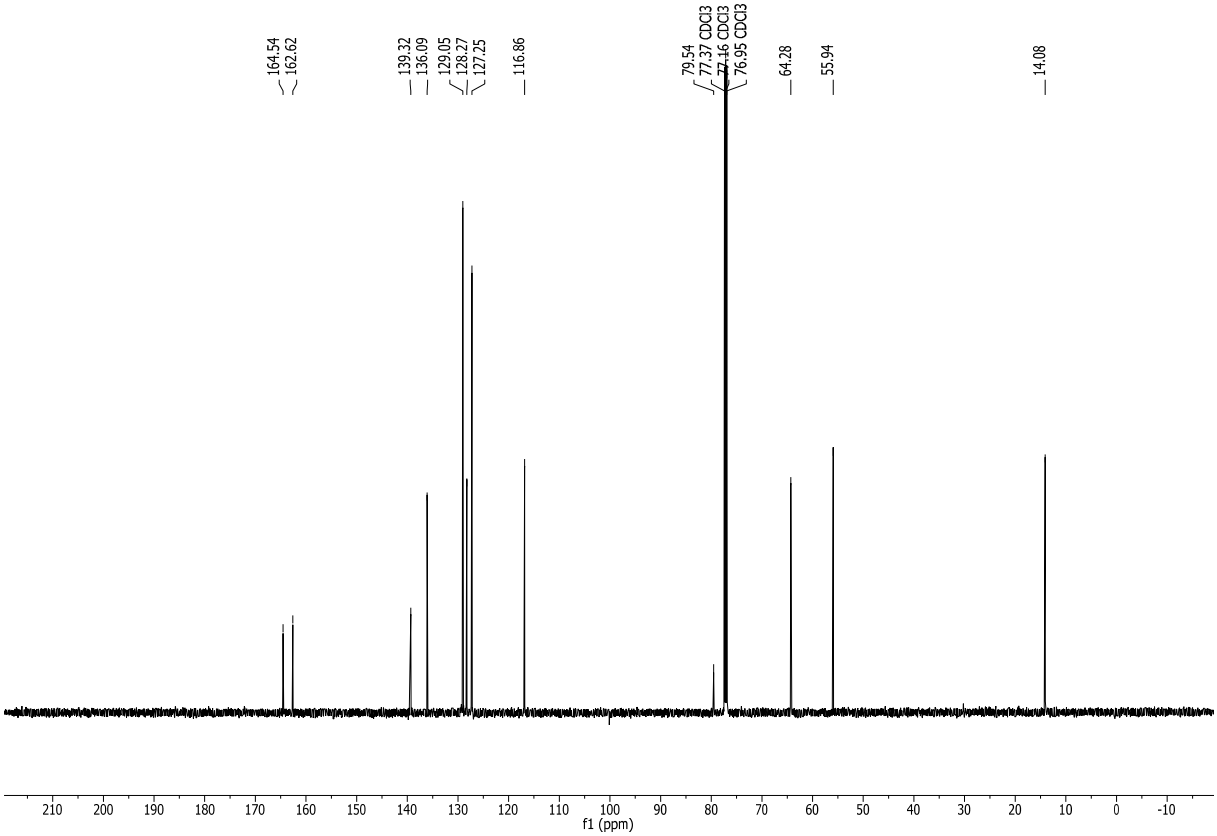

164.62 163.27
136.33 133.48 128.81 128.20 126.62 123.85
79.61 77.37 CDCl3 77.16 CDCl3 76.95 CDCl3
64.34
42.24
14.19
f1 (ppm)

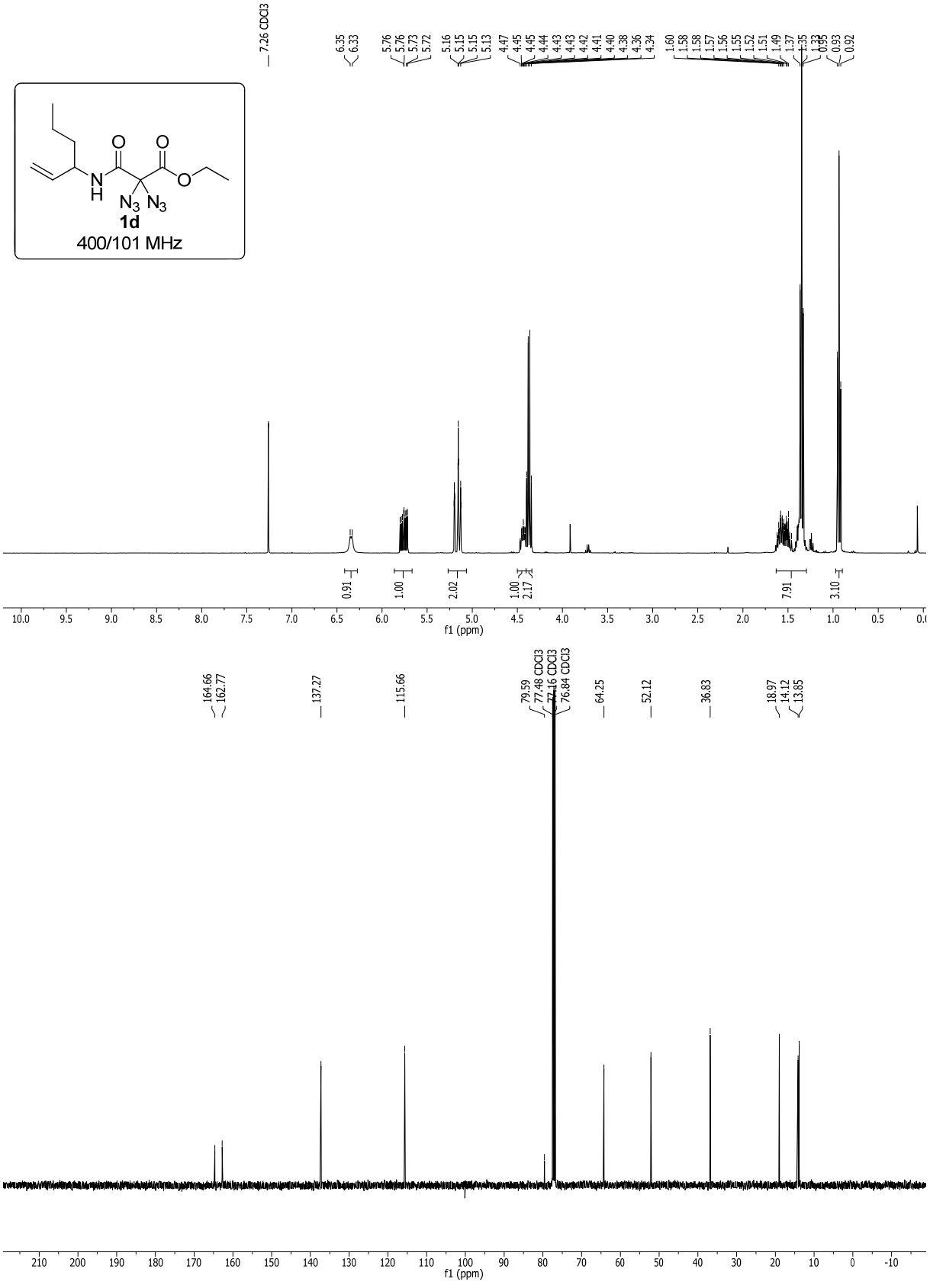


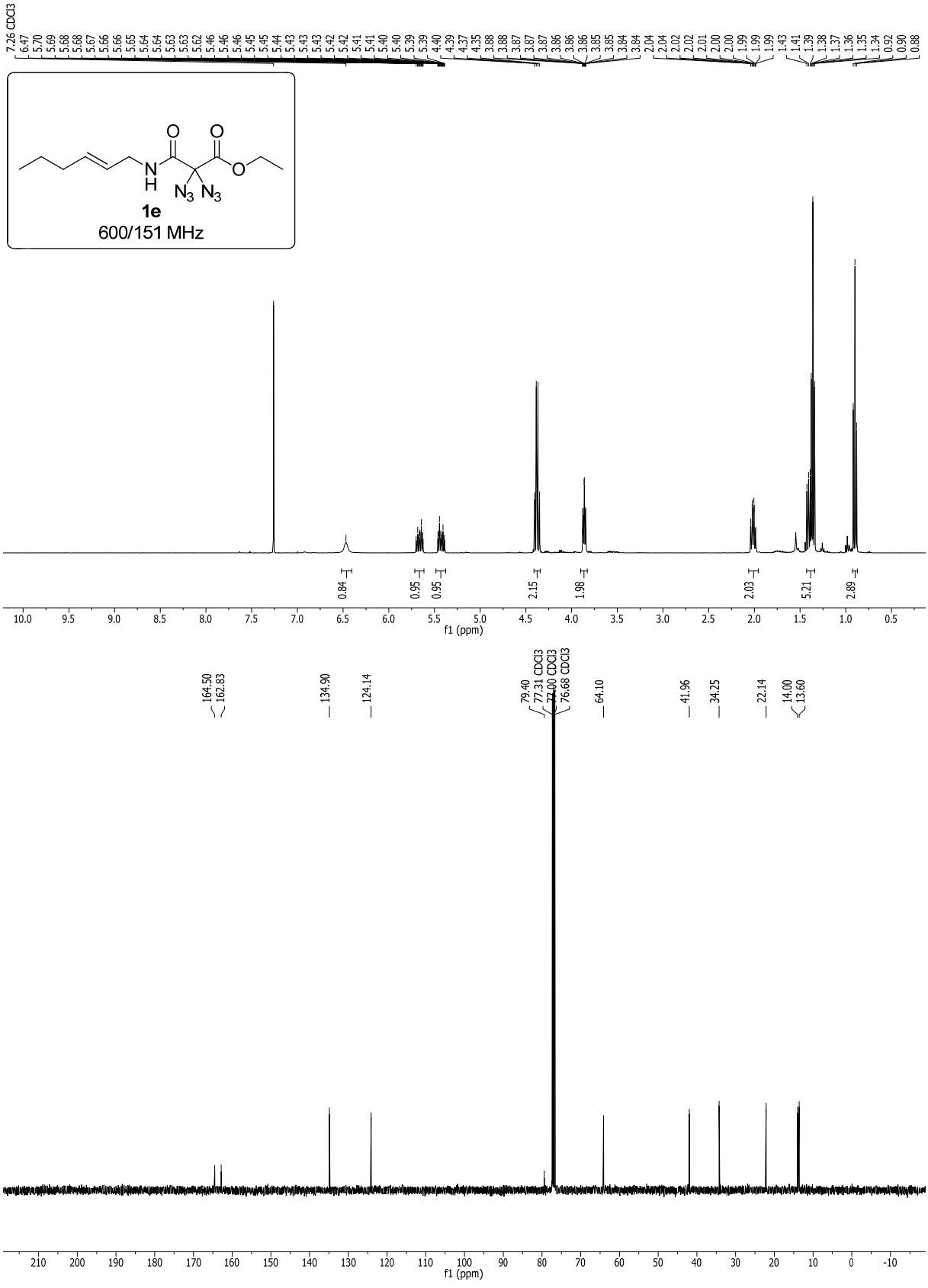


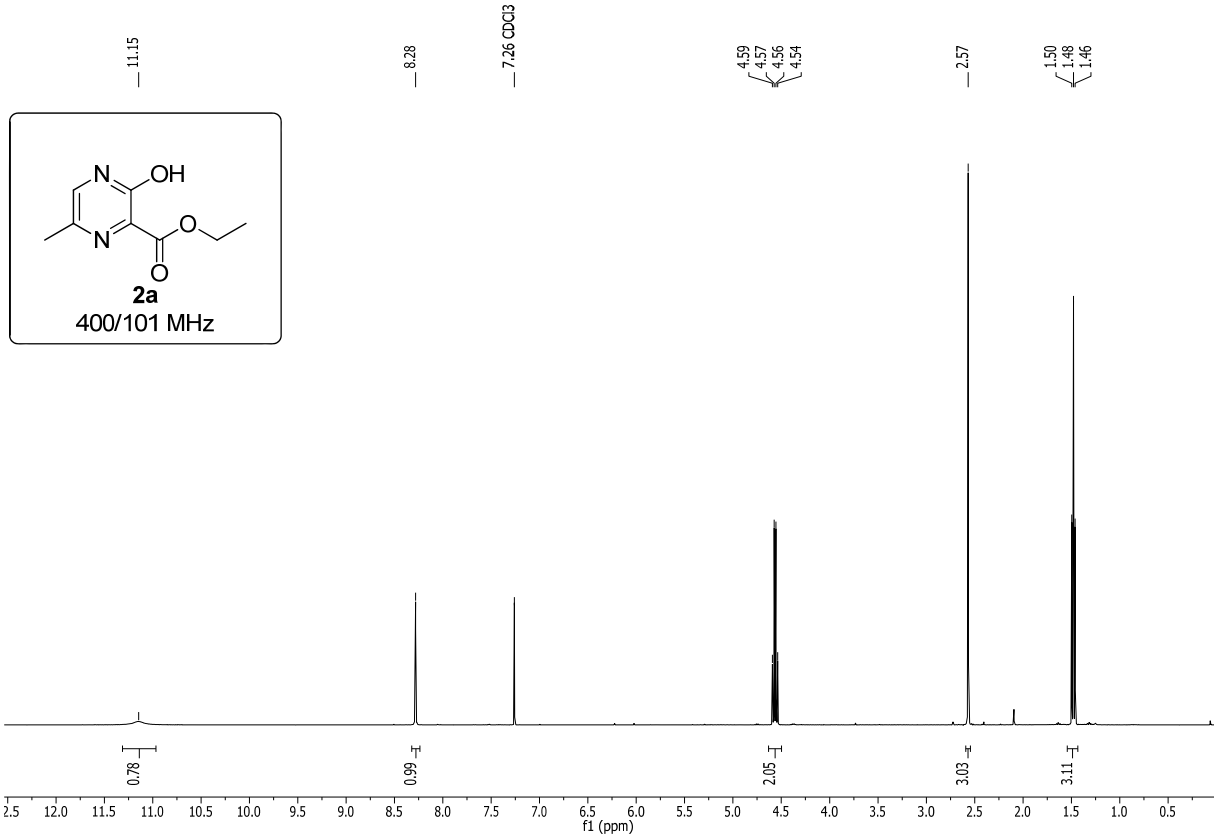
1c

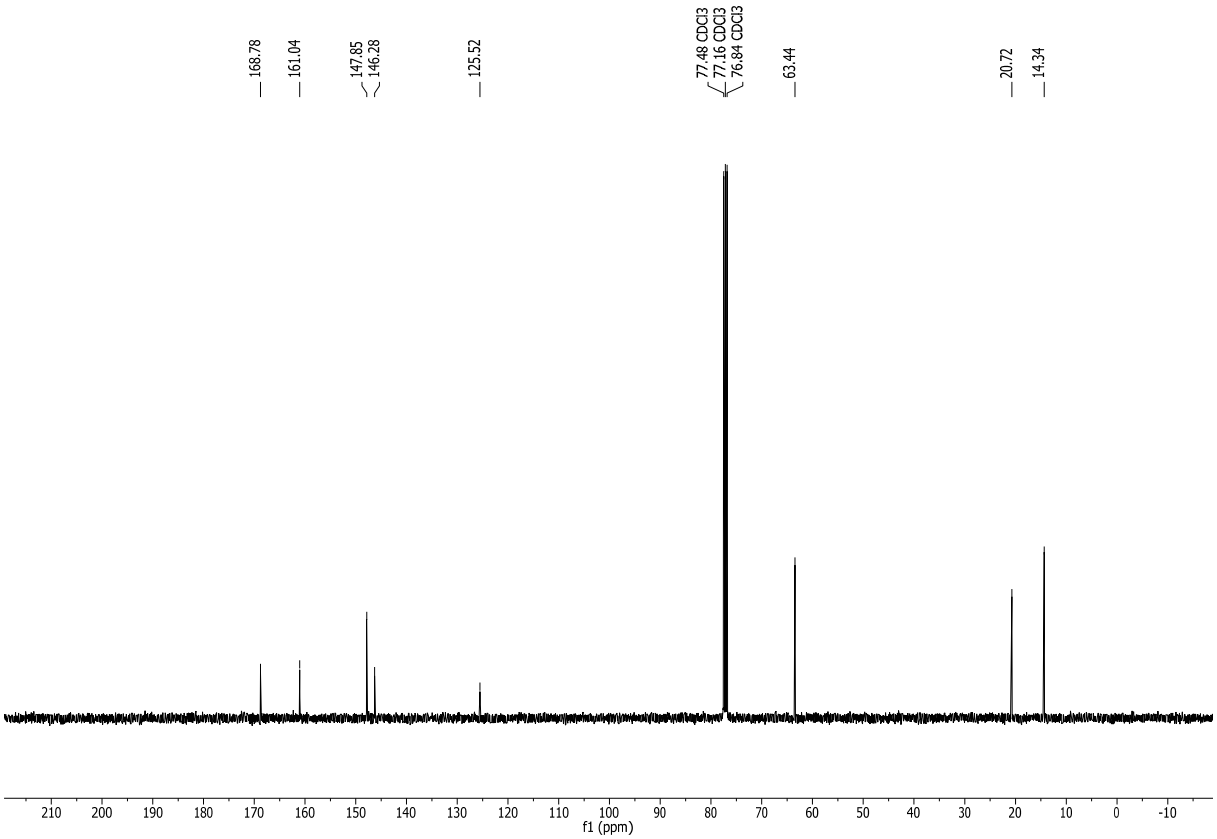
600/151 MHz

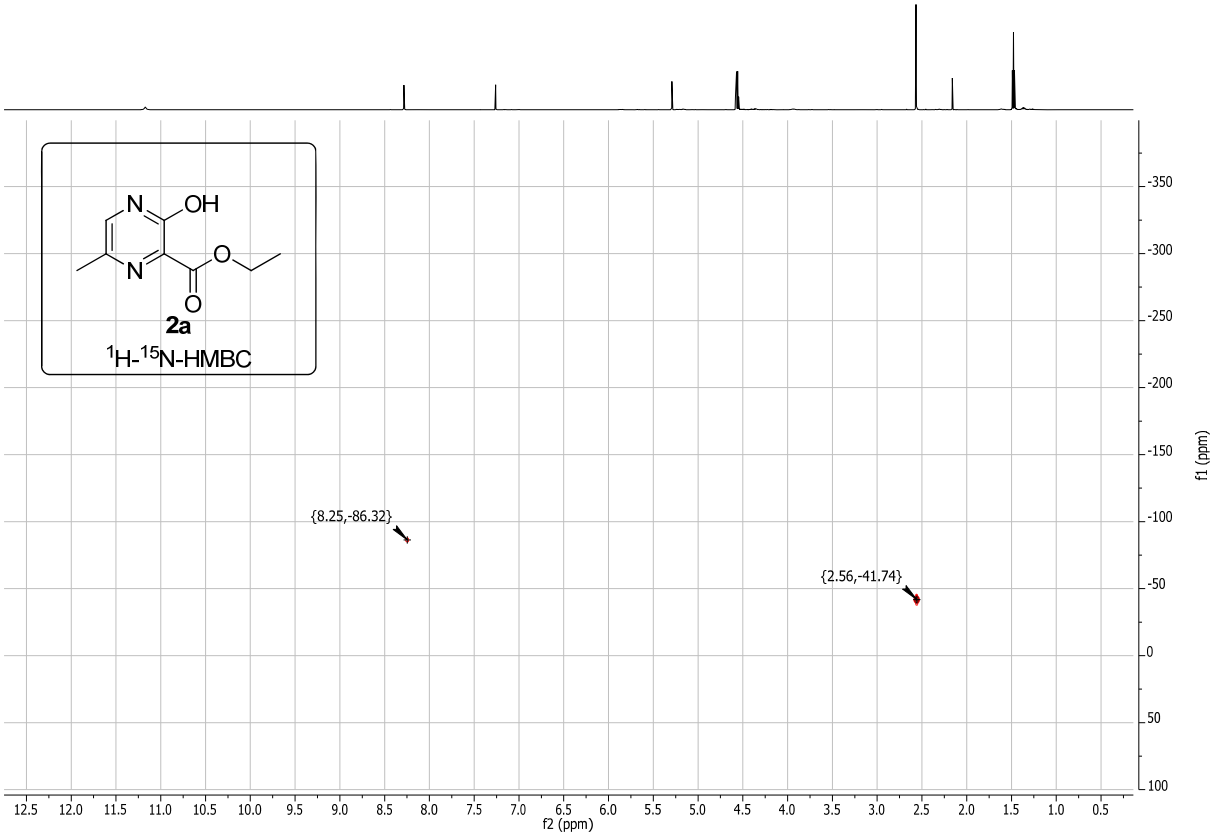


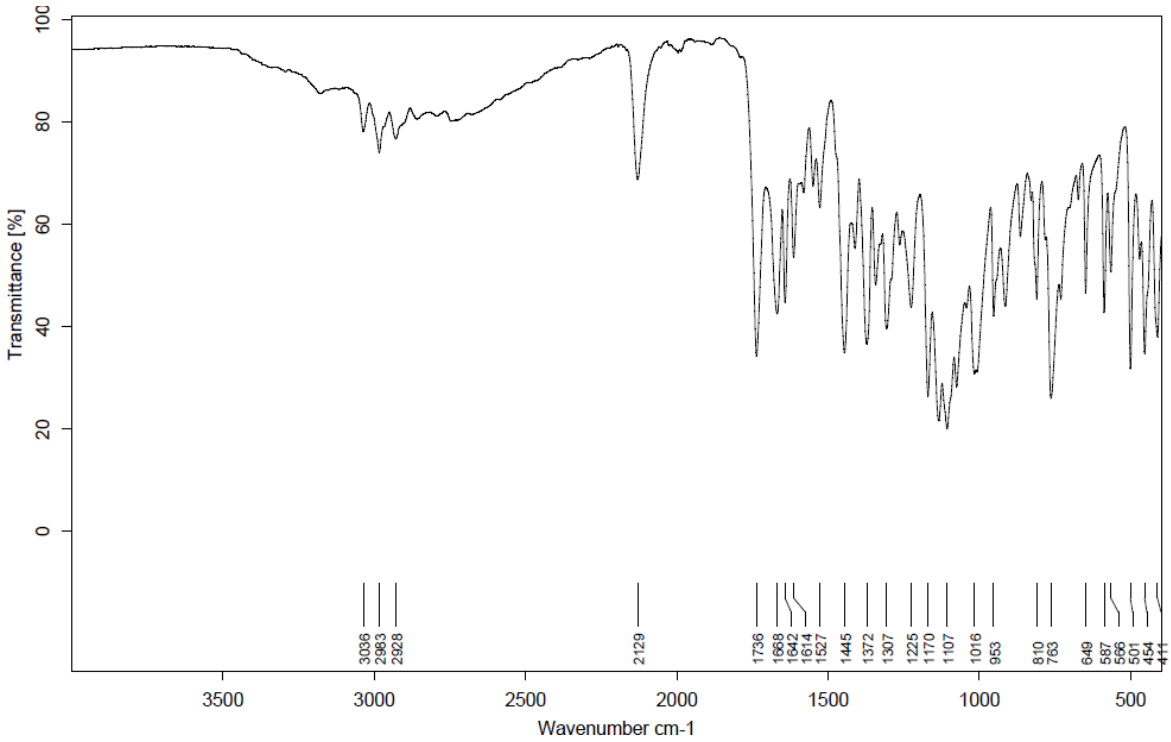

7.26 CDCl3
6.35
6.33
5.76
5.76
5.73
5.72
5.16
5.15
5.15
5.13
4.47
4.45
4.45
4.44
4.43
4.43
4.42
4.41
4.40
4.38
4.36
4.34
1.60
1.58
1.58
1.57
1.56
1.55
1.52
1.51
1.49
1.37
1.35
1.33
0.95
0.93
0.92
O
O
N
H
O
N3 N3
1d
400/101 MHz
0.91
1.00
2.02
1.00
2.17
7.91
3.10
f1 (ppm)
164.66
162.77
137.27
115.66
79.59
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.25
52.12
36.83
18.97
14.12
13.85
f1 (ppm)

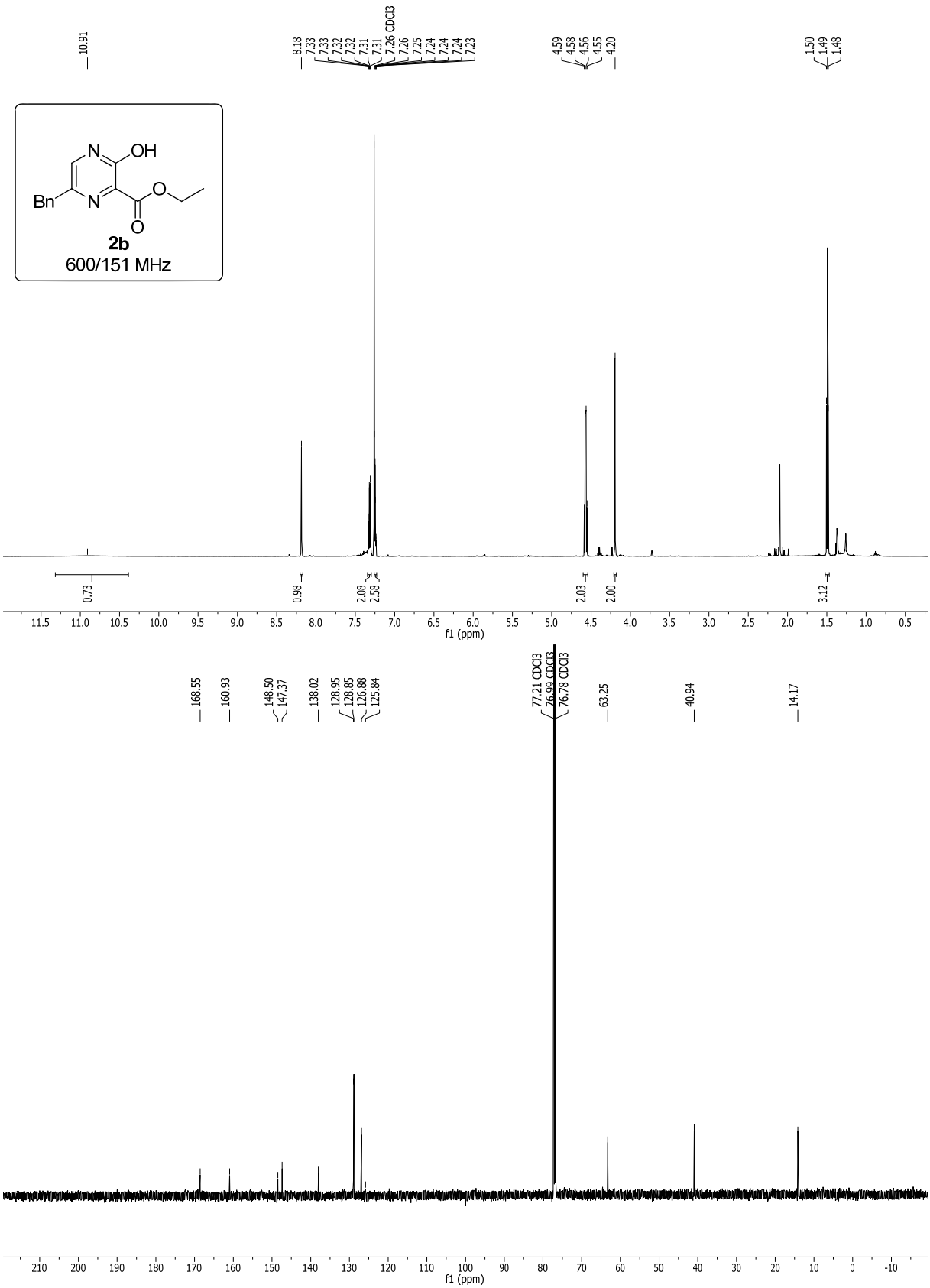

7.26 CDCl3
6.47 5.70 5.69 5.68 5.68 5.67 5.66 5.66 5.65 5.64 5.64 5.63 5.63 5.62 5.46 5.46 5.45 5.45 5.44 5.43 5.43 5.43 5.42 5.42 5.41 5.41 5.40 5.40 5.39 5.39 4.40 4.39 4.37 4.35 3.88 3.87 3.87 3.87 3.86 3.86 3.86 3.85 3.84 3.84 2.04 2.04 2.02 2.02 2.01 2.00 2.00 1.99 1.99 1.99 1.43 1.41 1.39 1.38 1.37 1.36 1.35 1.34 0.92 0.90 0.88
O
O
N
H
N3 N3
O
1e
600/151 MHz
0.84
0.95
0.95
2.15
1.98
2.03
5.21
2.89
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
164.50
162.83
134.90
124.14
79.40
77.31 CDCl3
77.00 CDCl3
76.68 CDCl3
64.10
41.96
34.25
22.14
14.00
13.60
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

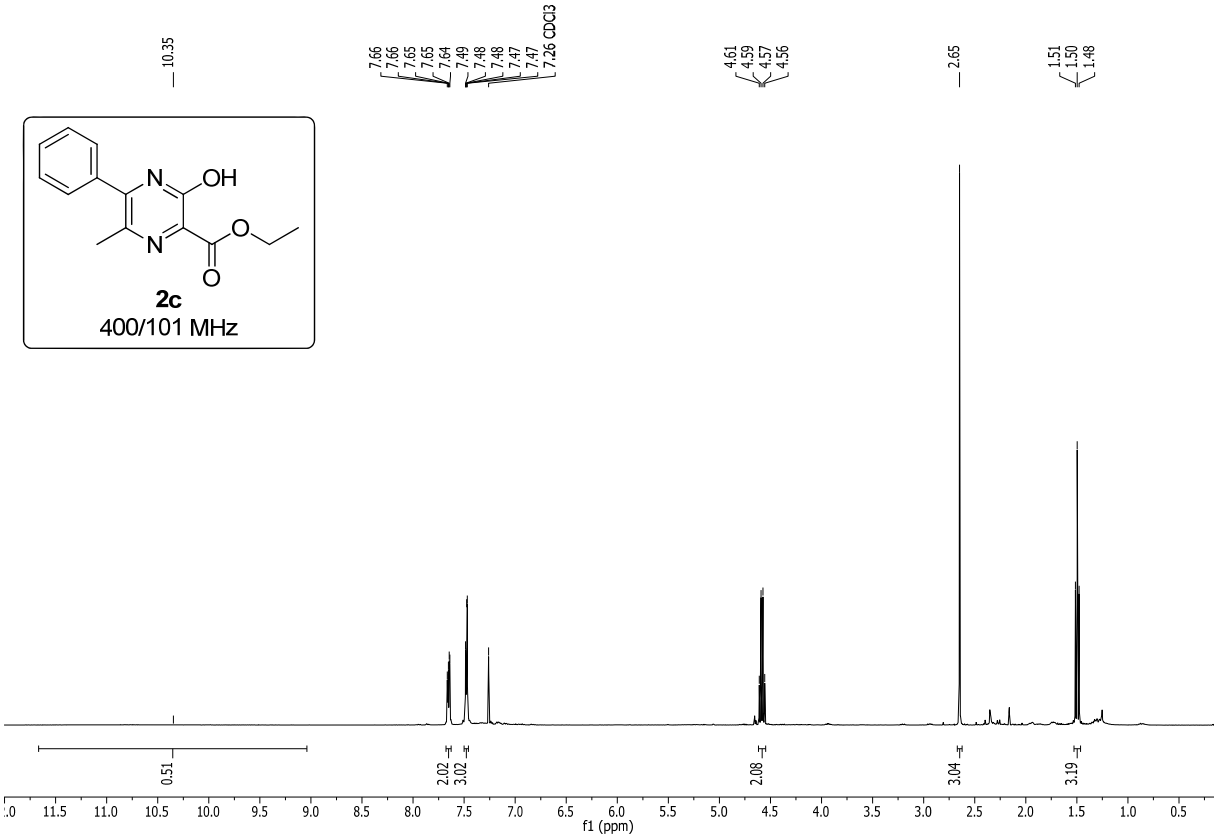

11.15
8.28
7.26 CDCl3
4.59
4.57
4.56
4.54
2.57
1.50
1.48
1.46
N
OH
N
O
O
2a
400/101 MHz
0.78
0.99
2.05
3.03
3.11
f1 (ppm)

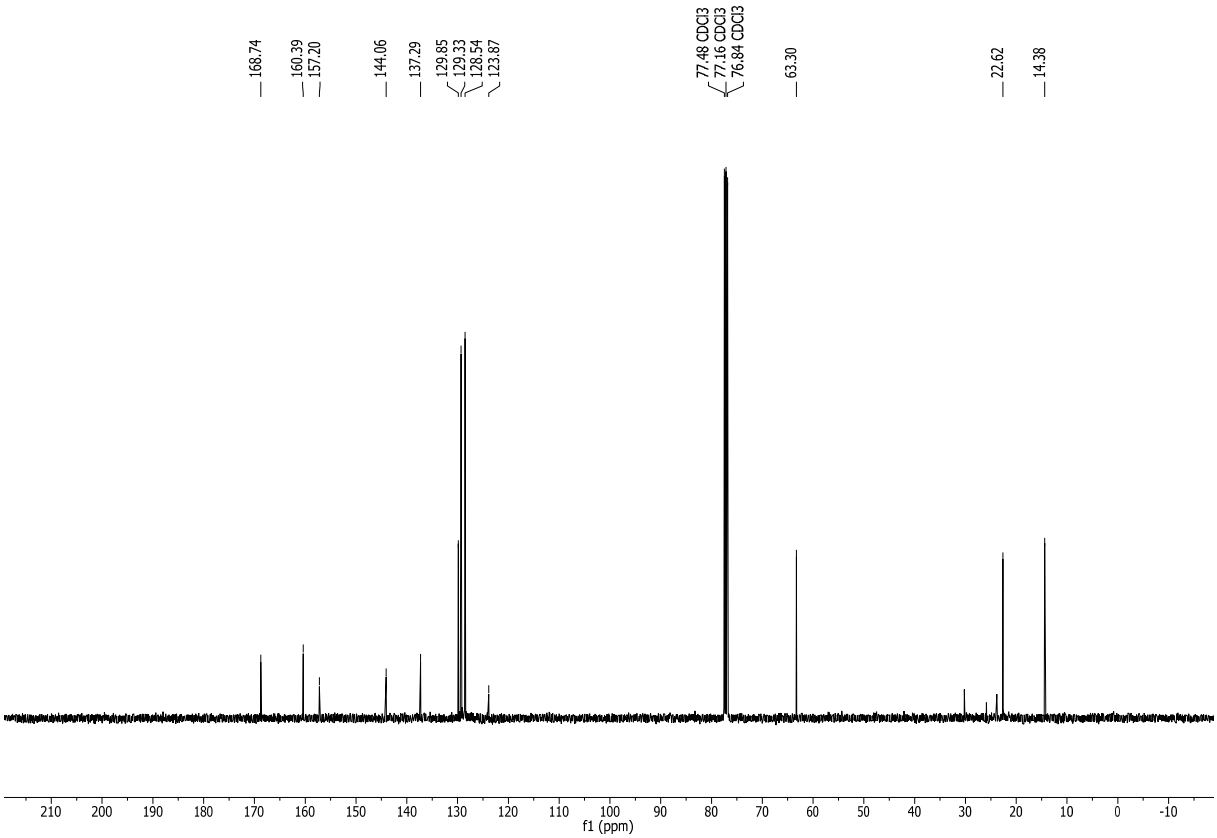

168.78
161.04
147.85
146.28
125.52
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
63.44
20.72
14.34
f1 (ppm)

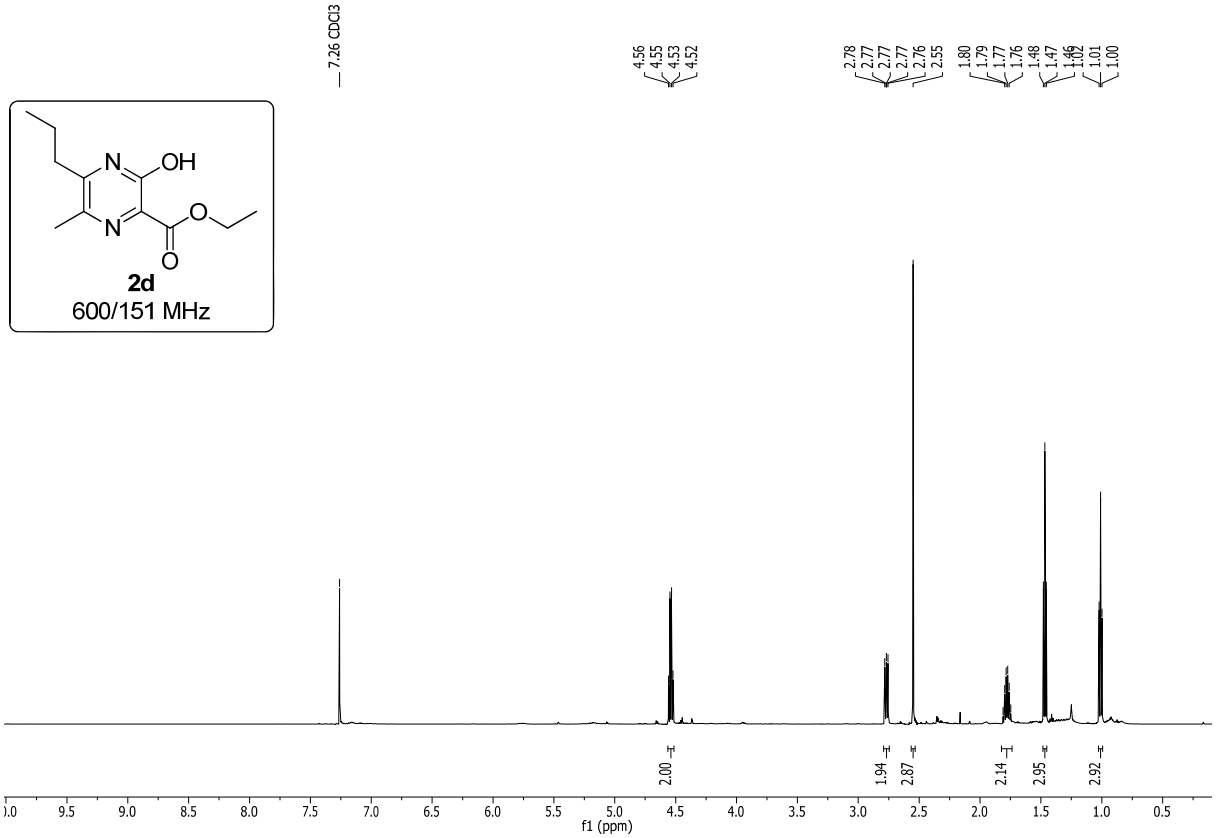

OH
N
N
O
O
2a
^{1}H-^{15}N-HMBC
{8.25,-86.32}
{2.56,-41.74}
f2 (ppm)
f1 (ppm)

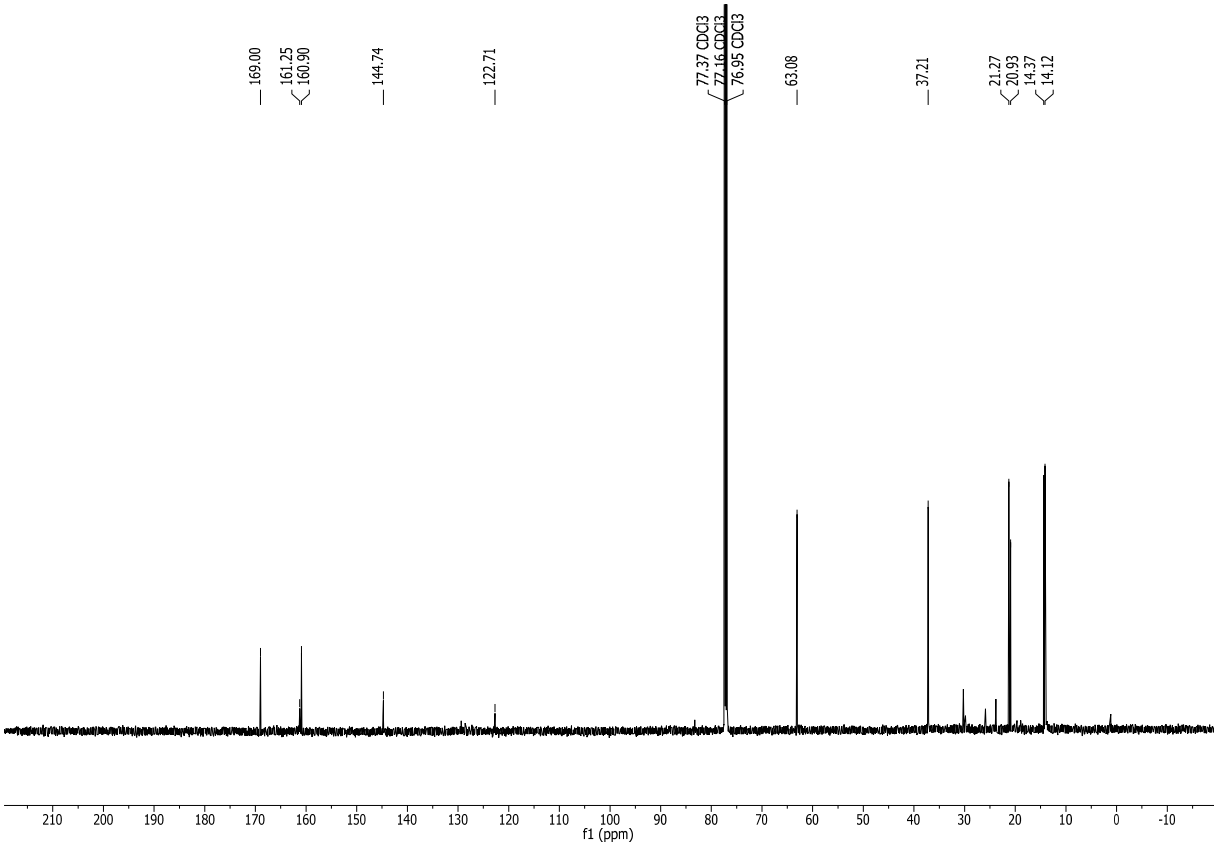

Transmittance [%]
Wavenumber cm-1
3036
2983
2928
2129
1736
1668
1642
1614
1527
1445
1372
1307
1225
1170
1107
1016
953
810
763
649
587
566
501
454
411

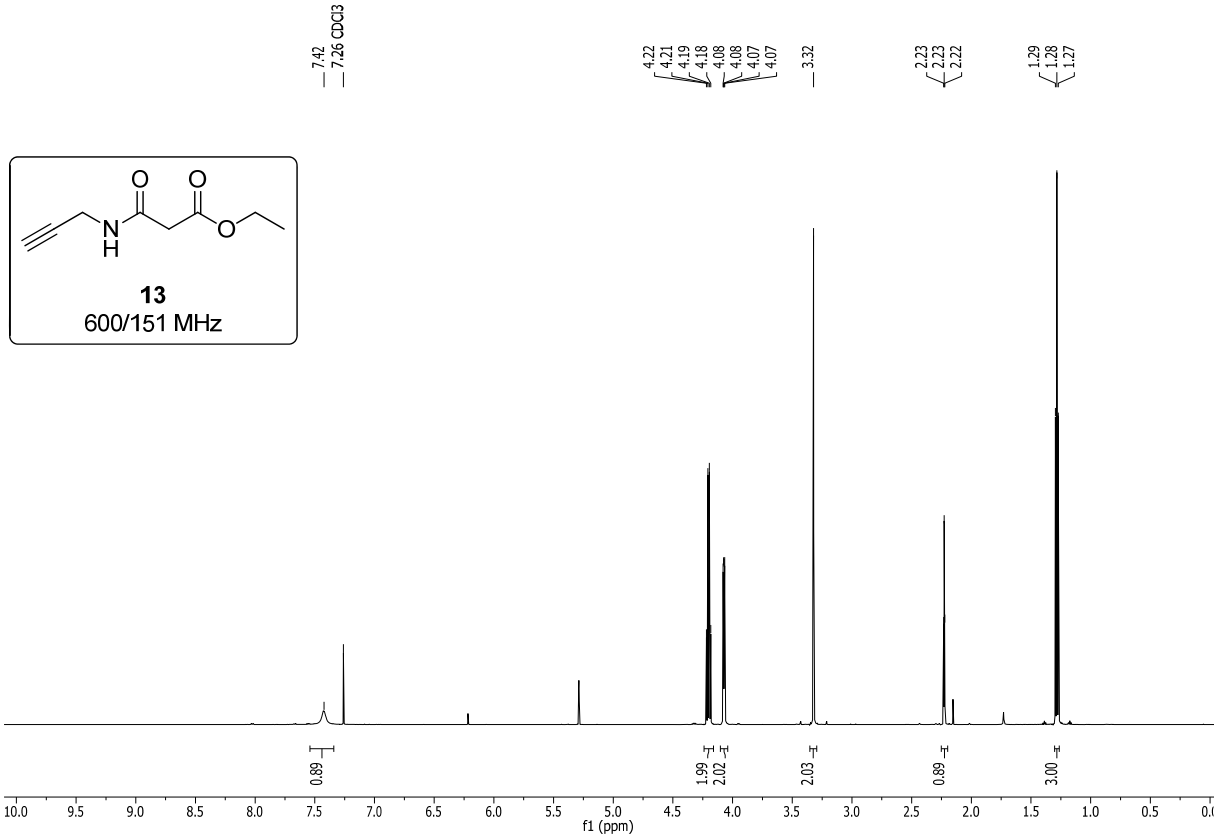

10.91
8.18
7.33
7.33
7.32
7.32
7.31
7.31
7.26 CDCl3
7.26
7.25
7.24
7.24
7.24
7.23
4.59
4.58
4.56
4.55
4.20
1.50
1.49
1.48
N
OH
Bn
N
O
O
2b
600/151 MHz
0.73
0.98
2.08
2.58
2.03
2.00
3.12
f1 (ppm)
168.55
160.93
148.50
147.37
138.02
128.95
128.85
126.88
125.84
77.21 CDCl3
76.99 CDCl3
76.78 CDCl3
63.25
40.94
14.17
f1 (ppm)

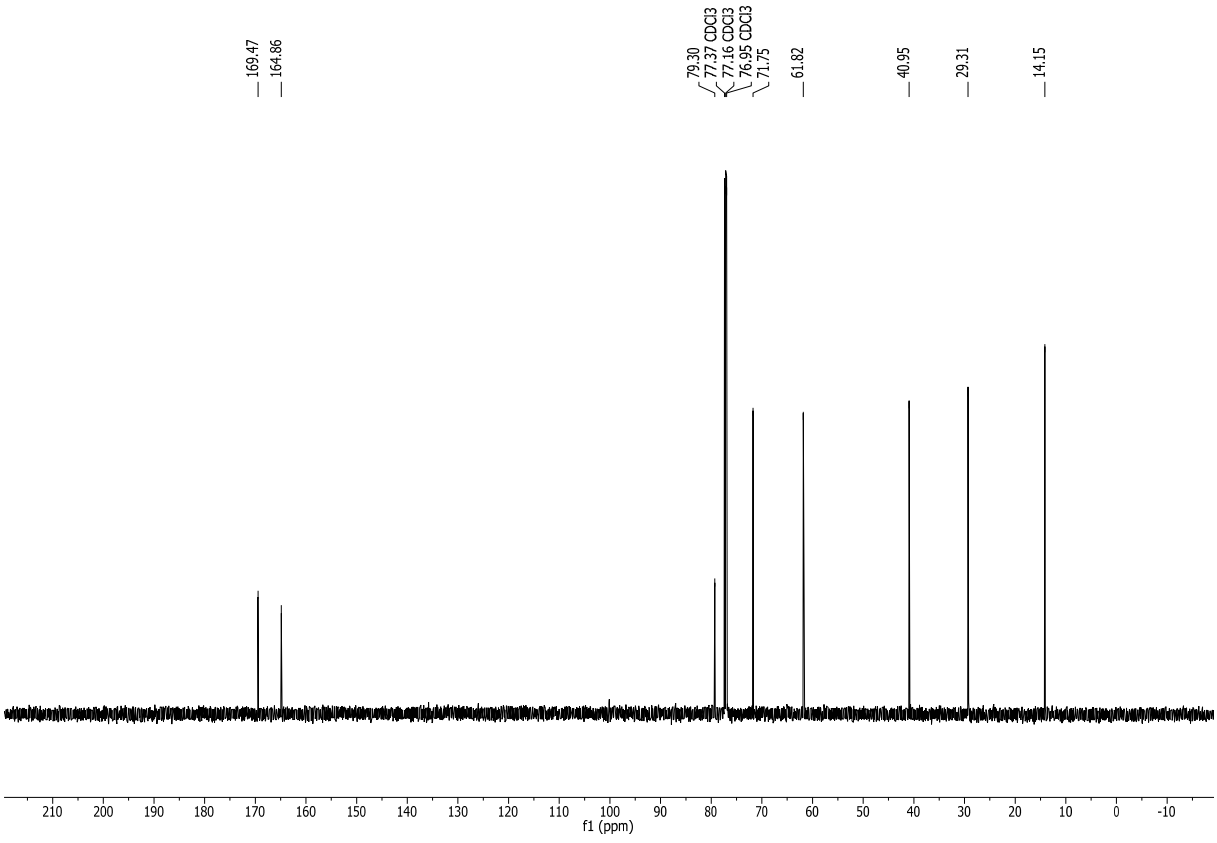

10.35
7.66
7.66
7.65
7.65
7.64
7.49
7.48
7.48
7.47
7.47
7.26 CDCl3
4.61
4.59
4.57
4.56
2.65
1.51
1.50
1.48
N
OH
N
O
O
2c
400/101 MHz
0.51
2.02
3.02
2.08
3.04
3.19
f1 (ppm)

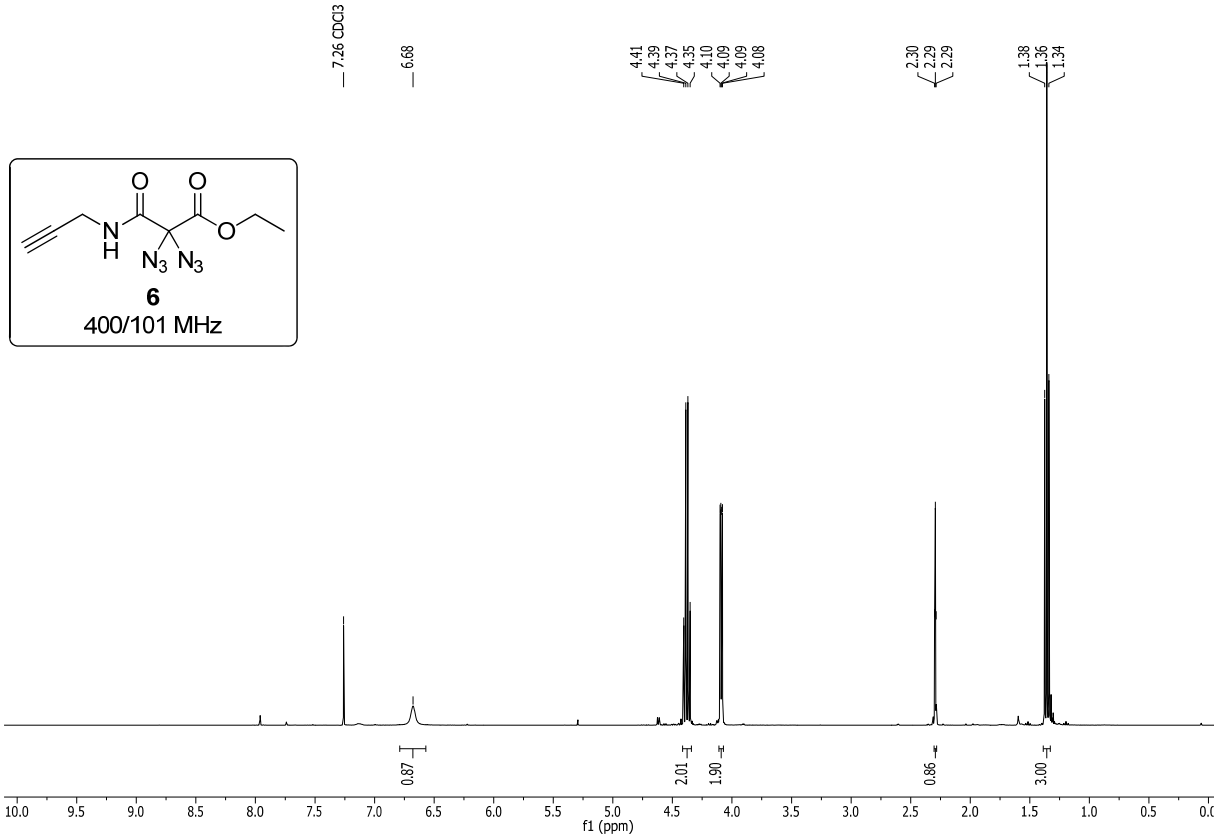

168.74
160.39
157.20
144.06
137.29
129.85
129.33
128.54
123.87
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
63.30
22.62
14.38
f1 (ppm)

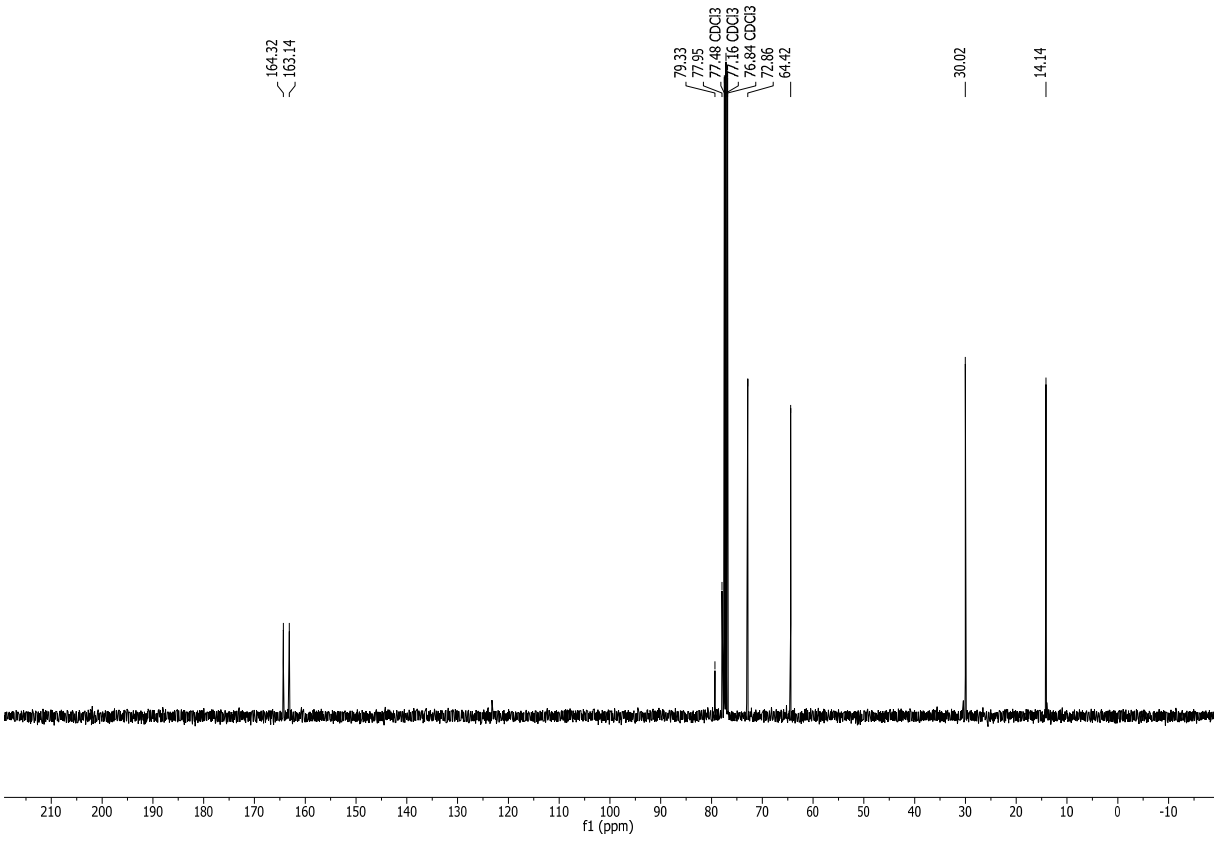

7.26 CDCl3
4.56
4.55
4.53
4.52
2.78
2.77
2.77
2.77
2.76
2.55
1.80
1.79
1.77
1.76
1.48
1.47
1.46
1.02
1.01
1.00
N
OH
N
O
O
2d
600/151 MHz
2.00
1.94
2.87
2.14
2.95
2.92
f1 (ppm)

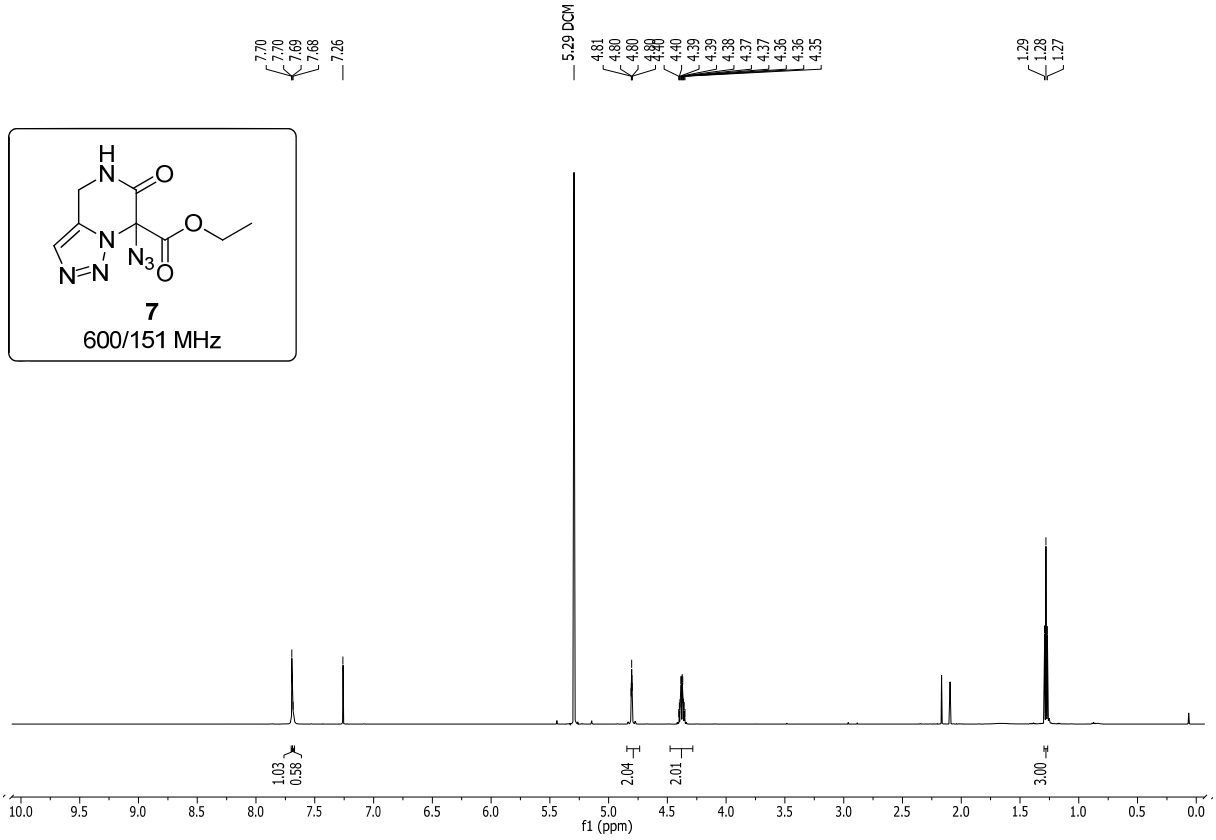

169.00
161.25
160.90
144.74
122.71
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
63.08
37.21
21.27
20.93
14.37
14.12
f1 (ppm)

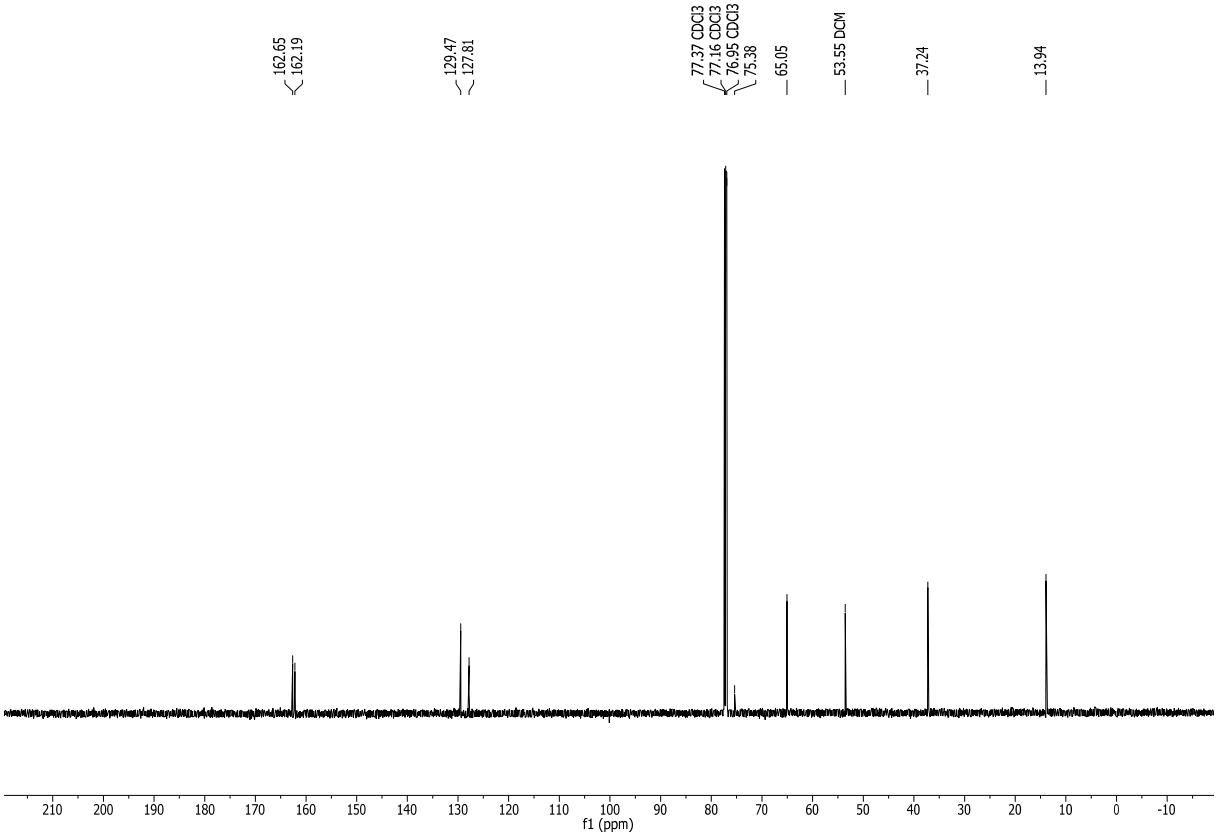

7.42
7.26 CDCl3
4.22
4.21
4.19
4.18
4.08
4.08
4.07
4.07
3.32
2.23
2.23
2.22
1.29
1.28
1.27
O
O
N
H
O
13
600/151 MHz
0.89
1.99
2.02
2.03
0.89
3.00
f1 (ppm)

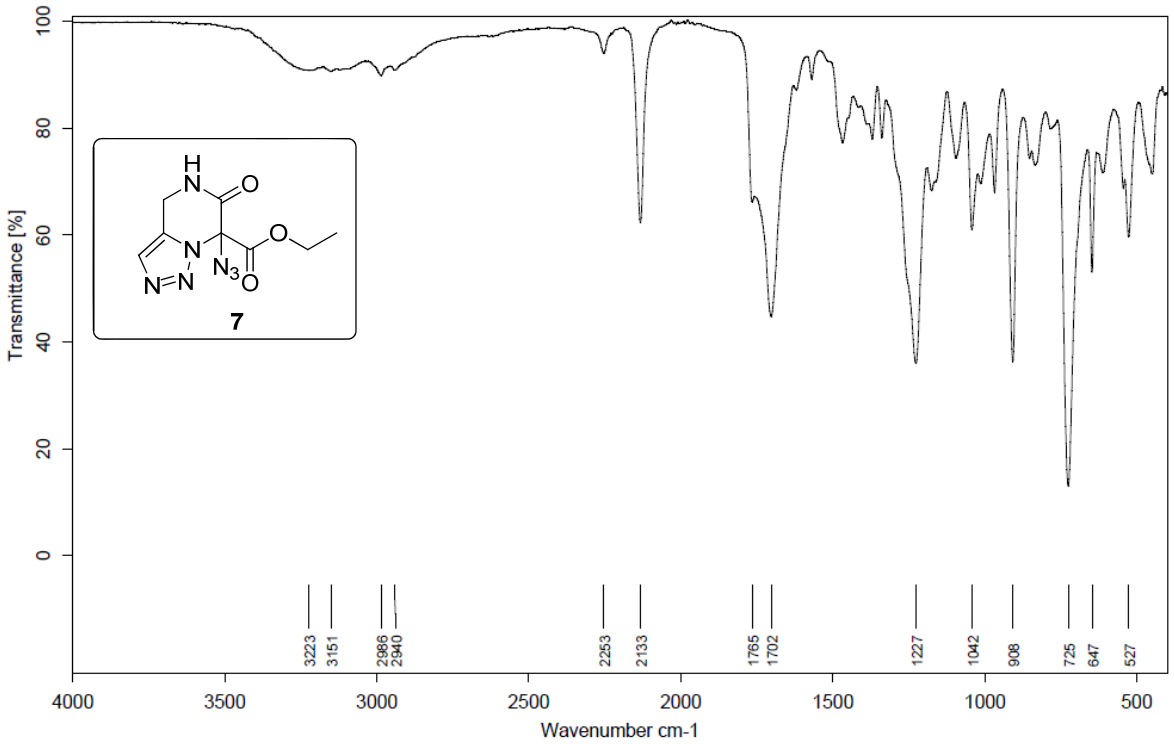

169.47
164.86
79.30
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
71.75
61.82
40.95
29.31
14.15
f1 (ppm)

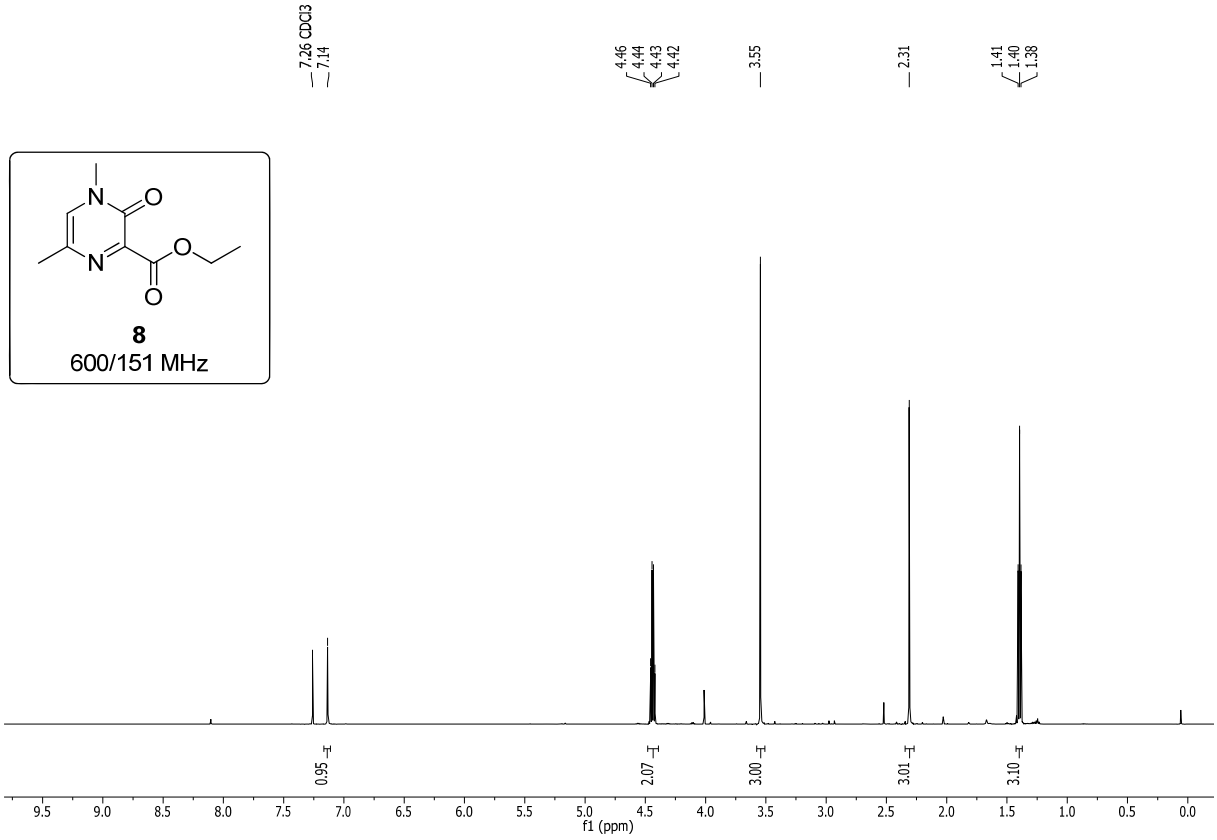

7.26 CDCl3
6.68
4.41
4.39
4.37
4.35
4.10
4.09
4.09
4.08
2.30
2.29
2.29
1.38
1.36
1.34
O
O
N
H
O
N3 N3
6
400/101 MHz
0.87
2.01
1.90
0.86
3.00
f1 (ppm)

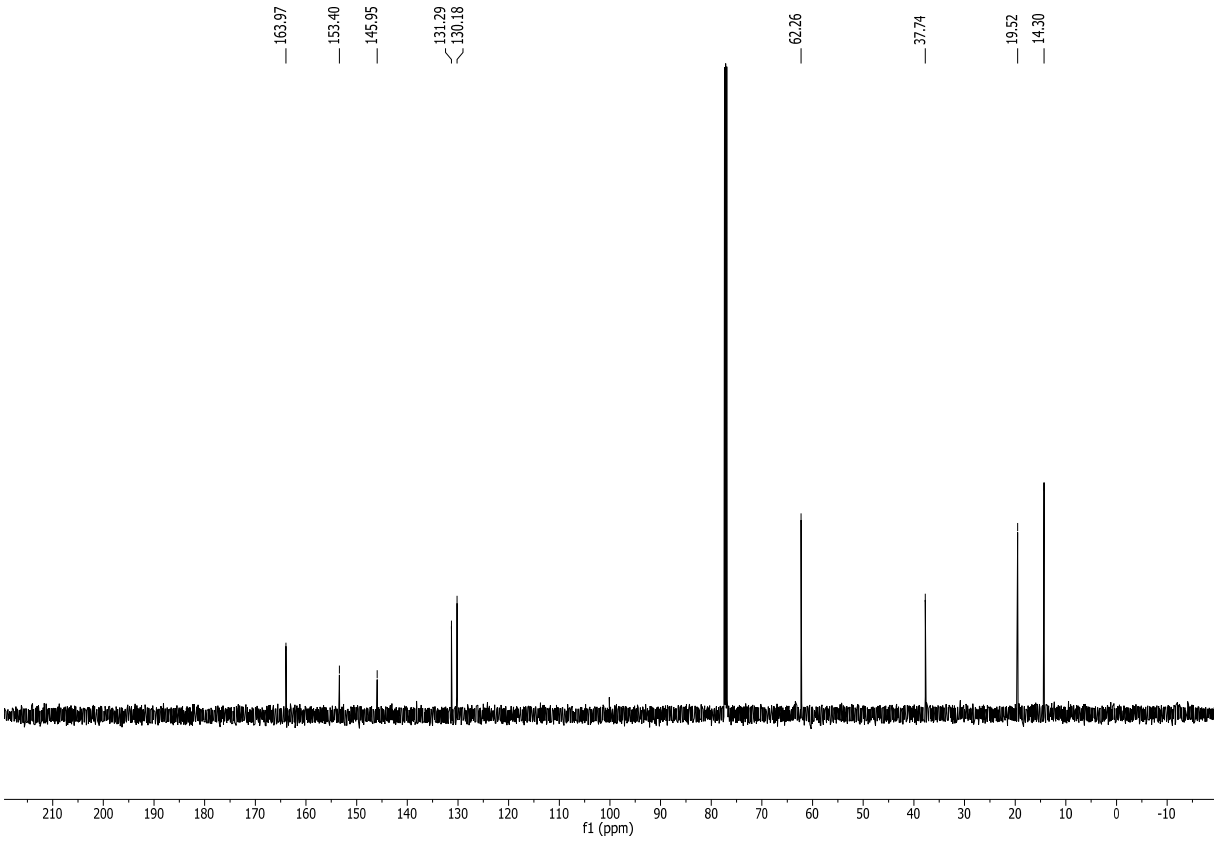

164.32
163.14
79.33
77.95
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
72.86
64.42
30.02
14.14
f1 (ppm)

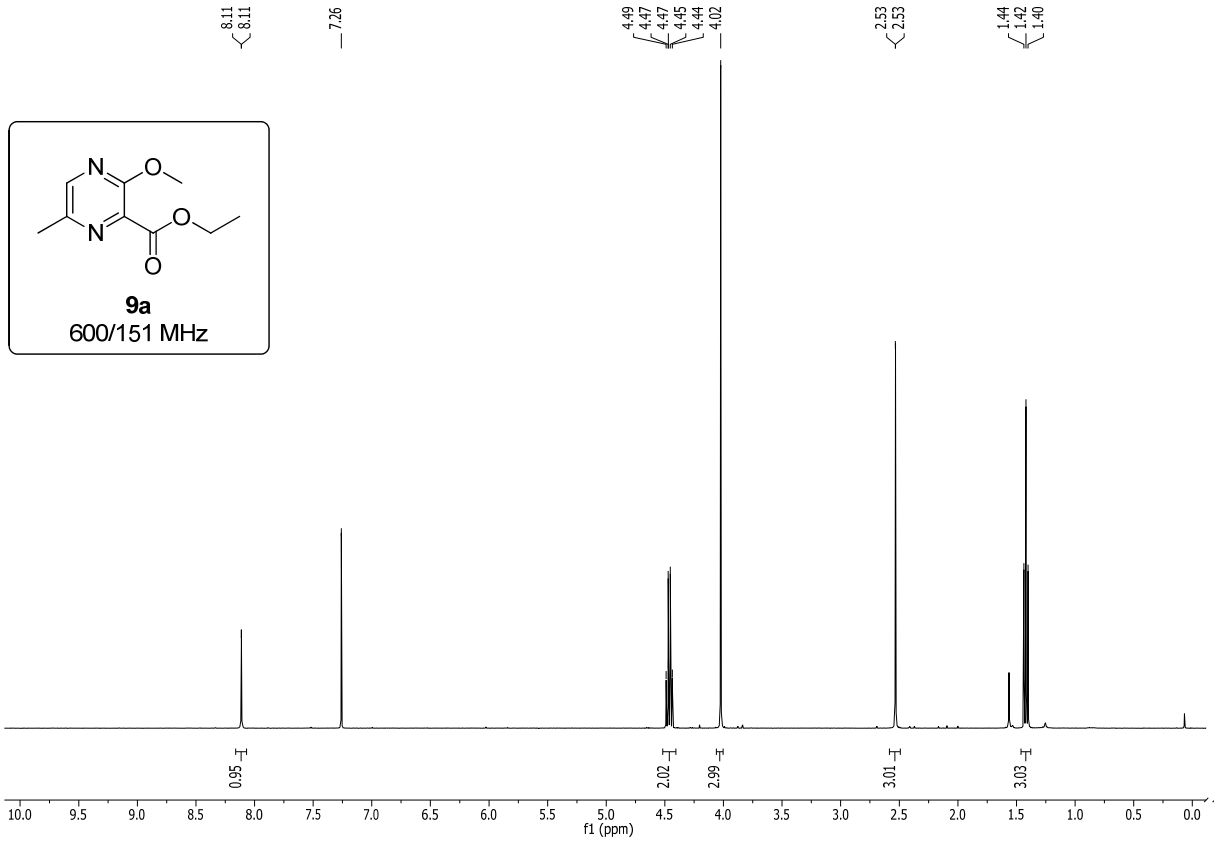

7.70
7.70
7.69
7.68
7.26
5.29 DCM
4.81
4.80
4.40
4.39
4.39
4.38
4.37
4.37
4.36
4.36
4.35
1.29
1.28
1.27
7
600/151 MHz
1.03
0.58
2.04
2.01
3.00
f1 (ppm)

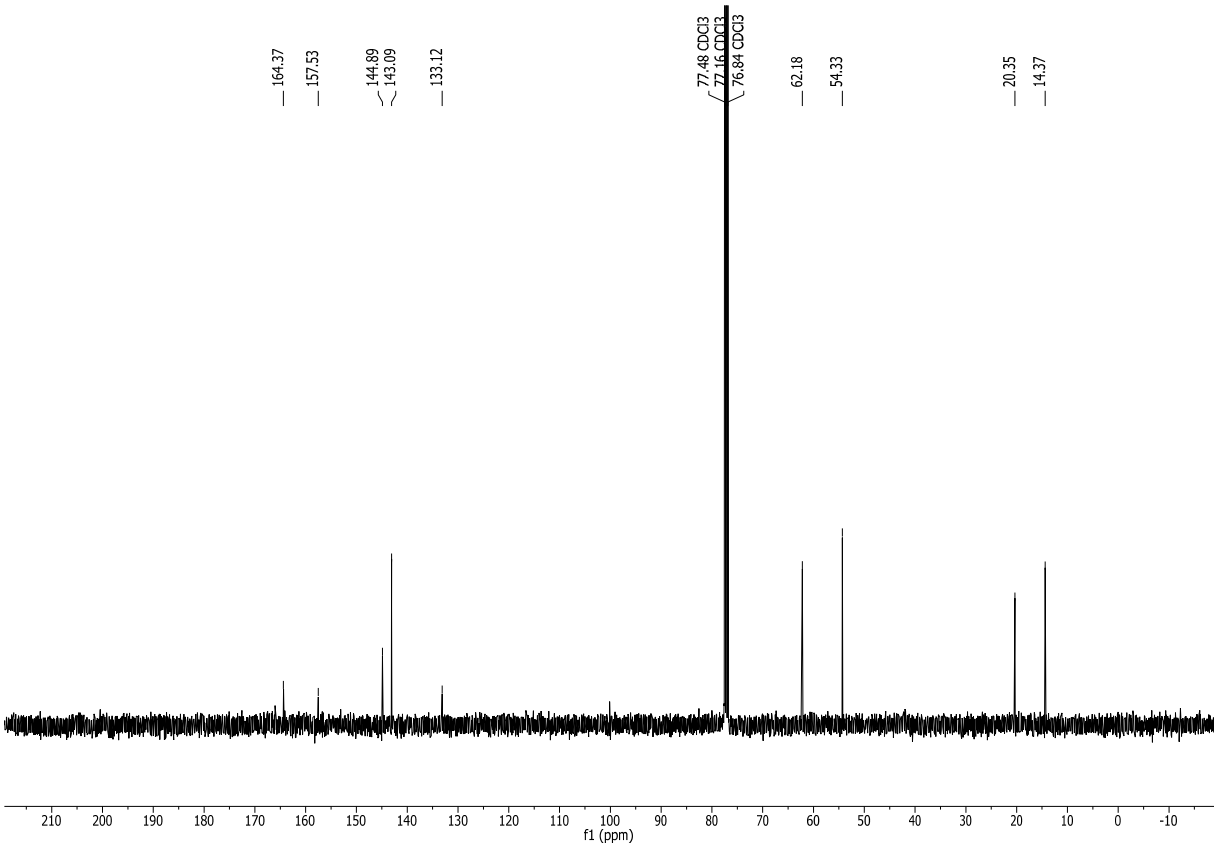

162.65
162.19
129.47
127.81
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
75.38
65.05
53.55 DCM
37.24
13.94
f1 (ppm)

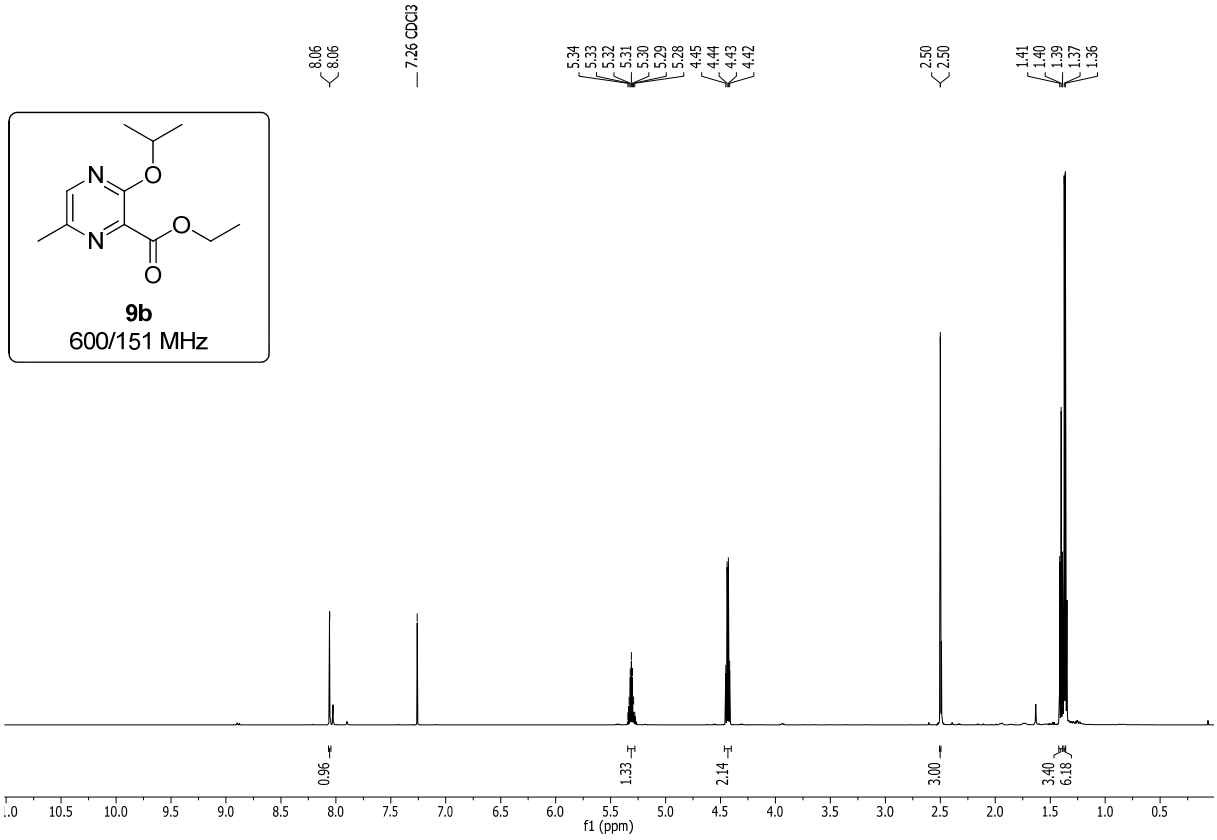

Transmittance [%]
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
3223
3151
2986
2940
2253
2133
1765
1702
1227
1042
908
725
647
527
7

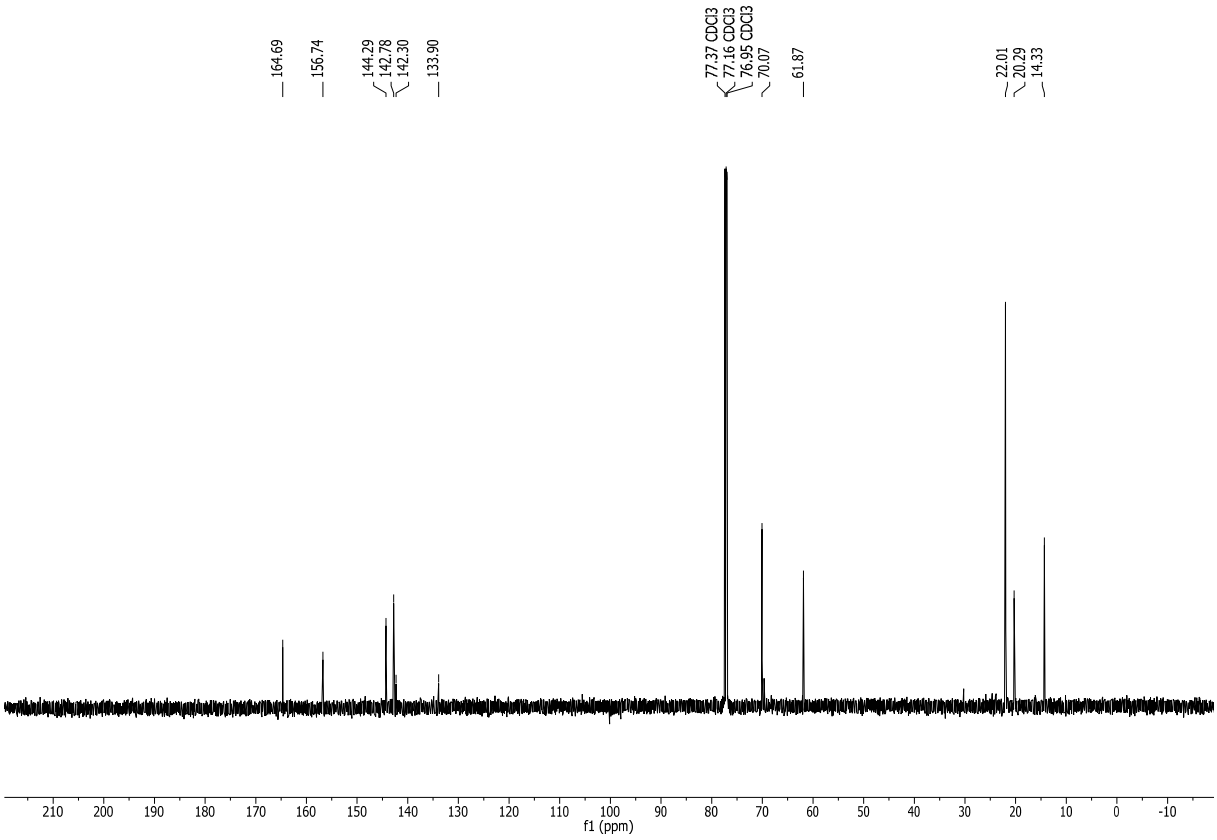

7.26 CDCl3
7.14
4.46
4.44
4.43
4.42
3.55
2.31
1.41
1.40
1.38
8
600/151 MHz
0.95
2.07
3.00
3.01
3.10
f1 (ppm)

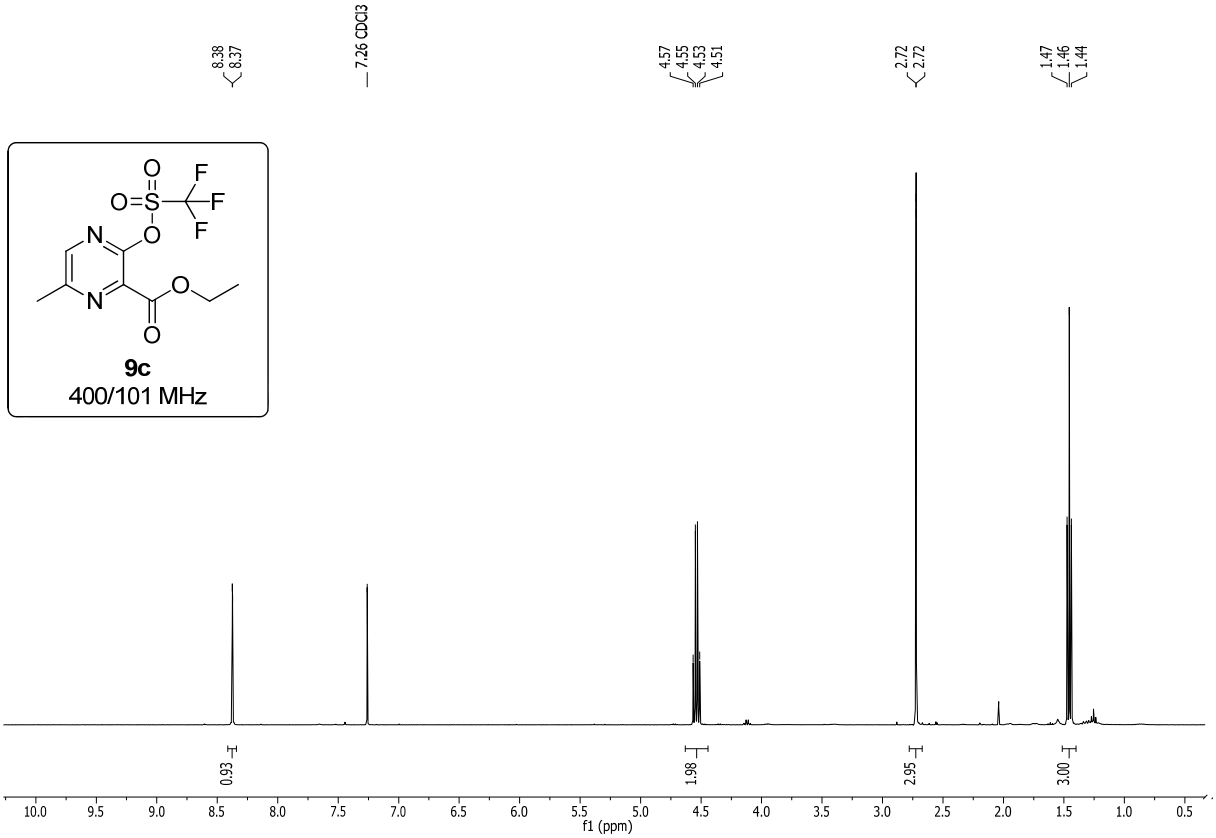

163.97
153.40
145.95
131.29
130.18
62.26
37.74
19.52
14.30
f1 (ppm)

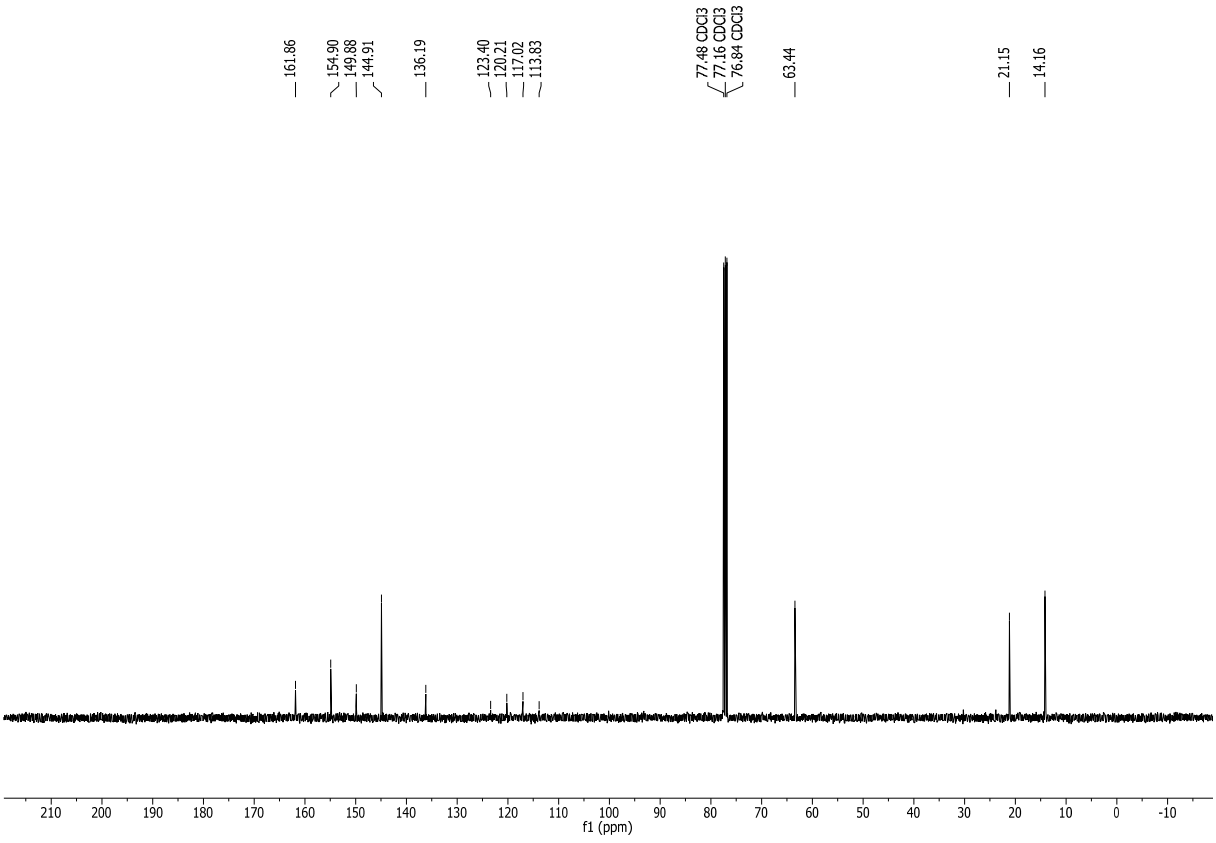

8.11
8.11
7.26
4.49
4.47
4.47
4.45
4.44
4.02
2.53
2.53
1.44
1.42
1.40
N
O
N
O
O
9a
600/151 MHz
0.95
2.02
2.99
3.01
3.03
f1 (ppm)

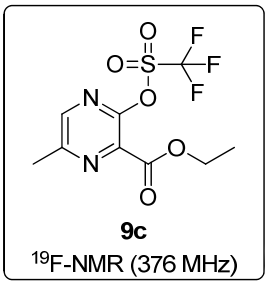

164.37
157.53
144.89
143.09
133.12
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.18
54.33
20.35
14.37
f1 (ppm)


8.06
8.06
7.26 CDCl3
5.34
5.33
5.32
5.31
5.30
5.29
5.28
4.45
4.44
4.43
4.42
2.50
2.50
1.41
1.40
1.39
1.37
1.36
9b
600/151 MHz
0.96
1.33
2.14
3.00
3.40
6.18
f1 (ppm)


164.69
156.74
144.29
142.78
142.30
133.90
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
70.07
61.87
22.01
20.29
14.33
f1 (ppm)

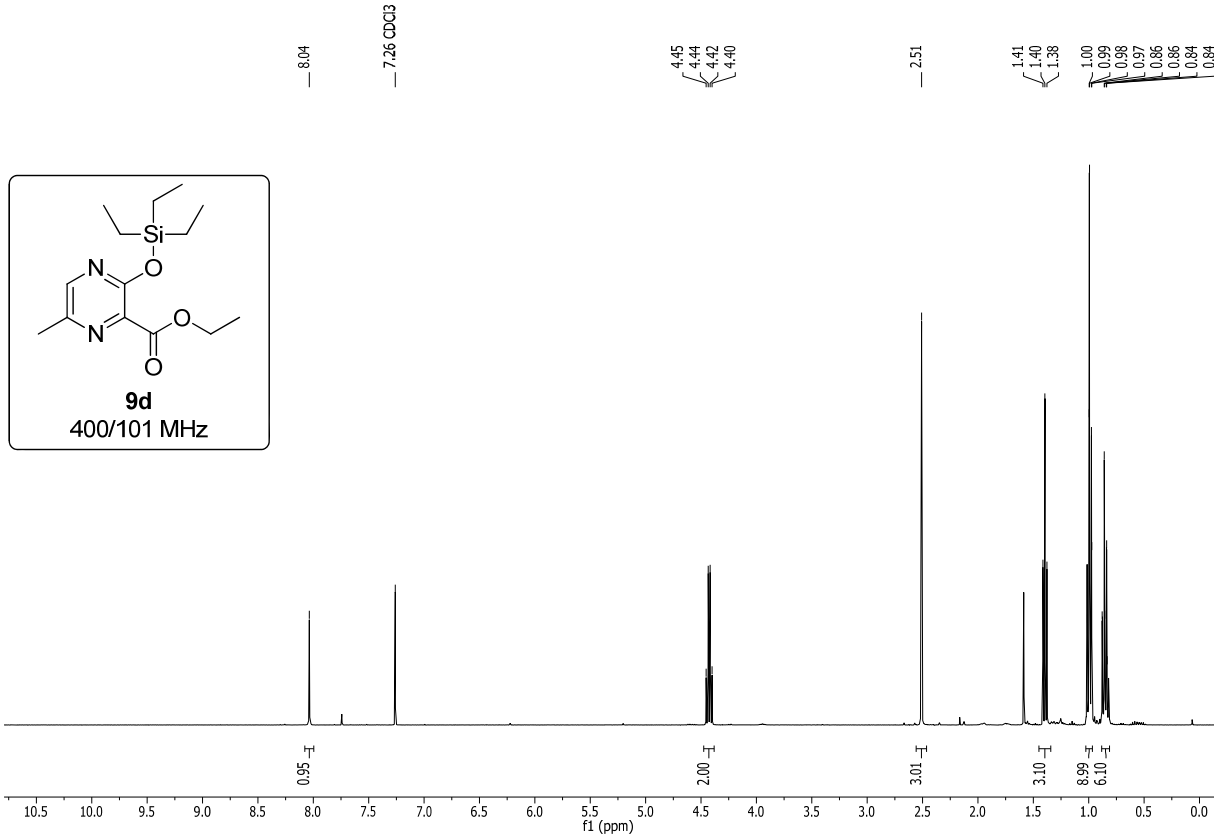

8.38
8.37
7.26 CDCl3
4.57
4.55
4.53
4.51
2.72
2.72
1.47
1.46
1.44
9c
400/101 MHz
0.93
1.98
2.95
3.00
f1 (ppm)


161.86
154.90
149.88
144.91
136.19
123.40
120.21
117.02
113.83
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
63.44
21.15
14.16
f1 (ppm)

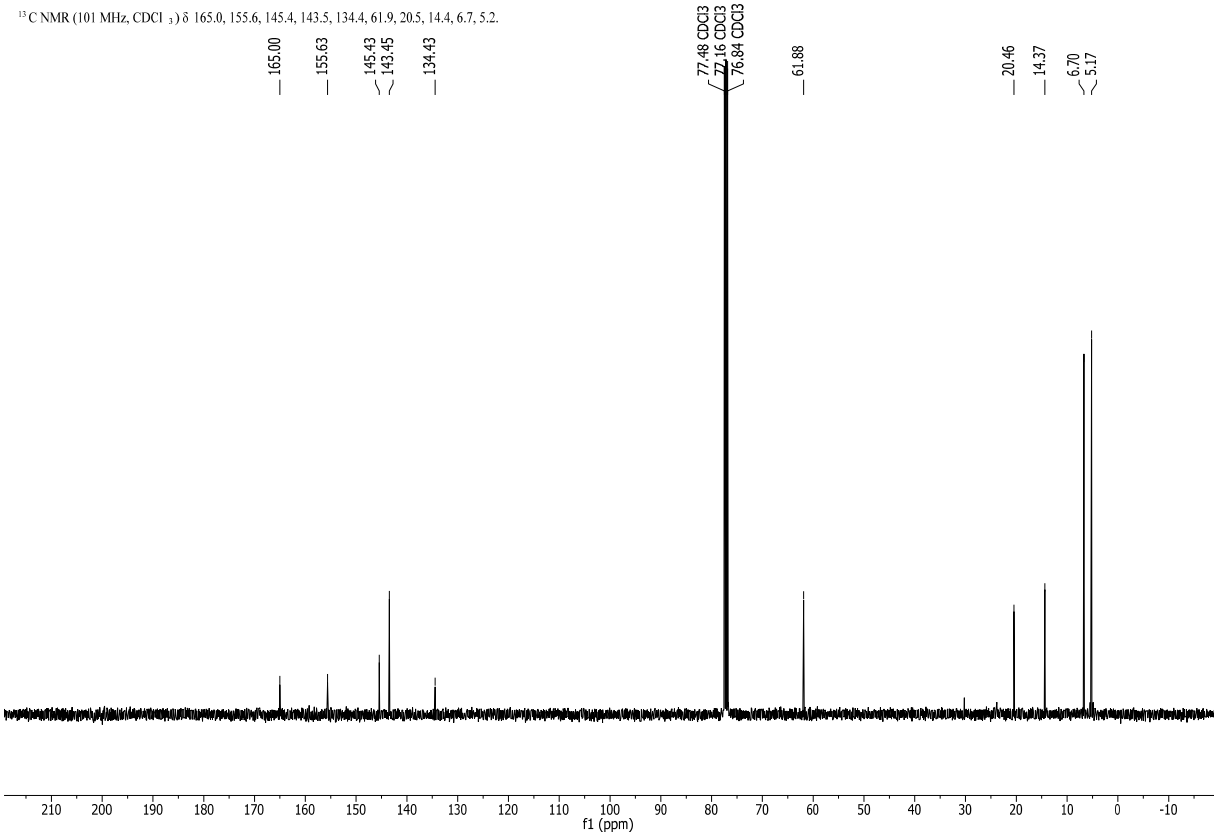


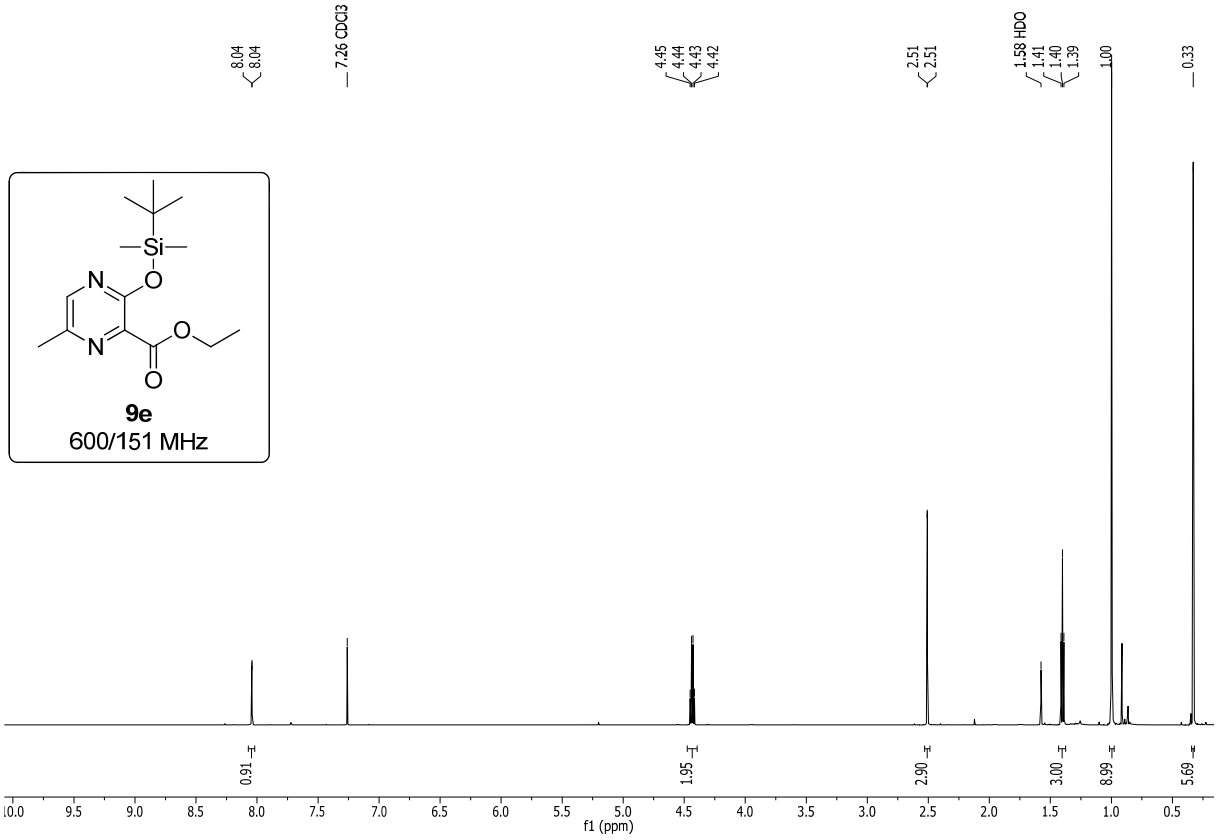
9c

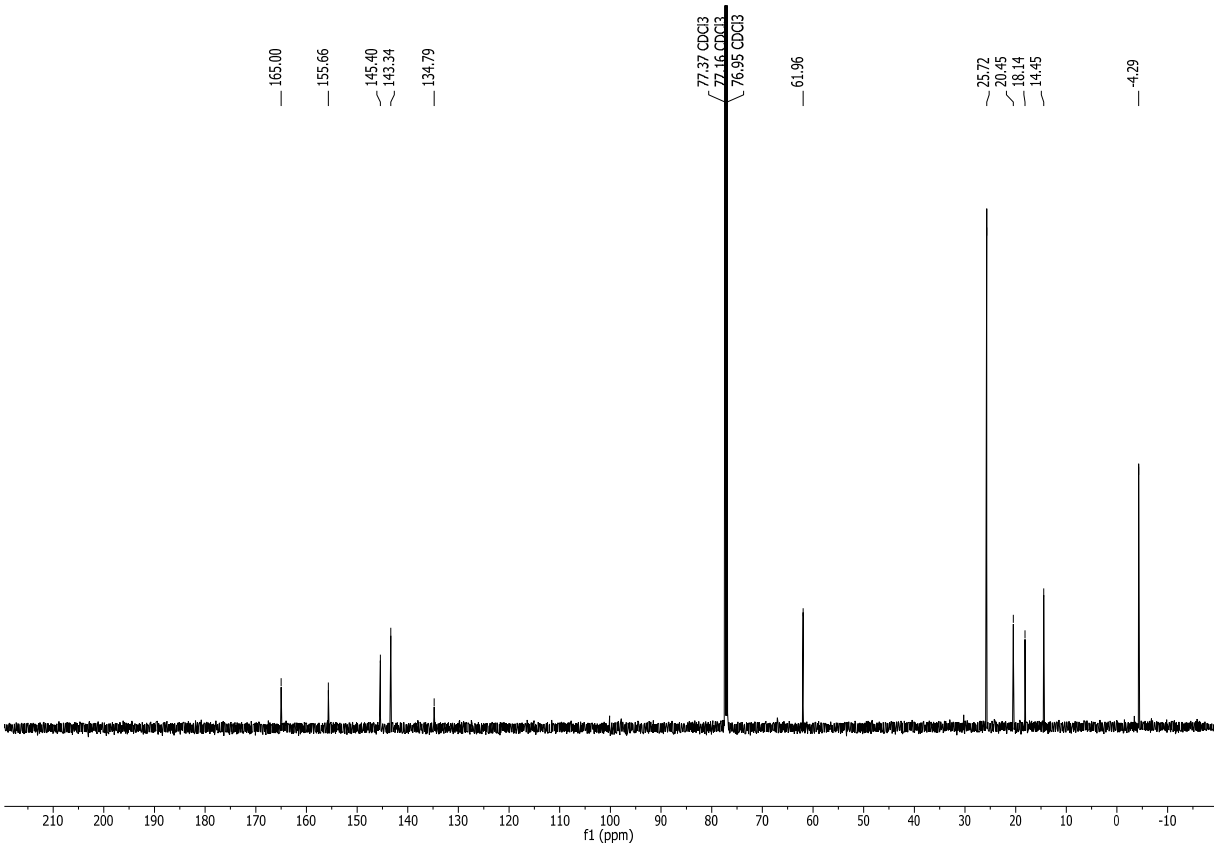
^{19}F-NMR (376 MHz)

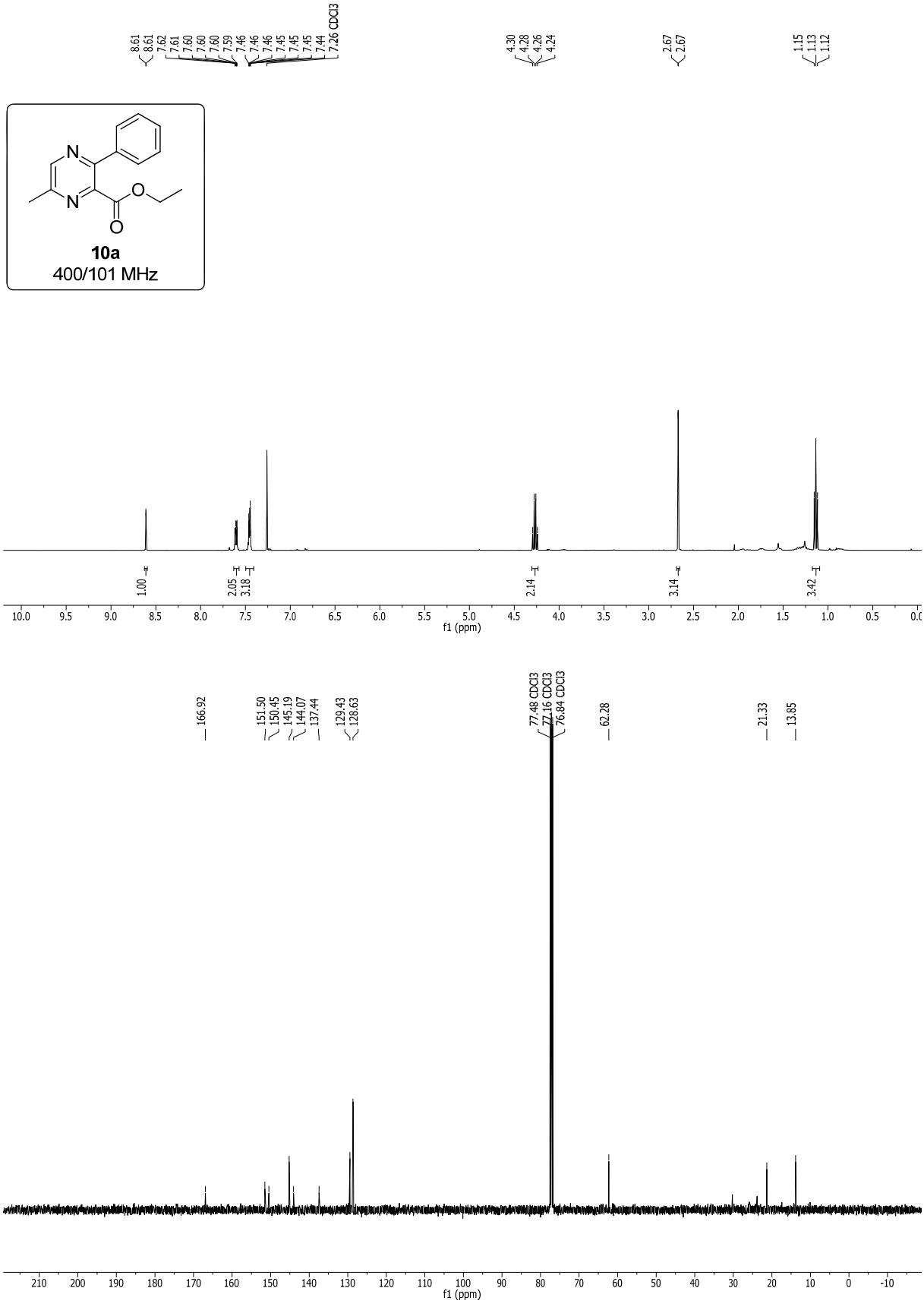


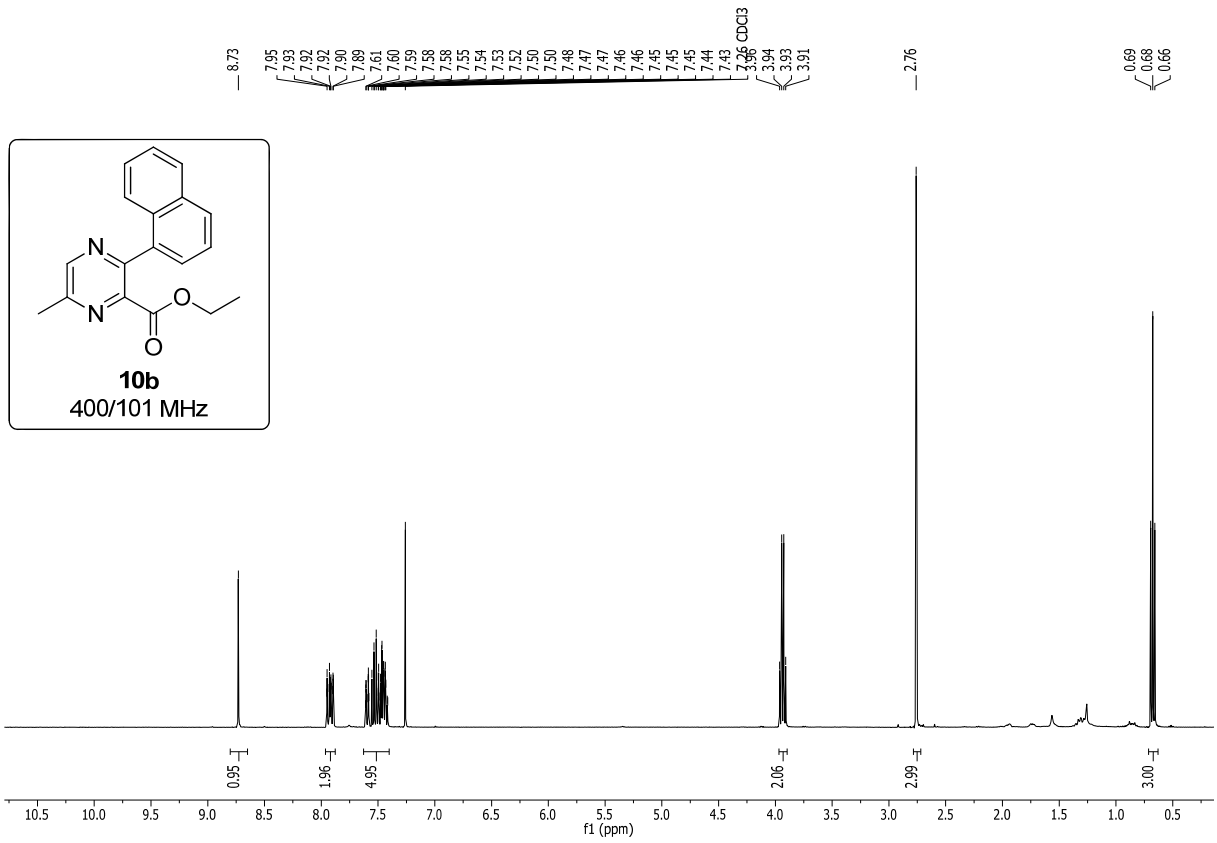
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 155.6, 145.4, 143.5, 134.4, 61.9, 20.5, 14.4, 6.7, 5.2.

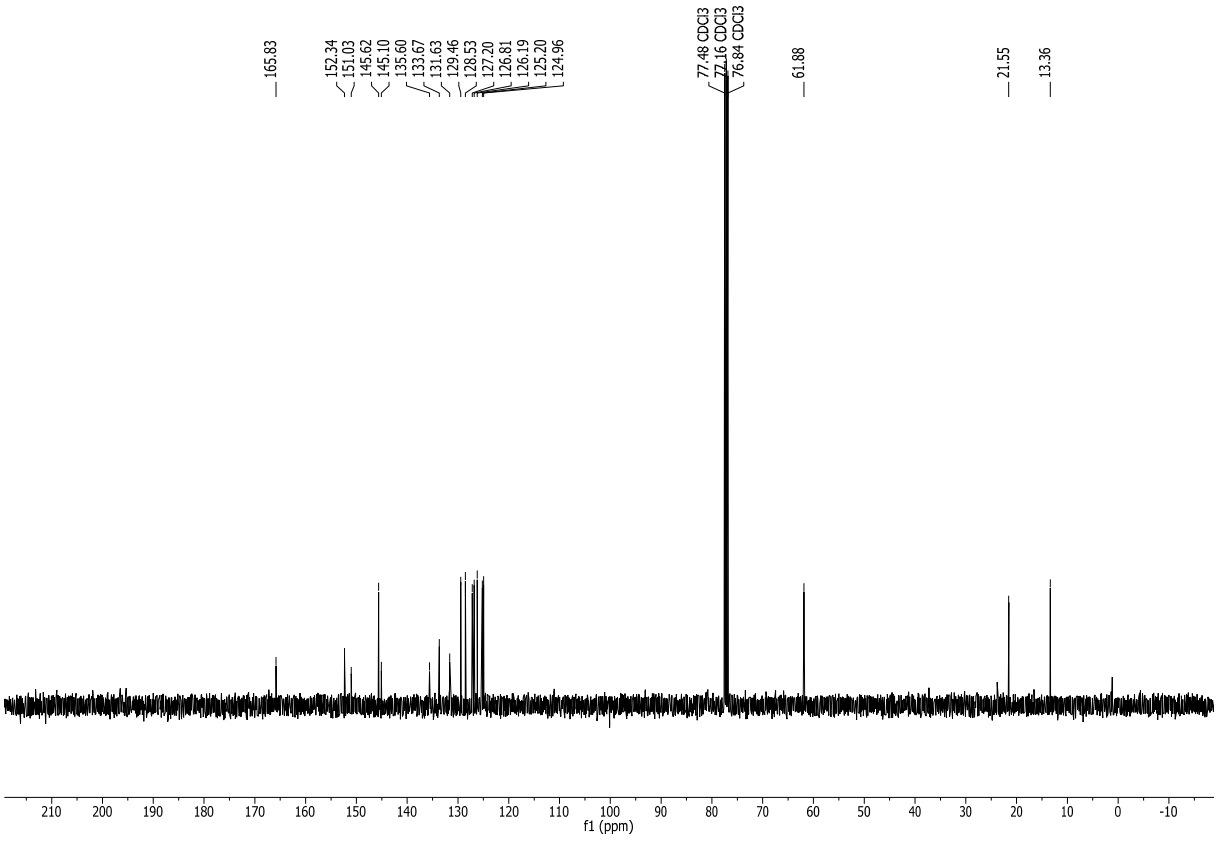


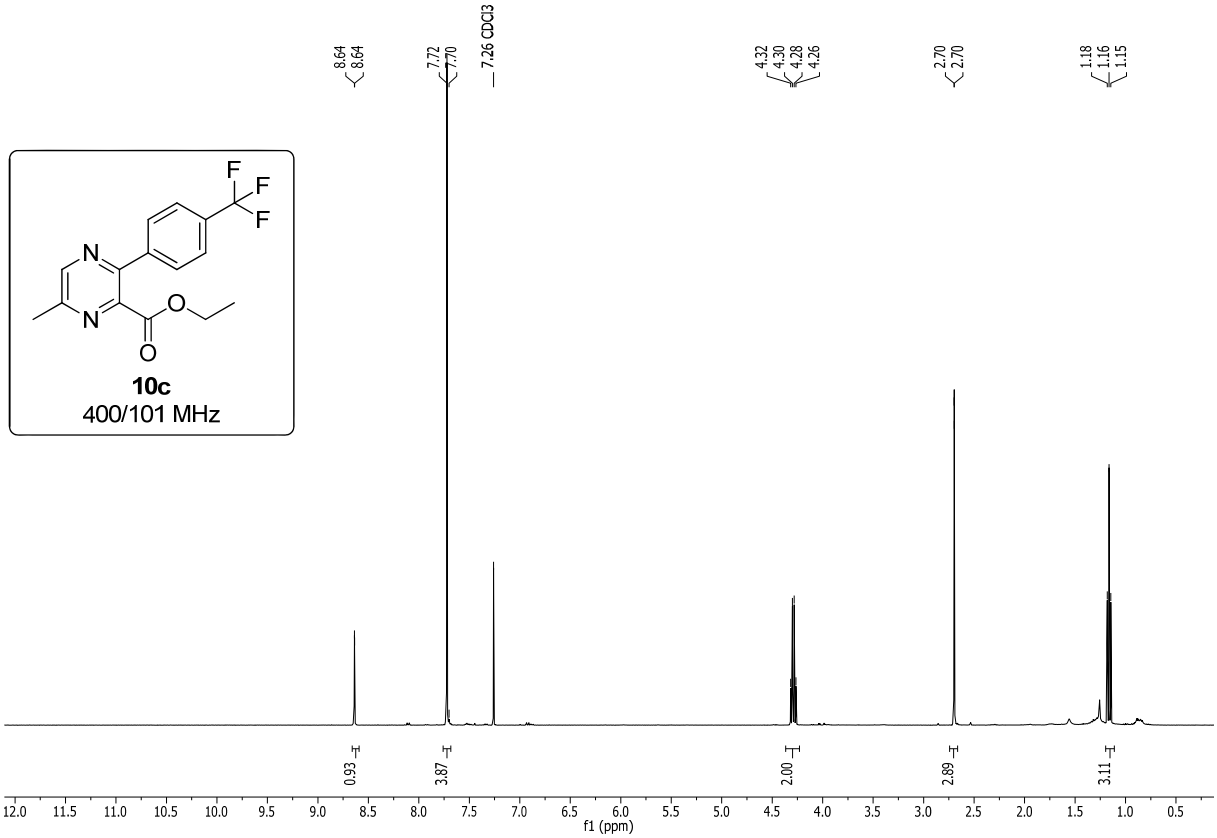

8.04
8.04
7.26 CDCl3
4.45
4.44
4.43
4.42
2.51
2.51
1.58 HDO
1.41
1.40
1.39
1.00
0.33
9e
600/151 MHz
0.91
1.95
2.90
3.00
8.99
5.69
f1 (ppm)

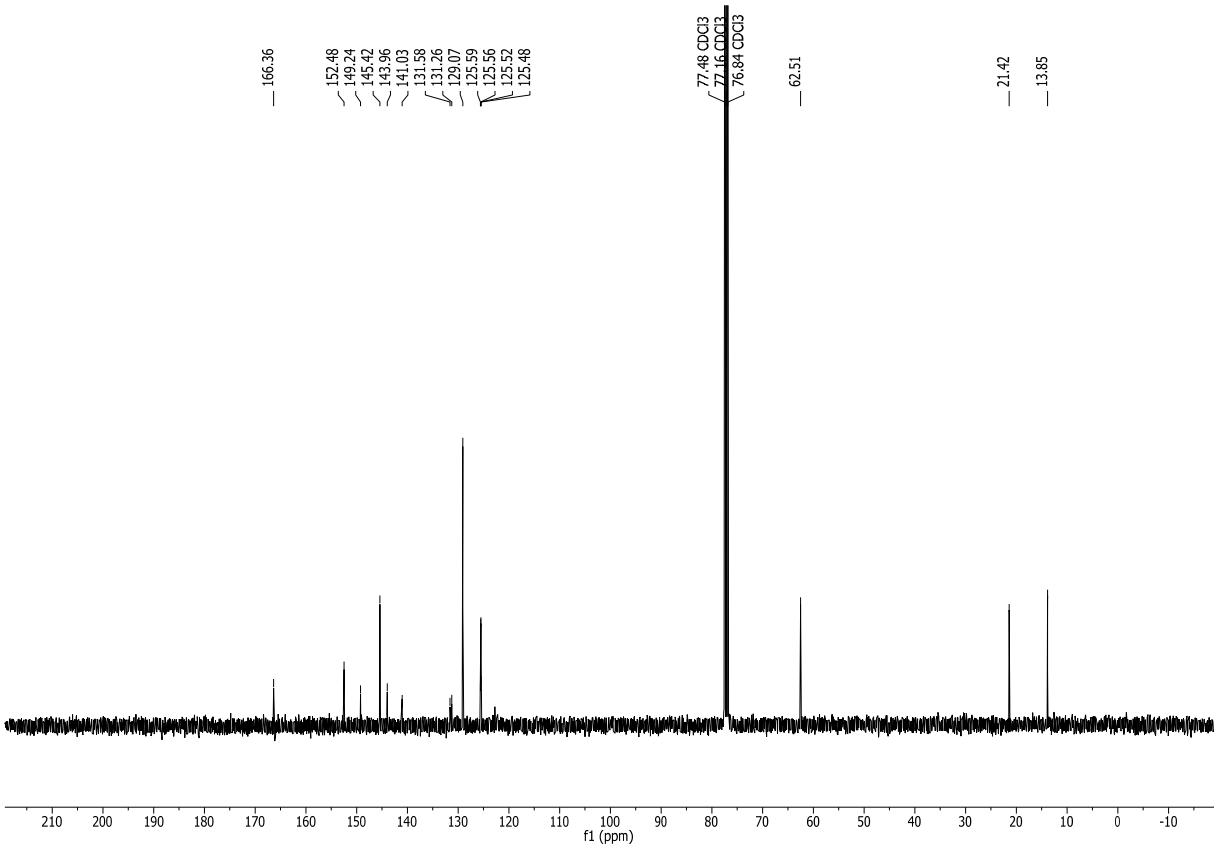

165.00
155.66
145.40
143.34
134.79
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
61.96
25.72
20.45
18.14
14.45
-4.29
f1 (ppm)

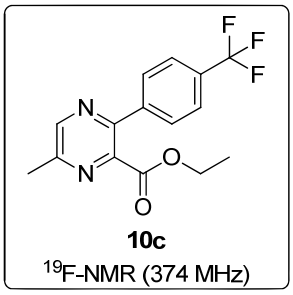

8.61
8.61
7.62
7.61
7.60
7.60
7.60
7.59
7.46
7.46
7.46
7.45
7.45
7.45
7.44
7.26 CDCl3
4.30
4.28
4.26
4.24
2.67
2.67
1.15
1.13
1.12
N
N
O
O
10a
400/101 MHz
1.00
2.05
3.18
2.14
3.14
3.42
f1 (ppm)
166.92
151.50
150.45
145.19
144.07
137.44
129.43
128.63
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.28
21.33
13.85
f1 (ppm)


8.73
7.95
7.93
7.92
7.92
7.90
7.89
7.61
7.60
7.59
7.58
7.58
7.55
7.54
7.53
7.52
7.50
7.50
7.48
7.47
7.47
7.46
7.46
7.45
7.45
7.45
7.44
7.43
7.26 CDCl3
3.96
3.94
3.93
3.91
2.76
0.69
0.68
0.66
10b
400/101 MHz
0.95
1.96
4.95
2.06
2.99
3.00
f1 (ppm)


165.83
152.34
151.03
145.62
145.10
135.60
133.67
131.63
129.46
128.53
127.20
126.81
126.19
125.20
124.96
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.88
21.55
13.36
f1 (ppm)

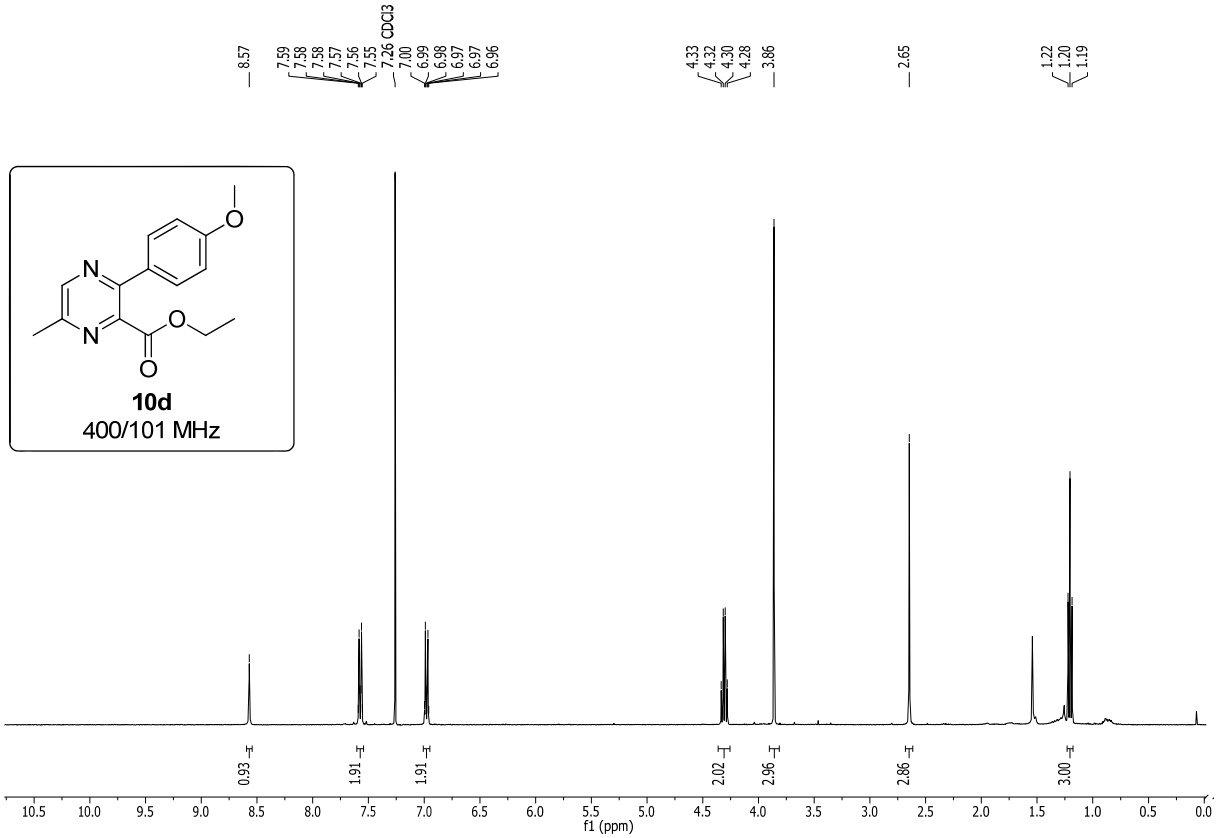

8.64
8.64
7.72
7.70
7.26 CDCl3
4.32
4.30
4.28
4.26
2.70
2.70
1.18
1.16
1.15
F
F
F
N
N
O
O
10c
400/101 MHz
0.93
3.87
2.00
2.89
3.11
f1 (ppm)

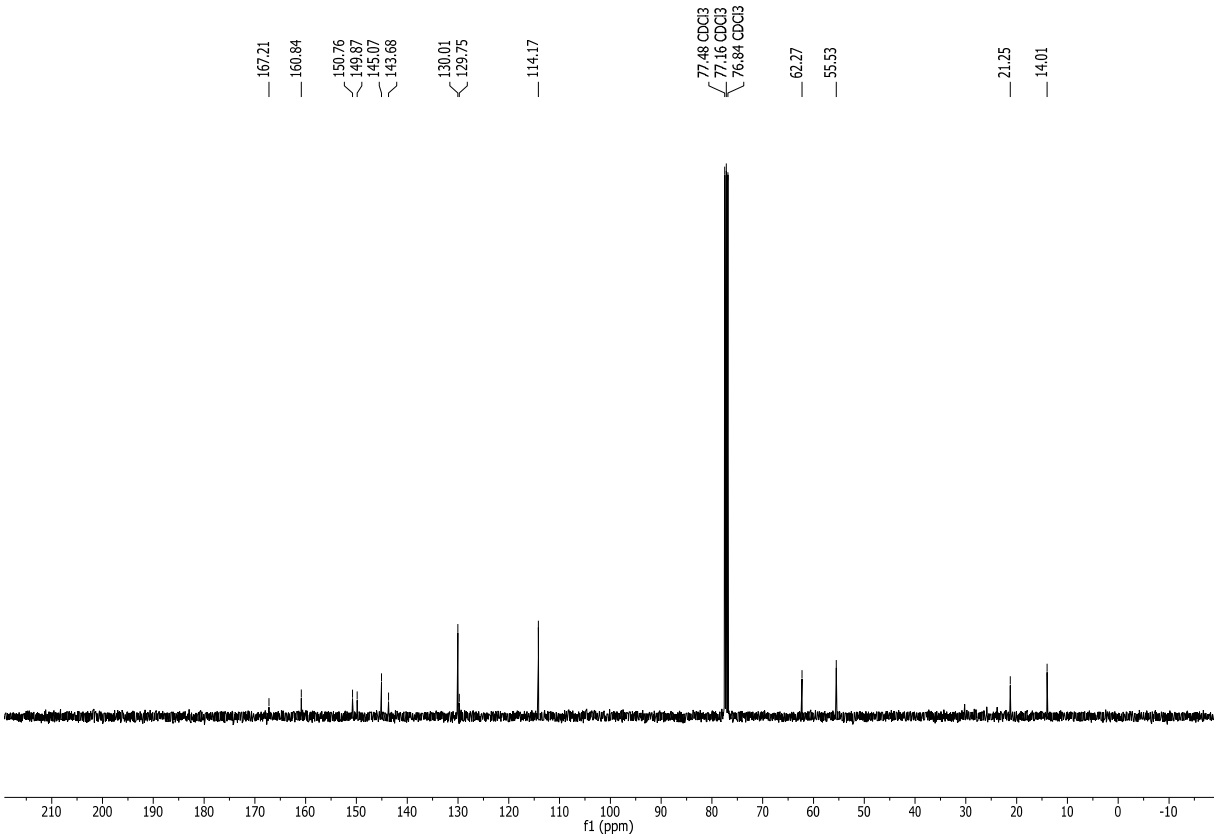

166.36
152.48
149.24
145.42
143.96
141.03
131.58
131.26
129.07
125.59
125.56
125.52
125.48
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.51
21.42
13.85
f1 (ppm)

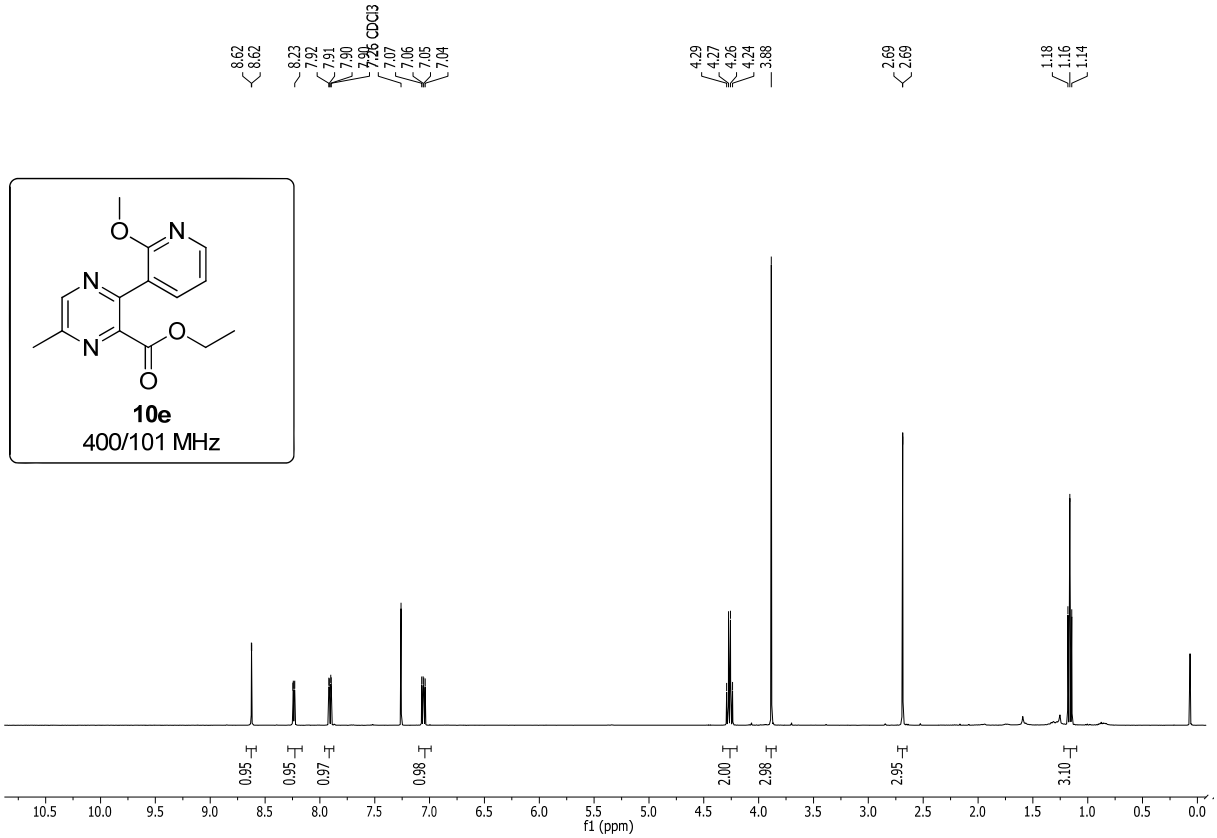


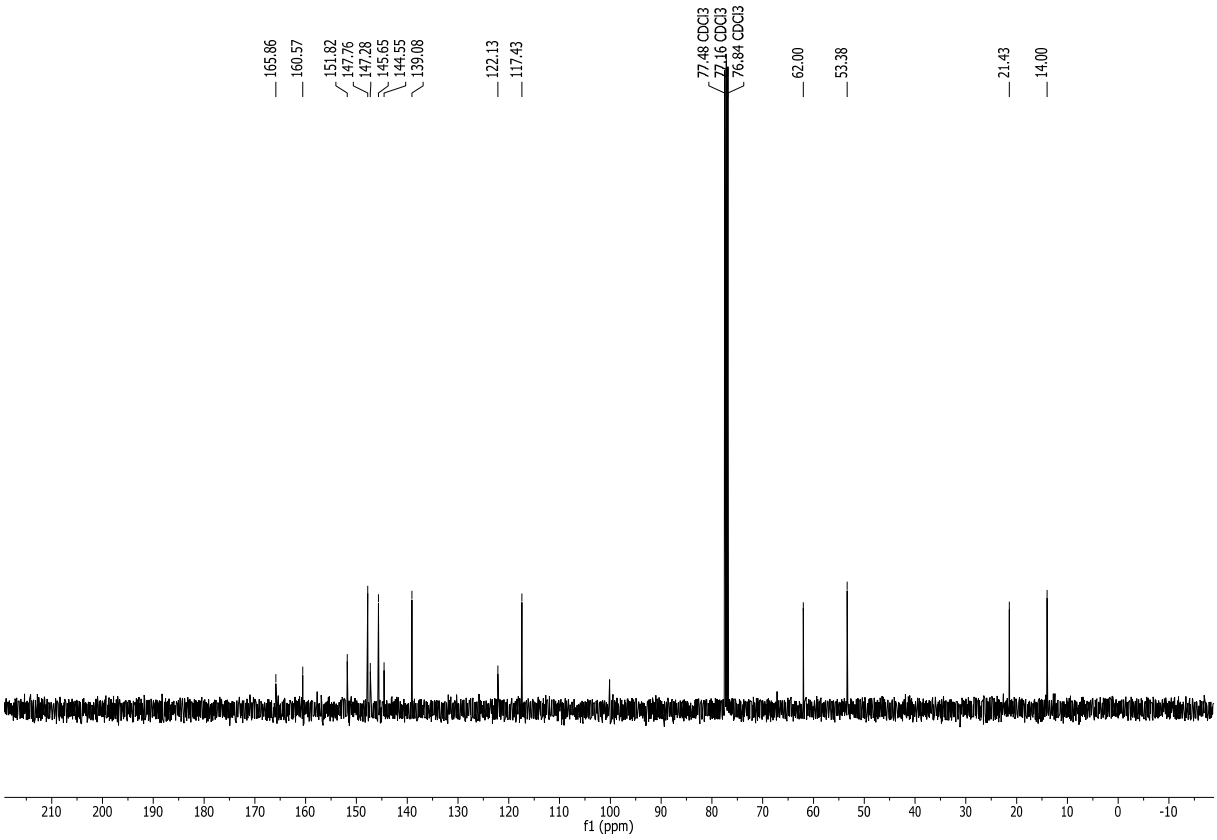
10c

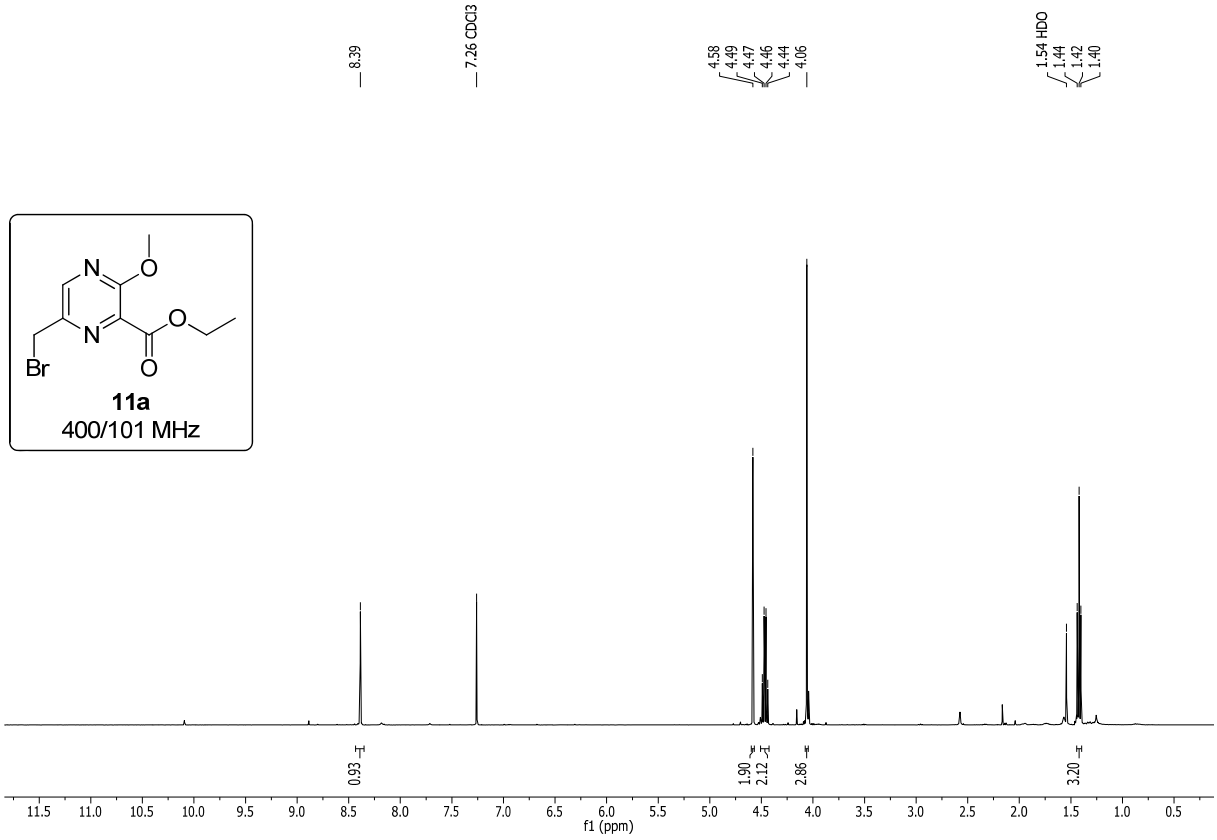
^{19}F-NMR (374 MHz)

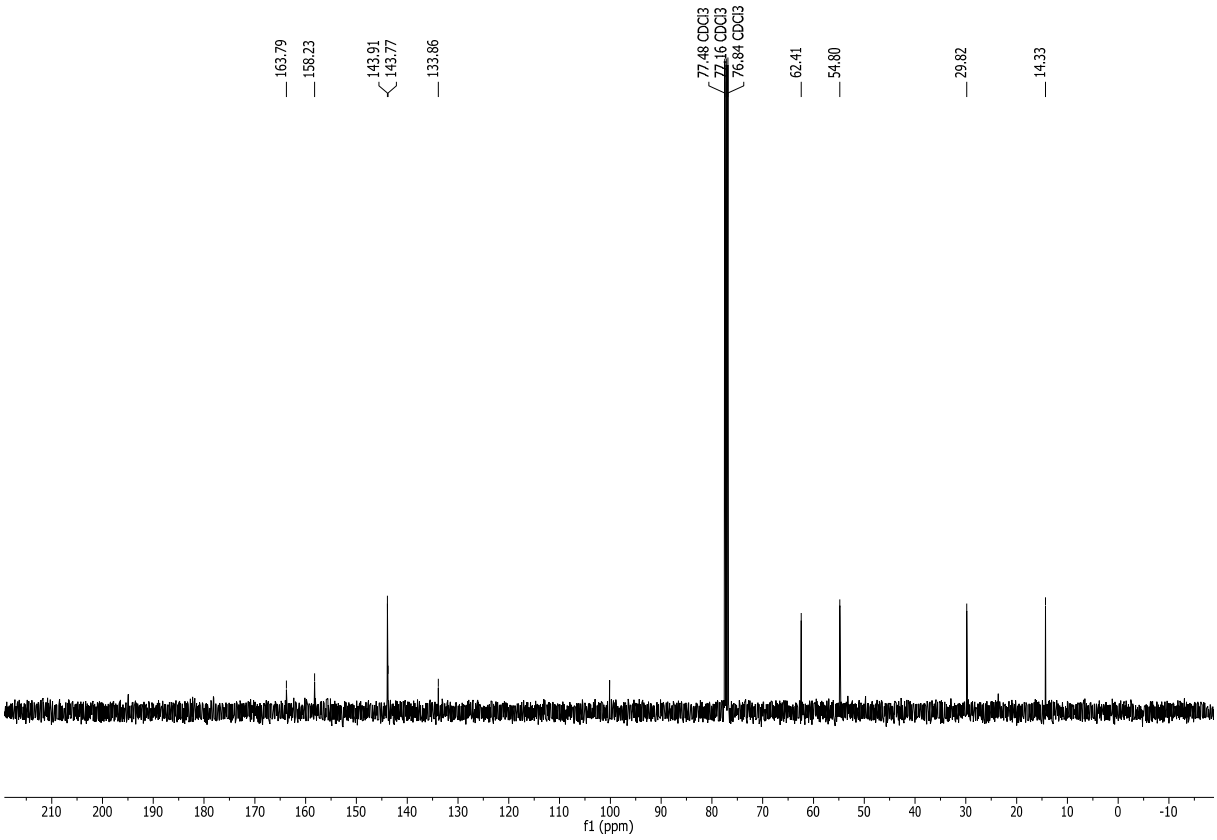

8.57
7.59
7.58
7.58
7.57
7.56
7.55
7.26 CDCl3
7.00
6.99
6.98
6.97
6.97
6.96
4.33
4.32
4.30
4.28
3.86
2.65
1.22
1.20
1.19
10d
400/101 MHz
0.93
1.91
1.91
2.02
2.96
2.86
3.00
f1 (ppm)

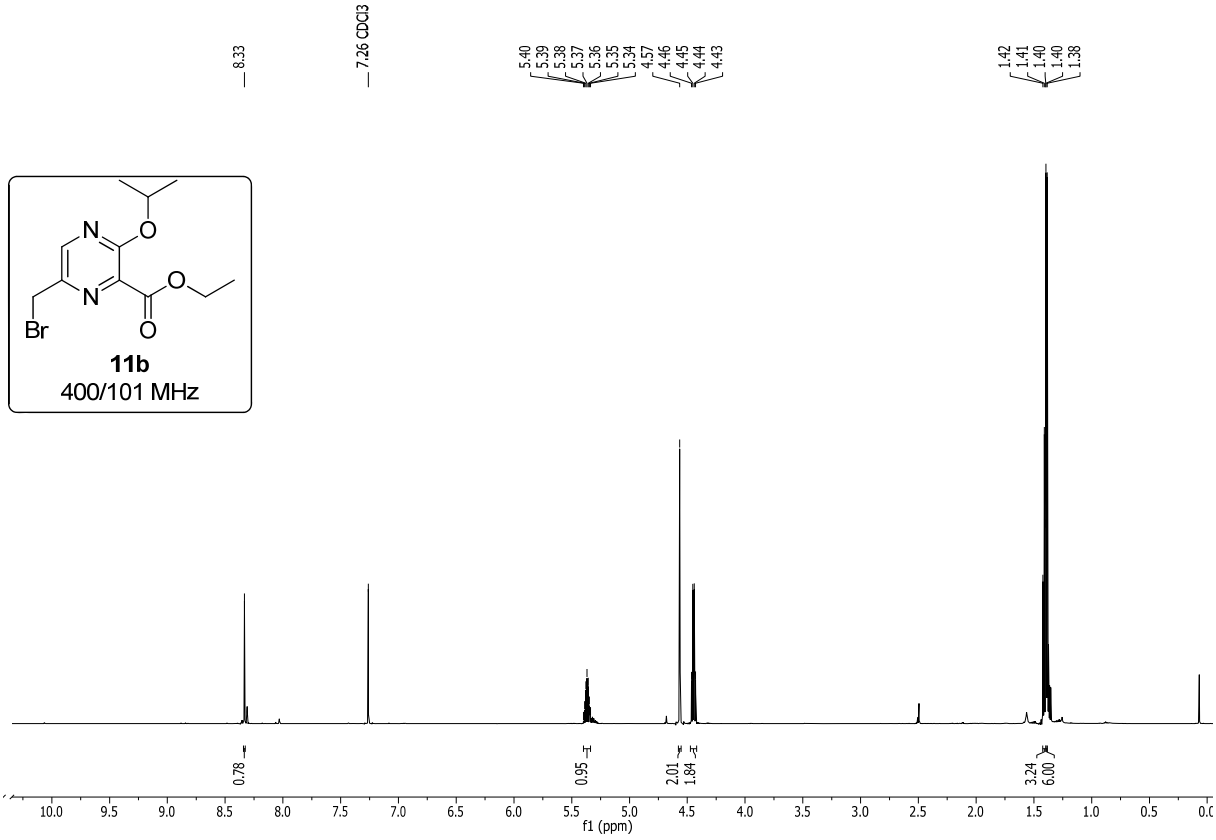

167.21
160.84
150.76
149.87
145.07
143.68
130.01
129.75
114.17
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.27
55.53
21.25
14.01
f1 (ppm)

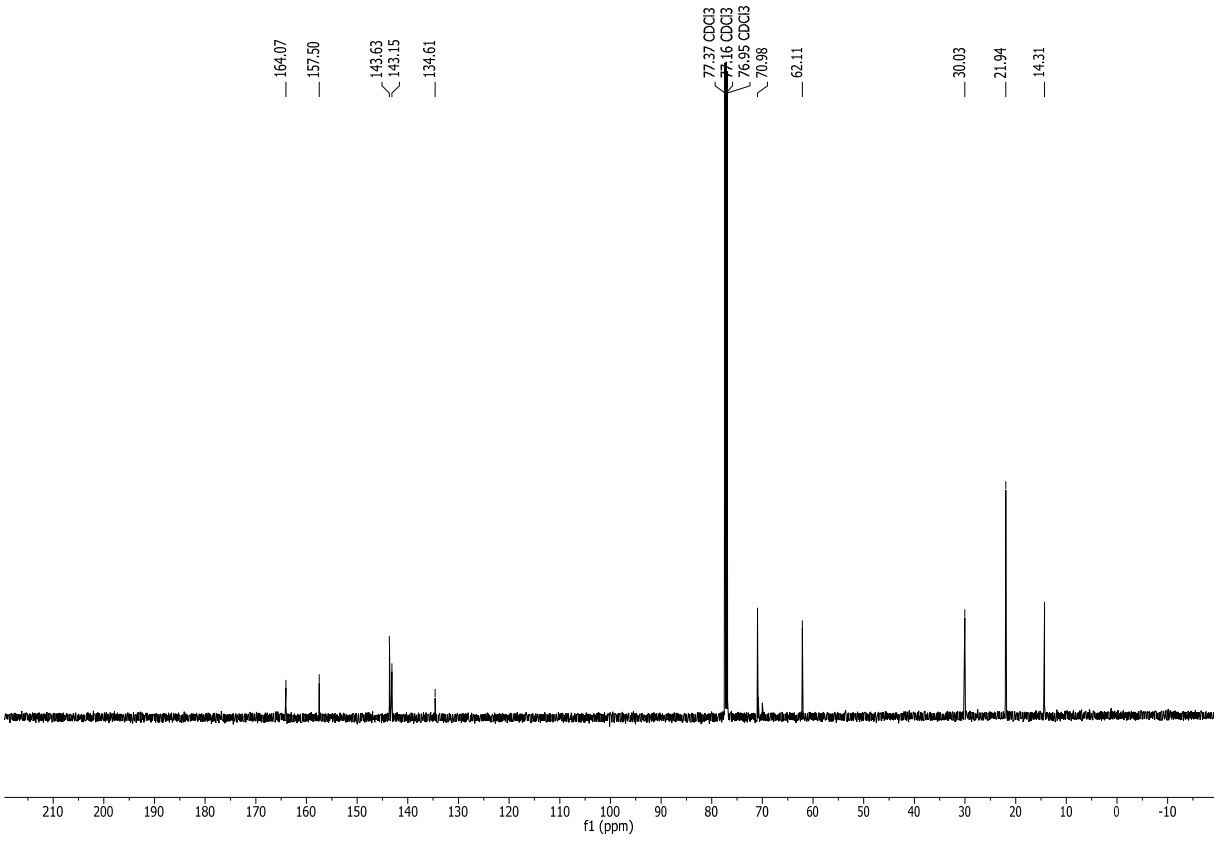

8.62
8.62
8.23
7.92
7.91
7.90
7.26 CDCl3
7.07
7.06
7.05
7.04
4.29
4.27
4.26
4.24
3.88
2.69
2.69
1.18
1.16
1.14
10e
400/101 MHz
0.95
0.95
0.97
0.98
2.00
2.98
2.95
3.10
f1 (ppm)

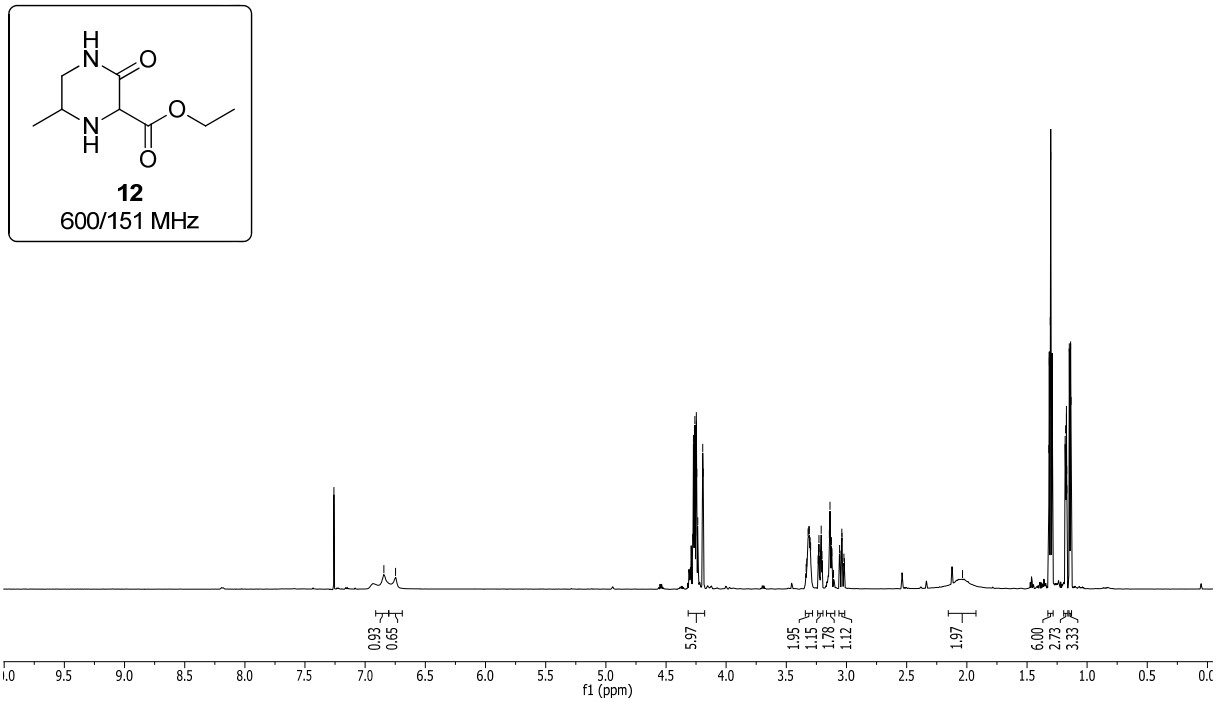

165.86
160.57
151.82
147.76
147.28
145.65
144.55
139.08
122.13
117.43
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.00
53.38
21.43
14.00
f1 (ppm)


8.39
7.26 CDCl3
4.58
4.49
4.47
4.46
4.44
4.06
1.54 HDO
1.44
1.42
1.40
11a
400/101 MHz
0.93
1.90
2.12
2.86
3.20
f1 (ppm)


163.79
158.23
143.91
143.77
133.86
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.41
54.80
29.82
14.33
f1 (ppm)


8.33
7.26 CDCl3
5.40
5.39
5.38
5.37
5.36
5.35
5.34
4.57
4.46
4.45
4.44
4.43
1.42
1.41
1.40
1.40
1.38
N
O
N
O
Br
O
11b
400/101 MHz
0.78
0.95
2.01
1.84
3.24
6.00
f1 (ppm)


164.07
157.50
143.63
143.15
134.61
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
70.98
62.11
30.03
21.94
14.31
f1 (ppm)



12
600/151 MHz