ppm Pd-Catalyzed, Cu-Free Sonogashira Couplings in Water Using Commercially Available Catalyst Precursors

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Electronic Supplementary Information (ESI)

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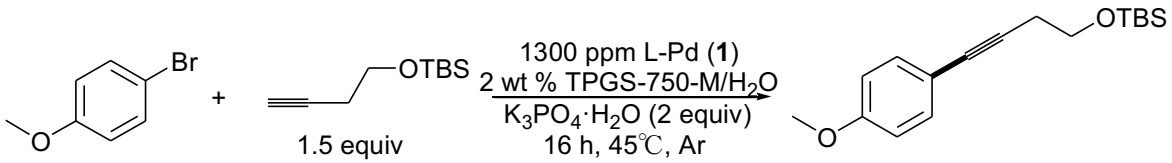
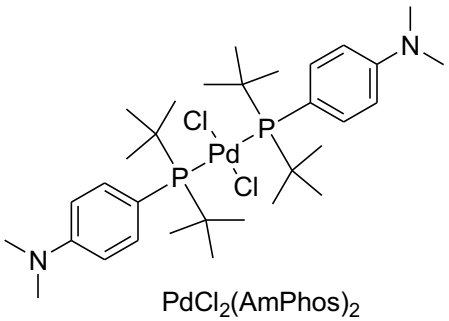
General Information

All reactions were performed under an atmosphere of argon. A solution of 2 wt % TPGS-750-M/H_2O was prepared by dissolving TPGS-750-M in degassed HPLC grade water and was stored under argon. TPGS-750-M was made as previously described[1] and is available from Sigma Aldrich® (catalog numbers 733857 and 763918). All commercially available reagents were used without further purification. Thin layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Merck, 0.25mm thick). Flash column chromatography was conducted in glass columns using Silica Gel 60 (EMD, 40-63 μm). Tetrahydrofuran (THF), taken from an Innovative Technologies Solvent Purification System (SPS), was further degassed by sparging with argon for 2 h while stirring. Diethyl ether, ethyl acetate, methylene chloride and hexanes were purchased from Fisher Scientific. N,N-dimethylformamide (DMF) and triethylamine were purchased from Merck. $K_3PO_4 \bullet H_2O$ was purchased from Acros Organics. MeMgBr was purchased from Sigma-Aldrich, in Et_2O (3 M). Palladium catalysts were purchased from Sigma Aldrich or generously donated by Johnson Matthey. BRIDP ligands were supplied by Takasago, Neolyst™ CX31 and Neolyst™ CX32 from Umicore AG & Co. KG. Reagents were purchased from Sigma-Aldrich, Combi-Blocks, Alfa Aesar, or Acros Organics. NMR solvents were purchased from Cambridge Isotope Laboratories. GC-MS data were recorded on an Agilent Technologies 7890A GC system coupled with Agilent Technologies 5975C mass spectrometer using HP-5MS column (30 m x 0.250 mm, 0.25 micron) purchased from Agilent Technologies. ^1H and ^{13}C NMR were recorded at 25 °C on a Varian Unity Inova 400 MHz or a Varian Unity Inova 500MHz spectrometers in $CDCl_3$ with residual $CHCl_3$ (^1H = 7.26 ppm, ^{13}C= 77.16 ppm) as internal standards. ^{19}F NMR was recorded at 25 °C on a Varian Unity Inova 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dddd = doublet of doublet of doublet of doublets, t = triplet, td = triplet of doublets, tt = triplet of triplets, q = quartet, p = pentet, m = multiplet), coupling constant (if applicable) and integration.

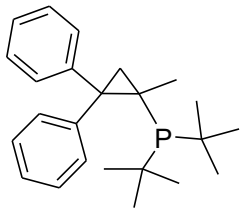
Reaction Optimization

a. Ligand Screening

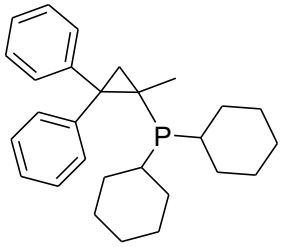




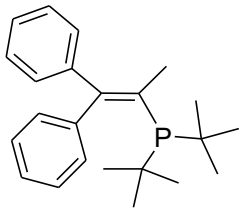
$PdCl_2(AmPhos)_2$



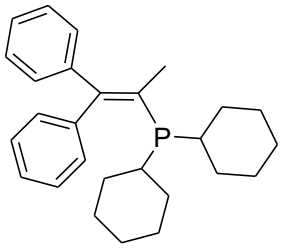
L1
(cBRIDP)



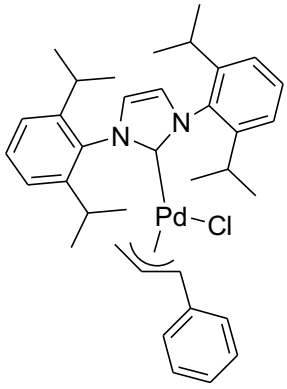
L2
(Cy-cBRIDP)



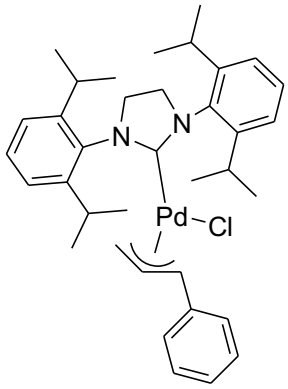
L3
(vBRIDP)



L4
(Cy-vBRIDP)



[(IPr)Pd(Cinnamyl)Cl]
(Umicore Neolyst CX31)

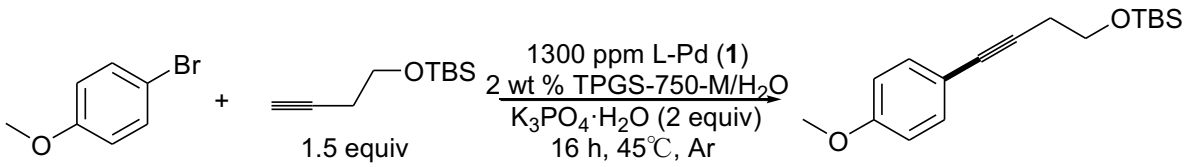


[(sIPr)Pd(Cinnamyl)Cl]
(Umicore Neolyst CX32)

Entry	palladium catalyst	GC yield (%)
1	$PdCl_2(AmPhos)_2$	30
2	$Pd(OAc)_2$/**L1**=1:2	85(76*)
3	$Pd(OAc)_2$/**L2**=1:2	trace
4	$Pd(OAc)_2$/**L3**=1:2	19
5	$Pd(OAc)_2$/**L4**=1:2	trace
6	[(IPr)Pd(Cinnamyl)Cl]	trace
7	[(sIPr)Pd(Cinnamyl)Cl]	trace

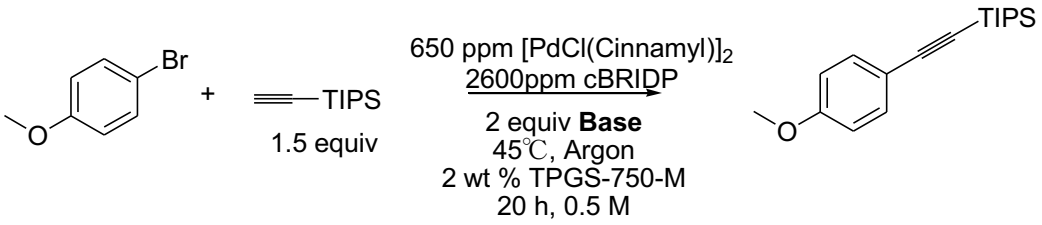
*Isolated yield

b. Screening of Palladium Source



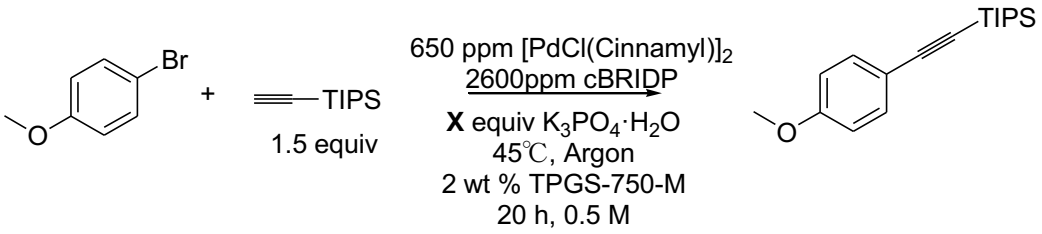
entry	palladium source	GC yield (%)
1	$PdCl_2(CH_3CN)_2$	23
2	$Pd(OAc)_2$	85
3	$[PdCl(allyl)]_2$	67
4	$[PdCl(crotyl)]_2$	83
5	$[PdCl(cinnamyl)]_2$	95

c. Screening of Base



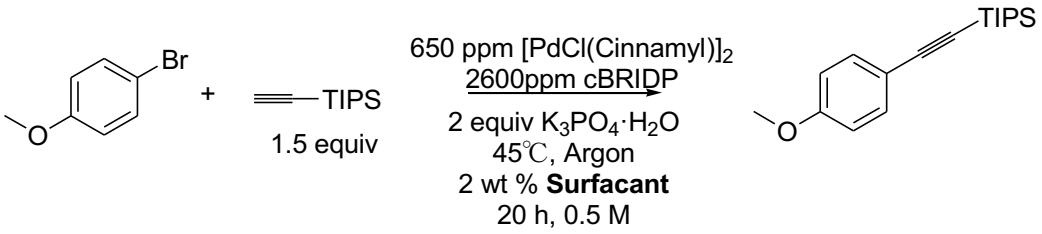
entry	base	GC yield (%)
1	$K_3PO_4•H_2O$	75
2	Et_3N	60
3	DABCO	40
4	NaOH	39
5	K_2CO_3	28

d. Screening of Equivalents of Base needed



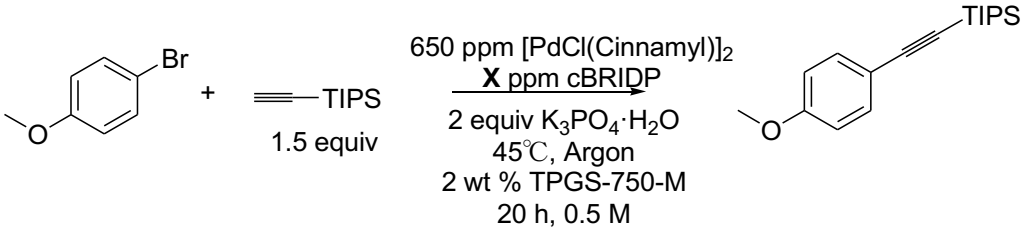
entry	base (equiv)	GC yield (%)
1	$K_3PO_4•H_2O$ (1.5)	73
2	$K_3PO_4•H_2O$ (2.0)	75
3	$K_3PO_4•H_2O$ (2.5)	50

e. Surfactant Screening



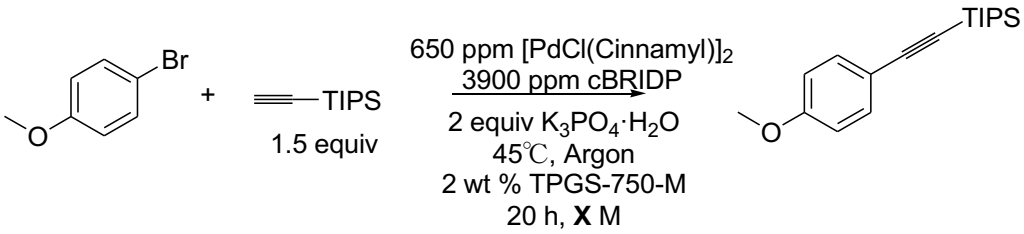
entry	surfactant (2 wt %)	GC yield (%)
1	TPGS-750-M	75
2	PTS	72
3	cremophor EL	33
4	Triton X-100	6
5	Brij 30	38
6	Pluronic	66

f. Screening of Ligand Equivalents



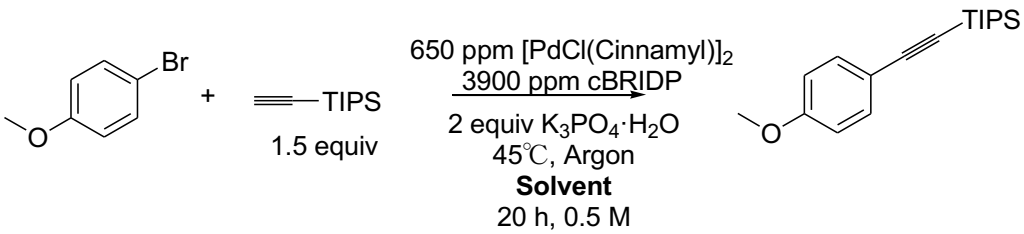
eentry	ligand equivalence to Pd	GC yield (%)
1	1.0	24
2	1.5	36
3	2.0	75
4	3.0	93
5	4.0	65

g. Screening of Global Concentration



entry	global concentration (M)	GC yield (%)
1	0.4	83
2	0.5	93
3	0.75	75
4	1.0	49

h. Co-solvent Screening



entry	solvent	GC yield (%)
1	2 wt % TPGS-750-M	75
2	2 wt % TPGS-750-M/THF (9:1)	17
3	H_2O/THF (1:9)	trace

General Procedure

Preparation of a stock solution of catalyst.

In a 4 mL reaction vial containing a PTFE coated magnetic stir bar, cBRIDP (10.6 mg, 0.030 mmol) and [(cinnamyl)PdCl]$_2$ (2.6 mg, 0.005 mmol) were added in a glove box. The reaction vial was sealed with a rubber septum and degassed, after which anhydrous THF (2 mL) was added via syringe. The mixture was stirred for 5 min at rt. A yellow stock solution was obtained for subsequent Sonogashira reactions (**Always use fresh stock solution because it is unstable at rt as indicated by the color change from yellow to orange to black within one week**).

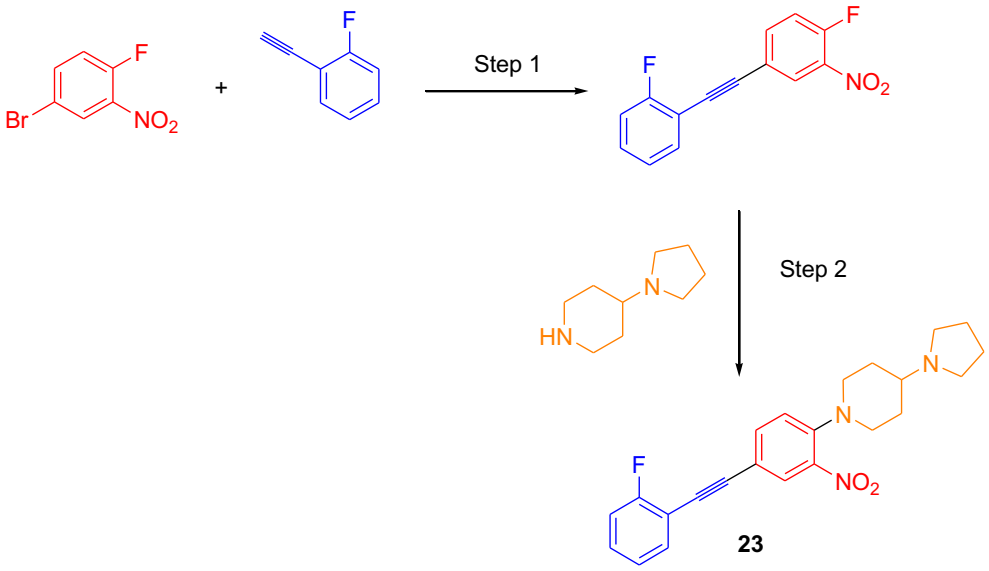
Procedure for Sonogashira reactions.

To a 4 mL reaction vial containing a PTFE coated magnetic stir bar, 100 µL of stock solution (1000 ppm palladium) or 150 µL of stock solution (1500 ppm palladium) was added and the THF was removed *in vacuo,* after which the reaction vial was backfilled with dry argon. All solid starting materials (bromide, terminal alkyne) and (or) base were added under an argon flow. The reaction vial was then evacuated and backfilled with dry argon three times. A solution of 2 wt % TPGS-750-M (1.0 mL) and liquid starting material (bromide, terminal alkyne) and/or base were added via syringe. The reaction mixture was then stirred vigorously at 45 ℃ (or at a different temperature as indicated) for a given time. After complete consumption of bromide, as monitored by TLC and/or GCMS, the reaction mixture was extracted with EtOAc (1.0 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography over silica gel to afford pure product.

Gram Scale Reaction

In an oven-dried 50 mL round bottom flask charged with a PTFE coated magnetic stir bar, 5-bromo-2-(1-piperidinyl)pyrimidine (1210.5 mg, 5.0 mmol), [(cinnamyl)PdCl]$_2$ (1.3 mg, 0.0025 mmol, 500 ppm) and cBRIDP (5.3 mg, 0.015 mmol, 3000 ppm) were added. The flask was evacuated and refilled with argon three times. 4-Ethynylanisole (780 µL, 6.0 mmol, 1.2 equiv), Et_3N (1.4 mL, 10.0 mmol, 2.0 equiv) and 2 wt % TPGS/H_2O (10 mL) were added via syringe. The reaction mixture was heated at 45 °C for 8 h with vigorous stirring then allowed to cool to rt. The mixture was extracted with EtOAc (10 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent was removed *in vacuo*. Crude product was purified with flash column chromatography to give 1272.1 mg (87%) of 5-(2-(4-methoxyphenyl)ethynyl)-2-(piperidin-1-yl)pyrimidine (**13**) as a pale yellow solid (hexane/ether: 90/10).

2-Step, 1-pot reaction



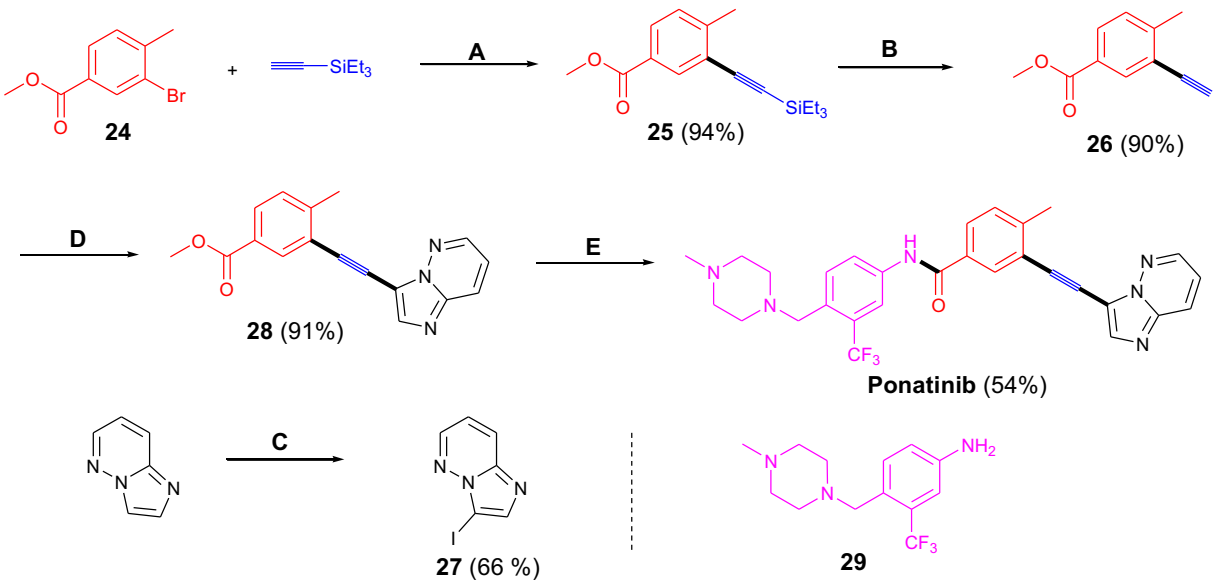
Step 1:

In a 4 mL reaction vial, 4-bromo-1-fluoro-2-nitrobenzene (62 µL, 0.5 mmol), 1-ethynyl-2-fluorobenzene (62 µL, 0.55 mmol, 1.1 equiv), 100 µL stock solution (1000 ppm Pd) and $K_3PO_4 \cdot H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 ℃ for 20 h following the general procedure above.

Step 2:

4-(1-Pyrrolidinyl)piperidine (77 mg, 0.5 mmol, 1.0 equiv) and THF (0.2 mL) were added and the reaction mixture was heated at 45 ℃ for another 5 h. EtOAc (1 mL x 5) was used to extract the aqueous layer and the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and crude product was purified by flash column chromatography to afford 186.7 mg (95%) of 1-(4-(2-(2-fluorophenyl)ethynyl)-2-nitrophenyl)-4-pyrrolidin-1-yl)piperidine (**23**) as an orange solid (hexane/EtOAc : 50/50).

Synthesis of ponatinib



Step **A**:

Following the standard procedure, methyl 3-bromo-4-methylbenzoate (78 µL, 0.5 mmol), (triethylsilyl)acetylene (179 µL, 1.0 mmol, 2.0 equiv) , 150 µL stock solution (1500 ppm Pd) and Et_3N (140 µL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 ℃ for 45 h yielding 135.7 mg (94%) of methyl 4-methyl-3-(2-(triethylsilyl)ethynyl)benzoate (**25**) as a yellow oil (hexane/ether : 97/3).

Step **B**:

In a 50 mL oven-dried round bottom flask containing a PTFE coated magnetic stir bar, methyl 4-methyl-3-(2-(triethylsilyl)ethynyl)benzoate (1.344 g, 4.67 mmol), K_2CO_3 (129 mg, 0.934 mmol, 0.2 equiv) and 1:1 MeOH/THF (5 mL + 5 mL) were added and reaction mixture was heated at 45 ℃ for 5 h. Upon completion of the reaction as monitored by TLC, the mixture was allowed to cool to rt. Ether (10 mL) and satd. aqueous NH_4Cl solution (10 mL) were added. The organic layer was extracted, washed with satd. aqueous NH_4Cl solution (5 mL x 2) and dried over anhydrous Na_2SO_4. Solvent was removed *in vacuo* and the crude product was purified over flash column chromatography to yield 731.2 mg (90%) of methyl 3-ethynyl-4-methylbenzoate (**26**) as a white solid (hexane/ether: 95/5).

Step **C**:

A 50 mL oven-dried round bottom flask containing a PTFE magnetic stir bar was evacuated and refilled with argon for three times. Imidazo[1,2-b]pyridazine (952.8 mg, 8.0 mmol) and N-Iodosuccinimide (2.16 g, 9.6 mmol, 1.2 equiv) were added under an argon flow and DMF (15 mL) was added via syringe. The reaction mixture was heated at 80 ℃ overnight. The flask was cooled to rt and the reaction mixture was poured into a 125 mL separatory funnel. Water (30 mL) and DCM (30 mL) were added. The organic layer was extracted and washed with water (20 mL x 5) and dried over anydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified over flash column chromatography to yield 1.29 g (66%) of 3-Iodoimidazo[1,2-b]pyridazine (**27**) as a brown solid (hexane/EtOAc: 50/50).

Step **D**:

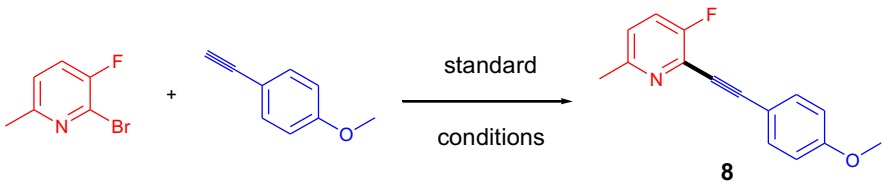
Following the standard procedure, **27** (245 mg, 1.0 mmol) and **26** (209 mg, 1.2 mmol, 1.2 equiv), 300 µL stock solution (1500 ppm Pd) and Et_3N (280 µL, 2.0 mmol, 2.0 equiv) in 2.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 47 h yielding 264.8 mg (91%) of methyl 3-(2-(imidazo[1,2- b]pyridazin-3-yl)ethynyl)-4-methylbenzoate (**28**) as a yellow solid

(hexane/DCM : 65/35).

Step **E**:

A 25 mL oven-dried round bottom flask containing a PTFE magnetic stir bar was evacuated and refilled with argon for three times. Methyl 3-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)-4-methylbenzoate (**28**) (145.7 mg, 0.5 mmol, 1.0 equiv) and 4-(4-Methylpiperazinomethyl)-3-(trifluoromethyl)aniline (**29**) (136.7 mg, 0.5 mmol, 1.0 equiv) were charged under argon flow. Anhydrous THF (3.0 mL) was added via syringe and the reaction mixture was stirred at rt for 5 minutes until a yellow homogeneous solution was obtained. KOtBu (112.2 mg, 1.0 mmol, 2.0 equiv) was then charged under argon flow and the reaction mixture was stirred at rt for 12h. Upon complete consumption of methyl ester monitored by TLC the solvent was removed in vacuo. H_2O (5 mL) was added and the aqueous layer was extracted with DCM (5 mL X 3). Organic layers were combined and solvent was removed in vacuo. Crude product was purified by flash column chromatography to afford 143.9 mg (54%) of ponatinib as a yellow solid. (EtOAc:DCM:MeOH=8:2:1)

E Factor determination and recycling study



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Initial Reaction:

Following the standard procedure, 2-bromo-3-fluoro-6-methylpyridine (95 mg, 0.5 mmol), 4-ethynylanisole (68 µL, 0.525 mmol, 1.05 equiv), 100 µL stock solution (1000 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 ℃ for 4 h then allowed to cool to rt. The reaction mixture was then transferred to a short pipette loaded with cotton. Liquid was collected and saved for recycle and the solid in the pipette was washed with 1 mL DI water and air-dry to dryness to give 114.3 mg of the crude 3-fluoro-2-(2-(4-methoxyphenyl)ethynyl)-6-methylpyridine (**8**) as a yellow solid.

E Factor calculation:

Density of THF = 0.889 g/mL

$$\text{E factor} = \frac{Waste\ (mg)}{Product\ (mg)}$$

$$\frac{(0.10\ mL\ THF)(0.889\frac{g}{mL})}{0.1143\ g} = 0.78$$

1st Recycle:

A solution of TPGS-750-M was obtained from the initial reaction and was briefly degassed and then used as the reaction medium (about 0.8-0.9 mL). To this was added fresh 2 wt % TPGS/H_2O solution to maintain the original volume. Following the standard procedure, to a new 4 mL reaction vial containing a PTFE magnetic stir bar 2-bromo-3-fluoro-6-methylpyridine (95 mg, 0.5 mmol), 4-ethynylanisole (68 µL, 0.525 mmol, 1.05 equiv), 100 µL stock solution (1000 ppm Pd), K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) and 1 mL recycled TPGS/H_2O solution were heated at 45 ℃ for 4 h then allowed to cool to rt. The reaction mixture was then transferred to a short pipette loaded with

cotton. Liquid was collected and saved for the next recycle while the solid in the pipette was washed with 1 mL DI water and air-dried to dryness to give the crude product.

2nd and 3rd Recycle: Repeat 1st recycle.

1st recycle: 89% yield

2nd recycle: 92% yield

3rd recycle: 92% yield

Residual Palladium

Robertson Microlit Laboratories

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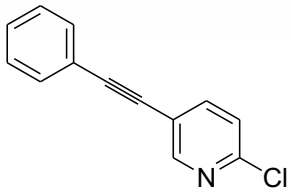

CIB001

Sample #: REILJO3-002-EXP002 **Test #:** 1 **Received:** 04/11/2018 **Completed:** 04/12/2018

ICP-MS: Palladium = 1 ppm

Services
ICP-MS

Palladium = 1000 ppm

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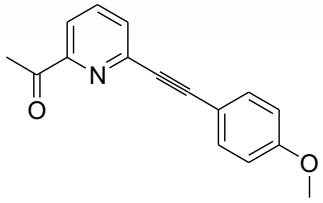


CIB001

Sample #: REILJO3-002-EXP004 **Test #:** 1 **Received:** 04/11/2018 **Completed:** 04/12/2018

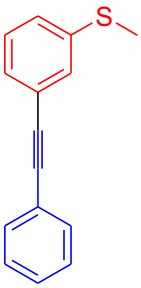
ICP-MS: Palladium = < 1 ppm

Services
ICP-MS

Palladium = 1000 ppm

Analytical data

Methyl (3-(2-phenylethynyl)phenyl)sulfane (2)



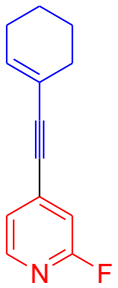
3-Bromothioanisole (67µL, 0.5 mmol), phenylacetylene (66 µL, 0.6 mmol, 1.2 equiv), 100 µL stock solution (1000 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 5 h yielding 107.7 mg (96%) of methyl (3-(2-phenylethynyl)phenyl)sulfane as a brown oil (hexane/ether: 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 2H), 7.42 (t, *J* = 1.7 Hz, 1H), 7.36 (dd, *J* = 5.1, 2.1 Hz, 3H), 7.32 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.23 (dt, *J* = 7.9, 1.7 Hz, 1H), 2.51 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.02, 131.77, 129.15, 128.78, 128.52, 128.50, 128.32, 126.61, 124.08, 123.19, 89.88, 89.07, 15.79.

HRMS: (EI, [$C_{15}H_{12}S$]) calcd, 224.0660; found *m/z*: 224.0661.

4-(2-Cyclohexenylethynyl)-2-fluoropyridine (3)



4-Bromo-2-fluoropyridine (51 µL, 0.5 mmol), 1-ethynylcyclohexene (71 µL, 0.6 mmol, 1.2 equiv), 100 µL stock solution (1000 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 16 h yielding 87.4 mg (87%) of 4-(2-cyclohexenylethynyl)-2-fluoropyridine as a yellow oil (hexane/ether: 90/10).

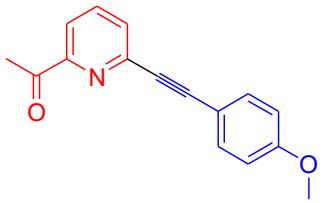
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 5.2 Hz, 1H), 7.13 (dt, *J* = 5.2, 1.6 Hz, 1H), 6.89 (d, *J* = 1.7 Hz, 1H), 6.31 (tt, *J* = 3.8, 1.7 Hz, 1H), 2.22 – 2.18 (m, 2H), 2.18 – 2.13 (m, 2H), 1.73 – 1.64 (m, 2H), 1.64 – 1.59 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.83, 162.94, 147.66, 147.53, 138.46, 137.16, 137.09, 123.43, 123.40, 120.03, 111.51, 111.20, 97.51, 83.55, 83.51, 28.88, 26.00, 22.25, 21.42.

^{19}F NMR (376 MHz, $CDCl_3$) δ -68.15.

HRMS: (EI, [$C_{13}H_{12}FN$]) calcd, 201.0954; found *m/z*: 201.0949.

1-(6-(2-(4-Methoxyphenyl)ethynyl)pyridin-2-yl)ethanone (4)



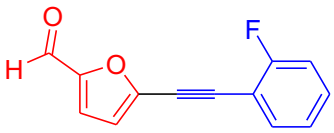
2-Acetyl-6-bromopyridine (100 mg, 0.5 mmol), 4-ethynylanisole (78 µL, 0.6 mmol, 1.2 equiv), 100 µL stock solution (1000 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 3 h yielding 110.4 mg (88%) of 1-(6-(2-(4-methoxyphenyl)ethynyl)pyridin-2-yl)ethanone as a white solid (hexane/ether : 80/20).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.80 (t, *J* = 7.8 Hz, 1H), 7.65 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.59 – 7.54 (m, 2H), 6.94 – 6.87 (m, 2H), 3.84 (s, 3H), 2.76 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.02, 160.51, 153.94, 143.36, 137.08, 133.84, 130.46, 120.40, 114.25, 114.08, 90.28, 87.37, 55.47, 25.98.

HRMS: (ESI, [$C_{16}H_{13}NO_2$ + Na]) calcd, 274.0844; found *m/z*: 274.0853.

5-(2-(2-Fluorophenyl)ethynyl)furan-2-carbaldehyde (5)



5-Bromo-2-furaldehyde (87.5 mg, 0.5 mmol), 1-ethynyl-2-fluorobenzene (68 µL, 0.6 mmol, 1.2 equiv), 100 µL stock solution (1000 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 18 h yielding 87.6 mg (82%) of 5-(2-(2-fluorophenyl)ethynyl)furan-2-carbaldehyde as a yellow solid (hexane/ether: 90/10).

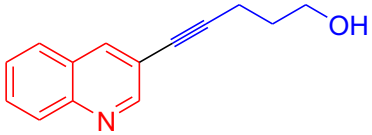
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.52 (td, *J* = 7.3, 1.8 Hz, 1H), 7.39 (dddd, *J* = 8.4, 7.3, 5.3, 1.8 Hz, 1H), 7.25 (d, *J* = 3.7 Hz, 1H), 7.18 – 7.08 (m, 2H), 6.82 (d, *J* = 3.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.41, 163.87, 161.85, 152.76, 141.61, 133.61, 133.60, 131.69, 131.62, 124.38, 124.35, 121.28, 117.67, 115.98, 115.82, 110.18, 110.06, 89.96, 83.24, 83.21.

^{19}F NMR (376 MHz, $CDCl_3$) δ -108.47, -108.49, -108.50, -108.51, -108.51, -108.53.

HRMS: (ESI, [$C_{13}H_7FO_2$ + Na]) calcd, 237.0328; found *m/z*: 237.0337.

5-(Quinolin-3-yl)pent-4-yn-1-ol (6) CAS: 178762-64-6



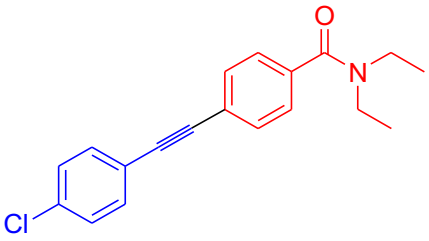
3-Bromoquinoline (68 µL, 0.5 mmol), 4-pentyn-1-ol (56 µL, 0.6 mmol, 1.2 equiv), 100 µL stock solution (1000 ppm Pd) and Et_3N (140 µL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 12 h yielding 78.3 mg (74%) of 5-(quinolin-3-yl)pent-4-yn-1-ol as a yellow oil (hexane/EtOAc: 60/40).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.1 Hz, 1H), 8.13 (d, *J* = 2.1 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.72 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 3.85 (t, *J* = 6.2 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.57(br s, 1H), 1.91 (p, *J* = 6.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.48, 146.60, 138.25, 129.90, 129.31, 127.55, 127.44, 127.29, 118.10, 93.32, 78.42, 61.54, 31.47, 16.21.

Jean, A.; Blanchet, J.; Rouden, J.; Maddaluno, J.; De Paolis, M. *Chem. Commun.* **2013**, *49*, 1651.

4-(2-(4-Chlorophenyl)ethynyl)-*N,N*-diethylbenzamide (7)



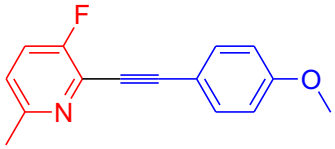
4-Bromo-*N,N*-diethylbenzamide (128 mg, 0.5 mmol), 1-chloro-4-ethynylbenzene (102.5 mg, 0.75 mmol, 1.5 equiv), 100 µL stock solution (1000 ppm Pd) and Et_3N (140 µL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 22 h yielding 153.5 mg (98%) of 4-(2-(4-chlorophenyl)ethynyl)-*N,N*-diethylbenzamide as a white solid (hexane/EtOAc : 70/30).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.34 (dd, *J* = 17.1, 8.4 Hz, 4H), 3.54 (s, 2H), 3.25 (s, 2H), 1.24 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.67, 137.23, 134.66, 132.97, 131.73, 128.87, 126.60, 123.96, 121.58, 89.76, 89.49, 43.41, 39.46, 14.35, 13.01.

HRMS: (ESI, [$C_{19}H_{18}ClNO$ + Na]) calcd, 334.0975; found *m/z*: 334.0970.

3-Fluoro-2-(2-(4-methoxyphenyl)ethynyl)-6-methylpyridine (8)



2-Bromo-3-fluoro-6-methylpyridine (95 mg, 0.5 mmol), 4-ethynylanisole (78 µL, 0.6 mmol, 1.2 equiv), 100 µL stock solution (1000 ppm Pd) and Et_3N (140 µL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 3 h yielding 117.1 mg (97%) of 3-fluoro-2-(2-(4-methoxyphenyl)ethynyl)-6-methylpyridine as a yellow solid (hexane/ether : 75/25).

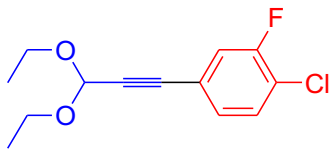
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.54 (m, 2H), 7.30 (t, *J* = 8.5 Hz, 1H), 7.07 (dd, *J* = 8.5, 3.8 Hz, 1H), 6.90 – 6.86 (m, 2H), 3.82 (s, 3H), 2.55 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.47, 159.63, 157.58, 154.67, 154.63, 133.84, 131.76, 131.64, 123.57, 123.54, 123.38, 123.23, 114.24, 114.16, 95.38, 95.34, 81.99, 81.95, 55.43, 23.94, 23.93.

^{19}F NMR (376 MHz, $CDCl_3$) δ -123.59, -123.60, -123.61, -123.62.

HRMS: (ESI, [$C_{15}H_{12}FNO$ + H]) calcd, 242.0981; found *m/z*: 242.0984.

1-Chloro-4-(3,3-diethoxyprop-1-ynyl)-2-fluorobenzene (9)

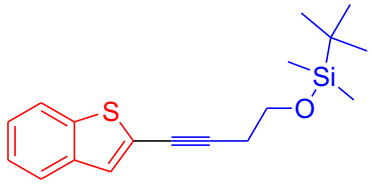


4-Bromo-1-chloro-2-fluorobenzene (61 µL, 0.5 mmol), 3,3-diethoxy-1-propyne (108 µL, 0.75 mmol, 1.5 equiv), 100 µL stock solution (1000 ppm Pd) and Et_3N (140 µL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 43 h yielding 89.6 mg (70%) of 1-chloro-4-(3,3-diethoxyprop-1-ynyl)-2-fluorobenzene as a colorless liquid (hexane/ether : 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 1H), 7.24 (dd, *J* = 9.4, 1.8 Hz, 1H), 7.19 (ddd, *J* = 8.3, 1.8, 0.9 Hz, 1H), 5.46 (s, 1H), 3.79 (dq, *J* = 9.4, 7.1 Hz, 2H), 3.65 (dq, *J* = 9.4, 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 6H).

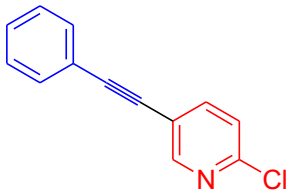
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.73, 156.74, 130.74, 128.61, 128.58, 122.34, 122.26, 122.20, 120.09, 119.91, 91.76, 91.74, 86.31, 83.08, 83.06, 61.23, 15.21.
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.71, -114.73, -114.75.
HRMS: (CI, [$C_{13}H_{14}ClFO_2$ + H]) calcd, 257.0745; found *m/z*: 257.0739.

(4-(Benzo[b]thiophen-2-yl)but-3-ynyloxy)(*t*-butyl)dimethylsilane (10)



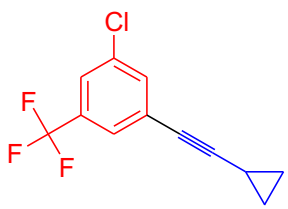
2-Bromobenzothiophene (106.5 mg, 0.5 mmol), 4-(*t*-butyldimethylsilyloxy)-1-butyne (155 µL, 0.75 mmol, 1.5 equiv), 100 µL stock solution (1000 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 43 h yielding 152.3 mg (96%) of (4-(benzo[b]thiophen-2-yl)but-3-ynyloxy)(*t*-butyl)dimethylsilane as a yellow oil (hexane/ether : 97/3).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.69 (m, 2H), 7.39 – 7.31 (m, 3H), 3.86 (t, *J* = 6.9 Hz, 2H), 2.70 (t, *J* = 6.9 Hz, 2H), 0.95 (s, 9H), 0.13 (s, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 139.97, 139.26, 128.02, 125.22, 124.69, 124.07, 123.69, 122.07, 93.80, 75.31, 61.75, 26.06, 24.35, 18.51, -5.07.
HRMS: (EI, [$C_{18}H_{24}OSSi$]) calcd, 316.1317; found *m/z*: 316.1319.

2-Chloro-5-(2-phenylethynyl)pyridine (11)



5-Bromo-2-chloropyridine (96.2 mg, 0.5 mmol), phenylacetylene (66 µL, 0.6 mmol, 1.2 equiv), 100 µL stock solution (1000 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 5 h yielding 93.3 mg (88%) of 2-chloro-5-(2-phenylethynyl)pyridine as a white solid (hexane/ether : 97/3).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, J = 2.4 Hz, 1H), 7.75 (dd, J = 8.2, 2.4 Hz, 1H), 7.54 (dd, J = 6.7, 3.0 Hz, 2H), 7.38 (dd, J = 5.0, 1.9 Hz, 3H), 7.32 (d, J = 8.2 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 152.19, 150.57, 141.02, 131.84, 129.18, 128.64, 124.04, 122.33, 119.53, 93.88, 84.83.
HRMS: (EI, [$C_{13}H_8ClN$]) calcd, 213.0345; found *m/z*: 213.0347.

1-Chloro-3-(2-cyclopropylethynyl)-5-(trifluoromethyl)benzene (12)



3-Bromo-5-chlorobenzotrifluoride (76 µL, 0.5 mmol), cyclopropylacetylene (46 µL, 0.55 mmol, 1.1 equiv), 100

µL stock solution (1000 ppm Pd) and Et_3N (140 µL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 35 °C for 13 h yielding 104.9 mg (86%) of 1-chloro-3-(2-cyclopropylethynyl)-5-(trifluoromethyl)benzene as a colorless oil (hexane).

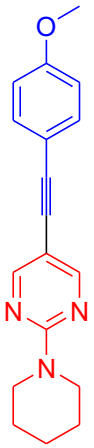
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.48 (m, 2H), 7.47 (d, *J* = 1.9 Hz, 1H), 1.45 (tt, *J* = 8.3, 5.0 Hz, 1H), 0.95 – 0.89 (m, 2H), 0.85 – 0.80 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.84, 134.68 (q, *J* = 1.2 Hz), 132.32 (q, *J* = 33.1 Hz), 126.86, 126.77 (q, *J* = 3.8 Hz), 124.51 (q, *J* = 3.8 Hz), 123.17 (q, *J* = 272.9 Hz), 97.15, 73.51, 8.94, 0.23.

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.18.

HRMS: (EI, [$C_{12}H_8ClF_3$]) calcd, 244.0267; found *m/z*: 244.0259.

5-(2-(4-Methoxyphenyl)ethynyl)-2-(piperidin-1-yl)pyrimidine (13)



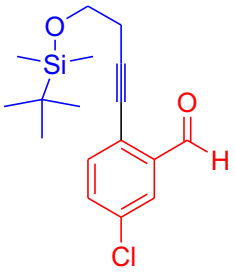
5-Bromo-2-(1-piperidinyl)pyrimidine (121 mg, 0.5 mmol), 4-ethynylanisole (78 µL, 0.6 mmol, 1.2 equiv), 100 µL stock solution (1000 ppm Pd) and Et_3N (140 µL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 8 h yielding 140.1 mg (95%) of 5-(2-(4-methoxyphenyl)ethynyl)-2-(piperidin-1-yl)-pyrimidine as a pale yellow solid (hexane/ether: 85/15).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 2H), 7.45 – 7.41 (m, 2H), 6.88 – 6.84 (m, 2H), 3.81 (d, *J* = 2.3 Hz, 7H), 1.72 – 1.65 (m, 2H), 1.64 – 1.57 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.88, 159.65, 159.61, 132.92, 115.48, 114.13, 106.32, 91.87, 83.34, 55.42, 45.04, 25.88, 24.92.

HRMS: (ESI, [$C_{18}H_{19}N_3O$ + H]) calcd, 294.1606; found *m/z*: 294.1603.

2-(4-(*t*-Butyldimethylsilyloxy)but-1-ynyl)-5-chlorobenzaldehyde (14)



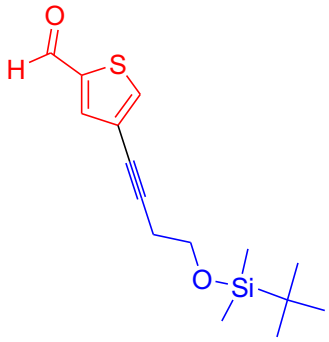
2-Bromo-5-chlorobenzaldehyde (110 mg, 0.5 mmol), 4-(*t*-butyldimethylsilyloxy)-1-butyne (155 µL, 0.75 mmol, 1.5 equiv), 150 µL stock solution (1500 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 50 h yielding 134.2 mg (83%) of 2-(4-(*t*-butyldimethyl-silyloxy)but-1-ynyl)- 5-chlorobenzaldehyde as a yellow oil (hexane/ether : 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.85 (d, *J* = 2.2 Hz, 1H), 7.48 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 3.84 (t, *J* = 6.7 Hz, 2H), 2.69 (t, *J* = 6.8 Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.90, 137.26, 134.69, 134.64, 133.82, 127.06, 125.97, 96.34, 76.49, 61.59, 25.99, 24.20, 18.46, -5.15.

HRMS: (ESI, [$C_{17}H_{23}ClO_2Si$ + Na]) calcd, 345.1053; found *m/z*: 345.1057.

4-(4-(*t*-Butyldimethylsilyloxy)but-1-ynyl)thiophene-2-carbaldehyde (15)



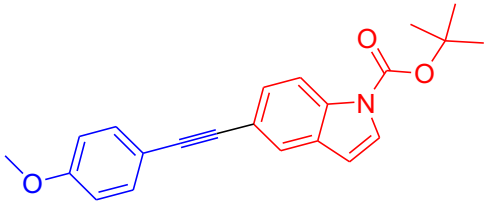
4-Bromo-2-thiophenecarboxaldehyde (95.5 mg, 0.5 mmol), 4-(*t*-butyldimethylsilyloxy)-1-butyne (155 µL, 0.75 mmol, 1.5 equiv), 150 µL stock solution (1500 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 44 h yielding 119.3 mg (81%) of 4-(4-(*t*-butyldimethyl-silyloxy)but-1-ynyl)thiophene- 2-carbaldehyde as a pale yellow oil (hexane/ether : 95/5).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (d, *J* = 1.2 Hz, 1H), 7.70 (d, *J* = 1.7 Hz, 2H), 3.81 (t, *J* = 6.9 Hz, 2H), 2.60 (t, *J* = 6.9 Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 182.68, 143.40, 138.66, 136.69, 124.54, 88.52, 75.29, 61.78, 26.02, 23.86, 18.50, -5.10.

HRMS: (CI, [$C_{15}H_{22}O_2SSi$ + H]) calcd, 295.1188; found *m/z*: 295.1177.

***t*-Butyl 5-(2-(4-methoxyphenyl)ethynyl)-1H-indole-1-carboxylate (16)**



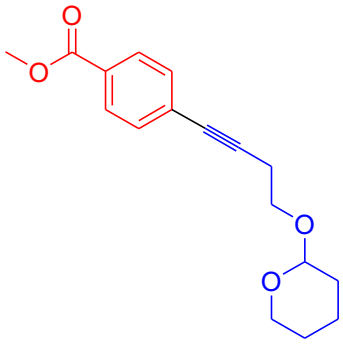
N-Boc-5-bromoindole (148 mg, 0.5 mmol), 4-Ethynylanisole (98 µL, 0.75 mmol, 1.5 equiv), 150 µL stock solution (1500 ppm Pd) and Et_3N (140 µL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 48 h yielding 151.0 mg (93%) of *t*-butyl 5-(2-(4-methoxyphenyl)ethynyl)-1H-indole-1-carboxylate as a white solid (hexane/ether : 95/5).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 3.7 Hz, 1H), 7.51 – 7.46 (m, 3H), 6.91 – 6.87 (m, 2H), 6.56 (d, *J* = 3.7 Hz, 1H), 3.83 (s, 3H), 1.68 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.58, 149.65, 134.75, 133.09, 130.66, 127.80, 126.84, 124.34, 117.87, 115.85, 115.26, 114.12, 107.24, 88.84, 88.12, 84.11, 55.42, 28.31.

HRMS: (EI, [$C_{22}H_{21}NO_3$ –Boc + H]) calcd, 247.0997; found *m/z*: 247.1001.

Methyl 4-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-ynyl)benzoate (17)



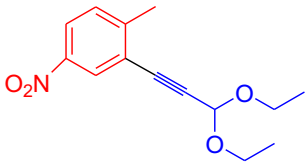
Methyl 4-bromobenzoate (107.5 mg, 0.5 mmol), 2-(3-Butynyloxy)tetrahydro-2H-pyran (118 µL, 0.75 mmol, 1.5 equiv), 150 µL stock solution (1500 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 44 h yielding 126.7 mg (88%) of methyl 4-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-ynyl)benzoate as a pale yellow oil (hexane/ether: 75/25).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 4.68 (t, *J* = 3.6 Hz, 1H), 3.95 – 3.84 (m, 5H), 3.65 (dt, *J* = 9.7, 7.0 Hz, 1H), 3.52 (dddd, *J* = 10.7, 6.4, 4.3, 2.6 Hz, 1H), 2.73 (t, *J* = 7.1 Hz, 2H), 1.83 (ddd, *J* = 9.8, 7.8, 4.8 Hz, 1H), 1.78 – 1.68 (m, 1H), 1.66 – 1.47 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.71, 131.62, 129.51, 129.17, 128.64, 98.90, 90.60, 81.02, 65.62, 62.32, 52.26, 30.68, 25.54, 21.15, 19.49.

HRMS: (ESI, [$C_{17}H_{20}O_4$ + Na]) calcd, 311.1259; found *m/z*: 311.1249.

2-(3,3-Diethoxyprop-1-ynyl)-1-methyl-4-nitrobenzene (18)



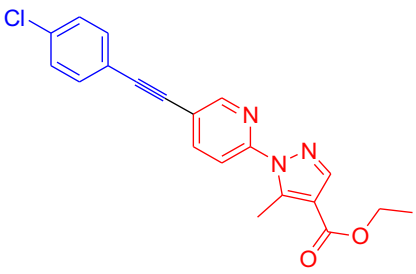
2-Bromo-4-nitrotoluene (108 mg, 0.5 mmol), 3,3-diethoxy-1-propyne (108 µL, 0.75 mmol, 1.5 equiv), 150 µL stock solution (1500 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 51 h yielding 81.2 mg (62%) of 2-(3,3-diethoxyprop-1-ynyl)-1-methyl-4-nitrobenzene as a yellow oil (hexane/ether : 90/10).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 2.5 Hz, 1H), 8.07 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 5.53 (s, 1H), 3.83 (dq, *J* = 9.5, 7.1 Hz, 2H), 3.69 (dq, *J* = 9.5, 7.1 Hz, 2H), 2.54 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.08, 146.14, 130.46, 127.35, 123.59, 123.44, 91.80, 90.84, 81.78, 61.32, 21.16, 15.26.

HRMS: (CI, [$C_{14}H_{17}NO_4$ + H]) calcd, 264.1236; found *m/z*: 264.1235.

Ethyl 1-(5-(2-(4-chlorophenyl)ethynyl)pyridin-2-yl)-5-methyl-1H-pyrazole-4-carboxylate (19)



Ethyl 1-(5-bromopyridin-2-yl)-5-methylpyrazole-4-carboxylate (155 mg, 0.5 mmol),

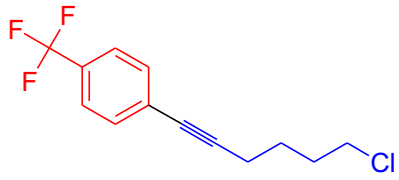
1-chloro-4-ethynylbenzene (102.5 mg, 0.75 mmol, 1.5 equiv), 150 µL stock solution (1500 ppm Pd) and Et_3N (140 µL, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 42 h yielding 179.5 mg (98%) of ethyl 1-(5-(2-(4-chlorophenyl)ethynyl)pyridin- 2-yl)-5-methyl-1H-pyrazole-4-carboxylate as a yellow solid (hexane/EtOAc : 90/10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 1.6 Hz, 1H), 8.03 (s, 1H), 7.94 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.95 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.72, 151.92, 150.30, 145.79, 142.84, 141.01, 135.17, 133.02, 129.00, 120.99, 118.75, 116.86, 114.60, 92.31, 86.42, 60.23, 14.53, 13.39.

HRMS: (EI, [$C_{20}H_{16}ClN_3O_2$]) calcd, 365.0931; found *m/z*: 365.0915.

1-(6-Chlorohex-1-ynyl)-4-(trifluoromethyl)benzene (20) CAS: 1440538-43-1



4-Bromobenzotrifluoride (70 µL, 0.5 mmol), 6-chloro-1-hexyne (91 µL, 0.75 mmol, 1.5 equiv), 150 µL stock solution (1500 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 45 h yielding 107.5 mg (83%) of 1-(6-chlorohex-1-ynyl)-4-(trifluoromethyl)benzene as a colorless oil (hexane/ether : 99/1).

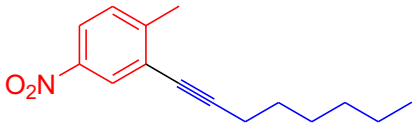
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 1.97 (ddt, *J* = 9.4, 8.1, 6.4 Hz, 2H), 1.84 – 1.73 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.92, 129.96, 129.70, 129.44, 129.19, 127.81, 127.79, 127.39, 125.33, 125.30, 125.27, 125.23, 125.22, 123.06, 120.90, 92.27, 80.25, 80.24, 44.59, 44.58, 31.76, 25.86, 18.89.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.77.

Dai, J.-J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z.-J.; Lu, X.; Liu,L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, 135, 8436.

1-Methyl-4-nitro-2-(oct-1-ynyl)benzene (21)



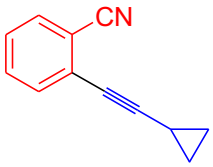
2-Bromo-4-nitrotoluene (108 mg, 0.5 mmol), 1-octyne (110 µL, 0.75 mmol, 1.5 equiv), 150 µL stock solution (1500 ppm Pd) and K_3PO_4•H_2O (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 50 h yielding 121.0 mg (98%) of 1-methyl-4-nitro-2-(oct-1-ynyl)benzene as a yellow solid (hexane/ether : 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 2.5 Hz, 1H), 7.98 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 2.49 (s, 3H), 2.46 (t, *J* = 7.1 Hz, 2H), 1.63 (dt, *J* = 14.9, 7.1 Hz, 2H), 1.51 – 1.42 (m, 2H), 1.40 – 1.27 (m, 4H), 0.94 – 0.85 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.64, 146.09, 130.17, 130.02, 126.76, 126.67, 125.54, 122.21, 122.17, 97.51, 77.69, 31.44, 28.69, 22.67, 21.18, 21.08, 19.61, 14.15.

HRMS: (EI, [$C_{15}H_{19}NO_2$]) calcd, 245.1416; found *m/z*: 245.1405.

2-(2-Cyclopropylethynyl)benzonitrile (22)



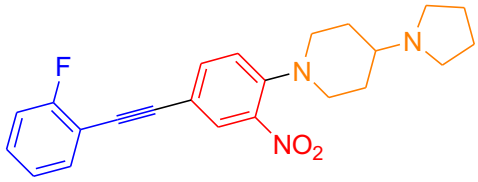
2-Bromobenzonitrile (91 mg, 0.5 mmol), cyclopropylacetylene (51 µL, 0.75 mmol, 1.5 equiv), 150 µL stock solution (1500 ppm Pd) and $K_3PO_4 \bullet H_2O$ (230 mg, 1.0 mmol, 2.0 equiv) in 1.0 mL 2 wt % TPGS/H_2O were reacted at 45 °C for 45 h yielding 73.5 mg (88%) of 2-(2-cyclopropylethynyl)benzonitrile as a pale yellow oil (hexane/ether : 98/2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.31 (td, *J* = 7.4, 1.9 Hz, 1H), 1.51 (tt, *J* = 8.1, 5.2 Hz, 1H), 0.99 – 0.86 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 132.53, 132.32, 132.21, 128.10, 127.50, 117.84, 115.38, 101.33, 72.42, 9.29, 0.45.

HRMS: (EI, [$C_{12}H_9N$]) calcd, 167.0735; found *m/z*: 167.0729.

1-(4-(2-(2-Fluorophenyl)ethynyl)-2-nitrophenyl)-4-(pyrrolidin-1-yl)piperidine (23)



For details, see the 2-step, 1-pot section.

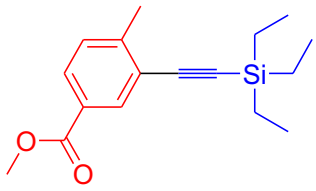
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.93 (m, 1H), 7.54 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.31 (q, *J* = 6.8 Hz, 1H), 7.10 (dt, *J* = 14.6, 8.2 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 1H), 3.34 (d, *J* = 12.6 Hz, 2H), 2.93 (t, *J* = 11.3 Hz, 2H), 2.65 – 2.51 (m, 4H), 2.18 (ddd, *J* = 14.2, 10.0, 3.6 Hz, 1H), 1.96 (dd, *J* = 13.5, 3.8 Hz, 2H), 1.87 – 1.65 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.72, 161.71, 145.99, 141.02, 136.31, 133.47, 133.46, 130.29, 130.23, 129.79, 124.16, 124.13, 120.45, 115.77, 115.61, 114.44, 111.75, 111.63, 92.56, 92.53, 83.22, 61.17, 51.54, 50.22, 31.42, 23.40.

^{19}F NMR (376 MHz, $CDCl_3$) δ -109.78, -109.80, -109.80, -109.81, -109.81, -109.82, -109.83, -109.84.

HRMS: (ESI, [$C_{23}H_{24}FN_3O_2$ + H]) calcd, 394.1931; found m/z: 394.1940.

Methyl 4-methyl-3-(2-(triethylsilyl)ethynyl)benzoate (25)

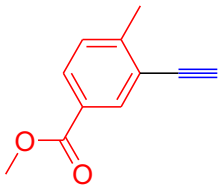


For details, section on see the ponatinib synthesis.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 1.9 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.28 – 7.25 (m, 1H), 3.90 (s, 3H), 2.49 (s, 3H), 1.06 (t, *J* = 7.9 Hz, 9H), 0.69 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.67, 145.95, 133.57, 129.64, 129.43, 127.86, 123.72, 104.09, 96.99, 52.23, 21.16, 7.67, 4.59.

Methyl 3-ethynyl-4-methylbenzoate (26)

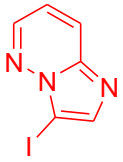


For details, section on see the ponatinib synthesis.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 1.9 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H), 3.31 (s, 1H), 2.50 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.54, 146.14, 133.88, 129.84, 129.77, 127.99, 122.48, 81.95, 81.62, 52.28, 20.99.

3-Iodoimidazo[1,2-b]pyridazine (27)

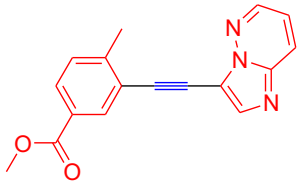


For details, section on see the ponatinib synthesis.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.90 (dd, *J* = 9.1, 1.6 Hz, 1H), 7.84 (s, 1H), 7.06 (dd, *J* = 9.1, 4.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.90, 141.43, 140.41, 125.70, 117.21, 68.32.

Methyl 3-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)-4-methylbenzoate (28)



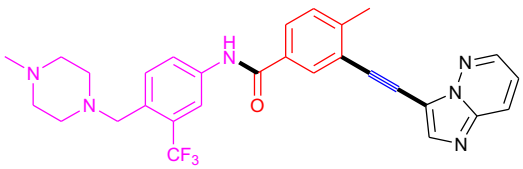
For details, section on see the ponatinib synthesis.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.26 (d, *J* = 1.8 Hz, 1H), 8.05 (s, 1H), 8.00 (dd, *J* = 9.1, 1.6 Hz, 1H), 7.92 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.33 (dt, *J* = 8.1, 0.7 Hz, 1H), 7.13 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.92 (s, 3H), 2.63 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.51, 145.54, 143.96, 139.79, 138.42, 133.16, 129.83, 129.82, 128.05, 126.00, 122.84, 117.77, 113.28, 96.84, 80.57, 52.26, 21.18.

HRMS: (ESI, [$C_{17}H_{13}N_3O_2$ + H]) calcd, 292.1086; found *m/z*: 292.1077.

Ponatinib



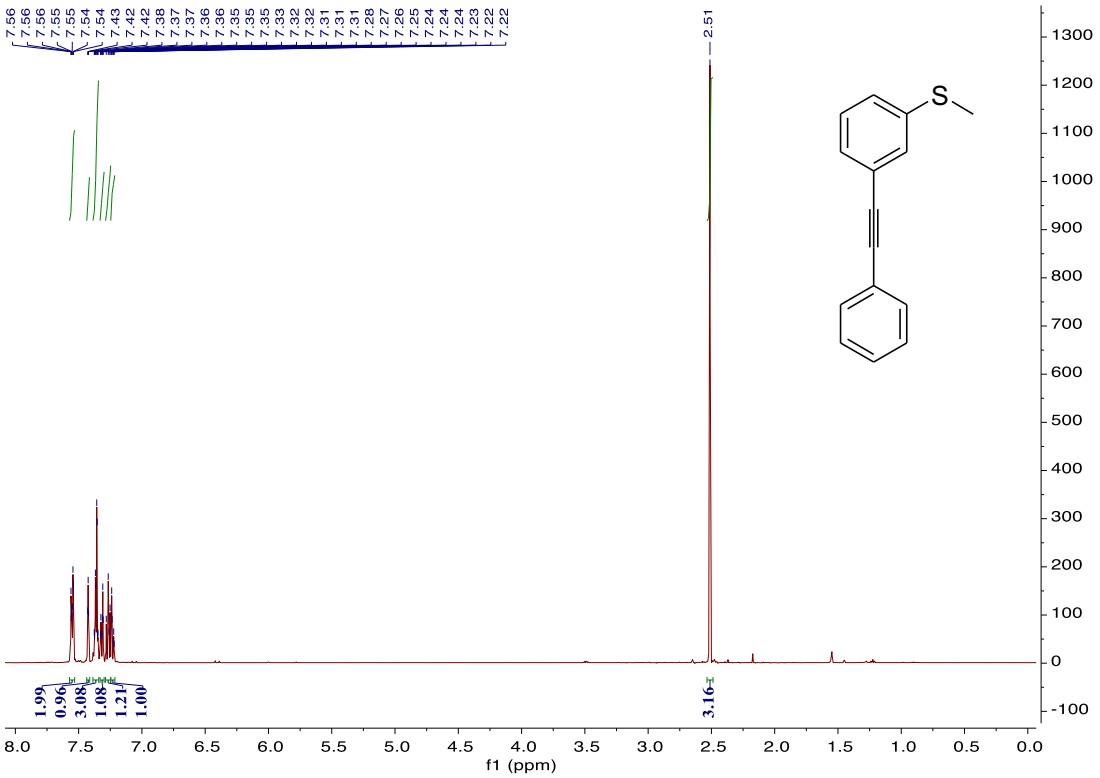
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.42 (dd, J = 4.4, 1.7 Hz, 1H), 8.07 (s, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.96 (d, J = 7.3 Hz, 2H), 7.82 (ddd, J = 9.6, 8.5, 1.8 Hz, 2H), 7.71 (d, J = 8.5 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.06 (dd, J = 9.2, 4.4 Hz, 1H), 3.60 (s, 2H), 2.55 (s, 3H), 2.49 (s, 8H), 2.29 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 165.53, 144.45, 144.03, 139.75, 138.23, 137.22, 133.48, 132.28, 131.40, 130.29, 130.18, 129.58, 129.34, 129.09, 128.86, 128.24, 125.82, 125.28, 123.60, 123.10, 122.60, 117.98, 113.23, 96.77, 80.62, 57.87, 55.22, 52.97, 45.97, 20.94.
^{19}F NMR (376 MHz, $CDCl_3$) δ -59.40.
HRMS: (ESI, [$C_{29}H_{27}F_3N_6O$ + H]) calcd, 533.2277; found *m/z*: 533.2266.

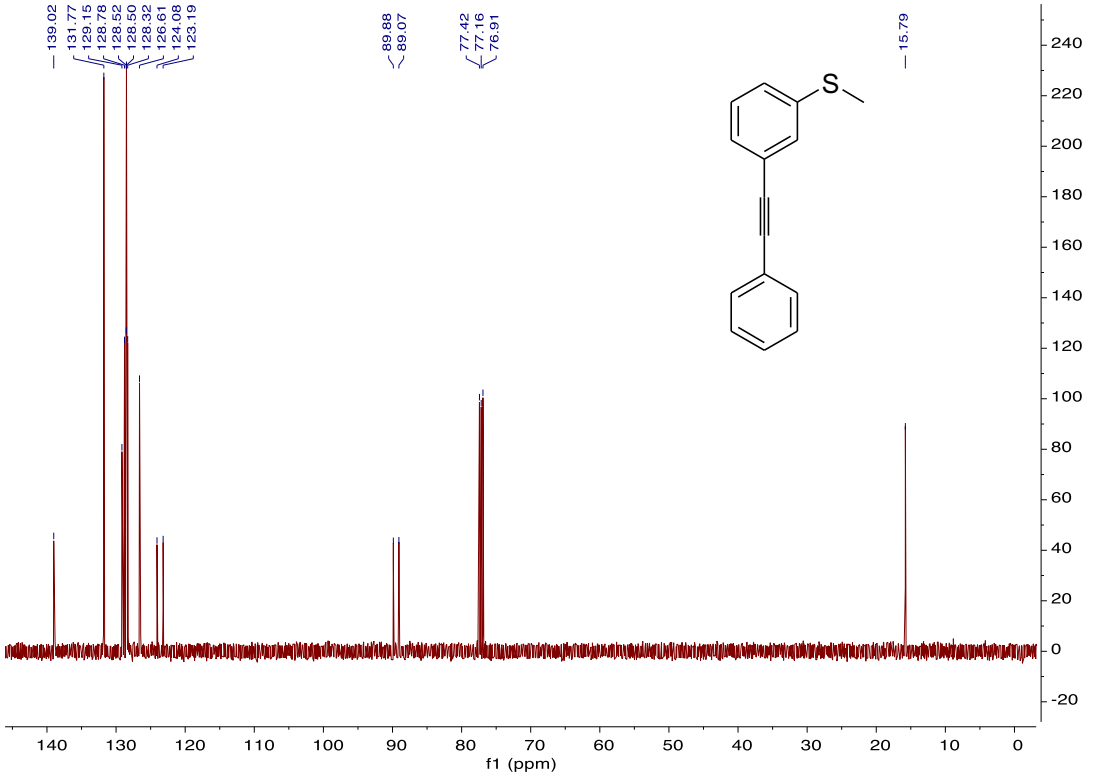
References

1. B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R. D. Gaston and R. C. Gadwood, *J. Org. Chem.*, **2011**, *76*, 4379.

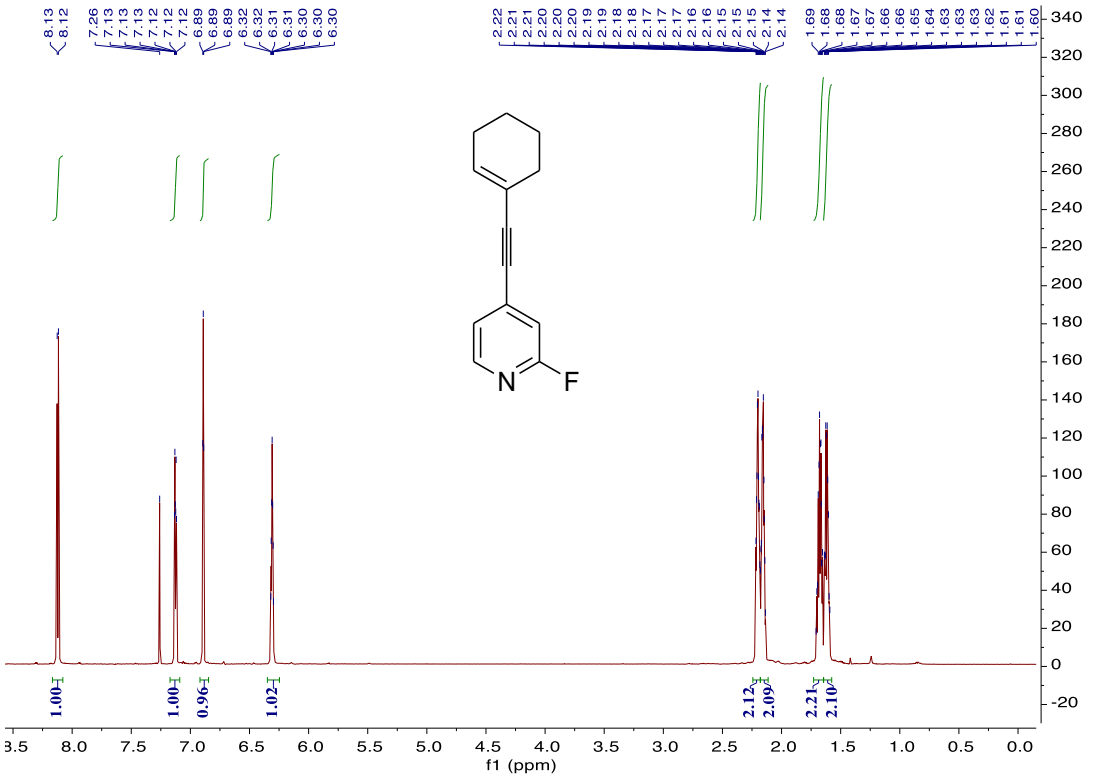
NMR Spectra

Methyl(3-(2-phenylethynyl)phenyl)sulfane (**2**)





4-(2-Cyclohexenylethynyl)-2-fluoropyridine (**3**)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0.96
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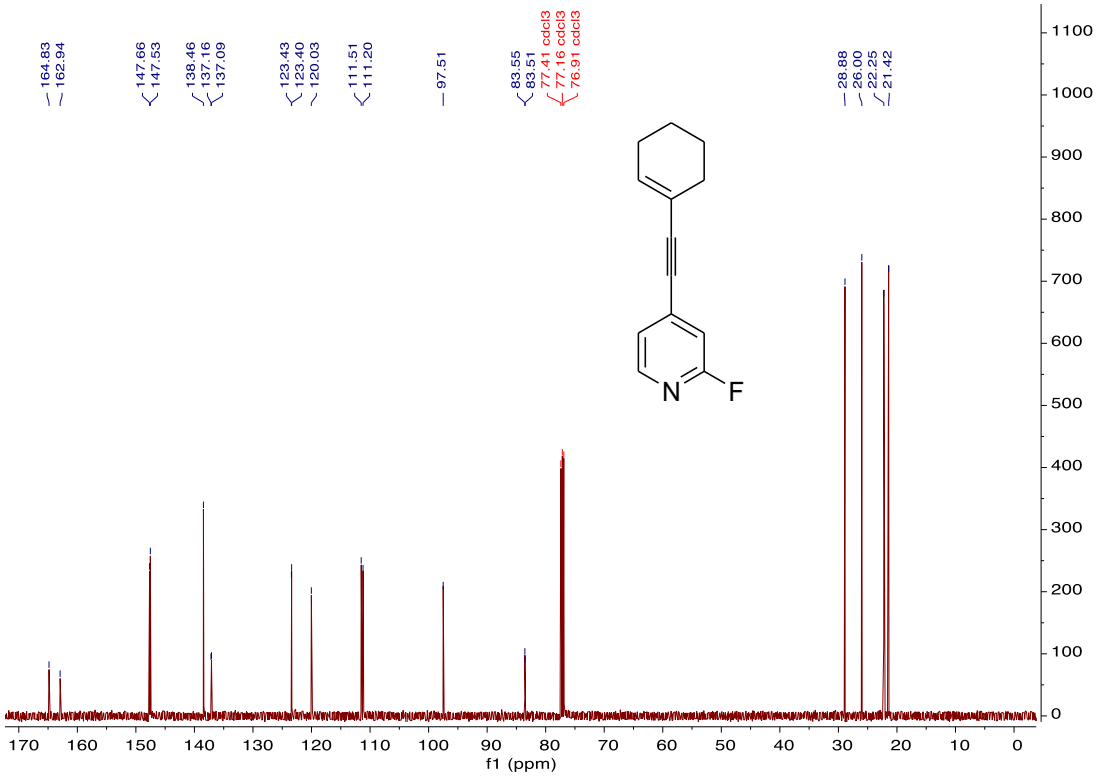
2.09
2.21
2.10
f1 (ppm)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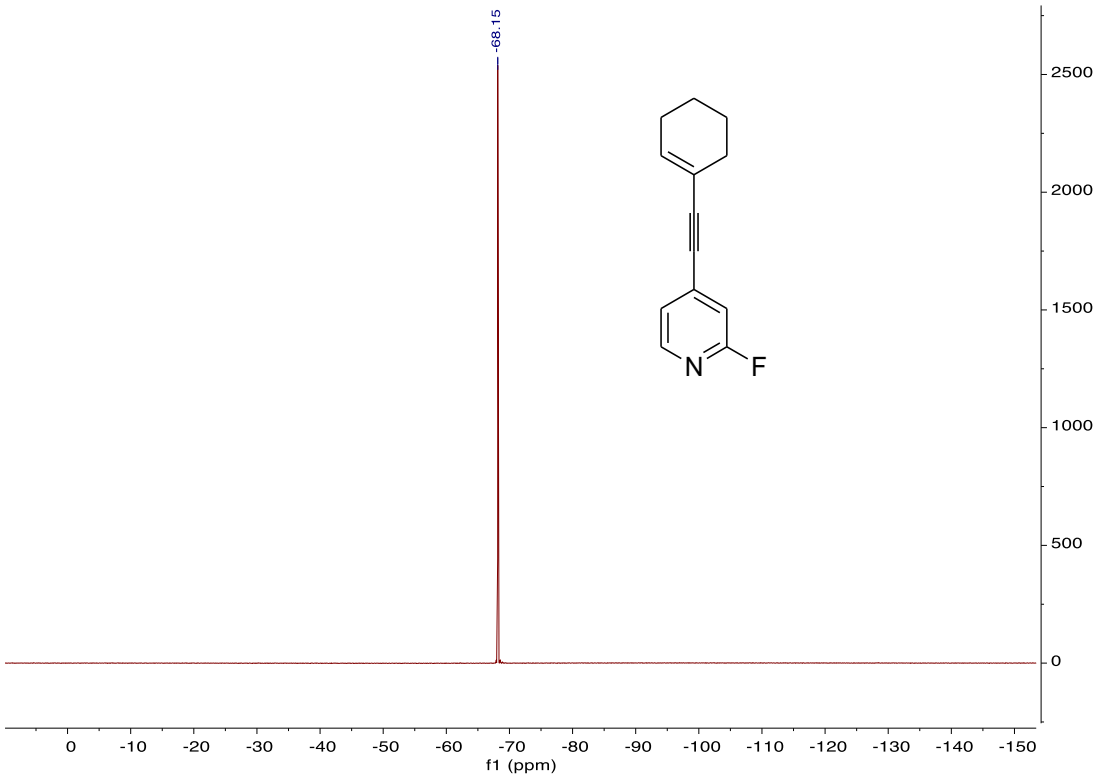
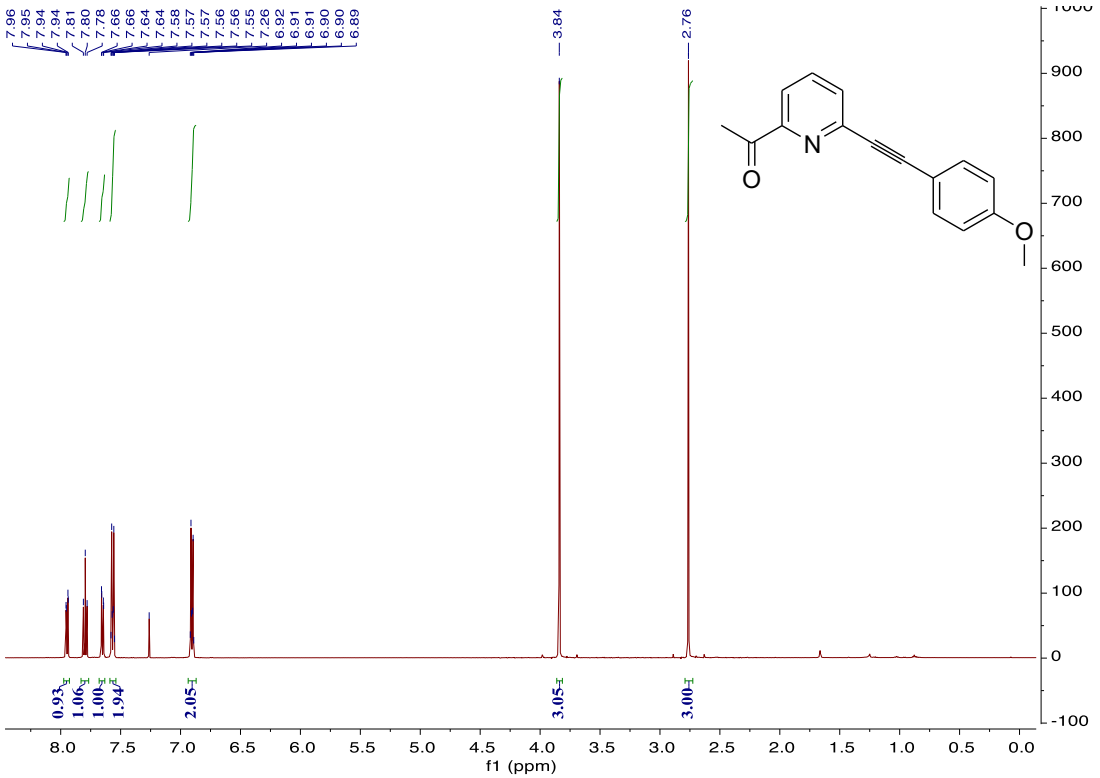
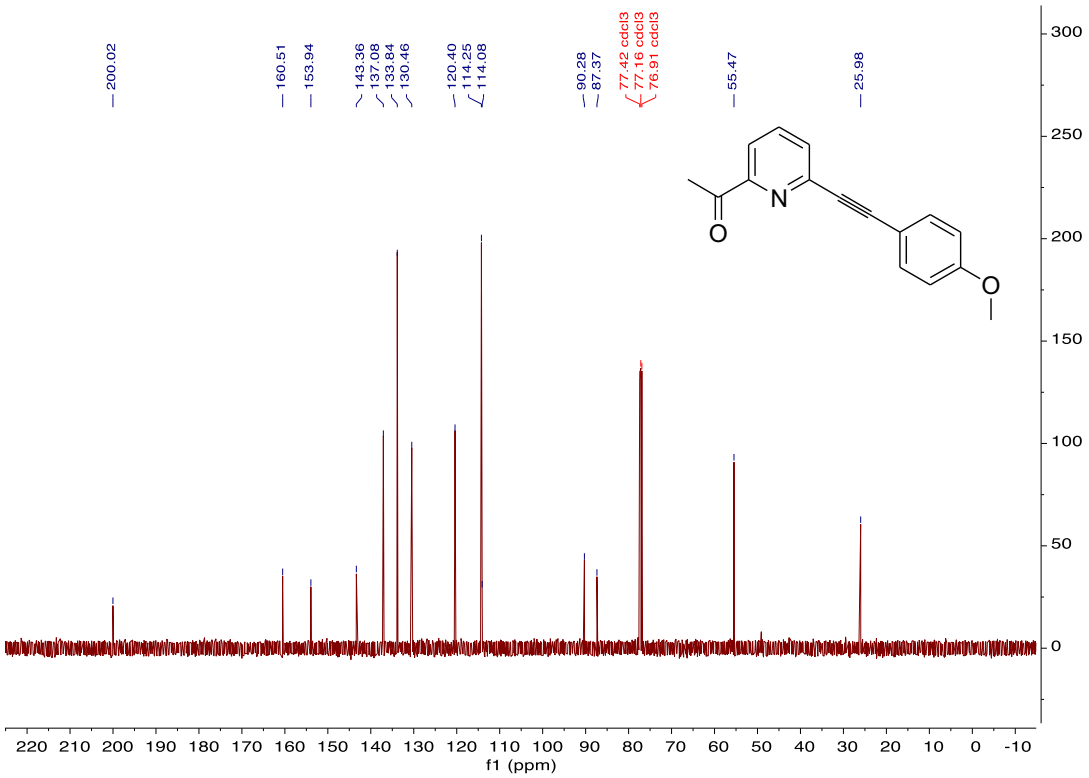
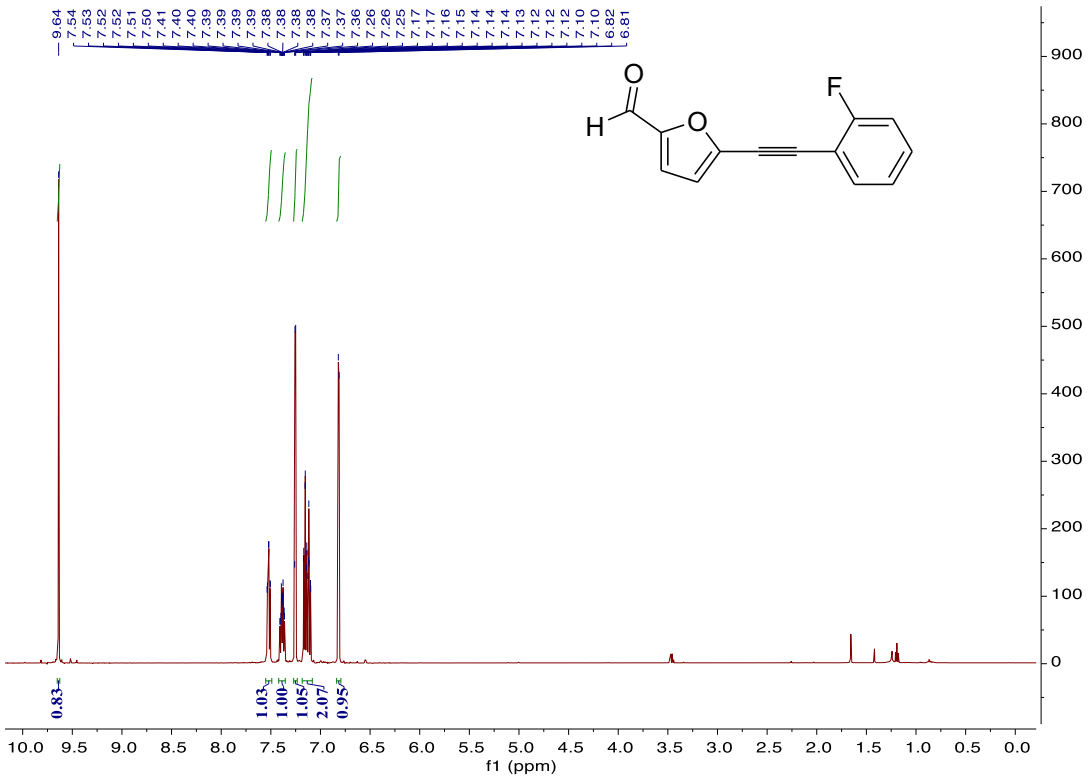


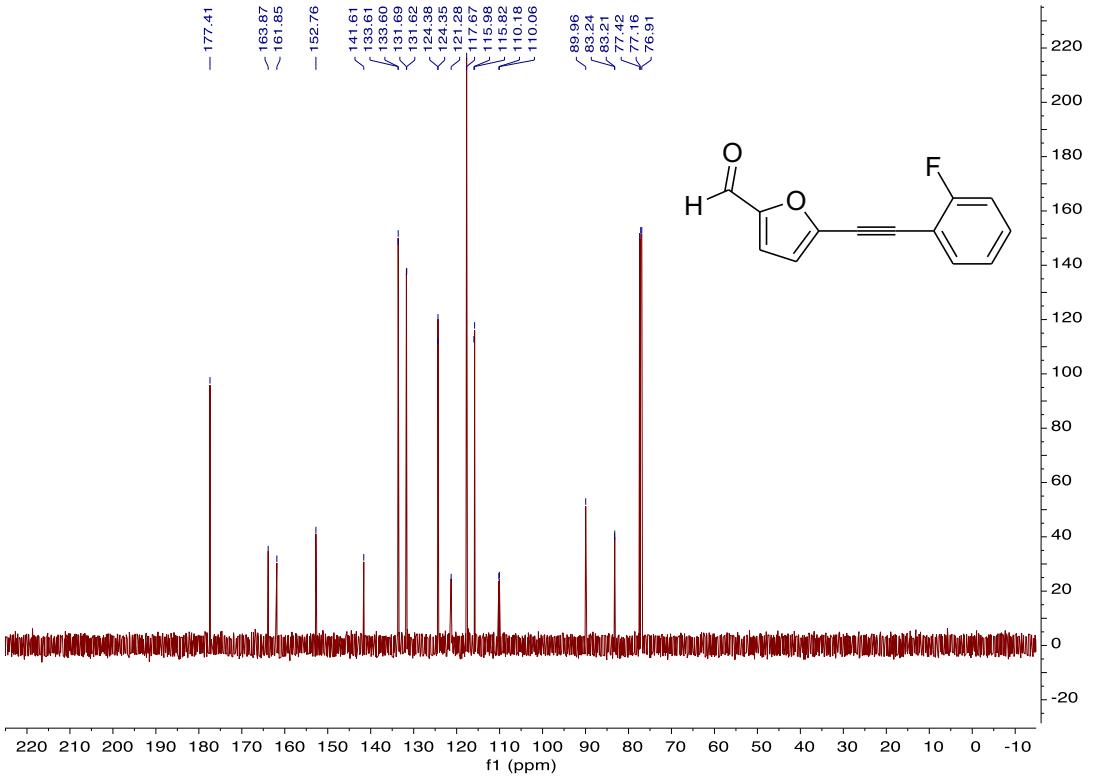
1-(6-(2-(4-Methoxyphenyl)ethynyl)pyridin-2-yl)ethanone (**4**)

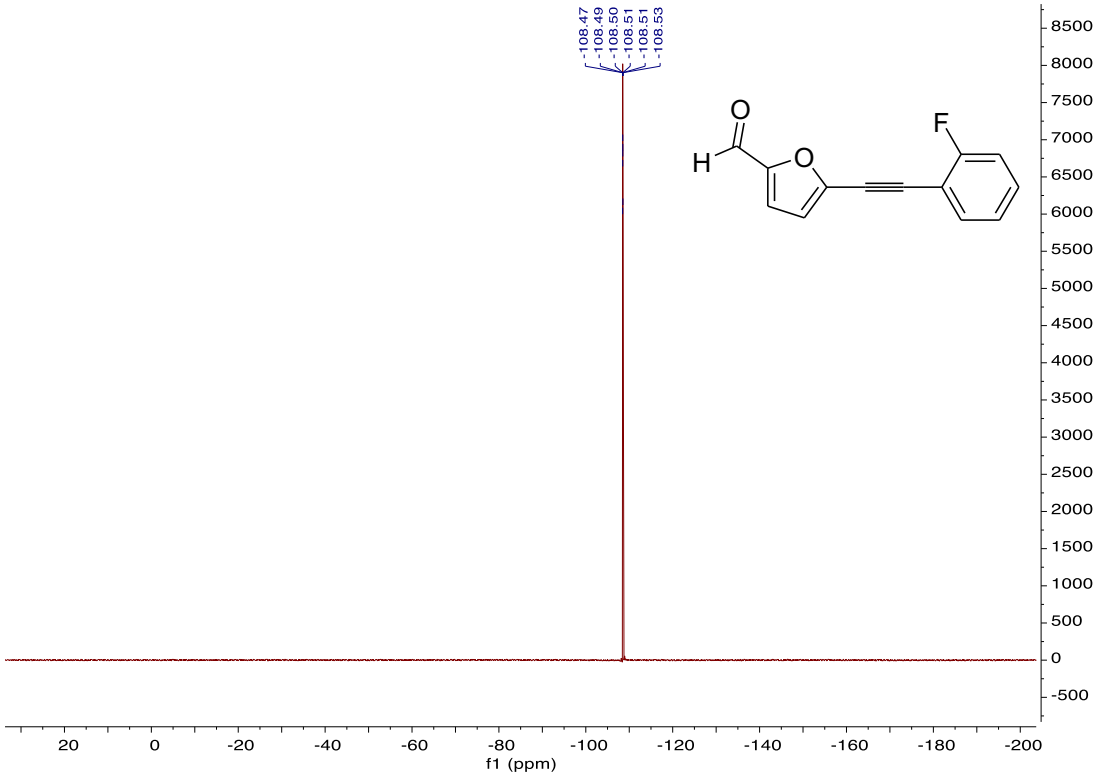




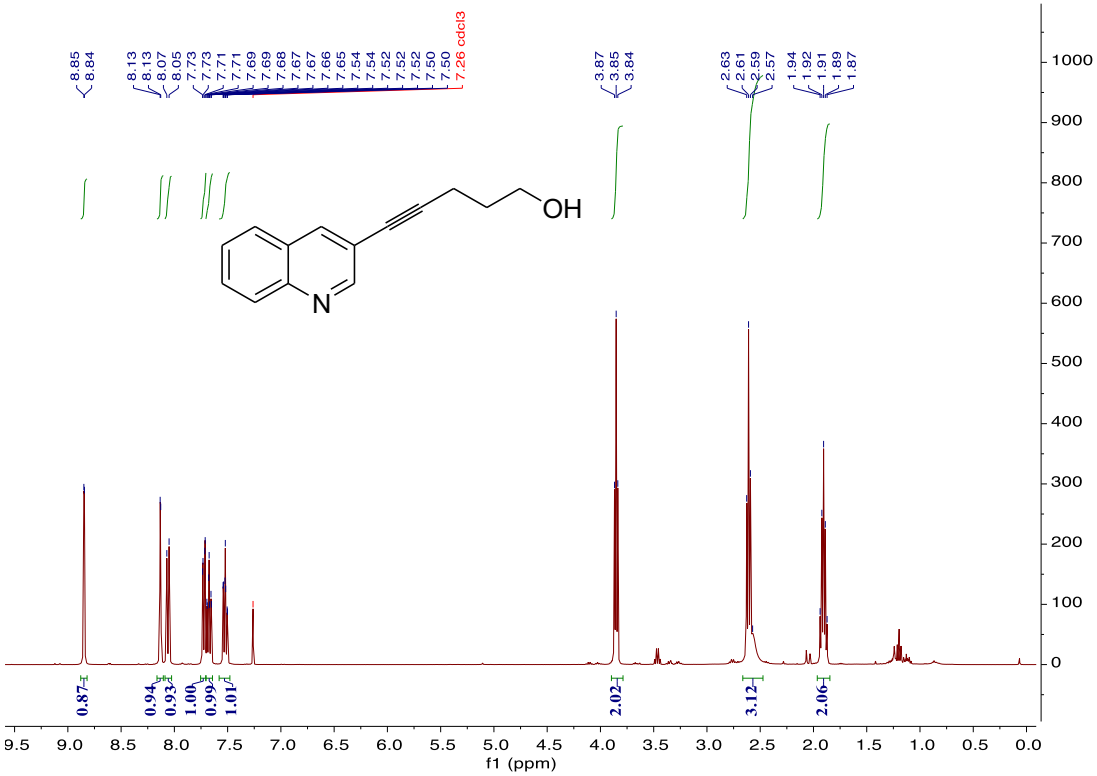
5-(2-(2-Fluorophenyl)ethynyl)furan-2-carbaldehyde (**5**)

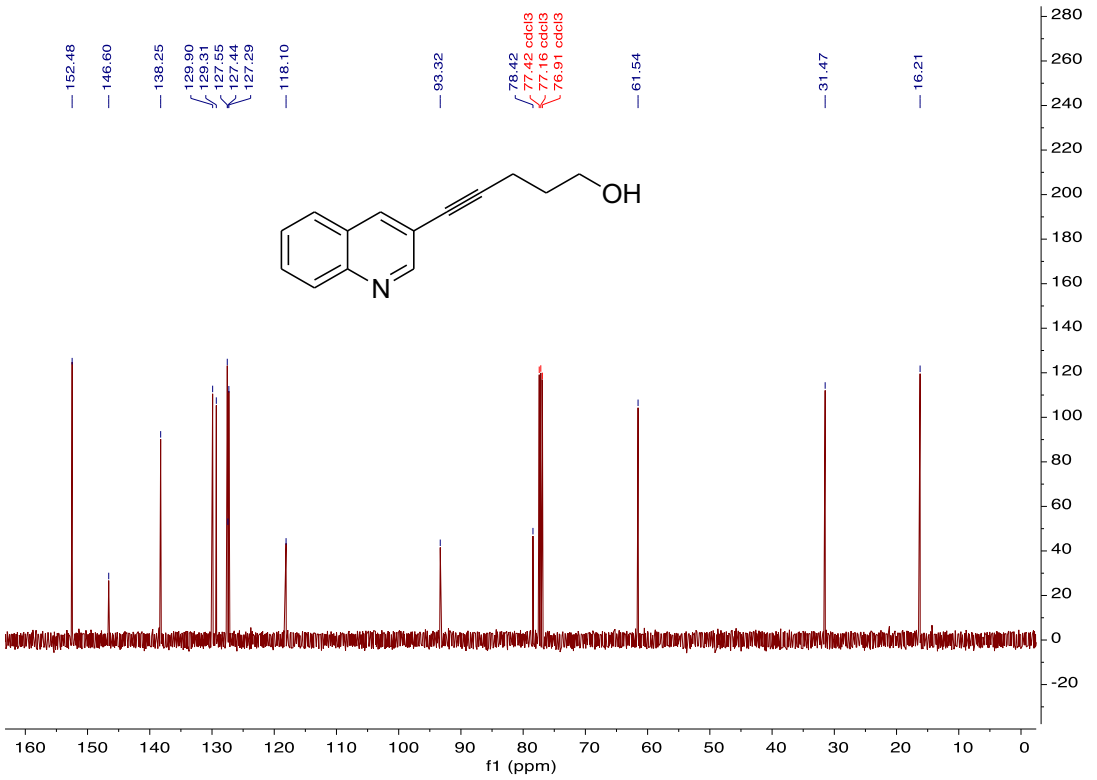



177.41
163.87
161.85
152.76
141.61
133.61
133.60
131.69
131.62
124.38
124.35
121.28
117.67
115.98
115.82
110.18
110.06
89.96
83.24
83.21
77.42
77.16
76.91
O
H
O
F
f1 (ppm)

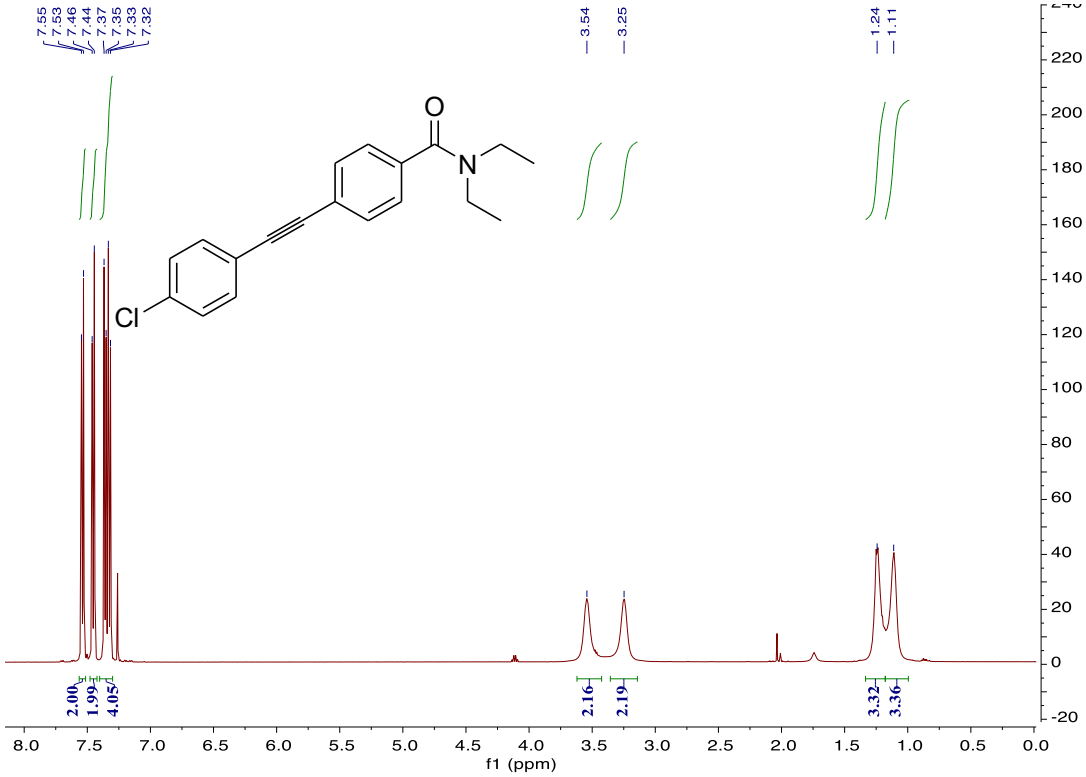

-108.47
-108.49
-108.50
-108.51
-108.51
-108.53
O
H
O
F
f1 (ppm)

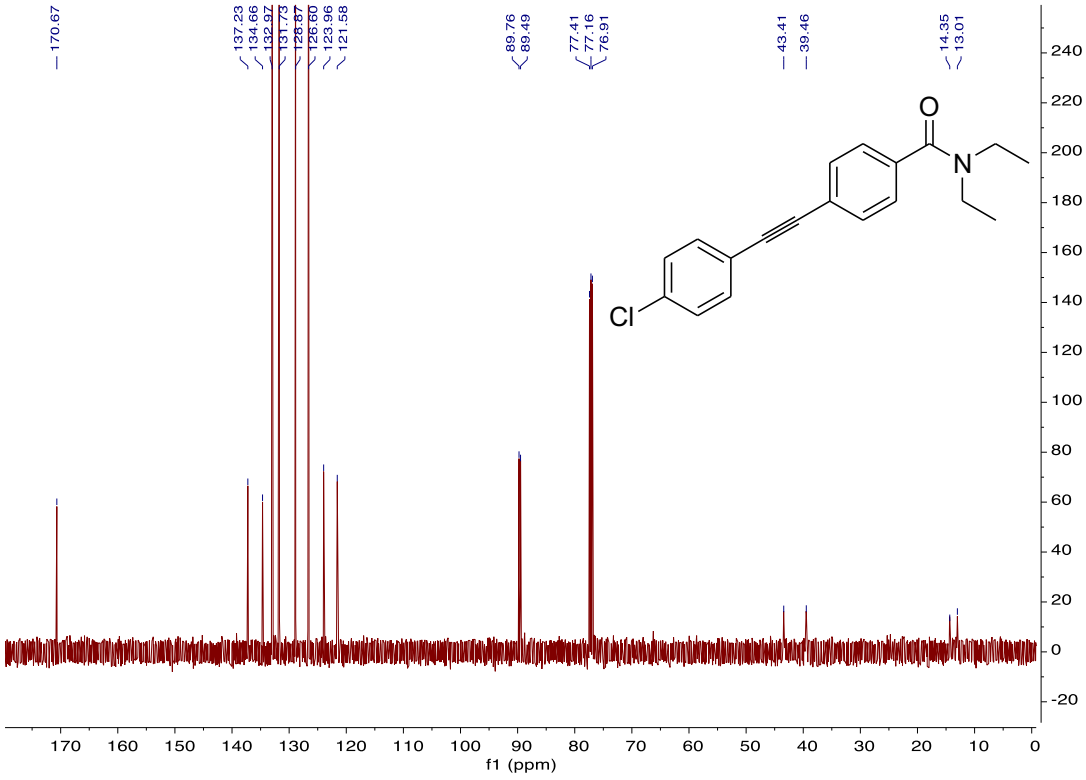
5-(quinolin-3-yl)pent-4-yn-1-ol (**6**)



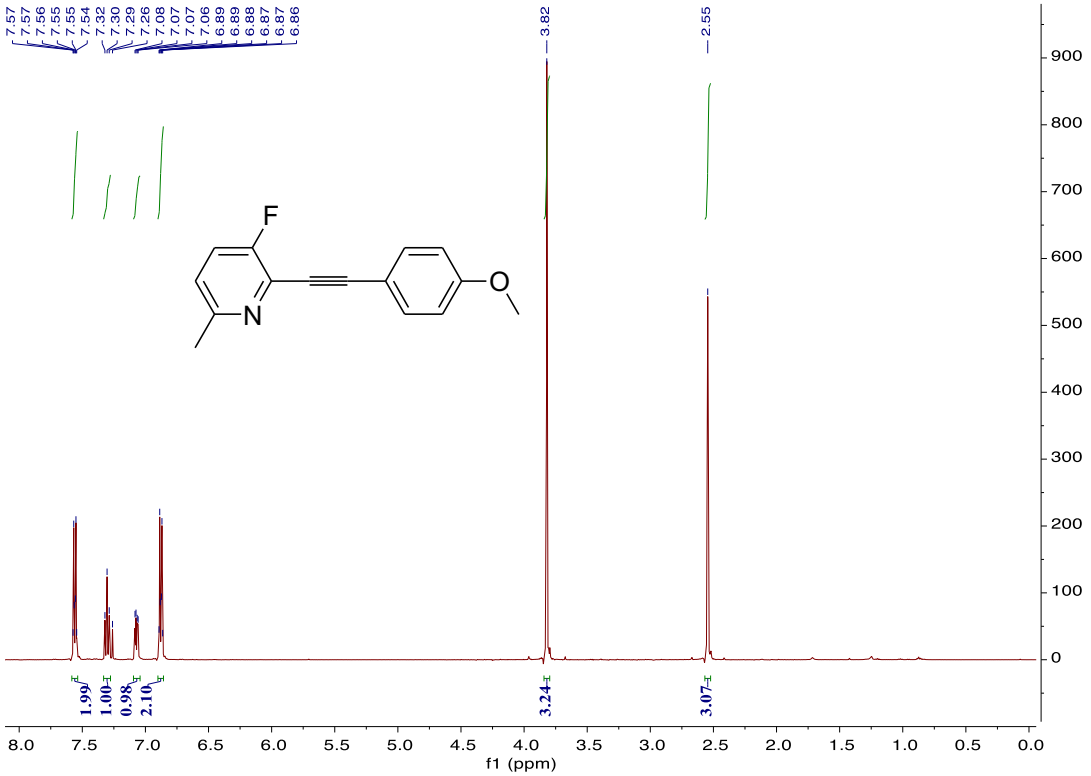


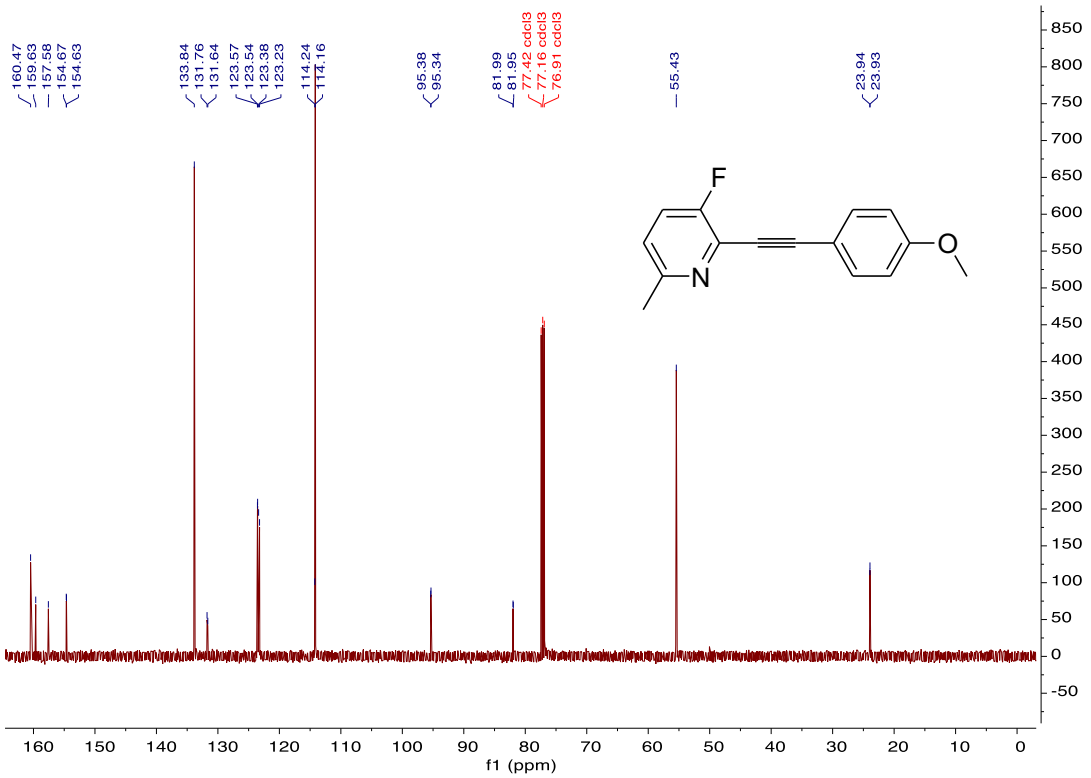
4-(2-(4-Chlorophenyl)ethynyl)-N,N-diethylbenzamide (**7**)

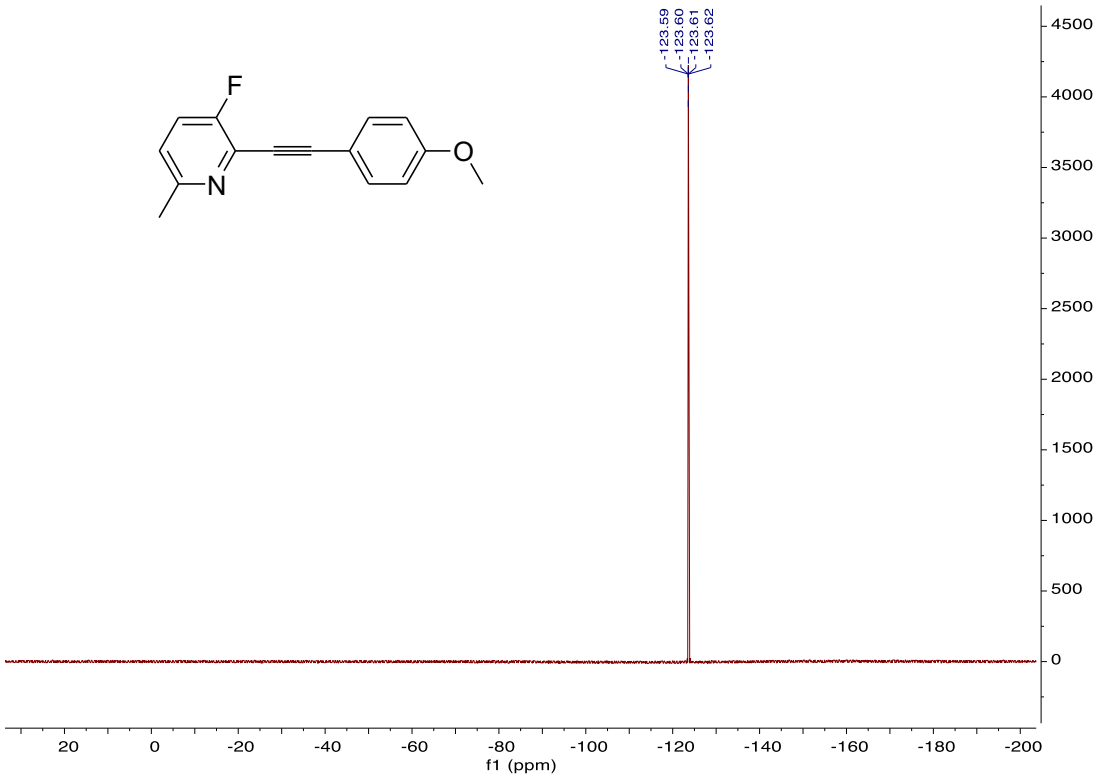




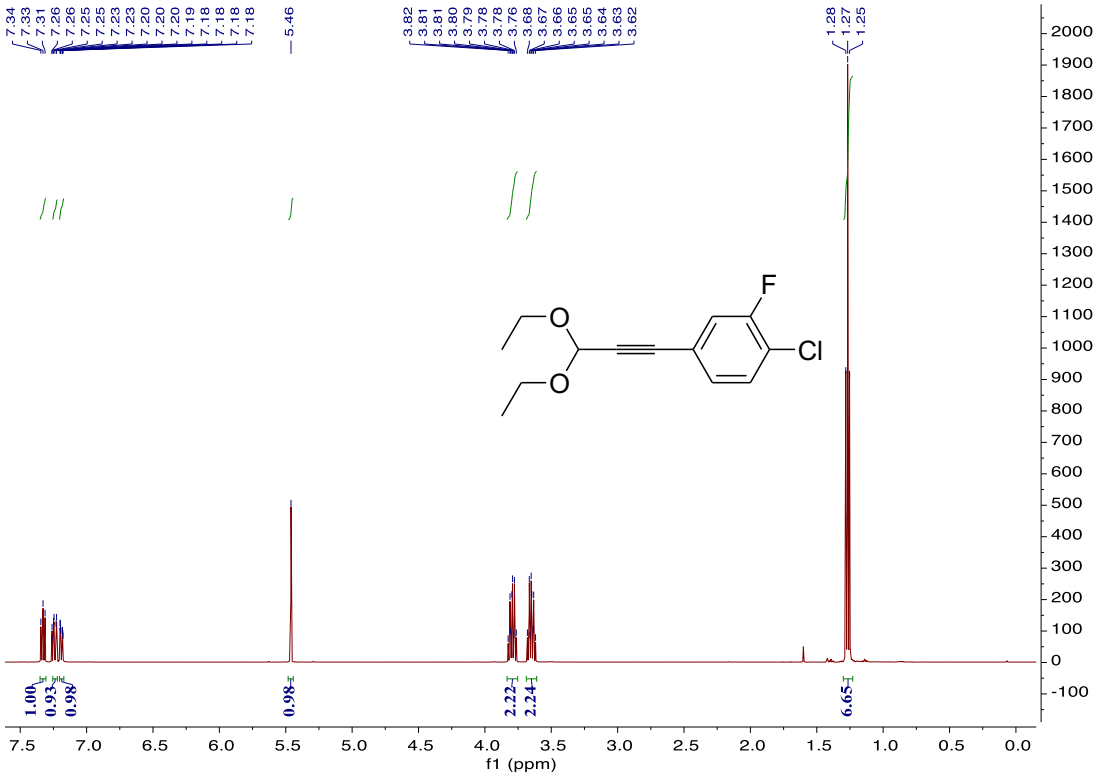
3-Fluoro-2-(2-(4-methoxyphenyl)ethynyl)-6-methylpyridine (**8**)

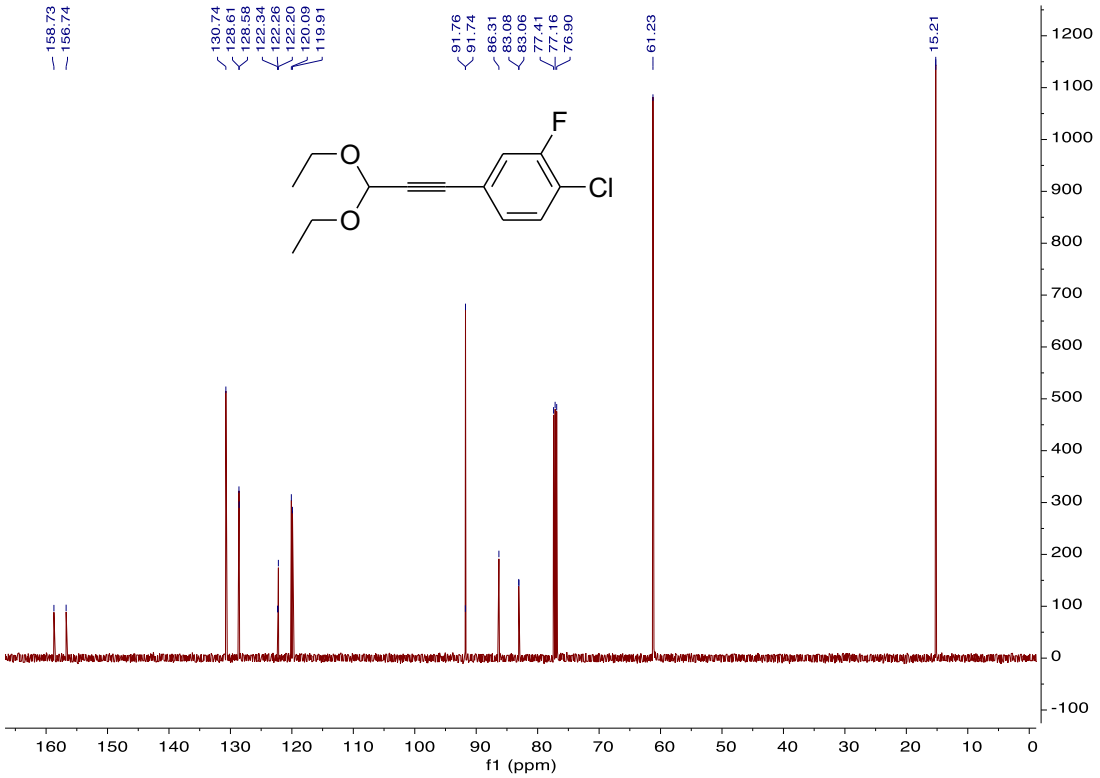


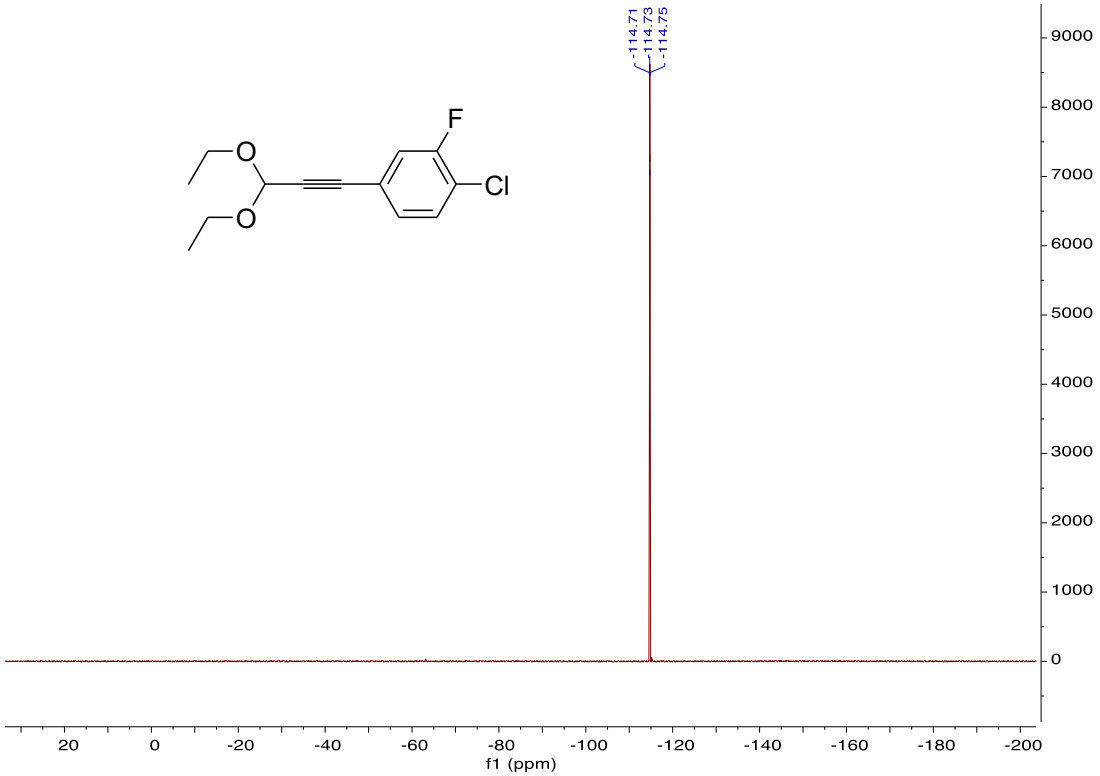




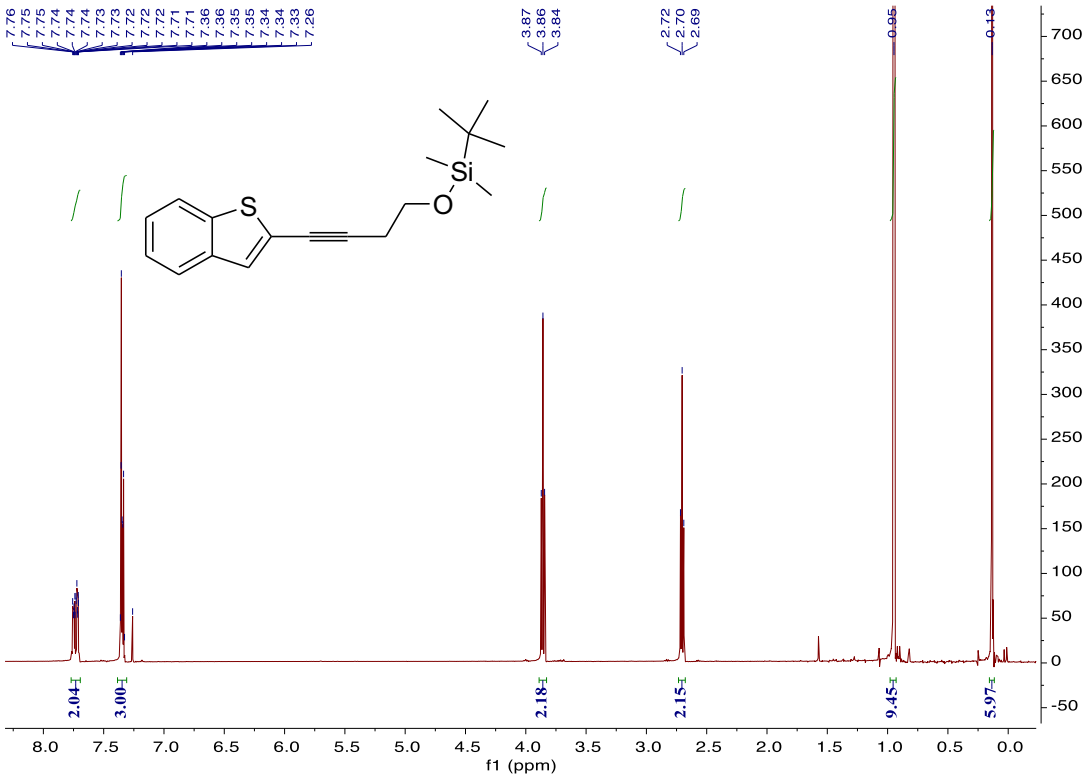
1-Chloro-4-(3,3-diethoxyprop-1-ynyl)-2-fluorobenzene (**9**)

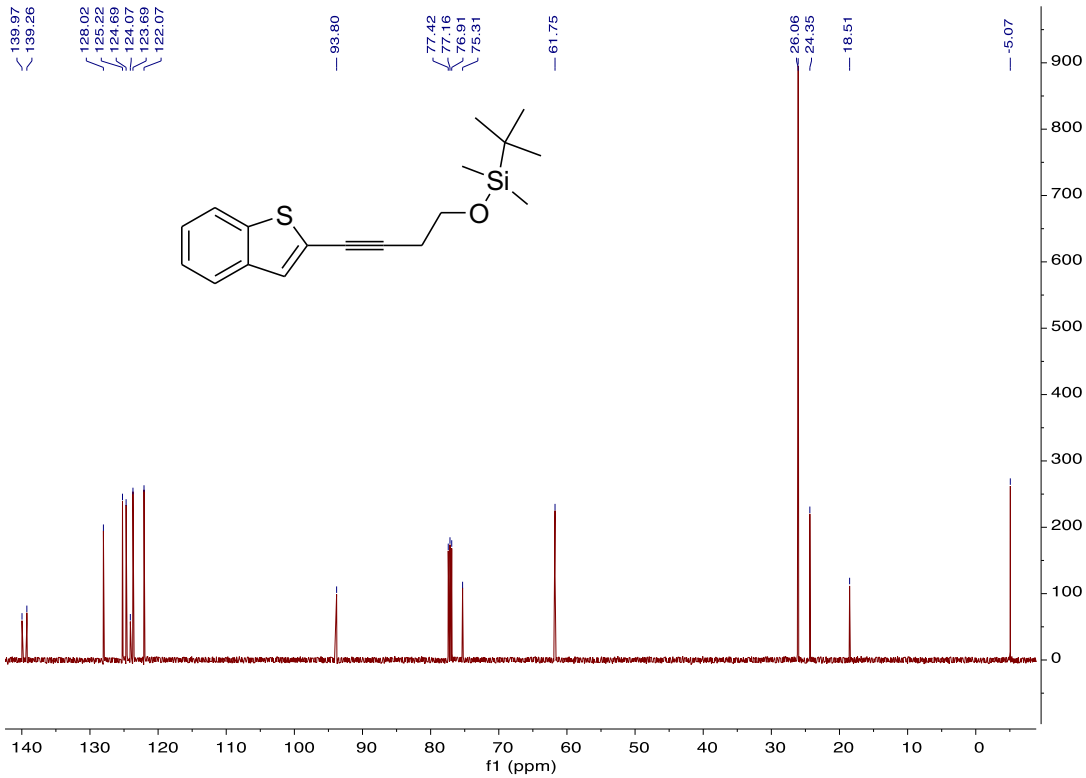



158.73
156.74
130.74
128.61
128.58
122.34
122.26
122.20
120.09
119.91
91.76
91.74
86.31
83.08
83.06
77.41
77.16
76.90
61.23
15.21
F
Cl
O
O
f1 (ppm)

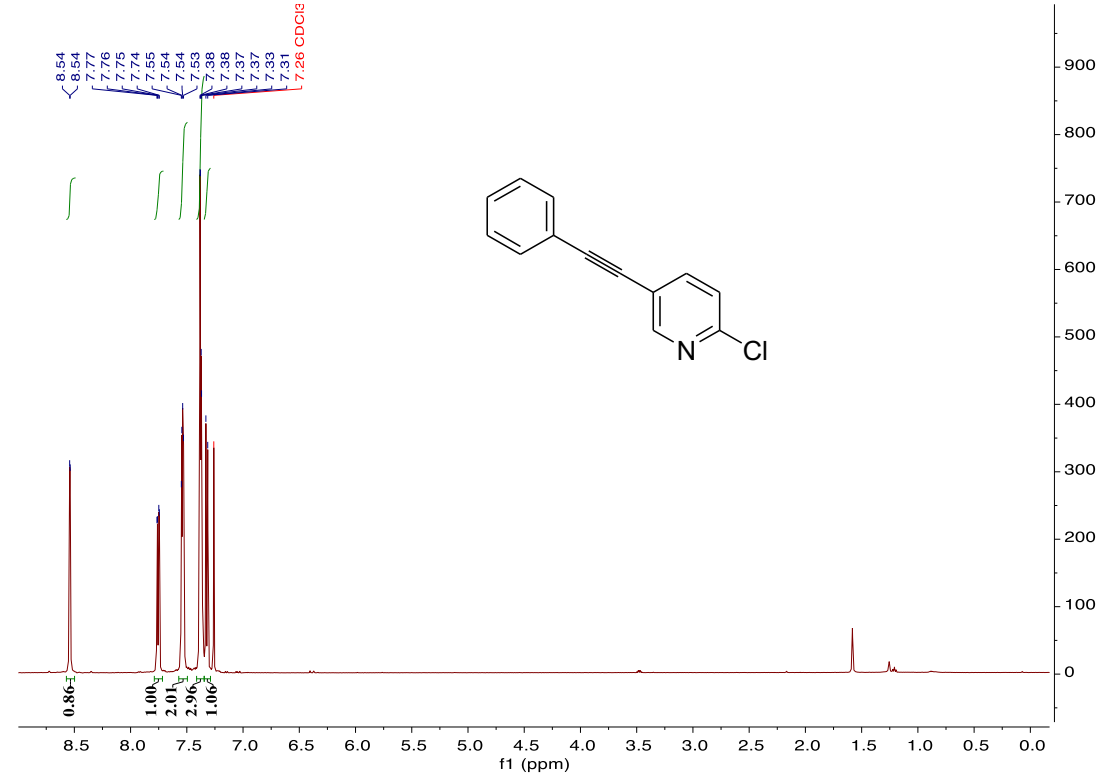

-114.71
-114.73
-114.75
F
Cl
O
O
f1 (ppm)

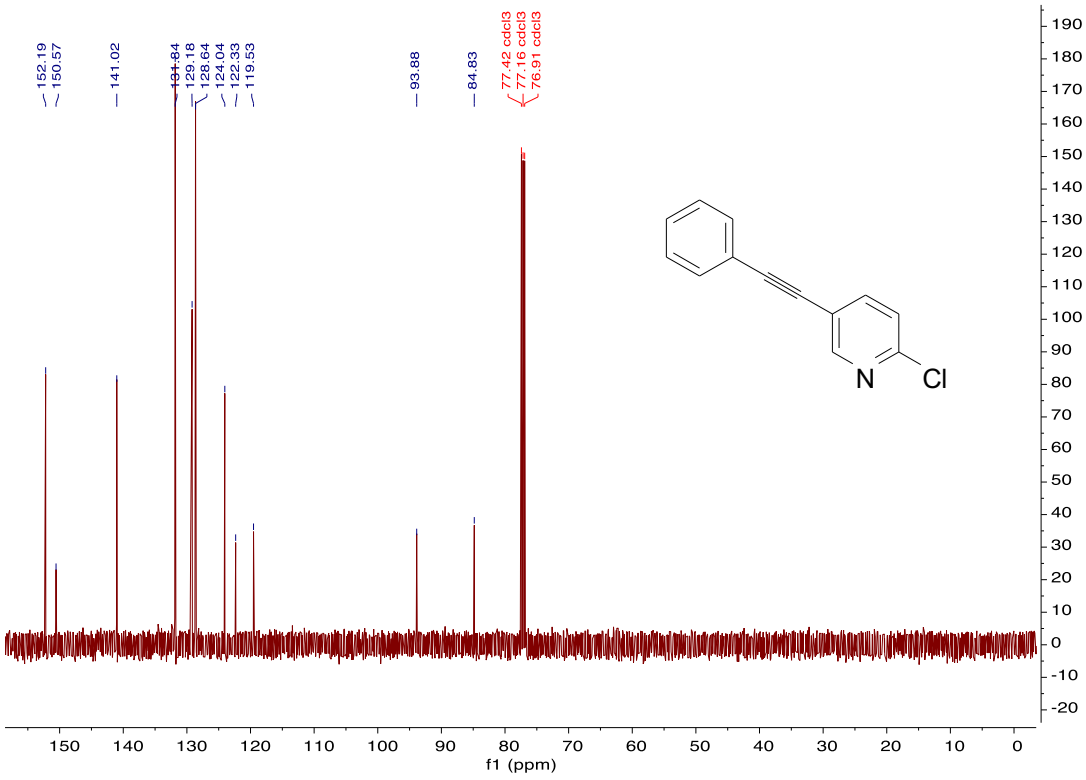
(4-(Benzo[b]thiophen-2-yl)but-3-ynyloxy)(tert-butyl)dimethylsilane (**10**)



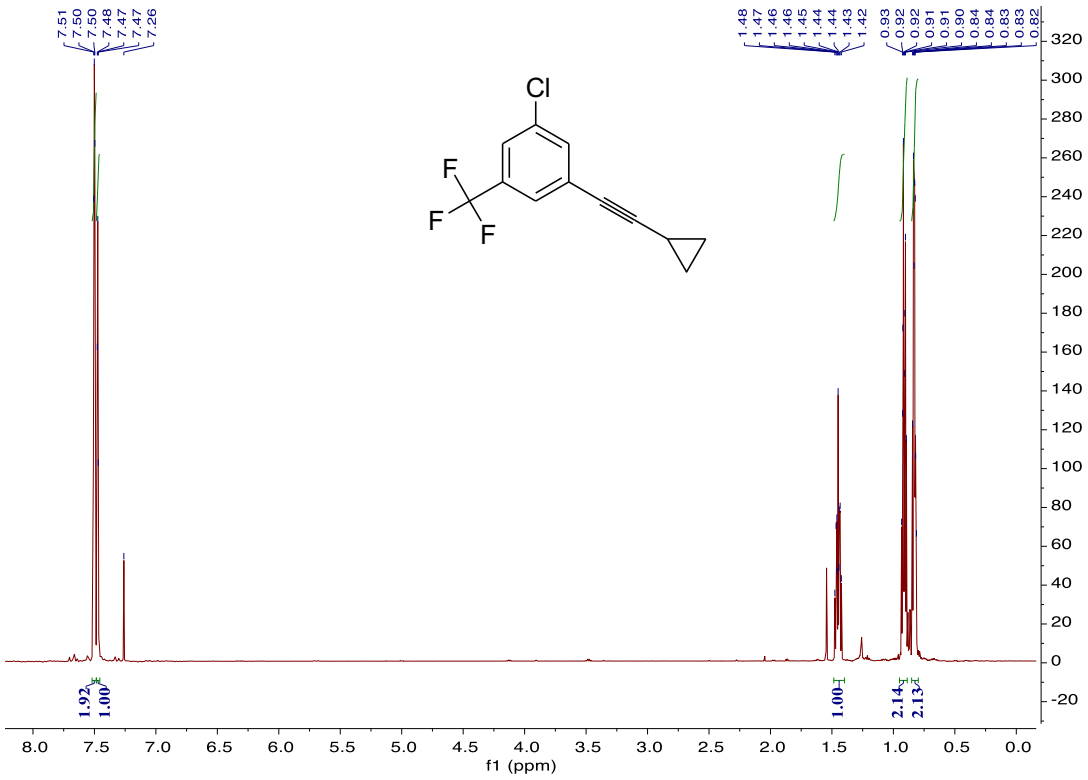


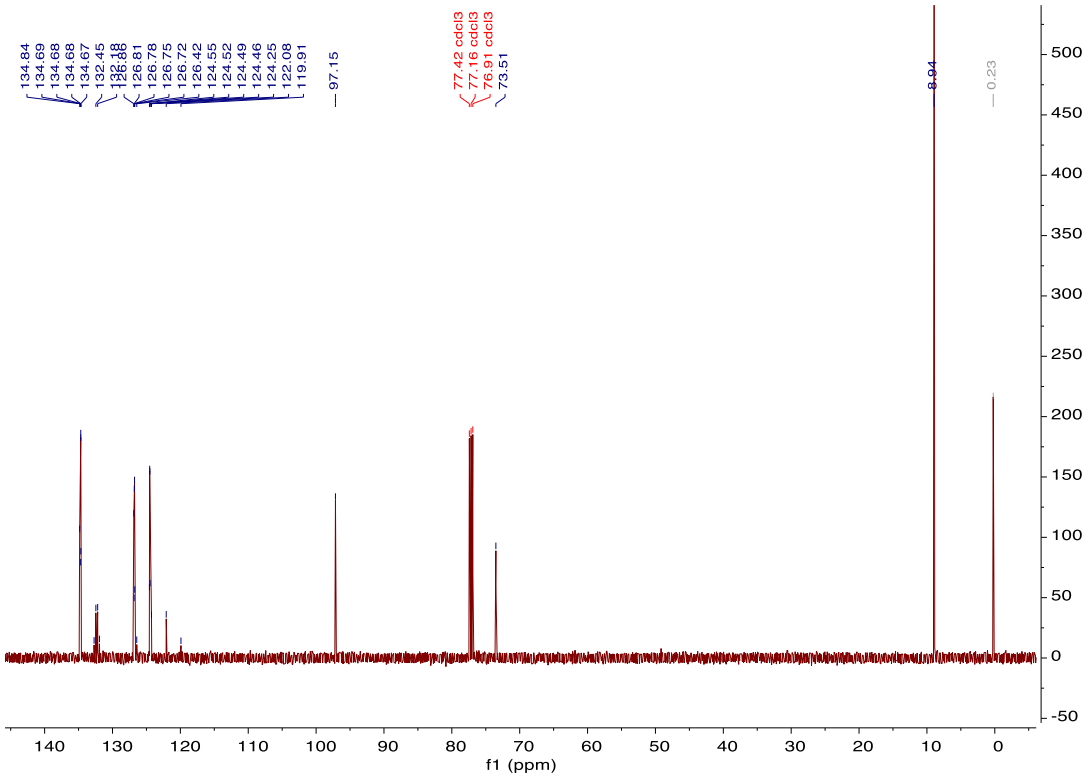
2-Chloro-5-(2-phenylethynyl)pyridine (**11**)

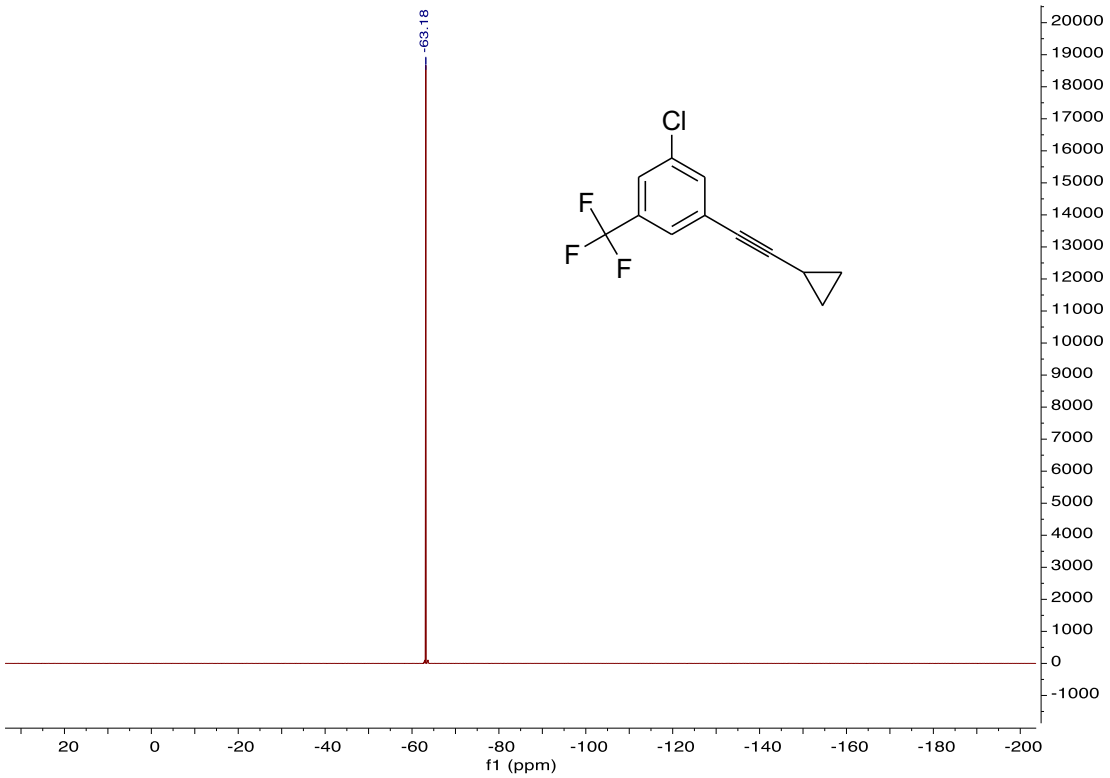




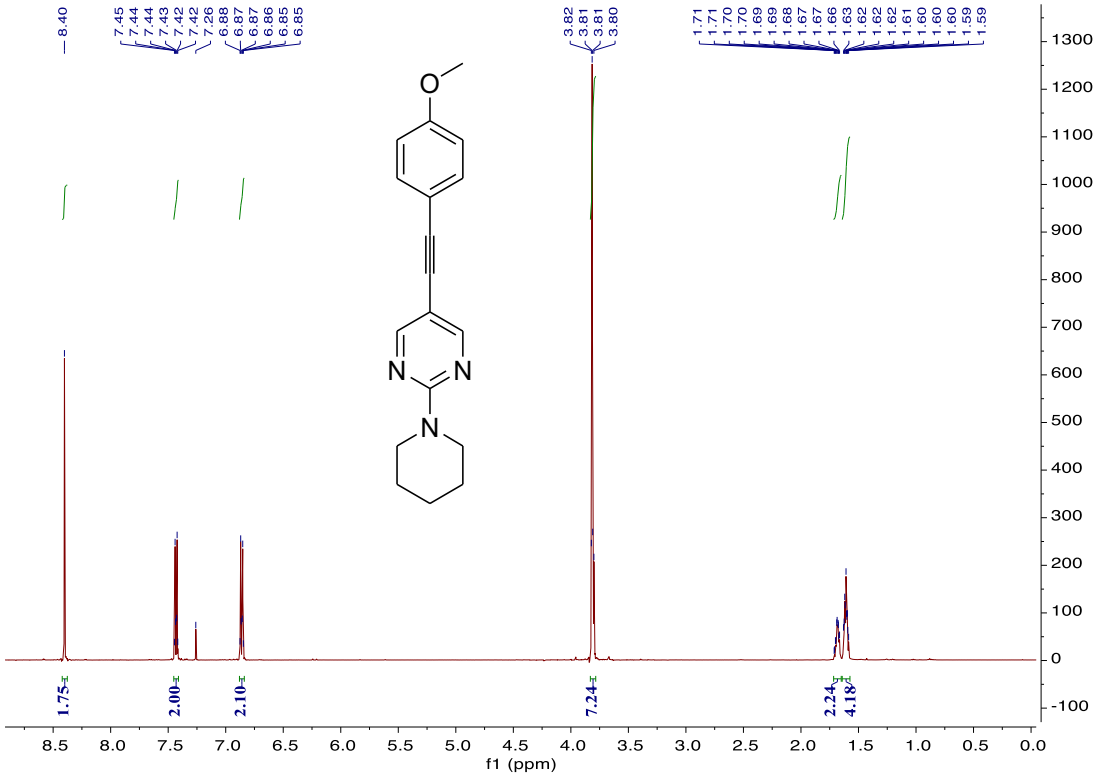
1-Chloro-3-(2-cyclopropylethynyl)-5-(trifluoromethyl)benzene (**12**)

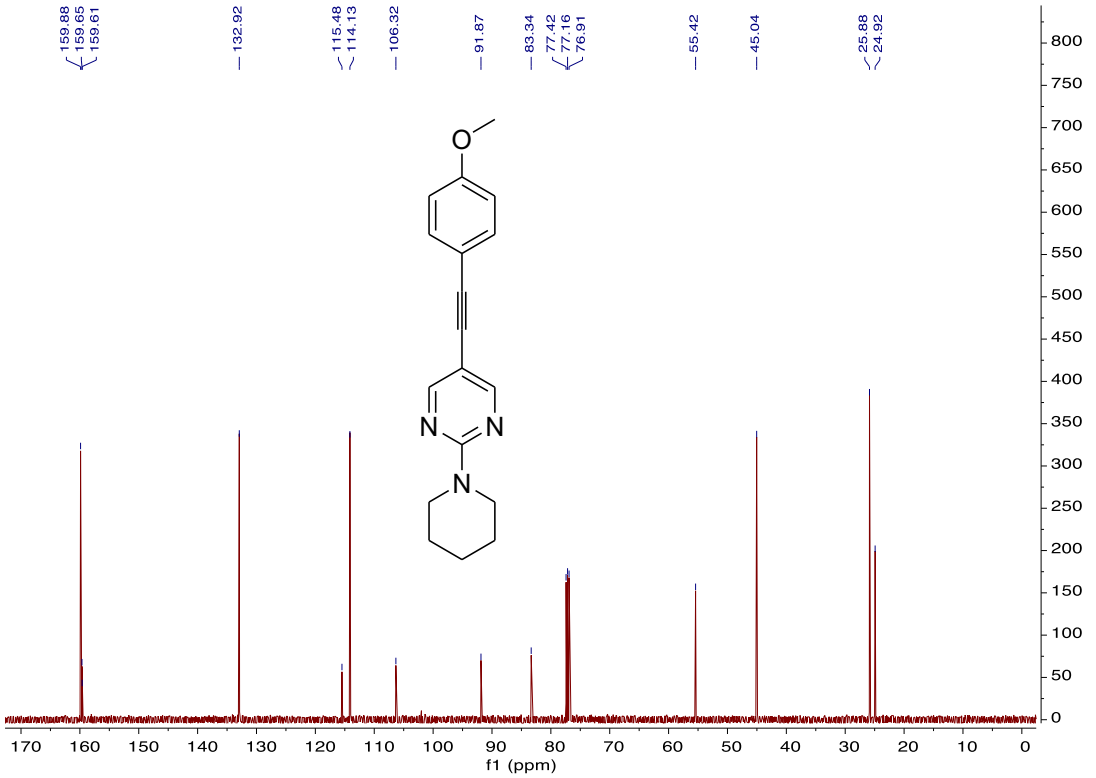




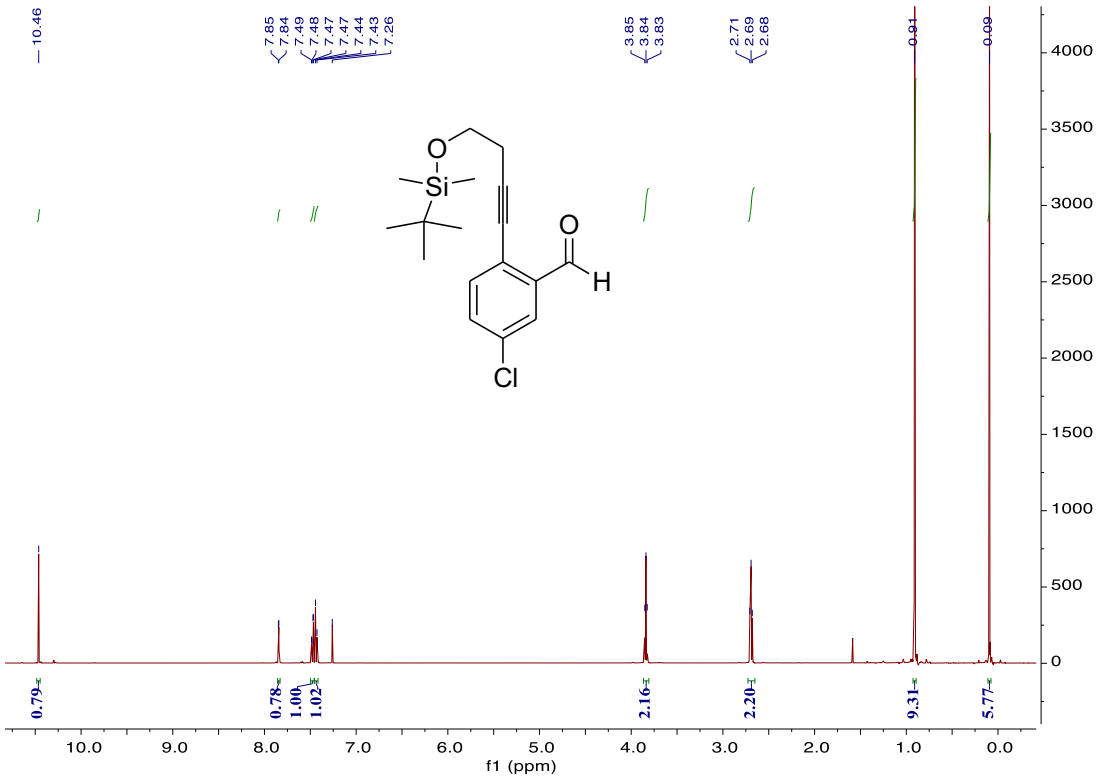


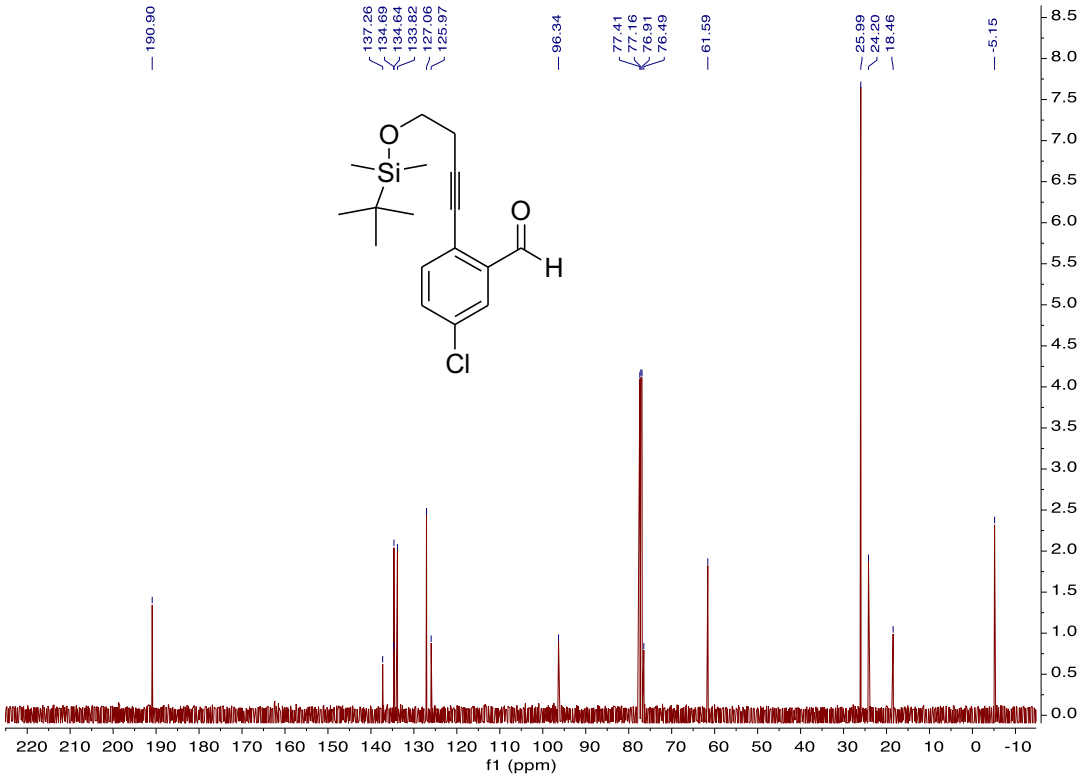
5-(2-(4-Methoxyphenyl)ethynyl)-2-(piperidin-1-yl)pyrimidine (**13**)



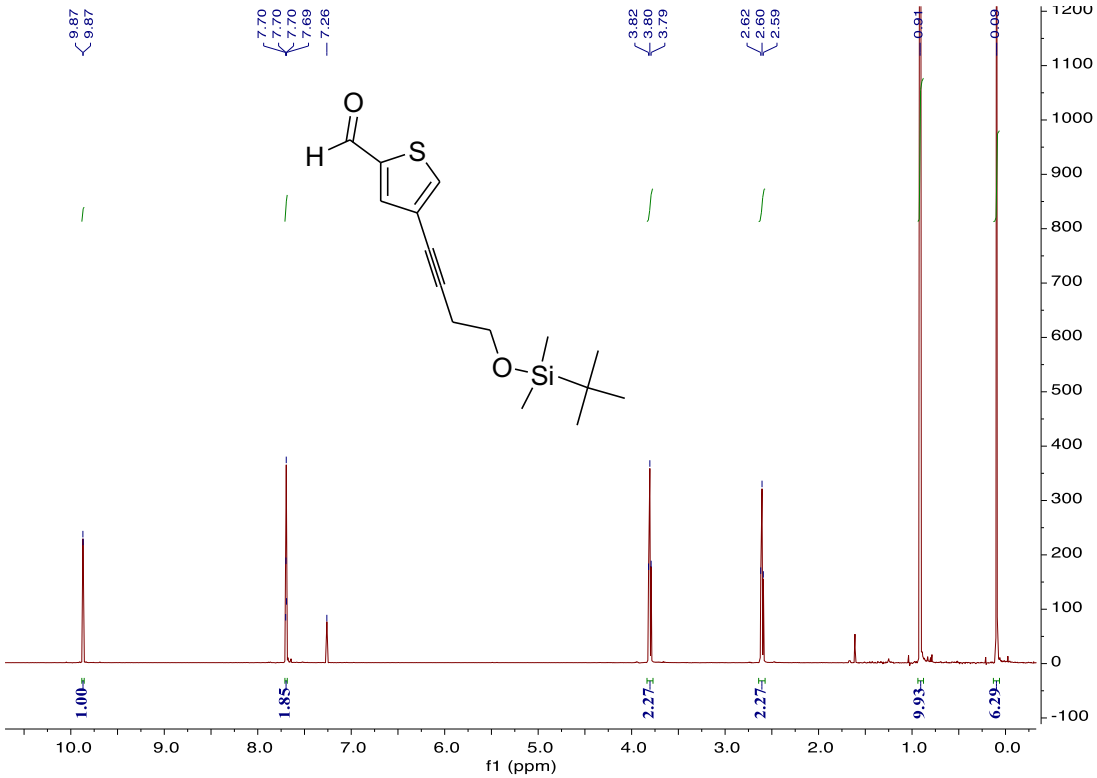


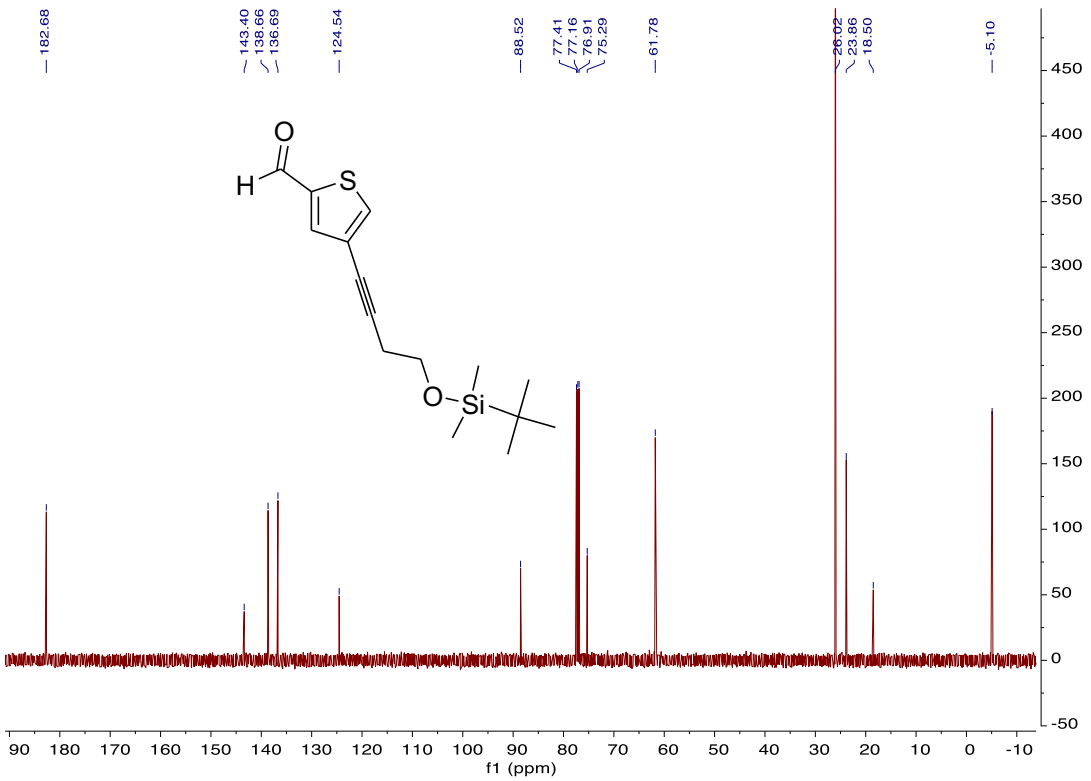
2-(4-(Tert-butyldimethylsilyloxy)but-1-ynyl)-5-chlorobenzaldehyde (**14**)



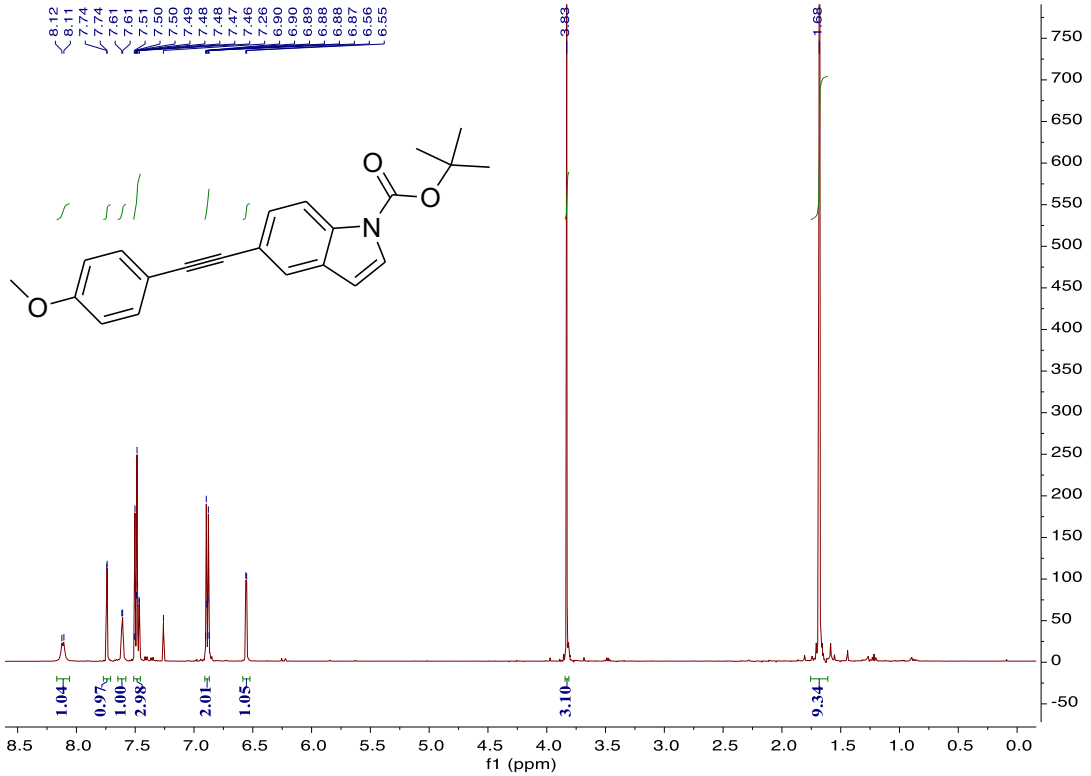


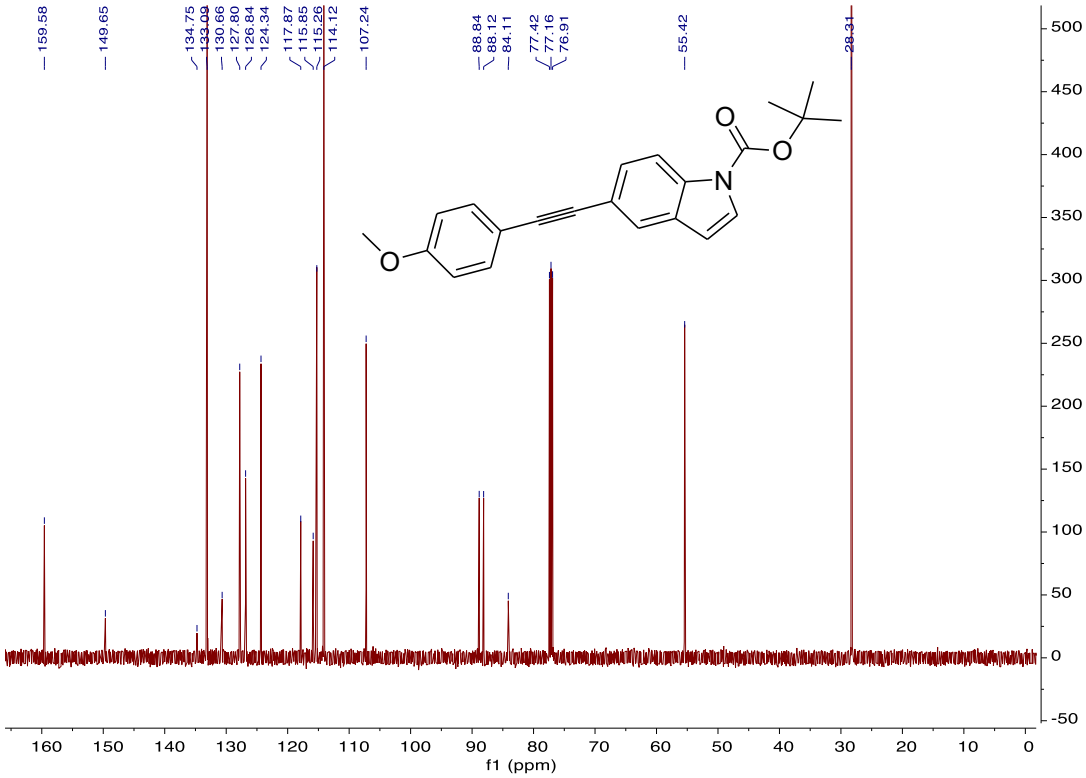
4-(4-(Tert-butyldimethylsilyloxy)but-1-ynyl)thiophene-2-carbaldehyde (**15**)



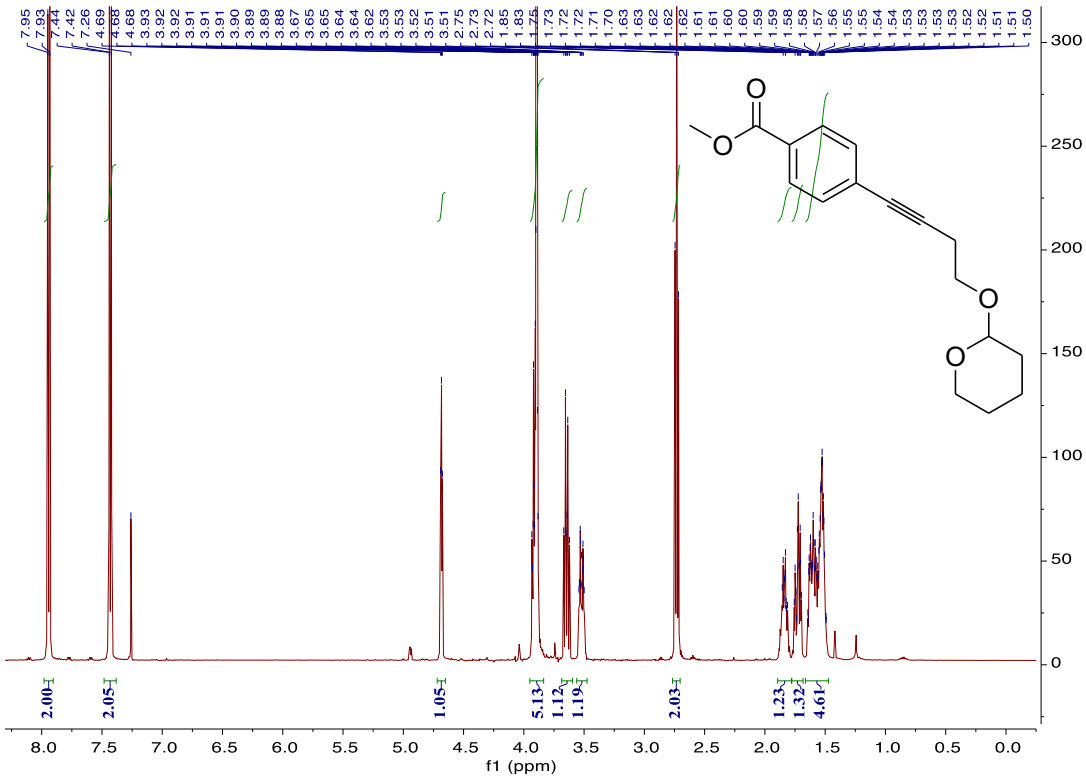


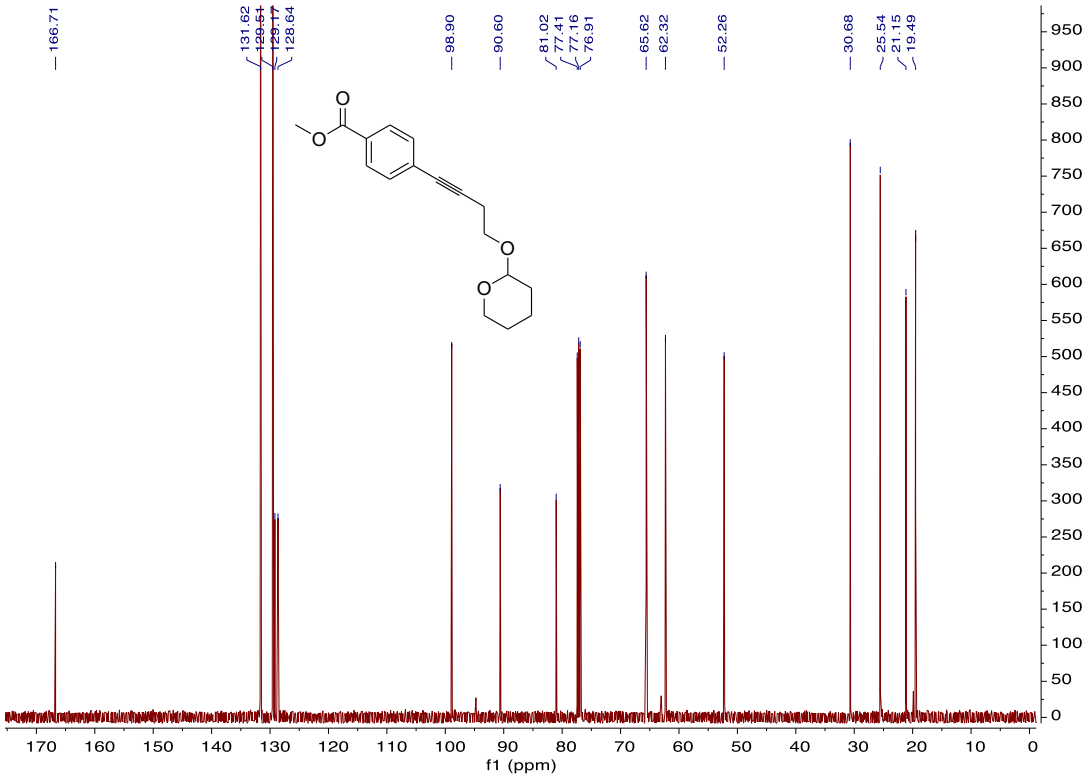
Tert-butyl 5-(2-(4-methoxyphenyl)ethynyl)-1H-indole-1-carboxylate (**16**)



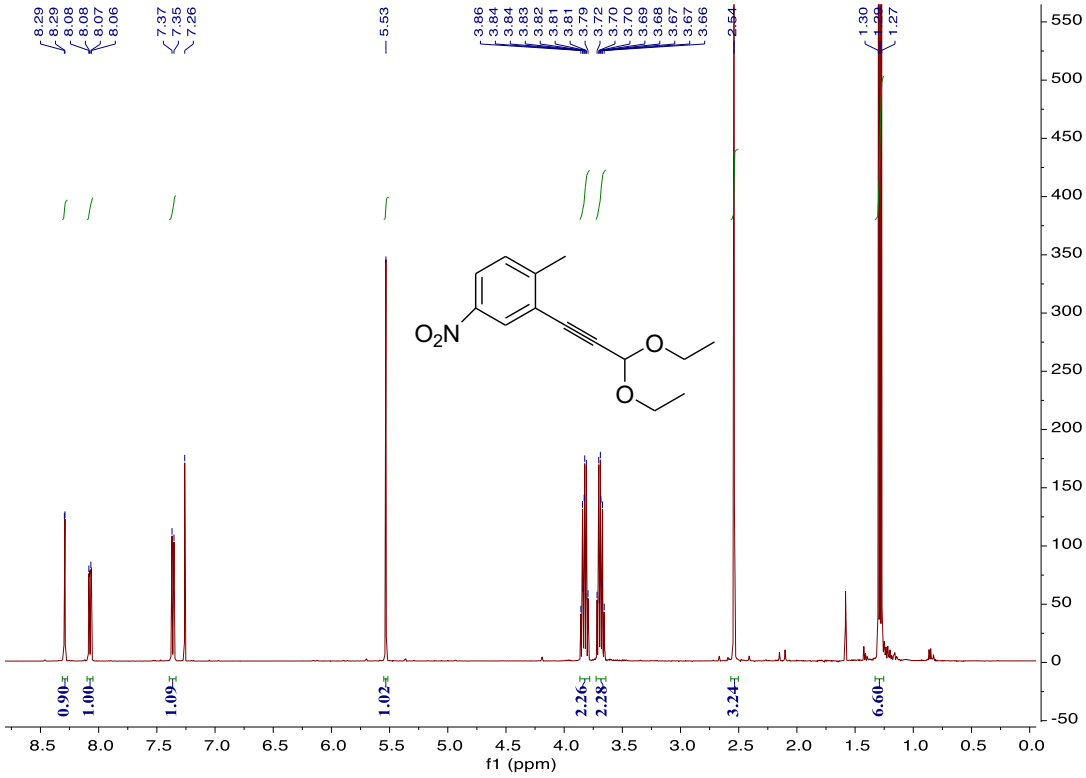


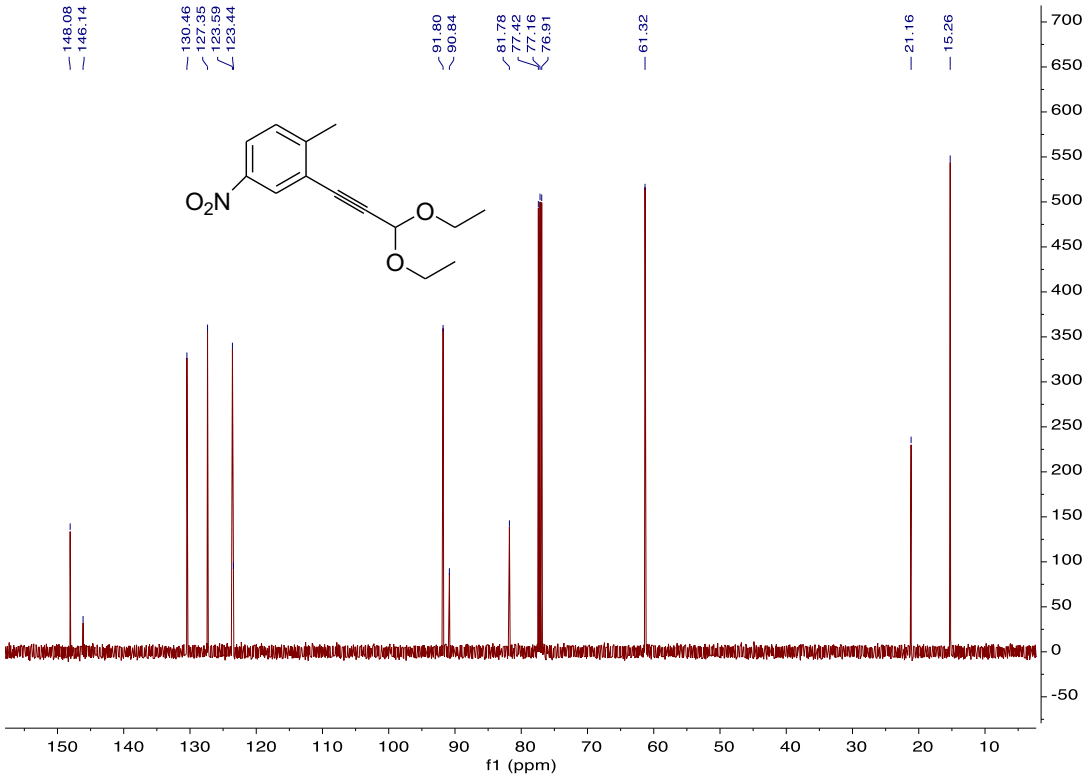
Methyl 4-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-ynyl)benzoate (**17**)



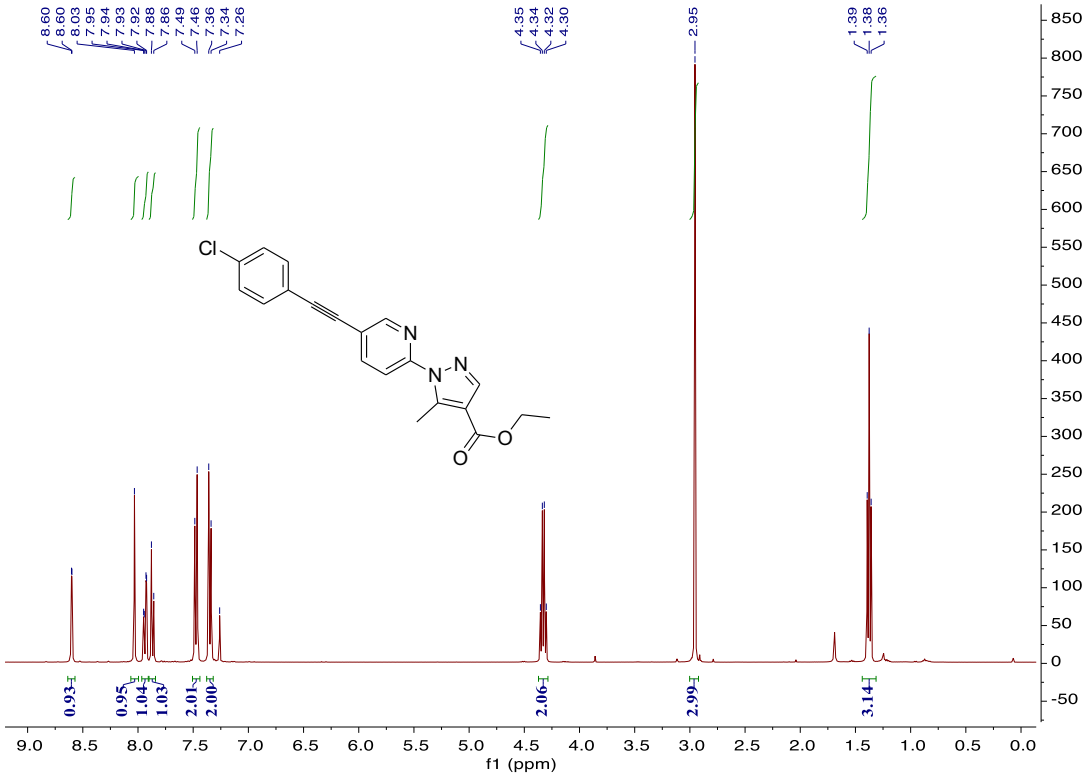


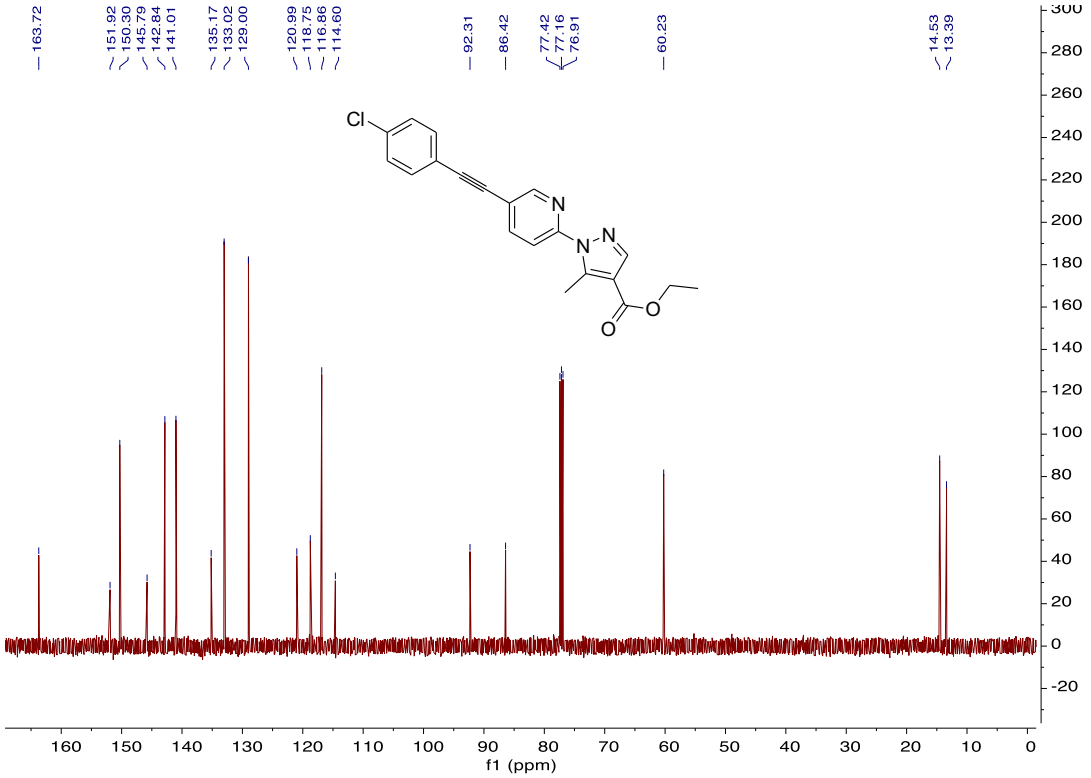
2-(3,3-Diethoxyprop-1-ynyl)-1-methyl-4-nitrobenzene (**18**)



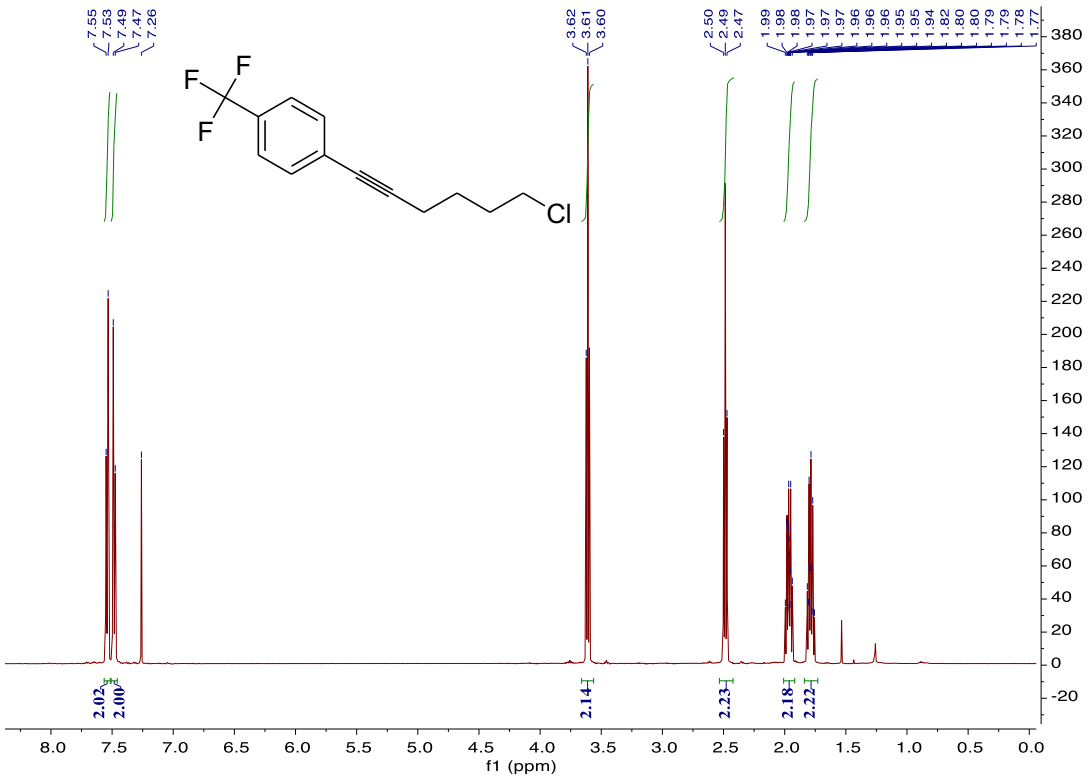


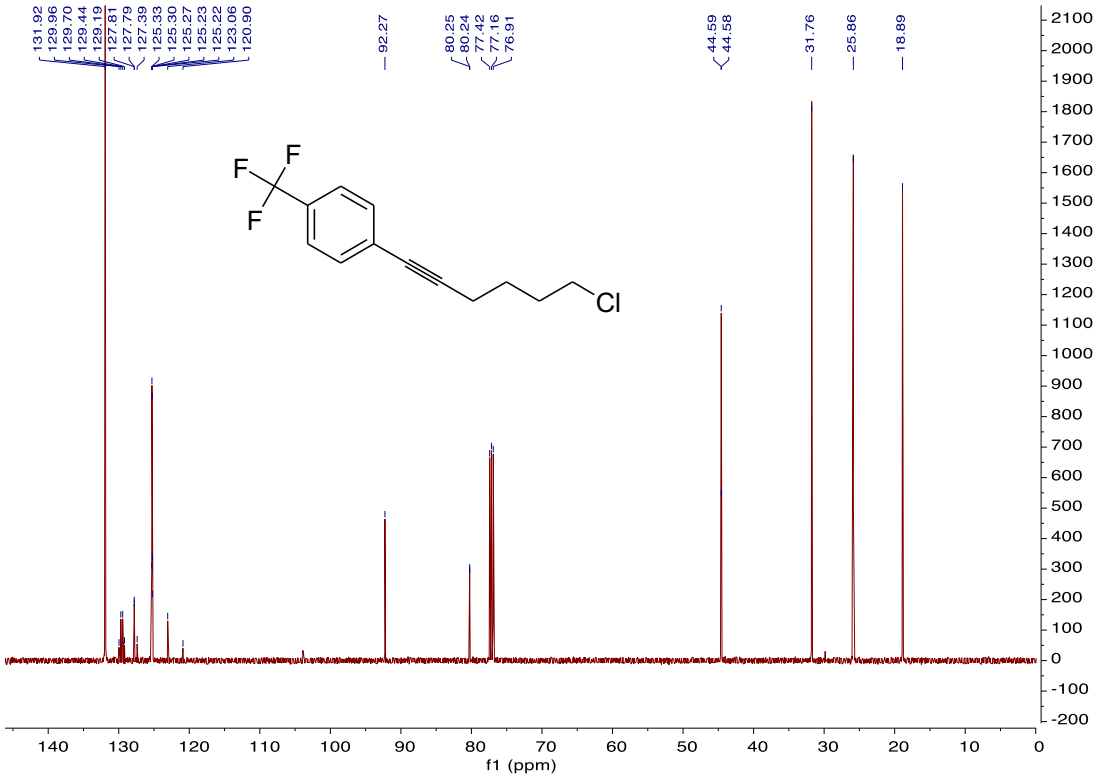
Ethyl 1-(5-(2-(4-chlorophenyl)ethynyl)pyridin-2-yl)-5-methyl-1H-pyrazole-4-carboxylate (**19**)

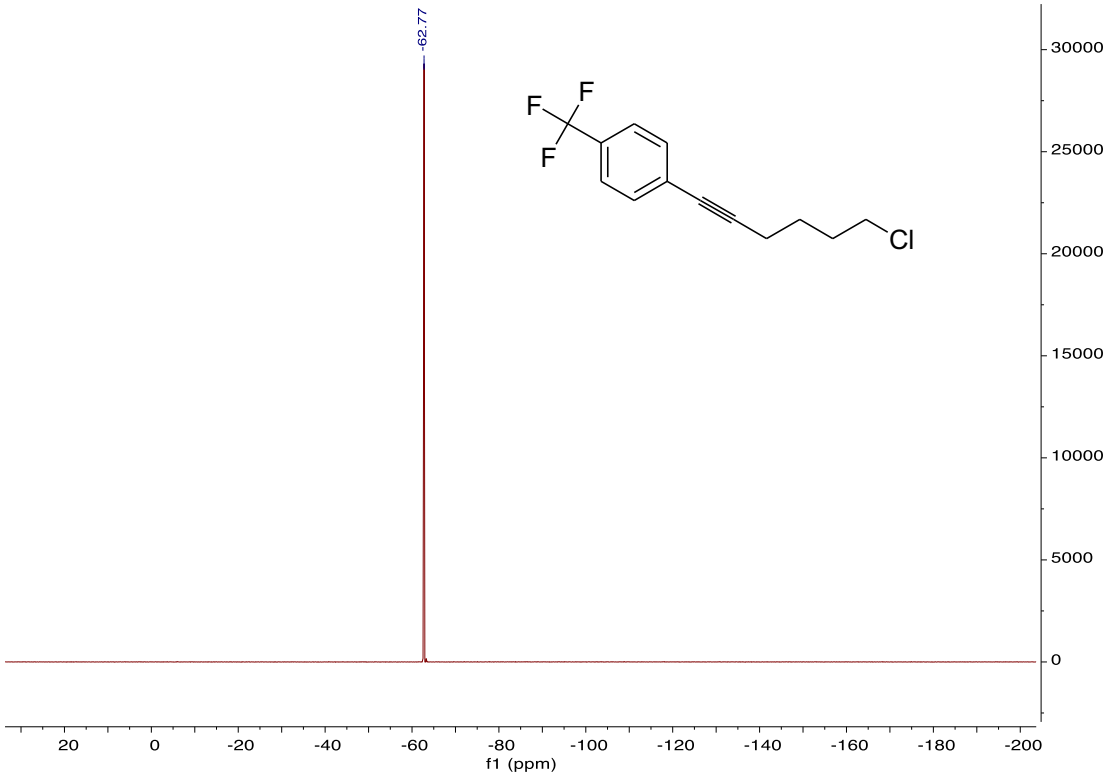




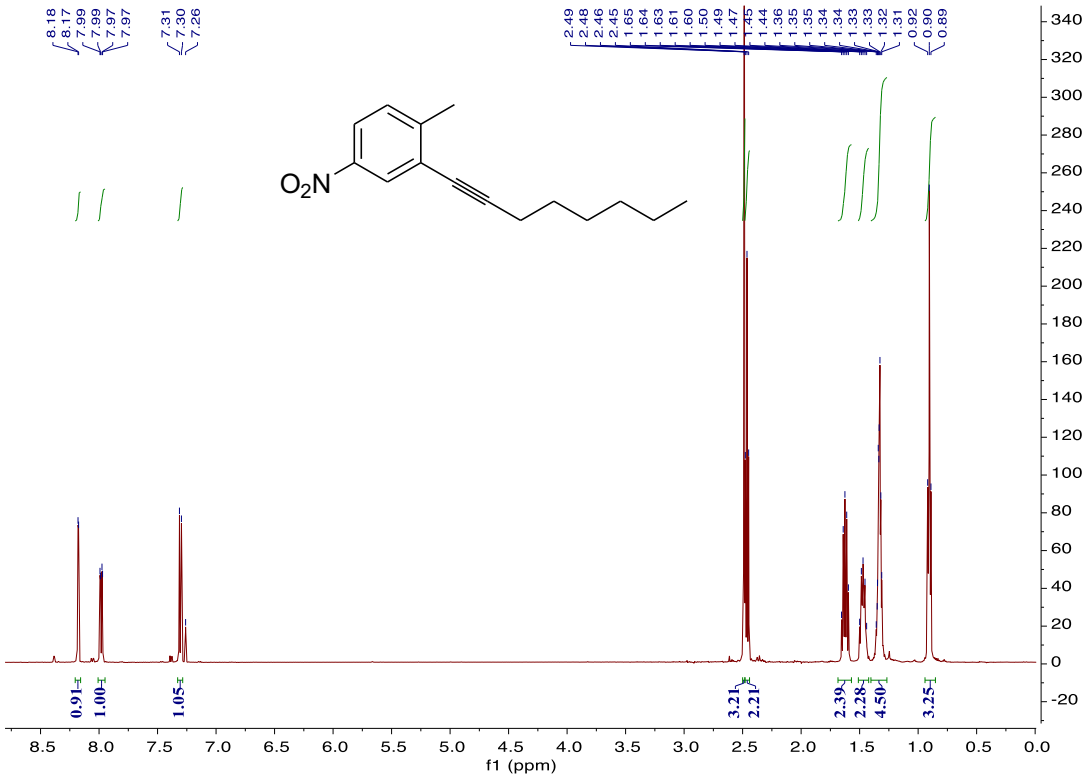
1-(6-Chlorohex-1-ynyl)-4-(trifluoromethyl)benzene (**20**)

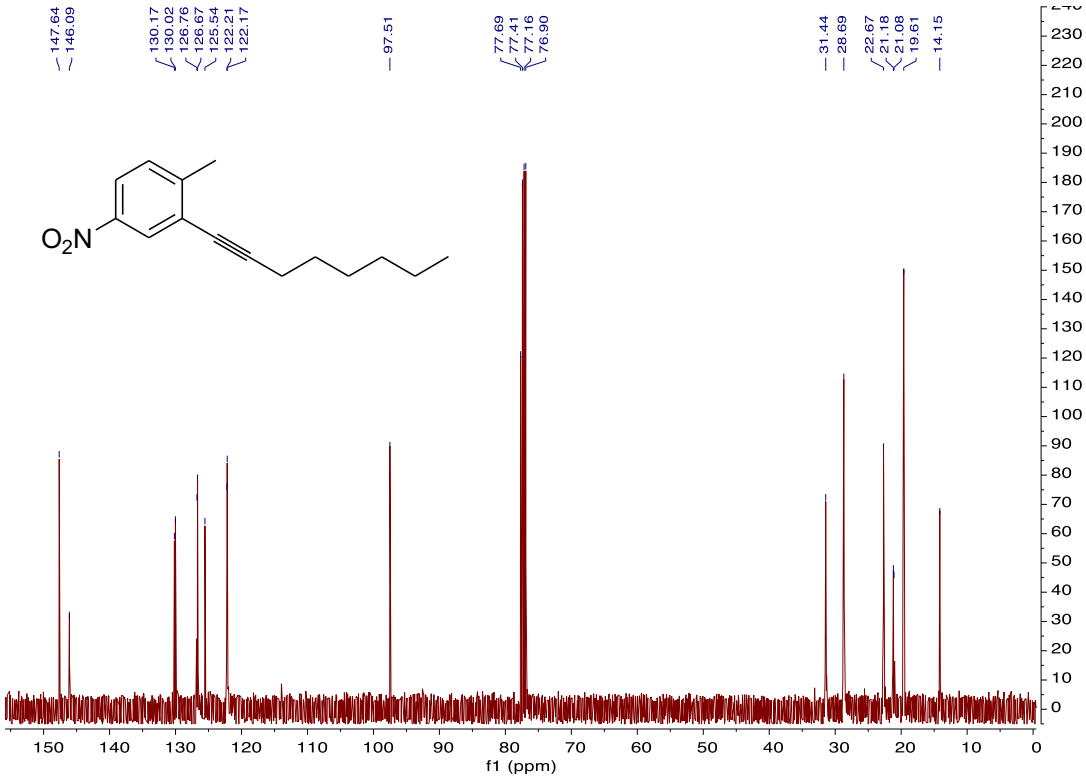



131.92
129.96
129.70
129.44
129.19
127.81
127.79
127.39
125.33
125.30
125.27
125.23
125.22
123.06
120.90
92.27
80.25
80.24
77.42
77.16
76.91
44.59
44.58
31.76
25.86
18.89
F
F
F
Cl
f1 (ppm)

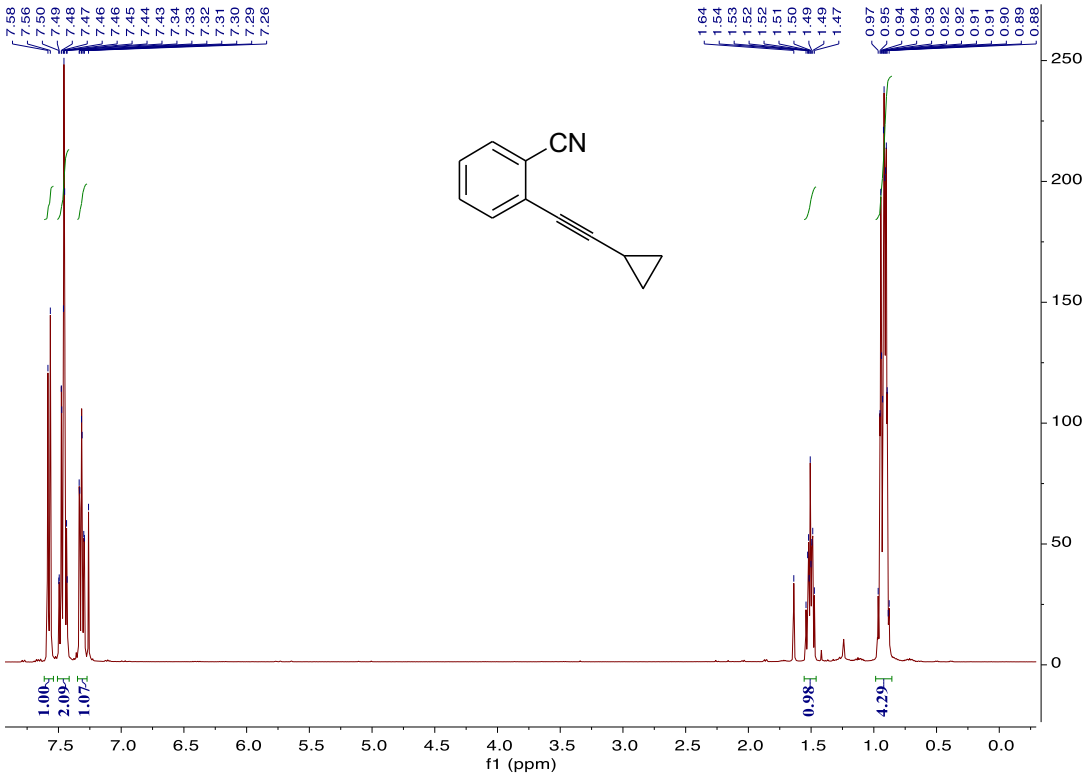

-62.77
F
F
F
Cl
f1 (ppm)

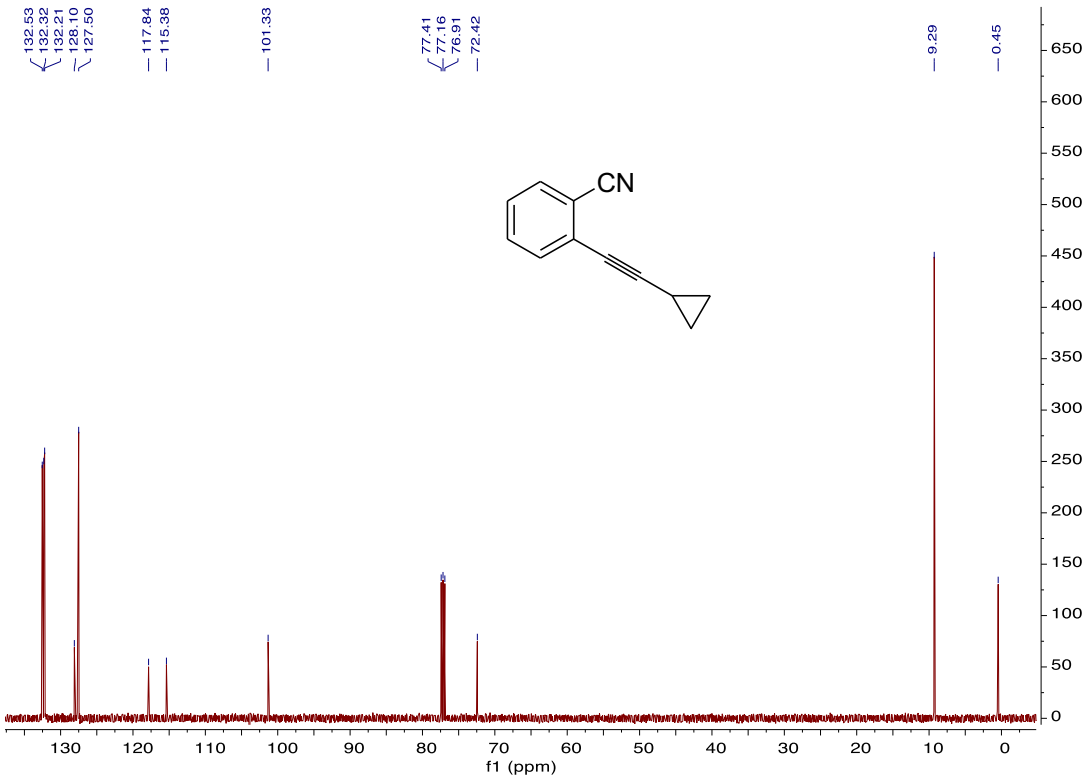
1-Methyl-4-nitro-2-(oct-1-ynyl)benzene (**21**)



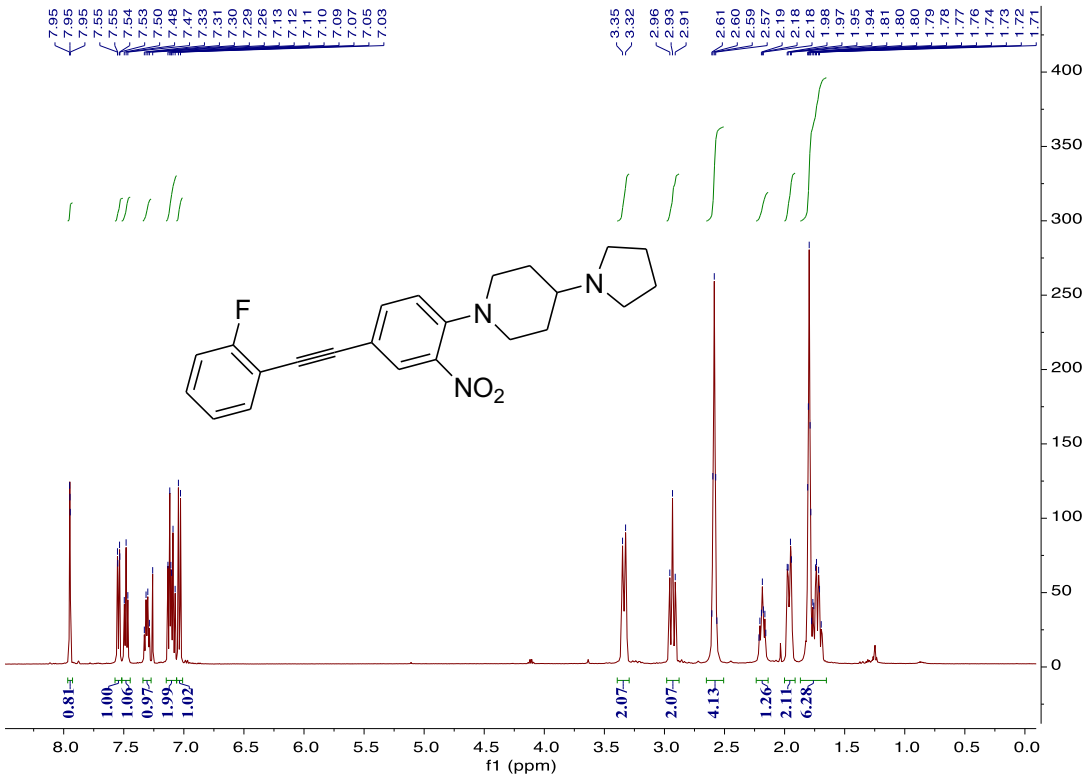


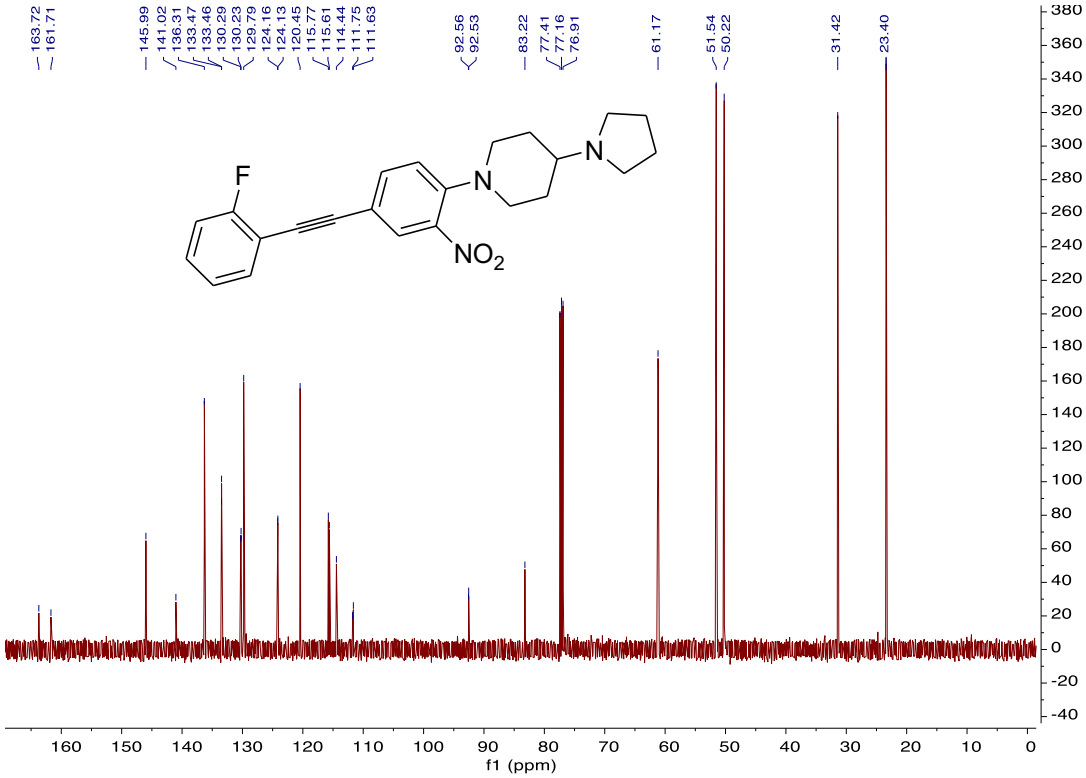
2-(2-Cyclopropylethynyl)benzonitrile (**22**)

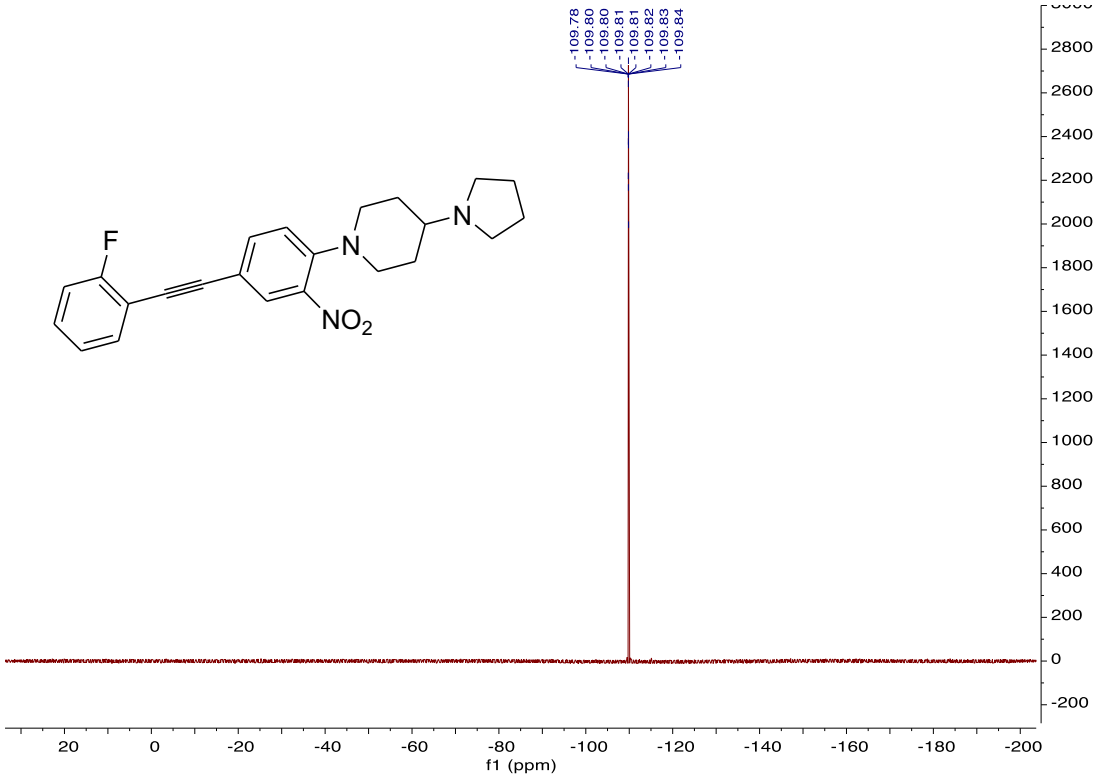




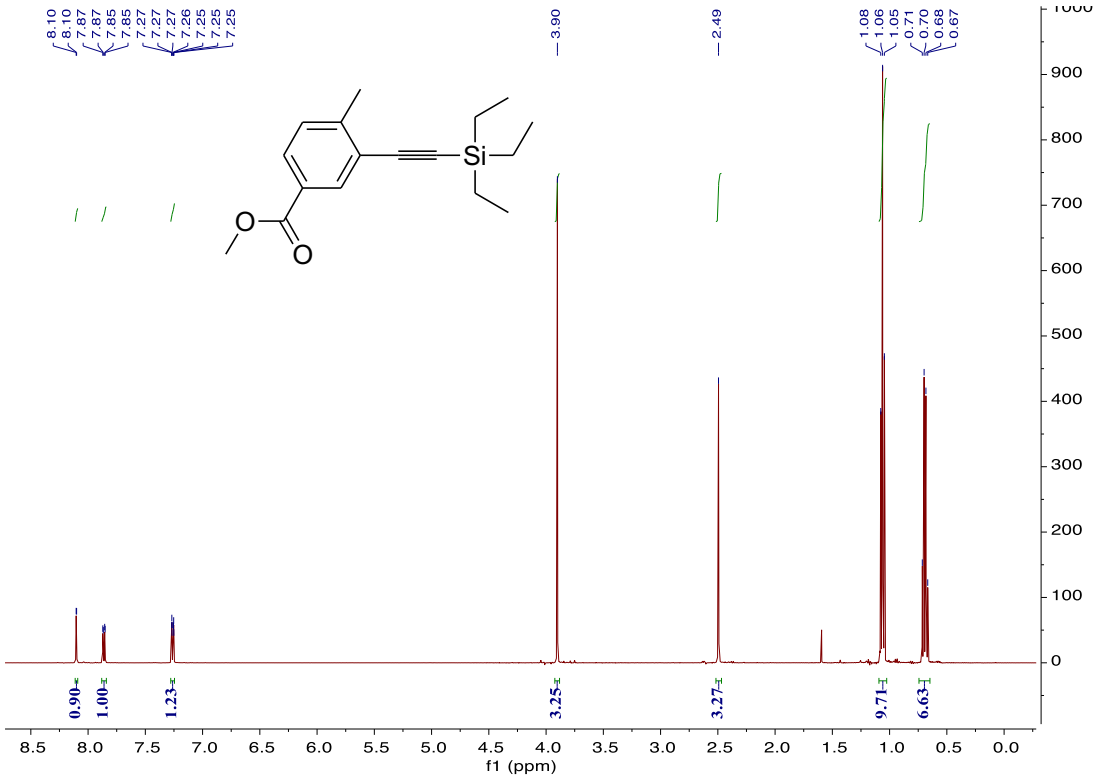
1-(4-(2-(2-Fluorophenyl)ethynyl)-2-nitrophenyl)-4-(pyrrolidin-1-yl)piperidine (**23**)

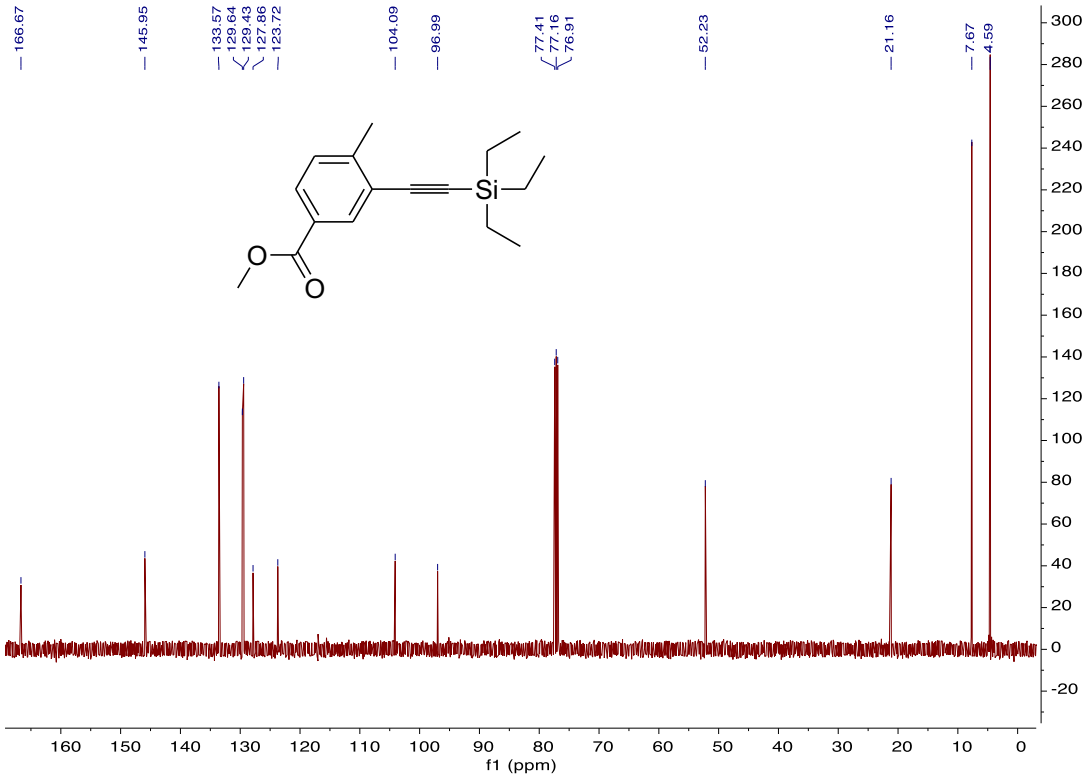




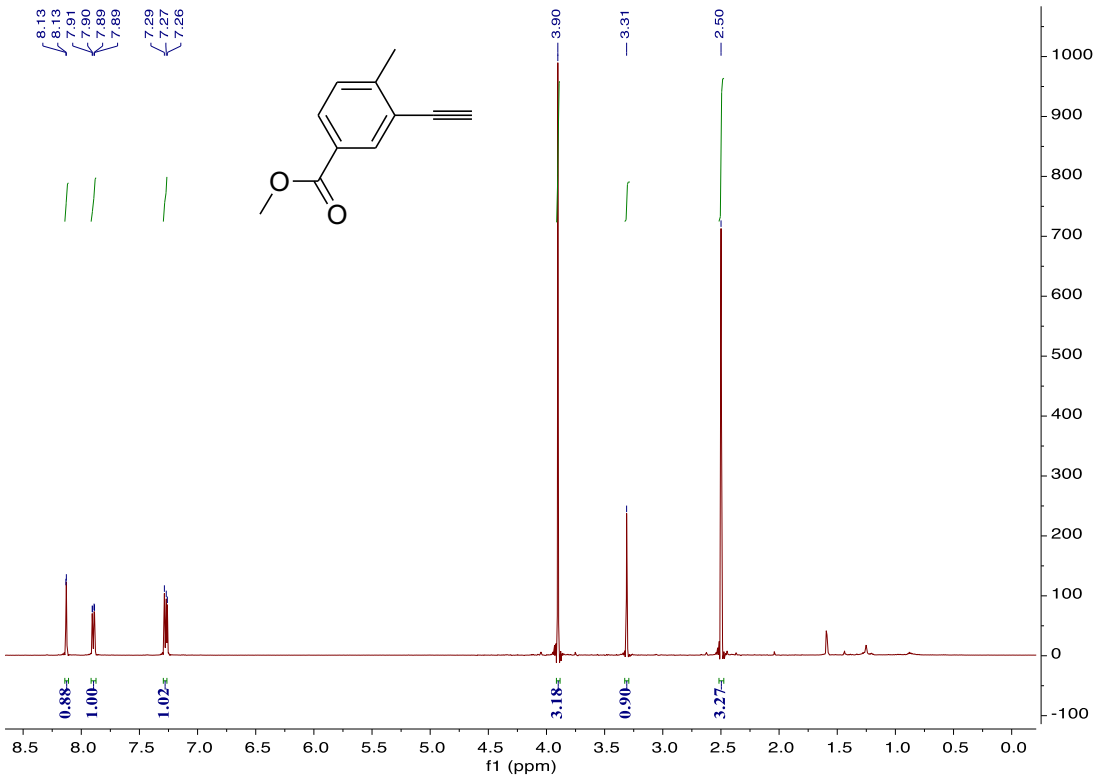


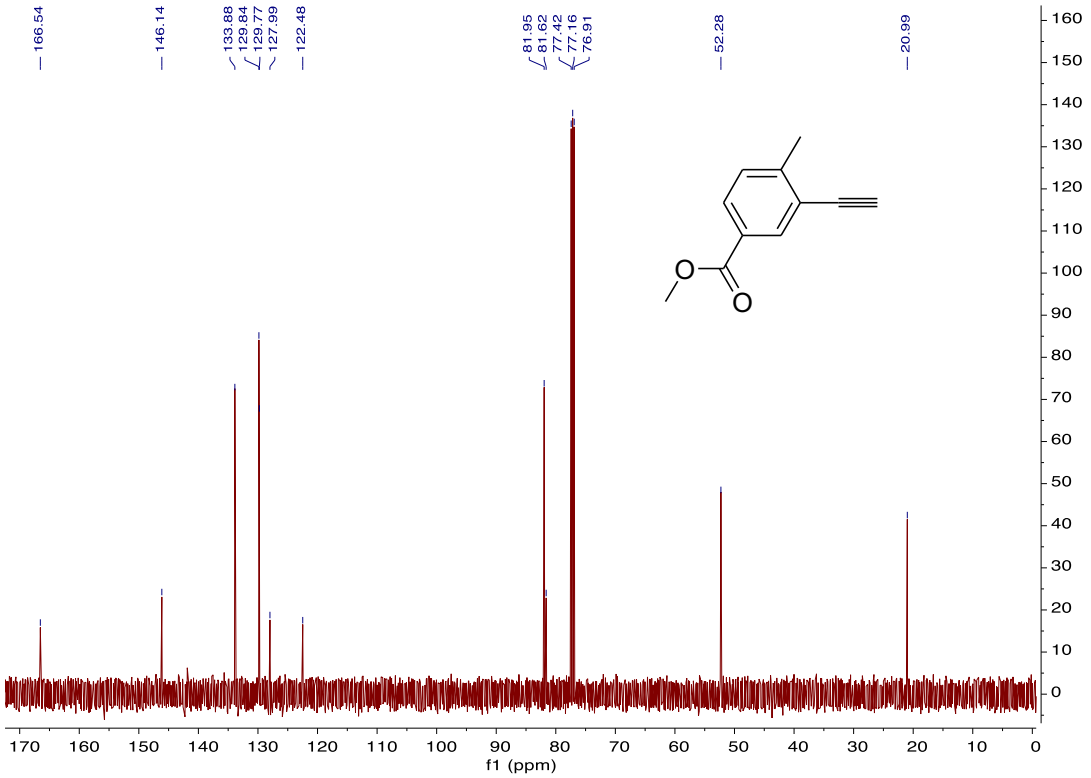
Methyl 4-methyl-3-(2-(triethylsilyl)ethynyl)benzoate (**25**)



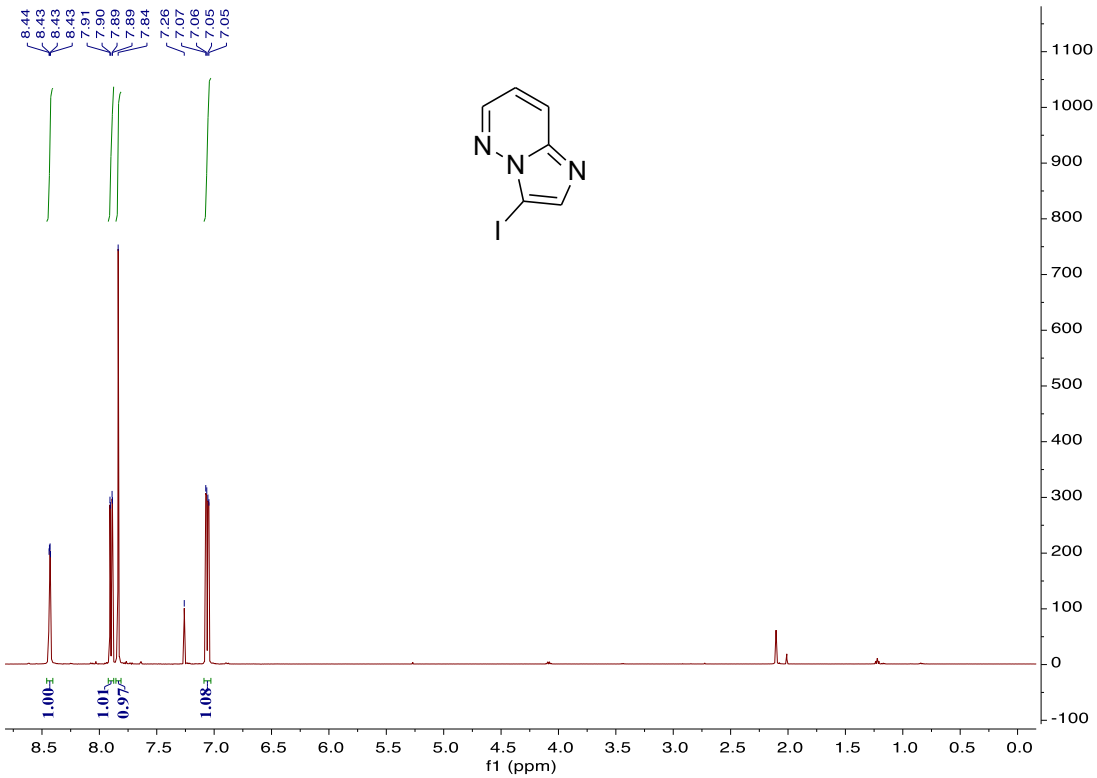


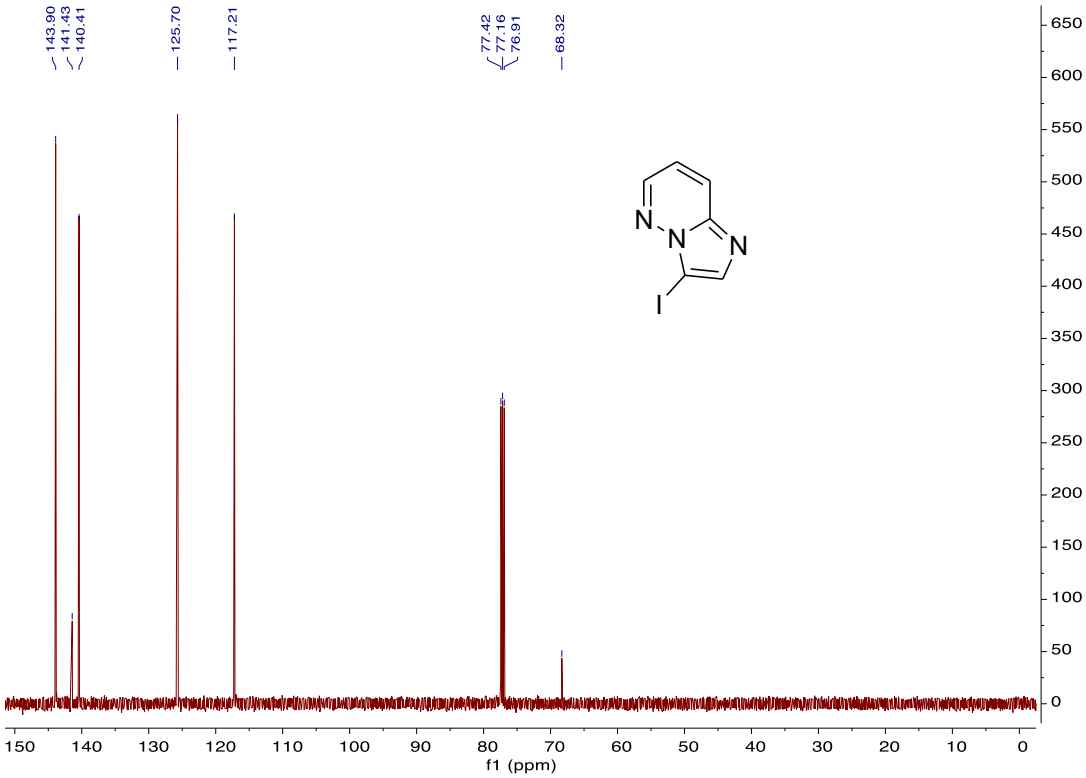
Methyl 3-ethynyl-4-methylbenzoate (**26**)



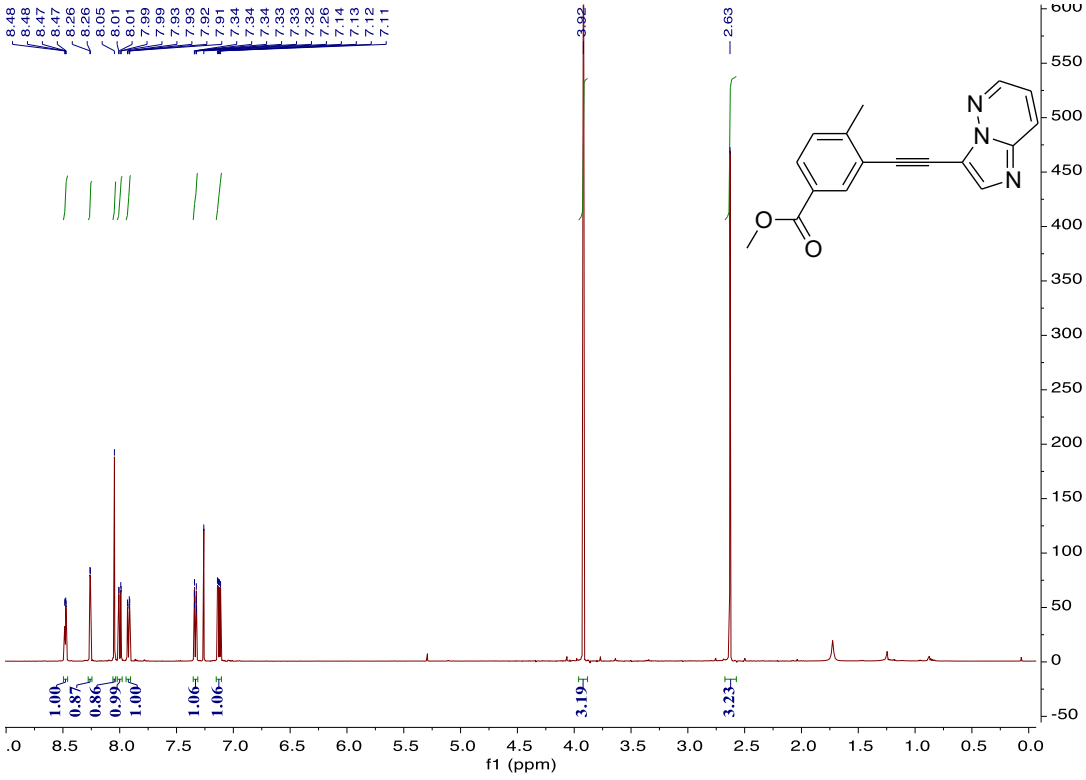


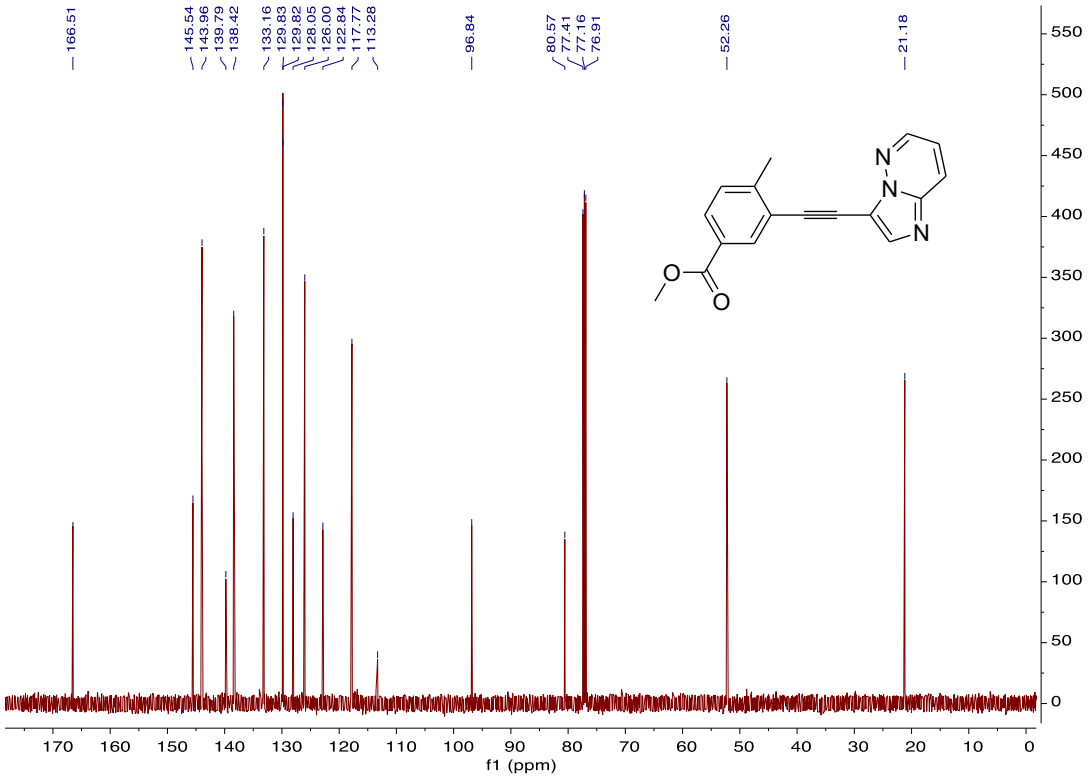
3-Iodoimidazo[1,2-b]pyridazine (**27**)



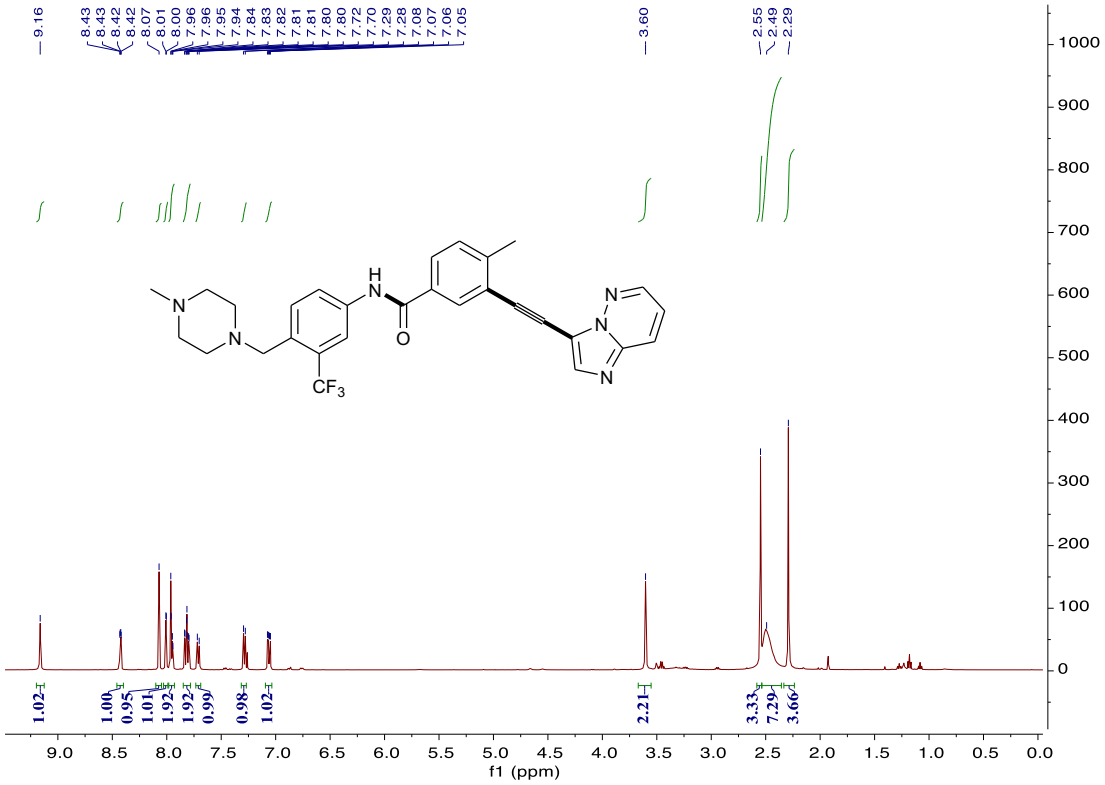


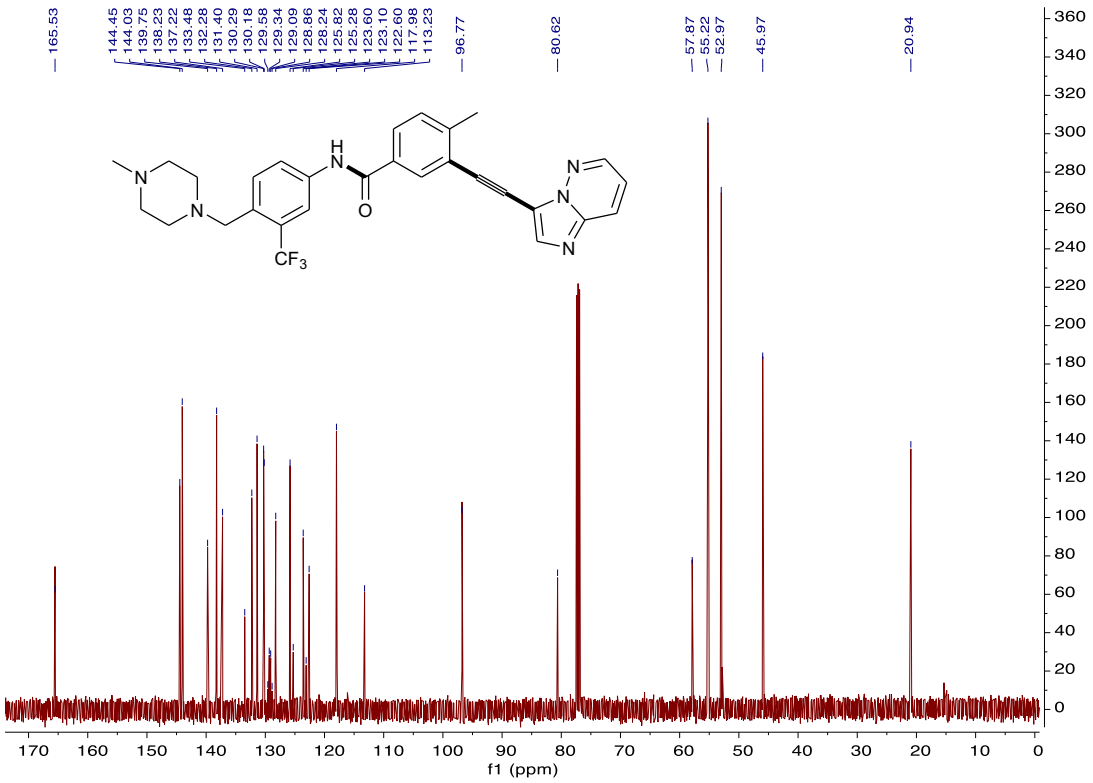
Methyl 3-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)-4-methylbenzoate (**28**)

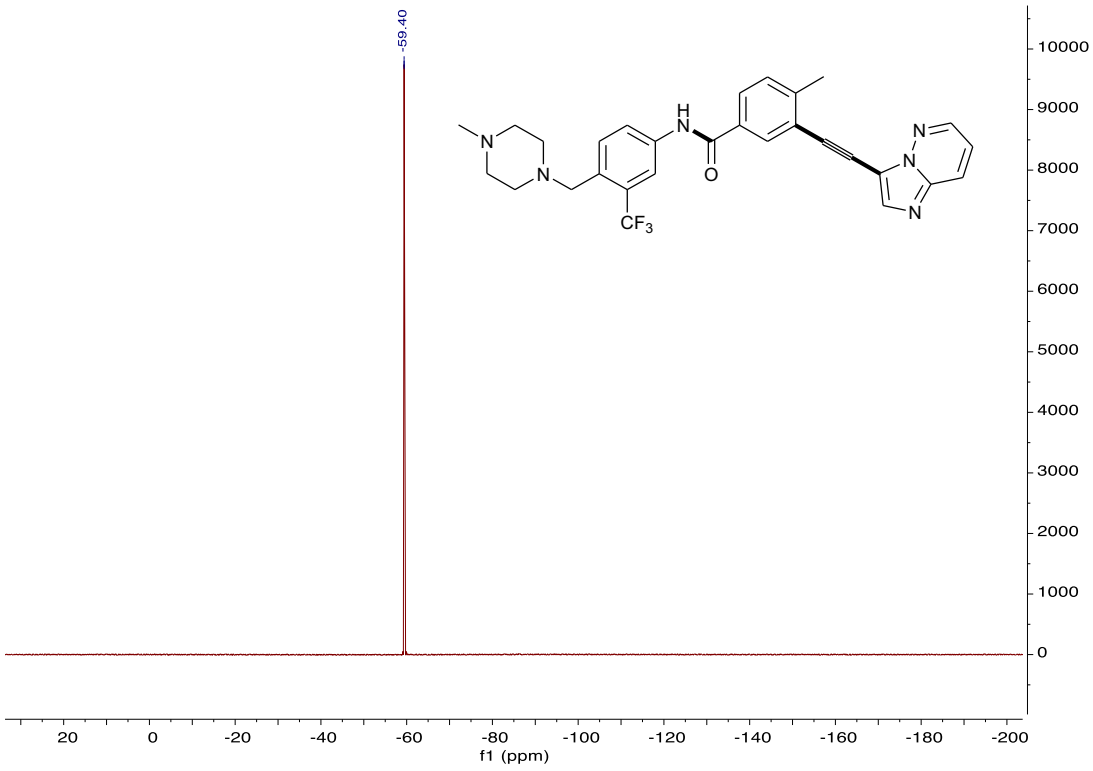



166.51
145.54
143.96
139.79
138.42
133.16
129.83
129.82
128.05
126.00
122.84
117.77
113.28
96.84
80.57
77.41
77.16
76.91
52.26
21.18
f1 (ppm)

Ponatinib


9.16
8.43
8.43
8.42
8.42
8.07
8.01
8.00
7.96
7.96
7.95
7.94
7.84
7.83
7.82
7.81
7.81
7.80
7.80
7.72
7.70
7.29
7.28
7.08
7.07
7.06
7.05
3.60
2.55
2.49
2.29
1.02
1.00
0.95
1.01
1.92
1.92
0.99
0.98
1.02
2.21
3.33
7.29
3.66
f1 (ppm)


165.53
144.45
144.03
139.75
138.23
137.22
133.48
132.28
131.40
130.29
130.18
129.58
129.34
129.09
128.86
128.24
125.82
125.28
123.60
123.10
122.60
117.98
113.23
96.77
80.62
57.87
55.22
52.97
45.97
20.94
f1 (ppm)


-59.40
f1 (ppm)