Inverse Electron-Demand-[4+2]-Cycloadditions of Ynamides: Access to Novel Pyridine Scaffolds

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Supporting information

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1. Material and methods

NMR spectra were recorded on Brucker AV 300 or AV 400 spectrometer at 300 MHz or 400 MHz for ^{1}H NMR, at 75 or 100 MHz for ^{13}C NMR and at 376 MHz or 282 MHz for ^{19}F NMR. The spectra were calibrated using undeuterated solvent as internal reference, unless otherwise indicated. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad. Coupling constant (*J*) were reported in Hertz. High resolution mass spectra (HRMS) in positive mode were recorded using a 6520 series quadrupole time-of-flight (Q-TOF) mass spectrometer (Agilent) fitted with a multimode ion source (in mixed mode that enables both electrospray ionization, ESI, and atmospheric pressure chemical ionization, APCI). Samples were directly infused into the source using 50/50-methanol/formic acid 0.2 % in water. Melting points were recorded on a Büchi 510 melting point apparatus. Tetrahydrofuran (THF) was distilled under nitrogen from sodium-benzophenone. Reagents were purchased from Aldrich, Apollo Scientific or Alfa Aesar and used without further purification, unless otherwise noted. All non-commercially available homopropargylic alcohols were prepared using literature procedure.[1] Microwave reactions were performed in a CEM Intelligent Explorer (Model 541416) microwave. Yields refer to chromatographically and spectroscopically (^{1}H, ^{13}C and ^{19}F NMR) homogeneous materials, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck TLC silica gel 60 F254 aluminum plates, using UV light or potassium permanganate as visualizing agents. All separations were performed by chromatography on Merck silica gel 60 (40-63 μm), on a Combiflash Companion from Teledyne Isco or by preparative TLC chromatography (layer thickness of 500 μm).

2. Experimental details and analytical data

General procedure A: SNAr of 2-chloro-4-trifluoromethylpyrimidine.

Sodium hydride (1.4 eq., 1.1 g, 28.0 mmol) was suspended in THF (65 mL, 0.3 M) at 0 °C under nitrogen in a round bottom flask equipped with a magnetic stirring bar. Homopropargylic alcohol (1.4 eq., 2.1 mL, 28.0 mmol) was then added and the solution left stirring for 30 minutes. 2-Chloro-4-trifluoromethylpyrimidine **1a** (1 eq., 2.4 mL, 20.0 mmol) was added dropwise and a colour change from yellow to deep red was observed. Once the addition was complete, the solution was left stirring at room temperature for 17 hours until complete consumption of the starting materials as indicated by TLC. The reaction mixture was concentrated in vacuo and quenched with water and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude product was purified using flash chromatography on silica gel (Petroleum ether/EtOAc: 7:3). **2a** was isolated as colourless oil (4 g, 94 %).

General procedure B: Synthesis of ynamide 3f using Stahl's conditions.

In a round bottomed flask flushed with oxygen and equipped with a magnetic stirrer bar were placed oxazolidinone (5 eq., 262 mg, 3.0 mmol), $CuCl_2$ (2 eq., 161 mg, 1.2 mmol) and Cs_2CO_3 (2 eq., 392 mg, 1.2 mmol). DMSO (2.9 mL) was then added via syringe and the suspension was heated at 70 °C, under an atmosphere of oxygen (balloon). A solution of alkyne **2f** (1 eq., 100 mg, 0.6 mmol) in DMSO (2.9 mL) was then slowly added to the reaction mixture via syringe pump addition over 4 hours and then stirring was continued at 70 °C until TLC showed complete consumption of alkyne **2f**. The reaction mixture was allowed to cool to room temperature and pyridine (2.4 mL, 50 eq) was added and the solution was stirred for ten more minutes. The reaction mixture was quenched with water and the aqueous layer was extracted using AcOEt. The combined

[1] a) F. Lehrich, H. Hopf, J. Grunenberg, *Eur. J. Org. Chem.* **2011**, *2011*, 2705-2718; b) J. Fu, H. Shang, Z. Wang, L. Chang, W. Shao, Z. Yang, Y. Tang, *Angew. Chem. Int. Ed.* **2013**, *52*, 4198-4202; c) T. O. Painter, J. R. Bunn, F. J. Schoenen, J. T. Douglas, V. W. Day, C. Santini, *J. Org. Chem.* **2013**, *78*, 3720-3730.

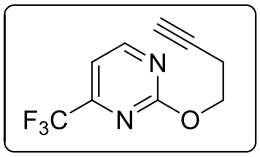
organic phases were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified using flash chromatography on silica gel (Petroleum ether/EtOAc: 8/2). **3f** was isolated as a white solid (116 mg, 77 %).

General procedure C: [4+2] cycloaddition of ynamide 3a under microwave conditions.

In a microwaveable tube equipped with a magnetic stirrer bar, ynamide **3a** (1 eq., 30 mg, 0.01 mmol) was dissolved in sulfolane (2.4 ml, 0.04 M) that had been dried over molecular sieves (4 Å). The tube was sealed, placed in the microwave and heated at either 210 °C for 30 minutes or 255 °C for 1 minute, both with a maximal power of 300 W. After completion of the reaction, the mixture was then quenched with warm saturated solution of K_2CO_3 (50 °C). The aqueous phase was extracted with methyl *t*-butyl ether. The combined organic phases were washed warm water (50 °C), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified using flash chromatography on silica gel (Petroleum Ether/EtOAc: 7/3). **4a** was isolated as a yellow solid (16 mg, 60 %).

2-(But-3-ynyloxy)-4-(trifluoromethyl)pyrimidine (**2a**)

Compound 2a was obtained from the corresponding 2-Chloro-4-trifluoromethylpyrimidine **1a** (3.6 g, 2.38 mL, 19.7 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **2a** was isolated as colorless oil (3.33 g, 78 % yield).



$C_9H_7F_3N_2O$
216,16 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.78 (d, *J* = 4.9 Hz, 1H); 7.29 (d, *J* = 4.9 Hz, 1H); 4.6 (t, *J* = 7.1 Hz, 2H); 2.76 (dt, *J* = 2.6 Hz, 7.1 Hz, 2H); 2.04 (t, *J* = 2.6 Hz, 1H)

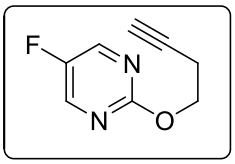
^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 165.2; 162.3; 157.6 (q, *J* = 36.8 Hz, *C*H); 120.2 (q, *J* = 275.0 Hz, *C*F_3); 110.9; 79.9; 70.3, 66.1; 19.0

^{19}F NMR ($CDCl_3$, 376MHz, ppm) δ: -65.8 ppm

HRMS-ESI *m/z* calcd for $[M+H]^+$ 217.0583, found 217.0578

2-(But-3-ynyloxy)-5-fluoropyrimidine (**2f**)

Compound 2f was obtained from **1f** (400 mg, 0.2 mL, 3.02 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 8:2), **2f** was isolated as colorless oil (396 mg, 78 % yield). The spectroscopic data obtained for this compound are in agreement with the literature.[2]



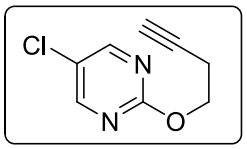
$C_8H_7FN_2O$
166,15 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.78 (s, 2H); 4.58 (t, *J* = 6.9 Hz, 2H); 2.76 (dt, *J* = 2.7 Hz, 7.09 Hz, 2H); 2.04 (t, *J* = 2.7 Hz, 1H)

2-(But-3-ynyloxy)-5-chloropyrimidine (**2i**)

Compound 2i was obtained from **1i** (700 mg, 4.7 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **2a** was isolated as colorless oil (787 mg, 92 % yield).
The spectroscopic data obtained for this compound are in agreement with the literature.[2]

[2] R. E. Martin, F. Morawitz, C. Kuratli, A. M. Alker, A. I. Alanine, *Eur. J. Org. Chem.* **2012**, 47-52.

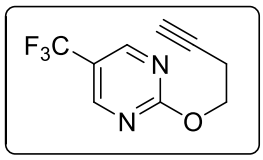


$C_8H_7ClN_2O$
182,61 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.45 (s, 2H); 4.46 (t, J = 7.1 Hz, 2H); 2.71 (dt, J = 2.7 Hz, 7.1 Hz, 2H); 2.02 (t, J = 2.7 Hz, 1H)

2-(But-3-ynyloxy)-5-(trifluoromethyl)pyrimidine (**2j**)

Compound 2j was obtained from the corresponding 2-Chloro-5-trifluoromethylpyrimidine **1j** (250 mg, 1.37 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **2j** was isolated as colorless oil (239 mg, 81 % yield).



$C_9H_7F_3N_2O$
216,16 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.78 (s, 2H); 4.58 (t, J = 7.0 Hz, 2H); 2.76 (dt, J = 2.7 Hz, 7.0 Hz, 2H); 2.04 (t, J = 2.7 Hz, 1H)

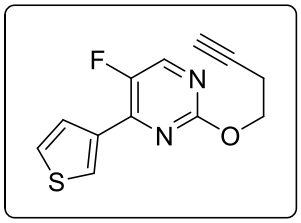
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 166.8; 157.5 (q, J = 3.3 Hz, *C*H); 122.3 (q, J = 270.6 Hz, *C*F_3); 119.7 (q, J = 34.0 Hz, *C*H); 79.9; 70.7; 66.5; 19.3

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -61.4 ppm

HRMS-ESI *m/z* calcd for $[M+H]^+$ 217.0583, found 217.0576

2-(But-3-ynyloxy)-5-fluoro-4-(thiophen-3-yl)pyrimidine (**2k**)

Compound 2k was obtained from 2-(but-3-ynyloxy)-5-fluoro-4-(thiophen-3-yl)pyrimidine (200 mg, 0.932 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 9:1), **2k** was isolated as colorless oil (185 mg, 84 % yield).



$C_{12}H_9FN_2OS$
248,28 g/mol

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.37 (d, J = 3.0 Hz, 1H); 8.27 (m, 1H); 7.86 (d, J = 4.8 Hz, 1 H); 7.40 (dd, J = 3.0 Hz, 5.3 Hz, 1 H); 4.51 (t, J = 7.3 Hz, 2H); 2.75 (dt, J = 2.6 Hz, 7.3 Hz, 2H); 2.04 (t, 2.6 Hz, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 160.8; 151.6 (d, J = 259 Hz, *C*F_3); 149.3; 147.7; 135.1; 130.59 (d, J = 11.0 Hz, *C*H); 127.7 (d, J = 5.1 Hz, *C*H); 126.3; 80.4; 70.4; 66.0; 19.4

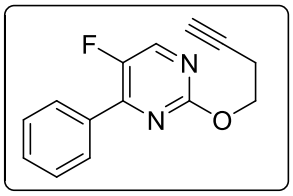
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -148.1 ppm

HRMS-EIC *m/z* calcd for $[M+H]^+$ 249.0472, found 249.0485

2-(But-3-ynyloxy)-5-fluoro-4-phenylpyrimidine (**2l**)

Compound 2l was obtained from 2-chloro-5-fluoro-4-phenylpyrimidine[3] (284 mg, 1.43 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 9:1), **2l** was isolated as colorless oil (234 mg, 71 % yield).

[3] G. I. Stevenson, A. Garavelas, K. L. Cosgrove, K. A. Reynolds, N. C. Franken, L. R. Whittell, H. P. Wijesekera, WO2014/41349 A1

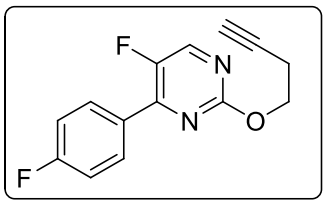


$C_{14}H_{11}FN_2O$
242,25 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.42 (d, J = 3.1 Hz, 1H); 8.15-8.12 (m, 2H); 7.53-.749 (m, 3H); 4.55 (t, J = 7.3 Hz, 2H); 2.77 (dt, 3.2 Hz, 7.3 Hz, 2H); 2.05 (t, J = 3.2 Hz, 1H)

2-(But-3-ynyloxy)-5-fluoro-4-(4-fluorophenyl)pyrimidine (**2m**)

Compound 2m was obtained from 2-chloro-5-fluoro-4-(4-fluorophenyl)pyrimidine[3] (500 mg, 2.21 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 9:1), **2m** was isolated as colorless oil (274 mg, 48 % yield).

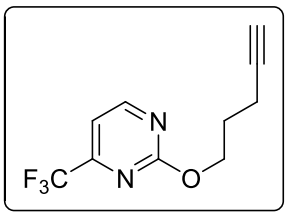


$C_{14}H_{10}F_2N_2O$
260,24 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.36 (d, J = 3.2 Hz, 1H); 8.12 (dd, J = 5.5, 8.5 Hz, 2H); 7.14 (t, J = 8.5 Hz, 2H); 4.48 (t, J = 7.4 Hz, 2H); 2.72 (d, J = 2.7, 7.4 Hz, 2H), 2.03 (t, J = 2.7 Hz, 1H)

2-(Pent-4-ynyloxy)-4-(trifluoromethyl)pyrimidine (**2n**)

Compound 2n was obtained from the corresponding 2-chloro-4-trifluoromethylpyrimidine **1a** (1 g, 0.66 mL, 7.67 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **2n** was isolated as colorless oil (1.01 g, 80 % yield).



$C_{10}H_9F_3N_2O$
230,19 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.78 (d, J = 4.9 Hz, 1H); 7.30 (d, J = 4.9 Hz, 1H); 4.57 (t, J = 6.9 Hz, 2H); 2.76 (dt, J = 3.1, 6.9 Hz, 2H); 2.04 (m, 2H), 1.9 (t, J = 2.1 Hz, 1H)

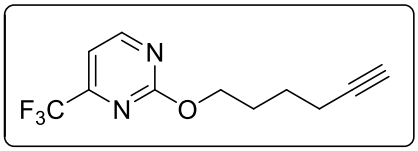
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 165.7; 162.2; 157.8 (q, J = 39.0 Hz, *C*H); 120.3 (q, J = 275.0 Hz, *C*F_3); 110.6 (d, J = 2.2 Hz, *C*H); 83.2; 69.2; 67.1; 27.8; 15.3

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -71.4 ppm

HRMS-EIC *m/z* calcd for $[M+H]^+$ 231.0740, found 231.0727

2-(Hex-5-ynyloxy)-4-(trifluoromethyl)pyrimidine (**2o**)

Compound 2o was obtained from the corresponding 2-Chloro-4-trifluoromethylpyrimidine **1a** (200 mg, 0.13 mL, 3.84 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **2o** was isolated as colorless oil (256 mg, 96 % yield).



$C_{11}H_{11}F_3N_2O$
244,21 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.77 (d, J = 4.8 Hz, 1H), 7.26 (d, J = 4.8 Hz, 1H), 4.47 (t, J = 6.4 Hz, 2H), 2.29 (td, J = 2.6 Hz, 6.9 Hz, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.80-1.72 (m, 4H)

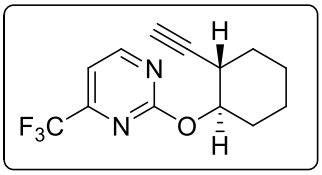
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 165.7; 162.2; 157.8 (q, J = 35.2 Hz, *C*H); 120.3 (q, J = 275.6 Hz, *C*F_3); 110.4 (d, J = 3.3 Hz, *C*H); 83.9; 68.9; 68.1; 27.8; 25.0; 18.2

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: – 71.5 ppm

HRMS-EIC *m/z* calcd for $[M+H]^+$ 245.0812, found 258.0886

2-(2-Ethynylcyclohexyloxy)-4-(trifluoromethyl)pyrimidine (**2p**)

Compound 2p was obtained from the corresponding 2-chloro-4-trifluoromethylpyrimidine **1a** (472 mg, 0.31 mL, 2.6 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **2p** was isolated as colorless oil (554 mg, 79 % yield).



$C_{13}H_{13}F_3N_2O$
270,25 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.75 (d, J = 4.9 Hz, 1H), 7.24 (d, J = 4.9 Hz, 1H), 5.19 (td, J = 3.6 Hz, 8.1 Hz, 1H), 2.79-2.74 (m, 1H), 2.18-2.12 (m, 2H), 2.03 (d, J = 2.4 Hz, 1H), 1.60-1.55 (m, 2H), 1.43-1.36 (m, 4H)

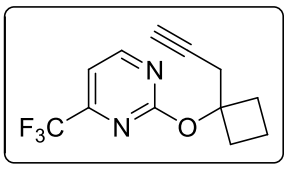
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 165.3; 162.2; 157.9 (q, J = 35.2 Hz, *C*H); 140.8 (q, J = 275.1 Hz, *C*F_3); 110.5; 85.1; 77.9; 70.3; 34.1; 30.1; 29.4; 23.7; 23.0

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -71.4

HRMS-ESI *m/z* calcd for $[M+H]^+$ 271.1140, found 271.1140

2-(1-(Prop-2-ynyl)cyclobutoxy)-4-(trifluoromethyl)pyrimidine (**2r**)

Compound 2r was obtained from the corresponding 2-chloro-4-trifluoromethylpyrimidine **1a** (828 mg, 0.55 mL, 4.5 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 85:15), **2r** was isolated as colorless oil (900 mg, 90 % yield).



$C_{12}H_{11}F_3N_2O$
256,22 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.72 (d, J = 4.7 Hz, 1H), 7.22 (d, J = 4.7 Hz, 1H), 3.02 (d, J = 2.8 Hz, 2H), 2.45 (t, J = 9.1 Hz, 4H), 1.93 (t, J = 2.8 Hz, 1H), 1.88-1.80 (m, 1H), 1.78-1.68 (m, 1H)

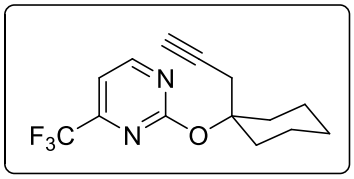
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 163.9, 162.0, 157.3 (q, J = 36.7 Hz, *C*H), 121.4 (q, J = 275.1 Hz, *C*F_3), 110.2 (q, J = 2.9 Hz, *C*H), 82.0, 79.6, 69.8, 33.3, 25.4, 13.3

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -71.6

HRMS-ESI *m/z* calcd for $[M]^+$ 256.0823, found 256.0829

2-(1-(Prop-2-ynyl)cyclohexyloxy)-4-(trifluoromethyl)pyrimidine (**2s**)

Compound 2s was obtained from the corresponding 2-chloro-4-trifluoromethylpyrimidine **1a** (396 mg, 0.26 mL, 2.17 mmol) following the general procedure A. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **2s** was isolated as colorless oil (309 mg, 50 % yield).



$C_{14}H_{15}F_3N_2O$
284,28 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.74 (d, J = 4.8 Hz, 1H); 7.23 (d, J = 4.8 Hz, 1H); 3.11 (d, J = 2.8 Hz, 2H); 2.49 (d, J = 12.1 Hz, 2H); 1.94 (t, J = 2.8 Hz, 1H); 1.76-1.26 (m, 8H)

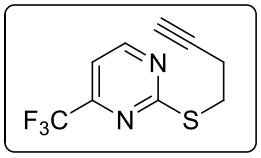
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 165.0; 162.1; 167.5 (q, 32.3 Hz, *C*H); 120.4 (q, 273.6 Hz, *C*F_3), 110.4; 84.2; 80.1; 71.1; 34.3; 28.0; 25.6; 22.0

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -71.4

HRMS-ESI *m/z* calcd for $[M]^+$ 284.1136, found 284.1145

2-(But-3-ynylthio)-4-(trifluoromethyl)pyrimidine (2**v**)

In a 25 mL dried sealed tube equipped with a magnetic stirring bar were placed 4-(trifluoromethyl)-2-pyrimidinethiol (1 eq., 400 mg, 2.22 mmol) and K_2CO_3 (2 eq., 614 mg, 4.44 mmol) dissolved in THF (4.4 mL). Then 4-bromobut-1-yne (1 eq., 295 mg, 2.22 mmol) was added to the stirring mixture which was allowed to react at 80 °C for 17 hours until complete consumption of the starting materials as indicated by TLC. The reaction mixture was concentrated in vacuo and quenched with water and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude product was purified using flash chromatography on silica gel (Petroleum ether/EtOAc: 6:4). **2v** was isolated as colourless oil



$C_9H_7F_3N_2S$
232,23 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.75 (d, , J = 5.0 Hz, 1H); 7.28 (d, J = 5.0 Hz, 1H); 3.32 (t, J = 7.2 Hz, 2H); 2.6 (dt, J = 2.6, 7.2 Hz); 2.04 (t, J = 2.6 Hz, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 173.7; 159.8; 156.0 (q, J = 36.2 Hz); 120.4 (q, J = 274.4 Hz); 112.2 (d, J = 2.7 Hz); 82.3; 70.1; 30.3; 19.2

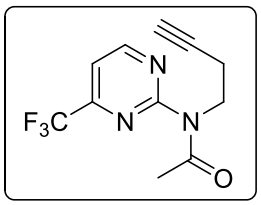
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: – 71.4

HRMS-EIC *m/z* calcd for $[M+H]^+$ 233.0355, found 233.0357

N-(But-3-ynyl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)acetamide (2**w**)

Sodium hydride (1 eq., 116 mg, and 2.9 mmol) was suspended in THF (9.6 mL, 0.3 M) at 0 °C under nitrogen in a round bottom flask equipped with a magnetic stirring bar. 4-Aminobut-3-yne (1 eq., 200 mg, 2.9 mmol) was then added and the solution left stirring for 30 minutes. 2-Chloro-4-trifluoromethylpyrimidine **1a** (1 eq., 0.35 mL, 2.9 mmol) was added dropwise. Once the addition was complete, the solution was left stirring at 50 °C for 17 hours until complete consumption of the starting materials as indicated by TLC. The reaction mixture was concentrated in vacuo and quenched with water and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude was then dissolved in acetic anhydride (18 mL, 0.2 M) in a 25 mL dried sealed tube equipped with a magnetic stirring bar. A drop of sulfuric acid was added and the mixture was allowed to stir overnight at 80 °C. When complete consumption of the starting materials as indicated by TLC was observed the reaction was quenched with water and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and

concentrated in vacuo. The resulting crude product was purified using flash chromatography on silica gel (Petroleum ether/EtOAc: 6:4). **2w** was isolated as colourless oil (513 mg, 55 % over two steps)



$C_{11}H_{10}F_3N_3O$
257,21 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.87 (d, J = 5.0 Hz, 1H); 7.34 (d, J = 4.9 Hz, 1H); 4.32 (t, J = 7.3 Hz, 2H); 2.59 (dt, 2.8, 7.2 Hz, 2H); 2.54 (s, 3H); 1.9 (t, J = 2.1 Hz, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 172.6; 161.4; 160.7; 156.5 (t, J = 35.7 Hz); 120.3 (q, J = 273.9 Hz); 111.8 (d, J = 2.2 Hz); 81.5; 70.1; 44.8; 26.8; 18.4

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: −71.3

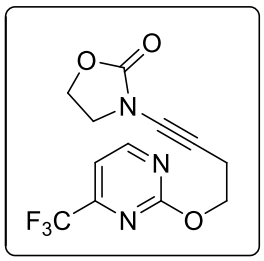
HRMS-EIC *m/z* calcd for $[M+H]^+$ 258.0849, found 258.0856

3-(4-(4-(Trifluoromethyl)pyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3a**)

Compound 3a was either obtained from **2a** (400 mg, 1.3 mmol) following the general procedure B or according to Evano's conditions.[4]

From procedure B: After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 6:4), **3a** was isolated as a white solid (136 mg, 45 % yield).

From Evano's conditions: In a 100 mL round bottom flask equipped with a magnetic stirrer were placed 2-(but-3-yn-1-yloxy)-4-trifluoromethylpyrimidine (1 eq., 1.6 g, 7.4 mmol) dissolved in a mixture of ethanol (21 mL) and a 32% hydroxyamonium solution (18 mL). The mixture was stirred for few minutes and then was added CuI (2 eq., 2.8 g, 14.8 mmol) and stirring was allowed to continue until complete consumption of starting material. The crude green mixture was filtrated over büchner and washed with an aqueous solution of NH_4OH (32%), H_2O, ethanol and finally Et_2O. In a 100 mL round bottom flask equipped with a magnetic stirrer was placed the alkynylcopper (1 eq., 1.6 g, 5.7 mmol) and 2-oxazolidinone (5 eq., 2.5 g, 28.7 mmol). MeCN (14.5 mL, 0.4 M) was added and the reaction mixture was allowed to stir under an oxygen atmosphere for few minutes. TMEDA (1 eq., 0.27 mL, 1.79 mmol) was finally added and the mixture was stirred overnight at room temperature under an atmosphere of oxygen. The deep blue crude mixture was concentrated in vacuo and quenched with water. The aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude product was purified by flash chromatography on silica gel (Petroleum ether/EtOAc: 7/3). **3a** was isolated as a white solid (1.47 g, 66 % over two steps).



$C_{12}H_{10}F_3N_3O_3$
301,22 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.78, (d, J = 4.9 Hz, 1H); 7.29 (d, J = 4.9 Hz, 1H); 4.55 (t, J = 7.9 Hz, 2H); 4.42 (t, J = 7.7 Hz, 2H); 3.89 (t, J = 7.9 Hz, 2H); 2.88 (t, J = 7.0 Hz, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 165.4; 162.4; 158.1 (q, J = 34.6 Hz, *C*H); 156.8; 120.3 (q, J = 273.4, *C*F_3); 111.0; 72.0; 67.1; 66.5; 63.3; 47.1; 19.3

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -70.2 ppm

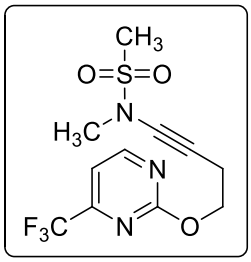
Mp: 97 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 302.0747, found 302.0747

[4] K. Jouvin, J. Heimburger, G. Evano, *Chem. Sci.* **2012**, 756-760

N-Methyl-*N*-(4-(4-(trifluoromethyl)pyrimidin-2-yloxy)but-1-ynyl)methanesulfonamide (**3b**)

Compound 3b was obtained from **2b** (200 mg, 0.925 mmol) and *N*-methyl-*N*-mesylamine following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 1:1), **3b** was isolated as a yellow oil (136 mg, 45 % yield).



$C_{11}H_{12}F_3N_3O_3S$
323,29 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.74 (d, *J* = 4.9 Hz, 1H); 7.26 (d; *J* = 4.9 Hz, 1H); 4.49 (t, *J* = 7.0 Hz, 2H); 3.11 (s, 3H); 3.01 (s, 3H); 2.81 (t, *J* = 7.0 Hz, 2H)

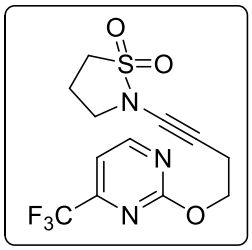
^{13}C NMR ($CDCl_3$, 75 MHz, ppm) *δ*:165.3; 162.4; 157.7 (q, *J* = 36.4 Hz, *C*H); 120.6 (q, 275,9 Hz, *C*F_3); 110.9 (d, *J* = 2.8 Hz, *C*H); 70.0; 66.5; 65.0; 39.2; 36.4; 19.1

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: -70.2 ppm

HRMS-ESI *m/z* calcd for $[M+Na]^+$ 346.0453, found 346.0344

2-(4-{[4-(Trifluoromethyl)pyrimidin-2-yl]oxy}but-1-yn-1-yl)-1,2-thiazolidine-1,1-dione (**3c**)

Compound 3c was obtained from **2c** (200 mg, 0.560 mmol) and 1,2-thiazolidine-1,1-dione following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 1:1), **3c** was isolated as a yellow solid (240 mg, 77 % yield).



$C_{12}H_{12}F_3N_3O_3S$
335,30 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.75 (d, *J* = 4.9 Hz, 1H); 7.28 (d, *J* = 4.9 Hz, 1H); 4.51 (t, 7.0 Hz, 2H); 3.65 (t, *J* = 7.0 Hz, 2H); 2.20 (t, *J* = 7.3 Hz, 2H); 2.84 (t, *J* = 7.0 Hz, 2H); 2.42 (m, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 164.9; 161.9; 157.5 (q, *J* = 35.9 Hz, *C*H); 119.2 (q, *J* = 275.6 Hz, *C*F_3); 110.4 (2.5 Hz, *C*H); 71.2; 66.6; 61.2; 49.4; 45.8; 19.0; 18.9

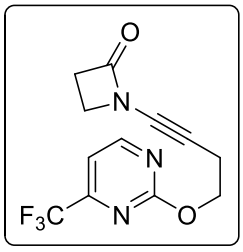
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: -71.2

Mp: 124 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 336.0624, found 336.0627

1-(4-(4-(Trifluoromethyl)pyrimidin-2-yloxy)but-1-ynyl)azetidin-2-one (**3d**)

Compound 3d was obtained from **2d** (377 mg, 1.32 mmol) and azetidinone following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 6:4), **3d** was isolated as a white solid (301 mg, 60 % yield).



$C_{12}H_{10}F_3N_3O_2$
285,22 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.72 (d, *J* = 5.0 Hz, 1H); 7.24 (d, *J* = 5.0 Hz, 1H); 4.46 (t, 7.1 Hz, 2H); 3.53 (d, *J* = 4.6 Hz, 2H); 2.95 (t, *J* = 3.0 Hz, 2H); 2.79 (t, 7.1 Hz, 2H)

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) *δ*:167.4; 165.2; 162.3; 157.8 (q, *J* = 36.4 Hz, *C*H); 122.0 (q, 275.9 Hz, *C*F_3); 110.9 (d, *J* = 2.5 Hz, *C*H), 71.7; 63.34; 65.8; 43.0; 37.8; 19.1

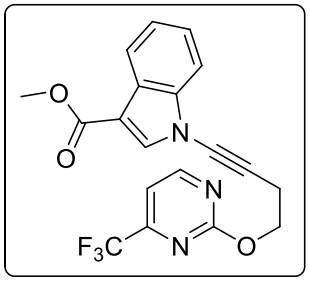
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: -71.2

Mp: 87 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 286.0798, found 286.0802

Methyl 1-(4-(4-(trifluoromethyl)pyrimidin-2-yloxy)but-1-ynyl)-1H-indole-3-carboxylate (**3e**)

Compound 3e was obtained from **2e** (500 mg, 2.31 mmol) and 1H-indole-3-carboxylate following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3e** was isolated as a white solid (451 mg, 50 % yield).



$C_{19}H_{14}F_3N_3O_3$
389,33 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.18 (d, *J* = 5.0 Hz, 1H); 7.54 (m, 1H); 6.94 (m, 1H); 6.79-6.65 (4H); 4.07 (t, *J* = 6.8 Hz, 2H); 3.31 (s, 3H); 2.45 (t, *J* = 6.8 Hz, 2H)

^{13}C NMR ($CDCl_3$, 75 MHz, ppm) *δ*: 165.0; 164.2; 162.0; 157.6 (q, *J* = 35.9 Hz, *C*H); 138.0.; 134.8; 125.0; 124.2; 123.4 (q, 273 Hz, *C*F_3); 123.3; 121.6; 111.2; 110.9; 110.2; 71.9; 67.4; 65.9; 51.1; 18.9

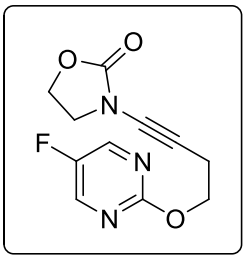
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: -71.2 ppm

Mp: 121 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 390.1060, found 390.1067

3-(4-(5-Fluoropyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3f**)

Compound 3f was obtained from **2f** (100 mg, 0.40 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 6:4), **3f** was isolated as a white solid (116 mg, 77 % yield).



$C_{11}H_{10}FN_3O_3$
251,21g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) ***δ***: 8.30 (s, 2H); 4.36 (t, *J* = 7.5 Hz, 4H); 3.83 (t, *J* = 7.9 Hz, 2H); 2.76 (t, *J* = 7.2 Hz, 2H)

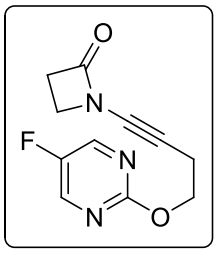
^{13}C NMR ($CDCl_3$, 75 MHz, ppm) ***δ*:** 161.1; 156.5 (d, *J* = 35.9 Hz, *C*H); 152.8; 146.7 (d, *J* = 19.5 Hz, *C*H); 71.7; 67.0; 66.2; 63.2; 47.0; 19.1

^{19}F NMR ($CDCl_3$, 376MHz, ppm) ***δ*:** -150.8

HRMS-ESI *m/z* calcd for $[M+Cl]^+$ 286.1167, found 286.1160

1-(4-(5-Fluoropyrimidin-2-yloxy)but-1-ynyl)azetidin-2-one (**3g**)

Compound 3g was obtained from **2g** (107 mg, 0.45 mmol) and azetidinone following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 6:4), **3g** was isolated as a white solid (40 mg, 57 % yield).



$C_{11}H_{10}FN_3O_2$
235,21 g/mol

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) *δ*: 8.36 (s, 2H); 4.41 (t, *J* = 7.0 Hz, 2H); 3.57 (t, *J* = 5.0 Hz, 2H); 2.99 (t, *J* = 5.0 Hz, 2H); 2.80 (t, *J* = 7.0 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*:167.4, 161.3, 155.9; 153.4 (d, *J* = 19.8 Hz, *C*H); 71.6; 63.3; 66.1; 43.1; 37.0; 19.3

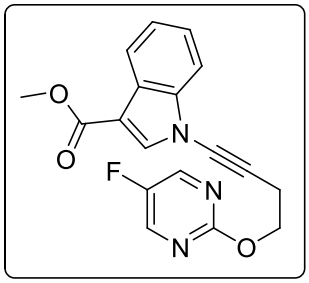
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: -150.7

Mp: 78 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 236.0830, found 236.0860

Methyl 1-(4-(5-fluoropyrimidin-2-yloxy)but-1-ynyl)-1H-indole-3-carboxylate (**3h**)

Compound 3h was obtained from **2h** (790 mg, 2.33 mmol) and 1H-indole-3-carboxylate following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3h** was isolated as a yellow solid (137 mg, 45 % yield).



$C_{18}H_{14}FN_3O_3$
339,32 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.42 (s, 2H); 8.16 (m, 1H); 7.89 (s, 1H); 7.57 (dd, *J* = 1.9 Hz, 6.6 Hz, 1H); 7.38-7.32 (m, 2H); 4.59 (t; *J* = 7.0 Hz, 2H); 3.93 (s, 3H), 3.04 (t, *J* = 7.0 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*:164.80; 161.4; 156.1; 153.6; 147.1 (d, *J* = 22.0 Hz, *C*H); 138.8; 135.4; 125.5; 124.7; 123.9; 122.3; 111.8; 72.4; 68.1; 66.4; 51.7; 19.5

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: -150.5

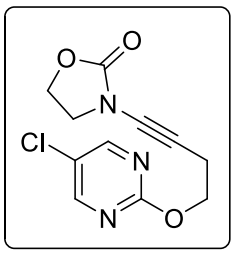
Mp: 87 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 340.1092, found 340.1099

3-(4-(5-Chloropyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3i**)

Compound **3i** was obtained according to Evano's conditions.[4] In a 100 mL round bottom flask equipped with a magnetic stirrer were placed 2-(but-3-yn-1-yloxy)-5-chloropyrimidine (1 eq., 500 mg, 2.74 mmol) dissolved in a mixture of ethanol (10 mL) and a 32% hydroxyamonium solution (17 mL). The mixture was stirred for few minutes and then was added CuI (2 eq., 1042 mg, 5.48 mmol) and stirring was allowed to continue until complete consumption of starting material. The crude green mixture was filtrated over büchner and washed with an aqueous solution of NH_4OH (32%), H_2O, ethanol and finally Et_2O.

In a 100 mL round bottom flask equipped with a magnetic stirrer was placed the alkynylcopper (1 eq., 438 mg, 1.79 mmol) and 2-oxazolidinone (5 eq., 777 mg, 8.92 mmol). MeCN (4.5 mL, 0.4 M) was added and the reaction mixture was allowed to stir under an oxygen atmosphere for few minutes. TMEDA (1 eq., 0.27 mL, 1.79 mmol) was finally added and the mixture was stirred overnight at room temperature under an atmosphere of oxygen. The deep blue crude mixture was concentrated in vacuo and quenched with water. The aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude product was purified by flash chromatography on silica gel (Petroleum ether/EtOAc: 7/3). **3i** was isolated as a white solid (402 mg, 55 % over two steps).



$C_{11}H_{10}ClN_3O_3$
267,67 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.44 (s, 2H); 4.47-4.39 (4H); 3.87 (t, *J* =8.4 Hz, 2H); 2.83 (t, *J* = 7.0 Hz, 2H)

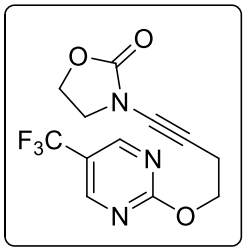
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*:163.4; 157.89; 156.8; 124.6; 71.9; 67.2; 66.33; 63.2; 47.1; 19.3

Mp: 117 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 268.0451, 268.0543

3-(4-(5-(Trifluoromethyl)pyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3j**)

Compound 3j was obtained from **2j** (190 mg, 0.88 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3j** was isolated as a white solid (92 mg, 35 % yield).



$C_{12}H_{10}F_3N_3O_3$
301,22 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.73 (s, 2H); 4.52 (t, *J* = 7.2 Hz, 2H); 4.40 (t, 8.3 Hz, 2H); 3.86 (t, *J* = 8.3 Hz, 2H); 2.84 (t, 7.2 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*:166.6; 157.4 (d *J* = 3.3 Hz, *C*H); 156.7; 128.7 (d, *J* = 184.4 Hz); 123.4 (q, 270.8 Hz, *C*F_3); 119.5 (q, 34.4 Hz, , *C*H); 72.0; 66.84; 66.6; 63.3; 47.1; 19.1

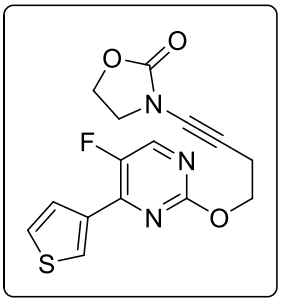
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: -62.5

Mp: 97 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 302.0747, found 302.0756

3-(4-(5-Fluoro-4-(thiophen-3-yl)pyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3k**)

Compound 3k was obtained from **2k** (200 mg, 0.81 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3k** was isolated as a white solid (170 mg, 63 % yield).



$C_{15}H_{12}FN_3O_3S$
333,34 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.37 (d, *J* = 3.0 Hz, 1H); 8.29 (ddd, *J* = 1.1 Hz, 2.6 Hz, 4.1 Hz, 1H); 7.87 (dt, *J* = 1.3 Hz, 5.3 Hz, 1H); 7.42 (dd, *J* = 3.0 Hz, 5.3 Hz, 1H); 4.51 (dd, *J* = 7.5 Hz, 9.2 Hz, 2H); 4.41 (dd, *J* = 7.7 Hz, 9.4 Hz, 2H); 3.89 (dd, *J* = 6.6 Hz, 8.3 Hz, 2H); 2.88 (t, *J* = 7.2 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*:160.9, 156.8; 151.7 (d, *J* = 256.0 Hz, *C*H); 149.4 (d, *J* = 12.5 Hz, *C*H); 135.1 (d, *J* = 5.1 Hz, *C*H); 135.9; 132.4; 130.6 (d, *J* = 10.3 Hz, *C*H); 127.8 (d, *J* = 4.4 Hz); 126.4; 71.8; 67.4; 66.3; 47.2; 19.4

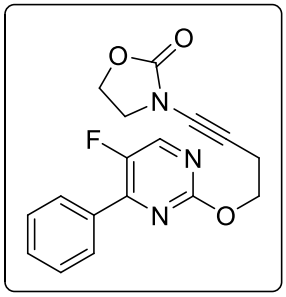
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: -148.1

Mp: 74 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 334.0656, found 334.0663

3-(4-(5-Fluoro-4-phenylpyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3l**)

Compound 3l was obtained from **2l** (214 mg, 0.88 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3l** was isolated as a white solid (195 mg, 67 % yield).



$C_{17}H_{14}FN_3O_3$
327,31 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.42 (d, *J* = 3.0 Hz, 1H); 8.16-8.13 (m, 2H); 7.54-7.50 (m, 3H); 4.55 (t, *J* = 7.2 Hz, 2H); 4.42 (t, *J* = 7.9 Hz, 2H); 3.90 (t, *J* = 7.9 Hz, 2H); 2.90 (t, *J* = 7.2 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*:160.9; 156.8; 153.1; (d, *J* = 256.0 Hz); 153.6 (d, *J* = 9.5 Hz, *C*H); 148.5 (d, *J* = 27.9 Hz, *C*H); 133.2 (d, *J* = 5.1 Hz, *C*H); 131.7; 129.5; 129.1; 71.8; 67.5; 66.41; 63.2; 47.2; 19.5

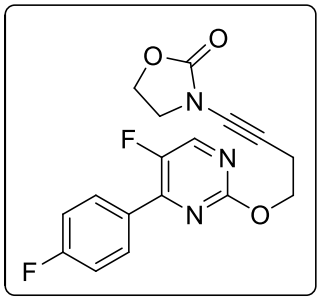
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -148.7

Mp: 135 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 328.1098, found 328.1092

3-(4-(5-Fluoro-4-(4-fluorophenyl)pyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3m**)

Compound 3m was obtained from **2m** (200 mg, 0.77 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3m** was isolated as a white solid (210 mg, 79 % yield).



$C_{17}H_{13}F_2N_3O_3$
345,30 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.43 (d, *J* = 3.4 Hz, 1H); 8.2 (dd, *J* = 2.8 Hz, 5.7 Hz, 2H); 7.22 (dd ap t, *J* = 8.9 Hz, 2H); 4.55 (t, *J* = 7.2 Hz, 2H); 4.44 (t, *J* = 7.7 Hz, 2H); 3.91 (t, *J* = 8.3 Hz, 2H); 2.91 (t, *J* = 7.2 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 165.3; 165.9; 162.4; 154.8; 142.0 (d, *J* = 9.6 Hz); 132.3; 131.0 (t, *J* = 8.8 Hz); 116.6; 115.7 (d, *J* = 23.5 Hz); 70.5; 63.6; 46.6 (d, *J* = 6.6 Hz); 30.0; 28.7

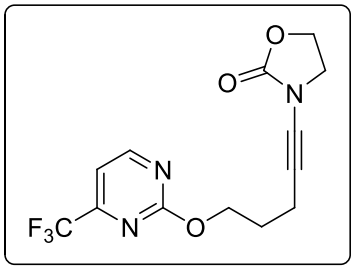
^{19}F NMR ($CDCl_3$, 37 6MHz, ppm) *δ*: -108.91; - 148.80

Mp: 120 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 346.1004, found 346.0998

3-(5-(4-(Trifluoromethyl)pyrimidin-2-yloxy)pent-1-ynyl)oxazolidin-2-one (**3n**)

Compound 3n was obtained from **2n** (180 mg, 0.78 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 6:4), **3n** was isolated as a white solid (185 mg, 75 % yield).



$C_{13}H_{12}F_3N_3O_3$
315,25 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.7 (d, *J* = 5.3 Hz, 1H); 7.2 (d, *J* = 5.3 Hz, 1H); 4.45 (t, *J* = 6.2 Hz, 2H); 4.34 (t, *J* = 9.0 Hz, 2H); 3.81 (t, *J* = 6.8 Hz, 2H); 2.46 (t, *J* = 6.6 Hz, 2H); 2.01-1.95 (2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 165.5; 162.2; 157.6 (q, *J* = 37.9 Hz, *C*H); 156.7; 120.3 (q, *J* = 275.5 Hz, *C*F_3); 110.6 (d, *J* = 3.3 Hz, *C*H); 71.0; 69.8; 67.1; 63.1; 47.1; 28.0; 15.3

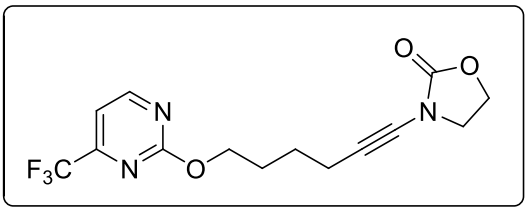
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: -71.3

Mp: 130 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 316.0904, found 316.0895

3-(6-(4-(Trifluoromethyl)pyrimidin-2-yloxy)hex-1-ynyl)oxazolidin-2-one (**3o**)

Compound 3o was obtained from **2o** (180 mg, 0.74 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 6:4), **3o** was isolated as a white solid (920 mg, 79 % yield).



$C_{14}H_{14}F_3N_3O_3$
329,27 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.75 (d, J = 4.8 Hz, 1H), 7.25 (d, J = 4.8 Hz, 1H), 4.46 (t, J = 6.2 Hz, 2H), 4.42 (t, J = 7.1 Hz, 2H), 3.87 (t, J = 8.3 Hz, 2H), 2.41 (t, J = 6.9 Hz, 2H), 2.01-1.92 (2H), 1.79-1.69 (2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 165.5; 162.2; 157.5 (q, J = 36.8 Hz, *C*H); 156.7; 120.2 (q, J = 275.5 Hz, *C*F_3); 110.4 (d, J = 3.2 Hz, *C*H); 70.8; 70.3; 68.0; 63.1; 47.1; 27.8; 25.2; 16.11

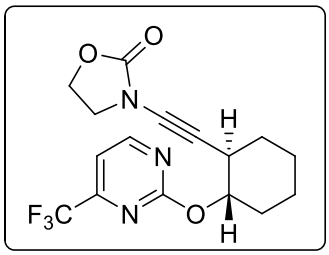
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -71.3

Mp: 142 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 330.0605, found 330.0616

3-((2-(4-(Trifluoromethyl)pyrimidin-2-yloxy)cyclohexyl)ethynyl)oxazolidin-2-one (**3p**)

Compound 3p was obtained from **2p** (200 mg, 0.74 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3p** was isolated as a white solid (139 mg, 53 % yield).



$C_{16}H_{16}F_3N_3O_3$
355,31g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.74 (d, J = 4.5 Hz, 1H), 7.23 (d, J = 4.5 Hz, 1H), 5.15 (td, J = 8.5 Hz, 3.8 Hz, 1H), 4.33 (t, J = 8.1 Hz, 2H), 3.74 (td, J = 8.3 Hz, 1.8 Hz, 2H), 2.86 (td, J = 4.3 Hz, 8.5 Hz, 1H), 2.17-2.03 (m, 2H), 1.75-1.69 (m, 2H), 1.60-1.49 (m, 2H), 1.43-1.29 (m, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 170.9, 155.1, 146.0 (q, J = 35.8 Hz, *C*H), 142.7; 122.8, 121.5 (q, J = 275.2 Hz, *C*F_3), 107.8 (d, J = 2.9 Hz, *C*H), 90.00, 63.0; 49.08, 46.2, 30.7, 30.05, 28.1, 25.9, 24.6

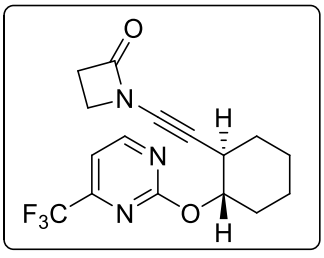
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -69.8

Mp: 133 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 356.1217, found 356.1225

1-((2-(4-(Trifluoromethyl)pyrimidin-2-yloxy)cyclohexyl)ethynyl)azetidin-2-one (**3q**)

Compound 3q was obtained from **2q** (100 mg, 0.37 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3q** was isolated as a yellow solid (80 mg, 64 % yield).



$C_{16}H_{16}F_3N_3O_2$
339,31 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.76 (d, J = 4.9 1H), 7.23 (d, J = 4.9 Hz, 1H), 5.16 (td, J = 8.31 Hz, 3.8 Hz, 1H), 3.48 (td, J = 1.0 Hz, 5.0 Hz, 2H), 2.94 (t, J = 4.8 Hz, 2H), 2.88 (m, 1H), 2.19-2.04 (2H), 1.86-1.68 (2H), 1.65-1.52 (2H), 1.48-1.34 (2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 166.8; 165.1; 161.9; 157.7; (q, J = 35.2 Hz, *C*H); 120.1 (q, 273.6 Hz, *C*F_3); 110.2; 77.8; 71.8; 70.4; 42.8; 37.5; 34.0; 30.1; 29.4; 23.7; 22.9

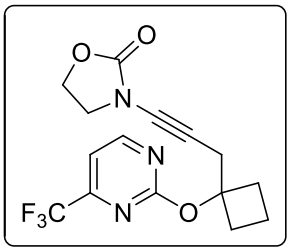
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -71.2 ppm

Mp: 124 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 340.1275, found 340.1267

3-(3-(1-(4-(Trifluoromethyl)pyrimidin-2-yloxy)cyclobutyl)prop-1-ynyl)oxazolidin-2-one (**3r**)

Compound 3r was obtained from **2r** (200 mg, 0.78 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3r** was isolated as a yellow solid (190 mg, 71 % yield).



$C_{15}H_{14}F_3N_3O_3$
341,29 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ : 8.72 (d, J = 4.9 Hz, 1H), 7.24 (d, J = 4.9 Hz, 1H), 4.39 (t, J = 8.2 Hz, 2H), 3.85 (t, J = 8.2 Hz, 2H), 3.18 (s, 2H), 2.48 (t, J = 8.9 Hz, 4H), 1.95-1.67 (m, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 164.1; 162.2; 157.6 (q, J = 36.0 Hz, *C*H); 156.8; 120.3 (q, J = 275.8 Hz, *C*F_3); 110.6; 82.4; 71.6; 70.0; 64.0; 47.1; 33.7; 25.7; 13.6

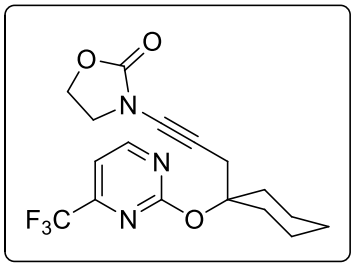
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -71.4 ppm

Mp: 125 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 342.1060, found 342.1071

3-(3-(1-(4-(Trifluoromethyl)pyrimidin-2-yloxy)cyclohexyl)prop-1-ynyl)oxazolidin-2-one (**3s**)

Compound 3s was obtained from **2s** (200 mg, 0.70 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3s** was isolated as a yellow solid (87 mg, 44 % yield).



$C_{17}H_{18}F_3N_3O_3$
369,34 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.71 (d, J = 4.9 Hz, 1H); 7.22 (d, J = 4.7 Hz, 1H); 4.36 (t, J = 8.0 Hz, 2H); 3.78 (t, J = 8.0 Hz, 2H); 3.19 (s, 2H); 2.50-2.45 (m, 2H); 1.73-1.27 (m, 8H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 164.9; 162.0; 156.7; 157.4 (q, J = 36.7 Hz, *C*H); 120.4 (q, J = 275.0 Hz, *C*F_3); 110.4 (d, J = 3.3 Hz, *C*H); 84.4; 82.6; 72.56; 67.00; 63.1; 47.1; 34.4; 27.9; 25.5; 22.0

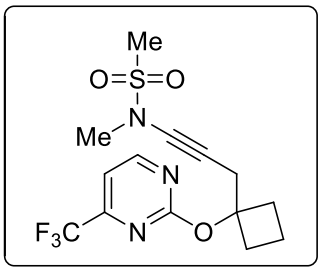
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -71.3

Mp: 119 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 370.1373, found 370.1376

N-Methyl-*N*-(3-(1-(4-(trifluoromethyl)pyrimidin-2-yloxy)cyclobutyl)prop-1-ynyl)methanesulfonamide (**3t**)

Compound 3t was obtained from **2t** (209 mg, 0.78 mmol) and *N*-methyl-*N*-mesylamine following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3t** was isolated as a yellow solid (90 mg, 32 % yield).



$C_{14}H_{16}F_3N_3O_3S$
363,36 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.71 (d, J = 4.9 Hz, 1H), 7.23 (d, J = 4.9 Hz, 1H), 3.16 (s, 3H); 3.12 (s, 3H), 3.01 (s, 3H), 2.48-2.43 (m, 4H), 1.89 (m, 1H), 1.74 (m, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 164.5; 162.2; 157.8 (q, J = 36.7 Hz, *C*H); 120.4 (q, J = 275.1 Hz, *C*F_3); 110.6 (d, J = 2.9 Hz, *C*H), 82.6; 75.9; 65.3; 39.3; 36.5; 33.8; 25.8; 13.7

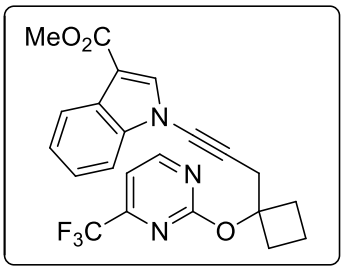
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -71.4 ppm

Mp: 111 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 364.0937, found 364.0947

Methyl-1-(3-(1-(4-(trifluoromethyl)pyrimidin-2-yloxy)cyclobutyl)prop-1-ynyl)-1H-indole-3-carboxylate (**3u**)

Compound 3u was obtained from **2u** (200 mg, 0.78 mmol) and 1H-indole-3-carboxylate following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 7:3), **3u** was isolated as a yellow solid (152 mg, 44 % yield).



$C_{22}H_{18}F_3N_3O_3$
429,39 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.77 (d, J = 4.8 Hz, 1H); 8.15 (dd, J = 1.3 Hz, 6.8 Hz, 1H); 7.88 (s, 1H); 7.54 (dd, J = 1.3 Hz, 7.1 Hz, 1H); 7.34 (dq, 1.3 Hz, 8.8 Hz, 2 H); 7.28 (d, J = 4.8 Hz, 1H); 3.92 (s, 3H); 3.38 (s, 2H); 2.61 (d, J = 6.6 Hz, 2H); 2.58 (d, J = 6.6 Hz, 2H); 2.04-1.79 (2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 164.7; 164.3; 162.3; 157.5 (q, J = 37.4 Hz, *C*H); 138.8; 135.3; 152.5; 124.7; 123.7; 122.1; 120.7 (q J = 275 Hz, *C*F_3); 111.8; 110.7; 110.5; 82.4; 72.0; 67.8; 51.6; 33.9; 25.9; 13.8;

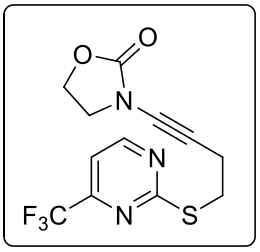
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -71.3 ppm

Mp: 87 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 430.1373, found 430.1381

3-(4-(4-(Trifluoromethyl)pyrimidin-2-ylthio)but-1-ynyl)oxazolidin-2-one (**3v**)

Compound 3v was obtained from **2v** (400 mg, 1.72 mmol) following the general procedure B using 10 eq. (1.5 g, 17.22 mmol) of oxazolidinone and adding 2v over 12 hours. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 1:1), **3v** was isolated as a white solid (378 mg, 69 % yield).



$C_{12}H_{10}F_3N_3O_2S$
317,29 g/mol

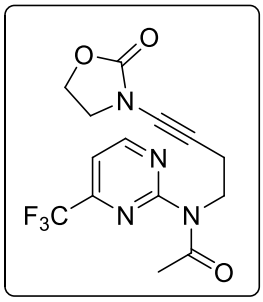
^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.76 (d, J = 5.0 Hz, 1H); 7.29 (d, J = 5.0 Hz, 1 H); 4.43 (t, J = 6.6 Hz, 2H); 3.9 (t, J = 6.6 Hz, 2H); 3.35 (t, J = 7.0 Hz, 2H); 2.82 (t, 6.8 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 173.6; 159.9; 156.1 (q, J = 36.2 Hz); 154.6; 123.9; 120.4 (q, J = 273.3 Hz); 112.4 (d, J = 3.8 Hz); 112.3; 63.1; 44.4; 35.2; 28.2

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: −70.33

N-(4-(2-Oxooxazolidin-3-yl)but-3-ynyl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)acetamide (**3w)**

Compound 3w was obtained from **2w** (150 mg, 0.58 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 6:4), **3w** was isolated as a white solid (47 mg, 25 % yield).



$C_{14}H_{13}F_3N_4O_3$
342,27 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.86 (d, J = 4.9 Hz, 1H); 7.33 (d, J = 4.9 Hz, 1H); 4.36 (t, J = 8.1 Hz); 4.29 (t, J = 7.4 Hz, 2H); 3.78 (t, J = 8.1 Hz); 2.68 (t, J = 7.4 Hz, t), 2.50 (s, 3H)

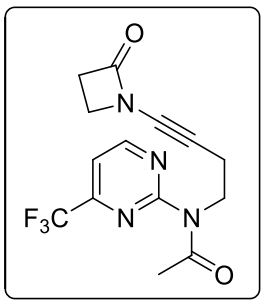
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 172.6; 161.2; 160.9; 156.6; 156.3 (q, J = 39.5 Hz); 120.4 (q, J = 273.9 Hz); 118.8 (d, J = 3.8 Hz); 71.8; 68.36; 47.1; 44.9; 26.7; 18.4

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: −71.3

HRMS-ESI *m/z* calcd for $[M+Na]^+$ 365.0832, found 365.0831

N-(4-(2-Oxoazetidin-1-yl)but-3-ynyl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)acetamide (**3x**)

Compound 3x was obtained from **2w** (200 mg, 0.78 mmol) following the general procedure B. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 6:4), **3x** was isolated as a white solid (145 mg, 54 % yield).



$C_{14}H_{13}F_3N_4O_2$
326,27g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 8.7 (d, J = 4.9 Hz, 1H); 7.33 (d, J = 4.9 Hz, 1H); 4.29 (t, J = 7.3 Hz, 2H); 3.48 (t, J = 4.7 Hz, 2H); 2.94 (t, J = 4.7 Hz, 2H); 2.67 (t, J = 7.3 Hz, 2H); 2.5 (s, 3H)

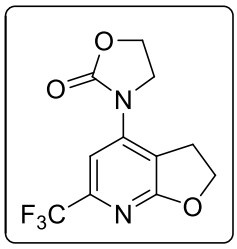
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 172.6; 167.2; 161.3; 160.8; 156.3 (q, J = 35.1 Hz); 120.4 (q, J = 274.4 Hz); 111.8 (d, J = 3.3 Hz); 71.7; 67.3; 45.0; 43.0; 37.8; 26.7; 18.4

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: −71.3

HRMS-ESI *m/z* calcd for $[M+Na]^+$ 349.0883, found 349.0890

3-(6-(Trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4a**)

Compound 4a was obtained from **3a** (30 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4a** was isolated as a white solid (16 mg, 60 % yield).



$C_{11}H_9F_3N_2O_3$
274,20 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 7.19 (s, 1H); 4.68 (t, J = 8.7 Hz, 2H); 4.56 (t, J = 7.2 Hz, 9.6 Hz, 2H); 4.17 (t, J = 7.2 Hz, 2H); 3.43 (t, J = 8.7 Hz, 2 H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 171.0; 154.2; 146.83 (q, J = 35.2 Hz, *C*H); 143.7; 124.22 (q, J = 274.4 Hz, *C*F_3); 115.3; 106.1 (d, J = 5.1 Hz, *C*H); 70.0; 62.7; 46.1; 29.2

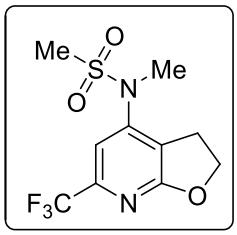
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: - 69.1

Mp : 127 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 275.0638, found 275.0644

N-Methyl-*N*-(6-(Trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)methanesulfonamide (**4b**)

Compound 4b was obtained from **3b** (36 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4b** was isolated as a yellow oil (7 mg, 21 % yield).



$C_{10}H_{11}F_3N_2O_3S$
296,27 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 7.08 (s, 1H); 4.73 (t, J = 8.7 Hz, 2H); 3.50 (t, J = 8.7 Hz, 2H); 3.31 (s, 3H); 2.99 (s, 3H)

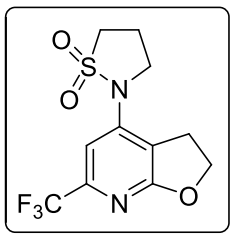
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 171.1; 147.5; 147.4 (q, J = 24.2 Hz, *C*H); 123.7; 121.4 (q, J = 274.4 Hz, *C*F_3); 110.4 (d, J = 2.9 Hz, *C*H); 70.4; 37.9; 36.9; 28.3

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: - 67.9

HRMS-ESI *m/z* calcd for $[M+H]^+$ 297.0515, found 297.0506

2-(4-{[4-(Trifluoromethyl)pyrimidin-2-yl]oxy}but-1-yn-1-yl)-2-thiazolidine-1,1-dione (**4c**)

Compound 4c was obtained from **3c** (34 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 2:8), **4c** was isolated as a yellow solid (16 mg, 52 % yield).



$C_{11}H_{11}F_3N_2O_3S$
308,28 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 6.87 (s, 1H); 4.68 (t, J = 8.5 Hz, 2H); 3.93 (t, J = 7.2 Hz, 2H); 3.57 (t, J = 8.5 Hz, 2H); 3.41 (t, J = 7.2 Hz, 2H); 2.64 (q, J = 7.2 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 170.5; 146.7 (q, J = 34.5 Hz, *C*H); 143.9; 121.3 (q, J = 272.9 Hz, *C*F_3) 112.4; 103.6 (d, J = 3.7 Hz, *C*H); 69.6; 48.6; 47.6; 29.4; 19.3

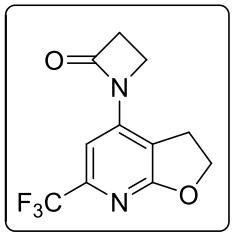
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: - 69.1

Mp : 132 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 309.0515, found 309.0516

1-(6-(Trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)azetidin-2-one (**4d**)

Compound 4d was obtained from **3d** (31 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4d** was isolated as a white powder (18 mg, 65 % yield).



$C_{11}H_9F_3N_2O_2$
258,20 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 7.28 (s, 1H); 4.68 (t, J = 8.7 Hz, 2H); 3.83 (t, J = 4.9 Hz, 2H); 3.54 (t, J = 8.7 Hz, 2H); 3.21 (t, J = 4.9 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 170.8; 164.9; 147.2 (q, J = 31.5 Hz, *C*H); 143.1; 121.6 (q, J = 274.4 Hz); 108.8; 103.7 (d, J = 4.4 Hz, *C*H); 69.9; 39.7; 37.3; 28.6

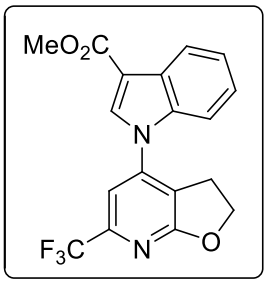
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: -69.2

Mp : 91 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 259.0689, found 259.0679

Methyl 1-(6-(trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)-1H-indole-3-carboxylate (**4e**)

Compound 4e was obtained from **3e** (39 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4e** was isolated as a yellow solid (18 mg, 49 % yield).



$C_{18}H_{13}F_3N_2O_3$
362,30 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) ***δ***: 8.30 (m, 1H); 7.97 (s, 1H); 7.43-7.36 (4 H); 4.82 (t, *J* = 8.5 Hz, 2H); 3.97 (s, 3H); 3.37 (t, *J* = 8.5 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) ***δ*:** 171.5; 165.0; 148.0 (q, *J* = 35.9 Hz, *C*H); 144.2; 136.0; 132.4; 127.2; 124.9; 123.4 (d, *J* = 102.0 Hz, *C*H); 121.3 (q, 273.6 Hz, *C*F_3); 118.4; 111.9; 111.3; 110.8 (q, *J* = 2.2 Hz, *C*H); 70.4; 51.8; 30.0; 27.9

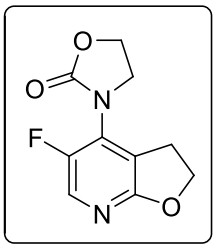
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) ***δ*:** - 69.0

Mp: 158 °C

HRMS-APCI *m/z* calcd for $[M+H]^+$ 363.0951, found 363.0944

3-(5-Fluoro-2,3-dihydrofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4f**)

Compound 4f was obtained from **3f** (13 mg, 0.05 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4f** was isolated as a white powder (8 mg, 71 % yield). Due to limited amount of this cycloadduct, only partial ^{13}C NMR data have been obtained.



$C_{10}H_9FN_2O_3$
224,19 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 7.90 (bs, 1H); 4.70 (t, *J* = 8.5 Hz, 2H); 4.58 (t, *J* = 7.6 Hz, 2H); 4.15 (t, *J* = 7.6 Hz, 2H); 3.35 (t, *J* = 8.5 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm (partial data)) *δ*: 165.8; 154.3; 131.1 (d, *J* = 12.5 Hz, *C*H); 70.2; 63.3; 46.1 (d, *J* = 7.4 Hz, *C*H); 28.5

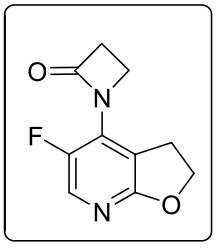
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: - 149.1 ppm

Mp: 97 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 225.0670, found 225.0659

1-(5-Fluoro-2,3-dihydrofuro[2,3-b]pyridin-4-yl)azetidin-2-one (**4g**)

Compound 4g was obtained from **3g** (12 mg, 0.05 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4g** was isolated as a yellow solid (9 mg, 90 % yield). Due to limited amount of this cycloadduct, only partial ^{13}C NMR data have been obtained.



$C_{10}H_9FN_2O_2$
208,19 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 7.78 (d, *J* = 3.0 Hz, 1H); 4.62 (t, 8.5 Hz, 2H); 3.94 (t, *J* = 4.8 Hz, 2H); 3.50 (t, *J* = 8.5 Hz, 2H); 3.19 (t, *J* = 4.8 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm (partial data)) *δ*: 165.8; 154.3; 131.1 (d, *J* = 12.5 Hz, *C*H); 70.2; 63.3; 46.1 (d, *J* = 7.4 Hz, *C*H); 28.5

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 162.4; 151.1; 134.4 (q, *J* = 27.9 Hz, *C*H); 70.5; 63.6; 46.4; 28.8

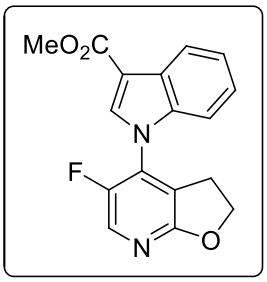
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: - 154.9 ppm

Mp : 91 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 209.1825, found 209.1831

Methyl 1-(5-fluoro-2,3-dihydrofuro[2,3-b]pyridin-4-yl)-1H-indole-3-carboxylate (**4h**)

Compound 4h was obtained from **3h** (34 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4h** was isolated as a yellow solid (17 mg, 54 % yield).



$C_{17}H_{13}FN_2O_3$
312,30 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) ***δ***: 8.28 (m, 1H); 8.11 (s, 1H); 7.92 (d, *J* = 1.2 Hz, 1H); 7.40 - 7.35 (2H); 7.18 (m, 1H); 4.75 (t, *J* = 8.6 Hz, 2H); 3.96 (s, 3H); 3.22 (t, *J* = 8.6 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) ***δ*:** 164.8; 161.4; 156.1; 147.0 (d, *J* = 19.8 Hz, *C*H); 138.8; 135.4; 125.5; 124.7; 123.9; 122.2; 111.8; 110.7; 72.3; 68.1; 66.4; 51.7; 19.5

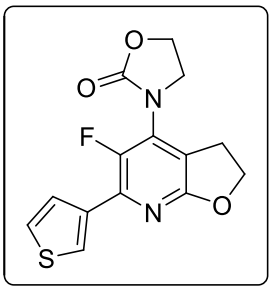
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) ***δ*:** - 148.1

Mp : 147 °C

HRMS-ESI *m/z* calcd for $[M+H]^+$ 313.0983, found 313.0979

3-(5-Fluoro-6-(thiophen-3-yl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4k**)

Compound 4k was obtained from **3k** (17 mg, 0.05 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4k** was isolated as a yellow solid (11 mg, 72 % yield).



$C_{14}H_{11}FN_2O_3S$
306,31 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 7.99 (t, *J* = 1.4 Hz, 1H); 7.76 (dt, *J* = 1.4 Hz, 5.1 Hz, 1H); 7.36 (dd, *J* = 3.0 Hz, 5.1 Hz, 1H); 4.71 (t, *J* = 8.4 Hz, 2H); 4.59 (t, *J* = 7.6 Hz, 2H); 4.18 (t, *J* = 7.6 Hz, 2H); 3.34 (t, *J* = 8.4 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 164.8; 154.82; 147.8 (d, *J* = 246.5 Hz, *C*H); 138.9 (d, *J* = 11.7 Hz, *C*H); 136.6; 132.16; 127.94 (d, *J* = 1.9 Hz); 126.5 (d; *J* = 5.9 Hz, *C*H); 125.6; 115.9; 70.4; 63.6; 46.6 (d; *J* = 7.4 Hz, *C*H); 28.8

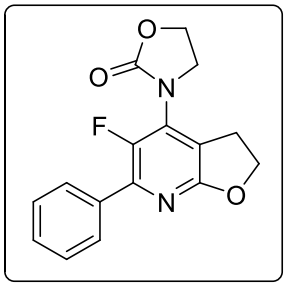
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: - 144.2

Mp : 92 °C

HRMS- ESI *m/z* calcd for $[M+H]^+$ 307.0544, found 307.0547

3-(5-Fluoro-6-phenyl-2,3-dihydrofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4l**)

Compound 4l was obtained from **3l** (33 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4l** was isolated as a yellow solid (25 mg, 82 % yield).



$C_{16}H_{13}FN_2O_3$
300,28 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 7.91 – 7.88 (2H); 7.49-7.41 (3H); 4.70 (t, *J* = 8.6 Hz, 2H); 4.57 (t, *J* = 7.6 Hz, 2H); 4.15 (t, *J* = 7.6 Hz, 2H); 3.35 (t, *J* = 8.6 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 165.0; 154.8; 148.4 (d, *J* = 250.9 Hz, *C*H); 143.0 (d, *J* = 13.9 Hz, *C*H); 135.0 (d, *J* = 4.4 Hz, *C*H); 132.1 (d, *J* = 13.9 Hz, *C*H); 129.3 (d, *J* = 49.9 Hz); 129.0; 128.6; 116.5; 70.4; 63.6; 46.5 (d, *J* = 7.3 Hz, *C*H); 28.7

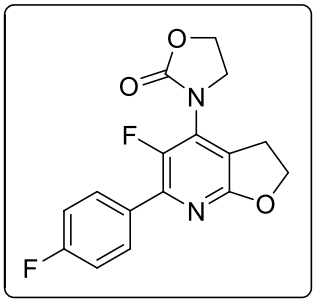
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: - 148.7

Mp : 142 °C

HRMS- ESI *m/z* calcd for $[M+H]^+$ 301.0983, found 301.0983

3-(5-Fluoro-6-(4-fluorophenyl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4m**)

Compound 4m was obtained from **3m** (35 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4m** was isolated as a yellow solid (23 mg, 72 % yield).



$C_{16}H_{12}F_2N_2O_3$
318,27 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 7.92 (dd, *J* = 7.0 Hz, 8.8 Hz, 2H); 7.14 (t, *J* = 8.7 Hz, 2H); 4.72 (t, *J* = 8.7 Hz, 2H); 4.60 (t, *J* = 7.7 Hz, 2H); 4.18 (t, *J* = 7.7 Hz, 2H); 3.36 (t, *J* = 8.7 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 165.3; 165.0; 162.0; 154.8; 148.3 (d, *J* = 244.8 Hz, *C*H); 141.9 (d, *J* = 1.4 Hz, *C*H); 132.2 (d, *J* = 13.7 Hz, *C*H); 131.0 (t, *J* = 6.6 Hz, *C*H); 116.6; 115.70 (d, *J* = 22.5 Hz, *C*H); 70.5; 63.6; 46.6 (d, *J* = 7.1 Hz, *C*H); 28.8

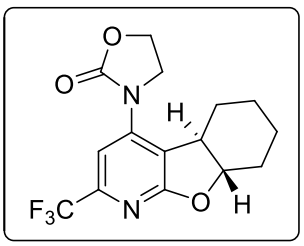
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: - 112.9; - 145.9

Mp : 139 °C

HRMS- ESI *m/z* calcd for $[M+H]^+$ 319.0889, found 319.0878

3-(2-(Trifluoromethyl)-4b,5,6,7,8,8a-hexahydrobenzofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4p**)

Compound 4p was obtained from **3p** (36 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4p** was isolated as a yellow solid (25 mg, 72 % yield).



$C_{15}H_{15}F_3N_2O_3$
328,29 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 7.01 (s, 1H); 4.64-4.51 (2H); 4.31 (q, *J* = 8.8 Hz, 1H); 4.06-3.87 (2H); 3.17 (1H); 2.40-2.24 (2H); 1.91-1.83 (2H); 1.66-1.52 (m, 2H); 1.46-1.39 (2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 170.8, 165.7, 146.0 (q, J = 34.5 Hz, *C*H), 142.2, 130.3 (q, J = 14.0 Hz, *C*H), 121.6 (q, J = 274.4 Hz, *C*F_3), 117.2, 105.6 (q, J = 2.9 Hz, *C*H), 89.7, 48.7, 40.2, 37.2, 30.7, 21.1, 24.6

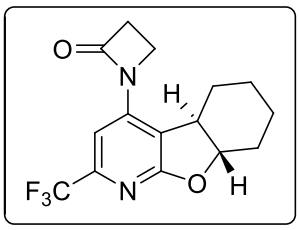
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: - 68.6

Mp : 142 °C

HRMS- ESI *m/z* calcd for $[M+H]^+$ 329.1112, found 329.1108

1-(2-(Trifluoromethyl)-4b,5,6,7,8,8a-hexahydrobenzofuro[2,3-b]pyridin-4-yl)azetidin-2-one (**4q**)

Compound 4q was obtained from **3q** (25 mg, 0.074 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4q** was isolated as a yellow solid (18 mg, 78 % yield).



$C_{15}H_{15}F_3N_2O_2$
312,2870 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 7.87 (bs, 1H); 4.63-4.50 (2H); 4.36 (t, *J* = 8.1 Hz, 1H); 4.00 (t, *J* = 10.9 Hz, 1H), 3.76-3.72 (2H), 2.36-2.17 (4H), 1.87-1.83 (4H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 170.8; 155.1; 145.9 (q, *J* = 35.9 Hz, *C*H); 142.7; 122.5 (q, *J* = 283.9 Hz, *C*F_3); 107.9 (d, *J* = 2.9 Hz, *C*H); 90.0; 63.0; 49.1; 45.8; 46.1; 30.6; 28.0; 25.9; 24.5

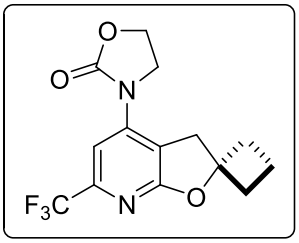
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: - 69.1

Mp : 136 °C

HRMS- ESI *m/z* calcd for $[M+H]^+$ 313.1158, found 313.1163

3-(6'-(Trifluoromethyl)-3'H-spiro[cyclobutane-1,2'-furo[2,3-b]pyridine]-4'-yl)oxazolidin-2-one (**4r**)

Compound 4r was obtained from **3r** (34 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 4:6), **4r** was isolated as a white solid (29 mg, 91 % yield).



$C_{14}H_{13}F_3N_2O_3$
314,26 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 7.13 (s, 1H), 4.57 (t, *J* = 8.0 Hz, 2H), 4.16 (t, *J* = 8.0 Hz, 2H), 3.52 (s, 2H), 2.69-2.58 (2H), 2.27-2.18 (2H), 1.93 (m, 1H), 1.72 (m, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 169.1; 153.9; 146.4 (q, *J* = 35.2 Hz, *C*H); 143.1; 121.6 (q, *J* = 275.8 Hz, *C*F_3); 114.8; 105.7 (d, *J* = 2.9 Hz, *C*H); 87.2; 62.4; 45.7; 40.9; 36.6; 12.2

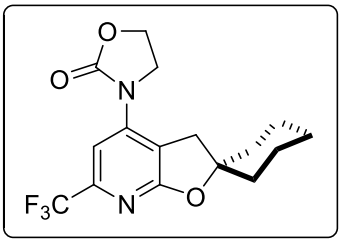
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: - 69.1

Mp : 129 °C

HRMS- ESI *m/z* calcd for $[M+H]^+$ 315.0951, found 315.0948

3-(6'-(Trifluoromethyl)-3'H-spiro[cyclohexane-1,2'-furo[2,3-b]pyridine]-4'-yl)oxazolidin-2-one (**4s**)

Compound 4s was obtained from **3s** (19 mg, 0.05 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4s** was isolated as a white solid (11 mg, 64 % yield).



$C_{16}H_{17}F_3N_2O_3$
342,31g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 7.12 (s, 1H), 4.60 (br t, *J* = 8.9 Hz, 2H); 4.15 (d, 8.9 Hz, 2H); 3.16 (s, 2H); 2.96-1.56 (8H); 1.59-1.39 (2H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 169.5; 162.0; 154.2; 146.9 (q, *J* = 32.0 Hz, *C*H); 143.7; 121.6; 115.6 (q, 275.3 Hz, *C*F_3); 105.7 (d, *J* = 3.2 Hz, *C*H); 88.7; 62.7; 46.1; 41.0; 37.7; 34.5; 25.2; 22.8

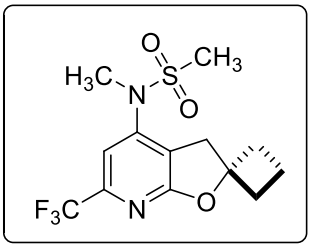
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: - 69.1

Mp : 164 °C

HRMS- ESI *m/z* calcd for $[M+H]^+$ 343.1264, found 343.1268

N-Methyl-*N*-(6'-(trifluoromethyl)-3'H-spiro[cyclobutane-1,2'-furo[2,3-b]pyridine]-4'-yl)methanesulfonamide (**4t**)

Compound 4t was obtained from **3t** (15 mg, 0.05 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4t** was isolated as a yellow solid (11 mg, 84 % yield).



$C_{13}H_{15}F_3N_2O_3S$
336,33 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 7.06 (s, 1H); 3.54 (s, 2H); 3.30 (s, 3H); 2.97 (s, 3H); 2.62 (2H); 2.26-2.20 (2H); 1.85 (m, 1H); 1.71 (m, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 169.6; 147.3 (q, *J* = 33.7 Hz, *C*H); 147.2; 123.7; 121.5 (q, *J* = 272.9 Hz, *C*F_3); 110.2 (q, *J* = 2.9 Hz, *C*H), 88.1, 40.2; 40.0; 36.9; 36.8; 12.5

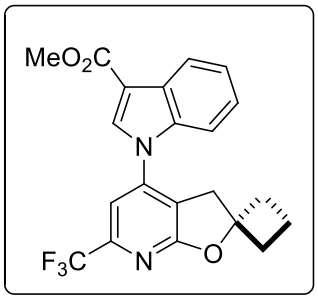
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: - 68.9 ppm

Mp : 164 °C

HRMS- ESI *m/z* calcd for $[M+H]^+$ 337.0828, found 337.834

Methyl 1-(6'-(trifluoromethyl)-3'H-spiro[cyclobutane-1,2'-furo[2,3-b]pyridine]-4'-yl)-1H-indole-3-carboxylate (**4u**)

Compound 4u was obtained from **3u** (33 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 3:7), **4u** was isolated as a yellow solid (28 mg, 92 % yield).



$C_{21}H_{17}F_3N_2O_3$
402,37 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 8.29 (t, *J* = 4.0 Hz, 1H), 7.96 (s, 1H), 7.44-7.36 (4H), 3.98 (s, 3H), 3.41 (s, 2H), 2.73-2.65 (2H), 2.29-2.21 (m, 2H), 1.99 (m, 1H), 1.72 (m, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 169.1, 165.1; 148.4 (q, *J* = 32.6 Hz, *C*H); 147.7; 147.4; 143.9; 136.0; 132.4; 127.2; 124.9; 123.8; 122.9; 120.0; 121.2 (q, *J* = 276.0 Hz, *C*F_3); 110.7 (d, *J* = 3.7 Hz, *C*H); 83.4; 51.8; 39.7; 36.9; 12.5

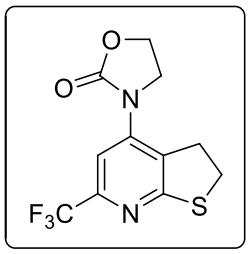
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: - 69.1 ppm

Mp : 169 °C

HRMS- ESI *m/z* calcd for $[M+H]^+$ 403.1257, found 403.1264

3-(6-(Trifluoromethyl)-2,3-dihydrothieno[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4v**)

Compound 4v was obtained from **3v** (32 mg, 0.1 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 4:6), **4v** was isolated as a yellow oil (20.5 mg, 71 % yield).



$C_{11}H_9F_3N_2O_2S$
290,26 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) *δ*: 7.15 (s, 1H); 4.56 (t, *J* = 7.9 Hz, 2H); 4.11 (t, *J* = 8.1 Hz, 2H); 3.44 (br m, 4H)

^{13}C NMR ($CDCl_3$, 100 MHz, ppm) *δ*: 171.0; 154.2; 147.8 (q, *J* = 36.7 Hz); 141.3; 131.2; 121.1 (q, *J* = 262.6 Hz); 109.2 (d, *J* = 3.8 Hz); 62.6; 46.1; 33.1; 30.1

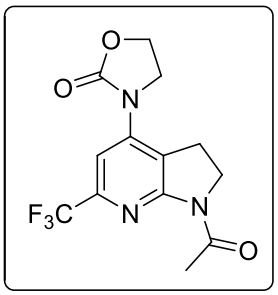
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) *δ*: –67.91

HRMS-ESI *m/z* calcd for $[M+H]^+$ 291.04096, found 291.04098

3-(1-acetyl-6-(trifluoromethyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4w**)

Compound 4w was obtained from **3w** (21 mg, 0.06 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 2:8), **4w** was isolated as a yellow solid (18mg, 93 % yield).

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 7.21 (s, 1H); 4.58 (t, J = 8.5 Hz, 2H), 4.19-4.13 (4H); 3.2 (t, J = 8.5 Hz, 2H), 2.70 (s, 3H)



$C_{13}H_{12}F_3N_3O_3$
315,25 g/mol

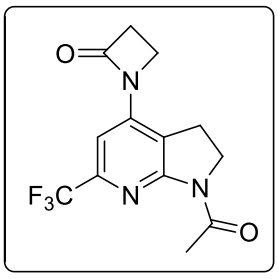
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 170.3; 158.3; 153.9; 146.2 (q, J = 36.2 Hz); 142.8; 121.7; 121.2 (q, J = 273.3 Hz); 107.2 (d, J = 5.5 Hz); 62.5; 45.8; 45.7; 25.2; 24.5

^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: −69.3

HRMS-ESI *m/z* calcd for $[M+Na]^+$ 338.0723, found 338.0727

3-(1-Acetyl-6-(trifluoromethyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4x**)

Compound 4x was obtained from **3w** (13.5 mg, 0.04 mmol) following the general procedure C. After purification of the crude material by column chromatography (Petroleum ether/EtOAc: 2:8), **4x** was isolated as a yellow oil (8.2 mg, 66 % yield).



$C_{13}H_{12}F_3N_3O_2$
299,25 g/mol

^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 7.5 (s, 1H); 4.14 (t, J = 8.1 Hz, 2H); 3.88 (t, J = 4.7 Hz, 2H); 3.33 (t, J = 8.1 Hz, 2H); 3.23 (t, J = 4.7 Hz, 2H); 2.68 (s, 3H)

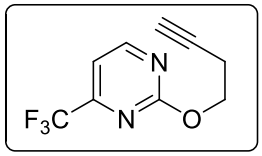
^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ: 170.7; 165.1; 158.3; 146.8 (q, J = 38.1 Hz); 147.8; 121.6 (q, J = 271.4 Hz); 114.4; 104.9 (d, J = 4.4 Hz); 46.0; 40.3; 37.7; 25.5; 24.2

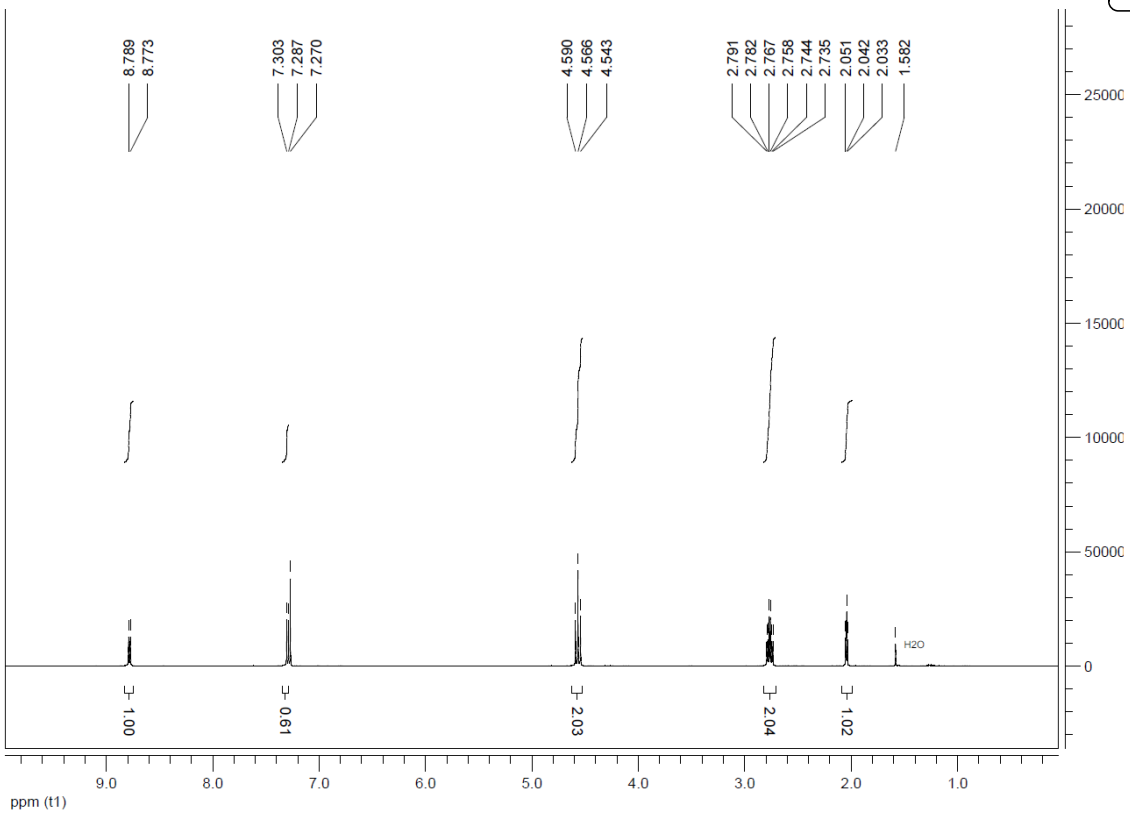
^{19}F NMR ($CDCl_3$, 376 MHz, ppm) δ: −68.4

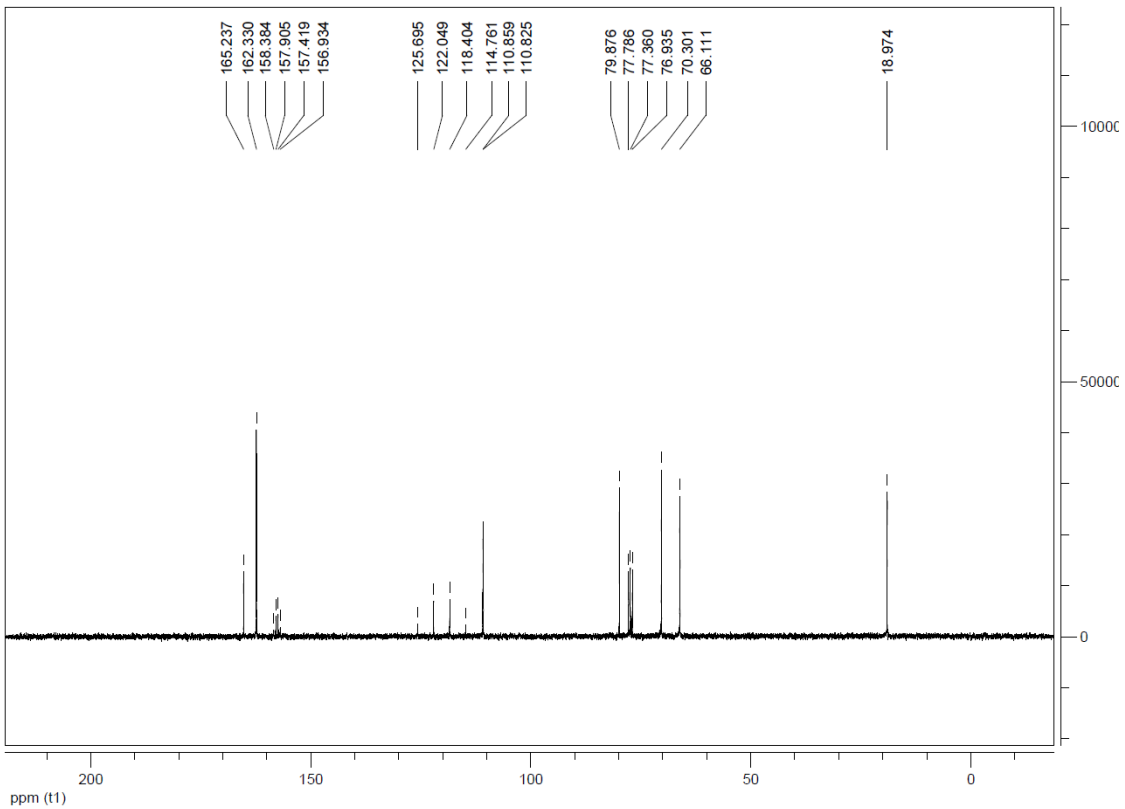
HRMS-ESI *m/z* calcd for $[M+H]^+$ 300.09837, found 300.09523

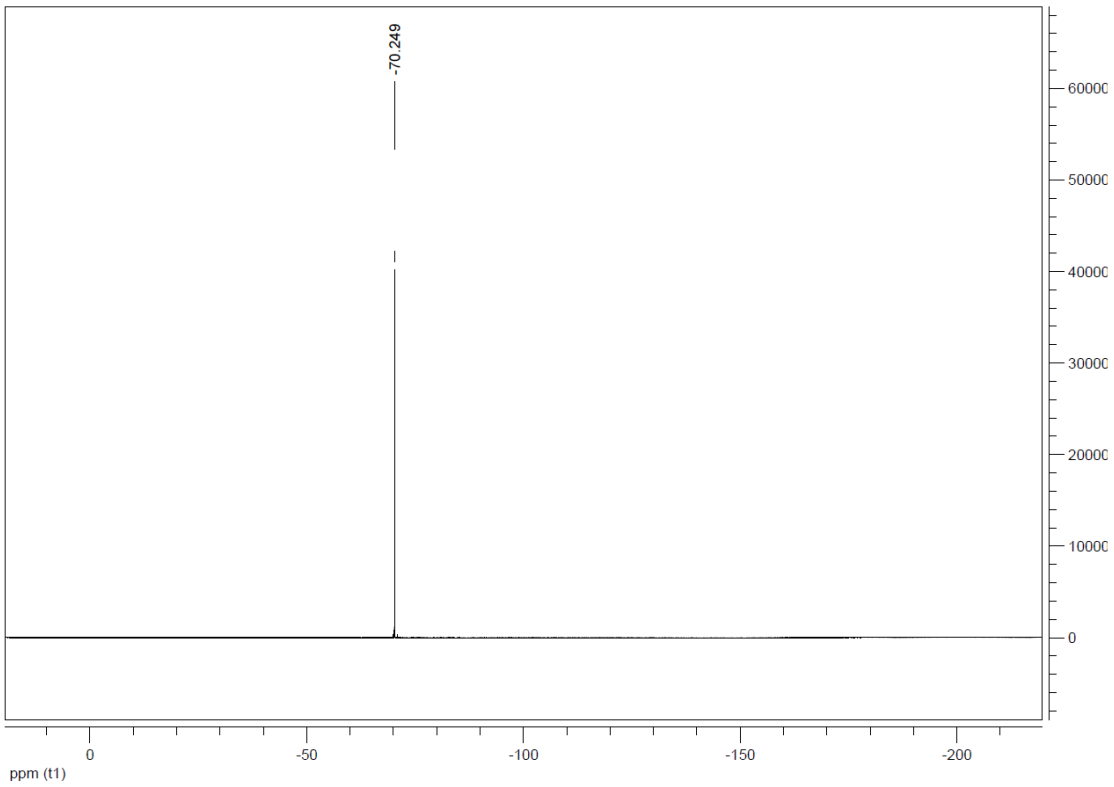
2. NMR Spectra

2-(But-3-ynyloxy)-4-(trifluoromethyl)pyrimidine (**2a**)

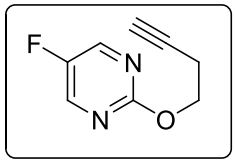


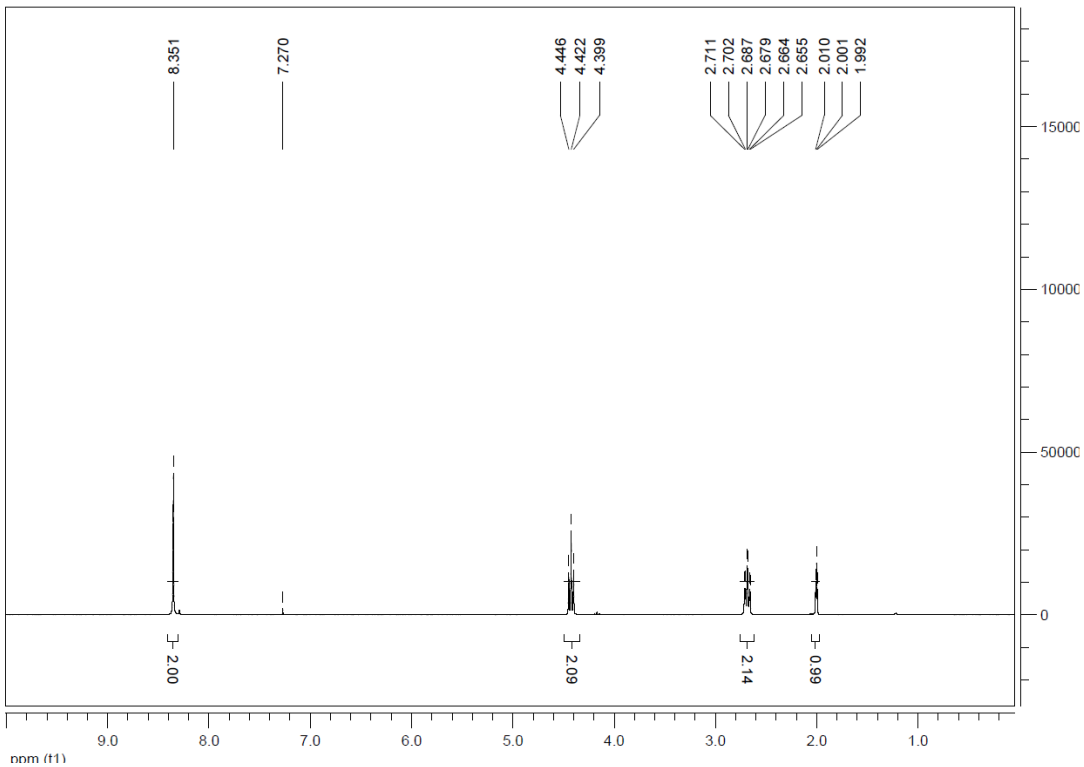




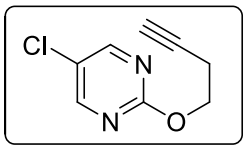


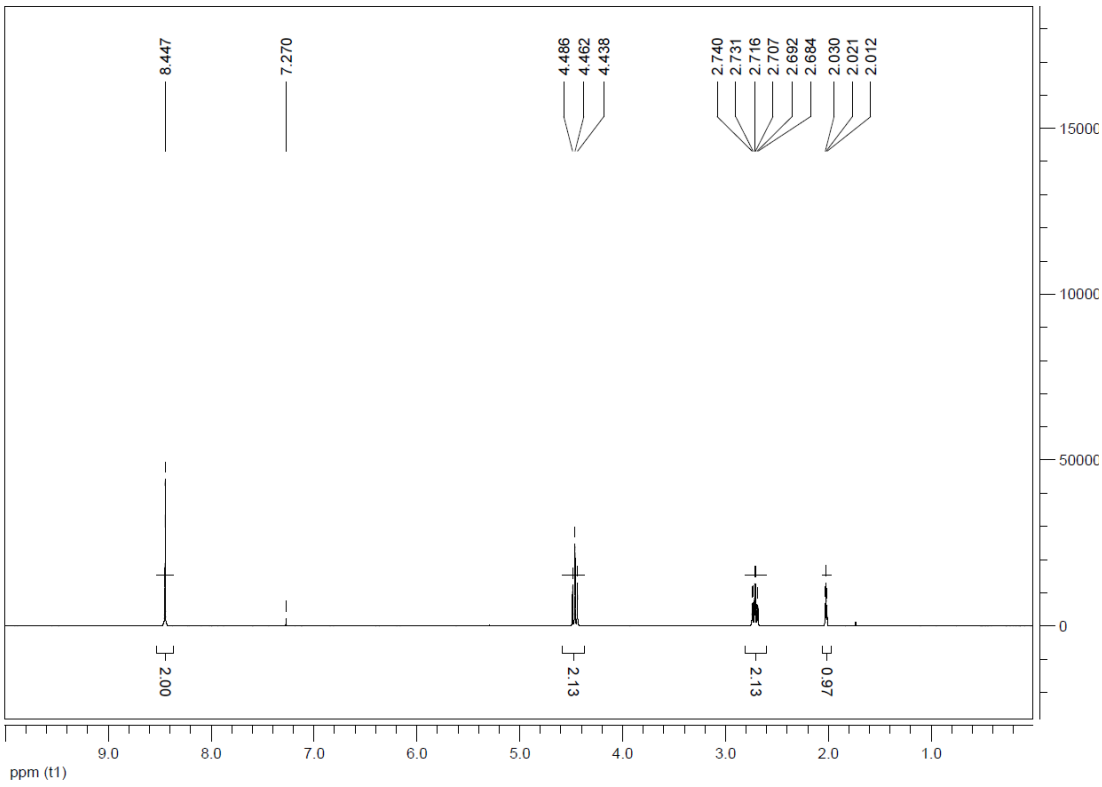
2-(But-3-ynyloxy)-5-fluoropyrimidine (**2f**)



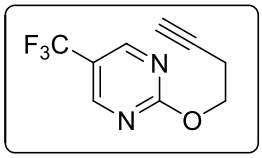


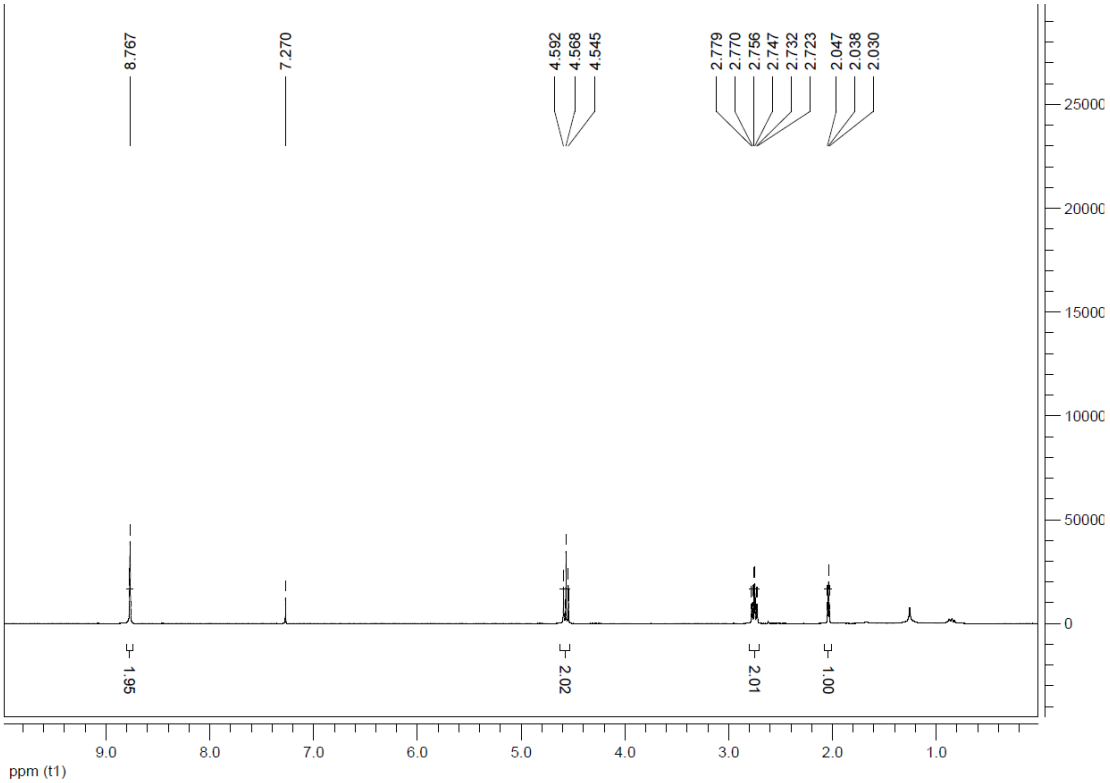
2-(But-3-ynyloxy)-5-chloropyrimidine (**2i**)

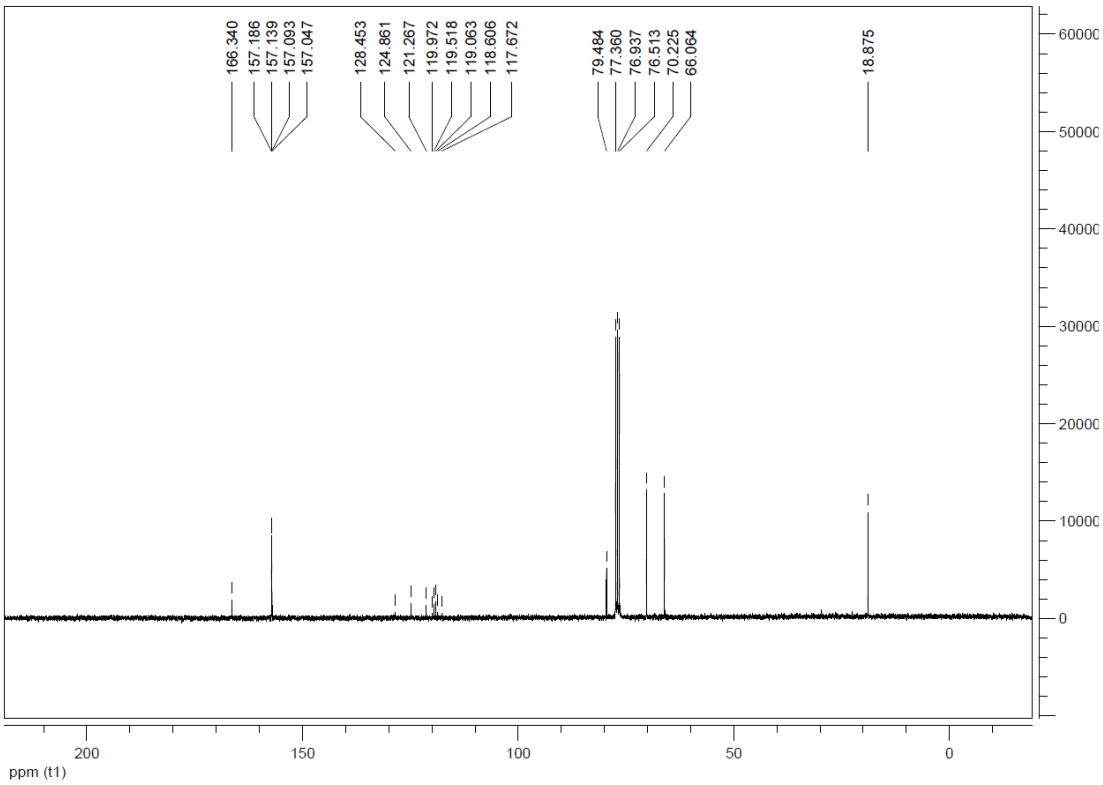




2-(But-3-ynyloxy)-5-(trifluoromethyl)pyrimidine (**2j**)



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157.139
157.093
157.047
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121.267
119.972
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119.063
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117.672
79.484
77.360
76.937
76.513
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66.064
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50000
40000
30000
20000
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150
100
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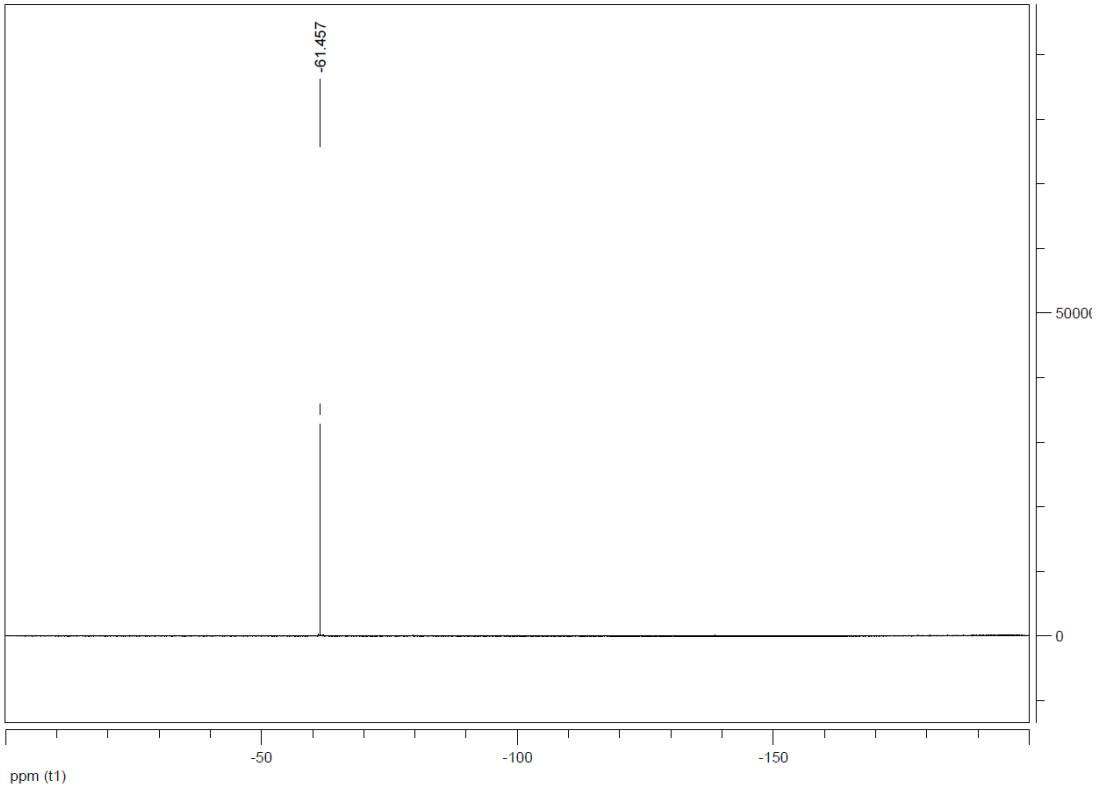
0
ppm (t1)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-100
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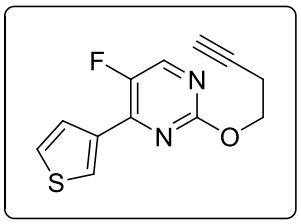
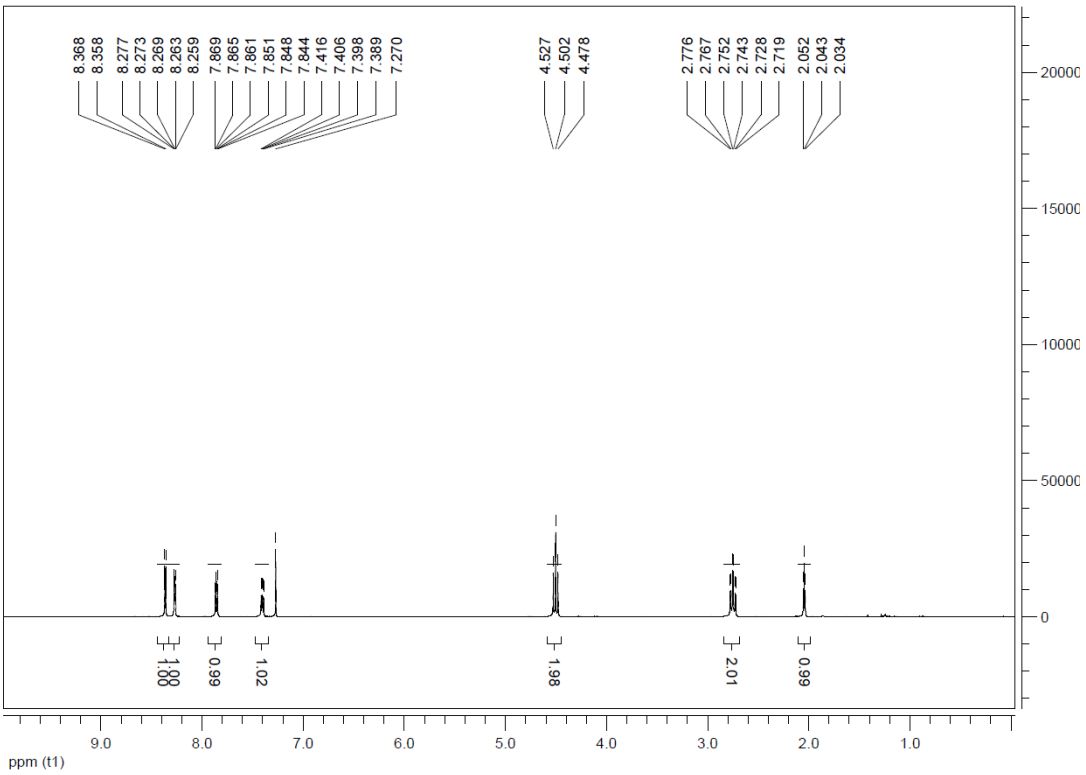
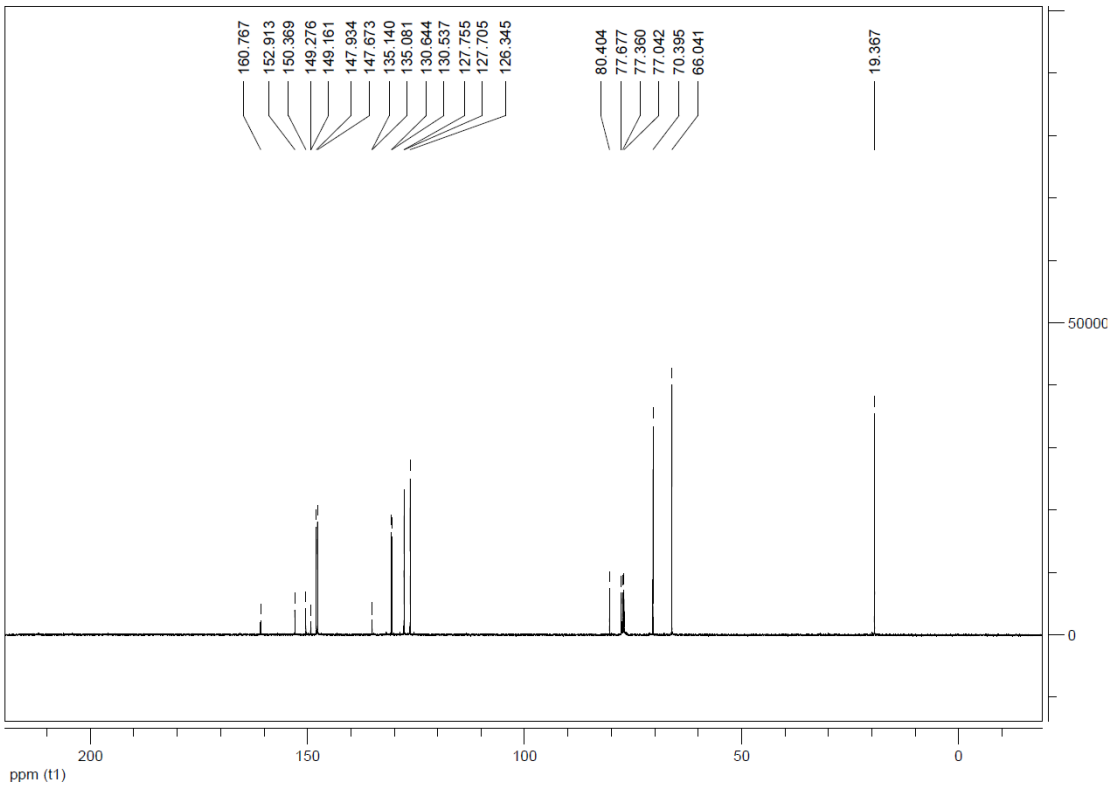
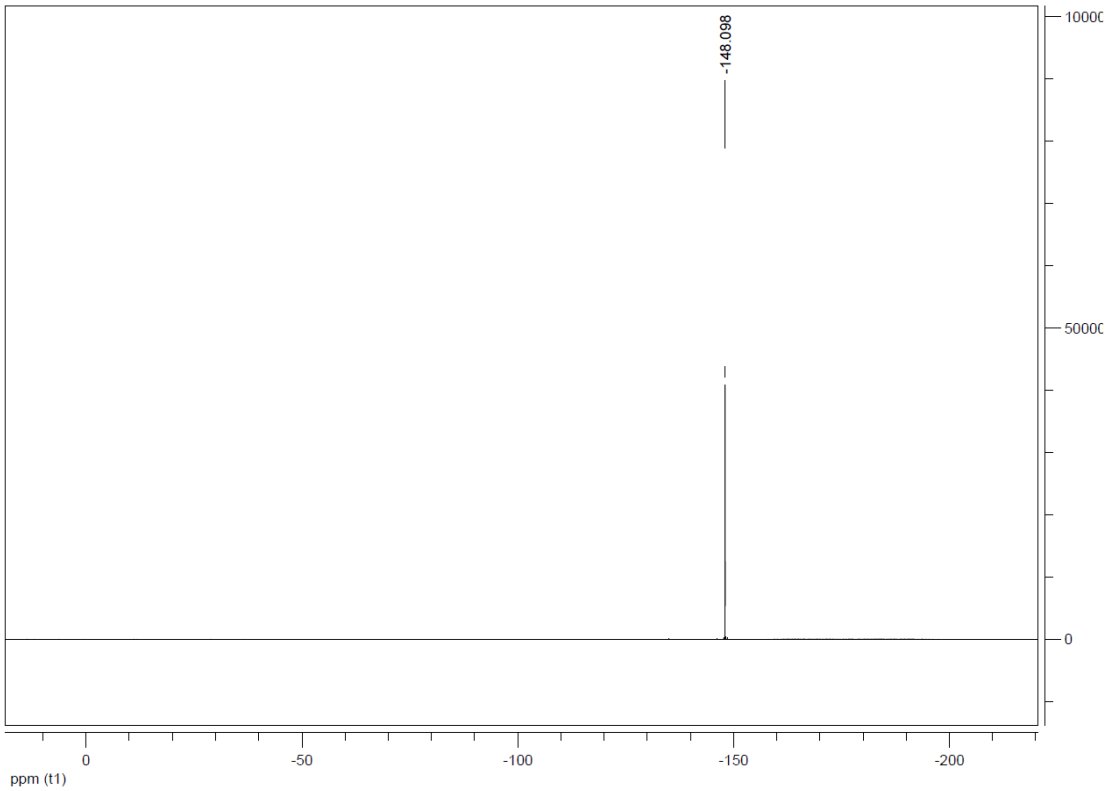
ppm (t1)



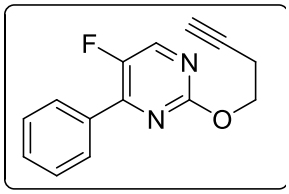
2-(But-3-ynyloxy)-5-fluoro-4-(thiophen-3-yl)pyrimidine (**2k**)

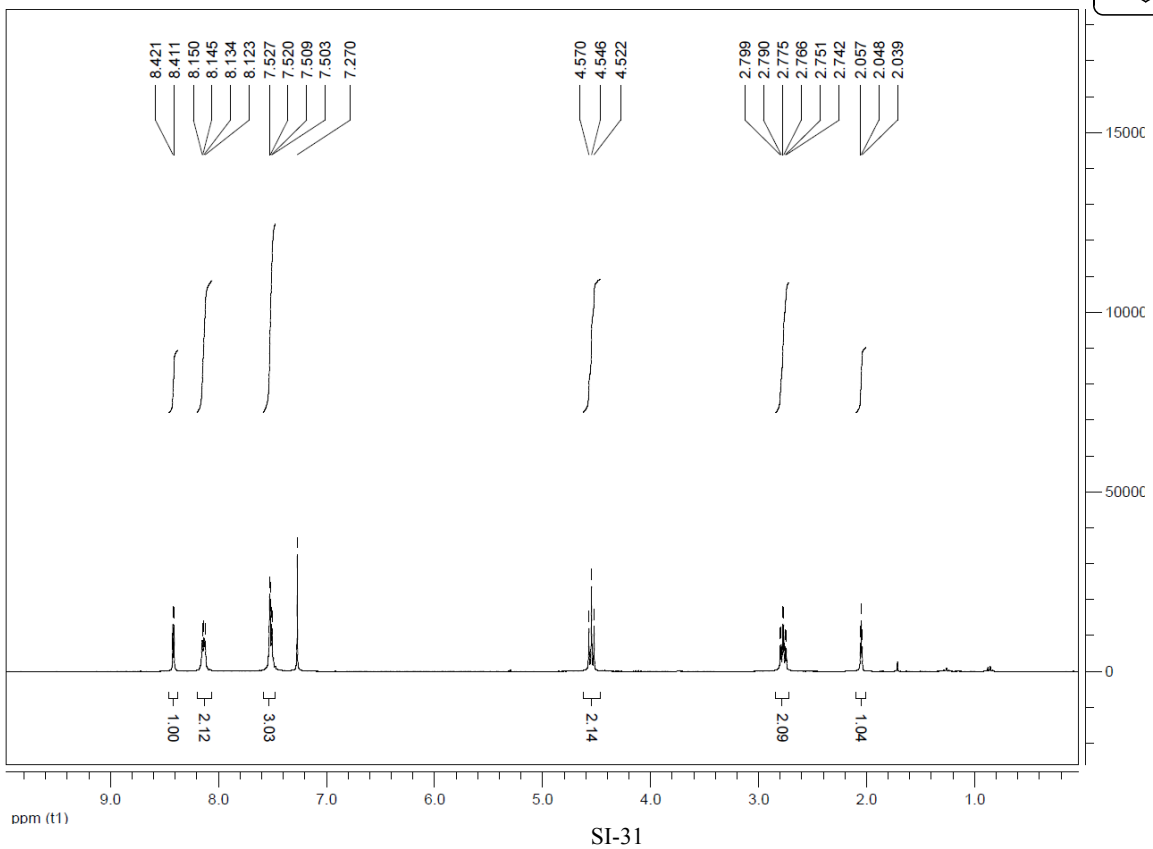




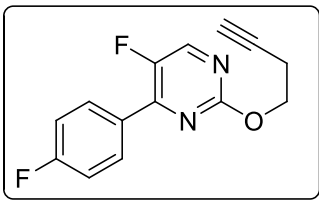


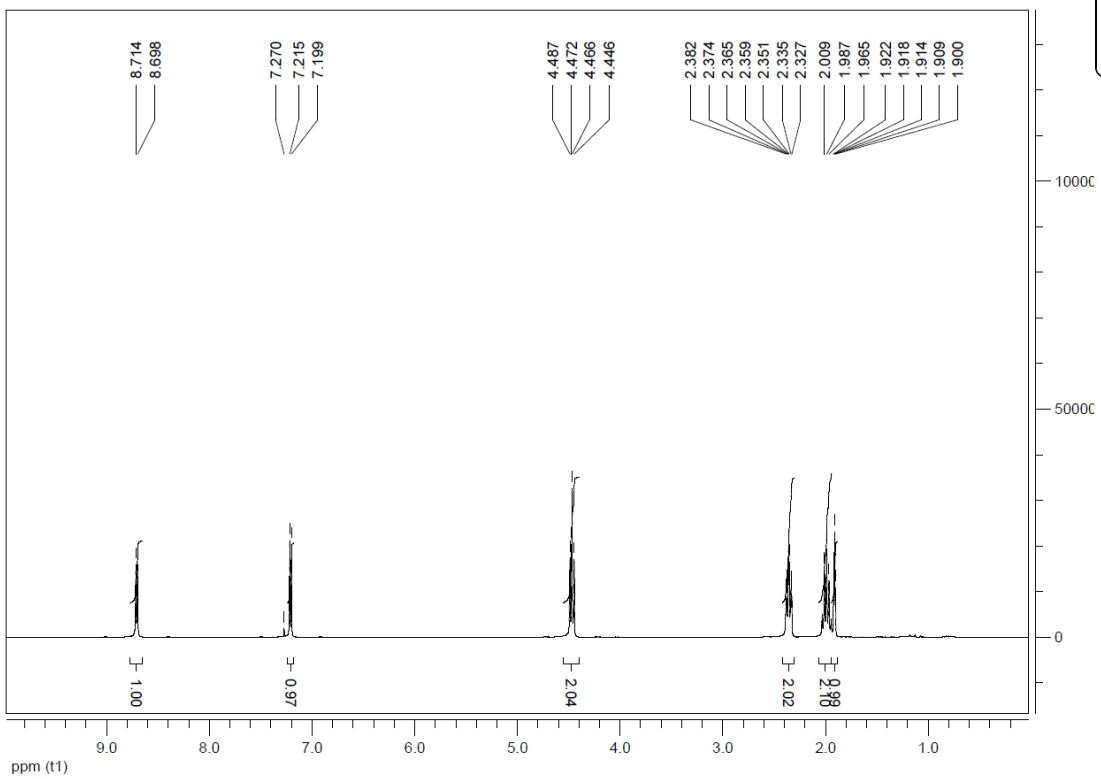
2-(But-3-ynyloxy)-5-fluoro-4-phenylpyrimidine (**2l**)



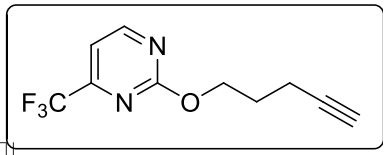


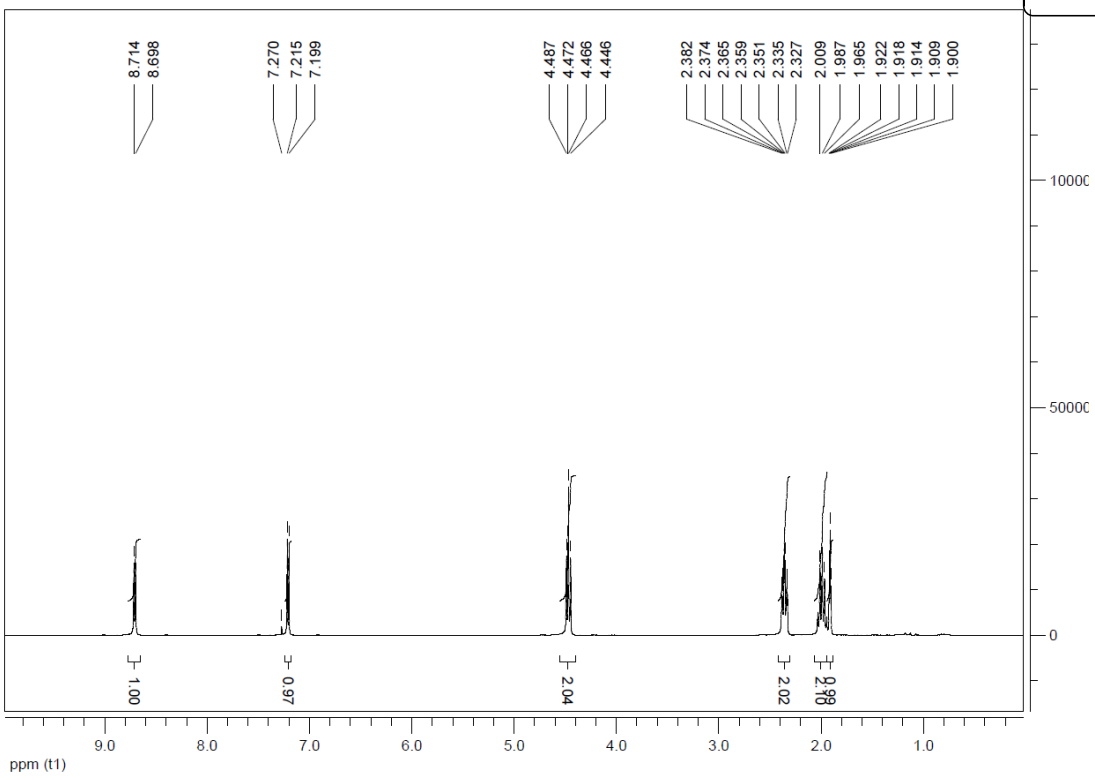
2-(But-3-ynyloxy)-5-fluoro-4-(4-fluorophenyl)pyrimidine (**2m**)

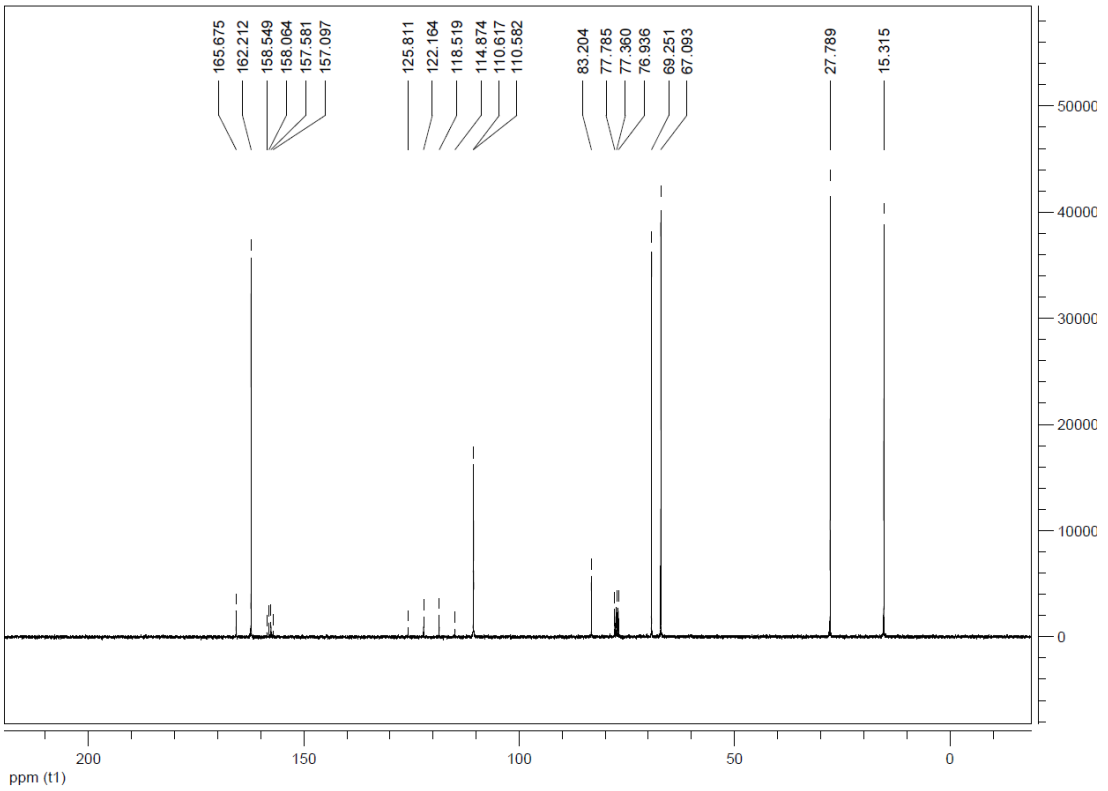




2-(Pent-4-ynyloxy)-4-(trifluoromethyl)pyrimidine (**2n**)



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122.164
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110.617
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83.204
77.785
77.360
76.936
69.251
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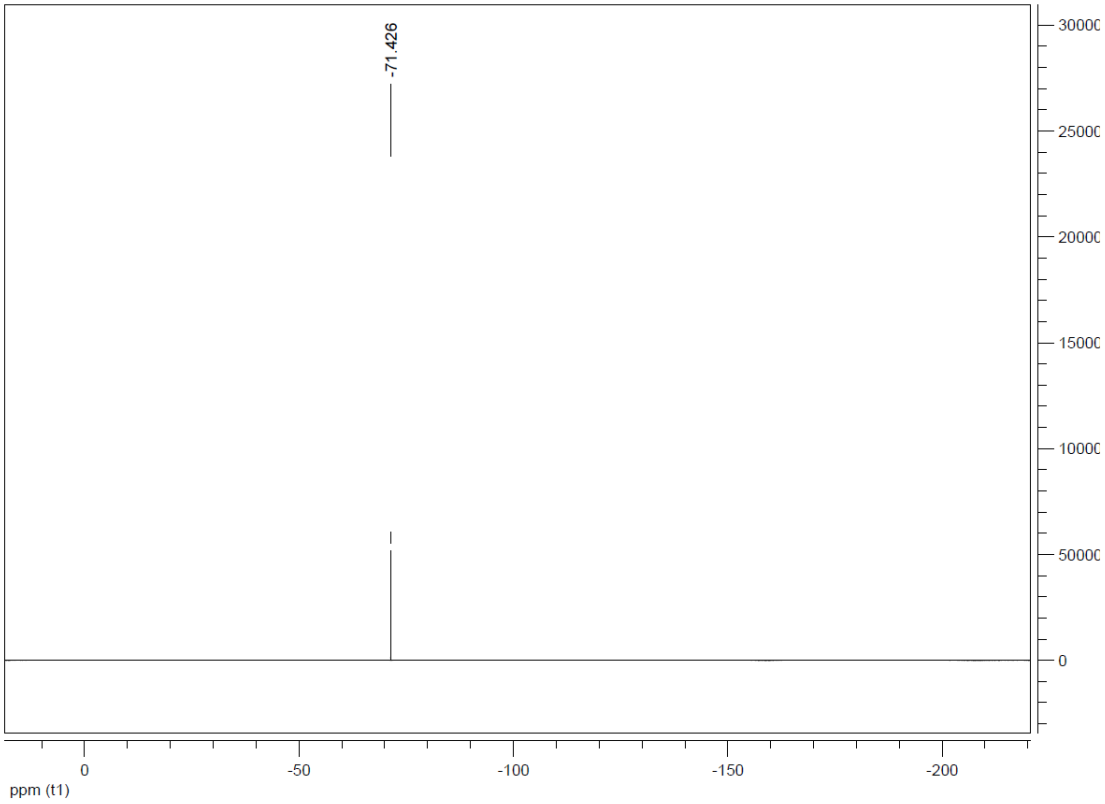
ppm (t1)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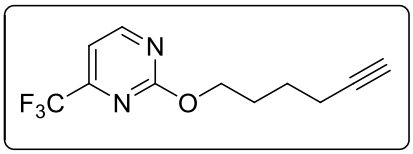
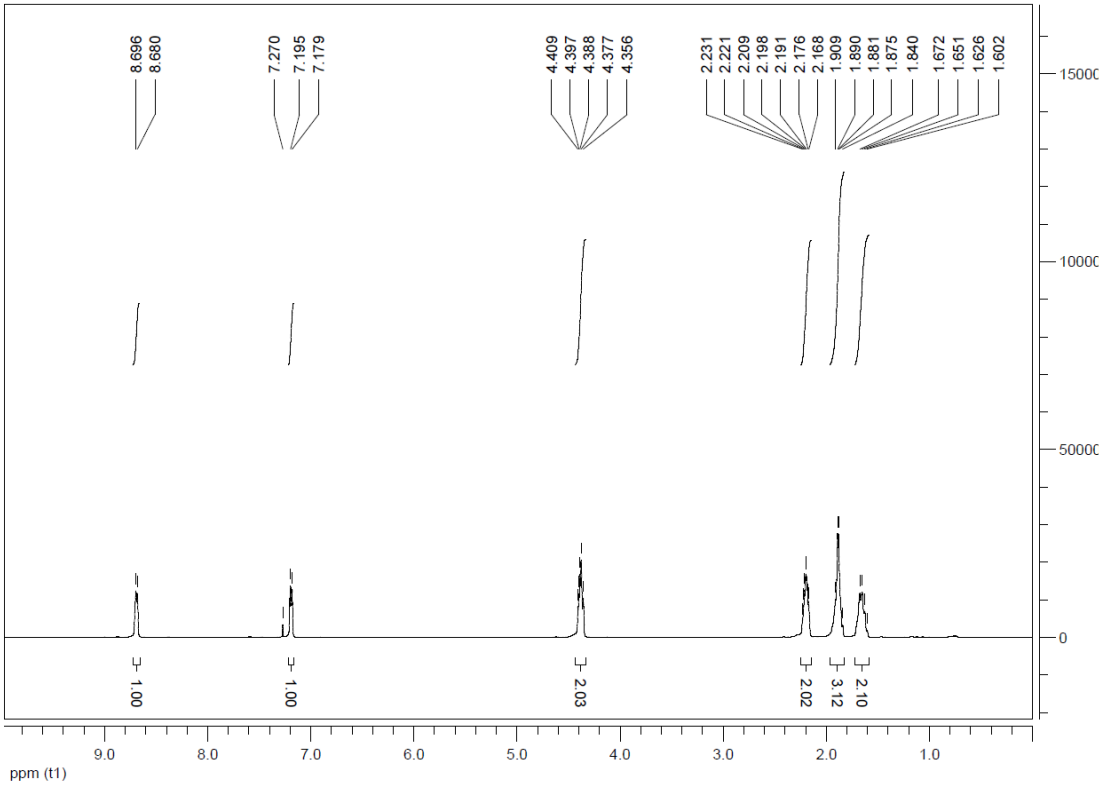
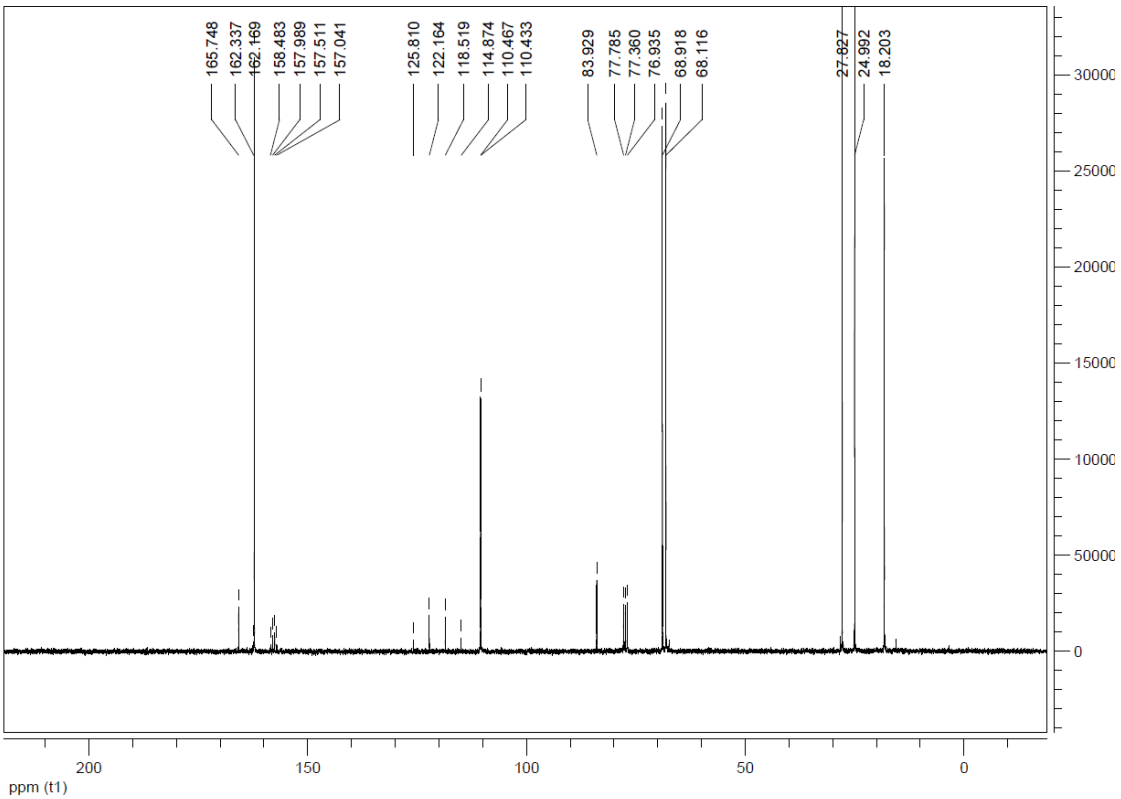
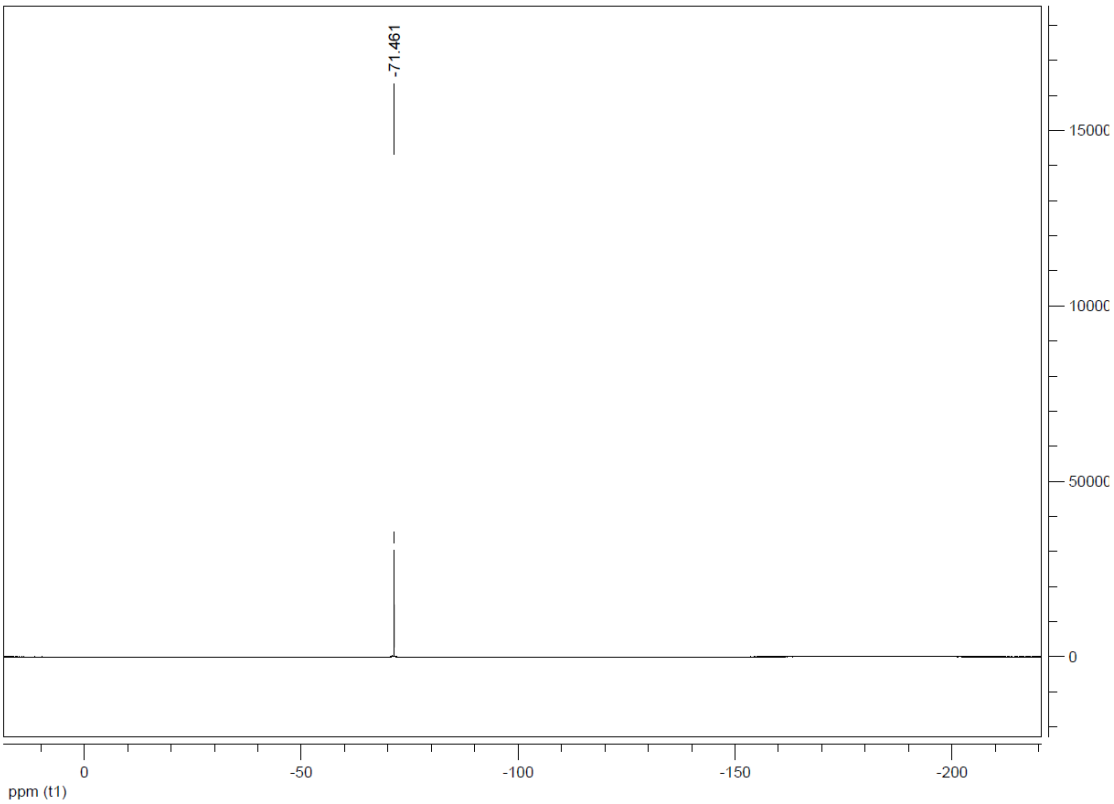
ppm (t1)

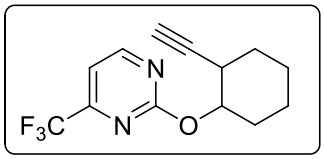
2-(Hex-5-ynyloxy)-4-(trifluoromethyl)pyrimidine (**2o**)



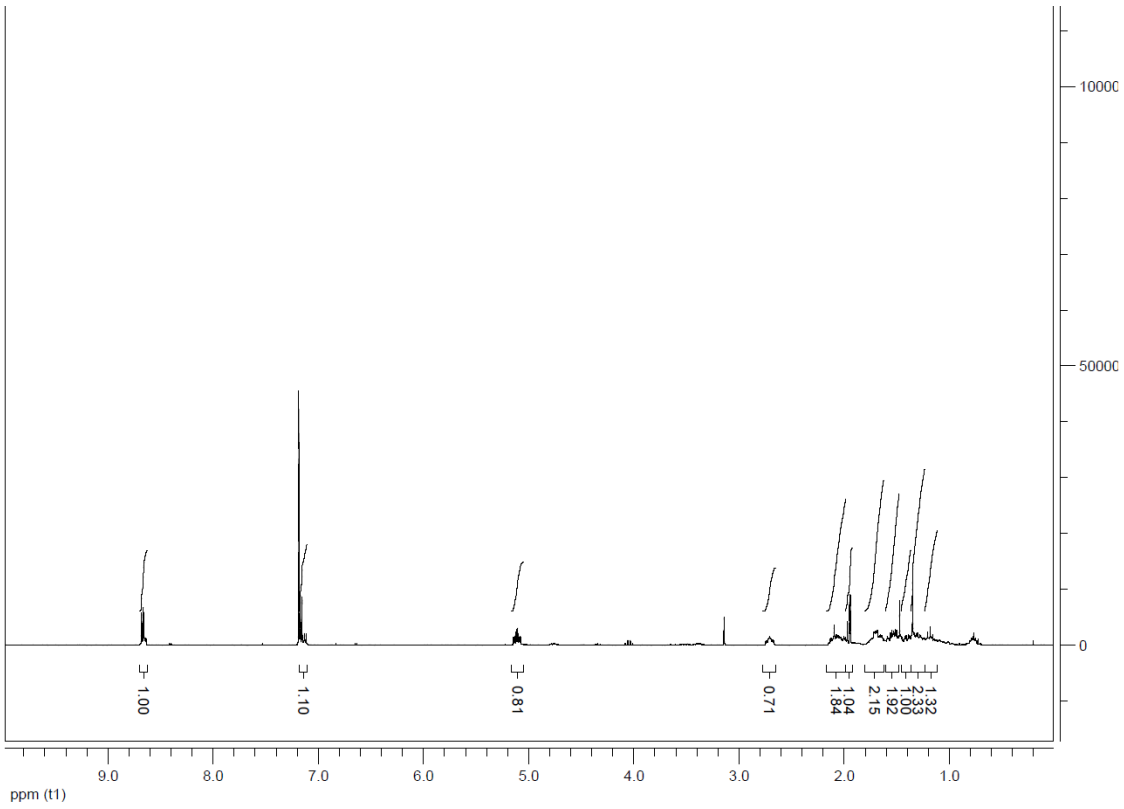


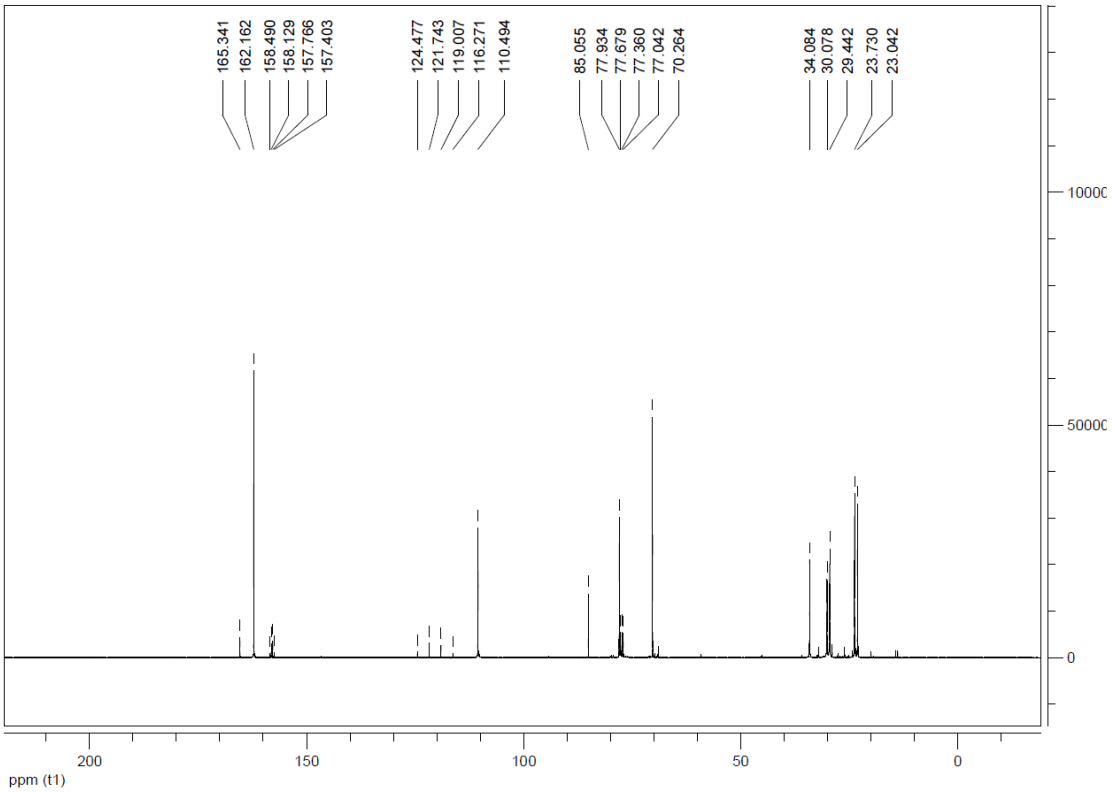






2-(2-Ethynylcyclohexyloxy)-4-(trifluoromethyl)pyrimidine (**2p**)

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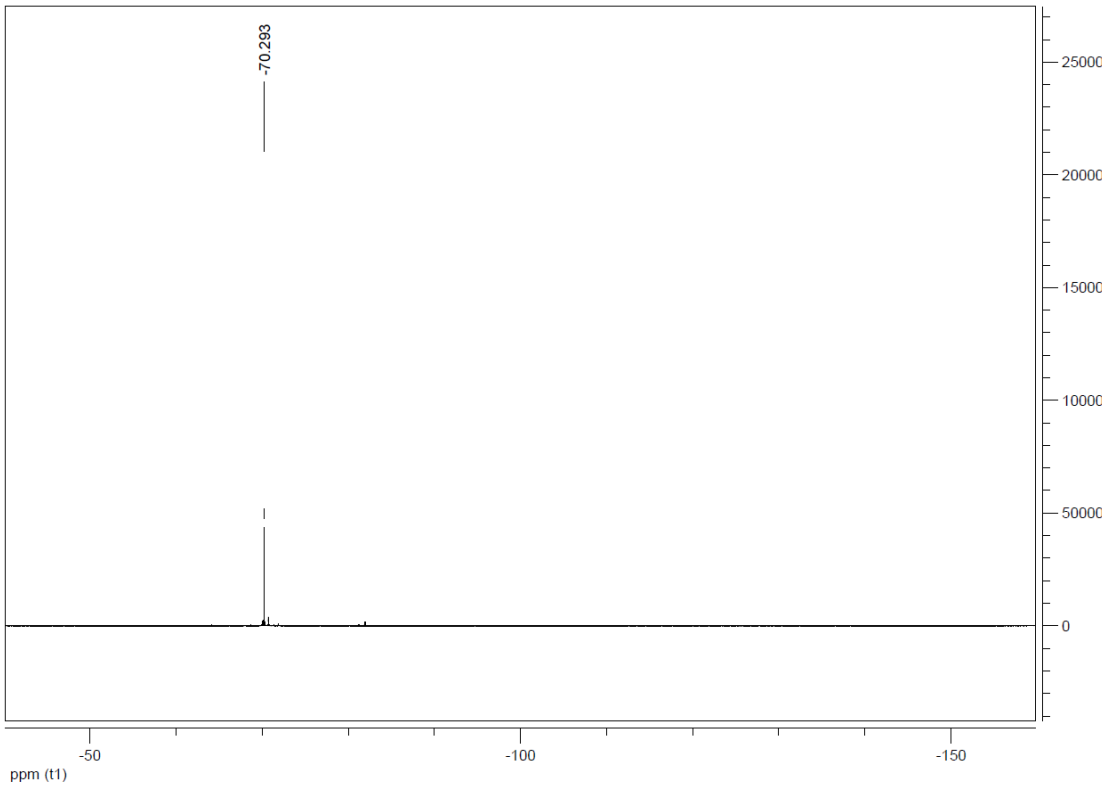
ppm (t1)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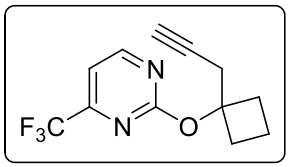
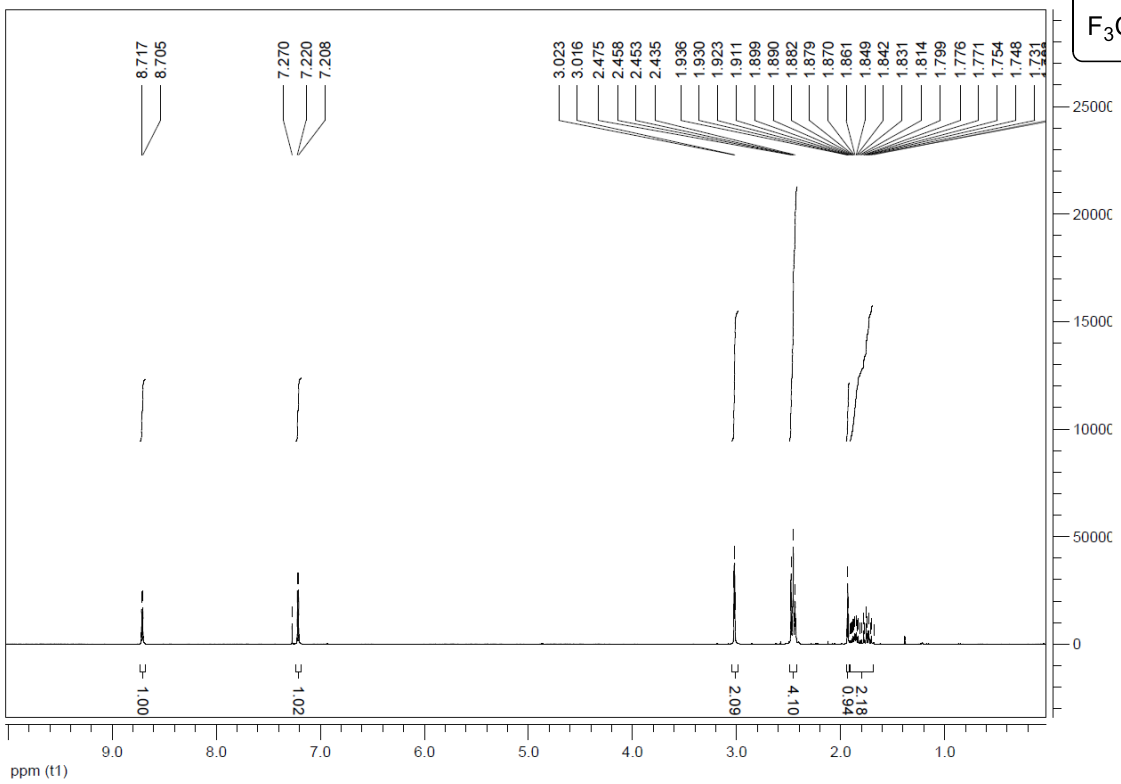
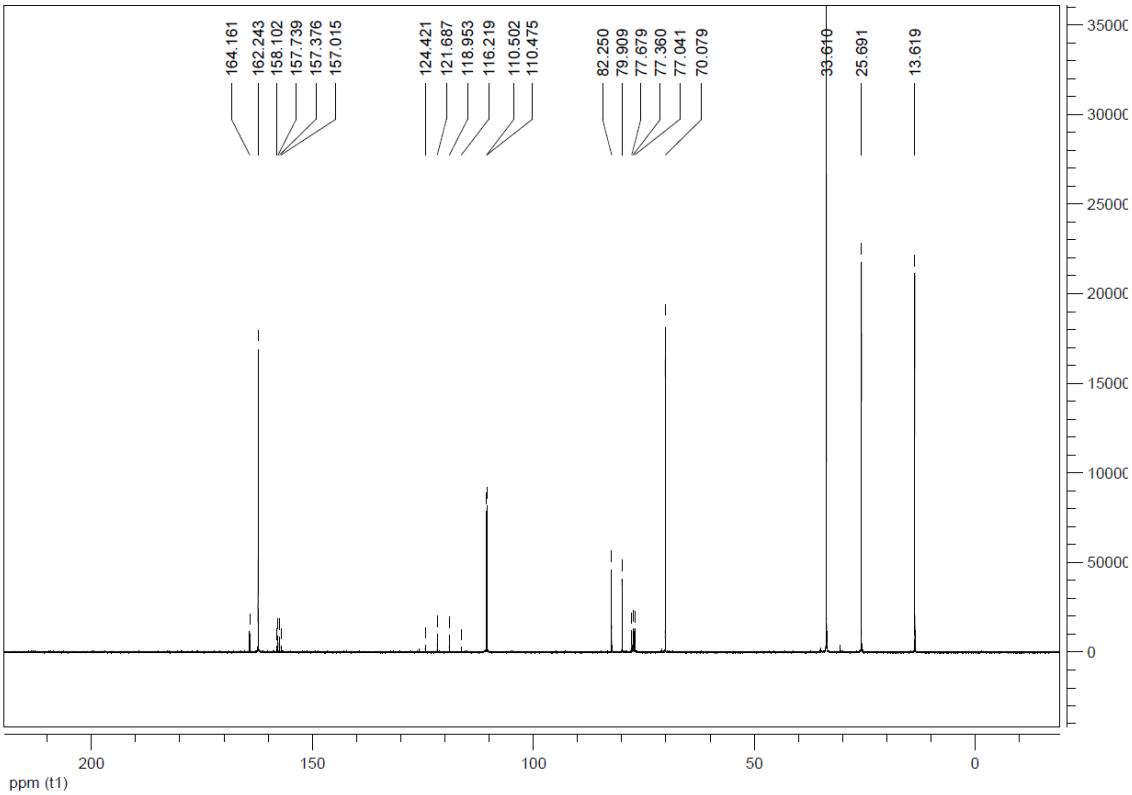
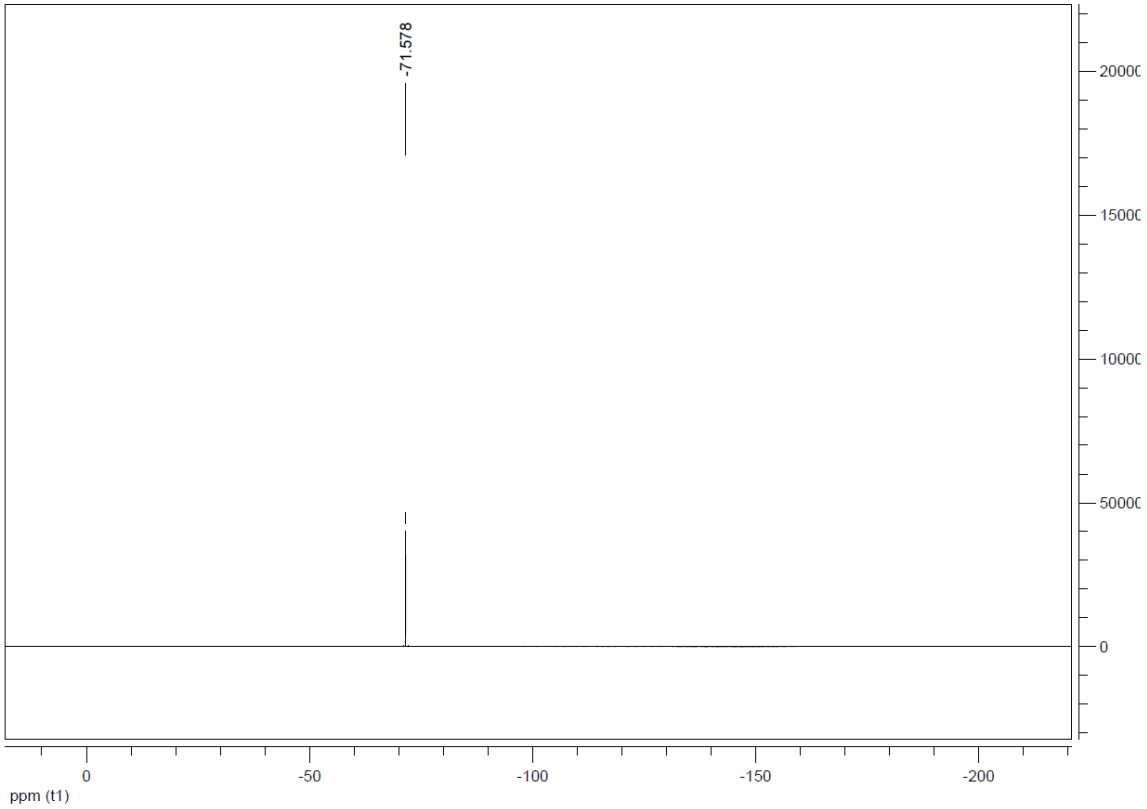
ppm (t1)

2-(1-(Prop-2-ynyl)cyclobutoxy)-4-(trifluoromethyl)pyrimidine (**2r**)

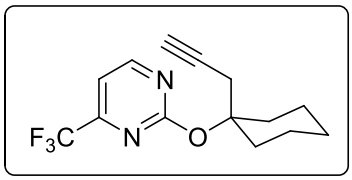


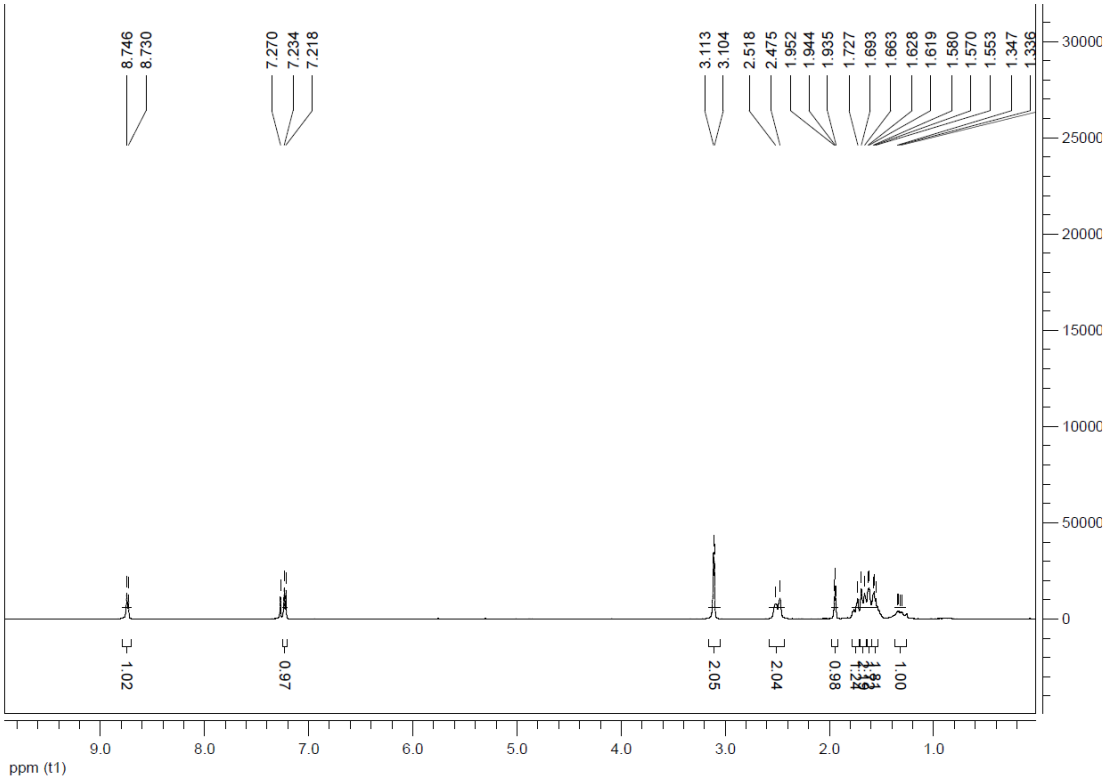


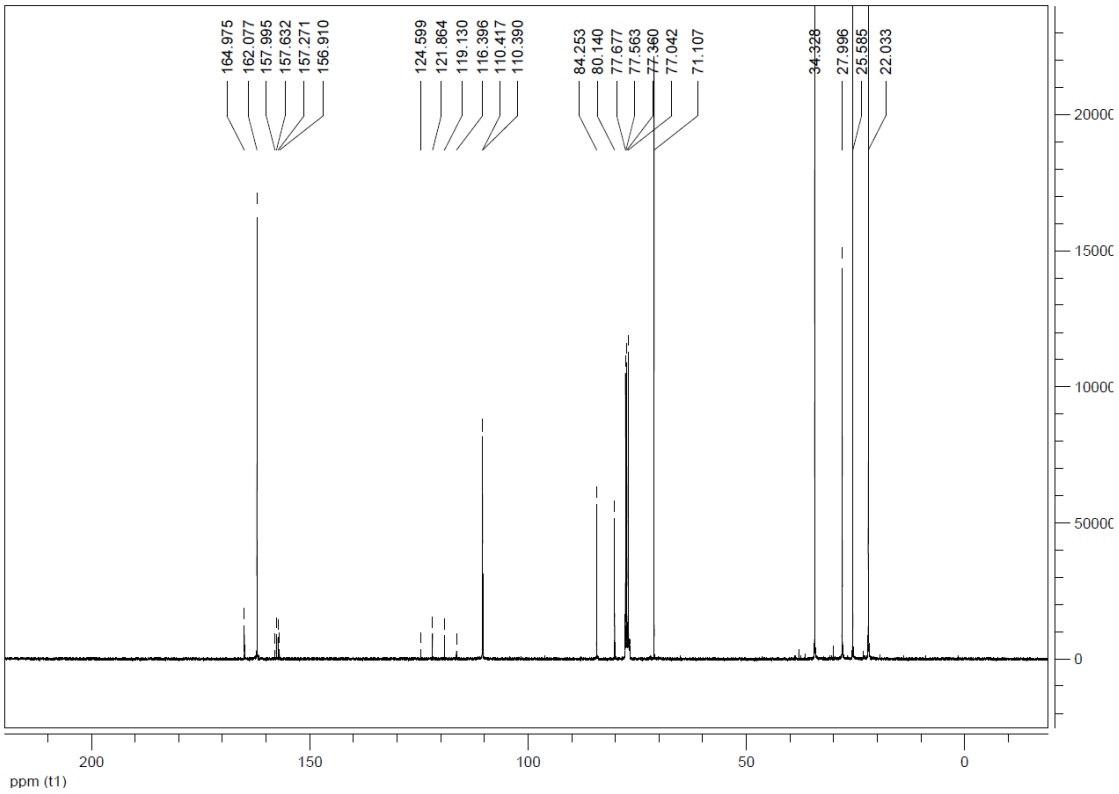


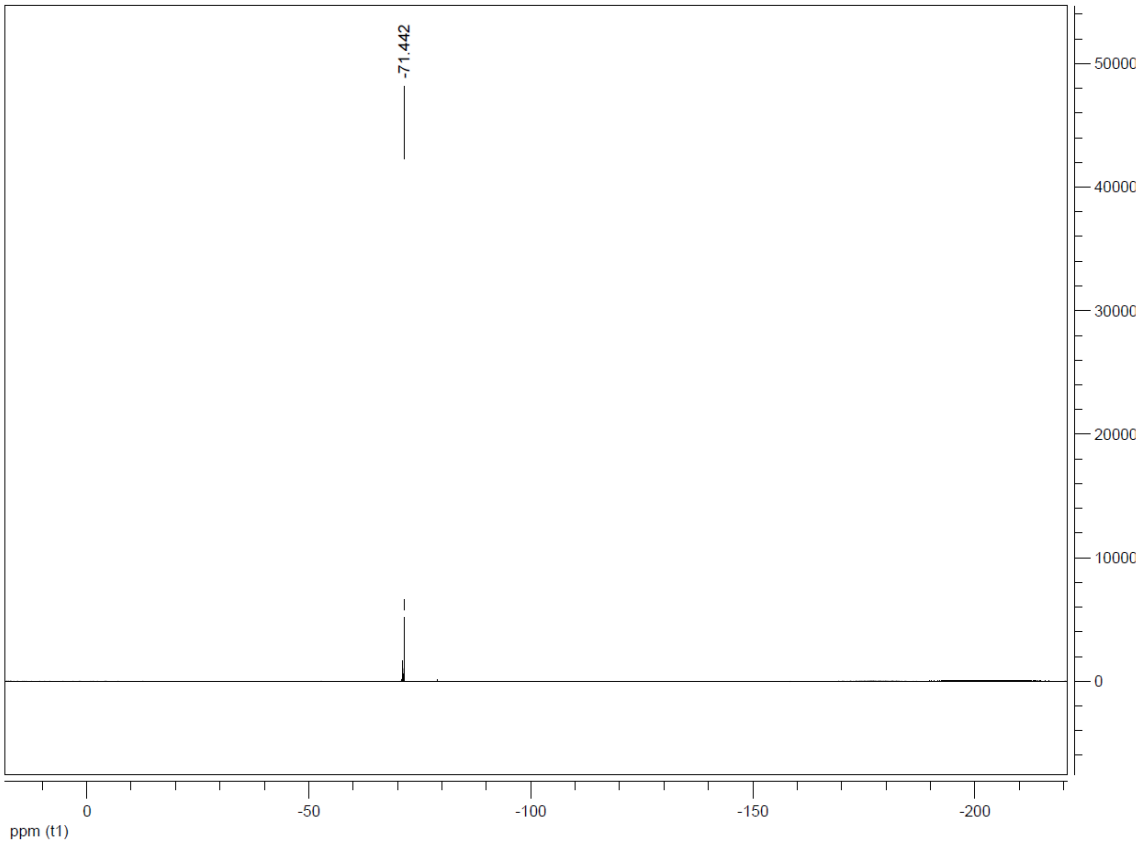


2-(1-(Prop-2-ynyl)cyclohexyloxy)-4-(trifluoromethyl)pyrimidine (**2s**)

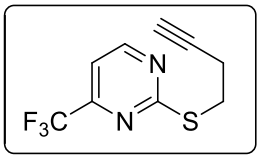


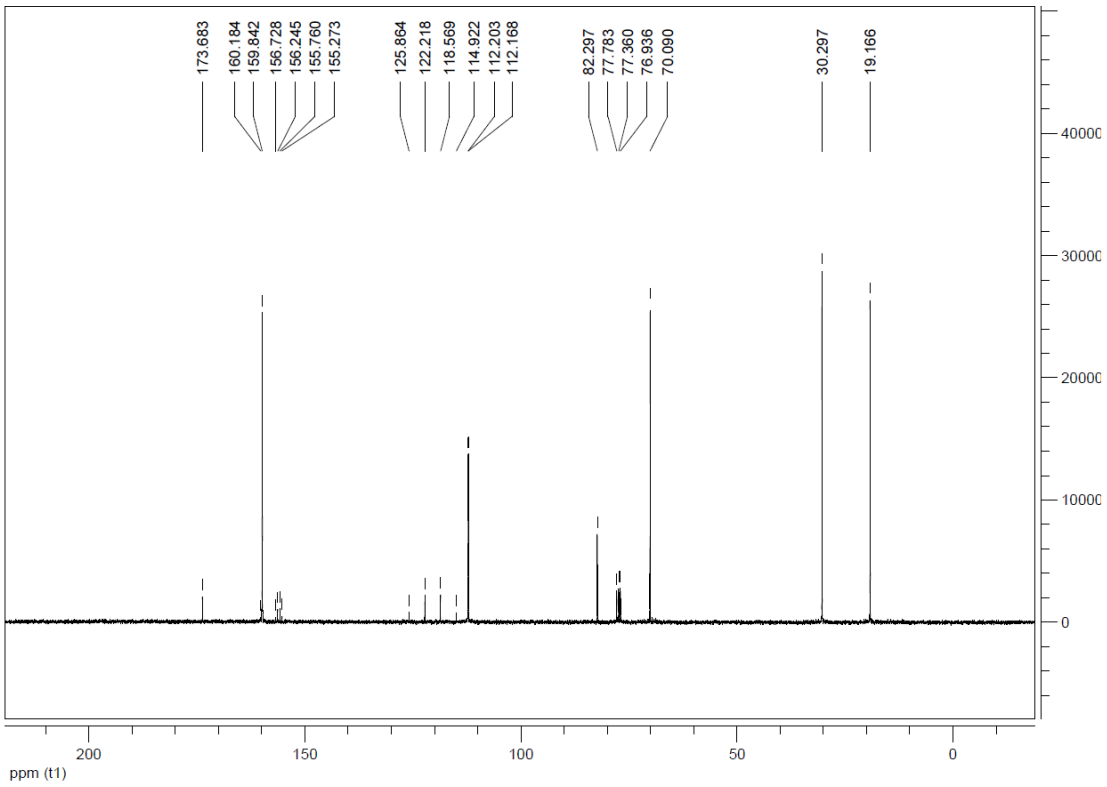


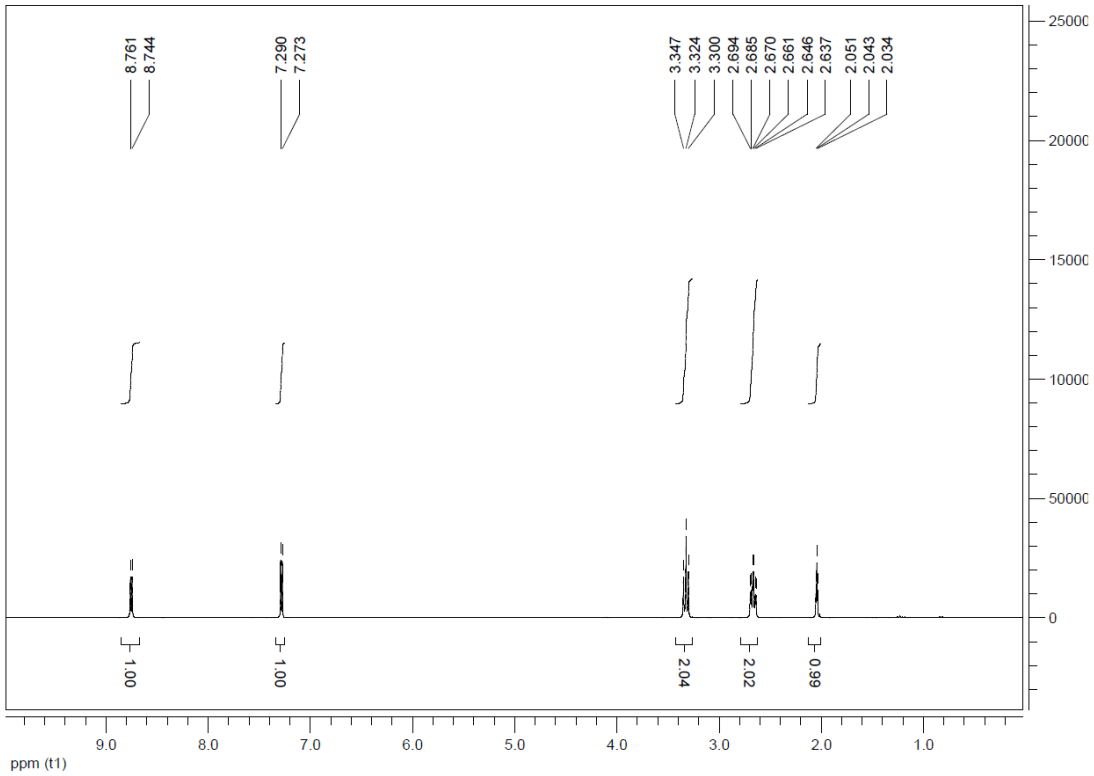

164.975
162.077
157.995
157.632
157.271
156.910
124.599
121.864
119.130
116.396
110.417
110.390
84.253
80.140
77.677
77.563
77.360
77.042
71.107
34.328
27.996
25.585
22.033
200
150
100
50
0
ppm (t1)

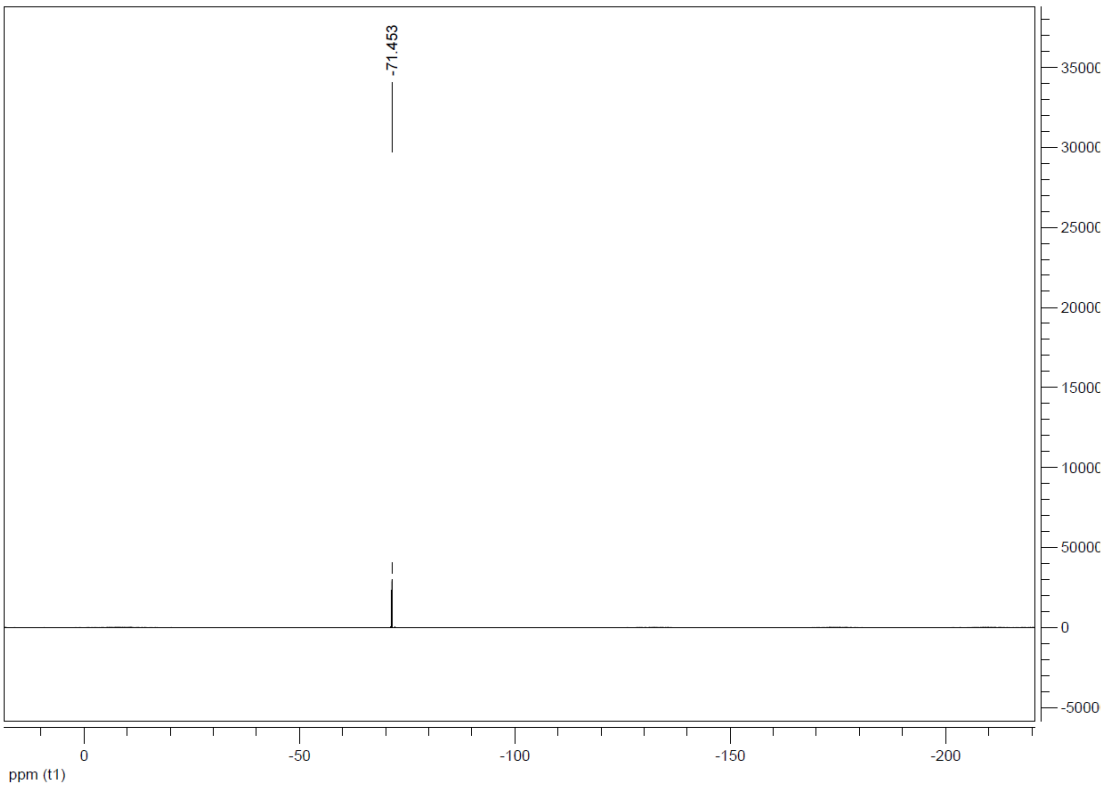

-71.442
0
-50
-100
-150
-200
ppm (t1)

2-(but-3-ynylthio)-4-(trifluoromethyl)pyrimidine (**2v**)

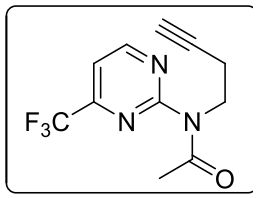


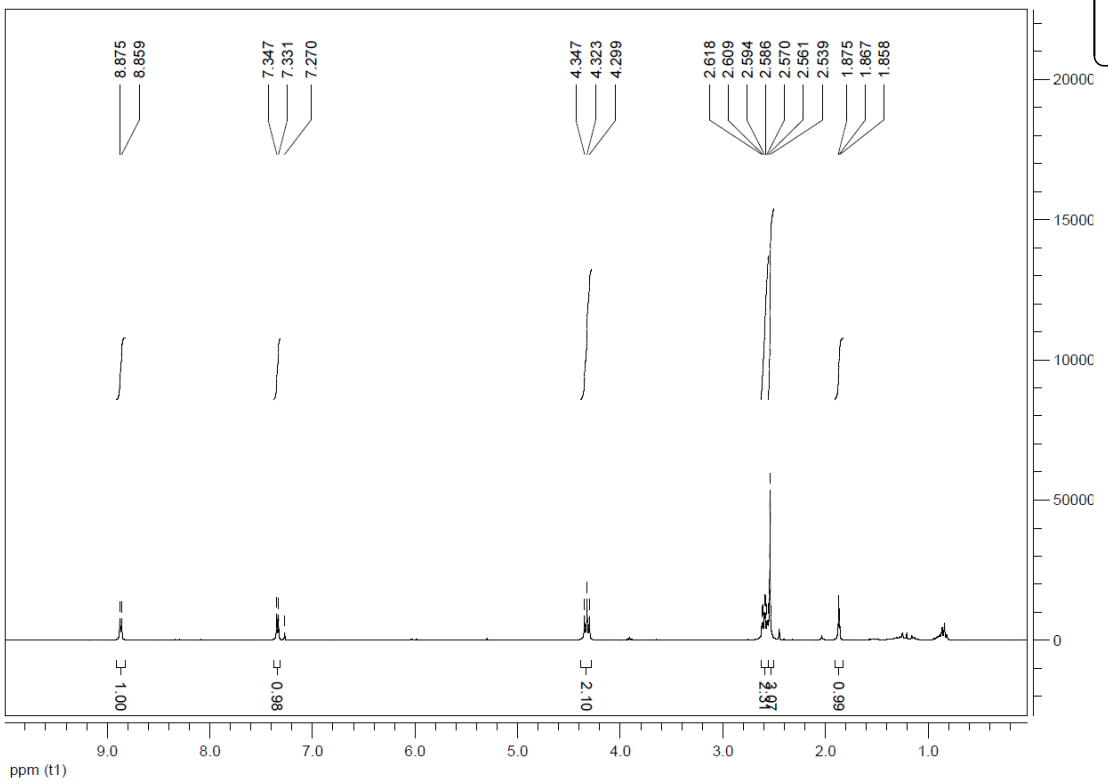


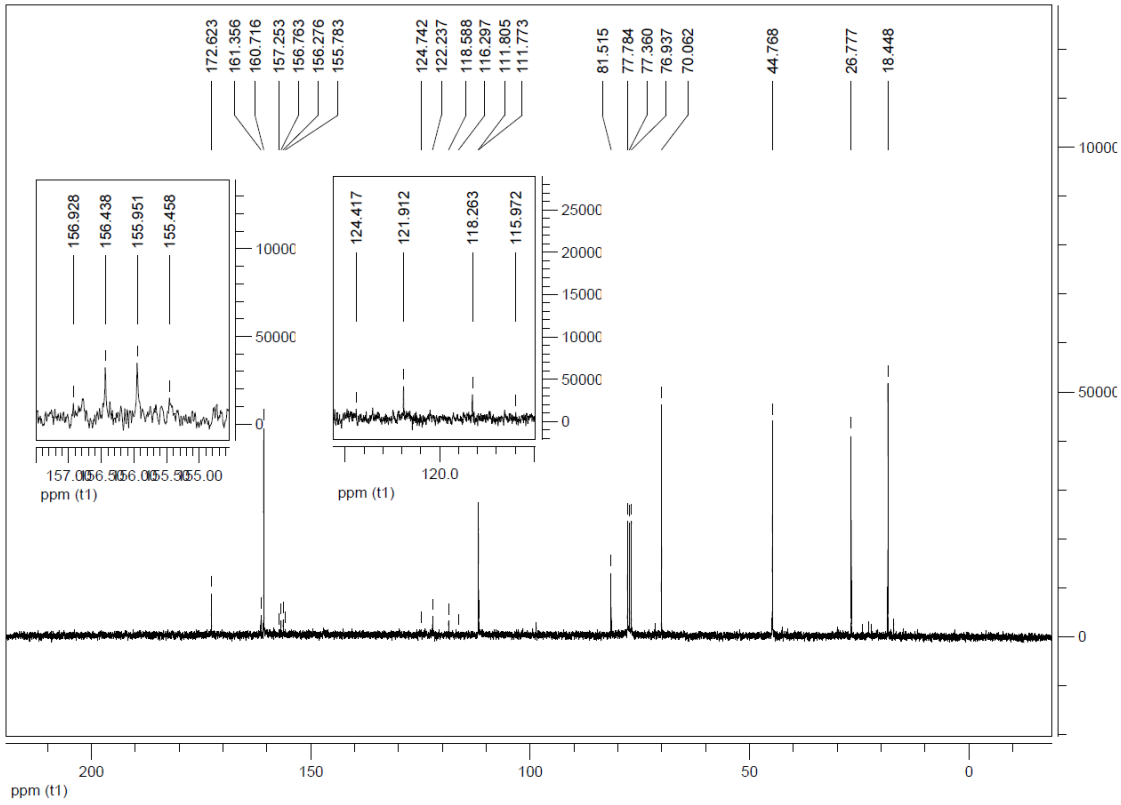


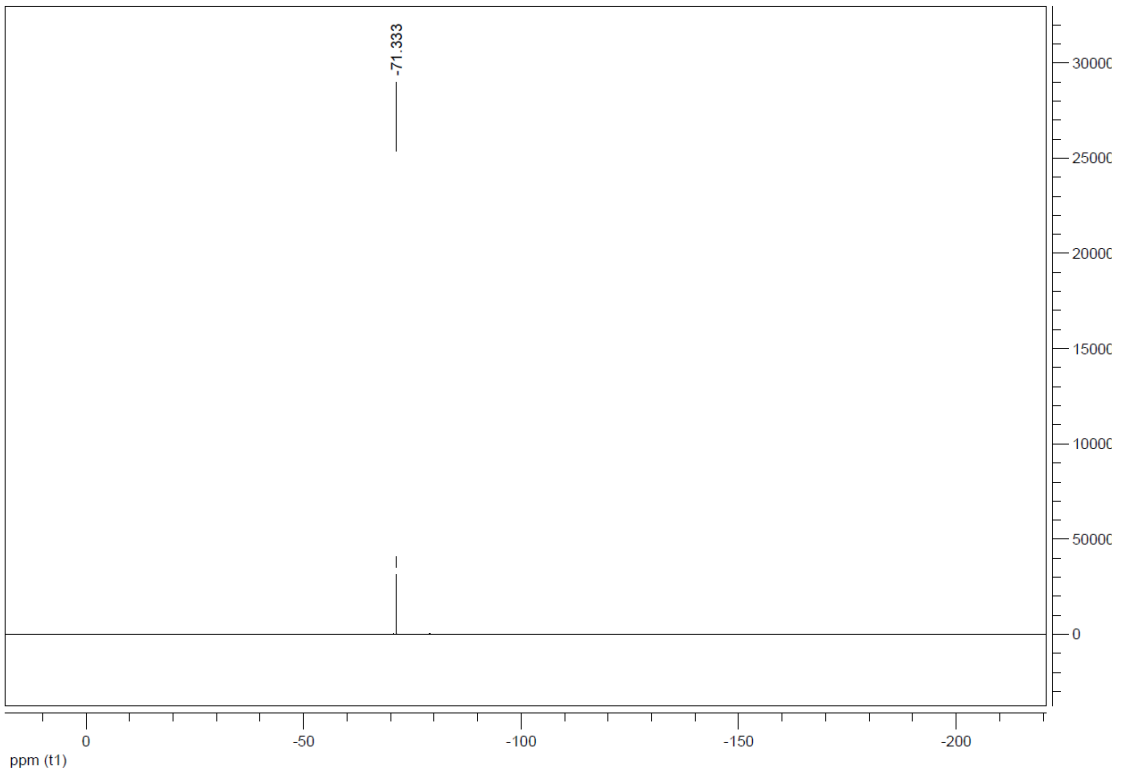


N-(but-3-ynyl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)acetamide (**4w**)

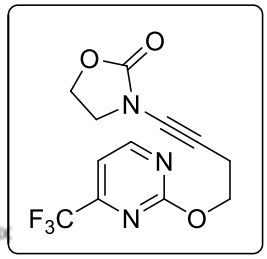


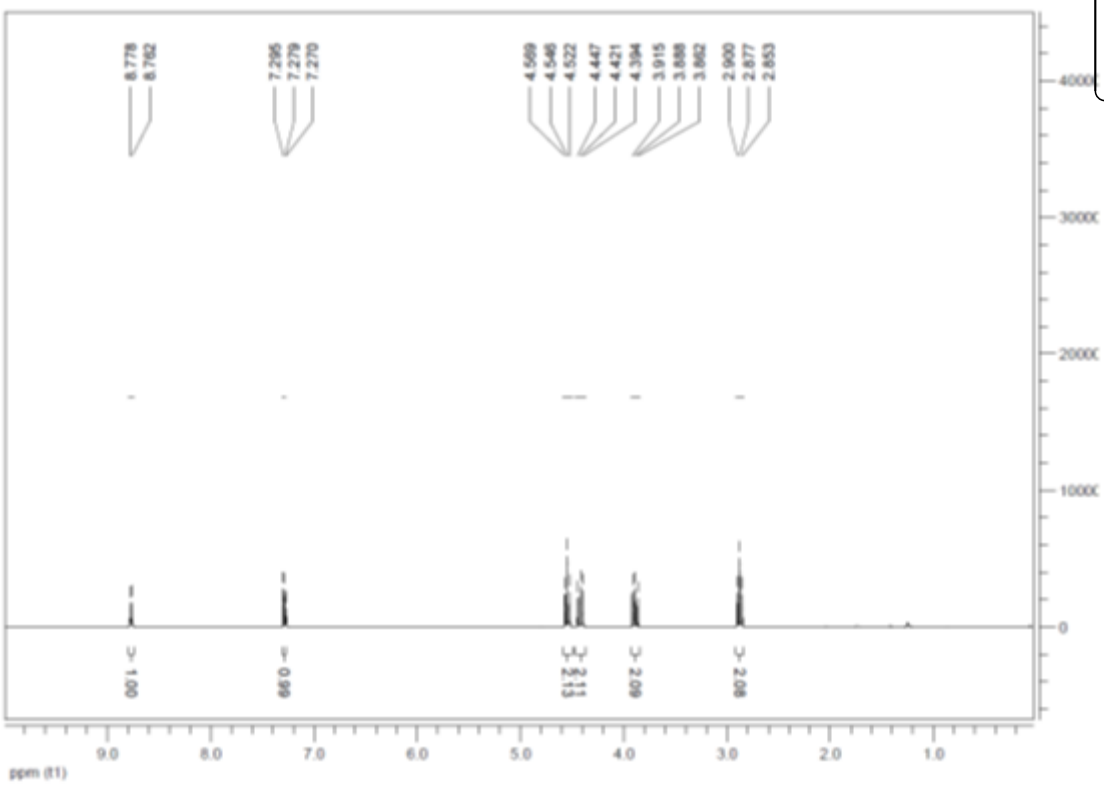


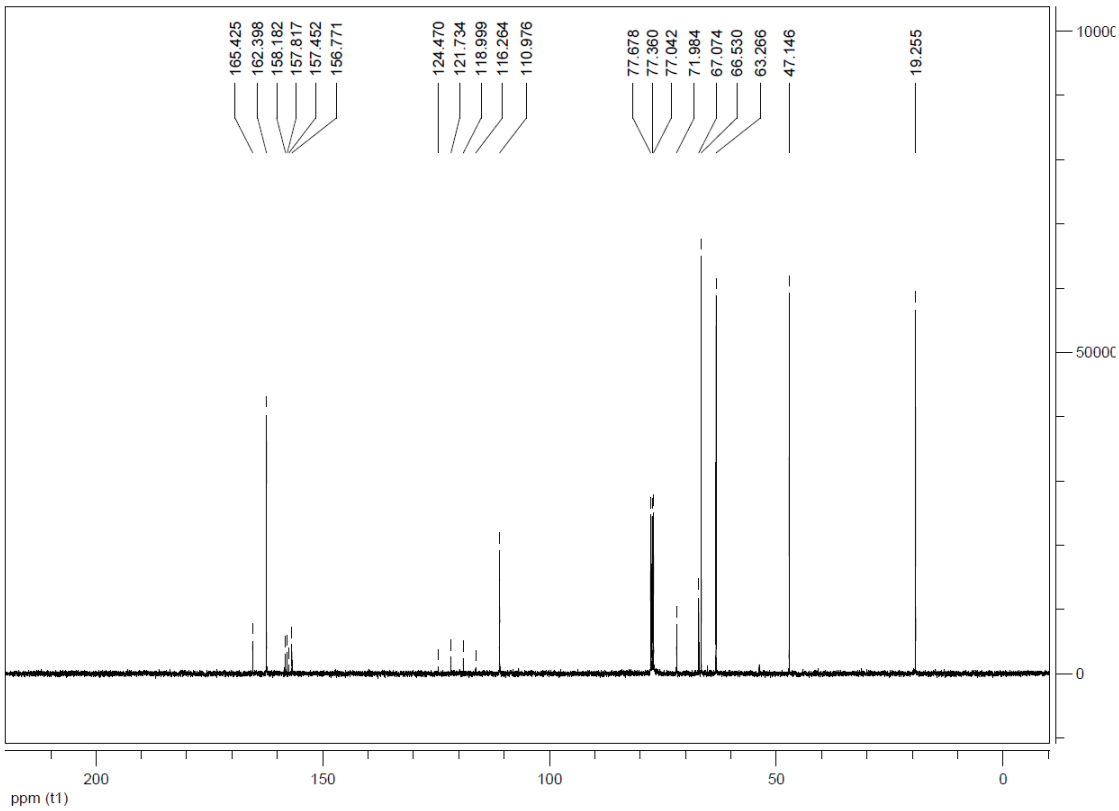

172.623
161.356
160.716
157.253
156.763
156.276
155.783
124.742
122.237
118.588
116.297
111.805
111.773
81.515
77.784
77.360
76.937
70.062
44.768
26.777
18.448
156.928
156.438
155.951
155.458
124.417
121.912
118.263
115.972
ppm (t1)
200
150
100
50
0

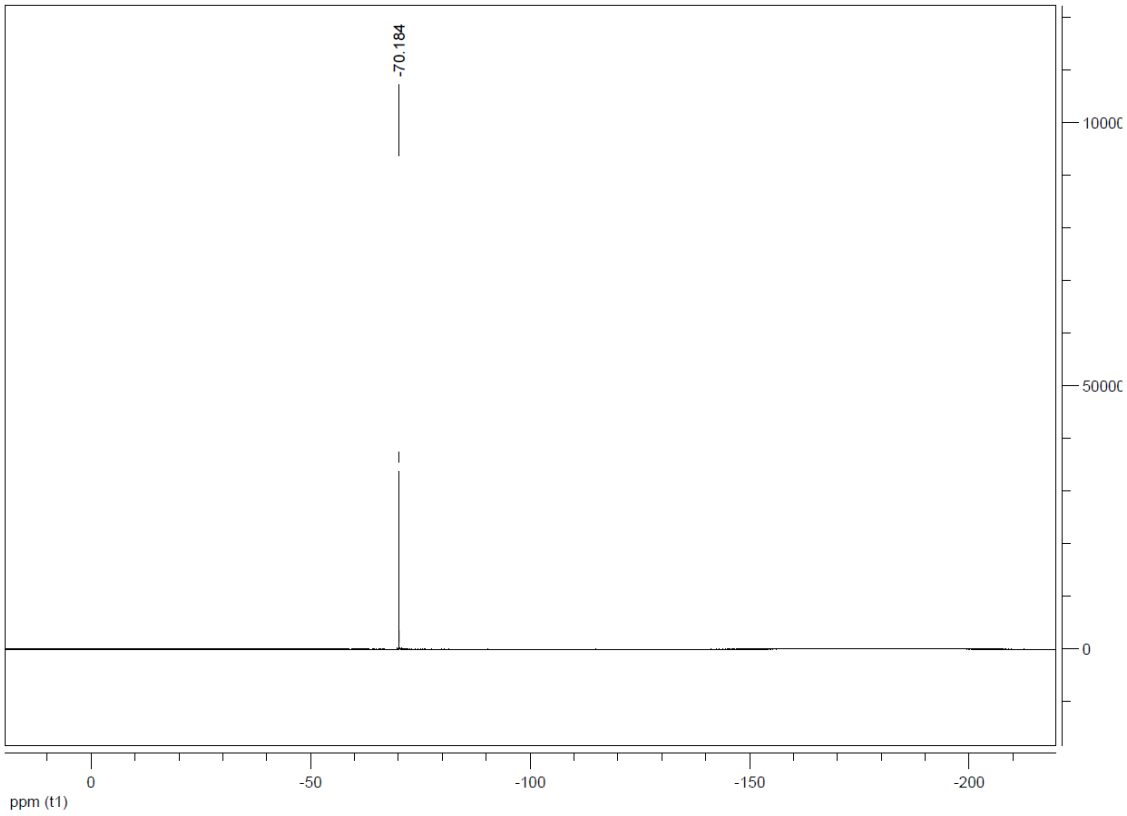

-71.333
ppm (t1)
0
-50
-100
-150
-200

3-(4-(4-(Trifluoromethyl)pyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3a**)

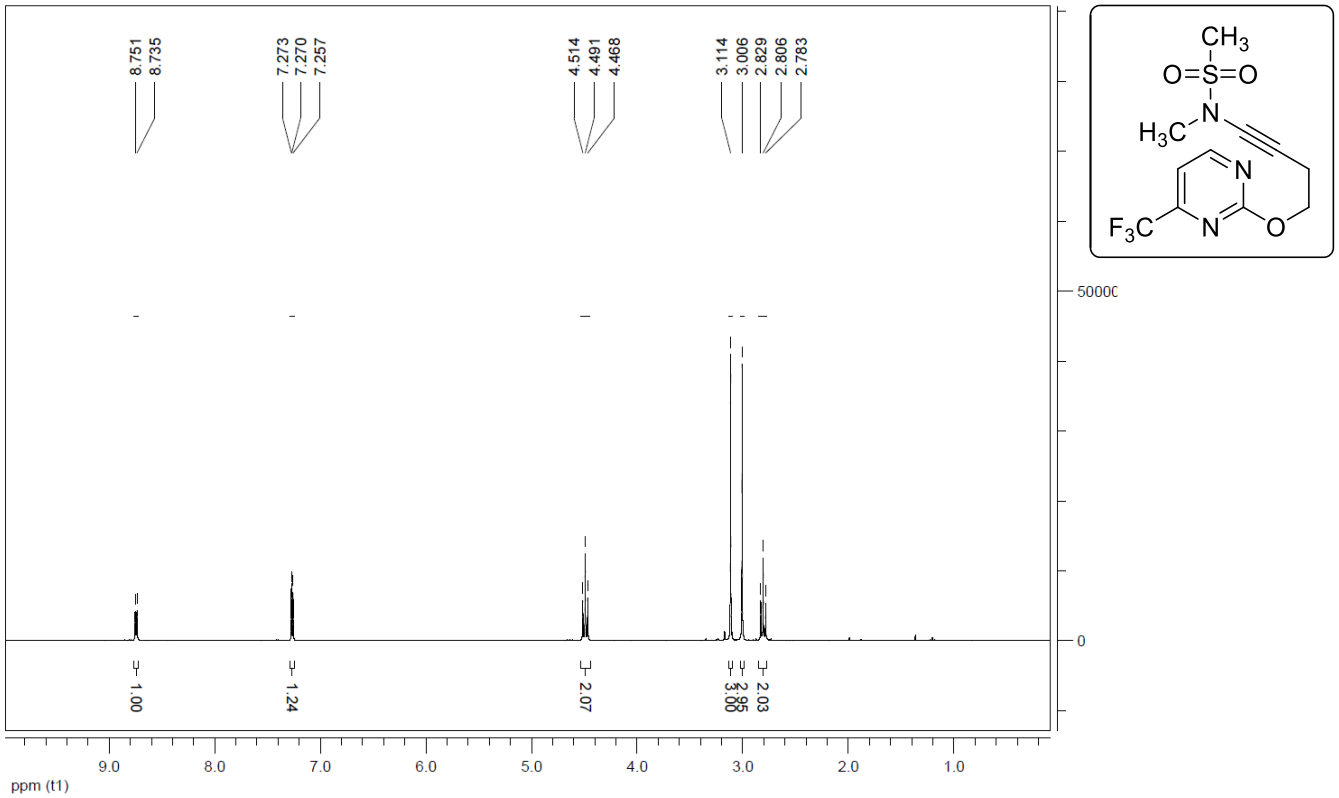


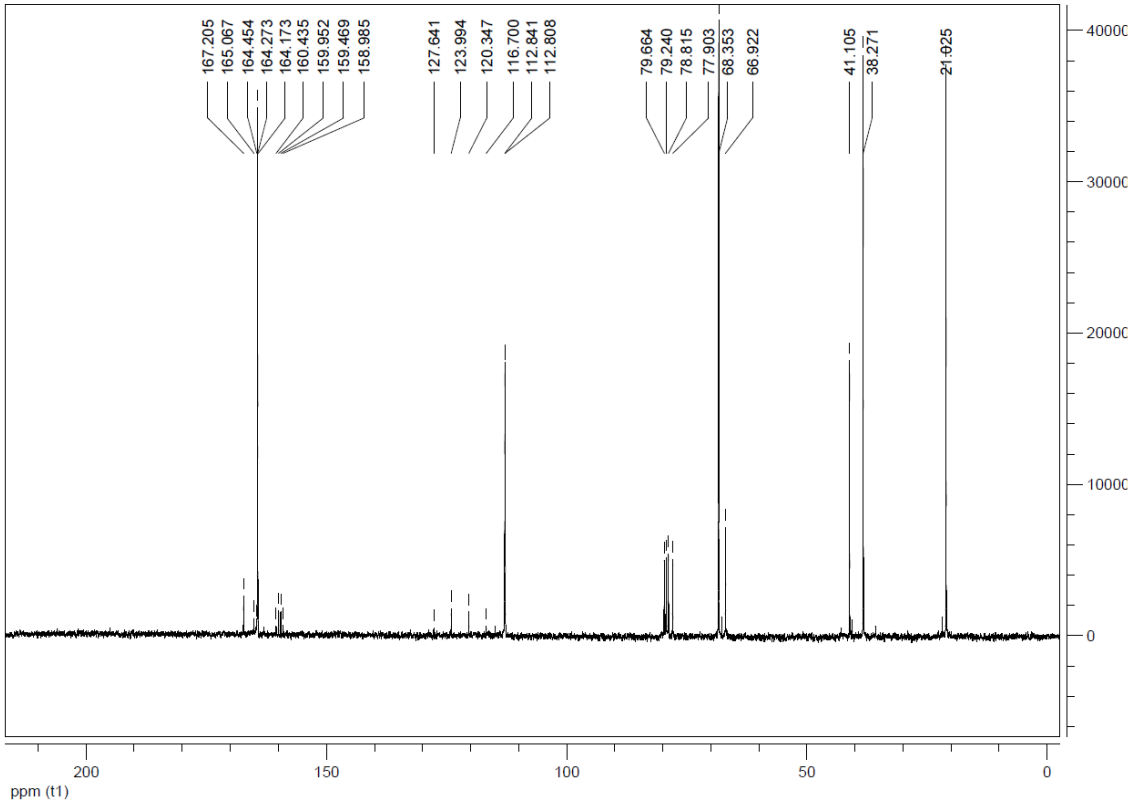


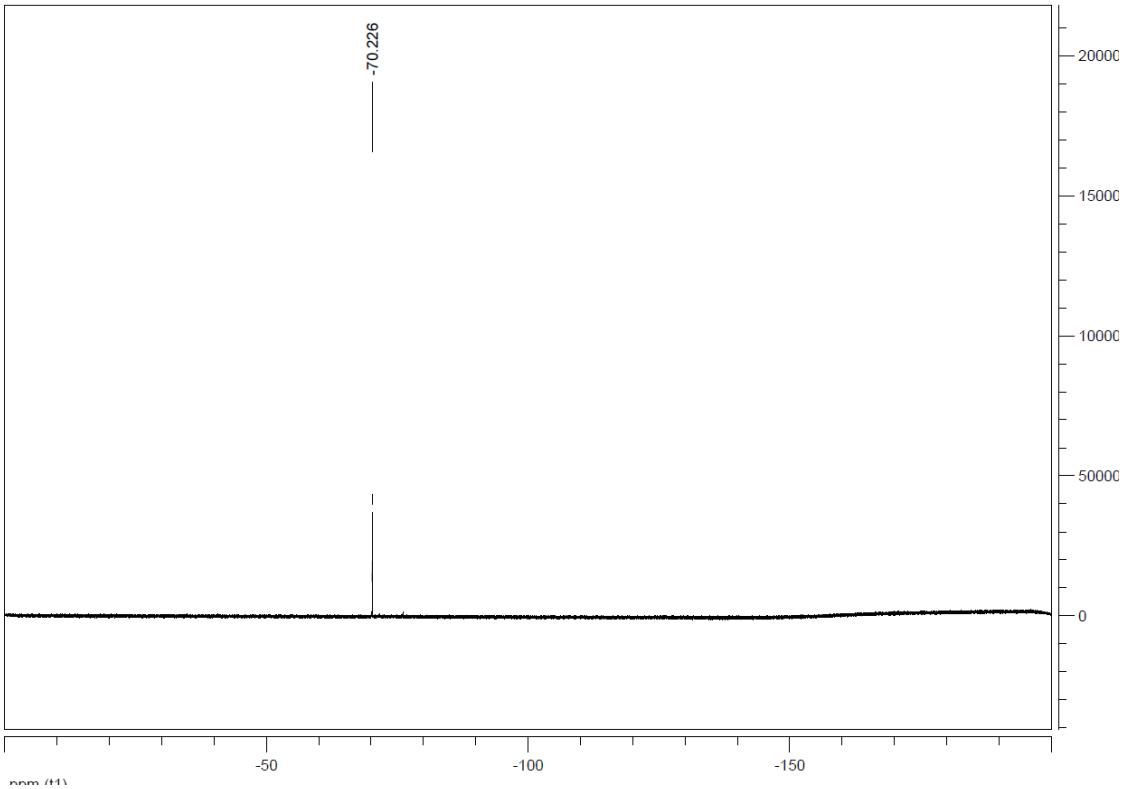




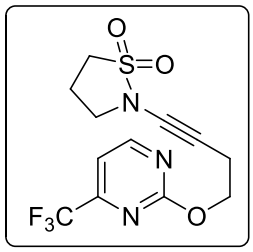
N-Methyl-*N*-(4-(4-(trifluoromethyl)pyrimidin-2-yloxy)but-1-ynyl)methanesulfonamide (**3b**)

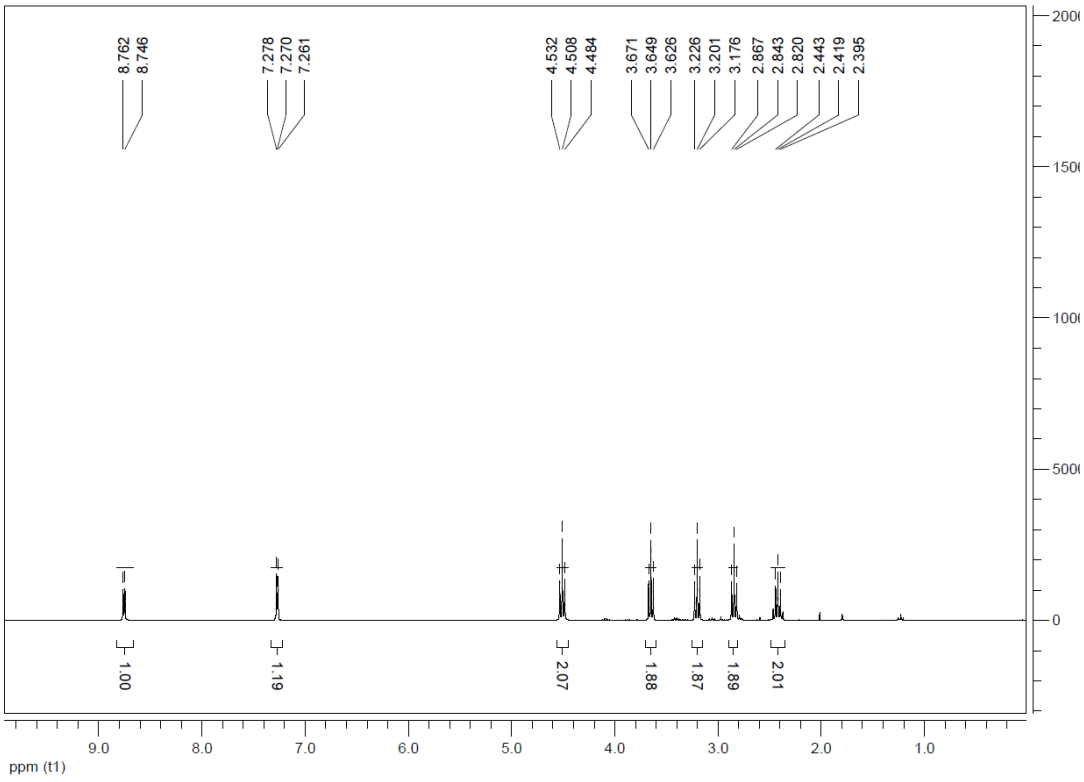


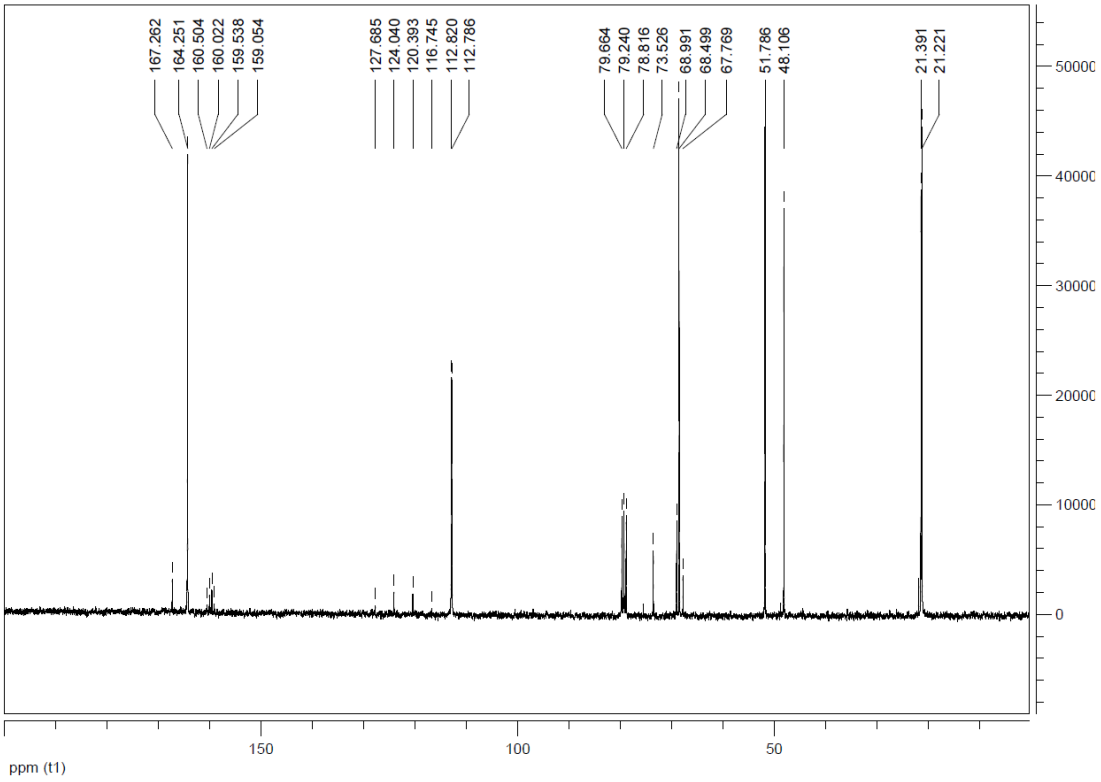

167.205
165.067
164.454
164.273
164.173
160.435
159.952
159.469
158.985
127.641
123.994
120.347
116.700
112.841
112.808
79.664
79.240
78.815
77.903
68.353
66.922
41.105
38.271
21.925
40000
30000
20000
10000
0
200
150
100
50
0
ppm (t1)

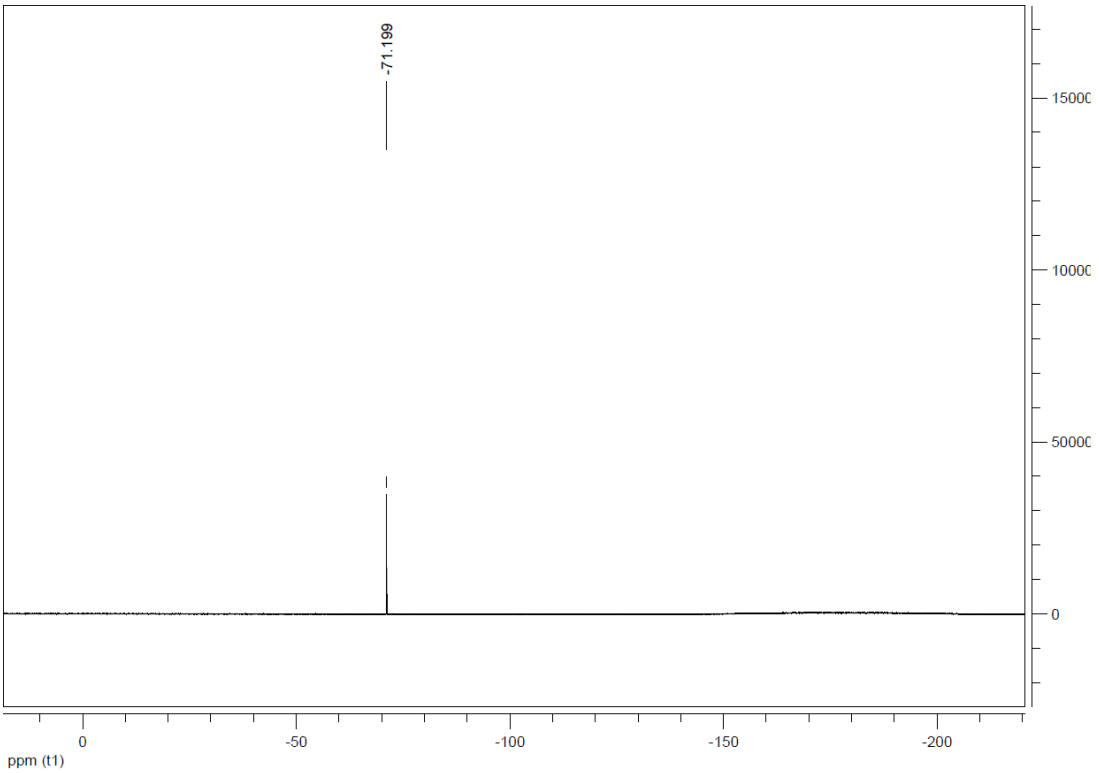

-70.226
20000
15000
10000
50000
0
-50
-100
-150

2-(4-{[4-(Trifluoromethyl)pyrimidin-2-yl]oxy}but-1-yn-1-yl)-1,2-thiazolidine-1,1-dione (**3c**)

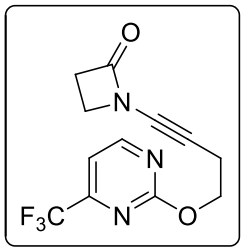


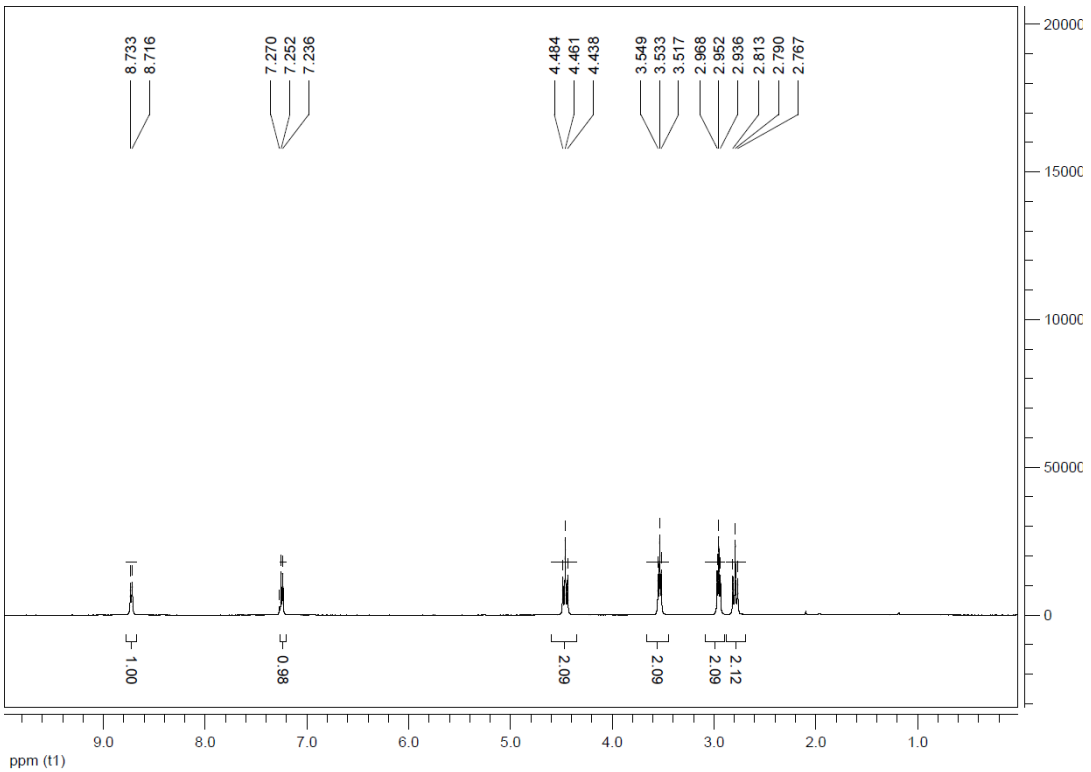


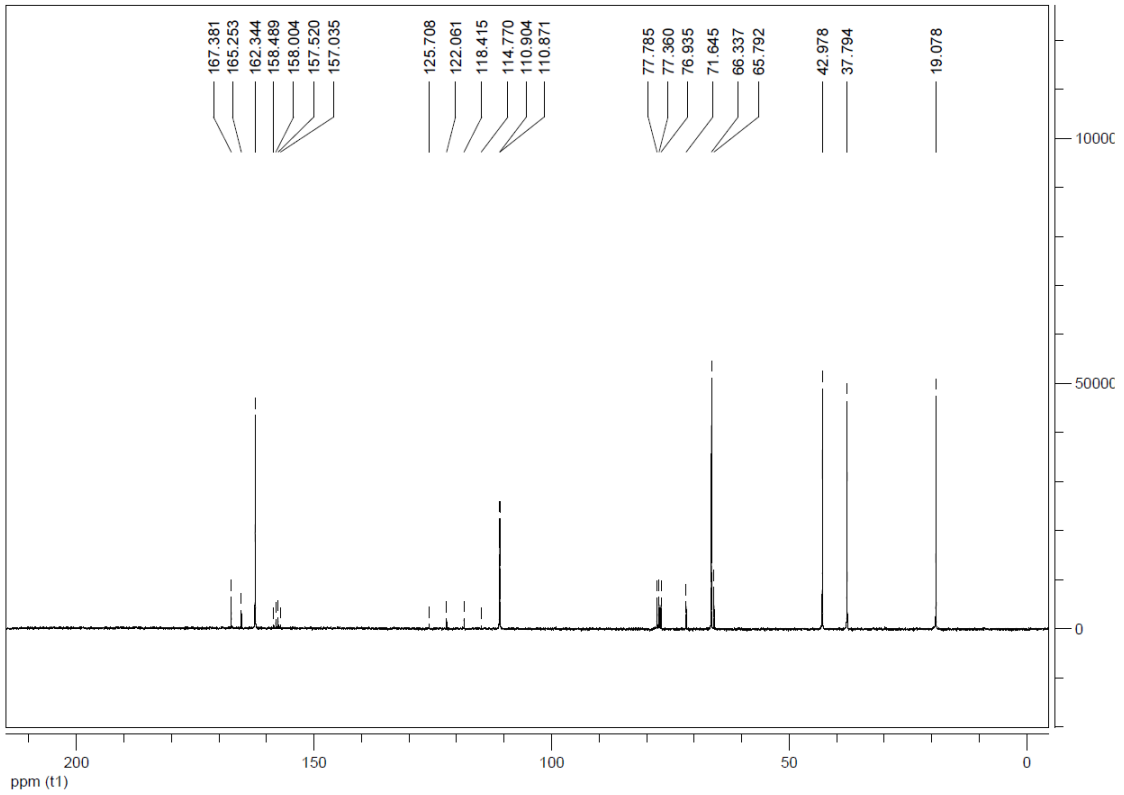


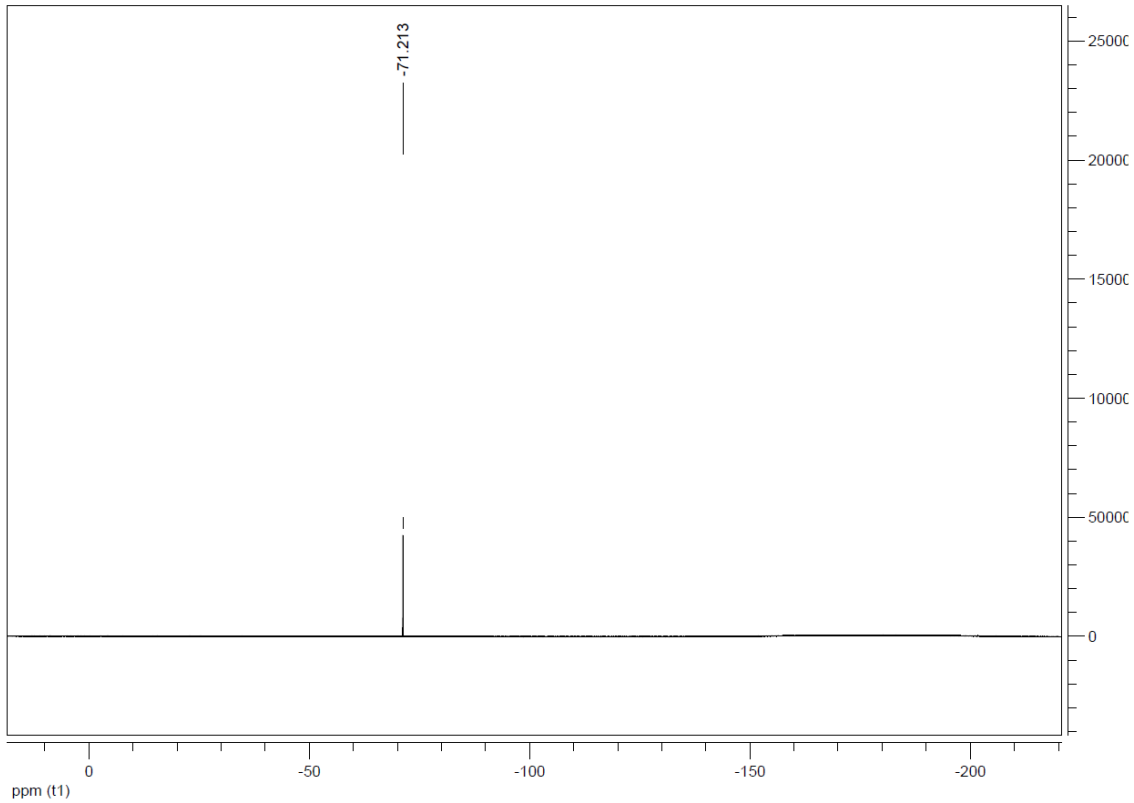


1-(4-(4-(Trifluoromethyl)pyrimidin-2-yloxy)but-1-ynyl)azetidin-2-one (**3d**)

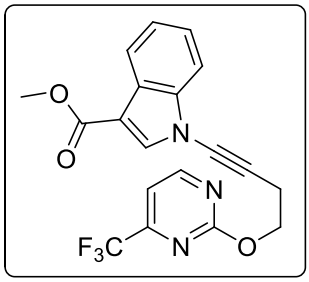


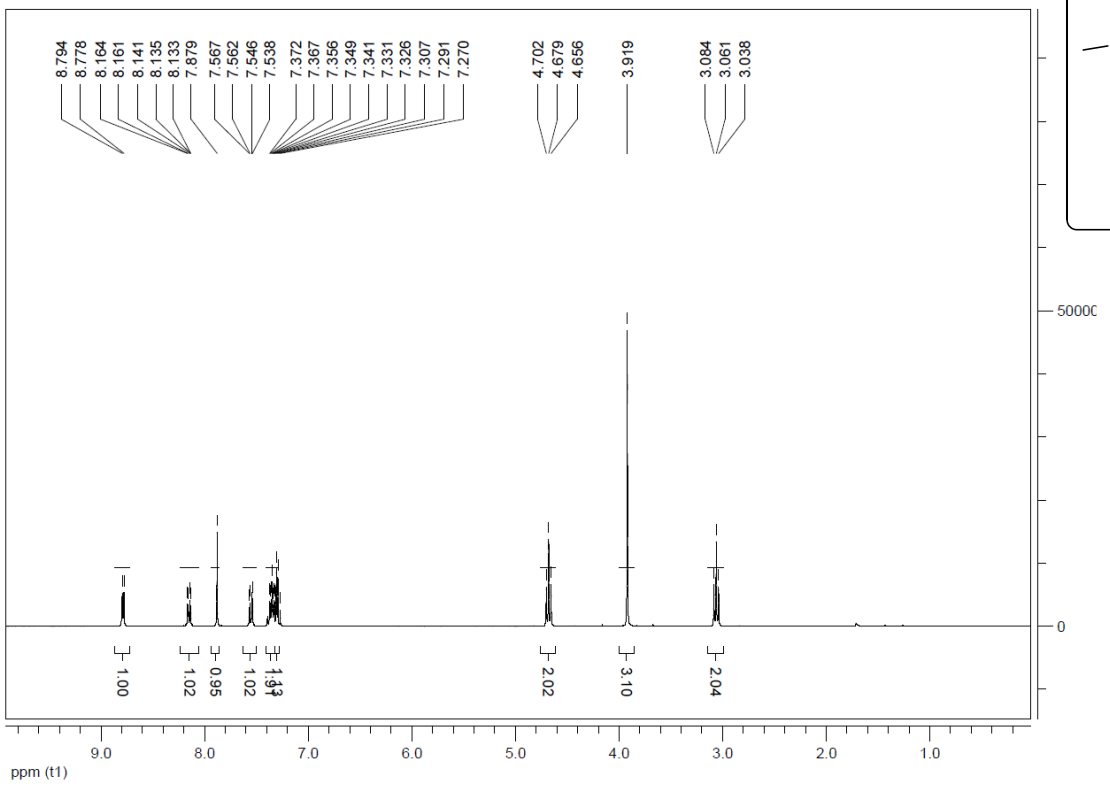


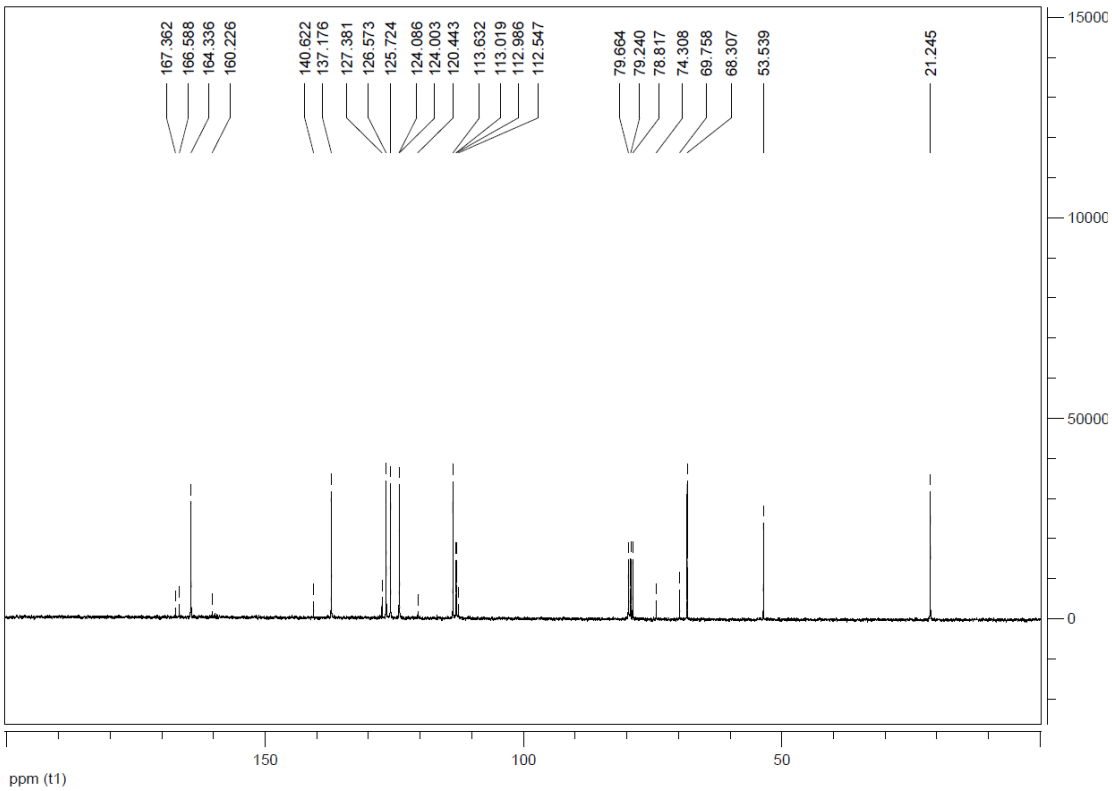

167.381
165.253
162.344
158.489
158.004
157.520
157.035
125.708
122.061
118.415
114.770
110.904
110.871
77.785
77.360
76.935
71.645
66.337
65.792
42.978
37.794
19.078
10000
5000
0
200
150
100
50
0
ppm (t1)

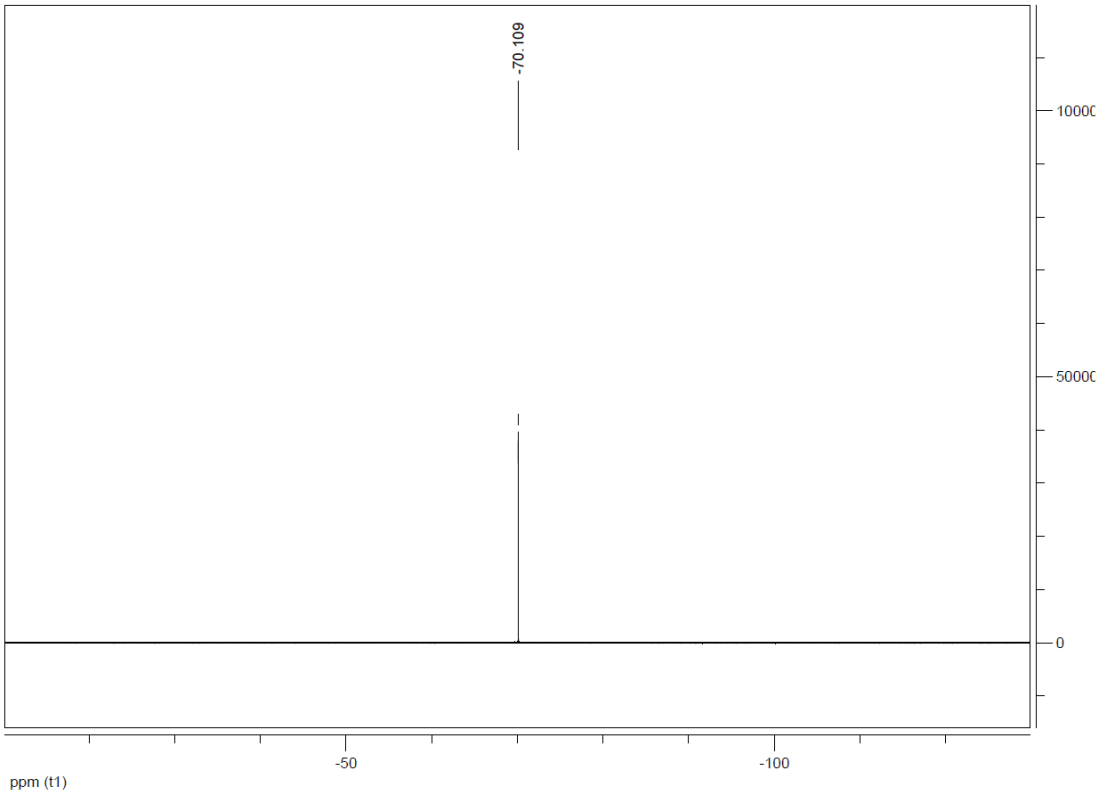

-71.213
25000
20000
15000
10000
5000
0
0
-50
-100
-150
-200
ppm (t1)

Methyl 1-(4-(4-(trifluoromethyl)pyrimidin-2-yloxy)but-1-ynyl)-1H-indole-3-carboxylate (**3e**)

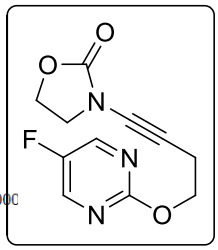


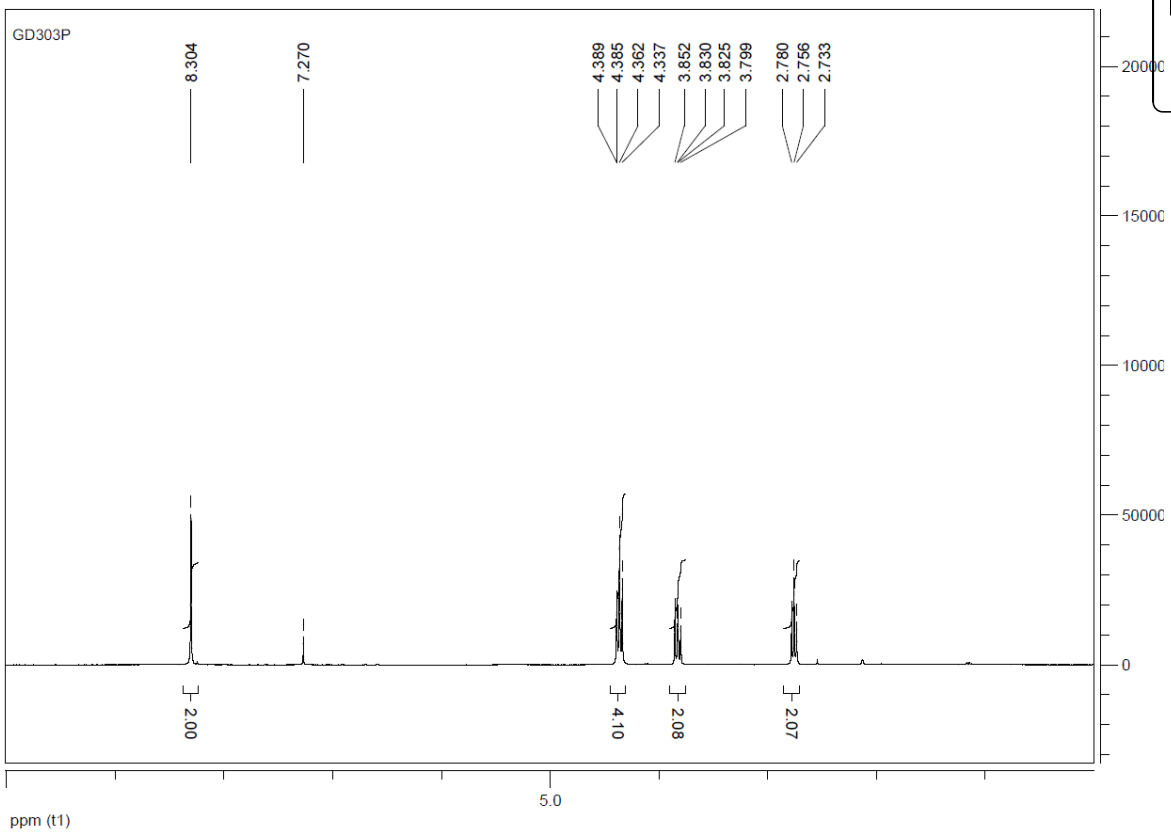


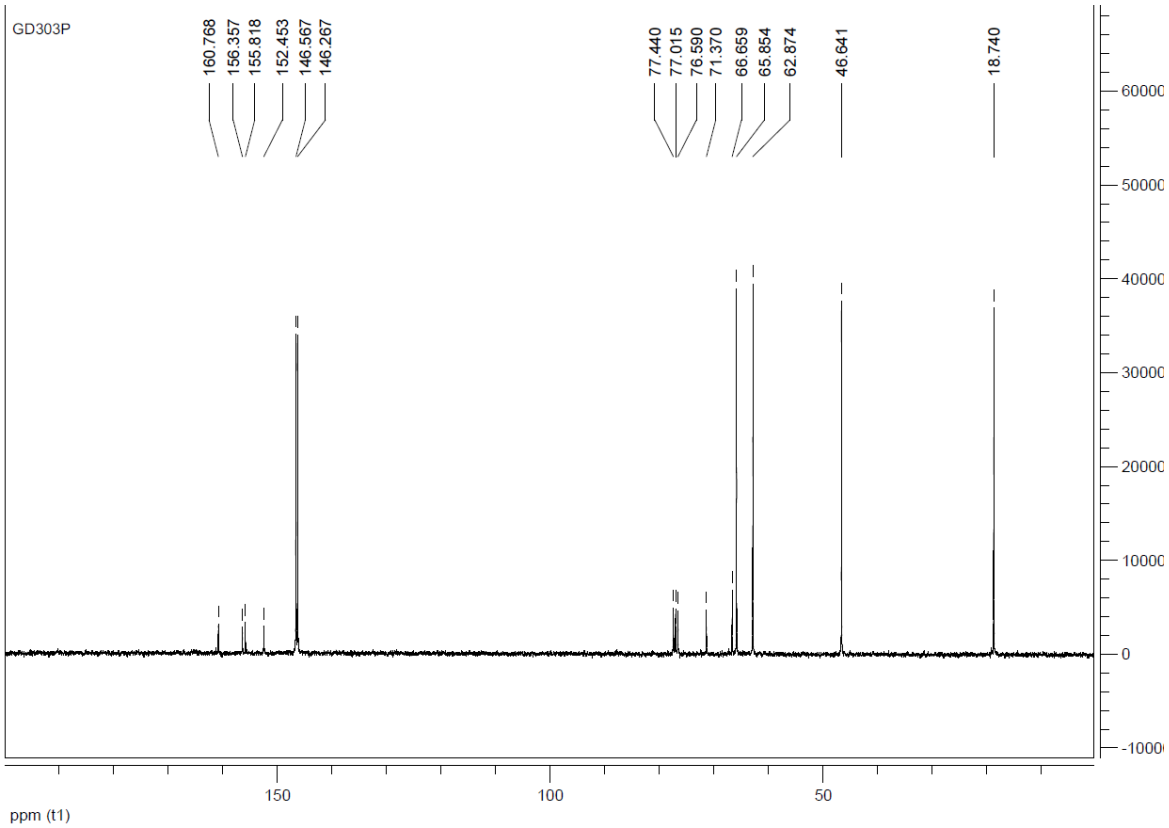


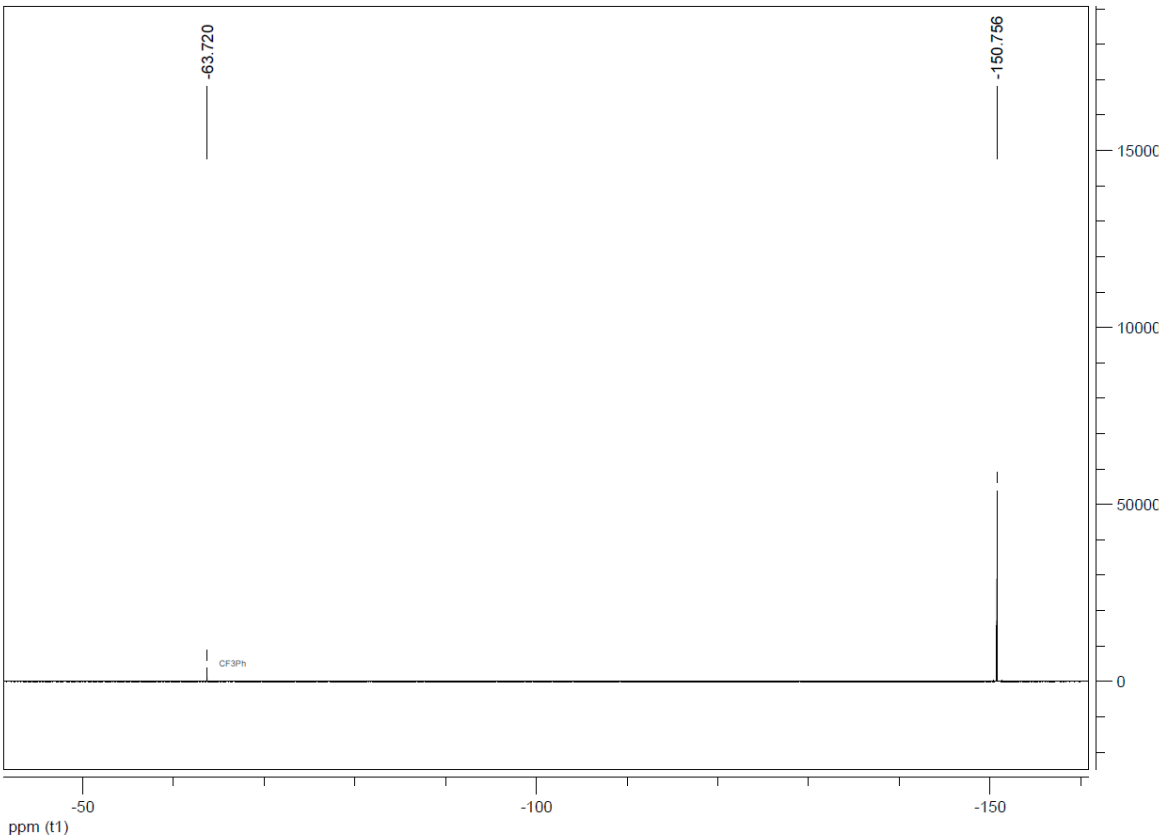


3-(4-(5-Fluoropyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3f**)

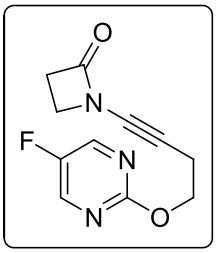


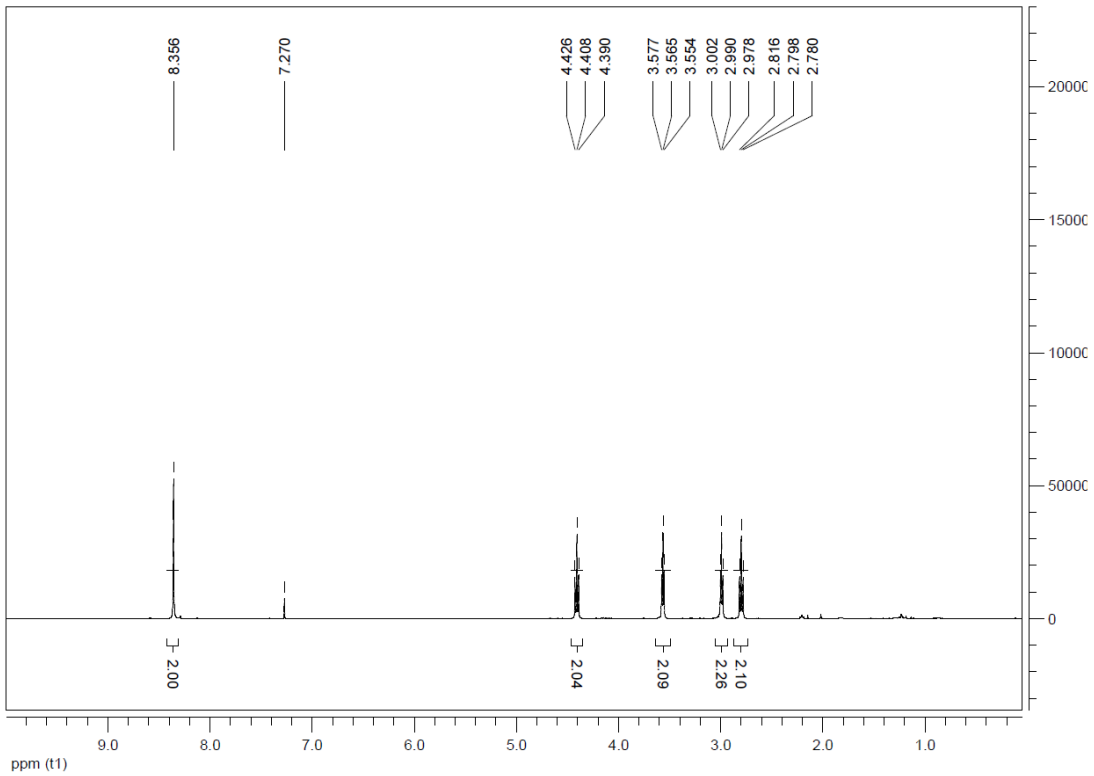


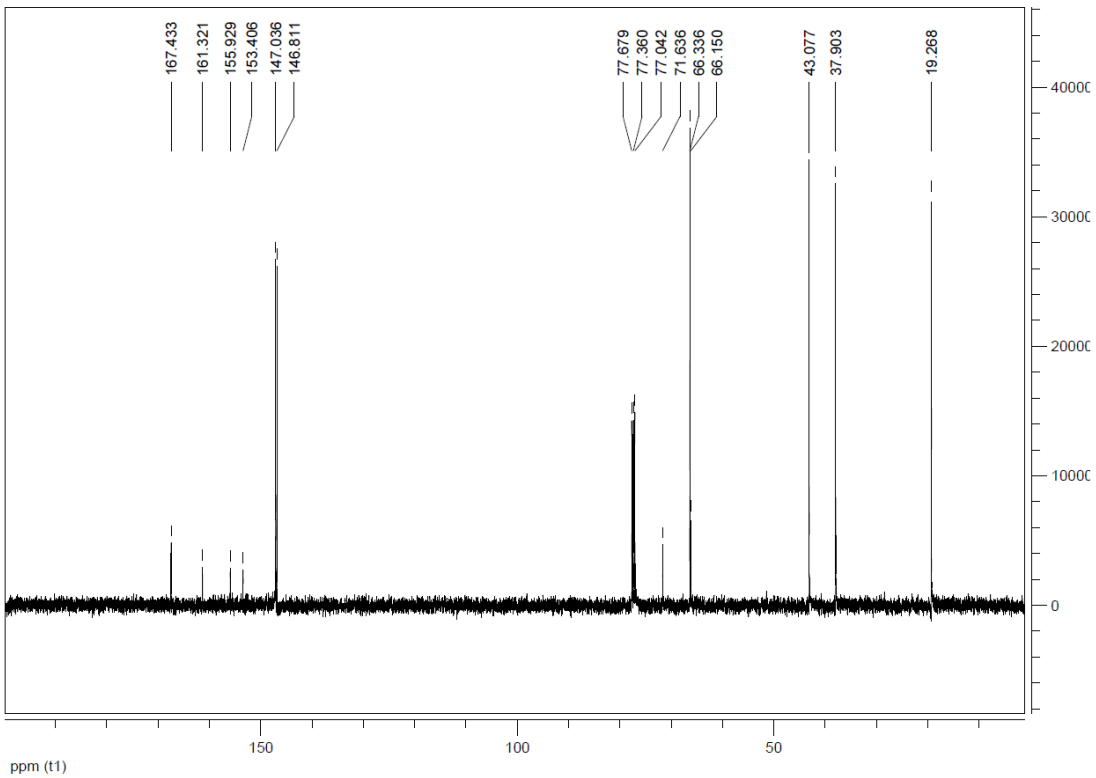

GD303P
160.768
156.357
155.818
152.453
146.567
146.267
77.440
77.015
76.590
71.370
66.659
65.854
62.874
46.641
18.740
60000
50000
40000
30000
20000
10000
0
-1000
150
100
50
ppm (t1)

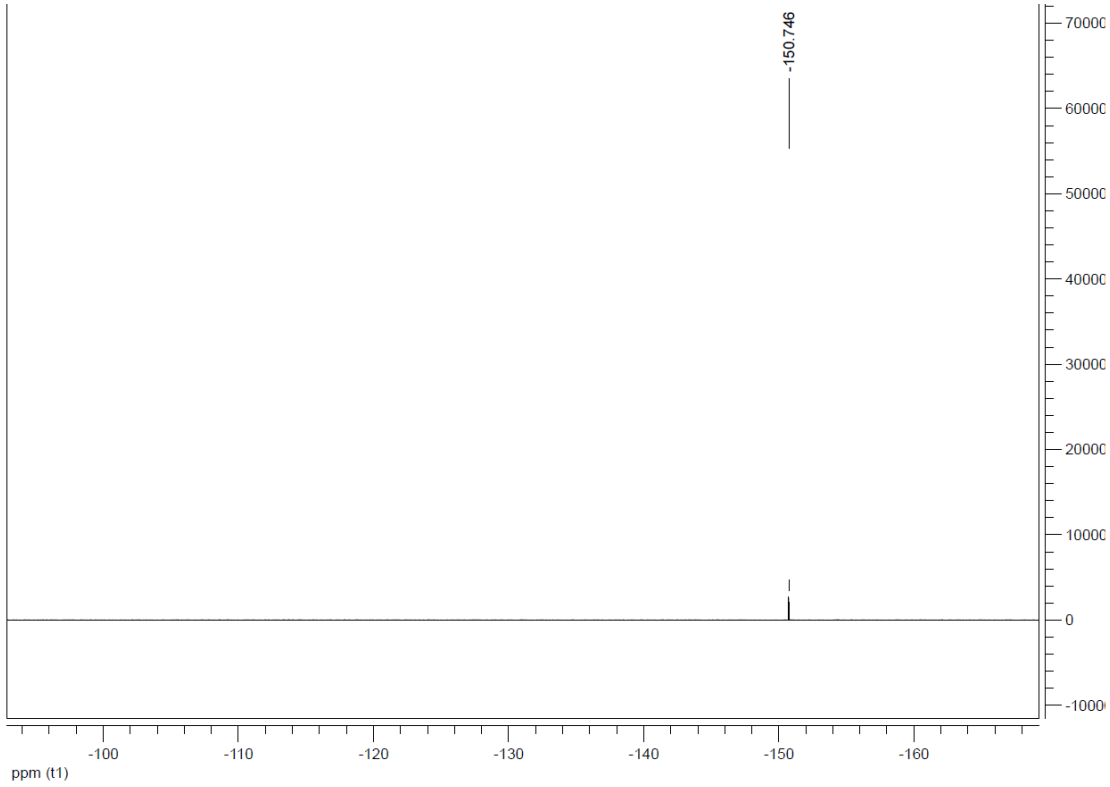

-63.720
-150.756
15000
10000
50000
0
CF3Ph
-50
-100
-150
ppm (t1)

1-(4-(5-Fluoropyrimidin-2-yloxy)but-1-ynyl)azetidin-2-one (**3g**)

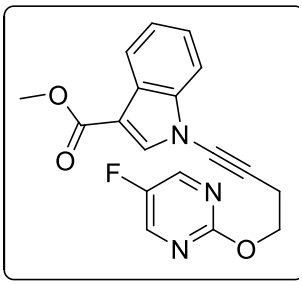


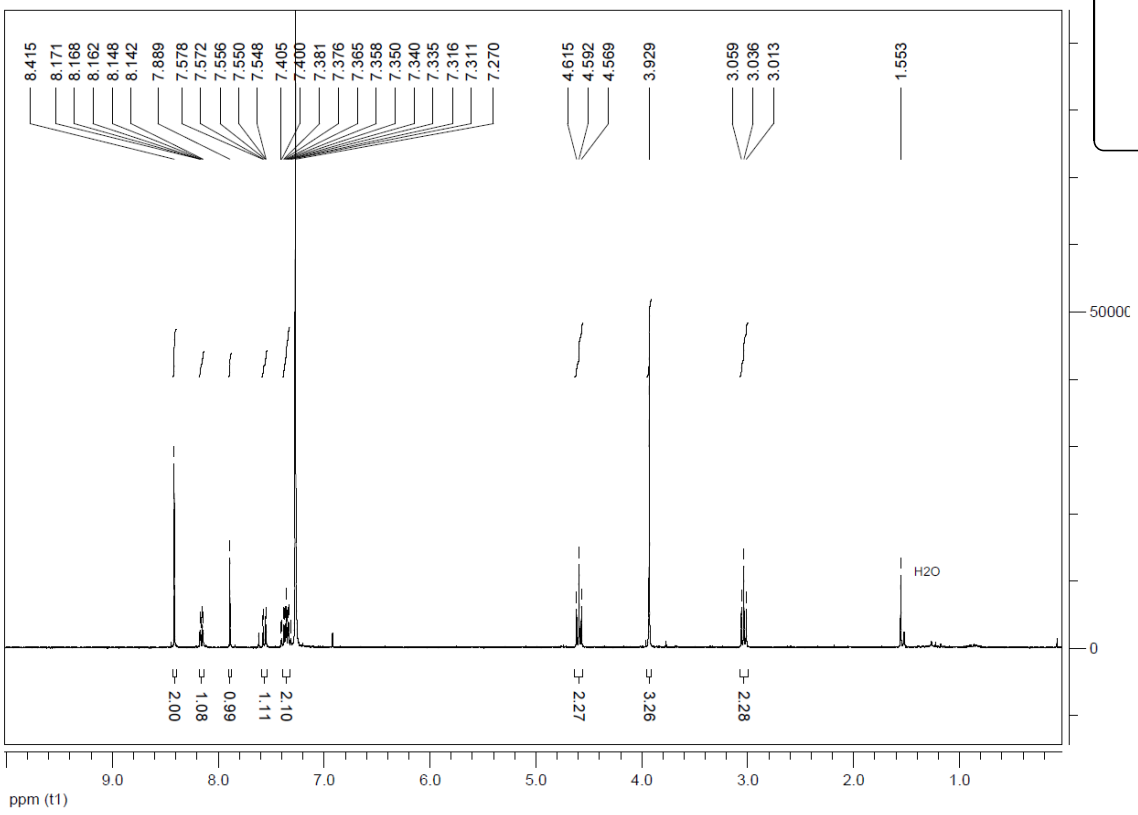


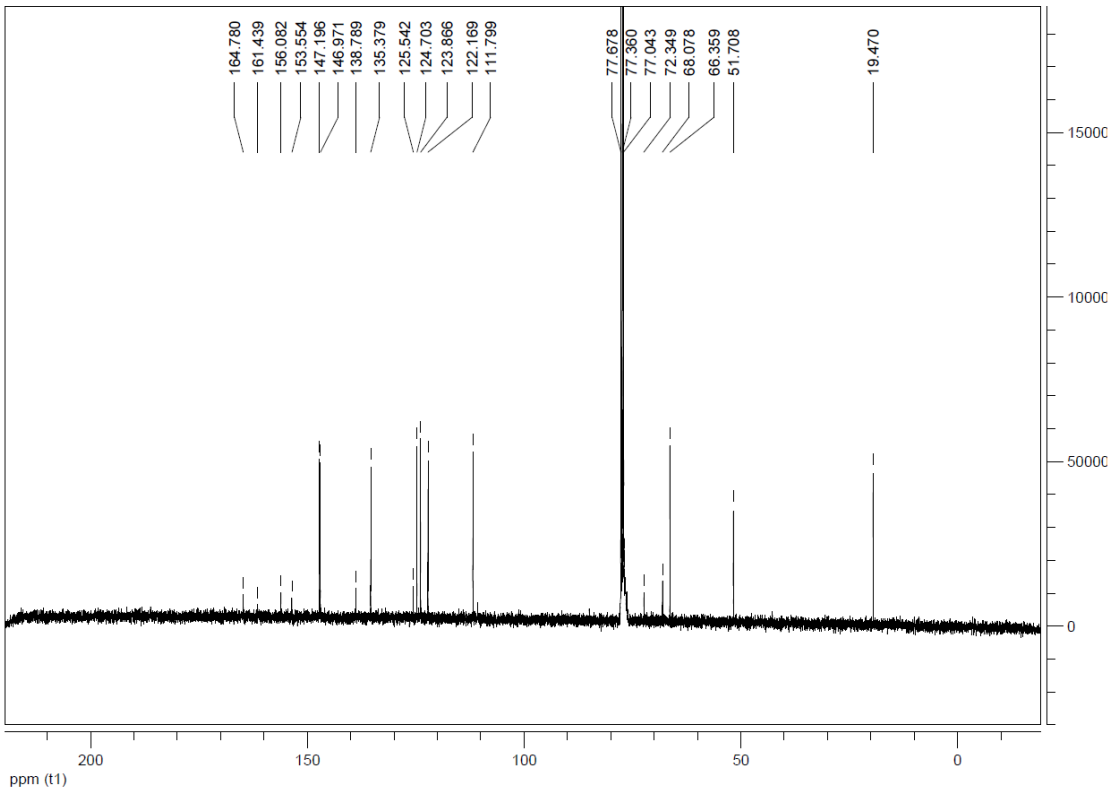


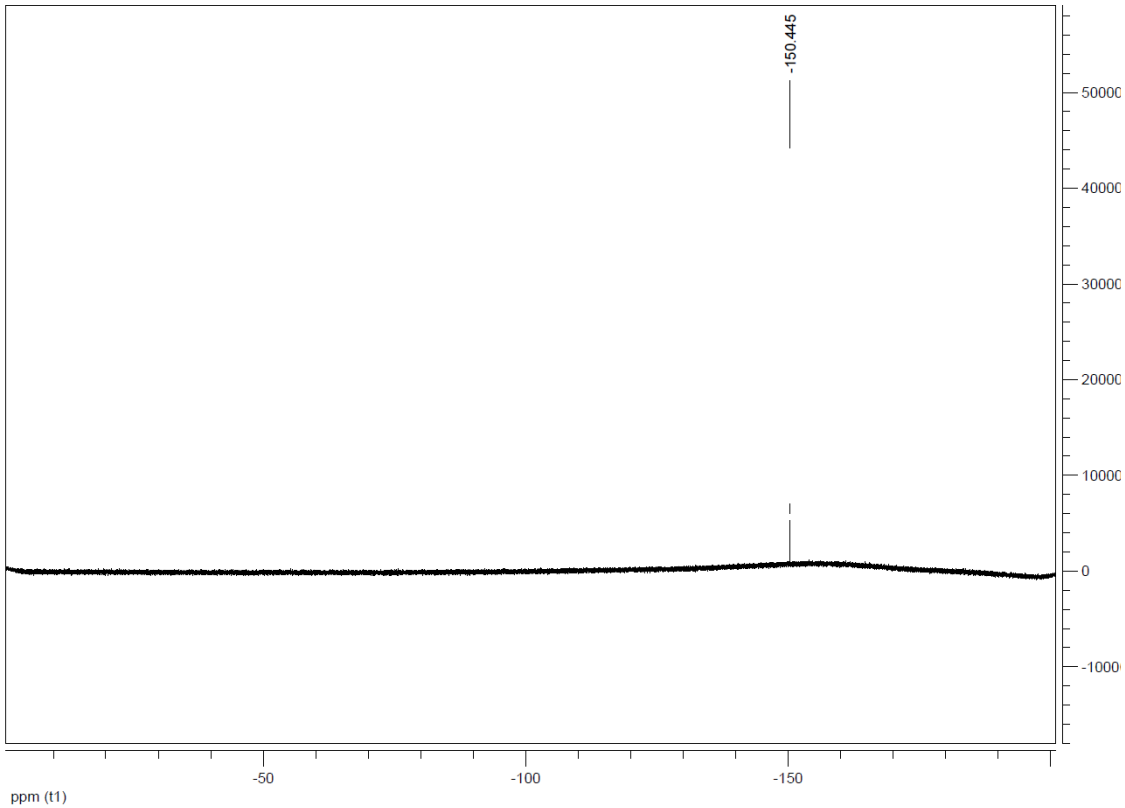


Methyl 1-(4-(5-fluoropyrimidin-2-yloxy)but-1-ynyl)-1H-indole-3-carboxylate (**3h**)

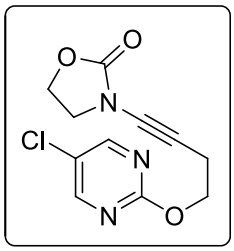


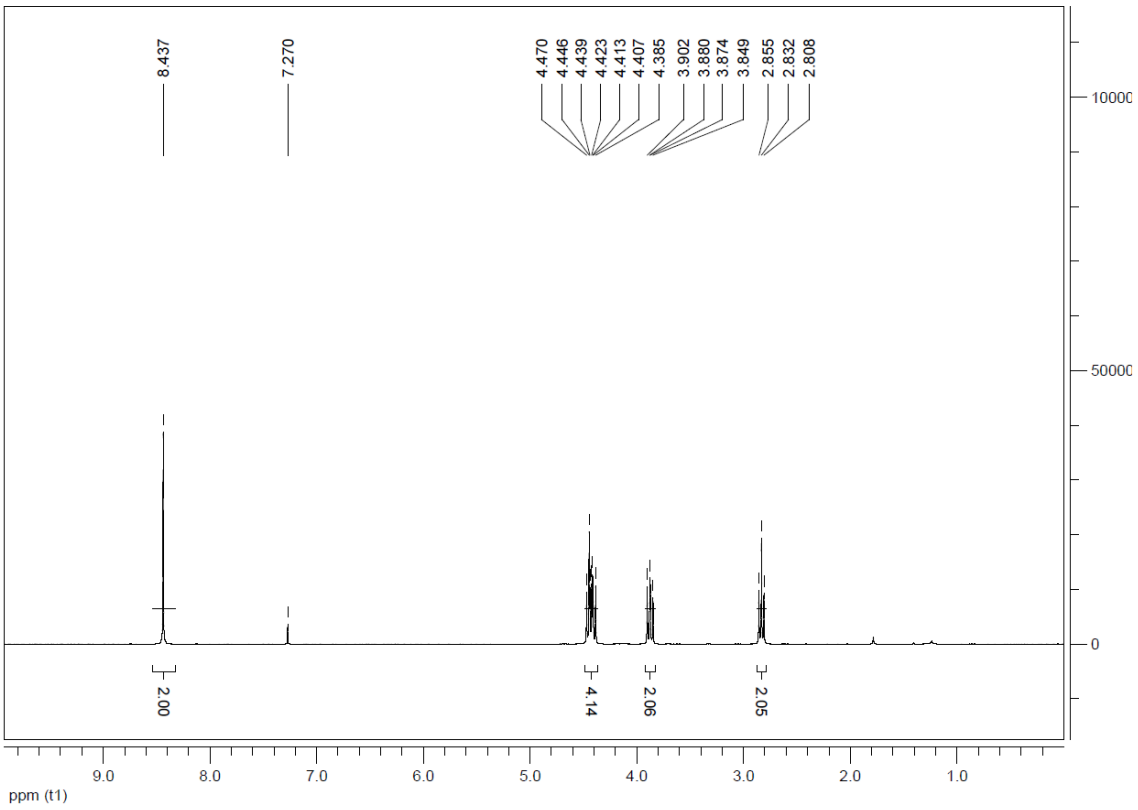


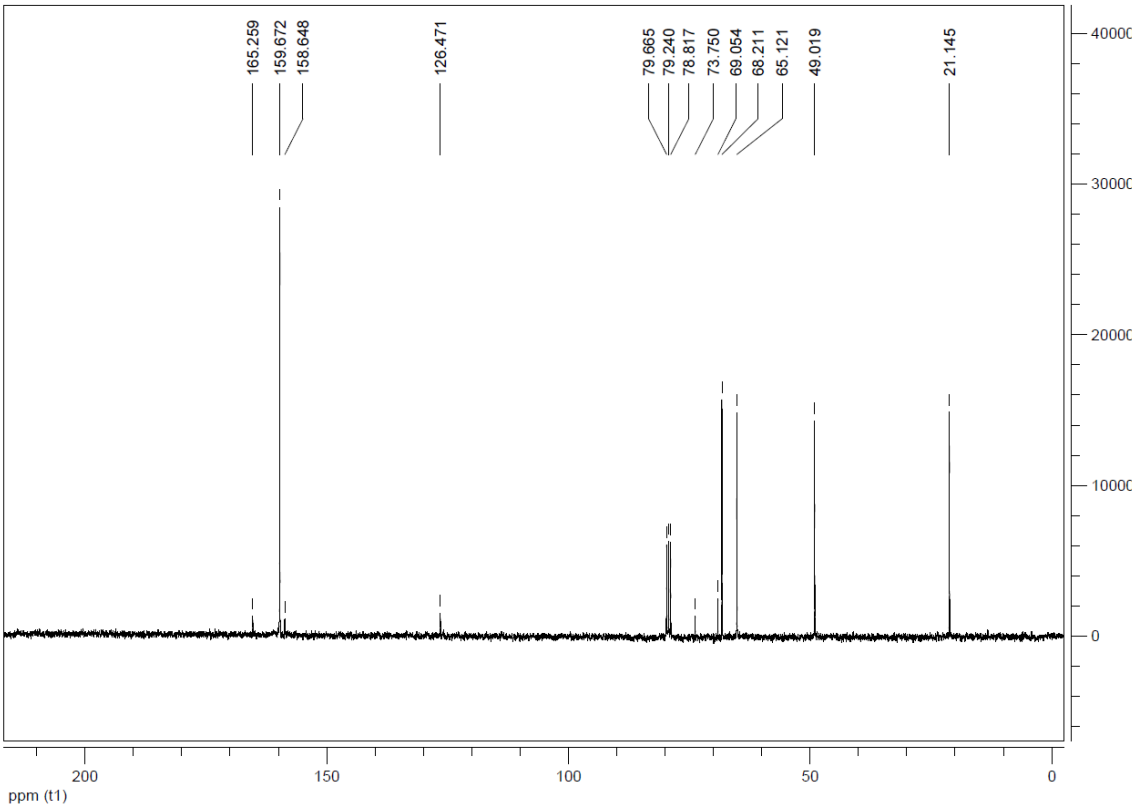

164.780
161.439
156.082
153.554
147.196
146.971
138.789
135.379
125.542
124.703
123.866
122.169
111.799
77.678
77.360
77.043
72.349
68.078
66.359
51.708
19.470
150000
100000
50000
0
200
150
100
50
0
ppm (t1)


-150.445
50000
40000
30000
20000
10000
0
-10000
-50
-100
-150
ppm (t1)

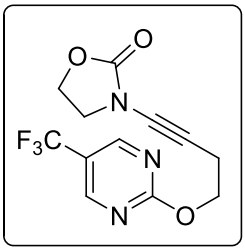
3-(4-(5-Chloropyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3i**)

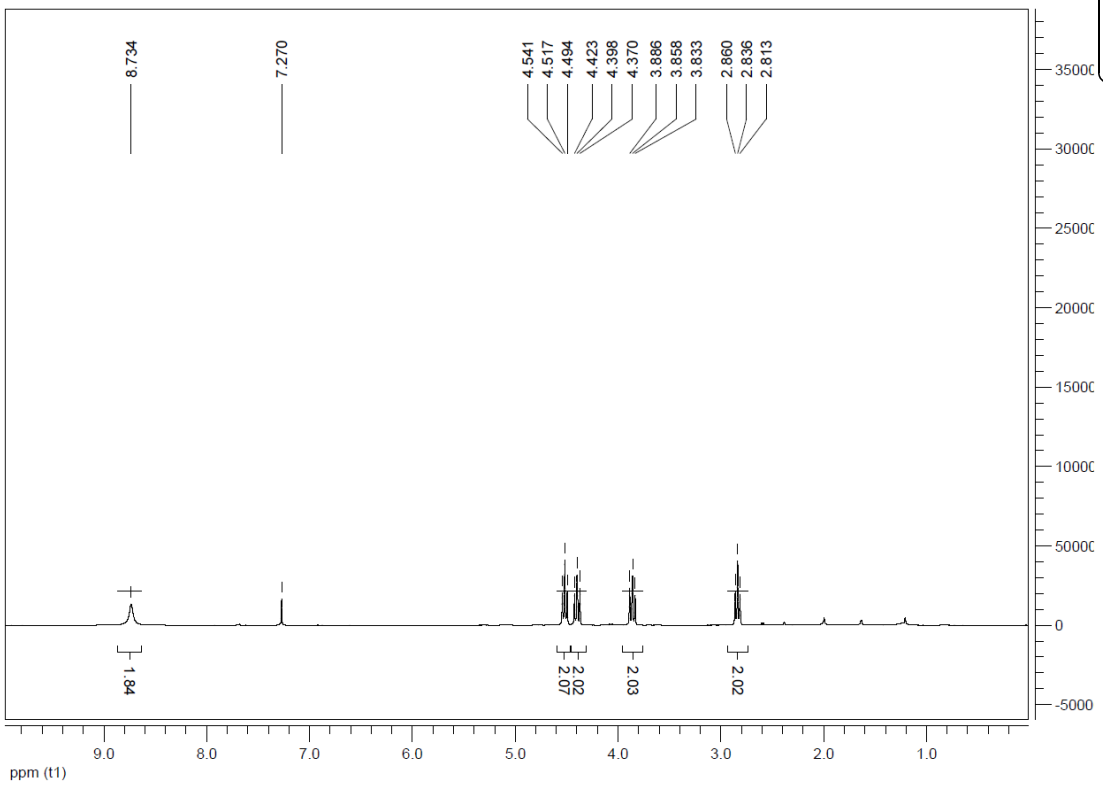


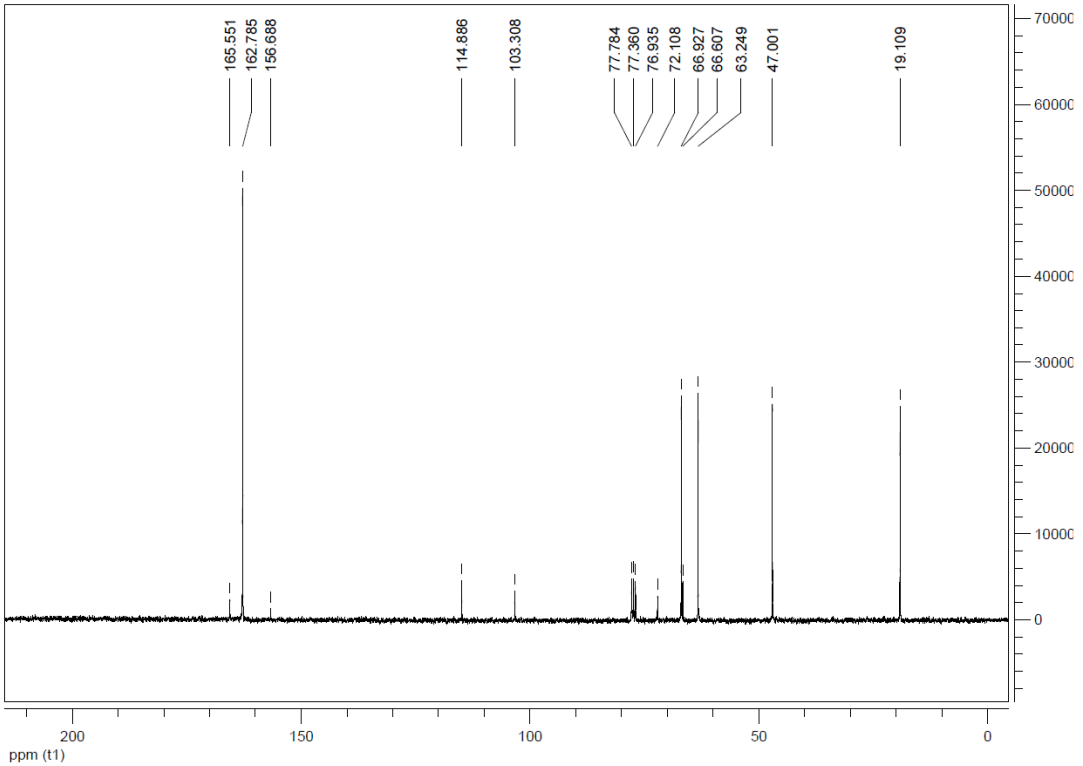


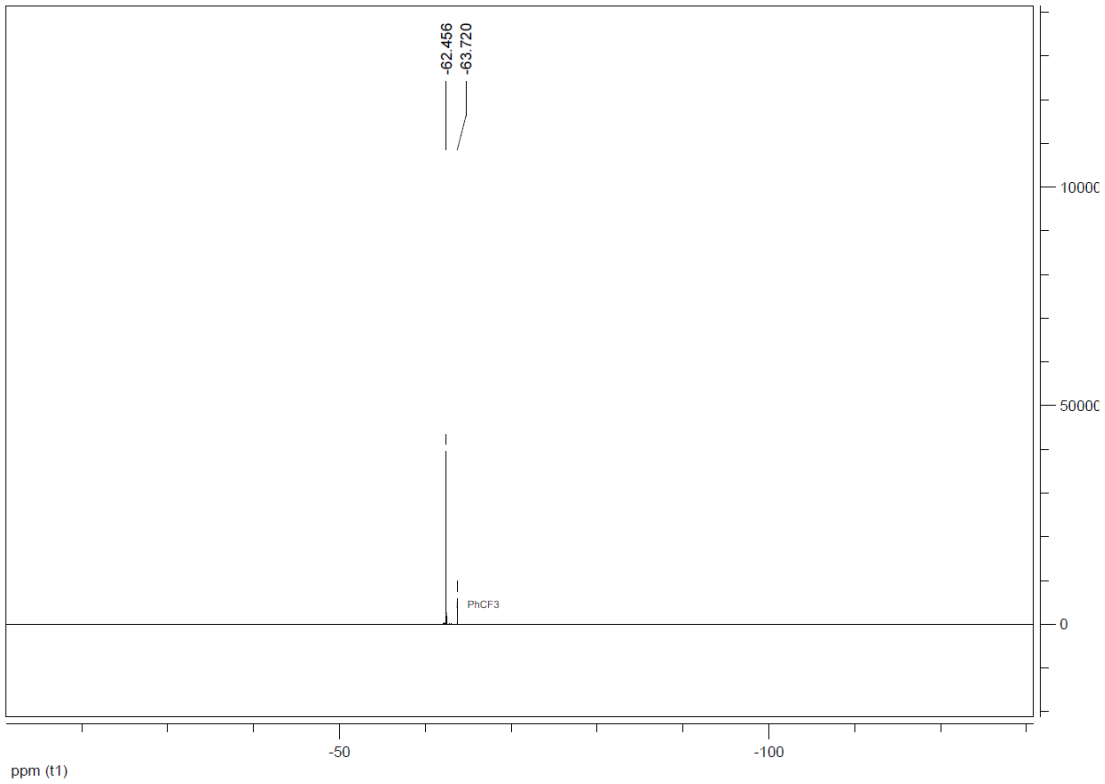


3-(4-(5-(Trifluoromethyl)pyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3j**)

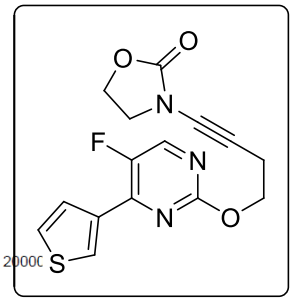


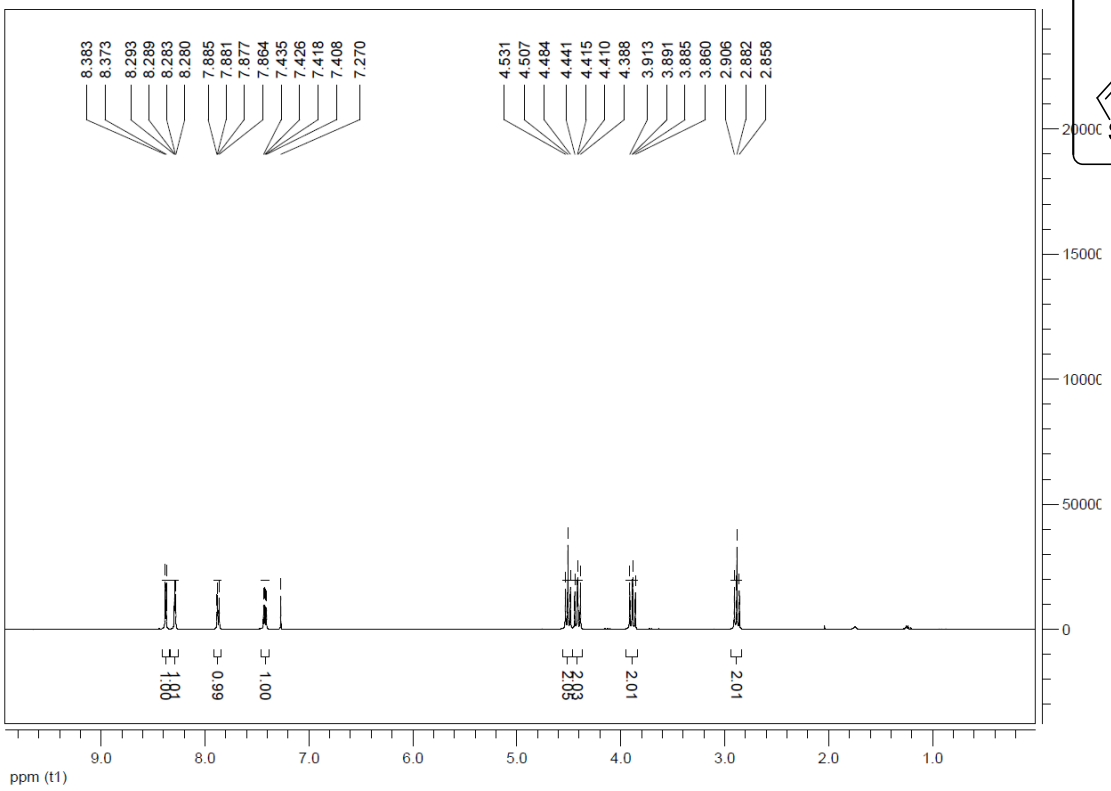


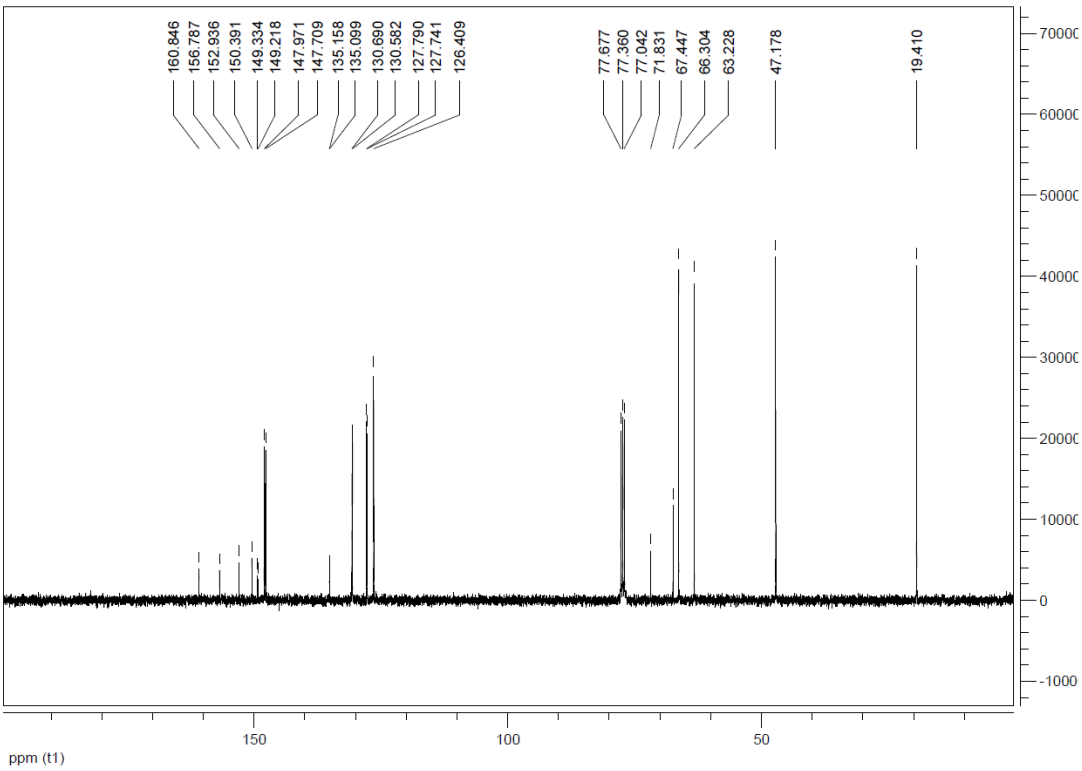




3-(4-(5-Fluoro-4-(thiophen-3-yl)pyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3k**)



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150.391
149.334
149.218
147.971
147.709
135.158
135.099
130.690
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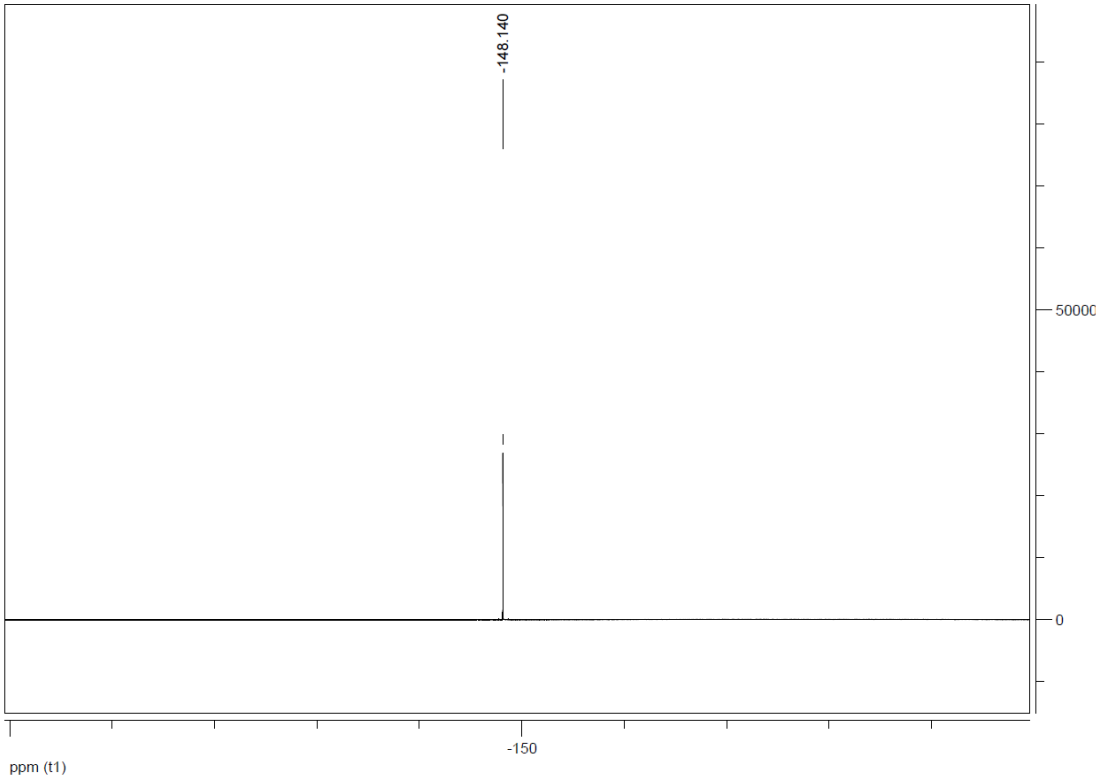
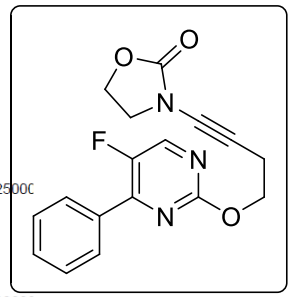
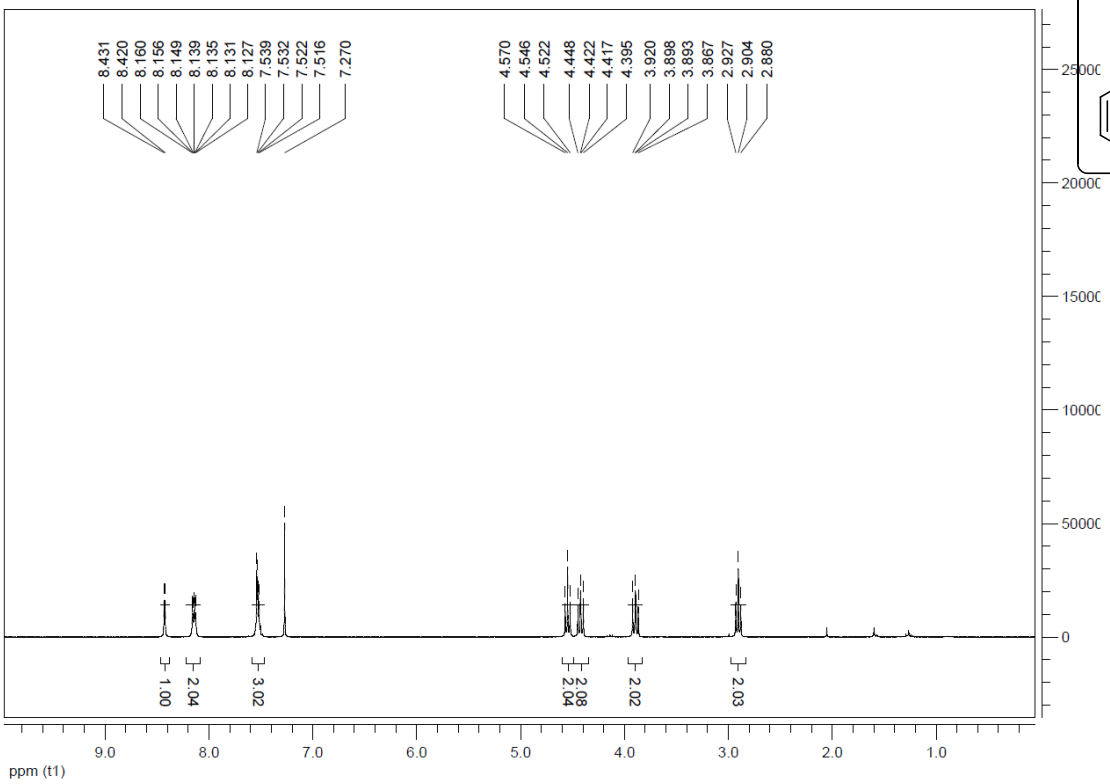
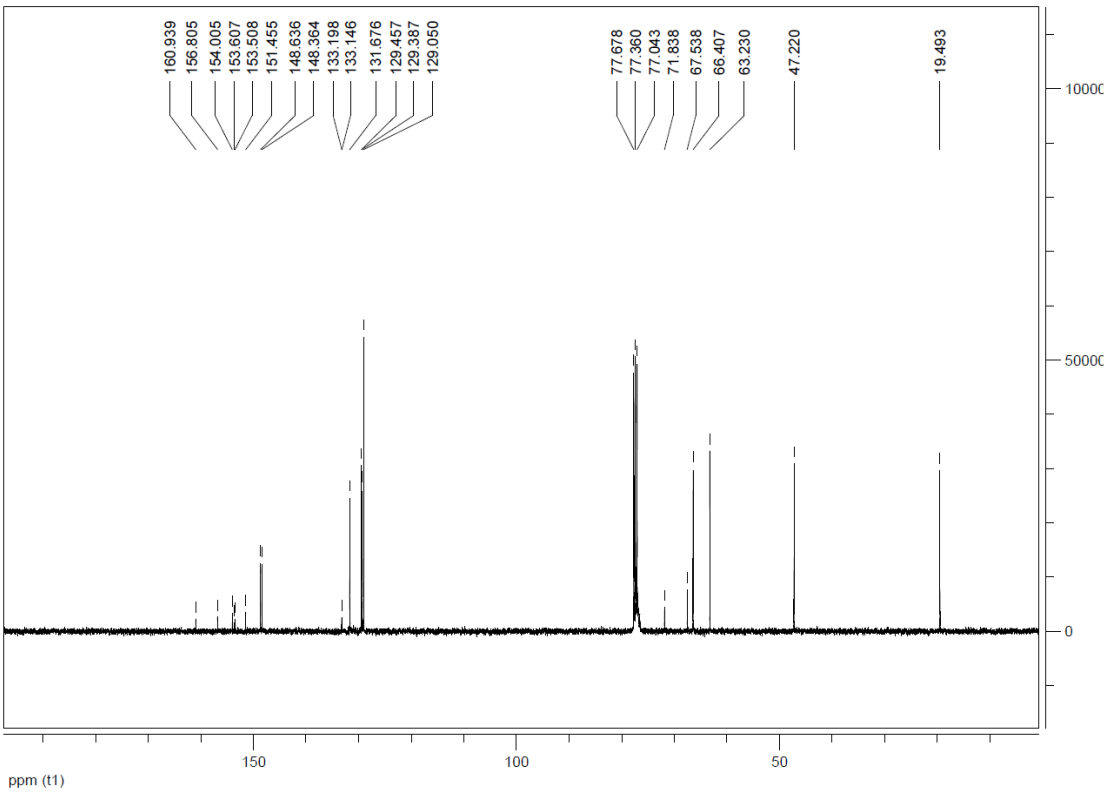
127.790
127.741
126.409
77.677
77.360
77.042
71.831
67.447
66.304
63.228
47.178
19.410
70000
60000
50000
40000
30000
20000
10000
0
-1000
150
100
50
ppm (t1)

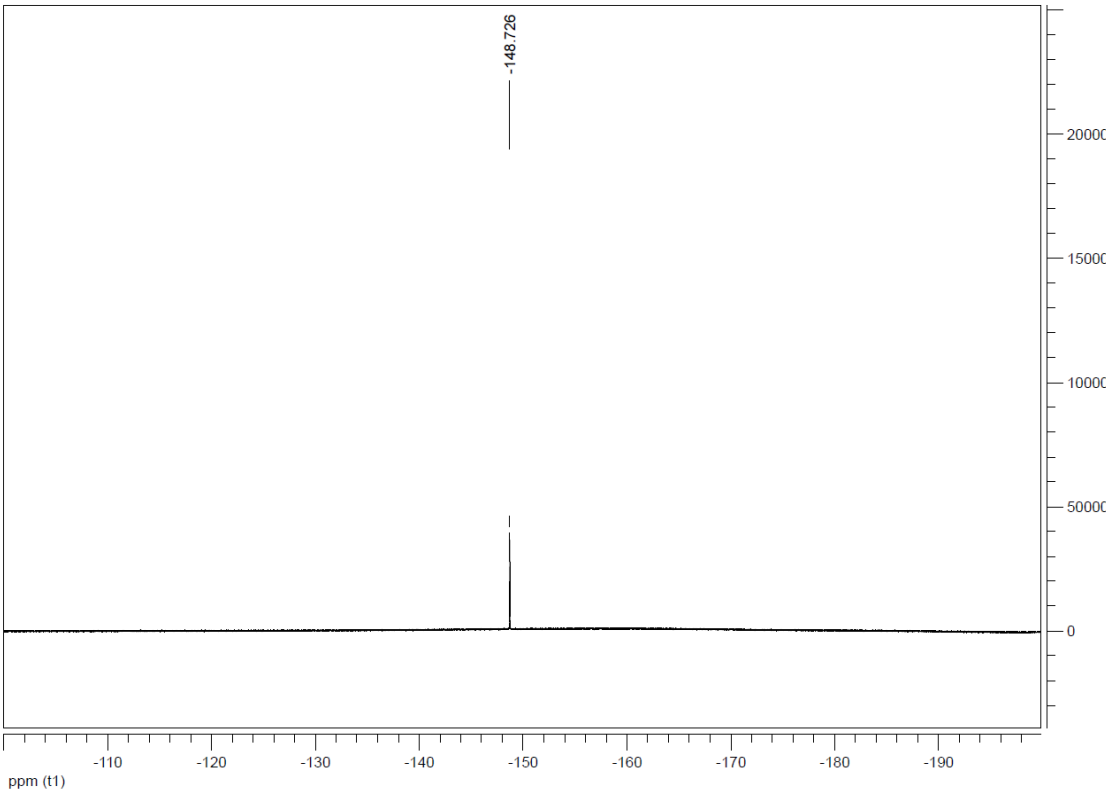

-148.140
50000
0
-150
ppm (t1)

3-(4-(5-Fluoro-4-phenylpyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3l**)

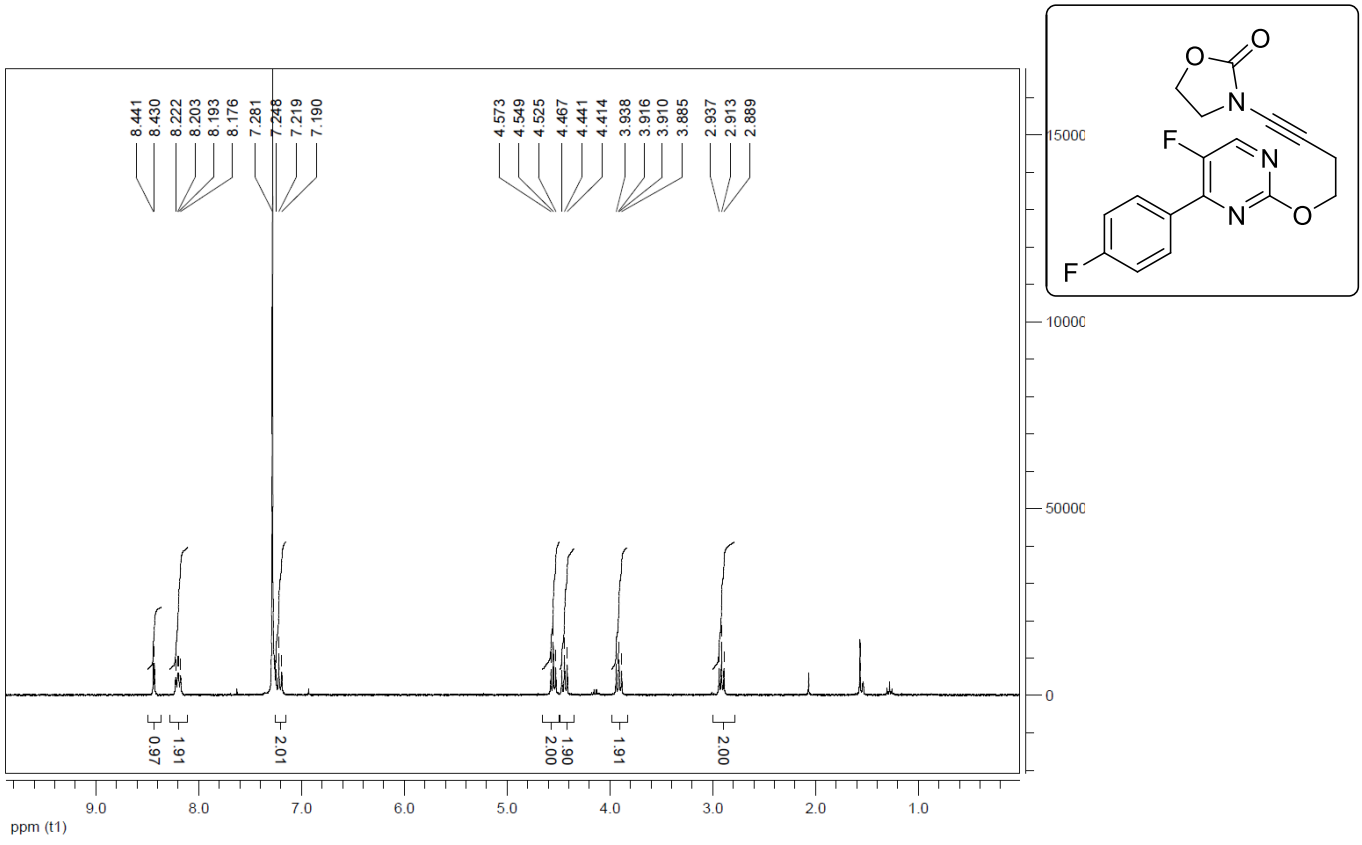


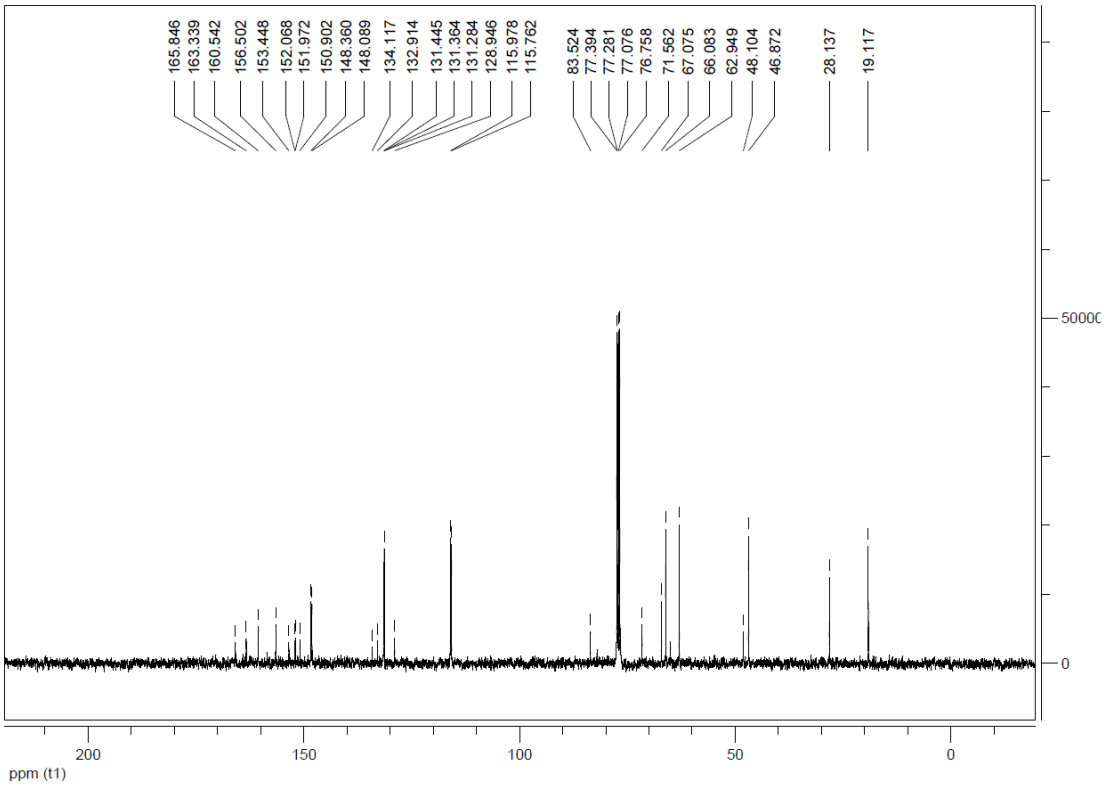


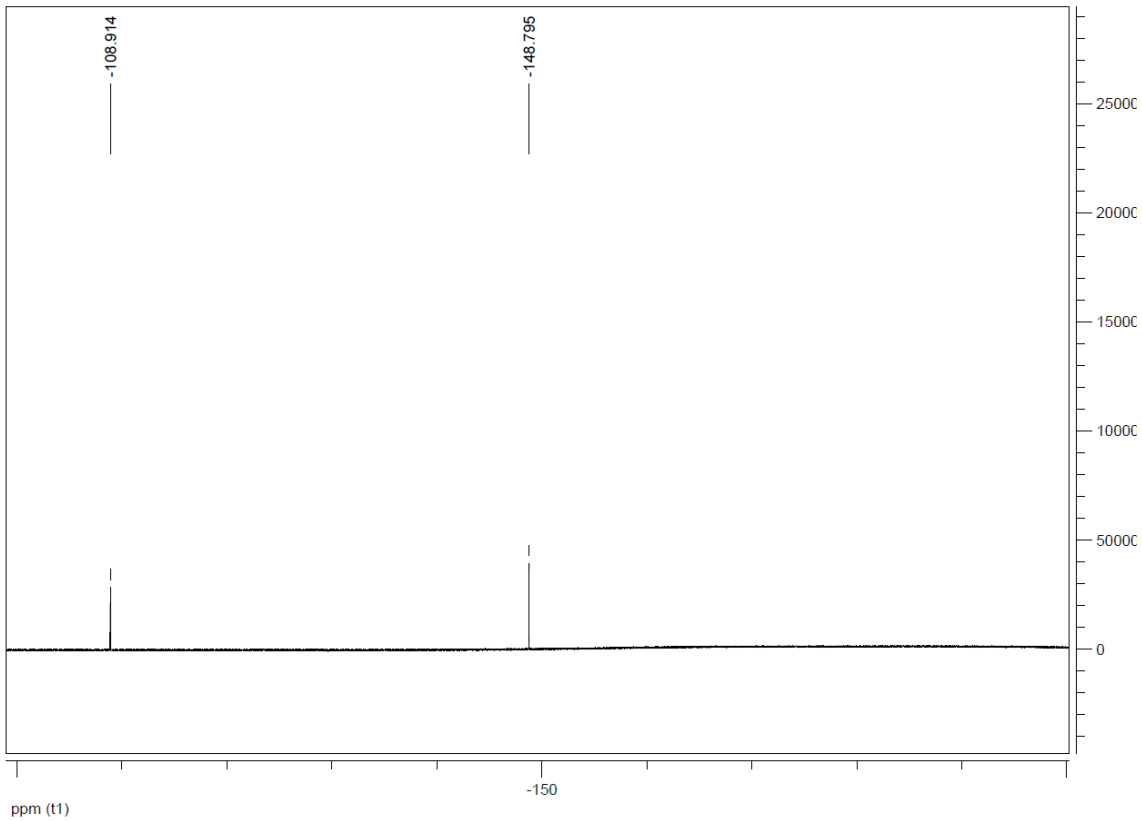




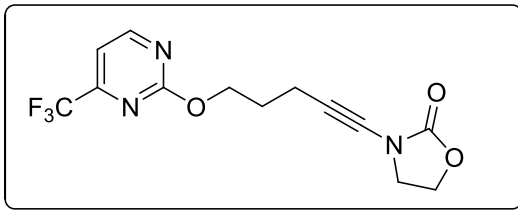
3-(4-(5-Fluoro-4-(4-fluorophenyl)pyrimidin-2-yloxy)but-1-ynyl)oxazolidin-2-one (**3m**)

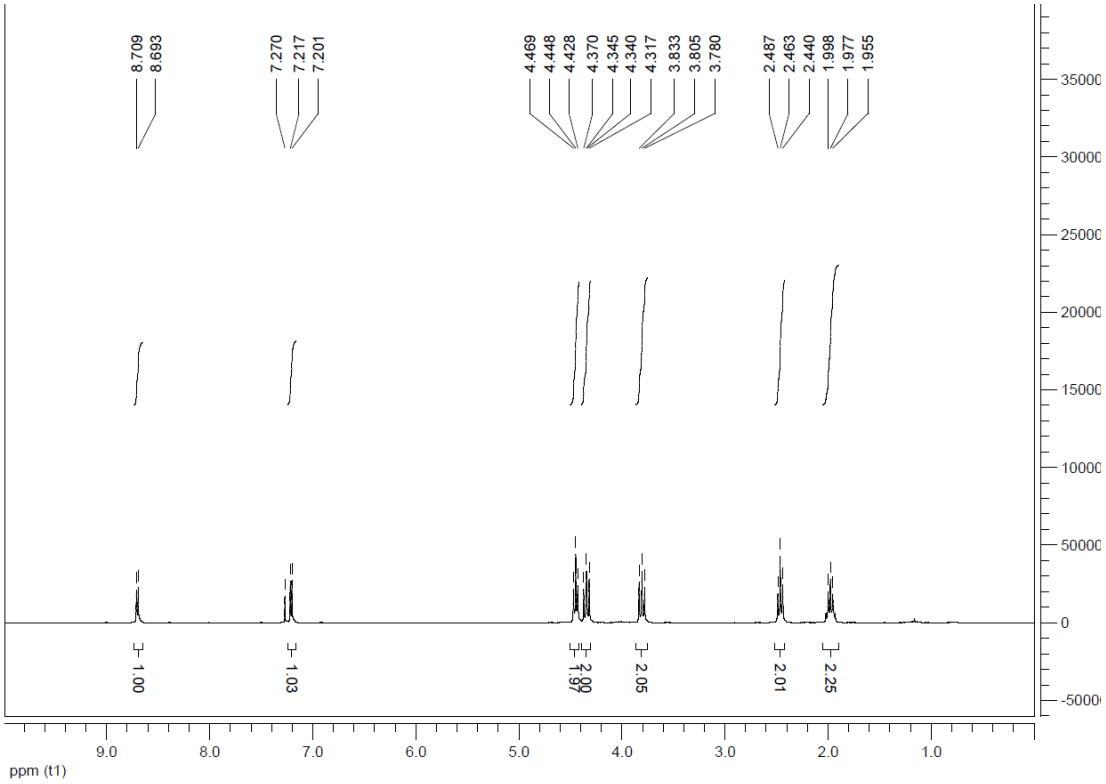


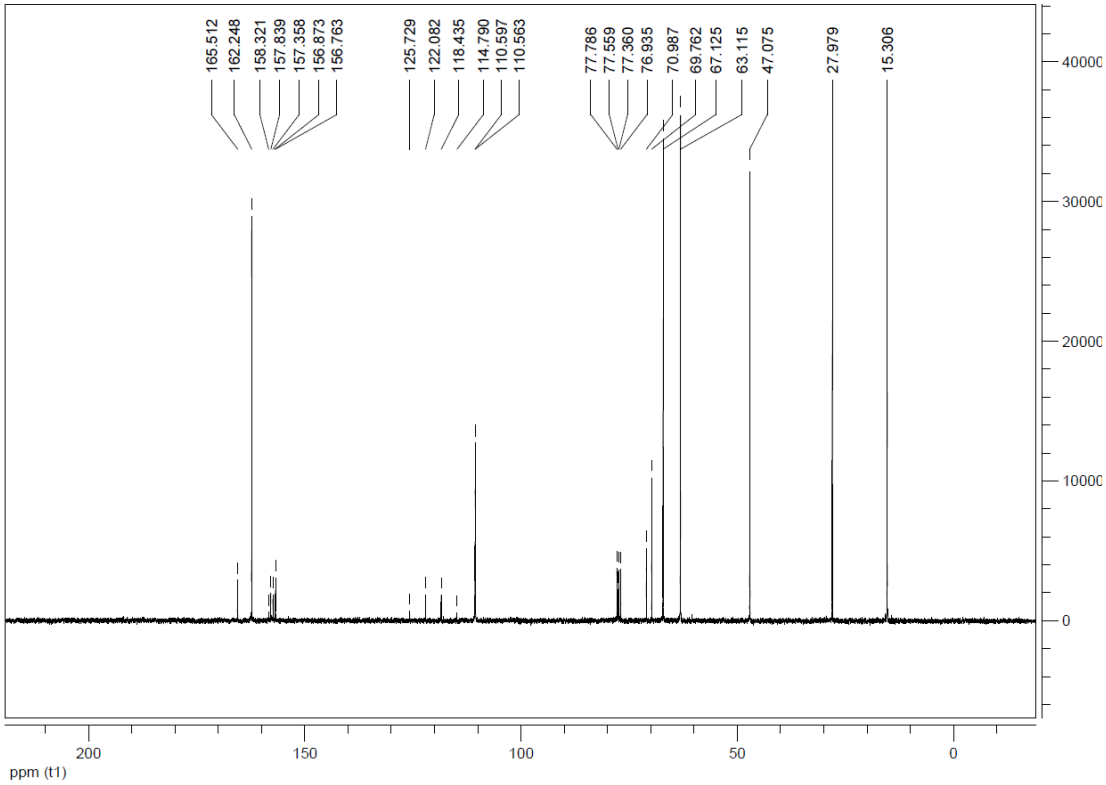

165.846
163.339
160.542
156.502
153.448
152.068
151.972
150.902
148.360
148.089
134.117
132.914
131.445
131.364
131.284
128.946
115.978
115.762
83.524
77.394
77.281
77.076
76.758
71.562
67.075
66.083
62.949
48.104
46.872
28.137
19.117
50000
0
200
150
100
50
0
ppm (t1)

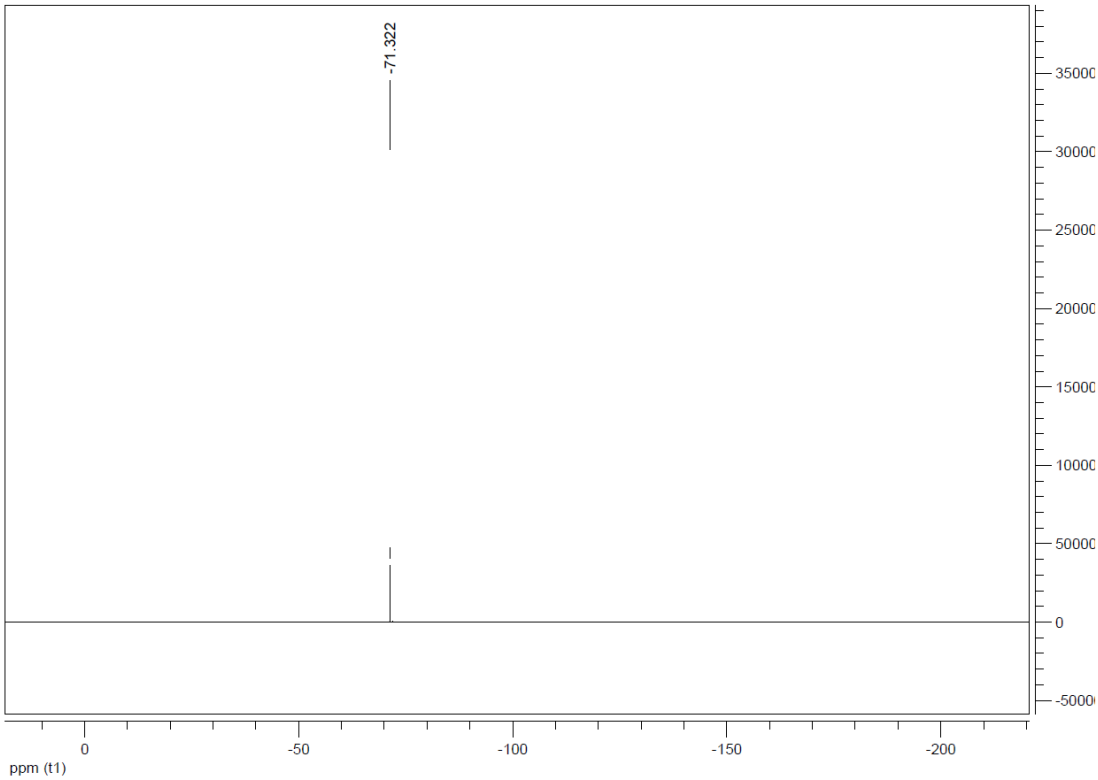

-108.914
-148.795
25000
20000
15000
10000
50000
0
-150
ppm (t1)

3-(5-(4-(Trifluoromethyl)pyrimidin-2-yloxy)pent-1-ynyl)oxazolidin-2-one (**3n**)

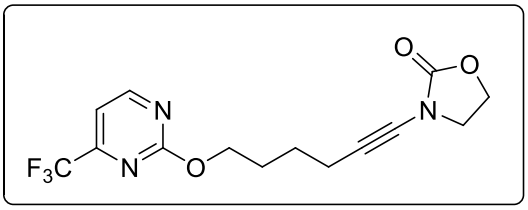


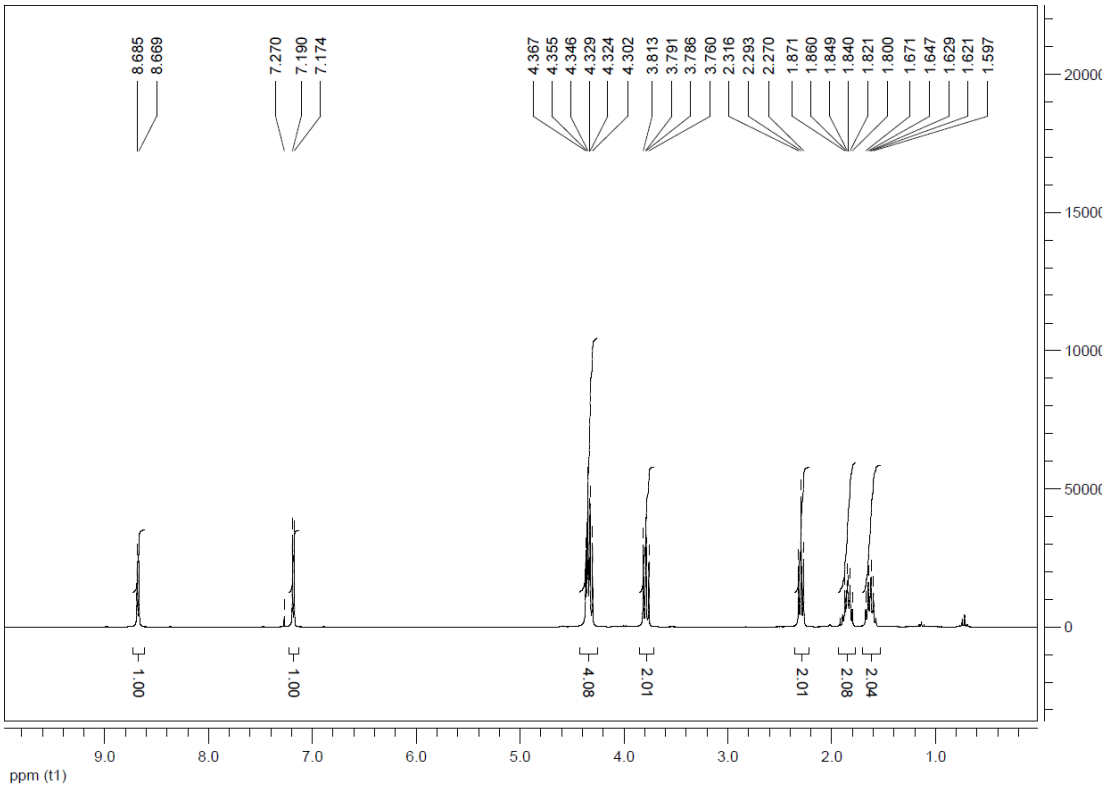


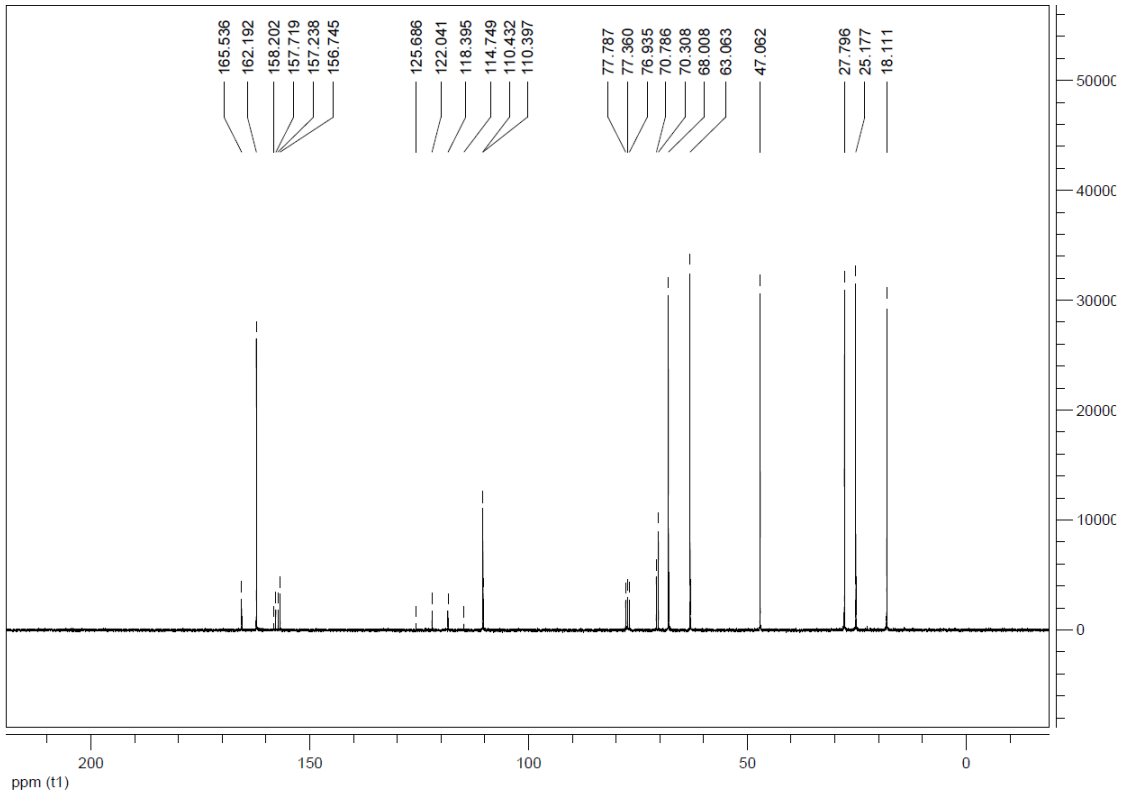




3-(6-(4-(Trifluoromethyl)pyrimidin-2-yloxy)hex-1-ynyl)oxazolidin-2-one (**3o**)



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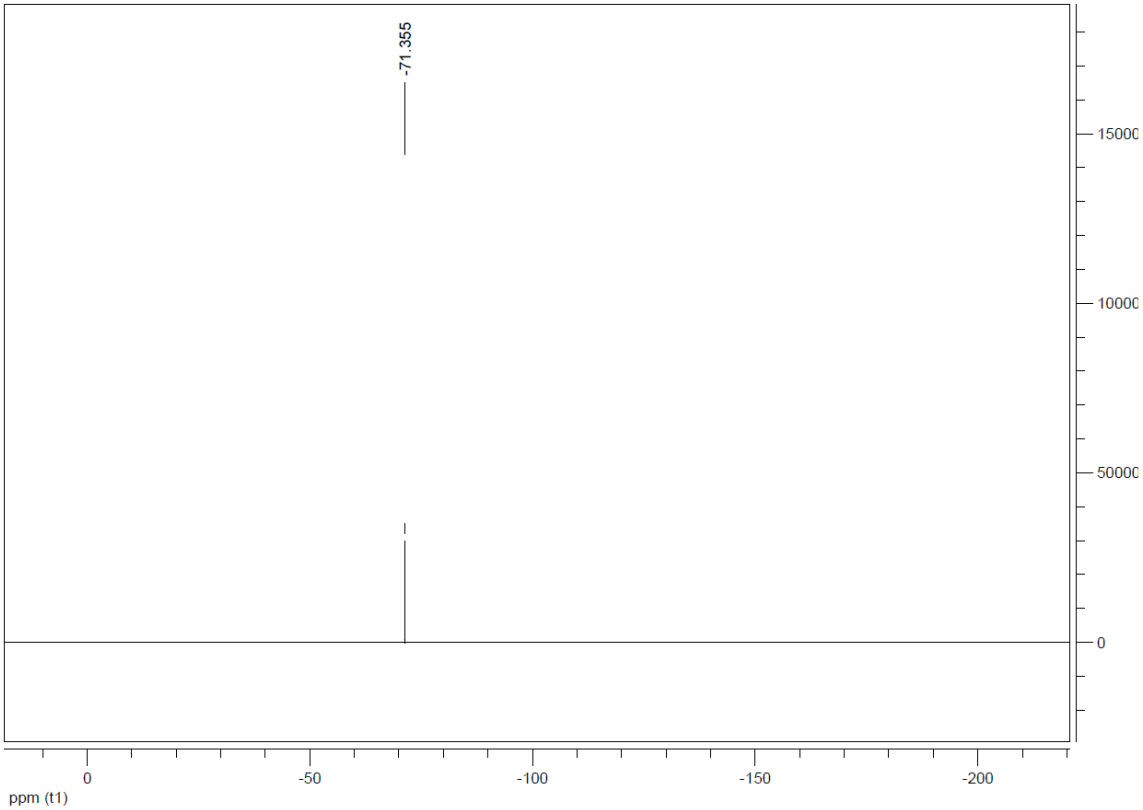
158.202
157.719
157.238
156.745
125.686
122.041
118.395
114.749
110.432
110.397
77.787
77.360
76.935
70.786
70.308
68.008
63.063
47.062
27.796
25.177
18.111
50000
40000
30000
20000
10000
0
200
150
100
50
0
ppm (t1)


-71.355
15000
10000
50000
0
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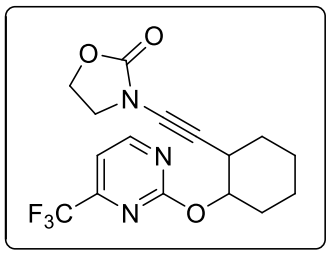
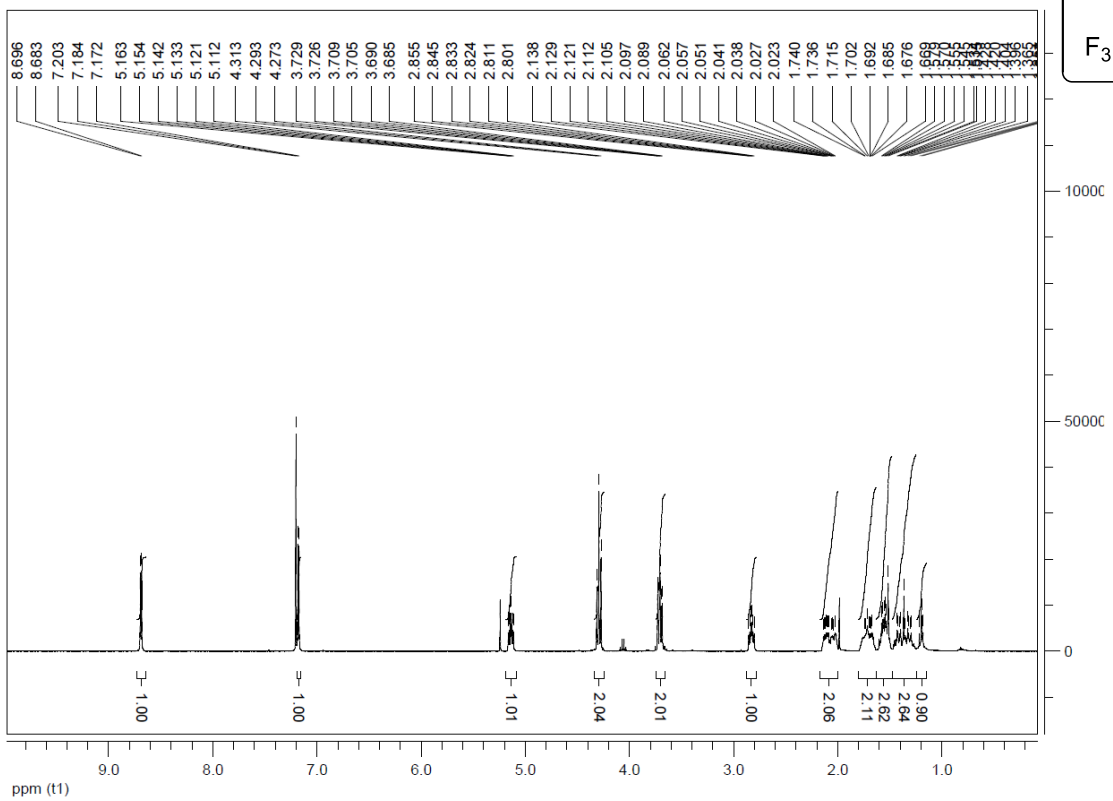
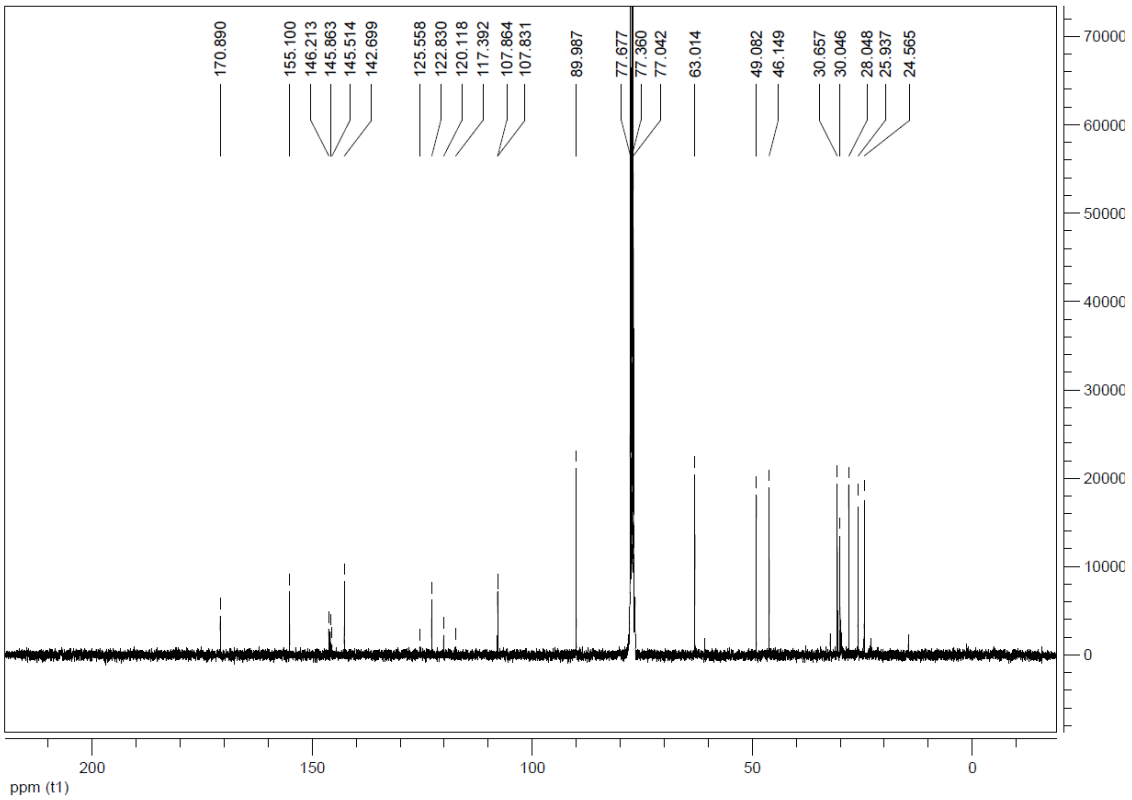
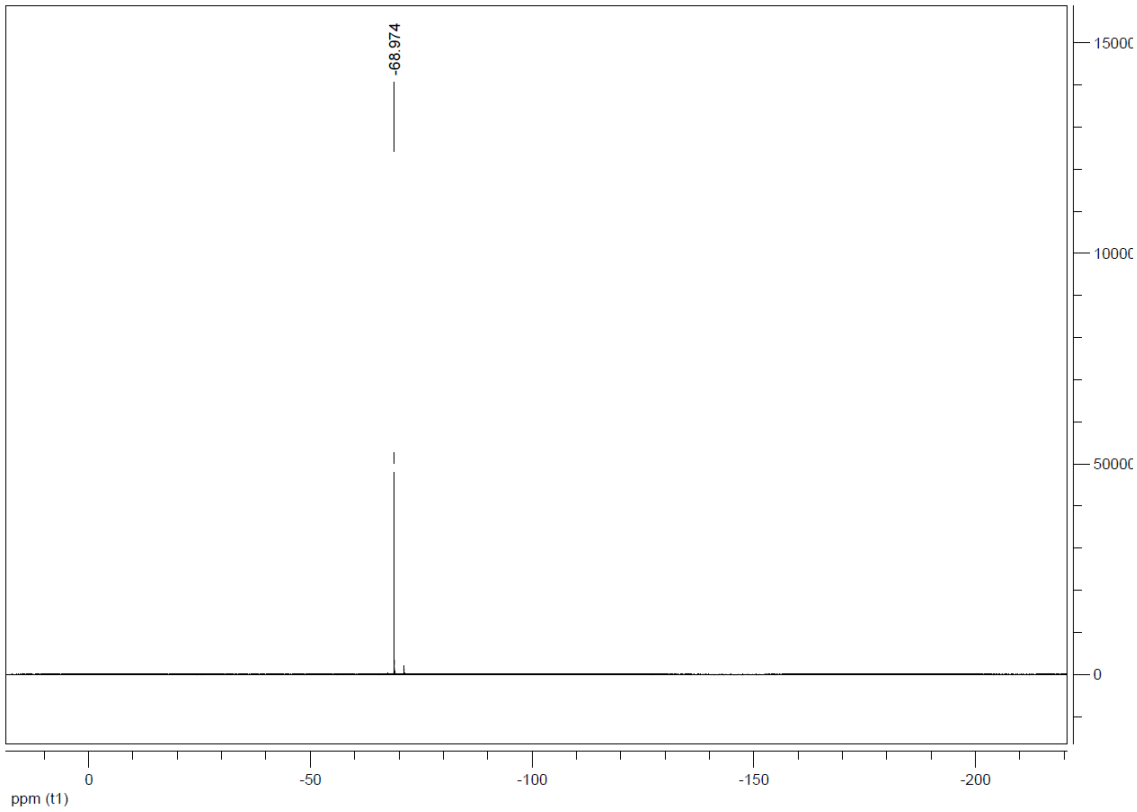
-50
-100
-150
-200
ppm (t1)

3-((2-(4-(Trifluoromethyl)pyrimidin-2-yloxy)cyclohexyl)ethynyl)oxazolidin-2-one (**3p**)

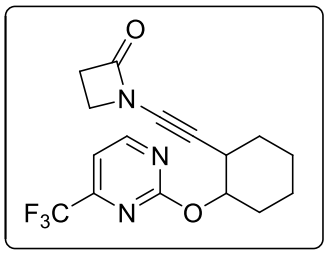


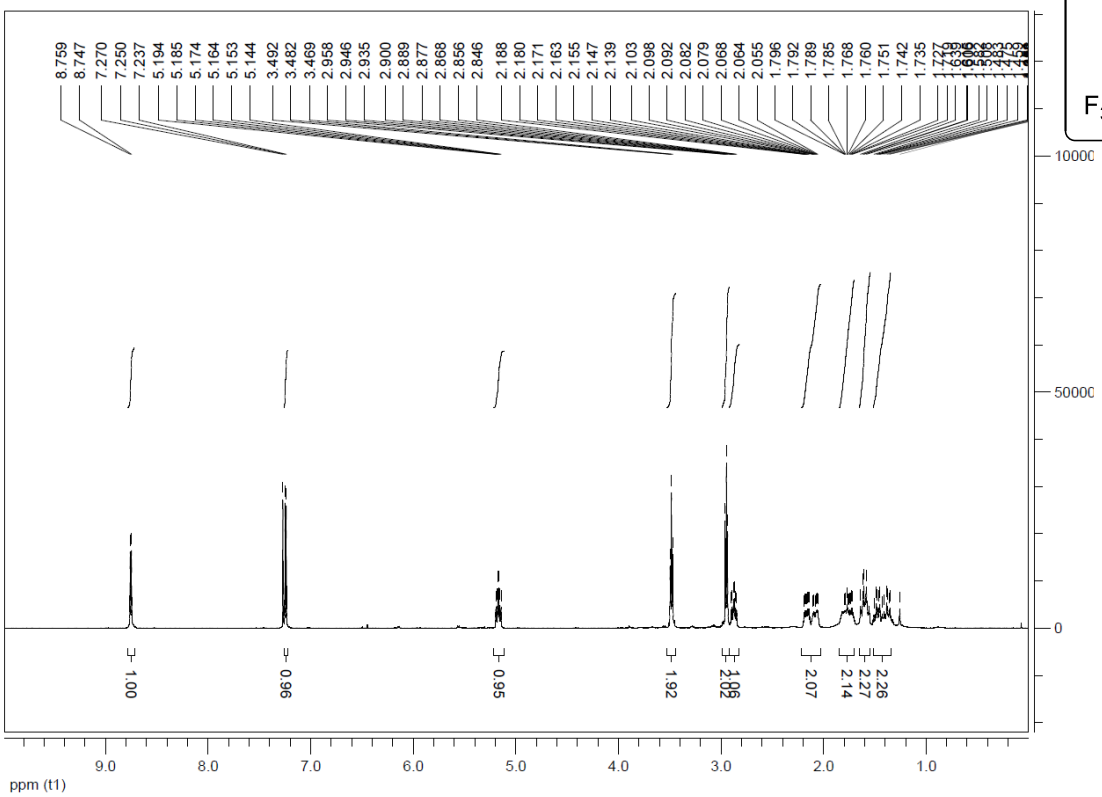


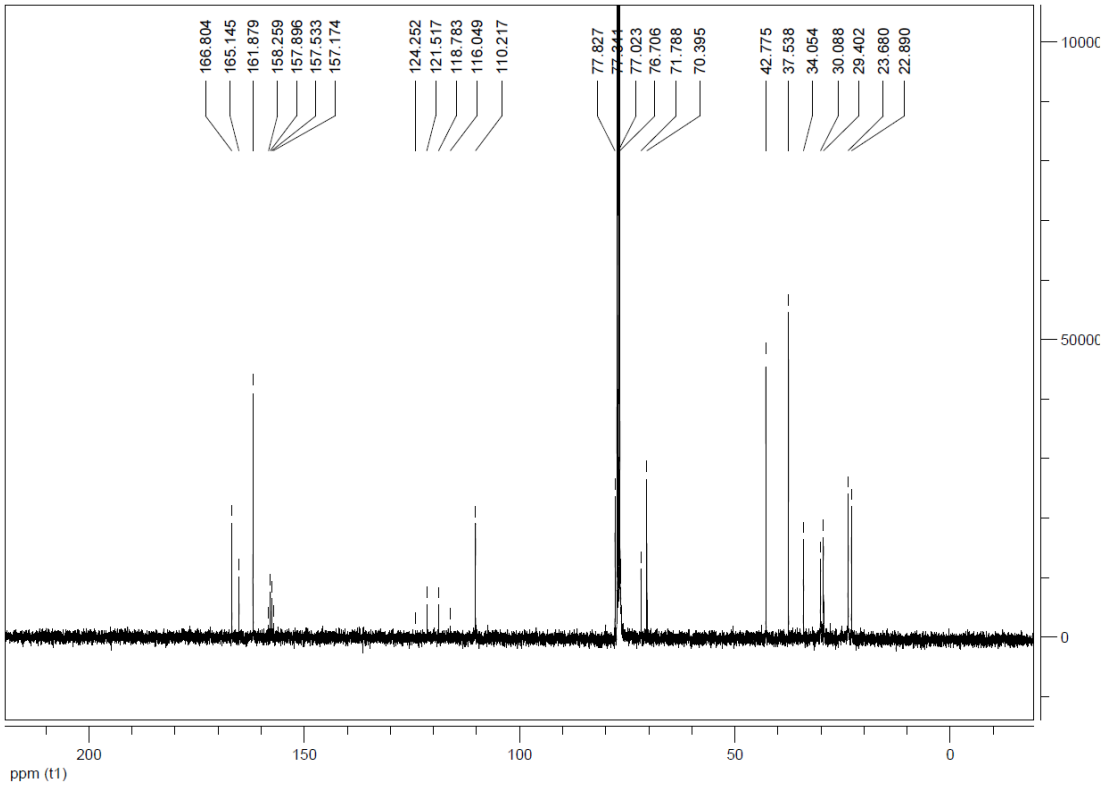




1-((2-(4-(Trifluoromethyl)pyrimidin-2-yloxy)cyclohexyl)ethynyl)azetidin-2-one (**3p**)



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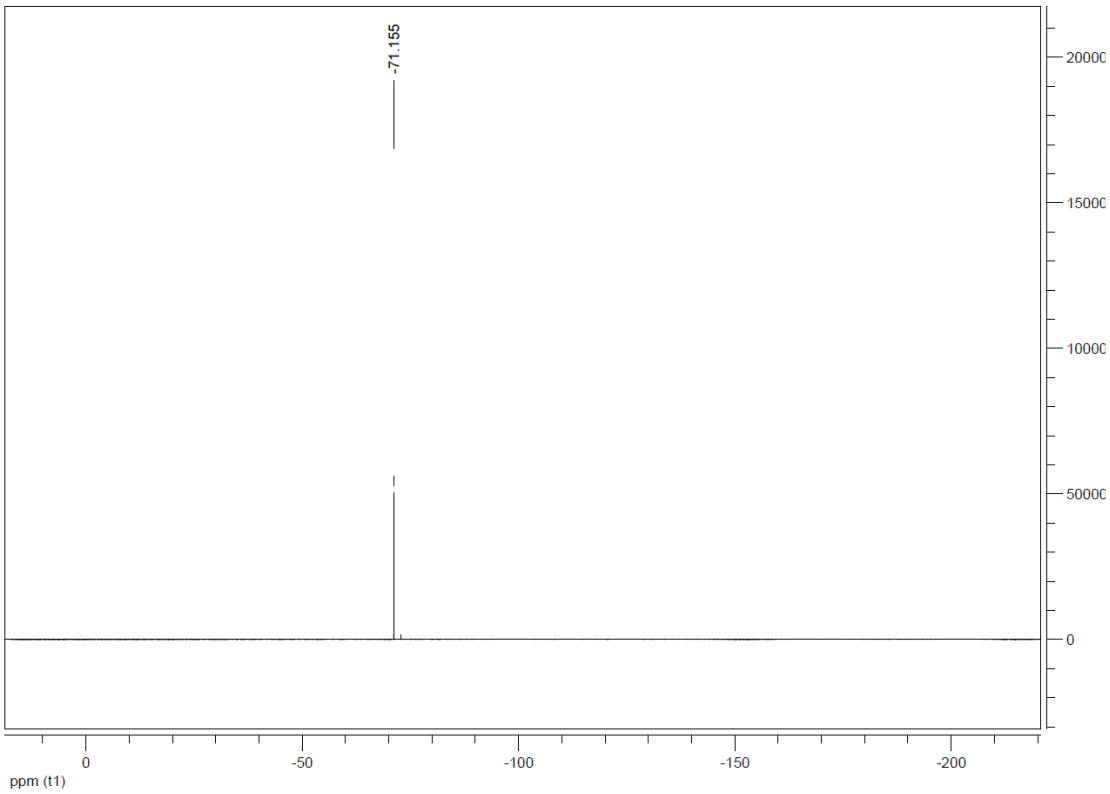
161.879
158.259
157.896
157.533
157.174
124.252
121.517
118.783
116.049
110.217
77.827
77.341
77.023
76.706
71.788
70.395
42.775
37.538
34.054
30.088
29.402
23.680
22.890
10000
50000
0
200
150
100
50
0
ppm (t1)


-71.155
20000
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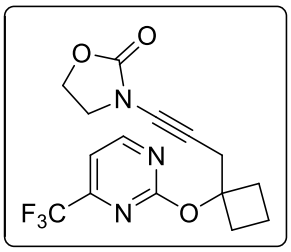
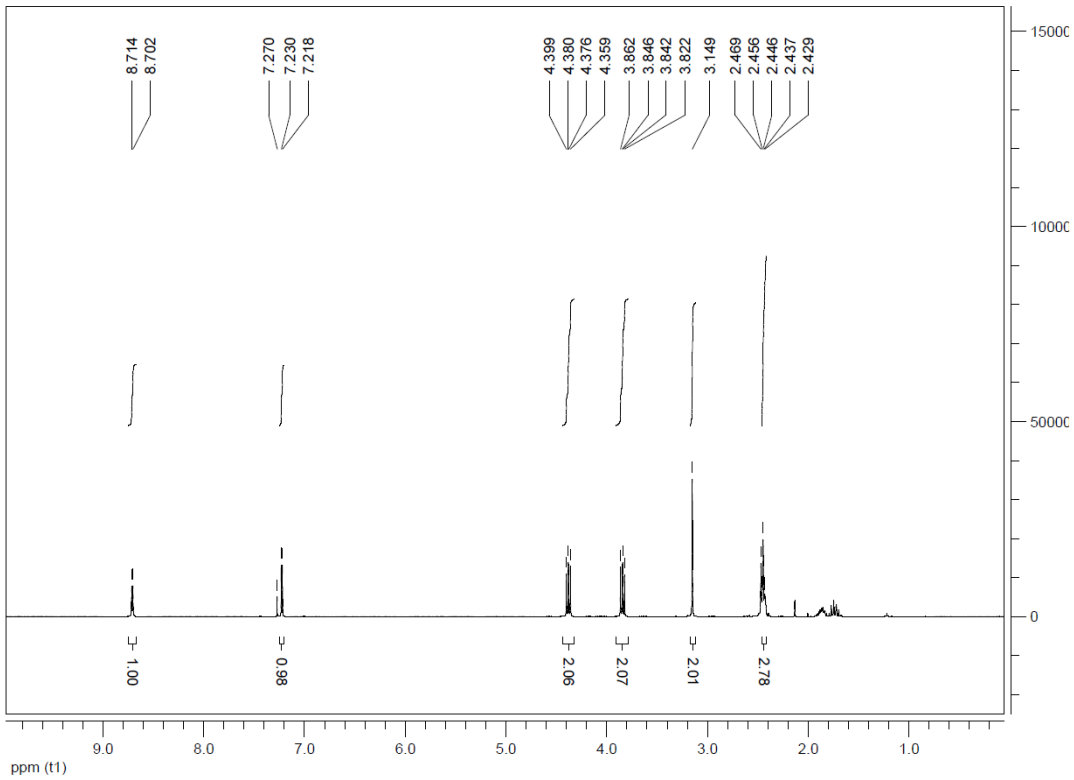
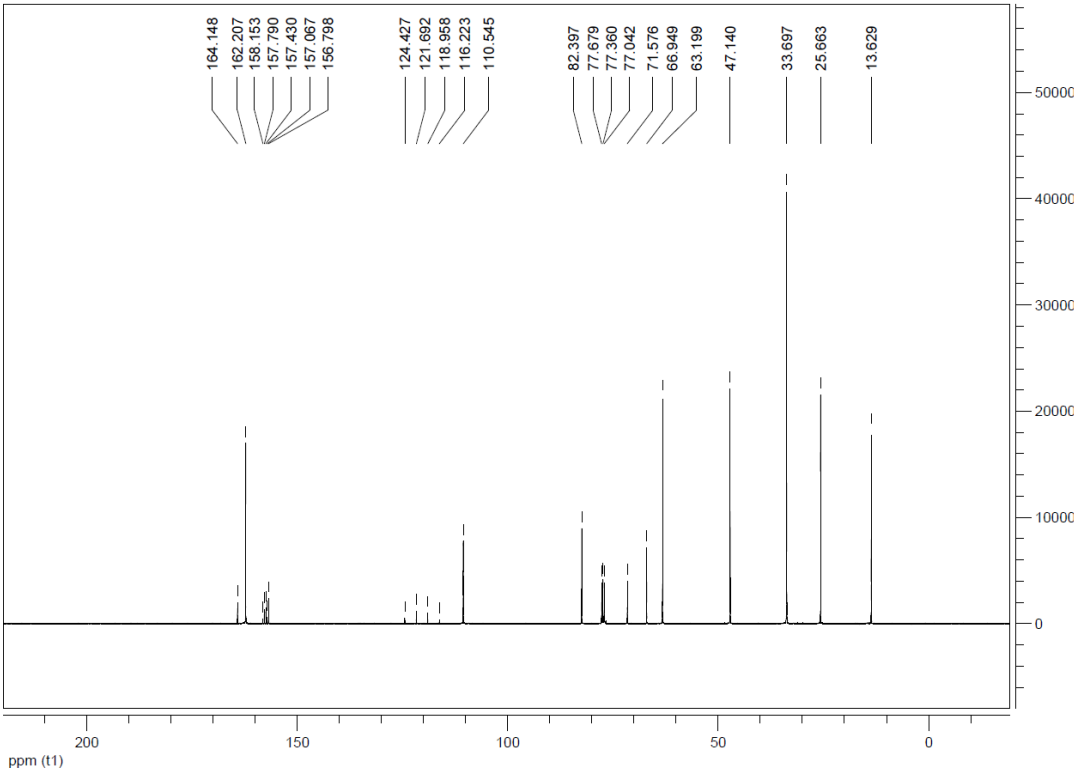
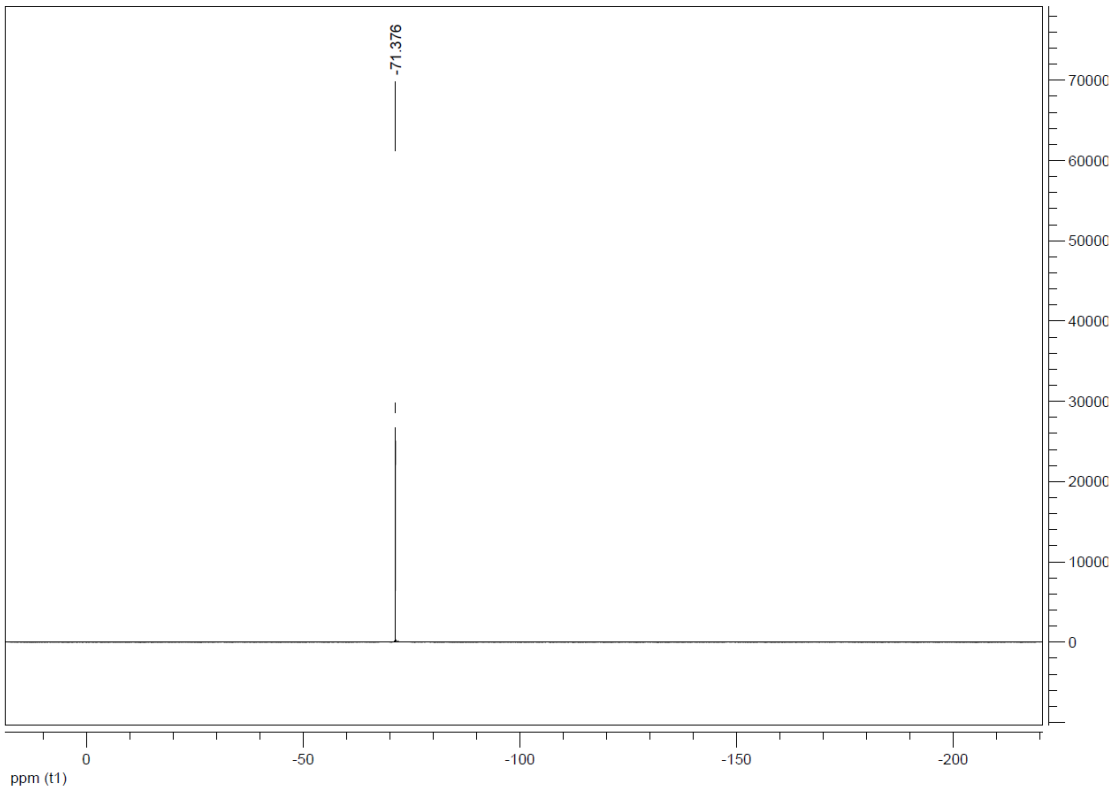
10000
50000
0
0
-50
-100
-150
-200
ppm (t1)

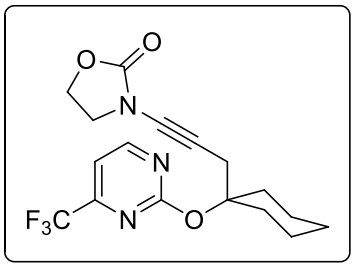
3-(3-(1-(4-(Trifluoromethyl)pyrimidin-2-yloxy)cyclobutyl)prop-1-ynyl)oxazolidin-2-one (**3r**)



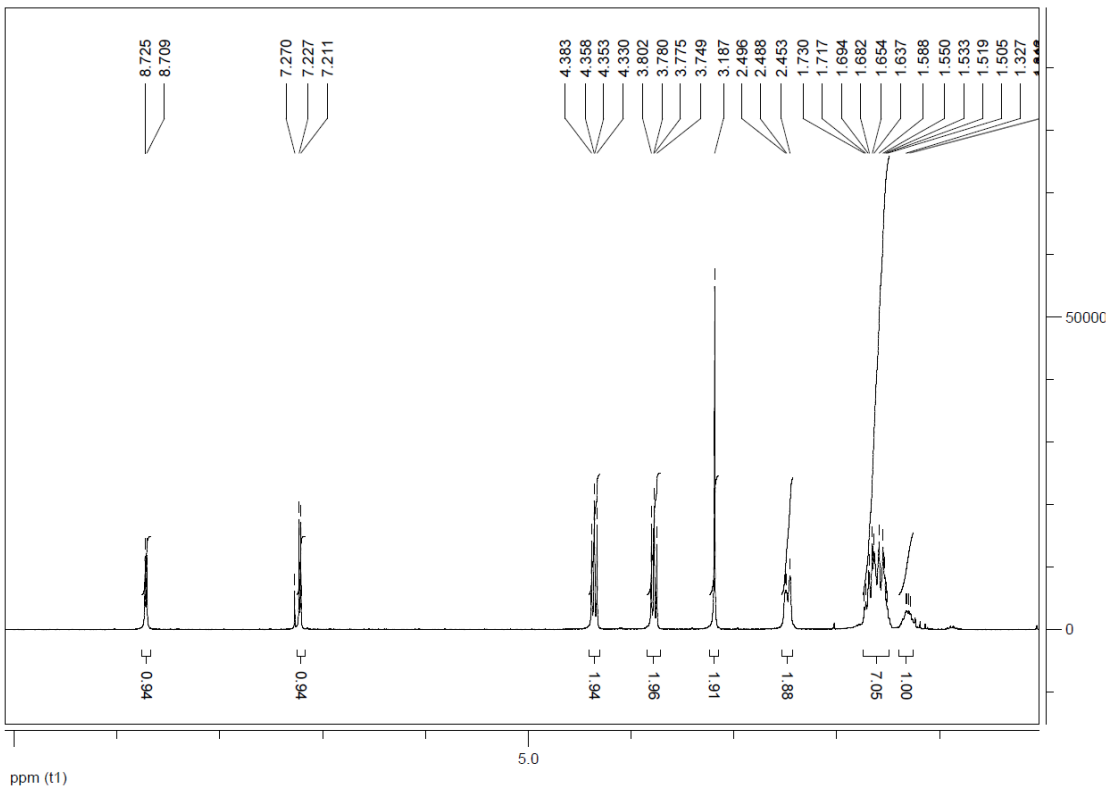


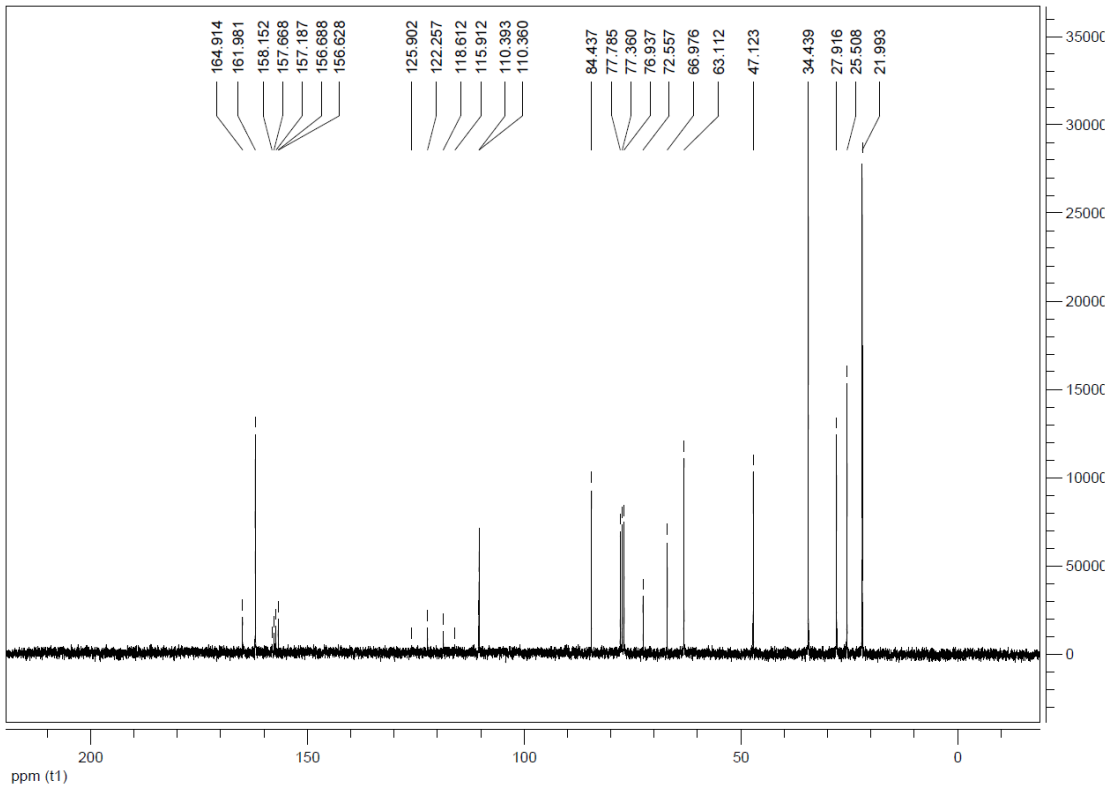






3-(3-(1-(4-(Trifluoromethyl)pyrimidin-2-yloxy)cyclohexyl)prop-1-ynyl)oxazolidin-2-one (**3s**)

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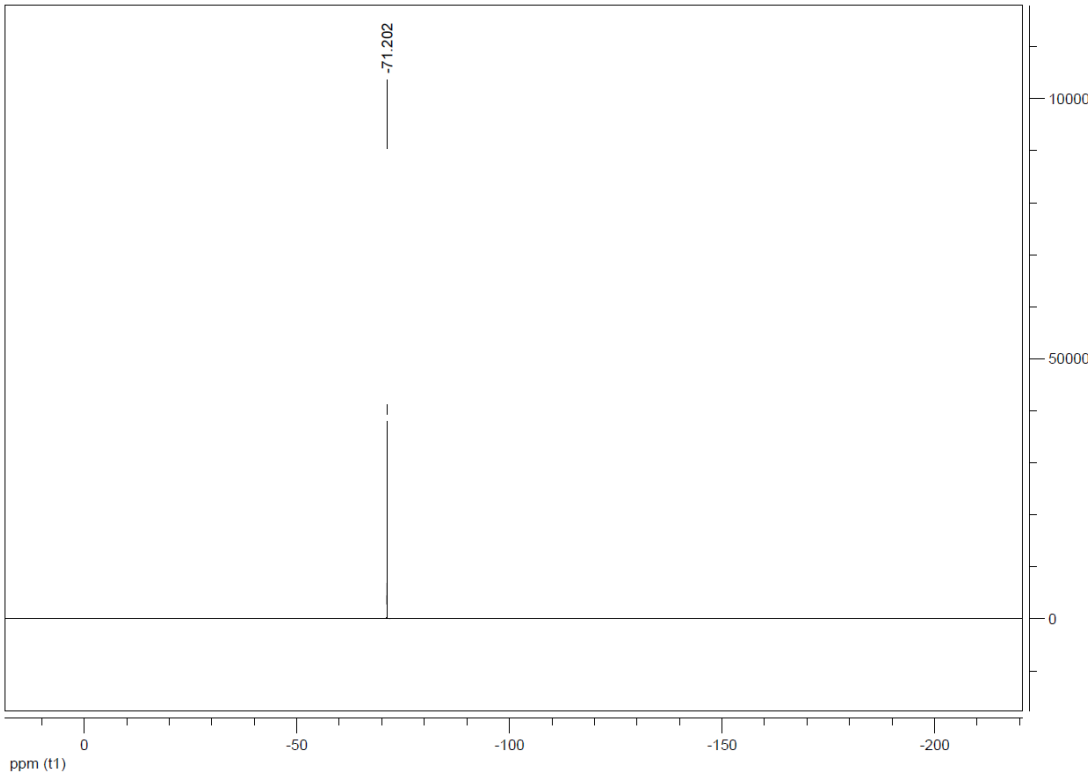
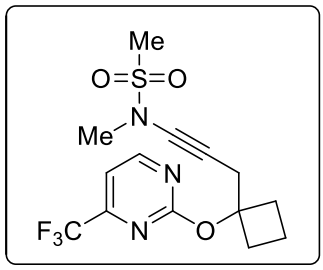
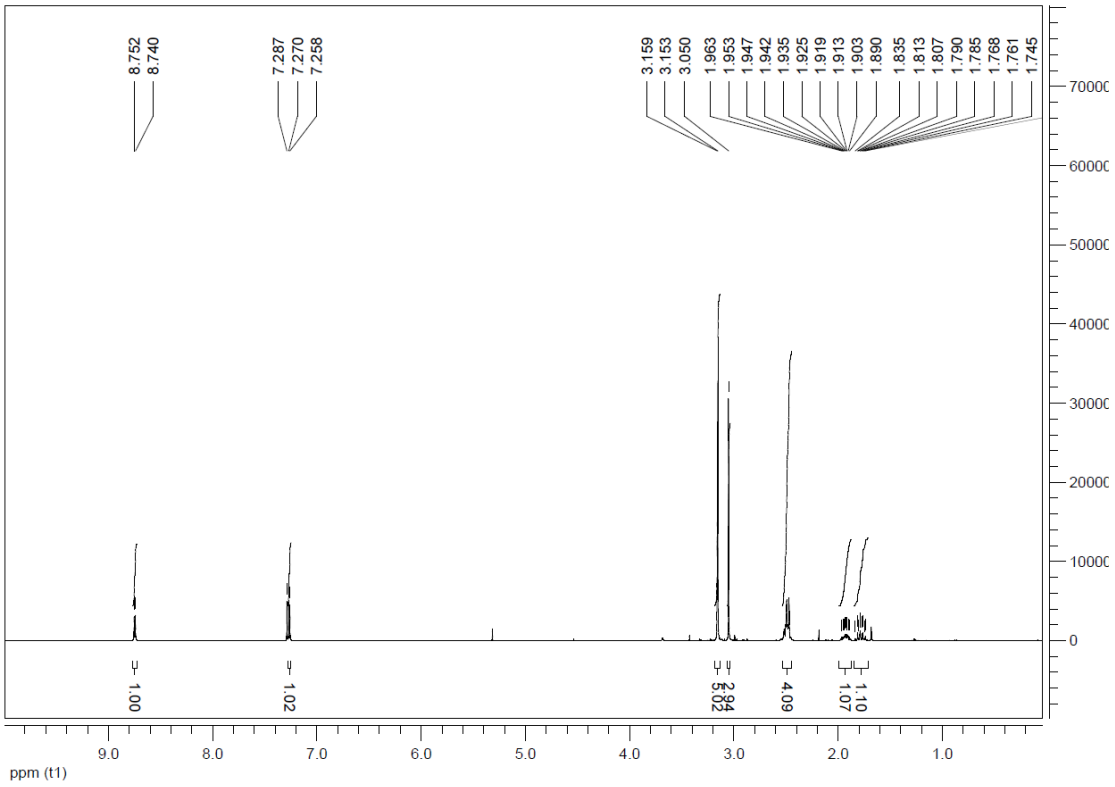
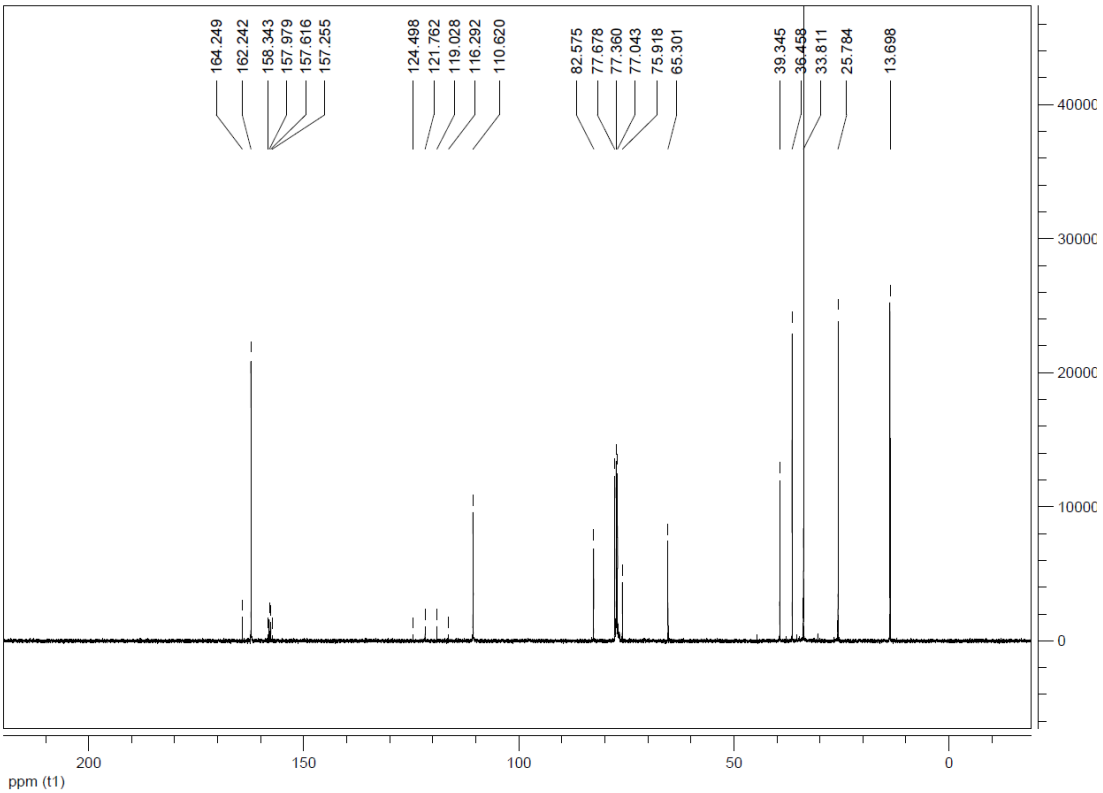
158.152
157.668
157.187
156.688
156.628
125.902
122.257
118.612
115.912
110.393
110.360
84.437
77.785
77.360
76.937
72.557
66.976
63.112
47.123
34.439
27.916
25.508
21.993
35000
30000
25000
20000
15000
10000
50000
0
200
150
100
50
0
ppm (t1)

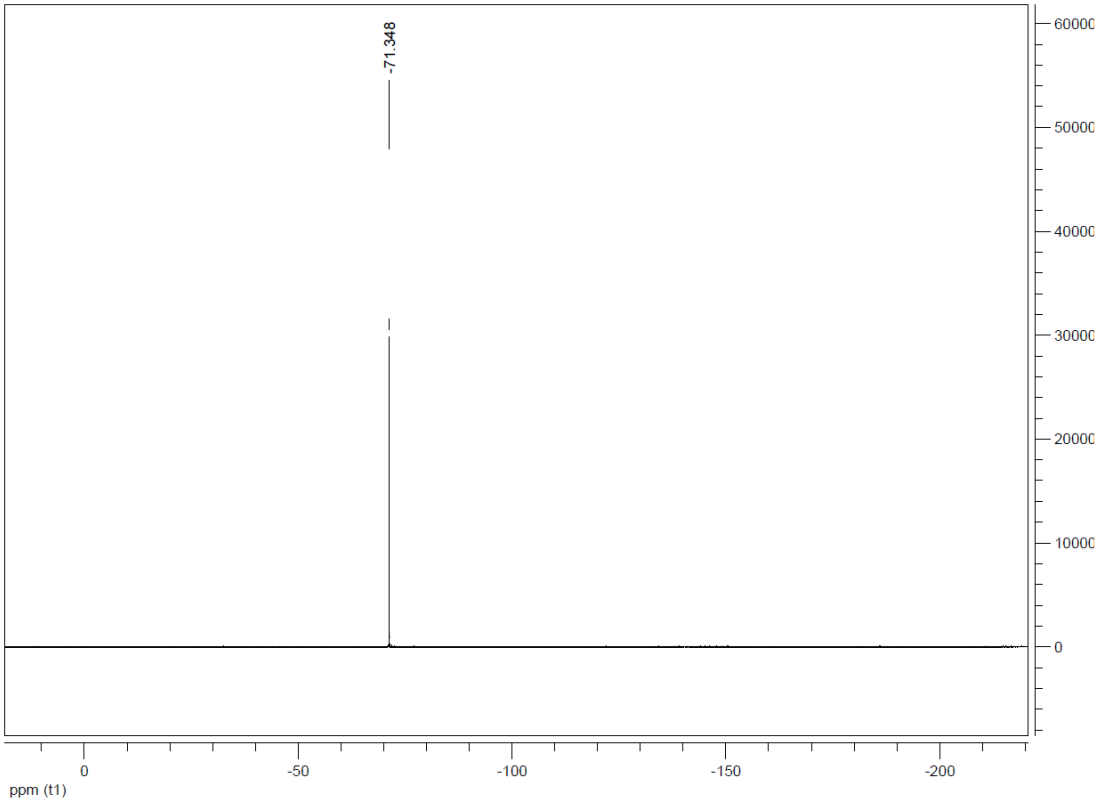

-71.202
10000
50000
0
0
-50
-100
-150
-200
ppm (t1)

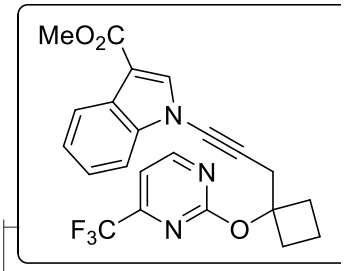
N-Methyl-*N*-(3-(1-(4-(trifluoromethyl)pyrimidin-2-yloxy)cyclobutyl)prop-1-ynyl)methanesulfonamide (**3t**)



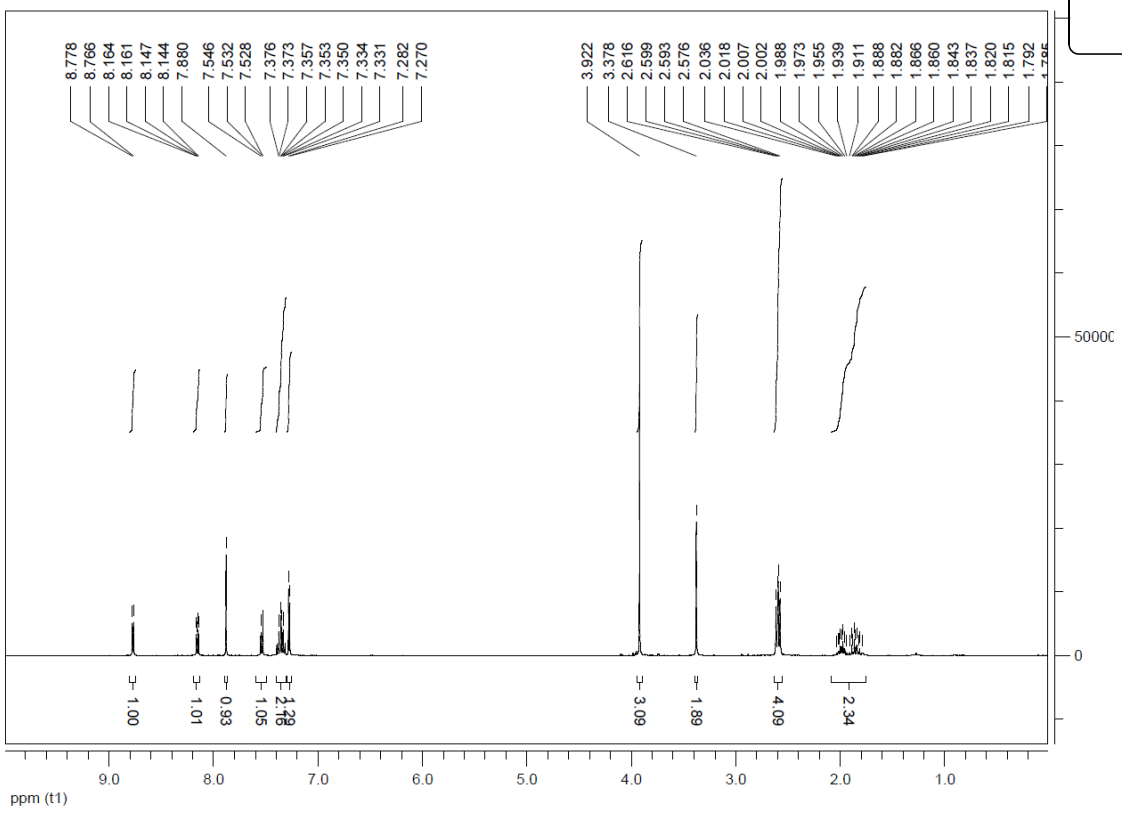


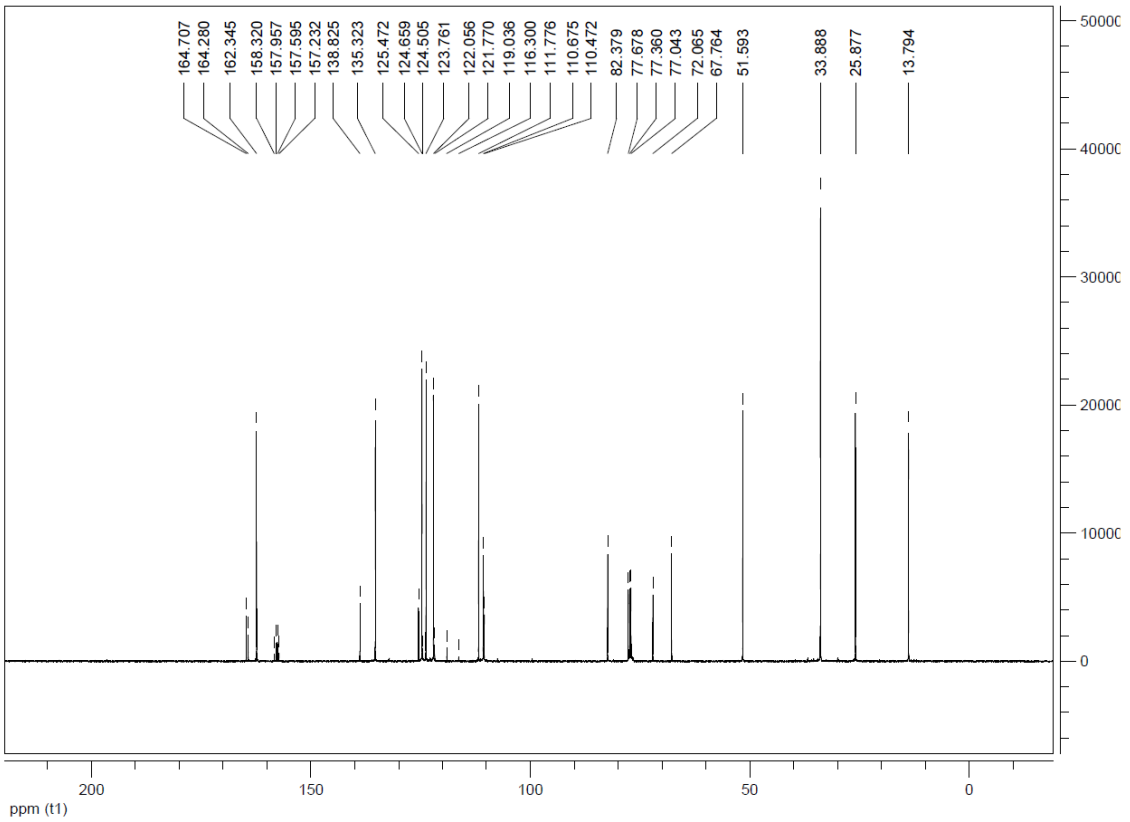


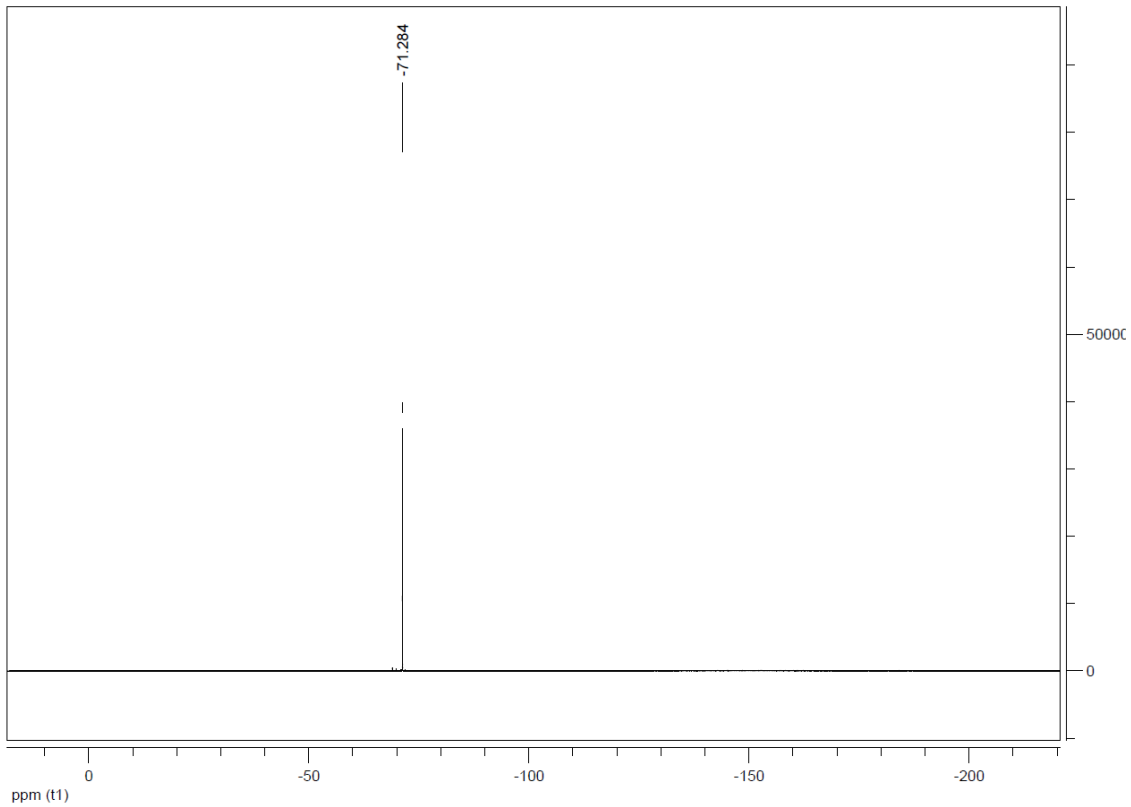




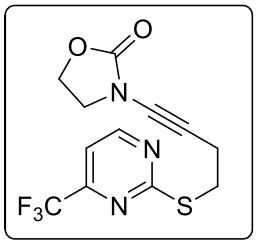
Methyl 1-(3-(1-(4-(trifluoromethyl)pyrimidin-2-yloxy)cyclobutyl)prop-1-ynyl)-1H-indole-3-carboxylate (**3u**)

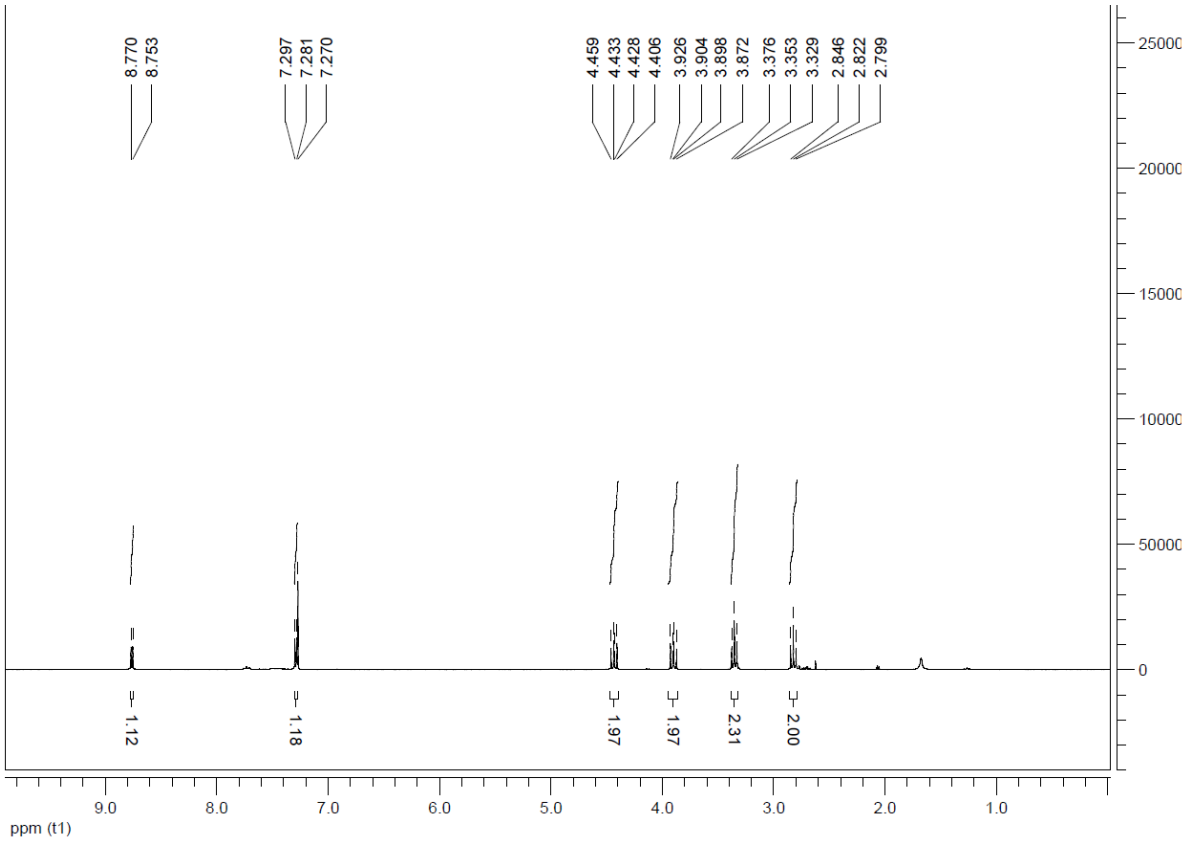


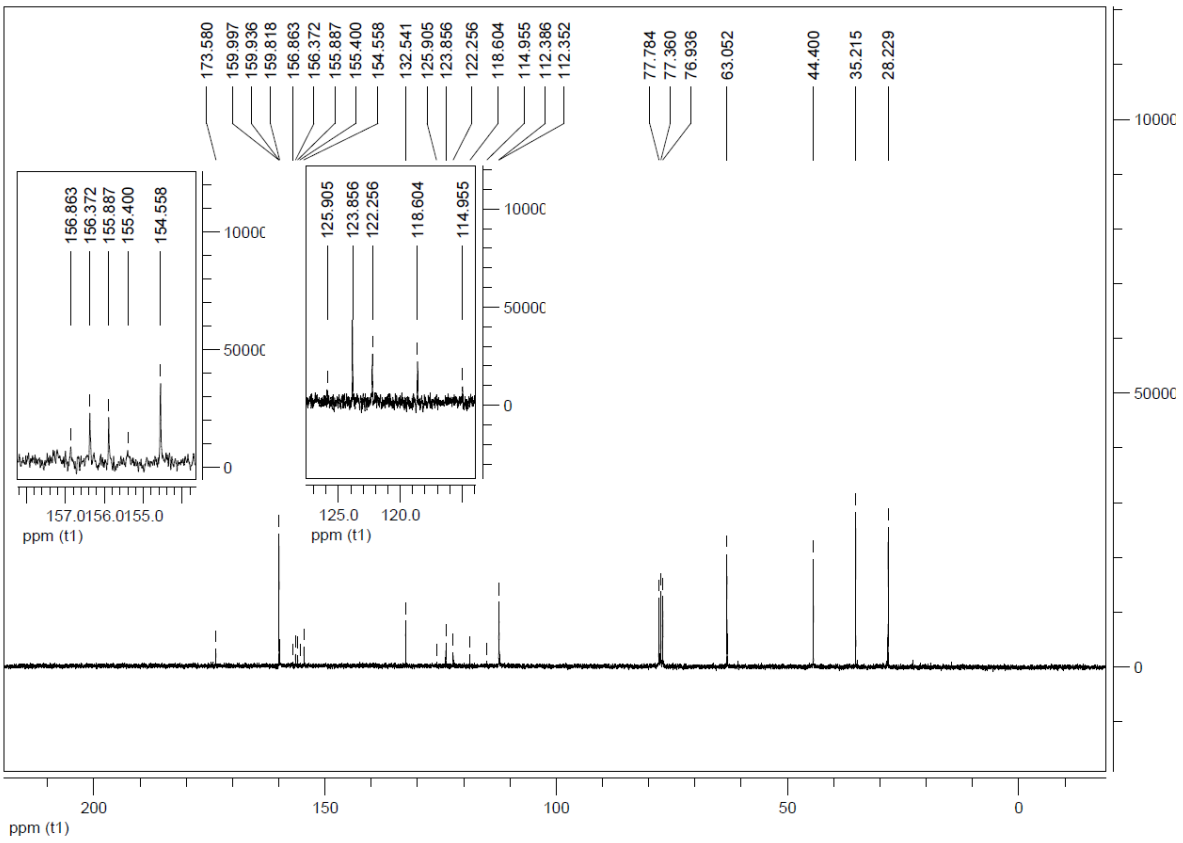

164.707
164.280
162.345
158.320
157.957
157.595
157.232
138.825
135.323
125.472
124.659
124.505
123.761
122.056
121.770
119.036
116.300
111.776
110.675
110.472
82.379
77.678
77.360
77.043
72.065
67.764
51.593
33.888
25.877
13.794
50000
40000
30000
20000
10000
0
200
150
100
50
0
ppm (t1)

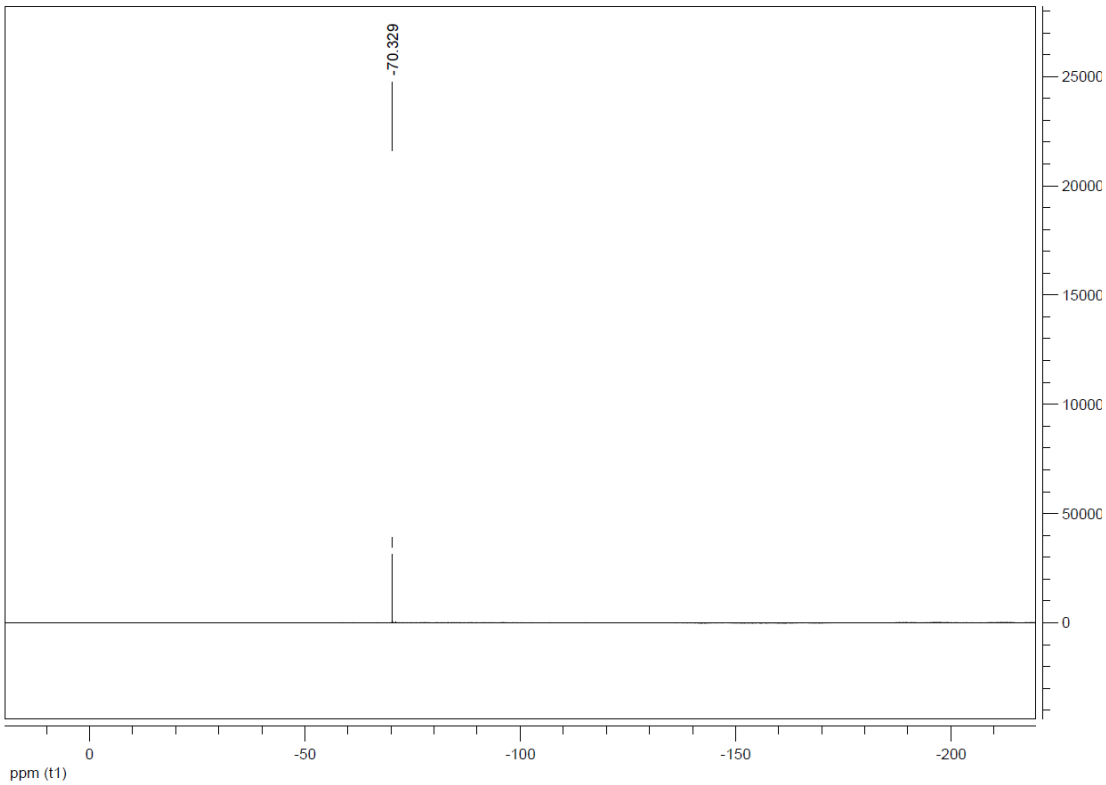

-71.284
50000
0
0
-50
-100
-150
-200
ppm (t1)

3-(4-(4-(trifluoromethyl)pyrimidin-2-ylthio)but-1-ynyl)oxazolidin-2-one (**3v**)

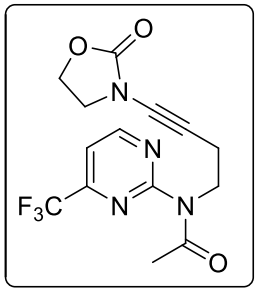


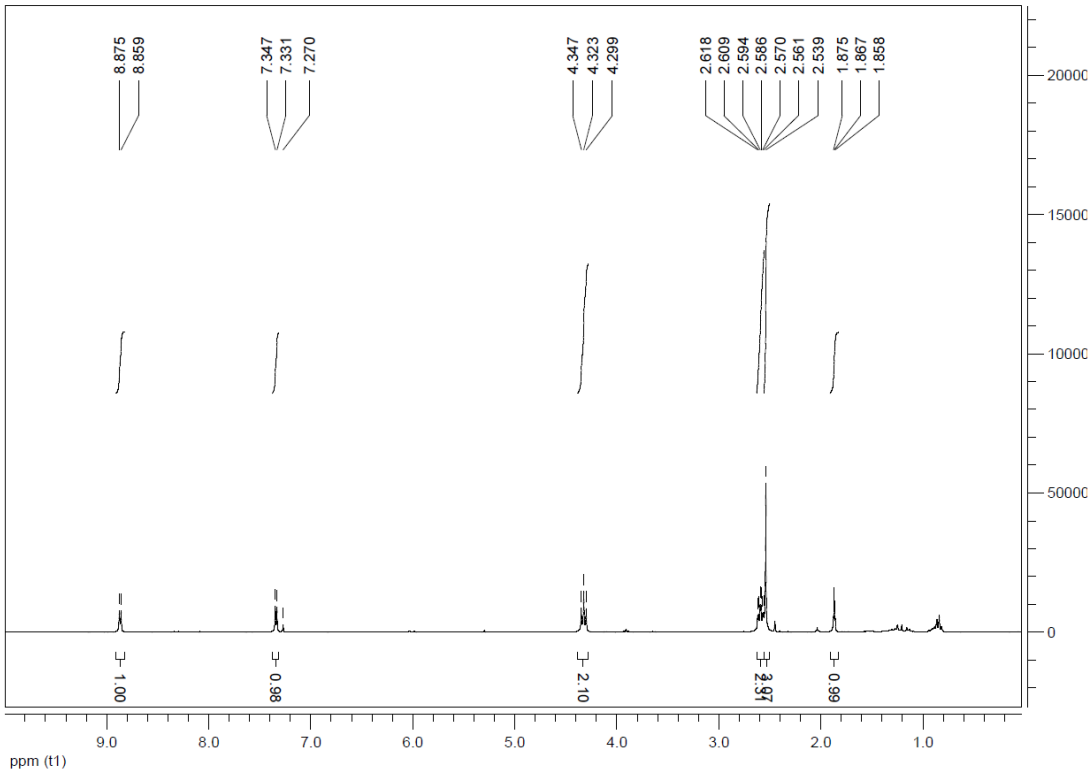


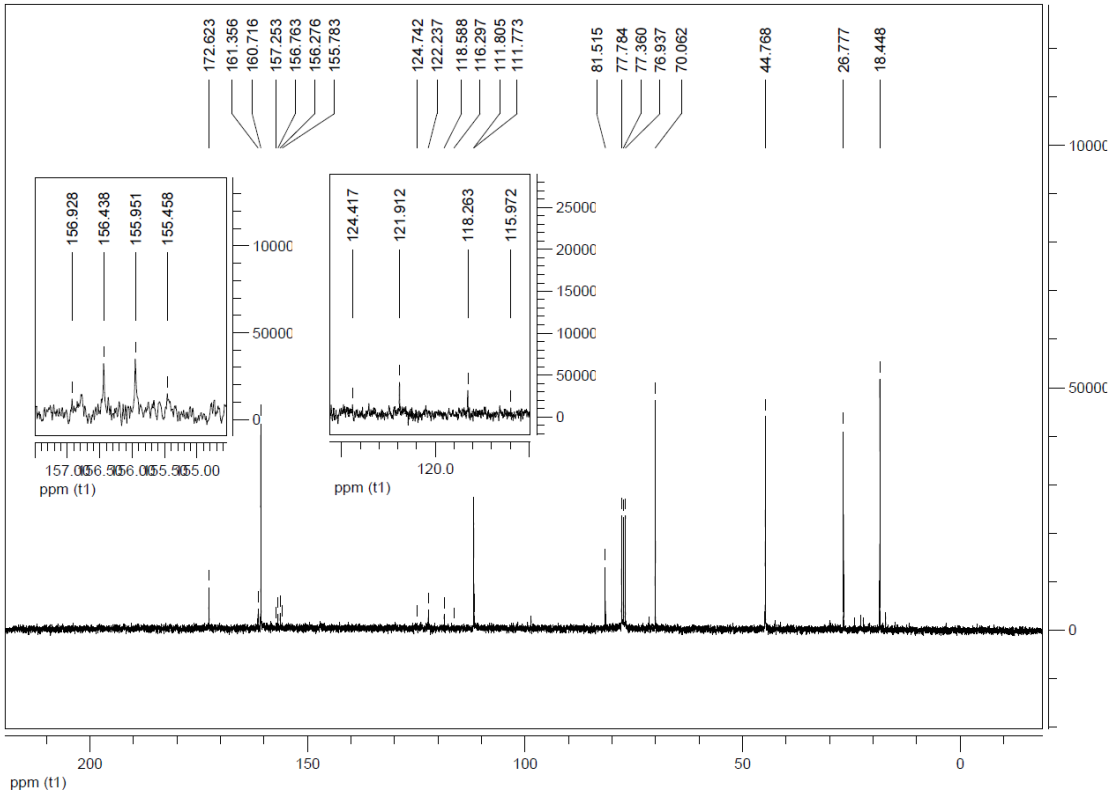


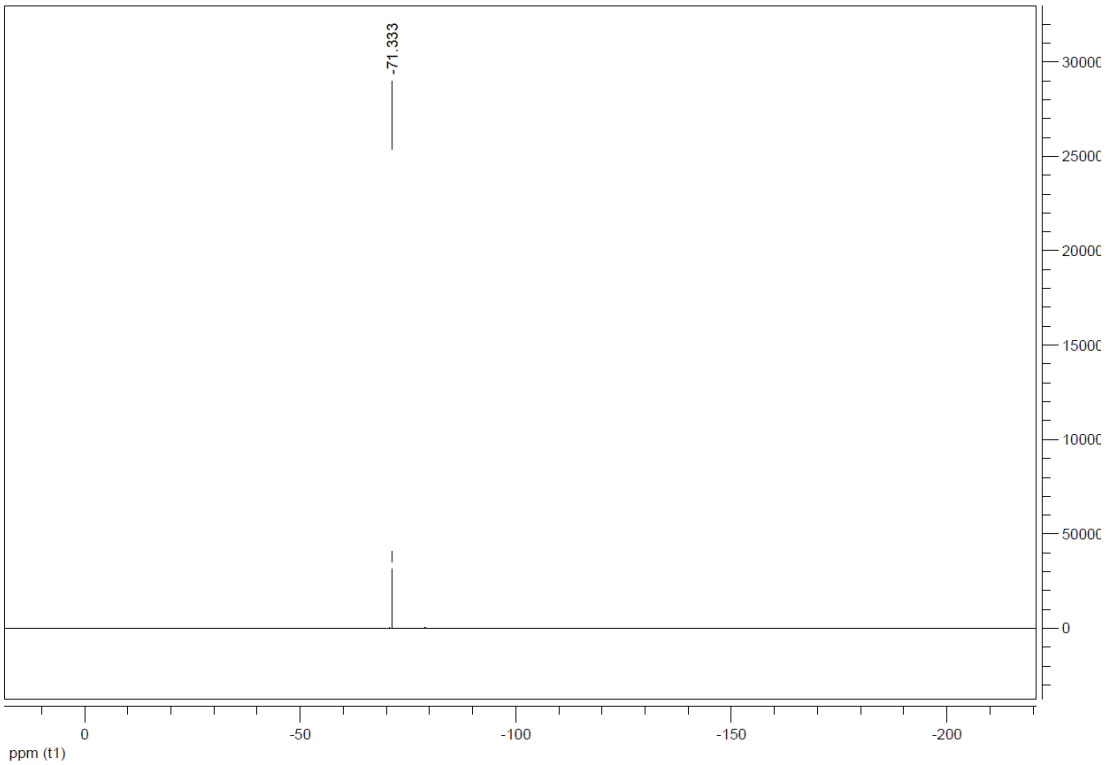


N-(4-(2-oxooxazolidin-3-yl)but-3-ynyl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)acetamide (**3w**)

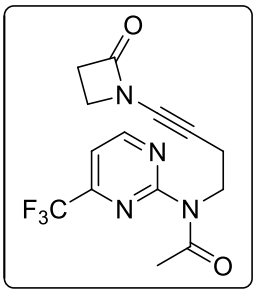


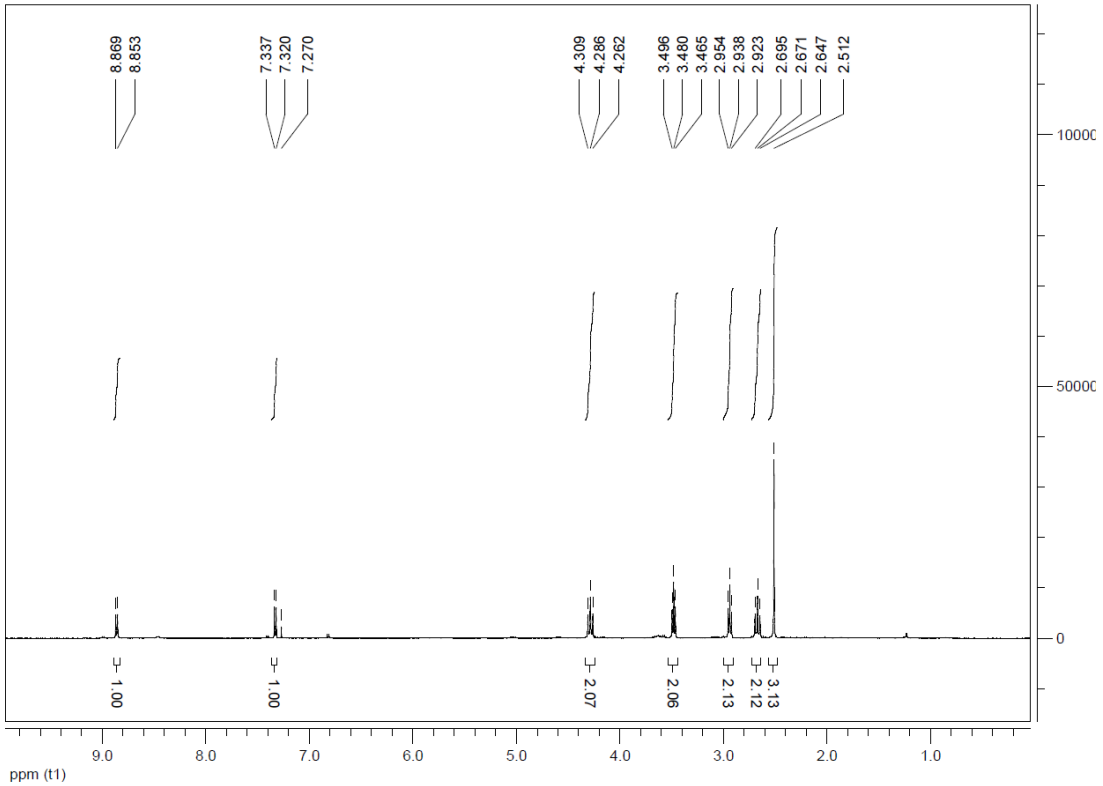


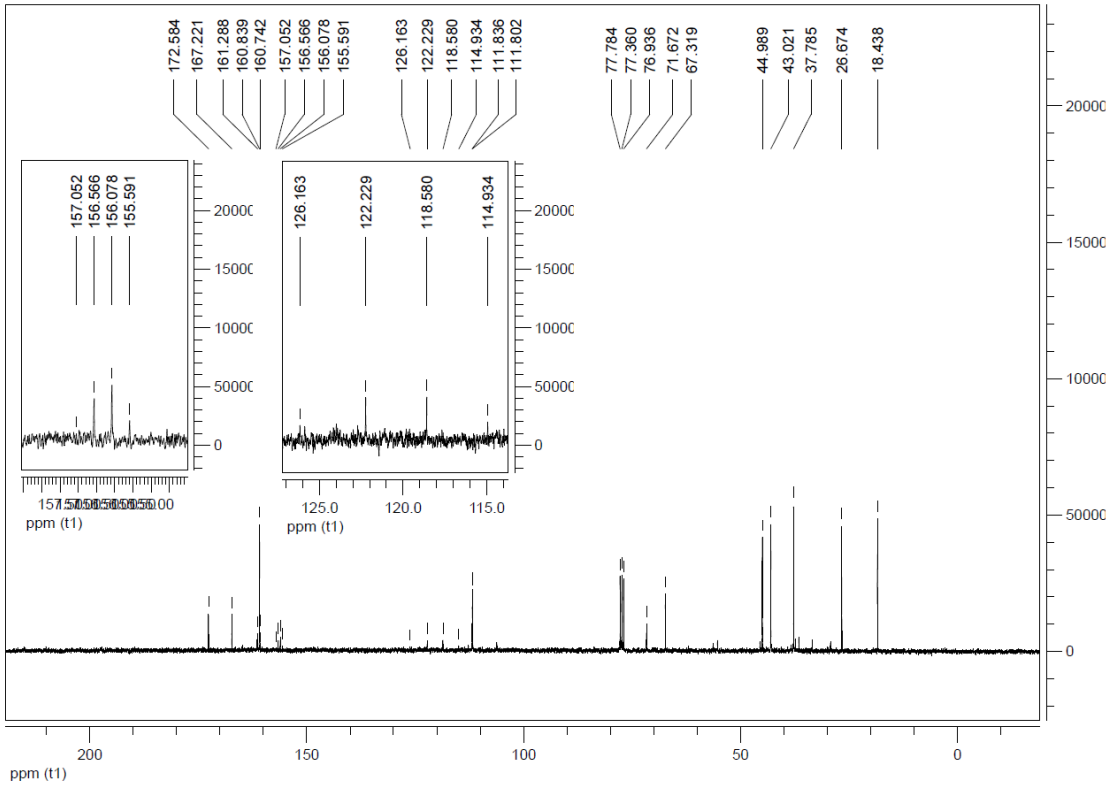

172.623
161.356
160.716
157.253
156.763
156.276
155.783
124.742
122.237
118.588
116.297
111.805
111.773
81.515
77.784
77.360
76.937
70.062
44.768
26.777
18.448
156.928
156.438
155.951
155.458
124.417
121.912
118.263
115.972
ppm (t1)
200
150
100
50
0

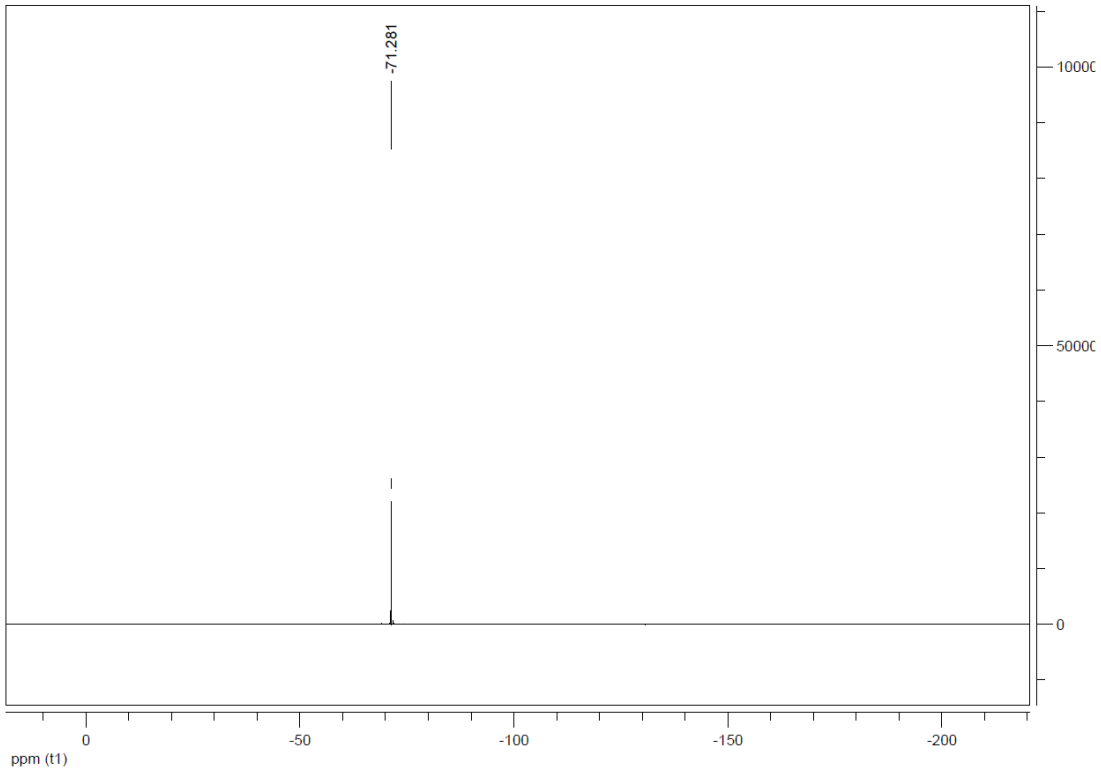

-71.333
ppm (t1)
0
-50
-100
-150
-200

N-(4-(2-oxoazetidin-1-yl)but-3-ynyl)-N-(4-(trifluoromethyl)pyrimidin-2-yl)acetamide (**3x**)

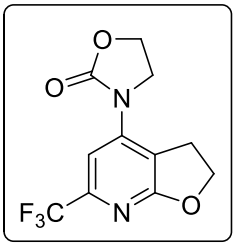


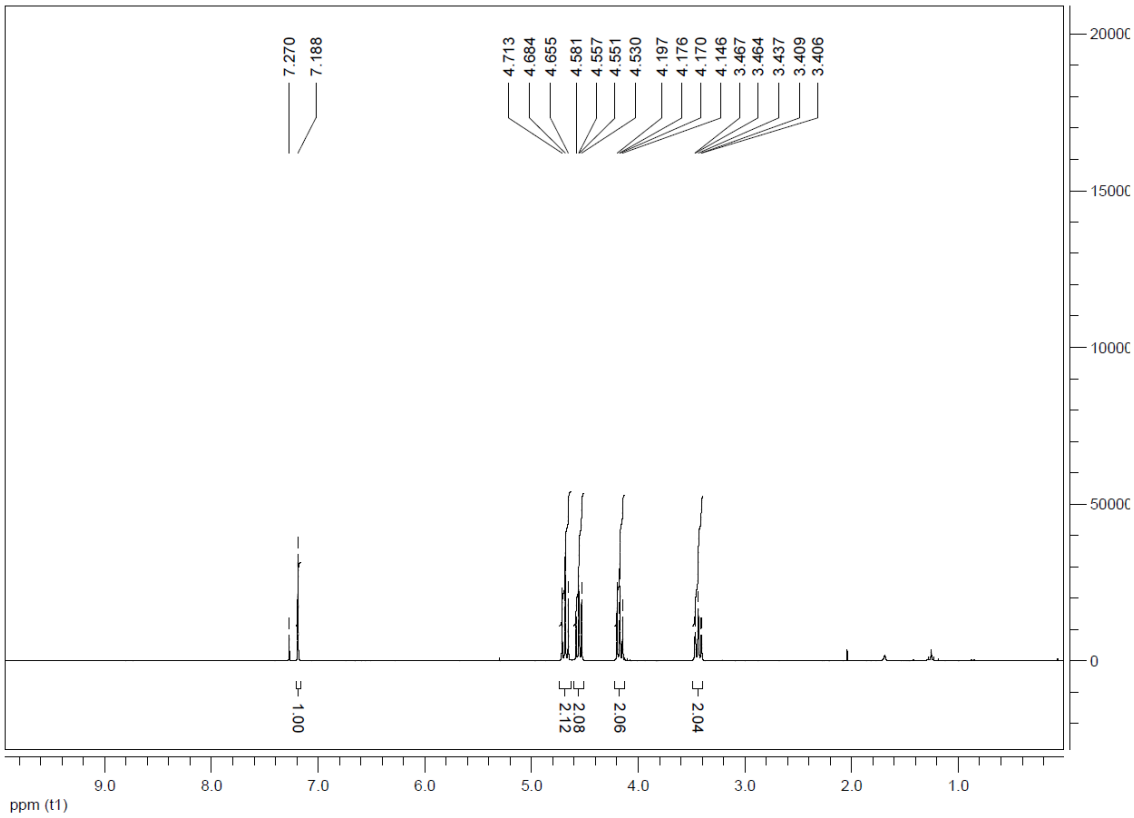


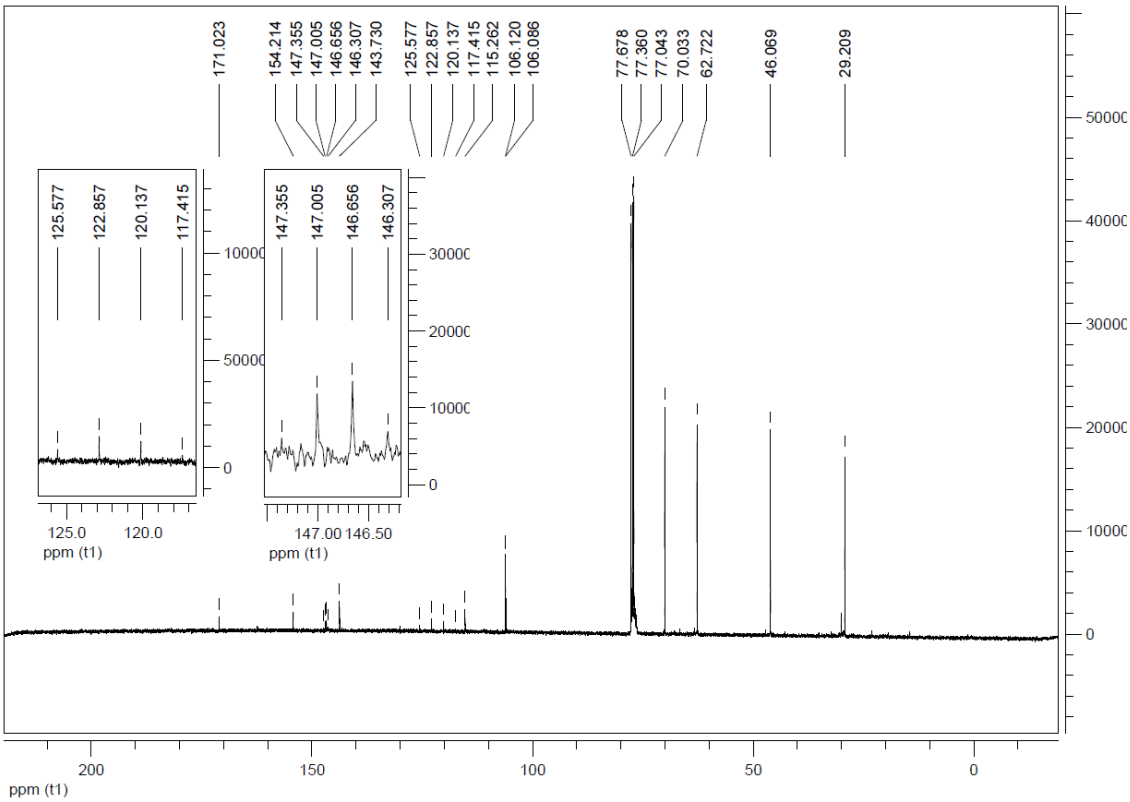


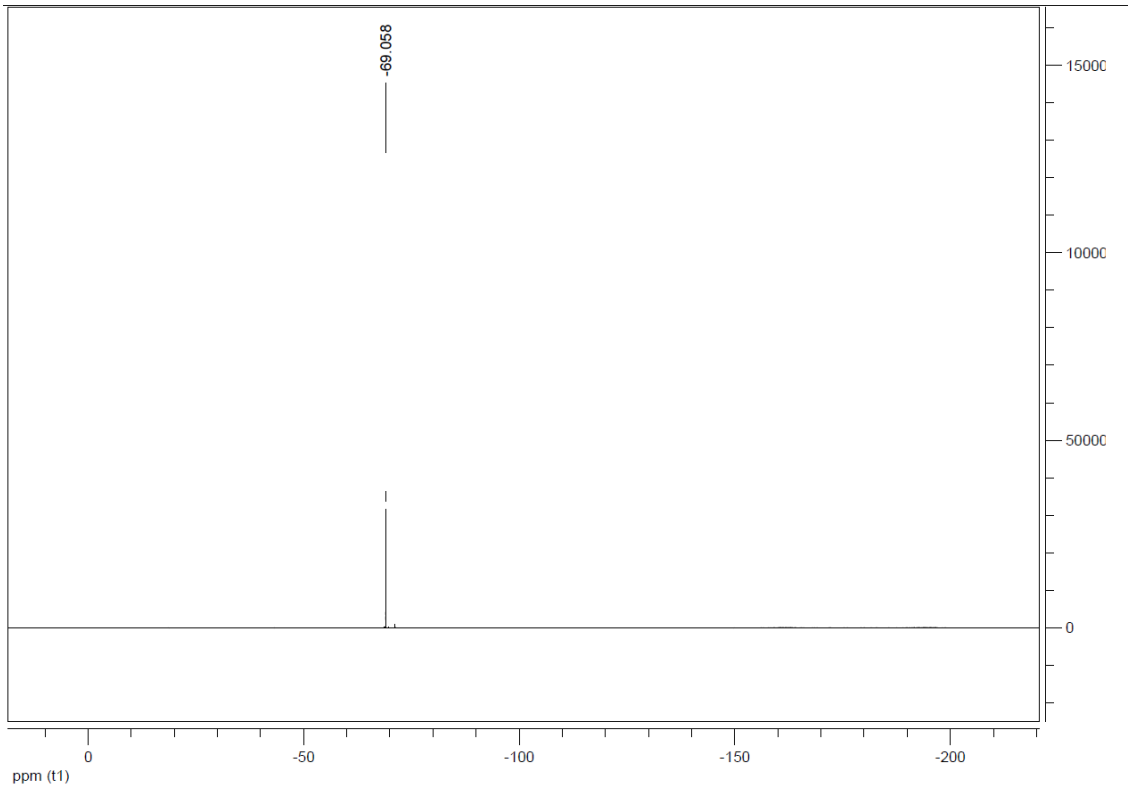


3-(6-(Trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4a**)

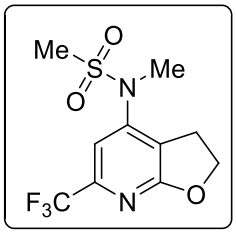


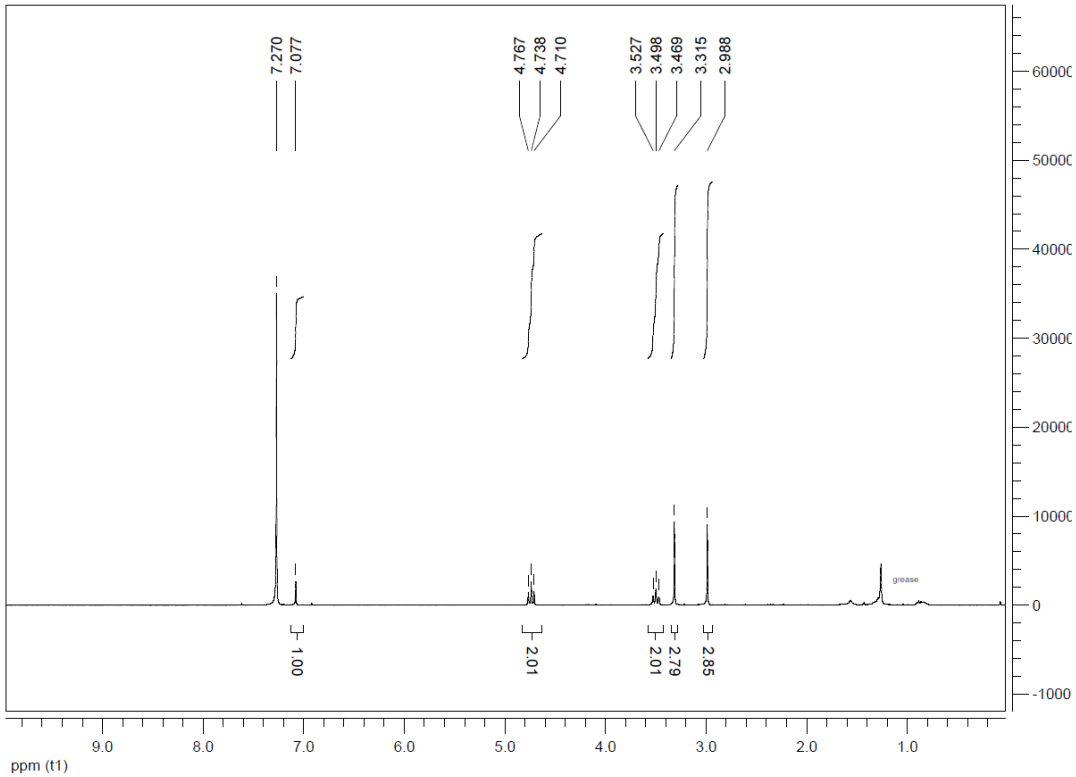


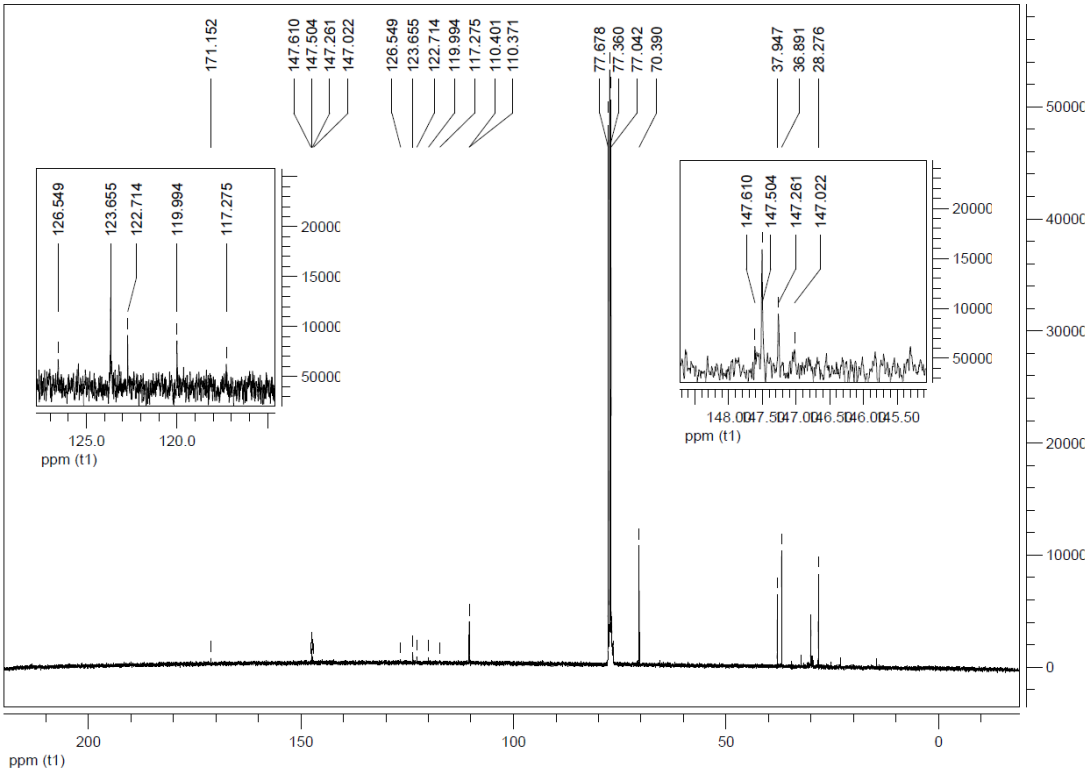

171.023
154.214
147.355
147.005
146.656
146.307
143.730
125.577
122.857
120.137
117.415
115.262
106.120
106.086
77.678
77.360
77.043
70.033
62.722
46.069
29.209
ppm (t1)

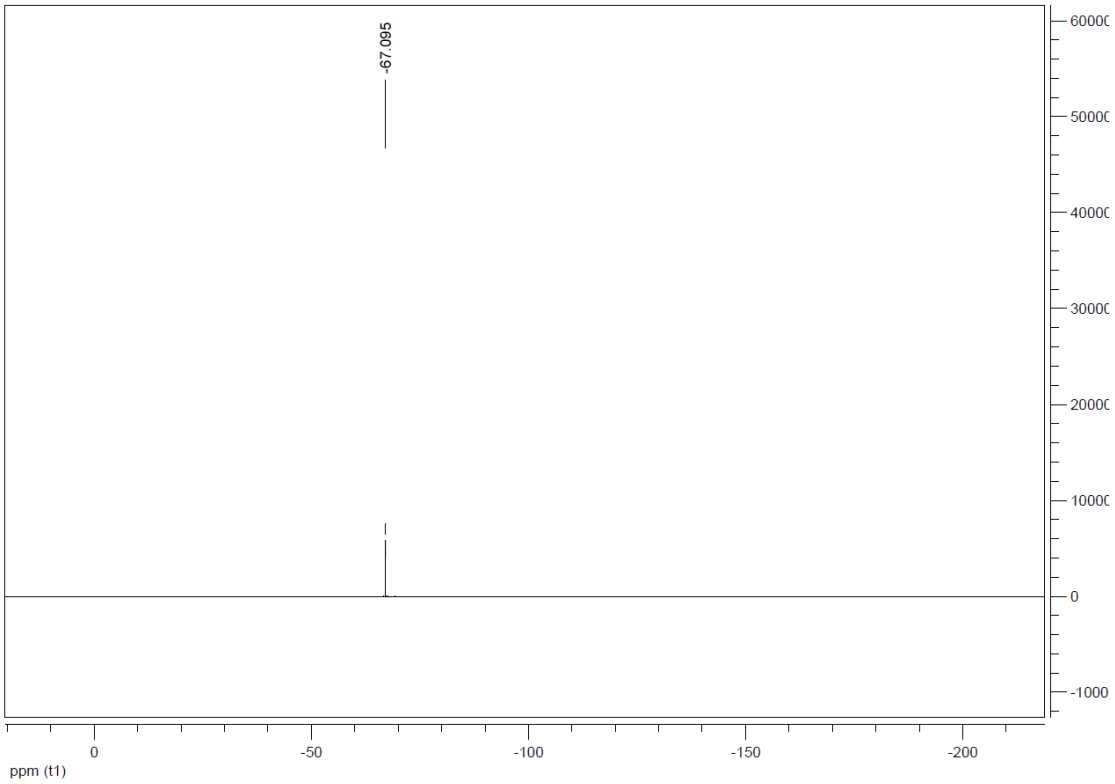

-69.058
ppm (t1)

N-Methyl-*N*-(6-(trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)methanesulfonamide (**4b**)

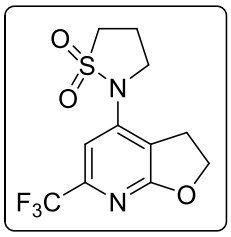


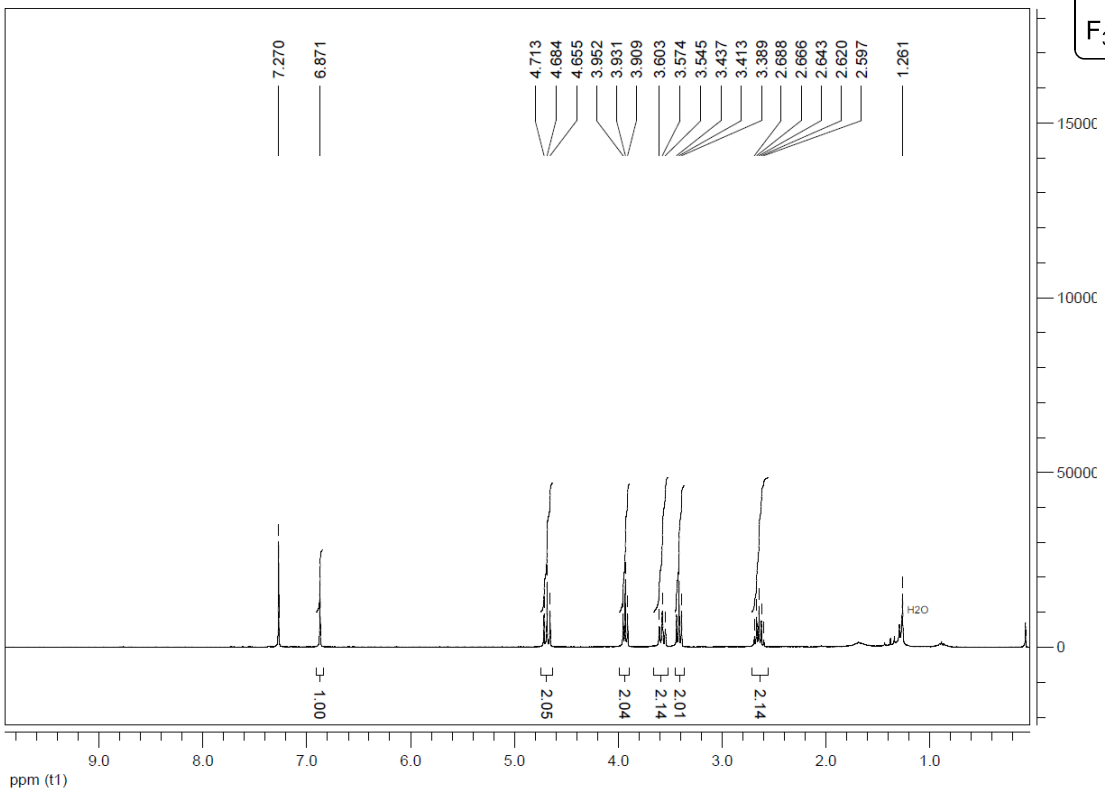


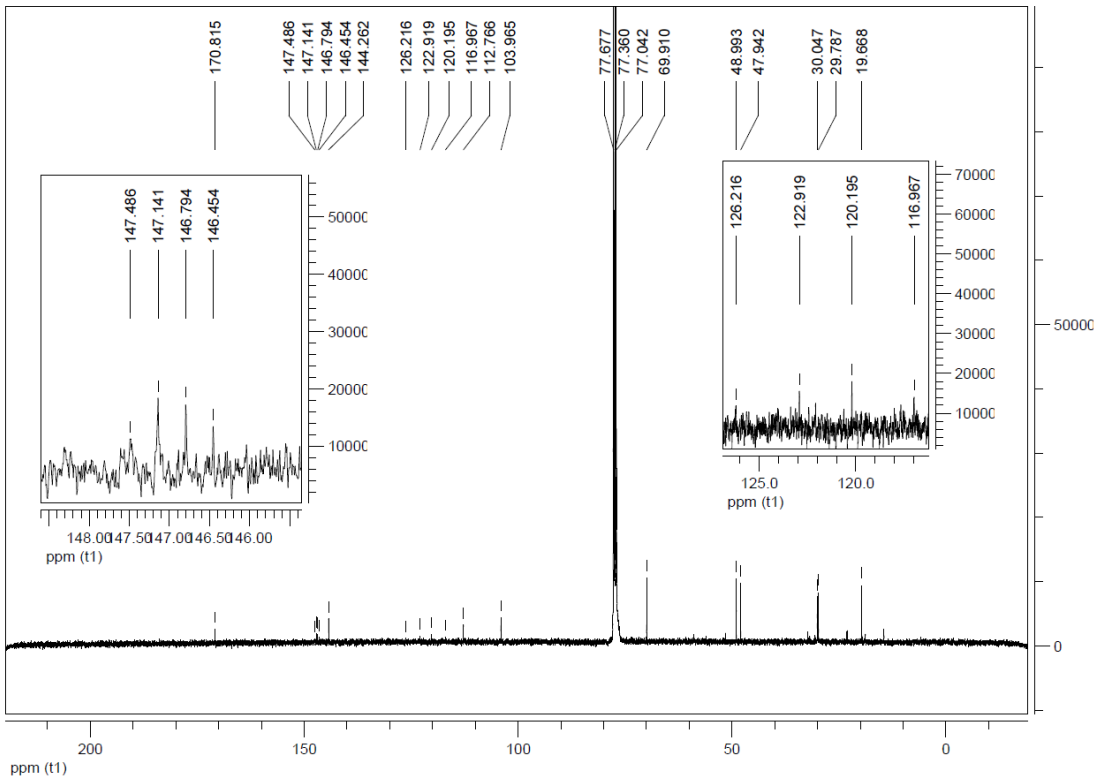




2-(4-{[4-(Trifluoromethyl)pyrimidin-2-yl]oxy}but-1-yn-1-yl)-2-thiazolidine-1,1-dione (**4c**)






170.815
147.486
147.141
146.794
146.454
144.262
126.216
122.919
120.195
116.967
112.766
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77.042
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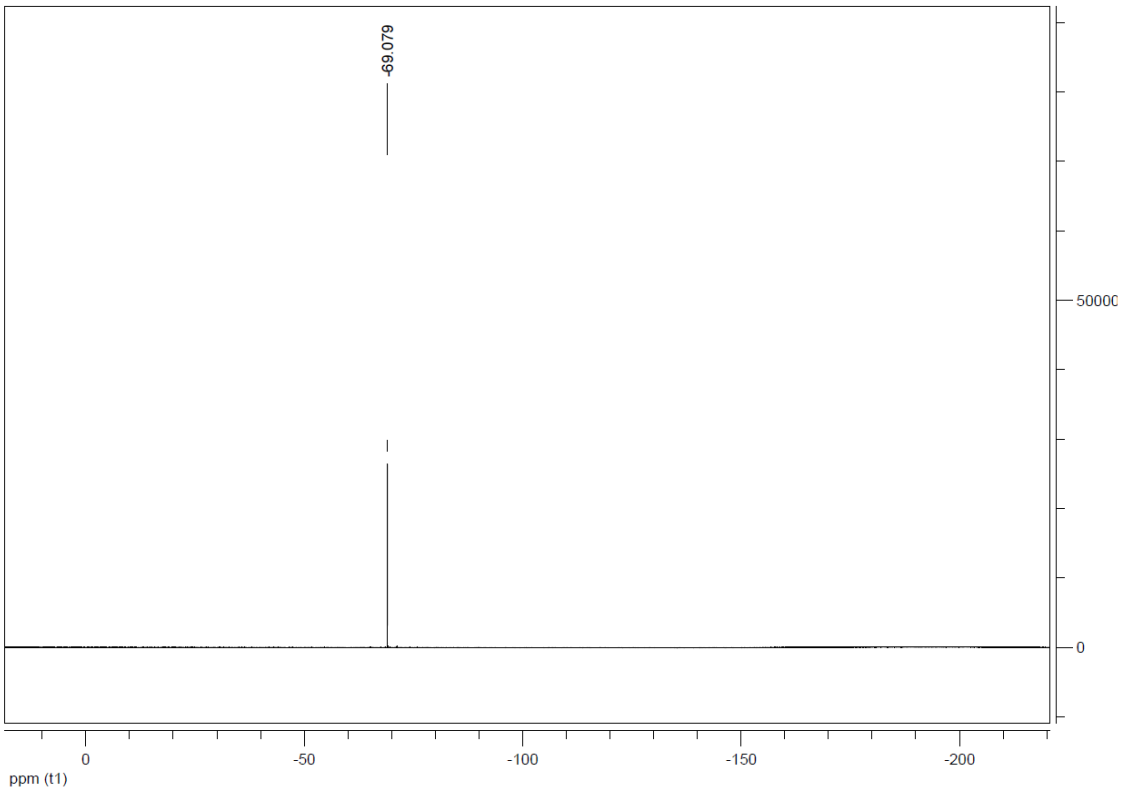
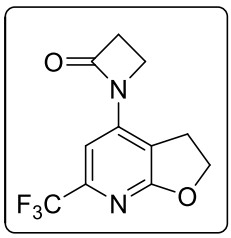
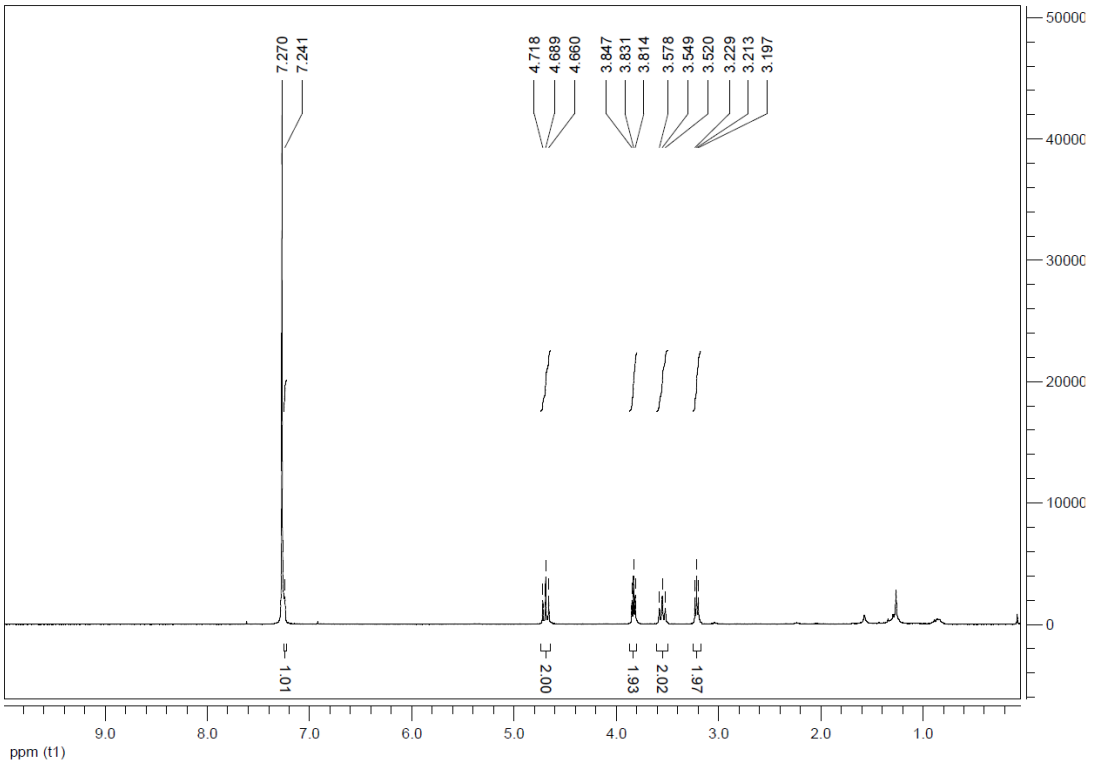
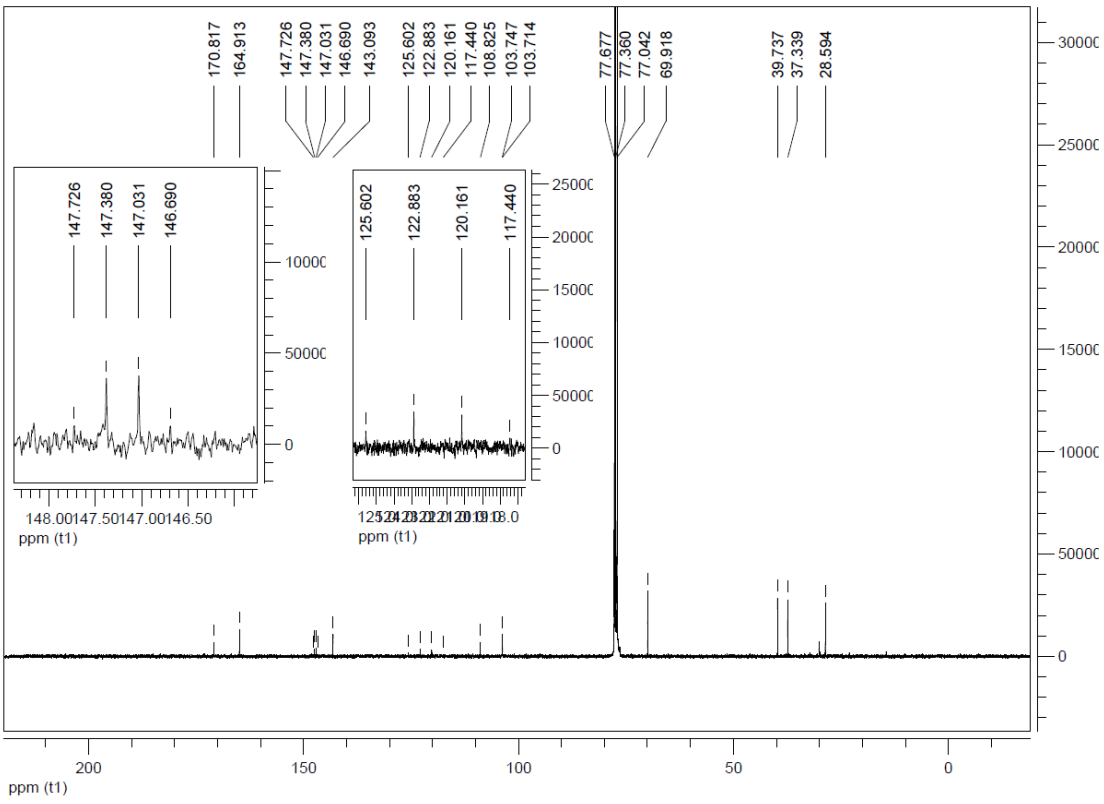
47.942
30.047
29.787
19.668
ppm (t1)

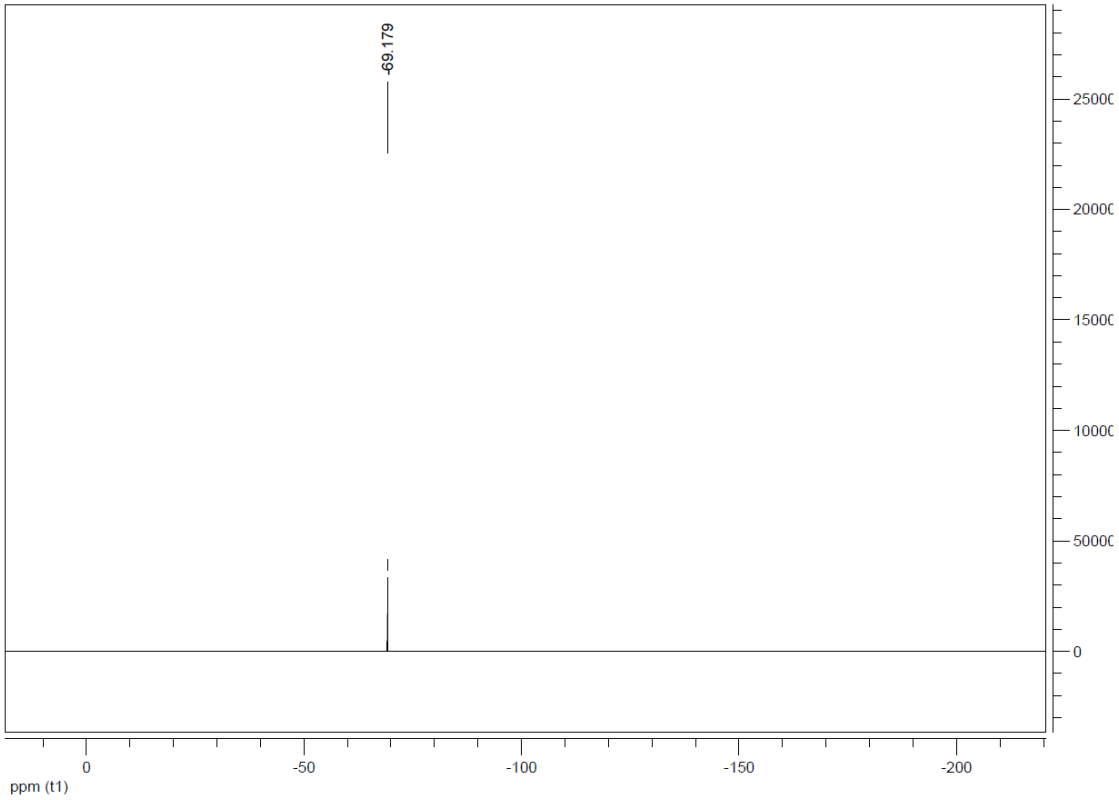

-69.079
ppm (t1)

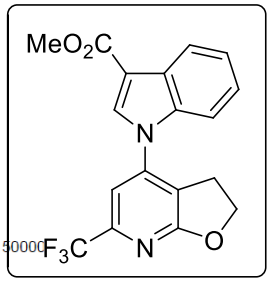
1-(6-(Trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)azetidin-2-one (**4d**)



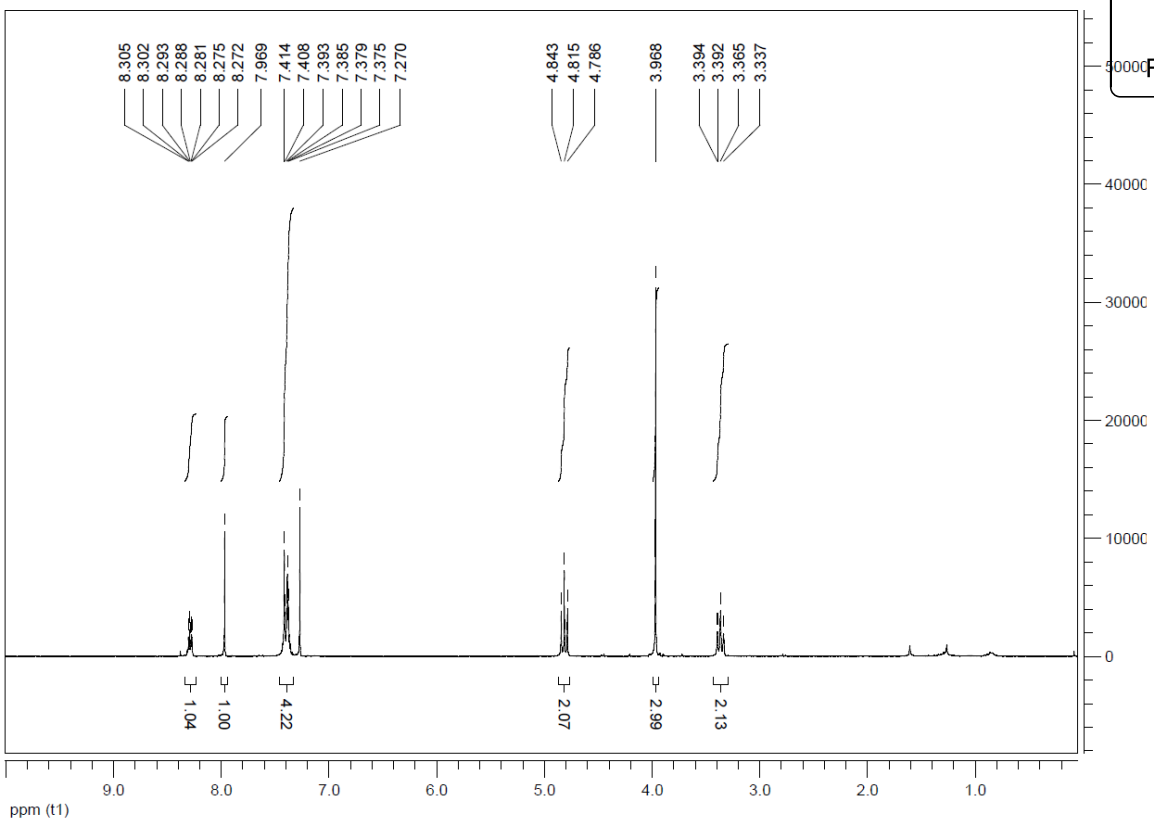


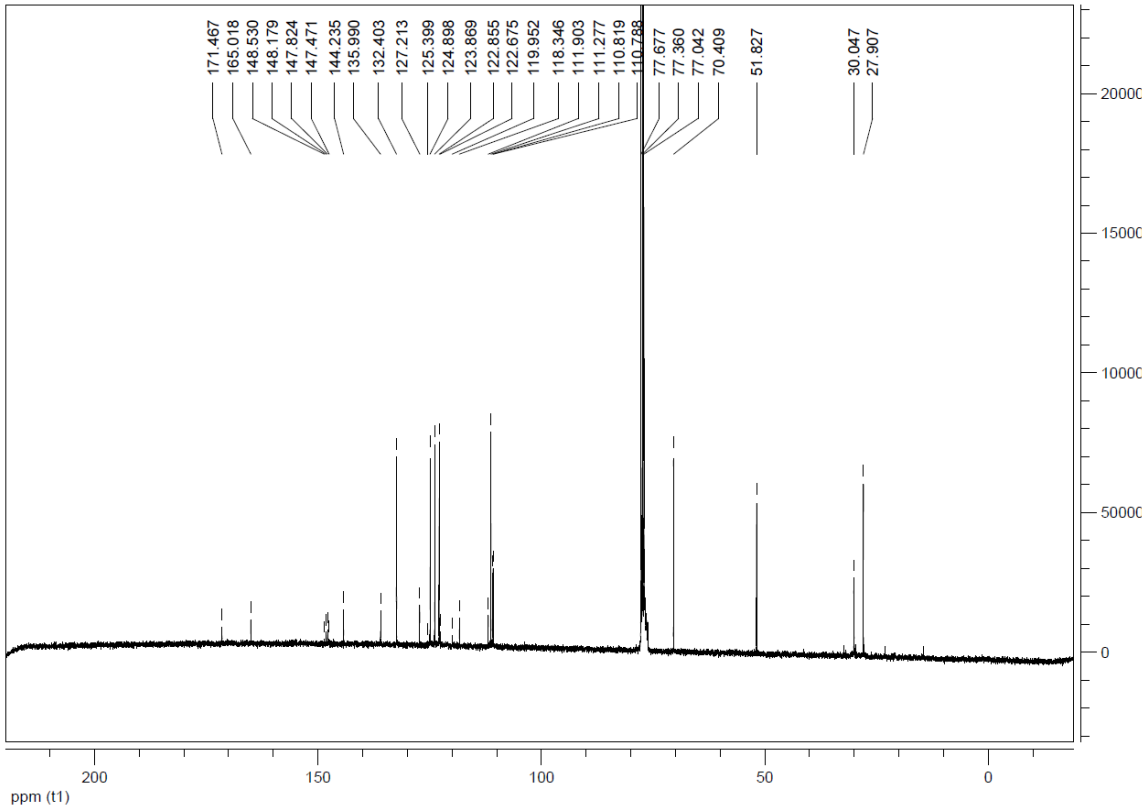


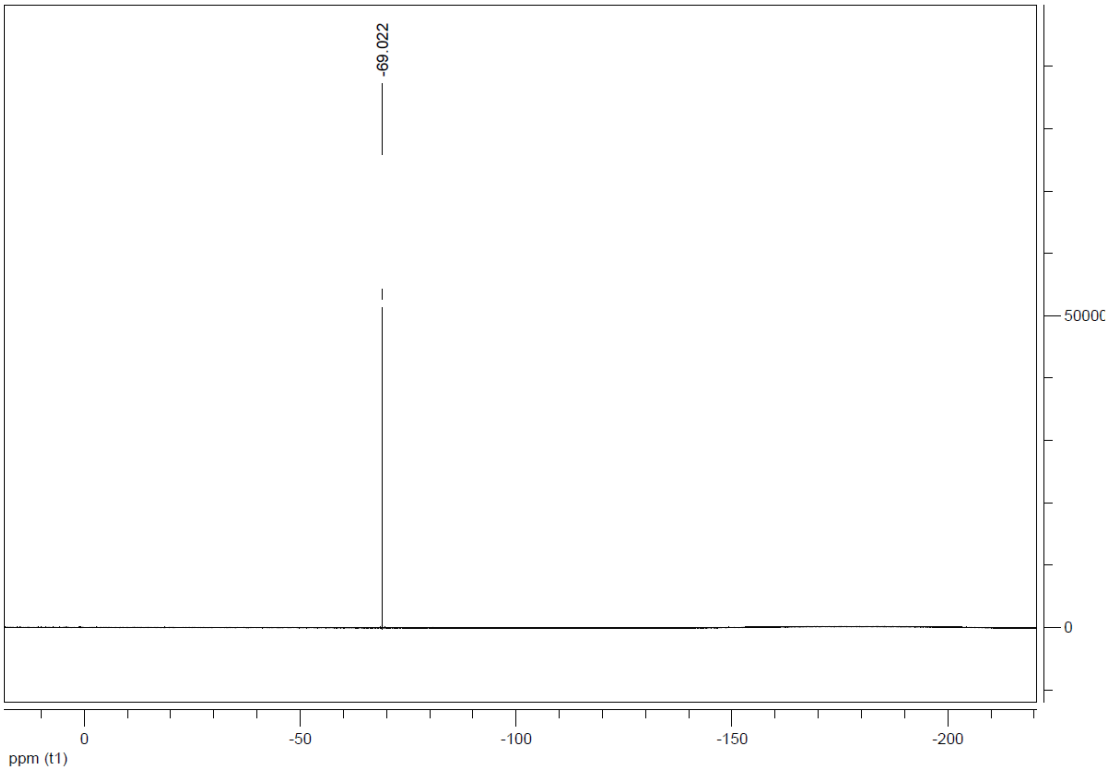




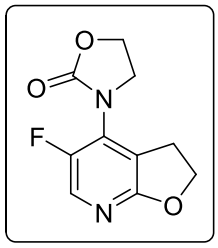
Methyl 1-(6-(trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)-1H-indole-3-carboxylate (**4e**)

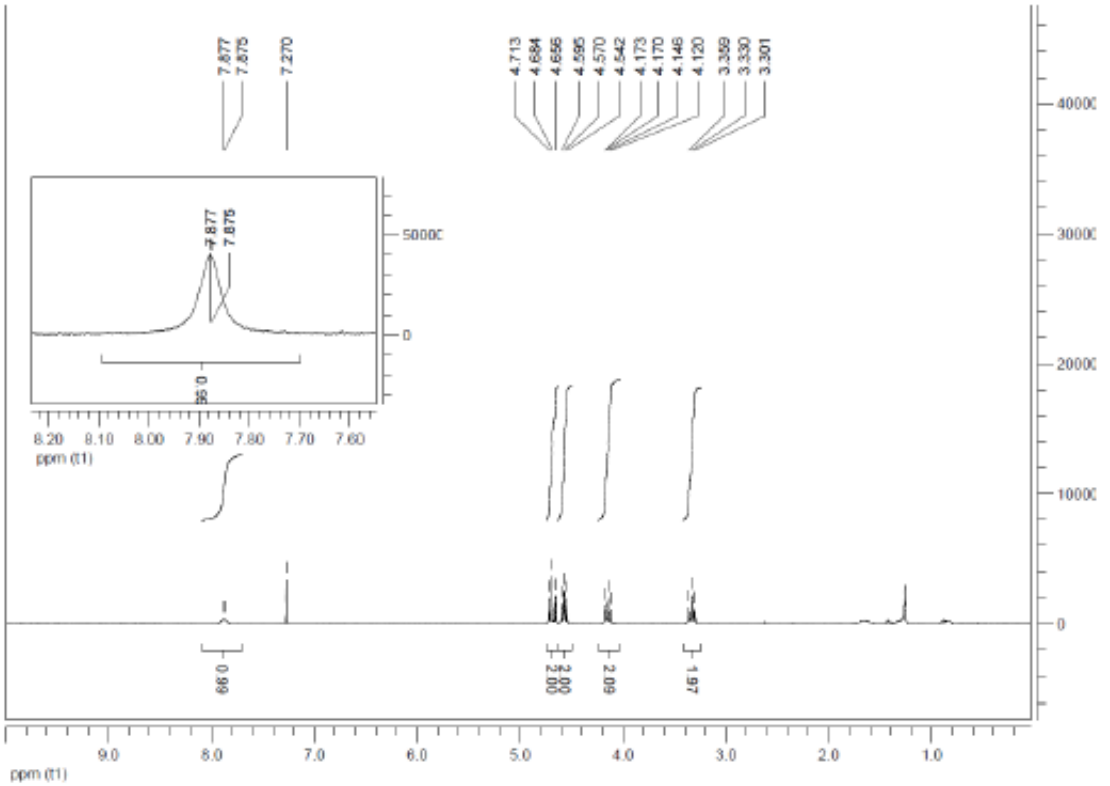


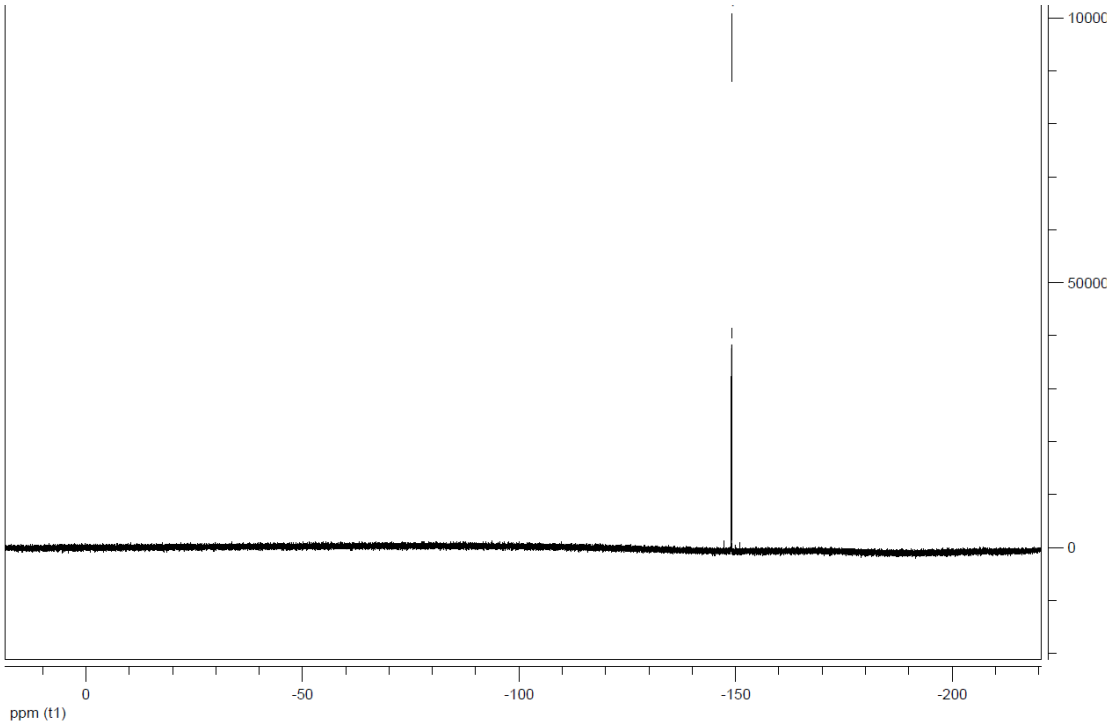

171.467
165.018
148.530
148.179
147.824
147.471
144.235
135.990
132.403
127.213
125.399
124.898
123.869
122.855
122.675
119.952
118.346
111.903
111.277
110.819
110.788
77.677
77.360
77.042
70.409
51.827
30.047
27.907
20000
15000
10000
50000
0
200
150
100
50
0
ppm (t1)


-69.022
50000
0
0
-50
-100
-150
-200
ppm (t1)

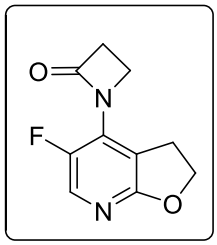
3-(5-Fluoro-2,3-dihydrofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4f**)

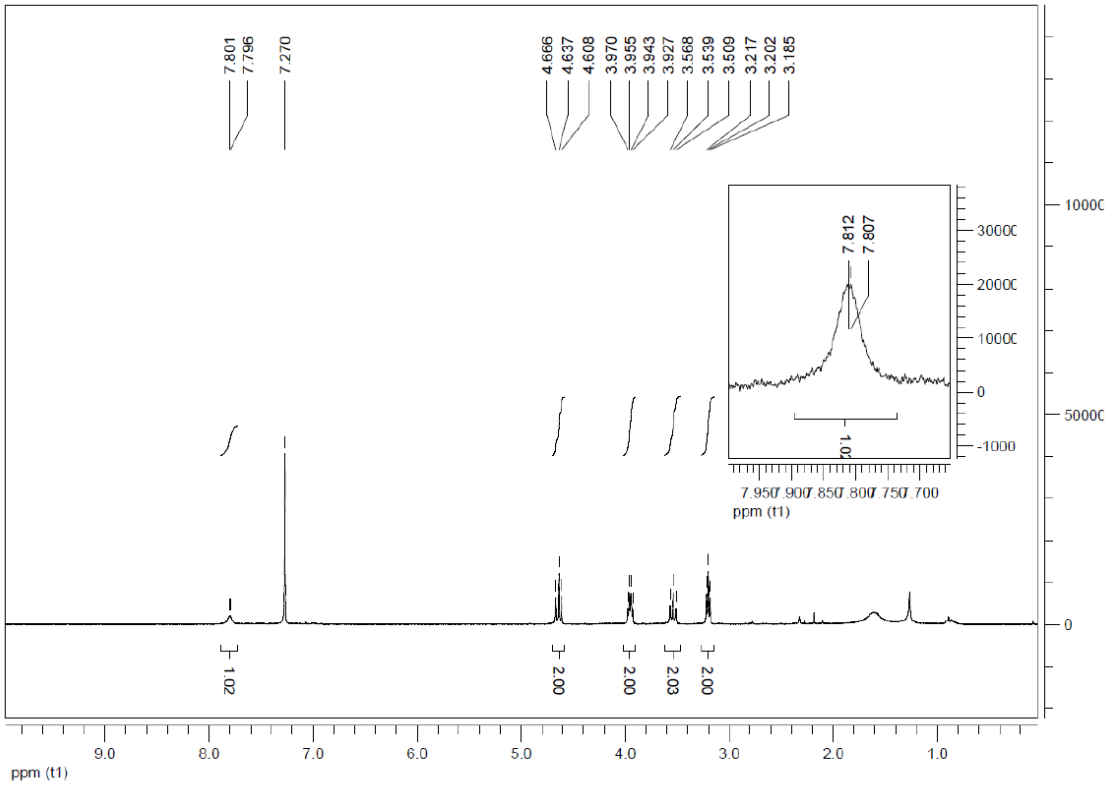


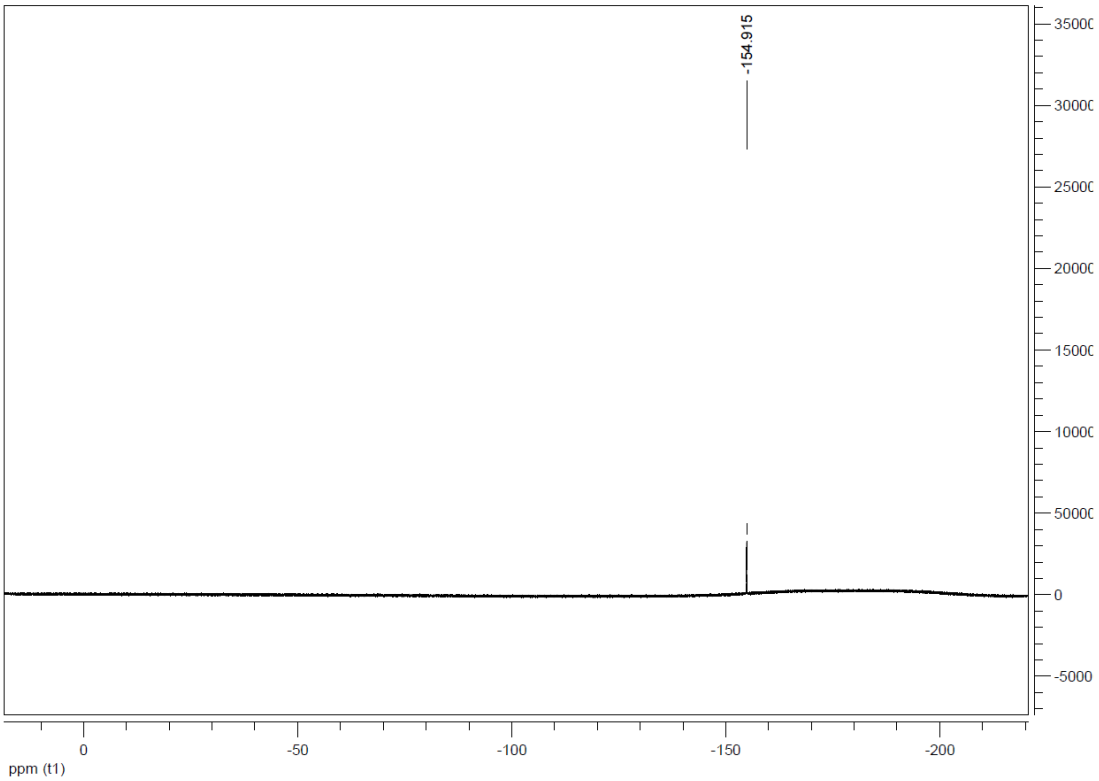




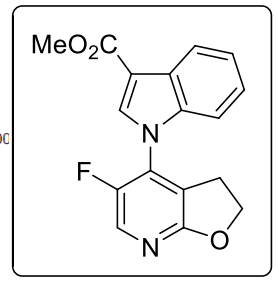
1-(5-Fluoro-2,3-dihydrofuro[2,3-b]pyridin-4-yl)azetidin-2-one (**4g**)

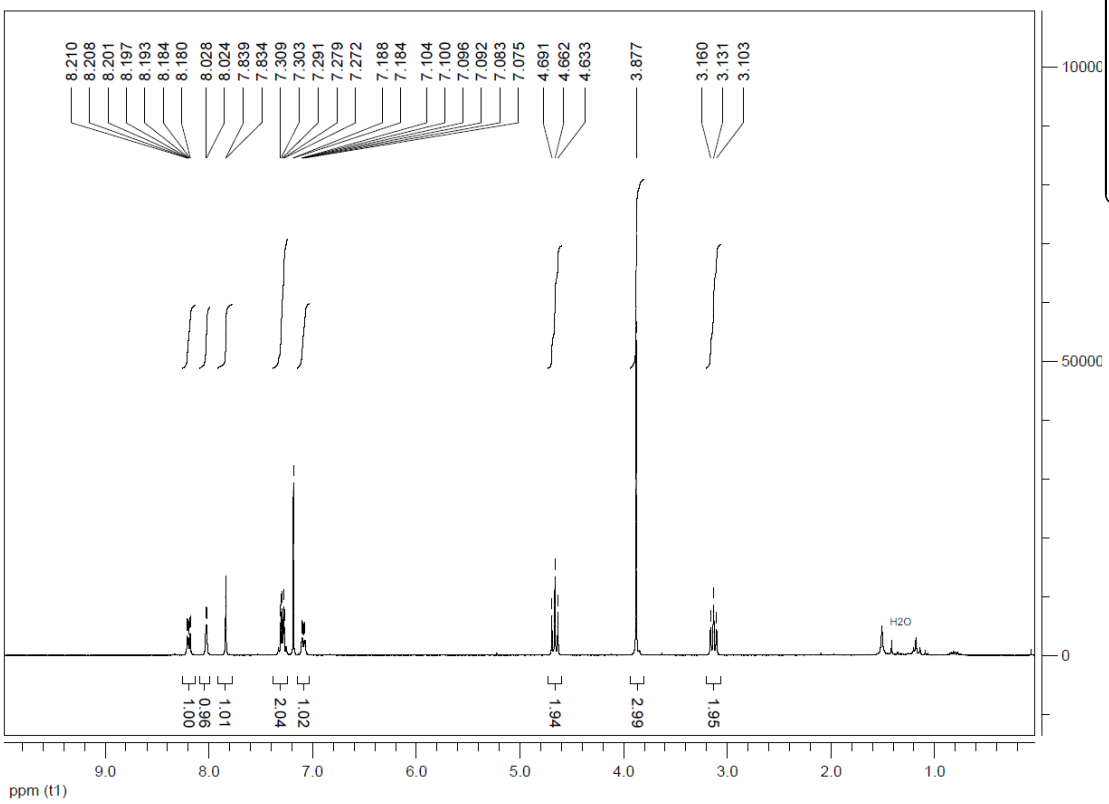


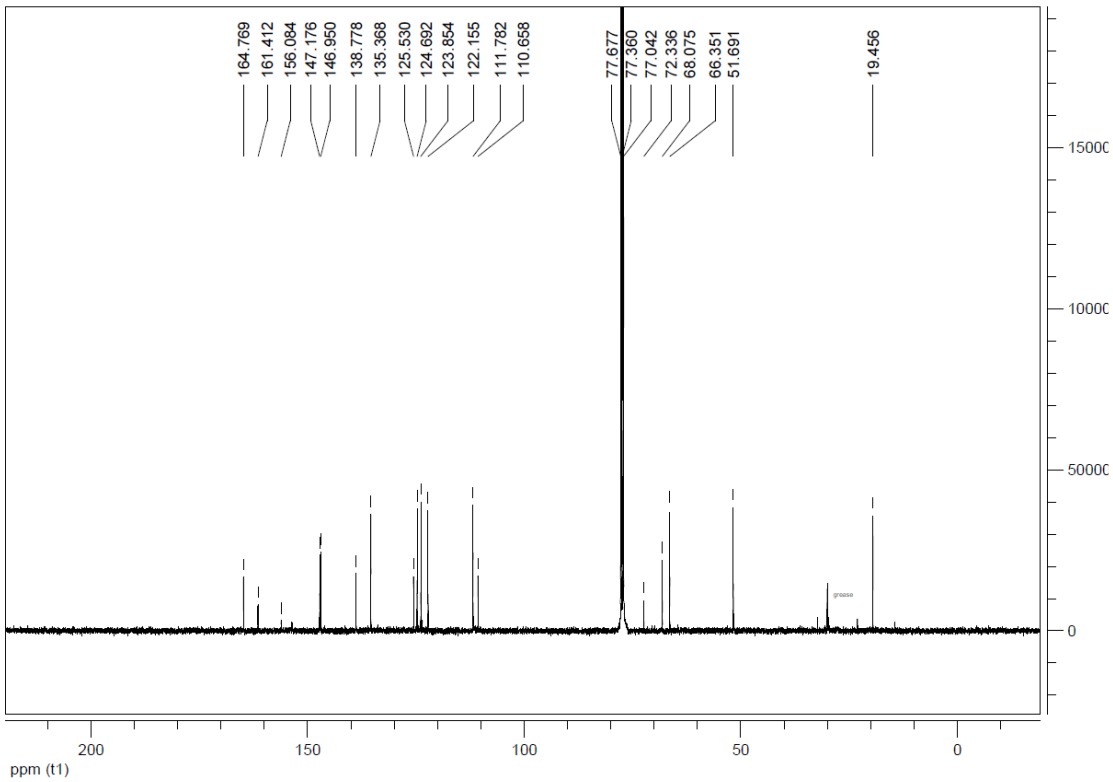


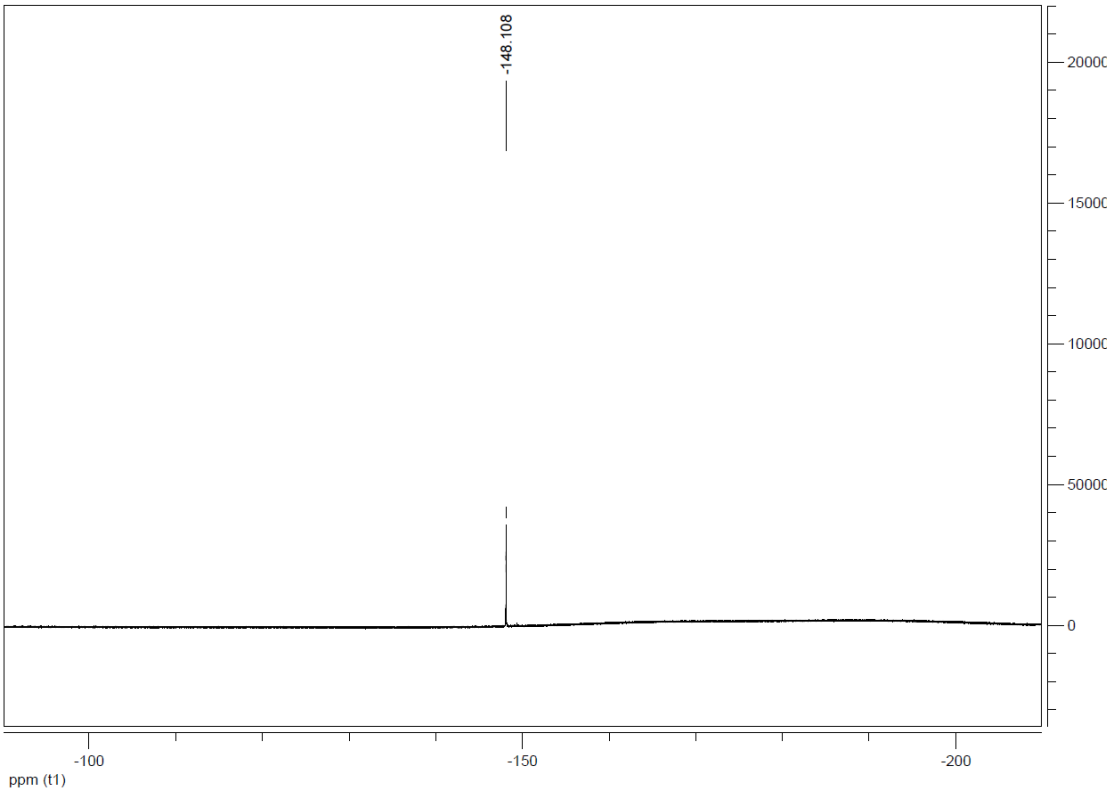


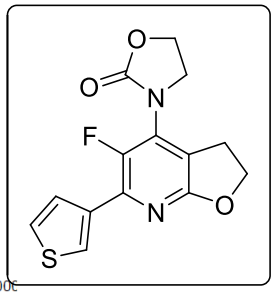
Methyl 1-(5-fluoro-2,3-dihydrofuro[2,3-b]pyridin-4-yl)-1H-indole-3-carboxylate (**4h**)



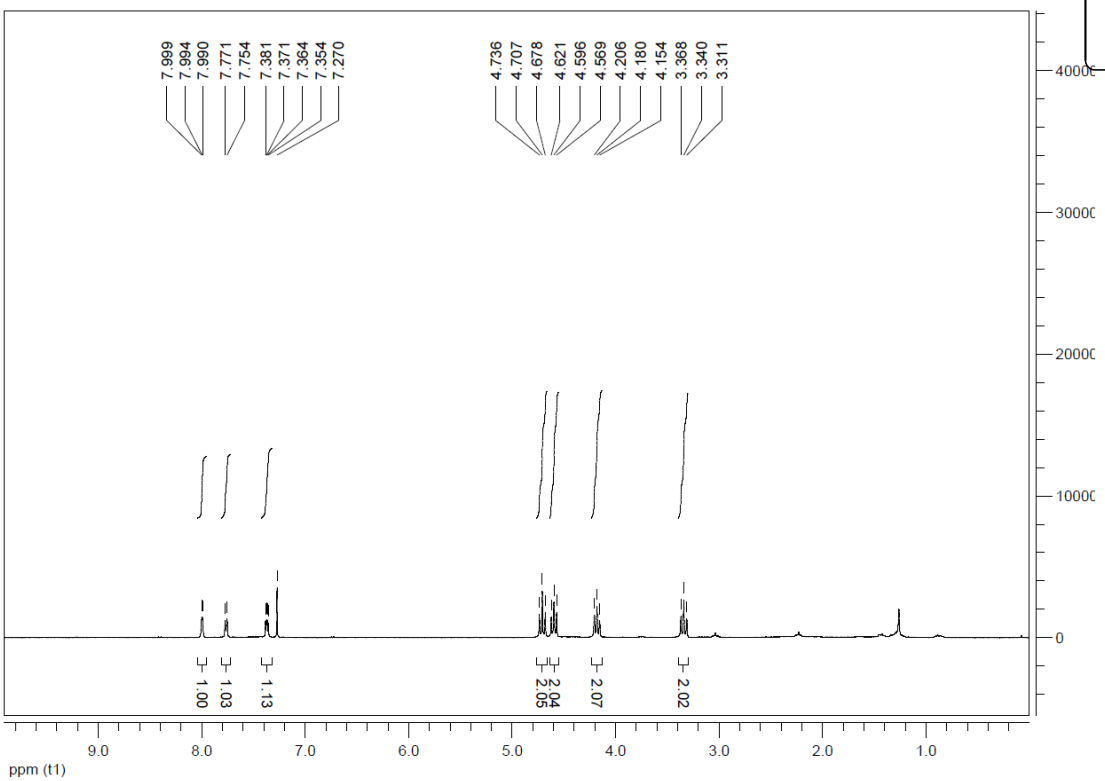


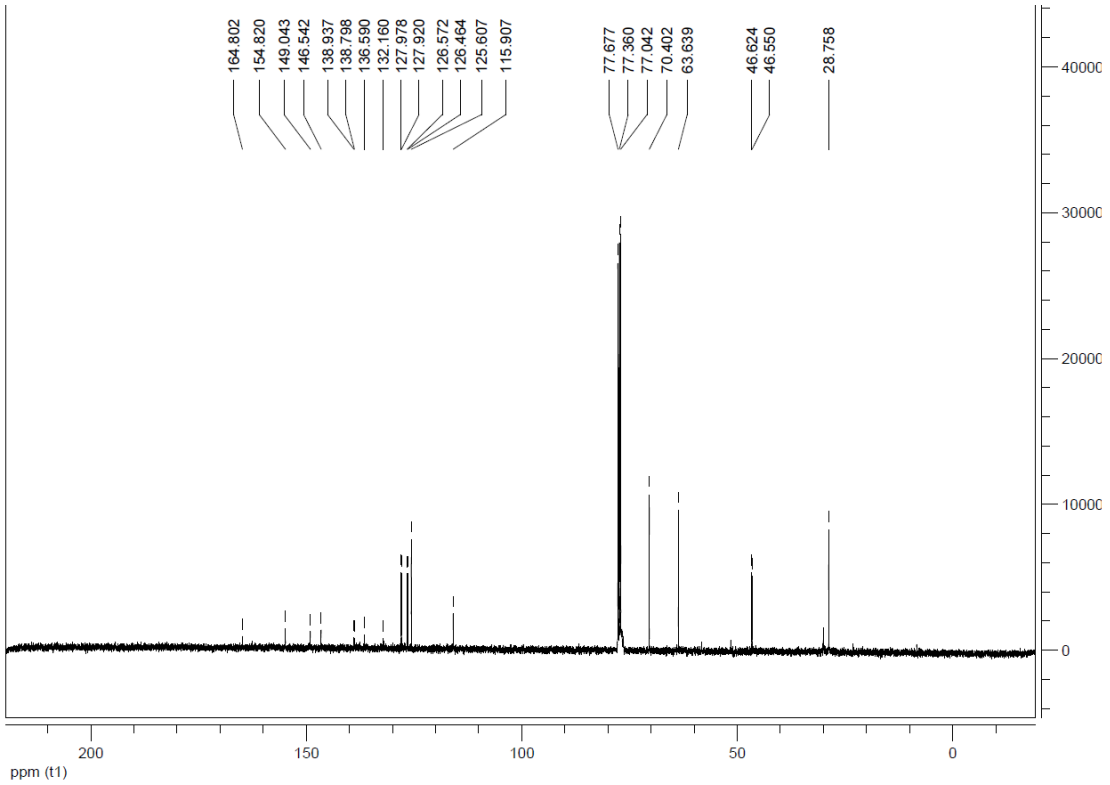


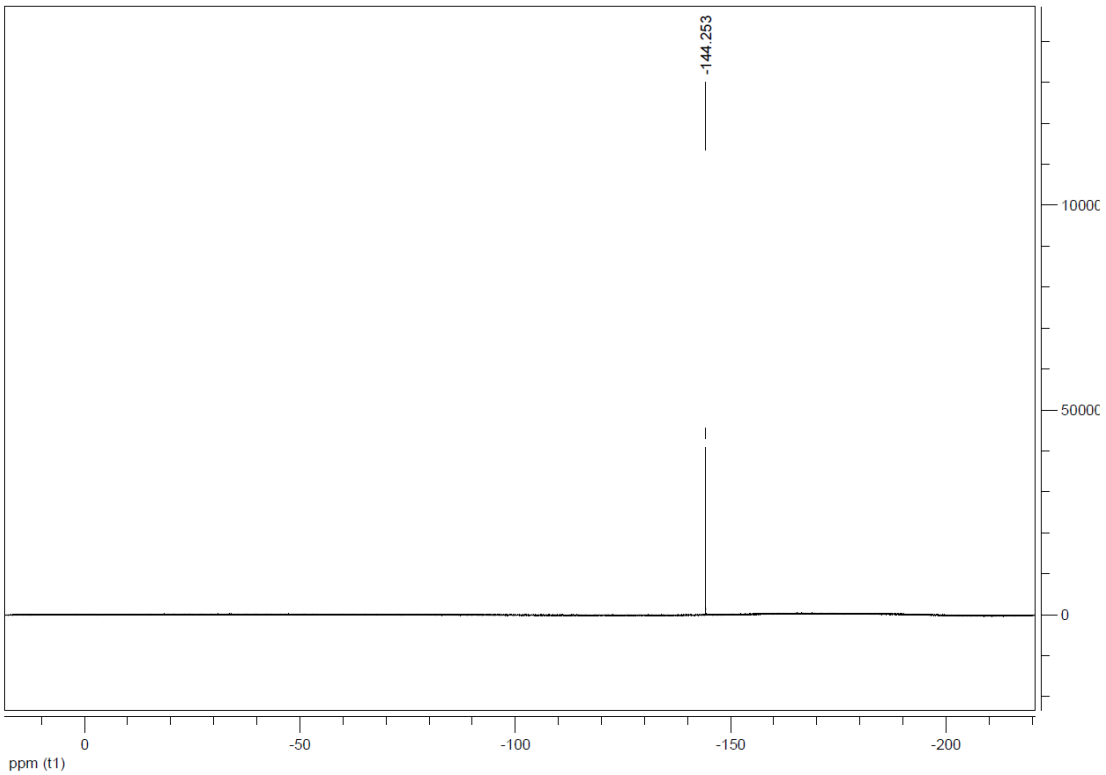




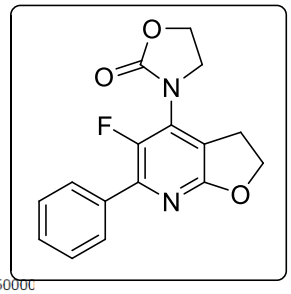
3-(5-Fluoro-6-(thiophen-3-yl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4k**)

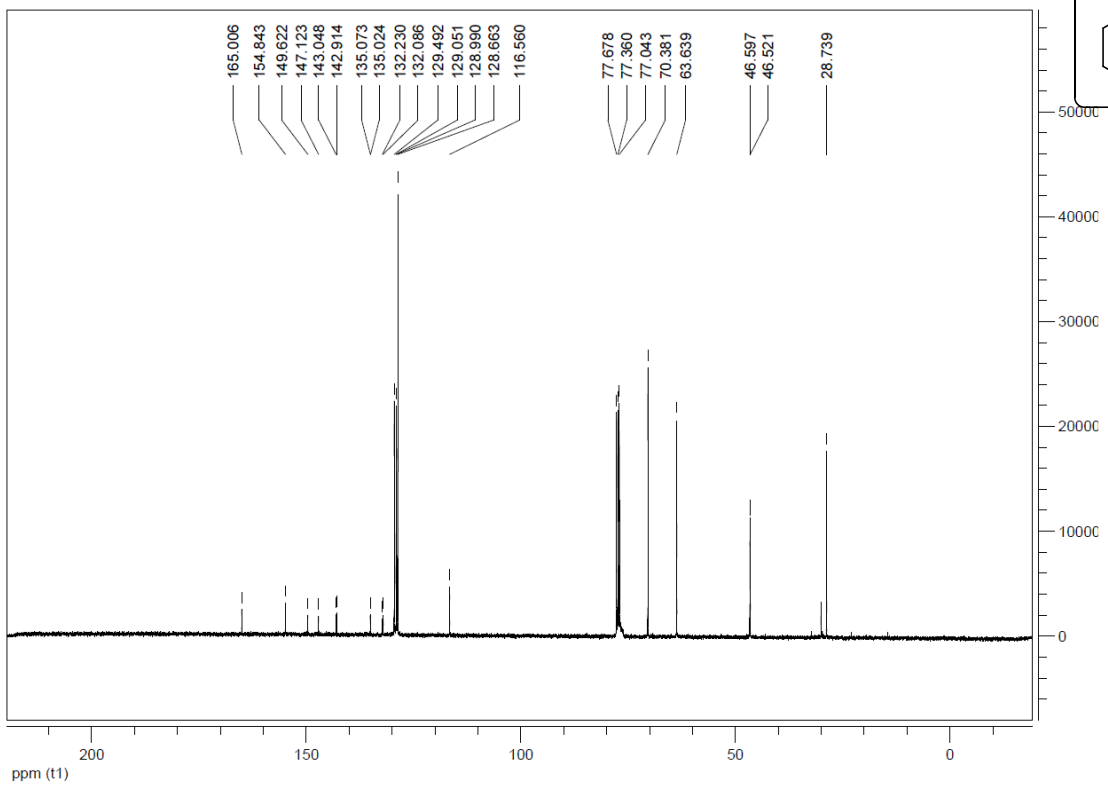


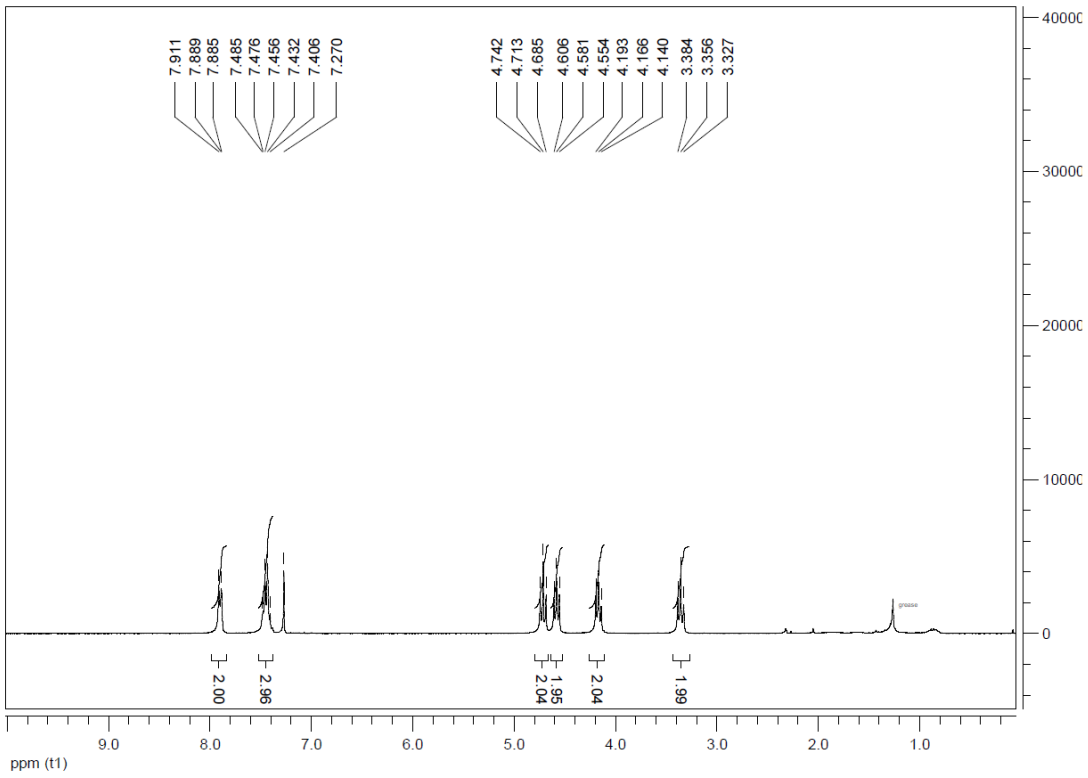

164.802
154.820
149.043
146.542
138.937
138.798
136.590
132.160
127.978
127.920
126.572
126.464
125.607
115.907
77.677
77.360
77.042
70.402
63.639
46.624
46.550
28.758
40000
30000
20000
10000
0
200
150
100
50
0
ppm (t1)

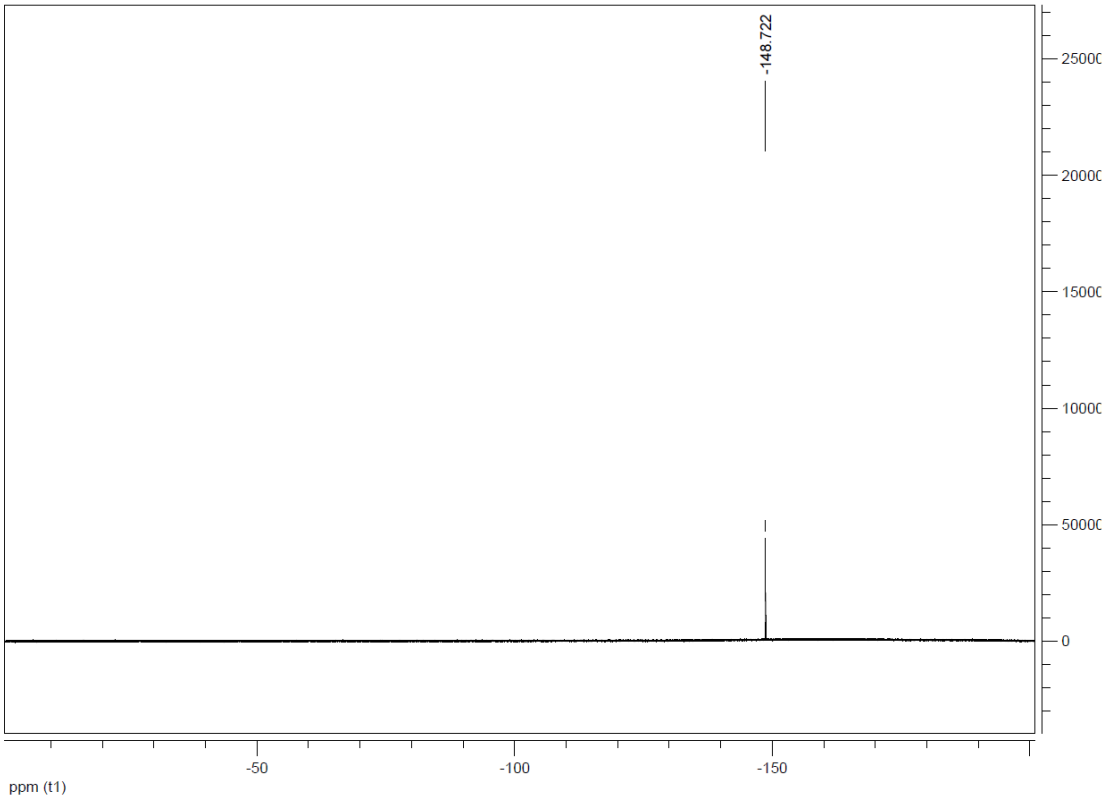

-144.253
10000
5000
0
0
-50
-100
-150
-200
ppm (t1)

3-(5-fluoro-6-phenyl-2,3-dihydrofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4l**)

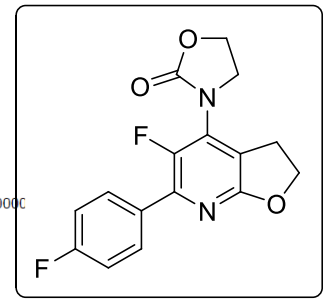


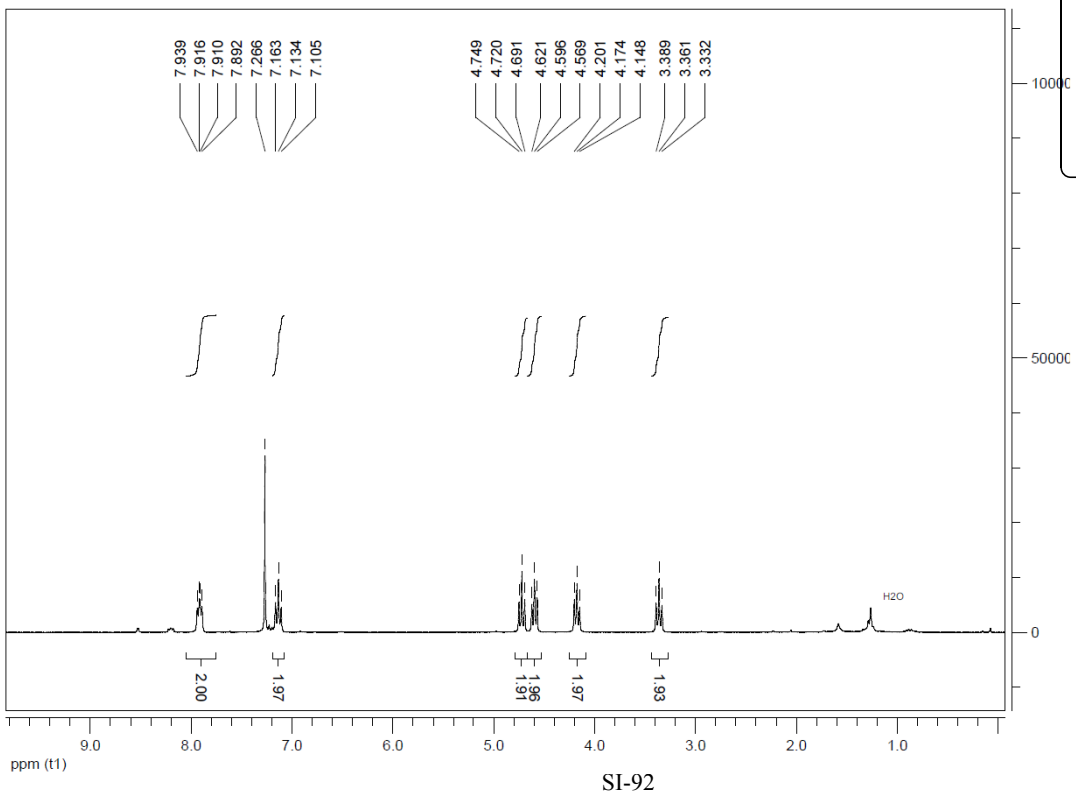


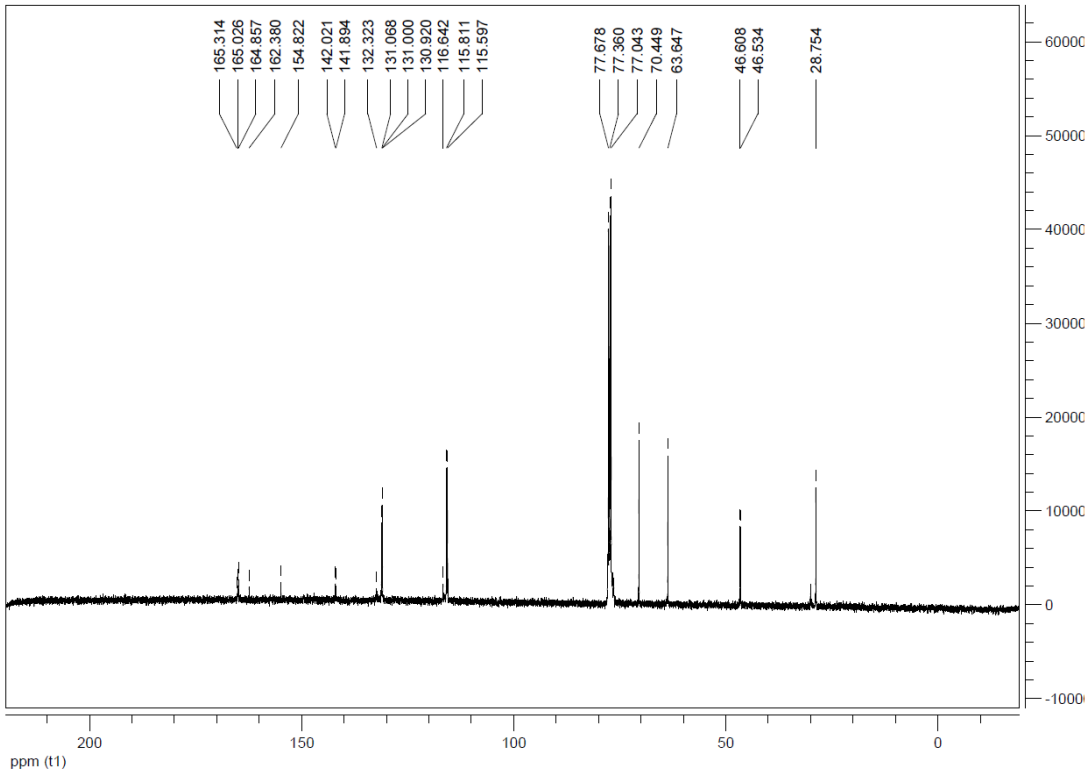


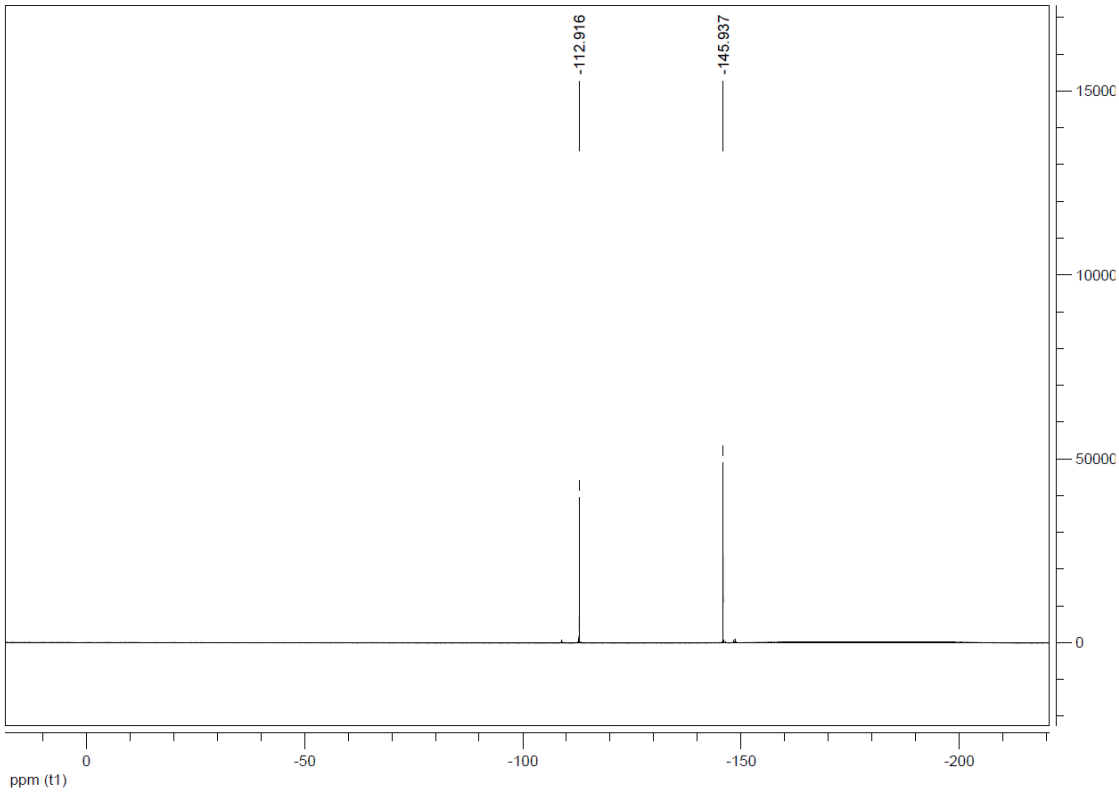


3-(5-Fluoro-6-(4-fluorophenyl)-2,3-dihydrofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4m**)

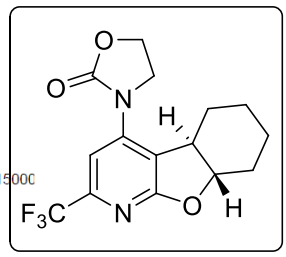


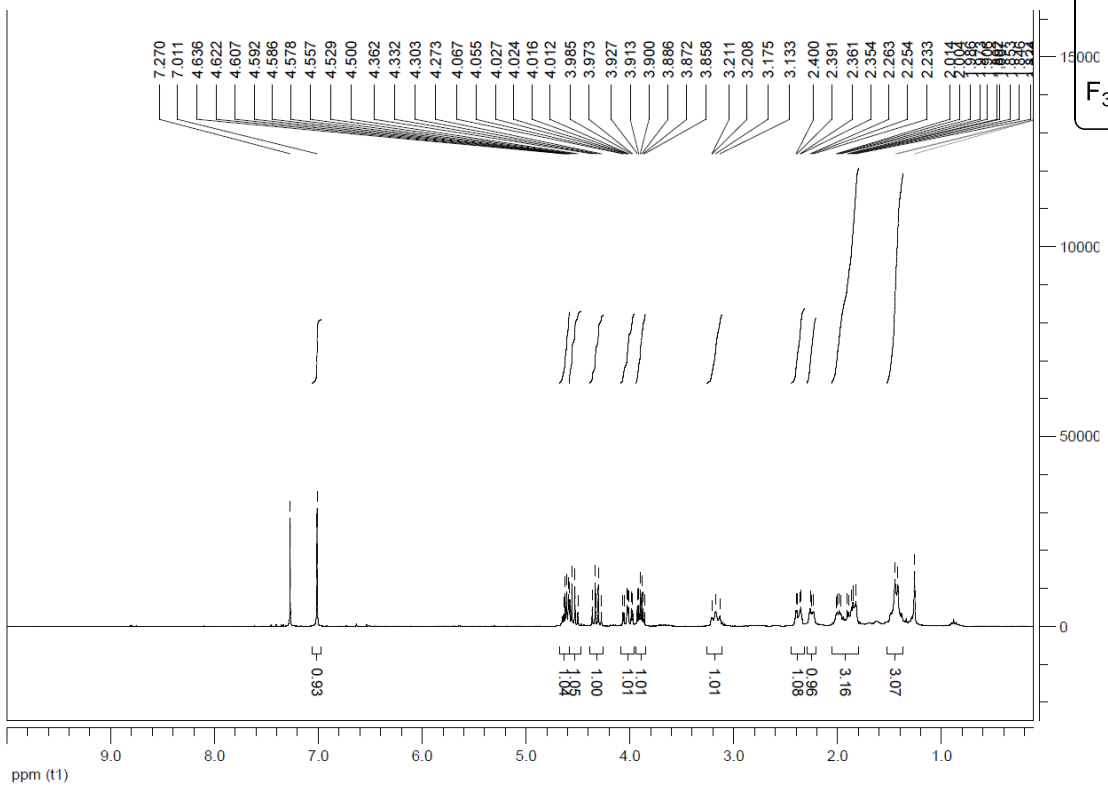


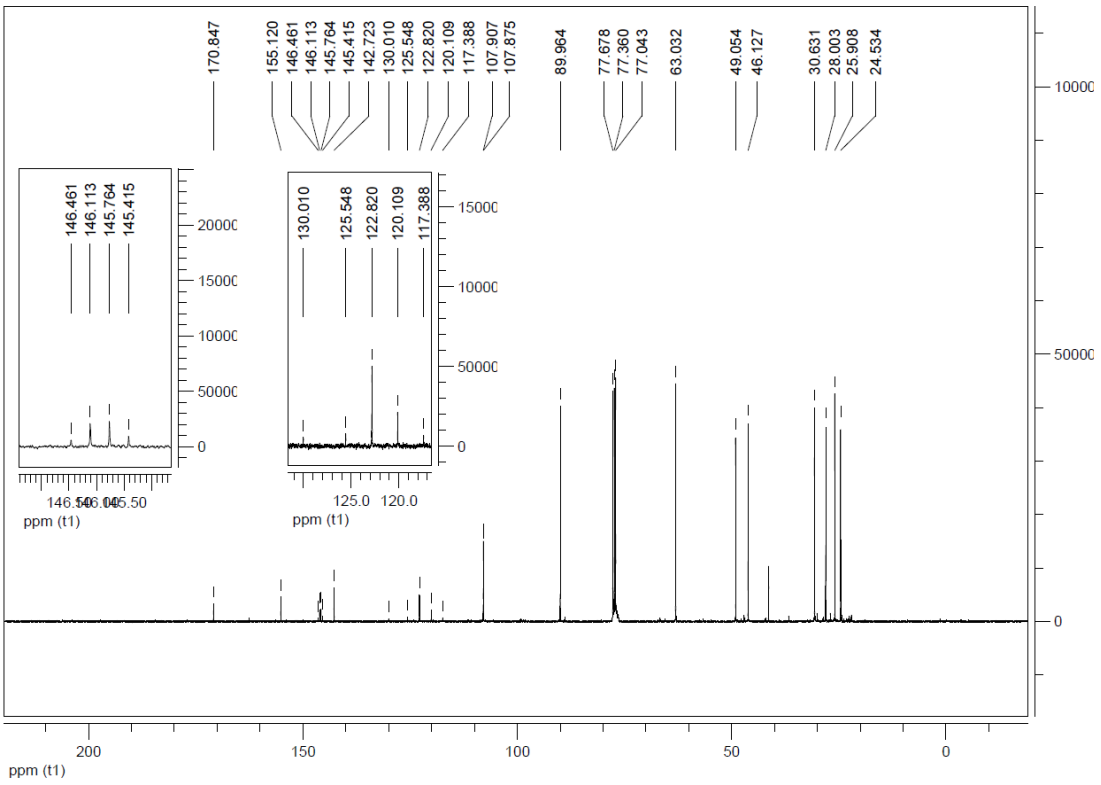

165.314
165.026
164.857
162.380
154.822
142.021
141.894
132.323
131.068
131.000
130.920
116.642
115.811
115.597
77.678
77.360
77.043
70.449
63.647
46.608
46.534
28.754
60000
50000
40000
30000
20000
10000
0
-1000
200
150
100
50
0
ppm (t1)

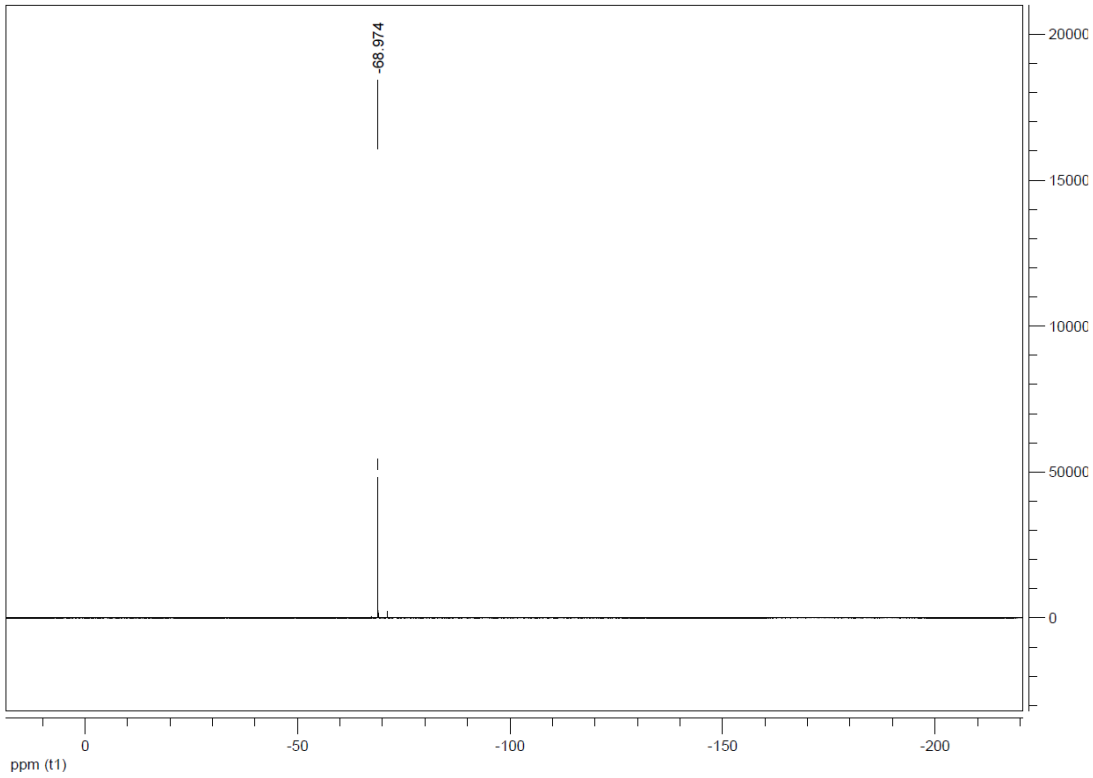

-112.916
-145.937
15000
10000
50000
0
0
-50
-100
-150
-200
ppm (t1)

3-(2-(Trifluoromethyl)-4b,5,6,7,8,8a-hexahydrobenzofuro[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4p**)

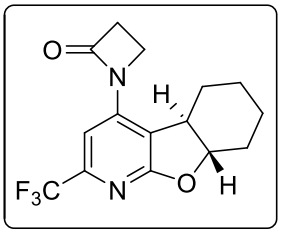


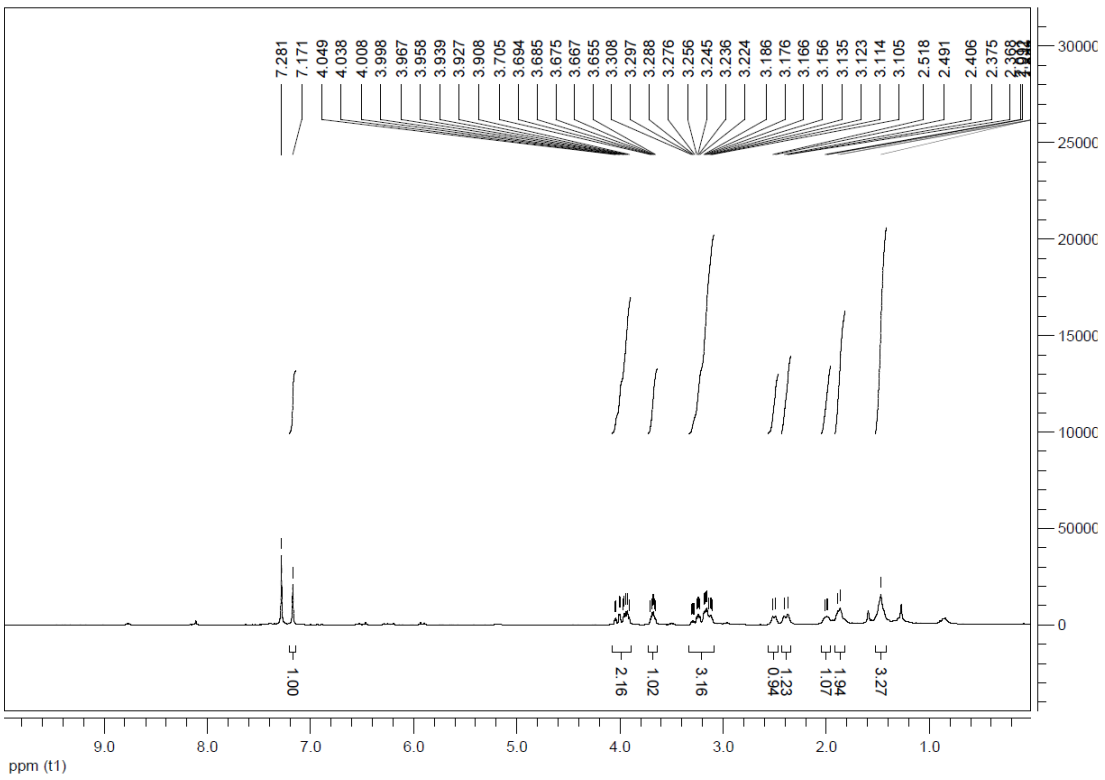


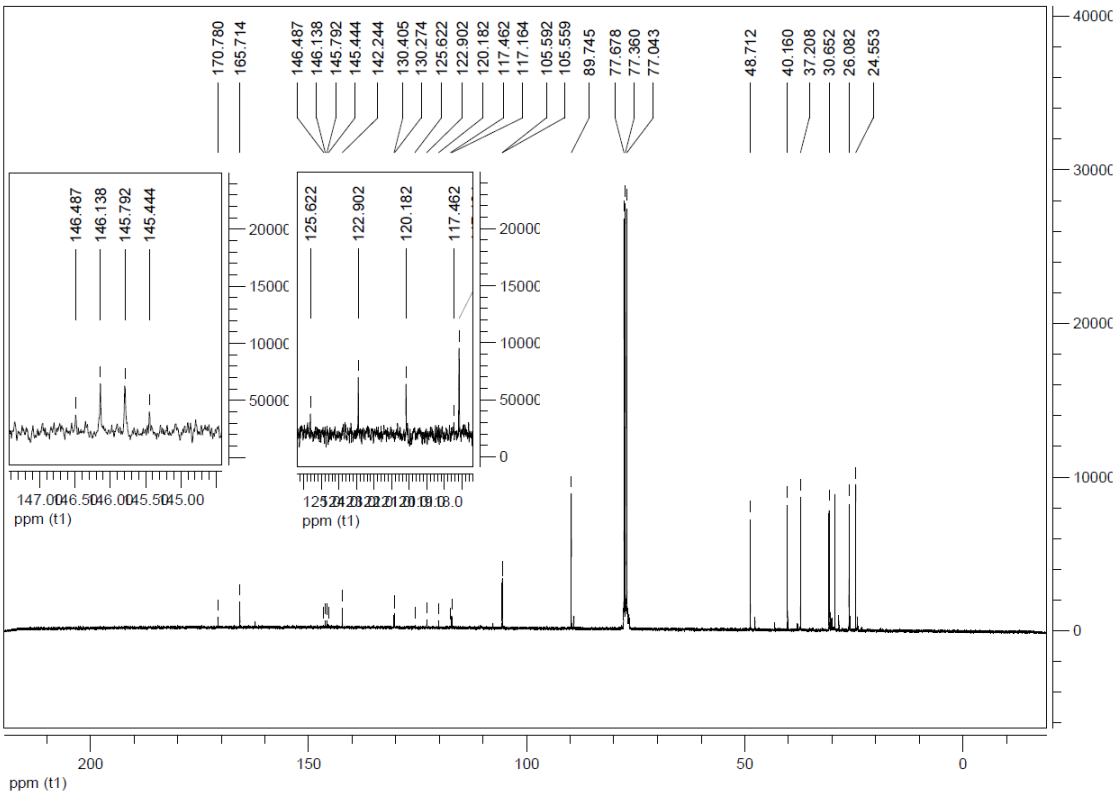


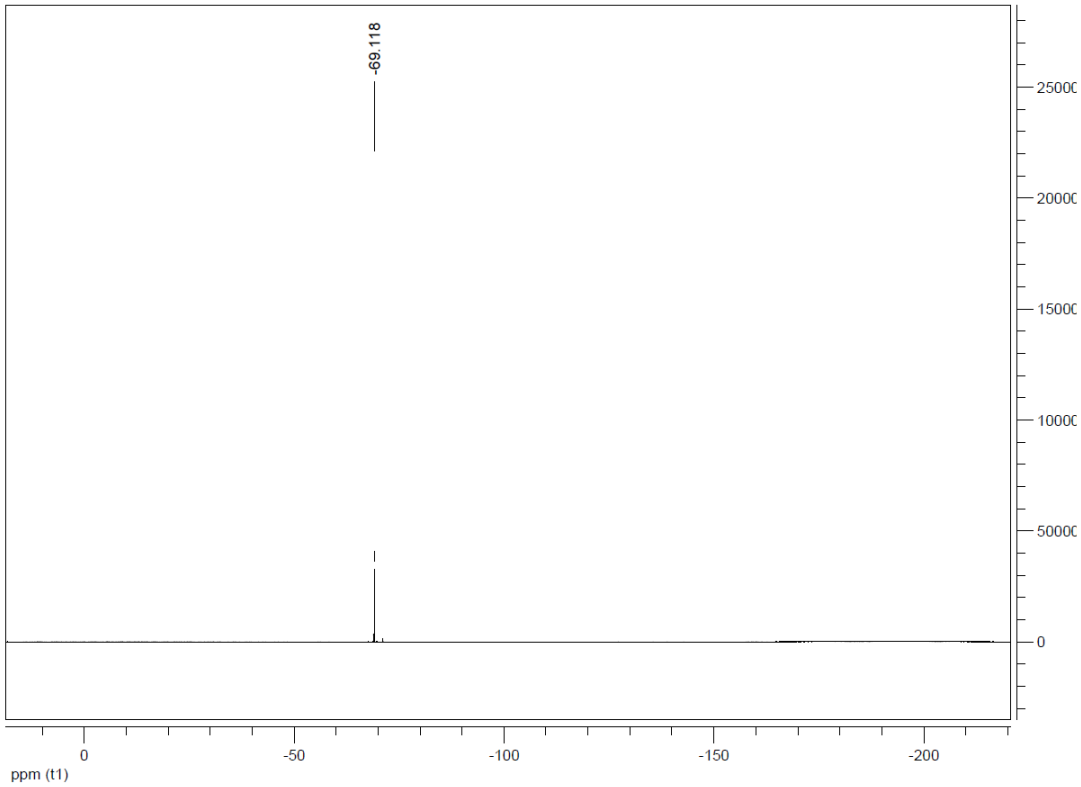


1-(2-(Trifluoromethyl)-4b,5,6,7,8,8a-hexahydrobenzofuro[2,3-b]pyridin-4-yl)azetidin-2-one (**4q**)

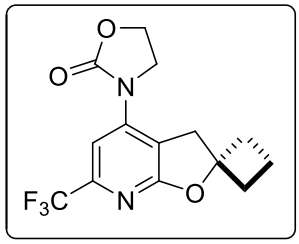


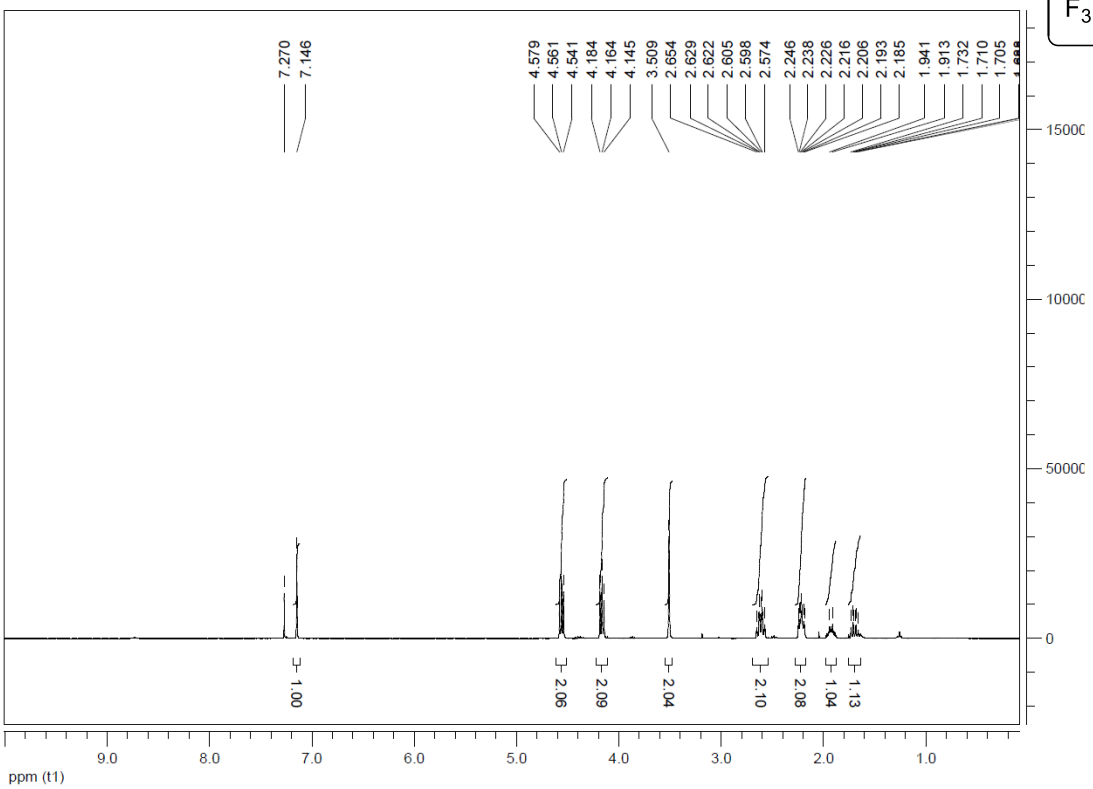


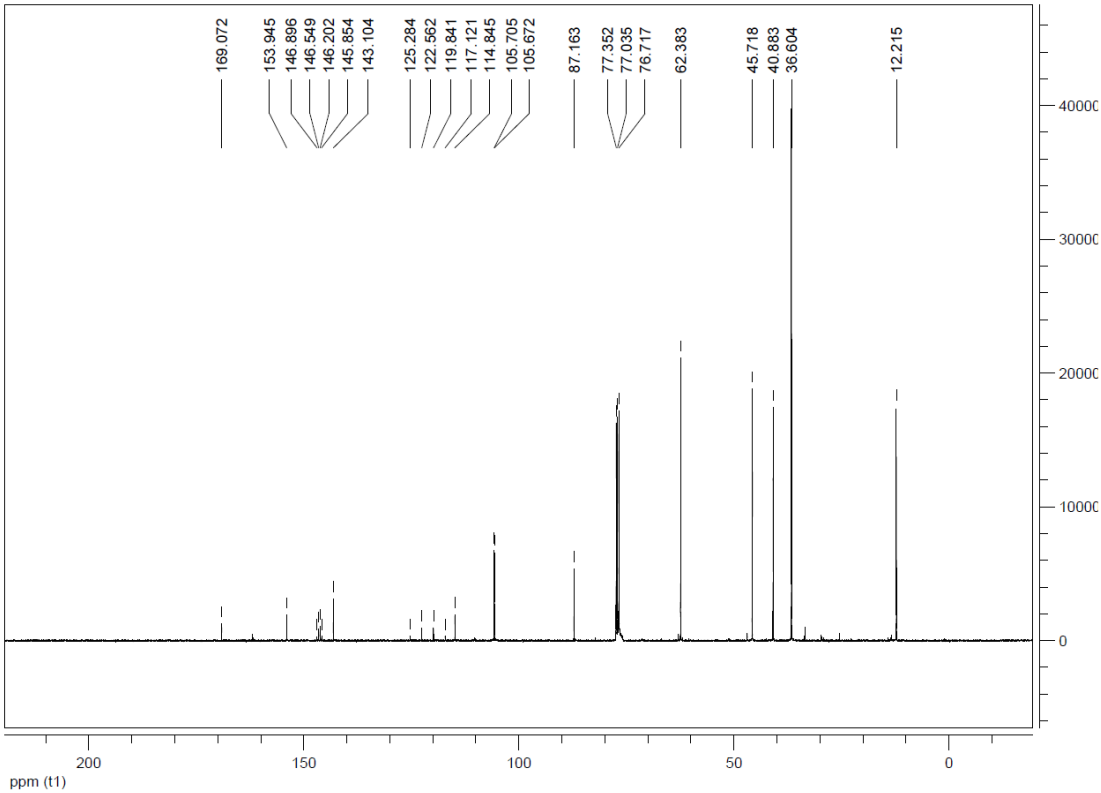

170.780
165.714
146.487
146.138
145.792
145.444
142.244
130.405
130.274
125.622
122.902
120.182
117.462
117.164
105.592
105.559
89.745
77.678
77.360
77.043
48.712
40.160
37.208
30.652
26.082
24.553
ppm (t1)

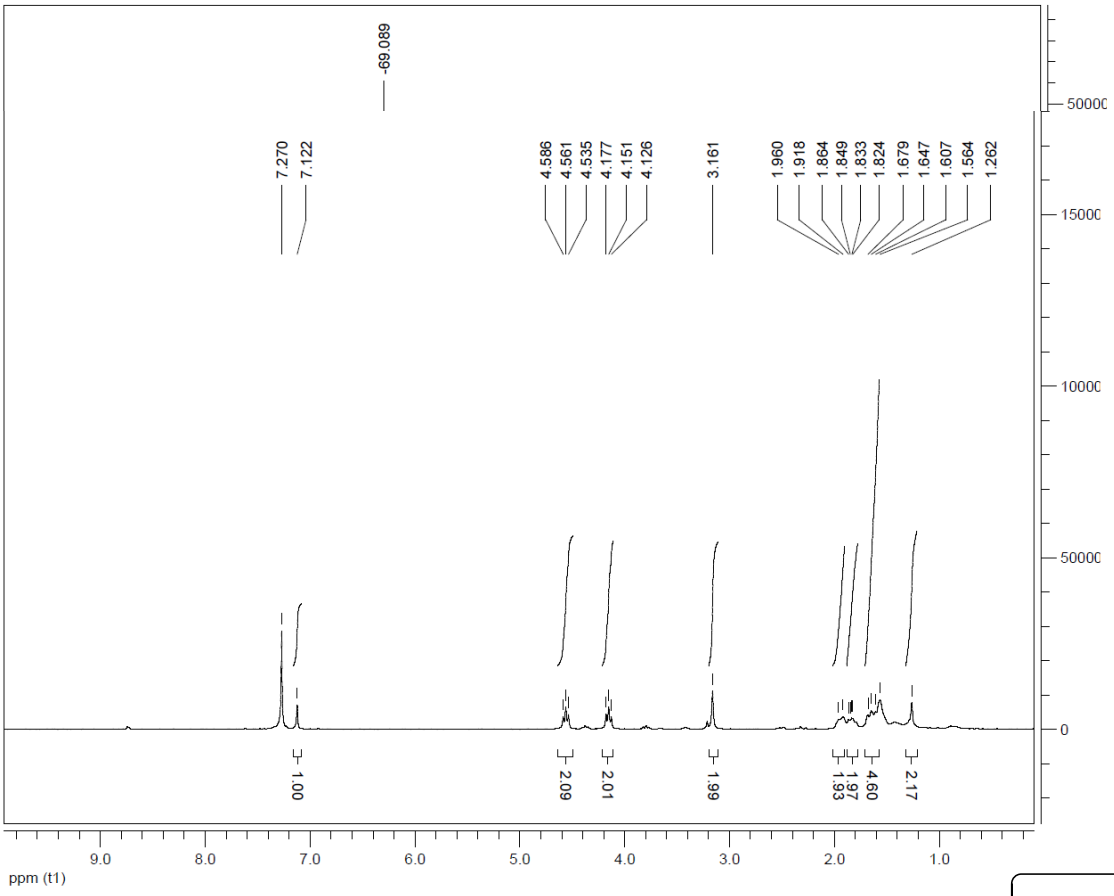

-69.118
ppm (t1)

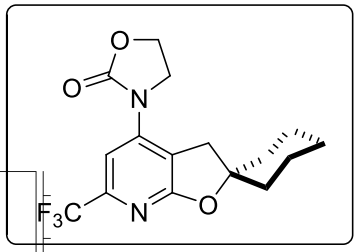
3-(6'-(Trifluoromethyl)-3'H-spiro[cyclobutane-1,2'-furo[2,3-b]pyridine]-4'-yl)oxazolidin-2-one (**4r**)



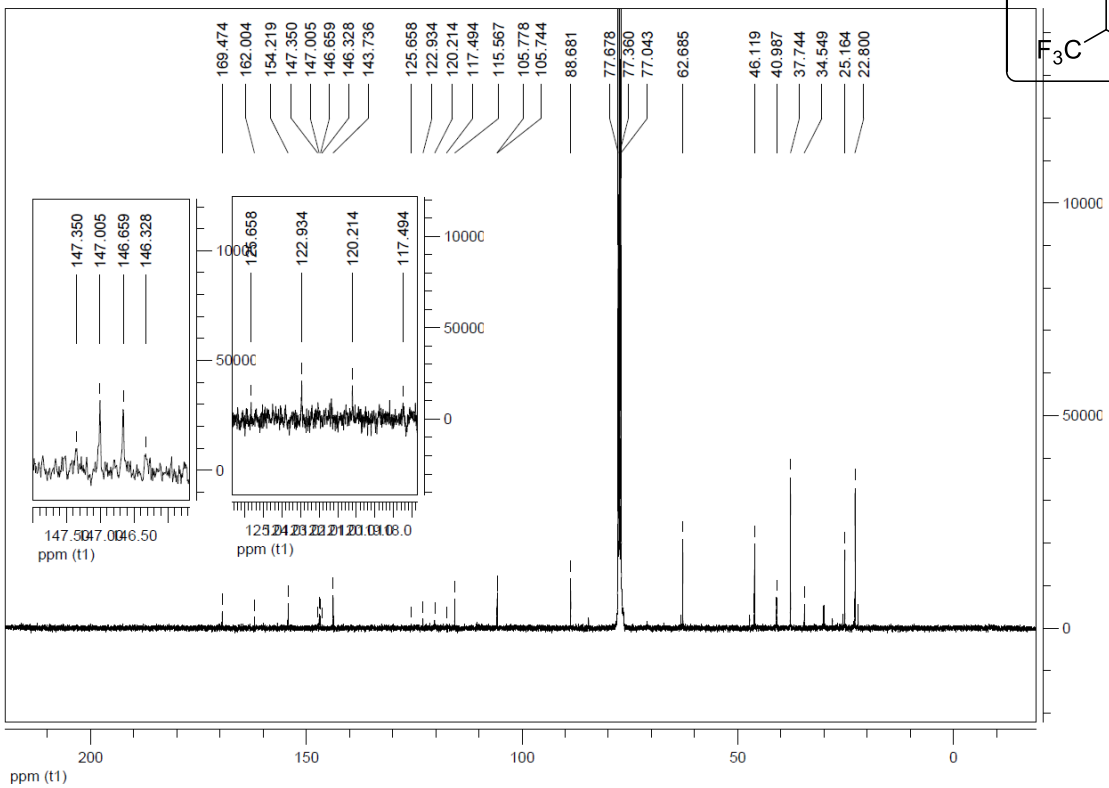


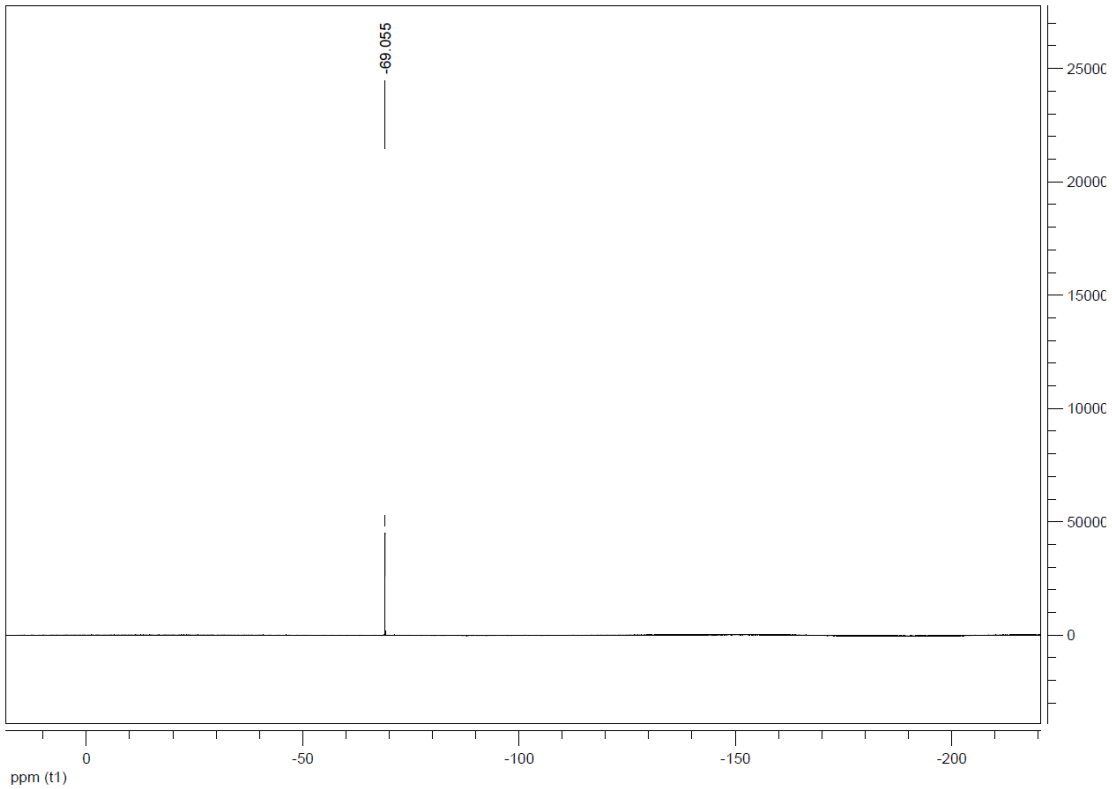




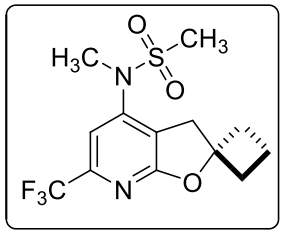


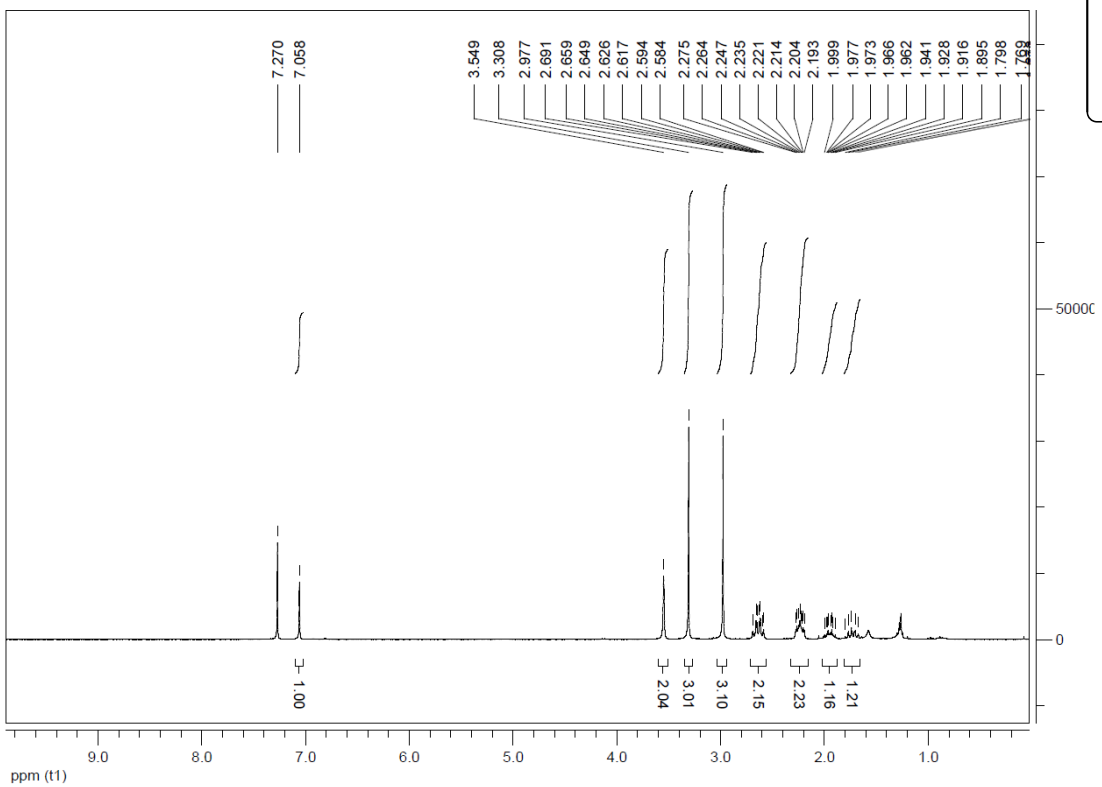
3-(6'-(Trifluoromethyl)-3'H-spiro[cyclohexane-1,2'-furo[2,3-b]pyridine]-4'-yl)oxazolidin-2-one (**4s**)

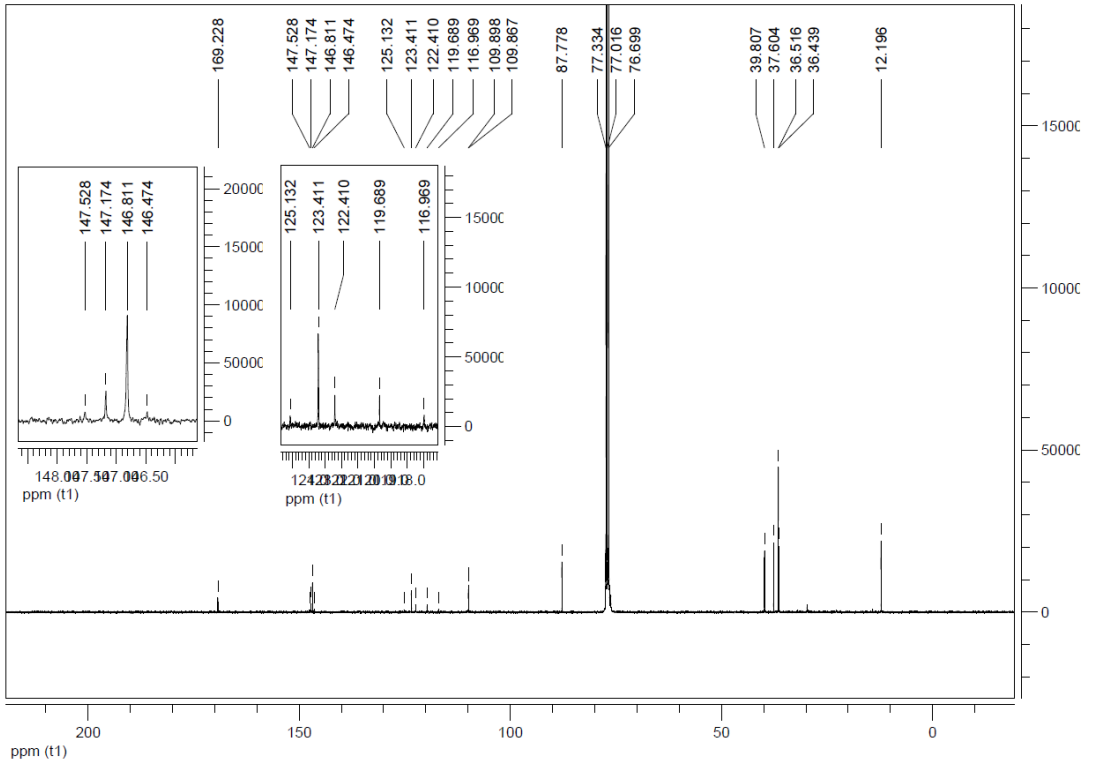


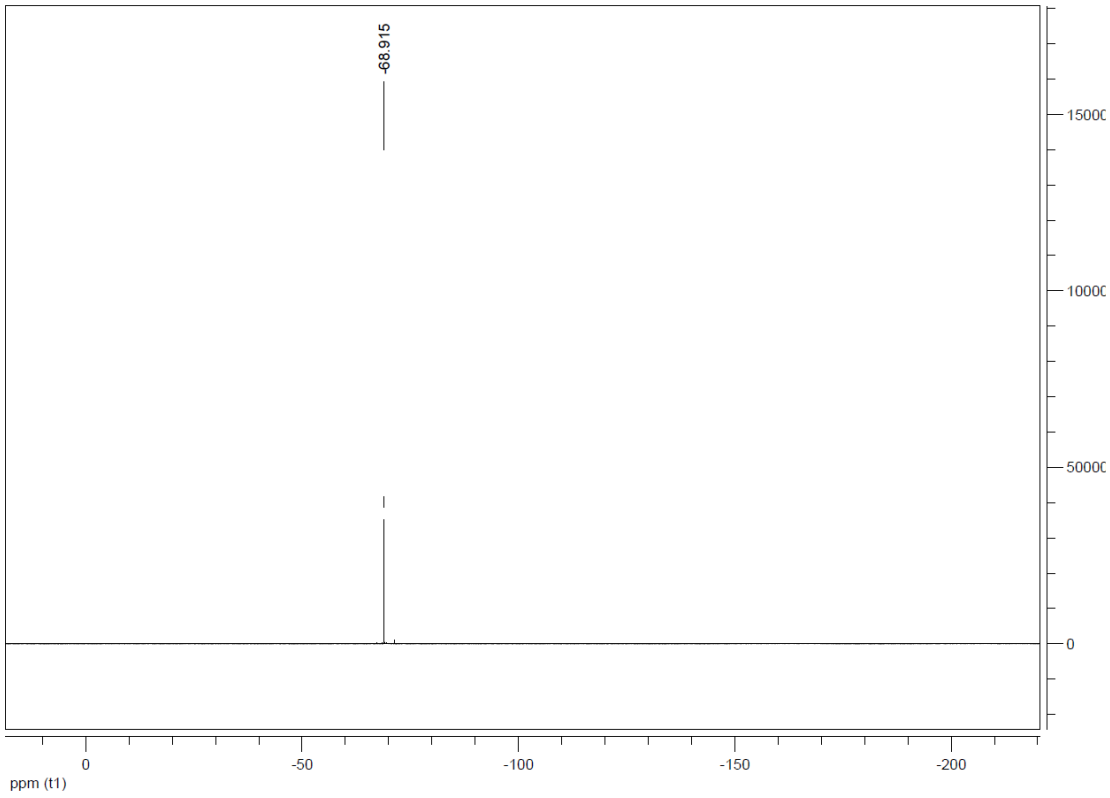


N-Methyl-*N*-(6'-(trifluoromethyl)-3'H-spiro[cyclobutane-1,2'-furo[2,3-b]pyridine]-4'-yl)methanesulfonamide (**4t**)

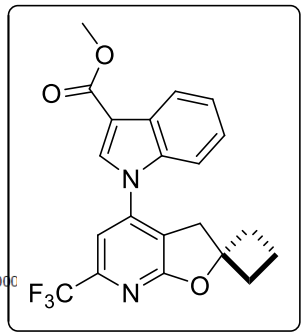


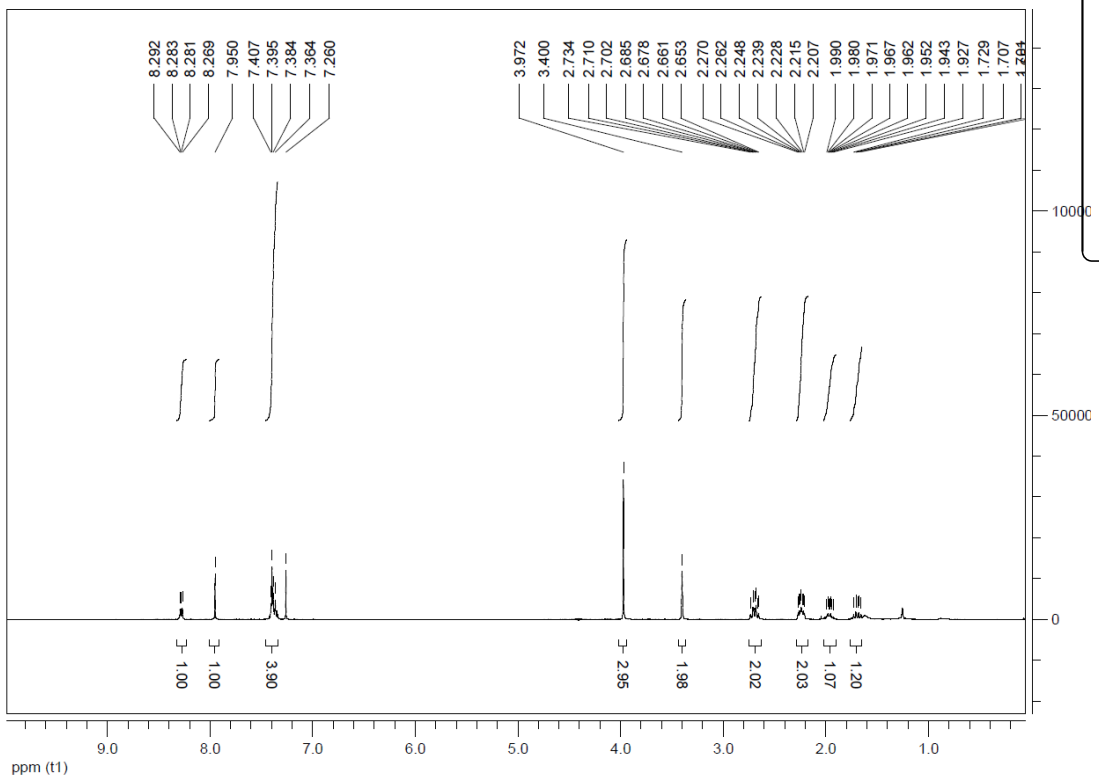


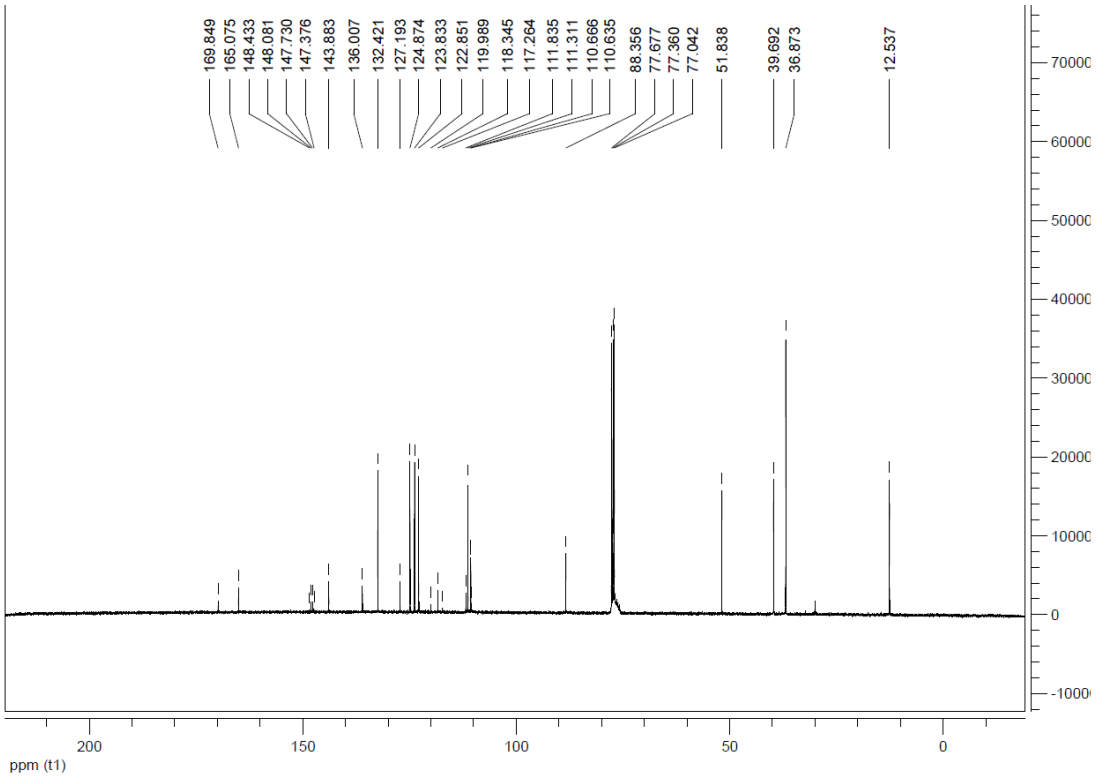

169.228
147.528
147.174
146.811
146.474
125.132
123.411
122.410
119.689
116.969
109.898
109.867
87.778
77.334
77.016
76.699
39.807
37.604
36.516
36.439
12.196
ppm (t1)
200
150
100
50
0

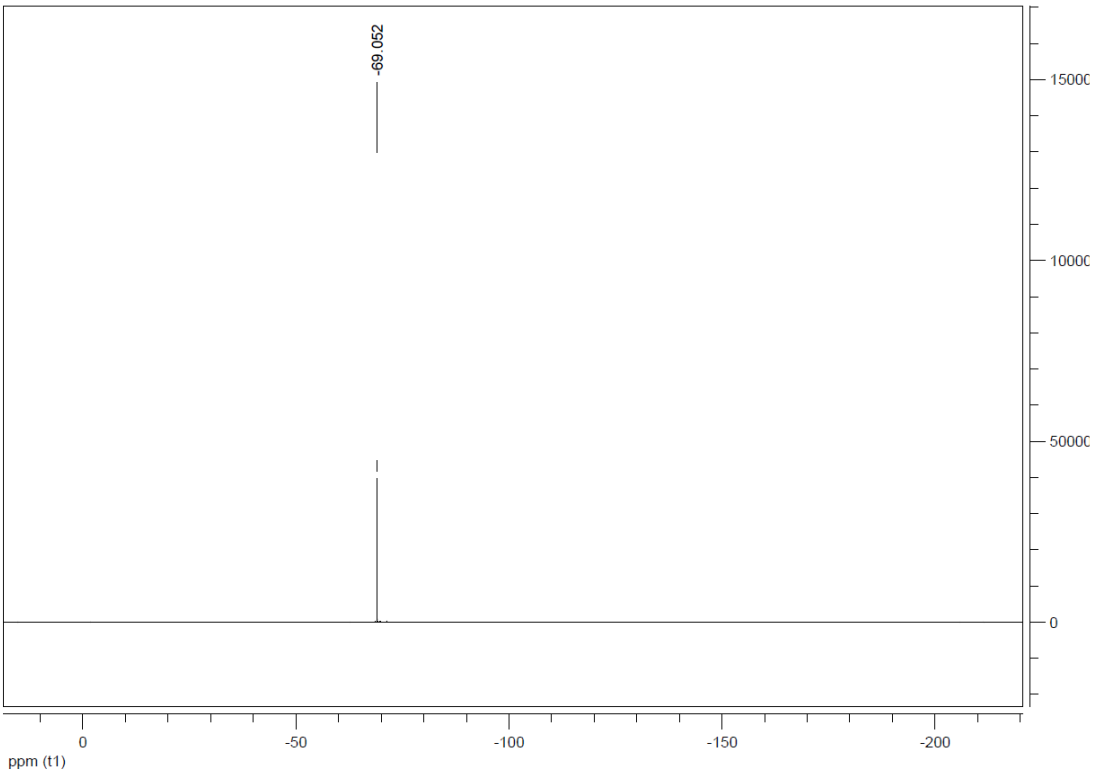

-68.915
ppm (t1)
0
-50
-100
-150
-200

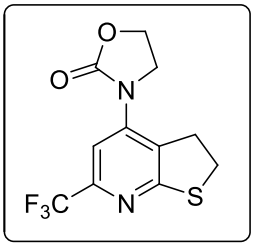
Methyl 1-(6'-(trifluoromethyl)-3'H-spiro[cyclobutane-1,2'-furo[2,3-b]pyridine]-4'-yl)-1H-indole-3-carboxylate (**4u**)



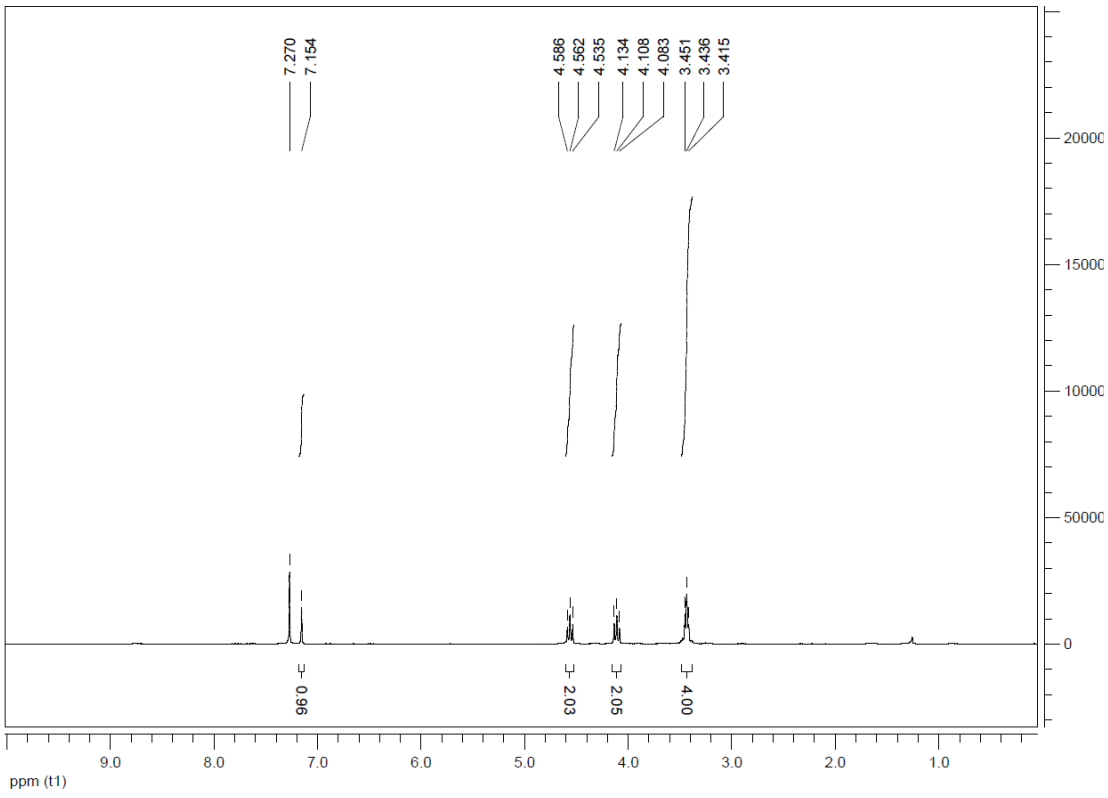


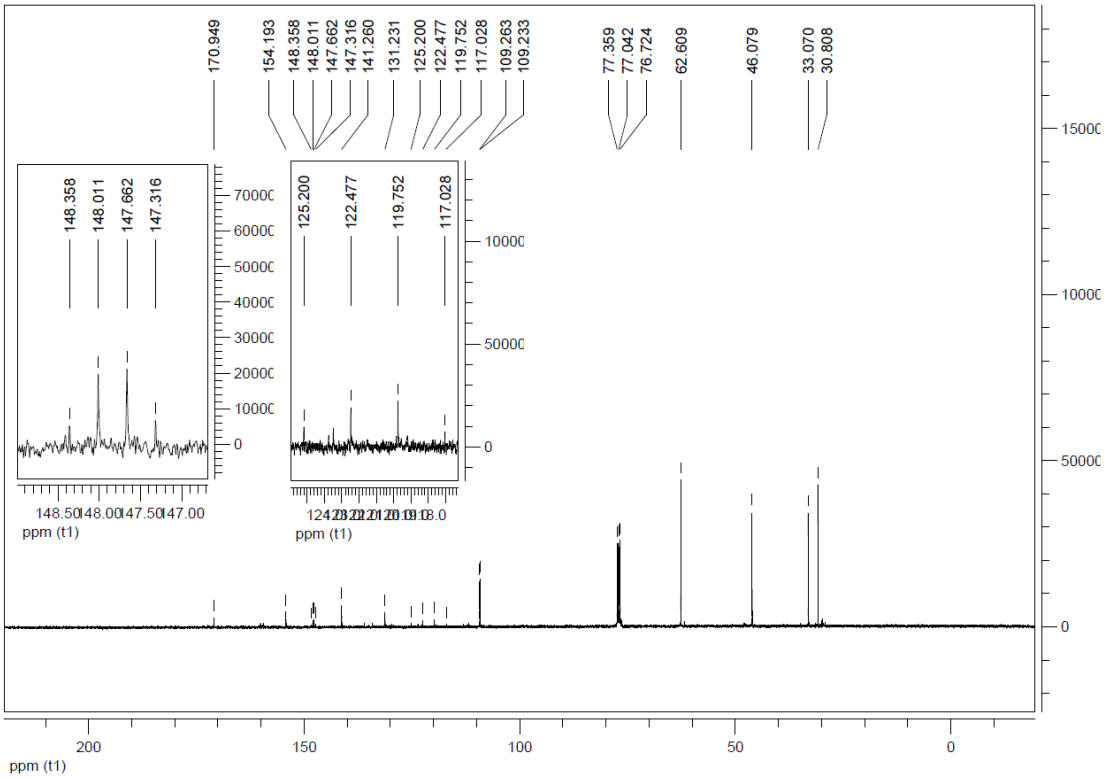


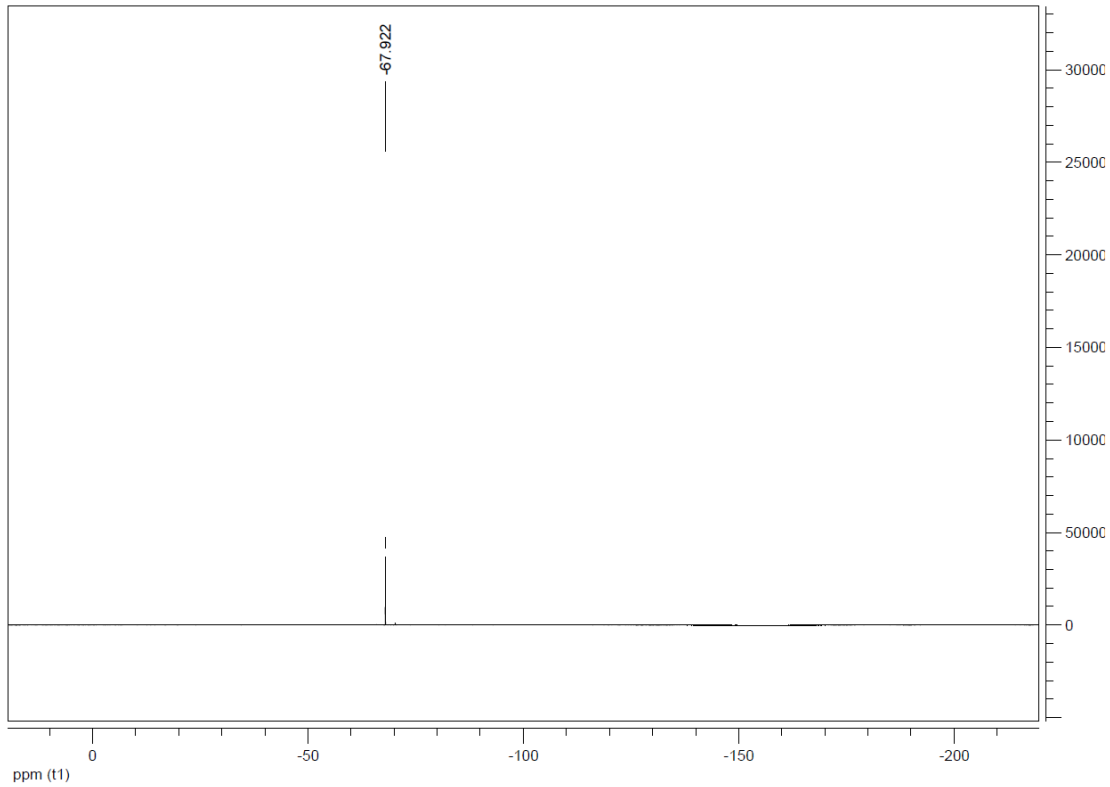




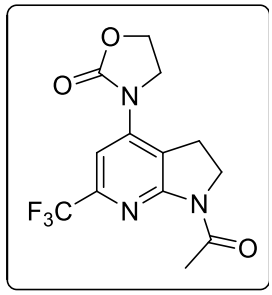
3-(6-(trifluoromethyl)-2,3-dihydrothieno[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4v**)

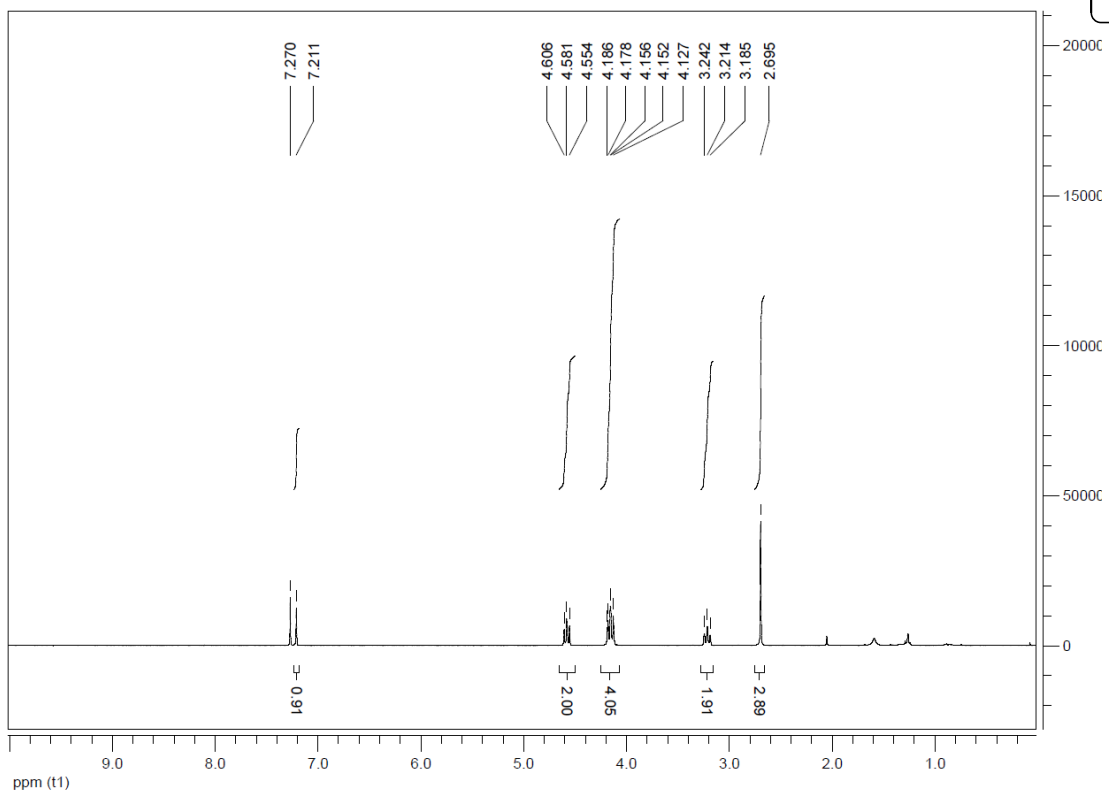


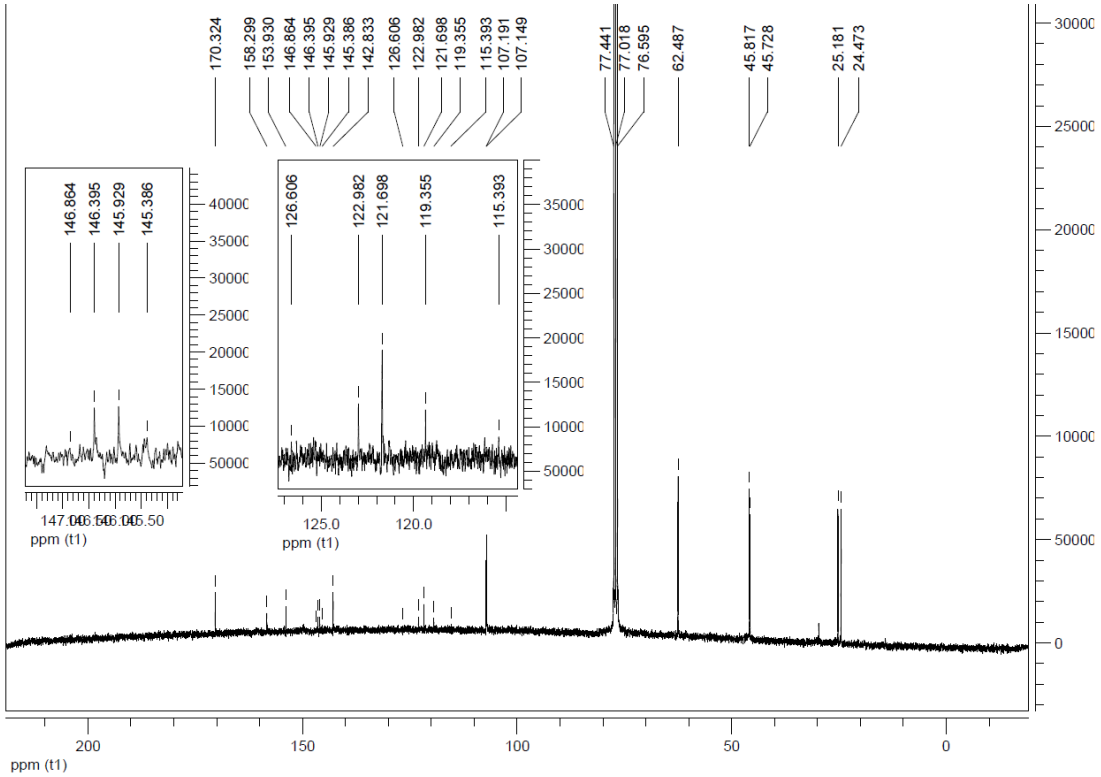

170.949
154.193
148.358
148.011
147.662
147.316
141.260
131.231
125.200
122.477
119.752
117.028
109.263
109.233
77.359
77.042
76.724
62.609
46.079
33.070
30.808
ppm (t1)

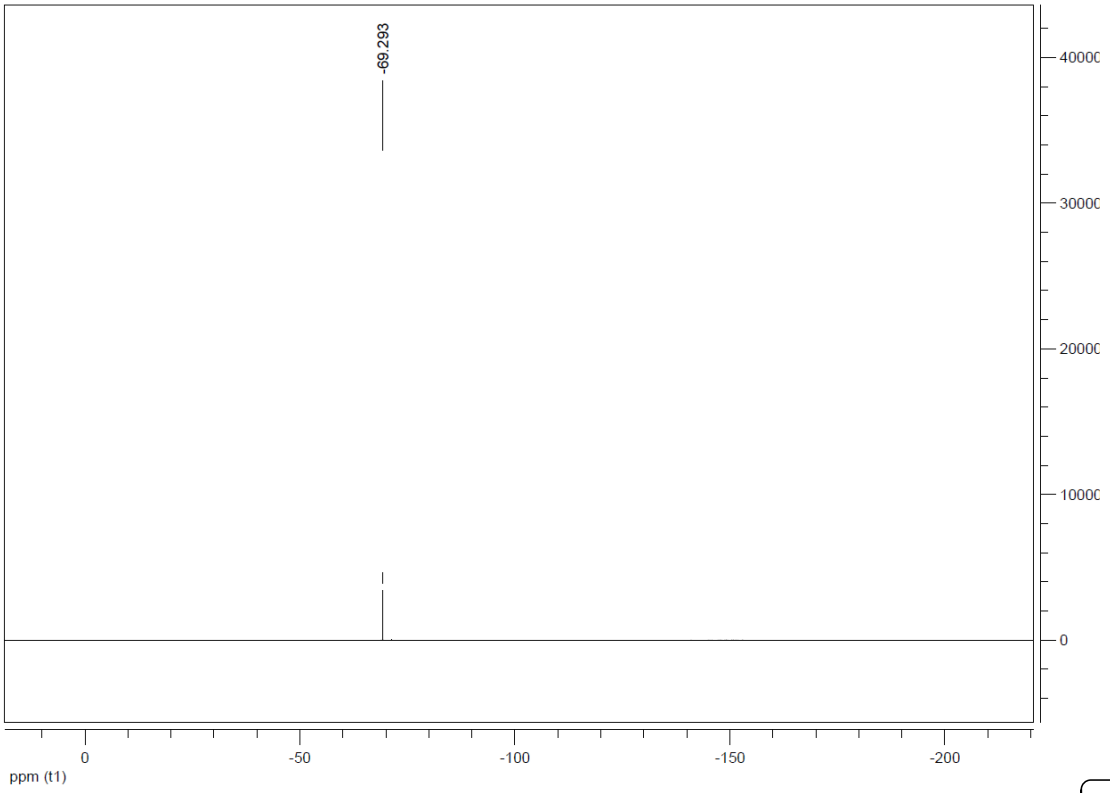

-67.922
ppm (t1)

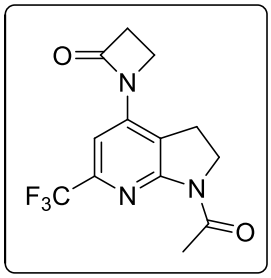
3-(1-acetyl-6-(trifluoromethyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxazolidin-2-one (**4w**)



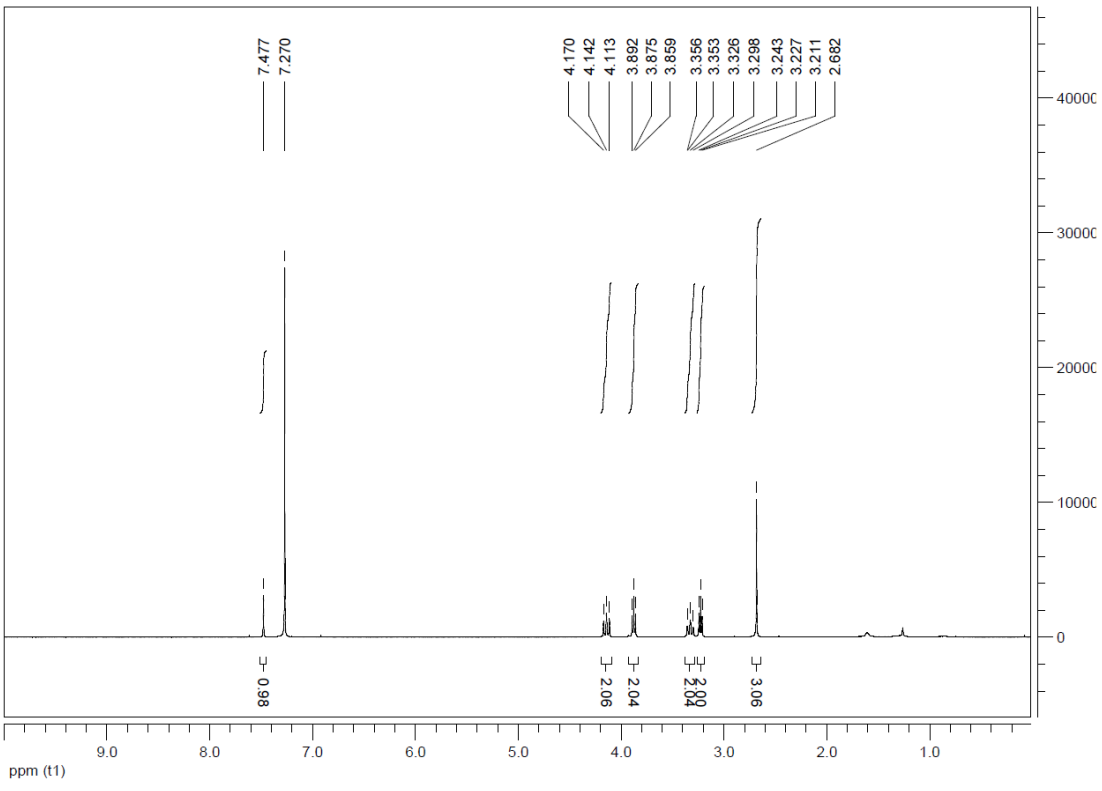


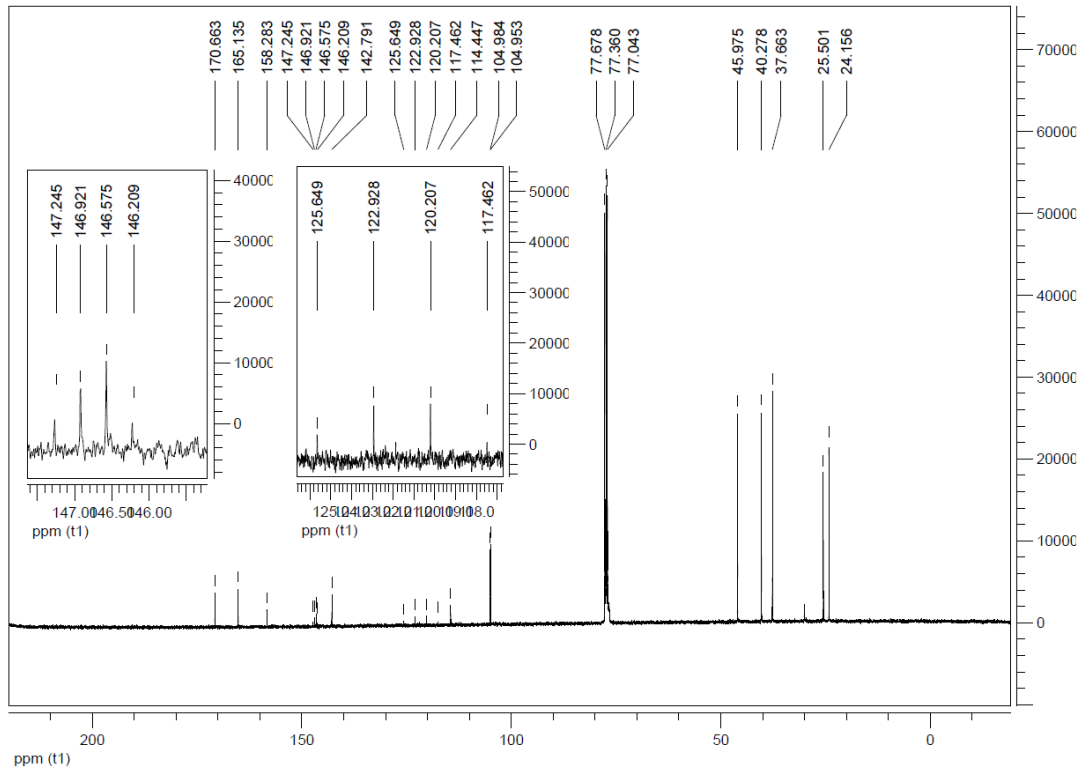


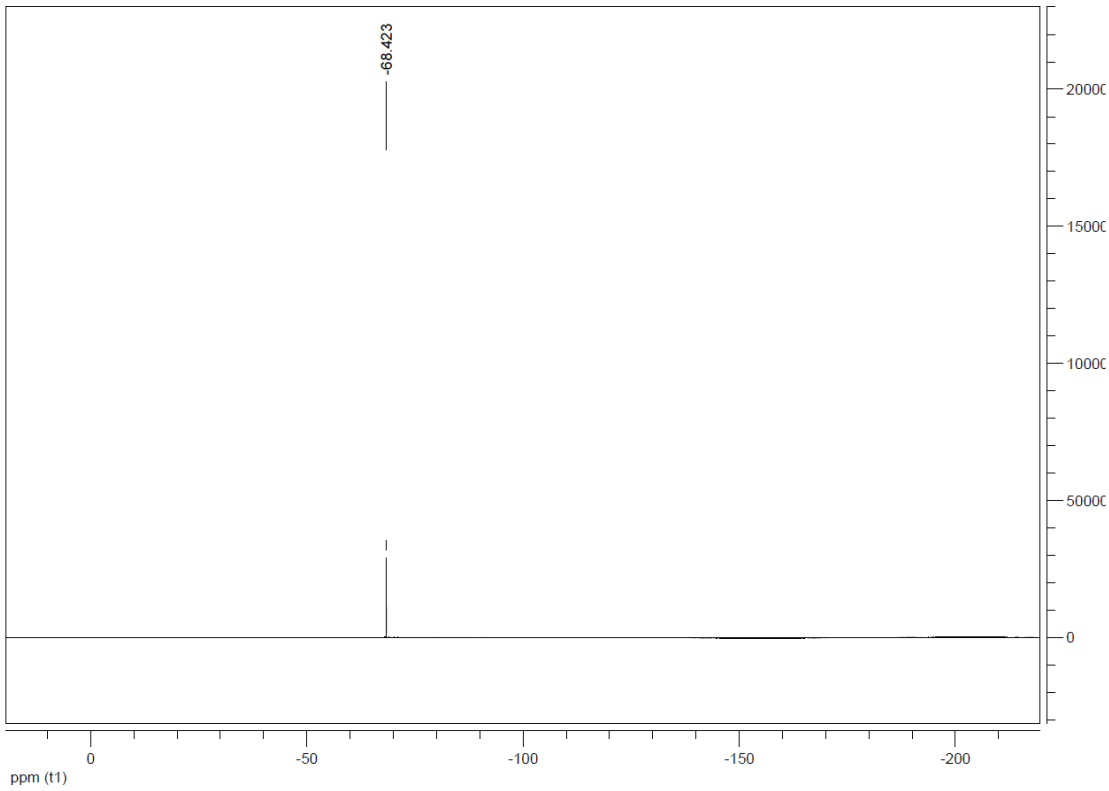




1-(1-acetyl-6-(trifluoromethyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl)azetidin-2-one (**4x**)




170.663
165.135
158.283
147.245
146.921
146.575
146.209
142.791
125.649
122.928
120.207
117.462
114.447
104.984
104.953
77.678
77.360
77.043
45.975
40.278
37.663
25.501
24.156
ppm (t1)


-68.423
ppm (t1)