Electronic Supplementary Information

Concise synthesis of rare pyrido[1,2-*a*]pyrimidin-2-ones and related nitrogen-rich bicyclic scaffolds with a ring-junction nitrogen

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General experimental details

All non-aqueous reactions were performed under a constant stream of dry nitrogen using oven-dried glassware. Standard practices were employed when handling moisture and air-sensitive materials.

Room temperature (r.t.) refers to ambient temperature. All temperatures below 0 °C are those of the external baths. Temperatures of 0 °C were maintained using an ice-water bath. Temperatures below 0 °C were maintained using an acetone-cardice bath (-78 ^{o}C) or acetonitrile-cardice (-40 ^{o}C).

All reagents and solvents were used as received unless otherwise stated. Toluene was distilled from calcium hydride. Tetrahydrofuran was dried over sodium metal wire and distilled from a mixture of lithium aluminium hydride and calcium hydride with triphenylmethane as indicator. Petroleum ether was distilled before use. *n*-Butyllithium in hexanes and LDA (2.0 M in THF/heptane/ethylbenzene) (Aldrich) were titrated with *N*-benzylbenzamide before use.[1] Sodium hydride was used without hexane washes. Magnesium turnings were used for the preparation of all Grignard reagents.

Yields refer to chromatographically and spectroscopically pure compounds (purity of at least 95%) unless otherwise stated, in which case corrected with respect to percentage weight purity (in cases where a purity is stated). Where possible, reactions were monitored by thin layer chromatography (TLC) performed on commercially prepared glass plates pre-coated with Merck silica gel 60 F254 or aluminium oxide 60 F254. Visualisation was by the quenching of UV fluorescence (ν_{max} = 254 nm) or by staining with potassium permanganate or by liquid chromatography mass spectrometry (LC-MS) using a Waters Micromass ZQ spectrometer. Retention factors (R_f) are quoted to 0.01.

Flash column chromatography was carried out using slurry-packed Merck 9385 Kieselgel 60 SiO_2 (230-400 mesh) under a positive pressure of compressed air, or Combiflash Companion automated purification columns (GRADE silica columns).

Melting points were obtained on a Buchi B-545 melting point apparatus and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer Spectrum One spectrometer with internal referencing. Selected absorption maxima (vmax) are reported in wavenumbers (cm^{-1}) with the following abbreviations: w, weak; med, medium; str, strong; br, broad.

Proton magnetic resonance spectra were recorded using an internal deuterium lock at ambient probe temperatures (unless otherwise stated) on the following instruments: Bruker DPX-400 (400 MHz), Bruker Avance 400 QNP (400 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz). Chemical shifts (δ_H) are quoted in ppm, to the nearest 0.01 ppm, and are referenced to the residual non-deuterated solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. Data are reported as follows: chemical shift, integration, multiplicity (br = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; or as a combination of these), coupling constant(s) and assignment. The numbering/lettering on selected structures does not follow the IUPAC naming system and is used for the assignment of the ^{1}H NMR and ^{13}C NMR spectra. Proton assignments were determined either on the basis of unambiguous chemical shift, coupling pattern, by patterns observed in 2D experiments (^{1}H-^{1}H COSY, HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds.

Carbon magnetic resonance spectra were recorded by broadband proton spin decoupling at ambient probe temperatures using an internal deuterium lock on the following instruments: Bruker DPX-400 (100 MHz), Bruker Avance 400 QNP (100 MHz) and Bruker Avance 500 Cryo Ultrashield (125 MHz). Chemical shifts (δ_C) are quoted in ppm, to the nearest 0.1 ppm, and are referenced to the residual non-deuterated solvent peak. Assignment was based on chemical shift, DEPT editing and where appropriate, HMQC and HMBC experiments or by analogy to fully interpreted spectra of related compounds.

Fluorine magnetic resonance spectra were recorded on a Bruker DPX-400 (162 MHz) instrument. Chemical shifts (δ_F) are quoted in ppm to the nearest 0.1 ppm and are referenced to $CFCl_3$.

High resolution mass spectrometry (HRMS) measurements were recorded on a Bruker Bioapex 4.7e FTICR or a Micromass LCT Premier spectrometer or a Waters Xevo G2 Qtof spectrometer. Mass values are quoted within the error limits of ± 5 ppm mass units. ToF ES+ or FTMS ESI+ refers to the mass ionisation technique.

Microwave reactions were carried out in a CEM Discover Microwave or in a Biotage Initiator Classic.

LC-MS chromatographs were recorded on an HP/Agilent MSD LC-MS APCI 120-1000 full gradient ACq T = 1 min 1 μL. Retention times are reported to the nearest 0.1 min. Preparative HPLC chromatography was carried out on a Dionex Ultimate 3000 loaded with a Reprosil Chiral NR 250 x 4.6 mm column, eluting with an isocratic 40-60% EtOH/heptane (with 0.01 mol/L NH_4OAc) over 60 mins or on a Reprosil Chiral NR 250 x 30 mm column, eluting with a 1.60 mL of the same conditions as above or on a Phenomenex Gemini-NX axia Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length, using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Retention times are reported to the nearest 0.01 min.

General methods

General method 1: Acylation of aminoazines

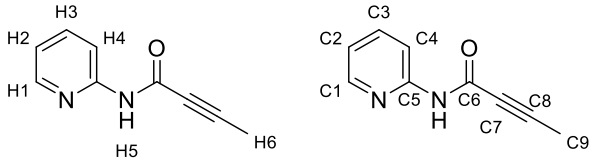
To a stirred solution of aminoazine (1 eq.) in anhydrous THF (reaction molarity of approx. 0.25 M) at -78 ^{o}C was added dropwise the solution of lithium base (2.1 eq.). The reaction was left to stir at -78 ^{o}C for 30 mins. The electrophile (1.2 eq.) was then added at -78 ^{o}C, and the reaction was left to warm to room temperature over 1 hour. The reaction was then quenched with AcOH (approx.1 mL) and diluted with CH_2Cl_2 (approx. 20 mL) and water (approx. 20 mL). The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3 x 20 mL). The combined organic layers were then dried ($MgSO_4$) and the solvent removed under reduced pressure at low temperature (<25 ^{o}C) to yield the crude product which was purified by column chromatography. Note – for highest and most reproducible yields reaction and purification should be carried out within six hours.

General method 2: Cyclisation of heterocyclic amides

A stirred solution of heterocyclic ynone in DMSO was heated to 85 or 100 ^{o}C until TLC/LC-MS showed complete consumption of starting material (see manuscript for times and temperatures). The solvent was then removed under a stream of N_2 gas overnight and the residue purified by column chromatography or preparative HPLC if required.

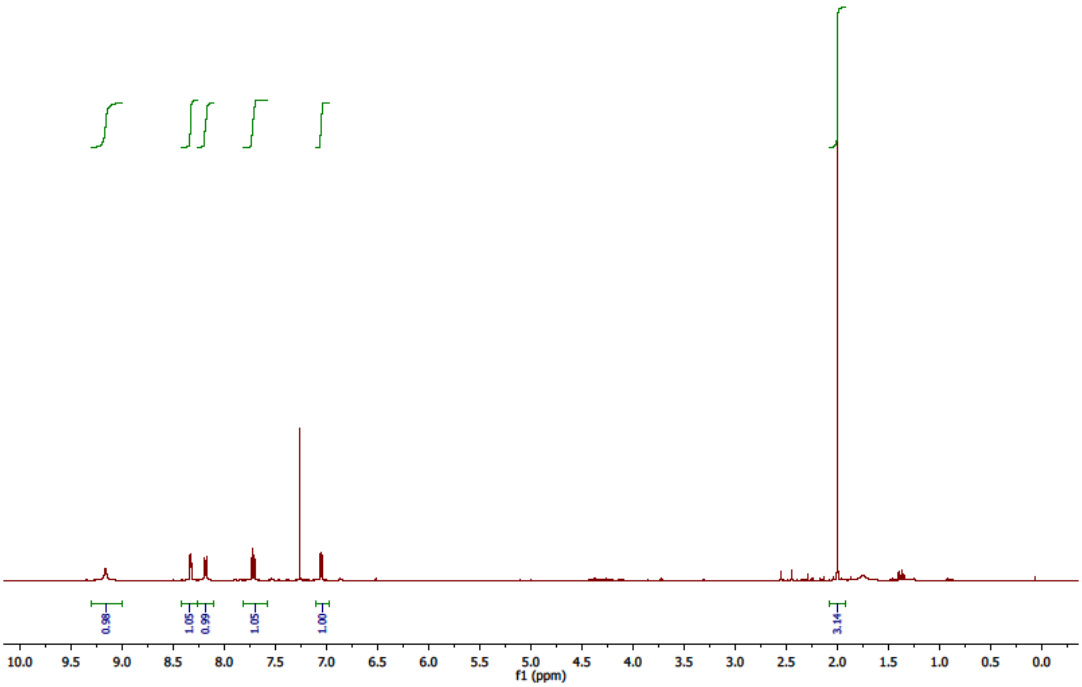
Experimental details and NMR spectra

N-(2-Pyridyl)but-2-ynamide **(25)**

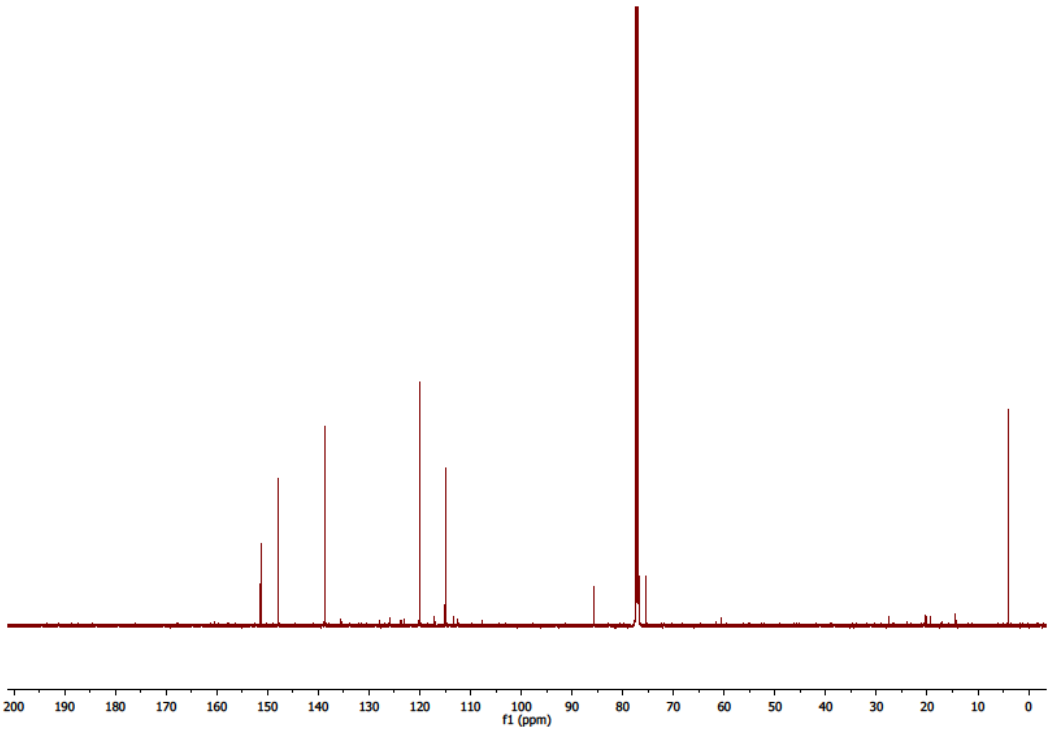


Prepared according to General Method 1 from 2-aminopyridine **23** (0.14 g, 1.43 mmol *n*BuLi (1.88 mL, 3.00 mmol) and ethyl 2-butynoate **24** (0.20 mL, 1.72 mmol). The crude product was purified by Combiflash Companion (SiO_2, 20 g, 0-50% EtOAc in heptane) to yield a yellow solid (0.10 g, 0.63 mmol, 44%). R_f = 0.26 (1:1 heptane: EtOAc). Mpt (CH_2Cl_2): 130-131 ^oC. IR ν_{max}/cm^{-1} (neat): 2956 (m, br, C-H/N-H), 2236 (med, C≡C), 1665 (str, C=O), 1581 (str, C=C), 1534 (str, C=C), 1437 (str, C=C). ^1H NMR (500 MHz, $CDCl_3$): δ_H 9.15 (1H, br s, H5), δ_H 8.32 (1H, dd, *J* = 4.9, 0.9 Hz, H1), δ_H 8.17 (1H, d, *J* = 8.4 Hz, H4), δ_H 7.70 (1H, ddd, *J* = 8.4, 7.5, 1.9 Hz, H3), δ_H 7.03 (1H, ddd, *J* = 7.3, 5.0, 0.9 Hz, H2), δ_H 1.99 (3H, s, H6). ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 151.3 (C5), δ_c 151.2 (C6), δ_c 147.8 (C1), δ_c 138.6 (C3), δ_c 119.9 (C2), δ_c 114.8 (C4), δ_c 85.5 (C7), δ_c 75.3 (C8), δ_c 3.8 (C9). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 161.0716, $C_9H_9N_2O^+$ required 161.0715, Δ ppm = 0.6 ppm.

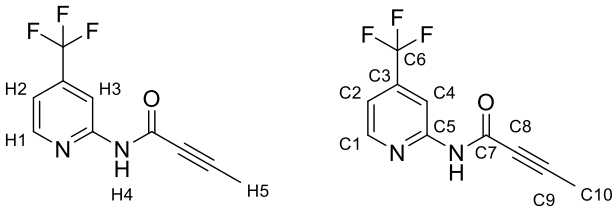
^{1}H NMR



^{13}C NMR

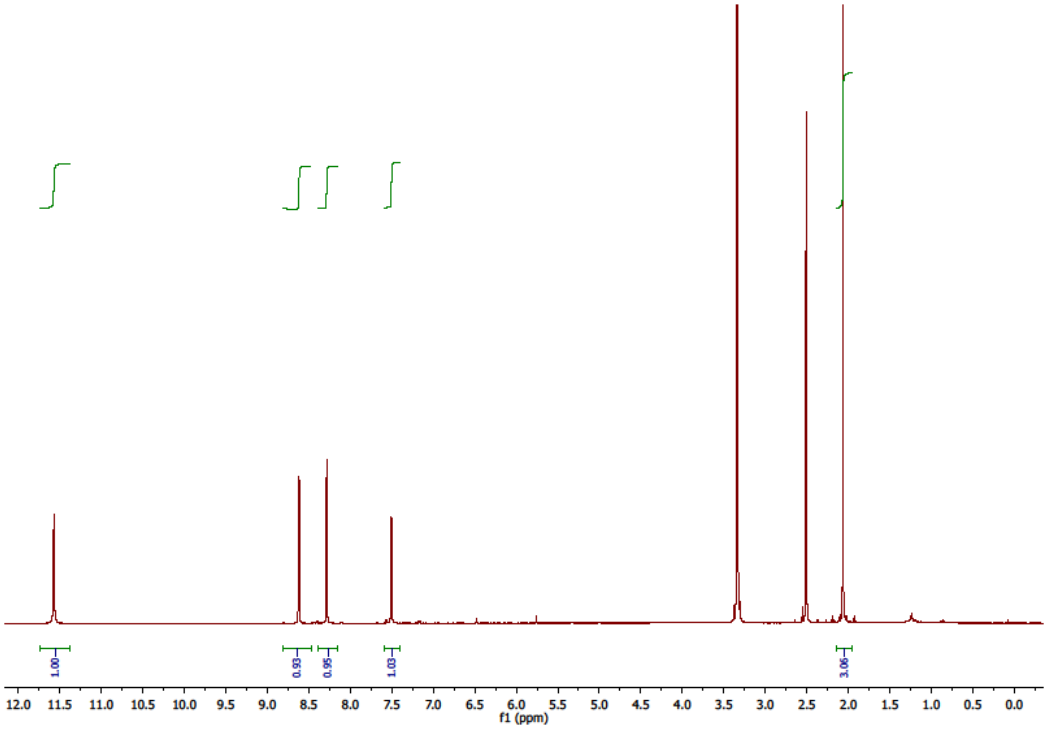


N-(4-(trifluoromethyl)pyridin-2-yl)but-2-ynamide **(43)**

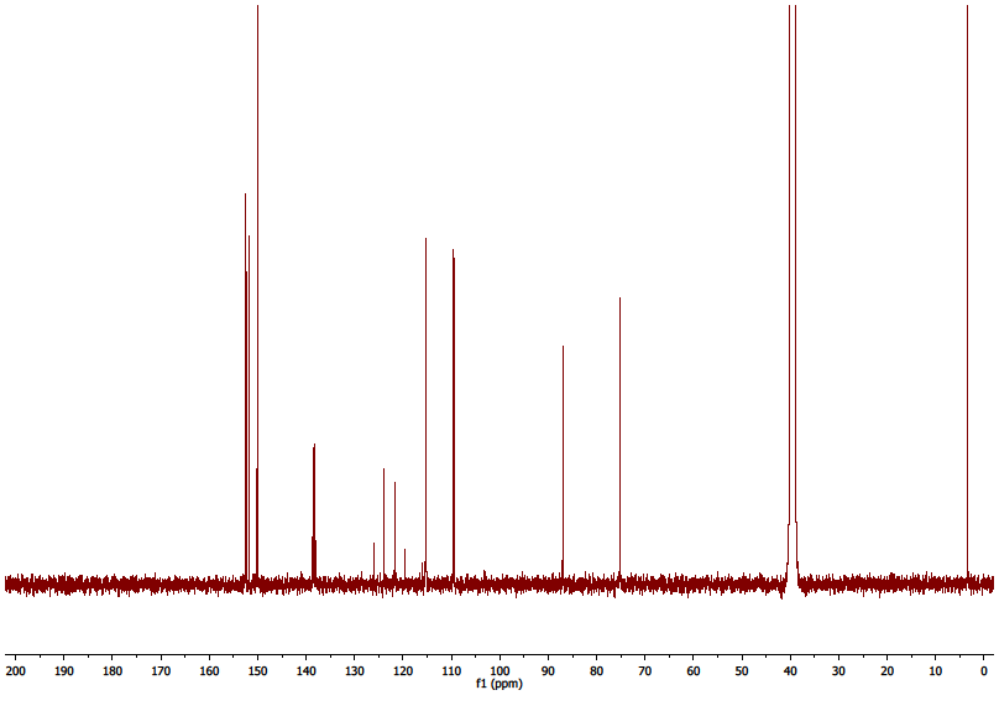


Prepared according to General Method 1 from 2-amino-4-(trifluoromethyl)pyridine **27** (0.10 g, 0.62 mmol), *n*BuLi (1.30 mmol) and ethyl 2-butynoate **24** (0.09 mL, 0.74 mmol). The crude product was purified by column chromatography (SiO_2, 20 g, 4:1 then 7:3 40-60 petroleum ether: EtOAc) to yield a beige solid (0.11 g, 0.50 mmol, 82%). R_f = 0.60 (1:1 40-60 petroleum ether: EtOAc). Mpt (CH_2Cl_2): darkens >120 ^oC, melts 129-131 ^oC. IR ν_{max}/cm^{-1} (neat): 3165 (w, N-H/C-H), 3125 (w, C-H), 2979 (w, C-H), 2241 (med, C≡C), 1679 (med, C=O), 1670 (med, C=O), 1618 (w), 1579 (str, C=C), 1529 (str, C=C/C=N), 1467 (w), 1420 (str), 1336 (str), 1309 (w), 1291 (med), 1275 (str), 1230 (str), 1165 (str), 1127 (str), 1087 (str), 1068 (str). ^1H NMR (500 MHz, d^6-DMSO): δ_H 11.55 (1H, s, H4), δ_H 8.60 (1H, d, J = 5.1 Hz, H1), δ_H 8.26 (1H, app s, H3), δ_H 7.48 (1H, dd, J = 5.1, 0.9 Hz, H2), δ_H 2.04 (3H, s, H5). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 152.5 (C5), δ_C 151.8 (C7), δ_C 150.2 (C1), δ_C 138.4 (q, $^2J_{C\text{-}F}$ = 33 Hz, C3), δ_C 122.8 (q, $^1J_{C\text{-}F}$ = 273 Hz, C6), δ_C 115.3 (d, $^3J_{C\text{-}F}$ = 3 Hz, C2), δ_C 109.6 ($^3J_{C\text{-}F}$ = 4 Hz, C4), δ_C 87.0 (C8), δ_C 75.3 (C9), δ_C 3.5 (C10). ^{19}F NMR (162 MHz, d^6-DMSO): δ_F -63.91 (s, CF_3). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 229.0579, $C_{10}H_8ON_2F_3^+$ required 229.0579, Δ ppm = -2.1 ppm.

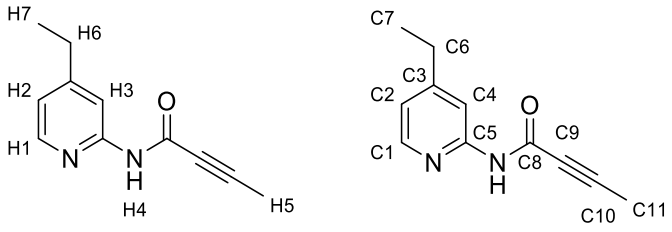
^{1}H NMR



^{13}C NMR

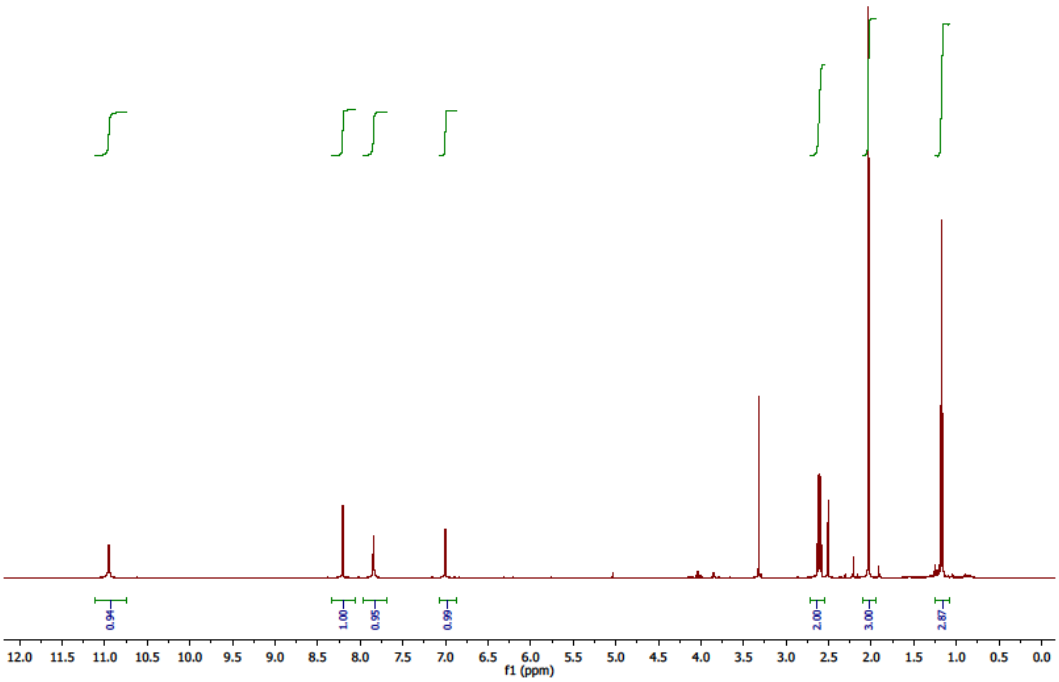


N-(4-ethylpyridin-2-yl)but-2-ynamide **(44)**

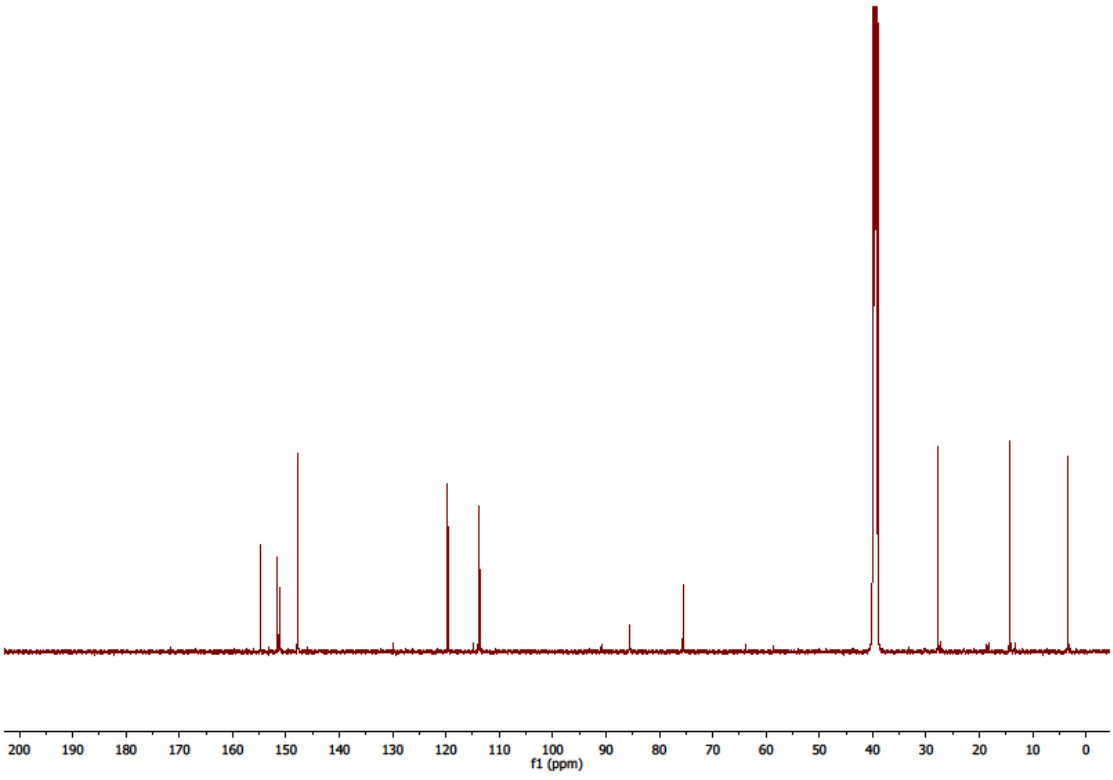


Prepared according to General Method 1 from 2-amino-4-ethylpyridine **28** (0.30 g, 2.46 mmol), *n*BuLi (5.16 mmol) and ethyl 2-butynoate **24** (0.34 mL, 2.95 mmol). The crude product was purified by column chromatography (SiO_2, 20 g, 7:3 40-60 petroleum ether: EtOAc) to yield a yellow solid (0.20 g, 90% purity, 0.98 mmol, 40%). R_f = 0.50 (1:1 40-60 petroleum ether: EtOAc). Mpt (CH_2Cl_2): 112-114 ^oC. IR ν_{max}/cm^{-1} (neat): 3100 (w, N-H/C-H), 3031 (w, C-H), 2972 (w, C-H), 2938 (w, C-H), 2781 (w), 2243 (w, C≡C), 2228 (w, C≡C), 1695 (w), 1660 (str, C=O), 1610 (med, C=C), 1565 (str, C=C), 1530 (str, C=C/C=N), 1466 (w), 1453 (w), 1416 (str), 1377 (w), 1296 (med), 1284 (w), 1270 (med), 1251 (str), 1164 (med), 1122 (w), 1071 (w), 1061 (w), 1001 (w). ^1H NMR (500 MHz, d^6-DMSO): δ_H 10.94 (1H, s, H4), δ_H 8.18 (1H, d, *J* = 5.0 Hz, H1), δ_H 7.82 (1H, app s, H3), δ_H 6.98 (1H, dd, *J* = 5.0, 1.5 Hz, H2), δ_H 2.59 (2H, q, *J* = 7.5 Hz, H6), δ_H 2.01 (3H, s, H5), δ_H 1.15 (3H, t, *J* = 7.5 Hz, H7). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 154.8 (C3), δ_C 151.7 (C8), δ_C 151.3 (C5), δ_C 147.9 (C1), δ_C 119.8 (C2), δ_C 113.8 (C4), 85.6 (C9), δ_C 75.6 (C10), δ_C 27.8 (C6), δ_C 14.4 (C7), δ_C 3.4 (C11). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 189.1030, $C_{11}H_{13}ON_2^+$ required 189.1028, Δ ppm = 1.1 ppm.

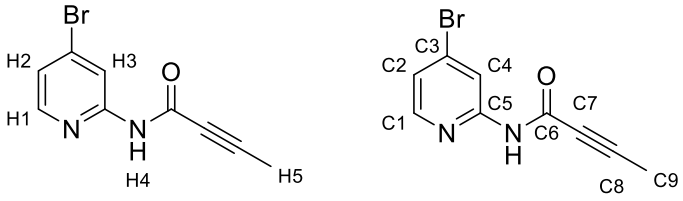
^{1}H NMR



^{13}C NMR

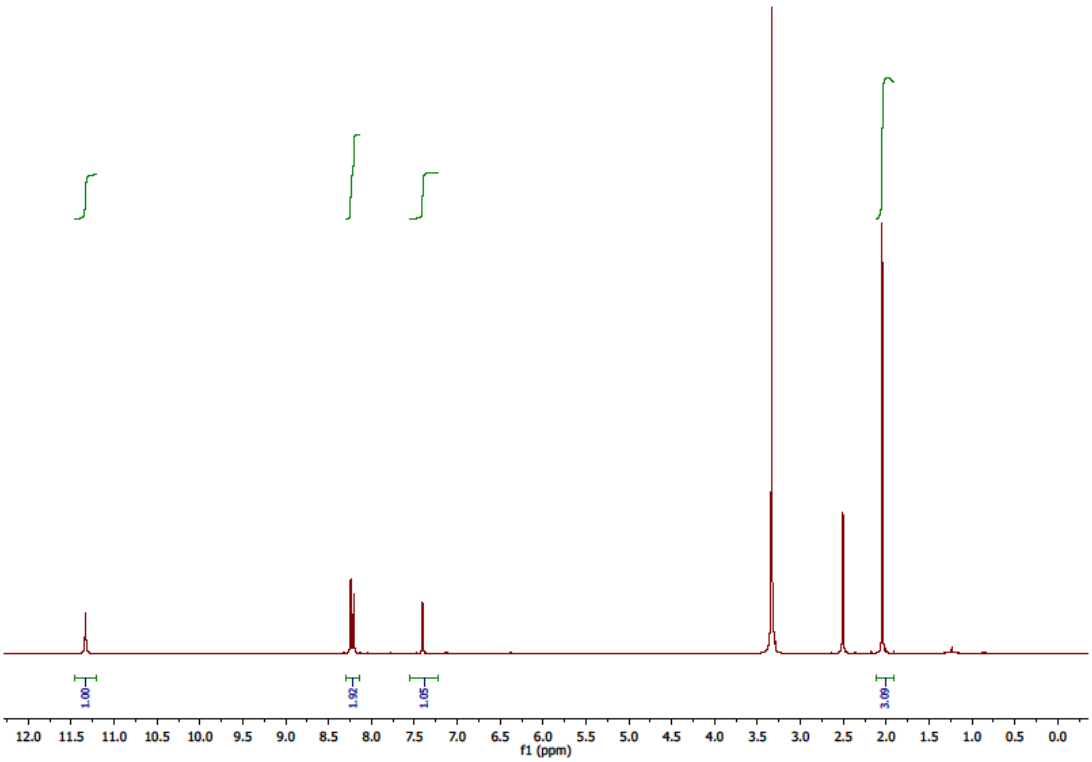


N-(4-Bromopyridin-2-yl)but-2-ynamide **(45)**

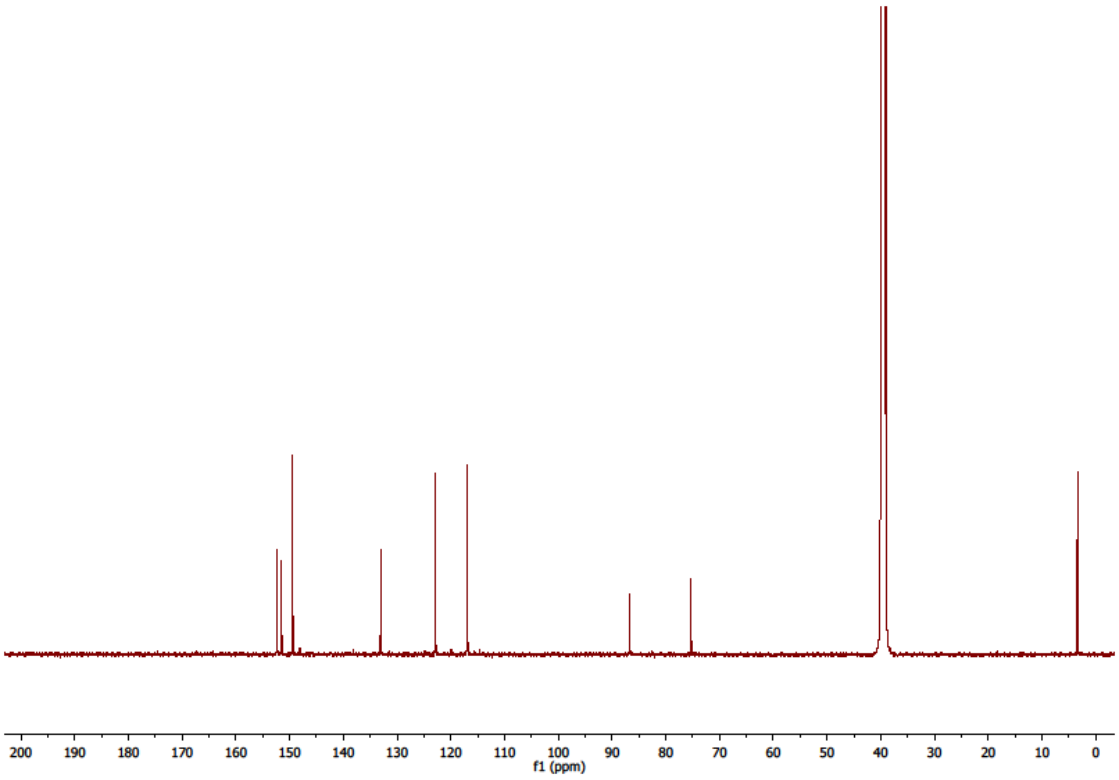


Prepared according to General Method 1 from 2-amino-4-bromopyridine **29** (1 g, 5.78 mmol), LDA (12.14 mmol) and ethyl 2-butynoate **24** (0.808 mL, 6.94 mmol). The crude product was purified by column chromatography (SiO_2, 0 to 30% EtOAc in heptane) to yield a yellow solid (0.698 g, 51%). This can be titurated with heptane if required. R_f = 0.65 (1:1 40-60 petroleum ether: EtOAc). Mpt (CH_2Cl_2): darkens >160 ^oC, melts 227-230 ^oC. IR ν_{max}/cm^{-1} (neat): 3199 (w, C-H/N-H), 3147 (w, C-H/N-H), 3052 (w, C-H), 3010 (w, C-H), 2236 (med, C≡C), 1659 (str, C=O), 1571 (str, C=C), 1511 (str, C=C), 1455 (w), 1419 (w), 1402 (str), 1290 (med), 1271 (str), 1251 (med), 1224 (med), 1122 (w), 1093 (med), 1066 (med), 1026 (w). ^1H NMR (500 MHz, d^6-DMSO): δ_H 11.31 (1H, s, H4), δ_H 8.24 (1H, d, J = 5.3 Hz, H1), δ_H 8.21 (1H, d, J = 1.2 Hz, H3), δ_H 7.40 (1H, dd, J = 5.3, 1.8 Hz, H2), δ_H 2.05 (3H, s, H5). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 152.4 (C5), δ_C 151.6 (C6), δ_C 149.5 (C1), δ_C 133.1 (C3), δ_C 122.9 (C2), δ_C 117.0 (C4), 86.8 (C7), δ_C 75.3 (C8), δ_C 3.5 (C9). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 238.9825, $C_9H_8ON_2{}^{79}Br^+$ required 238.9820, Δ ppm = 2.1 ppm.

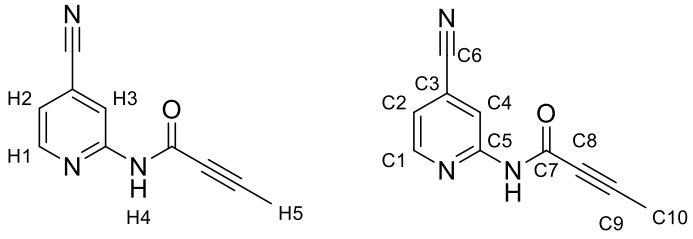
^{1}H NMR



^{13}C NMR

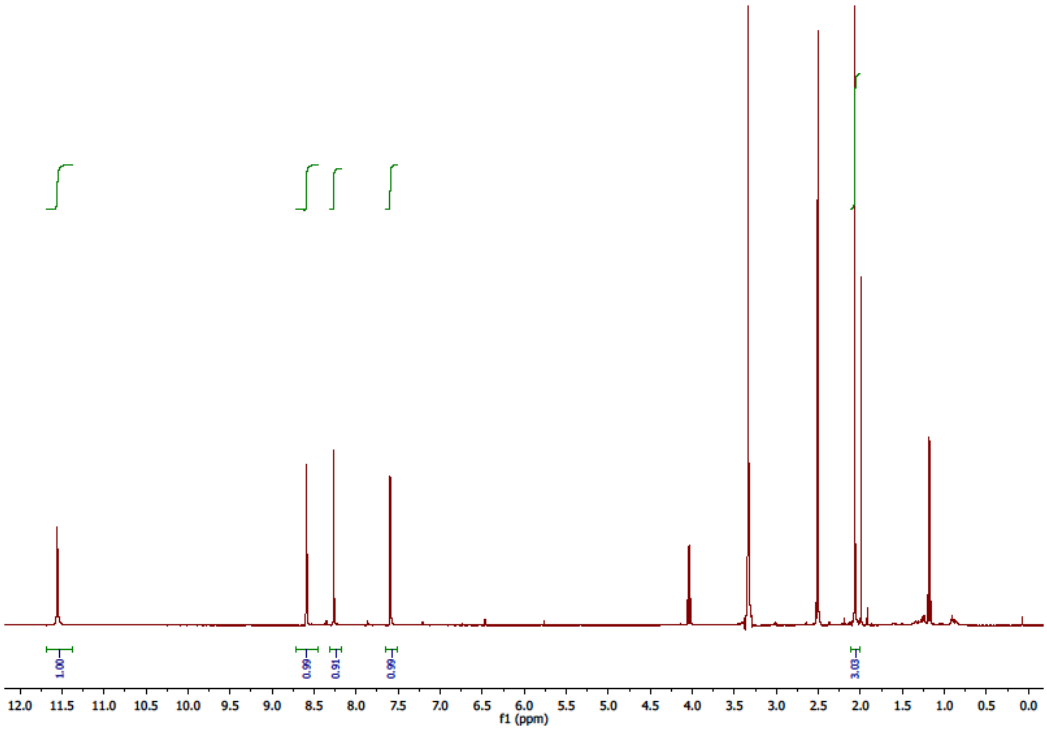


N-(4-cyanopyridin-2-yl)but-2-ynamide **(46)**

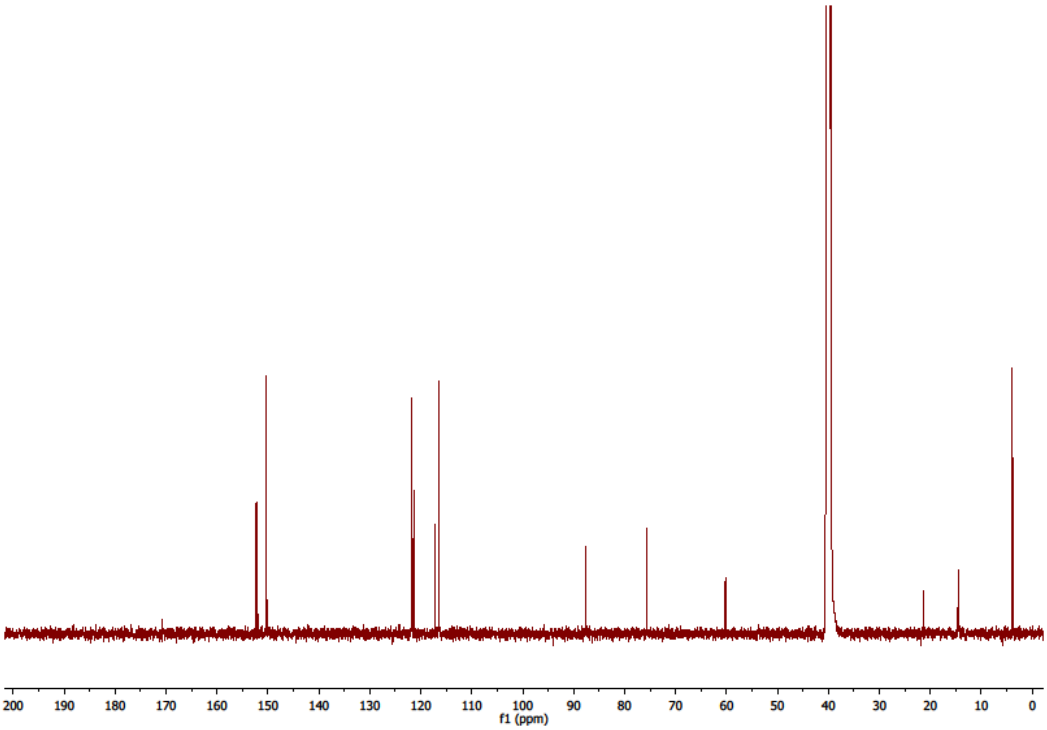


Prepared according to General Method 1 from 2-amino-4-cyanopyridine **30** (0.10 g, 0.84 mmol), LDA (1.76 mmol) and ethyl 2-butynoate **24** (0.12 mL, 1.01 mmol). The crude product was purified by column chromatography (SiO_2, 20 g, 7:3 40-60 petroleum ether: EtOAc) to yield a yellow solid (0.06 g, 0.30 mmol, 36%). R_f = 0.35 (1:1 40-60 petroleum ether: EtOAc). Mpt (CH_2Cl_2): darkens >140 ^oC, decomp. >297 ^oC. IR ν_{max}/cm^{-1} (neat): 3075 (w, br), 2230 (med, C≡C/C≡N), 1676 (str, C=O), 1600 (w, C=C), 1559 (str, C=C), 1521 (med, C=C), 1420 (str, C=C/C=N), 1293 (w), 1262 (str), 1231 (med), 1150 (med), 1067 (med). ^1H NMR (500 MHz, d^6-DMSO): δ_H 11.53 (1H, s, H4), δ_H 8.57 (1H, dd, *J* = 5.0, 0.3 Hz, H1), δ_H 8.24 (1H, s, H3), δ_H 7.57 (1H, dd, *J* = 5.0, 1.4 Hz, H2), δ_H 2.04 (3H, s, H5). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 152.1 (C7), δ_C 151.7 (C5), δ_C 149.9 (C1), δ_C 121.4 (C2), δ_C 121.0 (C3), δ_C 116.9 (C6), δ_C 116.1 (C4), δ_C 87.2 (C8), δ_C 75.2 (C9), δ_C 3.5 (C10). HRMS (FTMS ESI+) m/z found $[M+H]^+$ 186.0658, $C_{10}H_8ON_3^+$ required 186.0658, Δ ppm = -1.98 ppm.

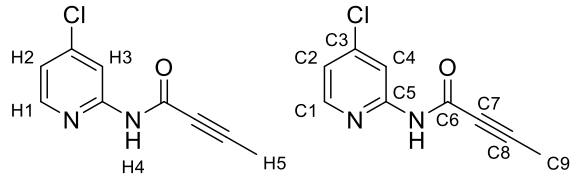
^1H NMR


1.00
0.99
0.91
0.99
3.03
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

^{13}C NMR

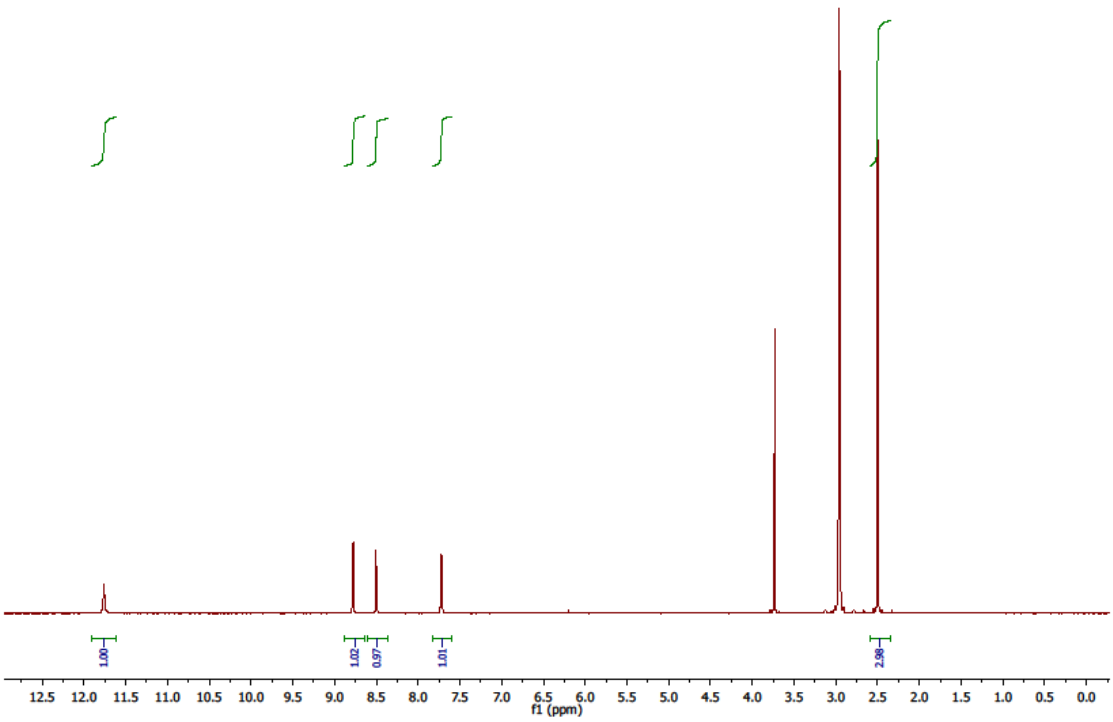

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

N-(4-chloropyridin-2-yl)but-2-ynamide **(47)**

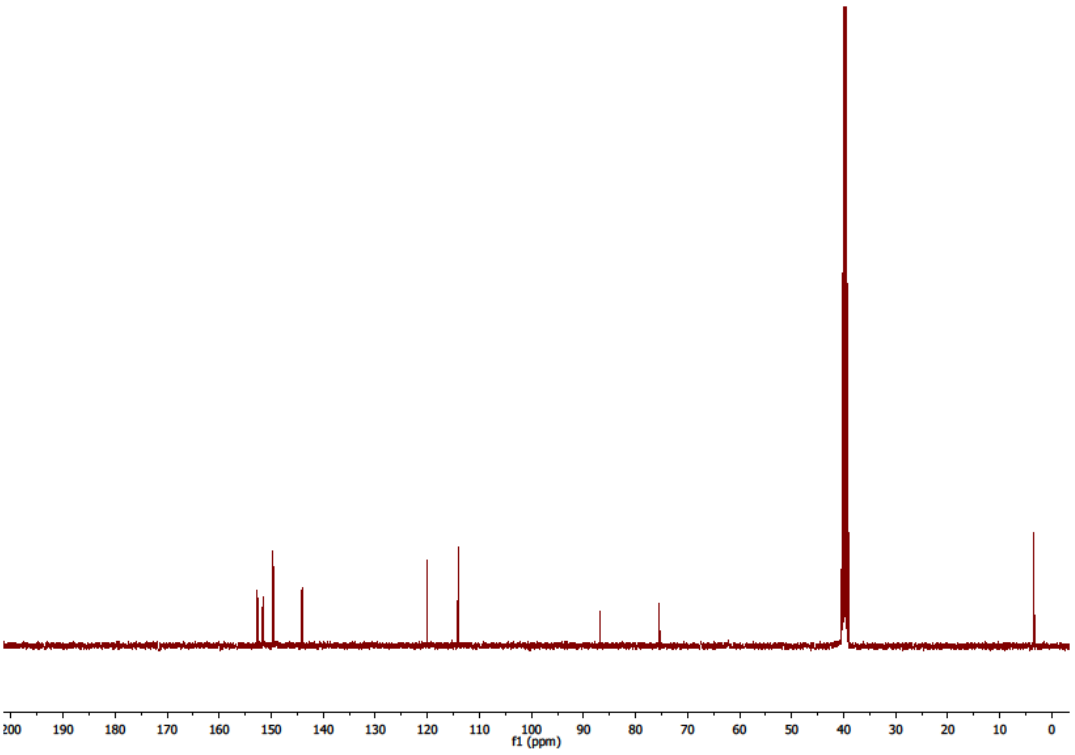


Prepared according to General Method 1 from 2-amino-4-chloropyridine **31** (1.00 g, 7.78 mmol), LDA (16.33 mmol) and ethyl 2-butynoate **24** (1.09 mL, 9.33 mmol). The crude product was purified by Combiflash Companion (SiO_2, 50 g, 0-100% EtOAc in heptane) to yield a cream solid (0.88 g, 4.52 mmol, 58%). R_f = 0.18 (3:1 heptane: EtOAc). Mpt (CH_2Cl_2): decomp 150-165 ^oC. IR ν_{max}/cm^{-1} (neat): 2983 (w, br, N-H/C-H), 2326 (w, br, C≡C), 2232 (med, C≡C), 1664 (str, C=O), 1575 (str, C=C), 1522 (str, C=C/C=N), 1406 (str), 1274 (str), 1230 (med), 1098 (med), 1071 (med). ^1H NMR (400 MHz, d^6-DMSO): δ_H 11.31 (1H, s, H4), δ_H 8.32 (1H, d, *J* = 5.4 Hz, H1), δ_H 8.05 (1H, d, *J* = 2.0 Hz, H3), δ_H 7.27 (1H, dd, *J* = 5.4, 1.9 Hz, H2), δ_H 2.04 (3H, s, H5). ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 152.7 (C5), δ_C 151.6 (C6), δ_C 149.6 (C1), δ_C 144.1 (C3), δ_C 120.0 (C2), δ_C 114.1 (C4), δ_C 86.8 (C7), δ_C 75.4 (C8), δ_C 3.9 (C9). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 195.0329, $C_9H_8N_2O^{35}Cl^+$ required 195.0325, Δ ppm = 2.1 ppm.

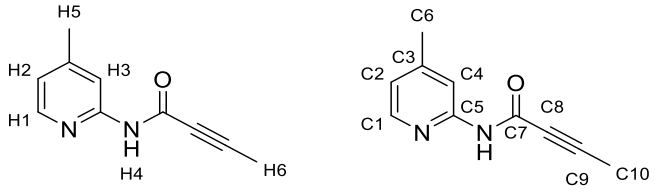
^{1}H NMR



^{13}C NMR

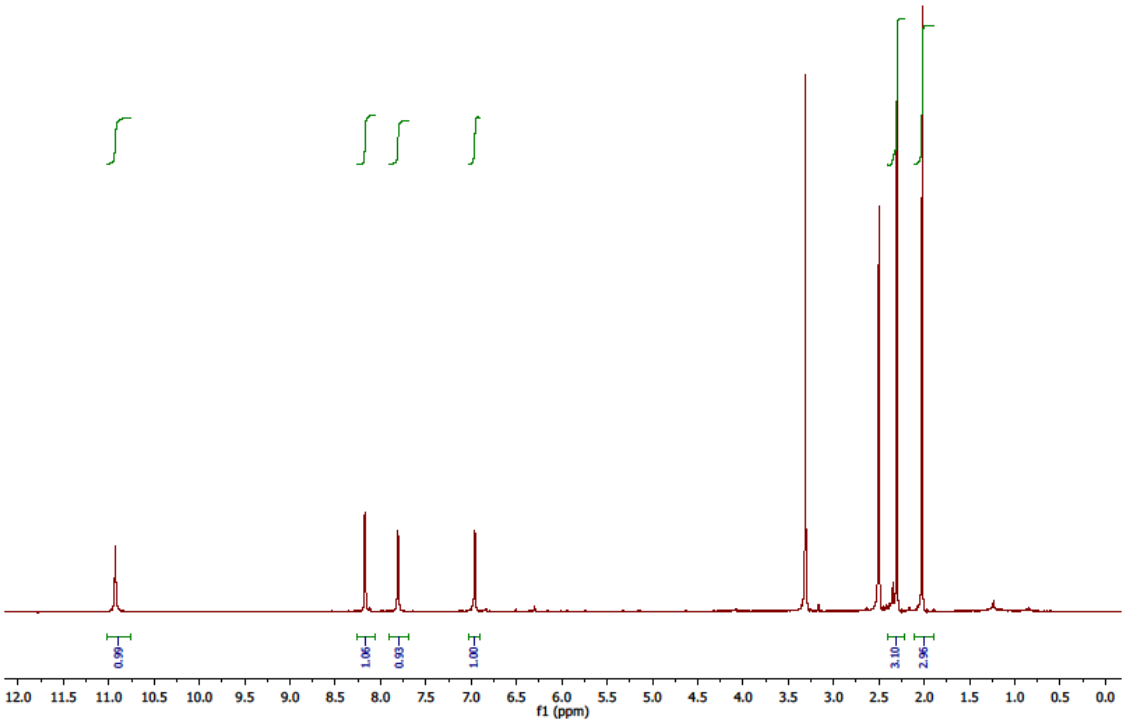


N-(4-methylpyridin-2-yl)but-2-ynamide **(48)**

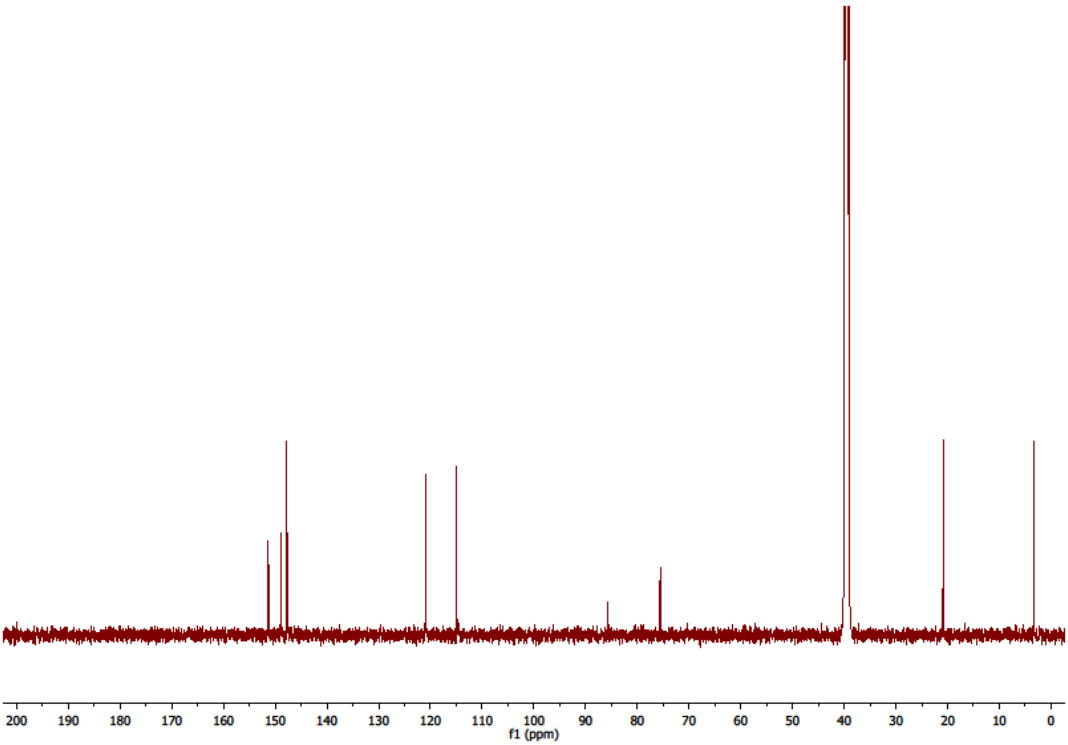


Prepared according to General Method 1 from 2-amino-4-methylpyridine **32** (1.004 g, 9.28 mmol), *n*BuLi (19.50 mmol) and ethyl 2-butynoate **24** (1.299 mL, 11.14 mmol). The crude product was purified by column chromatography (SiO_2, elution gradient 0 to 30% EtOAc in heptane) to yield a yellow solid. This was triturated with heptane to yield a yellow powder (0.624g, 39%). R_f = 0.35 (1:1 40-60 petroleum ether: EtOAc). Mpt (CH_2Cl_2): darkens >120 ^oC, melts 220-225 ^oC. IR ν_{max}/cm^{-1} (neat): 3114 (w, N-H/C-H), 2959 (w, C-H), 2917 (w, C-H), 1662 (str, C=O), 1612 (str, C=C), 1571 (str, C=C), 1533 (str, C=C/C=N), 1470 (med), 1410 (str), 1293 (str), 1284 (med), 1267 (str), 1259 (str), 1236 (str), 1166 (med), 1122 (w), 1074 (w), 1023 (w), 1000 (w). ^1H NMR (500 MHz, d^6-DMSO): δ_H 10.93 (1H, s, H4), δ_H 8.16-8.14 (1H, m, H1), δ_H 7.79 (1H, s, H3), δ_H 6.95-6.94 (1H, m, H2), δ_H 2.28 (3H, s, H5), δ_H 2.01 (3H, s, H6). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 151.5 (C7), δ_C 151.3 (C5), δ_C 149.0 (C3), δ_C 147.8 (C1), δ_C 121.0 (C2), δ_C 115.0 (C4), δ_C 85.7 (C8), δ_C 75.6 (C9), δ_C 20.9 (C6), δ_C 3.4 (C10). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 175.0859, $C_{10}H_{11}ON_2^+$ required 175.0866, Δ ppm = -4.1 ppm.

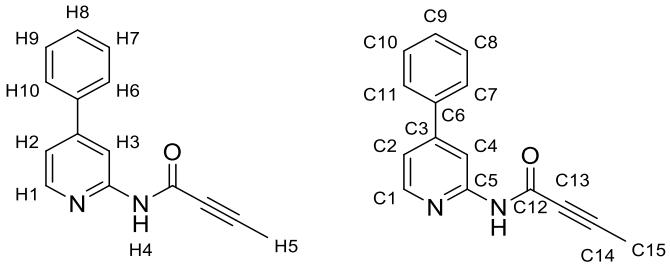
^{1}H NMR



^{13}C NMR

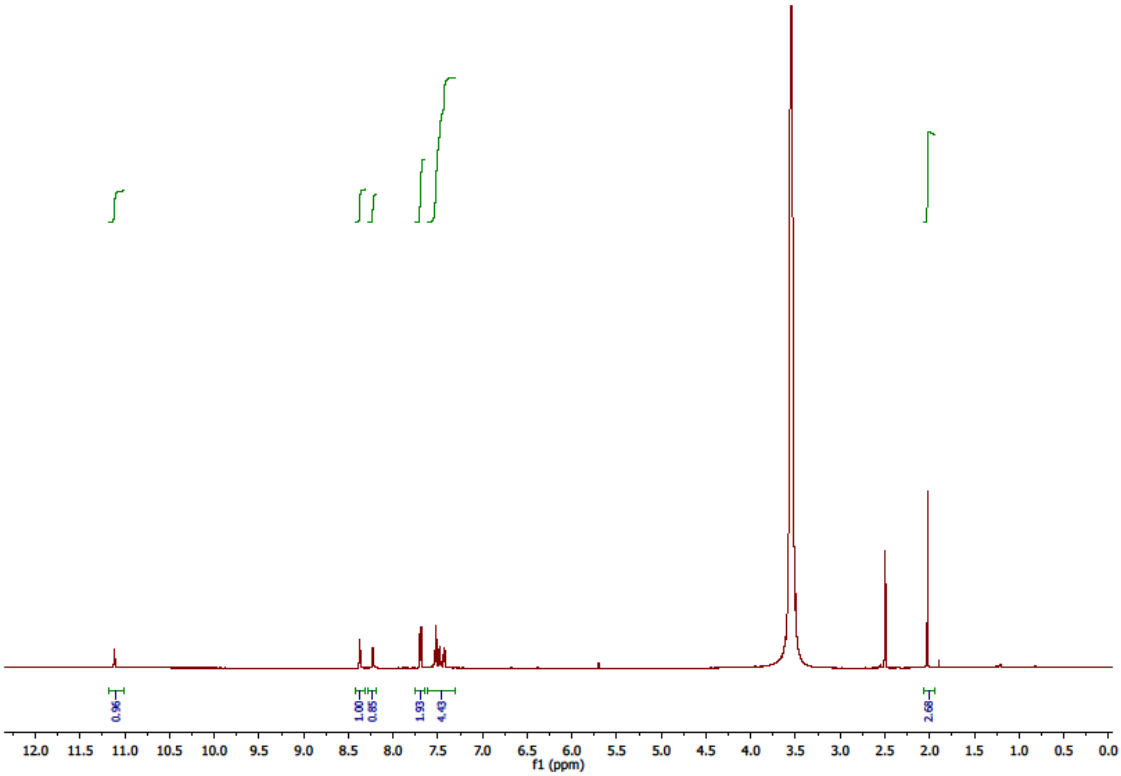


N-(4-phenylpyridin-2-yl)but-2-ynamide **(49)**

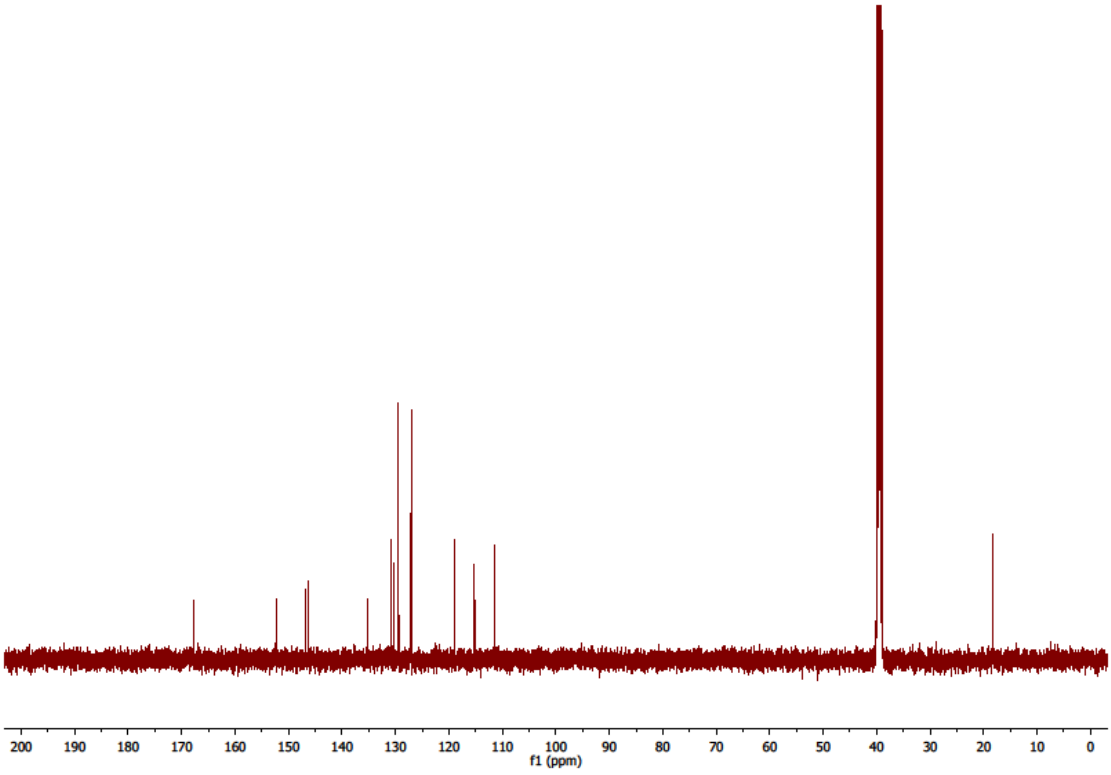


Prepared according to General Method 1 from 2-amino-4-phenylpyridine **33** (0.15 g, 0.88 mmol), ^{n}BuLi (1.85 mmol) and ethyl 2-butynoate **24** (0.12 mL, 1.06 mmol). The crude product was purified by column chromatography (SiO_2, 20 g, 3:2 40-60 petroleum ether: EtOAc) to yield a pale yellow solid (0.07 g, 0.28 mmol, 32%). R_f = 0.57 (1:1 40-60 petroleum ether: EtOAc). Mpt (CH_2Cl_2): darkens >142 ^{o}C, melts 210-213 ^{o}C. IR ν_{max}/cm^{-1} (neat): 2979 (w, br), 2357 (w, C≡C), 2343 (w, C≡C), 2229 (w, C≡C), 1663 (str, C=O), 1605 (med, C=C), 1557 (str, C=C), 1530 (med), 1493 (w), 1463 (w), 1448 (w), 1408 (str), 1318 (w), 1282 (w), 1264 (str), 1230 (med), 1074 (med). ^{1}H NMR (500 MHz, d^{6}-DMSO): δ_H 11.16 (1H, s, H4), δ_H 8.39 (1H, app dd, *J* = 5.2, 0.6 Hz, H1), δ_H 8.28-8.26 (1H, m, H3), δ_H 7.74-7.71 (2H, m, H6+H10), δ_H 7.57-7.47 (3H, m, H7+H8+H9), δ_H 7.45 (1H, dd, *J* = 5.2, 0.6 Hz, H2), δ_H 2.03 (3H, s, H5). ^{13}C NMR (125 MHz, d^{6}-DMSO): δ_C 167.5 (C12), δ_C 152.4 (C5), δ_C 149.4 (C3), δ_C 148.8 (C1), δ_C 137.5 (C6), δ_C 129.4 (C8+C10), δ_C 127.1 (C9), δ_C 126.9 (C7+C11), δ_C 117.8 (C2), δ_C 111.9 (C4), δ_C 86.0 (C13), δ_C 75.6 (C14), δ_C 3.5 (C15). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 237.1026, $C_{15}H_{13}ON_2^+$ required 237.1028, Δ ppm = -0.8 ppm.

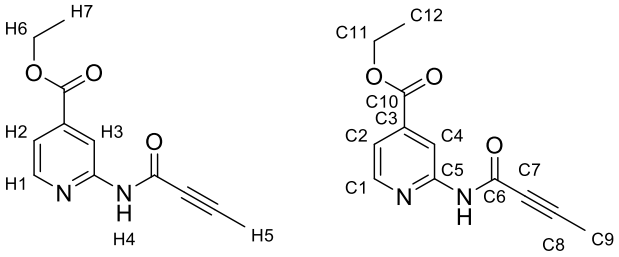
^{1}H NMR



^{13}C NMR

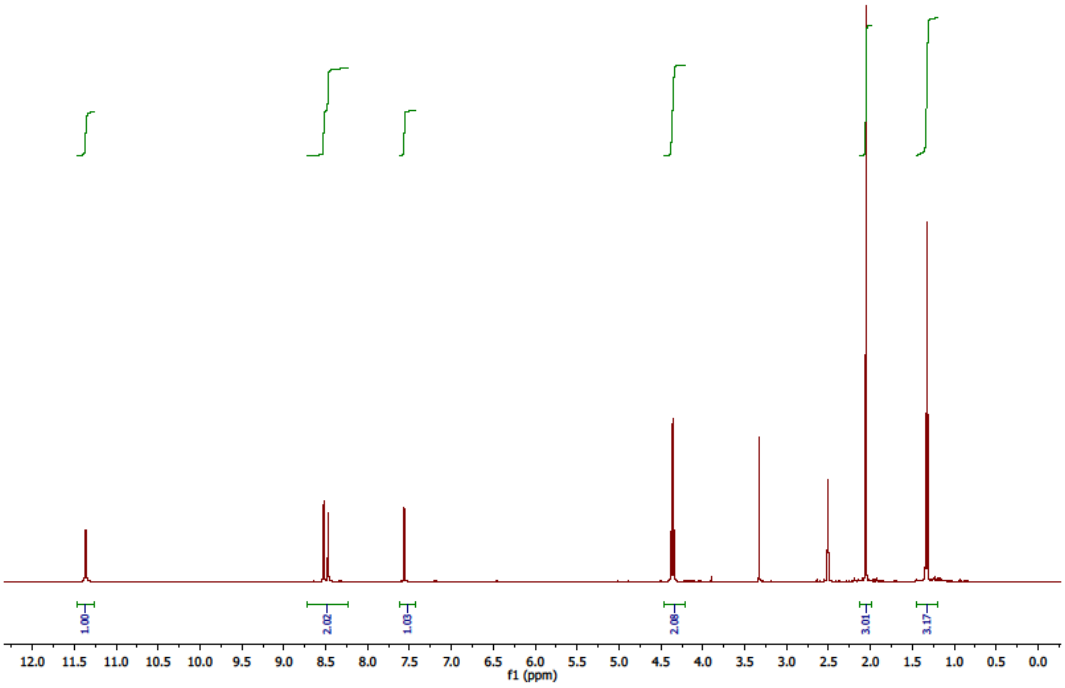


Ethyl 2-(but-2-ynamido)isonicotinate **(50)**

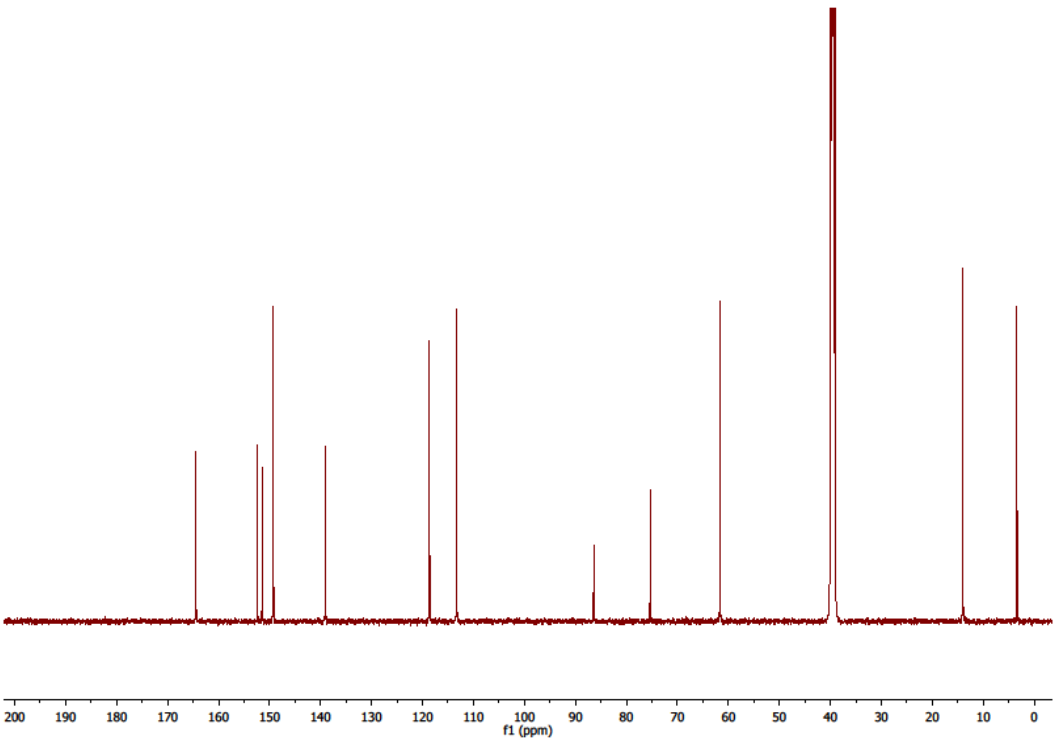


Prepared according to General Method 1 from 2-amino-isonicotinic acid ethyl ester **34**(0.10 g, 0.60 mmol), LDA (1.26 mmol) and ethyl 2-butynoate **24** (0.08 mL, 0.72 mmol). The crude product was purified by column chromatography (SiO_2, 20 g, 3:2 40-60 petroleum ether: EtOAc) to yield a yellow solid (0.04 g, 0.18 mmol, 30%). R_f = 0.44 (1:1 40-60 petroleum ether: EtOAc). Mpt (CH_2Cl_2): phase change >117 ^oC, melts 124-125 ^oC. IR ν_{max}/cm^{-1} (neat): 3161 (w, N-H), 3127 (w, C-H/N-H), 2980 (w, C-H), 2357 (w, C≡C), 1722 (str, C=O), 1665 (str, C=O), 1608 (w), 1572 (str, C=C), 1530 (str, C=C), 1461 (w), 1407 (str), 1369 (w), 1303 (w), 1287 (str), 1270 (str, C-O), 1232 (str), 1215 (str), 1173 (w), 1121 (w), 1104 (med), 1071 (med), 1016 (med). ^1H NMR (500 MHz, d^6-DMSO): δ_H 11.36 (1H, s, H4), δ_H 8.53 (1H, app dd, J = 5.1, 0.8 Hz, H1), δ_H 8.47 (1H, app s, H3), δ_H 7.56 (1H, dd, J = 5.1, 1.5 Hz, H2), δ_H 4.36 (2H, q, J = 7.1 Hz, H6), δ_H 2.05 (3H, s, H5), δ_H 1.33 (3H, t, J = 7.1 Hz, H7). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 164.5 (C10), δ_C 152.5 (C5), δ_C 151.5 (C6), δ_C 149.3 (C1), δ_C 139.2 (C3), δ_C 118.7 (C2), δ_C 113.4 (C4), 86.5 (C7), δ_C 75.4 (C8), δ_C 61.7 (C11), δ_C 14.1 (C12), δ_C 3.5 (C9). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 233.0936, $C_{12}H_{13}O_3N_2^+$ required 233.0926, Δ ppm = 4.3 ppm.

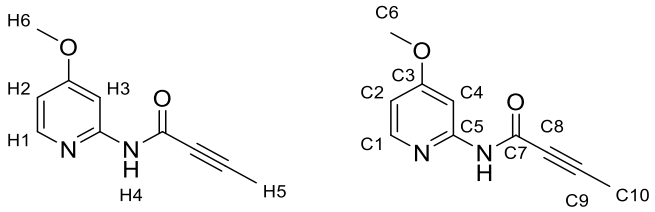
^{1}H NMR



^{13}C NMR

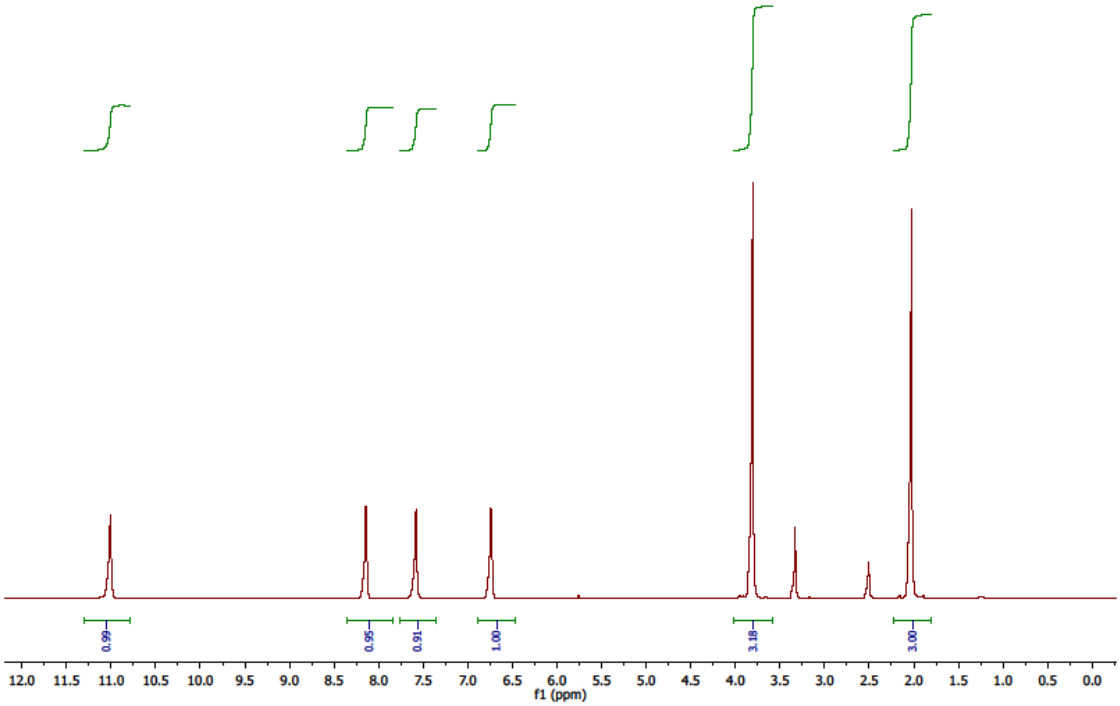


N-(4-Methoxypyridin-2-yl)but-2-ynamide **(51)**

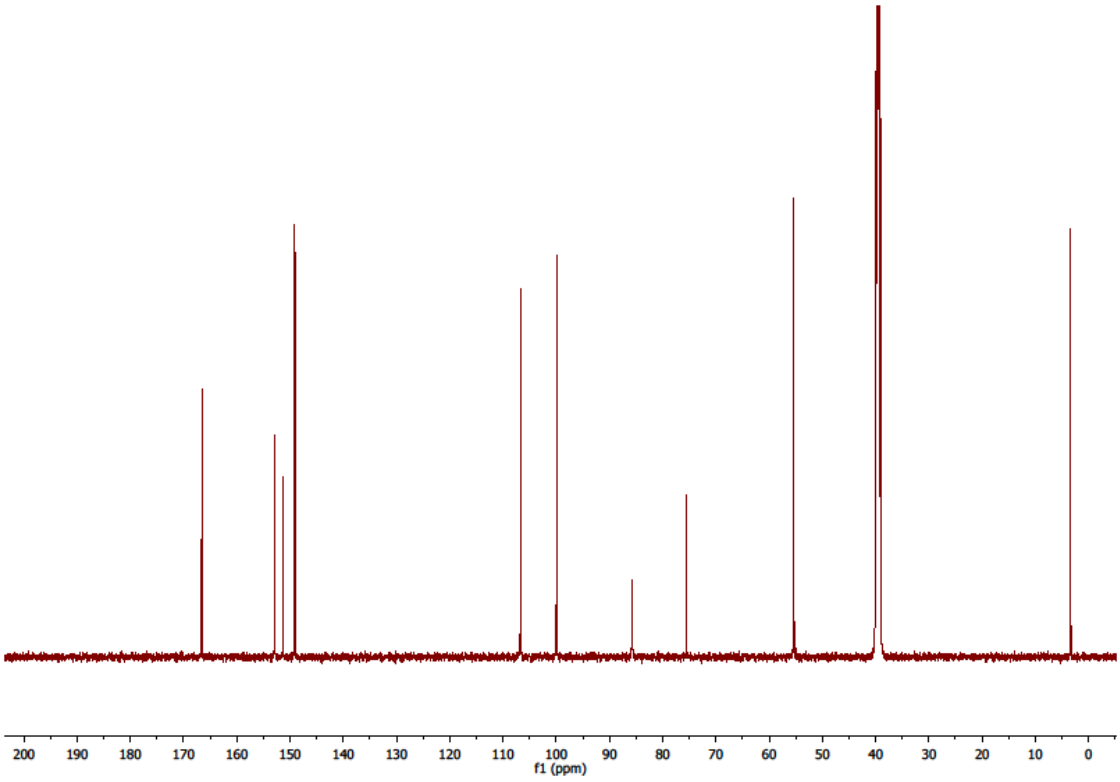


Prepared according to General Method 1 from 2-amino-4-methoxypyridine **35** (0.30 g, 2.42 mmol), ^{n}BuLi (5.07 mmol) and ethyl 2-butynoate **24** (0.34 mL, 2.90 mmol). The crude product was purified by column chromatography (SiO_2, 20 g, 3:2 then 1:1 40-60 petroleum ether: EtOAc) to yield a beige solid (0.15 g, 0.81 mmol, 34%). R_f = 0.28 (1:1 40-60 petroleum ether: EtOAc). Mpt (CH_2Cl_2): darkens >140 ^{o}C, melts 149-150 ^{o}C. IR ν_{max}/cm^{-1} (neat): 3117 (w, N-H/C-H), 2980 (w, C-H), 2230 (w, C≡C), 1655 (str, C=O), 1577 (str, C=C), 1533 (str, C=C), 1472 (w), 1452 (med), 1426 (med), 1311 (med), 1297 (w), 1279 (str), 1250 (str), 1196 (str), 1164 (str), 1133 (w), 1046 (str). ^{1}H NMR (500 MHz, d^{6}-DMSO): δ_H 10.99 (1H, s, H4), δ_H 8.12 (1H, d, *J* = 5.8 Hz, H1), δ_H 7.56 (1H, app s, H3), δ_H 6.72 (1H, dd, *J* = 5.8, 2.4 Hz, H2), δ_H 3.78 (3H, s, H6), δ_H 2.01 (3H, s, H5). ^{13}C NMR (125 MHz, d^{6}-DMSO): δ_C 167.1 (C3), δ_C 153.4 (C5), δ_C 151.8 (C7), δ_C 149.6 (C1), δ_C 107.2 (C2), δ_C 100.4 (C4), δ_C 86.2 (C8), δ_C 76.0 (C9), δ_C 55.8 (C6), δ_C 3.8 (C10). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 191.0824, $C_{10}H_{11}O_2N_2^+$ required 191.0815, Δ ppm = 4.8 ppm.

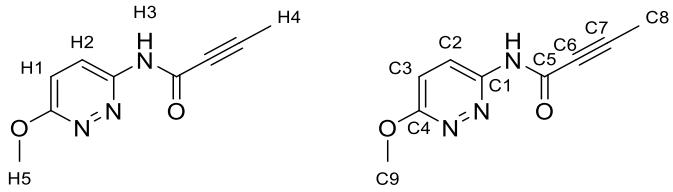
^{1}H NMR



^{13}C NMR



N-(6-Methoxypyridazin-3-yl)but-2-ynamide **(52)**



Prepared according to General Method 1 from 6-methoxypyridazin-3-amine **36** (150 mg, 1.20 mmol), *n*BuLi (2.52 mmol) and ethyl 2-butynoate **24** (0.168 mL, 1.44 mmol). Note – solvent should be evaporated at ambient temperature to avoid cyclisation. The crude product was purified by column chromatography (SiO_2, elution gradient 0 to 50% EtOAc in heptane) to yield an off-white solid solid (150 mg, 60%). R_f = 0.23 (1:1 EtOAc: heptane). Mpt (CH_2Cl_2): decomp. >110 ^oC. IR ν_{max}/cm^{-1} (neat): 3038 (m), 2942 (w, C-H), 2238 (w, C≡C), 1645 (str, C=O), 1603 (w), 1562 (w), 1504 (str), 1457 (med), 1408 (w), 1392 (str), 1340 (w), 1321 (w), 1305 (str), 1269 (med), 1251 (med), 1227 (med), 1210 (str), 1139 (w), 1112 (w), 1071 (w), 1051 (w), 1006 (str). ^1H NMR (400 MHz, d^6-DMSO): δ_H 11.41 (1H, s, H3), δ_H 8.07 (1H, d, *J* = 9.5 Hz, H2), δ_H 7.22 (1H, d, *J* = 9.5 Hz, H1), δ_H 3.98 (3H, s, H5), δ_H 2.03 (3H, s, H4). ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 167.3, 151.4, 150.1, 135.2, 123.7, 118.6, 113.6, 54.9, 54.3, 17.4, 3.3. HRMS (TOF ES+) *m/z* found $[M+H]^+$ 192.0776, $C_9H_{10}N_3O_2^+$ required 192.0773, Δ ppm = 1.6 ppm.

AstraZeneca

Name thomas alanine
M No kgbw666
Notebook Ref en07919–63–1
proton.az DMSO /opt/topspin2.1 chem 12

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EXPNO                120
PROCNO                 1
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Time                11.20
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PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    32
DS                     0
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ             3.9584243 sec
RG                  1024
DW                60.400 usec
DE                 6.00 usec
TE                303.1 K
D1            3.00000000 sec
TD0                    1

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P1                 11.00 usec
PL1                -2.00 dB
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SI                 32768
SF           400.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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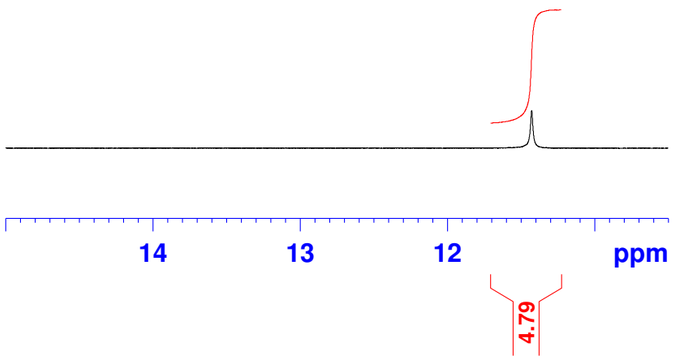
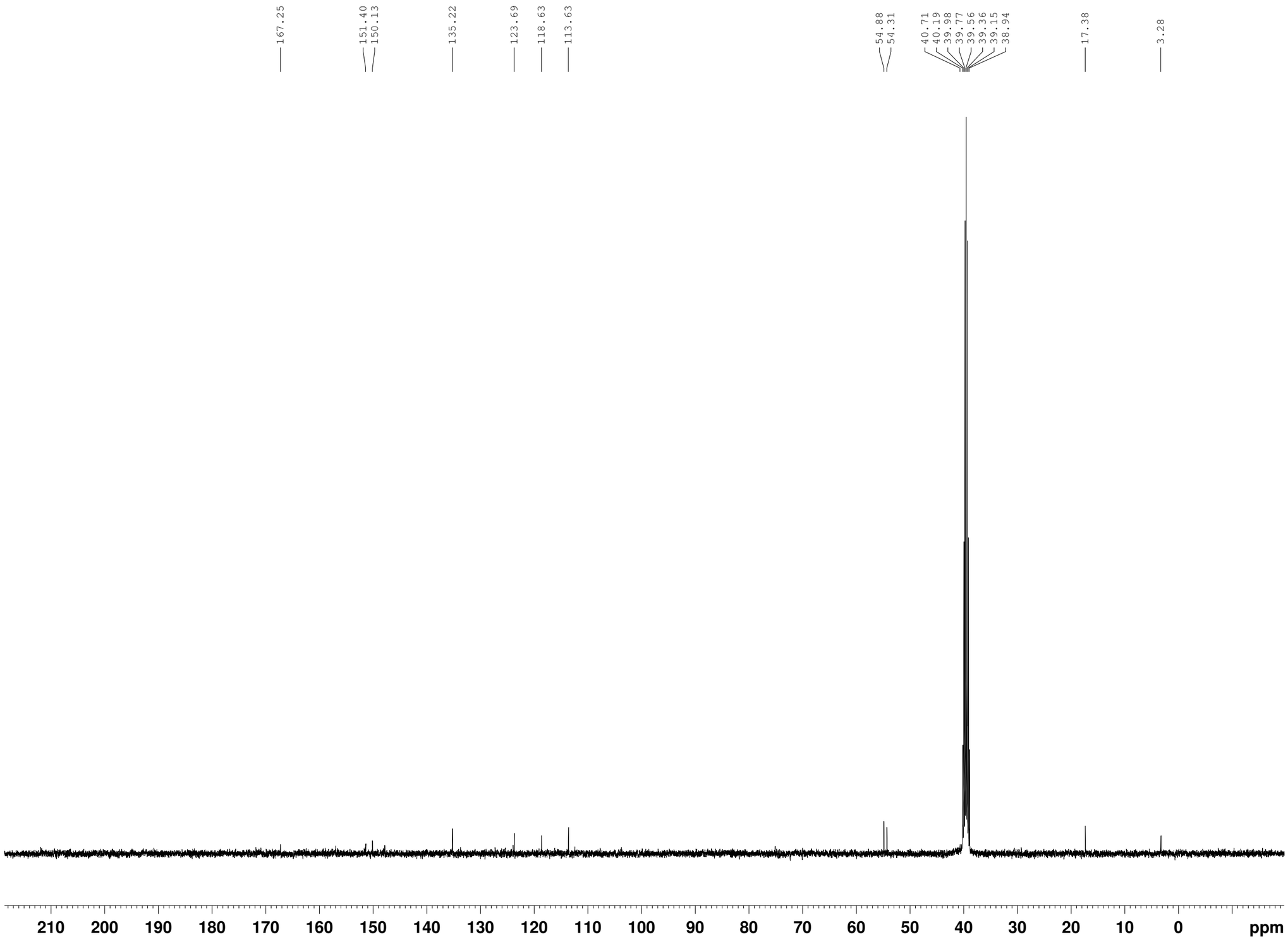


Signed By:–

Name thomas alanine
M No kgbw666
Notebook Ref en07919-63-1
carbon.az DMSO /opt/topspin2.1 chem 12



AstraZeneca

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AQ	1.3664756 sec
RG	23170.5
DW	20.850 use
DE	20.00 use
TE	303.1 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
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P1	11.00 use
PL1	3.70 dB
SFO1	100.6228298 MHz
======== CHANNEL f2 =======	
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NUC2	1H
PCPD2	95.00 use
PL2	-2.00 dB
PL12	15.00 dB
PL13	16.00 dB
SFO2	400.1316005 MHz
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SSB	0
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GB	0
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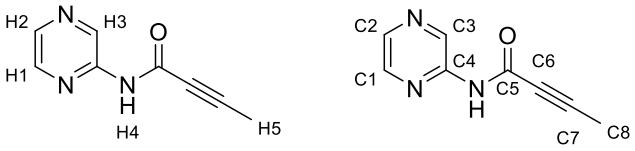
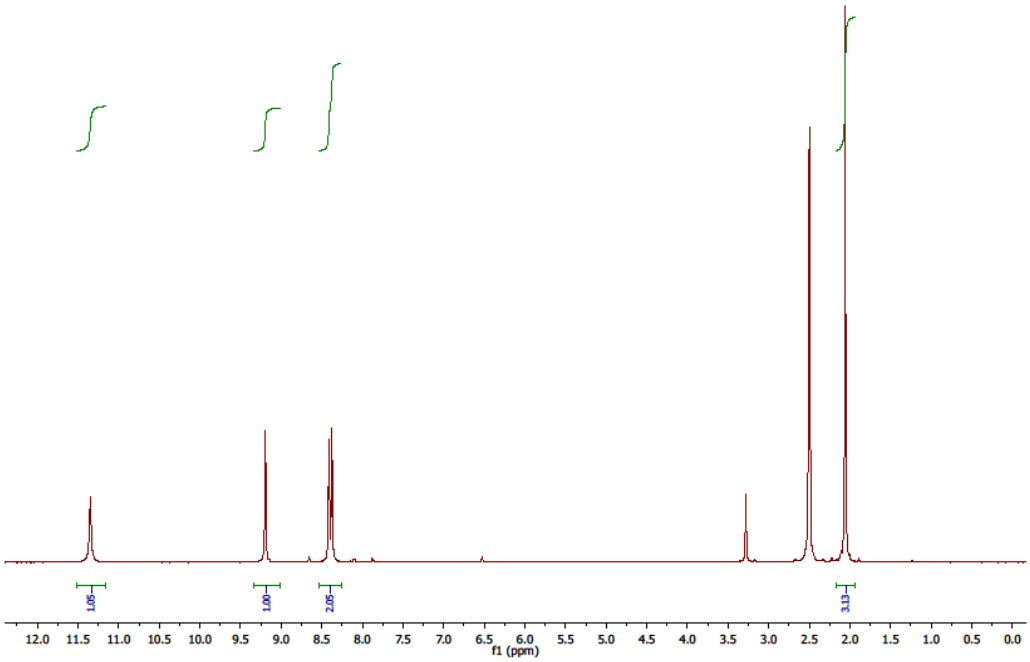
N-(Pyrazin-2-yl)but-2-ynamide **(53)**

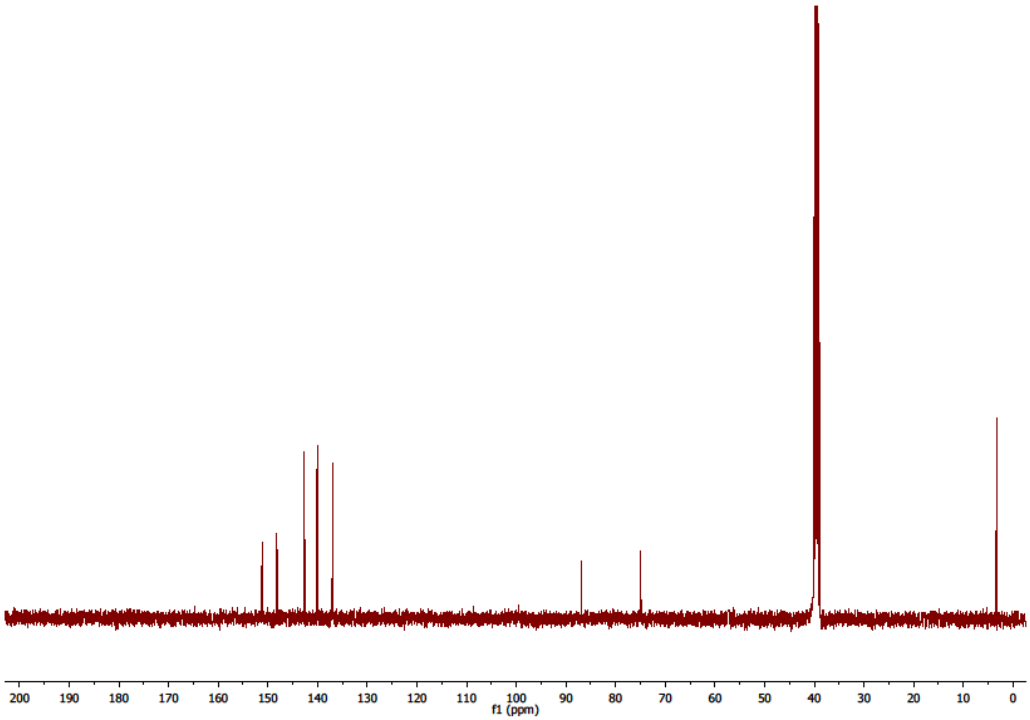


Prepared according to General Method 1 from aminopyrazine **37** (0.10 g, 1.05 mmol), ^{n}BuLi (2.21 mmol) and ethyl 2-butynoate **24** (0.15 mL, 1.26 mmol). The crude product was purified by Combiflash Companion (SiO_2, 12 g, 0-50% EtOAc in heptane) to yield a white solid (0.13 g, 0.79 mmol, 75%). R_f = 0.27 (1:1 heptane: EtOAc). Mpt (H_2O/MeCN): decomp. >150 ^{o}C. IR ν_{max}/cm^{-1} (neat): 3210 (med, br, N-H/C-H), 2238 (med, C≡C), 1667 (str, C=O), 1594 (w), 1551 (w), 1528 (w), 1488 (med, C=N), 1417 (str), 1344 (med), 1296 (w), 1257 (med), 1199 (med), 1143 (w), 1120 (med), 1077 (w), 1049 (w), 1013 (w). ^{1}H NMR (400 MHz, d^{6}-DMSO): δ_H 11.35 (1H, s, H4), δ_H 9.19 (1H, s, H3), δ_H 8.41 (1H, s, H1 or H2), δ_H 8.38 (1H, s, H1 or H2), δ_H 2.06 (3H, s, H5). ^{13}C NMR (100 MHz, d^{6}-DMSO): δ_C 151.2 (C4 or C5), δ_C 147.8 (C4 or C5), δ_C 142.6 (C1 or C2), δ_C 140.1 (C1 or C2), δ_C 137.0 (C3), δ_C 87.0 (C6), δ_C 75.0 (C7), δ_C 3.3 (C8). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 162.0672, $C_8H_8N_3O^+$ required 162.0667, Δ ppm = 3.1 ppm.

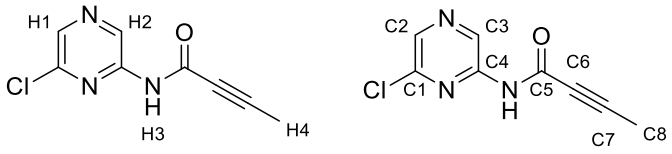
^{1}H NMR



^{13}C NMR

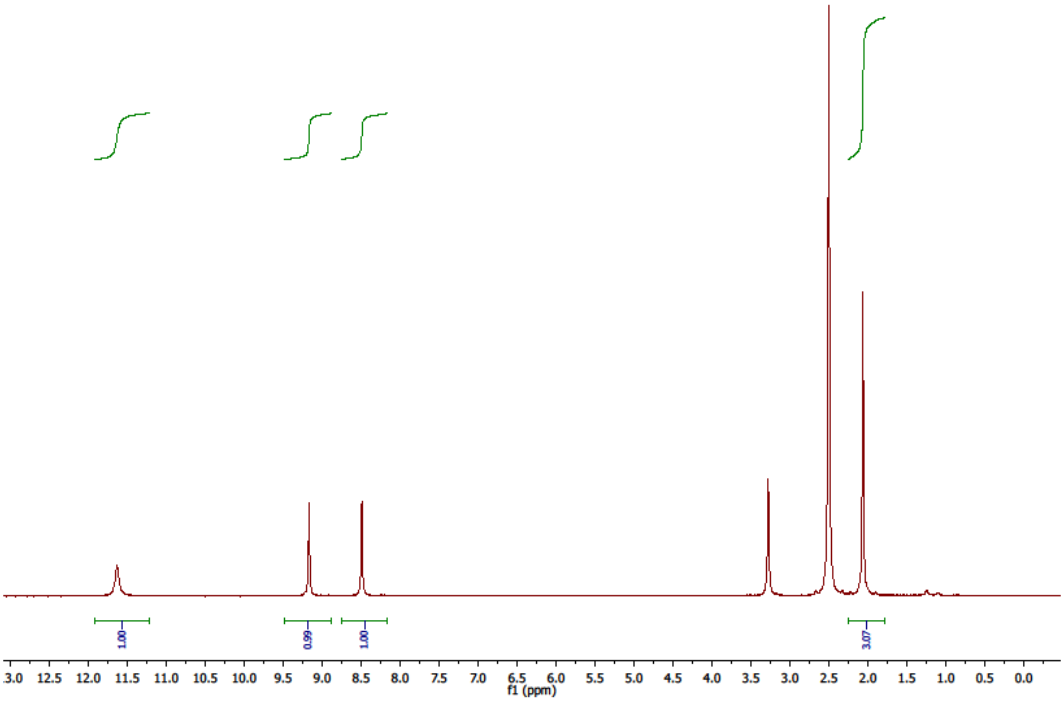


N-(6-Chloropyrazin-2-yl)but-2-ynamide **(54)**

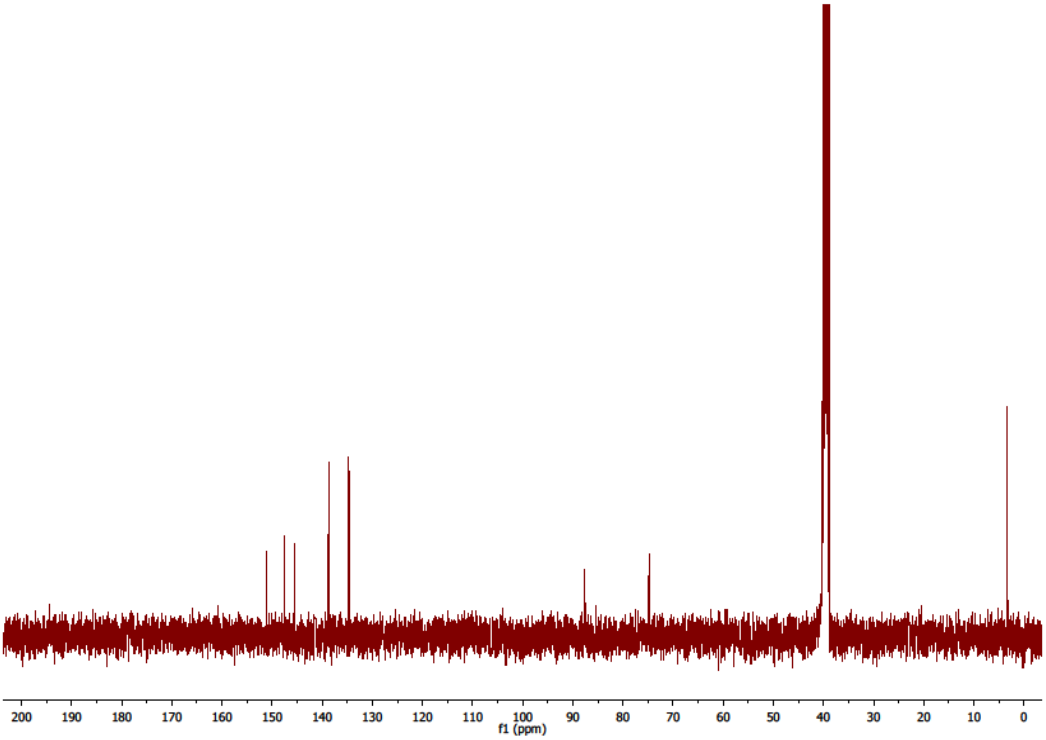


Prepared according to General Method 1 from 2-amino-6-chloropyrazine **38** (0.19 g, 1.43 mmol), LDA (3.00 mmol) and ethyl 2-butynoate **24** (0.20 mL, 1.72 mmol). The crude product was purified by Combiflash Companion (SiO_2, 12 g, 0-50% EtOAc in heptane) to yield orange flakes (0.12 g, 0.59 mmol, 41%). R_f = 0.71 (1:1 heptane: EtOAc). Mpt (H_2O/MeCN): phase change >150 ^oC, then melted 185-187 ^oC. IR ν_{max}/cm^{-1} (neat): 3207 (med, N-H), 2968 (med, C-H), 2236 (med, C≡C), 1668 (str, C=O), 1582 (w), 1556 (w), 1527 (w), 1486 (w), 1416 (str), 1398 (str), 1344 (med), 1297 (w), 1258 (med), 1198 (med), 1145 (w), 1120 (med), 1077 (w), 1047 (w), 1003 (w). ^1H NMR (400 MHz, d^6-DMSO): δ_H 11.63 (1H, s, H3), δ_H 9.17 (1H, s, H2), δ_H 8.49 (1H, s, H1), δ_H 2.06 (3H, s, H4). ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 151.1 (C4 or C5), δ_C 147.5 (C4 or C5), δ_C 145.4 (C1), δ_C 138.6 (C3), δ_C 134.7 (C2), δ_C 87.7 (C6), δ_C 74.8 (C7), δ_C 3.3 (C8). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 196.0279, $C_8H_7N_3O^{35}Cl^+$ required 196.0278, Δ ppm = 0.5 ppm.

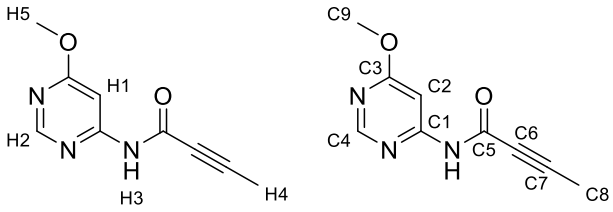
^{1}H NMR



^{13}C NMR

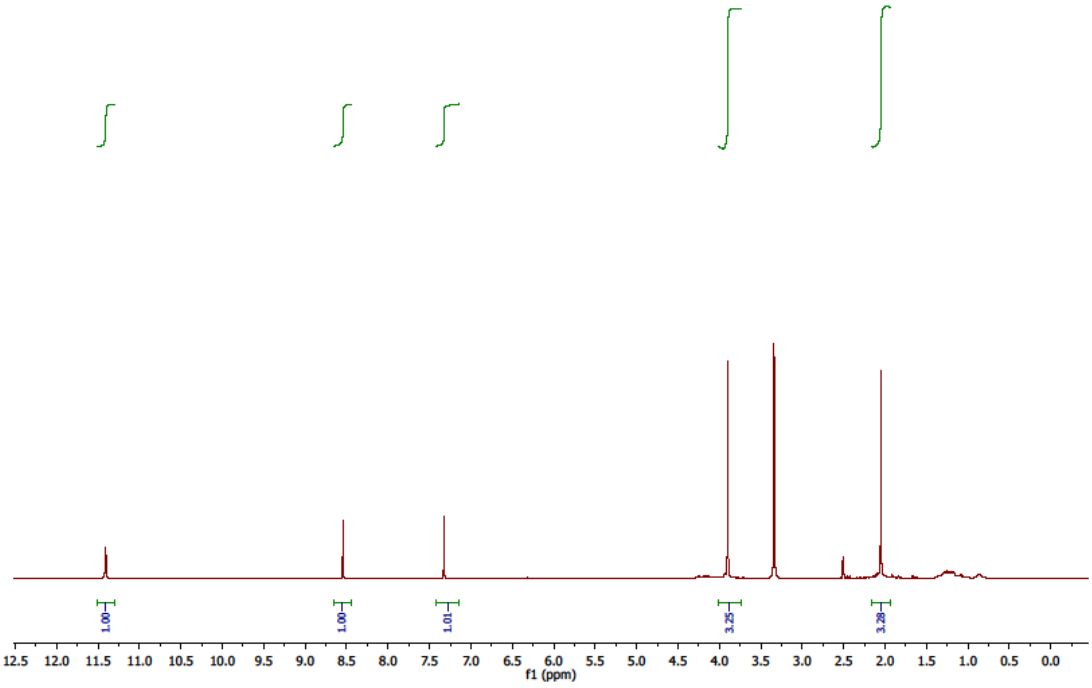


N-(6-Methoxypyrimidin-4-yl)but-2-ynamide **(55)**

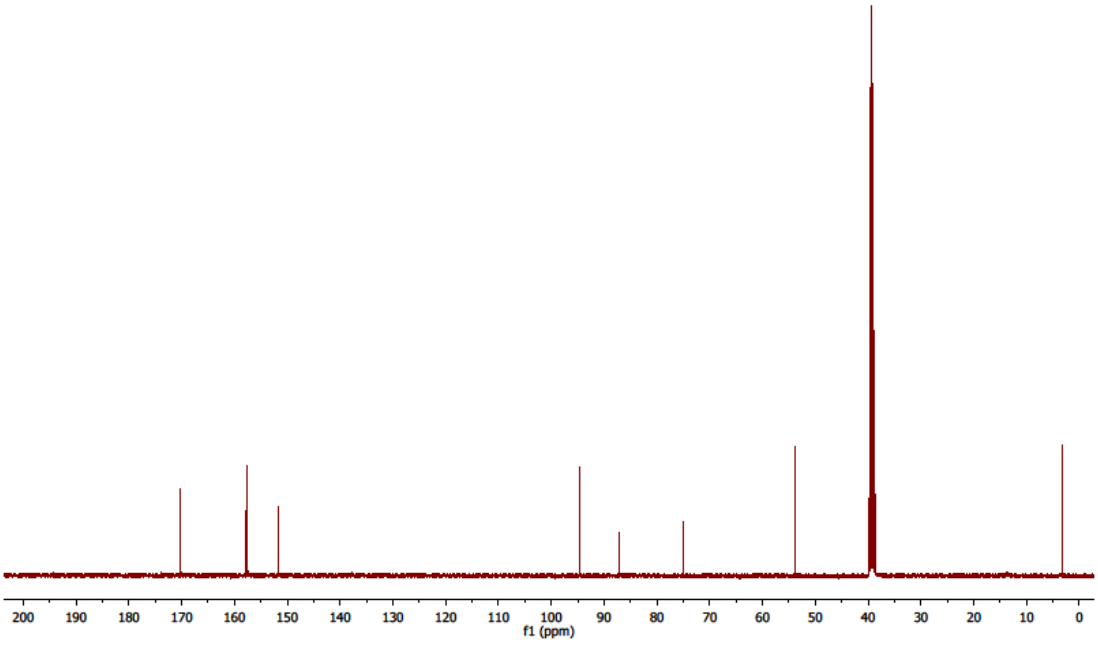


Prepared according to General Method 1 from 6-methoxypyrimidin-4-amine **39** (0.30 g, 2.40 mmol), *n*BuLi (5.03 mmol) and ethyl 2-butynoate **24** (0.34 mL, 2.88 mmol). The crude product was purified by column chromatography (SiO_2, 30 g, 7:3 40-60 petroleum ether: EtOAc) to yield a pale brown solid (0.24 g, 1.36 mmol, 53%). R_f = 0.47 (1:1 40-60 petroleum ether: EtOAc). Mpt (CH_2Cl_2): darkens >170 ^oC, decomp. >220 ^oC. IR ν_{max}/cm^{-1} (neat): 3362 (w, br, N-H), 3203 (w, N-H), 3004 (w, C-H), 2228 (w, C≡C), 1677 (str, C=O), 1603 (med, C=C), 1570 (str, C=C), 1511 (str), 1482 (str, C=C/C=N), 1397 (str, C-O), 1329 (w), 1301 (w), 1262 (str), 1226 (med), 1193 (str), 1170 (med), 1073 (w), 1036 (med). ^1H NMR (400 MHz, d^6-DMSO): δ_H 11.41 (1H, s, H3), δ_H 8.54 (1H, s, H2), δ_H 7.32 (1H, s, H1), δ_H 3.90 (3H, s, H5), δ_H 2.05 (3H, s, H4). ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 170.2 (C3), δ_C 157.9 (C1), δ_C 157.5 (C4), δ_C 151.8 (C5), δ_C 94.6 (C2), δ_C 87.1 (C6), δ_C 74.9 (C7), δ_C 53.8 (C9), δ_C 3.5 (C8). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 192.0766, $C_9H_{10}O_2N_3^+$ required 192.0768, Δ ppm = -0.9 ppm.

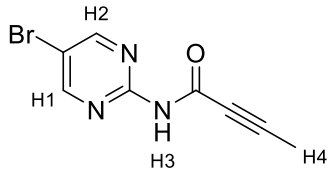
^1H NMR

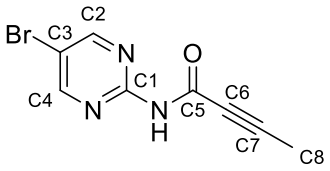

1.00
1.00
1.01
3.25
3.28
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

^{13}C NMR


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

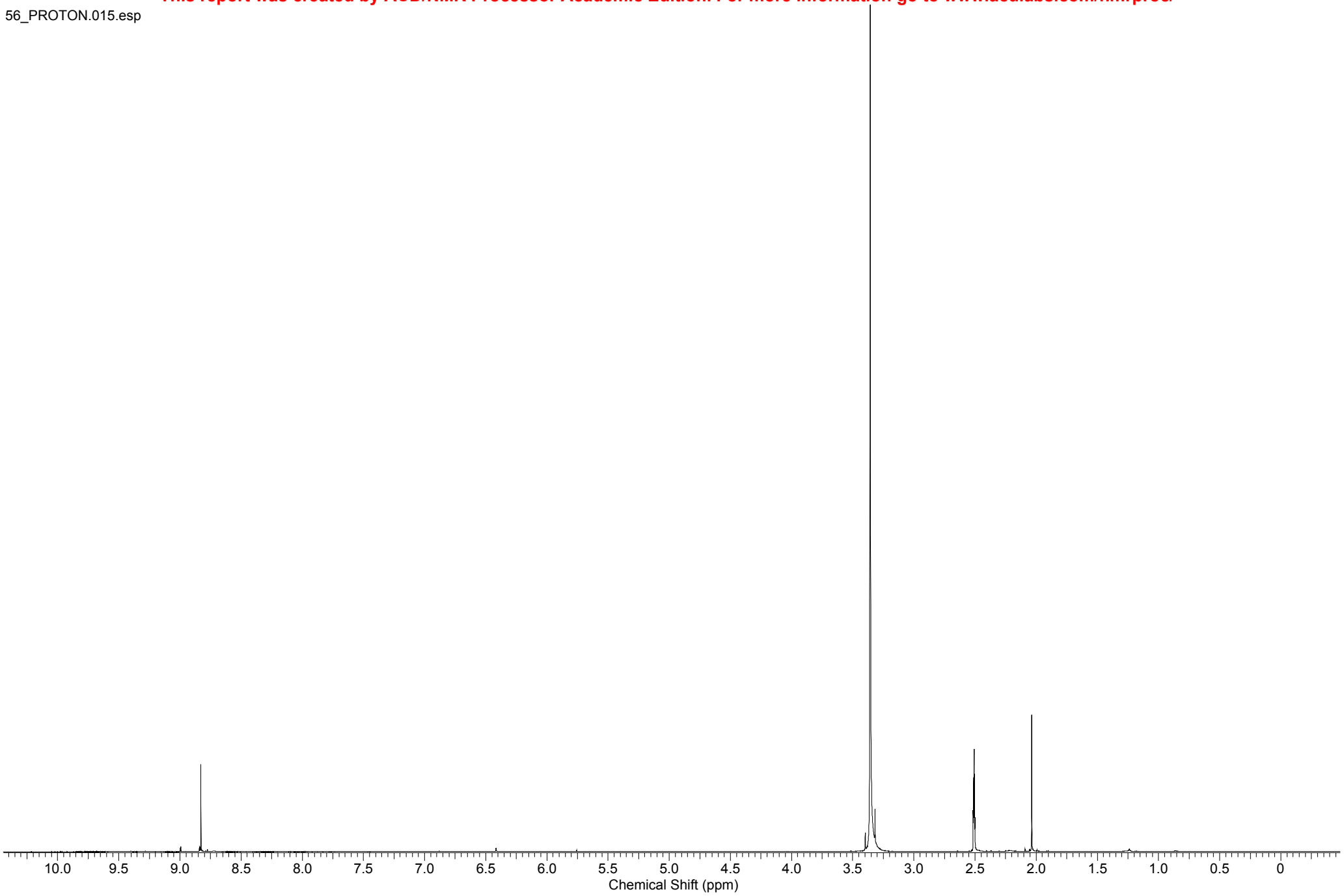
N-(5-Bromopyrimidin-2-yl)but-2-ynamide **(56)**



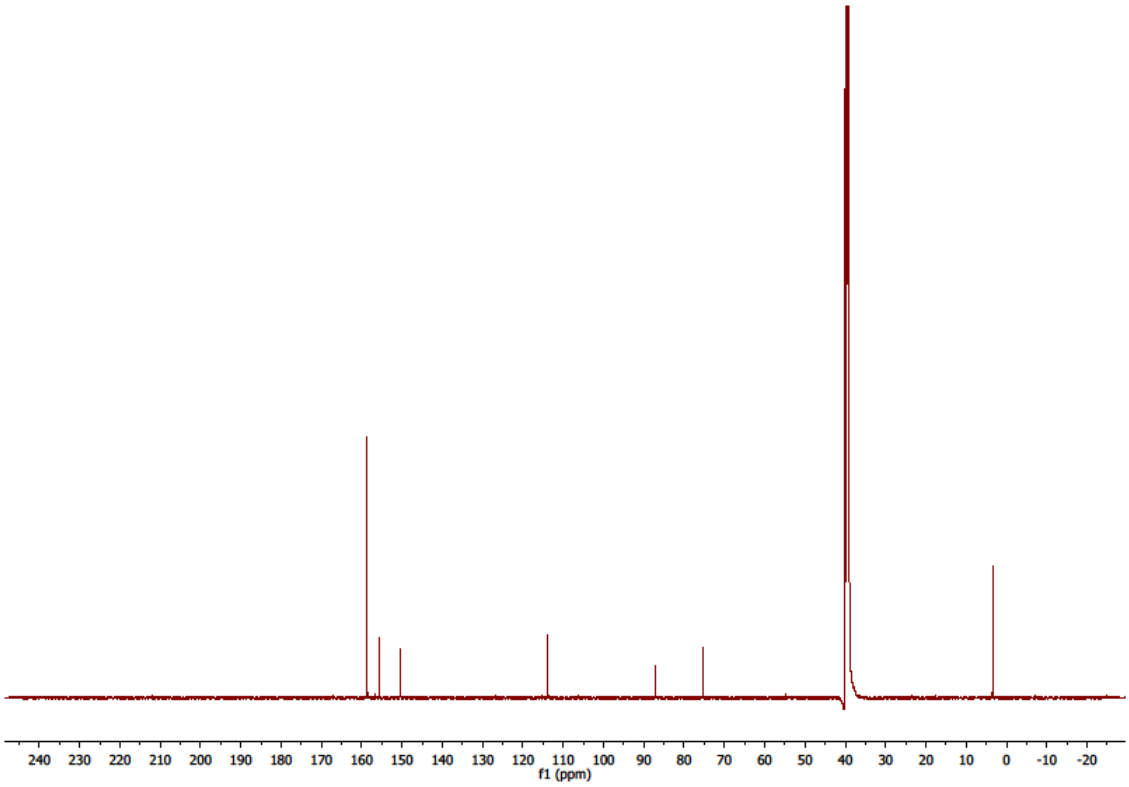


Prepared according to General Method 1 from 2-amino-5-bromopyrimidine **40** (0.10 g, 0.58 mmol), ^{n}BuLi (1.21 mmol) and ethyl 2-butynoate **24** (0.08 mL, 0.69 mmol). The crude product was purified by column chromatography (SiO_2, 20 g, 1:1 40-60 petroleum ether: EtOAc) to yield a beige solid wax (0.09 g, 94% purity with CH_2Cl_2, 0.33 mmol, 58%). Further purification by preparative HPLC yielded spectroscopically pure material. R_f = 0.41 (1:1 40-60 petroleum ether: EtOAc). Mpt (CH_2Cl_2): darkens >130-147 ^{o}C, melts 152-155 ^{o}C. IR ν_{max}/cm^{-1} (neat): 3220 (w, N-H), 3151 (w, C-H/N-H), 3071 (w, C-H), 2915 (w, C-H), 2227 (w, C≡C), 1684 (str, C=O), 1583 (med, C=C), 1560 (med, C=C), 1491 (str, C=C/C=N), 1455 (w), 1428 (str), 1373 (str), 1329 (med), 1266 (med), 1234 (str), 1167 (med), 1124 (med), 1067 (med), 1025 (w), 1007 (w). ^{1}H NMR (500 MHz, d^{6}-DMSO): δ_H 11.35 (1H, s, H3), δ_H 8.81 (2H, s, H1+H2), δ_H 2.02 (3H, s, H4). ^{13}C NMR (125 MHz, d^{6}-DMSO): δ_C 158.8 (C2+C4), δ_C 155.8 (C1), δ_C 150.6 (C5), δ_C 113.9 (C3), δ_C 87.2 (C6), δ_C 75.5 (C7), δ_C 3.5 (C8). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 239.9768, $C_8H_7ON_3{}^{79}Br^+$ required 239.9772, Δ ppm = -1.7 ppm.

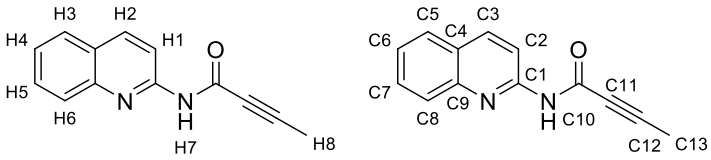
56_PROTON.015.esp



^{13}C NMR

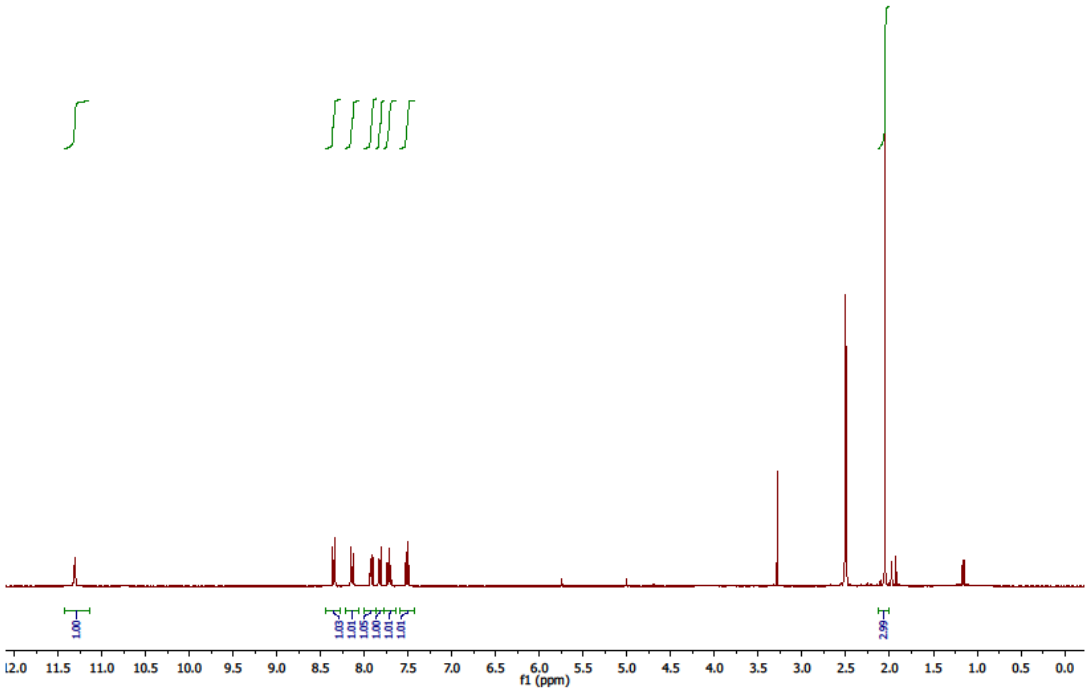

240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

N-(Quinolin-2-yl)but-2-ynamide **(57)**

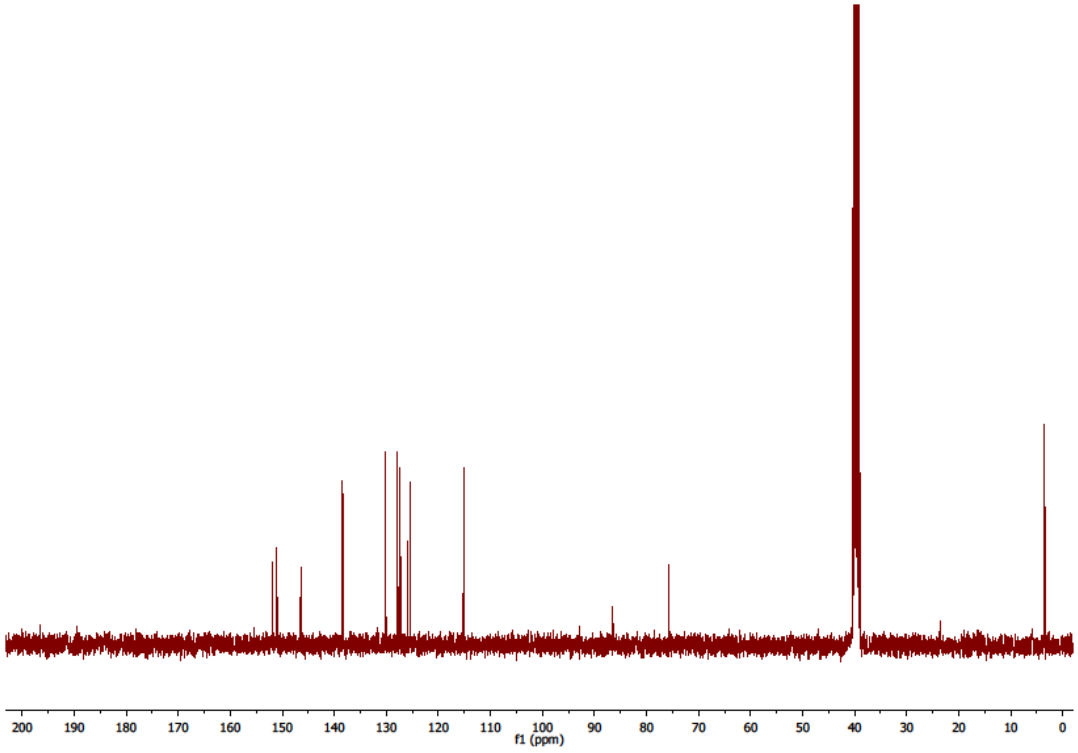


Prepared according to General Method 1 from 2-aminoquinoline **41** (0.21 g, 1.43 mmol), LDA (3.00 mmol) and ethyl 2-butynoate **24** (0.20 mL, 1.72 mmol). The crude product was purified by Combiflash Companion (SiO_2, 12 g, 0-25% EtOAc in heptane) to yield an ochre solid (0.22 g, 1.06 mmol, 74%). R_f = 0.50 (1:1 EtOAc: heptane). Mpt (CH_2Cl_2): phase change >100 ^oC then melted 157-159 ^oC. IR ν_{max}/cm^{-1} (neat): 3127 (w) 2941 (w, br, C-H), 2238 (w, C≡C), 1671 (str, C=O), 1618 (w), 1594 (str, C=C), 1577 (str, C=C), 1548 (w), 1526 (med), 1499 (str), 1425 (str), 1381 (w), 1320 (str), 1291 (str), 1264 (str), 1249 (str), 1237 (str), 1157 (w), 1146 (w), 1121 (str), 1087 (w), 1017 (w). ^1H NMR (400 MHz, d^6-DMSO): δ_H 11.31 (1H, s, H7), δ_H 8.35 (1H, d, *J* = 9.0 Hz, H2), δ_H 8.14 (1H, d, *J* = 9.0 Hz, H1), δ_H 7.92 (1H, dd, *J* = 8.1, 1.1 Hz, H3 or H6), δ_H 7.83-7.81 (1H, m, H3 or H6), δ_H 7.72 (1H, ddd, *J* = 8.4, 6.9, 1.5 Hz, H5), δ_H 7.51 (1H, ddd, *J* = 8.1, 6.9, 1.2, H4), δ_H 2.05 (3H, s, H8). ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 151.9 (C1 or C10), δ_C 151.1 (C1 or C10), δ_C 146.4 (C3), δ_C 138.4 (C9), δ_C 130.2 (C7), δ_C 127.9 (C5 or C8), δ_C 127.3 (C5 or C8), δ_C 125.9 (C4), δ_C 125.4 (C6), δ_C 115.1 (C2), δ_C 86.5 (C11), δ_C 75.7 (C12), δ_C 3.5 (C13). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 211.0859, $C_{13}H_{11}N_2O^+$ required 211.0866, Δ ppm = -3.1 ppm.

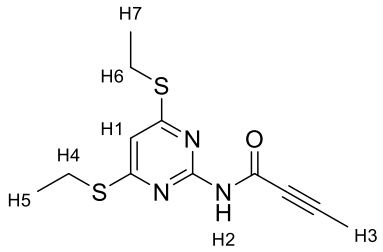
^{1}H NMR

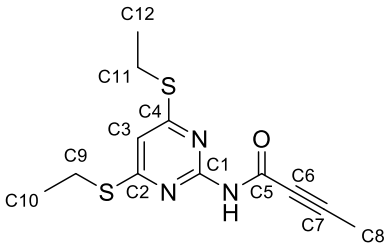


^{13}C NMR



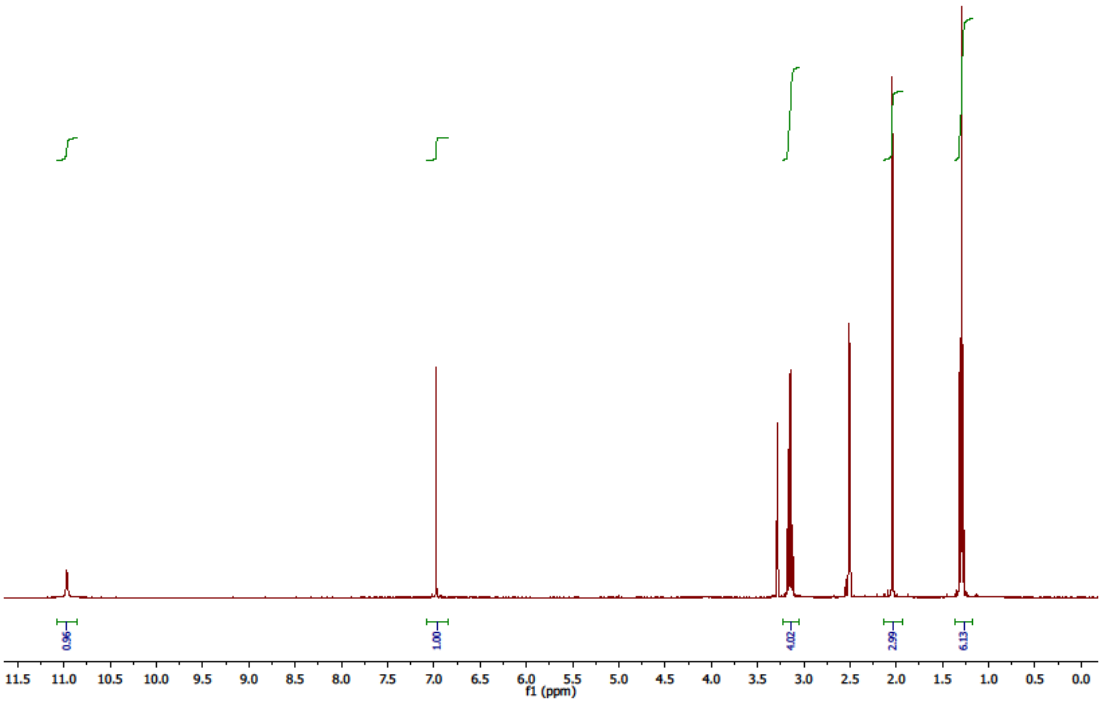
N-(4,6-bis(ethylthio)pyrimidin-2-yl)but-2-ynamide **(58)**



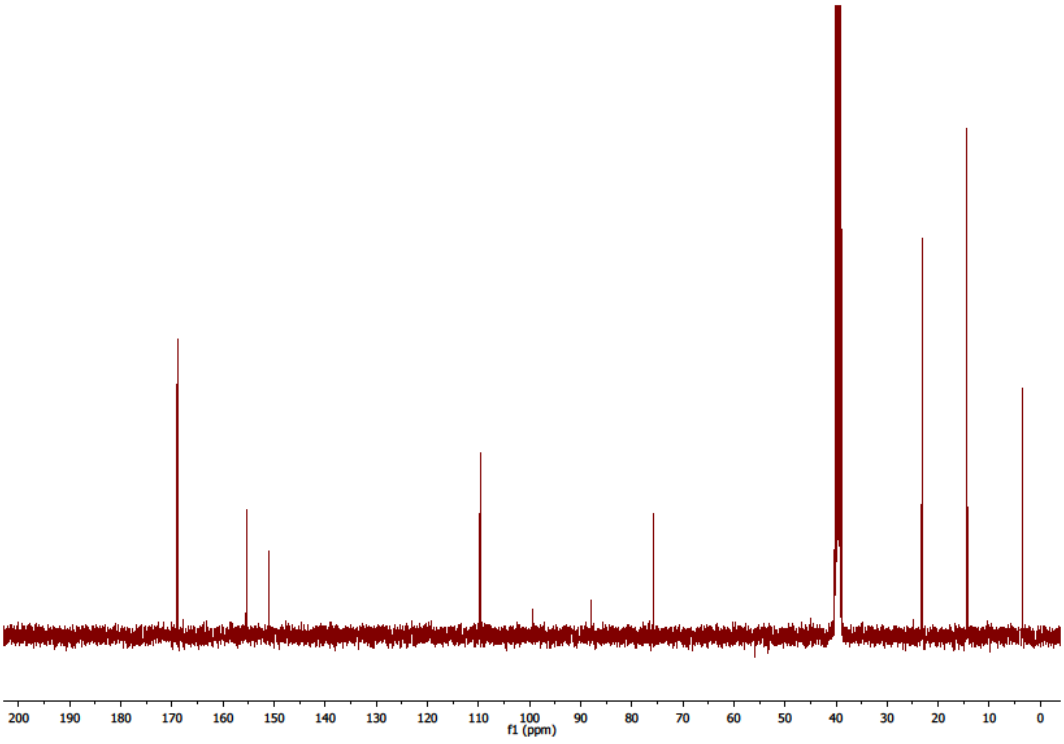


Prepared according to General Method 1 from 2-amino-4,6-bis(ethylthio)pyrimidine **42** (0.31 g, 1.43 mmol), LDA (3.00 mmol) and ethyl 2-butynoate **24** (0.20 mL, 1.72 mmol). The crude product was purified by Combiflash Companion (SiO_2, 24 g, 0-50% EtOAc in heptane) to yield a red gum (0.12 g, 0.44 mmol, 31%). R_f = 0.28 (3:1 heptane: EtOAc). IR ν_{max}/cm^{-1} (neat): 3284 (w), 3181 (w), 3100 (w), 3036 (w), 2966 (w, C-H), 2925 (w, C-H), 2864 (w, C-H), 2236 (med, C≡C), 1650 (str, C=O), 1554 (str, C=C), 1515 (str, C=C), 1494 (str, C=C), 1454 (w), 1427 (med), 1398 (w), 1377 (w), 1341 (str), 1330 (str), 1261 (str), 1229 (str), 1109 (str), 1082 (str), 1002 (w). ^{1}H NMR (400 MHz, d^6-DMSO): δ_H 10.97 (1H, s, H2), δ_H 6.97 (1H, s, H1), δ_H 3.15 (4H, q, *J* = 7.3 Hz, H4+H6), δ_H 2.04 (3H, s, H3), δ_H 1.29 (6H, t, *J* = 7.3 Hz, H5+H7). ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 168.9 (C2+C4), δ_C 155.4 (C1), δ_C 150.9 (C5), δ_C 109.7 (C3), δ_C 87.9 (C6), δ_C 75.6 (C7), δ_C 23.1 (C9+C11), δ_C 14.4 (C10+C12), δ_C 3.5 (C8). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 282.0740, $C_{12}H_{16}ON_3S_2^+$ required 282.0735, Δ ppm = 1.8 ppm.

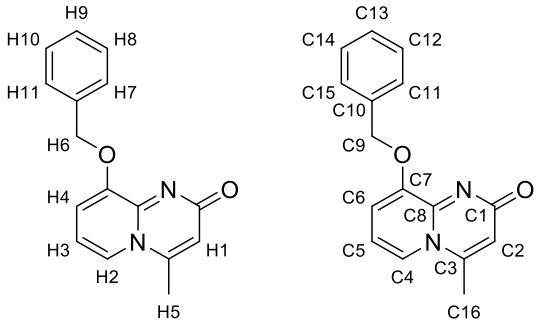
^{1}H NMR



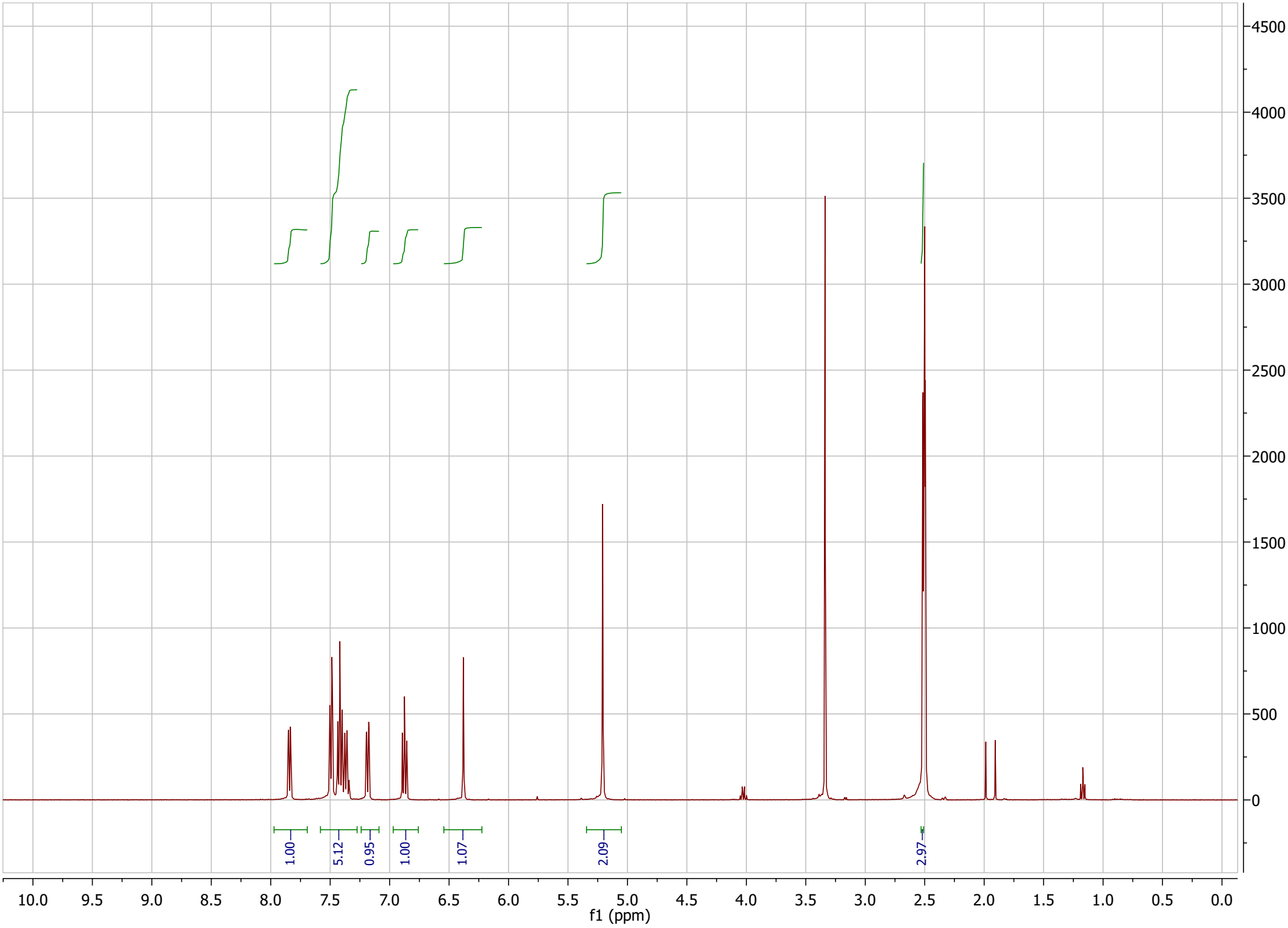
^{13}C NMR



9-(Benzyloxy)-4-methyl-2*H*-pyrido[1,2-a]pyrimidin-2-one **(62)**



Prepared according to General Method 1 from 2-amino-3-benzyloxypyridine **59** (700 mg, 3.50 mmol), *n*BuLi (7.34 mmol) and ethyl 2-butynoate **24** (0.489 mL, 4.20 mmol). The crude product was purified by column chromatography (SiO_2, elution gradient 0 to 100% EtOAc in heptane, followed by a second column, elution gradient 0 to 10% MeOH in CH_2Cl_2) to yield a sticky cream foam (320 mg, 34%). R_f = 0.58 (8:2 CH_2Cl_2:MeOH). IR ν_{max}/cm^{-1} (neat): 3479 (w), 3347 (w), 3262 (w), 3085 (w), 3034 (w, C-H), 2916 (w, C-H), 2871 (w, C-H), 1640 (str, C=O), 1588 (w), 1560 (str), 1470 (str), 1451 (str), 1435 (str), 1392 (med), 1374 (str), 1290 (w), 1268 (str), 1218 (w), 1198 (med), 1163 (str), 1098 (w), 1041 (med), 1015 (str). ^{1}H NMR (400 MHz, d^6-DMSO): δ_H 7.94-7.79 (1H, m, H2), δ_H 7.56-7.45 (2H, m, H7+H11), δ_H 7.45-7.39 (2H, m), δ_H 7.39-7.33 (1H, m), δ_H 7.23-7.09 (1H, m), δ_H 6.87 (1H, t, *J* = 7.4 Hz), δ_H 6.47-6.34 (1H, m), δ_H 5.21 (2H, s, H6), δ_H 2.51 (3H, s, H5). ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 168.8, 148.1, 146.9, 146.6, 136.1, 128.4, 128.1, 127.9, 121.9, 115.2, 112.4, 111.4, 70.3, 18.9. HRMS (TOF ES+) *m/z* found $[M+H]^+$ 267.1135, $C_{16}H_{15}N_2O_2^+$ required 267.1134, Δ ppm = 0.4 ppm.


4500
4000
3500
3000
2500
2000
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1000
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1.00
5.12
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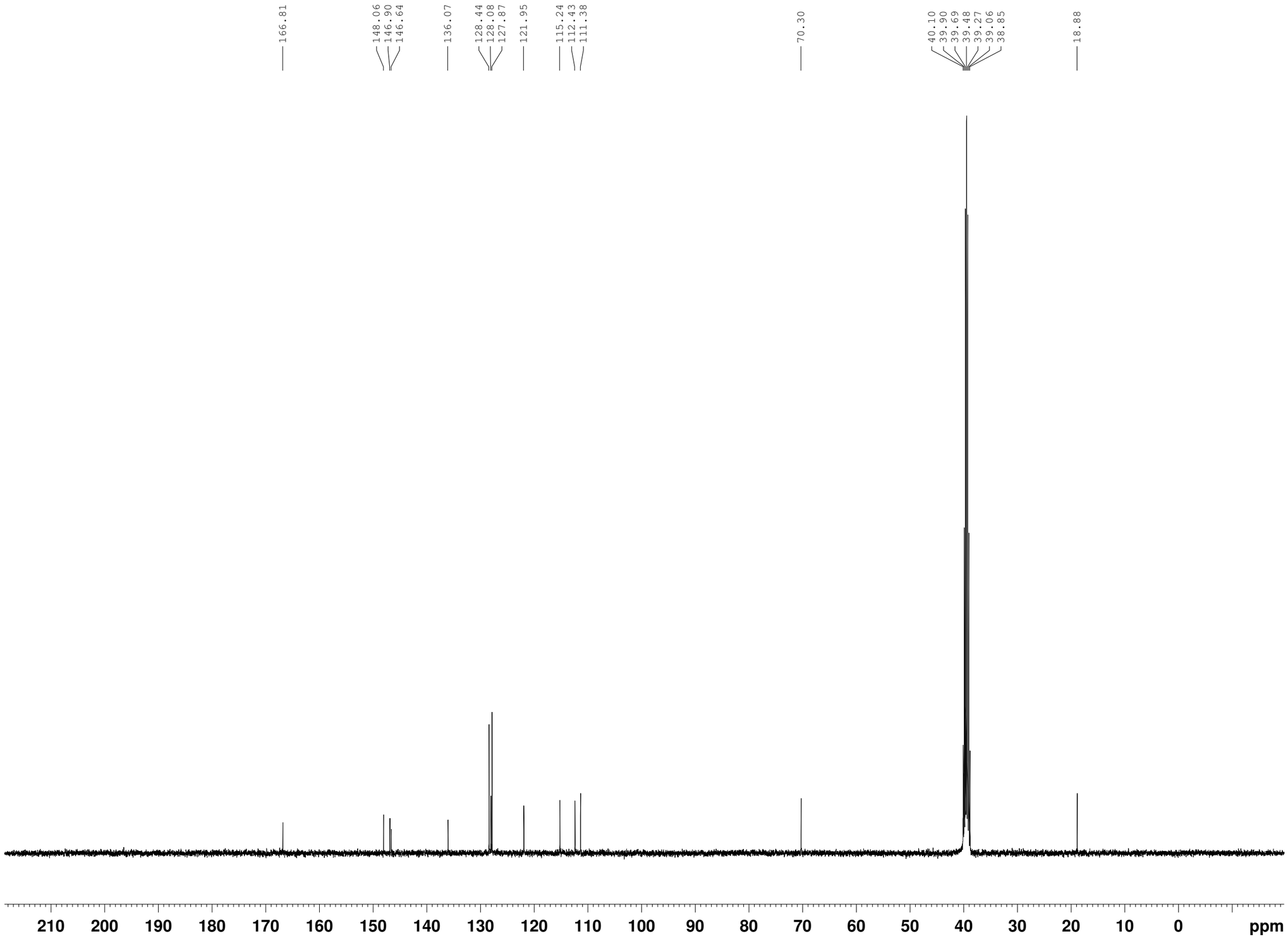
1.00
1.07
2.09
2.97
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

Name thomas alanine
M No kgbw666
Notebook Ref EN07919–84–01
carbon.az DMSO /opt/topspin2.1 chem 8



AstraZeneca

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PROCNO	1
Date_	20151019
Time	19.50
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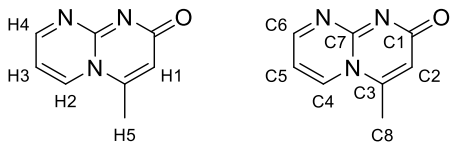
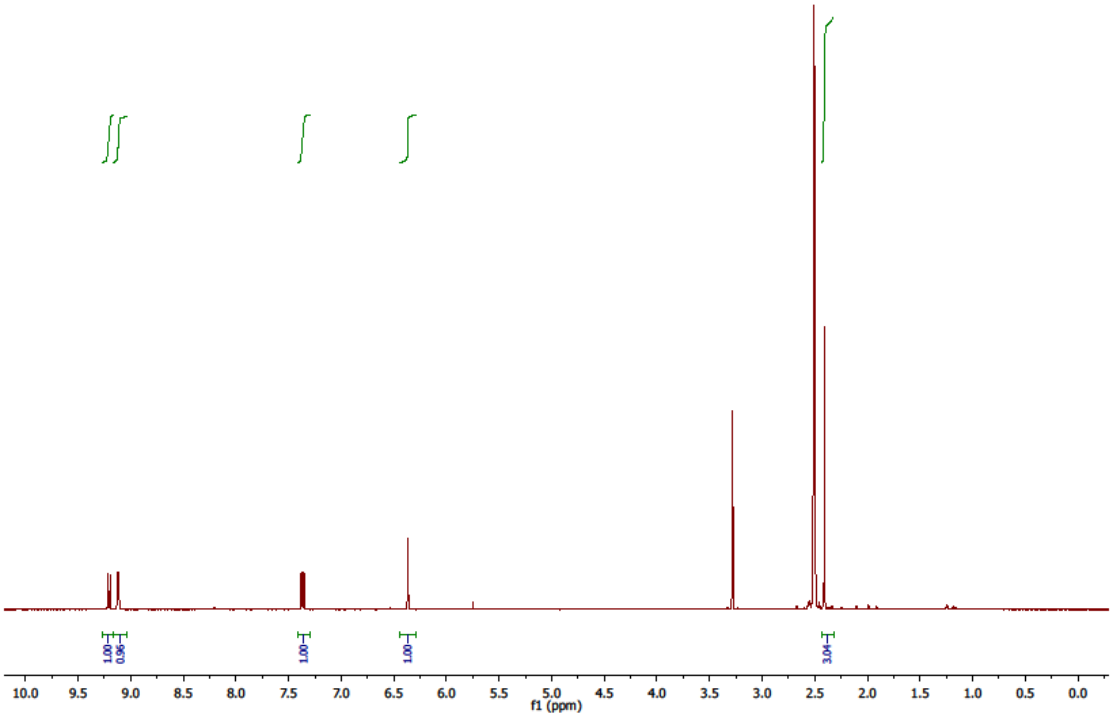
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	800
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	29193
DW	20.850 use
DE	20.00 use
TE	295.0 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 =======	
NUC1	13C
P1	11.00 use
PL1	3.70 dB
SFO1	100.6228298 MHz
======== CHANNEL f2 =======	
CPDPRG2	waltz16
NUC2	1H
PCPD2	95.00 use
PL2	-2.00 dB
PL12	15.00 dB
PL13	16.00 dB
SFO2	400.1316005 MHz
SI	32768
SF	100.6128193 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

4-Methyl-2*H*-pyrimido[1,2-a]pyrimidin-2-one **(63)**

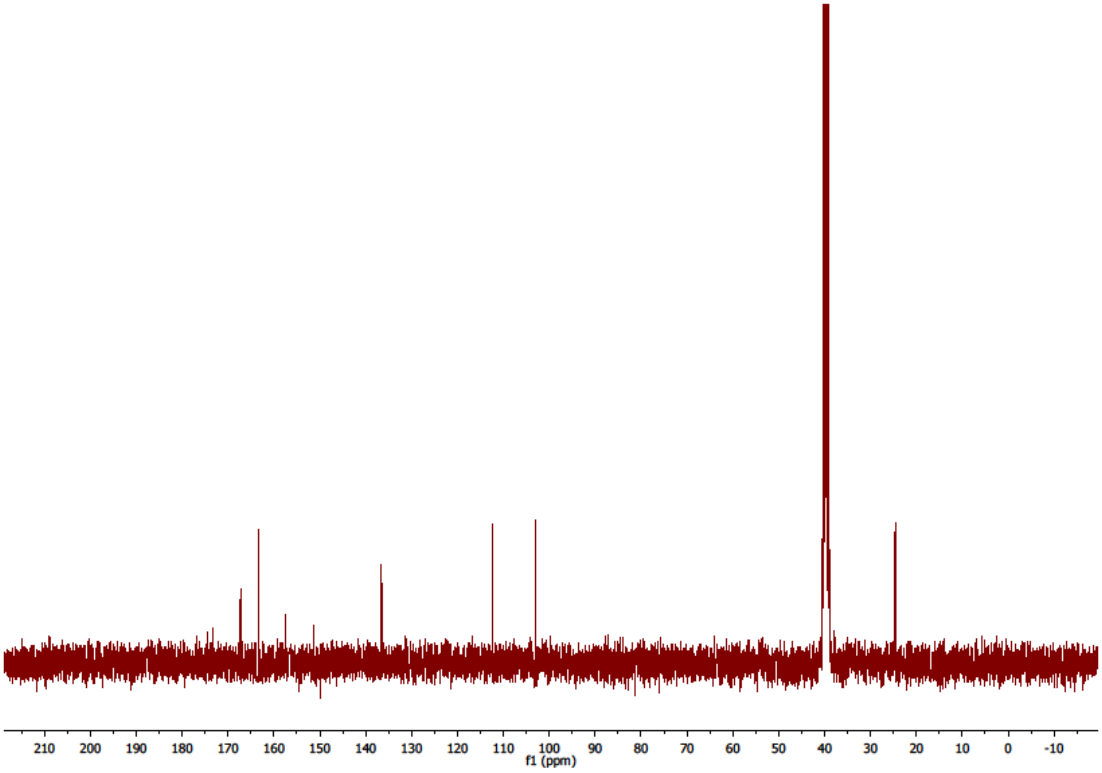


Prepared according to General Method 1 from 2-aminopyrimidine **60** (0.14 g, 1.43 mmol), LDA (3.00 mmol) and ethyl 2-butynoate **24** (0.20 mL, 1.72 mmol). The crude product was purified by Combiflash Companion (SiO_2, 12 g, EtOAc) to yield an orange solid (0.04 g, 0.25 mmol, 17%). R_f = 0.12 (EtOAc). Mpt (CH_2Cl_2): 159-162 ^oC. IR ν_{max}/cm^{-1} (neat): 3105 (w, C-H), 3074 (w, C-H), 3012 (w, C-H), 2917 (w, C-H), 1683 (str, C=O), 1627 (med, C=O), 1565 (med, C=C), 1529 (str, C=C), 1461 (str), 1402 (str), 1352 (str), 1260 (w), 1235 (med), 1199 (w), 1188 (w), 1168 (med), 1125 (med), 1074 (w), 1042 (w), 1025 (w). ^1H NMR (400 MHz, d^6-DMSO): δ_H 9.21 (1H, dd, *J* = 7.0, 2.3 Hz, H2 or H4), δ_H 9.12 (1H, dd, *J* = 3.9, 2.3 Hz, H2 or H4), δ_H 7.37 (1H, dd, *J* = 7.0, 3.9 Hz, H3), δ_H 6.37 (1H, s, H1), δ_H 2.41 (3H, s, H5). ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 167.3 (C1 or C7), δ_C 163.3 (C4), δ_C 157.4 (C1 or C7), δ_C 151.2 (C3), δ_C 136.6 (C6), δ_C 112.4 (C5), δ_C 102.9 (C2), δ_C 24.6 (C8). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 162.0673, $C_8H_8N_3O^+$ required 162.0667, Δ ppm = 3.7 ppm.

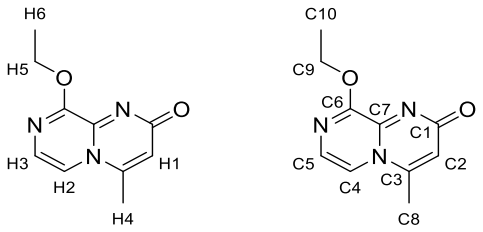
^{1}H NMR



^{13}C NMR

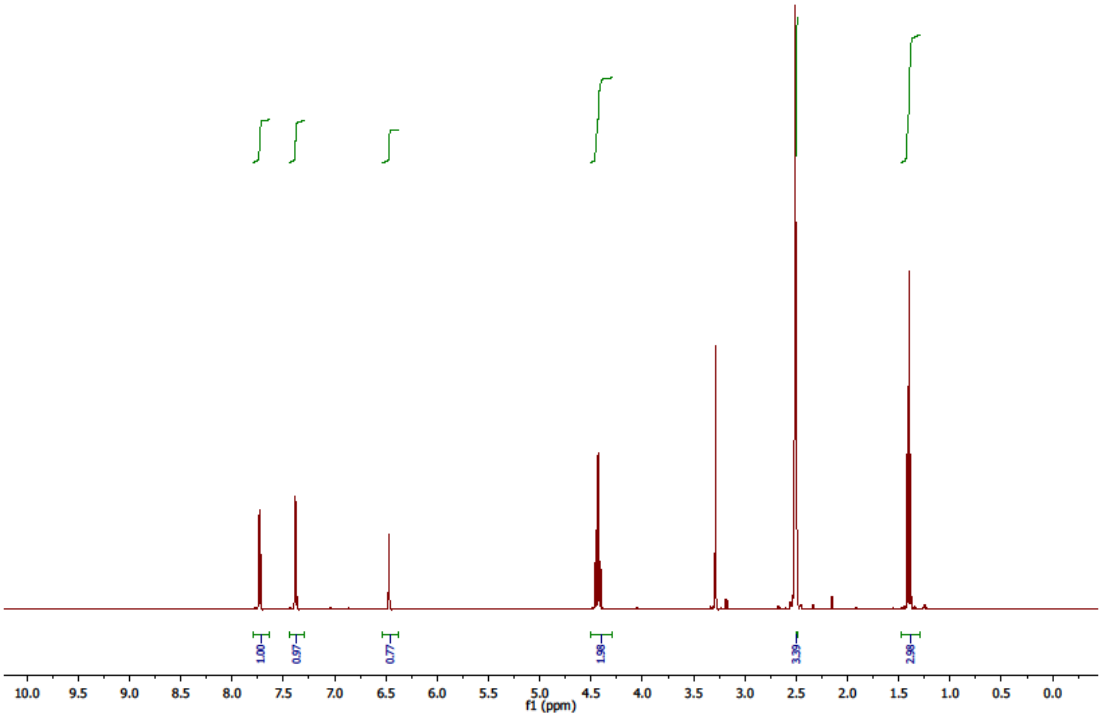


9-Ethoxy-4-methyl-2*H*-pyrazino[1,2-a]pyrimidin-2-one **(64)**

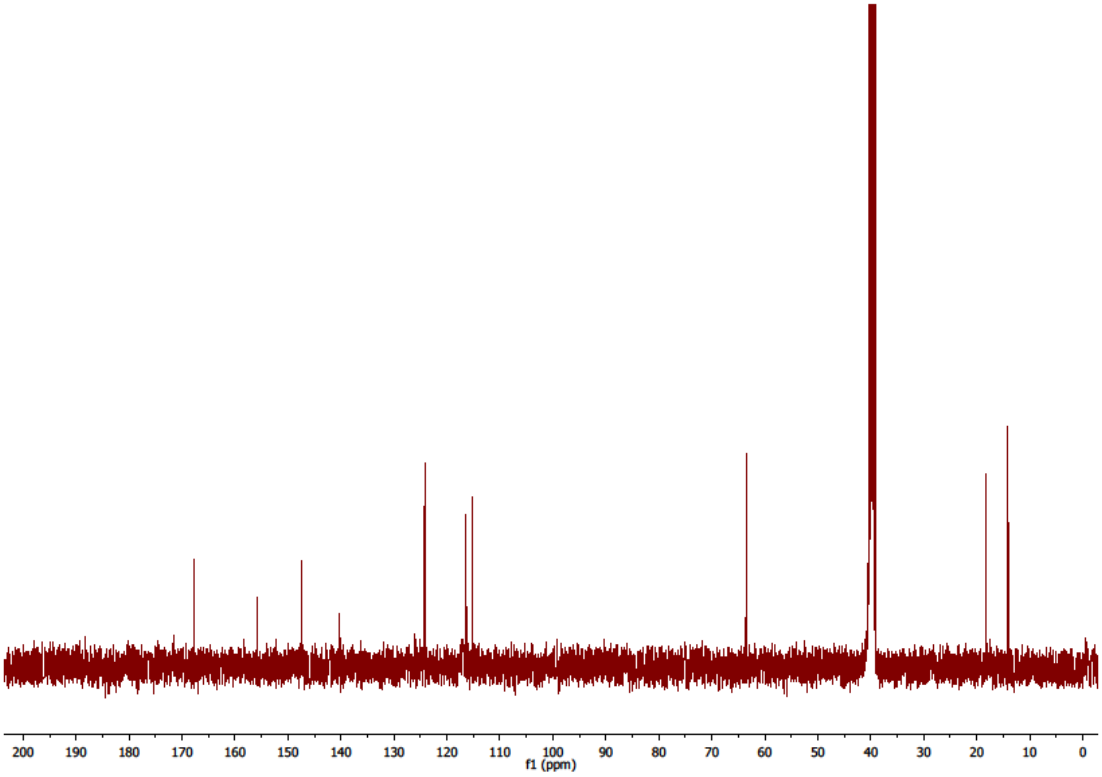


Prepared according to General Method 1 from 2-amino-3-ethoxypyrazine **61** (0.14 g, 1.43 mmol), LDA (3.00 mmol) and ethyl 2-butynoate **24** (0.20 mL, 1.72 mmol). The crude product was purified by Combiflash Companion (SiO_2, 12 g, 0-50% EtOAc in heptane) to yield a pale yellow solid (0.11 g, 0.54 mmol, 38%). R_f = 0.17 (9:1 CH_2Cl_2: MeOH). Mpt (H_2O/MeCN): 213-214 ^oC. IR ν_{max}/cm^{-1} (neat): 3126 (w, C-H), 2997 (w, C-H), 1646 (str, C=O), 1592 (str, C=C), 1541 (str, C=C), 1476 (str), 1432 (w), 1406 (w), 1393 (med), 1369 (str), 1326 (str), 1303 (w), 1272 (w), 1245 (w), 1216 (w), 1201 (w), 1184 (str), 1139 (w), 1041 (med), 1021 (med). ^1H NMR (400 MHz, d^6-DMSO): δ_H 7.73 (1H, d, *J* = 5.0 Hz, H2), δ_H 7.38 (1H, d, *J* = 5.0 Hz, H3), δ_H 6.47 (1H, d, *J* = 0.9 Hz, H1), δ_H 4.44 (2H, q, *J* = 7.1 Hz, H5), δ_H 1.41 (3H, t, *J* = 7.1 Hz, H6). H4 obscured by DMSO signal. ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 167.7 (C6), δ_C 155.8 (C1), δ_C 147.3 (C3), δ_C 140.3 (C7), δ_C 124.2 (C5), δ_C 116.5 (C2), δ_C 115.2 (C4), δ_C 63.5 (C9), δ_C 18.2 (C8), δ_C 14.2 (C10). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 206.0938, $C_{10}H_{12}N_3O_2^+$ required 206.0930, Δ ppm = 3.9 ppm and $[M+Na]^+$ 228.0758, $C_{10}H_{11}N_3O_2Na^+$ required 228.0749, Δ ppm = 3.9 ppm.

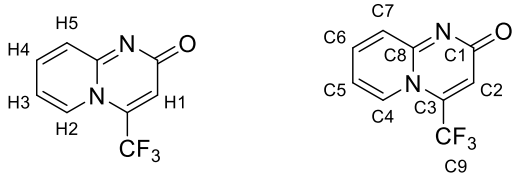
^{1}H NMR



^{13}C NMR

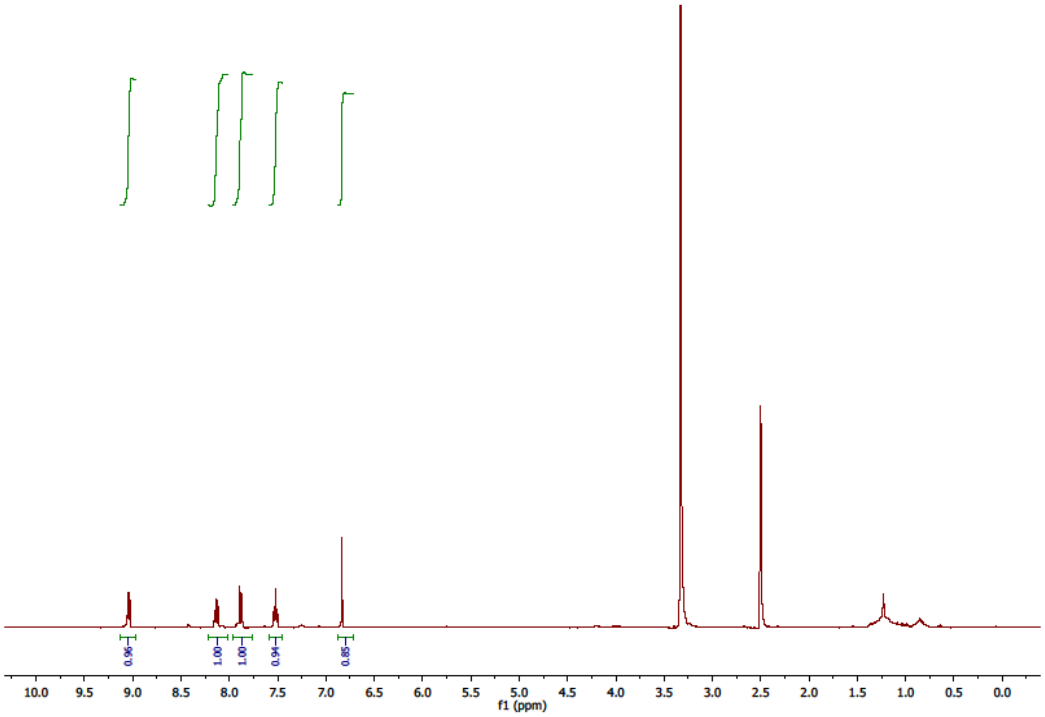


4-(Trifluoromethyl)-2*H*-pyrido[1,2-a]pyrimidin-2-one **(66)**

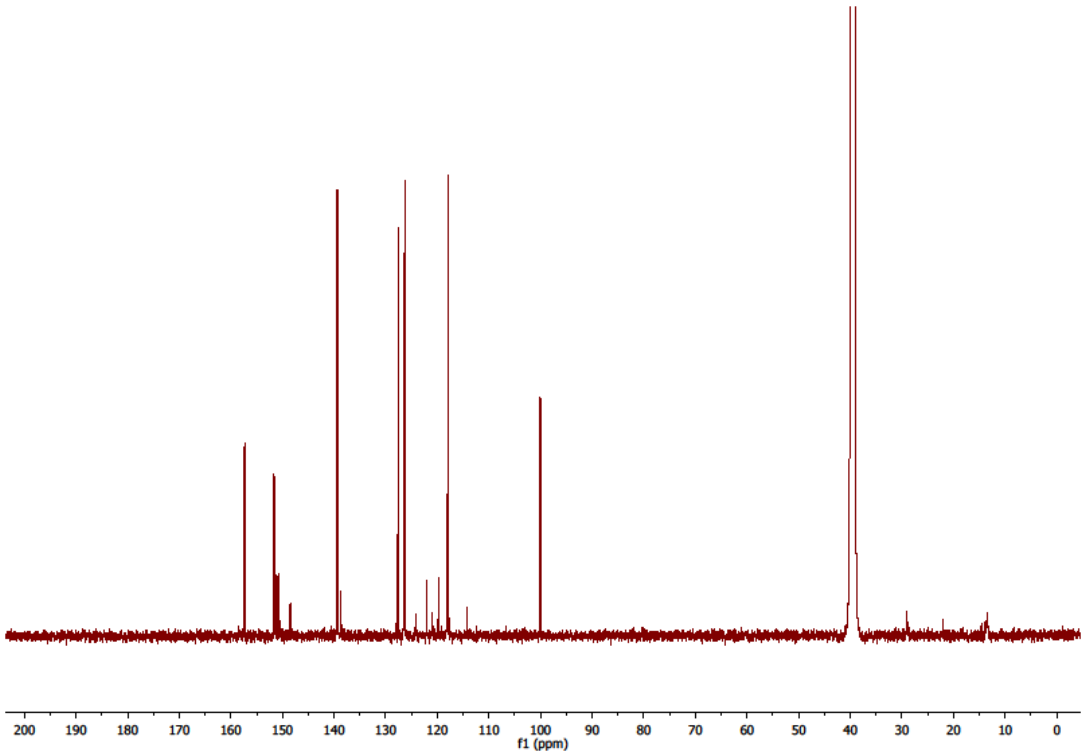


Prepared according to General Method 1 from 2-aminopyridine **23** (0.10 g, 1.06 mmol), *n*BuLi (2.23 mmol) and ethyl 4,4,4-trifluoromethylpropynoate **65** (0.18 mL, 1.28 mmol). The crude product was purified by column chromatography (SiO_2, 20 g, 3:1 40-60 petroleum ether: EtOAc) to yield a yellow wax (0.10 g, 96% purity with 2-aminopyridine, 0.42 mmol, 40%). R_f = 0.32 (3:1 40-60 petroleum ether: EtOAc). IR ν_{max}/cm^{-1} (neat): 3066 (w, C-H), 2924 (w, C-H), 1700 (str, C=O), 1638 (med, C=C), 1576 (w), 1534 (w), 1483 (str), 1456 (str), 1437 (med), 1365 (w), 1284 (str), 1252 (w), 1173 (str), 1133 (str), 1098 (str), 1020 (w). ^{1}H NMR (500 MHz, d^6-DMSO): δ_H 9.06-9.04 (1H, m, H2), δ_H 8.14 (1H, ddd, *J* = 8.6, 6.8, 1.6 Hz, H4), δ_H 7.89 (1H, d, *J* = 8.8 Hz, H5), δ_H 7.53 (1H, app dt, *J* = 1.3, 7.0 Hz, H3), δ_H 6.84 (1H, s, H1). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 157.4 (C1), δ_C 151.7 (C8), δ_C 151.0 (q, $^2J_{C-F}$ = 34 Hz, C3), δ_C 139.4 (C6), δ_C 127.7 (C4), δ_C 126.4 (C7), δ_C 120.9 (q, $^1J_{C-F}$ = 276 Hz, C9), δ_C 118.1 (C5), δ_C 100.1 (C2). ^{19}F NMR (162 MHz, d^6-DMSO): δ_F -68.66. HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 215.0417, $C_9H_6ON_2F_3^+$ required 215.0427, Δ ppm = -4.5 ppm. Data consistent with literature values.[2]

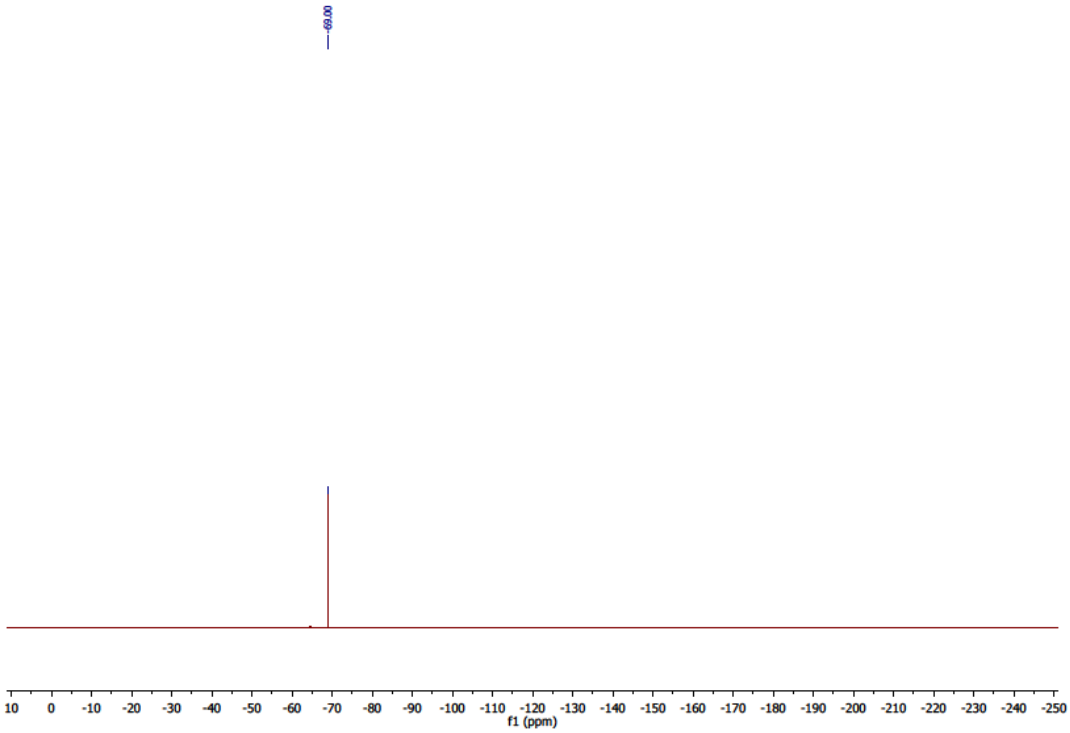
^{1}H NMR



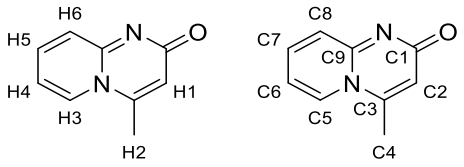
^{13} C NMR



^{19}F NMR

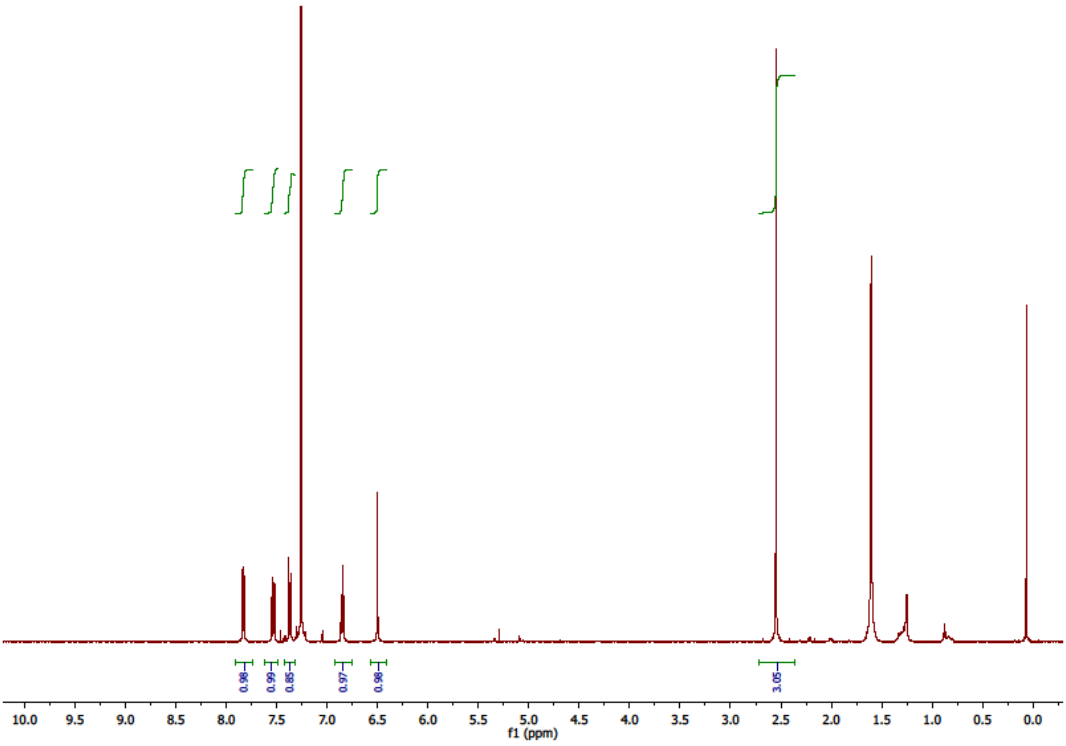

-69.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

4-Methyl-2*H*-pyrido[1,2-a]pyrimidin-2-one **(67)**

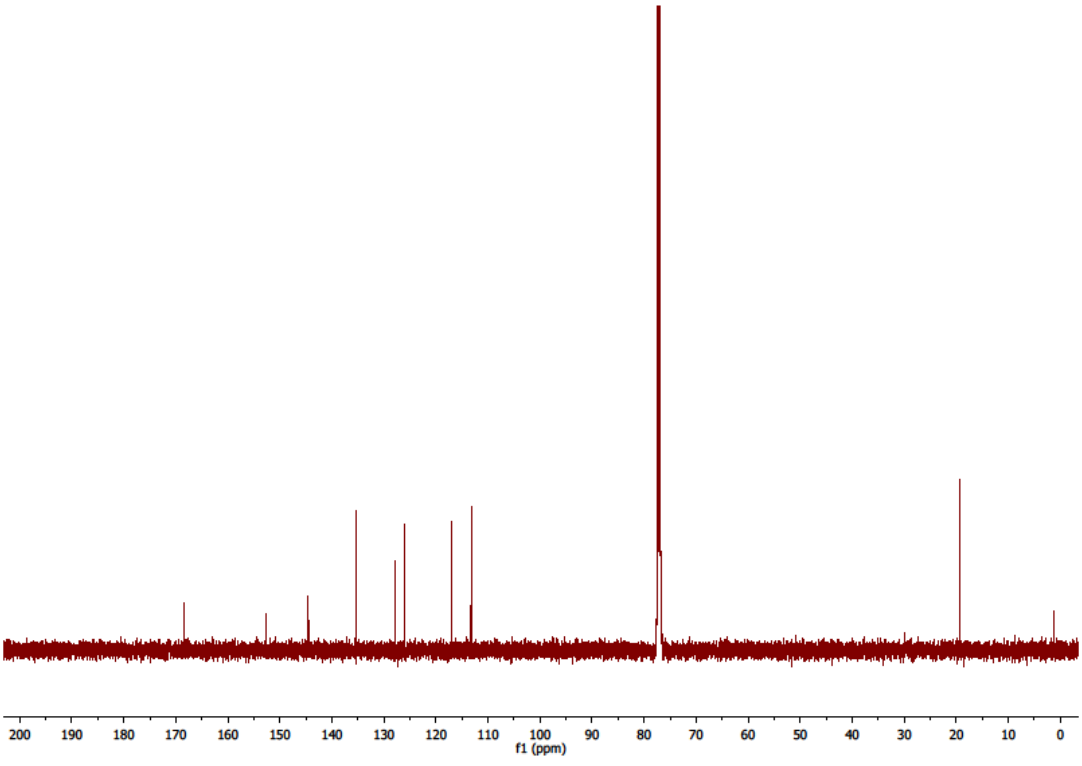


Prepared according to General Method 2 from **25**. The crude product was purified by column chromatography (SiO_2, 20 g, 93:7 CH_2Cl_2: MeOH) to yield a yellow solid (85%). R_f = 0.26 (9:1 CH_2Cl_2: MeOH). Mpt (CH_2Cl_2): >195 ^oC (decomp) (Lit 120-120.5 ^oC[3]). IR ν_{max}/cm^{-1} (neat): 1661 (str, C=O), 1645 (med, C=C/C=O), 1595 (str, C=C), 1547 (med, C=C), 1466 (str, C=C). ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.82 (1H, d, *J* = 7.2 Hz, H6), δ_H 7.54-7.50 (1H, m, H4), δ_H 7.39-7.35 (1H, m, H3), δ_H 6.83 (1H, app td, *J* = 7.0, 2.5 Hz, H5), δ_H 6.49 (1H, d, *J* = 0.6 Hz, H1), δ_H 2.54 (3H, d, *J* = 0.7 Hz, H2). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 168.3 (C1), δ_C 152.5 (C9), δ_C 144.4 (C3), δ_C 135.3 (C7), δ_C 127.7 (C5), δ_C 125.8 (C8), δ_C 116.9 (C2), δ_C 113.1 (C6), δ_C 19.1 (C4). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 161.0708, $C_9H_9N_2O^+$ required 161.0715, Δ ppm = -0.4 ppm. Data consistent with literature values.[3]

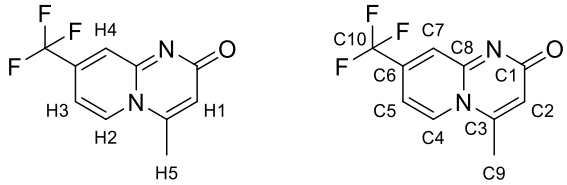
^{1}H NMR



^{13}C NMR

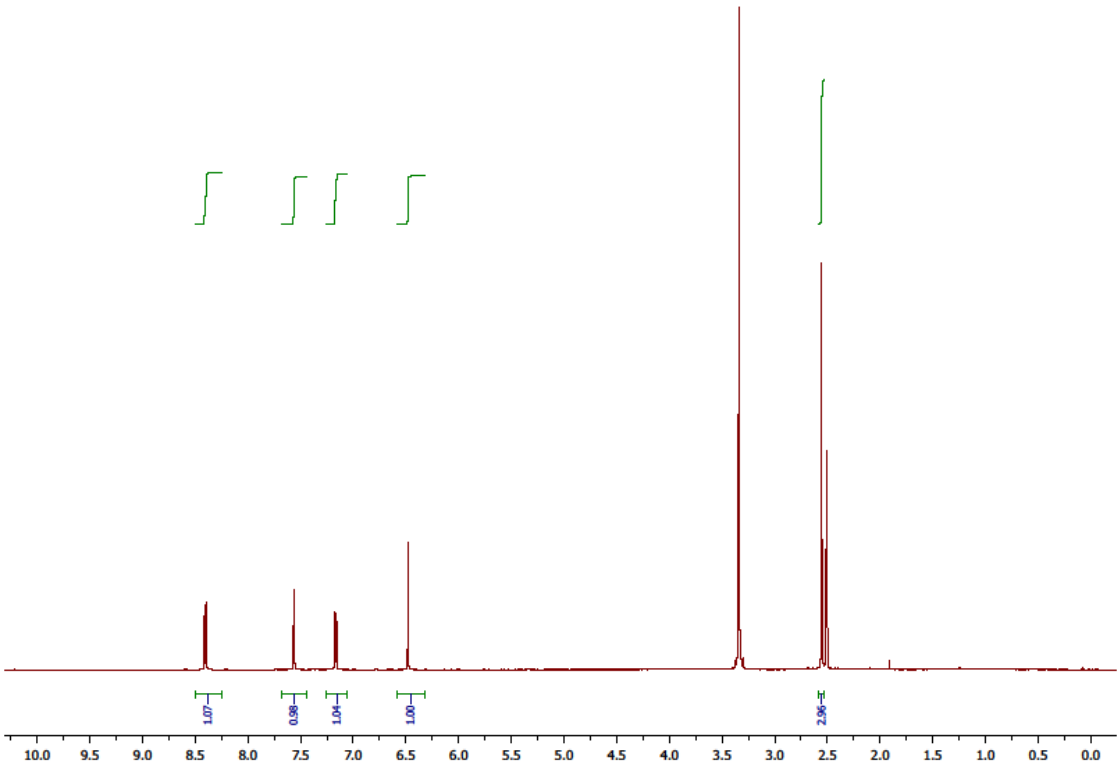


4-Methyl-8-(trifluoromethyl)-2*H*-pyrido[1,2-a]pyrimidin-2-one **(68)**

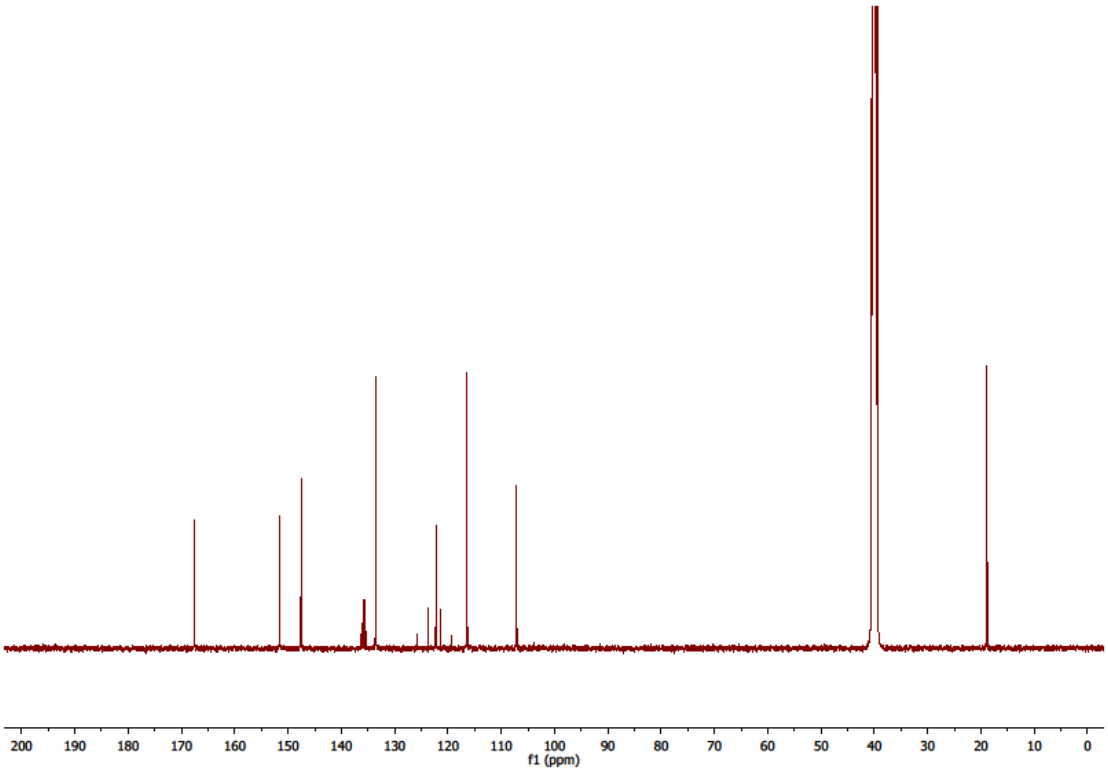


Prepared according to General Method 2 from **43**. The crude product was purified by column chromatography (SiO_2, 10 g, 100:0, 95:5 then 9:1 CH_2Cl_2: MeOH) to yield an ochre solid (quantitative). R_f = 0.23 (9:1 CH_2Cl_2: MeOH). Mpt (CH_2Cl_2): darkens >200 ^oC, melts 274-275 ^oC. IR ν_{max}/cm^{-1} (neat): 3063 (w, C-H), 1653 (str, C=O), 1614 (str, C=C), 1553 (w, C=C), 1474 (str, C=C/C=N), 1445 (med), 1392 (med), 1359 (str), 1301 (str, C-O), 1287 (str), 1243 (med), 1175 (med), 1159 (str), 1129 (str), 1077 (str), 1050 (w), 1026 (str). ^1H NMR (500 MHz, d^6-DMSO): δ_H 8.40 (1H, d, *J* = 7.5 Hz, H2), δ_H 7.58-7.55 (1H, m, H4), δ_H 7.17 (1H, dd, *J* = 7.5, 2.2 Hz, H3), δ_H 6.48 (1H, d, *J* = 0.6 Hz, H1), δ_H 2.55 (3H, d, *J* = 0.5 Hz, H5). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 167.2 (C1), δ_C 151.2 (C8), δ_C 147.2 (C3), δ_C 135.2 (q, $^2J_{C-F}$ = 34 Hz, C6), δ_C 133.2 (C4), δ_C 122.1 (q, $^1J_{C-F}$ = 273.6 Hz, C10), δ_C 121.8 (d, $^3J_{C-F}$ = 4.6 Hz, C7), δ_C 116.0 (C2), δ_C 106.8 (d, $^3J_{C-F}$ = 1.5 Hz, C5), δ_C 18.5 (C9). ^{19}F NMR (376 MHz, d^6-DMSO): δ_F -65.72 (CF_3). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 229.0576, $C_{10}H_8ON_2F_3^+$ required 229.0583, Δ ppm = -3.3 ppm.

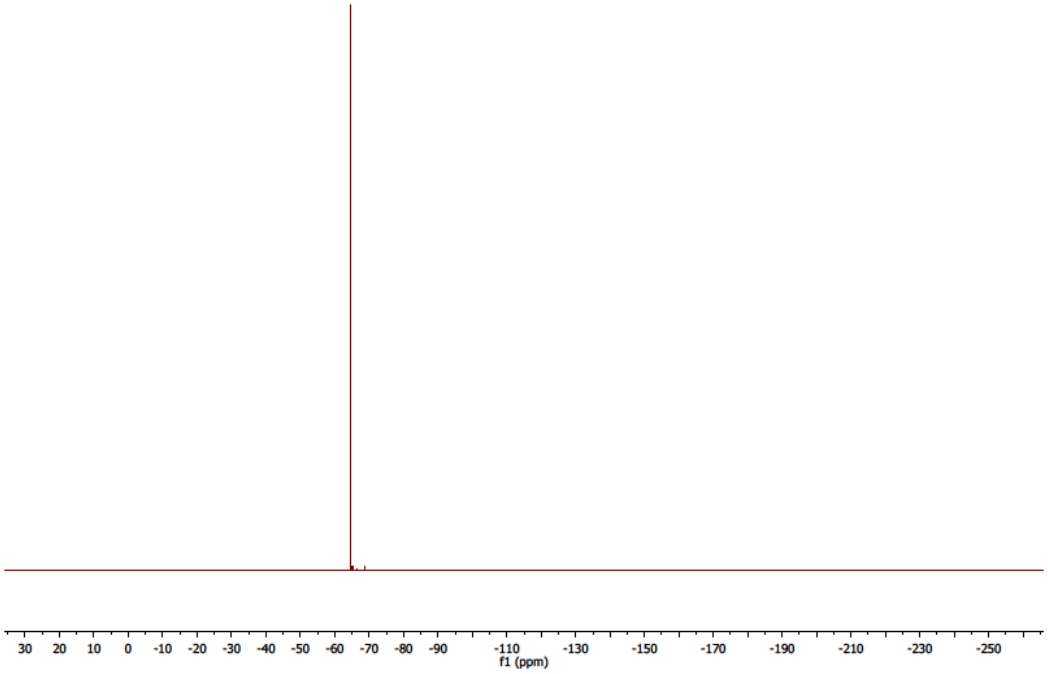
^{1}H NMR



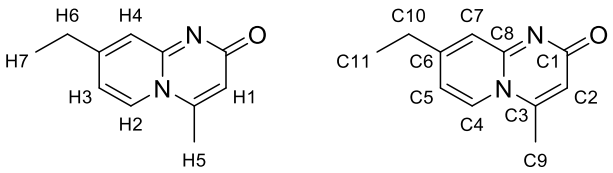
^{13}C NMR



^{19}F NMR

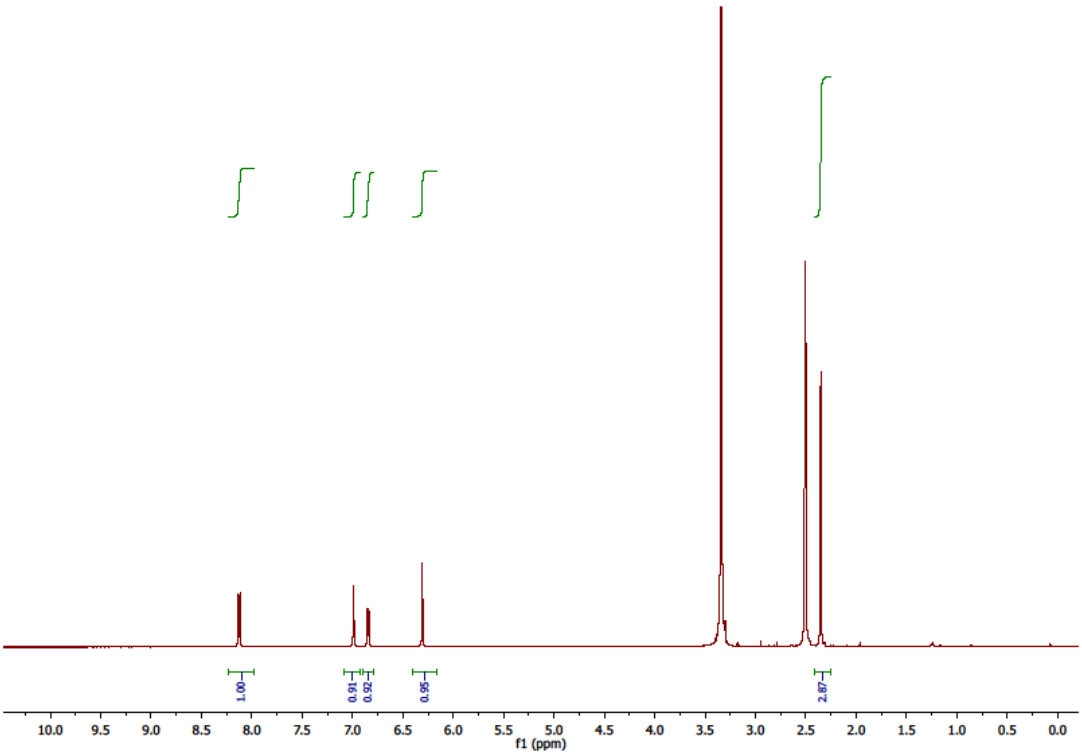

30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -110 -130 -150 -170 -190 -210 -230 -250
f1 (ppm)

8-Ethyl-4-methyl-2H-pyrido[1,2-a]pyrimidin-2-one **(69)**

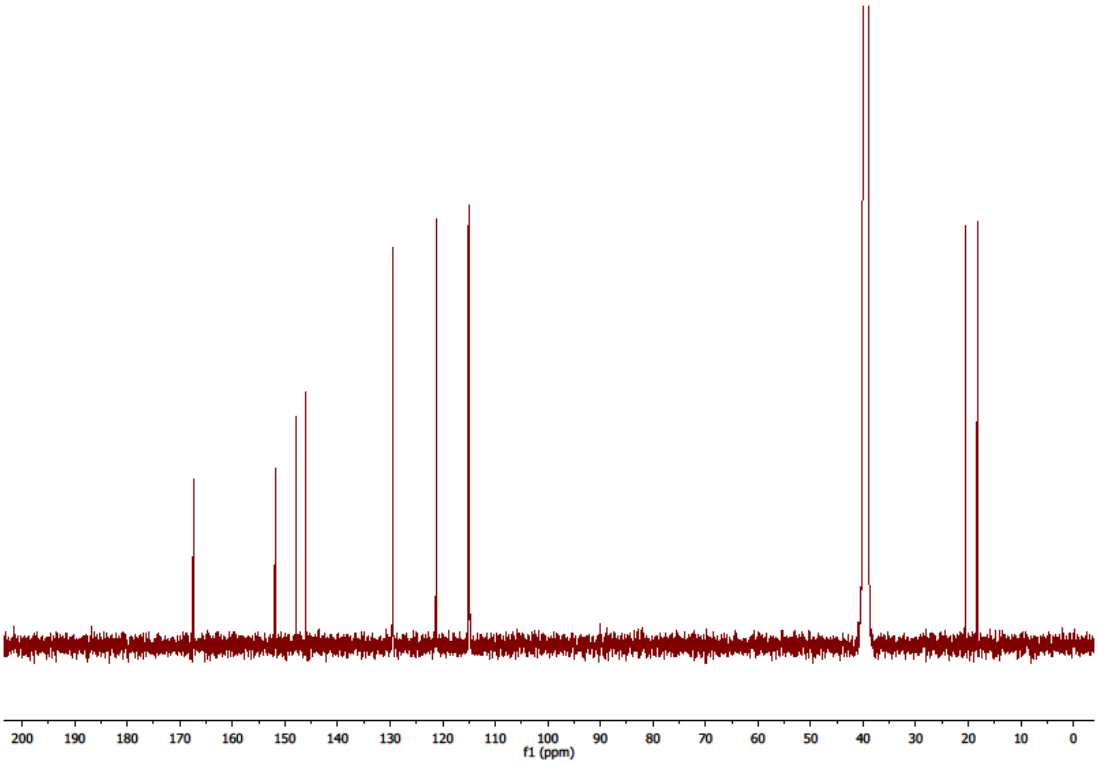


Prepared according to General Method 2 from **44**. The crude product was purified by column chromatography (SiO_2, 30 g, 19:1 CH_2Cl_2: MeOH) to yield a yellow wax (quantitative). R_f = 0.57 (9:1 CH_2Cl_2: MeOH). IR ν_{max}/cm^{-1} (neat): 3494 (w, br), 3082 (w, C-H), 1642 (str, C=O), 1591 (str, C=C), 1546 (w), 1479 (w), 1456 (str, C=C/C=N), 1440 (str), 1389 (str), 1365 (med), 1315 (w), 1283 (str), 1250 (med), 1200 (med), 1165 (med), 1138 (w), 1062 (w), 1051 (w), 1034 (w), 1006 (w). ^{1}H NMR (500 MHz, d^6-DMSO): δ_H 8.14 (1H, d, *J* = 7.3 Hz, H2), δ_H 6.97-6.96 (1H, m, H4), δ_H 6.89 (1H, dd, *J* = 7.3, 2.0 Hz, H3), δ_H 6.31 (1H, d, *J* = 0.8 Hz, H1), δ_H 2.65 (2H, dq, *J* = 0.6, 7.5 Hz, H6), δ_H 2.50 (3H, d, *J* = 0.8 Hz, H5), δ_H 1.20 (3H, t, *J* = 7.5 Hz, H7). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 167.5 (C1), δ_C 153.3 (C6), δ_C 152.1 (C8), δ_C 145.8 (C3), δ_C 129.9 (C4), δ_C 119.9 (C7), δ_C 115.0 (C2), δ_C 114.1 (C5), δ_C 27.4 (C10), δ_C 18.4 (C9), δ_C 13.4 (C11). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 189.1019, $C_{11}H_{13}ON_2^+$ required 189.1028, Δ ppm = -4.8 ppm.

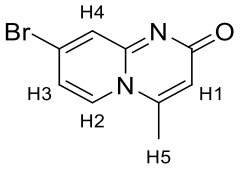
^{1}H NMR

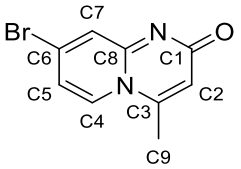


^{13}C NMR



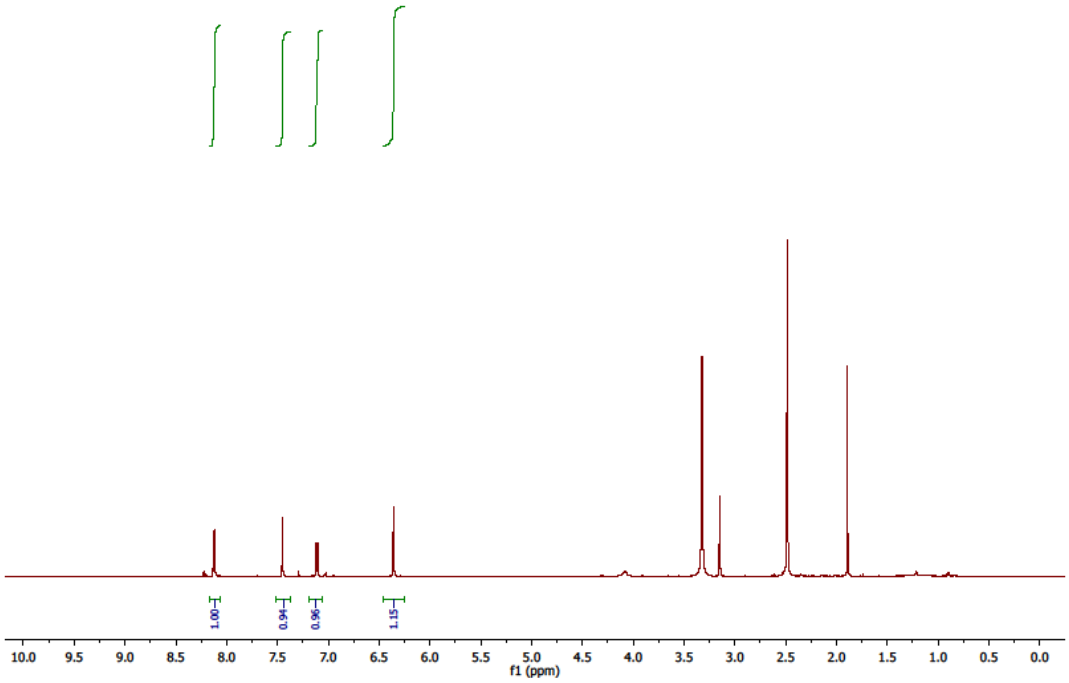
8-Bromo-4-methyl-2*H*-pyrido[1,2-a]pyrimidin-2-one **(70)**



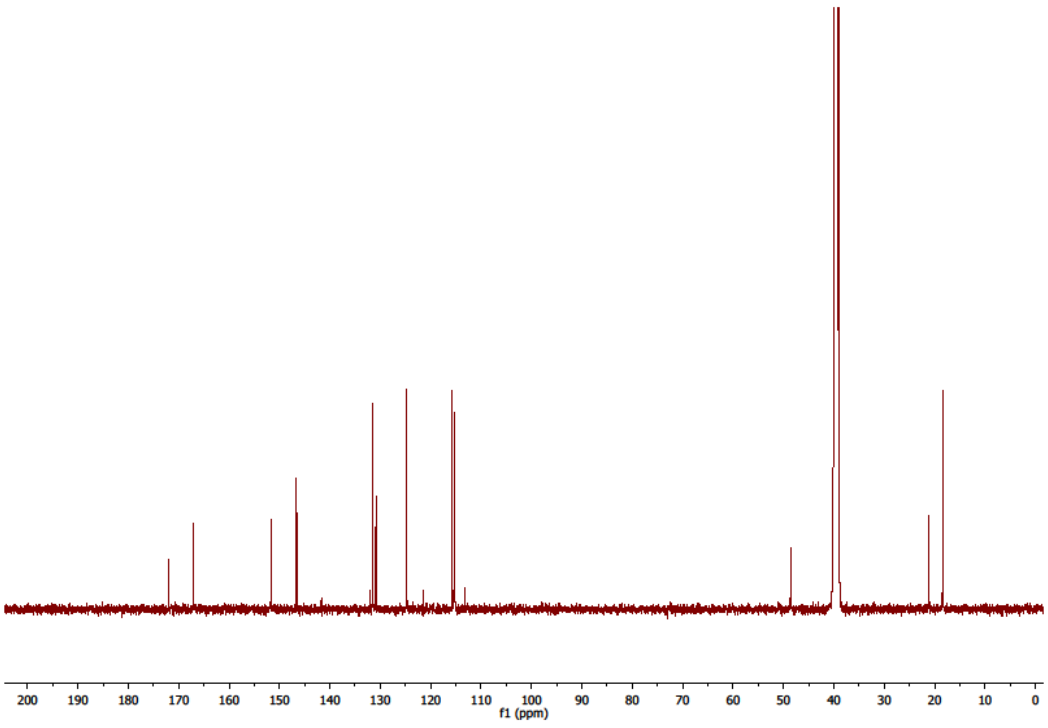


Prepared according to General Method 2 from **45**. The crude product was purified by column chromatography (SiO_2, 30 g, 1:0, 97:3, then 19:1 CH_2Cl_2: MeOH) to yield a brown wax (0.09g, 89% purity with **45** and methanol, 1.33 mmol, 19%). Further purification by preparative HPLC yielded spectroscopically pure material. R_f = 0.42 (9:1 CH_2Cl_2: MeOH). IR ν_{max}/cm^{-1} (neat): 3360 (w, br), 3045 (w, C-H), 3001 (w, C-H), 1724 (med), 1652 (str, C=O), 1574 (str, C=C), 1534 (w, C=C), 1456 (str, C=C/C=N), 1372 (str), 1354 (str), 1311 (w), 1285 (str), 1257 (w), 1193 (med), 1164 (w), 1104 (w), 1078 (w), 1057 (w), 1024 (med). ^{1}H NMR (500 MHz, d^6-DMSO): δ_H 8.12 (1H, d, *J* = 7.6 Hz, H2), δ_H 7.45 (1H, d, *J* = 2.2 Hz, H4), δ_H 7.11 (1H, dd, *J* = 7.6, 2.3 Hz, H3), δ_H 6.36 (1H, s, H1), H5 obscured by DMSO signal. ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 167.2 (C1), δ_C 151.8 (C8), δ_C 146.7 (C3), δ_C 131.6 (C4), δ_C 130.9 (C6), δ_C 124.9 (C7), δ_C 115.8 (C5), δ_C 115.4 (C2), δ_C 18.4 (C9). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 238.9805, $C_9H_8ON_2{}^{79}Br^+$ required 238.9815, Δ ppm = -4.1 ppm.

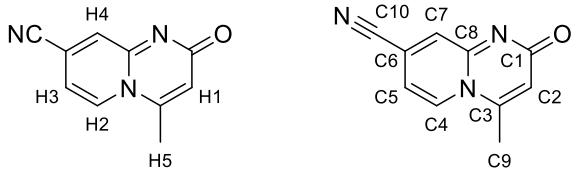
^{1}H NMR



^{13}C NMR

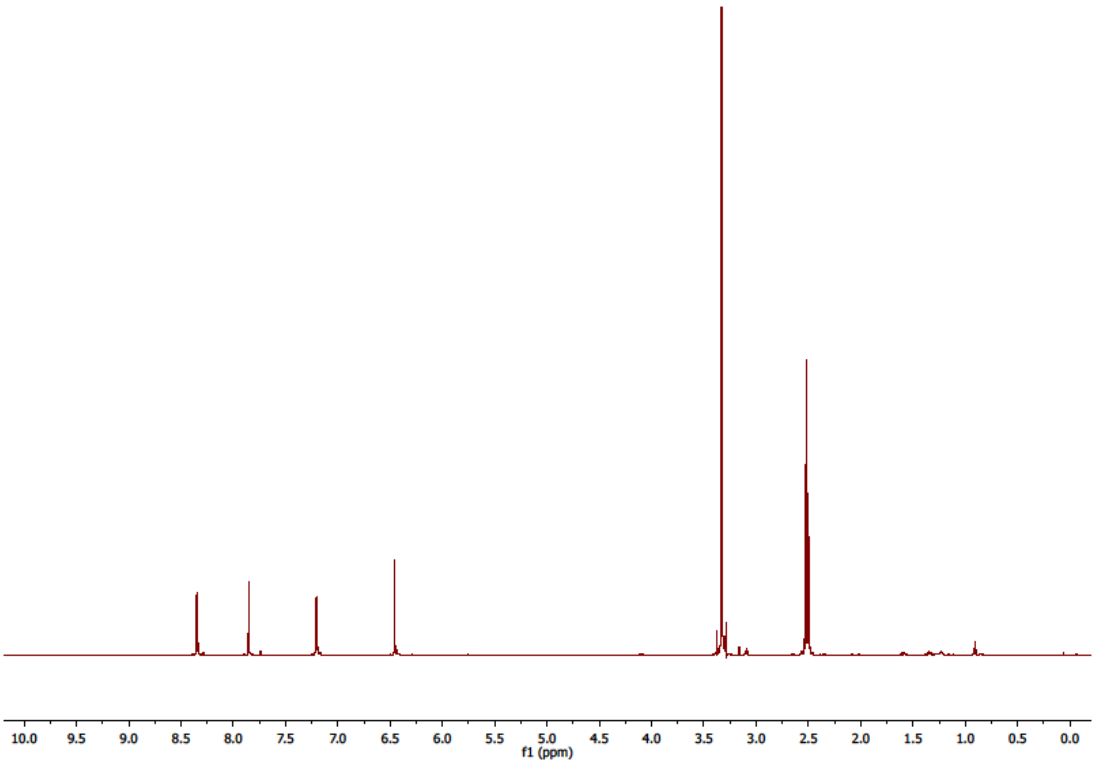


4-Methyl-2-oxo-2*H*-pyrido[1,2-a]pyrimidine-8-carbonitrile **(71)**

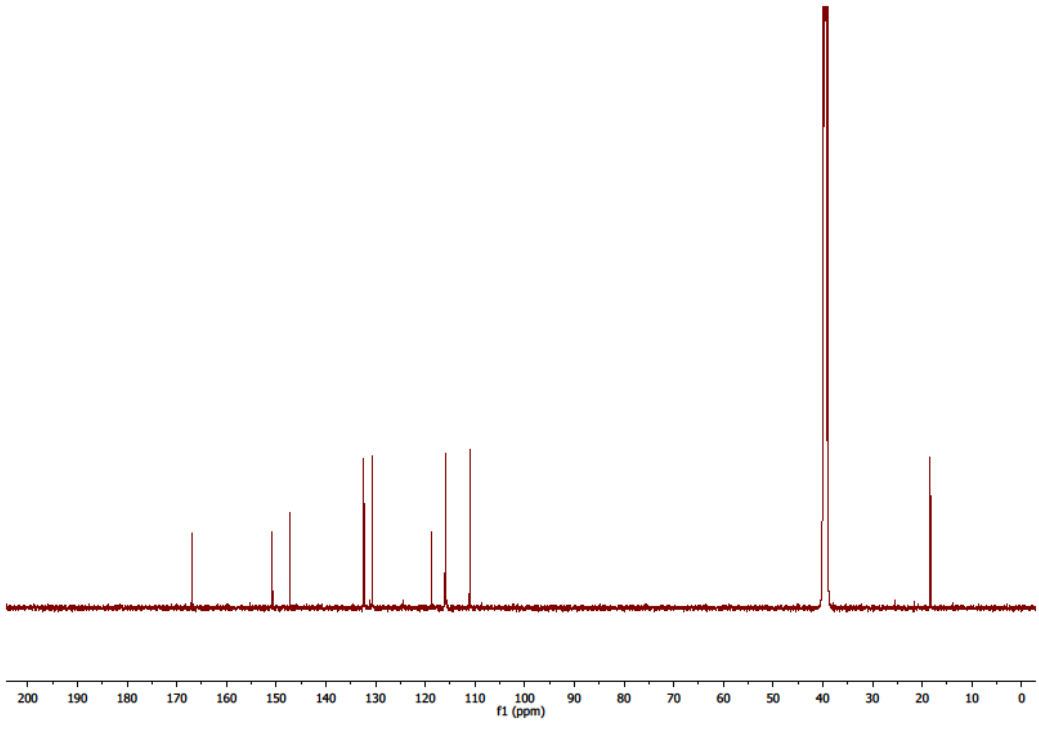


Prepared according to General Method 2 from **46**. The crude product was purified by column chromatography (SiO_2, 30 g, 19:1 CH_2Cl_2: MeOH) to yield a yellow wax (61%). R_f = 0.46 (9:1 CH_2Cl_2: MeOH). Mpt (CH_2Cl_2): phase change >240 ^oC, melts 299-301 ^oC. IR ν_{max}/cm^{-1} (neat): 3068 (w, C-H), 3040 (w, C-H), 2926 (w, C-H), 2237 (w, C≡C), 1685 (w), 1655 (med), 1642 (med, C=O), 1598 (str, C=C), 1532 (w), 1466 (str, C=N/C=C), 1399 (med), 1366 (med), 1291 (med), 1251 (w), 1206 (med), 1170 (w), 1064 (str), 1031 (med). ^1H NMR (500 MHz, d^6-DMSO): δ_H 8.35 (1H, d, *J* = 7.1 Hz, H2), δ_H 7.85 (1H, app dd, *J* = 2.0, 0.7 Hz, H4), δ_H 7.20 (1H, dd, *J* = 7.4, 2.0 Hz, H3), δ_H 6.46 (1H, d, *J* = 0.8 Hz, H1), δ_H 2.52 (3H, d, *J* = 0.7 Hz, H5). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 167.1 (C1), δ_C 150.8 (C8), δ_C 147.3 (C3), δ_C 132.4 (C4), δ_C 130.8 (C7), δ_C 118.9 (C6), δ_C 116.1 (C2), δ_C 116.0 (C10), δ_C 111.1 (C5), δ_C 18.4 (C9). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 186.0656, $C_{10}H_8ON_3^+$ required 186.0662, Δ ppm = -3.2 ppm.

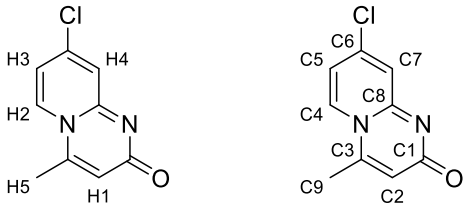
^{1}H NMR



^{13}C NMR

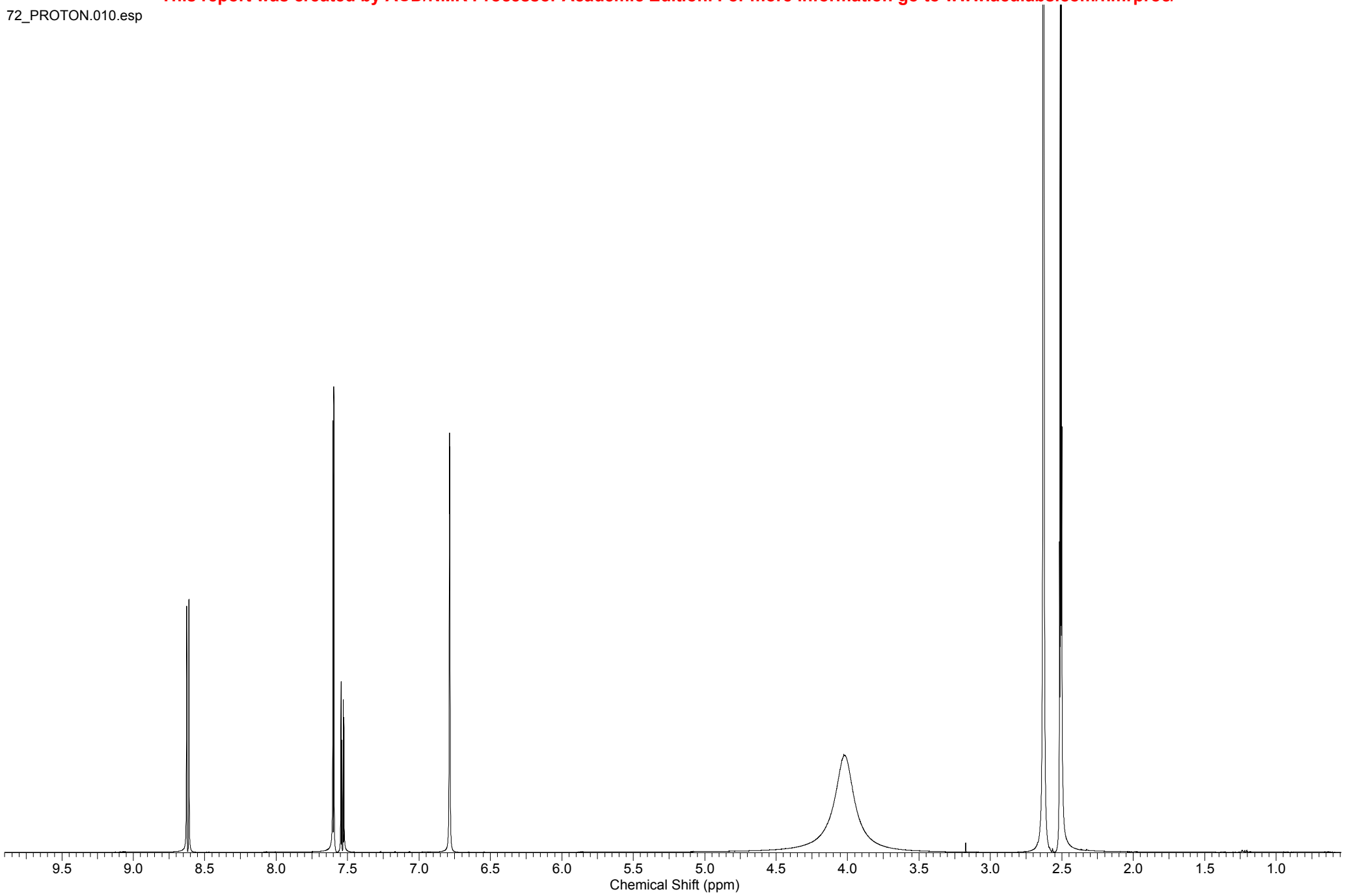


8-Chloro-4-methyl-2*H*-pyrido[1,2-a]pyrimidin-2-one **(72)**

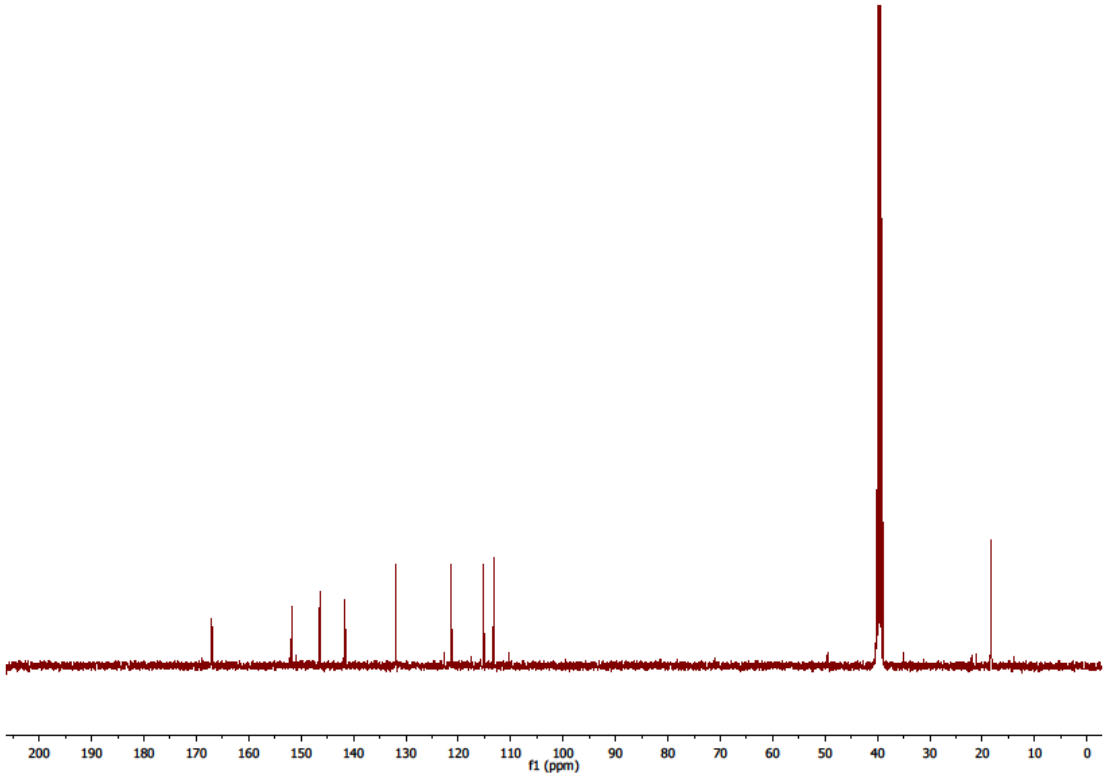


Prepared according to General Method 2 from **47**. The crude product was purified by Combiflash Companion (SiO_2, 12 g, 0-10% MeOH in CH_2Cl_2) to yield a pink solid (5.44 g, 87% purity, 24.33 mmol, 80%). Further purification by preparative HPLC yielded spectroscopically pure material. R_f = 0.23 (9:1 CH_2Cl_2: MeOH). Mpt (CH_2Cl_2/MeOH): phase change >165 ^oC, melts >300 ^oC. IR ν_{max}/cm^{-1} (neat): 3072 (w, C-H), 1640 (str, C=O), 1601 (str, C=C), 1540 (w), 1520 (w), 1464 (str, C=C/C=N), 1391 (str), 1372 (med), 1286 (str), 1251 (w), 1193 (med), 1166 (w), 1089 (w), 1065 (w), 1026 (w). ^1H NMR (400 MHz, d^6-DMSO): δ_H 8.23 (1H, d, *J* = 7.7 Hz, H2), δ_H 7.30 (1H, d, *J* = 2.3 Hz, H4), δ_H 7.03 (1H, dd, *J* = 7.6, 2.4 Hz, H3), δ_H 6.36 (1H, s, H1), H5 obscured by DMSO signal.^{13}C NMR (100 MHz, d^6-DMSO): δ_C 167.0 (C1), δ_C 151.7 (C8), δ_C 146.4 (C3), δ_C 141.6 (C6), δ_C 131.9 (C4), δ_C 121.3 (C7), δ_C 115.1 (C2), δ_C 113.2 (C5), δ_C 18.3 (C9). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 195.0333, $C_9H_8N_2O^{35}Cl^+$ required 195.0325, Δ ppm = 4.1 ppm.

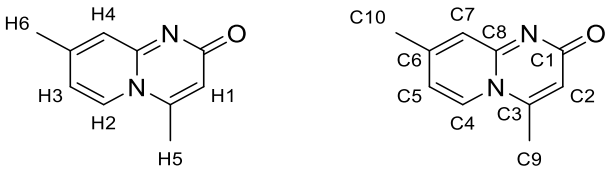
72_PROTON.010.esp



^{13}C NMR

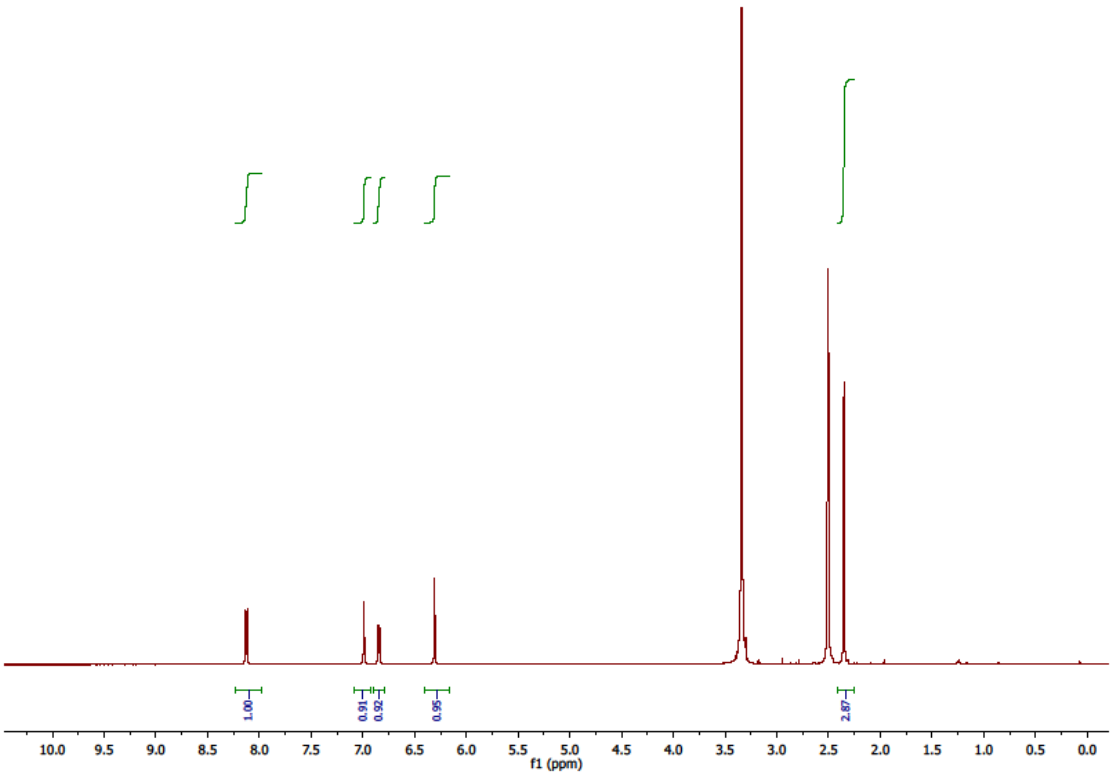

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

4,8-Dimethyl-2*H*-pyrido[1,2-a]pyrimidin-2-one **(73)**

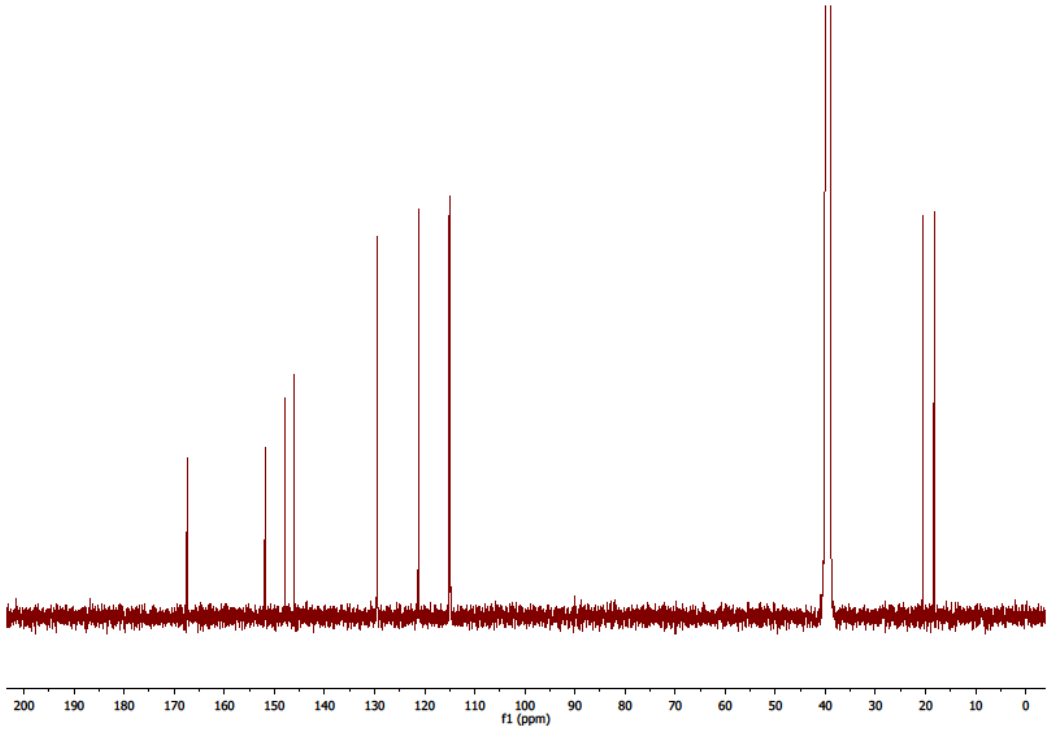


Prepared according to General Method 2 from **18**. The crude product was purified by Combiflash Companion (SiO_2, 24 g, 0-10% MeOH/CH_2Cl_2) to yield a white solid (53%). R_f = 0.26 (9:1 CH_2Cl_2: MeOH). Mpt (CH_2Cl_2): phase change >180 ^oC, melts 230-232 ^oC. IR ν_{max}/cm^{-1} (neat): 3233 (w, br, C-H), 3045 (w, C-H), 2955 (w, C-H), 1646 (str, C=O), 1592 (str, C=C), 1543 (w), 1466 (str, C=N/C=C), 1395 (str, C=C/C=N), 1372 (str), 1292 (med), 1253 (med), 1206 (med), 1175 (w), 1067 (str), 1043 (w). ^1H NMR (500 MHz, d^6-DMSO): δ_H 8.10 (1H, d, *J* = 7.3 Hz, H2), δ_H 6.97 (1H, s, H4), δ_H 6.82 (1H, dd, *J* = 7.3, 1.9 Hz, H3), δ_H 6.28 (1H, s, H1), δ_H 2.33 (3H, s, H6). H5 obscured by DMSO signal. ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 167.5 (C1), δ_C 152.0 (C8), δ_C 148.0 (C6), δ_C 146.1 (C3), δ_C 129.6 (C4), δ_C 121.3 (C7), δ_C 115.2 (C2 or C5), δ_C 115.0 (C2 or C5), δ_C 20.7 (C10), δ_C 18.4 (C9). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 175.0861, $C_{10}H_{11}ON_2^+$ required 175.0866, Δ ppm = -2.6 ppm.

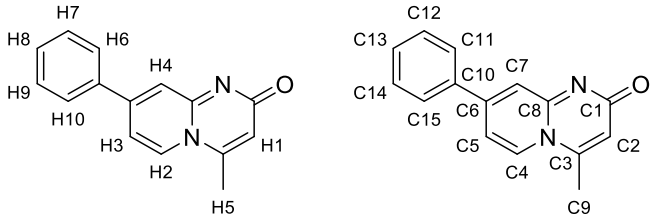
^{1}H NMR



^{13}C NMR

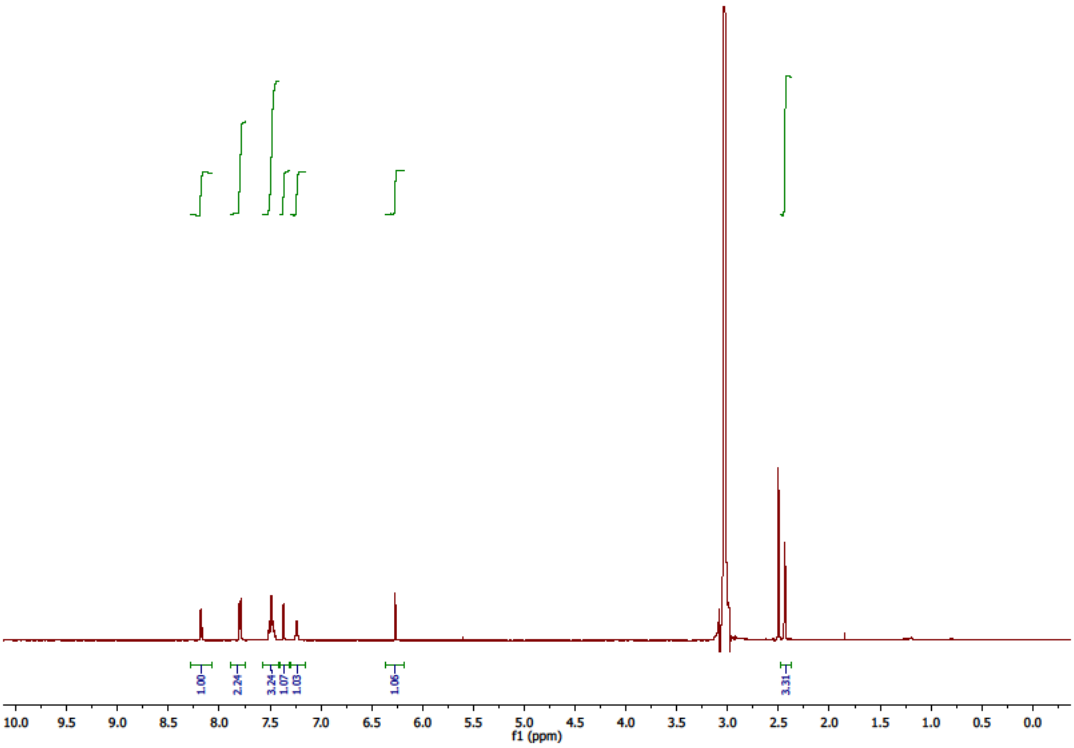


4-Methyl-8-phenyl-2H-pyrido[1,2-a]pyrimidin-2-one **(74)**

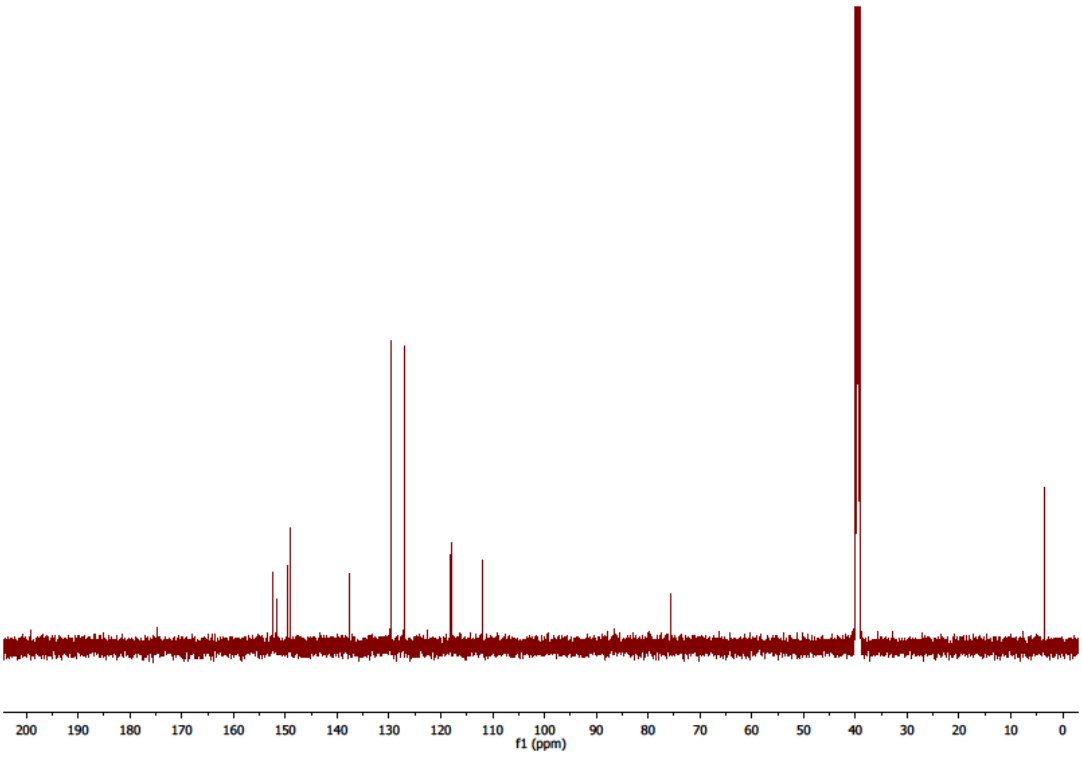


Prepared according to General Method 2 from **49**. The crude product was purified by column chromatography (SiO_2, 30 g, 19:1 CH_2Cl_2: MeOH) to yield a beige solid (94%). R_f = 0.49 (9:1 CH_2Cl_2: MeOH). Mpt (CH_2Cl_2): 189-192 ^oC. IR ν_{max}/cm^{-1} (neat): 3062 (w, br, C-H), 2923 (w, C-H), 2853 (w, C-H), 1708 (w), 1639 (str, C=O), 1576 (med, C=C), 1505 (w), 1449 (w), 1435 (w), 1393 (med), 1370 (med), 1256 (med), 1238 (med), 1191 (med), 1175 (med), 1073 (w), 1032 (w), 1017 (w). ^1H NMR (500 MHz, d^6-DMSO): δ_H 8.50 (1H, d, *J* = 7.5 Hz, H2), δ_H 7.95-7.88 (2H, m, H6+H10), δ_H 7.60-7.52 (3H, m, H7+H8+H9), δ_H 7.49 (1H, d, *J* = 2.0 Hz, H4), δ_H 7.37 (1H, dd, *J* = 7.5, 2.2 Hz, H3), δ_H 6.37 (1H, d, *J* = 0.8 Hz, H1), δ_H 2.56 (3H, d, *J* = 0.5 Hz, H5). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 167.4 (C1), δ_C 152.3 (C8), δ_C 146.6 (C6), δ_C 146.2 (C3), δ_C 135.2 (C10), δ_C 130.7 (C4), δ_C 130.2 (C13), δ_C 129.3 (C12+C14), δ_C 127.0 (C11+C15), δ_C 118.9 (C7), δ_C 115.2 (C2), δ_C 111.2 (C5), δ_C 18.3 (C9). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 237.1019, $C_{15}H_{13}ON_2^+$ required 237.1028, Δ ppm = -3.8 ppm.

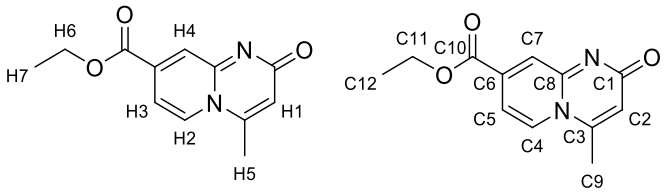
^{1}H NMR



^{13}C NMR

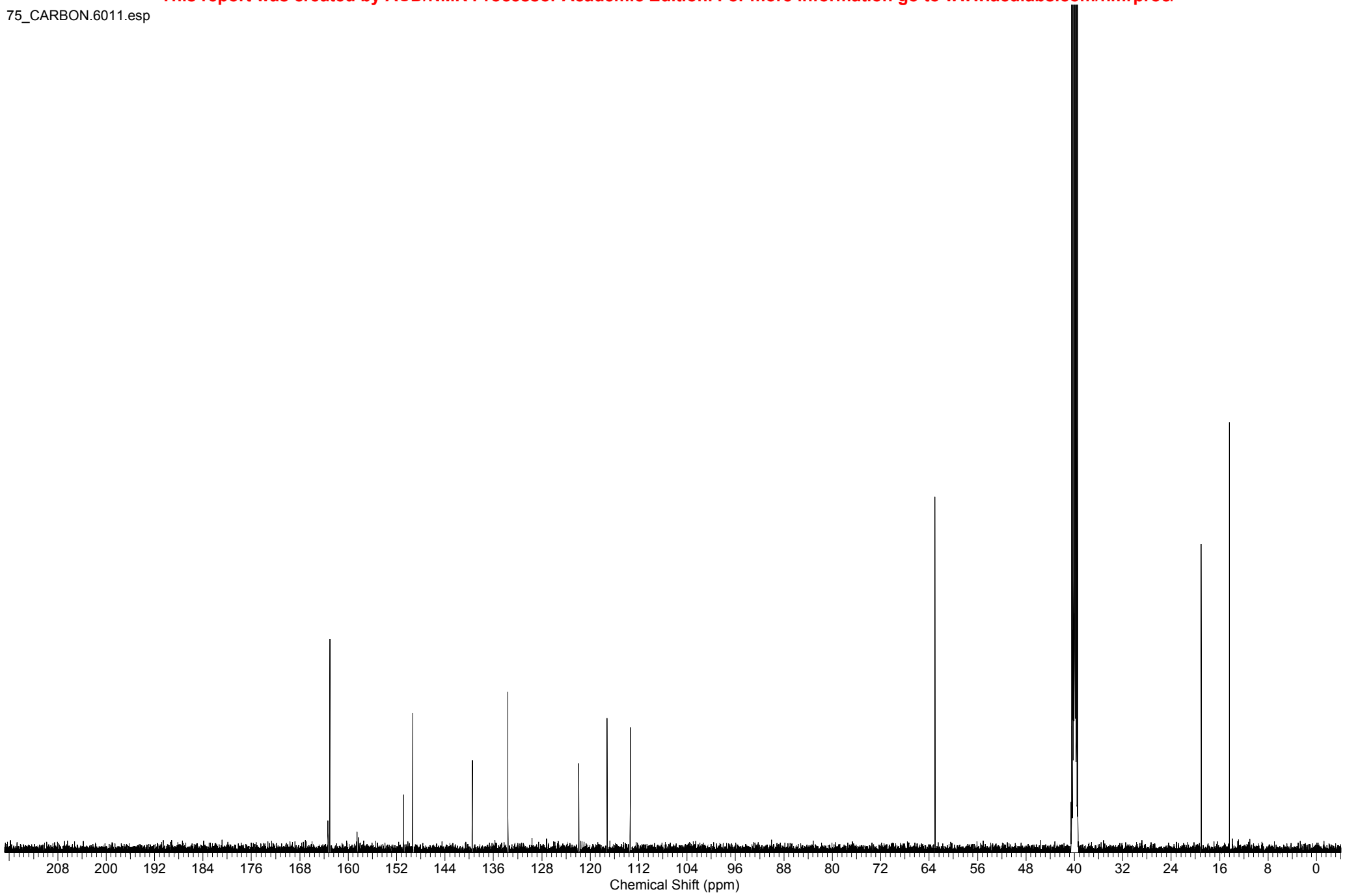


Ethyl 4-methyl-2-oxo-2*H*-pyrido[1,2-a]pyrimidine-8-carboxylate **(75)**

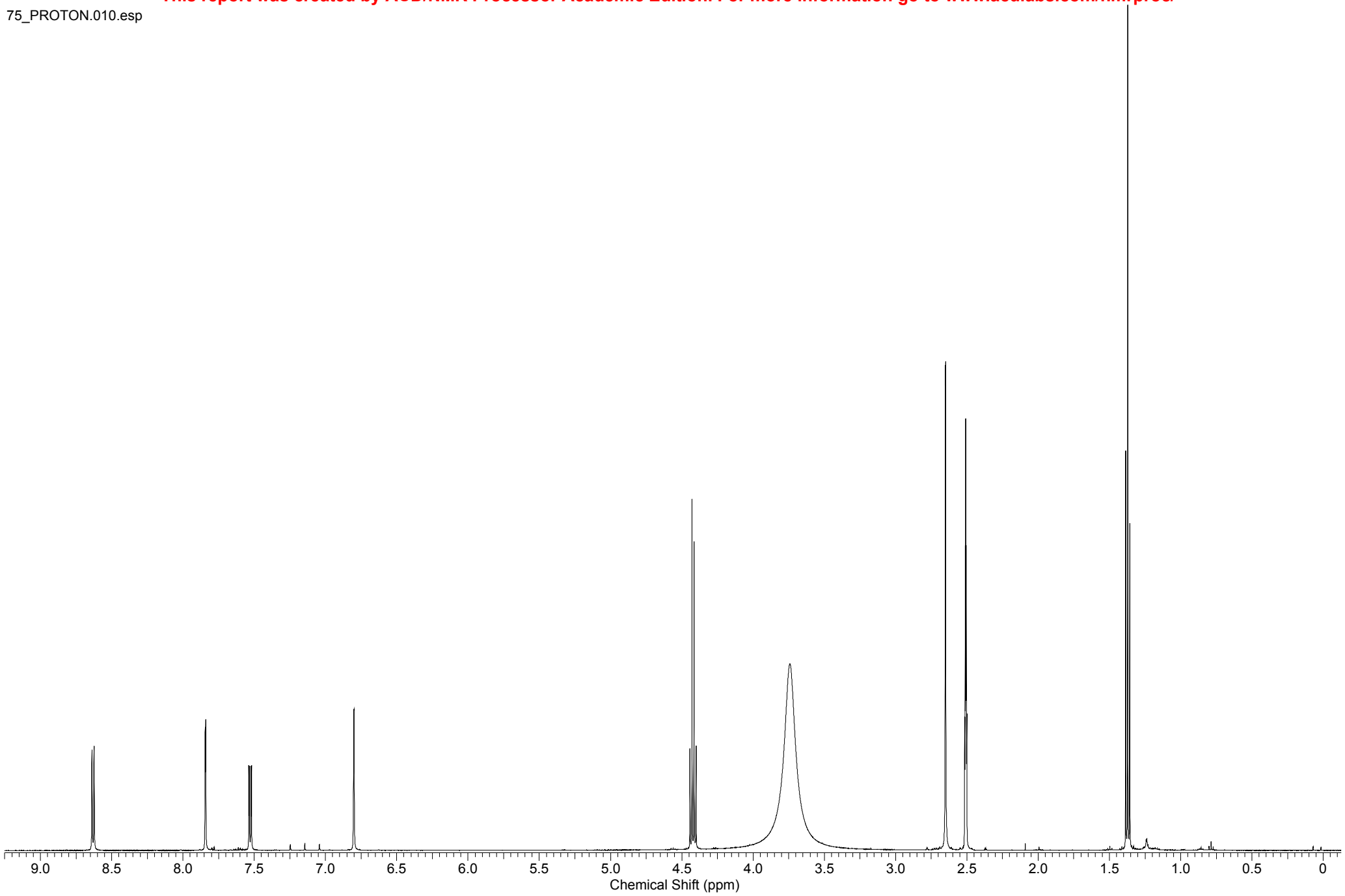


Prepared according to General Method 2 from **50**. The crude product was purified by column chromatography (SiO_2, 30 g, 19:1 CH_2Cl_2: MeOH) to yield a pale yellow solid (0.30 g, 88% purity, 1.15 mmol, 87%). Further purification by preparative HPLC yielded spectroscopically pure material. R_f = 0.43 (9:1 CH_2Cl_2: MeOH). Mpt (CH_2Cl_2): darkens >170 ^oC, decomp, >210 ^oC. IR ν_{max}/cm^{-1} (neat): 3330 (w, br), 3098 (w, C-H), 2911 (w, C-H), 2927 (w, C-H), 2870 (w, C-H), 1724 (med, C=O), 1660 (str, C=O), 1640 (str, C=O), 1619 (str, C=C), 1546 (w), 1471 (str, C=C/C=N), 1438 (med, C=C/C=N), 1392 (med), 1365 (med), 1344 (w), 1271 (med), 1258 (med), 1232 (str, C-O), 1188 (w), 1148 (med), 1100 (med), 1057 (w), 1031 (w), 1012 (med). ^1H NMR (500 MHz, d^6-DMSO): δ_H 8.30 (1H, d, *J* = 7.4 Hz, H2), δ_H 7.58 (1H, app dd, *J* = 2.0, 0.5 Hz, H4), δ_H 7.18 (1H, dd, *J* = 7.4, 2.0 Hz, H3), δ_H 6.43 (1H, d, *J* = 0.7 Hz, H1), δ_H 4.36 (2H, q, *J* = 7.1 Hz, H6), δ_H 2.52 (3H, d, *J* = 0.7 Hz, H5), δ_H 1.34 (3H, t, *J* = 7.1 Hz, H7). ^{13}C NMR (125 MHz, d^6-DMSO): δ_C 167.3 (C1), δ_C 163.3 (C10), δ_C 151.8 (C8), δ_C 147.0 (C3), δ_C 136.5 (C6), δ_C 131.7 (C4), δ_C 125.4 (C7), δ_C 115.9 (C2), δ_C 109.9 (C5), δ_C 62.2 (C11), δ_C 18.5 (C9), δ_C 14.0 (C12). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 233.0911, $C_{12}H_{13}O_3N_2^+$ required 233.0921, Δ ppm = -4.1 ppm.

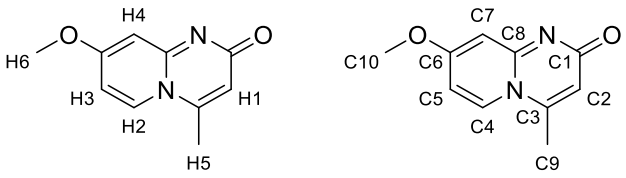
75_CARBON.6011.esp



75_PROTON.010.esp

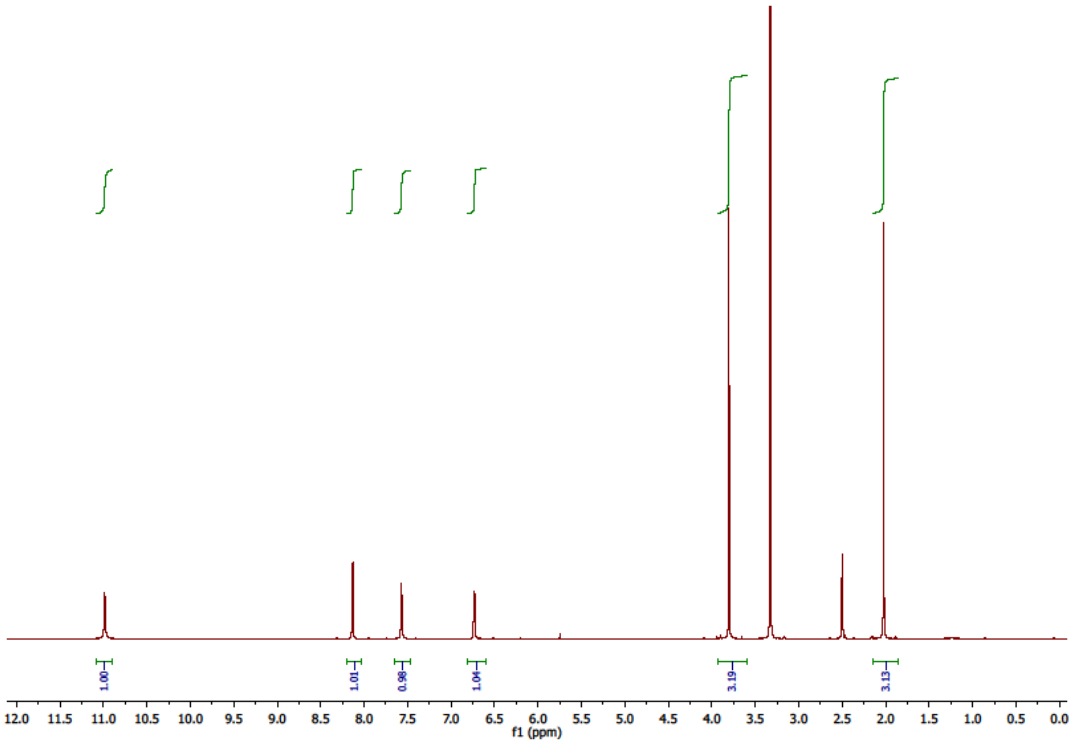


8-Methoxy-4-methyl-2H-pyrido[1,2-a]pyrimidin-2-one **(76)**

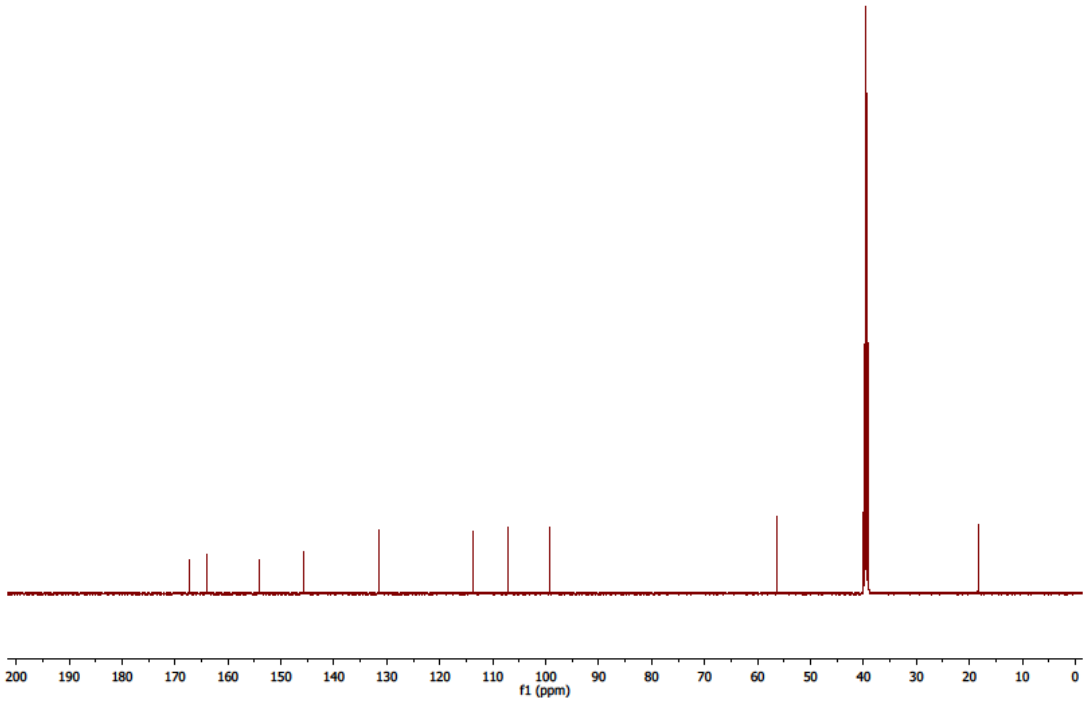


Prepared according to General Method 2 from **51**. The crude product was purified by column chromatography (SiO_2, 30 g, 92:8 CH_2Cl_2: MeOH) to yield a beige solid (quantitative). R_f = 0.42 (9:1 CH_2Cl_2: MeOH). Mpt (CH_2Cl_2): darkens >180 ^oC, melts 201-203 ^oC. IR ν_{max}/cm^{-1} (neat): 3488 (w), 3082 (w, C-H), 1642 (str, C=O), 1579 (str, C=C), 1555 (med, C=C), 1456 (str, C=C/C=N), 1445 (str, C=C/C=N), 1395 (str), 1362 (str), 1261 (str), 1223 (str), 1198 (med), 1184 (med), 1152 (w), 1071 (w), 1057 (w), 1006 (med). ^1H NMR (400 MHz, d^6-DMSO): δ_H 8.10 (1H, d, *J* = 8.0 Hz, H2), δ_H 6.67 (1H, dd, *J* = 8.0, 3.2 Hz, H3), δ_H 6.51 (1H, d, *J* = 3.2 Hz, H4), δ_H 6.20 (1H, d, *J* = 0.8 Hz, H1), δ_H 3.90 (3H, s, H6), δ_H 2.46 (3H, d, *J* = 0.8 Hz, H5). ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 167.4 (C1), δ_C 164.2 (C6), δ_C 154.2 (C8), δ_C 145.8 (C3), δ_C 131.6 (C4), δ_C 113.8 (C2), δ_C 107.2 (C5), δ_C 99.4 (C7), δ_C 56.5 (C10), δ_C 18.5 (C9). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 191.0814, $C_{10}H_{11}O_2N_2^+$ required 191.0815, Δ ppm = -0.4 ppm.

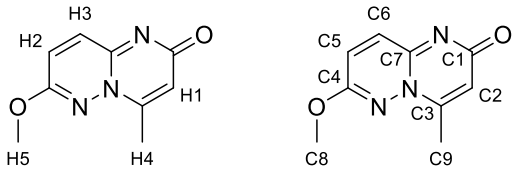
^{1}H NMR



^{13}C NMR

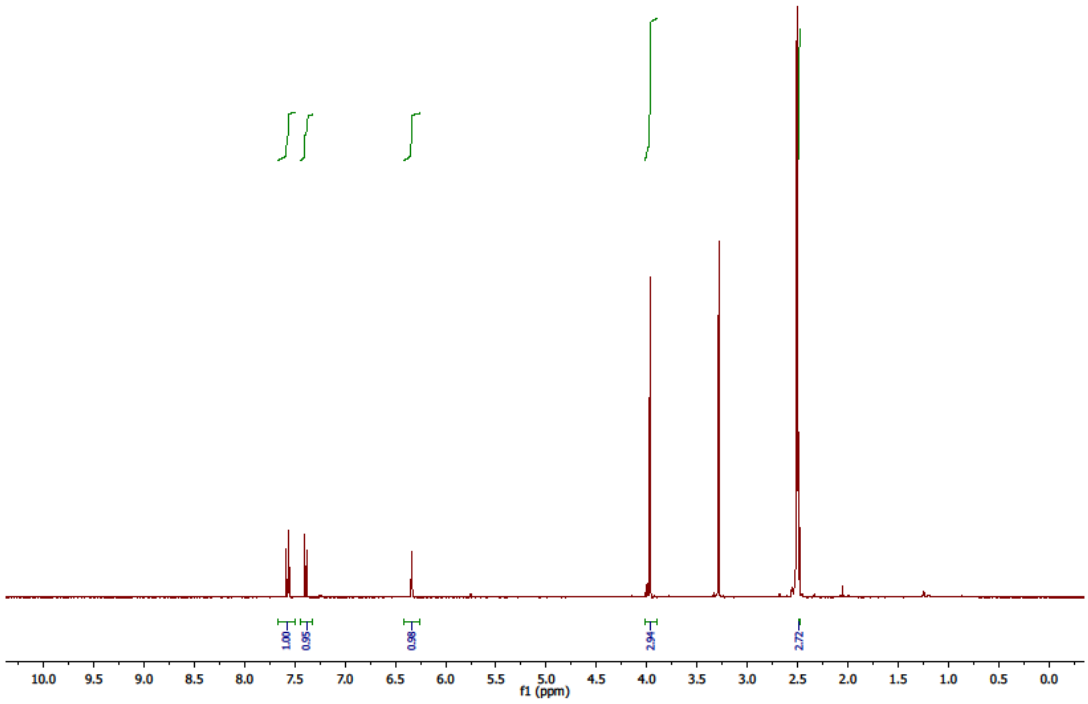


7-Methoxy-4-methyl-2*H*-pyrimido[1,2-b]pyridazin-2-one **(77)**

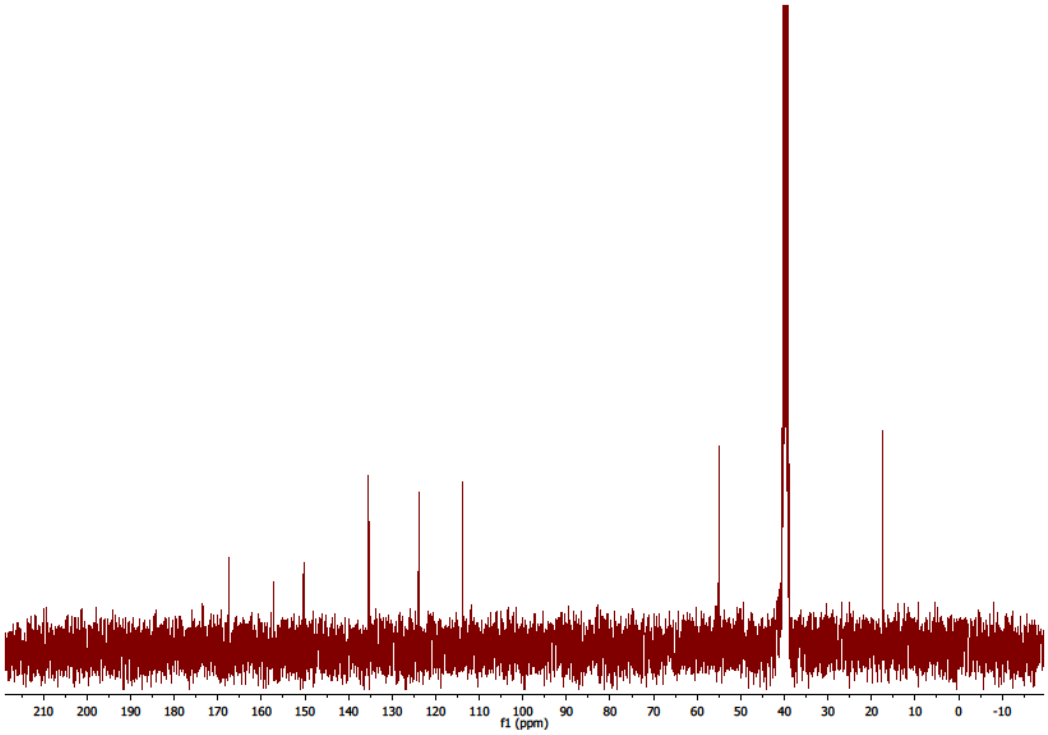


Prepared according to General Method 2 from **52**. The crude product was purified by column chromatography (SiO_2, 10 g, 19:1 CH_2Cl_2: MeOH) to yield an off-white solid (85%). R_f = 0.38 (9:1 CH_2Cl_2: MeOH). Mpt (CH_2Cl_2): phase change >170-220 ^oC then melt/decomposition >255 ^oC. IR ν_{max}/cm^{-1} (neat): 3284 (w), 3181 (w), 3100 (w), 3036 (w), 2966 (w, C-H), 2925 (w, C-H), 2864 (w, C-H), 2236 (med, C≡C), 1650 (str, C=O), 1554 (str, C=C), 1515 (str, C=C), 1494 (str, C=C), 1454 (w), 1427 (med), 1398 (w), 1377 (w), 1341 (str), 1330 (str), 1261 (str), 1229 (str), 1109 (str), 1082 (str), 1002 (w). ^1H NMR (400 MHz, d^6-DMSO): δ_H 7.57 (1H, d, *J* = 8.6 Hz, H2), δ_H 7.39 (1H, d, *J* = 8.6 Hz, H3), δ_H 6.34 (1H, s, H1), δ_H 3.97 (3H, s, H5), δ_H 2.50 (3H, s, H4). ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 167.5 (C4), δ_C 157.0 (C1), δ_C 150.1 (C3 or C7), δ_C 150.0 (C3 or C7), δ_C 135.6 (C5), δ_C 123.9 (C6), δ_C 113.7 (C2), δ_C 54.8 (C8), δ_C 17.4 (C9). HRMS (FTMS ESI+) *m/z* found $[M+H]^+$ 192.0780, $C_9H_{10}N_3O_2^+$ required 192.0773, Δ ppm = 3.6 ppm.

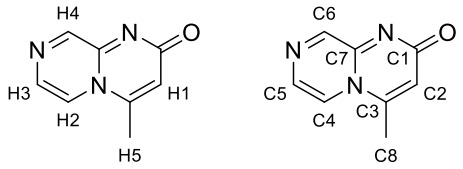
^{1}H NMR



^{13}C NMR

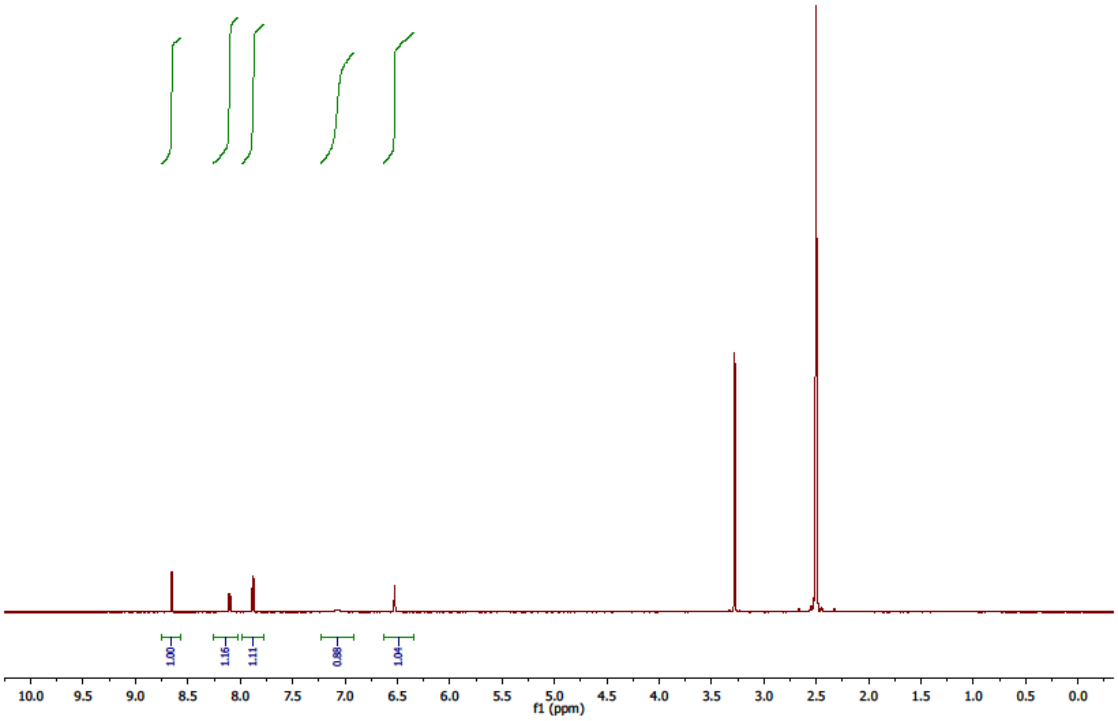


4-Methyl-2*H*-pyrazino[1,2-a]pyrimidin-2-one **(78)**

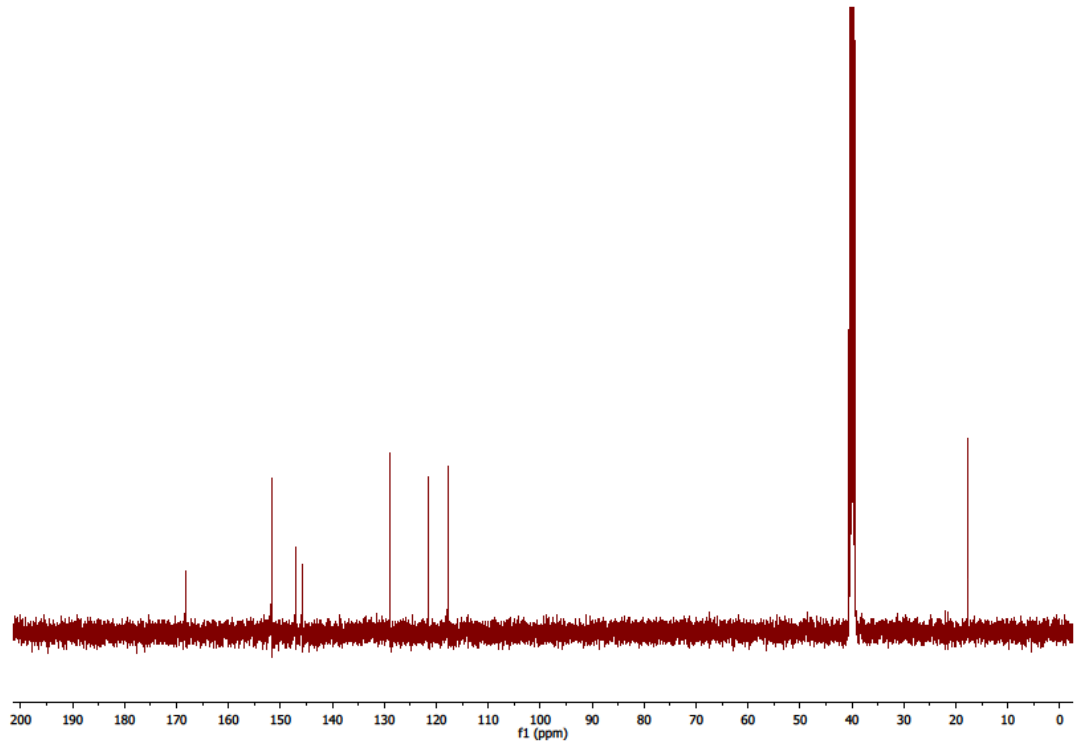


Prepared according to General Method 2 from **53**. The crude product was purified by Combiflash Companion (SiO_2, 12 g, 0-10% MeOH in CH_2Cl_2) to yield a light brown solid (quantitative). R_f = 0.06 (9:1 CH_2Cl_2: MeOH). Mpt (H_2O/MeCN): decomp. >165 ^oC. IR ν_{max}/cm^{-1} (neat): 3127 (w, C-H), 3038 (w, C-H), 1651 (str, C=O), 1607 (str), 1513 (str), 1485 (str), 1448 (w), 1408 (w), 1395 (str), 1371 (med), 1312 (w), 1279 (med), 1250 (w), 1239 (w), 1191 (med), 1109 (w), 1062 (med), 1042 (w). ^1H NMR (400 MHz, d^6-DMSO): δ_H 8.66 (1H, d, *J* = 1.2 Hz, H4), δ_H 8.11 (1H, dd, *J* = 4.9, 1.2 Hz, H3), δ_H 7.88 (1H, d, *J* = 4.9 Hz, H2), δ_H 6.53 (1H, d, *J* = 1.0 Hz, H1), H5 obscured by DMSO signal. ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 167.6 (C1), δ_C 151.1 (C6), δ_C 146.4 (C3), δ_C 145.1 (C7), δ_C 128.2 (C5), δ_C 120.8 (C4), δ_C 116.8 (C2), δ_C 17.3 (C8). HRMS (FTMS ESI+) m/z found [M+H]+ 162.0657, $C_8H_8N_3O^+$ required 162.0662, Δ ppm = -3.9 ppm.

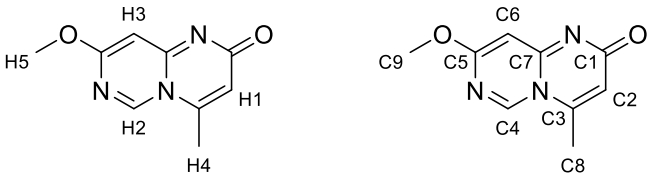
^{1}H NMR



^{13}C NMR

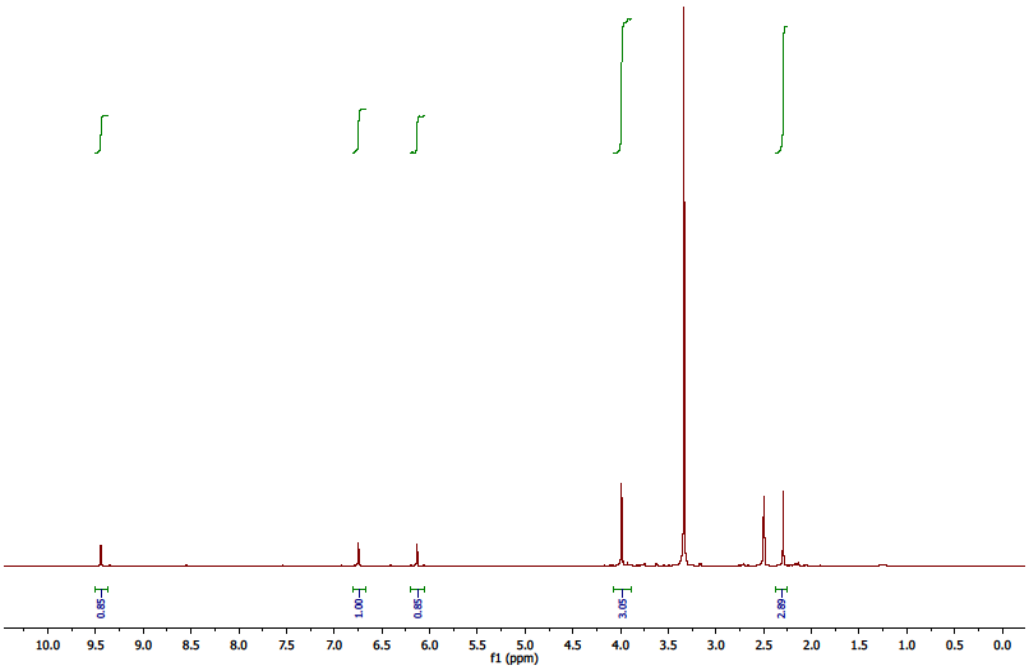


8-Methoxy-4-methyl-2*H*-pyrimido[1,6-a]pyrimidin-2-one **(79)**

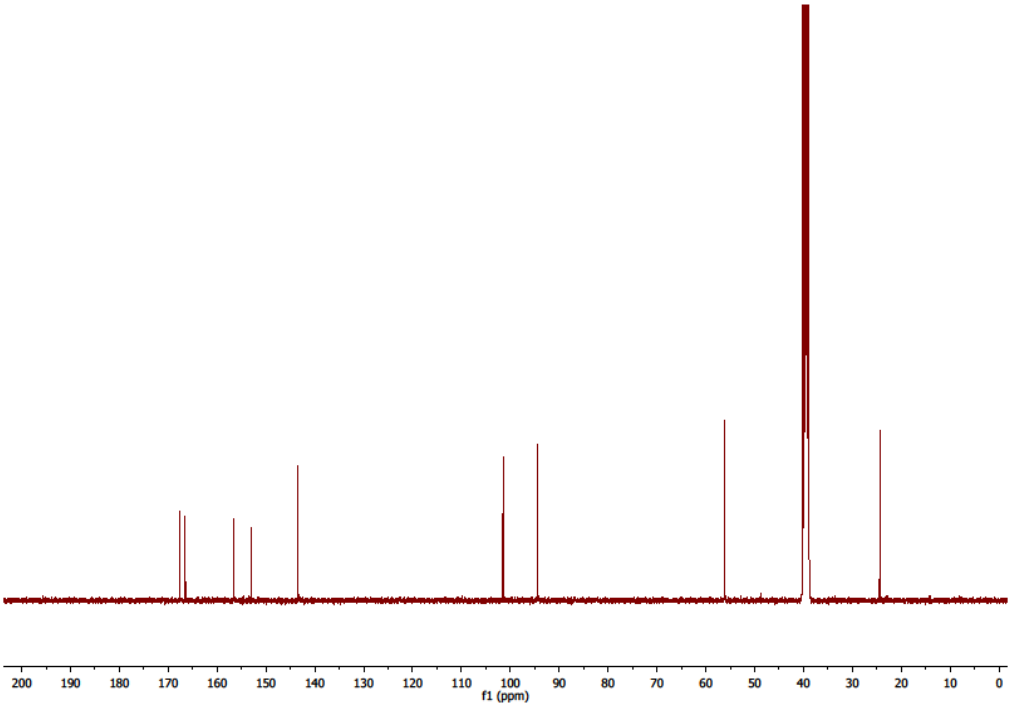


Prepared according to General Method 2 from **55**. The crude product was spectroscopically pure and used without further purification as a yellow solid (quantitative). R_f = 0.23 (1:1 40-60 petroleum ether: EtOAc). Mpt (CH_2Cl_2): 183-185 ^oC. IR ν_{max}/cm^{-1} (neat): 3057 (w, C-H), 1691 (str, C=O), 1618 (str), 1573 (str, C=C/C=N), 1546 (w), 1463 (str), 1394 (str), 1288 (w), 1244 (str), 1231 (str, C-O), 1195 (w), 1177 (w), 1158 (med), 1093 (str), 1011 (med). ^1H NMR (400 MHz, d^6-DMSO): δ_H 9.45 (1H, s, H2), δ_H 6.75 (1H, s, H3), δ_H 6.13 (1H, s, H1), δ_H 3.99 (3H, s, H5), δ_H 2.30 (3H, s, H4). ^{13}C NMR (100 MHz, d^6-DMSO): δ_C 167.7 (C5), δ_C 166.6 (C1), δ_C 156.7 (C3), δ_C 153.1 (C7), δ_C 143.5 (C4), δ_C 101.6 (C2), δ_C 94.5 (C6), δ_C 56.2 (C9), δ_C 24.5 (C8). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 192.0780, $C_9H_{10}O_2N_3^+$ required 192.0773, Δ ppm = -3.6 ppm.

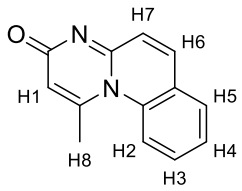
^{1}H NMR

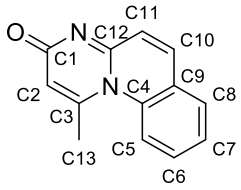


^{13}C NMR



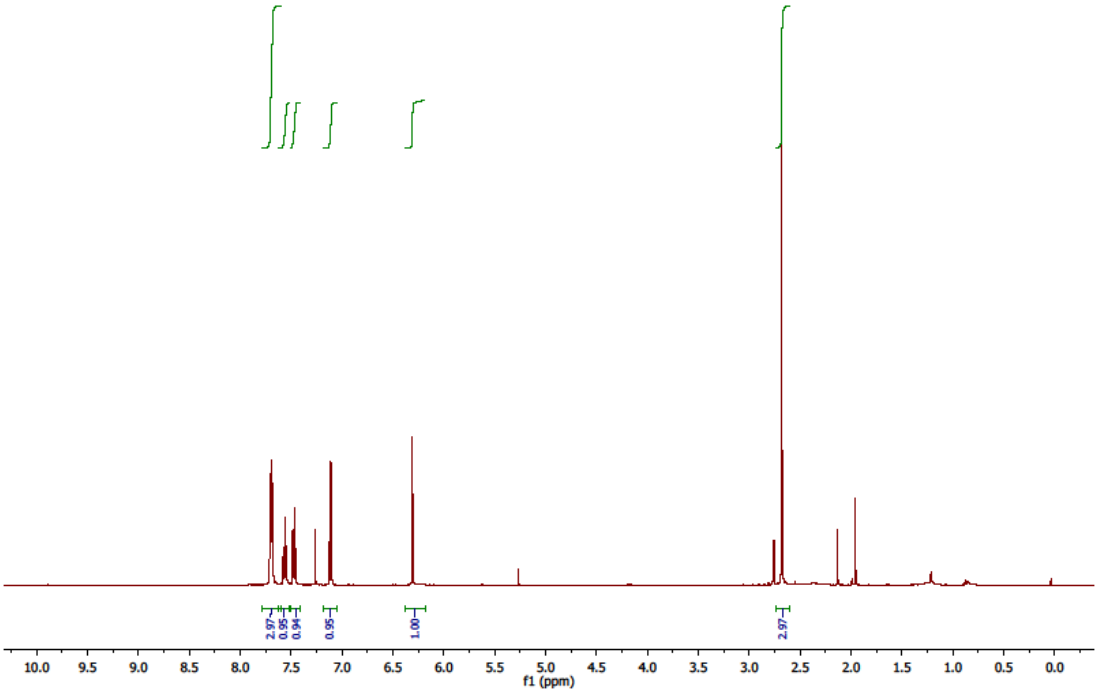
1-Methyl-3H-pyrimido[1,2-a]quinolin-3-one **(80)**



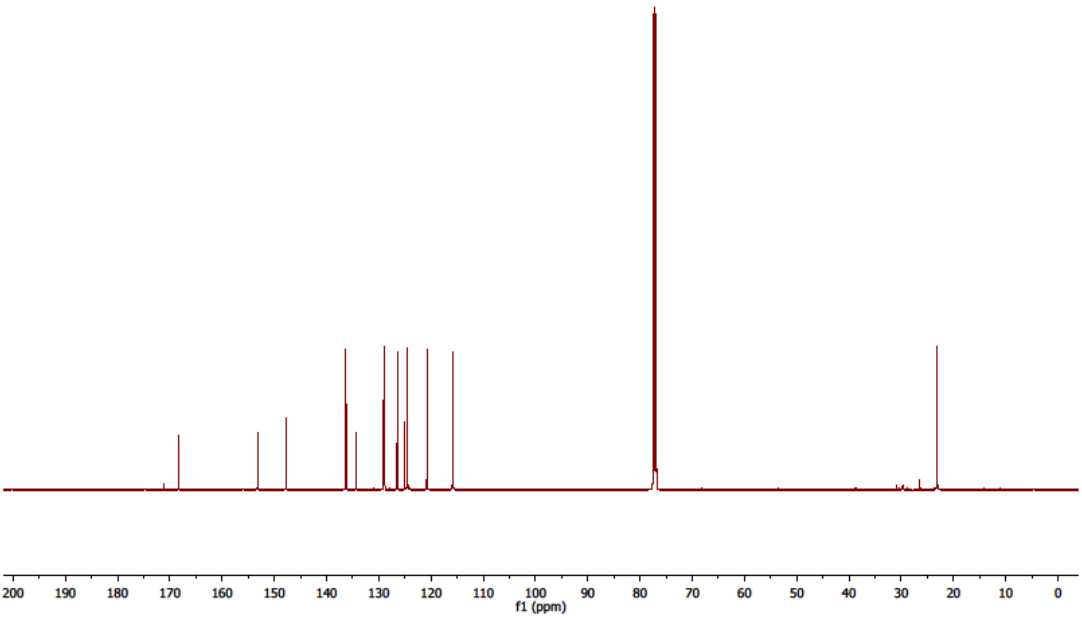


Prepared according to General Method 2 from **57**. The crude product was purified by column chromatography (SiO_2, 20 g, 97:3 then 19:1 CH_2Cl_2: MeOH) to yield a brown wax (50%). R_f = 0.76 (9:1 CH_2Cl_2: MeOH). IR ν_{max}/cm^{-1} (neat): 3390 (w, br, C-H), 3053 (w, C-H), 2980 (w, C-H), 1628 (str, C=O), 1598 (str, C=C), 1561 (w), 1516 (str, C=C), 1470 (med), 1441 (str), 1407 (med), 1389 (med), 1369 (med), 1291 (w), 1262 (w), 1219 (w), 1188 (w), 1164 (w), 1138 (w), 1049 (w), 1025 (w), 1006 (w). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.72-7.66 (3H, m, H2+H5+H6), δ_H 7.56 (1H, ddd, *J* = 8.7, 7.3, 1.5 Hz, H3), δ_H 7.47 (1H, app td, *J* = 7.3, 0.9 Hz, H4), δ_H 7.11 (1H, d, *J* = 9.3 Hz, H7), δ_H 6.31 (1H, d, *J* = 0.7 Hz, H1), δ_H 2.68 (3H, d, *J* = 0.6 Hz, H8). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 168.2 (C1), δ_C 153.1 (C12), δ_C 147.7 (C3), δ_C 136.2 (C10), δ_C 134.4 (C4), δ_C 129.0 (C8), δ_C 128.9 (C6), δ_C 126.4 (C7), δ_C 125.0 (C9), δ_C 124.4 (C11), δ_C 120.7 (C5), δ_C 115.8 (C2), δ_C 23.1 (C13). HRMS (TOF ES+) *m/z* found $[M+H]^+$ 211.0879, $C_{13}H_{11}ON_2^+$ required 211.0871, Δ ppm = 3.8 ppm.

^{1}H NMR



^{13}C NMR



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