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Supplementary Information

Synthesis of two 'heteroaromatic rings of the future' for applications in medicinal chemistry

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1. Materials and instrumentation:

Analytical Equipment

The proton Nuclear Magnetic Resonance spectra (^{1}H NMR) were recorded at 300 and 500 MHz spectrometer. The ^{13}C Nuclear Magnetic Resonance spectra (^{13}C NMR) were recorded at 75 and 125 MHz spectrometer. The chemical shift values (δ) are reported in parts per million (ppm), using tetramethylsilane as the reference (TMS). The signal multiplicities are shown in parentheses (s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet), using as internal standard the values of the coupling constant (*J*) are data in Hertz (*Hz*) and number of protons deduced from the full- on.

The mass analysis by mass spectrometry using electrospray ionization (IES-EM) were realized in a IES-TOF Mass Spectrometer.

Equipments

Below is presented the description of equipments used during synthetic procedures wich is detailed in the experimental section.

Analytical Balance Mettler PE 400 / Sartorius BP 121S

Apparatus meter • Melting point: 381 Marconi AM

Biotage Microwave synthesiser

Chromatographic columns (Vidrolabor)

DSC (NOME)

E2M5 high vacuum pump (Edwards)

Genevac

H-Cube

High Vacuum Pump: V-700 Büchi

ISCO purification system

ISOLUTE 103 for the extraction of water soluble compounds

Jones Flash Master

Magnetic stirrer: IKA C-MAG H57

OA purification system

Reverse phase column- C18

Rotary evaporator with vacuum controller: Büchi R-210

Si-TMT for Pd / Ir removal

System water purifier reverse osmosis LX 0510 (Gehaka)

Solvents and Reagents

The solvents used in extraction and synthesis were properly separated and sent to the waste treatment center. All of the reagents were obtained commercially.

Software

The 3D structures of heterocycles **1** and **2** were constructed and optimized using Spartan'10 software [1]. Initially, a conformational search was carried out using Merck Molecular Force Field (MMFF) [2] and, after, the geometry was optimized and the electronic structure was determined using Density Functional Theory (DFT) [3-5] calculations with B3LYP functional [6-8] and 6-31G* basis set [9-11].

[1] Spartan'10, Wavefunction, Inc., Irvine, CA, 2010.

[2] Halgren, T A. (1996) J. Comp. Chem. 17:490-519.

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[5] Parr RG, Yang W (1989) Density-functional theory of atoms and molecules. Oxford University Press, Oxford

[6] Lee C, Yang W, Parr RG (1988) Phys Rev B 37:785–789

[7] Miehlich B, Savin A, Stoll H, Preuss H (1989) Chem Phys Lett 157:200–206

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[9] R. Ditchfield, W. J. Hehre, and J. A. Pople, "Self-Consistent Molecular Orbital Methods. 9. Extended Gaussian-type basis for molecular-orbital studies of organic molecules," J. Chem. Phys., 54 (1971) 724.

[10] W. J. Hehre, R. Ditchfield, and J. A. Pople, "Self-Consistent Molecular Orbital Methods. 12. Further extensions of Gaussian-type basis sets for use in molecular-orbital studies of organic-molecules," J. Chem. Phys., 56 (1972) 2257.

[11] P. C. Hariharan and J. A. Pople, "Influence of polarization functions on molecular-orbital hydrogenation energies," Theor. Chem. Acc., 28 (1973) 213-22.

2. Synthetic procedure

All solvents used for extraction and chromatography procedures were used as received from commercial suppliers without further purification. All reagents were purchased and used as received unless otherwise noted. The physicochemical properties were calculated using Vortex (2015.07.42634) from Dotmatics Ltd. and MarvinSketch (15.7.20, 2015), ChemAxon.

N-(6-methoxy-4-methylpyridin-3-yl)acetamide (8) 7 (10 g, 72.4 mmol) was added to a round-bottom flask via syringe and fitted with a rubber septum. The flask was purged with nitrogen and dry DCM (60 mL, 1.8M) was added. Acetic anhydride (8.19 mL, 87 mmol) was added and the reaction was stirred at room temperature for 2 hours and monitored by LCMS. Upon completion of the reaction, the mixture was washed with 2M Na_2CO_3 solution, the organic layer was dried with $MgSO_4$ and the solvent removed under reduced pressure to give 13.03g (100%) of crude product, a pale solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ = 2.19(s,3H), 2.21(s,3H), 3.91 (s,3H),), 6.61 (s,1H), 7.27 (s,1H), 8.12 (s,1H). ^{13}C NMR (125 MHz, Methanol-d_4) δ = 169.6, 162.3, 146.7, 143.2, 126.9, 111.5, 77.3, 77.1, 76.8, 53.9, 23.5, 18.0. IR (solid, ν/cm^{-1}): 3307, 3163, 2916, 2846, 2355, 1481, 1359, 1149, 935, 941, 771, 399. HRMS (EI) m/z [M$^+$] calcd for $C_7H_8N_3O^+$:181.0972; found: 181.0971.

1-(5-methoxy-1H-pyrazolo[3,4-c]pyridin-1-yl)ethan-1-one (12) $NaNO_2$ (34.9g, 507 mmol) was added a solution of **7** (13.03 g, 72.4 mmol) and acetic anhydride (30 mL, 318 mmol) in DCM (30 mL) at vigorous stirring at room temperature for 3 hours and after this time the mixture was heated at 50 ^{o}C for 30 minutes. The reaction was monitored by LCMS. Upon completion the reaction, the solvent removed under reduced pressure to give 11.9 g (86%) of crude product, a brown solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ = 2.77 (s,3H), 4.06 (s,3H), 7.03 (s,1H), 8.09 (s,1H), 9.44 (s,1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 7.7, 23.4, 53.5, 111.4, 126.7, 143.8, 145.8, 162.5, 169.5. MS (70 eV) m/z 192.1 (M$^+$, 100), 193.1 (20).

5-methoxy-1H-pyrazolo[3,4-c]pyridine (11) The solution of **12** (8 g, 41.9 mmol) in 32% HCl (15 mL) was heated at 50 °C for 1 hour. The reaction was monitored by LCMS. Upon completion of the reaction, the mixture was cooled to room temperature and basified with 1 M aq. NaOH to pH 10, extracted with chloroform (4x40mL), dried with $MgSO_4$ and evaporated under reduced pressure. The product was purified by Flash chromatography (Hex:EtOAc, 2:1) to give 5.18 g (83%) of orange solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ= δ 8.55 (s,1H), 7.97(s,1H), 7.01(s,1H), 3.86(s,3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.1, 135.9, 133.9, 132.6, 1325, 96.4, 55.5. IR (solid, ν/cm^{-1}): 3307, 3163, 2916, 2846, 2355, 1481, 1359, 1149, 935, 941, 771, 399. HRMS (EI) m/z [M$^+$] calcd for $C_7H_8N_3O^+$: 150.0662; found: 150.0654.

1-(5-chloro-1H-pyrazolo[3,4-c]pyridin-1-yl)ethan-1-one (14) Acetic anhydride (10 mL, 105 mmol) was added to **13** (300 mg, 2.1 mmol) under N_2 atmosphere, the reaction as stirred for 2 hours at room temperature. Then, $NaNO_2$ (653 mg, 9,46 mmol) was added to the mixture at vigorous stirring at room temperature for 3 hours and after this time the mixture was heated to reflux and stirred overnight.

The reaction mixture was concentrated under reduced pressure and the residue was suspense in EtOAc and washed with water. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure resulting in the crude product used as starting material for the next step, 374 mg (89%). HRMS (EI) m/z [M+H$^+$] calcd. To $C_8H_7ClN_3O^+$: 196.0272; found: 196.0308.

5-chloro-1H-pyrazolo[3,4-c]pyridine (15) The solution of **14** (50 mg, 0,14mmol) in 32% HCl (5 mL) was heated at 50 °C for 1 hour. The reaction was monitored by LCMS. Upon completion of the reaction, the mixture was cooled to room temperature and basified with 1 M aq. NaOH to pH 10, extracted with chloroform (4x40mL), dried with $MgSO_4$ and evaporated under reduced pressure. The product was purified by Flash chromatography (DCM:MeOH, 19:1) to give 20 mg (92%) of white solid. ^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ 8.70 (s,1H), 8.06 (s,1H), 7.72 (s,1H). ^{13}C NMR (101 MHz, Methanol-*d*$_4$) δ 141.0, 137.6, 135.1, 134.2, 131.2, 115.6. HRMS (EI) m/z [M+H$^+$] calcd. to $C_6H_5ClN_3^+$: 154.0167; found: 154.0188.

5-amino-4-methylpyridin-2-ol (17) To a solution of **16** (260 mg, 1.69 mmol) in methanol (5 mL) was added Raney 2800 nickel (excess, slurry in methanol) at rt. This suspension was purged with hydrogen and stirred under hydrogen atmosphere for 2 h. Solid material was filtered off and the filtrate was concentrated. The crude solid was taking as starting material for the next step (193 mg, 92%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 6.73 (s, 1H), 6.10 (s, 1H), 2.01 (s, 3H).^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 159.7, 144.5, 130.1, 118.4, 117.9, 18.2.

1,1'-(5-oxo-1*H*-pyrazolo[3,4-c]pyridine-1,6(5H)-diyl)bis(ethan-1-one) (18) Acetic anhydride (7.4 mL, 78.1 mmol) was added to a round bottom flask with **17** (193 mg, 1.55 mmol) under nitrogen atmosphere, the reaction as stirred for 2 hours at room temperature. Then, $NaNO_2$ (536.4, 7.78 mmol) was added to the mixture at vigorous stirring at room temperature for 1 hours and after this time the mixture was refluxed for 17 hours. The reaction was monitored by LCMS. Upon completion of the reaction, the solvent removed under reduced pressure to give the crude product, a brown solid. The crude product was used as starting material for the next step. **18** can by purified by flash chromatography (DCM:MeOH, 9:1), orange solid,125 mg (36%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (d, *J* = 0.5 Hz, 1H), 8.18 (s, 1H), 7.42 (s, 1H), 2.80 (s, 3H), 2.38 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 169.3, 152.9, 138.4, 136.7, 134.5, 134.3, 106.6, 22.4, 21.2. HRMS (EI) m/z [M+] calcd for $C_{10}H_9N_3NaO_3^+$: 242.0536; found: 242.0543.

Intermediate -N-(6-hydroxy-4-methylpyridin-3-yl)acetamide: ^{1}H NMR (500 MHz, Methanol-*d*$_4$) δ 7.44 (s, 1H), 6.43 (s, 1H), 2.17 (s, 3H), 2.12 (s, 3H).^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ 171.8, 163.1, 152.3, 131.4, 119.4, 118.3, 21.2, 17.0. HRMS (EI) m/z [M$^+$] calcd for $C_8H_{11}N_2O_2^+$: 167.0815; found: 167.0819

1*H*-Pyrazolo[3,4-c]pyridin-5-ol (1) The solution of **18** (50 mg, 0.22 mmol) in 32% HCl (5 mL) was stirred for 2 hours at room temperature. The reaction was monitored by TLC. Upon completion of the reaction, the solvent was evaporated under reduced pressure. The product was purificated by flash chromatography (DCM:MeOH, 4:1), orange solid, 28 mg (90%). ^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ 8.89 (s, 1H),

8.30 (s, 1H), 7.44 (s, 1H).^{13}C NMR (101 MHz, Methanol-d_4) δ 152.6, 135.1, 134.2, 133.0, 127.5, 99.5. IR (solid, ν/cm^{-1}): 3154, 1656, 1537, 1402, 607. HRMS (EI) m/z [M$^+$] calcd for $C_6H_6N_3O^+$: 136.0505; found: 136.0506.

***No Needed Purification Route*- 1*H*-Pyrazolo[3,4-c]pyridin-5-ol (1)** To a solution of **16** (3.52 g, 22.83 mmol) in methanol (500 mL) was added Raney 2800 nickel (excess, 15 mL of the slurry in water) at rt. This suspension was purged with hydrogen and stirred under hydrogen atmosphere for 5 h. Solid material was filtered off and the filtrate was concentrated. Acetic anhydride (80 mL, 846 mmol) was added to the crude solid, the reaction as stirred for 17 hours at room temperature. Then, $NaNO_2$ (7.879 g, 114.2 mmol) was added to the mixture at vigorous stirring at room temperature for 3 hours and after this time the mixture was heated to 90°C for 3 hours. The reaction was monitored by TLC (EtOAc). Upon completion of the reaction, the insoluble material was filtered off using silica gel and washed with EtOAc (3x20 mL), the solvent was removed under reduced pressure to give the crude product, a brown solid. 1 N HCl (100 mL) aqueous solution was added to crude product and it was stirred for 17 hours at room temperature. The reaction was monitored by TLC (EtOAc). Upon completion of the reaction, the solvent was evaporated under reduced pressure resulting in the crude hydrochloride form. The product was purified by flash chromatography (DCM to remove impurities, and them DCM:MeOH, 4:1), orange solid, 3.23 g (82%).^{1}H NMR (400 MHz, Methanol-d_4) δ 8.89 (s, 1H), 8.30 (s, 1H), 7.44 (s, 1H).^{13}C NMR (101 MHz, Methanol-d_4) δ 152.6, 135.1, 134.2, 133.0, 127.5, 99.5. IR (solid, ν/cm^{-1}): 3154, 1656, 1537, 1402, 607. HRMS (EI) m/z [M$^+$] calcd for $C_6H_6N_3O^+$: 136.0505; found: 136.0506.

3-(2-ethoxy-2-oxoethyl)pyridine 1-oxide (22) A solution of m-CPBA (91 mmol, 15.67 g) in chloroform (100 mL) was dropped by addition funnel to a solution of **21** (60.6 mmol, 10g) at stirring at room temperature. The reaction was followed by LCMS. After 6 hours the reaction was completed, the solvent was removed under reduced pressure and then solved in 2M Na_2CO_3 solution and extracted with chloroform (3x 20 mL). The organic layer was dried with $MgSO_4$ and the solvent removed under reduced pressure to give 9.98 g (91%) of white crystal. m.p. 103 °C. ^{1}H NMR (500 MHz, $CDCl_3$):δ = 1.24 (t, J= 5 Hz, 3H), 3.57 (s. 2H), 4.36 (q, J= 5Hz, 2H), 7.26 (s, 1H), 7.26 (s, 1H), 8.19 (s, 1H), 8.2 (s, 1H).^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 139.8, 137.9, 133.6, 128.0, 125.8, 61.7, 38.0, 14.1. IR (solid, ν/cm^{-1}): 3377, 2330, 1724, 1442, 1263, 1159, 1022, 769. HRMS (EI) m/z [M$^+$] calcd for $C_9H_{12}NO_3^+$: 182,0812; found: 182,0814.

1-ethoxy-3-(2-ethoxy-2-oxoethyl)pyridin-1-ium iodide (23) Iodoethane (15 mL, 188 mmol) was added to **22** (9.87 g, 54.53 mmol), the mixture was stirred for 6 hours at 40 °C under nitrogen atmosphere. The mixture was concentred under reduced pressure, resulting in 17.45g (95%) of crude product, dark orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, J= 5 Hz, 3H), 3.57 (s, 2H), 4.36 (q, J= 5Hz, 2H), 7.26 (s, 1H), 7.26 (s, 1H), 8.19 (s, 1H), 8.2 (s, 1H).

ethyl 2-(4-cyanopyridin-3-yl)acetate (20) KCN solution (3.55 g, 54.5 mmol) in water (20 mL) was added by dropwise for 20 minutes to a solution of **23** (18.37, 54.5 mmol) in EtOH:H_2O (7:3, 30 mL) at stirring at 50 °C for 4 hours. The reaction was followed by LCMS. The reaction mixture was poured in ice and extracted with DCM (3x30), dried with $MgSO_4$ and concentrated under reduced pressure. The

product was purified by Flash chromatography (Hex:EtOAct, 6:4) to give 7.14 g (69%) of dark orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J*= 6 Hz, 3H), 3.82 (s, 2H), 4.45 (q, *J*= 6Hz, 2H), 7.5 (d, *J*=2Hz, 1H), 8.65 (d, *J*=6Hz, 1H), 8.68 (s, 1H). IR (solid, *v*/cm^{-1}): 2355, 1732, 1166, 1024, 773, 769, 578. HRMS (EI) m/z [M+] calcd. for $C_{10}H_{11}N_2O_2^+$: 191.0815; found: 191.0831.

1,4-dihydro-2,6-naphthyridin-3(2H)-one (19) A solution of **20** (5.98 g, 31.4 mmol) in acetic acid:ethanol (150 ml, 1:4) was hydrogenated by H-Cube for 24h at 30 bar and 35 °C with a Pd/C 10% (30 mm) column. The reaction was monitored by TLC (EtOAc). Upon completion of the reaction, the mixture was removed from the H-Cube and the solvent was evaporated under reduced pressure. The residue was solved in potassium carbonate 10% and then extracted with $CHCl_3$ (6 x 20 mL), dried over $MgSO_4$ and evaporated to afford 4.36 g (94%) of pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.24 (t, *J*= 6 Hz, 3H), 3.82 (s, 2H), 4.45 (q, *J*= 6Hz, 2H), 7.5 (d, *J*=2Hz, 1H), 8.65 (d, *J*=6Hz, 1H), 8.68 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 32.4, 44.5, 120.5, 127.6, 140.4, 146.8, 147.8, 176.2. IV (solid, *v*/cm^{-1}): 3398, 2357, 1647, 1217, 1020, 771, 667, 576. HRMS (EI) m/z [M$^+$] calcd. for $C_8H_9N_2O^+$:149.0709; found: 149.0711.

2,6-naphthyridin-3-ol (2) ***Method A***- Activated carbon (4 mg) was added to a solution of **19** (4 mg, 0.02 mmol) in xylene (3 mL) at 120°C under oxygen saturated atmosphere. The reaction was stirred for 24h under air bubbling and followed by TLC (EtOAc). The reaction was filtered by celite and washed with EtOAc. The solvent was removed under reduced pressure and the product was purified by flash chromatography (EtOAc) to give 3 mg (79%) of yellow solid. ***Method B***- Activated carbon (460 mg) was added to a solution of **19** (4.6 g, 31 mmol) in xylene (150 mL) at 120 °C. The reaction was stirred for 24h under air bubbling and followed by TLC (EtOAc). The reaction was filtered by celite and washed with EtOAc. The solvent was removed under reduced pressure and the product was purified by flash chromatography (EtOAc) to give 1,62 g (36%) of yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.07 (s, 1H), 7.82 (d, *J* = 5.7 Hz, 1H), 8.35 (d, *J* = 5.7 Hz, 1H), 9.05 (s, 1H), 9.21 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) = δ 161.5, 150.9, 150.3, 140.2, 133.7, 124.6, 119.1, 99.4. IR (solid, *v*/cm^{-1}): 3261, 2914, 771, 669, 399. HRMS (EI) m/z [M$^+$] calcd. for $C_8H_7N_2O^+$:147.0553; found: 147.0548.

3. Aqueous solubility measure

In order to access water solubility of the three heterocyclic systems we used absorption spectroscopy. For that, a saturated solution of each compound was prepared by stirring approximately 10 mg of the compound in 1 mL of water for 48 hours, followed by filtration of the non-soluble material using 0.2uM siringe filter (Sartorius AG, Goettingen, Germany). A calibration curve was prepared by using standard aqueous solutions which were prepared using analytical balances and glassware. By analyzing absorbance in of diverse dilutions of the saturated solution and comparing to the calibration curve it was possible to obtain the solubility (Supplementary Table 1).

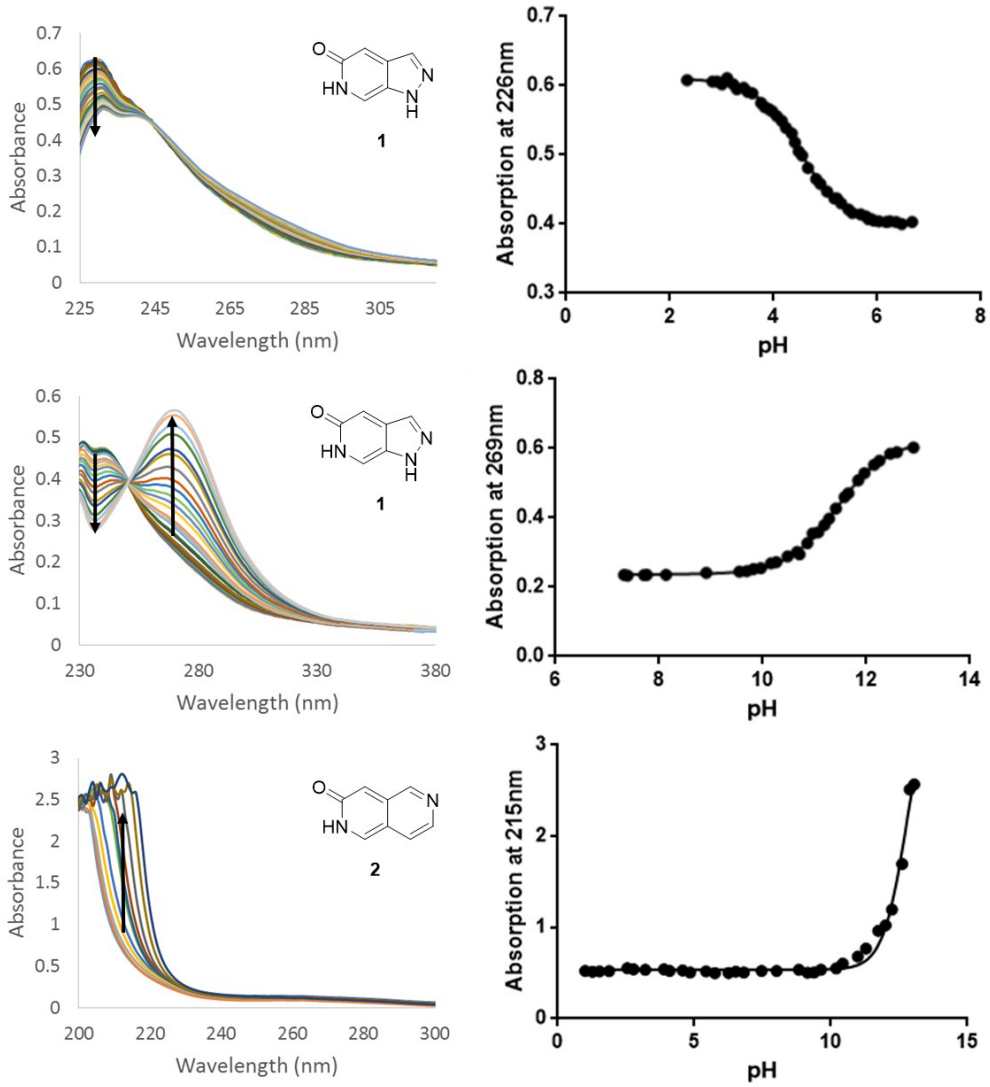
Supplementary Table 1. Aqueous solubility data.

Scaffold	***Wavelength***	***Calibration curve***			***Exp. Water Solubility (g/L)***	***Calcd. Water Solubility (g/L)***
		R^2	Intercept	Slope		
1	222 nm	0.992	0.005	12.61	301	37.32
2	220 nm	0.993	-0.007	35.44	2.1	10.52
3	Pearlman, R.S.; Yalkowsky, S.H.; Banerjee, S. J. Phys. Chem. Ref. Data. 1984, 13, 555.				0.83	3.47
4	**data not available**					
5	3-Hydroxyisoquinoline; MSDS No. A0338 [Online]; Alfa Aesar: Karsruhe, Germany. Jun 27, 2008. http://www.alfa.com/content/msds/english/L19428.pdf (accessed Oct 7, 2015).				Insoluble	0.76
6	Pearlman, R.S.; Yalkowsky, S.H.; Banerjee, S. J. Phys. Chem. Ref. Data. 1984, 13, 555.				4.5	0.98

4. pKa assays

In order to analyze the process of protonation and deprotonation, solutions of each compound in Britton-Robinson buffer were prepared and pH was adjusted to **1** using concentrated HCl. Using a concentrated solution of NaOH, the solution's pH was slowly enhanced till pH 13, with concomitant obtainment of absorption spectra in several values of pH. In the pH range studied it was possible to observe one spectral change in **2**, while two were observed for compound **1**. These spectral changes can be reasoned as different states of ionization and, to calculate the pKa, a sigmoid function was fitted to the experimental data and inflection point was calculated. Regarding compound **1**, the first pKA was around 4.5 while the second one was around 11.4. Once the curve for compound **2** did not reach a plateau between pH 1 and 13 it was not possible to calculate the exact pKa, however we can observe a turning point with a pKa over 12. Spectral changes, plotted data and fitted curves are shown in the figure S1.

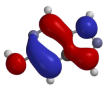
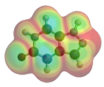
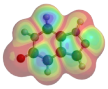
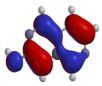
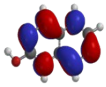
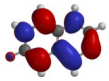
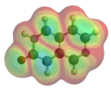
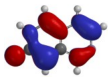
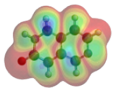
Figure S1. Spectral changes plotted data and fitted curves.



5. Calculated highest occupied molecular orbitals (HOMOs) and lowest unoccupied molecular orbitals (LUMOs)

We carried out molecular orbital calculations (Supplementary Table 2) for both tautomers of **1** and **2**, **1a** and **2a** respectively, aiming to evaluate the electron density variation according to the proton position.

Supplementary Table 2. Calculated highest occupied molecular orbitals (HOMOs) and lowest unoccupied molecular orbitals (LUMOs) for heterocycles 1, 1a, 2 and 2a, and maps indicating the electron density of the LUMO. (color range: 0 = red to 0.026 = blue) using Spartan'10 software (B3LYP/6-31g*).

	HOMO	HOMO map	LUMO	LUMO map
1	E_{HOMO} (eV) -5.85			E_{LUMO} (eV) -1.31	
1a	E_{HOMO} (eV) -5.62			E_{LUMO} (eV) -2.38	
2	E_{HOMO} (eV) -6.11			E_{LUMO} (eV) -1.90		
2a	E_{HOMO} (eV) -5.62			E_{LUMO} (eV) -2.38		

6. Atom coordinates

Supplementary Table 3. Atom coordinates for compounds 1.

Center Number	Atomic Number	Coordinates (Angstroms)		
		x	y	z
1	6	-0.788929049	-1.172.409.288	0.000000000
2	6	-0.308561154	1.583.857.946	0.000000000
3	6	1.845.179.949	-1.279.023.111	0.000000000
4	6	0.533543385	-0.709030843	0.000000000
5	6	0.766575426	0.690076977	0.000000000
6	6	-1.781.520.459	-0.197980186	0.000000000
7	7	2.780.144.930	-0.342677096	0.000000000
8	7	-1.558.825.077	1.131.368.836	0.000000000
9	7	2.130.544.137	0.843949537	0.000000000
10	1	-1.049.069.226	-2.224.820.644	0.000000000
11	1	-0.171436016	2.663.774.778	0.000000000
12	1	2.131.025.605	-2.322.258.773	0.000000000
13	1	2.671.784.558	1.694.278.155	0.000000000
14	1	-3.604.291.228	0.236912498	0.000000000
15	8	-3.084.291.056	-0.585778572	0.000000000

Supplementary Table 4. Atom coordinates for compounds 1a.

Center Number	Atomic Number	Coordinates (Angstroms)		
		x	y	z
1	6	-0.798587993	-1.210.146.207	0.000000000
2	6	-0.306872246	1.591.973.828	0.000000000
3	6	1.810.973.339	-1.280.653.570	0.000000000
4	6	0.486102816	-0.710771812	0.000000000
5	6	0.735687818	0.705693662	0.000000000
6	6	-1.930.900.249	-0.315866350	0.000000000
7	7	2.742.149.391	-0.351077269	0.000000000
8	7	2.110.370.218	0.847509678	0.000000000
9	1	-1.010.679.454	-2.273.056.015	0.000000000
10	1	-0.213920724	2.672.163.920	0.000000000
11	1	2.090.572.155	-2.325.410.372	0.000000000
12	1	2.663.340.575	1.688.968.053	0.000000000
13	8	-3.124.875.933	-0.610531947	0.000000000
14	7	-1.563.931.915	1.065.422.029	0.000000000
15	1	-2.366.457.017	1.684.703.966	0.000000000

Supplementary Table 5. Atom coordinates for compounds 2.

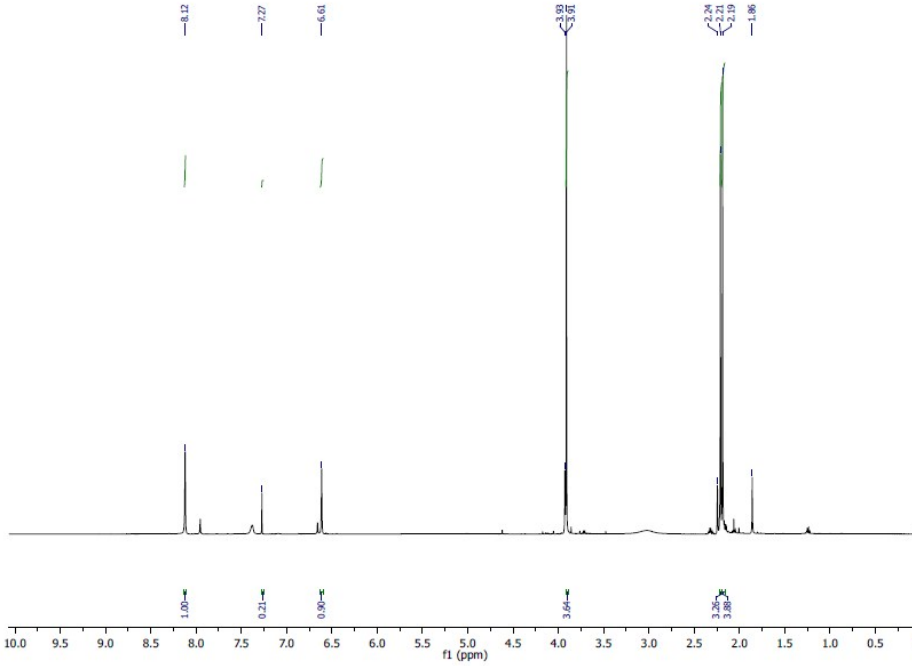
Center Number	Atomic Number	Coordinates (Angstroms)		
		x	y	z
1	6	1.841.353.357	-1.259.165.142	0.000000000
2	6	-1.018.734.761	1.129.311.827	0.000000000
3	6	2.875.454.571	-0.353338308	0.000000000
4	6	-0.644757976	-1.600.892.522	0.000000000
5	6	1.464.728.388	1.461.021.632	0.000000000
6	6	0.509063750	-0.776752174	0.000000000
7	6	0.300622915	0.634295915	0.000000000
8	6	-2.053.469.278	0.211477237	0.000000000
9	7	2.694.969.860	0.999577656	0.000000000
10	7	-1.876.894.927	-1.130.866.789	0.000000000
11	1	2.036.225.491	-2.328.515.740	0.000000000
12	1	-1.226.151.954	2.194.221.273	0.000000000
13	1	3.910.220.075	-0.686894672	0.000000000
14	1	-0.535147010	-2.685.374.942	0.000000000
15	1	1.344.041.651	2.545.053.763	0.000000000
16	8	-3.335.926.230	0.642227751	0.000000000
17	1	-3.888.001.888	-0.160080041	0.000000000

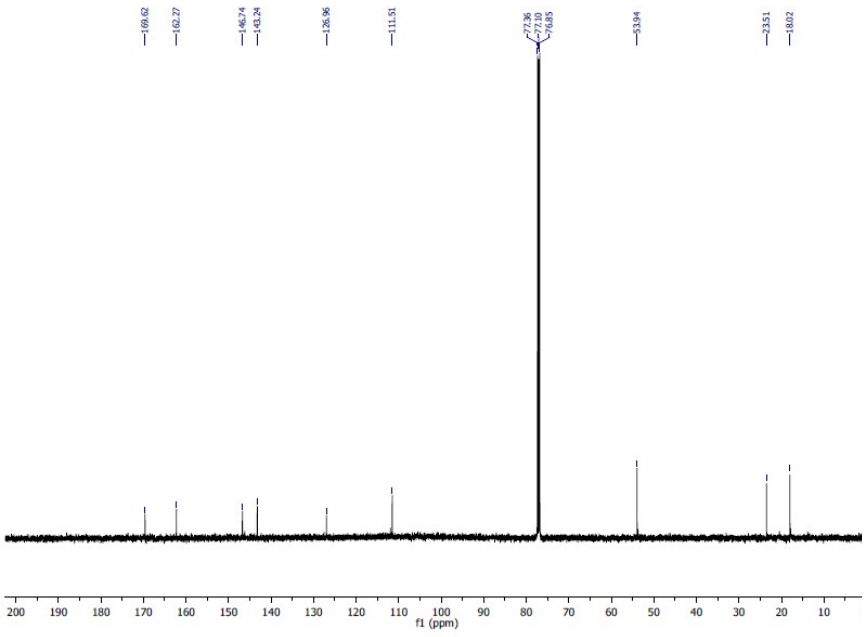
Supplementary Table 6. Atom coordinates for compounds 2a.

Center Number	Atomic Number	Coordinates (Angstroms)		
		x	y	z
1	6	1.835.656.323	-1.266.723.442	0.000000000
2	6	-1.016.031.716	1.162.967.079	0.000000000
3	6	2.858.013.230	-0.363727697	0.000000000
4	6	-0.629218261	-1.608.821.166	0.000000000
5	6	1.450.461.664	1.462.442.363	0.000000000
6	6	0.487432380	-0.791243184	0.000000000
7	6	0.262772904	0.636598402	0.000000000
8	6	-2.187.117.954	0.329336949	0.000000000
9	7	2.669.424.092	1.004.233.804	0.000000000
10	7	-1.862.667.287	-1.067.147.492	0.000000000
11	8	-3.367.914.688	0.661368719	0.000000000
12	1	2.033.999.567	-2.335.384.741	0.000000000
13	1	-1.179.530.562	2.235.486.870	0.000000000
14	1	3.895.133.720	-0.686890861	0.000000000
15	1	-0.565570761	-2.692.661.947	0.000000000
16	1	1.324.856.646	2.546.190.856	0.000000000
17	1	-2.682.135.901	-1.666.223.428	0.000000000

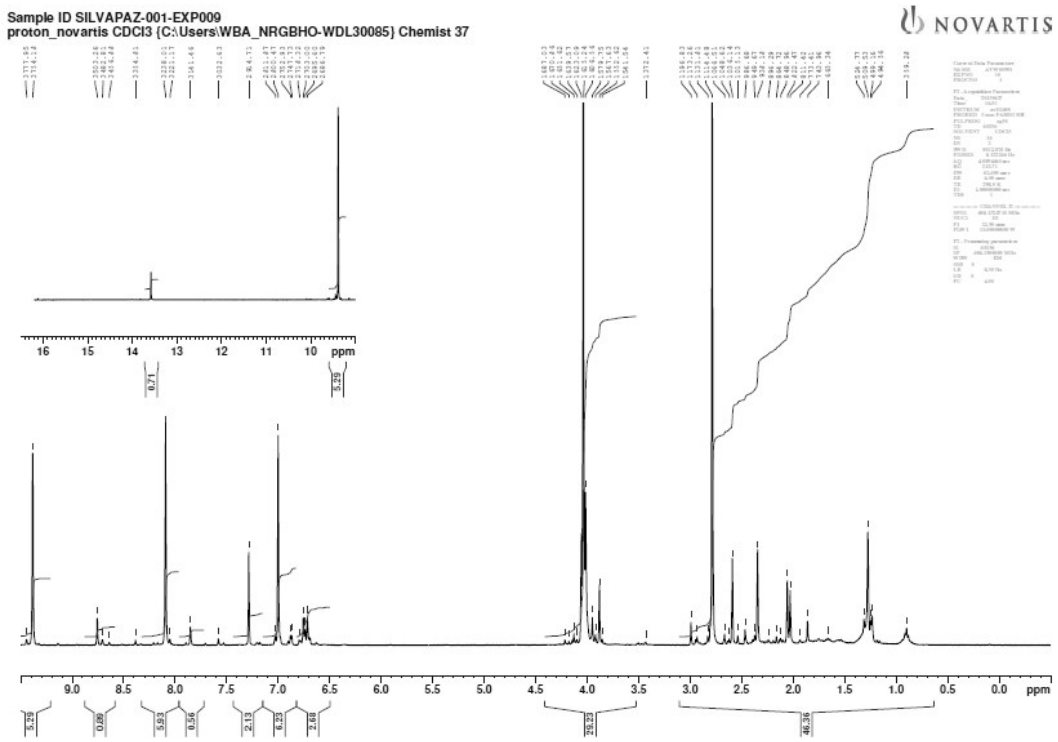
7. NMR-spectra

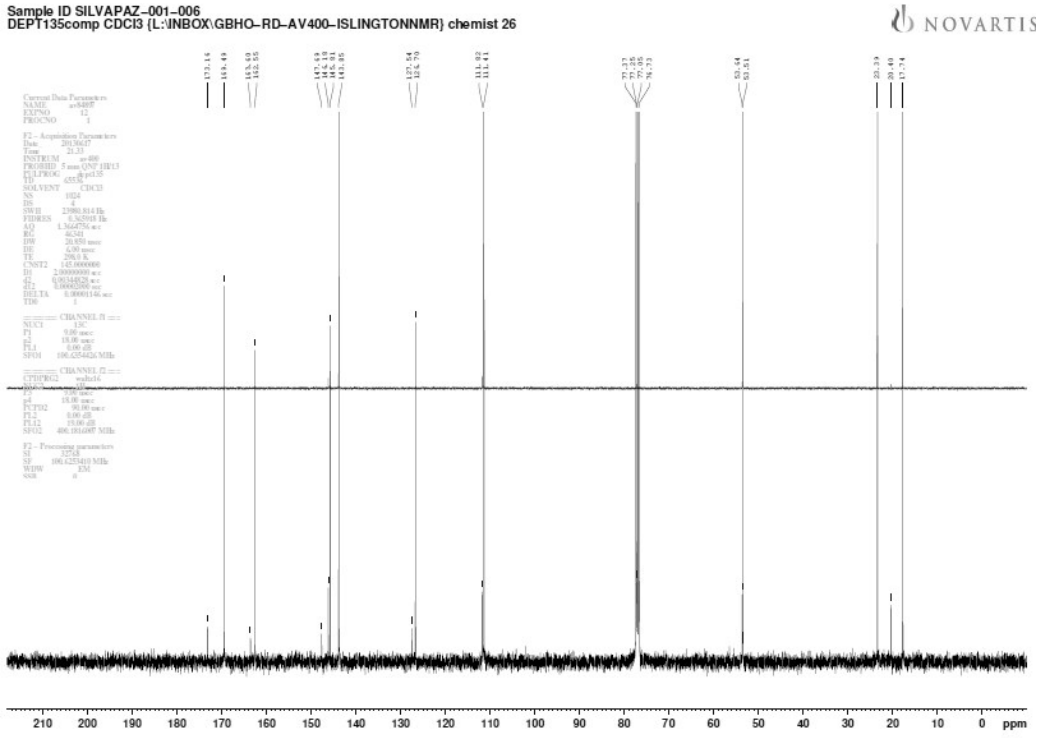
N-(6-methoxy-4-methylpyridin-3-yl)acetamide **(8)**



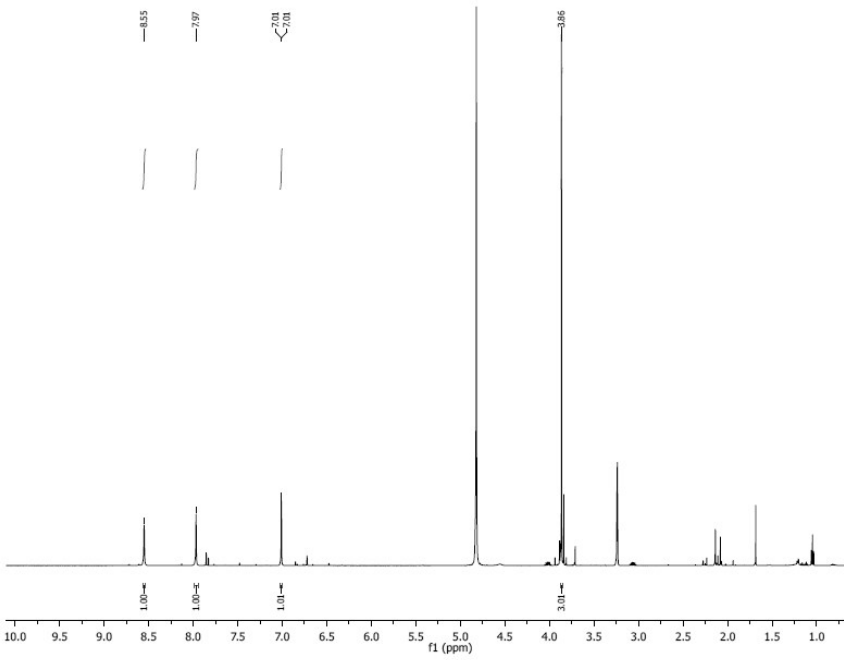


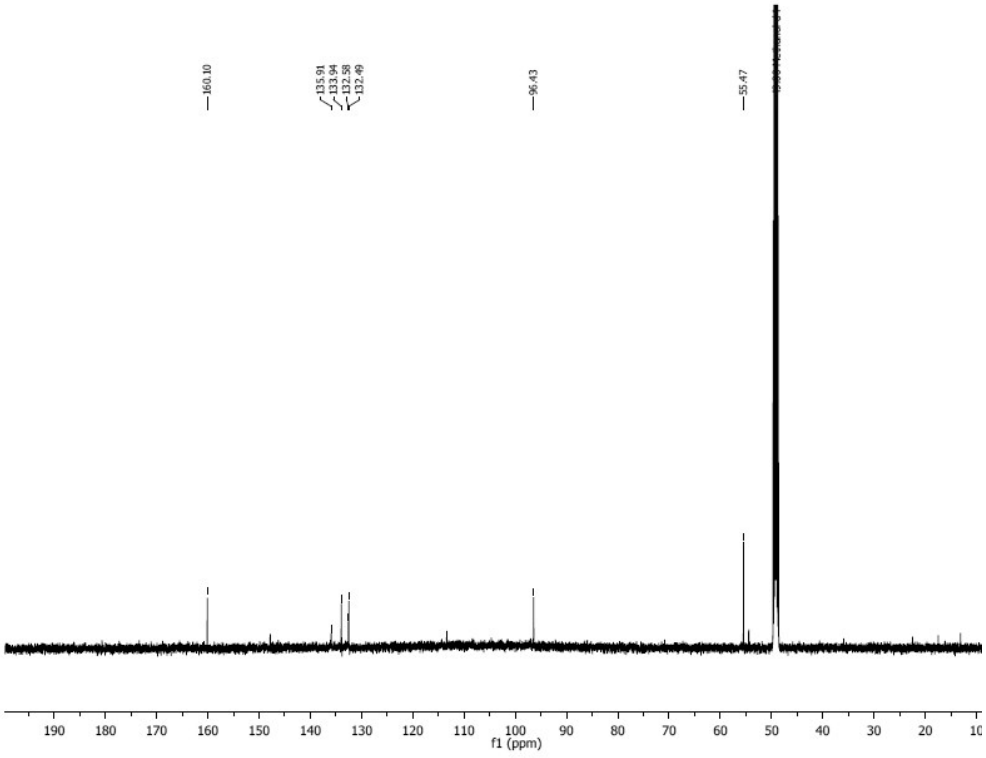
1-(5-methoxy-1H-pyrazolo[3,4-c]pyridin-1-yl)ethan-1-one (12)



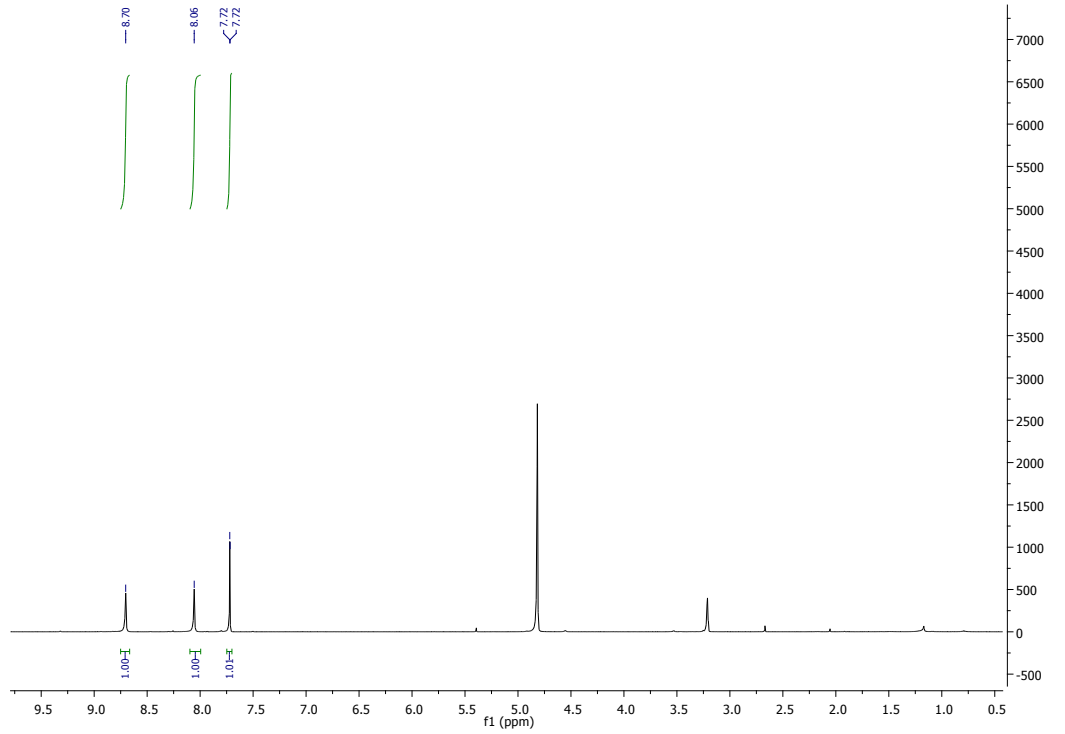


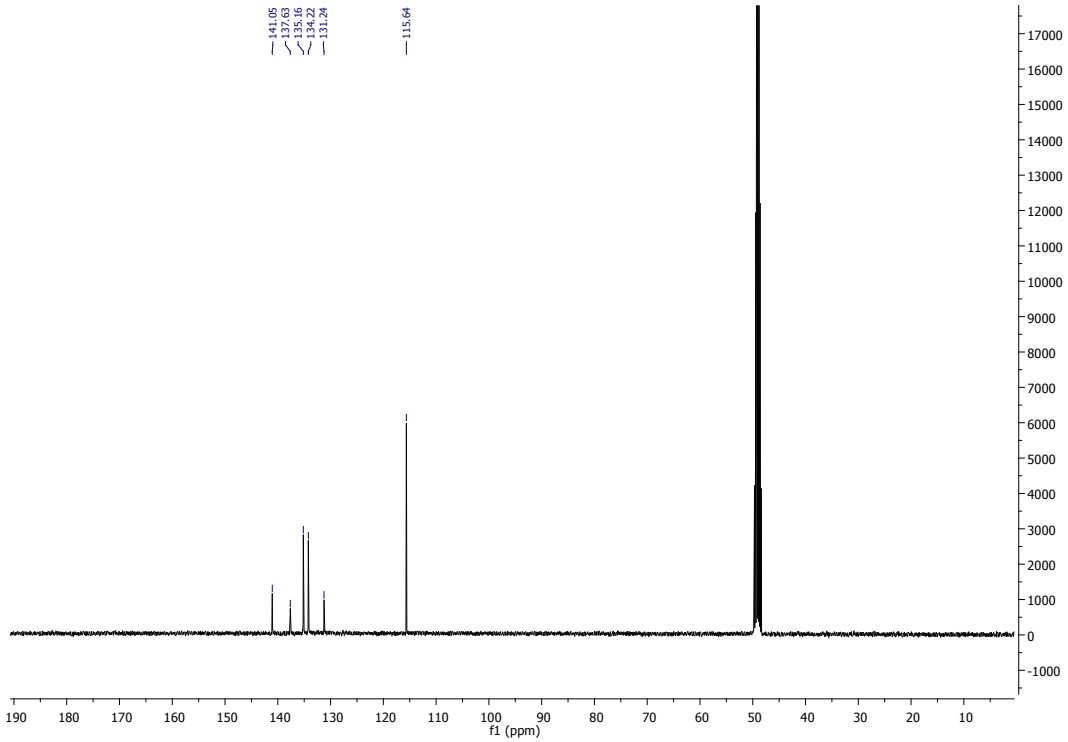
5-methoxy-1H-pyrazolo[3,4-c]pyridine (11)



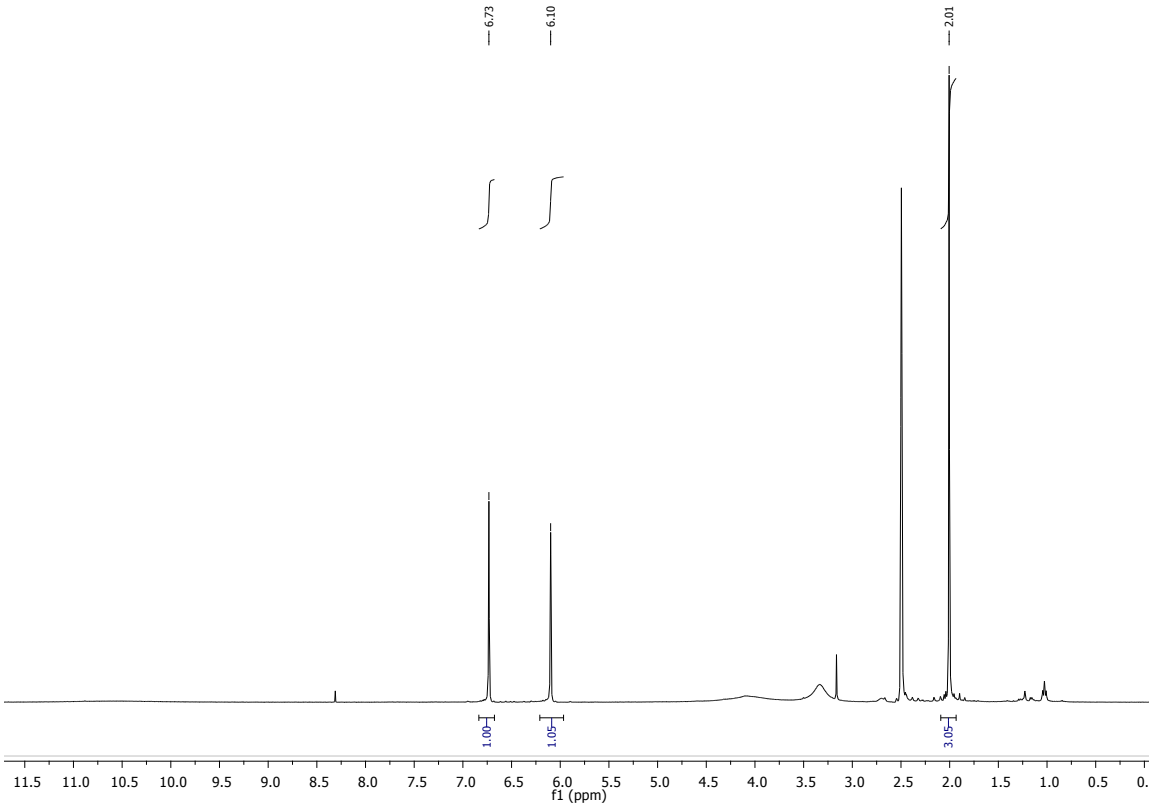


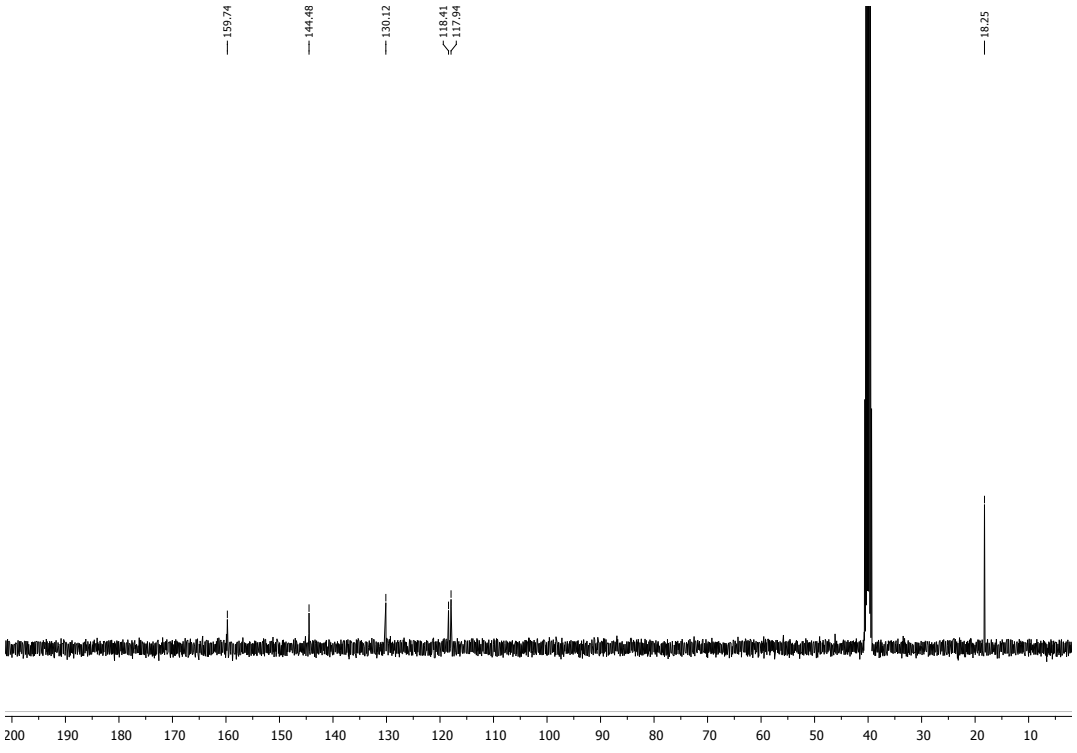
5-chloro-1H-pyrazolo[3,4-c]pyridine (15)



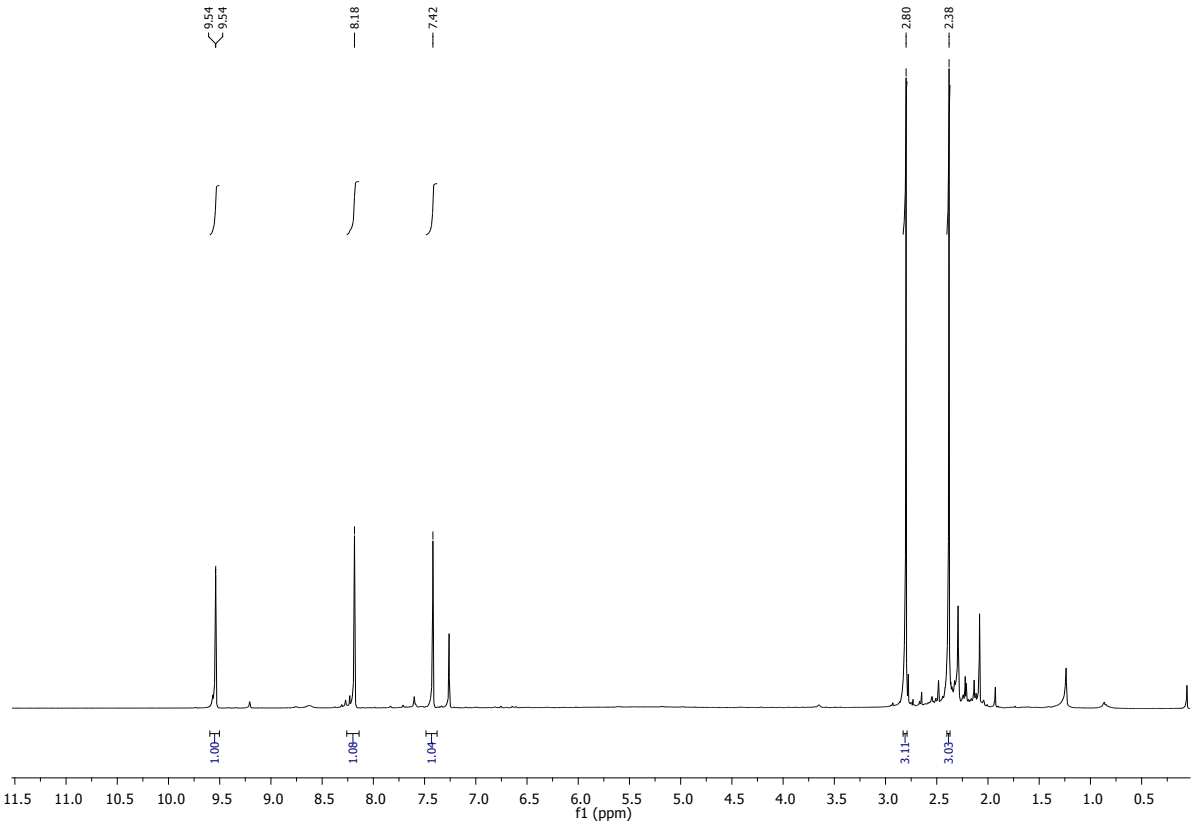


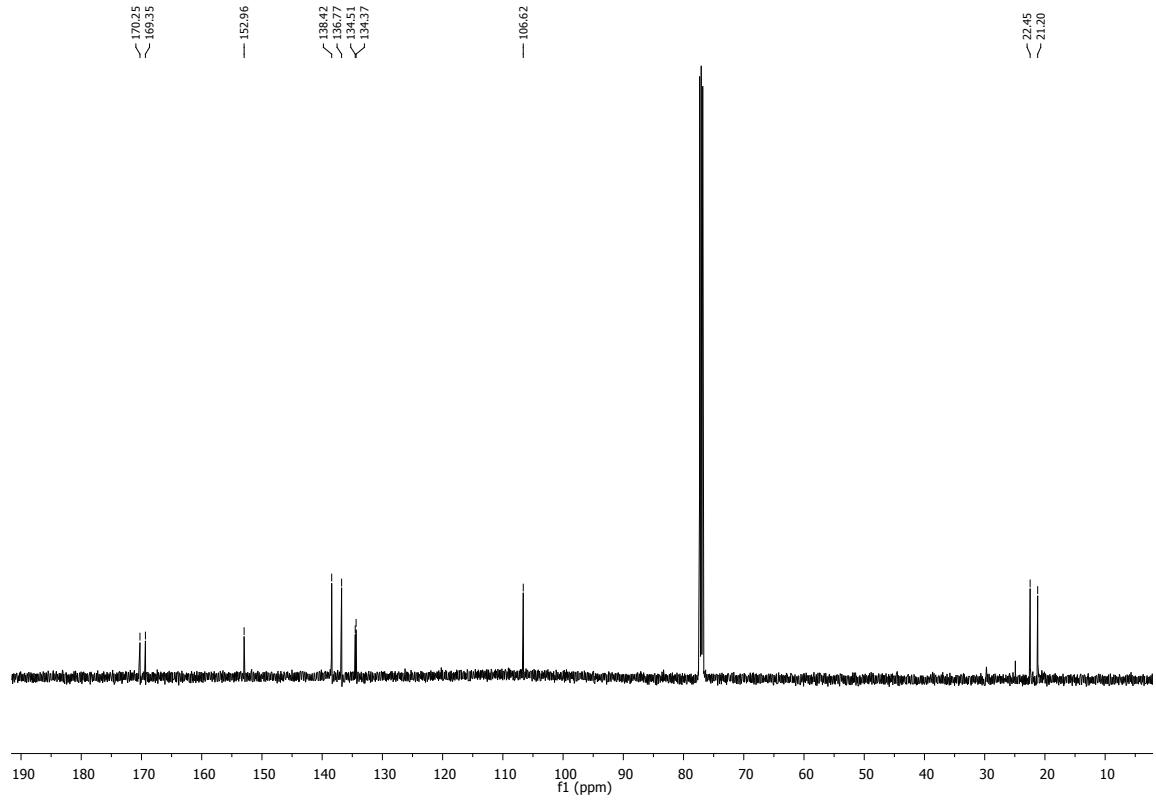
5-amino-4-methylpyridin-2-ol (17)



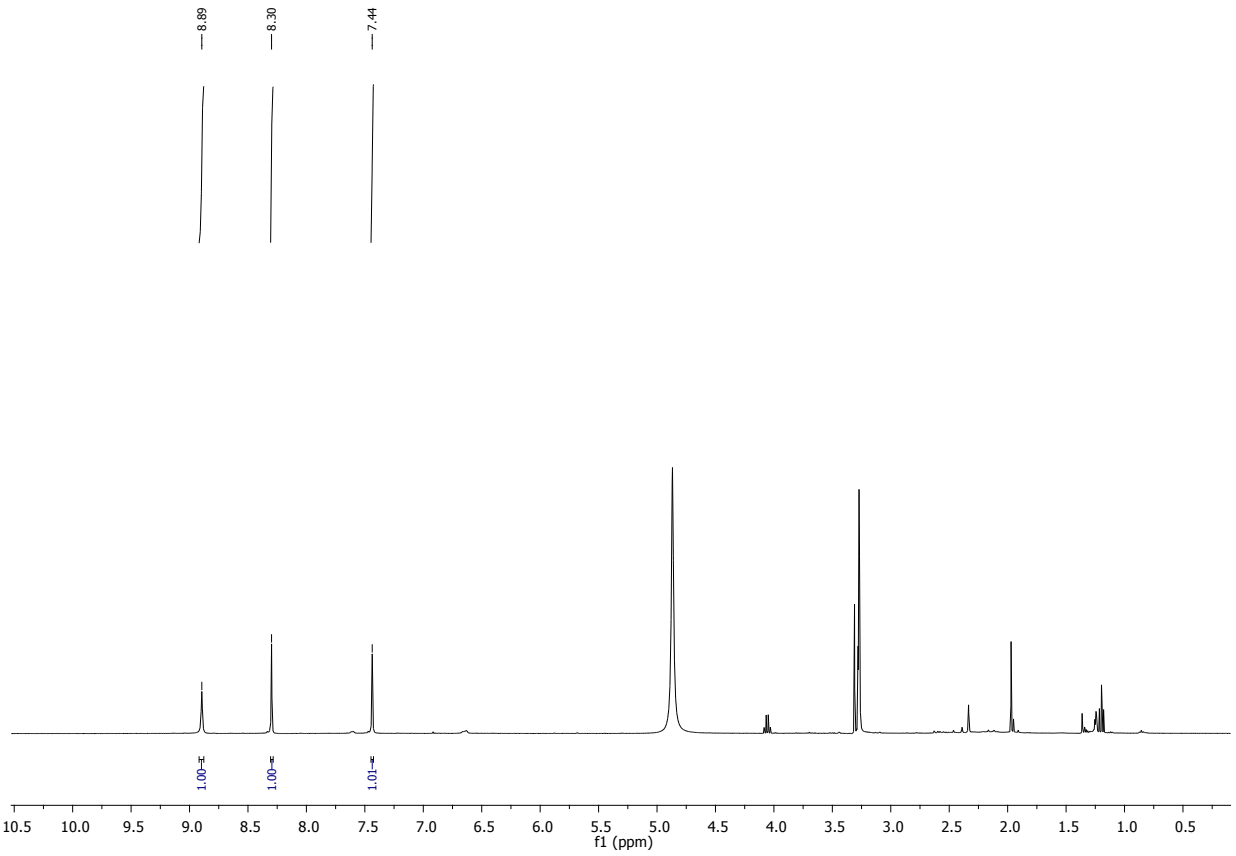


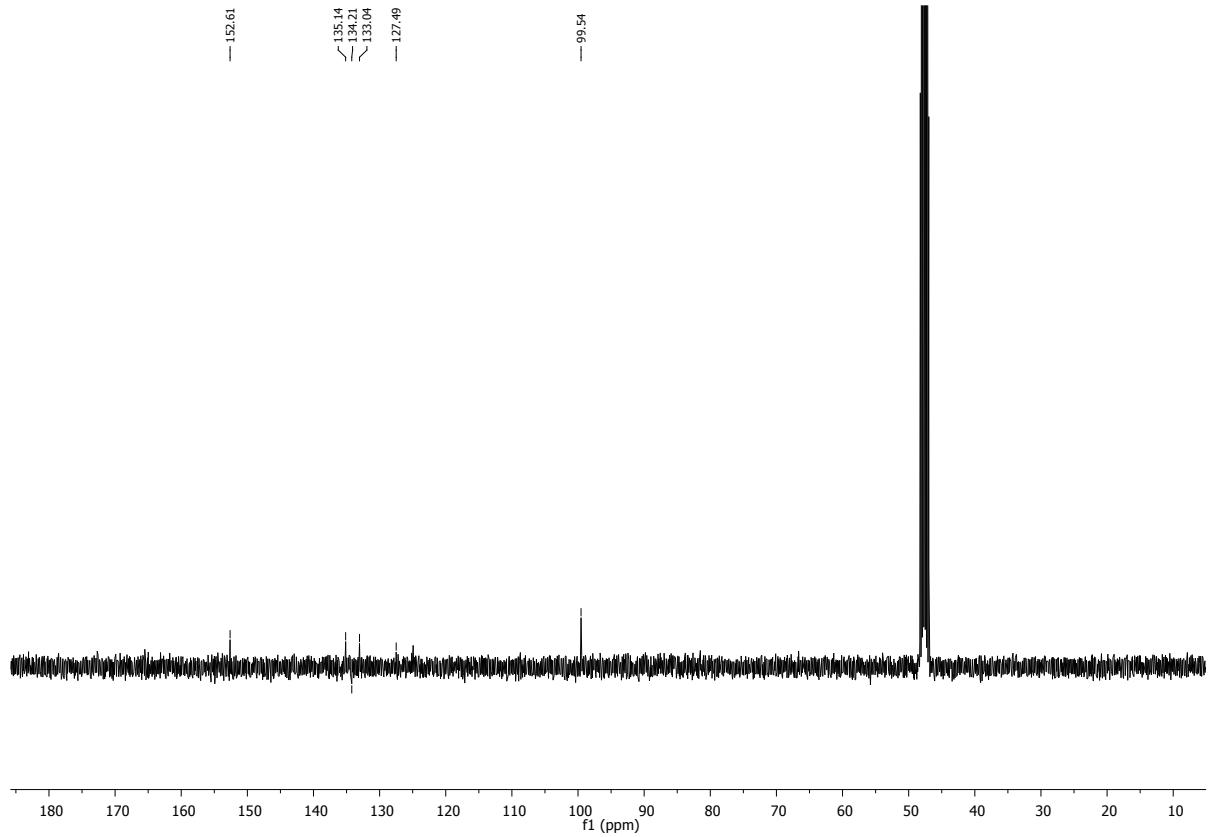
1,1'-(5-oxo-1H-pyrazolo[3,4-c]pyridine-1,6(5H)-diyl)bis(ethan-1-one) (18)



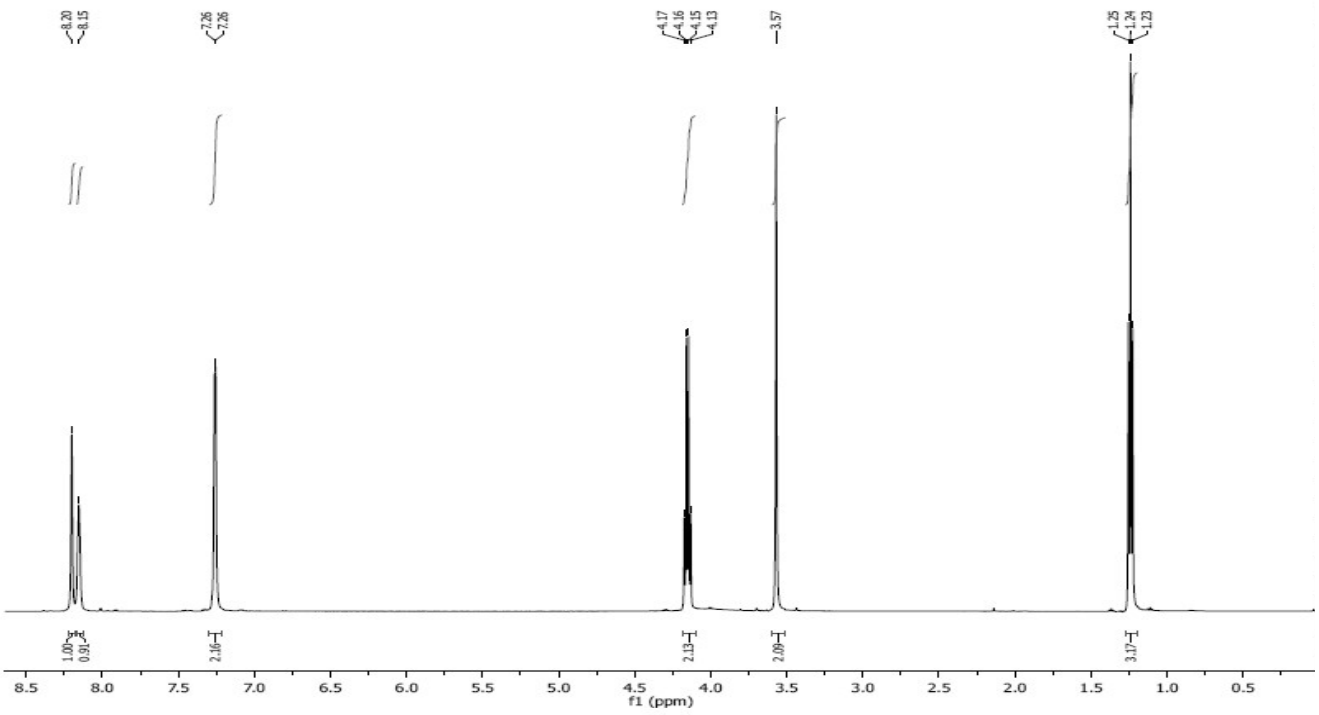


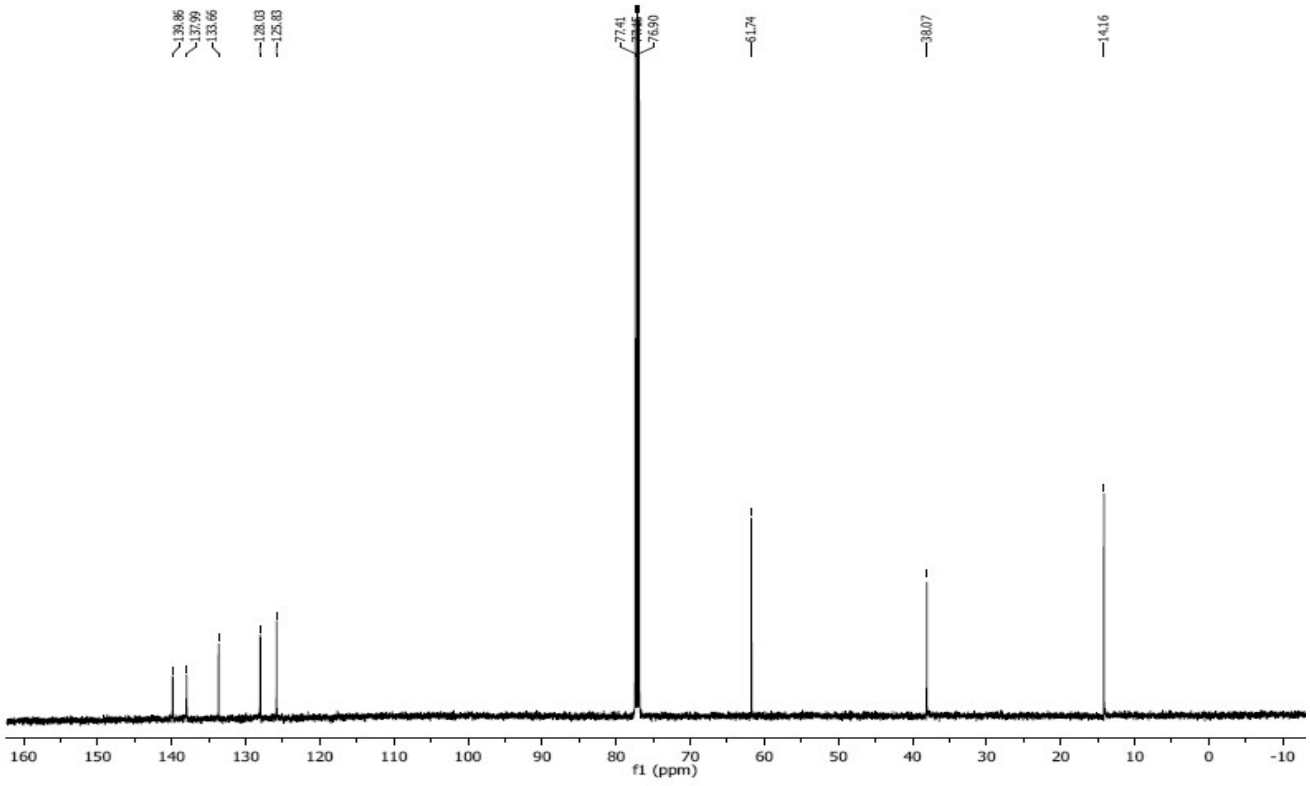
1H-Pyrazolo[3,4-c]pyridin-5-ol (1)



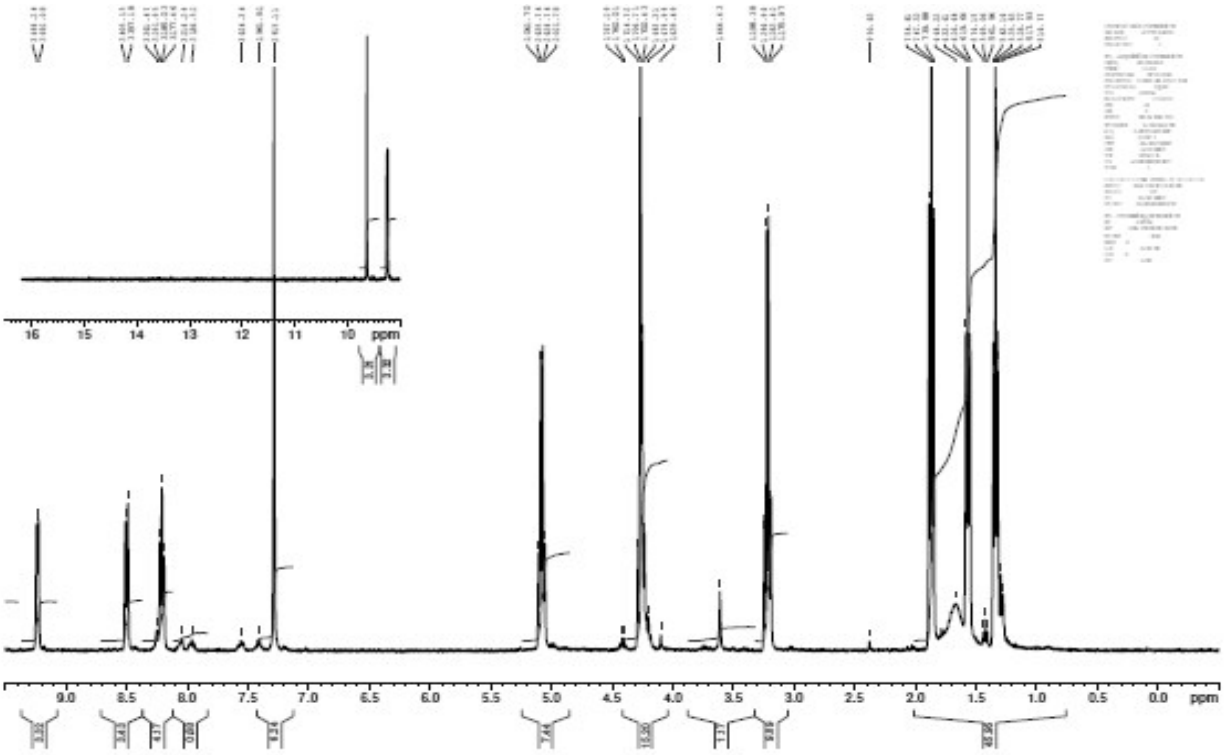


3-(2-ethoxy-2-oxoethyl)pyridine 1-oxide (22)

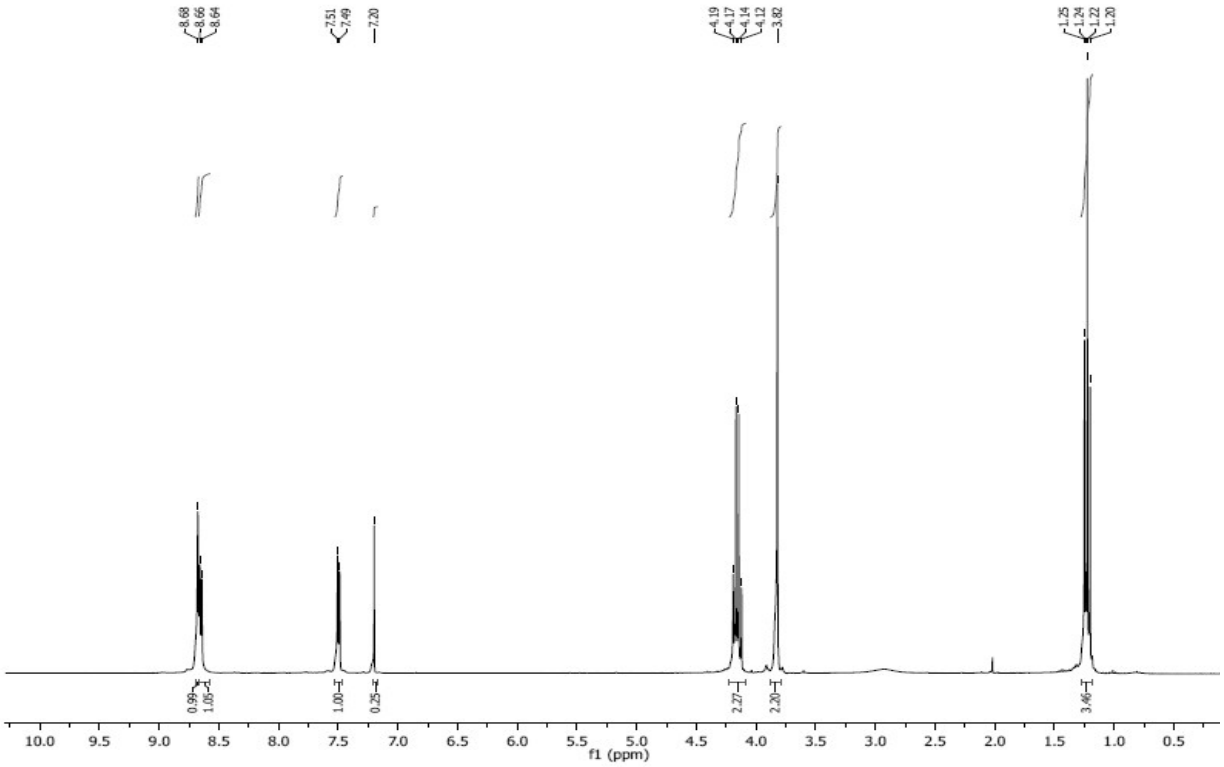




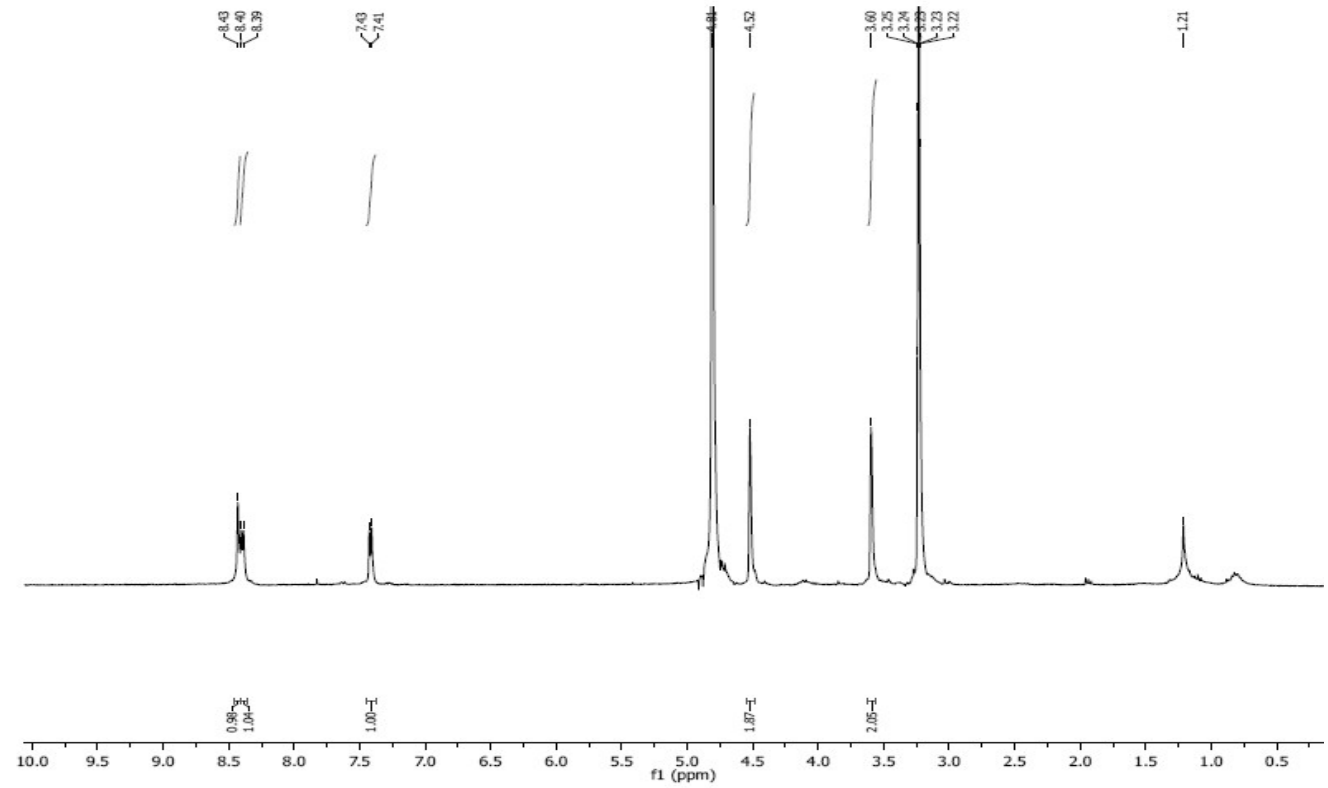
1-ethoxy-3-(2-ethoxy-2-oxoethyl)pyridin-1-ium iodide (23)

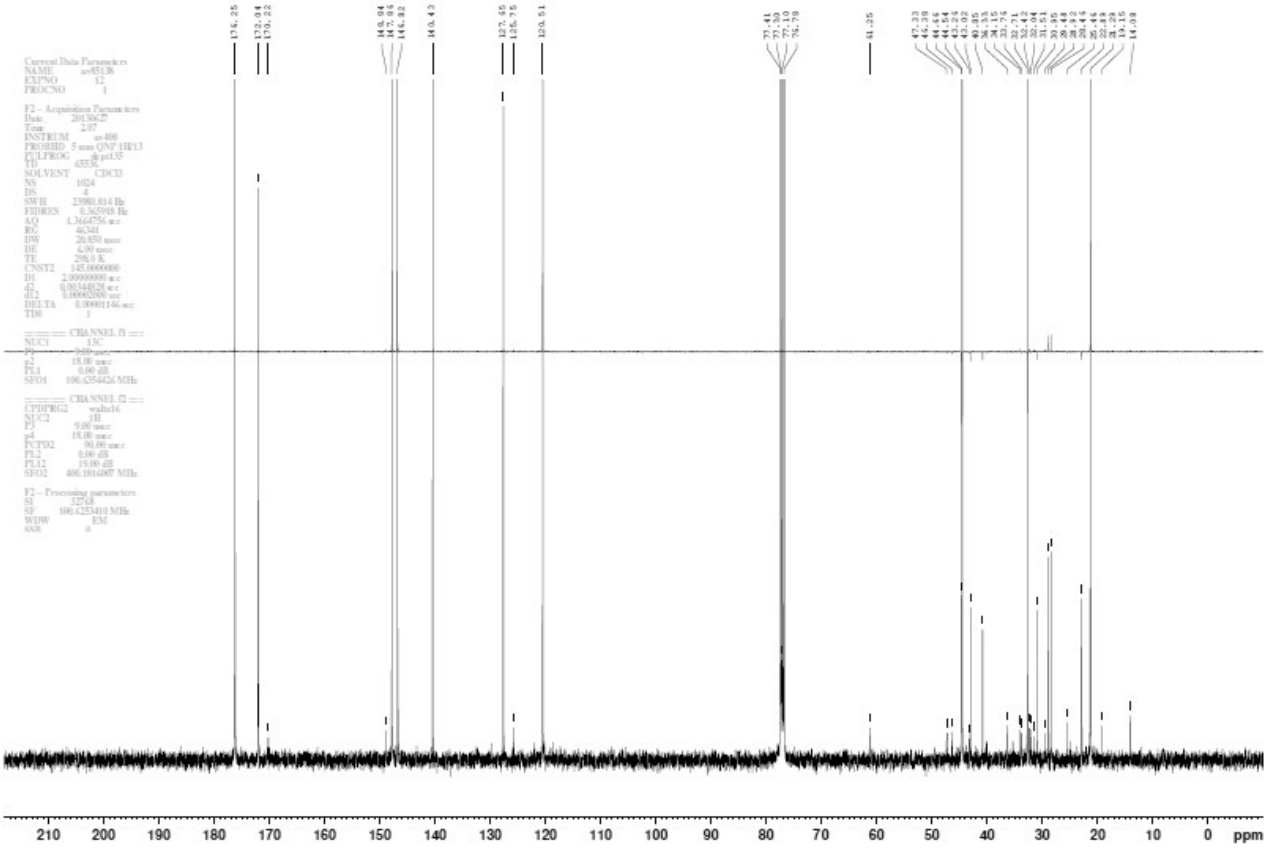


ethyl 2-(4-cyanopyridin-3-yl)acetate (20)



1,4-dihydro-2,6-naphthyridin-3(2H)-one (19)





2,6-naphthyridin-3-ol (2)