# A Mild Synthesis of Substituted 1,8-Naphthyridines

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## 1. General

### 1.1 Reagents

All reagents and solvents were obtained from commercial suppliers, and were used without further purification unless otherwise stated.

### 1.2 Experimental Details

All reactions were carried out using conventional glassware, or Reacti-Vials™, at ambient temperature under an air atmosphere, and with no special attention given to the exclusion of moisture, unless otherwise stated.

### 1.3 Purification of Products

i) Thin layer chromatography was carried out using Merck TLC silica gel 60 $F_{254}$ aluminium sheets. These were analysed under 254 nm UV light or developed using potassium permanganate solution.

ii) Column chromatography was carried out using Fluorochem Silicagel 60A 40-63µ.

### 1.4 Analysis of Products

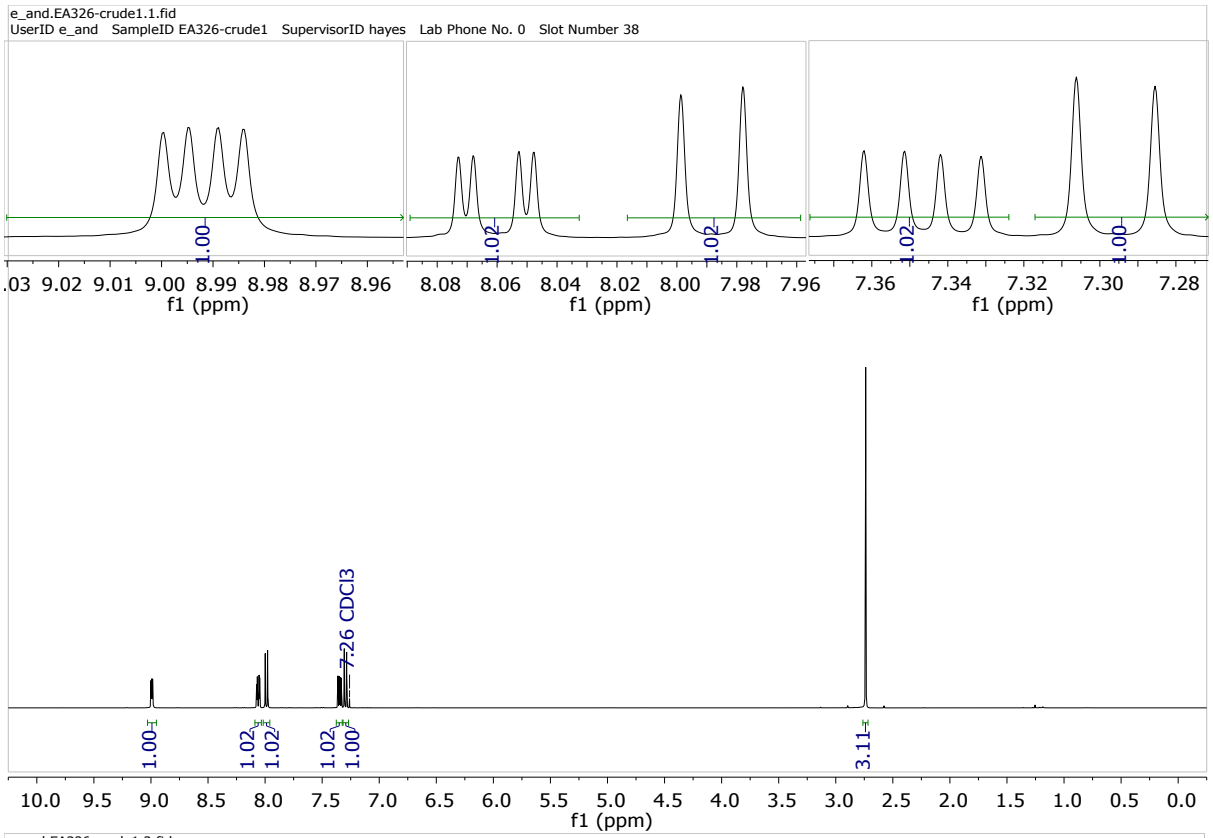
i) Fourier-transformed infrared (FTIR) spectra were obtained using a Bruker ALPHA FTIR spectrometer with a single reflection attenuated total reflectance (ATR) module.

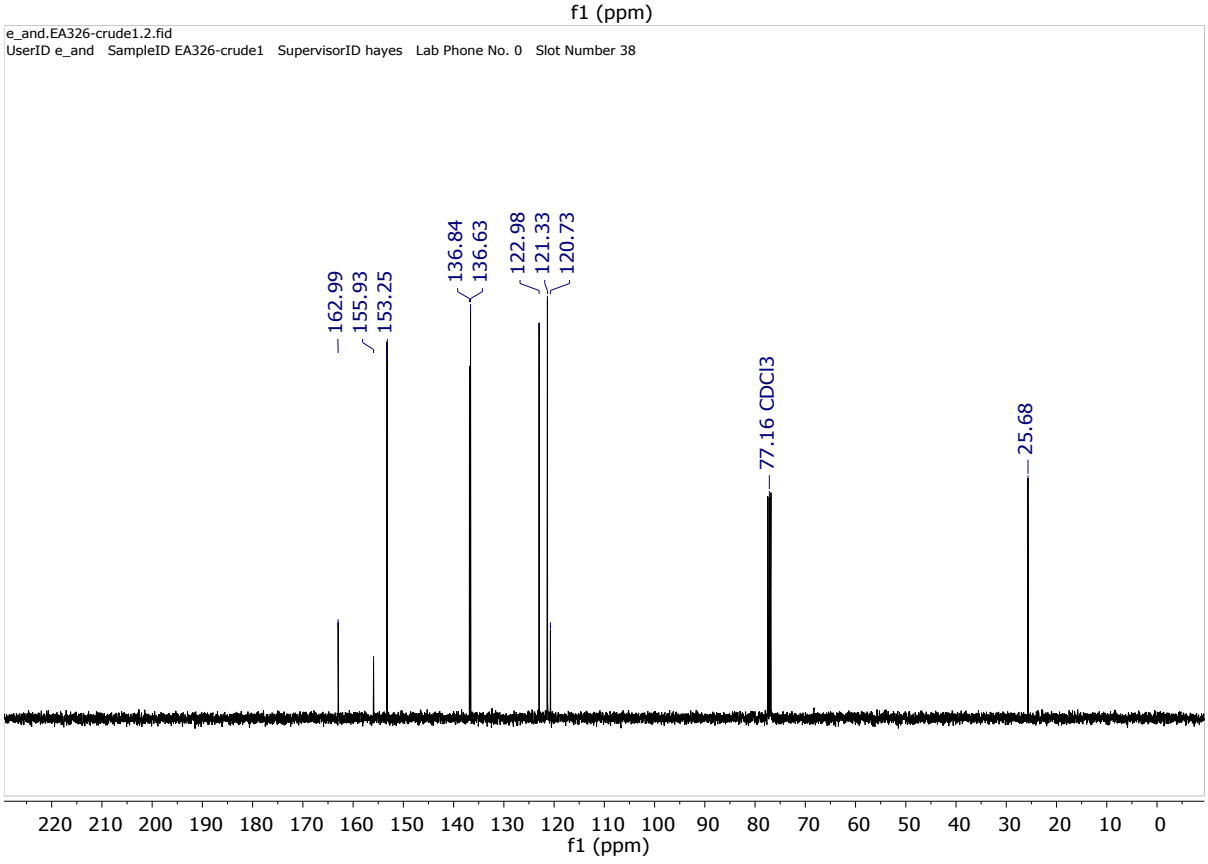
ii) $^{1}H$ and $^{13}C$ NMR spectra were obtained on a Bruker AV 400 at 400 MHz and 100 MHz respectively. Chemical shifts are reported in ppm, and coupling constants are reported in Hz, with $CHCl_3$/$CDCl_3$ referenced at 7.26 ($^{1}H$) and 77.16 ($^{13}C$).

iii) High resolution mass spectra were obtained using a Bruker MicroTOF mass spectrometer using electrospray ionisation.

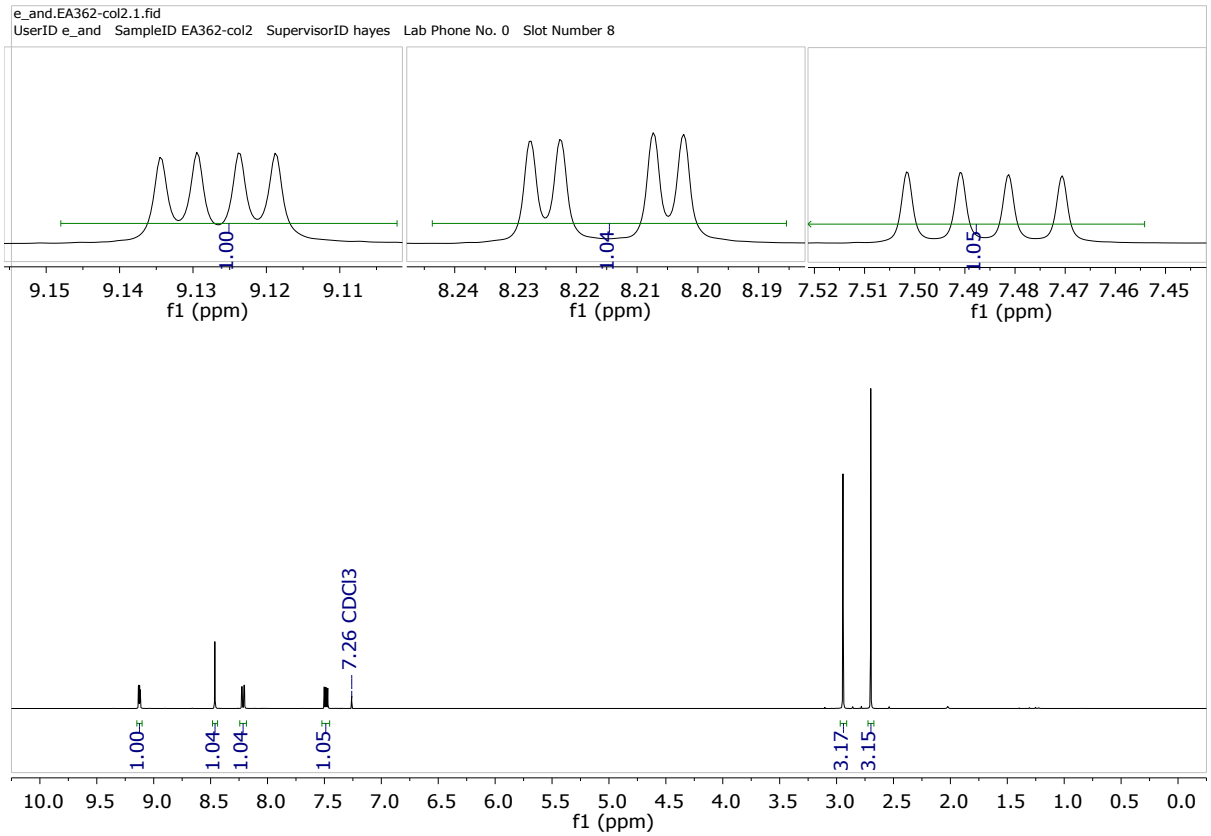
## 2. NMR Data

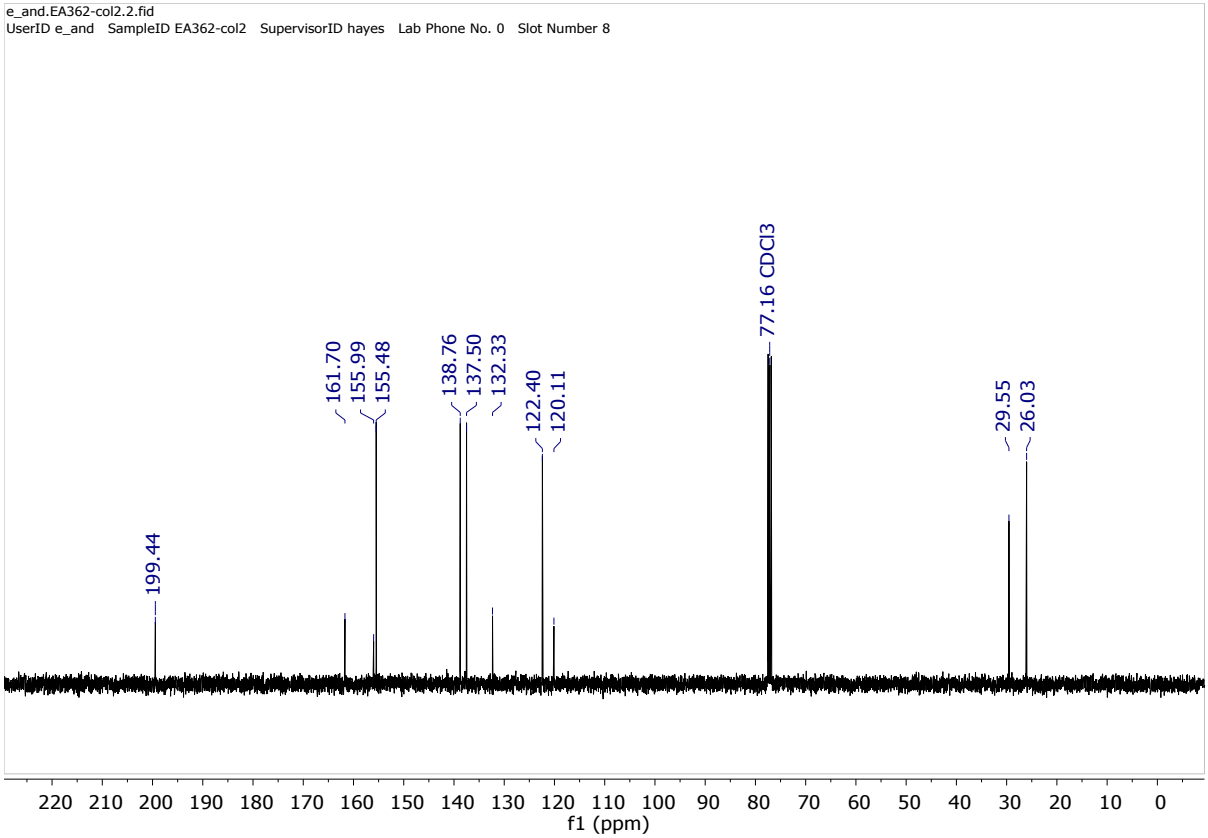
## 2-Methyl-1,8-naphthyridine (13)



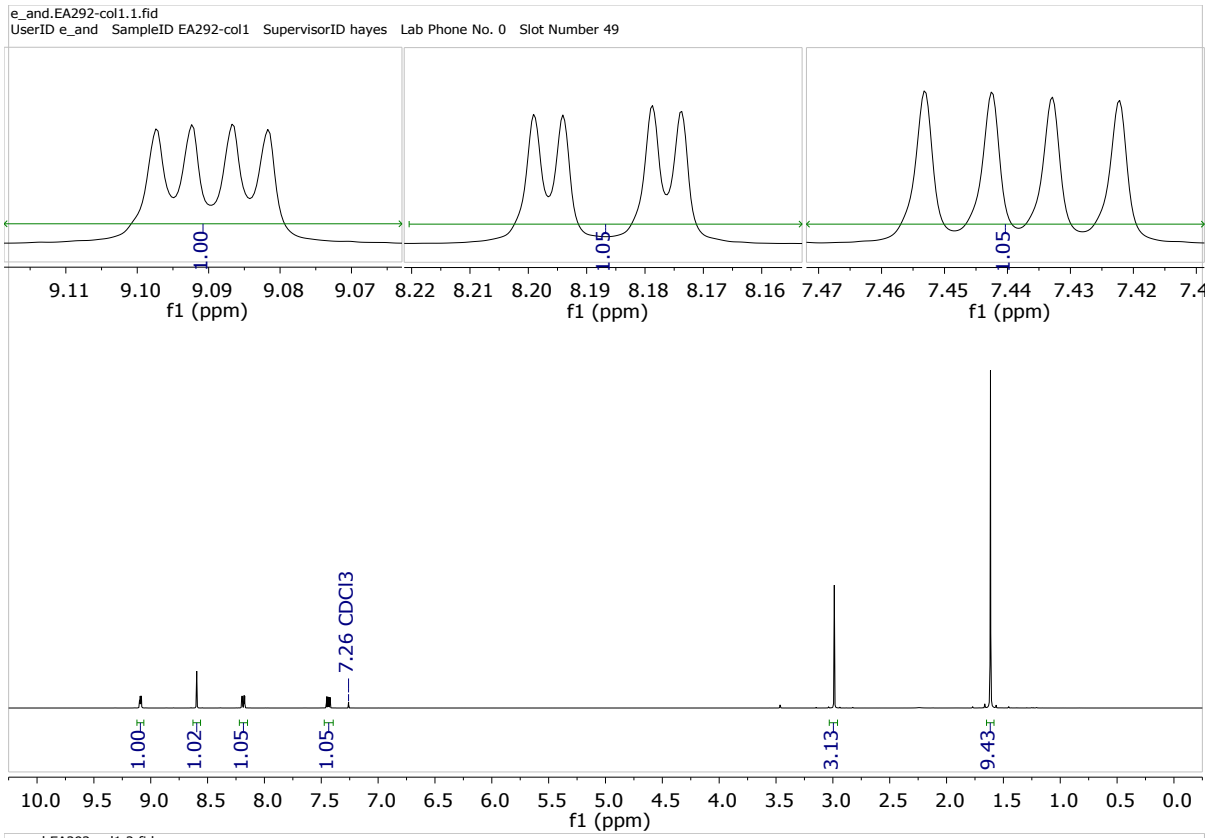



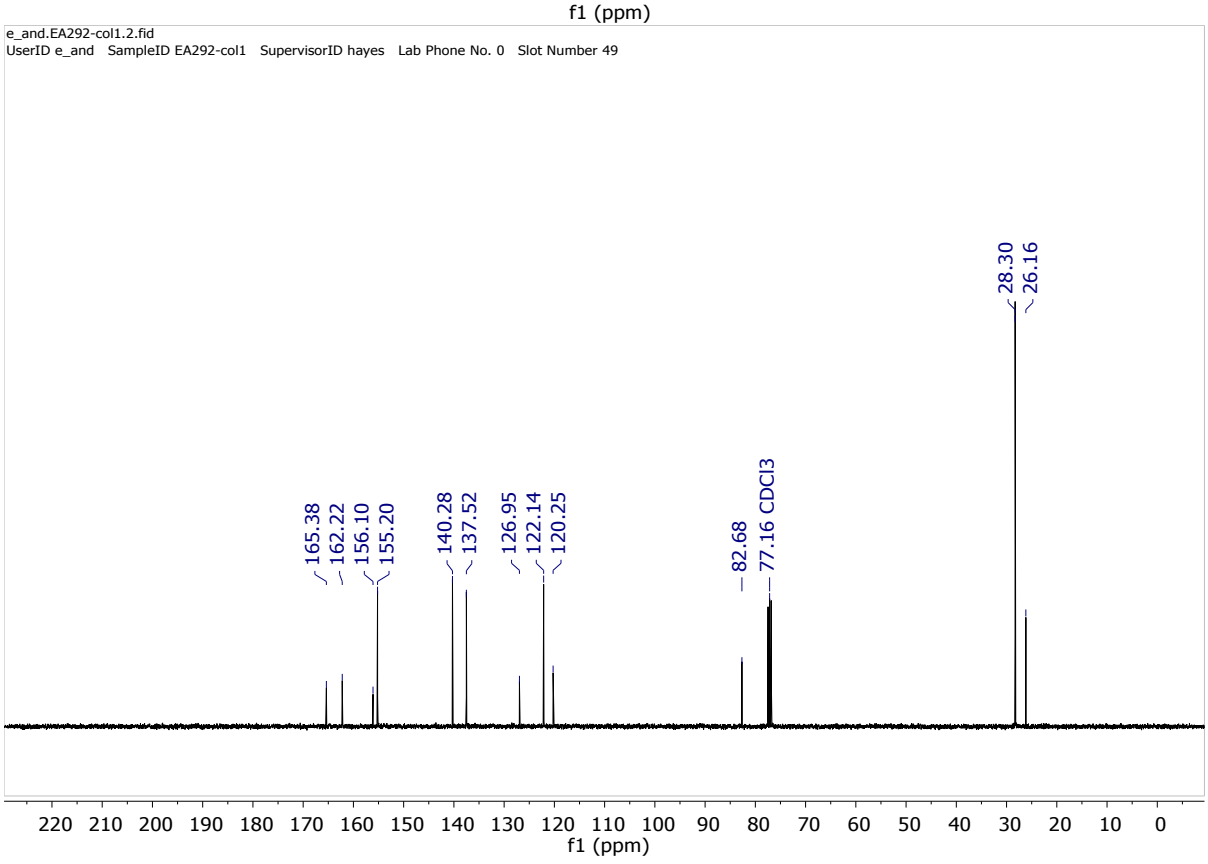
## 1-(2-Methyl-1,8-naphthyridin-3-yl)ethan-1-one (15a)



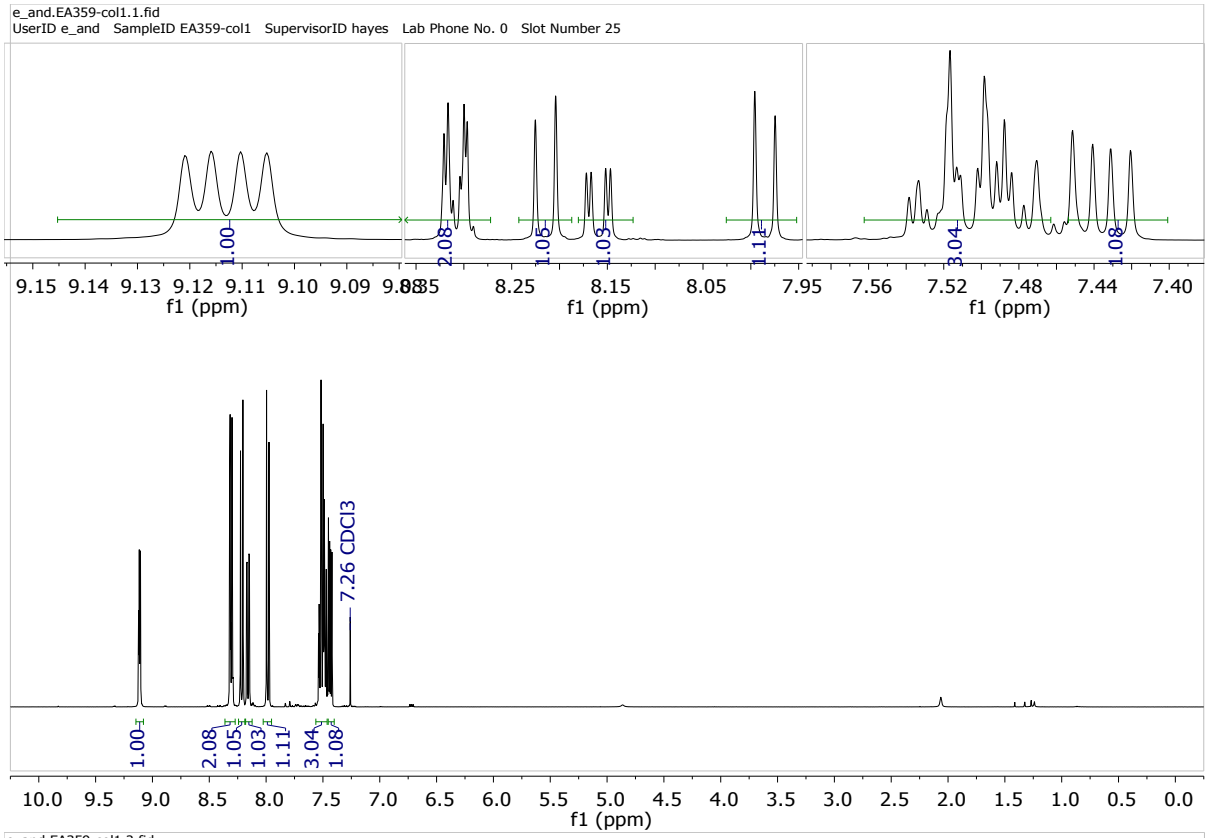



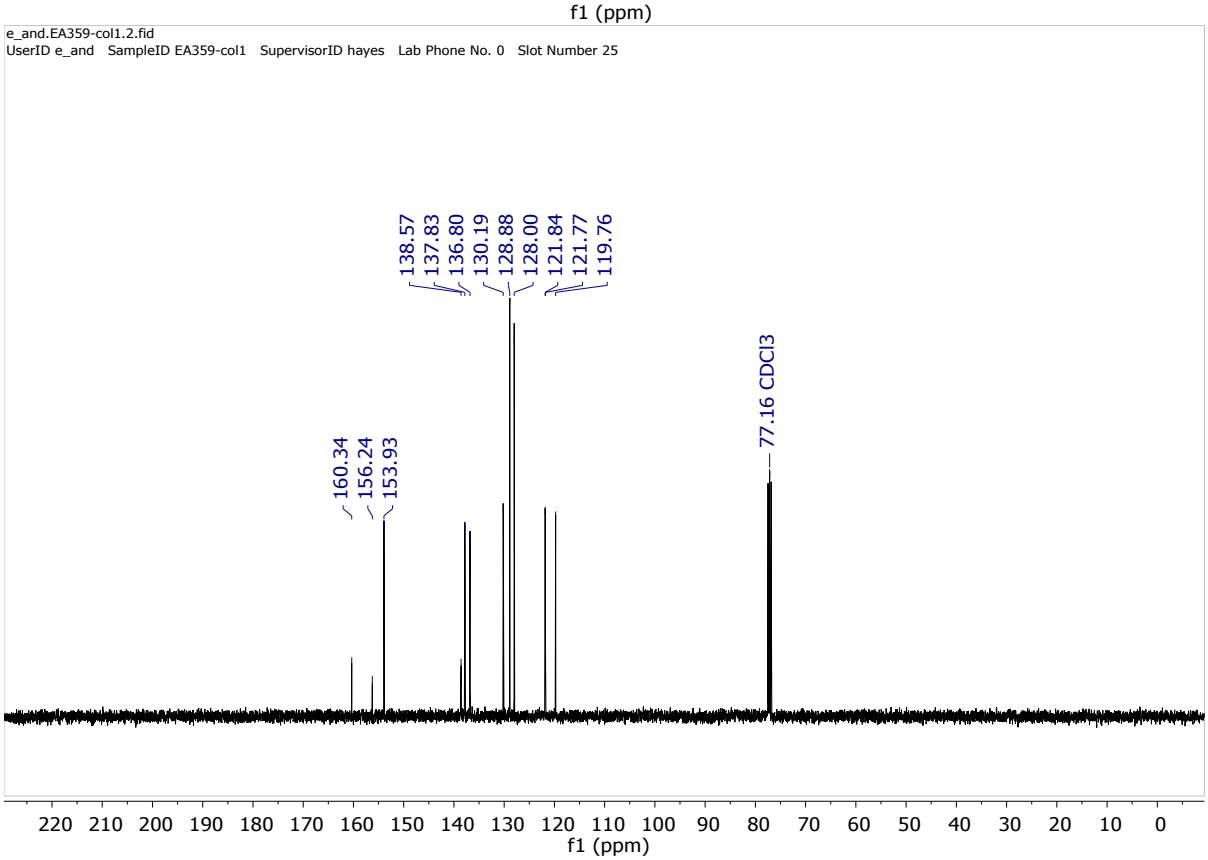
## *tert*-Butyl 2-methyl-1,8-naphthyridine-3-carboxylate (15b)



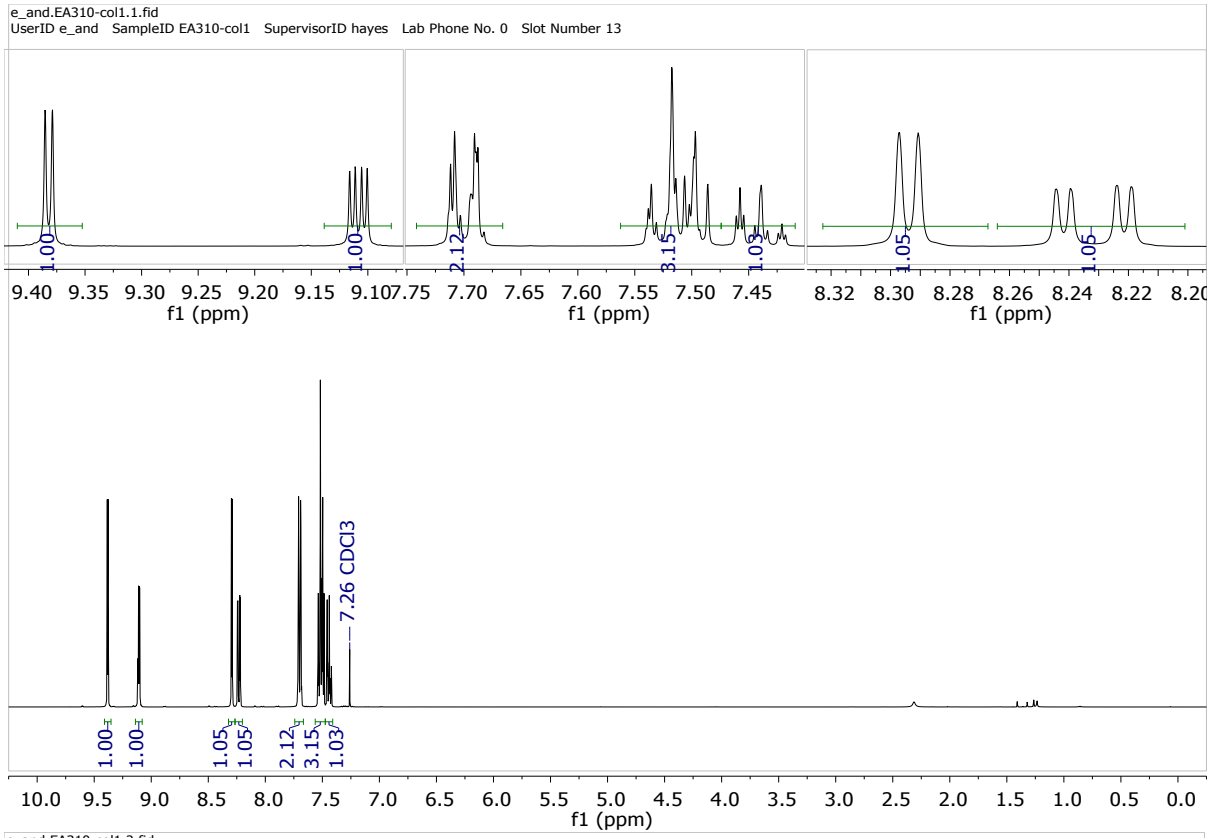



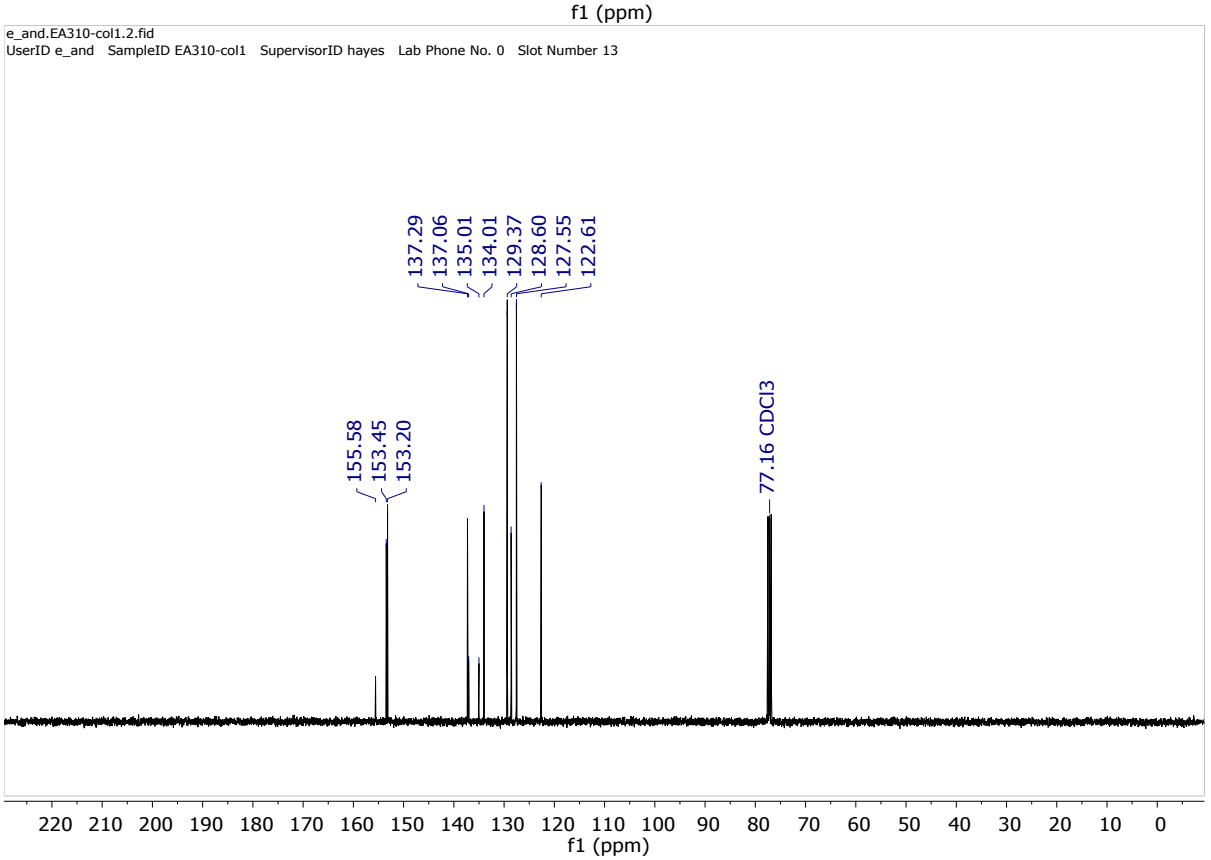
## 2-Phenyl-1,8-naphthyridine (15c)



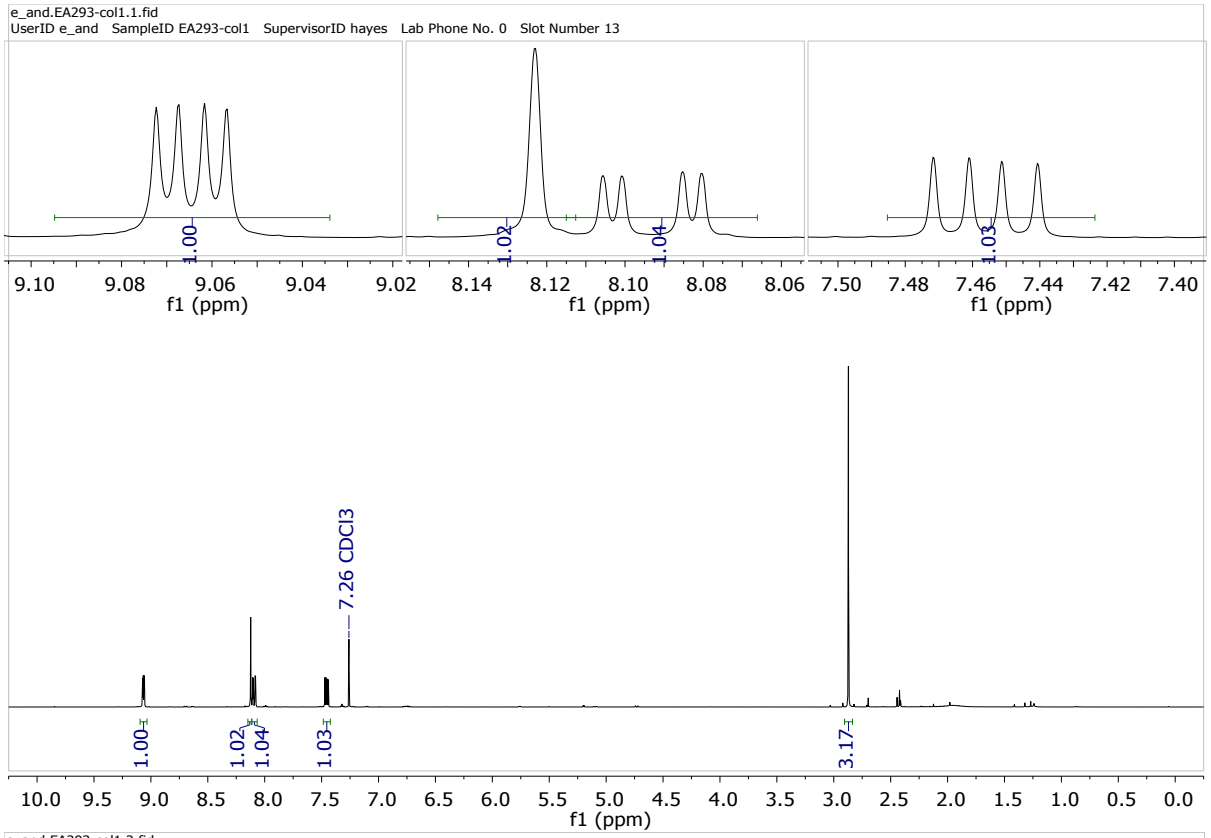



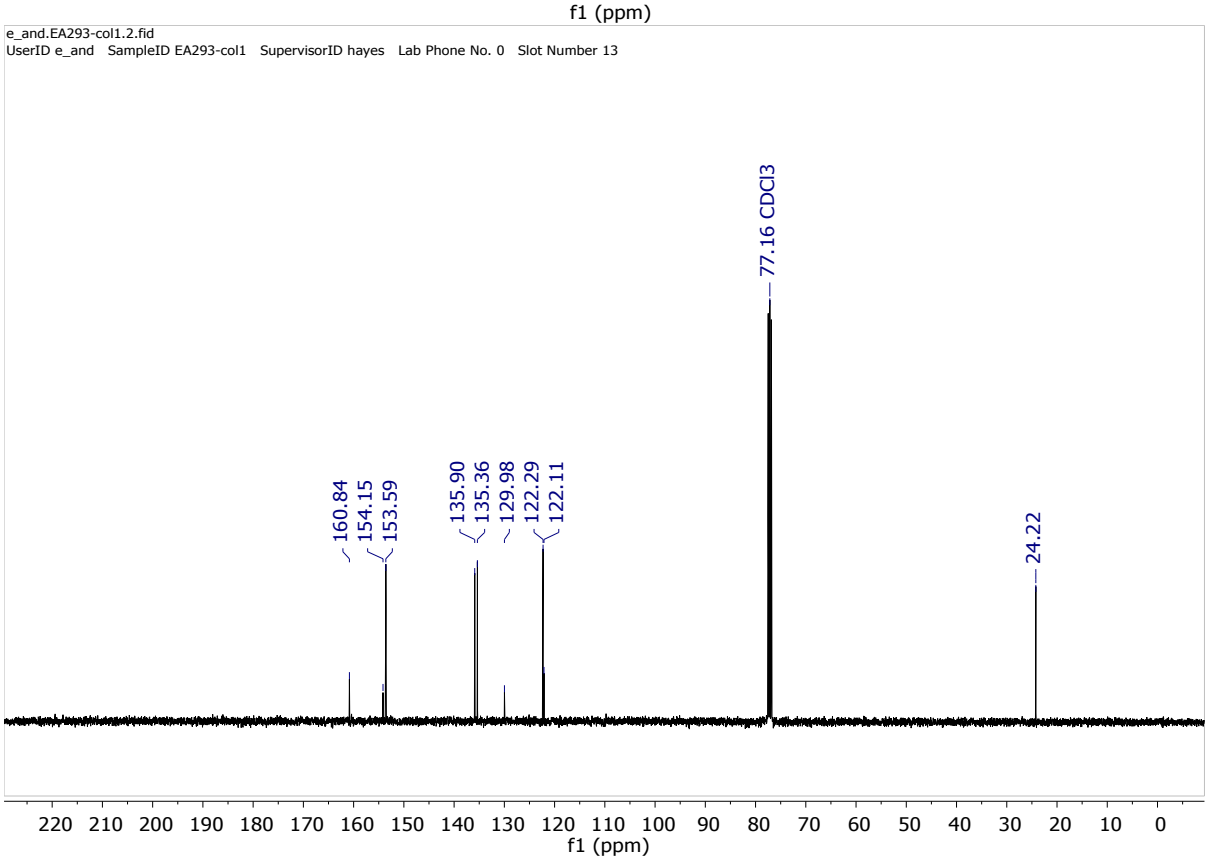
## 3-Phenyl-1,8-naphthyridine (15d)



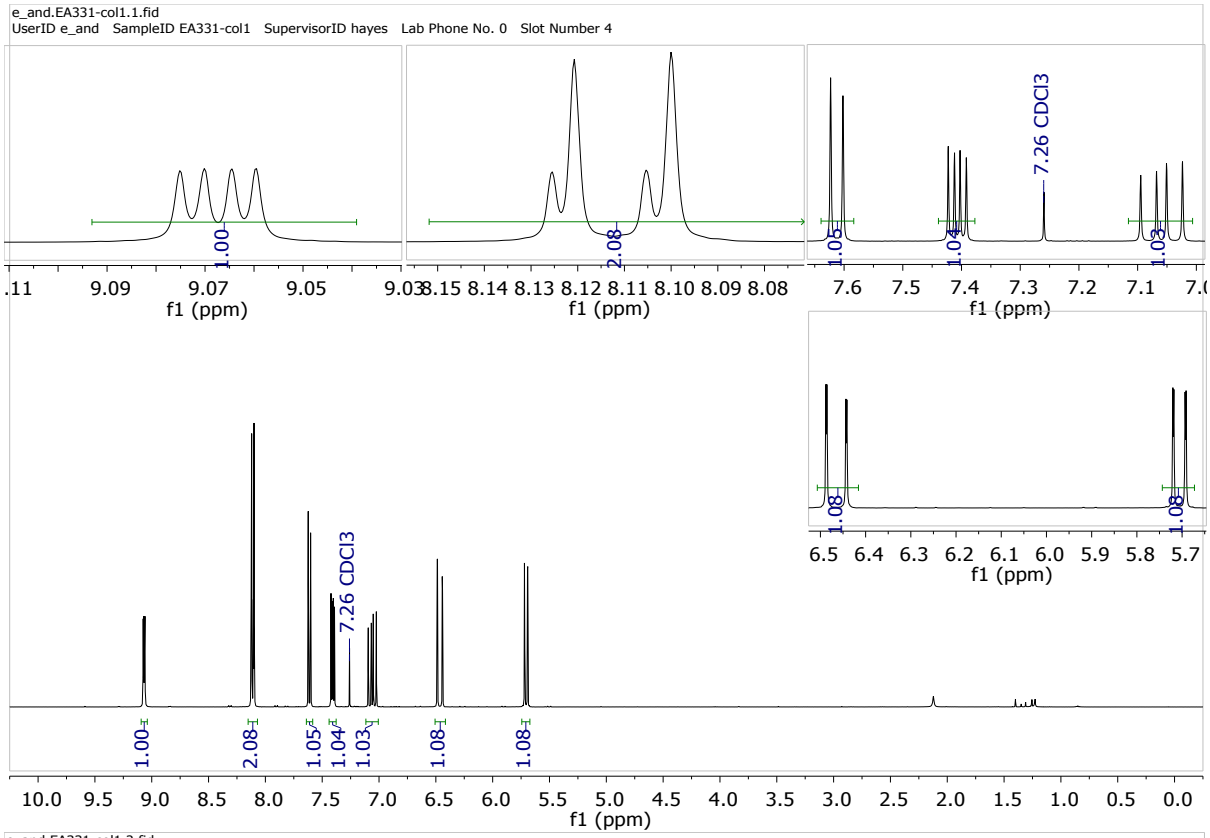



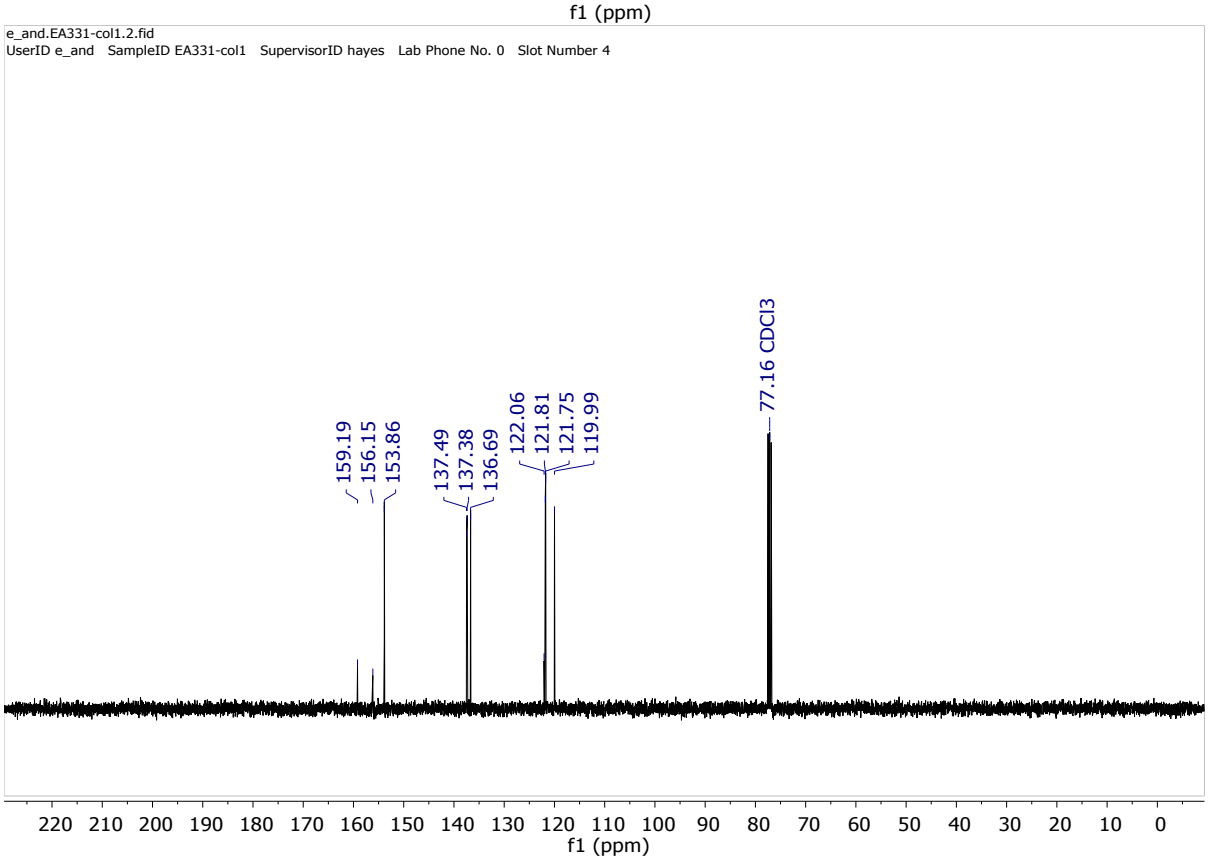
## 3-Chloro-2-methyl-1,8-naphthyridine (15e)



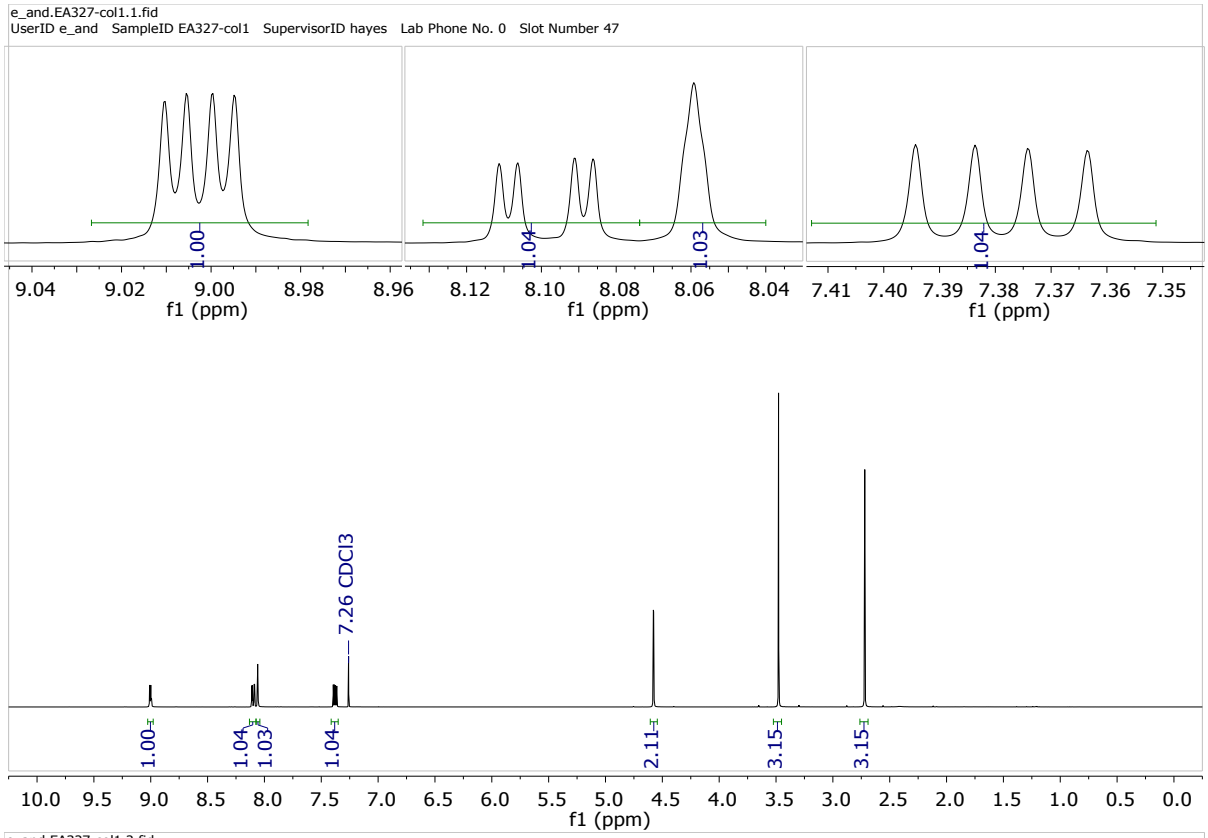



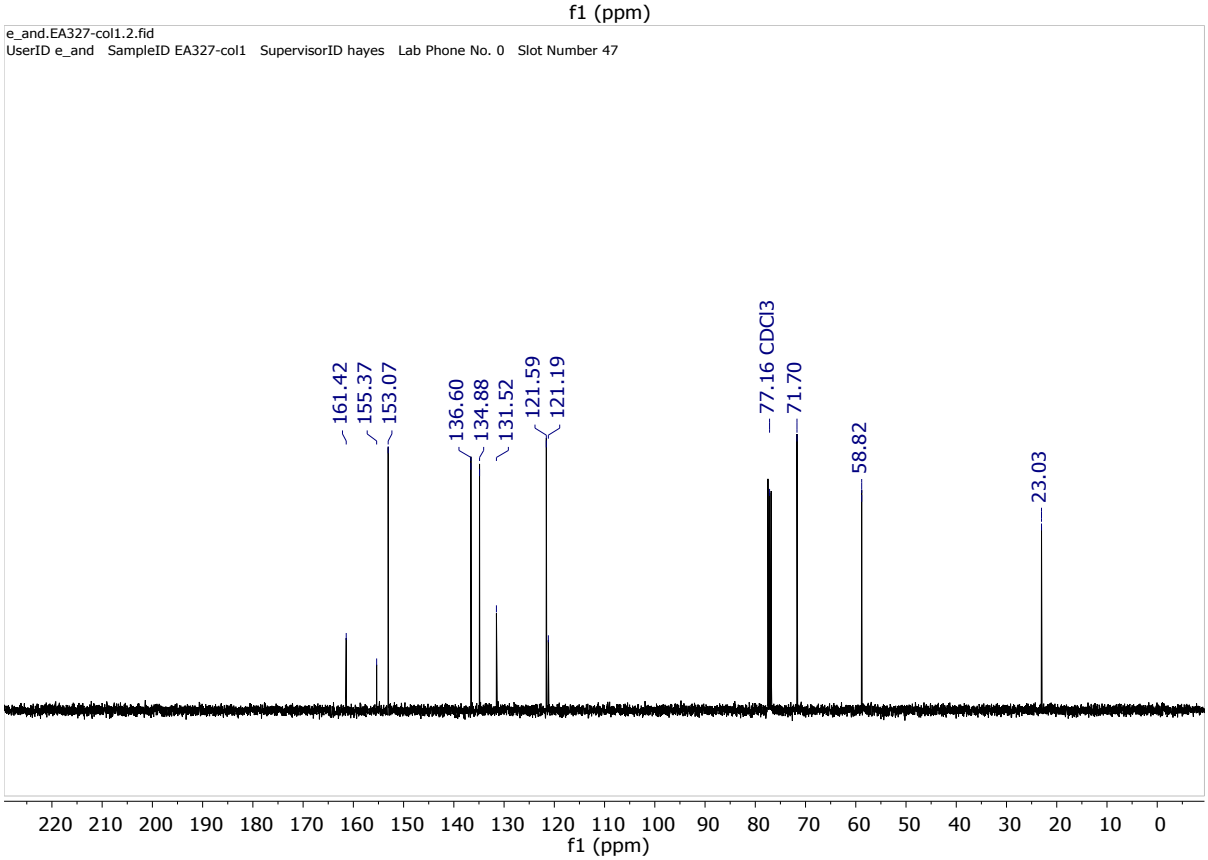
## 2-Vinyl-1,8-naphthyridine (15f)



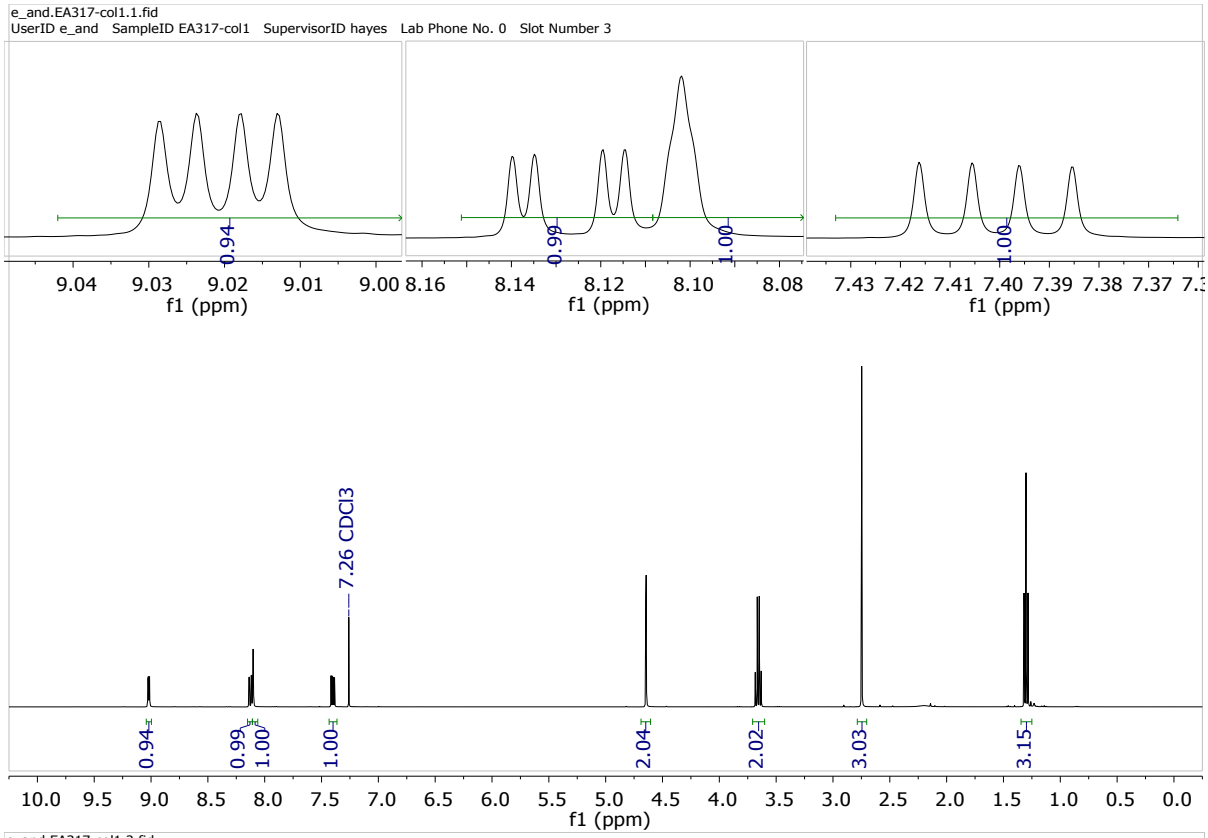



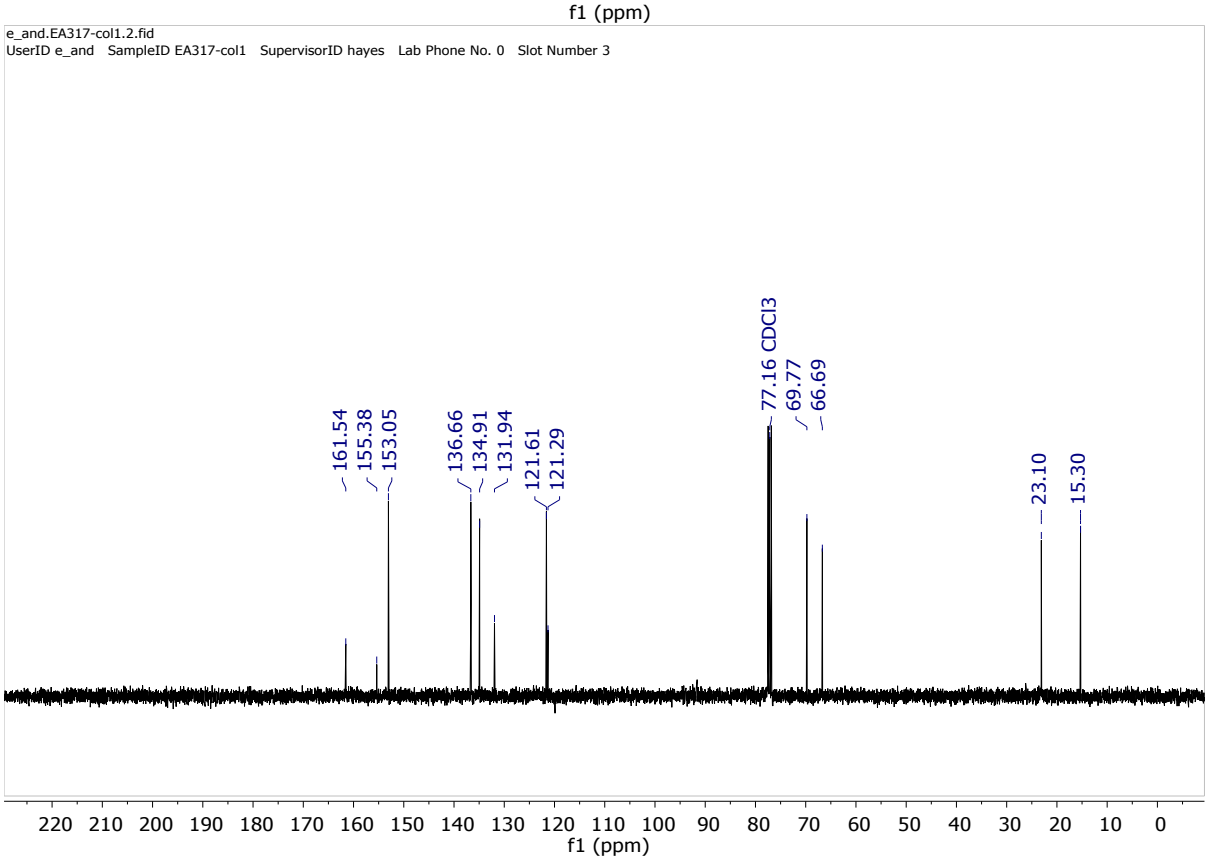
## 3-(Methoxymethyl)-2-methyl-1,8-naphthyridine (15g)



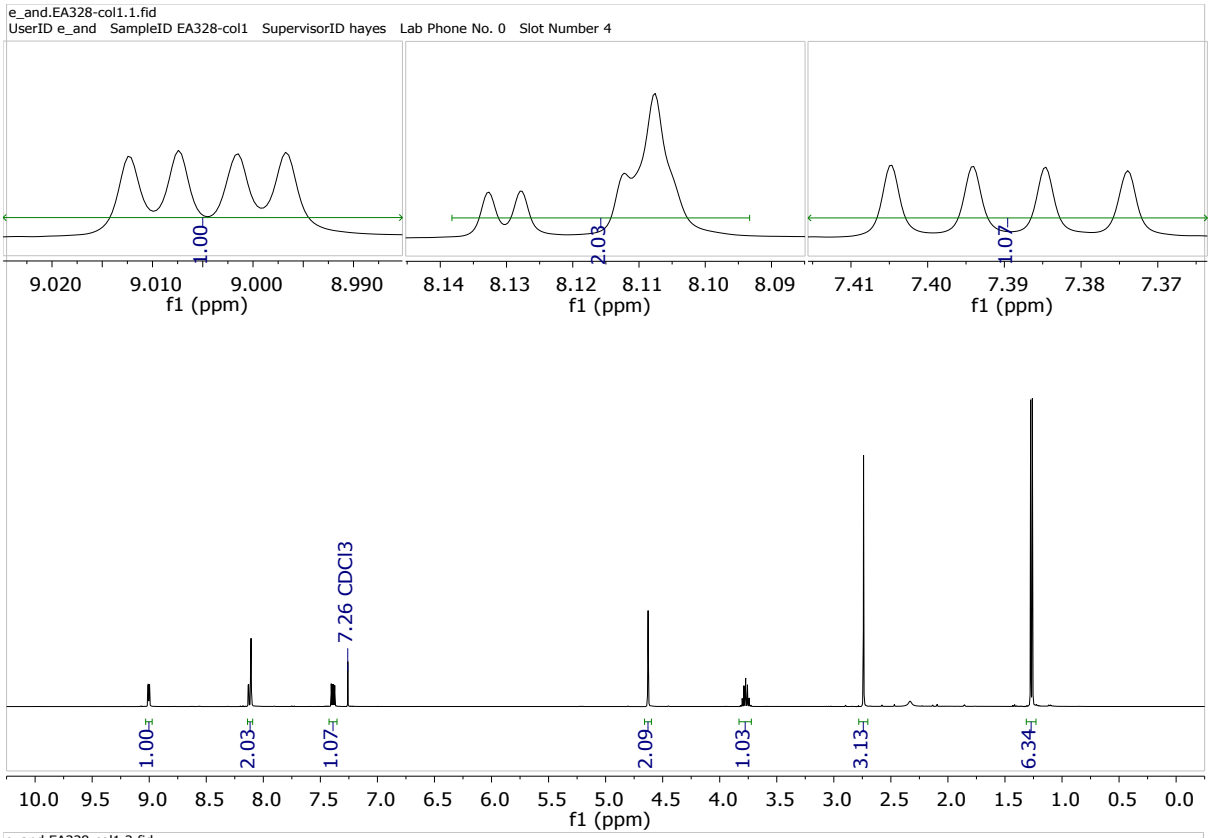



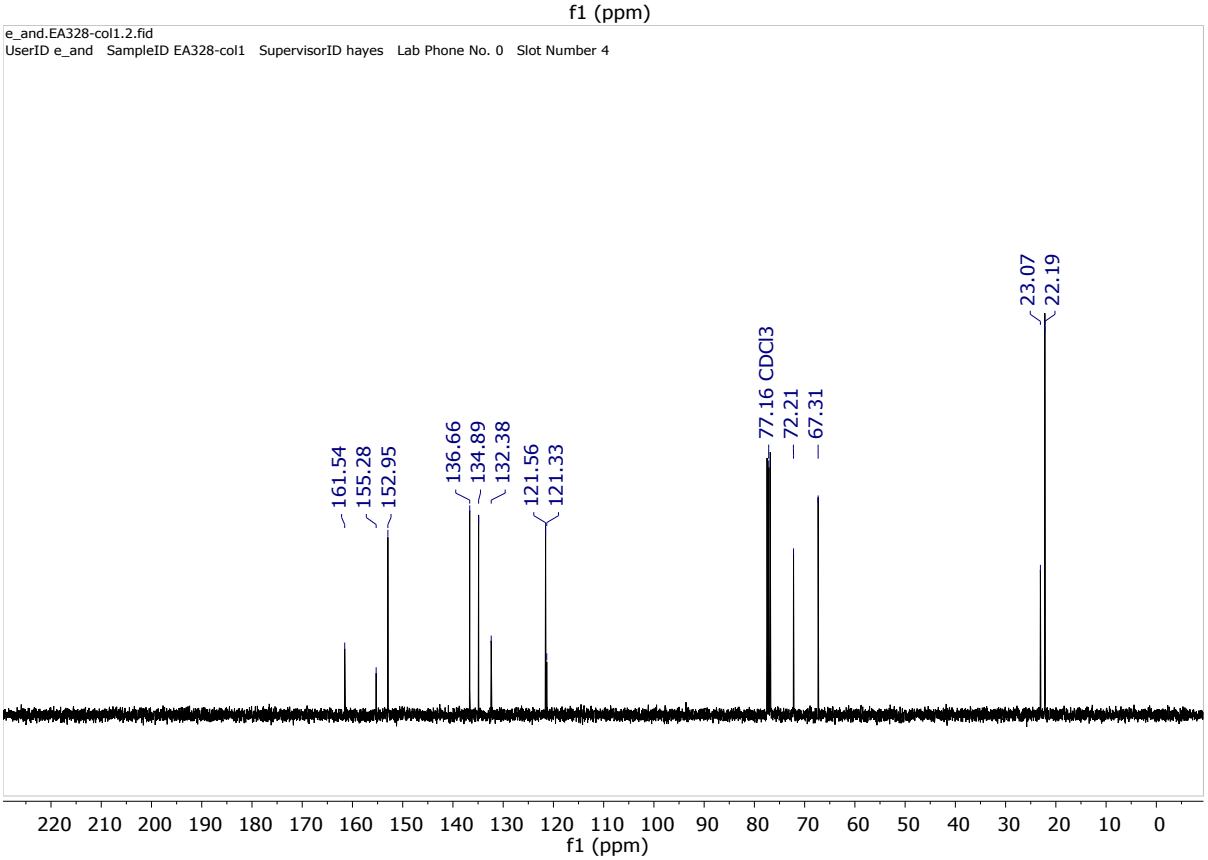
## 3-(Ethoxymethyl)-2-methyl-1,8-naphthyridine (15h)



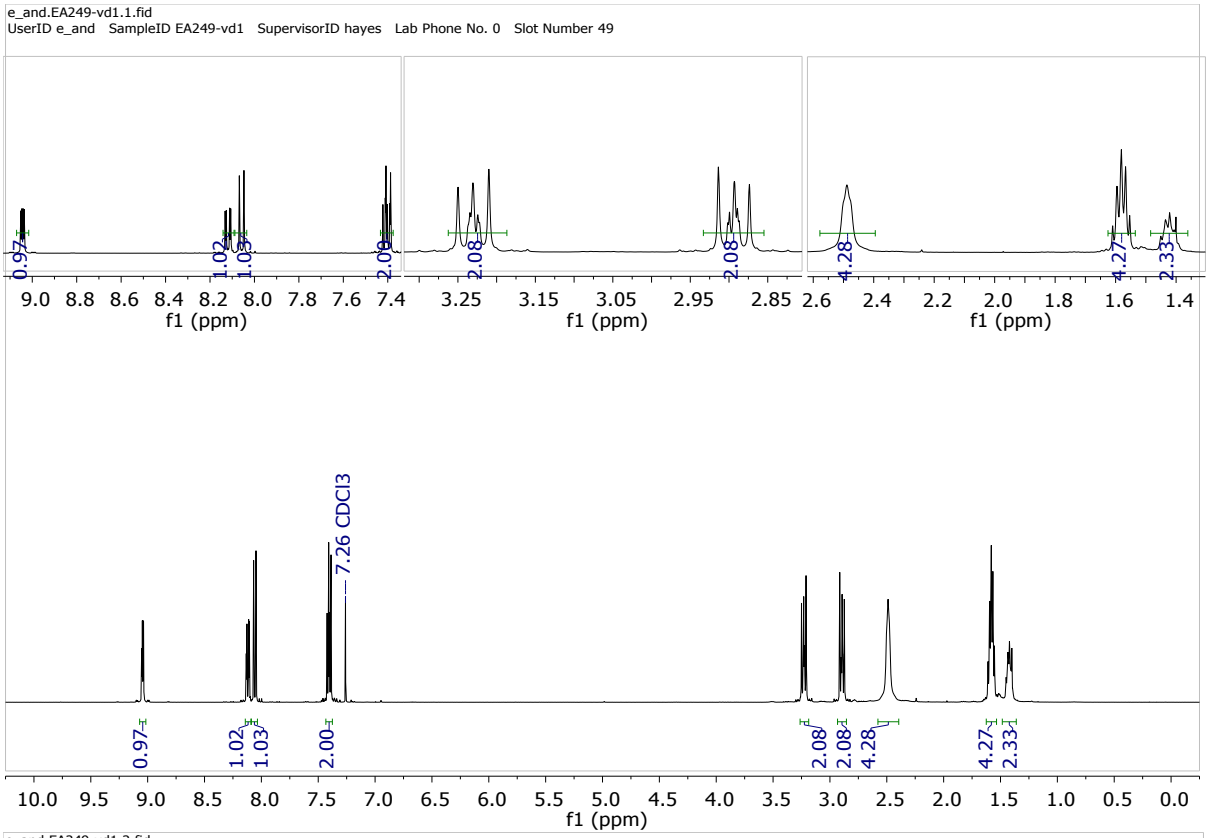



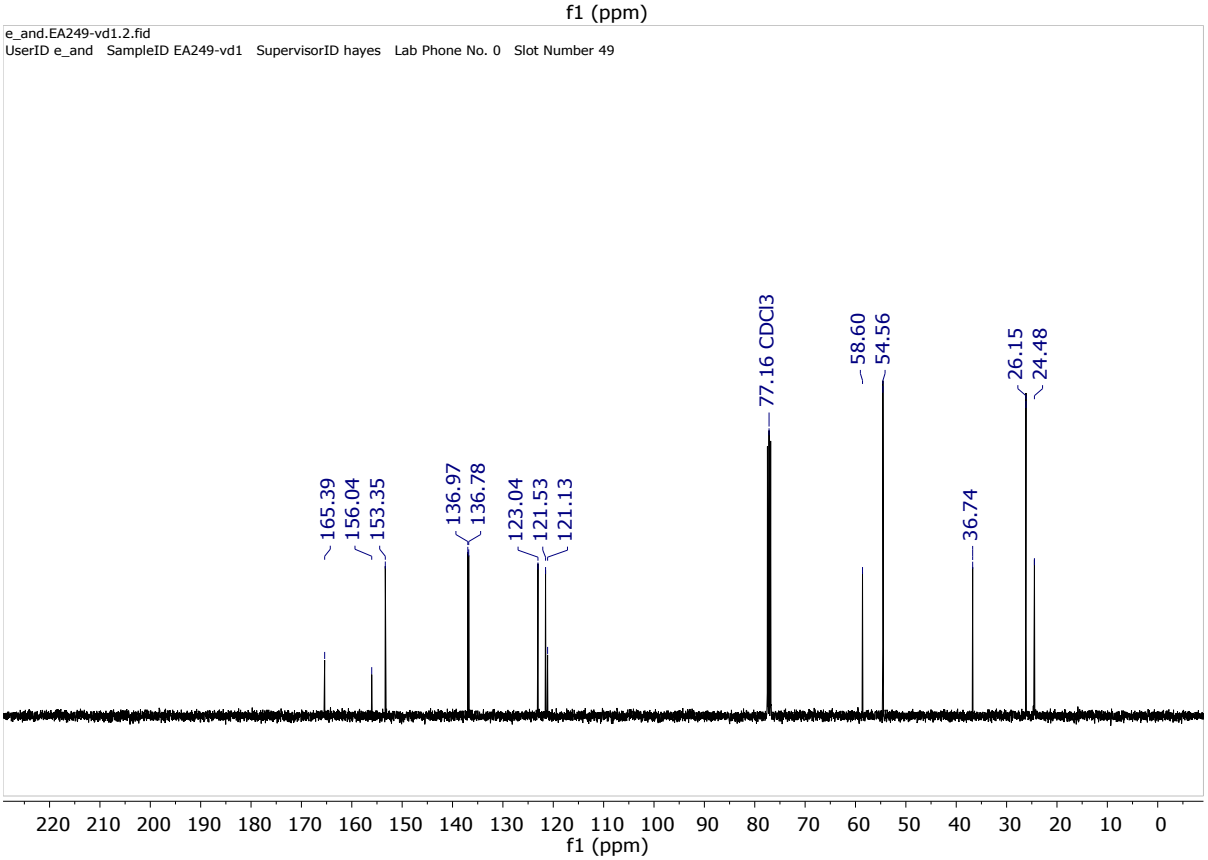
## 3-(*iso*-Propoxymethyl)-2-methyl-1,8-naphthyridine (15i)



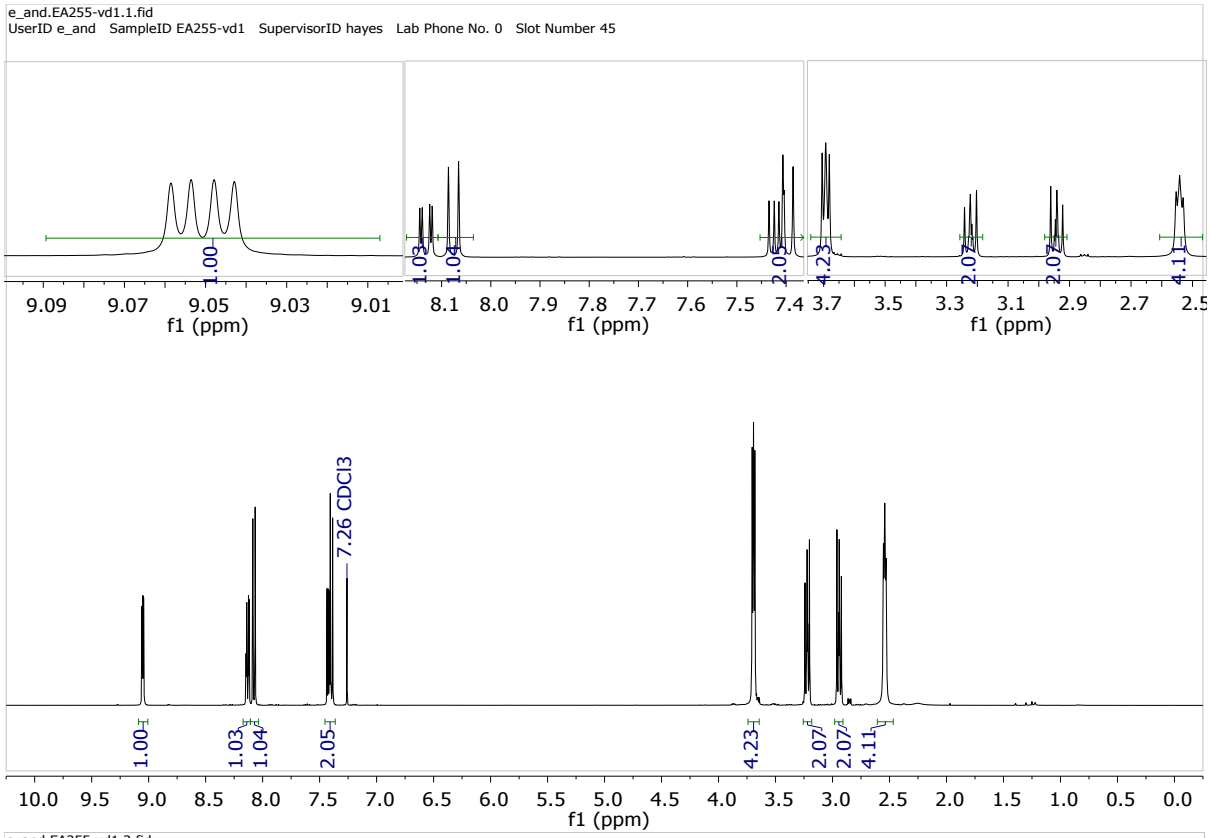



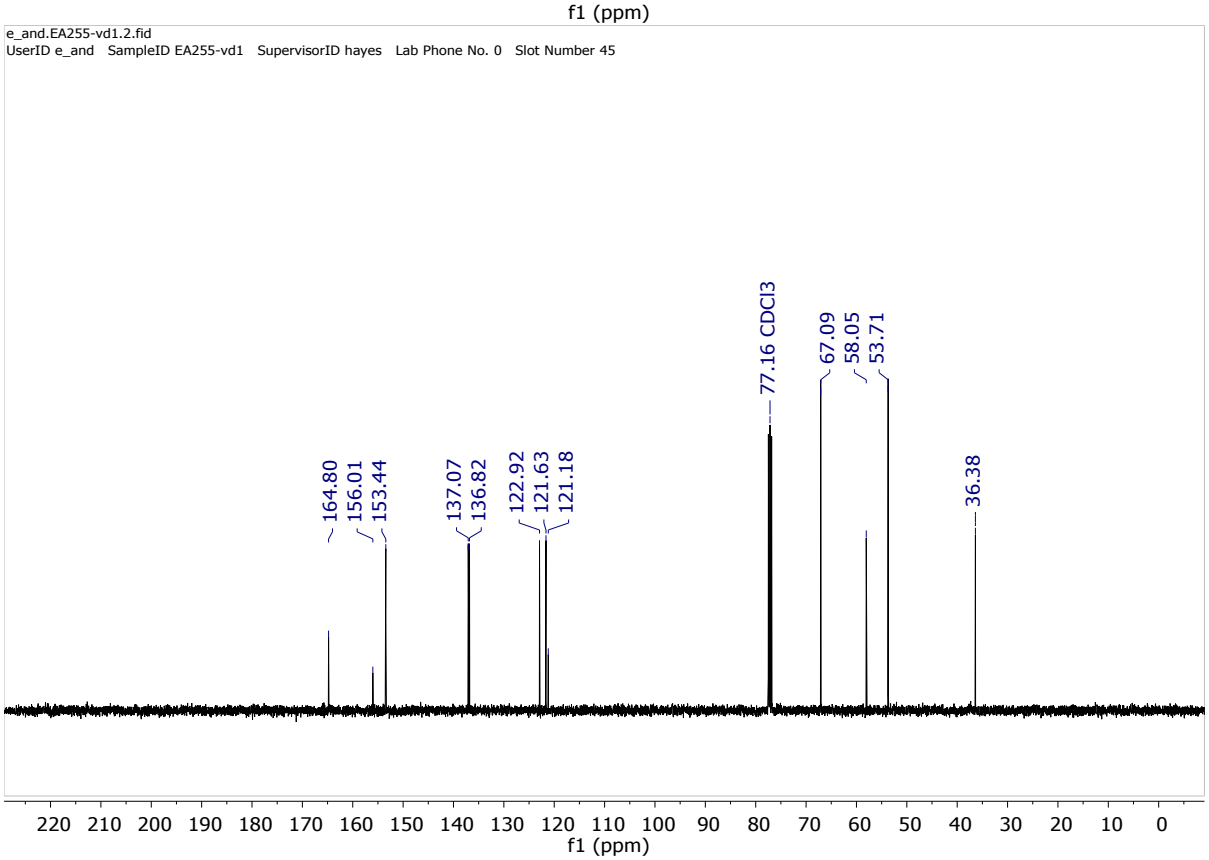
## 2-(2-(Piperidin-1-yl)ethyl)-1,8-naphthyridine (17a)



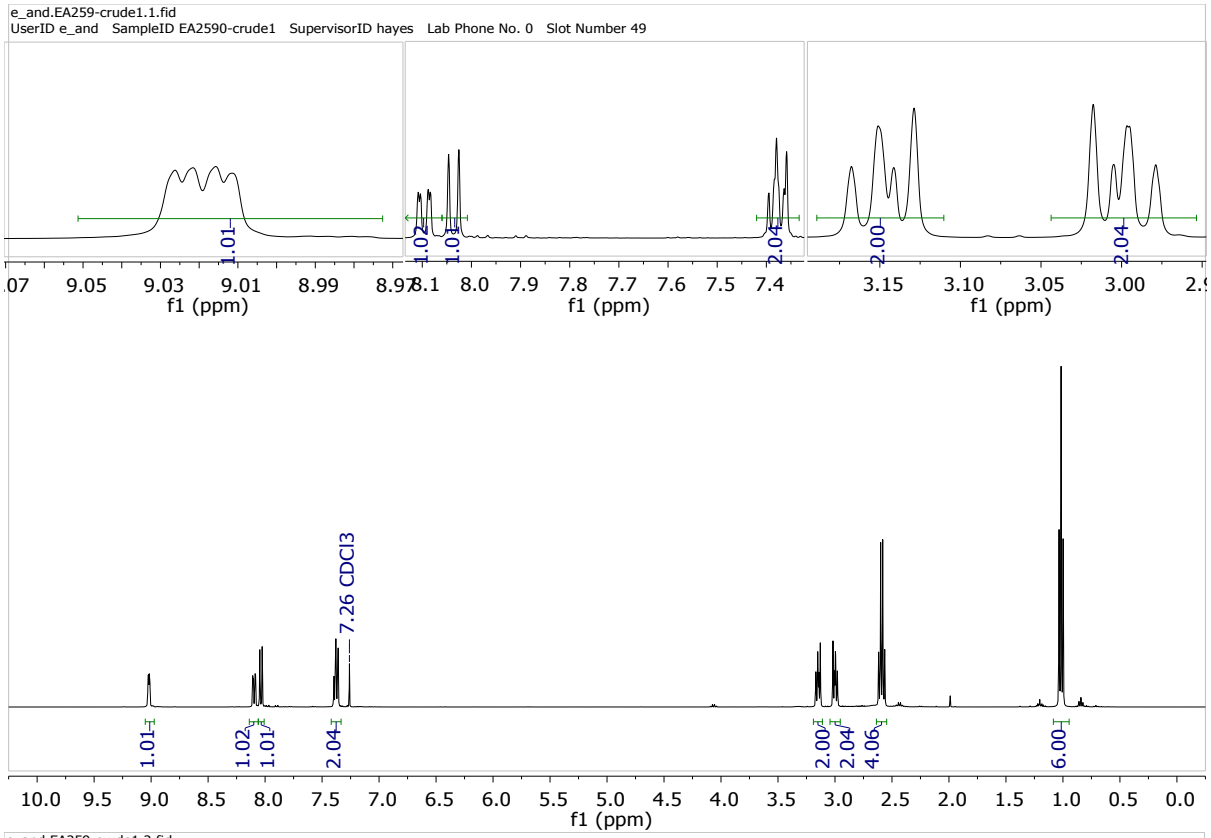



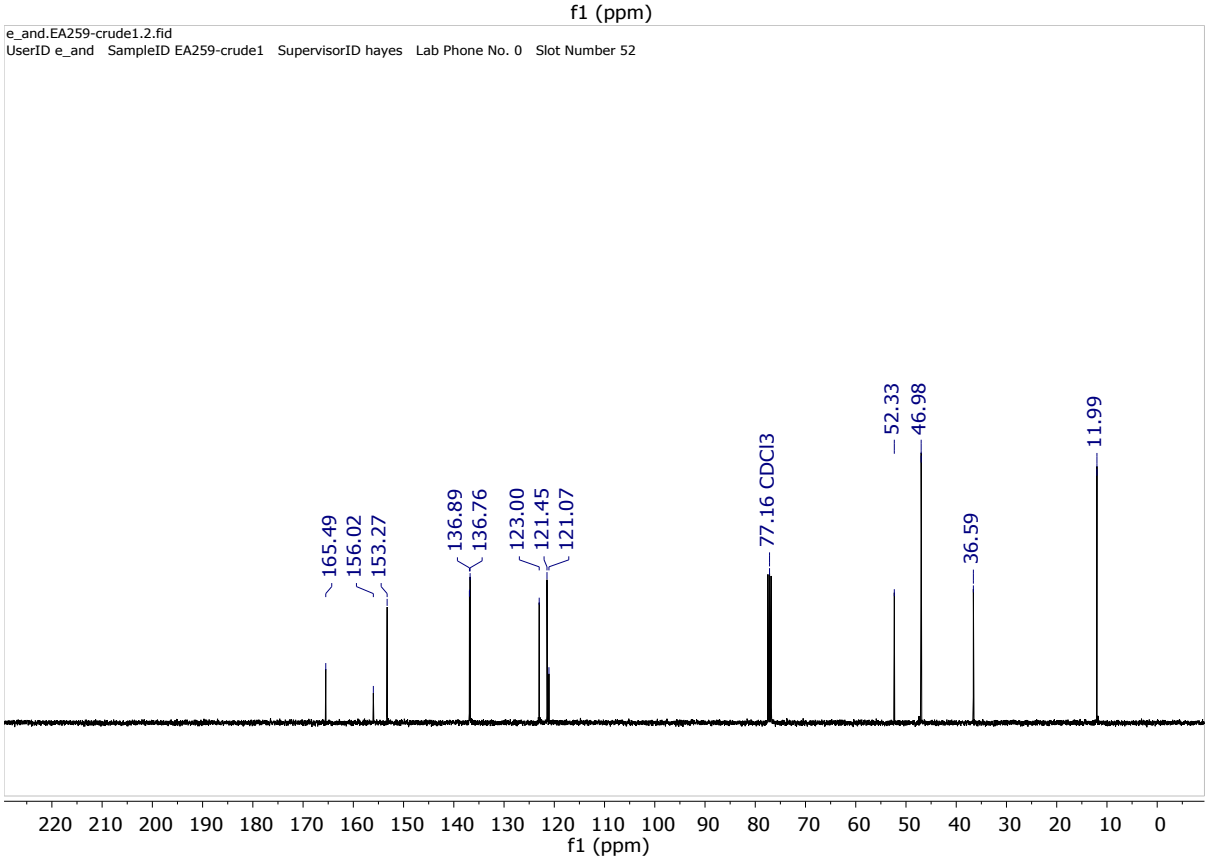
## 4-(2-(1,8-Naphthyridin-2-yl)ethyl)morpholine (17b)



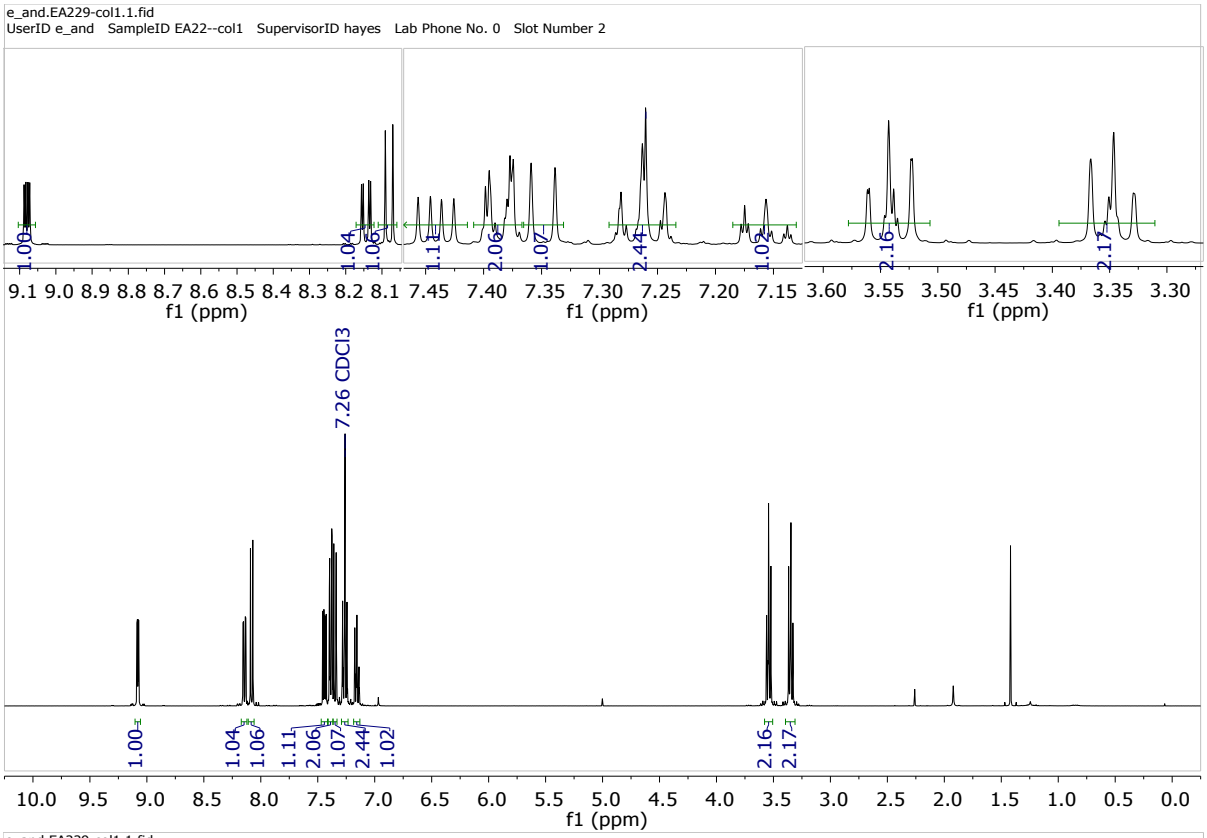



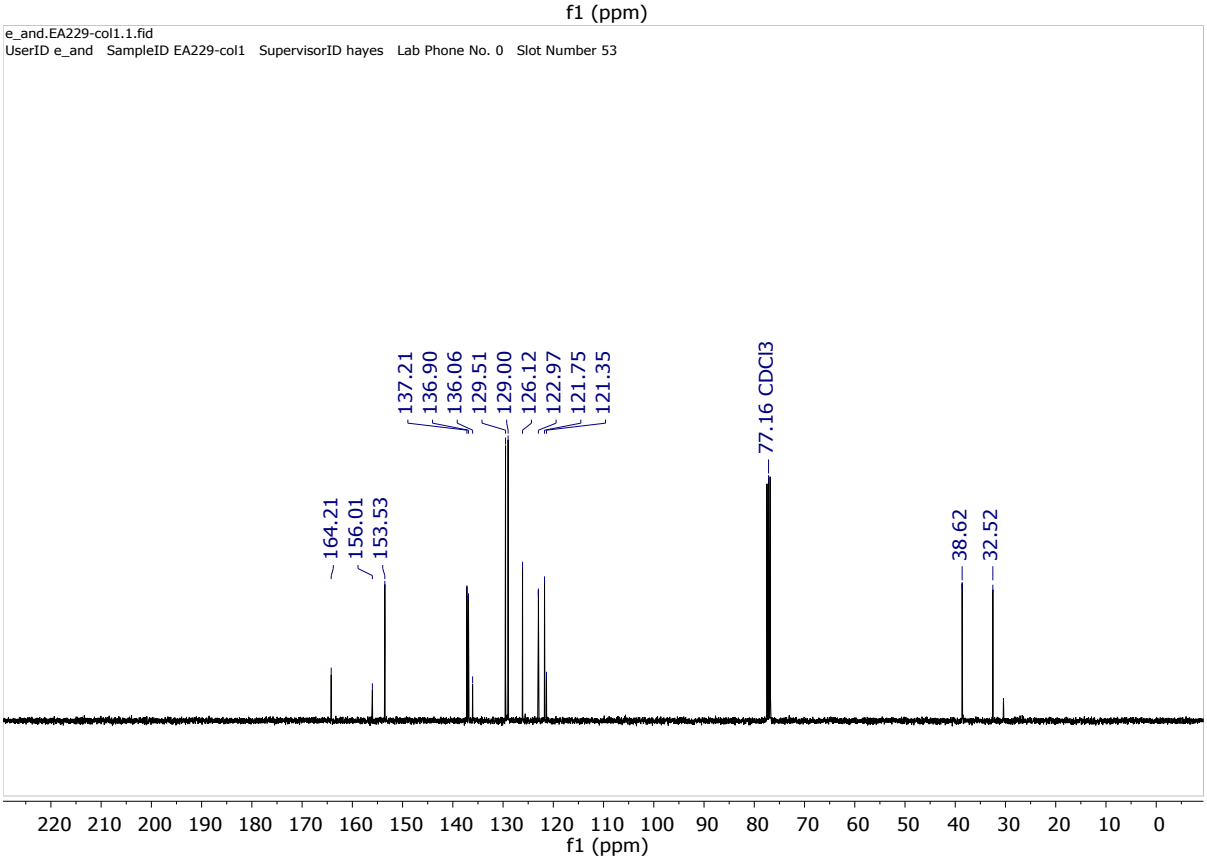
## *N*,*N*-Diethyl-2-(1,8-naphthyridin-2-yl)ethan-1-amine (17c)



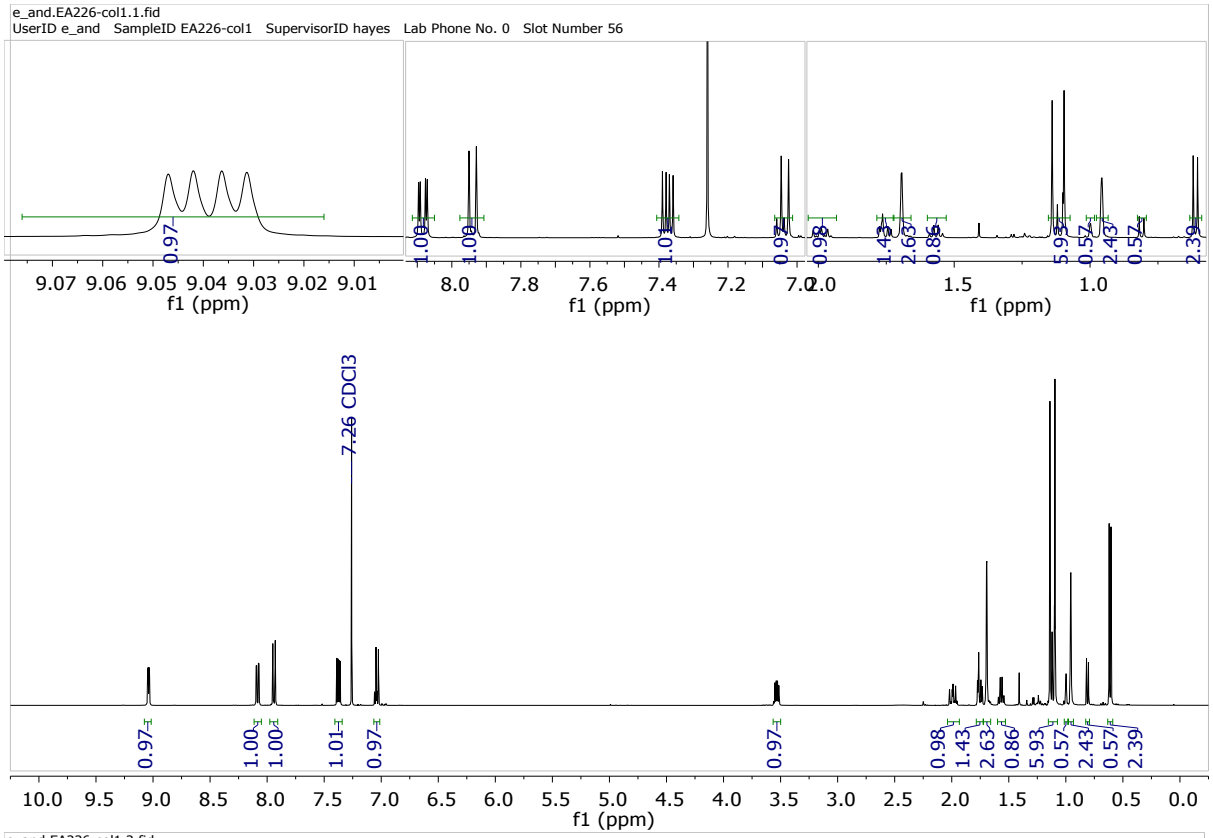



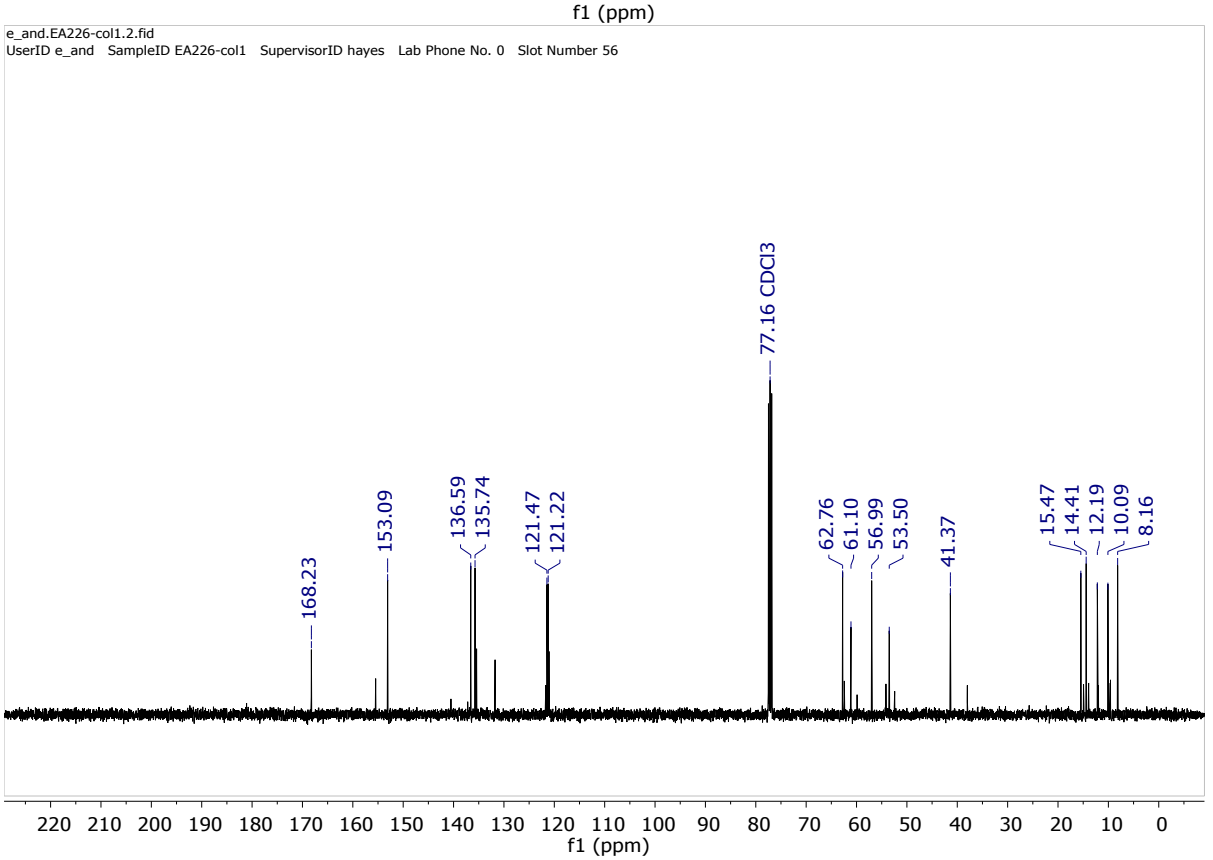
## 2-(2-(Phenylthio)ethyl)-1,8-naphthyridine (17d)



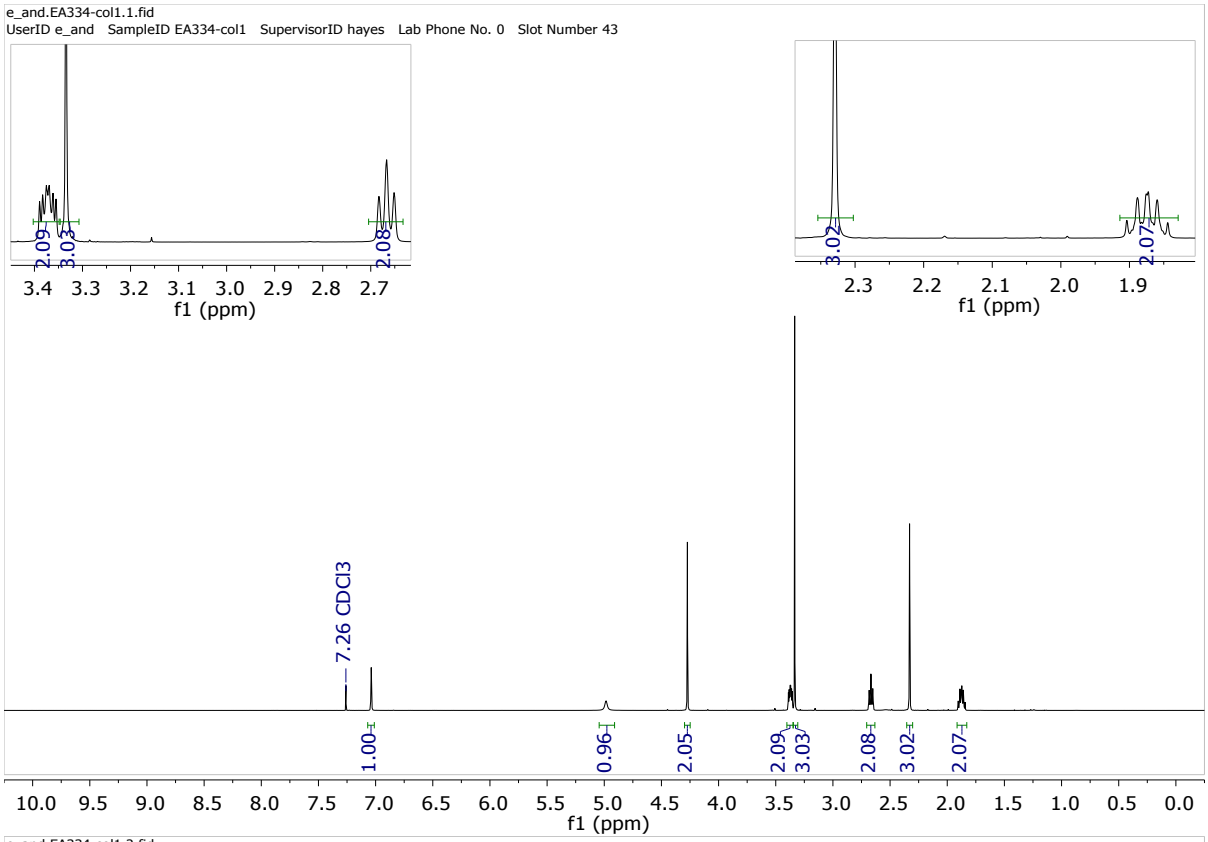



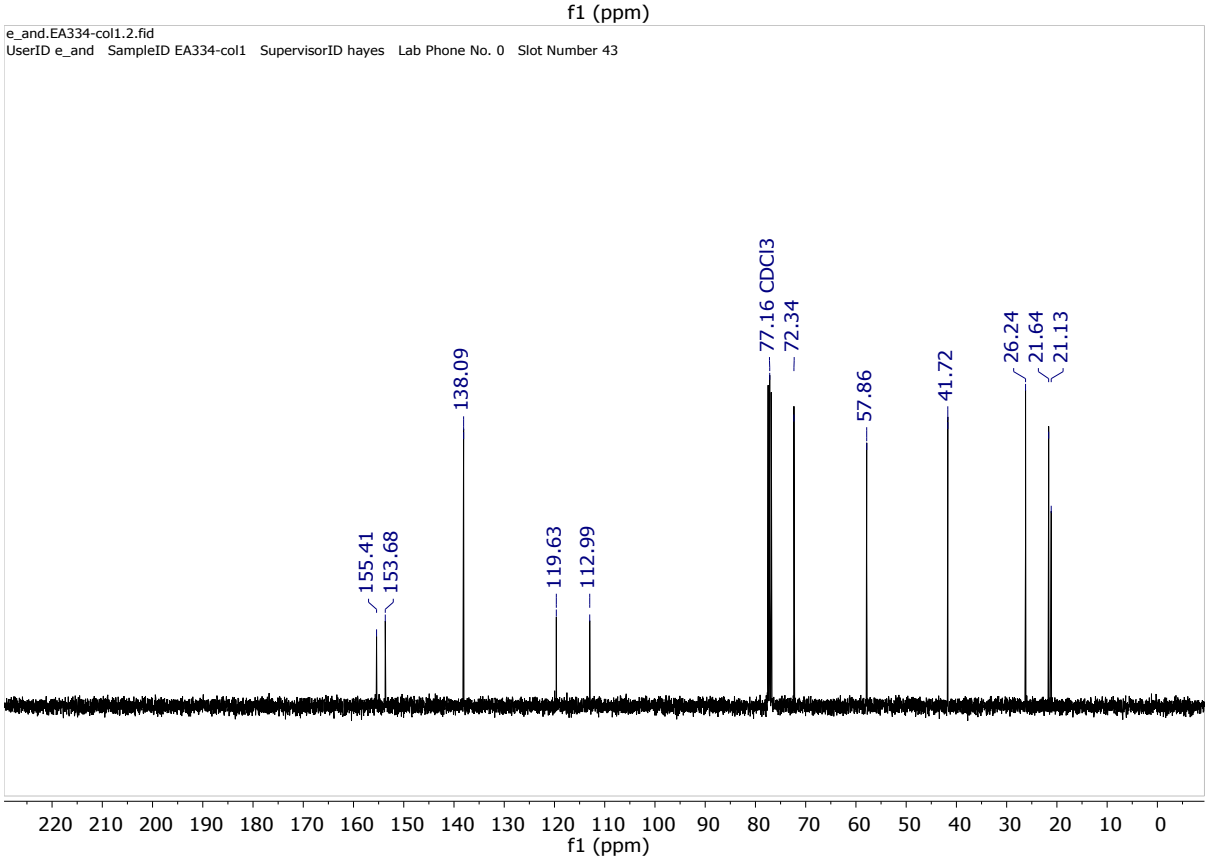
## 2-(1,4,5,6,7-Pentamethylbicyclo[2.2.1]hept-5-en-2-yl)-1,8-naphthyridine (17e)



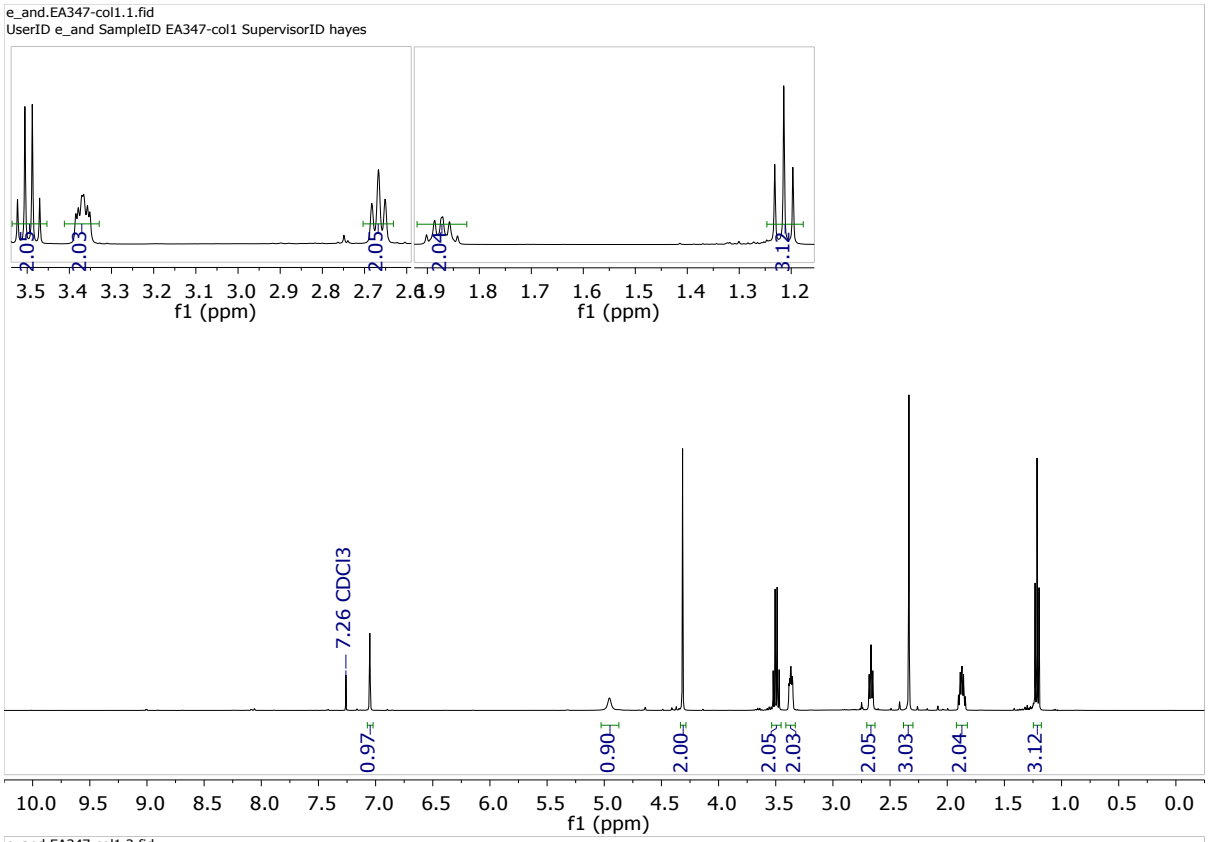



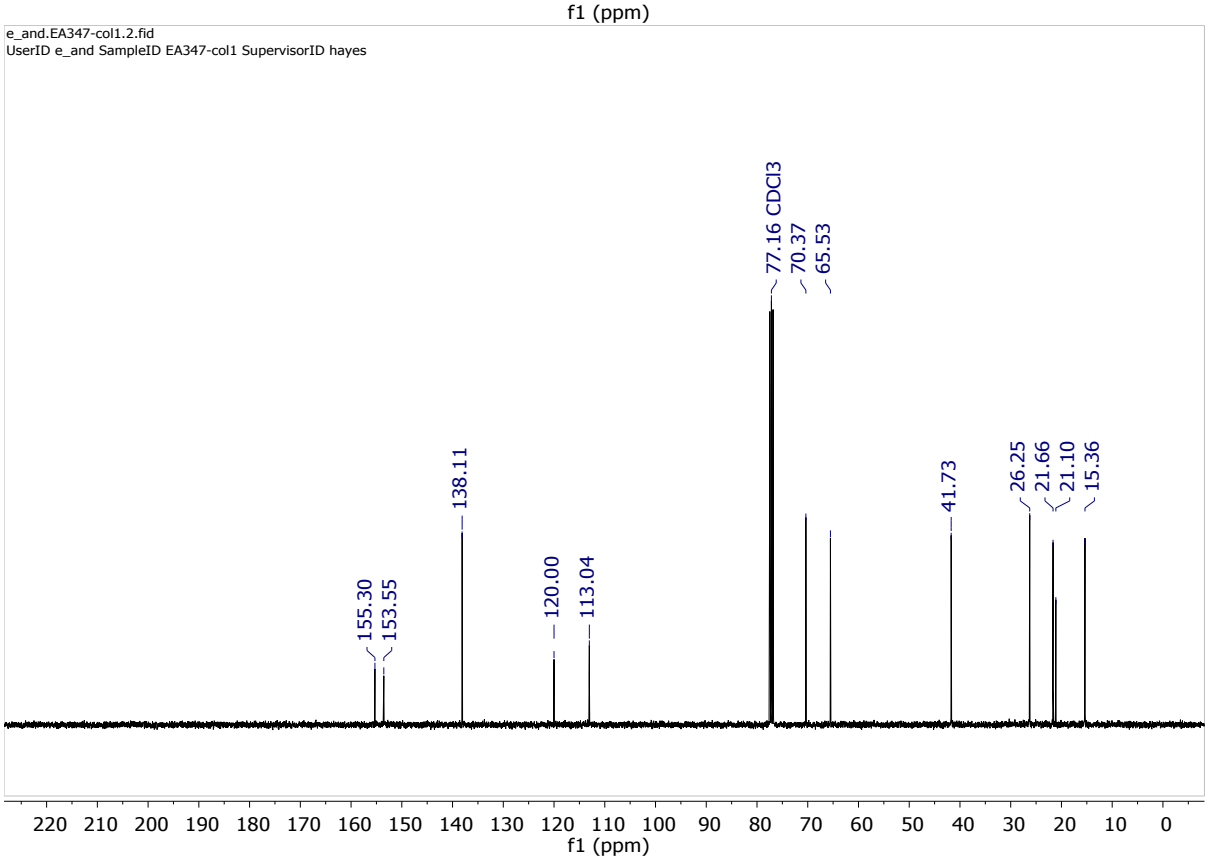
## 6-(Methoxymethyl)-7-methyl-1,2,3,4-tetrahydro-1,8-naphthyridine (18a)



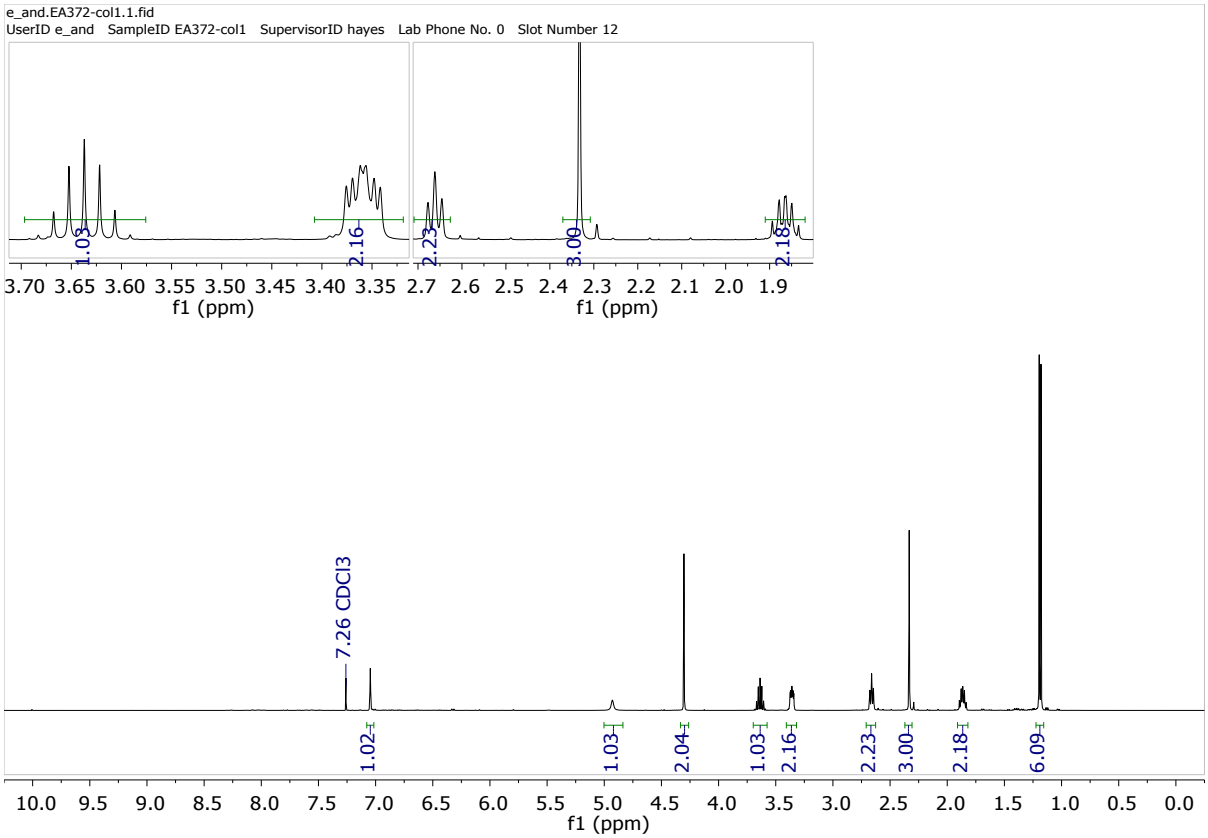



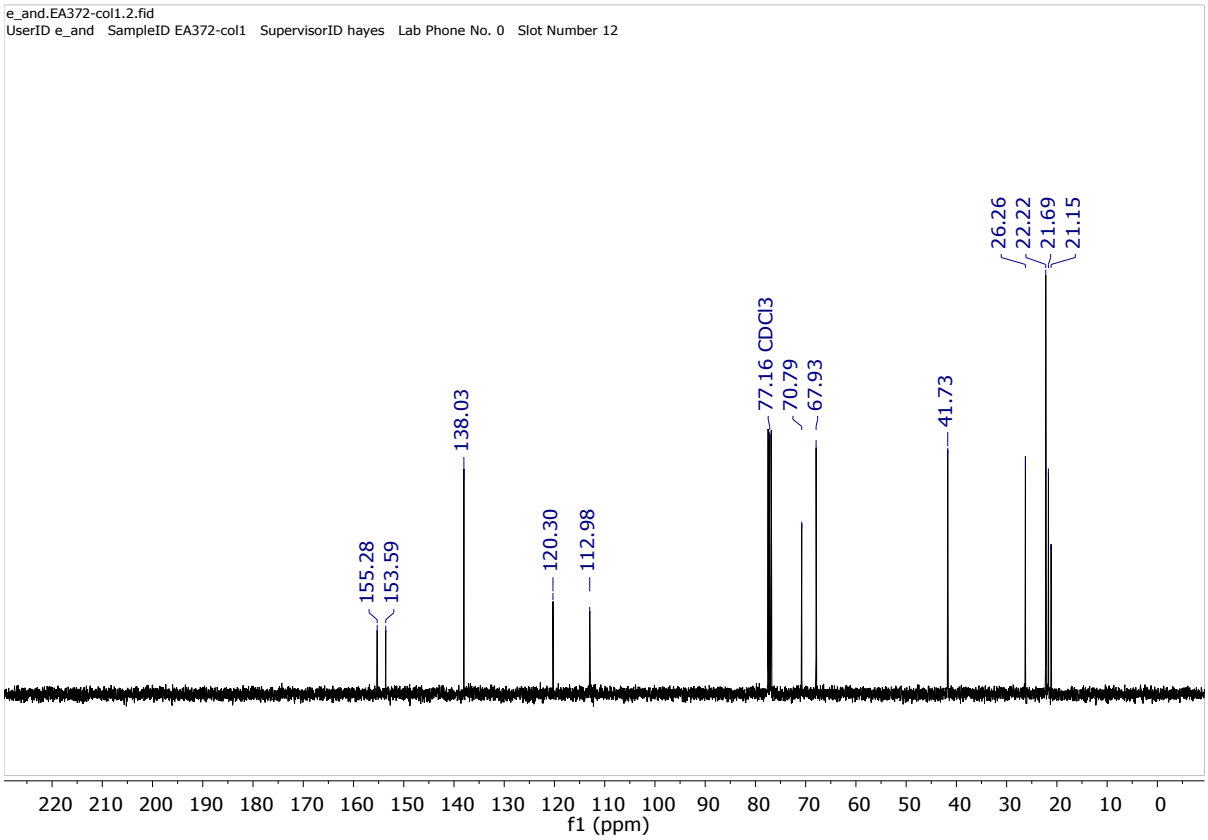
## 6-(Ethoxymethyl)-7-methyl-1,2,3,4-tetrahydro-1,8-naphthyridine (18b)



## 6-(*iso*-Propoxymethyl)-7-methyl-1,2,3,4-tetrahydro-1,8-naphthyridine (18c)



## 3. Metric Calculations

### 3.1 General

Molecular weights and Atom Economy[1] calculations were performed with values conforming to 2 decimal places, with the result quoted to the nearest integer. E-Factor[2] and process mass intensity (PMI)[3] calculations were performed with values conforming to 3 significant figures, with the result quoted to the nearest integer. Effective mass yield[4] values were rounded to the nearest integer percentage, and any reagents that were treated as benign in the referenced document were assumed as benign for the purposes of our calculations. EcoScale[5] values are correct as of 19/07/2018 or 26/11/2018. GREEN MOTION™[6] values are correct as of 20/07/2018, 26/11/2018, or 03/12/2018.

### 3.2 Atom Economy

$$Atom\ Economy = \frac{molecular\ mass\ of\ desired\ product}{molecular\ mass\ of\ all\ reactants} \times 100\%$$

### 3.3 Process Mass Intensity (PMI)

$$PMI = \frac{mass\ of\ all\ reactants, reagents, and\ solvents\ (kg)}{mass\ of\ desired\ product\ (kg)}$$

The PMI calculations were performed excluding purification methods. This decision was made in order to give the fairest comparison between methods, as specific data for purification was absent from some of the literature examples.

### 3.4 E-Factor

$$E-Factor = \frac{(mass\ of\ all\ reactants, reagents, and\ solvents) - mass\ of\ desired\ product\ (kg)}{mass\ of\ desired\ product\ (kg)}$$

The E-Factor calculations were performed excluding purification methods. This decision was made in order to give the fairest comparison between methods, as specific data for purification was absent from some of the literature examples.

Further, it can be shown from the equations above that E-Factor and PMI have the following relationship:

$$E-Factor = PMI - 1$$

### 3.5 Effective Mass Yield (EMY)

$$EMY = \frac{mass\ of\ desired\ product\ (kg)}{mass\ of\ non-benign\ reagents\ (kg)} \times 100\%$$

### 3.6 EcoScale

$$EcoScale = 100 - \sum(penalty\ points)$$

### 3.7 GREEN MOTION™

$$GREEN\ MOTION^{TM} = 100 - \sum(penalty\ points)$$

GREEN MOTION™ values were calculated using SDS data from Sigma Aldrich as of 20/07/2018, using only the data for the reaction step, as it is a step-by-step analysis method, and using ideal reaction conditions, e.g. the starting material is available from hemisynthesis.

### 3.8 Literature Examples & Calculations

Data from the following methods were used:

**Bera *et al.***[7]

2-Methyl-1,8-naphthyridine: 2-Aminonicotinaldehyde (10 g, 0.082 mol) was taken in a flame dried 250 mL two necked round-bottomed flask and dissolved in 100 mL of dry acetone. Then it was refluxed for 5 minutes under nitrogen atmosphere. A freshly prepared saturated solution of KOH in dry MeOH (0.5 mL) was then added to the refluxing solution. Immediately, the color of the solution was changed to brown. Reflux was continued for 24 hours to produce a dark brown solution. After that, it was cooled to room temperature and the solvent was removed by means of rotary evaporation. Finally, it was dried under vacuum and purified by column chromatography using silica gel as stationary phase and pure EtOAc as eluent to afford a brown solid. Yield: 11.14 g (94%).

| **Reaction component** | **MWt (g mol$^{-1}$)** | **Mass (g)** | **Benign/Non-benign** |
|---|---|---|---|
| 2-Aminonicontinaldehyde | 122.13 | 10.0 | Non-benign |
| KOH | 56.11 | 0.0605[a] | Non-benign |
| MeOH | 32.04 | 0.396[b] | Non-benign |
| Acetone (solvent) | 58.08 | 74.2[c] | Benign |
| Acetone (reagent consumed) | 58.08 | 4.8 | Benign |
| 2-Methyl-1,8-naphthyridine | 144.18 | 11.1 | Non-benign (product) |

[a]The mass of KOH present was calculated using the solubility of KOH in MeOH[8]; [b]The mass of MeOH present was calculated using the remainder of the 0.5 mL of KOH in MeOH and *d* = 0.791 g mL$^{-1}$; [c]The mass of acetone present was calculated using *d* = 0.791 g mL$^{-1}$.

***Atom Economy***

$$Atom\ Economy = \frac{144.18}{122.13 + 58.08} \times 100\% = \frac{144.18}{180.21} \times 100\% = 0.80 \times 100\% = 80\%$$

### *Atom Economy (including catalyst)*

$$Atom\ Economy = \frac{144.18}{122.13 + 58.08 + 56.11} \times 100\% = \frac{144.18}{236.32} \times 100\% = 0.61 \times 100\% = 61\%$$

### *Process Mass Intensity (PMI)*

$$E - Factor\ = \frac{10.0 + 0.0605 + 79.0 + 0.396}{11.1} = \frac{89.5}{11.1} = 8.06 \approx 8$$

### *E-Factor*

$$E - Factor = 8 - 1 = 7$$

### *Effective Mass Yield*

$$EMY = \frac{11.1}{10.0 + 0.0605 + 0.396} \times 100\% = \frac{11.1}{10.5} \times 100\% = \ 105.7\% \ \approx \ 106\%$$

### *Effective Mass Yield (considering acetone consumed)*

$$EMY = \frac{11.1}{10.0 + 0.0605 + 4.8 + 0.396} \times 100\% = \frac{11.1}{15.3} \times 100\% = \ 72.5\% \ \approx \ 73\%$$

# *EcoScale 19/07/2018*

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## Ecoscale calculator

### Reagents

Link

| | identifier* | name | MF* | MW | density | purity* | ml | g | mmoles | equiv. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | 2-Amino-3-pyridinecarboxaldehyde | C6H6N2O | 122.12644 | | 100% | 0 | 10 | 81.882350783 | 1 |
| 2 | | Potassium hydroxide | HKO | 56.10564 | | 100% | 0 | 0.0605 | 1.078322963 | 0.013169174 |
| 3 | | Acetone | C3H6O | 58.08004 | 0.79 | 100% | 100 | 79 | 1360.191900 | 16.61153945 |
| 4 | | Methanol | CH4O | 32.04216 | 0.791 | 100% | 0.500632 | 0.396 | 12.358717389 | 0.150932615 |

### Products

| identifier*: | name: | MF*: | MW: | g: | mmoles: | g theor: | yield: |
|---|---|---|---|---|---|---|---|
| | 2-Methyl-1,8-naphthyridine | C9H8N2 | 144.17592 | 11.14 | 77.266716938 | 11.805463 | 94.3631 |

### Conditions

| Reagents | Name | mmoles | eq. | Bp | Hazard | Price | |
|---|---|---|---|---|---|---|---|
| | 2-Amino-3-pyridinecarboxaldehyde | 7.35 | 1 | | | | |
| | Potassium hydroxide | 0.09 | 0.01 | 106 | | | |
| | Acetone | 122.09 | 16.61 | 56 | | | |
| | Methanol | 1.1 | 0.15 | 64.7 | | | |
| Yield | 94 | | | | | | -3 |
| Price / availability | | | | | | | -3 |
| Safety | | | | | | | -25 |
| Technical setup | Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique | Selected items: Common set-up | | | | | 0 |
| Temperature / time | Possible items: Room temperature, < 24h; Heating, < 1h; Heating, > 1h | Selected items: Heating, > 1h | | | | | -3 |
| Workup and purification | Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography | Selected items: Cooling to room temperature; Removal of solvent with bp < 150°C; Classical chromatography | | | | | -10 |
| EcoScale | | | | | | | 56 |

***GREEN MOTION™ 20/07/2018***


Raw materials origin: Raw material obtained by hemisynthesis

Renewable carbon percentage: 100

GHS pictograms of final product: Corrosive, Nocive (Exclamation point)

Is this process step natural?: No

Tick GHS pictograms visible on the reagents and solvent labels: Nocive (Exclamation point) [2-aminonicotinaldehyde, acetone, potassium hydroxide], Flammable [acetone, methanol], Corrosive [potassium hydroxide], Dangerous for health (CMR) Cat. 2 [methanol], Toxic [methanol]

Tick the solvents used during this step: Acetone, Methanol

Step yield: 94

Number of solvents used: 2

Atom Economy: 0.80

Is it a protection or deprotection step?: No

Is it a: [no answer selected]

Step duration (hours): 24

Reaction step under pressure?: Process at atmospheric pressure

Ways of heating: Electrical resistance

Ways of cooling: No cooling

Distillation conditions: No distillation

Does the step belong to the following list? If yes, tick its name: [no answer selected]

Last process review date: 20/07/2018

E-Factor: 7

**Campbell and Jones**[9]

2-methyl-1,8-naphthyridine: A solution of 2-aminonicotinaldehyde (11.10 g, 91 mmol), acetone (15.83 g, 272.9 mmol), and L-proline (11.40 g, 100.1 mmol) in ethanol (120 mL) was stirred at reflux for 16 h. The reaction solution was then cooled to room temperature, concentrated and the residue was dissolved in dichloromethane (100 mL) and filtrated. The filtrate was washed with water (3 x 100 mL) and the organic phase was dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with ethyl acetate:petrol ether (1:10) to give the title compound as a white solid (13.0 g, 99%).

| **Reaction component** | **MWt (g mol$^{-1}$)** | **Mass (g)** | **Benign/Non-benign** |
|---|---|---|---|
| 2-Aminonicontinaldehyde | 122.13 | 11.1 | Non-benign |
| (*S*)-Proline | 115.13 | 11.4 | Benign[a] |
| Acetone (solvent) | 58.08 | 10.5 | Benign |
| Acetone (reagent consumed) | 58.08 | 5.3 | Benign |
| EtOH | 46.07 | 94.7 | Benign |
| 2-Methyl-1,8-naphthyridine | 144.18 | 13.0 | Non-benign (product) |

[a]Assumed benign due to lack of hazardous SDS data; [b]The mass of EtOH present was calculated using $d$ = 0.789 g mL$^{-1}$.

***Atom Economy***

$$Atom\ Economy = \frac{144.18}{122.13 + 58.08} \times 100\% = \frac{144.18}{180.21} \times 100\% = 0.80 \times 100\% = 80\%$$

***Atom Economy (including catalyst)***

$$Atom\ Economy = \frac{144.18}{122.13 + 58.08 + 115.13} \times 100\% = \frac{144.18}{295.34} \times 100\% = 0.49 \times 100\% = 49\%$$

***Process Mass Intensity***

$$E - Factor\ = \frac{11.1 + 11.4 + 15.8 + 94.7}{13.0} = \frac{133}{13.0} = 10.2 \approx 10$$

***E-Factor***

$$E - Factor = 10 - 1 = 9$$

***Effective Mass Yield***

$$EMY = \frac{13.0}{11.1} \times 100\% = 117.1\% \approx 117\%$$

***Effective Mass Yield (Considering acetone consumed)***

$$EMY = \frac{13.0}{11.1 + 5.3} \times 100\% = \frac{13.0}{16.4} \times 100\% = 79.3\% \approx 79\%$$

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Reagents

Link

| | identifier* | name | MF* | MW | density | purity* | ml | g | mmoles | equiv. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | 2-Amino-3-pyridinecarboxaldehyde | C6H6N2O | 122.12644 | | 100% | 0 | 11.1 | 90.889409369 | 1 |
| 2 | | Acetone | C3H6O | 58.08004 | 0.79 | 100% | 20.037975 | 15.83 | 272.55490870 | 2.9987532166 |
| 3 | | L(-)-Proline | C5H9NO2 | 115.13196 | 1.35 | 100% | 767.510313 | 1036.138922 | 8999.5768483 | 99.016782162 |
| 4 | | Ethanol | C2H6O | 46.06904 | 0.79 | 100% | 120 | 94.8 | 2057.7811041 | 22.640493743 |

Products

| identifier*: | name: | MF*: | MW: | g: | mmoles: | g theor: | yield: |
|---|---|---|---|---|---|---|---|
| | 2-Methyl-1,8-naphthyridine | C9H8N2 | 144.17592 | 13 | 90.167622998 | 13.104064 | 99.2059 |

Conditions

Reagents

| Name | mmoles | eq. | Bp | Hazard | Price |
|---|---|---|---|---|---|
| 2-Amino-3-pyridinecarboxaldehyde | 6.99 | 1 | | | |
| Acetone | 20.96 | 2.99 | 56 | | |
| L(-)-Proline | 692.27 | 99.01 | | | |
| Ethanol | 158.29 | 22.64 | | | |

Yield 99 → 0

Price / availability → -8

Safety → -15

Technical setup
Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique
Selected items: Common set-up → 0

Temperature / time
Possible items: Heating, > 1h; Cooling to 0°C; Cooling, < 0°C
Selected items: Heating, > 1h → -3

Workup and purification
Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography
Selected items: Simple filtration; Liquid - liquid extraction or washing; Classical chromatography → -13

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7/19/2018 The EcoScale

EcoScale 61

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***GREEN MOTION™ 20/07/2018***


Raw materials origin: Raw material obtained by hemisynthesis

Renewable carbon percentage: 100

GHS pictograms of final product: Corrosive, Nocive (Exclamation point)

Is this process step natural?: No

Tick GHS pictograms visible on the reagents and solvent labels: Nocive (Exclamation point) [2-aminonicotinaldehyde, acetone, ethanol], Flammable [acetone, ethanol]

Tick the solvents used during this step: Ethanol

Step yield: 99

Number of solvents used: 1

Atom Economy: 0.80

Is it a protection or deprotection step?: No

Is it a: [no answer selected]

Step duration (hours): 16

Reaction step under pressure?: Process at atmospheric pressure

Ways of heating: Electrical resistance

Ways of cooling: No cooling

Distillation conditions: No distillation

Does the step belong to the following list? If yes, tick its name: [no answer selected]

Last process review date: 20/07/2018

E-Factor: 9

**Matveeva *et al.***[10]

A solution of 2-amino-3-formylpyridine (7.32 g, 60 mmol) and piperidine (5.6 g, 66 mmol) in acetone (40 ml) was heated in a sealed tube at 100 °C for 5 h. The solvent was removed *in vacuo*, and the residue was recrystallized from methyl-*tert*-butyl ether. The product was obtained as a light yellow crystalline compound. Yield: 7 g, 81%.

| **Reaction component** | **MWt (g mol$^{-1}$)** | **Mass (g)** | **Benign/Non-benign** |
|---|---|---|---|
| 2-Aminonicontinaldehyde | 122.13 | 7.32 | Non-benign |
| Piperidine | 85.15 | 5.60 | Non-benign |
| Acetone (solvent) | 58.08 | 28.1[a] | Benign |
| Acetone (reagent consumed) | 58.08 | 3.5 | Benign |
| 2-Methyl-1,8-naphthyridine | 144.18 | 7.00 | Non-benign (product) |

[a]The mass of acetone present was calculated using $d$ = 0.791 g mL$^{-1}$.

***Atom Economy***

$$Atom\ Economy\ =\ \frac{144.18}{122.13+58.08}\times 100\%\ =\ \frac{144.18}{180.21}\times 100\%\ =\ 0.80\times 100\%\ =\ 80\%$$

***Atom Economy (including catalyst)***

$$Atom\ Economy = \frac{144.18}{122.13+58.08+85.15}\times 100\% = \frac{144.18}{265.36}\times 100\% = 0.54\times 100\% = 54\%$$

***Process Mass Intensity***

$$PMI\ =\ \frac{7.32+5.60+31.6}{7.00} = \frac{44.5}{7.00} = 6.36 \approx 6$$

***E-Factor***

$$E-Factor = 6-1 = 5$$

***Effective mass Yield***

$$EMY = \frac{7.00}{7.32+5.60}\times 100\% = \frac{7.00}{12.9}\times 100\ \% = 54.3\%\ \approx 54\%$$

***Effective mass Yield (considering acetone consumed)***

$$EMY = \frac{7.00}{7.32+5.60+3.5}\times 100\% = \frac{7.00}{16.4}\times 100\ \% = 42.6\%\ \approx 43\%$$

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## Ecoscale calculator

### Reagents

Link

| | identifier* | name | MF* | MW | density | purity* | ml | g | mmoles | equiv. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | 2-Amino-3-pyridinecarboxaldehyde | C6H6N2O | 122.12644 | | 100% | 0 | 7.32 | 59.937880773 | 1 |
| 2 | | Acetone | C3H6O | 58.08004 | 0.79 | 100% | 40 | 31.6 | 544.07676027 | 9.0773439644 |
| 3 | | Piperidine | C5H11N | 85.14904 | 0.8622 | 100% | 6.495013 | 5.6 | 65.767036246 | 1.0972532795 |

### Products

| identifier*: | name: | MF*: | MW: | g: | mmoles: | g theor: | yield: |
|---|---|---|---|---|---|---|---|
| | 2-Methyl-1,8-naphthyridine | C9H8N2 | 144.17592 | 7 | 48.551796999 | 8.641599 | 81.003499999 |

### Conditions

| Reagents | Name | mmoles | eq. | Bp | Hazard | Price |
|---|---|---|---|---|---|---|
| | 2-Amino-3-pyridinecarboxaldehyde | 8.56 | 1 | | | |
| | Acetone | 77.72 | 9.07 | 56 | | |
| | Piperidine | 9.39 | 1.09 | 106 | | |

| | | |
|---|---|---|
| Yield | 81 | -9 |
| Price / availability | | -3 |
| Safety | | -15 |
| Technical setup | Possible items: Unconventional activation technique; Pressure equipment, > 1 atm; Any additional special glassware<br>Selected items: Pressure equipment, > 1 atm | -3 |
| Temperature / time | Possible items: Heating, > 1h; Cooling to 0°C; Cooling, < 0°C<br>Selected items: Heating, > 1h | -3 |
| Workup and purification | Possible items: Crystallization and filtration; Removal of solvent with bp > 150°C; Solid phase extration<br>Selected items: Cooling to room temperature; Removal of solvent with bp < 150°C; Crystallization and filtration | -1 |
| EcoScale | | 66 |

***GREEN MOTION™ 03/12/2018***


Raw materials origin: Raw material obtained by hemisynthesis

Renewable carbon percentage: 100

GHS pictograms of final product: Corrosive, Nocive (Exclamation point)

Is this process step natural?: No

Tick GHS pictograms visible on the reagents and solvent labels: Nocive (Exclamation point) [2-aminonicotinaldehyde, acetone], Flammable [acetone, piperidine], Toxic [piperidine], Corrosive [piperidine]

Tick the solvents used during this step: Acetone

Step yield: 81

Number of solvents used: 1

Atom Economy: 0.80

Is it a protection or deprotection step?: No

Is it a: [no answer selected]

Step duration (hours): 5

Reaction step under pressure?: Process under pressure

Ways of heating: Electrical resistance

Ways of cooling: No cooling

Distillation conditions: No distillation

Does the step belong to the following list? If yes, tick its name: [no answer selected]

Last process review date: 03/12/2018

E-Factor: 5

**Anderson, Sneddon, and Hayes (this work) – 0.5 M**

To a stirred mixture of 2-aminonicotinaldehyde (122 mg, 1.00 mmol) and LiOH•$H_2O$ (4.2 mg, 100 μmol) in $H_2O$ (2 mL) was added acetone (77.1 μL, 61.0 mg, 1.05 mmol) and the reaction mixture allowed to stir at ambient temperature for 5 h. The reaction mixture was diluted with sat. aq. $Na_2CO_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated under reduced pressure to give **13** as a yellow solid (140 mg, 97%).

| Reaction component | MWt (g mol$^{-1}$) | Mass (g) | Benign/Non-benign |
|---|---|---|---|
| 2-Aminonicontinaldehyde | 122.13 | 0.122 | Non-benign |
| LiOH•$H_2O$ | 41.96 | 0.00420 | Non-benign |
| Acetone | 58.08 | 0.0610[a] | Benign |
| Water | 18.02 | 2.00[b] | Benign |
| 2-Methyl-1,8-naphthyridine | 144.18 | 0.140 | Non-benign (product) |

[a]The mass of acetone present was calculated using $d$ = 0.791 g mL$^{-1}$; [b]The mass of water present was calculated using $d$ = 1.00 g mL$^{-1}$.

***Atom Economy***

$$Atom\ Economy = \frac{144.18}{122.13 + 58.08} \times 100\% = \frac{144.18}{180.21} \times 100\% = 0.80 \times 100\% = 80\%$$

***Atom Economy (including catalyst)***

$$Atom\ Economy = \frac{144.18}{122.13 + 58.08 + 41.96} \times 100\% = \frac{144.18}{222.17} \times 100\% = 0.65 \times 100\% = 61\%$$

***Process Mass Intensity***

$$PMI = \frac{0.122 + 0.00420 + 0.0610 + 2.00}{0.140} = \frac{2.19}{0.140} = 15.6 \approx 16$$

***E-Factor***

$$E - Factor = 16 - 1 = 15$$

***Effective Mass Yield***

$$EMY = \frac{0.140}{0.122 + 0.0042} \times 100\% = \frac{0.140}{0.126} \times 100\ \% = 111.1\% \approx 111\%$$

***Effective Mass Yield (considering acetone consumed)***

$$EMY = \frac{0.140}{0.122 + 0.00420 + 0.0610} \times 100\% = \frac{0.140}{0.187} \times 100\ \% = 74.9\% \approx 75\%$$

# *EcoScale 19/07/2018*




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## Ecoscale calculator

### Reagents

Link

| | identifier* | name | MF* | MW | density | purity* | ml | g | mmoles | equiv. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | 2-Amino-3-pyridinecarboxaldehyde | C6H6N2O | 122.12644 | | 100% | 0 | 0.122126 | 1.0000003330 | 1 |
| 2 | | Lithium hydroxide monohydrate | HLiO.H2O | 41.96362 | 1.51 | 100% | 0.002779 | 0.004196 | 0.1000000333 | 0.1 |
| 3 | | Acetone | C3H6O | 58.08004 | 0.79 | 100% | 0.077195 | 0.060984 | 1.0500003497 | 1.05 |
| 4 | | Water | H2O | 18.01528 | 1 | 100% | 2 | 2 | 111.01687012 | 111.01683314 |

### Products

| identifier*: | name: | MF*: | MW: | g: | mmoles: | g theor: | yield: |
|---|---|---|---|---|---|---|---|
| | 2-Methyl-1,8-naphthyridine | C9H8N2 | 144.17592 | 0.141 | 0.9779719109 | 0.144176 | 97.7971 |

### Conditions

**Reagents**

| Name | mmoles | eq. | Bp | Hazard | Price |
|---|---|---|---|---|---|
| 2-Amino-3-pyridinecarboxaldehyde | 7.09 | 1 | | | |
| Lithium hydroxide monohydrate | 0.7 | 0.1 | 106 | | |
| Acetone | 7.44 | 1.05 | 56 | | |
| Water | 787.35 | 111.01 | | | |

| | | |
|---|---|---|
| Yield | 98 | -1 |
| Price / availability | | -6 |
| Safety | | -5 |
| Technical setup | Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique — Selected items: Common set-up | 0 |
| Temperature / time | Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h — Selected items: Room temperature, < 24h | -1 |
| Workup and purification | Possible items: Simple filtration; Removal of solvent with bp < 150°C; Crystallization and filtration — Selected items: Liquid - liquid extraction or washing; Removal of solvent with bp < 150°C | -3 |





EcoScale 84

***GREENMOTION™ 26/11/2018***


Raw materials origin: Raw material obtained by hemisynthesis

Renewable carbon percentage: 100

GHS pictograms of final product: Corrosive, Nocive (Exclamation point)

Is this process step natural?: No

Tick GHS pictograms visible on the reagents and solvent labels: Nocive (Exclamation point) [2-aminonicotinaldehyde, acetone, $LiOH•H_2O$], Flammable [acetone], Corrosive [$LiOH•H_2O$]

Tick the solvents used during this step: Water

Step yield: 97%

Number of solvents used: 1

Atom Economy: 0.80

Is it a protection or deprotection step?: No

Is it a: [no answer selected]

Step duration (hours): 5

Reaction step under pressure?: Process at atmospheric pressure

Ways of heating: No heating

Ways of cooling: No cooling

Distillation conditions: No distillation

Does the step belong to the following list? If yes, tick its name: [no answer selected]

Last process review date: 20/07/2018

E-Factor: 15

**Anderson, Sneddon, and Hayes (this work) – 1 M**

To a stirred mixture of 2-aminonicotinaldehyde (122 mg, 1.00 mmol) and LiOH•$H_2O$ (4.2 mg, 100 μmol) in $H_2O$ (1 mL) was added acetone (77.1 μL, 61.0 mg, 1.05 mmol) and the reaction mixture allowed to stir at ambient temperature for 2 h. The reaction mixture was diluted with sat. aq. $Na_2CO_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated under reduced pressure to give **13** as a yellow solid (141 mg, 98%).

| Reaction component | MWt (g mol$^{-1}$) | Mass (g) | Benign/Non-benign |
|---|---|---|---|
| 2-Aminonicontinaldehyde | 122.13 | 0.122 | Non-benign |
| LiOH•$H_2O$ | 41.96 | 0.00420 | Non-benign |
| Acetone | 58.08 | 0.0610[a] | Benign |
| Water | 18.02 | 1.00[b] | Benign |
| 2-Methyl-1,8-naphthyridine | 144.18 | 0.141 | Non-benign (product) |

[a]The mass of acetone present was calculated using $d$ = 0.791 g mL$^{-1}$; [b]The mass of water present was calculated using $d$ = 1.00 g mL$^{-1}$.

***Atom Economy***

$$Atom\ Economy = \frac{144.18}{122.13 + 58.08} \times 100\% = \frac{144.18}{180.21} \times 100\% = 0.80 \times 100\% = 80\%$$

***Atom Economy (including catalyst)***

$$Atom\ Economy = \frac{144.18}{122.13 + 58.08 + 41.96} \times 100\% = \frac{144.18}{222.17} \times 100\% = 0.65 \times 100\% = 61\%$$

***Process Mass Intensity***

$$PMI = \frac{0.122 + 0.00420 + 0.0610 + 1.00}{0.141} = \frac{1.19}{0.141} = 8.44 \approx 8$$

***E-Factor***

$$E - Factor = 8 - 1 = 7$$

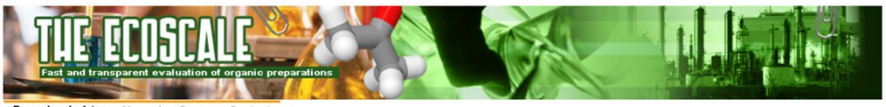
***Effective Mass Yield***

$$EMY = \frac{0.141}{0.122 + 0.0042} \times 100\% = \frac{0.141}{0.126} \times 100\ \% = 111.9\% \approx 112\%$$

***Effective Mass Yield (considering acetone consumed)***

$$EMY = \frac{0.141}{0.122 + 0.00420 + 0.0610} \times 100\% = \frac{0.141}{0.187} \times 100\ \% = 75.4\% \approx 75\%$$

# *EcoScale 26/11/2018*

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## Ecoscale calculator

### Reagents

Link

| | identifier* | name | MF* | MW | density | purity* | ml | g | mmoles | equiv. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | 2-Amino-3-pyridinecarboxaldehyde | C6H6N2O | 122.12644 | | 100% | 0 | 0.122126 | 1 | 1 |
| 2 | | Lithium hydroxide monohydrate | HLiO.H2O | 41.96362 | 1.51 | 100% | 0.002779 | 0.004196 | 0.1 | 0.1 |
| 3 | | Acetone | C3H6O | 58.08004 | 0.79 | 100% | 0.077195 | 0.060984 | 1.05 | 1.05 |
| 4 | | Water | H2O | 18.01528 | 1 | 100% | 1 | 1 | 55.508435061 | 55.508435061 |

### Products

| identifier*: | name: | MF*: | MW: | g: | mmoles: | g theor: | yield: |
|---|---|---|---|---|---|---|---|
| | 2-Methyl-1,8-naphthyridine | C9H8N2 | 144.17592 | 0.141 | 0.9779719109 | 0.144176 | 97.7971 |

### Conditions

Reagents

| Name | mmoles | eq. | Bp | Hazard | Price |
|---|---|---|---|---|---|
| 2-Amino-3-pyridinecarboxaldehyde | 7.09 | 1 | | | |
| Lithium hydroxide monohydrate | 0.7 | 0.1 | | | |
| Acetone | 7.44 | 1.05 | 56 | | |
| Water | 393.67 | 55.5 | | | |

| | | | |
|---|---|---|---|
| Yield | 98 | | -1 |
| Price / availability | | | -5 |
| Safety | | | -5 |
| Technical setup | Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique | Selected items: Common set-up | 0 |
| Temperature / time | Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h | Selected items: Room temperature, < 24h | -1 |
| Workup and purification | Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography | Selected items: Removal of solvent with bp < 150°C; Liquid - liquid extraction or washing | -3 |
| EcoScale | | | 85 |

***GREENMOTION™ 26/11/2018***


Raw materials origin: Raw material obtained by hemisynthesis

Renewable carbon percentage: 100

GHS pictograms of final product: Corrosive, Nocive (Exclamation point)

Is this process step natural?: No

Tick GHS pictograms visible on the reagents and solvent labels: Nocive (Exclamation point) [2-aminonicotinaldehyde, acetone, $LiOH•H_2O$], Flammable [acetone], Corrosive [$LiOH•H_2O$]

Tick the solvents used during this step: Water

Step yield: 98%

Number of solvents used: 1

Atom Economy: 0.80

Is it a protection or deprotection step?: No

Is it a: [no answer selected]

Step duration (hours): 2

Reaction step under pressure?: Process at atmospheric pressure

Ways of heating: No heating

Ways of cooling: No cooling

Distillation conditions: No distillation

Does the step belong to the following list? If yes, tick its name: [no answer selected]

Last process review date: 26/11/2018

E-Factor: 7

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