Supporting Information

Synthesis of substituted 4-, 5-, 6- and 7-azaindoles from aminopyridines *via* a cascade C-N cross-coupling/Heck reaction

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General information

All reagents and solvents were acquired commercially and usually used without further purification. The solvents used during the reactions were dried and distilled using typical methods. Analytical TLC was performed on Merck Keiselgel GF 254, 0.2 mm plates supported on aluminum. Preparative TLC was performed using Merk Keiselgel $60GS_{254}$ silica gel for TLC supported on a glass surface with the described eluent for each case. Column chromatography was performed using Merck Keiselgel 60A silica gel (70-200 mesh) or aluminium oxide 90 active neutral 0.063-0.200 mm (70-230 mesh ASTM from Merck) and the described eluent for each case.

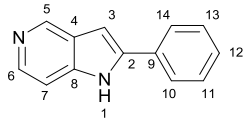
Melting points were measured using a Reichert Thermovar melting point apparatus, equipped with a Kofler plate. Measured melting points were not corrected.

NMR spectra were acquired with Bruker ARX 400 or Bruker Avance III 400 spectrometers. ^{1}H-RMN and ^{13}C-RMN spectra were measured at 400 and 101 MHz, respectively. The samples were prepared on 5 or 3 mm NMR tubes using $CDCl_3$ or DMSO-d_6 as solvents and the corresponding trace $CHCl_3$ or DMSO as reference signals. The NMR signals are described with chemical shift (δ, in ppm), source of signal (R-H) and relative intensity of signal multiplicity (nH, with n being the number of protons) of NMR signals are described as singlet (s), broad singlet (br s), doublet of doublets (dd), triplet of doublets (td), doublet (d), triplet (t) and multiplet (m) with coupling constant (J) being given in Hz.

General procedure for the cascade C-N cross-coupling/Heck with amino-*o*-bromopyridines

A sealed tube equipped with a magnetic stir bar was charged with Pd_2dba_3 (4 mol %), XPhos (8 mol %), *t*-BuONa (3 equiv) and amino-*o*-bromopyridine (1 equiv). The tube was sealed with a suba-seal, evacuated and backfilled with nitrogen thrice. *t*-BuOH (c = 0.1 M) was then added, followed by the alkenyl bromide compound (1.5 equiv) and the reaction was stirred for 24 h at 110 ^{o}C. The solution was allowed to cool to room temperature and concentrated; the residue was then diluted on ethyl acetate and a saturated solution of NH_4Cl was added. Aqueous layer was extracted several times (at least 4) until all the reaction products were recovered. Combined organic layers were dried with anhydrous sodium sulphate, filtered and concentrated. The desired product was isolated after purification by chromatography.[1]

2-Phenyl-5-azaindole (4a)[1]



Purification: Silica gel, dichloromethane/methanol with gradient

Appearance: White solid

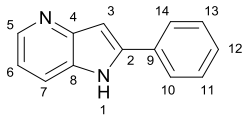
Yield: 57% (19.1 mg of **4a** from 30 mg of starting 4-amino-3-bromopyridine)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.97 (s, N*H,* 1H), 8.82 (s, H_5, 1H), 8.17 (d, *J* = 4.3 Hz, H_6, 1H), 7.90 (d, *J* = 7.3 Hz, Ar-$H_{14,10}$, 2H), 7.49 (t, *J* = 7.7 Hz, Ar-$H_{13,11}$, 2H), 7.38 – 7.35 (m, Ar-H_{12}, H_7, 2H), 7.04 (s, H_3, 1H)

^{13}C NMR (101 MHz, DMSO-d_6) δ: 142.95 (C_5), 140.46 (C_6), 140.36 (C_8), 138.87 (C_2), 131.42 (C_9), 129.01 ($C_{13,11}$), 128.08 (C_{12}), 125.74 (C_4), 125.36 ($C_{10,14}$), 106.59 (C_7), 97.57 (C_3).

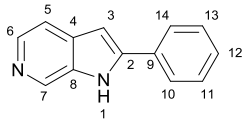
[1] **NOTE:** 2-Phenyl-4-azaindole (**4b**), 2-phenyl-6-azaindole (**4c**) and 7-azaindole (**4e**) when purified by silica gel tend to protonate; this was confirmed by NMR and with the addition of a drop of DBU (1,8-DiazabicycloUndec-7-ene) on the NMR tube, by comparison with the spectra reported for the azaindoles.

2-Phenyl-4-azaindole (4b)[1]



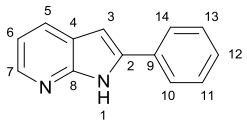
Purification: Neutral aluminium oxide, ethyl acetate/hexane (1:1)
Appearance: Yellow solid
Yield: 82% (27.5 mg of **4b** from 30 mg of starting 3-amino-2-bromopyridine)
^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.79 (s, N*H*, 1H), 8.31 (d, *J* = 3.5 Hz, H_5, 1H), 7.93 (d, *J* = 7.4 Hz, $H_{14,10}$, 2H), 7.76 (d, *J* = 8.0 Hz, H_7, 1H), 7.50 (t, *J* = 7.6 Hz, $H_{13,11}$, 2H), 7.39 (t, *J* = 7.3 Hz, H_{12}, 1H), 7.10 (dd, *J* = 8.1, 4.6 Hz, H_6, 1H), 7.06 (s, H_3, 1H)
^{13}C NMR (101 MHz, DMSO-d_6) δ: 146.94 (C_4), 142.87 (C_5), 140.83 (C_2), 131.49 (C_9), 129.89 (C_8), 128.99 ($C_{13,11}$), 128.25 (C_{12}), 125.39 ($C_{10,14}$), 118.03 (C_7), 116.63 (C_6), 99.13 (C_3).

2-Phenyl-6-azaindole (4c)[1]



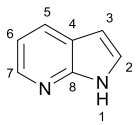
Purification: Neutral aluminium oxide, ethyl acetate/hexane (1:1)
Appearance: Beige solid
Yield: 48% (26.7 mg of **4c** from 50 mg of starting 3-amino-4-bromopyridine)
^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.02 (s, N*H,* 1H), 8.75 (s, H_7, 1H), 8.09 (d, *J* = 5.3 Hz, H_6, 1H), 7.94 (d, *J* = 7.3 Hz, $H_{10,14}$, 2H), 7.55 – 7.47 (m, H_5, $H_{11,13}$, 3H), 7.40 (t, *J* = 7.3 Hz, H_{12}, 1H), 6.97 (s, H_3, 1H)
^{13}C NMR (101 MHz, DMSO-d_6) δ: 141.25 (C_2), 138.26 (C_6), 134.23 (C_7), 133.43 (C_8)*, 132.74 (C_4), 131.30 (C_9), 129.05 ($C_{11,13}$), 128.56 (C_{12}), 125.77 ($C_{10,14}$), 114.41 (C_2), 97.90 (C_3)
*Observed on HMBC experiment, but it was not observed on ^{13}C.

2-Phenyl-7-azaindole (4d)[2]



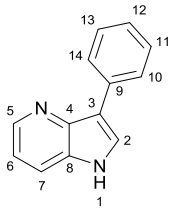
Purification: Silica gel, dichloromethane/ethyl acetate with gradient
Appearance: Dark beige solid
Yield: 19**%** (10.7 mg of **4d** from 50 mg of starting 2-amino-3-bromopyridine)
^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.13 (s, N*H,* 1H), 8.21 (d, *J* = 3.6 Hz, H_7, 1H), 7.98 – 7.89 (m, H_5, $H_{10,14}$, 3H), 7.47 (t, *J* = 7.6 Hz, $H_{11,13}$, 2H), 7.35 (t, *J* = 7.3 Hz, H_{12}, 1H), 7.06 (dd, *J* = 7.7, 4.7 Hz, H_6, 1H), 6.93 (s, H_3, 1H)
^{13}C NMR (101 MHz, DMSO-d_6) δ: 149.66 (C_8), 142.80 (C_7), 138.20 (C_2), 131.59 (C_9), 128.90 ($C_{11,13}$), 127.98 (C_{12}), 127.80 (C_5), 125.32 ($C_{10,14}$), 120.90 (C_4), 116.01 (C_6), 97.08 (C_3).

7-azaindole[3]



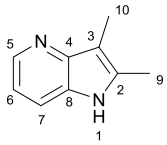
Purification: Silica gel, ethyl acetate/hexane (2:1) gave the protonated form
Appearance: Beige/yellow solid
Yield: 9**%** (3.2 mg of 7-azaindole from 50 mg of starting 2-amino-3-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (dd, *J* = 4.7, 1.2 Hz, H_7, 1H), 7.94 (dd, *J* = 7.8, 1.4 Hz, H_5, 1H), 7.34 (d, *J* = 3.5 Hz, H_3, 1H), 7.07 (dd, *J* = 7.8, 4.8 Hz, H_6, 1H), 6.49 (d, *J* = 3.5 Hz, H_2, 1H) and DBU
^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.56 (C_8), 142.99 (C_7), 128.98 (C_5), 124.96 (C_2), 120.32 (C_4), 116.02 (C_6), 100.88 (C_3) and DBU.

3-Phenyl-4-azaindole[4]



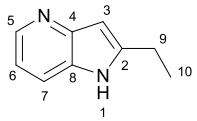
Purification: Silica gel, hexane/ethyl acetate with gradient
Appearance: Beige solid
Yield: 2% (0.7 mg of 3-phenyl-4-azaindole from 30 mg of starting 3-amino-2-bromopyridine)
^{1}H NMR (400 MHz, MeOD) δ: 8.38 (d, *J* = 4.2 Hz, H_5, 1H), 7.97 – 7.90 (m, $H_{10,14}$, 2H), 7.89 – 7.82 (m, H_7, H_2, 2H), 7.41 (t, *J* = 7.7 Hz, $H_{11,13}$, 2H), 7.27 – 7.17 (m, H_{12}, H_6, 2H).

2,3-Dimethyl-4-azaindole (4e)[5]



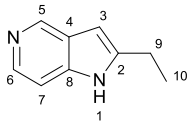
Purification: Silica gel, chloroform/methanol 3%
Appearance: Beige solid
Yield: 28% (7.1 mg of **4e** from 30 mg of starting 3-amino-2-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (dd, *J* = 4.6, 1.0 Hz, H_5, 1H), 8.15 (br s, N*H,* 1H), 7.51 (dd, *J* = 8.0, 1.0 Hz, H_7, 1H), 7.00 (dd, *J* = 8.0, 4.8 Hz, H_6, 1H), 2.42 (s, 3xH_9, 3H), 2.32 (s, 3xH_{10}, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 146.94 (C_4), 142.10 (C_5), 135.54 (C_2), 128.56 (C_8), 117.04 (C_7), 115.82 (C_6), 108.20 (C_3), 12.26(C_9), 7.59 (C_{10}).

2-Ethyl-4-azaindole (4f)[6]



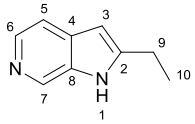
Purification: Neutral aluminium oxide, hexane/ethyl acetate with gradient
Appearance: Pale brown solid
Yield: 21% (9 mg of **4f** from 50 mg of starting 3-amino-2-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.18 (br s, N*H,* 1H), 8.38 (dd, *J* = 4.6, 1.2 Hz, H_5, 1H), 7.57 (d, *J* = 8.0 Hz, H_7, 1H), 7.02 (dd, *J* = 8.1, 4.8 Hz, H_6, 1H), 6.45 (s, H_3, 1H), 2.85 (q, *J* = 7.5 Hz, H_9, 2H), 1.36 (t, *J* = 7.6 Hz, H_{10}, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.32 (C_4), 146.23 (C_2), 142.42 (C_5), 129.25 (C_8), 117.62 (C_7), 115.90 (C_6), 99.51 (C_3), 21.97 (C_9), 13.17 (C_{10}).

2-Ethyl-5-azaindole (4g)



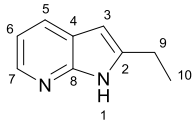
Purification: Neutral aluminium oxide, chloroform 100%
Appearance: Brown solid
Yield: 23% (9.6 mg of **4g** from 50 mg of starting 4-amino-3-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.39 (br s, N*H*, 1H), 8.83 (s, H_5, 1H), 8.24 (d, *J* = 5.7 Hz, H_6, 1H), 7.23 (d, *J* = 5.7 Hz, H_7, 1H), 6.33 (s, H_3, 1H), 2.84 (td, *J* = 14.5, 7.3 Hz, H_9, 2H), 1.37 (t, *J* = 7.6 Hz, H_{10}, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.13 (C_2), 142.39 (C_5), 140.14 (C_8), 140.03 (C_6), 126.02 (C_4), 106.13 (C_7), 97.69 (C_3), 21.51 (C_9), 13.21 (C_{10}).

2-Ethyl-6-azaindole (4h)[7]



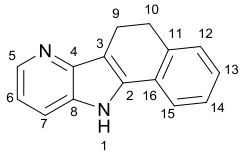
Purification: Neutral aluminium oxide, chloroform/methanol with gradient
Appearance: Brown solid
Yield: 22% (9.1 mg of **4h** from 50 mg of starting 3-amino-4-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (s, H_7, 1H), 8.18 (d, J = 5.5 Hz, H_6, 1H), 7.45 (d, J = 5.2 Hz, H_5, 1H), 6.28 (s, H_3, 1H), 2.88 (q, J = 7.6 Hz, H_9, 2H), 1.39 (t, J = 7.6 Hz, H_{10}, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.00 (C_2), 137.95 (C_6), 134.24 (C_8), 133.64 (C_4), 132.74 (C_7), 114.63 (C_5), 98.40 (C_3), 21.77 (C_9), 13.23 (C_{10}).

2-Ethyl-7-azaindole (4i)[8]



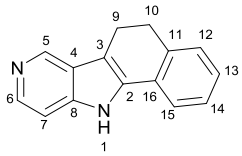
Purification: Neutral aluminium oxide, hexane/ethyl acetate with gradient followed by PTLC using dichloromethane/ethyl acetate (10%)
Appearance: Brown solid
Yield: 15% (6.5 mg of **4i** from 50 mg of starting 2-amino-3-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.84 (br s, N*H*, 1H), 8.21 (d, J = 3.6 Hz, H_7, 1H), 7.83 (dd, J = 7.7, 1.0 Hz, H_5, 1H), 7.03 (dd, J = 7.7, 4.8 Hz, H_6, 1H), 6.20 (s, H_3, 1H), 2.89 (q, J = 7.5 Hz, H_9, 2H), 1.40 (dd, J = 18.9, 11.3 Hz, H_{10}, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.14 (C_8), 142.86 (C_2), 141.05 (C_7), 127.75 (C_5), 121.78 (C_4), 115.76 (C_6), 96.74 (C_3), 21.92 (C_9), 13.24 (C_{10}).

6,11-Dihydro-5*H*-benzo[*g*]pyrido[3,2-*b*]indole (4j)[5]



Purification: Neutral aluminium oxide, dichloromethane followed by PTLC using chloroform/methanol (7%)
Appearance: White solid
Yield: 85% (32.5 mg of **4j** from 30 mg of starting 3-amino-2-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (br s, N*H*, 1H), 8.44 (d, J = 3.8 Hz, H_5, 1H), 7.67 (d, J = 7.1 Hz, H_7, 1H), 7.45 (d, J = 7.1 Hz, H_{15}, 1H), 7.32 – 7.19 (m, H_{14}, H_{13}, H_{12}, 3H + $CDCl_3$), 7.09 (dd, J = 8.1, 4.7 Hz, H_6, 1H), 3.17 – 3.04 (m, 2x H_9, 2x H_{10}, 4H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.83 (C_4), 143.02 (C_5), 137.75 (C_2), 137.11 (C_{11}), 130.60 (C_8), 128.94 (Ar-C), 128.29 (C_{16}), 128.10 (Ar-C), 126.86 (Ar-C), 120.40 (C_{15}), 118.38 (C_7), 116.95 (C_6), 112.41 (C_3), 29.47 (CH_2), 18.74 (CH_2)
IR (cm^{-1}) (NaCl): 3050, 2925, 2849, 1466
M.p.: 228-230 ºC (lit.: 254-256 ºC).

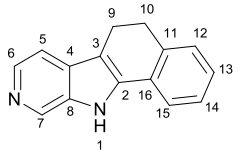
6,11-Dihydro-5*H*-benzo[*g*]pyrido[4,3-*b*]indole (4k)[5]



Purification: PTLC using chloroform/methanol (7%)
Appearance: Beige solid
Yield: 19% (7.1 mg of **4k** from 30 mg of starting 4-amino-3-bromopyridine)

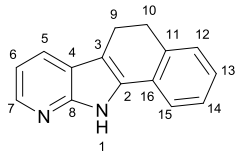
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.84 (s, H_5, 1H), 8.24 (d, *J* = 3.8 Hz, H_6, 1H), 7.45 (d, *J* = 7.0 Hz, H_{15}, 1H), 7.36 – 7.17 (m, H_{14}, H_{13}, H_{12}, H_7, 4H + $CDCl_3$), 3.12 – 2.97 (m, 2xH_9, 2xH_{10}, 4H)
IR (cm^{-1}) (NaCl): 2964, 2915, 2853, 1461
M.p.: 243-245 °C (lit.: 250-252 °C).

6,11-Dihydro-5*H*-benzo[*g*]pyrido[3,4-*b*]indole (4l)



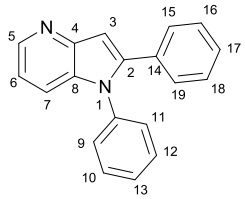
Purification: Neutral aluminium oxide, hexane/ethyl acetate with gradient until chloroform/methanol (10%) followed by PTLC using chloroform/methanol (7%)
Appearance: Beige solid
Yield: 28% (14.3 mg of **4l** from 40 mg of starting 3-amino-4-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.93 (s, H_7, 1H), 8.05 (d, *J* = 5.3 Hz, H_6, 1H), 7.88 – 7.78 (m, H_{15}, 1H), 7.41 (d, *J* = 5.6 Hz, H_5, 1H), 7.24 – 7.12 (m, H_{14}, H_{13}, H_{12}, 3H + $CDCl_3$), 3.03 – 2.85 (m, 2xH_9, 2xH_{10}, 4H)
^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.03 (C_2), 137.68 (C_{11}), 134.14 (C_6), 134.02 (C_8), 132.93 (C_4), 131.15 (C_7), 128.73 (C_{16}), 128.47 (C-Ar), 127.78 (C-Ar), 127.16 (C-Ar), 123.10 (C_{15}), 113.62 (C_5), 111.01 (C_3), 29.28 (CH_2), 19.35 (CH_2).
IR (cm^{-1}) (NaCl): 3157, 3059, 2934, 2898, 2840, 1644, 1545, 1470, 1434
M.p.: 149-151 °C.

6,11-Dihydro-5*H*-benzo[*g*]pyrido[2,3-*b*]indole (4m)[9]



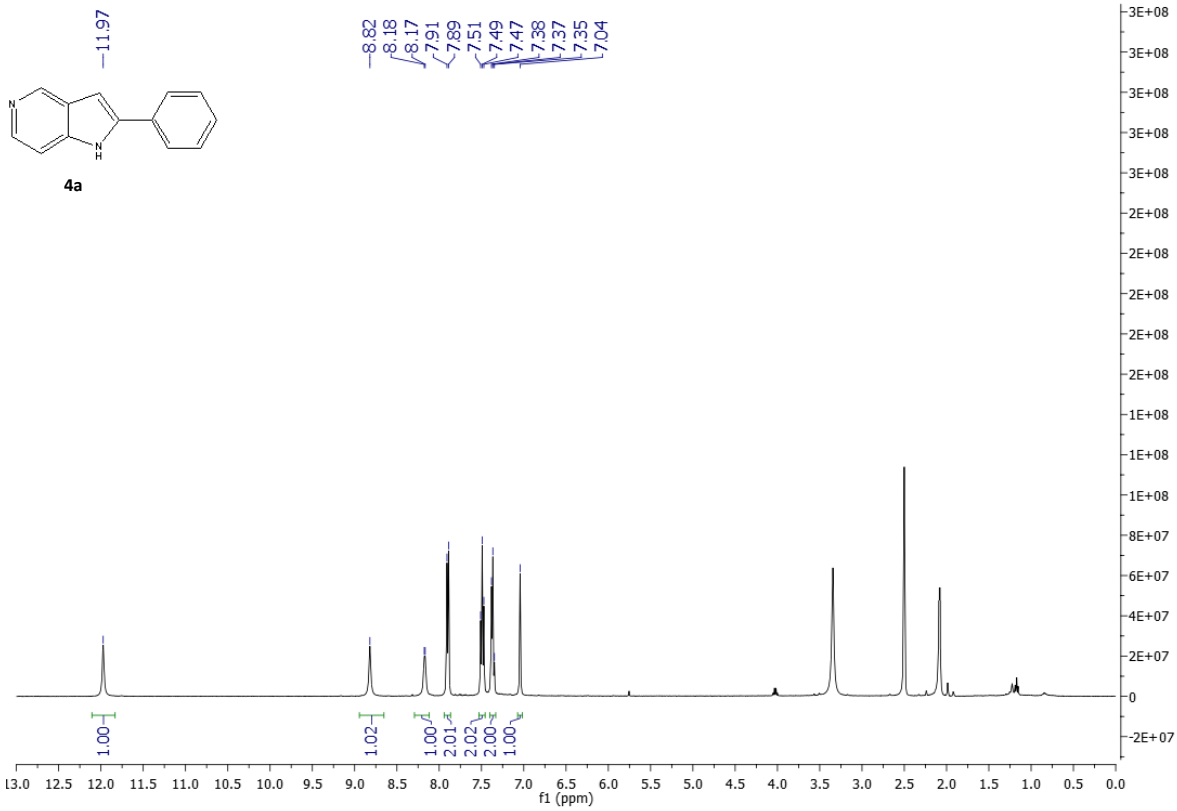
Purification: Neutral aluminium oxide, hexane/ethyl acetate with gradient followed by PTLC using cyclohexane/ethyl acetate 3:1
Appearance: White solid
Yield: 21% (10.6 mg of **4m** from 40 mg of starting 2-amino-3-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 3.9 Hz, H_7, 1H), 7.82 (dd, *J* = 8.0, 1.2 Hz, H_5, 1H), 7.56 (d, *J* = 7.3 Hz, H_{15}, 1H), 7.33 – 7.16 (m, H_{12}, H_{13}, H_{14}, 3H + $CDCl_3$), 7.05 (dd, *J* = 7.7, 4.8 Hz, H_6, 1H), 3.01 – 2.92 (m, 2xH_9, 2xH_{10}, 4H) and DBU
IR (cm^{-1}) (NaCl): 3147, 3121, 3047, 2920, 2893, 2848, 1581, 1470 (protonated form)
M.p.: 191-193 °C (protonated form) (lit.: 210-211 °C).

1,2-Diphenyl-4-azaindole[10]

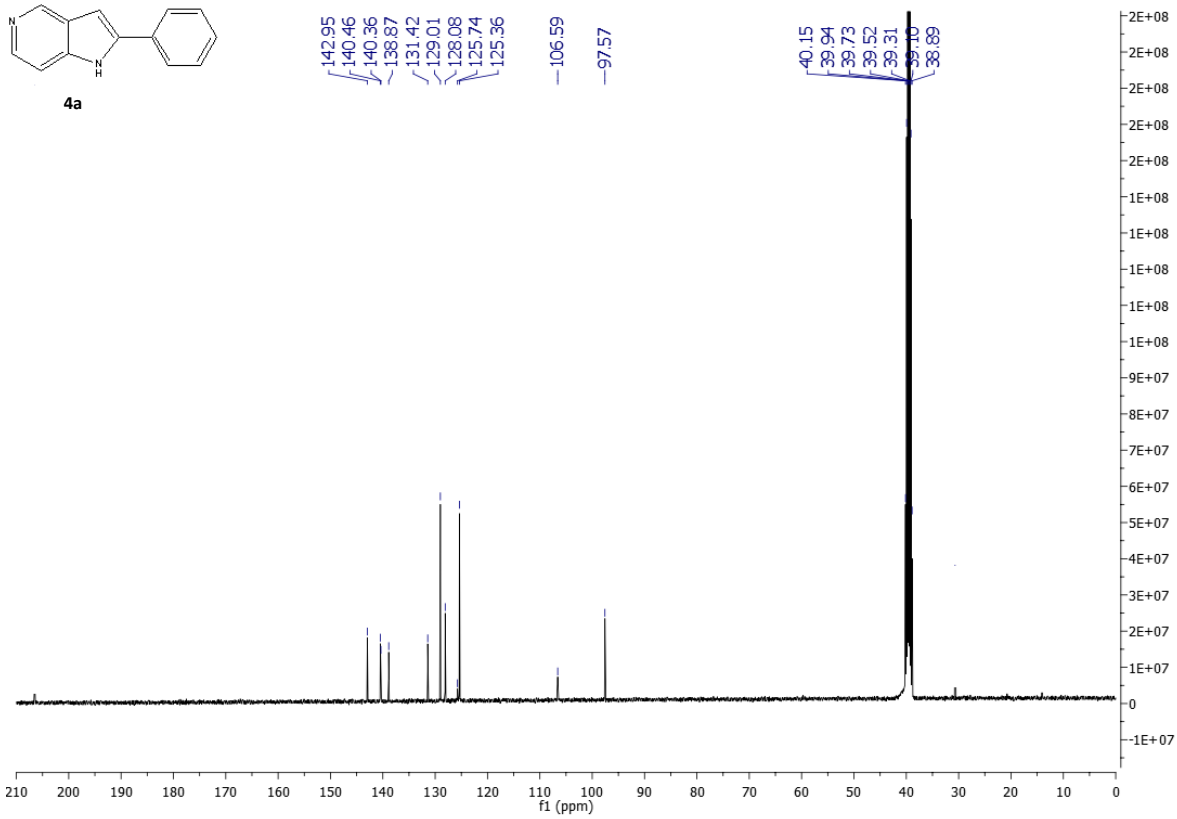


Purification: Neutral aluminium oxide, hexane/ethyl acetate with gradient followed by PTLC using hexane/ethyl acetate 2:1
Appearance: Beige solid
Yield: 5% (1.6 mg of 1,2- diphenyl-4-azaindole from 30 mg of starting 3-amino-2-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, *J* = 3.5 Hz, H_5, 1H), 7.57 (d, *J* = 8.1 Hz, H_7, 1H), 7.46 – 7.38 (m, *Ar-H*, 3H), 7.28 – 7.22 (m, *Ar-H*, 7H + $CDCl_3$), 7.11 (dd, *J* = 8.0, 4.4 Hz, H_6, 1H), 7.02 (s, H_3, 1H).

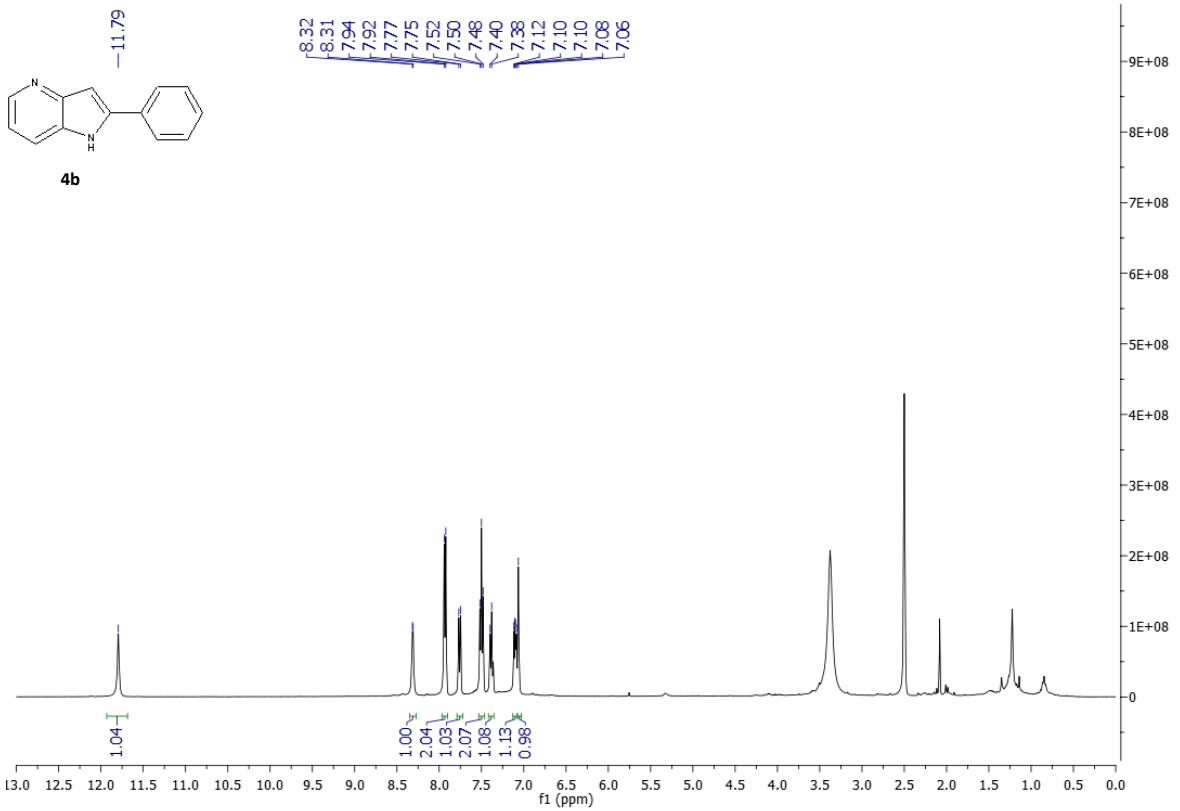
NMR spectra of azaindoles

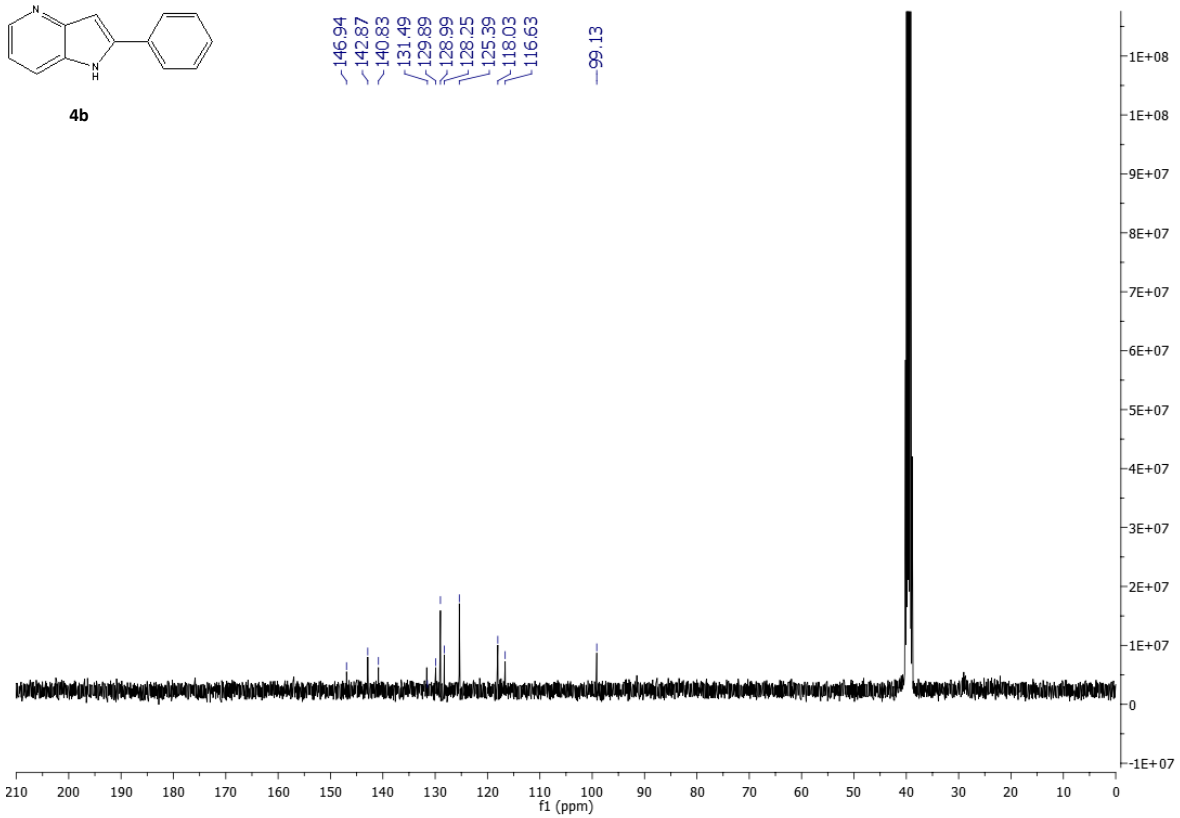


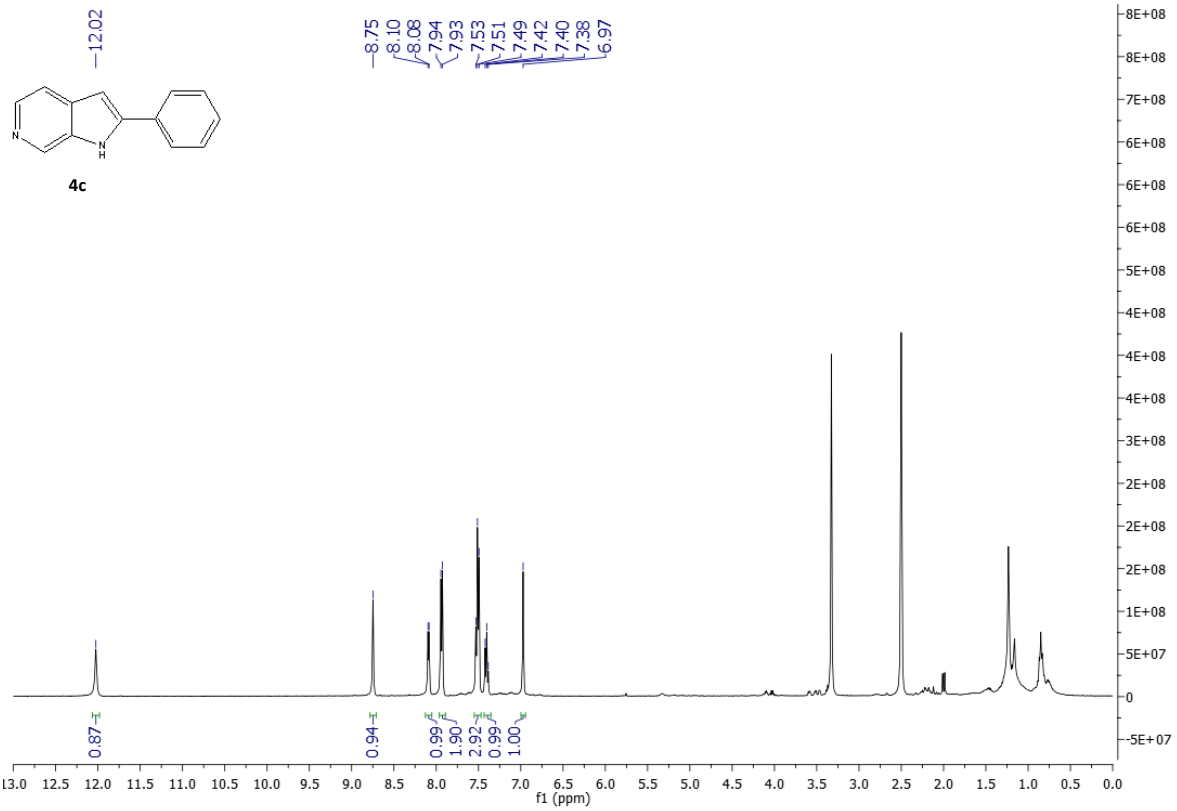
4a

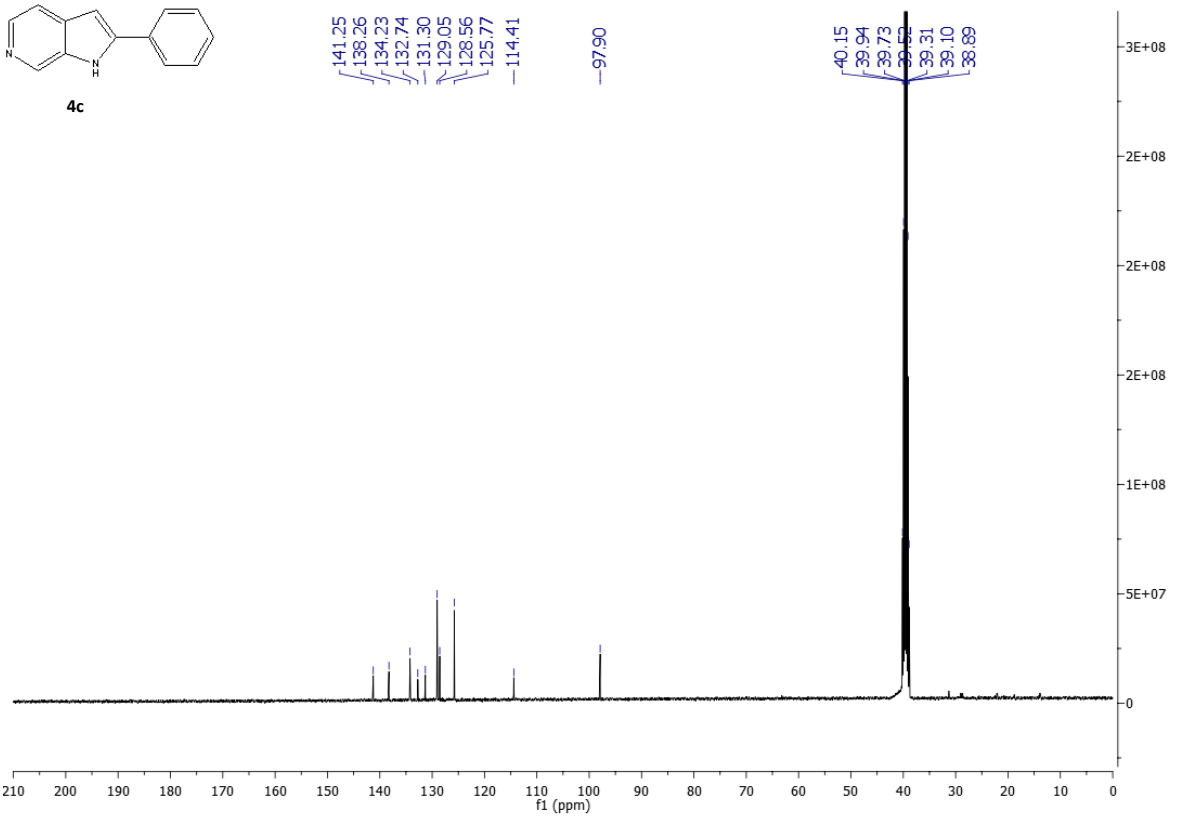


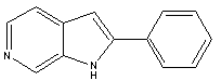
4a


11.79
8.32
8.31
7.94
7.92
7.77
7.75
7.52
7.50
7.48
7.40
7.38
7.12
7.10
7.10
7.08
7.06
4b
1.04
1.00
2.04
1.03
2.07
1.08
1.13
0.98
f1 (ppm)

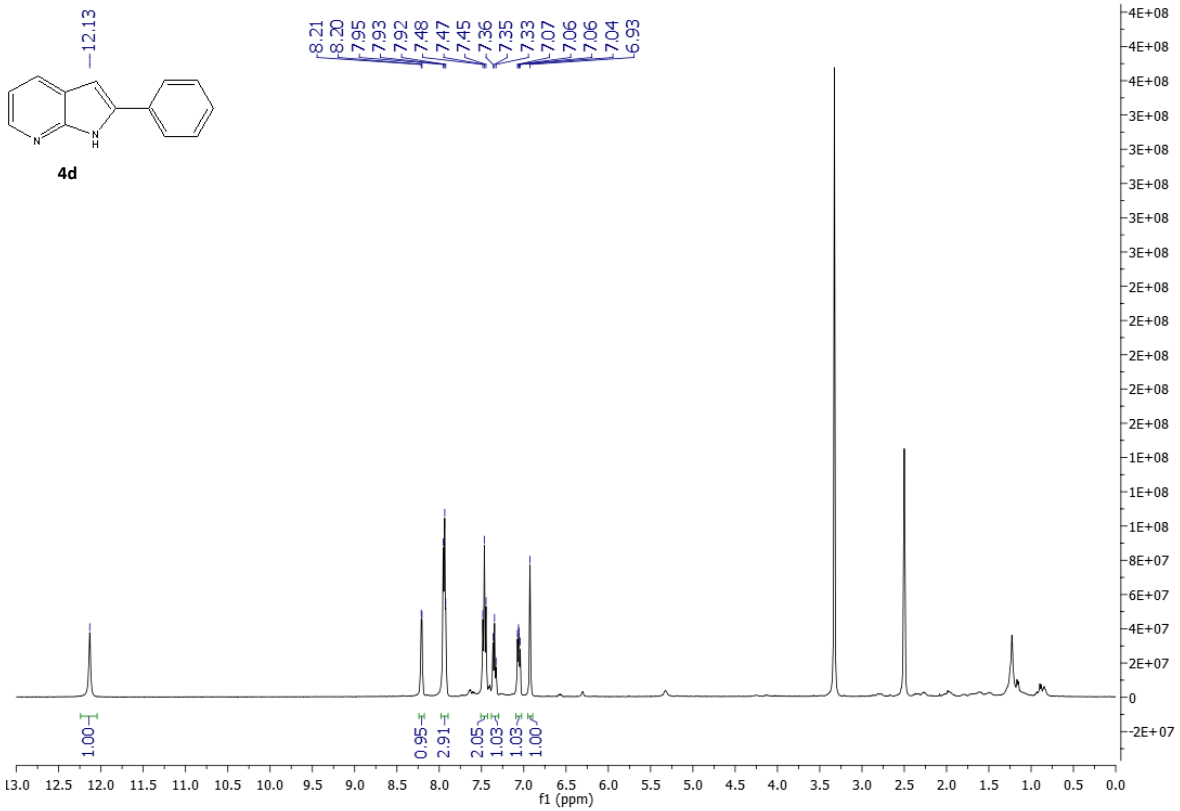

146.94
142.87
140.83
131.49
129.89
128.99
128.25
125.39
118.03
116.63
99.13
4b
f1 (ppm)

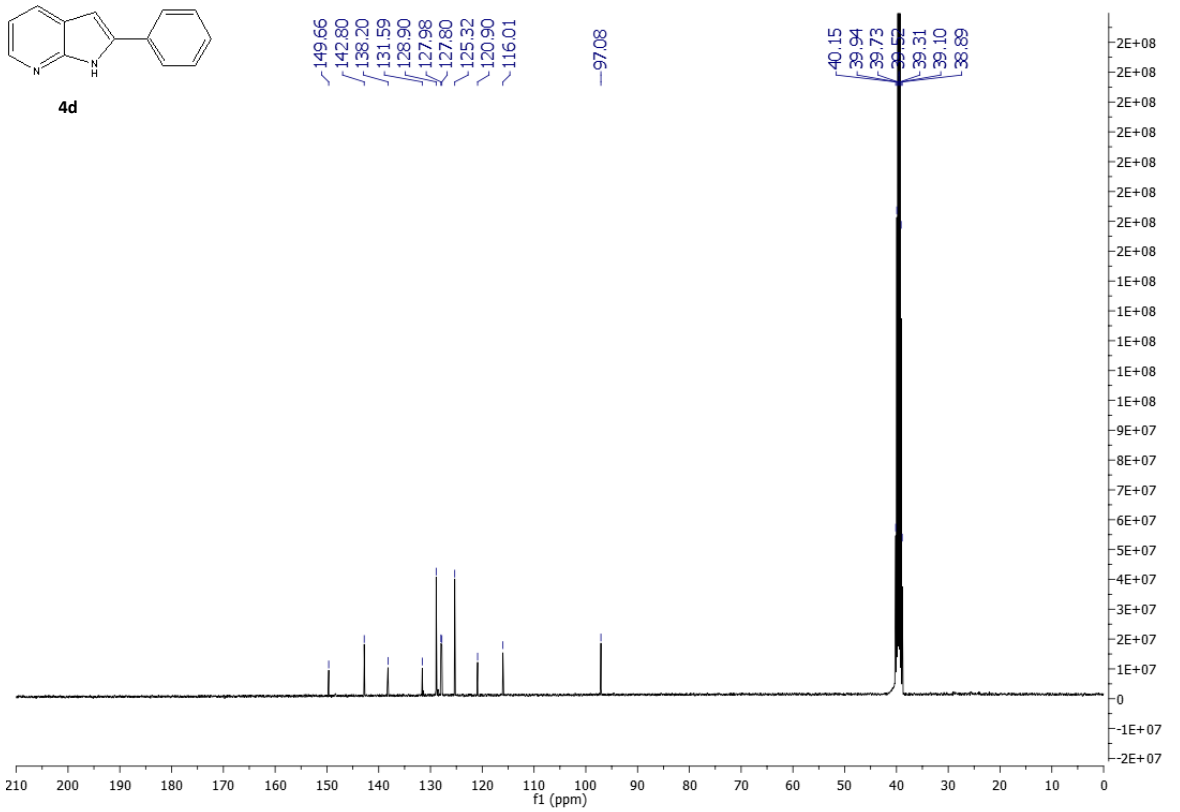

12.02
8.75
8.10
8.08
7.94
7.93
7.53
7.51
7.49
7.42
7.40
7.38
6.97
4c
0.87
0.94
0.99
1.90
2.92
0.99
1.00
f1 (ppm)


141.25
138.26
134.23
132.74
131.30
129.05
128.56
125.77
114.41
97.90
40.15
39.94
39.73
39.52
39.31
39.10
38.89
4c
f1 (ppm)



4c


12.13
8.21
8.20
7.95
7.93
7.92
7.48
7.47
7.45
7.36
7.35
7.33
7.07
7.06
7.06
7.04
6.93
4d
1.00
0.95
2.91
2.05
1.03
1.03
1.00
f1 (ppm)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142.80
138.20
131.59
128.90
127.98
127.80
125.32
120.90
116.01
97.08
40.15
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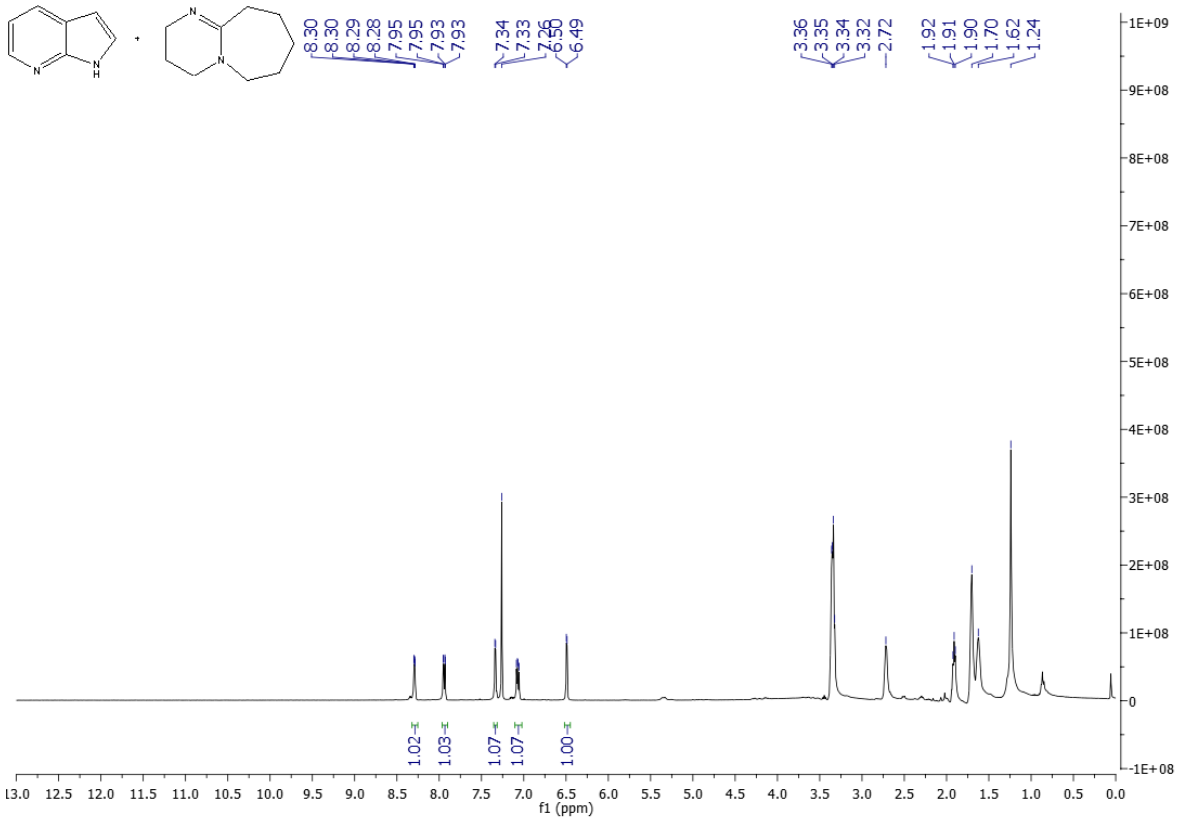
39.31
39.10
38.89
4d
f1 (ppm)


8.30
8.30
8.29
8.28
7.95
7.95
7.93
7.93
7.34
7.33
7.26
6.50
6.49
3.36
3.35
3.34
3.32
2.72
1.92
1.91
1.90
1.70
1.62
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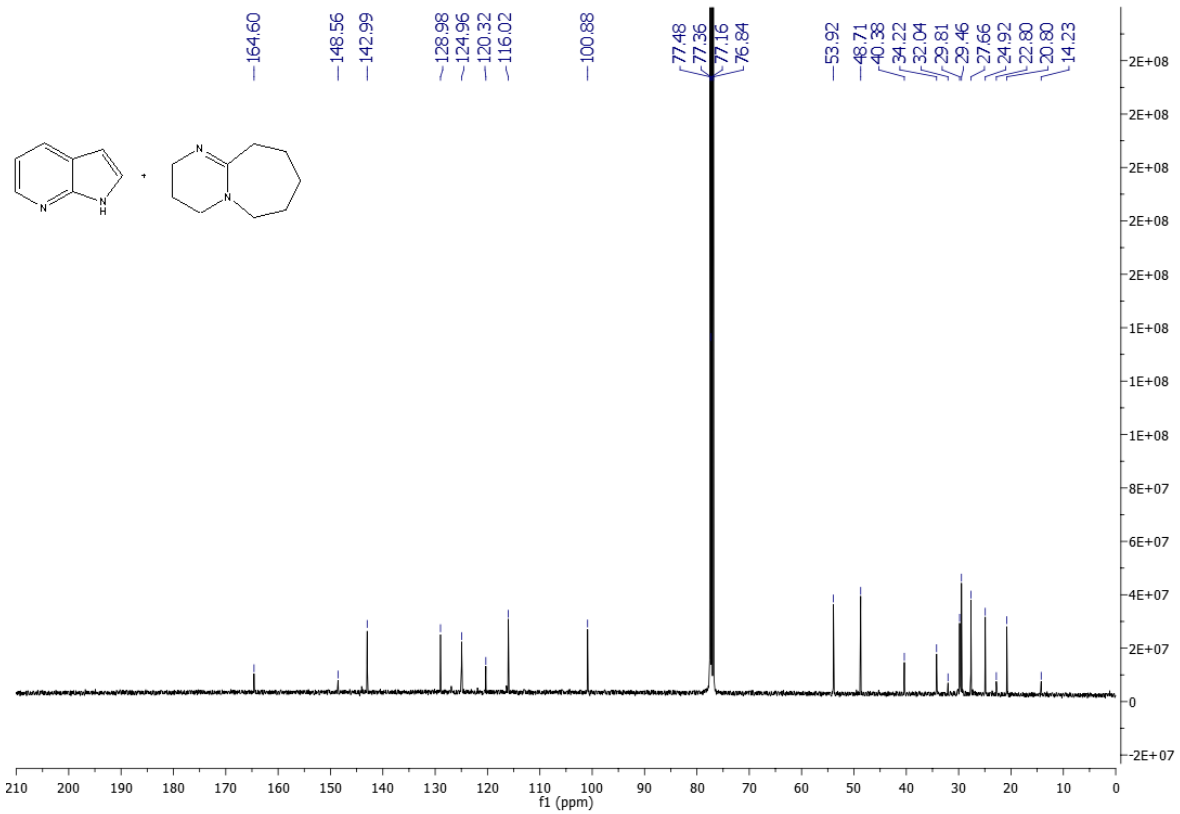
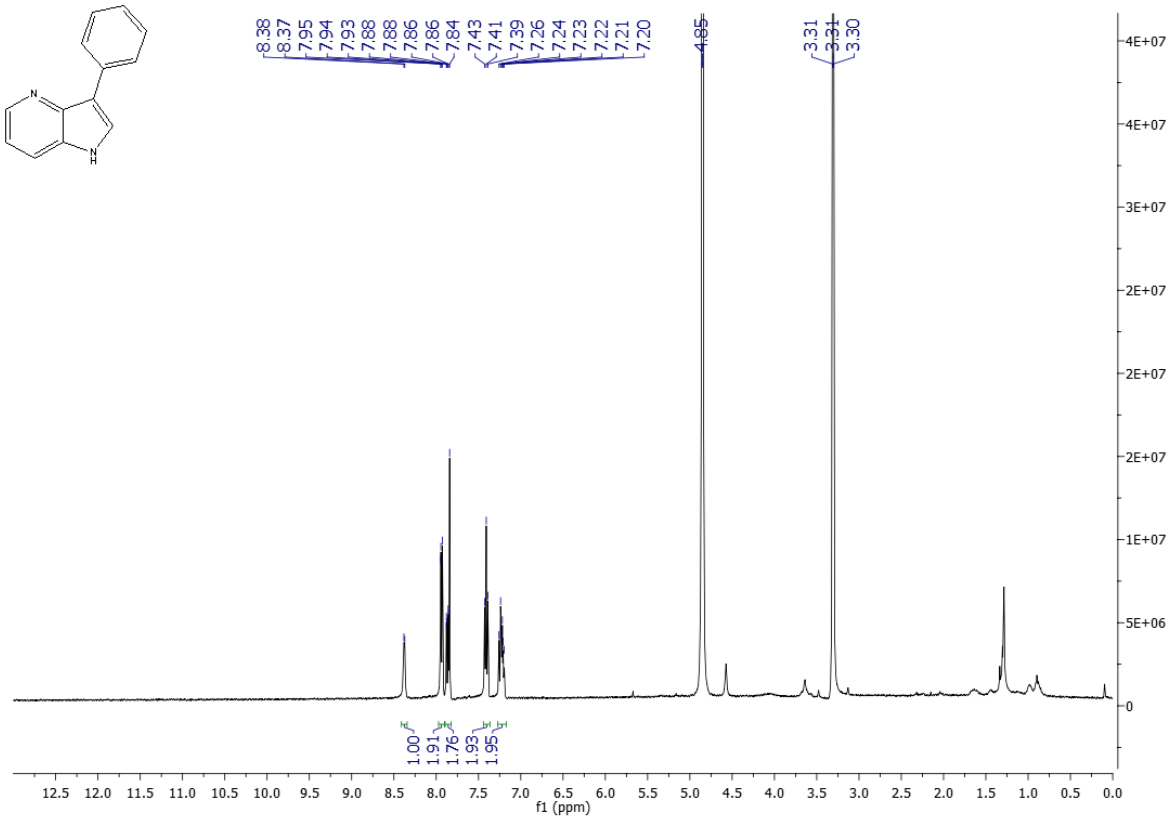
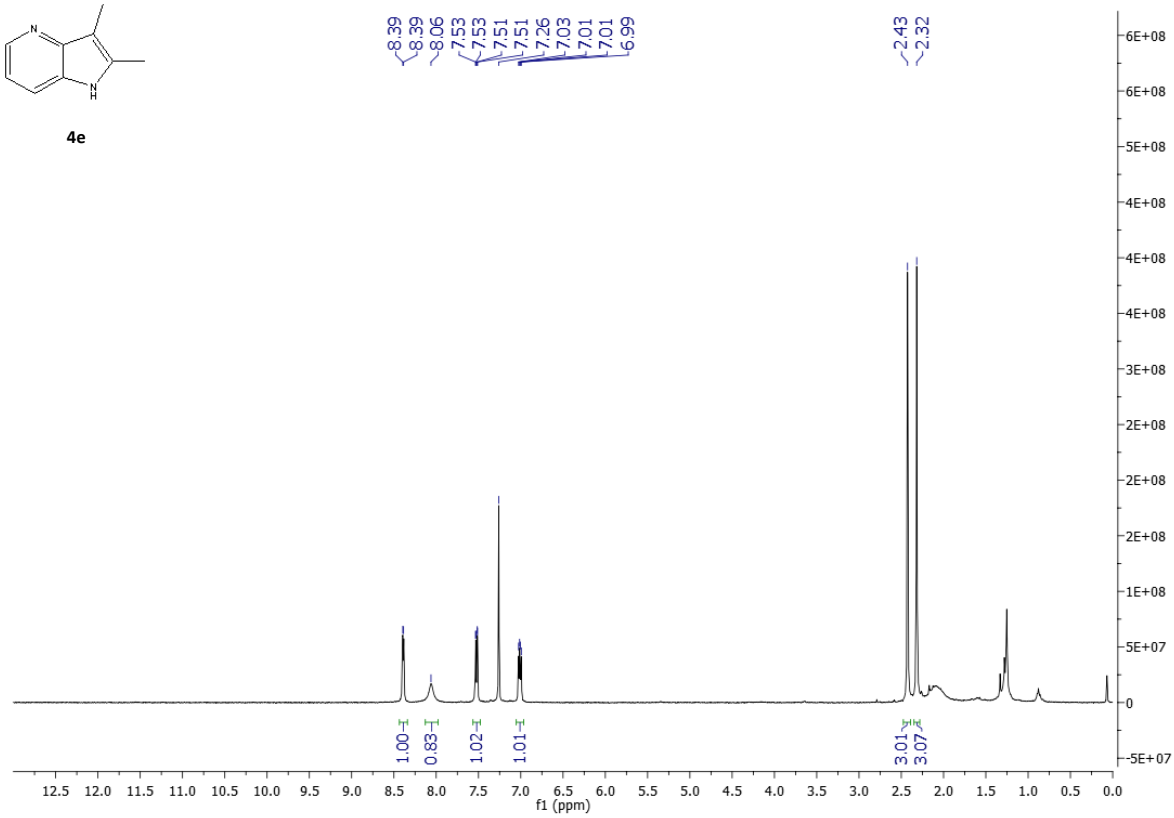
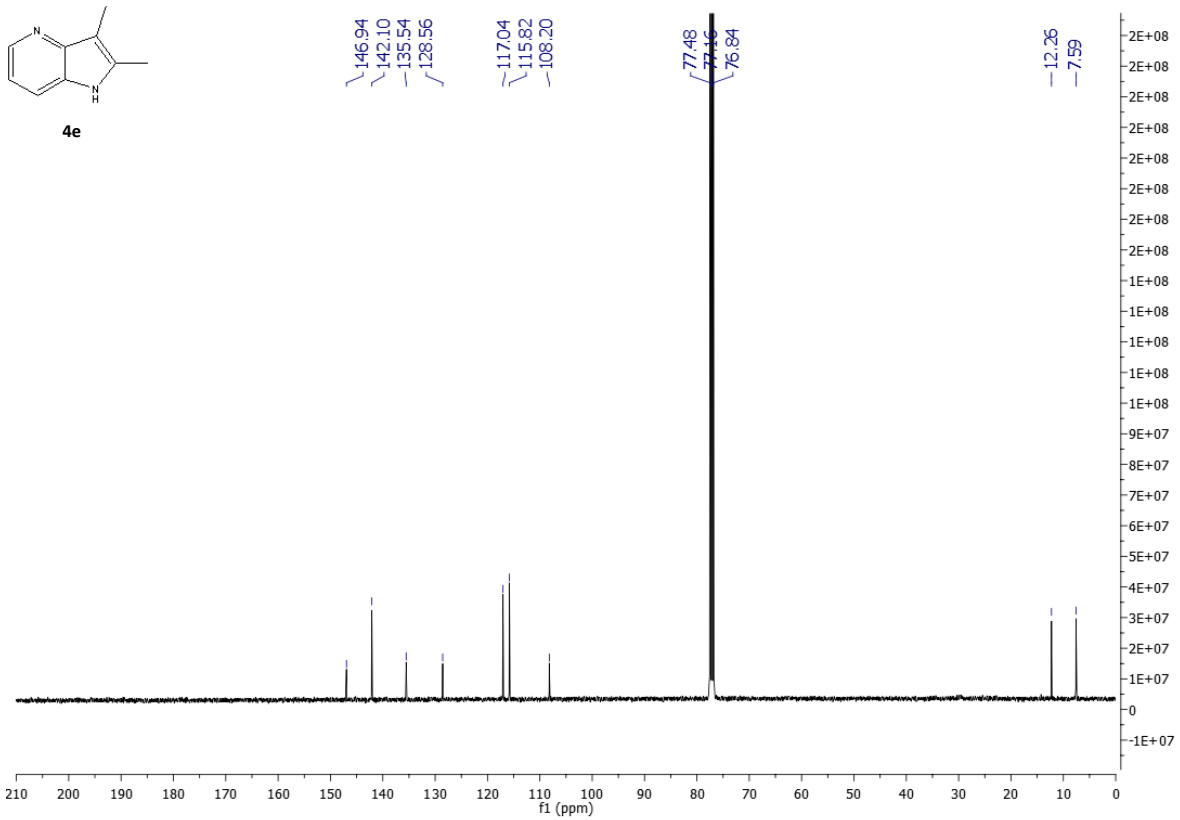
1.02
1.03
1.07
1.07
1.00
f1 (ppm)

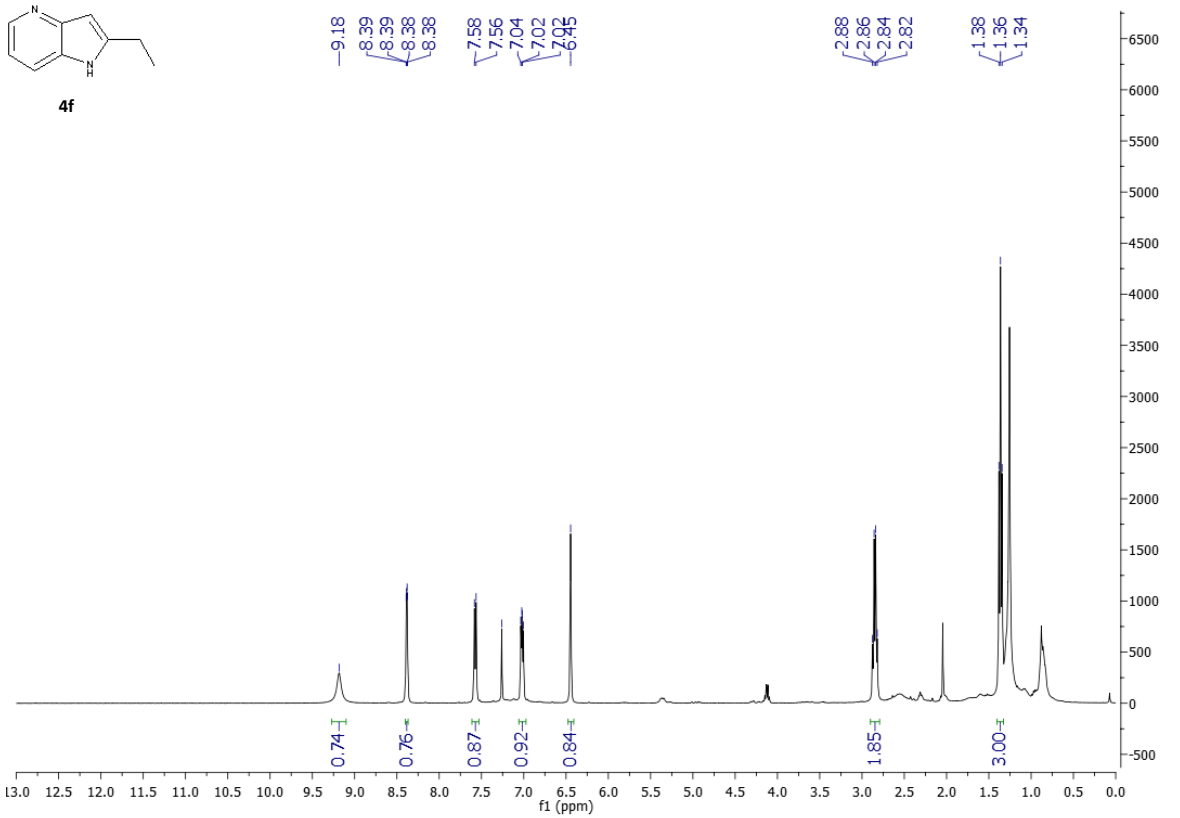

164.60
148.56
142.99
128.98
124.96
120.32
116.02
100.88
77.48
77.36
77.16
76.84
53.92
48.71
40.38
34.22
32.04
29.81
29.46
27.66
24.92
22.80
20.80
14.23
f1 (ppm)

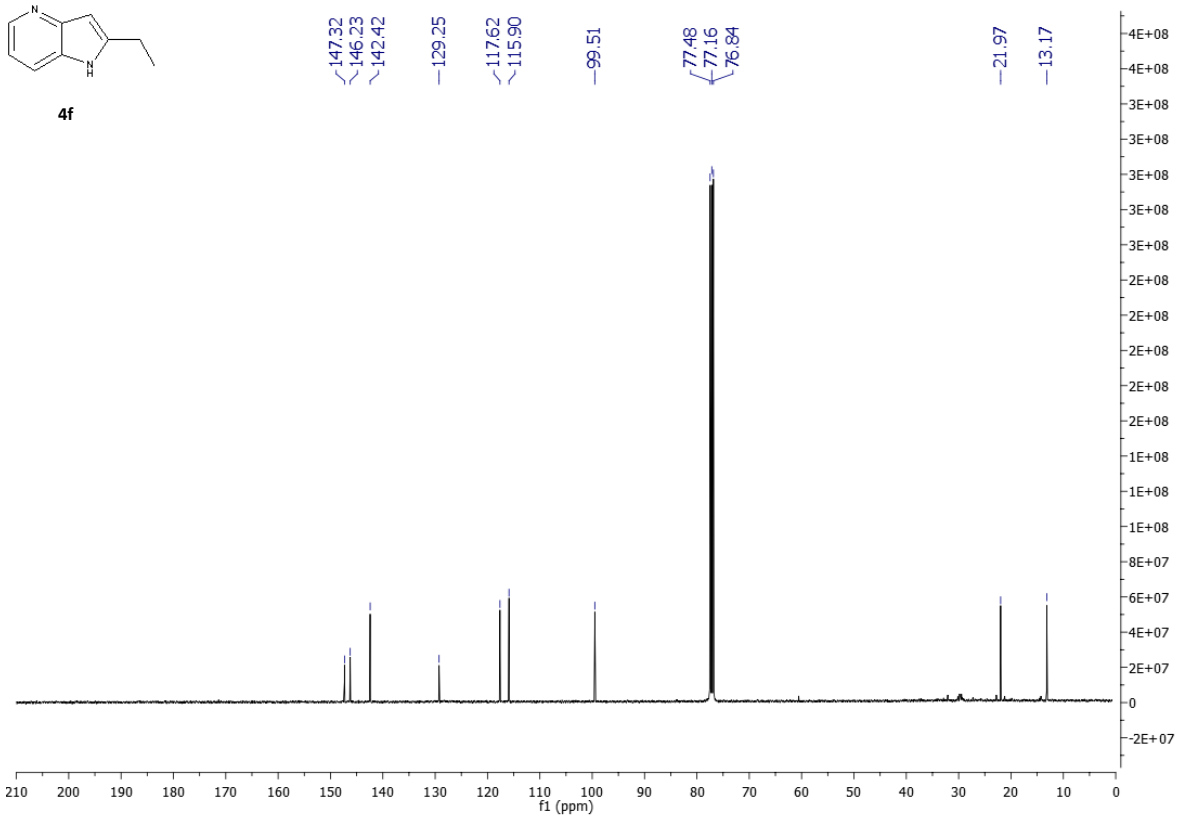

8.38
8.37
7.95
7.94
7.93
7.88
7.88
7.86
7.86
7.84
7.43
7.41
7.39
7.26
7.24
7.23
7.22
7.21
7.20
4.85
3.31
3.31
3.30
1.00
1.91
1.76
1.93
1.95
f1 (ppm)

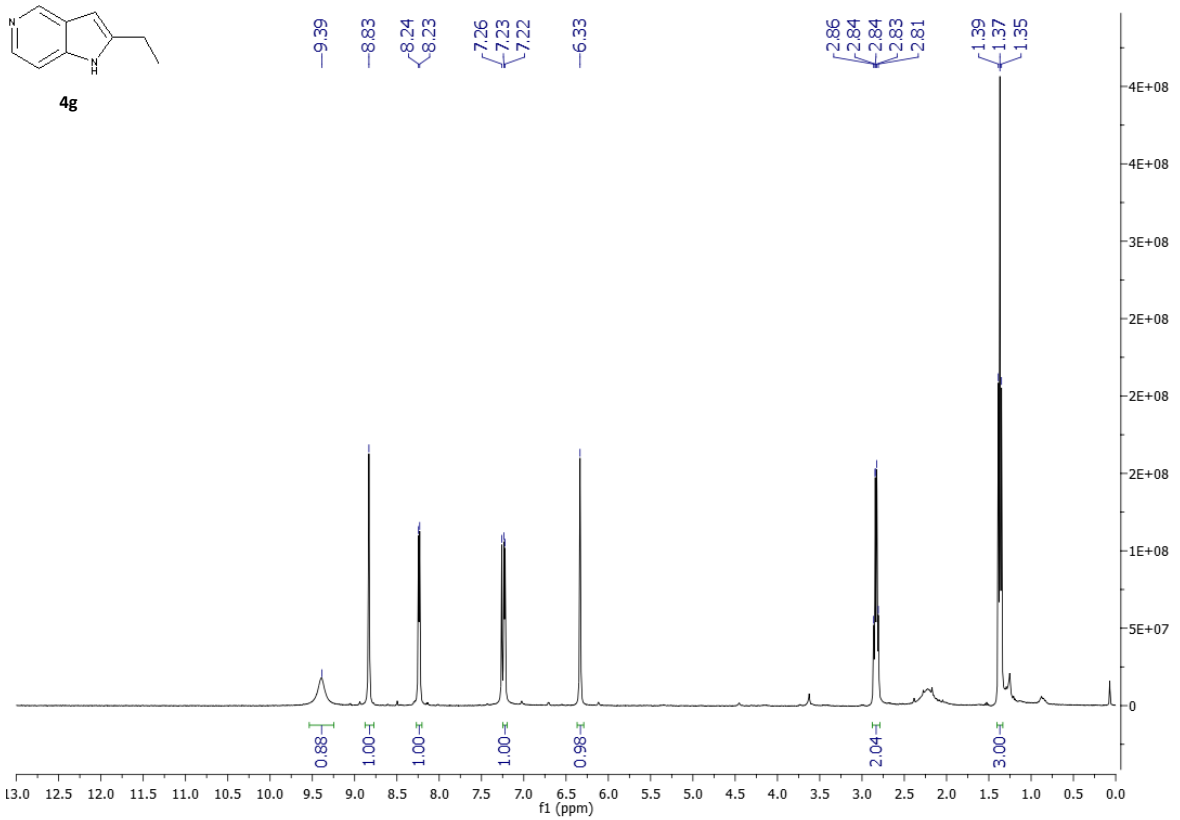

8.39
8.39
8.06
7.53
7.53
7.51
7.51
7.26
7.03
7.01
7.01
6.99
2.43
2.32
1.00
0.83
1.02
1.01
3.01
3.07
f1 (ppm)

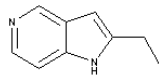
4e


4e
146.94
142.10
135.54
128.56
117.04
115.82
108.20
77.48
77.16
76.84
12.26
7.59
f1 (ppm)


4f
9.18
8.39
8.39
8.38
8.38
7.58
7.56
7.04
7.02
7.02
6.45
2.88
2.86
2.84
2.82
1.38
1.36
1.34
0.74
0.76
0.87
0.92
0.84
1.85
3.00
f1 (ppm)

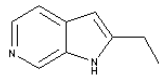

4f
147.32
146.23
142.42
129.25
117.62
115.90
99.51
77.48
77.16
76.84
21.97
13.17
f1 (ppm)


4g
9.39
8.83
8.24
8.23
7.26
7.23
7.22
6.33
2.86
2.84
2.84
2.83
2.81
1.39
1.37
1.35
0.88
1.00
1.00
1.00
0.98
2.04
3.00
f1 (ppm)



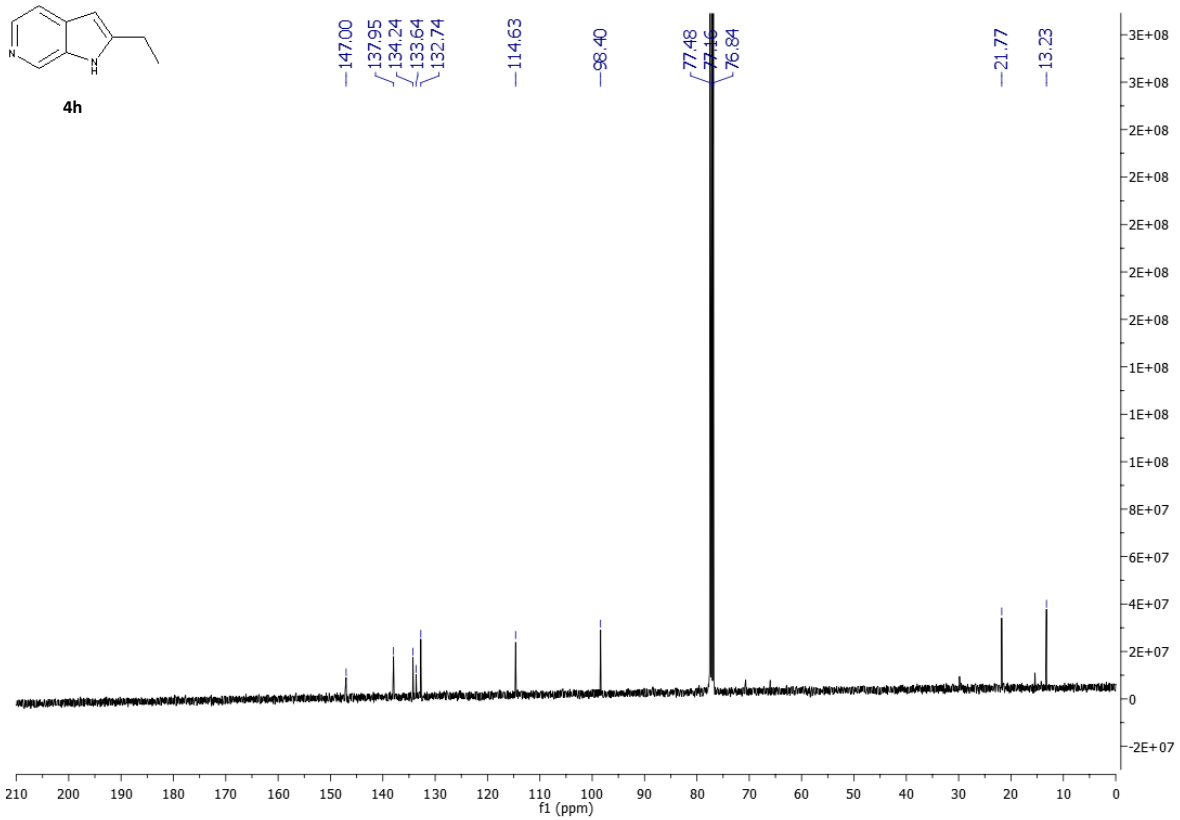
4g

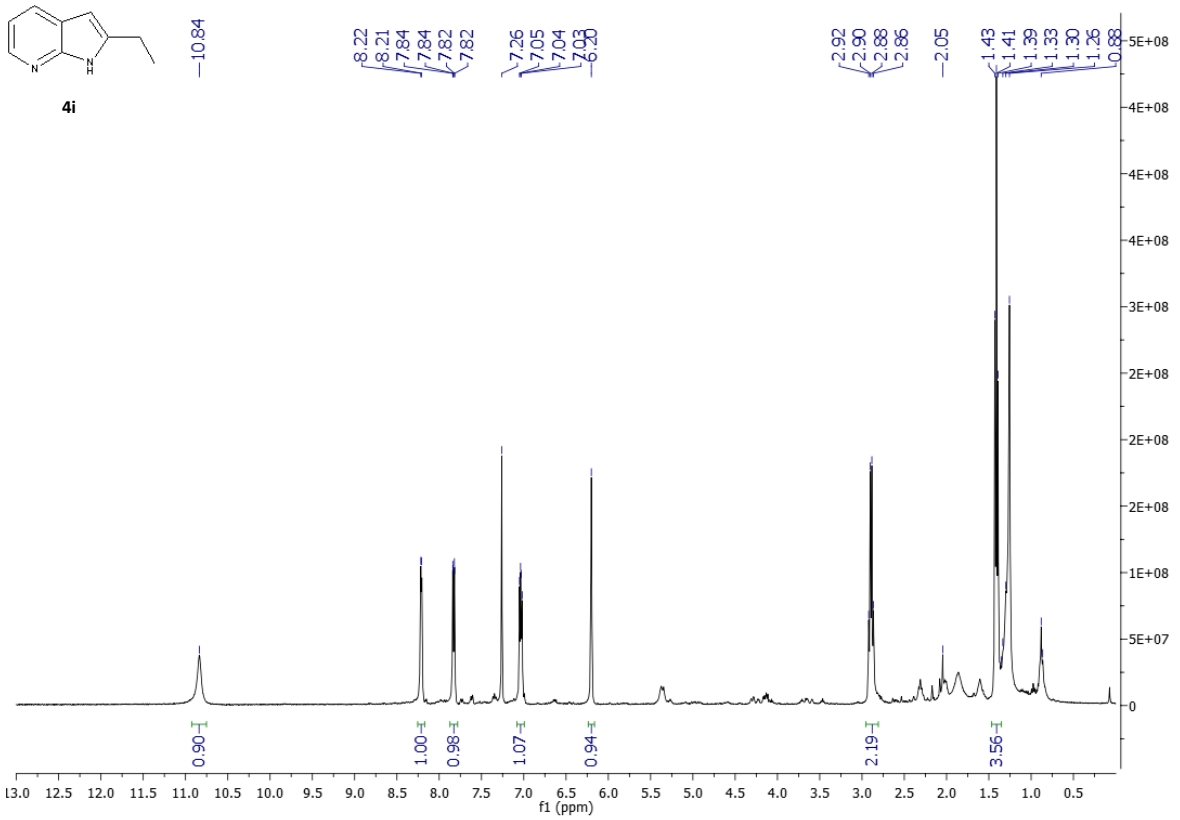
143.13
142.39
140.14
140.03
126.02
106.13
97.69
77.48
77.16
76.84
21.51
13.21
4E+08
3E+08
2E+08
1E+08
5E+07
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

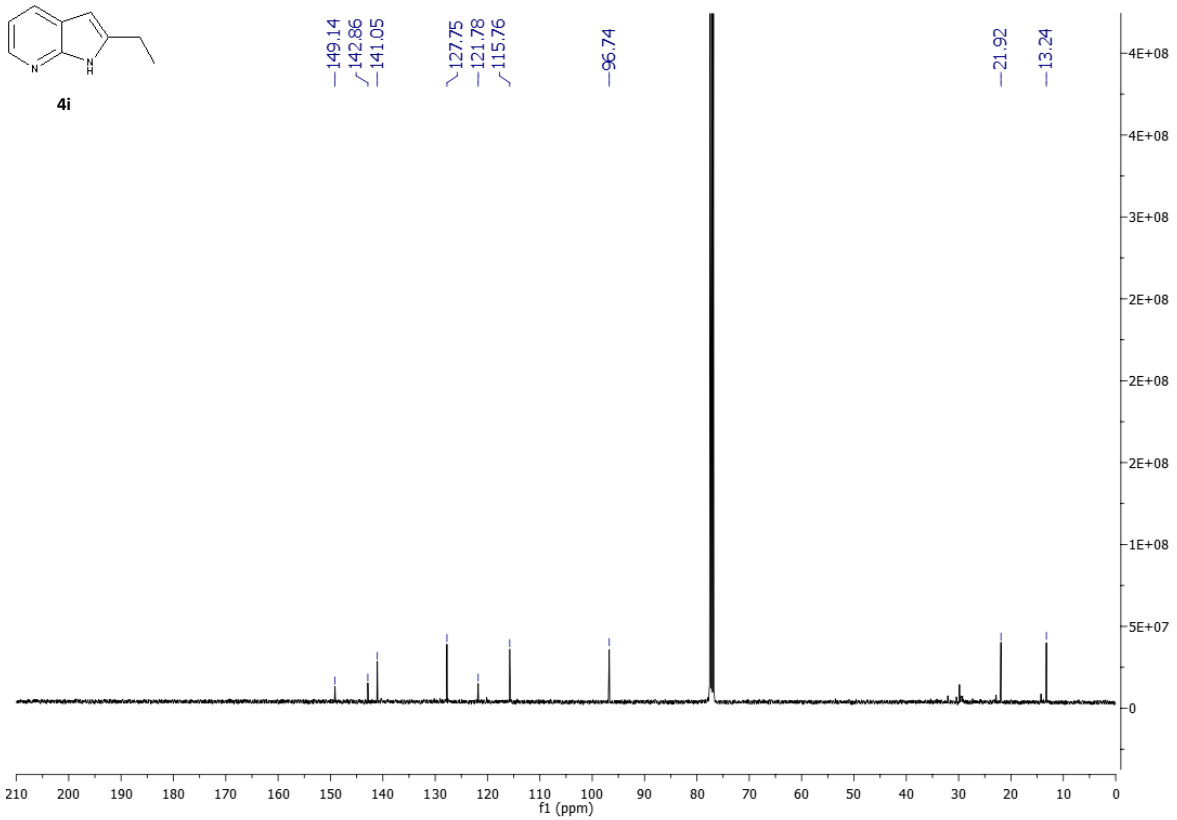


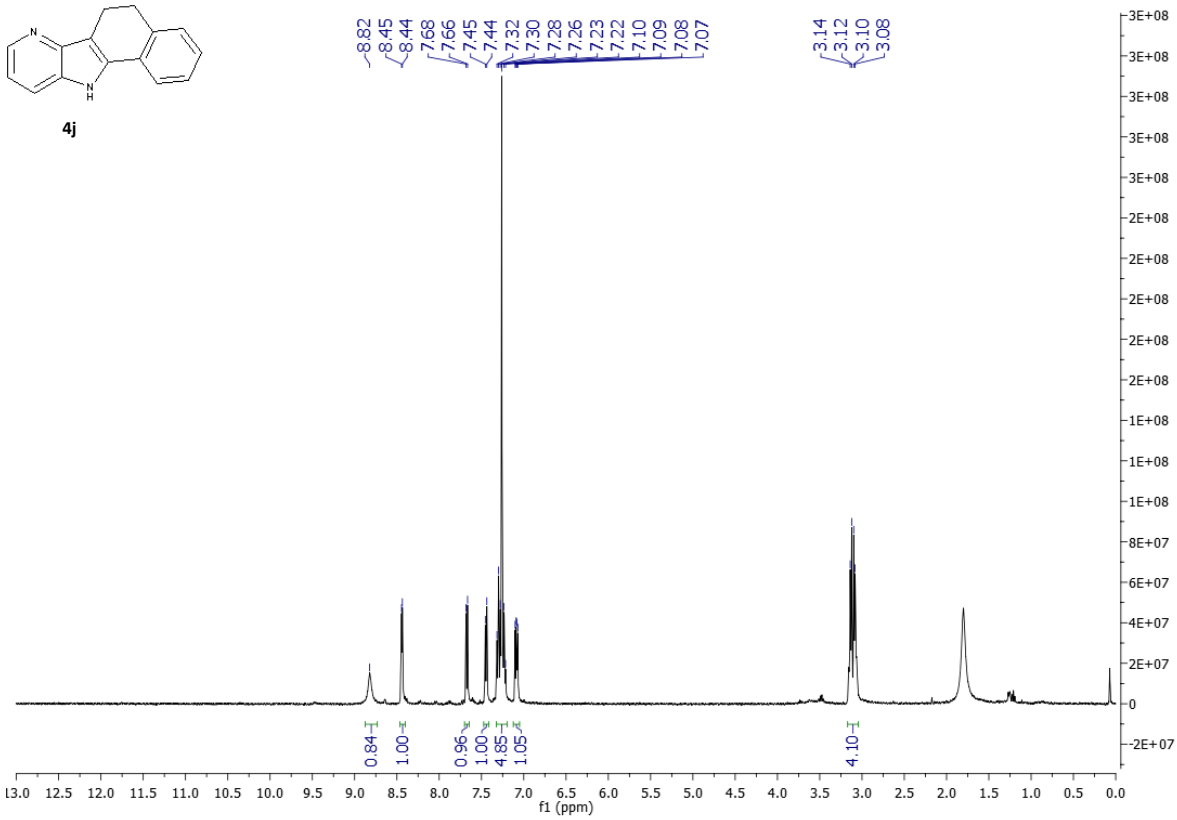
4h

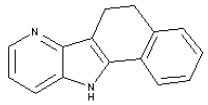
8.75
8.19
8.17
7.46
7.45
7.26
6.28
2.91
2.89
2.87
2.85
1.41
1.39
1.37
1.00
1.02
0.98
0.97
2.14
3.04
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
5E+07
0
-5E+07
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


4h
147.00
137.95
134.24
133.64
132.74
114.63
98.40
77.48
77.16
76.84
21.77
13.23
f1 (ppm)


4i
10.84
8.22
8.21
7.84
7.84
7.82
7.82
7.26
7.05
7.04
7.03
6.20
2.92
2.90
2.88
2.86
2.05
1.43
1.41
1.39
1.33
1.30
1.26
0.88
0.90
1.00
0.98
1.07
0.94
2.19
3.56
f1 (ppm)

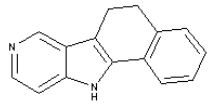

4i
149.14
142.86
141.05
127.75
121.78
115.76
96.74
21.92
13.24
f1 (ppm)


4j
8.82
8.45
8.44
7.68
7.66
7.45
7.44
7.32
7.30
7.28
7.26
7.23
7.22
7.10
7.09
7.08
7.07
3.14
3.12
3.10
3.08
0.84
1.00
0.96
1.00
4.85
1.05
4.10
f1 (ppm)



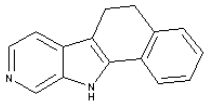
4j

144.83
143.02
137.75
137.13
130.60
128.94
128.29
128.10
126.86
120.40
118.38
116.95
112.41
77.48
77.16
76.84
29.47
18.74
f1 (ppm)



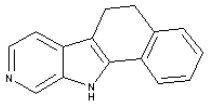
4k

8.84
8.24
7.46
7.44
7.33
7.32
7.30
7.28
7.26
7.23
7.21
7.20
3.08
3.07
3.03
3.01
1.25
0.07
1.00
1.12
1.14
5.47
4.15
f1 (ppm)



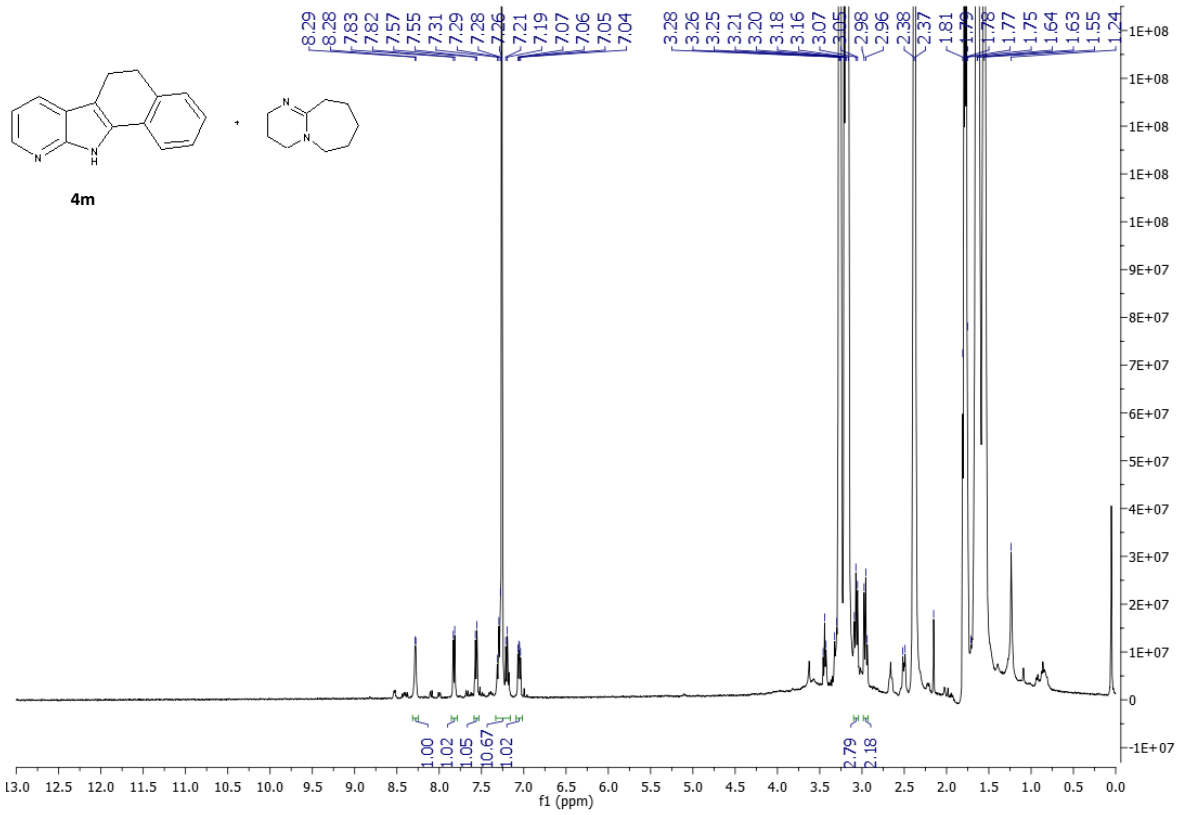
4l

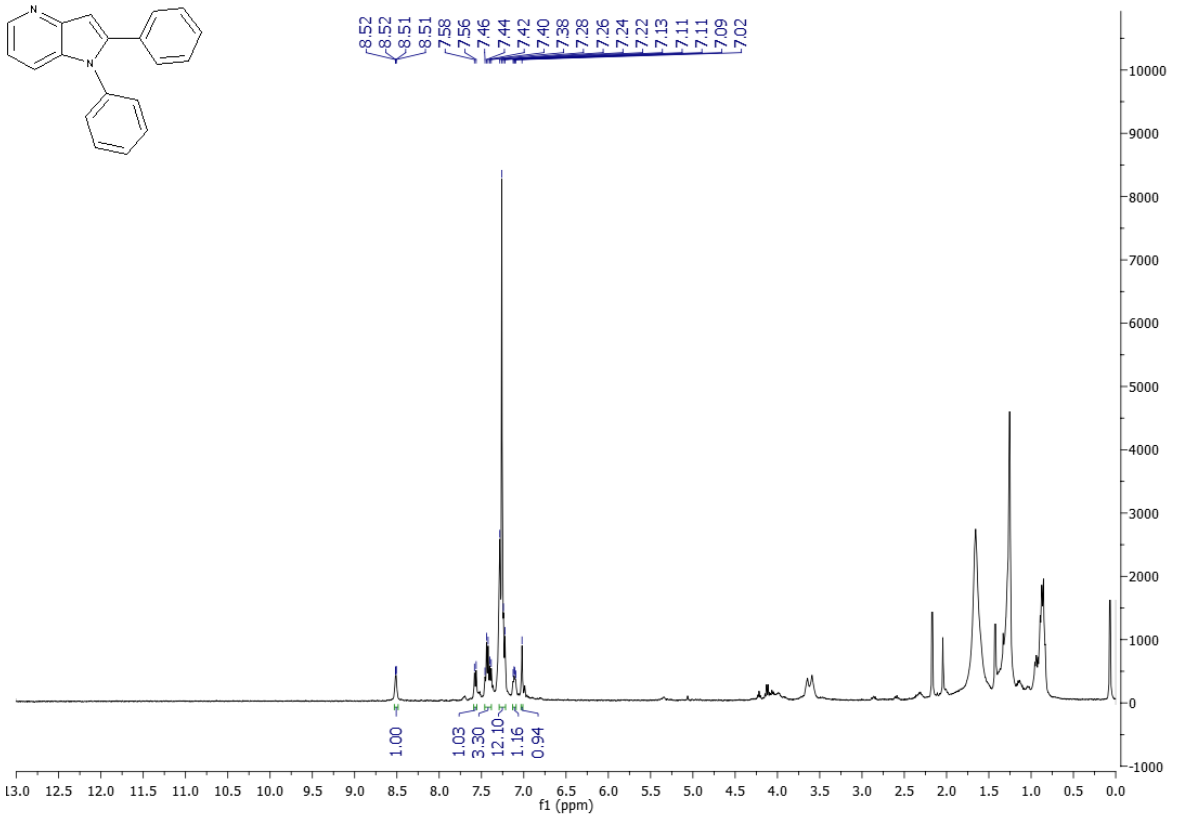
8.93
8.06
8.04
7.86
7.85
7.84
7.42
7.41
7.26
7.23
7.21
7.19
7.19
7.18
7.17
3.01
2.99
2.97
2.90
2.88
2.86
1.00
0.97
1.06
1.04
3.08
4.06
f1 (ppm)



4l

141.03
137.68
134.14
134.02
132.93
131.15
128.73
128.47
127.78
127.16
123.10
113.62
111.01
29.28
19.35
f1 (ppm)

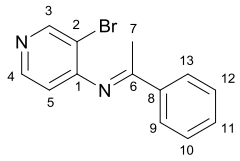

4m
f1 (ppm)


f1 (ppm)

Other information

(*E*)-*N*-(3-Bromopyridin-4-yl)-1-phenylethan-1-imine (3a)

This imine was isolated with 50% yield (24 mg) from the same reaction procedure previously mentioned for the 2-phenyl-5-azaindole synthesis, when performed in toluene using DavePhos as ligand, starting from 30 mg of 4-amino-3-bromopyridine.



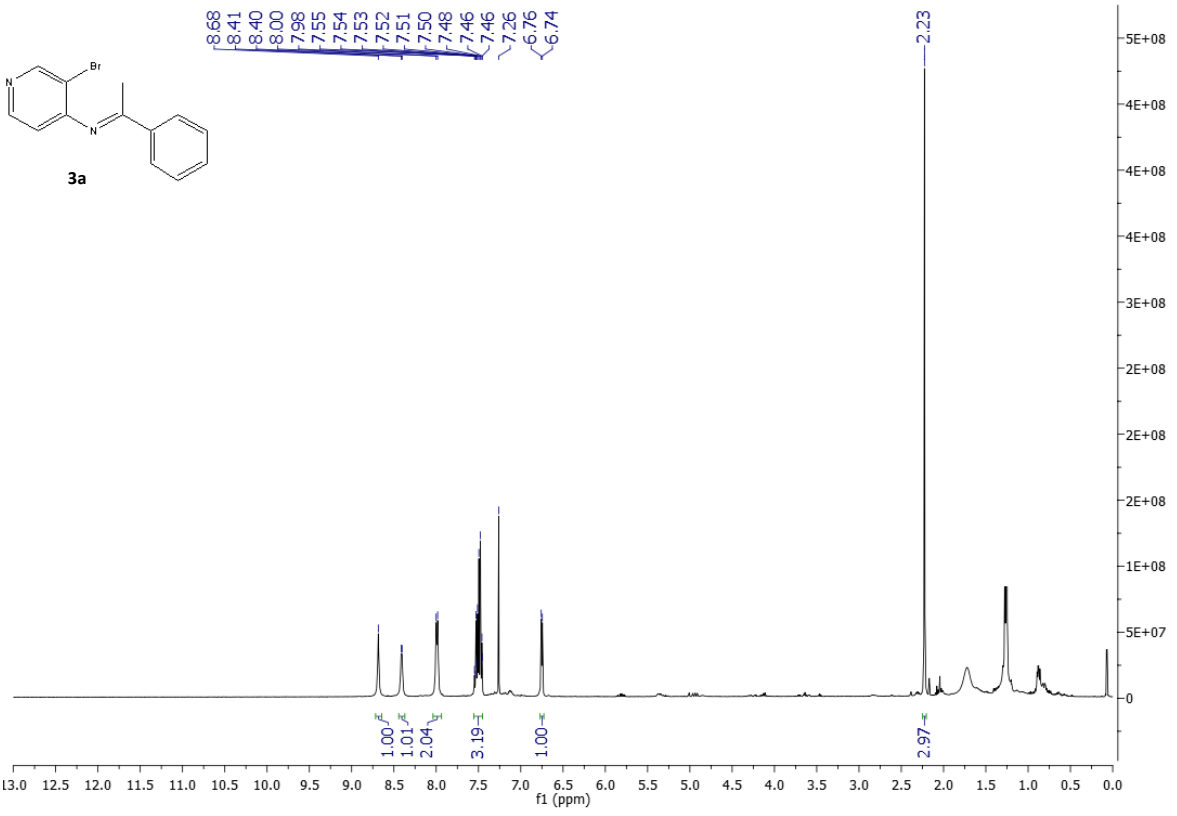
Purification: Neutral aluminium oxide, hexane/ethyl acetate with gradient

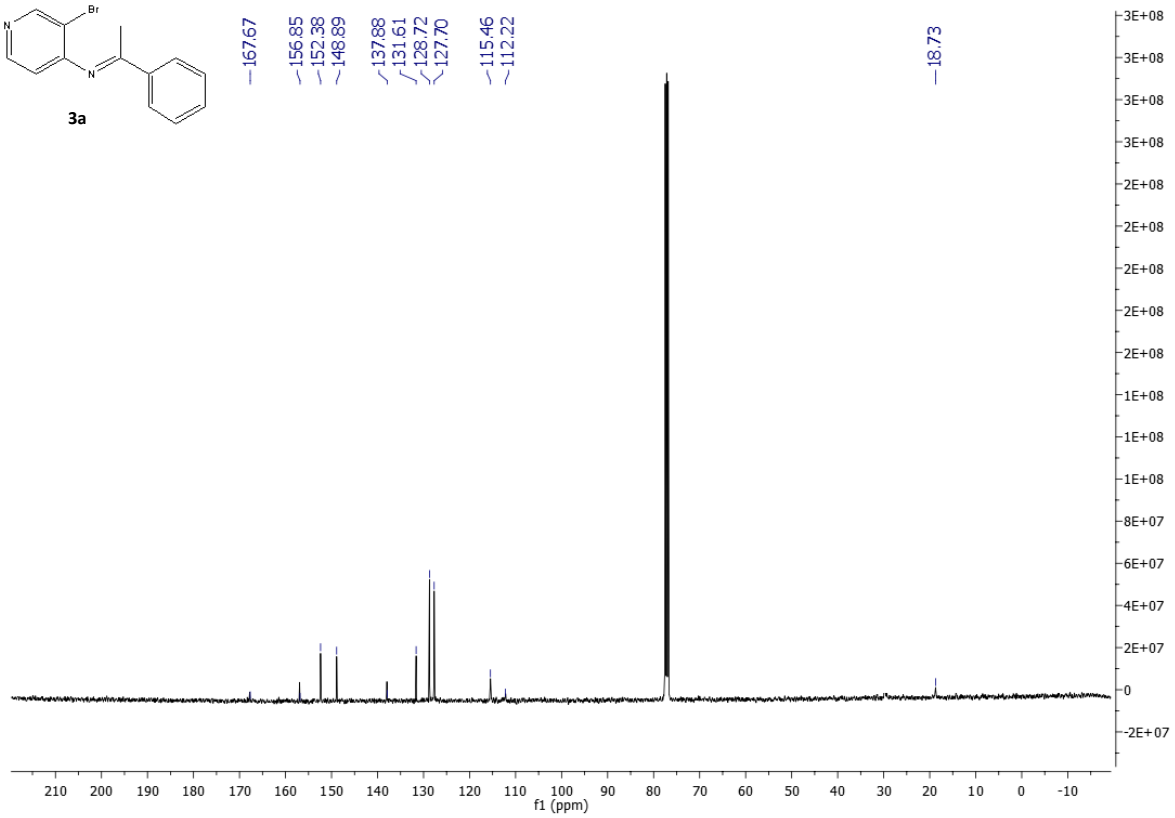
Appearance: Yellow Oil

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (s, H_3, 1H), 8.41 (d, J = 4.1 Hz, H_4, 1H), 7.99 (d, J = 6.2 Hz, $H_{9,13}$, 2H), 7.55 – 7.46 (m, $H_{10,12}$, H_{11}, 3H), 6.75 (d, J = 5.0 Hz, H_5, 1H), 2.23 (s, H_7, 3H).

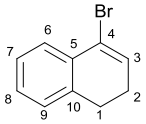
^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.67 (C_6), 156.85 (C_1), 152.38 (C_3), 148.89 (C_4), 137.88 (C_8), 131.61 (C_{11}), 128.72 ($C_{10,12}$), 127.70 ($C_{9,13}$), 115.46 (C_5), 112.22 (C_2), 18.73 (C_7).

IR (cm^{-1}) (NaCl): 1643 (imine).





4-Bromo-1,2-dihydronaphthalene[11]



1,2-Dihydronaphtalene (1.5 mmol) was dissolved in dichloromethane (7 mL), then Br_2 (2 equiv) was added dropwise at 0 °C. After 2 h 30 min the reaction the reaction was quenched with a saturated aq. solution of sodium thiosulphate (7 mL) and stirred for 15 minutes. The organic layer was extracted and the aqueous layer was washed twice with dichloromethane. The combined organic layers were washed twice with a saturated aq. solution of sodium thiosulphate and brine; then dried over anhydrous $MgSO_4$, filtered and dried under vacuum. The product 1,2-dibromo-1,2,3,4-tetrahydronaphtalene (436 mg) was used for the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 – 7.08 (m, 4H), 5.68 – 5.64 (m, 1H), 4.98 – 4.90 (m, 1H), 3.28 (ddd, *J* = 17.7, 11.9, 6.1 Hz, 1H), 2.95 (dd, *J* = 17.4, 5.8 Hz, 1H), 2.90 – 2.76 (m, 1H), 2.26 – 2.14 (m, 1H).[12]

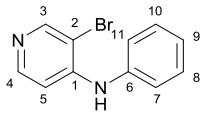
To a round-bottom flask charged with piperidine (3 equiv) at 0 °C was added a solution of the crude product 1,2-dibromo-1,2,3,4-tetrahydronaphtalene (400 mg) in dry toluene (0.8 mL) dropwise for 2 hours (about 66 µL/10 minutes). The reaction was left overnight at room temperature and then heated for 2 h 30 min at 90 °C. The reaction crude was neutralized by slowly adding this mixture to a solution of 1 M HCl (3.45 mL). The organic layer was separated and the aqueous was washed thrice with Et_2O. The combined organic layers were washed with water, then dried over anhydrous $MgSO_4$, filtered and dried under vacuum. The desired product was isolated after a fast purification by a large and short column chromatography (silica gel, hexane) and attained as unstable colourless oil in 67% yield (192 mg).[13]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, *J* = 7.5 Hz, 1H), 7.25 – 7.14 (m, 2H), 7.07 (d, *J* = 7.1 Hz, 1H), 6.42 (t, *J* = 4.8 Hz, 1H), 2.82 (t, *J* = 8.0 Hz, 2H), 2.34 (td, *J* = 8.1, 4.9 Hz, 2H).[11]

General procedure for *N*-arylation of amino-*o*-bromopyridines

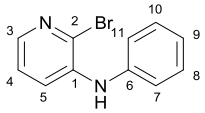
A sealed tube equipped with a magnetic stir bar was charged with Pd_2dba_3 (4 mol %), XantPhos (8 mol %), *t*-BuONa (2 equiv) and amino-*o*-bromopyridine (1 equiv) and dry toluene (c = 0.2 M), followed by iodobenzene (1.2 equiv). The reaction was stirred for 6 hours at 110 °C. The crude reaction product was filtered through a celite pad. The desired product was isolated after purification by column chromatography (silica gel, EtOAc: hexane with gradient).

3-Bromo-*N*-phenylpyridin-4-amine (5a)[14]



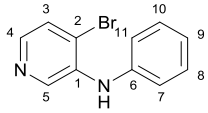
Appearance: Beige solid
Yield: 87% (124.8 mg of **5a** from 100 mg of starting 4-amino-3-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (s, H_3, 1H), 8.13 (d, *J* = 5.6 Hz, H_4, 1H), 7.41 (t, *J* = 7.8 Hz, $H_{10,8}$, 2H), 7.31 – 7.15 (m, $H_{7,11,9}$, 3H), 6.91 (d, *J* = 5.7 Hz, H_5, 1H), 6.57 (s, N*H*, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 151.43 (C_3), 148.68 (C_4), 148.31 (C_1), 138.47 (C_6), 129.87 ($C_{8,10}$), 125.69 (C_9), 123.56 ($C_{7,11}$), 108.42 (C_2), 107.83 (C_5).

2-Bromo-*N*-phenylpyridin-3-amine (5b)[14]



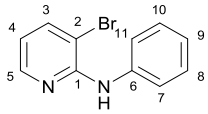
Appearance: Yellow solid
Yield: 99% (143.4 mg of **5b** from 100 mg of starting 3-amino-2-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (dd, *J* = 4.5, 1.5 Hz, H_3, 1H), 7.42 (dd, *J* = 8.1, 1.5 Hz, H_5, 1H), 7.35 (t, *J* = 7.9 Hz, $H_{10,8}$ 2H), 7.18 – 7.04 (m, $H_{11,7}$, H_9, H_4, 4H), 6.14 (br s, N*H*, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 140.04 (C_6), 139.85 (C_3), 139.48 (C_1), 131.71 (C_2), 129.77 ($C_{10,8}$), 124.05 (C_9), 123.45 (C_4), 121.32 ($C_{11,7}$), 121.23 (C_5).

4-Bromo-*N*-phenylpyridin-3-amine (5c)[14]



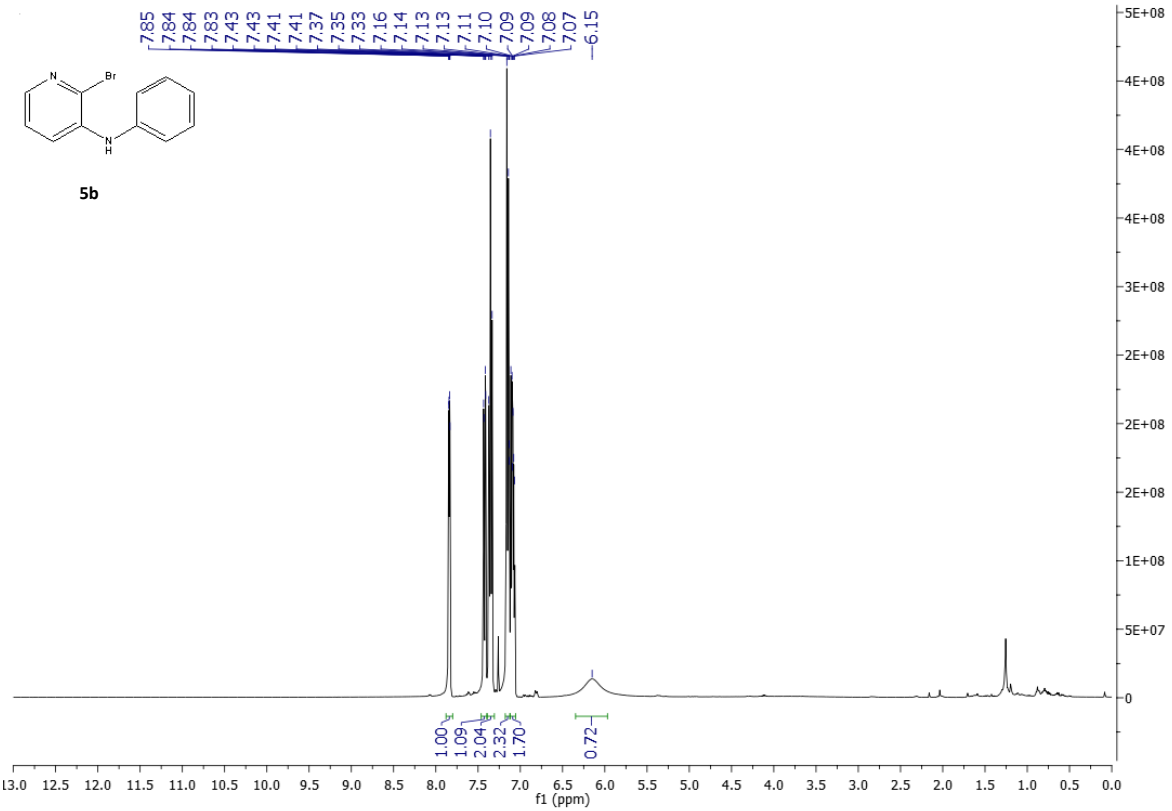
Appearance: Beige solid
Yield: 79% (113.4 mg of **5c** from 100 mg of starting 3-amino-4-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (s, H_5, 1H), 7.92 (d, *J* = 5.1 Hz, H_4, 1H), 7.45 (d, *J* = 5.1 Hz, H_3, 1H), 7.35 (t, *J* = 7.9 Hz, $H_{10,8}$, 2H), 7.18 (d, *J* = 7.7 Hz, $H_{11,7}$, 2H), 7.10 (t, *J* = 7.4 Hz, H_9, 1H), 5.96 (s, N*H*, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.29 (C_4), 140.58 (C_6), 138.91 (C_1), 137.95 (C_5), 129.85 ($C_{10,8}$), 127.74 (C_3), 123.83 (C_9), 121.11 (C_2), 120.73 ($C_{11,7}$).

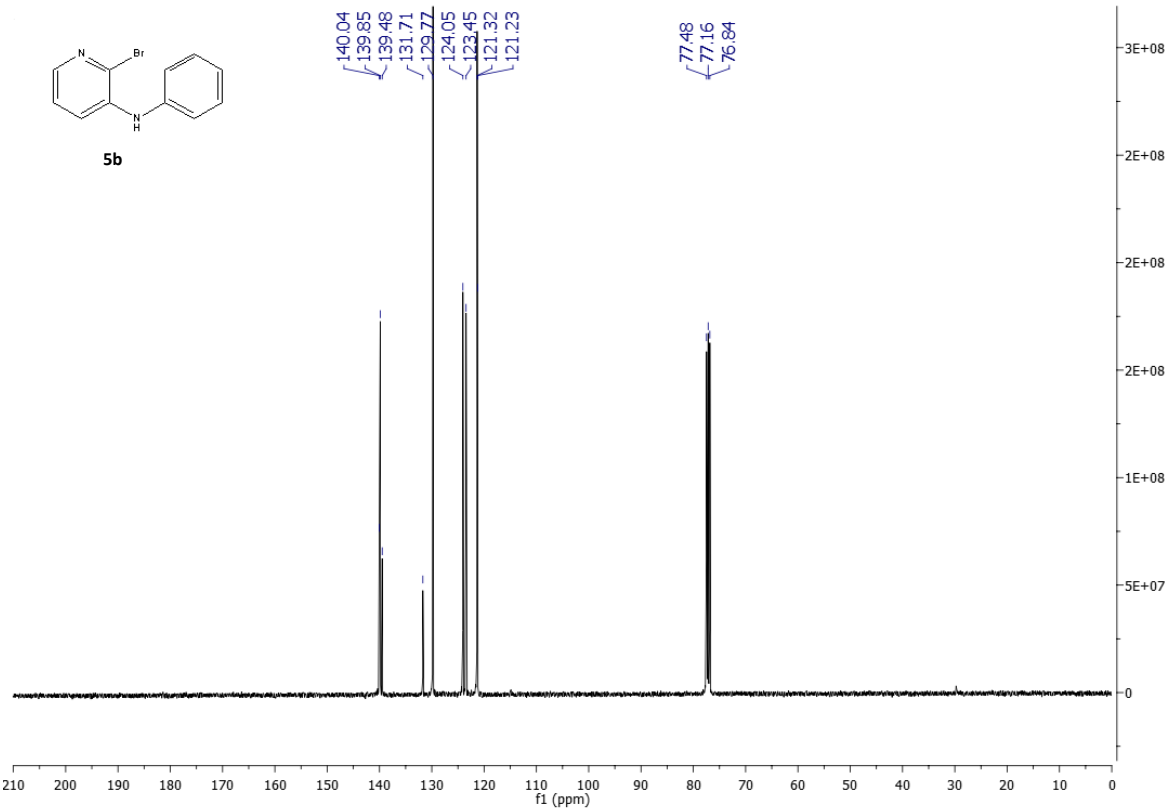
3-Bromo-*N*-phenylpyridin-2-amine (5d)[14]

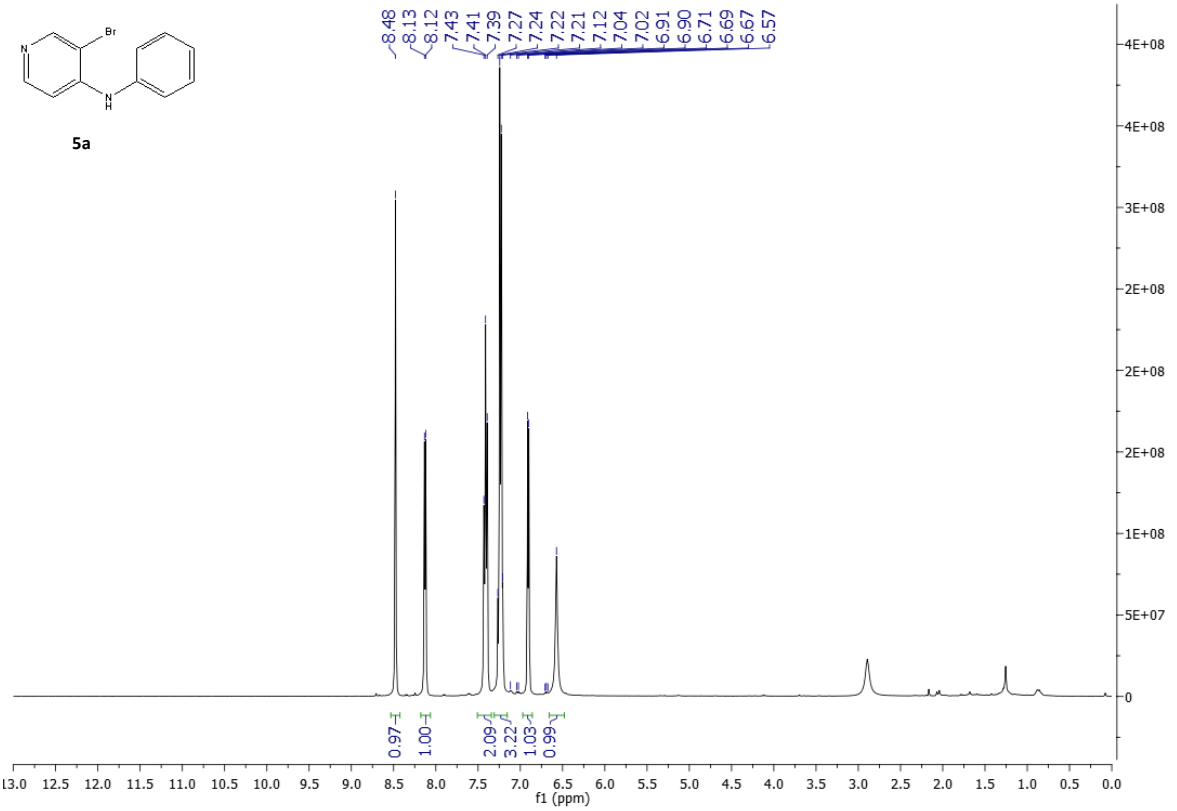


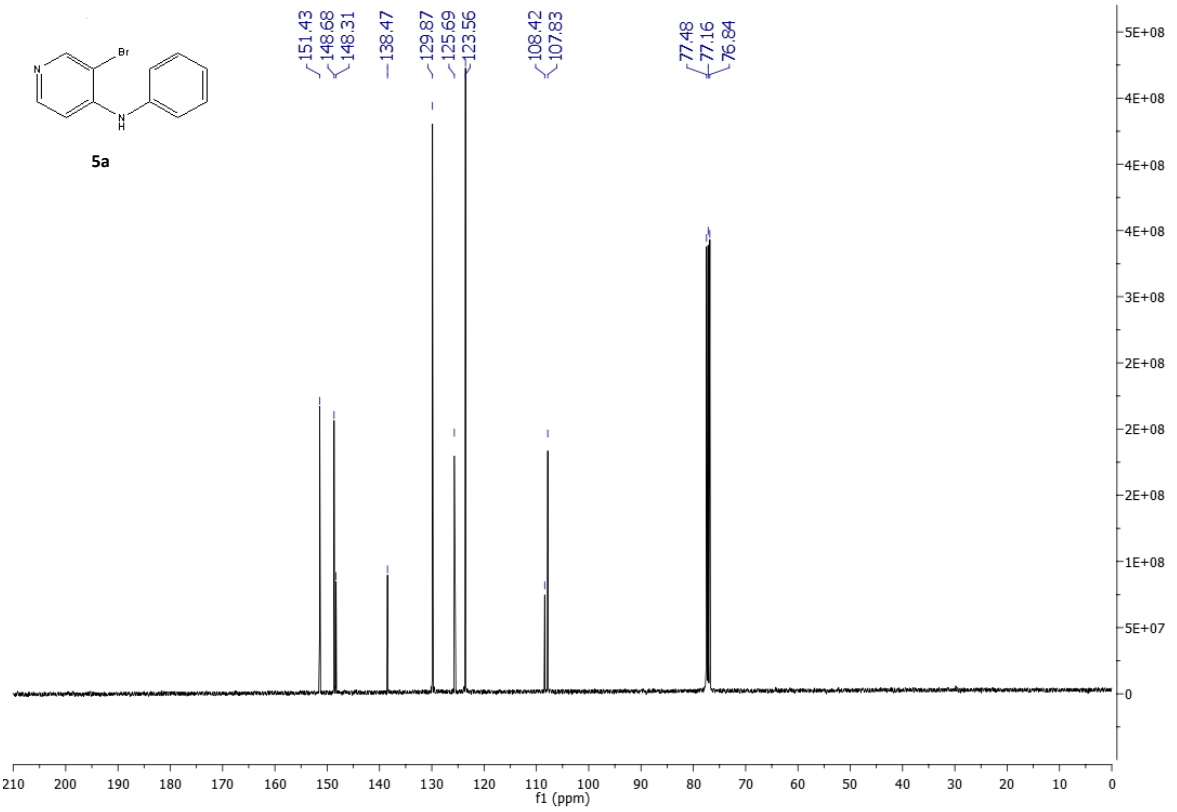
Appearance: Oil
Yield: 94% (142.8 mg of **5d** from 100 mg of starting 2-amino-3-bromopyridine)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (dd, *J* = 4.7, 1.3 Hz, H_5, 1H), 7.74 (dd, *J* = 7.7, 1.4 Hz, H_3, 1H), 7.63 (d, *J* = 7.8 Hz, $H_{11,7}$, 2H), 7.36 (t, *J* = 7.9 Hz, $H_{10,8}$, 2H), 7.11 – 6.99 (m, H_9, N*H*, 2H), 6.64 (dd, *J* = 7.7, 4.8 Hz, H_4, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 151.96(C_1), 146.52(C_5), 140.33(C_3), 139.81(C_6), 129.03($C_{10,8}$), 122.98(C_9), 120.14($C_{11,7}$), 115.72(C_4), 106.47(C_2).

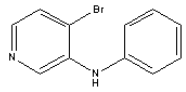
NMR spectra of *N*-phenyl amino-*o*-bromopyridines





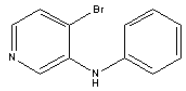

5a
8.48
8.13
8.12
7.43
7.41
7.39
7.27
7.24
7.22
7.21
7.12
7.04
7.02
6.91
6.90
6.71
6.69
6.67
6.57
0.97
1.00
2.09
3.22
1.03
0.99
f1 (ppm)


5a
151.43
148.68
148.31
138.47
129.87
125.69
123.56
108.42
107.83
77.48
77.16
76.84
f1 (ppm)



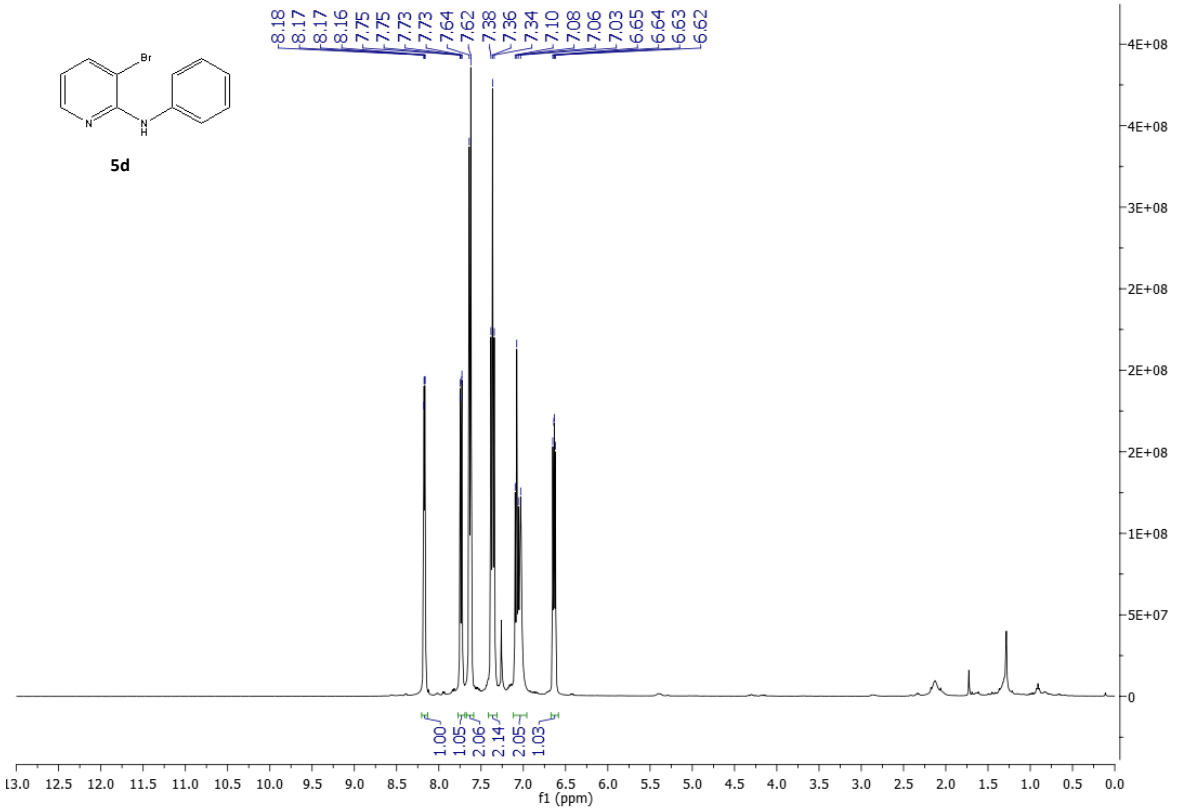
5c

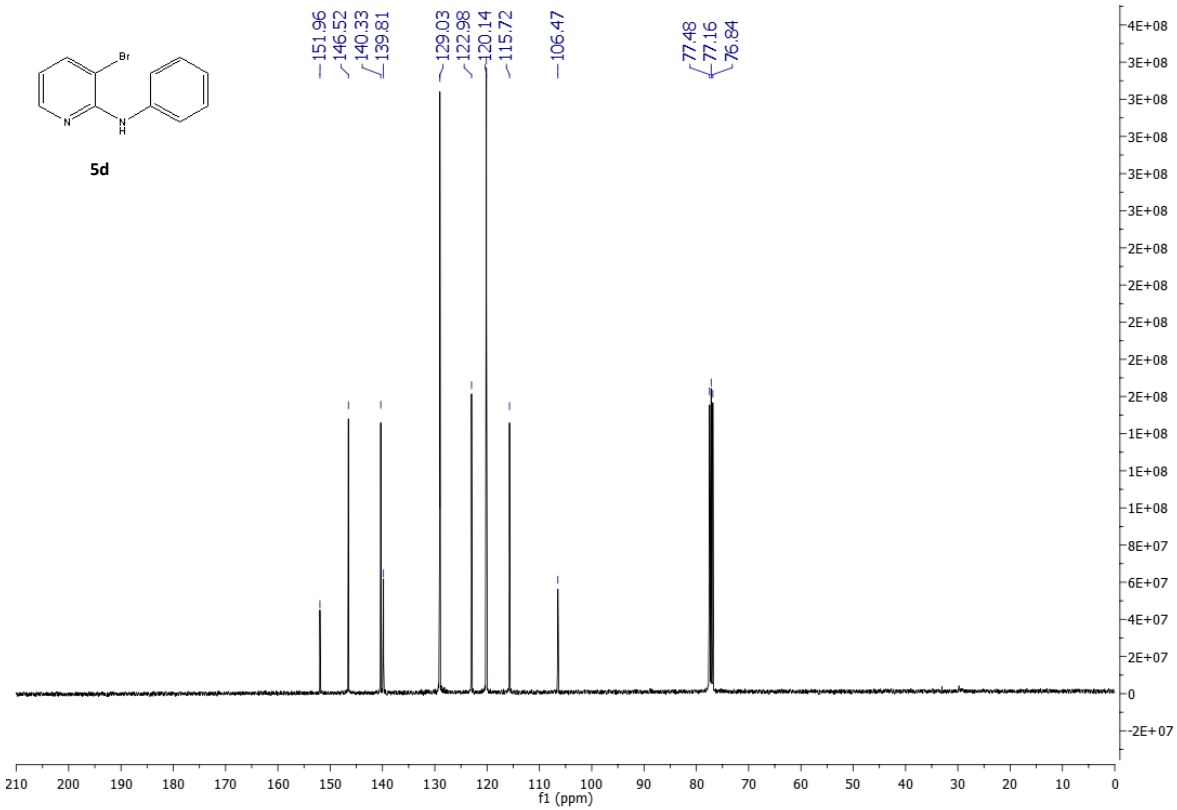
8.50
7.93
7.92
7.46
7.45
7.35
7.34
7.19
7.17
7.10
5.96
1.00
1.00
1.01
2.05
2.08
1.07
0.92
f1 (ppm)



5c

141.29
140.58
138.91
137.95
129.85
127.74
123.83
121.11
120.73
77.48
77.16
76.84
f1 (ppm)


8.18
8.17
8.17
8.16
7.75
7.75
7.73
7.73
7.64
7.62
7.38
7.36
7.34
7.10
7.08
7.06
7.03
6.65
6.64
6.63
6.62
Br
N
H
5d
1.00
1.05
2.06
2.14
2.05
1.03
f1 (ppm)


151.96
146.52
140.33
139.81
129.03
122.98
120.14
115.72
106.47
77.48
77.16
76.84
Br
N
H
5d
f1 (ppm)

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