Silver Promoted Synthesis of Pyrroles via Three Component Reaction Involving an Unusual Imidazole Ring Opening

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Supporting Information

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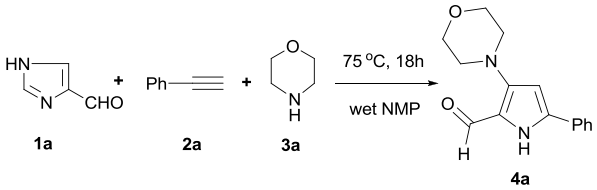
Section A: General Information

General: All the reactions were carried out in a flame or oven dried glassware under an argon or nitrogen atmosphere with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Organic solutions were concentrated under reduced pressure by rotary evaporation with a water bath (temperature below 40 °C). Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60–F254) using UV light at 254 nm as a visualizing agent and a $KMnO_4$ solution as stain. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). Technical grade solvents were used for chromatography and were distilled prior to use. IR spectra were recorded using FTIR Restige-21 (Shimadzu). NMR spectra were recorded at room temperature on 300 MHz Bruker ACF 300, 400 MHz Bruker DPX 400, 400MHz Bruker BPO 400 NMR spectrometers. The residual solvent signals were taken as the reference (7.26 ppm for 1H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). Sometimes the TMS signal at 0.0 ppm was used an internal standard for ^1H NMR spectra. Chemical shift (δ) is reported in ppm, coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal. HR-MS (ESI) spectra were recorded on a Waters Q-Tof premierTM mass spectrometer. Powder X-ray diffraction (XRD) was collected from Shimadzu 6000 diffractometer. X-ray crystallographic data was collected by using a Bruker X8 Apex diffractometer with Mo K/radiation (graphite monochromator). Melting points (m.p.) are uncorrected, and recorded on a Buchi B-540 melting point apparatus.

Section B: Reaction Optimization[a]



Entry	Promoter (equiv)	Additive (equiv)	Yield (%)[b,c]
1	$AgBF_4$ (0.2)	-	11 (4)
2	AgOTf (1.2)	-	48
3	$AgBF_4$ (1.2)	-	53
4	$AgBF_4$ (1.2)	DIPEA (1.5)	62
5	**$AgBF_4$ (0.2)**	**$AgNO_3$ (1.2), DIPEA (1.5)**	**61 (16)**
6	$AgBF_4$ (0.2)	Ag_2CO_3 (1.2), DIPEA (1.5)	60
7	$AgBF_4$ (0.2)	Ag_2O (1.2), DIPEA (1.5)	35
8	$AgBF_4$ (0.2)	AgOAc (1.2), DIPEA (1.5)	47
9	$AgBF_4$ (0.2)	AgF (1.2), DIPEA (1.5)	53
10[d]	$AgBF_4$ (0.2)	$AgNO_3$ (1.2), DIPEA (1.5)	trace
11[e]	$AgBF_4$ (0.2)	$AgNO_3$ (1.2), DIPEA (1.5)	31
12[f]	$AgBF_4$ (0.2)	$AgNO_3$ (1.2), DIPEA (1.5)	23

[a] Unless otherwise specified, all reactions were carried out using **1a** (0.3 mmol, 1 equiv), **2a** (0.45 mmol, 1.5 equiv) and **3a** (0.36 mmol, 1.2 equiv) with promoter and additive in wet NMP (NMP:H_2O = 20:1, 0.6 mL) at 75 ºC. [b] Isolated yields. [c] Numbers in brackets indicated the isolated yields of **5**. [d] Reaction was carried out in anhydrous NMP. [e] Reaction was carried out in wet toluene. [f] Reaction was carried out in wet DCE

The reaction with catalytic amount (0.2 equiv) of $AuCl_3$, $NaAuCl_4$, $Cu(OTf)_2$, CuOTf (toluene complex) and AgOTf gave the desired product less than 20% yield. The use of quantitative amount of $AgBF_4$ in wet N-methyl-2-pyrrolidinone (NMP) at 75 ºC resulted in formation of the desired pyrrole in 53% yield. 1.5 Equivalents of diisopropylethylamine (DIPEA) as the additive increased the yield to 62%, while other bases including triethylamine, pyridine and diazabicyclooctane (DABCO) gave slightly lower yields. Further optimizations revealed that when catalytic amount of $AgBF_4$ (0.2 equiv) was used in combination with 1.2 equivalents of other silver additives with none or weak Lewis acidity such as $AgNO_3$, Ag_2CO_3**,** Ag_2O and AgF, the desired pyrrole was still obtained in acceptable yields. Among the silver additives tested, $AgNO_3$ was found to be most compatible with this system, displaying the highest efficiency. With respect to solvents, polar solvents such as DMF and DMA gave good results, while toluene and DCE were inferior due to the poor solubility of imidazole-4-carboxyaldehyde. Interestingly, when anhydrous solvents were used instead of wet solvents, only trace amount of the desired pyrrole was observed.

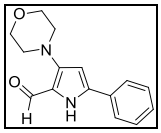
Section C: Experimental Procedures and characterization data

a. General Procedure for the Three Component Reaction: Synthesis of pyrrole 4a.

To a suspension of imidazole-4-carboxaldehyde (28.8 mg, 0.3 mmol), $AgBF_4$ (11.5mg, 0.2 equiv, 0.06 mmol) and $AgNO_3$ (61.2 mg, 1.2 equiv, 0.36 mmol.) in wet NMP (NMP:H_2O = 20:1, 0.6 mL) was added DIPEA (78.3 μL, 1.5 equiv, 0.45 mmol), Phenylacetylene (60 μL, 1.5 equiv, 0.45 mmol) and morpholine (31 μL, 1.2 euiv, 0.36 mmol). The reaction mixture was stirred at 75 °C for 18h, then filtered through celite. The filtrate was diluted with EtOAc (5 mL), washed with water (3mL × 3) and brine, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was carefully purified by flash column chromatography on silica gel (EtOAc:hexane = 1:1 to 3:1) to afford **4a** (46.8 mg, 61%) as a yellow solid and **5** (9.5 mg, 16%) as a yellow solid.

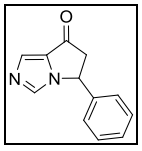
b. Characterization of Pyrrole Products

3-Morpholino-5-phenyl-1H-pyrrole-2-carbaldehyde 4a



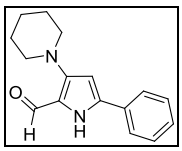
^{1}H NMR (300,/r2MHz, $CDCl_3$,) δ 3.25 (t, *J* 4.8 Hz, 4H), 3.89 (t, *J* 4.8 Hz, 4H), 6.19 (d, *J* 3.0 Hz, 1H), 7.36-7.46 (m, 3H), 7.57-7.60 (m, 2H), 9.19 (br s, 1H), 9.65 (s, 1H);
^{13}C NMR (75 MHz, $CDCl_3$) δ 52.8, 66.6, 98.1, 119.3, 122.5, 125.2, 128.9, 130.5, 139.5, 175.7;
FT-IR (KBr): ν_{max} 3244, 2960, 2825, 1622, 1600, 1512, 1458, 921, 721 cm^{-1};
ESI–MS m/z 603.3 $[M+Na]^+$.
mp 156-157 °C.
HR/MS (ESI) calcd for $C_{15}H_{16}N_2O_2Na$ $[M+Na]^+$ 279.1109, found 279.1118.

5-Phenyl-5H-pyrrolo[1,2-c]imidazol-7(6H)-one 5



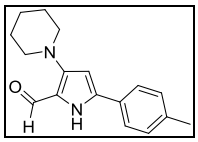
^{1}H NMR (400 MHz, $CDCl_3$,) δ 3.12 (dd, *J* 4.2, 18.5 Hz, 1H), 3.67 (dd, *J* 8.1, 18.5 Hz, 1H), 5.53 (dd, *J* 4.2, 8.1 Hz, 1H), 7.14-7.17 (m, 2H), 7.38-7.42 (m, 3H), 7.56 (s, 1H), 8.16 (s, 1 H);
^{13}C NMR (100MHz, $CDCl_3$) 50.9, 56.9, 126.0, 127.6, 129.2, 129.6, 133.6, 135.9, 139.0, 186.1 ppm;
FT-IR (KBr): ν_{max}, 3115, 1714, 1531, 1107, 939 cm^{-1};
mp 148-149 °C.
HR/MS (ESI) calcd for $C_{12}H_{11}N_2O$ $[M+H]^+$ 199.0871, found 199.0875.

5-Phenyl-3-(piperidin-1-yl)-1H-pyrrole-2-carbaldehyde 4b



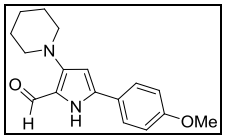
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54-1.60 (m, 2H), 1.68-1.74 (m, 4H), 3.21 (t, *J* 5.2 Hz, 4H), 6.10 (d, *J* 2.9 Hz, 1H), 7.29 (t, *J* 7.4 Hz, 1H), 7.37 (m, 2H), 7.66 (d, *J* 7.8 Hz, 2H), 9.66 (s, 1H), 10.07 (br s, 1H);
^{13}CNMR (100MHz, $CDCl_3$) δ 24.0, 25.7, 54.1, 98.1, 122.6, 125.5, 128.6, 128.9, 130.8, 140.1, 175.7;
FT-IR (KBr): ν_{max} 3242, 2933, 2850, 1620, 1610, 1490, 1128, 1026, 916, 692 cm^{-1};
mp 130 °C.
HR/MS (ESI) calcd for $C_{16}H_{18}N_2ONa$ $[M+Na]^+$ 277.1317, found 277.1327.

3-(Piperidin-1-yl)-5-*p*-tolyl-1H-pyrrole-2-carbaldehyde 4c



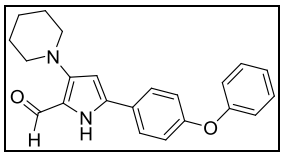
^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.58-1.63 (m, 2H), 1.70-1.76 (m, 4H), 2.37 (s, 3H), 3.24 (t, *J* 5.3 Hz, 4H), 6.10 (d, *J* 2.9 Hz, 1H), 7.21 (d, *J* 8.1 Hz, 2H), 7.47 (d, *J* 8.1 Hz, 2H), 9.16 (br s, 1H), 9.61 (s, 1H);
^{13}CNMR (100MHz, $CDCl_3$) δ 21.7, 23.9, 25.8, 53.7, 97.8, 122.2, 125.4, 128.3, 129.8, 138.8, 139.8, 152.0, 175.9;
FT-IR (KBr): ν_{max} 3242, 2935, 2846, 1610, 1519, 1379, 1128, 918, 785 cm^{-1};
mp 155-156 °C.
HR/MS (ESI) calcd for $C_{17}H_{21}N_2O$ $[M+H]^+$ 269.1654, found 269.1660.

5-(4-Methoxyphenyl)-3-(piperidin-1-yl)-1H-pyrrole-2-carbaldehyde 4d



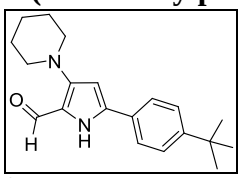
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59-1.63 (m, 2H), 1.71-1.76 (m, 4H), 3.24 (t, *J* 5.4 Hz, 4H), 3.83 (s, 3H), 6.05 (d, *J* 2.9 Hz, 1H), 6.93 (d, *J* 8.8 Hz, 2H), 8.27 (d, *J* 8.8 Hz, 2H), 9.11 (br s, 1H), 9.59 (s, 1H);
^{13}C NMR (100MH_Z, $CDCl_3$) δ 23.9, 25.6, 53.8, 55.4, 97.2, 114.5, 122.0, 123.4, 126.6, 139.8, 160.1, 175.2;
FT-IR (KBr): ν_{max} 3379, 2933, 2852, 1593, 1517, 1477, 1375, 1182, 1029, 918, 788 cm^{-1};
mp 166-167 °C.
HR/MS (ESI) calcd for $C_{17}H_{20}N_2O_2Na$ $[M+Na]^+$ 307.1422, found 307.1427.

5-(4-Phenoxyphenyl)-3-(piperidin-1-yl)-1H-pyrrole-2-carbaldehyde 4e



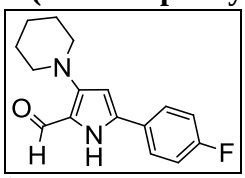
^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58-1.61 (m, 2H), 1.68-1.75 (m, 4H), 3.22 (t, *J* 5.2 Hz, 4H), 6.06 (d, *J* 2.8 Hz, 1H), 6.98-7.04 (m, 4H), 7.10-7.14 (m, 1H), 7.32-7.37 (m, 2H), 7.54-7.57 (m, 2H), 9.38 (br s, 1H), 9.59 (s, 1H);
^{13}C NMR (100MH_Z, $CDCl_3$) δ 23.9, 25.6, 53.9, 97.7, 118.9, 119.4, 122.3, 123.9, 125.7, 126.9, 129.9, 139.5, 152.2, 156.5, 158.0, 175.4;
FT-IR (KBr): ν_{max} 3238, 2933, 2806, 1610, 1587, 1473, 1240, 692 cm^{-1};
mp 147-148 °C.
HR/MS (ESI) calcd for $C_{22}H_{23}N_2O_2$ $[M+H]^+$ 347.1760, found 347.1774.

5-(4-*tert*-Butylphenyl)-3-(piperidin-1-yl)-1H-pyrrole-2-carbaldehyde 4f



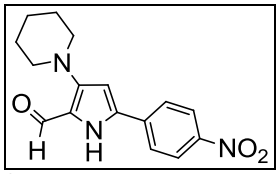
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.60-1.63 (m, 2H), 1.71-1.77 (m, 4H), 3.25 (t, *J* 5.3 Hz, 4H), 6.06 (d, *J* 2.8 Hz, 1H), 7.05-7.10 (m, 2H), 7.55-7.59 (m, 2H), 9.40 (br s, 1H), 9.60 (s, 1H);
^{13}C NMR (100MHz, $CDCl_3$):23.9, 25.6, 31.2, 34.8, 53.8, 97.7, 122.1, 124.9, 126.0, 127.8, 139.7, 151.1, 152.0, 175.5;
FT-IR (KBr): $\nu_{max,}$ 3446, 2933, 2856, 1597, 1477, 1379, 1211, 798 cm^{-1};
mp 198-199 °C.
HR/MS (ESI) calcd for $C_{20}H_{27}N_2O$ $[M+H]^+$ 311.2123, found 311.2137.

5-(4-Fluorophenyl)-3-(piperidin-1-yl)-1H-pyrrole-2-carbaldehyde 4g



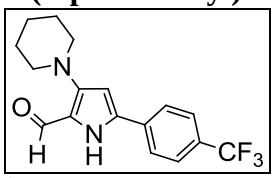
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58-1.60 (m, 2H), 1.70-1.73 (m, 4H), 3.22 (t, *J* 5.3 Hz, 4H), 6.05 (d, *J* 2.9 Hz, 1H), 6.93 (d, *J* 8.8 Hz, 2H), 8.27 (d, *J* 8.8 Hz, 2H), 9.11 (br s, 1H), 9.59 (s, 1H);
^{13}C NMR (100MHz, $CDCl_3$) δ 23.9, 25.6, 53.9, 98.0, 115.9, 116.2, 122.4, 127.1, 127.2, 138.9, 162.9 (d, $^1J_{CF}$ 247.6 Hz), 175.7;
FT-IR (KBr): ν_{max} 3242, 2935, 2850, 1606, 1517, 1450, 1377, 1159, 918, 796 cm^{-1};
mp 151-152 °C.
HR/MS (ESI) calcd for $C_{16}H_{18}N_2OF$ $[M+H]^+$ 273.1403, found 273.1415.

5-(4-Nitrophenyl)-3-(piperidin-1-yl)-1H-pyrrole-2-carbaldehyde 4h



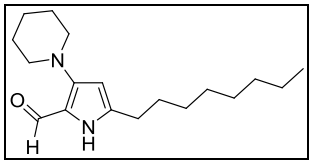
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61-1.65 (m, 2H), 1.74-1.78 (m, 4H), 3.26 (t, *J* 5.4 Hz, 4H), 6.30 (d, *J* 2.8 Hz, 1H), 7.80 (d, *J* 8.7 Hz, 2H), 8.27 (d, *J* 8.7 Hz, 2H), 9.72 (s, 1H), 9.83 (br s, 1H);
^{13}C NMR (100MHz, $CDCl_3$) δ 23.8, 25.6, 53.9, 100.1, 123.6, 124.4, 125.7, 136.7, 136.8, 147.2, 151.1, 176.7.
FT-IR (KBr): ν_{max} 3419, 2922, 1647, 1579, 1554, 1508, 1384, 1220, 1107 cm^{-1};
mp 217-218 °C.
HR/MS (ESI) calcd for $C_{16}H_{18}N_3O_3$ $[M+H]^+$ 300.1348, found 300.1354.

3-(Piperidin-1-yl)-5-(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbaldehyde 4i



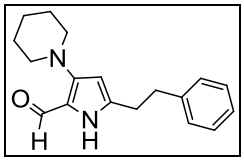
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62-1.65 (m, 2H), 1.73-1.79 (m, 4H), 3.24-3.26 (m, 4H), 6.23 (d, *J* 2.6 Hz, 1H), 7.65 (d, *J* 8.2 Hz, 2H), 7.80 (d, *J* 8.2 Hz, 2H), 9.69 (s, 1H), 10.26 (br s, 1H);
^{13}C NMR (75MHz, $CDCl_3$) δ 23.9, 25.7, 54.1, 99.1, 123.1, 124.0 (q, $^1J_{CF}$ 270.5 Hz), 125.4, 125.8 (q, $^3J_{CF}$ 3.1 Hz), 130.0 (q, $^2J_{CF}$ 32.6 Hz), 134.2, 138.3, 151.7, 176.2;
FT-IR (KBr): ν_{max} 3419, 3261, 2937, 2810, 1610, 1560, 1379, 1325, 1122, 1016, 794 cm^{-1};
mp 168-169 °C.
HR/MS (ESI) calcd for $C_{17}H_{18}N_2OF3$ $[M+H]^+$ 323.1371, found 323.1375.

5-Octyl-3-(piperidin-1-yl)-1H-pyrrole-2-carbaldehyde 4j



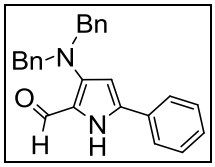
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* 6.5 Hz, 3H), 1.26-1.31 (m, 10H), 1.57-1.63 (m, 4H), 1.68-1.75 (m, 4H), 2.52 (t, *J* 7.6 Hz, 2H), 3.18 (t, *J* 5.3 Hz, 4H), 5.59 (d, *J* 2.6 Hz, 1H), 8.76 (br s, 1H), 9.49 (s, 1H);
^{13}C NMR (100MHz, $CDCl_3$) δ 14.1, 22.6, 23.9, 25.6, 28.2, 28.6, 29.1, 29.2, 29.3, 31.8, 53.5, 98.5, 120.7, 143.2, 151.2, 174.7 ppm;
FT-IR (KBr): ν_{max} 3446, 3242, 2926, 2852, 1614, 1555, 1377, 1126, 798 cm^{-1};
mp 43-44 °C.
HR/MS (ESI) calcd for $C_{18}H_{30}N_2ONa$ $[M+Na]^+$ 313.2256, found 313.2266.

5-Phenethyl-3-(piperidin-1-yl)-1H-pyrrole-2-carbaldehyde 4k



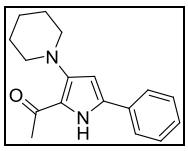
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62-1.65 (m, 2H), 1.67-1.73 (m, 4H), 2.83 (t, *J* 7.4 Hz, 2H), 2.93 (t, *J* 7.4 Hz, 2H), 3.18 (t, *J* 5.4 Hz, 4H), 5.61 (d, *J* 2.3 Hz, 1H), 7.16-7.17 (m, 2H), 7.21-7.23 (m, 1H), 7.27-7.32 (m, 2H), 8.69 (br s, 1H), 9.50 (s, 1H);
^{13}C NMR (100MHz, $CDCl_3$): δ 23.9, 25.6, 30.1, 35.0, 53.6, ;
FT-IR (KBr): ν_{max} 3439, 3240, 2933, 2806, 1598, 1556, 1494, 1377, 698 cm^{-1};
mp 126-127 °C.
HR/MS (ESI) calcd for $C_{18}H_{23}N_2O$ $[M+H]^+$ 283.1810, found 283.1818.

3-(Dibenzylamino)-5-phenyl-1H-pyrrole-2-carbaldehyde 4l



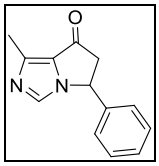
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (s, 4H), 6.05 (d, *J* 2.4 Hz, 1H), 7.20-7.30 (m, 6H), 7.34-7.44 (m, 7H), 7.52-7.54 (m, 2H), 9.10 (br s, 1H), 9.23 (s, 1H);
^{13}C NMR (100MHz, $CDCl_3$) δ 57.0, 96.3, 120.5, 125.3, 126.7, 128.8, 128.9, 129.0, 130.5, 136.9, 140.2, 149.0, 175.2;
FT-IR (KBr): ν_{max} 3423, 3253, 2854, 1587, 1556, 1452, 1382, 1265, 1201, 696 cm^{-1};
mp 143-144 °C.
HR/MS (ESI) calcd for $C_{25}H_{22}N_2ONa$ $[M+Na]^+$ 389.1630, found 389.1646.

1-(5-Phenyl-3-(piperidin-1-yl)-1H-pyrrol-2-yl)ethanone 12a



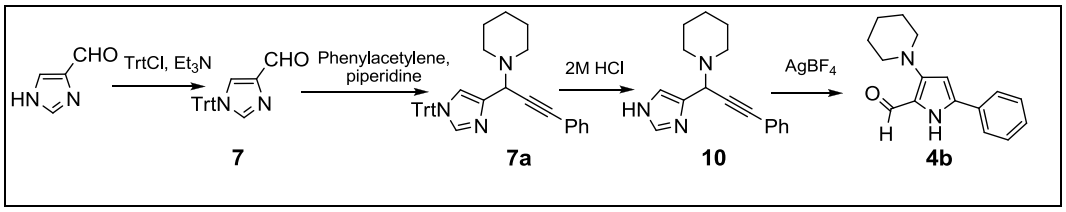
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57-1.60 (m, 2H), 1.71-1.77 (m, 4H), 2.58 (s, 3H), 2.97 (t, *J* 5.1 Hz, 4H), 6.37 (d, *J* 3.0 Hz, 1H), 7.31-7.33 (t, *J* 7.5 Hz, 1H), 7.40 (dd, *J* 7.5, 7.8 Hz, 2H), 7.58 (d, *J* 7.8 Hz, 1H), 9.40 (br s, 1H);
^{13}C NMR (100MHz, $CDCl_3$) δ 24.1, 26.0, 26.2, 56.0, 100.4, 124.3, 124.9, 128.1, 128.9, 131.1, 136.4, 149.7, 186.5;
FT-IR (KBr): ν_{max} 3273, 2933, 2850, 2796, 1612, 1595, 1469, 1452, 1273, 975, 761, 690cm^{-1};
mp 108-109 °C.
HR/MS (ESI) calcd for $C_{17}H_{21}N_2O$ $[M+H]^+$ 269.1654, found 269.1663.

1-methyl-5-phenyl-5H-pyrrolo[1,2-c]imidazol-7(6H)-one 9c



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.07 (dd, *J* 4.3, 18.4 Hz, 1H), 3.62 (dd, *J* 8.2, 18.4 Hz, 1H), 5.56 (dd, *J* 4.3, 8.2 Hz, 1H), 7.14-7.18 (m, 2H), 7.36-7.42 (m, 4H);
^{13}C NMR (100MHz, $CDCl_3$) δ 13.9, 50.9, 56.5, 126.0, 129.1, 129.5, 129.8, 134.7, 139.3, 139.8, 186.2;
FT-IR (KBr): ν_{max} 2858, 1705, 1610, 1568, 1456, 1323, 1228, 700 cm^{-1};
mp 160-161 °C.
HR/MS (ESI) calcd for $C_{13}H_{12}N_2ONa$ $[M+H]^+$ 235.0847, found 235.0841.

c. Reaction with substituted imidazole-4-carboxaldehyde.



7: To a solution of imidazole-4-carboxaldehyde (961 mg, 10 mmol) and triethylamine (2.1 mL, 15 mmol) in anhydrous DMF (50 mL) was added TrtCl (4.18 g, 15 mmol) in portions at 0 °C under nitrogen. The mixture was allowed to warm to rt. and stirred for overnight, then diluted with ether (50 mL) and washed with water (50 mL × 3), the organic phase was washed brine, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:5) to afford **7** (2.77 g, 82%) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09-7.11 (m, 6H), 7.32-7.36 (m, 9H), 7.53 (s, 1H), 7.60 (s, 1H), 9.87 (s, 1H);
^{13}C NMR (100MHz, $CDCl_3$) δ 126.8, 128.4, 128.6, 129.7, 140.6, 140.9, 141.5, 186.6;
FT-IR (KBr): ν_{max} 3420, 2816, 1693, 1535, 1490, 1448, 1298, 1120, 700 cm^{-1};
mp 196-197 °C.
HR/MS (ESI) calcd for $C_{23}H_{18}N_2ONa$ $[M+Na]^+$ 361.1317, found 361.1312.

7a: To a suspension of **7** (338 mg, 1.0 mmol) and $AgBF_4$ (38.6, 0.2 equiv, 0.2 mmol) in toluene (3 mL) was added phenylacetylene (0.2 mL, 1.5 equiv, 1.5 mmol) and piperidine (0.12 mL, 1.2 euiv, 1.2 mmol). The reaction mixture was stirred for 18h at 75 ^{o}C then filtered through celite. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to afford **7a** (365 mg, 72%) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.43 (m, 2H), 1.58-1.66 (m, 4H), 2.56-2.60 (m, 4H), 4.82 (s, 1H), 6.94 (s, 1H), 7.15-7.18 (m, 6H), 7.24-7.26 (m, 3H), 7.32-7.36 (m, 12H), 7.41-7.42 (m, 1H);
^{13}C NMR (100MHz, $CDCl_3$) δ 24.5, 26.1, 50.6, 57.2, 75.4, 85.7, 86.3, 102.8, 127.9, 128.0, 128.1, 129.8, 131.8, 138.8, 142.5;
FT-IR (KBr): ν_{max} 2933, 1635, 1489, 1442, 1128, 754, 700 cm^{-1};
mp 76-77 °C.
HR/MS (ESI) calcd for $C_{36}H_{33}N_3Na$ $[M+Na]^+$ 530.2572, found 530.2566.

10: To a solution of **7a** (507 mg, 1 mmol) in THF (5 mL) was adde 2M HCl (2 mL), the reaction mixture was stirred at 50 ^{o}C for 2 h, then cooled down to room temperature and neutralized with saturated aqueous $NaHCO_3$. The solution was extracted with EtOAc (5 mL × 3), washed with brine, dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 5:1) to afford **10** (172 mg, 65%) as a yellow iol.

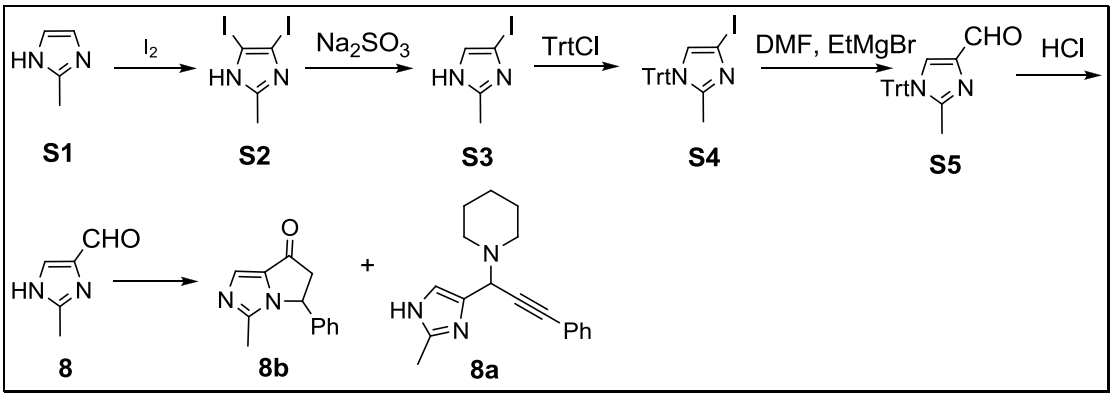
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.43 (m, 2H), 1.54-1.63 (m, 4H), 2.60-2.63 (m, 4H), 4.86 (s, 1H), 7.16 (s, 1H), 7.22-7.32 (m, 3H), 7.42-7.46 (m ,2H), 7.63 (s, 1H), 8.41 (br s, 1H);

^{13}C NMR (100MHz, $CDCl_3$) δ 24.3, 26.0, 50.4, 56.0, 85.1, 86.2, 120.0, 123.0, 128.2, 128.3, 131.8, 134.3, 135.4;

FT-IR (KBr): ν_{max} 3078, 2933, 2852, 1597, 1489, 1442, 1089, 985, 756, 690cm^{-1};

HR/MS (ESI) calcd for $C_{17}H_{19}N_3Na$ $[M+Na]^+$ 288.1477, found 288.1483.

4b To a suspension of **10** (79.5 mg, 0.3 mmol), $AgBF_4$ (11.5mg, 0.2 equiv, 0.06 mmol) and $AgNO_3$ (61.2 mg, 1.2 equiv, 0.36 mmol.) in anhydrous toluene (0.6 mL) was added DiPEA (78.3 μL, 1.5 equiv, 0.45 mmol) and H_2O (or D_2O or $H_2{}^{18}O$, 54 μL, 3 mmol). The reaction mixture was stirred for 18h at 75 ^{o}C then filtered through celite. The filtrate was dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was carefully purified by flash column chromatography on silica gel (EtOAc:hexane = 1:3 to EtOAc:hexane = 1:1) to afford **4b** (46.8 mg, 64%) as a yellow solid.



S2: To a slightly yellow homogenous solution of 2-methylimidazole (1.64 g, 20 mmol) in dioxane (30 mL) and distilled water (30 mL)was added successively sodium carbonate (6.36 g, 60 mmol) and iodine (11 g, 44 mmol) at room temperature. The resulting reaction mixture was further stirred at room temperature for 24 h under nitrogen. EtOAc (90 mL) was then added followed by saturated aqueous $Na_2S_2O_3$ (50 mL), the organic phase was separated and washed with saturated aqueous $Na_2S_2O_3$ (30 mL) and brine, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product (5.8g, 87%) which used in the next step without further purification.

S3[1] A solution of above crude product and Na_2SO_3 (17 g) in 30% aqueous EtOH (60 mL) was refluxed for 24 h. The solvent was removed almost to dryness to prevent the inorganic salts from precipitating. The solid was filtered, washed with water and dried to give a white powder

^{1}HNMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.10 (s, 1H), 12.52 (br s, 1H);

^{13}CNMR (100 MHz, $CDCl_3$) δ 14.0, 123.3, 147.1, 151.2;

FT-IR (KBr): ν_{max} 3415, 2924, 2854, 1643, 1558, 1408, 1172, 945, 748 cm^{-1};

mp 146-147 °C.

HR/MS (ESI) calcd for $C_4H_6N_2I$ $[M+H]^+$ 208.9576, found 208.9582.

S4: To a solution of **S3** (670 mg, 3.2 mmol) and triethylamine (0.53 mL, 3.9 mmol) in anhydrous DMF (10 mL) was added TrtCl (1.07 g, 3.9 mmol) in portions at 0 °C under nitrogen. The mixture was allowed to warm to rt. and stirred for overnight, then diluted with ether (20 mL) and washed with water (10 mL × 3), the organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to afford **S4** (1.02 mg, 70%) as a yellow solid.

^{1}HNMR (400 MHz, $CDCl_3$) δ 1.64 (s, 3H), 6.78 (s, 1H), 7.10-7.13 (m, 6H), 7.30-7.32 (m, 9H);

^{13}CNMR (100 MHz, $CDCl_3$) δ 17.3, 75.5, 78.7, 126.8, 128.1, 128.2, 129.9, 141.8, 149.3;

FT-IR (KBr): ν_{max} 2943, 2852, 1492, 1444, 1217, 941, 748, 702 cm^{-1};

mp 219-220 °C.

HR/MS (ESI) calcd for $C_{23}H_{19}N_2INa$ $[M+Na]^+$ 473.0491, found 473.0488.

S5: To a solution of **S4** (275 mg, 0.5 mmol) in anhydrous DCM (3 mL) was added EtMgBr (3 M in ether, 0.2 mL, 0.6 mmol) at room temperature. The reaction mixture was stirred for 4 h at room temperature and then added anhydrous DMF (77 μL, 1 mmol). The reaction mixture was stirred overnight, quenched with sat. aq. NH_4Cl and extracted with DCM ((30 mL × 3), the organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to afford **S5** (141 mg, 80%) as a yellow solid.

^{1}HNMR (400 MHz, $CDCl_3$) δ 1.69 (s, 3H), 7.11-7.13 (m, 7H), 7.35-7.41 (m, 8H), 7.51 (s, 1H), 9.78 (s, 1H);

^{13}CNMR (100 MHz, $CDCl_3$) δ 17.4, 127.9, 128.0, 128.1, 128.4, 129.9, 130.0, 138.4, 141.2, 149.5, 185.7;

FT-IR (KBr): ν_{max}, 2821, 2765, 1685, 1541, 1492, 1446, 1151, 748, 702 cm^{-1};

mp 192-193 °C.

HR/MS (ESI) calcd for $C_{24}H_{20}N_2ONa$ $[M+Na]^+$ 375.1473, found 375.1460.

8 To a solution of **S5** (352 mg, 1.0 mmol) in THF (5 mL) was adde 2M HCl (2 mL),

[1] M. D. Cliff, S. G. Pyne, *Synthesis-Stuttgart* **1994**, 681-682

the reaction mixture was stirred at 50 °C for 2 h, then cooled down to room temperature and neutralized with saturated aqueous $NaHCO_3$. The solution was extracted with EtOAc (5 mL × 3), washed with brine, dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (DCM:MeOH = 20:1) to afford **8** (67 mg, 61%) as a white solid.

^{1}HNMR (400 MHz, DMSO-d6) δ 2.32 (s, 3H), 7.83 (s, 1H), 9.60 (s, 1h), 12.74 (br s, 1H);

^{13}CNMR (100 MHz, DMSO-d6) δ 14.2, 126.7, 132.7, 149.2, 182.7;

FT-IR (KBr): ν_{max} 2868, 1653 cm^{-1};

mp 161-162 °C.

HR/MS (ESI) calcd for $C_5H_6N_2ONa$ $[M+Na]^+$ 133.0378, found 133.0381.

8a and **8b** were prepared according to the general procedure:

8a ^{1}HNMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 3.06 (dd, *J* 3.5, 18.5 Hz, 1H), 3.70 (dd, *J* 8.3, 18.5 Hz, 1H), 5.53 (dd, *J* 3.5, 8.3 Hz, 1H), 7.10-7.13 (m, 2H), 7.31-7.42 (m, 3H), 7.56 (s, 1H);

^{13}CNMR (100 MHz, $CDCl_3$) δ 13.1, 51.6, 56.5, 125.9, 127.2, 129.0, 129.6, 133.8, 145.8, 186.0;

FT-IR (KBr): ν_{max} 2929, 1705, 1537, 1498, 1456, 1300, 1149, 1018, 700 cm^{-1};

mp 110-111 °C.

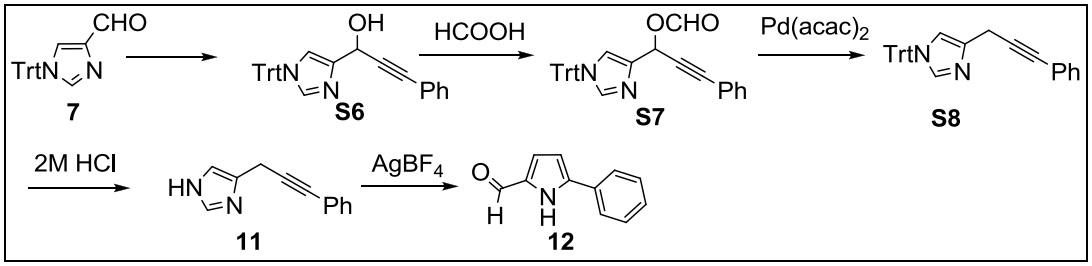
HR/MS (ESI) calcd for $C_{13}H_{13}N_2O$ $[M+H]^+$ 213.1028, found 213.1035.

8b: ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.42-1.46 (m, 2H), 1.57-1.66 (m, 4H), 2.42 (s, 3H), 2.61-2.67 (m, 4H), 4.81 (s, 1H), 7.00 (br s, 1H), 7.03 (s, 1H), 7.30-7.32 (m, 3H), 7.45-7.48 (m, 2H);

^{13}CNMR (100 MHz, $CDCl_3$) δ 14.2, 24.2, 25.9, 50.5, 55.8, 84.2, 86.6, 120.1, 121.5, 122.8, 128.3, 131.8, 144.7;

FT-IR (KBr): ν_{max} 3339, 2933, 2806, 1637, 1489, 756, 690 cm^{-1};

HR/MS (ESI) calcd for $C_{18}H_{11}N_3$ $[M+H]^+$ 280.1814, found 280.1804.



S6: To a solution of phenylacetylene (0.66 mL, 6 mmol) in anhydrous THF (3 mL) was add droppwise *n*-butyllithium (2 M in cyclohexhane, 3mL, 6 mmol) at -78 °C. The reaction mixture was stirred at this temperature for 1h, and then a solution of **7** (1.6 g, 5 mmol) in anhydrous THF (7 mL) was added via syringe. The reaction mixture was stirred for another 1 h at -78 °C then allowed to warm to room temperature and stirred for 1 h. the reaction was quenched with saturated aquous.

NH_4Cl and extracted with DCM (10 mL × 3), the organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to afford **S6** (1.7 g, 77%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (br s, 1H), 5.72 (s, 1H), 6.99 (s, 1H), 7.13-7.15 (m, 6H), 7.24-7.26 (m, 4H), 7.32-7.36 (m, 10H), 7.46 (s, 1H);

^{13}C NMR (100MHz, $CDCl_3$) δ 58.6, 75.6, 84.3, 88.9, 119.0, 122.9, 128.1, 128.2, 129.9, 131.8, 139.3, 141.7, 142.2;

FT-IR (KBr): ν_{max} 3419, 2854, 1647, 1595, 1489, 1444, 1128, 746, 702 cm^{-1};

mp 164-165 °C.

HR/MS (ESI) calcd for $C_{31}H_{24}N_2ONa$ $[M+Na]^+$ 463.1786, found 463.1792.

S7[2]: To a solution of 2-hydroxypyridine (59.4 mg, 0.6 mmol) and DCC (153.0 mg, 0.7 mmol) in DCM (1 mL) was added dropwise formic acid (25.7 μL, 0.7 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 2h, then **S7** (220.0 mg, 0.5 mmol) was added to the mixture at 0 ^{o}C. After the reaction was allowed to warm to room temperature and stirred overnight, the mixture was filtered through celite, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to afford **S7** (150.0 g, 64%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (s, 1H), 6.78 (s, 1H), 7.15-7.17 (m, 8H), 7.25-7.40 (m, 12H), 7.49 (s, 1H), 8.18 (s, 1H);

^{13}C NMR (100MHz, $CDCl_3$) δ 60.7, 75.7, 84.0, 86.2, 121.2, 127.2, 127.9, 128.1, 128.2, 128.8, 129.8, 131.9, 139.7, 142.1, 159.9;

FT-IR (KBr): ν_{max} 2962, 2850, 2231, 1730, 1643, 1489, 1261, 798, 702 cm^{-1};

HR/MS (ESI) calcd for $C_{32}H_{25}N_2O_2$ $[M+H]^+$ 469.1916, found 469.1920.

S8[3]: A solution of **S7** (242.0 mg, 0.51 mmol), $Pd(acac)_2$ (15.7 mg, 0.05 mmol) and DPPPE (22.0 mg, 0.05 mmol) in toluene (5 mL) was stirred overnight at 50 ^{o}C under argon. The reaction mixture was filtered through celite, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to afford **S8** (155.8 g, 72%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 2H), 6.82 (s, 1H), 7.13-7.17 (m, 7 H), 7.23-7.25 (m, 3H), 7.31-7.33 (m, 10H), 7.37 (s, 1H);

^{13}C NMR (100MHz, $CDCl_3$) δ 19.8, 75.3, 81.4, 87.1, 118.6, 123.7, 126.2, 127.7, 128.0, 128.1, 128.4, 129.8, 129.9, 131.6, 137.2, 138.8, 142.5;

mp 131-132 °C.

FT-IR (KBr): ν_{max} 2927, 1689, 1597, 1490, 1452, 1444, 756, 702 cm^{-1};

HR/MS (ESI) calcd for $C_{31}H_{25}N_2$ $[M+H]^+$ 425.2018, found 425.2036.

11: To a solution of **S8** (180 mg, 0.4 mmol) in THF (2 mL) was adde 2M HCl (0.5 mL), the reaction mixture was stirred at 50 ^{o}C for 2 h, then cooled down to room

2 H. Ohmiya, M. Yang, Y. Yamauchi, Y. Ohtsuka, M. Sawamura, *Org. Lett.* **2010**, *12*, 1796-1799.

temperature and neutralized with saturated aqueous $NaHCO_3$. The solution was extracted with EtOAc (2 mL × 3), washed with brine, dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc) to afford **11** (46.7 mg, 62%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 (s, 2H), 6.99 (s, 1H), 7.22-7.24 (m, 3H), 7.35-7.37 (m, 2H), 7.59 (s, 1H), 10.66 (br s, 1H);

^{13}C NMR (100MHz, $CDCl_3$) δ 18.6, 81.6, 86.7, 115.6, 123.5, 127.9, 128.2, 131.6, 134.4, 135.0;

FT-IR (KBr): ν_{max} 3404, 2883, 1653, 1597, 1489, 765, 690cm^{-1};

mp 116-117 °C.

HR/MS (ESI) calcd for $C_{12}H_{11}N_2$ $[M+H]^+$ 183.0922, found 183.0923.

12: To a suspension of **11** (30 mg, 0.16 mmol), $AgBF_4$ (6.2 mg, 0.03 mmol) and $AgNO_3$ (27.0 mg, 0.16 mmol.) in wet NMP (NMP:H_2O = 20:1, 0.5 mL) was added DIPEA (33.0 μL, 0.19 mmol). The reaction mixture was stirred for 24h at 75 ^{o}C then filtered through celite. The filtrate was dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was carefully purified by flash column chromatography on silica gel (EtOAc:hexane = 1:3 to 1:1) to afford **12** (5.7 mg, 21%) as a yellow solid.

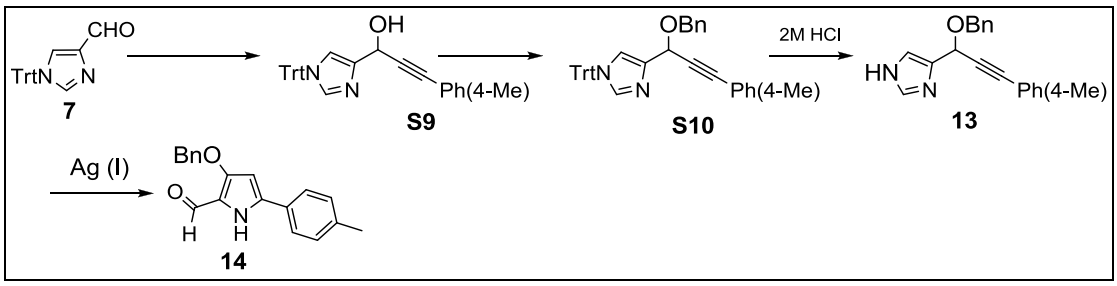
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (dd, *J* 2.7, 3.8 Hz, 1H), 7.02 (dd, *J* 2.4, 3.9 Hz, 1H), 7.37 (d, *J* 7.2 Hz, 1H), 7.42-7.46 (m, 2H), 7.60 (d, *J* 7.2 Hz, 2H), 9.51 (s, 1H), 9.53 (br s, 1H);

^{13}C NMR (100MHz, $CDCl_3$) δ 109.0, 122.6, 125.2, 128.7, 129.2, 130.6, 133.3, 139.8, 178.8;

FT-IR (KBr): ν_{max} 3419, 2924, 1643, 1469, 1263, 758 cm^{-1};

mp 136-137 °C.

HR/MS (ESI) calcd for $C_{11}H_{19}NONa$ $[M+Na]^+$ 194.0582, found 194.0587.



S9: To a solution of *p*-methylphenylacetylene (1.3 g, 12.0 mmol) in anhydrous THF (10 mL) was add droppwise *n*-butyllithium (2 M in cyclohexhane, 6.5 mL, 13.0 mmol) at -78 ^{o}C. The reaction mixture was stirred at this temperature for 1h, and then a solution of **7** (3.4 g, 10.0 mmol) in anhydrous THF (7 mL) was added *via* syringe. The reaction mixture was stirred for another 1 h at -78 ^{o}C then allowed to warm to room temperature and stirred for 1 h. the reaction was quenched with sat. aq. NH_4Cl and extracted with DCM (10 mL × 3), the organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The

residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to afford **S9** (3.7 g, 81%) as a yellow solid.
^{1}H NMR (400 MHz, CDCl3) δ 2.32 (s, 3H), 4.63 (br s, 1H), 5.73 (s, 1H), 6.99 (s, 1H), 7.05-7.07 (m, 2H), 7.13-7.17 (m, 6H), 7.23 (s, 1H), 7.25-7.27 (m, 1H), 7.31-7.35 (m, 9 H), 7.46 (d, *J* 1.4 Hz, 1H);
^{13}C NMR (100MHz, $CDCl_3$) δ 21.5, 59.0, 75.6, 84.8, 87.6, 118.9, 128.1, 128.2, 128.9, 129.9, 131.7, 139.3, 142.2;
FT-IR (KBr): ν_{max} 3439, 2868, 1635, 1508, 1444, 700 cm^{-1};
mp 217-218 °C.
HR/MS (ESI) calcd for $C_{32}H_{26}N_2ONa$ $[M+Na]^+$ 477.1943, found 477.1936.

S10 To a solution of **S9** (136 mg, 0.3 mmol) in anhydrous DMF (1 mL) was added NaH (60% in oil, 18 mg, 0.45 mmol) at 0 ^{o}C, the reaction mixture was stirred for 1h at this temperature and then allowed to warm to room temperature and stirred overnight. The mixture was quenched with cold water and diluted with DCM (1 mL), the organic phase was separated, the aqueous phase was extracted with DCM (1 mL × 3), the combined organic phase were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to afford **S10** (140 g, 88%) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.76 (d, *J* 11.6 Hz, 1H), 4.80 (d, *J* 11.6 Hz, 1H), 5.49 (s, 1H), 7.06-7.08 (m, 4H), 7.10-7.17 (m, 7H), 7,23-7.35 (m, 12H), 7.39-7.44 (m, 3H);
^{13}C NMR (100MHz, $CDCl_3$) δ 21.5, 66.1, 69.9, 75.6, 85.9, 86.4, 119.6, 120.4, 127.6, 127.7, 1228.1, 128.3, 128.6, 129.7, 129.9, 131.8, 138.0, 138.5, 139.2, 139.3, 142.4, 142.5;
FT-IR (KBr): ν_{max} 2922, 2860, 2225, 1597, 1492, 1444, 1128, 699 cm^{-1};
mp 53-54 °C.
HR/MS (ESI) calcd for $C_{39}H_{32}N_2ONa$ $[M+Na]^+$ 567.2412, found 567.2410.

13: To a solution of **S10** (270 mg, 0.5 mmol) in THF (2 mL) was adde 2M HCl (0.5 mL), the reaction mixture was stirred at 50 ^{o}C for 2 h, then cooled down to room temperature and neutralized with saturated aqueous $NaHCO_3$. The solution was extracted with EtOAc (2 mL × 3), washed with brine, dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (DCM:MeOH = 20:1) to afford **13** (98 mg, 65%) as a yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 4.68 (d, *J* 11.4 Hz, 1H), 4.75 (d, *J* 11.4 Hz, 1H), 5.52 (s, 1H), 7.05 (s, 1H), 7.07 (s, 1H), 7.21 (s, 1H), 7.22-7.35 (m, 7H), 7.50 (s, 1H), 9.78(br s, 1H);
^{13}C NMR (100MHz, $CDCl_3$) δ 21.5, 65.3, 70.0, 85.5, 86.8, 117.3, 119.3, 127.8, 128.4, 128.5, 128.6, 131.7, 135.8, 137.7, 138.8;
FT-IR (KBr): ν_{max} 3412, 2862, 2225, 1653, 1508, 1053, 815, 698 cm^{-1};
HR/MS (ESI) calcd for $C_{20}H_{19}N_2O$ $[M+H]^+$ 303.1497, found 303.1507.

14: To a suspension of **13** (110 mg, 0.36 mmol), $AgBF_4$ (14.1 mg, 0.07 mmol) and $AgNO_3$ (73.4 mg, 0.43 mmol.) in wet NMP (NMP : H_2O= 20:1, 0.8 mL) was added DIPEA (94.0 μL, 0.54 mmol). The reaction mixture was stirred for 20h at 75 ^oC then filtered through celite. The filtrate was dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was carefully purified by flash column chromatography on silica gel (EtOAc:hexane = 1:5 to 1:2) to afford **14** (44.1 mg, 42%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 5.17 (s, 2H), 6.19 (d, *J* 2.8 Hz, 1H), 7.21-7.24 (m, 2H) 7.33-7.37 (m, 2H), 7.39-7.46 (m, 5H), 8.95 (br s, 1H), 9.59 (s, 1H);

^{13}C NMR (100MHz, $CDCl_3$) δ 21.3, 72.8, 94.1, 119.7, 124.9, 127.5, 127.6, 128.3, 128.7, 129.9, 136.3, 139.2, 174.9;

FT-IR (KBr): ν_{max} 3396, 2854, 1614, 1504, 1454, 1108, 975, 734, 696 cm^{-1};

HR/MS (ESI) calcd for $C_{26}H_{27}O_4FNa[M+Na]^+$ 445.1791, found 445.1797.

mp 140-141 °C.

HR/MS (ESI) calcd for $C_{19}H_{17}NO_2Na$ $[M+Na]^+$ 314.1157, found 314.1168.

Section D. X-ray Date of 4a

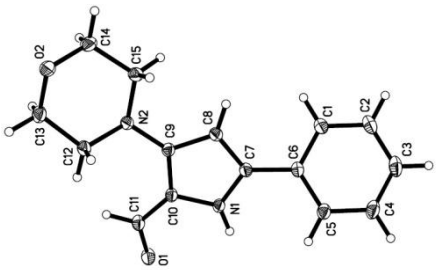


Table 1. Crystal data and structure refinement for **4a**.

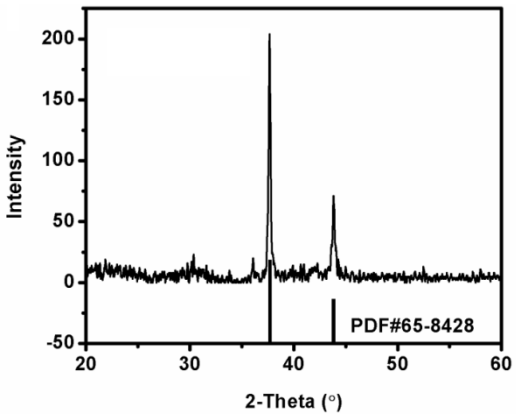
Empirical formula	C15 H16 N2 O2	
Formula weight	256.30	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.2571(2) Å	α= 106.2790(10)°.
	b = 11.7675(2) Å	β= 109.1210(10)°.
	c = 13.4040(3) Å	γ = 99.1840(10)°.
Volume	1272.36(5) $Å^3$	
Z	4	
Density (calculated)	1.338 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	544	
Crystal size	0.40 x 0.36 x 0.12 mm^3	
Theta range for data collection	1.72 to 31.12°.	
Index ranges	-13<=h<=13, -17<=k<=17, -19<=l<=19	
Reflections collected	27401	
Independent reflections	8115 [R(int) = 0.0356]	
Completeness to theta = 31.12°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9893 and 0.9648	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8115 / 0 / 343	
Goodness-of-fit on F^2	1.089	
Final R indices [I>2sigma(I)]	R1 = 0.0447, wR2 = 0.1226	
R indices (all data)	R1 = 0.0610, wR2 = 0.1442	
Largest diff. peak and hole	0.492 and -0.381 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **4a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8135(1)	3817(1)	1915(1)	18(1)
C(2)	7566(2)	3828(1)	2758(1)	22(1)
C(3)	8510(2)	3700(1)	3743(1)	25(1)
C(4)	10021(2)	3568(1)	3887(1)	24(1)
C(5)	10601(1)	3566(1)	3052(1)	18(1)
C(6)	9656(1)	3686(1)	2053(1)	16(1)
C(7)	10225(1)	3684(1)	1154(1)	15(1)
C(8)	9318(1)	3326(1)	0(1)	16(1)
C(9)	10364(1)	3510(1)	-538(1)	14(1)
C(10)	11928(1)	3991(1)	323(1)	15(1)
C(11)	13410(1)	4512(1)	328(1)	17(1)
C(12)	10836(1)	2714(1)	-2261(1)	20(1)
C(13)	10295(1)	2697(1)	-3461(1)	21(1)
C(14)	7769(2)	2760(1)	-3550(1)	23(1)
C(15)	8190(1)	2821(1)	-2342(1)	19(1)
C(16)	7262(1)	10006(1)	2753(1)	19(1)
C(17)	7405(2)	10426(1)	1910(1)	21(1)
C(18)	6656(2)	9666(1)	780(1)	22(1)
C(19)	5729(2)	8482(1)	498(1)	23(1)
C(20)	5569(1)	8057(1)	1336(1)	20(1)
C(21)	6357(1)	8808(1)	2477(1)	15(1)
C(22)	6318(1)	8344(1)	3377(1)	15(1)
C(23)	6939(1)	8987(1)	4545(1)	16(1)
C(24)	6698(1)	8122(1)	5058(1)	15(1)
C(25)	5943(1)	6967(1)	4194(1)	15(1)
C(26)	5414(1)	5815(1)	4290(1)	17(1)
C(27)	5665(2)	8331(1)	6510(1)	24(1)
C(28)	6145(2)	8513(1)	7752(1)	27(1)
C(29)	8734(2)	9599(1)	8183(1)	26(1)
C(30)	8343(2)	9453(1)	6957(1)	23(1)
N(1)	11779(1)	4060(1)	1338(1)	15(1)
N(2)	9909(1)	3312(1)	-1683(1)	16(1)
N(3)	5701(1)	7135(1)	3179(1)	15(1)

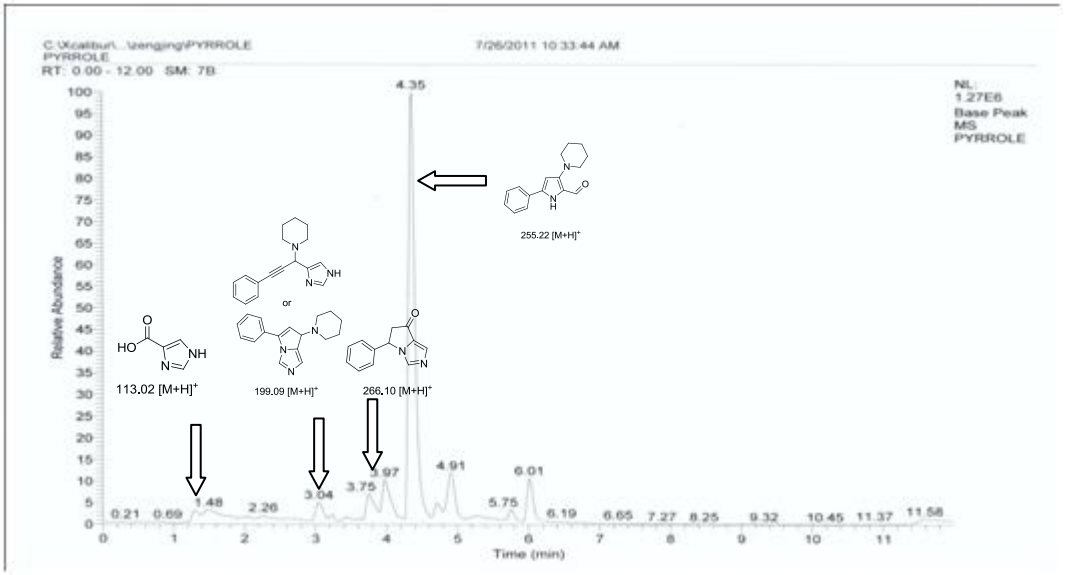
N(4)	7063(1)	8324(1)	6213(1)	16(1)
O(1)	14652(1)	5042(1)	1199(1)	21(1)
O(2)	8642(1)	2095(1)	-4078(1)	21(1)
O(3)	4542(1)	4856(1)	3498(1)	20(1)
O(4)	7368(1)	9635(1)	8447(1)	29(1)

Section E. X-ray diffraction profile of the precipitated powder and the reference pattern (vertical bars) of the JCPDS cards (Card No. 65-8428).

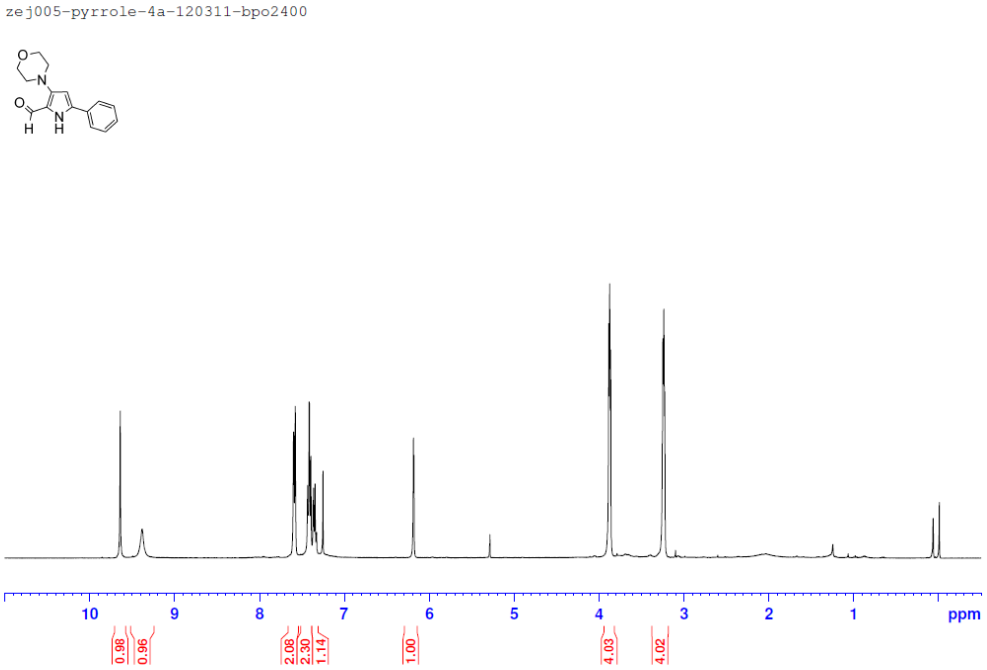


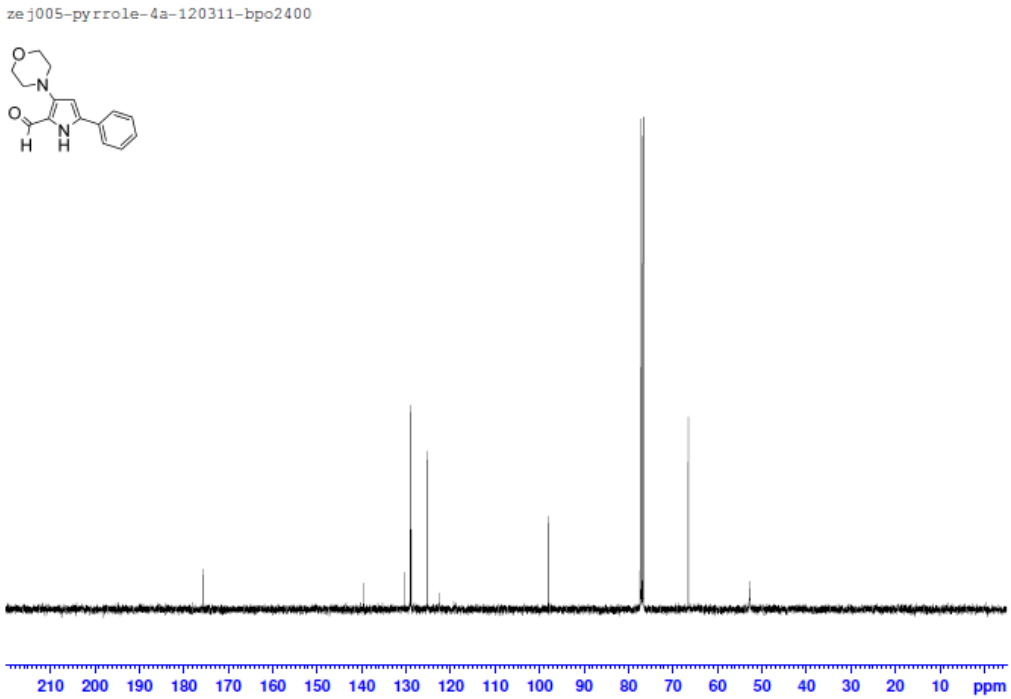
Two obvious peaks corresponding to the metallic Ag (111) and Ag (200) planes at 2θ values around 38.4 and 44.3 respectively were observed. The XRD pattern is in good agreement with the standard value (JCPDS card No. 65-8428), which strongly suggested that the Ag (I) was reduced to Ag (0) in the reaction. This process could explain the rationale behind the need for quantitative amount of silver salt.

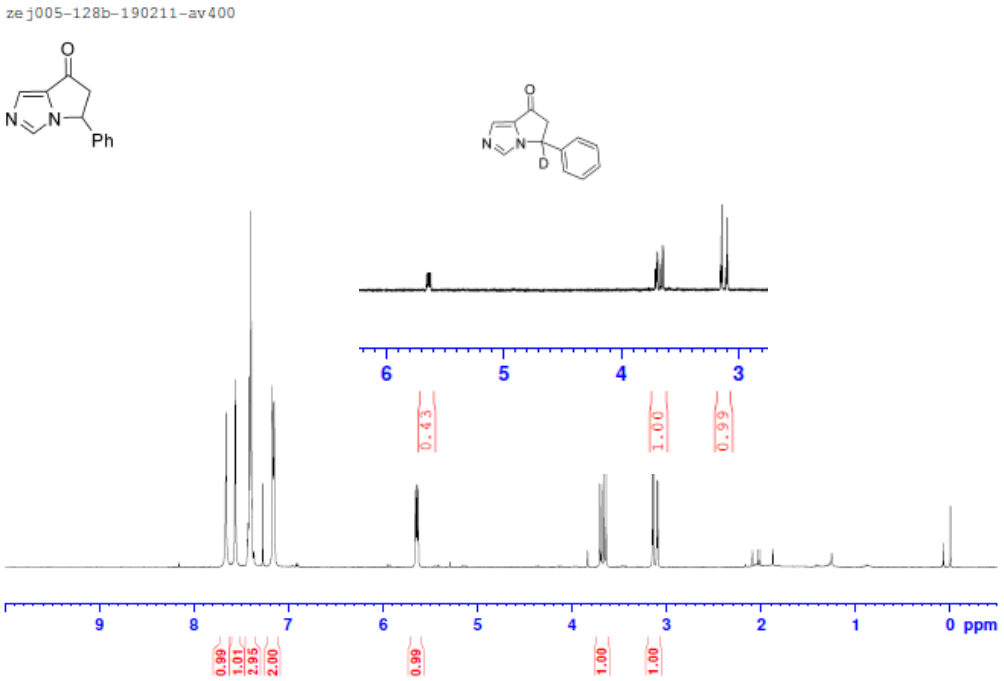
Section F. LCMs of reaction mixture



Section G. Copies of ^{1}H NMR and ^{13}C NMR Spectra



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N
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Ph
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N
N
D
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5
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3
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0.99
9
8
7
6
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2.95
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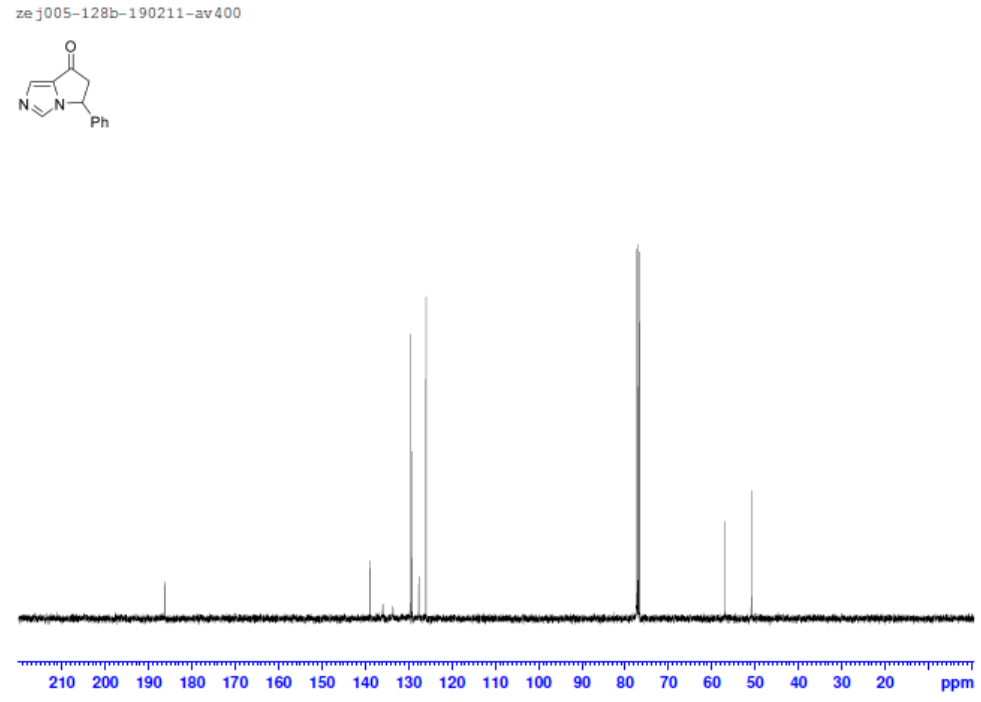
1.00
1.00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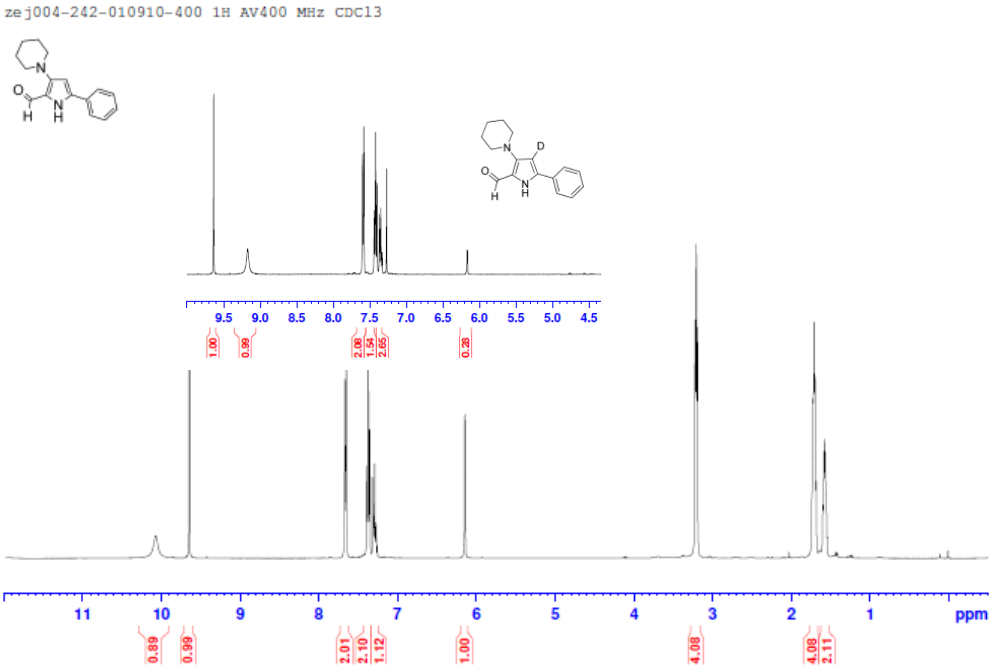
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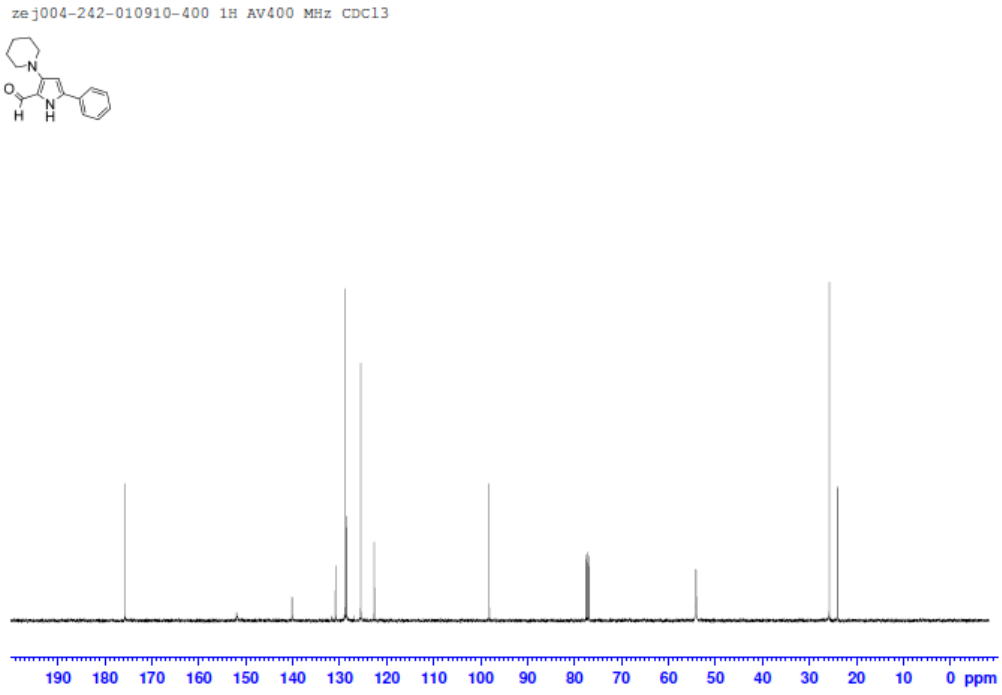
ppm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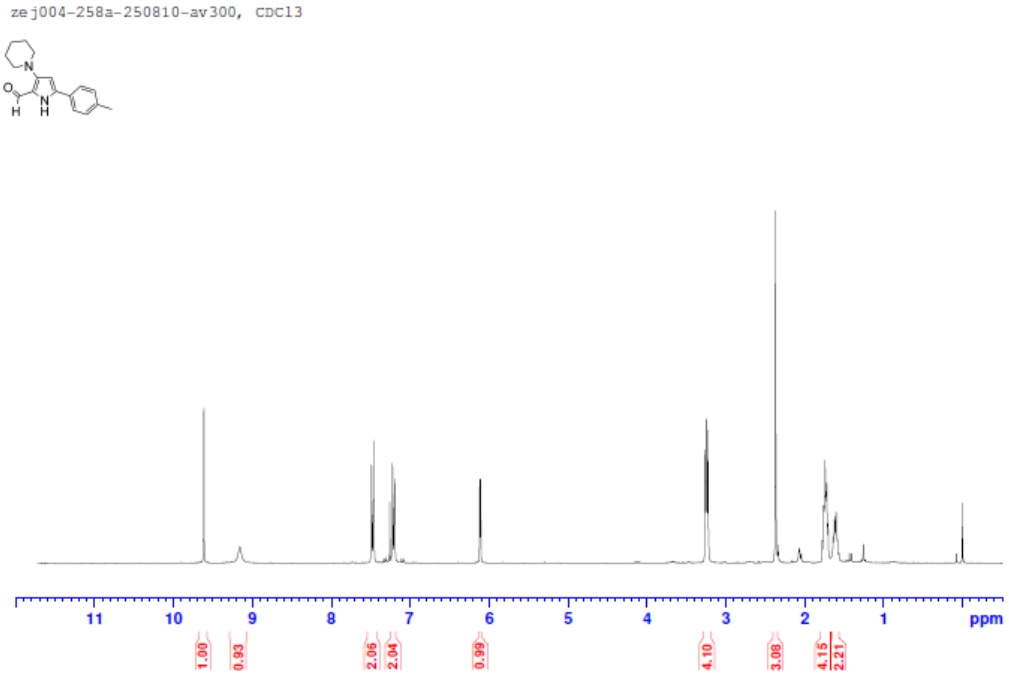
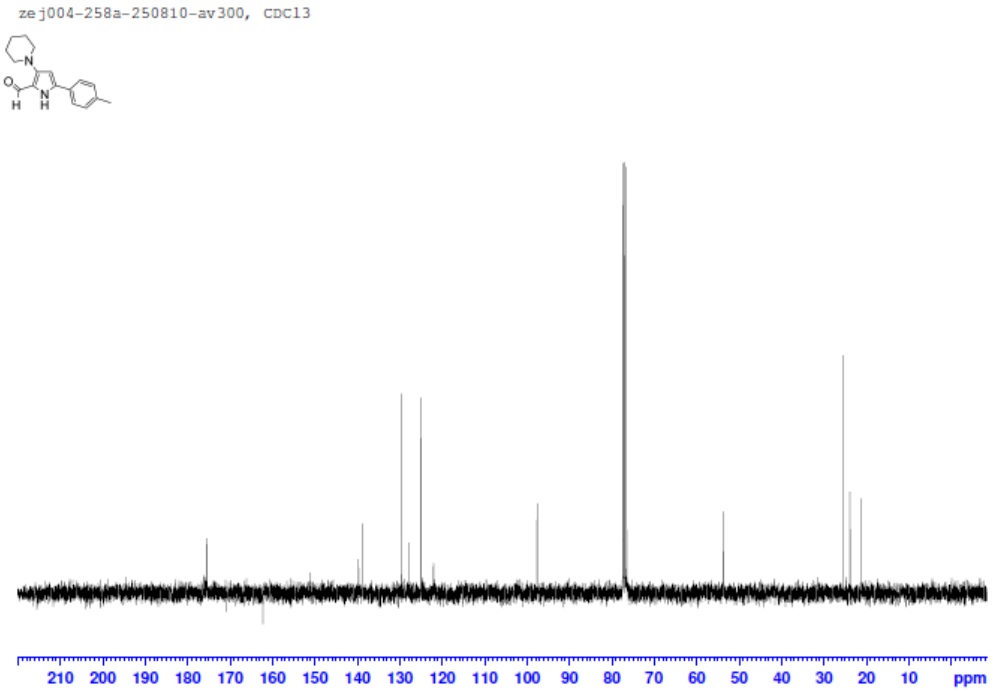
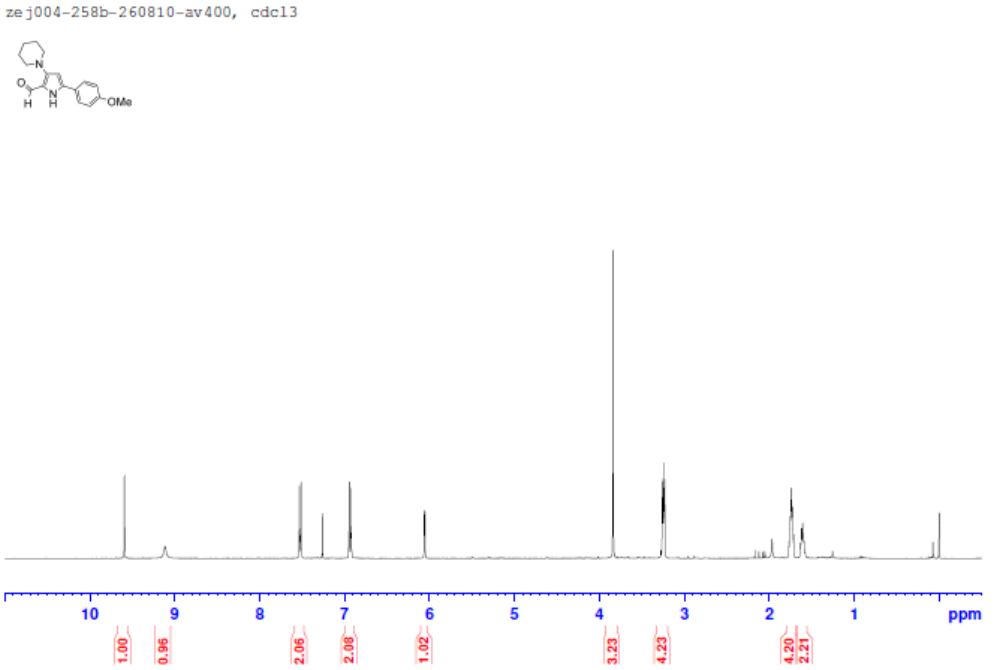
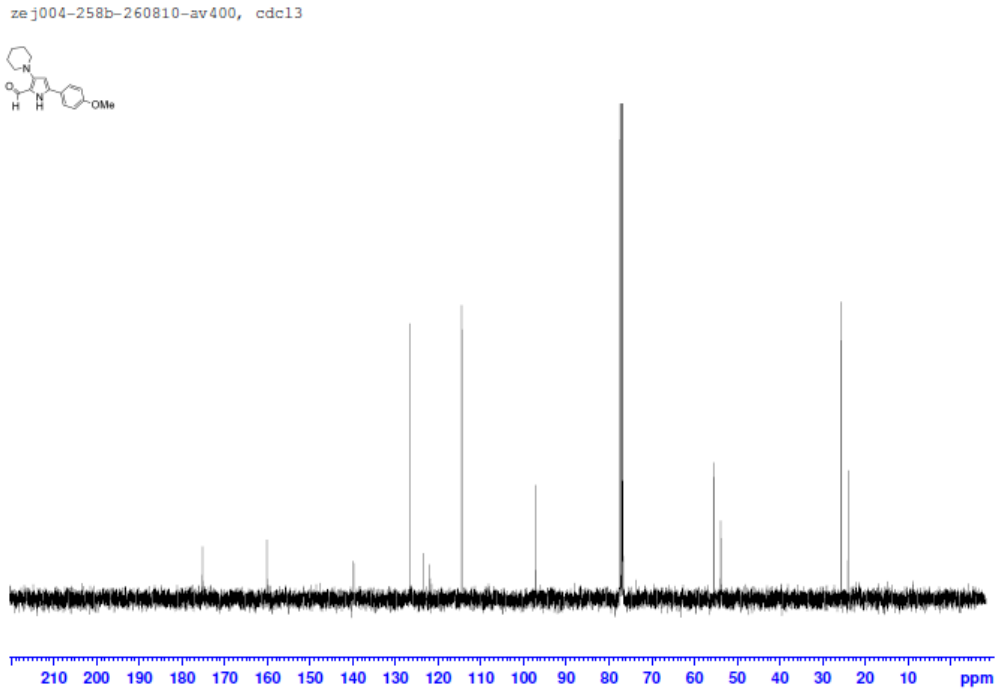
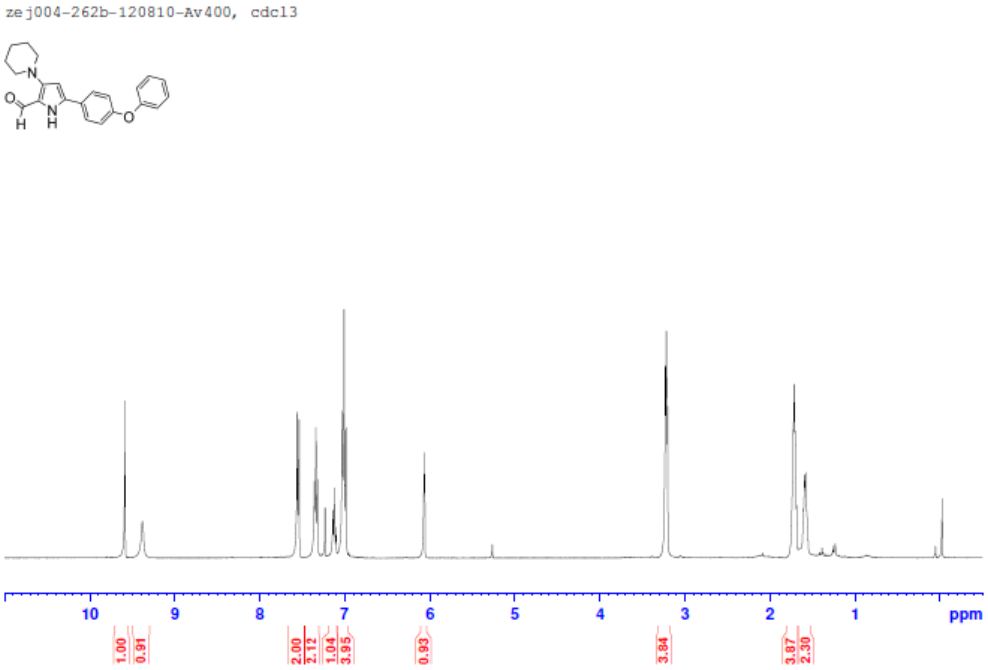
ppm

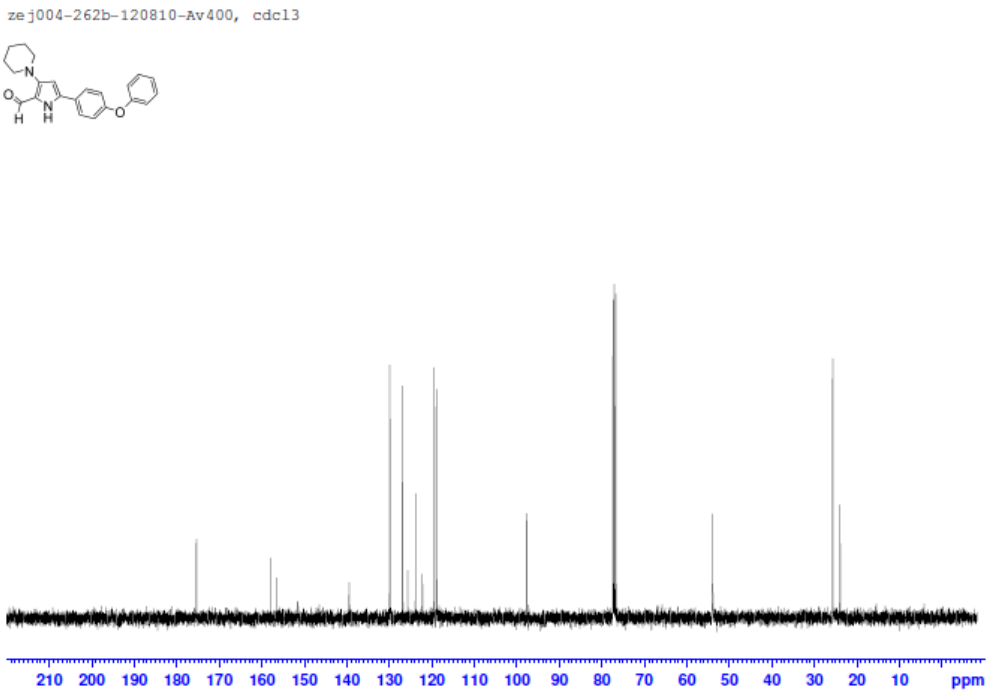


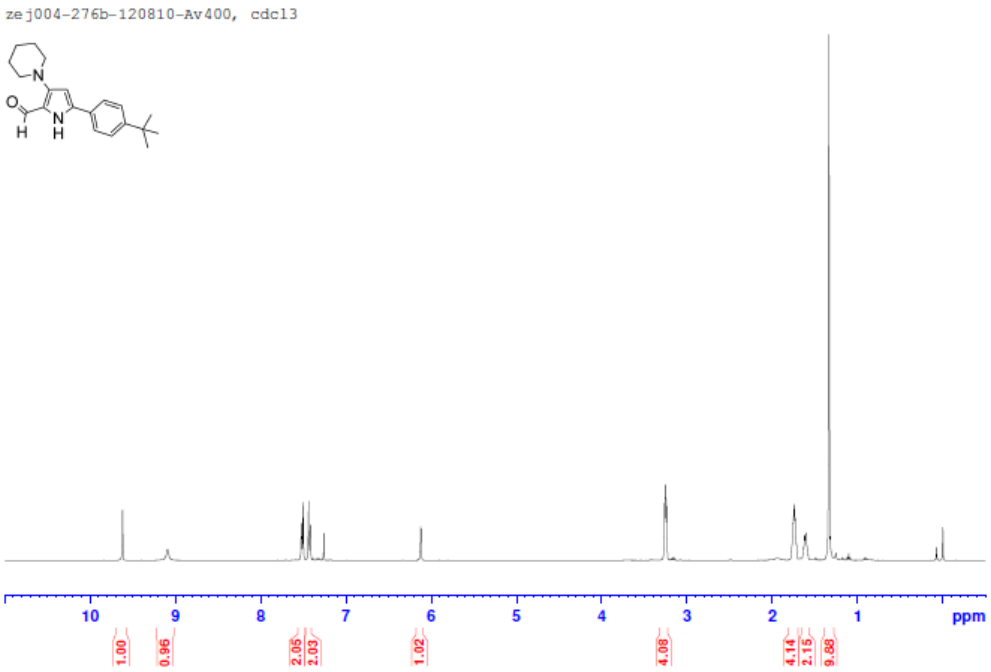








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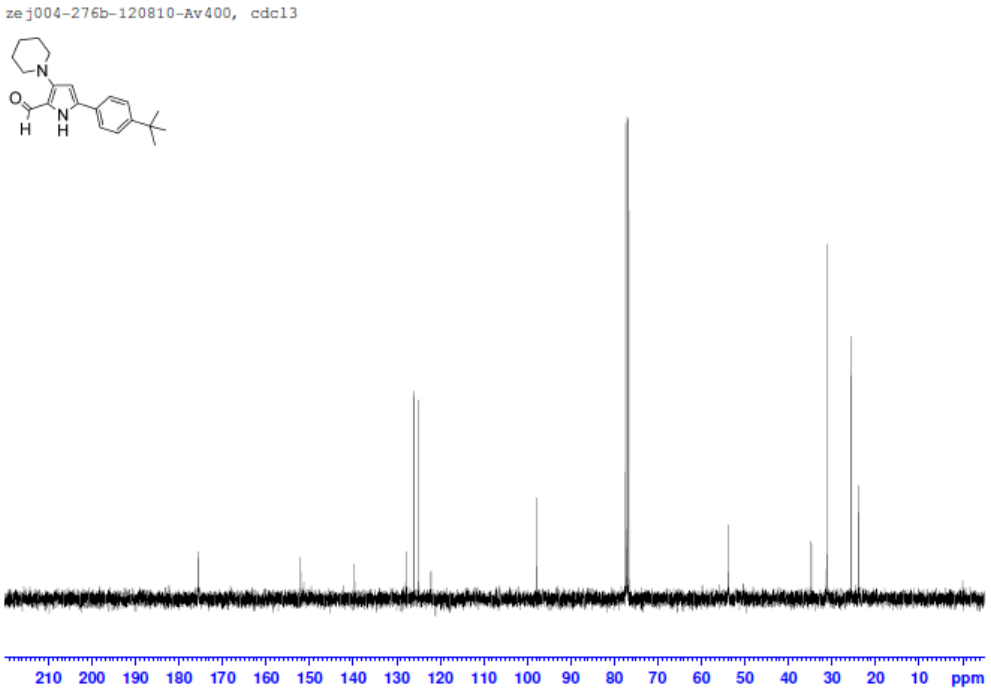
1.00 0.96 2.05 2.03 1.02 4.08 4.14 2.15 9.88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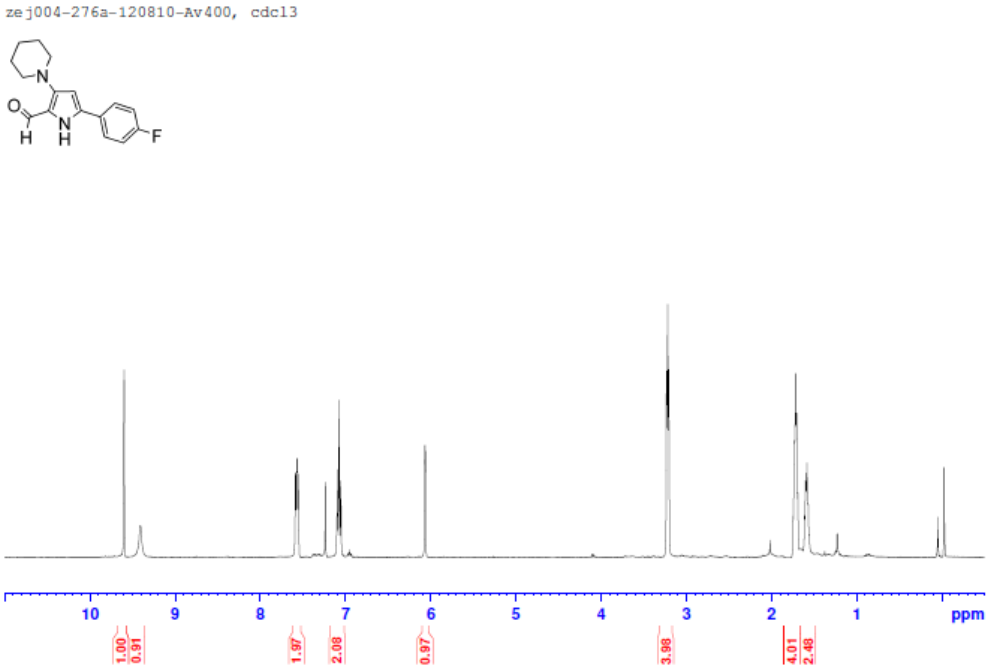
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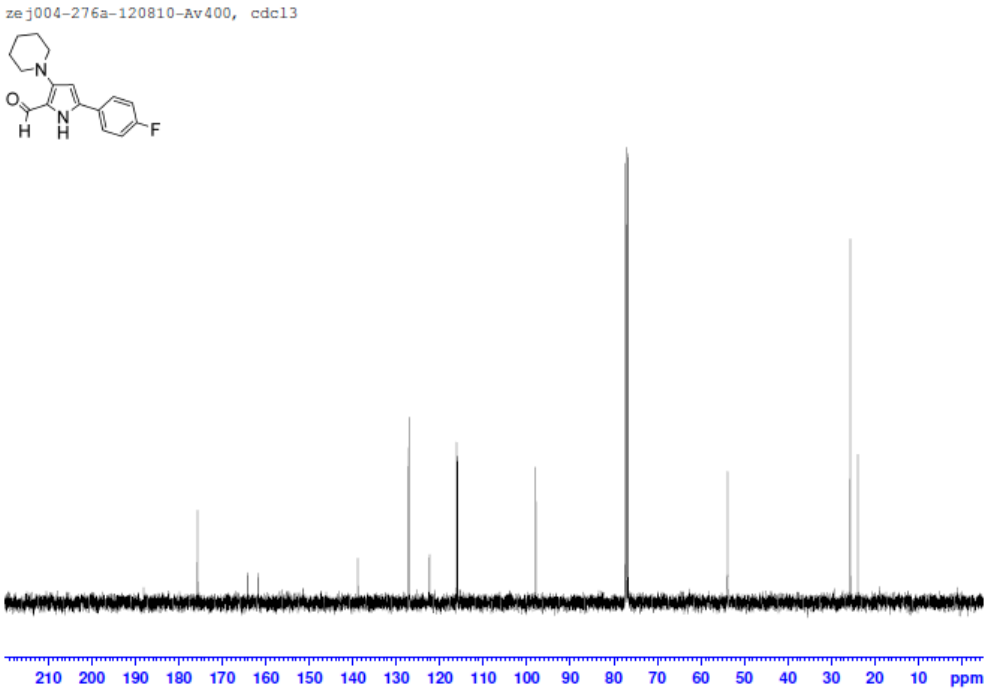
4.01
2.48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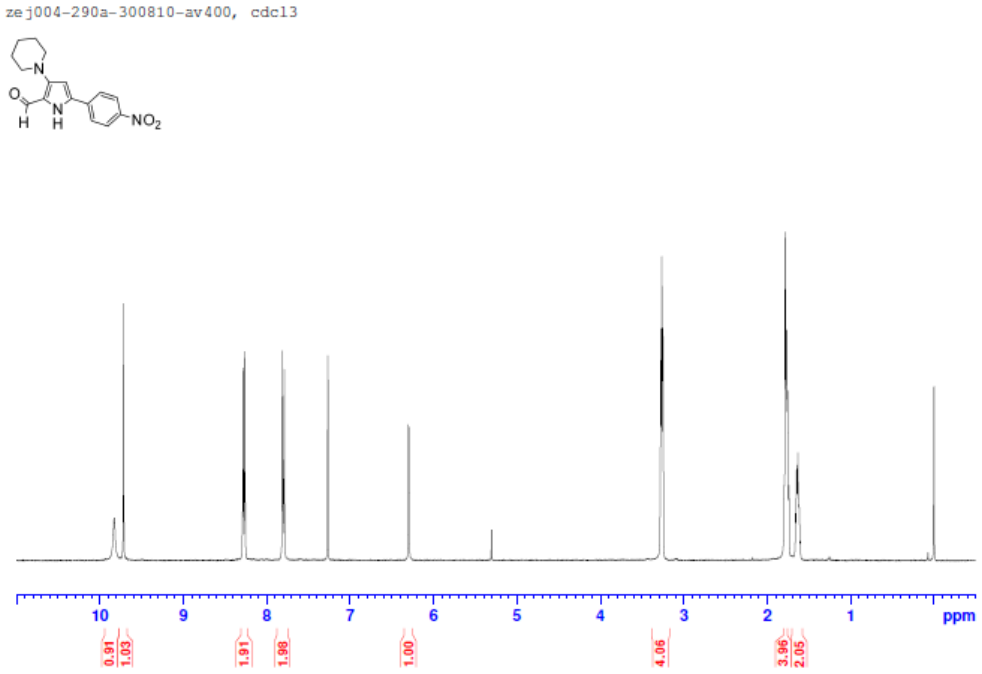

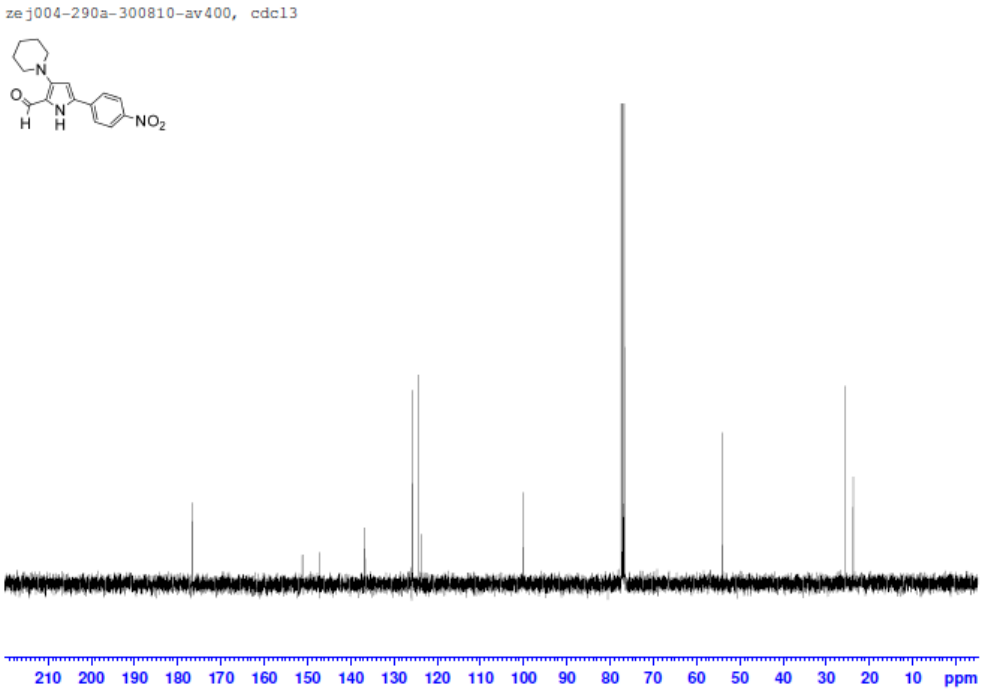

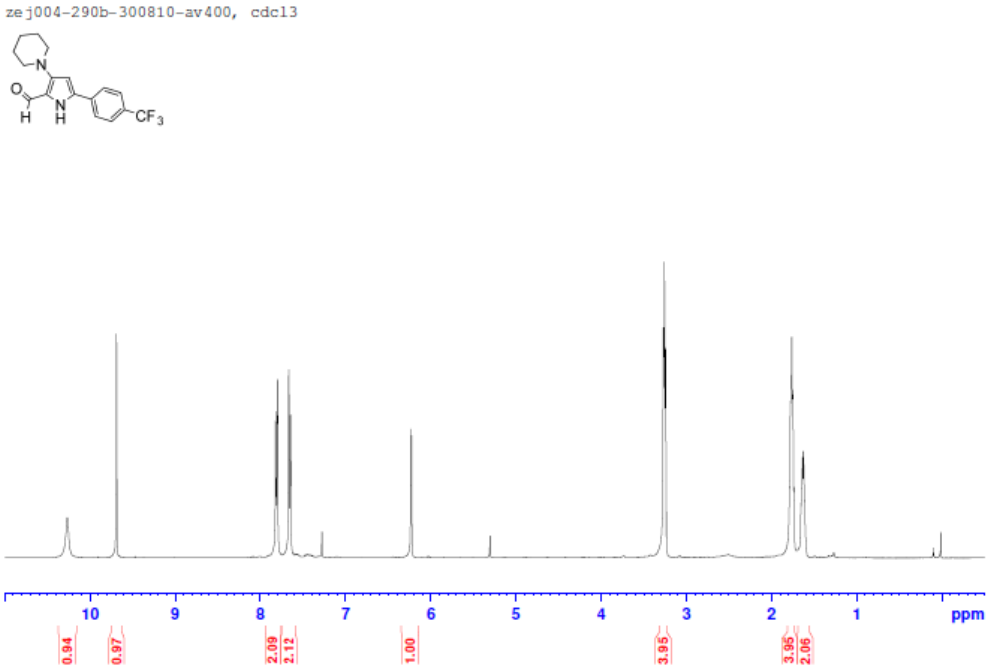

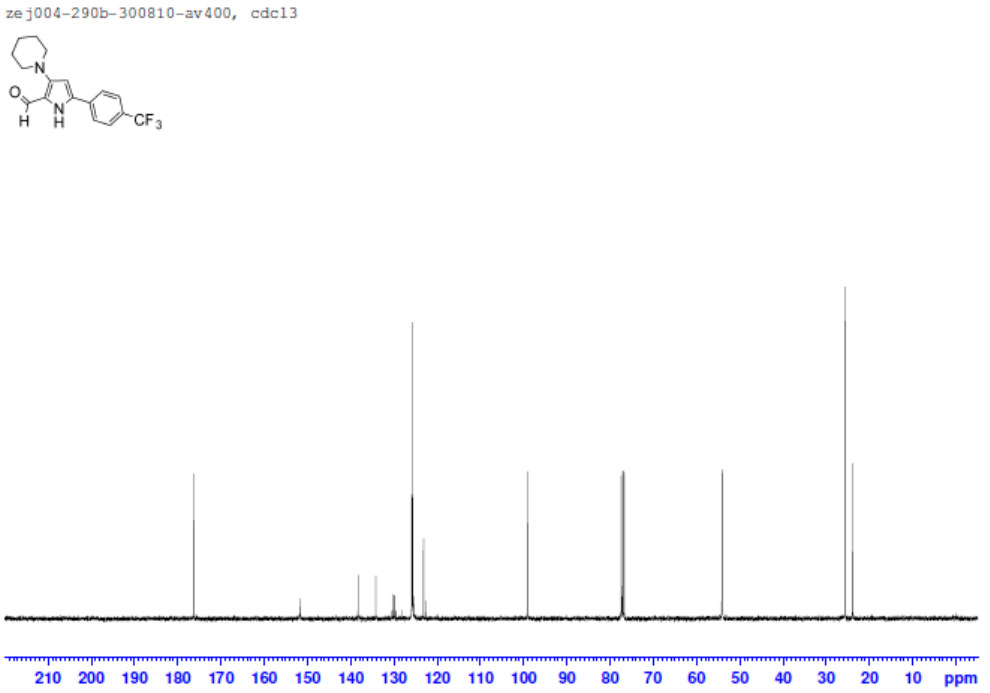

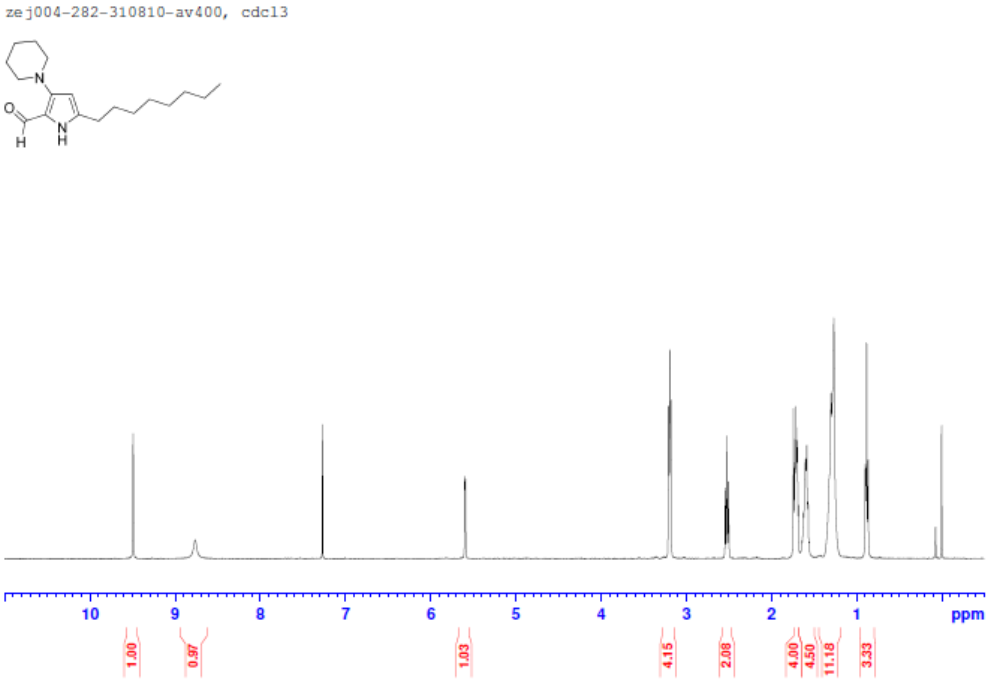

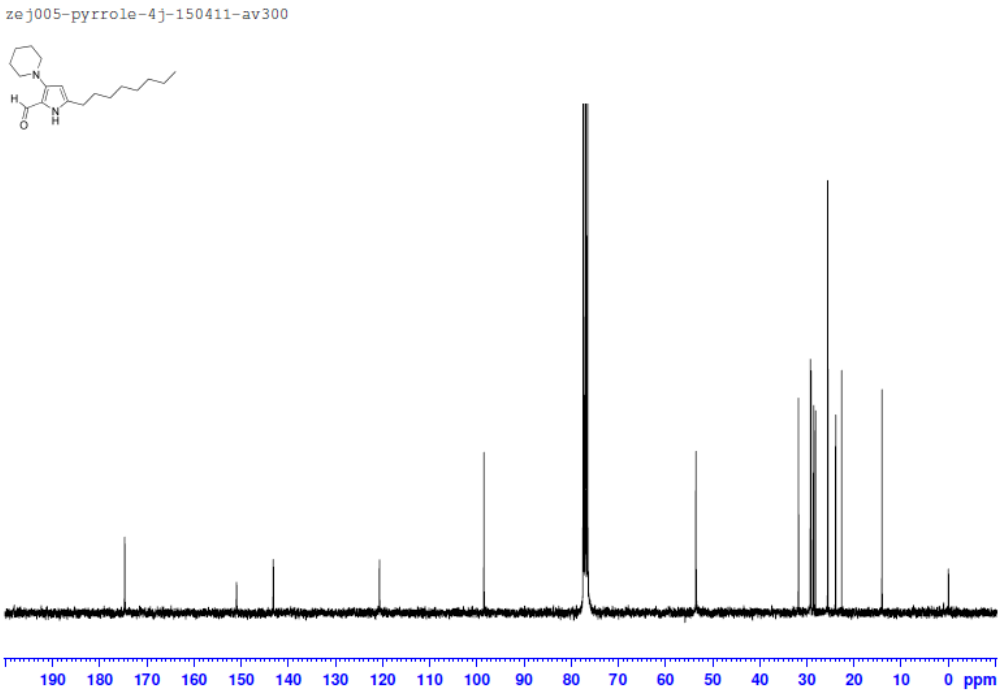

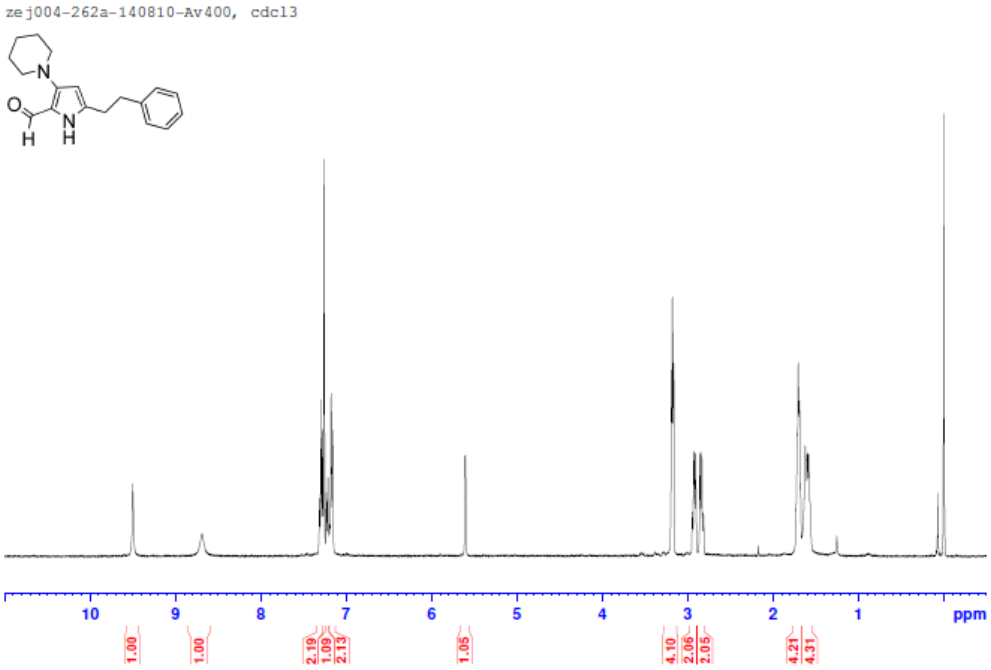

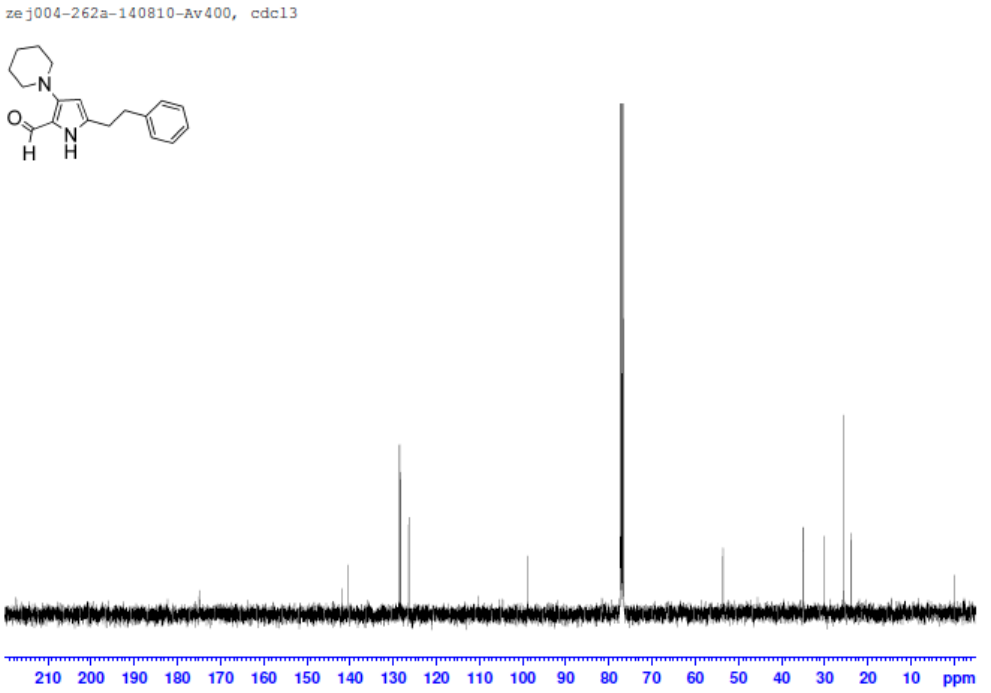

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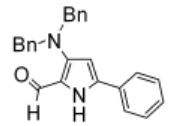
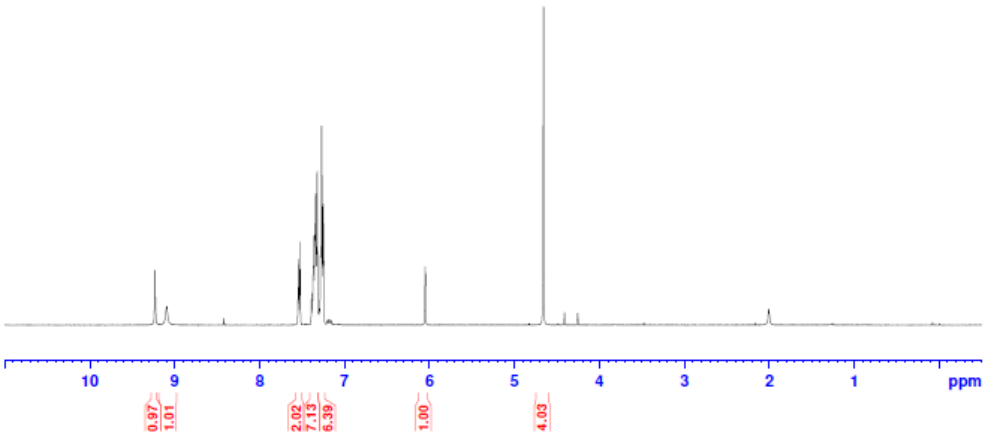
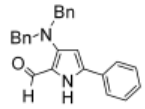
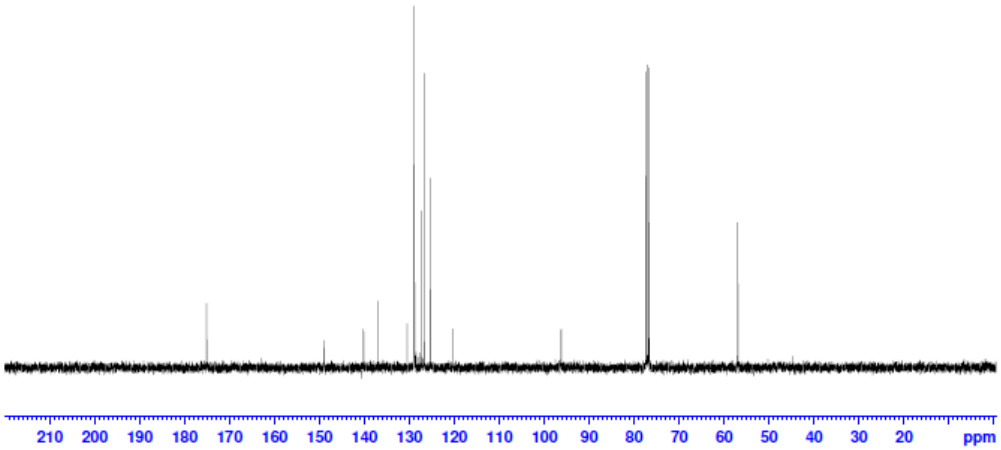
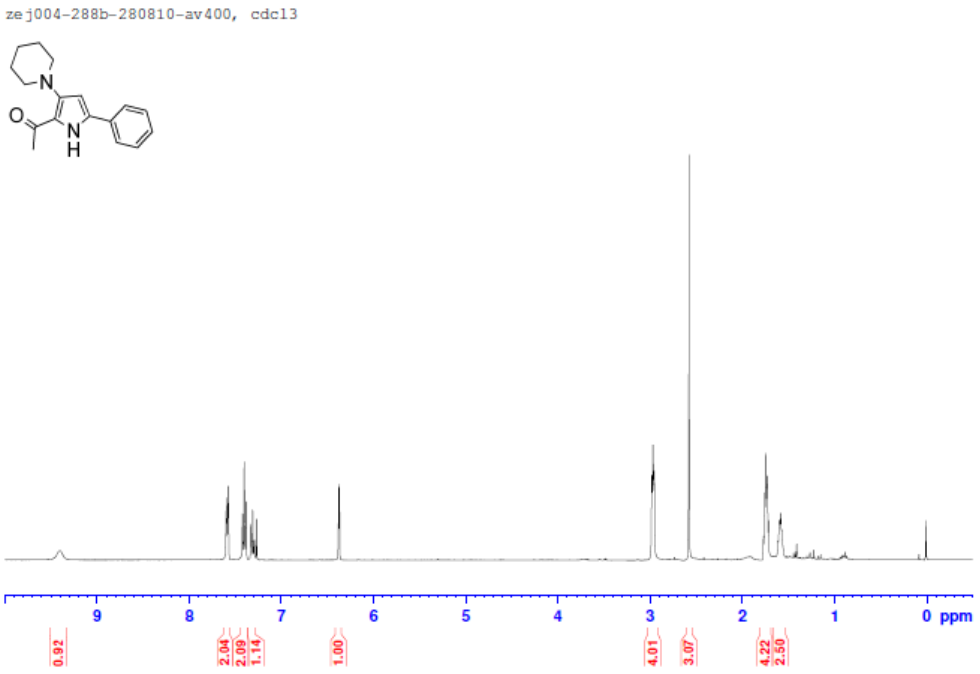


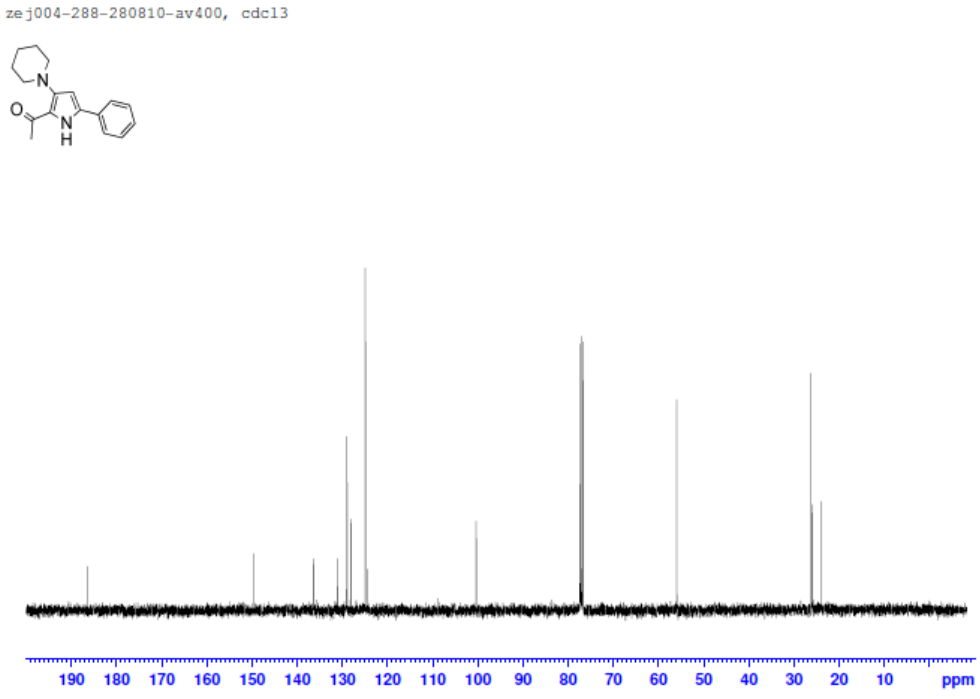


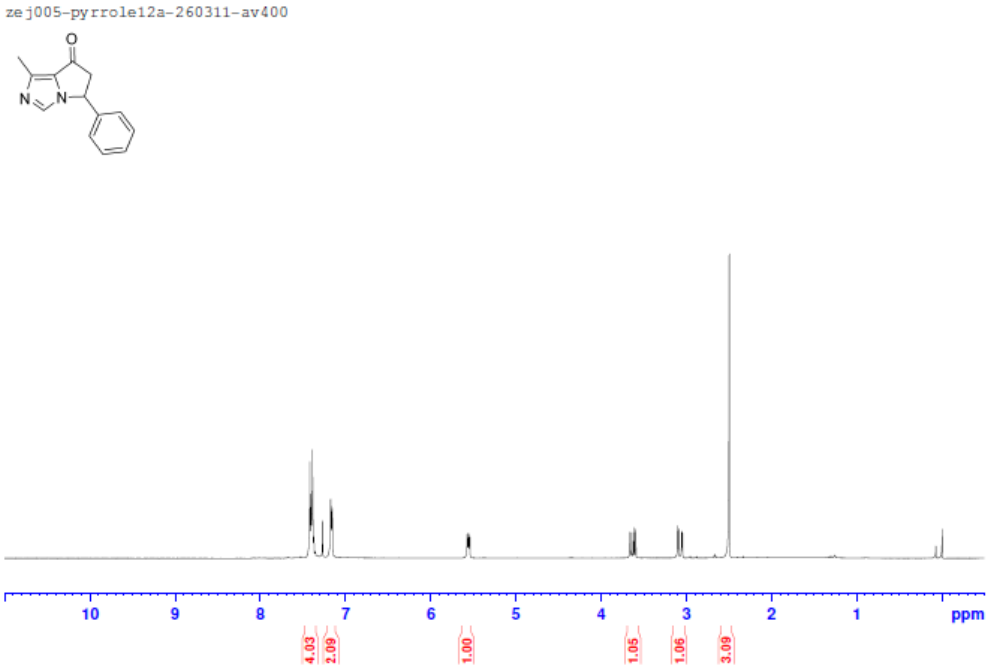
zej004-288a-180910-400 13c AV400 MHz CDCl3

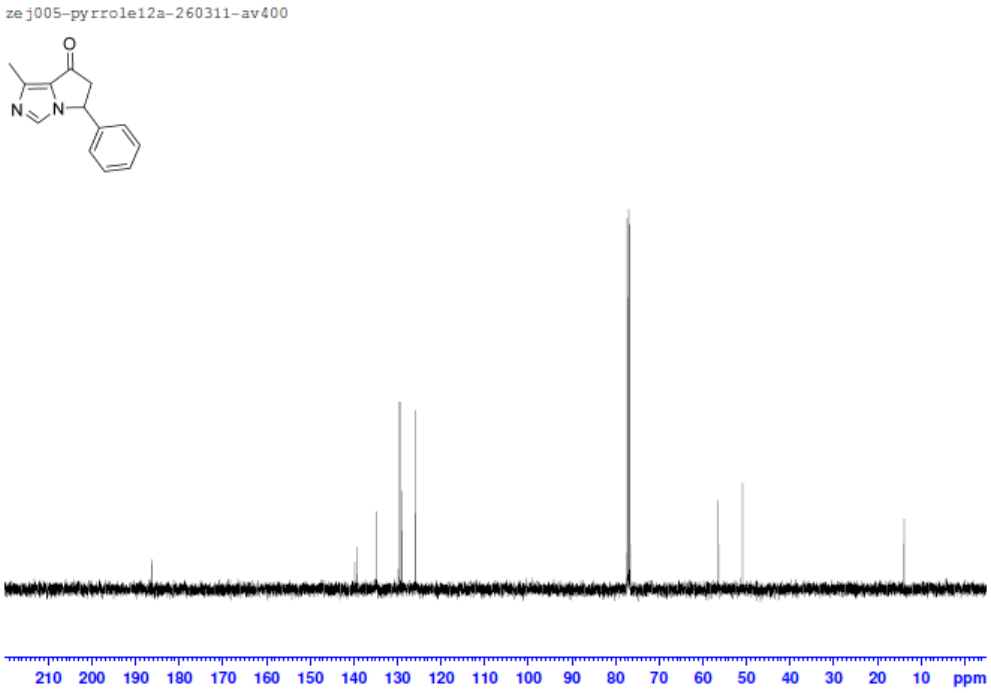


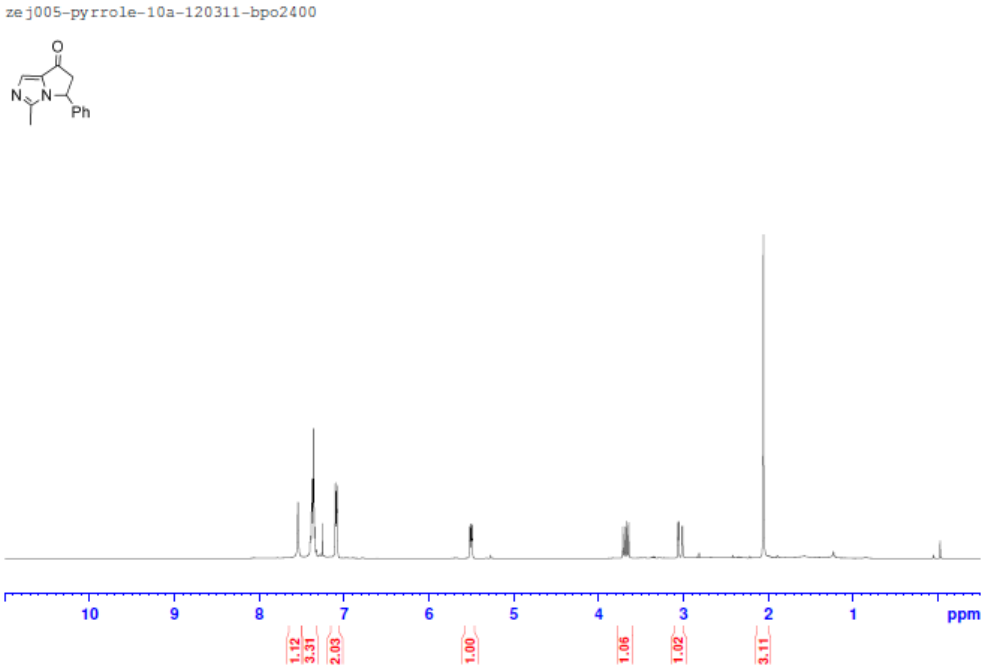


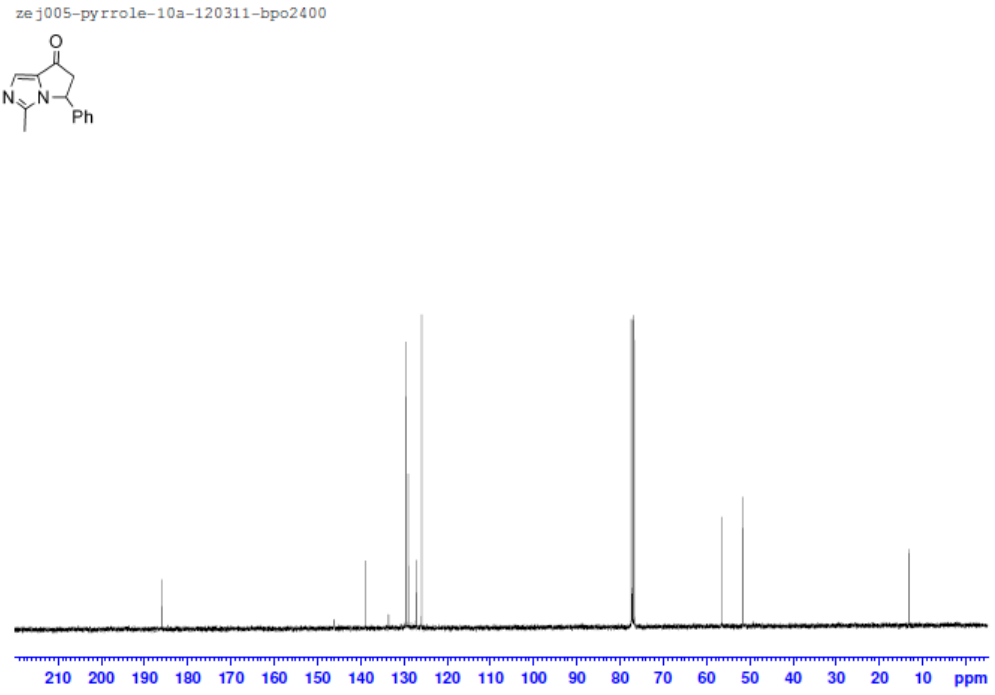

zej004-288b-280810-av400, cdcl3
9
8
7
6
5
4
3
2
1
0 ppm
0.92
2.04
2.09
1.14
1.00
4.01
3.07
4.22
2.50

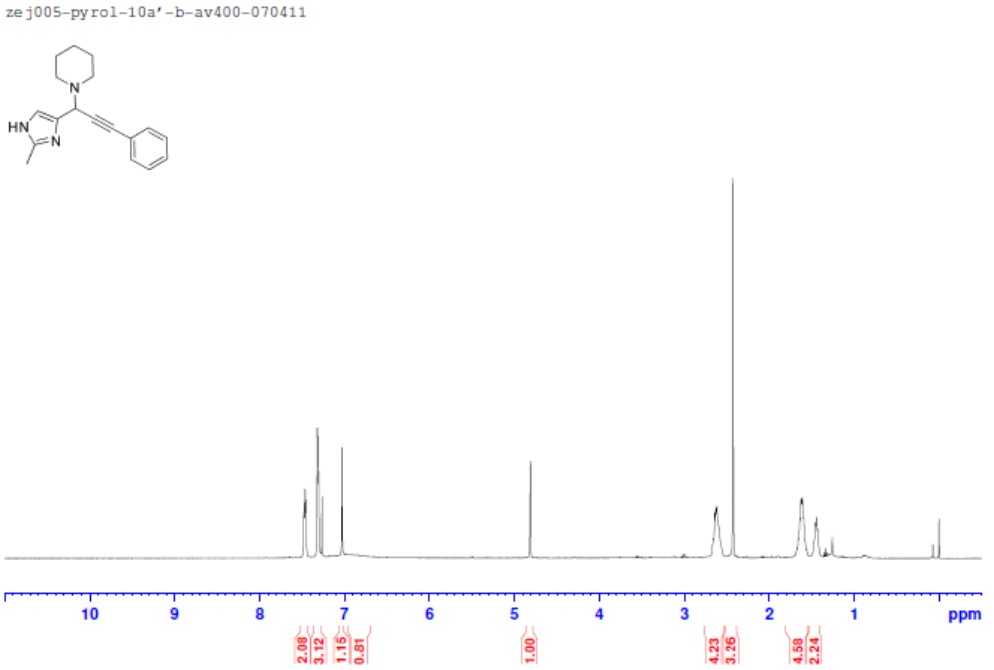

zej004-288-280810-av400, cdcl3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

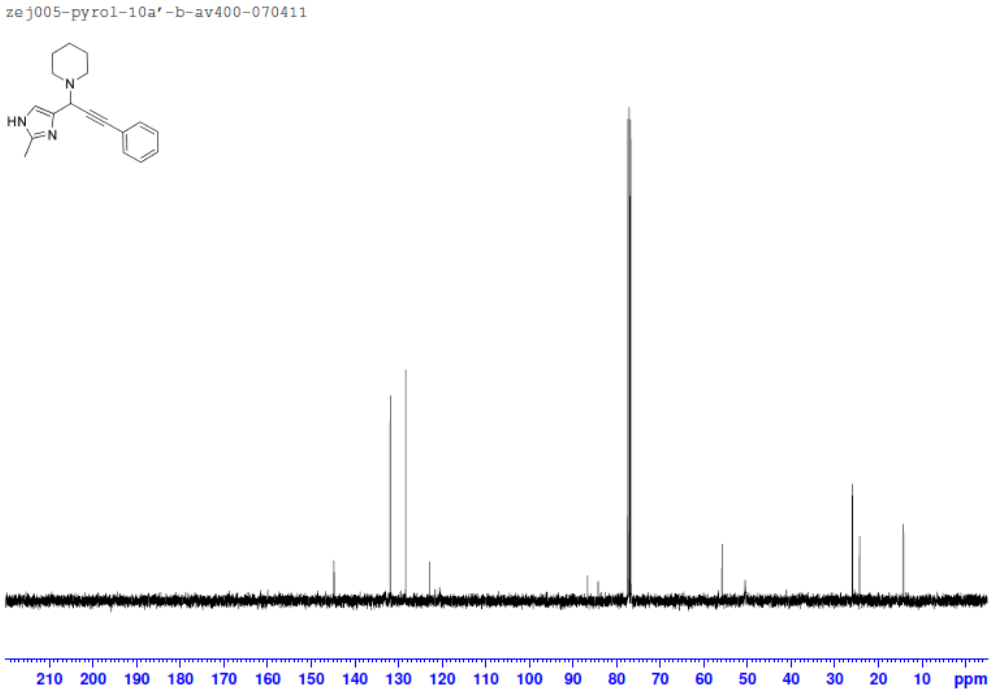


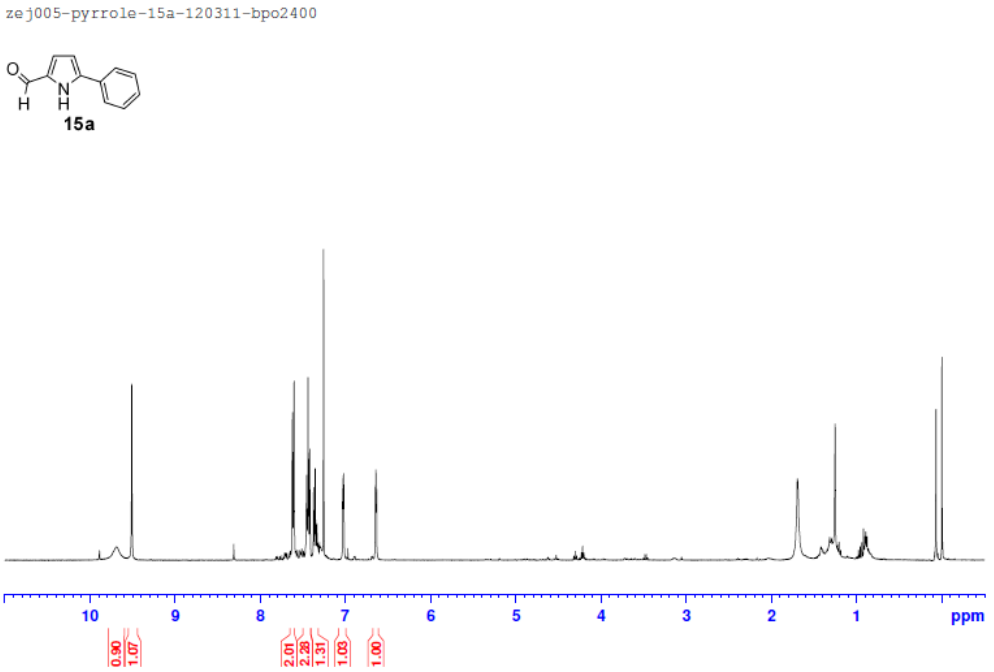


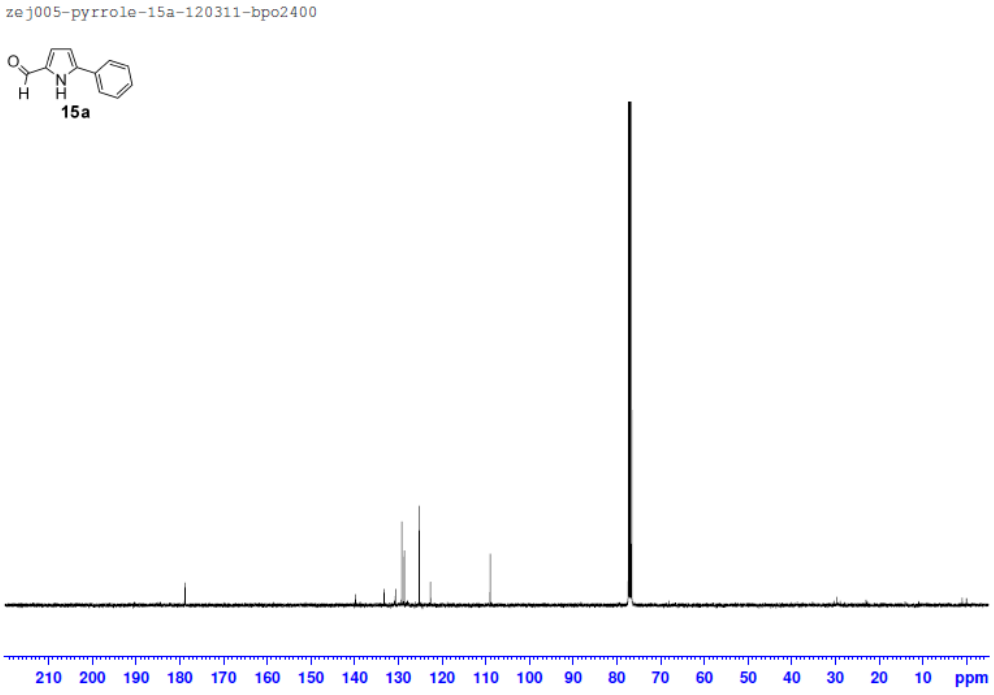

zej005-pyrrole-10a-120311-bpo2400
O
N
N
Ph
10
9
8
7
6
5
4
3
2
1
ppm
1.12
3.31
2.03
1.00
1.06
1.02
3.11

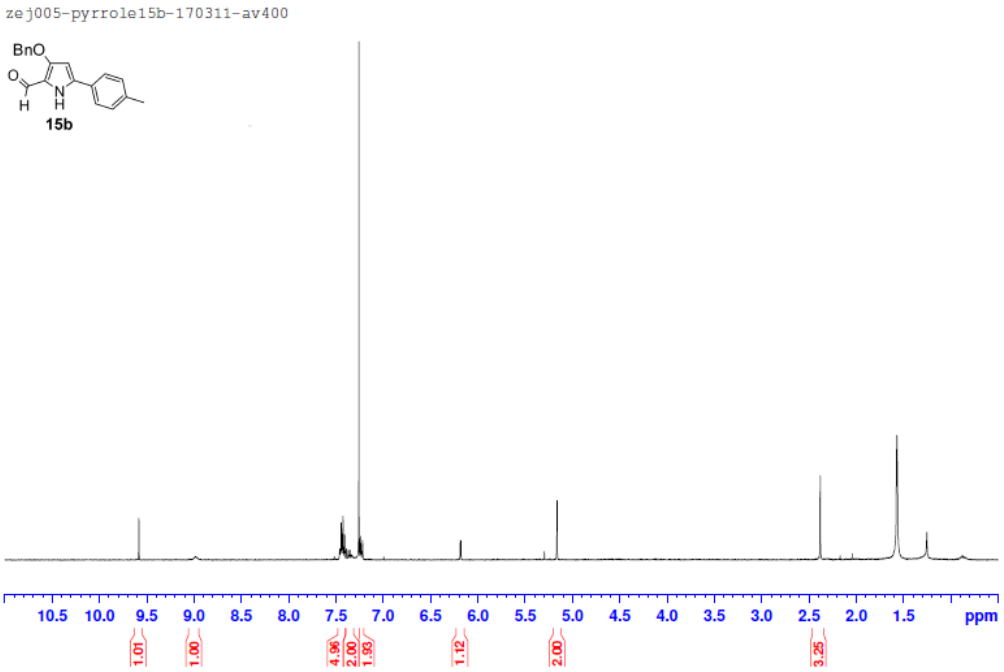

zej005-pyrrole-10a-120311-bpo2400
O
N
N
Ph
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

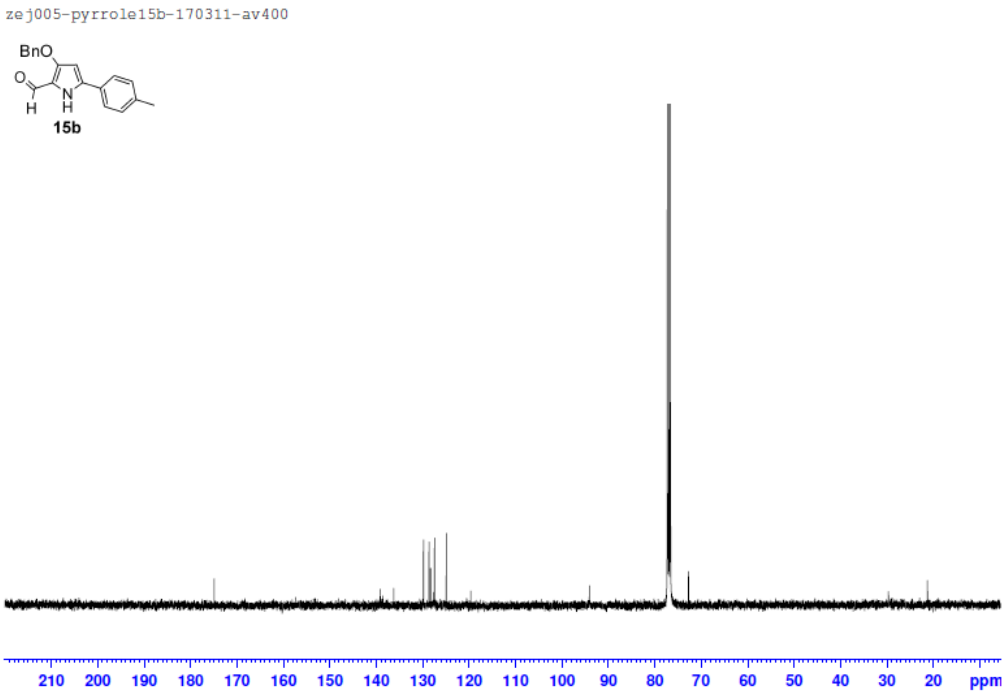

zej005-pyrol-10a'-b-av400-070411
HN
N
10
9
8
7
6
5
4
3
2
1
ppm
2.08
3.12
1.15
0.81
1.00
4.23
3.26
4.58
2.24


zej005-pyrol-10a'-b-av400-070411
HN
N
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm






zej005-pyrrole15b-170311-av400
BnO
O
H
N
H
15b
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 ppm
1.01
1.00
4.96
2.00
1.93
1.12
2.00
3.25


zej005-pyrrole15b-170311-av400
BnO
O
H
N
H
15b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm