Supporting Information

Synthetic Entries to Substituted Bicyclic Pyridones.

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The numbering system used in the Supporting Information is that used in the accompanying paper. Additional numbers have been assigned to intermediates (not shown in the paper) and these are linked clearly to the structure involved.

General Experimental Details:

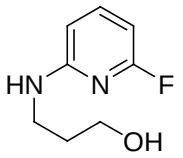
Starting materials sourced from commercial suppliers were used as received. Dry solvents, where necessary, were obtained by distillation using standard procedures or by passage through a column of anhydrous alumina using equipment from Anhydrous Engineering based on the Grubbs' design. Petroleum ether refers to the fraction of petroleum ether boiling in the range of 40-60 °C. The removal of solvents *in vacuo* was achieved using both a Büchi rotary evaporator (bath temperatures up to 40 °C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump), as appropriate, and a high vacuum line at room temperature. Reactions requiring anhydrous conditions were run under an atmosphere of dry nitrogen; glassware, syringes and needles were either flame dried immediately prior to use or placed in an oven (150 °C) for at least 2 hours and allowed to cool either in desiccators or under an atmosphere of dry nitrogen; liquid reagents, solutions or solvents were added *via* syringe through rubber septa; solid reagents were added *via* Schlenk type adapters. Commercially available Merck Kieselgel $60F_{254}$ aluminium backed plates were used for TLC analysis. Visualisation was achieved by either UV fluorescence, acidic $KMnO_4$ solution and heat, ninhydrin stain and heat, ammonium molybdate solution and heat or iodine vapour. Flash column chromatography (FCC) was performed using Fluorochem 60 silica: 230-400 mesh (40-63 μm). The crude material was applied to

the column as a solution in CH_2Cl_2 or by pre-adsorption onto silica, as appropriate. Analytical HPLC was performed on a Hiatchi D700 series apparatus fitted with a UV detector and an Agilent Zorbax Eclipse XDB-C8 column (4.6 × 150 mm), eluting at 1mL/min at 20 °C. Retention times (t_R) are quoted with the eluting solvent with the following notation; "95/5-5/95(15) H_2O/MeCN + TFA" meaning the eluting solvent gradient was from 95% H_2O to 95% MeCN, plus 0.01% TFA, over 15 minutes. Melting points were determined using a Reichert melting point table and temperature controller and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Elemental analysis was performed by the University of Bristol microanalytical service. Infra-red spectra were recorded in the range 4000-600 cm^{-1} on a Perkin Elmer Spectrum either as neat oils, solids compressed onto a diamond window or as thin films after the evaporation of loading solvent (solvents used are shown in parentheses). Abbreviations used are: w (weak), m (medium), s (strong) and br (broad). NMR spectra were recorded on a JEOL GX270, JEOL GX400, JEOL Lambda 300, JEOL Eclipse 400, JEOL Eclipse 300 or JEOL Alpha 500 spectrometer. Chemical shifts are quoted in parts per million (ppm); ^1H NMR spectra are referenced to TMS or residual protons of the deuterated solvent; ^{13}C NMR are referenced to TMS or the deuterated solvent. Coupling constants (*J*) are quoted to the nearest 0.5 Hz. Other abbreviations used are: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet) m (multiplet) and br (broad). Assignments of ^1H NMR and ^{13}C NMR signals were made where possible, using COSY, DEPT, HMQC and HMBC experiments.. Mass spectra were determined by the University of Bristol mass spectrometry service by either electron impact (EI) or chemical ionisation (CI) using a Fisons VG Analytical Autospec spectrometer, or by electrospray ionisation (ESI) using a Brüker Daltonics Apex IV spectrometer.

General procedure for reaction of amino alcohols with 2,6-difluoropyridine

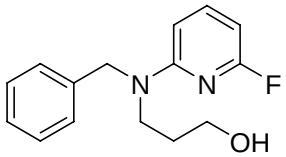
The requisite amino alcohol was added to a solution of 2,6-difluoropyridine **5** in ethanol or dioxane. This mixture was degassed using a sonic bath and then transferred into a sealed tube and heated until TLC showed starting material had been consumed; temperature and time used are indicated in each case. The reaction mixture was preabsorbed onto silica gel using a rotary evaporator, and purified by the column chromatography; eluent and R_f values are indicated in each case. Details for individual compounds, together with characterization data of adducts are presented below.

2-Fluoro-6-(*N*-3-hydroxypropyl)aminopyridine (6)



3-Amino-1-propanol (3.8 mL, 50 mmol) and 2,6-difluoropyridine (0.454 mL, 5 mmol) in ethanol (10 mL) were heated at 90 °C for 2 hours. Chromatography (eluting with ethyl acetate; $R_f = 0.4$) gave the title compound **6** (0.81 g, 95 %) as colorless crystals. m.p 50 °C (ethyl acetate). (Found: C, 56.32; H, 6.66; N, 16.33. $C_8H_{11}FN_2O$ requires C, 56.46; H, 6.51; N, 16.46); (Found: M^++H, 171.0939. $C_8H_{12}FON_2$ requires 171.0934); υ_{max} (CH_2Cl_2) /cm^{-1} 3320, 2944, 2832, 1227, 927; δ_H (400 MHz, $CDCl_3$) 7.43 (1H, q , *J* 8 Hz), 6.20 (1H, dd, *J* 8, 2 Hz), 6.10 (1 H, dd, *J* 8, 2 Hz), 4.80 (1 H, br), 3.70 (2 H, q, *J* 6 Hz), 3.47 (2H, q, *J* 6 Hz), 1.79 (2H, quin, *J* 6 Hz); δ_C (100.5 MHz, $CDCl_3$) 163.2 (d, *J* 236 Hz), 158.4 (d, *J* 16 Hz), 141.7 (d, *J* 8 Hz), 103.4 (d, *J* 5 Hz), 95.5 (d , *J* 36 Hz), 59.6; 38.9; 32.1.

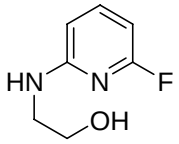
2-Fluoro-6-(*N*-benzyl-*N*-3-hydroxypropyl)aminopyridine (10)



N-Benzyl-3-amino-1-propanol (0.779 g, 4.7 mmol) and 2,6-difluoropyridine (0.288 g , 2.5 mmol) in dioxane (10 mL) were heated at 140 °C for 48 hours. Chromatography (eluting with 1:1 ethyl acetate/petroleum ether; $R_f = 0.5$) gave the title compound **10** (0.57 g, 87 %) as a colorless oil. (Found: C, 69.32; H, 6.61; N, 10.82 $C_{15}H_{17}FN_2O$

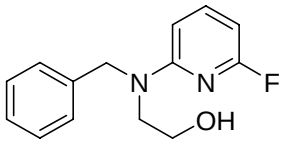
requires C, 69.21; H, 6.58; N, 10.76); (Found: M^++H, 261.1393 $C_{15}H_{17}FN_2O$ requires 261.1403); υ_{max} (neat) /cm^{-1} 3332, 1619, 1502; δ_H (270 MHz, $CDCl_3$) 7.45-7.16 (6H, m), 6.22 (1H, dd, *J* 8, 3 Hz), 6.10 (1H, dd, *J* 8, 3 Hz), 4.60 (2H, s), 3.74 (2H, t, *J* 6 Hz), 3.60 (2H, q, *J* 6 Hz), 1.78 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 162.7 (d, *J* 237 Hz), 158.1 (d, *J* 15 Hz), 141.9 (d, *J* 8 Hz),137.0, 128.7, 127.1, 126.3, 102.3(d, *J* 4 Hz), 94.7(d, *J* 36 Hz), 58.5, 51.6, 44.5, 30.5.

2-Fluoro-6-(*N*-2-hydroxyethyl)aminopyridine (8)



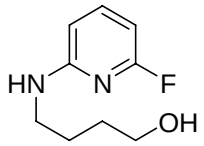
Ethanolamine (12 mL, 0.2 mol) and 2,6-difluoropyridine (1.83 mL, 20 mmol) in ethanol (40 mL) were heated at 90 °C for 18 hours. Chromatography (eluting with ethyl acetate; R_f = 0.40) gave the title compound **8** (3.11 g, 99 %) as a colorless oil. (Found: C, 53.56; H, 5.97; N, 18.23; $C_7H_9FN_2O$ requires C, 53.84; H, 5.81; N, 17.94); υ_{max} (neat) /cm^{-1} 3326, 2931, 2877, 1222; δ_H (400 MHz, $CDCl_3$) 7.44 (1H, app. q, *J* 8 Hz), 6.25 (1H, d, *J* 8 Hz), 6.13 (1H, d, *J* 8 Hz), 3.81 (2H, t, *J* 5 Hz), 3.47 (2H, t, *J* 5 Hz); δ_C (100.6 MHz, $CDCl_3$): 163.3 (d, *J* 239 Hz), 158.2, 141.7, 103.6, 95.7 (d, *J* 36 Hz), 61.9, 44.4.

2-Fluoro-6-(*N*-benzyl-*N*-3-hydroxyethyl)aminopyridine (9)



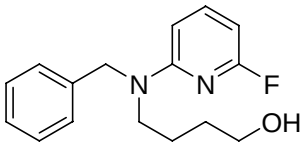
N-Benzylethanolamine (18 g, 0.12 mol) and 2,6-difluoropyridine (1.10 mL, 12 mmol) in ethanol (10 mL) were heated at 120 °C for 72 hours. Chromatography (eluting with 1:1 ethyl acetate/ petroleum ether; R_f = 0.42) gave the title compound **9** (2.95 g, 81 %) as a pale yellow oil. (Found: M^++H, 247.1237. $C_{14}H_{16}FN_2O$ requires 247.1247); υ_{max} (neat) /cm^{-1} 3365, 2927, 2880, 1223; δ_H (400 MHz, CD_3OD) 7.49 (1H, app. q, *J* 8.5 Hz), 7.32-7.25 (2H, m), 7.24-7.18 (3H, m), 6.38 (1H, dd, *J* 8, 2.5 Hz), 6.11 (1H, dd, *J* 8, 2.5 Hz), 4.78 (2H, s), 3.74 (2H, t, *J* 6 Hz), 3.66 (2H, t, *J* 6 Hz); δ_C (100.6 MHz, CD_3OD) 162.9 (d, *J* 234 Hz), 157.8 (d, *J* 16 Hz), 141.7, 138.3, 128.3, 126.8, 126.6, 102.3, 94.0 (d, *J* 37 Hz), 59.3, 52.3, 50.6.

2-Fluoro-6-(*N*-4'-hydroxybutyl)aminopyridine (11)



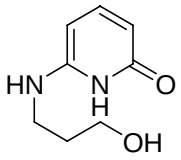
4-Aminobutan-1-ol (0.8 mL, 8.86 mmol) and 2,6-difluoropyridine (78 μL, 0.868 mmol) in ethanol (2 mL) were heated at 120 °C for 3 hours. Chromatography (eluting, with ethyl actetate; $R_f = 0.5$) gave the title compound **11** (0.132 g, 83 %) as a colorless oil. (Found: M^++H 184.1007 $C_9H_{13}FN_2O$ requires 184.1012); υ_{max}(neat) /cm^{-1} 3266, 2935, 1619, 1439; δ_H (270 MHz, $CDCl_3$) 7.45 (1H, q, *J* 8 Hz), 6.18 (2H, dd, *J* 8, 2 Hz), 6.11 (2H, dd, *J* 8, 2 Hz), 4.84 (1H, br), 3.69 (2H, t, *J* 6, 5 Hz), 3.29 (2H, d, *J* 6, 5 Hz), 2.25 (1H, br), 1.59-1.75 (4H, m); δ_C (100.6 MHz, $CDCl_3$) 163.3 (d, *J* 237 Hz); 158.2 (d, *J* 17 Hz), 141.8 (d, *J* 9 Hz), 102.6, 95.4, 62.4, 41.9, 29.9, 25.9.

2-Fluoro-6-(*N*-benzyl-*N*-3'-hydroxybutyl)aminopyridine (12)



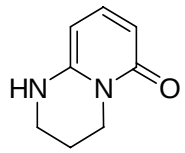
N-benzylaminobutan-1-ol (1.13 g, 6.29 mmol) and 2,6-difluoropyridine (57 μL, 0.629 mmol) and in ethanol (3 mL) were heated at 120 ºC for 72 hours. Chromatography (eluting with 1:1 ethyl actetate/ petroleum ether; $R_f = 0.44$) gave **12** (0.141 g, 82 %) as a colorless oil. (Found: M^+ , 274.1480 $C_{16}H_{19}FN_2O$ requires 274.1481), υ_{max} (neat)/cm^{-1}: 2936, 1615, 1496, 1434, 1222, 770; δ_H (400 MHz, $CDCl_3$) 7.40 (4H, q, *J* 8 Hz), 7.24 (5H, m), 6.20 (1H, dd, *J* 8, 2.5 Hz), 6.07 (1H, dd, *J* 8, 2.5 Hz), 4.66 (2H, s), 3.67 (2H, m), 3.53 (2H, m), 1.70 (2H, m), 1.56 (2H, m); δ_C (101 MHz, $CDCl_3$) 162.9 (d, *J* 235 Hz), 157.6 (d, *J* 17 Hz), 141.5 (d, *J* 8.5 Hz), 138.1, 128.6, 127.1, 126.8, 102.1 (d, *J* 4 Hz), 94.5 (d, *J* 38 Hz), 62.5, 51.9, 48.3, 29.7, 23.7.

6-(3'-Hydroxypropyl)amino-1*H*-pyridin-2-one (7)



2-Fluoro-6-(3-hydroxypropyl)aminopyridine **6** (0.219 g 1.2 mmol) was added to aqueous HCl (from 0.5 mL concentrated HCl and 3.5 mL of water). The mixture was heated, degassed using a sonic bath then transferred to a sealed tube and heated at 140 °C in a microwave reactor (at 160 W) for 30 minutes. The mixture was neutralized using saturated aqueous $NaHCO_3$ (to pH 7) and extracted with ethyl acetate (50 mL). The aqueous phase was concentrated *in vacuo* and the resulting dark yellow solid was dissolved in hot ethanol (50 mL). The insoluble material was removed by filtration and the filtrate was concentrated then preabsorbed onto silica gel. Chromatography (eluting with 10:100:1 methanol/CH_2Cl_2/aq NH_3; R_f = 0.08) gave **7** (0.111 g, 55 %) as pale yellow crystals. m.p 136 °C (CH_2Cl_2). (Found: C, 57.33; H, 7.29; N, 16.82. $C_8H_{12}O_2N_2$ requires C, 57.13; H, 7.19; N, 16.66); (Found: M^+ +H, 169.0976. $C_8H_{13}O_2N_2$ requires 169.0977); $\upsilon_{max}(CH_2Cl_2)$ /cm^{-1} 3332, 2883, 1227, 1621, 903; δ_H (400 MHz, CD_3OD): 7.38 (1H, t, *J* 12 Hz), 5.68 (1H, d, *J* 12z), 5.54 (1H, d, *J* 12 Hz), 4.87 (2H, br, NH), 3.66 (2H, t, *J* 9 Hz), 3.24 (2H, t, *J* 10 Hz), 1.81 (2H, quin, J 10 Hz); δ_C (100.5 MHz, CD_3OD): 164.3, 151.8, 144.4, 101.7, 86.9, 58.9, 39.0, 31.2.

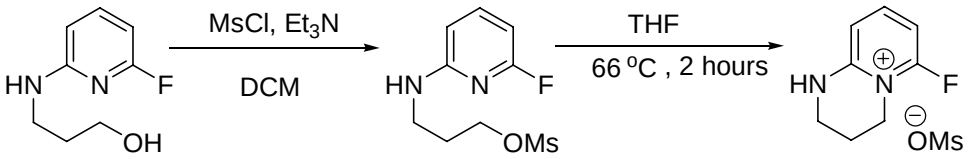
1,2,3,4-Tetrahydropyrido[1,2-*a*]pyrimidin-6-one (2a)



(i) Under Mitsunobu conditions: A solution of pyridin-2-one **7** (0.064 g, 0.38 mmol) and triphenylphosphine (0.150 g, 0.57 mmol) in dry THF (10 mL) was cooled to 0 °C and DIAD (0.075 mL, 0.57 mmol) in THF (3 mL) was added dropwise over 25 minutes. After this time, the solution was warmed to room temperature and stirred for 2 hours. The mixture was concentrated and the residue was purified by chromatography (eluting with 1:10 methanol/CH_2Cl_2 (R_f = 0.34) to give **2a** (0.048 g, 85 %) as colorless crystals. m.p 167 °C (CH_2Cl_2). (Found: C, 63.69; H, 6.51; N, 18.55. $C_8H_{10}N_2O$ requires C, 63.98; H, 6.71; N, 18.65); (Found: M^+, 150.0788. $C_8H_{10}ON_2$ requires 150.0793); $\upsilon_{max}(CH_2Cl_2)$ /cm^{-1} 3326, 1645, 767; δ_H (400 MHz, $CDCl_3$) 7.10 (1H, t, *J* 8 Hz), 5.89 (1H, br), 5.72 (1H, dd, *J* 8, 2 Hz), 5.37 (1H, dd, *J* 8, 2 Hz), 4.03 (2H, t, *J* 6 Hz), 3.37 (2H, dd, *J* 6 Hz), 2.05 (2H, quin, *J* 6 Hz); δ_C (100.5 MHz, $CDCl_3$) 162.5 (d, *J* 2 Hz), 150.3, 140.6, 101.2, 88.1, 39.4, 38.9, 20.6.

(ii) "One-pot" procedure: 2-Fluoro-6-(3-hydroxypropyl)aminopyridine **6** (0.240 g, 1.4 mmol) was mixed with triethylamine (0.98 mL, 7.0 mmol) in dry CH_2Cl_2 at 0 °C. Mesyl chloride (0.12mL, 1.55mmol) was added dropwise over 2 minutes and the mixture was stirred vigorously at 0 °C for 30 minutes. After removal of the CH_2Cl_2 *in vacuo* (at 40 °C), dry THF (10 mL) was added and the resulting mixture was heated at reflux for 2 hours, until ^{1}H NMR showed complete salt formation (see below). Solvents were removed *in vacuo* and saturated aqueous $NaHCO_3$ (15 mL) was added, and the mixture was heated at 60 °C for 3 hours. The reaction mixture was then neutralized with 1M HCl solution (to pH 7) and extracted with ethyl acetate (3 × 50mL). The extracts were washed with brine, dried (Na_2SO_4), concentrated and purification of the residue by chromatography (eluting with 1: 10 methanol/CH_2Cl_2; R_f = 0.34**)** gave **2a** (0.174 g, 83 %) as colorless crystals. Characterization data for **2a** is described above.

Monitoring the formation of mesylate 34 and cyclisation to give pyridinium 14.

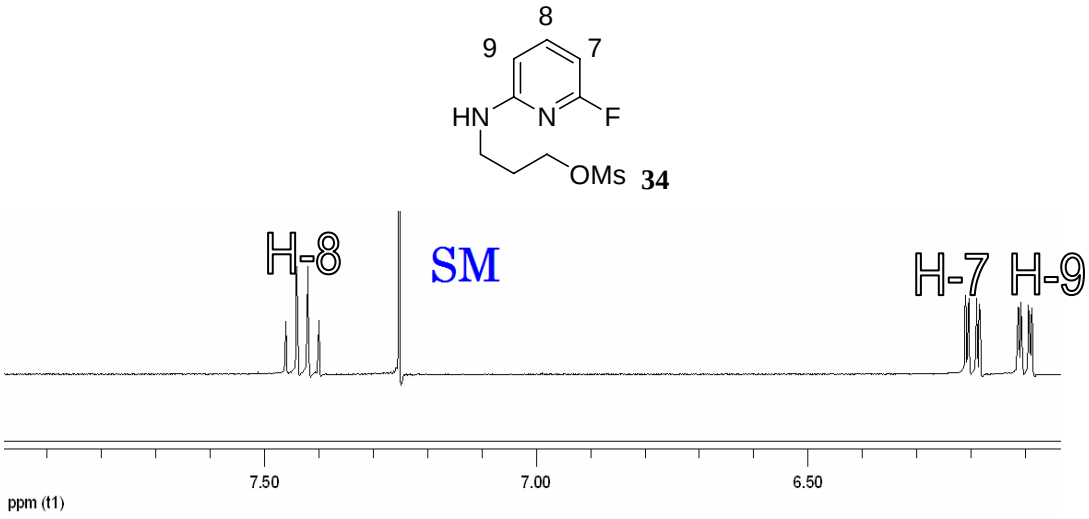


6 **34** **14**

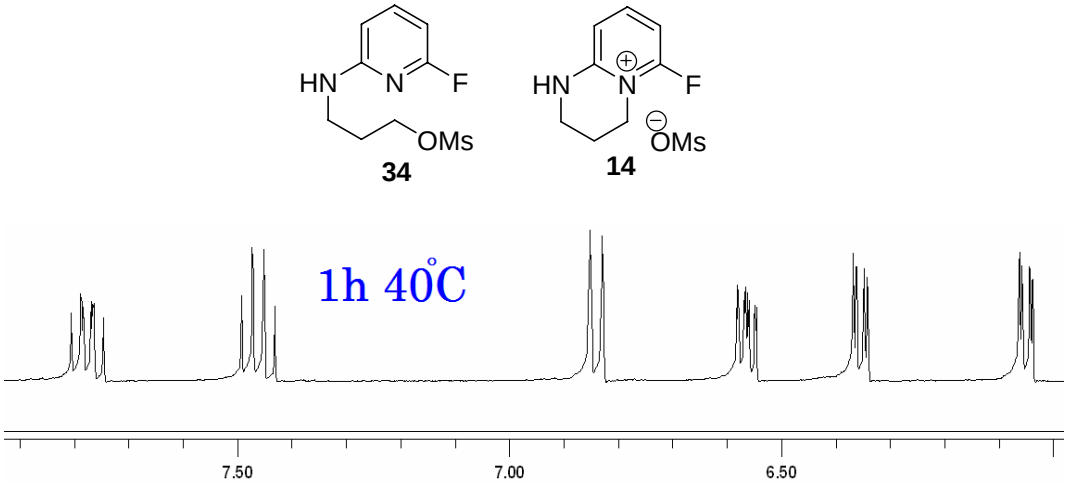
The course of the reaction sequence shown above was followed by ^{1}H NMR using the three ring protons of the pyridine ring (see **Figure 1**). Protons H-7, H-8, H-9 of **34** are shown in spectrum (A). After heating at 40 °C for 1 hour, another set of signals appeared at low field in spectrum (B), and these new peaks are attributed to salt **14.** After 2 hours at 66 °C (in THF), only the low field protons remained in spectrum (C), consistent with complete formation of **14**.

Figure 1: Following the formation of **14** by ^{1}H NMR spectroscopy

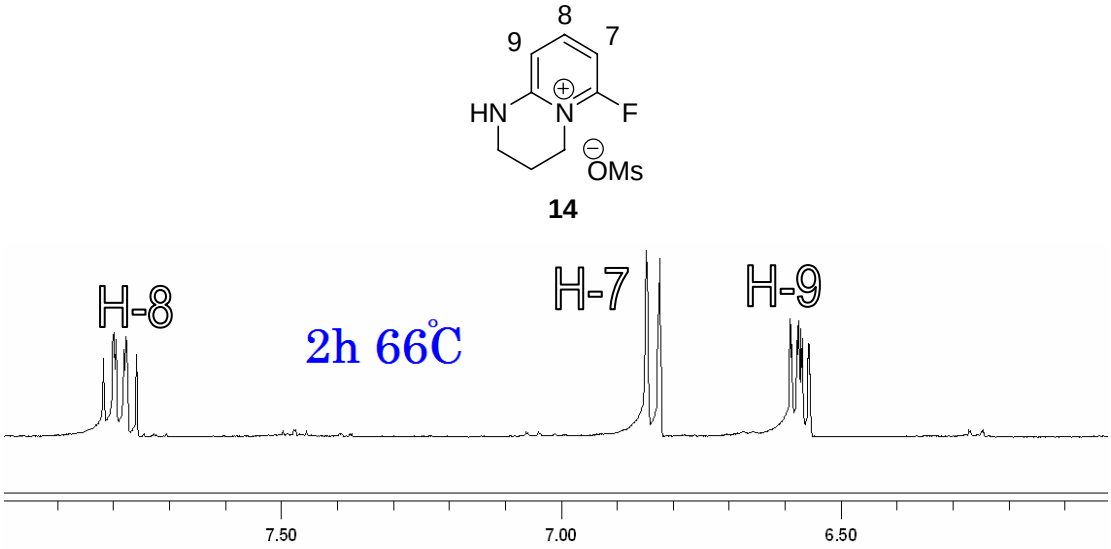
(A): ^{1}H NMR of mesylate **34** (only the aryl proton region is shown)



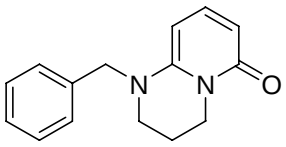
(B): ^{1}H NMR after heating at 40 °C for 1 hour; showing partial conversion to **14**.



(C): ^{1}H NMR after heating at 66 °C for 2 hours; cyclisation to **14** complete.

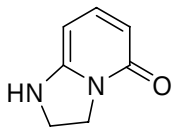


1-Benzyl-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-6-one (2b)



Pyridine **10** (0.505 g, 1.93 mmol) was mixed with triethylamine (0.81 mL, 5.8 mmol) in dry CH_2Cl_2 at 0 °C. Mesyl chloride (0.18 mL, 2.3 mmol) was added dropwise over 2 minutes, and the mixture was stirred vigorously for 30 minutes. The solvent was removed *in vacuo* and anhydrous methanol (10 mL) was added. After 24 hours at room temperature, the solvent was removed and saturated aqueous $NaHCO_3$ (25 mL) was added. The mixture was heated at 80 °C for 2 hours. After this time the mixture was neutralized with 1M HCl solution (to pH 7) and extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the residue purified by chromatography (eluting with 8:100 methanol/ CH_2Cl_2, R_f = 0.32) to give the title compound (0. 40 g, 86 %) as colorless crystals. m.p 112-114 °C (ethyl acetate/petroleum ether). (Found: C, 74.97; H, 6.71; N, 11.66. $C_{15}H_{16}N_2O$ requires C, 74.82; H, 6.66; N, 11.52); (Found: M^++H, 241.1332. $C_{15}H_{17}N_2O$ requires 241.1341.); υ_{max} (neat) /cm^{-1} 3456, 2970, 1641; δ_H (400 MHz, $CDCl_3$) 7.39-7.20 (5H, m), 7.11 (1H, t, *J* 8 Hz), 5.87 (1H, dd, *J* 8, 1 Hz), 5.34 (1H, dd, *J* 8, 1 Hz), 4.52 (2H, s), 4.13 (2H, t, *J* 6 Hz), 3.42 (2H, q, *J* 6 Hz), 2.11 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 162.7, 150.5, 140.4, 136.0, 129.1, 127.7, 126.5, 103.6, 86.8, 55.1, 47.3, 39.5, 21.4.

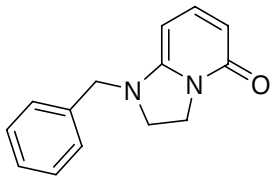
2,3-Dihydro-1*H*-imidazo[1,2-*a*]pyridin-5-one (3a)



Pyridine **8** (2.20 g, 8.9 mmol) was mixed with triethylamine (1.87 mL, 13.4 mmol) in dry CH_2Cl_2 (80 mL) at 0 °C. Mesyl chloride (0.10 mL, 1.34 mmol) was added dropwise and the solution was stirred for 30 minutes before being added to ice/water (60 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude mesylate as a yellow oil. The mesylate was dissolved in dry THF (40 mL) and heated at reflux for 12 hours. After this time, cyclisation to the pyridinium salt was shown to be complete by HPLC

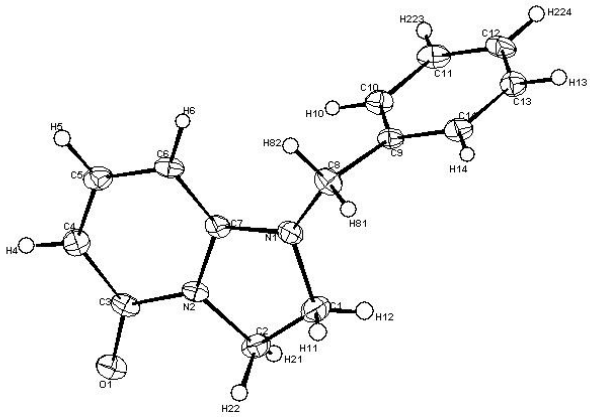
(t_R = 12.6 minutes (vs. 14.6 minutes), 95/5-90/10(8)-5/95(15) H_2O/MeCN + TFA) and the product appeared as a cream-colored precipitate which was isolated by filtration. A portion of this solid (2 g) was dissolved in water (100 mL) containing NaOH (2.05 g, 51.2 mmol). The mixture was stirred at room temperature for 30 minutes, after which time reaction was shown to be complete by HPLC (t_R = 4.19 minutes, 95/5-90/10(8)-5/95(15) H_2O/MeCN + TFA). The dark red solution was neutralized with concentrated HCl and solvent was removed *in vacuo*. The resulting solid was suspended in CH_2Cl_2, filtered through a pad of celite and washed with aliquots of CH_2Cl_2. The filtrate was dried (Na_2SO_4) and concentrated to give pyridone **3a** (1.033 g, 88 %) as a cream solid which was unstable towards chromatography. m.p 92-93 ºC (ethyl acetate/petroleum ether); (Found: M^+, 136.0634. $C_7H_8N_2O$ requires 136.0636); υ_{max}(neat) /cm^{-1} 3169, 3076, 2897, 1644, 1532, 1149; δ_H (400 MHz, CD_3OD) 7.30 (1H, app. t, *J* 8.5 Hz), 5.68 (1H, d, *J* 9 Hz), 5.56 (1H, d, *J* 8 Hz), 4.16 (2H, t, *J* 9 Hz), 3.71 (2H, t, *J* 9 Hz); δ_C (100.6 MHz, CD_3OD) 162.6, 154.6, 143.5, 102.4, 85.3, 44.6, 42.0.

2,3-Dihydro-1-benzylimidazo[1,2-*a*]pyridin-5-one (3b)



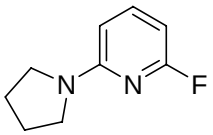
Pyridine **9** (0.246 g, 1 mmol) was mixed with triethylamine (0.12 mL, 0.21 mmol) in dry CH_2Cl_2 (6 mL) at 0 ºC. Mesyl chloride (0.12 mL, 1.5 mmol) was added dropwise and the solution was stirred for 10 minutes then added to ice/water (20 mL). The organic phase was quickly separated, dried (Na_2SO_4) and the solvent was removed *in vacuo* to give the crude mesylate (1:1 ethyl acetate/petroleum ether; R_f = 0.45) as a colorless oil which turned purple over time. The mesylate spontaneously cyclized to the pyridinium salt (0.323 g, quantitative) over 3 hours in methanol solution; the completion of cyclisation was monitored by ^{1}H NMR. [Partial data for intermediate pyridinium salt: δ_H (270 MHz, CD_3OD) 8.00 (1H, app. td *J* 7, 8 Hz), 6.82 (1H, d, *J* 8.5 Hz), 6.66 (1H, d d, *J* 4, 8 Hz), 4.87(2H, s), 4.71 (2H, t, *J* 10 Hz), 4.08 (2H, t, *J* 10 Hz), 2.69 (3H, s)]. A portion of the pyridinium salt (0.293 g, 0.9 mmol) in water (3 mL) and 1M NaOH (3 mL) was stirred at room temperature for 20 minutes, after which time reaction was shown to be complete by TLC (1:10 methanol/CH_2Cl_2, R_f = 0.4). The solution was neutralized with 1M HCl and extracted with ethyl acetate (3 ×

10 mL). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* and trituration (with hexane) gave pyridone **3b** (0.178 g, 86 %) as a cream solid. m.p 94-95 ºC (ethyl acetate/petroleum ether). (Found: M^+, 226.1104. $C_{14}H_{14}N_2O$ requires 226.1106) υ_{max}(neat) /cm^{-1} 2839, 1645, 1539, 1147; δ_H (400 MHz, CD_3OD) 7.39-7.25 (6H, m), 5.74 (2H, d, *J* 8.5 Hz), 5.62 (2H, d, *J* 8 Hz), 4.39 (2H, s), 4.08 (2H, t, *J* 9 Hz), 3.56 (2H, t, *J* 9 Hz); δ_C (100.6 MHz, CD_3OD) 163.9, 154.7, 144.7, 144.5, 137.2, 129.9, 129.0, 104.7, 85.4, 51.3, 48.2, 44.5.



The structure of **3b** is shown above.

2-Fluoro-6-pyrrolidin-1-ylpyridine (15)

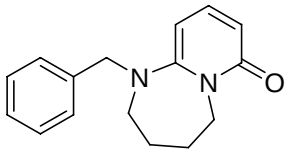


To a solution of pyridine **11** (0.2 g, 1.08 mmol) in CH_2Cl_2 (5 mL) at 0 ºC was added triethylamine (219 mg, 2.17 mmol) followed by dropwise addition of mesyl chloride (0.249 g, 2.17 mmol) over 3 minutes. After 15 minutes, further mesyl chloride (0.124 g, 1.08 mmol) was added and solution was stirred at room temperature for 1.5 hours then added to ice/water (20 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in methanol (10 mL) and stirred at room temperature for 24 hours, and following removal of solvent, the residue was dissolved in water (5.4 mL), 1M NaOH (3 mL) and THF (4 mL) and stirred at room temperature for 20 minutes. The reaction mixture was then neutralized with saturated aqueous ammonium chloride and extracted with ethyl actetate (4 × 20 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography (1:1 ethyl acetate/petroleum ether, R_f = 0.65) to give **15**

(0.064 g, 35 %) as a pale yellow oil. (Found: M^+ +H, 166.0900. $C_9H_{11}FN_2$ requires 166.0906); υ_{max} (neat) /cm^{-1} 2857, 1500, 1434, 1233; δ_H (400 MHz, $CDCl_3$) 7.45 (1H, app. q, *J* 8.0 Hz), 6.11 (1H, dd, *J* 8.0, 2.5 Hz), 6.04 (1H, dd, *J* 8.0, 2.5 Hz), 3.41 (4H, t, *J* 6.5 Hz), 1.98 (4H, m); δ_C (100.6 MHz, $CDCl_3$) 162.86 (d, *J* 234.5 Hz), 156.10 (d, *J* 17 Hz), 140.71 (d, *J* 9 Hz), 102.1 (d, *J* 4 Hz), 93.2 (d, *J* 38 Hz), 46.4, 25.1.

2-Fluoro-6-pyrrolidin-1-ylpridine was prepared by an independent route: n-Butyl lithium (0.35 mL, 2.5 M in THF) was added dropwise to a stirred solution of pyrrolidine (0.068 g, 0.96 mmol) in dry THF (10 mL) at 0 ºC. After 20 minutes, 2,6-difluoropyridine (0.10 g, 0.88 mmol) was added dropwise and the solution was stirred at 0 ºC for 30 minutes. Water (4 mL) was added and product was extracted with diethyl ether (3 × 10 mL). The combined extracts were dried (Na_2SO_4), solvents were removed *in vacuo* and purified by chromatography (eluting with 1:1 ethyl acetate/petroleum ether; R_f = 0.65) to give 2-fluoro-6-pyrrolidin-1-ylpridine (0.144 g, 99 %), the spectroscopic and analytical characteristics of which were identical to that described above.

1-Benzyl-2,3,4,5-tetrahydropyrido[1,2-*a*][1,3]diazepin-7-one (4b)

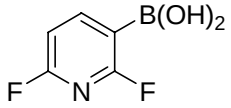


Pyridine **12** (328 mg, 1.2 mmol) was dissolved in aqueous HCl (from 0.5 mL concentrated HCl and 3 mL of water). The mixture was heated and degassed using a sonic bath then transferred to a sealed tube and heated at 120 ºC (at 160 W) for 30 min. The pink reaction mixture was neutralized using saturated aqueous $NaHCO_3$ (to pH 8) and extracted with ethyl acetate (3 × 50 mL). The extracts were evaporated *in vacuo* (to give a purple solid) which was purified by chromatography (eluting with MeOH/ethyl acetate 1:1) to give **15** (60 mg, 30%) which was identical to that obtained earlier.

Continued elution gave **4b** (15 mg, 5%) as a pink solid m.p. 77 ºC (ethyl acetate/petroleum ether); R_f = 0.3; (Found M^+ 254.1428. $C_{16}H_{18}N_2O$ requires 254.1419); υ_{max} (neat) /cm^{-1} 2924, 1623, 1574, 695; δ_H (400 MHz, $CDCl_3$) 7.16 - 7.35

(6H, m), 5.78 (1H, d, *J* 9 Hz), 5.37 (1H, d, *J* 7.5 Hz), 4.53 (2H, s), 3.72 (2H, t, *J* 6 Hz), 3.58 (2H, t, *J* 7.5Hz), 1.81 (2H, m), 1.61 (2H, m); δ_C (100.5 MHz, $CDCl_3$) 164.8, 151.5, 143.2, 136.4, 128.8, 127.5, 126.4, 102.4, 89.1, 61.8, 53.1, 49.5, 28.9, 24.3.

2, 6-Difluoropyridine-3-boronic acid (16)



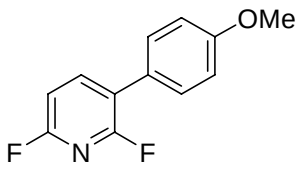
n-Butyl lithium (6.85 mL, 13.7 mmol, 2.0 M in hexanes) was added dropwise to a solution of diisopropylamine (1.93 mL, 13.7 mmol) in THF (10 mL) at 0 ºC under nitrogen. After stirring at 0 ºC for 20 minutes, this solution was added by cannula to a solution of 2,6-difluoropyridine (1.0 mL, 11.4 mmol) in THF (10 mL) at -78 ºC. The resulting solution was stirred at -78 ºC for 30 minutes, then trimethylborate (1.55 mL, 13.7 mmol) in THF (5 mL) was added dropwise. The mixture was warmed to room temperature over 1 hour and then quenched with 1M NaOH (40 mL). The aqueous layer was separated and treated with 2M HCl solution to pH 8. The resulting aqueous solution was extracted with ethyl acetate (30 mL) and this extract was discarded. The aqueous phase was then taken to pH 6.5 (solution went cloudy), and extracted several times with ethyl acetate (30 mL). The aqueous phase was taken to pH 4 and the extraction process was repeated. The combined organic extracts (taken at pH 6.5 to 4) were combined, dried (Na_2SO_4), concentrated *in vacuo*, and the residue was recrystallised from ethyl acetate/diethyl ether to give the boronic acid **16** (1.54 g, 85 %) as a colorless solid. m.p 168 ºC (ethyl acetate/diethyl ether). (Found: C, 37.69; H, 2.29; N, 8.57; $C_5H_4BF_2NO_2$ requires C, 37.79; H, 2.54; N, 8.81); (Found: M^++H, 160.0379. $C_5H_5BF_2NO_2$ requires 160.0381); υ_{max} (neat) /cm^{-1} 3383, 1267, 1380, 995; δ_H (400 MHz, CD_3OD) 8.15 (1H, q, *J* 8.5 Hz), 6.87 (1H, dd, *J* 8.5, 2.0 Hz); δ_C (100.5 MHz, CD_3OD) 164.4 (dd, *J* 247, 15 Hz), 162.9 (dd, *J* 247, 15 Hz), 151.8 (d, *J* 8 Hz), 105.5 (dd, *J* 33, 5 Hz) (C(3) was not observed); δ_B (128 MHz, CD_3OD) 26.1(s).

General Suzuki coupling of 2,6-difluoropyridine-3-boronic acid 16.

Boronic acid **16** (0.31 g, 1.95 mmol), aryl iodide (2.1 mmol) and tetrakis(triphenylphosphino)palladium(0) (5 mol% relative to boronic acid **16**) were added sequentially to degassed DME (30 mL) and this mixture was stirred at 30 °C

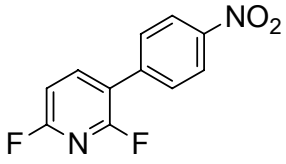
for 20 minutes. Na_2CO_3 (250 mol% relative to boronic acid **16**) was dissolved in water, degassed, added to the reaction mixture and the mixture was heated under nitrogen at 85 °C for 5 hours; conversion was readily monitored by TLC. After concentration *in vacuo*, ethyl acetate was added and insoluble components were removed by filtration. The filtrate was washed with brine, dried (Na_2SO_4) and concentrated. Purification (column chromatography; ethyl acetate – petroleum ether) gave the Suzuki adduct and characterization data for individual compounds is presented below.

2, 6-Difluoro-3-(4'-methoxyphenyl)pyridine (17a)



The title compound **17** was prepared using the general procedure and isolated in 89 % yield as colorless crystals. m.p 89 ºC (ethyl acetate). (Found: C, 65.34; H, 3.87; N, 6.26 $C_{12}H_9F_2NO$ requires C, 65.16; H, 4.10; N, 6.33); (Found: M^+, 221.0652. $C_{12}H_9F_2NO$ requires 221.0652); $\upsilon_{max}(CH_2Cl_2)$ /cm^{-1} 2838, 1606, 992; δ_H (400 MHz, $CDCl_3$) 7.92 (1H, q, *J* 8 Hz), 7.46-7.42 (2H, m), 7.00-6.95 (2H, m), 6.88 (1H, dt, *J* 8, 3 Hz), 3.85 (3H, s); δ_C (100.5 MHz, $CDCl_3$) 160.1 (dd, *J* 246, 14.5 Hz), 159.9, 157.8 (dd, *J* 250, 17 Hz), 144.6 (dd, *J* 7.5, 4 Hz), 129.9 (d , *J* 3 Hz), 125.2 (d, *J* 5 Hz), 120.4 (dd, *J* 25.5, 6 Hz), 114.4, 106.5 (d d, *J* 34.5, 6 Hz), 55.4.

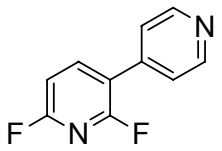
2, 6-Difluoro-3-(4'-nitrophenyl)pyridine (17b)



The title compound was prepared using the general procedure and isolated in 94 % yield as colorless crystals. m.p 168-170 °C (CH_2Cl_2/diethyl ether). (Found: C, 55.93; H, 2.25; N, 12.15; $C_{11}H_6F_2N_2O_2$ requires C, 55.94; H, 2.56; N, 11.86); (Found: M^+, 236.0394. $C_{11}H_6F_2N_2O_2$ requires 236.0397); $\upsilon_{max}(CH_2Cl_2)$ /cm^{-1} 2844, 1616, 982, 847; δ_H (400MHz, $CDCl_3$) 8.34-8.31 (2H, m), 8.03 (1H, dt, *J* 10.0, 8Hz), 7.73-7.69 (2H,

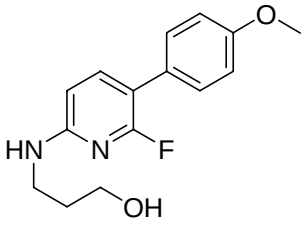
m), 7.00 (1H, dd, *J* 8, 3 Hz); δ_C (125.7 MHz, $CDCl_3$) 161.4 (dd, *J* 250, 14 Hz), 158.0 (dd, *J* 249, 15 Hz), 147.8, 145.0 (d, *J* 4 Hz), 139.3 (d, *J* 5 Hz), 129.6 (d, *J* 3.5 Hz), 124.1, 118.5 (dd, *J* 32.1, 6.5 Hz), 107.2 (dd, *J* 35, 6.5 Hz).

2, 6-Difluoro-3-(4'-pyridyl)pyridine (17c)

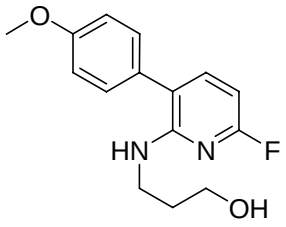


The title compound was prepared using the general procedure and isolated in 95 % yield as colorless crystals, m.p 128-130 °C ($CHCl_3$); (Found: C, 62.30; H, 3.05; N, 14.32; $C_{10}H_6F_2N_2$ requires C, 62.50; H, 3.15; N, 14.58); (Found: M^+ 192.0490. $C_{10}H_6F_2N_2$ requires 192.0499); υ_{max} ($CHCl_3$) /cm^{-1} 2822, 1605, 857; δ_H (400 MHz, $CDCl_3$) 8.76 (2H, d, *J* 6 Hz), 8.07 (1H, dt, *J* 16, 6 Hz), 7.50 (2H, d, *J* 4.5 Hz), 7.20 (1H, dd, *J* 8, 2.8 Hz); δ_C (75.5 MHz, $CDCl_3$) 161.4 (dd, *J* 249.5, 14 Hz), 158.1 (dd, *J* 235, 14.5 Hz), 150.4, 144.7(dd, *J* 8, 3.5 Hz), 140.5 (d, *J* 5 Hz), 123.0, 117.9 (dd, *J* 25, 6.0 Hz), 107.1 (dd, *J* 34.5, 5.5 Hz).

6-(3''-Hydroxylpropyl)amino-2-fluoro-3-(4'-methoxyphenyl)pyridine (18a)



18a



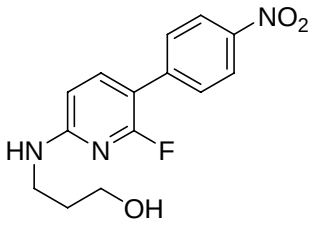
18a-A

Pyridine **17a** (1.11g, 5 mmol) and 3-amino-1-propanol (3.8 mL, 50 mmol) in ethanol (10 mL) were heated at 90 °C for 8 hours, followed by chromatography (eluting with 1:1 ethyl acetate/petroleum ether; R_f = 0.40) gave <u>minor</u> regioisomer 6-(3-Hydroxylpropyl)amino-2-fluoro-5-(4-methoxyphenyl)pyridine **18a-A** (0.417 g, 31%) as colorless crystals. mp: 110 °C (Ethyl acetate/Petroleum ether); (Found: C, 65.18; H, 6.30; N, 10.41; $C_{15}H_{17}FN_2O_2$ requires C, 65.20; H, 6.20; N, 10.14); (Found: M+Na^+, 299.1162. $C_{15}H_{17}FN_2NaO_2$ requires 299.1166); υ_{max}(neat) /cm^{-1} 3391, 2936, 1243, 2838, 1606, 1579, 926; δ_H (400MHz, $CDCl_3$) 7.28 (1H, q, *J* 8 Hz) 7.28-7.24 (2H, m),

7.00-6.96 (2H, m), 6.16 (1H, dd, *J* 8, 2.8 Hz), 4.94 (1H, br, NH), 3.84 (3H, s), 3.64 (2H, t, *J* 5.6 Hz), 3.47 (2H, br); 1.71 (2H, quin, *J* 6 Hz); δ_C (100.5 MHz, $CDCl_3$) 162.7 (d, *J* 235.8 Hz), 159.4; 155.7 (d, *J* 16 Hz), 141.6 (d, *J* 8.6 Hz), 130.3, 129.1, 118.4 (d, *J* 4.7 Hz), 114.9, 94.8 (d, *J* 36.0 Hz), 59.3, 55.5, 38.0, 33.4.

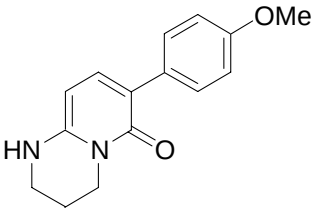
Continued elution (R_f = 0.18) gave the title and major regioisomer **18a** (0.876 g, 63%) as colorless crystals. m.p 110 °C (ethyl acetate); (Found: C, 64.97; H, 6.13; N, 9.91; $C_{15}H_{17}FN_2O_2$ requires C, 65.20; H, 6.20; N, 10.14); (Found: M+Na^+, 299.1163. $C_{15}H_{17}FN_2NaO_2$ requires 299.1166); $\upsilon_{max}(CH_2Cl_2)$ /cm^{-1} 3327, 2935, 1244, 2837, 1606, 926; δ_H (400MHz, $CDCl_3$) 7.59 (1H, dd, *J* 8, 1 Hz), 7.45-7.42 (2H, m), 6.99-6.95 (2H, m), 6.34 (1H, dd, *J* 8, 2 Hz), 3.88 (3H, s), 3.77 (2H, t, *J* 5.5 Hz), 3.47 (2H, t, *J* 5.5 Hz), 1.85 (2H, quin, *J* 6 Hz); δ_C (100.5 MHz, $CDCl_3$) 159.6 (d, *J* 238.5 Hz), 158.6, 157.0 (d, *J* 16 Hz), 141.6 (d, *J* 5.5 Hz), 129.4, 127.4, 114.1, 109.7 (d, *J* 26 Hz), 104.3 (d, *J* 3 Hz), 59.8, 55.3, 38.8, 32.6.

6-(3”-Hydroxylpropyl)amino-2-fluoro-3-(4’-nitrophenyl)pyridine (18b)



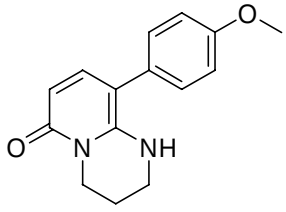
Pyridine **17b** (0.232 g 0.98 mmol) and 3-amino-1-propanol (0.74 g, 9.8 mmol) in ethanol (10 mL) were heated at 90 °C for 4 hours, followed by chromatography (eluting with 1:1 ethyl acetate/petroleum ether; R_f = 0.2) gave **18b** (0.233 g, 83 %) as colorless crystals. m.p 103-105 °C (CH_2Cl_2/diethyl ether). (Found: C, 57.93; H, 4.65; N, 14.14. $C_{14}H_{14}FN_3O_3$ requires C, 57.73; H, 4.84; N, 14.43); (Found: M^+, 291.1021. $C_{14}H_{14}FN_3O_3$ requires 291.1019). $\upsilon_{max}(CH_2Cl_2)$ /cm^{-1} 3400, 2936, 1622; δ_H (400 MHz, $CDCl_3$) 8.25-8.22 (2H, m), 7.77-7.61 (3H, m), 6.37 (1H, dd, *J* 8.5, 2 Hz), 5.19 (1H, br), 3.76 (2H, t, *J* 5.5 Hz), 3.54 (2H, q, *J* 5.5 Hz), 1.85 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 160.0 (d, *J* 241 Hz), 158.3(d, *J* 17 Hz), 146.4, 141.8 (d, *J* 6 Hz), 141.5 (d, *J* 5 Hz), 128.6 (d, *J* 4 Hz), 124.0, 107.3 (d, *J* 26 Hz), 104.9 (d, *J* 2.5 Hz), 60.7, 39.1, 32.3.

3-(4'-Methoxyphenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidine-6-one (19a)



Pyridine **18a** (0.158g, 0.57 mmol) was mixed with triethylamine (0.24 mL, 1.71 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. Mesyl chloride (0.049 mL, 0.63 mmol) was added to the mixture dropwise over 2 minutes and was stirred vigorously for 30 minutes. The solvent was removed *in vacuo*, THF (10 mL) was added and the mixture was heated at reflux for 2 hours. After this time, the mixture was concentrated and the reaction mixture was treated with saturated aqueous $NaHCO_3$ (15 mL) and heated at 60 °C for 3 hours during which time a yellow precipitate formed. The mixture was neutralized using 1M HCl solution (to pH 7) and extracted with ethyl acetate (5 × 10 mL). The organic layer was washed with brine, dried (Na_2SO_4), and the residue was purified by chromatography (eluting with ethyl acetate, $R_f = 0.16$**)** to give the title compound **19a** (0.118 g, 81 %) as colorless crystals. m.p 212 °C (decomp., ethyl acetate). (Found: C, 70.12; H, 6.47; N, 10.98 $C_{15}H_{16}N_2O_2$ requires C, 70.29; H, 6.29; N, 10.93); (Found: $M+Na^+$, 279.1106. $C_{15}H_{16}N_2NaO_2$ requires 279.1104); υ_{max}(neat) /cm^{-1} 3515, 2995, 1247, 1770; δ_H (400 MHz, $CDCl_3$) 7.62-7.58 (2H, m), 7.31 (1H, d, *J* 8 Hz), 6.90-6.87 (2H, m), 5.37 (1H, d, *J* 8 Hz), 4.72 (1H, br, NH), 4.10 (2H, t, *J* 6 Hz), 3.80 (3H, s), 3.36 (2H, dd, *J* 6, 2 Hz), 2.08 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, d_6-acetone) 160.1, 157.5, 150.1, 137.9, 132.0, 128.4, 113.0, 111.2, 86.6, 54.6, 39.5, 38.6, 20.8.

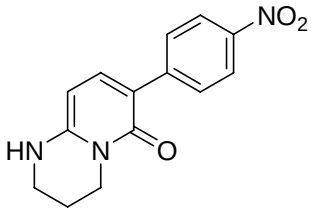
9-(4'-Methoxyphenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-6-one (31)



Using the procedure described above, minor regioisomer **18a-A** (0.172g) reacted with tiethylamine (0.26mL, 1.75mmol) and Mesyl chloride (0.053mL, 0.67mmol) gave the title compound **31** (0.124g, 78 %) as colorless crystals. m.p 206-208 °C (CH_2Cl_2); (Found: C, 70.43; H, 6.60; N, 10.89. $C_{15}H_{16}O_2N_2$ requires C, 70.29; H, 6.29; N, 10.93); (Found: M^++Na, 279.1111. $C_{15}H_{16}N_2NaO_2$ requires 279.1104); υ_{max}(CH_2Cl_2) /cm^{-1}

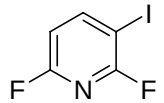
3279, 2964, 1642; δ_H (400 MHz, $CDCl_3$) 7.23-7.19 (2H, m), 7.09 (1H, d, *J* 9 Hz), 6.97-6.93 (2H, m), 5.87 (1H, d, *J* 9 Hz), 4.11 (2H, t, *J* 6 Hz), 3.83 (3H, s), 3.33 (2H, td, *J* 6, 3 Hz), 2.07 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 161.9, 158.7, 146.9, 141.9, 130.8, 129.1, 114.7, 102.4, 100.9, 55.4, 39.9, 39.3, 20.6.

3-(4'-Nitrophenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidine-6-one (19b)



Pyridine **18b** (0.20 g, 0.68 mmol) was mixed with triethylamine (0.29 mL, 1.84 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C ice bath. Mesyl chloride (0.058 mL, 0.75 mmol) was added to the mixture dropwise over 2 minutes and was stirred vigorously for 30 minutes. The solvent was removed *in vacuo* and THF (10 mL) was added and the mixture was heated at reflux for 2 hours. After the solvent was removed, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (150 mL) and heated at 60 °C for 5 hours. This reaction mixture was neutralized using 1M HCl (to pH 7) and extracted with ethyl acetate (500 mL). The organic layer was washed with brine, dried (Na_2SO_4), and the residue was purified by chromatography (eluting with 1:10 methanol/CH_2Cl_2, R_f = 0.30**)** to give the title compound **19b** (0.134 g, 73 %) as colorless crystals. m.p >220 °C (CH_2Cl_2) (Found: C, 61.87; H, 4.79; N, 15.44 $C_{14}H_{13}N_3O_3$ requires C, 61.99; H, 4.83; N, 15.49); (Found: M^+, 271.0947. $C_{14}H_{13}N_3O_3$ requires 271.0952); υ_{max}(methanol) /cm^{-1} 3401, 2250, 1739; δ_H (270 MHz, d5-pyridine) 8.44-8.39 (2H, m), 8.32-8.27 (2H, m), 7.72 (1H, d, *J* 8.5 Hz), 5.72 (1H, d, *J* 8.5 Hz), 5.03 (1H, br), 4.08 (2H, t, *J* 6 Hz), 3.20 (2H, m), 1.78 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, d5-pyridine) 160.4, 152.4, 150.1, 147.2, 144.2, 139.8, 126.7, 107.3, 89.7, 39.8, 38.4, 20.3.

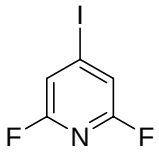
3-Iodo-2,6-difluoropyridine (20)



n-Butyl lithium (7.5mL, 12 mmol, 1.6 M in hexane) was added dropwise to a solution of diisopropylamine (1.7 mL, 12 mmol) in THF (10 mL) at -78 °C under nitrogen, After 20 min, 2,6-difluoropyridine (1.1 mL, 12 mmol) was added dropwise and after a

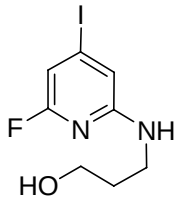
further 1 hour, a solution of iodine (3.2 g, 13.5 mmol) in THF (5 mL) was added over 10 minutes at -78 °C. The solution was allowed to warm to room temperature over 1 hour, was washed with 10% aqueous Na_2SO_3 (10 mL) and extracted with ethyl acetate (50 mL). The organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue was recrystallized from petroleum ether to give **20** (2.72 g, 94 %) as colorless crystals. m.p 38-40 °C (petroleum ether). (Found: C, 24.94; H, 1.04; N, 5.38; $C_5H_2F_2IN$ requires C, 24.92; H, 0.84; N, 5.81); (Found: M^+, 240.9192. $C_5H_2F_2IN$ requires 240.9200); υ_{max} (petroleum ether) /cm^{-1} 1596, 1446, 1302 ; δ_H (400 MHz, $CDCl_3$) 8.23 (1H, td, *J* 8, 8 Hz), 6.71(1H, dd, *J* 8, 3 Hz); δ_C (100.5 MHz, $CDCl_3$) 162.1 (dd, *J* 247, 13 Hz), 160.3 (dd, *J* 241, 15 Hz), 153.6 (dd, *J* 7.5, 3.0 Hz), 108.4 (dd, *J* 35, 6 Hz), 69.3 (dd, *J* 40, 6 Hz). (see Schlosser, M.; Rausis, T. *Eur. J. Org. Chem.* **2004**, 1018-1024.)

4-Iodo-2,6-difluoropyridine (21)



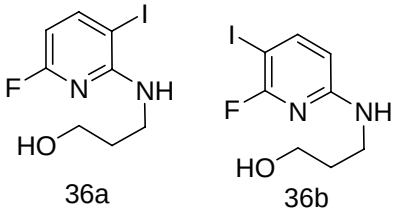
n-Butyl lithium (6.5 mL, 10.4 mmol, 1.6 M in hexane) was added dropwise to a solution of diisopropylamine (1.5 mL, 4.8 mmol) in THF (5 mL) at -78 °C under nitrogen. After 20 minutes pyridine **20** (2.46 g, 10.4 mmol) in THF (12 mL) was added dropwise into this mixture by cannula. After 10 hours at -78 °C, H_2O (0.51 g, 28 mmol) in THF (5 mL) was added and the mixture was warmed to room temperature over 1 hour. The mixture was washed with 10 % aqueous Na_2SO_3 (10 mL) and extracted with ethyl acetate (150 mL). The organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue was purified by chromatography (eluting with 5:95 ethyl acetate/petroleum ether; R_f = 0.6) to give **21** (1.72 g, 70 %) as colorless crystals. m.p 80-82 °C (petroleum ether). (Found: C, 25.22; H, 0.63; N, 5.50; $C_5H_2F_2IN$ requires C, 24.92; H, 0.84; N, 5.81); (Found: M^+, 240.9195. $C_5H_2F_2IN$ requires 240.9200); υ_{max}(petroleum ether) /cm^{-1} 1569, 1392, 1267; δ_H (400 MHz, $CDCl_3$) 7.26 (2H, t, *J* 1 Hz); δ_C (100.6 MHz, $CDCl_3$): 161.3 (dd, *J* 251, 16 Hz), 115.8 (dd, *J* 28, 14 Hz), 110.15 (dd, *J* 44, 7 Hz). (see Schlosser, M.; Rausis, T. *Eur. J. Org. Chem.* **2004**, 1018-1024.)

2-(*N*-3'-Hydroxypropyl)-6-fluoro-4-iodopyridine (35)



A solution of 4-iodo-2,6-difluoropyridine (0.70 g, 2.9 mmol) and 3-amino-1-propanol (1.1 mL, 14.5 mmol) in ethanol (12 mL) was degassed and then transferred to a sealed tube and heated at 70 °C (oil bath temperature) for 2 hours. The reaction mixture was preabsorbed onto silica gel and chromatography (eluting with ethyl acetate, R_f = 0.44) gave the title compound **35** (0.765 g, 96%) as colorless crystals. m.p 86-88 °C (petroleum ether). (Found: C, 32.61; H, 3.25; N, 9.30. $C_8H_{10}FIN_2O$ requires C, 32.45; H, 3.40; N, 9.46). (Found: M^++H, 296.9889. $C_8H_{11}FIN_2O$ requires 296.9900); υ_{max}(petroleum ether) /cm^{-1} 3327, 2935; δ_H (400 MHz, $CDCl_3$) 6.63 (1H, t, *J* 1 Hz), 6.52 (1H, dd, *J* 2, 1 Hz), 3.75 (2H, t, *J* 6 Hz), 3.45 (2H, q, *J* 6 Hz), 1.80 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 162.6 (d, *J* 242 Hz), 158.2 (d, *J* 18 Hz), 112.4 (d, *J* 4 Hz), 108.1 (d, *J* 9 Hz), 104.9 (d, *J* 39 Hz), 60.1, 39.1, 32.2.

2-(*N*-3'-Hydroxypropyl)-6-fluoro-3-iodopyridine (36a) and 2-(*N*-3'-hydroxypropyl)-6-fluoro-5-iodopyridine (36b)



A solution of 3-iodo-2,6-difluoropyridine (0.36 g, 1.5 mmol) and 3-amino-1-propanol (0.63 mL, 8.25 mmol) in CH_2Cl_2 (10 mL) was degassed, transferred to a sealed tube and heated at 50 °C for 50 hours. Work-up (as described for **35**) and column chromatography (eluting with 1:1 ethyl acetate/ petroleum ether, R_f = 0.46) gave the title compound **36a** (0.38 g, 87 %) as colorless crystals. m.p 50-52 °C (CH_2Cl_2/ petroleum ether). (Found: C, 32.45; H, 3.40; N, 9.15. $C_8H_{10}FIN_2O$ requires C, 32.45; H, 3.40; N, 9.46); (Found: M^++H, 296.9896. $C_8H_{11}FIN_2O$ requires 296.9900); υ_{max}(CH_2Cl_2) /cm^{-1} 3409, 2940, 1607; δ_H (400 MHz, $CDCl_3$) 7.84 (1H, t, *J* 8.0 Hz), 6.01 (1H, dd, *J* 8, 2.8 Hz), 5.38 (1H, br), 3.72 (2H, t, *J* 6 Hz), 3.61 (2H, t, *J* 6 Hz), 2.81 (1H, t, *J* 6 Hz, OH), 1.85 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 163.7 (d, *J*

238.5 Hz), 156.2 (d, *J* 17 Hz), 150.2 (d, *J* 8.5 Hz), 97.6 (d, *J* 37.5 Hz), 71.6 (d, *J* 4.5 Hz), 59.9, 39.3, 32.7.

Continued elution (R_f = 0.26) gave **2-(*N*-3'-hydroxypropyl)-6-fluoro-5-iodopyridine 36b** (0.04g, 9%) as colorless crystals. m.p 82-84 °C (CH_2Cl_2/petroleum ether). (Found: C, 32.36; H, 3.48; N, 9.12. $C_8H_{10}FIN_2O$ requires C, 32.45; H, 3.40; N, 9.46); (Found: M^++H, 296.9892. $C_8H_{11}FIN_2O$ requires 296.9900); $\upsilon_{max}(CH_2Cl_2)$ /cm^{-1} 3330, 2942, 1511; δ_H (400 MHz, $CDCl_3$) 7.70 (1H, t, *J* 8 Hz), 6.11 (1H, dd, *J* 8, 2 Hz), 4.92 (1H, br), 3.76 (2H, t, *J* 6 Hz), 3.49 (2H, m, *J* 6 Hz), 2.38 (1H, br, OH), 1.84 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 161.5 (d, *J* 233 Hz), 158.1 (d, *J* 15.5 Hz), 149.7 (d, *J* 4 Hz), 106.2 (d, *J* 4 Hz), 60.2, 54.9 (d, *J* 43 Hz), 39.1, 32.3.

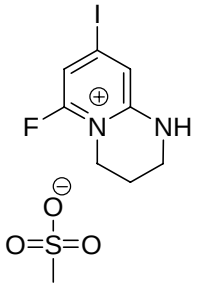
Other results using different solvents system are listed below:

Solvent	Reaction temp.	Reaction time	Yield of **36a**	Yield of **36b**
Ethanol	90 °C	5 hours	65 %	34 %
Methanol/ CH_2Cl_2 (1:1)	80 °C	7 hours	74 %	18 %

General procedure for iodopyridium salt formation (10mmol scale)

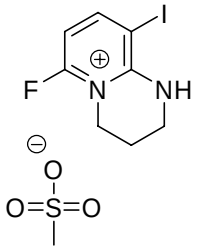
A stirred solution of the requisite iodopyridine (see Scheme 4) and triethylamine (3 eq) in dry CH_2Cl_2 was cooled to 0 °C and mesyl chloride (1.2 eq) was added dropwise over 5 minutes. After 1 hour, the mixture was washed with brine, the organic phase was separated, evaporated and then taken up in methanol, stirred for 20 hours at room temperature, after which time salt formation was completed as judged by TLC. Characterization data for each system are provided below.

6-Fluoro-8-iodo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium mesylate (22)



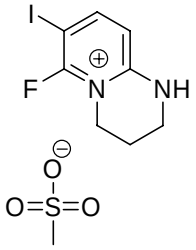
Isolated in 99 % yield as colorless crystals. m.p. >220 °C (CH_2Cl_2); (Found: C, 28.93; H, 3.51; N, 7.55. $C_9H_{12}FIN_2O_3S$ requires C, 28.89; H, 3.23; N, 7.49); (Found: M^+, 278.9794. $C_8H_9FIN_2$ requires 278.9789); υ_{max}(methanol) /cm^{-1} 3411, 2502, 1661; δ_H (400 MHz, $CDCl_3$) 7.31 (1H, d, *J* 2 Hz), 7.03 (1H, dd, *J* 8, 2 Hz), 4.23 (2H, t, *J* 6 Hz), 3.52 (2H, t, *J* 6 Hz), 2.70 (3H, s), 2.21 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 155.3 (d, *J* 271 Hz), 152.5 (d, *J* 17 Hz), 120.3, 112.0 (d, *J* 11 Hz), 104.6 (d, *J* 17 Hz), 44.6 (d, *J* 8 Hz), 39.5, 39.1, 18.3.

6-Fluoro-9-iodo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium mesylate (24)



Isolated in 99 % yield as colorless crystals. m.p. >220 °C (CH_2Cl_2); (Found: C, 28.83; H, 3.41; N, 7.57. $C_9H_{12}FIN_2O_3S$ requires C, 28.89; H, 3.23; N, 7.49); (Found: M^+, 278.9793. $C_8H_9FIN_2$ requires 278.9789); υ_{max}(methanol) /cm^{-1} 3244, 1656, 1170; δ_H (400 MHz, CD_3OD) 8.43 (1H, dd, *J* 8, 7 Hz), 6.55 (1H, dd, *J* 8, 5 Hz), 4.37 (2H, t, *J* 6 Hz), 3.66 (2H, t, *J* 6 Hz), 2.67 (3H, s), 2.23 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, CD_3OD) 157.6 (d, *J* 268 Hz); 154.6 (d, *J* 11 Hz), 152.3, 97.1 (d, *J* 23 Hz), 75.9 (d, *J* 5 Hz), 46.1, 40.9, 39.7, 18.7.

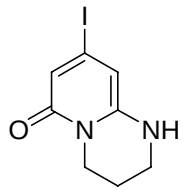
6-Fluoro-7-iodo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium mesylate (25)



Isolated in 99 % yield as colorless crystals. m.p. >220 °C (CH_2Cl_2); (Found: C, 28.67; H, 3.25; N, 7.37 $C_9H_{12}FIN_2O_3S$ requires C, 28.89; H, 3.23; N, 7.49); (Found: M^+, 278.9798. $C_8H_9FIN_2$ requires 278.9789); υ_{max}(methanol) /cm^{-1} 3411, 2502, 1661; δ_H

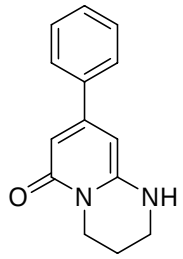
(400 MHz, CD_3OD) 8.00 (1H, dd, *J* 8, 5.5 Hz), 6.71 (1H, dd, *J* 8, 5 Hz), 4.33 (2H, t, *J* 6 Hz), 3.54 (2H, t, *J* 6 Hz), 2.70 (3H, s), 2.21 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, CD_3OD) 155.9 (d, *J* 257 Hz), 153.4, 151.3 (d, *J* 6 Hz), 113.0 (d, *J* 5 Hz), 54.1 (d, *J* 28 Hz), 45.8 (d, *J* 8 Hz), 39.7, 39.2, 18.7.

8-Iodo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-6-one (23)



Mesylate **22 (**0.624 g, 1.67 mmol) in 1M NaOH (10 mL) was heated at 80 °C for 4 hours. After this time 12M HCl was added (to pH 4), and the product was extracted with ethyl acetate (200 mL). The extracts were washed with brine, dried (Na_2SO_4), and the residue was purified by column chromatography (eluting with 1:10 methanol/ CH_2Cl_2; R_f = 0.42**)** to give pyridone **23** (0.160 g, 84 %) as colorless crystals. m.p 180 °C (decomp., CH_2Cl_2). (Found: C, 34.44; H, 3.50; N, 10.35; $C_8H_9IN_2O$ requires C, 34.80; H, 3.29; N, 10.15); (Found: M^++H, 276.9831, $C_8H_{10}IN_2O$ requires 276.9838); υ_{max}(neat) /cm^{-1} 786, 2995; δ_H (400 MHz, d_5-pyridine) 6.54 (1H, d, *J* 2 Hz), 5.99 (1H, d, *J* 2 Hz), 3.96 (2H, t, *J* 6 Hz), 3.13 (2H, td, *J* 6, 3 Hz), 1.71 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, d_5-pyridine) 160.7, 150.9, 110.9, 109.7, 96.2, 39.5, 38.6, 20.2.

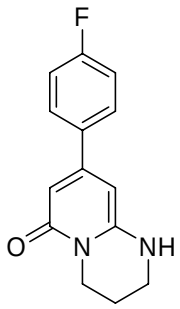
General Suzuki coupling procedure for pyridium salts. 8-Phenyl-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-6-one (27)



Salt **22** (0.135 g, 0.360 mmol) and tetrakis(triphenylphosphino)palladium(0) (0.020 g, 0.018 mmol, 5 mol% relative to **22**) in methanol (2 mL) were degassed and heated at 40 °C for 10 minutes. Phenylboronic acid (0.066 g, 0.54 mmol) and Na_2CO_3 (0.114 g, 1.1 mmol) in methanol (1:1, 4 mL) were added and the reaction mixture was heated under nitrogen at 85 °C for 5 hours. After this time, solvents were removed and ethyl acetate (40 mL) was added. The mixture was filtered and the filtrate was dried

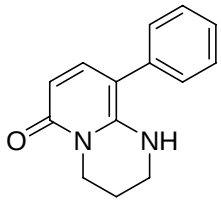
(Na_2SO_4), concentrated and purification by chromatography (eluting with 15:100 methanol/ether; R_f = 0.30) gave **27** (0.063 g, 75 %) as colorless crystals. m.p >220 °C (CH_2Cl_2); (Found: M^++H, 227.1166. $C_{14}H_{15}ON_2$ requires 227.1169); υ_{max}(CH_2Cl_2) /cm^{-1} 3016, 1738, 1366; δ_H (400 MHz, CD_3OD) 7.56-7.38 (5H, m), 5.89 (1H, d, *J* 2 Hz), 5.80 (1H, d, *J* 2 Hz), 4.00 (2H, t, *J* 6 Hz), 3.36 (2H, d, *J* 6 Hz), 2.04 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, CD_3OD) 163.8, 154.4, 151.5, 139.5, 129.5, 129.2, 126.9; 97.4, 89.4, 40.5, 39.0, 20.7.

8-(4'-Fluorophenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-6-one (28)



Using the procedure described above, reaction of **22** with (4-fluorophenyl)boronic acid gave **28** in 80 % yield as colorless crystals. m.p >220 °C (CH_2Cl_2). (Found: M^+, 244.1009. $C_{14}H_{13}FN_2O$ requires 244.1012); υ_{max}(neat) /cm^{-1} 3244, 1651, 1548; δ_H (400 MHz, $CDCl_3$), 7.43 (2H, dd, *J* 9, 5 Hz), 7.00 (2H, t, *J* 8 Hz), 6.26 (1H, br), 5.94 (1H, d, *J* 2. Hz), 5.61 (1H, d, *J* 2 Hz), 4.05 (2H, t, *J* 6 Hz), 3.40 (2H, d, *J* 6 Hz), 2.05 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 163.1 (d, *J* 248 Hz), 162.5, 151.8, 150.0, 135.1 (d, *J* 3 Hz), 128.1 (d, *J* 9 Hz); 115.4 (d, *J* 21 Hz), 98.9, 87.1, 39.4, 39.0, 20.5.

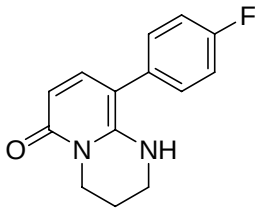
9-Phenyl-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-6-one (29)



Using the procedure described above, reaction of **24** with phenylboronic acid gave the title compound **29** in 75 % yield as colorless crystals. m.p >220 °C (CH_2Cl_2). (Found: M^++H, 227.1180. $C_{14}H_{15}ON_2$ requires 227.1184); υ_{max} (CH_2Cl_2) /cm^{-1} 786, 2541, 2995; δ_H (400 MHz,$CDCl_3$) 7.44-7.40 (2H, m), 7.32- 7.28 (3H, m), 7.13 (1H, d, *J* 9 Hz), 5.87 (1H, d, *J* 9 Hz), 5.17 (1H, br), 4.09 (2H, t, *J* 6 Hz), 3.34 (2H, t, *J* 6 Hz); 2.07 (2H,

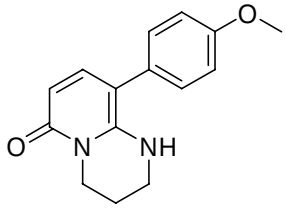
quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 162.0, 146.9, 142.0, 137.2, 129.5, 129.4, 127.2, 102.7, 101.4, 40.0, 39.3, 20.6.

9-(4'-Fluorophenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-6-one (30)

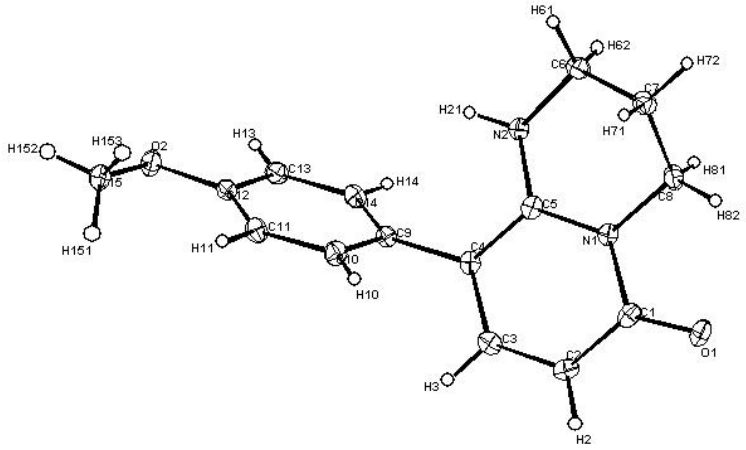


Using the procedure described above, reaction of **24** with 4-fluorophenylboronic acid gave the title compound **30** in 84% yield as colorless crystals. m.p >220 °C (CH_2Cl_2). (Found: M^+, 244.1010. $C_{14}H_{13}FN_2O$ requires 244.1012); $\upsilon_{max}(CH_2Cl_2)$ /cm^{-1} 3291, 2964, 1633; δ_H (400 MHz,$CDCl_3$) 7.30-7.26 (2H, m); 7.15-7.09 (3H, m); 5.89 (1H, d *J* 8 Hz); 4.95 (1H, br); 4.11 (2H, t, *J* 6 Hz); 3.36 (2H, d, *J* 6 Hz); 2.09 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 161.9 (d, *J* 247 Hz); 161.8, 146.8, 141.8, 132.9 (d, *J* 4 Hz), 131.8(d, *J* 8 Hz), 116.2 (d, *J* 21 Hz), 102.7, 100, 39.9, 39.3, 20.5.

9-(4'-Methoxyphenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-6-one (31)

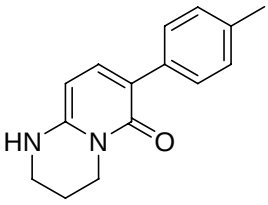


Using the procedure described above, reaction of **24** with (4-methoxyphenyl)boronic acid gave the title compound **31** in 82 % yield as colorless crystals. m.p 206-208 °C (CH_2Cl_2); (Found: C, 70.43; H, 6.60; N, 10.89. $C_{15}H_{16}O_2N_2$ requires C, 70.29; H, 6.29; N, 10.93); (Found: M^++Na, 279.1111. $C_{15}H_{16}N_2NaO_2$ requires 279.1104); $\upsilon_{max}(CH_2Cl_2)$ /cm^{-1} 3279, 2964, 1642; δ_H (400 MHz, $CDCl_3$) 7.23-7.19 (2H, m), 7.09 (1H, d, *J* 9 Hz), 6.97-6.93 (2H, m), 5.87 (1H, d, *J* 9 Hz), 4.11 (2H, t, *J* 6 Hz), 3.83 (3H, s), 3.33 (2H, td, *J* 6, 3 Hz), 2.07 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CDCl_3$) 161.9, 158.7, 146.9, 141.9, 130.8, 129.1, 114.7, 102.4, 100.9, 55.4, 39.9, 39.3, 20.6.



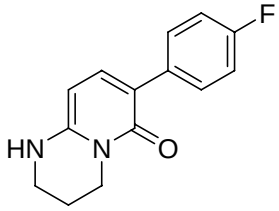
The structure of **31** is shown above.

3-(4'-Methylphenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidine-6-one (32)



Using the procedure described above, reaction of **25** with (4-methylphenyl)boronic acid gave the title compound **32** in 72 % yield as colorless crystals. m.p >220 °C (methanol/$CHCl_3$). (Found: C, 74.63; H, 6.63; N, 11.89. $C_{15}H_{16}N_2O$ requires C, 74.97; H, 6.71; N, 11.66); (Found: M^+, 240.1256. $C_{15}H_{16}N_2O$ requires 240.1263); $\upsilon_{max}(CH_2Cl_2)$ /cm^{-1} 3016, 1738, 1366; δ_H (400 MHz, $CD_3OD/CDCl_3$) 7.58 (2H, d, *J* 8.0Hz), 7.36 (1H, d, *J* 8 Hz), 7.17 (2H, d, *J* 8 Hz), 5.40 (1H, d *J* 8 Hz), 4.12 (2H, t, *J* 6 Hz), 3.21 (2H, d, *J* 6 Hz), 2.36 (3H, s), 2.10 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CD_3OD/CDCl_3$) 160.7, 149.0, 139.0, 135.6, 135.2, 128.7, 127.8, 113.9, 87.8, 39.8, 39.0, 21.1, 20.9.

3-(4'-Fluorophenyl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidine-6-one (33)

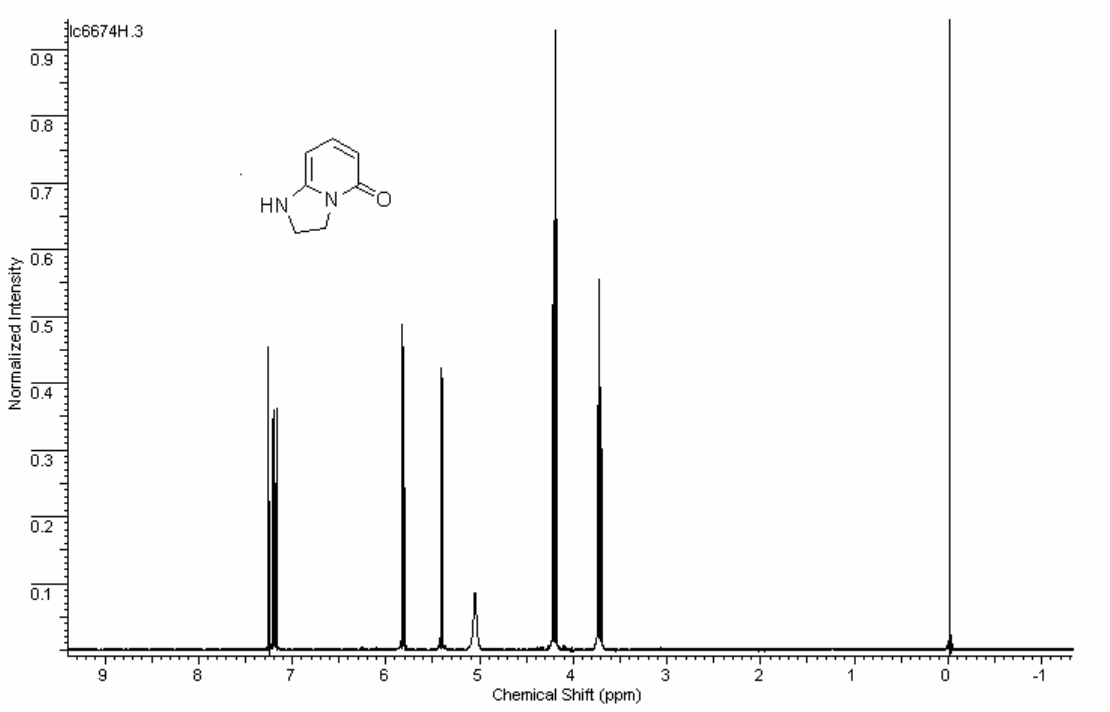


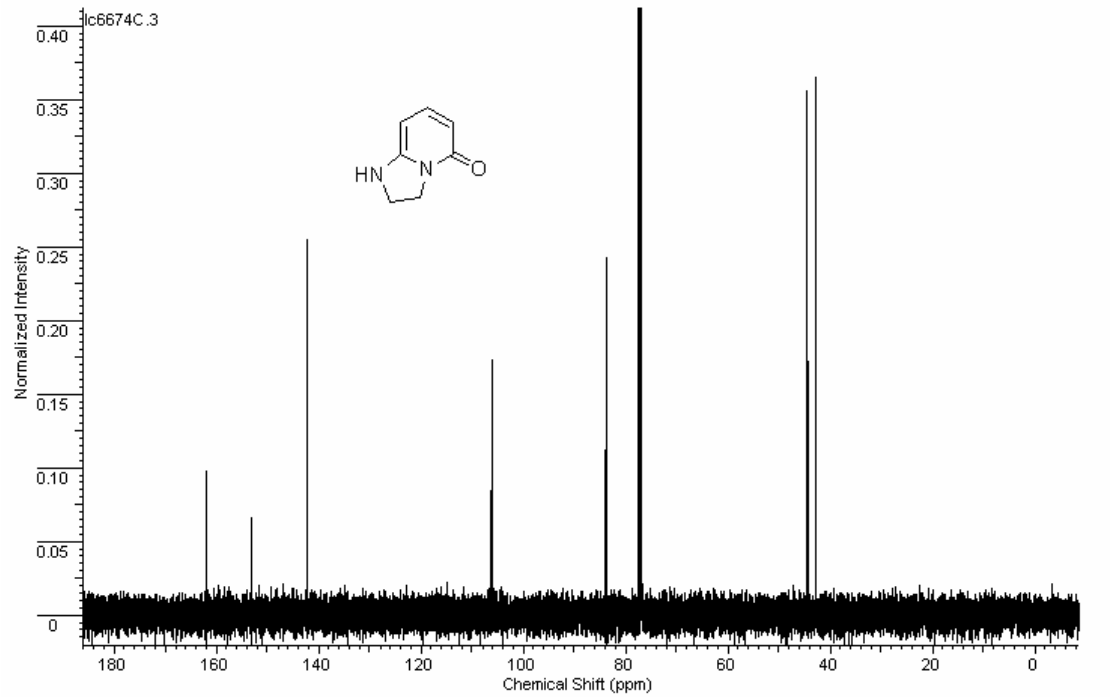
Using the procedure described above, reaction of **25** with (4-fluorophenyl)boronic acid gave the title compound **33** in 75 % yield as colorless crystals. m.p >220 °C

(methanol/$CHCl_3$). (Found: M^+, 244.1007. $C_{14}H_{13}FN_2O$ requires 244.1012); υ_{max}(methanol) /cm^{-1} 3245, 1635, 1473; δ_H (400 MHz, $CD_3OD/CDCl_3$) 7.42-7.39 (2H, m), 7.19 (1H, d, *J* 8 Hz), 6.89-6.85 (2H, m), 5.41 (1H, d, *J* 8 Hz), 4.14 (1H, br, NH), 3.92 (2H, t, *J* 6 Hz), 3.21 (2H, d, *J* 6 Hz), 1.94 (2H, quin, *J* 6 Hz); δ_C (100.6 MHz, $CD_3OD/CDCl_3$) 161.1(d, *J* 243 Hz), 159.9, 150.1, 140.0, 134.5 (d, *J* 3 Hz), 129.4 (d, *J* 7 Hz), 114.5 (d, *J* 21 Hz), 111.2, 89.7, 40.1, 38.4, 20.4.

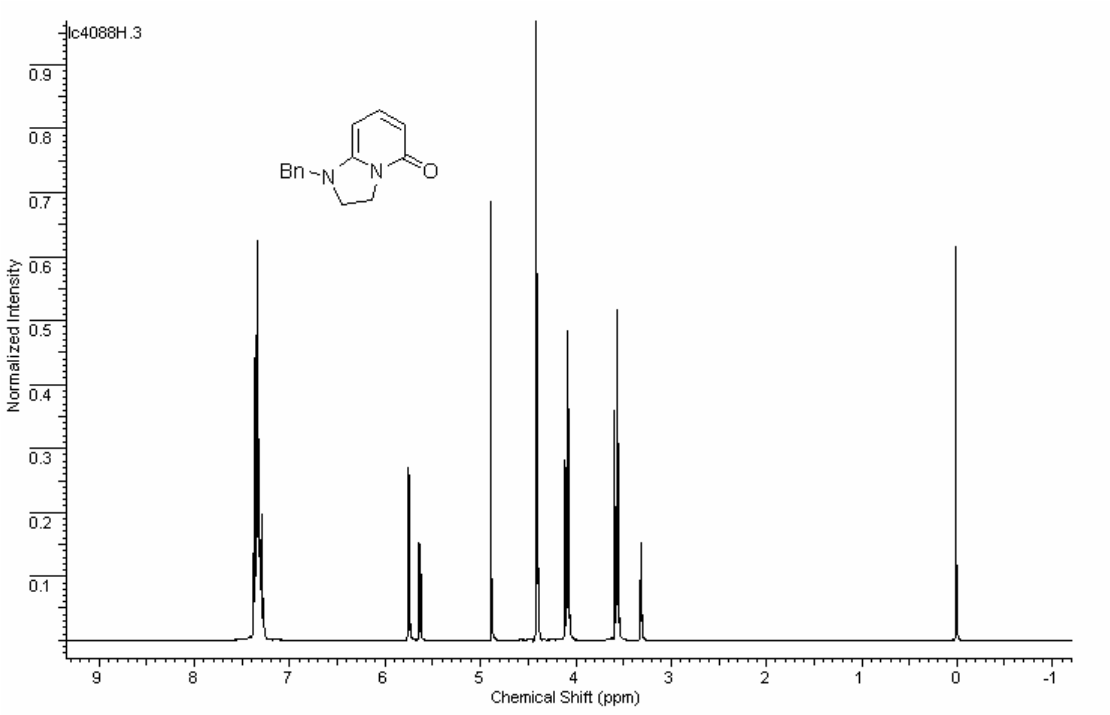
Copies of ^{1}H and ^{13}C NMR spectra

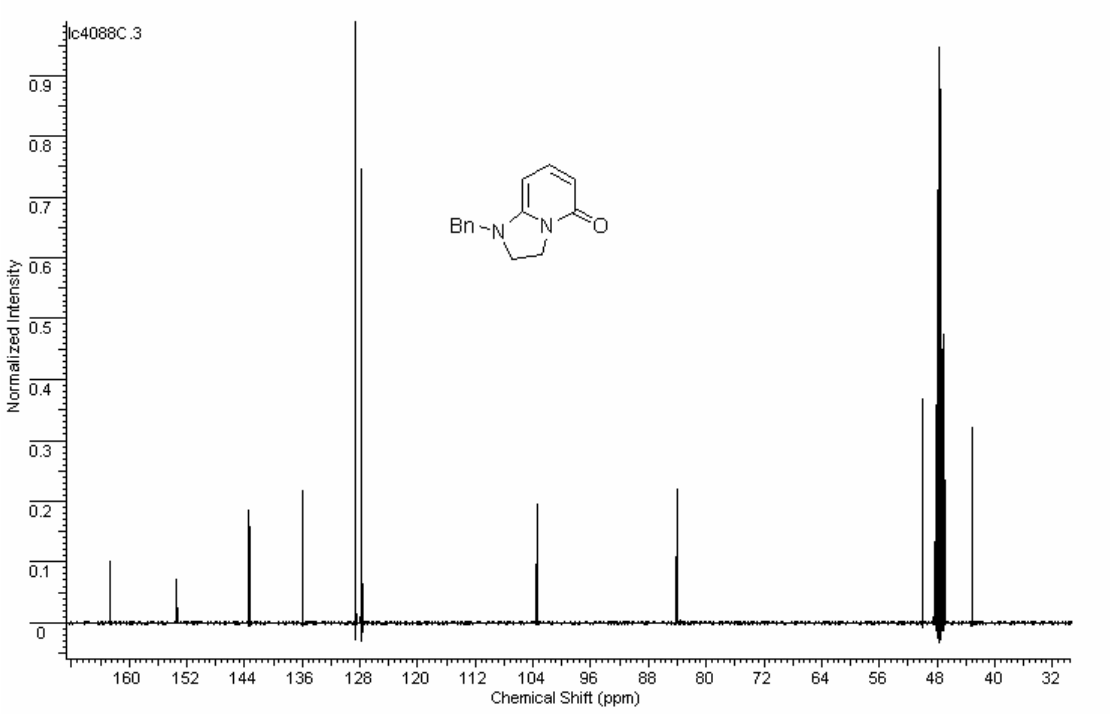
Compound 3a


lc6674H.3
Normalized Intensity
Chemical Shift (ppm)
HN
N
O

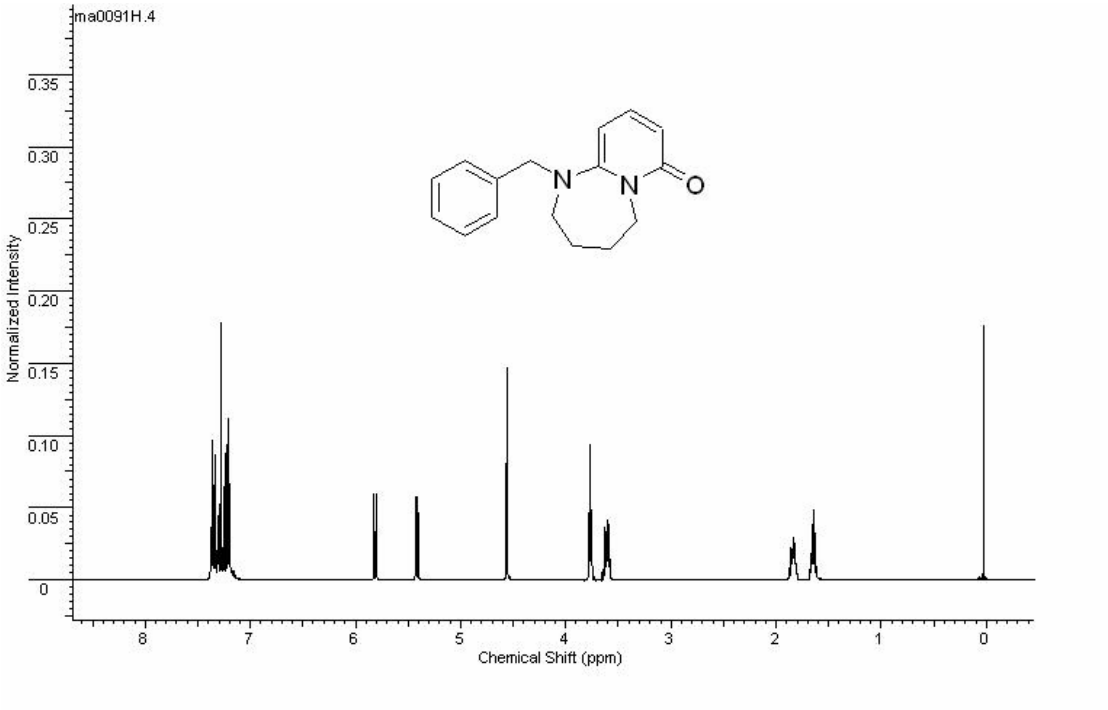

lc6674C.3
Normalized Intensity
Chemical Shift (ppm)
HN
N
O

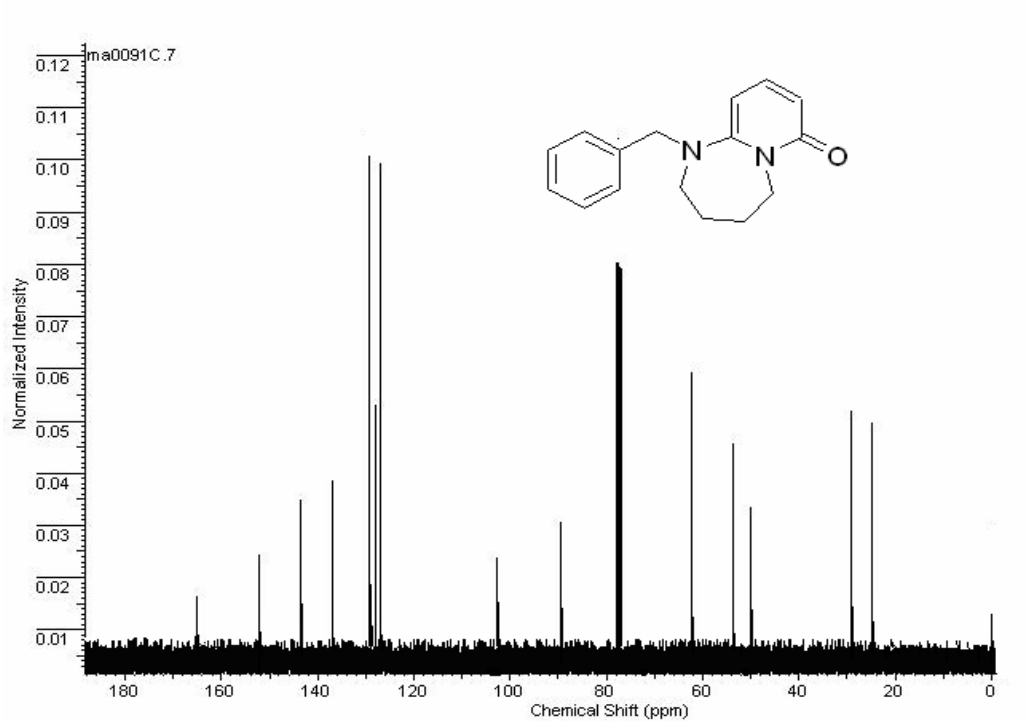
Compound 3b


lc4088H.3
Bn
N
N
O
Normalized Intensity
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
9
8
7
6
5
4
3
2
1
0
-1
Chemical Shift (ppm)

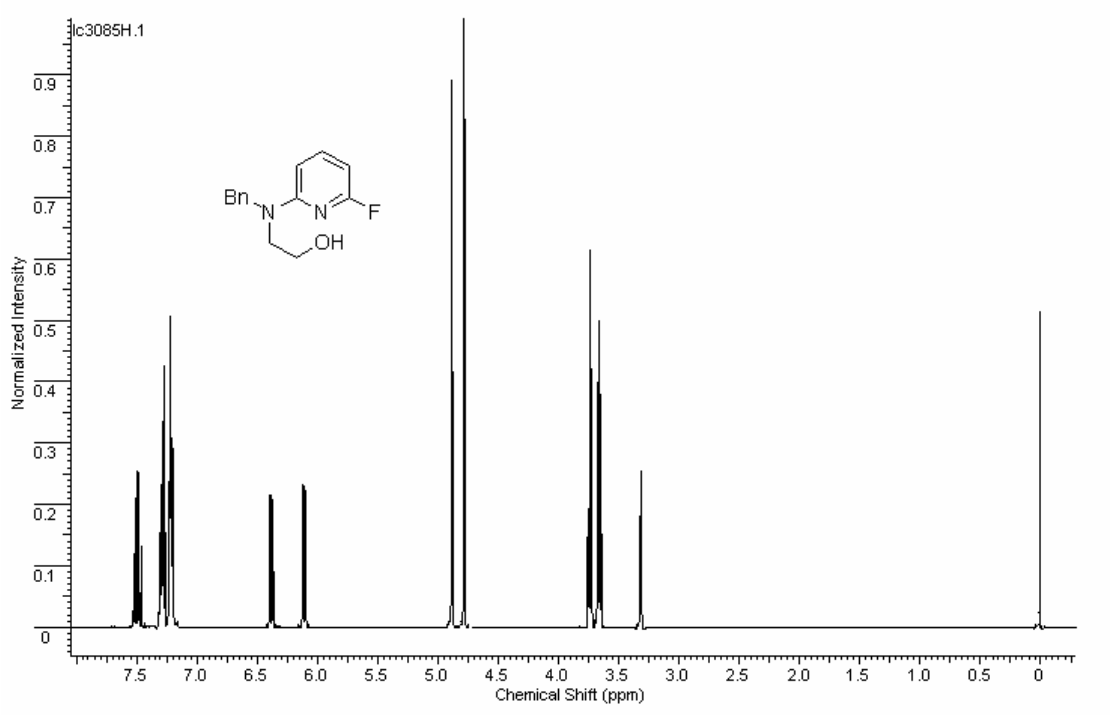

lc4088C.3
Bn
N
N
O
Normalized Intensity
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)

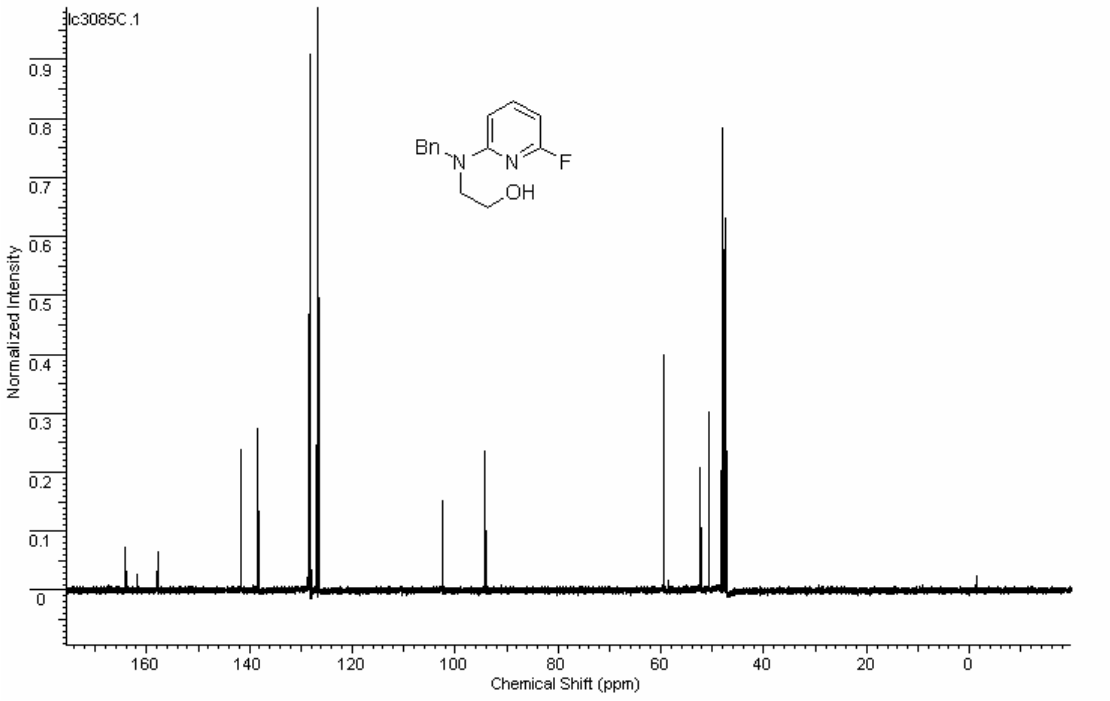
Compound 4b


ma0091H.4
Normalized Intensity
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
N
N
O

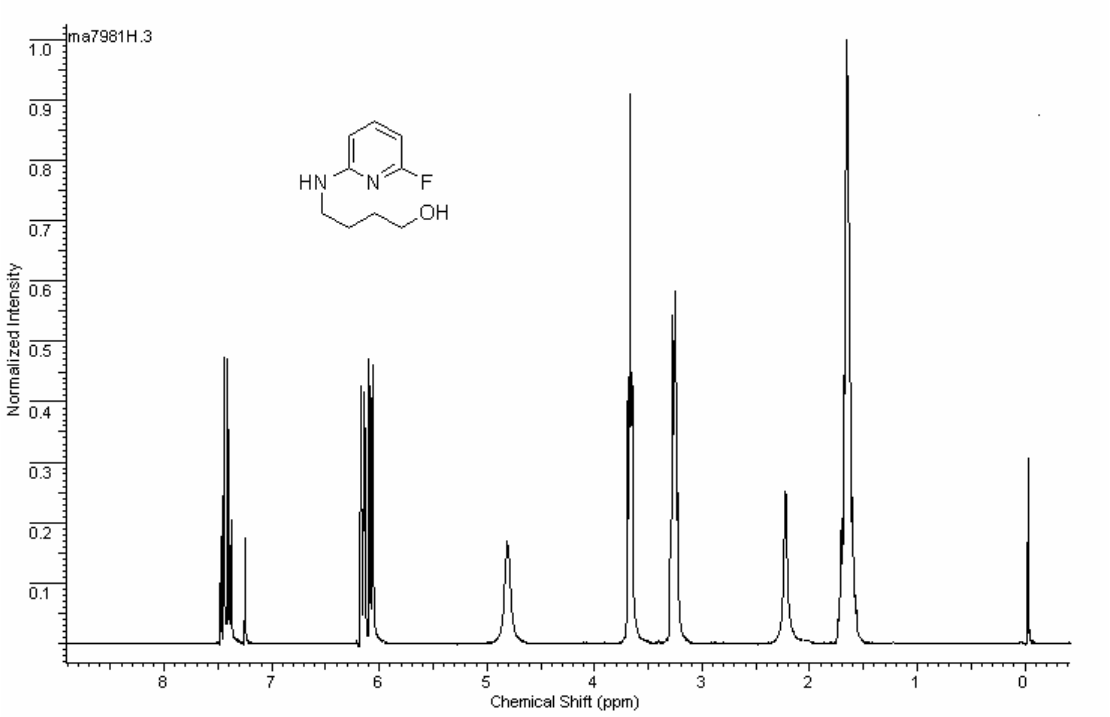

ma0091C.7
Normalized Intensity
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)
N
N
O

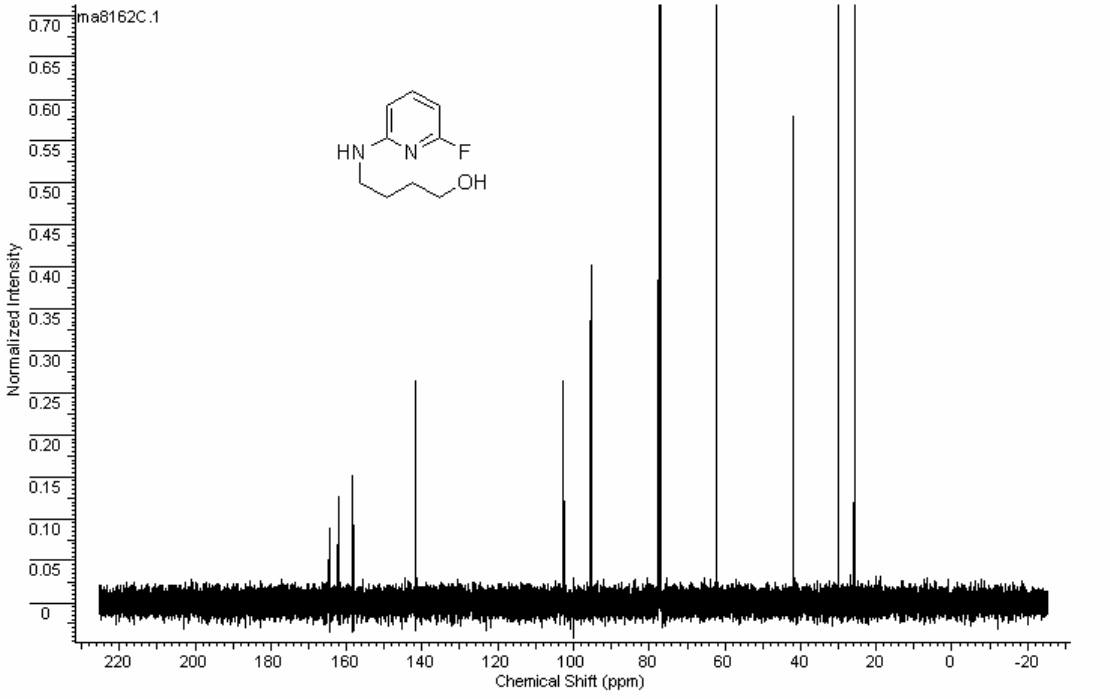
Compound 9


lc3085H.1
Bn
N
N
F
OH
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
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
Chemical Shift (ppm)

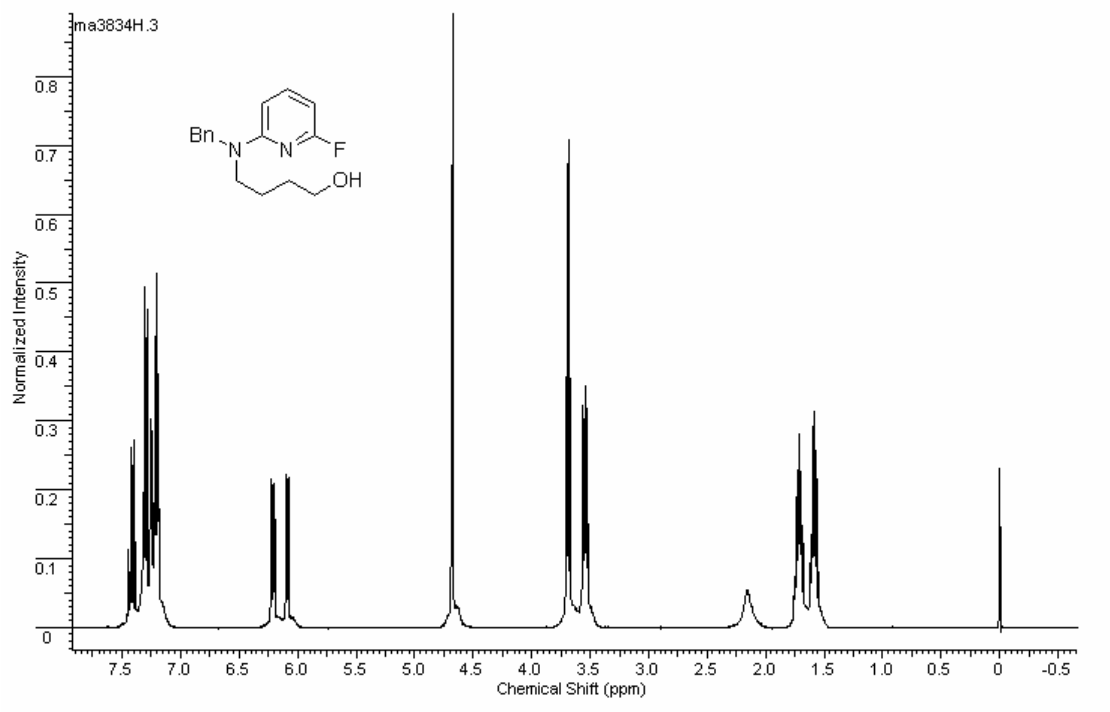

lc3085C.1
Bn
N
N
F
OH
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

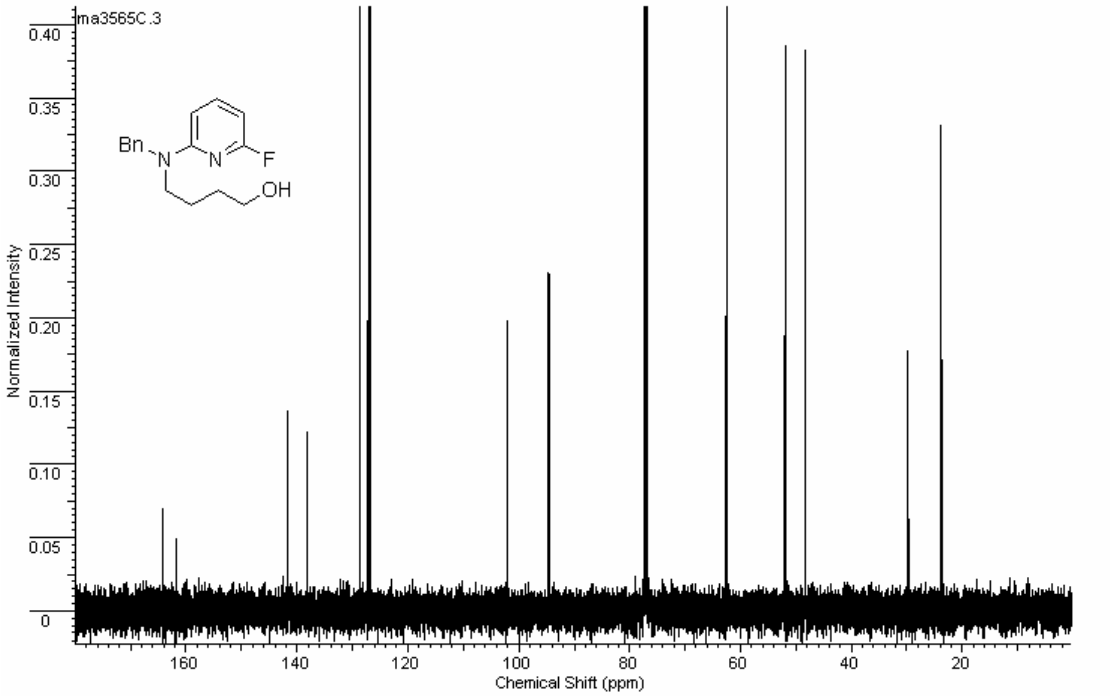
Compound 11


ma7981H.3
HN
N
F
OH
Normalized Intensity
Chemical Shift (ppm)

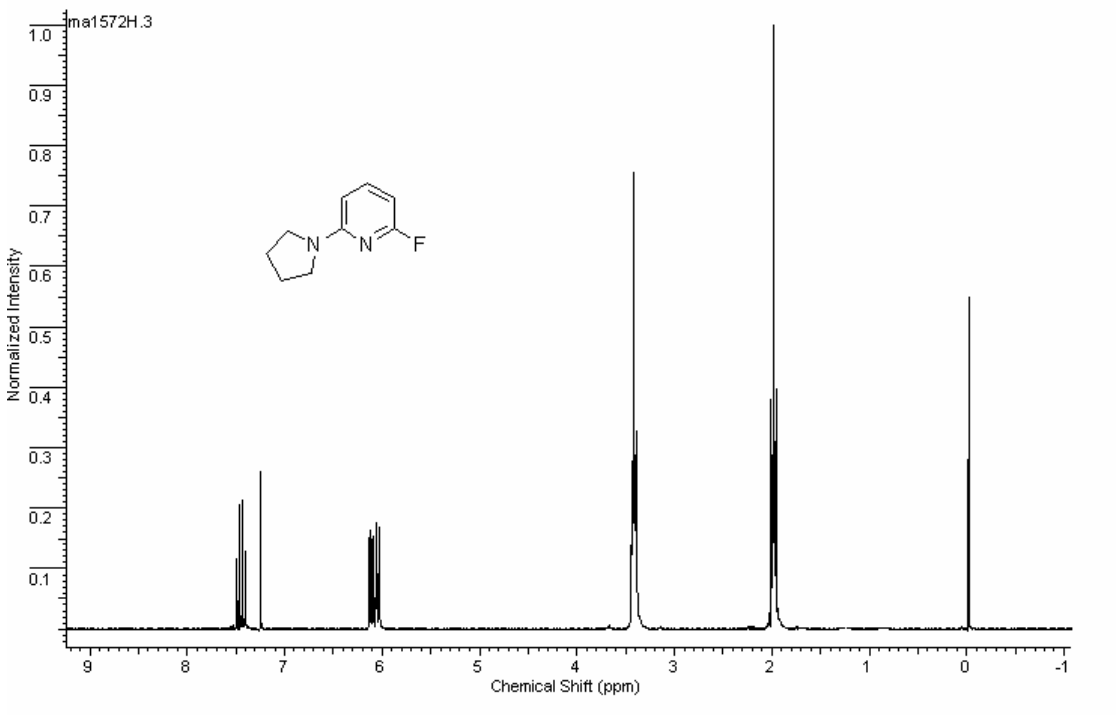

ma8162C.1
HN
N
F
OH
Normalized Intensity
Chemical Shift (ppm)

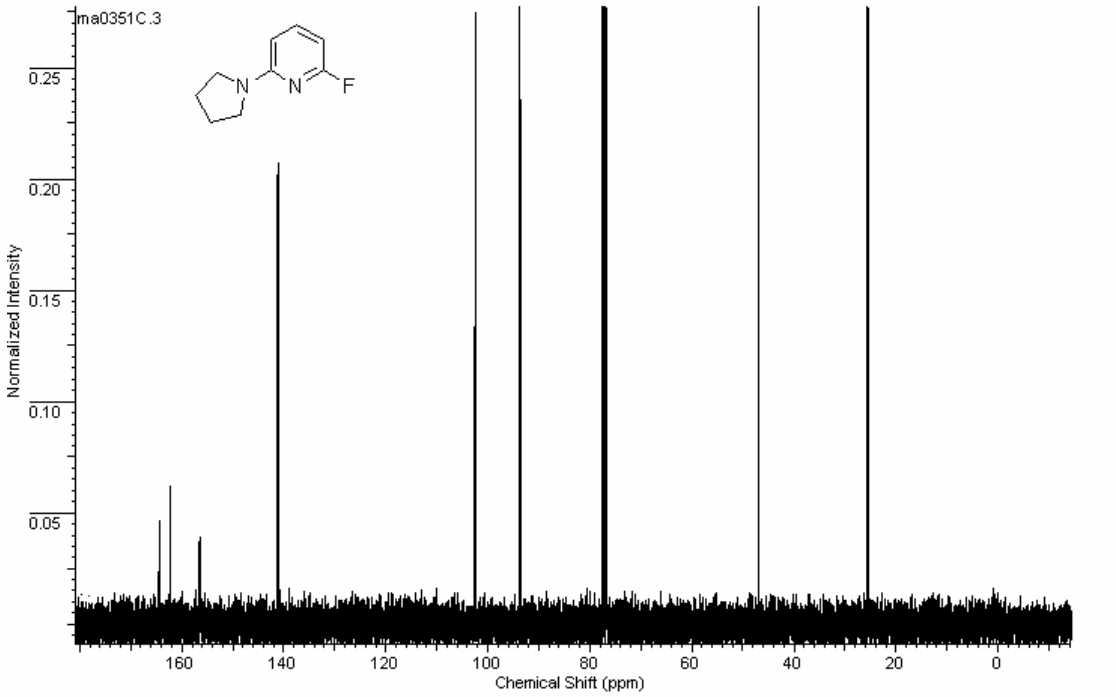
Compound 12


ma3834H.3
Bn
N
N
F
OH
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
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
-0.5
Chemical Shift (ppm)

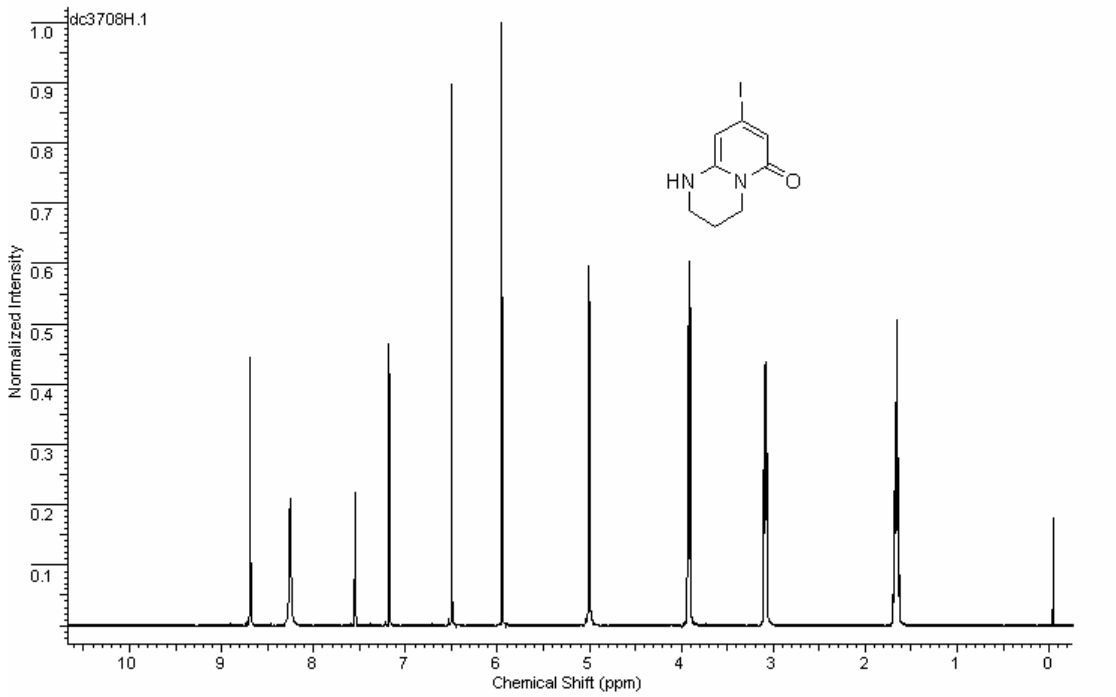

ma3565C.3
Bn
N
N
F
OH
Normalized Intensity
0
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

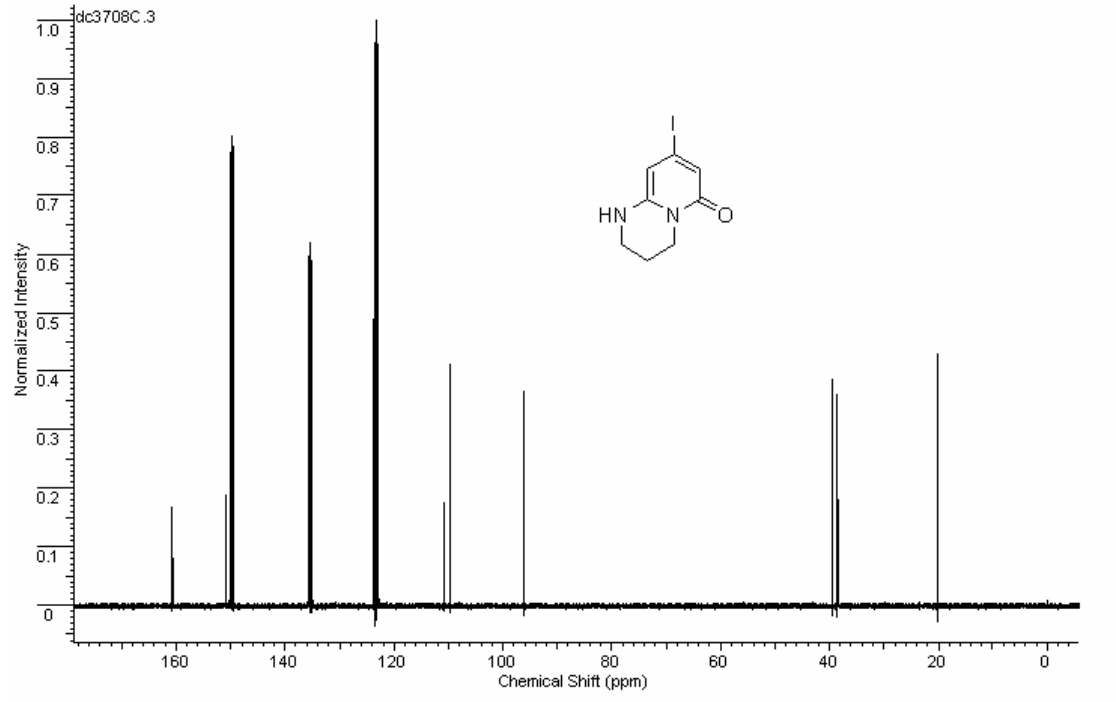
Compound 15


ma1572H.3
Normalized Intensity
Chemical Shift (ppm)
N
N
F

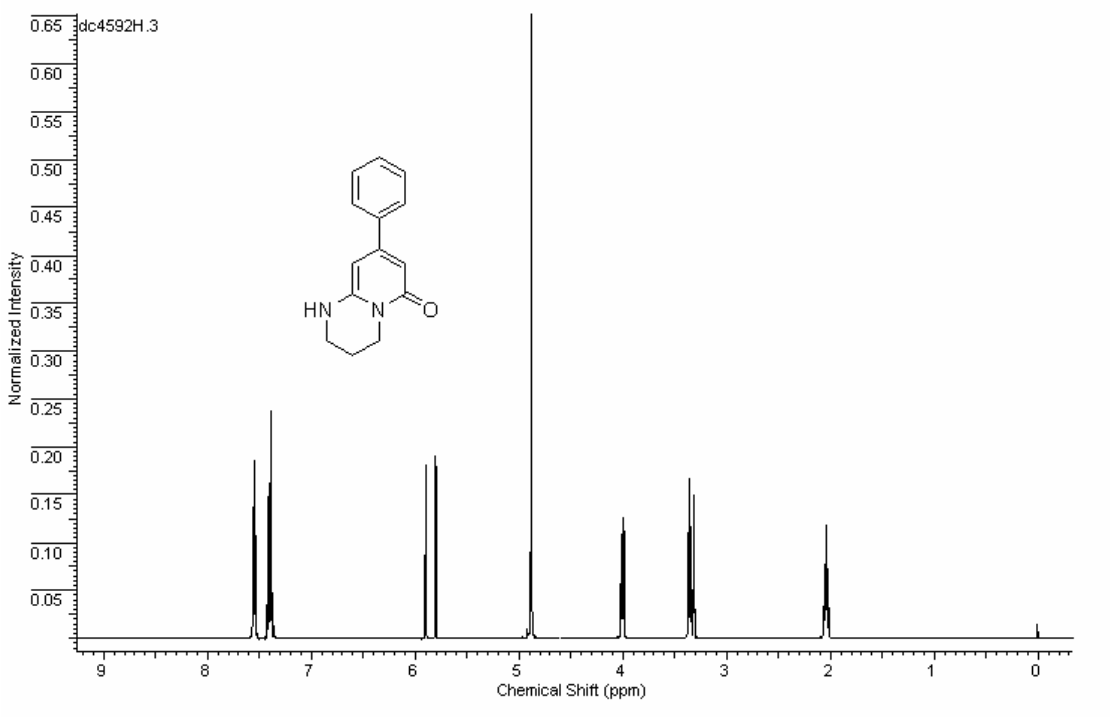

ma0351C.3
Normalized Intensity
Chemical Shift (ppm)
N
N
F

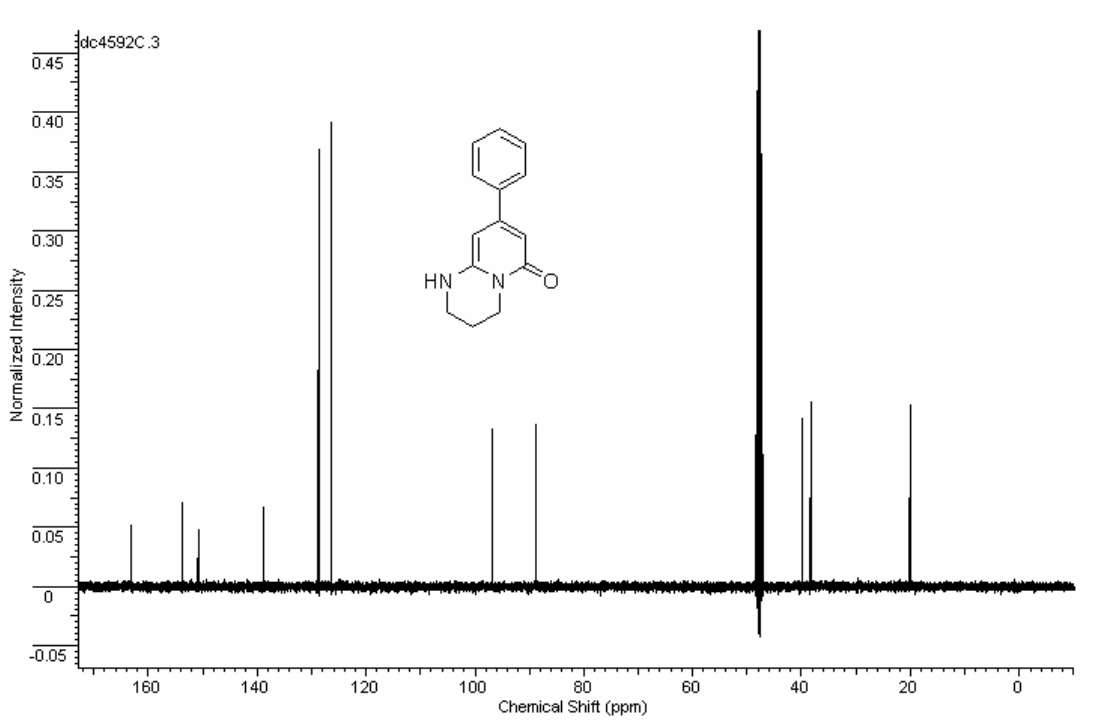
Compound 23


dc3708H.1
Normalized Intensity
Chemical Shift (ppm)
I
HN
N
O

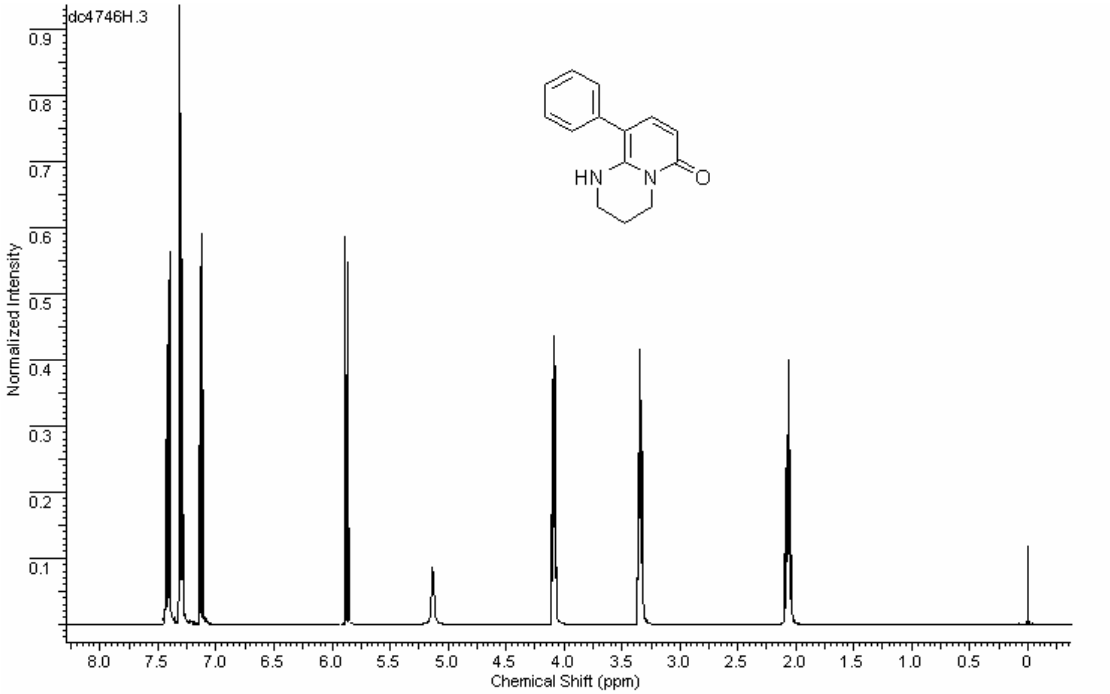

dc3708C.3
Normalized Intensity
Chemical Shift (ppm)
I
HN
N
O

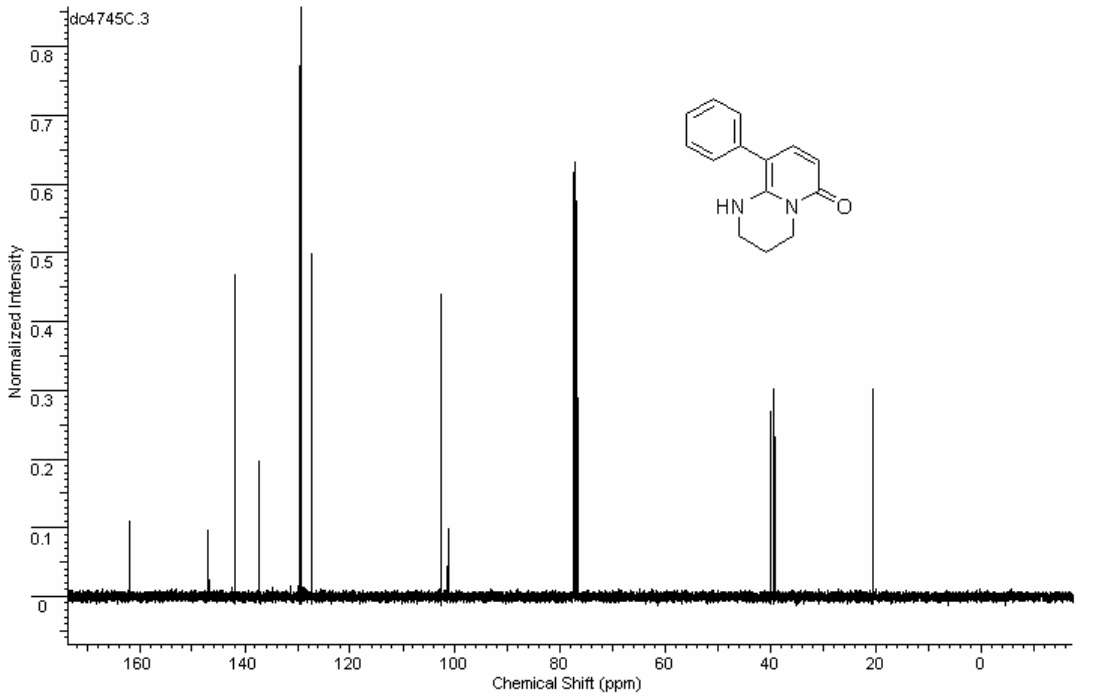
Compound 27


dc4592H.3
Normalized Intensity
Chemical Shift (ppm)
HN
N
O

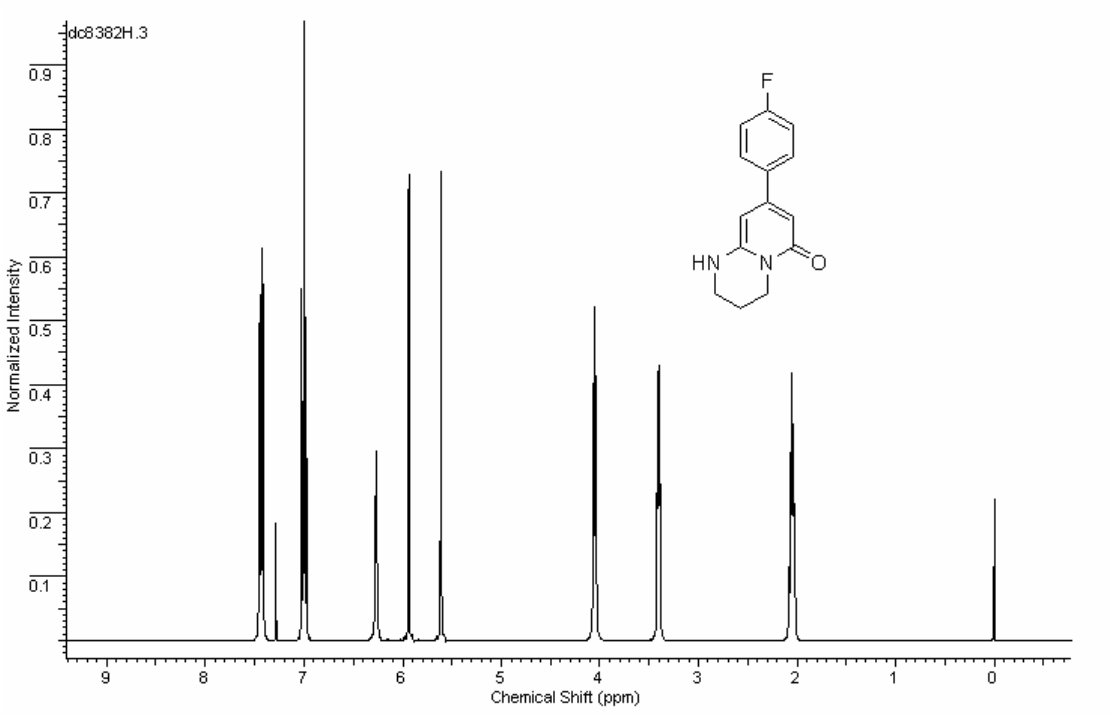

dc4592C.3
Normalized Intensity
Chemical Shift (ppm)
HN
N
O

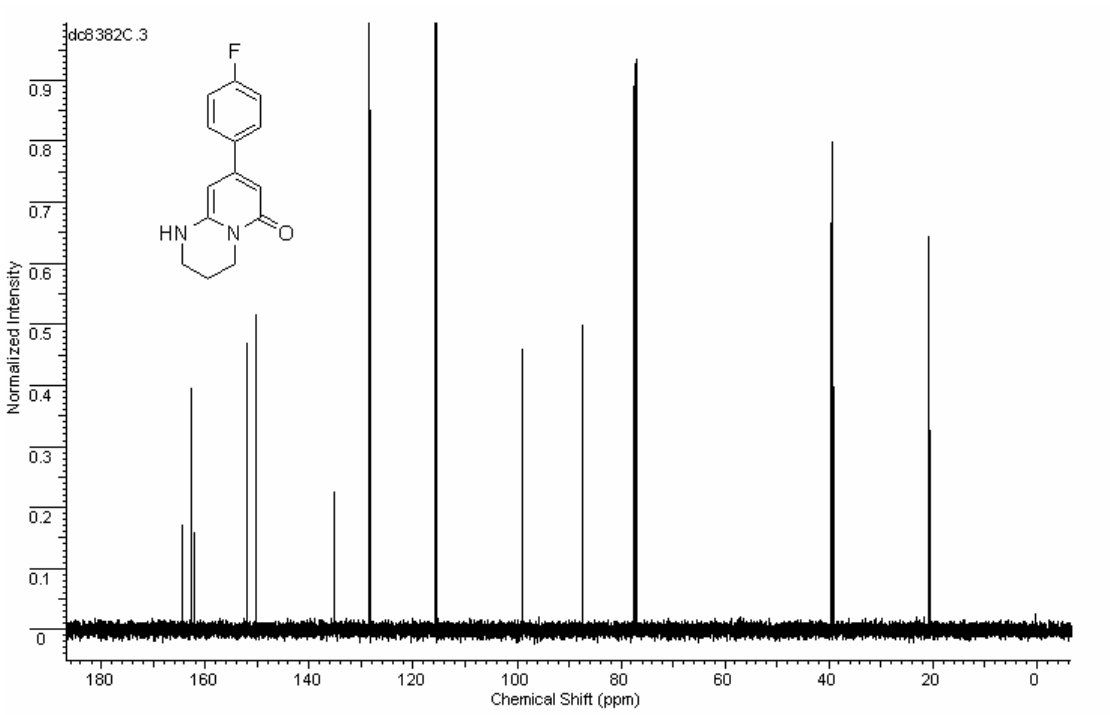
Compound 29


dc4746H.3
Normalized Intensity
Chemical Shift (ppm)
HN
N
O

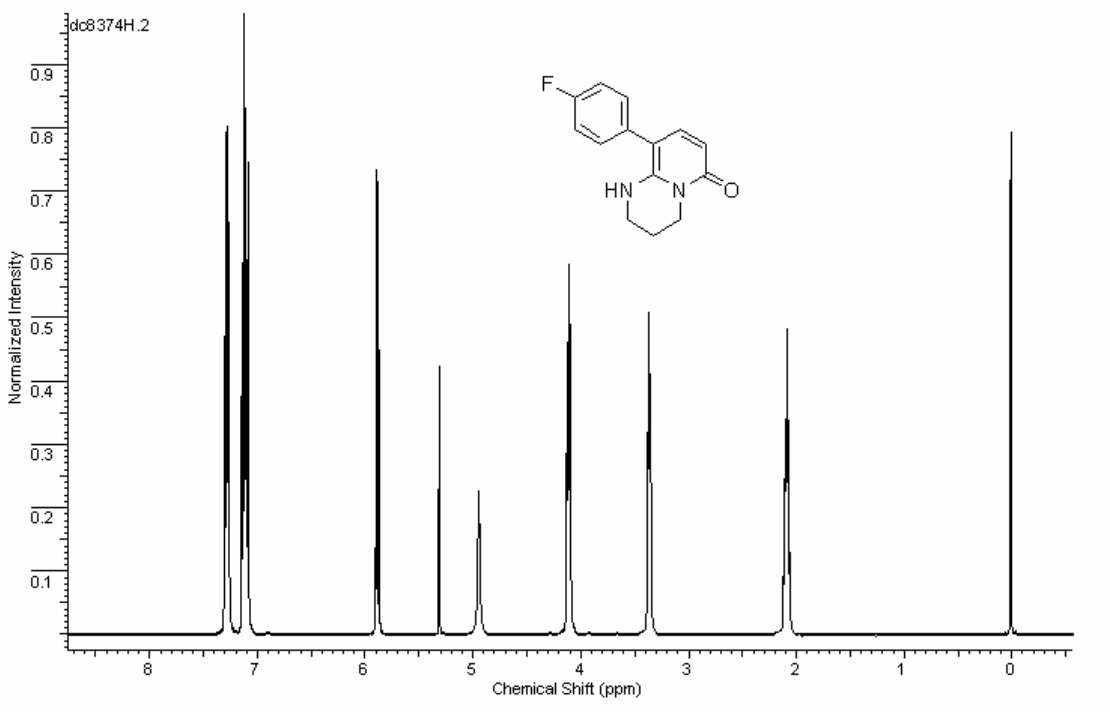

dc4745C.3
Normalized Intensity
Chemical Shift (ppm)
HN
N
O

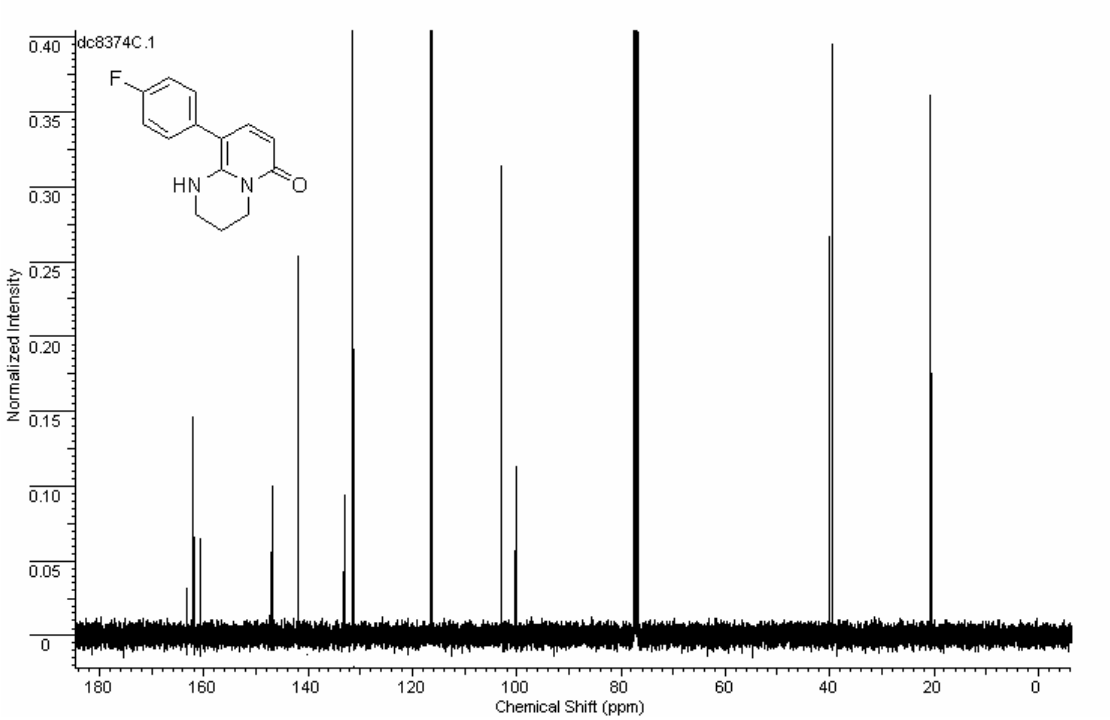
Compound 28


dc8382H.3
Normalized Intensity
Chemical Shift (ppm)
F
HN
N
O

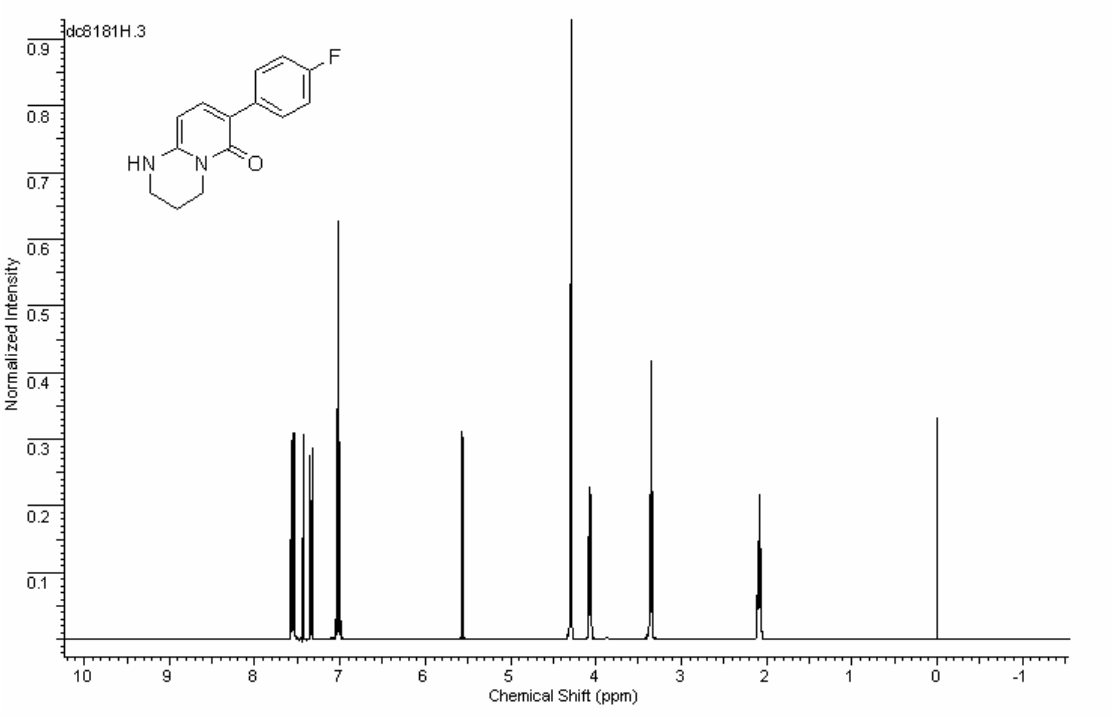

dc8382C.3
Normalized Intensity
Chemical Shift (ppm)
F
HN
N
O

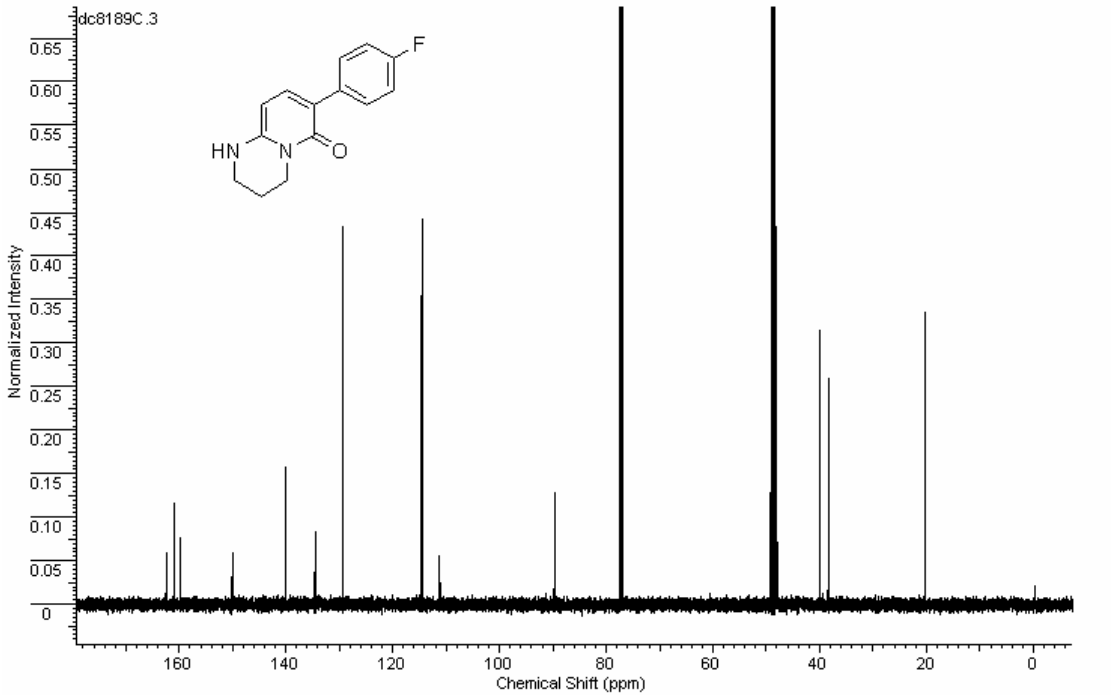
Compound 30


dc8374H.2
F
HN
N
O
Normalized Intensity
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


dc8374C.1
F
HN
N
O
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

Compound 33


dc8181H.3
F
HN
N
O
Normalized Intensity
Chemical Shift (ppm)


dc8189C.3
F
HN
N
O
Normalized Intensity
Chemical Shift (ppm)