1,1’-Carbonyldiimidazole (CDI) Mediated Coupling and Cyclization to Generate [1,2,4]Triazolo[4,3-*a*]pyridines

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Supporting Information

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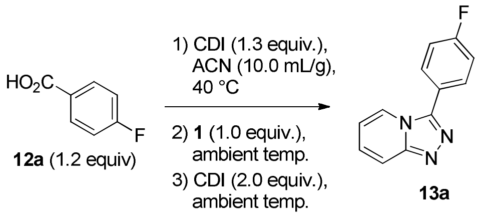
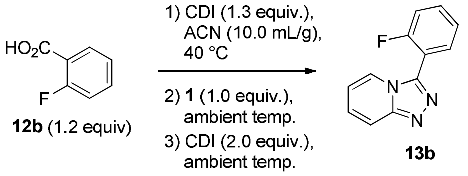
General Experimental Details:

All commercially obtained reagents were used as received. Reactions were performed in anhydrous solvents (solvent passed through activated-alumina columns or used “as is” from sure seal bottles). Silica chromatography was performed using Adlrich Merck Grade 9385 60Å (230-400 mesh size) silica. Heating was performed utilizing aluminum vial plates controlled by an IKA temperature control/stir unit. HPLC determination of reaction conversion and product purity was performed on an Agilent 1260 Infinity/6120 Quadrupole LC/MS system using a Halo C18 3x30 mm column. Flow chemistry was performed with Syrris Asia Syringe pumps using 1.0 mL capacity syringe volumes. NMR spectra were recorded at 400 MHz and are reported relative to signals of the deuterated solvent. IR spectra were recorded as thin films using a Thermo Nicolet 6700 FT-IR spectrometer. Concentrations were carried out at reduced pressure using a rotary evaporator.

Experimental Procedures:



To a 20 mL vial with a PTFE/Silicone cap and equipped with a magnetic stir-bar and placed under nitrogen (with a back-pressure bubbler) was charged 381 mg (2.75 mmol, 1.2 eq) 3-chlorobenzoic acid and 2.5 mL acetonitrile (10.0 mL/g). 483 mg (2.98 mmol, 1.3 eq) CDI was charged to the solution (CAUTION: Gas Evolution)[1] and the reaction mixture was aged at 40 °C for 30 minutes. The reaction was cooled to ambient temperature and 250 mg (2.29 mmol, 1.0 eq) 2-pyridylhydrazine was charged to the vial. The reaction mixture was aged for 60 min at ambient temperature. An additional 743 mg (4.58 mmol, 2.0 eq) of CDI was charged and the reaction was aged at ambient temperature for 3 hours to slowly generate a slurry. 4.5 mL DI water was charged to the slurry (CAUTION: Gas Evolution) and the slurry was aged for an additional 2 h. The solids were isolated by filtration and the cake was washed with 2 x 2 mL DI water and 2 x 2 mL heptane. The solids were then dried in a 40 °C vacuum oven with a nitrogen bleed overnight to afford compound **13a** as a white powder (473 mg, 89%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.23 (m, 3 H) 7.87 (t, *J*=7.38, 7.38 Hz, 1 H) 8.03 (m, 3 H) 8.62 (dd, *J*=4.69, 0.98 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 113.41, 116.29, 116.51, 119.37, 119.40, 121.82, 128.64, 128.73, 138.67, 148.17, 148.93, 150.40, 153.46, 163.76, 166.28; IR (neat): 1774.31, 1584.41, 1436.30, 1349.81, 1225.44, 1072.59, 994.80, 767.55, 740.08 cm^{-1}; HRMS (ES+) m/z calcd for C$_{12}$H$_9$FN$_3$ (M+H) 214.07750, found 214.21781.



To a 20 mL vial with a PTFE/Silicone cap and equipped with a magnetic stir-bar and placed under nitrogen (with a back-pressure bubbler) was charged 374 mg (2.67 mmol, 1.2 eq) 2-fluorobenzoic acid and 2.5 mL acetonitrile (10.0 mL/g). 468 mg (2.89 mmol, 1.3 eq) CDI was charged to the solution (CAUTION: Gas Evolution)[1] and the reaction was aged at 40 °C for 20 minutes. The reaction was cooled to ambient temperature and 250 mg (2.22 mmol, 1.0 eq) 2-pyridylhydrazine was charged to the vial. The reaction mixture was aged for 30 min at ambient temperature. An additional 720 mg (4.44 mmol, 2.0 eq) CDI was charged and the reaction was aged at ambient temperature for 1 hour. 8.0 ml DI water was charged to the reaction mixture (CAUTION: Gas Evolution), and the resulting slurry was aged an additional 1 hour. The solids were isolated by filtration and the cake was washed with 2 x 2 mL DI water and 2 x 2 mL heptane. The solids were then dried in a 40 °C vacuum oven with a nitrogen bleed overnight to afford the compound **13b** as a tan powder (378 mg, 80%): ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.24-7.33 (m, 3 H) 7.53-7.60 (m, 1 H) 7.89 (ddd, *J*=8.31, 7.43, 1.86 Hz, 1 H) 7.96-8.04 (m, 2 H) 8.60-8.66 (m, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 111.72, 111.83, 113.67, 116.97, 117.17, 121.94, 124.57, 124.61, 129.08, 133.86, 133.95, 138.72, 148.27, 148.99, 150.15, 151.29, 159.03, 161.61; IR (neat): 1793.17, 1588.31, 1470.39, 1436.34, 1368.71, 967.86, 829.66, 768.25, 735.38 cm^{-1}; HRMS (ES+) m/z calcd for C$_{12}$H$_9$FN$_3$ (M+H) 214.07750, found 214.07697.

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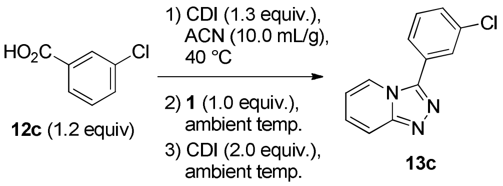
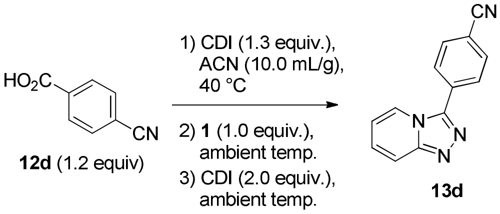
[1] For larger scale experiments, the authors recommend portion wise addition of CDI to control gas evolution.



To a 20 mL vial with a PTFE/Silicone cap and equipped with a magnetic stir-bar and placed under nitrogen (with a back-pressure bubbler) was charged 430 mg (2.75 mmol, 1.2 eq) 3-chlorobenzoic acid and 2.5 mL acetonitrile (10.0 mL/g). 483 mg (2.98 mmol, 1.3 eq) CDI was charged to the solution (CAUTION: Gas Evolution)[1] and the reaction mixture was aged at 40 °C for 30 minutes. The reaction was cooled to ambient temperature and 250 mg (2.29 mmol, 1.0 eq) 2-pyridylhydrazine was charged to the vial. The reaction mixture was aged for 30 min at ambient temperature. An additional 743 mg (4.58 mmol, 2.0 eq) of CDI was charged and the reaction was aged at ambient temperature for 4 hours to slowly generate a slurry. 4.5 mL DI water was charged to the slurry (CAUTION: Gas Evolution) and the slurry was aged for an additional 45 min. The solids were isolated by filtration and the cake was washed with 2 x 2 mL DI water and 2 x 2 mL heptane.[2] The solids were then dried in a 40 °C vacuum oven with a nitrogen bleed overnight to afford compound **13c** as a white powder (473 mg, 90%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.29 (m, 1H) 7.51 (m, 2H) 7.89 (m, 2H) 8.05 (m, 2 H) 8.63 (dd, *J*=4.6, 1.47 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 113.42, 121.92, 124.32, 124.71, 126.25, 130.30, 132.21, 135.25, 138.68, 148.05, 148.94, 150.17, 152.99; IR (neat): 1774.31, 1600.63, 1584.41, 1474.35, 1436.30, 1369.17, 1349.81, 1225.44, 1165.43, 994.80, 841.86 cm^{-1}; HRMS (ES+) m/z calcd for $C_{12}H_9ClN_3$ (M+H) 230.04795, found 230.67241.



To a 20 mL vial with a PTFE/Silicone cap and equipped with a magnetic stir-bar and placed under nitrogen (with a back-pressure bubbler) was charged 396 mg (2.67 mmol, 1.2 eq) 4-cyanobenzoic acid and 2.5 mL acetonitrile (10.0 mL/g). 468 mg (2.89 mmol, 1.3 eq) CDI was charged to the solution (CAUTION: Gas Evolution)[1] and the reaction mixture was aged at 40 °C for 30 minutes. The reaction was cooled to ambient temperature and 250 mg (2.22 mmol, 1.0 eq) 2-pyridylhydrazine was charged to the vial. The reaction mixture was aged for 20 min at ambient temperature. An additional 720 mg (4.44 mmol, 2.0 eq) of CDI was charged and the reaction was aged at ambient temperature for 3 hours. 5 ml DI water was charged to the solution (CAUTION: Gas Evolution) and the resulting slurry was aged for an additional 3 hours. The solids were isolated by filtration and the cake was washed with 2 x 2 mL DI water followed by 2 x 2 mL heptane. The solids were then dried in a 40 °C vacuum oven with a nitrogen bleed overnight to afford compound **13d** as a white powder (470 mg, 96%): ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.31 (ddd, *J*=7.34, 4.89, 0.88 Hz, 1 H) 7.82 (d, *J*=8.06 Hz, 2 H) 7.87-7.95 (m, 1 H) 8.04 (d, *J*=8.41 Hz, 1 H) 8.14 (d, *J*=7.98 Hz, 2 H) 8.61-8.66 (m, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 113.61, 115.67, 117.66, 119.67, 122.28, 126.75, 127.03, 132.77, 138.86, 147.92, 149.06, 150.03, 152.56; IR (neat) 3109, 1780, 1649, 1470, 1436, 1334, 946, 771, 738 cm^{-1}; HRMS (ES+) m/z calcd for $C_{13}H_9N_4$ (M+H) 221.08217, found 221.08175.

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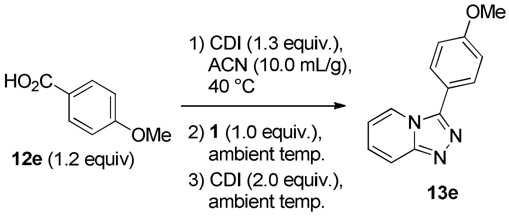
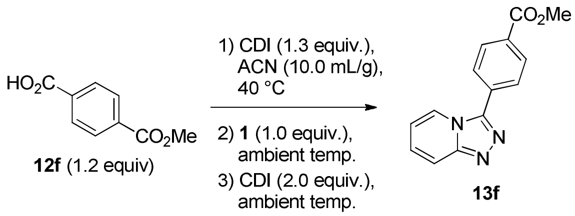
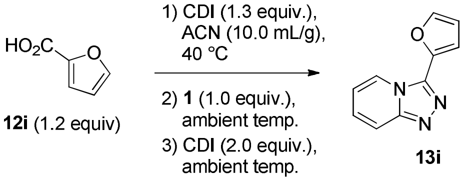
[2] During filtration, additional precipitation of solids occurred in the receiving flask. These solids were collected and charged to the primary cake before cake washing operations.



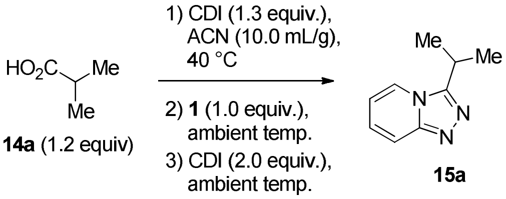
To a 20 mL vial with a PTFE/Silicone cap and equipped with a magnetic stir-bar and placed under nitrogen (with a back-pressure bubbler) was charged 418 mg (2.75 mmol, 1.2 eq) 4-methoxybenzoic acid and 2.5 mL acetonitrile (10.0 mL/g). 483 mg (2.98 mmol, 1.3 eq) CDI was charged to the solution (CAUTION: Gas Evolution)[1] and the reaction mixture was aged at 40 °C for 30 minutes. The reaction was cooled to ambient temperature and 250 mg (2.29 mmol, 1.0 eq) 2-pyridylhydrazine was charged to the vial. The reaction mixture was aged for 30 min at ambient temperature. An additional 743 mg (4.58 mmol, 2.0 eq) of CDI was charged and the reaction was aged at ambient temperature for 4 hours to slowly generate a slurry. 4.5 mL DI water was charged to the slurry (CAUTION: Gas Evolution) and the slurry was aged for an additional 45 min. The solids were isolated by filtration and the cake was washed with 2 x 2 mL DI water and 2 x 2 mL heptane. The solids were then dried in a 40 °C vacuum oven with a nitrogen bleed overnight to afford compound **13e** as a white powder (473 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.99 (m, 2H) 7.23 (ddd, *J*=7.34, 4.89, 0.88 Hz, 1H) 7.84 (ddd, *J*=8.36, 7.38, 1.86 Hz, 1H) 7.94 (m, 2 H) 8.03 (d, *J*=8.41 Hz, 1 H) 8.60 (dd, *J*=4.6, 1.47 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 55.43, 113.32, 114.41, 115.40, 121.54, 128.16, 138.56, 148.34, 148.87, 150.63, 154.26, 162.70; IR (neat): 1774.31, 1584.41, 1506.44, 1474.35, 1436.30, 1225.44, 1165.43, 1072.59, 994.80, 841.86, 767.55 cm^{-1}; HRMS (ES+) m/z calcd for $C_{13}H_{12}N_3O$ (M+H) 226.09749, found 226.25333.



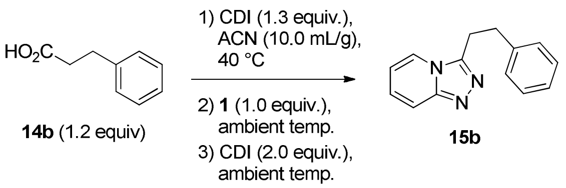
To a 20 mL vial with a PTFE/Silicone cap equipped with a magnetic stir-bar and placed under nitrogen (with a back-pressure bubbler) was charged 495 mg (2.67 mmol, 1.2 eq) monomethyl terephthalate and 2.5 mL acetonitrile (10.0 mL/g). 468 mg (2.89 mmol, 1.3 eq) CDI was charged to the solution (CAUTION: Gas Evolution)[1] and the reaction mixture was aged at 40 °C for 20 minutes. The reaction was cooled to ambient temperature and 250 mg (2.22 mmol, 1.0 eq) 2-pyridylhydrazine was charged to the vial. The reaction mixture was aged for 20 minutes at ambient temperature. An additional 720 mg (4.44 mmol, 2.0 eq) CDI was charged and the reaction was aged at ambient temperature for 2 hours. 5.0 mL DI water was charged to the reaction mixture (CAUTION: Gas Evolution), and the resulting slurry stirred was aged for an additional 2 hours. The solids were isolated by filtration and the cake was washed with 2 x 2 mL DI water and 2 x 2 mL heptane. The solids were then dried in a 40 °C vacuum oven with a nitrogen bleed overnight to afford the compound **13f** as a white powder (560 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.97 (s, 3 H) 7.30 (ddd, *J*=7.43, 4.89, 0.78 Hz, 1 H) 7.90 (t, *J*=7.77 Hz, 1 H) 8.06 (d, *J*=8.41 Hz, 1 H) 8.09-8.13 (m, 2 H) 8.16-8.21 (m, 2 H) 8.64 (dt, *J*=4.89, 0.88 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 52.56, 113.62, 122.12, 126.34, 126.96, 130.22, 133.35, 138.83, 148.17, 149.09, 150.37, 153.49, 165.99; IR (neat): 1774.65, 1722.41, 1580.23, 1360.68, 1275.42, 1104.13, 995.55, 773.30, 736.00, 695.34 cm^{-1}; HRMS (ES+) m/z calcd for $C_{14}H_{12}N_3O_2$ (M+H) 254.09240, found 254.09206.



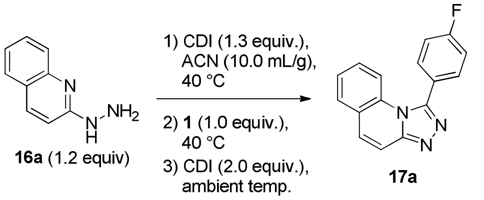
To a 20 mL vial with a PTFE/Silicone cap and equipped with a magnetic stir-bar and placed under nitrogen (with a back-pressure bubbler) was charged 299 mg (2.67 mmol, 1.2 eq) 2-furancarboxylic acid and 2.5 mL acetonitrile (10.0 mL/g). 468 mg (2.89 mmol, 1.3 eq) CDI was charged to the solution (CAUTION: Gas Evolution)[1] and the reaction was aged at 40 °C for 20 minutes. The reaction was cooled to ambient temperature and 250 mg (2.22 mmol, 1.0 eq) 2-pyridylhydrazine was charged to the vial. The reaction was aged 30 min at ambient temperature. An additional 720 mg (4.44 mmol, 2.0 eq) CDI was charged and the reaction was aged at ambient temperature for 1 hour. The reaction was concentrated to remove approx. 1 ml solvent, and 3.0 ml DI water was charged to the reaction (CAUTION: Gas Evolution). The resulting slurry was aged an additional 2 hours. The solids were isolated by filtration and the cake was washed with 2 x 2 mL DI water and 2 x 2 mL heptane. The solids were dried in a 50 °C vacuum oven with a nitrogen bleed overnight to afford the compound **13i** as a white powder (361 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.61 (dd, *J*=3.52, 1.76 Hz, 1 H) 7.18 (d, *J*=3.52 Hz, 1 H) 7.25-7.29 (m, 1 H) 7.66 (d, *J*=1.76 Hz, 1 H) 7.87 (ddd, *J*=8.26, 7.48, 1.86 Hz, 1 H) 8.02 (d, *J*=8.22 Hz, 1 H) 8.60-8.64 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 112.18, 113.35, 114.99, 121.87, 138.39, 138.66, 146.21, 147.50, 148.98, 149.68. IR (neat): 3108.71, 1779.57, 1649.30, 1469.51, 1435.61, 1333.59, 945.95, 771.23, 737.76 cm^{-1}. HRMS (ES+) m/z calcd $C_{10}H_8N_3O$ (M+H) 186.06619, found 186.06572.



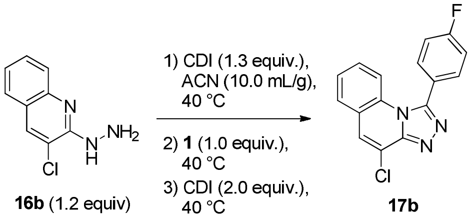
To a 20 mL vial with a PTFE/Silicone cap and equipped with a magnetic stir-bar and placed under nitrogen (with a back-pressure bubbler) was charged 247 µl (2.67 mmol, 1.2 eq) isobutyric acid and 2.5 mL acetonitrile (10.0 mL/g). 468 mg (2.89 mmol, 1.3 eq) CDI was charged to the solution (CAUTION: Gas Evolution)[1] and the reaction mixture was aged at 40 °C for 50 minutes. The reaction was cooled to ambient temperature and 250 mg (2.22 mmol, 1.0 eq) 2-pyridylhydrazine was charged to the vial. The reaction mixture was aged for 30 min at ambient temperature. An additional 720 mg (4.44 mmol, 2.0 eq) CDI was charged and the reaction was aged at ambient temperature for 2 hours. The crude reaction mixture was concentrated to an oil and purified by silica chromatography (25% to 33% ethyl acetate in heptane). The desired fractions were collected and concentrated to afford compound **15a** as a pale yellow oil (276 mg, 77%). ^{1}H NMR (400 MHz, CDCl3) δ ppm: 1.38 (d, *J*=6.85 Hz, 6 H) 3.02 (dt, *J*=14.04, 6.97 Hz, 1H) 7.22 (ddd, *J*=7.38, 4.94, 0.78 Hz, 1 H) 7.82 (t, *J*=7.81 Hz, 1 H) 7.97 (d, *J*=8.41 Hz, 1 H) 8.56 (dd, *J*=4.89, 0.98 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3) δ ppm: 18.91, 27.20, 113.18, 121.50, 138.56, 148.21, 148.87, 151.08, 161.33; IR (neat): 2982.23, 1772.73, 1584.35, 1434.44, 1350.98, 950.10, 780.32, 743.73 cm^{-1}; HRMS: (ES+) m/z calcd for $C_9H_{12}N_3$ (M+H) 162.10257, found 162.10213.



To a 20 mL vial with a PTFE/Silicone cap and equipped with a magnetic stir-bar and placed under nitrogen (with a back-pressure bubbler) was charged 413 mg (2.75 mmol, 1.2 eq) hydrocinnamic acid and 2.5 mL acetonitrile (10.0 mL/g). 483 mg (2.98 mmol, 1.3 eq) CDI was charged to the solution (CAUTION: Gas Evolution)[1] and the reaction was aged at 40 °C for 60 minutes. The reaction was cooled to ambient temperature and 250 mg (2.29 mmol, 1.0 eq) 2-pyridylhydrazine was charged to the vial. The reaction was aged for 30 min at ambient temperature. An additional 743 mg (4.58 mmol, 2.0 eq) of CDI was charged and the reaction was aged at ambient temperature for 30 min. 5.0 mL DI water was charged to form a biphasic mixture (CAUTION: Gas Evolution). The organic phase was separated and the aqueous phase was extracted with dichloromethane 2 x 5 mL. The combined organic layers were dried with anhydrous sodium sulfate and concentrated to afford a pale yellow oil. The crude product was purified by silica chromatography (40% ethyl acetate:heptanes) to yield **15b** as a white/slight yellow semi-solid (453 mg, 89% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 3.04 (m, 4H) 7.24 (m, 6H) 7.81 (ddd, *J*=8.31, 7.34, 1.96 Hz, 1H) 7.96 (d, *J*=8.22 Hz, 1H) 8.54 (dq, *J*=4.9x(4) Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm:28.24, 31.50, 112.94, 121.53, 126.53, 126.70, 128.12, 128.67, 138.54, 138.88, 147.96, 148.77, 150.79, 156.71; IR (neat): 1774.31, 1622.78, 1584.41, 1506.44, 1474.35, 1436.30, 1349.81, 1225.44, 1165.43, 994.80, 841.86, 767.55 cm^{-1}; HRMS (ES+) m/z calcd for $C_{14}H_{14}N_3$ (M+H) 224.11822, found 224.28051.



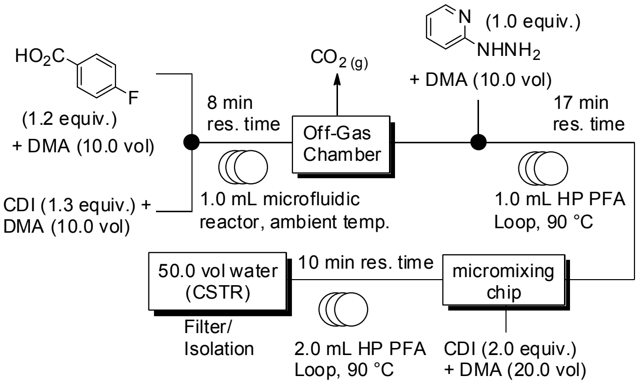
To a 20 mL vial with a PTFE/Silicone cap and equipped with a stir-bar and placed under nitrogen (with a back-pressure bubbler) was charged 264 mg (1.89 mmol, 1.2 eq) 4-fluorobenzoic acid and 4.0 mL acetonitrile. 331 mg (2.04 mmol, 1.3 eq) CDI was charged to the solution (CAUTION: Gas Evolution)[1] and the reaction mixture was aged at 40 °C for 50 minutes. The reaction was cooled to ambient temperature and 250 mg (1.57 mmol, 1.0 eq) 2-hydrazinoquinoline was charged to the vial. The reaction was aged at 40 °C for 1.5 hours. The reaction was cooled to ambient temperature and an additional 510 mg (3.14 mmol, 2.0 eq) CDI was charged to the vial. The reaction was aged at ambient temperature for an additional 30 minutes. 4.0 ml DI water was charged to the reaction (CAUTION: Gas Evolution), and the resulting slurry was aged for 1 hour. The solids were isolated by filtration and the cake was washed with 2 x 2 mL DI water and 2 x 2 mL heptane. The solids were dried in a 50 °C vacuum oven with a nitrogen bleed overnight to afford compound **17a** as an off-white powder (410 mg, 99%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm: 7.23 (m, 2 H) 7.59 (t, *J*=7.28 Hz, 1 H) 7.79 (td, *J*=7.73, 1.37 Hz, 1 H) 7.88 (d, *J*=8.02, 1 H) 8.06-8.12 (m, 2 H) 8.18-8.25 (m, 2 H) 8.35 (d, *J*=9.00 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ ppm: 112.40, 116.34, 116.56, 119.38, 126.74, 127.53, 128.88, 129.00, 130.61, 139.39, 146.65, 147.03, 150.70, 153.78, 163.88, 166.41; IR (neat): 1777.72, 1599.04, 1505.49, 1368.52, 1341.35, 1238.85, 1000.59, 825.58, 743.74, 606.48 cm^{-1}; HRMS [ES+] m/z calcd for $C_{16}H_{11}FN_3$ (M+H) 264.09315, found 264.09245.

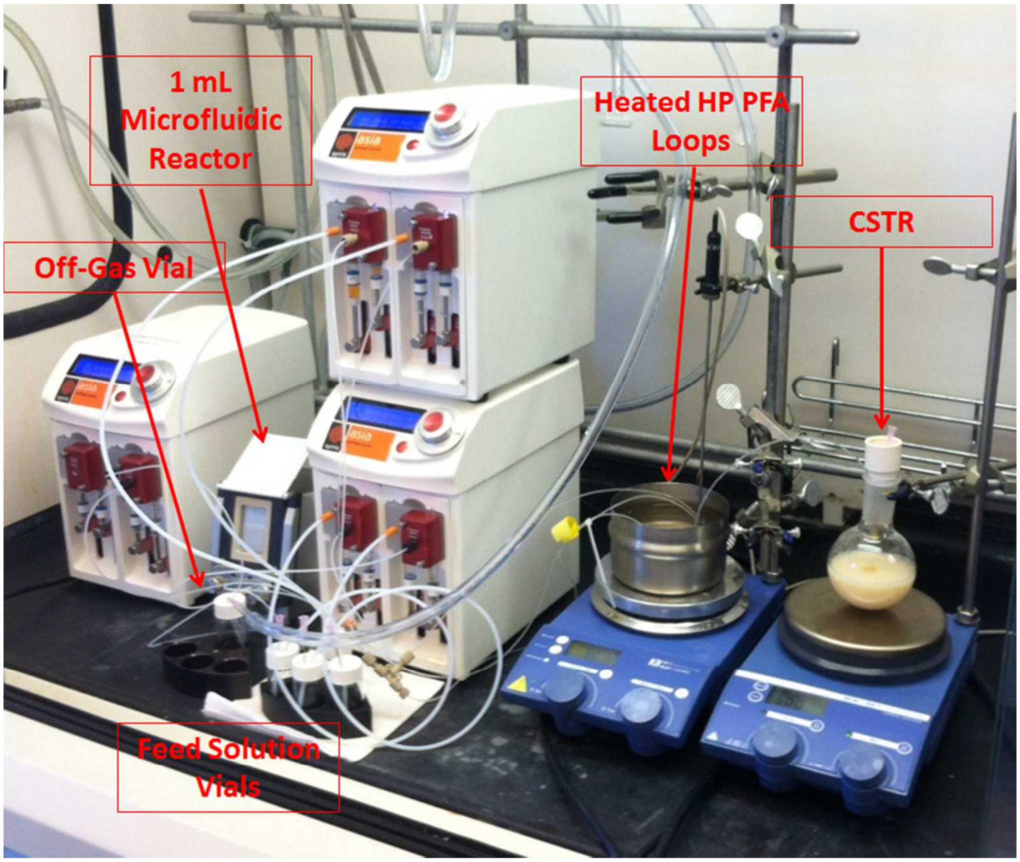


16b (1.2 equiv) **17b**

To a 20 mL vial with a PTFE/Silicone cap and equipped with a magnetic stir-bar and placed under nitrogen (with a back-pressure bubbler) was charged 278 mg (1.99 mmol, 1.2 eq) 4-fluorobenzoic acid and 5.0 mL acetonitrile. 350 mg (2.15 mmol, 1.3 eq) CDI was added to the solution (CAUTION: Gas Evolution)[1] and the reaction was aged at 40 °C for 20 minutes. The reaction was cooled to ambient temperature and 250 mg (1.65 mmol, 1.0 eq) 3-chloro-2-hydrazinopyridine was charged and the reaction was aged at 40 °C for 1 hour. The reaction was cooled to ambient temperature and an additional 617 mg (3.80 mmol, 2.3 eq) CDI was charged to the vial. The reaction was aged at 40 °C for 3.5 hours. 9.0 ml DI water was charged to the reaction mixture (CAUTION: Gas Evolution), and the resulting slurry was aged an additional 1 hour. The solids were isolated by filtration and the cake was washed with 2 x 2 mL DI water and 2 x 2 mL heptane. The solids were dried in a 50 °C vacuum oven with a nitrogen bleed overnight to afford the compound **17b** as a white powder (380 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.17-7.25 (m, 2 H) 7.44 (dd, *J*=8.12, 4.60 Hz, 1 H) 7.92-8.01 (m, 3 H) 8.57 (dd, *J*=4.69, 1.56 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 116.35, 116.57, 119.67, 125.70, 128.44, 128.52, 140.00, 144.85, 147.58, 150.63, 154.12, 163.73, 166.26. IR (neat): 1789.26, 1618.88, 1503.22, 1415.26, 1340.61, 1222.41, 1157.43, 978.72, 841.07, 797.41, 736.46 cm^{-1}; HRMS (ES+) m/z calcd for $C_{12}H_8ClFN_3$ 248.03853 (M+H), found 248.03798.

3. Continuous Flow Experimental Procedure





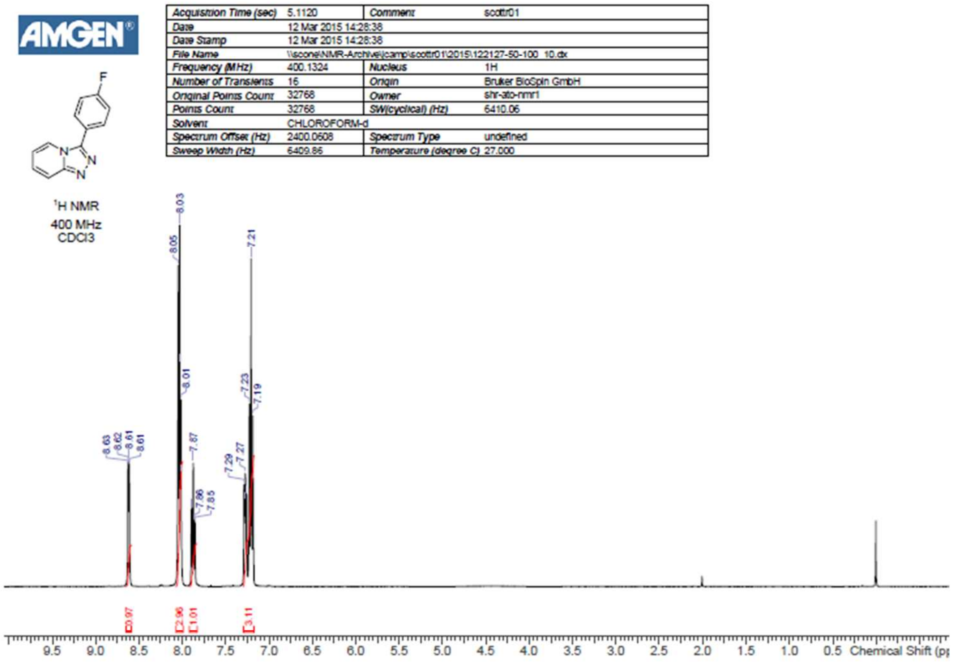
4-Fluorobenzoic acid (770 mg, 5.50 mmol, 1.2 equiv.), CDI charge-1 (966 mg, 5.96 mmol, 1.3 equiv.), and 2-pyridyl hydrazine (500 mg, 4.58 mmol, 1.0 equiv.) were charged to individual 20 mL vials with a PTFE/Silicone membrane cap. DMA (5.0 mL, 10.0 mL/g) was charged into each 20 mL vial to create homogeneous solutions. CDI charge-2 (1486 mg, 9.16 mmol, 2.0 equiv) was charged into an individual 20 mL vial and dissolved in 10.0 mL (20.0 mL/g) DMA and sealed with a PTFE/Silicone membrane cap. All septum were pierced with a large bore needle and pump intake Teflon tubing was inserted through the pierced septum into the solutions. An additional needle was placed through the septum to avoid vacuum during operation (See Feed Solutions Vials labeled above). 50 mL (100.0 mL/g) deionized water (DI) water was charged to a 150 mL RBF containing a magnetic stir bar. The solution was stirred at a moderate rate at ambient temperature (See CSTR labeled above).

The 4-fluorobenzoic acid and CDI charge-1solutions were flowed through a 1 mL quartz micro-reactor at ambient temperature (8 min residence time). The resulting segmented flow was flowed into a 20 mL vial through a pierced PTFE/Silicone membrane cap. The vial was allowed to partially fill, and the solution was pumped out of the vial and flowed through a static micromixing tee with the 2-pyridylhydrazine solution, and this solution was flowed through a 1.0 mL capacity HP PFA reactor at 90 °C (17 min residence time).

This solution and the CDI charge-2 solution were flowed through a quartz micromixing chip and a 2.0 mL capacity HP PFA reactor at 90 °C (10 min residence time). The triazolopyridine product was precipitated by feeding this final crude product solution into the continuous stirred-tank reactor (CSTR) containing DI water at ambient temperature. The crude reaction mixture purity at steady state (before water precipitation) was 84 $LCAP_{254}$. The final purity profile of the isolated solids was upgraded to 100 $LCAP_{254}$ after continuous precipitation (producing 2 mg/min final product). See Sections **2** and **4** for product characterization information (compound **13a**).

4. ^{1}H and ^{13}C NMR Spectra:

Compound 13a



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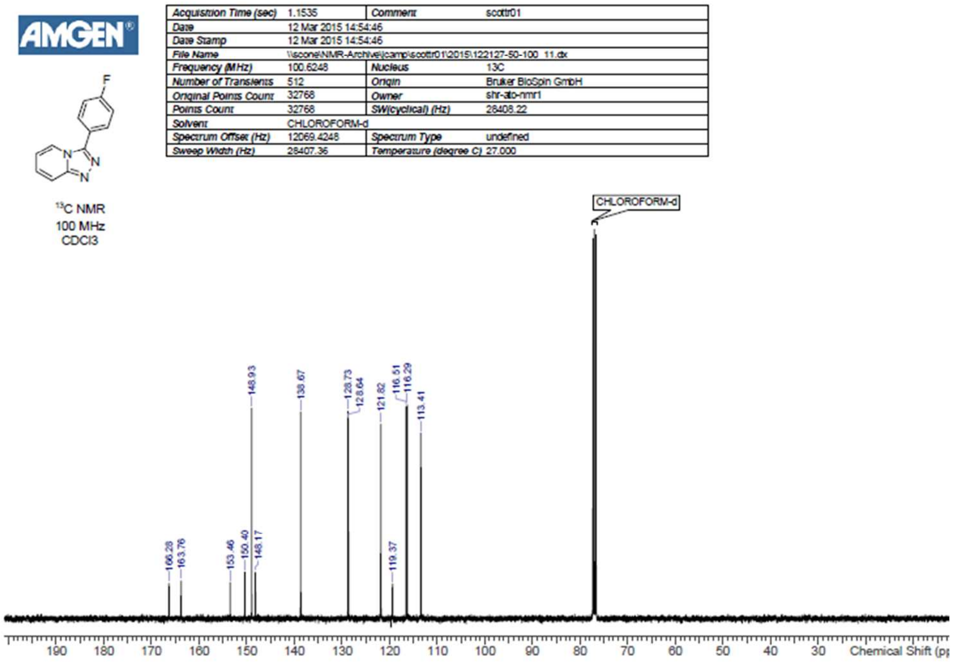
^{13}C NMR: 13a



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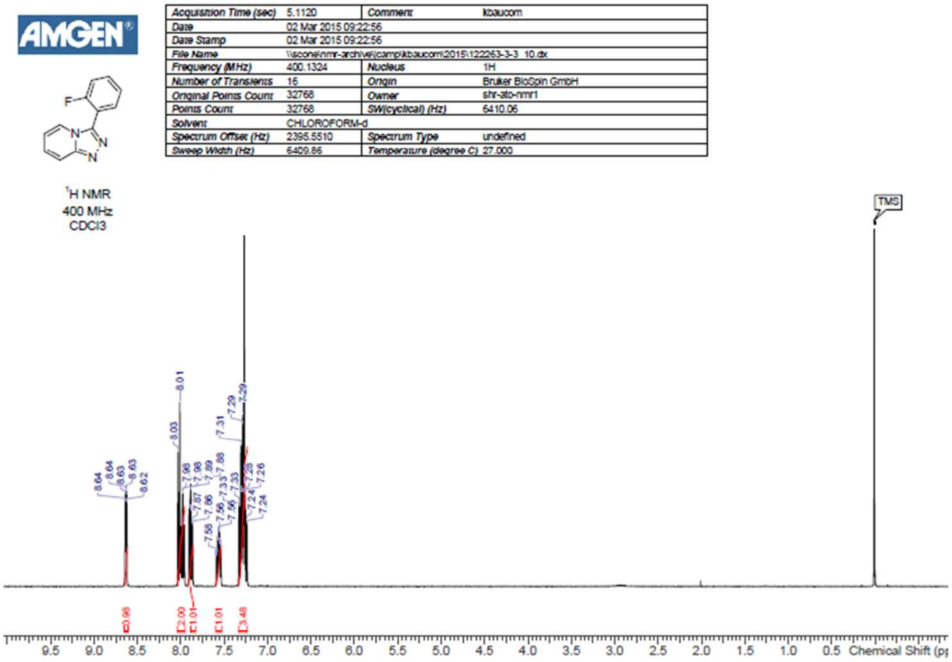
^{1}H NMR: 13b



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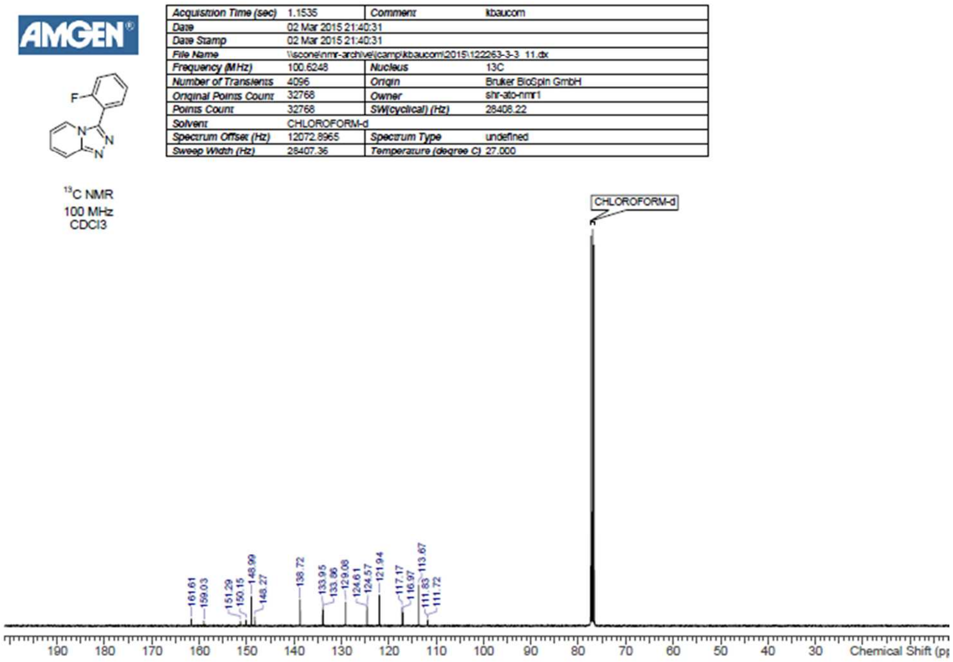
^{13}C NMR: 13b



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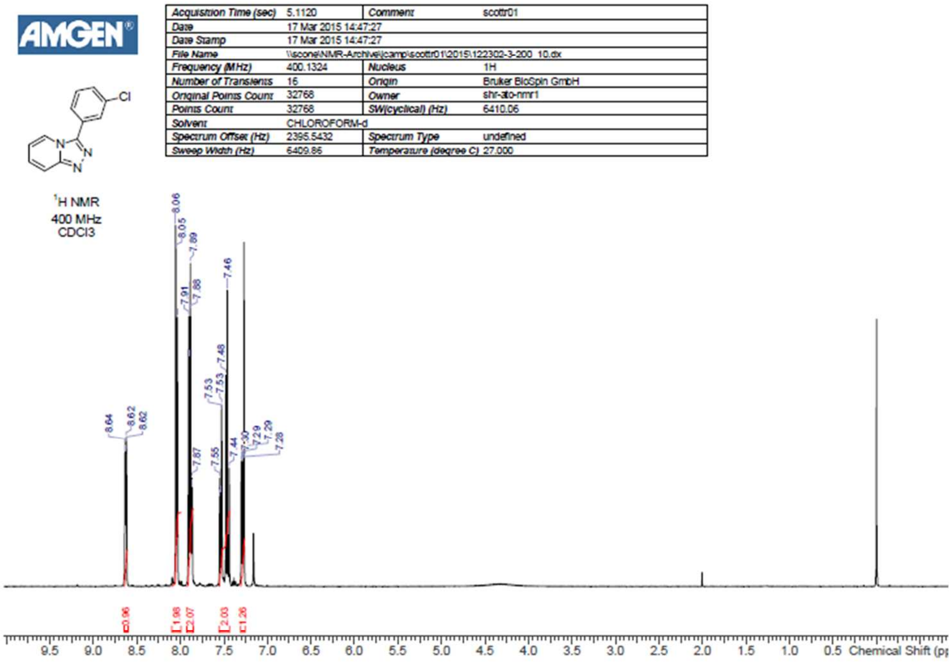
^{1}H NMR: 13c



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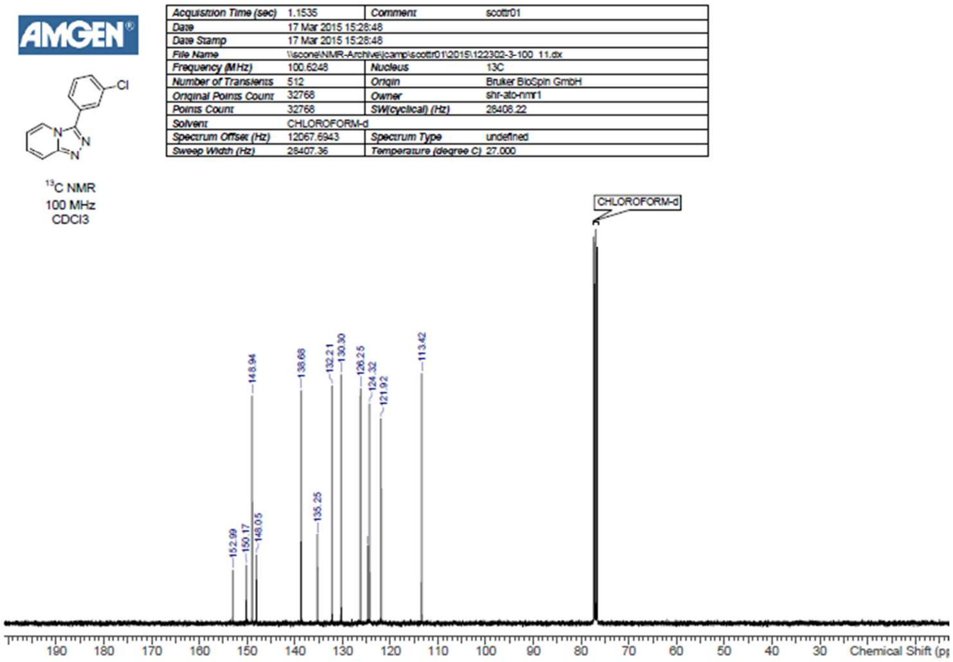
^{13}C NMR: 13c



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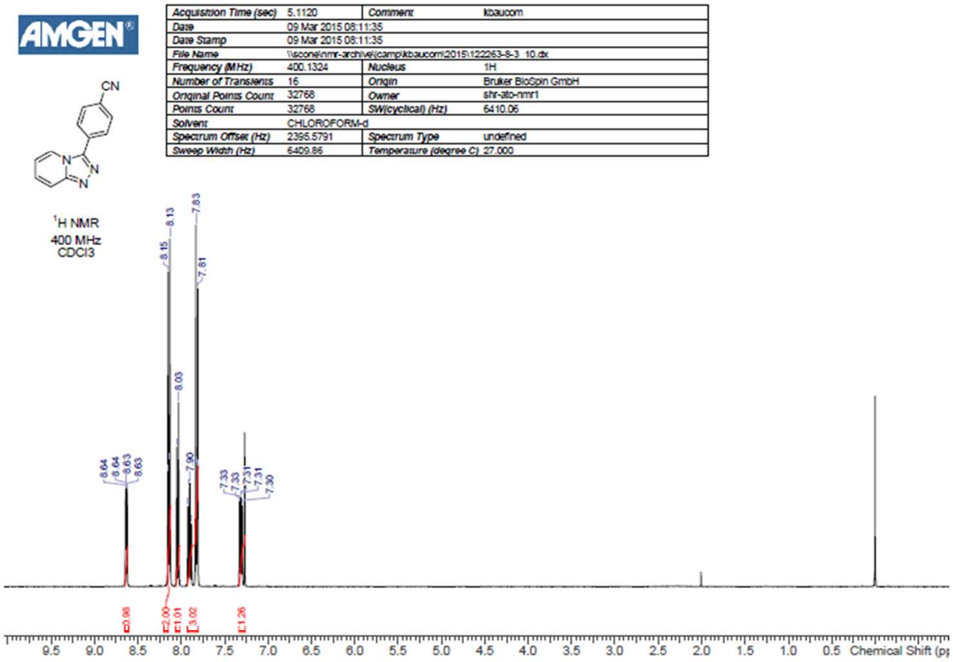
^{1}H NMR: 13d



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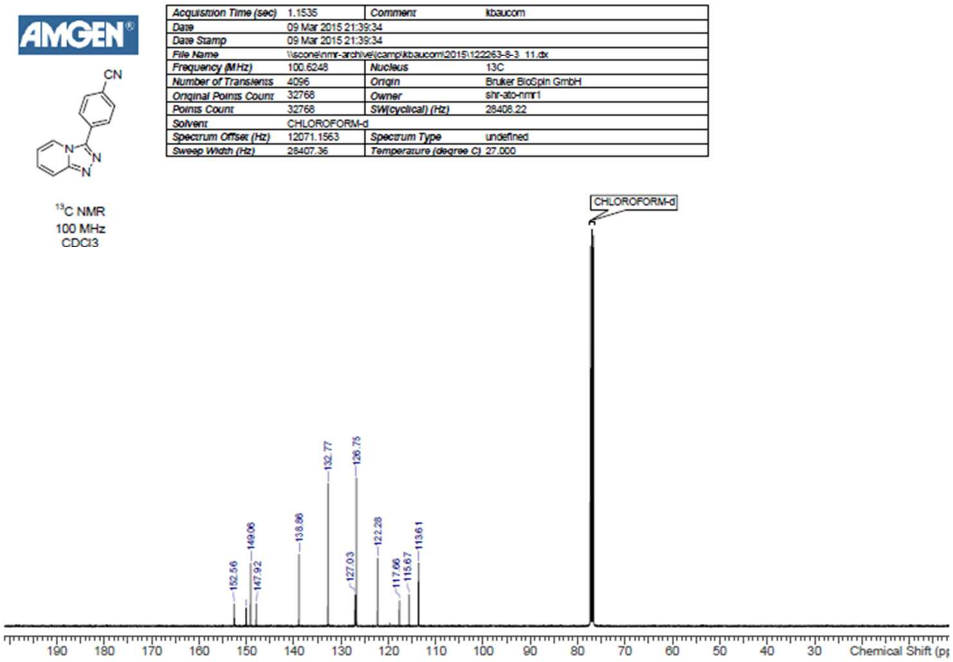
^{13}C NMR: 13d



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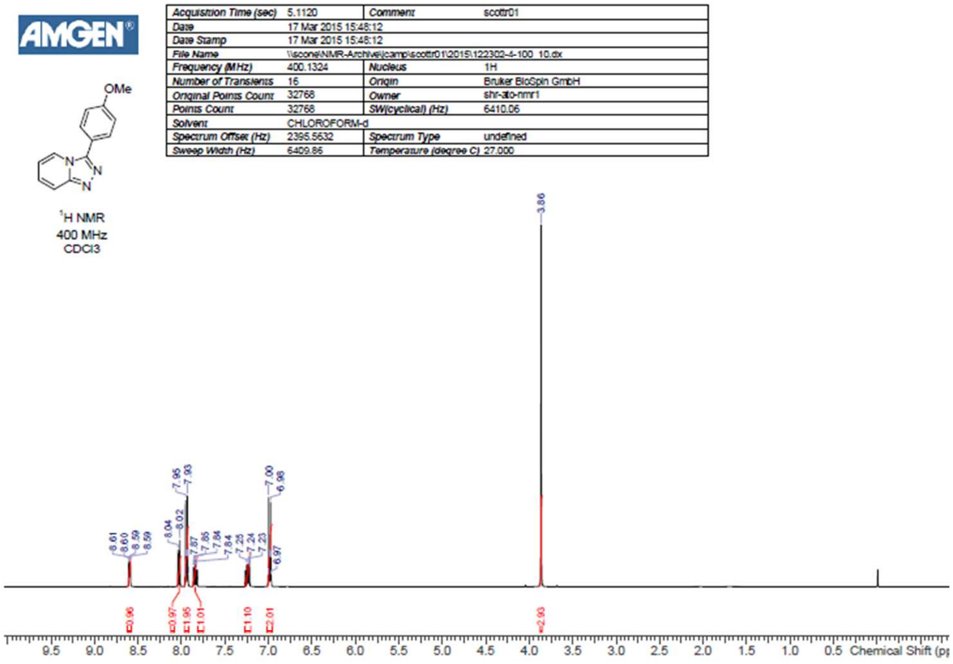
^{1}H NMR: 13e



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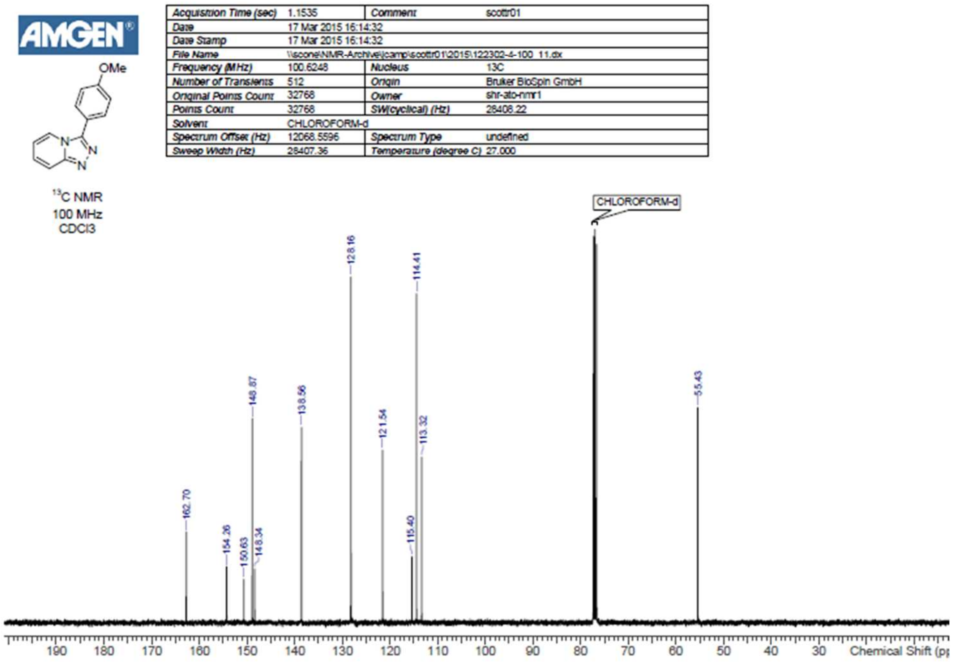
^{13}C NMR: 13e



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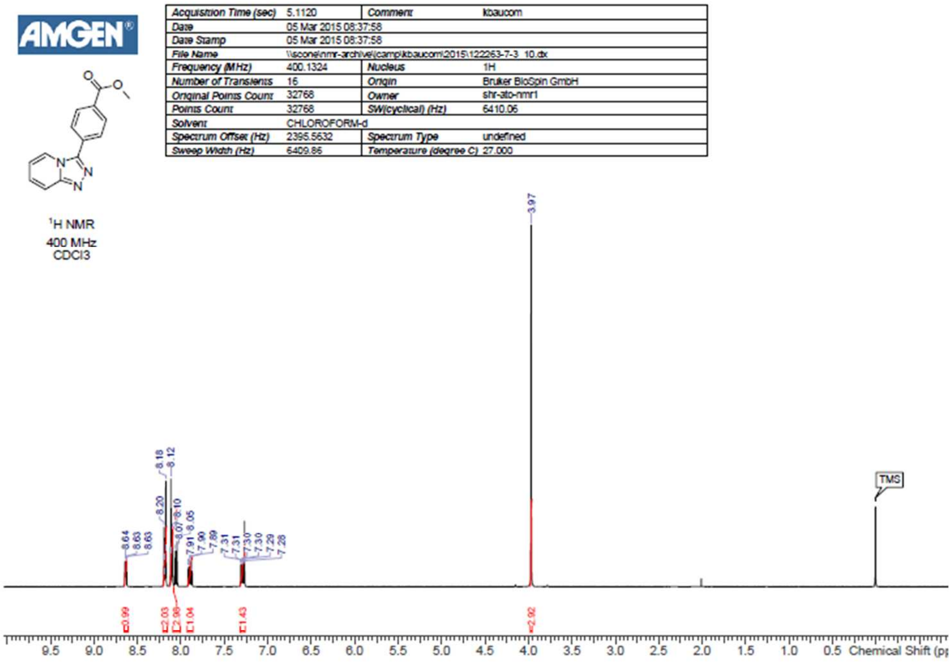
^{1}H NMR: 13f



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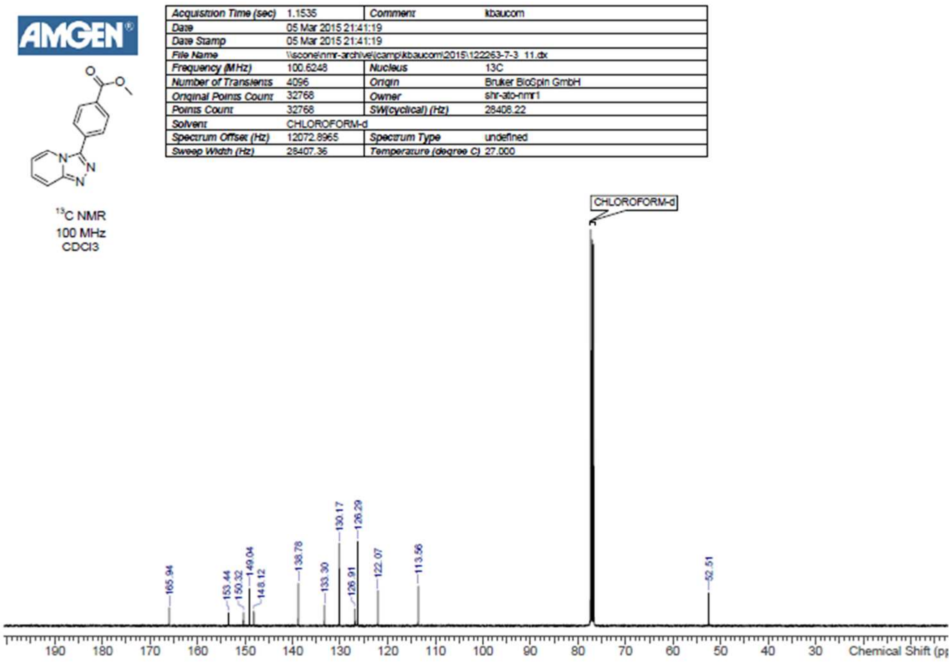
^{13}C NMR: 13f



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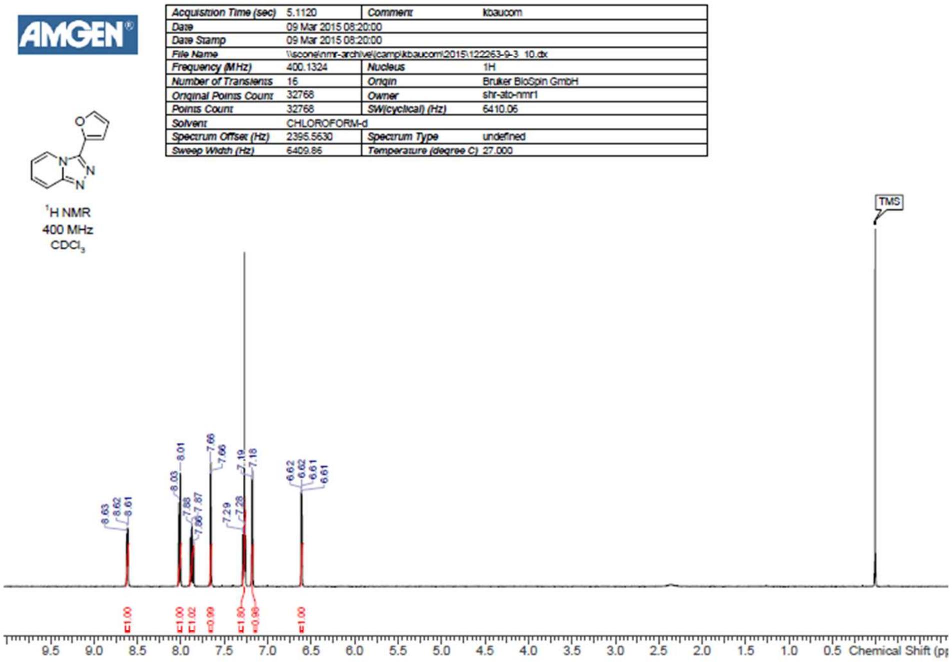
^{1}H NMR: 13i



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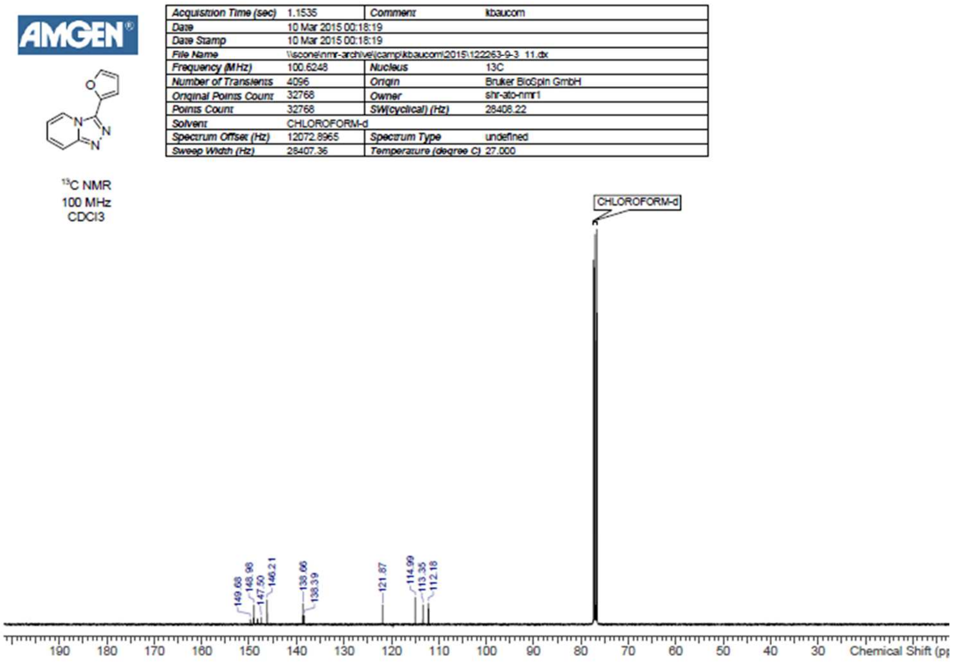
^{13}C NMR: 13i



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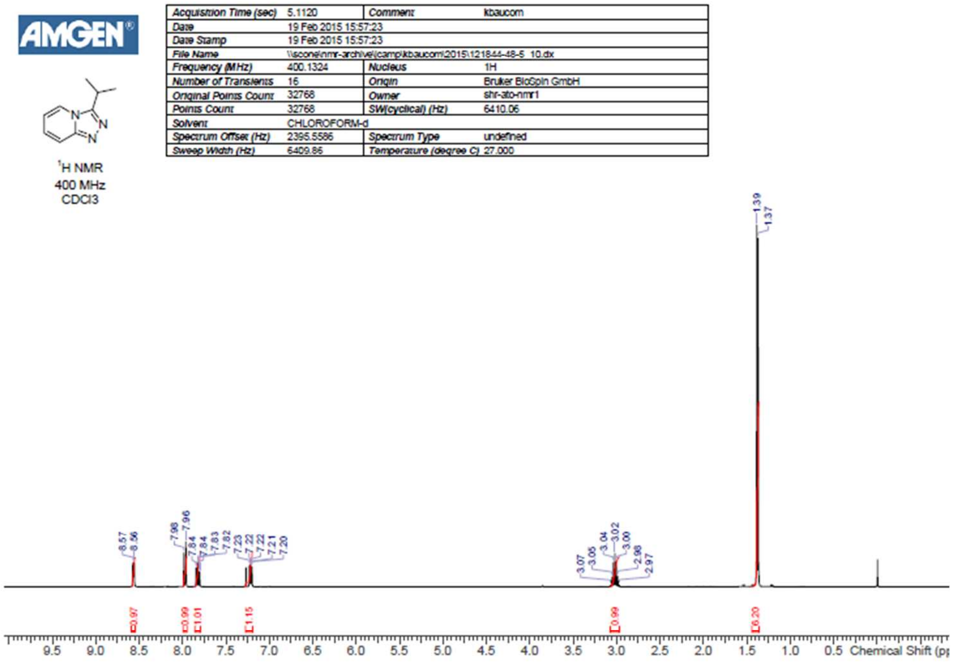
^{1}H NMR: 15a



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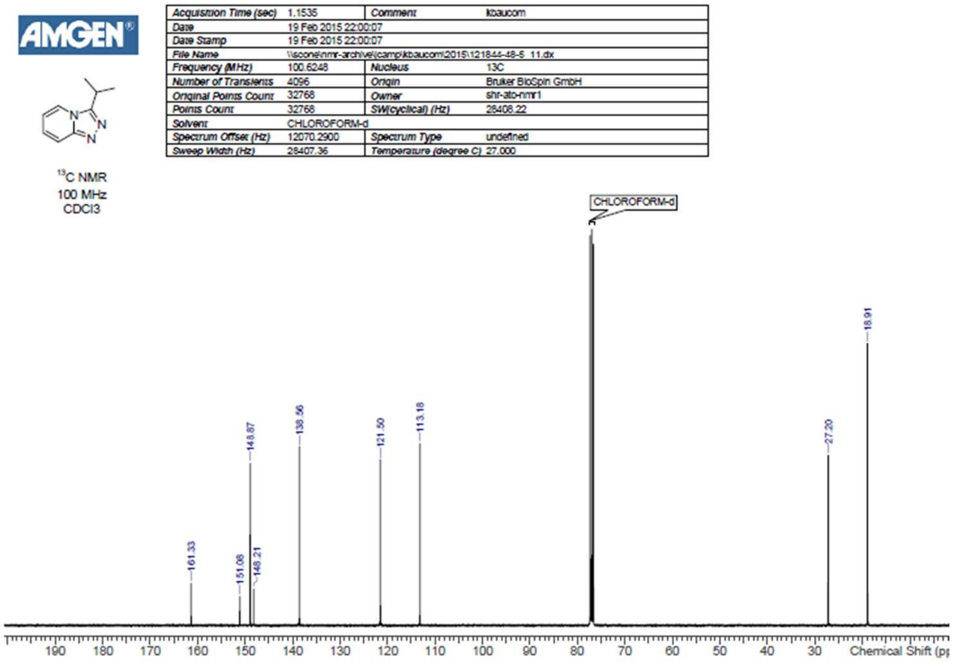
^{13}C NMR: 15a



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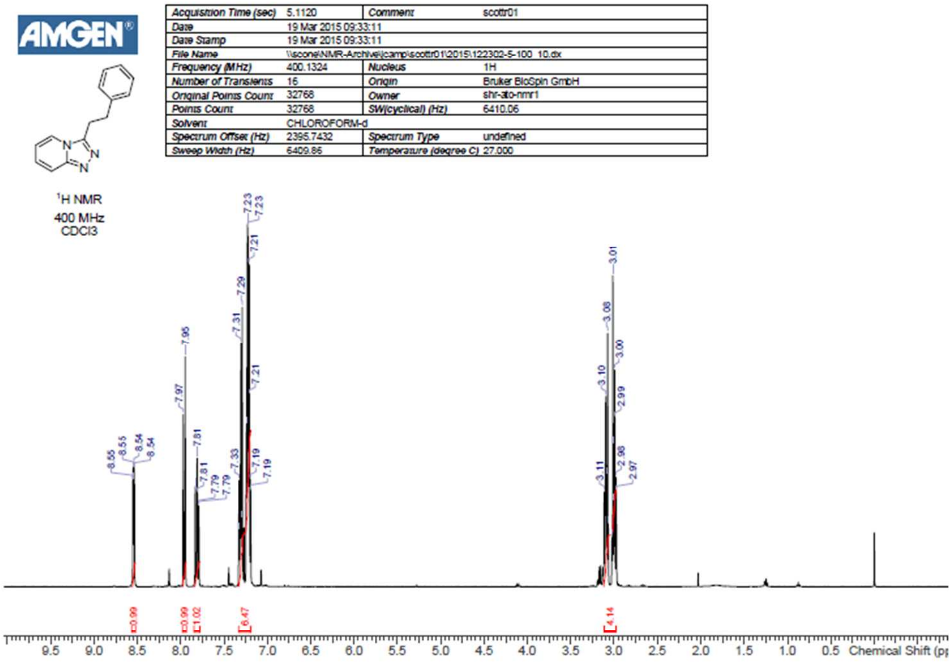
^{1}H NMR: 15b



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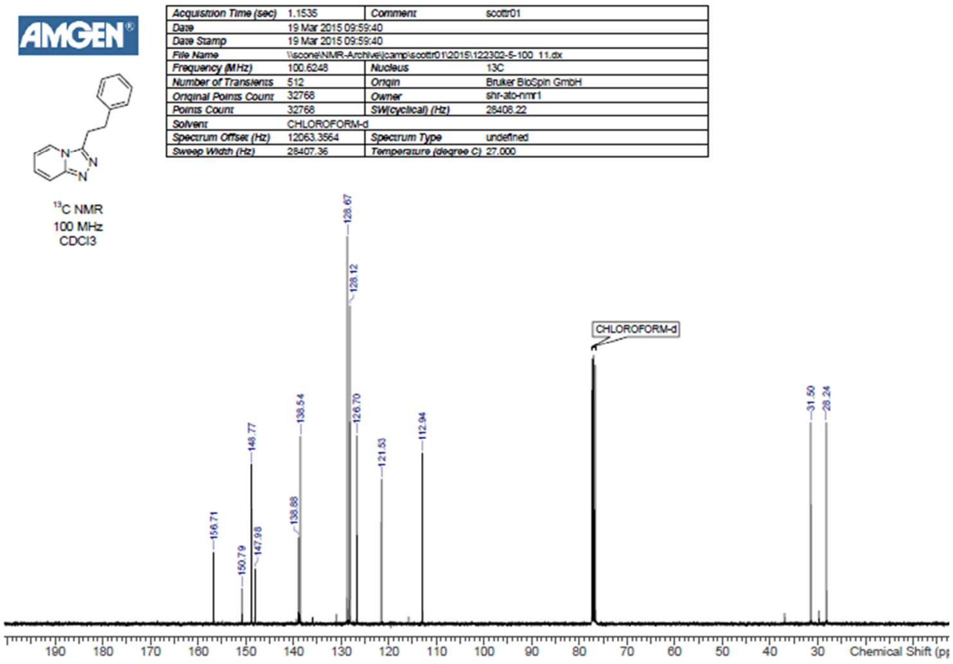
^{13}C NMR: 15b



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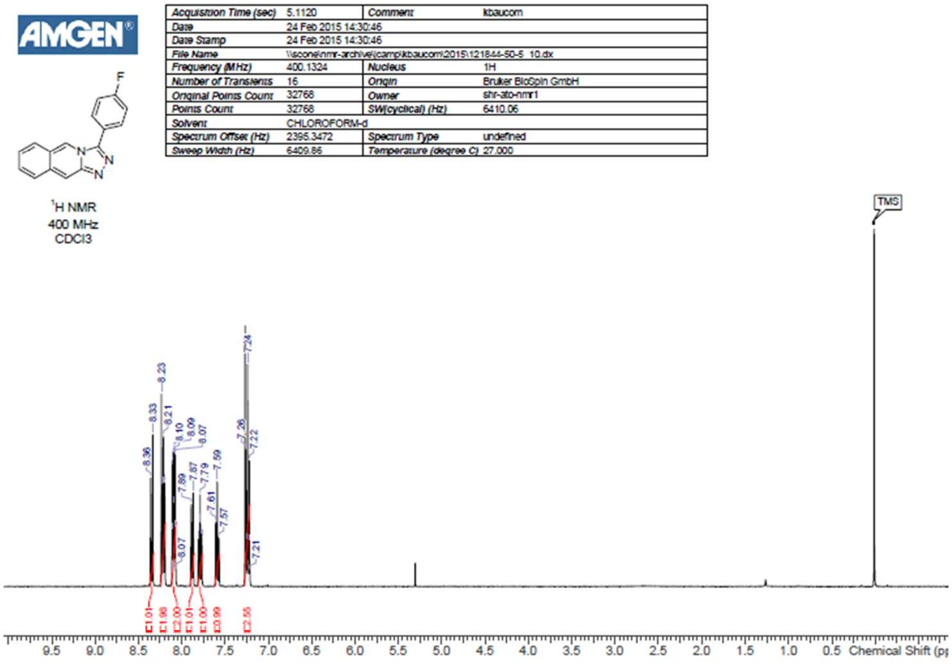
^1H NMR: 17a



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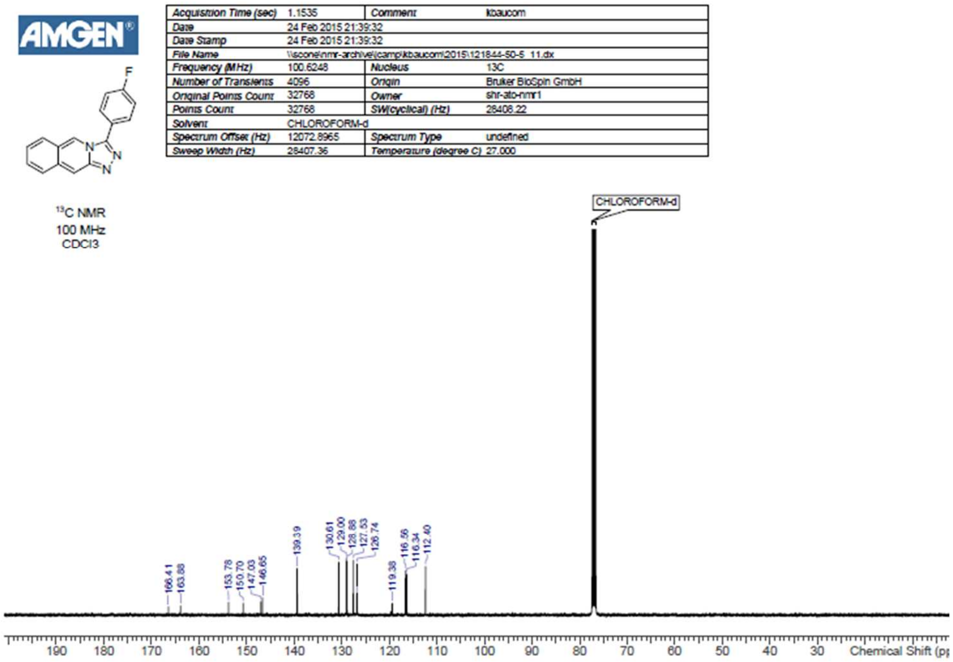
^{13}C NMR: 17a



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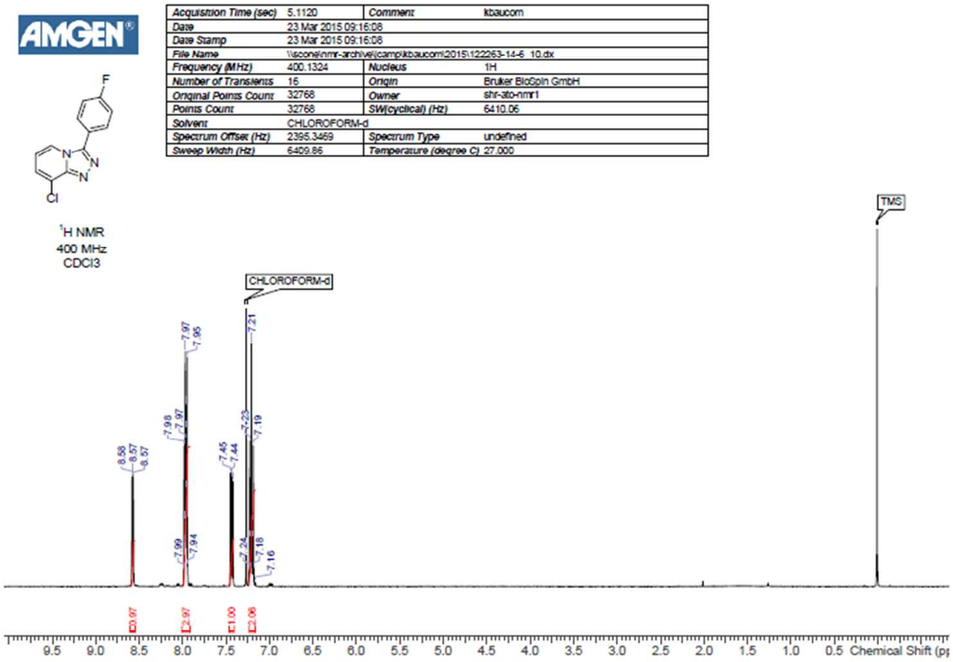
^{1}H NMR: 17b



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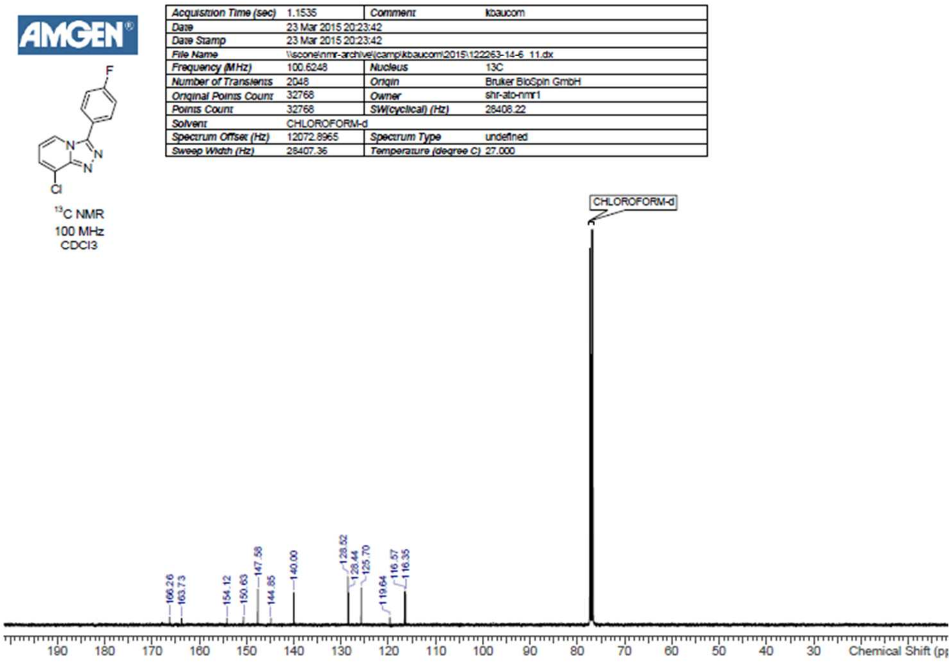
^{13}C NMR: 17b



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