Exploring Structural Effects in a New Class of NRF2 Inhibitors

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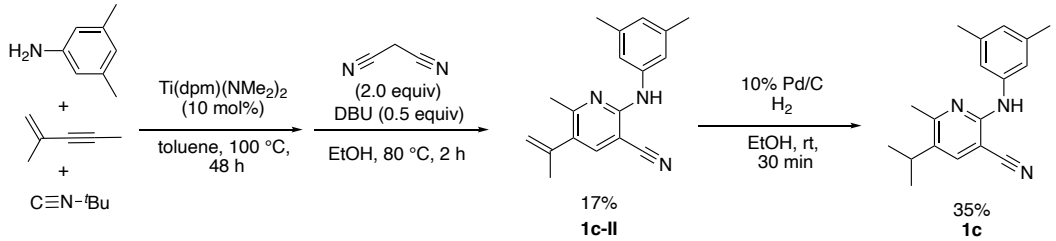

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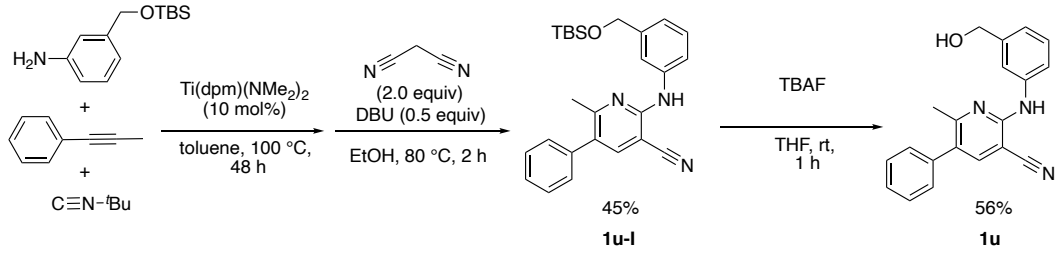

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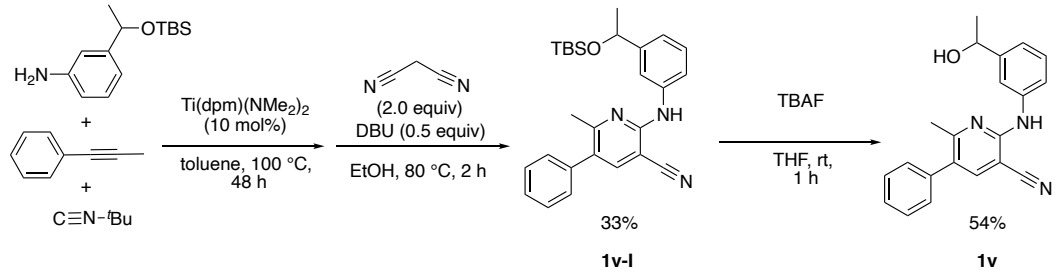

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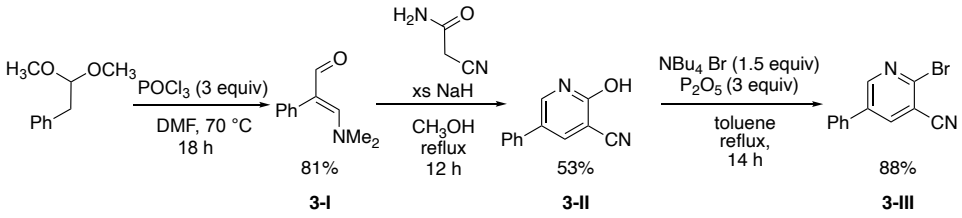
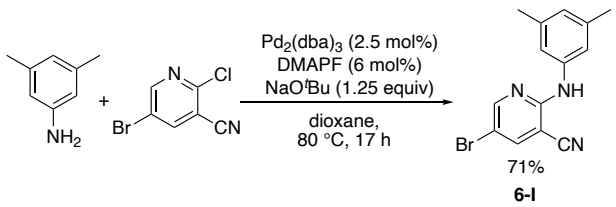
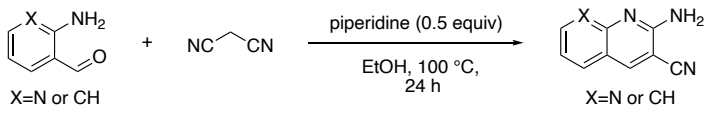


*Synthesis of 5-bromo-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**6-I**).*



Synthesis of 2-amino-3-cyano quinoline and 1,8-napthyridine

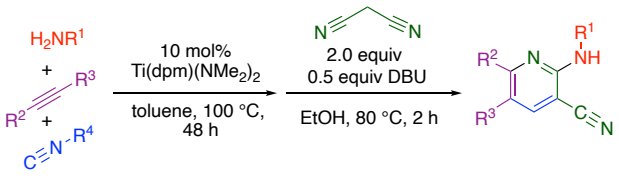


General Considerations

All manipulations were carried out under an inert dinitrogen atmosphere in an MBraun glovebox or using standard Schlenk techniques. Toluene was sparged with dinitrogen and passed over an activated alumina column prior to use. Tetrahydrofuran, *n*-hexane, and 1,4-dioxane were dried over sodium-benzophenone radical, refluxed, and distilled under dinitrogen prior to use. Ethanol was dried over magnesium, refluxed, and distilled under dinitrogen prior to use. *p*-Cymene was sparged with dinitrogen and distilled from CaH_2 prior to use. All deuterated NMR solvents were purchased from Cambridge Isotope Laboratories. Benzene-d_6 was dried over CaH_2 and distilled under dinitrogen. $CDCl_3$ was dried over P_2O_5 and distilled under dinitrogen. Synthesis of *tert*-butylisonitrile was done according to the literature procedure and purified by distillation under dry dinitrogen.[1] Synthesis of $Ti(dpm)(NMe_2)_2$ and $Ti(NMe_2)_3/SiO_2{}^{700}$ was done according to the literature procedures.[2, 3] $Ti(NMe_2)_4$ was purchased from Gelest and used as received. Palladium acetate was purchased from Strem and used as received. Tris(dibenzylideneacetone)dipalladium was purchased from Oakwood and used as received. BINAP was purchased from Alfa Aesar Chemicals and used as received. DMAPF was purchased from Sigma Aldrich and used as received. 1-phenyl-1-propyne and phenylacetylene were purchased from Combi-blocks and distilled from BaO prior to use. The kinetic solubilities were measured in the MSU Medicinal Chemistry Facility. For % activity,[4] MCF-7 cells stably transfected with a NRF2 luciferase construct were treated with 5 μmol/L of compounds and 20 μmol/L *tert*-butylhydroquinone (an NRF2 activator) for 24 h.[4] Luciferase activity was normalized to the DMSO control.

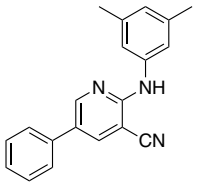
Synthesis of Compounds

General procedure A: Synthesis of 2-amino-nicotinonitrile derivatives via titanium-catalyzed multicomponent coupling



In the glovebox, a 15 mL pressure tube equipped with a stir bar was loaded with $Ti(dpm)(NMe_2)_2$ (32 mg, 0.1 mmol, 10 mol%) in dry toluene (2 mL). To the solution was added arylamine (1.0 mmol, 1.0 equiv), alkyne (1.0 mmol, 1.0 equiv), and *tert*-butylisonitrile (1.5 mmol, 1.5 equiv). The pressure tube was sealed with a Teflon screw cap and taken out of the glovebox. With stirring, the solution was heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2.0 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), and ethanol (2 mL). The mixture was heated for 2-12 h at 80 °C in an oil bath. The crude product was purified by column chromatography (silica gel, hexanes:EtOAc 10:1) to afford the desired products.

*2-((3,5-dimethylphenyl)amino)-5-phenylnicotinonitrile (**1b**)*

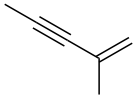


General procedure A was followed using 3,5-dimethylaniline (125 µL, 1.0 mmol, 1.0 equiv), phenylacetylene (110 µL, 1.0 mmol, 1.0 equiv), *tert*-butylisonitrile (170 µL, 1.5 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (32 mg, 0.1 mmol, 10 mol%), and 2 mL of dry toluene. The second step used malononitrile (132 mg, 2.0 mmol, 2.0 equiv), DBU (76 mg, 0.5 mmol, 0.5 equiv), molecular sieves (200 mg), 2 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white solid (58 mg, 19%). M.p.: 114-115 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): 8.63 (s, 1H), 7.98 (s, 1H), 7.52-7.43 (m, 3H), 7.42-7.38 (m, 1H), 7.23 (s, 2H), 6.95 (s, 1H), 6.80 (s, 1H), 2.35 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C):

155.34, 151.00, 139.78, 138.96, 138.71, 136.27, 129.39, 128.07, 127.56, 126.40, 126.22, 118.99, 116.61, 115.71, 21.61. LRMS (EI): calc'd: 299, found: 298.

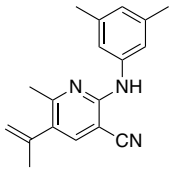
Alternative method: A 15 mL pressure tube was charged with $Ti(NMe_2)_3/SiO_2^{700}$ (320 mg), 2,6-dimethylphenylamidate (26 mg, 0.10 mmol), p-cymene (1 mL), and a Teflon coated stir bar. This mixture was stirred at room temperature for 5 min. Separately, a solution containing 3,5-dimethylaniline (242 mg, 2.0 mmol), CyNC (218 mg, 2.0 mmol), and phenylacetylene (408 mg, 4.0 mmol) in p-cymene was prepared (with a total volume of ~2 mL). This solution was added to the contents of the pressure tube, which immediately resulted in a color change from pale yellow-orange to bright red. The tube was sealed and transferred from the glovebox to a preheated aluminum block (180 °C) where it was heated and stirred for 2 h. GC-FID of the crude 3CC reaction mixture at this point showed ~90% yield of the 3CC product. The tube was removed from heat and allowed to cool to room temperature before being opened in air. The following reagents were then added: 200 mg of activated 3 Å molecular sieves, 3 mL of dry EtOH, DBU (151 mg, 1 mmol), and malononitrile (264 mg, 4 mmol). The tube was once again sealed and heated to 80 °C in an oil bath, with stirring, for 2 h. After 2 h the reaction was cooled. The crude product could be identified by GC-MS as the targeted pyridine. The contents of the pressure tube were transferred to a round bottom flask, and the volatiles removed by rotary evaporation. This resulted in ~2 mL of a viscous brown oil, which was purified by column chromatography (hexanes, gradient with 0-10% EtOAc, Al_2O_3 packing, product fluoresces under long-UV, Rf ~0.5). From the column fractions, solvent was removed by rotary evaporation to yield the product as a waxy tan solid. This waxy solid was washed with hexanes to afford an off-white powder that was pure by several methods of characterization. Yield: 62 mg, 11%. Additionally, from this powder, X-ray quality crystals were grown from a solution of acetone and diethyl ether layered with hexane and stored at –20 °C overnight.

*2-methyl-1-penten-3-yne (**1c-I**)*



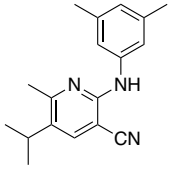
In the glovebox, a 100 mL, 1-neck Schlenk flask equipped with a stir bar was loaded with 2-methyl-1-buten-3-yne (4.78 g, 72.4 mmol) in dry THF (30 mL). The flask was placed inside a liquid nitrogen-cooled cold-well for 10 min. Then, the flask was removed from the cold-well, and n-butyllithium (2.5 M in hexane, 32 mL, 80 mmol) was added dropwise in 3 portions (10 mL each portion). The solution was cooled in the in the cold-well for 5 min between each portion. After the addition was completed, the mixture was stirred in the cold-well for 1 h. With stirring, iodomethane (11.3 g, 79.6 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 1 h. The flask was taken out of glovebox and water (30 mL) was added. The organic layer was collected and dried over Na_2SO_4. The product was obtained from fractional distillation (3.1 g, 38.8 mmol, 53.5%). ^{1}H NMR and ^{13}C NMR were consistent with those previously reported.[5] ^{1}H NMR (CDCl3, 500 MHz, 21 °C): δ 5.17 (s, 1H), 5.12 (s, 1H), 1.92 (s, 3H), 1.84 (d, *J*=1.2 Hz, 3H).

*2-((3,5-dimethylphenyl)amino)-6-methyl-5-(prop-1-en-2-yl)nicotinonitrile (**1c-II**)*



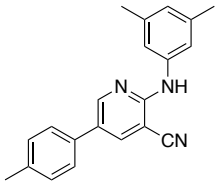
General procedure A was followed using 3,5-dimethylaniline (125 μL, 1.0 mmol, 1.0 equiv), 2-methyl-1-penten-3-yne **1c-I** (106 μL, 1.0 mmol, 1.0 equiv), *tert*-butylisonitrile (170 μL, 1.5 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (31 mg, 0.1 mmol, 10 mol%), and 2 mL of dry toluene. The second step used malononitrile (132 mg, 2.0 mmol, 2.0 equiv), DBU (76 mg, 0.5 mmol, 0.5 equiv), molecular sieves (200 mg), 2 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a yellow oil (47 mg, 17%). ^{1}H NMR (CDCl3, 500 MHz, 21 °C): δ 7.50 (s, 1H), 7.28 (s, 2H), 6.82 (s, 1H), 6.74 (s, 1H), 5.28-5.22 (m, 1H), 4.91 (dd, *J*=1.6, 0.8 Hz, 1H), 2.50 (s, 3H), 2.33 (s, 6H), 2.02-2.01 (m, 3H). LRMS (EI): 276. The NMR shows a compound with modest purity, that was used without further purification in the next step.

*6-Methyl-2-[(3,5-dimethylphenyl)amino]-5-(isopropyl)nicotinonitrile (**1c**)*



6-Methyl-2-[(3,5-dimethylphenyl)amino]-5-(prop-1-en-2-yl)nicotinonitrile **1c-II** (80 mg, 0.28 mmol) was dissolved in dry ethanol (6 mL) in a 100 mL Schlenk flask. Palladium on carbon (10%, 100 mg) was added. The flask was flushed with purified dinitrogen, then with dihydrogen gas. The joint was fit with an adaptor for a hydrogen-filled balloon and was stirred at room temperature (25 °C) for 30 min. Purification was accomplished by filtration through neutral alumina, followed by column chromatography (neutral alumina, hexanes:EtOAc 10:1), which afforded the desired compound as a yellow liquid (35%, 28 mg, 0.1 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): 7.59 (s, 1H), 7.29 (s, 2H), 6.77 (s, 1H), 6.73 (s, 1H), 3.06 (hept, *J*=6.9 Hz, 1H), 2.54 (s, 3H), 2.34 (s, 6H), 1.22 (d, *J*=6.9 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): 160.1, 153.4, 139.2, 138.6, 138.1, 132.5, 124.9, 117.7, 117.3, 90.6, 29.8, 28.5, 23.0, 21.6 LRMS (EI): calc'd: 279; found: 278.

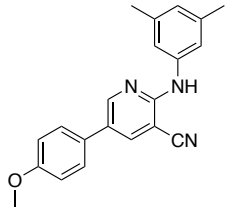
*2-((3,5-dimethylphenyl)amino)-5-(p-tolyl)nicotinonitrile (**1d**)*



General procedure A was followed using 3,5-dimethylaniline (125 μL, 1.0 mmol, 1.0 equiv), 4-ethynyltoluene (127 μL, 1.0 mmol, 1.0 equiv), *tert*-butylisonitrile (170 μL, 1.5 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (32 mg, 0.1 mmol, 10 mol%), and dry toluene (2 mL). The second step used malononitrile (132 mg, 2.0 mmol, 2.0 equiv), DBU (76 mg, 0.5 mmol, 0.5 equiv), molecular sieves (200 mg), 2 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white solid (31 mg, 10%). M.p.: 112-113 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.62 (d, *J*=2.5 Hz, 1H), 7.95 (d, *J*=2.5 Hz, 1H), 7.39 (d, *J*=8.1 Hz, 2H), 7.28 (d, *J*=7.9 Hz, 2H), 7.23 (s, 2H), 6.94 (s, 1H), 6.79 (s, 1H), 2.41 (s, 3H), 2.35 (s,

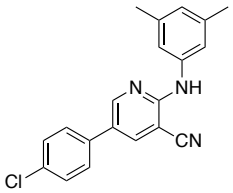
6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 150.79, 139.53, 138.41, 137.99, 133.34, 130.07, 127.53, 126.21, 126.09, 118.88, 116.66, 21.60, 21.27. LRMS (EI): calc'd: 313; found: 312.

*2-((3,5-dimethylphenyl)amino)-5-(4-methoxyphenyl)nicotinonitrile (**1e**)*



General procedure A was followed using 3,5-dimethylaniline (125 μL, 1.0 mmol, 1.0 equiv), 4-ethynylanisole (130 μL, 1.0 mmol, 1.0 equiv), *tert*-butylisonitrile (170 μL, 1.5 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (32 mg, 0.1 mmol, 10 mol%), and dry toluene (2 mL). The second step used malononitrile (132 mg, 2.0 mmol, 2.0 equiv), DBU (76 mg, 0.5 mmol, 0.5 equiv), molecular sieves (200 mg), 2 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white solid (39 mg, 12%). M.p.: 141-142 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.59 (d, *J*=2.4 Hz, 1H), 7.92 (d, *J*=2.9 Hz, 1H), 7.42 (d, *J*=8.5 Hz, 2H), 7.23 (s, 2H), 7.00 (d, *J*=8.6 Hz, 2H), 6.92 (s, 1H), 6.79 (s, 1H), 3.86 (s, 3H), 2.34 (s, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 159.71, 154.94, 150.59, 139.32, 138.94, 138.46, 128.73, 127.54, 127.37, 126.07, 118.85, 116.70, 114.82, 93.19, 55.55, 21.61. LRMS (EI): calc'd: 329; found: 328..

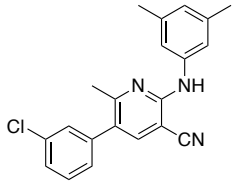
*5-(4-chlorophenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**1f**)*



General procedure A was followed using 3,5-dimethylaniline (125 μL, 1.0 mmol, 1.0 equiv), 1-chloro-4-ethynylbenzene (136 mg, 1.0 mmol, 1.0 equiv), *tert*-butylisonitrile (170 μL, 1.5 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (32 mg, 0.1 mmol, 10 mol%), and dry toluene (2 mL). The second step used malononitrile (132 mg, 2.0 mmol, 2.0 equiv), DBU (76 mg, 0.5 mmol, 0.5 equiv), molecular sieves (200 mg), 2 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as light yellow crystals (55 mg, 17%).

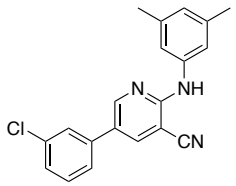
M.p.: 147-148 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.59 (d, *J*=2.5 Hz, 1H), 7.93 (d, *J*=2.5 Hz, 1H), 7.47-7.38 (m, 4H), 7.23 (s, 2H), 6.99 (s, 1H), 6.80 (s, 1H), 2.35 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 155.42, 150.78, 139.58, 138.95, 138.17, 134.69, 134.20, 129.56, 127.57, 126.32, 126.28, 119.03, 116.40, 93.27, 21.59. . LRMS (EI): calc'd: 333; found: 332.

*5-(3-chlorophenyl)-2-((3,5-dimethylphenyl)amino)-6-methylnicotinonitrile (**1g**)*



General procedure A was followed using 3,5-dimethylaniline (250 μL, 2.0 mmol, 1.0 equiv), 1-chloro-3-(prop-1-yn-1-yl)benzene (300 mg, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv), Ti(dpm)(NMe_2)$_2$ (64 mg, 0.2 mmol, 10 mol%), and 4 mL of dry toluene. The second step used malononitrile (264 mg, 4.0 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (400 mg), 4 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white solid (127 mg, 18%). M.p.: 136-137 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.60 (s, 1H), 7.38-7.34 (m, 2H), 7.31 (s, 2H), 7.29-7.27 (m, 1H), 7.19-7.13 (m, 1H), 6.92 (s, 1H), 6.77 (s, 1H), 2.46 (s, 3H), 2.34 (s, 7H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 154.56, 142.24, 140.06, 138.80, 138.63, 134.63, 130.03, 129.32, 127.96, 127.48, 126.59, 125.64, 118.27, 116.60, 90.52, 24.19, 21.65. One quaternary carbon was not found.

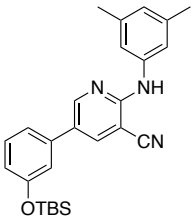
*5-(3-chlorophenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**1h**)*



General procedure A was followed using 3,5-dimethylaniline (125 μL, 1.0 mmol, 1.0 equiv), 1-chloro-3-ethynylbenzene (136 mg, 1.0 mmol, 1.0 equiv), *tert*-butylisonitrile (170 μL, 1.5 mmol, 1.5 equiv), Ti(dpm)(NMe_2)$_2$ (32 mg, 0.1 mmol, 10 mol%), and 2 mL of dry toluene. The second step used malononitrile (132 mg, 2.0 mmol, 2.0 equiv), DBU (76 mg, 0.5 mmol, 0.5 equiv), molecular sieves (200 mg), 2 mL of

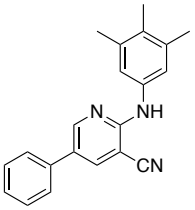
ethanol and was heated for 2 h. Removal of solvent afforded product as a white solid (76 mg, 23%). M.p.: 125-126 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.60 (s, 1H), 7.96 (s, 1H), 7.53-7.46 (m, 1H), 7.45-7.32 (m, 3H), 7.23 (s, 2H), 6.99 (s, 1H), 6.81 (s, 1H), 2.35 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 155.47, 150.82, 139.62, 138.87, 137.99, 137.94, 130.50, 127.95, 126.37, 126.27, 125.98, 124.35, 118.96, 116.22, 93.18, 21.47. One quaternary carbon was not found. LRMS (EI): calc'd: 333; found: 332.

*5-(3-((tert-butyldimethylsilyl)oxy)phenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**1i**)*



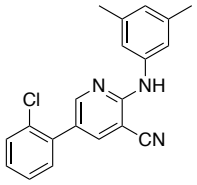
General procedure A was followed using 3,5-dimethylaniline (250 μL, 2.0 mmol, 1.0 equiv), *tert*-butyl(3-ethynylphenoxy)dimethylsilane (464 mg, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv), Ti(dpm)$(NMe_2)_2$ (64 mg, 0.2 mmol, 10 mol%), and 5 mL of dry toluene. The second step used malononitrile (264 mg, 4.0 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (200 mg), 2 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white solid (160 mg, 19%). M.p.: 104-105 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C):δ 8.61 (d, *J*=2.4 Hz, 1H), 7.94 (d, *J*=2.5 Hz, 1H), 7.32 (t, *J*=7.9 Hz, 1H), 7.23 (s, 2H), 7.08 (d, *J*=7.8 Hz, 1H), 6.99-6.94 (m, 2H), 6.86 (dd, *J*=8.1, 1.7 Hz, 1H), 6.80 (s, 1H), 2.35 (s, 6H), 1.01 (s, 9H), 0.24 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 156.54, 155.36, 150.96, 139.74, 138.95, 138.33, 137.63, 130.38, 127.32, 126.20, 119.70, 119.36, 118.99, 118.12, 116.61, 93.17, 25.81, 21.60, 18.37, -4.20.

*5-phenyl-2-((3,4,5-trimethylphenyl)amino)nicotinonitrile (**1j**)*



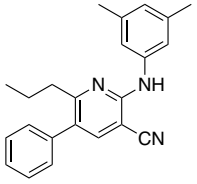
General procedure A was followed using 3,4,5-trimethylaniline (140 μL, 1.0 mmol, 1.0 equiv), phenylacetylene (110 μL, 1.0 mmol, 1.0 equiv), *tert*-butylisonitrile (170 μL, 1.5 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (32 mg, 0.1 mmol, 10 mol%), and 2 mL of dry toluene. The second step used malononitrile (132 mg, 2.0 mmol, 2.0 equiv), DBU (76 mg, 0.5 mmol, 0.5 equiv), molecular sieves (200 mg), 2 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white solid (43 mg, 14%). ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.61 (s, 1H), 7.96 (s, 1H), 7.54-7.43 (m, 4H), 7.39 (t, *J*=7.7 Hz, 1H), 7.23 (s, 2H), 6.91 (s, 1H), 2.32 (s, 6H), 2.17 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 155.58, 151.00, 139.62, 137.25, 136.23, 135.18, 131.60, 129.24, 127.85, 127.10, 126.22, 121.06, 116.61, 92.73, 20.83, 15.04. LRMS (EI): calc'd: 313; found: 312.

*5-(2-chlorophenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**1k**)*



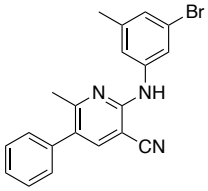
General procedure A was followed using 3,5-dimethylaniline (250 μL, 1.0 mmol, 1.0 equiv), 1-chloro-3-ethynylbenzene (272 mg, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (64 mg, 0.2 mmol, 10 mol%), and 5 mL of dry toluene. The second step used malononitrile (264 mg, 4.0 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (400 mg), 4 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white solid (149 mg, 22%). M.p.: 139-140 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.46 (d, *J*=1.9 Hz, 1H), 7.99-7.85 (m, 1H), 7.53-7.47 (m, 1H), 7.39-7.28 (m, 3H), 7.24 (s, 2H), 6.99 (s, 1H), 6.81 (s, 1H), 2.35 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 155.26, 152.76, 142.17, 138.85, 138.03, 135.24, 134.99, 130.90, 130.32, 129.49, 127.37, 126.24, 119.04, 116.33, 109.53, 92.40, 21.47. One quaternary carbon was not found. LRMS (EI): calc'd: 333; found: 332.

*2-((3,5-dimethylphenyl)amino)-5-phenyl-6-propylnicotinonitrile (**1l**)*



General procedure A was followed using 3,5-dimethylaniline (125 μL, 1.0 mmol, 1.0 equiv), 1-phenyl-1-pentyne (160 μL, 1.0 mmol, 1.0 equiv), *tert*-butylisonitrile (170 μL, 1.5 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (31 mg, 0.1 mmol, 10 mol%), and 2 mL of dry toluene. The second step used malononitrile (132 mg, 2.0 mmol, 2.0 equiv), DBU (76 mg, 0.5 mmol, 0.5 equiv), molecular sieves (200 mg), 2 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white powder (113 mg, 34%). M.p.: 126-127 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.60 (s, 1H), 7.43 (t, *J*=7.2 Hz, 2H), 7.38 (t, *J*=7.3 Hz, 1H), 7.36 (s, 2H), 7.26 (d, 2H), 6.92 (s, 1H), 6.75 (s, 1H), 2.70 (t, *J*=7.6 Hz, 2H), 2.34 (s, 6H), 1.79 (h, *J*=7.4 Hz, 2H), 0.90 (t, *J*=7.4 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 163.60, 154.38, 142.28, 138.96, 138.61, 138.39, 129.35, 128.67, 128.15, 127.69, 125.10, 117.95, 116.90, 90.13, 37.73, 21.78, 21.59, 14.08. LRMS (EI): calc'd: 341; found: 340.

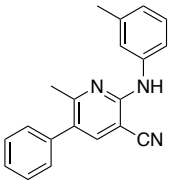
*2-((3-bromo-5-methylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1m**)*



The general procedure A was followed using 3-bromo-5-methylaniline (370 mg, 2.0 mmol, 1.0 equiv), 1-phenyl-1-propyne (250 μL, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (62 mg, 0.2 mmol, 10 mol%), and 5 mL of dry toluene. The second step used malononitrile (264 mg, 4.0 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (400 mg), 4 mL of ethanol and was heated for 12 h. Removal of solvent afforded product as a white powder (168 mg, 19%). M.p.: 161-162 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.63 (s, 1H), 7.46 (s, 2H), 7.44 (t, *J*=7.4 Hz, 2H), 7.38 (t, *J*=7.3 Hz, 1H), 7.27 (d, *J*=8.5 Hz, 2H), 6.87 (s, 1H), 2.78 (s, 3H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR

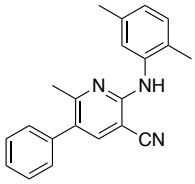
($CDCl_3$, 126 MHz, 21 °C): δ 160.36, 154.07, 142.26, 138.87, 138.18, 137.55, 130.20, 129.20, 128.79, 128.42, 127.86, 121.36, 119.96, 116.73, 90.67, 29.71, 24.25. One quaternary carbon was not found. LRMS (EI): calc'd: 377; found: 378.

*6-methyl-5-phenyl-2-(m-tolylamino)nicotinonitrile (**1n**)*



General procedure A was followed using *m*-toluidine (214 μL, 2.0 mmol, 1.0 equiv), 1-phenyl-1-propyne (250 μL, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (62 mg, 0.2 mmol, 10 mol%), and 5 mL of dry toluene. The second step used malononitrile (264 mg, 4.0 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (400 mg), 4 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white powder (155 mg, 29%). M.p.:117-118 °C ^1H NMR ($CDCl_3$, 500 MHz, 21 °C):δ 7.64 (s, 1H), 7.59 (d, *J*=8.1 Hz, 1H), 7.49-7.42 (m, 3H), 7.39 (t, *J*=8.0 Hz, 1H), 7.31-7.23 (m, 4H), 6.94 (s, 1H), 6.93 (s, 1H), 2.49 (s, 3H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 160.36, 154.29, 142.23, 139.00, 138.95, 138.31, 129.23, 128.95, 128.75, 128.18, 127.78, 124.40, 120.85, 117.36, 116.85, 90.48, 24.28, 21.74. LRMS (EI): calc'd: 299; found: 298.

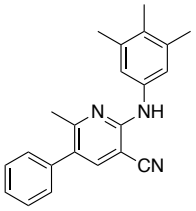
*2-((2,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1o**)*



General procedure A was followed using 2,5-xylidine (249 μL, 2.0 mmol, 1.0 equiv), 1-phenyl-1-propyne (250 μL, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (62 mg, 0.2 mmol, 10 mol%), and 5 mL of dry toluene. The second step used malononitrile (264 mg, 4.0 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (400 mg), 4 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white powder (96 mg, 15%). M.p.: 128-129 °C.

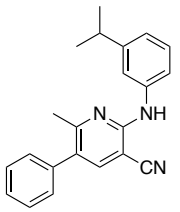
^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C):δ 7.81 (s, 1H), 7.62 (s, 1H), 7.44 (t, *J*=7.3 Hz, 2H), 7.41-7.35 (m, 1H), 7.30-7.26 (m, 2H), 7.13 (d, *J*=7.7 Hz, 1H), 6.92 (d, *J*=8.4 Hz, 1H), 6.79 (s, 1H), 2.43 (s, 3H), 2.36 (s, 3H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 160.48, 154.88, 142.24, 138.39, 136.92, 136.36, 130.57, 129.24, 128.73, 127.95, 127.73, 126.91, 125.43, 123.25, 116.89, 90.25, 24.29, 21.44, 17.81. LRMS (EI): calc'd: 313; found: 312.

*6-methyl-5-phenyl-2-((3,4,5-trimethylphenyl)amino)nicotinonitrile (**1p**)*



General procedure A was followed using 3,4,5-trimethylaniline (280 μL, 2.0 mmol, 1.0 equiv), 1-phenyl-1-propyne (250 μL, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (62 mg, 0.2 mmol, 10 mol%), and 5 mL of dry toluene. The second step used malononitrile (264 mg, 4.0 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (400 mg), 4 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white powder (98 mg, 15%). M.p.: 167-177 °C ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.61 (s, 1H), 7.48-7.42 (m, 2H), 7.41-7.36 (m, 1H), 7.34 (s, 2H), 7.29-7.27 (m, 2H), 6.84 (s, 1H), 2.52 (s, 3H), 2.31 (s, 6H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 160.38, 154.55, 142.20, 138.44, 137.13, 135.96, 130.65, 129.24, 128.72, 127.79, 127.69, 119.89, 116.99, 90.10, 24.29, 20.99, 15.08. LRMS (EI): calc'd: 327; found: 326.

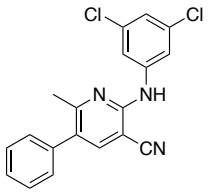
*2-((3-isopropylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1q**)*



General procedure A was followed using 3-isopropylaniline (281 μL, 2.0 mmol, 1.0 equiv), 1-phenyl-1-propyne (250 μL, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv),

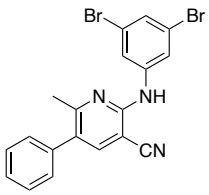
$Ti(dpm)(NMe_2)_2$ (62 mg, 0.2 mmol, 10 mol%), and 5 mL of dry toluene. The second step used malononitrile (264 mg, 4.0 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (400 mg), 4 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white powder (120 mg, 18%). M.p.: 114-115 °C ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.64 (s, 1H), 7.59-7.51 (m, 2H), 7.44 (t, *J*=7.3 Hz, 2H), 7.38 (t, *J*=7.3 Hz, 1H), 7.32-7.27 (m, 3H), 7.26 (s, 1H), 6.99 (s, 1H), 6.97 (s, 1H), 2.93 (hept, *J*=7.5 Hz, 1H), 2.47 (s, 3H), 1.29 (d, *J*=6.9 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 154.30, 149.95, 142.24, 139.00, 138.32, 130.13, 129.23, 128.96, 128.76, 128.15, 127.78, 121.93, 118.35, 117.70, 116.88, 90.42, 34.30, 24.28, 24.11. LRMS (EI): calc'd: 327; found: 326.

*2-((3,5-dichlorophenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1r**)*



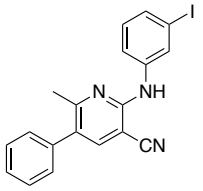
General procedure A was followed using 3,5-dichloroaniline (324 mg, 2.0 mmol, 1.0 equiv), 1-phenyl-1-propyne (250 μL, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (62 mg, 0.2 mmol, 10 mol%), and dry toluene (5 mL). The second step used malononitrile (264 mg, 4.0 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (400 mg), 4 mL of ethanol and was heated for 12 h. Removal of solvent afforded product as a white powder (200 mg, 28%). M.p.: 211-212 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.72 (d, *J*=1.7 Hz, 2H), 7.68 (s, 1H), 7.45 (t, *J*=7.2 Hz, 2H), 7.40 (t, *J*=7.3 Hz, 1H), 7.28 (d, *J*=6.9 Hz, 2H), 7.08 (t, *J*=1.8 Hz, 1H), 6.98 (s, 1H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 160.36, 153.33, 142.43, 140.94, 137.77, 135.26, 129.50, 129.16, 128.88, 128.10, 123.20, 118.09, 116.21, 91.46, 24.16. LRMS (EI): calc'd: 353; found: 352.

*2-((3,5-dibromophenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1s**)*



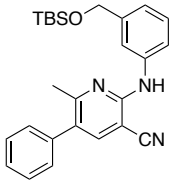
General procedure A was followed using 3,5-dibromoaniline (502 mg, 2.0 mmol, 1.0 equiv), 1-phenyl-1-propyne (250 μL, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (62 mg, 0.2 mmol, 10 mol%), and dry toluene (5 mL). Then, malononitrile (264 mg, 4.0 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (400 mg), 4 mL of ethanol were added, and the solution was heated for 12 h. Removal of solvent afforded product as a white powder (168 mg, 19%). M.p.: 202-203 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.91 (d, *J*=1.5 Hz, 2H), 7.68 (s, 1H), 7.45 (t, *J*=7.3 Hz, 2H), 7.40 (t, *J*=7.3 Hz, 1H), 7.37 (t, *J*=1.5 Hz, 1H), 7.28 (d, *J*=6.9 Hz, 2H), 6.98 (s, 1H), 2.51 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 160.44, 153.29, 142.32, 141.33, 137.82, 129.51, 129.16, 128.86, 128.50, 128.07, 123.01, 121.30, 116.25, 91.40, 24.22. LRMS (EI): calc'd: 443; found: 443.

*2-((3-iodophenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1t**)*



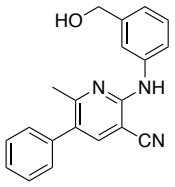
General procedure A was followed using 3-iodoaniline (438 mg, 2.0 mmol, 1.0 equiv), 1-phenyl-1-propyne (250 μL, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv), $Ti(dpm)(NMe_2)_2$ (62 mg, 0.2 mmol, 10 mol%), and dry toluene (5 mL). The second step used malononitrile (264 mg, 4.0 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (400 mg), 4 mL of ethanol and was heated for 6 h. Removal of solvent afforded product as a white powder (310 mg, 38%). M.p.: 144-145 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.25-8.21 (m, 1H), 7.66 (s, 1H), 7.62 (ddd, *J*=8.2, 2.2, 0.8 Hz, 1H), 7.47-7.41 (m, 3H), 7.41-7.37 (m, 1H), 7.30-7.27 (m, 2H), 7.08 (t, *J*=8.0 Hz, 1H), 6.94 (s, 1H), 2.50 (s, 3H).^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 160.39, 153.71, 142.27, 140.30, 138.04, 132.29, 130.50, 129.19, 128.90, 128.81, 128.76, 127.94, 119.18, 116.52, 94.29, 90.94, 24.24.

*2-((3-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1u-I**)*



General procedure A was followed using 3-(((tert-butyldimethylsilyl)oxy)methyl)aniline (474 mg, 2.0 mmol, 1.0 equiv), 1-phenyl-1-propyne (250μL, 2.0 mmol, 1.0 equiv), *tert*-butylisonitrile (340 μL, 3.0 mmol, 1.5 equiv), Ti(dpm)(NMe_2)$_2$ (64 mg, 0.2 mmol, 10 mol%), and 4 mL of dry toluene. The second step used malononitrile (264 mg, 4 mmol, 2.0 equiv), DBU (152 mg, 1.0 mmol, 0.5 equiv), molecular sieves (400 mg), 4 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as light yellow oil (384 mg, 45%). ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.64 (s, 2H), 7.61 (d, *J*=7.6 Hz, 1H), 7.44 (t, *J*=7.3 Hz, 2H), 7.38 (t, *J*=7.4 Hz, 1H), 7.32 (t, *J*=7.8 Hz, 1H), 7.28 (d, *J*=6.8 Hz, 2H), 7.06 (d, *J*=7.6 Hz, 1H), 7.00 (s, 1H), 4.77 (s, 2H), 2.47 (s, 3H), 0.96 (s, 9H), 0.13 (s, 6H). The NMR shows a compound with modest purity, that was used without further purification in the next step.

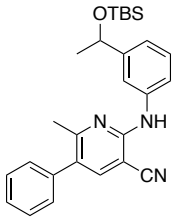
*2-((3-(hydroxymethyl)phenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1u**)*



In a 20 mL glass vial, 2-((3-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1u-I**) (400 mg, 0.93 mmol) was dissolved in 5 mL of THF with a stir bar. To this solution, 3 mL of 1 M TBAF solution (3.0 mmol) in THF was added dropwise under room temperature. The colorless solution became bright orange. After 1 h of stirring, the solvent was removed and crude product was purified by column chromatography (silica hexanes:EtOAc 4:1), which afforded the desired compound as colorless crystals (54%, 163 mg). M.p.: 114-115 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, 21 °C): δ 8.34 (s, 1H), 8.20 (s, 1H), 8.13 (d, *J*=9.6 Hz, 1H), 8.02 (t, *J*=7.2 Hz, 3H), 7.95 (t, *J*=7.4 Hz, 1H), 7.94-7.90 (m, 2H), 7.87 (t, *J*=7.8 Hz, 1H), 7.62 (d, *J*=8.6 Hz, 1H), 5.22-5.09 (m, 2H), 3.77 (t, *J*=6.0 Hz, 1H),

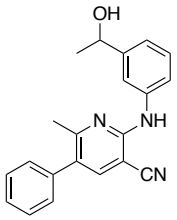
2.94 (s, 3H). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6, 126 MHz, 21 °C): δ 159.72, 154.42, 143.04, 142.86, 139.61, 138.32, 129.18, 128.55, 127.99, 127.56, 121.52, 119.81, 119.41, 116.35, 90.76, 63.68, 23.28. One quaternary carbon was not found.

*2-((3-(1-((tert-butyldimethylsilyl)oxy)ethyl)phenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1v-I**)*



General procedure A was followed using 3-(1-((*tert*-butyldimethylsilyl)oxy)ethyl)aniline (251 mg, 1.0 mmol, 1.0 equiv), 1-phenyl-1-propyne (125 μL, 1.0 mmol, 1.0 equiv), *tert*-butylisonitrile (170 μL, 1.5 mmol, 1.5 equiv), Ti(dpm)$(NMe_2)_2$ (32 mg, 0.1 mmol, 10 mol%), and 2 mL of dry toluene. The second step used malononitrile (132 mg, 2 mmol, 2.0 equiv), DBU (76 mg, 0.5 mmol, 0.5 equiv), molecular sieves (200 mg), 2 mL of ethanol and was heated for 2 h. Removal of solvent afforded product as a white powder (146 mg, 33%). M.p.: 69-70 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.63 (d, *J*=8.4 Hz, 2H), 7.59 (s, 1H), 7.44 (t, *J*=7.4 Hz, 2H), 7.38 (t, *J*=7.4 Hz, 1H), 7.31 (t, *J*=7.9 Hz, 1H), 7.28 (d, *J*=7.1 Hz, 2H), 7.08 (d, *J*=7.6 Hz, 1H), 6.98 (s, 1H), 4.89 (q, 1H), 2.47 (s, 3H), 1.44 (d, *J*=6.3 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.01 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 160.34, 154.29, 148.08, 142.24, 138.86, 138.31, 129.23, 128.86, 128.75, 128.20, 127.78, 120.58, 118.58, 117.27, 116.85, 90.48, 70.92, 27.42, 26.06, 24.29, 18.45, –4.56, –4.66.

*2-((3-(1-hydroxyethyl)phenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1v**)*

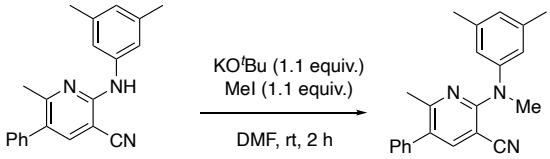


In a 20 mL glass vial, 2-((3-(1-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1v-I**) (50 mg, 0.11 mmol) was dissolved in 5 mL of THF with a stir bar. To this

solution, 1 mL of 1 M TBAF solution (1.0 mmol) in THF was added dropwise under room temperature. The colorless solution became bright orange. After 1 h of stirring, the solvent was removed and crude product was purified by column chromatography (silica hexanes:EtOAc 3:1), which afforded the desired compound as colorless crystals (54%, 20 mg). M.p.: 194-195 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, 21 °C): δ 11.25 (s, 1H), 8.29 (s, 1H), 8.06 (s, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.63 (s, 2H), 7.50-7.43 (m, 4H), 7.37 (ddd, *J*=8.6, 5.6, 2.3 Hz, 1H), 7.24 (t, *J*=7.8 Hz, 1H), 6.93 (d, *J*=7.6 Hz, 1H), 4.70 (q, *J*=6.4 Hz, 1H), 2.42 (s, 3H), 1.34 (d, *J*=6.4 Hz, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz, 21 °C): δ 170.01, 156.86, 153.28, 148.09, 140.25, 139.06, 138.69, 129.33, 128.37, 127.00, 125.89, 118.60, 117.27, 116.22, 107.79, 68.16, 25.98, 23.47. . LRMS (EI): calc'd: 329; found: 328.

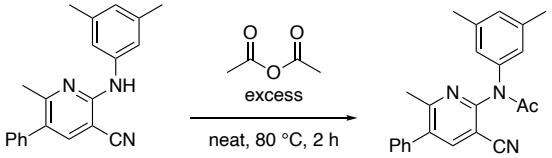
Post functionalization of MSU38225

*2-((3,5-dimethylphenyl)(methyl)amino)-6-methyl-5-phenylnicotinonitrile (**2a**)*



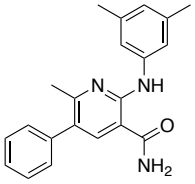
The procedure was adapted from a literature procedure.[6] In a 20 mL glass vial, 2-((3,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (80 mg, 1.0 equiv), potassium *tert*-butoxide (32 mg, 1.1 equiv), and 3 mL of DMF were loaded with a stir bar. The mixture was stirred under room temperature for 10 min before methyl iodide (40 mg, 1.1 equiv) was added dropwise. The mixture was stirred for another 2 h under room temperature. The reaction mixture was poured onto water and extracted with 20 mL of EtOAc. The organic layer was washed with brine, dried with sodium sulfate, and evaporated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford pure product as a white solid (46 mg, 55%). M.p.: 106-107 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.52 (s, 1H), 7.42 (t, *J*=7.6 Hz, 2H), 7.35 (t, *J*=7.3 Hz, 1H), 7.28 (d, *J*=7.9 Hz, 2H), 6.94 (s, 1H), 6.89 (s, 2H), 3.52 (d, *J*=1.5 Hz, 3H), 2.47 (d, *J*=1.5 Hz, 3H), 2.33 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 159.35, 157.10, 146.51, 144.88, 139.60, 138.52, 129.21, 128.65, 128.56, 127.53, 127.29, 124.04, 116.72, 92.44, 40.73, 24.15, 21.53. LRMS (EI): calc'd: 327; found: 327.

*N-(3-cyano-6-methyl-5-phenylpyridin-2-yl)-N-(3,5-dimethylphenyl)acetamide (**2b**)*



The procedure was adapted from a literature procedure.[7] In a 15 mL pressure tube, 2-((3,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (100 mg, 0.32 mmol) and acetic anhydride (2 mL, 21 mmol) were loaded with a stir bar. The tube was sealed and heated in an oil bath at 80 °C for 2 h. After the reaction was cooled to room temperature, the reaction mixture was poured onto water and extracted with 20 mL of EtOAc. The organic layer was washed with brine, dried with sodium sulfate, and evaporated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford pure product as a white solid (78 mg, 69%). M.p.: 161-162 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.83 (s, 1H), 7.51-7.43 (m, 3H), 7.32-7.28 (m, 2H), 7.18 (s, 2H), 7.02 (s, 1H), 2.51 (s, 3H), 2.36 (s, 6H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 171.42, 161.32, 154.59, 142.53, 140.61, 139.55, 137.22, 136.30, 130.42, 128.95, 128.60, 126.50, 115.94, 106.44, 24.14, 22.99, 21.38. LRMS (EI): calc'd: 355; found: 355.

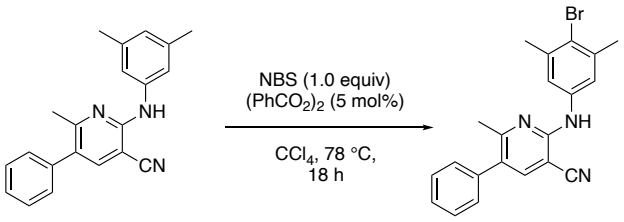
*2-((3,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinamide (**2c**)*



2-((3,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (110 mg, 0.35 mmol) was placed in a 50 mL round bottom flask with a stir bar and 4 mL of EtOH. This solution was stirred, and tetrabutylammonium hydroxide solution (0.5 mL, 40% in water) was added. An air condenser was attached to the flask, and the solution was heated, in air, until it was actively refluxing. The solution was sampled at 30 min intervals and checked by TLC for completion (watched the starting pyridine disappear). When the starting material no longer appeared by TLC, the reaction was removed from heat and allowed to cool (~4

h). Once cooled, the solution was neutralized with ammonium chloride until the pH was between 7 and 8. The crude solution was then extracted with DCM several times (5 mL × 5). The combined organic fractions were dried over Na_2SO_4, filtered to remove the drying agent, and concentrated by rotary evaporation. This provided the crude product as a sticky orange oil. This oil was washed with water to remove excess N^nBu_4Cl generated during neutralization. The resulting residue was rinsed with hexanes and dried once more by rotary evaporation. This provided the product as a yellow powder (yield: 27 mg, 23%). From this powder, X-ray quality crystals were grown from a solution of $CHCl_3$ layered with n-pentane at –20 °C for 3 d. The crystals contain $CHCl_3$ in the lattice, so this method of purification is undesirable for biological samples due to this solvation. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): 10.52 (s, 1H), 7.54 (s, 1H), 7.47-7.40 (m, 4H), 7.39-7.34 (m, 1H), 7.34-7.29 (m, 2H), 6.67 (s, 1H), 5.77 (s (br), 2H), 2.47 (s, 3H), 2.33 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.48, 159.57, 154.20, 140.25, 139.65, 138.34, 137.73, 129.38, 128.63, 127.32, 126.31, 124.07, 118.08, 106.60, 23.88, 21.70. LRMS (EI): calc'd: 331; found: 331.

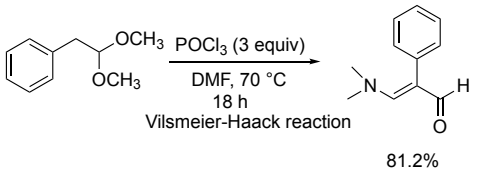
*2-((4-bromo-3,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (**2d**)*



In a 50 mL round bottom flask, N-bromosuccinimide (66 mg, 0.37 mmol, 1.0 equiv) and benzoyl peroxide (5.0 mg, 0.05 equiv) was dissolved in 3 mL of CCl_4 with a stir bar. A solution of 2-((3,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (115 mg, 0.37 mmol, 1.0 equiv) in 3 mL of CCl_4 was added. The round bottom flask was fixed with a condenser and heated in an oil bath at 78 °C for 18 h. After the reaction was cooled to room temperature, the reaction mixture was diluted by adding 50 mL of EtOAc, then washed with brine. The organic layer was dried with sodium sulfate and evaporated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford pure product as an off-white solid (124 mg, 86%). ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.63 (s, 1H), 7.46 (s, 2H), 7.44 (t, *J*=7.5 Hz, 2H), 7.38 (t, *J*=7.3 Hz, 1H), 7.28 (s, 1H), 6.87 (s, 1H), 2.47 (s, 3H), 2.43 (s, 6H).

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 160.36, 154.07, 142.26, 138.87, 138.18, 137.55, 129.20, 128.78, 128.40, 127.86, 121.36, 119.96, 116.73, 90.67. LRMS (EI): calc'd: 391; found: 392.

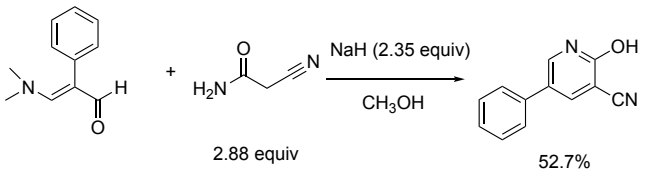
*Synthesis of 3-(dimethylamino)-2-phenylacrylaldehyde (**3-I**)*



81.2%

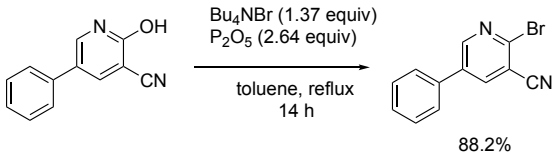
The procedure was adapted from a literature procedure.[8] A 250 mL Schlenk flask was loaded with $POCl_3$ (41.39 g, 0.27 mol, 3 equiv) and a magnetic stir bar. Then, the flask was flushed with dry dinitrogen for 5 min and set in a room temperature water bath. With vigorous stirring, dimethylformamide (24 g, 0.33 mol, 3.67 equiv) was then added dropwise to $POCl_3$. The mixture was stirred under room temperature for 5 min. After 5 min, phenylacetaldehyde dimethyl acetal (15 g, 0.09 mol, 1 equiv) in 45 mL dimethylformamide was added dropwise for about 5 min. The resulting solution was stirred at 70 °C for 18 h before it was poured into 375 mL ice and neutralized by the addition of anhydrous potassium carbonate till pH is around 7. Then the solution was slowly added sodium hydroxide (50 g, 1.25 mol), and 50 mL of water and heated at 50 °C with stirring for 1 h. The mixture was cooled and extracted with DCM (50 mL × 2) and washed with water thoroughly (50 mL × 3). The excess solvent was removed *in vacuo*, resulting a red-brown oil. The crude product was used in the next step without further purification. Further purification can be achieved by cooling concentrated ether solution in a freezer (–30 °C) overnight to afford a red-brown oil (12.79 g, 0.073 mol, 81.2%). ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 9.10 (s, 1H), 7.31-7.35 (m, 2H), 7.22-7.25 (m, 1H), 7.16-7.20 (m, 2H), 6.78 (s, 1H, br), 2.81 (s, 1H, br). 13C{1H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ188.96, 158.60, 133.73, 130.81, 127.45, 126.36, 125.23, 114.86. LRMS (EI): calc'd: 175; found: 175.

*Synthesis of 2-hydroxy-5-phenylnicotinonitrile (**3-II**)*



The procedure was adapted from a literature procedure.[9] A 500 mL Schlenk flask was loaded with NaH (3.22 g, 0.134 mol, 2.35 equiv) and a magnetic stir bar before 130 mL of MeOH slowly was added. After 10 min of stirring at room temperature, cyanoacetamide (13.78 g, 0.164 mol, 2.88 equiv), and 3-(dimethylamino)-2-phenylprop-2-enal **c-I** (10 g, 0.0571 mol, 1.0 equiv) was added. The mixture was stirred at room temperature for 1.5 h and then refluxed overnight. After cooling to room temperature, 100 mL of water was added, and the mixture was acidified with 1 M HCl solution. While adding acid, a large amount of yellow solid precipitated out. The solid was filtered and washed with water (20 mL × 3), methanol (5mL × 3), ether (5mL × 3) and hexane (5mL × 3) to afford a light-yellow product. (5.91 g, 0.03 mol, 52.7%). M.p.: 226-227 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 13.61 (s, 1H, br), 8.23 (s, 1H), 7.99 (s, 1H), 7.45-7.51 (m, 2H), 7.38-7.45 (m, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ162.11, 147.96, 137.47, 134.04, 129.55, 128.54, 125.88, 121.76, 115.21, 105.35. One quaternary carbon was not found. LRMS (EI): calc'd: 196; found: 196.

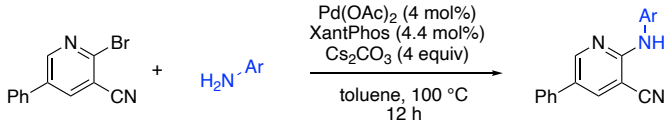
*Synthesis of 2-bromo-5-phenylnicotinonitrile (**3-III**)*



A 250 mL Schlenk flask was charged with 2-hydroxy-5-phenylnicotinonitrile **c-II** (2.14 g, 10.9 mmol), Bu_4NBr (4.8 g, 14.9 mmol), P_2O_5 (4.1 g, 28.8 mmol), toluene (110 mL), and a magnetic stir bar. The mixture was heated for 14 h under reflux. Then, the toluene layer was decanted and washed with 30 mL of saturated $NaHCO_3$ solution and then 50 mL of water. 50 mL of water and powered $NaHCO_3$ was added till no gas was evolved. The mixture was extracted with 250 mL DCM, washed with 2 × 50 mL of brine, and washed with 30 mL of water. The organic layers were combined and dried with $MgSO_4$. Removal of the solvent in

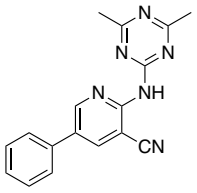
vacuo afforded a light-yellow power. Further purification can be achieved by chromatography (1:10 EtOAc:hexane). (2.48 g, 9.61 mmol, 88.2%). M.p.: 139-140 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.76 (s, 1H), 8.10 (s, 1H), 7.48-7.57 (m, 5H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ151.33, 142.07, 140.50, 136.33, 134.41, 129.76, 129.73, 127.15, 115.90, 114.29, 24.99. LRMS (EI): calc'd: 258; found: 259.

General procedure B: synthesis of 2-amino-5-phenylnicotinonitrile derivatives via Buchwald-Hartwig coupling



The procedure was adapted from a literature procedure.[10] In a glove box, palladium(II) acetate (9.0 mg, 0.04 mmol, 4 mol%) and Xantphos (25.4 mg, 0.044 mmol, 4.4 mol%) were dissolved in 2 mL of dry toluene in a 35 mL pressure tube. The mixture was stirred for 2 min before 2-bromo-5-phenylnicotinonitrile (259 mg, 1.0 mmol, 1.0 equiv), aryl amine (1.2 mmol, 1.2 equiv), and cesium carbonate (1312 mg, 4.0 mmol, 4.0 equiv) were added to the pressure tube. Then, another 3 mL of dry toluene were added. The reaction was then removed from the glovebox and heated in an oil bath at 110 °C for 14 h. After the reaction was cooled to room temperature, the reaction mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate).

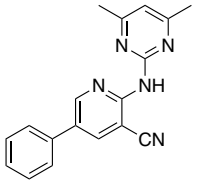
*2-((4,6-dimethyl-1,3,5-triazin-2-yl)amino)-5-phenylnicotinonitrile (**3a**)*



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (300 mg, 1.16 mmol, 1.0 equiv), 4,6-dimethyl-1,3,5-triazin-2-amine (172 mg, 1.2 equiv), palladium(II) acetate (10.4 mg, 4 mol%), xantphos (29.5 mg, 4.4 mol%), cesium carbonate (1520 mg, 4.0 equiv), and 5 mL of dry toluene. Removal of solvent afforded product as an off-white powder (42 mg, 12%). M.p.: 225-226 °C. ^{1}H NMR ($CDCl_3$, 500

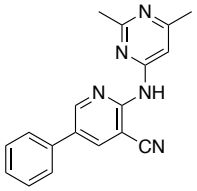
MHz, 21 °C): 9.36 (br s, 1H), 8.97 (d, *J*=2.3 Hz, 1H), 8.22 (d, *J*=2.3 Hz, 1H), 7.59 (d, *J*=7.4 Hz, 2H), 7.53 (t, *J*=7.5 Hz, 2H), 7.47 (t, *J*=7.3 Hz, 1H), 2.57 (s, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): 176.94, 163.43, 150.75, 150.34, 140.75, 135.21, 133.29, 129.46, 128.93, 126.85, 115.77, 103.84, 25.50. LRMS (EI): calc'd: 302; found: 301.

*2-((4,6-dimethylpyrimidin-2-yl)amino)-5-phenylnicotinonitrile (**3b**)*



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (200 mg, 1.0 equiv), 4,6-dimethylpyrimidin-2-amine (114 mg, 1.2 equiv), palladium(II) acetate (7 mg, 4 mol%), xantphos (19.6 mg, 4.4 mol%), cesium carbonate (1013 mg, 4.0 equiv), and 4 mL of dry toluene. Removal of solvent afforded product as an off-white powder (207 mg, 69%). M.p.: 215-216 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.82 (d, *J*=2.4 Hz, 1H), 8.25 (s, 1H), 8.13 (d, *J*=2.4 Hz, 1H), 7.56 (d, *J*=7.5 Hz, 2H), 7.50 (t, *J*=7.6 Hz, 2H), 7.43 (t, *J*=7.3 Hz, 1H), 6.69 (s, 1H), 2.44 (s, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 168.18, 157.97, 152.43, 150.58, 140.78, 135.86, 131.52, 129.47, 128.61, 126.84, 116.40, 114.81, 101.06, 23.99. LRMS (EI): calc'd: 301; found: 300.

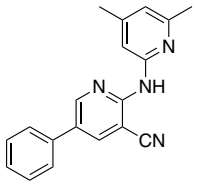
*2-((2,6-dimethylpyrimidin-4-yl)amino)-5-phenylnicotinonitrile (**3c**)*



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (300 mg, 1.16 mmol, 1.0 equiv), 2,6-dimethylpyrimidin-4-amine (170 mg, 1.2 equiv), palladium(II) acetate (10.4 mg, 4 mol%), xantphos (29.5 mg, 4.4 mol%), cesium carbonate (1520 mg, 4.0 equiv), and 5 mL of dry toluene. Removal of solvent afforded product as an off-white powder (74 mg, 21%). M.p.: 154-155 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): 8.77 (d, *J*=2.3 Hz, 1H), 8.11 (s, 1H), 8.09 (d, *J*=2.5 Hz, 1H), 7.86 (s, 1H), 7.41-7.57 (m, 5H),

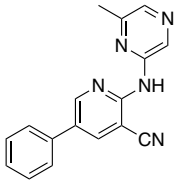
2.61 (s, 3H), 2.53 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): 151.33, 142.07, 140.50, 136.34, 134.42, 129.76, 129.73, 129.51, 128.70, 127.84, 127.15, 126.89, 119.25, 115.91, 114.30, 21.49. LRMS (EI): calc'd: 301; found: 300.

*2-((4,6-dimethylpyridin-2-yl)amino)-5-phenylnicotinonitrile (**3d**)*



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (160 mg, 0.62 mmol, 1.0 equiv), 4,6-dimethylpyridin-2-amine (91 mg, 1.2 equiv), palladium(II) acetate (5.5 mg, 4 mol%), xantphos (15.7 mg, 4.4 mol%), cesium carbonate (810 mg, 4.0 equiv), and 4 mL of dry toluene. The compound was purified by column chromatography on silica gel using40% EtOAc in hexanes. Removal of solvent afforded product as an off-white powder (93 mg, 50%). M.p.: 112-113 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.70 (d, *J*=2.4 Hz, 1H), 8.03 (d, *J*=2.4 Hz, 1H), 8.02 (s, 1H), 7.76 (s, 1H), 7.56-7.46 (m, 4H), 7.41 (t, *J*=7.2 Hz, 1H), 6.72 (s, 1H), 2.45 (s, 3H), 2.37 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 156.85, 153.80, 151.44, 150.41, 149.74, 140.08, 136.05, 129.44, 128.48, 128.28, 126.51, 119.63, 116.03, 110.74, 94.59, 24.06, 21.59. LRMS (EI): calc'd: 300; found: 299.

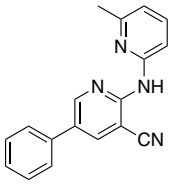
*2-((6-methylpyrazin-2-yl)amino)-5-phenylnicotinonitrile (**3e**)*



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (200 mg, 1.0 equiv), 6-methylpyrazin-2-amine (101 mg, 1.2 equiv), palladium(II) acetate (7 mg, 4 mol%), xantphos (19.6 mg, 4.4 mol%), cesium carbonate (1013 mg, 4.0 equiv), and 4 mL of dry toluene. Removal of solvent afforded product as a white powder (77 mg, 35%). M.p.: 160-161 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 9.59 (s, 1H), 8.74 (d, *J*=2.5 Hz, 1H), 8.18 (s, 1H), 8.08 (d, *J*=2.5 Hz, 1H), 7.72 (s, 1H), 7.54 (d, *J*=7.0 Hz, 2H),

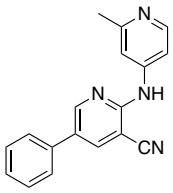
7.50 (t, *J*=7.6 Hz, 2H), 7.45-7.41 (m, 1H), 2.51 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 152.87, 152.09, 150.51, 148.05, 140.08, 138.13, 135.66, 132.55, 129.74, 129.53, 128.60, 126.65, 115.69, 94.97, 21.32. LRMS (EI): calc'd: 287; found: 286.

*2-((6-methylpyridin-2-yl)amino)-5-phenylnicotinonitrile (**3f**)*



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (259 mg, 1.0 equiv), 6-methylpyridin-2-amine (130 mg, 1.2 equiv), palladium(II) acetate (9 mg, 4 mol%), xantphos (25.5 mg, 4.4 mol%), cesium carbonate (1312 mg, 4.0 equiv), and 4 mL of dry toluene. Removal of solvent afforded product as a yellow powder (180 mg, 63%). M.p.: 145-146 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.68 (dd, *J*=2.3, 0.9 Hz, 1H), 8.20 (d, *J*=8.3 Hz, 1H), 8.04 (dd, *J*=2.4, 1.0 Hz, 1H), 7.81 (s, 1H), 7.61 (t, *J*=7.7 Hz, 1H), 7.56-7.45 (m, 4H), 7.41 (t, *J*=7.6 Hz, 1H), 6.87 (d, *J*=7.5 Hz, 1H), 2.49 (s, 3H).. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 157.32, 153.75, 151.36, 150.39, 140.05, 138.43, 135.99, 129.45, 128.63, 128.31, 126.52, 118.31, 116.00, 110.14, 94.62, 24.26. LRMS (EI): calc'd: 286; found: 285.

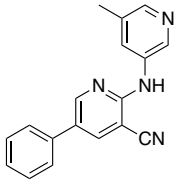
*2-((2-methylpyridin-4-yl)amino)-5-phenylnicotinonitrile (**3g**)*



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (147 mg, 1.0 equiv), 2-methylpyridin-4-amine (74 mg, 1.2 equiv), palladium(II) acetate (5 mg, 4 mol%), xantphos (15 mg, 4.4 mol%), cesium carbonate (744 mg, 4.0 equiv), and 3 mL of dry toluene. Removal of solvent afforded product as white crystals (110 mg, 68%). M.p.: 133-134 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): 8.74 (d, *J*=2.4 Hz, 1H), 8.42 (d, *J*=6.1 Hz, 1H), 8.06 (d, *J*=2.4 Hz, 1H), 7.55-7.46 (m, 6H), 7.43 (t, *J*=7.0 Hz, 1H), 7.16 (s, 1H), 2.58 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 159.63, 154.02, 150.55, 150.10,

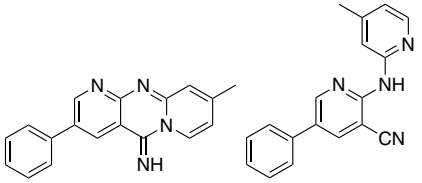
146.21, 139.89, 135.69, 129.54, 129.45, 128.59, 126.62, 115.93, 112.64, 110.93, 95.02, 24.83. LRMS (EI): calc'd: 286; found: 285.

*2-((5-methylpyridin-3-yl)amino)-5-phenylnicotinonitrile (**3h**)*



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (147 mg, 1.0 equiv), 5-methylpyridin-3-amine (74 mg, 1.2 equiv), palladium(II) acetate (5 mg, 4 mol%), xantphos (15 mg, 4.4 mol%), cesium carbonate (744 mg, 4.0 equiv), and 3 mL of dry toluene. Removal of solvent afforded product as white crystals (110 mg, 68%). M.p.: 180-181 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): 8.64 (d, *J*=2.4 Hz, 2H), 8.21 (s, 1H), 8.02 (d, *J*=2.5 Hz, 1H), 7.95 (s, 1H), 7.56-7.44 (m, 4H), 7.40 (t, *J*=7.7 Hz, 1H), 7.10 (s, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.76, 150.73, 145.65, 139.94, 139.80, 135.92, 135.11, 133.48, 129.44, 128.56, 128.38, 128.31, 126.46, 116.24, 93.84, 18.63. LRMS (EI): calc'd: 286; found: 285.

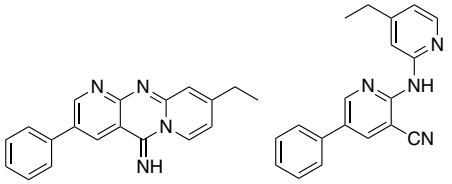
*2-((4-methylpyridin-2-yl)amino)-5-phenylnicotinonitrile (**3i**)*



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (259 mg, 1.0 equiv), 4-methylpyridin-2-amine (9 mg, 1.2 equiv), palladium(II) acetate (5 mg, 4 mol%), xantphos (25.5 mg, 4.4 mol%), cesium carbonate (1312 mg, 4.0 equiv), and 5 mL of dry toluene. Removal of solvent afforded product as an orange powder (109 mg, 42%). M.p.: 149-150 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 9.12 (s, 1H), 8.99 (d, *J*=7.0 Hz, 1H), 8.31 (s, 1H), 7.66 (d, *J*=7.8 Hz, 2H), 7.51 (t, *J*=7.6 Hz, 3H), 7.42 (t, *J*=7.1 Hz, 1H), 7.22 (s, 1H), 6.64 (d, *J*=7.5 Hz, 1H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 154.66, 154.27, 150.45, 147.79, 137.17, 132.38, 131.13, 129.43, 129.37, 128.24, 127.31, 127.06, 126.50,

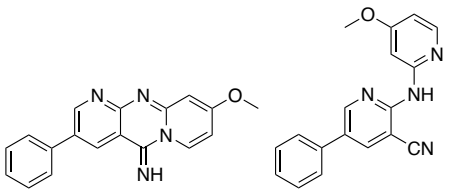
124.17, 115.35, 109.66, 21.54. ^{1}H NMR (500 MHz, DMSO, 21 °C) δ 10.03 (s, 1H), 9.12 (d, *J*=2.6 Hz, 1H), 9.07 (d, *J*=2.6 Hz, 1H), 8.97 (d, *J*=7.5 Hz, 1H), 7.90 (d, *J*=7.2 Hz, 2H), 7.54 (t, *J*=7.7 Hz, 2H), 7.43 (t, *J*=7.4 Hz, 1H), 7.14 (s, 1H), 6.82 (dd, *J*=7.5, 2.0 Hz, 1H), 2.37 (s, 3H). uncyclized form: 1H NMR (CDCl3, 500 MHz, 21 °C): δ 8.71 (d, J = 2.4 Hz, 1H), 8.22 (s, 1H), 8.17 (d, J = 5.1 Hz, 1H), 8.04 (d, J = 2.6 Hz, 1H), 7.81 (s, 1H), 7.65 (s, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 4.2 Hz, 1H), 2.41 (s, 3H). LRMS (EI): calc'd: 286; found: 285.

2-((4-ethylpyridin-2-yl)amino)-5-phenylnicotinonitrile ***(3j)***



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (100 mg, 1.0 equiv), 4-ethylpyridin-2-amine (58 mg, 1.2 equiv), palladium(II) acetate (5 mg, 4 mol%), xantphos (10 mg, 4.4 mol%), cesium carbonate (500 mg, 4.0 equiv), and 3 mL of dry toluene. Removal of solvent afforded product as an orange powder (35 mg, 30%). M.p.:122-123 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ 9.15 (s, 1H), 9.05 (d, J = 7.2 Hz, 1H), 8.39 (s, 1H), 7.70 (s, 2H), 7.53 (s, 2H), 7.44 (s, 1H), 7.29 (s, 1H), 6.72 (d, J = 8.3 Hz, 1H), 2.71 (q, J = 7.5 Hz, 2H), 1.33 (t, J = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 25 °C): δ 165.00, 154.38, 153.40, 137.20, 131.16, 129.45, 129.41, 128.29, 127.48, 127.11, 126.53, 125.69, 122.70, 120.92, 114.49, 28.43, 13.17. LRMS (EI): calc'd: 300; found: 300.

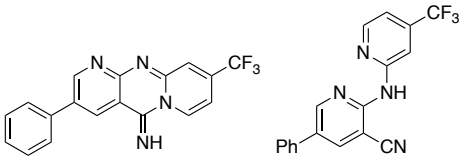
2-((4-methoxypyridin-2-yl)amino)-5-phenylnicotinonitrile ***(3k)***



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (100 mg, 1.0 equiv), 4-methoxylpyridin-2-amine (58 mg, 1.2 equiv), palladium(II) acetate (5 mg, 4 mol%), xantphos (10 mg, 4.4 mol%), cesium carbonate (500 mg, 4.0 equiv), and 3 mL of dry toluene. Removal of solvent afforded

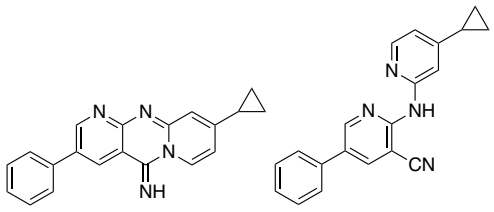
product as an orange powder (72 mg, 62%). M.p.: 188-189 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ 9.08 (d, J = 2.3 Hz, 1H), 9.01 (d, J = 8.1 Hz, 1H), 8.28 (s, 1H), 7.66 (d, J = 7.9 Hz, 2H), 7.58-7.47 (m, 2H), 7.42 (t, J = 7.4 Hz, 1H), 6.68 (d, J = 2.7 Hz, 1H), 6.52 (dd, J = 8.1, 2.9 Hz, 1H), 3.94 (s, 3H).. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 25 °C): δ 165.08, 156.46, 154.93, 154.29, 152.45, 137.31, 131.99, 131.18, 129.39, 128.19, 127.04, 126.56, 109.17, 108.48, 100.95. LRMS (EI): calc'd: 302; found: 302.

*5-phenyl-2-((4-(trifluoromethyl)pyridin-2-yl)amino)nicotinonitrile (**3l**)*



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (100 mg, 1.0 equiv), 4-(trifluoromethyl)pyridin-2-amine (75 mg, 1.2 equiv), palladium(II) acetate (4 mg, 4 mol%), xantphos (11 mg, 4.4 mol%), cesium carbonate (506 mg, 4.0 equiv), and 5 mL of dry toluene. Removal of solvent afforded product as an orange powder (101 mg, 77%). M.p.: 138-140 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ 8.81 (s, 1H), 8.79 (d, J = 2.6 Hz, 1H), 8.50 (d, J = 5.0 Hz, 1H), 8.12 (d, J = 2.6 Hz, 1H), 8.07 (s, 1H), 7.57 (d, J = 7.3 Hz, 2H), 7.53 (t, J = 7.6 Hz, 2H), 7.49-7.43 (m, 1H), 7.24 (d, J = 5.2 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 25 °C): δ 153.15, 152.98, 150.41, 149.30, 140.23, 140.08, 135.67, 129.69, 129.53, 128.61, 126.64, 115.60, 114.30, 114.27, 114.25, 114.22, 109.24, 109.21, 109.18, 109.15, 95.24. ^{19}F NMR (471 MHz, $CDCl_3$) δ -64.73.

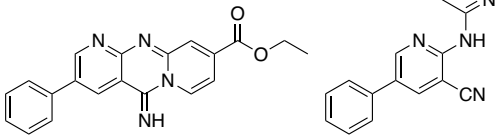
*5-phenyl-2-((4-(cyclopropyl)pyridin-2-yl)amino)nicotinonitrile (**3m**)*



General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (259 mg, 1.0 equiv), 4-cyclopropylpyridin-2-amine (134 mg, 1.2 equiv), palladium(II) acetate (5 mg, 4 mol%), xantphos (25 mg, 4.4 mol%), cesium carbonate (1312 mg, 4.0 equiv), and 5 mL of dry toluene. Removal of solvent afforded

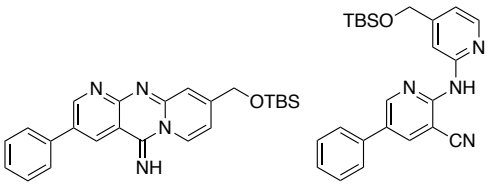
product as an orange powder (70 mg, 22%). M.p.: above 260 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, 25 °C): δ 9.25 (d, J = 2.5 Hz, 1H), 9.13 (d, J = 7.6 Hz, 1H), 9.07 (d, J = 2.5 Hz, 1H), 8.77 (d, J = 2.5 Hz, 1H), 7.86 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.8 Hz, 2H), 7.52-7.47 (m, 2H), 7.45 (d, J = 2.2 Hz, 1H), 7.35-7.28 (m, 3H), 7.26 (t, J = 7.2 Hz, 2H), 6.99 (dd, J = 7.8, 2.1 Hz, 1H), 2.24-2.18 (m, 1H), 1.26-1.19 (m, 2H), 1.10-1.03 (m, 2H). ^{13}C{^{1}H} NMR (DMSO-d_6, 151 MHz, 25 °C): δ 163.36, 155.71, 151.45, 149.01, 148.14, 141.04, 135.81, 132.99, 130.98, 129.80, 129.28, 129.15, 128.17, 127.48, 126.20, 119.87, 87.63, 16.90, 15.29, 10.79. LRMS (EI): calc'd: 312; found: 312.

*Ethyl 2-((3-cyano-5-phenylpyridin-2-yl)amino)isonicotinate (**3n**)*



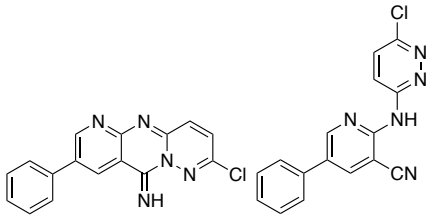
General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (300 mg, 1.0 equiv), ethyl 2-aminoisonicotinate (231 mg, 1.2 equiv), palladium(II) acetate (11 mg, 4 mol%), xantphos (27 mg, 4.4 mol%), cesium carbonate (1.5 g, 4.0 equiv), and 5 mL of dry toluene. Removal of solvent afforded product as an orange powder (60 mg, 15%). M.p.: 187-190 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ 8.40 (d, J = 5.2 Hz, 1H), 8.26-8.20 (m, 1H), 7.94 (ddd, J = 8.0, 2.2, 1.0 Hz, 1H), 7.81 (dt, J = 7.7, 1.3 Hz, 1H), 7.65-7.59 (m, 2H), 7.53 (dd, J = 5.6, 2.1 Hz, 3H), 7.46 (t, J = 7.9 Hz, 1H), 7.28 (s, 1H), 6.90 (d, J = 5.2 Hz, 1H), 4.48-4.34 (m, 2H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 25 °C): δ 166.41, 156.96, 155.06, 151.69, 138.99, 136.50, 131.53, 130.23, 129.21, 128.36, 125.32, 125.07, 121.99, 116.61, 115.40, 92.19, 61.30, 14.49. LRMS (EI): calc'd: 344; found: 344.

*2-((4-(((tert-butyldimethylsilyl)oxy)methyl)pyridin-2-yl)amino)-5-phenylnicotinonitrile (**3o**)*



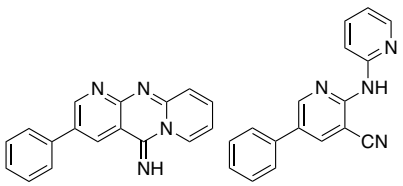
General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (300 mg, 1.0 equiv), 4-(((tert-butyldimethylsilyl)oxy)methyl)pyridin-2-amine (331 mg, 1.2 equiv), palladium(II) acetate (11 mg, 4 mol%), xantphos (32 mg, 4.4 mol%), cesium carbonate (1520 mg, 4.0 equiv), and 5 mL of dry toluene. Removal of solvent afforded product as a yellow powder (398 mg, 82%). Column condition: 40% EtOAc in hexanes. M.p.: 94-95 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ 9.13 (s, 1H), 9.05 (d, J = 7.9 Hz, 1H), 8.57 (s, 1H), 8.33 (s, 1H), 7.68 (d, J = 7.8 Hz, 2H), 7.58-7.49 (m, 2H), 7.48-7.40 (m, 2H), 6.70 (d, J = 7.6 Hz, 1H), 4.74 (s, 2H), 0.98 (s, 9H), 0.16 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 25 °C): δ 154.60, 154.33, 150.78, 150.64, 137.17, 132.61, 131.13, 129.40, 128.30, 127.71, 127.11, 121.12, 110.95, 109.82, 63.43, 26.00, 18.49, -5.23.

*2-((6-chloropyridazin-3-yl)amino)-5-phenylnicotinonitrile (**3p**)*



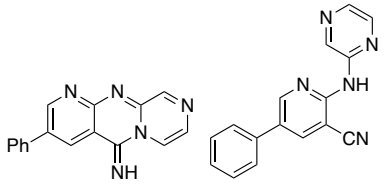
General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (200 mg, 1.0 equiv.), 6-chloropyridazin-3-amine (121 mg, 1.2 equiv.), palladium (II) acetate (7 mg, 4 mol%), Xantphos (19.6 mg, 4.4 mol%), cesium carbonate (1013 mg, 4.0 equiv), and 4 mL of dry toluene. Removal of solvent afforded product as an orange powder (55 mg, 23%). M.p.: 238-239 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ 9.18 (s, 1H), 9.04 (s, 1H), 7.74 (d, J = 7.4 Hz, 2H), 7.67 (d, J = 9.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.21 (d, J = 9.5 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 25 °C): δ 180.58, 154.11, 153.03, 150.56, 146.15, 145.28, 138.23, 136.57, 135.05, 133.19, 129.38, 129.22, 128.70, 127.34.

*5-phenyl-2-(pyridin-2-ylamino)nicotinonitrile (**3q**)*



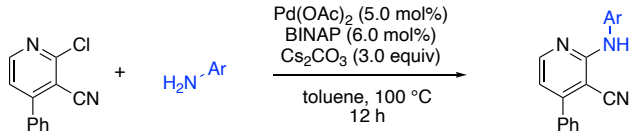
General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (200mg, 1.0 equiv), pyridin-2-amine (87 mg, 1.2 equiv), palladium(II) acetate (7 mg, 4 mol%), xantphos (20 mg, 4.4 mol%), cesium carbonate (1013 mg, 4.0 equiv), and 5 mL of dry toluene. Removal of solvent afforded product as an orange powder (40 mg, 19%). ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ 9.20-9.14 (m, 1H), 9.11 (d, J = 7.1 Hz, 1H), 8.36 (s, 1H), 7.69 (d, J = 7.5 Hz, 2H), 7.56-7.41 (m, 6H), 6.82 (t, J = 7.3 Hz, 1H). 1H NMR (DMSO-d_6, 500 MHz, 25 °C) δ 10.10 (s, 1H), 9.18-9.07 (m, 2H), 9.05 (d, J = 7.0 Hz, 1H), 7.90 (d, J = 7.1 Hz, 2H), 7.68 (ddd, J = 9.0, 6.4, 1.6 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.43 (t, J = 7.4 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.93 (ddd, J = 7.8, 6.5, 1.5 Hz, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz, 25 °C): δ 154.21, 153.90, 152.72, 150.11, 136.81, 136.39, 132.33, 130.96, 129.14, 127.97, 127.94, 126.63, 125.49, 112.29, 110.46. LRMS (EI): calc'd: 272; found: 272.

*5-phenyl-2-(pyrazin-2-ylamino)nicotinonitrile (**3r**)*



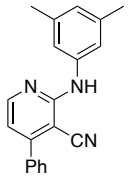
General procedure B was followed using 2-bromo-5-phenylnicotinonitrile (200 mg, 1.0 equiv), pyrazin-2-amine (88mg, 1.2 equiv), palladium(II) acetate (7 mg, 4 mol%), xantphos (20 mg, 4.4 mol%), cesium carbonate (1013 mg, 4.0 equiv), and 4 mL of dry toluene. Removal of solvent afforded product as an orange powder (85 mg, 40%). M.p.:166-167 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ 9.22 (s, 1H), 8.92 (s, 1H), 8.72 (s, 2H), 8.37 (s, 1H), 7.79 (d, J = 5.0 Hz, 1H), 7.69 (d, J = 7.6 Hz, 2H), 7.55 (t, J = 7.7 Hz, 2H), 7.48 (t, J = 7.7 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 25 °C): δ 154.67, 153.81, 148.93, 143.55, 141.91, 136.50, 134.92, 131.08, 129.58, 128.92, 128.45, 127.32, 126.66, 117.52. ^{1}H NMR (DMSO-d_6, 500 MHz,) δ 10.24 (s, 1H), 9.23 (s, 1H), 9.14 (d, J = 2.6 Hz, 1H), 8.78 (s, 1H), 8.68 (d, J = 5.1 Hz, 1H), 7.93 (d, J = 7.6 Hz, 2H), 7.79 (d, J = 5.0 Hz, 1H), 7.56 (t, J = 7.7 Hz, 2H), 7.46 (t, J = 7.3 Hz, 1H). LRMS (EI): calc'd: 273; found: 273.

General procedure C: synthesis of 2-amino-5-phenylnicotinonitrile derivatives via Buchwald-Hartwig coupling



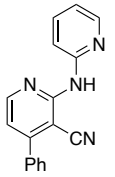
In a glove box, palladium(II) acetate (11.2 mg, 0.05 mmol, 5 mol%) and BINAP (37.7 mg, 0.06 mmol, 6.0 mol%) were dissolved in 2 mL of dry toluene in a 35 mL pressure tube. The mixture was stirred for 2 min before 2-chloro-4-phenylnicotinonitrile (214 mg, 1.0 mmol, 1.0 equiv), aryl amine (1.2 mmol, 1.2 equiv), and cesium carbonate (984 mg, 3.0 mmol, 3.0 equiv) were added to the pressure tube. Then, another 3 mL of dry toluene were added. The reaction was then removed from the glovebox and heated in an oil bath at 110 °C for 14 h. After the reaction was cooled to room temperature, the reaction mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate).

*2-((3,5-dimethylphenyl)amino)-4-phenylnicotinonitrile (**4a**)*



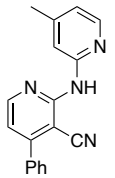
General procedure C was followed using 2-chloro-4-phenylnicotinonitrile (100 mg, 1.0 equiv), dimethyl aniline (73 μL, 1.2 equiv), palladium(II) acetate (5.2 mg, 5 mol%), BINAP (17.6 mg, 6 mol%), cesium carbonate (460 mg, 3.0 equiv), and 3 mL of dry toluene. Removal of solvent afforded product as white crystals (133 mg, 68%). M.p.: 143-144 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.37 (d, *J*=4.9 Hz, 1H), 7.61 (d, *J*=7.3 Hz, 2H), 7.56-7.48 (m, 3H), 7.24 (s, 2H), 7.12 (s, 1H), 6.83 (d, *J*=5.1 Hz, 1H), 6.80 (s, 1H), 2.35 (s, 6H).^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 157.40, 154.90, 151.82, 138.89, 138.49, 136.69, 130.08, 129.11, 128.34, 126.16, 119.20, 116.83, 114.64, 91.73, 21.60. LRMS (EI): calc'd: 299; found: 298.

*4-phenyl-2-(pyridin-2-ylamino)nicotinonitrile (**4b**)*



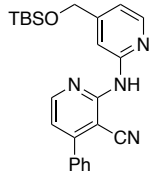
General procedure C was followed using 2-chloro-4-phenylnicotinonitrile (100 mg, 1.0 equiv), 2-aminopyridine (53 mg, 1.2 equiv), palladium(II) acetate (5.2 mg, 5 mol%), BINAP (17.6 mg, 6 mol%), cesium carbonate (460 mg, 3.0 equiv), and 3 mL of dry toluene. The compound was purified by column chromatography on silica gel using pure hexanes. Removal of solvent afforded product as white crystals (120 mg, 94%). M.p.: 150-151 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.50-8.38 (m, 2H), 8.32 (s, 1H), 8.02 (s, 1H), 7.73 (t, *J*=7.8 Hz, 1H), 7.65-7.57 (m, 2H), 7.52 (s, 3H), 7.05-6.99 (m, 1H), 6.95 (t, *J*=4.3 Hz, 1H).^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 155.86, 155.14, 152.30, 151.25, 148.24, 138.11, 136.41, 130.22, 129.16, 128.43, 118.77, 116.04, 115.93, 113.55, 93.24.

*2-((4-methylpyridin-2-yl)amino)-4-phenylnicotinonitrile (**4c**)*



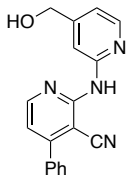
General procedure C was followed using 2-chloro-4-phenylnicotinonitrile (100 mg, 1.0 equiv), 4-methylpyridin-2-amine (61 mg, 1.2 equiv), palladium(II) acetate (5.2 mg, 5 mol%), BINAP (17.6 mg, 6 mol%), cesium carbonate (460 mg, 3.0 equiv), and 3 mL of dry toluene. The compound was purified by column chromatography on silica gel using 20% EtOAc in hexanes. Removal of solvent afforded product as white crystals (97 mg, 73%). M.p.: 123-124 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.47 (d, *J*=5.2 Hz, 1H), 8.25 (s, 1H), 8.19 (d, *J*=5.0 Hz, 1H), 7.99 (s, 1H), 7.67-7.59 (m, 2H), 7.58-7.49 (m, 3H), 6.95 (d, *J*=5.2 Hz, 1H), 6.89-6.82 (m, 1H), 2.43 (s, 3H).^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ. 13C NMR (126 MHz, cdcl3) δ 156.35, 155.92, 155.14, 152.34, 151.27, 149.54, 147.80, 136.44, 130.20, 129.15, 128.43, 120.08, 116.07, 115.80, 113.96, 21.73.

*2-((4-(((tert-butyldimethylsilyl)oxy)methyl)pyridin-2-yl)amino)-4-phenylnicotinonitrile (**4d-I**)*



General procedure C was followed using 2-chloro-4-phenylnicotinonitrile (200 mg, 1.0 equiv), 4-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridin-2-amine (267 mg, 1.2 equiv), palladium(II) acetate (10.4 mg, 5 mol%), BINAP (35.2 mg, 6 mol%), cesium carbonate (920 mg, 3.0 equiv), and 6 mL of dry toluene. The compound was purified by column chromatography on silica gel using 20% EtOAc in hexanes. Removal of solvent afforded product as white crystals (286 mg, 74%). M.p.: 102-103 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.49 (s, 1H), 8.42 (d, *J*=5.2 Hz, 1H), 8.24 (d, *J*=5.1 Hz, 1H), 8.05 (s, 1H), 7.65-7.58 (m, 2H), 7.57-7.49 (m, 3H), 6.96 (d, *J*=5.4 Hz, 1H), 6.94 (d, *J*=5.2 Hz, 1H), 4.81 (s, 2H), 1.00 (s, 9H), 0.15 (s, 6H)..^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 155.88, 155.08, 153.16, 152.49, 151.22, 147.86, 136.47, 130.18, 129.14, 128.43, 116.08, 115.87, 115.81, 110.12, 93.18, 63.92, 26.02, 18.51, -5.19.

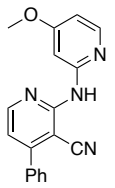
*2-((4-(hydroxymethyl)pyridin-2-yl)amino)-4-phenylnicotinonitrile (**4d**)*



In a 20 mL glass vial, 2-((4-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridin-2-yl)amino)-4-phenylnicotinonitrile **4d-I** (85 mg, 1.0 equiv) was dissolved in 5 mL of THF with a stir bar. To this solution, 3 mL of 1 M TBAF solution in THF was added dropwise under room temperature. The colorless solution became bright orange. After 4 h of stirring, the solvent was removed, and the crude product was purified by column chromatography (silica gel, gradient hexanes:EtOAc 1:1 to pure EtOAc), which afforded the desired compound as colorless crystals (75%, 46 mg). M.p.: 151-152 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.43 (d, *J*=5.2 Hz, 1H), 8.41 (s, 1H), 8.27 (d, *J*=5.1 Hz, 1H), 8.04 (s, 1H), 7.65-7.57 (m, 2H), 7.57-7.49 (m, 3H), 7.02 (d, *J*=5.7 Hz, 1H), 6.95 (d, *J*=5.2 Hz, 1H), 4.79 (s, 2H), 2.37 (s, 1H)..^{13}C{^{1}H}

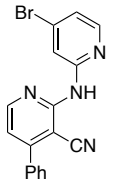
NMR ($CDCl_3$, 126 MHz, 21 °C): δ 155.81, 155.16, 152.56, 152.37, 151.26, 148.25, 136.35, 130.25, 129.16, 128.42, 116.45, 115.98, 110.66, 93.33, 64.11.

*2-((4-methoxypyridin-2-yl)amino)-4-phenylnicotinonitrile (**4e**)*



General procedure C was followed using 2-chloro-4-phenylnicotinonitrile (100 mg, 1.0 equiv), 4-methoxypyridin-2-amine (70 mg, 1.2 equiv), palladium(II) acetate (5.2 mg, 5 mol%), BINAP (17.6 mg, 6 mol%), cesium carbonate (460 mg, 3.0 equiv), and 3 mL of dry toluene. The compound was purified by column chromatography on silica gel using pure hexanes. Removal of solvent afforded product as white crystals (122 mg, 87%). M.p.: 144-145 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.45 (d, *J*=5.2 Hz, 1H), 8.14 (d, *J*=5.7 Hz, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.64-7.58 (m, 2H), 7.55-7.49 (m, 3H), 6.95 (d, *J*=5.2 Hz, 1H), 6.57 (dd, *J*=5.7, 2.1 Hz, 1H), 3.91 (s, 3H)..^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 167.45, 155.87, 155.14, 153.85, 151.20, 149.06, 136.43, 130.22, 129.16, 128.44, 115.99, 115.86, 105.72, 99.00, 55.49.

*2-((4-bromopyridin-2-yl)amino)-4-phenylnicotinonitrile (**4f**)*

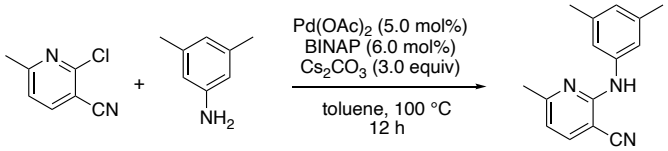


General procedure C was followed using 2-chloro-4-phenylnicotinonitrile (200 mg, 1.0 equiv), 4-bromopyridin-2-amine (267 mg, 1.2 equiv), tris(dibenzylideneacetone)dipalladium(0) (11 mg, 2.5 mol%), 1,1'-bis(bis(dimethylamino)phosphino)ferrocene (DMAPF, 12 mg, 6 mol%), sodium *tert*-butoxide (56 mg, 1.25 equiv), and 3 mL of dry toluene. The compound was purified by column chromatography on silica gel using 20% EtOAc in hexanes. Removal of solvent afforded product as white crystals (60 mg, 37%). M.p.: 166-167 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.76 (s, 1H), 8.50 (d, *J*=5.2 Hz, 1H), 8.13 (d, *J*=5.3 Hz, 1H), 8.07 (s, 1H), 7.66-7.58 (m, 2H), 7.58-7.50 (m, 3H), 7.17 (dd, *J*=5.3, 1.6 Hz, 1H), 7.01 (d, *J*=5.2 Hz,

1H)..$^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 155.37, 155.25, 153.05, 151.25, 148.67, 136.24, 134.25, 130.35, 129.22, 128.44, 121.96, 116.48, 116.39, 115.83, 93.61.

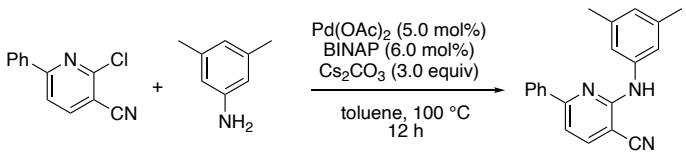
Synthesis of 2-((3,5-dimethylphenyl)amino)nicotinonitrile derivatives via Buchwald-Hartwig coupling

*2-((3,5-dimethylphenyl)amino)-6-methylnicotinonitrile (**5a**)*



In a glove box, palladium(II) acetate (11.2 mg, 0.05 mmol, 5 mol%) and BINAP (37.7 mg, 0.06 mmol, 6.0 mol%) were dissolved in 2 mL of dry toluene in a 35 mL pressure tube. The mixture was stirred for 2 min before 2-chloro-6-methylnicotinonitrile (152 mg, 1.0 mmol, 1.0 equiv), dimethyl aniline (73 μL, 1.2 mmol, 1.2 equiv), and cesium carbonate (984 mg, 3.0 mmol, 3.0 equiv) were added to the pressure tube. Then, another 3 mL of dry toluene were added. The reaction was then removed from the glovebox and heated in an oil bath at 110 °C for 14 h. After the reaction was cooled to room temperature, the reaction mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate). Removal of solvent afforded product as white crystals (132 mg, 56%). ^1H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 7.64 (d, J=7.8 Hz, 1H), 7.28 (s, 2H), 6.87 (s, 1H), 6.75 (s, 1H), 6.64 (d, J=7.8 Hz, 1H), 2.50 (s, 3H), 2.33 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz, 21 °C): δ 162.91, 155.68, 141.59, 138.75, 138.70, 125.44, 118.20, 117.10, 113.72, 89.91, 25.29, 21.62. LRMS (EI): calc'd: 237; found: 236.

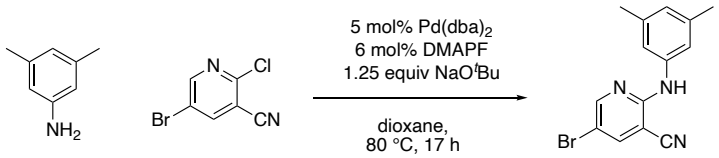
*2-((3,5-dimethylphenyl)amino)-6-phenylnicotinonitrile (**5b**)*



In a glove box, palladium(II) acetate (5.2 mg, 0.05 mmol, 5 mol%) and BINAP (17.6 mg, 6.0 mol%) were dissolved in 2 mL of dry toluene in a 35 mL pressure tube. The mixture was stirred for 2 min before 2-chloro-4-phenylnicotinonitrile (100 mg, 1.0 equiv), dimethylaniline (73 μL, 1.2 equiv), and cesium

carbonate (460 mg, 3.0 equiv) were added to the pressure tube. Then, another 3 mL of dry toluene were added. The reaction was then removed from the glovebox and heated in an oil bath at 110 °C for 14 h. After the reaction was cooled to room temperature, the reaction mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate). Removal of solvent afforded product as white crystals (133 mg, 95%). M.p.: 135-136 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.06 (dd, *J*=7.4, 2.0 Hz, 2H), 7.83 (d, *J*=8.1 Hz, 1H), 7.52-7.43 (m, 3H), 7.39 (s, 2H), 7.28 (d, *J*=8.1 Hz, 1H), 6.99 (s, 1H), 6.79 (s, 1H), 2.36 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 159.49, 155.53, 142.20, 138.56, 137.84, 130.36, 128.82, 127.37, 125.33, 118.32, 116.91, 110.24, 91.05, 21.50. One quaternary carbon was not found. LRMS (EI): calc'd: 299; found: 298.

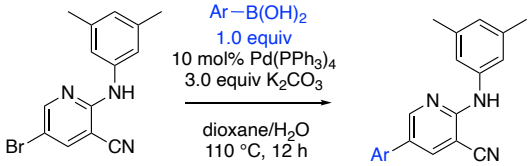
*Synthesis of 5-bromo-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**6-I**)*



The procedure was adapted from a literature procedure.[11] In a glove box, tris(dibenzylideneacetone)dipalladium(0) (23 mg, 0.05 mmol, 2.5 mol%) and DMAPF (25.3 mg, 0.06 mmol, 6 mol%) were dissolved in 2 mL of dry dioxane in a 35 mL pressure tube. The mixture was stirred for 2 min before 5-bromo-2-chloronicotinonitrile (217 mg, 1.0 mmol, 1.0 equiv), 3,5-dimethylaniline (125 μL, 1.0 mmol, 1.0 equiv), and sodium *tert*-butoxide (119 mg, 1.25 mmol, 1.25 equiv) were added to the pressure tube. Then, another 2 mL of dry dioxane was added. The reaction was then removed from the glovebox and heated in an oil bath at 70 °C for 15 h. After the reaction was cooled to room temperature, the reaction mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford pure product as an off-white solid (214 mg, 71%). M.p.: 145-147 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.39 (s, 1H), 7.84 (s, 1H), 7.15 (s, 2H), 6.90 (s, 1H), 6.81 (s, 1H), 2.33 (s, 7H). ^{13}C{^{1}H} NMR ($CDCl_3$,

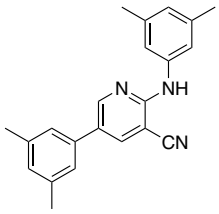
126 MHz, 21 °C): δ 154.89, 153.56, 143.17, 139.02, 137.80, 126.62, 119.20, 115.31, 107.29, 94.52, 21.57. LRMS (EI): calc'd: 301; found: 302.

General procedure D: synthesis of 3-cyano-pyridine derivatives via Suzuki coupling



The procedure was adapted from a literature procedure.[12] In a glove box, tetrakis(triphenylphosphine)palladium(0) (10 mol%), potassium carbonate (2.0 equiv), 5-bromo-2-((3,5-dimethylphenyl)amino)nicotinonitrile **6-I** (1.0 equiv), aryl boronic acid (1.0 equiv), and 3 mL of dioxane were added in a 50 mL Schlenk tube. The reaction was then removed from the glovebox and charged with water under a constant flow of dry dinitrogen. Then, the Schlenk tube was sealed and heated in an oil bath at 70 °C for 15 h. After the reaction was cooled to room temperature, the reaction mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford pure product.

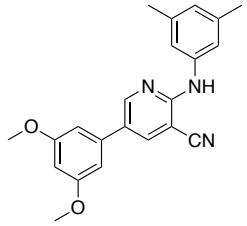
*5-(3,5-dimethylphenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**6a**)*



General procedure D was followed using 5-bromo-2-((3,5-dimethylphenyl)amino)nicotinonitrile **6-I** (50 mg, 1.0 equiv), (3,5-dimethylphenyl)boronic acid (25 mg, 1.0 equiv), tetrakis(triphenylphosphine)palladium(0) (19 mg, 10 mol%), potassium carbonate (69 mg, 3.0 equiv), 2 mL of dioxane, and 0.5 mL of water. Removal of solvent afforded product as a white powder (40 mg, 74 %). M.p.: 162-163 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.61 (d, *J*=2.4 Hz, 1H), 7.96 (d, *J*=2.5 Hz, 1H), 7.23 (s, 2H), 7.11 (s, 2H), 7.03 (s, 1H), 6.94 (s, 1H), 6.79 (s, 1H), 2.38 (s, 6H), 2.34 (s, 6H). ^{13}C{^{1}H} NMR

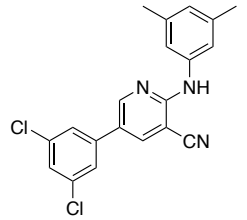
($CDCl_3$, 126 MHz, 21 °C): δ 155.10, 150.61, 140.02, 139.03, 138.96, 138.30, 136.08, 129.75, 127.79, 126.23, 124.27, 119.01, 116.54, 93.27, 21.60, 21.53. LRMS (EI): calc'd: 327; found: 326.

*5-(3,5-dimethoxyphenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**6b**)*



General procedure D was followed using 5-bromo-2-((3,5-dimethylphenyl)amino)nicotinonitrile **6-I** (80 mg, 1.0 equiv), (3,5-dimethoxyphenyl)boronic acid (25 mg, 1.0 equiv), tetrakis(triphenylphosphine)palladium(0) (30 mg, 10 mol%), potassium carbonate (110 mg, 3.0 equiv), 2 mL of dioxane, and 0.5 mL of water. Removal of solvent afforded product as a white powder (80 mg, 84 %). M.p.: 169-170 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.61 (d, *J*=2.3 Hz, 1H), 7.95 (d, *J*=2.4 Hz, 1H), 7.23 (s, 2H), 6.96 (s, 1H), 6.80 (s, 1H), 6.61 (s, 2H), 6.48 (s, 1H), 3.85 (s, 6H), 2.35 (s, 6H).^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 161.57, 155.46, 151.01, 139.86, 138.96, 138.29, 127.46, 126.23, 118.98, 116.57, 104.67, 99.76, 93.11, 55.62, 21.61. LRMS (EI): calc'd: 359; found: 358.

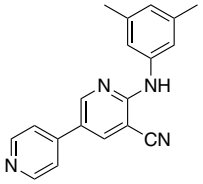
*5-(3,5-dichlorophenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**6c**)*



General procedure D was followed using 5-bromo-2-((3,5-dimethylphenyl)amino)nicotinonitrile **6-I** (80 mg, 1.0 equiv), (3,5-dichlorophenyl)boronic acid (51 mg, 1.0 equiv), tetrakis(triphenylphosphine)palladium(0) (30 mg, 10 mol%), potassium carbonate (110 mg, 3.0 equiv), 2 mL of dioxane, and 0.5 mL of water. Removal of solvent afforded product as a white powder (25 mg, 20 %). M.p.: 191-192 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.57 (d, *J*=2.4 Hz, 1H), 7.93 (d, *J*=2.5 Hz, 1H), 7.37 (s, 3H), 7.22 (s, 2H), 7.03 (s, 1H), 6.82 (s, 1H), 2.35 (s, 7H).^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C):

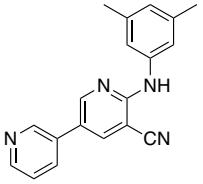
δ 211.98, 155.85, 150.92, 139.73, 139.22, 139.04, 137.92, 136.02, 127.95, 126.60, 124.80, 119.21, 116.13, 93.40, 21.60. LRMS (EI): calc'd: 367; found: 366.

*6-((3,5-dimethylphenyl)amino)-[3,4'-bipyridine]-5-carbonitrile (**6d**)*



General procedure D was followed using 5-bromo-2-((3,5-dimethylphenyl)amino)nicotinonitrile **6-I** (100 mg, 1.0 equiv), pyridin-4-ylboronic acid (41 mg, 1.0 equiv), tetrakis(triphenylphosphine)palladium(0) (38 mg, 10 mol%), potassium carbonate (137 mg, 3.0 equiv), 3 mL of dioxane, and 0.75 mL of water. Removal of solvent afforded product as a white powder (80 mg, 81 %). M.p.: 185-186 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.71-8.67 (m, 3H), 8.04 (d, *J*=2.5 Hz, 1H), 7.47-7.38 (m, 2H), 7.23 (s, 2H), 7.08 (s, 1H), 6.83 (s, 1H), 2.35 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 156.27, 151.04, 150.84, 143.50, 139.74, 139.06, 137.81, 126.76, 124.19, 120.46, 119.39, 116.12, 93.52, 21.59. LRMS (EI): calc'd: 300; found: 299.

*6-((3,5-dimethylphenyl)amino)-[3,3'-bipyridine]-5-carbonitrile (**6e**)*

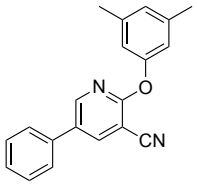


General procedure D was followed using 5-bromo-2-((3,5-dimethylphenyl)amino)nicotinonitrile **6-I** (71 mg, 1.0 equiv), pyridin-3-ylboronic acid (29 mg, 1.0 equiv), tetrakis(triphenylphosphine)palladium(0) (27 mg, 10 mol%), potassium carbonate (97 mg, 3.0 equiv), 2 mL of dioxane, and 0.5 mL of water. Removal of solvent afforded product as a yellow powder (mg, 79 %). M.p.: 93-95 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.81 (s, 1H), 8.65 (d, J=4.6 Hz, 1H), 8.64 (s, 1H), 8.00 (s, 1H), 7.87 (d, J=7.9 Hz, 1H), 7.46 (t, J=6.7, 5.9 Hz, 1H), 7.24 (s, 2H), 7.05 (s, 1H), 6.84 (app t, 1H), 2.36 (s, 7H).^{13}C{^{1}H} NMR ($CDCl_3$, 126

MHz, 21 °C): δ 155.75, 150.83, 148.31, 146.64, 139.67, 138.92, 137.78, 134.18, 132.34, 126.51, 124.17, 123.62, 119.16, 116.04, 93.42, 21.46. . LRMS (EI): calc'd: 300; found: 299.

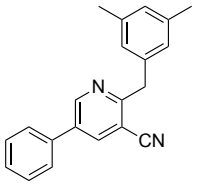
Replacements NH with O and CH_2 linkers

*2-(3,5-dimethylphenoxy)-5-phenylnicotinonitrile (**7a**)*



Under N_2, a 100 mL Schlenk flask was loaded with 2-bromo-5-phenylnicotinonitrile (500 mg, 1.94 mmol), 3,5-dimethylphenol (284 mg, 2.32 mmol, 1.2 equiv.), sodium hydride (93 mg, 3.88 mmol, 2.0 equiv.), 20 mL THF and a magnetic stir bar. The solution was heated to 60 °C and stirred for 3 hours. Then, the solvent was removed giving a light-yellow crude product. The crude product was purified by chromatography (EtOAc:hexane=1:10) and recrystallized from DCM/n-hexane. The product was formed as white crystals. (339 mg, 1.13 mmol, 58.2%). M.p.: 123-124 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.53 (s, 1H), 8.17 (s, 1H), 7.46-7.52 (m, 4H), 7.41-7.46 (m, 1H), 6.93 (s, 1H), 6.84 (s, 2H), 2.36 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ163.44, 152.94, 150.21, 142.05, 140.01, 135.78, 132.05, 129.75, 128.95, 128.10, 127.13, 119.51, 115.29, 97.97, 21.74. LRMS (EI): calc'd: 300; found: 300.

*2-(3,5-dimethylbenzyl)-5-phenylnicotinonitrile (**7b**)*



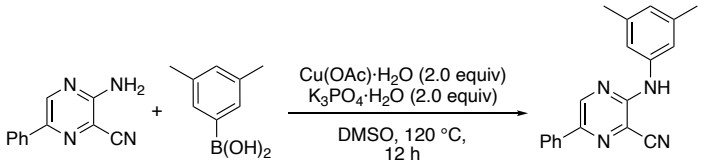
In a glovebox, a 20 ml scintillation vial was loaded with zinc dust (616 mg, 9.47 mmol, 5 equiv.), 3 mL of THF, and a micro magnetic stir bar. In another vial, 3,5-dimethylbenzyl bromide (490 mg, 2.46 mmol, 1.3 equiv.) was dissolved in 3 mL of THF. Then, 3,5-dimethylbenzyl bromide solution was added dropwise to the previous solution with a suspension of zinc dust. The mixture was stirred in room temperature for 10 minutes and filtered through celite, then added to a new vial loaded with 2-bromo-5-phenylnicotinonitrile

(0.500 g, 1.94 mmol, 1 equiv.), $Pd(PPh_3)_4$ (17.6 mg, 0.08 equiv.), 5 mL of THF and a micro magnetic stir bar. The mixture was let stir overnight before filtered through a short alumina column. The product was purified by recrystallization with DCM/pentane. White needle-like crystals were formed. (510 mg, 1.71 mmol, 88.3%). M.p.: 127-128 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.95 (s, 1H), 8.08 (s, 1H), 7.43-7.55 (m, 5H), 7.03 (s, 2H), 6.88 (s, 1H), 4.34 (s, 2H), 2.29 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ162.34, 151.30, 138.72, 138.45, 137.52, 135.63, 134.72, 129.55, 129.11, 128.82, 127.02, 117.24, 109.14, 42.75, 21.44. One quaternary carbon was not found. LRMS (EI): calc'd: 298; found: 298.

(Note: Zinc dust was activated by stirring in 1 mol/L HCl (aq.) for 10 minutes, then was washed with ether and dried in glovebox under vacuo.)

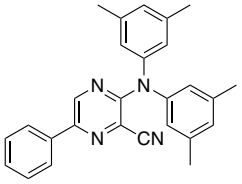
Synthesis of 3-amino-6-phenylpyrazine-2-carbonitrile derivatives via Chan-Lam coupling

*3-((3,5-dimethylphenyl)amino)-6-phenylpyrazine-2-carbonitrile (**8a**)*



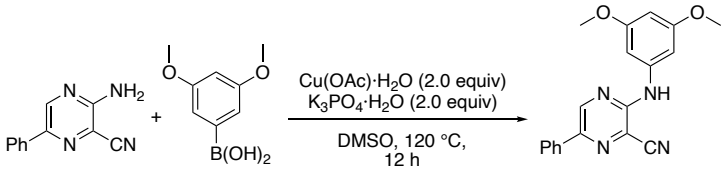
The procedure was adapted from a literature procedure.[13] In a 50 mL round bottom flask, 3-amino-6-phenylpyrazine-2-carbonitrile (392 mg, 2.0 mmol, 1.0 equiv), (3,5-dimethylphenyl)boronic acid (300 mg, 2.0 mmol, 1.0 equiv), copper(II) acetate monohydrate (800 mg, 4.0 mmol, 2.0 equiv), potassium phosphate monohydrate (920 mg, 4.0 mmol, 2.0 equiv), and 10 mL of DMSO were loaded with a stir bar. The solution had a dark green color. The reaction was heated in an oil bath at 120 °C for 12 h. After the reaction was cooled to room temperature, the reaction mixture was diluted by adding 50 mL of EtOAc, then washed with brine. The organic layer was dried with sodium sulfate and evaporated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford pure product as an off-white solid (53 mg, 9%). ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.78 (s, 1H), 7.92 (d, J=7.1 Hz, 2H), 7.49 (t, J=7.4 Hz, 2H), 7.44 (t, J=7.3 Hz, 1H), 7.21 (s, 2H), 7.03 (s, 1H), 6.84 (s, 1H), 2.36 (s, 6H).^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 152.40, 143.95, 143.03, 139.16, 137.42, 135.17, 129.48, 129.24, 126.80, 125.95, 119.06, 115.31, 114.41, 21.59. LRMS (EI): calc'd: 300; found: 299.

*3-(bis(3,5-dimethylphenyl)amino)-6-phenylpyrazine-2-carbonitrile (**8a-s**)*



The procedure to synthesize 3-((3,5-dimethylphenyl)amino)-6-phenylpyrazine-2-carbonitrile also generated an N,N-diaryl byproduct, which was isolated as well. Column chromatography also afforded side product as a white solid (16 mg, 4%). ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.75 (s, 1H), 7.94 (d, J=7.0 Hz, 2H), 7.49 (t, J=7.2 Hz, 2H), 7.46-7.42 (m, 1H), 6.90 (s, 2H), 6.80 (s, 4H), 2.30 (s, 13H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 152.39, 143.92, 143.01, 139.14, 137.43, 135.16, 129.47, 129.23, 126.78, 125.94, 119.04, 115.30, 114.40, 21.58. LRMS (EI): calc'd: 403; found: 403.

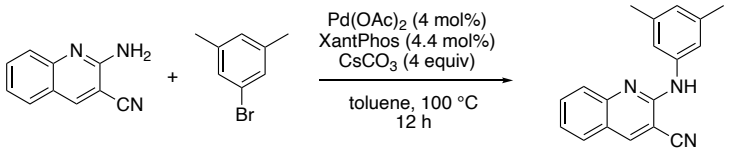
*3-((3,5-dimethoxyphenyl)amino)-6-phenylpyrazine-2-carbonitrile (**8b**)*



In a 50 mL round bottom flask, 3-amino-6-phenylpyrazine-2-carbonitrile (392 mg, 2.0 mmol, 1.0 equiv), (3,5-dimethoxyphenyl)boronic acid (364 mg, 2.0 mmol, 1.0 equiv), copper(II) acetate monohydrate (800 mg, 4.0 mmol, 2.0 equiv), potassium phosphate monohydrate (920 mg, 4.0 mmol, 2.0 equiv), and 10 mL of DMSO were added together with a stir bar. The reaction was heated in an oil bath at 120 °C for 12 h. After the reaction was cooled to room temperature, the reaction mixture was diluted by adding 50 mL of EtOAc, then washed with brine. The organic layer was dried with sodium sulfate and evaporated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford pure product as an off-white solid (73 mg, 11%). ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.79 (s, 1H), 7.92 (d, J=7.5 Hz, 2H), 7.50 (t, J=7.5 Hz, 2H), 7.44 (t, *J*=7.2 Hz, 1H), 7.09 (s, 1H), 6.84 (d, *J*=2.1 Hz, 2H), 6.29 (s, 1H), 3.83 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 161.36, 152.08, 144.24, 142.86, 139.40, 135.02, 129.61, 129.26, 126.01, 115.19, 114.69, 99.30, 96.61, 55.62. LRMS (EI): calc'd: 332; found: 332.

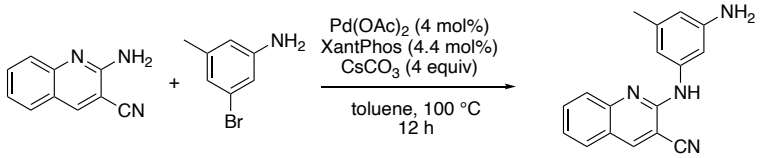
Synthesis of quinoline and 1,8-Naphthyridine derivatives

*2-((3,5-dimethylphenyl)amino)quinoline-3-carbonitrile (**9a**)*



In a glove box, palladium(II) acetate (9.0 mg, 0.04 mmol, 4 mol%) and xantphos (25.4 mg, 0.044 mmol, 4.4 mol%) were dissolved in 2 mL of dry toluene in a 35 mL pressure tube. The mixture was stirred for 2 min before 2-aminoquinoline-3-carbonitrile (169 mg, 1.0 mmol, 1.0 equiv), 1-bromo-3,5-dimethylbenzene (185 mg, 1.0 mmol, 1.0 equiv), and cesium carbonate (1312 mg, 4.0 mmol, 4.0 equiv) were added to the pressure tube. Then, another 3 mL of dry toluene were added. The reaction was then removed from the glovebox and heated in an oil bath at 100 °C for 12 h. After the reaction was cooled to room temperature, the reaction mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford pure product as an off-white powder (253 mg, 93 %). M.p.: 141-142 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 8.34 (s, 1H), 7.82 (d, *J*=8.5 Hz, 1H), 7.70 (t, *J*=7.6 Hz, 1H), 7.66 (d, *J*=8.0 Hz, 1H), 7.47 (s, 2H), 7.36 (t, *J*=7.5 Hz, 1H), 7.05 (s, 1H), 6.79 (s, 1H), 2.37 (s, 7H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 151.25, 144.31, 138.83, 133.26, 128.14, 127.67, 125.70, 124.59, 121.90, 118.18, 96.74, 21.69. LRMS (EI): calc'd: 273; found: 272.

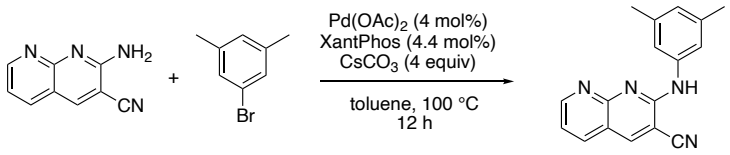
*2-((3-amino-5-methylphenyl)amino)quinoline-3-carbonitrile (**9b**)*



In a glove box, palladium(II) acetate (9.0 mg, 0.04 mmol, 4 mol%) and xantphos (25.4 mg, 0.044 mmol, 4.4 mol%) were dissolved in 2 mL of dry toluene in a 35 mL pressure tube. The mixture was stirred for 2 min before 2-aminoquinoline-3-carbonitrile (169 mg, 1.0 mmol, 1.0 equiv), 3-bromo-5-methylaniline (186 mg, 1.0 mmol, 1.0 equiv), and cesium carbonate (1312 mg, 4.0 mmol, 4.0 equiv) were added to the pressure

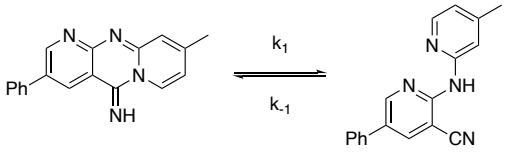
tube. Then, another 3 mL of dry toluene were added. The reaction was then removed from the glovebox and heated in an oil bath at 100 °C for 12 h. After the reaction was cooled to room temperature, the reaction mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford pure product as an off-white powder (170 mg, 62 %). M.p.: 159-160 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C) δ 8.33 (s, 1H), 7.83 (d, *J*=8.6 Hz, 1H), 7.70 (t, *J*=7.8 Hz, 1H), 7.66 (d, *J*=7.8 Hz, 1H), 7.36 (t, *J*=7.5 Hz, 1H), 7.30 (s, 1H), 7.02 (s, 1H), 6.89 (s, 1H), 6.31 (s, 1H), 3.77 (s, 1H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 147.19, 144.28, 139.99, 133.21, 128.15, 127.67, 124.59, 121.86, 116.40, 111.62, 111.35, 104.21, 21.76. LRMS (EI): calc'd: 274; found: 273.

*2-((3,5-dimethylphenyl)amino)-1,8-naphthyridine-3-carbonitrile (**9c**)*



In a glove box, palladium(II) acetate (11.0 mg, 4 mol%) and xantphos (30 mg, 4.4 mol%) were dissolved in 2 mL of dry toluene in a 35 mL pressure tube. The mixture was stirred for 2 min before 2-amino-1,8-naphthyridine-3-carbonitrile (200 mg, 1.0 equiv), 1-bromo-3,5-dimethylbenzene (218 mg, 1.0 equiv), and cesium carbonate (1543 mg, 4.0 equiv) were added to the pressure tube. Then, another 3 mL of dry toluene were added. The reaction was then removed from the glovebox and heated in an oil bath at 100 °C for 12 h. After the reaction was cooled to room temperature, the reaction mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to afford pure product as an off-white powder (96 mg, 30 %). M.p.: 182-183 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 21 °C): δ 9.02 (dd, *J*=4.4, 2.0 Hz, 1H), 8.35 (s, 1H), 8.03 (d, *J*=9.9 Hz, 1H), 7.49 (s, 2H), 7.32 (dd, *J*=8.0, 4.4 Hz, 1H), 7.23 (s, 1H), 6.82 (s, 1H), 2.37 (s, 6H). δ ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz, 21 °C): δ 156.68, 156.35, 153.84, 145.01, 139.03, 137.94, 137.43, 126.63, 120.16, 118.84, 116.46, 115.63, 98.22, 21.69. LRMS (EI): calc'd: 274; found: 273.

Kinetic Studies



A **B**

To a 20 mL glass vial, **3i** (2.2 mg) and ferrocene (1.0 mg) were added. The deuterated solvent (1.0 mL) was added using a volumetric syringe. The sample was made homogeneous by a glass pipette mixing, i.e., the solution was drawn up into the pipette and pushed back into the volumetric flask, until all solids were completely dissolved. The sample was filtered and transferred into an NMR tube. An array ^{1}H NMR experiment was set over a gradient range of time with 16 scans and 10 s of relaxation time. The relative concentrations of isomers vs internals standard ferrocene were monitored as a function of time. The fits of the exponential decay of **A** and growth of **B** were done using Kaleidagraph. The expression used to fit the data is shown in Eq S1, where Y = concentration of isomer A or B at time t (Y_t), infinity (Y_∞), or at the start of the reaction (Y_0). The rate constants were calculated by averaging the values of the decay of isomer **A** and the growth of isomer **B**. The forward and backward rate constants, k_1 and k_{-1}, were calculated from Eq S3 and Eq S4.[14]

$$Y_t = Y_\infty + (Y_0 - Y_\infty)e^{-(k_1+k_{-1})t} \qquad \textbf{Eq S1}$$

$$k_e = k_1 + k_{-1} \qquad \textbf{Eq S2}$$

$$k_1 = \frac{k_e}{1+K^{-1}} \qquad \textbf{Eq S3}$$

$$k_{-1} = \frac{k_e}{1+K} \qquad \textbf{Eq S4}$$

Solvent	k_1	k_{-1}	K_{eq}
toluene-d_8	4.82×10^{-5}	3.25×10^{-5}	1.48
$CDCl_3$	3.94×10^{-4}	5.06×10^{-4}	0.77
DMSO-d_6	1.49×10^{-5}	3.03×10^{-5}	0.49

k_1 and k_{-1} are from the fit of Eq S1, which provided $k_1 + k_{-1}$ (= k_e), then Eq S3 and S4 were used to separate the forward (k_1) and backward (k_{-1}) rate constants. The equilibrium constant (K) is measured from ^{1}H NMR spectroscopy on the equilibrium mixture at long times (after several days) in the solvent at room temperature.

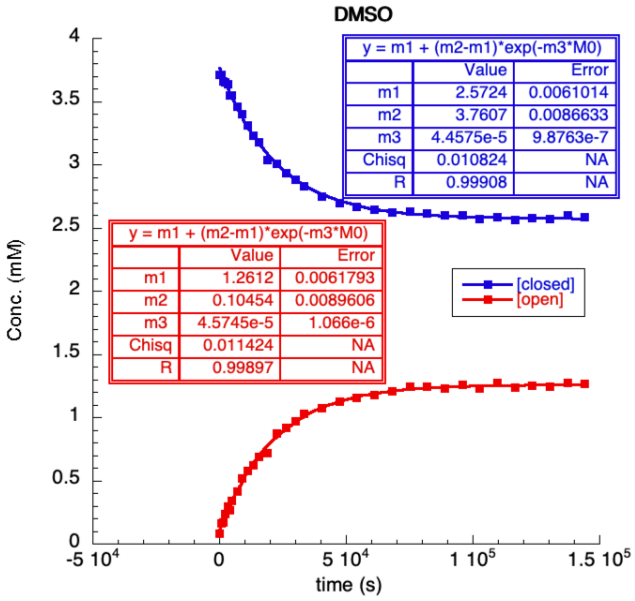


Fig. S1. Concentration of **A** (blue dots) and **B** (red dots) as a function of time in DMSO-d6. Internal standard (ferrocene) was omitted for clarification.

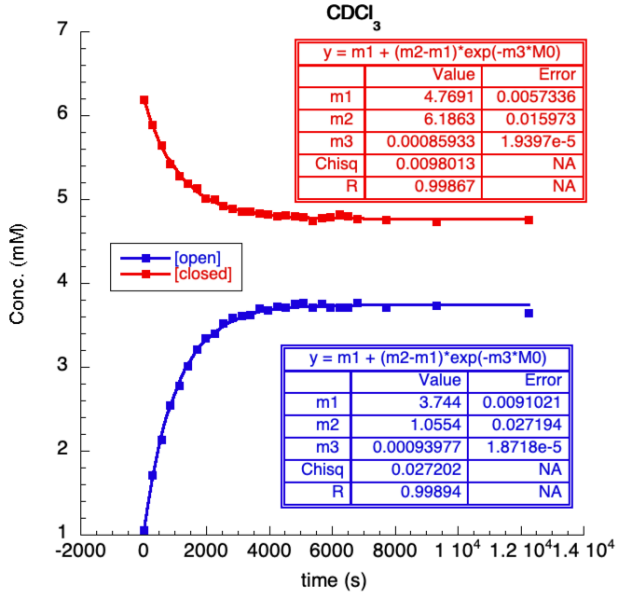


Fig. S2. Concentration of **A** (blue dots) and **B** (red dots) as a function of time in $CDCl_3$. Internal standard (ferrocene) was omitted for clarification.

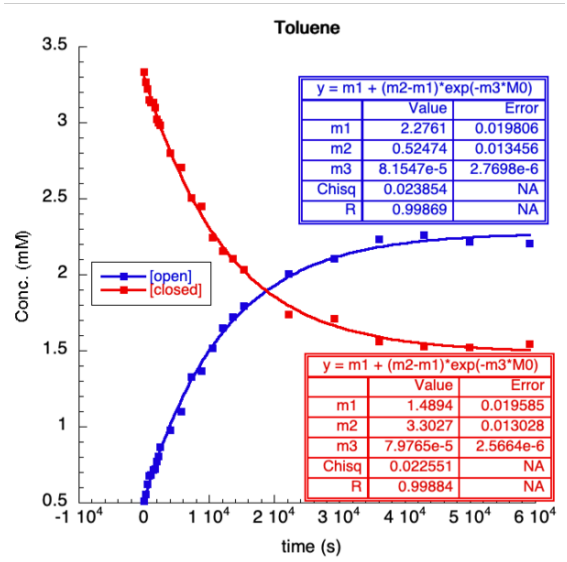
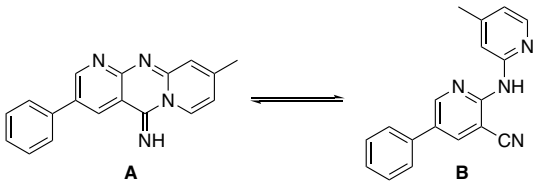


Fig. S3. Concentration of **A** (blue dots) and **B** (red dots) as a function of time in toluene-d_8. Internal standard (ferrocene) was omitted for clarification.

DFT Calculations for Equilibrium Constants for 3i in Various Media



Solvent	ΔG (kcal/mol)	
	cc-pvTZ	*6-311G++(p,d)*
gas phase	–4.68	–6.04
toluene	–2.16	–2.72
$CHCl_3$	–0.43	–1.91
DMSO	–0.09	–0.64
H_2O	1.10	0.49

The compound structures were optimized using DFT with B3PW91 functional and 6-311G+(d,p) basis set on all atoms with Gaussian16. Energy calculations were conducted using optimized geometry with 6-311G+(d,p) and cc-pvTZ basis set on all atoms. ΔG = Gibbs free energy of **B** minus the Gibbs free energy of **A**.

Table of Equilibrium Constants from DFT (B3PW91/cc-pvTZ) and Experiment

Solvent	K_{eq}	
	Experimental (25 °C)	*DFT*
toluene	1.48	38.4
$CHCl_3$	0.78	4.3
DMSO	0.49	1.16

The equilibrium constants were calculated using the van 't Hoff equation, $\Delta G° = -RT \ln K_{eq}$, where $R = 1.987 \times 10^{-3}$ kcal/mol and $T = 298$ K. The "Experimental" values are from ^{1}H NMR spectroscopy in the solvent after several days.

DFT Coordinates of Optimized Structures

*Cyclized Form (**A**)*

0 1

C	4.87301600	1.17789800	0.16209900
C	3.58762500	1.59985400	0.19095200
C	2.76050900	-0.65415900	-0.06772400
C	4.12334000	-1.08054900	-0.09915600
C	5.17291800	-0.21210100	0.01018700
C	1.19310200	1.24974800	0.11436100
C	0.50744800	-1.13047100	-0.14187100
C	0.14699100	0.23336700	-0.00102700
C	-1.21182400	0.56556100	0.04000300
H	-1.51550300	1.59759900	0.17236200
C	-2.18316900	-0.42302000	-0.06273500
C	-1.71348700	-1.74717800	-0.21523500
H	5.66788800	1.90731200	0.25495500
H	3.29931100	2.63293300	0.30151000
H	4.28172100	-2.14525200	-0.21550100
H	-2.42934700	-2.55696000	-0.32652700
N	-0.43868600	-2.09605700	-0.25366000
N	1.79877100	-1.55131200	-0.17539800
N	2.52673100	0.71725300	0.07808500
N	1.06645300	2.51766100	0.23908400
H	0.08795700	2.79302600	0.25180400
C	-3.63329700	-0.12030800	-0.02067100
C	-4.14090400	1.05426700	-0.60018300

C	-4.53503100	-0.99904200	0.60218000
C	-5.50317300	1.34141500	-0.55517000
H	-3.46916000	1.73956900	-1.10486700
C	-5.89776100	-0.71145000	0.64373800
H	-4.16868700	-1.90280500	1.07597900
C	-6.38830500	0.45974800	0.06620100
H	-5.87435000	2.25148500	-1.01394800
H	-6.57553200	-1.40054700	1.13589900
H	-7.44894100	0.68310000	0.09970400
C	6.60019000	-0.66897900	-0.02462700
H	6.67301000	-1.75003200	-0.15014100
H	7.13601500	-0.18279700	-0.84644200
H	7.11361300	-0.38704000	0.90051800

*Opem Form (**B**)*

0 1

C	5.55137400	-0.87588800	0.06763300
C	5.39256000	0.49878500	-0.02816900
C	3.10319700	0.33900900	-0.02041000
C	3.15958900	-1.05970800	0.07552300
C	4.40639600	-1.68206100	0.12123900
C	-0.03848800	3.14698600	-0.15747200
C	0.60175300	0.75015700	-0.04570000
C	-0.39493300	1.77254700	-0.09029200
C	-1.73966500	1.40654500	-0.07683900
H	-2.49237200	2.18398700	-0.12743200

C	-2.10397100	0.05923200	-0.01710100
C	-1.04723800	-0.85821400	0.03470700
H	6.25993300	1.15118600	-0.07176900
H	2.24930500	-1.63642800	0.11283600
H	-1.25830300	-1.92091900	0.10769100
N	0.24703000	-0.53529300	0.01997900
N	1.92749700	1.09938900	-0.07024600
N	4.20174200	1.10685700	-0.07192200
N	0.26784300	4.26183800	-0.21113100
H	2.13264300	2.09014300	-0.13146600
C	-3.52059200	-0.37763700	0.00269900
C	-3.92312100	-1.54699600	-0.66246200
C	-4.49233600	0.36814100	0.68926800
C	-5.25419400	-1.95825400	-0.63750900
H	-3.19732300	-2.12890200	-1.21946800
C	-5.82331300	-0.04263500	0.70953500
H	-4.20356800	1.26552800	1.22526700
C	-6.21025000	-1.20831100	0.04768300
H	-5.54522400	-2.86137800	-1.16296700
H	-6.55717200	0.54507600	1.25035700
H	-7.24619300	-1.52829800	0.06495400
H	6.54422000	-1.30969500	0.09978700
C	4.52029900	-3.17852700	0.22558700
H	3.53853400	-3.65389100	0.25903800
H	5.07189500	-3.58383500	-0.62845800
H	5.07244200	-3.46114100	1.12735200

Biological Assays

NRF2 Pathway Inhibition Assay

MCF-7 NRF2/ARE re-porter cells (10,000/well) were plated in a 96 well plate and treated with compounds for 24 h. tert-butylhydroquinone (tBHQ) was added 1 h after compounds to activate the NRF2 pathway. Cell viability was detected by Celltiter-fluor (Promega), and luciferase activity was detected by Steady-glo (Promega) using Synergy Neo HTS multi-mode microplate reader (BioTek). Experiments were per-formed in triplicate and results shown are mean ± standard error.

Cell Culture

MCF-7 NRF2/ARE, A549 and H460 cells were purchased from ATCC and cultured in complete F12K or RPMI media (Corning), respectively, containing 10% fetal bovine serum (FBS) (VWR) and 1% penicillin/streptomycin (Corning).

Western Blotting

A549 or H460 cells (6×10^5) were plated and allowed to attach for 24 h. Cells were then serum deprived in 1% FBS and treated with the indicated concentration of compounds for 24 h. Total cellular lysates were generated using RIPA buffer (5M NaCl, 1M Tris-Cl, 0.5M EDTA, 25mM deoxycholic acid, 1% Triton X-100 (v/v), 0.1% sodium dodecyl sulfate (w/v), pH 7.4) containing protease inhibitors (1 mM phenylmethylsulfonylfluoride, 2 mg/mL aprotinin, and 5 mg/mL leupeptin). A bicinchoninic acid assay (Sigma) was used to determine protein concentrations and 25 µg of total protein was separated by gel electrophoresis on 10% SDS-PAGE gels. Proteins were then transferred to nitrocellulose membranes and blocked with 5% powdered milk (w/v) in Tris-buffered saline containing 0.1% Tween-20 (v/v) for 1 h. Membranes were incubated with primary antibodies overnight at 4 C° {NRF2 (Novus Biologicals, 1:1000) and GAPDH (Santa Cruz Bio-technology, 1:4000)} and secondary antibodies {anti-mouse (GAPDH) or anti-rabbit (NRF2)} at room temperature for 1 h. Signal was detected with enhanced chemiluminescent substrate (GE Healthcare Life Sciences).

RT-PCR

A549 cells (6×10^5) were plated and allowed to adhere for 24 h. Cells were serum deprived in 1% FBS and treated with the indicated concentration of compounds for 24 h. RNA was isolated using TRIzol (Invitrogen) and 1 μg of RNA was converted to cDNA using a High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems) according to the manufacturer's protocol. Primers for each target were purchased from IDT. Fast SYBR Green Master Mix (Applied Biosystems) was used to run samples on the QuantStudio7 Flex RT-PCR system (Applied Biosystems) and relative gene expression calculated by normalizing CT values to GAPDH and vehicle (DMSO) control using ΔΔCT.

Viability Assay

For the initial proliferation assay, A549 cells were treated with 5 μM compounds for 72 h and cell proliferation evaluated with the MTT assay as described.[4] Next, A549 or H460 cells (2×10^3) were treated with increasing concentrations of compounds for 72 h. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, VWR) was added to cells for 4 h and cells were lysed in isopropanol mixed with 1N HCl (1:25). Colorimetric absorption at 570 nM was measured and percent viability calculated as compared to the vehicle control.[15]

Cell Cycle Analysis

Adherent A549 or H460 cells (4×10^5) were synchronized in 1% FBS media for 12 h, then treated for 24 h with compounds. Cells were stained in a cocktail of 10 μg/mL propidium iodide containing 0.1% (v/v) Triton-X100, and 100 μg/mL DNase-free RNase for 16 h. Sample data were acquired using a BD Accuri C6 Flow Cytometer and analyzed using FloJo, specifically univariate cell cycle analysis using a Watson Pragmatic model with G0/G1 and G2/M peak constraints.

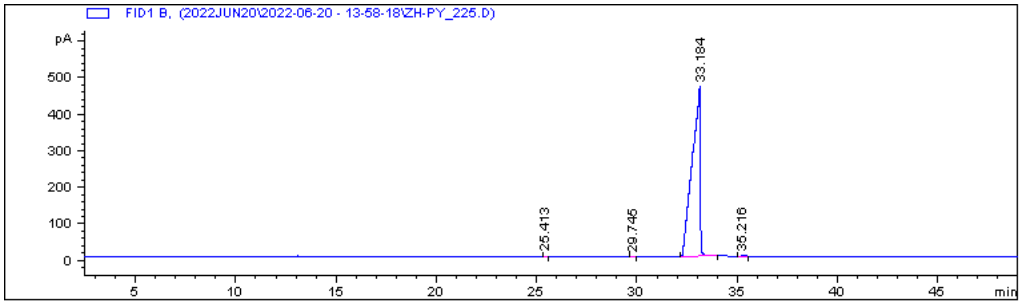
Transwell Migration Assays

A549 cells were dissociated and resuspended in serum free medium and 5×10^4 cells added to the upper chamber of each transwell (8 μm pore size, VWR). In the bottom chamber, medium containing 5% FBS was used as a chemoattractant. Vehicle control or compounds were added to both the upper and lower

cham-bers. After allowing cells to migrate for 24 h, transwell inserts were fixed with 3.7% formaldehyde, stained with DAPI (300 nM) and imaged with a BZ-X-800E all-in-one fluorescence microscope system (Keyence, Osaka, Japan). Images were analyzed with Fiji (NIH, Bethesda, MD) by stacking all images, converting to 8-bit and binary (using threshold setting “moments”), removing outliers (2.0 px, radius 50) and analyzing particles. The number of particles was taken as the number of migrated cells and was spot checked against unprocessed images to ensure accurate analysis.

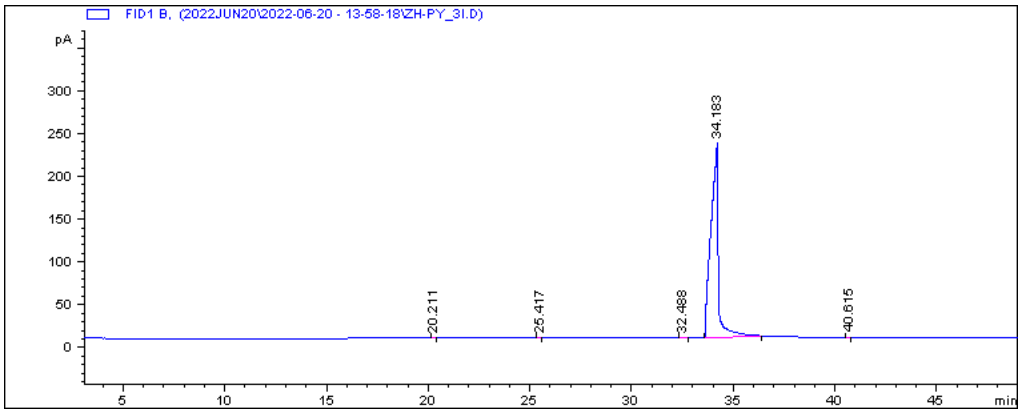
Representative GCFID traces of *in vitro* tested compounds

*2-((3,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1a**)*



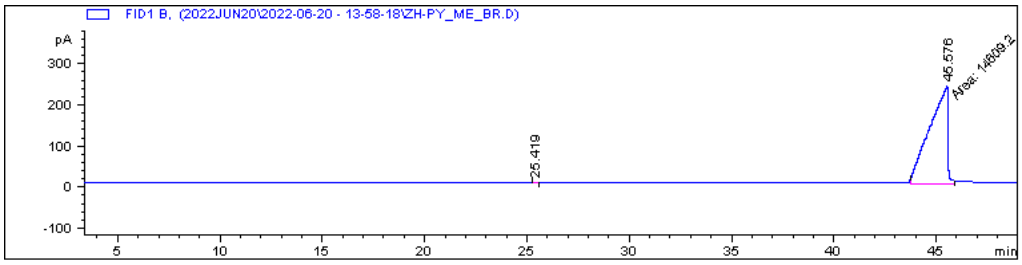
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	25.413	BB	0.0748	2.36111	4.52826e-1	0.01793
2	29.745	BB	0.1102	2.17632	2.34668e-1	0.01653
3	33.184	BB	0.3402	1.31608e4	462.23489	99.93699
4	35.216	BB	0.1934	3.75996	2.34031e-1	0.02855
Totals :				1.31691e4	463.15642	

*2-((4-methylpyridin-2-yl)amino)-5-phenylnicotinonitrile (**3i**)*



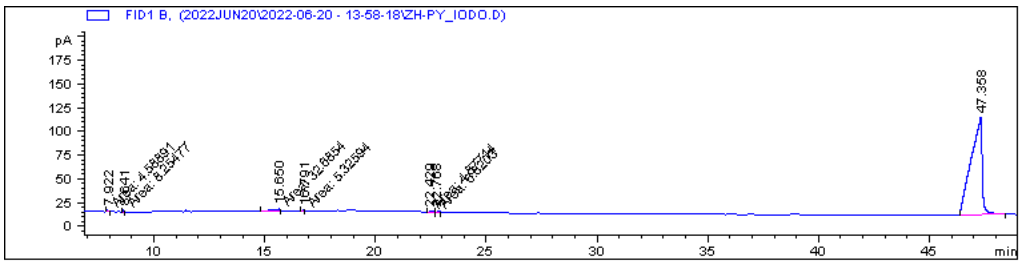
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	20.211	BB	0.0802	2.73983	4.55653e-1	0.04625
2	25.417	BB	0.0680	2.60465	5.15394e-1	0.04397
3	32.488	BB	0.1248	3.82046	3.75138e-1	0.06449
4	34.183	BB	0.3171	5910.37402	226.75180	99.76851
5	40.615	BV	0.0861	4.54871	7.46711e-1	0.07678
Totals :				5924.08767	228.84470	

*2-((3-bromo-5-methylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1m**)*



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	25.419	BB	0.0751	2.21302	4.15912e-1	0.01515
2	45.576	MM	1.0241	1.46092e4	237.75175	99.98485
Totals :				1.46114e4	238.16767	

*2-((3-iodophenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1t**).*

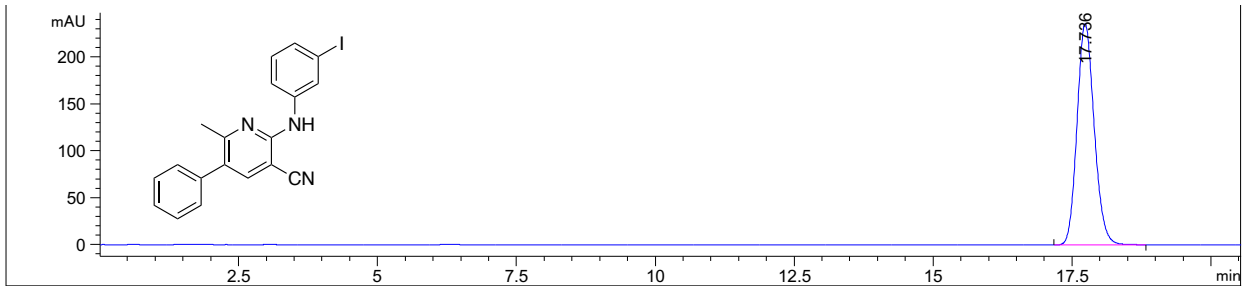


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	7.922	MM	0.0575	4.58891	1.32961	0.12639
2	8.641	MM	0.0498	8.25477	2.76174	0.22736
3	15.650	MM	0.2468	32.68540	2.20699	0.90024
4	16.791	MM	0.0739	5.32594	1.20055	0.14669
5	22.429	MM	0.1490	4.87714	5.45456e-1	0.13433
6	22.768	MM	0.1308	6.82030	8.68900e-1	0.18785
7	47.358	BB	0.4246	3568.18311	101.88271	98.27714
Totals :				3630.73557	110.79596	

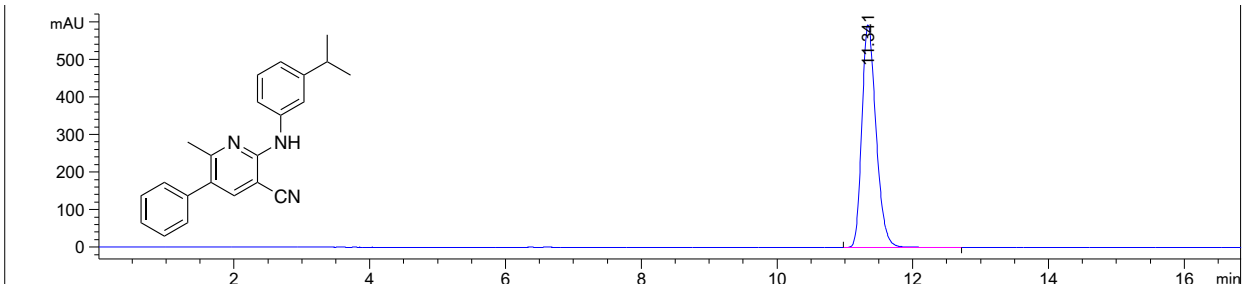
Representative HPLC traces of *in vitro* tested compounds

HPLC data was collected using AD-H column on Agilent 1260 HPLC. A mixture of hexanes and isopropanol (90:10) were used with 360 nm wavelength.

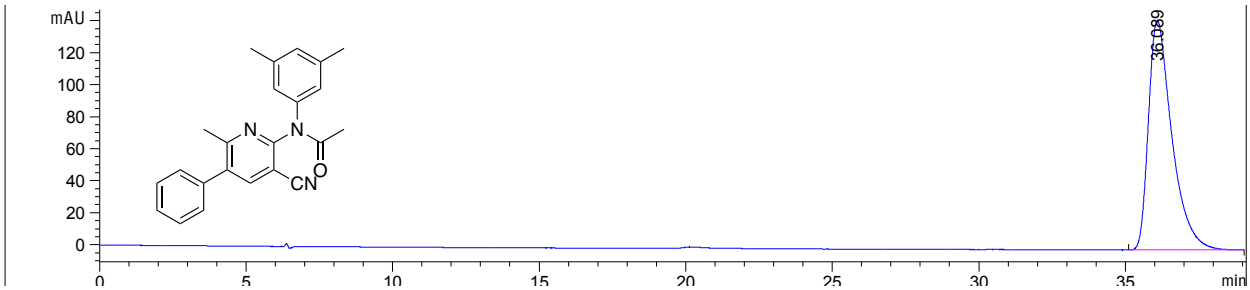
*2-((3-iodophenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1t**).*



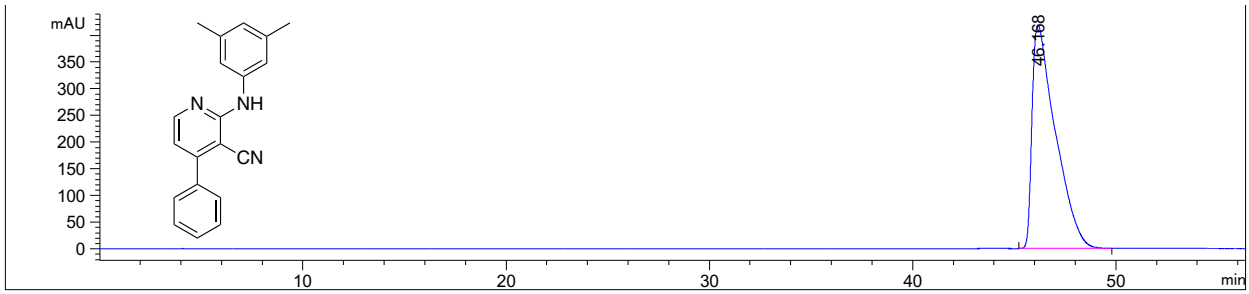
*2-((3-isopropylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1q**).*



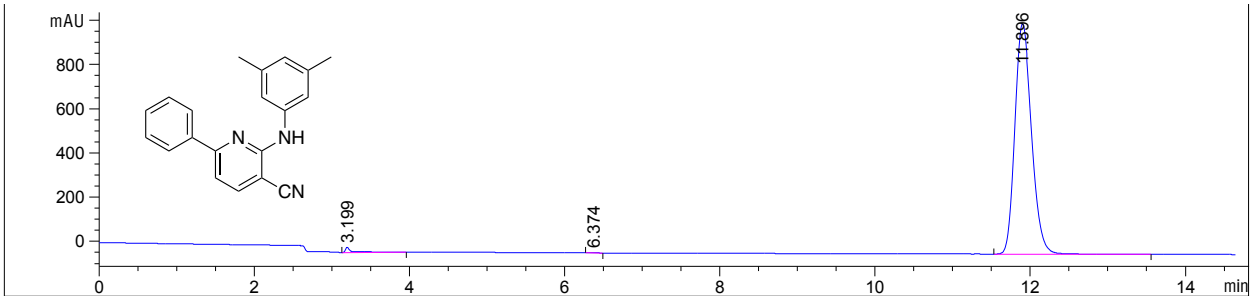
*N-(3-cyano-6-methyl-5-phenylpyridin-2-yl)-N-(3,5-dimethylphenyl)acetamide (**2b**).*



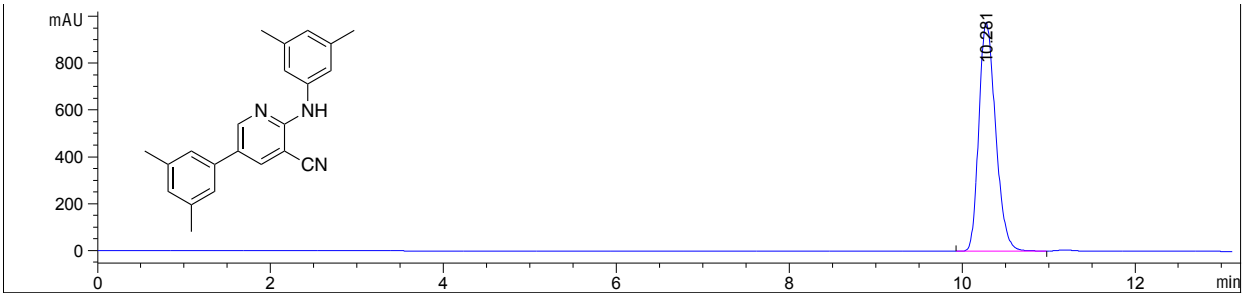
*2-((3,5-dimethylphenyl)amino)-4-phenylnicotinonitrile (**4a**).*



*2-((3,5-dimethylphenyl)amino)-6-phenylnicotinonitrile (**5b**).*

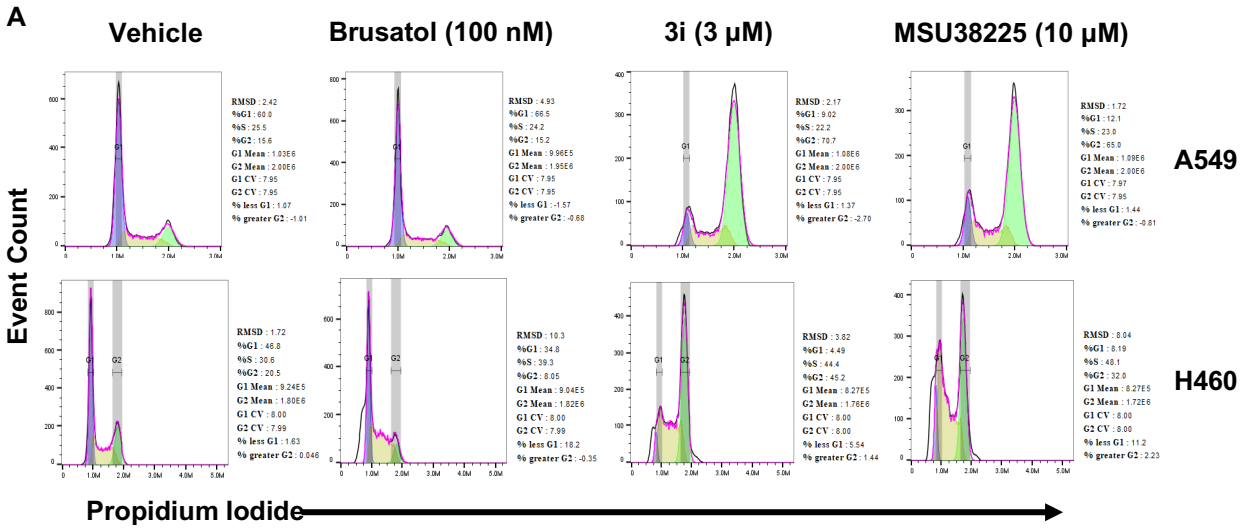


*5-(3,5-dimethylphenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**6a**).*



Compound 3i induces G2/M arrest in lung cancer cells

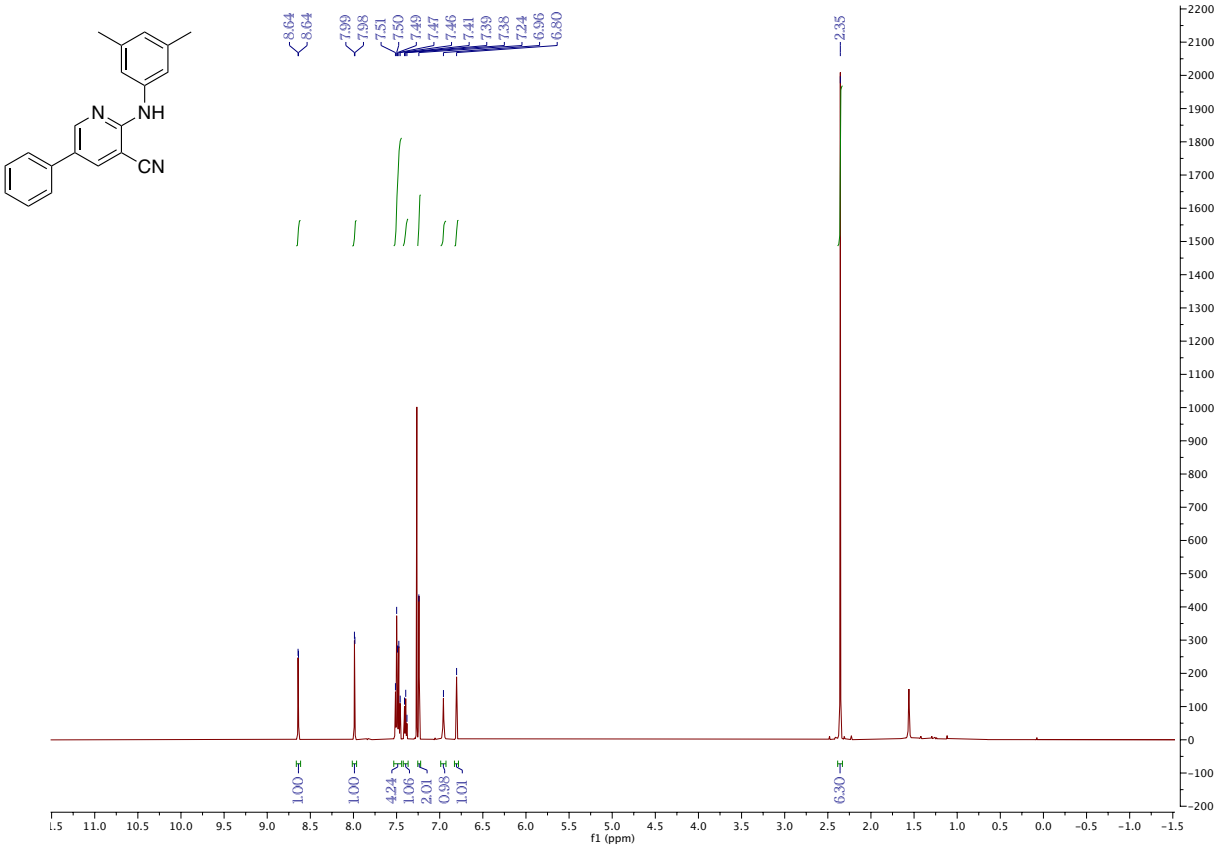
Raw cell cycle data from Fig. 2D.



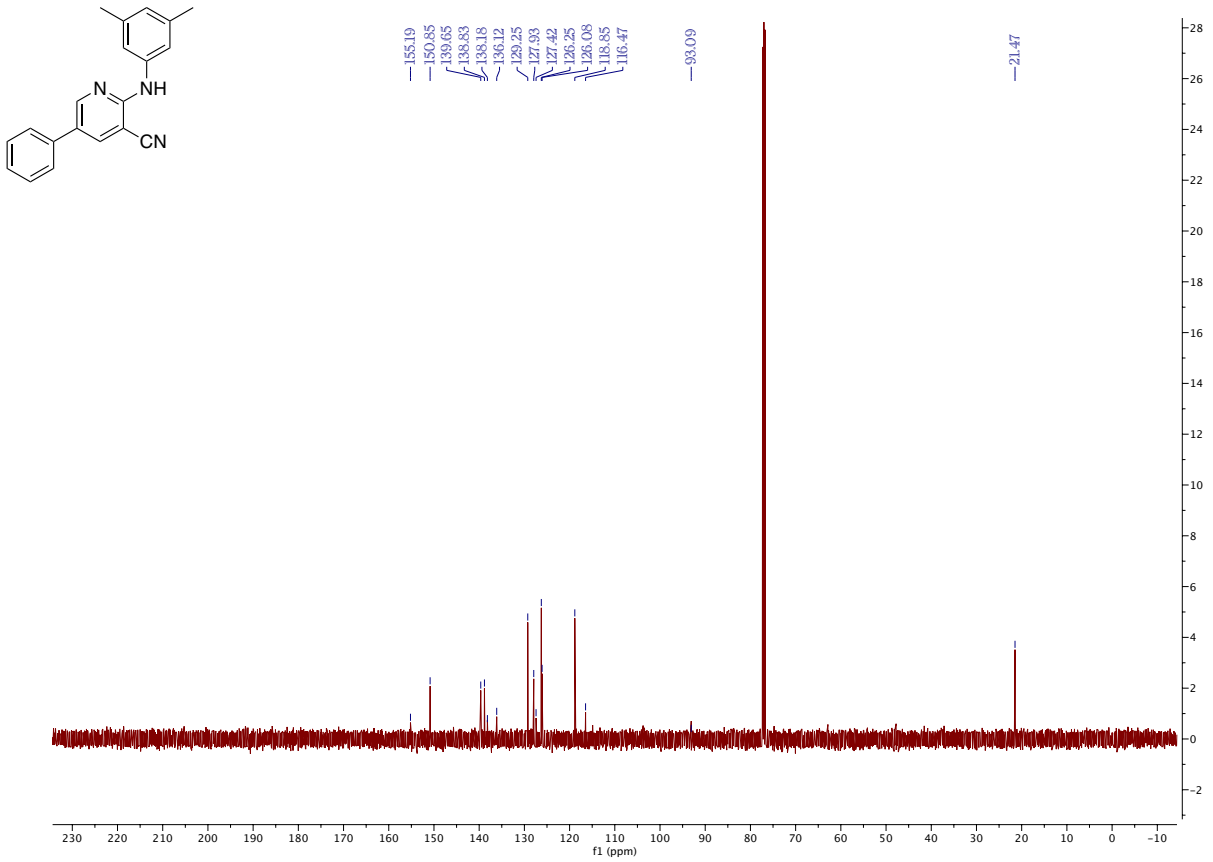
Spectral Data

*2-((3,5-dimethylphenyl)amino)-5-phenylnicotinonitrile (**1b**).*

^{1}H NMR

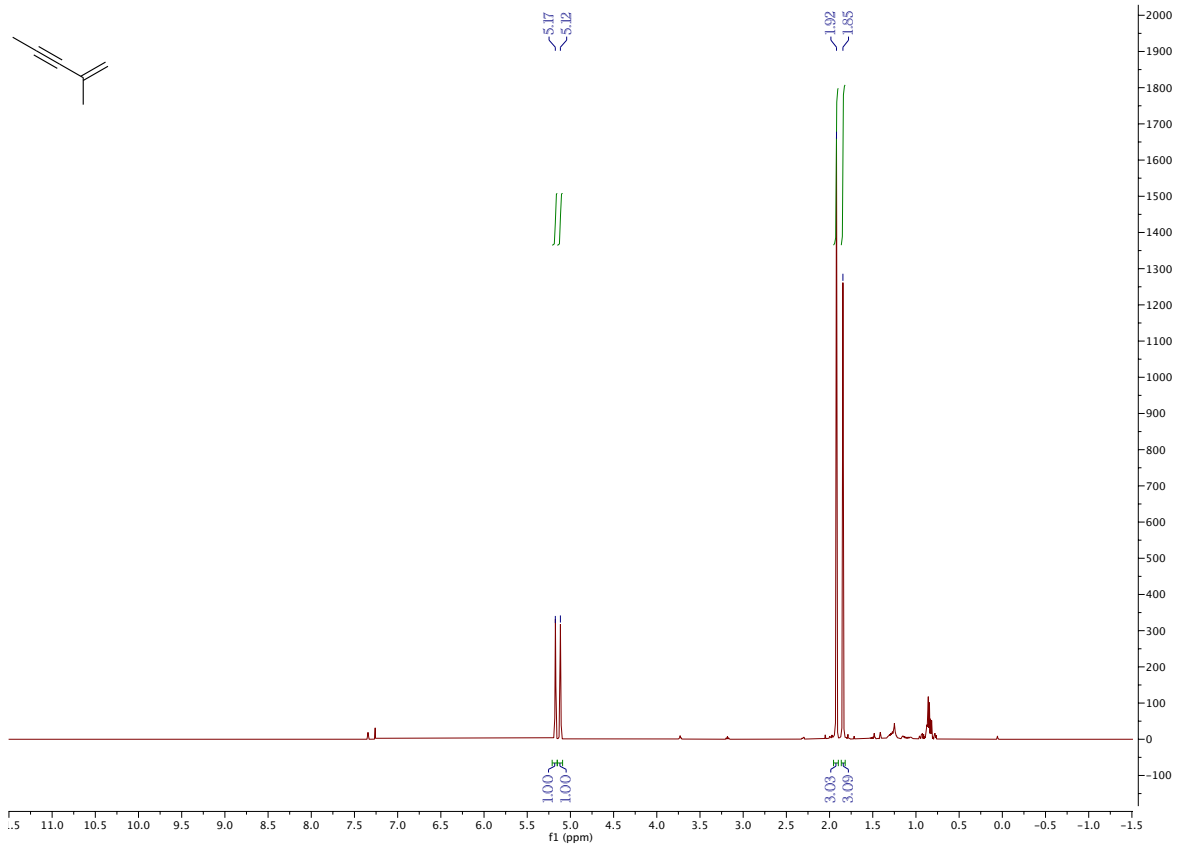


^{13}C NMR


155.19
150.85
139.65
138.83
138.18
136.12
129.25
127.93
127.42
126.25
126.08
118.85
116.47
93.09
21.47
NH
N
CN
f1 (ppm)

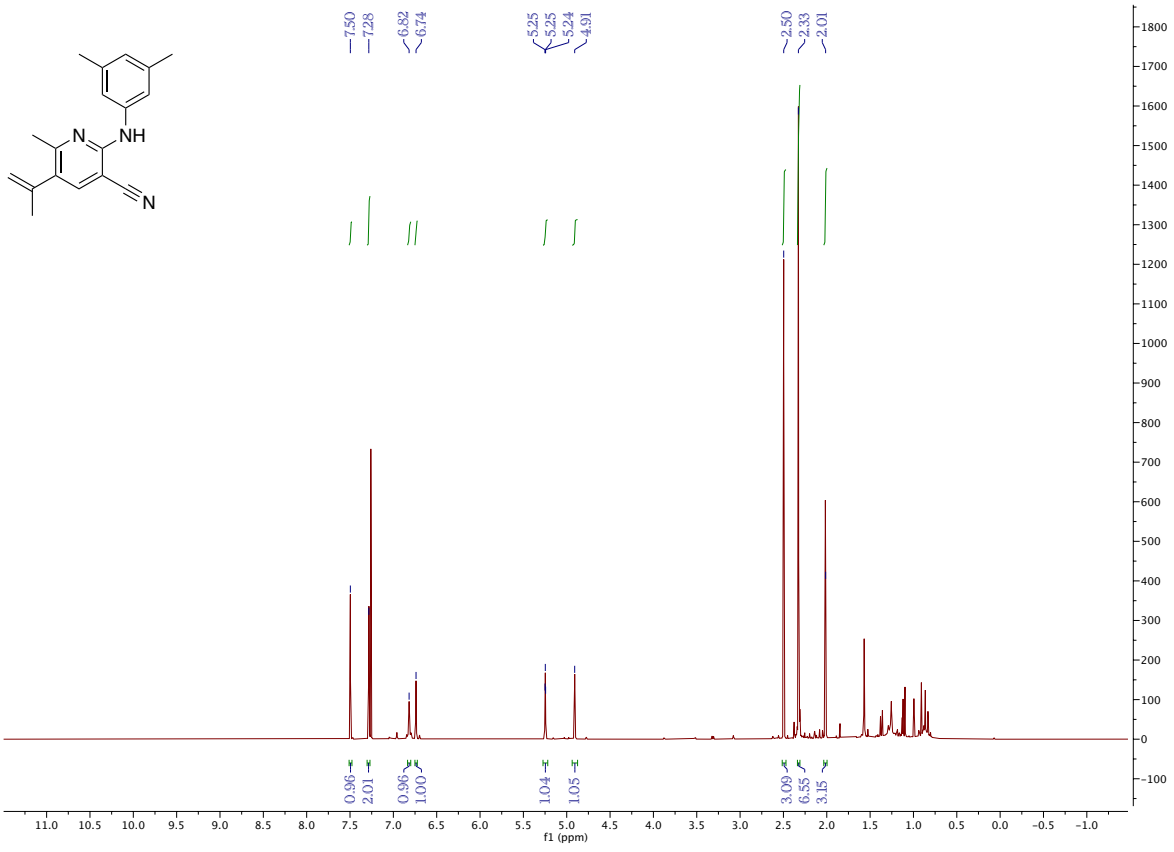
*2-methyl-1-penten-3-yne (**1c-I**).*

^{1}H NMR



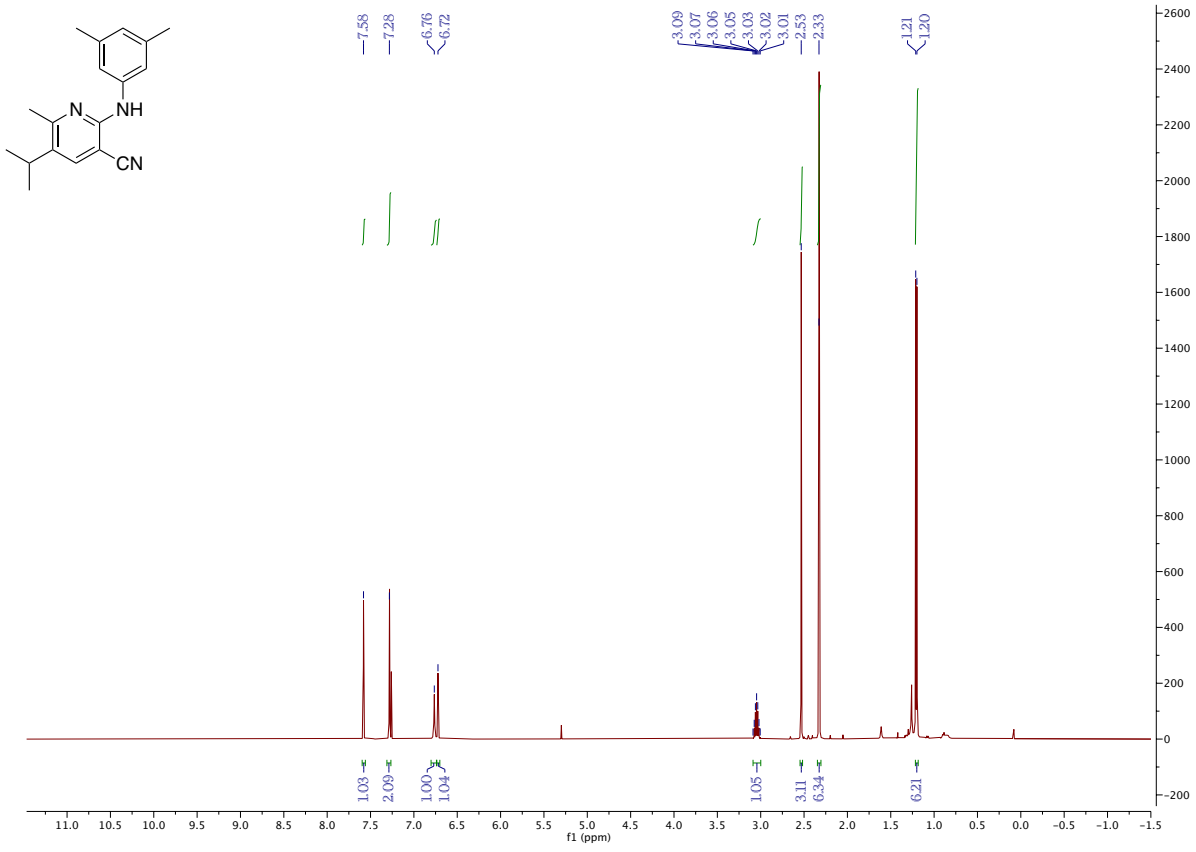
2-((3,5-dimethylphenyl)amino)-6-methyl-5-(prop-1-en-2-yl)nicotinonitrile ***(1c-II)***.

^{1}H NMR

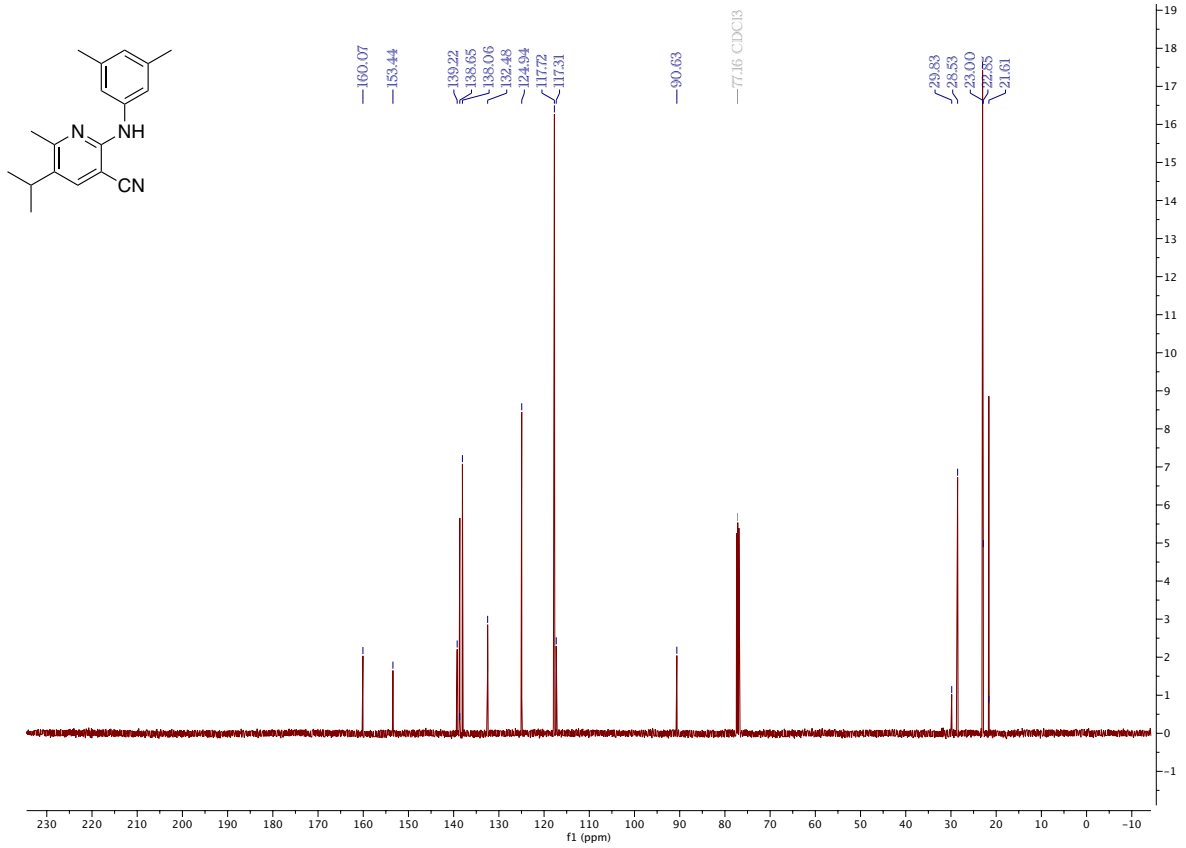


*6-Methyl-2-[(3,5-dimethylphenyl)amino]-5-(isopropyl)nicotinonitrile (**1c**).*

^{1}H NMR

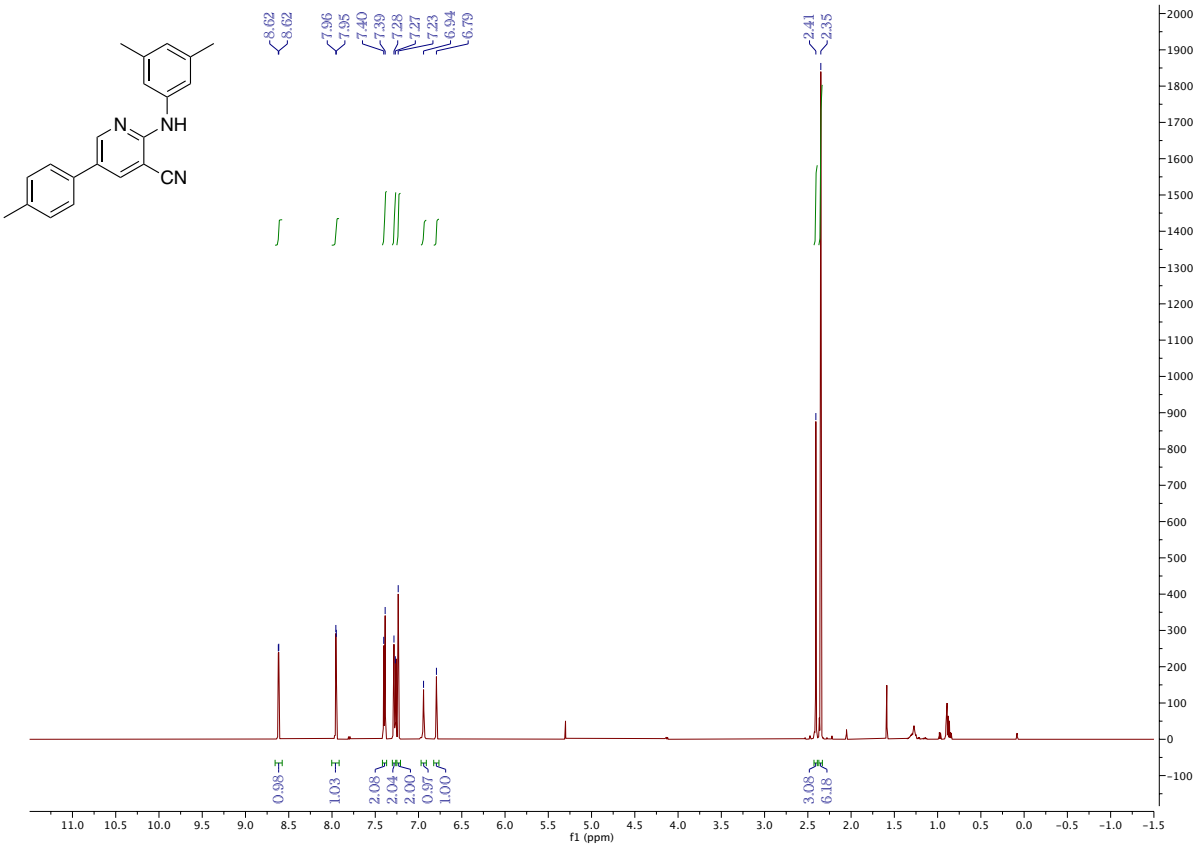


^{13}C NMR

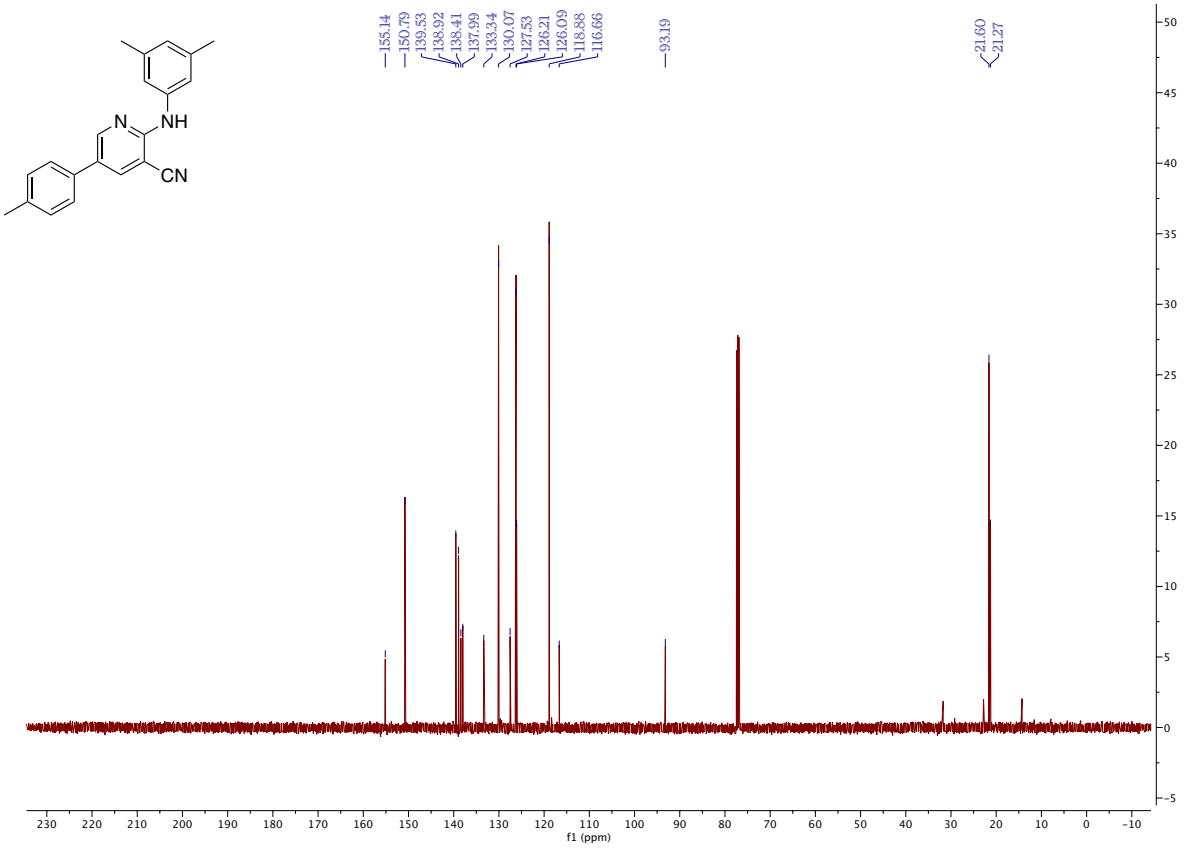

160.07
153.44
139.22
138.65
138.06
132.48
124.94
117.72
117.31
90.63
77.46 CDCl3
29.83
28.53
23.00
22.85
21.61
N
NH
CN
f1 (ppm)

*2-((3,5-dimethylphenyl)amino)-5-(p-tolyl)nicotinonitrile (**1d**).*

^{1}H NMR

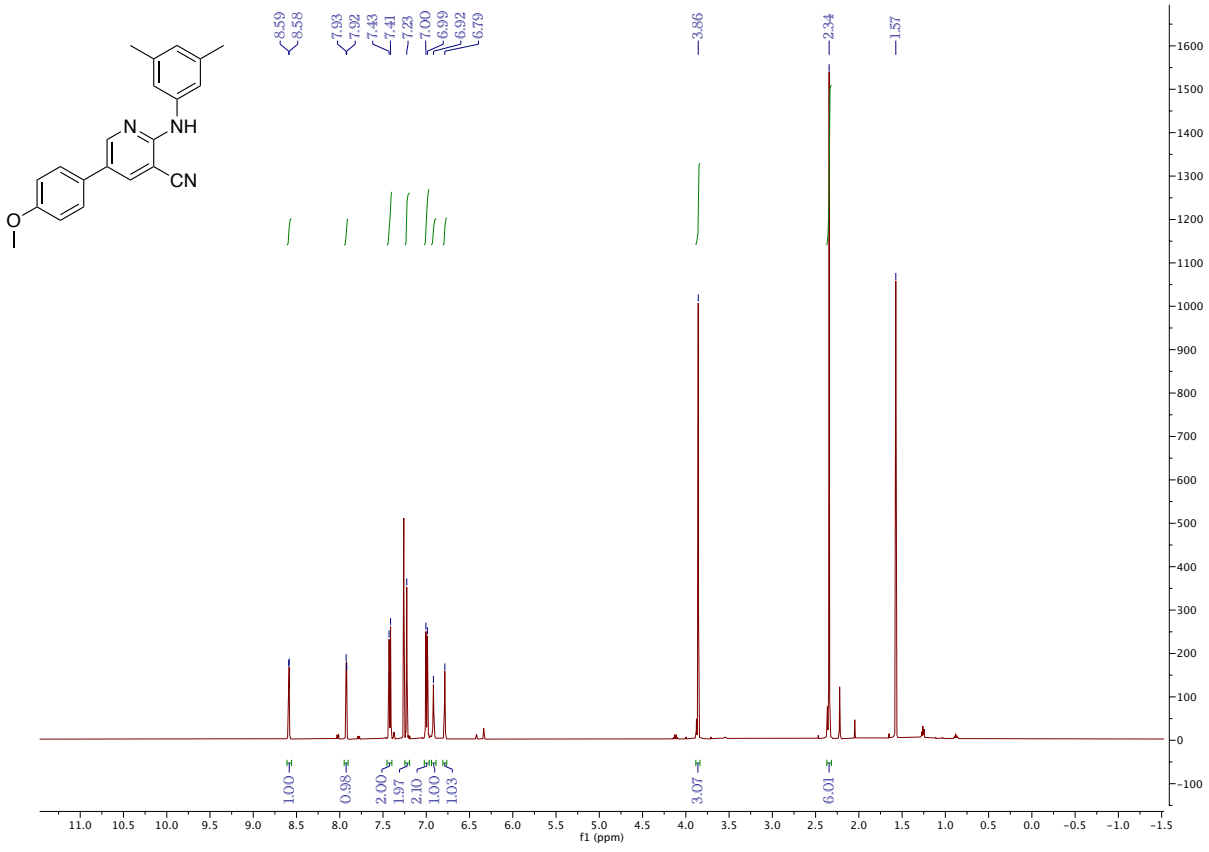


^{13}C NMR

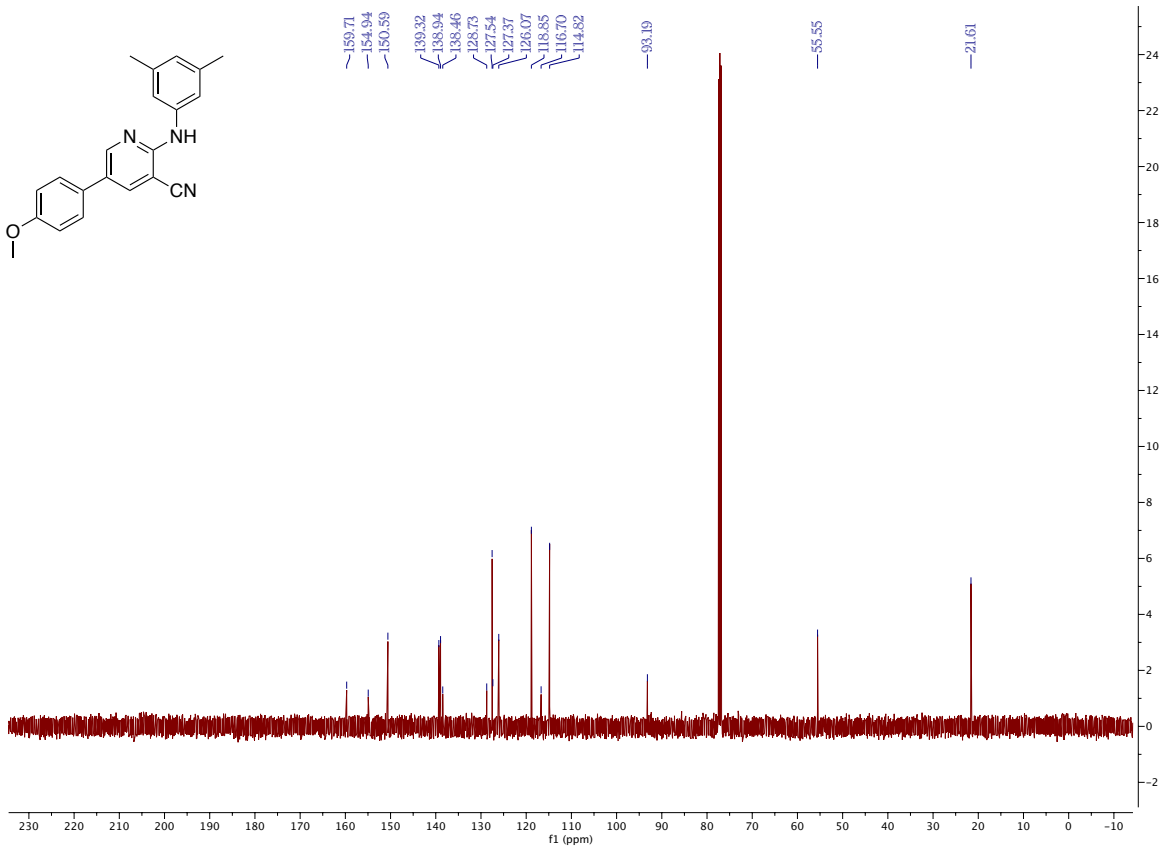

155.14
150.79
139.53
138.92
138.41
137.99
133.34
130.07
127.53
126.21
126.09
118.88
116.66
93.19
21.60
21.27
NH
N
CN
f1 (ppm)

*2-((3,5-dimethylphenyl)amino)-5-(4-methoxyphenyl)nicotinonitrile (**1e**).*

^{1}H NMR

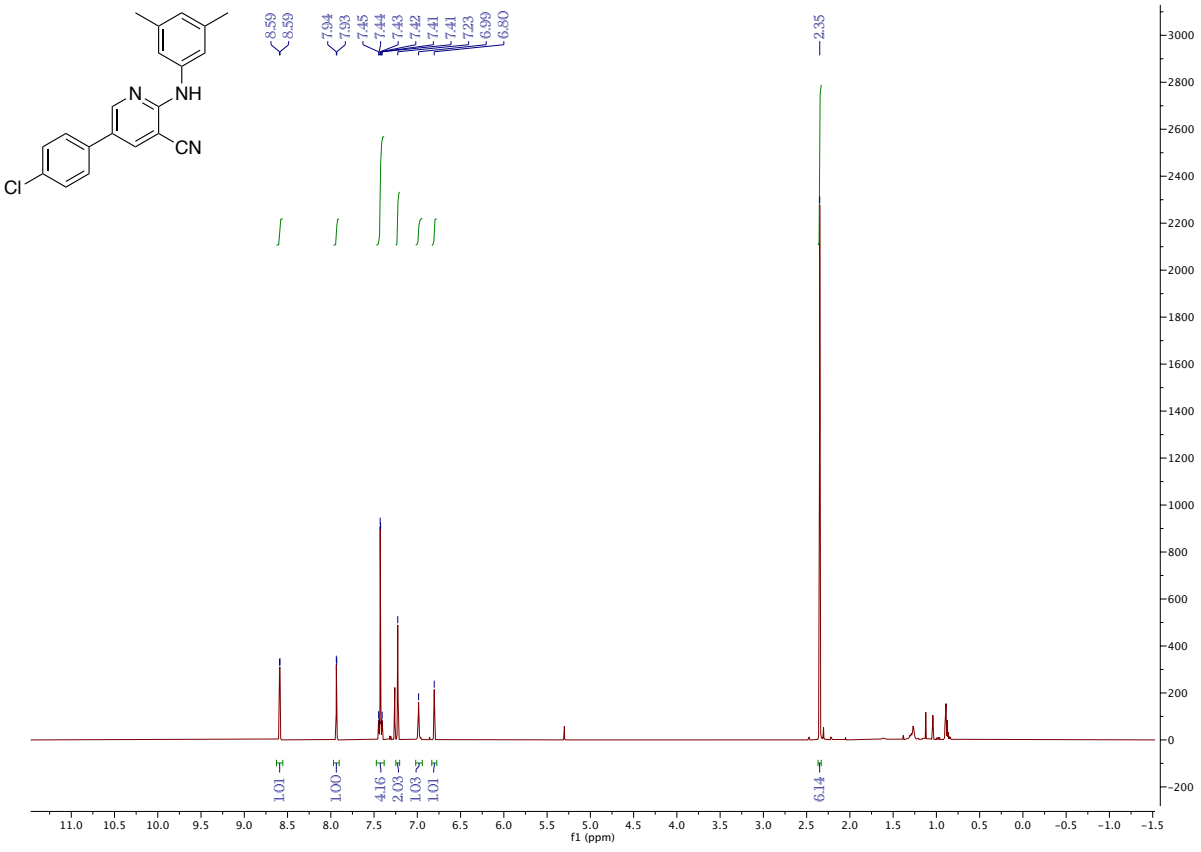


^{13}C NMR

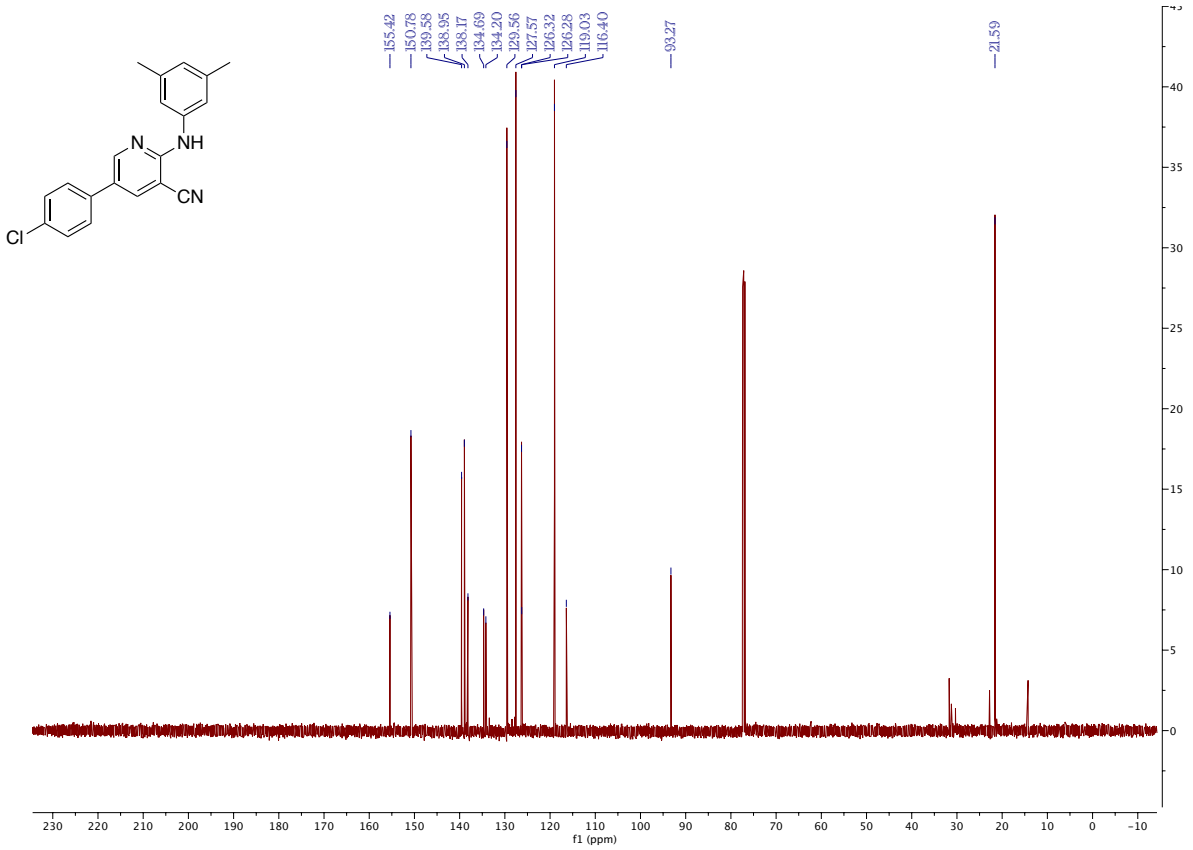

159.71
154.94
150.59
139.32
138.94
138.46
128.73
127.54
127.37
126.07
118.85
116.70
114.82
93.19
55.55
21.61
N
NH
CN
O
f1 (ppm)

*5-(4-chlorophenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**1f**).*

^{1}H NMR

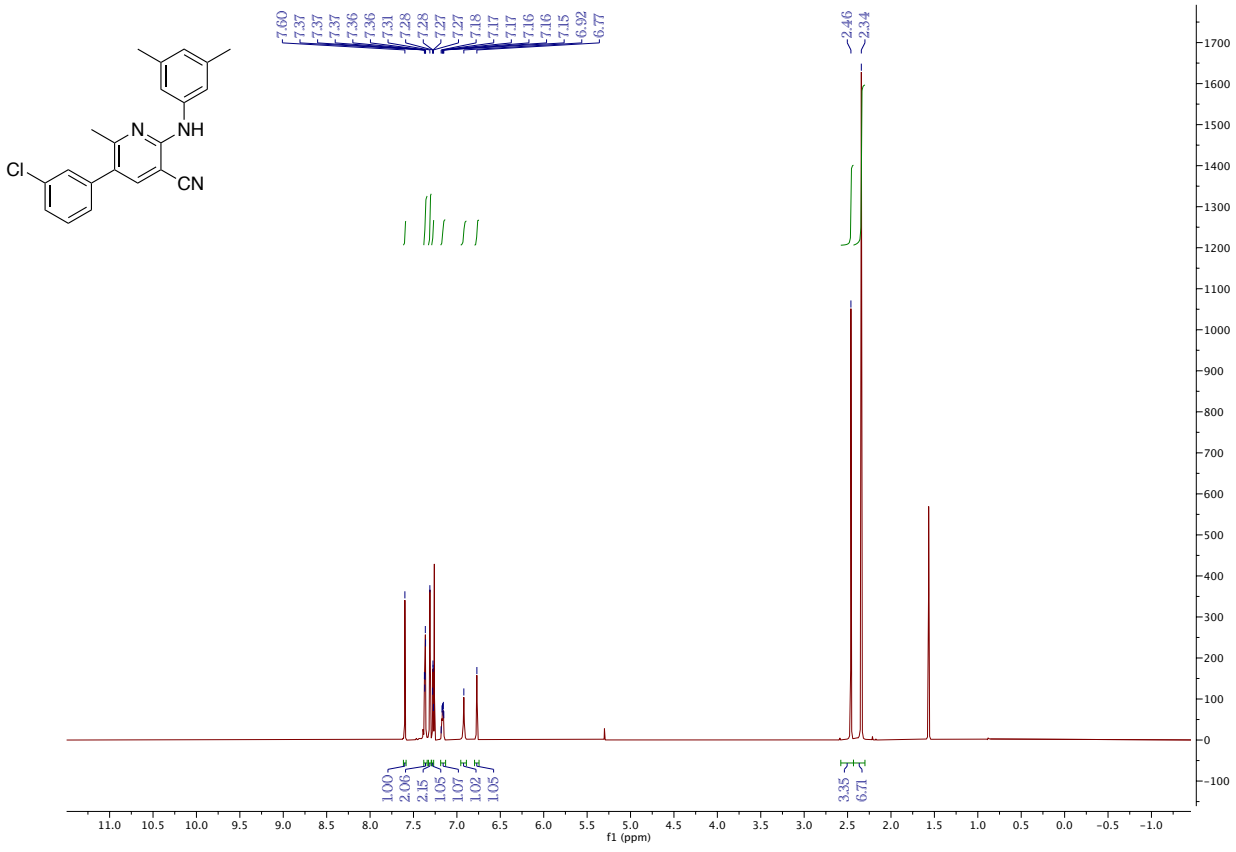


^{13}C NMR

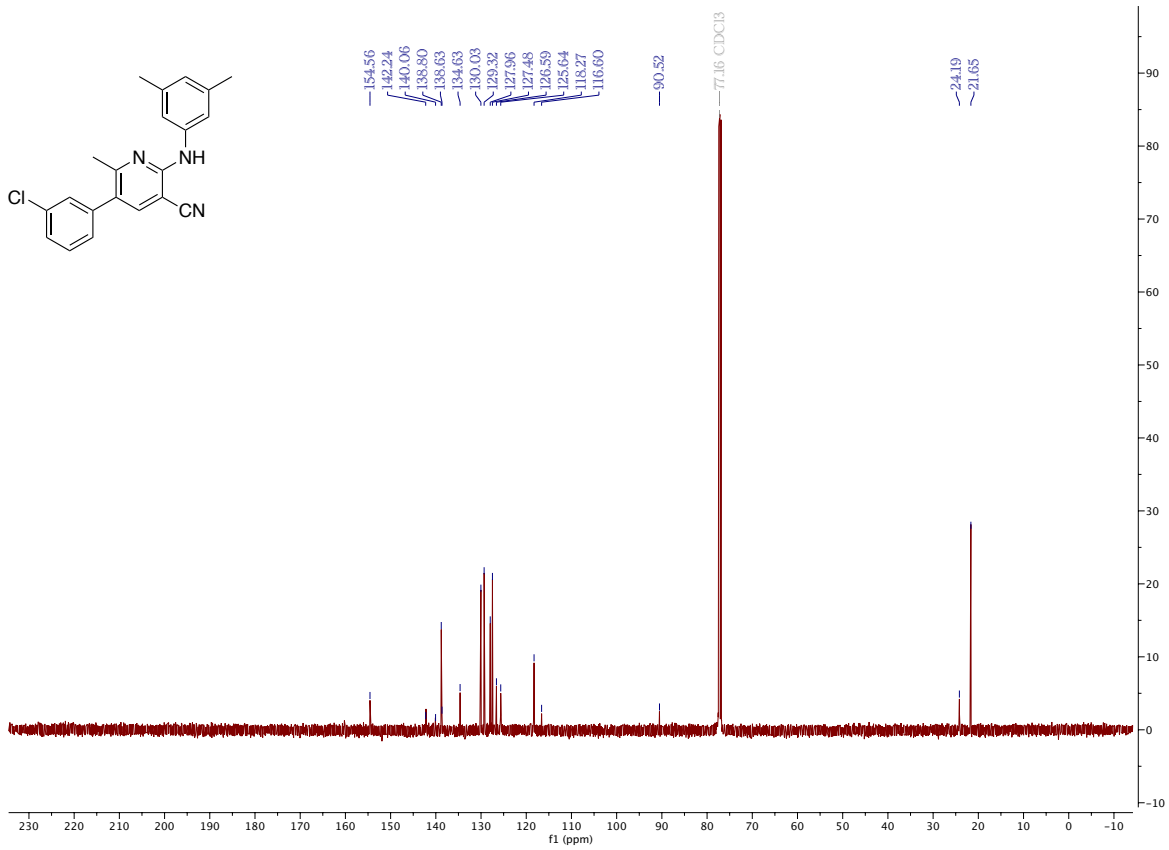

155.42
150.78
139.58
138.95
138.17
134.69
134.20
129.56
127.57
126.32
126.28
119.03
116.40
93.27
21.59
N
NH
CN
Cl
f1 (ppm)

*5-(3-chlorophenyl)-2-((3,5-dimethylphenyl)amino)-6-methylnicotinonitrile (**1g**).*

^{1}H NMR

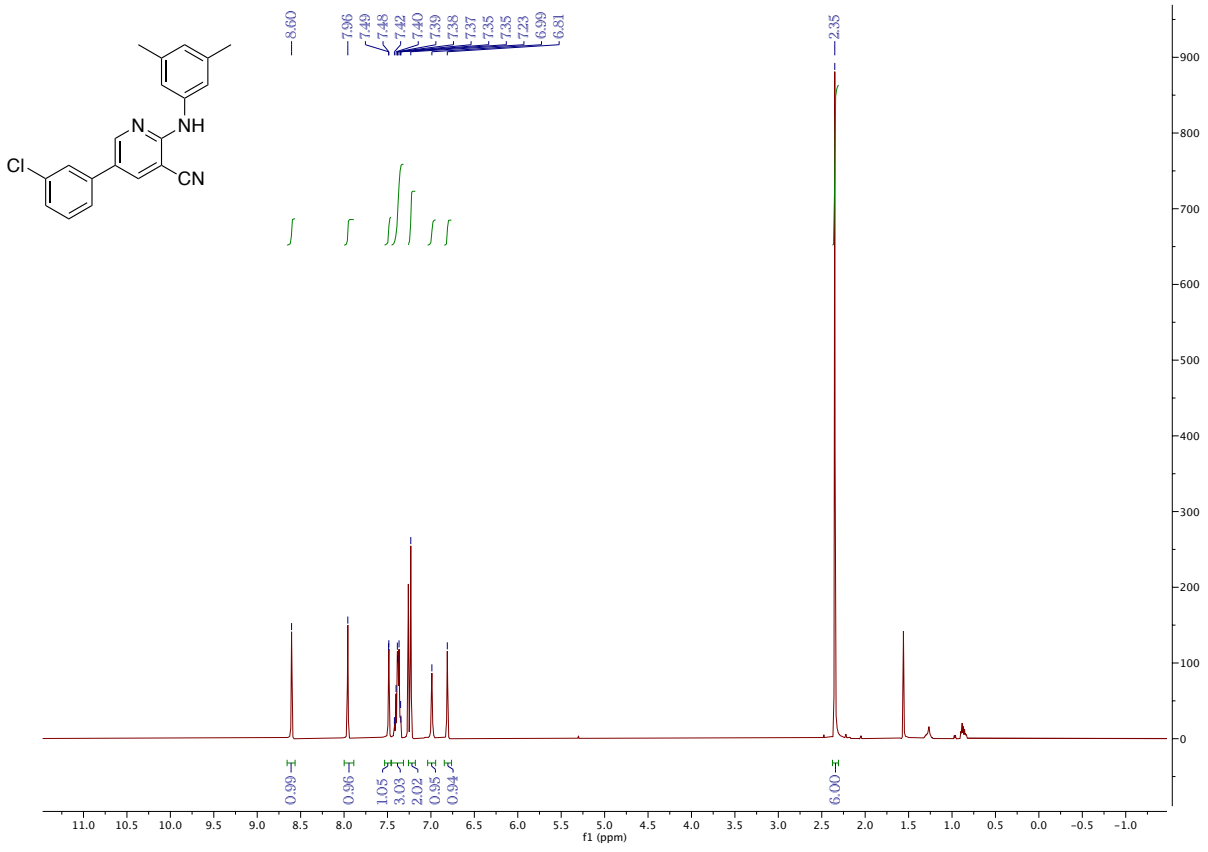


^{13}C NMR

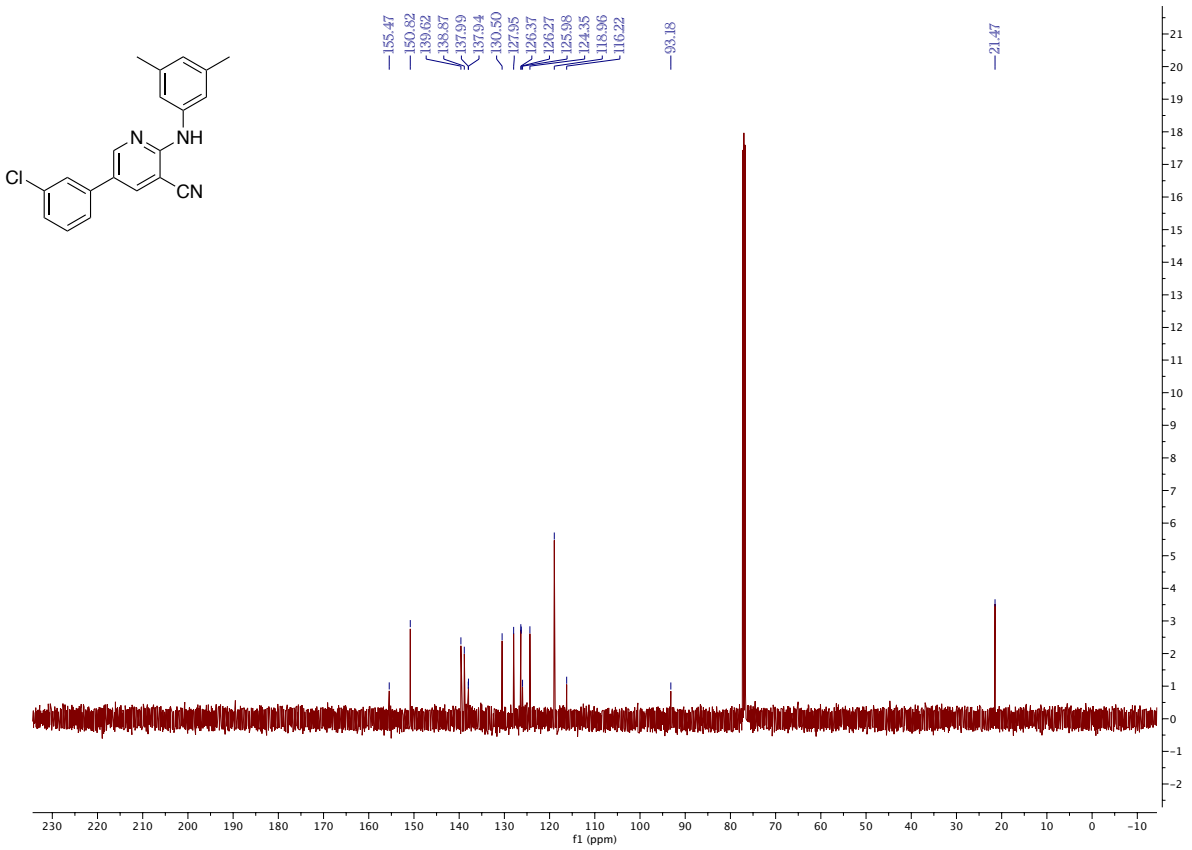

154.56
142.24
140.06
138.80
138.63
134.63
130.03
129.32
127.96
127.48
126.59
125.64
118.27
116.60
90.52
77.46 CDCl3
24.19
21.65
NH
N
Cl
CN
f1 (ppm)

*5-(3-chlorophenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**1h**).*

^{1}H NMR

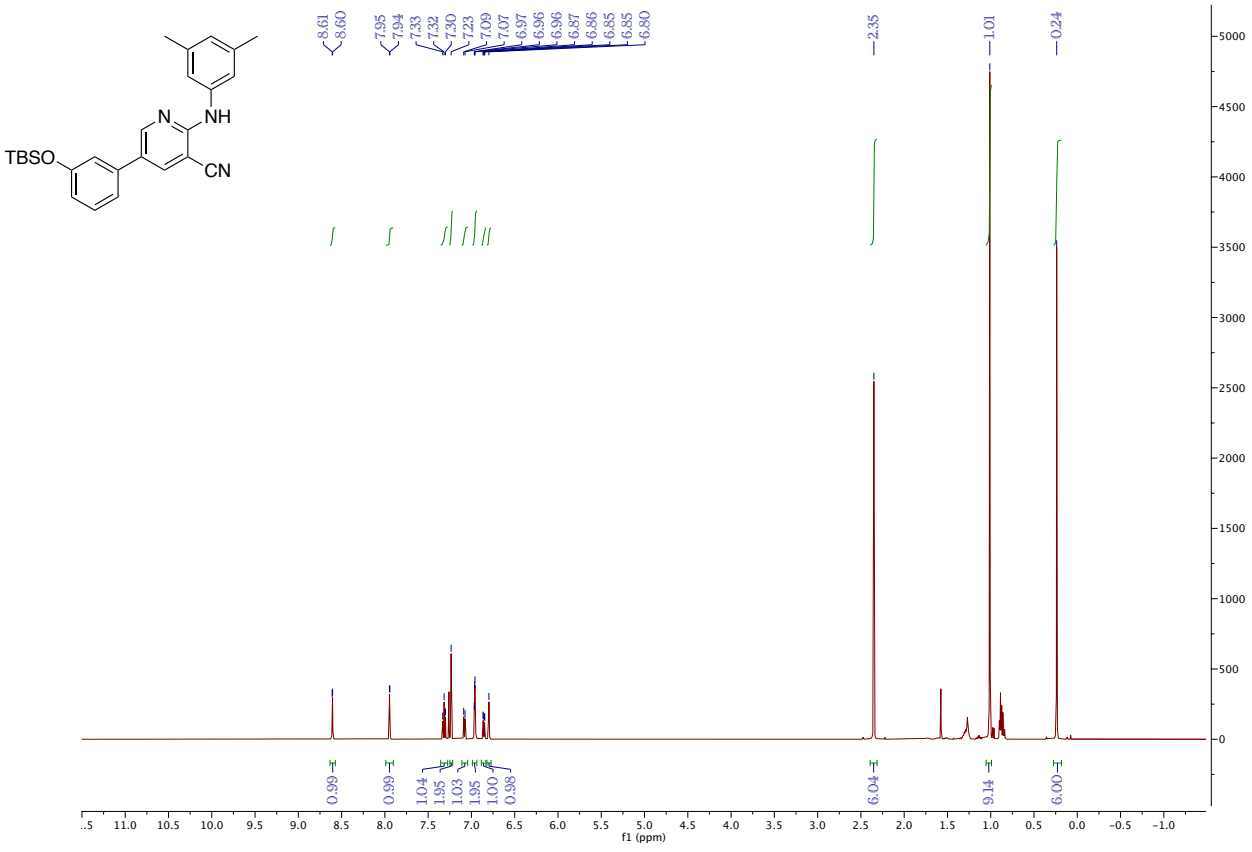


^{13}C NMR

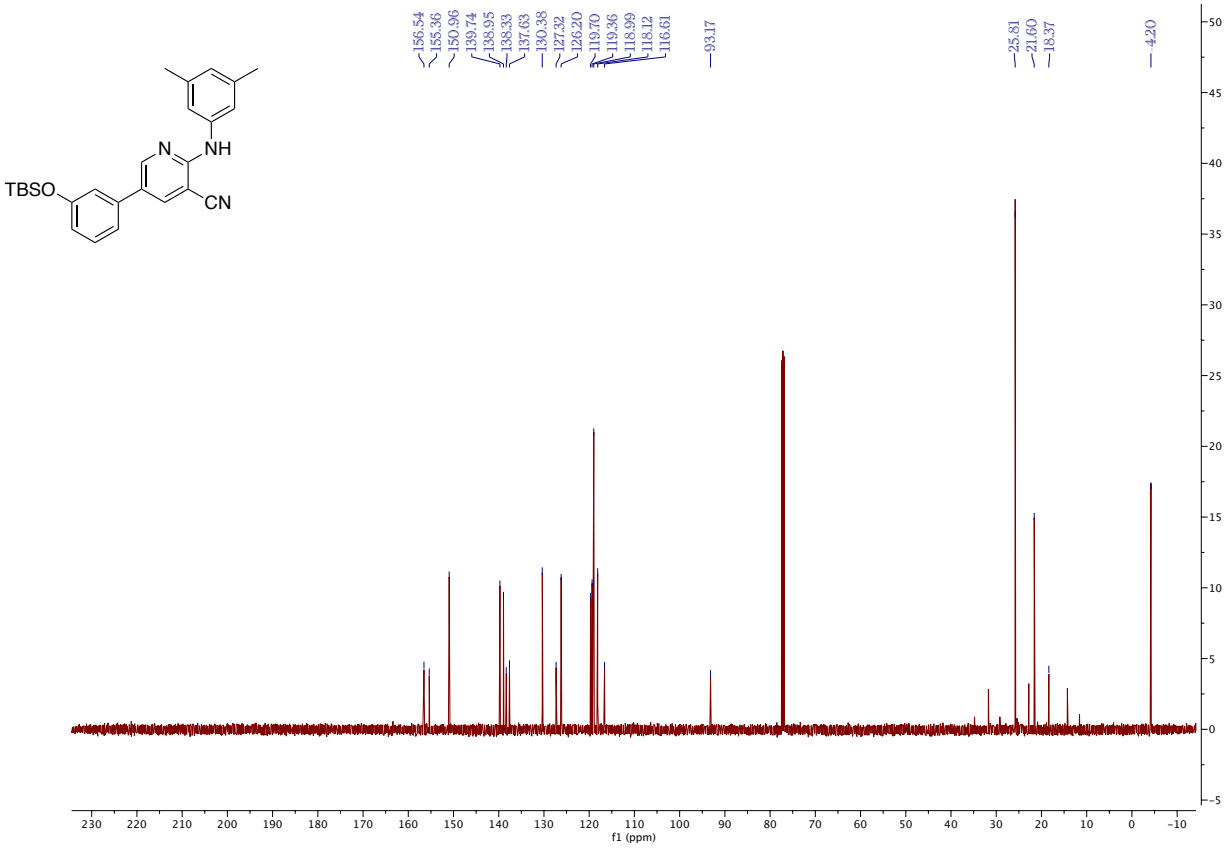

155.47
150.82
139.62
138.87
137.99
137.94
130.50
127.95
126.37
126.27
125.98
124.35
118.96
116.22
93.18
21.47
Cl
N
NH
CN
f1 (ppm)

*5-(3-((tert-butyldimethylsilyl)oxy)phenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**1i**).*

^{1}H NMR

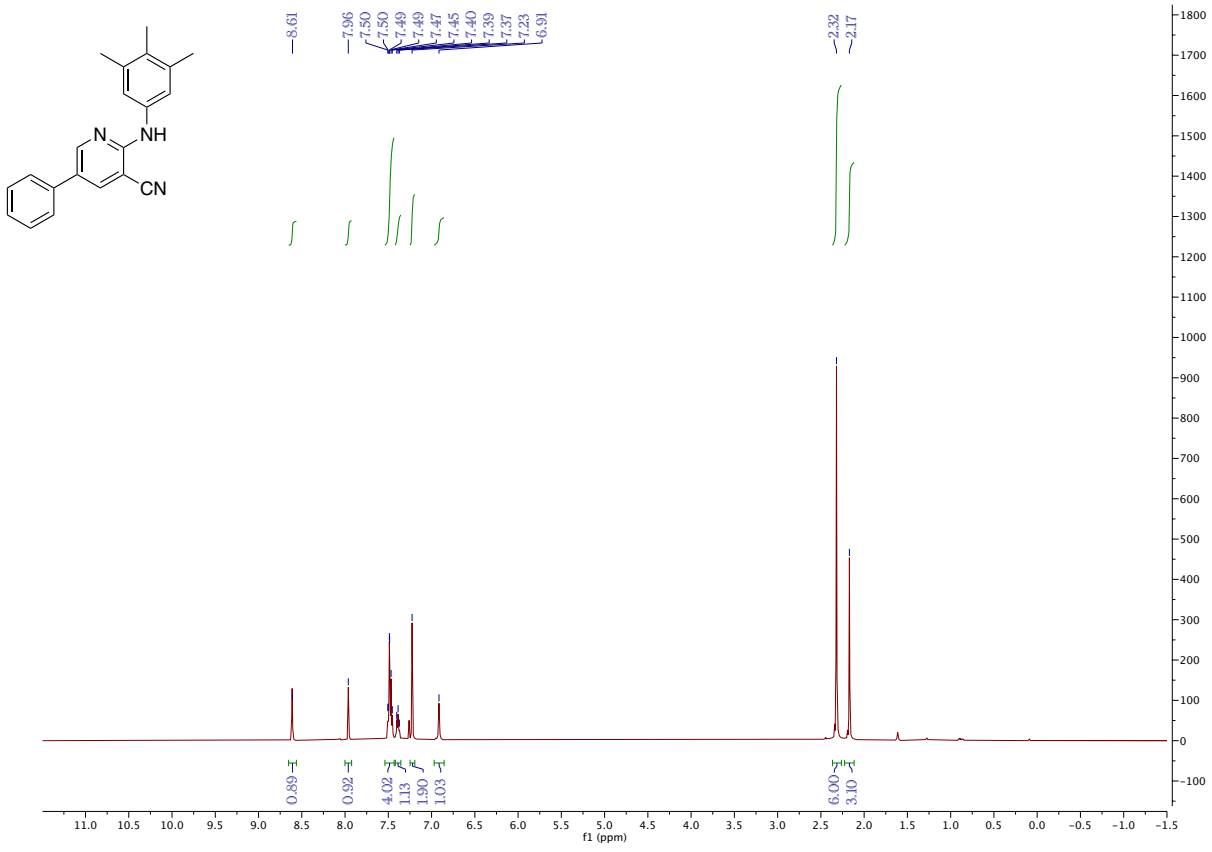


^{13}C NMR

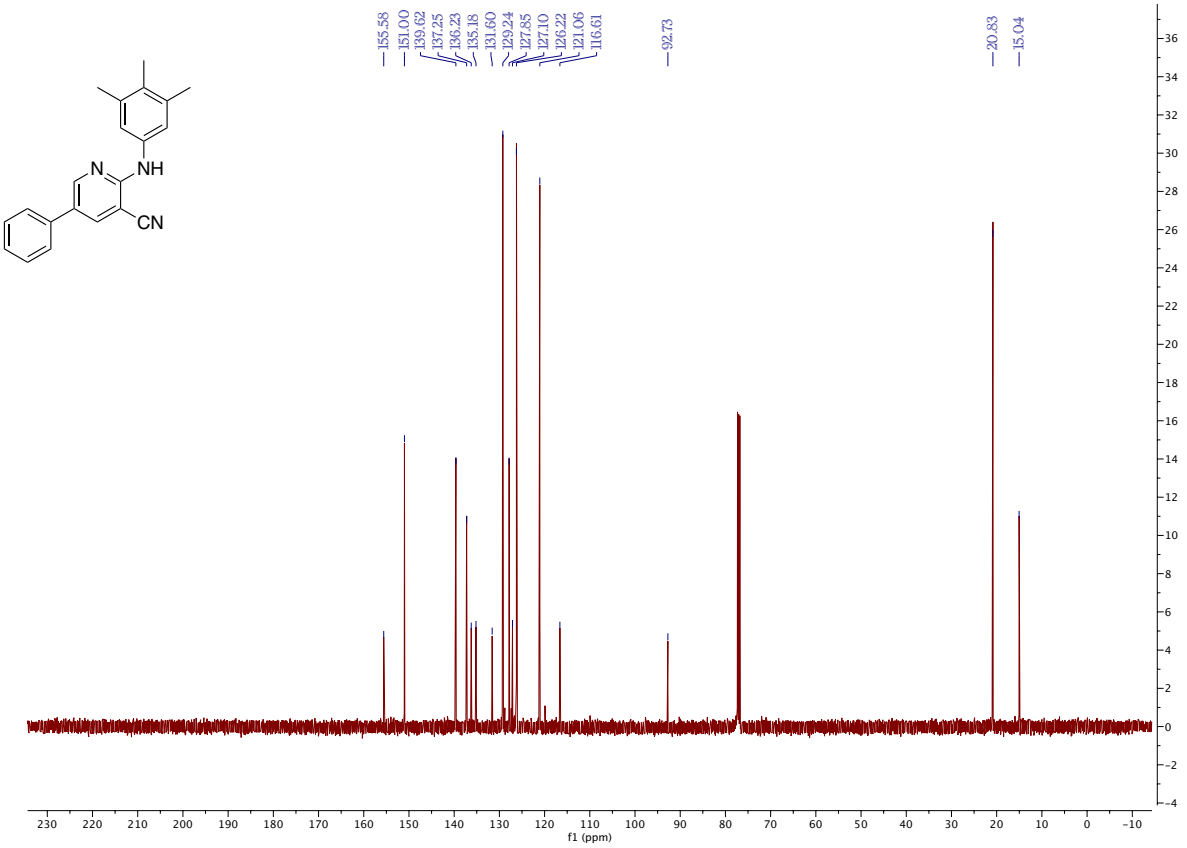

156.54
155.36
150.96
139.74
138.95
138.33
137.63
130.38
127.32
126.20
119.70
119.36
118.99
118.12
116.61
93.17
25.81
21.60
18.37
-4.20
TBSO
N
NH
CN
f1 (ppm)

*5-phenyl-2-((3,4,5-trimethylphenyl)amino)nicotinonitrile (**1j**).*

^{1}H NMR

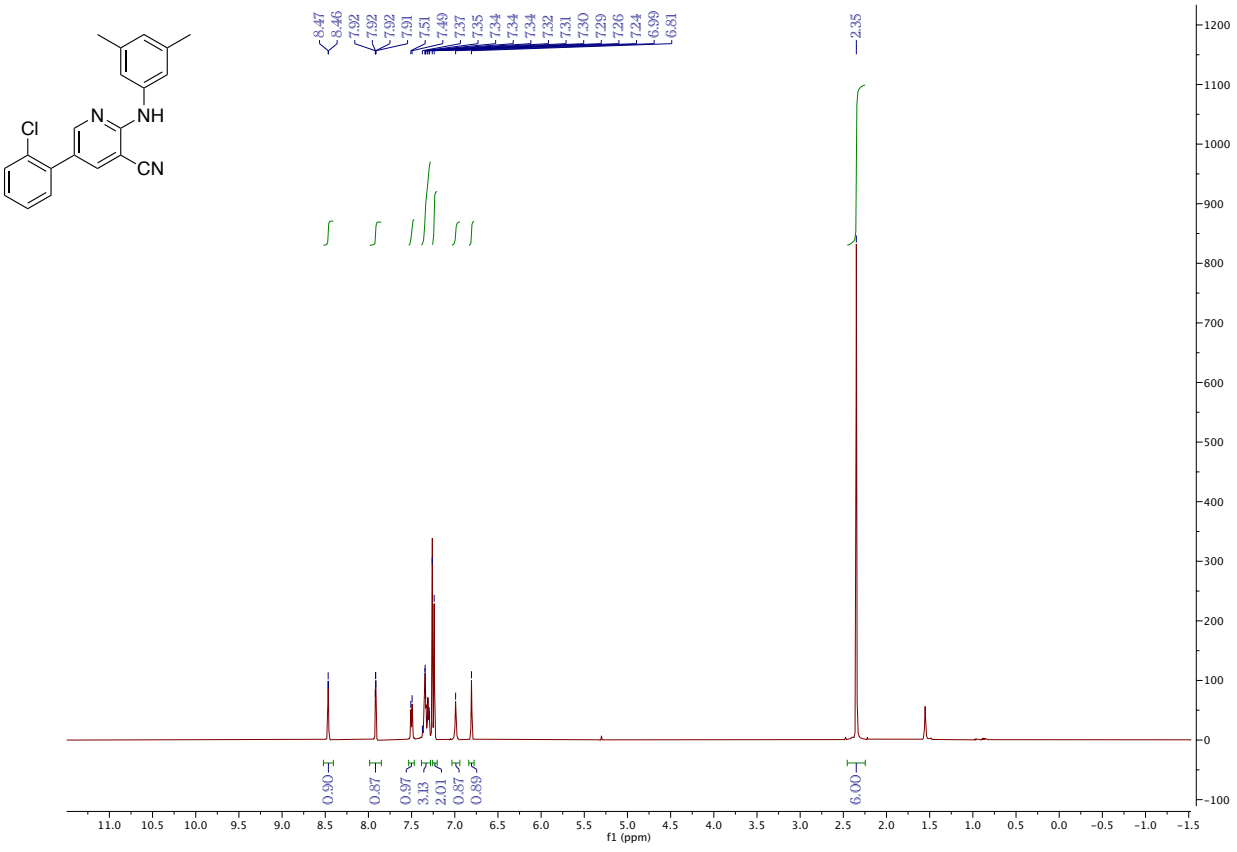


^{13}C NMR

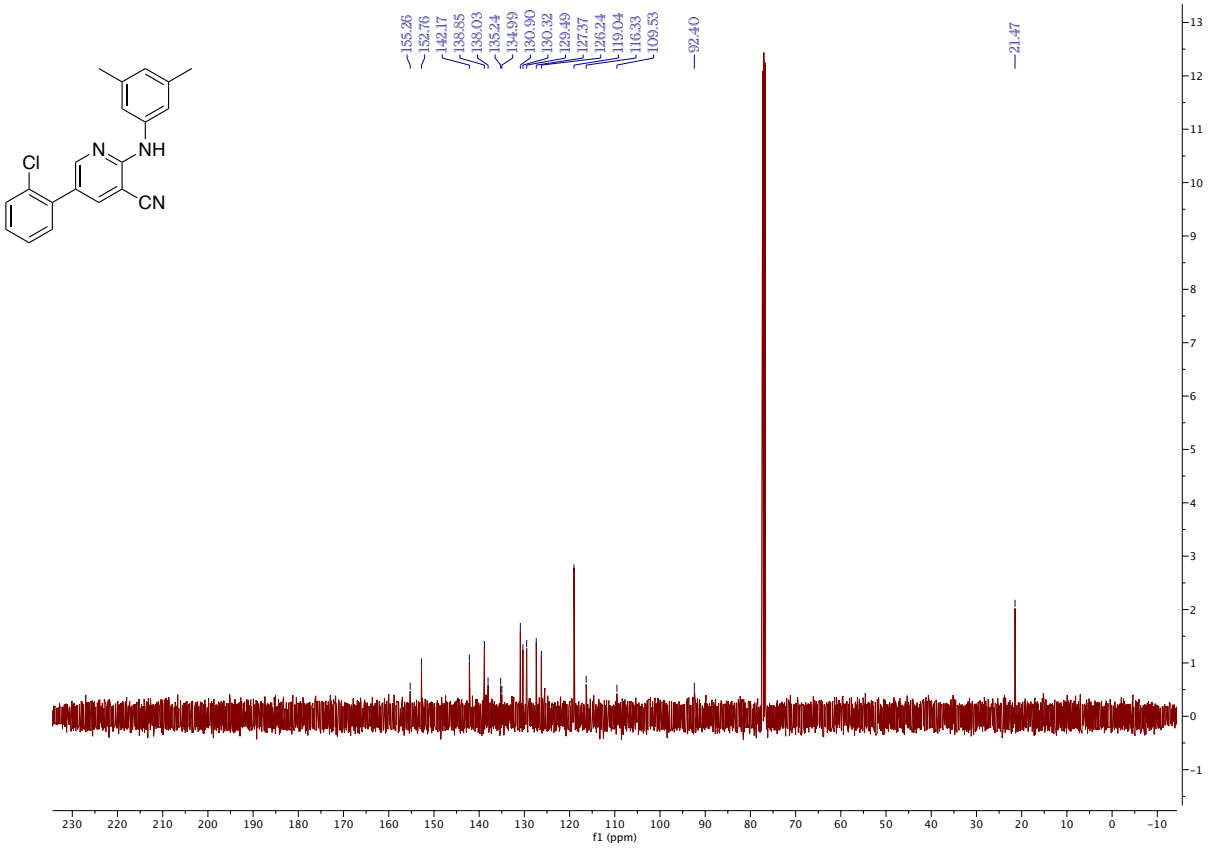

155.58
151.00
139.62
137.25
136.23
135.18
131.60
129.24
127.85
127.10
126.22
121.06
116.61
92.73
20.83
15.04
NH
N
CN
f1 (ppm)

*5-(2-chlorophenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**1k**).*

^{1}H NMR

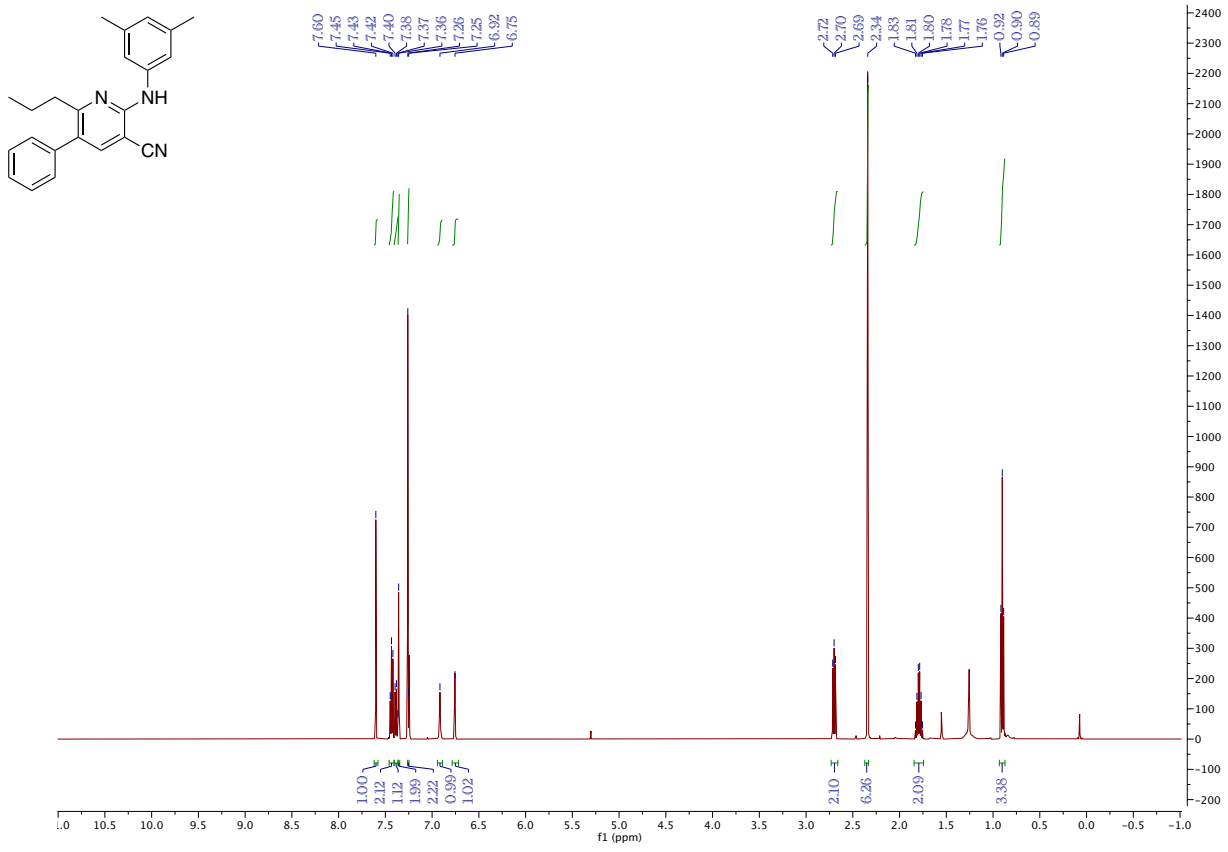


^{13}C NMR

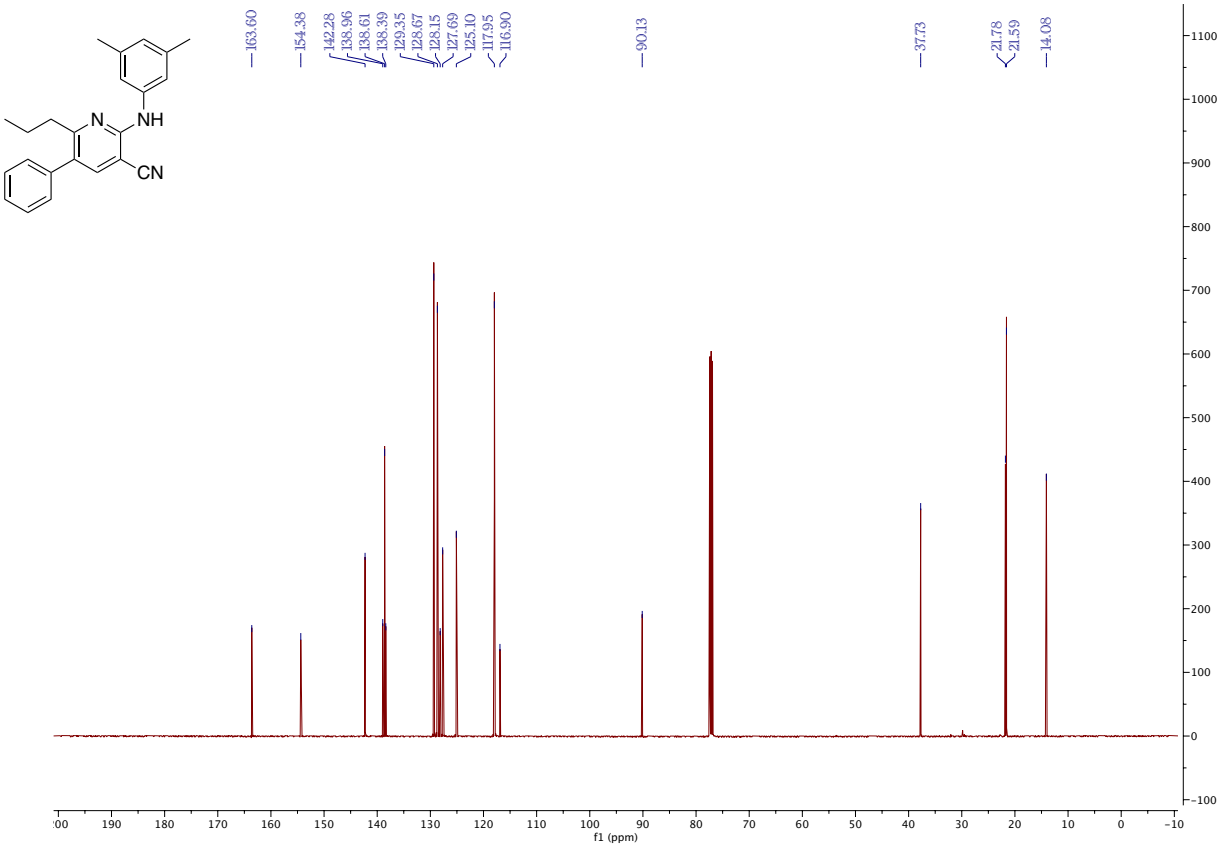

155.26
152.76
142.17
138.85
138.03
135.24
134.99
130.90
130.32
129.49
127.37
126.24
119.04
116.33
109.53
92.40
21.47
Cl
N
NH
CN
f1 (ppm)

*2-((3,5-dimethylphenyl)amino)-5-phenyl-6-propylnicotinonitrile (**11**).*

^{1}H NMR

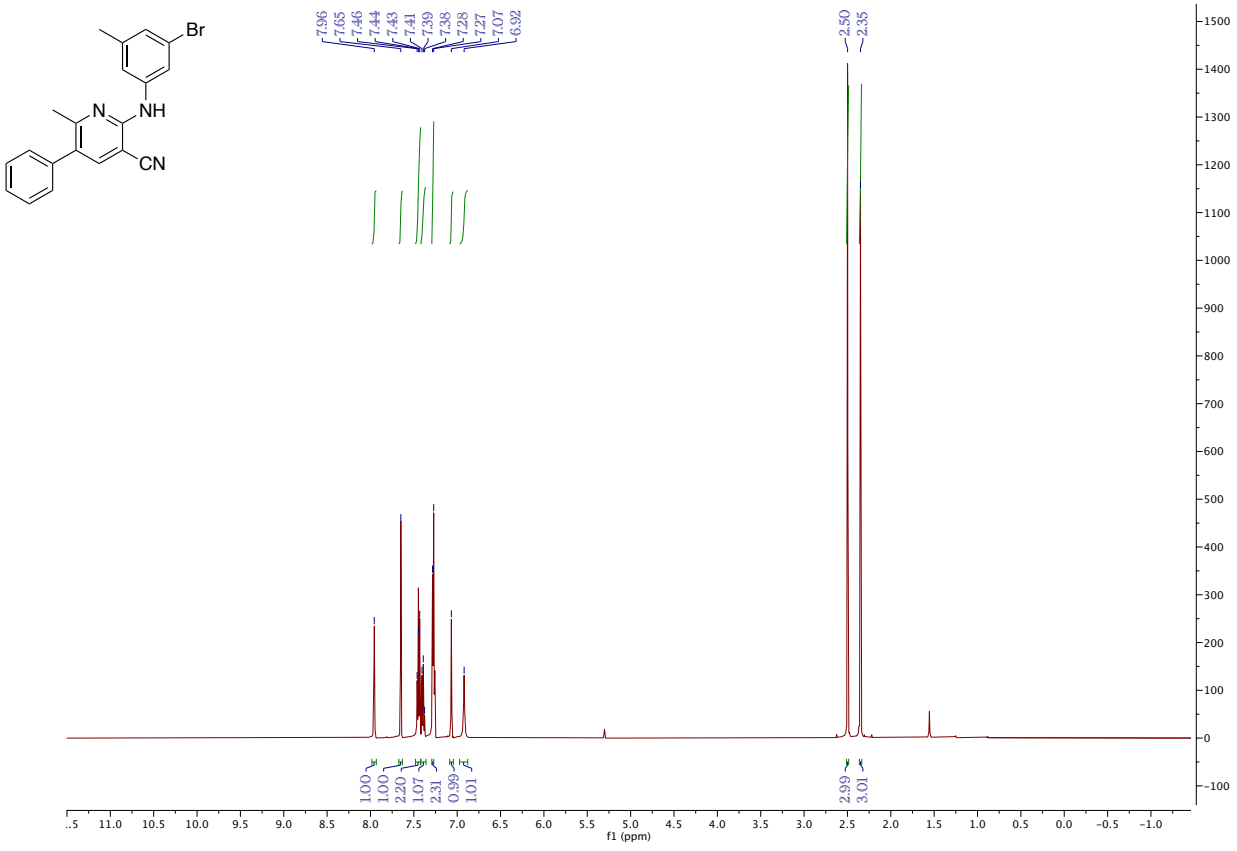


^{13}C NMR

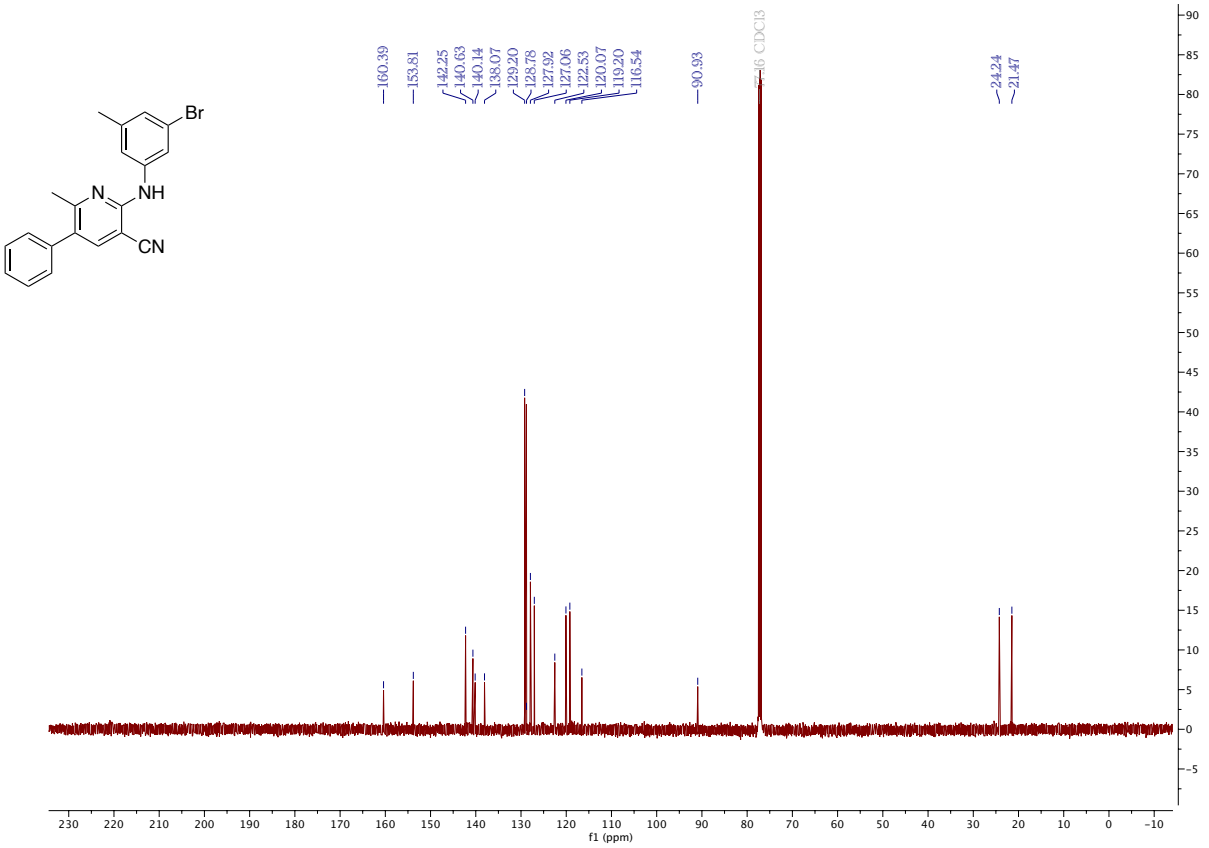

163.60
154.38
142.28
138.96
138.61
138.39
129.35
128.67
128.15
127.69
125.10
117.95
116.90
90.13
37.73
21.78
21.59
14.08
NH
N
CN
f1 (ppm)

*2-((3-bromo-5-methylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1m**).*

^{1}H NMR

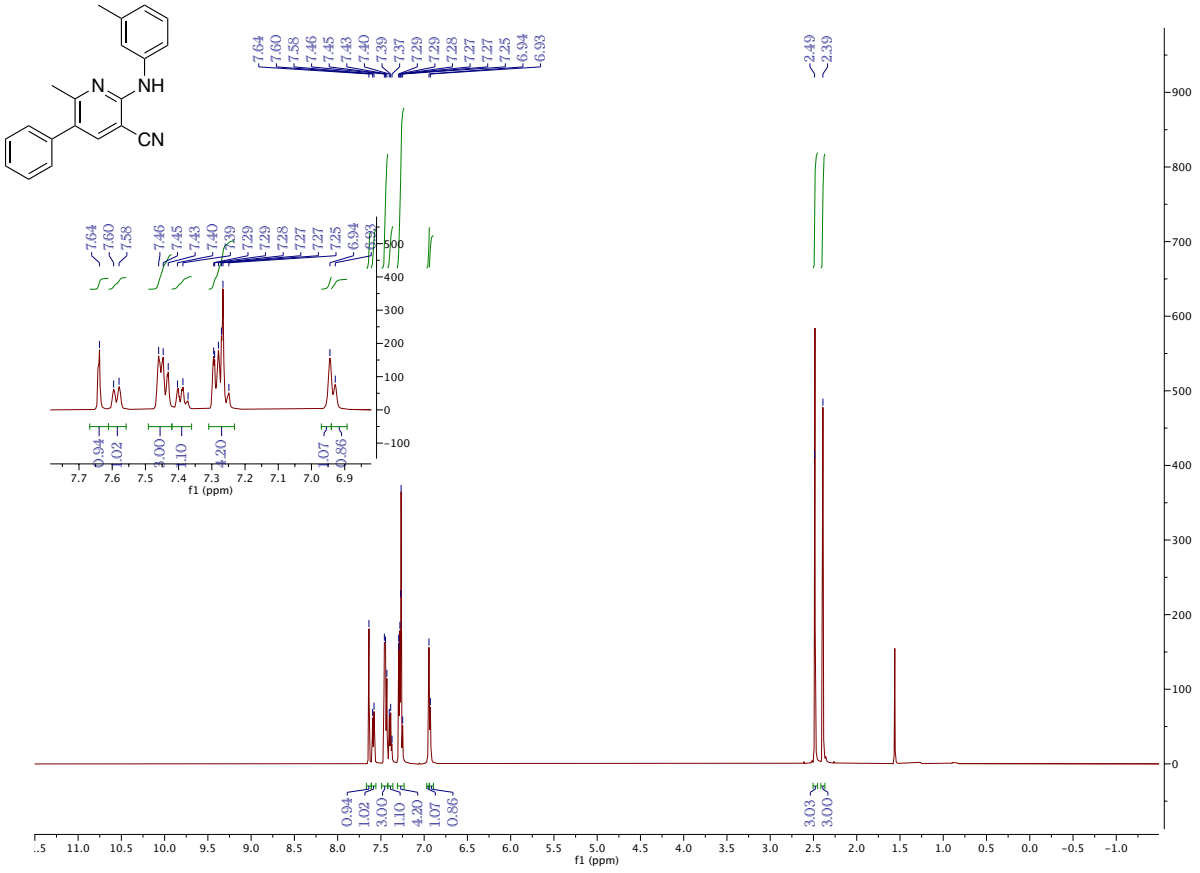


^{13}C NMR

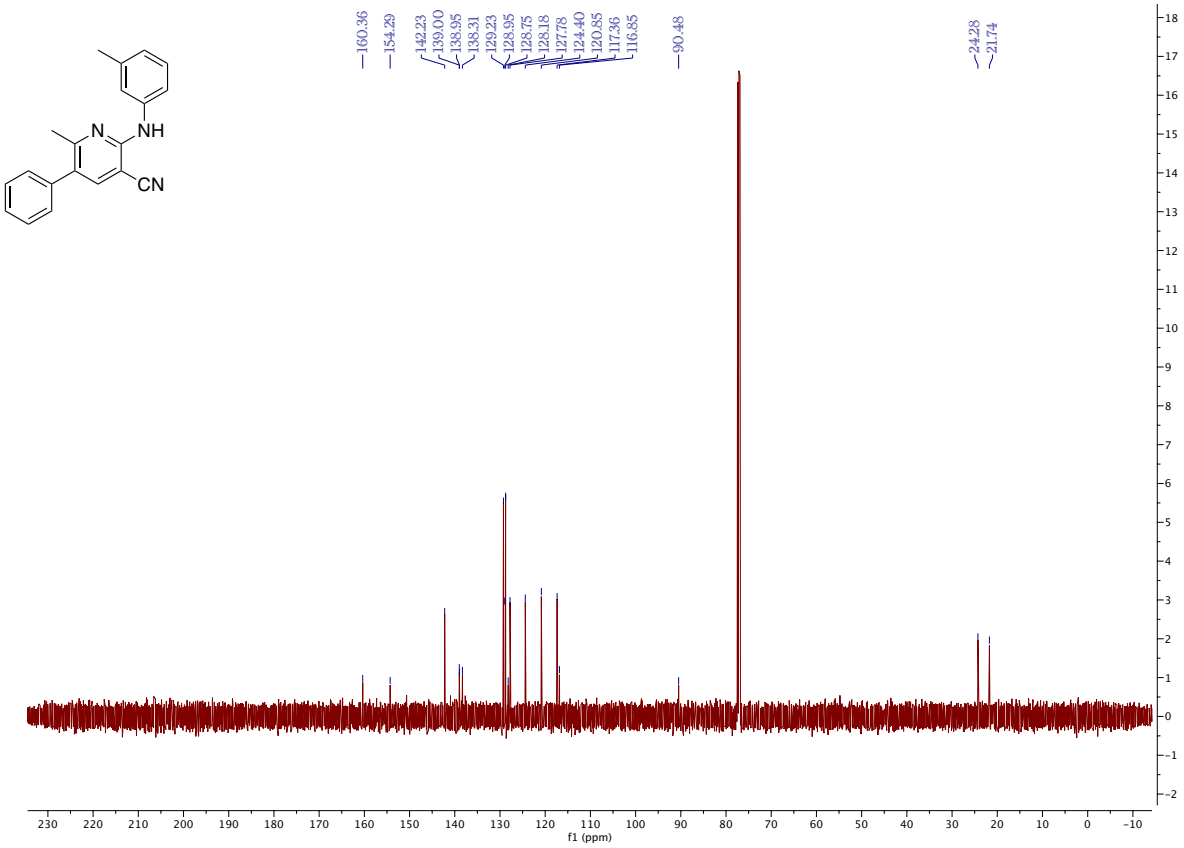

Br
N
NH
CN
160.39
153.81
142.25
140.63
140.14
138.07
129.20
128.78
127.92
127.06
122.53
120.07
119.20
116.54
90.93
77.16 CDCl3
24.24
21.47
f1 (ppm)

*6-methyl-5-phenyl-2-(m-tolylamino)nicotinonitrile (**1n**).*

^{1}H NMR

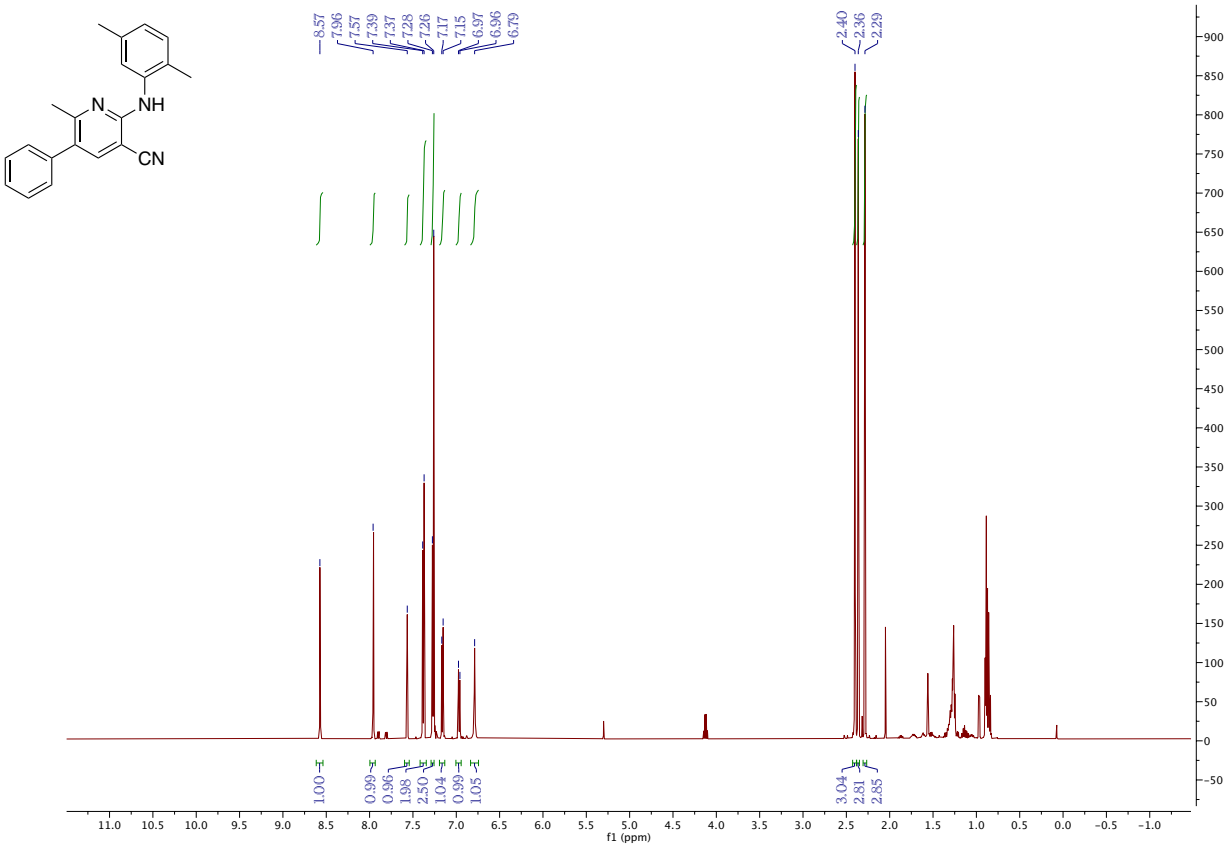


^{13}C NMR

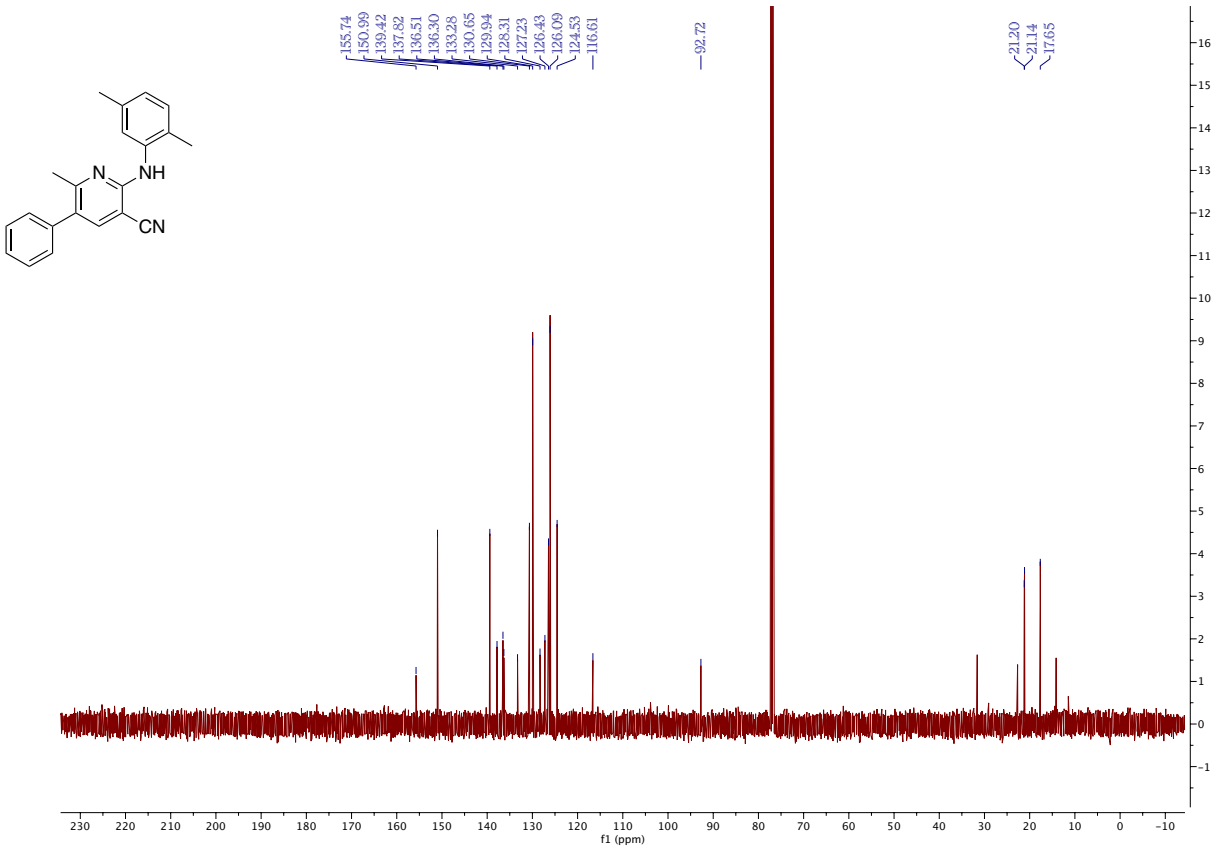

160.36
154.29
142.23
139.00
138.95
138.31
129.23
128.95
128.75
128.18
127.78
124.40
120.85
117.36
116.85
90.48
24.28
21.74
f1 (ppm)

*2-((2,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1o**).*

^{1}H NMR

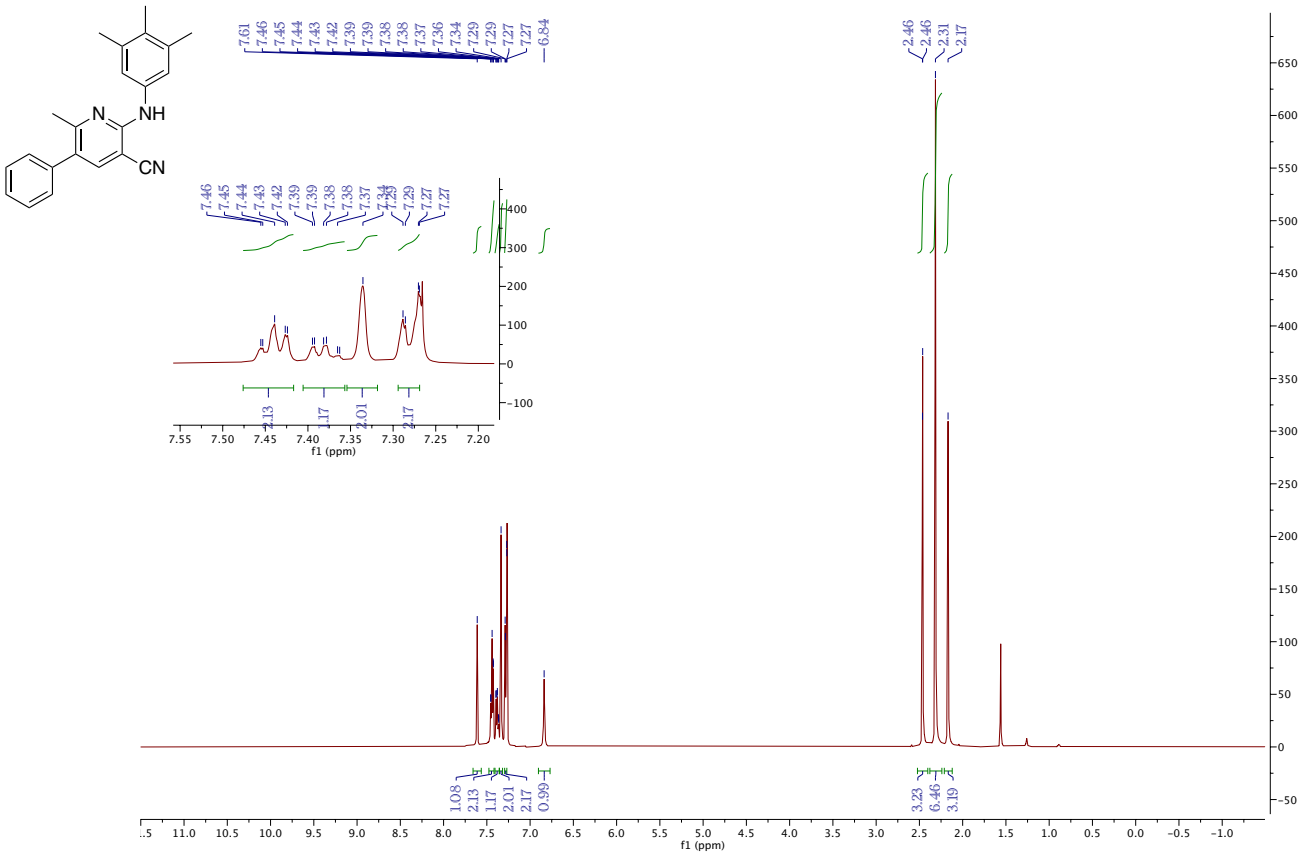


^{13}C NMR

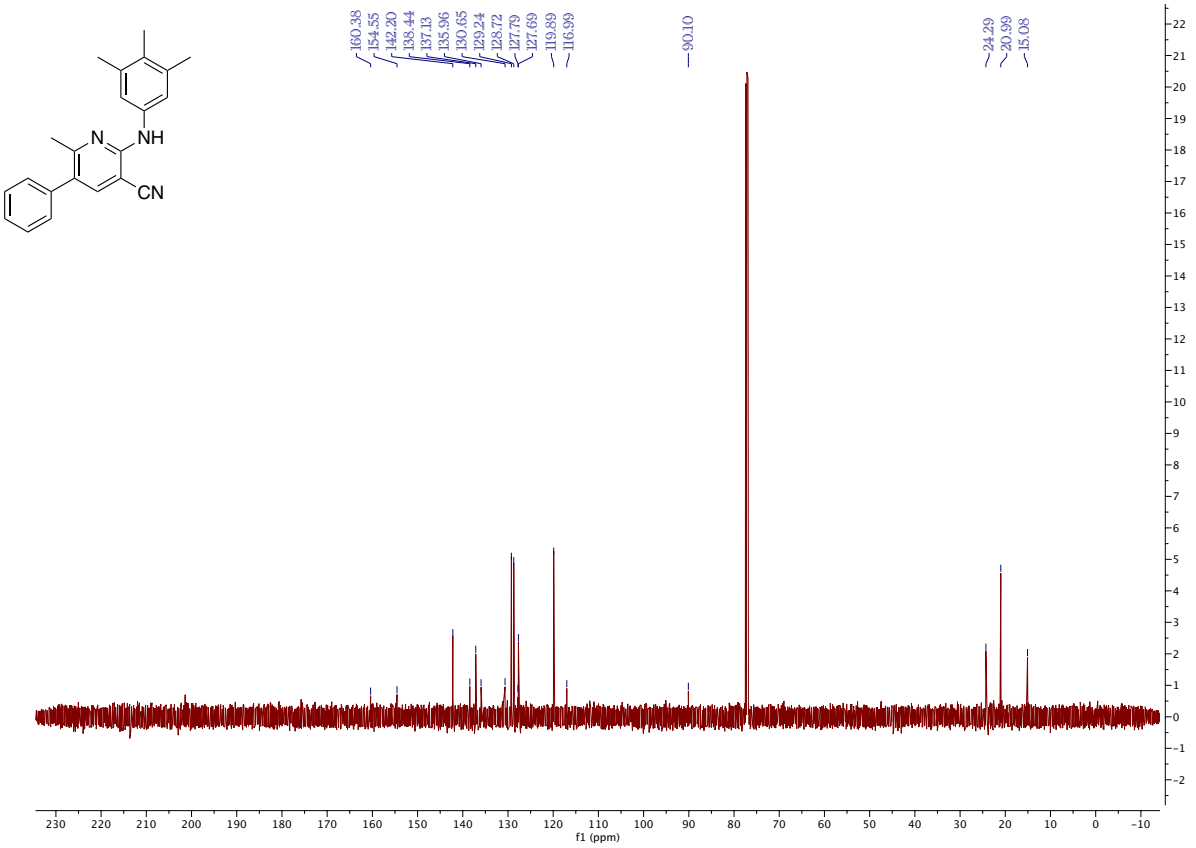

155.74
150.99
139.42
137.82
136.51
136.30
133.28
130.65
129.94
128.31
127.23
126.43
126.09
124.53
116.61
92.72
21.20
21.14
17.65
NH
N
CN
f1 (ppm)

*6-methyl-5-phenyl-2-((3,4,5-trimethylphenyl)amino)nicotinonitrile (**1p**).*

^{1}H NMR

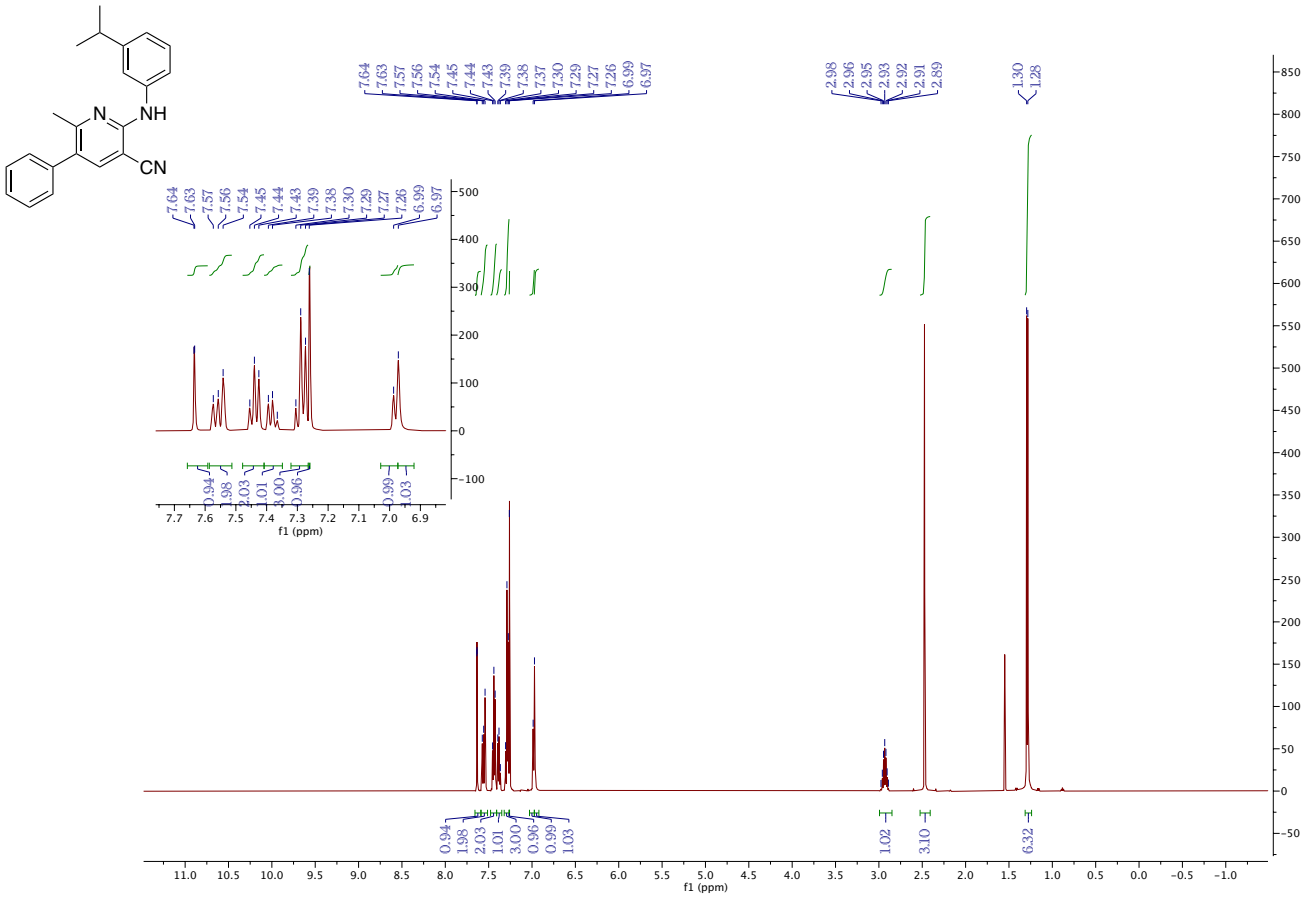


^{13}C NMR

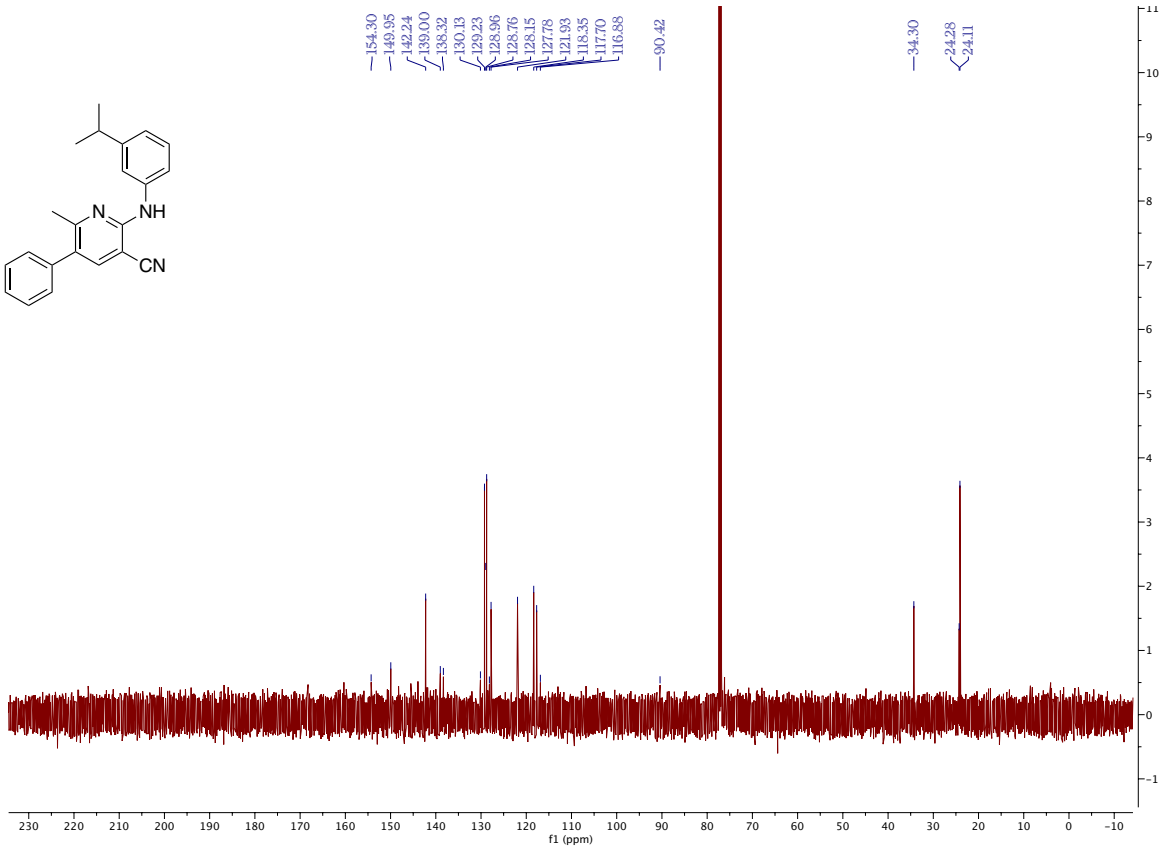

160.38
154.55
142.20
138.44
137.13
135.96
130.65
129.24
128.72
127.79
127.69
119.89
116.99
90.10
24.29
20.99
15.08
N
NH
CN
f1 (ppm)

*2-((3-isopropylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1q**).*

^{1}H NMR

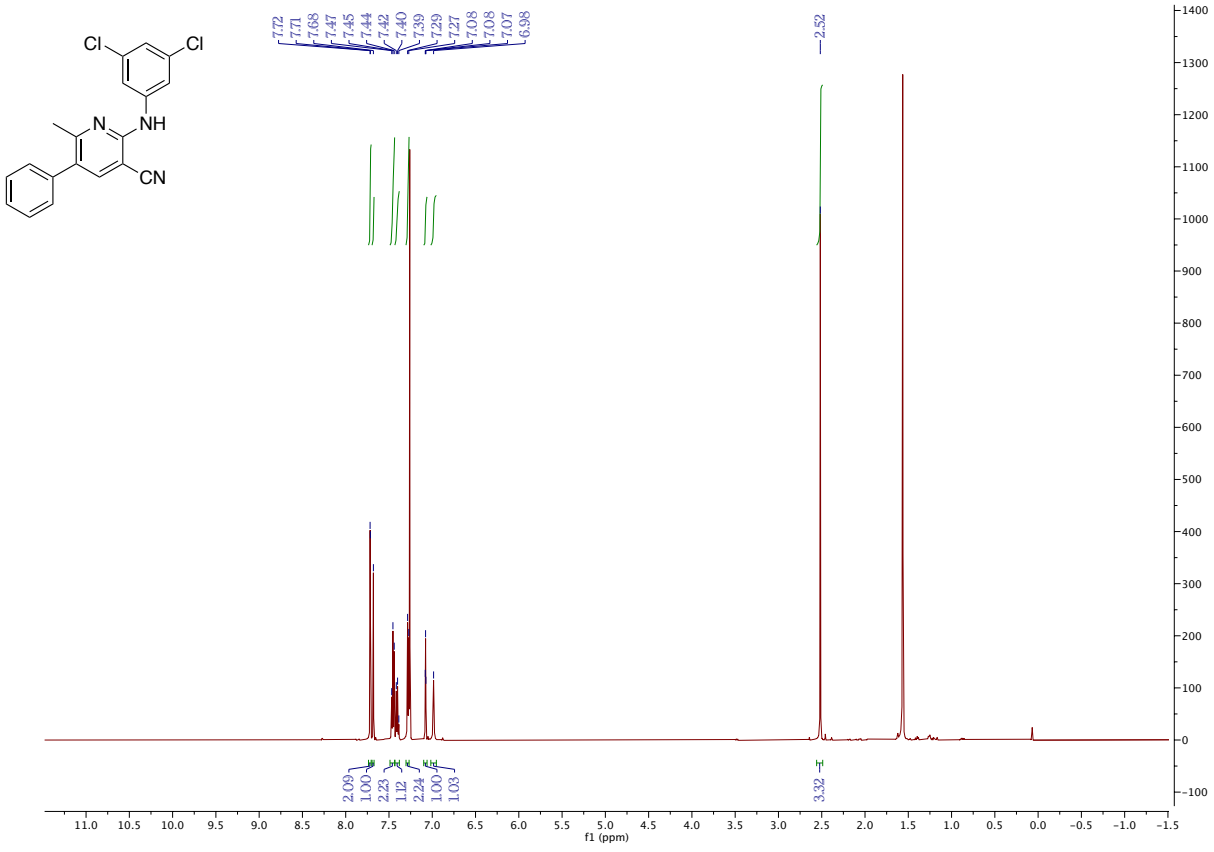


^{13}C NMR

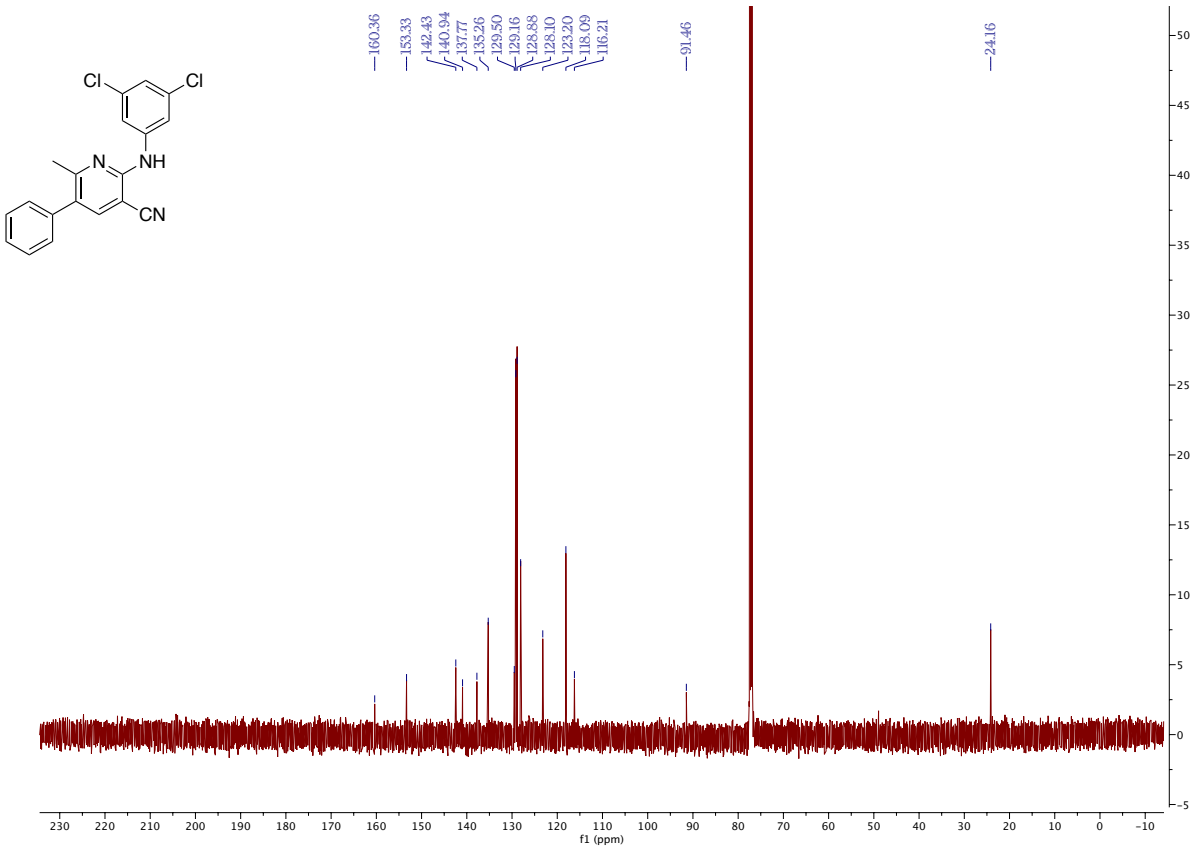

154.30
149.95
142.24
139.00
138.32
130.13
129.23
128.96
128.76
128.15
127.78
121.93
118.35
117.70
116.88
90.42
34.30
24.28
24.11
NH
N
CN
f1 (ppm)

*2-((3,5-dichlorophenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1r**).*

^{1}H NMR

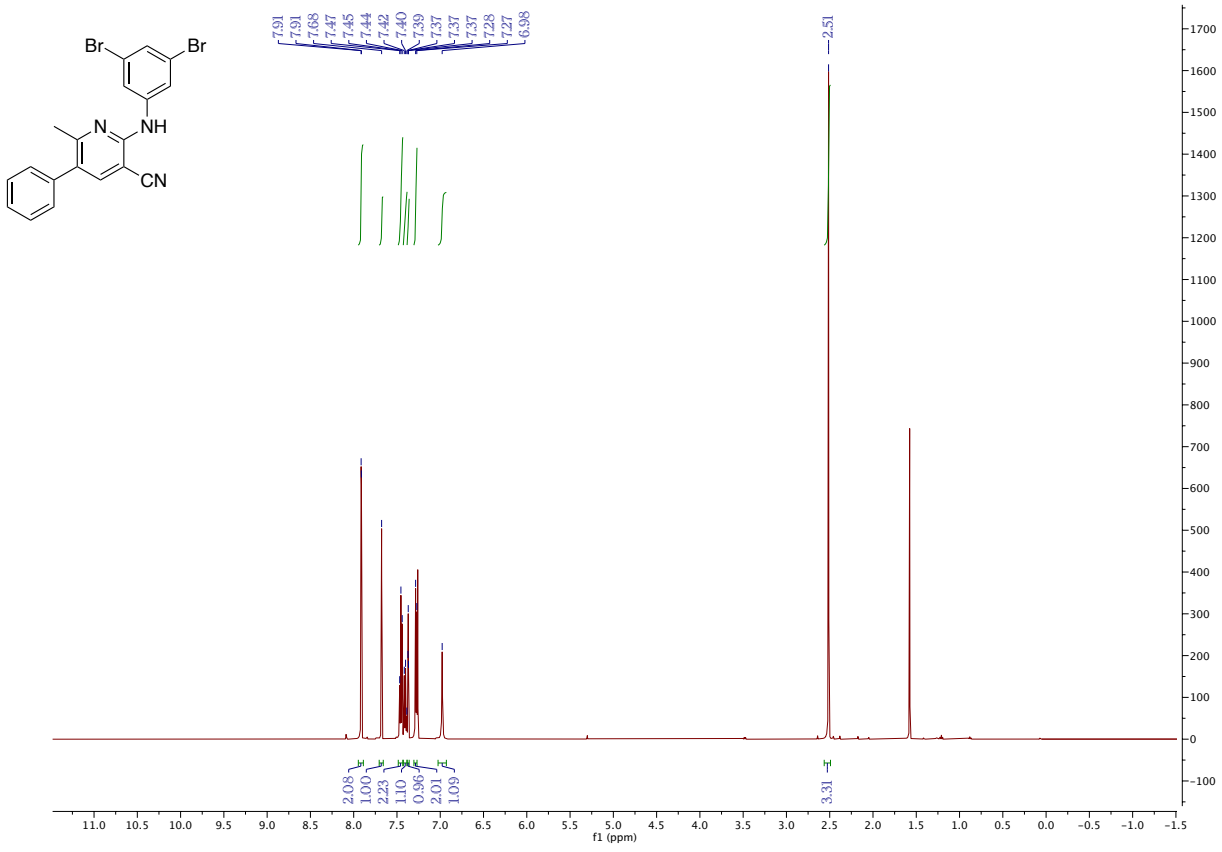


^{13}C NMR

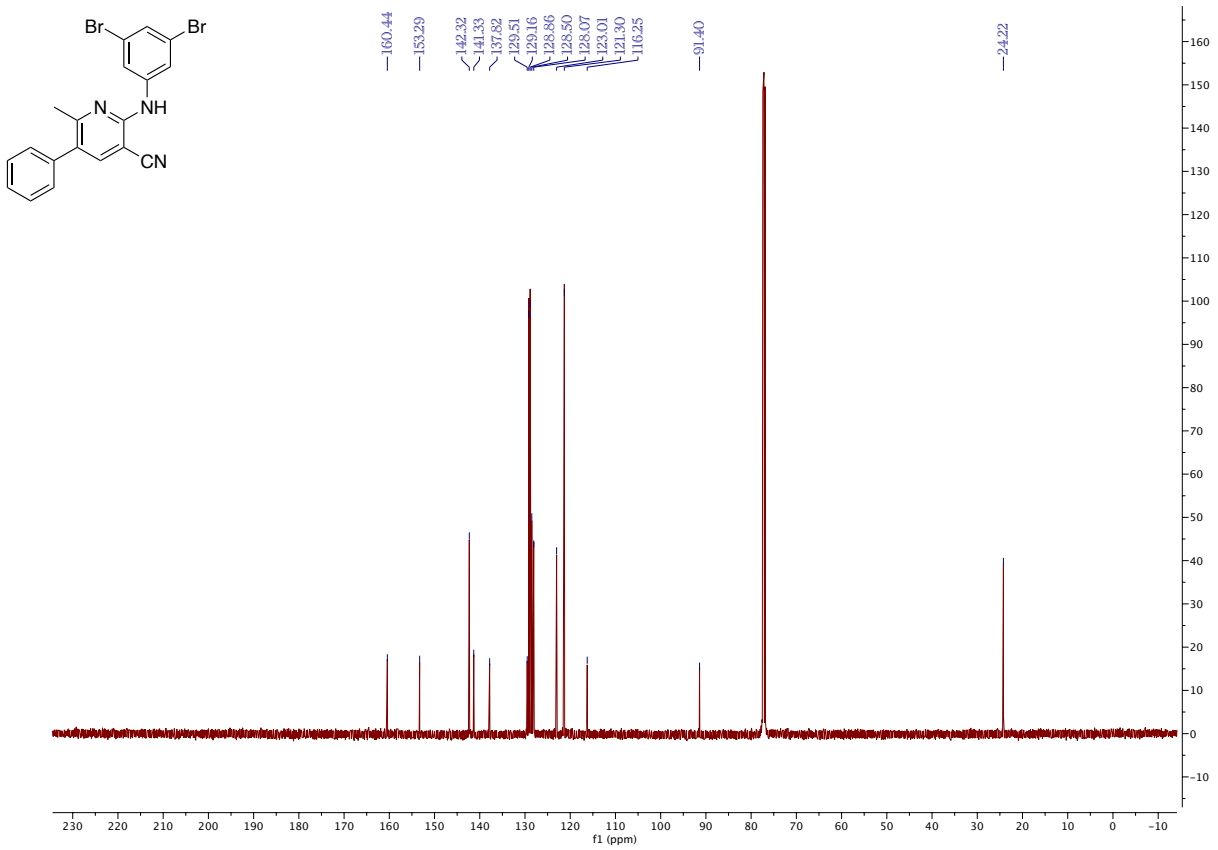

160.36
153.33
142.43
140.94
137.77
135.26
129.50
129.16
128.88
128.10
123.20
118.09
116.21
91.46
24.16
Cl
Cl
N
NH
CN
f1 (ppm)

*2-((3,5-dibromophenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1s**).*

^{1}H NMR

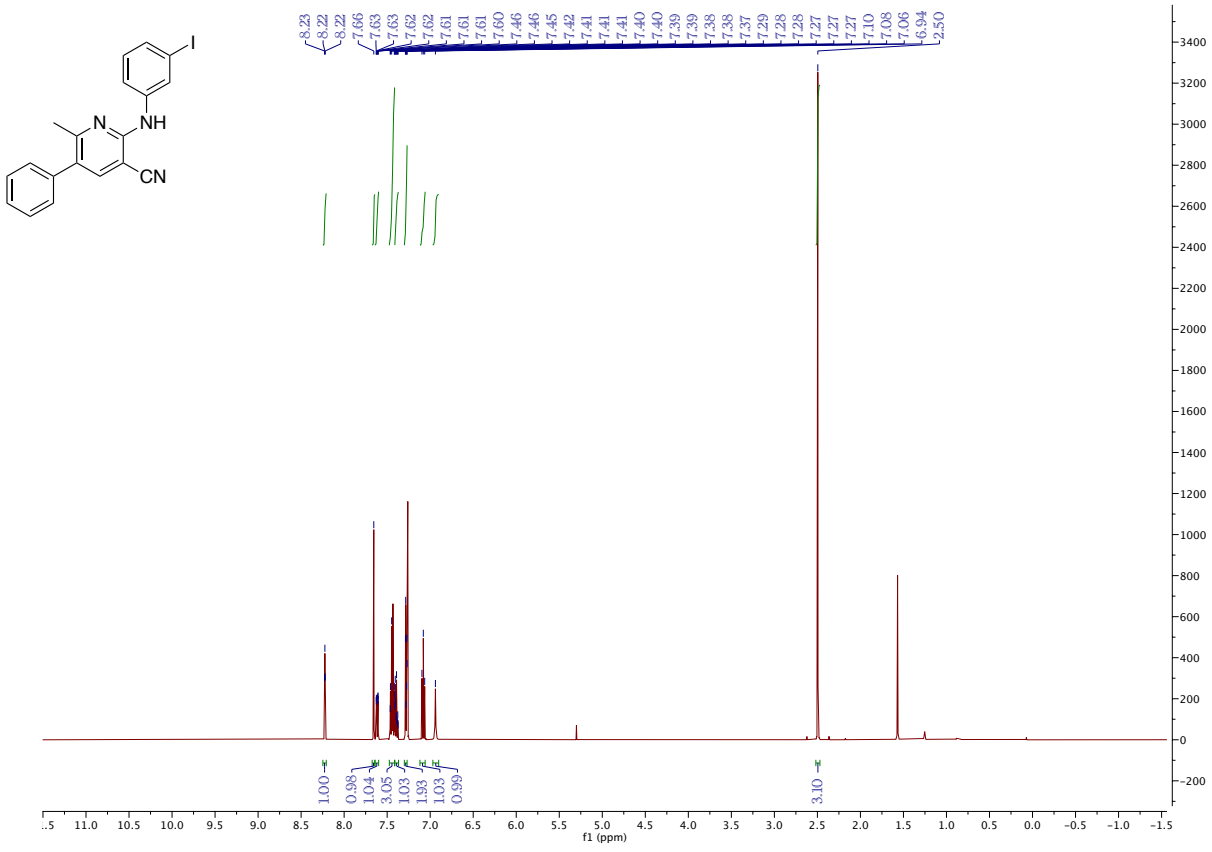


^{13}C NMR

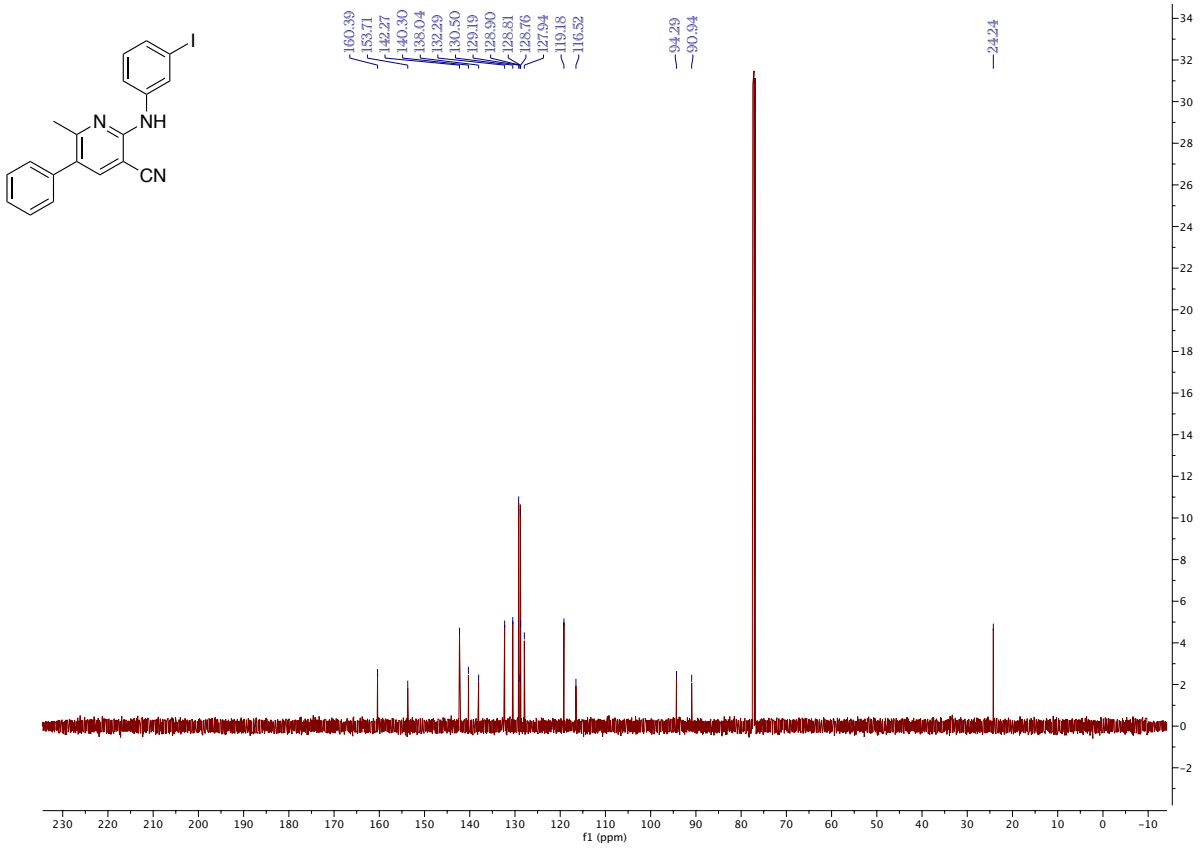

Br
Br
N
NH
CN
160.44
153.29
142.32
141.33
137.62
129.51
129.16
128.86
128.50
128.07
123.01
121.30
116.25
91.40
24.22
f1 (ppm)

*2-((3-iodophenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1t**).*

^{1}H NMR

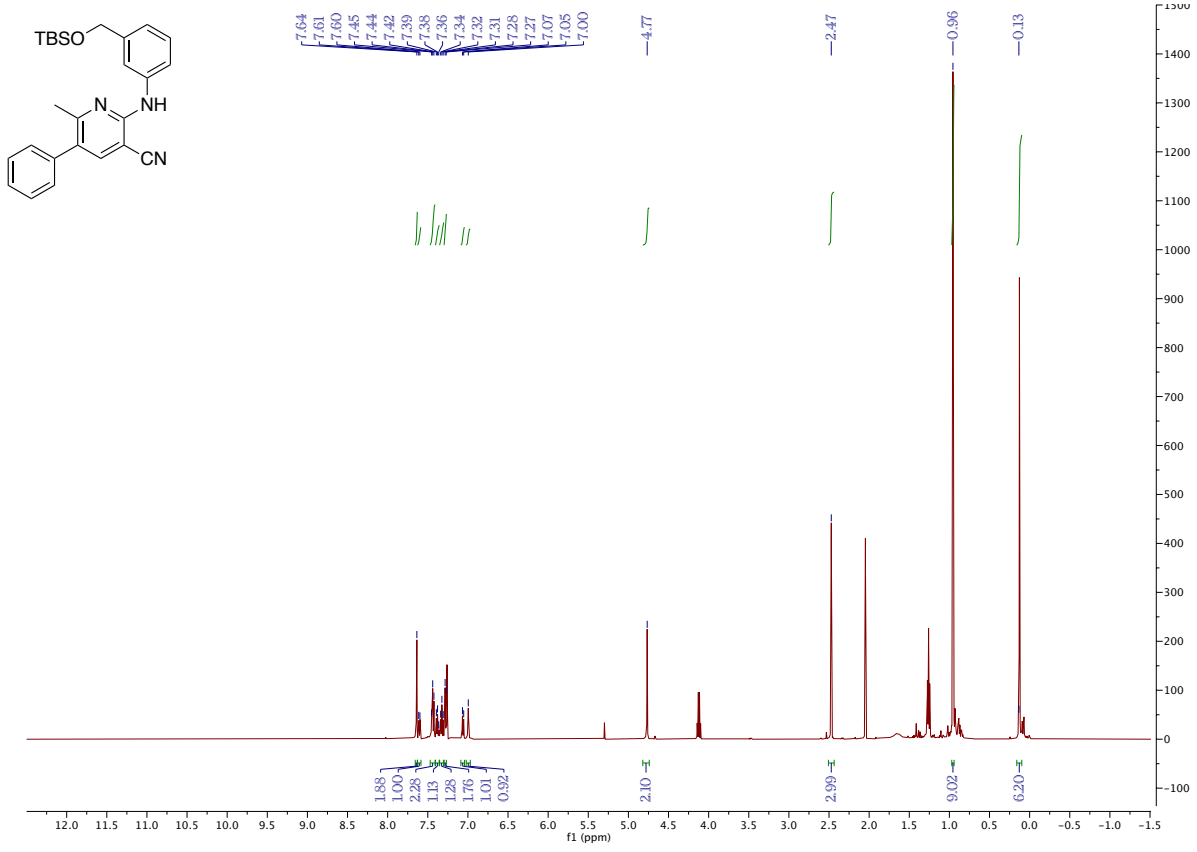


^{13}C NMR


160.39
153.71
142.27
140.30
138.04
132.29
130.50
129.19
128.90
128.81
128.76
127.94
119.18
116.52
94.29
90.94
24.24
I
NH
N
CN
f1 (ppm)

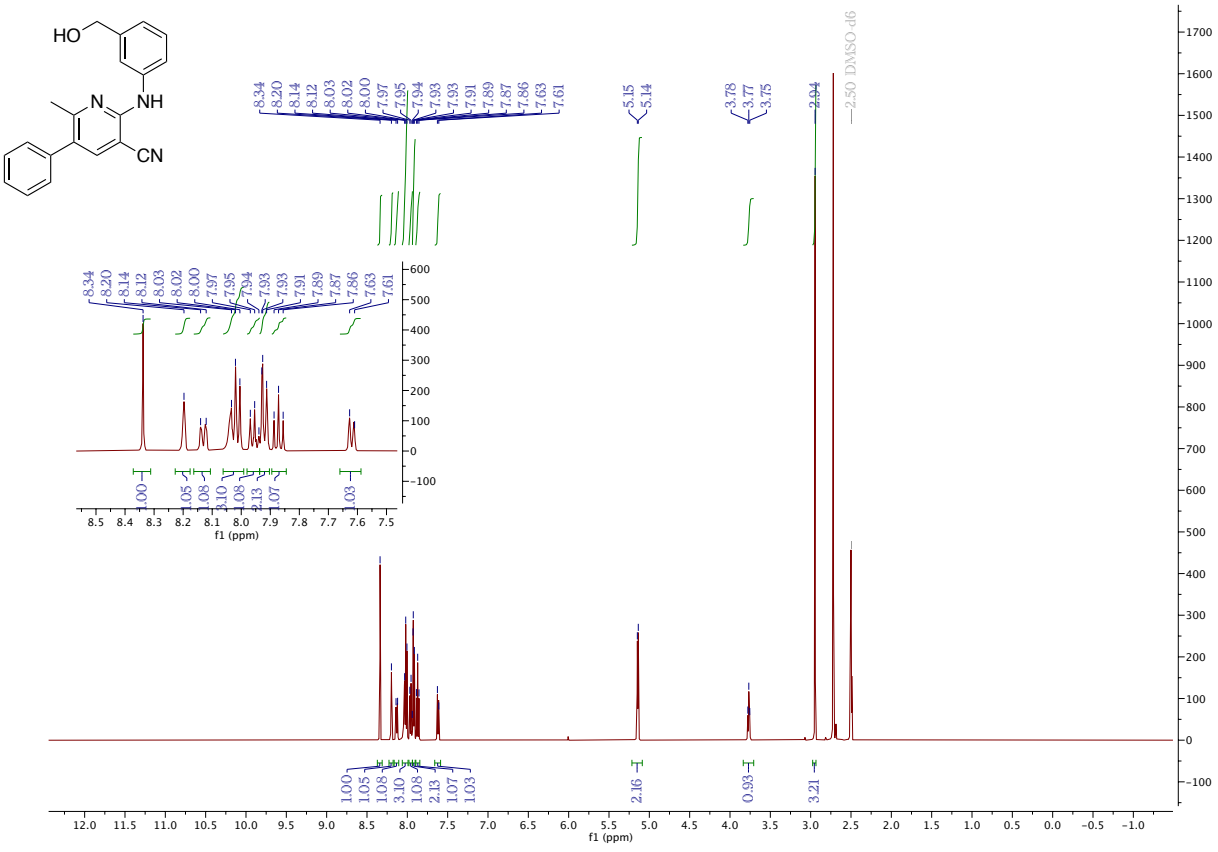
*2-((3-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1u-I**).*

^{1}H NMR

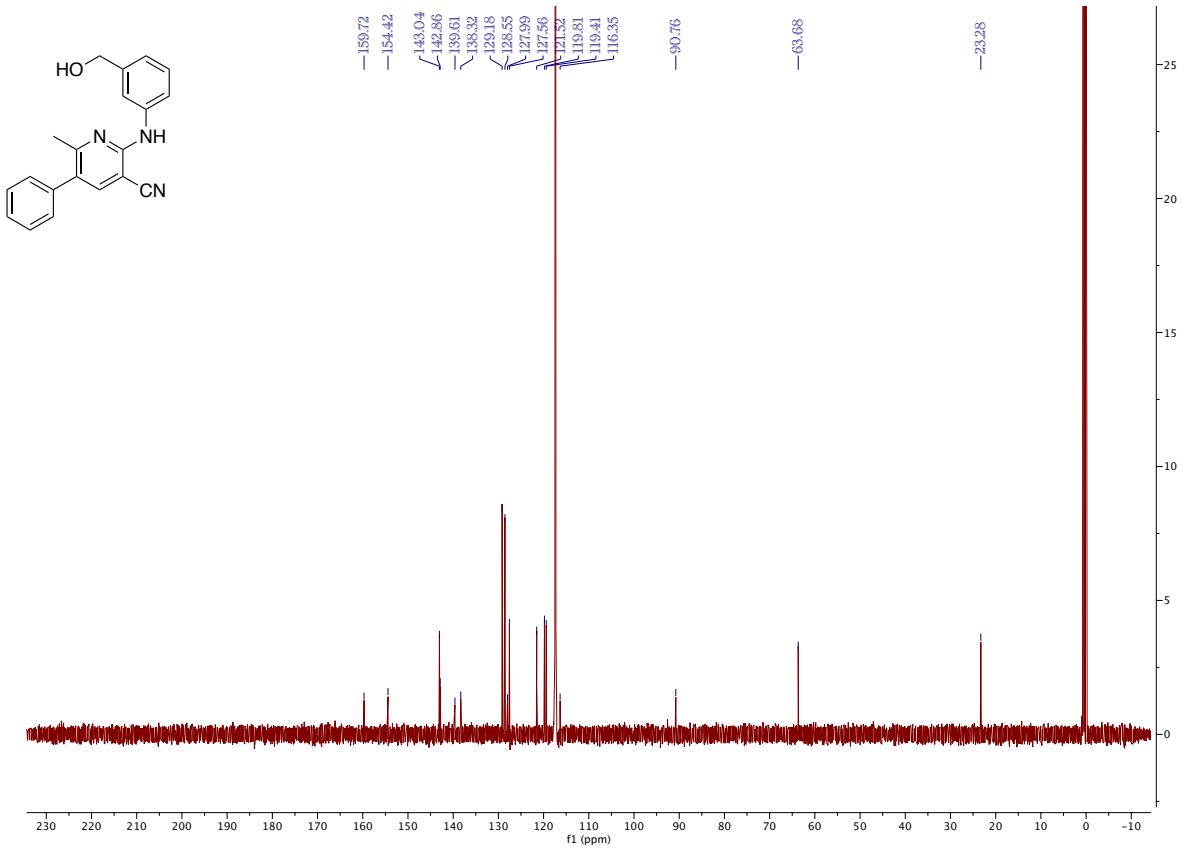


*2-((3-(hydroxymethyl)phenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1u**).*

^{1}H NMR

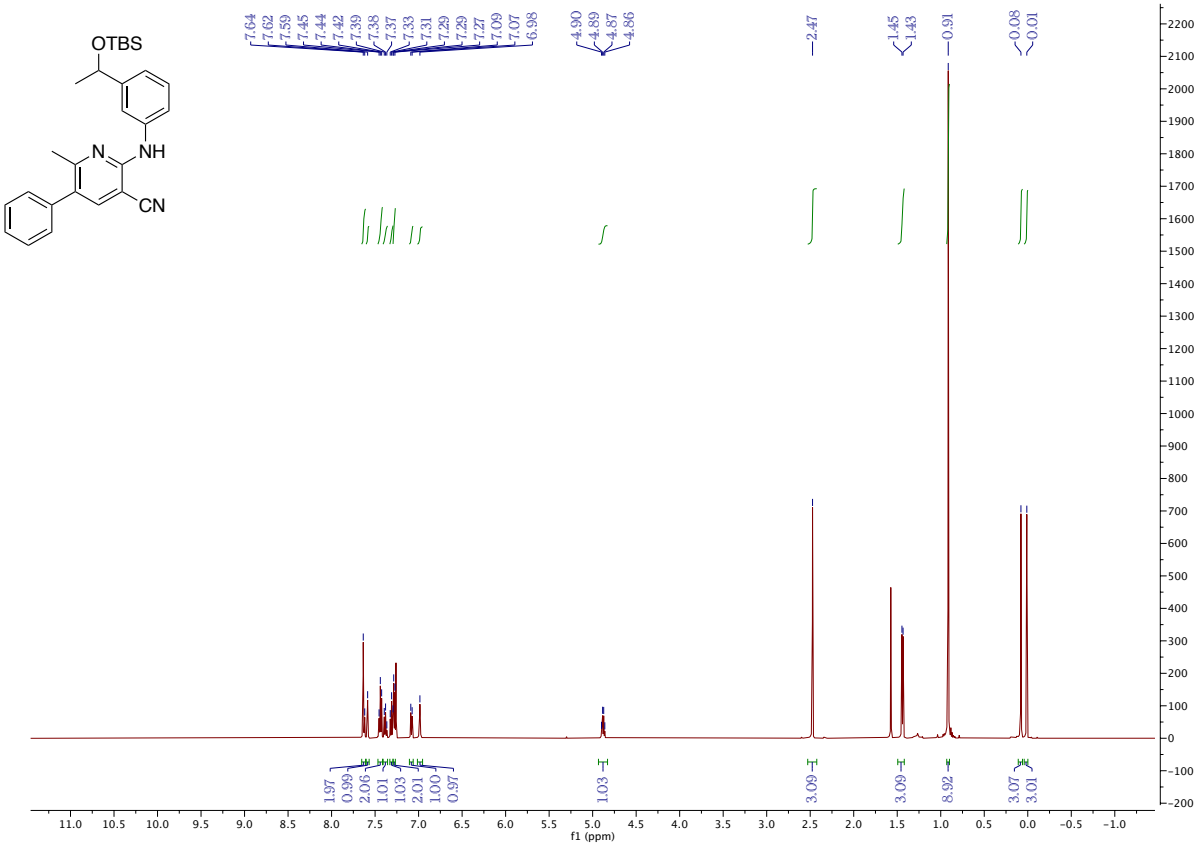


^{13}C NMR

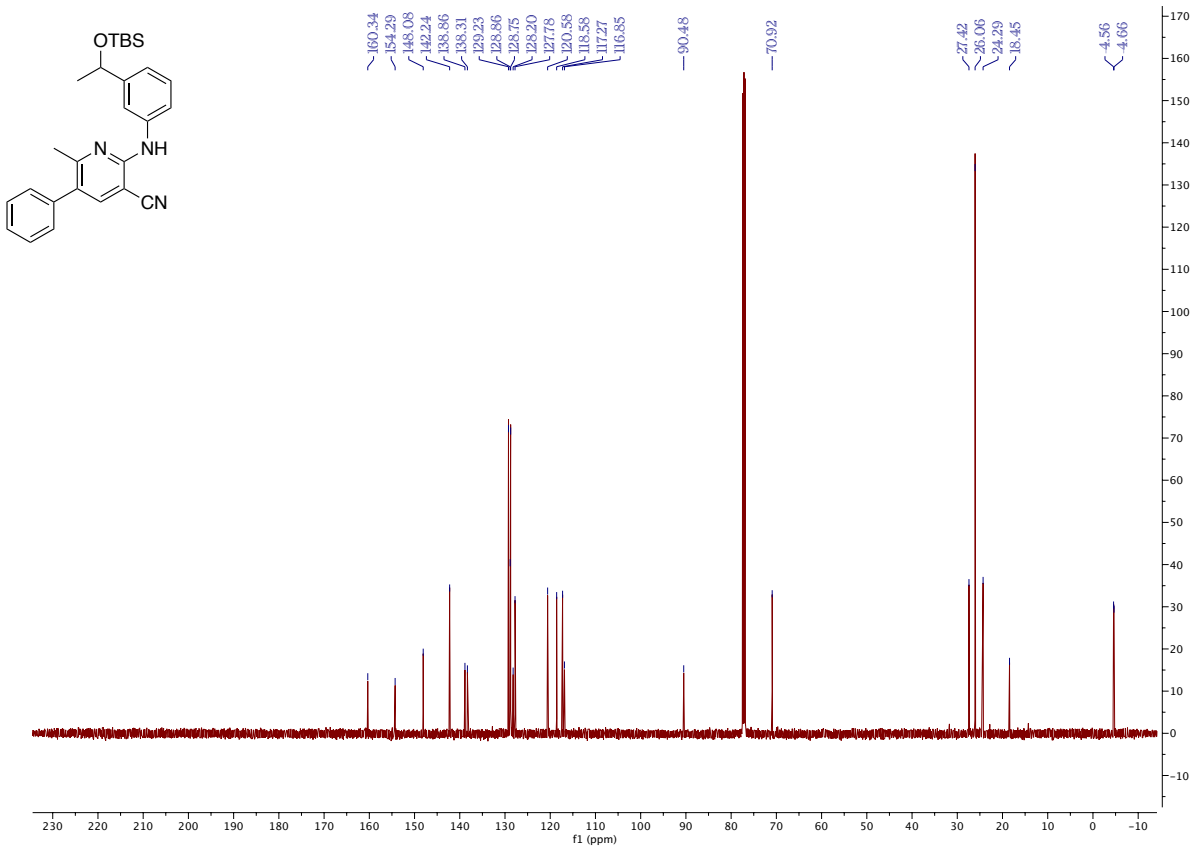

HO
N
NH
CN
159.72
154.42
143.04
142.86
139.61
138.32
129.18
128.55
127.99
127.56
121.52
119.81
119.41
116.35
90.76
63.68
23.28
f1 (ppm)

*2-((3-(1-((tert-butyldimethylsilyl)oxy)ethyl)phenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1v-I**).*

^{1}H NMR

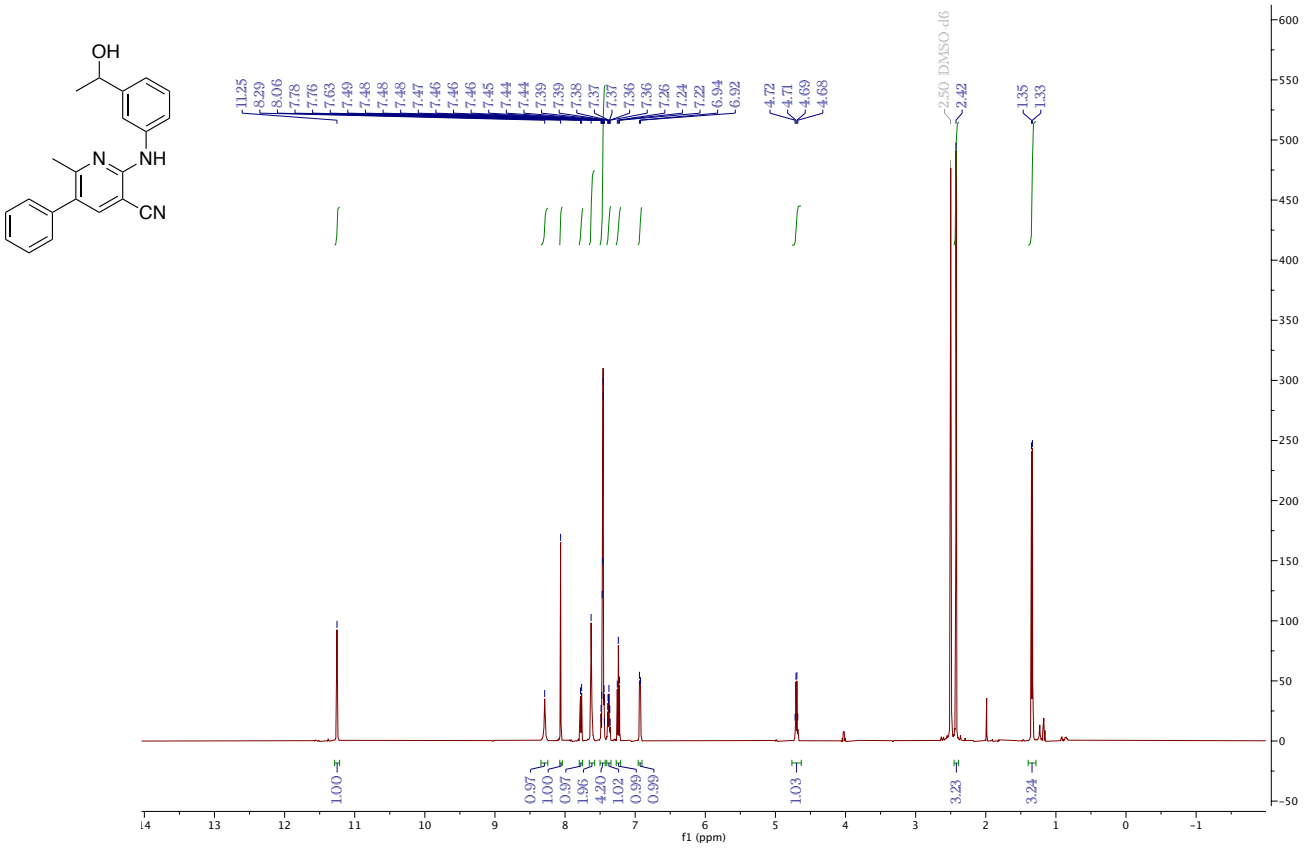


^{13}C NMR

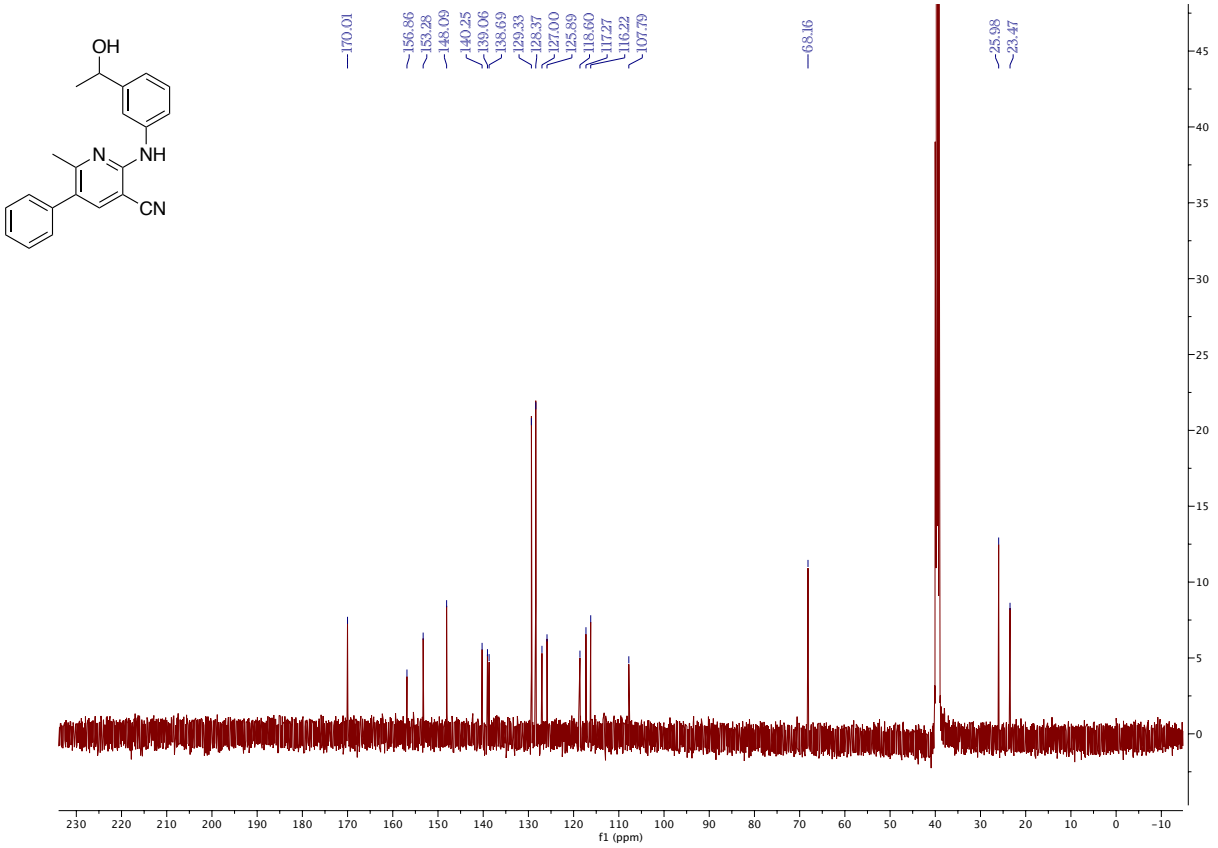

OTBS
N
NH
CN
160.34
154.29
148.08
142.24
138.86
138.31
129.23
128.86
128.75
128.20
127.78
120.58
118.58
117.27
116.85
90.48
70.92
27.42
26.06
24.29
18.45
-4.56
-4.66
f1 (ppm)

*2-((3-(1-hydroxyethyl)phenyl)amino)-6-methyl-5-phenylnicotinonitrile (**1v**).*

^{1}H NMR

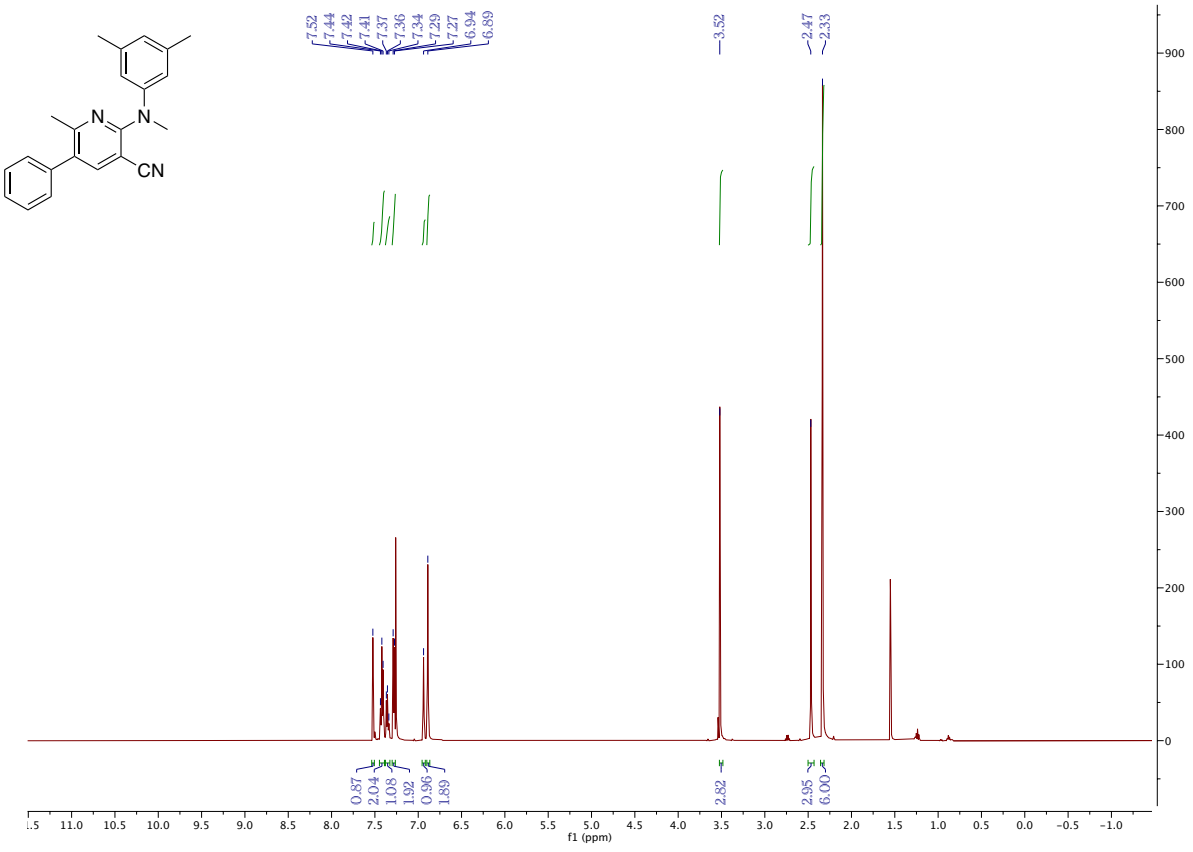


^{13}C NMR

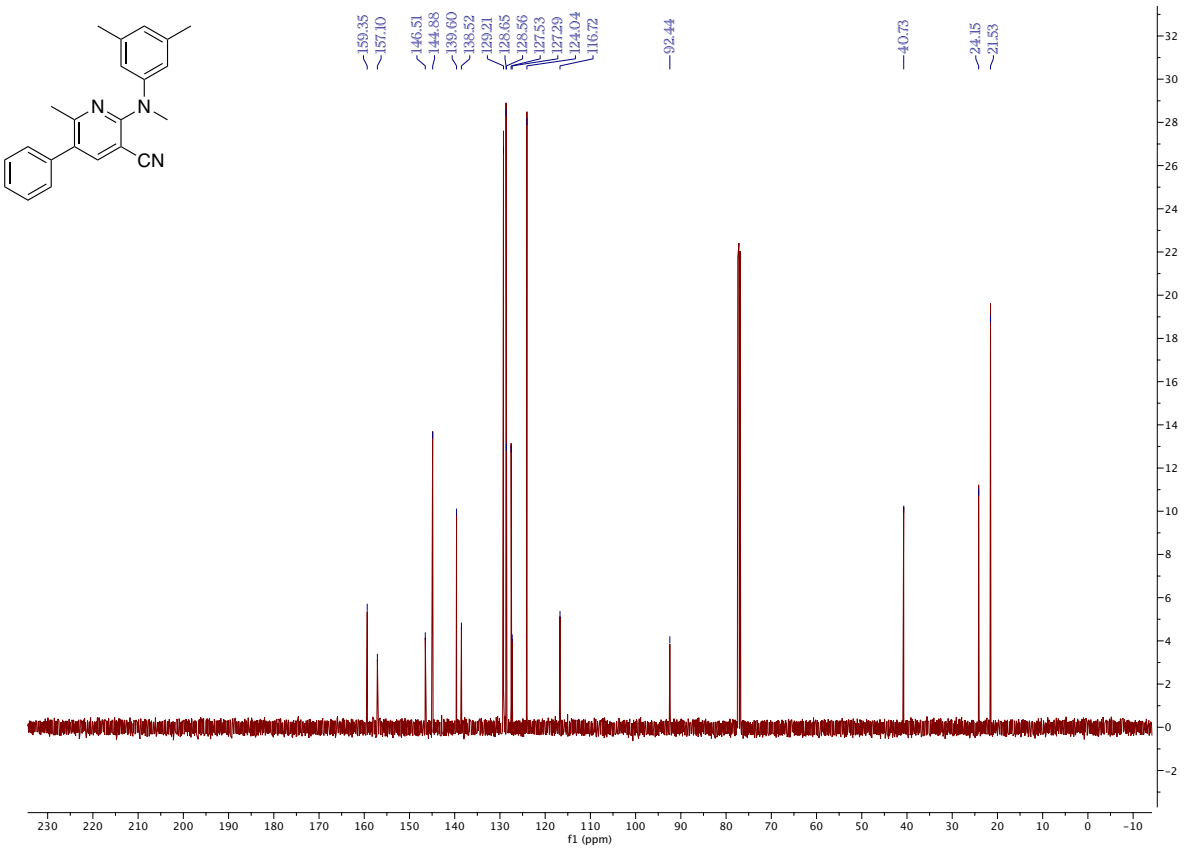

OH
N
NH
CN
170.01
156.86
153.28
148.09
140.25
139.06
138.69
129.33
128.37
127.00
125.89
118.60
117.27
116.22
107.79
68.16
25.98
23.47
f1 (ppm)

*2-((3,5-dimethylphenyl)(methyl)amino)-6-methyl-5-phenylnicotinonitrile (**2a**).*

^{1}H NMR

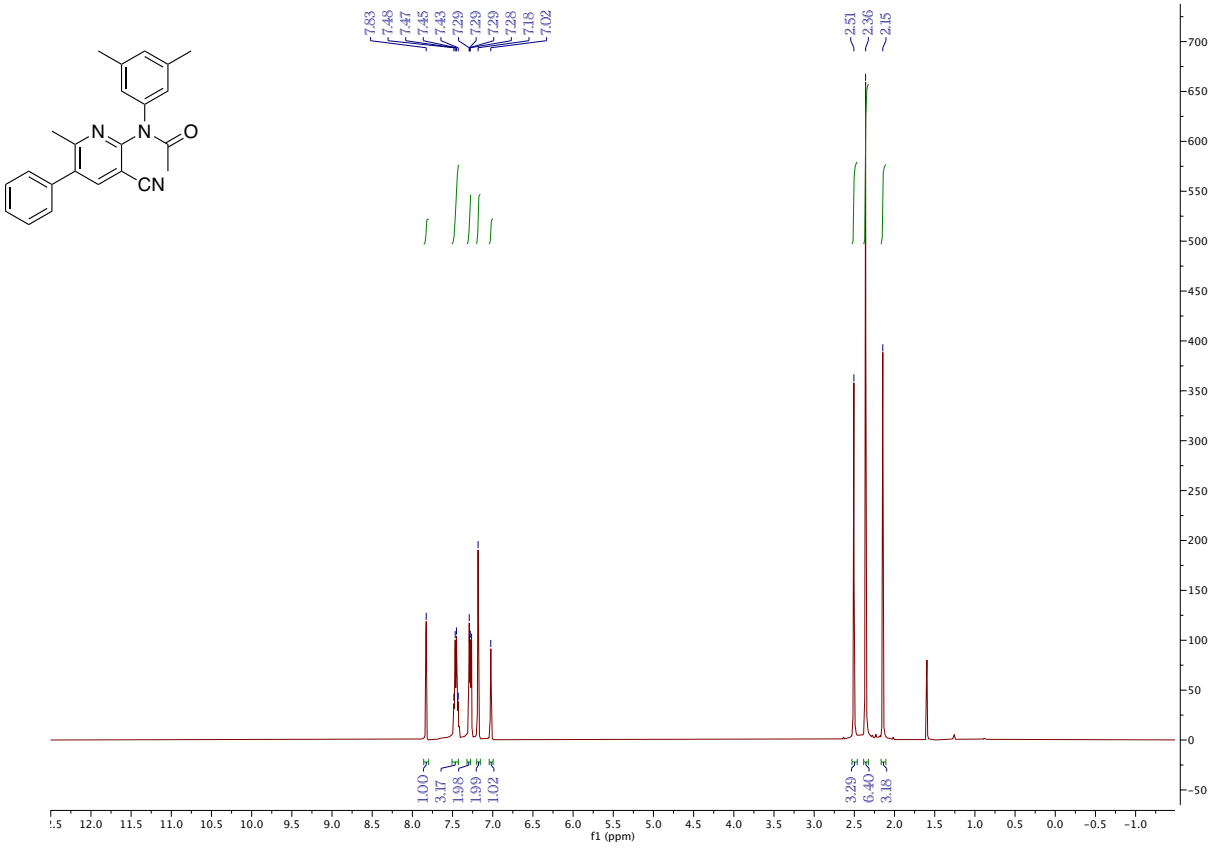


^{13}C NMR

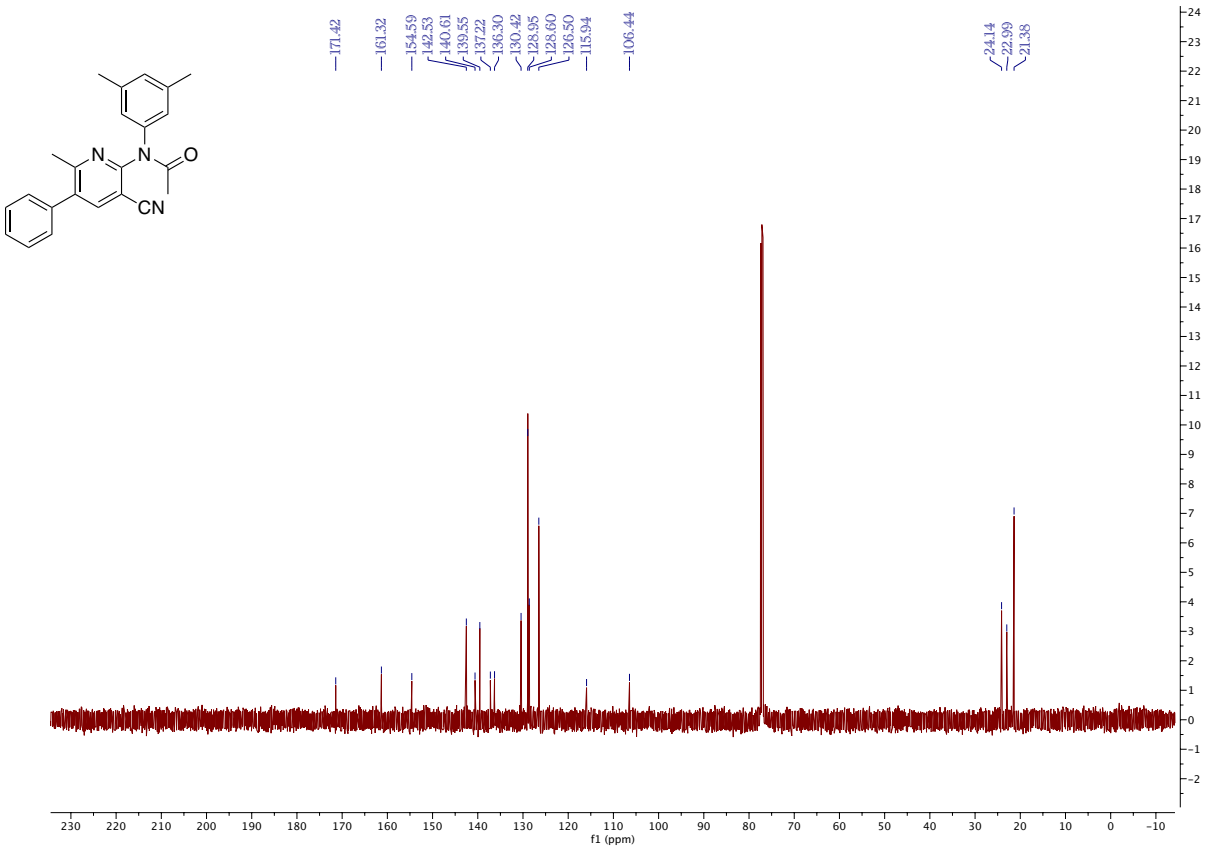

159.35
157.10
146.51
144.88
139.60
138.52
129.21
128.65
128.56
127.53
127.29
124.04
116.72
92.44
40.73
24.15
21.53
N
N
CN
f1 (ppm)

*N-(3-cyano-6-methyl-5-phenylpyridin-2-yl)-N-(3,5-dimethylphenyl)acetamide (**2b**).*

^{1}H NMR

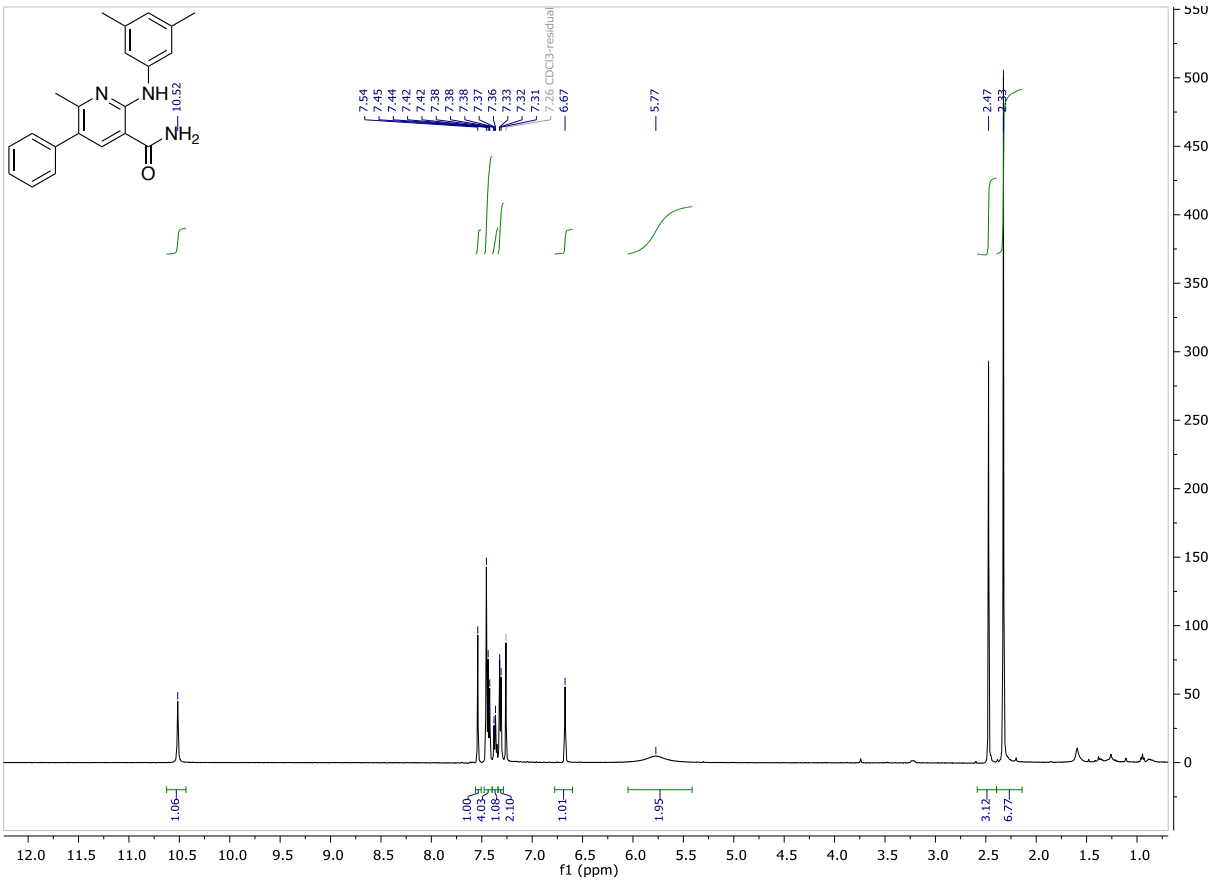


^{13}C NMR

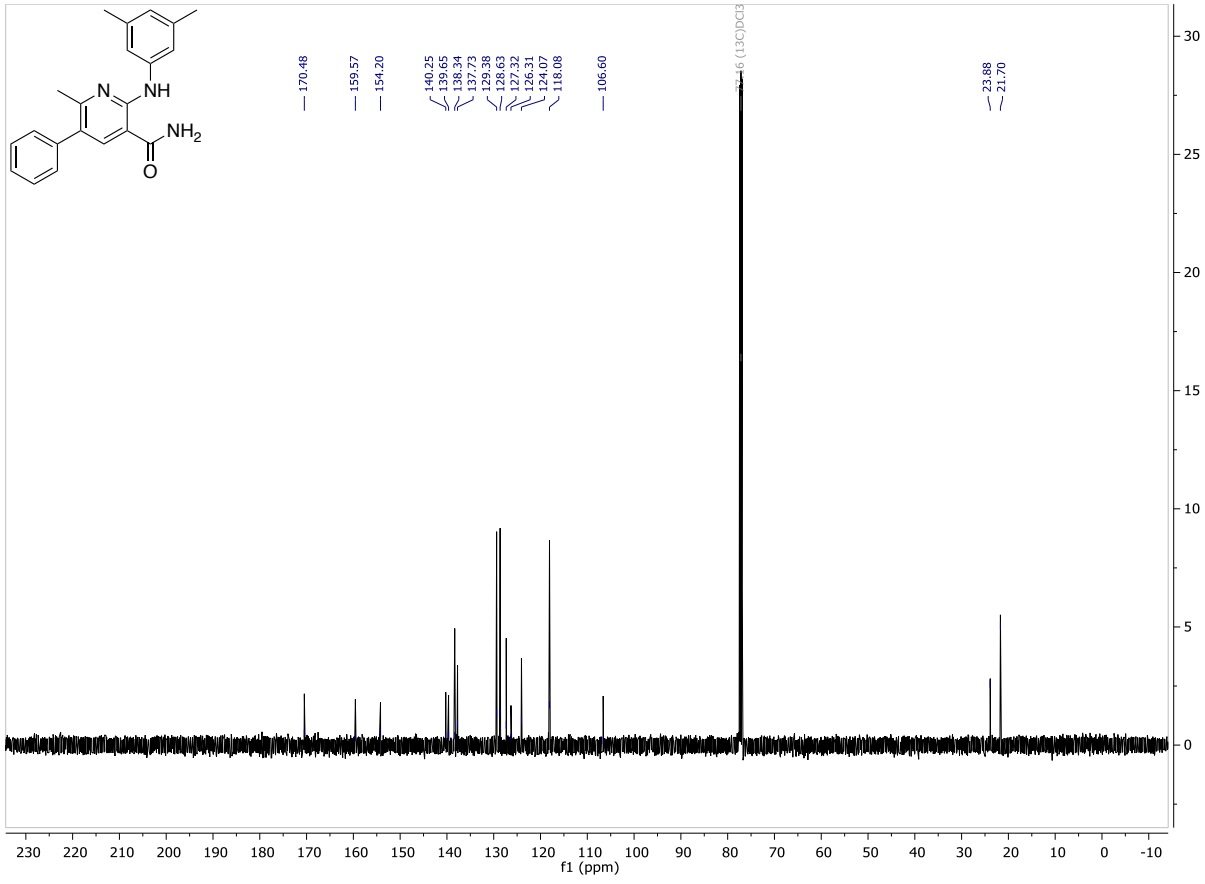

171.42
161.32
154.59
142.53
140.61
139.55
137.22
136.30
130.42
128.95
128.60
126.50
115.94
106.44
24.14
22.99
21.38
N
N
O
CN
f1 (ppm)

*2-((3,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinamide (**2c**).*

^{1}H NMR

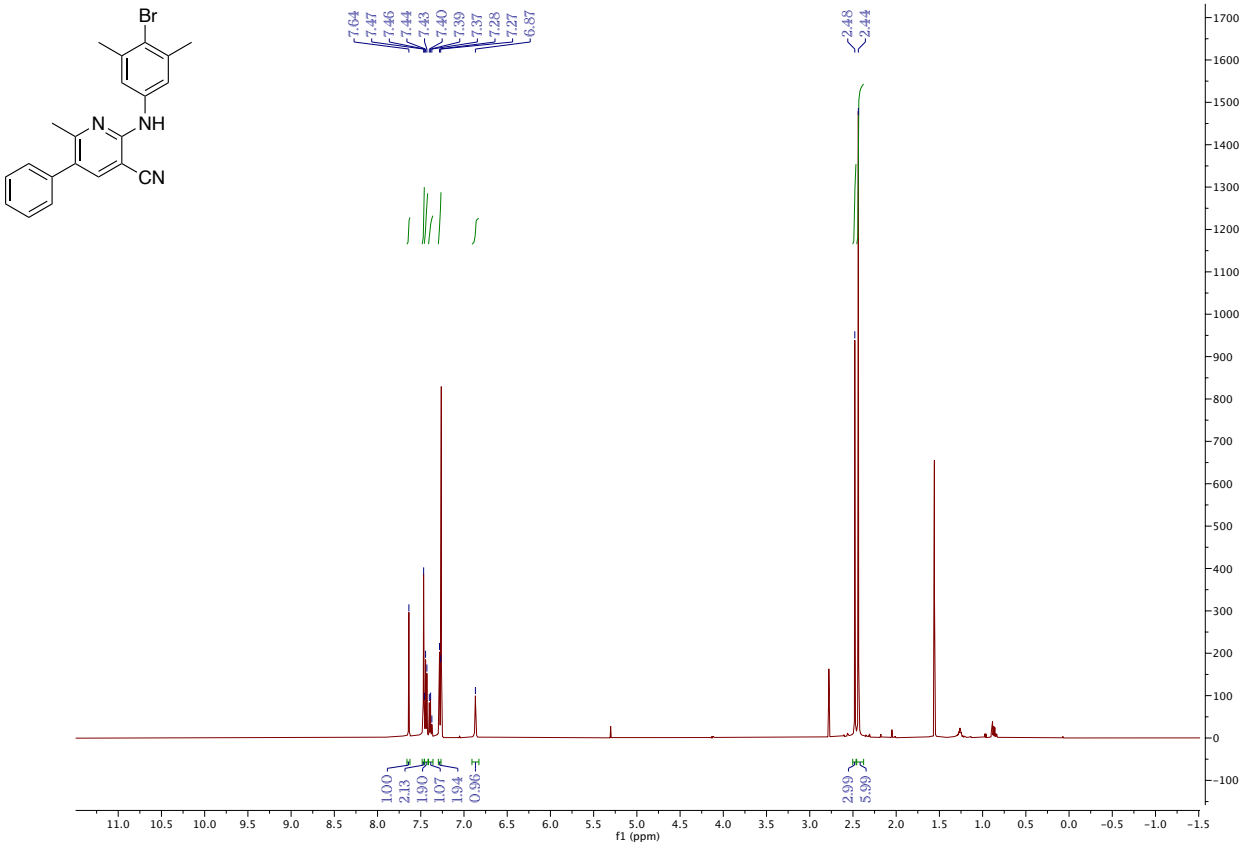


^{13}C NMR

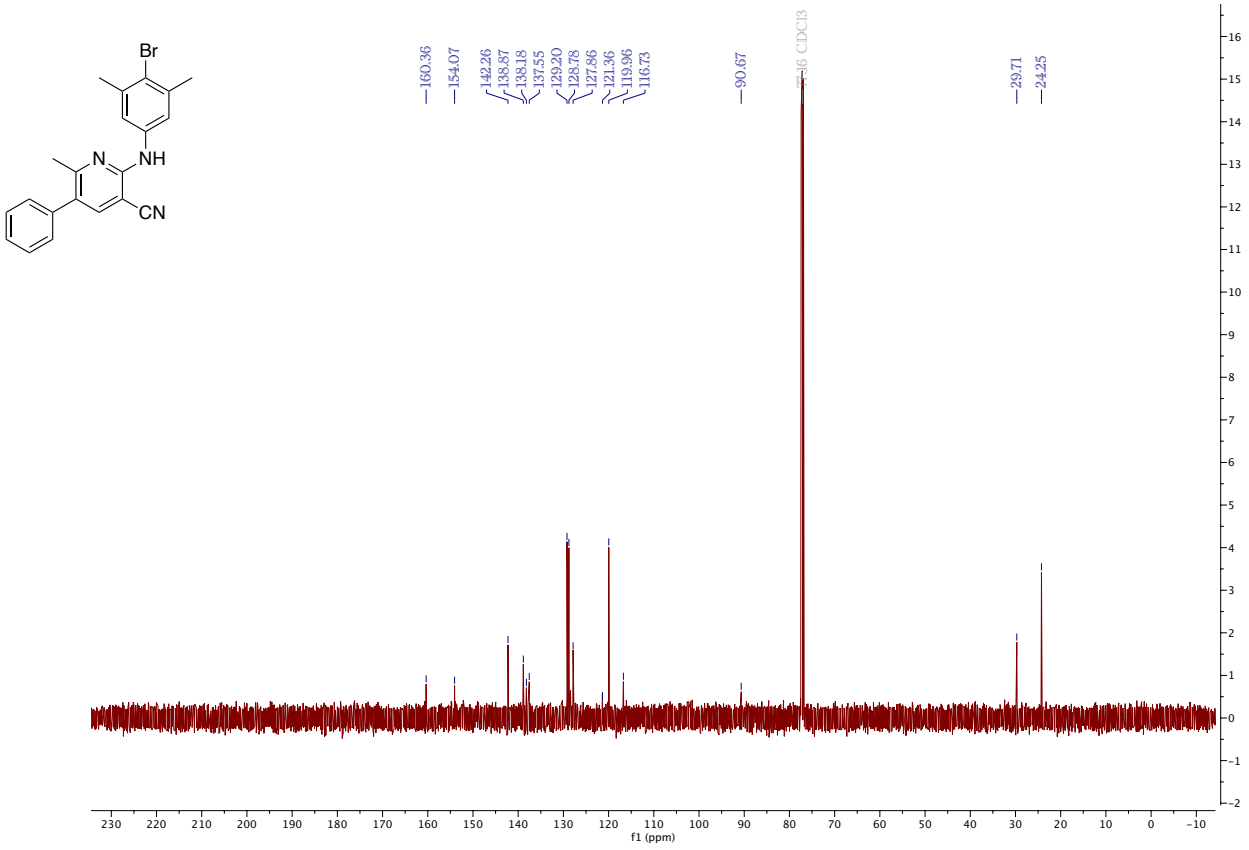

NH
N
NH2
O
170.48
159.57
154.20
140.25
139.65
138.34
137.73
129.38
128.63
127.32
126.31
124.07
118.08
106.60
77.16 (13C)CDCl3
23.88
21.70
f1 (ppm)

*2-((4-bromo-3,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (**2d**).*

^{1}H NMR

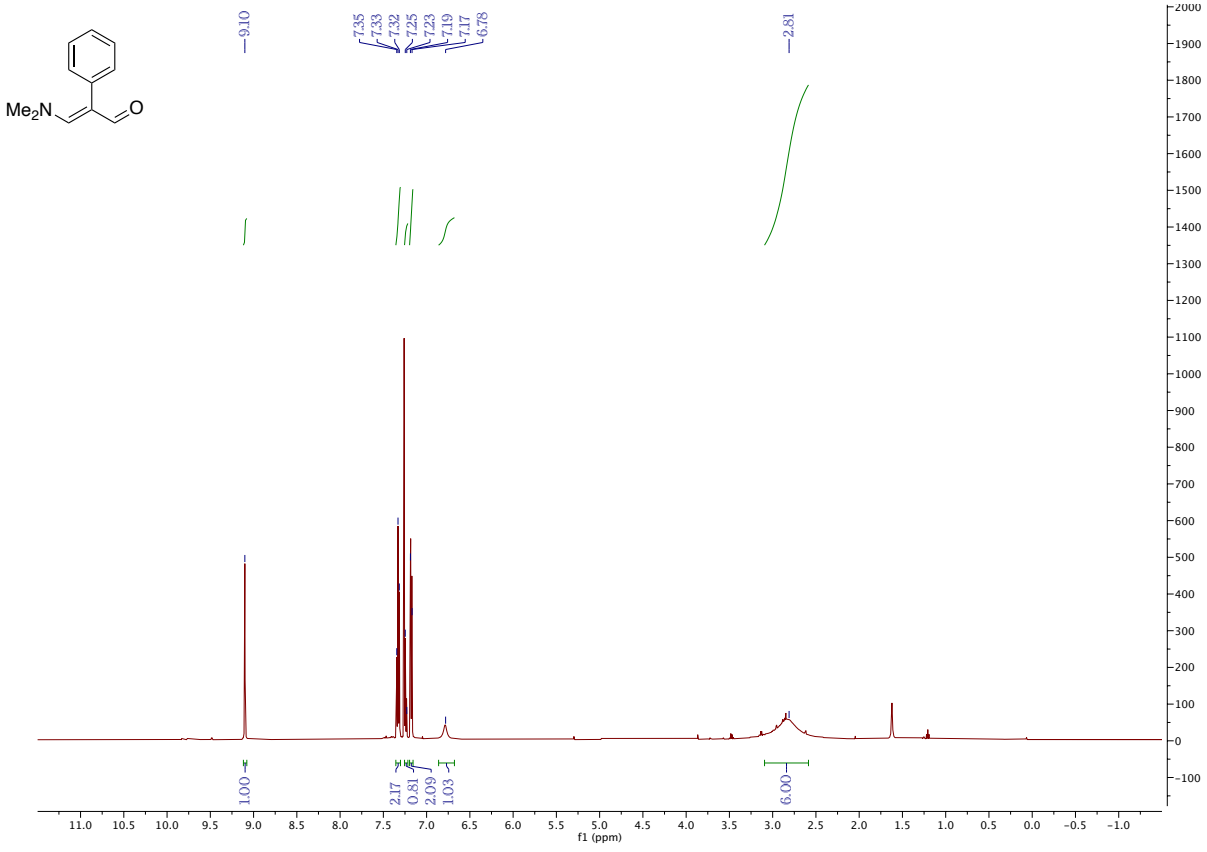


^{13}C NMR

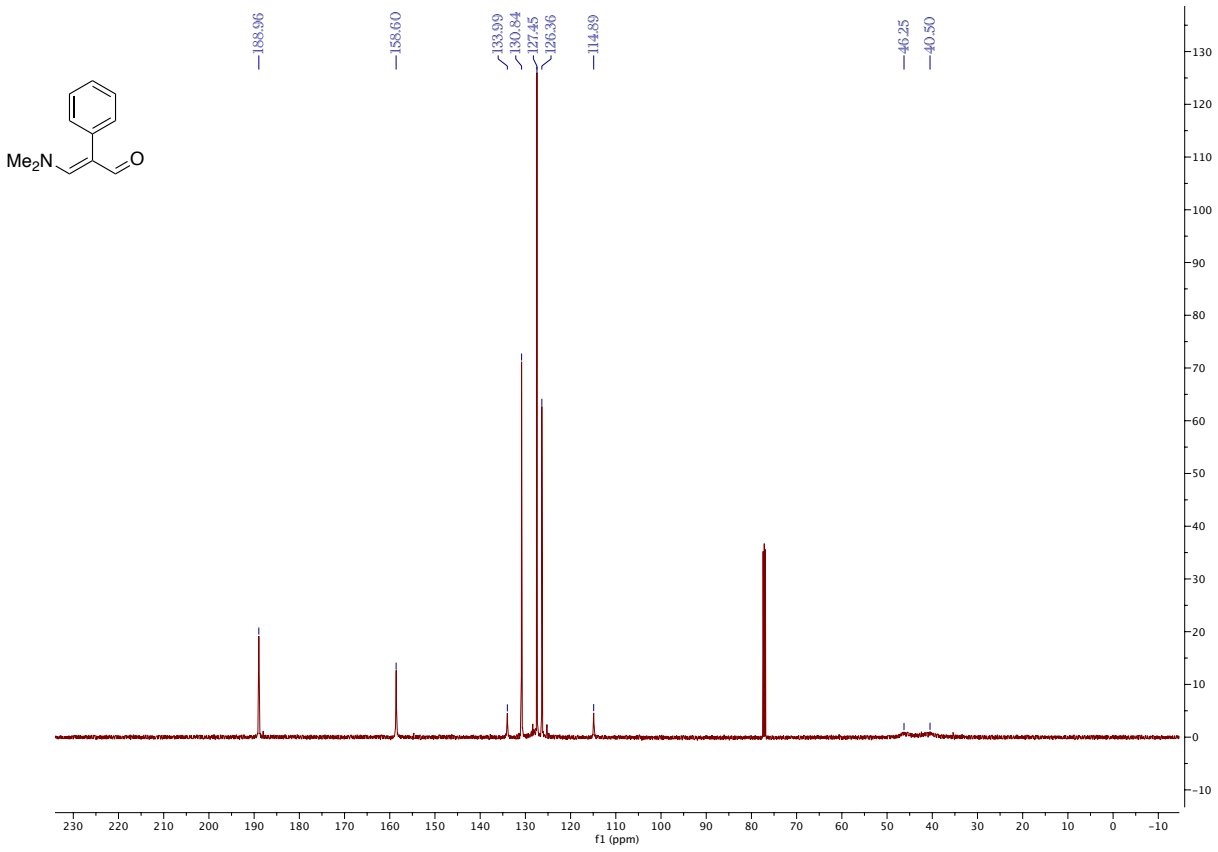

Br
N
NH
CN
160.36
154.07
142.26
138.87
138.18
137.55
129.20
128.78
127.86
121.36
119.96
116.73
90.67
77.46 CDCl3
29.71
24.25
f1 (ppm)

*3-(dimethylamino)-2-phenylacrylaldehyde (**3-I**).*

^{1}H NMR

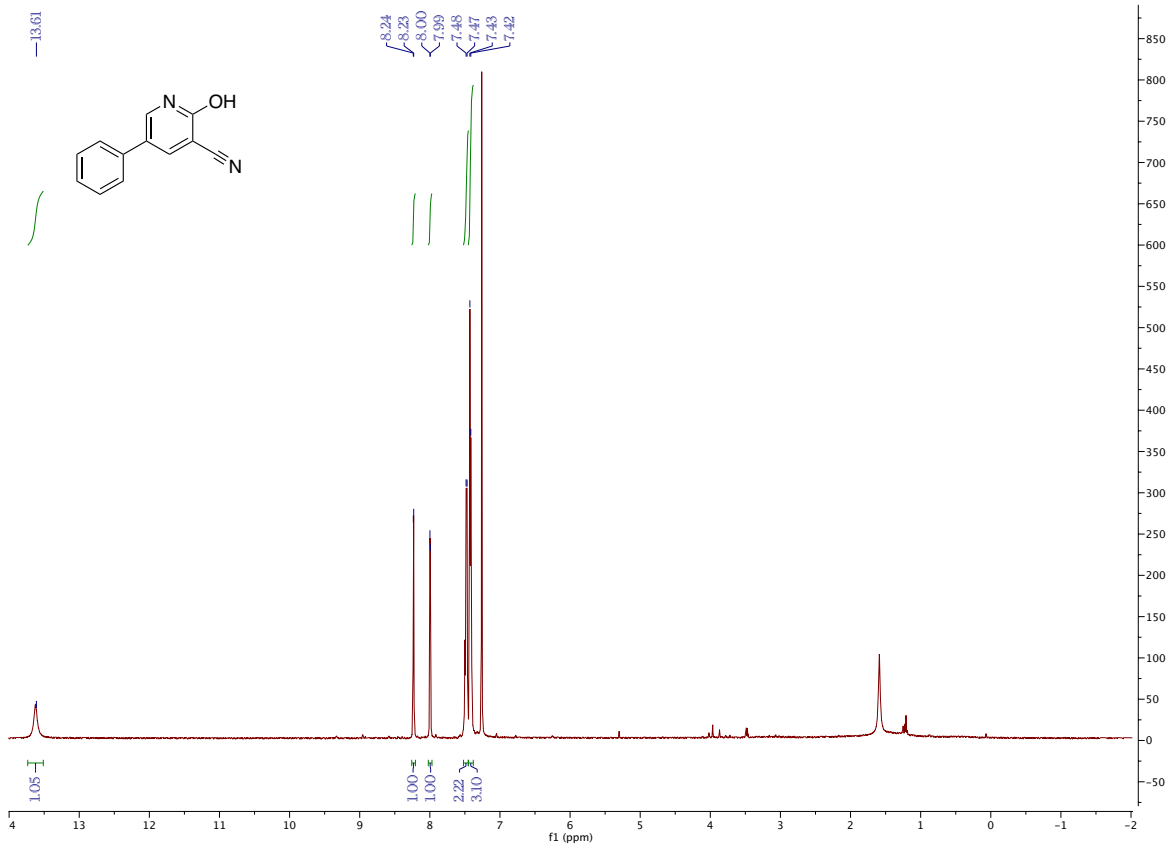


^{13}C NMR

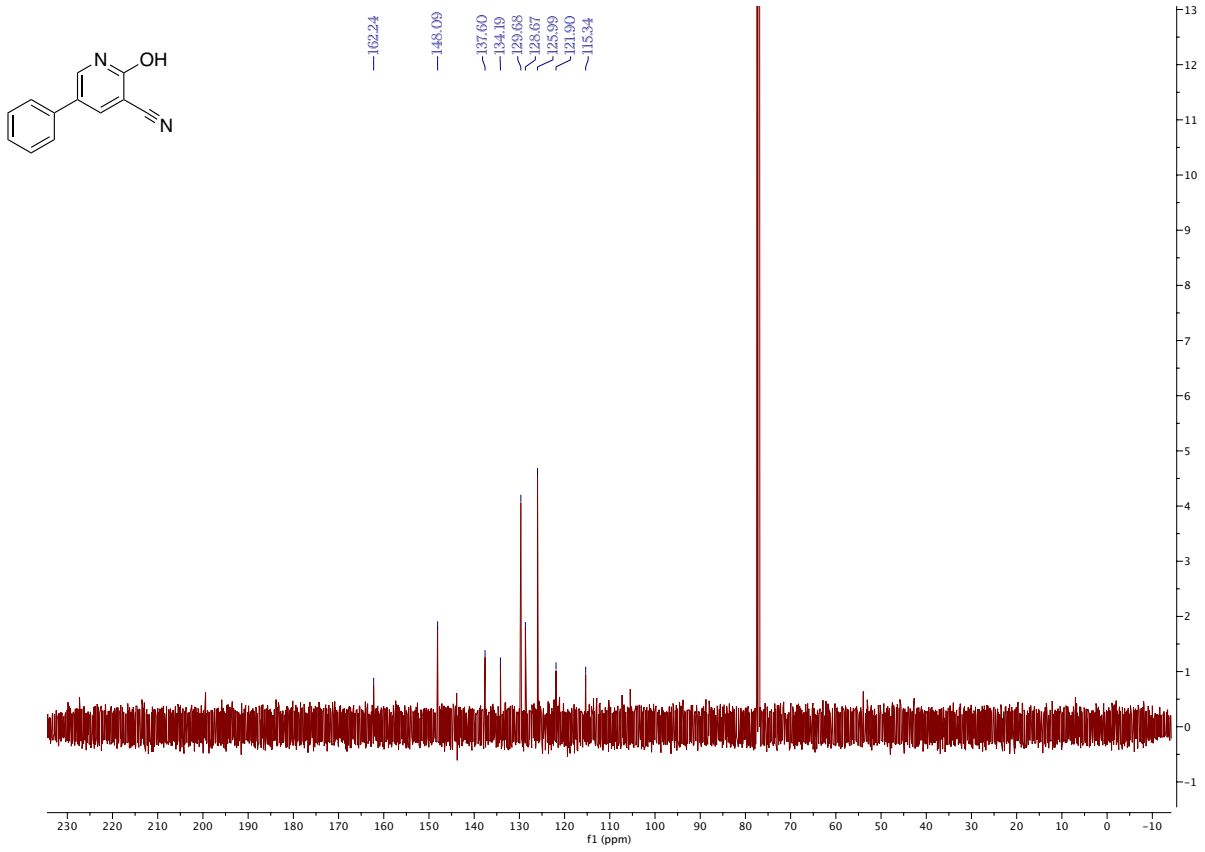

188.96
158.60
133.99
130.84
127.45
126.36
114.89
46.25
40.50
Me2N
O
f1 (ppm)

*2-hydroxy-5-phenylnicotinonitrile (**3-II**).*

^{1}H NMR

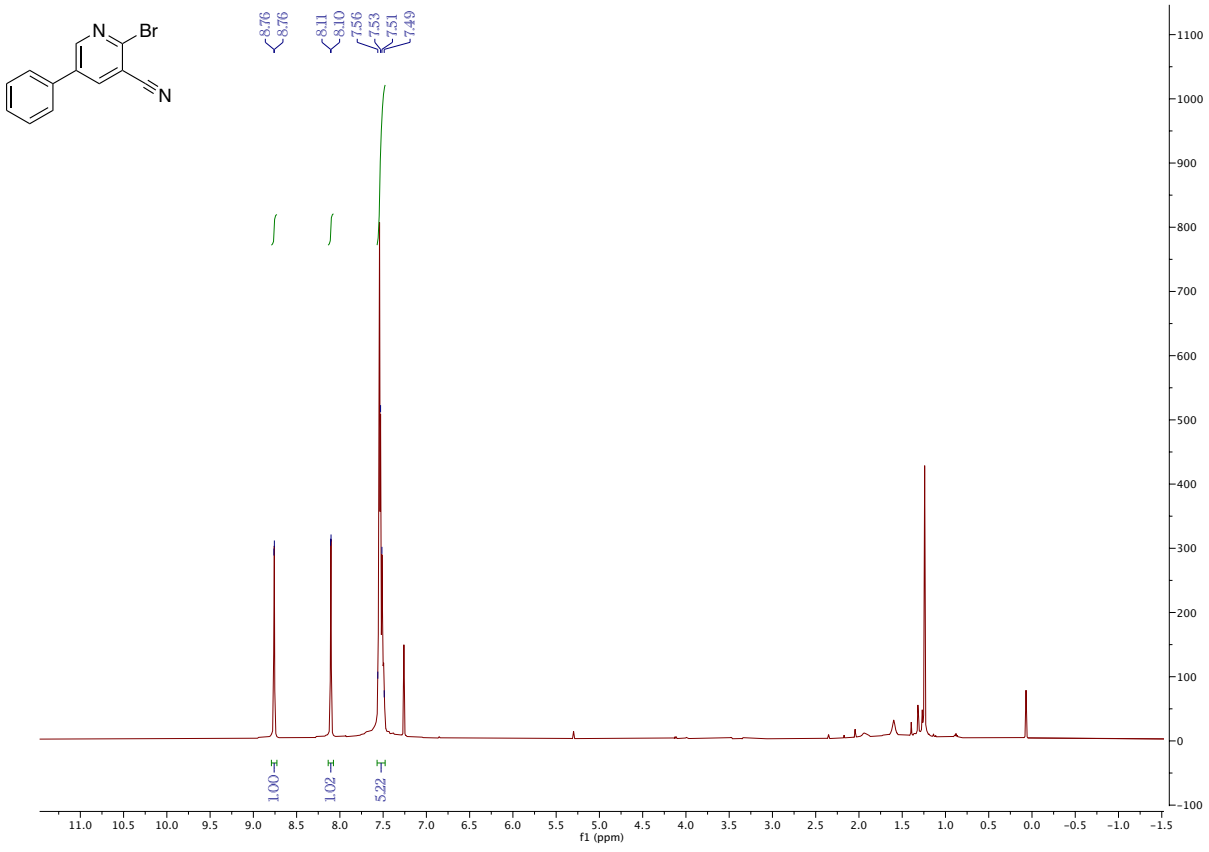


^{13}C NMR

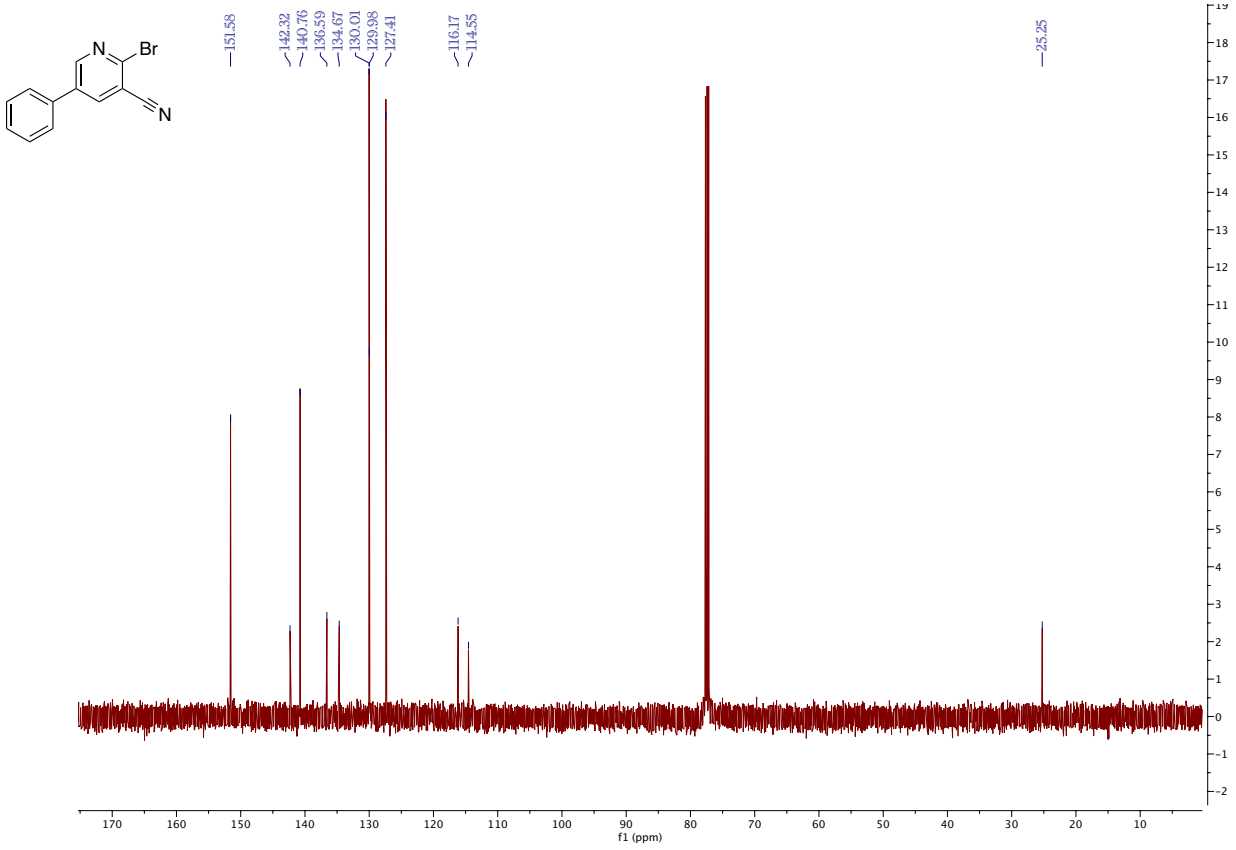

OH
N
N
162.24
148.09
137.60
134.19
129.68
128.67
125.99
121.90
115.34
f1 (ppm)

*2-bromo-5-phenylnicotinonitrile (**3-III**).*

^{1}H NMR

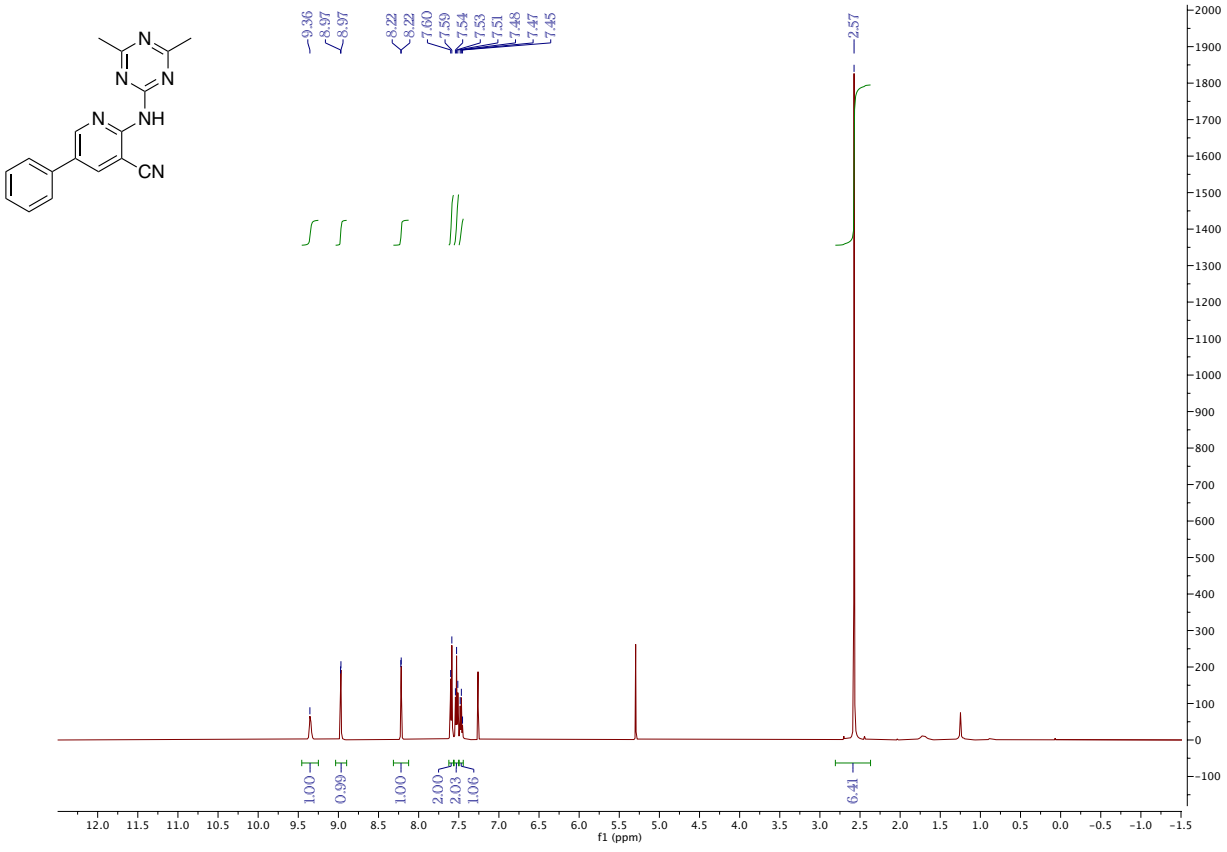


^{13}C NMR

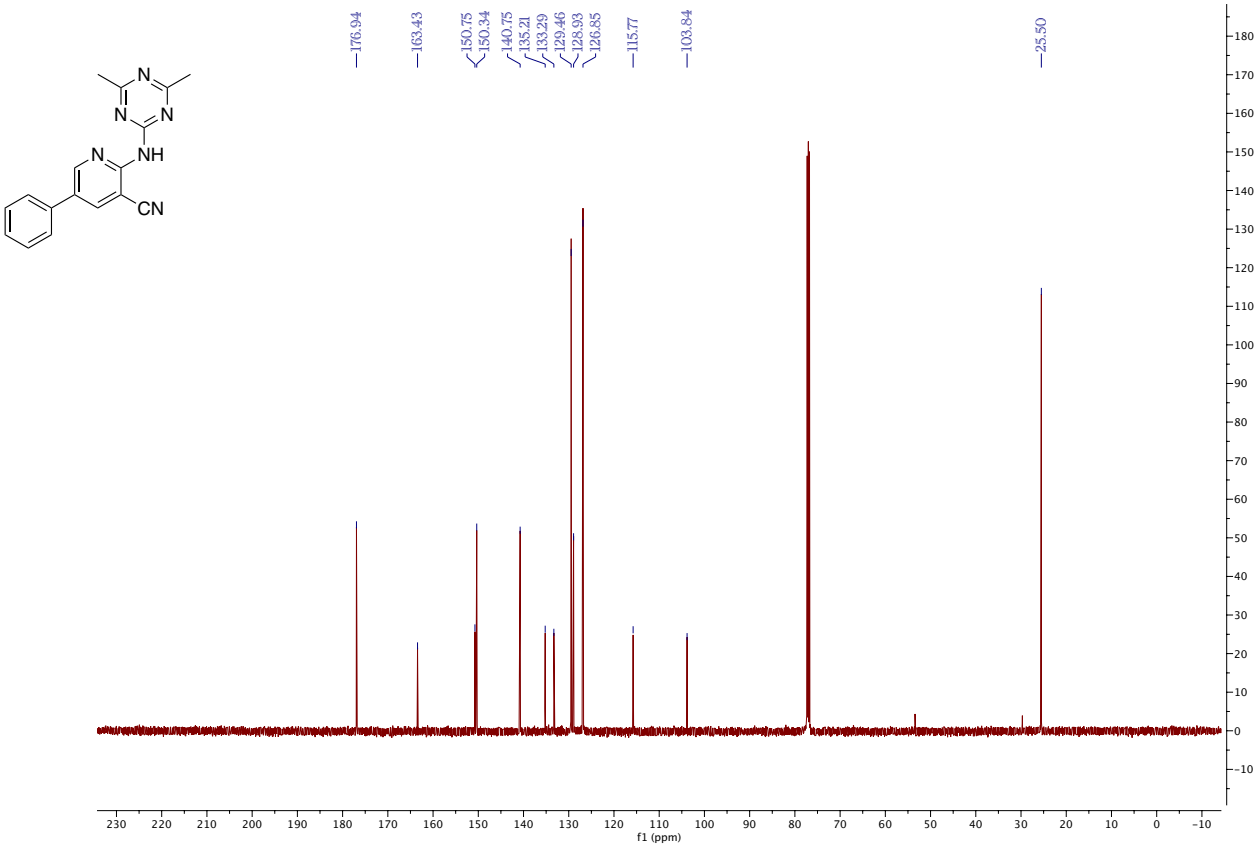

N
Br
N
151.58
142.32
140.76
136.59
134.67
130.01
129.98
127.41
116.17
114.55
25.25
f1 (ppm)

*2-((4,6-dimethyl-1,3,5-triazin-2-yl)amino)-5-phenylnicotinonitrile (**3a**).*

^{1}H NMR

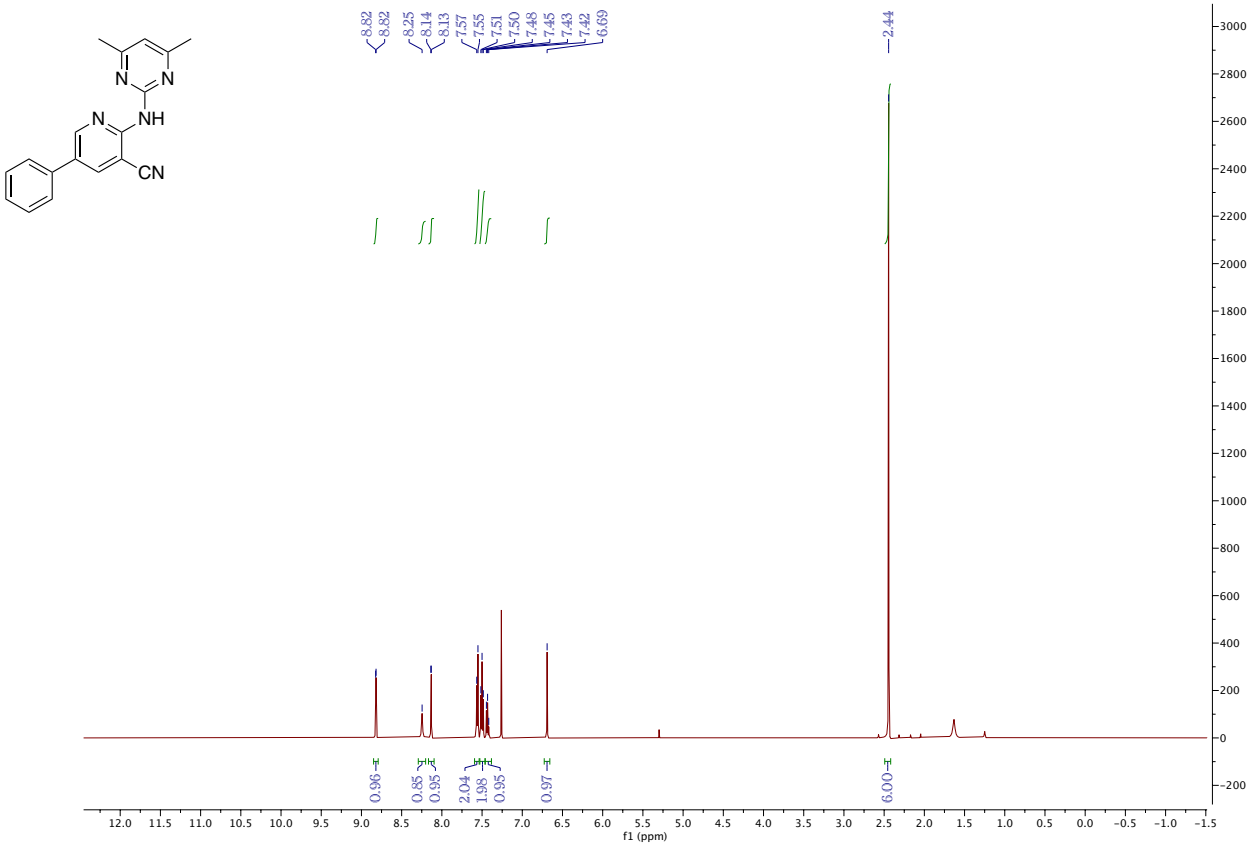


^{13}C NMR

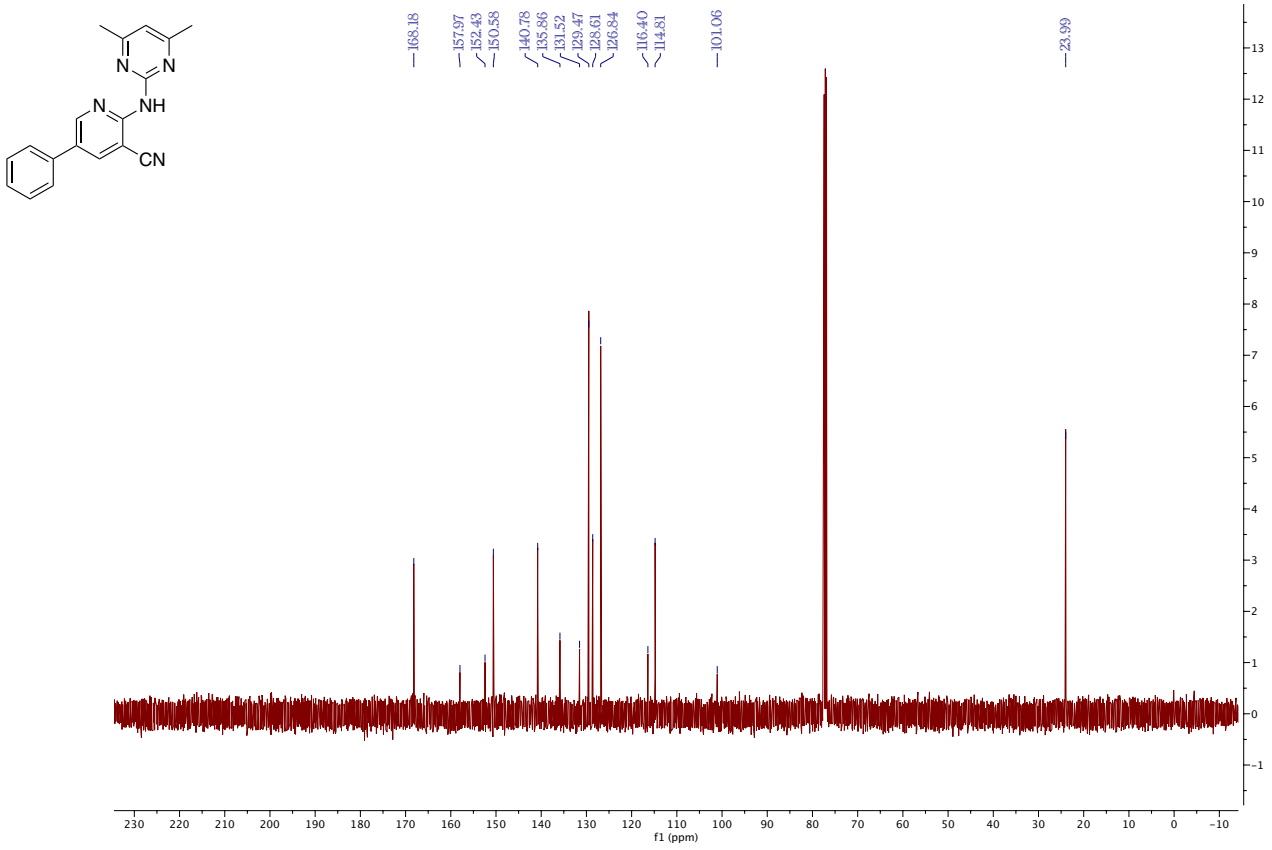

176.94
163.43
150.75
150.34
140.75
135.21
133.29
129.46
128.93
126.85
115.77
103.84
25.50
N
N
N
NH
N
CN
f1 (ppm)

*2-((4,6-dimethylpyrimidin-2-yl)amino)-5-phenylnicotinonitrile (**3b**).*

^{1}H NMR

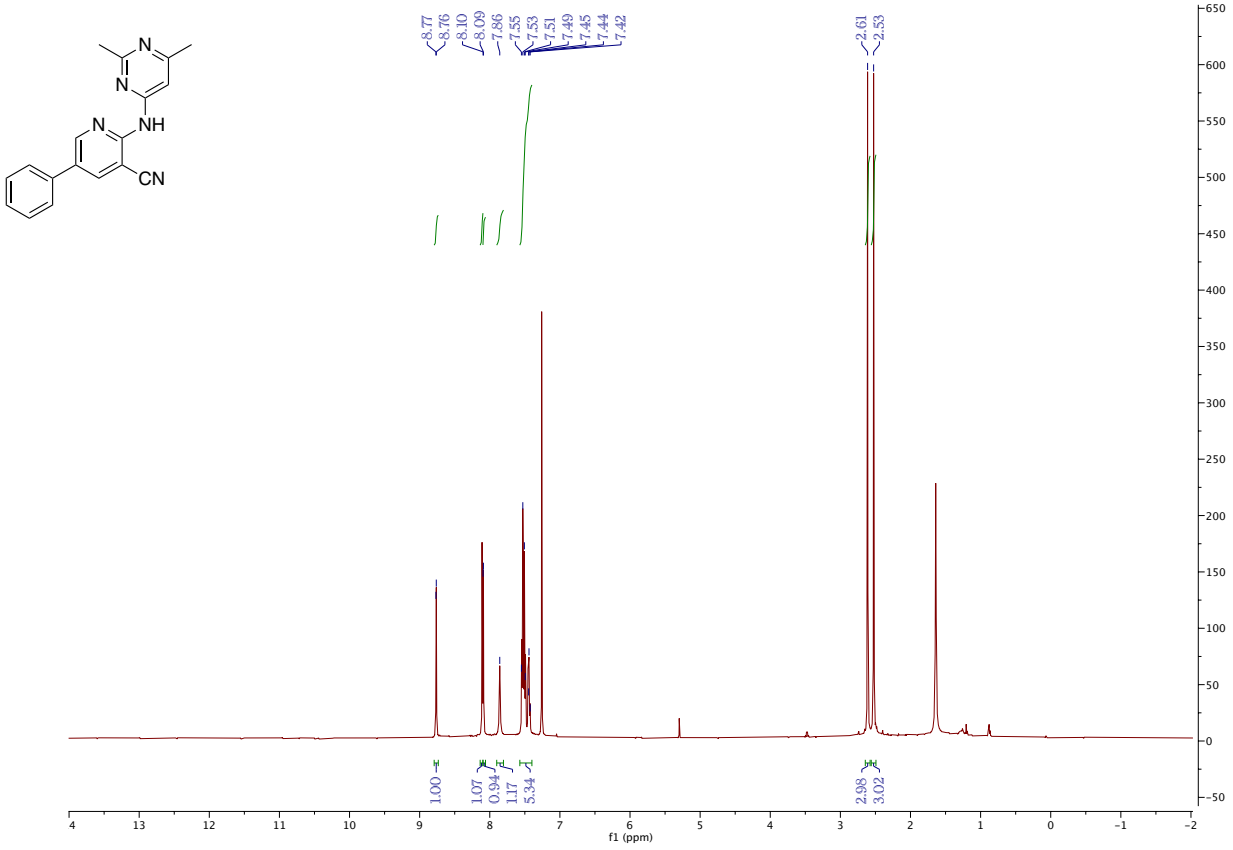


^{13}C NMR

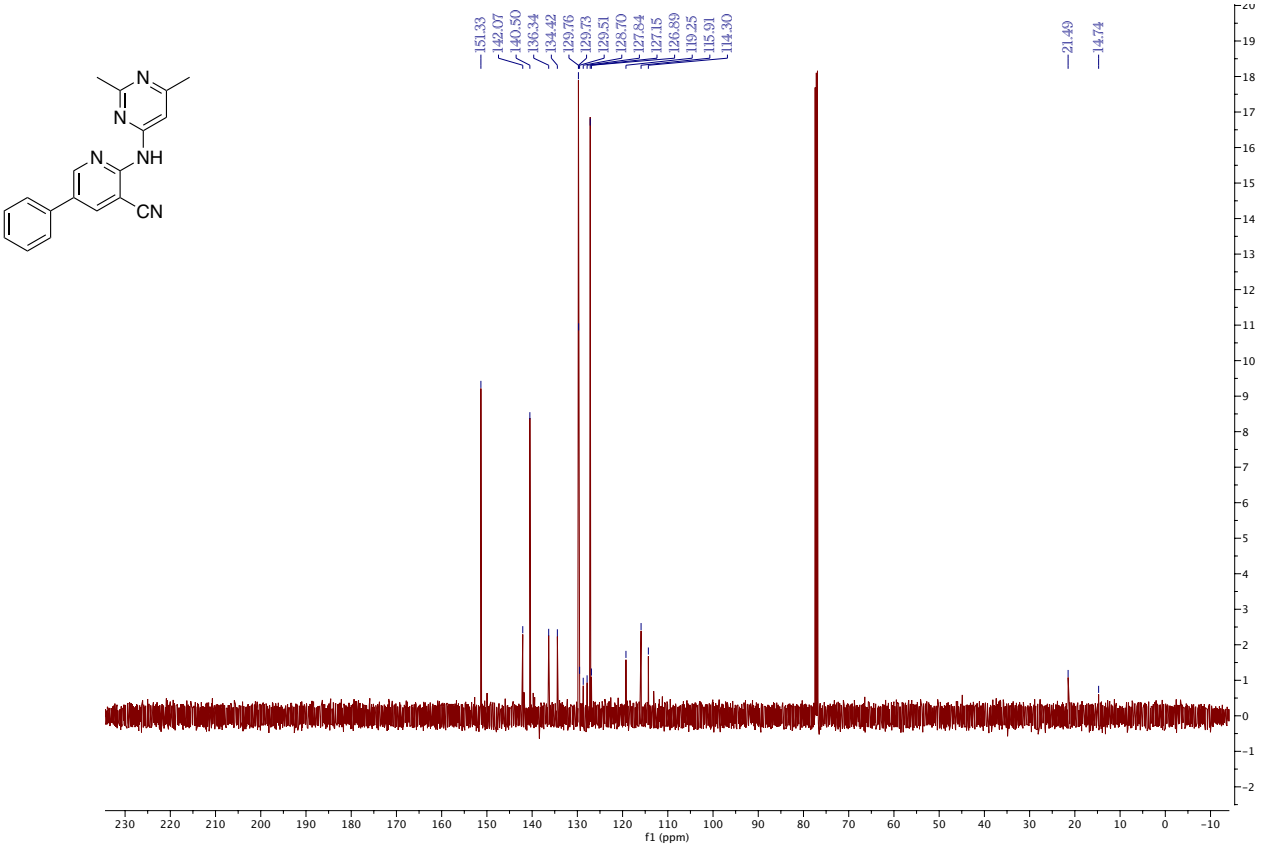

N
N
NH
N
CN
168.18
157.97
152.43
150.58
140.78
135.86
131.52
129.47
128.61
126.84
116.40
114.81
101.06
23.99
f1 (ppm)

*2-((2,6-dimethylpyrimidin-4-yl)amino)-5-phenylnicotinonitrile (**3c**).*

^{1}H NMR

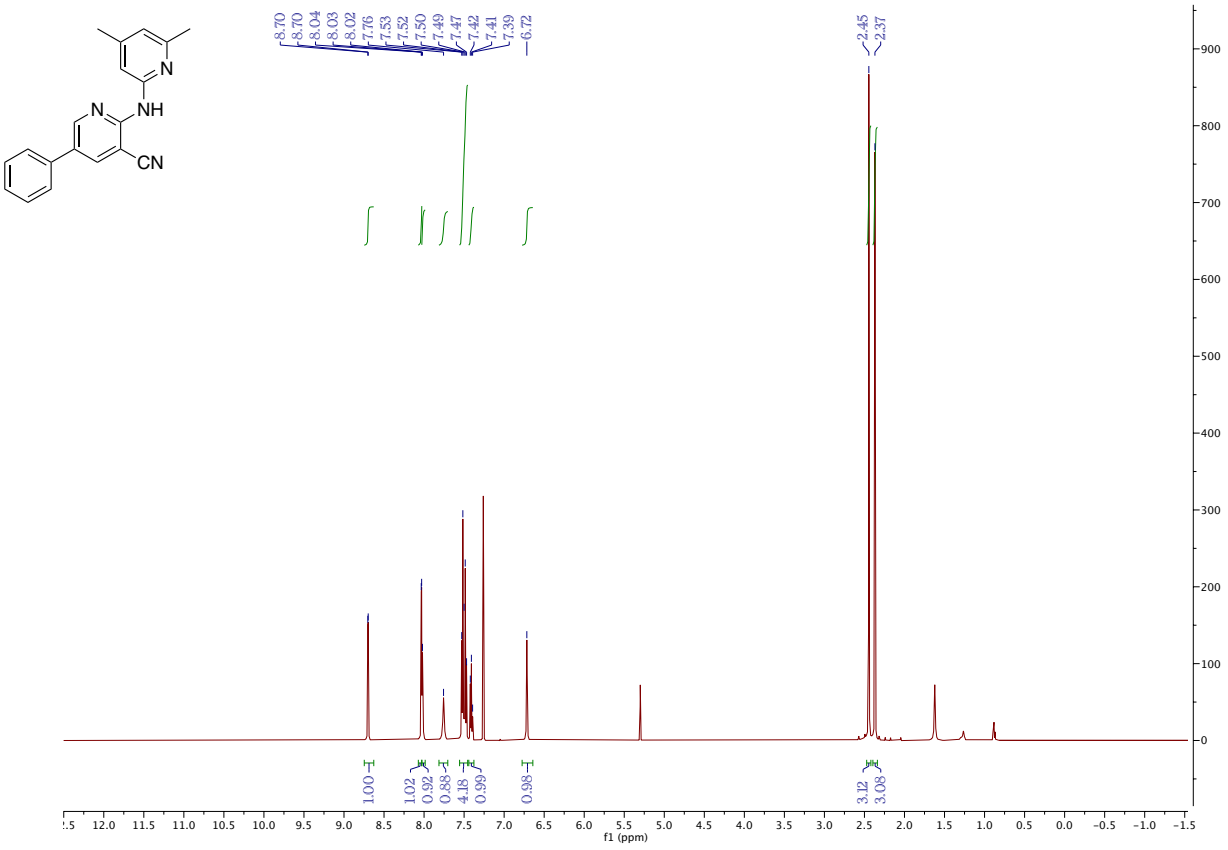


^{13}C NMR

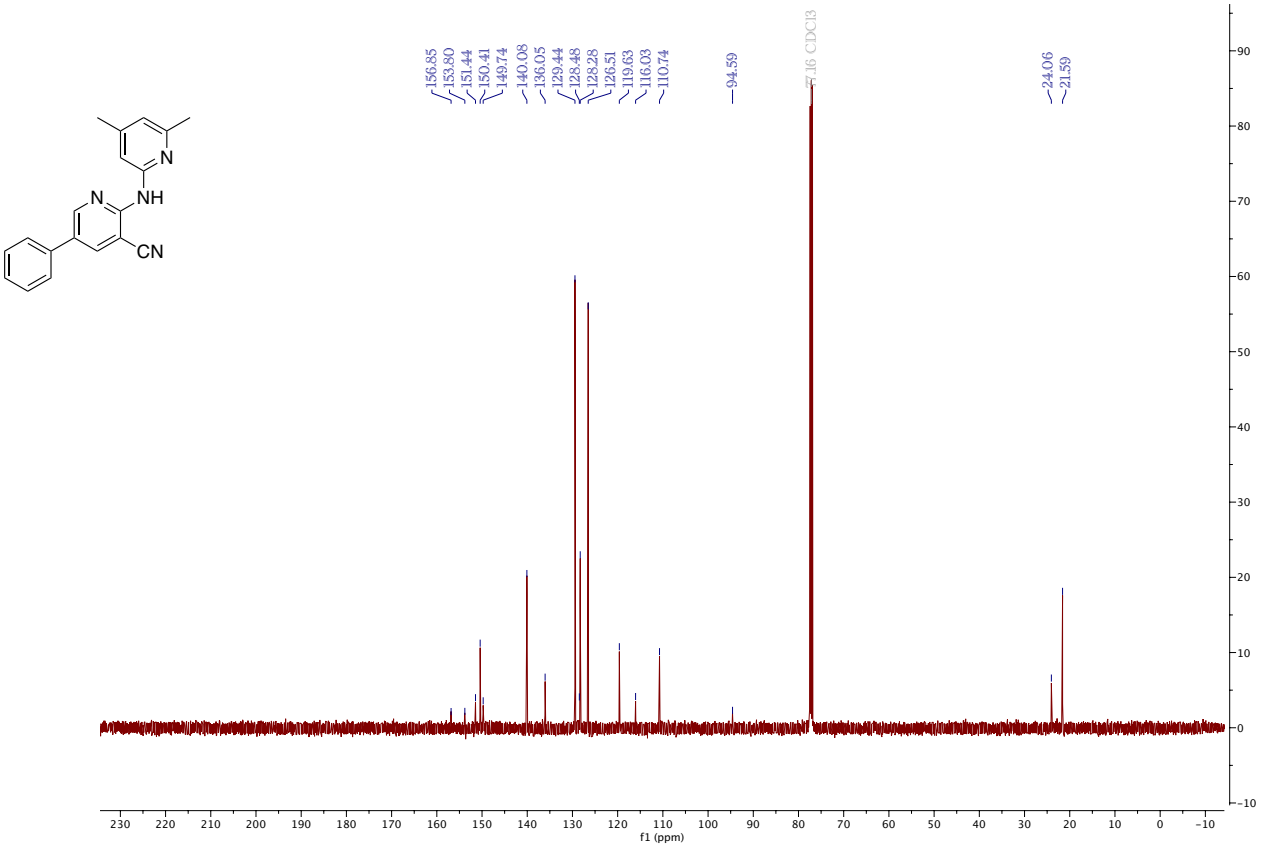

151.33
142.07
140.50
136.34
134.42
129.76
129.73
129.51
128.70
127.84
127.15
126.89
119.25
115.91
114.30
21.49
14.74
N
N
NH
N
CN
f1 (ppm)

*2-((4,6-dimethylpyridin-2-yl)amino)-5-phenylnicotinonitrile (**3d**).*

^{1}H NMR

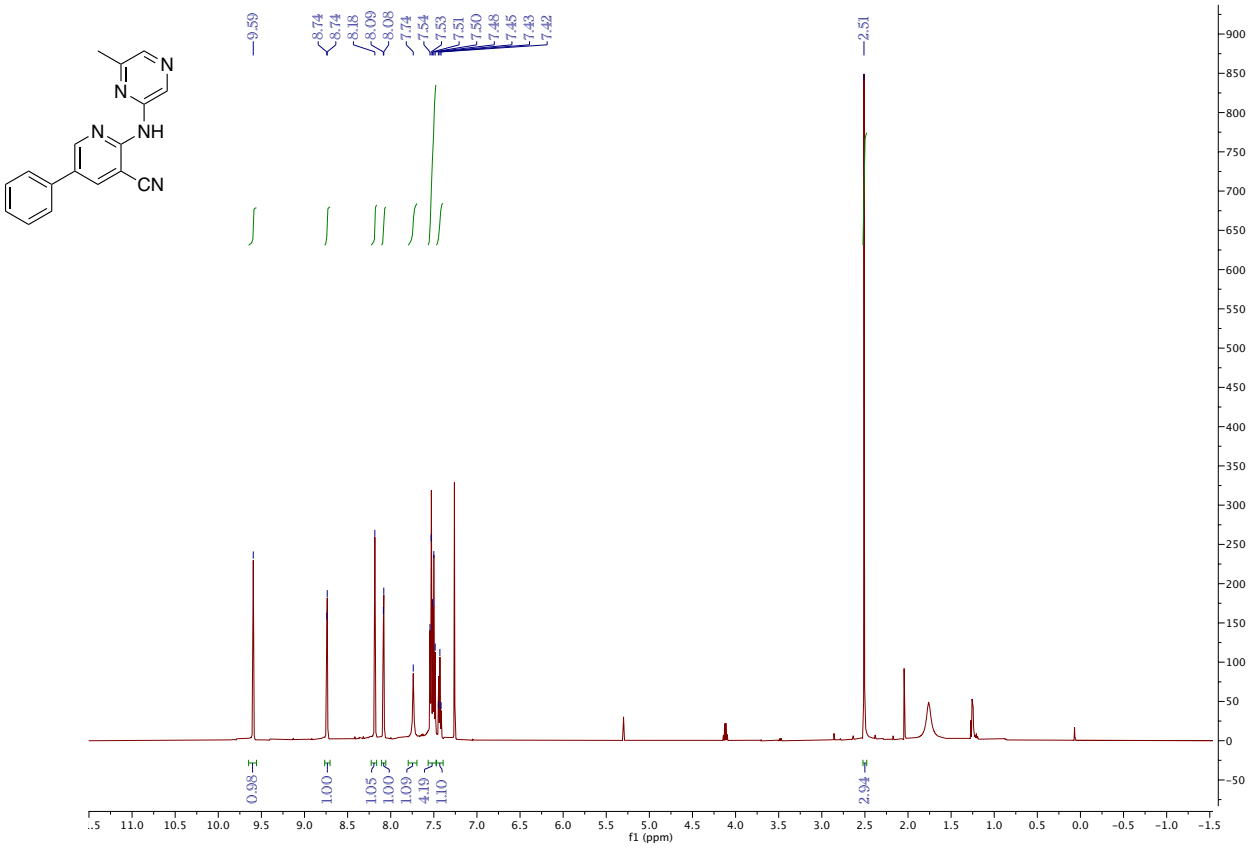


^{13}C NMR

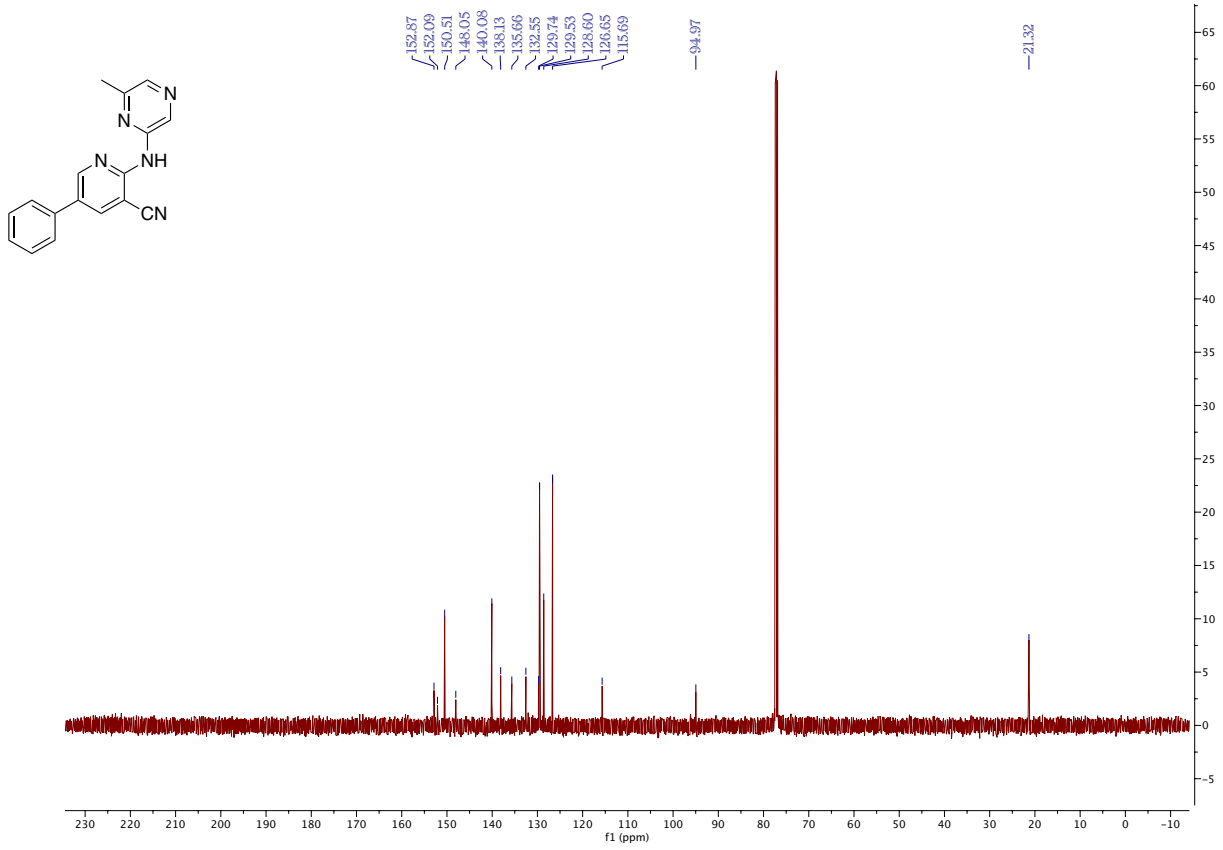

156.85
153.80
151.44
150.41
149.74
140.08
136.05
129.44
128.48
128.28
126.51
119.63
116.03
110.74
94.59
77.16 CDCl3
24.06
21.59
N
NH
N
CN
f1 (ppm)

*2-((6-methylpyrazin-2-yl)amino)-5-phenylnicotinonitrile (**3e**).*

^{1}H NMR

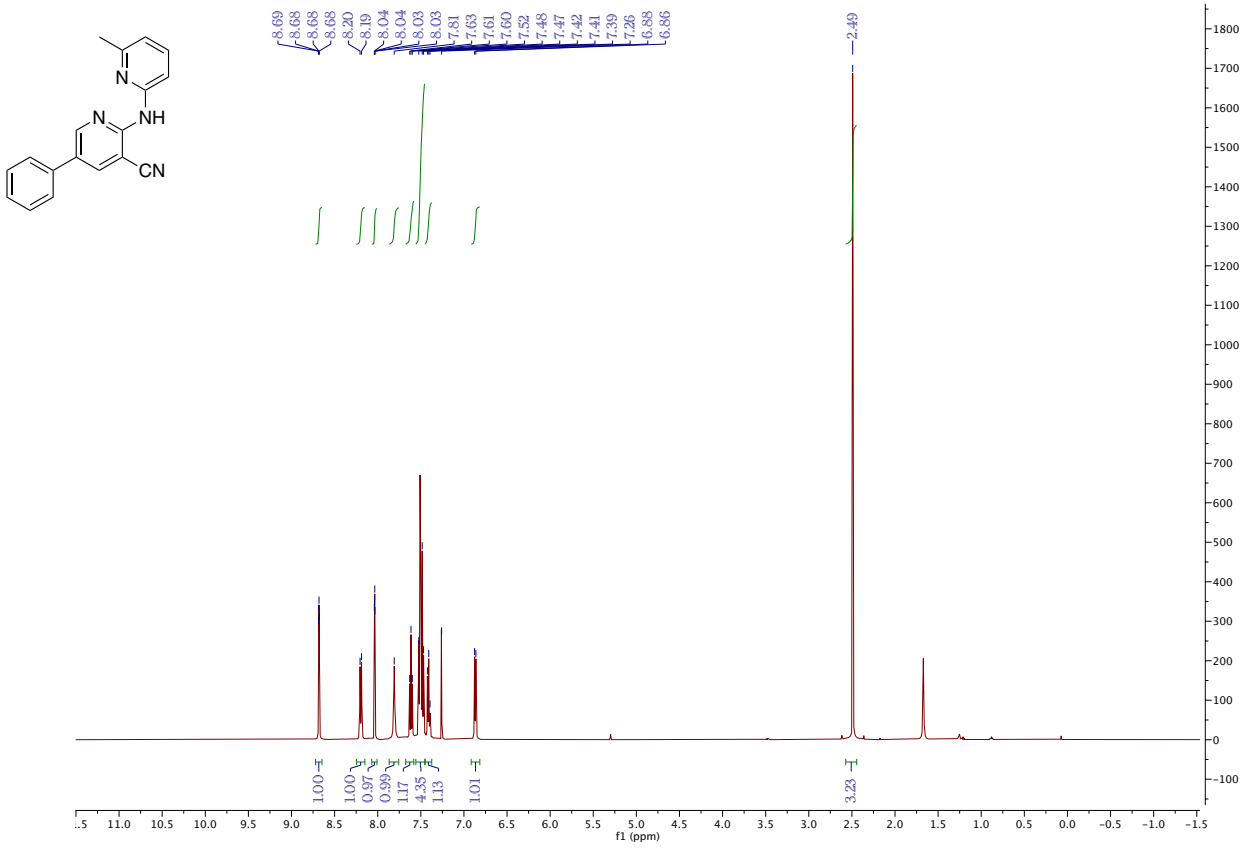


^{13}C NMR

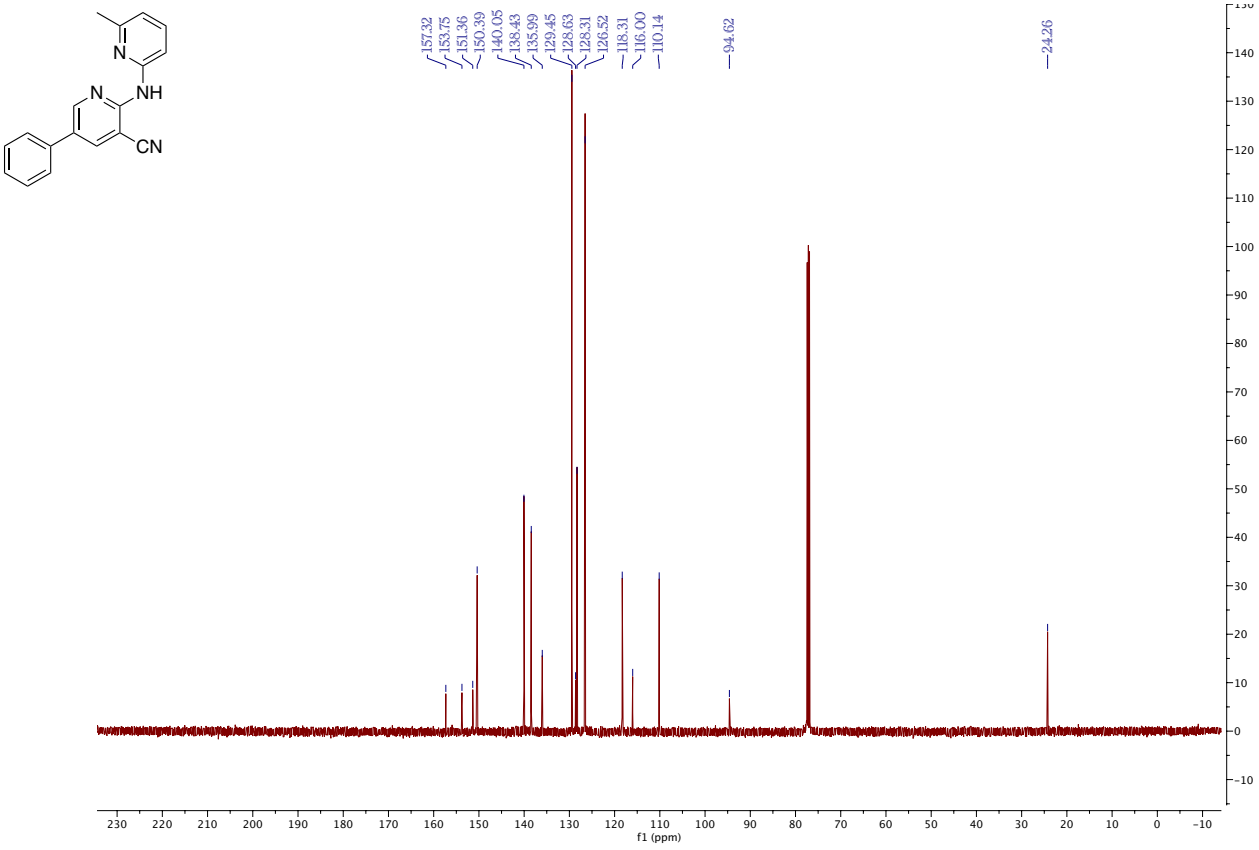

152.87
152.09
150.51
148.05
140.08
138.13
135.66
132.55
129.74
129.53
128.60
126.65
115.69
94.97
21.32
N
N
NH
N
CN
f1 (ppm)

*2-((6-methylpyridin-2-yl)amino)-5-phenylnicotinonitrile (**3f**).*

^{1}H NMR

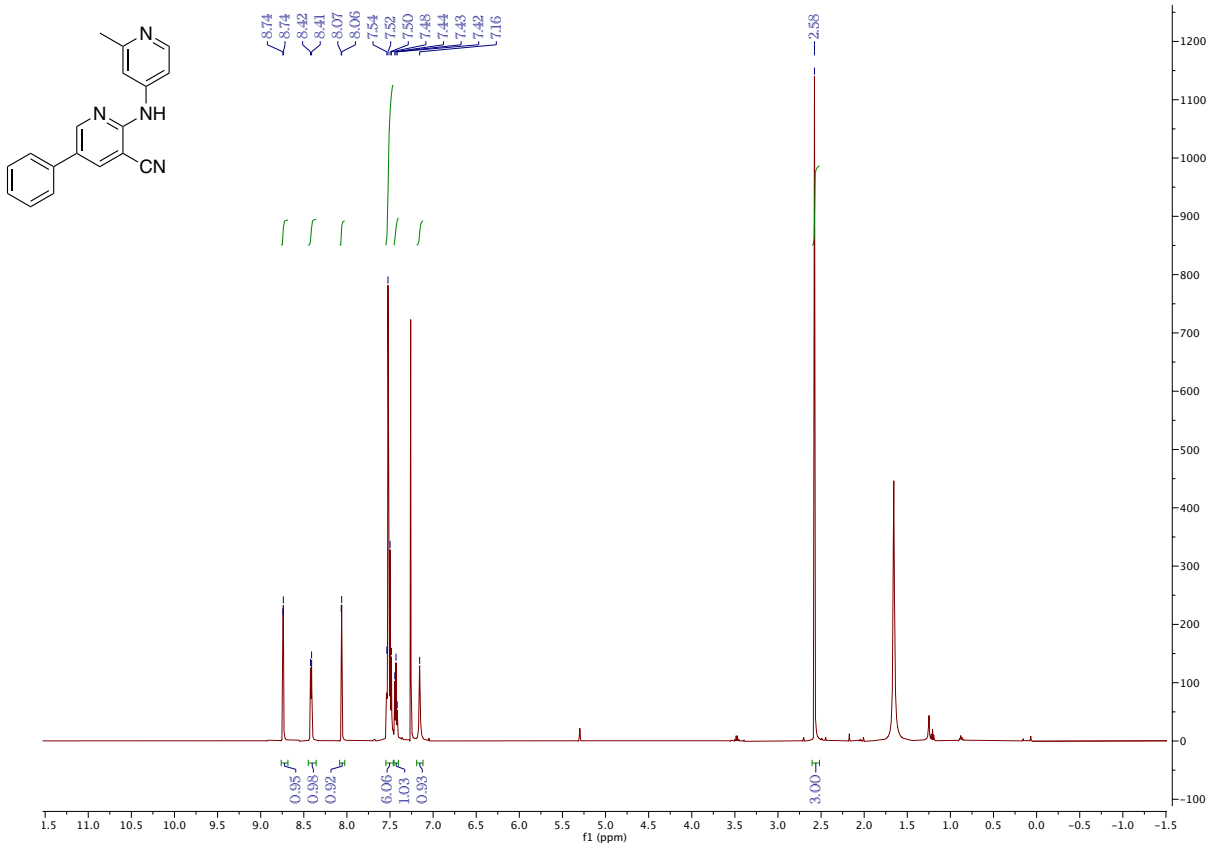


^{13}C NMR

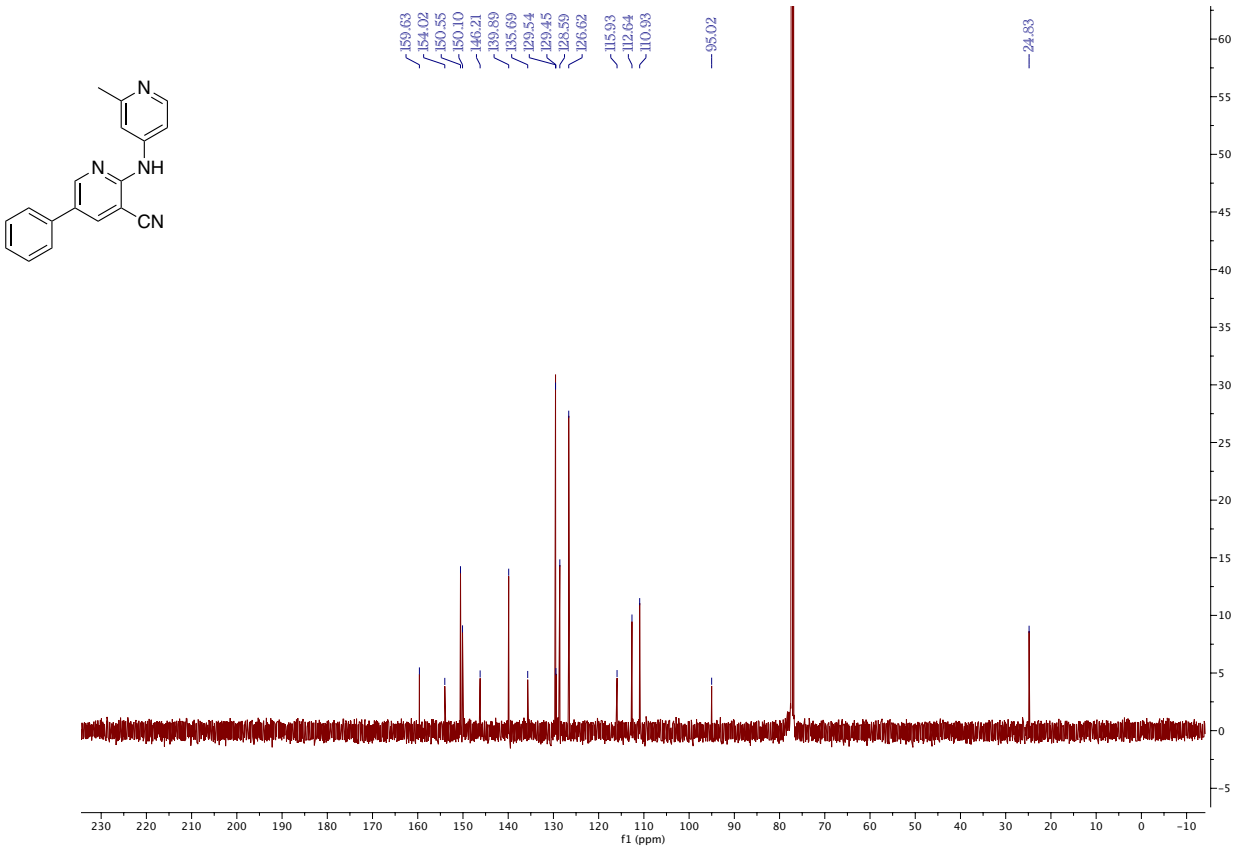

N
NH
N
CN
157.32
153.75
151.36
150.39
140.05
138.43
135.99
129.45
128.63
128.31
126.52
118.31
116.00
110.14
94.62
24.26
f1 (ppm)

*2-((2-methylpyridin-4-yl)amino)-5-phenylnicotinonitrile (**3g**).*

^{1}H NMR

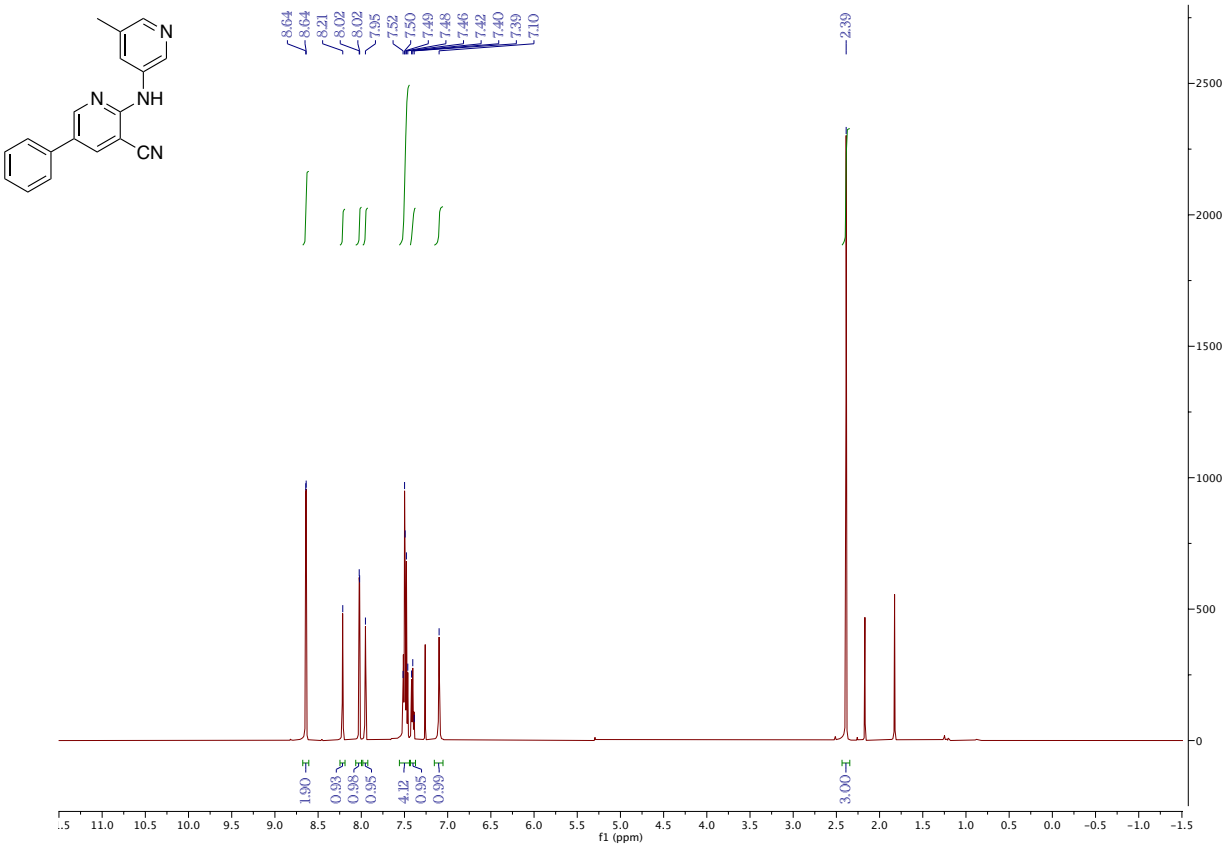


^{13}C NMR

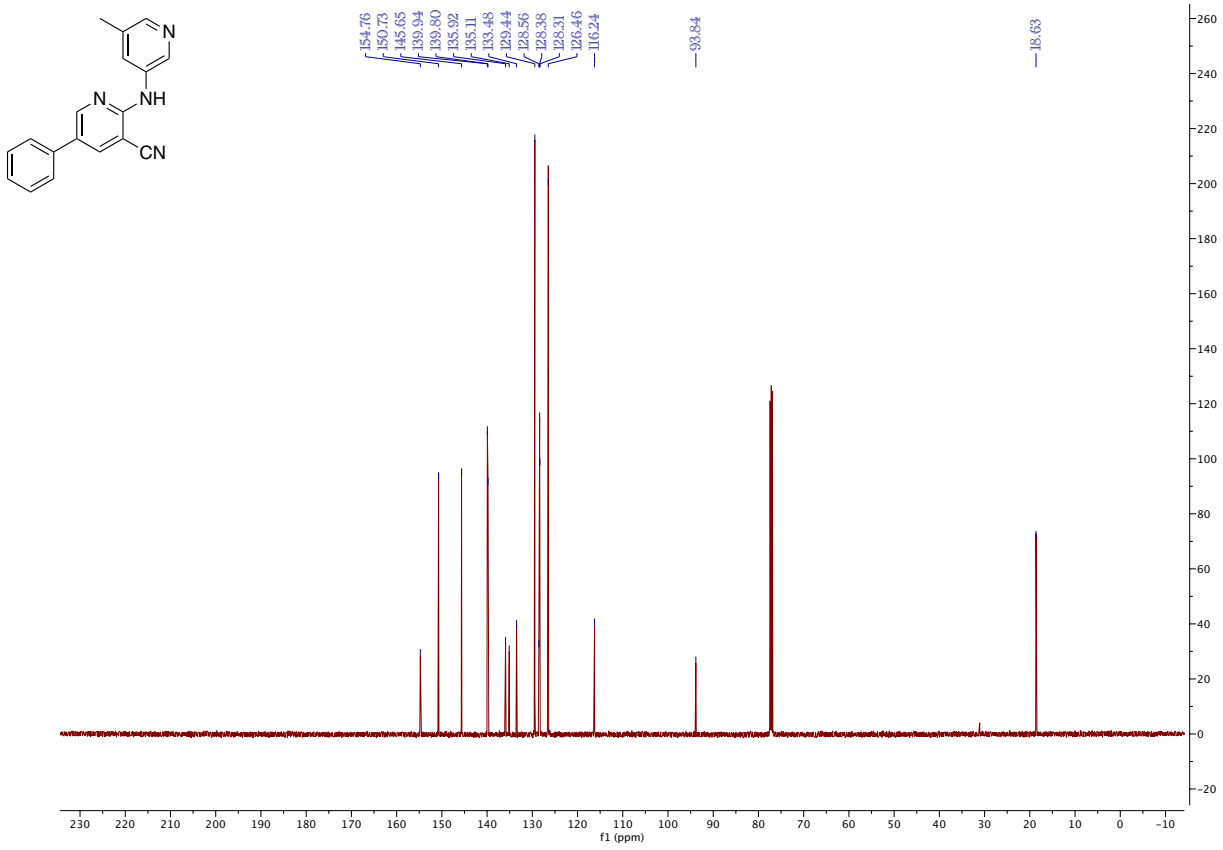

159.63
154.02
150.55
150.10
146.21
139.89
135.69
129.54
129.45
128.59
126.62
115.93
112.64
110.93
95.02
24.83
N
NH
N
CN
f1 (ppm)

*2-((5-methylpyridin-3-yl)amino)-5-phenylnicotinonitrile (**3h**).*

^{1}H NMR

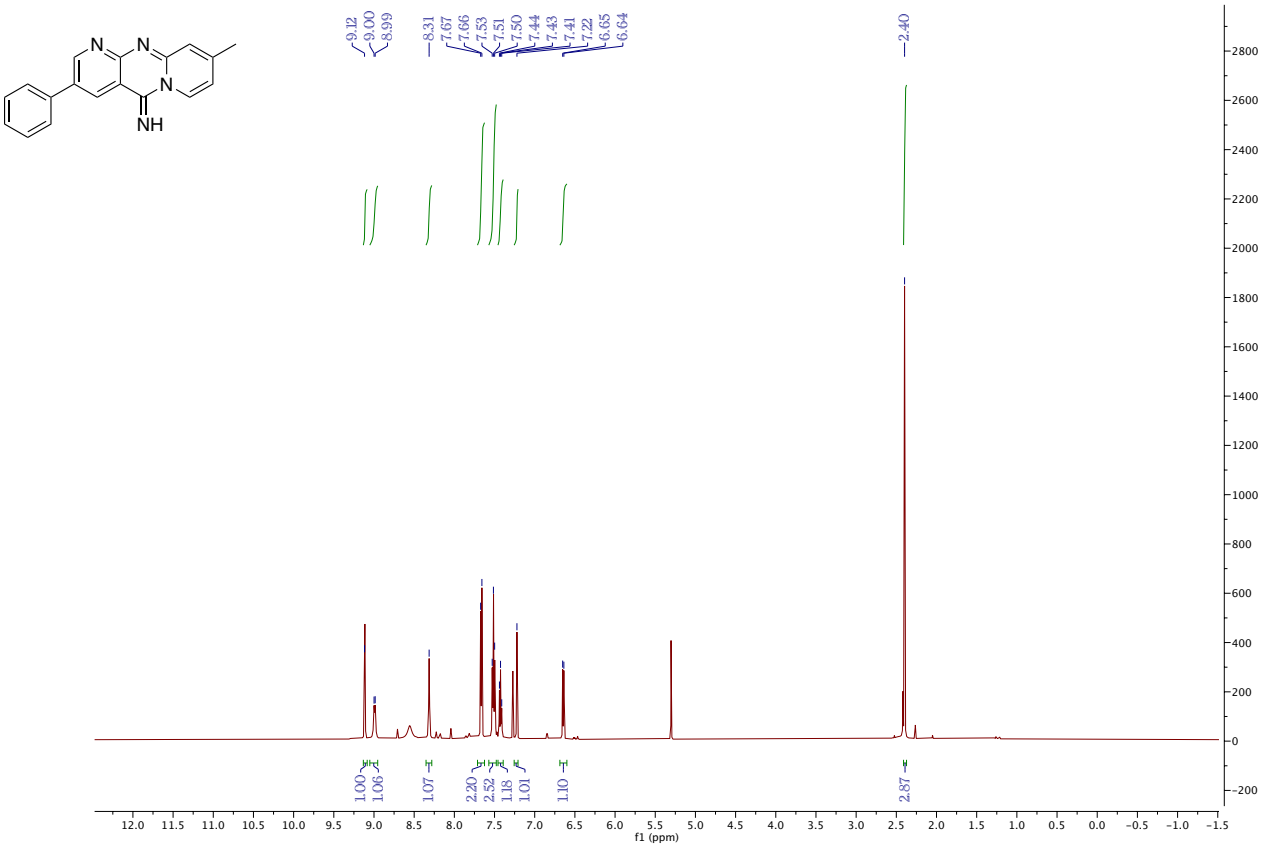


^{13}C NMR

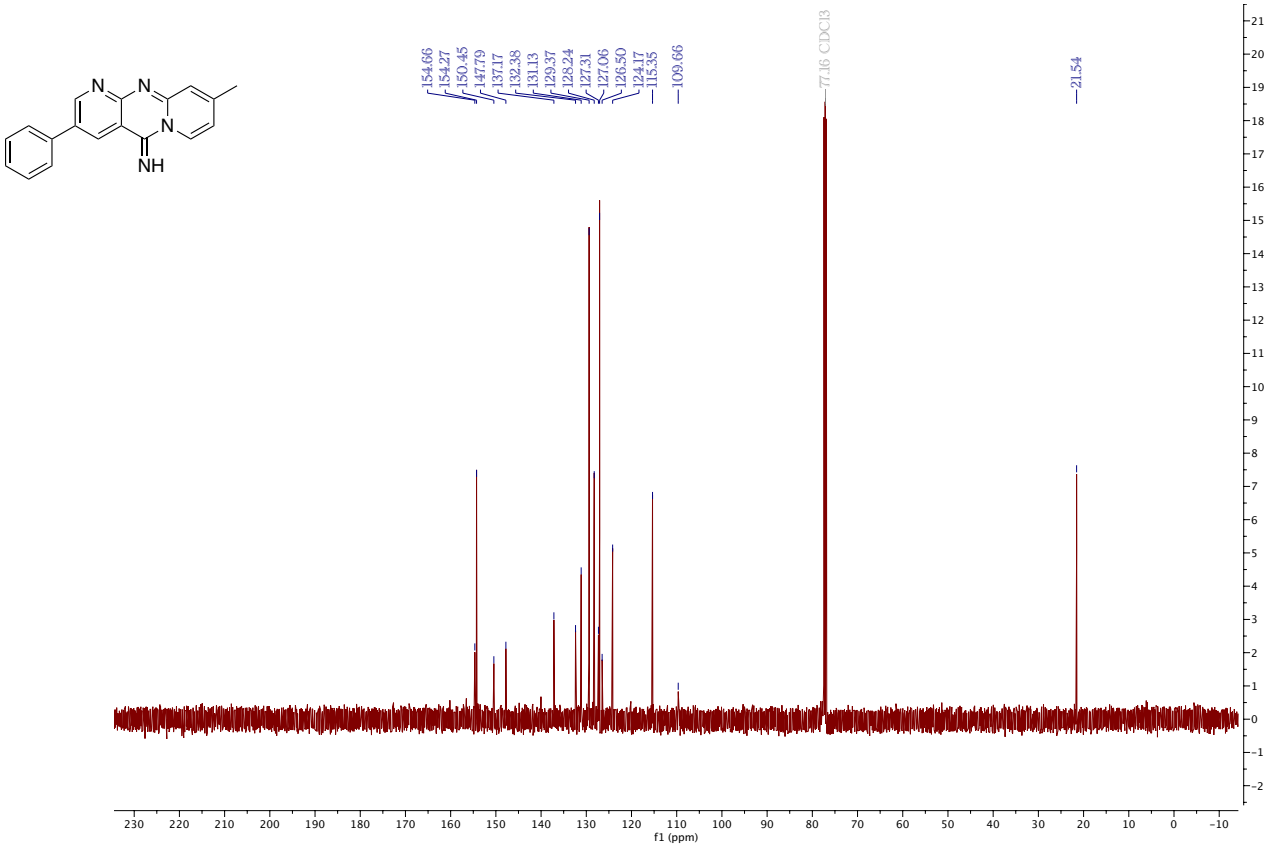

154.76
150.73
145.65
139.94
139.80
135.92
135.11
133.48
129.44
128.56
128.38
128.31
126.46
116.24
93.84
18.63
N
NH
N
CN
f1 (ppm)

*2-((4-methylpyridin-2-yl)amino)-5-phenylnicotinonitrile (**3i**).*

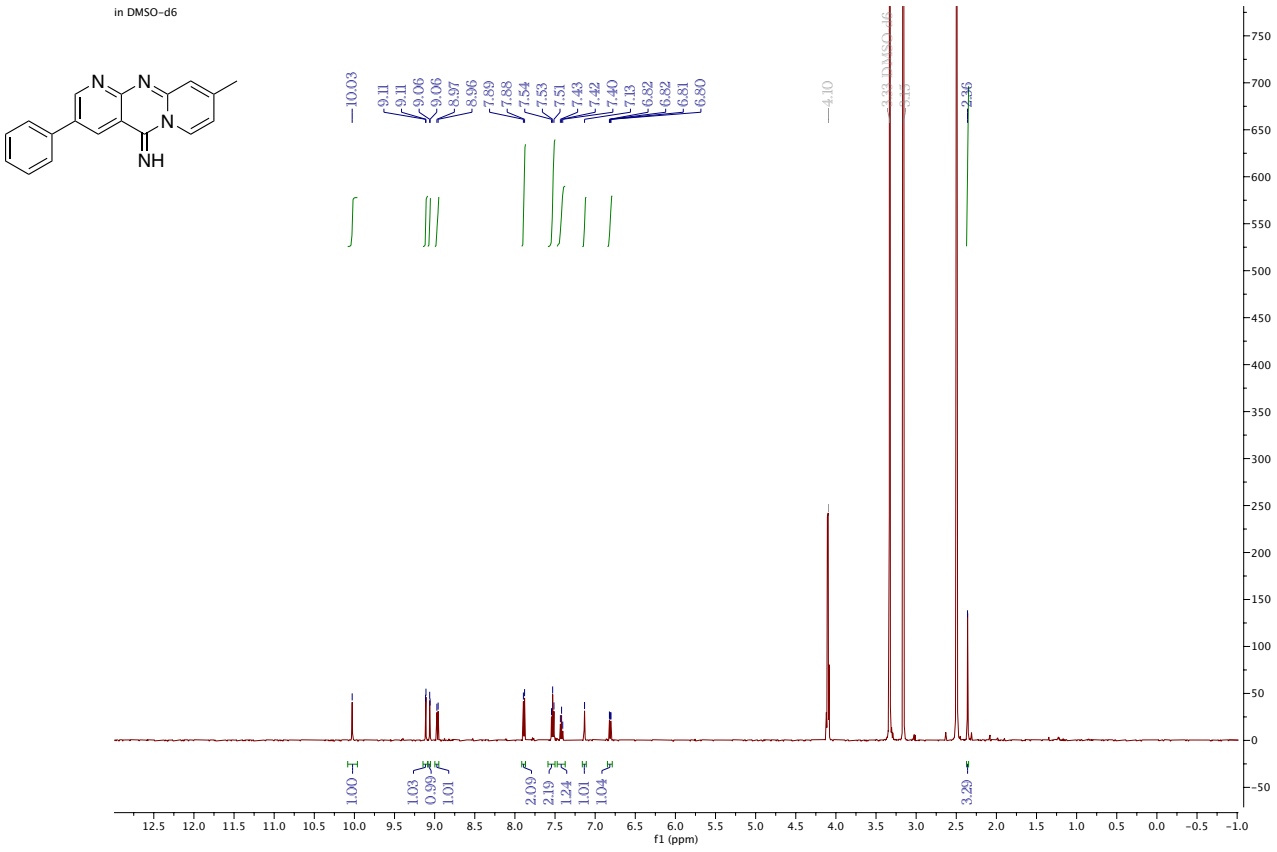
^{1}H NMR



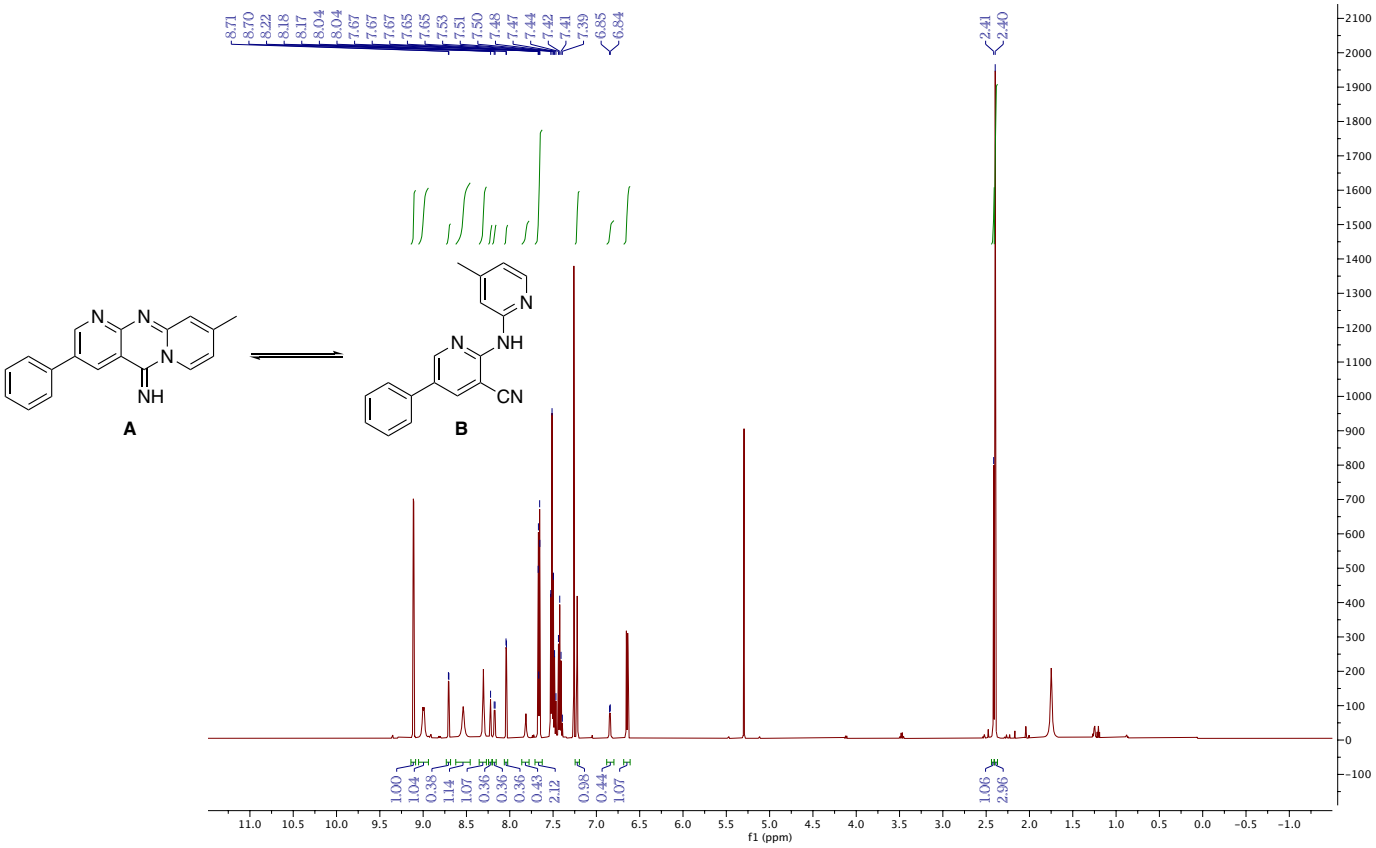
^{13}C NMR


154.66
154.27
150.45
147.79
137.17
132.38
131.13
129.37
128.24
127.31
127.06
126.50
124.17
115.35
109.66
77.16 CDCl3
21.54
f1 (ppm)

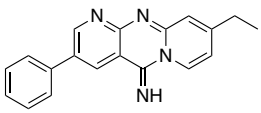
[1]H NMR in d6-DMSO



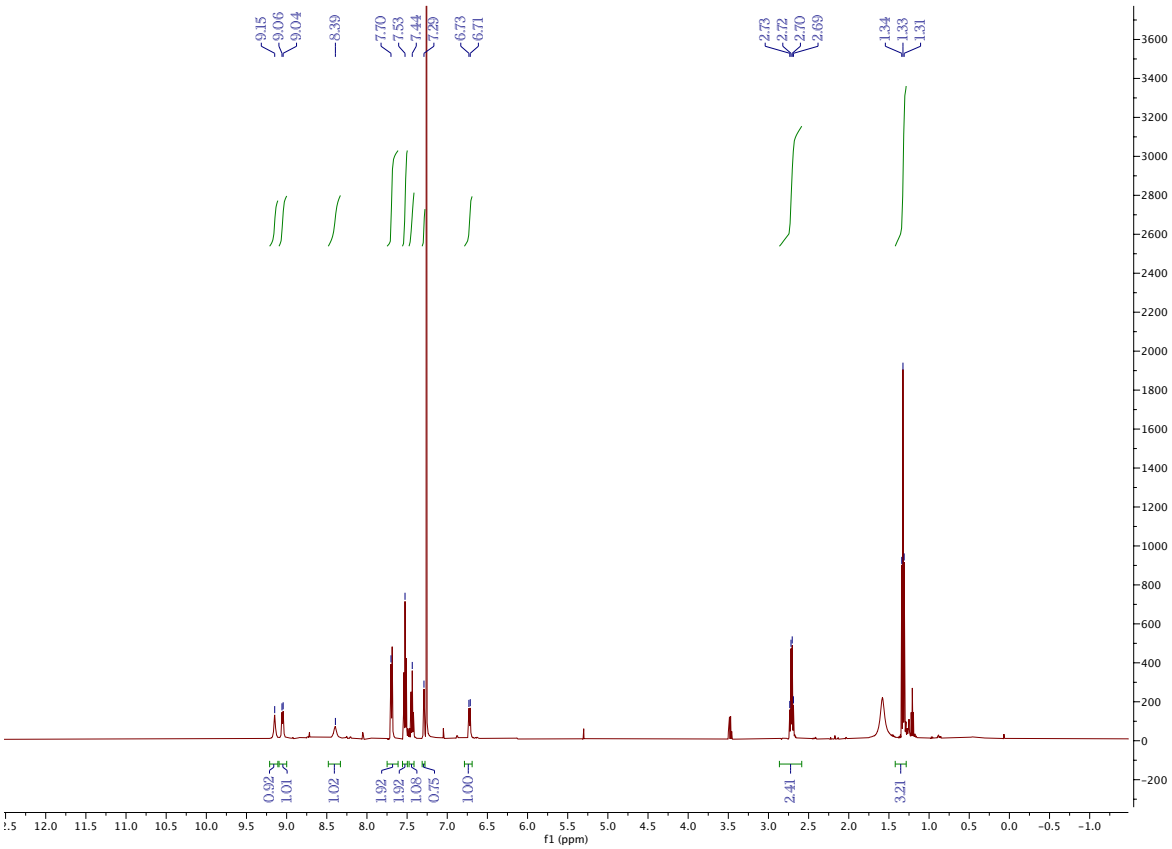
[1]H NMR isomer A and B mixture



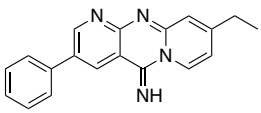
*2-((4-ethylpyridin-2-yl)amino)-5-phenylnicotinonitrile (**3j**)*

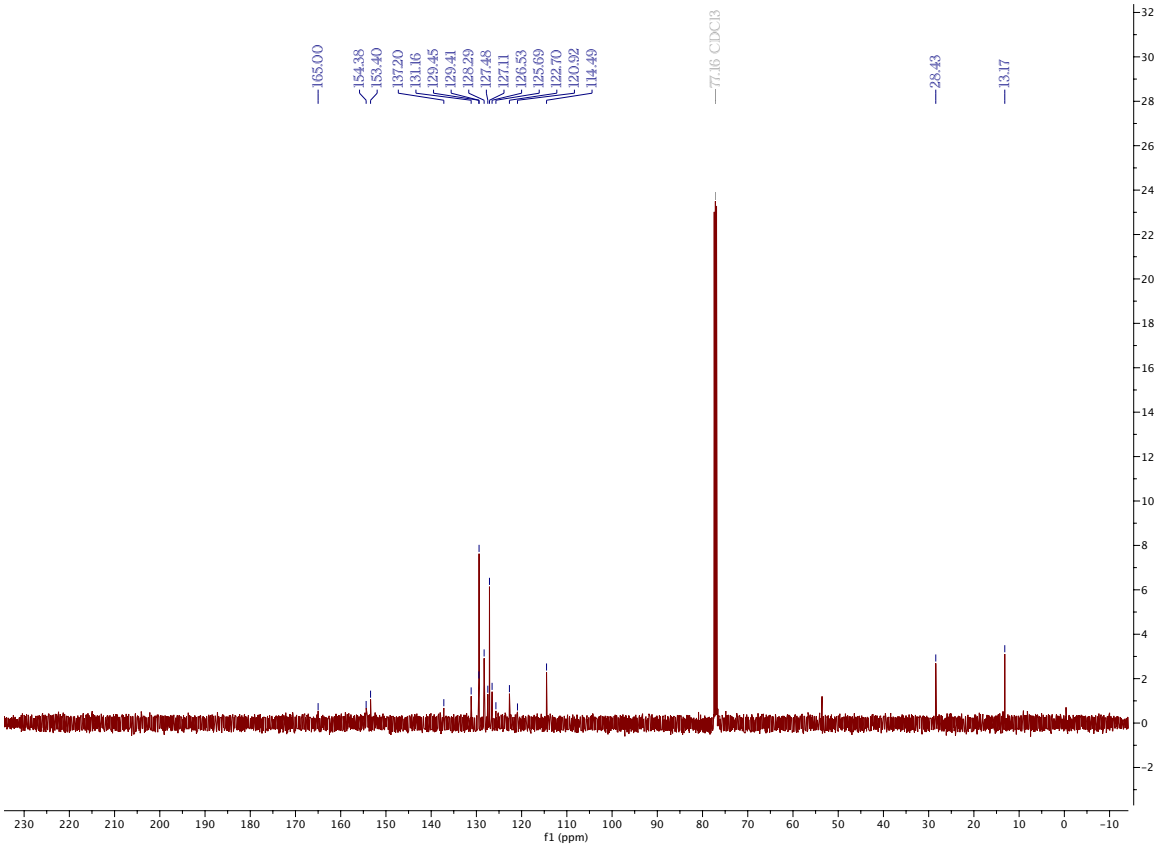


^{1}H NMR

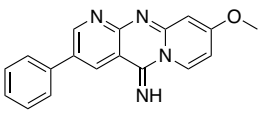


^{13}C NMR

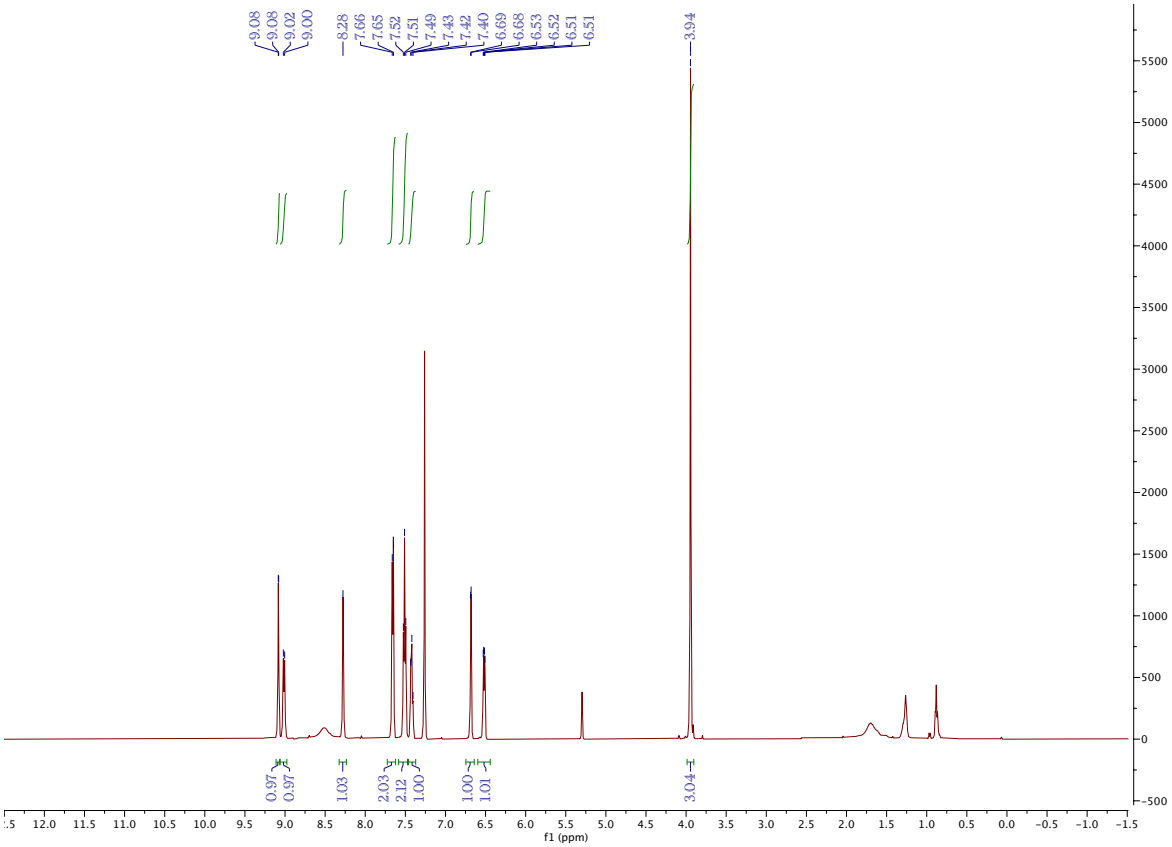

N
N
N
NH


165.00
154.38
153.40
137.20
131.16
129.45
129.41
128.29
127.48
127.11
126.53
125.69
122.70
120.92
114.49
77.16 CDCl3
28.43
13.17
f1 (ppm)

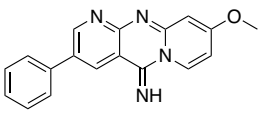
*2-((4-methoxypyridin-2-yl)amino)-5-phenylnicotinonitrile (**3k**)*

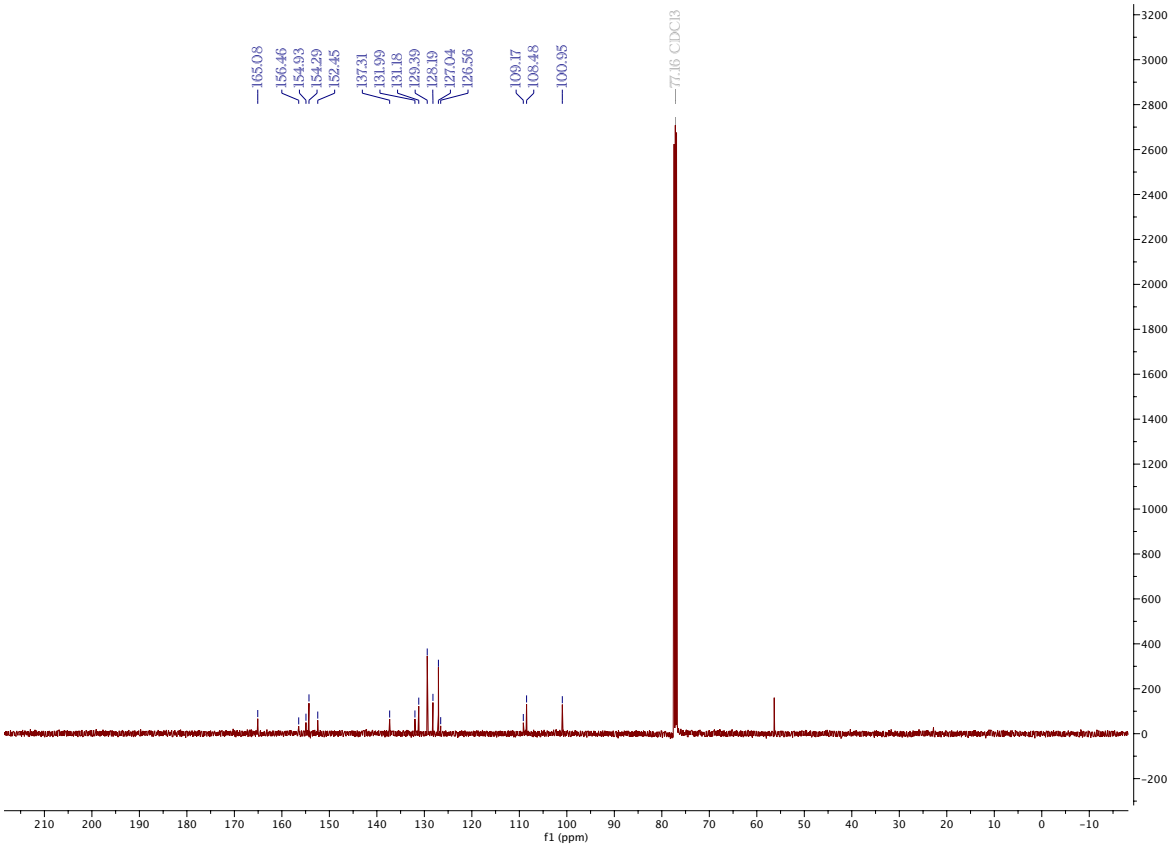


^{1}H NMR



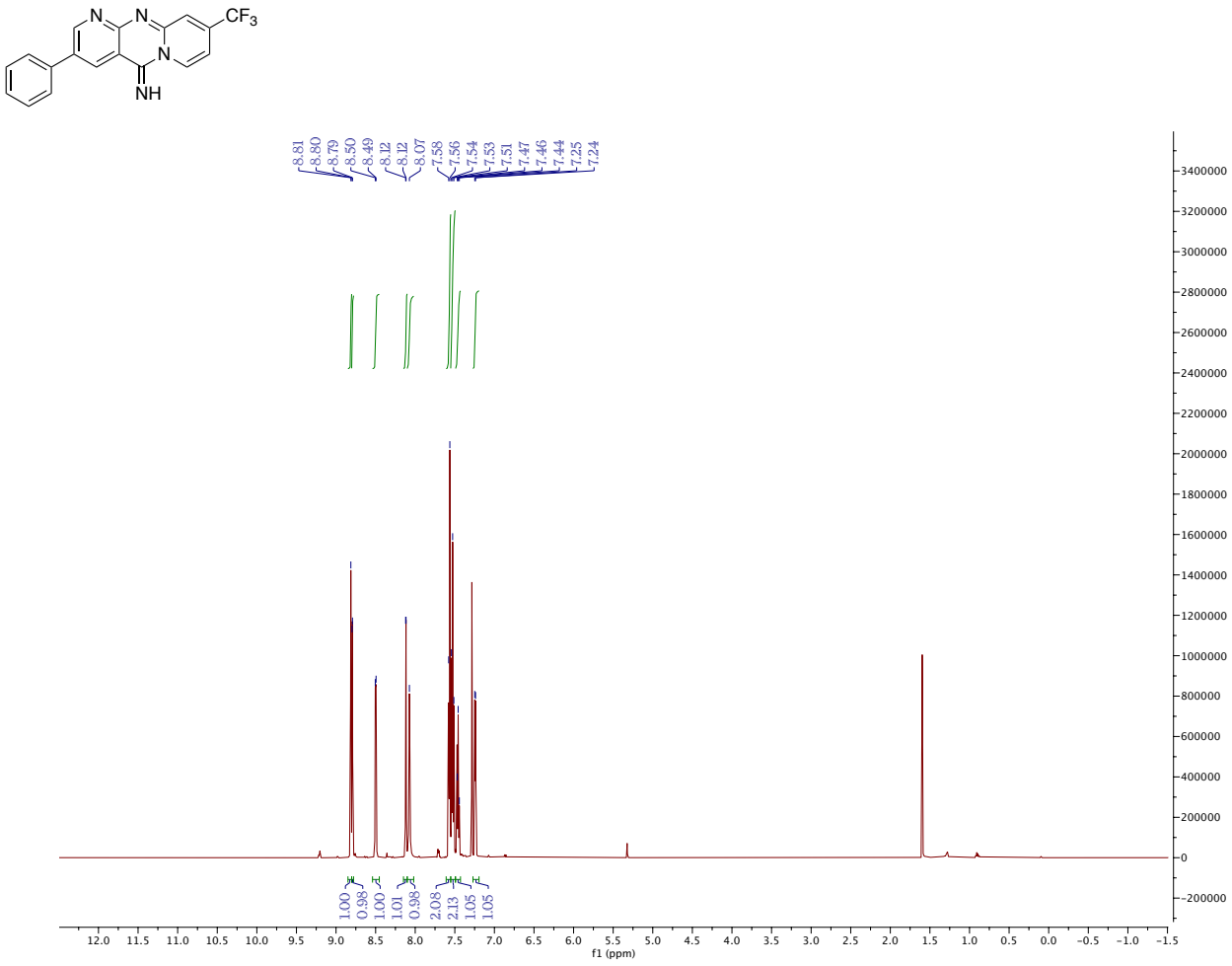
^{13}C NMR


N
N
O
N
NH

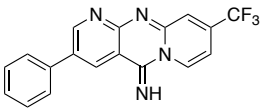

165.08
156.46
154.93
154.29
152.45
137.31
131.99
131.18
129.39
128.19
127.04
126.56
109.17
108.48
100.95
77.16 CDCl3
f1 (ppm)

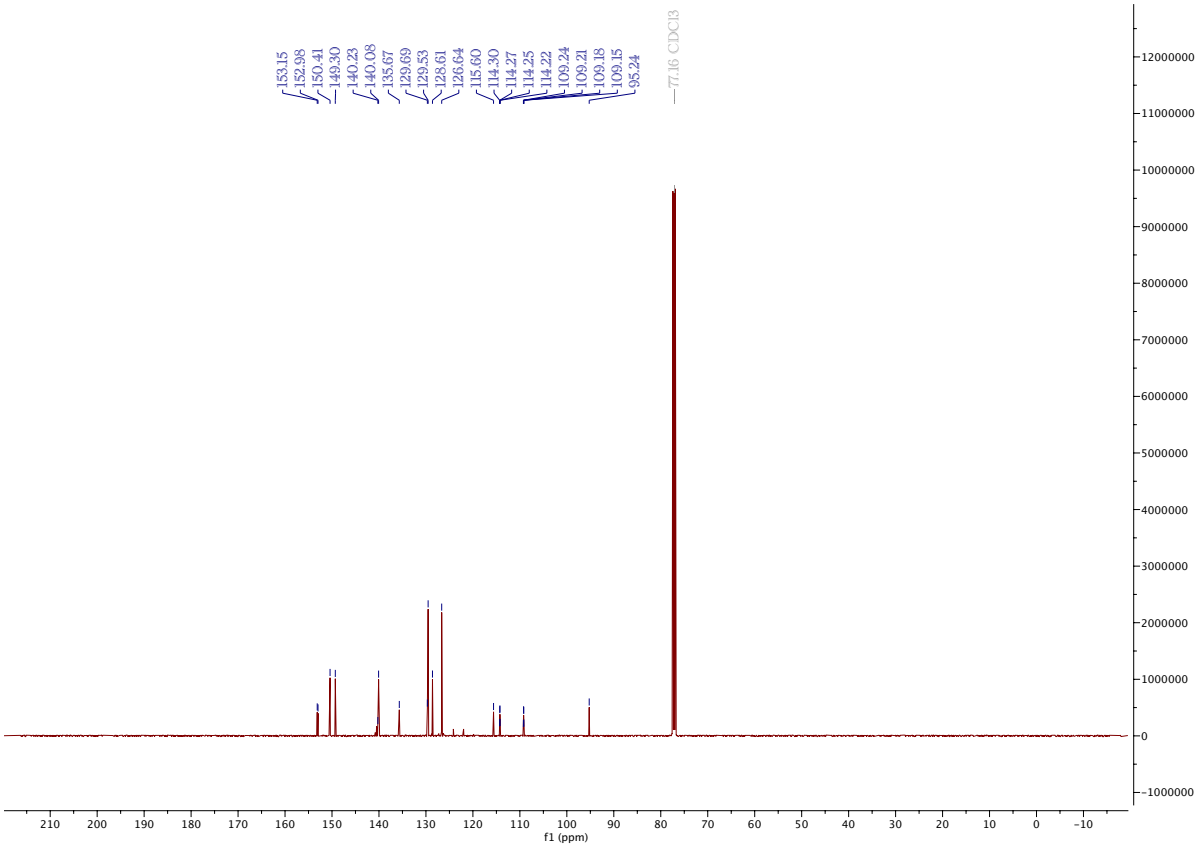
*5-phenyl-2-((4-(trifluoromethyl)pyridin-2-yl)amino)nicotinonitrile (**3l**)*

^{1}H NMR

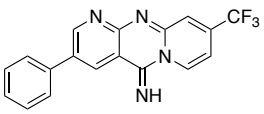


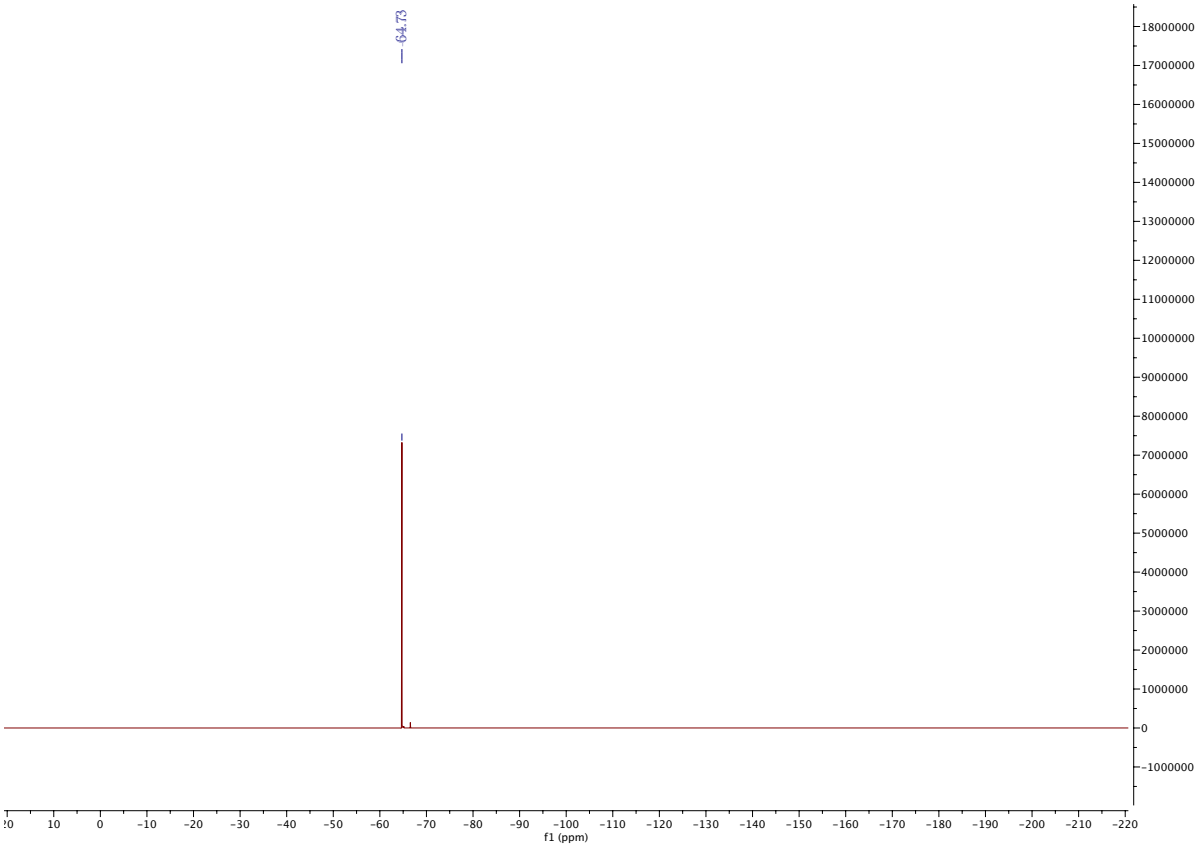
^{13}C NMR


N
N
CF3
N
NH

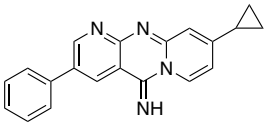

153.15
152.98
150.41
149.30
140.23
140.08
135.67
129.69
129.53
128.61
126.64
115.60
114.30
114.27
114.25
114.22
109.24
109.21
109.18
109.15
95.24
77.16 CDCl3
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

^{19}F NMR

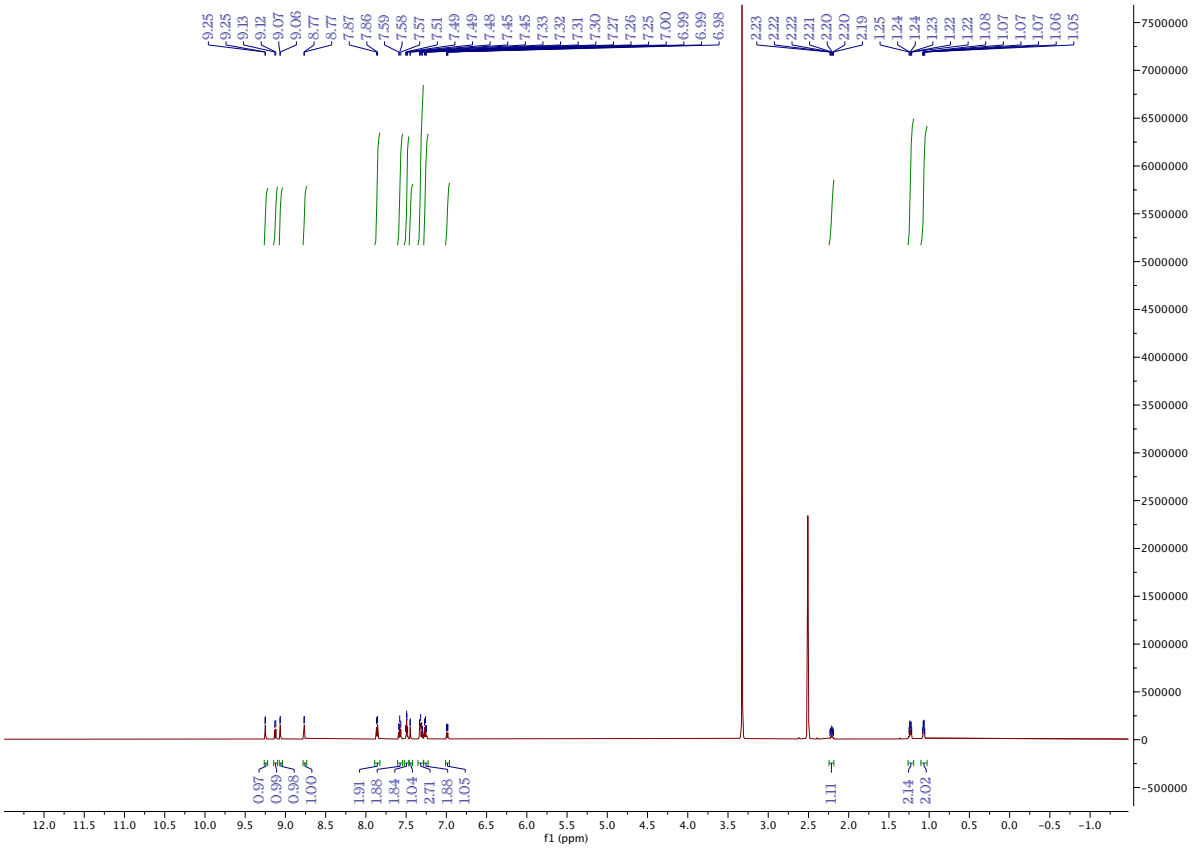

N
N
CF3
N
NH


-64.73
18000000
17000000
16000000
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)

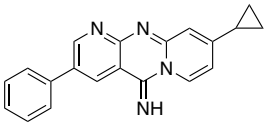
*5-phenyl-2-((4-(cyclopropyl)pyridin-2-yl)amino)nicotinonitrile (**3m**)*

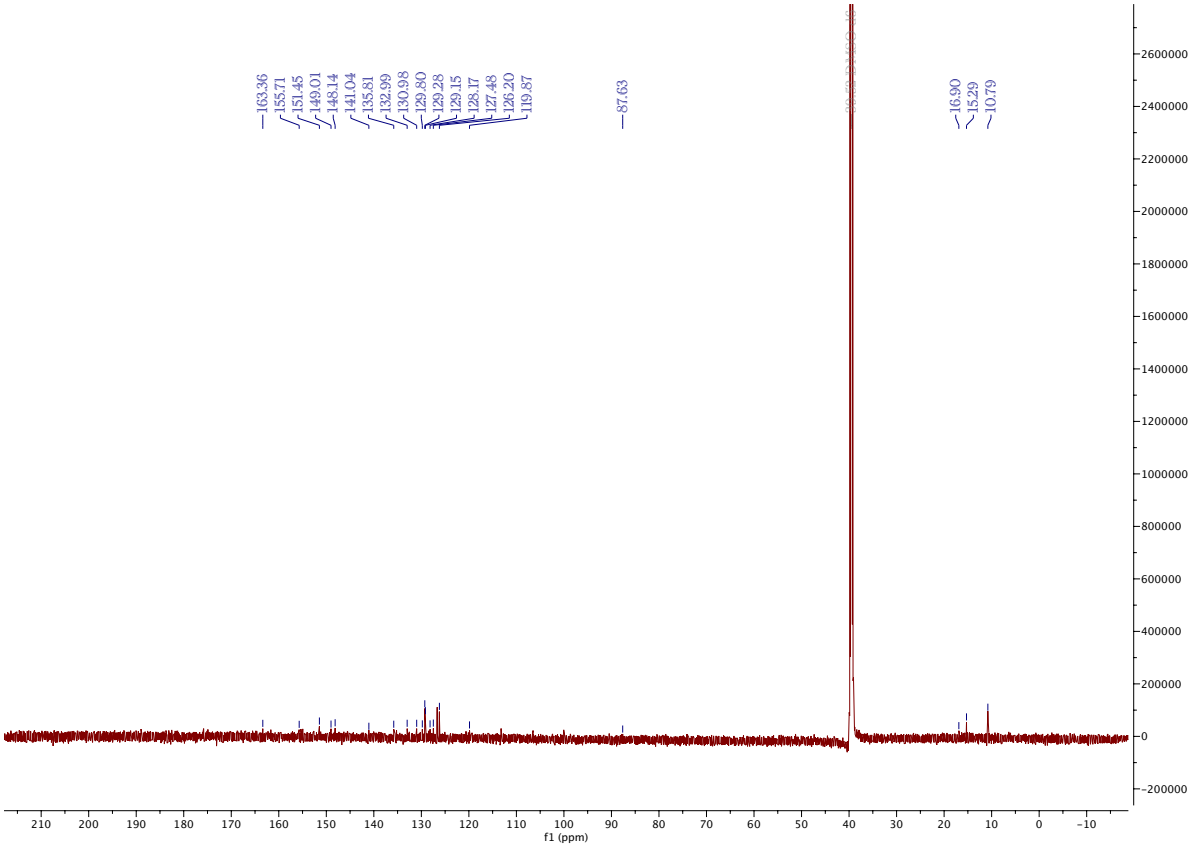


^{1}H NMR

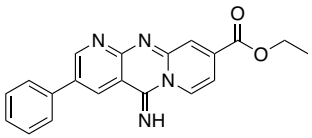


^{13}C NMR

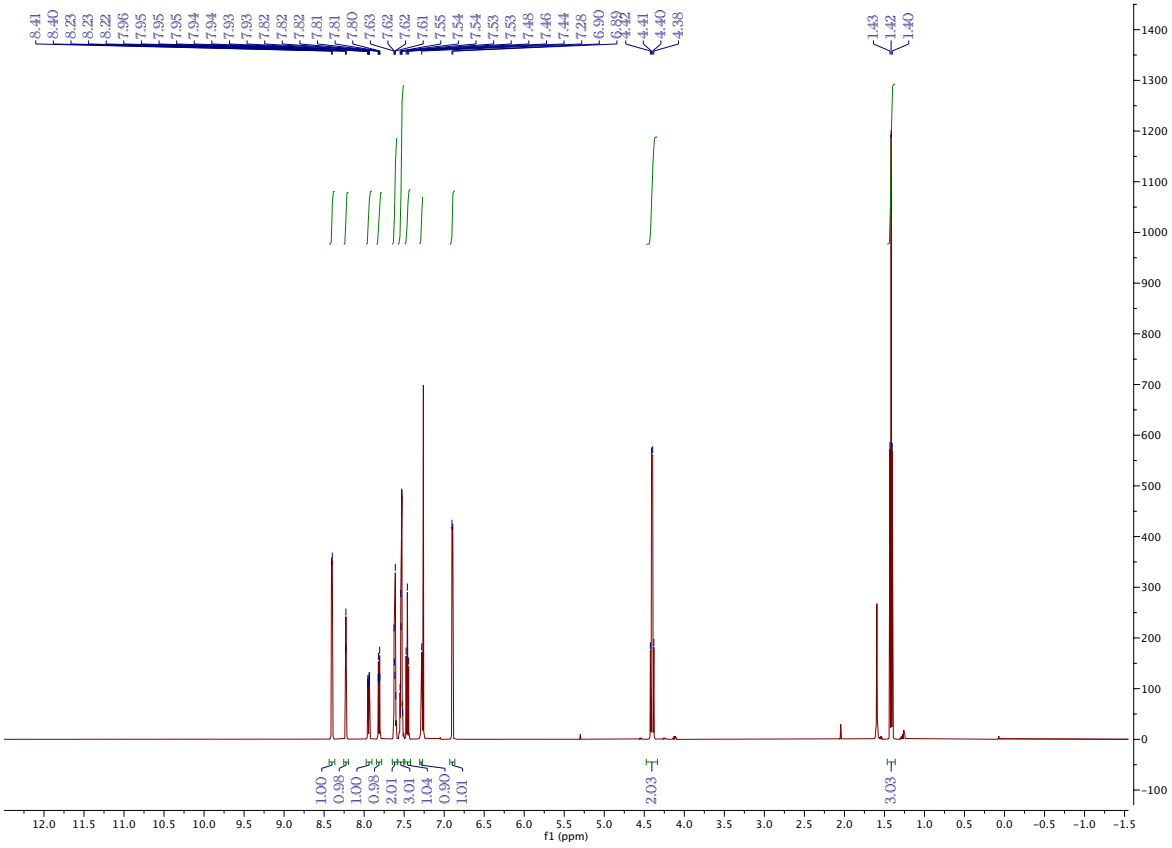

N
N
N
NH


163.36
155.71
151.45
149.01
148.14
141.04
135.81
132.99
130.98
129.80
129.28
129.15
128.17
127.48
126.20
119.87
87.63
16.90
15.29
10.79
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

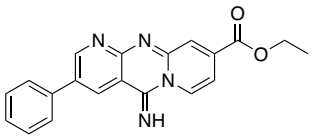
*Ethyl 2-((3-cyano-5-phenylpyridin-2-yl)amino)isonicotinate (**3n**)*

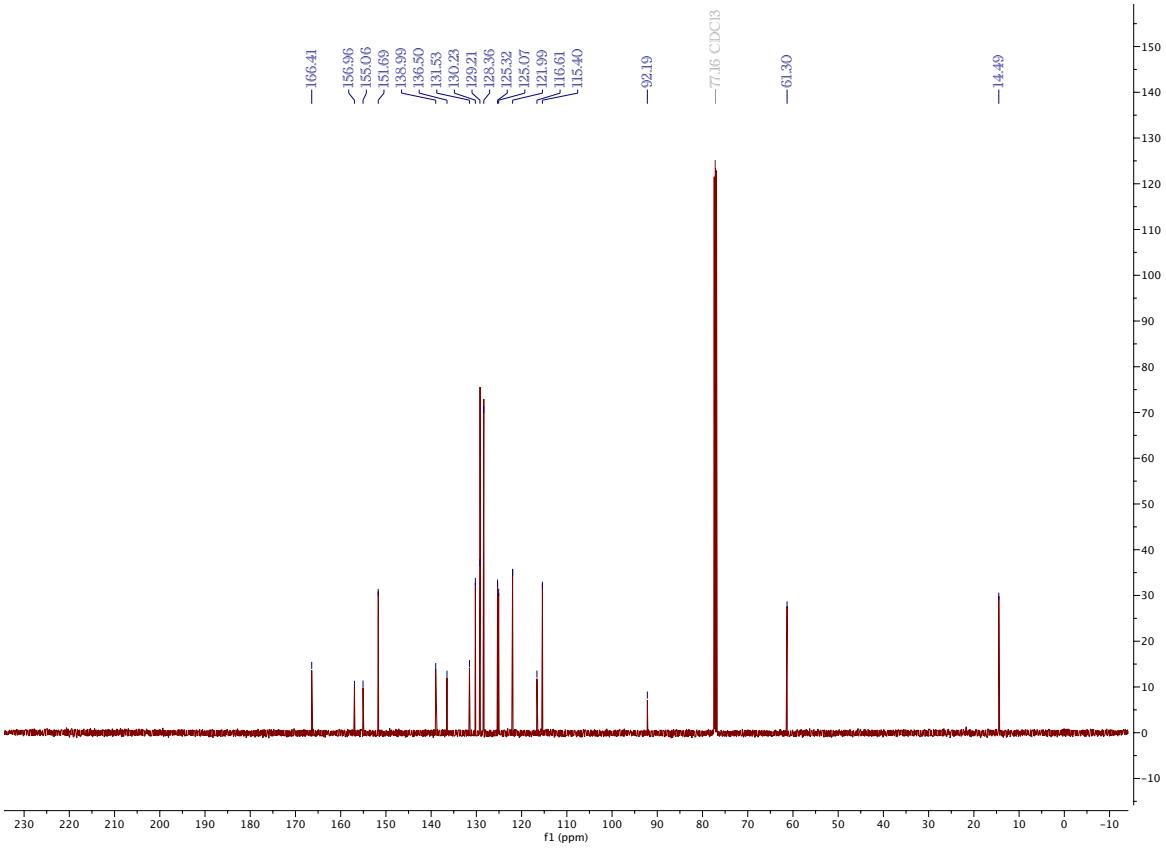


^{1}H NMR



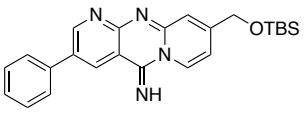
^{13}C NMR

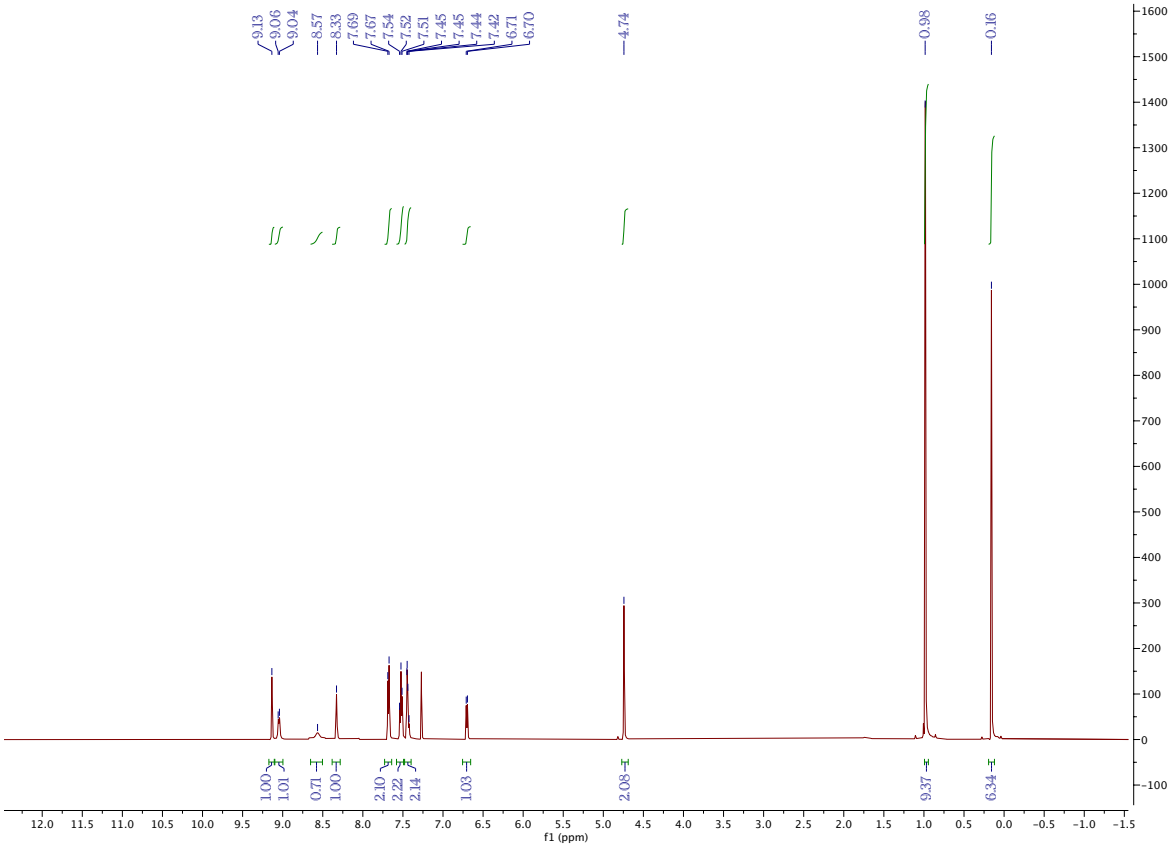

O
N
N
O
N
NH


166.41
156.96
155.06
151.69
138.99
136.50
131.53
130.23
129.21
128.36
125.32
125.07
121.99
116.61
115.40
92.19
77.16 CDCl3
61.30
14.49
f1 (ppm)

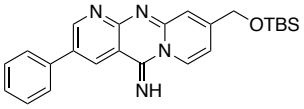
*2-((4-(((tert-butyldimethylsilyl)oxy)methyl)pyridin-2-yl)amino)-5-phenylnicotinonitrile (**3o**)*

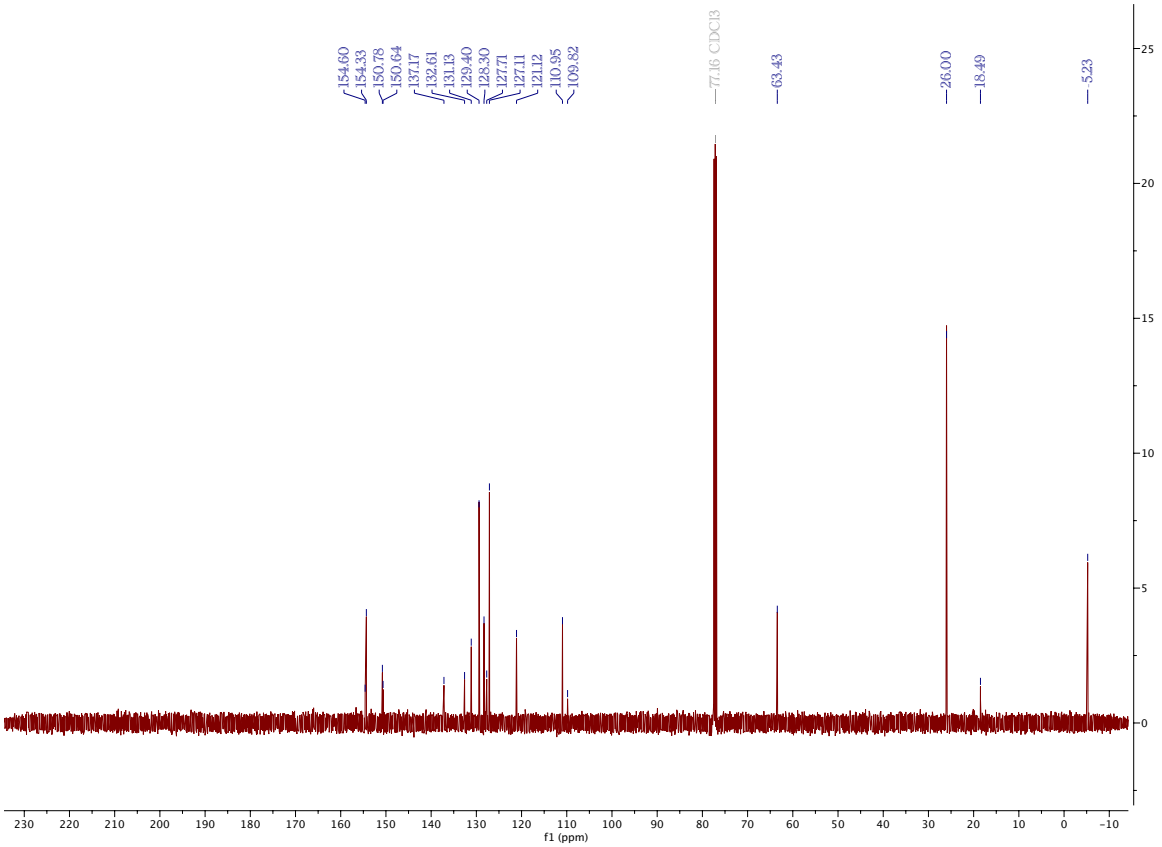
^{1}H NMR



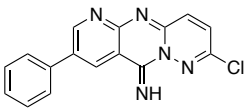


^{13}C NMR

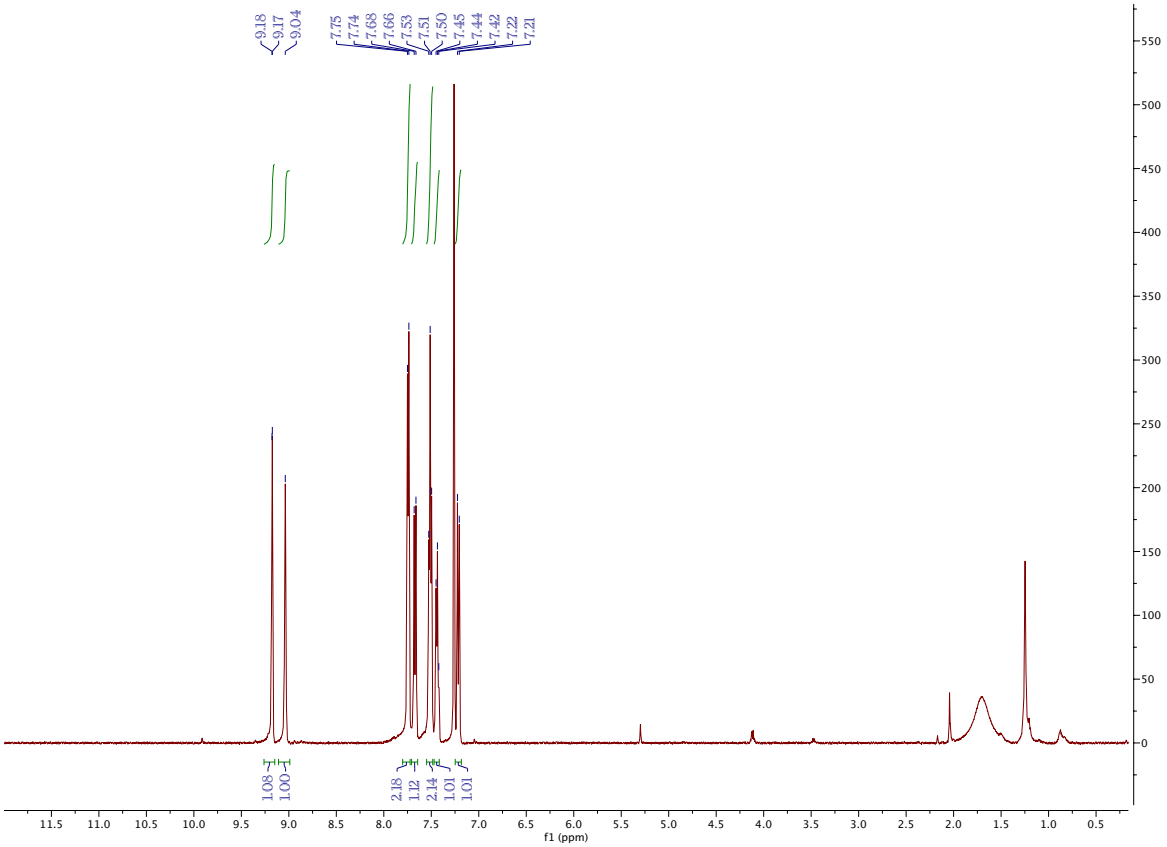

N
N
N
NH
OTBS


154.60
154.33
150.78
150.64
137.17
132.61
131.13
129.40
128.30
127.71
127.11
121.12
110.95
109.82
77.16 CDCl3
63.43
26.00
18.49
5.23
f1 (ppm)

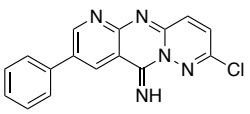
*2-((6-chloropyridazin-3-yl)amino)-5-phenylnicotinonitrile (**3p**)*

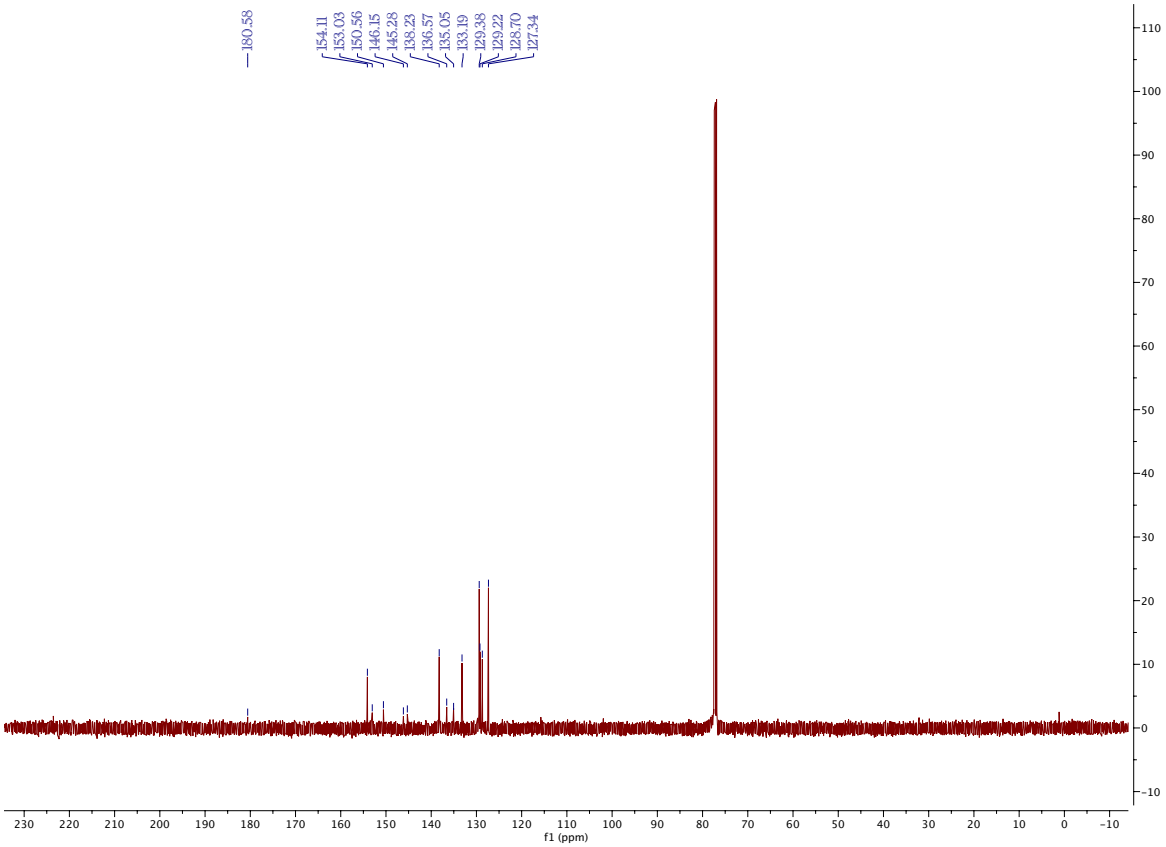


^{1}H NMR

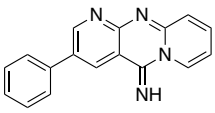


^{13}C NMR

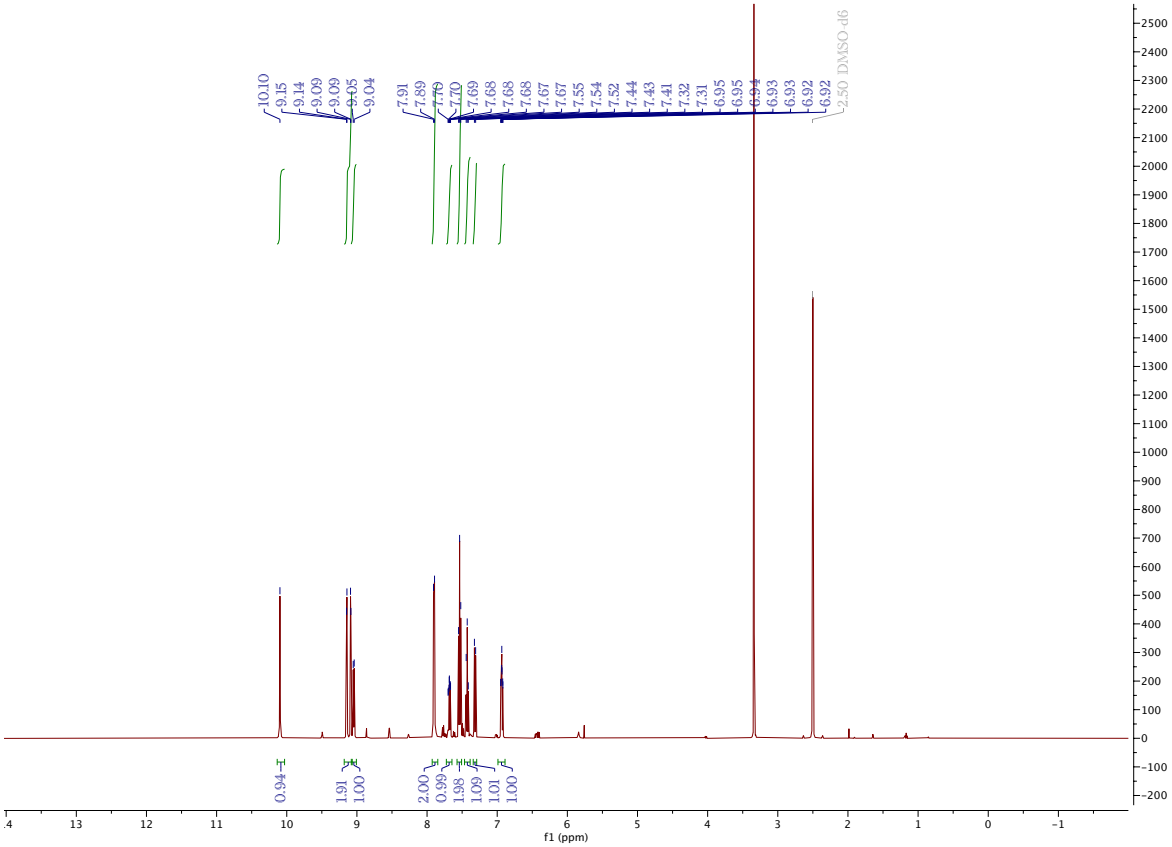

N
N
N
N
Cl
NH


180.58
154.11
153.03
150.56
146.15
145.28
138.23
136.57
135.05
133.19
129.38
129.22
128.70
127.34
110
100
90
80
70
60
50
40
30
20
10
0
-10
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

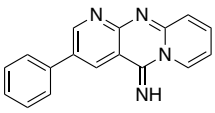
*5-phenyl-2-(pyridin-2-ylamino)nicotinonitrile (**3q**)*

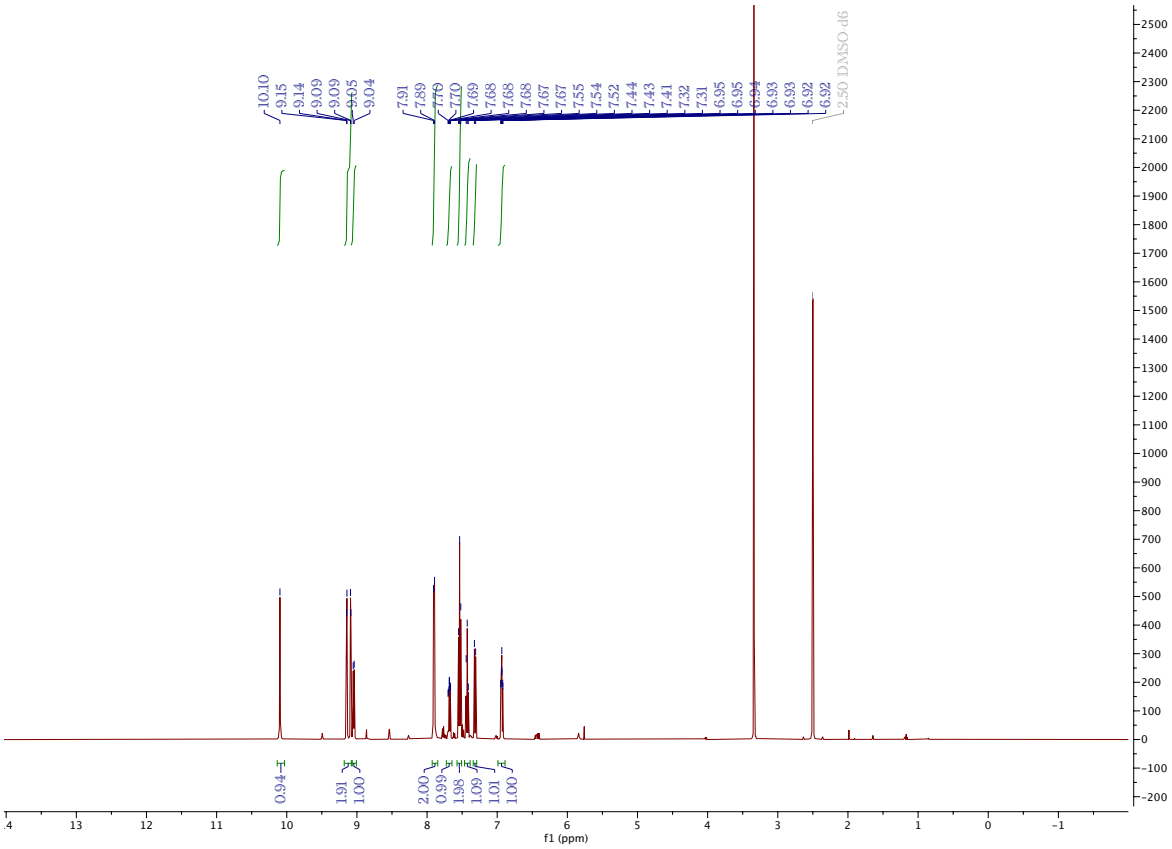


^{1}H NMR

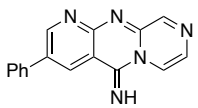


^{13}C NMR

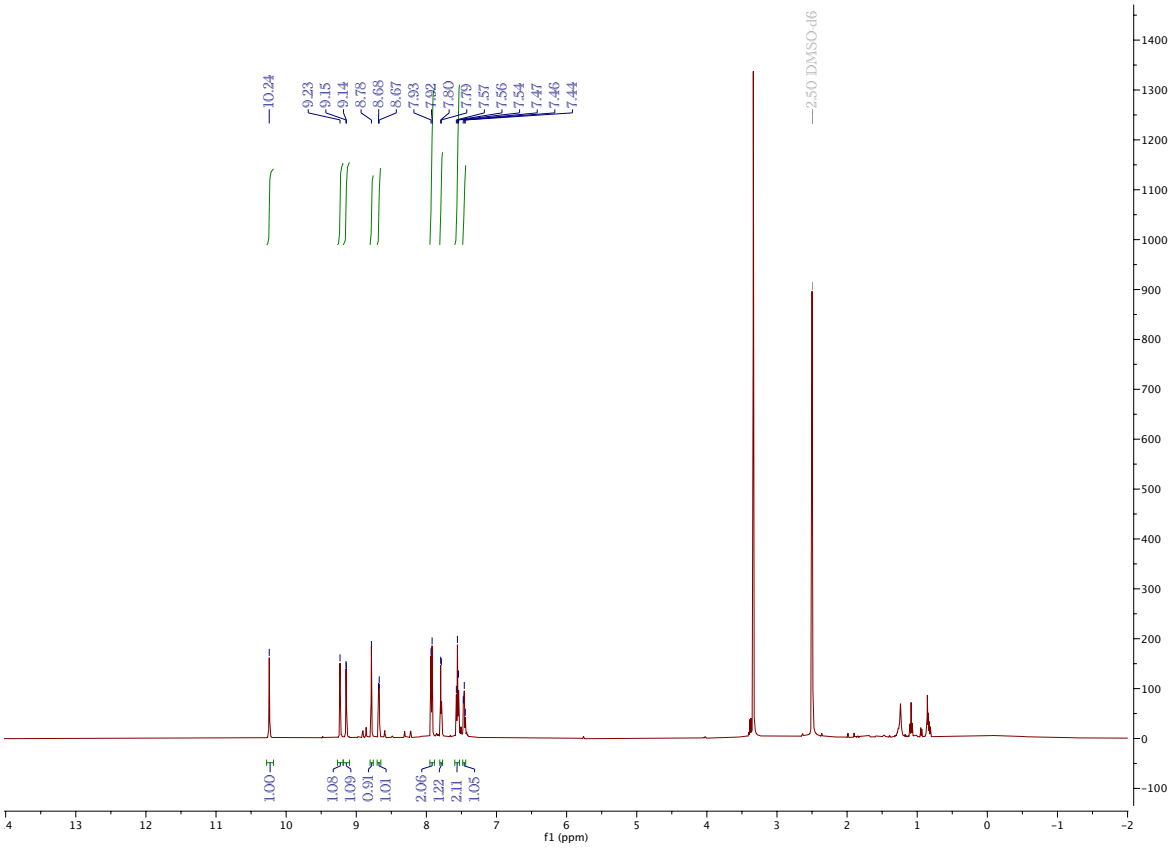

N
N
N
NH


10.10
9.15
9.14
9.09
9.09
9.05
9.04
7.91
7.89
7.79
7.70
7.69
7.68
7.68
7.68
7.67
7.67
7.55
7.54
7.52
7.44
7.43
7.41
7.32
7.31
6.95
6.95
6.94
6.93
6.92
6.92
2.50 DMSO-d6
0.94
1.91
1.00
2.00
0.99
1.98
1.09
1.01
1.00
f1 (ppm)

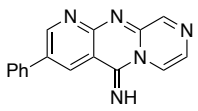
*5-phenyl-2-(pyrazin-2-ylamino)nicotinonitrile (**3r**)*

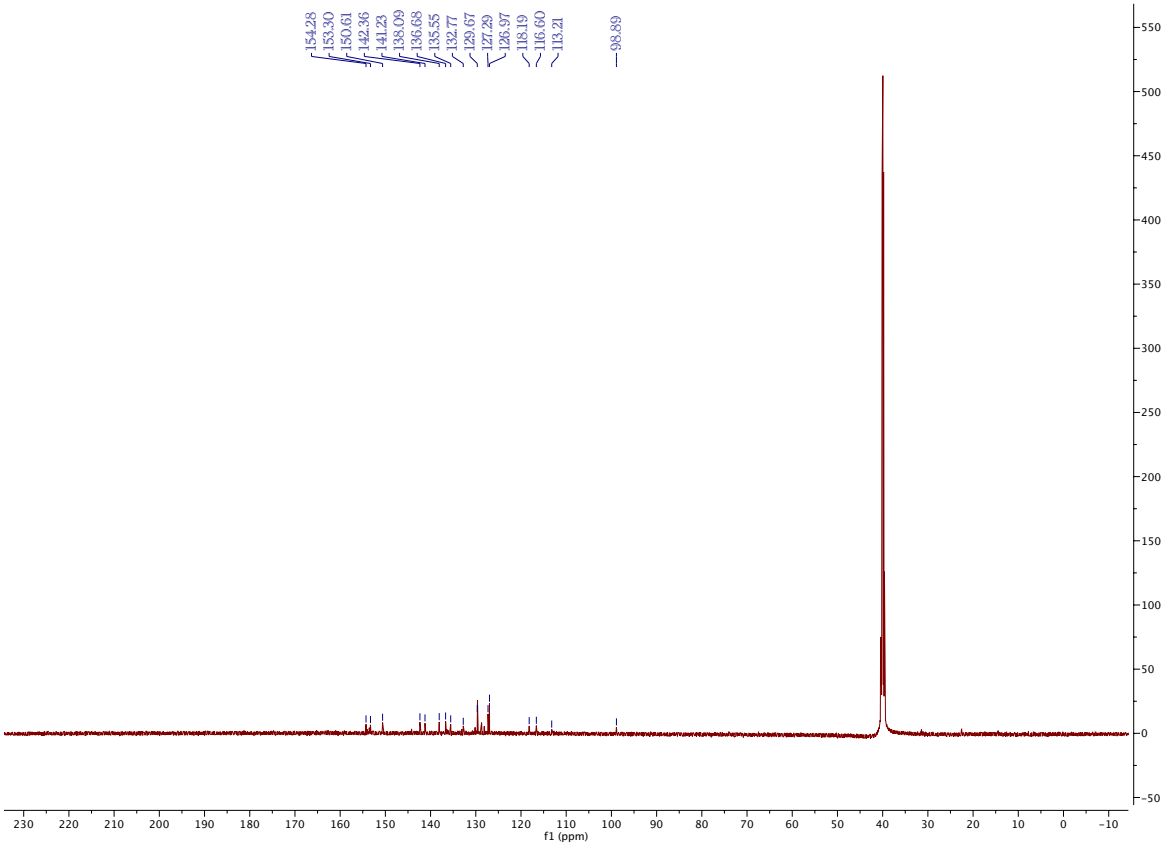


^{1}H NMR



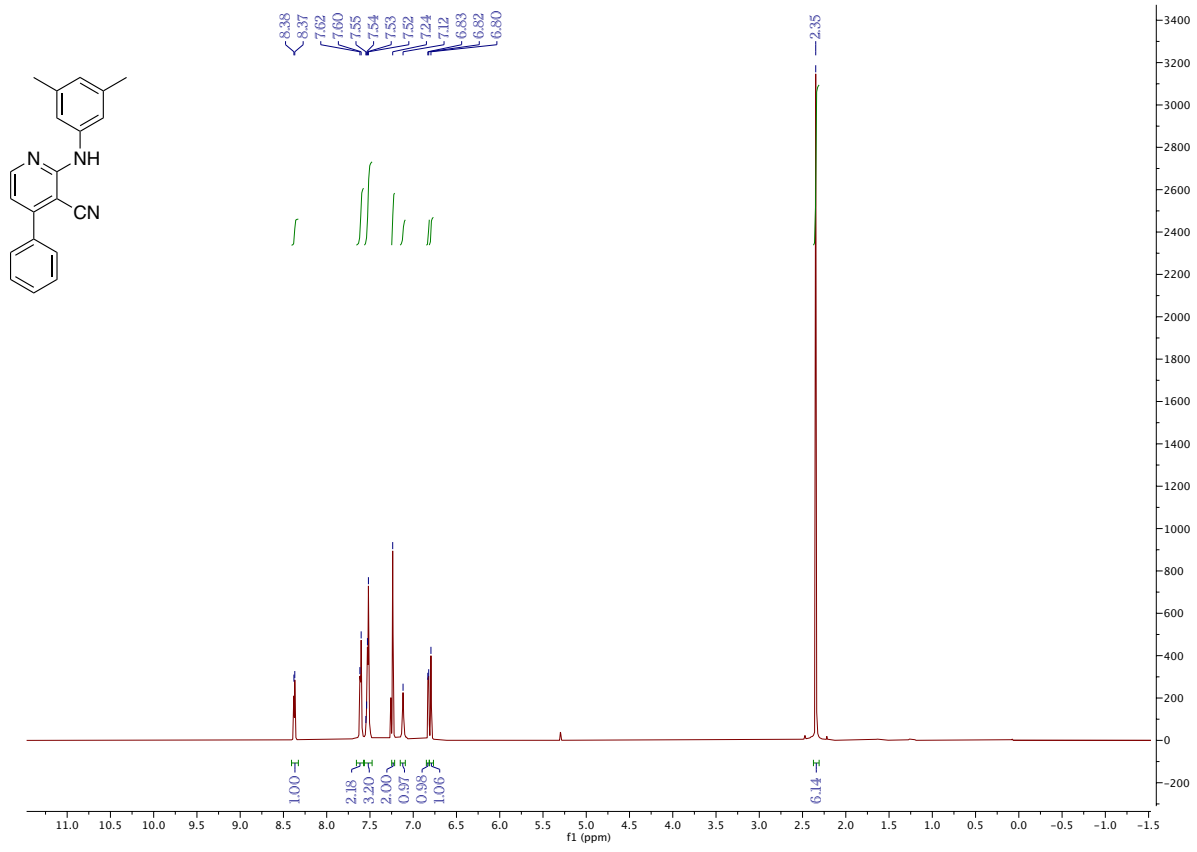
^{13}C NMR


N
N
N
N
Ph
NH

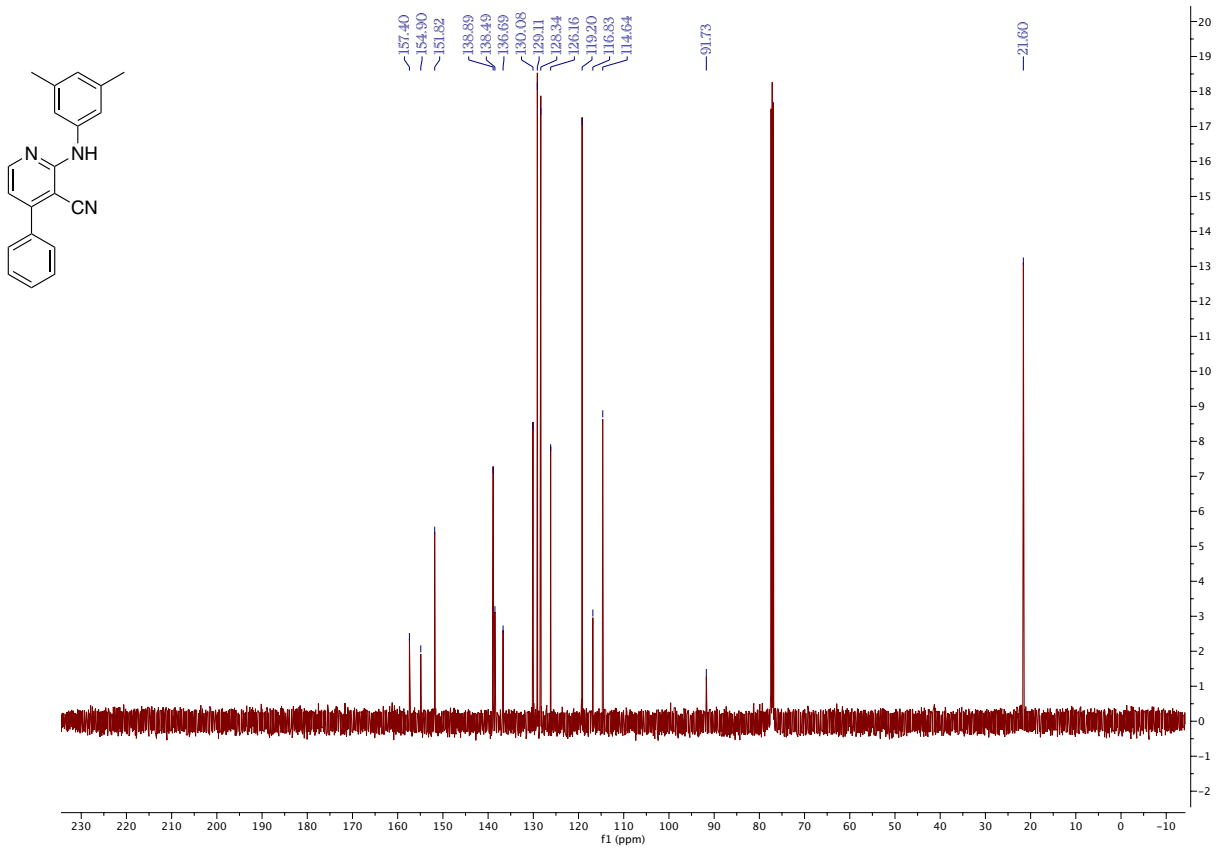

154.28
153.30
150.61
142.36
141.23
138.09
136.68
135.55
132.77
129.67
127.29
126.97
118.19
116.60
113.21
98.89
550
500
450
400
350
300
250
200
150
100
50
0
-50
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

*2-((3,5-dimethylphenyl)amino)-4-phenylnicotinonitrile (**4a**).*

^{1}H NMR

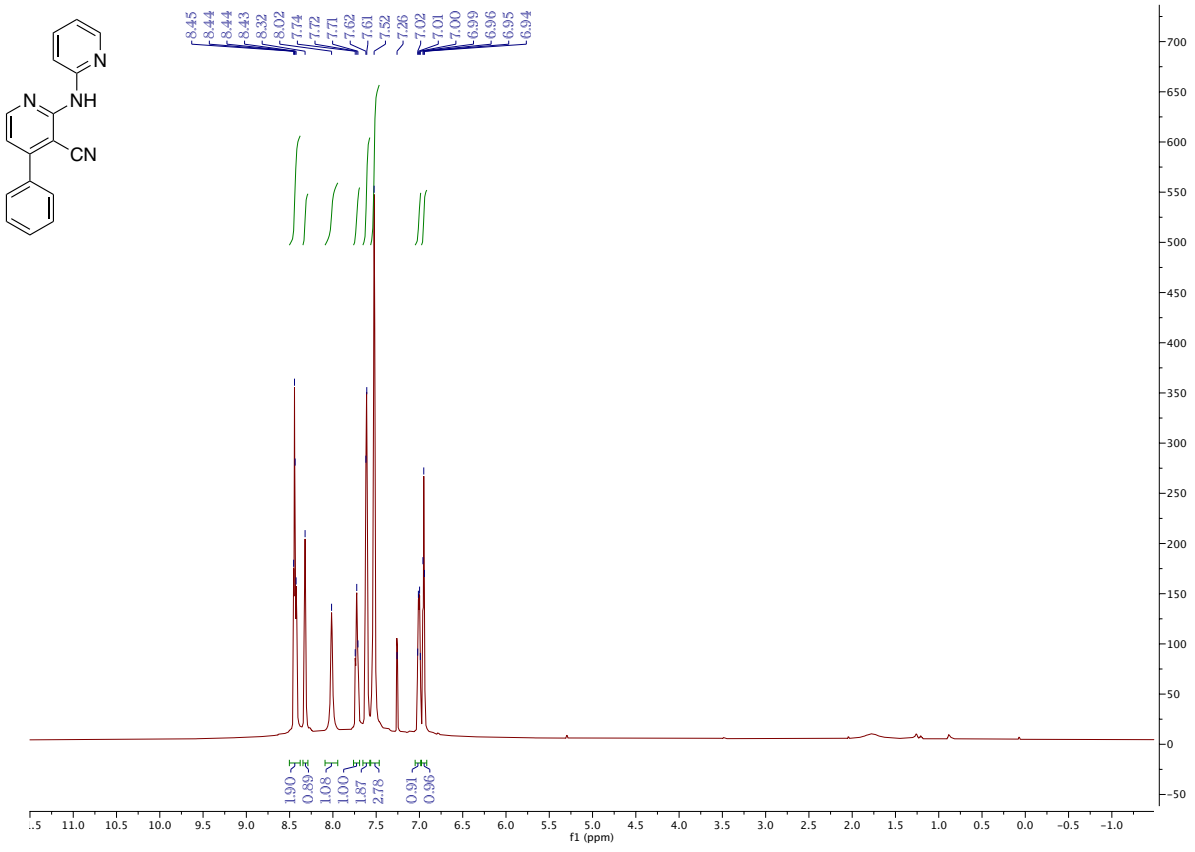


^{13}C NMR

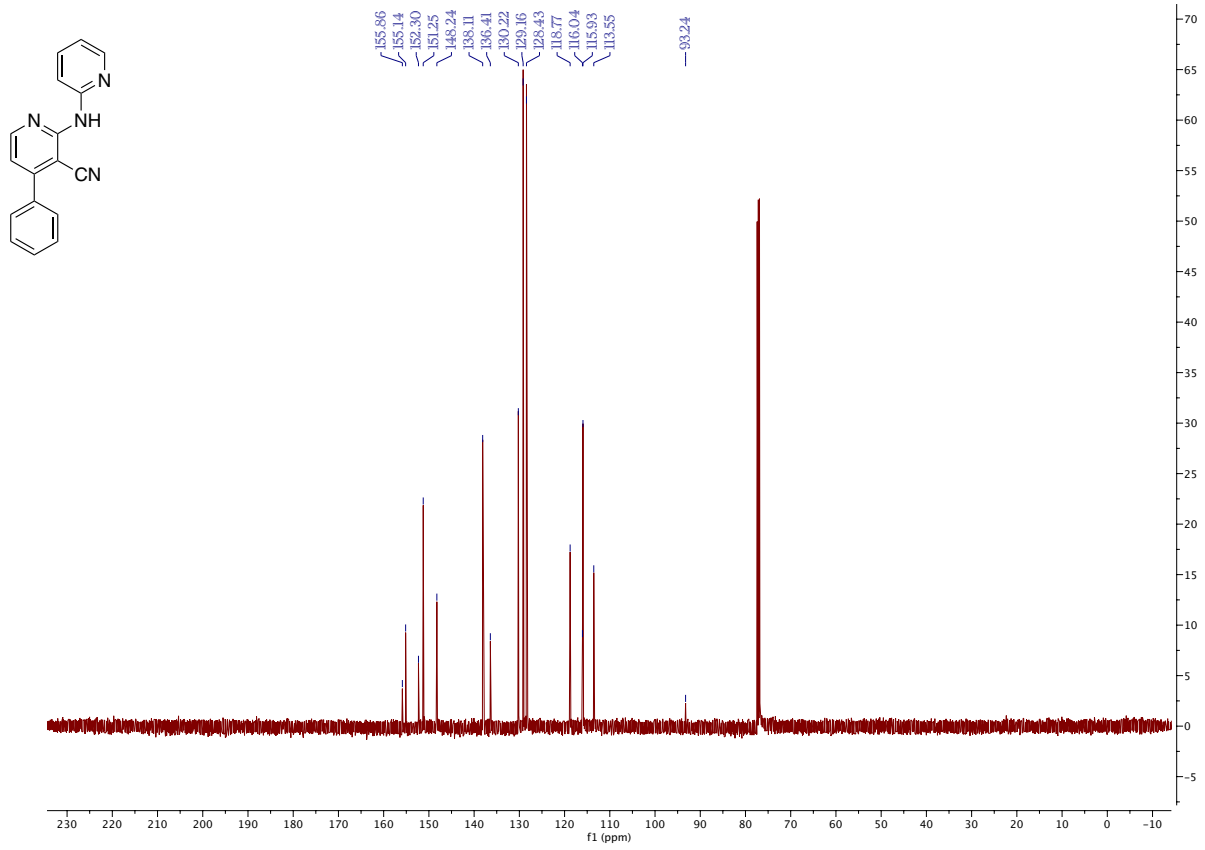

157.40
154.90
151.62
138.89
138.49
136.69
130.08
129.11
128.34
126.16
119.20
116.83
114.64
91.73
21.60
N
NH
CN
f1 (ppm)

*4-phenyl-2-(pyridin-2-ylamino)nicotinonitrile (**4b**).*

^{1}H NMR

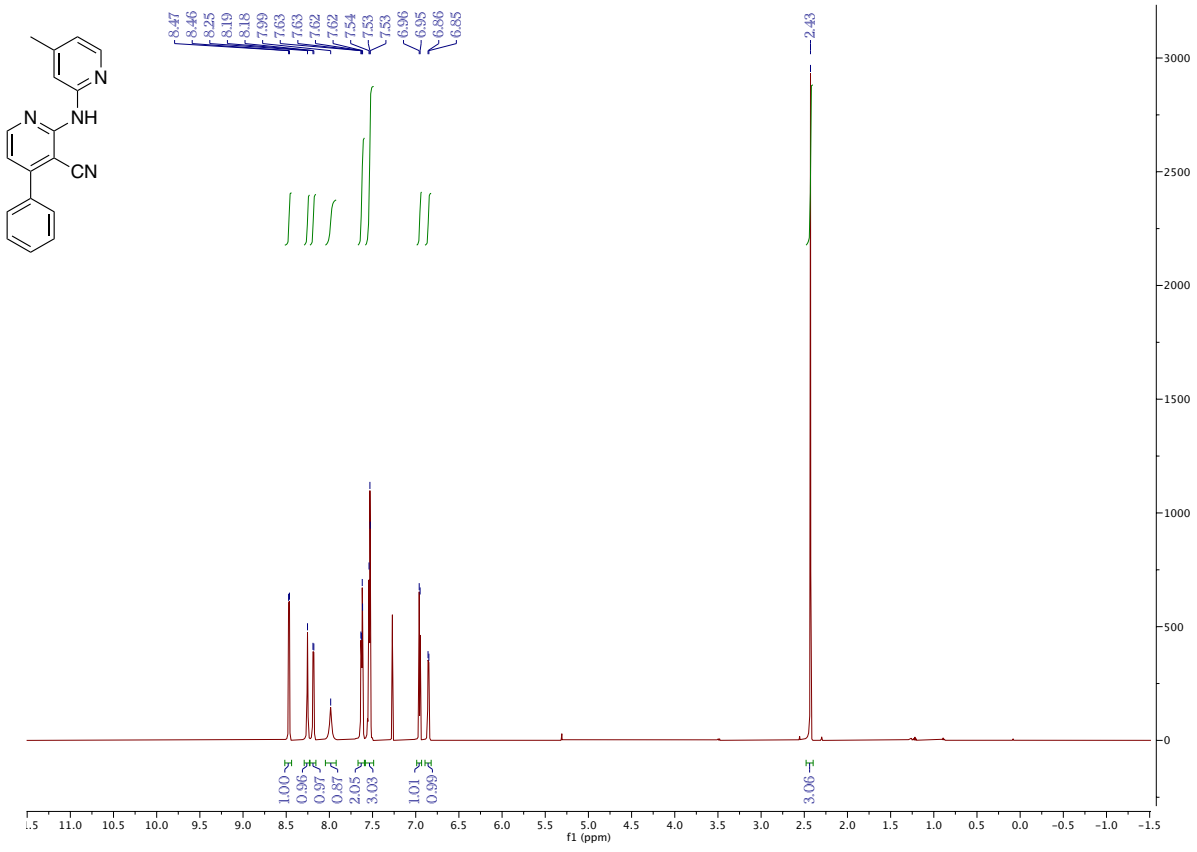


^{13}C NMR

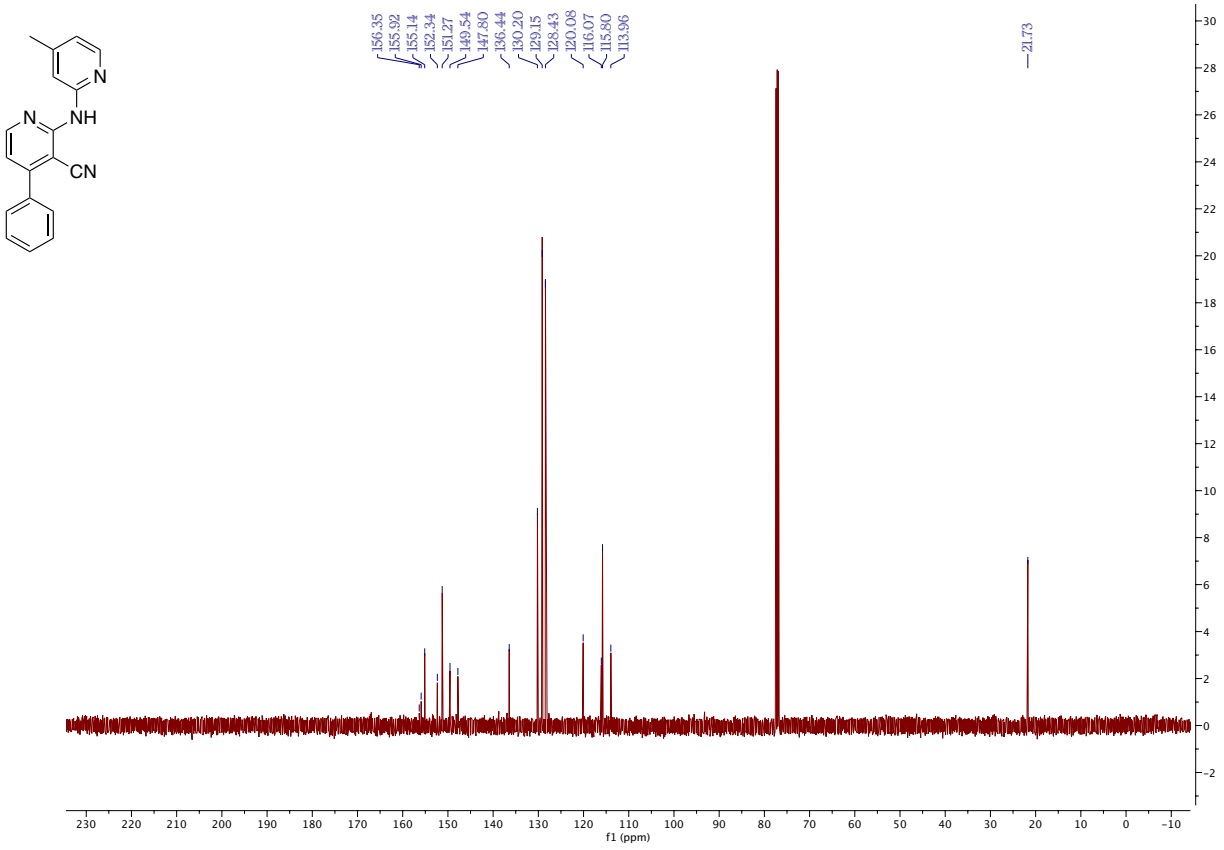

155.86
155.14
152.30
151.25
148.24
138.11
136.41
130.22
129.16
128.43
118.77
116.04
115.93
113.55
93.24
f1 (ppm)

*2-((4-methylpyridin-2-yl)amino)-4-phenylnicotinonitrile (**4c**).*

^{1}H NMR

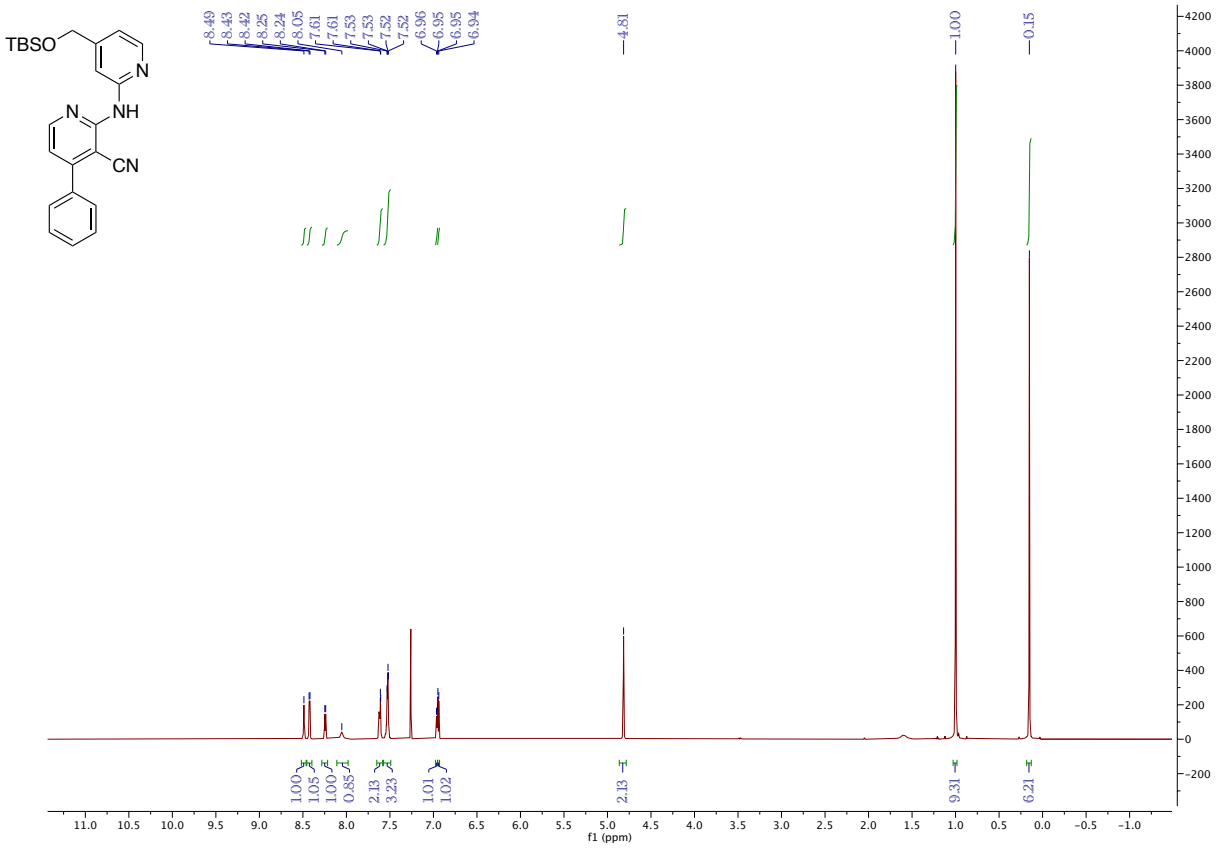


^{13}C NMR

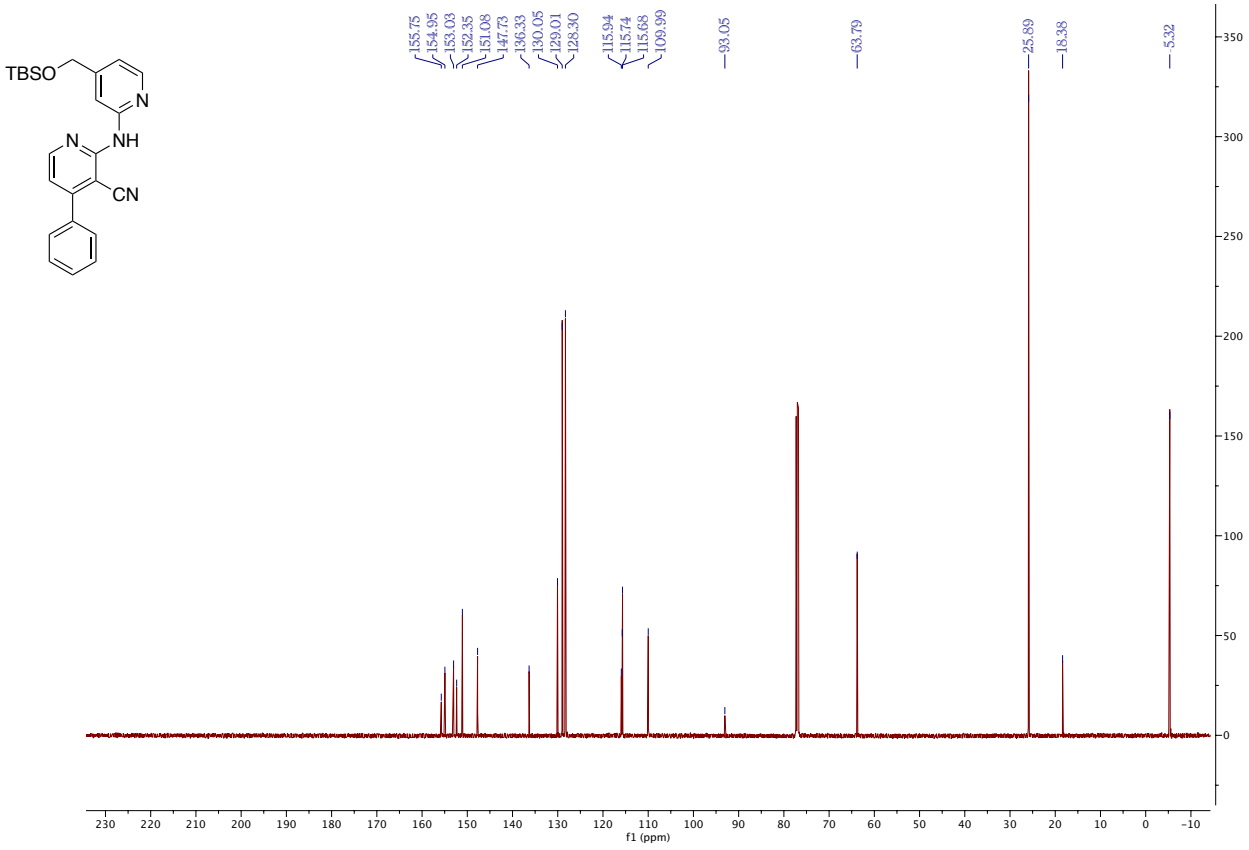

156.35
155.92
155.14
152.34
151.27
149.54
147.80
136.44
130.20
129.15
128.43
120.08
116.07
115.80
113.96
21.73
f1 (ppm)

*2-((4-(((tert-butyldimethylsilyl)oxy)methyl)pyridin-2-yl)amino)-4-phenylnicotinonitrile (**4e-I**).*

^{1}H NMR

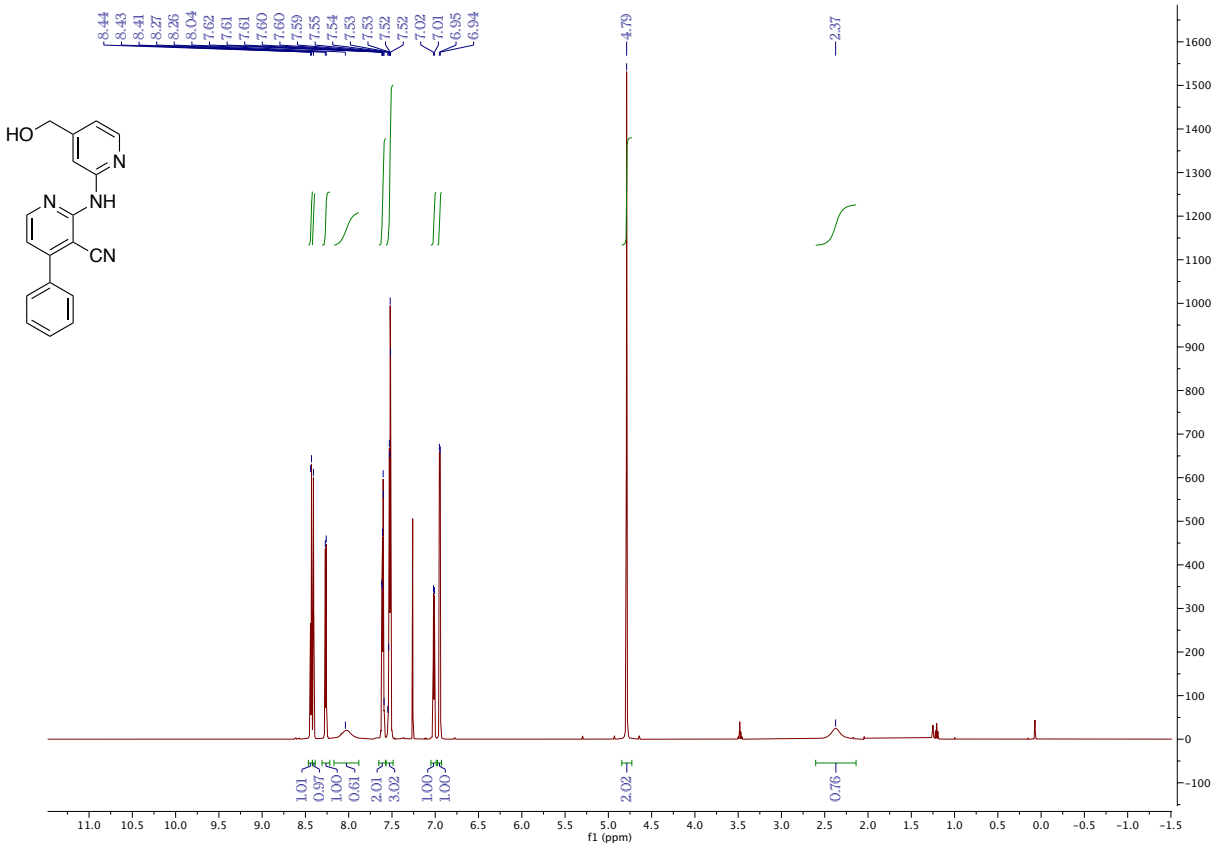


^{13}C NMR

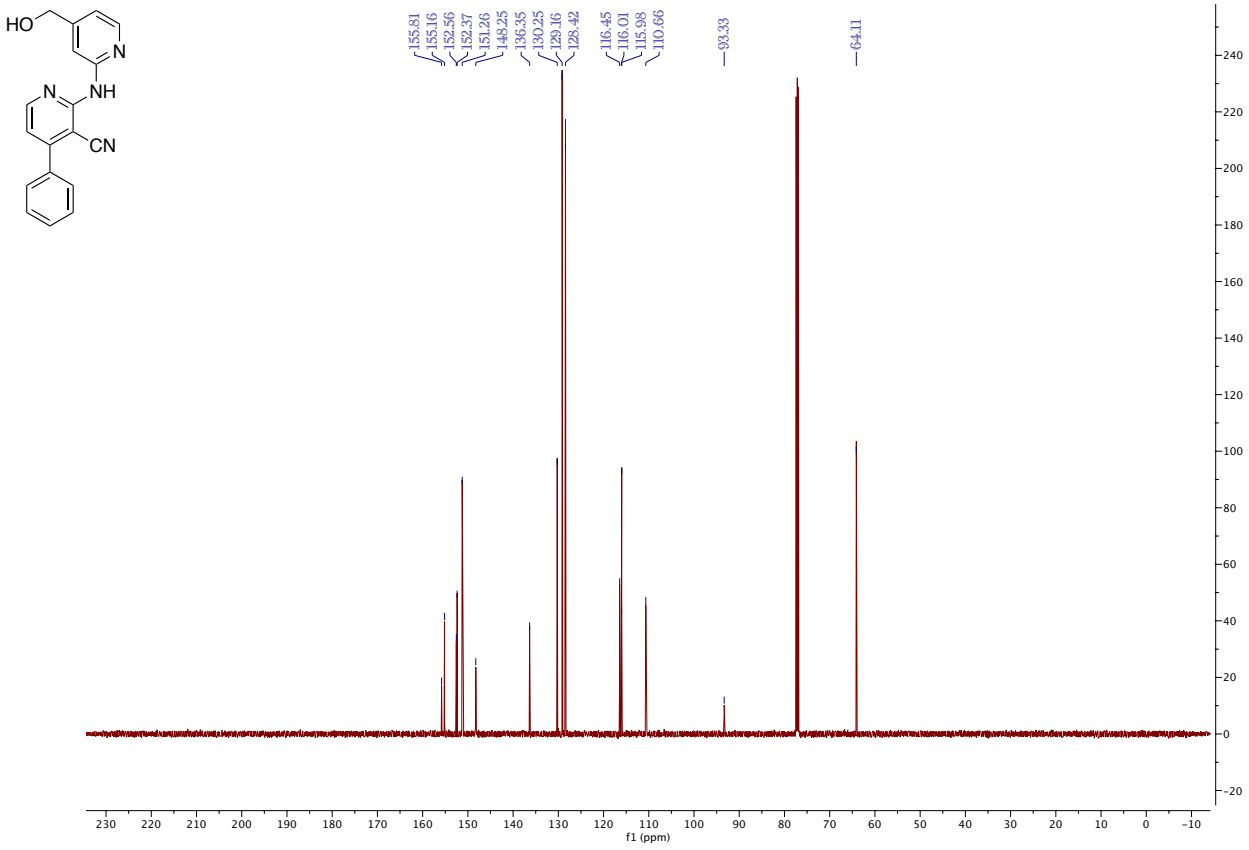

TBSO
N
NH
N
CN
155.75
154.95
153.03
152.35
151.08
147.73
136.33
130.05
129.01
128.30
115.94
115.74
115.68
109.99
93.05
63.79
25.89
18.38
-5.32
f1 (ppm)

*2-((4-(hydroxymethyl)pyridin-2-yl)amino)-4-phenylnicotinonitrile (**4e**).*

^{1}H NMR

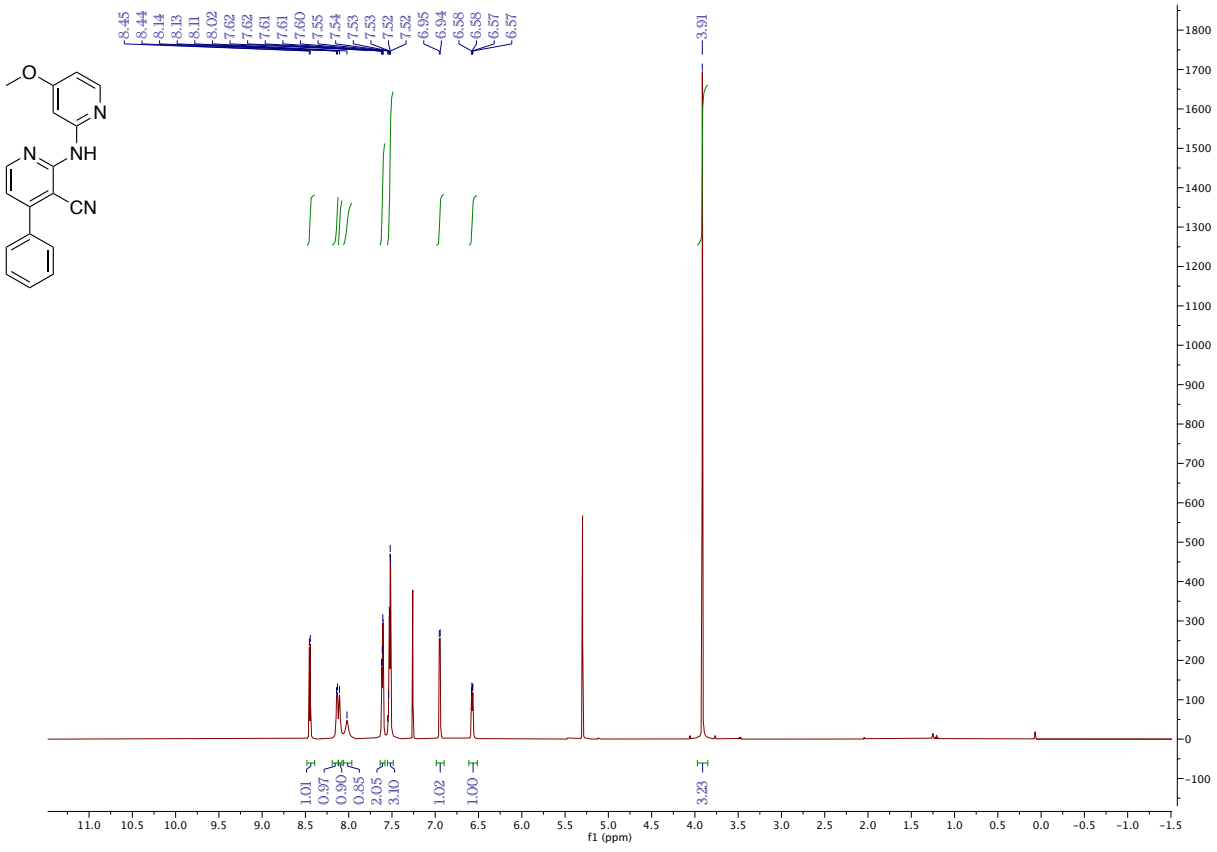


^{13}C NMR

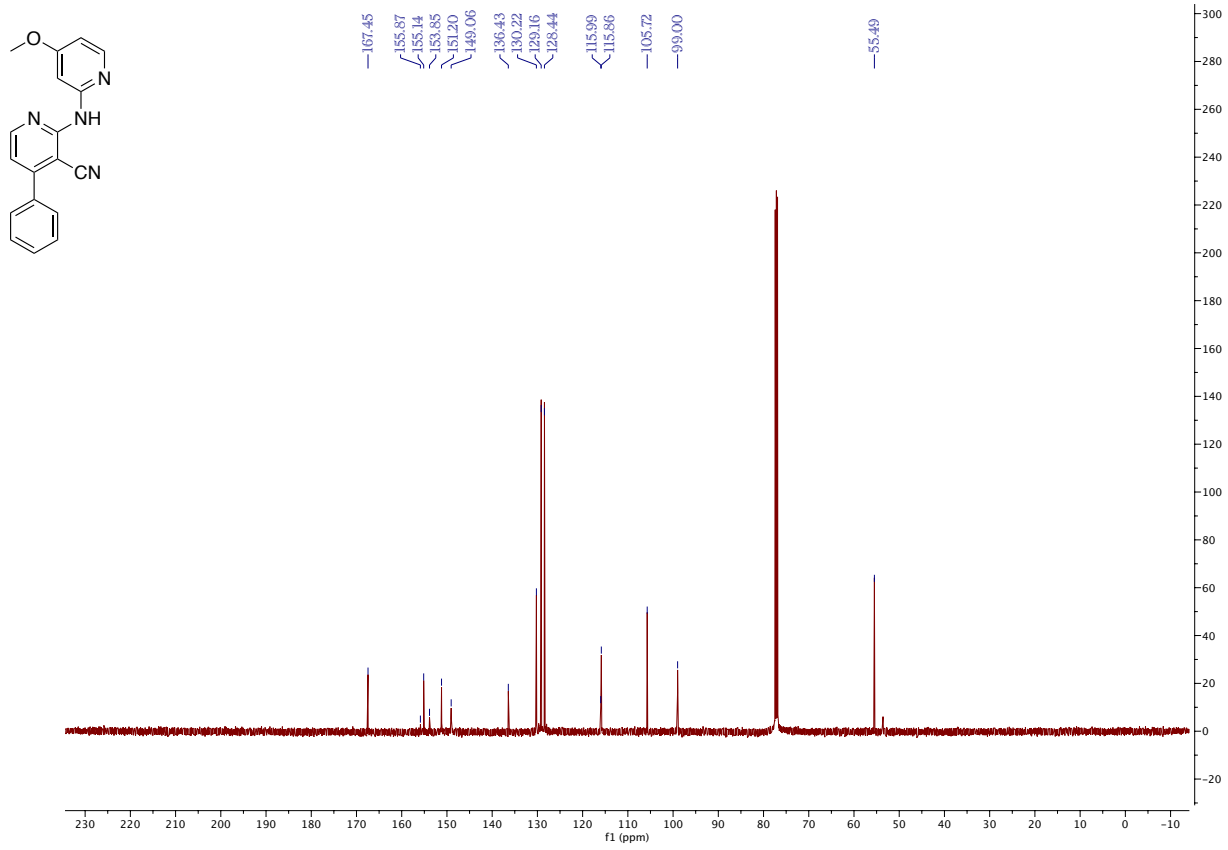

HO
N
NH
N
CN
155.81
155.16
152.56
152.37
151.26
148.25
136.35
130.25
129.16
128.42
116.45
116.01
115.98
110.66
93.33
64.11
f1 (ppm)

*2-((4-methoxypyridin-2-yl)amino)-4-phenylnicotinonitrile (**4f**).*

^{1}H NMR

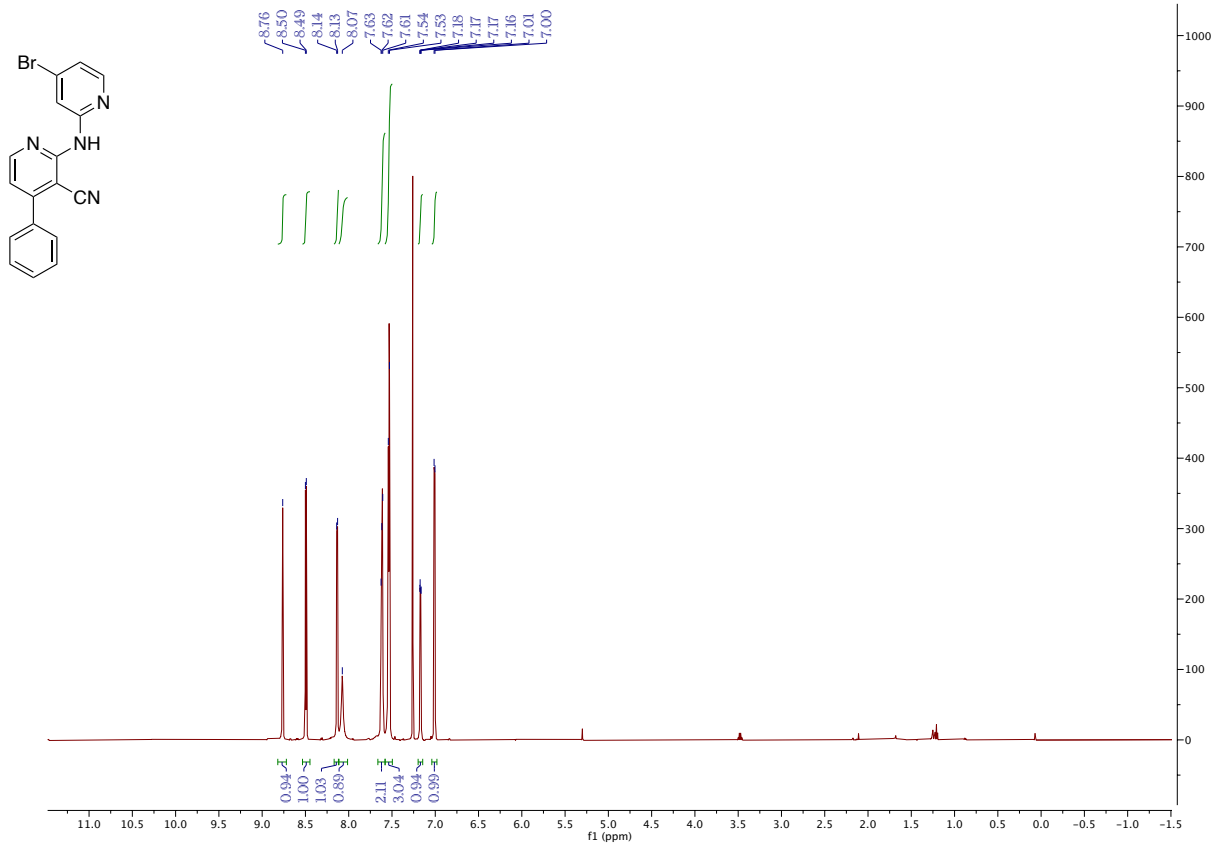


^{13}C NMR

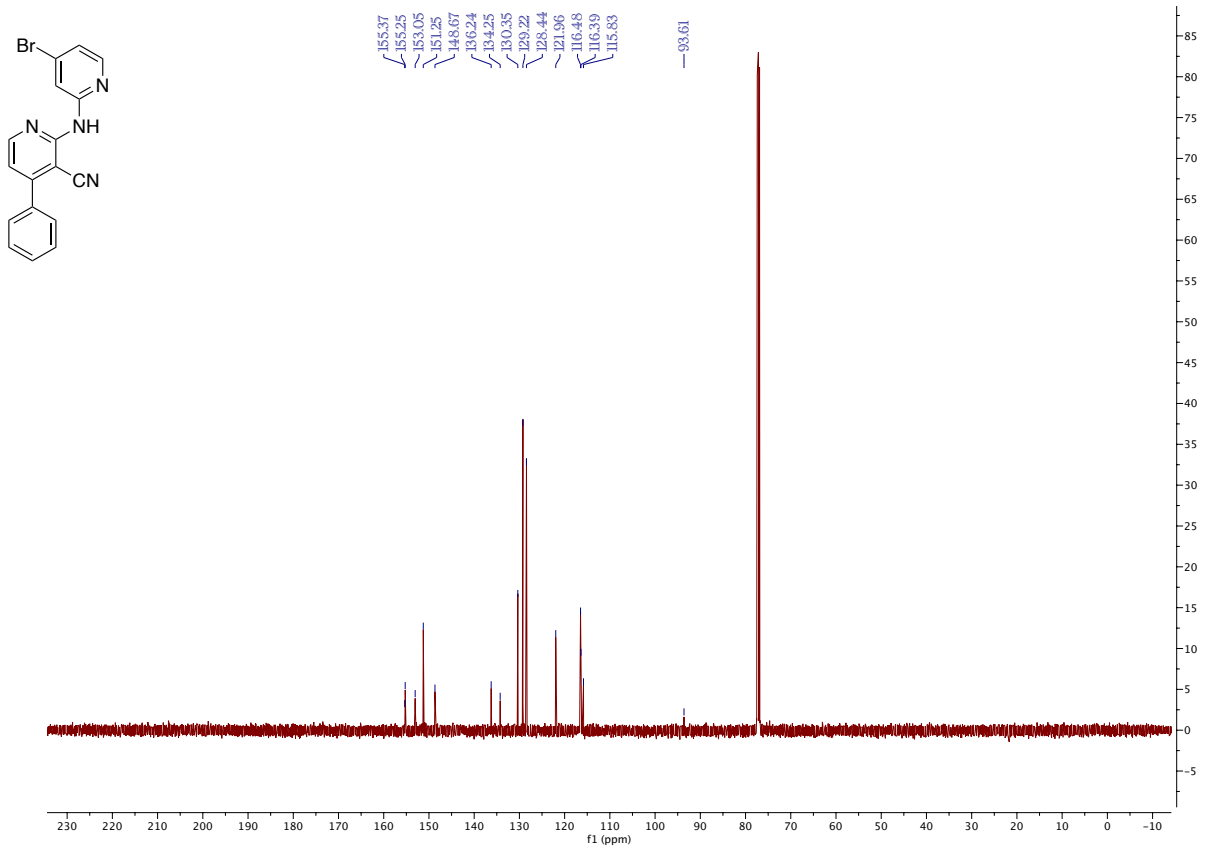

O
N
N
NH
CN
167.45
155.87
155.14
153.85
151.20
149.06
136.43
130.22
129.16
128.44
115.99
115.86
105.72
99.00
55.49
f1 (ppm)

*2-((4-bromopyridin-2-yl)amino)-4-phenylnicotinonitrile (**4g**).*

^{1}H NMR

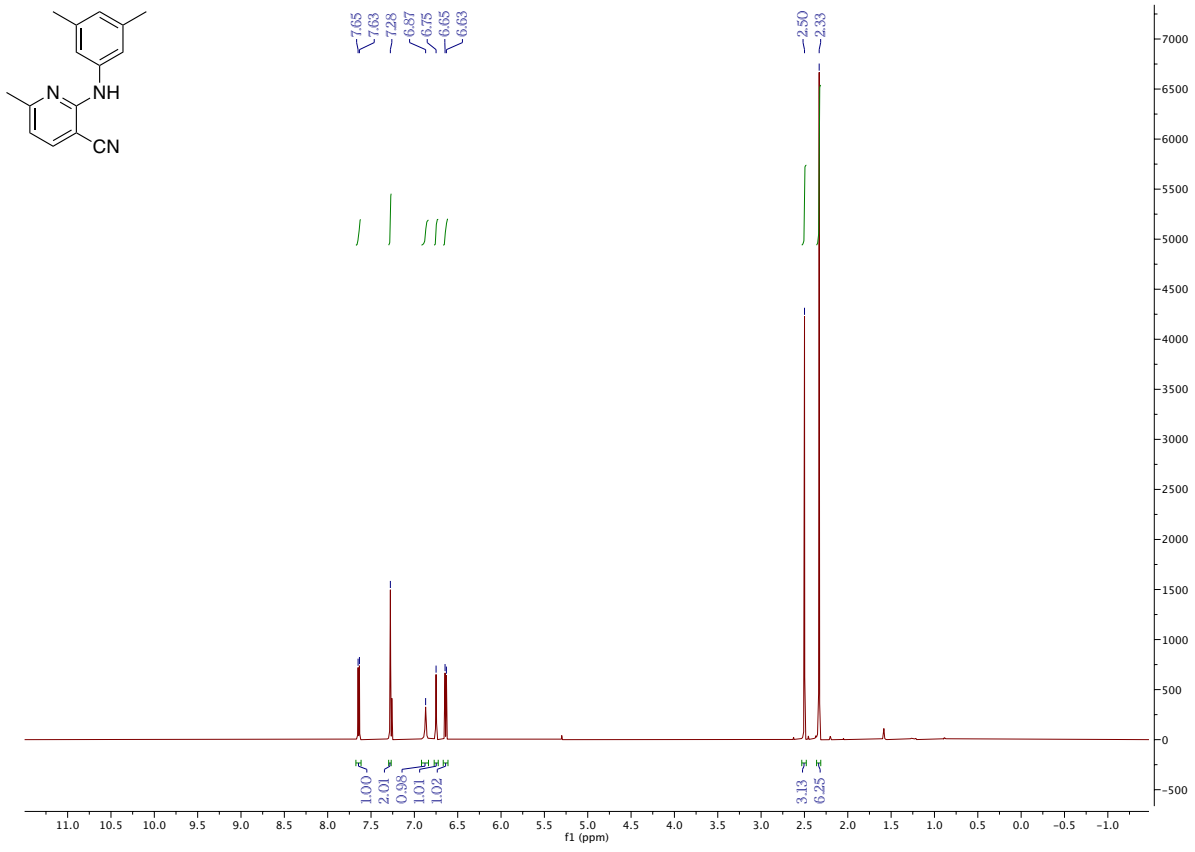


^{13}C NMR

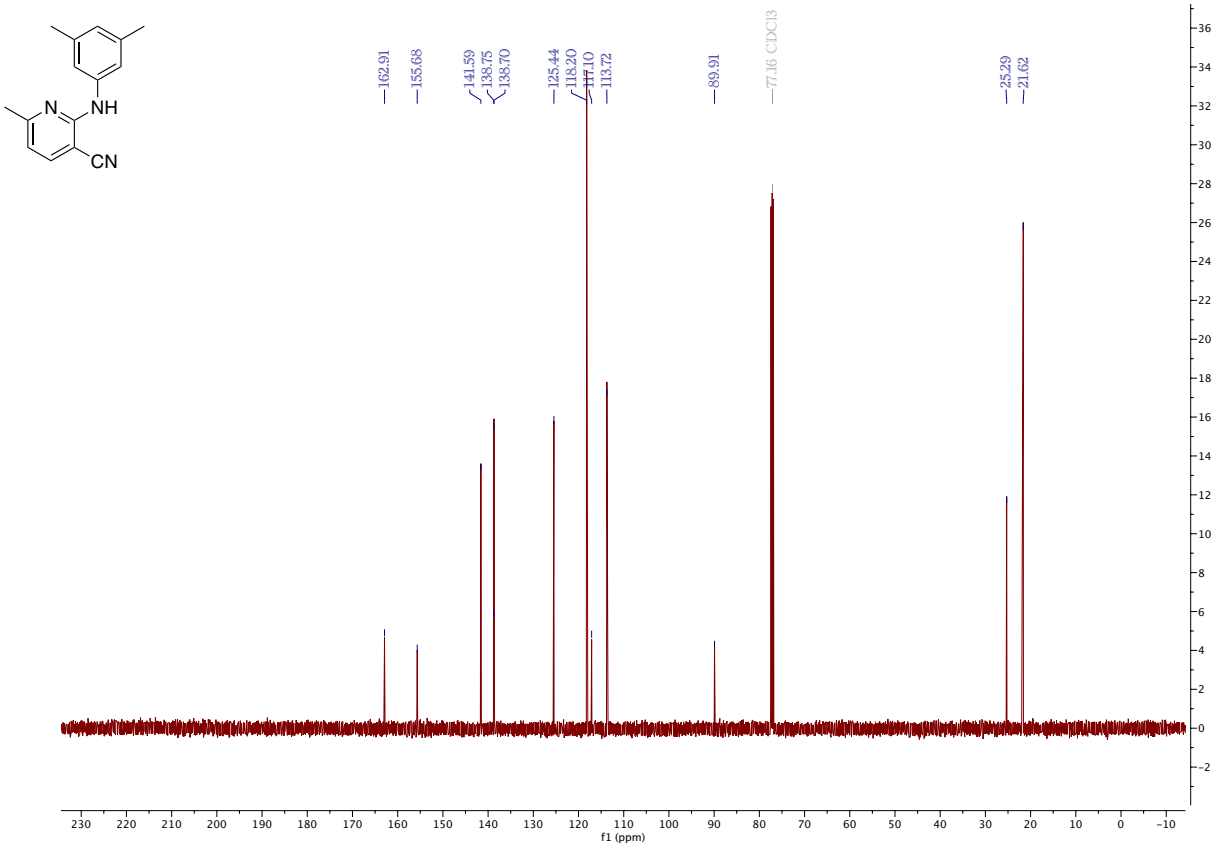

Br
N
N
NH
CN
155.37
155.25
153.05
151.25
148.67
136.24
134.25
130.35
129.22
128.44
121.96
116.48
116.39
115.83
93.61
f1 (ppm)

*2-((3,5-dimethylphenyl)amino)-6-methylnicotinonitrile (**5a**).*

^{1}H NMR

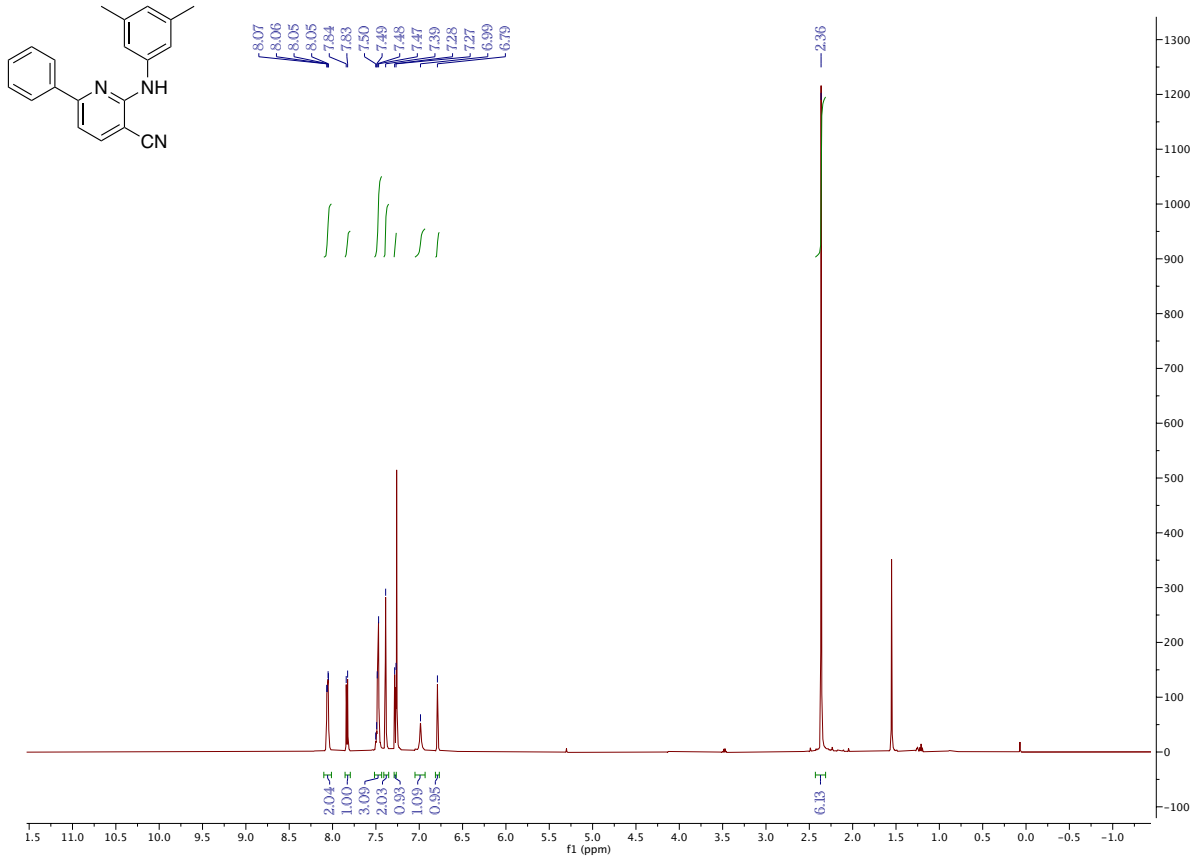


^{13}C NMR

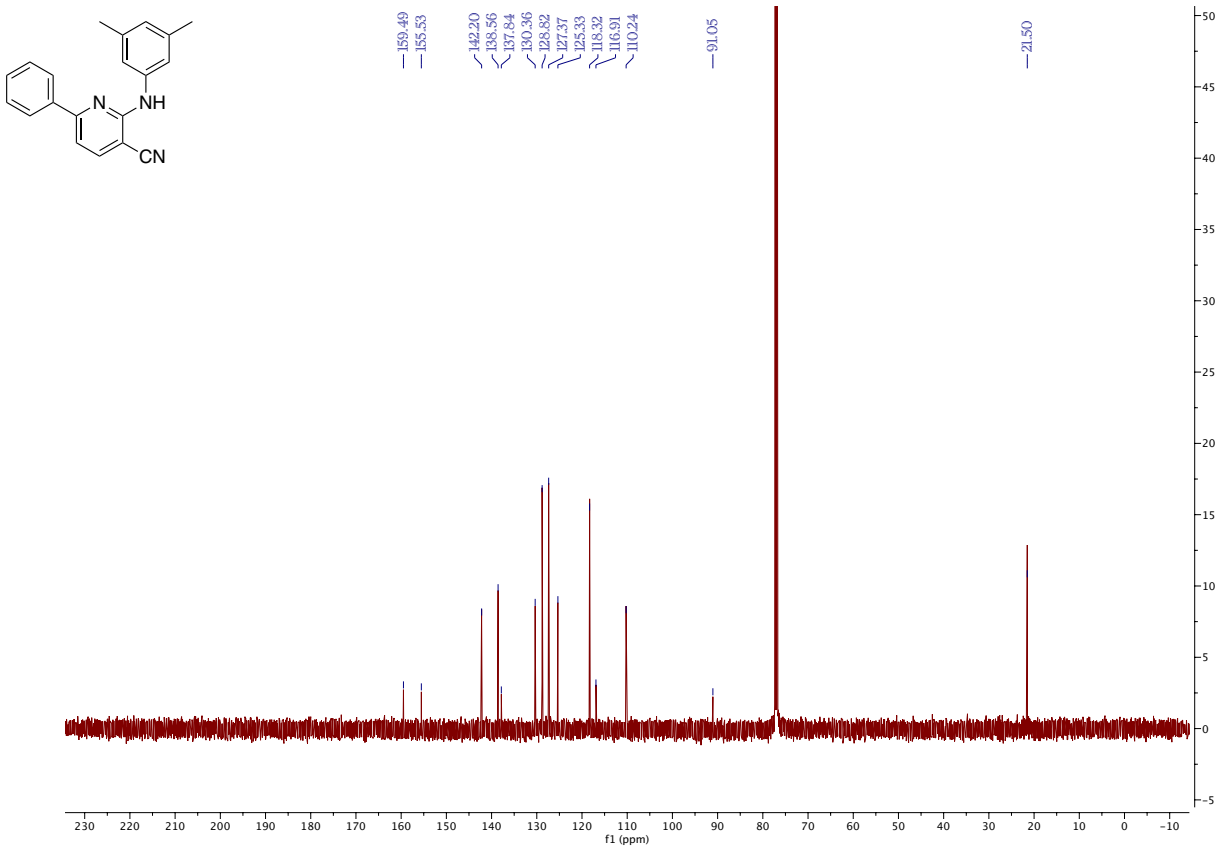

N
NH
CN
162.91
155.68
141.59
138.75
138.70
125.44
118.20
117.10
113.72
89.91
77.16 CDCl3
25.29
21.62
f1 (ppm)

*2-((3,5-dimethylphenyl)amino)-6-phenylnicotinonitrile (**5b**).*

^{1}H NMR

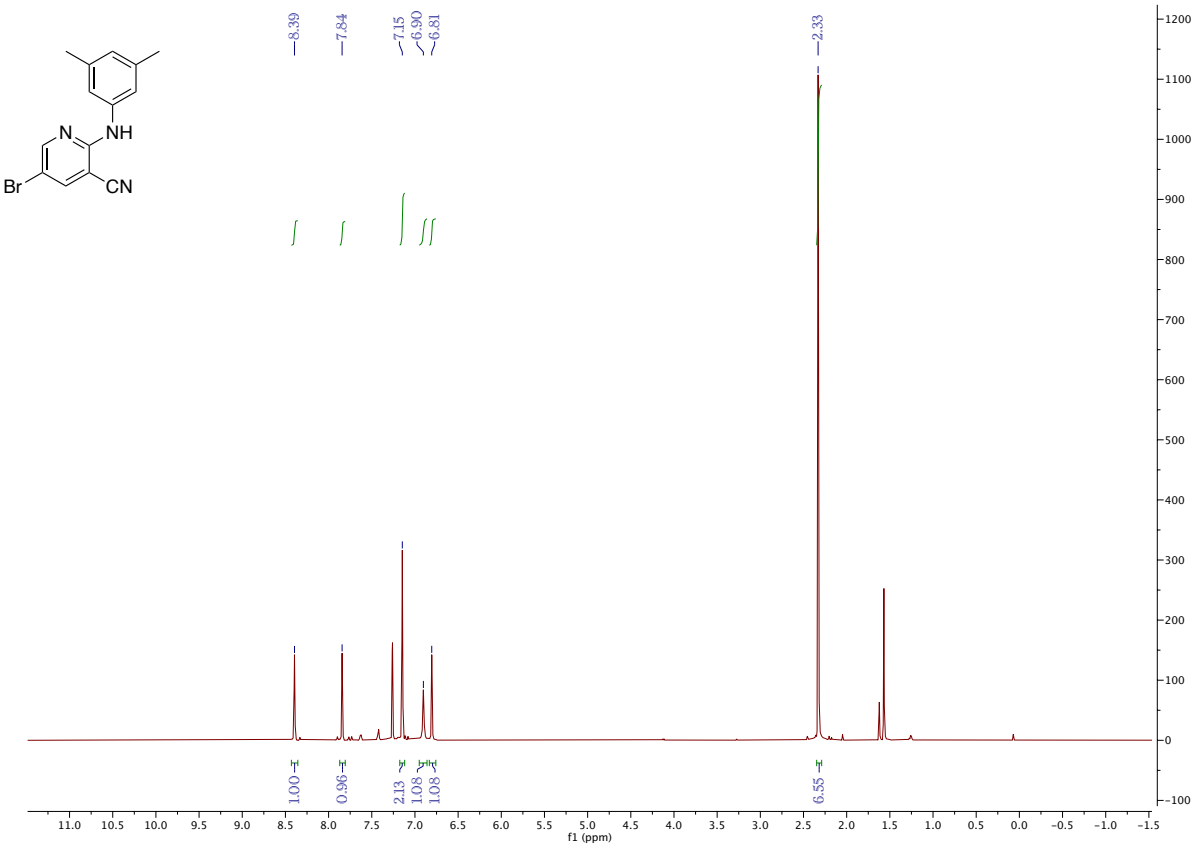


^{13}C NMR

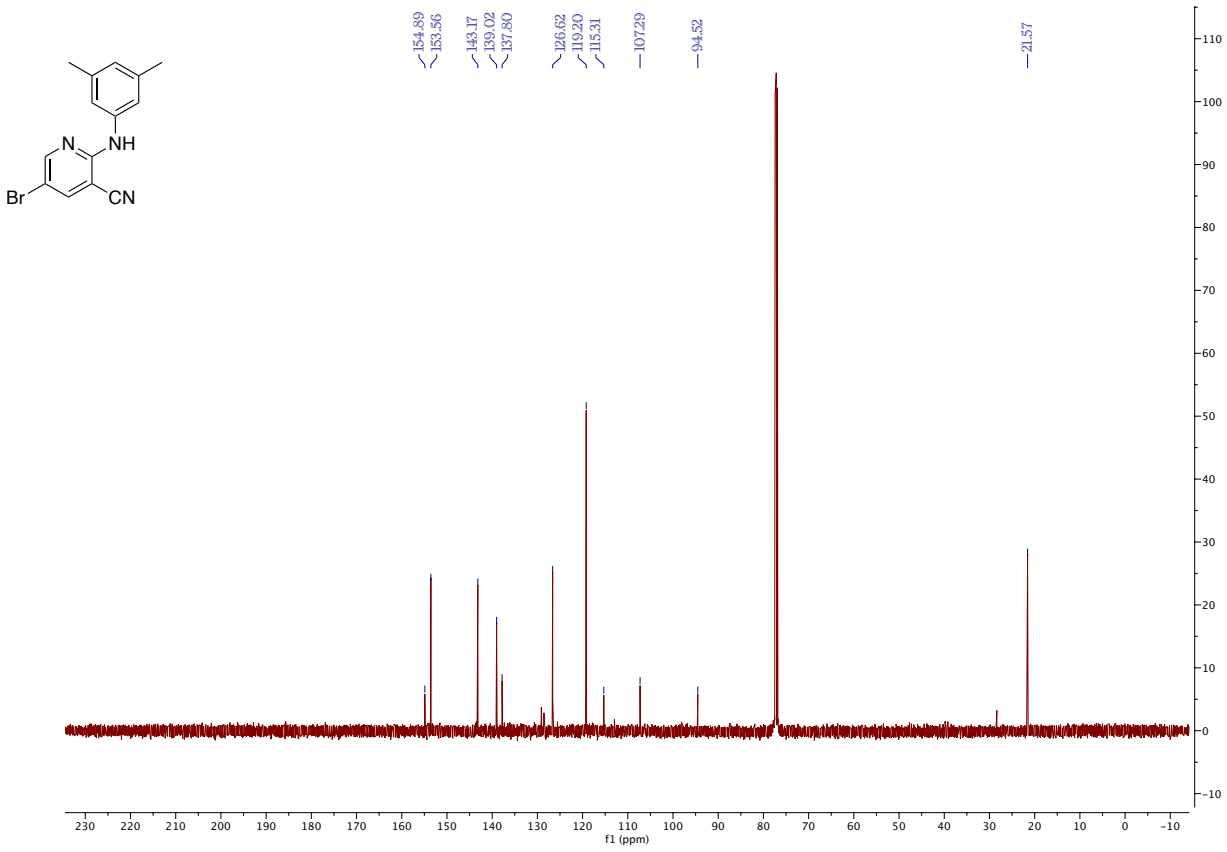

159.49
155.53
142.20
138.56
137.84
130.36
128.82
127.37
125.33
118.32
116.91
110.24
91.05
21.50
NH
N
CN
f1 (ppm)

*5-bromo-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**6-I**).*

^{1}H NMR

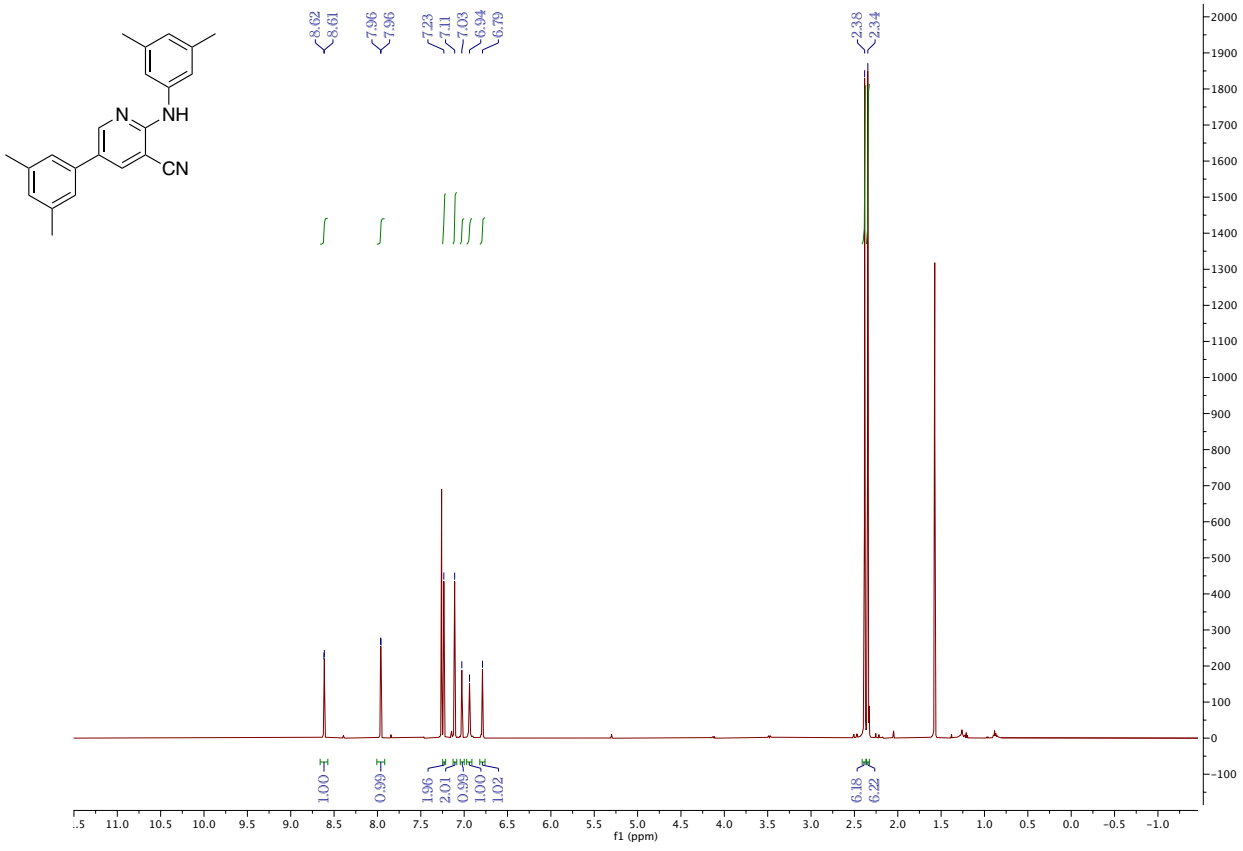


^{13}C NMR

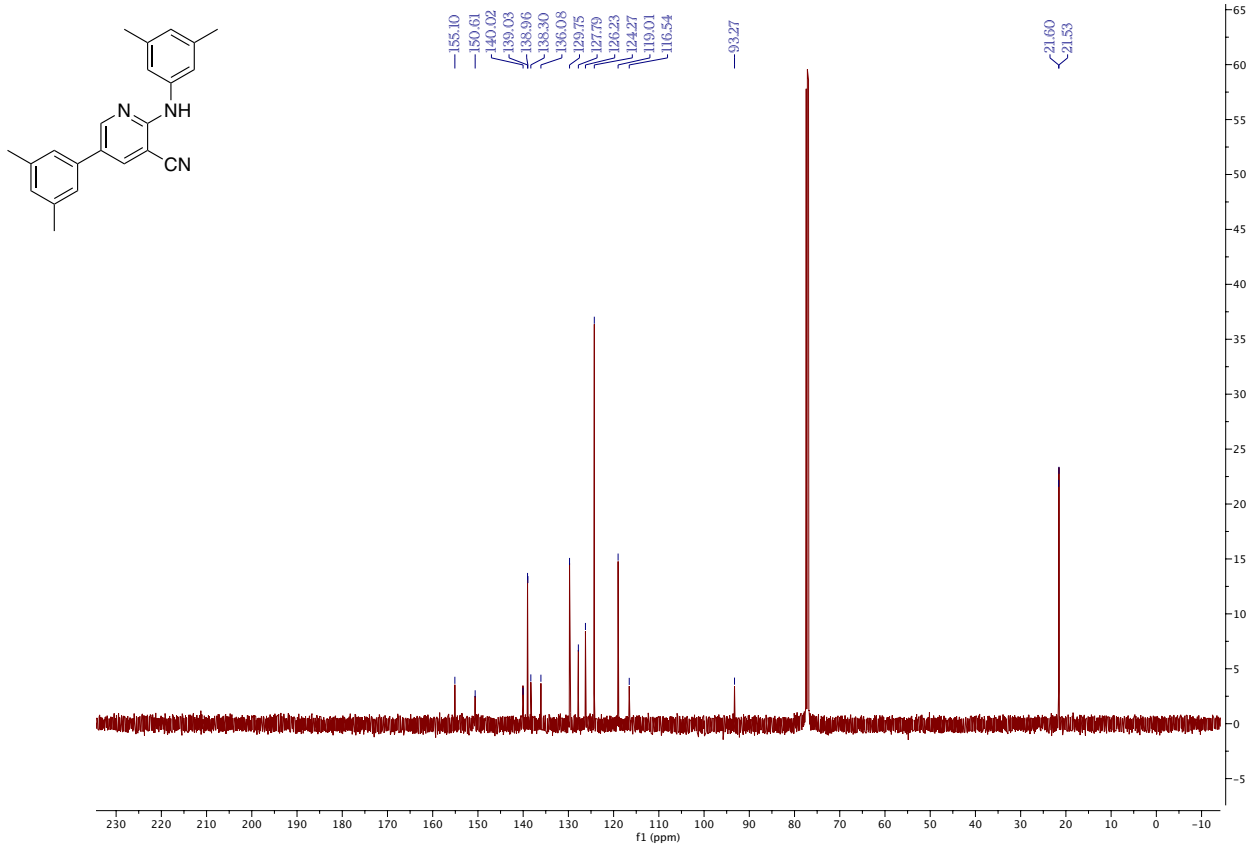

154.89
153.56
143.17
139.02
137.80
126.62
119.20
115.31
107.29
94.52
21.57
Br
CN
NH
N
f1 (ppm)

*5-(3,5-dimethylphenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**6a**).*

^{1}H NMR

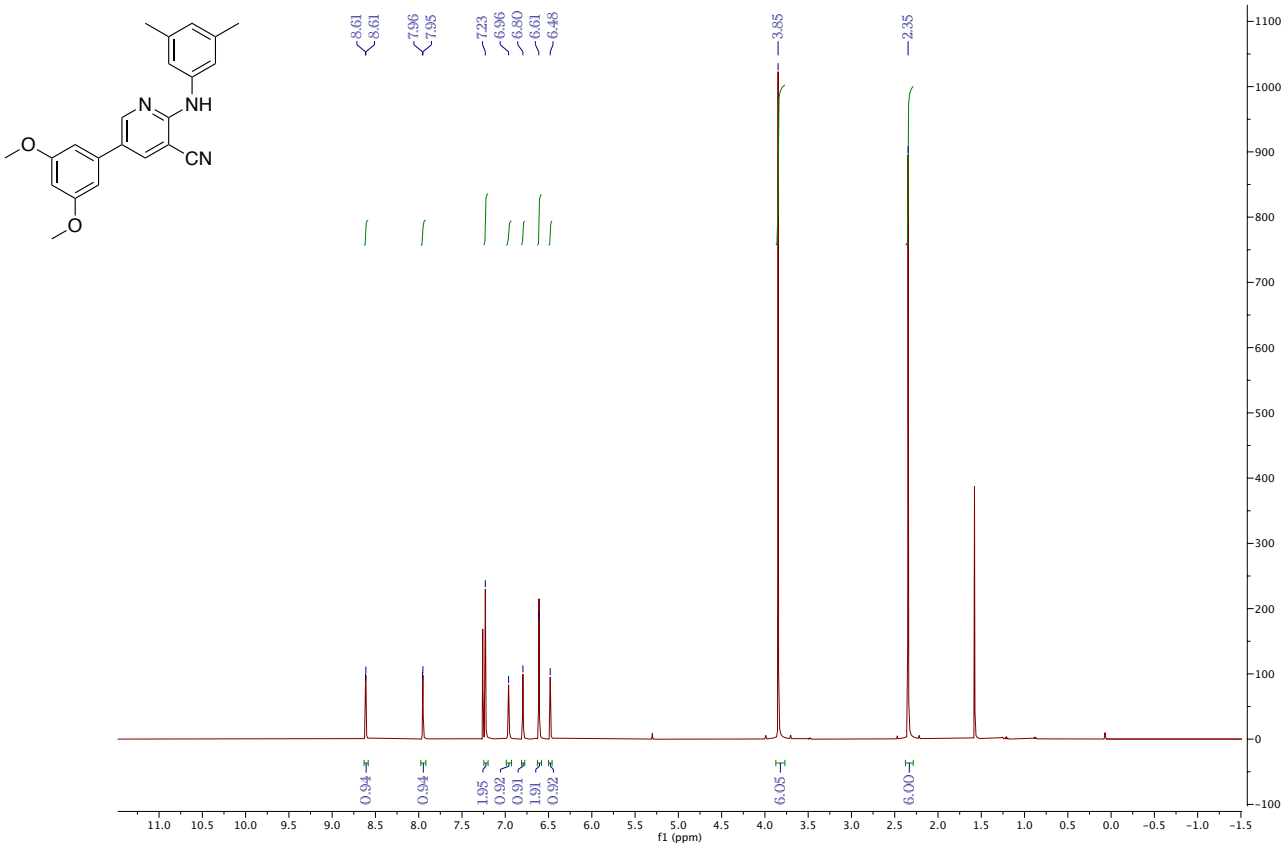


^{13}C NMR

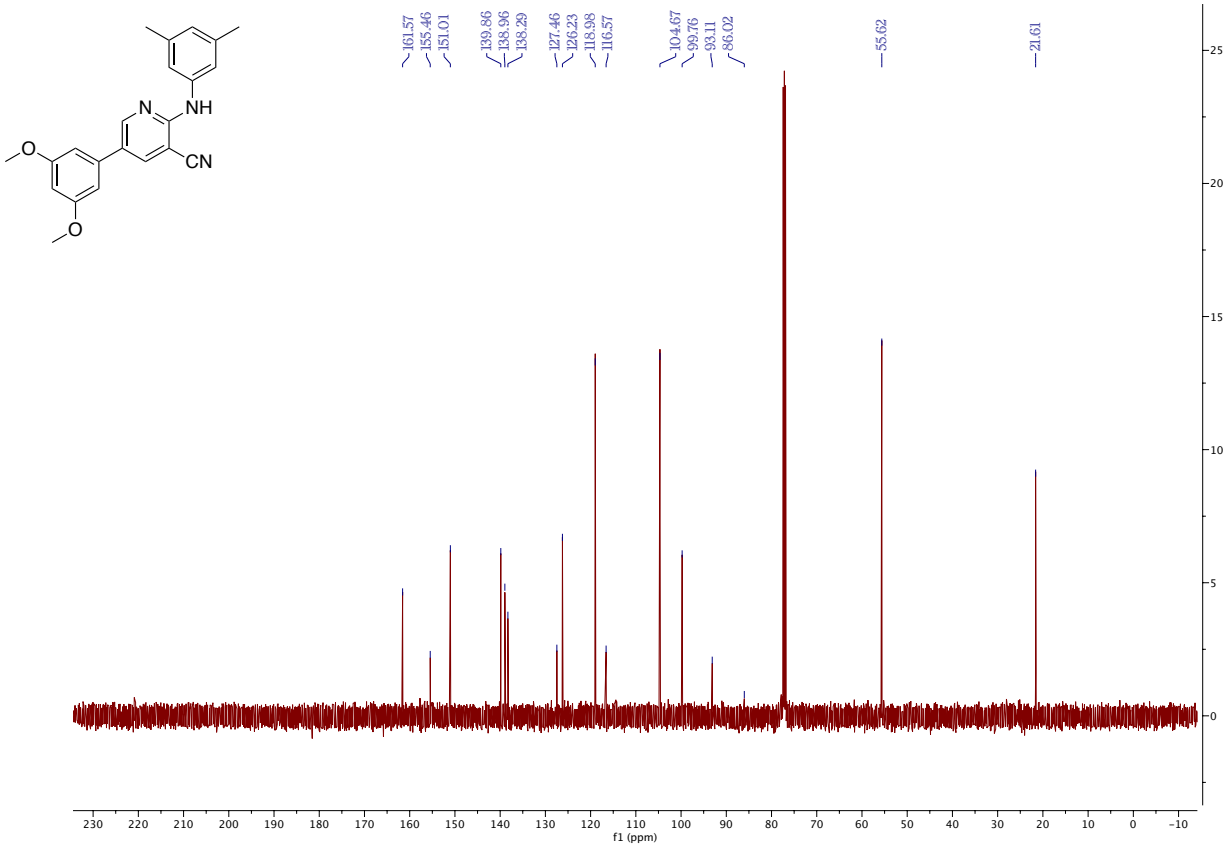

155.10
150.61
140.02
139.03
138.96
138.30
136.08
129.75
127.79
126.23
124.27
119.01
116.54
93.27
21.60
21.53
NH
N
CN
f1 (ppm)

*5-(3,5-dimethoxyphenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**6b**).*

^{1}H NMR

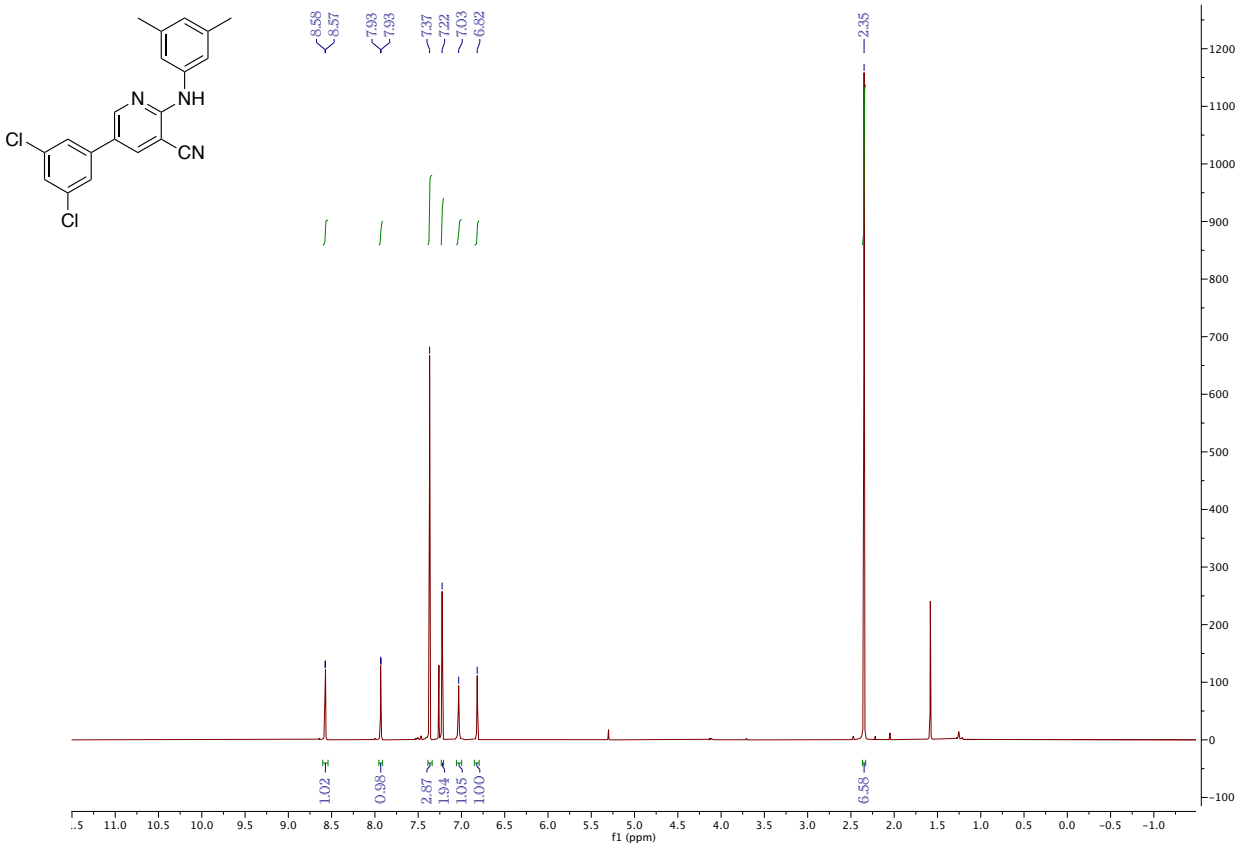


^{13}C NMR

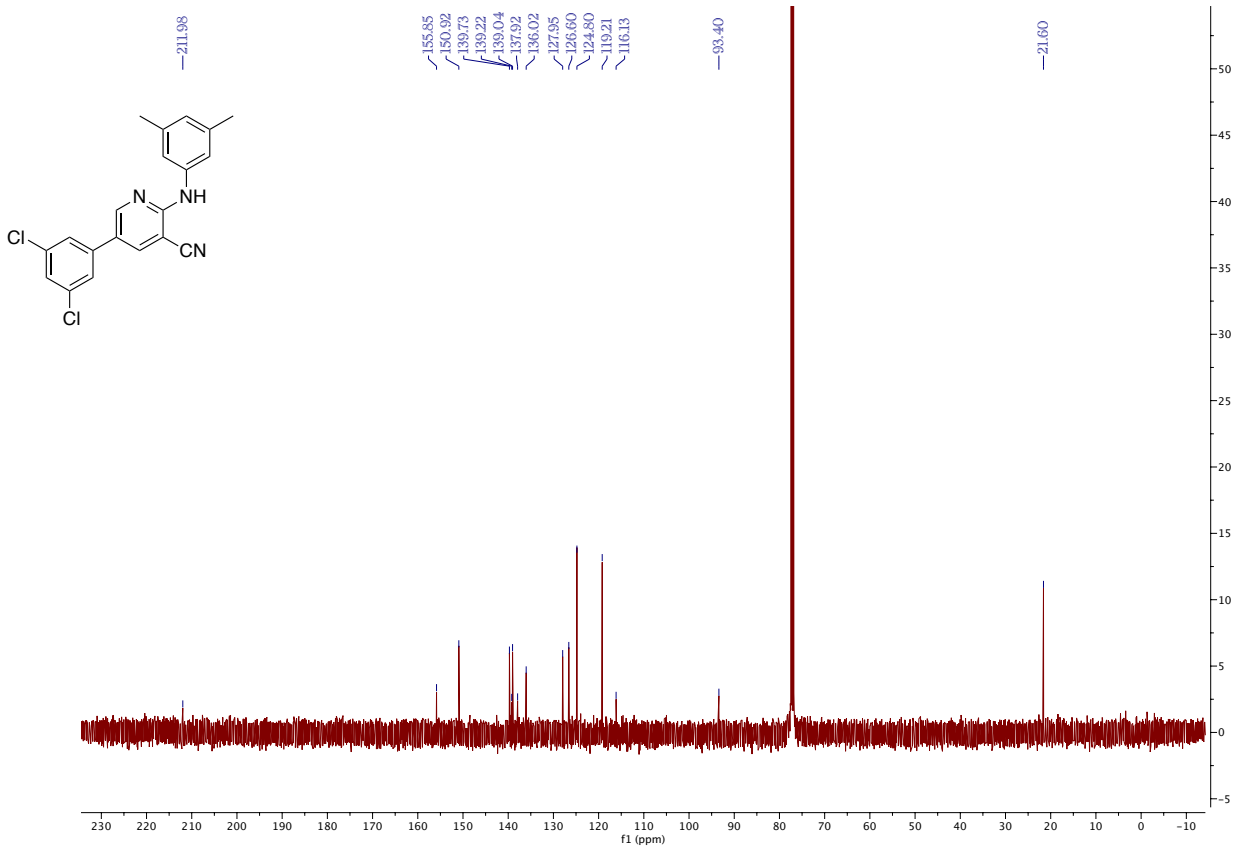

161.57
155.46
151.01
139.86
138.96
138.29
127.46
126.23
118.98
116.57
104.67
99.76
93.11
86.02
55.62
21.61
NH
N
CN
O
O
f1 (ppm)

*5-(3,5-dichlorophenyl)-2-((3,5-dimethylphenyl)amino)nicotinonitrile (**6c**).*

^{1}H NMR

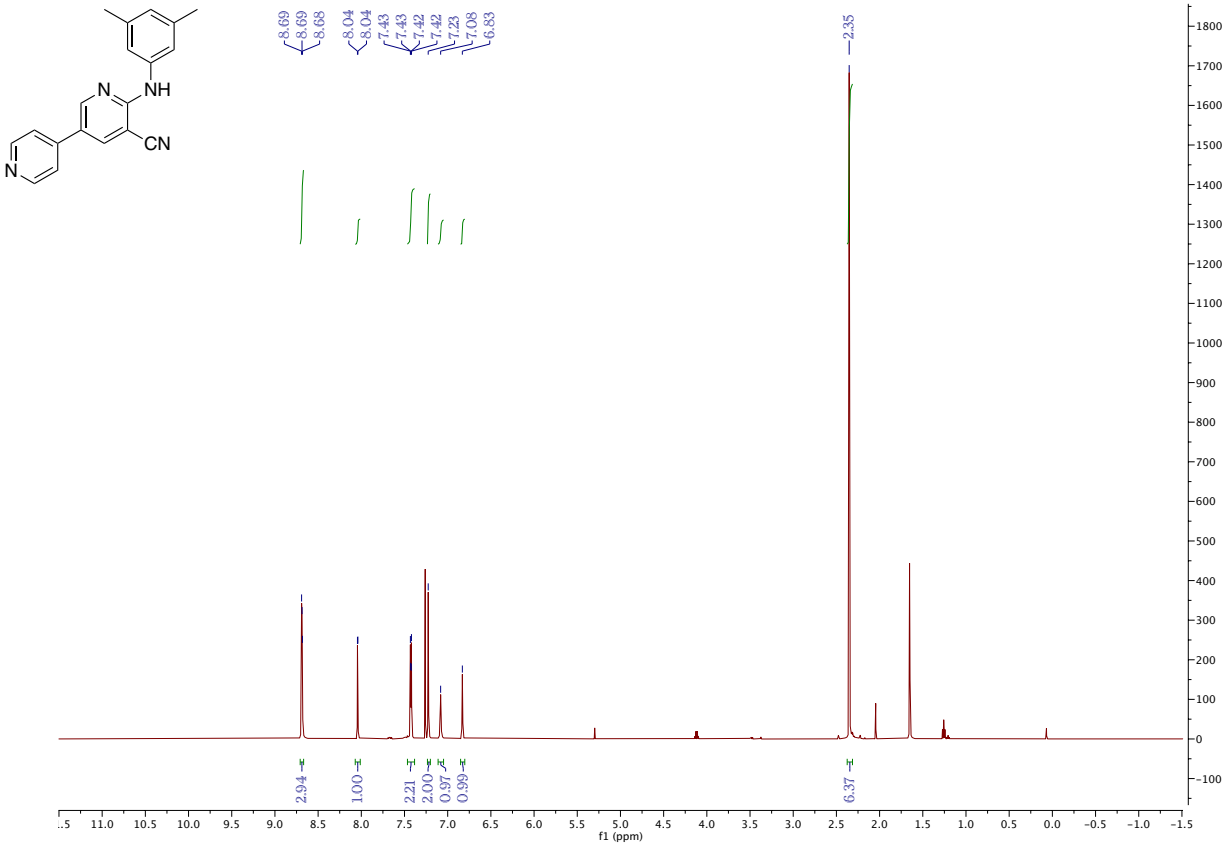


^{13}C NMR

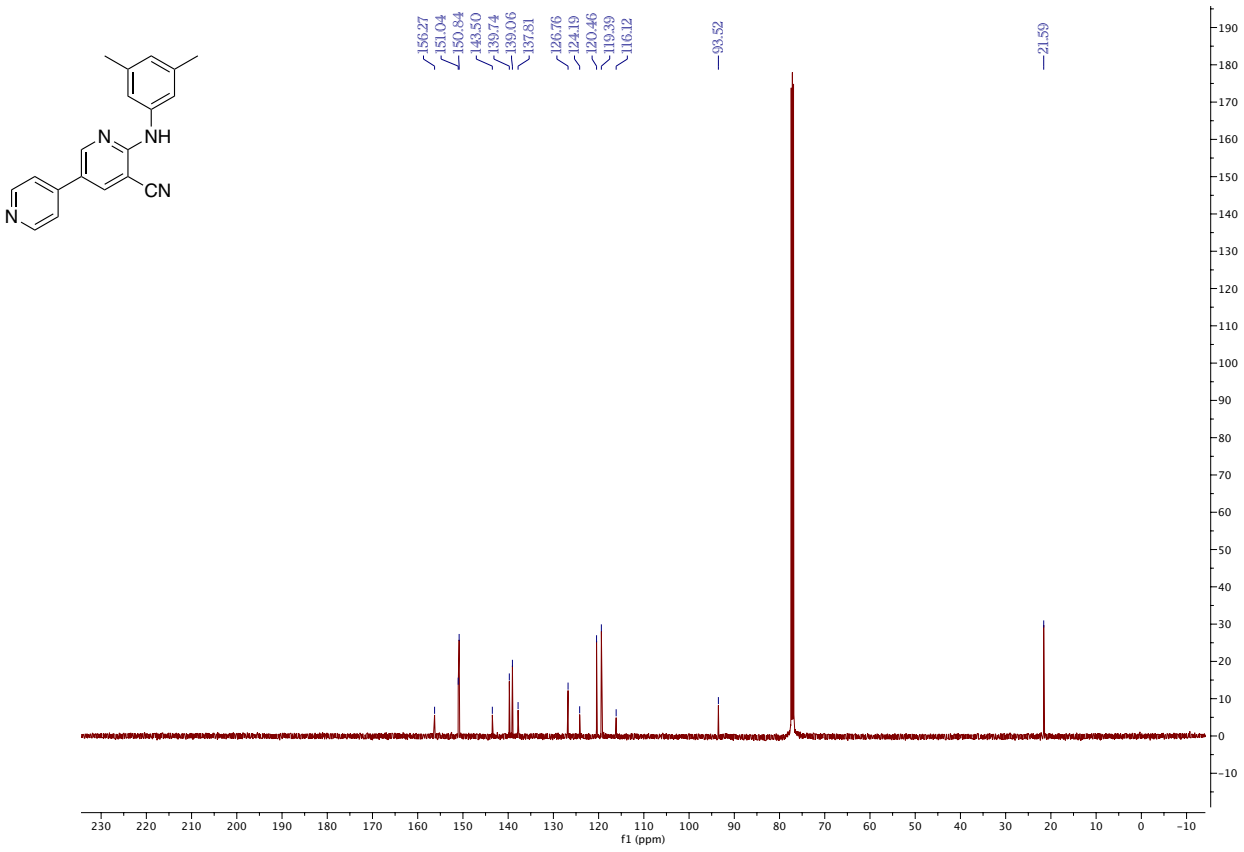

211.98
155.85
150.92
139.73
139.22
139.04
137.92
136.02
127.95
126.60
124.80
119.21
116.13
93.40
21.60
NH
N
Cl
CN
Cl
f1 (ppm)

*6-((3,5-dimethylphenyl)amino)-[3,4'-bipyridine]-5-carbonitrile (**6d**).*

^{1}H NMR

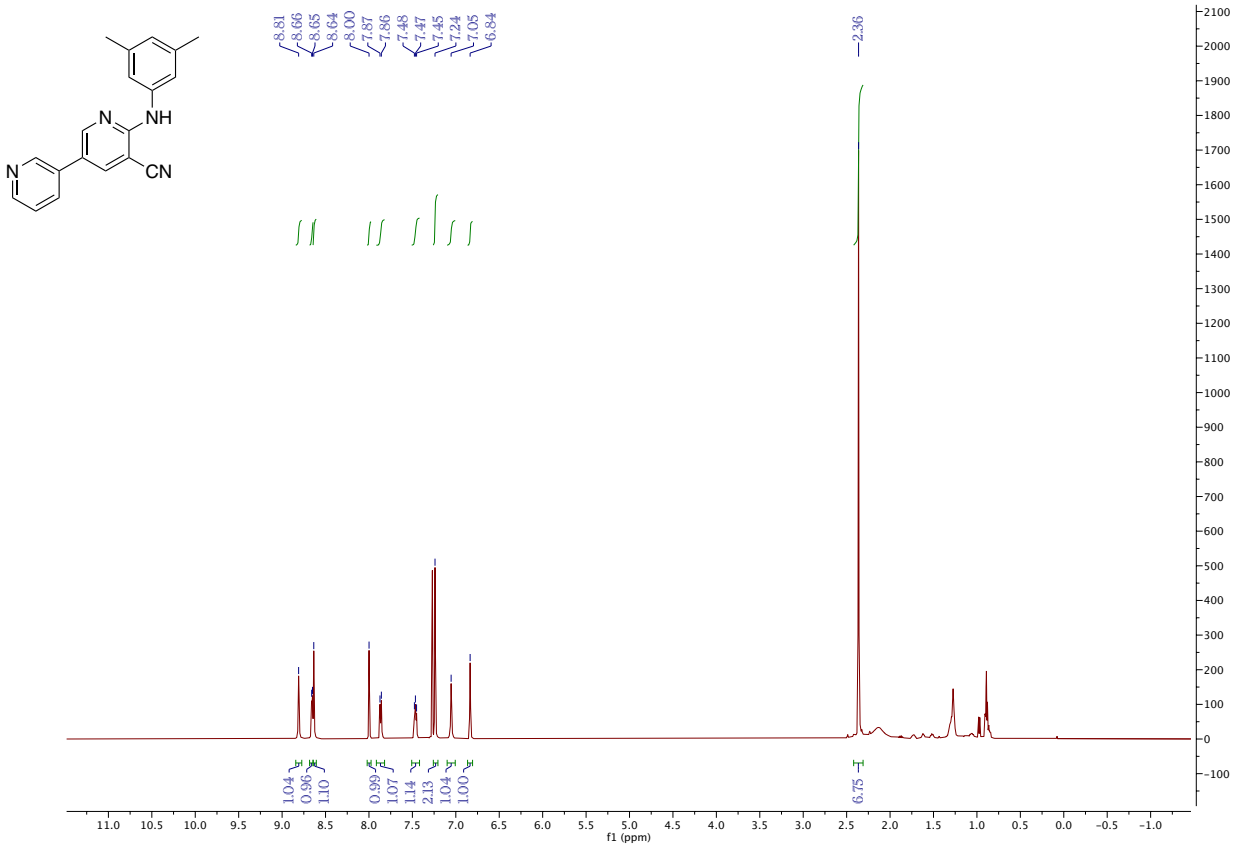


^{13}C NMR

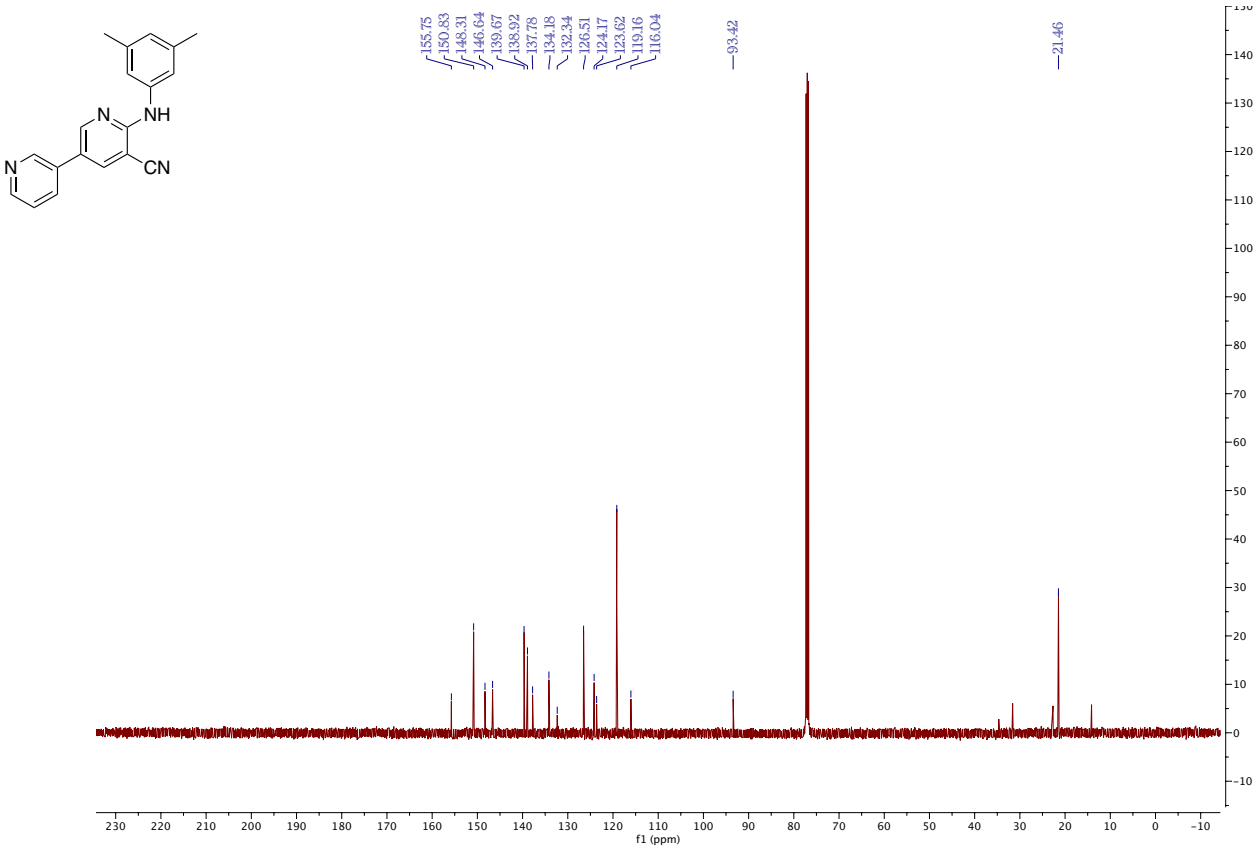

156.27
151.04
150.84
143.50
139.74
139.06
137.81
126.76
124.19
120.46
119.39
116.12
93.52
21.59
NH
N
CN
N
f1 (ppm)

*6-((3,5-dimethylphenyl)amino)-[3,3'-bipyridine]-5-carbonitrile (**6e**).*

^{1}H NMR

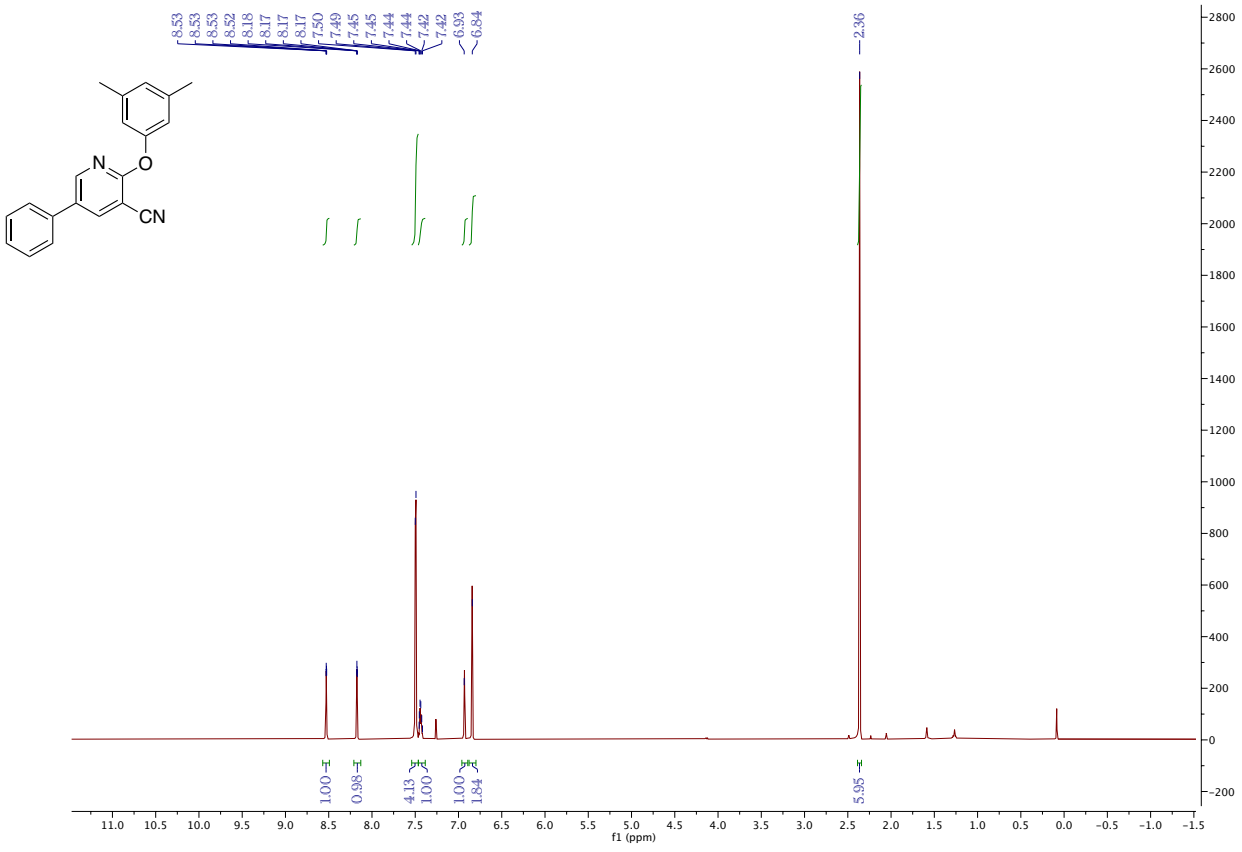


^{13}C NMR

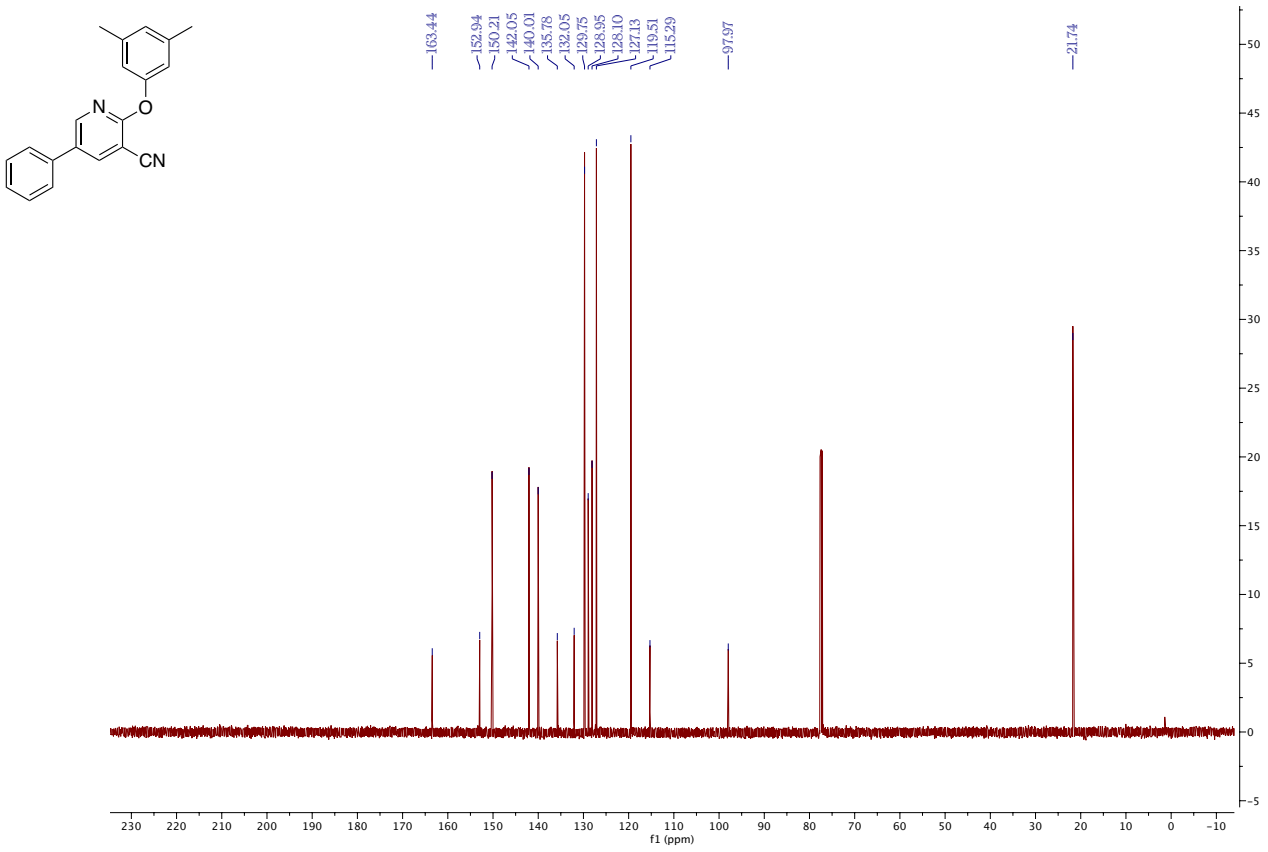

155.75
150.83
148.31
146.64
139.67
138.92
137.78
134.18
132.34
126.51
124.17
123.62
119.16
116.04
93.42
21.46
NH
N
CN
f1 (ppm)

*2-(3,5-dimethylphenoxy)-5-phenylnicotinonitrile (7**a**)*

^{1}H NMR

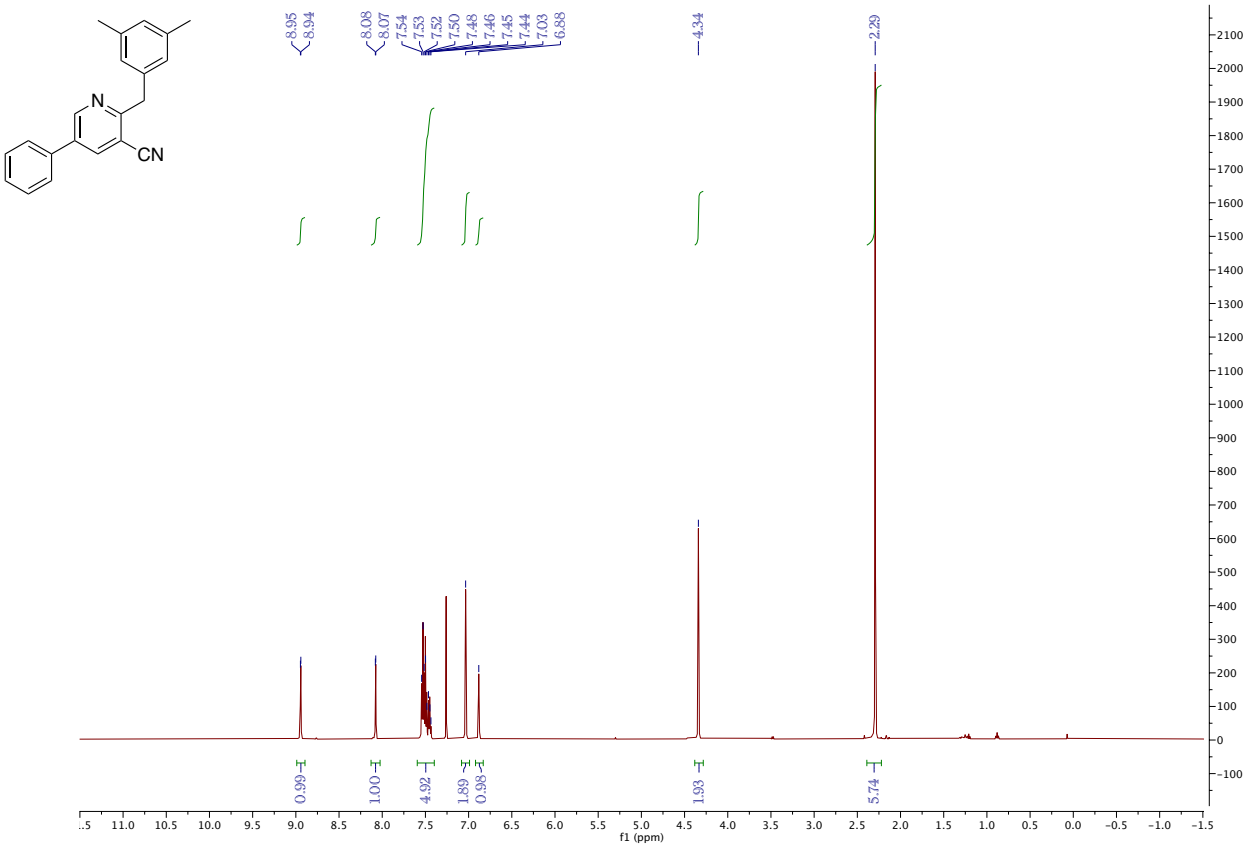


^{13}C NMR

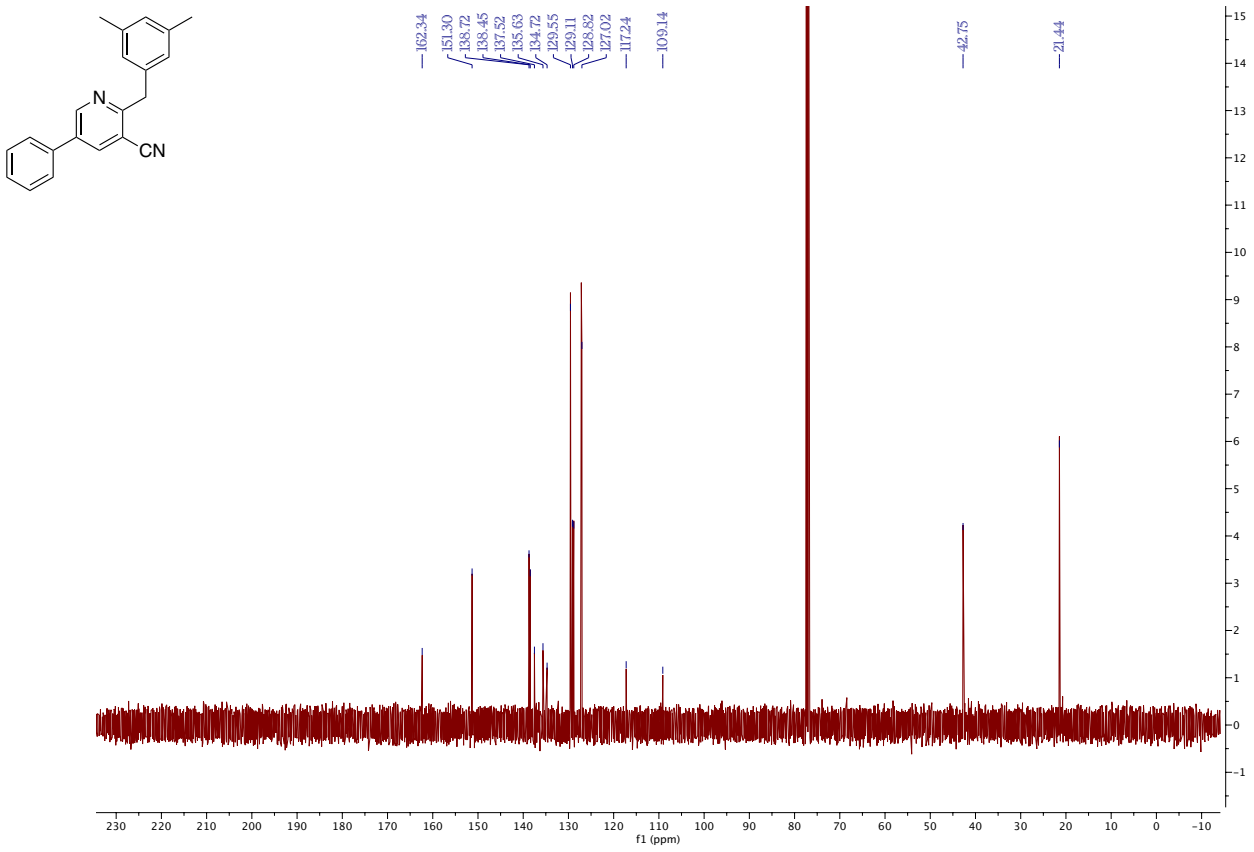

N
O
CN
163.44
152.94
150.21
142.05
140.01
135.78
132.05
129.75
128.95
128.10
127.13
119.51
115.29
97.97
21.74
f1 (ppm)

*2-(3,5-dimethylbenzyl)-5-phenylnicotinonitrile (7**b**).*

^{1}H NMR

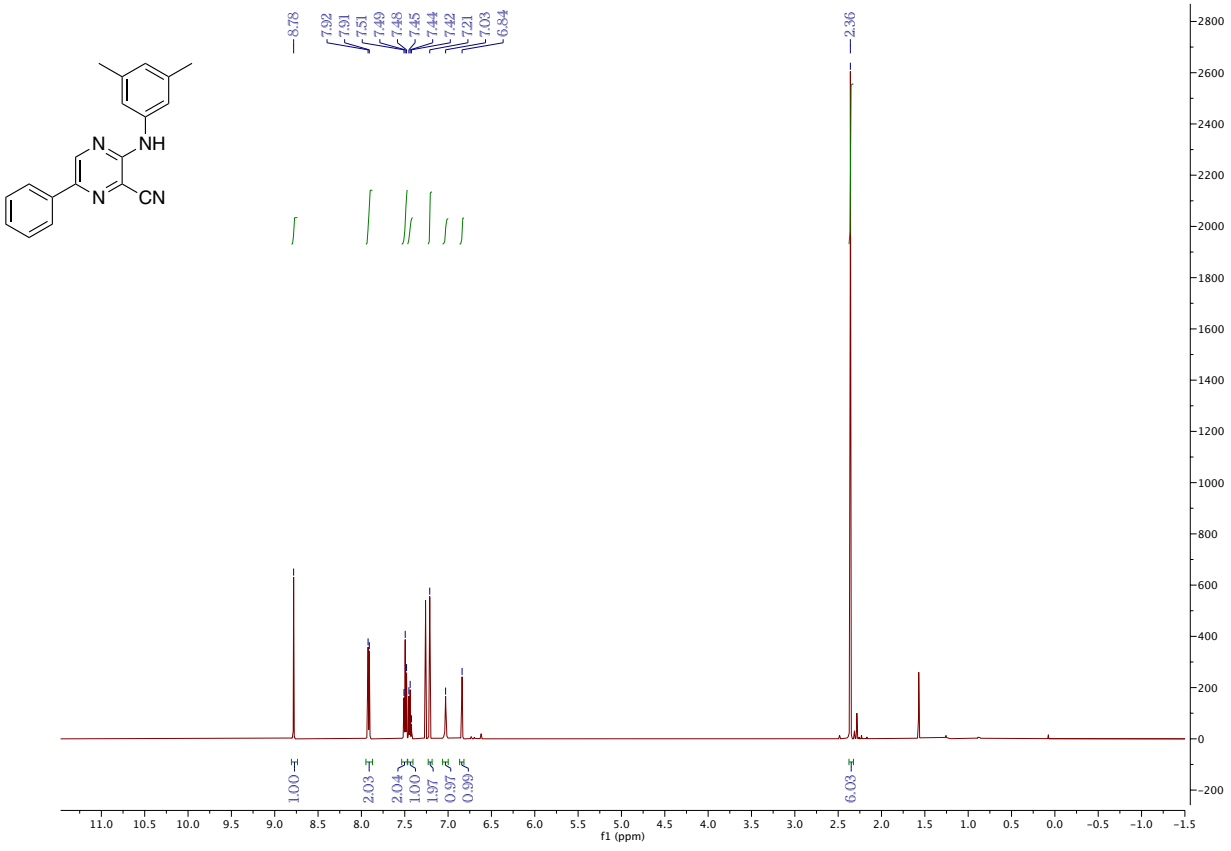


^{13}C NMR

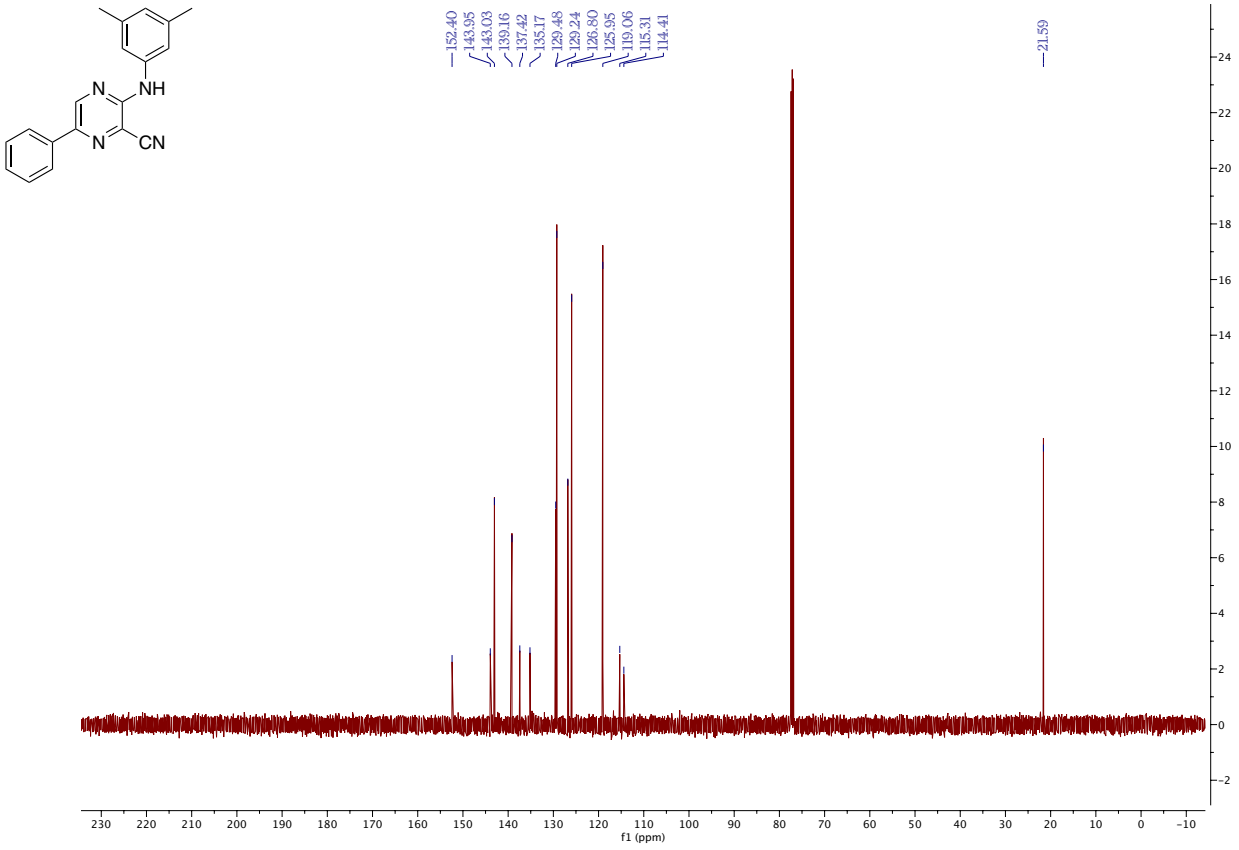

N
CN
162.34
151.30
138.72
138.45
137.52
135.63
134.72
129.55
129.11
128.82
127.02
117.24
109.14
42.75
21.44
f1 (ppm)

*3-((3,5-dimethylphenyl)amino)-6-phenylpyrazine-2-carbonitrile (**8a**).*

^{1}H NMR

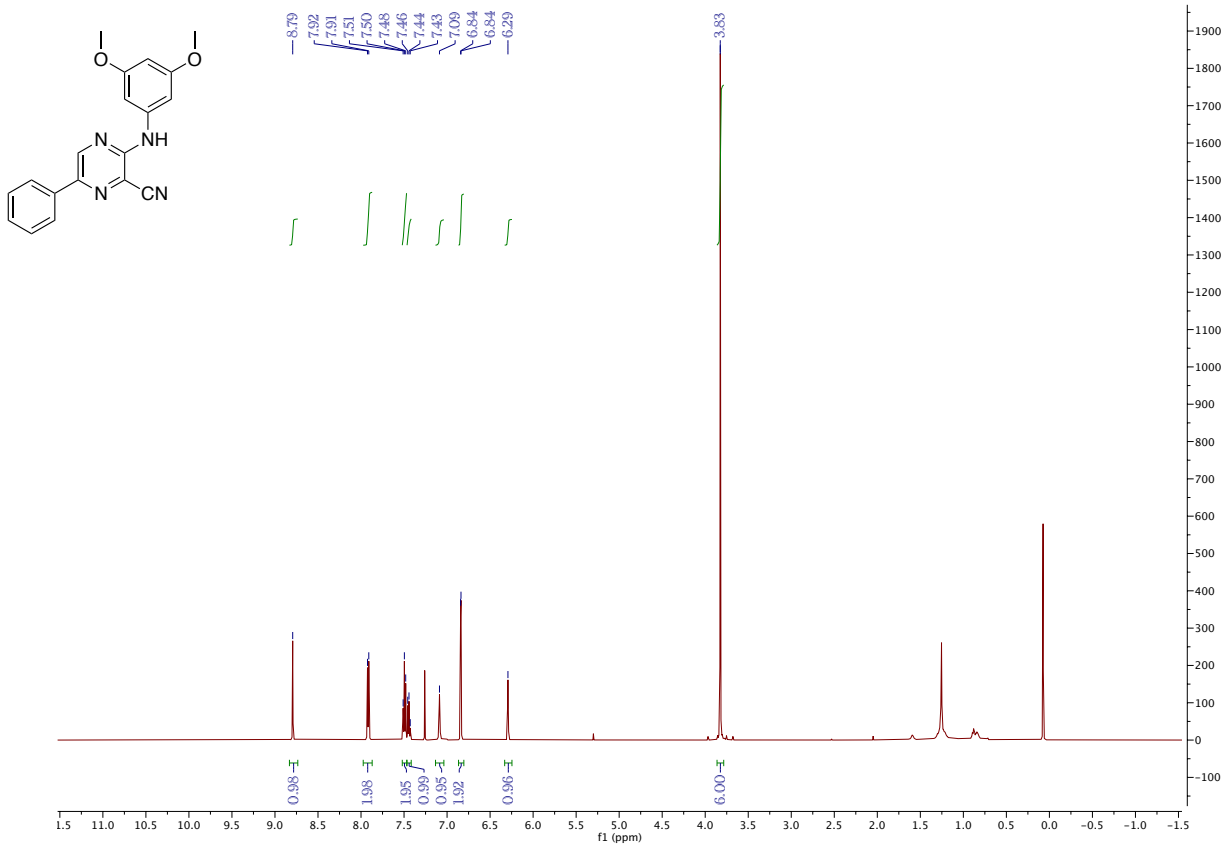


^{13}C NMR

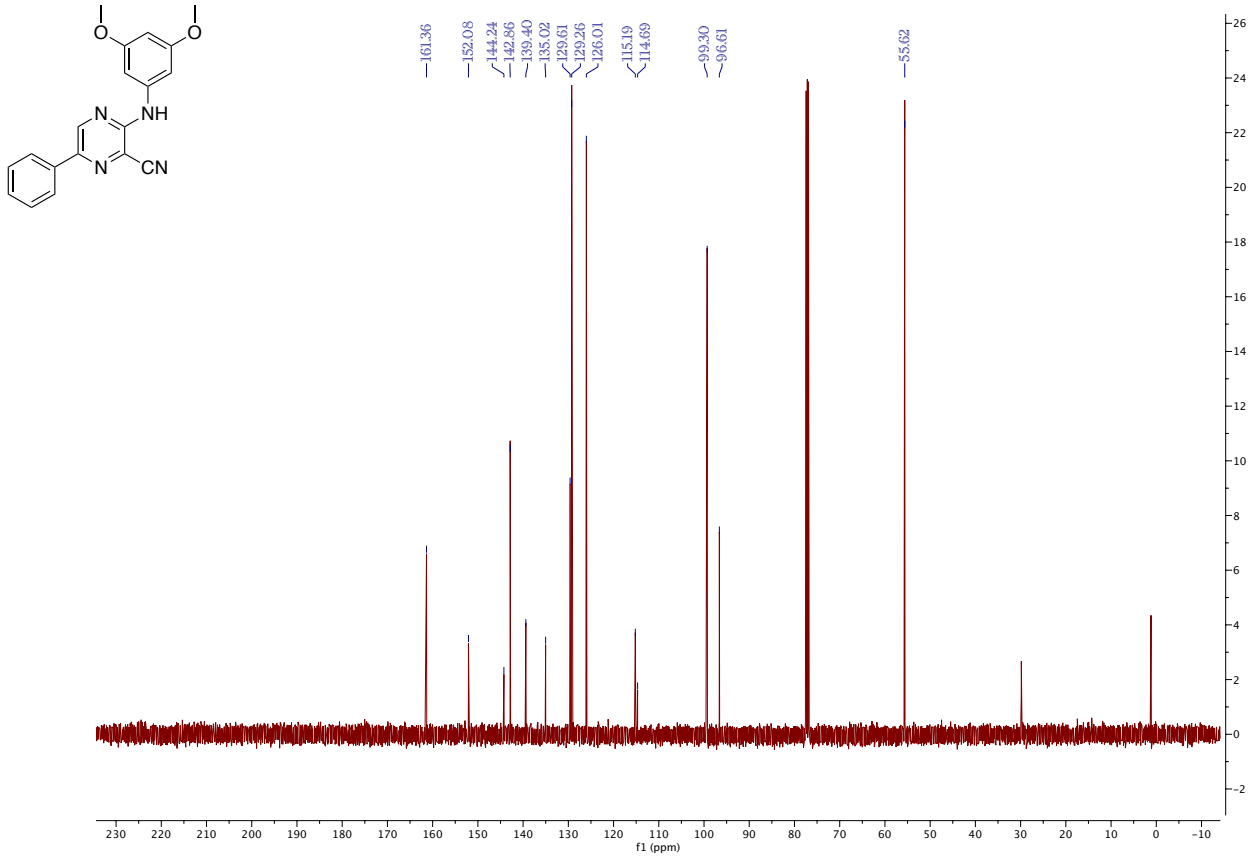

152.40
143.95
143.03
139.16
137.42
135.17
129.48
129.24
126.80
125.95
119.06
115.31
114.41
21.59
NH
N
N
CN
f1 (ppm)

*3-((3,5-dimethoxyphenyl)amino)-6-phenylpyrazine-2-carbonitrile (**8b**).*

^{1}H NMR

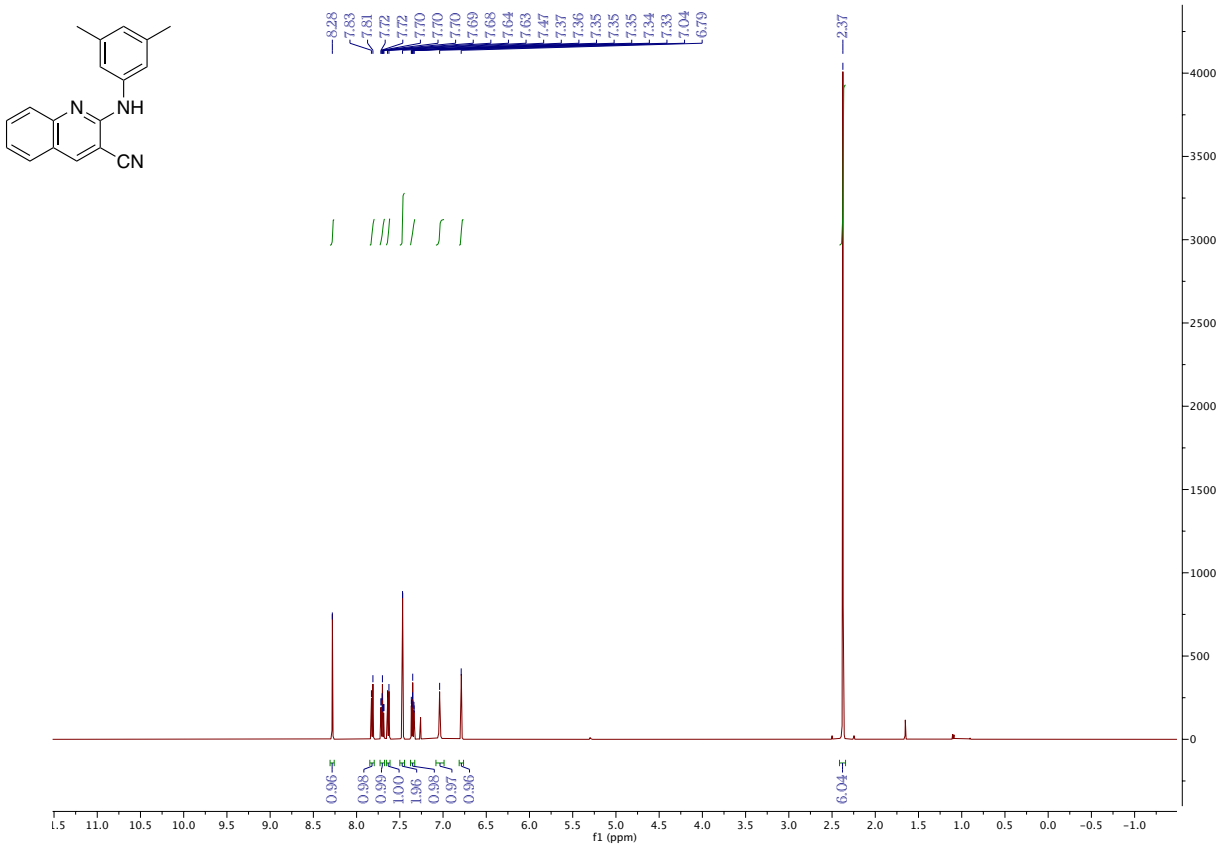


^{13}C NMR

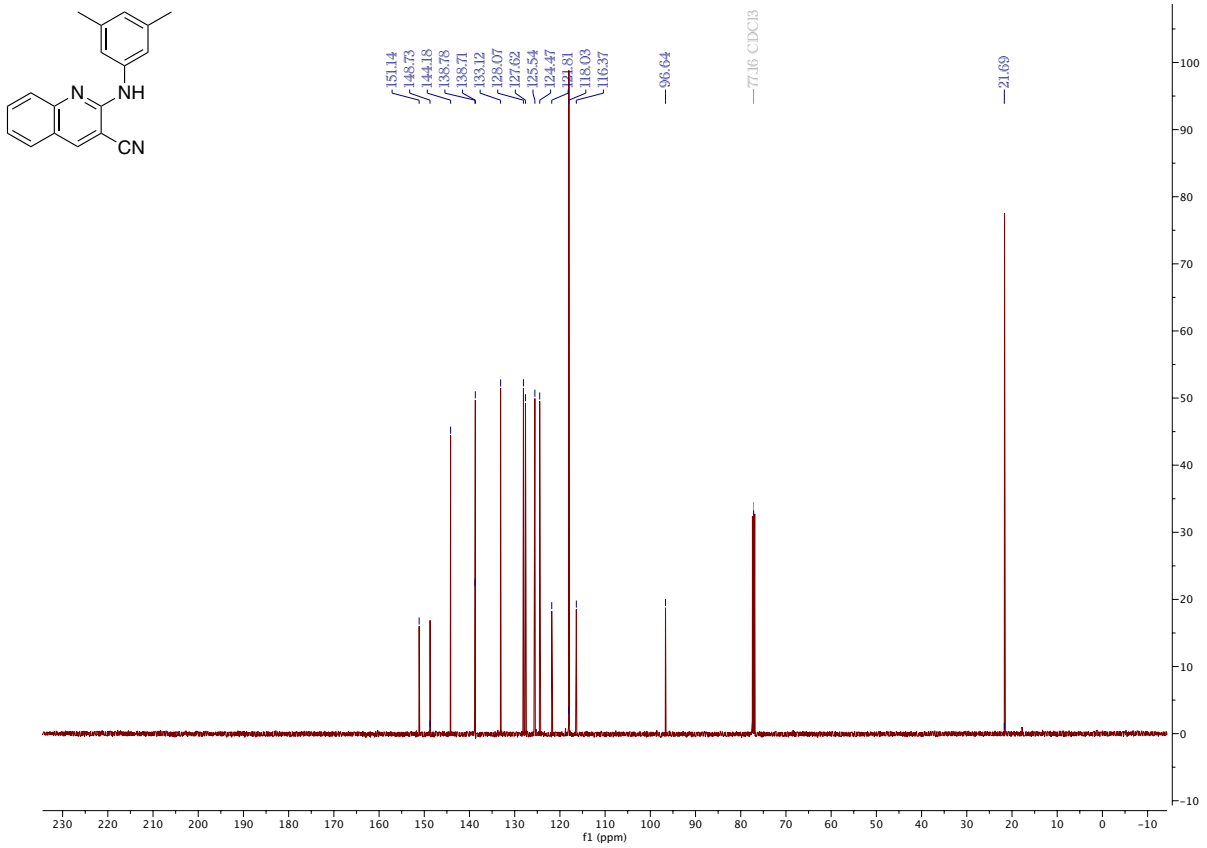

161.36
152.08
144.24
142.86
139.40
135.02
129.61
129.26
126.01
115.19
114.69
99.30
96.61
55.62
f1 (ppm)

*2-((3,5-dimethylphenyl)amino)quinoline-3-carbonitrile (**9a**).*

^{1}H NMR

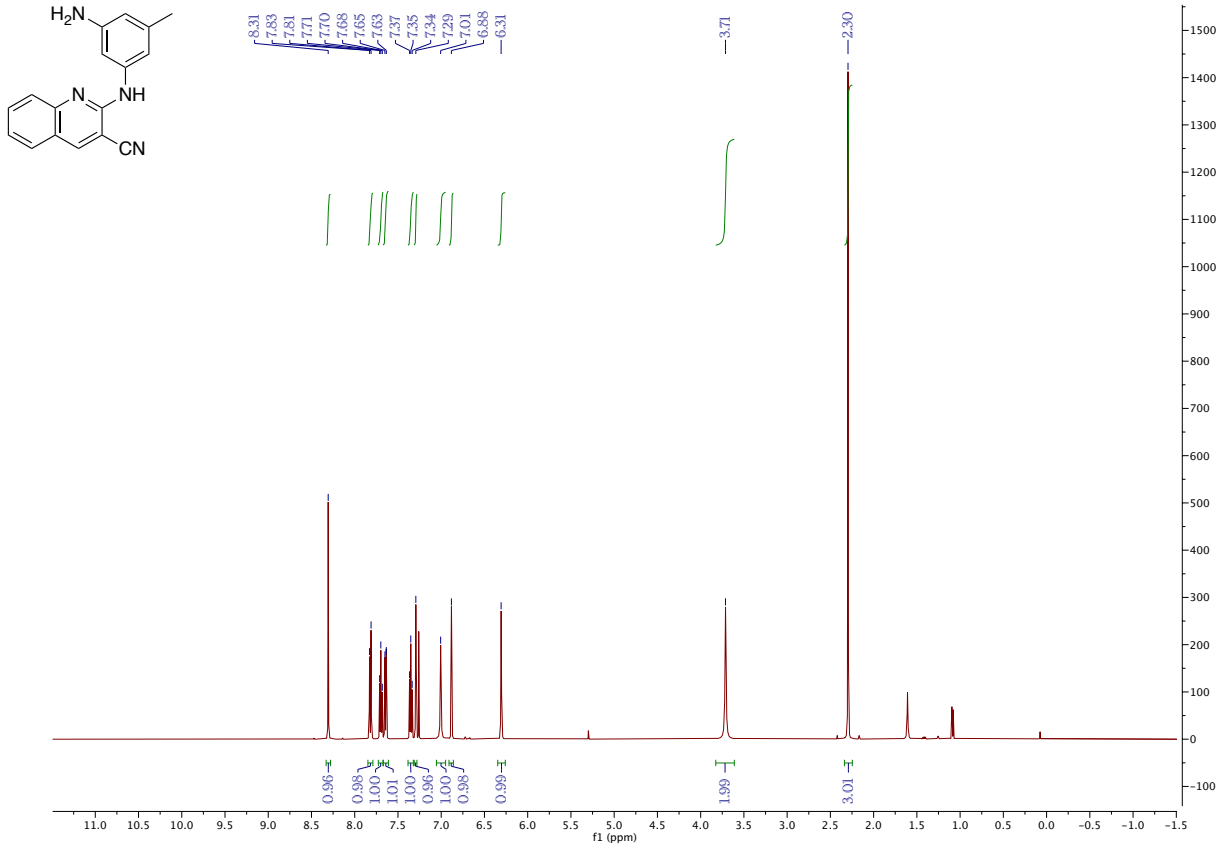


^{13}C NMR

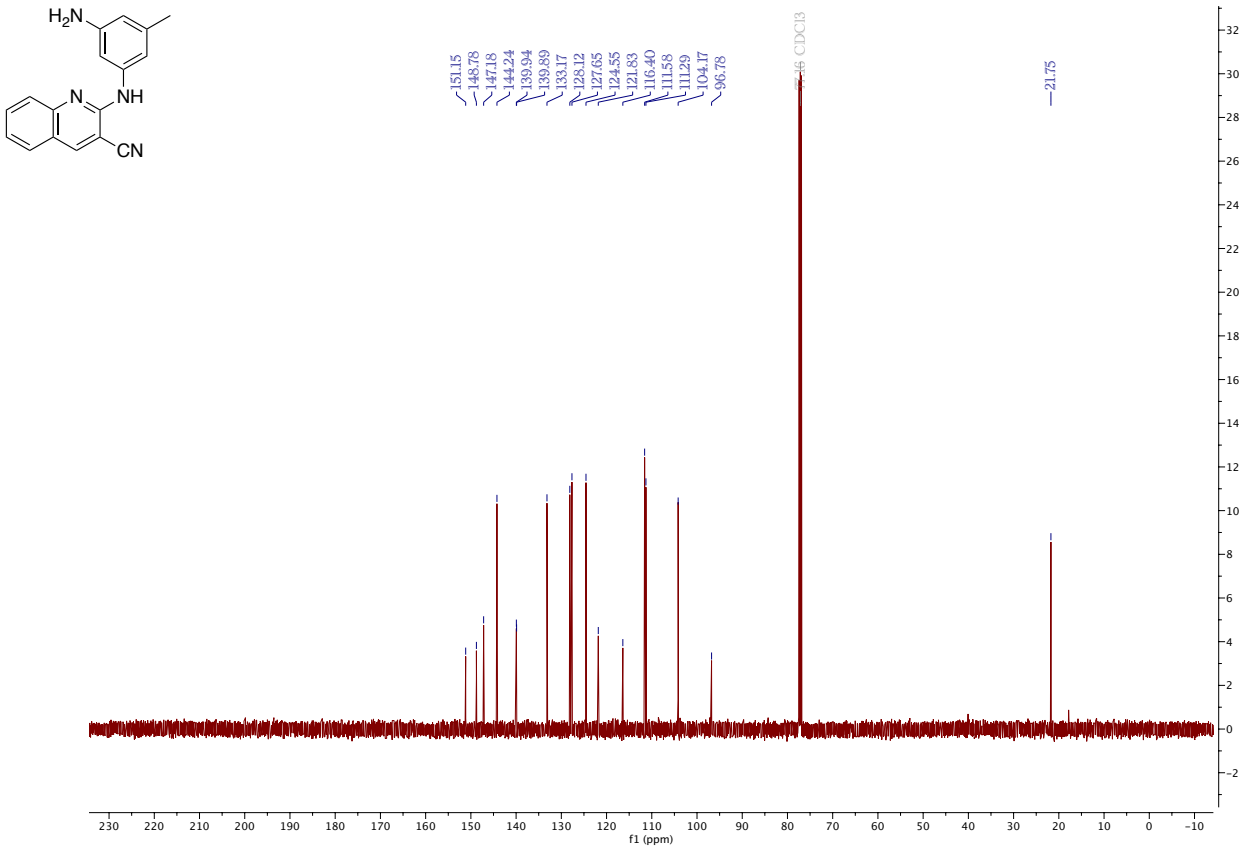

N
NH
CN
151.14
148.73
144.18
138.78
138.71
133.12
128.07
127.62
125.54
124.47
121.81
118.03
116.37
96.64
77.46 CDCl3
21.69
f1 (ppm)

*2-((3-amino-5-methylphenyl)amino)quinoline-3-carbonitrile (**9b**).*

^{1}H NMR

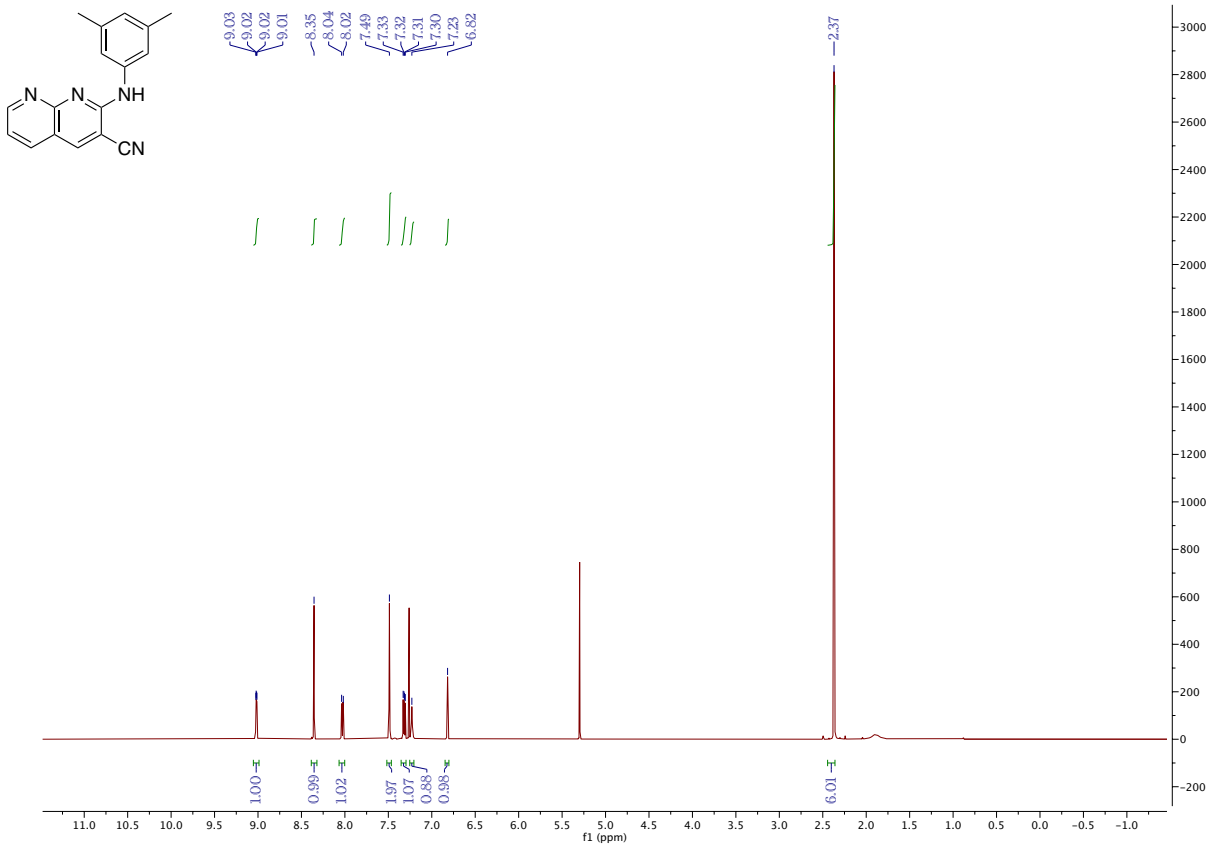


^{13}C NMR

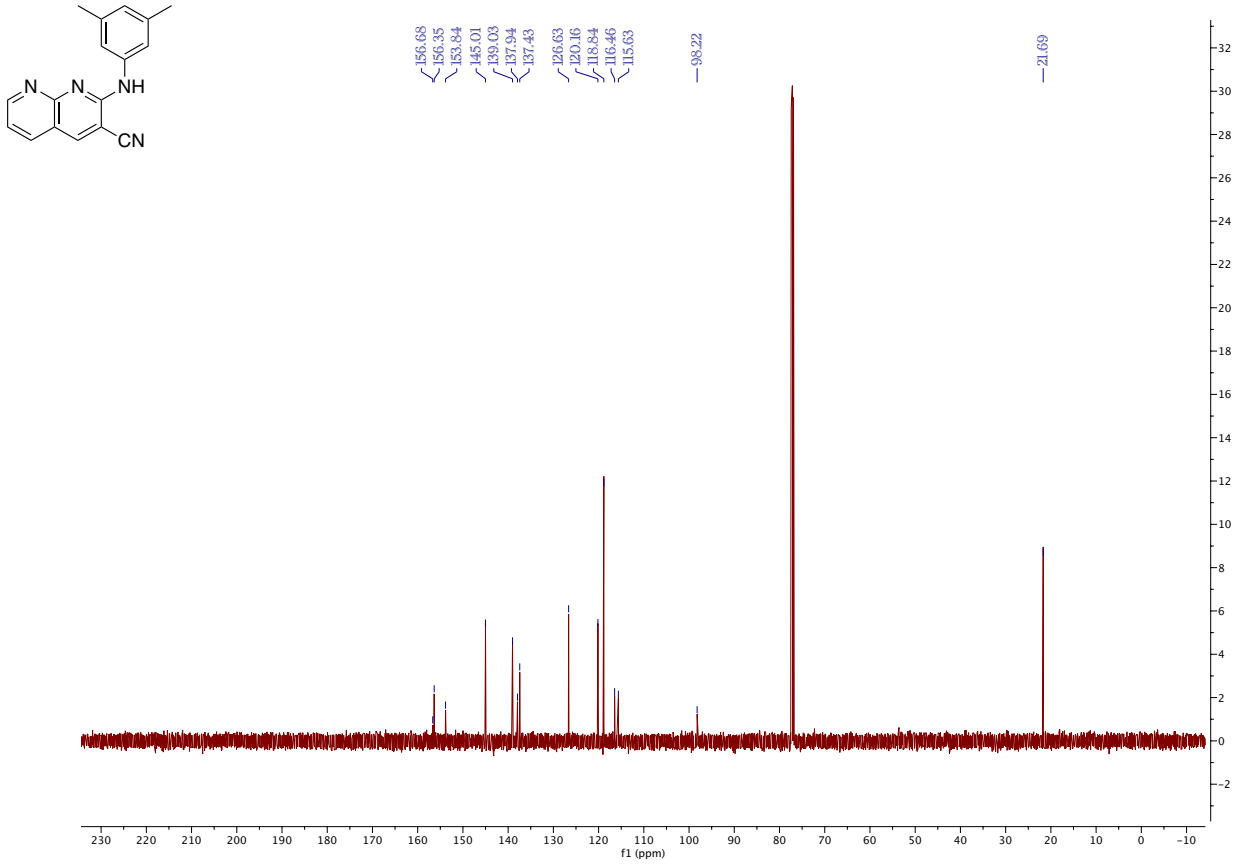

H2N
NH
N
CN
151.15
148.78
147.18
144.24
139.94
139.89
133.17
128.12
127.65
124.55
121.83
116.40
111.58
111.29
104.17
96.78
77.46 CDCl3
21.75
f1 (ppm)

*2-((3,5-dimethylphenyl)amino)-1,8-naphthyridine-3-carbonitrile (**9c**).*

^{1}H NMR



^{13}C NMR



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