A Simple, Modular Method for the Synthesis of 3,4,5-Trisubstituted Pyrazoles

Mark McLaughlin,* Karen Marcantonio, Cheng-yi Chen and Ian W. Davies

Department of Process Research, Merck Research Laboratories, Merck & Co., Inc. Rahway, NJ 07065

mark_mclaughlin@merck.com

Supporting Information

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General considerations: Screening reactions were conducted under a nitrogen atmosphere in 8 mL vials equipped with magnetic stir-bars and septa. Larger scale preparative reactions were conducted in standard RB-flasks under a nitrogen atmosphere. HPLC grade solvents were used with no additional purification/drying. K_3PO_4 was purchased as granular and ground to a powder before use. Stock solutions of HCl/MeOH were prepared by adding 10 mL AcCl to 100 mL MeOH over 5 min with ice-cooling. NMR spectra were recorded using a 400 MHz spectrometer; ^{1}H NMR recorded at 400 MHz and ^{13}C recorded at 100 MHz. TLC was performed using 2.5 cm × 7.5 cm glass-backed plates (silica gel 60, F_{254}, 250 μm thickness). Flash column chromatography was performed using silica gel 60, 230-400 mesh.

General Procedure A

Suzuki Cross-Coupling of Pyrazole Boronic Esters and HCl salt formation: To an 8 mL vial equipped with stir-bar and septum was charged the pyrazole boronate (**6** or **10a-f**) (1 mmol), aryl halide (1 mmol) K_3PO_4 (300 mol%), $Pd(dba)_2$ (2 mol%), $PCy_3.HBF_4$ (2.4 mol%) and 1,4-dioxane (3 mL). The heterogeneous mixture was agitated and purged with N_2 for 10 minutes before it was heated to 80 °C for 16 h. After this time, LC analysis of the gray mixture normally indicated > 98% conversion. The mixture was diluted with brine (30 mL) and MTBE (70 mL) and the separated organic was dried over Na_2SO_4. The filtered MTBE solution was concentrated under reduced pressure and the crude residue was treated with HCl in MeOH (10 mL of stock solution) at rt. Isolation of the HCl salts (**8**) was achieved by dilution with MTBE and filtration of the resultant slurry. Alternatively, the THP-protected compounds (**7**) could be isolated following flash chromatography on silica gel using an appropriate mixture of EtOAc/hexanes as the eluent.

General Procedure B

THP Switch: To an 8 mL vial equipped with stir-bar and septum was charged the substrate **7** (1 mmol) followed by toluene (3 mL), DHP (100 mol%) and TFA (5 mol%).

The mixture was heated at 60 °C for 3 h then LC analysis indicated complete switching of the THP group. The mixture was diluted into saturated aqueous $NaHCO_3$ (30 mL) and MTBE (70 mL) then the separated organic phase was washed with brine (30 mL) and dried over Na_2SO_4. The filtered MTBE solution was concentrated under reduced pressure and the switched THP product **9** was isolated following flash chromatography on silica gel using an appropriate mixture of EtOAc/hexanes as the eluent.

General Procedure C

Conversion of Mono-Arylpyrazole HCl Salts into Switched THP Products: The HCl salt **8** (5 mmol) was partitioned between saturated aqueous Na_2CO_3 (30 mL) and EtOAc (70 mL). The separated organic phase was washed with brine (30 mL) then dried over Na_2SO_4 before it was filtered and concentrated under reduced pressure. The crude residue was treated with DHP (110 mol%) and TFA (5 mol%) in MeCN (15 mL) at 70 °C until LC analysis indicated complete conversion to the switched THP product **9**. [CAUTION! – These small scale experiments were conducted using the "all-in" procedure described. Slow addition of DHP would likely be preferable on larger scale as a means to control any potential exotherm, such as that observed during the preparation of compound **6** (*vide infra*).] The mixture was diluted into saturated aqueous $NaHCO_3$ (30 mL) and MTBE (70 mL) then the separated organic phase was washed with brine (30 mL) and dried over Na_2SO_4. The filtered MTBE solution was concentrated under reduced pressure and the switched THP product **9** was isolated following flash chromatography on silica gel using an appropriate mixture of EtOAc/hexanes as the eluent.

General Procedure D

Lithiation/(i-$PrO)_3B$ *Quench of THP-Pyrazoles Using n-BuLi:* To a cooled (- 60 °C) THF solution of THP-pyrazole substrate (100 mol%, 10 mL/g, water content < 500 ppm) was charged *n*-BuLi (2.5 M in hexanes, 105 mol%), maintaining < - 40 °C. After 5 min, $B(Oi\text{-}Pr)_3$ (110 mol%) was added and the mixture was allowed to warm to rt. After 1 h, pinacol (110 mol%) and AcOH (200 mol%) were added and the mixture was stirred at rt

for a further 1 h. The mixture was diluted into water and MTBE and the separated organic phase was washed with brine then dried over Na_2SO_4. The filtered solution was solvent-switched into heptane and concentrated under reduced pressure to isolate the product by crystallization. Alternatively, in cases where the product **10** was an oil, the crude was purified by filtration over a pad of silica using an appropriate mixture of EtOAc/hexanes as the eluent.

General Procedure E

Lithiation/(i-PrO)$_3$B *Quench of THP-Pyrazoles Using LDA:* A 1 M THF solution of LDA was prepared by adding *n*-BuLi (2.5 M in hexanes, 120 mol%) to a THF solution of *i*-Pr_2NH (120 mol%) at - 60 °C. The LDA solution was allowed to warm to 0-20 °C for 10 min before it was added to a cooled (- 60 °C) THF solution of THP-pyrazole substrate (100 mol%, 10 mL/g, water content < 500 ppm) and B(O*i*-Pr)$_3$ (120 mol%) over 5 min. Upon complete addition of LDA, LC analysis indicated consumption of the starting pyrazole and the mixture was allowed to warm to room temperature. After 1 h, pinacol (110 mol%) and AcOH (200 mol%) were added and the mixture was stirred at rt for a further 1 h. The mixture was diluted into water and MTBE and the separated organic phase was washed with brine then dried over Na_2SO_4. The filtered solution was solvent-switched into heptane and concentrated under reduced pressure to isolate the product by crystallization. Alternatively, in cases where the product **10** was an oil, the crude was purified by filtration over a pad of silica using an appropriate mixture of EtOAc/hexanes as the eluent.

Preparation of Pyrazole Boronate 6:[1] To a 500 mL 3-neck R-B flask equipped with a dropping funnel, reflux condenser, temperature probe and nitrogen inlet was charged pyrazole (60.0 g, 0.88 mol, 100 mol%), toluene (100 mL) and TFA (3.40 mL, 44.1 mmol, 5 mol%). The slurry was heated to 80 °C then 3,4-dihydro-*2H*-pyran (DHP) (85 mL, 0.92

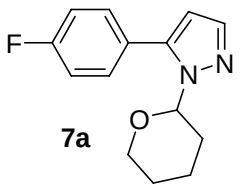
[1] Gerard, A.-L.; Bouillon, A.; Mahatsekake, C.; Collot, V.; Rault, S. *Tetrahedron Lett.*, **2006**, *47*, 4665 - 4669.

mol, 105 mol%) was added over 1 h using the dropping funnel. [CAUTION! - As indicated in the manuscript, when this reaction is conducted following an "all-in" procedure, an exotherm is observed around 60 °C that can increase the batch temperature to > 100 °C. At this stage, the toluene/DHP reflux can mediate the batch temperature however this procedure is not recommended. The controlled addition of DHP at 80 °C ensures steady conversion and no accumulation of unreacted reagents.] The resultant pale yellow solution was aged for a further 1 h then LC analysis indicated complete conversion to the THP-pyrazole. The mixture was concentrated under reduced pressure to leave a crude pale yellow liquid (140 g) that was suitable for direct use in the subsequent boronate formation.

To a 3 L 4-neck R-B flask equipped with an overhead stirrer, reflux condenser, temperature probe and nitrogen inlet was charged the crude THP-pyrazole (assume 0.88 mol, 100 mol%) and THF (1 L, 100 ppm H_2O). The solution was cooled to - 50 °C and *n*-BuLi (2.5 M, 370 mL, 0.925 mol, 105 mol%) was added over 30 min using a dropping funnel (maintaining < - 40 °C). The resultant light brown solution was aged for 10 min at - 50 °C before $B(O\textit{i}\text{-}Pr)_3$ (225 mL, 0.969 mol, 110 mol%) was added over 10 min using a dropping funnel (maintaining < - 30 °C). The solution was allowed to warm to room temperature then pinacol (115 g, 0.969 mol, 110 mol%) and AcOH (101 mL, 1.76 mol, 200 mol%) were added. (The addition of AcOH caused formation of a gel-like substance that is difficult to agitate unless an efficient overhead stirrer is used.) The mixture was aged at room temperature for 4 h before it was poured into saturated aqueous NH_4Cl (1 L) and heptane (1.2 L). The separated organic phase was washed with saturated aqueous $NaHCO_3$ (0.7 L) then brine (0.7 L) before it was dried over Na_2SO_4. The filtered solution was solvent-switched into heptane and concentrated under reduced pressure to isolate the product by crystallization at 5 °C. Filtration of the thick slurry afforded a cream solid, which was dried in a vacuum oven (with an N_2 bleed) at room temperature to give 196 g (80%): mp = 77-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 12 H), 1.48-1.58 (m, 1H), 1.59-1.76 (m, 2H), 1.90-1.99 (m, 1H), 2.00-2.10 (m, 1H), 2.35-2.50 (m, 1H), 3.59-3.70 (m, 1H), 3.97-4.07 (m, 1H), 5.83 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.72 (d, *J* = 1.6 Hz, 1H), 7.58 (d, *J* = 1.6 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.0, 24.6, 24.9, 25.1,

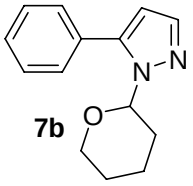
29.7, 67.9, 84.1, 86.3, 116.2, 139.2. HRMS calcd. for $C_8H_{14}BN_2O_3$ $[M+H\ (B(OH)_2)]^+$ 197.10975, found 197.11003.

Compounds 7a-g:



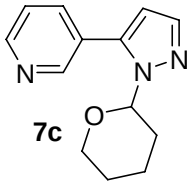
7a

5-(4-Fluoro-phenyl)-1-(tetrahydro-pyran-2-yl)-1*H*-pyrazole (7a): Following general procedure A, **7a** was obtained as a yellow solid (79%): mp = 58-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47-1.60 (m, 2H), 1.64-1.75 (m, 1H), 1.78-1.85 (m, 1H), 1.99-2.07 (m, 1H), 2.50-2.61 (m, 1H), 3.51-3.59 (m, 1H), 4.06-4.12 (m, 1H), 5.12 (d, *J* = 10.0, 2.4 Hz, 1H), 6.27 (d, *J* = 1.6 Hz, 1H), 7.08-7.14 (m, 2H), 7.45-7.50 (m, 2H), 7.56 (d, *J* = 1.6 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9, 24.8, 29.6, 67.6, 84.1, 106.5, 115.6 (d, J_{CF} = 20.1 Hz), 126.5 (d, J_{CF} = 10.0 Hz), 130.8 (d, J_{CF} = 10.0 Hz), 139.3, 143.1, 163.0 (d, J_{CF} = 251.6 Hz). HRMS calcd. for $C_9H_8FN_2$ $[(M\text{-}THP)+H]^+$ 163.06715, found 163.06792.



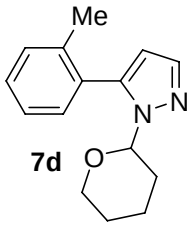
7b

5-Phenyl-1-(tetrahydro-pyran-2-yl)-1*H*-pyrazole (7b): Following general procedure A, **7b** was obtained as a beige solid (76%): mp = 92-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50-1.62 (m, 2H), 1.70-1.80 (m, 1H), 1.81-1.89 (m, 1H), 2.02-2.10 (m, 1H), 2.54-2.65 (m, 1H), 3.56-3.63 (m, 1H), 4.10-4.17 (m, 1H), 5.22 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.33 (d, *J* = 1.6 Hz, 1H), 7.40-7.49 (m, 3H), 7.51-7.55 (m, 2H), 7.61 (d, *J* = 1.6 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.1, 25.0, 29.9, 67.9, 84.3, 106.4, 128.7, 128.6, 129.2, 130.6, 139.6, 144.3. HRMS calcd. for $C_9H_9N_2$ $[(M\text{-}THP)+H]^+$ 145.07657, found 145.07703.



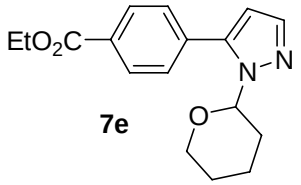
7c

3-[2-(Tetrahydro-pyran-2-yl)-2*H*-pyrazol-3-yl]-pyridine (7c): Following general procedure A, **7c** was obtained as a colorless oil (68%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52-1.65 (m, 2H), 1.68-1.82 (m, 1H), 1.85-1.93 (m, 1H), 2.04-2.14 (m, 1H), 2.53-2.65 (m, 1H), 3.55-3.65 (m, 1H), 4.09-4.17 (m, 1H), 5.16 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.41 (d, *J* = 2.0 Hz, 1H), 7.41 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.87 (ddd, *J* = 7.6, 2.4, 1.6 Hz, 1H), 8.67 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.78 (d, *J* = 2.4 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.0, 24.9, 29.7, 67.8, 84.5, 107.5, 123.5, 126.8, 136.4, 139.7, 140.9, 149.8 (2 overlapping signals). HRMS calcd. for $C_8H_8N_3$ $[(M\text{-}THP)+H]^+$ 146.07182, found 146.07130.



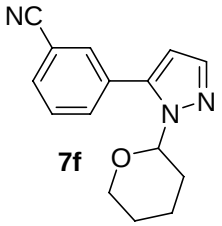
7d

1-(Tetrahydro-pyran-2-yl)-5-*o*-tolyl-1*H*-pyrazole (7d): Following general procedure A, **7d** was obtained as a yellow oil (77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.57 (m, 2H), 1.63-1.74 (m, 1H), 1.78-1.85 (m, 1H), 1.97-2.07 (m, 1H), 2.19 (s, 3H), 2.44-2.57 (m, 1H), 3.35-3.44 (m, 1H), 3.99-4.06 (m, 1H), 4.92 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.23 (d, *J* = 1.6 Hz, 1H), 7.21-7.39 (m, 4H), 7.65 (d, *J* = 1.6 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.1, 23.0, 25.0, 30.1, 68.0, 84.2, 107.1, 125.7, 129.1, 130.2, 130.3, 130.7, 138.0, 139.6, 142.7. HRMS calcd. for $C_{10}H_{11}N_2$ $[(M\text{-}THP)+H]^+$ 159.09222, found 159.09314.



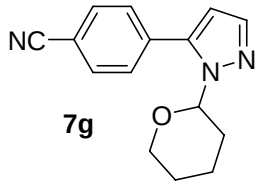
7e

4-[2-(Tetrahydro-pyran-2-yl)-2*H*-pyrazol-3-yl]-benzoic acid ethyl ester (7e): Following general procedure A, **7e** was obtained as a yellow oil (77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.2 Hz, 3H), 1.47-1.59 (m, 2H), 1.69-1.77 (m, 1H), 1.79-1.86 (m, 1H), 2.01-2.08 (m, 1H), 2.50-2.61 (m, 1H), 3.54-3.61 (m, 1H), 4.08-4.14 (m, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 5.17 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.37 (d, *J* = 2.0 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 2.0 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.4, 23.1, 24.9, 29.8, 61.2, 37.8, 84.5, 107.2, 129.0, 129.9, 130.6, 134.8, 139.6, 143.3, 166.2. HRMS calcd. for $C_{12}H_{13}N_2O_2$ $[(M\text{-}THP)+H]^+$ 217.09770, found 217.09848.



7f

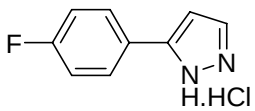
3-[2-(Tetrahydro-pyran-2-yl)-2*H*-pyrazol-3-yl]-benzonitrile (7f): Following general procedure A, **7f** was obtained as a yellow oil (80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50-1.61 (m, 2H), 1.65-1.76 (m, 1H), 1.80-1.88 (m, 1H), 2.01-2.11 (m, 1H), 2.49-2.61 (m, 1H), 3.55-3.63 (m, 1H), 4.08-4.15 (m, 1H), 5.09 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.37 (d, *J* = 1.6 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 1.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 7.6 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.8, 24.8, 29.5, 67.6, 84.4, 107.4, 113.0, 118.3, 129.7, 131.8, 132.0, 132.4, 133.3, 139.6, 141.8. HRMS calcd. for $C_{10}H_8N_3$ $[(M\text{-}THP)+H]^+$ 170.07182, found 170.07215.



7g

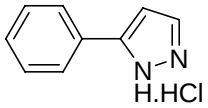
4-[2-(Tetrahydro-pyran-2-yl)-2*H*-pyrazol-3-yl]-benzonitrile (7g): Following general procedure A, **7g** was obtained as a yellow oil (81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50-1.65 (m, 2H), 1.68-1.79 (m, 1H), 1.83-1.90 (m, 1H), 2.03-2.16 (m, 1H), 2.50-2.64 (m, 1H), 3.53-3.66 (m, 1H), 4.08-4.18 (m, 1H), 5.14 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.40 (d, *J* = 1.6 Hz, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9, 24.9, 29.7, 67.8, 84.6, 107.7, 112.4, 118.5, 129.7, 132.6, 135.1, 139.7, 142.4. HRMS calcd. for $C_{10}H_8N_3$ $[(M\text{-}THP)+H]^+$ 170.07182, found 170.07240.

Compounds 8a-g:



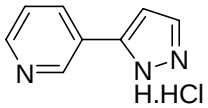
8a

5-(4-Fluoro-phenyl)-1*H*-pyrazole hydrochloride (8a): Following general procedure A, **8a** was obtained as an off-white solid (84%): mp = 162-163 °C; ^{1}H NMR (400 MHz, DMSO) δ 6.98 (d, *J* = 2.4 Hz, 1H), 7.28 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.98 (dd, *J* = 8.4, 5.6 Hz, 2H), 8.08 (d, *J* = 2.4 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 103.5, 116.1 (d, J_{CF} = 20.1 Hz), 126.0, 128.6 (d, J_{CF} = 10.0 Hz), 133.8, 146.1, 163.6 (d, J_{CF} = 251.6 Hz). HRMS calcd. for $C_9H_8FN_2$ $[M+H]^+$ 163.06715, found 163.06749.



8b

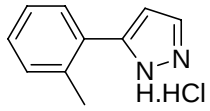
5-Phenyl-1*H*-pyrazole hydrochloride (8b):[2] Following general procedure A, **8b** was obtained as an off-white solid (81%): mp = 152-154 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.06 (d, *J* = 2.4 Hz, 1H), 7.29-7.41 (m, 3H), 7.93 (d, *J* = 7.2 Hz, 2H), 8.22 (d, *J* = 2.4 Hz); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 104.3, 126.8, 127.9, 129.3, 130.2, 134.6, 146.6. HRMS calcd. for $C_9H_9N_2$ $[M+H]^+$ 145.07657, found 145.07693.



8c

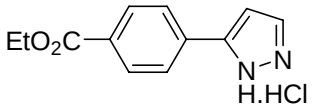
3-(2*H*-Pyrazol-3-yl)-pyridine hydrochloride (8c):[3] Following general procedure A, **8c** was obtained as an off-white solid (70%): mp = 263-264 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.09 (d, *J* = 2.4 Hz, 1H), 7.94 (d, *J* = 2.4 Hz, 1H), 8.08 (dd, *J* = 8.0, 5.6 Hz, 1H), 8.81 (d, *J* = 5.6 Hz, 1H), 8.94 (d, *J* = 8.0 Hz, 1H), 9.30 (s, 1H); ^{13}C {^{1}H} NMR (100

MHz, DMSO) δ 103.8, 127.6, 131.6, 133.0, 137.5, 139.6, 141.2, 143.9. HRMS calcd. for $C_8H_8N_3$ $[M+H]^+$ 146.07182, found 146.07270.



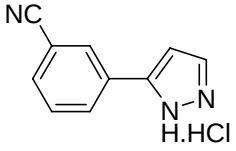
8d

5-*o*-Tolyl-1*H*-pyrazole hydrochloride (8d): Following general procedure A, **8d** was obtained as an off-white solid (81%): mp = 147-150 °C; ^{1}H NMR (400 MHz, DMSO) δ 2.39 (s, 3H), 6.73 (d, *J* = 2.4 Hz, 1H), 7.25-7.34 (m, 3H), 7.51 (d, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 2.4 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 20.6, 106.2, 126.1, 129.0, 129.2, 129.4, 130.9, 133.3, 136.0, 146.3. HRMS calcd. for $C_{10}H_{11}N_2$ $[M+H]^+$ 159.09222, found 159.09252.



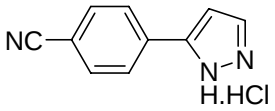
8e

4-(2*H*-Pyrazol-3-yl)-benzoic acid ethyl ester hydrochloride (8e): Following general procedure A, **8e** was obtained as an off-white solid (88%): mp = 194-195 °C; ^{1}H NMR (400 MHz, DMSO) δ 1.33 (t, *J* = 7.2 Hz, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 6.85 (d, *J* = 2.4 Hz, 1H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.93-8.01 (m, 4H); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 14.2, 60.7, 103.1, 125.4, 128.8, 129.7, 132.3, 136.8, 147.3, 165.5. HRMS calcd. for $C_{12}H_{13}N_2O_2$ $[M+H]^+$ 217.09770, found 217.09713.



8f

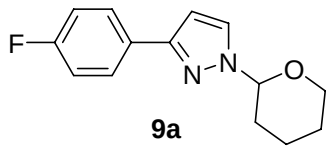
3-(2*H*-Pyrazol-3-yl)-benzonitrile hydrochloride (8f): Following general procedure A, **8f** was obtained as a white solid (82%): mp = 168-169 °C; ^{1}H NMR (400 MHz, DMSO) δ 6.98 (br s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.95 (br s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.29 (br s, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 103.6, 112.2, 118.7, 129.2, 130.2 (2 overlapping signals), 131.8, 132.6, 132.8, 146.2. HRMS calcd. for $C_{10}H_8N_3$ $[M+H]^+$ 170.07182, found 170.07101.



8g

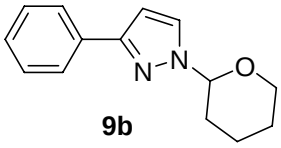
4-(2*H*-Pyrazol-3-yl)-benzonitrile hydrochloride(8g): Following general procedure A, **8g** was obtained as a white solid (85%): mp = 200-201 °C; ^{1}H NMR (400 MHz, DMSO) δ 6.96 (d, *J* = 2.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 2.4 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 104.0, 110.5, 118.9, 126.3, 132.8, 132.9, 135.8, 146.5. HRMS calcd. for $C_{10}H_8N_3$ $[M+H]^+$ 170.07182, found 170.07122.

Compounds 9a-f:



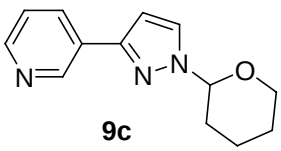
9a

3-(4-Fluoro-phenyl)-1-(tetrahydro-pyran-2-yl)-1*H*-pyrazole (9a): Following general procedure B, **9a** was obtained as a colorless oil (86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58-1.77 (m, 3H), 2.02-2.23 (m, 3H), 3.69-3.77 (m, 1H), 4.07-4.14 (m, 1H), 5.43 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 1H), 7.04-7.11 (m, 2H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.77-7.82 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.6, 25.1, 30.7, 68.0, 87.9, 103.3, 115.5 (d, J_{CF} = 20.1 Hz), 127.6, 129.1, 129.8, 150.9, 162.7 (d, J_{CF} = 241.5 Hz). HRMS calcd. for $C_9H_8FN_2$ $[(M\text{-}THP)+H]^+$ 163.06715, found 163.06724.



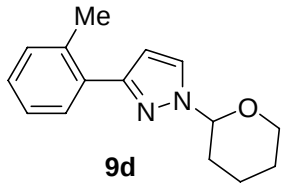
9b

3-Phenyl-1-(tetrahydro-pyran-2-yl)-1*H*-pyrazole (9b): Following general procedure B, **9b** was obtained as a colorless oil (78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56-1.74 (m, 3H), 2.00-2.23 (m, 3H), 3.67-3.76 (m, 1H), 4.06-4.14 (m, 1H), 5.43 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.64 (d, *J* = 2.4 Hz, 1H), 7.87 (d, *J* = 7.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.5, 25.0, 30.6, 67.9, 87.8, 103.4, 125.8, 127.7, 128.6, 128.9, 133.5, 151.5. HRMS calcd. for $C_9H_9N_2$ $[(M\text{-}THP)+H]^+$ 145.07657, found 145.07702.



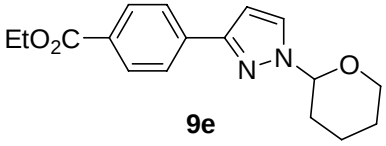
9c

3-[1-(Tetrahydro-pyran-2-yl)-1*H*-pyrazol-3-yl]-pyridine (9c): Following general procedure B, **9c** was obtained as a colorless oil (68%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45-1.63 (m, 3H), 1.89-2.12 (m, 3H), 3.57-3.64 (m, 1H), 3.94-4.01 (m, 1H), 5.32 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 7.20 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 8.03 (dt, *J* = 8.0, 2.0 Hz, 1H), 8.44 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.97 (d, *J* = 2.0 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.3, 24.8, 30.4, 67.7, 87.5, 103.3, 123.3, 129.2, 138.8, 147.1, 148.4, 148.6. HRMS calcd. for $C_8H_8N_3$ $[(M\text{-}THP)+H]^+$ 146.07182, found 146.07095.



9d

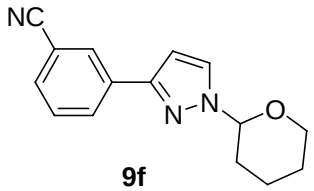
1-(Tetrahydro-pyran-2-yl)-3-*o*-tolyl-1*H*-pyrazole (9d): Following general procedure B, **9d** was obtained as a colorless oil (81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57-1.77 (m, 3H), 2.02-2.24 (m, 3H), 2.49 (s, 3H), 3.69-3.78 (m, 1H), 4.06-4.14 (m, 1H), 5.46 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 7.20-7.26 (m, 3H), 7.56-7.61 (m, 1H), 7.66 (d, *J* = 2.4 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.3, 22.6, 25.1, 30.7, 67.8, 87.8, 106.5, 125.8, 127.7, 127.9, 129.5, 130.8, 133.4, 136.2, 151.9. HRMS calcd. for $C_{10}H_{11}N_2$ $[(M\text{-}THP)+H]^+$ 159.09222, found 159.09259.



9e

4-[1-(Tetrahydro-pyran-2-yl)-1*H*-pyrazol-3-yl]-benzoic acid ethyl ester (9e): Following general procedure B, **9e** was obtained as a colorless oil (85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 1.51-1.70 (m, 3H), 1.95-2.18 (m, 3H), 3.63-3.70 (m, 1H), 4.01-4.07 (m, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 5.39 (dd, *J* = 9.6, 2.4 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 8.05 (d, *J* = 8.4 Hz,

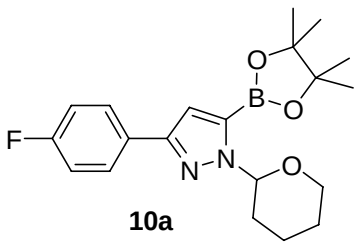
2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.4, 22.5, 25.0, 30.7, 60.9, 67.9, 87.9, 104.0, 125.6, 129.3, 129.5, 130.0, 137.8, 150.5, 166.6. HRMS calcd. for $C_{12}H_{13}N_2O_2$ [(M-THP)+H]$^+$ 217.09770, found 217.09813.



9f

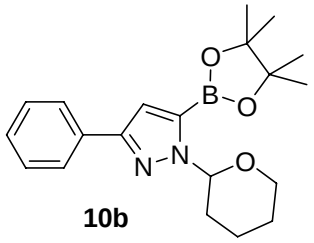
3-[1-(Tetrahydro-pyran-2-yl)-1*H*-pyrazol-3-yl]-benzonitrile (9f): Following general procedure B, **9f** was obtained as a white solid (83%): mp = 87-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55-1.75 (m, 3H), 1.98-2.21 (m, 3H), 3.66-3.74 (m, 1H), 4.03-4.10 (m, 1H), 5.39 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.60 (d, *J* = 2.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.53 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.11 (t, *J* = 1.6 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.4, 24.9, 30.5, 67.9, 87.8, 103.5, 112.6, 118.9, 129.2, 129.3, 129.5, 129.9, 130.9, 134.7, 149.3. HRMS calcd. for $C_{10}H_8N_3$ [(M-THP)+H]$^+$ 170.07182, found 170.07248.

Compounds 10a-f:



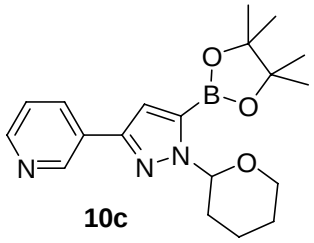
10a

3-(4-Fluoro-phenyl)-1-(tetrahydro-pyran-2-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazole (10a): Following general procedure D, **10a** was obtained as a white solid (79%): mp = 104-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 12H), 1.55-1.62 (m, 1H), 1.69-1.81 (m, 2H), 1.97-2.05 (m, 1H), 2.09-2.17 (m, 1H), 2.51-2.63 (m, 1H), 3.65-3.74 (m, 1H), 4.05-4.12 (m, 1H), 5.87 (dd, J = 10.0, 2.4 Hz, 1H), 7.00 (s, 1H), 7.02-7.09 (m, 2H), 7.77-7.85 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.0, 24.8, 25.0, 25.2, 29.8, 68.0, 84.3, 86.6, 113.3, 115.4 (d, J_{CF} = 20.1 Hz), 127.6 (d, J_{CF} = 10.0 Hz), 129.8, 150.6, 162.5 (d, J_{CF} = 251.6 Hz). HRMS calcd. for $C_{14}H_{17}BFN_2O_3$ [M+H ($B(OH)_2$)]$^{+}$ 291.13163, found 291.13291.



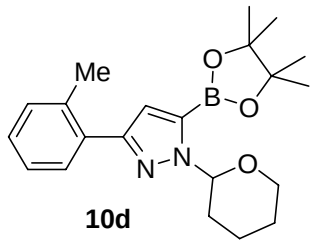
10b

3-Phenyl-1-(tetrahydro-pyran-2-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazole (10b): Following general procedure D, **10b** was obtained as a white solid (72%): mp = 99-100 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 12H), 1.56-1.63 (m, 1H), 1.70-1.82 (m, 2H), 1.99-2.07 (m, 1H), 2.11-2.19 (m, 1H), 2.55-2.66 (m, 1H), 3.65-3.75 (m, 1H), 4.04-4.14 (m, 1H), 5.89 (dd, J = 10.0, 2.4 Hz, 1H), 7.08 (s, 1H), 7.25-7.32 (t, J = 7.2 Hz, 1H), 7.38-7.42 (t, J = 7.2 Hz, 2H), 7.83-7.89 (d, J = 7.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 23.0, 24.8, 25.1, 25.2, 29.8, 67.9, 84.3, 86.6, 113.6, 126.1, 127.6, 128.5, 133.6, 151.5. HRMS calcd. for $C_{14}H_{18}BN_2O_3$ [M+H ($B(OH)_2$)]$^{+}$ 273.14105, found 273.14242.



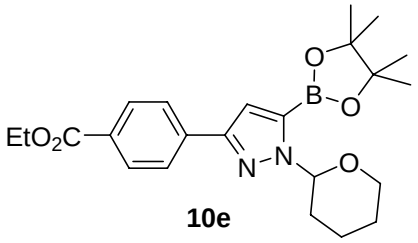
10c

3-[1-(Tetrahydro-pyran-2-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazol-3-yl]-pyridine (10c): Following general procedure D, **10c** was obtained as a colorless oil (67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 12H), 1.55-1.62 (m, 1H), 1.69-1.79 (m, 2H), 1.97-2.04 (m, 1H), 2.08-2.17 (m, 1H), 2.50-2.62 (m, 1H), 3.65-3.73 (m, 1H), 4.05-4.11 (m, 1H), 5.88 (dd, *J* = 10.0, 2.4 Hz, 1H), 7.09 (s, 1H), 7.29 (dd, *J* = 8.0, 4.0 Hz, 1H), 8.14 (ddd, *J* = 8.0, 4.0, 2.0 Hz, 1H), 8.51 (d, *J* = 4.0 Hz, 1H), 9.04 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9, 24.8, 25.0, 25.1, 29.7, 68.0, 84.4, 86.7, 113.6, 123.5, 129.4, 133.2, 147.5, 148.5, 148.6. HRMS calcd. for $C_{13}H_{17}BN_3O_3$ [M+H $(B(OH)_2)]^+$ 274.13630, found 274.1371.



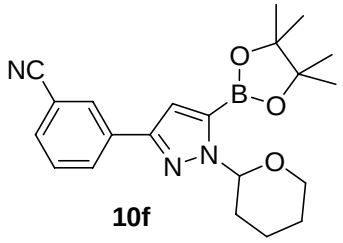
10d

1-(Tetrahydro-pyran-2-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3-*o*-tolyl-1*H*-pyrazole (10d): Following general procedure D, **10d** was obtained as a white solid (72%): mp = 109-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 12H), 1.55-1.62 (m, 1H), 1.69-1.79 (m, 2H), 2.01-2.09 (m, 1H), 2.10-2.18 (m, 1H), 2.51 (s, 3H), 2.53-2.59 (m, 1H), 3.67-3.75 (m, 1H), 4.05-4.11 (m, 1H), 5.90 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.92 (s, 1H), 7.18-7.25 (m, 3H), 7.56-7.61 (m, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.4, 22.9, 24.8, 25.1, 25.2, 29.7, 67.7, 84.2, 86.4, 116.5, 125.7, 127.5, 129.6, 130.7, 133.3, 136.3, 151.6. HRMS calcd. for $C_{15}H_{20}BN_2O_3$ [M+H $(B(OH)_2)]^+$ 287.15670, found 287.15720.



10e

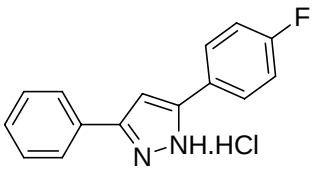
4-[1-(Tetrahydro-pyran-2-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazol-3-yl]-benzoic acid ethyl ester (10e): Following general procedure E, **10e** was obtained as a white solid (82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 12H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.55-1.62 (m, 1H), 1.68-1.81 (m, 2H), 1.91-2.06 (m, 1H), 2.08-2.16 (m, 1H), 2.51-2.63 (m, 1H), 3.64-3.74 (m, 1H), 4.04-4.13 (m, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 5.88 (dd, *J* = 10.0, 2.4 Hz, 1H), 7.12 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 8.05 (d, *J* = 8.4 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.5, 22.9, 24.8, 25.0, 25.1, 29.7, 60.9, 68.0, 84.4, 86.7, 114.1, 125.7, 129.3, 129.9, 137.8, 150.3, 166.7. HRMS calcd. for $C_{17}H_{22}BN_2O_5$ $[M+H\ (B(OH)_2)]^+$ 345.16218, found 345.16294.



10f

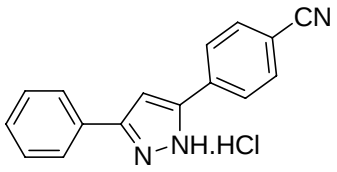
3-[1-(Tetrahydro-pyran-2-yl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazol-3-yl]-benzonitrile (10f): Following general procedure E, **10f** was obtained as a colorless oil (81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 12H), 1.54-1.63 (m, 1H), 1.66-1.82 (m, 2H), 1.96-2.04 (m, 1H), 2.07-2.17 (m, 1H), 2.48-2.60 (m, 1H), 3.65-3.74 (m, 1H), 4.03-4.12 (m, 1H), 5.88 (dd, *J* = 10.0, 2.4 Hz, 1H), 7.06 (s, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 8.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.16 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9, 24.8, 25.0, 29.7, 68.0, 84.5, 86.7, 112.7, 113.6, 119.0, 129.4, 129.5, 130.1, 130.8, 134.8, 149.2. HRMS calcd. for $C_{15}H_{17}BN_3O_3$ $[M+H\ (B(OH)_2)]^+$ 298.13630, found 298.13710.

Compounds 11a-f:



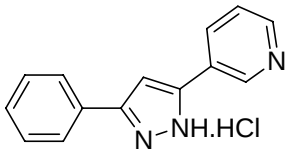
11a

5-(4-Fluoro-phenyl)-3-phenyl-1*H*-pyrazole hydrochloride (11a):[4] Following general procedure A, **11a** was obtained as a white solid (83%): mp = 227-228 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.26-7.35 (m, 3H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.94-7.99 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 100.4, 115.8, 115.9 (d, J_{CF} = 20.1 Hz), 125.7, 126.9, 127.9 (d, J_{CF} = 10.0 Hz), 128.7, 129.0, 129.8, 146.8 (d, J_{CF} = 20.1 Hz), 162.2 (d, J_{CF} = 251.5 Hz). HRMS calcd. for $C_{15}H_{12}FN_2$ $[M+H]^+$ 239.09845, found 239.09877.



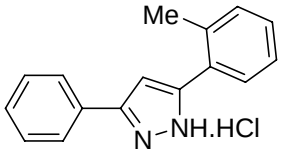
11b

4-(5-Phenyl-2*H*-pyrazol-3-yl)-benzonitrile hydrochloride (11b): Following general procedure A, **11b** was obtained as a white solid (88%): mp = 259-260 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.27-7.37 (m, 2H), 7.39-7.48 (m, 2H), 7.78-7.91 (m, 4H), 8.00-8.10 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 101.2, 110.3, 119.1, 125.6, 126.0, 128.5, 129.1, 130.0, 133.0, 136.2, 146.5, 147.1. HRMS calcd. for $C_{16}H_{12}N_3$ $[M+H]^+$ 246.10312, found 246.10405.



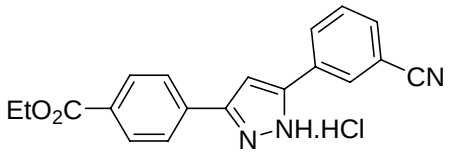
11c

3-(5-Phenyl-2*H*-pyrazol-3-yl)-pyridine hydrochloride (11c): Following general procedure A, **11c** was obtained as an off-white solid (78%): mp = 242-243 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.34 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.56 (s, 1H), 7.85 (d, *J* = 7.2 Hz, 2H), 8.10 (dd, *J* = 8.4, 5.6 Hz, 1H), 8.85 (d, *J* = 5.6 Hz, 1H), 8.97 (d, *J* = 8.4 Hz, 1H), 9.30 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 101.7, 125.5, 127.9, 128.6, 129.2, 129.3, 132.6, 137.5, 139.8, 141.3, 144.5, 145.6. HRMS calcd. for $C_{14}H_{12}N_3$ $[M+H]^+$ 222.10312, found 222.10415.



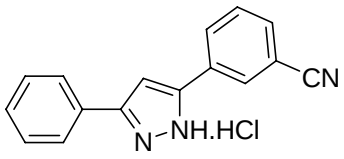
11d

3-Phenyl-5-*o*-tolyl-1*H*-pyrazole hydrochloride (11d): Following general procedure A, **11d** was obtained as a white solid (88%): 181-182 °C; ^{1}H NMR (400 MHz, DMSO) δ 2.45 (s, 3H), 7.10 (s, 1H), 7.26-7.34 (m, 3H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 20.9, 103.5, 125.9, 126.0, 128.8, 128.9, 129.1, 129.3, 129.8, 130.3, 131.1, 136.0, 146.8, 147.0. HRMS calcd. for $C_{16}H_{15}N_2$ $[M+H]^+$ 235.12352, found 235.12299.



11e

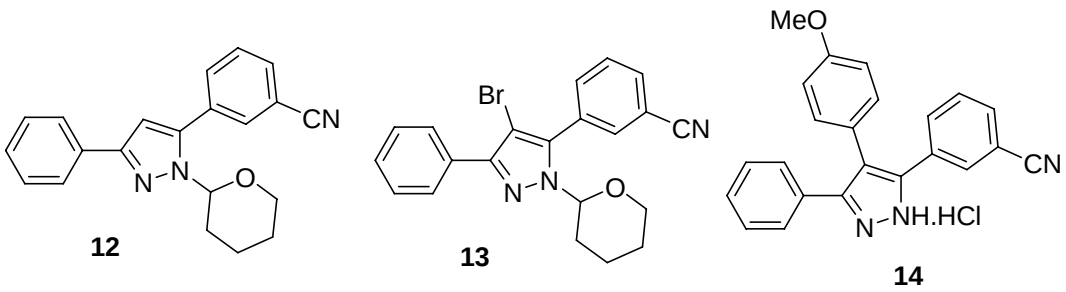
4-[5-(3-Cyano-phenyl)-1*H*-pyrazol-3-yl]-benzoic acid ethyl ester hydrochloride (11e): Following general procedure A, **11e** was obtained as an off-white solid (79%): mp = 234-235 °C; ^{1}H NMR (400 MHz, DMSO) δ 1.35 (t, *J* = 7.2 Hz, 3H), 4.34 (q, *J* = 7.2 Hz, 2H), 7.50 (s, 1H), 7.68 (t, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 8.05 (d, *J* = 8.4 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 1H), 8.30 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 14.1, 60.7, 101.5, 112.0, 118.6, 125.1, 128.5, 129.0, 129.5, 129.8, 130.1, 131.2, 132.6, 135.2, 146.2 (2 overlapping signals), 165.4. HRMS calcd. for $C_{19}H_{16}N_3O_2$ $[M+H]^+$ 318.12425, found 318.12478.



11f

3-(5-Phenyl-2*H*-pyrazol-3-yl)-benzonitrile hydrochloride (11f): Following general procedure A, **11f** was obtained as a white solid (81%): mp = 221-222 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.27-7.48 (m, 4H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.31 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO) δ 100.9, 112.1, 118.8, 125.6, 128.6, 128.9, 129.1, 129.9, 130.0, 130.2, 131.6, 132.8, 146.5, 146.7. HRMS calcd. for $C_{16}H_{12}N_3$ $[M+H]^+$ 246.10312, found 246.10421.

Compounds 12, 13 and 14:

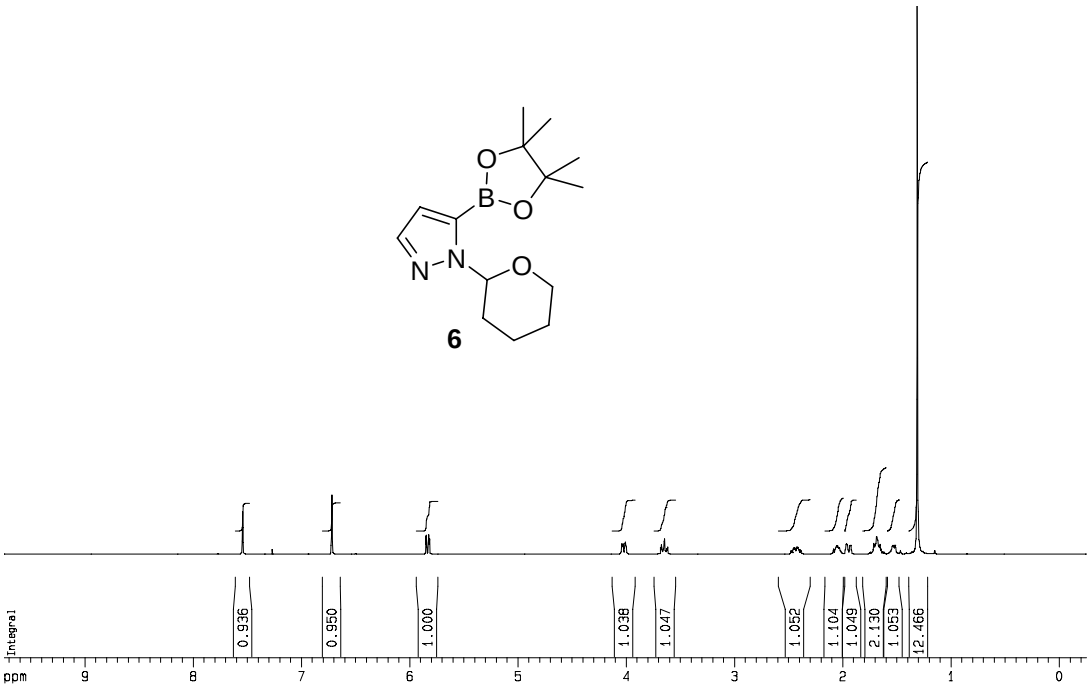


3-[5-phenyl-2-(tetrahydro-pyran-2-yl)-2*H*-pyrazol-3-yl]-benzonitrile (12): Following general procedure A, **12** was obtained as a white solid (81%): mp = 135-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53-1.68 (m, 2H), 1.71-1.86 (m, 1H), 1.87-1.97 (m, 1H), 2.08-2.22 (m, 1H), 2.61-2.76 (m, 1H), 3.56-3.69 (m, 1H), 4.14-4.24 (m, 1H), 5.16 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.71 (s, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.93 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.9, 24.9, 29.6, 67.7, 84.8, 104.7, 113.2, 118.5, 126.0, 128.1, 128.7, 129.8, 131.9, 132.2, 132.5, 133.0, 133.3, 143.3, 151.4. HRMS calcd. for $C_{16}H_{12}N_3$ $[M+H]^+$ 246.10312, found 246.10329.

3-[4-Bromo-5-phenyl-2-(tetrahydro-pyran-2-yl)-2*H*-pyrazol-3-yl]-benzonitrile (13): A solution of **12** (0.50 g, 1.52 mmol, 100 mol%) in EtOAc (5 mL) was treated with NBS (0.40 g, 2.28 mmol, 150 mol%) and heated to 50 °C. After 2 h, LC analysis indicated complete conversion to **13** and the mixture was diluted with aqueous NaOH (0.5 M, 30 mL) and EtOAc (70 mL). The separated organic was washed with brine then dried over Na_2SO_4 before it was filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel using an appropriate gradient of EtOAc/hexanes as the eluent. Compound **13** was isolated as a white solid (0.54 g, 87%): mp = 169-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52-1.61 (m, 2H), 1.67-1.78 (m, 1H), 1.85-1.93 (m, 1H), 2.07-2.16 (m, 1H), 2.53-2.65 (m, 1H), 3.50-3.58 (m, 1H), 4.09-4.16 (m, 1H), 5.08 (dd, *J* = 10.0, 2.4 Hz, 1H), 7.37-7.48 (m, 3H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.92-7.98 (m, 3H); ^{13}C {^{1}H} NMR

(100 MHz, $CDCl_3$) δ 22.7, 24.8, 29.1, 67.7, 85.5, 94.3, 113.2, 118.3, 128.2, 128.4, 128.6, 129.7, 130.1, 132.0, 132.9, 133.9, 134.7, 141.0, 149.1. HRMS calcd. for $C_{16}H_{11}BrN_3$ $[(M\text{-}THP)+H]^+$ 324.01363, found 324.01372.

3-[4-(4-Methoxy-phenyl)-5-phenyl-*2H*-pyrazol-3-yl]-benzonitrile hydrochloride (14): Following general procedure A, compound **14** was obtained as a white solid (72%): mp = 219-220 °C; ^1H NMR (400 MHz, DMSO) δ 3.77 (s, 3H), 6.94 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.26-7.38 (m, 5H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.69-7.75 (m, 2H); ^{13}C $\{^1H\}$ NMR (100 MHz, DMSO) δ 55.1, 111.5, 114.4, 117.0, 118.6, 125.0, 127.4, 128.0, 128.5, 129.7, 130.5, 131.0, 131.7, 131.8, 133.7, 143.4, 144.4, 158.6. HRMS calcd. for $C_{23}H_{18}N_3O$ $[M+H]^+$ 352.14499, found 352.14574.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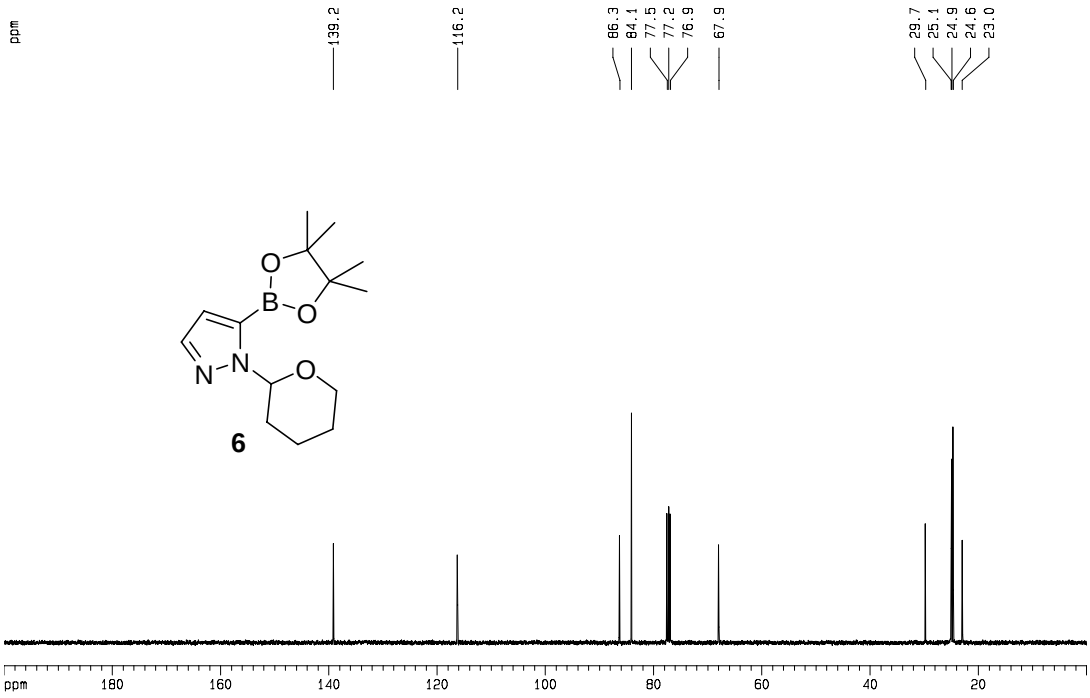
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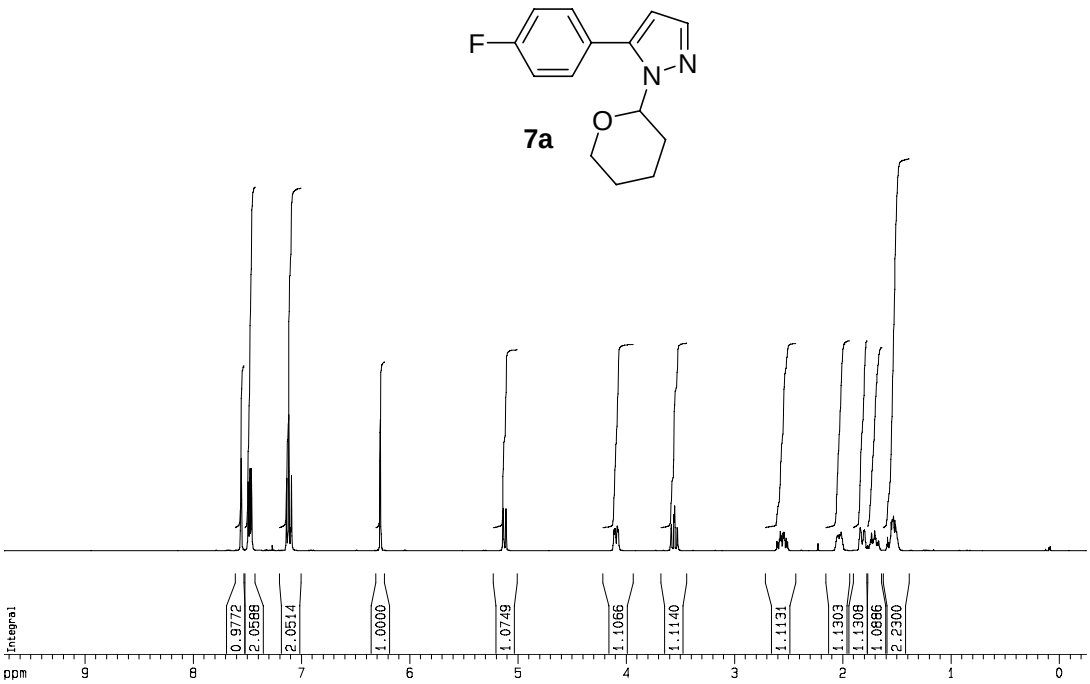
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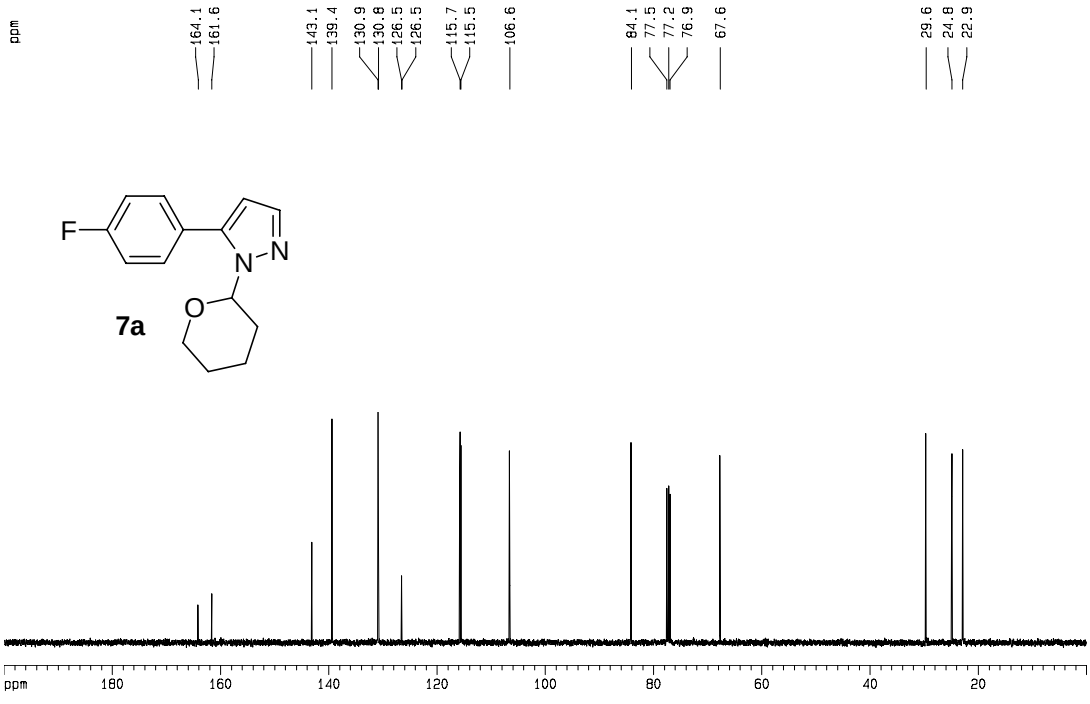
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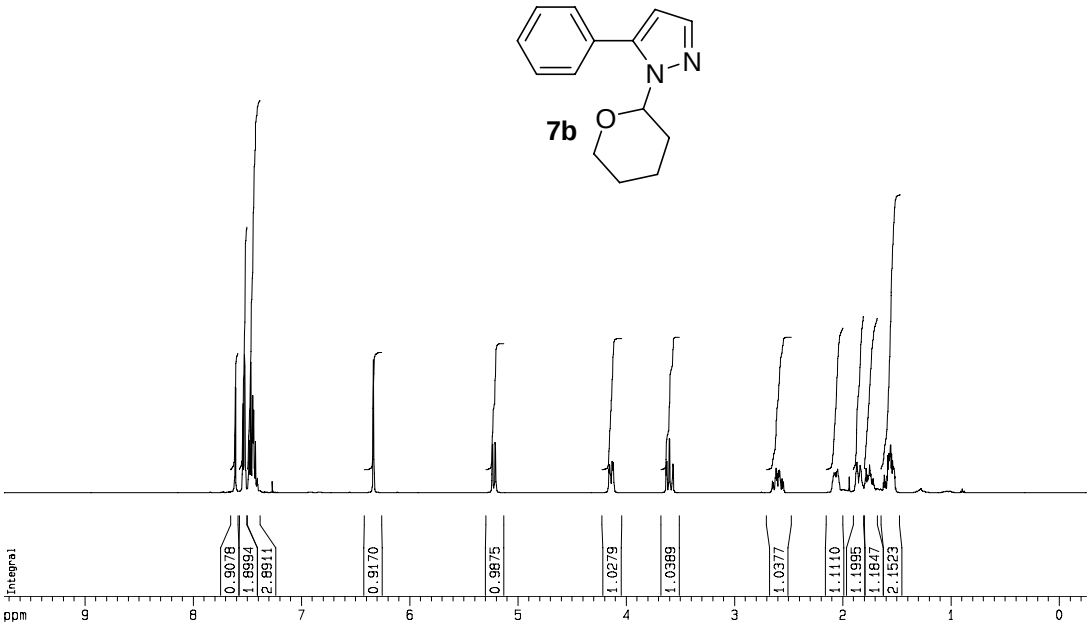
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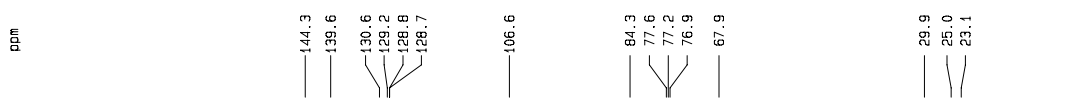
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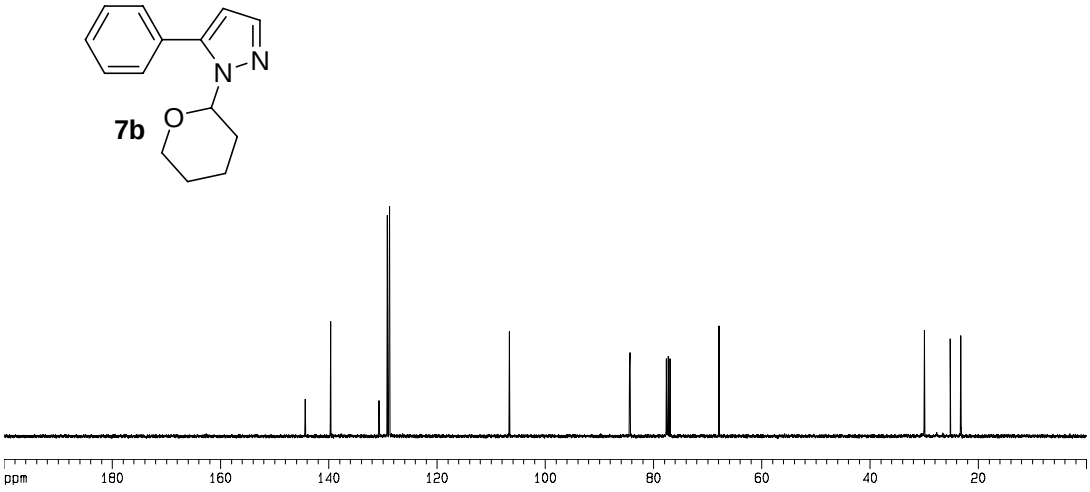
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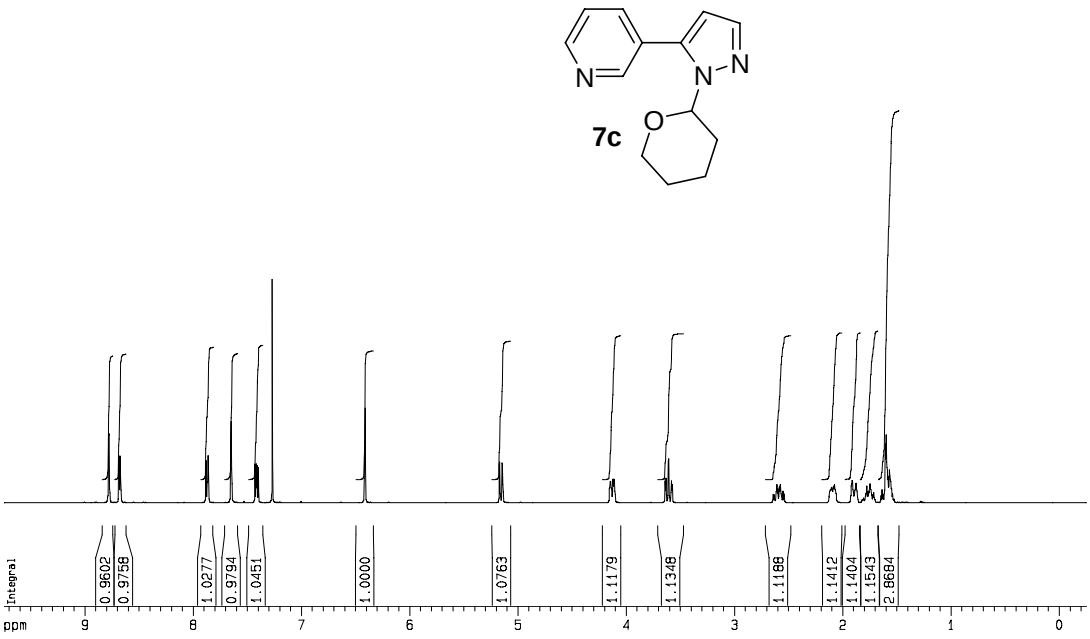
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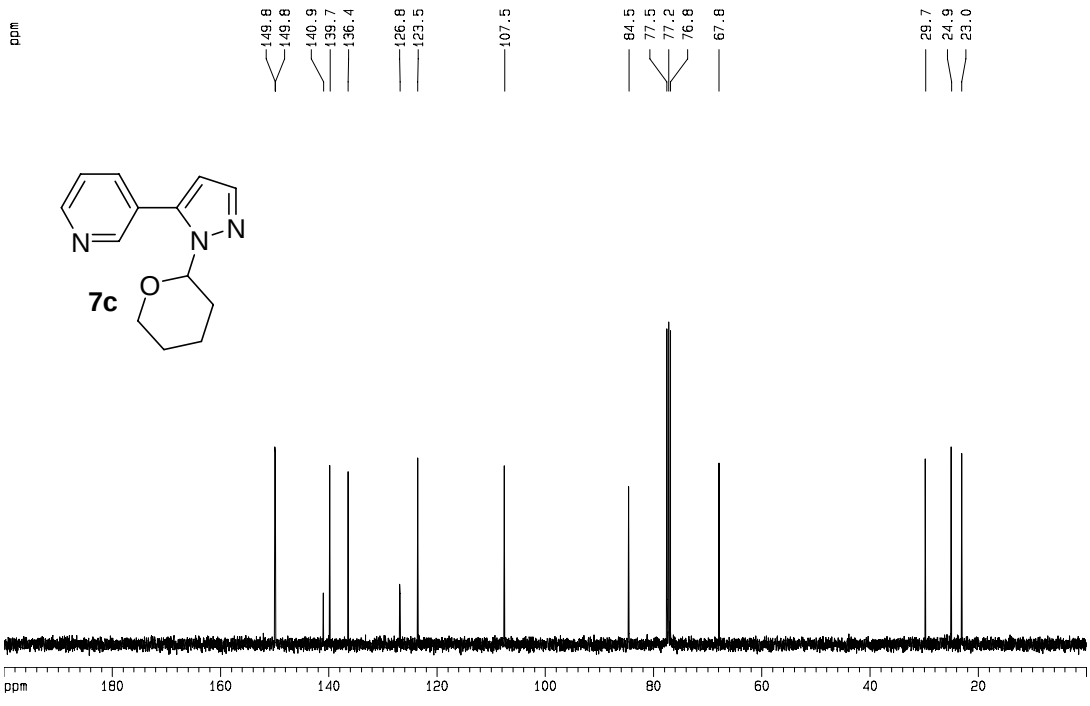
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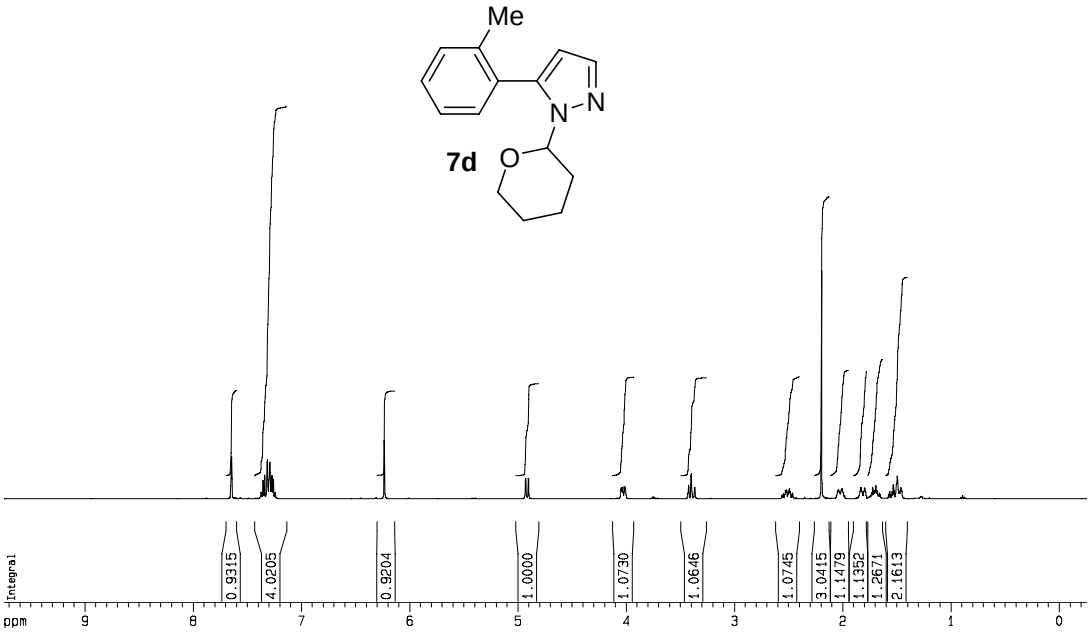
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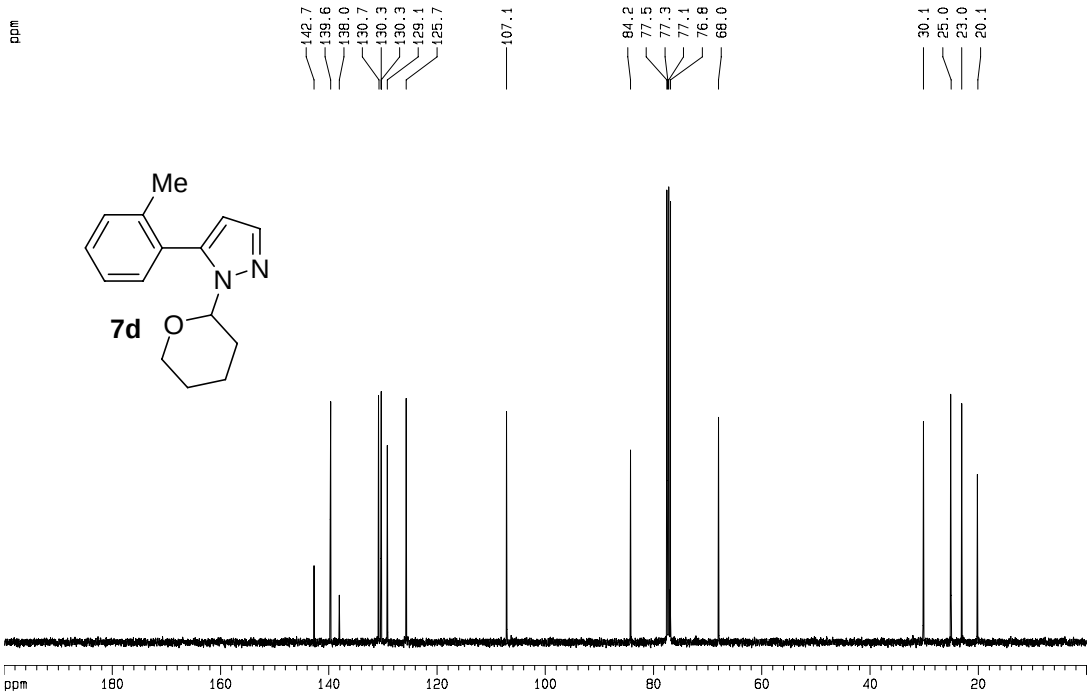
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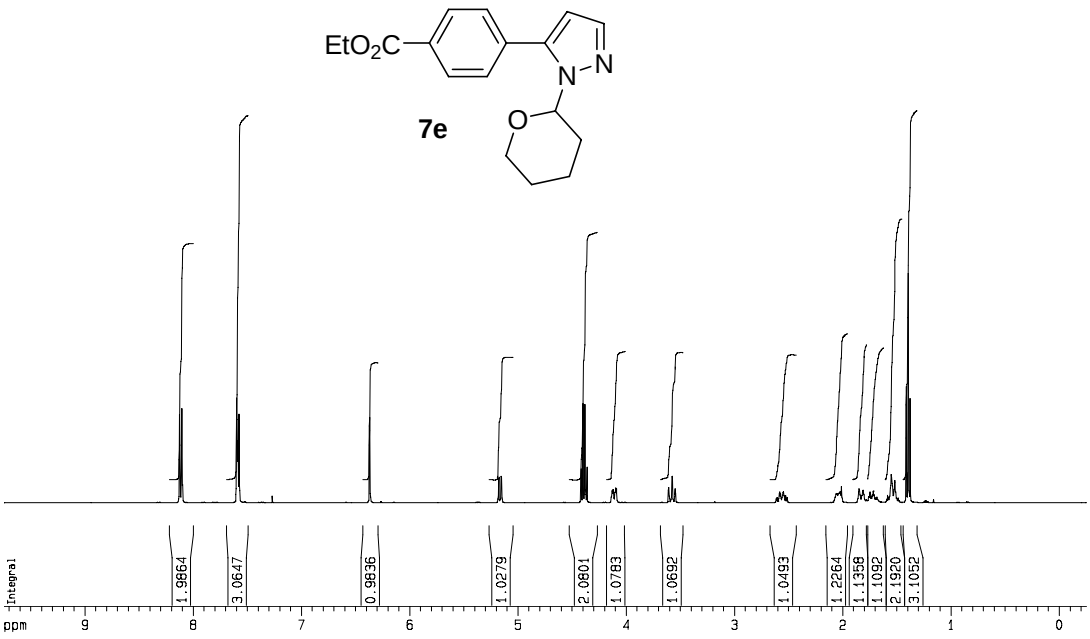
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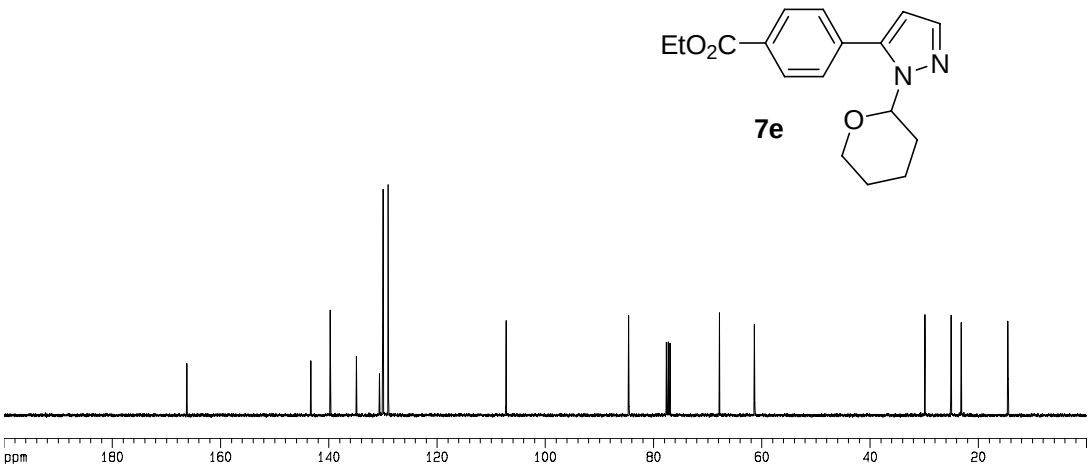
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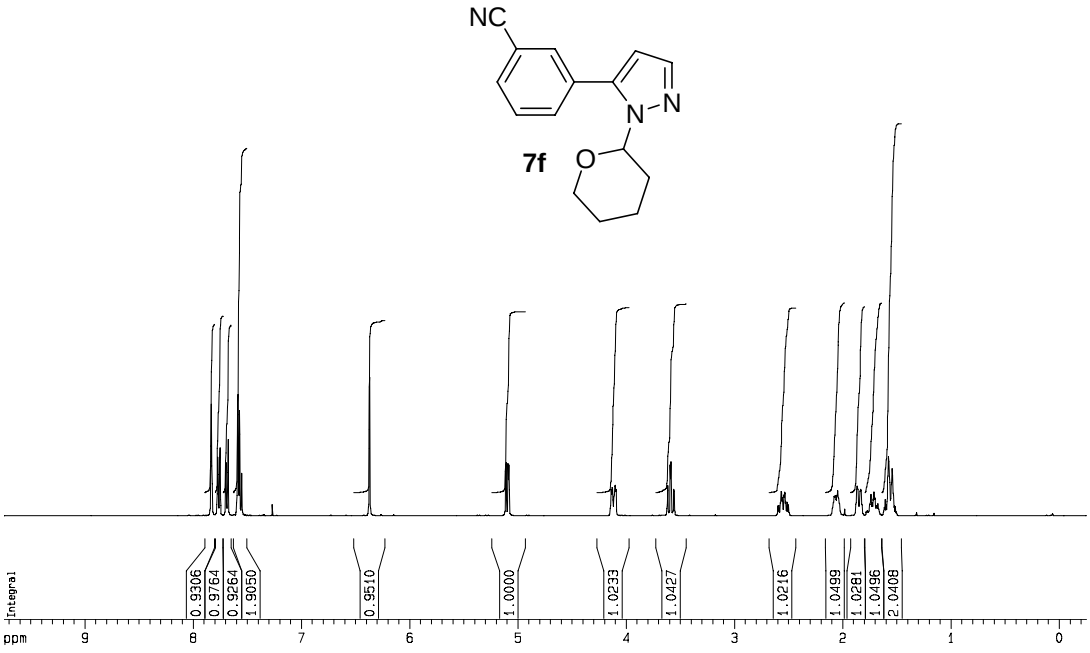
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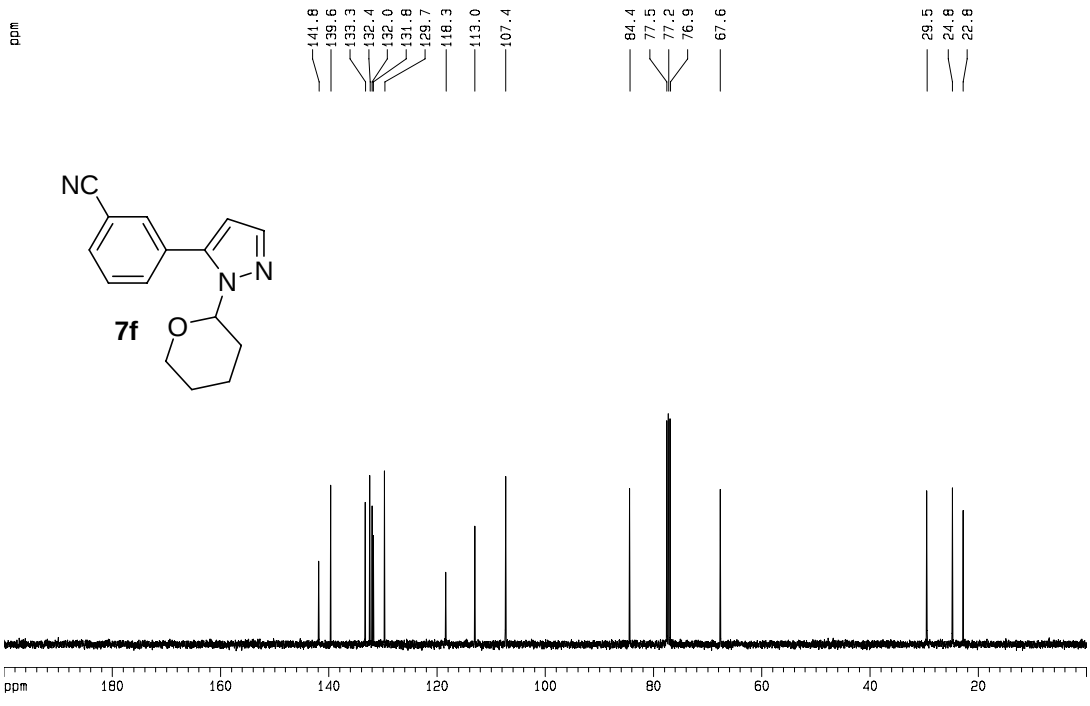
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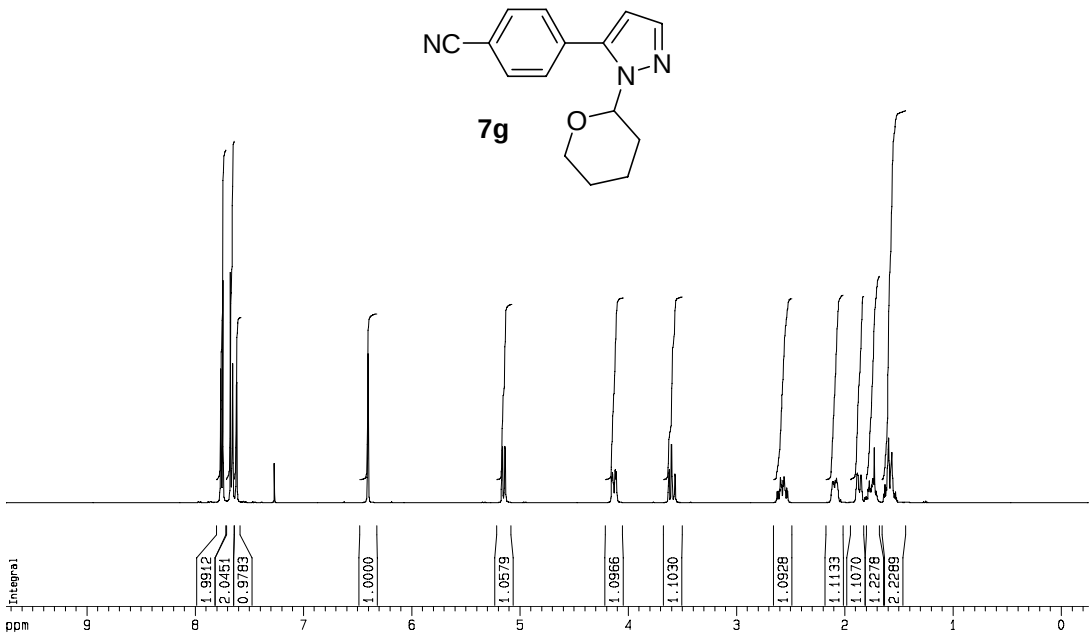
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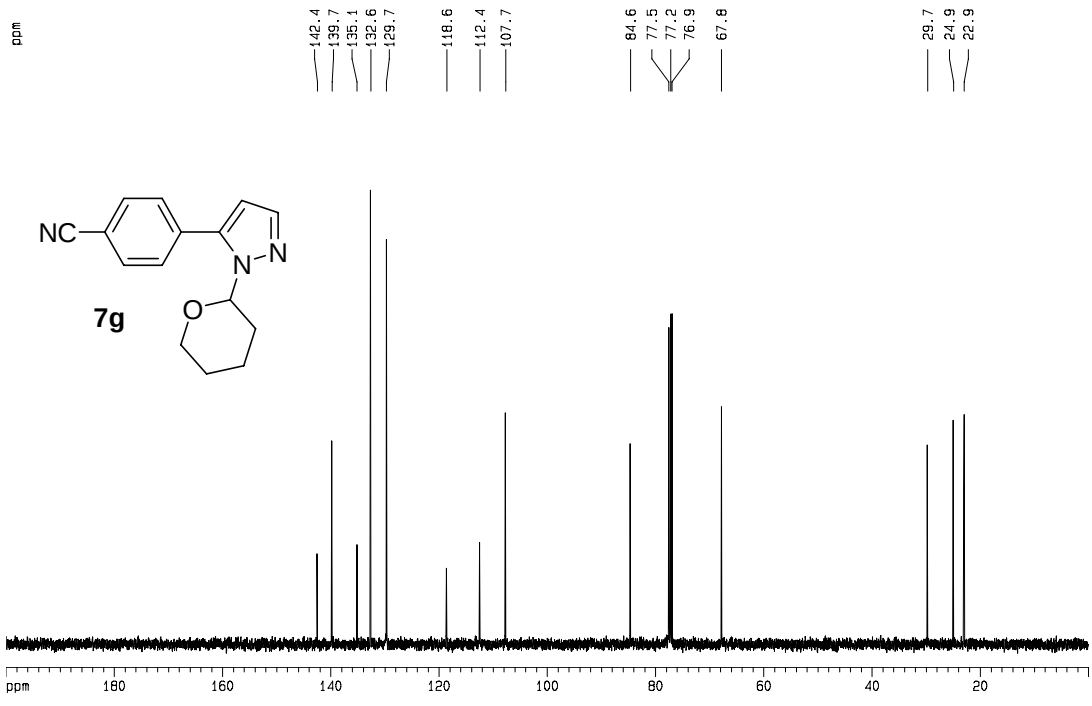
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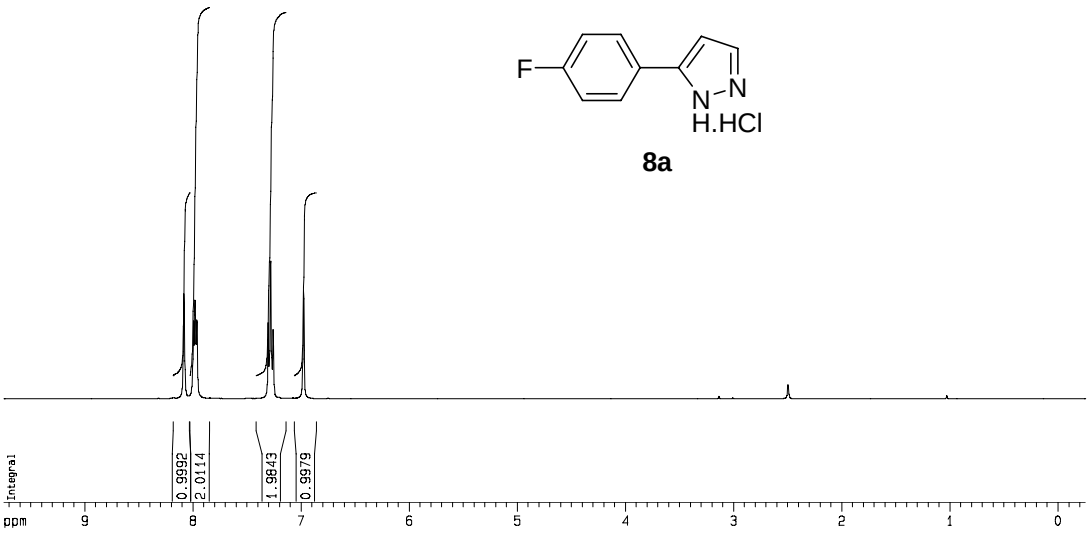
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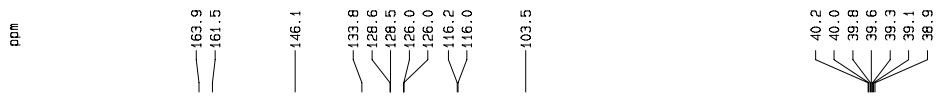
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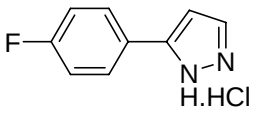
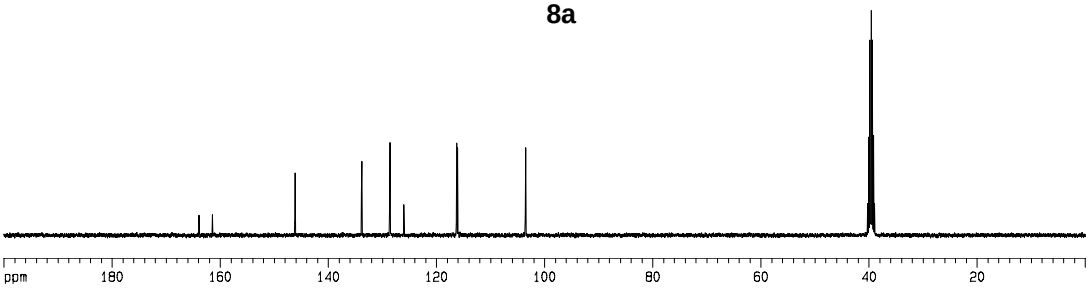
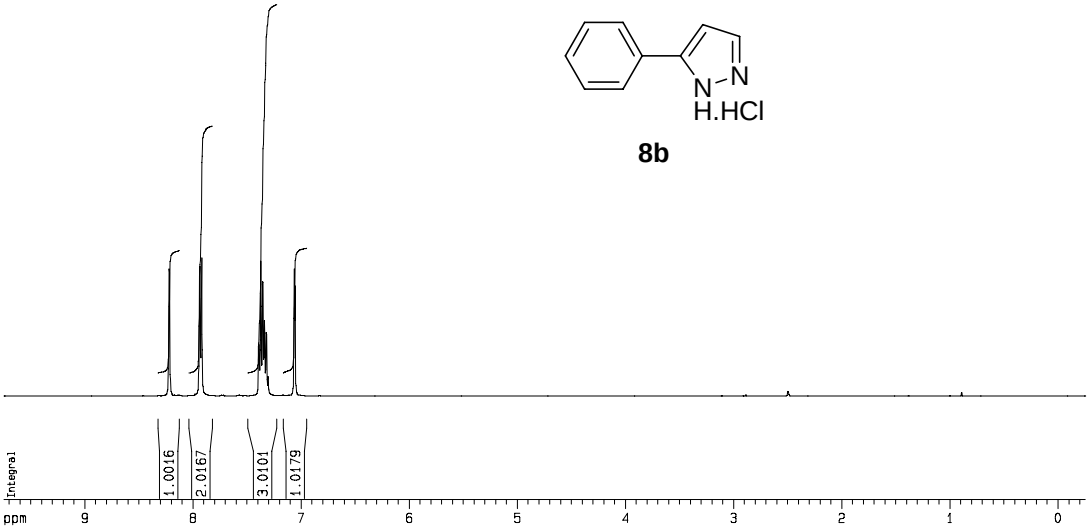
116.2
116.0
103.5
40.2
40.0
39.8
39.6
39.3
39.1
38.9

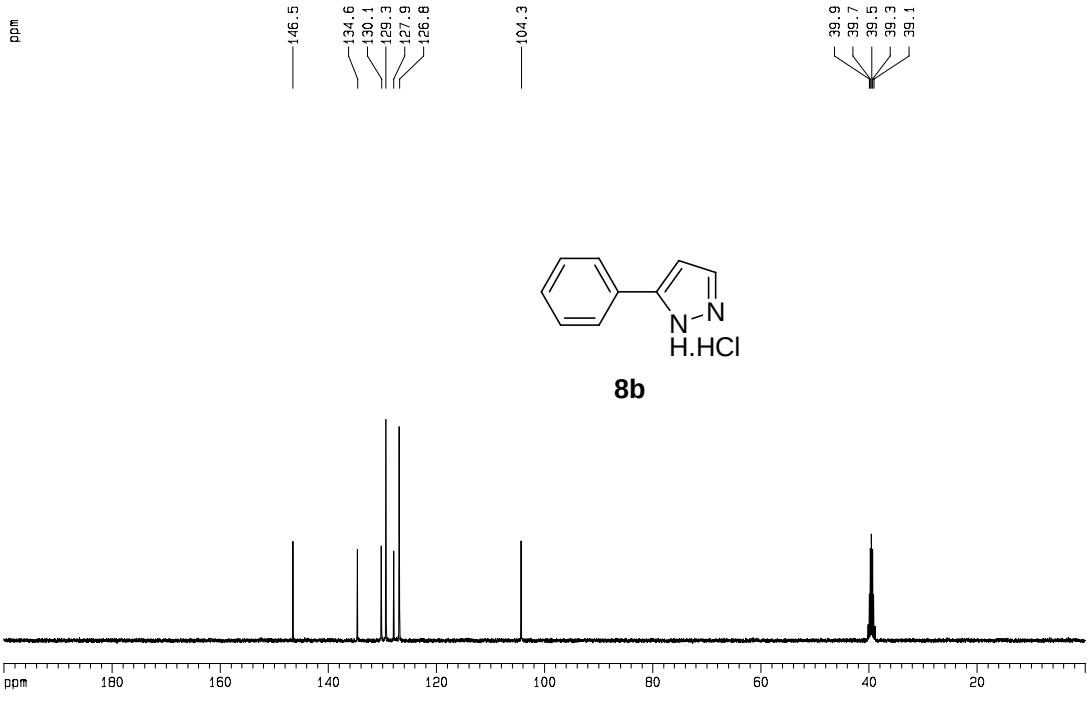

F
N
N
H.HCl

8a

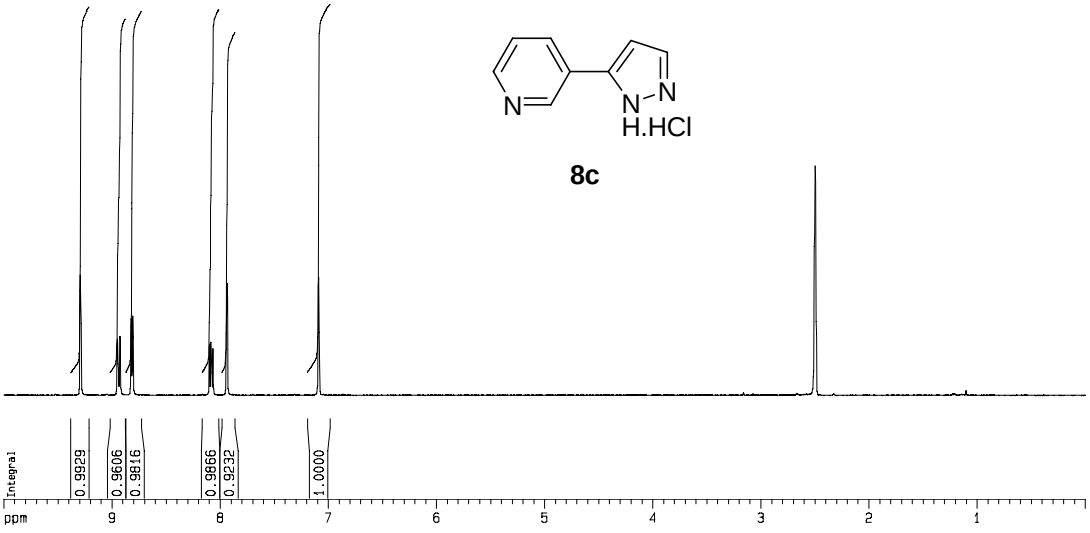

ppm
180
160
140
120
100
80
60
40
20


N
N
H.HCl
Integral
1.0016
2.0167
3.0101
1.0179
ppm
9
8
7
6
5
4
3
2
1
0

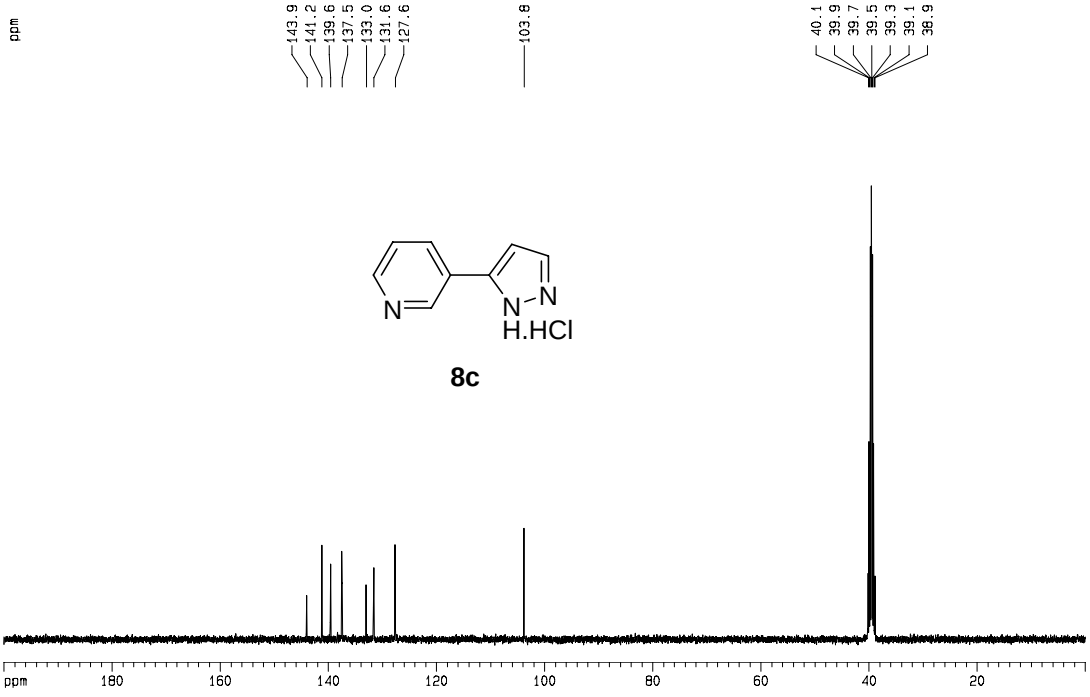
8b


ppm
146.5
134.6
130.1
129.3
127.9
126.8
104.3
39.9
39.7
39.5
39.3
39.1
N
N
H.HCl
ppm
180
160
140
120
100
80
60
40
20

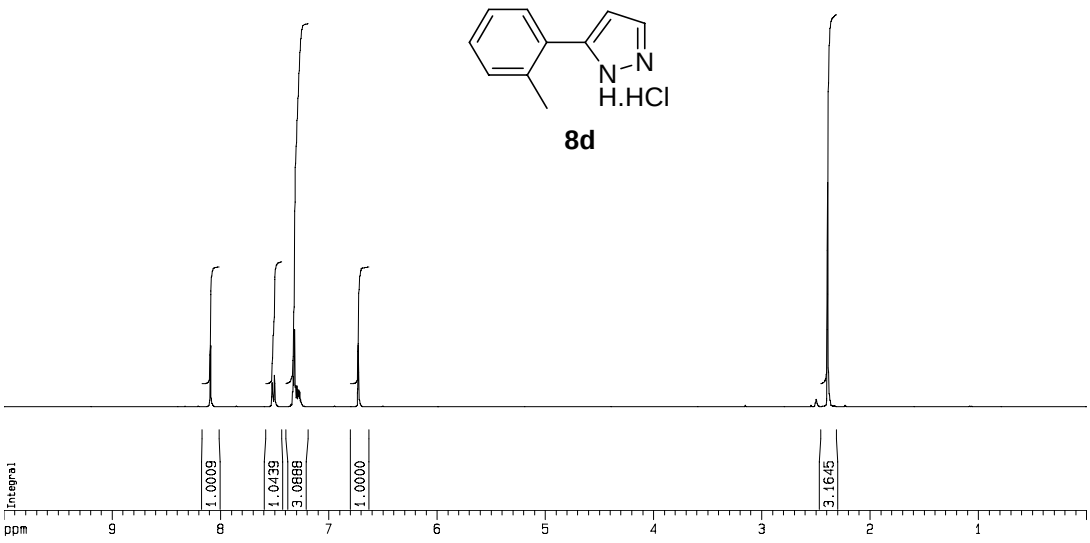
8b


N
N
N
H.HCl
Integral
0.9929
0.9606
0.9816
0.9866
0.9232
1.0000
ppm
9
8
7
6
5
4
3
2
1

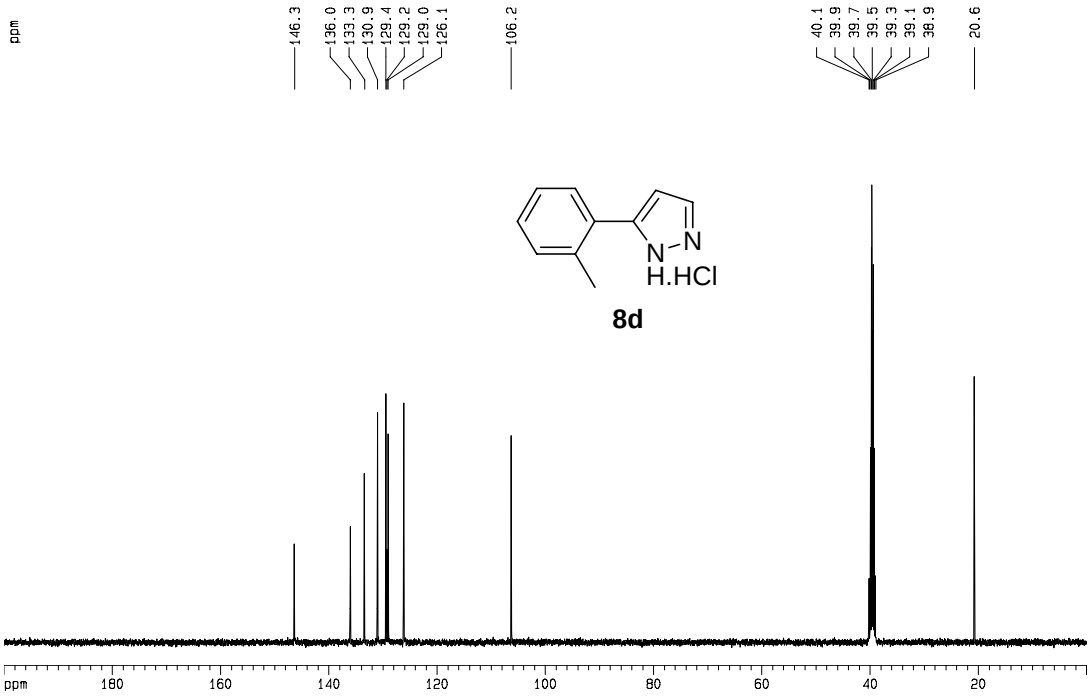
8c


ppm
143.9
141.2
139.6
137.5
133.0
131.6
127.6
103.8
40.1
39.9
39.7
39.5
39.3
39.1
38.9
N
N
N
H.HCl
ppm
180
160
140
120
100
80
60
40
20

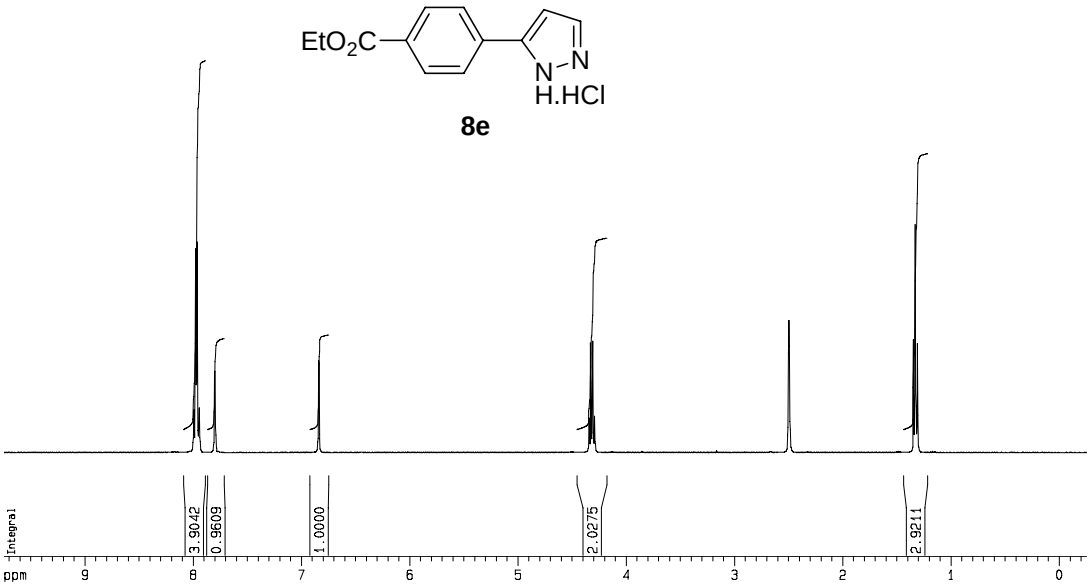
8c

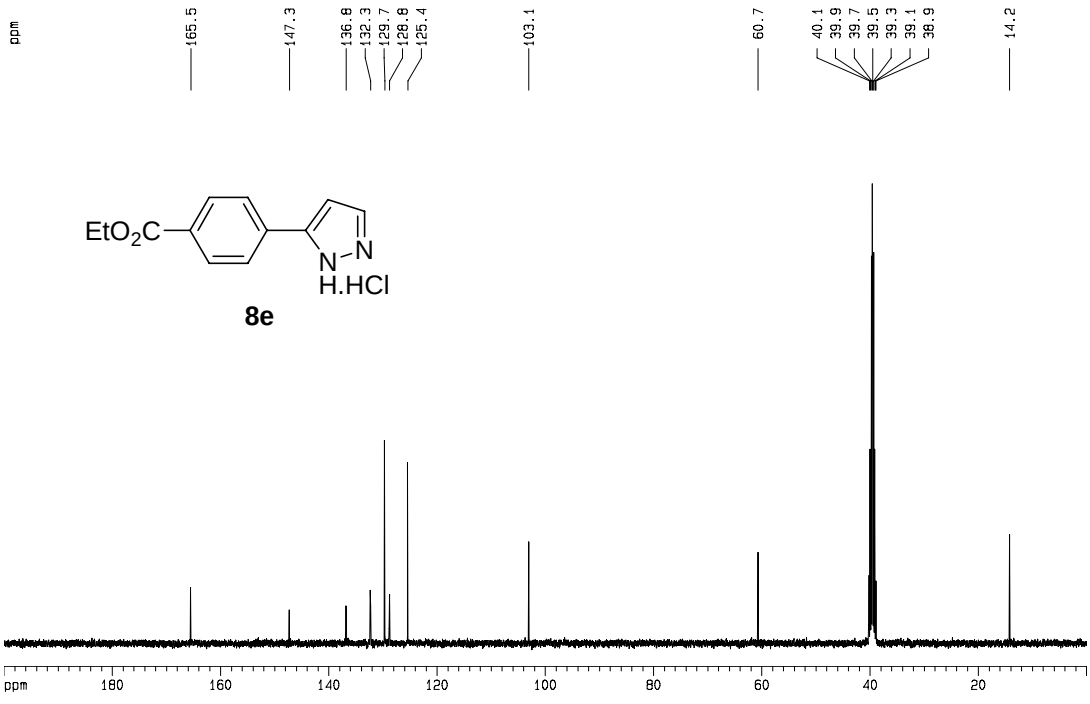

N
N
H.HCl
Integral
1.0009
1.0439
3.0888
1.0000
3.1645
ppm
9
8
7
6
5
4
3
2
1

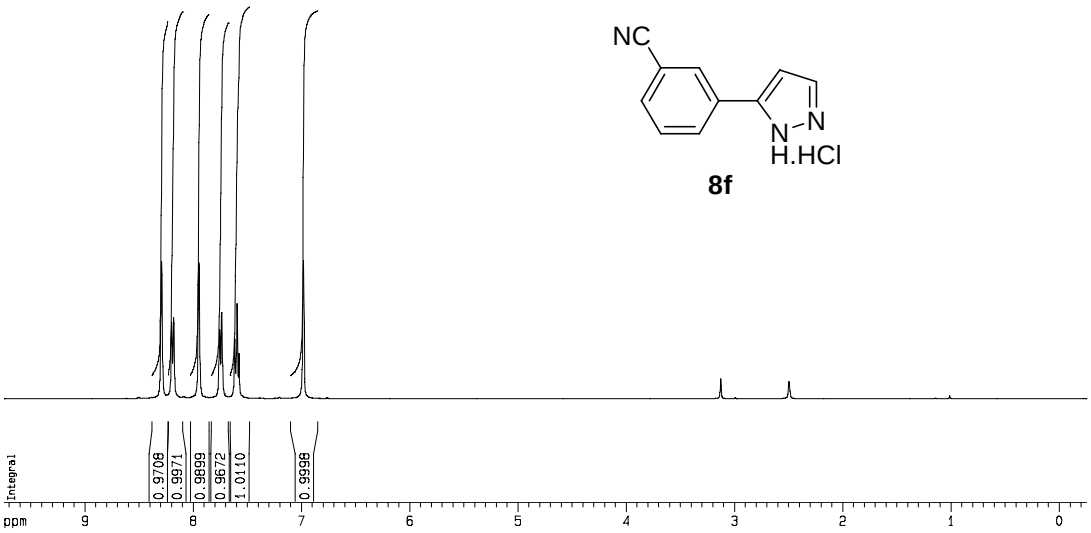
8d

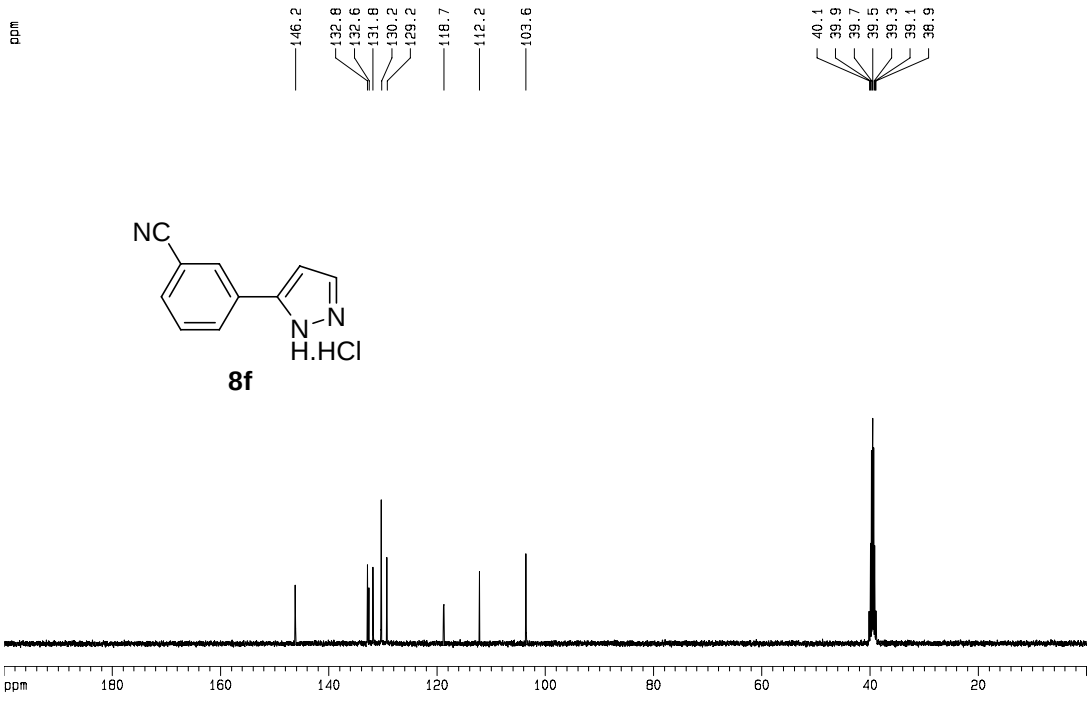

ppm
146.3
136.0
133.3
130.9
129.4
129.2
129.0
126.1
106.2
40.1
39.9
39.7
39.5
39.3
39.1
38.9
20.6
N
N
H.HCl
ppm
180
160
140
120
100
80
60
40
20

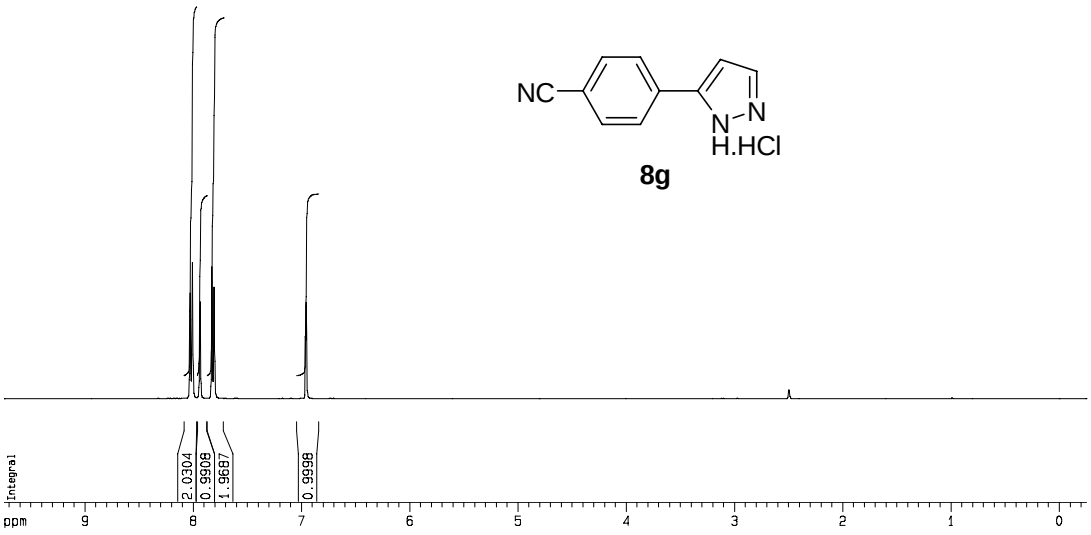
8d


EtO2C
N
N
H.HCl
8e
Integral
3.9042
0.9609
1.0000
2.0275
2.9211
ppm
9
8
7
6
5
4
3
2
1
0

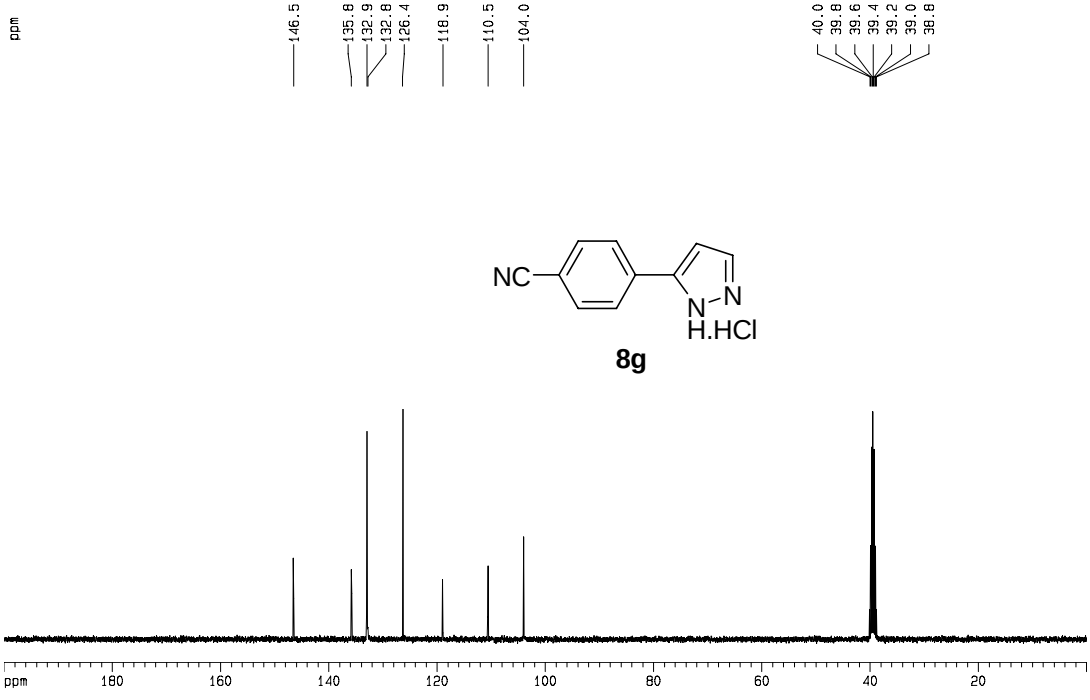

ppm
165.5
147.3
136.8
132.3
129.7
128.8
125.4
103.1
60.7
40.1
39.9
39.7
39.5
39.3
39.1
38.9
14.2
EtO2C
N
N
H.HCl
8e
ppm
180
160
140
120
100
80
60
40
20


NC
N
N
H.HCl
8f
Integral
0.9708
0.9971
0.9899
0.9672
1.0110
0.9998
ppm
9
8
7
6
5
4
3
2
1
0

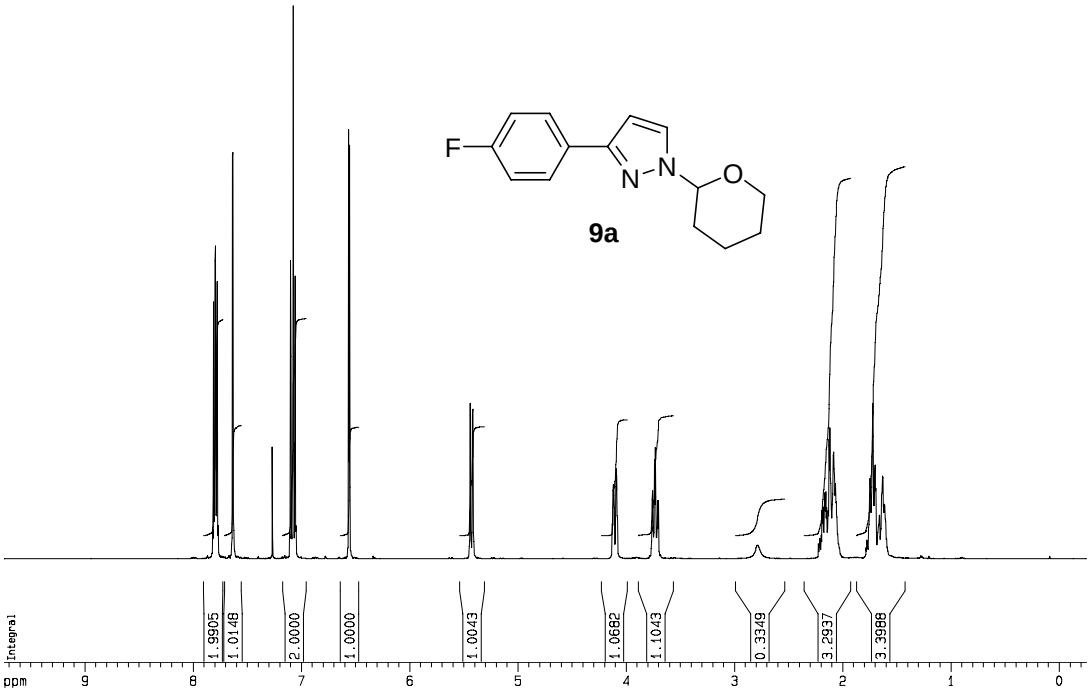

ppm
146.2
132.8
132.6
131.8
130.2
129.2
118.7
112.2
103.6
40.1
39.9
39.7
39.5
39.3
39.1
38.9
NC
N
N
H.HCl
8f
ppm
180
160
140
120
100
80
60
40
20

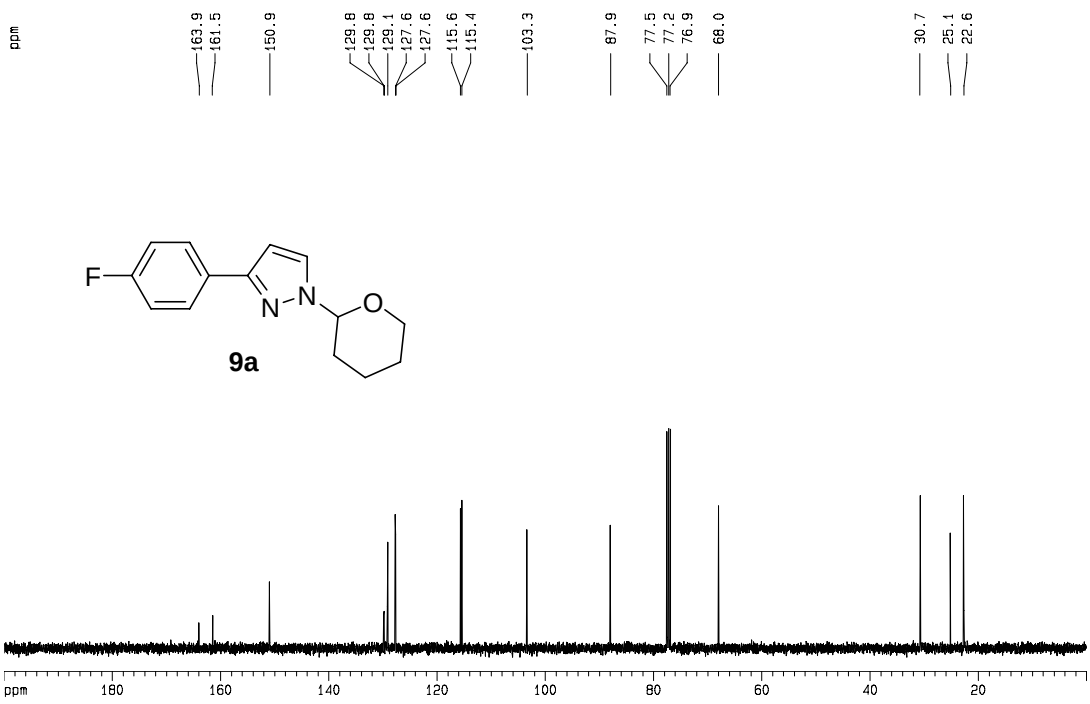

NC
N
N
H.HCl
Integral
2.0304
0.9908
1.9687
0.9998
ppm
9
8
7
6
5
4
3
2
1
0

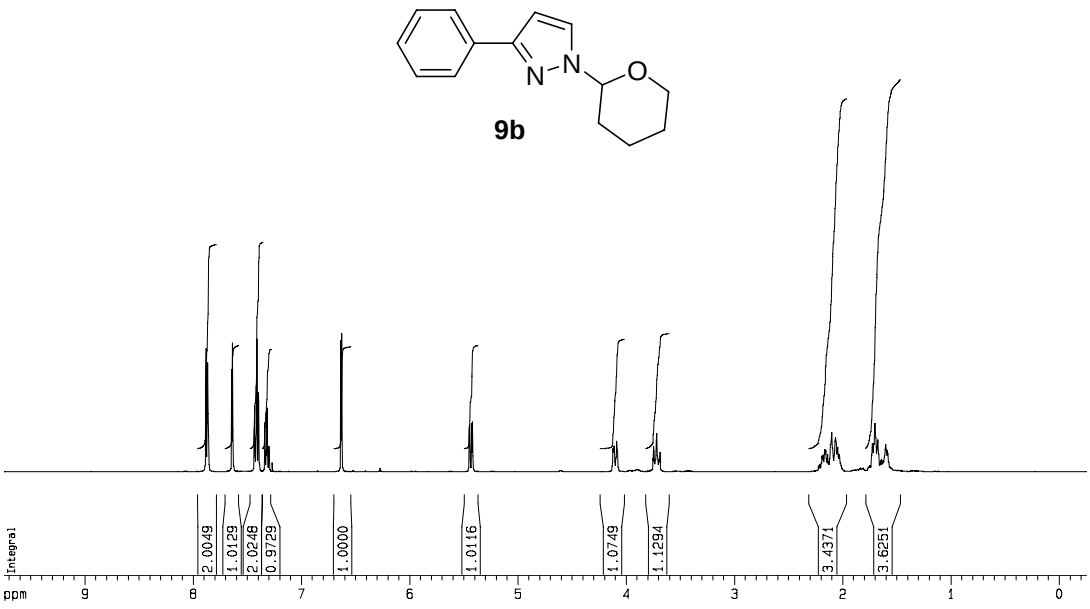
8g

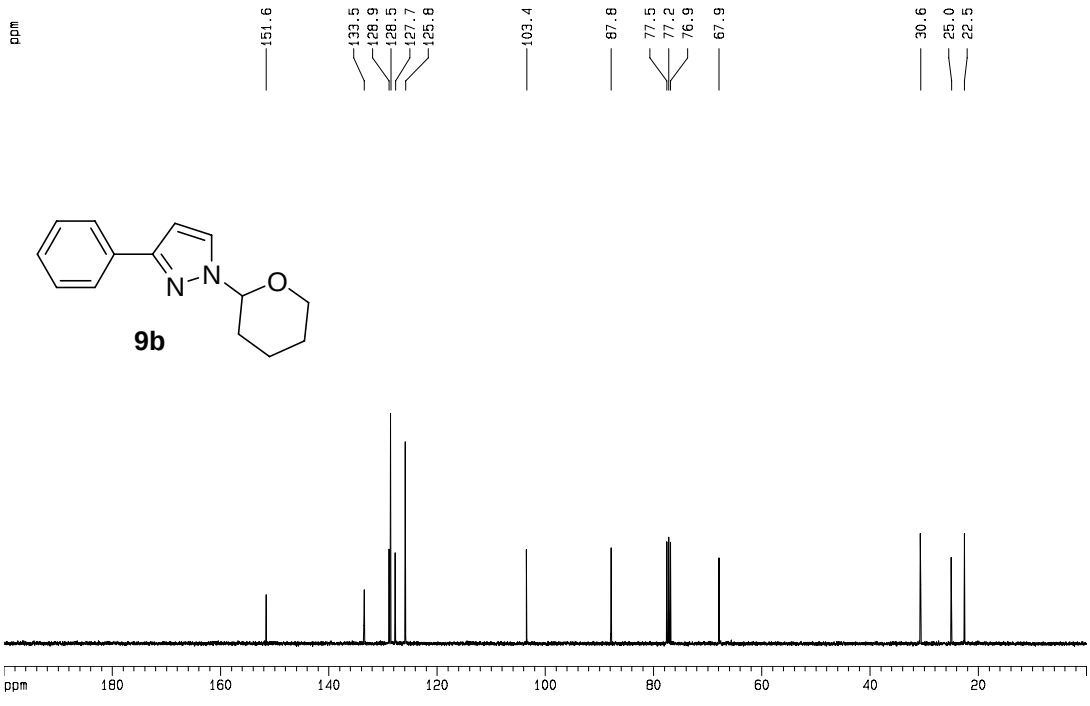

ppm
146.5
135.8
132.9
132.8
126.4
118.9
110.5
104.0
40.0
39.8
39.6
39.4
39.2
39.0
38.8
NC
N
N
H.HCl
ppm
180
160
140
120
100
80
60
40
20

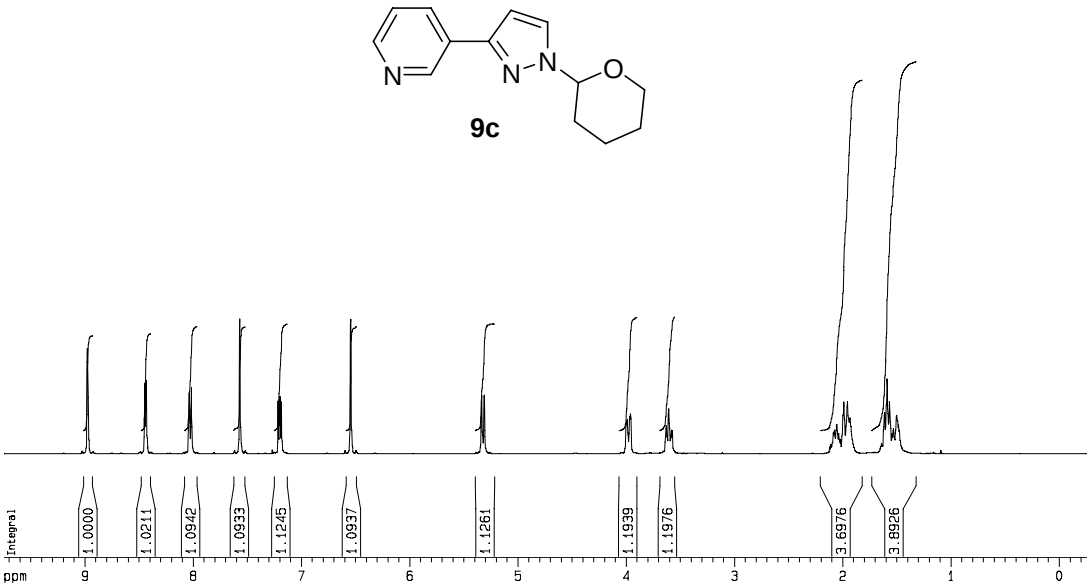
8g

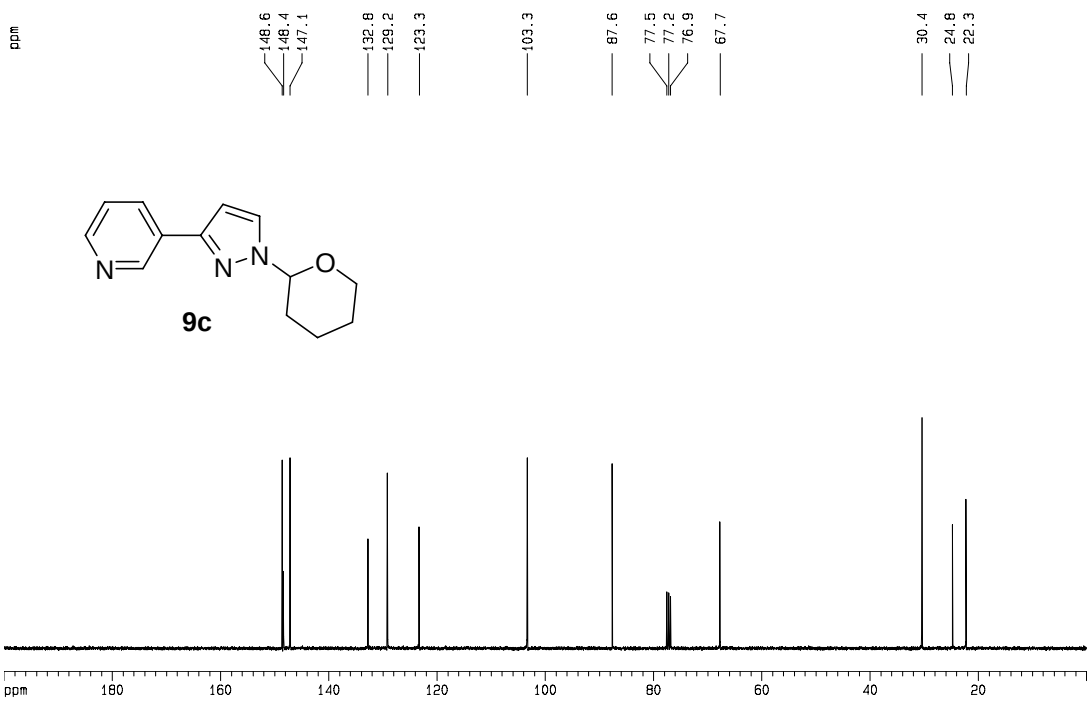

F
N
N
O
9a
Integral
1.9905
1.0148
2.0000
1.0000
1.0043
1.0682
1.1043
0.3349
3.2937
3.3988
ppm
9
8
7
6
5
4
3
2
1
0

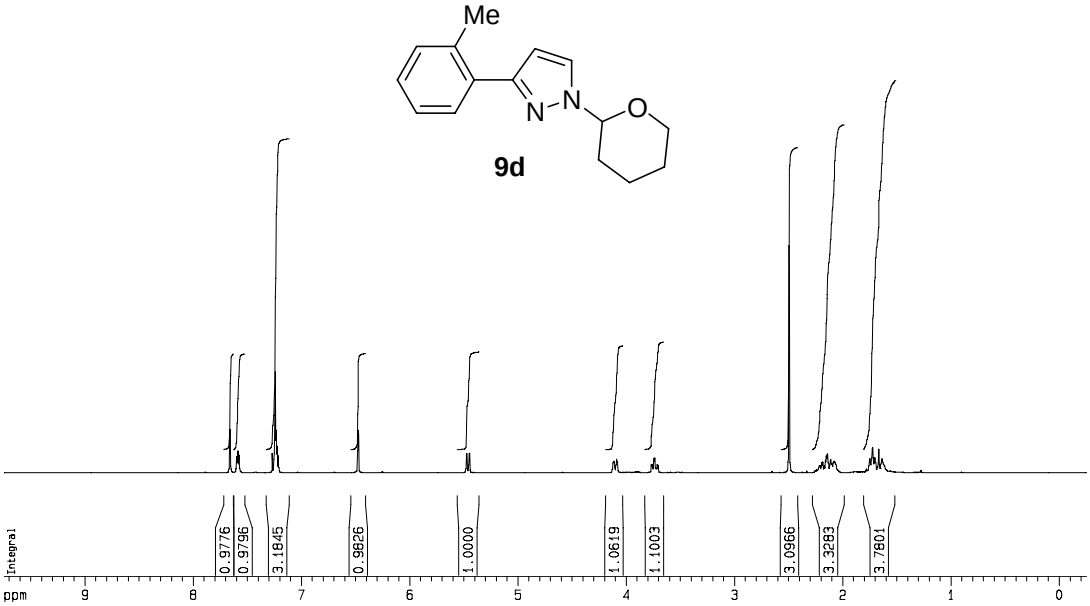

ppm
163.9
161.5
150.9
129.8
129.8
129.1
127.6
127.6
115.6
115.4
103.3
87.9
77.5
77.2
76.9
68.0
30.7
25.1
22.6
F
N
N
O
9a
ppm
180
160
140
120
100
80
60
40
20

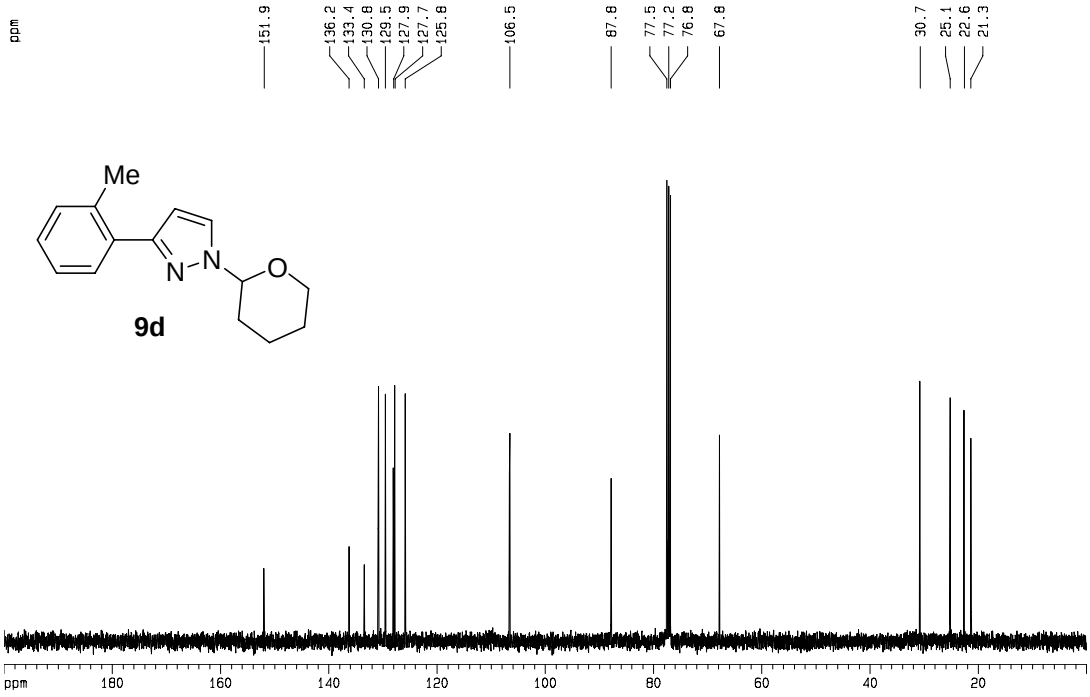

9b
Integral
2.0049
1.0129
2.0248
0.9729
1.0000
1.0116
1.0749
1.1294
3.4371
3.6251
ppm
9
8
7
6
5
4
3
2
1
0

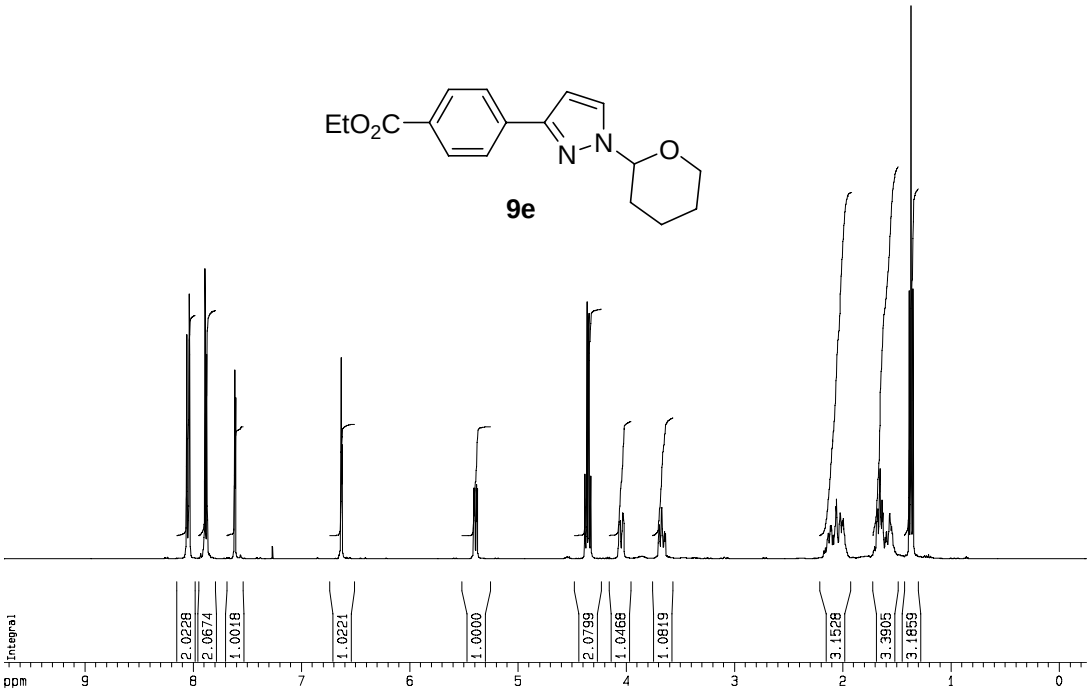

ppm
151.6
133.5
128.9
128.5
127.7
125.8
103.4
87.8
77.5
77.2
76.9
67.9
30.6
25.0
22.5
9b
ppm
180
160
140
120
100
80
60
40
20

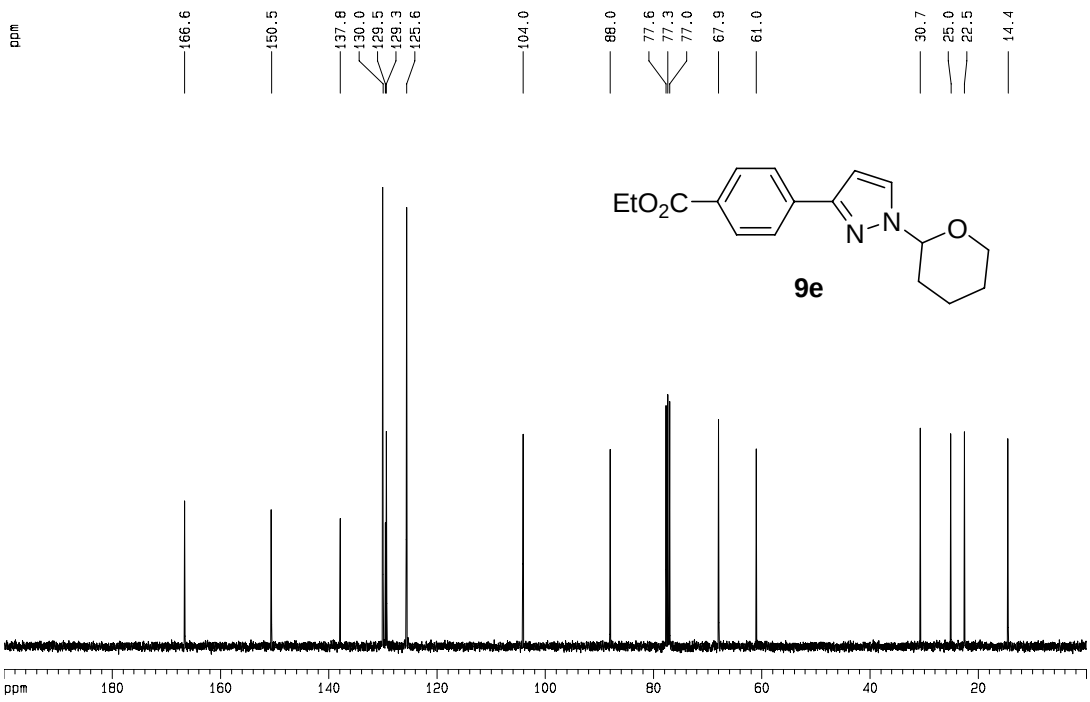

9c
Integral
1.0000
1.0211
1.0942
1.0933
1.1245
1.0937
1.1261
1.1939
1.1976
3.6976
3.8926
ppm
9
8
7
6
5
4
3
2
1
0


9c
ppm
148.6
148.4
147.1
132.8
129.2
123.3
103.3
87.6
77.5
77.2
76.9
67.7
30.4
24.8
22.3
ppm
180
160
140
120
100
80
60
40
20

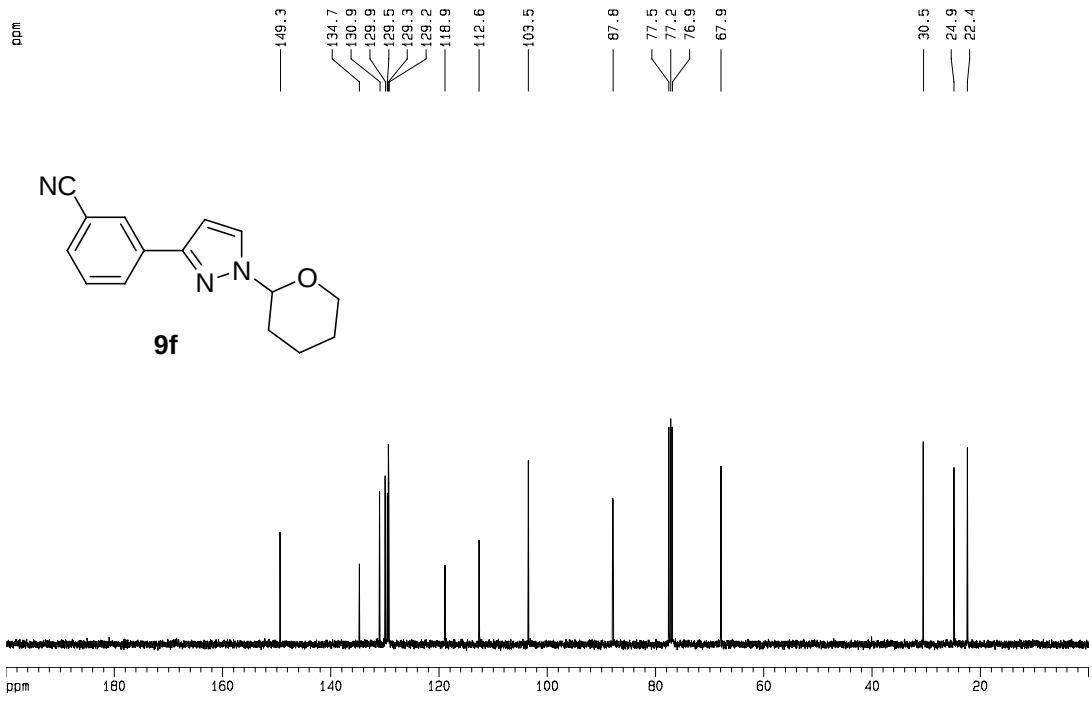

Me
N
N
O
9d
Integral
0.9776
0.9796
3.1845
0.9826
1.0000
1.0619
1.1003
3.0966
3.3283
3.7801
ppm
9
8
7
6
5
4
3
2
1
0

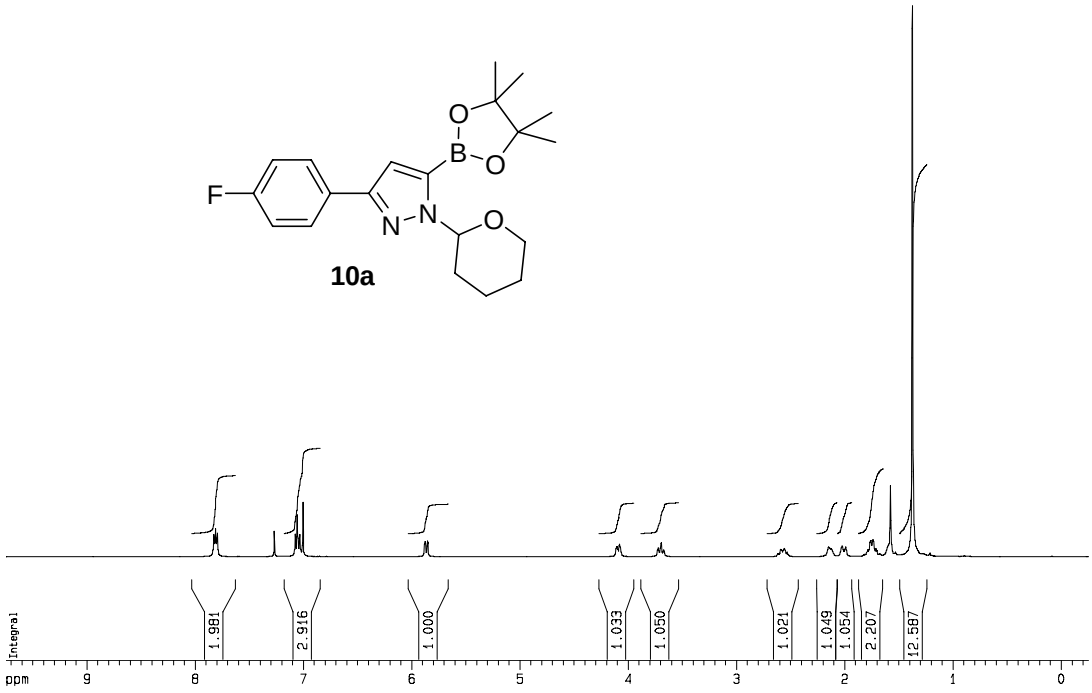

ppm
151.9
136.2
133.4
130.8
129.5
127.9
127.7
125.8
106.5
87.8
77.5
77.2
76.8
67.8
30.7
25.1
22.6
21.3
Me
N
N
O
9d
ppm
180
160
140
120
100
80
60
40
20


EtO2C
N
N
O
9e
Integral
2.0228
2.0674
1.0018
1.0221
1.0000
2.0799
1.0468
1.0819
3.1528
3.3905
3.1659
ppm
9
8
7
6
5
4
3
2
1
0


ppm
166.6
150.5
137.8
130.0
129.5
129.3
125.6
104.0
86.0
77.6
77.3
77.0
67.9
61.0
30.7
25.0
22.5
14.4
EtO2C
N
N
O
9e
ppm
180
160
140
120
100
80
60
40
20


NC
N
N
O
9f
Integral
0.9512
0.9970
1.0066
0.9598
1.0107
1.0042
1.0000
1.0532
1.0545
3.2493
3.2094
ppm
9
8
7
6
5
4
3
2
1
0


ppm
149.3
134.7
130.9
129.9
129.5
129.3
129.2
118.9
112.6
103.5
87.8
77.5
77.2
76.9
67.9
30.5
24.9
22.4
NC
N
N
O
9f
ppm
180
160
140
120
100
80
60
40
20


F
B
O
O
N
N
O
10a
Integral
1.981
2.916
1.000
1.033
1.050
1.021
1.049
1.054
2.207
12.587
ppm
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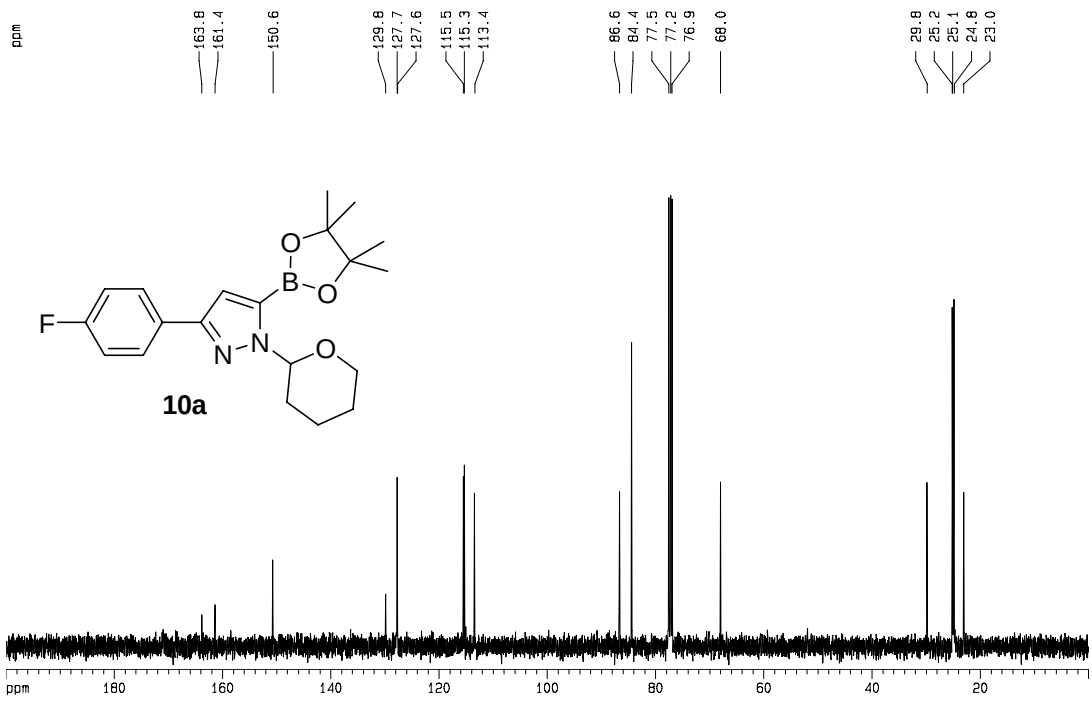
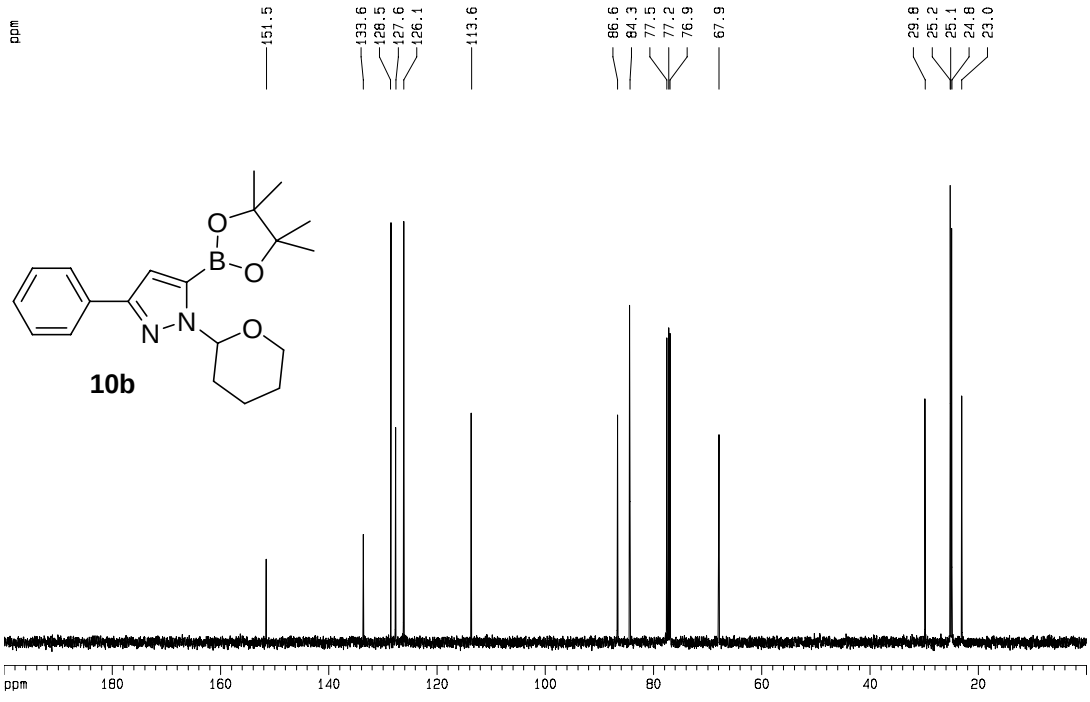
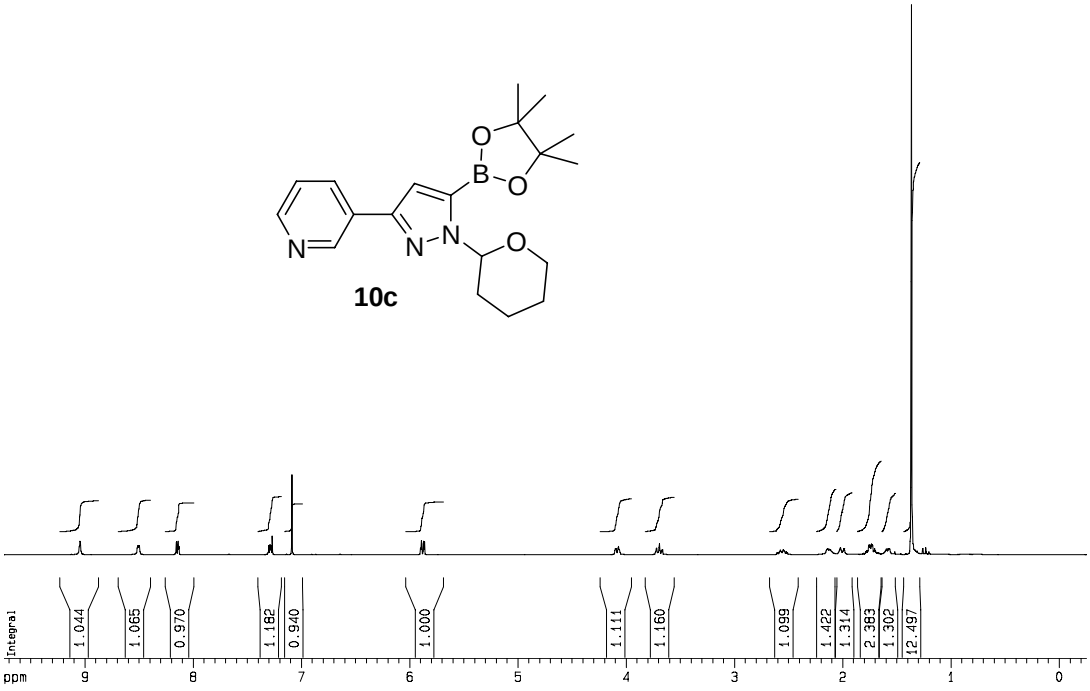
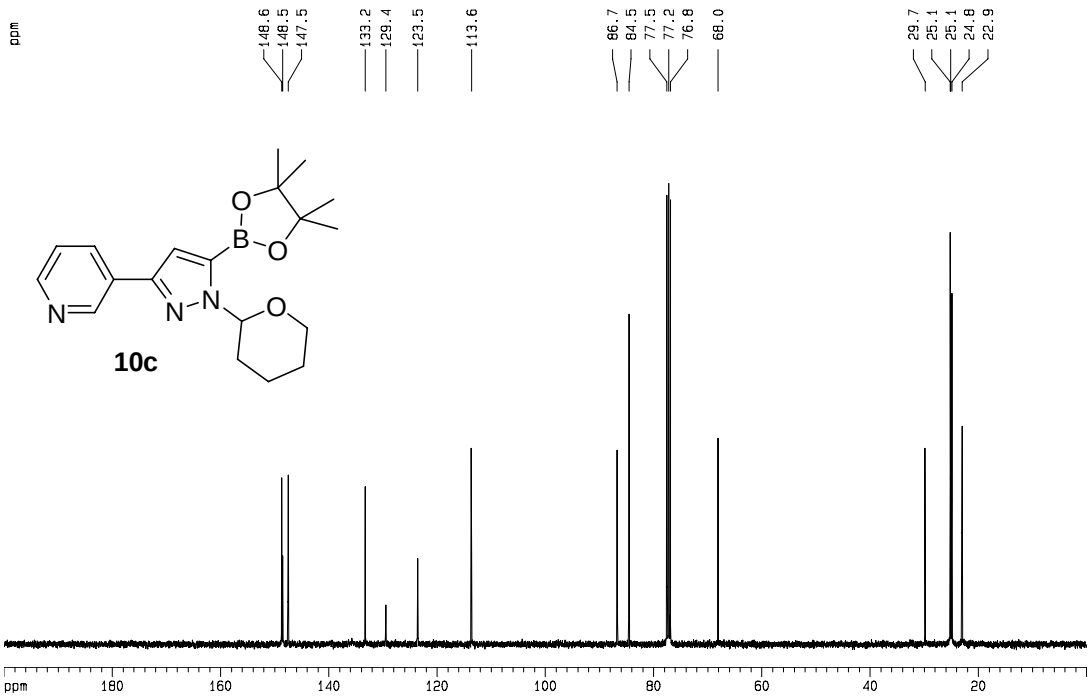
8
7
6
5
4
3
2
1
0


ppm
163.8
161.4
150.6
129.8
127.7
127.6
115.5
115.3
113.4
86.6
84.4
77.5
77.2
76.9
68.0
29.8
25.2
25.1
24.8
23.0
F
B
O
O
N
N
O
10a
ppm
180
160
140
120
100
80
60
40
20


O
B
O
N
N
O
10b
Integral
1.958
1.971
1.052
0.954
1.000
1.033
1.048
1.034
1.040
1.057
2.188
1.056
12.415
ppm
9
8
7
6
5
4
3
2
1
0


ppm
151.5
133.6
128.5
127.6
126.1
113.6
86.6
84.3
77.5
77.2
76.9
67.9
29.8
25.2
25.1
24.8
23.0
O
B
O
N
N
O
10b
ppm
180
160
140
120
100
80
60
40
20


10c
Integral
1.044
1.065
0.970
1.182
0.940
1.000
1.111
1.160
1.099
1.422
1.314
2.383
1.302
12.497
ppm
9
8
7
6
5
4
3
2
1
0


ppm
148.6
148.5
147.5
133.2
129.4
123.5
113.6
86.7
84.5
77.5
77.2
76.8
68.0
29.7
25.1
25.1
24.8
22.9
10c
ppm
180
160
140
120
100
80
60
40
20


Me
O
B
O
N
N
O
10d
Integral
0.977
2.914
0.930
1.000
1.036
1.057
4.047
1.038
1.042
2.084
1.138
12.420
ppm
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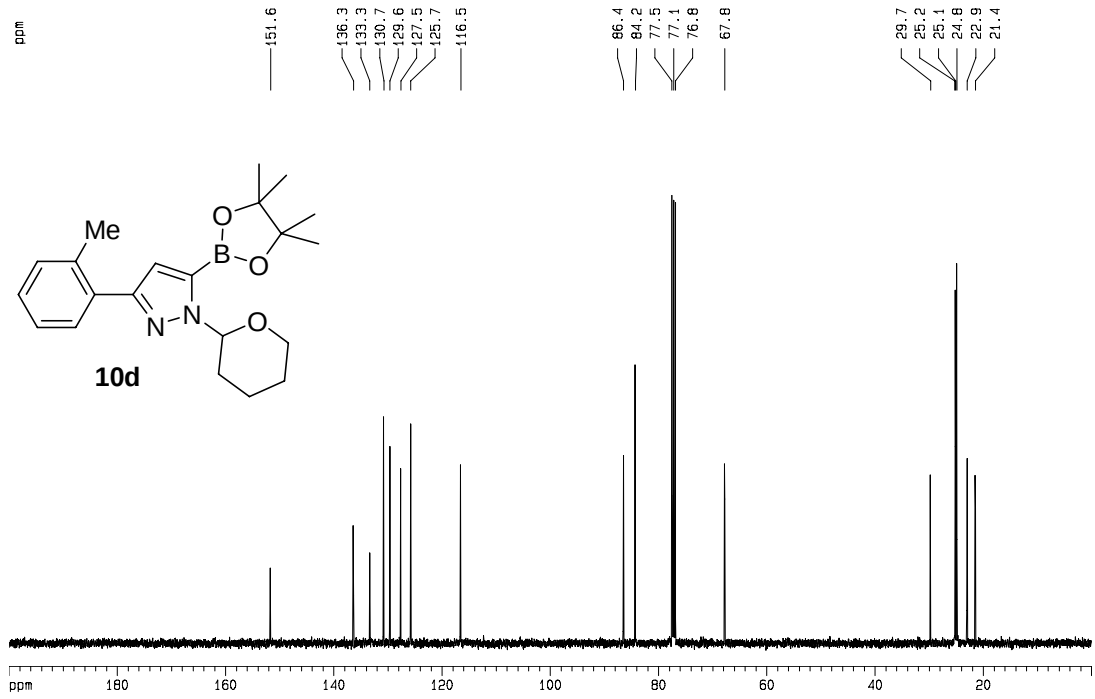
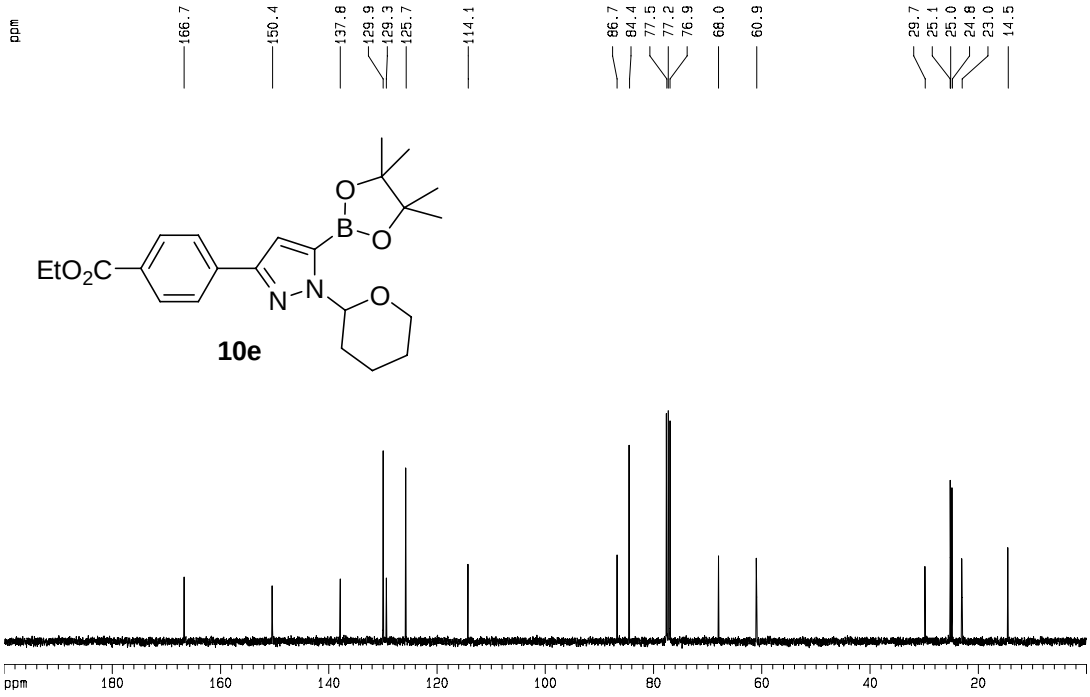
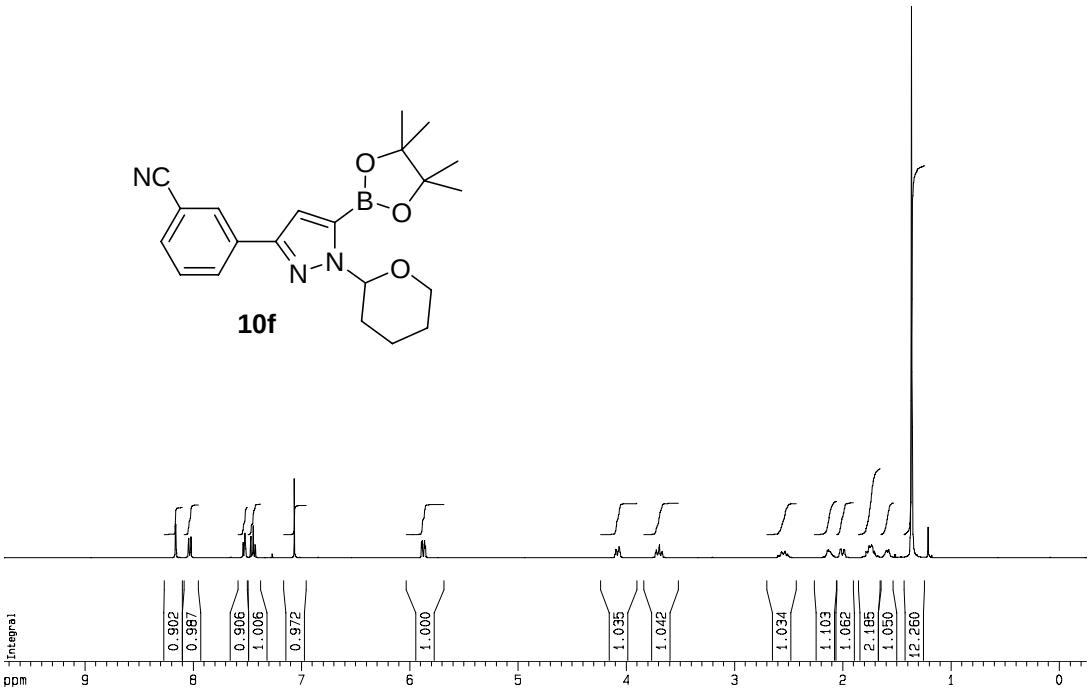
8
7
6
5
4
3
2
1
0


ppm
151.6
136.3
133.3
130.7
129.6
127.5
125.7
116.5
86.4
84.2
77.5
77.1
76.8
67.8
29.7
25.2
25.1
24.8
22.9
21.4
Me
O
B
O
N
N
O
10d
ppm
180
160
140
120
100
80
60
40
20


EtO2C
O
B
O
N
N
O
10e
Integral
1.976
2.016
0.982
1.000
2.027
1.030
1.052
1.035
1.038
1.043
2.041
1.078
3.329
11.713
ppm
9
8
7
6
5
4
3
2
1
0


ppm
166.7
150.4
137.8
129.9
129.3
125.7
114.1
86.7
84.4
77.5
77.2
76.9
68.0
60.9
29.7
25.1
25.0
24.8
23.0
14.5
EtO2C
O
B
O
N
N
O
10e
ppm
180
160
140
120
100
80
60
40
20


NC
O
B
O
N
N
O
10f
Integral
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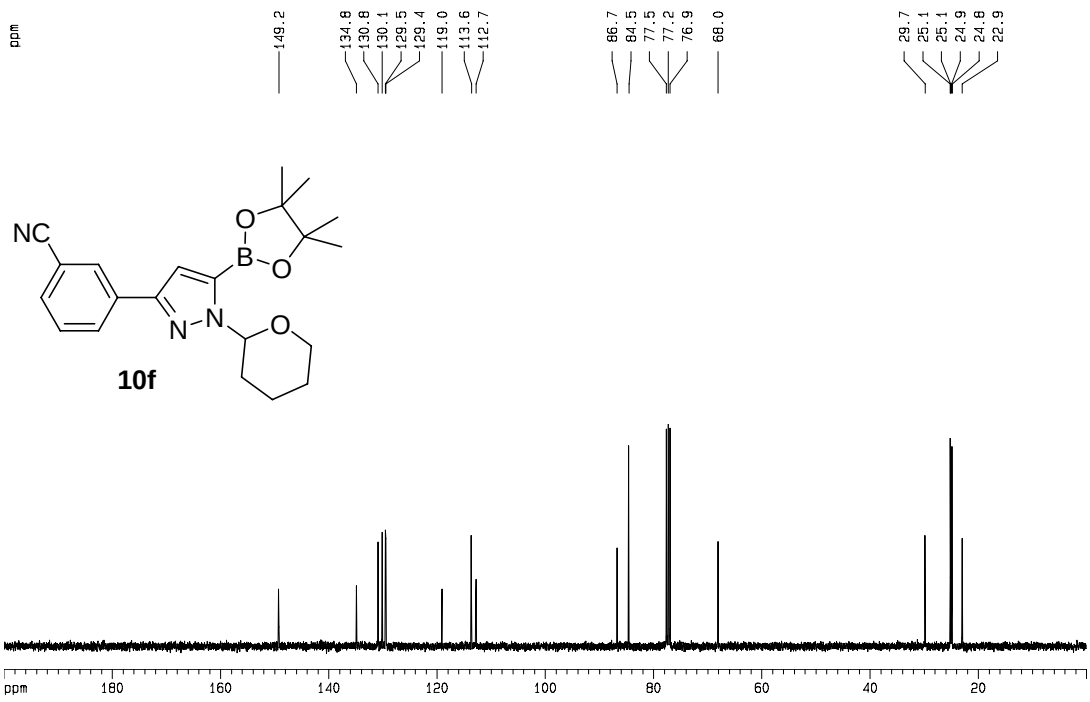
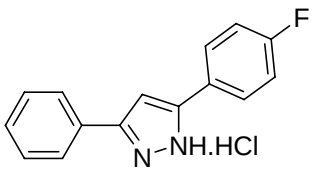
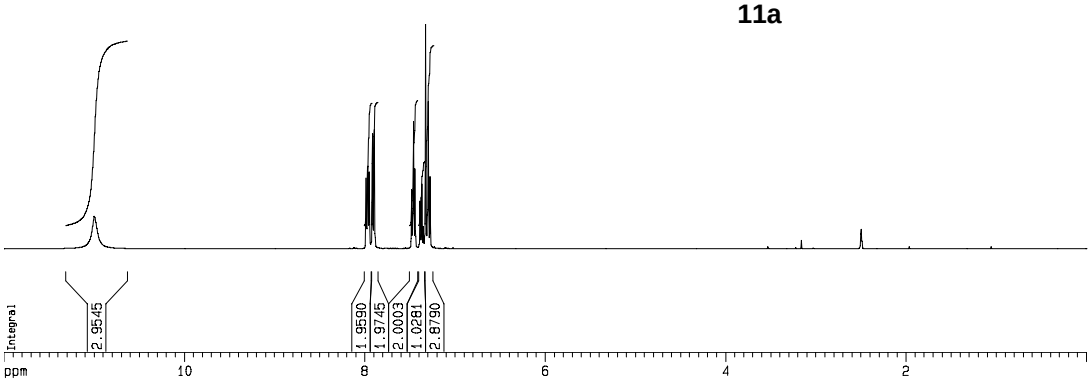
0.987
0.906
1.006
0.972
1.000
1.035
1.042
1.034
1.103
1.062
2.185
1.050
12.260
ppm
9
8
7
6
5
4
3
2
1
0


ppm
149.2
134.8
130.8
130.1
129.5
129.4
119.0
113.6
112.7
86.7
84.5
77.5
77.2
76.9
68.0
29.7
25.1
25.1
24.9
24.8
22.9
NC
O
B
O
N
N
O
10f
ppm
180
160
140
120
100
80
60
40
20


F
N
NH.HCl

11a


Integral
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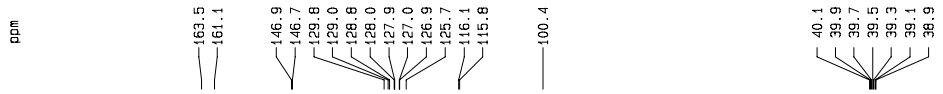
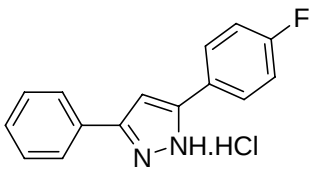
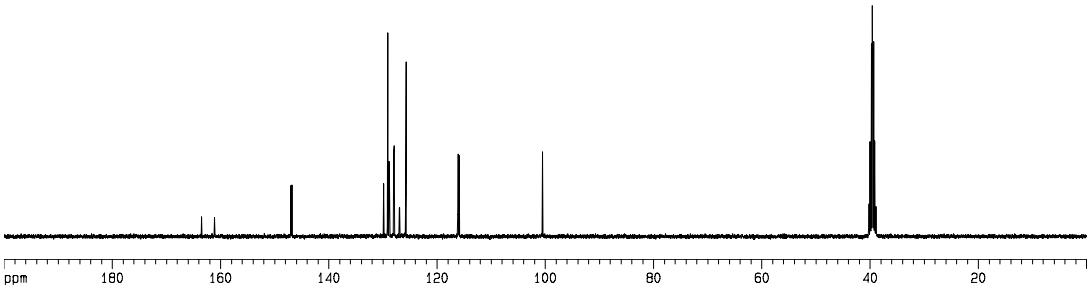
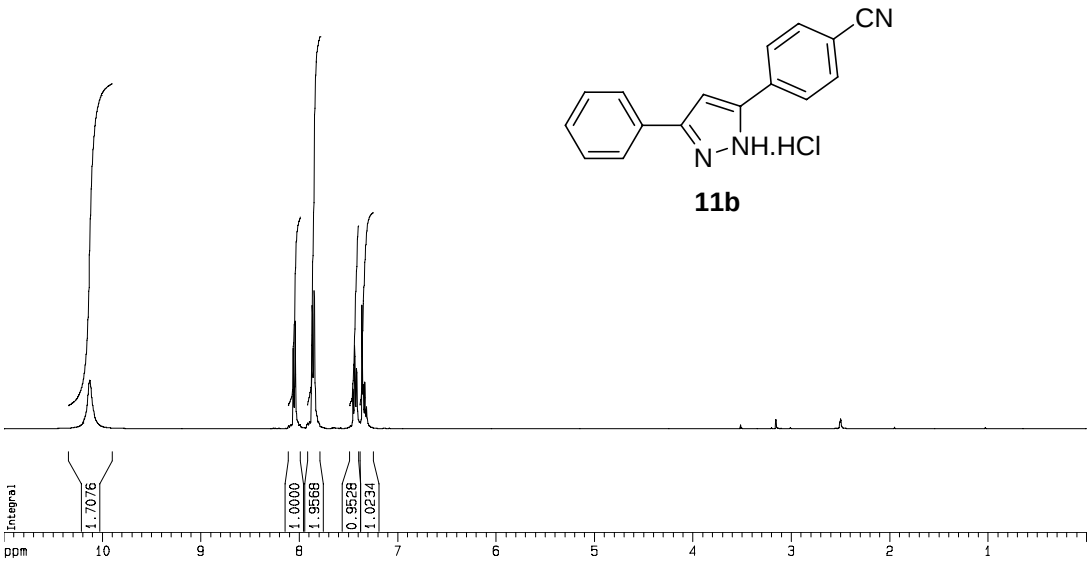
1.9590
1.9745
2.0003
1.0281
2.8790
ppm
10
8
6
4
2

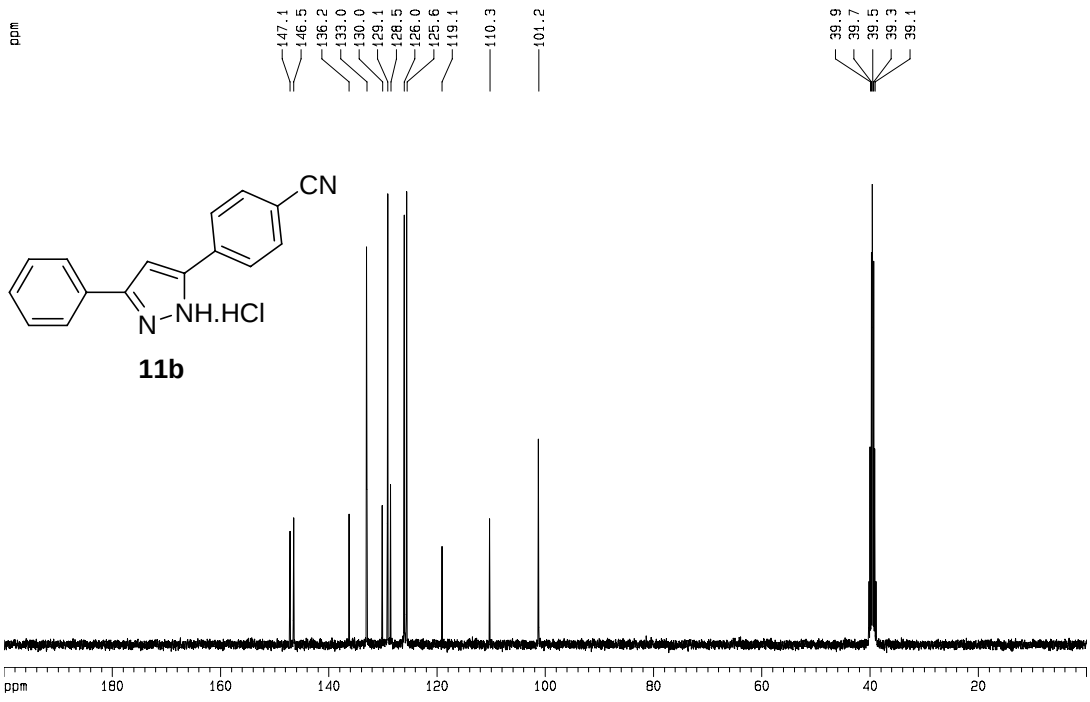

ppm
163.5
161.1
146.9
146.7
129.8
129.0
128.8
128.0
127.9
127.0
126.9
125.7
116.1
115.8
100.4
40.1
39.9
39.7
39.5
39.3
39.1
38.9

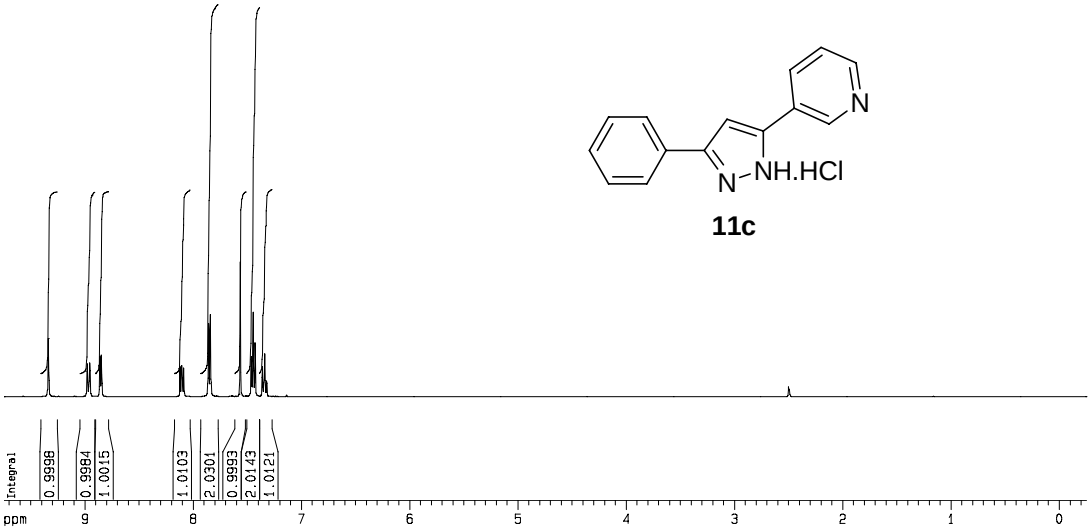

F
N
NH.HCl

11a

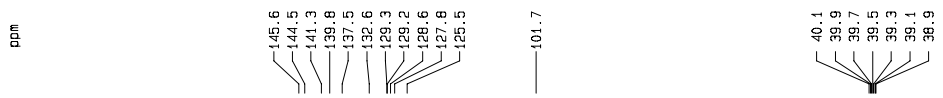

ppm
180
160
140
120
100
80
60
40
20

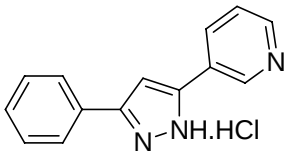

CN
NH.HCl
N
11b
Integral
1.7076
1.0000
1.9568
0.9528
1.0234
ppm
10
9
8
7
6
5
4
3
2
1


ppm
147.1
146.5
136.2
133.0
130.0
129.1
128.5
126.0
125.6
119.1
110.3
101.2
39.9
39.7
39.5
39.3
39.1
CN
NH.HCl
N
11b
ppm
180
160
140
120
100
80
60
40
20

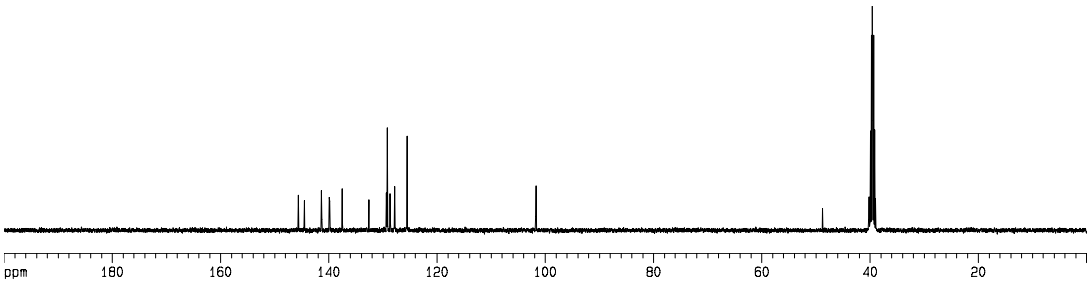

N
NH.HCl
N
Integral
0.9998
0.9984
1.0015
1.0103
2.0301
0.9993
2.0143
1.0121
ppm
9
8
7
6
5
4
3
2
1
0

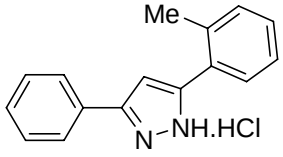
11c


ppm
145.6
144.5
141.3
139.8
137.5
132.6
129.3
129.2
128.6
127.8
125.5
101.7
40.1
39.9
39.7
39.5
39.3
39.1
38.9

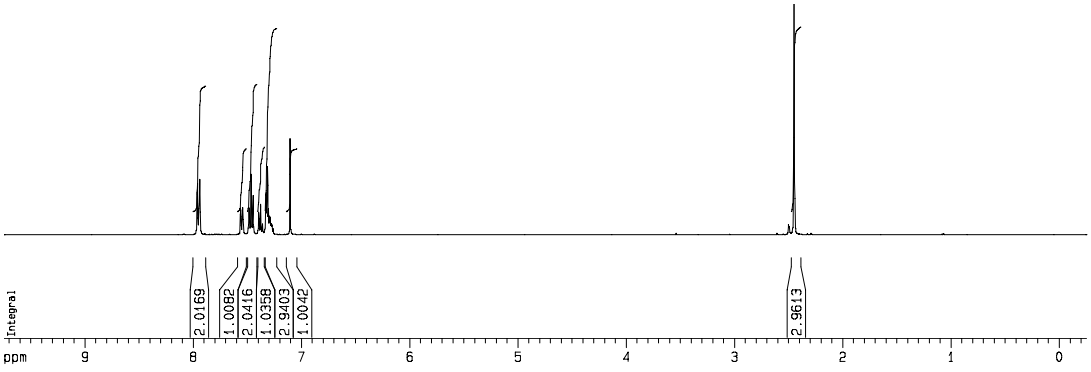

N
NH.HCl
N

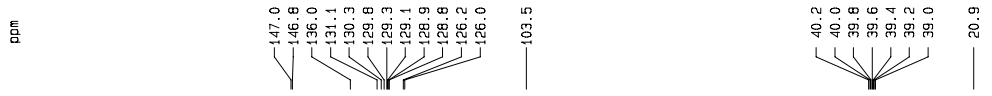
11c

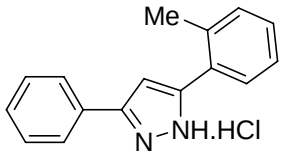

ppm
180
160
140
120
100
80
60
40
20


Me
N
NH.HCl

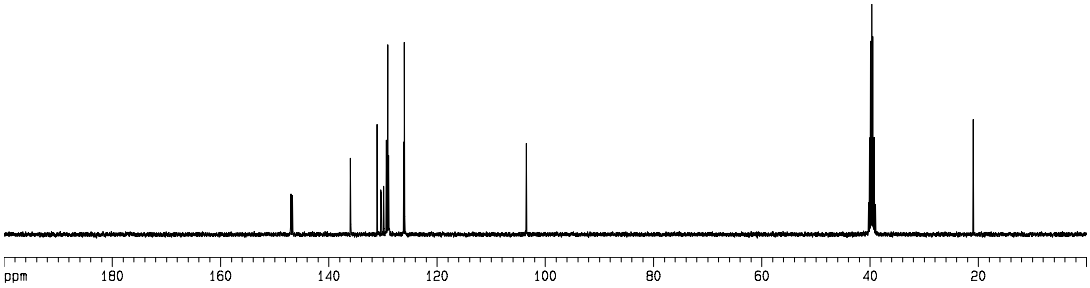
11d

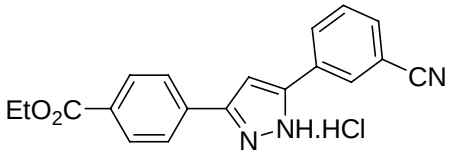

Integral
2.0169
1.0082
2.0416
1.0358
2.9403
1.0042
2.9613
ppm
9
8
7
6
5
4
3
2
1
0


ppm
147.0
146.8
136.0
131.1
130.3
129.8
129.3
129.1
128.9
128.8
126.2
126.0
103.5
40.2
40.0
39.8
39.6
39.4
39.2
39.0
20.9

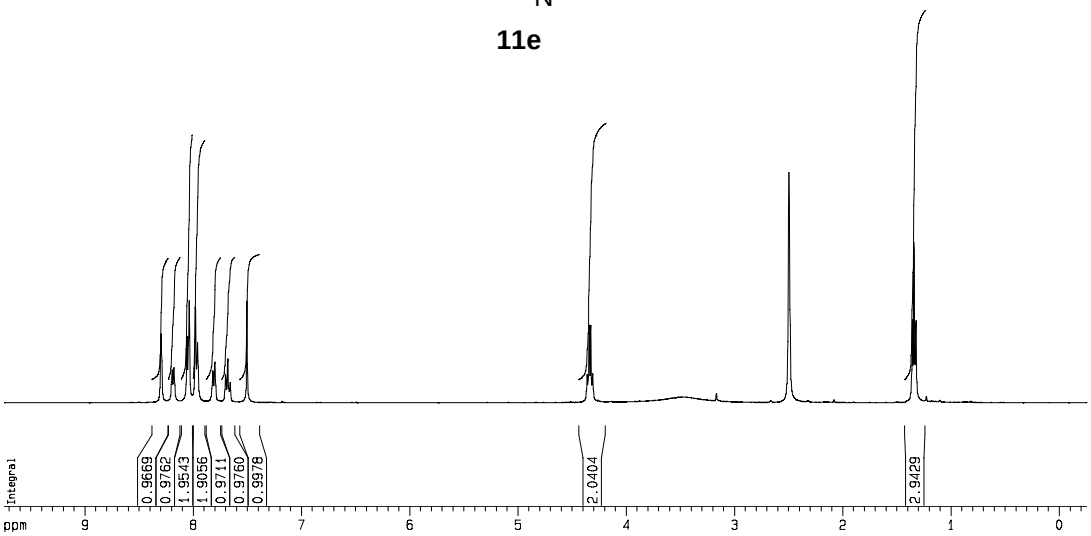

Me
N
NH.HCl

11d

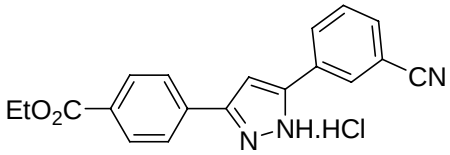

ppm
180
160
140
120
100
80
60
40
20


EtO2C
CN
N
NH.HCl

11e

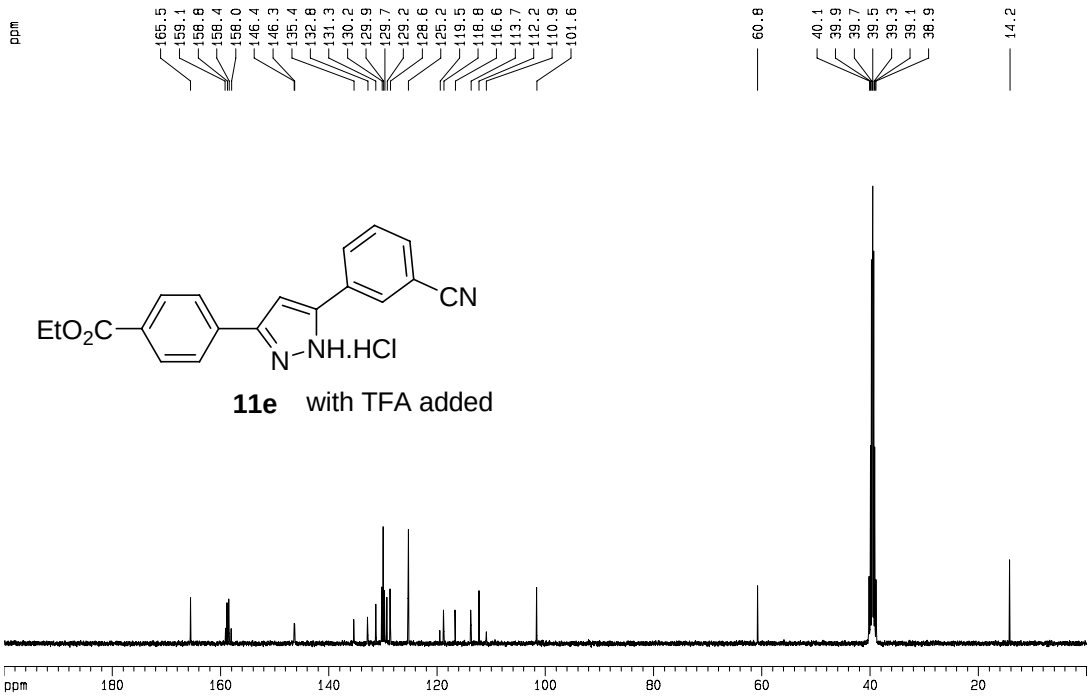

Integral
0.9669
0.9762
1.9543
1.9056
0.9711
0.9760
0.9978
2.0404
2.9429
ppm
9
8
7
6
5
4
3
2
1
0


ppm
165.4
146.2
135.2
132.6
131.2
130.1
129.8
129.5
129.0
128.5
125.1
118.6
112.0
101.5
60.7
40.1
39.9
39.7
39.5
39.3
39.1
38.9
14.1

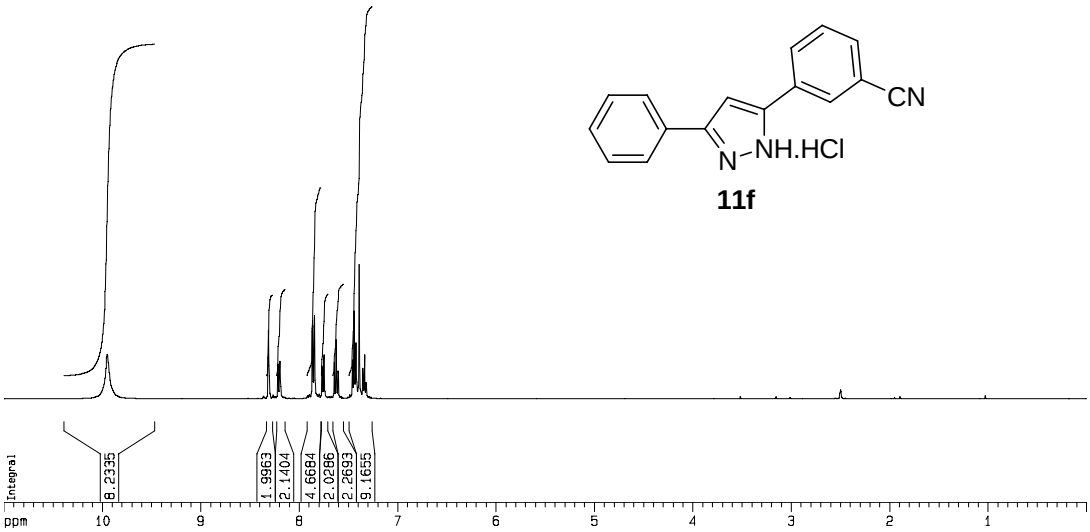

EtO2C
CN
N
NH.HCl

11e

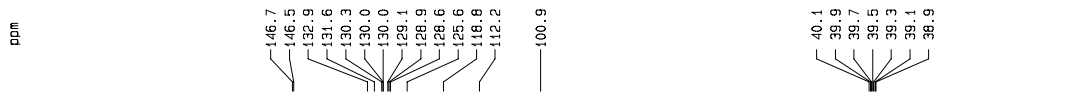
ppm
180
160
140
120
100
80
60
40
20

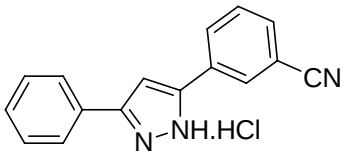


11e with TFA added

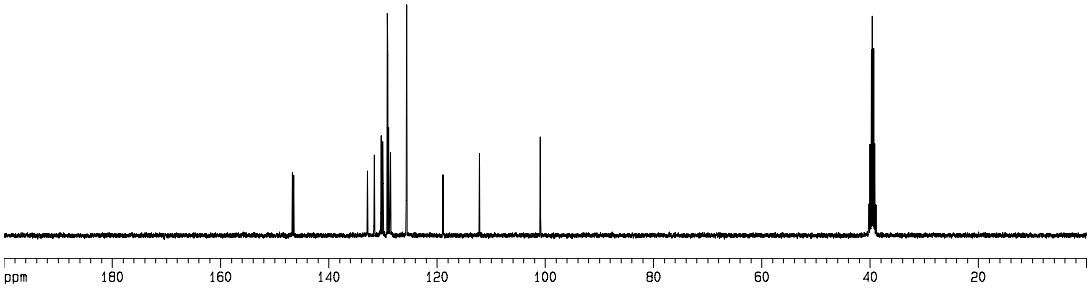

CN
NH.HCl
N
Integral
8.2335
1.9963
2.1404
4.6684
2.0286
2.2693
9.1655
ppm
10
9
8
7
6
5
4
3
2
1

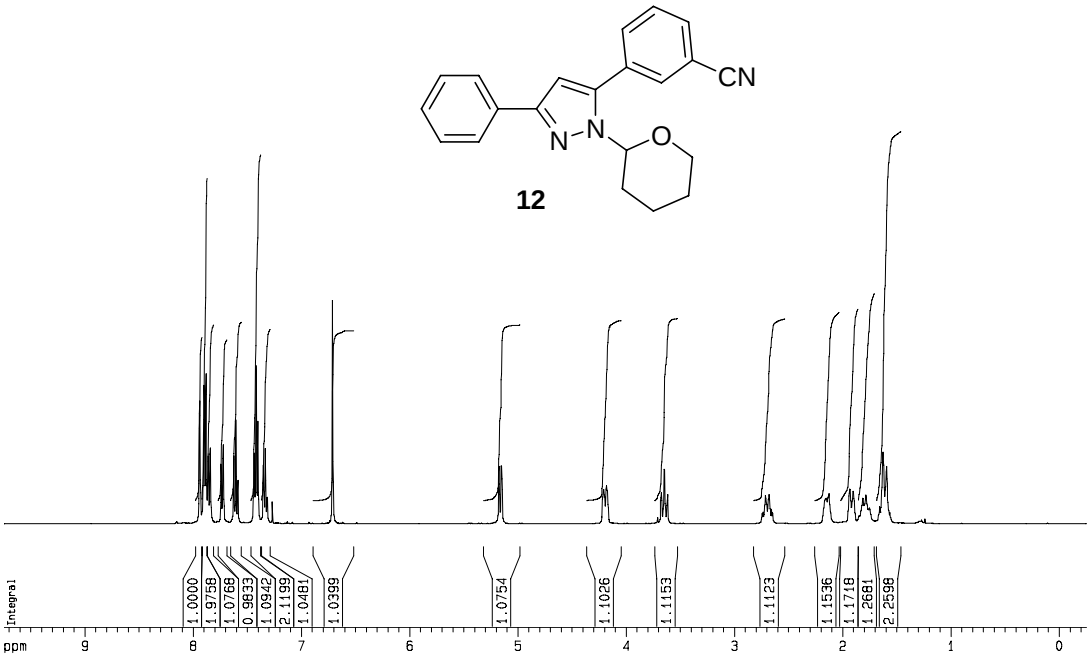
11f


ppm
146.7
146.5
132.9
131.6
130.3
130.0
130.0
129.1
128.9
128.6
125.6
118.8
112.2
100.9
40.1
39.9
39.7
39.5
39.3
39.1
38.9


CN
NH.HCl
N

11f


ppm
180
160
140
120
100
80
60
40
20


CN
N
N
O
12
Integral
1.0000
1.9758
1.0768
0.9833
1.0942
2.1199
1.0481
1.0399
1.0754
1.1026
1.1153
1.1123
1.1536
1.1718
1.2681
2.2598
ppm
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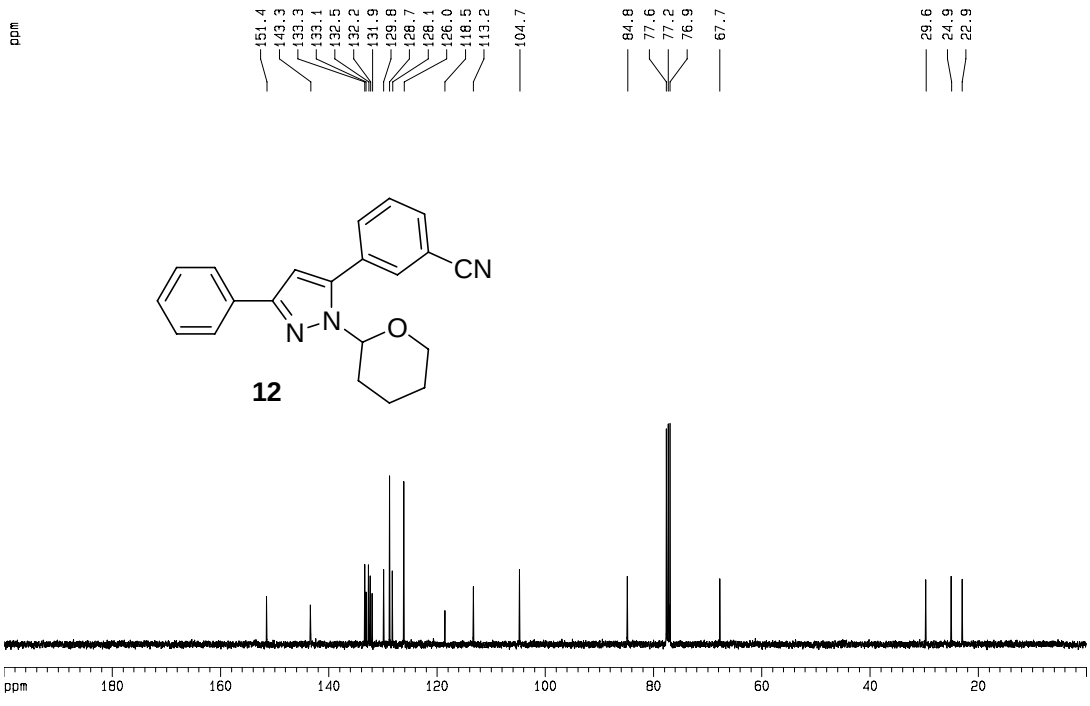
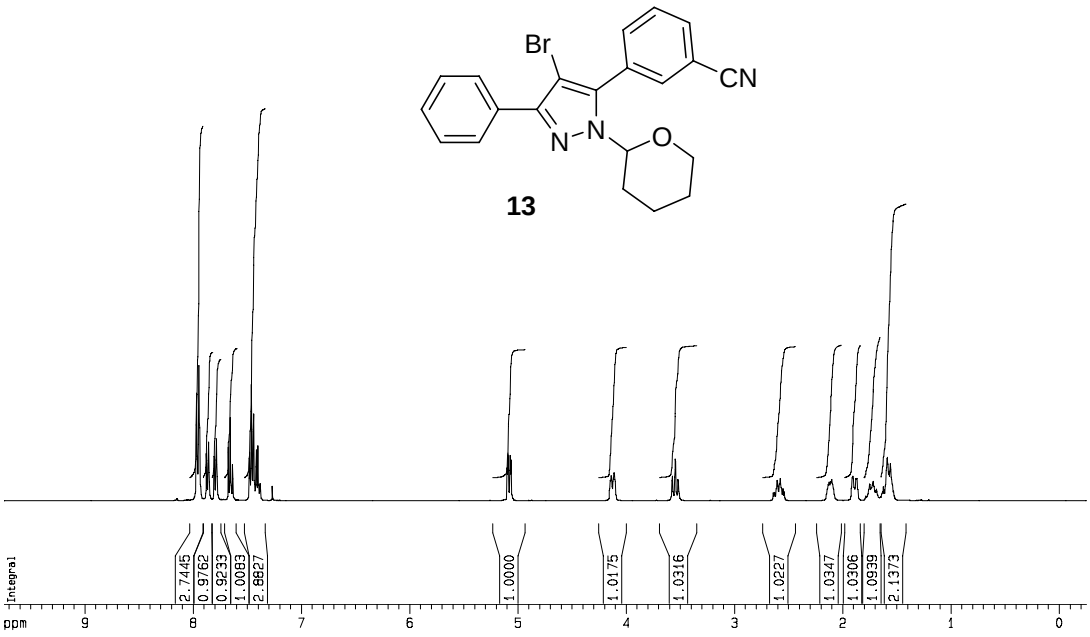
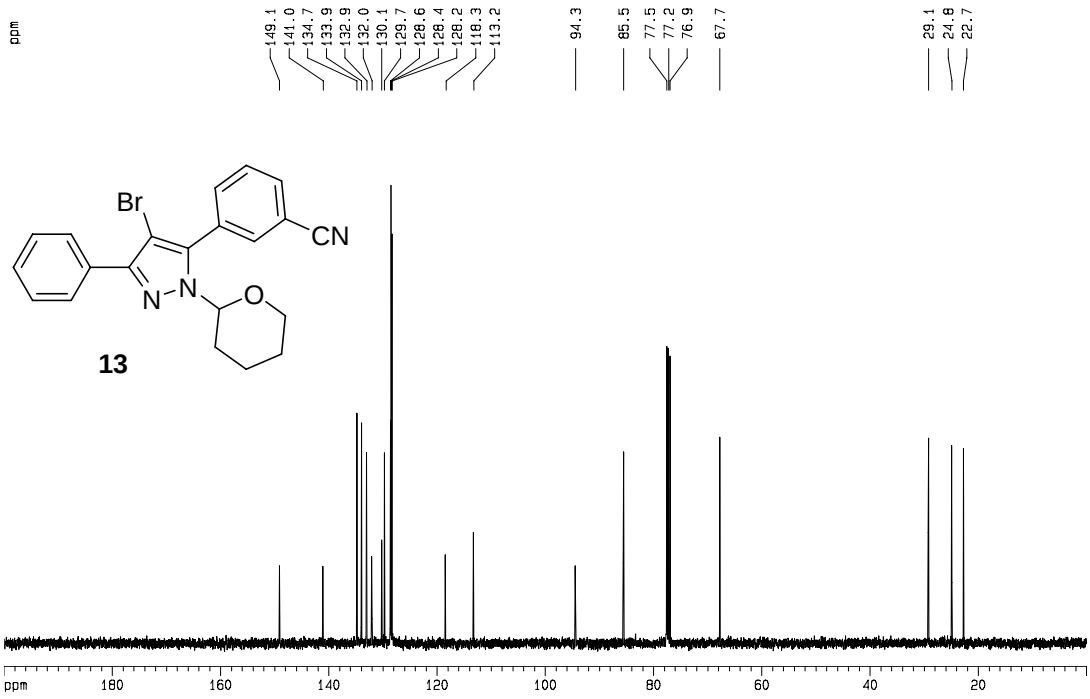
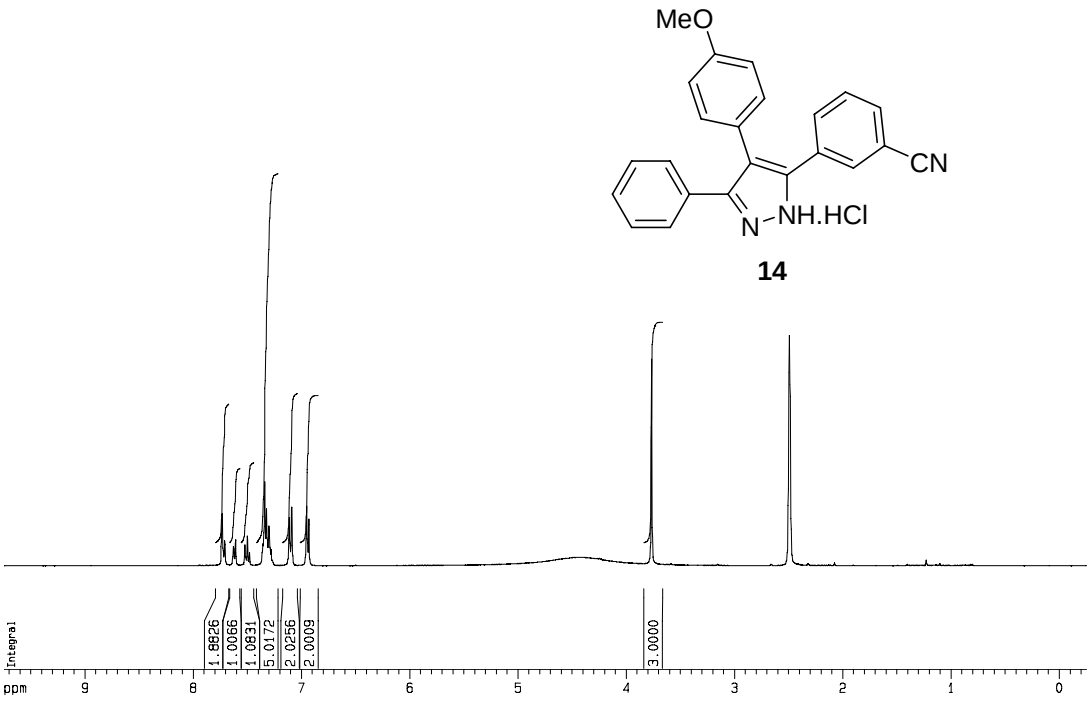
8
7
6
5
4
3
2
1
0

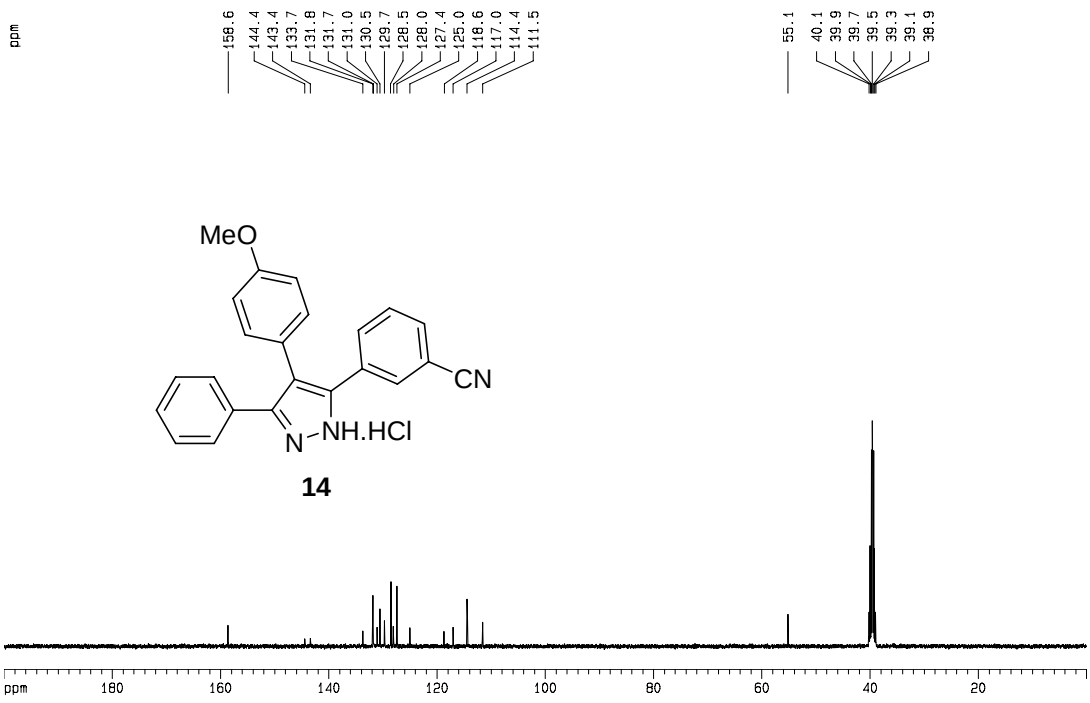

ppm
151.4
143.3
133.3
133.1
132.5
132.2
131.9
129.8
128.7
128.1
126.0
118.5
113.2
104.7
84.8
77.6
77.2
76.9
67.7
29.6
24.9
22.9
CN
N
N
O
12
ppm
180
160
140
120
100
80
60
40
20


Br
CN
N
N
O
13
Integral
2.7445
0.9762
0.9233
1.0083
2.8827
1.0000
1.0175
1.0316
1.0227
1.0347
1.0306
1.0939
2.1373
ppm
9
8
7
6
5
4
3
2
1
0


ppm
149.1
141.0
134.7
133.9
132.9
132.0
130.1
129.7
128.6
128.4
128.2
118.3
113.2
94.3
85.5
77.5
77.2
76.9
67.7
29.1
24.8
22.7
Br
CN
N
N
O
13
ppm
180
160
140
120
100
80
60
40
20


MeO
CN
N
NH.HCl
Integral
1.8826
1.0066
1.0831
5.0172
2.0256
2.0009
3.0000
ppm
9
8
7
6
5
4
3
2
1
0

14


ppm
158.6
144.4
143.4
133.7
131.8
131.7
131.0
130.5
129.7
128.5
128.0
127.4
125.0
118.6
117.0
114.4
111.5
55.1
40.1
39.9
39.7
39.5
39.3
39.1
38.9
MeO
CN
N
NH.HCl
ppm
180
160
140
120
100
80
60
40
20

14

References

1. Gérard, A.-L.; Bouillon, A.; Mahatsekake, C.; Collot, V.; Rault, S. *Tetrahedron Lett.* **2006**, *47*, 4665–4669.
2. Polevoi, L. G.; Kudrin, A. N.; Grandberg, I. I.; Kost, A. N. *Izvestiya Timiryazevskoi Sel'skokhozyaistvennoi Akademii* **1968**, 1, 192-207.
3. Schunack, W. *Archiv der Pharmazie (Weinheim, Germany)* **1973**, *306*, 934-942.
4. Joshi, K. C.; Pathak, V. N. *Indian Journal of Chemistry* **1973**, *11*, 398-399.