Supporting Information

Pd-catalyzed direct arylation of tautomerizable heterocycles with aryl boronic acids via C-OH bond activation using phosphonium salts

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I - General Methods

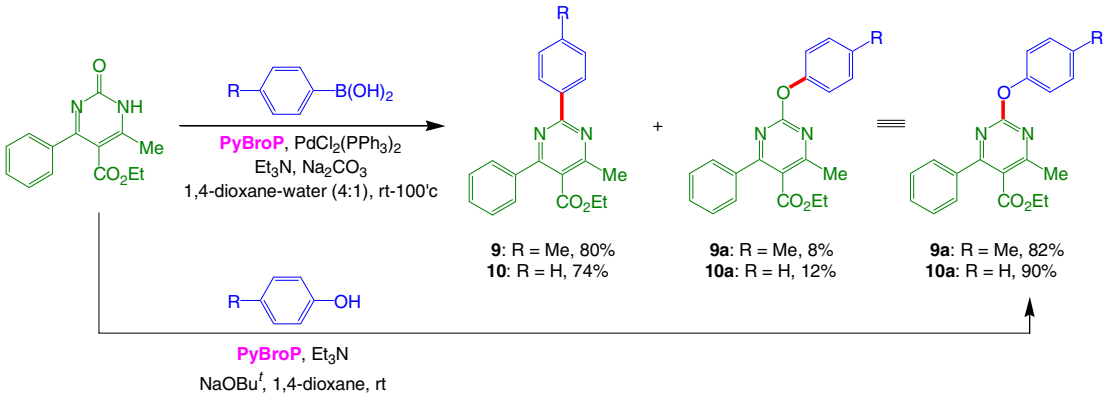
^{1}H NMR spectra were recorded at 400 MHz on a Bruker spectrometer, and were reported in ppm from tetramethylsilane on the scale. Data are reported as follows: chemical shift, multiplicity, coupling constants (Hz), and relative integration. ^{13}C NMR spectra were recorded at 100 MHz on a Bruker spectrometer, and were reported in ppm from the central deuterated solvent peak. LCMS was performed on an Agilent 1100 LC/MSD with an Agilent 1100 SL mass spectrometer. HRMS was performed on a Micromass Q-Tof API US hybrid quadrupole/time of flight mass spectrometer.

II - General Procedure for the Pd-catalyzed Direct Arylation of Tautomerizable Heterocycles with Aryl Boronic Acids via C-OH Bond Activation using PyBroP

A mixture of the tautomerizable heterocycle (0.5 mmol), PyBroP (1.2 eq) and Et_3N (3 eq) in 1,4-dioxane (4 mL) was stirred in a sealed tube at rt for 2h. Then, the aryl boronic acid (2 eq), Na_2CO_3 (5 eq), $PdCl_2(PPh_3)_2$ (5 mol%) and water (1 mL) were added, and the mixture was stirred at 100 °C in the sealed tube for 4h. After the mixture was cooled to rt, it was diluted with EtOAc, washed with water, and dried with brine and Na_2SO_4. Flash chromatography using an EtOAc/hexane mixture or HPLC using a MeCN/water mixture gave the biaryl product.

III - Direct Arylation versus Biaryl Ether Formation

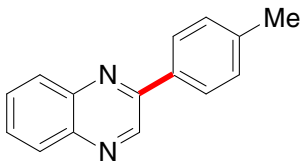
It is interesting to note that the direct arylation of the multi-functionalized 2-pyrimidinone with *p*-tolyl and phenyl boronic acids produced the unexpected biaryl ethers (**9a** and **10a**) (C-O bond formation) as the minor side products along with the desired biaryl products (**9** and **10**). To confirm their structures, the identical biaryl ethers **9a** and **10a** were alternatively prepared via our previous phosphonium coupling condition for the direct C-O bond formation by using the corresponding phenols (Kang, F.-A., *et al. J. Org. Chem.* **2005**, *70*, 1957). The reason for the biaryl ether formation on this substrate was unclear, and neither C-C nor C-O bond formation was observed in the absence of PyBroP.



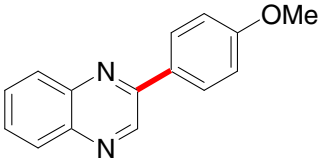
IV - Hydrogen-Deuterium Exchange Experiment

It is noteworthy that two carbons of compound **11** were found to overlap and show as a single peak at 129.24 ppm on the ^{13}C NMR spectrum in DMSO^{d6}, while addition of D_2O (two drops) in the hydrogen-deuterium exchange experiment (compound **11a**) caused the overlapped carbons to split as two peaks at 129.28 and 129.29 ppm respectively, see: the NMR data and spectra below.

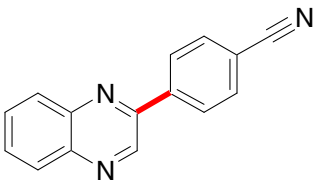
V - Characterization Data



2-*p*-Tolyl-quinoxaline
(Compound **1**): White solid; ^1H NMR ($CDCl_3$) δ 2.46 (s, 3H), 7.37 (d, 2H, *J* = 8.2 Hz), 7.75 (m, 2H), 8.10 (d, 1H, *J* = 8.2 Hz), 8.14 (m, 1H), 9.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 127.4, 129.1, 129.3, 129.5, 129.9, 130.2, 134.0, 140.5, 141.5, 142.4, 143.3, 151.9; MS *m/e* (MH^+) 221.

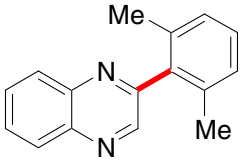


2-(4-Methoxyphenyl)-quinoxaline
(Compound **2**): White solid; ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 7.07 (d, 2H, *J* = 8.8 Hz), 7.73 (m, 2H), 8.10 (m, 2H), 8.17 (d, 2H, *J* = 8.8 Hz), 9.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.4, 114.6, 128.9, 129.0, 129.1, 129.3, 129.4, 130.2, 141.2, 142.3, 143.1, 151.4, 161.5; MS *m/e* (MH^+) 237.

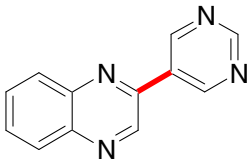


2-(4-Cyanophenyl)-quinoxaline

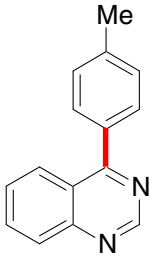
(Compound **3**): White solid; ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 2H), 7.85 (d, 2H, *J* = 8.6 Hz), 8.16 (m, 2H), 8.33 (d, 2H, *J* = 8.6 Hz), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 113.6, 118.5, 128.0, 129.2, 129.8, 130.5, 130.8, 132.8, 140.8, 142.0, 142.2, 142.7, 149.5; MS *m/e* (MH^+) 232.



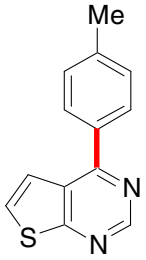
2-(2,6-Dimethylphenyl)-quinoxaline
(Compound **4**): White solid; ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 6H), 7.18 (d, 2H, *J* = 8.4 Hz), 7.27 (m, 1H), 7.81 (m, 2H), 8.18 (m, 2H), 8.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4, 128.0, 129.0, 129.3, 129.5, 129.9, 130.2, 136.3, 137.1, 141.2, 142.4, 146.4, 155.5; MS *m/e* (MH^+) 235.



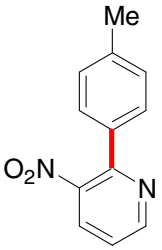
2-Pyrimidin-5-yl-quinoxaline
(Compound **5**): White solid; ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2H), 8.18 (m, 2H), 9.35 (s, 1H), 9.37 (s, 1H), 9.55 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 129.4, 129.8, 130.3, 130.8, 131.0, 142.0, 142.2, 142.3, 146.7, 155.5, 159.4; MS *m/e* (MH^+) 209.



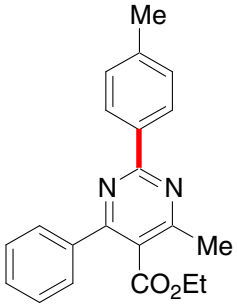
4-*p*-Tolyl-quinazoline
(Compound **6**): White solid; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 7.38 (d, 2H, *J* = 7.8 Hz), 7.61 (m, 1H), 7.70 (d, 2H, *J* = 7.8 Hz), 7.91 (m, 1H), 8.10 (d, 1H, *J* = 8.4 Hz), 8.16 (d, 1H, *J* = 8.4 Hz), 9.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 123.2, 127.2, 127.6, 128.9, 129.3, 130.0, 133.6, 134.3, 140.3, 151.1, 154.7, 168.4; MS *m/e* (MH^+) 221.



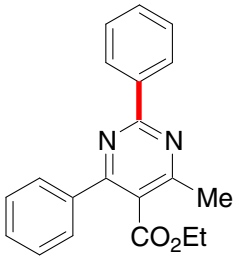
4-*p*-Tolyl-thieno[2,3-d]pyrimidine
(Compound **7**): White solid; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 7.35 (d, 2H, *J* = 8.2 Hz), 7.53 (d, 2H, *J* = 6.2 Hz), 7.59 (d, 1H, *J* = 6.2 Hz), 7.85 (d, 2H, *J* = 8.2 Hz), 9.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 121.1, 126.8, 127.7, 129.1, 129.6, 134.9, 140.8, 153.3, 160.9, 169.7; MS *m/e* (MH^+) 227.



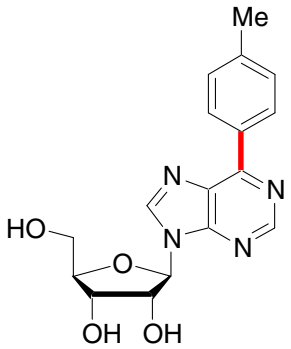
3-Nitro-2-*p*-tolyl-pyridine
(Compound **8**): Light yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 7.27 (d, 2H, *J* = 8.2 Hz), 7.39 (m, 1H), 7.47 (d, 2H, *J* = 8.2 Hz), 8.09 (dd, 1H, *J* = 8.0, 1.6 Hz), 8.83 (dd, 1H, *J* = 4.8, 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 122.1, 128.0, 129.5, 132.1, 133.4, 140.1, 146.2, 152.1, 152.8; MS *m/e* (MH^+) 215.



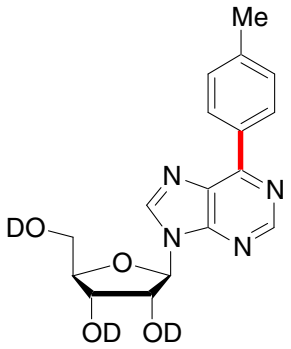
4-Methyl-6-phenyl-2-*p*-tolyl-pyrimidine-5-carboxylic acid ethyl ester
(Compound **9**): White solid; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, *J* = 7.0 Hz), 2.40 (s, 3H), 2.68 (s, 3H), 4.19 (q, 2H, *J* = 7.0 Hz), 7.27 (d, 2H, *J* = 8.2 Hz), 7.46 (m, 3H), 7.75 (m, 2H), 8.44 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6, 21.5, 22.9, 61.7, 123.0, 128.4, 128.6, 129.2, 129.9, 134.5, 138.3, 141.3, 163.5, 163.7, 165.3, 168.5; MS *m/e* (MH^+) 333.



4-Methyl-2,6-diphenyl-pyrimidine-5-carboxylic acid ethyl ester
(Compound **10**): White solid; ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3H, *J* = 7.2 Hz), 2.70 (s, 3H), 4.21 (q, 2H, *J* = 7.2 Hz), 7.49 (m, 6H), 7.76 (m, 2H), 8.56 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.9, 61.8, 123.4, 128.46, 128.48, 128.5, 128.6, 130.0, 131.0, 137.2, 138.3, 163.6, 163.7, 165.4, 168.5; MS *m/e* (MH^+) 319.

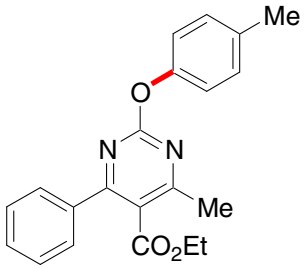


2-Hydroxymethyl-5-(6-p-tolyl-purin-9-yl)-tetrahydro-furan-3,4-diol
(Compound **11**): White solid; ^{1}H NMR (DMSO^{d6}) δ 2.42 (s, 3H), 3.61 (m, 1H), 3.71 (m, 1H), 4.00 (q, 1H, *J* = 3.6 Hz), 4.21 (q, 1H, *J* = 4.4 Hz), 4.66 (q, 1H, *J* = 6.0 Hz), 5.14 (t, 1H, *J* = 5.4 Hz), 5.24 (d, 1H, *J* = 4.4 Hz), 5.55 (d, 1H, *J* = 6.0 Hz), 6.09 (d, 1H, *J* = 5.6 Hz), 7.42 (d, 2H, *J* = 8.4 Hz), 8.75 (d, 2H, *J* = 8.4 Hz), 8.90 (s, 1H), 8.98 (s, 1H); ^{13}C NMR (DMSO^{d6}) δ 21.0, 61.1, 70.1, 73.6, 85.5, 87.5, 129.2, 130.5, 132.4, 141.1, 144.6, 151.8, 152.0, 152.9; MS *m/e* (MH^+) 343; HRMS (ESI) Calcd for $C_{17}H_{18}N_4O_4$ (MH^+) 343.1406, Found 343.1403.

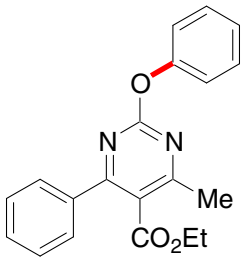


Hydrogen-deuterium exchange with D_2O in $(CD_3)_2SO$

2-Hydroxymethyl-5-(6-p-tolyl-purin-9-yl)-tetrahydro-furan-3,4-diol[d3]
(Compound **11a**): ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.62 (m, 1H), 3.73 (m, 1H), 4.04 (q, 1H, *J* = 4.0 Hz), 4.24 (t, 1H, *J* = 4.4 Hz), 4.67 (t, 1H, *J* = 5.4 Hz), 6.10 (d, 1H, *J* = 5.6 Hz), 7.43 (d, 2H, *J* = 8.2 Hz), 8.72 (d, 2H, *J* = 8.2 Hz), 8.88 (s, 1H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 61.0, 70.1, 73.5, 85.5, 87.6, 129.28, 129.29, 130.5, 132.3, 141.3, 144.6, 151.8, 151.9, 153.1.



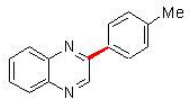
4-Methyl-6-phenyl-2-*p*-tolyloxy-pyrimidine-5-carboxylic acid ethyl ester
(Compound **9a**): Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, *J* = 7.0 Hz), 2.37 (s, 3H), 2.56 (s, 3H), 4.17 (q, 2H, *J* = 7.0 Hz), 7.12 (d, 2H, *J* = 8.6 Hz), 7.19 (d, 2H, *J* = 8.6 Hz), 7.41 (m, 3H), 7.59 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.6, 20.9, 22.8, 29.7, 61.8, 120.9, 121.2, 128.3, 128.4, 129.9, 130.2, 134.7, 137.4, 150.6, 164.1, 166.6, 168.1, 169.1; MS *m/e* (MH^+) 349.



4-Methyl-2-phenoxy-6-phenyl-pyrimidine-5-carboxylic acid ethyl ester

(Compound **10a**): White solid; ^{1}H NMR ($CDCl_3$) δ 1.06, (t, 3H, *J* = 7.0 Hz), 2.57 (s, 3H), 4.17 (q, 2H, *J* = 7.0 Hz), 7.25 (m, 3H), 7.42 (m, 5H), 7.59 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13,6, 22.8, 61.8, 121.0, 121.6, 125.2, 128.3, 128.4, 129.4, 130.3, 137.3, 152.8, 163.9, 166.6, 168.1, 169.2; MS *m/e* (MH^+) 335.

VI - NMR Spectra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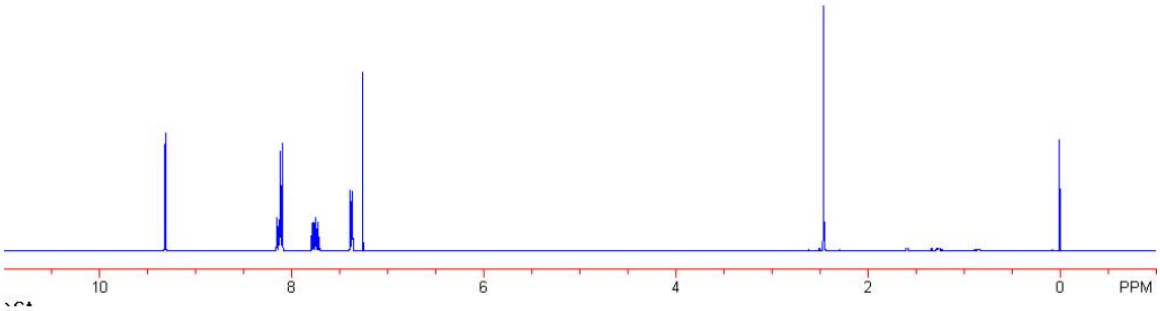
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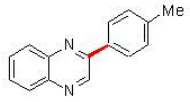
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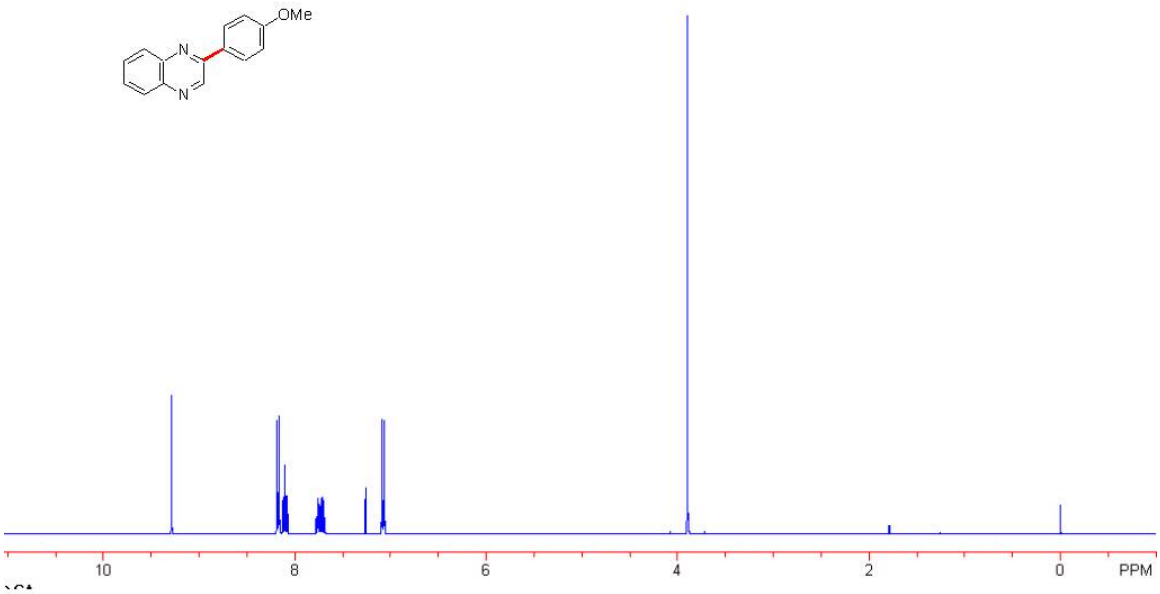
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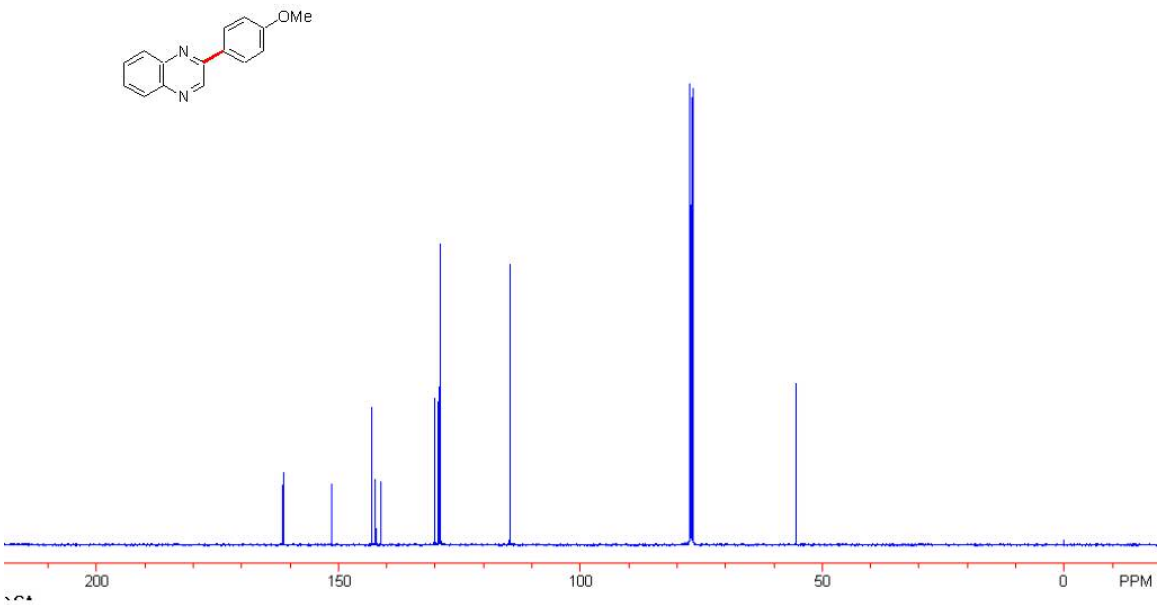
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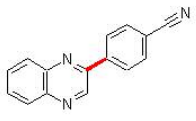
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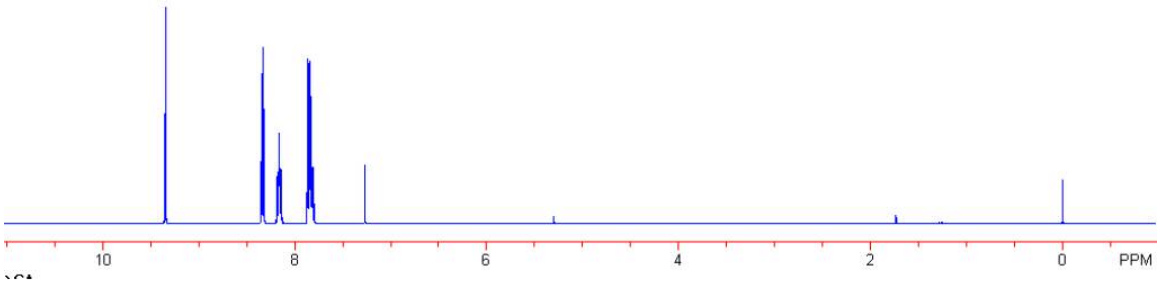
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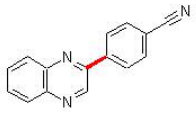
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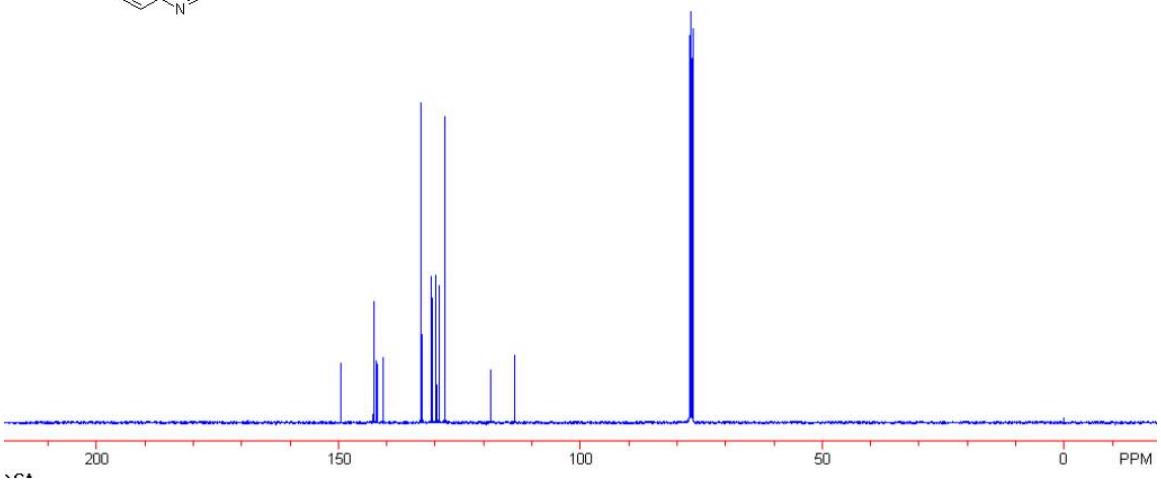
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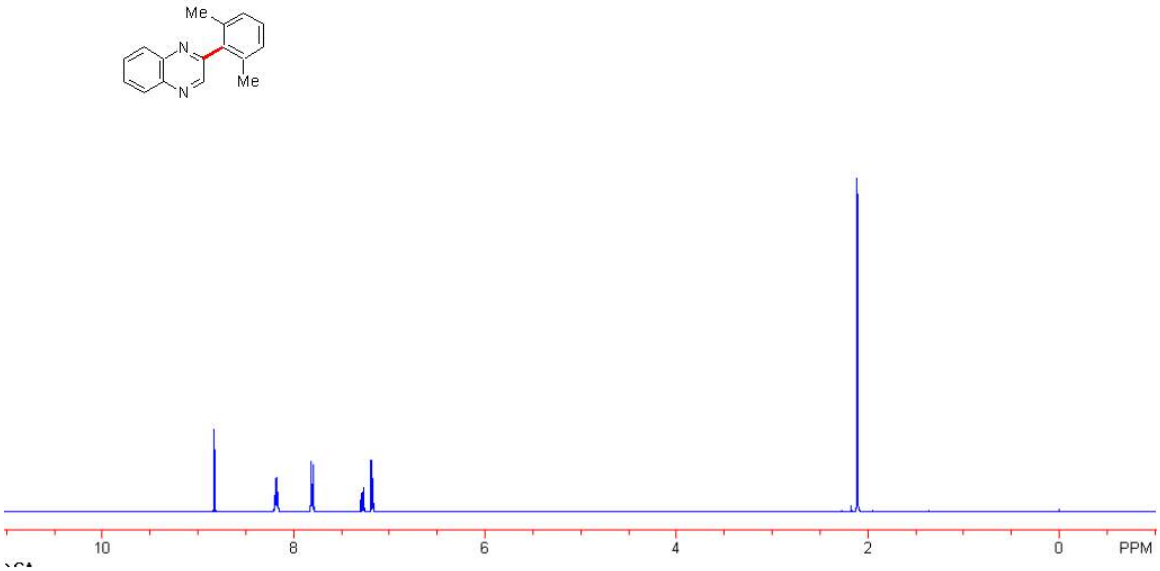
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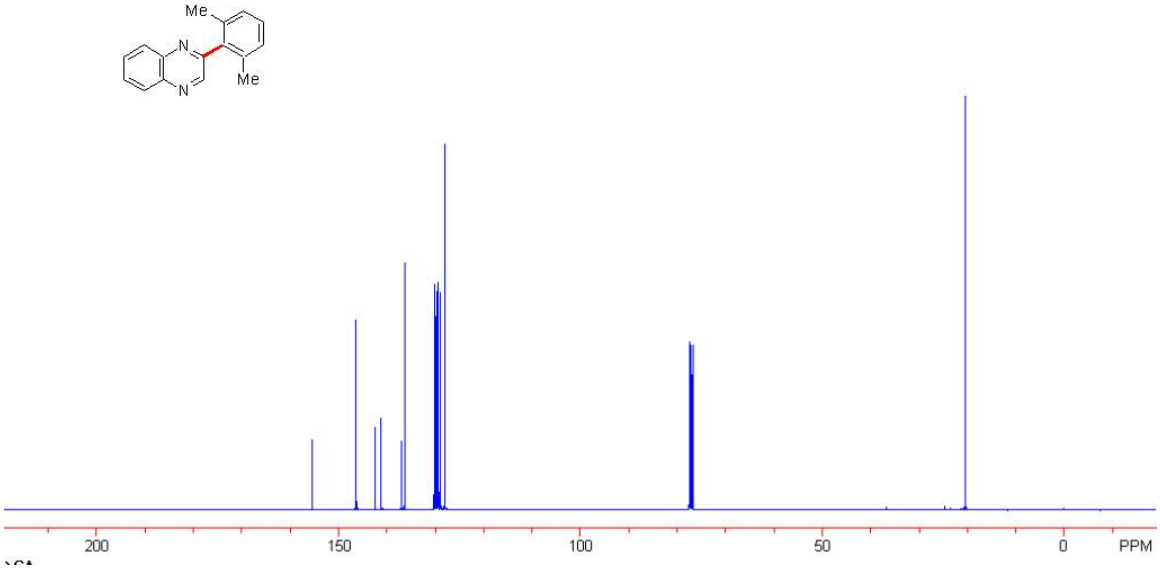
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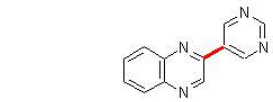

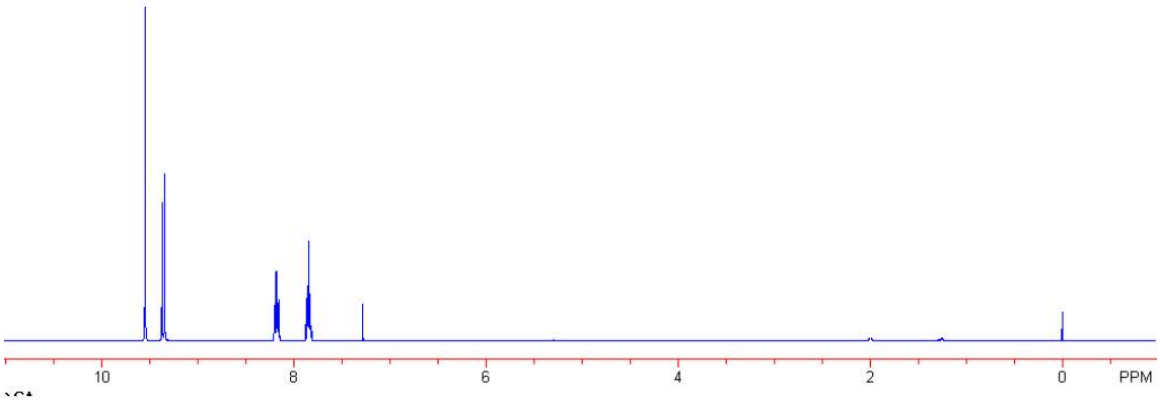
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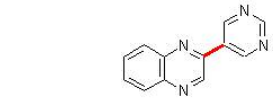

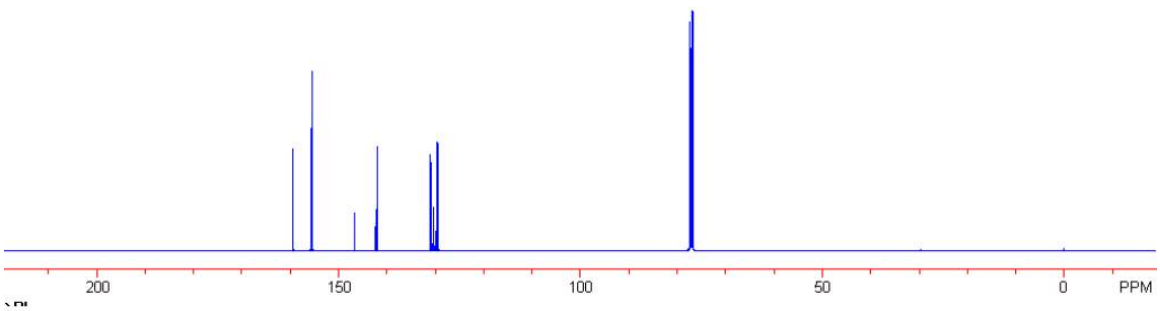
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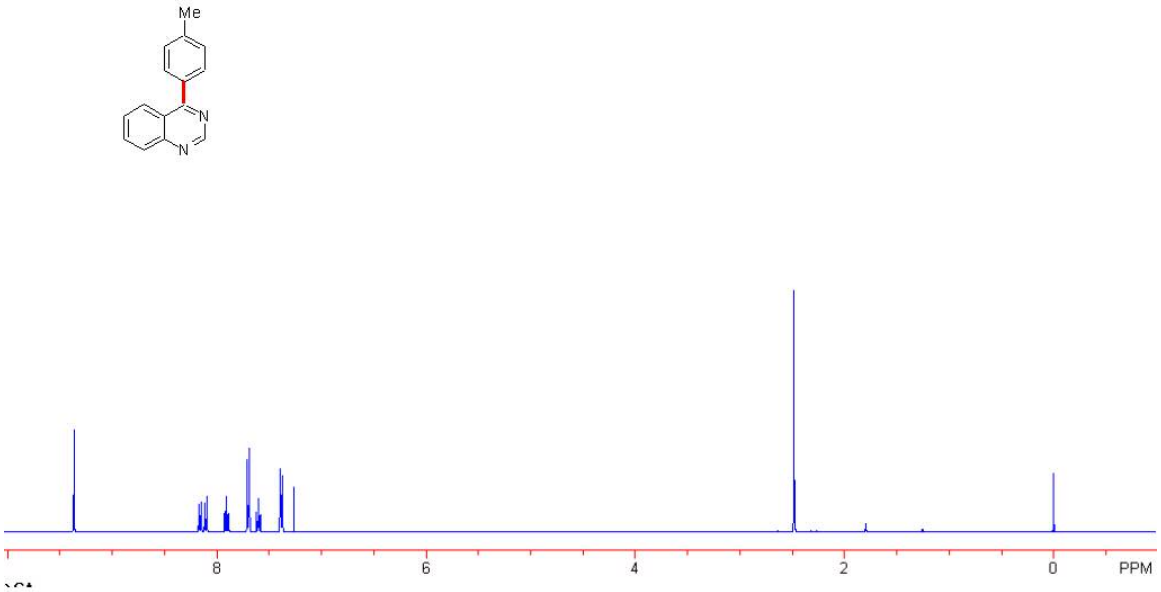
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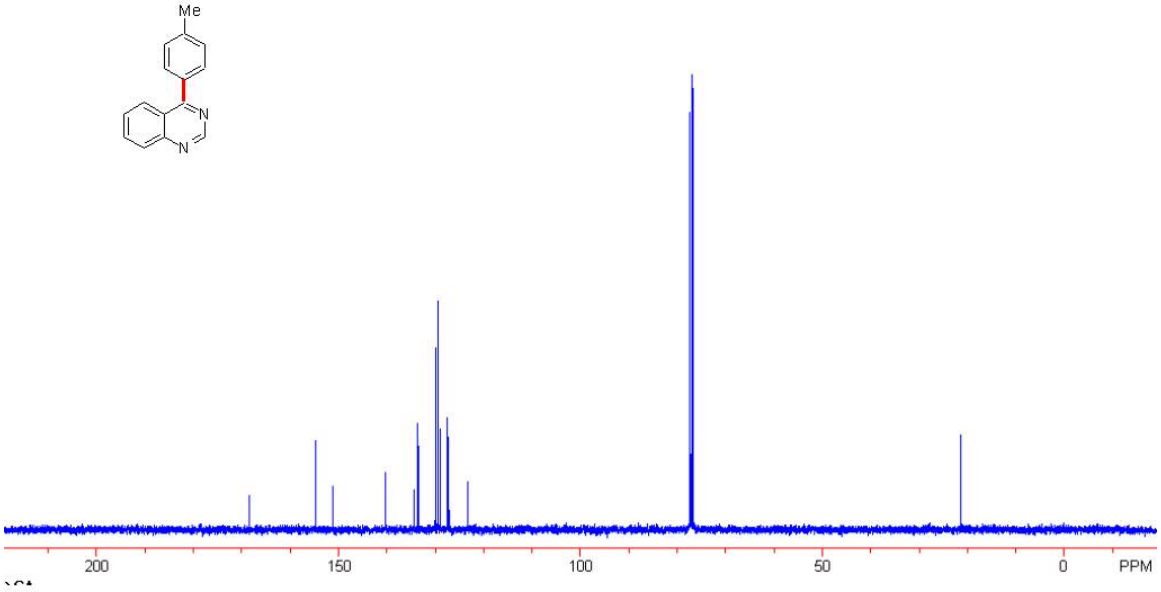
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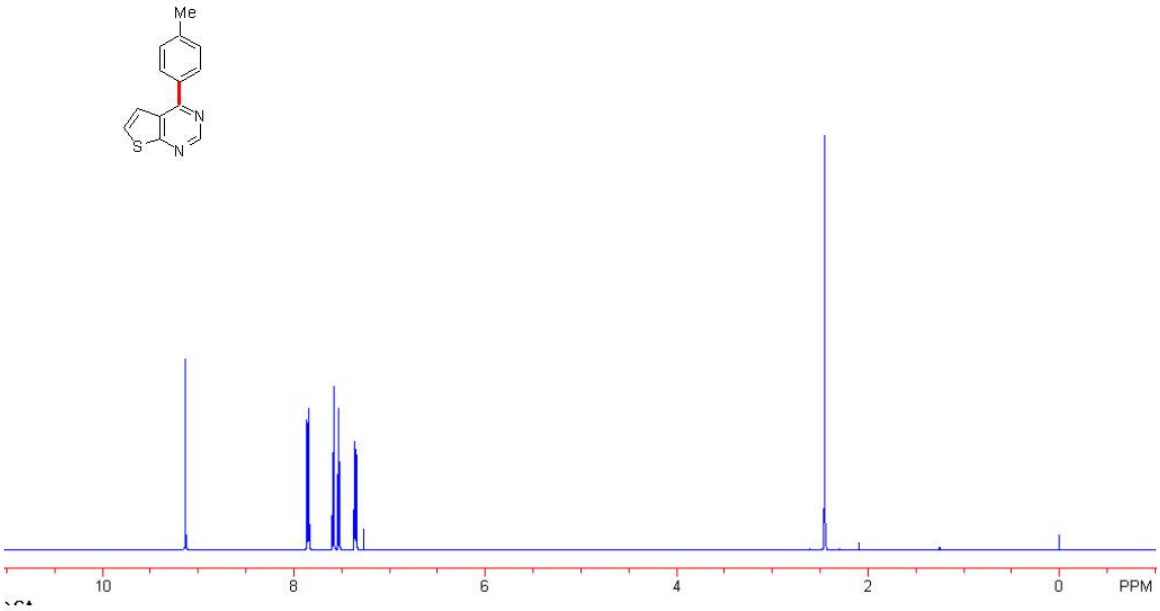
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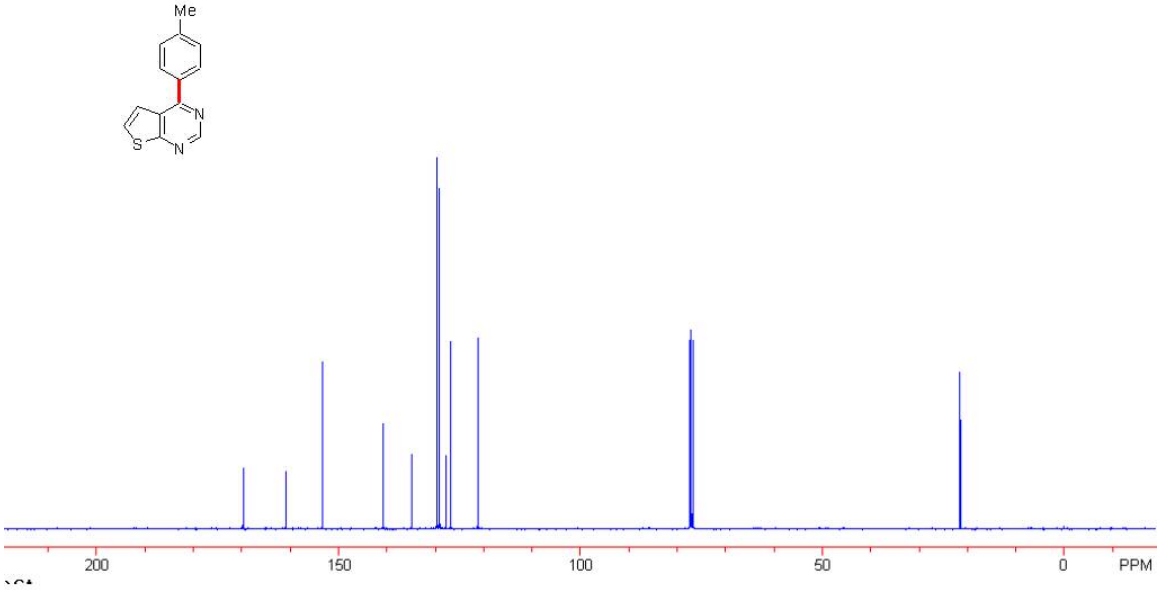
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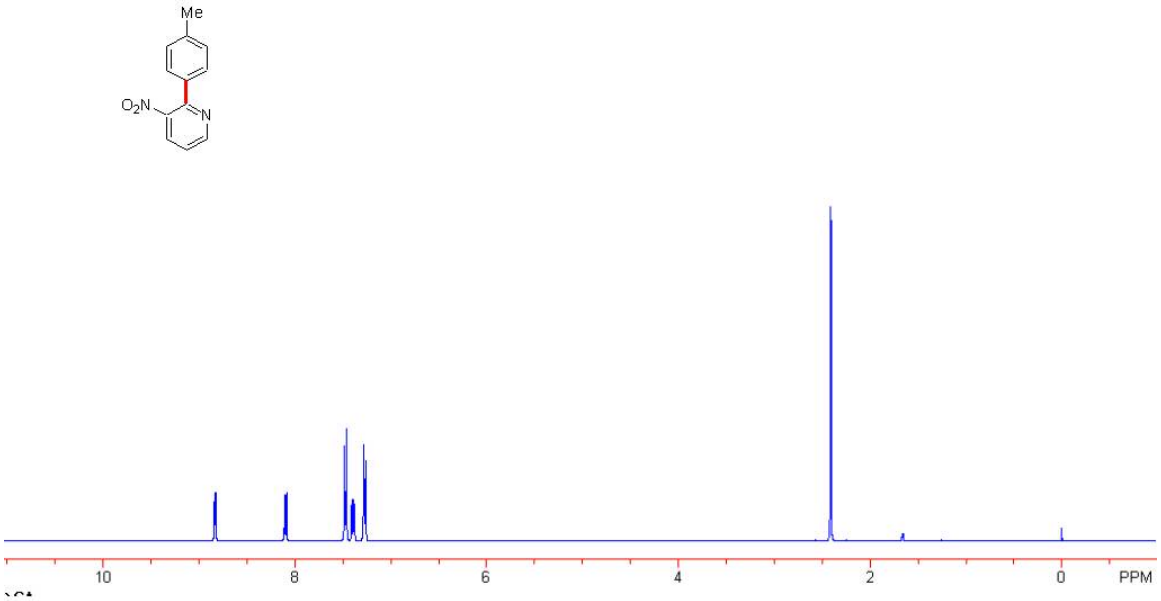
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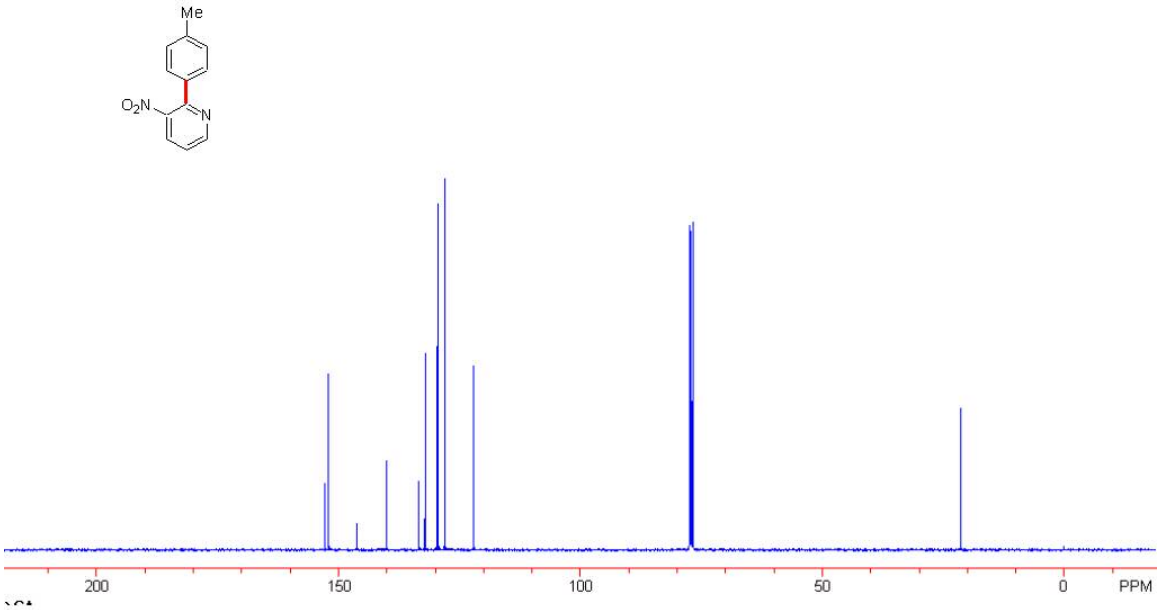
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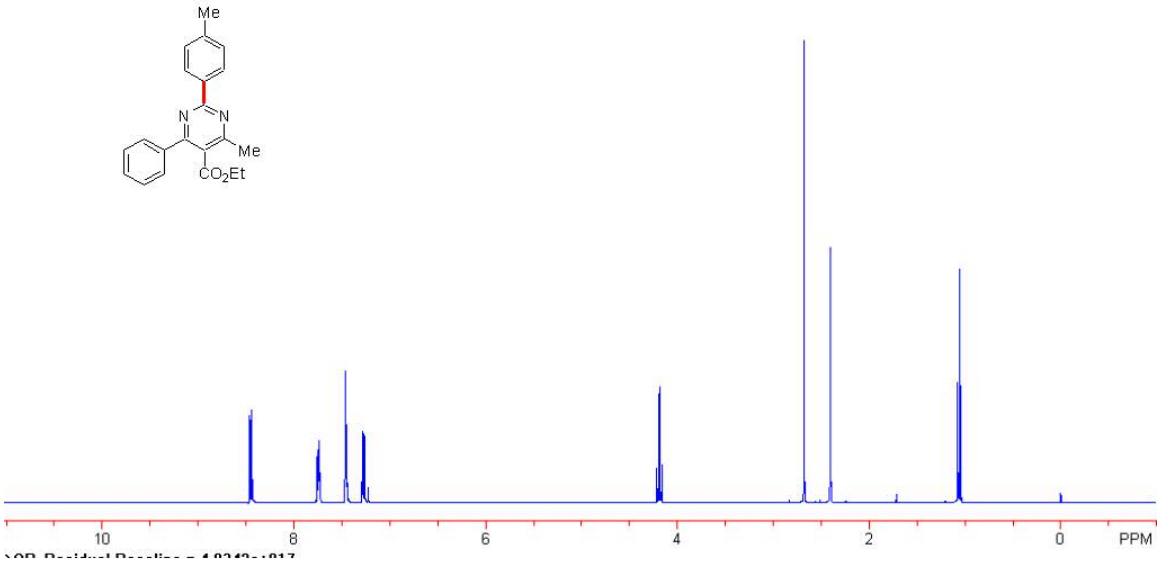
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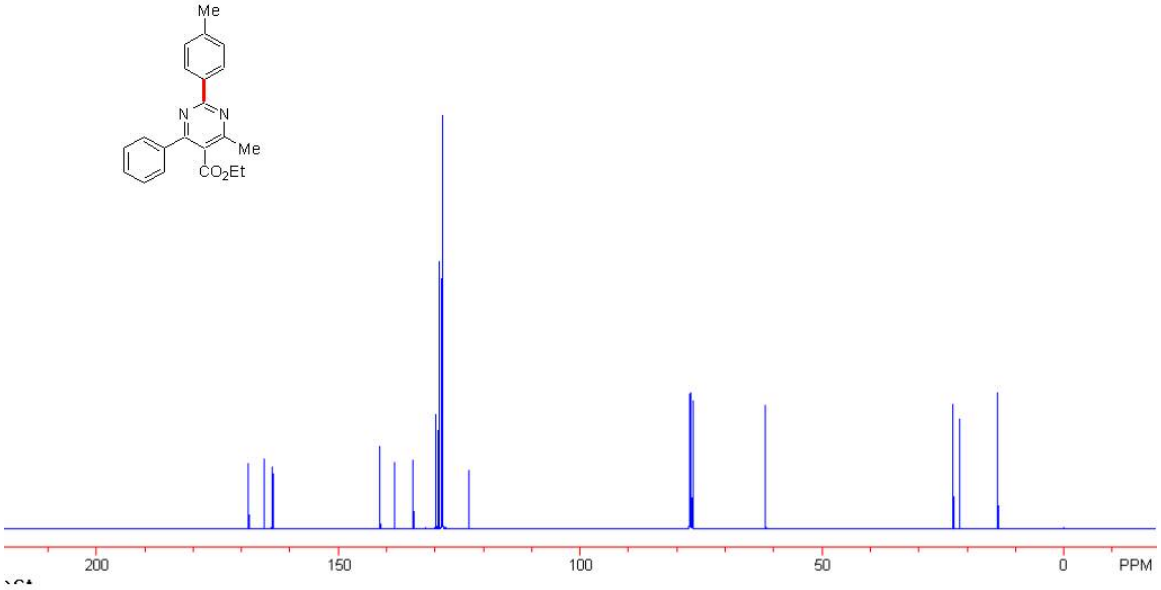
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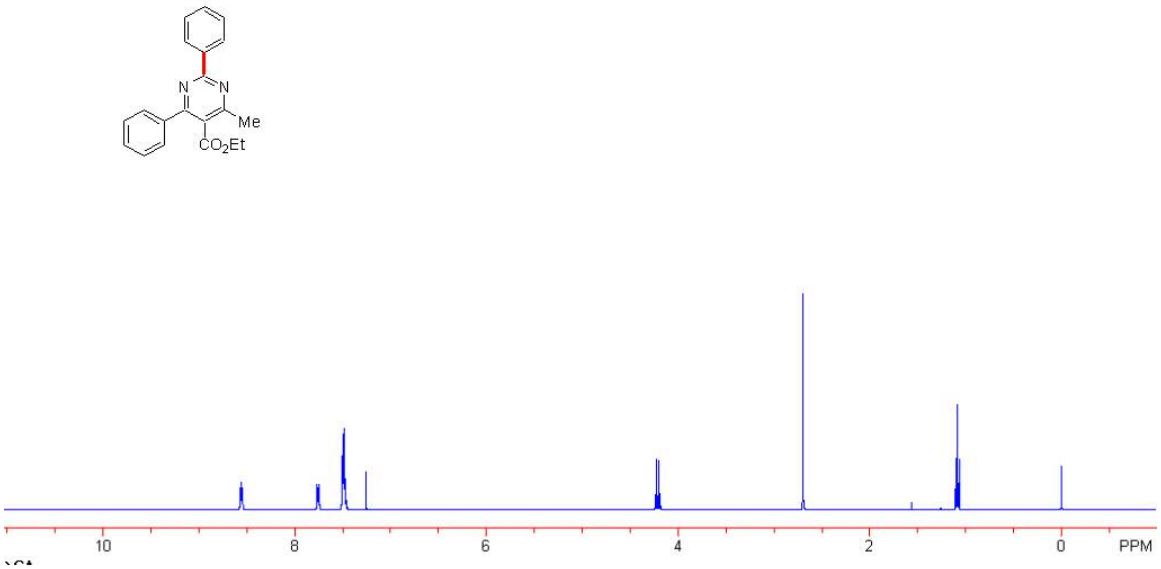
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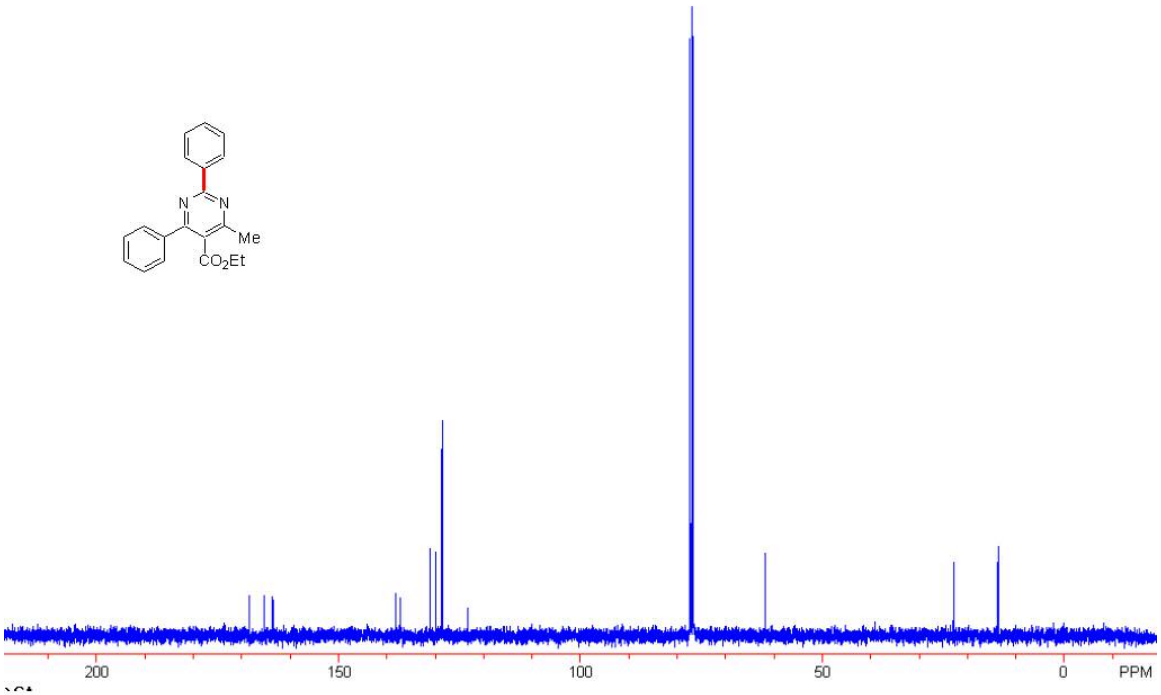
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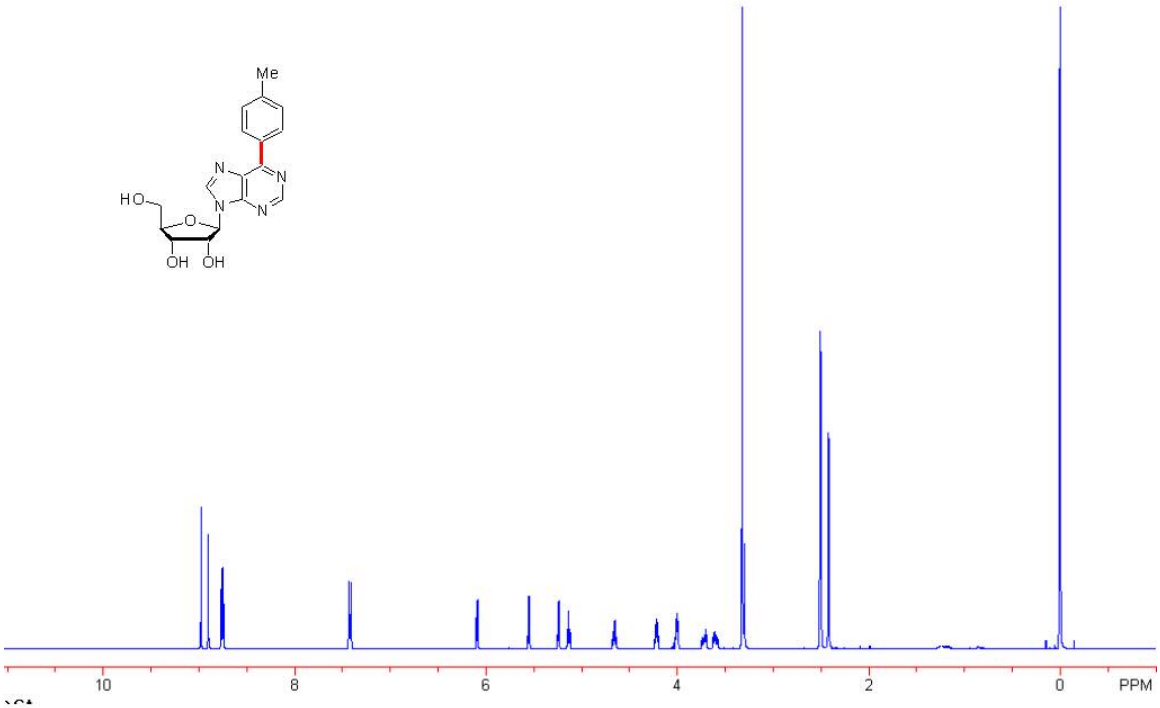
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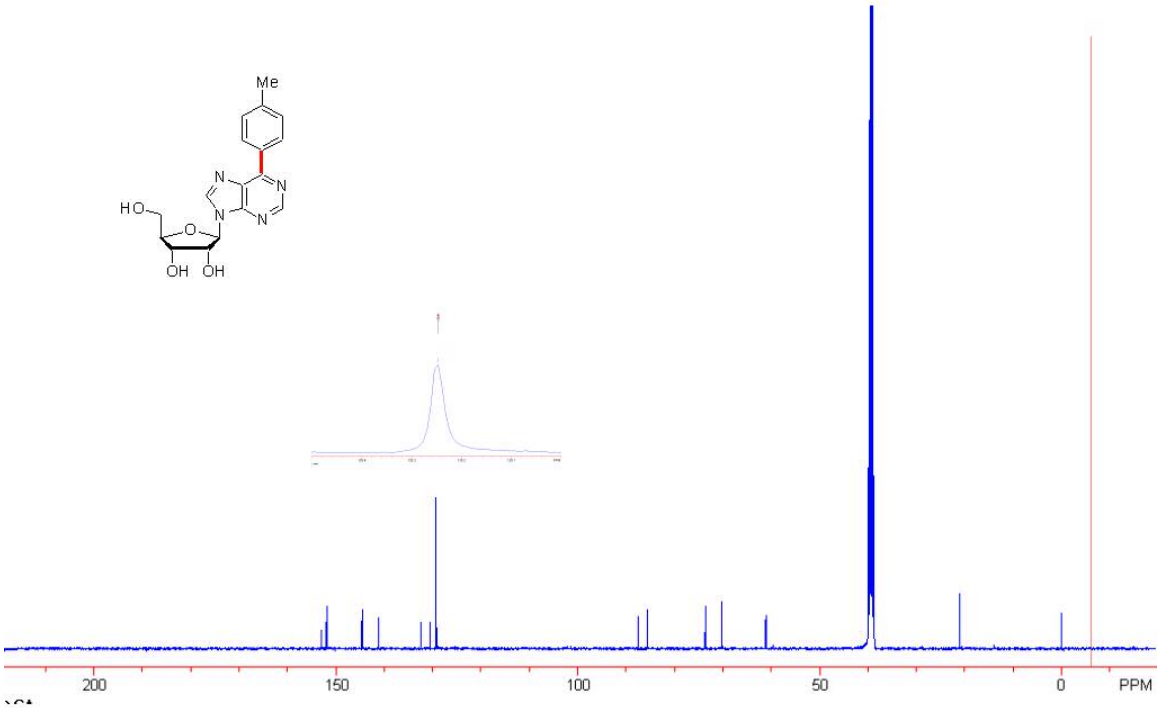
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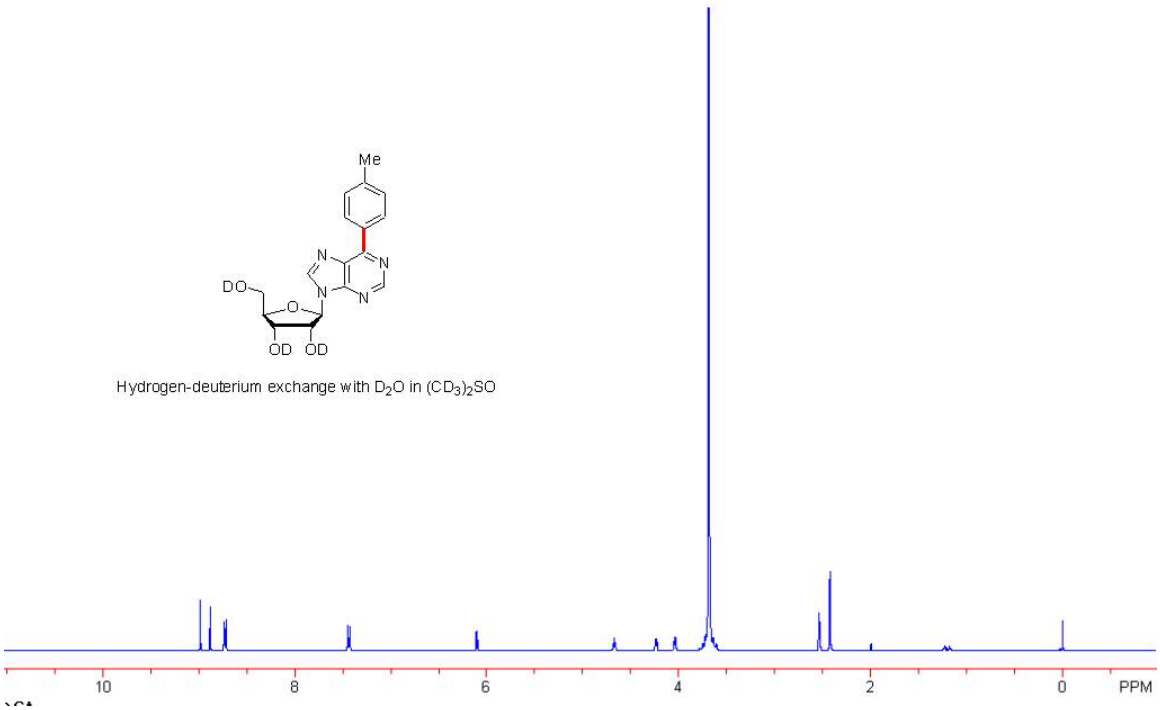
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DO
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Hydrogen-deuterium exchange with D_2O in $(CD_3)_2SO$
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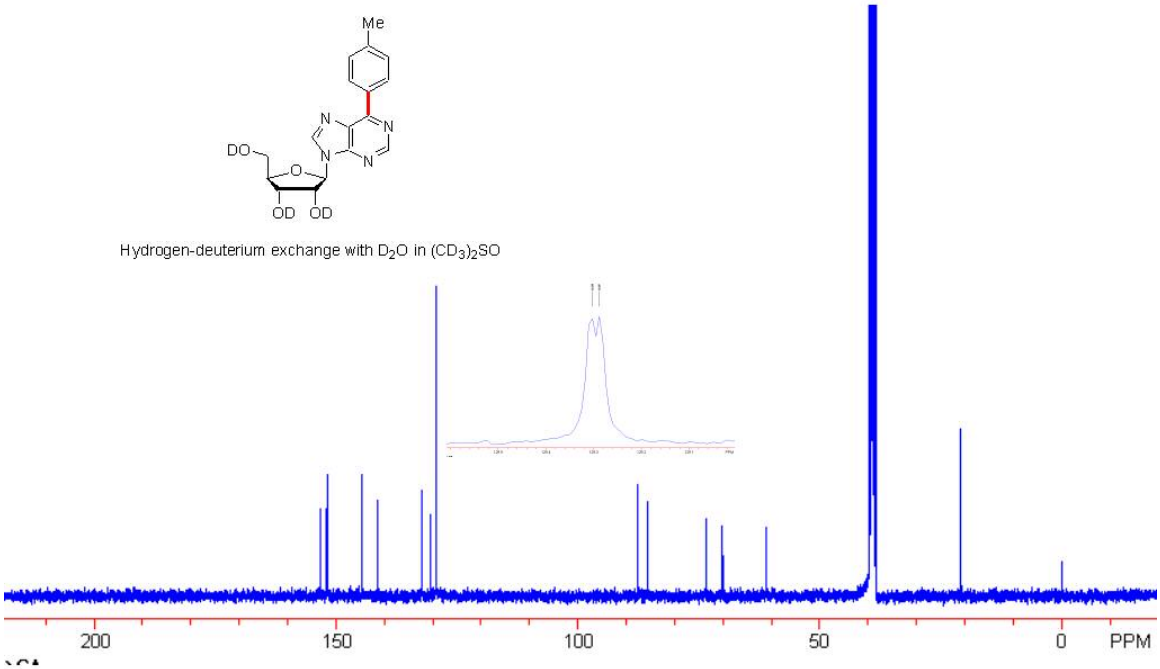
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DO
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Hydrogen-deuterium exchange with D_2O in $(CD_3)_2SO$
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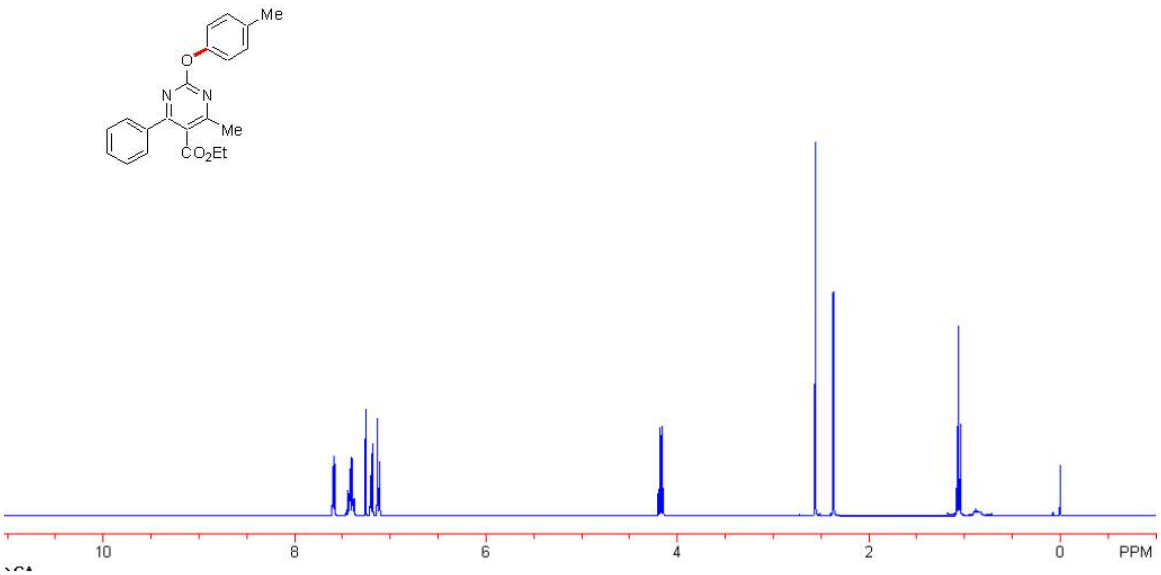
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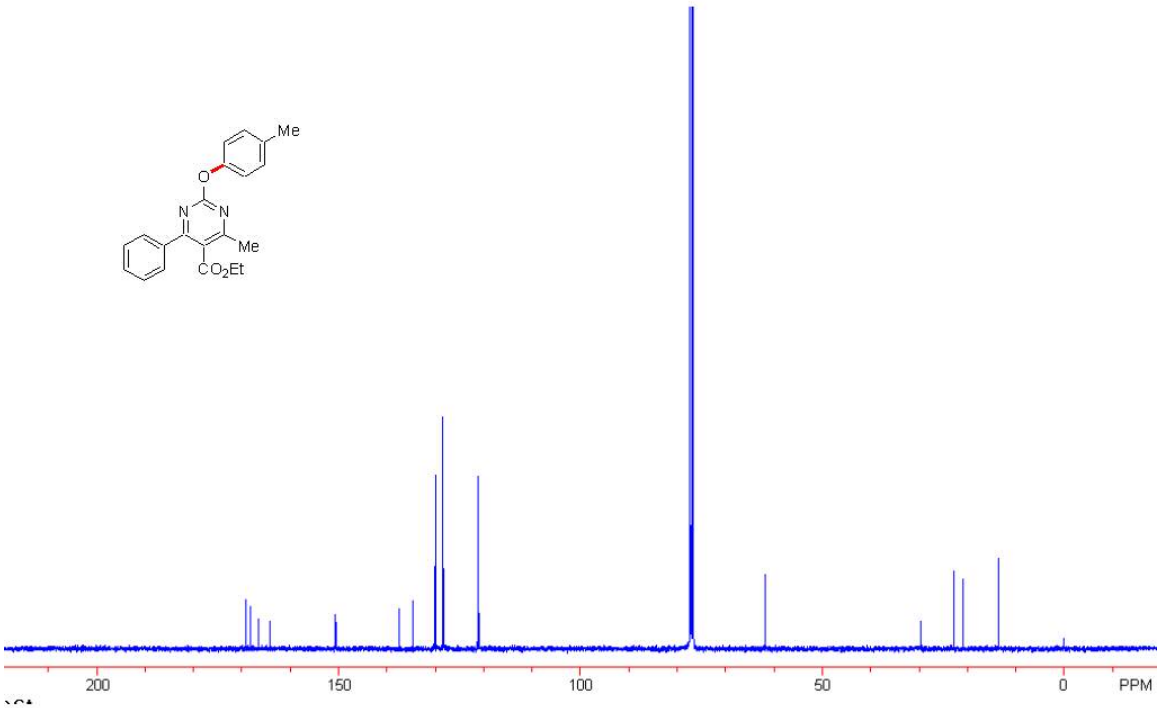
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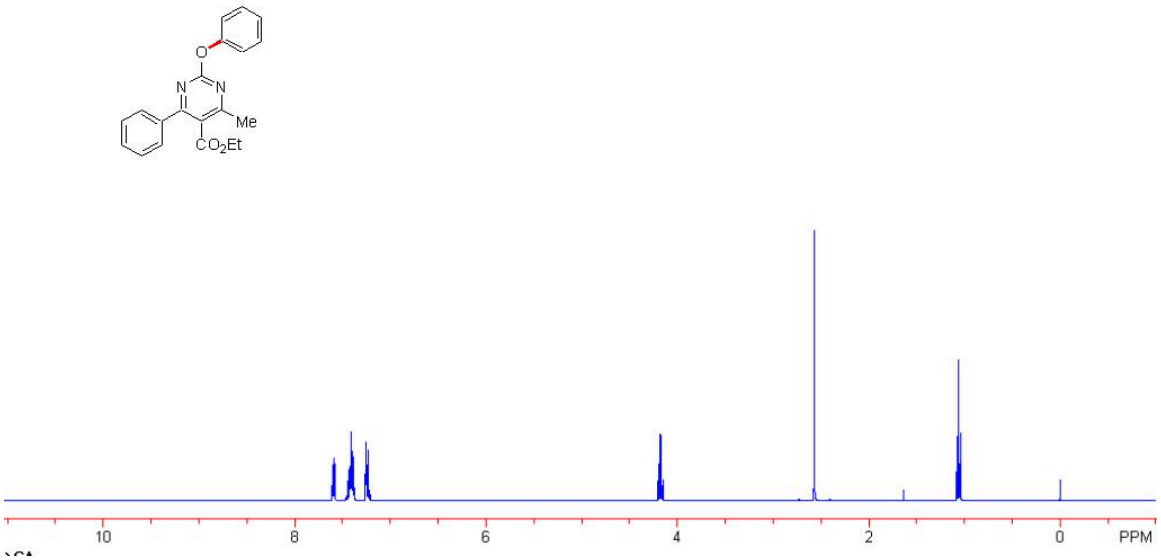
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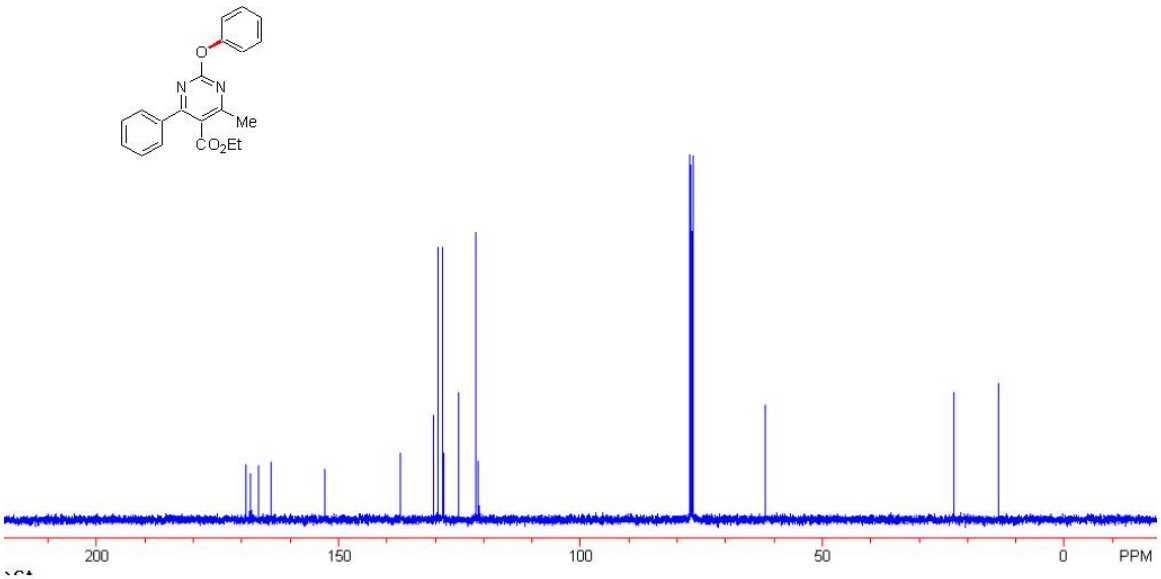
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