Electronic Supplementary Material (ESI) for Chemical Science.

Supporting Information

Radical Generation Enabled by Photoinduced N–O Bond Fragmentation

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Abstract: Recent advances in synthetic chemistry have seen a resurgence in the development of methods for visible light-mediated radical generation. Herein, we report the development of a photoactive ester based on the quinoline *N*-oxide core structure, that provides a strong oxidant in its excited state. The heteroaromatic *N*-oxide provides access to primary, secondary, and tertiary radical intermediates, and its application toward the development of a photochemical Minisci alkylation is reported.

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General Information

All chemicals were used as received unless otherwise noted. Reactions were monitored by TLC and visualized with a dual short wave/long wave UV lamp. Column flash chromatography was performed using 230-400 mesh silica gel or via automated column chromatography using Biotage Selekt or Biotage Isolera purification systems. Basic alumina was stored in an oven at 150° C until use. Preparative TLC purifications were run on silica plates of 1000 µm thickness. NMR spectra were recorded on Varian MR400, Varian Inova 500, Varian Vnmrs 600, Varian Vnmrs 500, or Varian Vnmrs 700 spectrometers. Chemical shifts for ^{1}H NMR were reported as δ, parts per million, relative to the signal of $CHCl_3$ at 7.26 ppm. Chemical shifts for ^{13}C NMR were reported as δ, parts per million, relative to the center line signal of the $CDCl_3$ triplet at 77.16 ppm. Chemical shifts for ^{19}F NMR were reported as δ, parts per million, relative to the signal of a trifluorotoluene internal standard at -63.72 ppm. The abbreviations s, br. s, d, dd, br. d, ddd, t, q, br. q, qi, m, and br. m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, quintet, multiplet and broad multiplet, respectively. IR spectra were recorded on a PerkinElmer Frontier FT-IR spectrometer with a universal ATR accessory. Mass Spectra were recorded with an Agilent 1290 Infinity II UPLC with a TOF 6230B Dual AJS Ion source, as well as at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPCL-MS with ESI high resolution mass spectrometer. Fluorescence measurements were performed with a Horiba Qunatamaster 8000 fluorimeter equipped with a Xe arc lamp. UV/VIS measurements were obtained on a Varian Cary-50 spectrophotometer. NMR reaction monitoring was carried out using an LED NMR ser-up that consisted of a Prizmatix High Power Microscope LED Head (430 nm), Prizmatix Low Noise Benchtop Mic-LED Current-Controller, and Prizmatix Fiber Coupling Adaptor. Irradiation of reactions was carried out using Kessil PR-160 lamps (390 nm, 427 nm, and 456 nm). Solvents were purified on a SciMatCo solvent purification system under a constant flow of argon prior to use.

Experimental Procedures

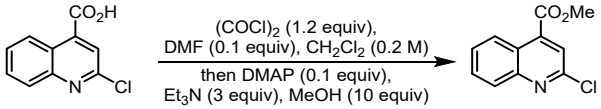
General Procedure A: Minisci Alkylation with PQCNO
To a flame dried 1-dram vial equipped with a magnetic stirbar was weighed substrate (0.2 mmol, 1 equiv), PQCNO (112 mg, 0.4 mmol, 2 equiv), acyl chloride (if solid) (0.44 mmol, 2.2 equiv) and calcium chloride (22.2 mg, 0.2 mmol, 1 equiv). The reaction vial was then sealed with a screw cap with a teflon lined septa top. The solids were evacuated and back filled with nitrogen 5 times. To the vial was then added 0.5 mL of MeCN, followed by acyl chloride (if liquid) (0.44 mmol, 2.2 equiv). The needle was removed from the septa cap and the cap sealed with a piece of electrical tape, followed by parafilm. The reaction mixture was then affixed to the stir plate by a piece of double-sided tape at a distance of 5-7 cm from the Kessil lamp. The reaction mixtures were irradiated for 30 mins at 100% power.

At the conclusion of the reaction, the reaction was taken up into 10 mL of saturated sodium bicarbonate. The aqueous mixture was extracted with 3 x 10 mL of DCM, the combined organic extracts were then washed with 1 x 10 mL of saturated sodium chloride and dried over sodium sulfate, filtered and concentrated *in vacou*. The crude organic material was purified by flash chromatography. Best results were obtained when running a column with 10-20% ethyl acetate in hexanes followed by a second column using 2-5% acetone in dichloromethane.

General Procedure B: Oxidation of Heteroaromatic *N*-oxides
To a round bottom flask equipped with a magnetic stir bar was added methyl 2-phenylquinoline-4-carboxylate (1 equiv). The solid was then taken up into DCM (0.2M) and the solution was cooled to 0 °C in an ice bath. To the cold solution was added *m*-CPBA in small batches over the course of 5 mins. The reaction was then sealed with a septa, transferred to a heating mantle and heated at 50 °C for 8-15 hours. [CAUTION!] The reaction builds up pressure during the heating process, the reaction should be removed from heat and vented prior to removing the septa. The cooled reaction mixture was then taken up into 50 mL of DCM and extracted 3 x 50 mL with saturated sodium bicarbonate. The combined aqueous layers were then extracted 3 times with 50 mL portions of DCM. The combined organic extracts were washed with 50 mL of saturated sodium chloride and dried over sodium sulfate. The combined organic layers were concentrated *in vacou* to give a crude golden oil. Heteroaromatic *N*-oxides were purified by flash chromatorgraphy on silica.

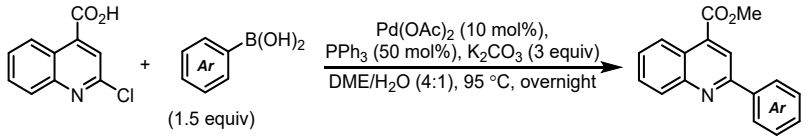
General Procedure C: Preparation of Acid Chlorides
To a flame dried 100 mL round bottom flask equipped with a stir bar was added carboxylic acid (1 equiv.), and DCM (0.2 M). The flask was then equipped with a septa and a vent needle. To this was added oxalyl chloride (1.1 equiv), followed by DMF (0.1 equiv, a few drops). At this point, the reaction mixture will begin to bubble vigorously. The reaction was allowed to stir at room temperature for 30 mins to 1 hour. At the conclusion of the reaction (when bubbling ceased), the crude reaction was concentrated *in vacou* to a small volume, and then run through a plug of basic alumina oxide (approx. 1 in L x 1 cm D). The organic layer was then concentrated *in vacou* and used without further purification. A crude ^{1}H NMR was acquired for each sample.

General Procedure D: Preparation of methyl 2-arylquinoline-4-carboxylate derivatives



To a flame dried 500 mL flask was weighed 10 g of 2-chloroquinoline-4-carboxylate (1 equiv). The solid was taken up into 250 mL of DCM and cooled in an ice bath. To the solution was added 5 mL of oxalyl chloride (1.2 equiv), followed by 200 μL of DMF. The reaction began to bubble vigorously. The reaction was removed from the ice bath and allowed to stir at room temperature until bubbling stopped (stirred for approximately 5 hours). At which point, the reaction was cooled in an ice bath and DMAP (0.1 equiv), methanol (10 equiv), and triethylamine (3 equiv) were added in order. The reaction formed a colorless cloud upon the addition of triethylamine. The reaction exothermed significantly and began to reflux the DCM solvent. Reaction was removed from the ice bath after ~1 hour, and then was allowed to stir overnight.

Reaction was concentrated to approximately half the volume, then washed with 2 x 100 mL water. The water was then back-extracted with 3 x 100 mL DCM. The combined organic layers were washed with sodium bicarbonate (3 x 100 mL), followed by brine (1 x 100 mL) and then dried over sodium sulfate. Pure product was obtained by column chromatography using 5% acetone in DCM as the mobile phase. Rf product ~0.75 in 5% acetone in DCM.

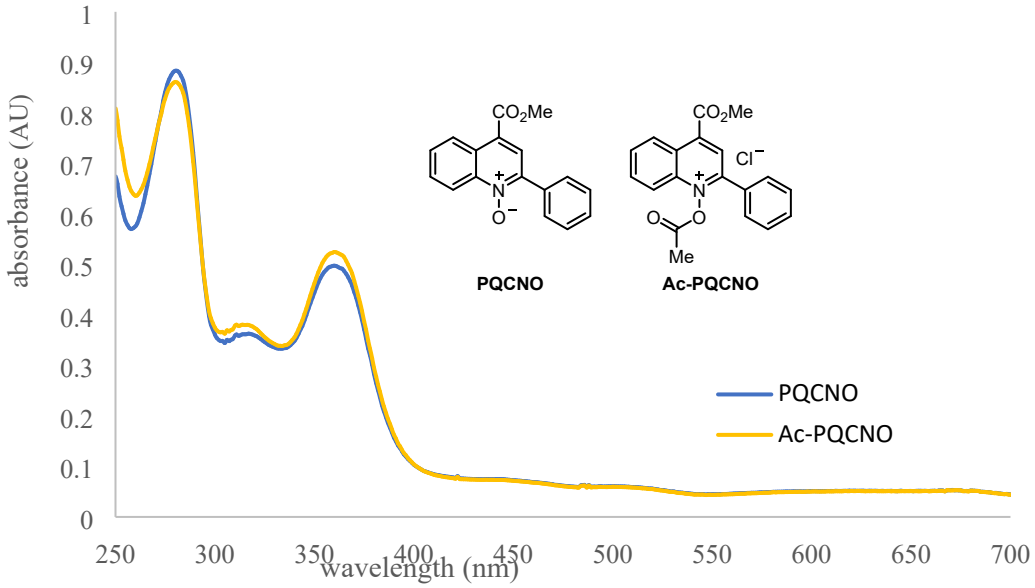


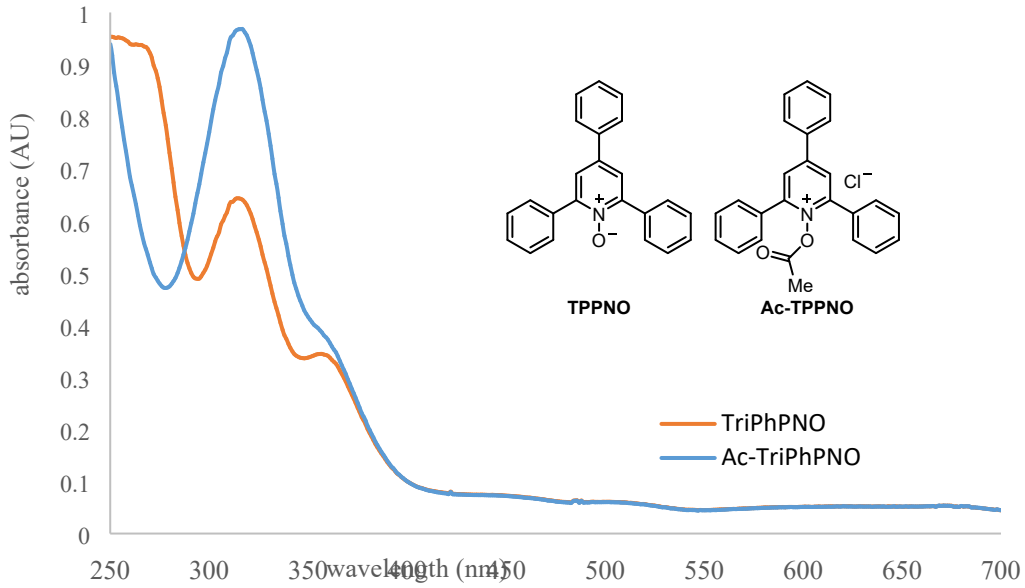
Reaction carried out according to: Qiao, K *et al. - Eur. J. Org. Chem.* **2016,** 1606–1611.[1]

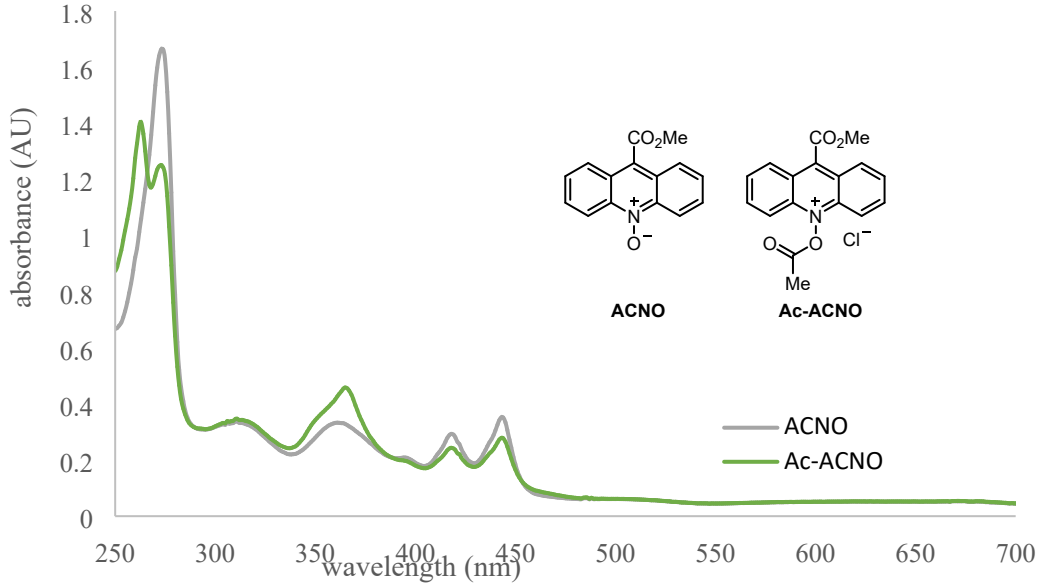
To a 100 mL sealed tube equipped with a Teflon lined stir bar and a Teflon cap was weighed methyl 2-chloroquinoline-4-carboxylate (1 equiv), boronic acid (1.5 equiv), potassium carbonate (3 equiv), palladium acetate (10 mol%), and triphenyl phosphine (50 mol%). To this was added DME, followed by water. The tube was sealed and placed into a pre-heated sand bath at 95 °C. The reaction was heated at 95 °C overnight. At the conclusion of the reaction period, the reaction was allowed to cool to rt, and then taken up into 30 mL of EtOAc. The reaction was extracted with 3 x 30 mL of EtOAc. The combined organic extracts were then washed with sodium bicarbonate, followed by saturated sodium chloride. The organic extracts were then dried over sodium sulfate. The crude reaction material was concentrated *in vacou*, and purified by column chromatography.

UV/Vis Analysis of Aromatic *N*-oxides

To a flame dried 1-dram vial was weighed heteroaromatic *N*-oxide (0.011 mmol), and this was taken up into 3 mL of MeCN. For measurements of acylated heteroaromatic *N*-oxides, acyl chloride (1.1 equiv) was added and the mixture was shaken vigorously, the solution was a clear and colorless. A 30 μM solution of heteroaromatic *N*-oxide was prepared by diluting 25 μL to a volume of 3 mL, and the mixture was shaken vigorously to ensure mixing. The final solution was then transferred to a quartz cuvette with a 1 cm path length. Measurements were taken using a Varian Cary-50 spectrophotometer. Data was exported as a .csv file and processed using Microsoft Excel.

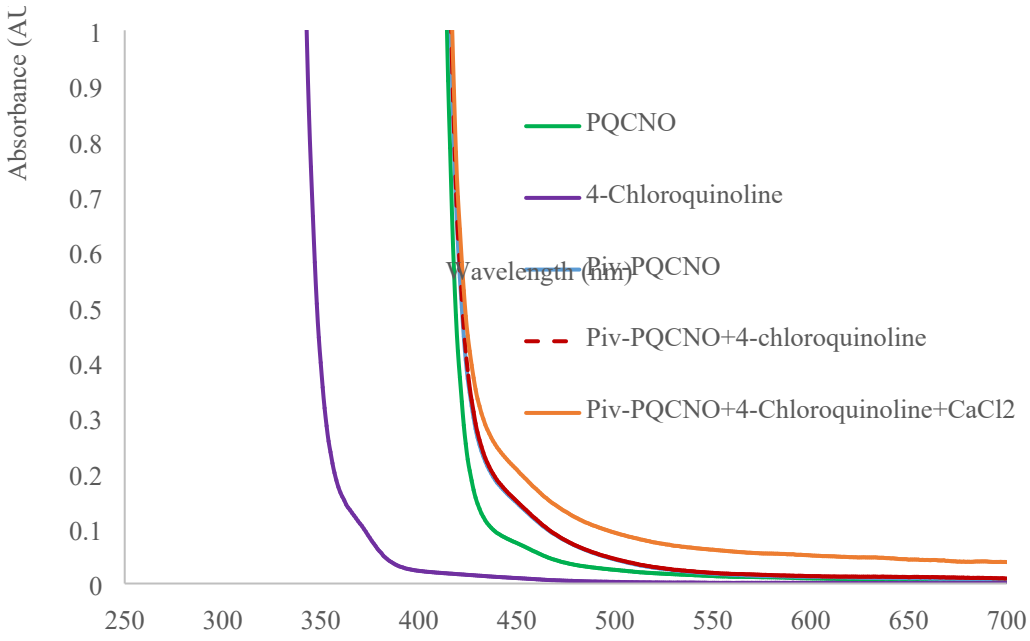






UV/Vis Analysis of Reaction Mixture

A 1 cm path length quartz cuvette was charged with PQCNO (0.200 mmol), 4-Chloroquonoline (0.200 mmol), and $CaCl_2$ (0.200 mmol) if applicable. The solid(s) were then dissolved in dry MeCN (3 mL) and sonicated for 30 seconds. Freshly distilled pivaloyl chloride (0.220 mmol) was then added via syringe if applicable. The mixture was shaken vigorously for 30 seconds before the absorbance was measured. Measurements were taken on a Varian Cary-50 spectrophotometer. Data was exported as a .csv file and processed using Microsoft excel.



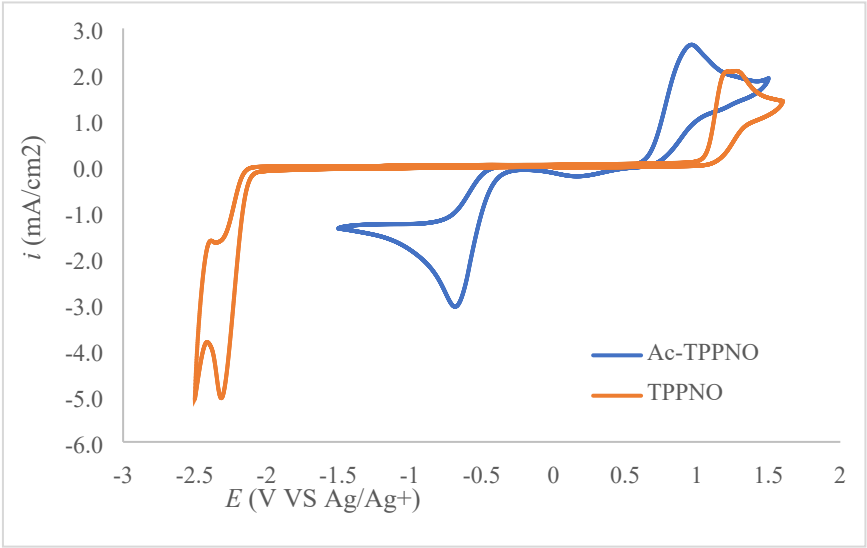
Cyclic Voltammetry of heteroaromatic *N*-oxides
Prior to cyclic voltammetry experiments, MeCN was sparged with an argon balloon for 15 mins.

To a flame dried 4-dram vial was weighed 1.2 mmol (930 mg) of tetra-butylammonium hexafluorophosphate (Bu_4NPF_6), and this was taken up in to 12 mL of dry, sparged MeCN. This solution was then used to prepare the heteroaromatic *N*-oxide samples for CV experiments.

To a flame dried 1-dram vial was weighed heteroaromatic *N*-oxide (0.3 mmol). The solid was then dissolved in 3 mL of the Bu_4NPF_6/MeCN electrolyte solution. The solution was transferred to 4-neck e-chem cell (pictured below) and equipped with a working (glassy carbon), counter (platinum), and reference (0.1 M $Ag/AgNO_3$) electrodes. The solution was sparged with nitrogen for 5 mins, then a CV experiment was run and data collected. Following collection of data for the free heteroaromatic *N*-oxide, 4.3 μL of acetyl chloride was added to the solution, and the solution was sparged for an additional 5 mins. A CV experiment was then run and data collected. Data was processed and plotted in Microsoft excel. Raw current was converted to current density.

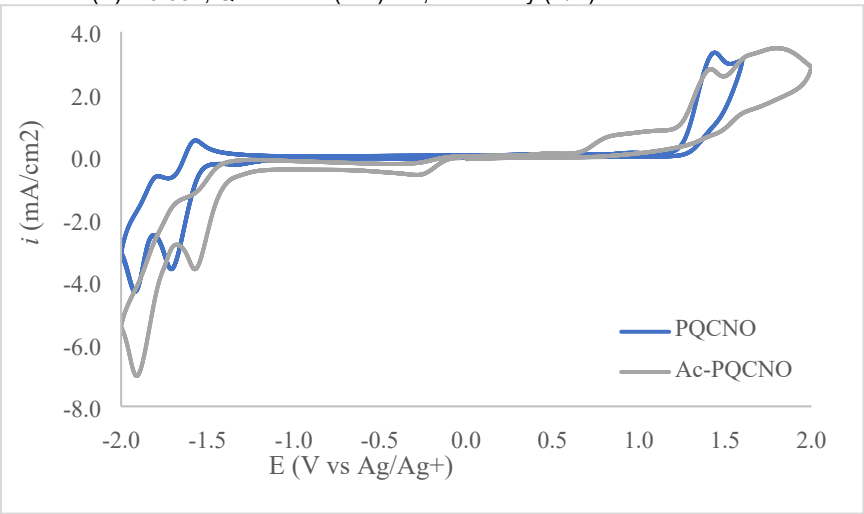
2,4,6-triphenylpyridine *N*-oxide (TPPNO)
Experimental parameters for TPPNO: Init E (V) = 0; High E (V) = 1.6; Low E (V) = -2.5; Final E (V) = 0; Init P/N = N; Scan; Rate (V/s) = 0.1; Segment = 3; Sample Interval (V) = 0.001; Quiet Time (sec) = 2; Sensitivity (A/V) = 1e-4

Experimental parameters for Ac-TPPNO: Init E (V) = 0; High E (V) = 1.5; Low E (V) = -1.5; Final E (V) = 0; Init P/N = P; Scan Rate (V/s) = 0.1; Segment = 3; Sample Interval (V) = 0.001; Quiet Time (sec) = 2; Sensitivity (A/V) = 1e-4



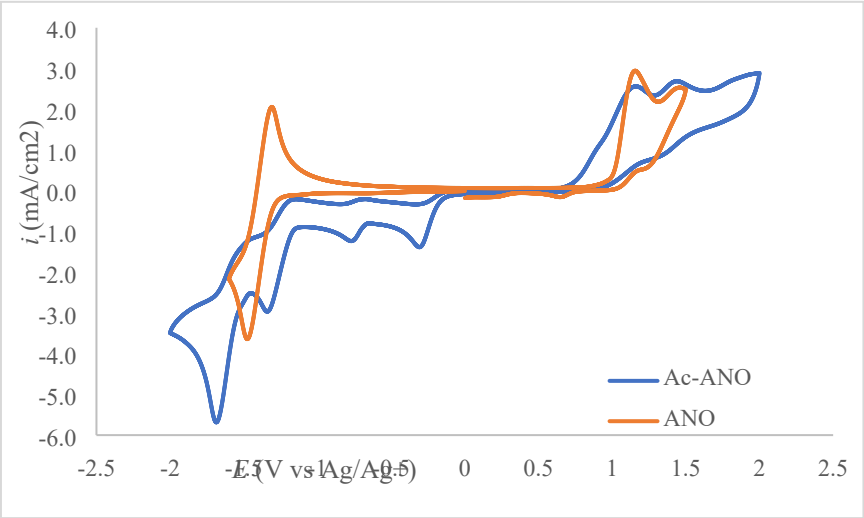
Methyl 2-phenylquinoline-4-carboxylate *N*-oxide (PQCNO)
Experimental parameters for PQCNO: Init E (V) = 0; High E (V) = 1.6; Low E (V) = -2; Init P/N = N; Scan Rate (V/s) = 0.1; Segment = 3; Sample Interval (V) = 0.001; Quiet Time (sec) = 2; Sensitivity (A/V) = 1e-4

Experimental parameters for Ac-PQCNO: Init E (V) = 0; High E (V) = 2; Low E (V) = -2; Final E (V) = 0; Init P/N = N; Scan Rate (V/s) = 0.1; Segment = 3; Sample Interval (V) = 0.001; Quiet Time (sec) = 2; Sensitivity (A/V) = 1e-4



Methyl acridine-9-carboxylate *N*-oxide (ACNO)
Experimental parameters for ACNO: Init E (V) = 0; High E (V) = 1.5; Low E (V) = -1.6; Final E (V) = 0; Init P/N = N; Scan Rate (V/s) = 0.1; Segment = 3; Sample Interval (V) = 0.001; Quiet Time (sec) = 2; Sensitivity (A/V) = 1e-4

Experimental parameters for Ac-ACNO: Init E (V) = 0; High E (V) = 2; Low E (V) = -2; Final E (V) = 0; Init P/N = P; Scan Rate (V/s) = 0.1; Segment = 3; Sample Interval (V) = 0.001; Quiet Time (sec) = 2; Sensitivity (A/V) = 1e-4

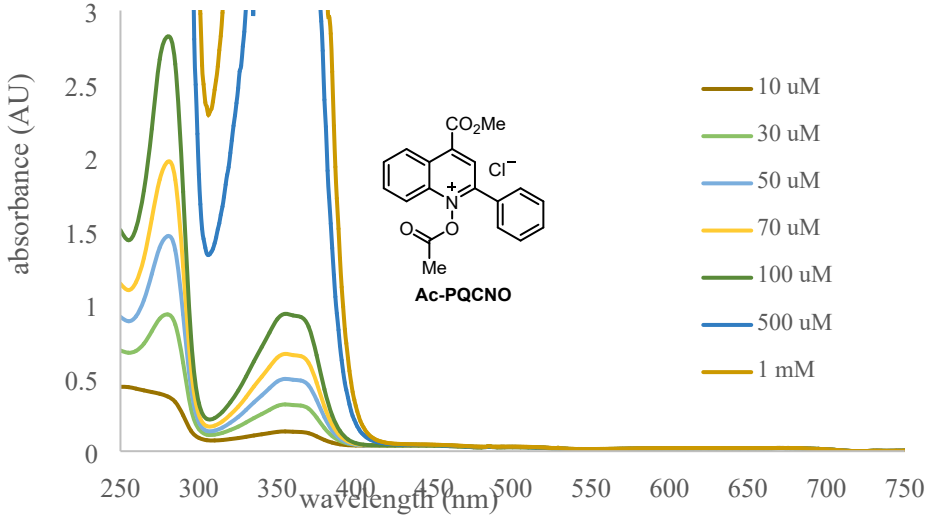


Determination of Molar Absorptivity of Ac-PQCNO
To a flame dried 1-dram vial was weighed heteroaromatic *N*-oxide (3 mg, 0.011 mmol), and this was taken up into 3 mL of MeCN. For measurements of acylated heteroaromatic *N*-oxides, acyl chloride (2 µL) was added and the mixture was shaken vigorously, the solution was a clear and colorless. Solutions of heteroaromatic *N*-oxide were prepared by diluting the stock solution to a volume of 3 mL, and the mixture was shaken vigorously to ensure mixing. The final solution was then transferred to a quartz cuvette with a 1 cm path length. Measurement were taken using a Varian Cary-50 spectrophotometer. Data was exported as a .csv file and processed using Microsoft Excel.

The molar absorptivity of Ac-PQCNO was determined by UV/vis spectroscopy. Measurements were taken at 10 µM, 30 µM, 50 µM, 70 µM, 100 µM, 500 µM, 1 mM, 10 mM, and 100 mM.

The following solutions were prepared by diluting the stock solution to a final volume of 3 mL.
10 µM - 8 µL of the stock solution was diluted to 3 mL

30 µM - 25 µL of the stock solution was diluted to 3 mL
50 µM - 42 µL of the stock solution was diluted to 3 mL
70 µM - 58 µL of the stock solution was diluted to 3 mL
100 µM - 83 µL of the stock solution was diluted to 3 mL
500 µM – 417 µL of the stock solution was diluted to 3 mL
1 mM – 833 µL of the stock solution was diluted to 3 mL

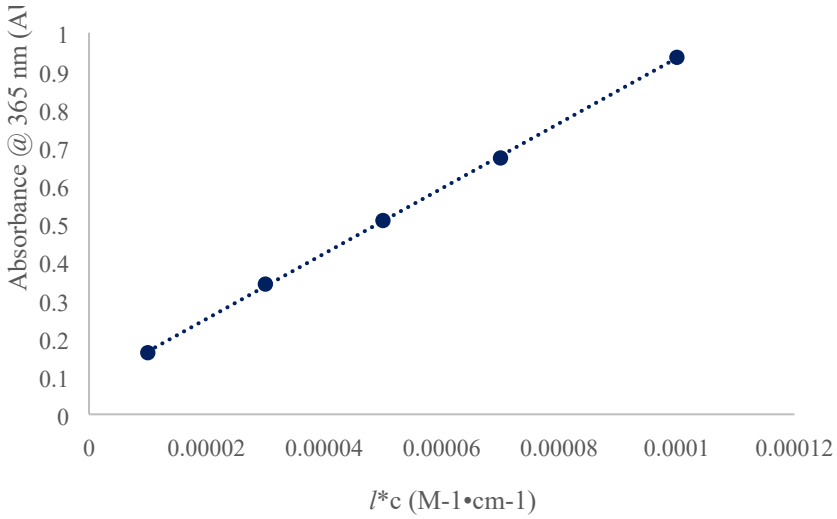


The molar absorptivity of the electronic transition at 365 nm was determined according to Beer's law:

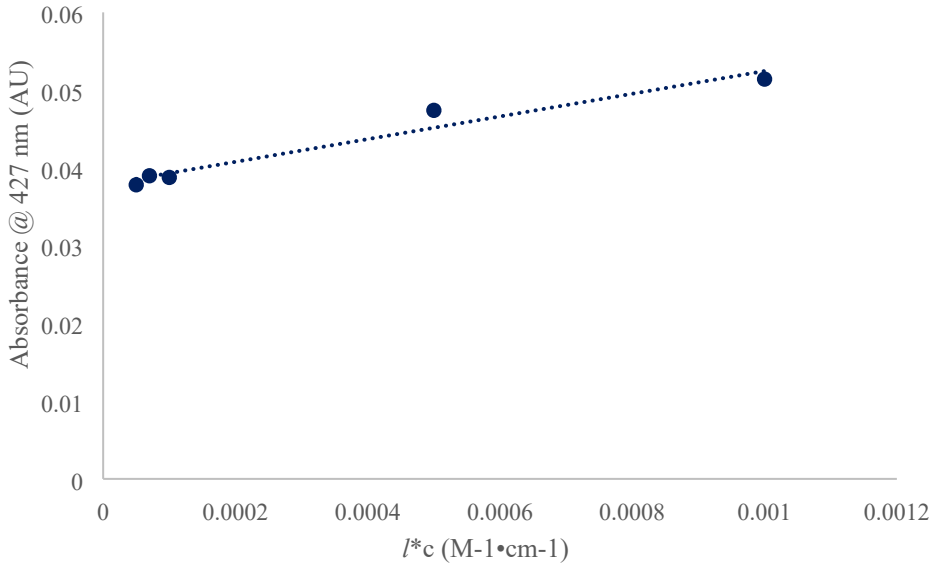
$$Beer's\ Law: A = \varepsilon lc$$

Where A = absorbance; ε = molar absorptivity; *l* = path length (1 cm); c = concentration. Plotting the absorbance vs concentration(c)•path length (*l*) gives a line with a slope that equals the molar absorptivity of the electronic transition. ($\varepsilon = \frac{A}{l \bullet c}$)

Molar absorptivity of Ac-PQCNO at 365 nm was determined to be 8,543 $M^{-1}cm^{-1}$



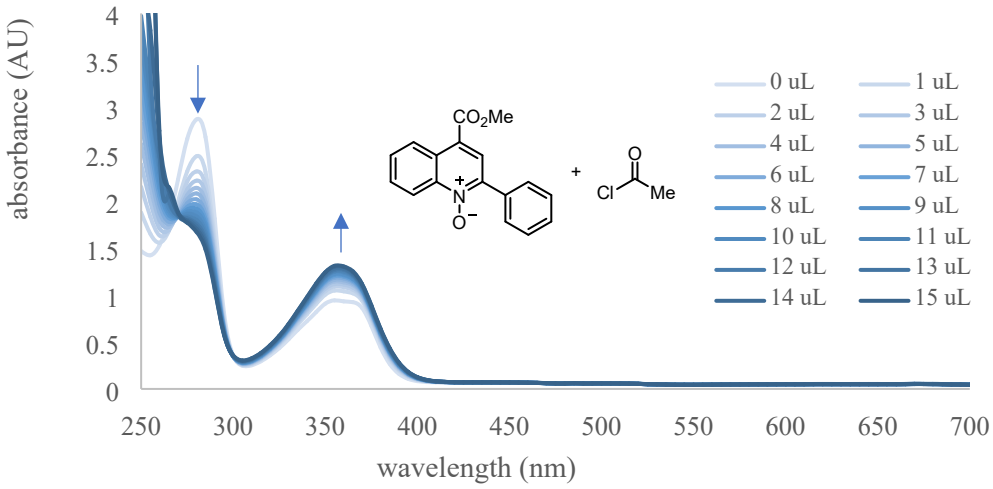
By this method, the molar absorptivity at 427 nm was determined to be 14 M^{-1} cm^{-1}.



UV/Vis Titration of PQCNO with Acetyl Chloride

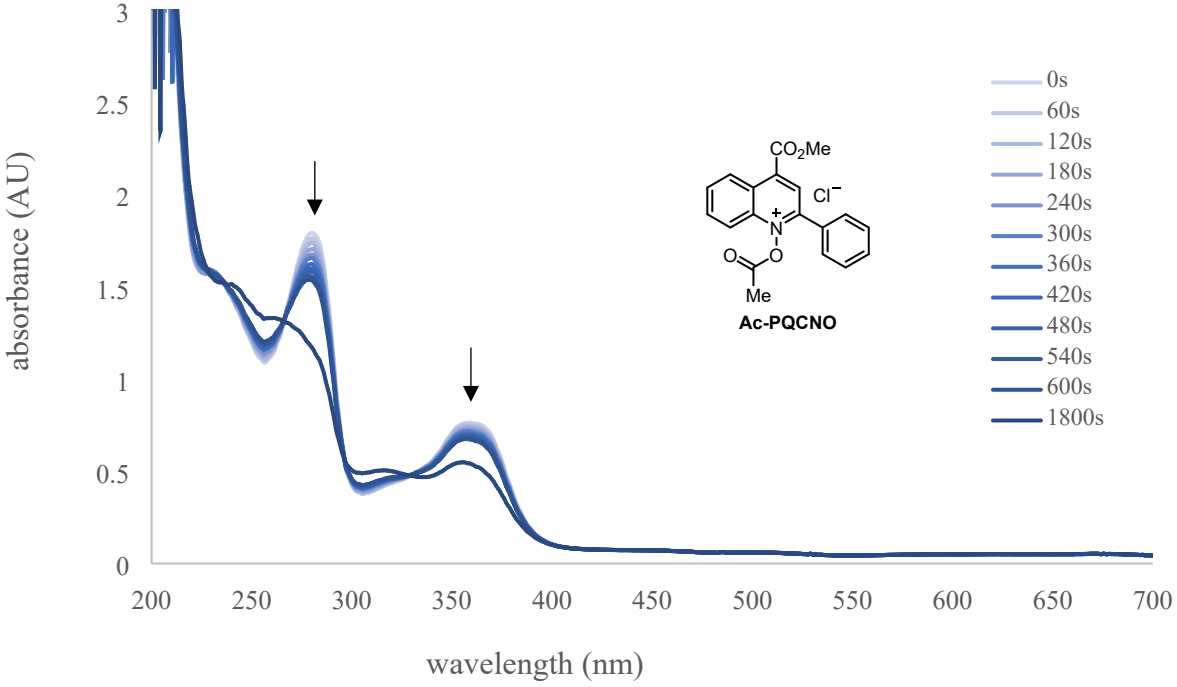
To a flame dried 1-dram vial was weighed heteroaromatic *N*-oxide (3 mg, 0.011 mmol), and this was taken up into 3 mL of MeCN. A 30 μM solution of PQCNO was prepared by diluting 25 μL to a volume of 3 mL, and the mixture was shaken vigorously to ensure mixing. The final solution was then transferred to a quartz cuvette with a 1 cm path length. Measurements were taken using a Varian Cary-50 spectrophotometer. Data was exported as a .csv file and processed using Microsoft Excel.

For measurements, 1 μL of acetyl chloride was added to the *N*-oxide sample, and the sample was shaken 5 times to ensure mixing. A UV/vis of the sample was then obtained. This process was repeated for additions of 1-15 μL of acetyl chloride.



UV/Vis Monitoring of Photochemical Decomposition of Ac-PQCNO

To a flame dried 1-dram vial was weighed PQCNO (3 mg, 0.011 mmol), and this was taken up into 3 mL of MeCN. For measurements of acylated PQCNO, acyl chloride (1.1 equiv) was added and the mixture was shaken vigorously, the solution was a clear and colorless. A 100 μM solution of PQCNO was prepared by diluting 83 μL to a volume of 3 mL, and the mixture was shaken vigorously to ensure mixing. The final solution was then transferred to a quartz cuvette with a 1 cm path length. UV/vis of the AcPQCNO material was obtained, then the sample was irradiated with a 427 nm Kessil lamp from 5 cm for 60 s, and a second UV/vis was obtained. This process was repeated for 10 times. The sample was then irradiated for 20 additional minutes, and a final UV/vis measurement was obtained. Measurement were taken using a Varian Cary-50 spectrophotometer. Data was exported as a .csv file and processed using Microsoft Excel.



Discussion – The above experiment supports the hypothesis that the decomposition of Ac-PQCNO species is a photo-induced reaction, as degradation could be observed by UV/vis after as little as 60s of irradiation from a 427 nm Kessil lamp. In the design of this study, we sought to observe PQCN derived fragmentation products with unique electronic structures (such as radical cation intermediates), however, no such products were observed.

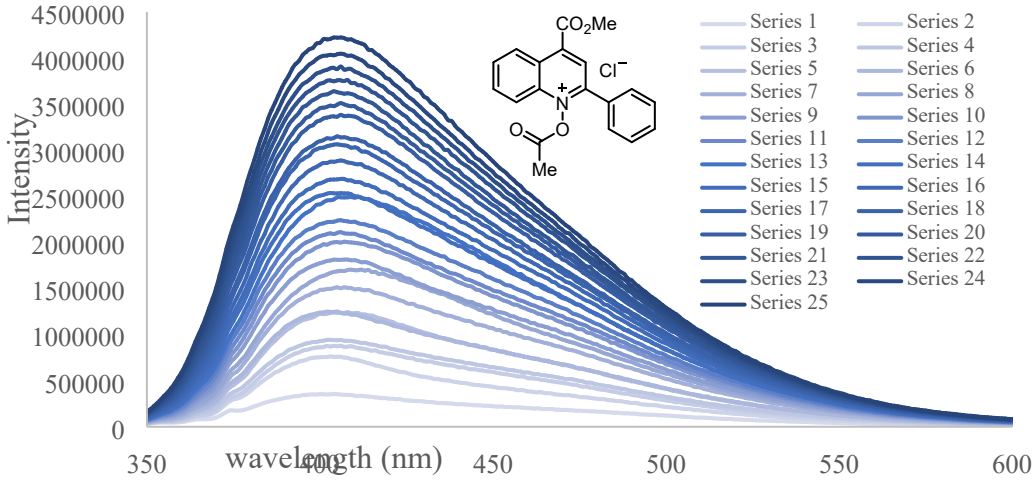
Fluorescence Spectroscopy

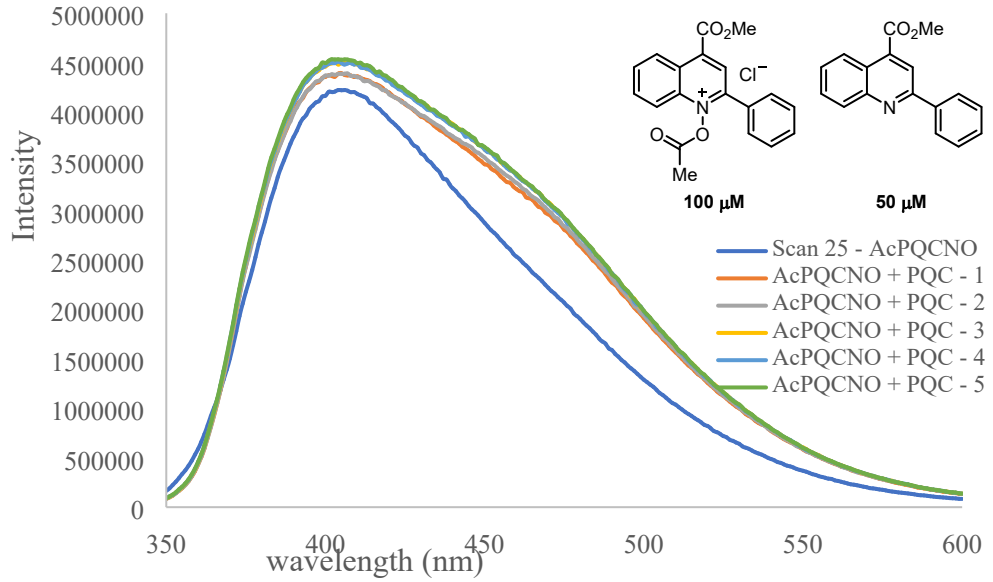
To a flame dried 1-dram vial was weighed heteroaromatic *N*-oxide, and this was taken up into 3 mL of sparged MeCN. A 100 μM solution of heteroaromatic *N*-oxide was prepared by diluting 83 μL to a volume of 3 mL, and the mixture was shaken vigorously to ensure mixing. The final solution was then transferred to a quartz cuvette with a 1 cm path length. For measurements of acylated heteroaromatic *N*-oxides, acyl chloride (1.1 equiv) was added to the cuvette and the mixture was shaken vigorously, the solution remained clear and colorless. Measurement were taken using a Horiba Quantamaster 8000 Fluorimeter. Data was exported as a .csv file and processed using Microsoft Excel.

Decomposition of PQCNO Monitored by Fluorescence Spectroscopy

To a flame dried 1-dram vial was weighed PQCNO (3 mg, 0.011 mmol), and this was taken up into 3 mL of sparged MeCN. Acetyl chloride (1.1 equiv) was added, and the mixture was shaken vigorously, the solution was a clear and colorless. A 100 μM solution of Ac-PQCNO was prepared by diluting 83 μL to a volume of 3 mL, and the mixture was inverted 15 times to ensure mixing. The final solution was then transferred to a quartz cuvette with a 1 cm path length. Fluorescence measurements were carried out in the dark. A fluorescence experiment was run, shaken with a gentle wrist flick 5 times and returned to the sample holder and a subsequent fluorescence measurement was taken. This was process was repeated 25 times. After the 25th experiment, 39 μL of a 0.0038 M (0.15 μmol, 0.5 equiv with respect to PQCNO) solution of methyl 2-phenylquinoline-4-carboxylate was added to the fluorescence sample, and the cuvette was vigorously shaken to ensure mixing. Five more fluorescence measurements were carried out.

Measurement were taken using a Horiba Quantamaster 8000 Fluorimeter. Data was exported as a .csv file and processed using Microsoft Excel. Excitation beam was set to 335 nm to minimize spectral distortions from Raman scattering of the acetonitrile solvent. Excitation 335 nm, slit width 3 nm. Emission was scanned from 350 nm to 500 nm, slit width of 5 nm.

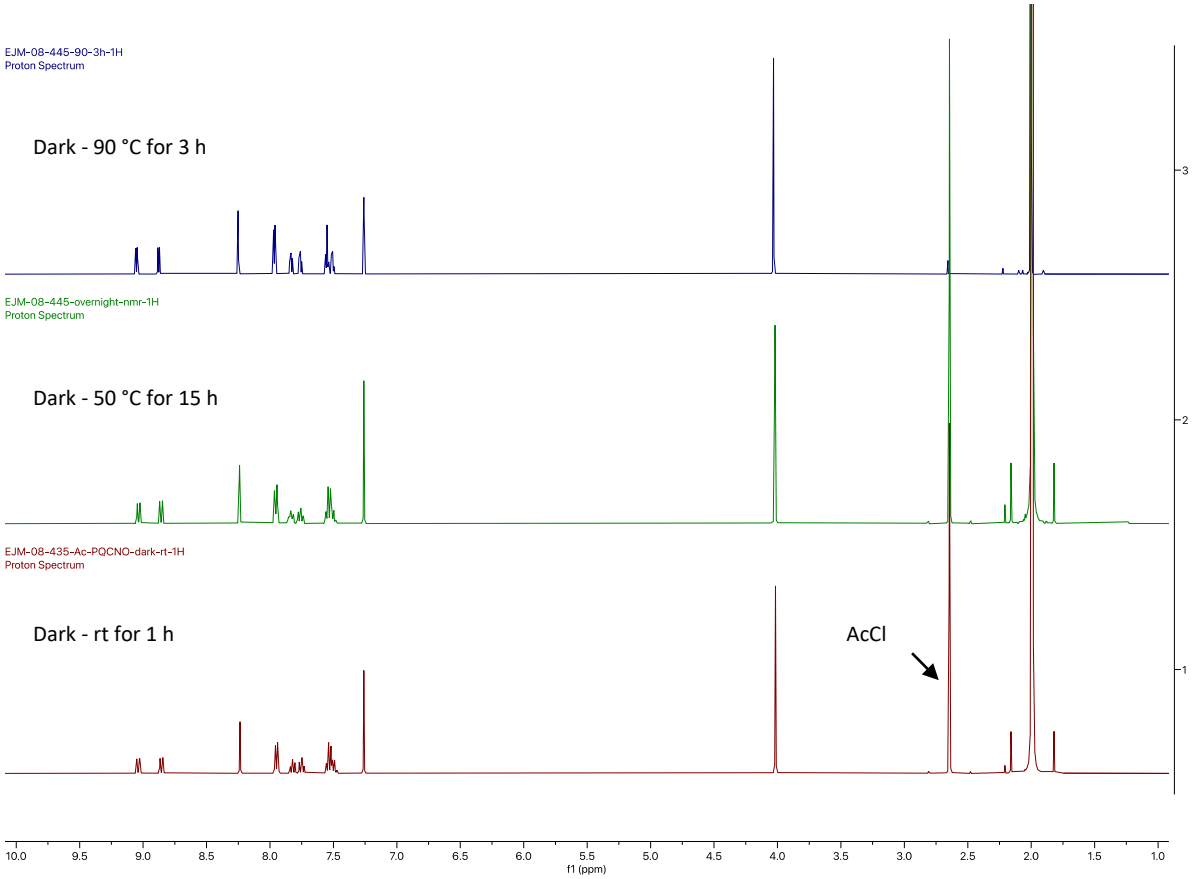




Discussion –Ac-PQCNO is observed to have an increase in fluorescence upon successive fluorescence experiments with an excitation at 335 nm. Addition of free quinoline (PQCN), which is the primary fragmentation product, to the sample results in an increase in the fluorescence maximum, with no change to the wavelength of maximum fluorescence. Together, this data supports the hypothesis that excitation of Ac-PQCNO results in a fast N–O bond homolysis, leading to decarboxylation and liberating an equivalent of PQCN. As successive fluorescence measurements are taken, PQCN builds up and becomes the primary fluorophore. Because fluorescence is the primary process that occurs upon excitation of the PQCN, it washes out fluorescence due to Ac-PQCNO. Additionally, the weak initial fluorescence that is attributed to Ac-PQCNO demonstrates that there is an excited state reaction pathway that competes with fluorescence upon excitation.

Investigation of Thermal Reactivity

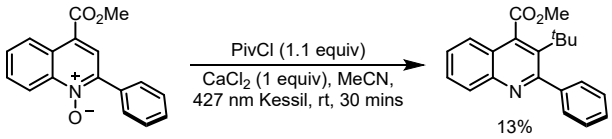
To a flame dried vial equipped with a stir bar was weighed 112 mg (1 equiv) PQCNO, and 22.2 mg (1 equiv) calcium chloride. The vial was capped with a septa cap, and the solids were evacuated and backfilled 5 times with nitrogen. 0.5 mL of acetonitrile followed by 35 μL of acetyl chloride were added and the vial was sealed under nitrogen with electrical tape and parafilm. The vial was then wrapped with aluminum foil and placed in the center of a stir plate. Aliquots of the reaction were taken after stirring for 1 h at room temperature, 50 °C for 15 hours, and 90 °C for 3 hours. No reactivity was observed, however, at elevated temperatures acetyl chloride was boiled off of the reaction solution.



Discussion – The above experiment demonstrates the thermal stability of PQCNO and Ac-PQCNO, as no thermal reactivity was observed upon heating the sample to 90 °C for 3 hours. Because the temperature and time far exceed that of the standard reaction (35-45 °C, 30 min to 1 h), we believe that this result demonstrates the observed decomposition of Ac-PQCNO is due to photochemical reactivity.

Investigation of PQCN Alkylation

A reaction was carried out according to **General Procedure A** in the absence of a substrate. The non-volatile organic products of the reaction were assessed. Methyl 3-(*tert*-butyl)-2-phenylquinoline-4-carboxylate was isolated as a minor product in 13% yield. No other functionalization products of PQCN were observed.



Discussion – The results of this reaction demonstrate that in the absence of substrates, alkylation of PQCN is still very slow and only occurs to a minor extent.

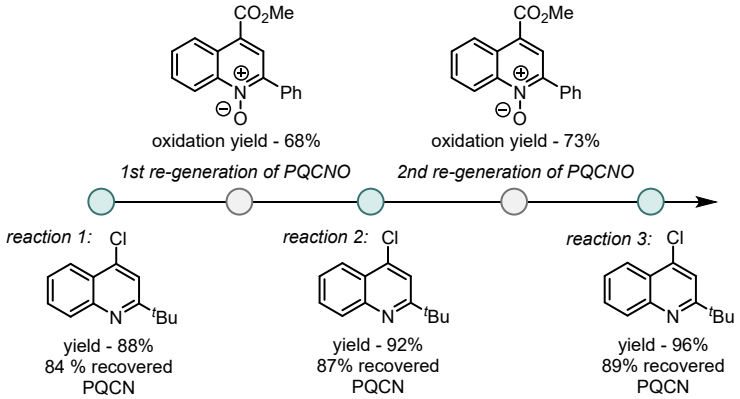
Recycling of PQCNO

To demonstrate the utility of PQCNO photo-active ester, a recycling experiment was performed in which the parent quinoline (PQCN) following the Minisci alkylation was recovered, re-oxidized to regenerate PQCNO, and re-subjected to Minisci alkylation reaction conditions. This process was carried for 3 consecutive Minisci alkylation reactions. Each of the Minisci alkylation reactions were carried out according to **General Procedure A** with the only alteration being to the scale of the reaction. Oxidation reactions were carried out according to **General Procedure B**.

1st Minisci alkylation was carried out on 1 mmol scale, reaction was run for 30 mins. 2-(*tert*-butyl)-4-chloroquinoline was isolated in 88% yield. 84% of deoxygenated PQCN was recovered.

2nd Minisci alkylation was carried out on 0.5 mmol scale, reaction was run for 30 mins. 2-(*tert*-butyl)-4-chloroquinoline was isolated in 92% yield. 87% of deoxygenated PQCN was recovered.

3rd Minisci alkylation was carried out on 0.29 mmol scale, reaction was run for 30 mins. 2-(*tert*-butyl)-4-chloroquinoline was isolated in 96% yield. 89% of deoxygenated PQCN was recovered.

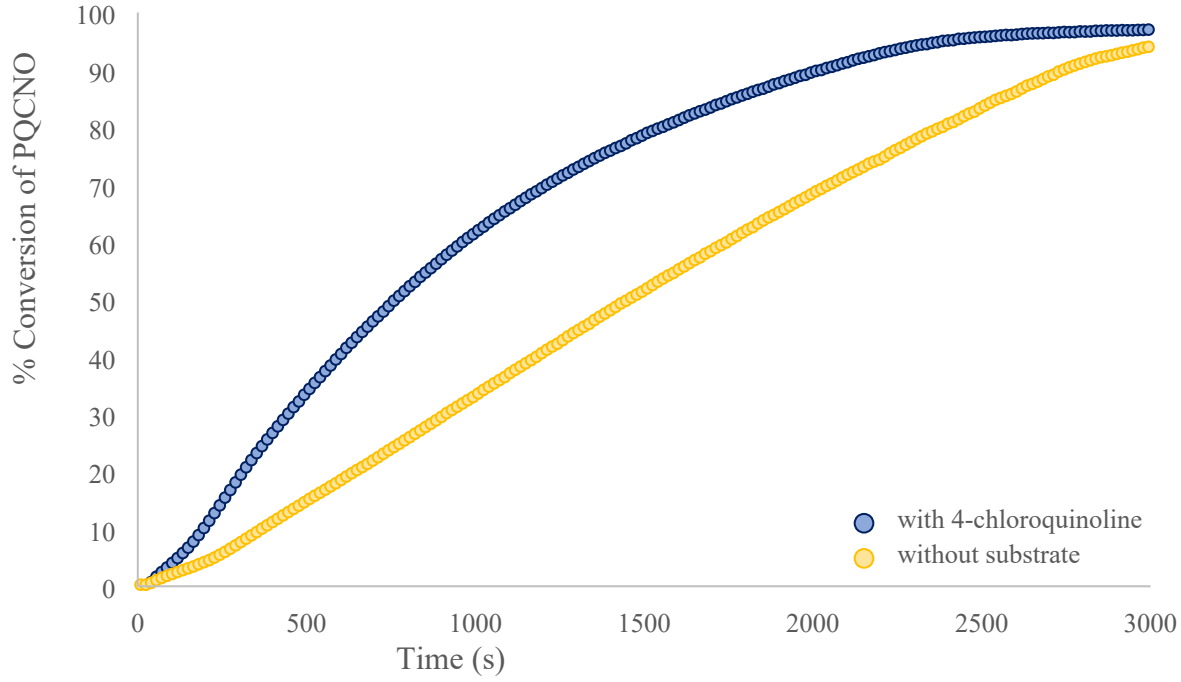


Discussion – These experiments demonstrate the potential applicability of PQCNO derived photo-active esters towards large scale synthesis. Importantly, our findings demonstrate that the deoxygenated quinoline material (PQCN) can be recovered and PQCNO regenerated in high yields with no loss of efficiency under Minisci alkylation conditions.

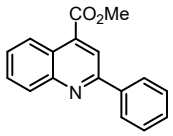
LED NMR Reaction Monitoring

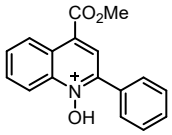
To a flame dried vial equipped with a stir bar was weighed out PQCNO (56 mg, 0.2 mmol, 1 equiv) and 4-chloroquinoline (16.4 mg, 0.1 mmol, 0.5 equiv). The vial was capped with a septa cap, and the solids were evacuated and backfilled 5 times with nitrogen. The mixture of solids was then taken up into 0.5 mL of MeCN, and 27 μL of PivCl followed by the addition of 16 μL of TFA. The reaction mixture was then sealed under nitrogen atmosphere with electrical tape and parafilm, and allowed to stir for 10 to 15 mins, or until the PQCNO had completely dissolved. A thin walled NMR tube that was purged with argon for 15 mins, at which point, the reaction solution was transferred to the NMR tube via a 1 mL syringe. The co-axial insert was added immediately, and the NMR tube was sealed with parafilm. The fiber optic cable was inserted to the co-axial insert and secured with a small piece of electrical tape prior to the NMR experiment. The NMR sample was inserted and at least one experiment was collected prior to starting irradiation with a 430 nm LED light source. Data was processed in MestraNova using the reaction monitoring plugin, the methyl ester signal corresponding to PQCNO and deoxygenated PQCNO was monitored to assess the conversion. In the presence of TFA, two equilibria states of PQCNO exist (free PQCNO and $PQCNOH^+$), the two integrals were summed to give an integration that was assumed to equal 100%. Data was plotted in Microsoft Excel.

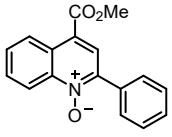
NMR parameters: Relaxation delay of 0.5 s, 45 ° pulse angle, acquisition time of 2.83 s, 2 steady state scans prior to each experiment, 4 scans per experiment, for a total of 16.98 s per experiment (.fid file). 200 experiments were collected for a total time of 57 mins.

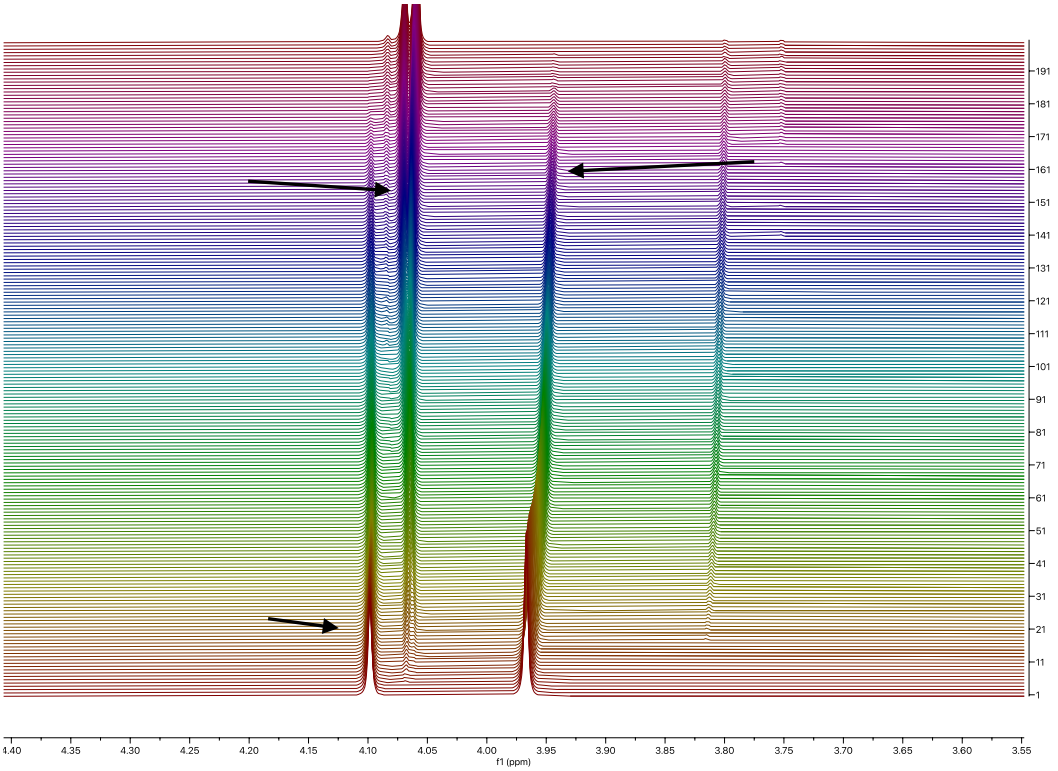


In the absence of 4-chloroquinoline

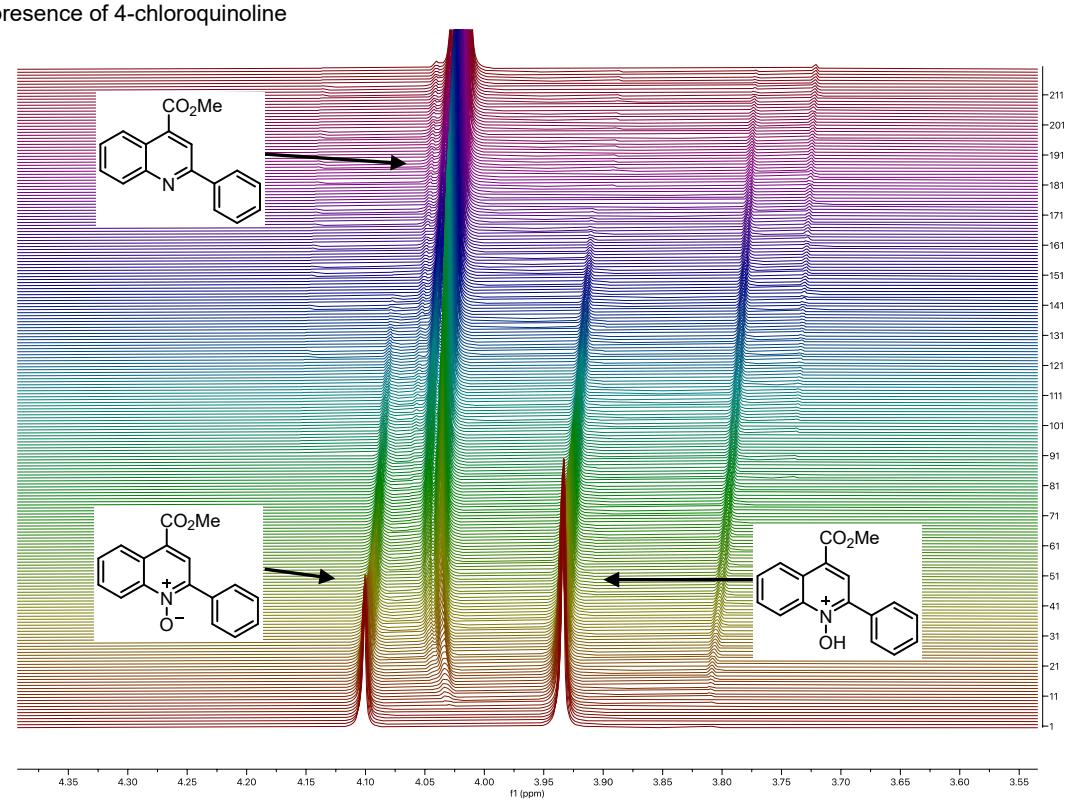








In the presence of 4-chloroquinoline



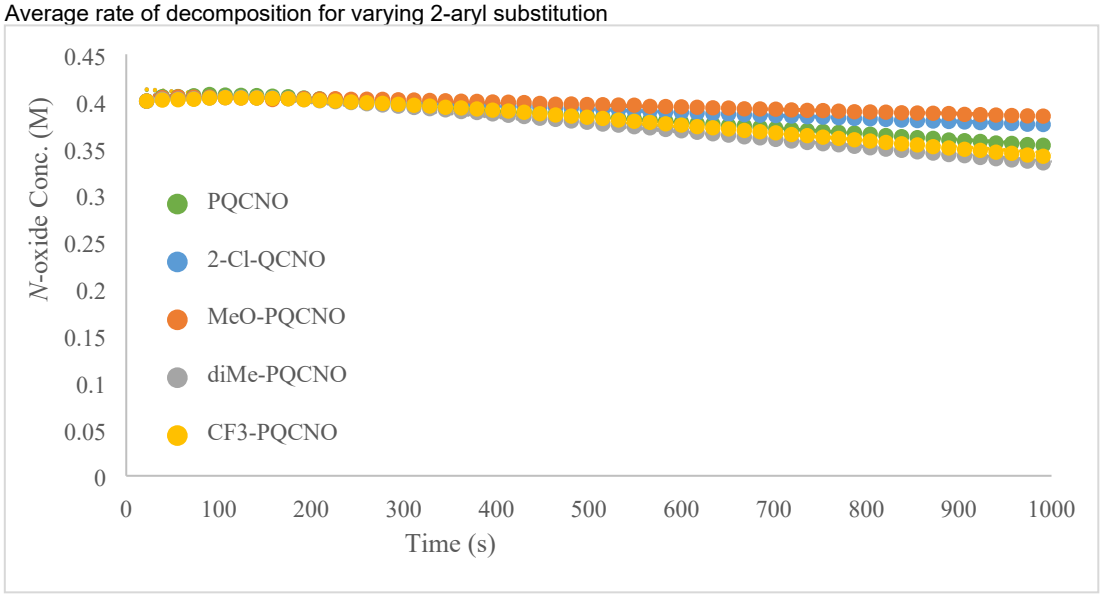
Discussion – The results of this experiment show that there is a change in the overall kinetics of the deoxygenation reaction in the presence/absence of a substrate. We believe that the observed change in the kinetic profile of the reaction is due to a background electron transfer from the substrate following radical addition to an equivalent of Piv-PQCNO, resulting in propagation of the reaction.

LED NMR Studies on Effect of 2-Aryl Substitution on Rate of Fragmentation

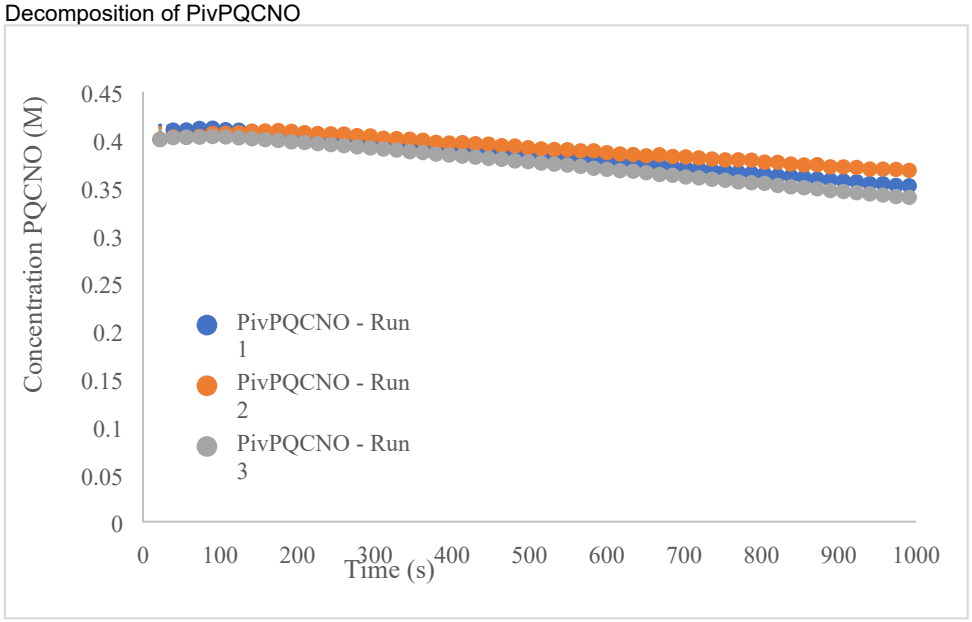
To a flame dried vial equipped with a stir bar was weighed out PQCNO (or derivative) (0.2 mmol, 1 equiv). The vial was capped with a septa cap, and the solids were evacuated and backfilled 5 times with nitrogen. The mixture of solids was then taken up into 0.5 mL of MeCN, and 27 μL of PivCl followed by the addition of 15 μL of TFA and 14 μL of dibromomethane internal standard. The reaction mixture was allowed to stir for 10 to 15 mins under an active stream of nitrogen, or until the PQCNO (or derivative) had completely dissolved. A thin-walled NMR tube was purged with a stream of nitrogen for 5 mins, at which point, the reaction solution was transferred to the NMR tube via a 1 mL syringe. The co-axial insert was added immediately, and the NMR tube was sealed with parafilm. The fiber optic cable was inserted to the co-axial insert and secured with a small piece of electrical tape prior to the NMR experiment. The NMR sample was inserted and the NMR array began data collection, 60 s was allowed to pass before turning on the 430 nm LED light source. Data was processed in MestraNova using the data analysis feature, the methyl ester signal corresponding to PQCNO (or derivative) and deoxygenated PQCNO (or derivative) was monitored to assess the conversion. Data was plotted in Microsoft Excel.

NMR parameters: Relaxation delay of 5 s, 45 ° pulse angle, acquisition time of 3.50 s, 2 steady state scans prior to each experiment, 2 scans per experiment, for a total of 17.28 s per experiment (.fid file). 60 experiments were collected for a total time of 17 mins 17 s.

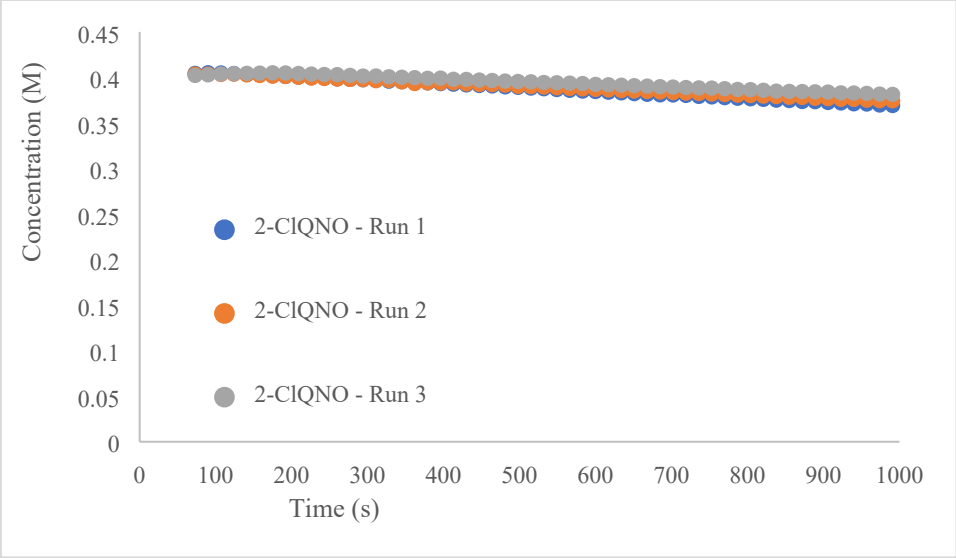
Average rate of decomposition for varying 2-aryl substitution



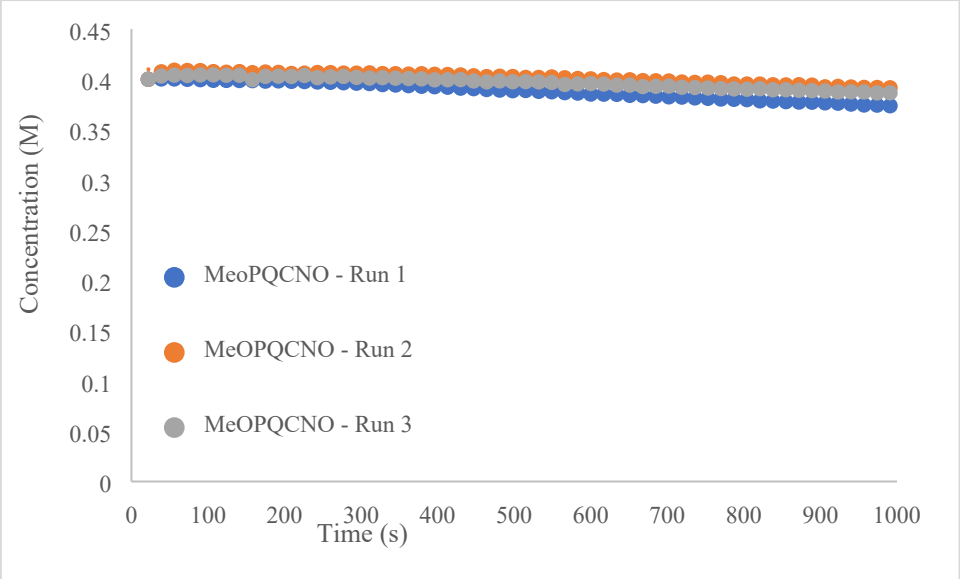
Decomposition of PivPQCNO



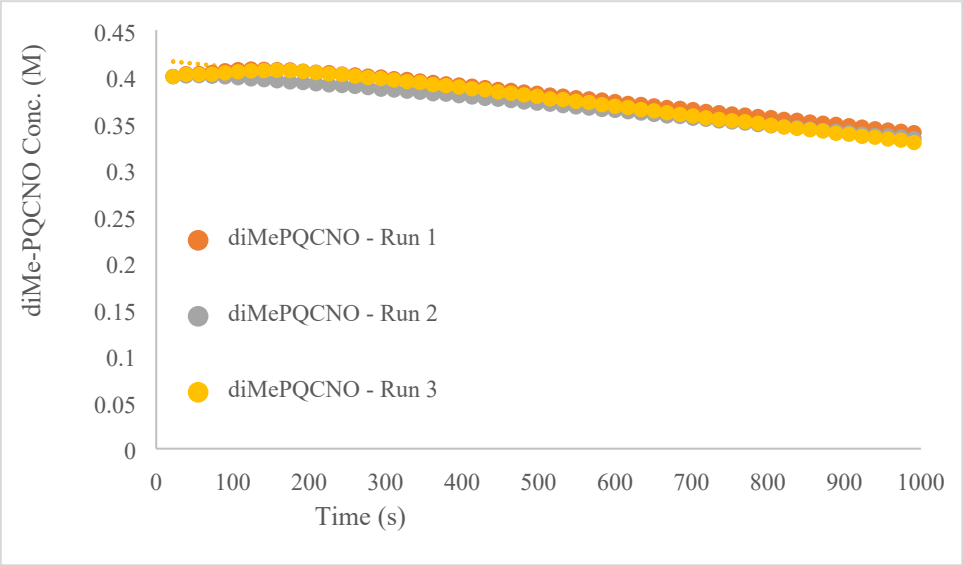
Decomposition of 2-chloroquinoline *N*-oxide/PivCl



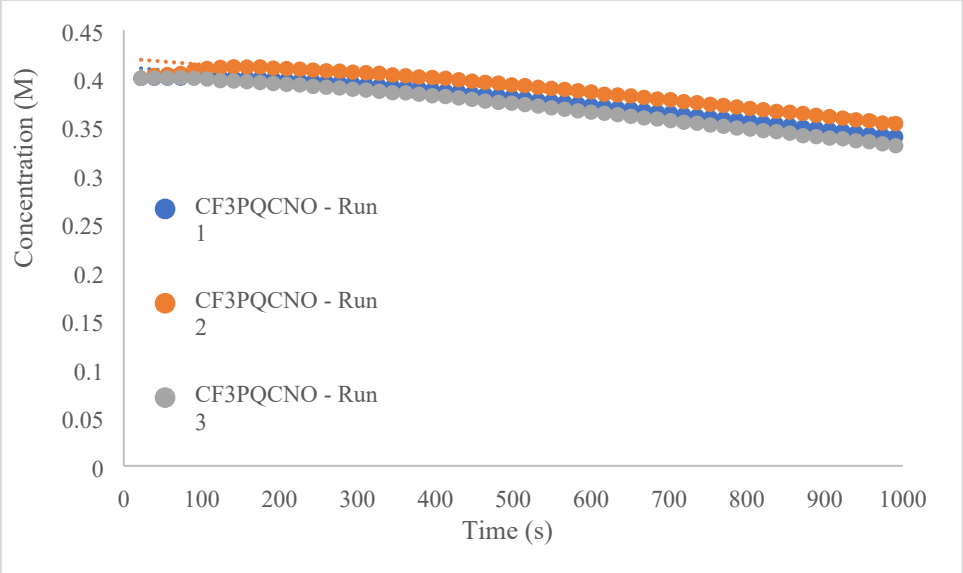
Decomposition of MeOPQCNO (methyl 2-(4'-methoxyphenyl)quinoline-4-carboxylate *N*-oxide)



Decomposition of diMePQCNO (methyl 2-(2',6'-dimethylphenyl)quinoline-4-carboxylate *N*-oxide)



Decomposition of CF_3PQCNO ((methyl 2-(4'-trifluoromethylphenyl)quinoline-4-carboxylate *N*-oxide)

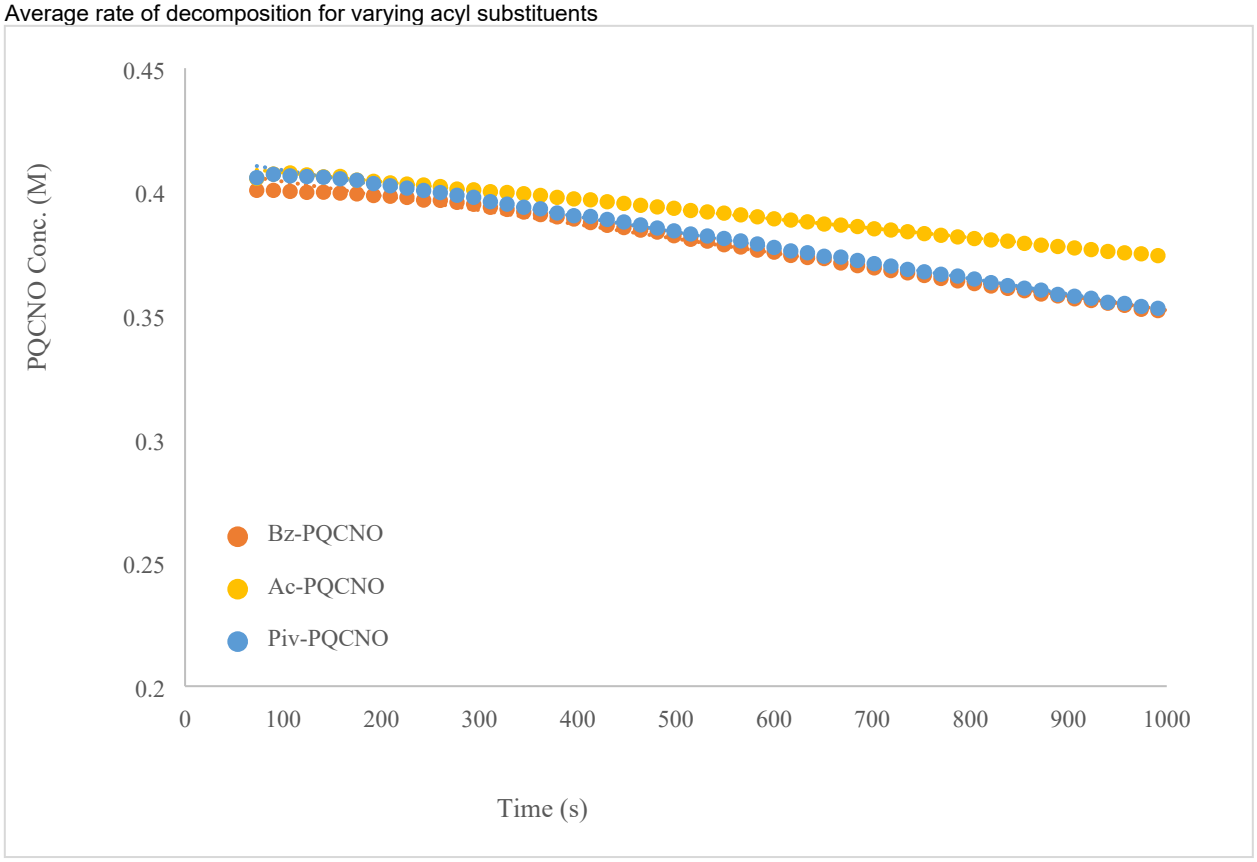


LED NMR Studies on Effect of Acyl Group on Rate of Fragmentation

To a flame dried vial equipped with a stir bar was weighed out PQCNO (56 mg, 0.2 mmol, 1 equiv). The vial was capped with a septa cap, and the solids were evacuated and backfilled 5 times with nitrogen. The mixture of solids was then taken up into 0.5 mL of MeCN, and 1.1 equiv of acyl chloride followed by the addition of 15 μL of TFA and 14 μL of dibromomethane internal standard. The reaction mixture was allowed to stir for 10 to 15 mins under an active stream of nitrogen, or until the PQCNO had completely dissolved. A thin-walled NMR tube was purged with a stream of nitrogen for 5 mins, at which point, the reaction solution was transferred to the NMR tube via a 1 mL syringe. The co-axial insert was added immediately, and the NMR tube was sealed with parafilm. The fiber optic cable was inserted to the co-axial insert and secured with a small piece of electrical tape prior to the NMR experiment. The NMR sample was inserted and the NMR array began data collection, 60 s was allowed to pass before turning on the 430 nm LED light source. Data was processed in MestraNova using the data analysis feature, the methyl ester signal corresponding to PQCNO and deoxygenated PQCNO was monitored to assess the conversion. Each experiment was carried out in triplicate, then the averages of the data compared. Data was plotted in Microsoft Excel.

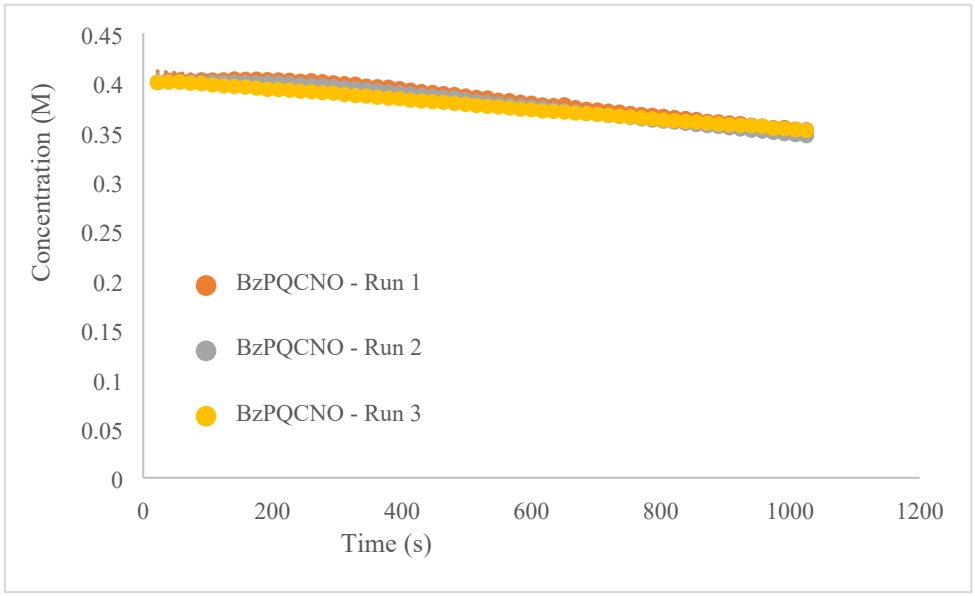
NMR parameters: Relaxation delay of 5 s, 45 ° pulse angle, acquisition time of 3.50 s, 2 steady state scans prior to each experiment, 2 scans per experiment, for a total of 17.28 s per experiment (.fid file). 60 experiments were collected for a total time of 17 mins and 17 s.

Average rate of decomposition for varying acyl substituents

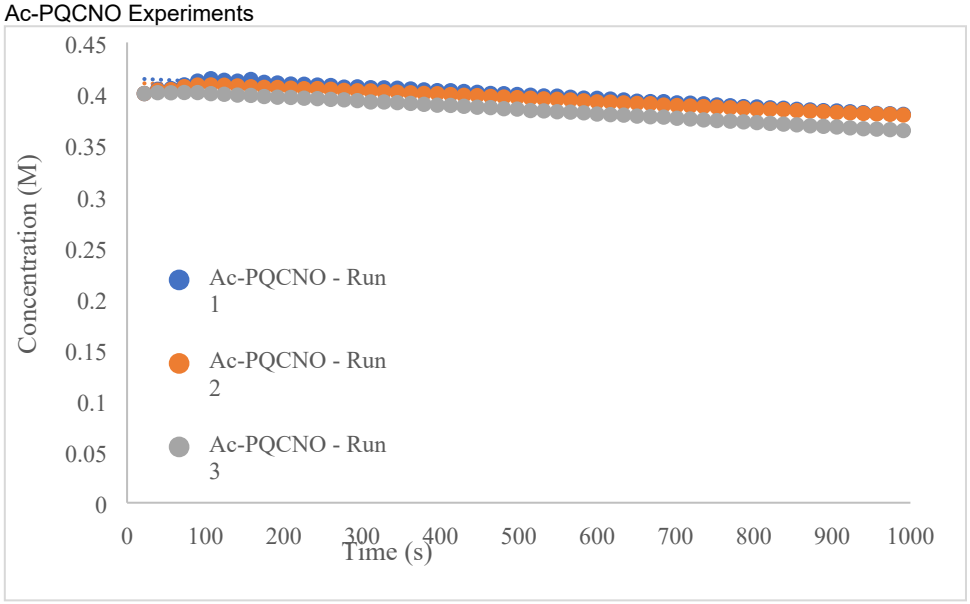


Piv-PQCNO Experiments (see above)

Bz-PQCNO Experiments



Ac-PQCNO Experiments



Quantum Yield Experiments

The experimental procedure was based on the report from Cismesia and Yoon.[2] Actinometry experiments were performed on a Horiba PTI QuantaMaster 8075-11 spectrofluorometer equipped with a 75W xenon arc lamp using a potassium ferrioxalate actinometer. Potassium ferrioxalate trihydrate was prepared according to the procedure reported by Johnson.[3] The actinometer was recrystallized from water three times and dehydrated by placing over high vacuum at 110 °C overnight prior to use. The ferrioxalate actinometer solution measures the decomposition of Fe(III) to Fe(II) ions, which are complexed by 1,10-phenanthroline and monitored by UV-Vis absorbance at 510 nm. The number of moles of Fe(II)-phenanthroline complex formed are directly proportional to moles of photons absorbed. The values of the quantum yield of potassium ferrioxalate are related to concentration and wavelength. The following solutions were prepared and stored in the dark:

1. **0.15 M Potassium ferrioxalate solution**: 655.8 mg of potassium ferrioxalate and 49 µL of sulfuric acid (96%) were added to a 10 mL volumetric flask and filled to the mark with HPLC grade water.
2. **Phenanthroline solution**: 50 mg of 1,10-phenanthroline, 11.25 g of sodium acetate, and 2.45 mL of sulfuric acid (96%) were added to a 50 mL volumetric flask and filled to the mark with HPLC grade water. It was then sonicated 10-15 minutes to dissolve any solids and allowed to rest 30 minutes for the volume to stabilize.

To determine the photon flux of the spectrophotometer, 2.0 mL of the 0.15 M potassium ferrioxalate solution was added to a quartz cuvette and irradiated for 90 s with a wavelength of λ = 436 nm using an emission slit width of 10.0 nm. Immediately following irradiation, 0.35 mL of the phenanthroline solution was added to the cuvette in one portion. The cuvette. The cuvette was then allowed to sit for 1 h to in the dark to allow the Fe(II) to coordinate to the phenanthroline. The solutions were then transferred to a 1 mm (0.1 cm) path length quartz cuvette and the absorbance of the solution was measured at 510 nm. A non-irradiated sample was also prepared and the absorbance at 510 nm measured. Light exclusion was achieved by wrapping the reaction in foil until the reaction was placed in the fluorimeter. All measurements were performed in the dark. Conversion was calculated according to eq. 1.

$$mol\ Fe(II) = \frac{V \cdot \Delta A}{l \cdot \varepsilon} = \frac{0.00235\ L\ \cdot 0.218172}{0.100\ cm\ \cdot 11{,}100\ L\ mol^{-1}\ cm^{-1}} = 4.62 \times 10^{-7}\ mol\ Fe(II)\ \ eq.1.$$

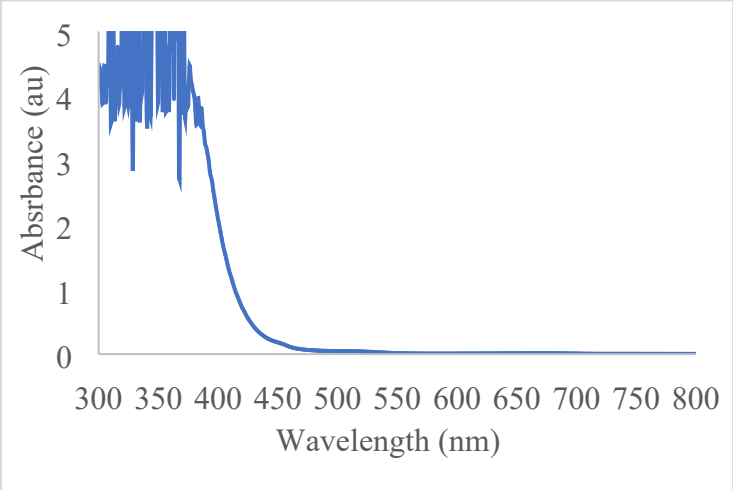
Where V is the volume in the cuvette (0.00235L) after the addition of phenanthroline solution, ΔA is the difference in absorbance at 510 nm between the irradiated and non-irradiated solutions, l is the path length of the cuvette (0.100 cm), and ε is the molar absorptivity at 510 nm (11,100 L mol^{-1} cm^{-1}).[4] Using the moles of Fe(II) produced, the photon flux can be calculated according to eq. 2.

$$photon\ flux = \frac{mol\ Fe(II)}{\Phi \cdot t \cdot f} = \frac{4.62 \times 10^{-7}\ mol}{1.01 \cdot 90\ s \cdot 0.615709} = 8.25 \times 10^{-9}\ einstein\ s^{-1}\ \ eq.2.$$

Where **Φ** is the quantum yield for the ferrioxalate actinometer (1.01 for a 0.15 M solution at λ = 436 nm)[4], t is the time the solution was irradiated (90 s), and f is the fraction of light absorbed at λ = 436 nm according to eq. 3.

$$f = 1 - 10^{-A} = 1 - 10^{-0.415339} = 0.615709\ \ eq.3.$$

Where A is the measured absorbance of the irradiated ferrioxalate solution at λ = 436 nm. The photon flux was calculated for an average of three experiments.
Absorbance spectrum for $K_3Fe(C_2O_4)_3$, 0.15 M in 0.05 M H_2SO_4.



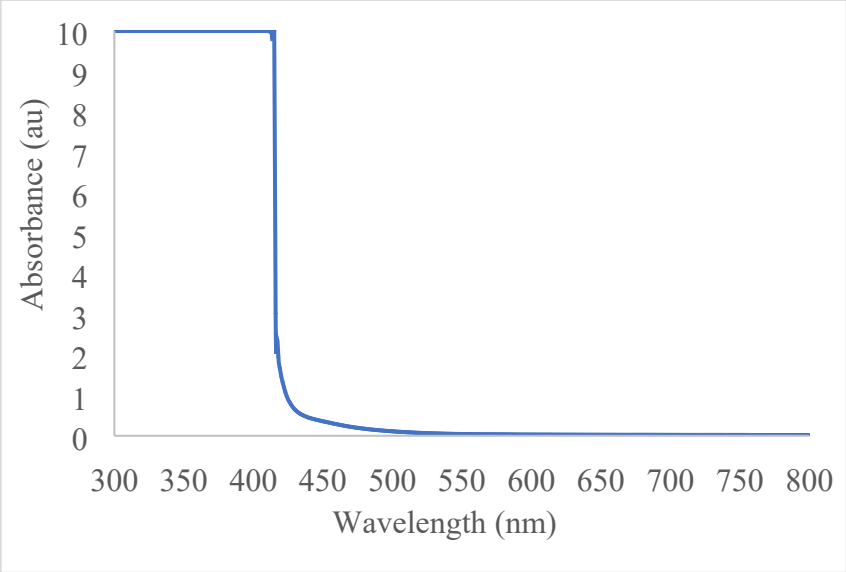
Reaction solution: In a dark room, a 1 cm path length quartz cuvette was charged with PQCNO (112 mg, 0.4 mmol, 2 equiv), 4-chloroquinoline (32.7 mg, 0.2 mmol, 1 equiv), calcium chloride (22 mg, 0.2 mmol, 1 equiv) and 3.0 mL of dry acetonitrile. The cuvette was fitted with a screw cap with a Teflon-lined septum top. The solution was sparged with nitrogen for 5 min before pivaloyl chloride (54 μL, 0.44 mmol, 2.2 equiv) freshly distilled under argon was added while under positive nitrogen pressure. The needle was removed, and the cap was quickly sealed with electrical tape and parafilm. Light exclusion was achieved by wrapping the reaction in foil until the reaction was placed in the fluorimeter. The samples were irradiated (λ = 436 nm, slit width = 10 nm) for the 8 h (28,800 s) before being removed from the fluorimeter. Immediately after irradiation the reactions were quenched with 0.5 mL of methanol and methyl *tert*-butyl ether (23.8 μL, 0.2 mmol) was added to the cuvette as an internal standard. A small aliquot was taken for analysis by ^{1}H NMR where the yield of deoxygenated PQCNO was determined by monitoring methyl ester signal. The reactions with and without 4-chloroquinoline present were performed in triplicate, and the average yield of deoxygenated PQCNO was used in the calculation of the quantum yield. The average reaction yield with 4-chloroquinoline present was 40% and without 4-chloroquinoline present was 10%.

Quantum Yield Calculation:
The quantum yield was calculated according to eq. 4.

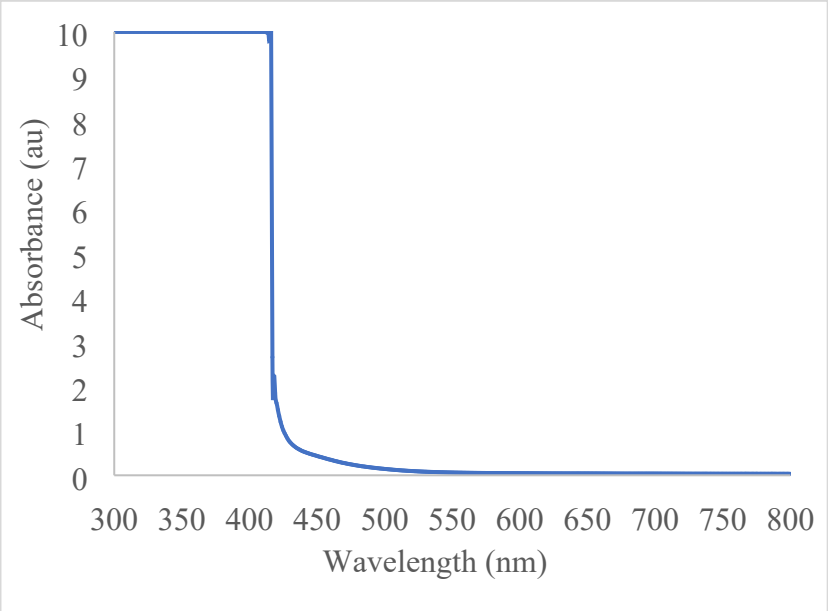
$$\Phi = \frac{mol\ product}{flux \cdot t \cdot f} = \frac{1.60 \times 10^{-4}\ mol}{8.25 \times 10^{-9}\ einstein\ s^{-1} \cdot 28{,}800\ s \cdot 0.684865} = 0.983\ \ eq.4.$$

Where **Φ** is the quantum yield, t is the irradiation time (28,800 s), and f is the fraction of light absorbed by the reaction solution (λ = 436 nm) according to eq. 3 (0.684865 with 4-chloroquinoline present, 0.746910 with no 4-chloroquinoline present).
$\Phi_{\text{4-chloroquinoline}}$: 0.983
$\Phi_{\text{no 4-chloroquinoline}}$: 0.218

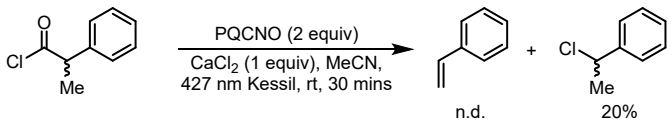
Absorbance spectrum of the full reaction mixture with 4-chloroquinoline (0.4 M in MeCN).



Absorbance spectrum of the full reaction mixture without 4-chloroquinoline (0.4 M in MeCN).



Reaction with 2-phenylpropionyl chloride



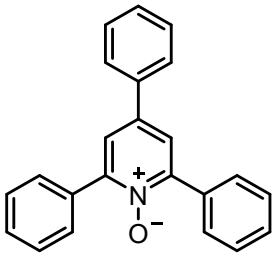
To a flame dried 1-dram vial equipped with a Teflon stir bar was weighed PQCNO (112 mg, 0.4 mmol, 1 equiv) and calcium chloride (0.5 equiv, 22.2 mg). The solids were evacuated and backfilled 5 times with nitrogen. To the vial was added 0.5 mL MeCN, followed by the addition of 2-phenylpropionyl chloride (1.1 equiv, 0.44 mmol, 74.2 mg). The vial was then sealed with a piece of electrical tape and

parafilm, and then irradiated with a 427 nm Kessil lamp for 30 min. At the conclusion of the reaction, 24 uL of MTBE was added as an internal standard and NMR was obtained in chloroform. Crude analysis showed the appearance of 1-chloro-1-phenylethane in 20% yield.

Discussion: We believe that this results demonstrates the ability of acylated-PQCNO to oxidize stabilized carbon centered radicals.

Compound Isolation and Characterization Data

2,4,6-triphenylpyridine *N*-oxide (TPPNO)



2,4,6-triphenylpyridine *N*-oxide was prepared according to Buchardt, *et al. Acta Chem. Scand.* **1970,** *24,* 3435-3443.[5]
2,4,6-triphenylpyridine *N*-oxide was isolated as an off-white amorphous solid.

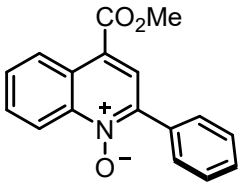
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 – 7.88 (m, 4H), 7.67 (d, *J* = 7.8 Hz, 4H), 7.53 – 7.42 (m, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 150.04, 136.85, 133.46, 129.75, 129.56, 129.38, 129.03, 128.32, 128.24, 126.57, 123.96 ppm.

IR(neat): 3057, 1620, 1577, 1549, 1495, 1452, 1402, 1341, 1304, 1254, 1182, 1163, 1075, 1028, 1015, 1001, 983, 878, 867, 838, 764, 728, 689 cm^{-1}.

HRMS: Calculated [M+H]+: 324.1383; Found [M+H]+: 324.1380.

Methyl 2-phenylquinoline-4-carboxylate *N*-oxide (PQCNO)



Preparation of PQCNO was carried out according to **General Procedure B**, using methyl 2-phenylquinoline-4-carboxylate as the starting material. PQCNO was isolated as an off-white amorphous solid.

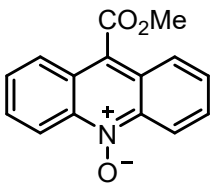
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (dt, *J* = 8.6, 1.7 Hz, 1H), 8.87 (d, *J* = 8.8 Hz, 1H), 8.24 (d, *J* = 1.1 Hz, 1H), 7.99 – 7.93 (m, 2H), 7.81 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H), 7.75 (ddd, *J* = 8.8, 6.9, 1.8 Hz, 1H), 7.58 – 7.46 (m, 3H), 4.02 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.50, 144.31, 143.20, 132.86, 130.75, 130.03, 129.86, 129.65, 128.59, 127.44, 126.89, 126.78, 122.63, 120.46, 52.77 ppm.

IR(neat): 3054, 2990, 2947, 1715, 1579, 1553, 1506, 1495, 1454, 1428, 1373, 1334, 1308, 1248, 1228, 1192, 1139, 1065, 1033, 1024, 929, 913, 862, 784, 765, 736, 723, 695, 678 cm^{-1}.

HRMS: Calculated [M+H]+: 280.0968; Found [M+H]+: 280.0963.

Methyl acridine-9-carboxylate *N*-oxide (ACNO)



Preparation of ACNO was carried out according to **General Procedure B**, using methyl acridine-9-carboxylate as the starting material. Methyl acridine-9-carboxylate *N*-oxide was isolated as a vibrant yellow amorphous solid.

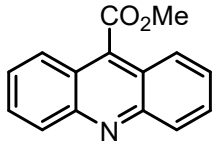
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.90 (d, *J* = 9.0 Hz, 3H), 8.12 (d, *J* = 8.7 Hz, 3H), 7.79 (ddd, *J* = 9.1, 6.6, 1.3 Hz, 3H), 7.64 (ddd, *J* = 8.8, 6.6, 1.2 Hz, 3H), 4.19 (d, *J* = 0.9 Hz, 5H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.33, 139.51, 130.94, 128.58, 126.15, 124.98, 124.37, 120.13, 53.21 ppm.

IR(neat): 2958, 1721, 1622, 1571, 1536, 1482, 1429, 1376, 1292, 1272, 1221, 1202, 1162, 1110, 926, 902, 842, 812, 783, 762, 743 cm^{-1}.

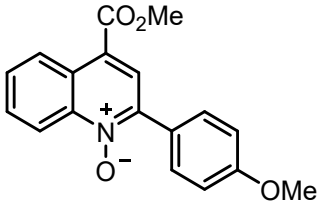
HRMS: Calculated [M+H]+: 254.0812; Found [M+H]+: 254.0809.

Methyl acridine-9-carboxylate



To a flame dried round bottom flask equipped with a magnetic stir bar was weighed acridine-9-carboxylate (1 equiv., 4.5 mmol, 1 g, pale yellow powder). The solid was taken up into 50 mL of DCM. Note: At this point the material was insoluble and the mixture was stirred as yellow solid floated on top of DCM. The round bottom flask was equipped with a septum with a vent needle, and oxalyl chloride (1.2 equiv., 5.4 mmol, 685 mg, 463 μL) was added. To the mixture was added DMF (0.1 equiv., ~5 drops), the acridine-9-carboxylate immediately went into solution and the reaction began to bubble vigorously. The reaction was allowed to stir for about 3 hours (when bubbling ceased), at which point methanol (5 mL) and sodium methoxide (2 equiv., 9 mmol, 486 mg) were added and the reaction mixture was allowed to stir for an additional 3 hours. Upon conclusion of the reaction, the mixture was taken up into saturated sodium bicarbonate (20 mL) and extracted with 3 portions of 20 mL DCM. [Note: An emulsion forms at this point. The reaction mixture is a dark orange in color at this point and both aqueous and organic layers will become colored. On several occasions, a solid yellow precipitate was observed to crash out of solution, this was collected with the DCM layers]. The combined organic extracts were washed with 20 mL saturated sodium chloride [Note: emulsion forms], and dried over sodium sulfate. The crude organic material was purified by column chromatography using DCM/Acetone as a mobile phase.

Methyl 2-(4'-methoxyphenyl)quinoline-4-carboxylate *N*-oxide



Preparation of methyl 2-(4'methoxyphenyl)quinoline-4-carboxylate was carried out according to **General Procedure D.** Preparation of methyl 2-(4'methoxyphenyl)quinoline-4-carboxylate *N*-oxide was carried out according to **General Procedure B.** 2-(4'methoxyphenyl)quinoline-4-carboxylate *N*-oxide was isolated as vibrant yellow amorphous solid.

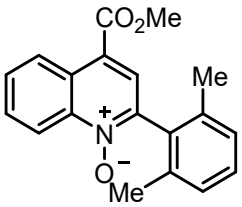
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.87 (dd, *J* = 8.8, 1.4 Hz, 1H), 8.25 (s, 1H), 8.01 (d, *J* = 8.9 Hz, 2H), 7.80 (ddd, *J* = 8.7, 6.9, 1.4 Hz, 1H), 7.72 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.06 (d, *J* = 8.9 Hz, 2H), 4.03 (s, 4H), 3.89 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.58, 160.93, 144.03, 143.20, 131.32, 130.72, 129.58, 127.06, 126.72, 126.69, 124.96, 122.75, 120.38, 113.99, 55.58, 52.77 ppm.

IR(neat): 2955, 2839, 2041, 1724, 1613, 1556, 1518, 1499, 1438, 1337, 1311, 1246, 1225, 1184, 1138, 1026, 926, 905, 816, 783, 766, 740, 685, 652 cm^{-1}.

HRMS: Calculated [M+H]+: 310.1074; Found [M+H]+: 310.1078.

Methyl 2-(2',6'-dimethylphenyl)quinoline-4-carboxylate *N*-oxide



Preparation of methyl 2-(2',6'-dimethylphenyl)quinoline-4-carboxylate was carried out according to **General Procedure D.** Preparation of methyl 2-(2',6'-dimethylphenyl)quinoline-4-carboxylate *N*-oxide was carried out according to **General Procedure B.** 2-(2',6'-dimethylphenyl)quinoline-4-carboxylate *N*-oxide was isolated as an off-white amorphous solid.

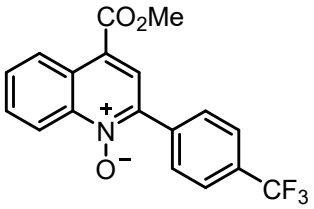
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.85 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.02 (s, 1H), 7.80 (dqd, *J* = 8.4, 6.9, 1.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 4.00 (s, 3H), 2.11 (s, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.36, 145.11, 142.91, 136.72, 132.66, 130.36, 129.84, 129.43, 127.74, 127.72, 127.14, 126.76, 121.81, 120.37, 52.59, 19.75 ppm.

IR(neat): 2963, 1699, 1594, 1557, 1505, 1469, 1449, 1434, 1378, 1354, 1326, 1240, 1193, 1179, 1168, 1056, 1032, 943, 928, 864, 823, 784, 772, 744, 730, 691 cm^{-1}.

HRMS: Calculated [M+H]+: 308.1281; Found [M+H]+: 308.1287.

Methyl 2-(4'-trifluoromethylphenyl)quinoline-4-carboxylate *N*-oxide



Preparation of methyl 2-(4'-trifluoromethylphenyl)quinoline-4-carboxylate was carried out according to **General Procedure D.** Preparation of methyl 2-(4'-trifluoromethylphenyl)quinoline-4-carboxylate *N*-oxide was carried out according to **General Procedure B.** 2-(4'-dimethylphenyl)quinoline-4-carboxylate *N*-oxide was isolated as an off-white amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (d, *J* = 8.5 Hz, 1H), 8.85 (d, *J* = 8.7 Hz, 1H), 8.23 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 2H), 7.87 – 7.74 (m, 4H), 4.03 (s, 3H) ppm.

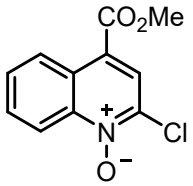
^{13}C NMR (126 MHz, $CDCl_3$) δ 165.15, 143.06, 142.71, 136.22, 131.61 (q, *J* = 32.8 Hz) 130.89, 130.18, 129.99, 127.58, 126.79, 126.29, 125.44 (q, *J* = 3.8 Hz), 124.93, 122.77, 122.66, 120.30, 52.75 ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -63.53 ppm.

IR(neat): 3066, 1724, 1707, 1616, 1556, 1505, 1442, 1322, 1308, 1254, 1229, 1195, 1172, 1144, 1112, 1071, 1059, 1014, 949, 868, 851, 784, 774, 736 cm^{-1}.

HRMS: Calculated [M+H]+: 348.0842; Found [M+H]+: 348.0848.

Methyl 2-chloroquinoline-4-carboxylate *N*-oxide



Preparation of methyl 2-chloroquinoline-4-carboxylate was carried out according to **General Procedure D.** Preparation of methyl 2-chloroquinoline-4-carboxylate *N*-oxide was carried out according to **General Procedure B.** 2-chloroquinoline-4-carboxylate *N*-oxide was isolated as an off-white amorphous solid.

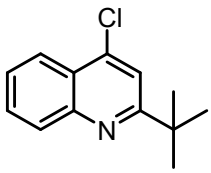
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (dd, *J* = 8.6, 1.4 Hz, 1H), 8.81 – 8.76 (m, 1H), 8.21 (s, 1H), 7.83 (ddd, *J* = 8.6, 7.0, 1.4 Hz, 1H), 7.76 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 4.03 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.39, 143.27, 137.47, 131.15, 129.99, 127.01, 126.55, 125.86, 122.85, 120.00, 52.90 ppm.

IR(neat): 3069, 2969, 1707, 1581, 1549, 1499, 1428, 1366, 1295, 1277, 1245, 1212, 1168, 1090, 1010, 944, 879, 819, 784, 761, 737 cm^{-1}.

HRMS: Calculated [M+H]+: 238.0265; Found [M+H]+: 238.0273.

2-(*tert*-butyl)-4-chloroquinoline



Reaction run according to **General Procedure A**. 2-(*tert*-butyl)-4-chloroquinoline was isolated as a colorless oil.

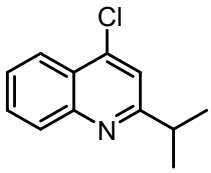
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.09 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.72 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.62 (s, 1H), 7.57 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 1.47 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.49, 148.47, 142.41, 130.05, 129.89, 126.74, 124.80, 123.84, 118.59, 38.39, 31.43, 31.26, 30.33, 30.13 ppm.

IR(neat): 3064, 2961, 2907, 2868, 1617, 1589, 1552, 1492, 1462, 1397, 1364, 1303, 1262, 1218, 1204, 1147, 1105, 1023, 977, 897, 868, 840, 757, 713 cm^{-1}

HRMS – Calculated [M+H]+: 220.0888; Found [M+H]+: 220.0880.

2-(*iso*-propyl)-4-chloroquinoline

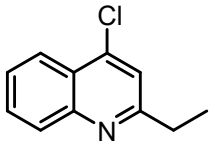


Reaction run according to **General Procedure A**. 2-*iso*propyl-4-chloroquinoline was isolated as a colorless oil. Characterization data is consistent with previously reported literature (Chen *et al. Chem. Sci.*, **2016,** *7,* 6407–6412.).[6]

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.73 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.57 (td, *J* = 7.5, 6.8, 1.2 Hz, 1H), 7.43 (s, 1H), 3.23 (p, *J* = 7.0 Hz, 1H), 1.39 (d, *J* = 6.9 Hz, 7H) ppm.

HRMS: Calculated [M+H]+: 206.0731; Found [M+H]+: 206.0733.

2-ethyl-4-chloroquinoline

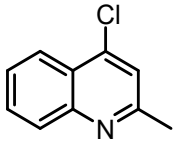


Reaction run according to **General Procedure A**. 2-ethyl-4-chloroquinoline was isolated as a colorless oil. Characterization data is consistent with previously reported literature (Chen *et al. Chem. Sci.*, **2016,** *7,* 6407–6412.). [6]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.73 (t, *J* = 8.5 Hz, 1H), 7.58 (t, *J* = 8.5 Hz, 1H), 7.41 (s, 1H), 2.98 (q, *J* = 7.7 Hz, 2H), 1.40 (t, *J* = 7.6 Hz, 3H) ppm.

HRMS: Calculated [M+H]+: 192.0575; Found [M+H]+: 192.0576

2-methyl-4-chloroquinoline

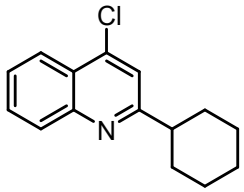


Reaction run according to **General Procedure A**, run for 1 hour. 2-methyl-4-chloroquinoline was isolated as a 1:2.5 inseparable mixture with 4-chloroquinoline. Characterization data is consistent with previously reported literature (Chen *et al. Chem. Sci.*, **2016,** *7,* 6407–6412.). [6]

^{1}H NMR (401 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 2.73 (s, 3 H) ppm.

HRMS: Calculated [M+H]+: 178.0418; Found [M+H]+: 178.0412.

2-(cyclohexyl)-4-chloroquinoline

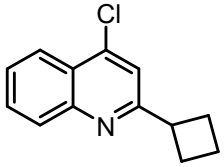


Reaction run according to **General Procedure A**. 2-cyclohexyl-4-chloroquinoline was isolated as a colorless amorphous solid. Characterization data is consistent with previously reported literature (Chen *et al. Chem. Sci.*, **2016,** *7,* 6407–6412.). [6]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.73 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.43 (s, 1H), 2.90 (tt, *J* = 12.0, 3.5 Hz, 1H), 2.03 (ddq, *J* = 11.9, 3.6, 1.9 Hz, 2H), 1.90 (dt, *J* = 13.0, 3.4 Hz, 2H), 1.79 (dtt, *J* = 11.5, 3.3, 1.6 Hz, 1H), 1.61 (qd, *J* = 12.6, 3.3 Hz, 2H), 1.46 (qt, *J* = 12.8, 3.4 Hz, 2H), 1.39 – 1.24 (m, 1H) ppm.

HRMS: Calculated [M+H]+: 246.1044; Found [M+H]+: 246.1051

2-(cyclobutyl)-4-chloroquinoline

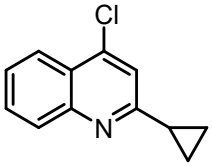


Reaction run according to **General Procedure A**. 2-cyclobutyl-4-chloroquinoline was isolated as a pale-yellow oil. Characterization data is consistent with previously reported literature (Chen *et al. Chem. Sci.*, **2016,** *7,* 6407–6412.). [6]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.72 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.56 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.43 (s, 1H), 3.88 – 3.78 (m, 1H), 2.45 (td, *J* = 9.0, 6.0 Hz, 4H), 2.13 (dq, *J* = 10.9, 9.0 Hz, 1H), 2.00 – 1.91 (m, 1H) ppm.

HRMS – Calculated [M+H]+: 218.0731; Found [M+H]+: 218.0731.

2-(cyclopropyl)-4-chloroquinoline

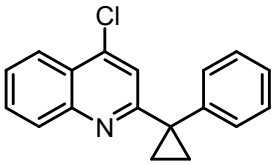


Reaction run according to **General Procedure A**. 2-cyclobutyl-4-chloroquinoline was isolated as a pale-yellow oil. Characterization data is consistent with previously reported literature (Chen *et al. Chem. Sci.*, **2016,** *7,* 6407–6412.). [6]

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.29 (s, 1H), 2.21 (s, 1H), 1.17 (dq, *J* = 5.4, 3.7, 2.7 Hz, 2H), 1.15 – 1.09 (m, 2H) ppm.

HRMS – Calculated [M+H]+: 204.0575; Found [M+H]+: 204.0579.

2-(1-phenylcyclopropyl)-4-chloroquinoline



Reaction run according to **General Procedure A**. 2-(1-phenylcyclopropyl)-4-chloroquinoline was isolated as a pale-yellow amorphous solid.

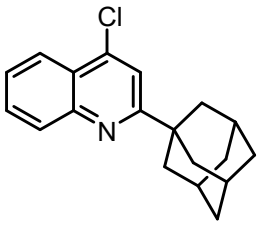
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.34 – 7.30 (m, 1H), 7.16 (s, 1H), 1.87 (q, *J* = 3.9 Hz, 2H), 1.41 (q, *J* = 3.9 Hz, 2H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$) δ 164.61, 142.92, 130.61, 130.33, 129.47, 128.91, 127.24, 126.60, 124.73, 124.00, 121.17, 32.31, 18.11 ppm.

IR(neat): 3061, 2923, 2867, 1719, 1584, 1549, 1492, 1446, 1406, 1322, 1244, 1205, 1172, 1145, 1090, 1076, 1059, 1025, 979, 937, 907, 860, 842, 753, 697 cm^{-1}

HRMS: Calculated [M+H]+: 280.0888; Found [M+H]+: 280.0892.

2-(1-adamantyl)-4-chloroquinoline



Reaction run according to **General Procedure A**. 2-(1-adamantyl)-4-chloroquinoline was isolated as a colorless amorphous solid.

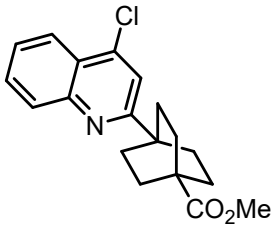
^{1}H NMR (401 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.57 (s, 1H), 7.56 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 2.19 – 2.13 (m, 4H), 2.10 (d, *J* = 2.9 Hz, 7H), 1.83 (t, *J* = 3.0 Hz, 7H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$) δ 169.30, 148.71, 142.48, 130.00, 129.87, 126.70, 124.96, 123.90, 118.33, 41.88, 40.03, 36.91, 28.89 ppm.

IR(neat): 2903, 2848, 1617, 1584, 1548, 1494, 1449, 1410, 1344, 1323, 1293, 1255, 1228, 1191, 1149, 1103, 1000, 970, 904, 868, 841, 756, 707, 662 cm^{-1}.

HRMS: Calculated [M+H]+: 298.1357; Found [M+H]+: 298.1359.

2-(methyl 4-[2.2.2]-bicyclooctyl-1-carboxylate)-4-chloroquinoline



Reaction run according to **General Procedure A**. 2-(methyl 4-[2.2.2]-bicyclooctyl-1-carboxylate)-4-chloroquinoline was isolated as a colorless amorphous solid.

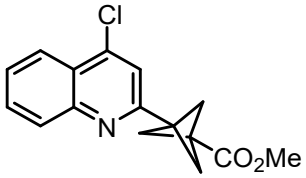
^{1}H NMR (500 MHz, $cdcl_3$) δ 8.15 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.56 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.51 (s, 1H), 3.69 (s, 3H), 2.04 (dd, *J* = 10.3, 5.2 Hz, 6H), 1.96 (dd, *J* = 10.4, 5.1 Hz, 6H) ppm.

^{13}C NMR (126 MHz, $cdcl_3$) δ 178.36, 167.74, 148.49, 142.51, 130.17, 129.75, 126.86, 124.89, 123.88, 118.72, 51.83, 39.47, 38.56, 30.57, 28.67 ppm.

IR(neat): 2945, 2920, 2868, 1718, 1615, 1586, 1551, 1493, 1455, 1437, 1414, 1402, 1300, 1254, 1237, 1218, 1192, 1170, 1075, 1006, 967, 922, 866, 841, 765, 704, 666 cm^{-1}.

HRMS – Calculated [M+H]+: 330.1255; Found [M+H]+: 330.1267.

2-(methyl 3-[1.1.1]-bicyclopentyl-1-carboxylate)-4-chloroquinoline



Reaction run according to **General Procedure A**. 2-(methyl 3-[1.1.1]-bicyclopentyl-1-carboxylate)-4-chloroquinoline was isolated as a colorless amorphous solid.

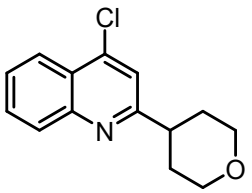
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.61 – 7.56 (m, 1H), 7.42 (s, 1H), 3.74 (s, 3H), 2.51 (s, 6H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.54, 158.69, 148.84, 142.99, 130.62, 129.66, 127.34, 125.38, 124.05, 119.08, 53.48, 51.92, 42.80, 37.42 ppm.

IR(neat): 2996, 2958, 2925, 1723, 1590, 1550, 1492, 1442, 1404, 1372, 1326, 1304, 1208, 1187, 1136, 1111, 1027, 976, 946, 871, 824, 790, 769, 718, 695 cm^{-1}.

HRMS – Calculated [M+H]+: 288.0786; Found [M+H]+: 288.0786.

2-(tetrahydro-2*H*-pyran-4-yl)-4-chloroquinoline



Reaction run according to **General Procedure A**. 2-(tetrahydro-*2H*-pyran-4-yl)-4-chloroquinoline was isolated as a colorless amorphous solid.

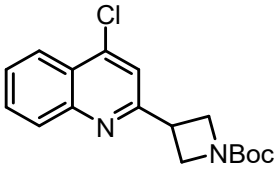
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.07 – 8.02 (m, 1H), 7.72 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.41 (s, 1H), 4.16 – 4.08 (m, 2H), 3.57 (td, *J* = 11.7, 2.2 Hz, 2H), 3.12 (tt, *J* = 11.9, 4.0 Hz, 1H), 2.00 (dtd, *J* = 13.3, 11.8, 4.4 Hz, 2H), 1.92 (ddd, *J* = 13.2, 4.2, 2.1 Hz, 2H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.59, 148.76, 143.02, 130.46, 129.48, 127.00, 125.30, 124.02, 119.63, 68.05, 44.23, 32.20 ppm.

IR(neat): 3064, 2953, 2842, 1730, 1615, 1589, 1553, 1494, 1465, 1443, 1411, 1386, 1298, 1237, 1212, 1150, 1128, 1085, 1011, 981, 939, 913, 869, 841, 820, 758, 730, 695, 672 cm^{-1}

HRMS - Calculated [M+H]+: 248.0837; Found [M+H]+: 248.0838.

***tert*-butyl 3-(4-chloroquinolin-2-yl)azetidine-1-carboxylate**



Reaction run according to **General Procedure A**. *tert*-butyl 3-(4-chloroquinolin-2-yl)azetidine-1-carboxylate was isolated as a pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.77 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.62 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.51 (s, 1H), 4.39 (t, *J* = 8.7 Hz, 2H), 4.28 (dd, *J* = 8.7, 5.9 Hz, 2H), 4.03 (dq, *J* = 12.8, 4.4, 3.0 Hz, 1H), 1.48 (s, 10H) ppm.

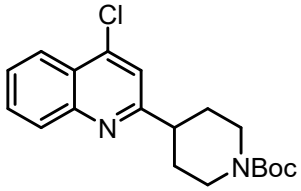
^{13}C NMR (151 MHz, $CDCl_3$) δ 161.28, 156.64, 148.66, 143.50, 130.81, 129.60, 127.46, 125.43, 124.12, 119.79, 79.83, 54.62, 35.78, 29.84, 28.57 ppm.

IR(neat): 3062, 2976, 2887, 1695, 1616, 1589, 1554, 1495, 1479, 1455, 1391, 1365, 1300, 1252, 1216, 1162, 1132, 1027, 971, 927, 863, 838, 760, 734 cm^{-1}.

HRMS – During MS analysis of with ESI source in positive mode, we observed Boc deprotection of the product.

Molecular Formula: $C_{12}H_{11}ClN_2$
Calculated [M+H]+: 219.0684; Found [M+H]+: 219.0688.

***tert*-butyl 4-(4-chloroquinolin-2-yl)piperidine-1-carboxylate**



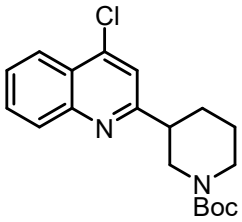
Reaction run according to **General Procedure A**. *tert*-butyl 4-(4-chloroquinolin-2-yl)piperidine-1-carboxylate was isolated as a pale yellow oil. Characterization data is consistent with previously reported literature (Wang et al. J. Org. Chem. **2019,** *84,* 11, 7532–7540.). [7]

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (dt, *J* = 8.4, 1.8 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.73 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1H), 7.57 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.39 (d, *J* = 1.8 Hz, 1H), 4.28 (s, 2H), 3.02 (td, *J* = 11.6, 5.8 Hz, 1H), 2.87 (s, 2H), 1.98 (d, *J* = 13.1 Hz, 2H), 1.82 (qd, *J* = 12.5, 4.4 Hz, 2H), 1.48 (s, 9H) ppm.

HRMS – During MS analysis of with ESI source in positive mode, we observed Boc deprotection of the product.

Molecular Formula: $C_{14}H_{15}ClN_2$
Calculated [M+H]+: 247.0997; Found [M+H]+: 247.1002.

***tert*-butyl 3-(4-chloroquinolin-2-yl)piperidine-1-carboxylate**



Reaction run according to **General Procedure A**. *tert*-butyl 3-(4-chloroquinolin-2-yl)piperidine-1-carboxylate was isolated as a pale yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.42 (s, 1H), 4.60-4.20 (m, 1H), 4.13 (bs, 1H), 3.42-3.03 (m, 1H), 3.04-2.95 (m, 1H), 2.85 (t, *J* = 12.8 Hz, 1H), 2.13 (d, *J* =13.2 Hz, 1H), 1.95-1.84 (m, 1H), 1.80 (d, *J* = 13.5 Hz, 1H), 1.68-1.57 (m, 1H), 1.47 (s, 9H) ppm.

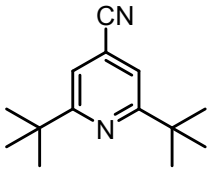
^{13}C NMR (176 MHz, $CDCl_3$) δ 163.03, 154.96, 148.87, 142.78, 130.42, 129.60, 127.06, 125.34, 124.04, 120.62, 79.69, 48.83, 44.84, 43.76, 30.82, 29.82, 28.59, 25.21ppm.

IR(neat): 2976, 2931, 2856, 1687, 1616, 1589, 1494, 1411, 1365, 1301, 1256, 1162, 1146, 1136, 1024, 977, 938, 864, 839, 759, 736, 702 cm^{-1}.

HRMS – During MS analysis of with ESI source in positive mode, we observed Boc deprotection of the product.

Molecular Formula: $C_{14}H_{15}ClN_2$
Calculated [M+H]+: 247.0997; Found [M+H]+: 247.1005.

2,6-di-*tert*-butylisonicotinonitrile



Reaction run according to **General Procedure A**. 2,6-bis(*tert*-butyl)-4-cyanopyridine was isolated as a colorless oil.

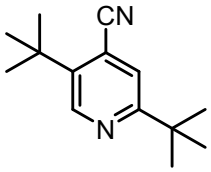
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 2H), 1.35 (s, 18H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.76, 120.67, 118.28, 117.78, 38.38, 30.17 ppm.

IR(neat):

HRMS – Calculated [M+H]+: 217.1699; Found [M+H]+: 217.1709.

2,5-di-*tert*-butylisonicotinonitrile

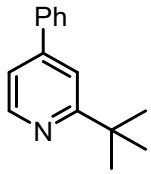


Reaction run according to **General Procedure A**. 2,5-bis(*tert*-butyl)-4-cyanopyridine was isolated as a 1:1 mixture with 2,6- bis(*tert*-butyl)-4-cyanopyridine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.54 (s, 1H), 1.54 (s, 9H), 1.37 (s, 9H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.06, 169.55, 147.27, 123.74, 37.38, 34.43, 31.07, 29.98, 29.97 ppm.

2-(*tert*-butyl)-4-phenylpyridine

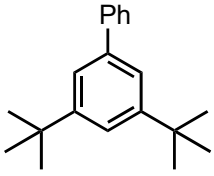


Reaction run according to **General Procedure A**. 2-(tert-butyl)-4-phenylpyridine was isolated as a colorless oil. Characterization data is consistent with previously reported literature (Stephenson et al. Org. Lett., 2018, 20, 3487–3490.). [8]

^{1}H NMR (401 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.1 Hz, 1H), 7.63 (dt, *J* = 8.1, 1.2 Hz, 2H), 7.54 (s, 1H), 7.52 – 7.43 (m, 3H), 7.31 (d, *J* = 4.9 Hz, 1H), 1.43 (d, *J* = 1.0 Hz, 9H) ppm.

HRMS – Calculated [M+H]+: 212.1434; Found [M+H]+: 212.1442.

2,6-bis(*tert*-butyl)-4-phenylpyridine

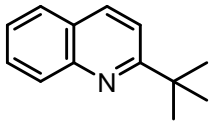


Reaction run according to **General Procedure A**. 2,6-bis(*tert*-butyl)-4-phenylpyridine was isolated as a colorless oil. Characterization data is consistent with previously reported literature (Stephenson et al. Org. Lett., 2018, 20, 3487–3490.). [8]

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.62-7.60 (m, 2H), 7.47 (t, *J* = 7.1 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 1 H), 7.29 (s, 2 H), 1.40 (s, 18 H) ppm.

HRMS – Calculated [M+H]+: 268.2060; Found [M+H]+: 268. 2072.

2-(*tert*-butyl)quinoline

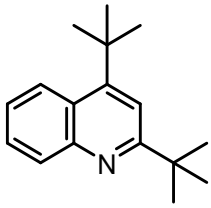


Reaction run according to **General Procedure A**. A mixture of 2-(tert-butyl)quinoline and 2,4-bis(tert-butyl)quinoline was isolated as a colorless oil. Characterization data is consistent with previously reported literature (Stephenson et al. Org. Lett., 2018, 20, 3487–3490.). [8]

^{1}H NMR (600 MHz, $cdcl_3$) δ 8.07 (dd, *J* = 8.6, 2.3 Hz, 2H), 7.77 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.48 – 7.42 (m, 1H, distorted by 2,4-bis(*tert*-butyl)quinoline), 1.48 (s, 18H, distorted by 2,4-bis(*tert*-butyl)quinoline) ppm.

HRMS – Calculated [M+H]+: 186.1277; Found [M+H]+: 186.1284.

2,4-bis(*tert*-butyl)quinoline

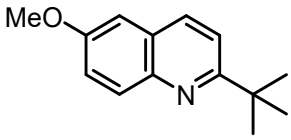


Characterization data is consistent with previously reported literature (Stephenson *et al. Org. Lett.*, **2018,** *20, 3487–3490.*). 2,4-bis(tert-butyl)quinoline was isolated as a colorless oil.

^{1}H NMR (600 MHz, $cdcl_3$) δ 8.34 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.09 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.60 (ddd, *J* = 8.3, 6.7, 1.4 Hz, 1H), 7.48 (s, 1H), 7.44 (ddd, *J* = 8.4, 6.7, 1.4 Hz, 1H), 1.62 (s, 10H), 1.47 (s, 11H) ppm.

HRMS – Calculated [M+H]+: 242.1903; Found [M+H]+: 242.1910.

2-(*tert*-butyl)-6-methoxyquinoline

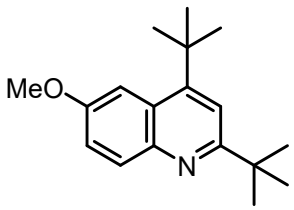


Reaction run according to **General Procedure A**. A mixture of 2-(tert-butyl)-6-methoxyquinoline and 2,4-bis(tert-butyl)-6-methoxyquinoline was isolated as a colorless oil. Characterization data is consistent with previously reported literature (Wojciechowski *et al. Syn. Lett.* **2012,** *23, 2682–2686.*). [9]

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.97 (d, *J* = 9.1Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H) 7.48 (d, *J* = 8.7 Hz, 1H), 7.32 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.04 (d, *J* = 2.8 Hz, 1H), 3.94 (s, 2H), 3.92 (s, 3H), 1.46 (s, 14H) ppm.

HRMS – Calculated [M+H]+: 216.1383; Found [M+H]+: 216.1389.

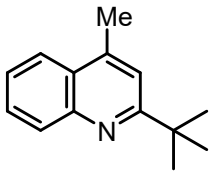
2,4-bis(*tert*-butyl)-6-methoxyquinoline



^{1}H NMR (401 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.2 Hz, 1H), 7.63 (d, *J* = 2.8 Hz, 1H), 7.45 (s, 1H), 7.29 (d, *J* = 2.6 Hz, 1H), 3.94 (s, 3H), 1.62 (s, 10H), 1.46 (s, 9H) ppm.

HRMS – Calculated [M+H]+: 272.2009; Found [M+H]+: 272.2017.

2-(*tert*-butyl)-4-methylquinoline

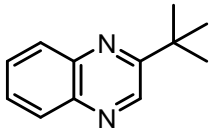


Reaction run according to **General Procedure A**. 2-(tert-butyl)-4-methylquinoline was isolated as a colorless oil. Characterization data is consistent with previously reported literature (Stephenson *et al. Org. Lett.*, **2018,** *20, 3487–3490.*). [8]

^{1}H NMR (401 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.94 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.66 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.35 (d, *J* = 1.2 Hz, 1H), 2.69 (d, *J* = 1.0 Hz, 3H), 1.46 (s, 9H) ppm.

HRMS – Calculated [M+H]+: 200.1434; Found [M+H]+: 200.1437.

2-(*tert*-butyl)quinoxaline

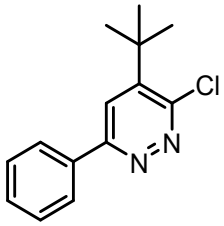


Reaction run according to **General Procedure A**. 2-(tert-butyl)-quinoxaline was isolated as a colorless oil. Characterization data is consistent with previously reported literature (Stephenson *et al. Org. Lett.*, **2018,** *20, 3487–3490.*). [8]

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.09 – 8.03 (m, 2H), 7.71 (dddd, *J* = 19.8, 8.3, 6.9, 1.6 Hz, 2H), 1.52 (s, 9H) ppm.

HRMS: Calculated [M+H]+: 187.1230; Found [M+H]+: 187.1234.

4-(*tert*-butyl)-3-chloro-6-phenylpyridazine

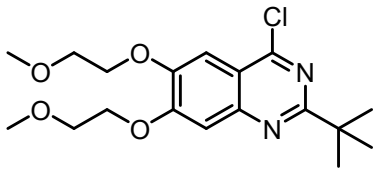


Reaction run according to **General Procedure A**. 4-(tert-butyl)-3-chloro-6-phenylpyridazine was isolated as a colorless, amorphous solid. Characterization data is consistent with previously reported literature (Stephenson *et al. ACS Catal.*, **2020,** *10, 12636–12641.*). [10]

^{1}H NMR (600 MHz, cdcl$_3$) δ 8.19 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.75 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.42 (s, 1H), 3.75 (s, 3H), 2.51 (s, 6H) ppm.

HRMS – Calculated [M+H]+: 288.0786; Found [M+H]+: 288.0786.

2-(*tert*-butyl)-4-chloro-6,7-bis(2-methoxyethoxy)quinazoline



Reaction run according to **General Procedure A**. 2-(tert-butyl)-4-chloro-6,7-bis(2-methoxyethoxy)quinazoline was isolated as a colorless, amorphous solid.

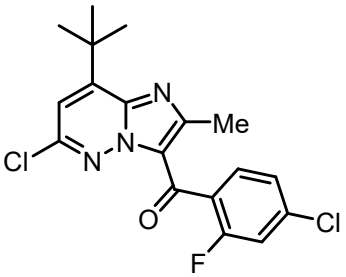
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.27 (s, 1H), 4.31 (dt, *J* = 9.7, 4.7 Hz, 4H), 3.89 – 3.85 (m, 4H), 3.49 (s, 2H), 3.48 (s, 1H), 1.45 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.76, 159.12, 156.04, 150.17, 149.22, 117.15, 107.99, 104.58, 70.79, 70.56, 68.94, 68.79, 59.54, 59.53, 39.46, 29.69 ppm.

IR(neat): 2958, 2928, 2896, 2821, 1617, 1571, 1497, 1452, 1416, 1350, 1235, 1219, 1175, 1125, 1098, 1053, 1032, 993, 933, 911, 868, 807, 731, 687 cm^{-1}

HRMS – Calculated [M+H]+: 369.1576; Found [M+H]+: 369.1578.

(8-(*tert*-butyl)-6-chloro-2-methylimidazo[1,2-*b*]pyridazin-3-yl)(4-chloro-2-fluorophenyl)methanone

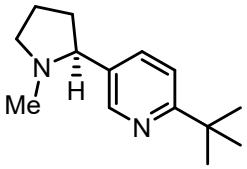


Reaction run according to **General Procedure A**. (8-(*tert*-butyl)-6-chloro-2-methylimidazo[1,2-*b*]pyridazin-3-yl)(4-chloro-2-fluorophenyl)methanone was isolated as a colorless, amorphous solid. Characterization data is consistent with previously reported literature (Stephenson *et al. Org. Lett.*, **2018,** *20, 3487–3490.*). [8]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.2, 7.5 Hz, 1H), 7.29 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.12 (dd, *J* = 9.9, 1.9 Hz, 1H), 6.98 (s, 1H), 2.67 (s, 3H), 1.58 (s, 9H) ppm.

HRMS – Calculated [M+H]+: 380.0727; Found [M+H]+: 380.0729.

(S)-2-(tert-butyl)-5-(1-methylpyrrolidin-2-yl)pyridine



Reaction run according to **General Procedure A**. (S)-2-(tert-butyl)-5-(1-methylpyrrolidin-2-yl)pyridine was isolated as a pale-yellow oil.

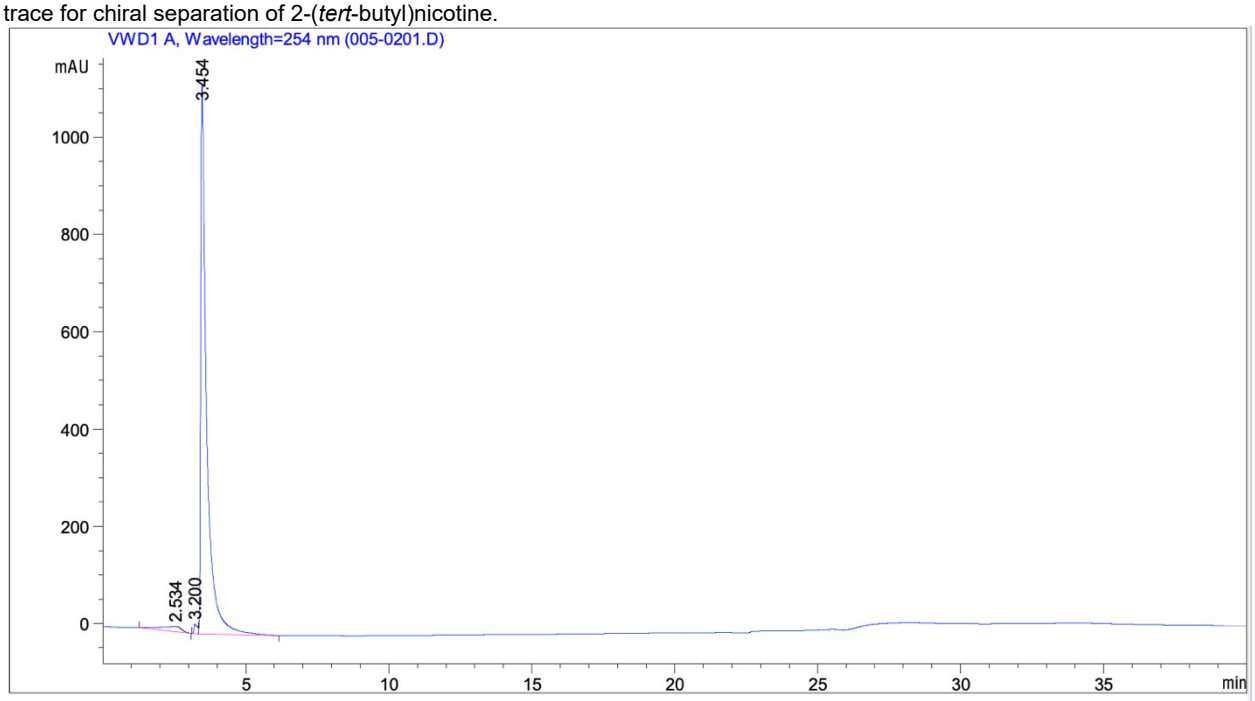
^{1}H NMR (600 MHz, C_6D_6) δ 8.71 (d, *J* = 2.4 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.13 (dd, *J* = 8.2, 0.8 Hz, 1H), 3.03 (td, *J* = 8.5, 2.2 Hz, 1H), 2.78 (t, *J* = 8.3 Hz, 1H), 2.03-1.97 (m, 4H), 1.84 (dddd, *J* = 14.6, 9.6, 6.0, 3.8 Hz, 1H), 1.77 – 1.65 (m, 1H), 1.61 – 1.51 (m, 1H), 1.48-1.41 (m, 10H) ppm.

^{13}C NMR (151 MHz, C_6D_6) δ 168.12, 148.59, 134.55, 118.51, 68.27, 56.56, 39.93, 37.15, 35.41, 30.14, 22.43 ppm.

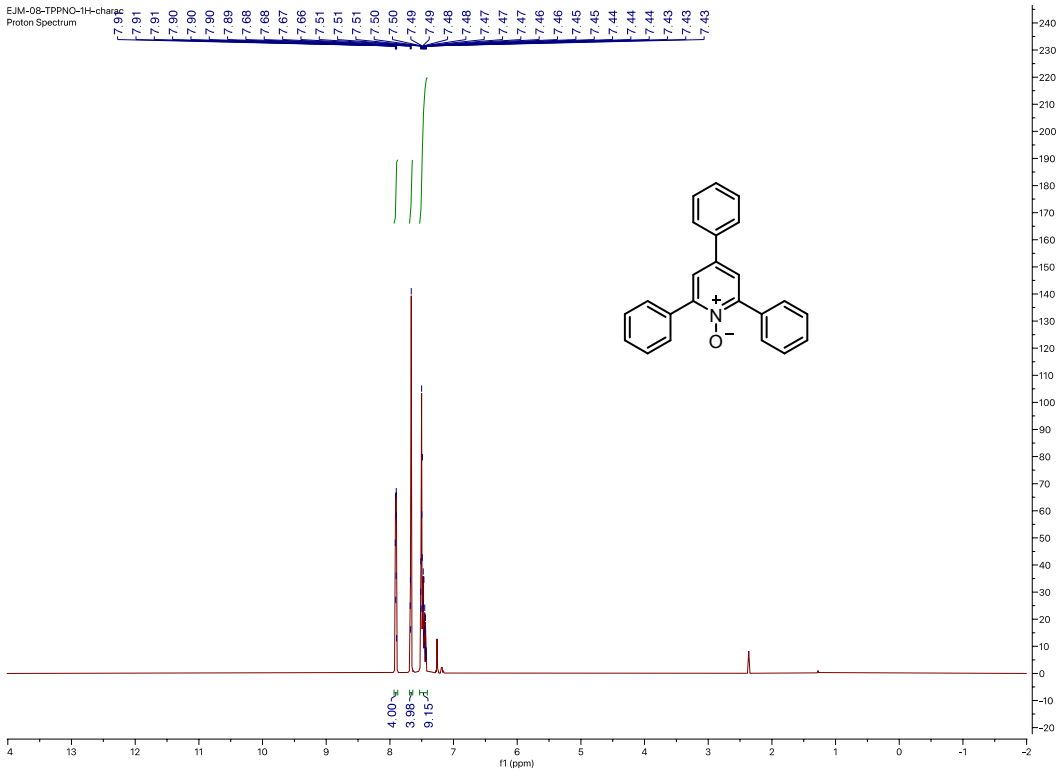
IR(neat): 2959, 2872, 2839, 2774, 1737, 1599, 1567, 1485, 1460, 1397, 1362, 1332, 1284, 1225, 1126, 1088, 1045, 1026, 904, 839, 733 cm^{-1}.

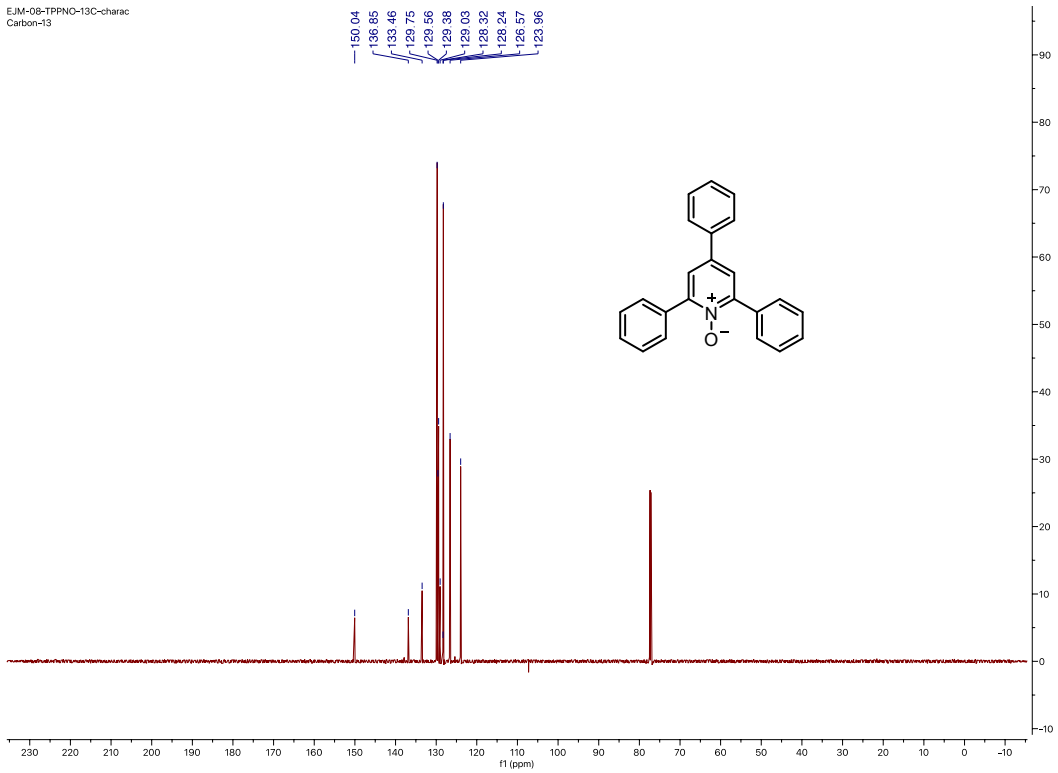
HRMS – Calculated [M+H]+: 219.1856; Found [M+H]+: 219.1857.

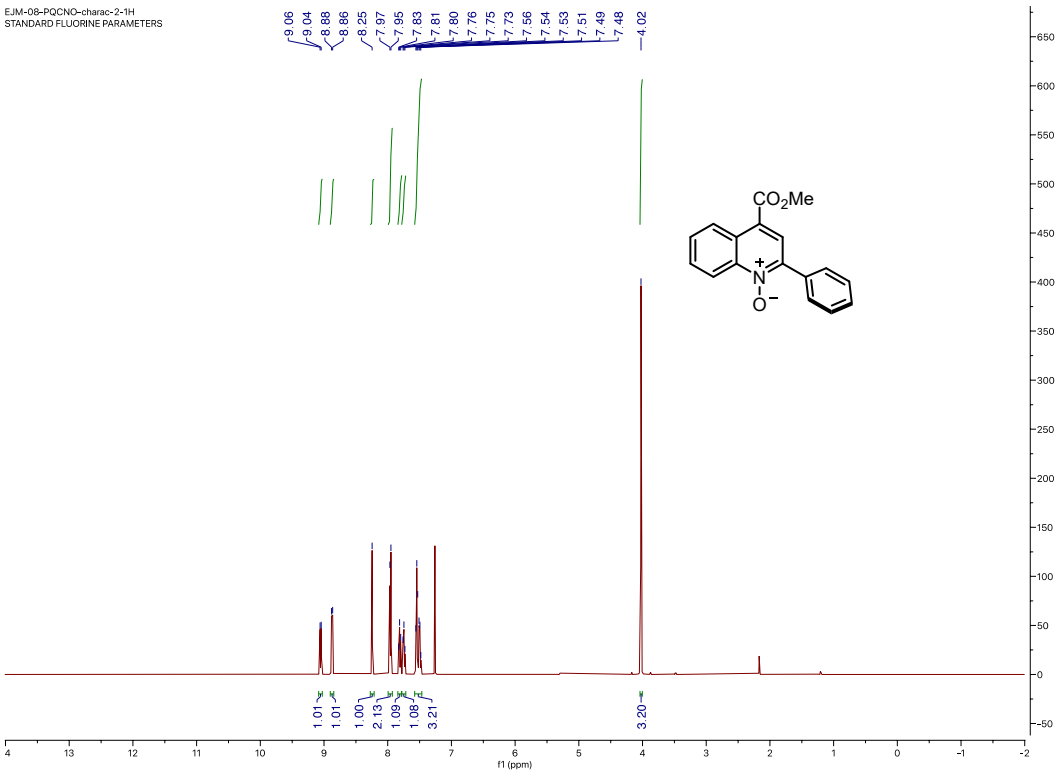
HPLC trace for chiral separation of 2-(*tert*-butyl)nicotine.

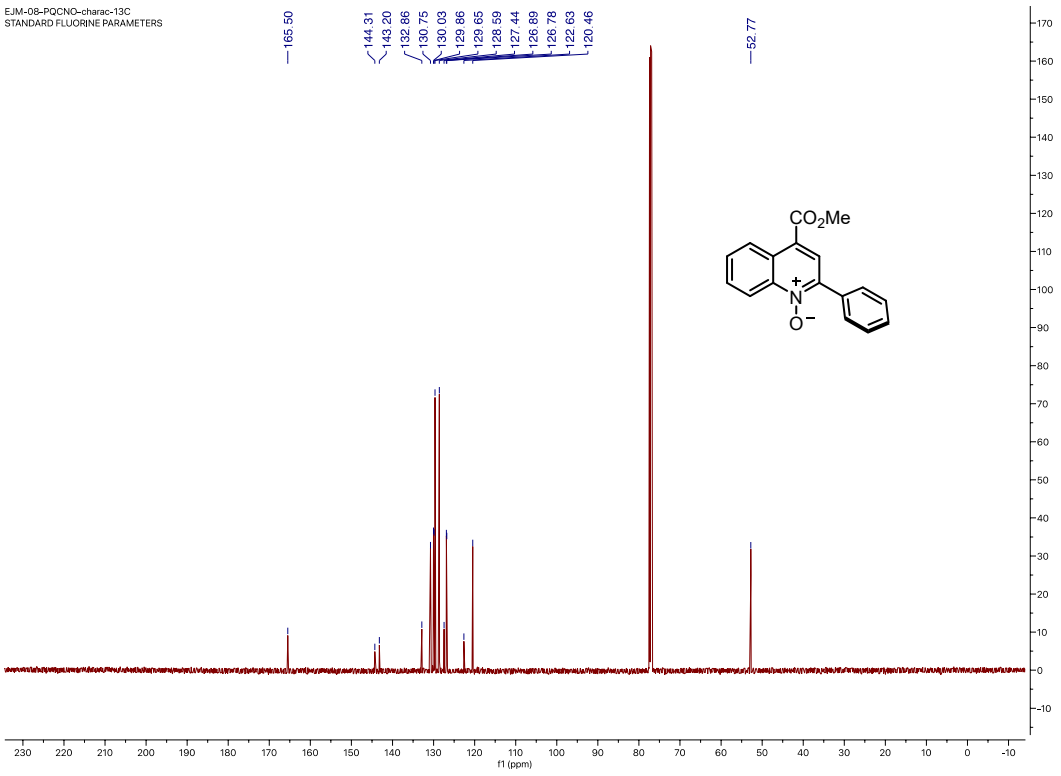


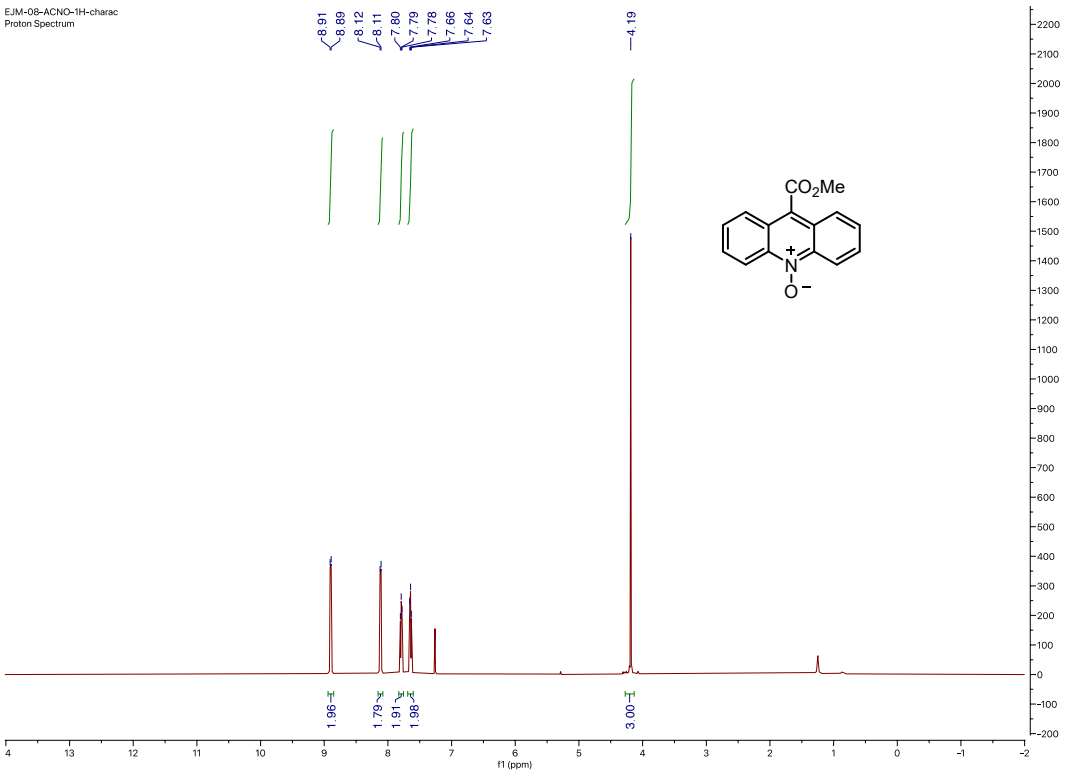
Experimental Spectra

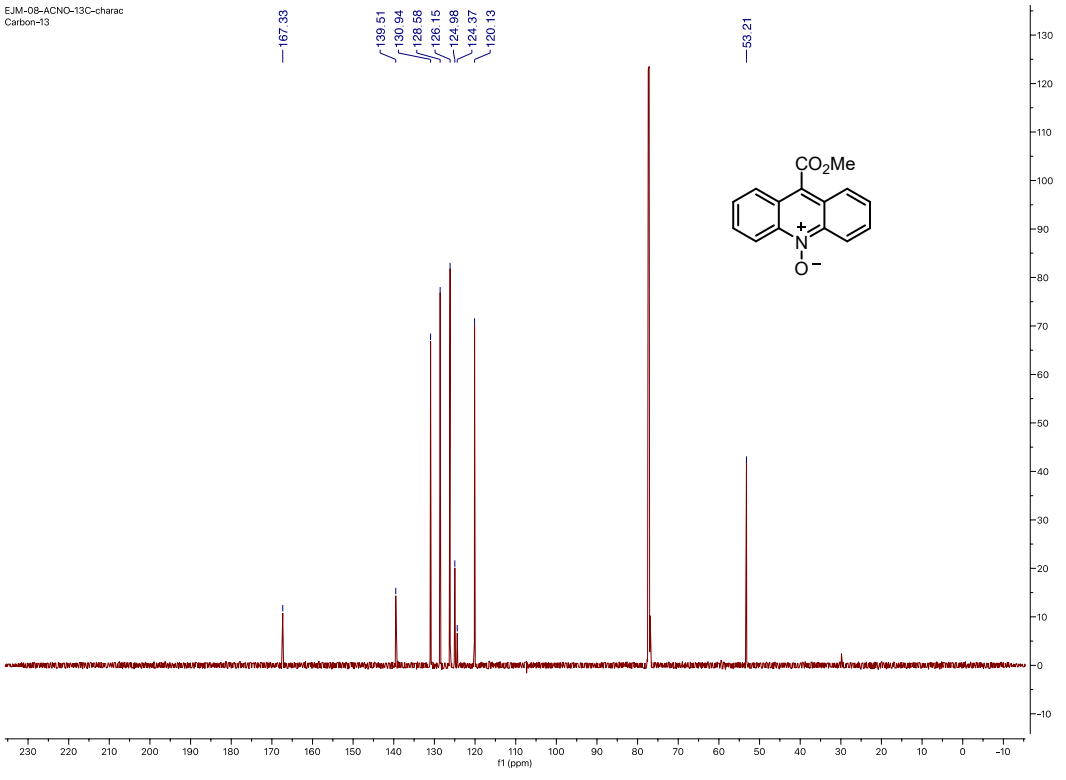


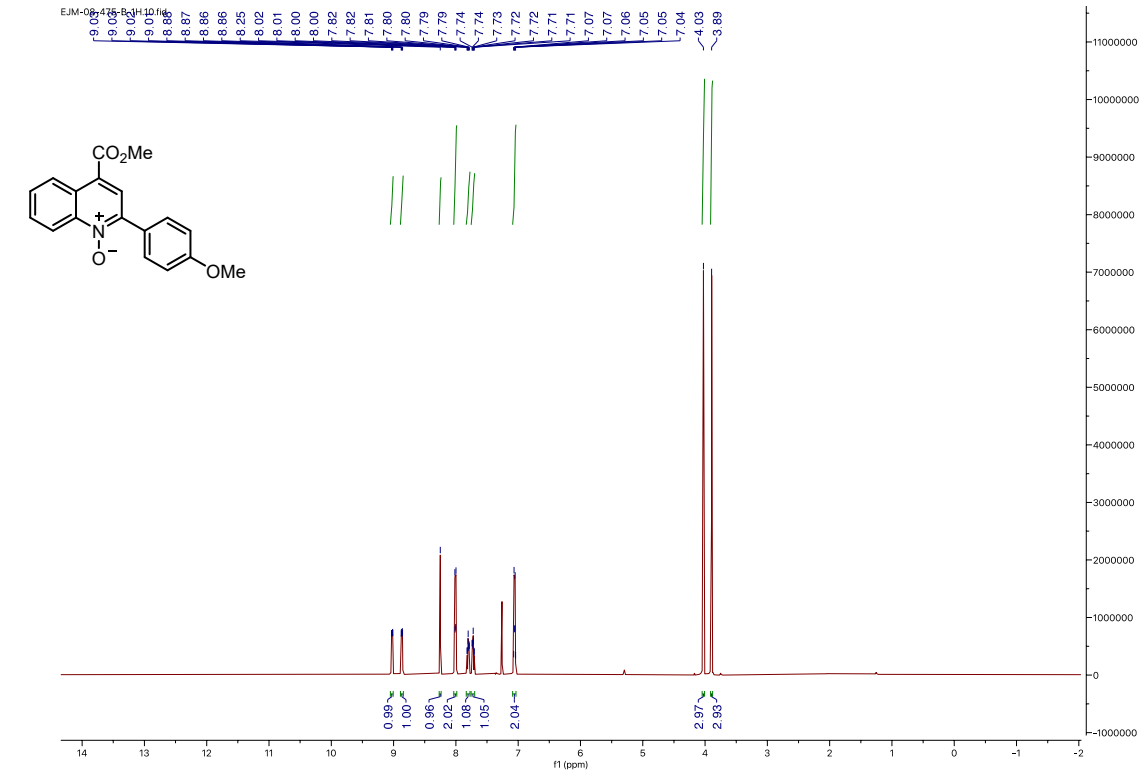


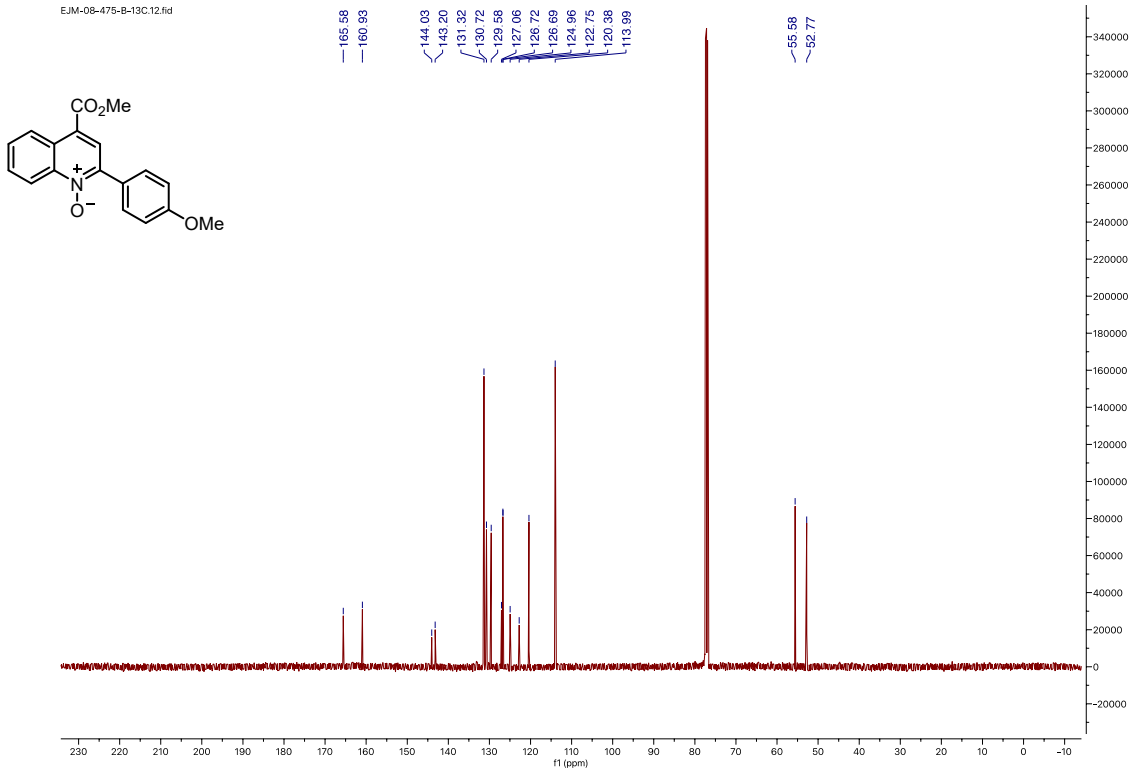

EJM-08-PQCNO-charac-2-1H
STANDARD FLUORINE PARAMETERS
9.06
9.04
8.88
8.86
8.25
7.97
7.95
7.83
7.81
7.80
7.76
7.75
7.73
7.56
7.54
7.53
7.51
7.49
7.48
4.02
CO2Me
1.01
1.01
1.00
2.13
1.09
1.08
3.21
3.20
f1 (ppm)

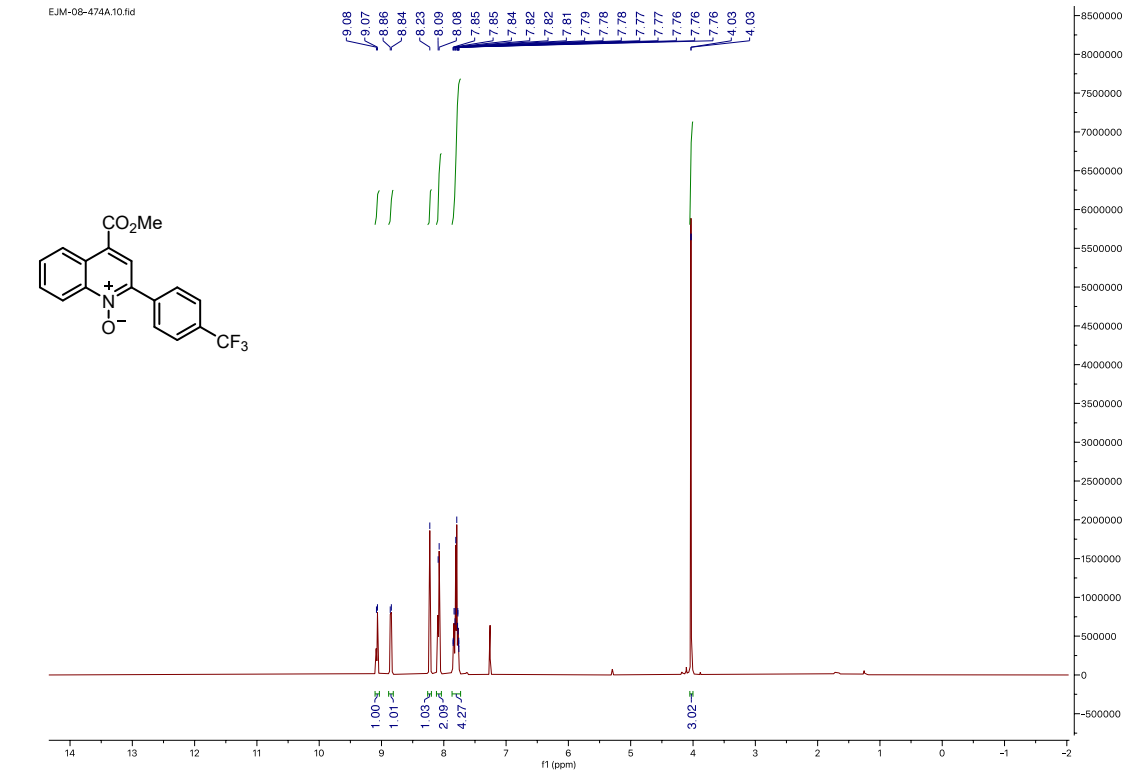

EJM-08-PQCNO-charac-13C
STANDARD FLUORINE PARAMETERS
165.50
144.31
143.20
132.86
130.75
130.03
129.86
129.65
128.59
127.44
126.89
126.78
122.63
120.46
52.77
CO2Me
f1 (ppm)

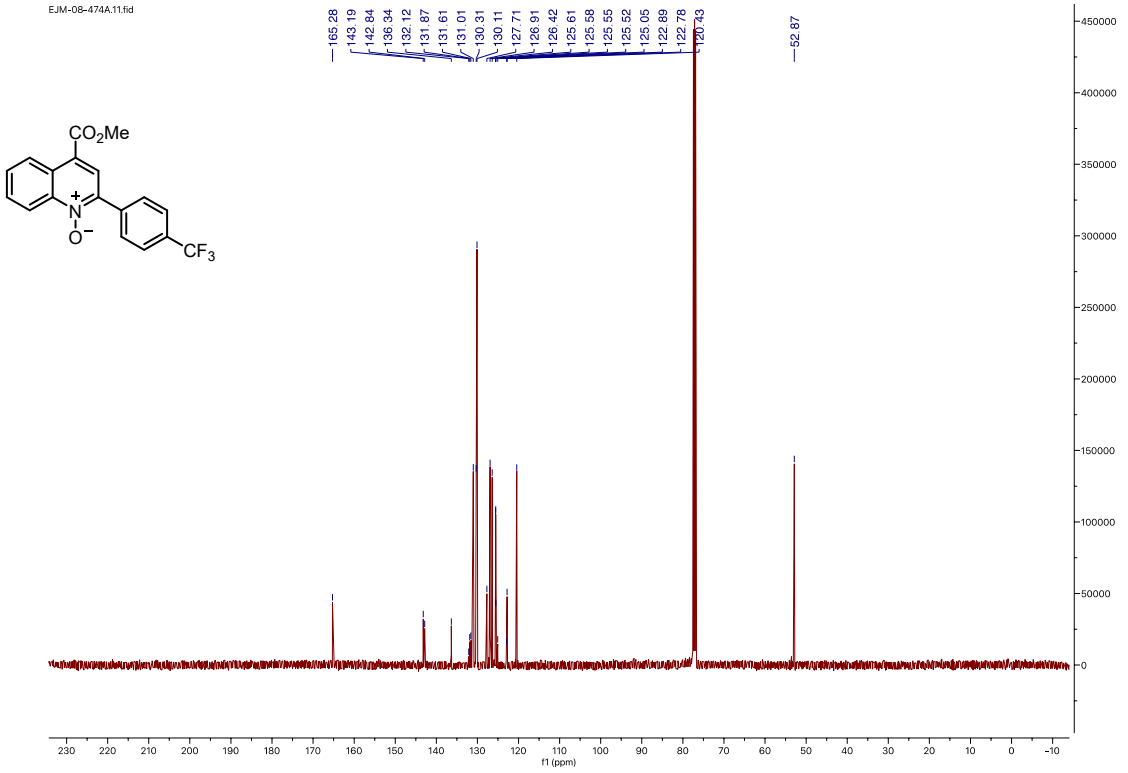

EJM-08-ACNO-1H-charac
Proton Spectrum
8.91
8.89
8.12
8.11
7.80
7.79
7.78
7.66
7.64
7.63
4.19
CO2Me
1.96
1.79
1.91
1.98
3.00
f1 (ppm)

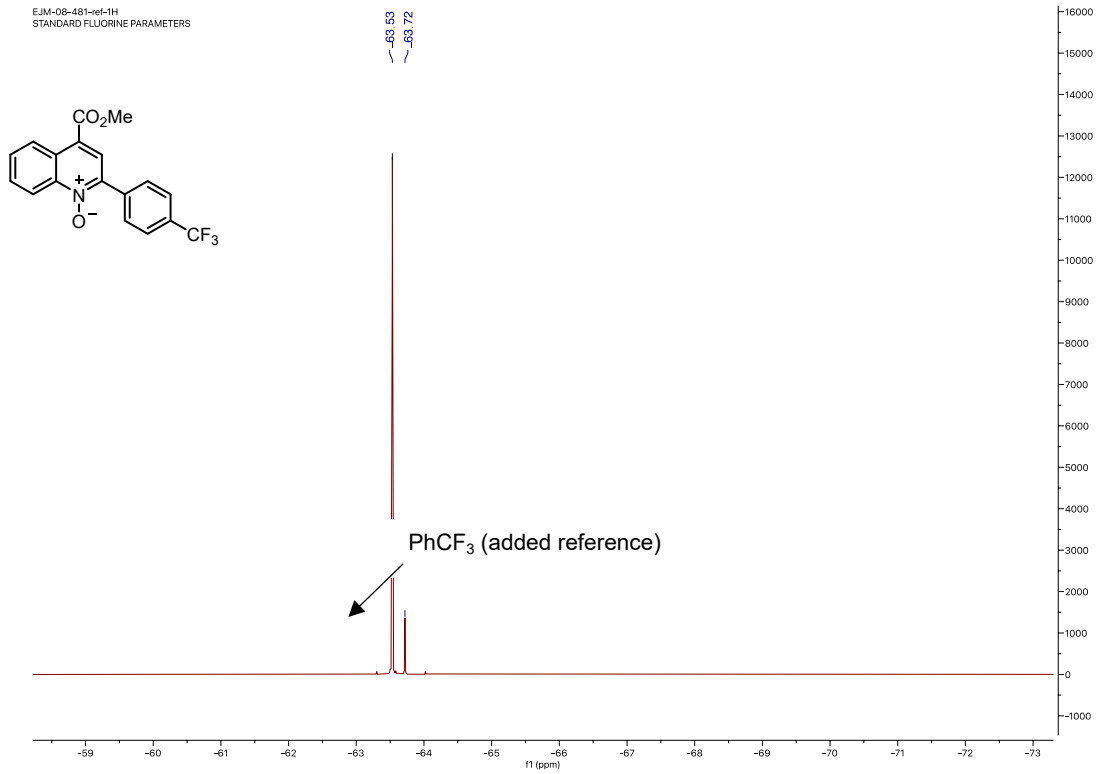

EJM-08-ACNO-13C-charac
Carbon-13
167.33
139.51
130.94
128.58
126.15
124.98
124.37
120.13
53.21
CO2Me
f1 (ppm)

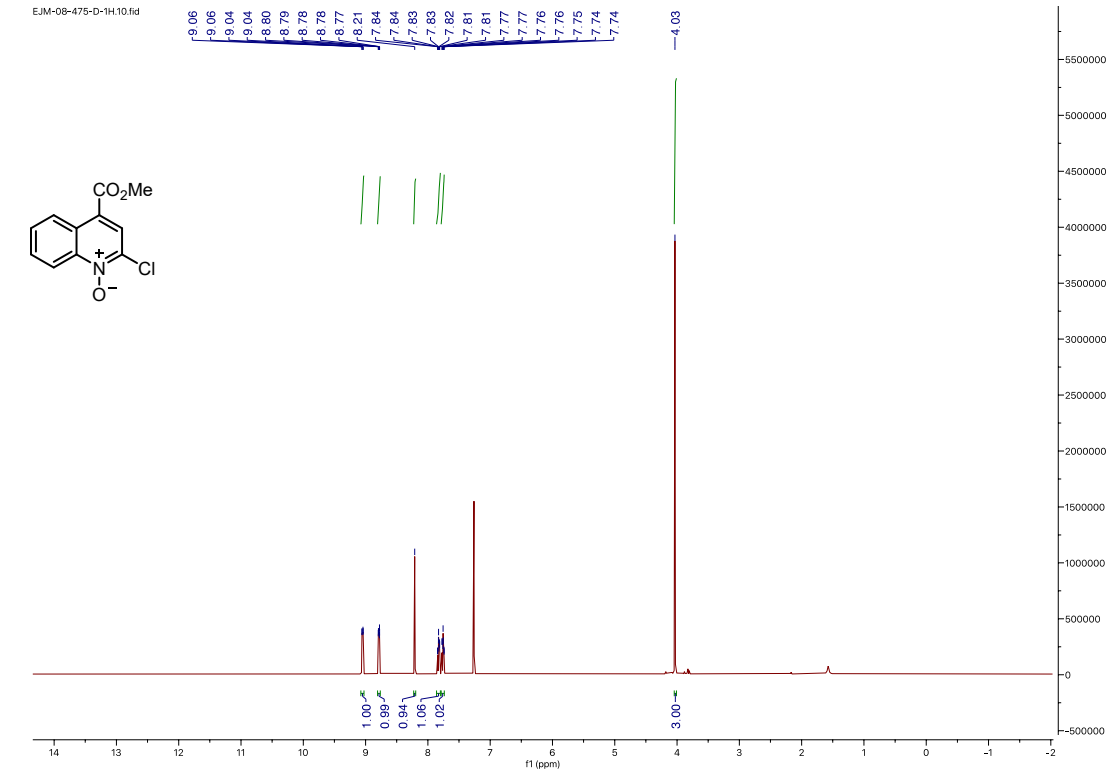

EJM-08-475-B-1H-10.fid
9.04
9.03
9.02
8.87
8.86
8.86
8.25
8.02
8.01
8.00
8.00
7.82
7.82
7.81
7.80
7.80
7.79
7.79
7.74
7.74
7.73
7.72
7.72
7.71
7.71
7.07
7.07
7.06
7.05
7.05
7.04
4.03
3.89
CO2Me
N
O
OMe
0.99
1.00
0.96
2.02
1.08
1.05
2.04
2.97
2.93
f1 (ppm)

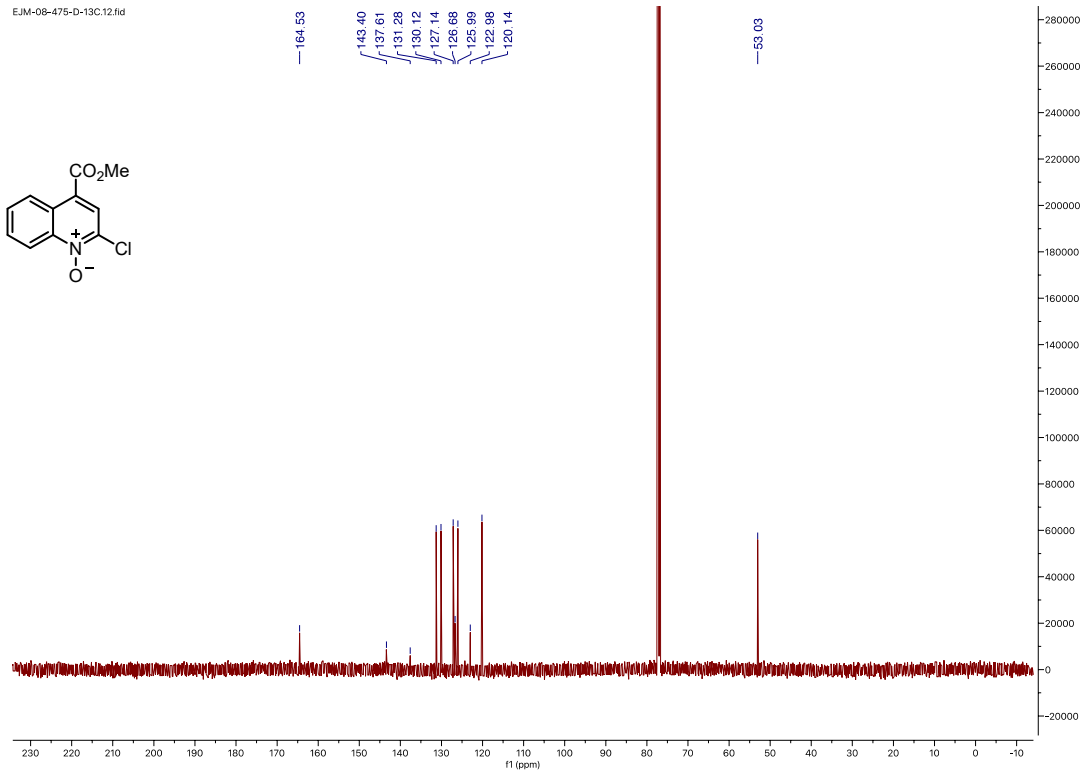

EJM-08-475-B-13C.12.fid
165.58
160.93
144.03
143.20
131.32
130.72
129.58
127.06
126.72
126.69
124.96
122.75
120.38
113.99
55.58
52.77
CO2Me
N
O
OMe
f1 (ppm)

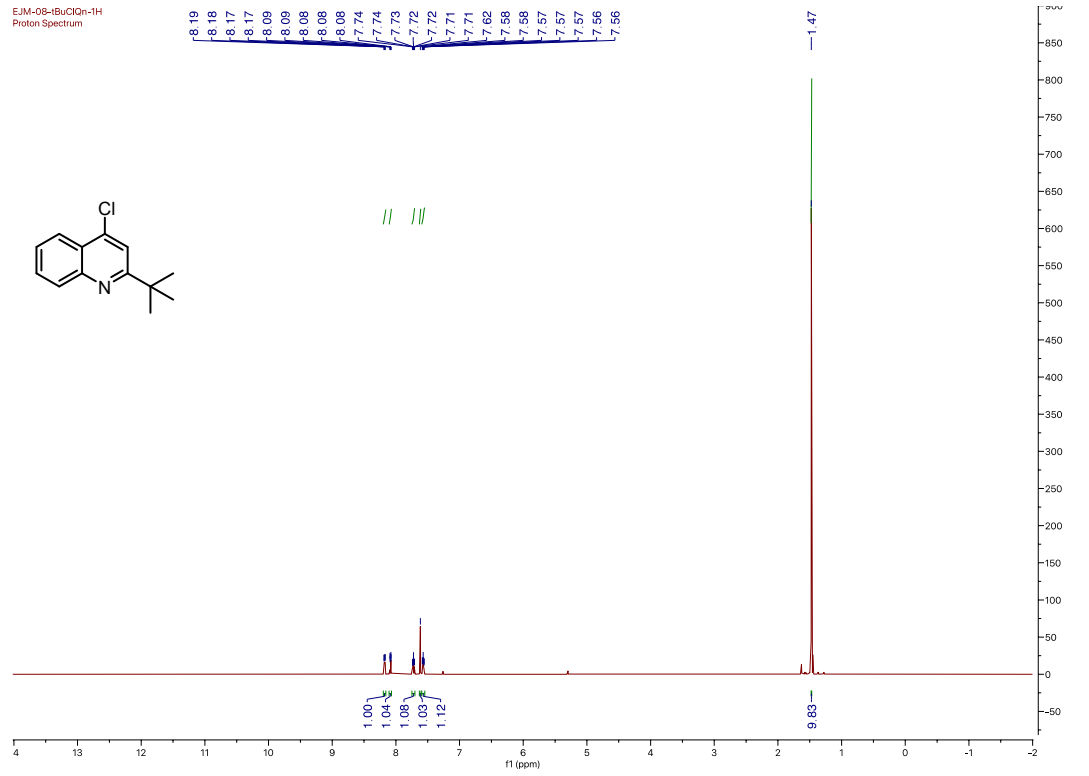

EJM-08-474A.10.fid
9.08
9.07
8.86
8.84
8.23
8.09
8.08
7.85
7.85
7.84
7.82
7.82
7.81
7.79
7.78
7.78
7.77
7.77
7.76
7.76
7.76
4.03
4.03
CO2Me
N
O
CF3
1.00
1.01
1.03
2.09
4.27
3.02
f1 (ppm)

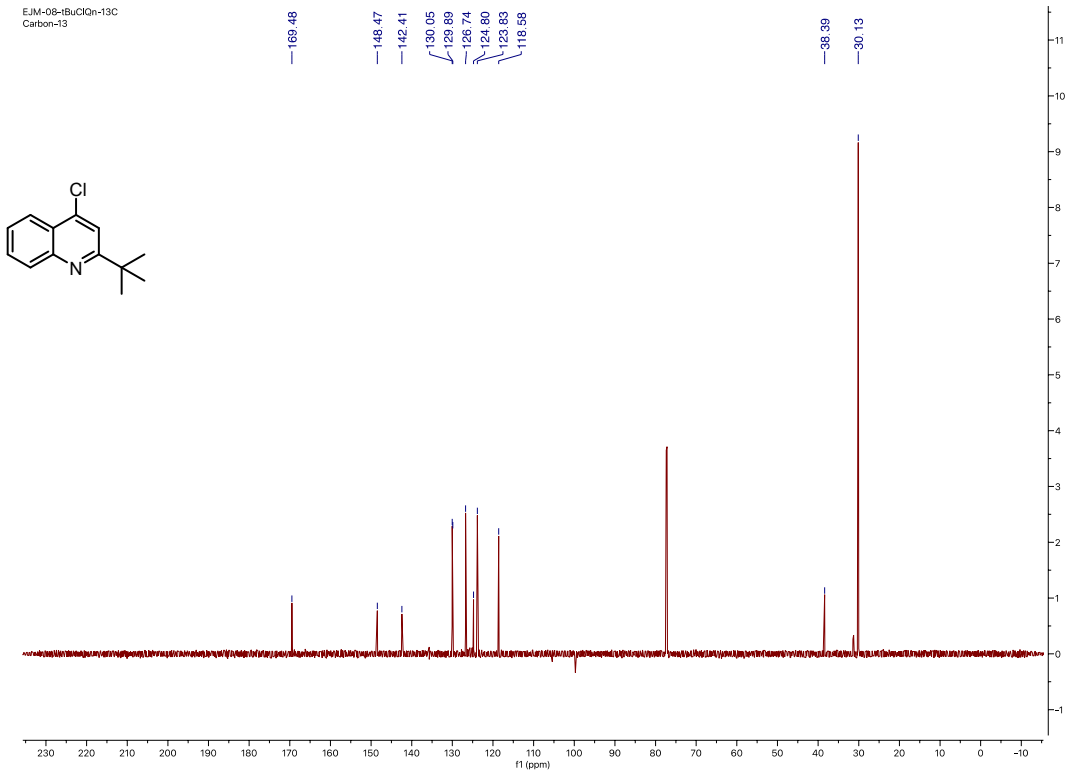

EJM-08-474A.11.fid
165.28
143.19
142.84
136.34
132.12
131.87
131.61
131.01
130.31
130.11
127.71
126.91
126.42
125.61
125.58
125.55
125.52
125.05
122.89
122.78
120.43
52.87
CO2Me
N
O
CF3
f1 (ppm)

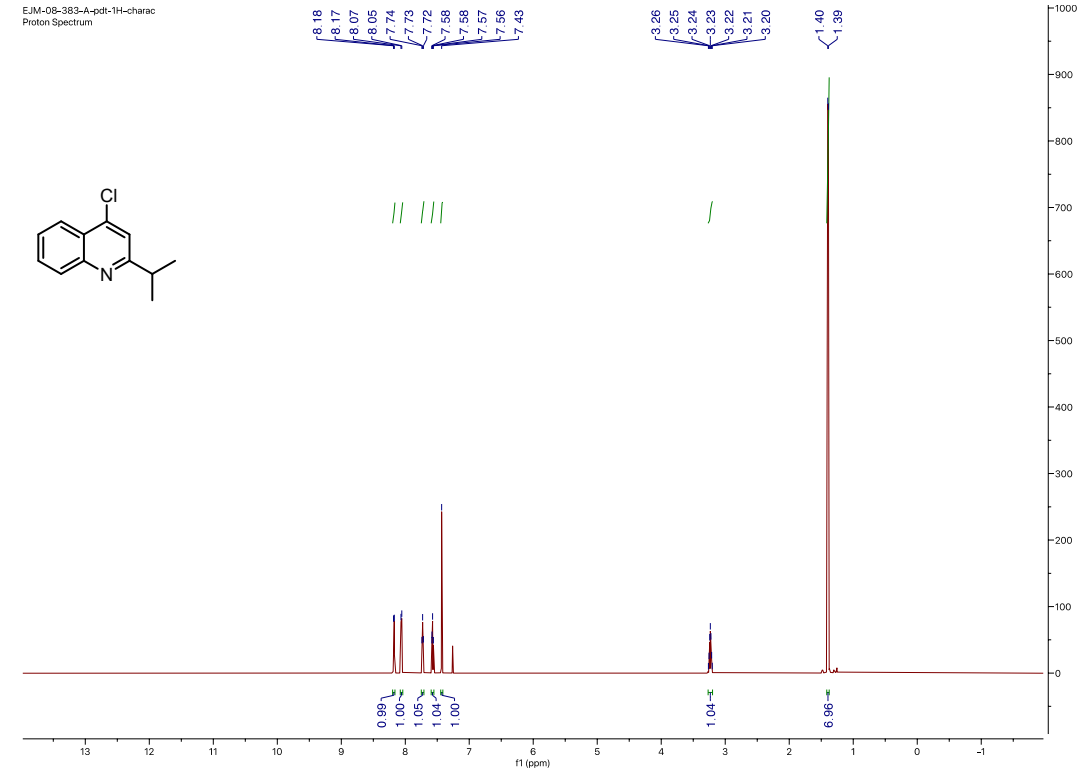

EJM-08-481-ref-1H
STANDARD FLUORINE PARAMETERS
CO2Me
N
O
CF3
-63.53
-63.72
PhCF3 (added reference)
f1 (ppm)

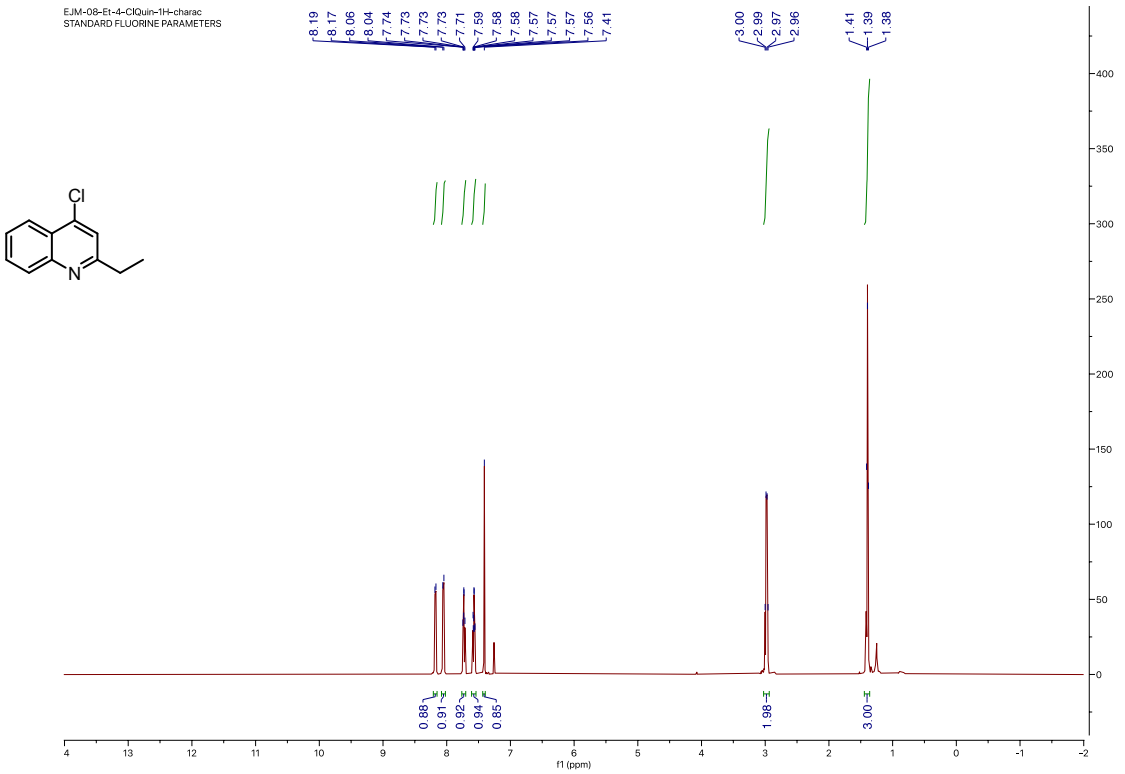

EJM-08-475-D-1H.10.fid
CO2Me
N
O
Cl
9.06
9.04
8.80
8.79
8.78
8.77
8.21
7.84
7.83
7.82
7.81
7.77
7.76
7.75
7.74
4.03
1.00
0.99
0.94
1.06
1.02
3.00
f1 (ppm)

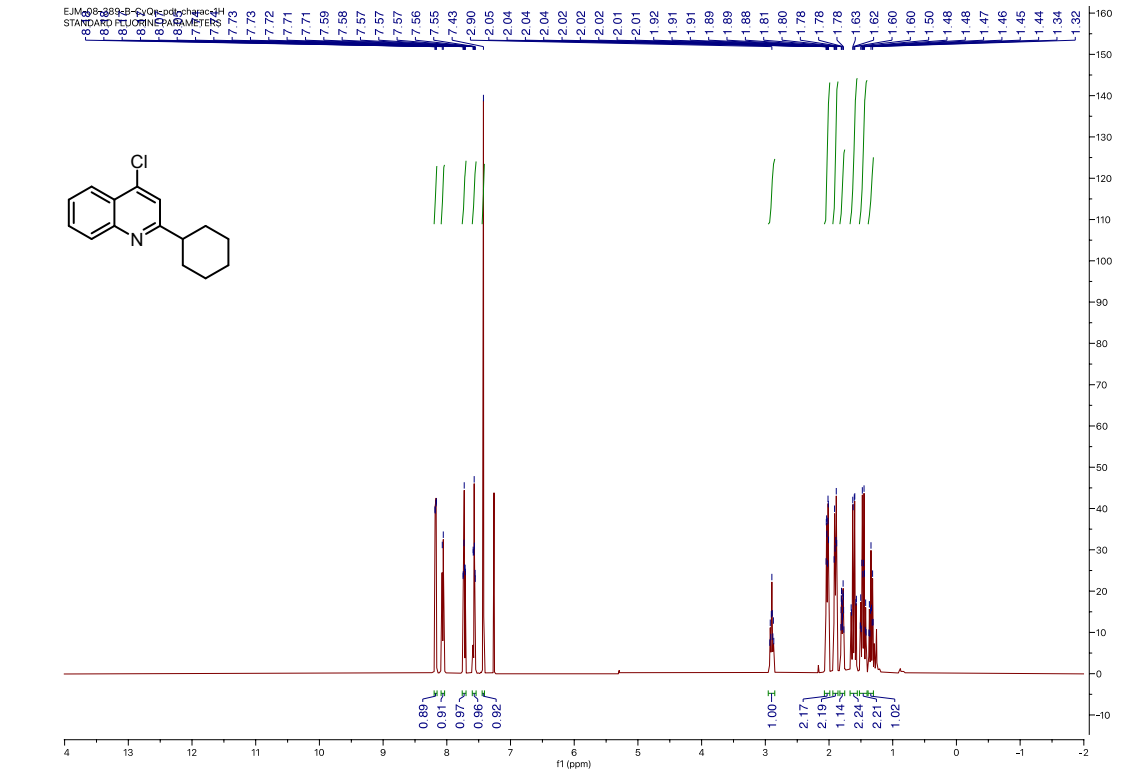

EJM-08-475-D-13C.12.fid
164.53
143.40
137.61
131.28
130.12
127.14
126.68
125.99
122.98
120.14
53.03
CO2Me
N
O
Cl
f1 (ppm)

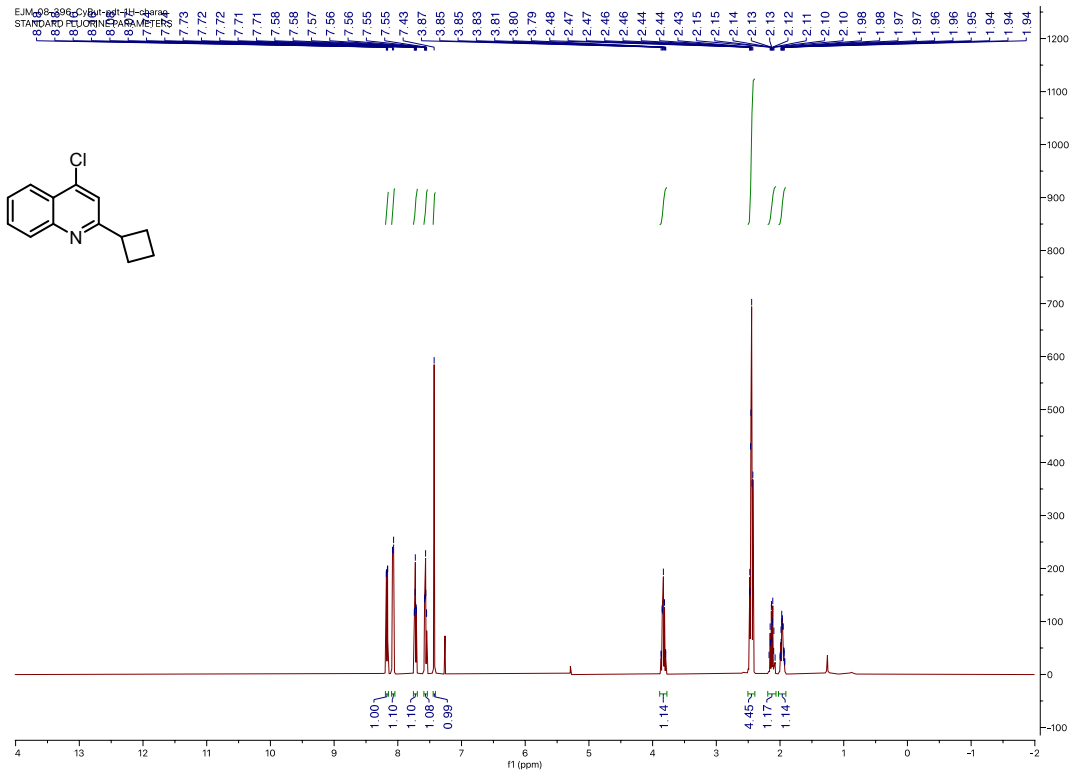

EJM-08-tBuClQn-1H
Proton Spectrum
8.19
8.18
8.17
8.17
8.09
8.09
8.08
8.08
8.08
7.74
7.74
7.73
7.72
7.72
7.71
7.71
7.62
7.58
7.58
7.57
7.57
7.57
7.56
7.56
1.47
Cl
N
1.00
1.04
1.08
1.03
1.12
9.83
f1 (ppm)

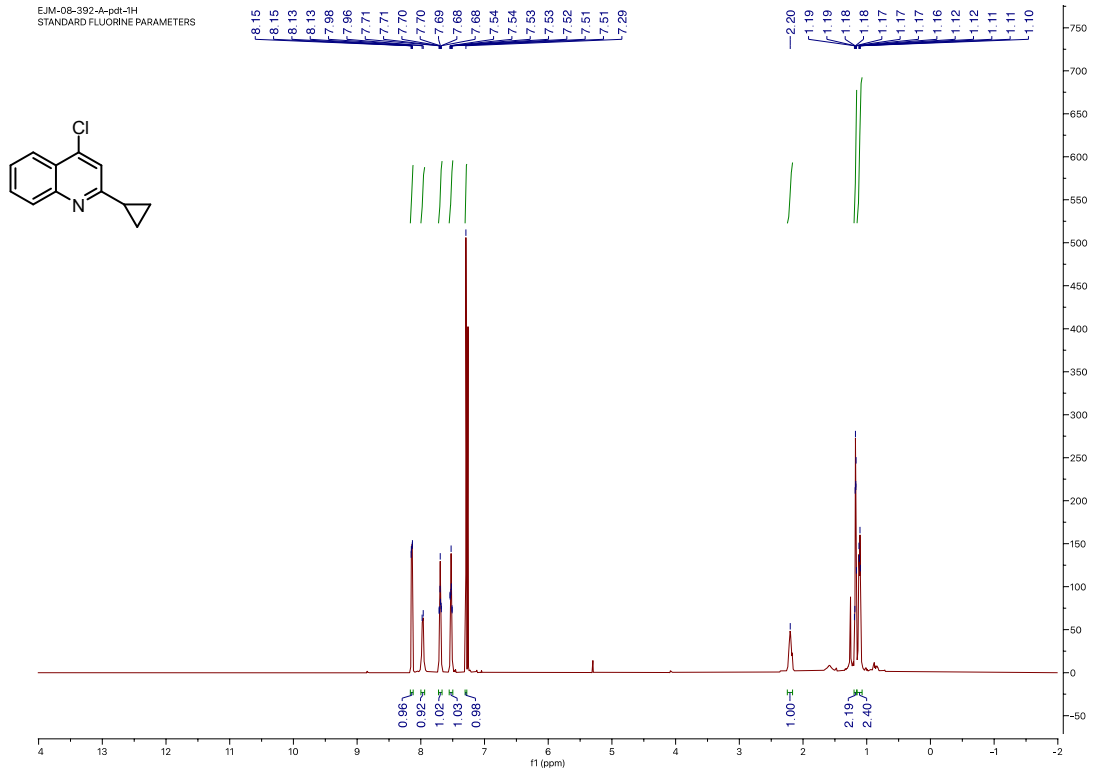

EJM-08-tBuClQn-13C
Carbon-13
169.48
148.47
142.41
130.05
129.89
126.74
124.80
123.83
118.58
38.39
30.13
Cl
N
f1 (ppm)

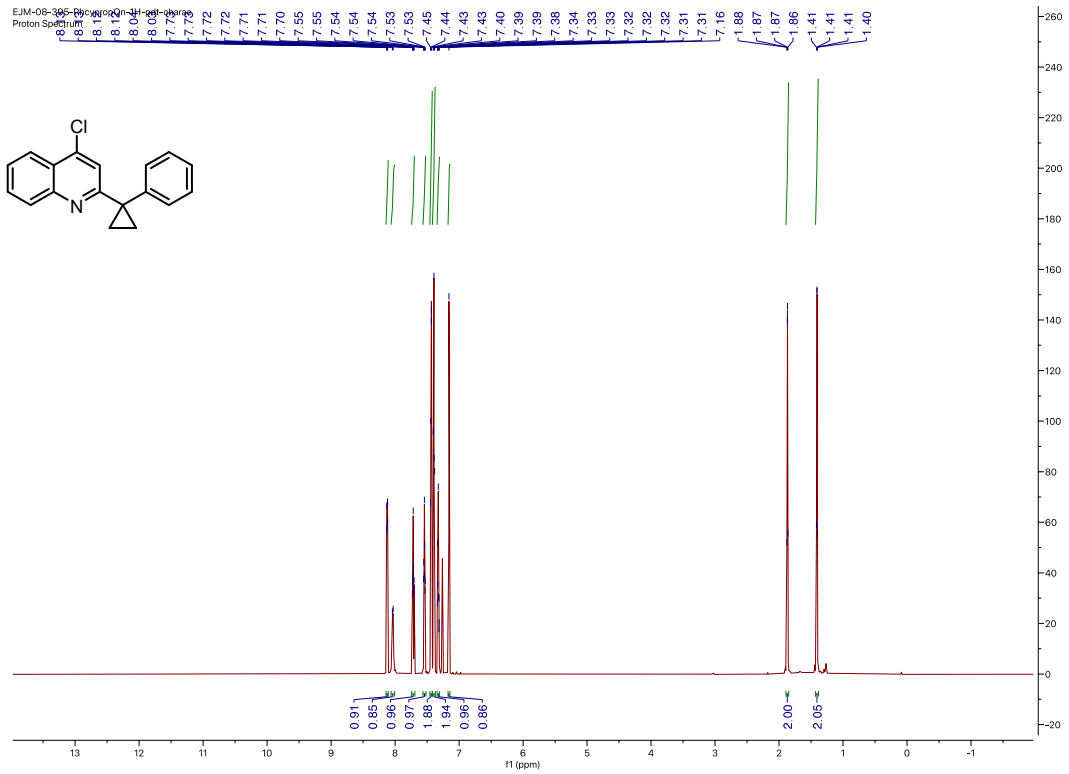

EJM-08-383-A-pdt-1H-charac
Proton Spectrum
8.18
8.17
8.07
8.05
7.74
7.73
7.72
7.58
7.58
7.57
7.56
7.43
3.26
3.25
3.24
3.23
3.22
3.21
3.20
1.40
1.39
0.99
1.00
1.05
1.04
1.00
1.04
6.96
Cl
N
f1 (ppm)

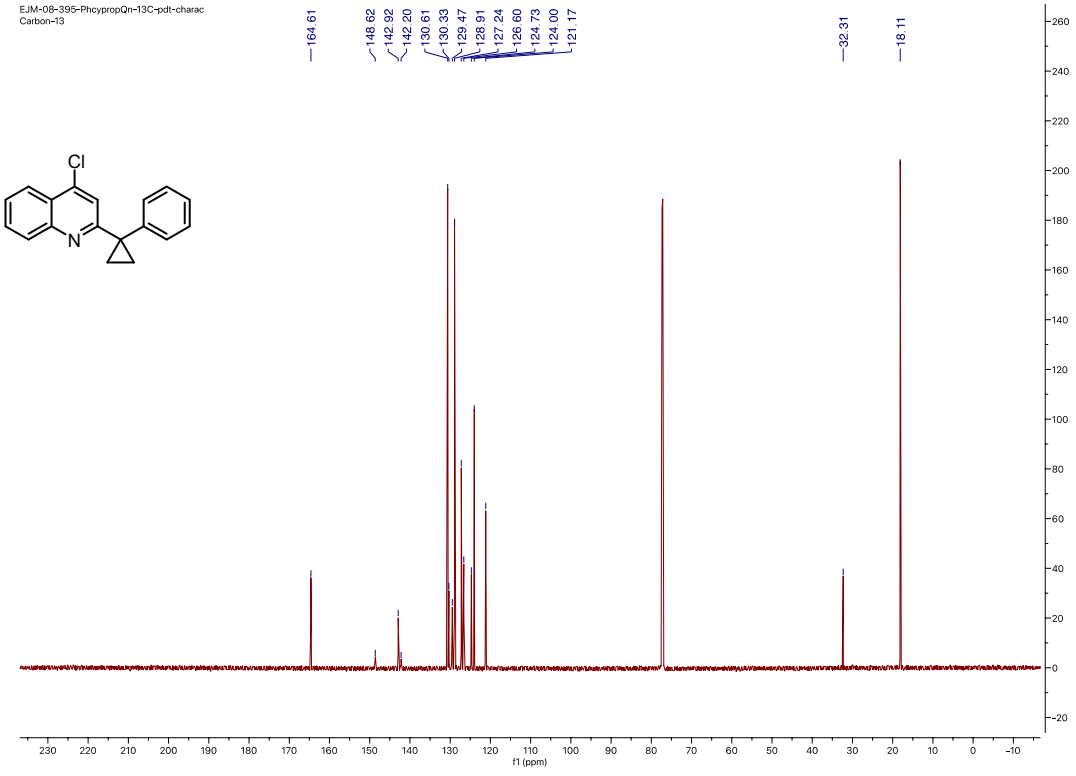

EJM-08-Et-4-ClQuin-1H-charac
STANDARD FLUORINE PARAMETERS
Cl
N
f1 (ppm)

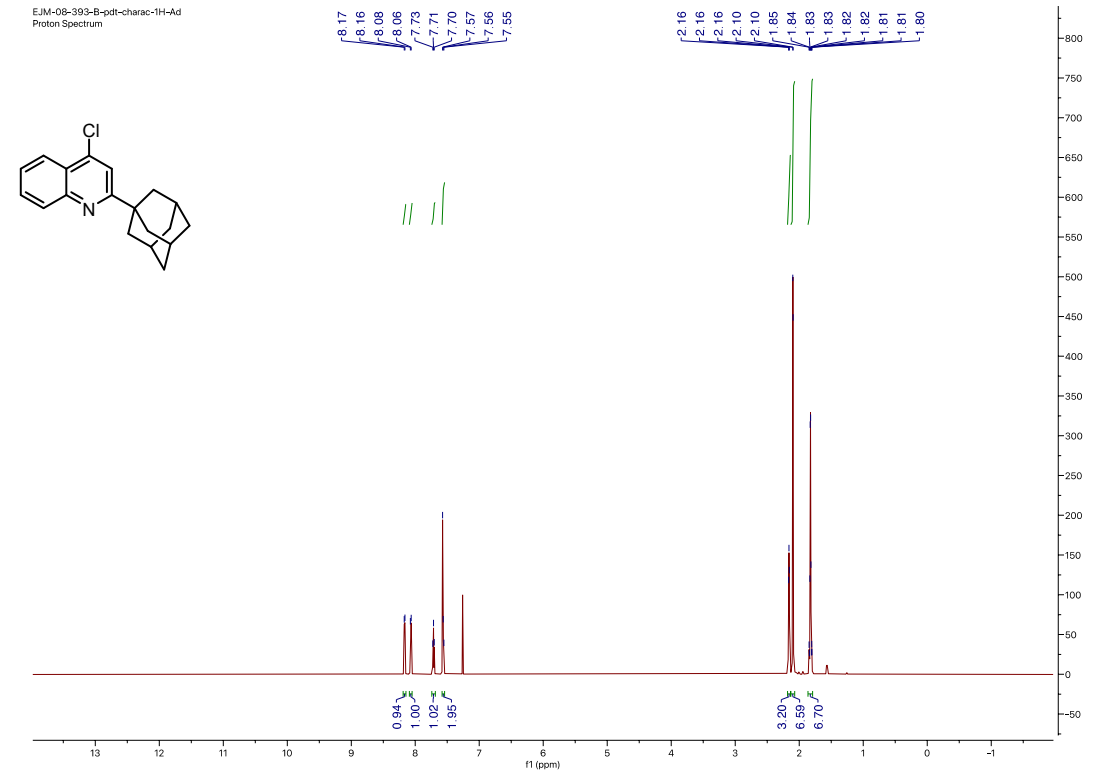

STANDARD FLUORINE PARAMETERS
Cl
N
f1 (ppm)

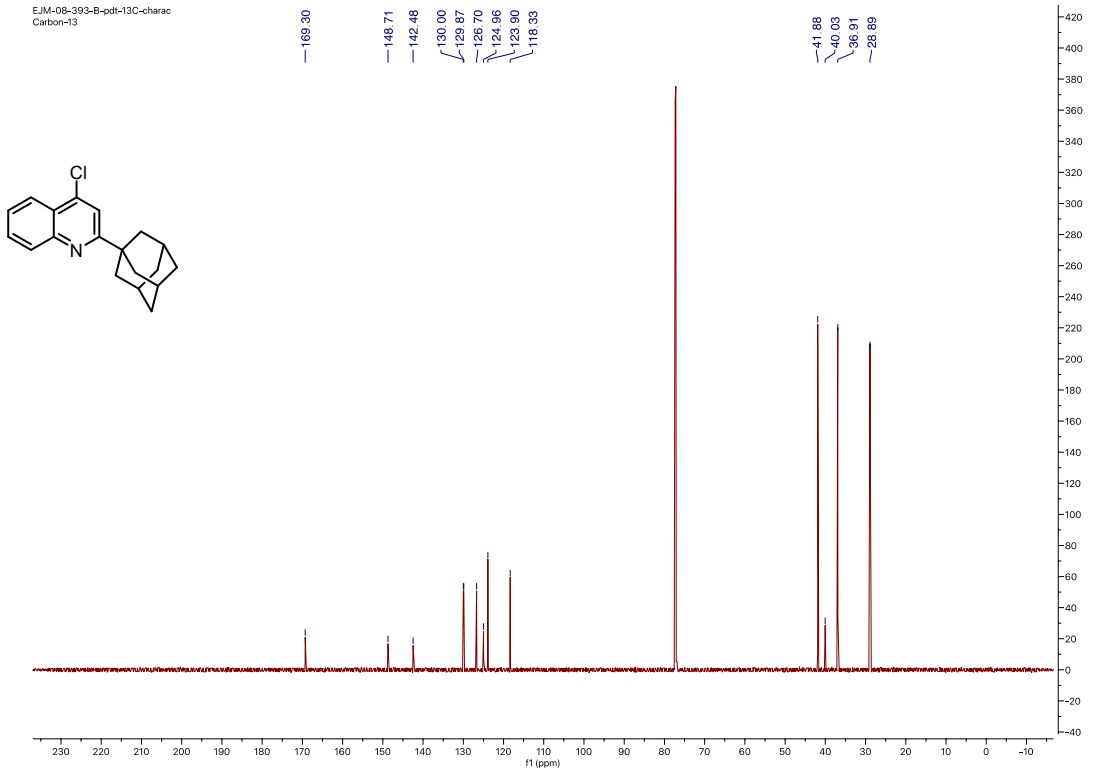

EJM-08-398-Crude-pdt-1H-charac
STANDARD FLUORINE PARAMETERS
Cl
N
1.00
1.10
1.10
1.08
0.99
1.14
4.45
1.17
1.14
f1 (ppm)

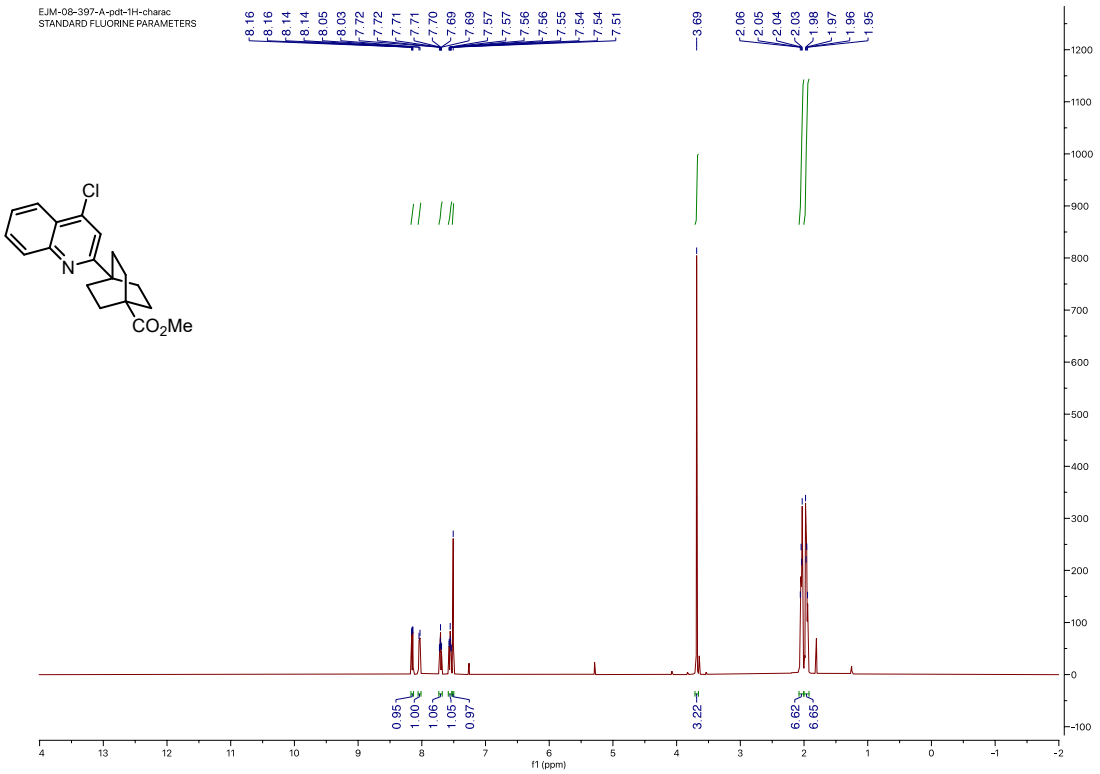

EJM-08-392-A-pdt-1H
STANDARD FLUORINE PARAMETERS
Cl
N
0.96
0.92
1.02
1.03
0.98
1.00
2.19
2.40
f1 (ppm)

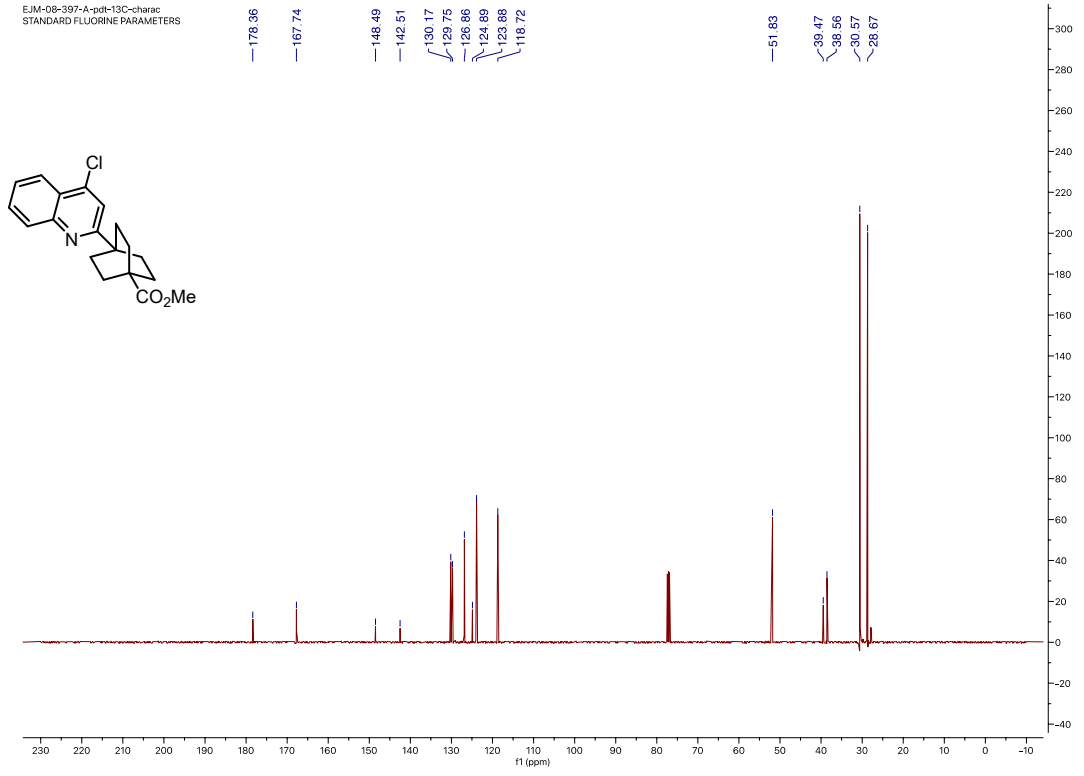

EJM-08-395-PhcypropQn-1H-pdt-charac
Proton Spectrum
Cl
N
0.91
0.85
0.96
0.97
1.88
1.94
0.96
0.86
2.00
2.05
f1 (ppm)

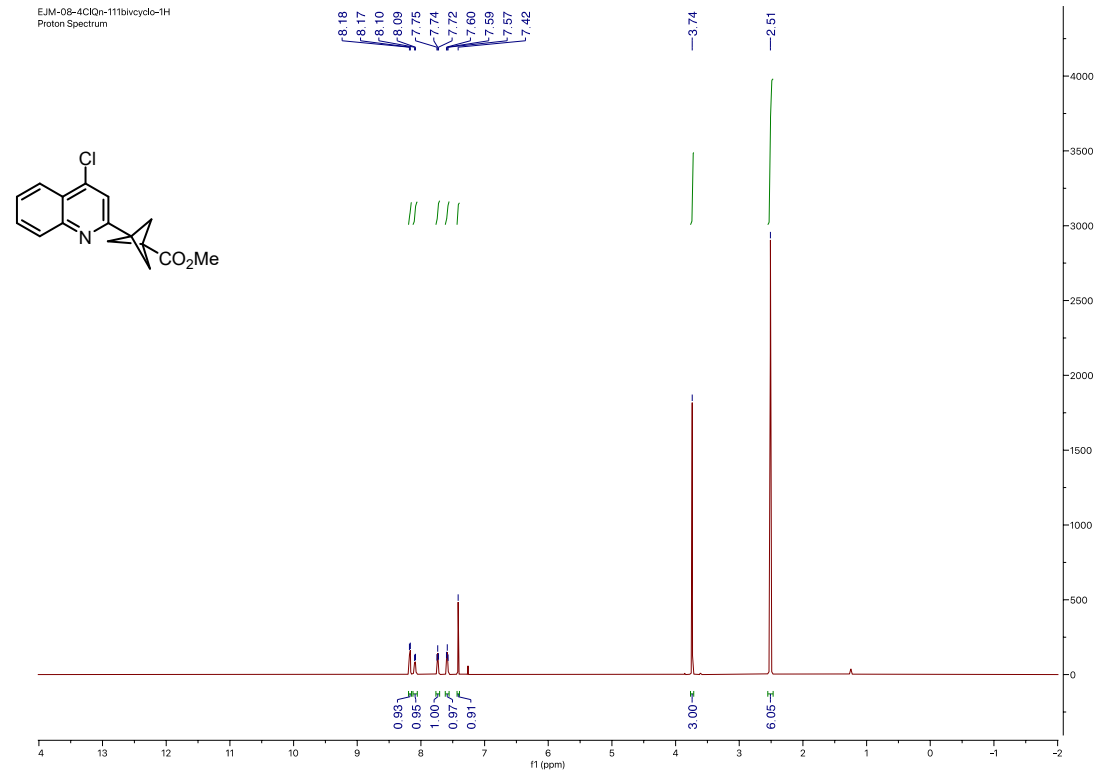

EJM-08-395-PhcypropQn-13C-pdt-charac
Carbon-13
164.61
148.62
142.92
142.20
130.61
130.33
129.47
128.91
127.24
126.60
124.73
124.00
121.17
32.31
18.11
Cl
N
f1 (ppm)

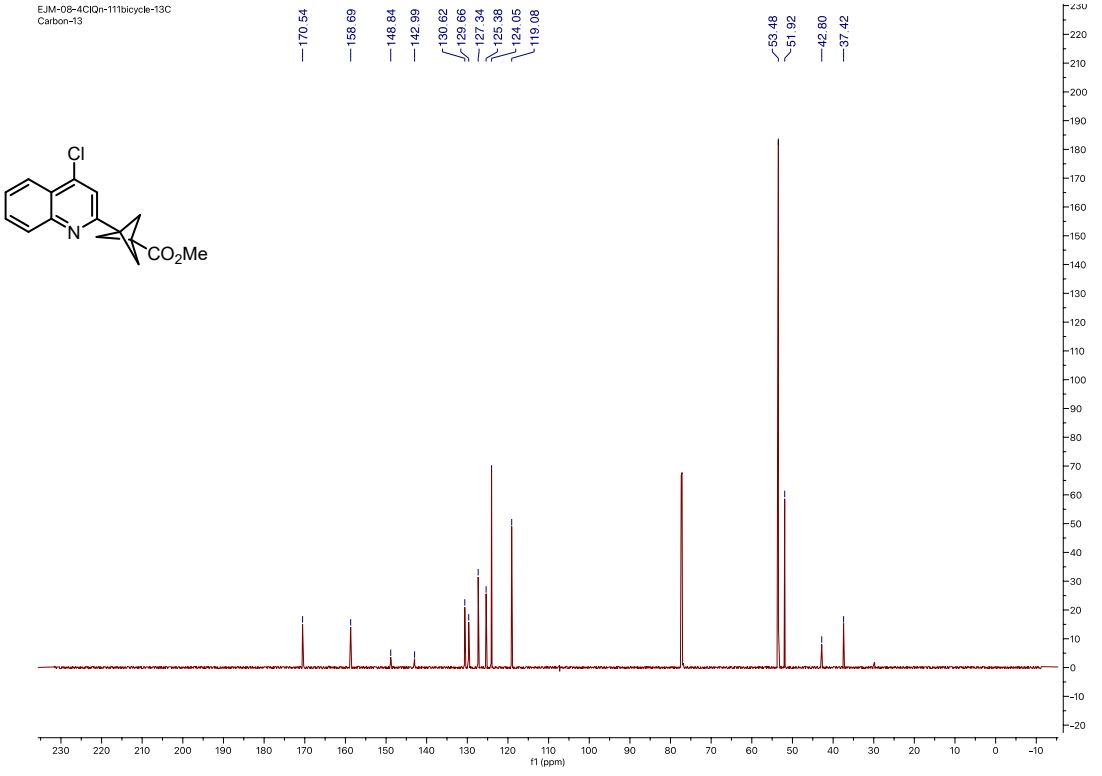

EJM-08-393-B-pdt-charac-1H-Ad
Proton Spectrum
Cl
N
8.17
8.16
8.08
8.06
7.73
7.71
7.70
7.57
7.56
7.55
2.16
2.16
2.16
2.10
2.10
1.85
1.84
1.83
1.83
1.82
1.82
1.81
1.81
1.80
0.94
1.00
1.02
1.95
3.20
6.59
6.70
f1 (ppm)

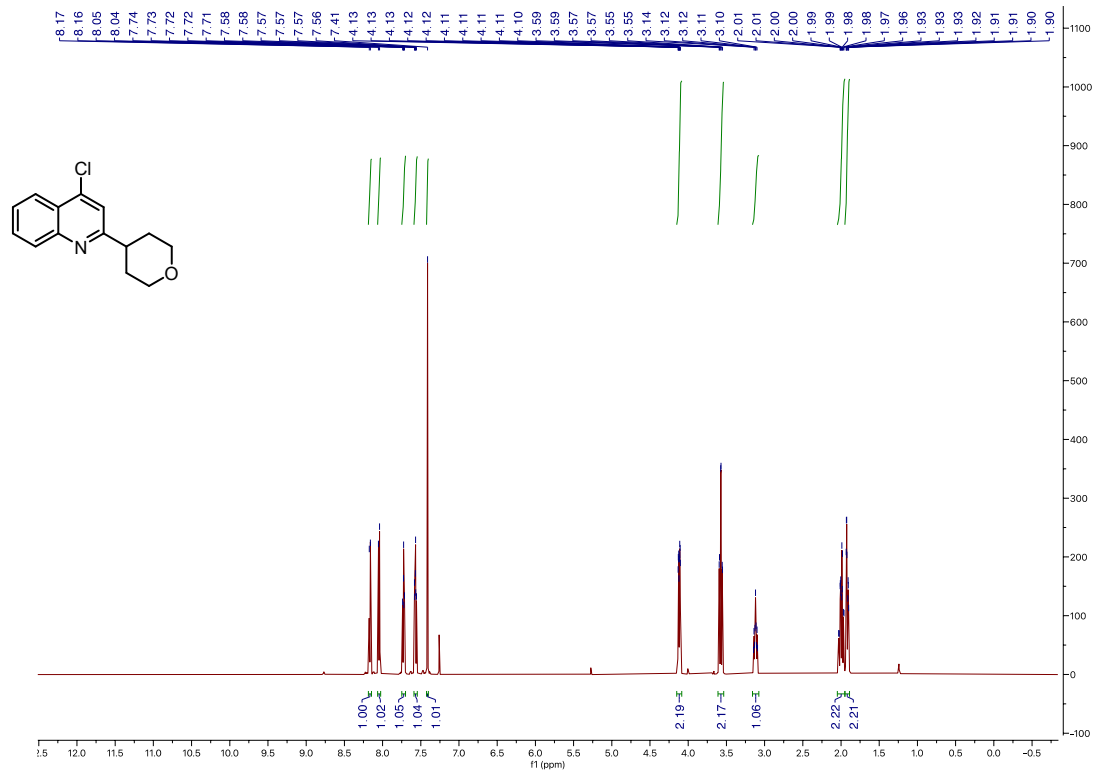

EJM-08-393-B-pdt-13C-charac
Carbon-13
Cl
N
169.30
148.71
142.48
130.00
129.87
126.70
124.96
123.90
118.33
41.88
40.03
36.91
28.89
f1 (ppm)

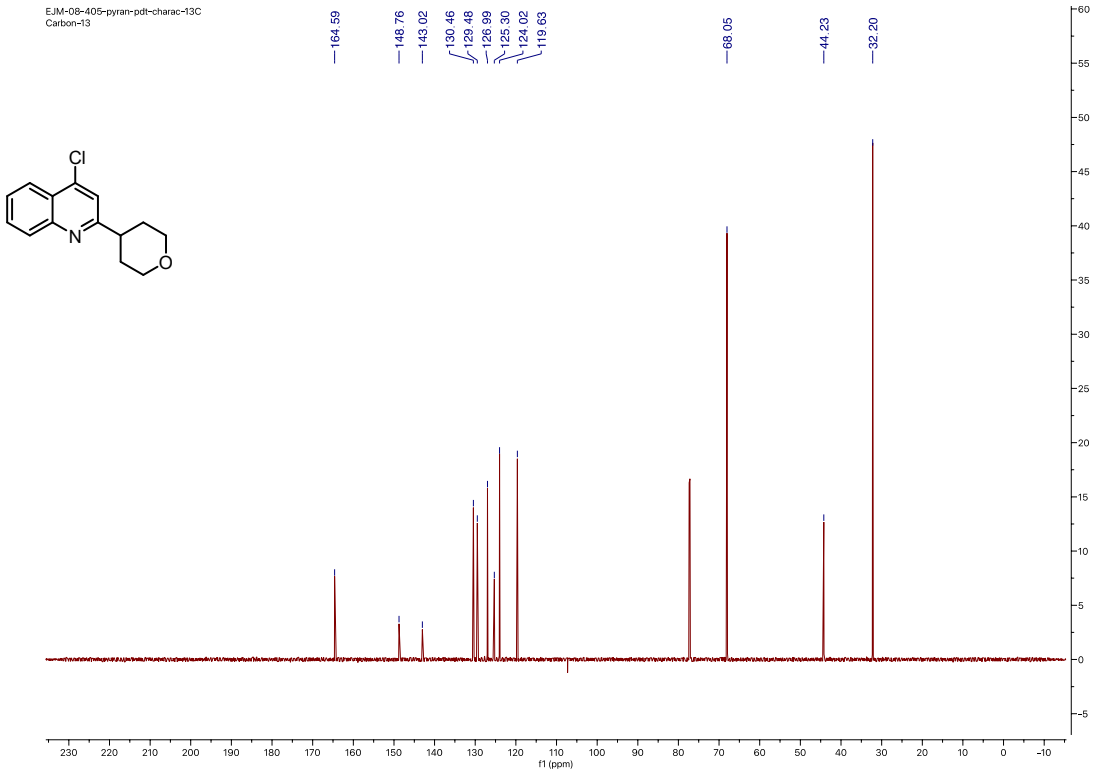

EJM-08-397-A-pdt-1H-charac
STANDARD FLUORINE PARAMETERS
8.16
8.16
8.14
8.14
8.05
8.03
7.72
7.72
7.71
7.71
7.70
7.69
7.69
7.57
7.57
7.56
7.56
7.55
7.54
7.54
7.51
3.69
2.06
2.05
2.04
2.03
1.98
1.97
1.96
1.95
Cl
N
CO2Me
0.95
1.00
1.06
1.05
0.97
3.22
6.62
6.65
f1 (ppm)

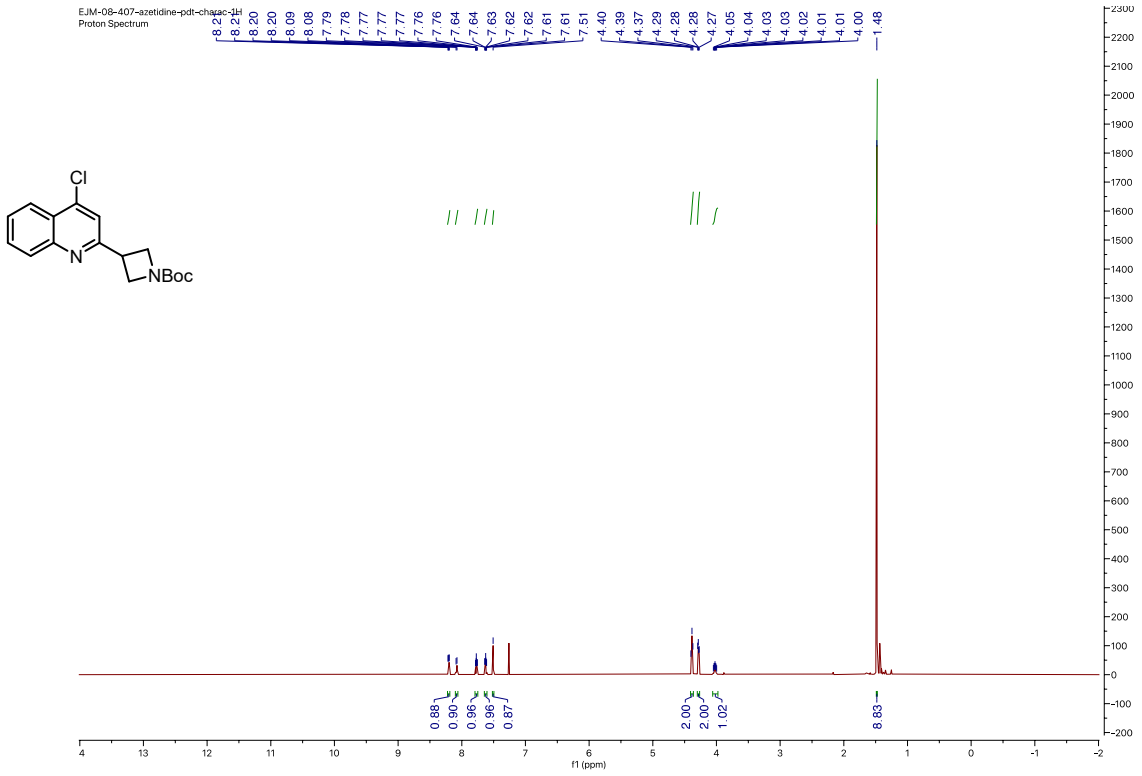

EJM-08-397-A-pdt-13C-charac
STANDARD FLUORINE PARAMETERS
178.36
167.74
148.49
142.51
130.17
129.75
126.86
124.89
123.88
118.72
51.83
39.47
38.56
30.57
28.67
Cl
N
CO2Me
f1 (ppm)

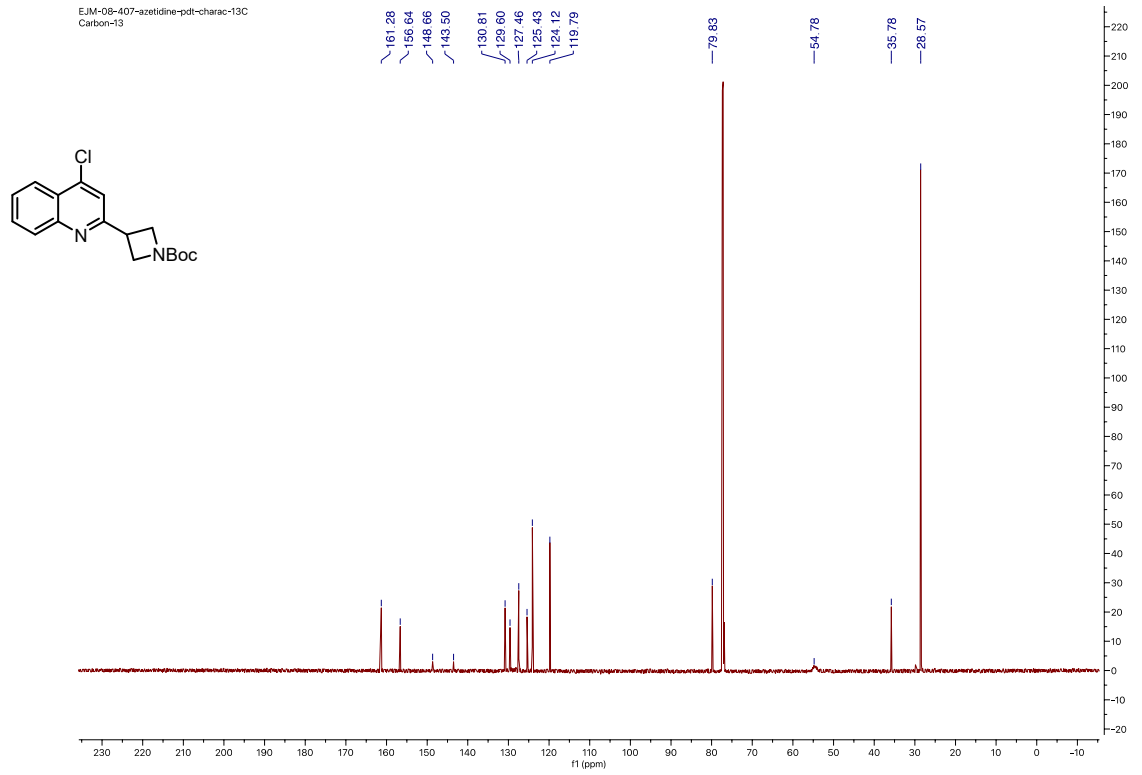

EJM-08-4ClQn-111bicyclo-1H
Proton Spectrum
8.18
8.17
8.10
8.09
7.75
7.74
7.72
7.60
7.59
7.57
7.42
3.74
2.51
Cl
N
CO2Me
0.93
0.95
1.00
0.97
0.91
3.00
6.05
f1 (ppm)


EJM-08-4ClQn-111bicycle-13C
Carbon-13
170.54
158.69
148.84
142.99
130.62
129.66
127.34
125.38
124.05
119.08
53.48
51.92
42.80
37.42
Cl
N
CO2Me
f1 (ppm)

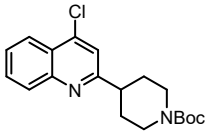

8.17 8.16 8.05 8.04 7.74 7.73 7.72 7.72 7.71 7.58 7.58 7.57 7.57 7.57 7.56 7.41 4.13 4.13 4.12 4.12 4.11 4.11 4.11 4.10 3.59 3.59 3.57 3.57 3.55 3.55 3.14 3.12 3.12 3.11 3.10 2.01 2.00 2.00 1.99 1.99 1.98 1.97 1.96 1.93 1.93 1.93 1.92 1.91 1.91 1.90 1.90
Cl
N
O
1.00 1.02 1.05 1.04 1.01 2.19 2.17 1.06 2.22 2.21
f1 (ppm)


EJM-08-405-pyran-pdt-charac-13C
Carbon-13
164.59 148.76 143.02 130.46 129.48 126.99 125.30 124.02 119.63 68.05 44.23 32.20
Cl
N
O
f1 (ppm)

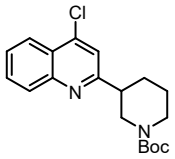

EJM-08-407-azetidine-pdt-charac-1H
Proton Spectrum
Cl
N
NBoc
f1 (ppm)

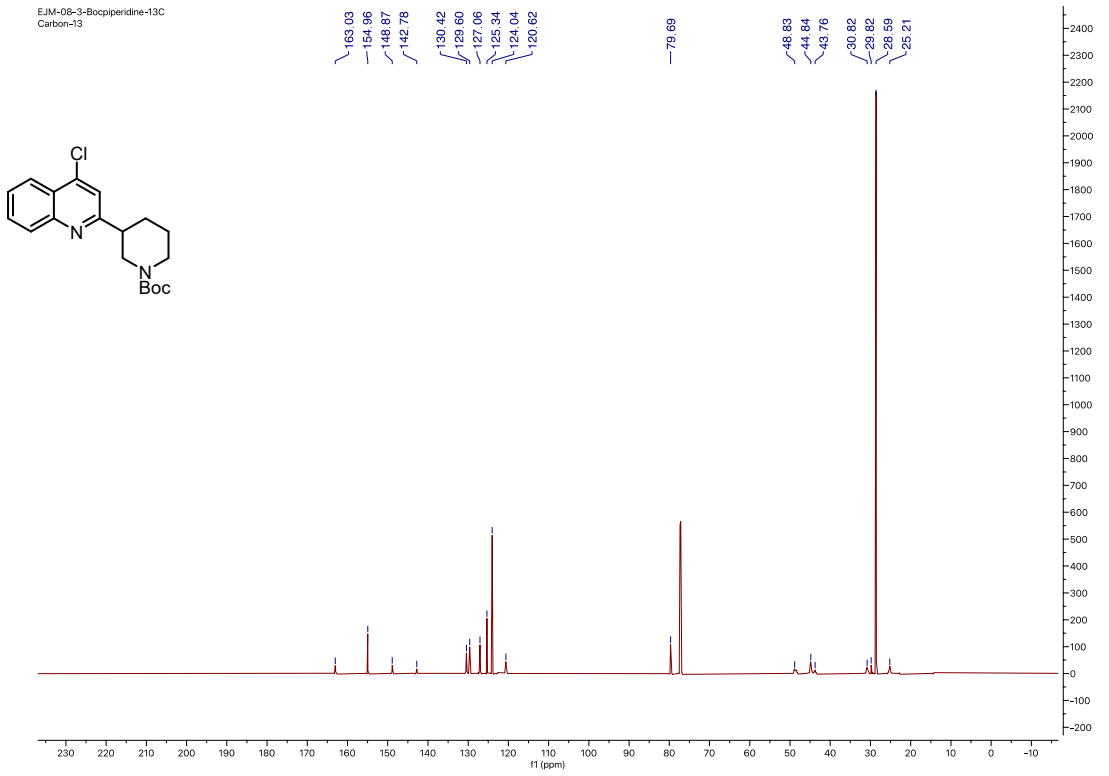

EJM-08-407-azetidine-pdt-charac-13C
Carbon-13
Cl
N
NBoc
f1 (ppm)

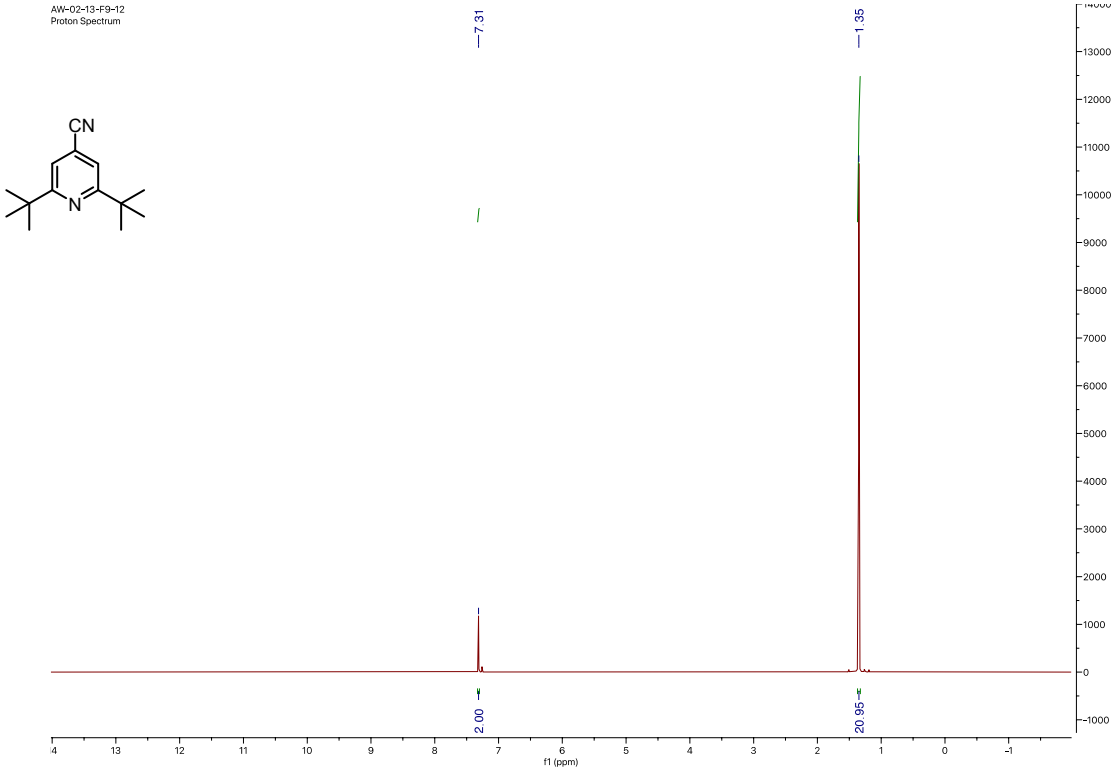
EJM-08-4Bocpiperidine-1H
Proton Spectrum

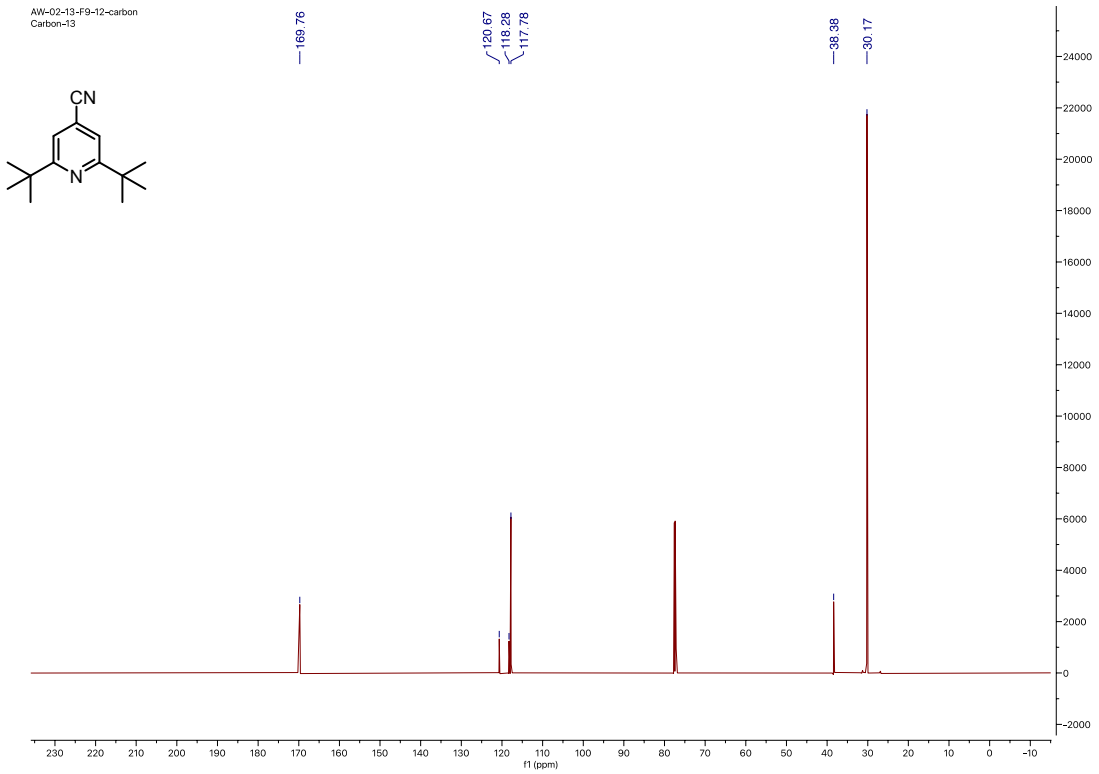


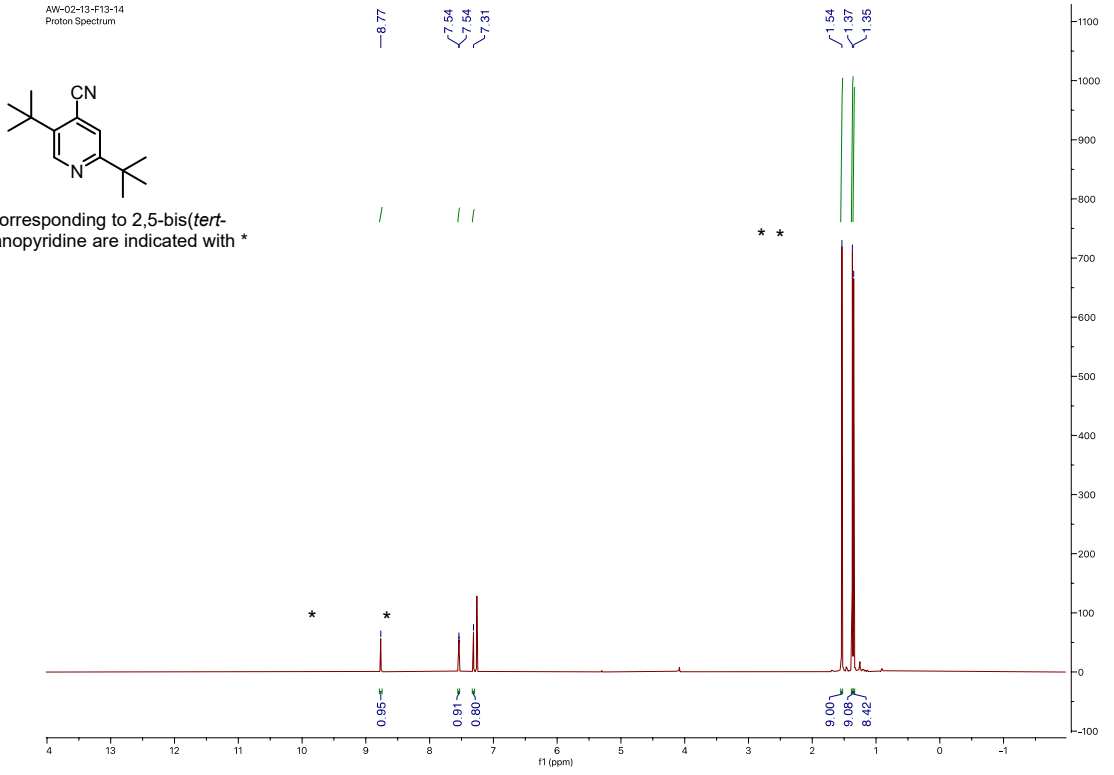
EJM-08-3Bocpiperidine-1H-3
Proton Spectrum



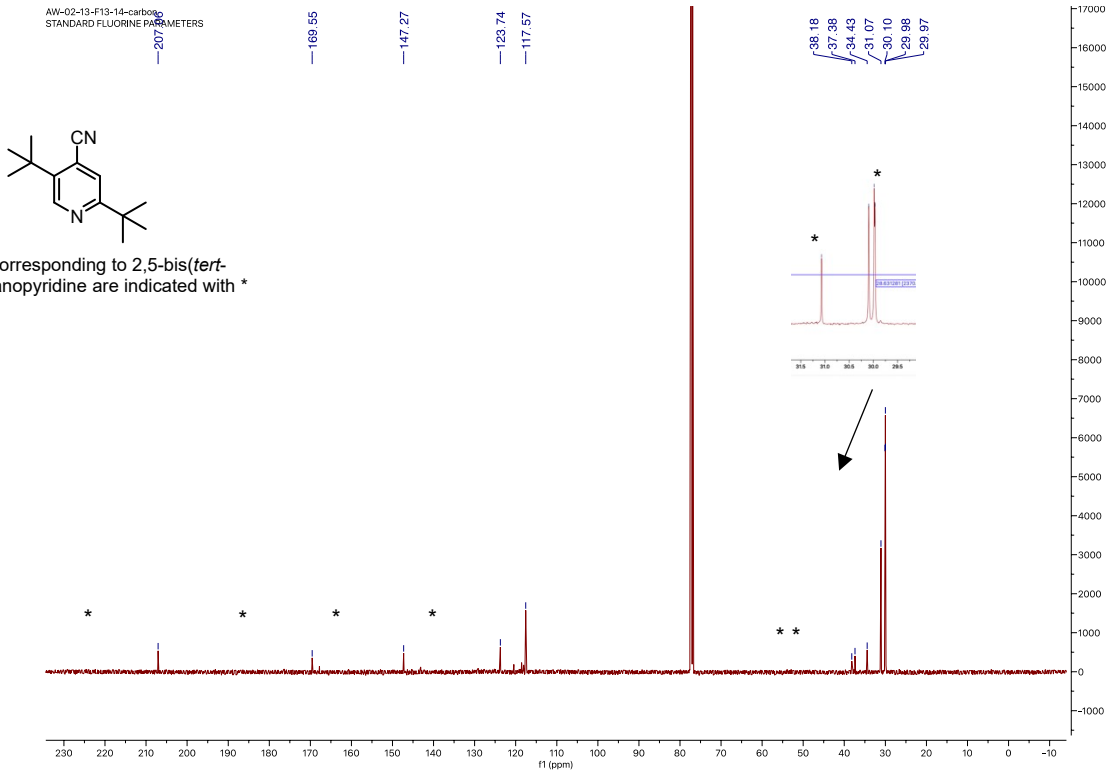

EJM-08-3-Bocpiperidine-13C
Carbon-13
163.03
154.96
148.87
142.78
130.42
129.60
127.06
125.34
124.04
120.62
79.69
48.83
44.84
43.76
30.82
29.82
28.59
25.21
Cl
N
N
Boc
f1 (ppm)


AW-02-13-F9-12
Proton Spectrum
7.31
1.35
CN
N
2.00
20.95
f1 (ppm)

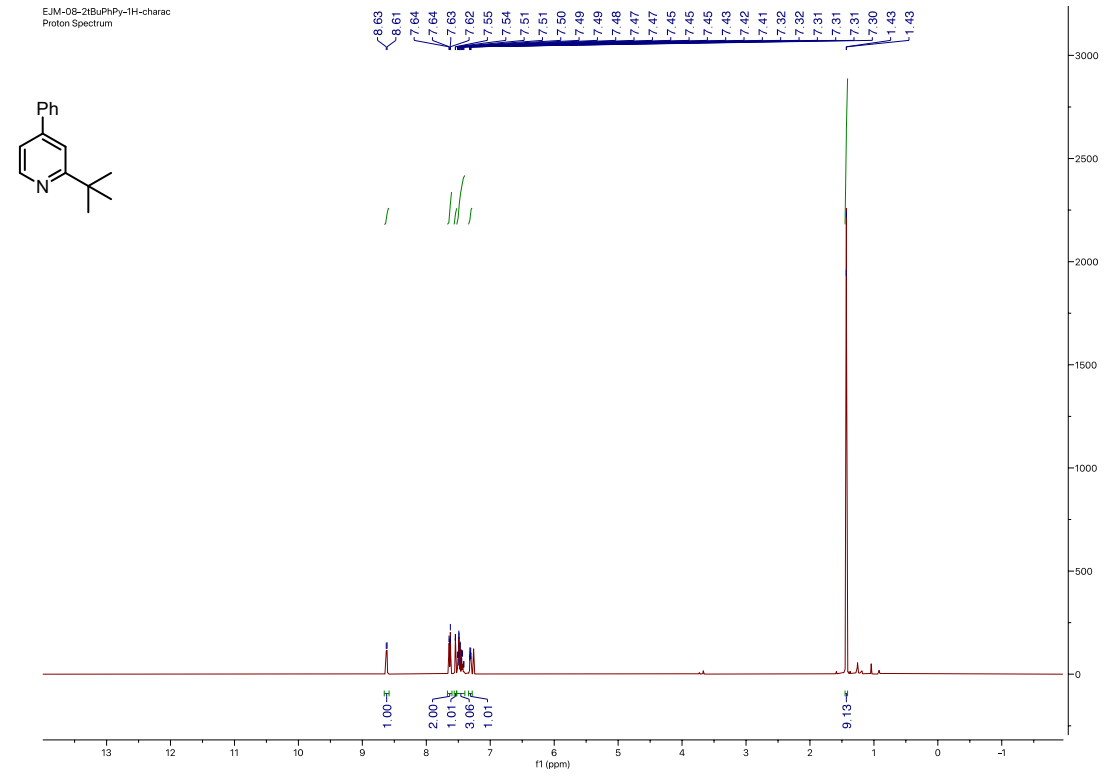


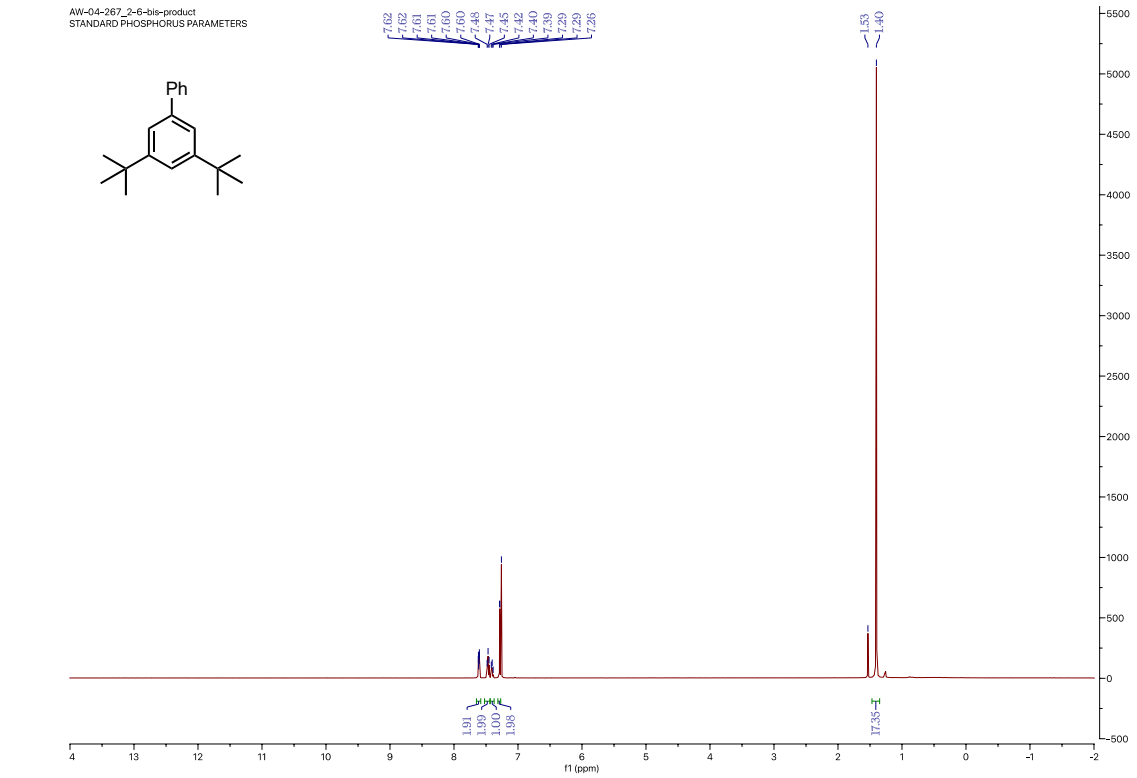


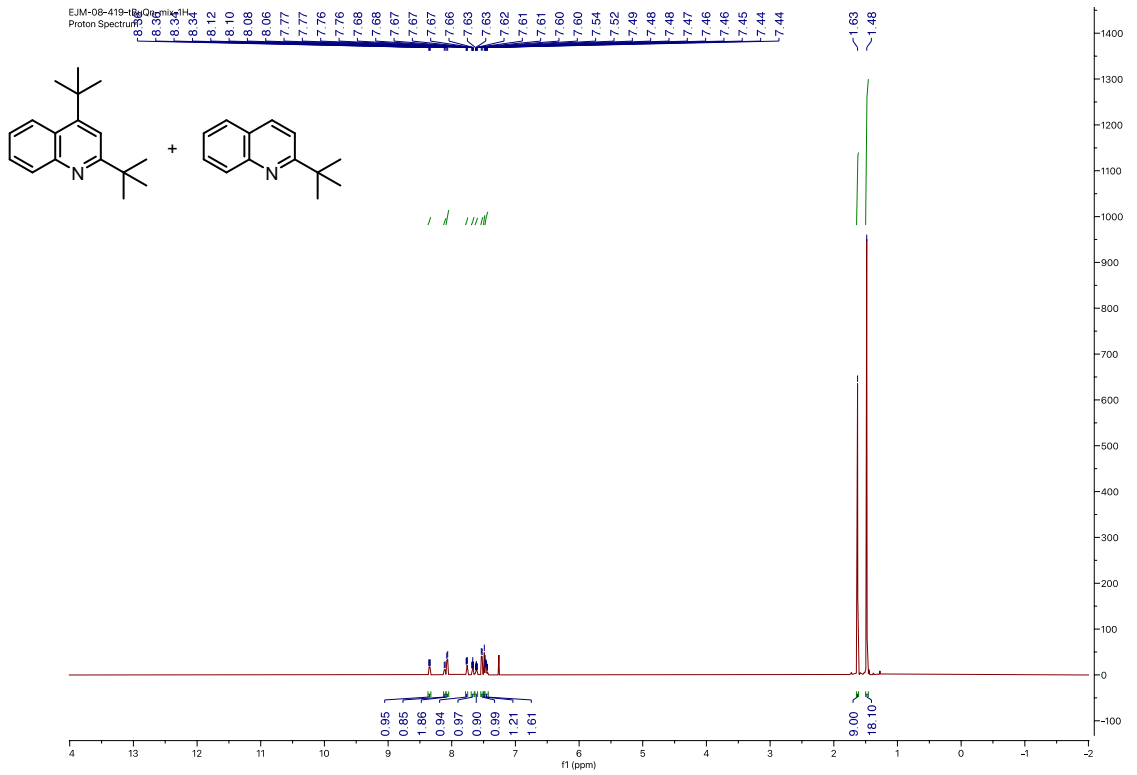
signals corresponding to 2,5-bis(*tert*-butyl)-4-cyanopyridine are indicated with *

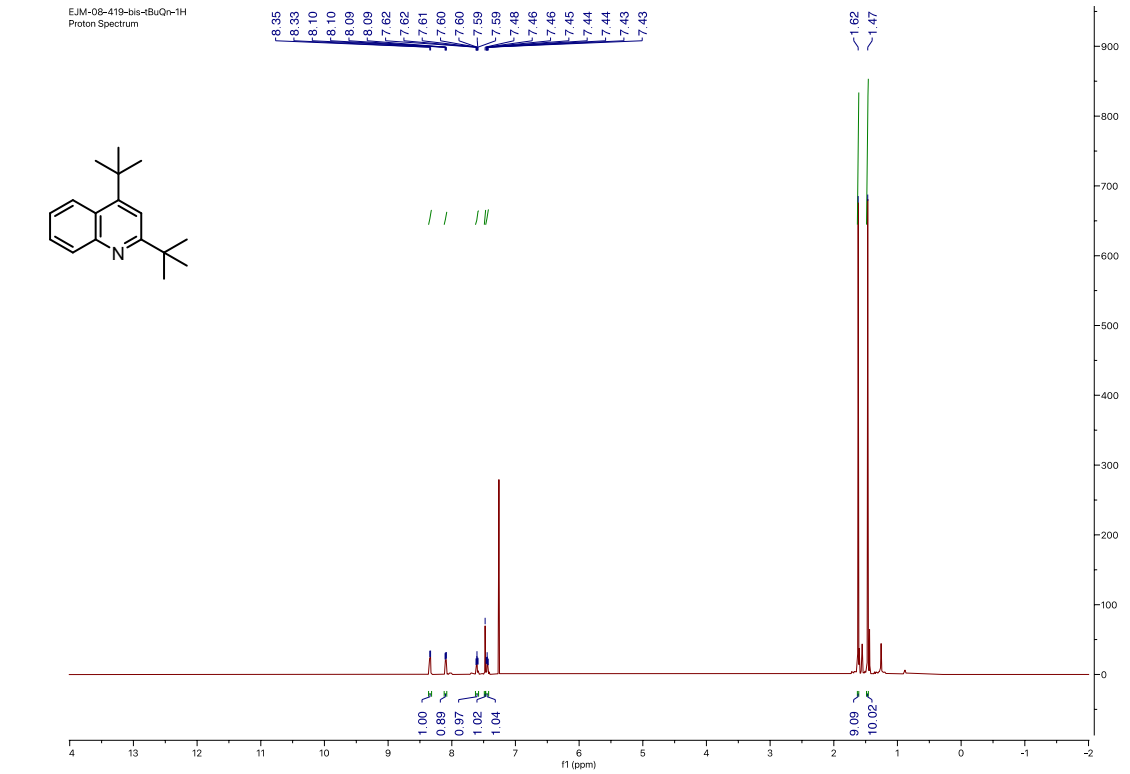


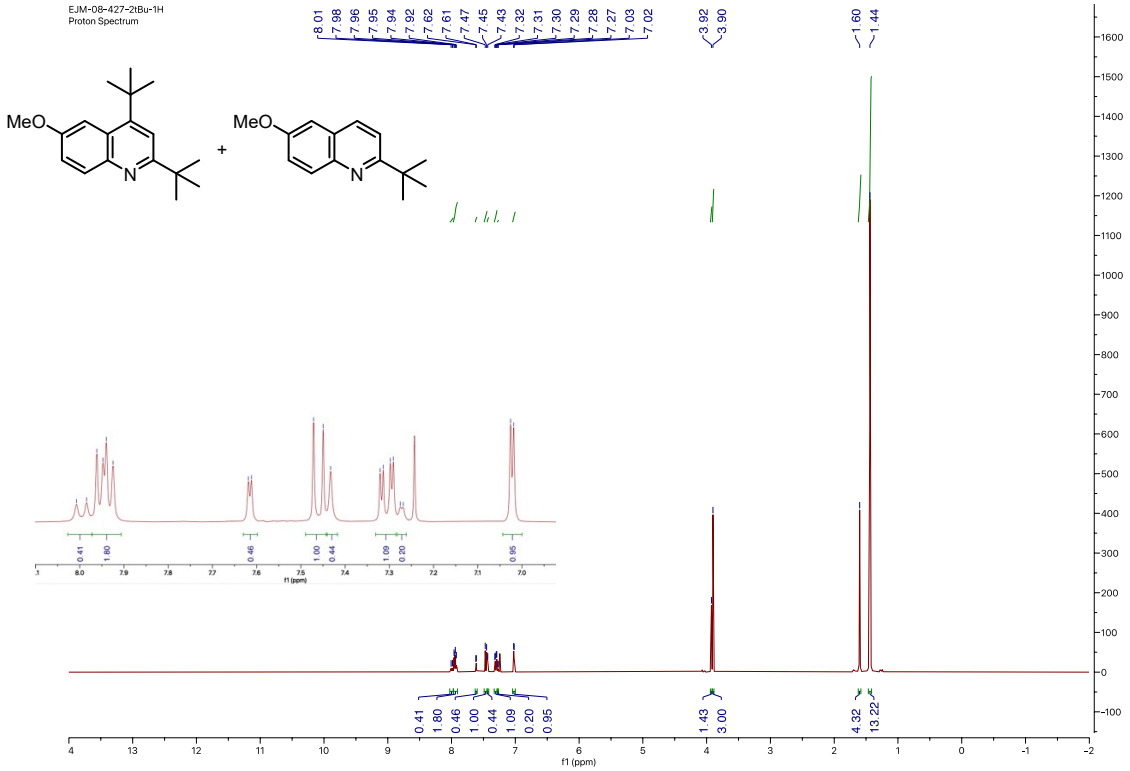
signals corresponding to 2,5-bis(*tert*-butyl)-4-cyanopyridine are indicated with *

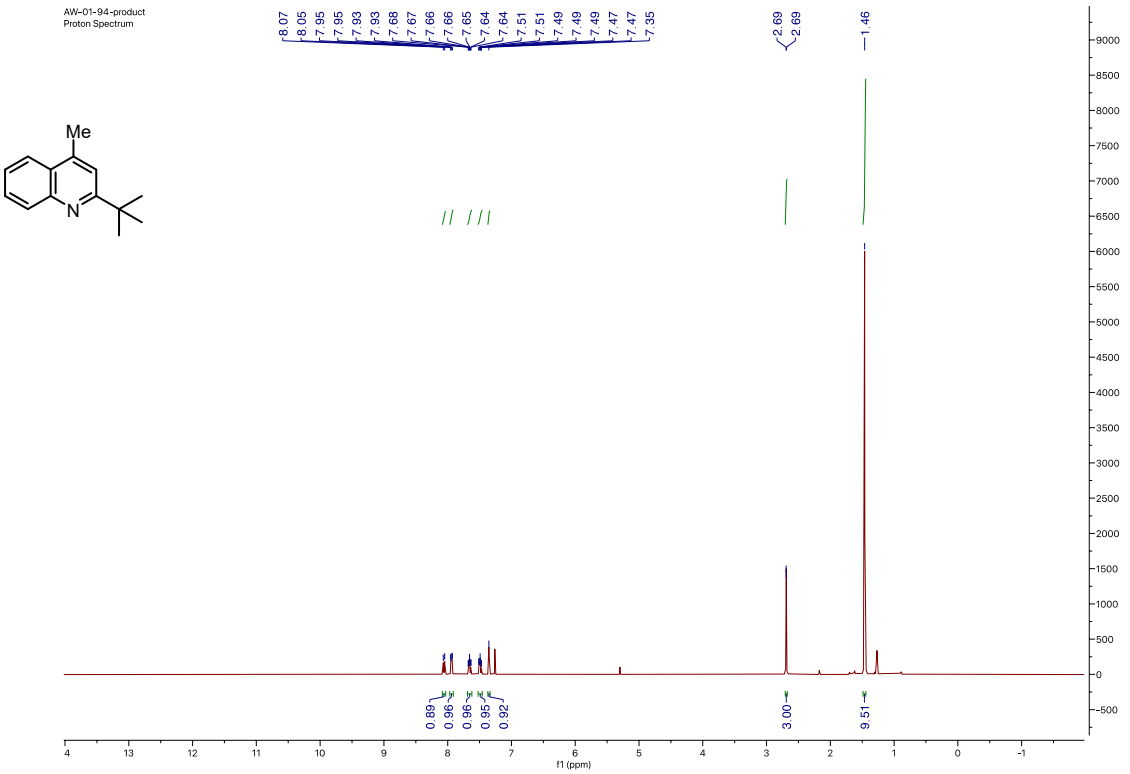


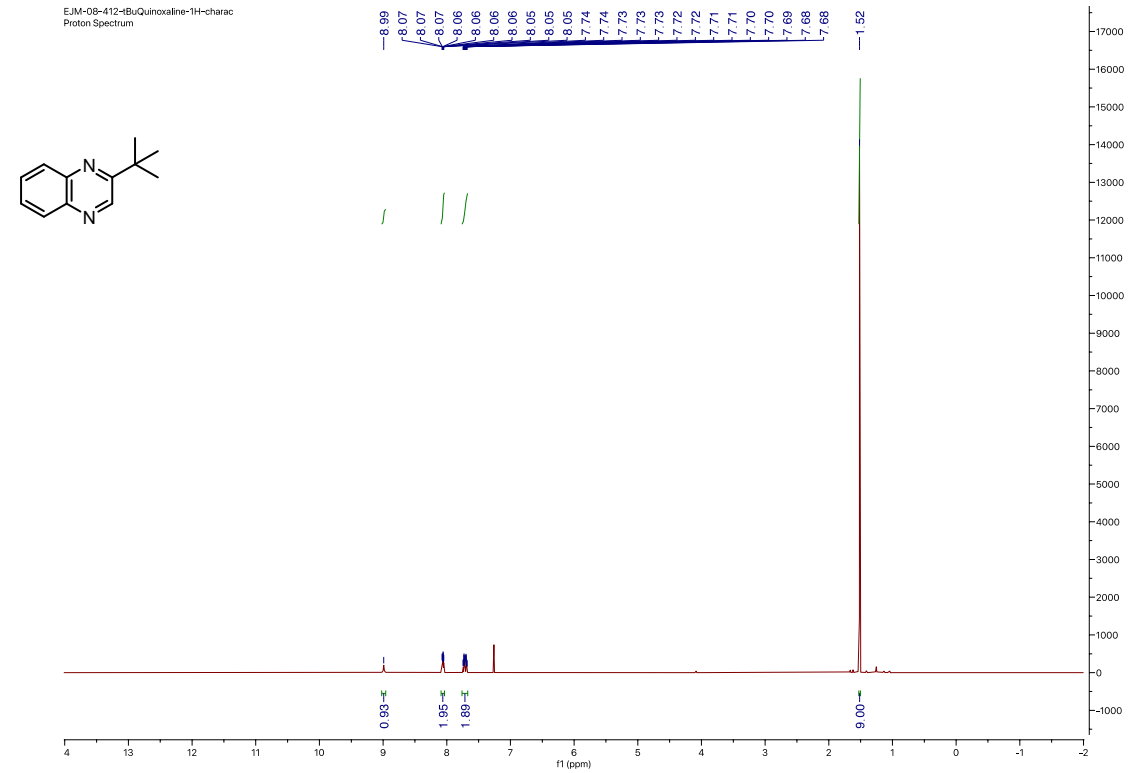

AW-04-267_2-6-bis-product
STANDARD PHOSPHORUS PARAMETERS
Ph
7.62
7.62
7.61
7.61
7.60
7.60
7.48
7.47
7.45
7.42
7.40
7.39
7.29
7.29
7.26
1.53
1.40
1.91
1.99
1.00
1.98
17.35
f1 (ppm)

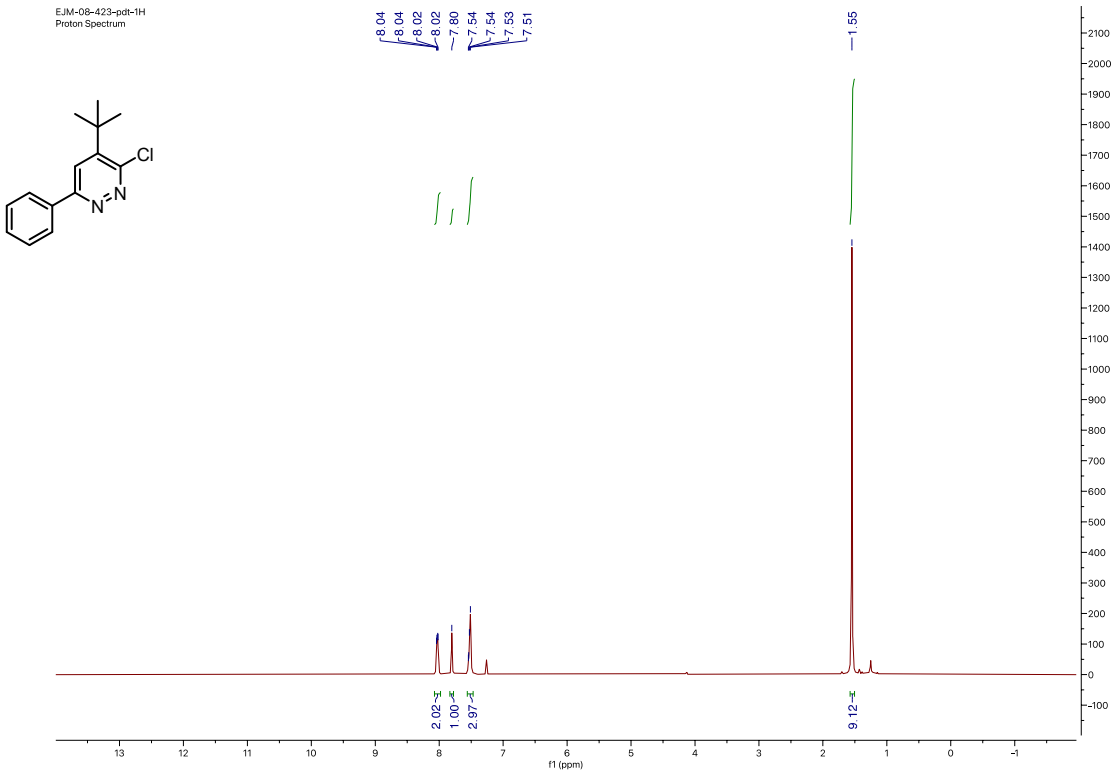

Proton Spectrum
8.35
8.34
8.34
8.12
8.10
8.08
8.06
7.77
7.77
7.76
7.76
7.68
7.68
7.67
7.67
7.67
7.66
7.63
7.63
7.62
7.61
7.61
7.60
7.60
7.54
7.52
7.49
7.48
7.48
7.47
7.46
7.46
7.45
7.44
7.44
1.63
1.48
0.95
0.85
1.86
0.94
0.97
0.90
0.99
1.21
1.61
9.00
18.10
f1 (ppm)

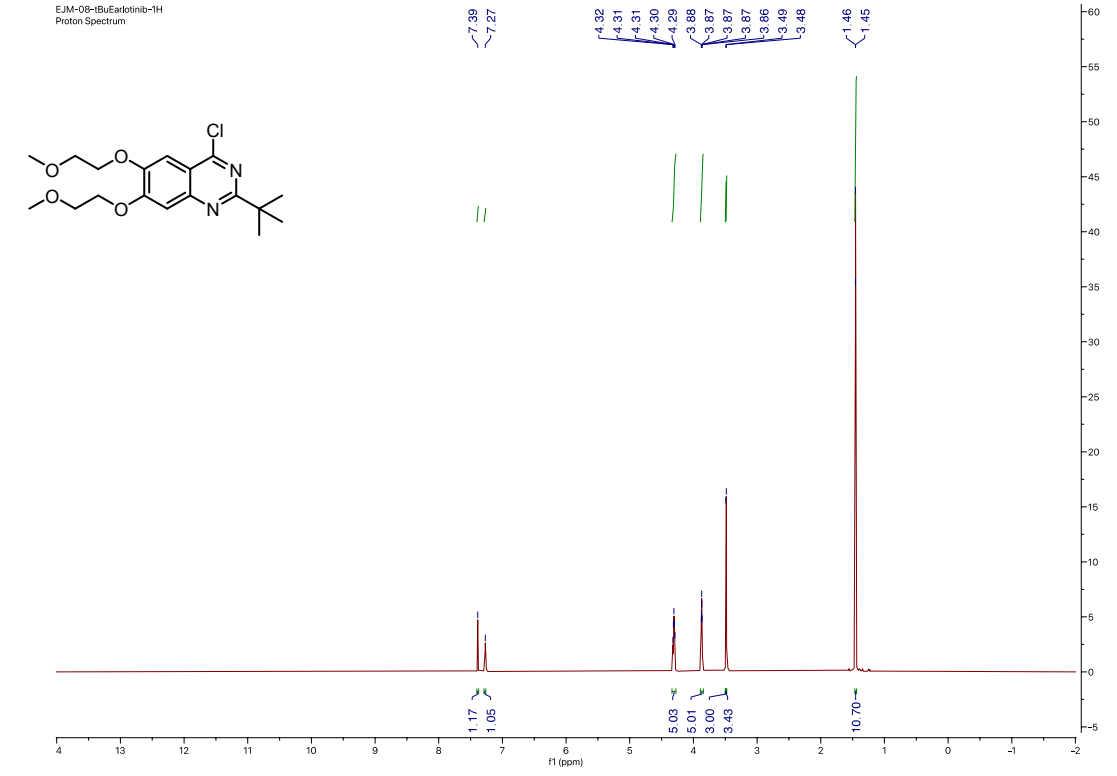

EJM-08-419-bis-tBuQn-1H
Proton Spectrum
8.35
8.33
8.10
8.10
8.09
8.09
7.62
7.62
7.61
7.60
7.60
7.59
7.59
7.48
7.46
7.46
7.45
7.44
7.44
7.43
7.43
1.62
1.47
N
1.00
0.89
0.97
1.02
1.04
9.09
10.02
f1 (ppm)

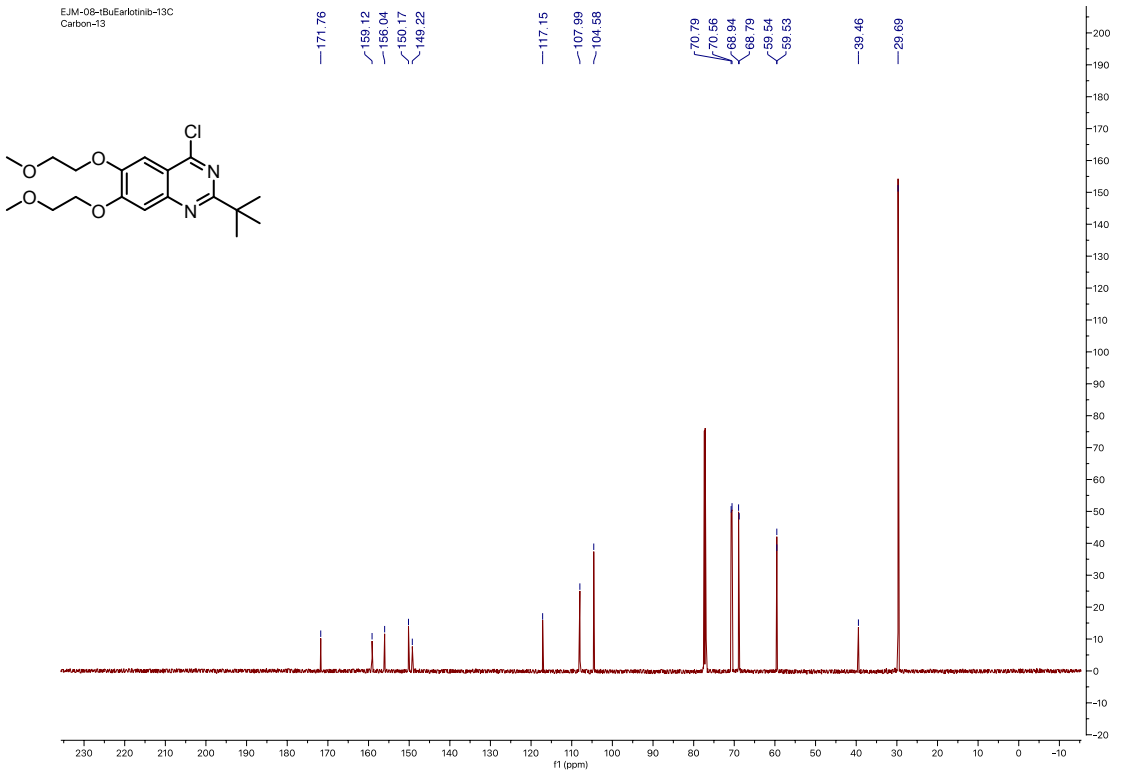

EJM-08-427-2tBu-1H
Proton Spectrum
8.01
7.98
7.96
7.95
7.94
7.92
7.62
7.61
7.47
7.45
7.43
7.32
7.31
7.30
7.29
7.28
7.27
7.03
7.02
3.92
3.90
1.60
1.44
MeO
N
+
MeO
N
0.41
1.80
0.46
1.00
0.44
1.09
0.20
0.95
1.43
3.00
4.32
13.22
f1 (ppm)

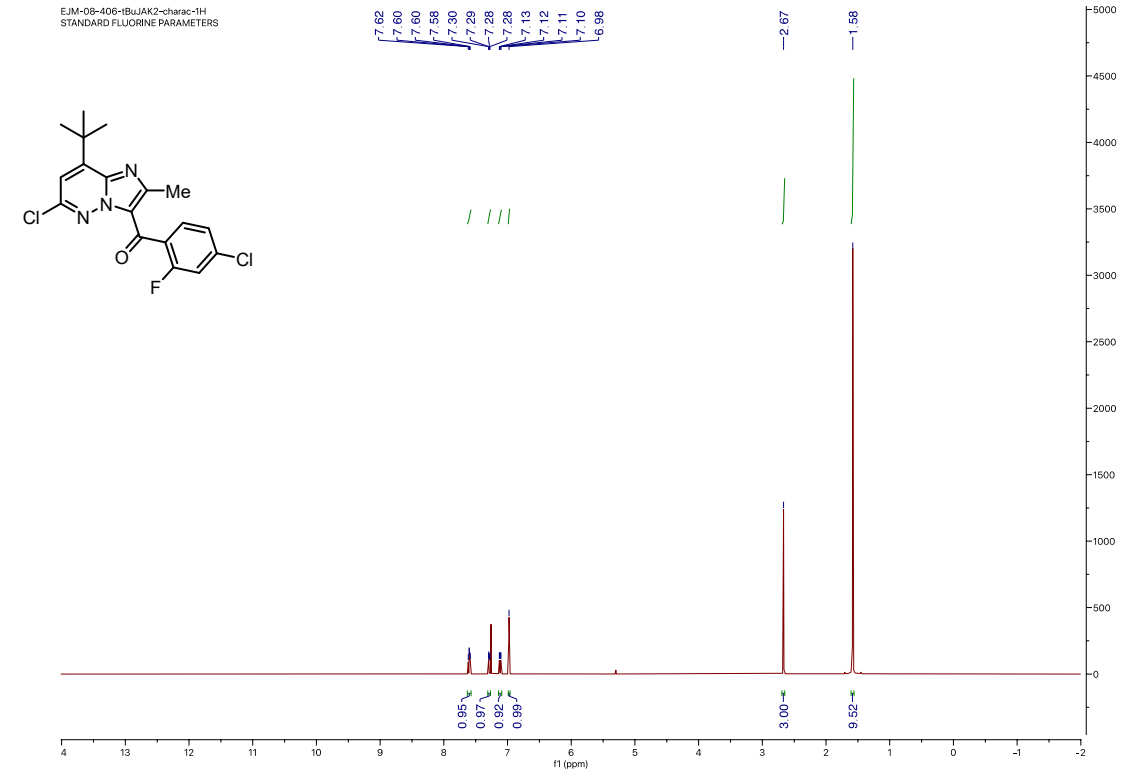

AW-01-94-product
Proton Spectrum
Me
N
8.07
8.05
7.95
7.95
7.93
7.93
7.68
7.67
7.66
7.66
7.65
7.64
7.64
7.51
7.51
7.49
7.49
7.49
7.47
7.47
7.35
2.69
2.69
1.46
0.89
0.96
0.96
0.95
0.92
3.00
9.51
f1 (ppm)

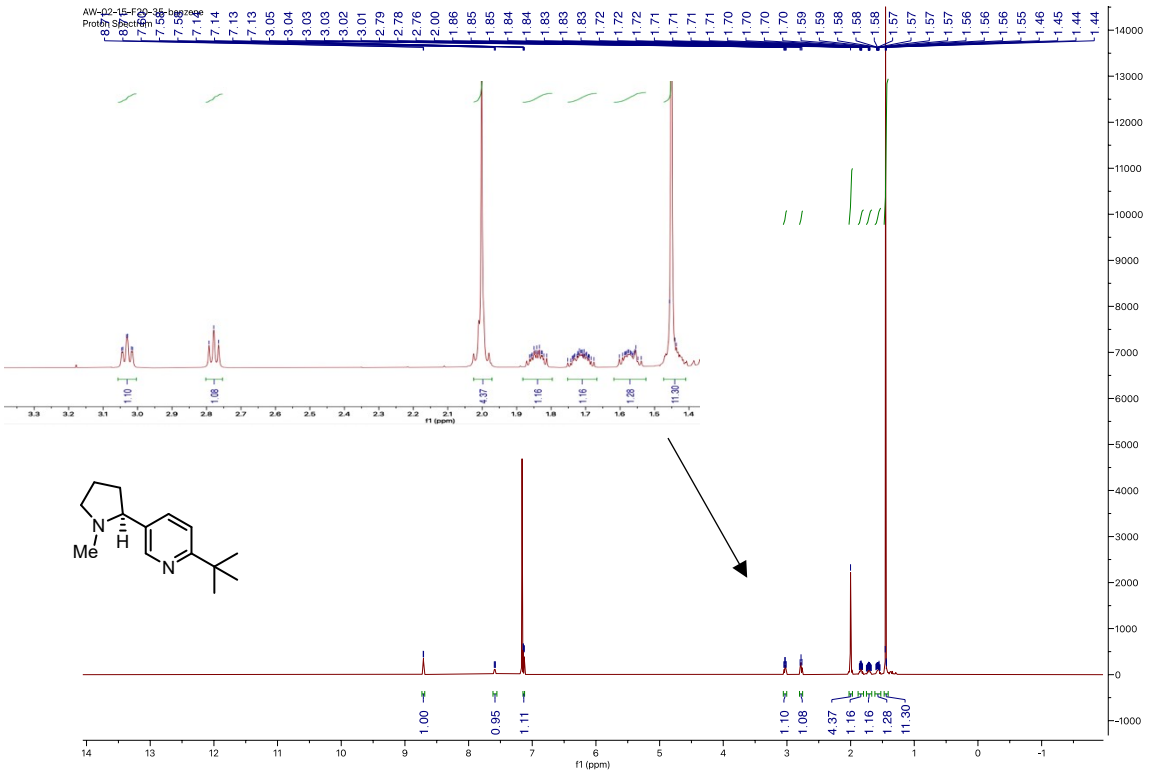

EJM-08-412-tBuQuinoxaline-1H-charac
Proton Spectrum
N
N
8.99
8.07
8.07
8.07
8.06
8.06
8.06
8.06
8.05
8.05
8.05
7.74
7.74
7.73
7.73
7.73
7.72
7.72
7.71
7.71
7.70
7.70
7.69
7.68
7.68
1.52
0.93
1.95
1.89
9.00
f1 (ppm)

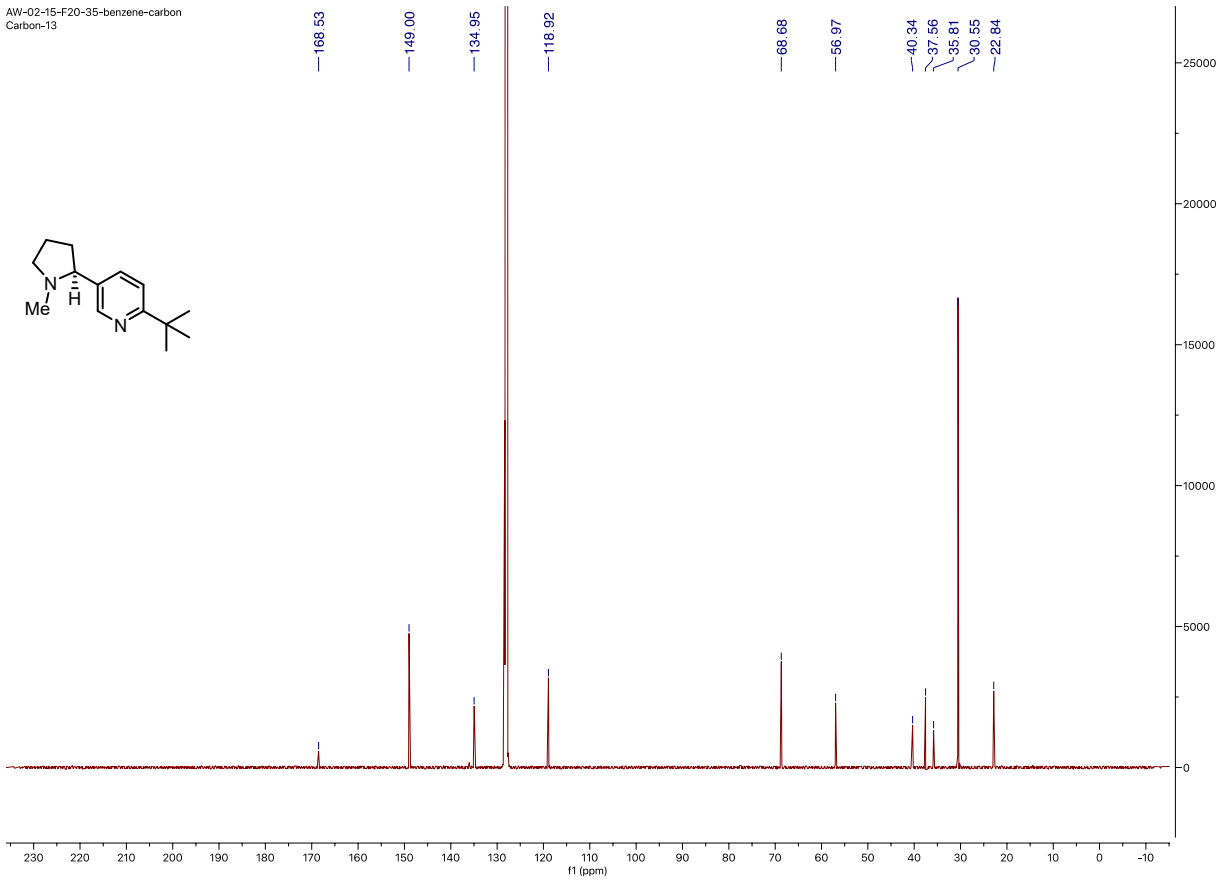

EJM-08-423-pdt-1H
Proton Spectrum
Cl
N
N
8.04
8.04
8.02
8.02
7.80
7.54
7.54
7.53
7.51
1.55
2.02
1.00
2.97
9.12
f1 (ppm)


EJM-08-tBuEarlotinib-1H
Proton Spectrum
Cl
O
O
O
O
N
N
7.39
7.27
4.32
4.31
4.31
4.30
4.29
3.88
3.87
3.87
3.87
3.86
3.49
3.48
1.46
1.45
1.17
1.05
5.03
5.01
3.00
3.43
10.70
f1 (ppm)


EJM-08-tBuErlotinib-13C
Carbon-13
171.76
159.12
156.04
150.17
149.22
117.15
107.99
104.58
70.79
70.56
68.94
68.79
59.54
59.53
39.46
29.69
Cl
O
O
O
O
N
N
f1 (ppm)


EJM-08-406-tBuJAK2-charac-1H
STANDARD FLUORINE PARAMETERS
7.62
7.60
7.60
7.58
7.30
7.29
7.28
7.28
7.13
7.12
7.11
7.10
6.98
2.67
1.58
0.95
0.97
0.92
0.99
3.00
9.52
Me
Cl
N
N
O
Cl
F
f1 (ppm)


Me
N
H
N
1.00
0.95
1.11
1.10
1.08
4.37
1.16
1.16
1.28
11.30
f1 (ppm)


AW-02-15-F20-35-benzene-carbon
Carbon-13
168.53
149.00
134.95
118.92
68.68
56.97
40.34
37.56
35.81
30.55
22.84
Me
N
H
N
f1 (ppm)

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Author Contributions

Edward J. McClain – Lead - Data curation, formal analysis, investigation, project administration, validation and writing of original draft
Alan K. Wortman – Supporting – Data curation, formal analysis, investigation
Corey R. J. Stephenson – Supporting – funding acquisition, project administration, validation, formal analysis