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Supporting Information

Photochemical C–H Hydroxyalkylation of Quinolines and Isoquinolines

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A. General Information

The NMR spectra were recorded at 300 MHz, 400 MHz and 500 MHz for ^{1}H, 101 MHz or 126 MHz for ^{13}C and 376 MHz or 470 MHz for ^{19}F. The chemical shift (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ @ 7.26 ppm ^{1}H NMR and 77.16 ppm ^{13}C NMR, CD_3CN @ 1.94 ppm ^{1}H NMR and 118.26, 1.32 ppm ^{13}C NMR and tetramethylsilane @ 0 ppm). Coupling constants are given in Hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; sept, septet; m, multiplet; bs, broad signal.

GC-MS analysis were performed by an Agilent Technology (7890A) equipped with an HP-5 column and MS spectrometer Agilent Technology 5975C.

High-resolution mass spectra (HRMS) were obtained from the ICIQ High Resolution Mass Spectrometry Unit on MicroTOF Focus and Maxis Impact (Bruker Daltonics) with electrospray ionization.

Cyclic voltammetry studies were carried out on a Princeton Applied Research PARSTAT 2273 potentiostat offering compliance voltage up to ± 100 V (available at the counter electrode), ± 10 V scan range and ± 2 A current range.

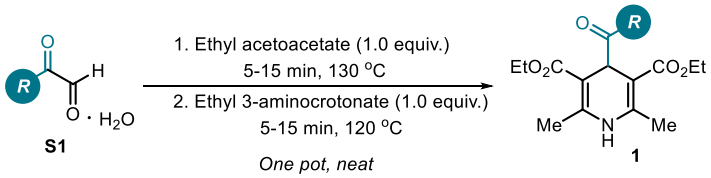
Continuous wave (CW) EPR spectra were obtained on a Bruker EMX Micro X-band bridge of 9.1-9.9 GHz, using a Bruker ER 1164 HS resonator and equipped with an ESR900 cryostat.

The authors are indebted to the team of the Research Support Area at ICIQ.

General Procedures. All reactions were set up under argon atmosphere in oven-dried glassware using standard Schlenk techniques, unless otherwise stated. Synthesis grade solvents were used as purchased. Anhydrous solvents were taken from a commercial SPS solvent dispenser. Chromatographic purification of products was accomplished using force-flow chromatography (FC) on silica gel (35-70 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck pre-coated TLC plates (silica gel 60 GF254, 0.25 mm) were employed, using UV light as the visualizing agent and acid solution of 2,4-dinitophenylhydrazine or basic aqueous potassium permanganate ($KMnO_4$) stain solutions and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator (in vacuo at 40 ºC, ≈5 mbar).

Materials. Commercial grade reagents and solvents were purchased at the highest commercial quality from Sigma-Aldrich, Apollo Scientific, Fluka, Alfa Aesar, Fluorochem, TCI and used without further purification, unless otherwise stated. Bosutinib was purchased from Carbosynth Ltd. 4-acyl-1,4-dihydropyridines **1a-x** were prepared from the corresponding glyoxals or glyoxal hydrates according to the procedure described in Section B, Scheme S1.

B. Preparation of 4-Acyl-1,4-dihydropyridines 1



Scheme S1. General procedure for preparation of **1**

Glyoxal hydrates **S1** were purchased from Sigma-Aldrich, Apollo Scientific or prepared using literature protocols *via* the Riley oxidation (vide infra), unless stated otherwise.[1] 2-Cyclopropyl-2-oxoacetaldehyde was used without further purification. Other glyoxal hydrates **S1** were recrystallized from boiling water before use in the next step.

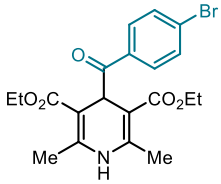
General Procedure for the Preparation of Glyoxal Hydrates via the Riley Oxidation

To a 250 mL round bottom flask, equipped with a magnetic stirrer and a reflux condenser, SeO_2 (1.2 equiv.) was added, followed by 1,4-dioxane/water (5 vol., 10:1 mixture) and the ketone (1.0 equiv.). The reaction mixture was refluxed under argon for 5-48 h until completion, as judged by TLC analysis, and then cooled to ambient temperature. The suspension was filtered through a plug of Celite and the solvent was removed by rotary evaporator. The residue was dried under high vacuum and dissolved in a minimum amount of boiling water. The mixture was slowly cooled to 0 °C and then the crystallized glyoxal hydrates were filtered off and dried.

General Procedure 1 for the Preparation of Acyl DHPs

Glyoxals or glyoxal hydrates **S1** (2 g, 1.0 equiv.) and ethyl acetoacetate (1.0 equiv.) were added to a 50 mL round bottom flask equipped with a magnetic stirrer. The mixture was slowly heated to 130 °C and kept under stirring for 5-30 min, until the condensation reaction was completed (as monitored by TLC analysis). The solution was then cooled to 80 °C. Ethyl 3-aminocrotonate (1.0 equiv.) was slowly added (exothermic reaction), then the mixture was slowly heated to 120 °C for 5-15 min and monitored by TLC. After completion, the reaction mixture was cooled to ambient temperature and the substrates **1** were purified by column chromatography (SiO_2, pentane/diethyl ether, gradient from 8:2 to 5:5), prior to recrystallization from cyclohexane/ethyl acetate (8:2).

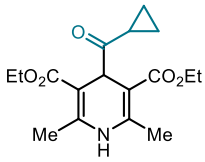
Diethyl 4-(4-bromobenzoyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1p)



2-(4-Bromophenyl)-2-oxoacetaldehydemonohydrate was prepared via Riley oxidation from 1-(4-bromophenyl)ethan-1-one and **1p** was prepared using the *General Procedure 1* to yield 1.53 g (2 g scale, 33% yield) of pure product (yellow crystalline solid).

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.17 – 7.87 (m, 2H), 7.71 – 7.51 (m, 2H), 6.77 (s, 1H), 5.66 (s, 1H), 4.12 – 3.89 (m, 4H), 2.29 (s, 6H), 1.07 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 203.4, 166.9, 147.0, 135.7, 131.3, 131.2, 128.0, 99.7, 60.0, 41.7, 19.4, 14.2. HRMS: Calculated for $C_{20}H_{22}BrNNaO_5$ $[M+Na]^+$: 458.0574, found: 458.0576.

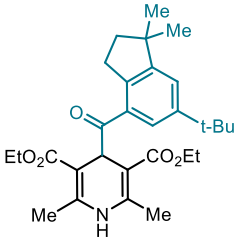
Diethyl 4-(cyclopropanecarbonyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1w)



2-Cyclopropyl-2-oxoacetaldehyde was prepared via Riley oxidation from 1-cyclopropylethan-1-one and **1w** was prepared using modified *General Procedure 1*. After the completion of the reaction, diethyl ether was added (25 mL) and solids were filtered off and dried to yield 2.4 g (2.8 g scale, 26% yield) of pure product (yellow crystalline solid).

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 6.87 (s, 1H), 5.06 (s, 1H), 4.33 - 4.03 (m, 4H), 2.33 (tt, *J* = 7.7, 4.6 Hz, 1H), 2.21 (s, 6H), 1.29 (*t*, J = 7.1 Hz, 6H), 0.99 – 0.85 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm): 213.3, 167.2, 146.5, 99.1, 59.9, 47.5, 19.6, 19.0, 14.4, 11.8. HRMS: Calculated for $C_{17}H_{22}NO_5$ $[M-H]^-$: 320.1503, found: 320.1495.

Diethyl 4-(6-(tert-butyl)-1,1-dimethyl-2,3-dihydro-1H-indene-4-carbonyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1x)



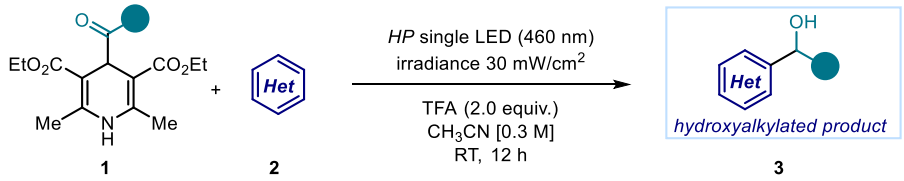
2-(6-(*tert*-Butyl)-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)-2-oxoacet aldehyde was prepared via Riley oxidation of celestolide and **1x** was prepared using modified *General Procedure 1* to yield 1.2 g (2.7 g scale, 23% yield) of pure product (yellow crystalline solid).

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.94 (d, *J* = 1.8 Hz, 1H), 7.28 (*d*, J = 1.8 Hz, 1H), 6.80 (s, 1H), 5.62 (s, 1H), 4.14 – 3.83 (m, 4H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.34 (s, 6H), 1.90 (t, *J* = 7.2 Hz, 2H), 1.37 (s, 9H), 1.25 (s, 6H), 1.00 (*t*, J = 7.1 Hz, 6H).); ^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm): 205.4, 166.9, 153.2, 149.2, 146.5, 140.2, 134.4, 124.7, 122.0, 99.3, 59.6, 44.3, 43.6, 41.4, 34.8, 31.6, 29.7, 28.8, 19.3, 14.2. HRMS: Calculated for $C_{29}H_{39}NNaO_5$ $[M+Na]^+$: 504.2720, found: 504.2716.

The remaining acyl-DHPs were prepared and characterized according to a literature protocol.[2]

C. Photochemical C-H Hydroxyalkylation of *N*-Heteroarenes

C.1 General Procedure



Scheme S2. Photochemical Hydroxyalkylations of heteroarenes

To a 8 mL vial, the heteroarene **2** (0.2 mmol, 1 equiv.) and acyl DHP **1** (0.24 mmol, 1.2 equiv.) was added. The vial was put under vacuum and backfilled with argon. Previously degassed CH_3CN (0.6 mL) and TFA (31 µL, 0.4 mmol, 2 equiv) were sequentially added. The vial was sealed with parafilm and placed inside a steel reactor fixed over an aluminium block equipped with a High Power single LED (λ = 460 nm), irradiance = 30 mW/cm^2 as controlled by an external power supply. The reaction was irradiated at ambient temperature for 12 h (unless otherwise stated). For the reaction carried out at lower temperature, the temperature was kept at -10 °C using a chiller connected to the steel reactor. To prevent moisture condensation, the reactor was placed inside a glass bell, which was kept under continuous air flow during the whole experiment (details of the set-up are shown in Figure S1).

The residue was purified by flash chromatography (Ø = 1.5 cm, h SiO_2 = 13 cm) upon direct loading on the silica column to afford products **3** in the stated yield.

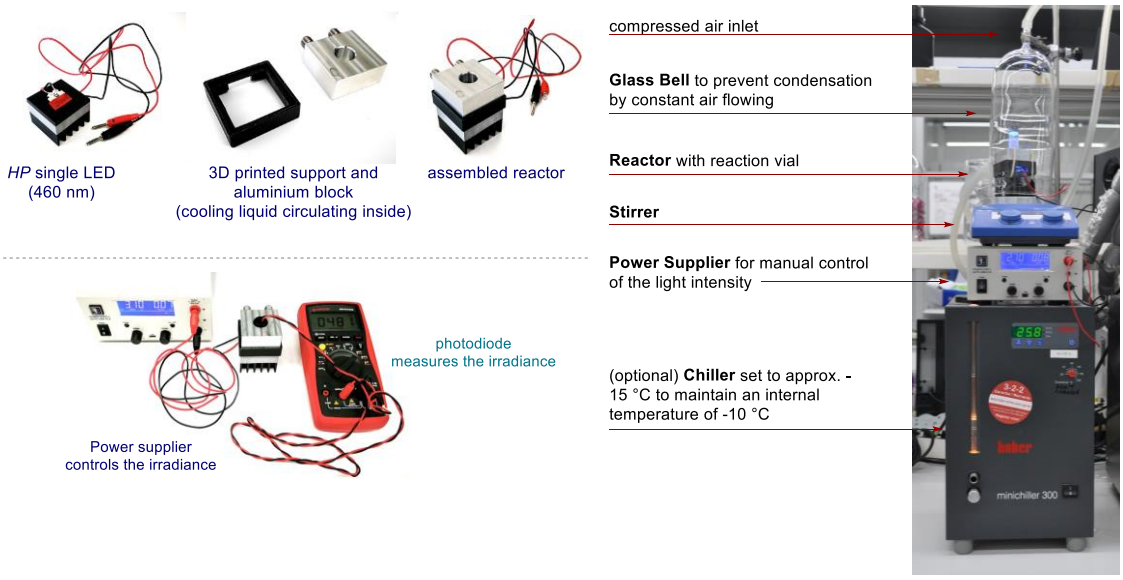
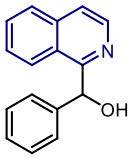


Figure S1. Detailed set-up and illumination system. The light source for illuminating the reaction vessel consisted of a 460 nm high-power single LED (OCU-440 UE420-X-T) purchased from OSA Opto Light.

C.2 Synthesis and Characterization of Products 3

Isoquinolin-1-yl(phenyl)methanol (3a)



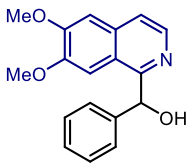
Prepared according to the *General Procedure* from isoquinoline **2a** (0.2 mmol, 26 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg)[2] and trifluoroacetic acid (0.4 mmol, 31 µL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 85:15) to give **3a** as a white solid (68 mg, 72% yield), average of two runs. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.57 (d, *J* = 5.7 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.73 – 7.62 (m, 2H), 7.55 – 7.45 (m, 1H), 7.40 – 7.24 (m, 5H), 6.39 (s, 1H).^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm): 159.2, 143.3, 140.0, 136.6, 130.3, 128.7, 127.9, 127.7, 127.5, 127.4, 125.2, 124.8, 121.1, 72.6. NMR shifts are consistent with the literature.[4]

1.5 Mmol scale reaction using a focused light beam EvoluChem™ LED photoreactor

An oven-dried 50 mL Schlenk tube was charged with isoquinoline **2a** (194 mg, 1.5 mmol) and acyl-DHP **1a** (643 mg, 1.8 mmol, 1.2 equiv.). The mixture was evacuated and filled with argon three times. Previously degassed acetonitrile (6 mL) and TFA (0.23 mL, 3 mmol, 2 equiv.) were sequentially added. The mixture was stirred at 25 °C in a commercially available EvoluChem™ LED 18W photoreactor (emission at 450-455 nm) for 12 h. The solvent was evaporated *in vacuo.* The resulting crude mixture was purified by column chromatography on silica gel (*n*-hexane/EtOAc/triethylamine, gradient from 95:5:0 to 80:20:1) to give the corresponding product **3a** as yellow solid (247 mg, 70% yield).

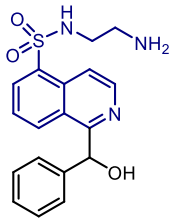
Photoreactor and specifications of the light source: EvoluChem™ LED photoreactor. Light source: P201-18-2 450-455 nm. Electric power: 18W. Total irradiance: 34 mW/cm^2. Beam Angle 25°. LED: CREE XPE.

(6,7-Dimethoxyisoquinolin-1-yl)(phenyl)methanol (3b)



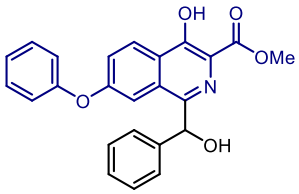
Prepared according to the *General Procedure* from 6,7-dimethoxyisoquinoline **2b** (0.2 mmol, 37.8 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg) and trifluoroacetic acid (0.4 mmol, 31 µL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 80:20) to give **3b** as a yellow solid (48 mg, 81% yield), average of two runs. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.39 (d, *J* = 5.6 Hz, 1H), 7.49 (d, *J* = 5.7 Hz, 1H), 7.36 – 7.19 (m, 5H), 7.05 (d, *J* = 6.1 Hz, 2H), 6.17 (s, 1H), 3.96 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm): 156.9, 153.0, 150.2, 143.8, 139.2, 133.9, 129.1, 128.3, 128.1, 121.3, 120.2, 105.6, 103.6, 73.2, 56.4, 56.2. HRMS: Calculated for $C_{18}H_{18}NO_3$ $[M+H]^+$: 296.1281, found: 296.1285.

N-(2-aminoethyl)-1-(hydroxy(phenyl)methyl)isoquinoline-5-sulfonamide (3c)



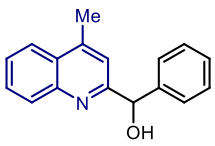
Prepared according to the *General Procedure* from N-(2-aminoethyl)isoquinoline-5-sulfonamide **2c** (0.2 mmol, 50.3 mg),[5] diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg) and trifluoroacetic acid (0.6 mmol, 46 µL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (DCM/MeOH, gradient from 95:5 to 90:10) to give **3c** as a yellow solid (39 mg, 55% yield), average of two runs. ^{1}H NMR (500 MHz, CD_3OD), δ (ppm): 8.73 – 8.67 (m, 2H), 8.57 (d, *J* = 6.2 Hz, 1H), 8.41 (d, *J* = 7.4 Hz, 1H), 7.69 (dd, *J* = 8.6, 7.4 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.35 – 7.31 (m, 2H), 7.29 – 7.23 (m, 1H), 6.56 (s, 1H), 3.02 (t, *J* = 6.3 Hz, 2H), 2.89 (t, *J* = 6.3 Hz, 2H). ^{13}C NMR (126 MHz, CD_3OD), δ (ppm): 162.4, 143.2, 142.4, 135.3, 133.2, 132.7, 132.0, 128.6, 127.7, 126.8, 126.6, 125.9, 117.7, 75.2, 41.6, 40.2. HRMS: Calculated for $C_{18}H_{20}N_3O_3S$ $[M+H]^+$: 358.1220, found: 358.1221.

Methyl 4-hydroxy-1-(hydroxy(phenyl)methyl)-7-phenoxyisoquinoline-3-carboxylate (3d)



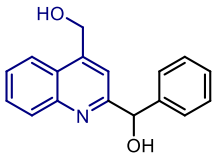
Prepared according to the *General Procedure* from methyl 4-hydroxy-7-phenoxyisoquinoline-3-carboxylate **3d** (0.2 mmol, 59 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg) and trifluoroacetic acid (0.4 mmol, 31 µL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 80:20) to give **3d** as a white solid (48 mg, 81% yield), average of two runs. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.36 (d, *J* = 9.1, 1H), 7.44 – 7.38 (m, 3H), 7.32 – 7.26 (m, 1H), 7.21 – 7.15 (m, 3H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.07 – 7.02 (m, 2H), 6.97 – 6.90 (m, 2H), 5.87 (s, 1H), 4.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$), δ (ppm): 171.2, 160.2, 157.0, 155.0, 149.2, 143.0, 130.7, 130.1, 129.1, 128.1, 127.9, 126.5, 125.5, 124.3, 122.9, 120.9, 117.6, 109.4, 73.0, 53.1. HRMS: Calculated for $C_{24}H_{19}NO_5$ $[M+H]^+$: 402.1336, found: 402.1320.

(4-Methylquinolin-2-yl)(phenyl)methanol (3e)



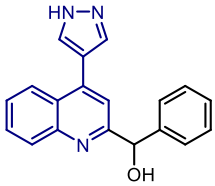
Prepared according to the *General Procedure 2* from 4-methylquinoline **2e** (0.2 mmol, 28.6 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg) and trifluoroacetic acid (0.4 mmol, 31 µL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 85:15) to give **3e** as a yellow solid (41 mg, 82% yield), average of two runs. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.18 (d, *J* = 8.3 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.81 - 7.74 (m, 1H), 7.64 – 7.56 (m, 1H), 7.48 – 7.41 (m, 2H), 7.41 – 7.30 (m, 3H), 7.04 (s, 1H), 5.85 (s, 1H), 2.64 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$), δ (ppm): 160.0, 145.6, 142.9, 129.7, 129.2, 128.6, 128.1, 128.0, 127.6, 127.5, 126.4, 123.8, 119.8, 74.9, 18.9. HRMS: Calculated for $C_{17}H_{16}NO$ $[M+H]^+$: 250.1226, found: 250.1230.

(4-(Hydroxymethyl)quinolin-2-yl)(phenyl)methanol (3f)



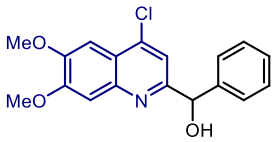
Prepared according to the *General Procedure* from quinolin-4-ylmethanol **2f** (0.2 mmol, 31.8 mg),[6] diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg) and trifluoroacetic acid (0.4 mmol, 31 µL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 85:15) to give **3f** as a yellow solid (29 mg, 54% yield), average of two runs. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.19 (d, *J* = 8.5, 1H), 7.94 – 7.87 (m, 1H), 7.77 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.58 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.37 – 7.28 (m, 4H), 6.09 (s, 1H), 5.85 (s, 1H), 5.12 (dd, *J* = 2.9, 1.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$), δ (ppm): 160.8, 147.5, 146.1, 143.0, 131.8, 130.1, 129.8, 129.0, 128.4, 127.8, 127.0, 123.1, 116.6, 75.6, 62.1. HRMS: Calculated for $C_{17}H_{16}NO_2$ $[M+H]^+$: 266.1176, found: 266.1168.

(4-(1H-Pyrazol-4-yl)quinolin-2-yl)(phenyl)methanol (3g)



Prepared according to the *General Procedure* from 4-(1H-pyrazol-4-yl)quinoline **2g** (0.2 mmol, 39.0 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg) and trifluoroacetic acid (0.8 mmol, 62 µL). Time of irradiation: 40 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 80:20) to give **3a** as a yellow solid (25 mg, 42% yield), average of two runs. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.19 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.09 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.81 (s, 2H), 7.79 – 7.72 (m, 1H), 7.59 – 7.52 (m, 1H), 7.45 – 7.39 (m, 2H), 7.35 – 7.30 (m, 2H), 7.30 – 7.25 (m, 1H), 7.14 (s, 1H), 5.90 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$), δ (ppm): 160.5, 146.9, 143.0, 140.9, 134.3, 130.3, 129.6, 129.1, 128.6, 128.4, 127.8, 127.2, 126.4, 125.6, 119.2, 118.7, 75.5. HRMS: Calculated for $C_{19}H_{16}N_3O$ $[M+H]^+$: 302.1288, found: 302.1284.

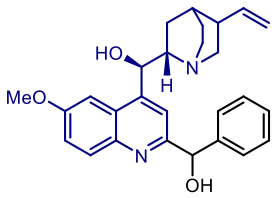
(4-Chloro-6,7-dimethoxyquinolin-2-yl)(phenyl)methanol (3h)



Prepared according to the *General Procedure* from 4-chloro-6,7-dimethoxyquinoline **2h** (0.2 mmol, 44.7 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg) and trifluoroacetic acid (0.4 mmol, 31 µL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 80:20) to give **3h** as a yellow solid (25 mg, 42% yield), average of two runs.

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.48 (s, 1H), 7.45 – 7.31 (m, 6H), 7.18 (s, 1H), 5.82 (s, 1H), 5.62 (s,1H), 4.10 (s, 3H), 4.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm): 158.6, 153.4, 150.7, 143.9, 142.5, 141.3, 128.7, 128.1, 127.3, 121.0, 117.5, 107.9, 101.9, 75.0, 56.4, 56.2. HRMS: Calculated for $C_{18}H_{17}ClNO_3$ $[M+H]^+$: 330.0891, found: 330.0882.

(4-((1R)-Hydroxy((2S)-5-vinylquinuclidin-2-yl)methyl)-6-methoxyquinolin-2-yl)(phenyl)methanol (3i)

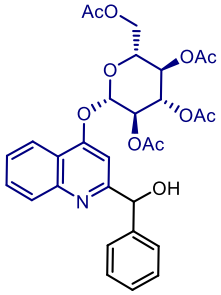


Prepared according to the *General Procedure* from quinine **2i** (0.2 mmol, 64.9 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg) and trifluoroacetic acid (0.4 mmol, 31 µL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 75:25) to give **3i** as a white solid (36 mg, 42% yield), average of two runs.

^{1}H NMR (500 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ (ppm): 8.21 - 8.11 (m, 2H), 7.98 (s, 1H), 7.80 (s, 1H), 7.48 – 7.40 (m, 4H), 7.36 – 7.21 (m, 8H), 7.20 – 7.10 (m, 2H), 6.36 – 6.23 (m, 4H), 5.58 – 5.43 (m, 2H), 5.31 (s, 2H), 5.07 – 4.94 (m, 4H), 4.27 (s, 2H), 3.75 (s, 3H), 3.72

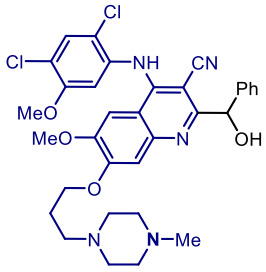
(s, 3H), 3.54 – 3.39 (m, 2H), 3.28 – 2.92 (m, 6H), 2.67 (s, 2H), 2.23 – 1.74 (m, 8H), 1.25 – 1.02 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ (ppm): 163.4, 163.1, 162.7, 162.4, 160.7, 160.5, 158.2, 154.7, 154.0, 140.0, 139.8, 137.4, 134.6, 134.5, 129.7, 129.7, 129.3, 129.1, 129.0, 127.4, 127.2, 127.0, 126.8, 126.1, 125.9, 125.1, 124.8, 121.2, 118.7, 118.5, 118.3, 117.9, 115.4, 112.5, 101.0, 100.9, 73.4, 73.1, 66.8, 66.6, 60.4, 60.3, 57.0, 56.8, 55.2, 53.9, 44.3, 37.4, 27.0, 27.0, 24.4, 18.2, 18.0. HRMS: Calculated for $C_{27}H_{31}N2O_3$ $[M+H]^+$: 431.2329, found: 431.2323.

(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-((2-(hydroxy(phenyl)methyl)quinolin-4-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3j)



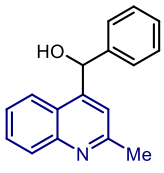
Prepared according to the *General Procedure* from (2R,3R,4S,5R,6S)-2 (acetoxymethyl)-6-(quinolin-4-yloxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate **2j**[7] (0.1 mmol, 35.0 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.12 mmol, 43 mg) and trifluoroacetic acid (0.4 mmol, 31 μL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 80:20 to 60:40) to give **3j** as a colourless solid (35 mg, 30% yield), average of two runs.
^{1}H NMR (500 MHz, $CDCl_3$), 1:1 mixture of diastereoisomers, δ (ppm): 8.15 - 8.07 (m, 2H), 8.06 – 8.00 (m, 2H), 7.82 -7.68 (m, 2H), 7.61 - 7.49 (m, 2H), 7.48 – 7.31 (m, 12H), 6.66 (s, 1H), 6.59 (s, 1H), 5.81 (s, 2H), 5.58 – 5.02 (m, 10H), 4.32 – 4.24 (m, 2H), 3.89 – 3.76 (m, 2H), 2.11 – 2.03 (m, 24H). ^{13}C NMR (126 MHz, , $CDCl_3$), 1:1 mixture of diastereoisomers, δ (ppm): 170.8, 170.5, 170.4, 169.7, 169.7, 169.6, 162.2, 162.0, 160.2, 159.9, 147.7, 147.6, 143.2, 142.9, 131.0, 130.9, 129.1, 129.0, 128.8, 128.6, 128.6, 127.8, 127.6, 126.9, 126.9, 122.0, 120.8, 120.7, 75.8, 72.8, 72.7, 72.6, 72.5, 71.0, 70.9, 68.5, 68.0, 62.2, 61.4, 60.7, 21.4, 21.1, 21.0, 21.0, 20.9, 20.9, 20.9, 20.9. HRMS: Calculated for $C_{30}H_{32}NO_{11}$ $[M+H]^+$: 582.1970, found: 582.1976.

4-((2,4-Dichloro-5-methoxyphenyl)amino)-2-(hydroxy(phenyl)methyl)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinoline-3-carbonitrile (3k)



Prepared according to the *General Procedure* from Bosutinib **2n** (0.1 mmol, 53.0 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.12 mmol, 43 mg) and trifluoroacetic acid (0.5 mmol, 39 μL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (CH_2Cl_2/MeOH, gradient from 95:5 to 90:10) to give **3n** as a yellow solid (21 mg, 33% yield), average of two runs. ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 7.79 (s, 1H), 7.45 – 7.40 (m, 5H), 7.29 (s, 1H), 7.09 (s, 1H), 6.68 (s, 1H), 6.56 (s, 1H), 5.76 (s, 1H), 4.13 (t, *J* = 6.5 Hz, 2H), 3.69 (s, 3H), 3.43 (s, 3H), 2.40 (m, 10H), 2.17 (s, 3H), 1.93 – 1.88 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6), δ (ppm): 164.1, 154.2, 152.8, 149.8, 149.0, 147.7, 138.0, 130.5, 129.2, 129.1, 127.7, 127.6, 119.7, 118.4, 112.1, 110.0, 109.9, 103.9, 103.2, 83.9, 67.2, 57.1, 55.4, 55.3, 55.0, 54.6, 52.9, 45.9, 26.4. HRMS: Calculated for $C_{33}H_{36}Cl_2N_5O_4$ $[M+H]^+$: 636.2139, found: 636.2129.

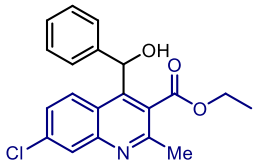
(2-Methylquinolin-4-yl)(phenyl)methanol (3l)



Prepared according to the *General Procedure* from 2-methylquinoline **2k** (0.2 mmol, 28.6 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg) and trifluoroacetic acid (0.4 mmol, 31 μL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 85:15) to give **3k** as a white solid (31 mg, 63% yield), average of two runs. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.03 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.47 – 7.28 (m, 6H), 6.48 (s, 1H), 2.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm): 159.0, 148.2, 148.0, 142.1, 129.2,

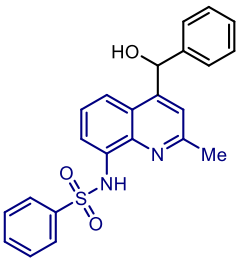
129.0, 128.8, 128.3, 127.3, 125.7, 123.9, 123.6, 119.3, 72.6, 25.5. HRMS: Calculated for $C_{17}H_{16}NO$ $[M+H]^+$: 250.1226, found: 250.1222.

Ethyl 7-chloro-4-(hydroxy(phenyl)methyl)-2-methylquinoline-3-carboxylate (3m)



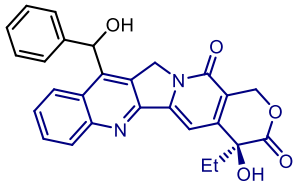
Prepared according to the *General Procedure* from ethyl 7-chloro-2-methylquinoline-3-carboxylate **2m** (0.2 mmol, 49.9 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg) and trifluoroacetic acid (0.4 mmol, 31 μL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 80:20) to give **3m** as a yellow solid (61 mg, 85% yield), average of two runs. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.13 – 8.05 (m, 2H), 7.62 – 7.56 (m, 1H), 7.53 – 7.46 (m, 2H), 6.81 – 6.64 (m, 3H), 6.57 (d, *J* = 2.1 Hz, 1H), 5.82 (s, 1H), 4.11 – 3.98 (m, 2H), 2.35 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$), δ (ppm): 167.4, 149.1, 137.8, 137.1, 133.8, 133.5, 129.9, 129.6, 129.1, 123.1, 118.8, 115.5, 96.0, 60.2, 45.5, 20.6, 14.0. HRMS: Calculated for $C_{20}H_{18}ClNNaO_3$ $[M+Na]^+$: 378.0867, found: 378.0876.

N-(4-(Hydroxy(phenyl)methyl)-2-methylquinolin-8-yl)benzenesulfonamide (3n)



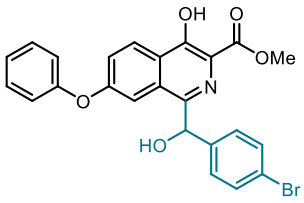
Prepared according to the *General Procedure* from N-(2-methylquinolin-8-yl)benzenesulfonamide **2l** (0.2 mmol, 59.7 mg)[8], diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.24 mmol, 86 mg) and trifluoroacetic acid (0.4 mmol, 31 μL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 90:10) to give **3l** as a yellow solid (52 mg, 64% yield), average of two runs. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.89 – 7.84 (m, 2H), 7.66 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.61 (d, *J* = 0.8 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 - 7.27 (m, 4H), 7.24 (s, 1H), 7.24 – 7.20 (m, 1H), 6.35 (s, 1H), 2.70 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$), δ (ppm): 158.1, 149.2, 142.0, 139.8, 138.3, 133.7, 133.2, 129.3, 129.2, 128.8, 127.6, 127.5, 126.2, 124.2, 120.3, 118.5, 115.3, 72.9, 25.6. HRMS: Calculated for $C_{23}H_{19}N_2O_3S$ $[M-H]^-$: 403.1122, found: 403.1124.

(*4S*)-4-Ethyl-4-hydroxy-11-(hydroxy(phenyl)methyl)-1,12-dihydro-14H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H)-dione (3o)



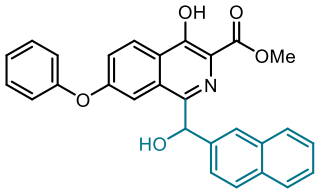
Prepared according to the *General Procedure* from Camptothecin **2o** (0.1 mmol, 35.0 mg), diethyl 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (0.12 mmol, 43 mg) and trifluoroacetic acid (0.4 mmol, 31 μL) using degassed $CHCl_3$ (0.6 mL) as a solvent. Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (DCM/MeOH, gradient from 98:2 to 85:15) to give **3o** as a yellow solid (14 mg, 31% yield), average of two runs. ^{1}H NMR (500 MHz, DMSO-*d*$_6$), 1:1 mixture of diastereoisomers, δ (ppm): 8.24 (dd, *J* = 8.7, 4.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.77 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.59 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.33 (s, 1H), 7.29 – 7.22 (m, 2H), 7.23 – 7.18 (m, 1H), 6.75 – 6.70 (m, 1H), 6.57 – 6.53 (m, 1H), 6.49 (d, *J* = 3.4 Hz, 1H), 5.57 – 5.30 (m, 4H), 1.93 – 1.76 (m, 2H), 0.91 – 0.82 (m, 3H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$), 1:1 mixture of diastereoisomers, δ (ppm): 173.3, 157.6, 153.9, 153.9, 150.8, 150.8, 149.3, 149.3, 146.4, 146.4, 146.1, 143.5, 130.7, 130.6, 129.3, 128.4, 128.3, 128.0, 127.9, 127.7, 126.0, 125.9, 119.8, 97.3, 73.2, 73.2, 71.7, 66.1, 52.3, 52.2, 31.2, 31.1, 8.6, 8.6. HRMS: Calculated for $C_{27}H_{22}N_2NaO_5$ $[M+Na]^+$: 477.1421, found: 477.1411.

Methyl 1-((4-bromophenyl)(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3-carboxylate (3p)



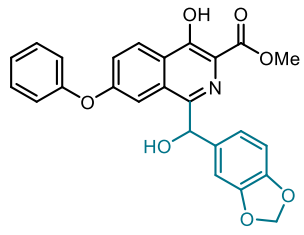
Prepared according to the *General Procedure* from methyl 4-hydroxy-7-phenoxyisoquinoline-3-carboxylate **2d** (0.2 mmol, 59.0 mg), diethyl 4-(4-bromobenzoyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1p** (0.24 mmol, 104.7 mg) and trifluoroacetic acid (0.4 mmol, 31 µL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was treated with acetonitrile (3 mL) and decanted off. Solids were washed with acetonitrile (2 x 2mL) to yield **3p** as white solid (91 mg, 95% yield), average of two runs. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 11.79 (s, 1H), 8.40 (d, *J* = 9.1 Hz, 1H), 7.55 – 7.43 (m, 3H), 7.39 – 7.30 (m, 3H), 7.03 (d, *J* = 2.4 Hz, 1H), 7.00 – 6.89 (m, 4H), 5.85 (s, 1H), 4.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm): 170.8, 160.1, 156.7, 154.6, 148.1, 141.7, 131.9, 130.4, 129.6, 129.2, 126.3, 125.3, 123.9, 122.7, 121.8, 120.6, 117.3, 108.8, 72.1, 52.8. HRMS: Calculated for $C_{24}H_{19}BrNO_5$ $[M+H]^+$: 480.0441, found: 480.0437.

Methyl 4-hydroxy-1-(hydroxy(naphthalen-2-yl)methyl)-7-phenoxyisoquinoline-3-carboxylate (3q)



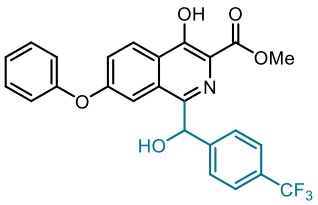
Prepared according to the *General Procedure* from methyl 4-hydroxy-7-phenoxyisoquinoline-3-carboxylate **2d** (0.2 mmol, 59.0 mg), diethyl 4-(2-naphthoyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1q**[2] (0.24 mmol, 97.8 mg) and trifluoroacetic acid (0.4 mmol, 31 µL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 90:10) to give **3q** as a yellow solid (78 mg, 88% yield), average of two runs. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 11.81 (s, 1H), 8.40 (d, *J* = 9.1 Hz, 1H), 7.83 – 7.67 (m, 3H), 7.58 – 7.55 (m, 1H), 7.51 – 7.43 (m, 3H), 7.28 (s, 1H), 7.24 – 7.18 (m, 3H), 7.16 (dd, J = 8.5, 1.8 Hz, 1H), 6.87 – 6.82 (m, 2H), 6.15 – 6.00 (m, 2H), 4.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm): 170.9, 159.9, 156.7, 154.5, 148.6, 140.0, 133.3, 133.0, 130.2, 129.9, 128.7, 128.3, 127.6, 126.9, 126.2, 126.1, 126.0, 125.1, 124.9, 123.9, 122.6, 120.3, 117.3, 109.0, 72.9, 52.7. HRMS: Calculated for $C_{28}H_{21}NNaO_5$ $[M+Na]^+$: 474.1312, found: 474.1313.

Methyl 1-(benzo[d][1,3]dioxol-5-yl(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3 carboxylate (3s)



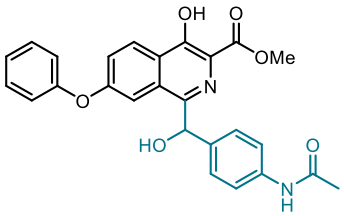
Prepared according to the *General Procedure* from methyl 4-hydroxy-7-phenoxyisoquinoline-3-carboxylate **2d** (0.2 mmol, 59.0 mg), diethyl 4-(benzo[d][1,3]dioxole-5-carbonyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1s**[2] (0.24 mmol, 96.3 mg) and trifluoroacetic acid (0.4 mmol, 31 µL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 90:10) to give **3s** as a yellow solid (67 mg, 75% yield), average of two runs. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 11.78 (s, 1H), 8.40 (d, *J* = 9.1 Hz, 1H), 7.52 – 7.42 (m, 3H), 7.37 – 7.30 (m, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.05 – 6.96 (m, 2H), 6.64 (d, *J* = 7.9 Hz, 1H), 6.57 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.52 (d, *J* = 1.7 Hz, 1H), 5.99 (d, *J* = 4.7 Hz, 1H), 5.93 (d, *J* = 1.4 Hz, 1H), 5.90 (d, *J* = 1.4 Hz, 1H), 5.82 (d, *J* = 4.1 Hz, 1H), 4.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm): 170.8, 159.9, 156.6, 154.7, 148.7, 147.8, 147.2, 136.8, 130.3, 129.7, 126.1, 125.2, 123.9, 122.5, 121.4, 120.6, 117.2, 109.1, 108.3, 107.7, 101.0, 72.3, 52.7. HRMS: Calculated for $C_{25}H_{19}NNaO_7$ $[M+Na]^+$: 468.1054, found: 468.1049.

Methyl 4-hydroxy-1-(hydroxy(4-(trifluoromethyl)phenyl)methyl)-7-phenoxyisoquinoline-3-carboxylate (3t)



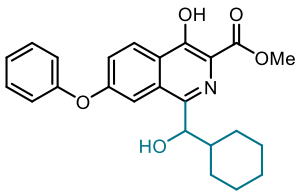
Prepared according to the *General Procedure* from methyl 4-hydroxy-7-phenoxyisoquinoline-3-carboxylate **2d** (0.2 mmol, 59.0 mg), diethyl 2,6-dimethyl-4-(4-(trifluoromethyl)benzoyl)-1,4-dihydropyridine-3,5-dicarboxylate **1t**[2] (0.24 mmol, 103 mg) and trifluoroacetic acid (0.4 mmol, 31 μL). Time of irradiation: 72 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 90:10) to give **3t** as a yellow solid (70 mg, 75% yield), average of two runs. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 11.80 (s, 1H), 8.41 (d, *J* = 9.1 Hz, 1H), 7.52 – 7.41 (m, 5H), 7.37 – 7.29 (m, 1H), 7.21 – 7.15 (m, 2H), 7.03 – 6.92 (m, 3H), 5.93 (s, 1H), 4.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 170.7, 160.3, 156.8, 154.5, 147.8, 146.5, 130.4, 130.1, 129.7, 129.6, 127.8, 126.3, 125.7, 125.7, 125.4, 123.9, 122.7, 120.7, 117.4, 108.5, 72.2, 52.8. ^{19}F NMR (376 MHz, $CDCl_3$), δ (ppm): -62.68. HRMS: Calculated for $C_{25}H_{19}F_3NO_5$ $[M+H]^+$: 470.1210, found: 470.1209.

Methyl 1-((4-acetamidophenyl)(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3-carboxylate (3u)



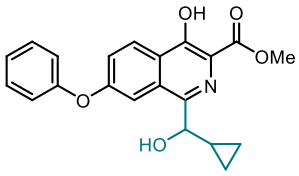
Prepared according to the *General Procedure* from methyl 4-hydroxy-7-phenoxyisoquinoline-3-carboxylate **2d** (0.2 mmol, 59.0 mg), diethyl 4-(4-acetamidobenzoyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1u**[2] (0.24 mmol, 86 mg) and trifluoroacetic acid (0.4 mmol, 31 μL). Time of irradiation: 72 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 90:10) to give **3u** as a white solid (56 mg, 61% yield), average of two runs. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.36 (d, *J* = 9.1 Hz, 1H), 7.45 – 7.41 (m, 3H), 7.34 – 7.27 (m, 3H), 7.16 (s, 1H), 7.12 – 7.05 (m, 1H), 7.00 – 6.92 (m, 4H), 5.84 (s, 1H), 4.07 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm): 171.2, 168.5, 160.3, 157.0, 154.9, 149.0, 138.9, 137.7, 131.4, 130.8, 128.6, 126.5, 125.6, 124.2, 122.9, 121.0, 120.3, 117.6, 109.3, 72.5, 53.1, 25.0. HRMS: Calculated for $C_{26}H_{22}N_2NaO_6$ $[M+Na]^+$: 481.1370, found: 481.1372.

Methyl 1-(cyclohexyl(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3-carboxylate (3v)



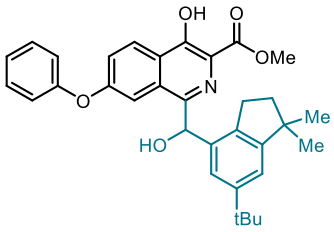
Prepared according to the *General Procedure* from methyl 4-hydroxy-7-phenoxyisoquinoline-3-carboxylate **2d** (0.2 mmol, 59.0 mg), diethyl 4-(cyclohexanecarbonyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1v**[2] (0.24 mmol, 87.2 mg) and trifluoroacetic acid (0.4 mmol, 31 μL). Time of irradiation: 12 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 90:10) to give **3v** as a white solid (61 mg, 75% yield), average of two runs. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 11.71 (s, 1H), 8.43 (d, *J* = 9.1 Hz, 1H), 7.56 – 7.41 (m, 3H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.31 – 7.23 (m, 1H), 7.19 – 7.09 (m, 2H), 4.91 (dd, *J* = 7.0, 3.2 Hz, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.06 (s, 3H), 1.83 – 1.48 (m, 6H), 1.23 – 0.98 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 171.0, 159.5, 156.0, 155.4, 150.4, 130.2, 130.0, 126.2, 125.0, 123.9, 122.4, 120.2, 117.7, 109.9, 73.6, 52.7, 44.8, 30.7, 26.7, 26.2, 26.0, 25.7. HRMS: Calculated for $C_{24}H_{25}NNaO_5$ $[M+Na]^+$: 430.1625, found: 430.1620.

Methyl 1-(cyclopropyl(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3-carboxylate (3w)



Prepared according to the modified *General Procedure* from methyl 4-hydroxy-7-phenoxyisoquinoline-3-carboxylate **2d** (0.2 mmol, 59.0 mg), diethyl 4-(cyclopropanecarbonyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1w** (0.24 mmol, 77.2 mg) and trifluoroacetic acid (0.4 mmol, 31 μL). Time of irradiation: 72 hours (460 nm, 30 mW/cm^2). The reaction was carried out at -10 °C using a chiller connected to the steel reactor. The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 90:10) to give **3w** as a white solid (30 mg, 41% yield), average of two runs. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 11.73 (s, 1H), 8.45 (d, *J* = 9.7 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.50 – 7.43 (m, 2H), 7.32 – 7.26 (m, 1H), 7.19 – 7.11 (m, 2H), 4.91 – 4.74 (m, 2H), 4.06 (s, 3H), 1.20 – 1.05 (m, 1H), 0.50 – 0.38 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$), δ (ppm): 170.9, 159.6, 156.2, 155.4, 150.9, 130.3, 130.0, 126.2, 125.0, 124.1, 122.6, 120.2, 117.7, 110.2, 70.7, 52.7, 17.9, 3.3, 1.7. HRMS: Calculated for $C_{21}H_{20}NO_5$ $[M+H]^+$: 366.1336, found: 366.1335.

Methyl 1-((6-(tert-butyl)-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3-carboxylate (3x)



Prepared according to the modified *General Procedure* from methyl 4-hydroxy-7-phenoxyisoquinoline-3-carboxylate **2d** (0.2 mmol, 59.0 mg), diethyl 4-(6-(tert-butyl)-1,1-dimethyl-2,3-dihydro-1H-indene-4-carbonyl)-2,6-dimethyl-1,4-dihydropyridine -3,5-dicarboxylate **1x** (0.24 mmol, 116 mg) and trifluoroacetic acid (0.4 mmol, 31 μL). Acetonitrile/DMSO (1.2 mL, 1:1) was used as reaction solvent. Time of irradiation: 48 hours (460 nm, 30 mW/cm^2). The reaction mixture was purified on silica gel (*n*-hexane/EtOAc, gradient from 95:5 to 90:10) to give **3x** as a white solid (49 mg, 47% yield), average of two runs. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 11.75 (s, 1H), 8.39 (d, *J* = 9.1 Hz, 1H), 7.42 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.23 (d, *J* = 2.3 Hz, 1H), 7.18 – 7.13 (m, 1H), 6.98 (d, *J* = 1.8 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.84 (d, *J* = 1.8 Hz, 1H), 6.02 (s, 1H), 5.86 (s, 1H), 4.08 (s, 3H), 2.61 – 2.42 (m, 2H), 1.78 – 1.70 (m, 2H), 1.17 (s, 3H), 1.13 (s, 3H), 1.12 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$), δ (ppm): 171.3, 159.3, 156.8, 155.8, 153.6, 150.3, 149.7, 138.4, 137.4, 130.5, 126.5, 124.9, 124.4, 123.3, 123.3, 119.8, 118.9, 117.7, 111.0, 71.7, 53.1, 44.0, 41.8, 34.9, 31.8, 29.1, 29.1, 28.0. HRMS: Calculated for $C_{33}H_{36}NO_5$ $[M+H]^+$: 526.2588, found: 526.2584.

C.3 Unsuccessful Substrates

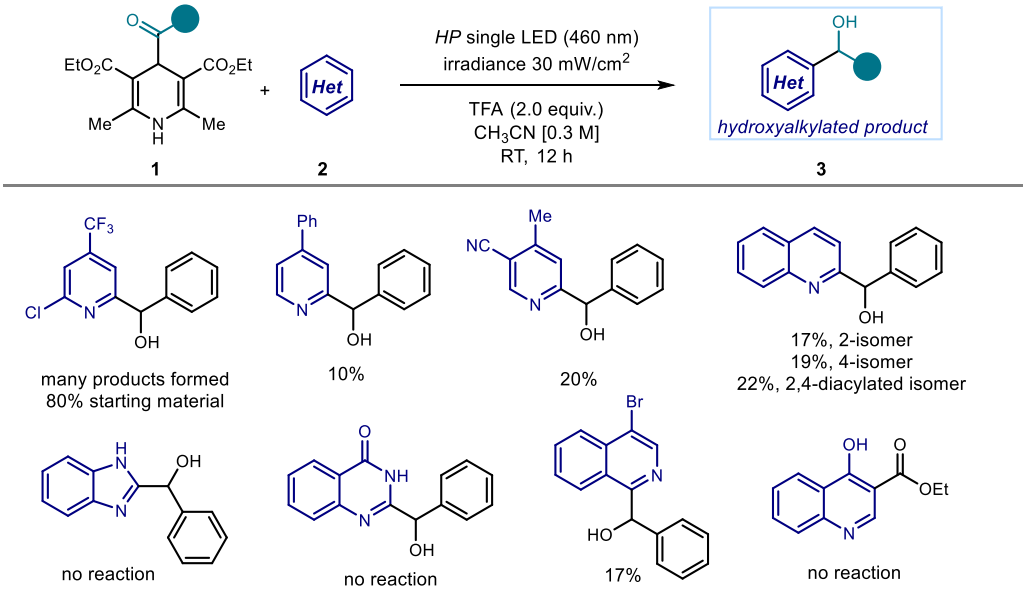


Figure S2. List of unsuccessful substrates. Yield determined by ^{1}H NMR analysis of the crude mixture using trichloroethylene as the internal standard.

D. Electrochemical measurements

For the cyclic voltammetry (CV) measurements, a glassy carbon disk electrode (diameter: 3 mm) was used as a working electrode. A silver wire coated with AgCl immersed in a 3 M aqueous solution of NaCl and separated from the analyte by a fritted glass disk was employed as the reference electrode. A Pt wire counter-electrode completed the electrochemical setup. For comparison, all the potentials in are quoted with respect to the saturated calomel electrode (SCE, +0.047 V vs. Ag/AgCl, 3 M NaCl).[1A] A scan rate of 500 mV/s was used for all CV experiments. Potentials are quoted with the following notation: E_p peak potential, $E_{p/2}$ half peak potential (half-maximum current), $E_{1/2}$ half-wave potential (average of anodic and catodic peak potentials, for reversible peaks). Protonated forms were prepared by addition of 1.0 equiv. of trifluoromethanesulfonic acid.

Table S1. Reduction potentials (reported vs. SCE) of representative pyridine, quinoline and isoquinoline derivatives and their protonated forms.

Heterocycle	Free Base		Protonated Form	
	E_p (V)	$E_{p/2}$ (V)	E_p (V)	$E_{p/2}$ (V)
Diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate **(1a)**	–2.32	–2.16	–1.09	–1.01
6,7-Dimethoxyisoquinoline **(2b)**	–2.63	–2.48	–1.41	–1.32
Isoquinoline **(2a)**	–2.38	–2.27	–1.16	–1.08
4-Methylquinoline **(2e)**	–2.40	–2.21	–1.08	–1.00

[A] Ferrocene (Fc) was used as an internal standard for potential calibration purposes. With respect to the Ag/AgCl reference electrode we employed, $E_{1/2}(Fc^+/Fc)$ = +0.427 V in acetonitrile. Knowing that $E_{1/2}(Fc^+/Fc)$ = +0.380 V vs. SCE (V. V Pavlishchuk, A. W. Addison, *Inorganica Chim. Acta* **2000**, *298*, 97–102), it follows that E(Ag/AgCl, 3 M NaCl) = –0.047 V + E(SCE).

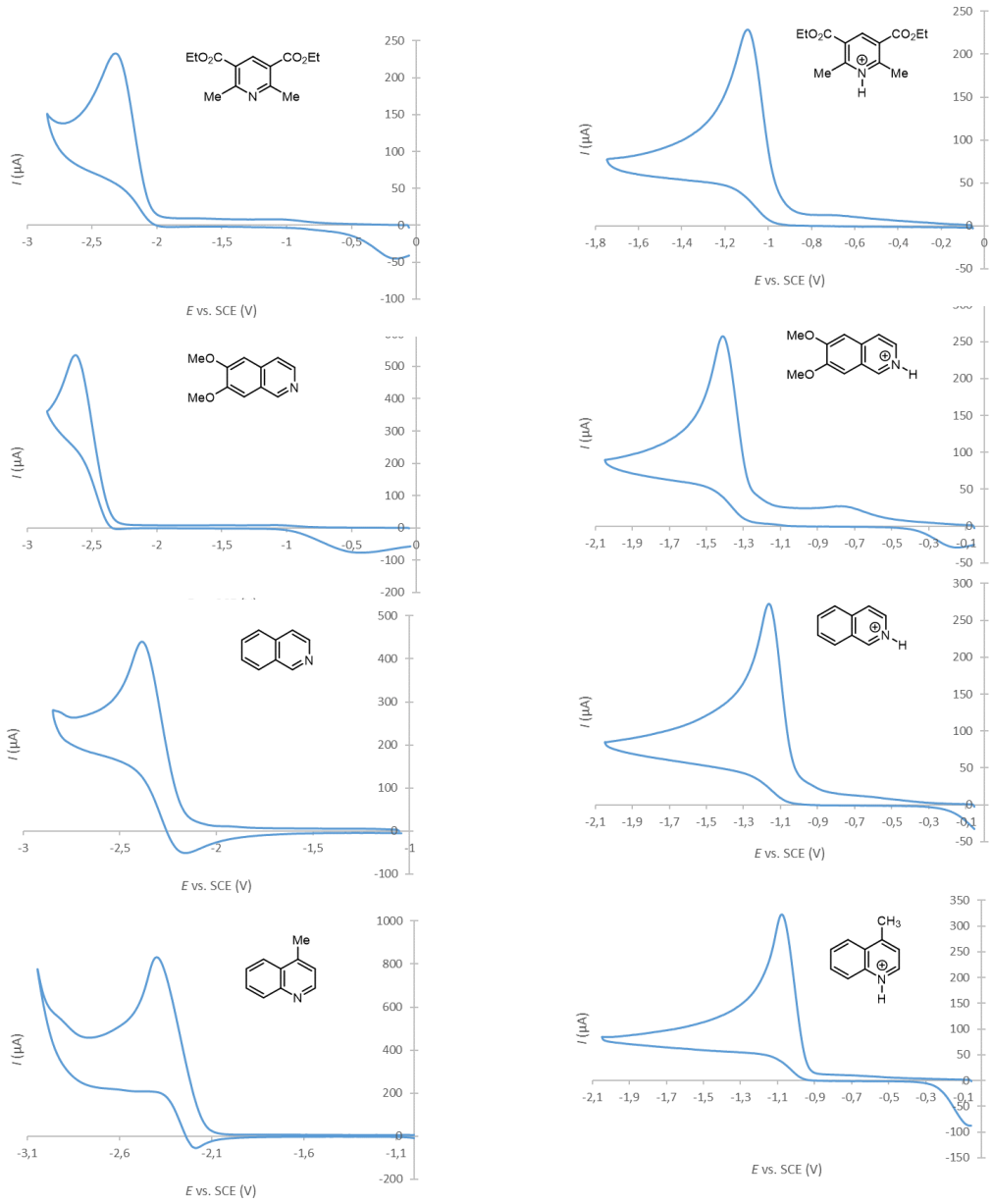


Figure S3. Cyclic voltammograms of **1a, 2a, 2b** and **2e** [0.02 M] as both free base and in protonated form in [0.1 M] $TBAPF_6$ in CH_3CN. Sweep rate: 20 mV/s, glassy carbon working electrode, Ag/AgCl (NaCl 3 M) reference electrode, Pt wire auxiliary electrode.

E. UV-vis Absorption Spectra of 1a

Solutions at different concentrations of **1a**, obtained by opportunely diluting an original stock solution ([**1a**] = 0.3 mM in CH_3CN) with acetonitrile, were introduced to a 1 cm path length quartz cuvette equipped with a Teflon® septum. The solution were analyzed using a Shimadzu 2401PC UV-Vis spectrophotometer.

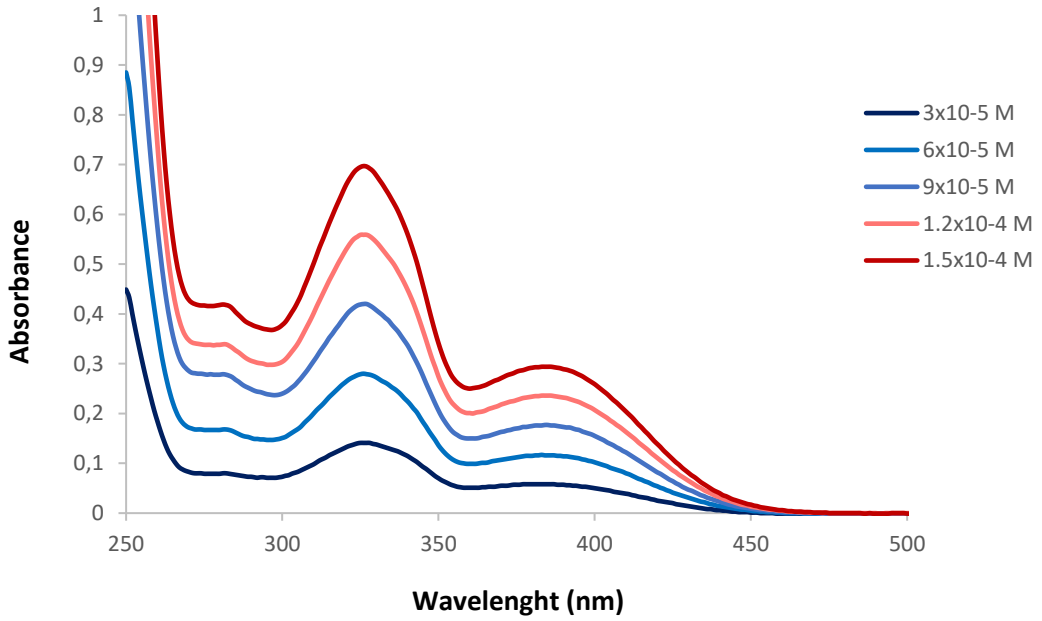
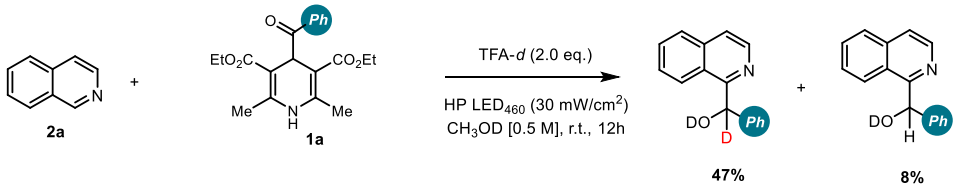


Figure S4. Absorption spectra of **1a** at different concentrations in CH_3CN. The tail wavelength of absorption was considered at 475 nm.

F. Deuterium Incorporation Studies



Scheme S3. Deuterium Incorporation Experiment

The 8 mL vial was charged with the isoquinoline **2a** (26 mg, 0.2 mmol, 1 equiv.) and 4-benzoyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1a** (86 mg, 0.24 mmol, 1.2 equiv.). The vial was put under vacuum and backfilled with argon three times. Finally the degassed CH_3OD (0.6 mL) and a TFA-*d* (31 µL, 0.4 mmol, 2 equiv) was added. The vial was sealed with parafilm and placed inside a steel reactor fixed over an aluminum block equipped with a High Power single LED (λ = 460 nm), irradiance = 30 mW/cm^2 as controlled by external power supply. The reaction was irradiated at ambient temperature for 12 h. The solvent was removed *in vacuo* and the residue was dissolved in $CDCl_3$. The degree of deuterium incorporation was determined by ^{1}H NMR spectroscopy (Figure S5).

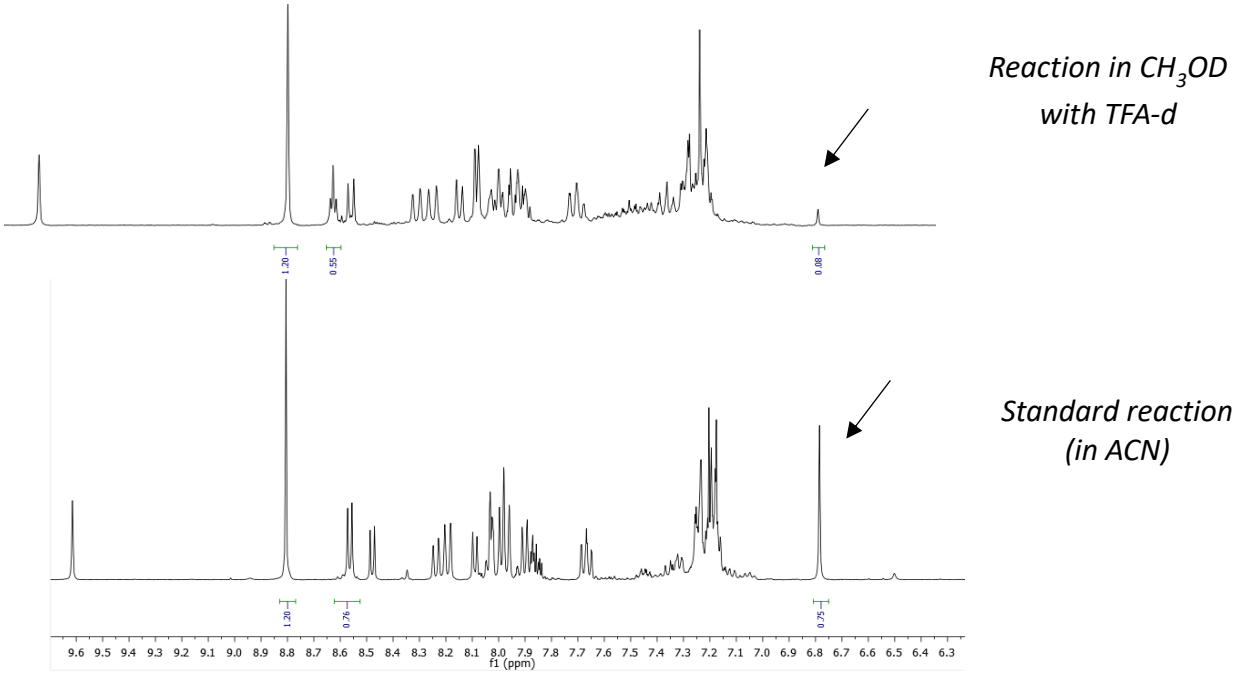


Figure S5. NMR spectra of crude mixtures. Above: the reaction carried out in CH_3OD as the solvent, showing deuterium incorporation in α-OH position (6.78 ppm). Below: the standard crude reaction mixture in acetonitrile for the reference.

The reaction carried out in CH_3OD produced 55% of the crude product, which is identical to the outcome of the reaction in CH_3OH. Clearly, deuterium incorporation in α-OH position could be observed, which accounted for 85% of the product.

G. Theoretical Studies

Computational Details

All DFT calculations were performed with the Gaussian09 suite of programs (Rev. A.01).[9] The structures of all the studied species were fully optimized without any symmetry constraint using the M06-2X functional[10] in conjunction with the split-valence 6-31+G(d) basis set (unrestricted spin mode). All stationary points were characterized as minima by harmonic frequency calculations. Computed harmonic frequencies were used to calculate the thermal contribution to Gibbs free energy with the usual approximations. Temperature and pressure were fixed at 298 K and 1 atm, respectively. To obtain more accurate electronic energies, single-point calculations were performed with the same functional and the larger 6-311+G(3df,2p) basis set. Bulk solvent effects were accounted for by the Polarizable Continuum Model in its Integral Equation Formalism variant (IEF-PCM), as implemented in Gaussian09.[11] The default parameters for acetonitrile were used.

Estimation of the Reduction Potential of Intermediate VII to give VIII

DFT-based computational approaches for the estimation of redox potentials in solution are well documented,[12] and they are especially useful to assess the redox properties of highly reactive intermediates that cannot be studied easily by electrochemical methods. Generally, results are accurate enough to support qualitative conclusions. For instance, the B3LYP/6-311++G(2df,2p)//B3LYP/6-31+G(d) model chemistry was suitable to predict redox potentials in acetonitrile with a mean unsigned error of 0.17 V over a large benchmark set of 270 organic molecules.[12a]

In line with the literature,[12] the reduction potential of intermediate **VII** to give **VIII** was estimated from the computed free energy difference between these two species. For referencing, the "absolute" potential of the saturated calomel electrode was estimated as $E_{SCE,abs}$ = +4.525 V (with free energy of the electron taken as zero) based on the reported accurate calculation of potential of the standard hydrogen electrode (SHE, $E_{SCE,abs}$ = +4.281 V)[13] and of the experimental potential the SCE vs. NHE (E_{SCE} = +0.244 V vs. SHE).[14]

More in detail, from the computed free energy difference ΔG(**VII**/**VIII**) = –105.7 kcal mol^{-1}, it follows that $E_{\mathbf{VII/VIII},abs}$ = +4.58 V and $E_{\mathbf{VII/VIII}}$ = +0.06 vs. SCE.

H. EPR Experiments

EPR experiments were conducted to evaluate how the presence of the protonated pyridine (**Pyr-H**$^+$), which arises from the photolysis of the benzoyl radical precursor **1a**, affected the rate of benzoyl radical generation via photolysis of **1a** (Figure S6).

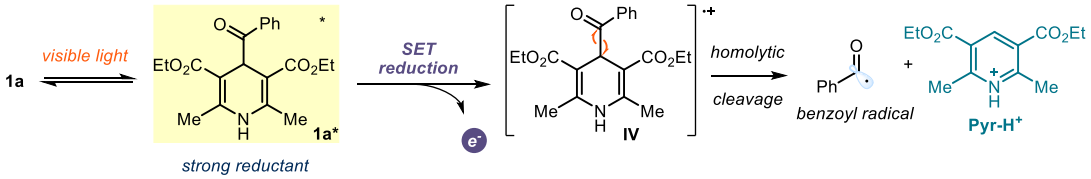


Figure S6. Photolysis of **1a** to afford the benzoyl radical and possible role of the pyridinium ion (Pyr-H$^+$) as electron acceptor.

EPR spectra were acquired on a Bruker EMX X-band EPR spectrometer with an ER 4116 HS cavity (9.86 GHz at room temperature) using 100 kHz field modulation (modulation amplitude: 5 G). A 150 mL Suprasil offset liquid nitrogen dewar flask (Wilmad-LabGlass) was used for low-temperature measurements. Individual EPR tubes were filled with ~0.7 mL of the solution and were placed at the same position of the resonant cavity for EPR spectral acquisition. The spectral data were collected at 298 K with the following spectrometer settings: microwave power = 0.6363 mW; center field = 3348 G, sweep width = 1000 G, sweep time = 30 s, modulation frequency = 100 KHz, modulation amplitude = 5 G, power attenuation = 25 dB, time constant = 0.01 ms.

Two samples were measured, containing a mixture of **1a** alone and a combination of **1a** and the protonated pyridine (**Pyr-H**$^+$). The samples were prepared as follow:
(1) **1a** (36 mg, 0.1 mmol) was dissolved in 1,4-dioxane (1 mL, [**1a**] = 100 mM). This solution was transferred into EPR Low Pressure/Vacuum Tube. The reaction mixture was degassed via a freeze-pump-thaw procedure. The tube was then inserted inside the EPR cavity for the EPR measurements.
(2) **Pyr-H**$^+$ was prepared by dissolving diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (25 mg, 0.1 mmol) in diethyl ether (0.5 mL) and adding trifluoroacetic acid (1.0 eq.). Diethyl ether was removed by rotary evaporator and dried under high vacuum to yield **Pyr-H**$^+$ as a yellow oil (36 mg, quant.). The mixture of **1a** + **Pyr-H**$^+$ was prepared by dissolving **1a** (36 mg, 0.1 mmol) in 1,4-dioxane, (1 mL, [**1a**] = 100 mM) and **Pyr-H**$^+$ (18 mg, 0.05 mmol, 50 mol%) was added. This solution was transferred into EPR Low Pressure/Vacuum Tube. The reaction mixture was degassed via a freeze-pump-thaw procedure. The tube was then inserted inside the EPR cavity for the EPR measurements.

Before acquiring the spectra, a 460 nm high power LED purchased from LEDENGIN was used to irradiate the samples. The LED was connected to the EPR cavity using an optical fibre supplied with the equipment from Bruker. EPR spectra were recorded after 0 and 15 minutes of irradiation (Figure S7). The spectrum at 15 min showed an isotropic X-band absorption and afforded a *g*-value of 2.004, which is consistent with literature data for the characterization of the benzoyl radical.[2] The signal reached a maximum of intensity after 7.5 min and it did not increase upon further irradiation. The peak corresponding to the generation of the benzoyl radical started to emerge at different rates after 2.5 min of irradiation for the **1a** solution (Figure S7, left) and the **1a** + **Pyr-H**$^+$ mixture (Figure S7, right). The irradiated solution of **1a** reached the point of saturation, where the signal did no longer increase in intensity, after 7.5 min, while the solution of **1a** + **Pyr-H**$^+$ (50 mol%) reached the point of saturation much earlier (after 3.5 min).

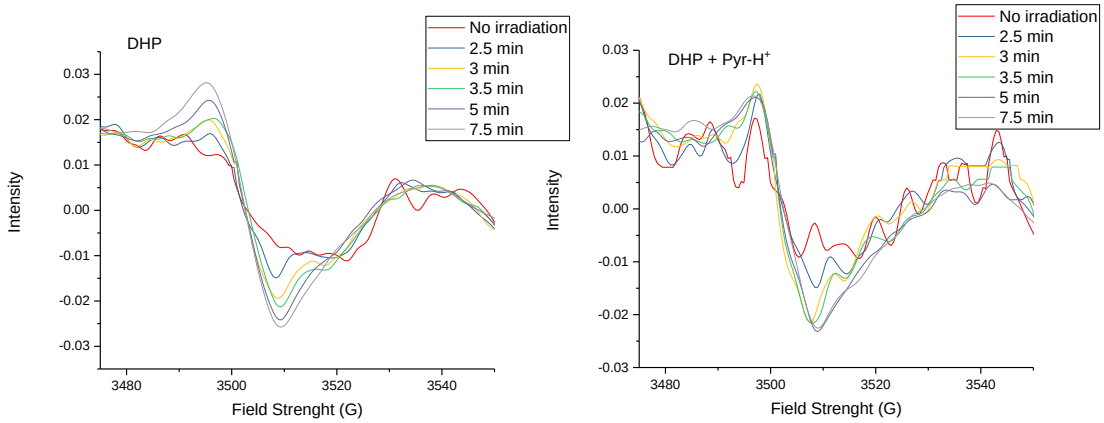


Figure S7. Normalised EPR signals corresponding to the benzoyl radical: left panel - irradiated soluiton of benzoyl-DHP **1a** (0.05 mM, 1,4-dioxane, 293 K, 460 nm, 52 mW/cm^2); right panel - solution of benzoyl-DHP **1a** + **Pyr-H$^+$** (50 mol%, 0.05 mM, 1,4-dioxane, 293 K, 460 nm LED, 52 mW/cm^2).

Figure S8 compares the amplitudes of signals corresponding to the benzoyl radical after 2.5 min (**A, D** left), 3.5 min (**B, E** center) and 2.5 min vs 12.5 min (**C, F** right) of irradiation for both the **1a** solution and the **1a** + **Pyr-H$^+$** (50 mol%) mixture. After 2.5 minutes of irradiation of **1a**, a small signal of intensity 0.003 was detected (Figure S8, **A**, top left). The signal slowly increased to 0.01 after 3.5 min (**B**) to reach its maximum of 0.017 after 7.5 min (**C**). On the other hand, the mixture **1a** + **Pyr-H$^+$** (50 mol%) generated a signal of higher amplitude (0.012) after 2.5 min. (Figure S8, **D,** bottom left), which reached the point of saturation after 3.5 min (amplitude of 0.017, **E**).

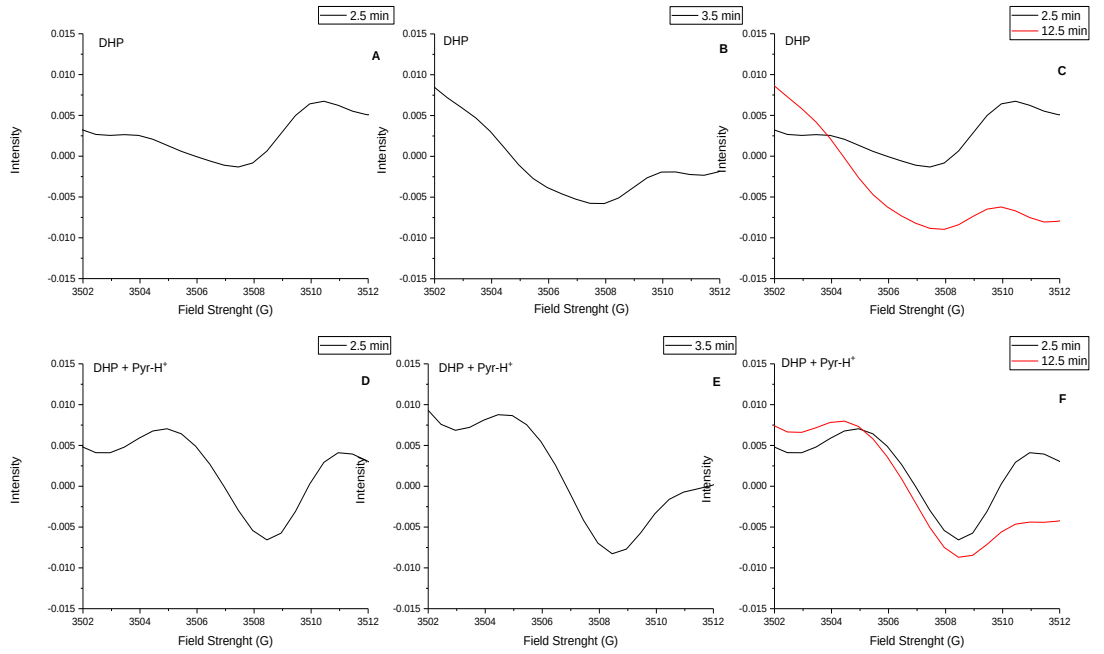


Figure S8. *In-situ* monitoring by EPR spectroscopy of benzoyl radical formation for a solution of **1a** (**A-C**) and for a mixture of **1a** + Pyr-H$^+$ (50 mol%) (**D-F**). **C** and **F** show the comparison between the initial signal measured after 2.5 min with the final signal after 12.5 min. EPR conditions: 0.05 mM, 1,4-dioxane, 293 K, 460 nm, 52 mW/cm^2. Signals obtained after subtraction of baseline and normalisation.

These experiments were repeated twice, giving similar results. Overall, the EPR experiments detailed in Figure S7 and S8 indicate that the addition of **Pyr-H**$^+$ (50 mol%) accelerates the initial rate of benzoyl radical formation upon irradiation with visible light. The addition of **Pyr-H**$^+$ (50 mol%) accelerates the radical generation process (**D, E** bottom) when compared to the irradiation of **1a** alone (**A, B** top). This observation is consistent with the mechanistic proposal that **Pyr-H**$^+$ acts as an electron acceptor from the excited **1a***, thus facilitating the photolysis of the benzoyl-DHP radical precursor **1a** (Figure S6).

I. References.

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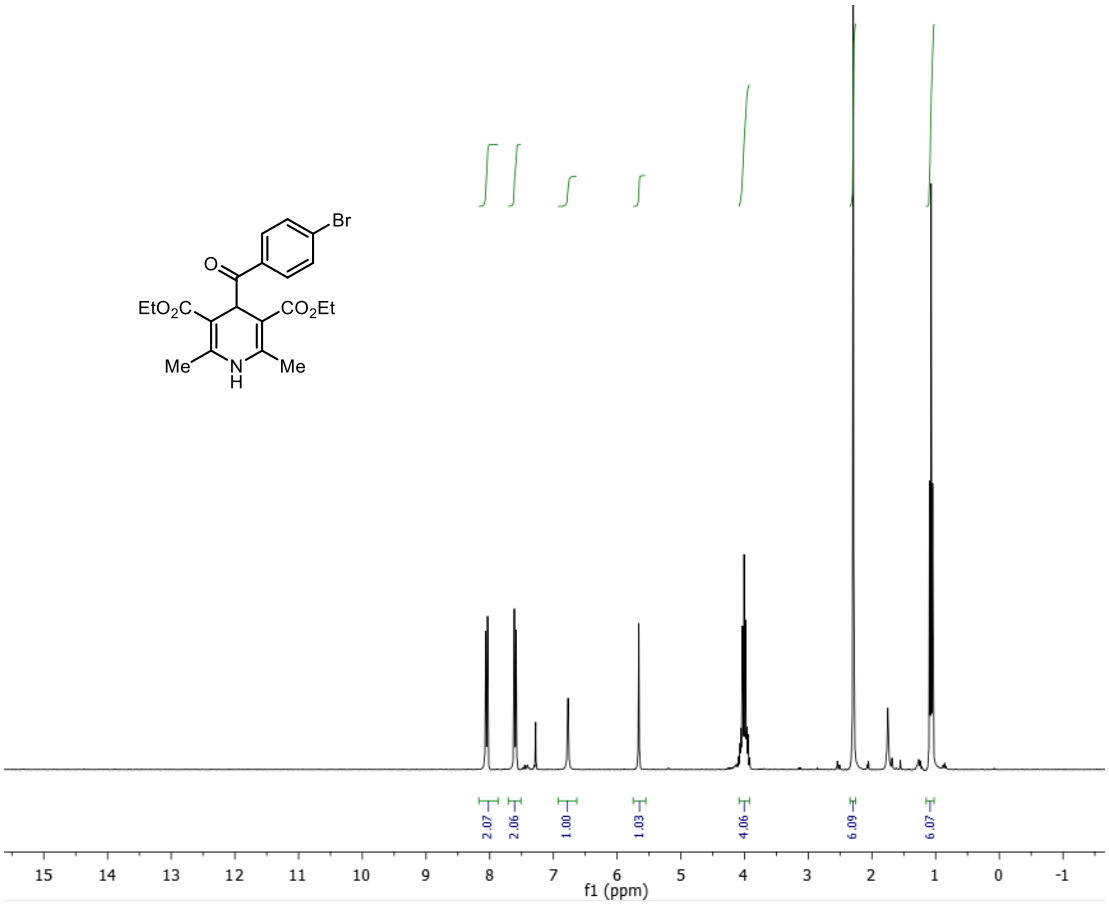
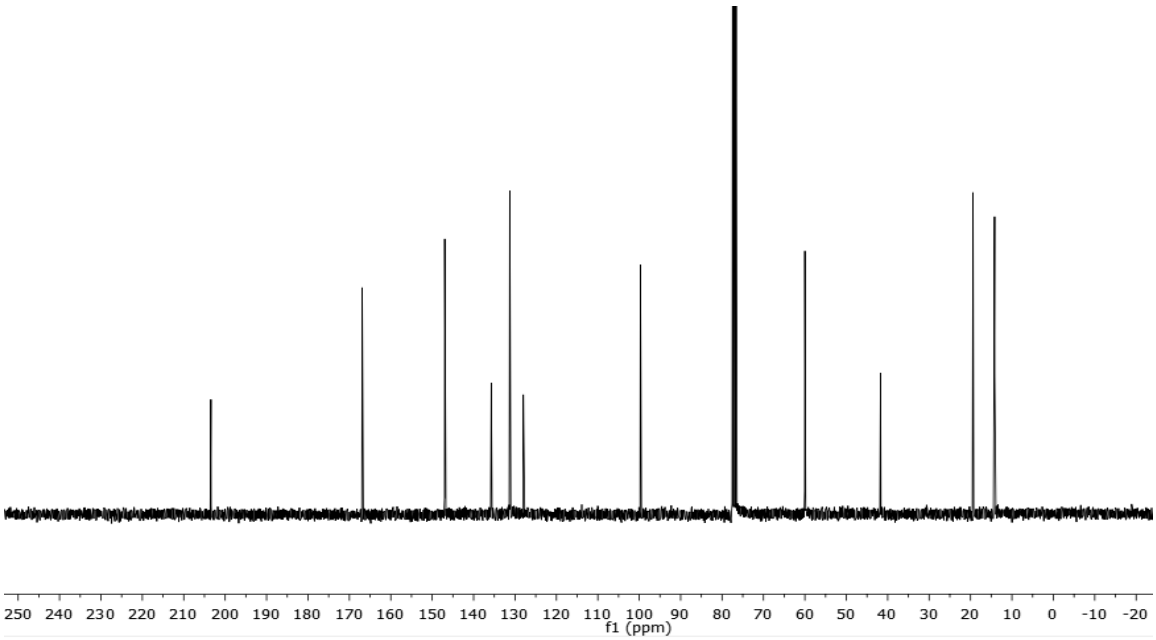
J. NMR Spectra

Diethyl 4-(4-bromobenzoyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1p)

^{1}H NMR (300 MHz, $CDCl_3$)

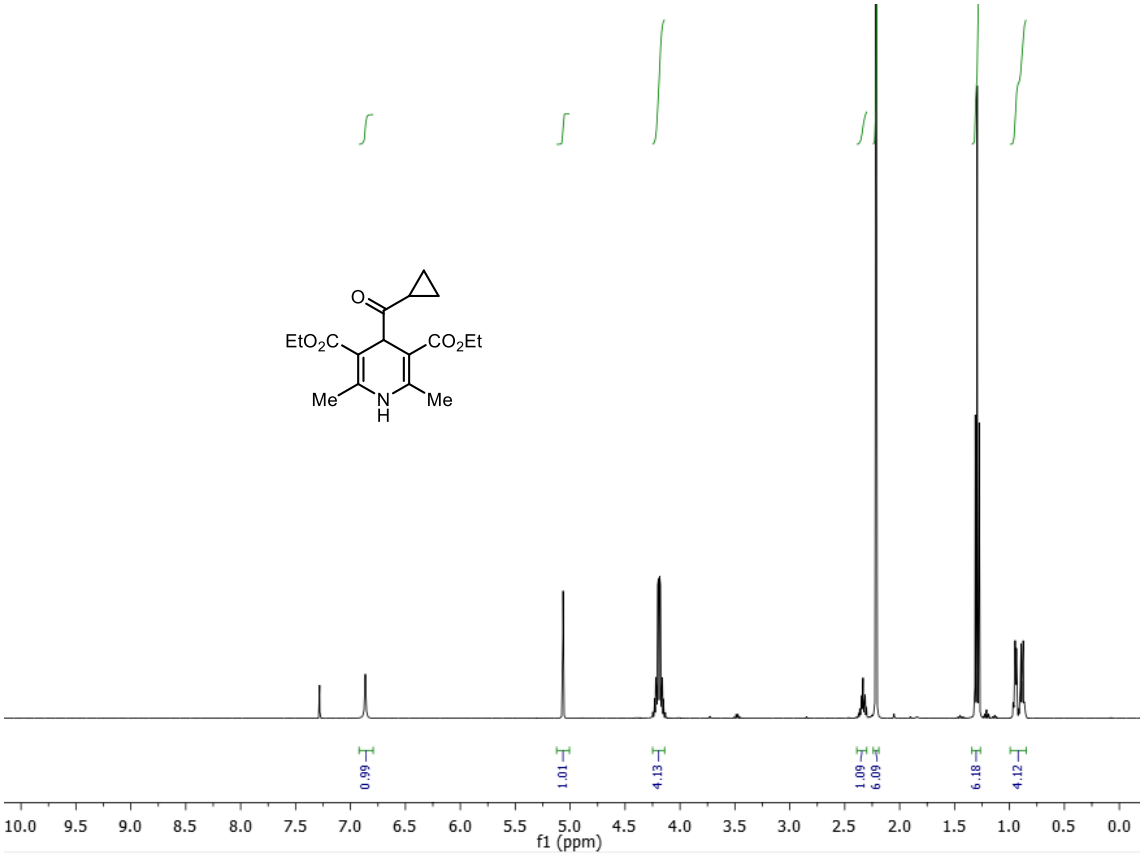


^{13}C NMR (75 MHz, $CDCl_3$)

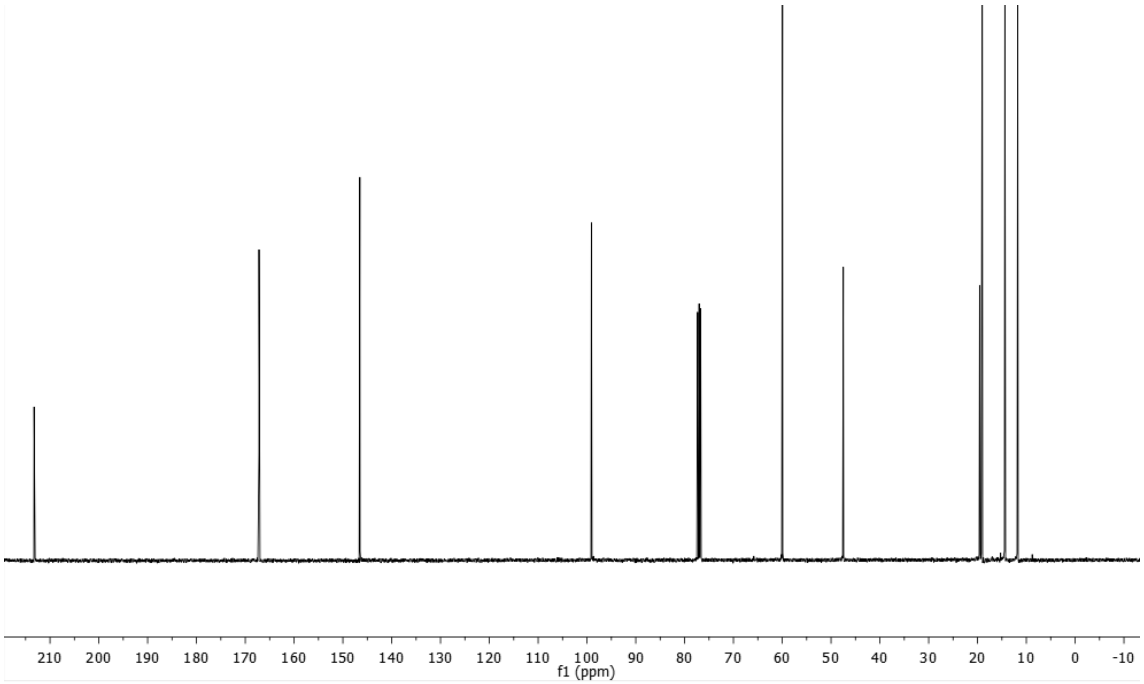


Diethyl 4-(cyclopropanecarbonyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1w)

^{1}H NMR (400 MHz, $CDCl_3$)

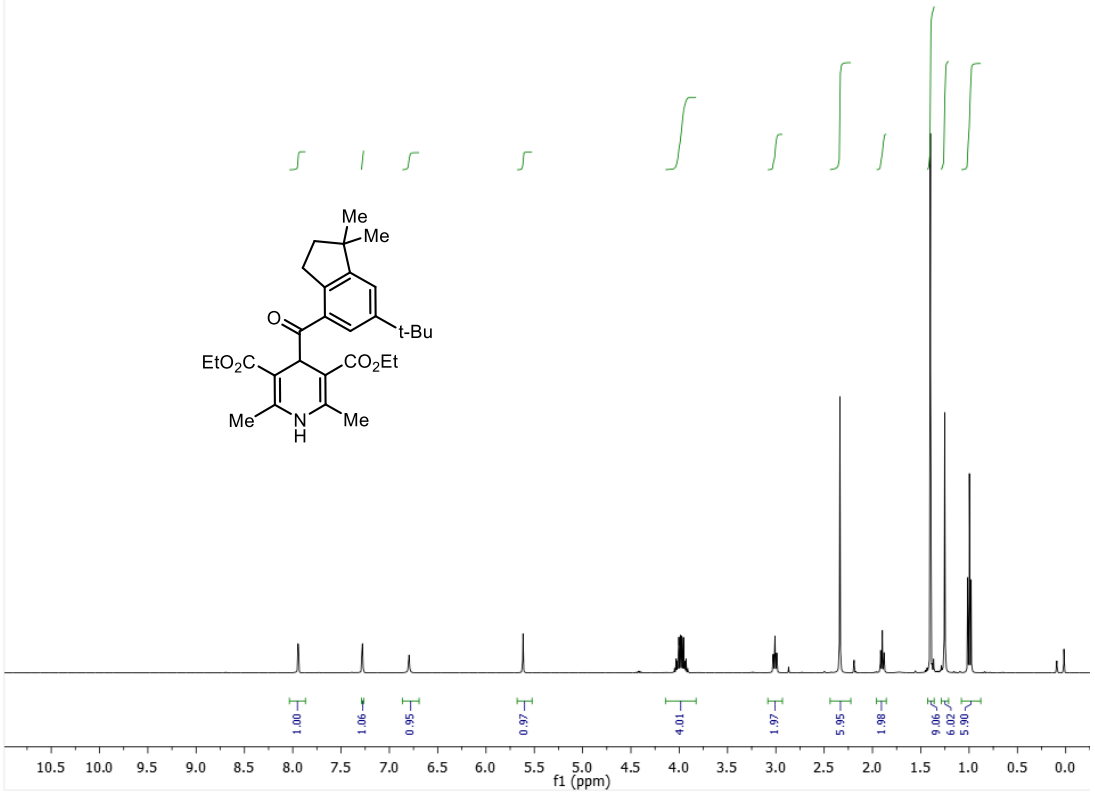


^{13}C NMR (101 MHz, $CDCl_3$)

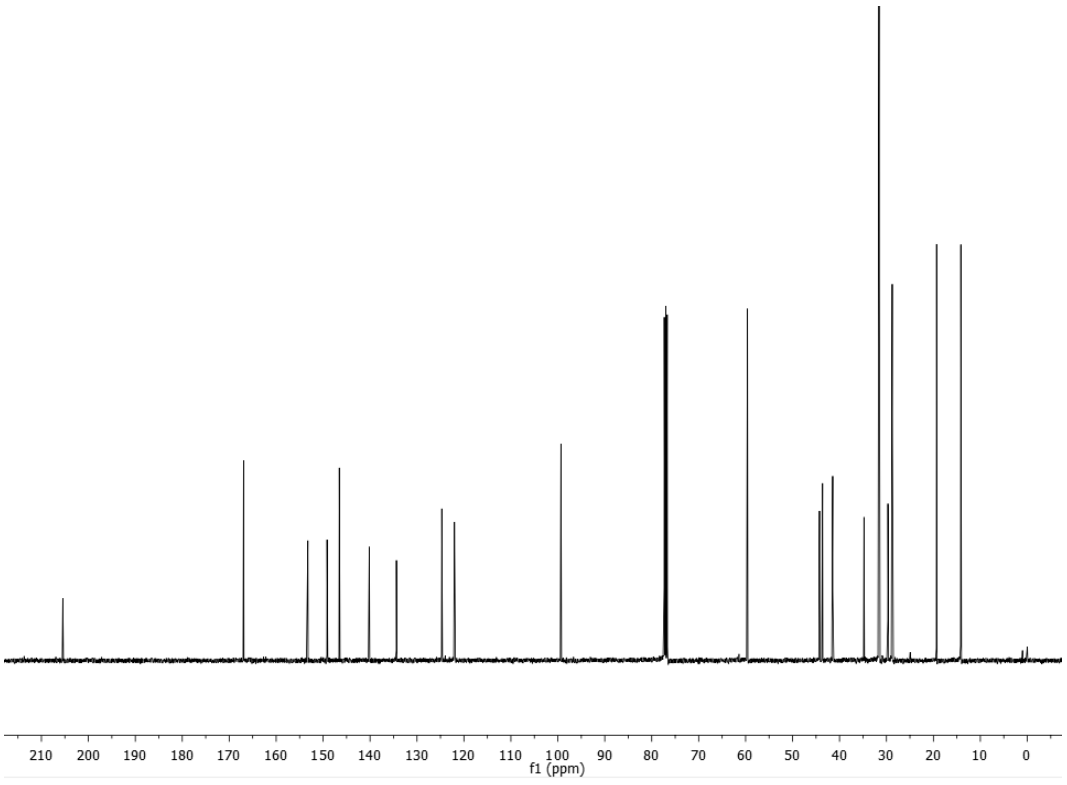


Diethyl 4-(6-(tert-butyl)-1,1-dimethyl-2,3-dihydro-1H-indene-4-carbonyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1x)

^{1}H NMR (400 MHz, $CDCl_3$)

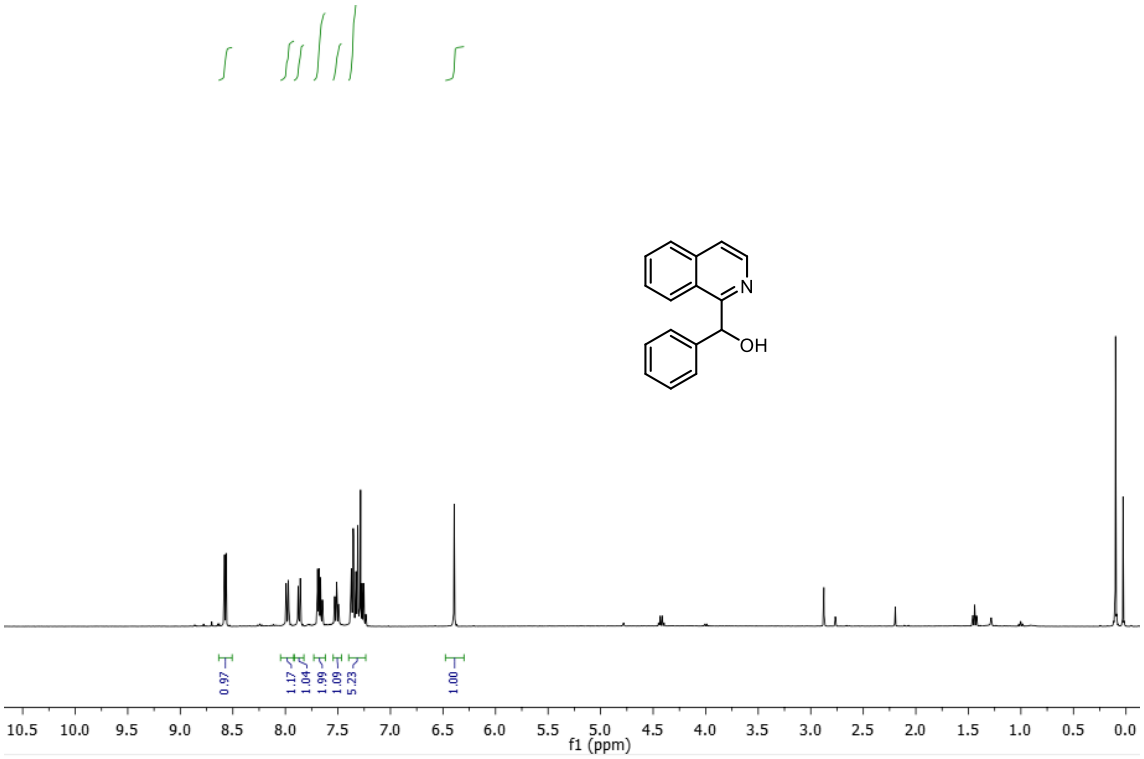


^{13}C NMR (101 MHz, $CDCl_3$)

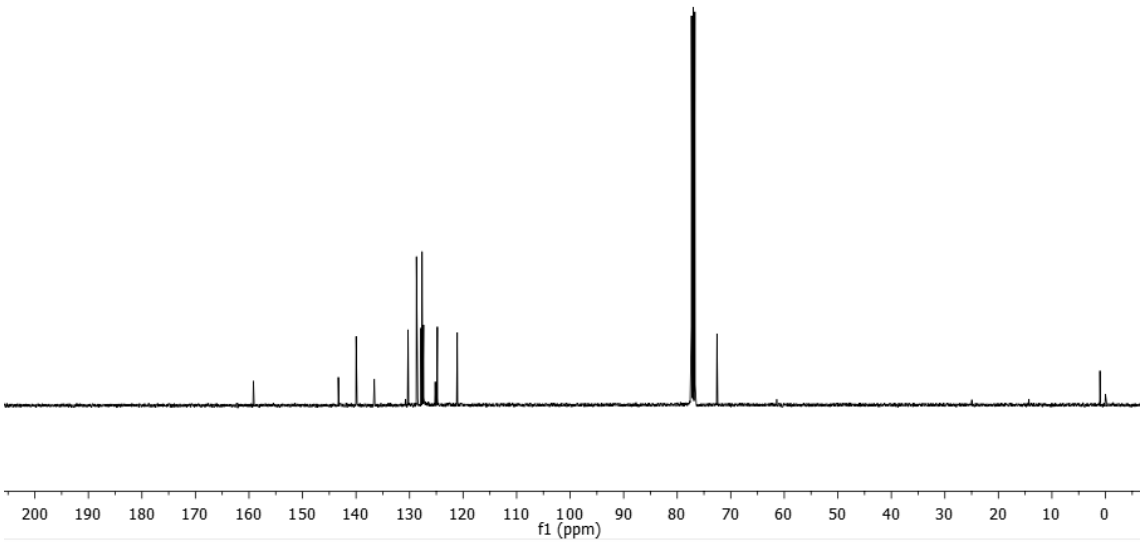


Isoquinolin-1-yl(phenyl)methanol (3a)

^{1}H NMR (400 MHz, $CDCl_3$)

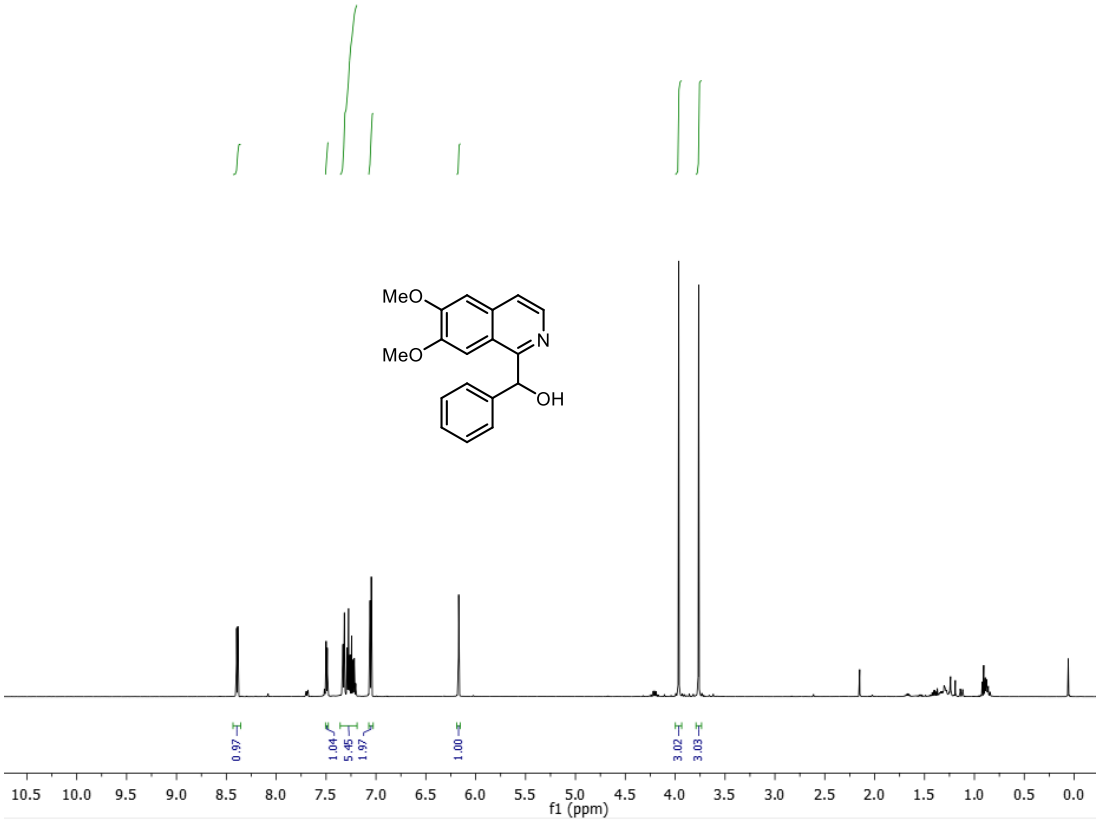


^{13}C NMR (101 MHz, $CDCl_3$)

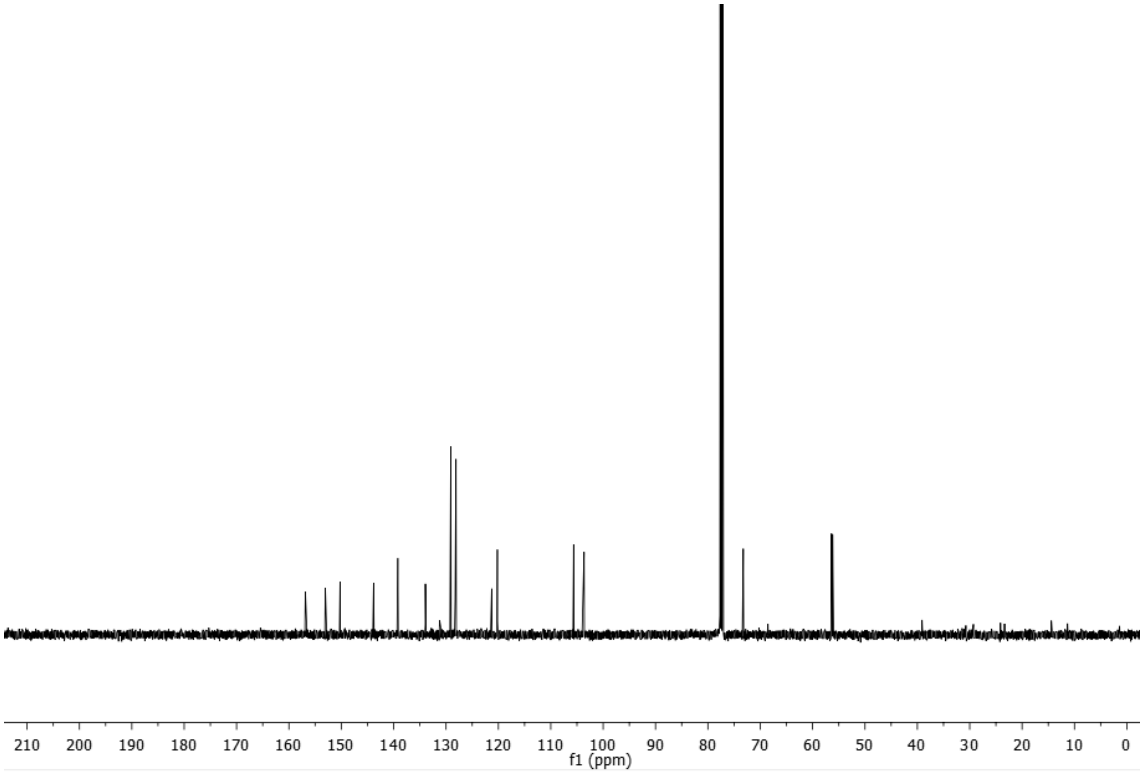


(6,7-Dimethoxyisoquinolin-1-yl)(phenyl)methanol (3b)

^{1}H NMR (500 MHz, $CDCl_3$)

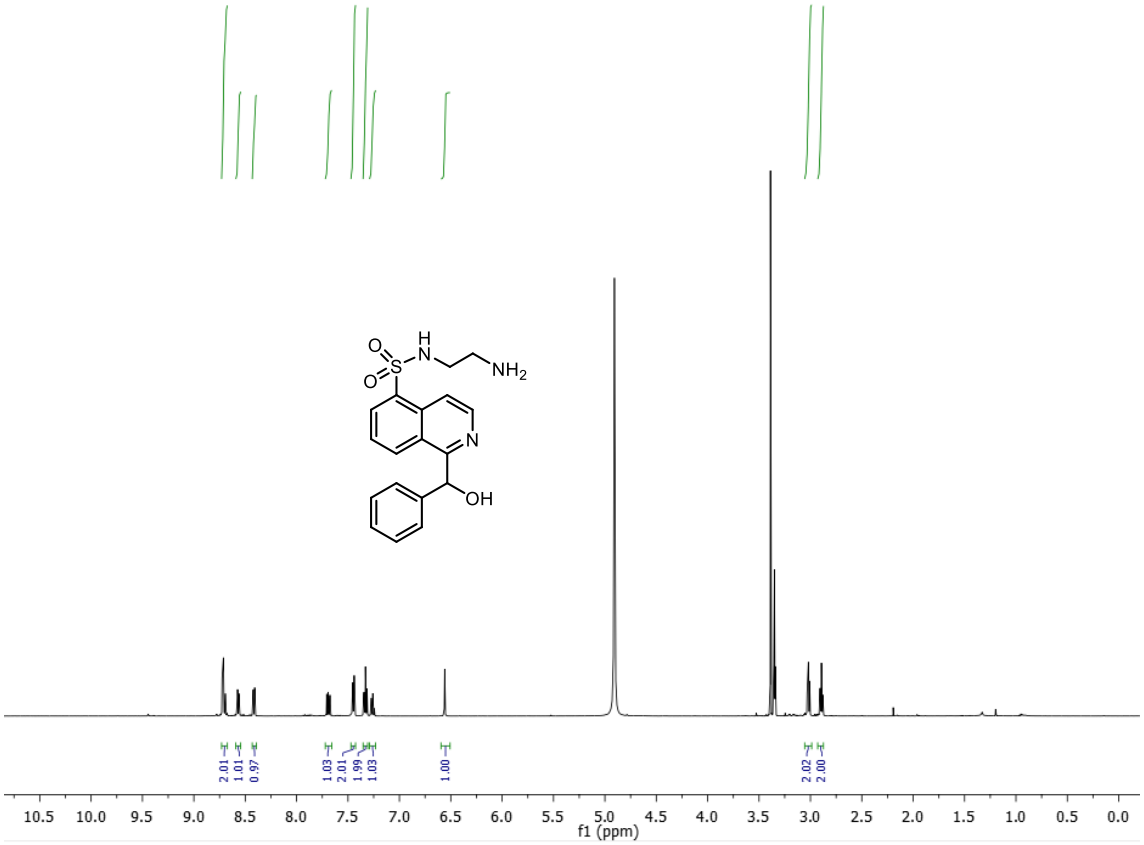


^{13}C NMR (101 MHz, $CDCl_3$)

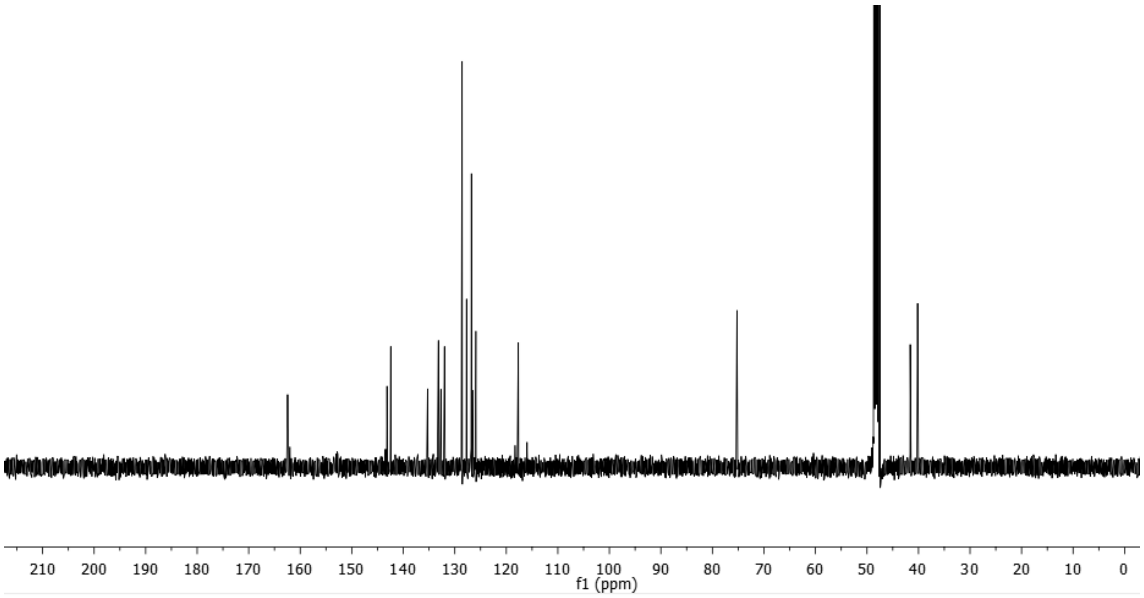


N-(2-Aminoethyl)-1-(hydroxy(phenyl)methyl)isoquinoline-5-sulfonamide (3c)

^{1}H NMR (500 MHz, CD_3OD)

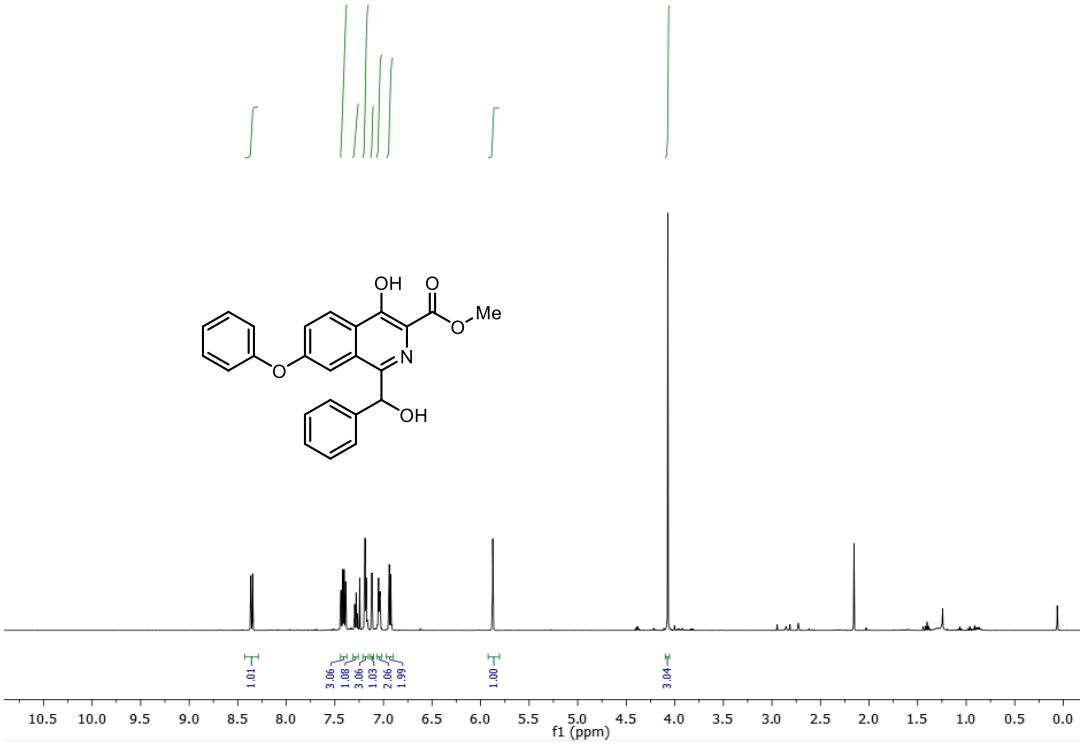


^{13}C NMR (126 MHz, CD_3OD)

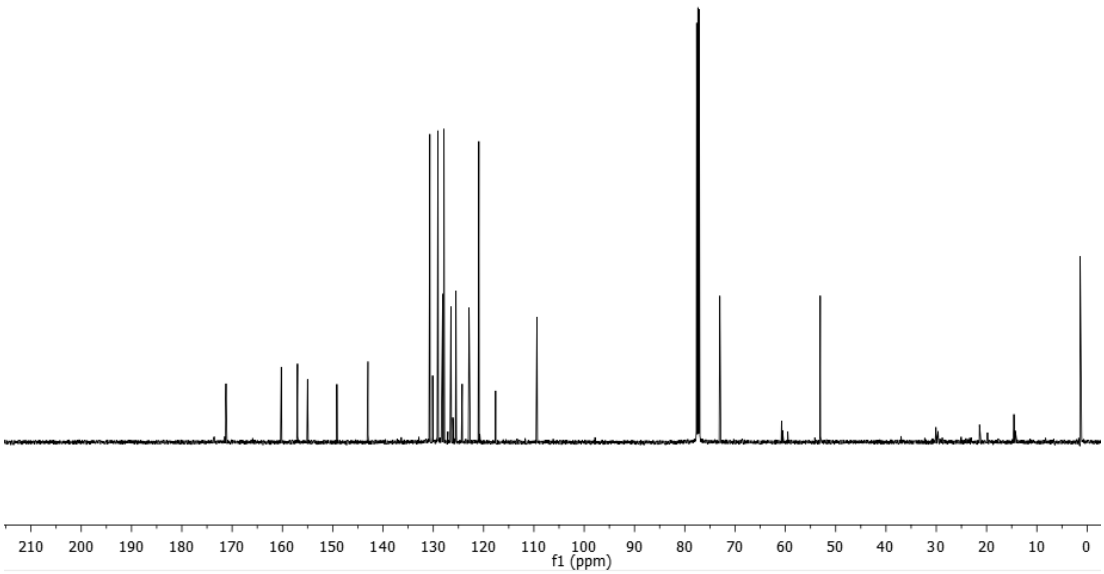


Methyl 4-hydroxy-1-(hydroxy(phenyl)methyl)-7-phenoxyisoquinoline-3-carboxylate (3d)

^{1}H NMR (500 MHz, $CDCl_3$)

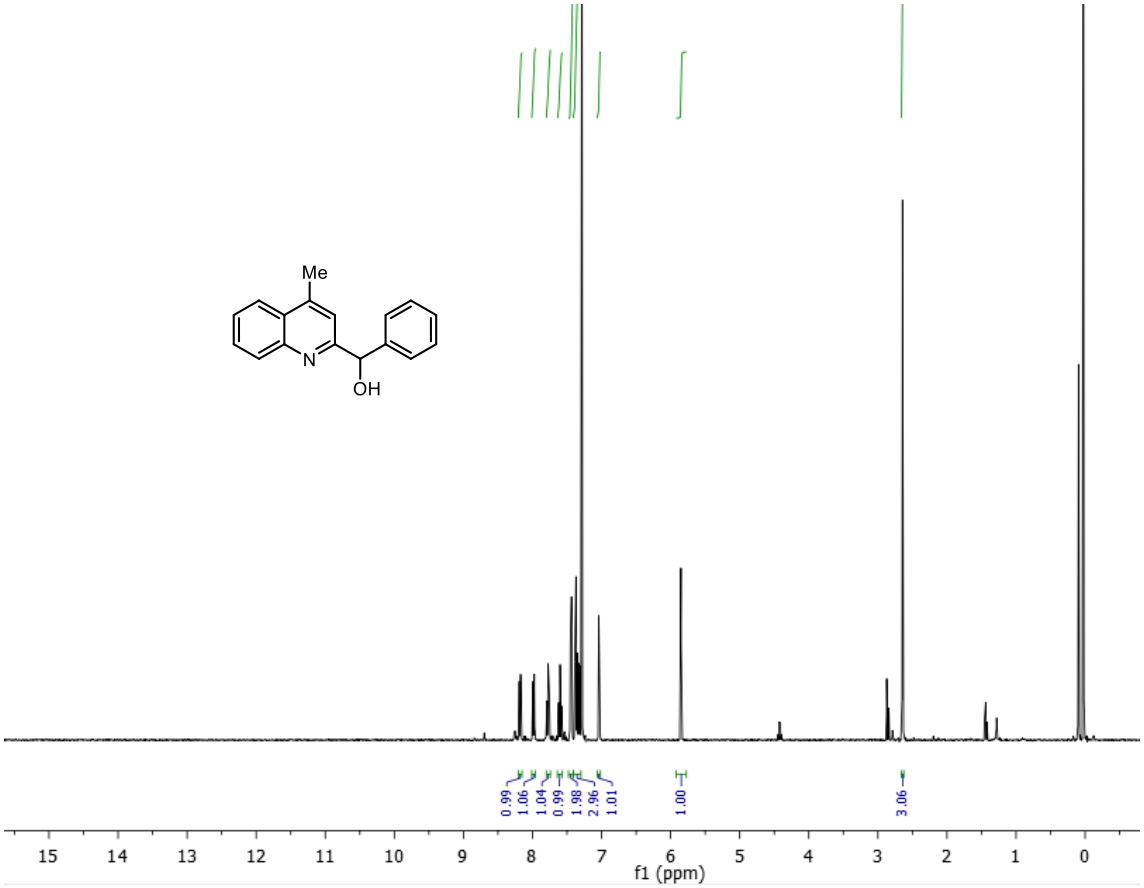


^{13}C NMR (126 MHz, $CDCl_3$)

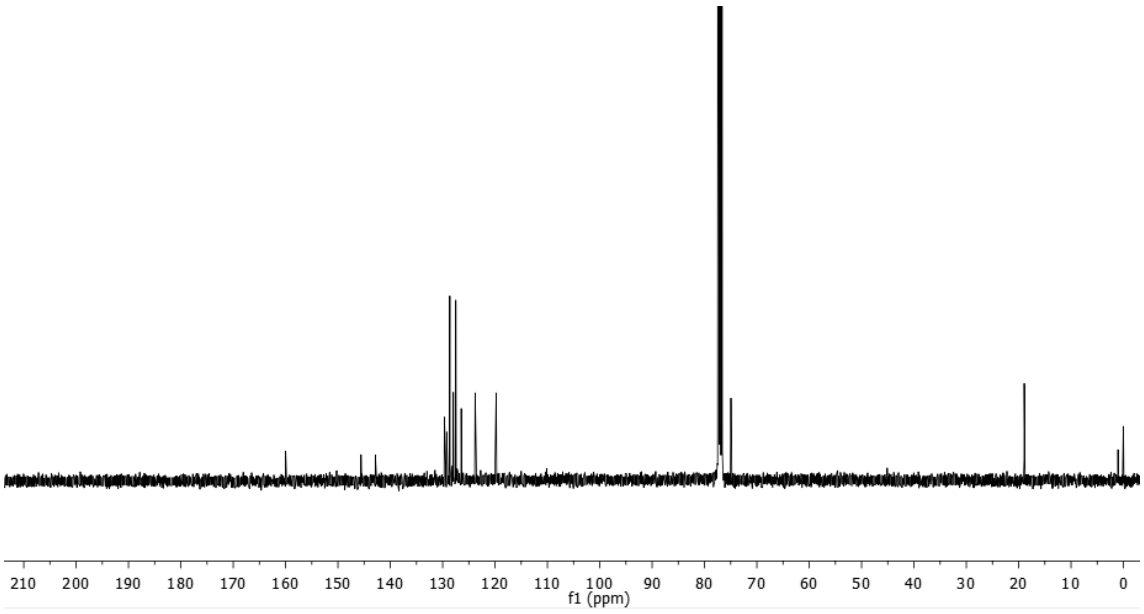


(4-Methylquinolin-2-yl)(phenyl)methanol (3e)

^{1}H NMR (400 MHz, $CDCl_3$)

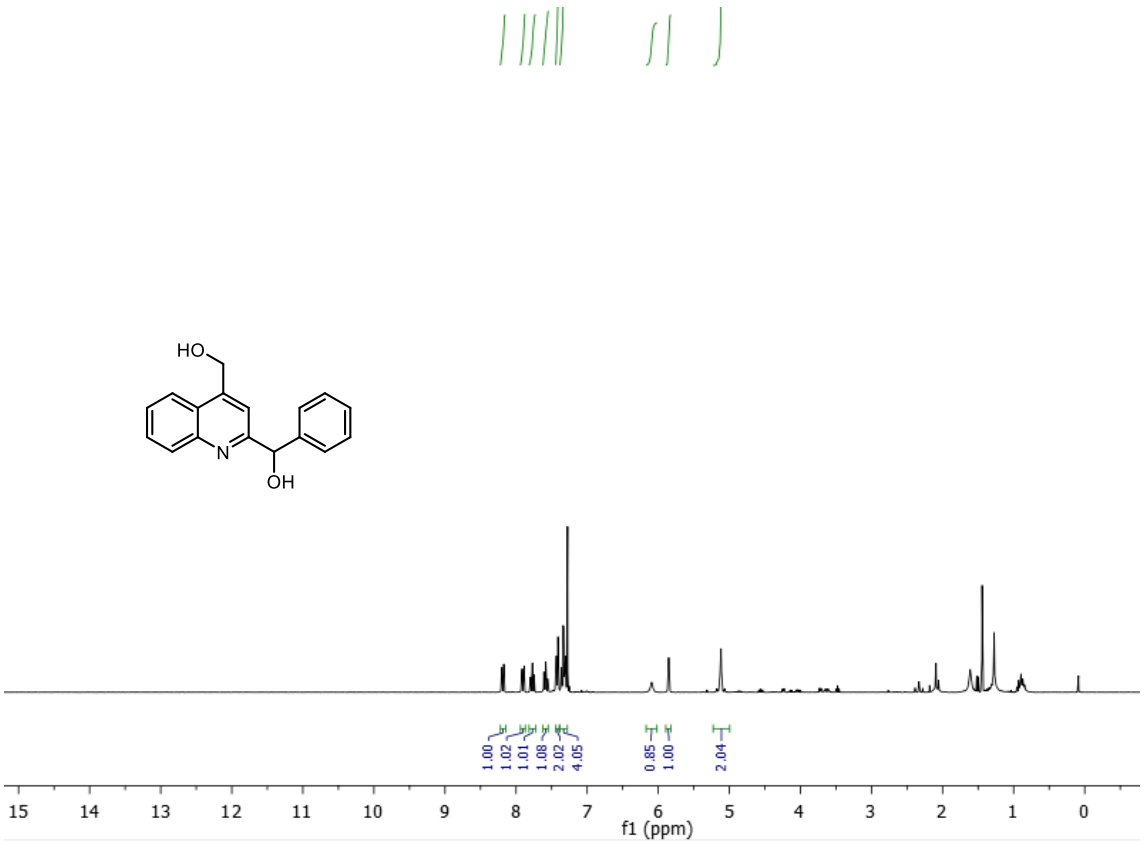


^{13}C NMR (101 MHz, $CDCl_3$)

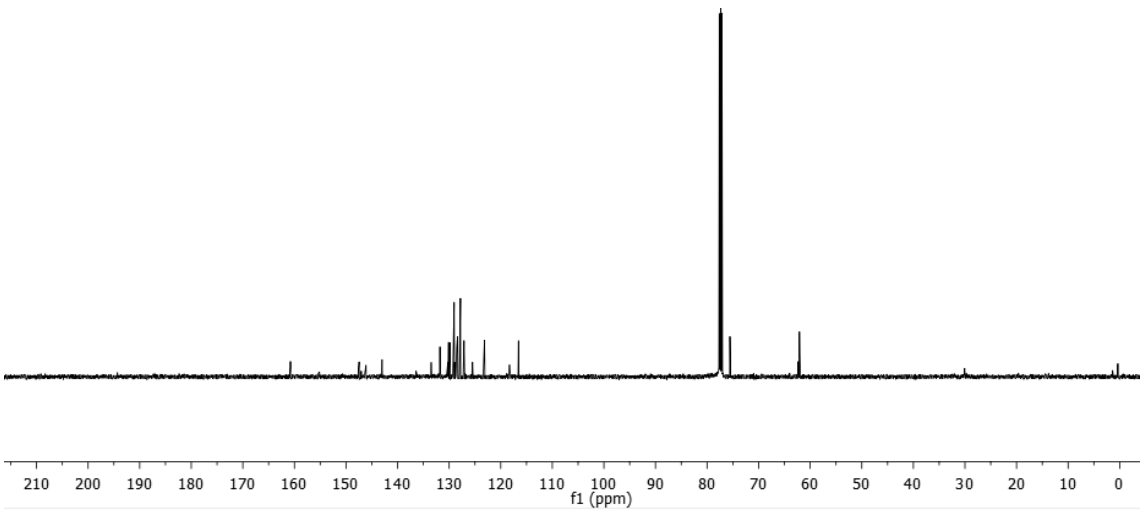


(4-(Hydroxymethyl)quinolin-2-yl)(phenyl)methanol (3f)

^{1}H NMR (500 MHz, $CDCl_3$)

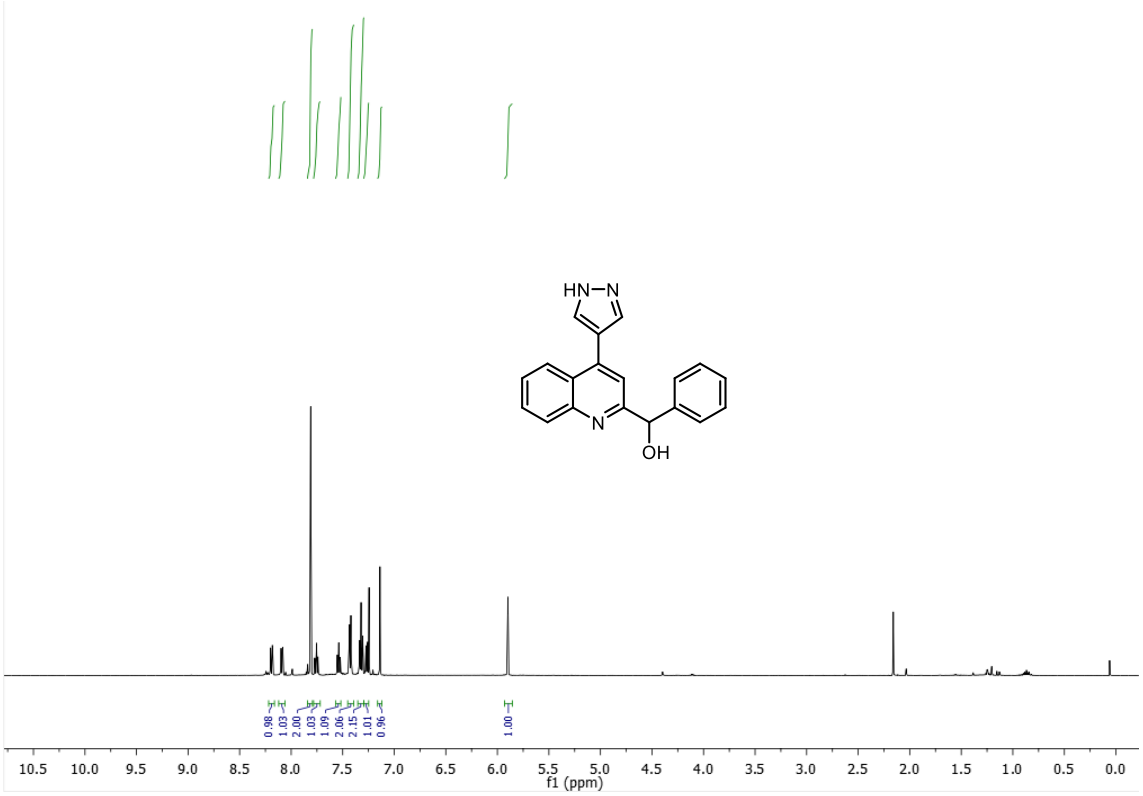


^{13}C NMR (101 MHz, $CDCl_3$)

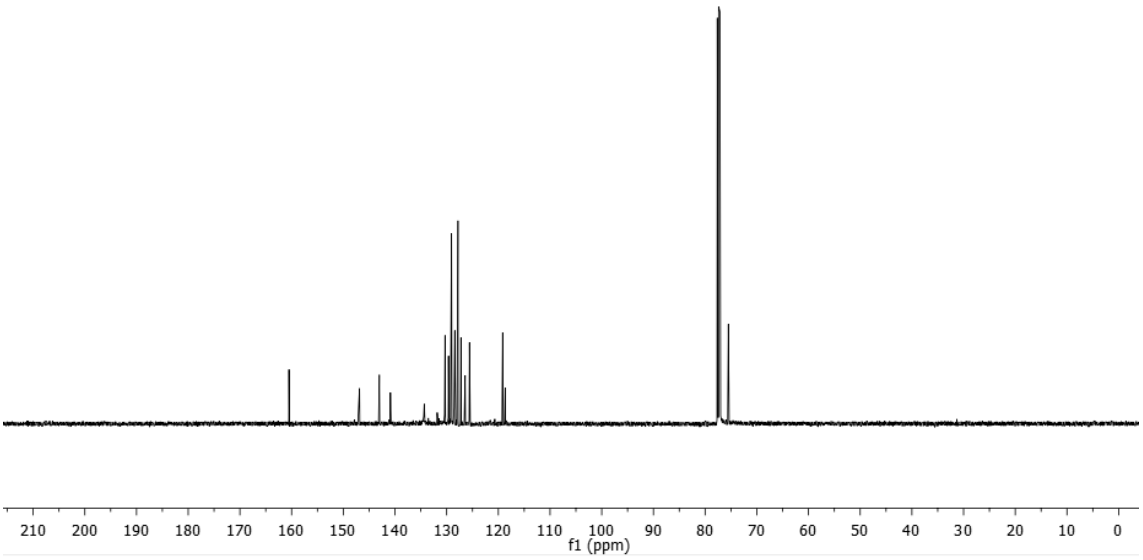


(4-(1H-Pyrazol-4-yl)quinolin-2-yl)(phenyl)methanol (3g)

^{1}H NMR (500 MHz, $CDCl_3$)

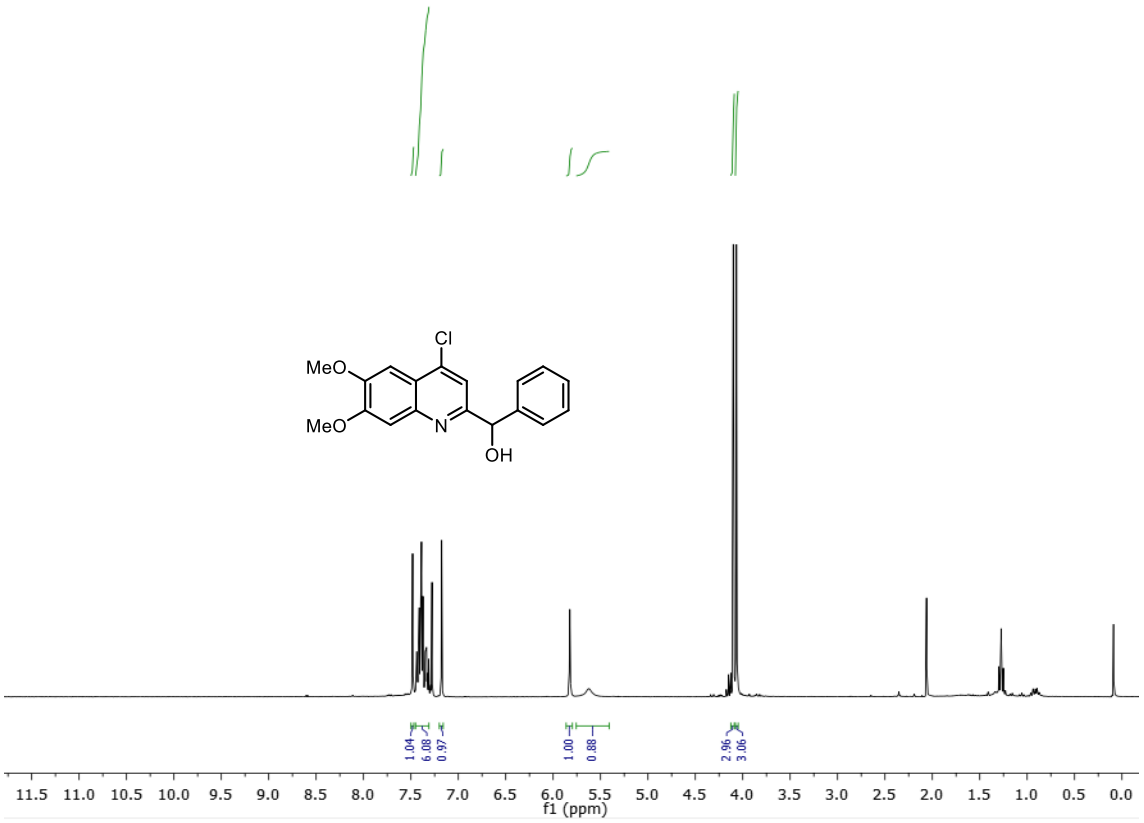


^{13}C NMR (126 MHz, $CDCl_3$)

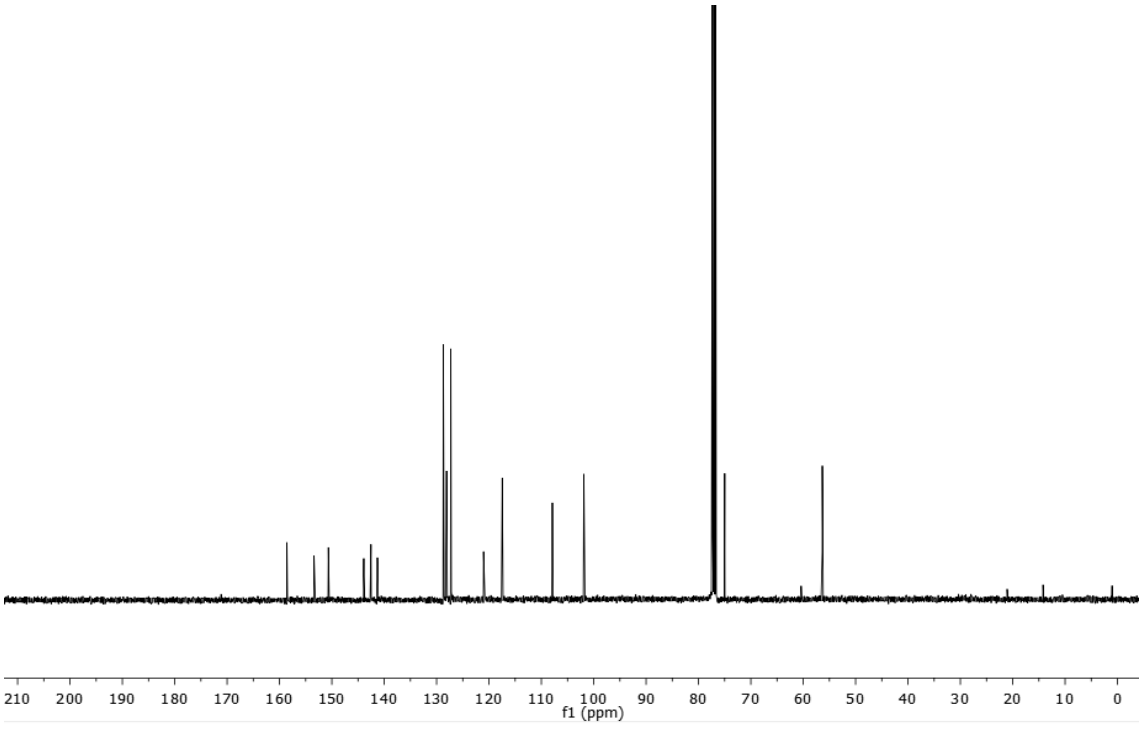


(4-Chloro-6,7-dimethoxyquinolin-2-yl)(phenyl)methanol (3h)

^{1}H NMR (300 MHz, $CDCl_3$)

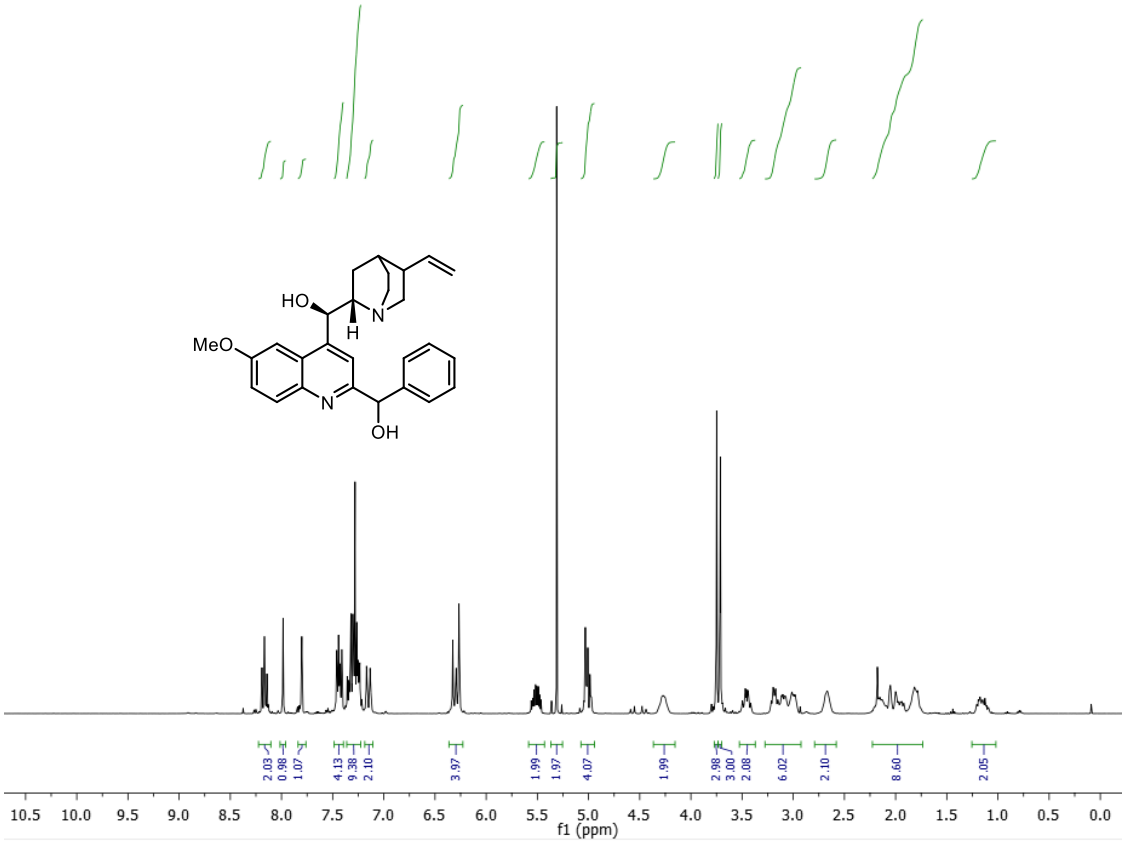


^{13}C NMR (126 MHz, $CDCl_3$)

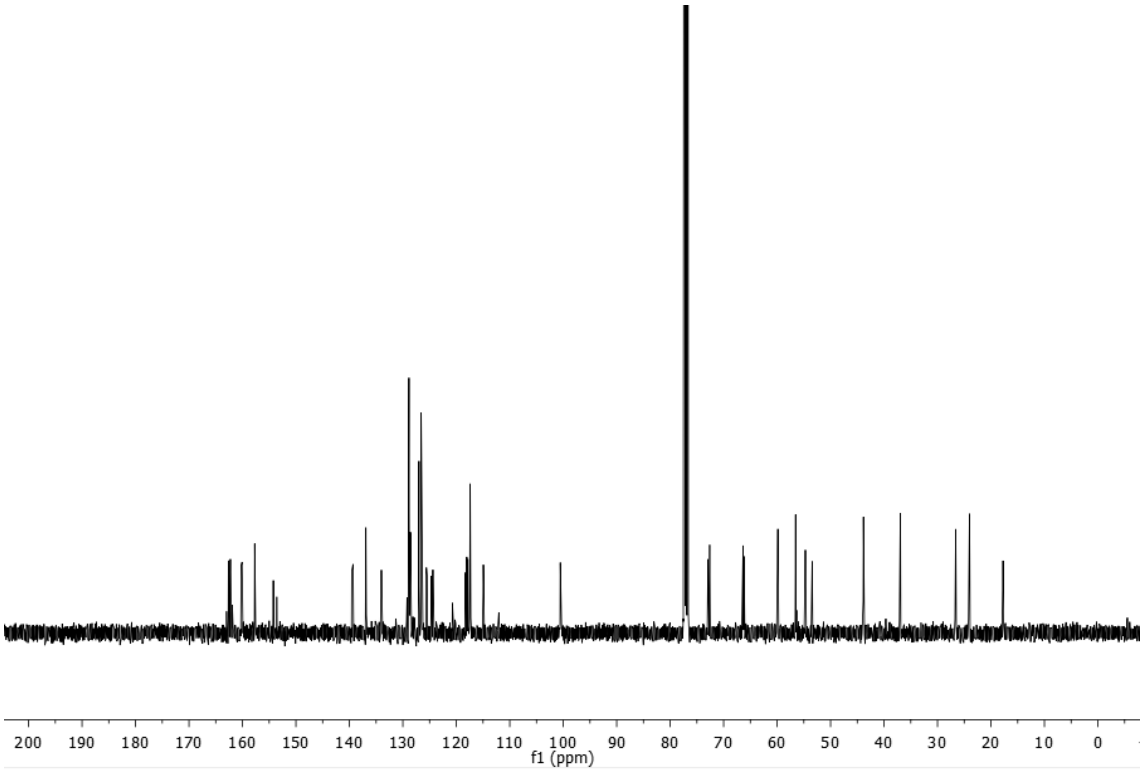


(4-((1R)-Hydroxy((2S)-5-vinylquinuclidin-2-yl)methyl)-6-methoxyquinolin-2-yl)(phenyl)methanol (3i)

^{1}H NMR (500 MHz, $CDCl_3$)

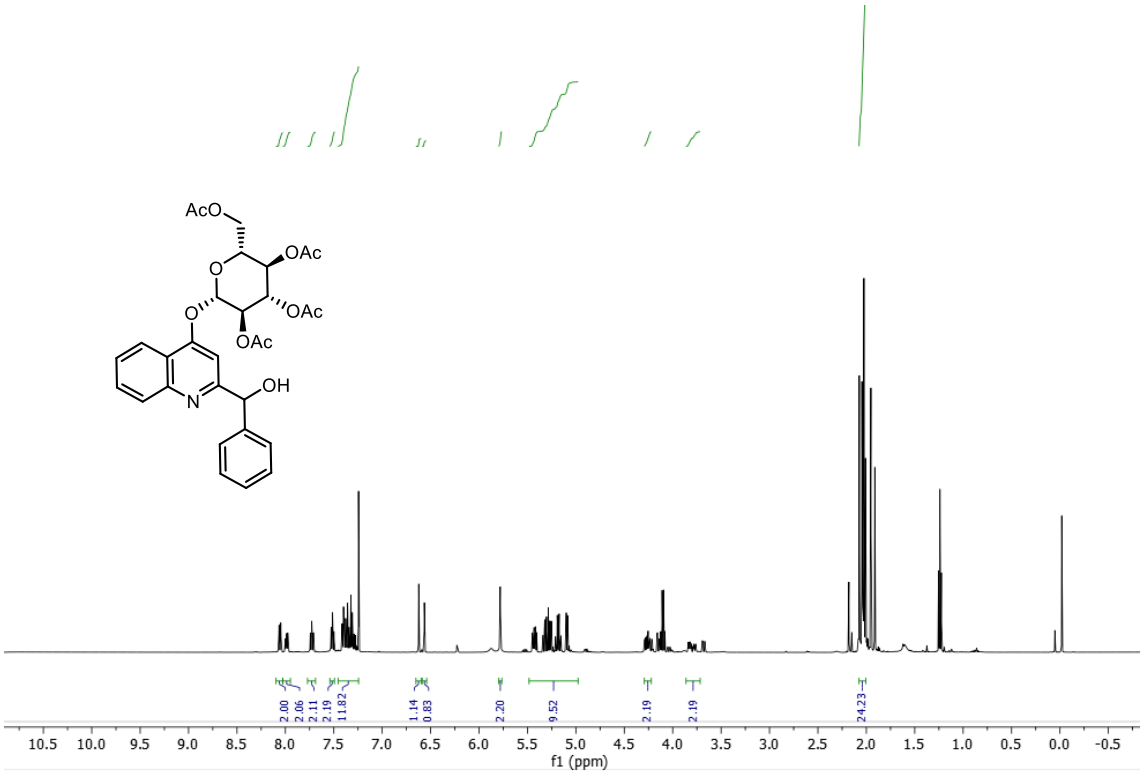


^{13}C NMR (126 MHz, $CDCl_3$)

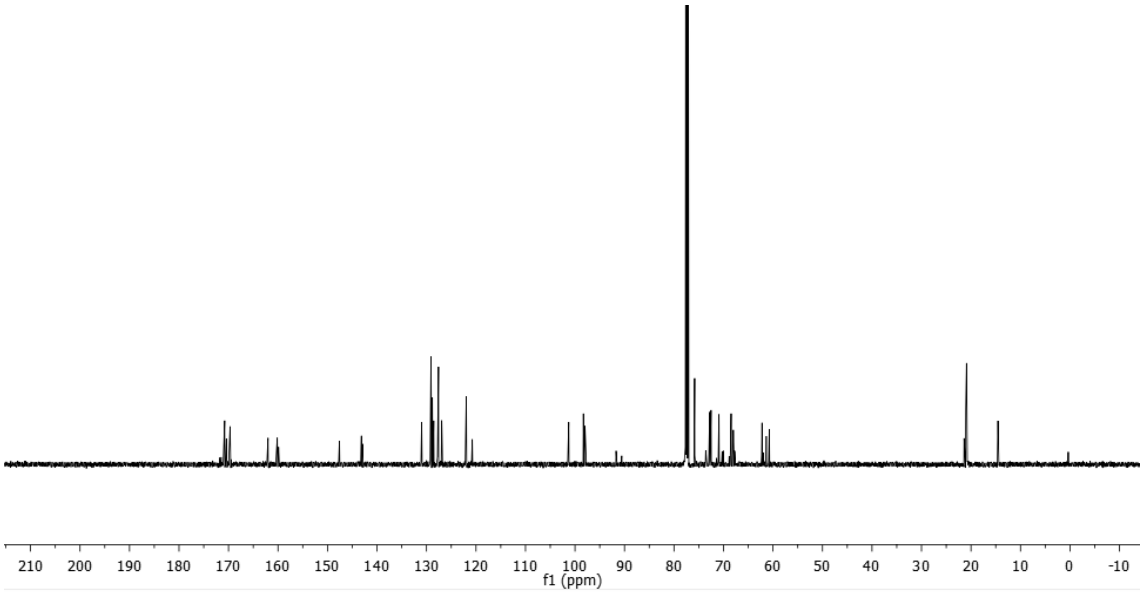


(2R,3R,4S,5R,6S)-2-(Acetoxymethyl)-6-((2-(hydroxy(phenyl)methyl)quinolin-4-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3j)

^{1}H NMR (500 MHz, $CDCl_3$)

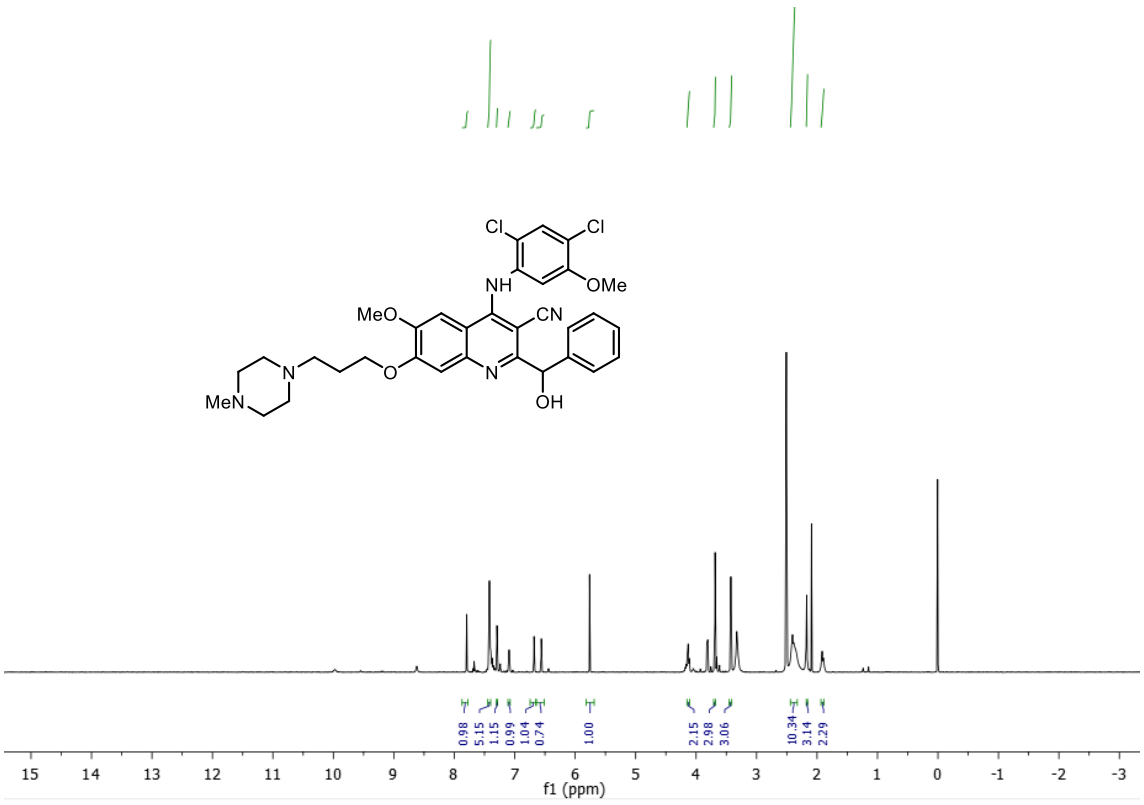


^{13}C NMR (126 MHz, $CDCl_3$)

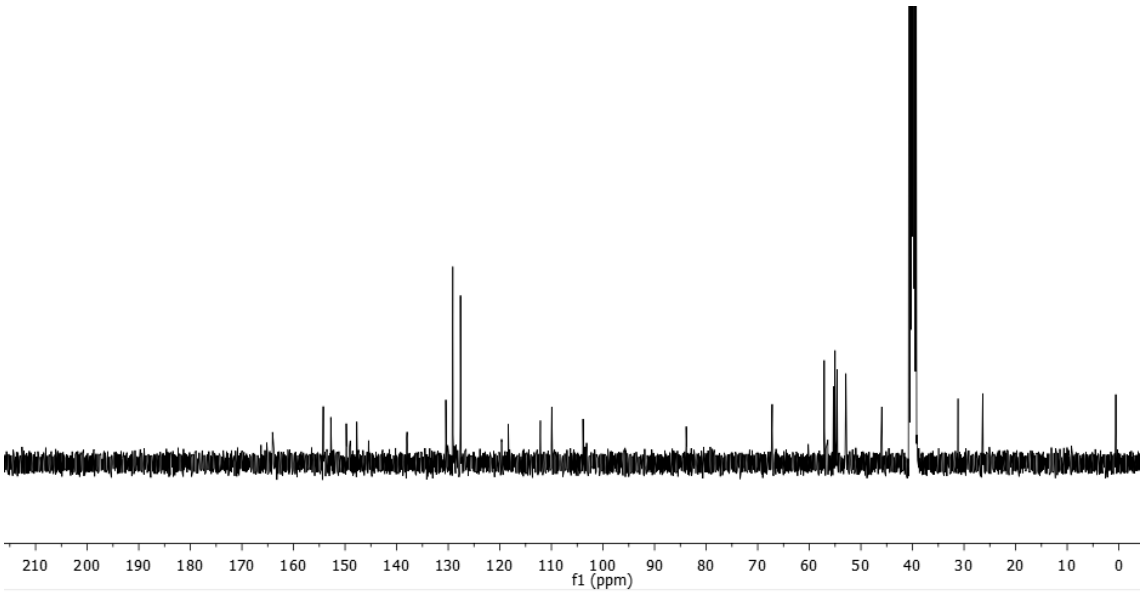


4-((2,4-Dichloro-5-methoxyphenyl)amino)-2-(hydroxy(phenyl)methyl)-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinoline-3-carbonitrile (3k)

^{1}H NMR (400 MHz, DMSO-d_6)

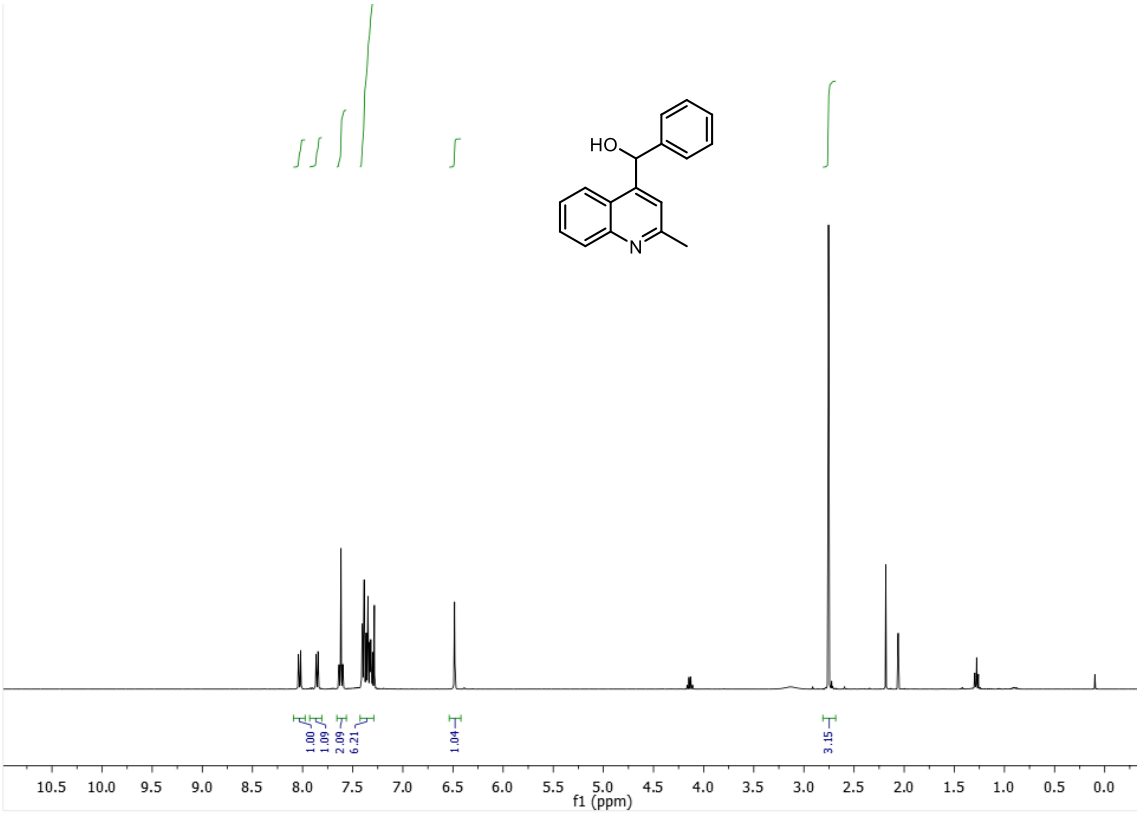


^{13}C NMR (101 MHz, DMSO-d_6)

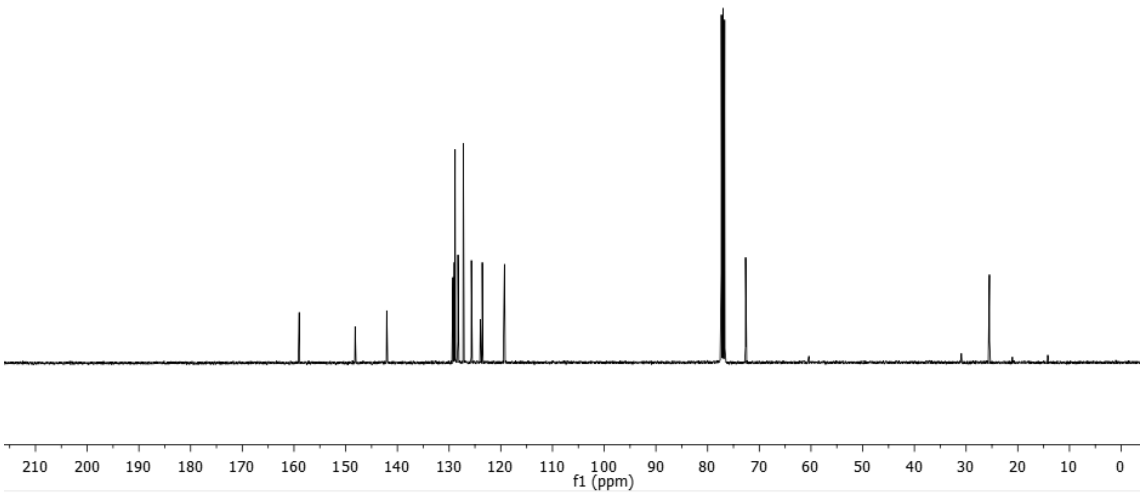


(2-Methylquinolin-4-yl)(phenyl)methanol (3l)

^{1}H NMR (400 MHz, $CDCl_3$)

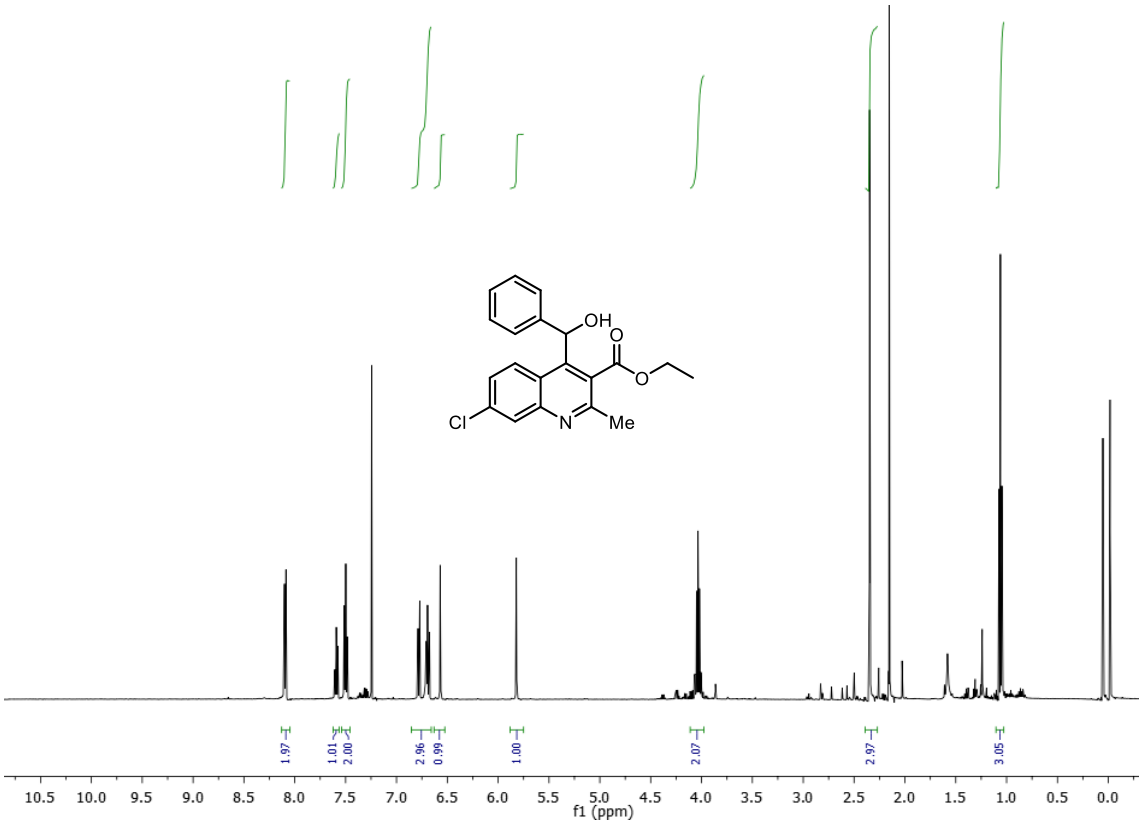


^{13}C NMR (101 MHz, $CDCl_3$)

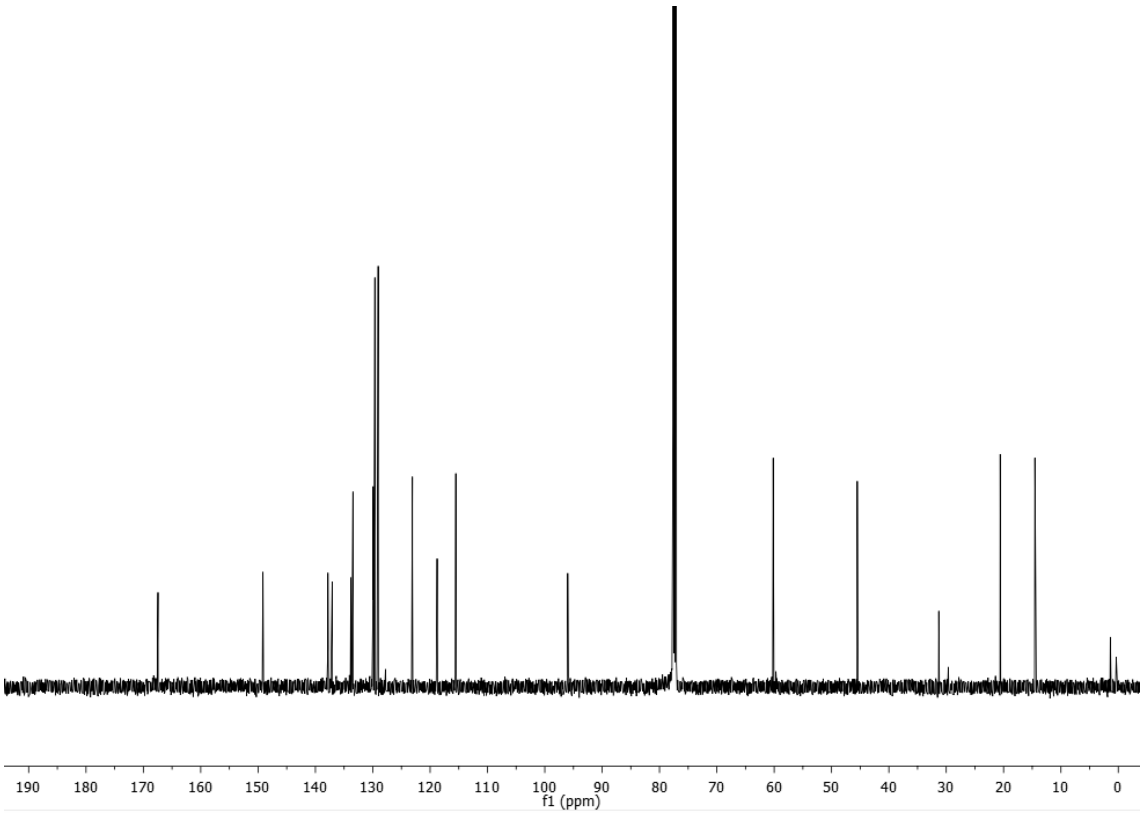


Ethyl 7-chloro-4-(hydroxy(phenyl)methyl)-2-methylquinoline-3-carboxylate (3m)

^{1}H NMR (500 MHz, $CDCl_3$)

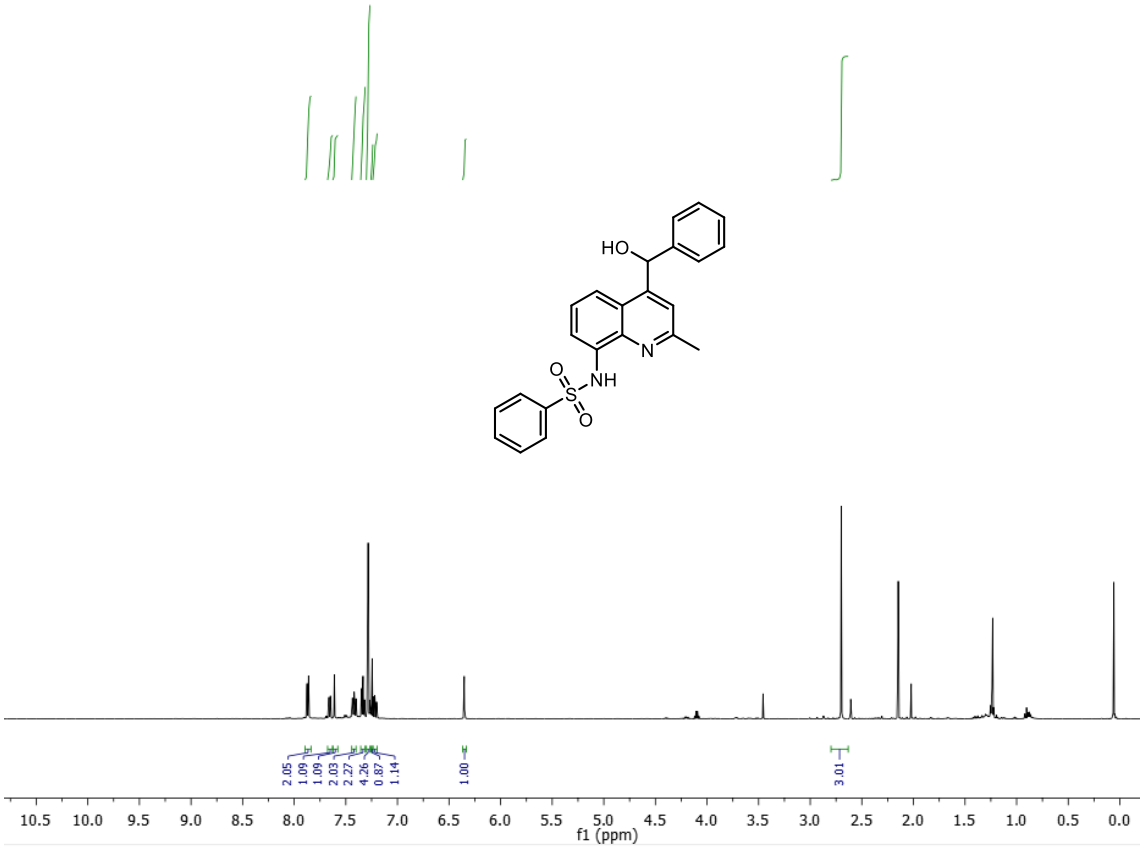


^{13}C NMR (126 MHz, $CDCl_3$)

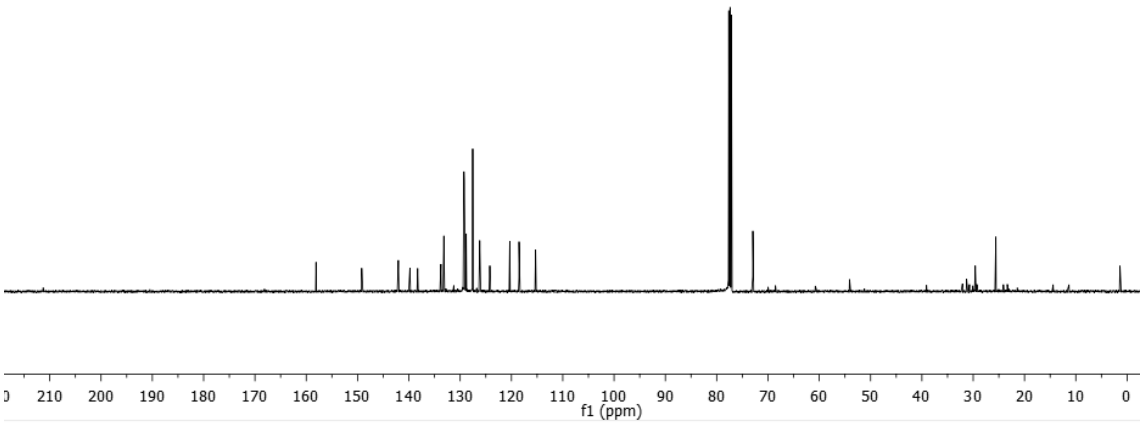


N-(4-(Hydroxy(phenyl)methyl)-2-methylquinolin-8-yl)benzenesulfonamide (3n)

^{1}H NMR (500 MHz, $CDCl_3$)

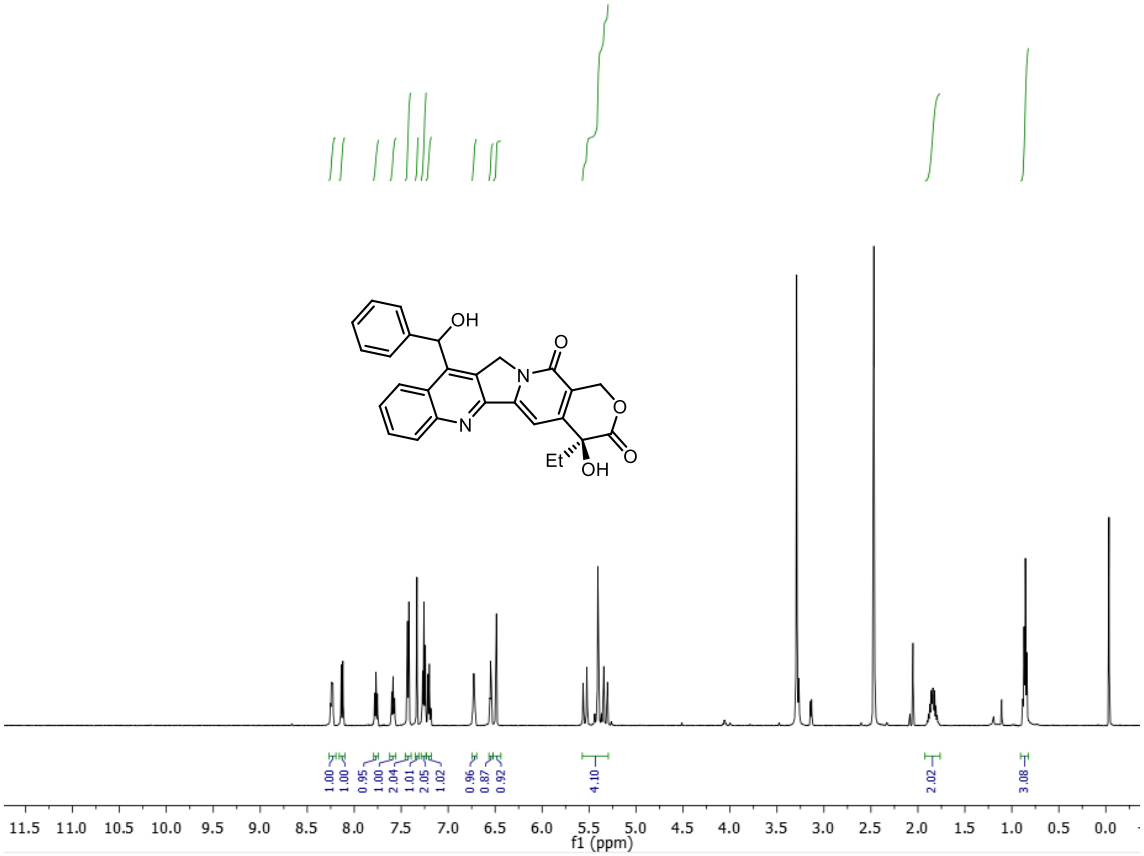


^{13}C NMR (126 MHz, $CDCl_3$)

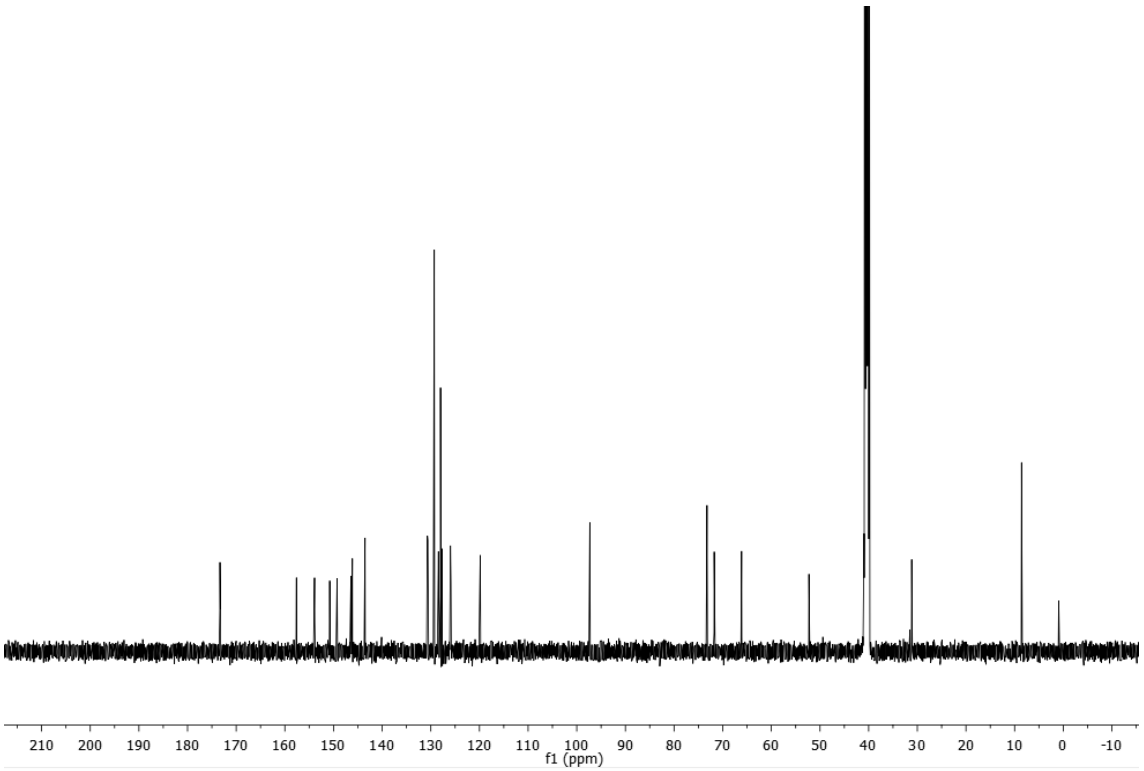


(*4S*)-4-Ethyl-4-hydroxy-11-(hydroxy(phenyl)methyl)-1,12-dihydro-14H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H)-dione (3o)

^{1}H NMR (400 MHz, DMSO-d_6)

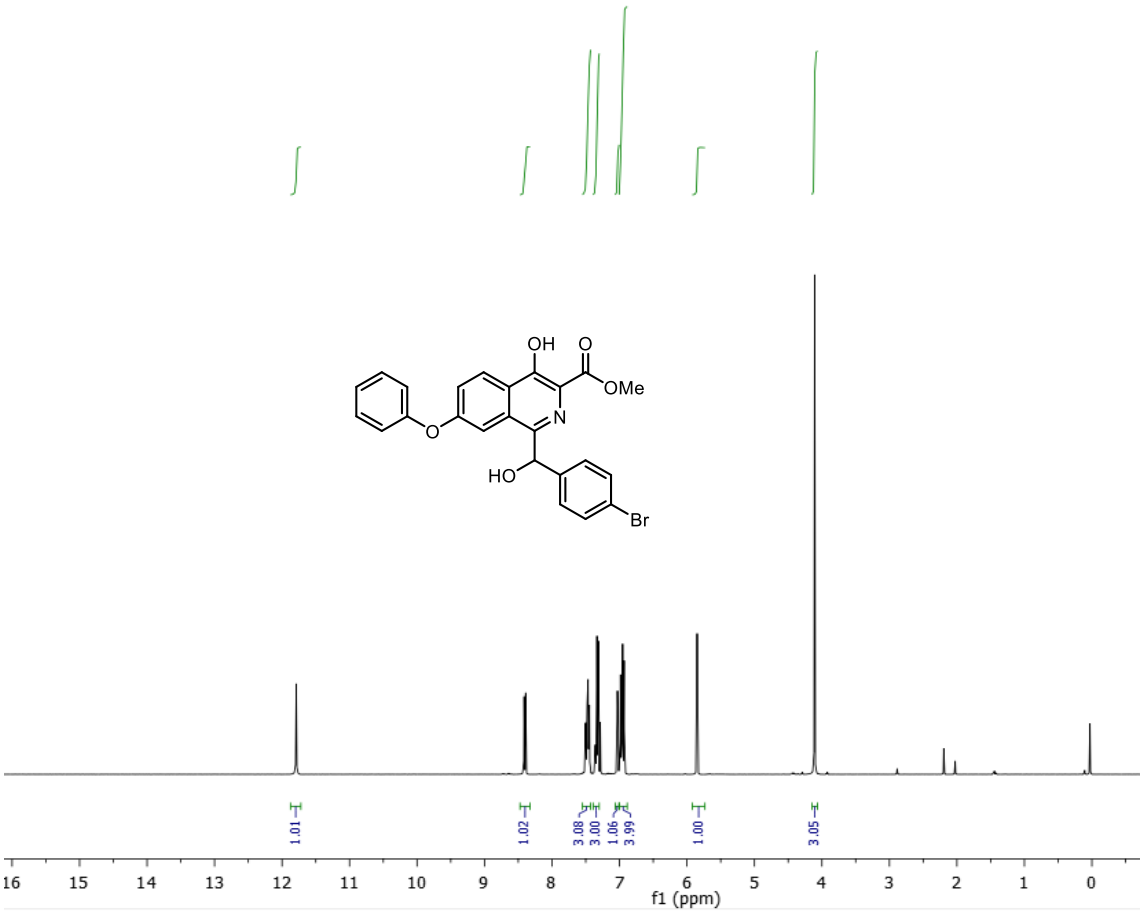


^{13}C NMR (126 MHz, DMSO-d_6)

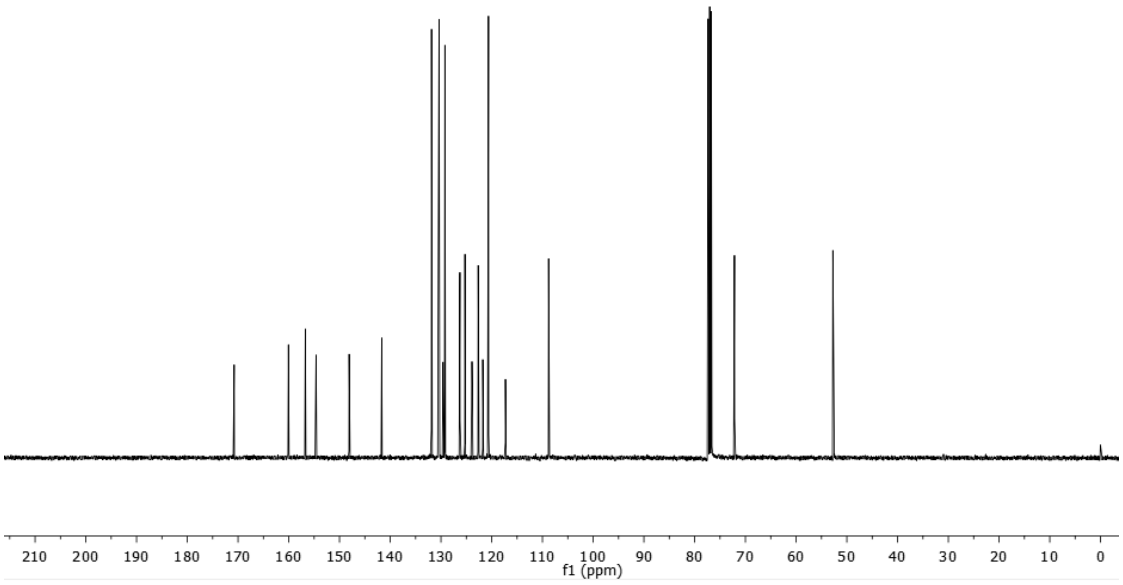


Methyl 1-((4-bromophenyl)(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3-carboxylate (3p)

^{1}H NMR (400 MHz, $CDCl_3$)

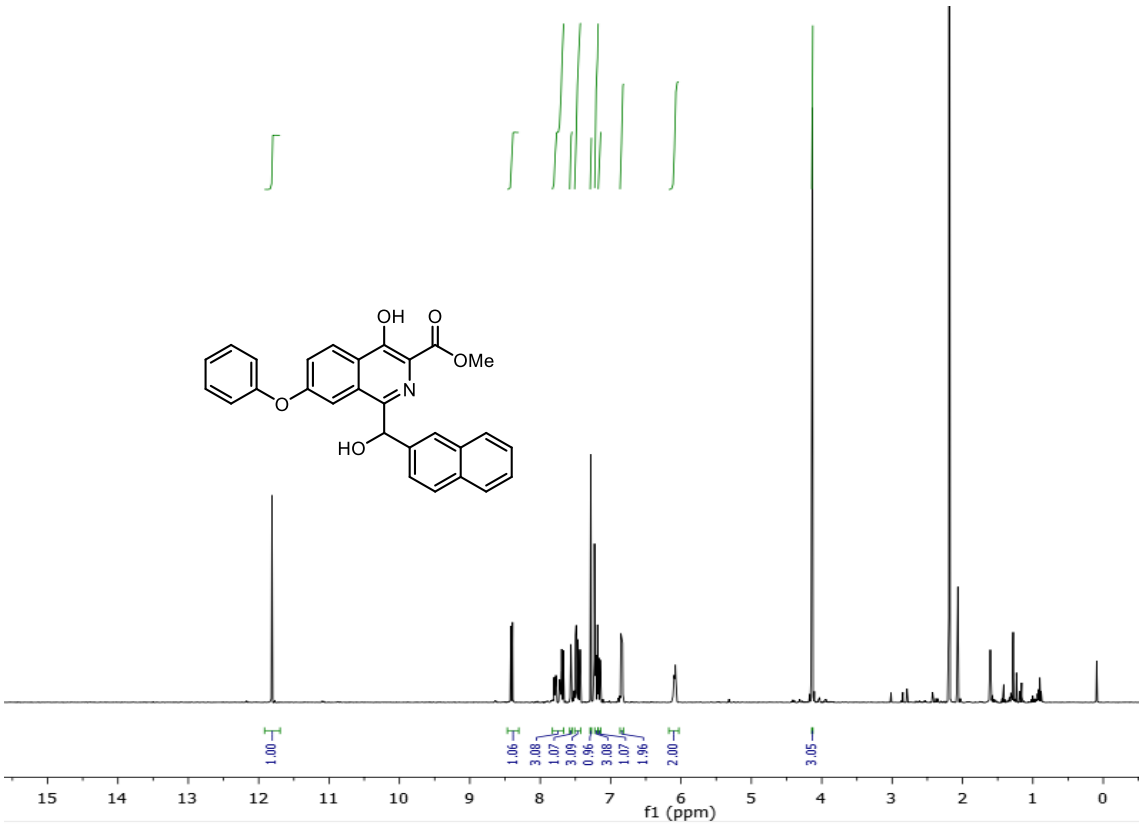


^{13}C NMR (101 MHz, $CDCl_3$)

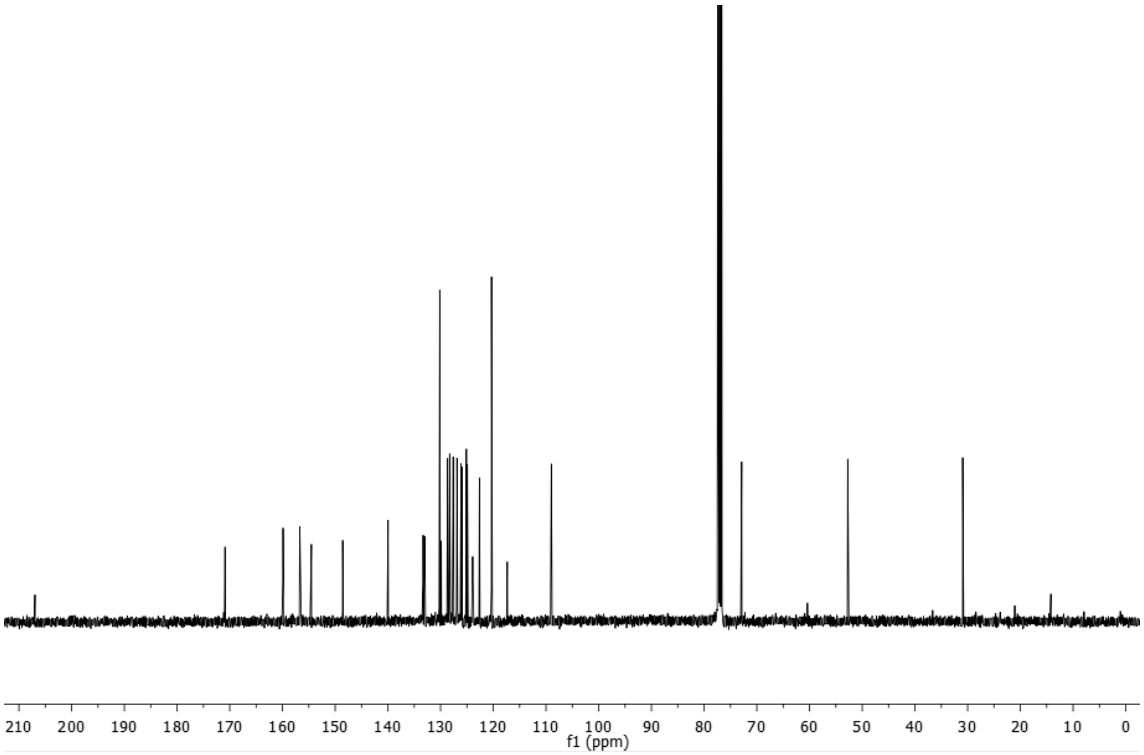


Methyl 4-hydroxy-1-(hydroxy(naphthalen-2-yl)methyl)-7-phenoxyisoquinoline-3-carboxylate (3q)

^{1}H NMR (400 MHz, $CDCl_3$)

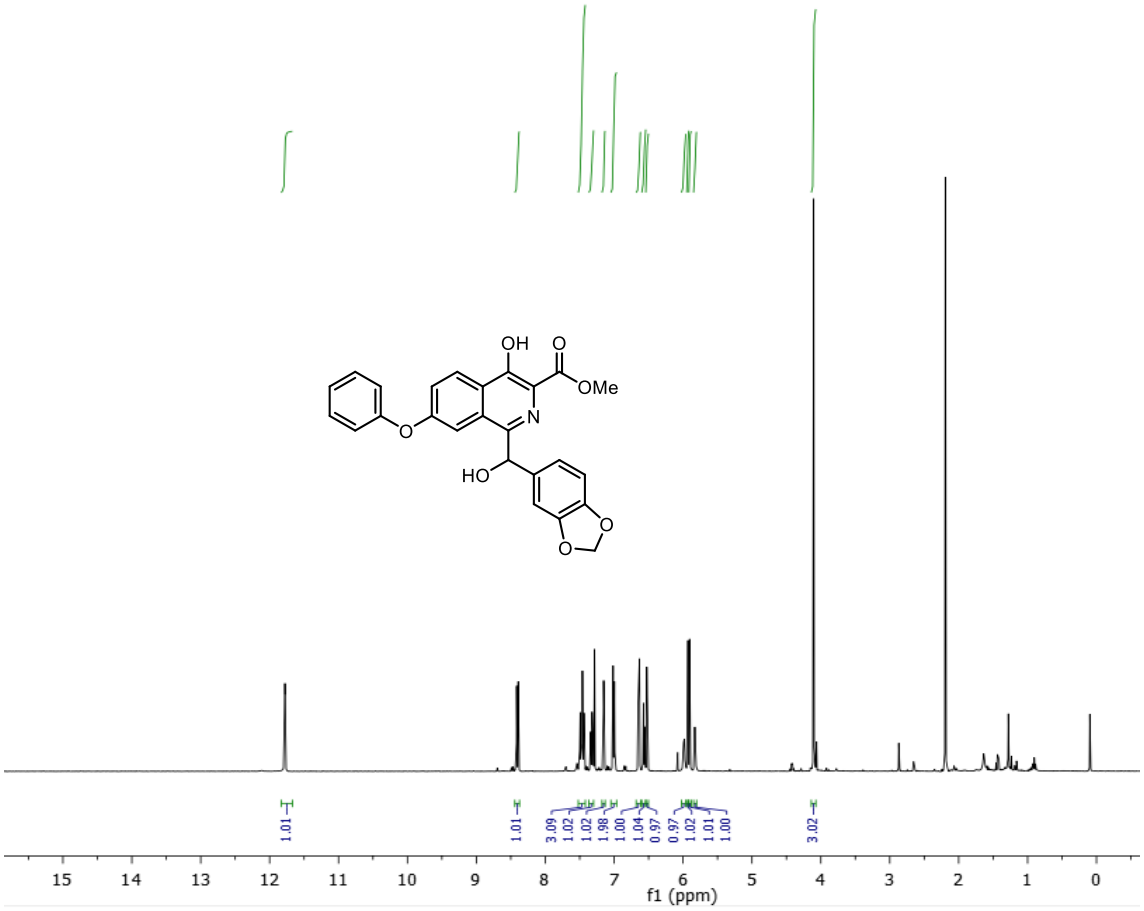


^{13}C NMR (101 MHz, $CDCl_3$)

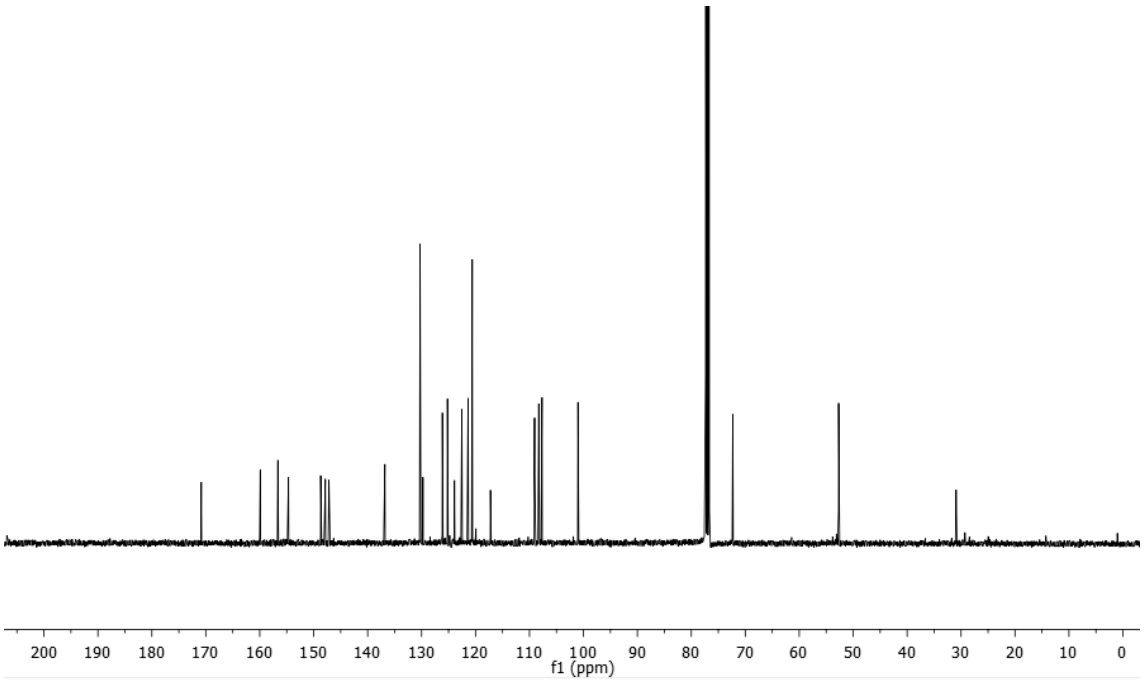


Methyl 1-(benzo[d][1,3]dioxol-5-yl(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3-carboxylate (3s)

^{1}H NMR (400 MHz, $CDCl_3$)

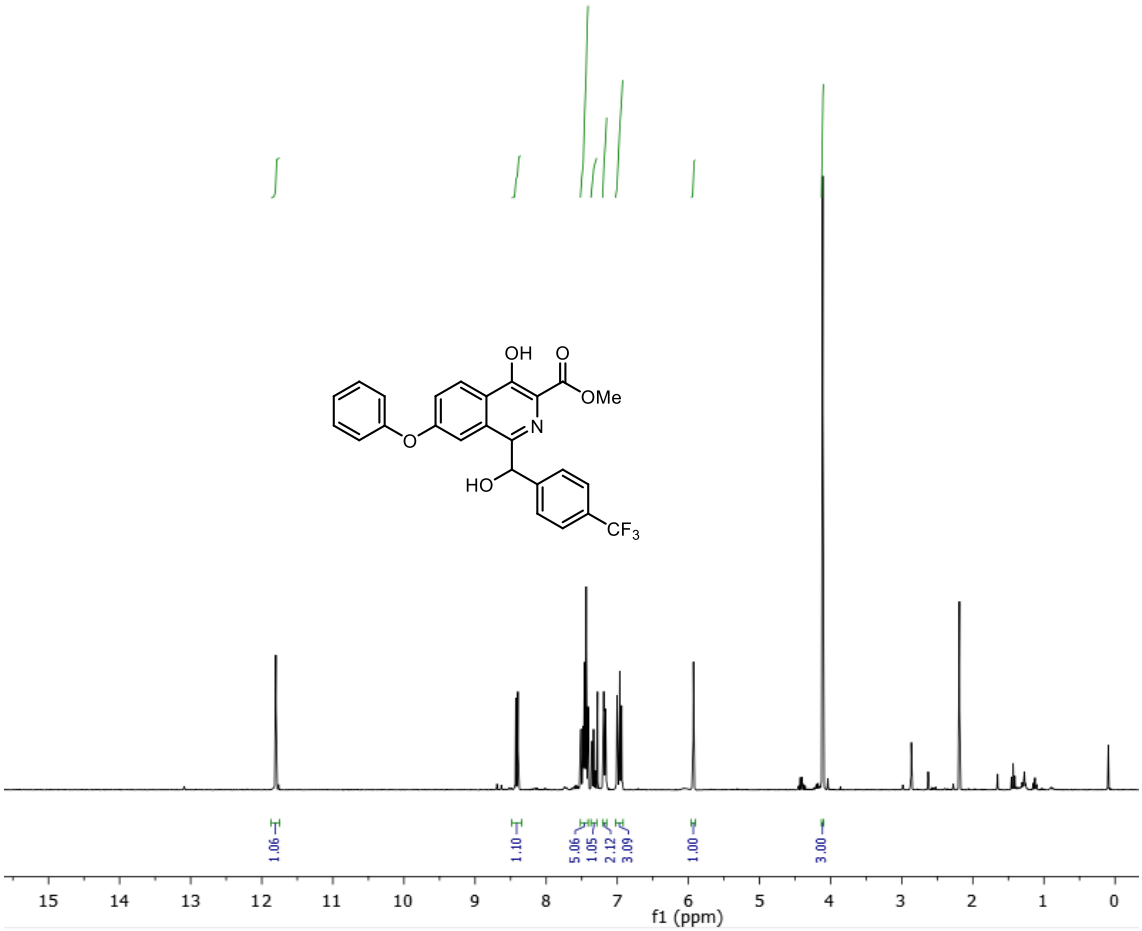


^{13}C NMR (101 MHz, $CDCl_3$)

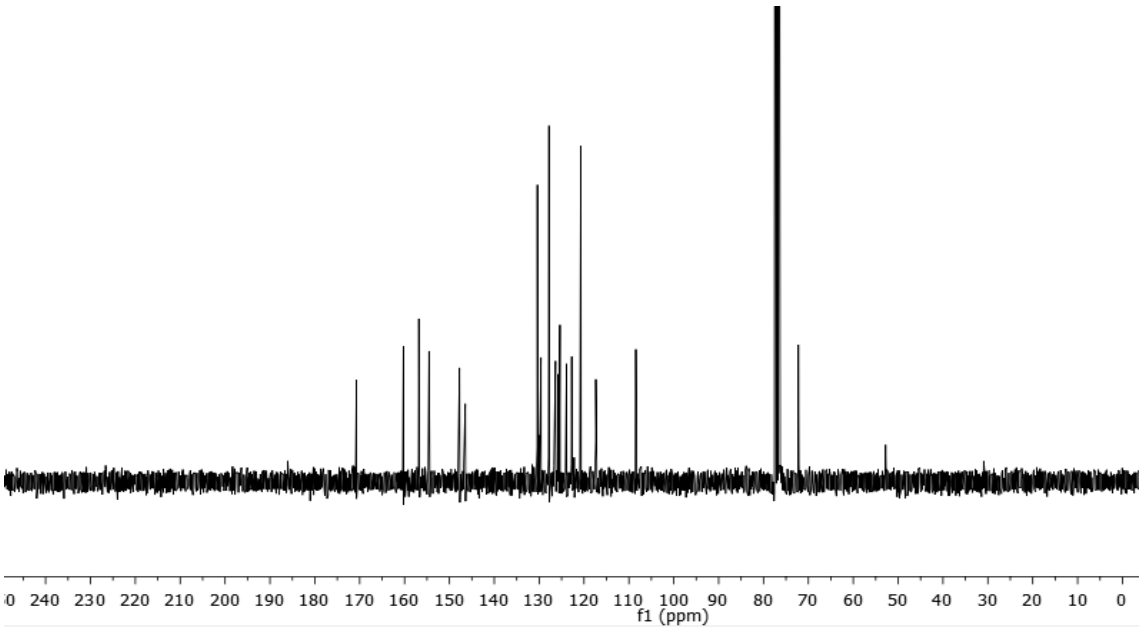


Methyl 4-hydroxy-1-(hydroxy(4-(trifluoromethyl)phenyl)methyl)-7-phenoxyisoquinoline-3-carboxylate (3t)

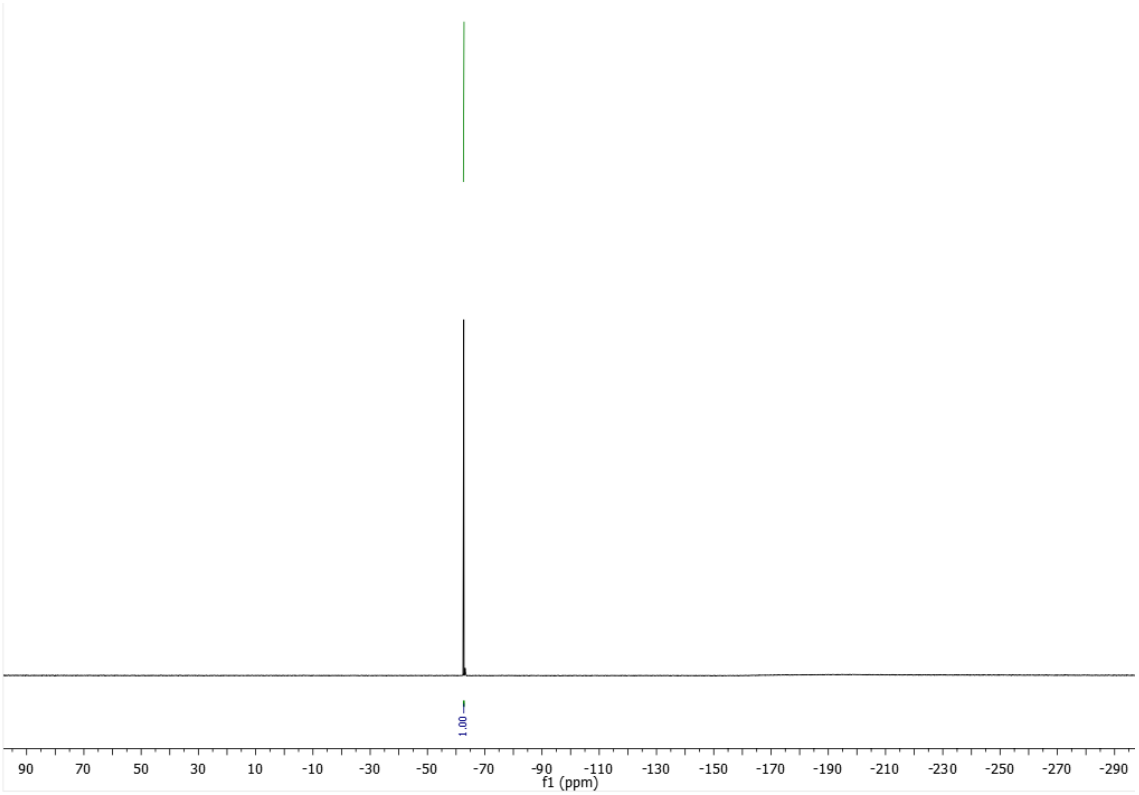
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)

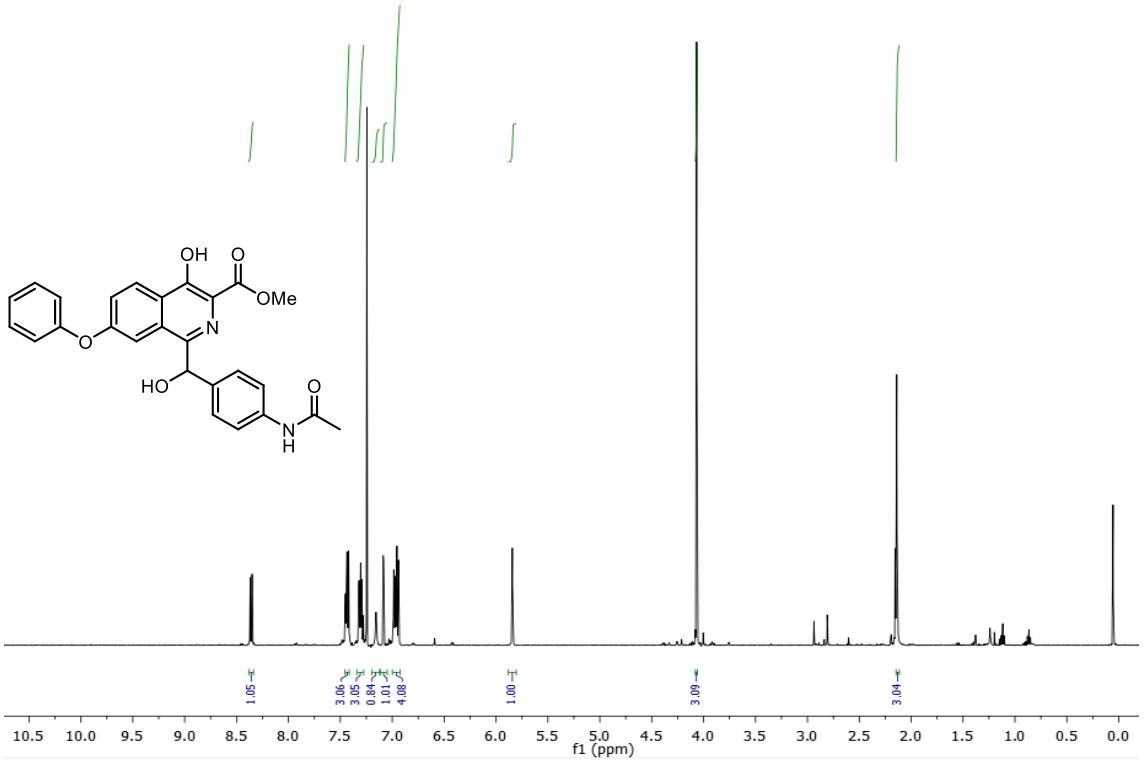


^{19}F NMR (373 MHz, $CDCl_3$)

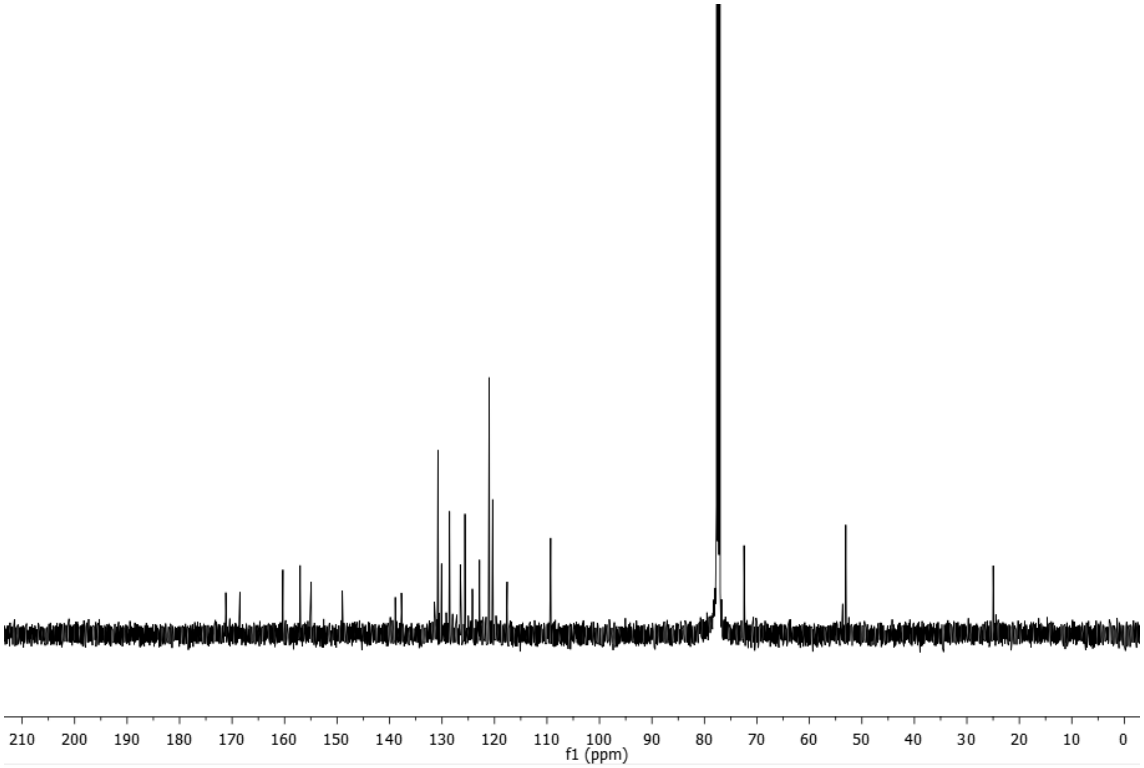


Methyl 1-((4-acetamidophenyl)(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3-carboxylate (3u)

^{1}H NMR (500 MHz, $CDCl_3$)

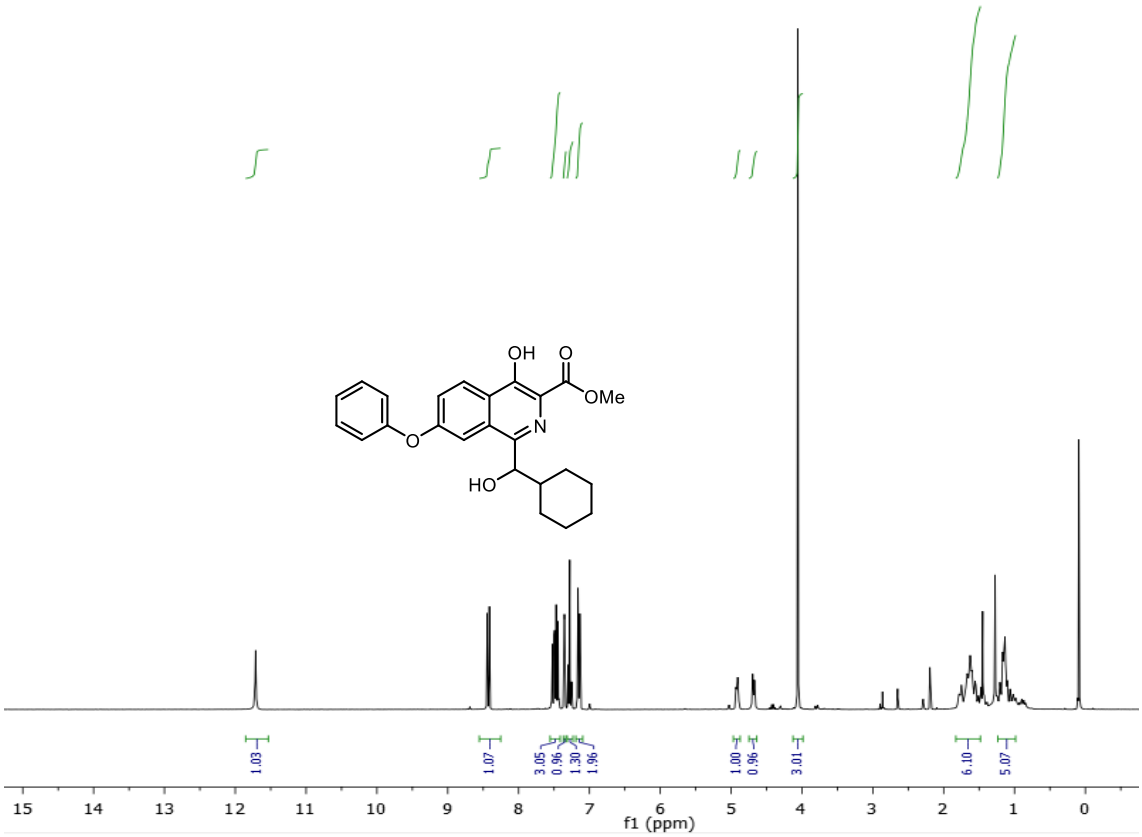


^{13}C NMR (126 MHz, $CDCl_3$)

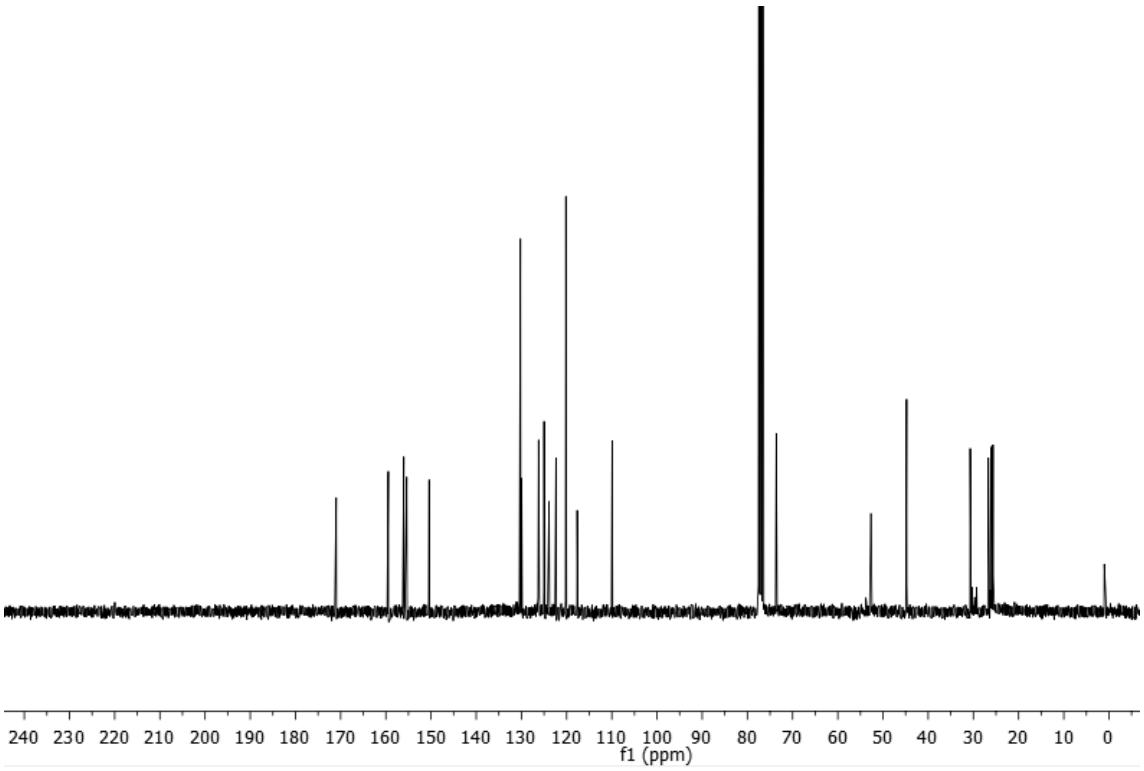


Methyl 1-(cyclohexyl(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3-carboxylate (3v)

^{1}H NMR (300 Mz, $CDCl_3$)

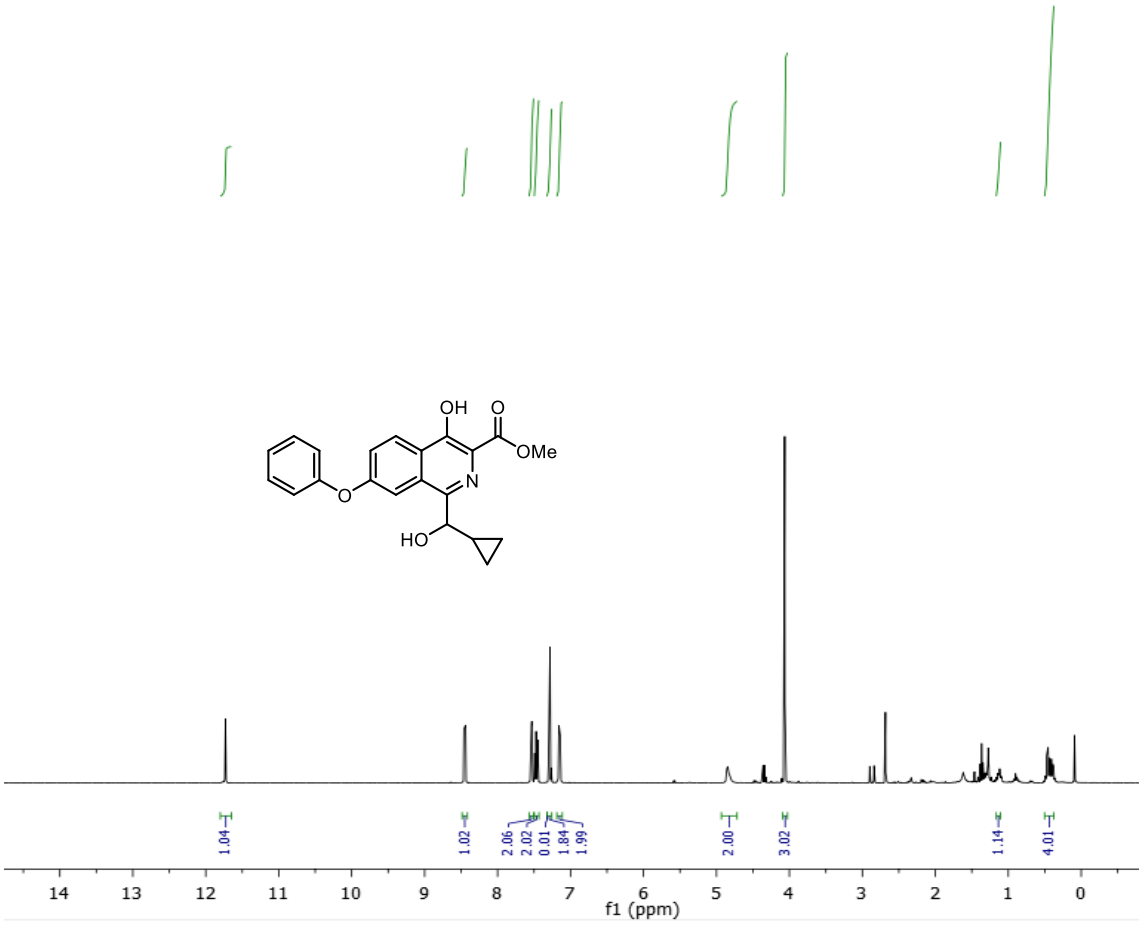


^{13}C NMR (75 MHz, $CDCl_3$)

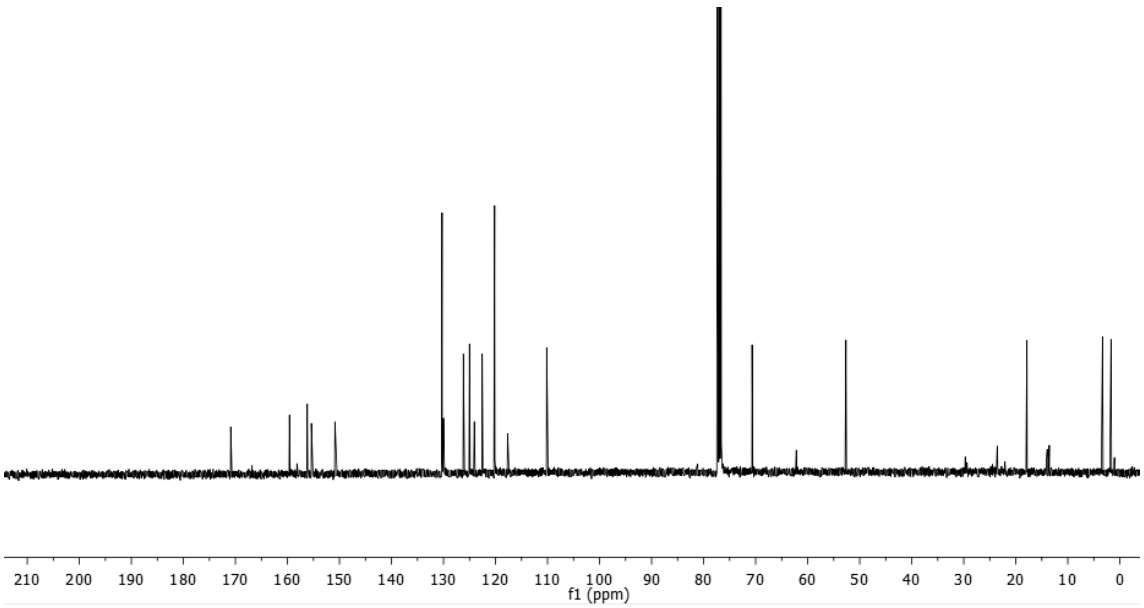


Methyl 1-(cyclopropyl(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3-carboxylate (3w)

^{1}H NMR (400 MHz, $CDCl_3$)

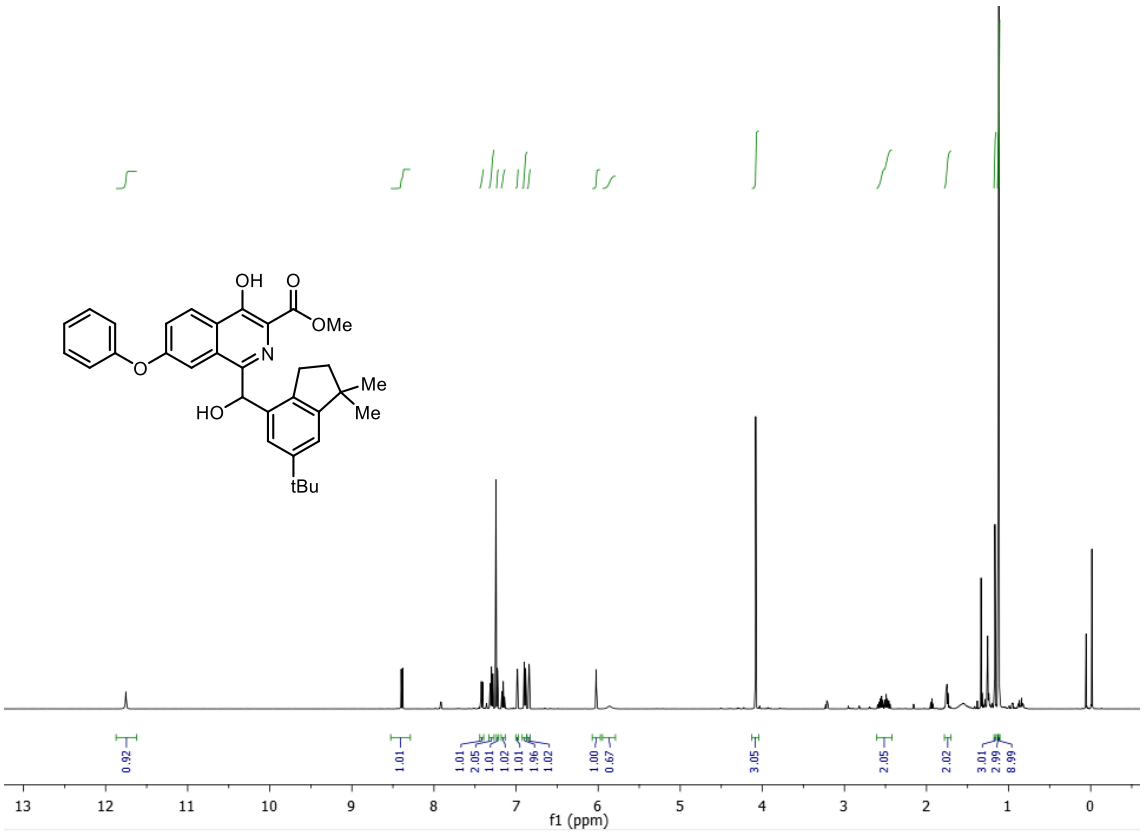


^{13}C NMR (101 MHz, $CDCl_3$)

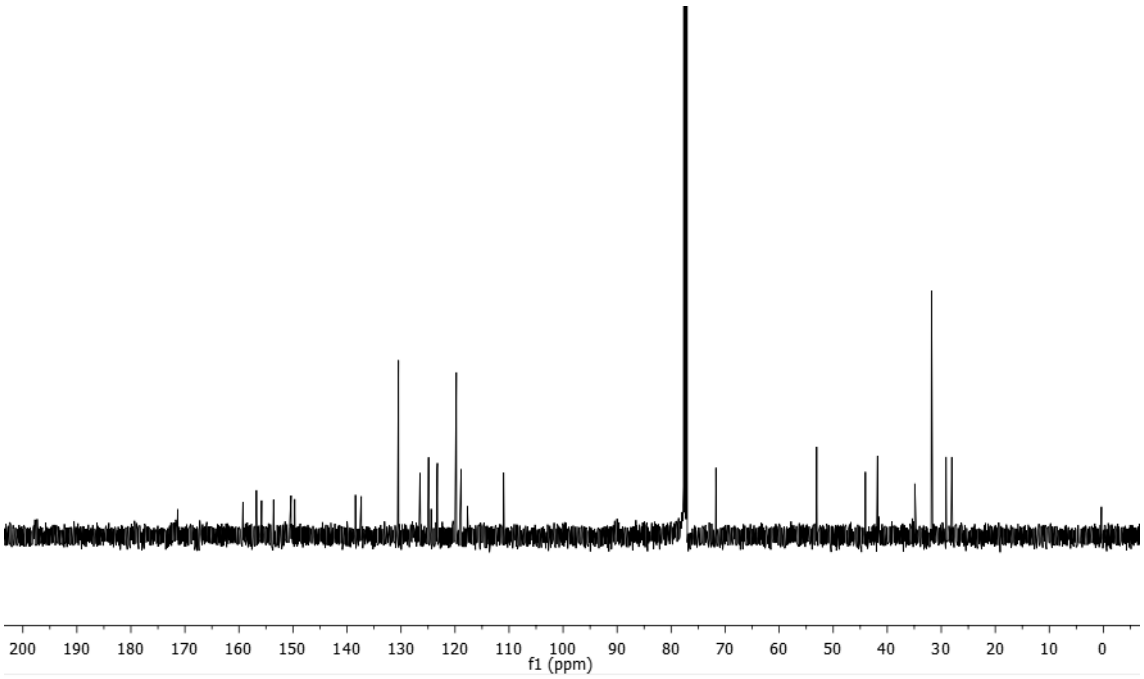


Methyl 1-((6-(tert-butyl)-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)(hydroxy)methyl)-4-hydroxy-7-phenoxyisoquinoline-3-carboxylate (3x)

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)



K. Cartesian Geometries and Absolute Energies

Here follow the computed absolute electronic energies (Table 3) and the Cartesian geometries (in Å) of all the species studied by DFT calculations.

Table 3 – Absolute electronic energies and thermal corrections to Enthalpy and Gibbs free energy of all the species studied by DFT calculations (in Hartree per particle).

Chemical species	M06-2X/6-31+G(d)			M06-2X/ 6-311+G(3df,2p)
	Electronic Energy	Thermal corr. to *G*	Thermal corr. to *H*	Electronic Energy
2a–H$^+$	–402.211439603	0.120179	0.159190	–402.330895397
Bz$^\bullet$	–344.786139256	0.067201	0.105788	–344.891765943
VI	–747.021382133	0.210936	0.267737	–747.244212074
I	–746.609796790	0.198270	0.254707	–746.832483865
CF_3COO^-	–526.203666033	-0.005310	0.033479	–526.390126822
CF_3COOH	–526.639611508	0.008253	0.046634	–526.833217226
VII	–747.038232424	0.211910	0.268259	–747.266012476
VIII	–747.203272872	0.209998	0.266642	–747.432460811

2a-H$^+$

C	-2.44156700	-0.73588800	0.00001300
C	-1.25300100	-1.41902100	0.00003300
C	-0.03244000	-0.69100200	0.00003600
C	-0.04210800	0.73494500	0.00002100
C	-1.28719300	1.40875400	0.00000000
C	-2.45516200	0.68412300	-0.00000400
H	-3.38151100	-1.27728000	0.00000600
H	-1.22625700	-2.50442200	0.00004100
C	1.20149000	1.42271900	0.00003000
H	-1.30206300	2.49411500	-0.00001600
H	-3.40894600	1.20222200	-0.00001800
C	2.37013500	0.72309400	0.00005900
H	1.22723600	2.50670400	0.00002600
H	3.35376700	1.17199700	0.00006800
H	3.21724100	-1.14977200	0.00007400
N	2.33214800	-0.64623900	0.00005900
C	1.20805100	-1.34794900	0.00004700
H	1.30034400	-2.42786700	0.00006100

Bz$^\bullet$

C	6.98889200	0.35503000	0.00012100
C	8.38597000	0.33435500	0.00053800
C	9.09103900	1.53564200	-0.00005700
C	8.39624600	2.74569900	-0.00106600
C	6.99760100	2.76490100	-0.00148500
C	6.28759000	1.57006100	-0.00089500
H	8.90483500	-0.62002700	0.00132300
H	10.17624900	1.52976200	0.00025900
H	8.94606600	3.68216200	-0.00153600
H	6.46705800	3.71196300	-0.00227600
H	5.20149000	1.56394500	-0.00120700
C	6.25456700	-0.92949900	0.00075400

O	5.08040300	-1.11560400	0.00045000

VI

C	2.92936500	1.37917000	-1.29034800
C	1.94037000	1.47103800	-0.31052100
C	1.54097500	0.33361900	0.38009100
C	2.14854000	-0.91644100	0.08877100
C	3.15005900	-0.98841900	-0.90678400
C	3.53365500	0.14942600	-1.59011600
H	3.23268900	2.27343100	-1.82489100
H	1.48639800	2.43236000	-0.08696700
C	1.73607700	-2.07502600	0.79875900
H	3.60776500	-1.94932000	-1.12176200
H	4.30062400	0.09410900	-2.35500900
C	0.72502500	-1.98955000	1.76010000
H	2.18997800	-3.03886100	0.60210000
H	0.38110700	-2.85822700	2.30985000
H	-0.57903100	-0.83500600	2.76366000
N	0.13279000	-0.84242600	2.03640200
C	-0.77893100	1.19782300	0.92000500
O	-0.87878600	2.36922200	1.21576000
C	-1.78446000	0.49353300	0.08399400
C	-1.49308000	-0.68403100	-0.61537900
C	-3.06039400	1.06574000	-0.01324500
C	-2.47009100	-1.28148600	-1.40705900
H	-0.50416000	-1.12934600	-0.57682100
C	-4.03765800	0.45806500	-0.79247300
H	-3.27319000	1.97921100	0.53327000
C	-3.74208000	-0.71514600	-1.49075000
H	-2.23683200	-2.18666500	-1.95814000
H	-5.02823500	0.89660100	-0.85777300
H	-4.50449600	-1.18746800	-2.10267600
C	0.47870500	0.44299300	1.44932200
H	0.84806200	1.08228300	2.26205600

I

C	3.64522300	-1.74502300	-0.10016800
C	2.28554100	-1.49792600	-0.21062900
C	1.77585300	-0.18550500	-0.08058600
C	2.69742400	0.87284100	0.17619900
C	4.07194000	0.59386900	0.27815900
C	4.54744700	-0.69922500	0.14058200
H	4.01091600	-2.76234900	-0.20300000
H	1.59945200	-2.31089700	-0.40113400
C	2.21017600	2.22055400	0.33624500
H	4.75668200	1.41566000	0.47104800
H	5.61113800	-0.90140600	0.22185800
C	0.88230100	2.46611800	0.23788400
H	2.90254900	3.03090300	0.53287500
H	0.44218500	3.45060800	0.33687700
H	-0.97449500	1.69113900	-0.11833800
N	0.00411400	1.45088500	-0.00401300
C	0.36044900	0.12526000	-0.16528400
C	-0.68960100	-0.82465400	-0.43005200
O	-0.46862400	-1.98460000	-0.84245900
C	-2.12318100	-0.40968200	-0.22818200
C	-2.56537200	0.19938800	0.95344500
C	-3.05593200	-0.73066600	-1.22166400
C	-3.91738200	0.49223700	1.13198300
H	-1.85533200	0.42454800	1.74648200
C	-4.40349900	-0.42511900	-1.04912200
H	-2.71298600	-1.22139200	-2.12825900
C	-4.83691600	0.18738200	0.12865100
H	-4.25127600	0.95285200	2.05692300

H	-5.11738100	-0.66730800	-1.83085900
H	-5.88860100	0.42069500	0.26563500

CF_3COO^-

C	-3.94379100	0.90394600	-0.03146000
O	-2.92871600	0.77361000	0.67273100
C	-4.62734800	2.30985300	0.01763100
O	-4.53117200	0.10537700	-0.78511800
F	-4.00762300	3.19028500	0.82013000
F	-5.90286500	2.22126800	0.45341000
F	-4.67961000	2.87477800	-1.20814600

CF_3COOH

C	-3.91768600	0.96142500	0.01072500
O	-2.93361000	0.74369600	0.65983900
C	-4.63746600	2.32743800	0.01770300
O	-4.55441300	0.13008300	-0.79687200
H	-4.10473800	-0.73686100	-0.80543200
F	-4.00806000	3.18115300	0.81714500
F	-5.89686300	2.19046600	0.44591300
F	-4.67302800	2.84485700	-1.21527600

VII

C	3.61370800	-1.77957900	-0.03027000
C	2.26223900	-1.52300200	-0.13777800
C	1.77472800	-0.19597800	-0.05367700
C	2.71224800	0.85841200	0.16443800
C	4.09059600	0.56401100	0.26155700
C	4.53754300	-0.73410200	0.16236100
H	3.96580700	-2.80396300	-0.09523200
H	1.57998700	-2.34650100	-0.28425700
C	2.25759800	2.20487900	0.30190100
H	4.78662800	1.38207300	0.42176200
H	5.59746700	-0.95422500	0.23936900
C	0.92807700	2.47753200	0.22121200
H	2.96650700	3.00650100	0.47197900
H	0.50241900	3.46845400	0.30721400
H	-0.93617300	1.72815500	-0.10690200
N	0.04172400	1.47129400	0.00558300
C	0.36956200	0.15087700	-0.13670500
C	-0.71068600	-0.73059100	-0.36419200
O	-0.43106100	-1.94526500	-0.83743500
C	-2.12337600	-0.37000000	-0.17840500
C	-2.56271400	0.27064400	0.99217200
C	-3.05466200	-0.73032600	-1.16611300
C	-3.91375800	0.55574500	1.16114500
H	-1.85369700	0.51359600	1.77962100
C	-4.40313200	-0.43869300	-0.98940300
H	-2.71826900	-1.20835700	-2.08258400
C	-4.83359400	0.20481700	0.17172700
H	-4.24947100	1.04141300	2.07160600
H	-5.11672500	-0.70728000	-1.76152600
H	-5.88667200	0.43021400	0.30723700
H	-1.21969700	-2.51625400	-0.81623900

VIII

C	3.66352944	-1.71642930	-0.45952552
C	2.30322147	-1.43268510	-0.55522132
C	1.79081067	-0.19130964	-0.14401405
C	2.69641000	0.79390175	0.33440570

C	4.06245870	0.48290966	0.43184534
C	4.54622494	-0.76076196	0.04779114
H	4.03168755	-2.68603897	-0.78135277
H	1.63206474	-2.18176958	-0.95144253
C	2.21611100	2.12321482	0.66877682
H	4.74370767	1.24358810	0.80546535
H	5.60662560	-0.98134601	0.13064080
C	0.94198292	2.44883925	0.36299797
H	2.89782863	2.86638556	1.06518231
H	0.53925147	3.44942730	0.47666832
H	-0.86894260	1.82112126	-0.36056726
N	0.07536574	1.52520983	-0.15358502
C	0.34542748	0.14216156	-0.16204276
C	-0.69571250	-0.72865181	-0.20354960
O	-0.45453580	-2.06759720	-0.45623250
C	-2.12507426	-0.35330618	-0.12142751
C	-2.60899747	0.52705819	0.86132566
C	-3.04636807	-0.94924357	-0.99805281
C	-3.96721355	0.82219129	0.94401518
H	-1.91705192	0.96272382	1.57802308
C	-4.40575697	-0.65591496	-0.91051864
H	-2.68782817	-1.63898571	-1.75754982
C	-4.87132972	0.23482798	0.05669220
H	-4.32256257	1.50113820	1.71363770
H	-5.10167074	-1.12146729	-1.60242344
H	-5.93053420	0.46376882	0.12493611
H	-1.11597928	-2.59845818	0.01526966