Phytomanagement Strategy Leads to Plant-Derived Catalysts for the Sustainable Synthesis of Oxidized Hantzsch Esters

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Supplementary methods

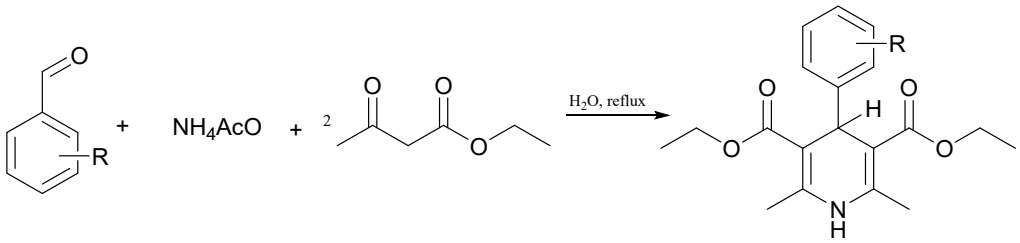
1. General Methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian VNMRS 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) instrument. The ^{1}H data is presented as follows: chemical shift (in ppm on the δ scale), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), the coupling constant (J, in Hertz) and integration. The ^{13}C data is reported as the ppm on the δ scale followed by interpretation. TLC was performed on Merck 60F254 silica plates and visualized by UV light. Melting points were measured on a MPA 100 OptiMelt® apparatus and are uncorrected. Flash chromatography was performed with a CombiFlash Rf Companion (Teledyne-Isco System) using RediSep packed silica columns.

Unless indicated otherwise, reagents and substrates were purchased from commercial sources and used as received. Solvents not required to be dry were purchased and used as received. All reported compounds were characterized by ^{1}H and ^{13}C NMR and compared with literature data.

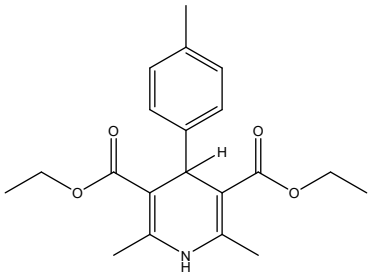
2. Synthesis of compounds

Hantzsch dihydropyridine derivatives synthesis[1]



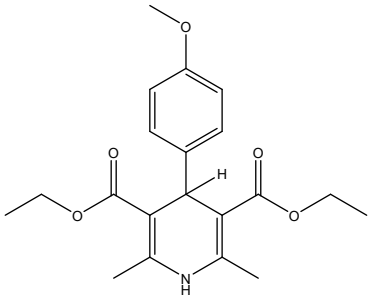
To a stirred solution of the aldehyde (6 mmol) in 15 mL of water, ammonium acetate (6 mmol) and ethyl acetoacetate (12 mmol) were added. The reaction mixture was heated under reflux for 1 hour. Upon completion, as monitored by TLC, the reaction mixture was cooled to room temperature, and the resulting precipitate was filtered, washed with cold water, and dried. The crude product was purified by recrystallization from ethanol to yield the desired derivative.

Diethyl 2,6-dimethyl-4-(*p*-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate 1a[2]



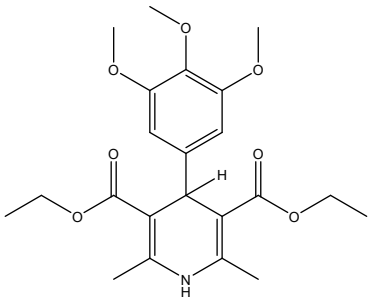
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.15 (m, 2H, Ar*H*), 7.08 – 6.96 (m, 2H, Ar*H*), 5.57 (d, *J* = 4.4 Hz, 1H, C*H*), 4.95 (s, 1H, N*H*), 4.11 – 3.93 (m, 4H, CH_2), 2.30 (s, 6H, CH_3), 2.28 (s, 3H, CH_3), 1.23 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.47 (2C), 141.49 (2C), 133.34 (C), 126.40 (2CH), 125.67 (2CH), 102.18 (2C), 57.53 (CH_2), 36.93 (CH), 18.89 (CH_3), 17.47 ($2CH_3$), 12.09 ($2CH_3$).

Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 1b[3]



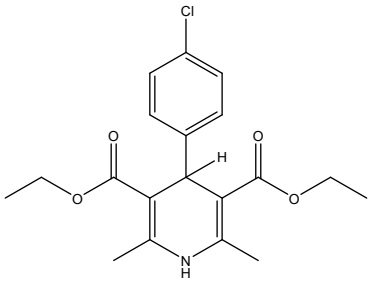
White solid. Yield 90%, 1.94 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.06 (m, 2H, Ar*H*), 6.84 – 6.63 (m, 2H, Ar*H*), 5.53 (s, 1H, N*H*), 4.93 (s, 1H, C*H*), 4.09 (qd, *J* = 7.1, 5.2 Hz, 4H, CH_2), 3.75 (s, 3H, CH_3), 2.33 (s, 6H_3), 1.22 (t, *J* = 7.1 Hz, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.78 (2C), 157.00 (C), 142.56 (2C), 139.42 (C), 128.08 (2CH), 112.30 (2CH), 103.59 (2C), 58.82 (CH), 54.26 (CH_3), 37.86 (2CH_2), 18.75 (2CH_3), 13.39 (2CH_3). M.p. (EtOH) = 137-139 °C.

Diethyl 2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate 1c[3]



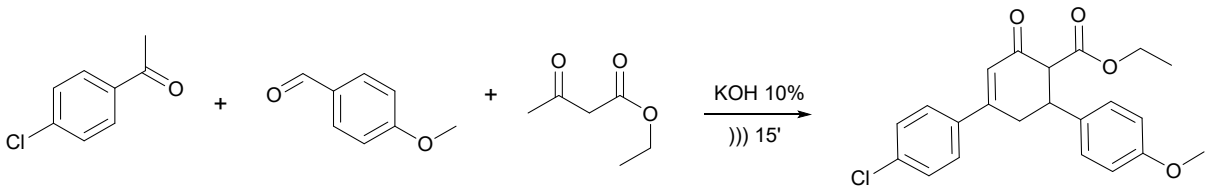
White solid. Yield 88%, 2.21 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (s, 2H, Ar*H*), 5.62 (s, 1H, N*H*), 4.98 (s, 1H, C*H*), 4.25 – 4.05 (m, 4H, CH_2), 3.80 (d, *J* = 1.0 Hz, 9H, CH_3), 2.35 (s, 6H, CH_3), 1.25 (t, *J* = 7.1 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.97 (2C), 151.00 (2C),142.05 (2C), 141.68 (C), 134.85 (C), 103.42 (2CH), 102.42 (2C), 59.10 (2CH_2), 58.12 (CH_3), 54.32 (2CH_3), 38.03 (CH_2), 17.98 (2CH_3), 12.72 (2CH_3). M.p. (EtOH) = 168-170°C.

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 1d [4]



White solid. Yield 85%, 1.84 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.05 (m, 4H, Ar*H*), 5.64 (s, 1H, N*H*), 4.96 (s, 1H, CH), 4.21 – 3.90 (m, 4H, CH_2), 2.33 (s, 6H, CH_3), 1.22 (t, *J* = 7.1 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.42 (2C), 146.32 (C), 143.94 (2C), 131.71 (C), 129.43 (2CH), 127.95 (2CH), 103.94 (2C), 59.83 (CH), 39.27 (2CH_2), 19.63 (2CH_3), 14.27 (2CH_3). M.p. (EtOH) = 153-155 °C.

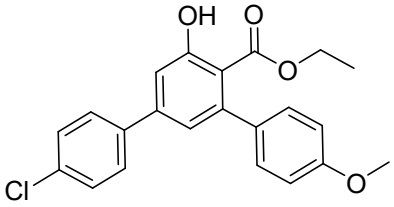
Synthesis of methyl 4-chloro-4''-methoxy-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate **5**[5]



Molecule **5** was synthesized via a one-pot, two-step ultrasound-assisted reaction. In a 100 mL reaction beaker, 4-chloroacetophenone (3 mmol) and 4-methoxybenzaldehyde (3 mmol) were dissolved in 10 mL of 10% aqueous KOH. The reaction mixture was subjected to ultrasonic irradiation at room temperature for 5 minutes, facilitating the initial aldol condensation. After completion of the first step, ethyl acetoacetate (3.3 mmol, 1.1 eq) was added to the reaction mixture, and the ultrasonic treatment was continued under the same conditions for another 10 minutes. Upon completion, the reaction was quenched by neutralizing with dilute HCl (10%). The crude product was isolated by filtration, washed with cold water, and dried. The final product was purified by recrystallization from ethanol, yielding white crystals.

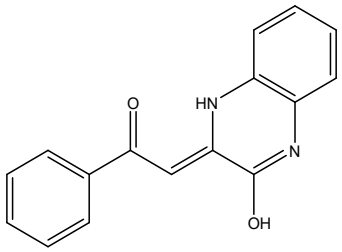
Yellow solid. Yield 65%, 0.75 g. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 (dd, *J* = 8.7, 1.7 Hz, 2H, Ar*H*), 7.36 (dd, *J* = 8.7, 1.7 Hz, 2H, Ar*H*), 7.27 – 7.12 (m, 3H, Ar*H*), 6.94 – 6.77 (m, 2H, C*H*), 6.50 (s, 1H, Ar*H*), 4.03 (dt, *J* = 7.1, 1.0 Hz, 2H, CH_2), 3.77 (d, *J* = 1.6 Hz, 4H, CH_2, C*H*), 3.14 – 2.82 (m, 2H, CH_3), 1.05 (td, *J* = 7.1, 1.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.02 (C), 167.19 (C), 156.87 (C), 155.19 (C), 134.10 (C), 130.85 (C), 127.12 (2CH), 126.29 (2CH), 125.43 (2CH), 122.26 (CH), 112.17 (2CH), 58.97 (CH), 57.82 ($2CH_2$), 53.26 (CH_3), 41.28 (CH_2), 34.19 (CH), 11.96 (CH_3).

Ethyl 4-chloro-5'-hydroxy-4''-methoxy-[1,1':3',1''-terphenyl]-4'-carboxylate 6[6]



White solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.95 (s, 1H, OH), 7.55 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.41 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.20 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.18 (d, *J* = 1.9 Hz, 1H, Ar*H*), 6.99 (d, *J* = 1.9 Hz, 1H, Ar*H*), 6.92 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.04 (d, *J* = 7.1 Hz, 2H, CH_2), 3.86 (s, 3H, CH_3), 0.85 (t, *J* = 7.1 Hz, 3H, CH_3).

(Z)-2-(3-hydroxyquinoxalin-2(1H)-ylidene)-1-phenylethan-1-one 8[7]



Orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.64 (s, 1H, O*H*), 12.04 (s, 1H, N*H*), 8.09 – 7.87 (m, 2H, Ar*H*), 7.62 – 7.51 (m, 2H, Ar*H*), 7.31 – 7.02 (m, 4H, Ar*H*), 6.79 (s, 1H, C*H*). ^{13}C NMR (100 MHz, dmso) δ 188.86 (C), 156.13 (C), 146.07 (C), 139.07 (C), 132.38 (C), 129.22 (2CH), 127.44 (2CH), 127.17 (C), 124.54 (CH), 124.46 (CH), 124.13 (CH), 117.03 (CH), 115.83 (CH), 89.53 (CH).

Quantification of Reaction Progress via ^{1}H-NMR

The oxidation of all substrates was quantitatively monitored using ^{1}H-NMR spectroscopy in $CDCl_3$ with an internal standard, TMS. Diagnostic signals for the starting material and the product were integrated, enabling calculation of conversion. Peak assignments were confirmed by recording reference spectra of pure starting material and product under identical conditions. Additionally, error minimization was ensured by setting identical acquisition parameters, including pulse angle, relaxation delay, and receiver gain, across all measurements.

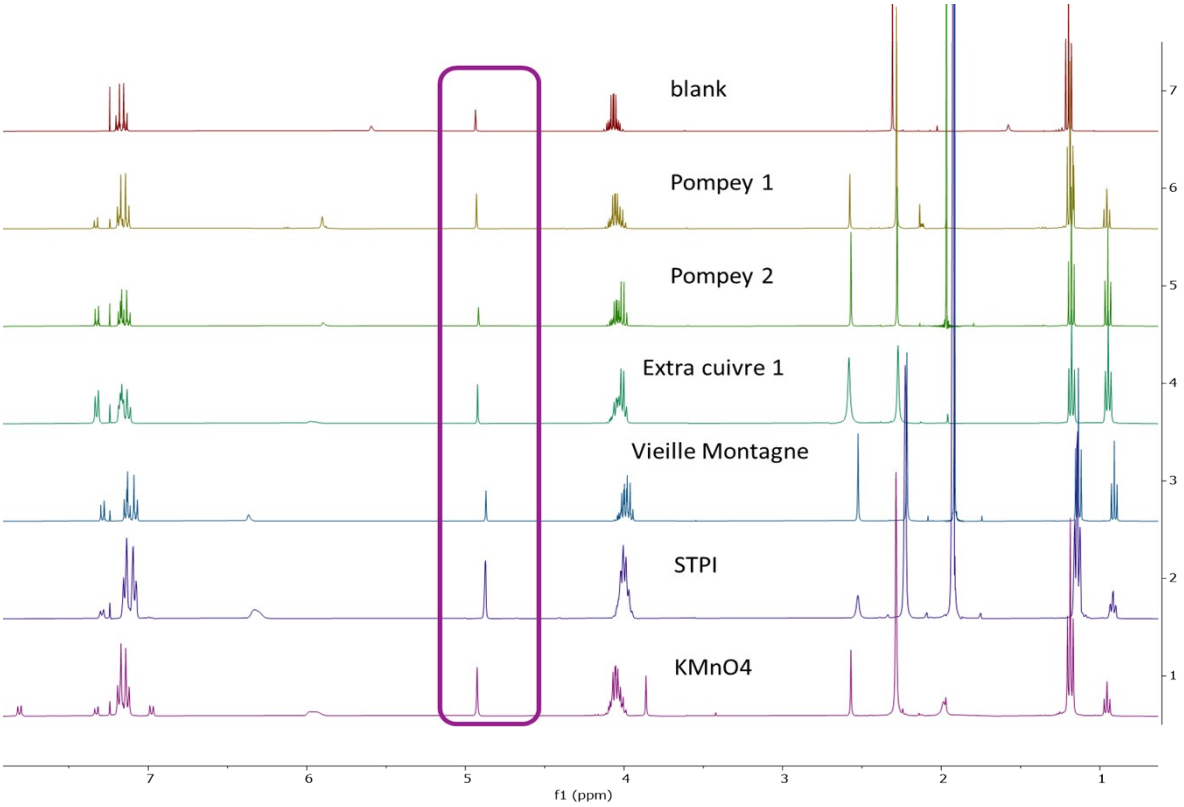


Fig. S1 Overlay of ^{1}H-NMR spectra of reaction mixtures showing the oxidation of Hantzsch ester **1d** using various studied catalysts, in acetonitrile

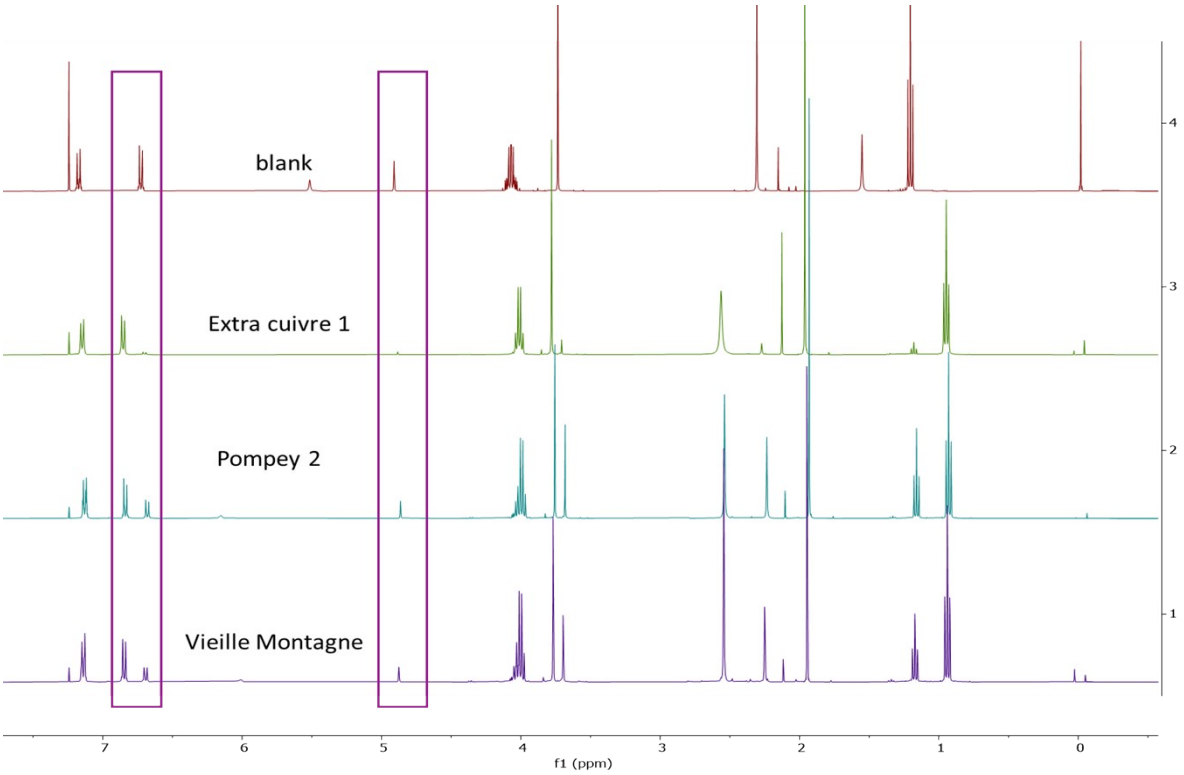


Fig. S2 Overlay of ^{1}H-NMR spectra of reaction mixtures showing the oxidation of Hantzsch ester **1b** of the most promising catalysts, in acetonitrile.

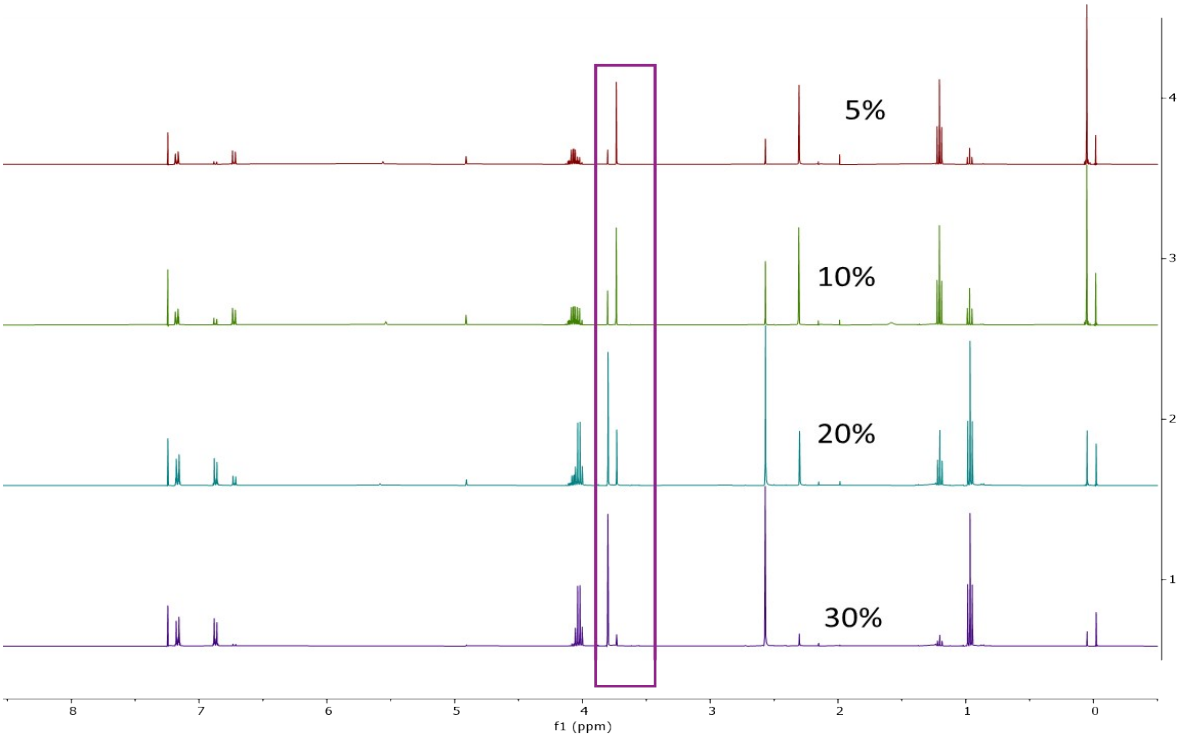


Fig. S3 Overlay of ^{1}H-NMR spectra showing the effect of catalyst loading on the oxidation of Hantzsch ester derivative **1b** using BIO-P2. Catalyst loadings of 5%, 10%, 20%, and 30% (relative to substrate weight)

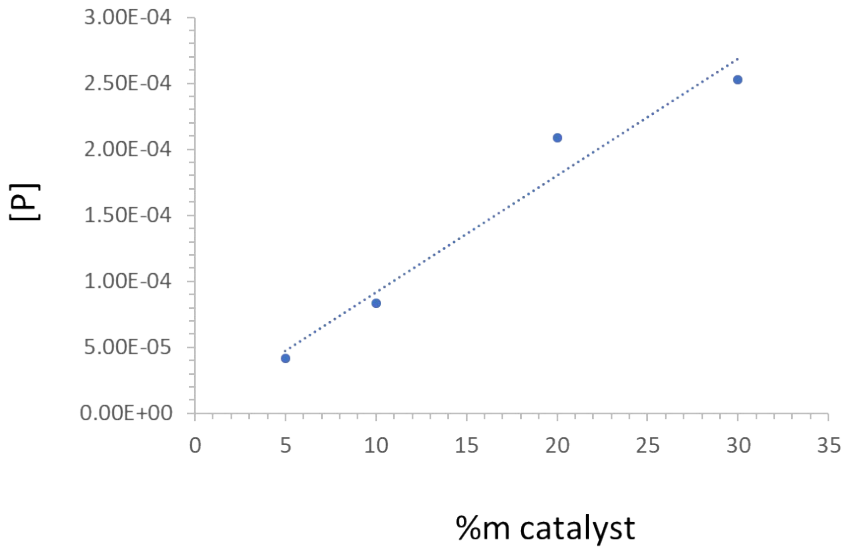


Fig. S4. Second-order kinetic plot for the oxidation of Hantzsch ester **1b** using BIO-P1 (20 wt%) under standard conditions, ACN, reflux.

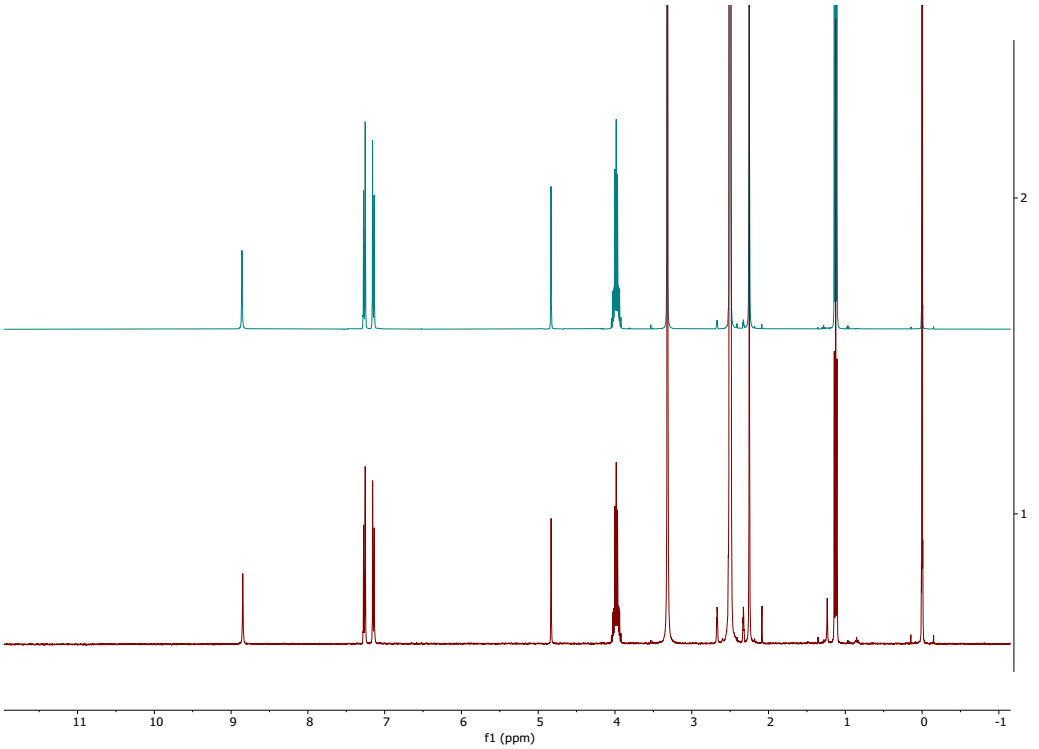


Fig. S5. Overlay of ^{1}H-NMR spectra showing the effect of catalyst loading on the oxidation of Hantzsch ester derivative **1d** using BIO-P2 and BIO-V, in water as solvent. Catalyst loadings of 5 wt%

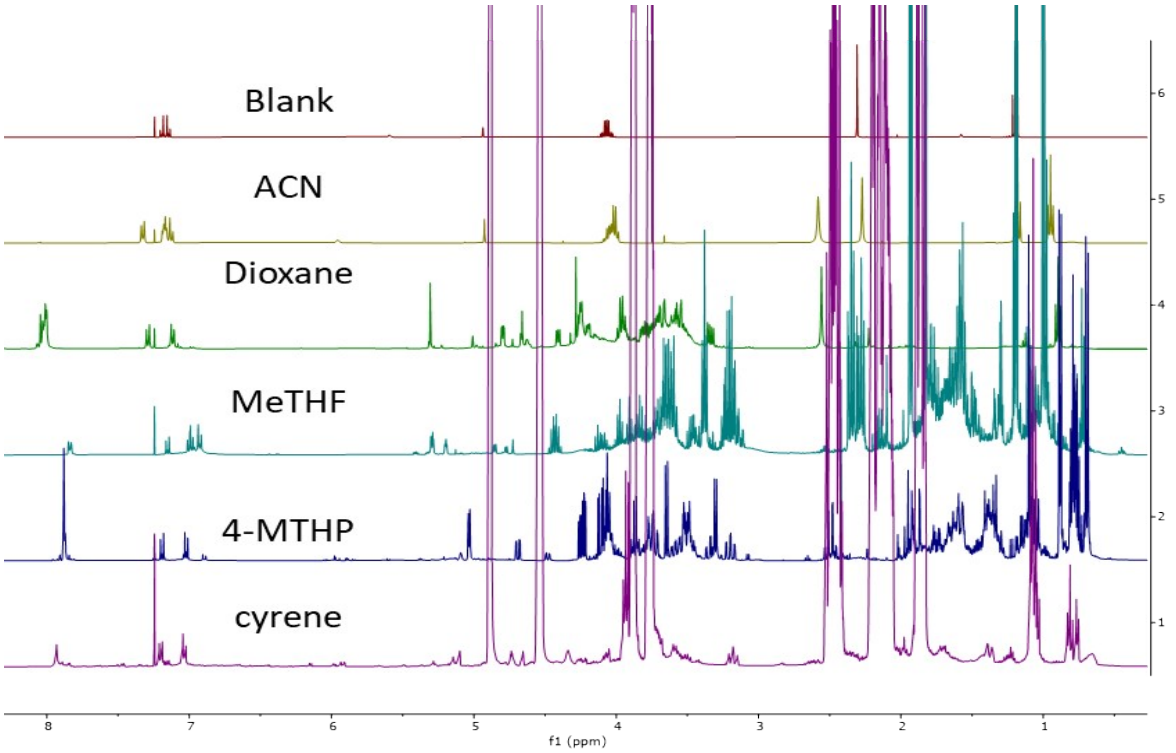


Fig.S6. Overlay of ^{1}H-NMR spectra of reaction mixtures showing the oxidation of Hantzsch ester derivative **1d** in different solvents (ACN, Dioxane, MeTHF, 4-MTHP, and Cyrene)

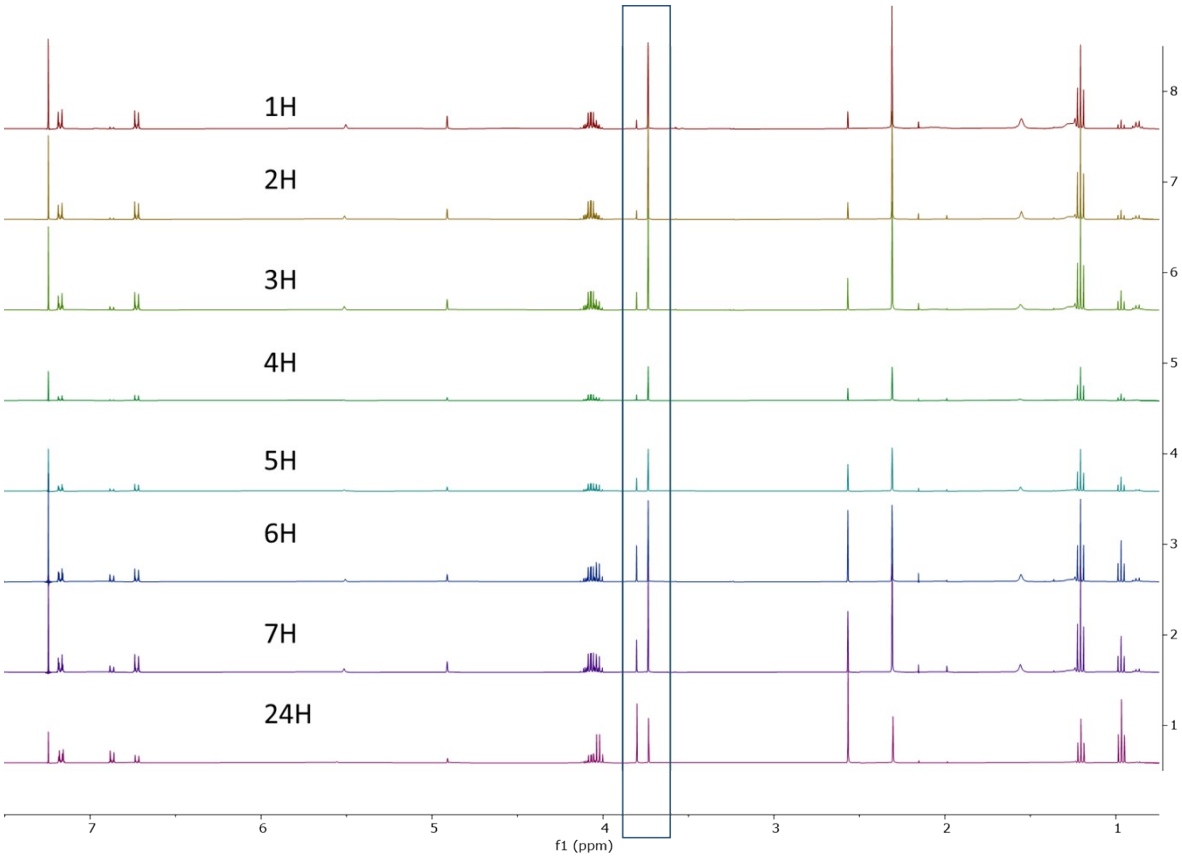


Fig. S7. Overlay of ^{1}H-NMR spectra illustrating the oxidation of dihydropyridine **1b** to pyridine **2b**. Each spectrum corresponds to a specific time interval (1H, 2H, 3H, etc.), showing the gradual disappearance of dihydropyridine signals and the emergence of characteristic pyridine signals.

Kinetics of DHP 1b oxidation in presence of BIO-P1

Time (hours)	% Product	Product Concentration (M)
1	6	1.648352e-05
2	10	2.747253e-05
3	14	3.846154e-05
4	16	4.395604e-05
5	18	4.945055e-05
6	25	6.868132e-05
7	32	8.791209e-05
24	65	1.785714e-04

Kinetic equations

Zero-order: $[A] = [A]_0 - kt$

First-order: $\ln([A]) = \ln([A]_0) - kt$

Second-order: $1/[A] = 1/[A]_0 + kt$

Kinetic plots

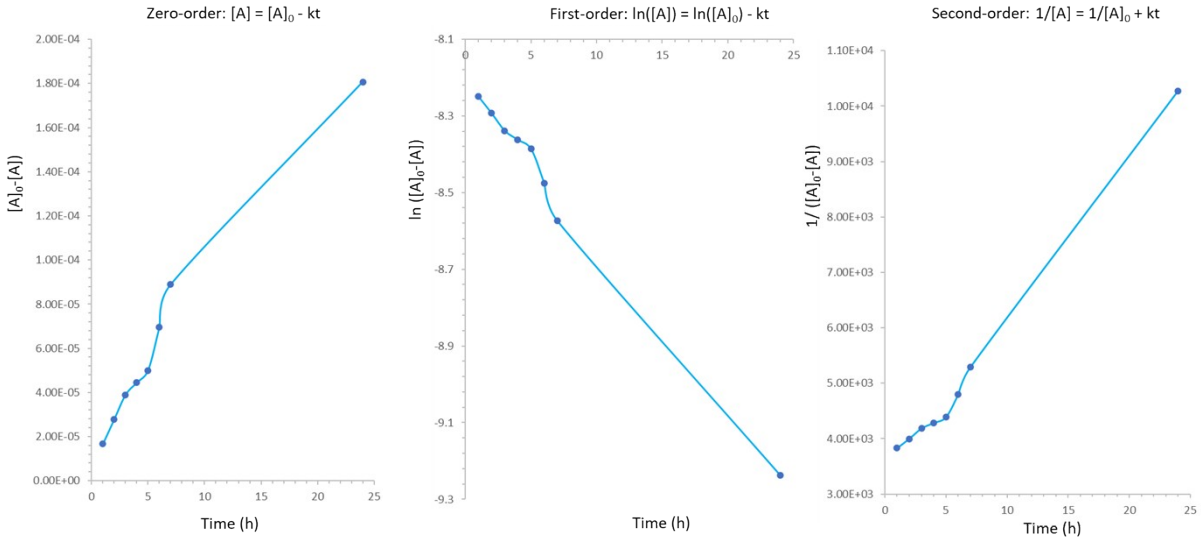


Fig. S8. Kinetic Plots for the Oxidation of **1b** to **2b**

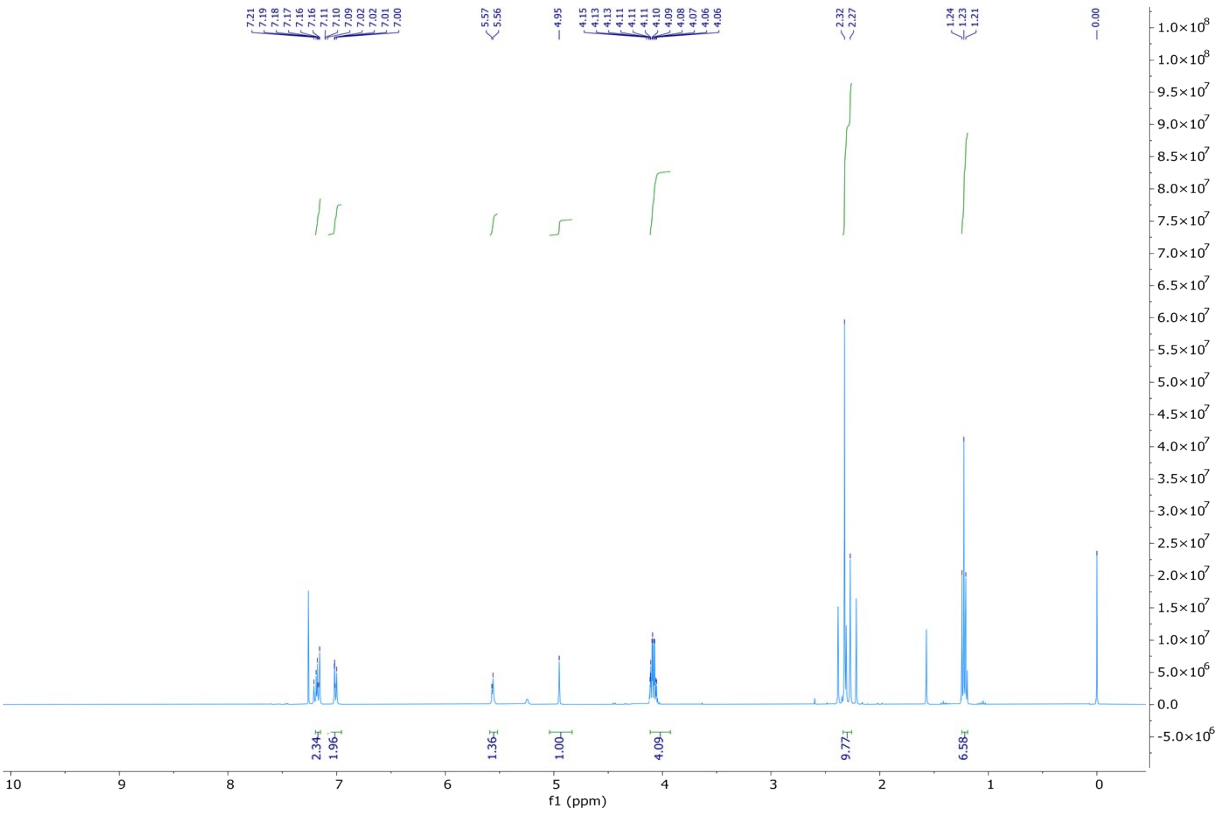
Rate Constant Determination

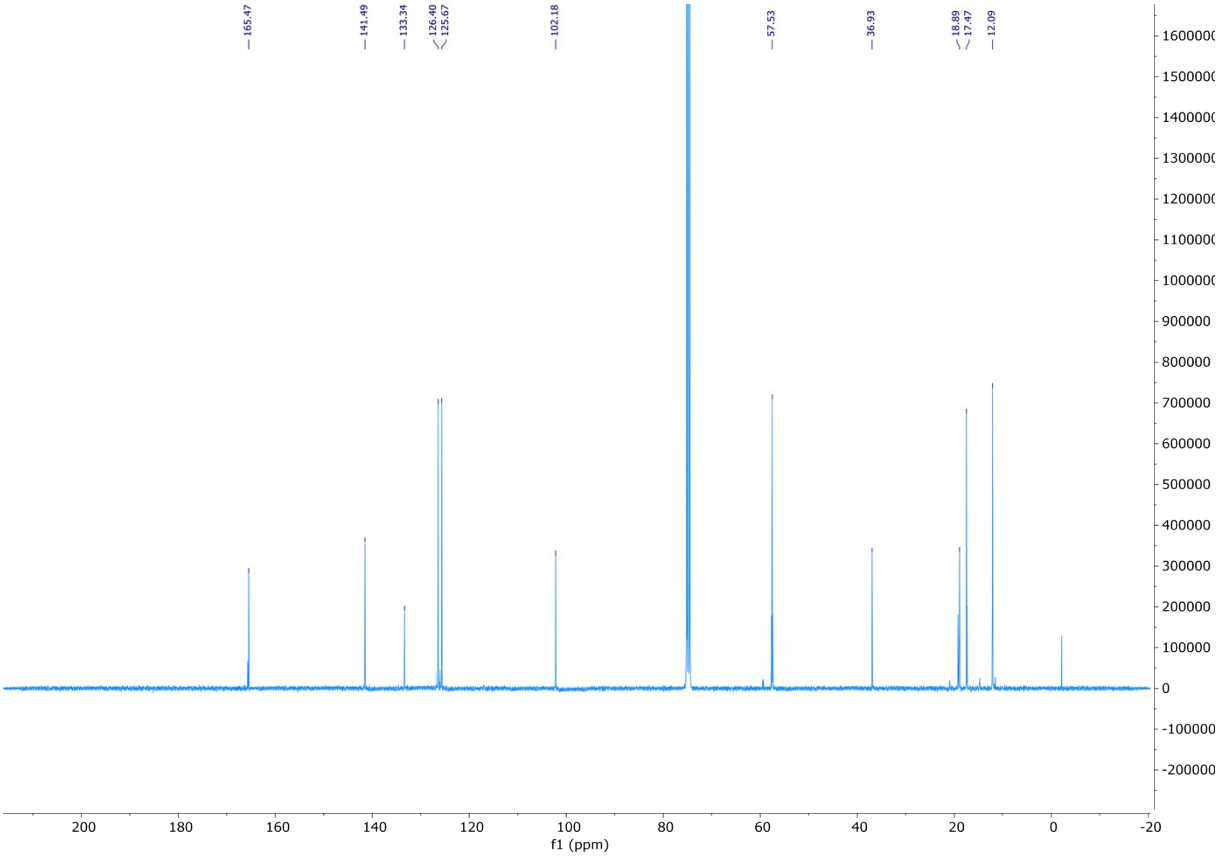
The reaction was determined to follow second-order kinetics. The rate constant (k) is:

Rate constant, k = 0.08021 $M^{-1}s^{-1}$ (T=355.15K)

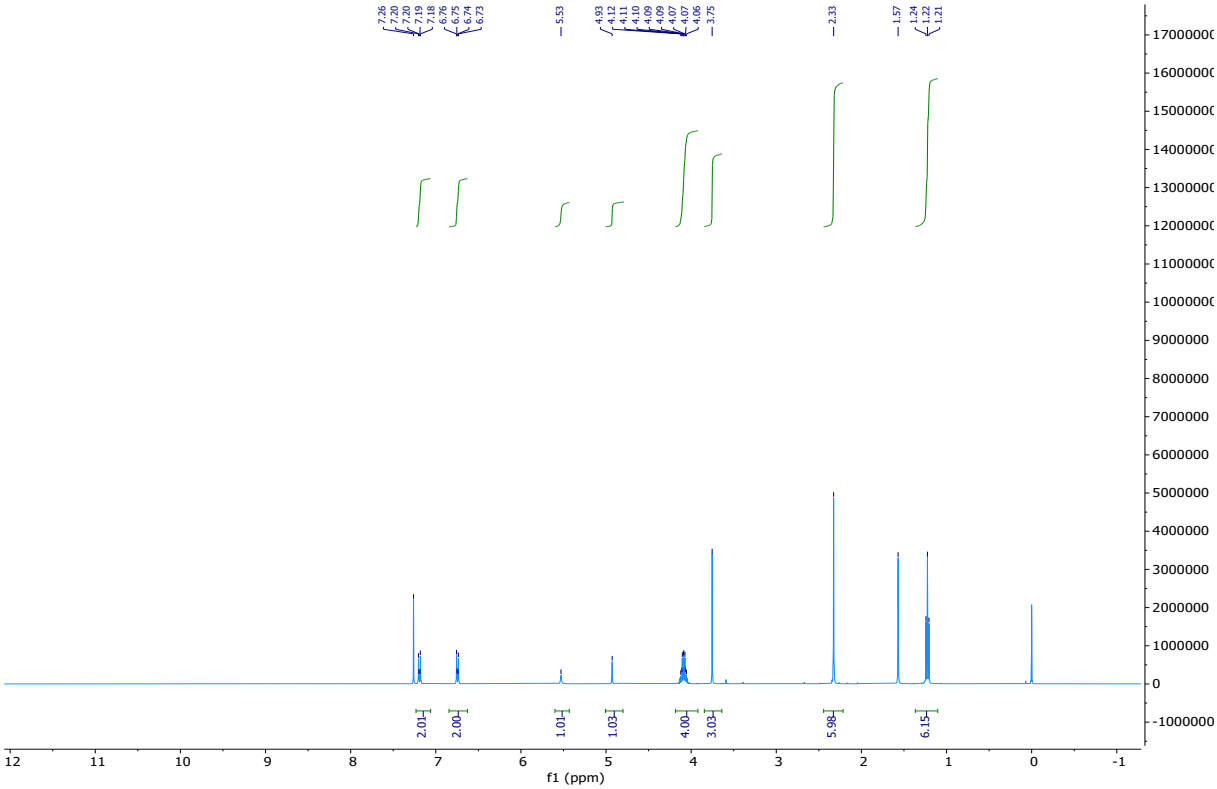
Supplementary figures

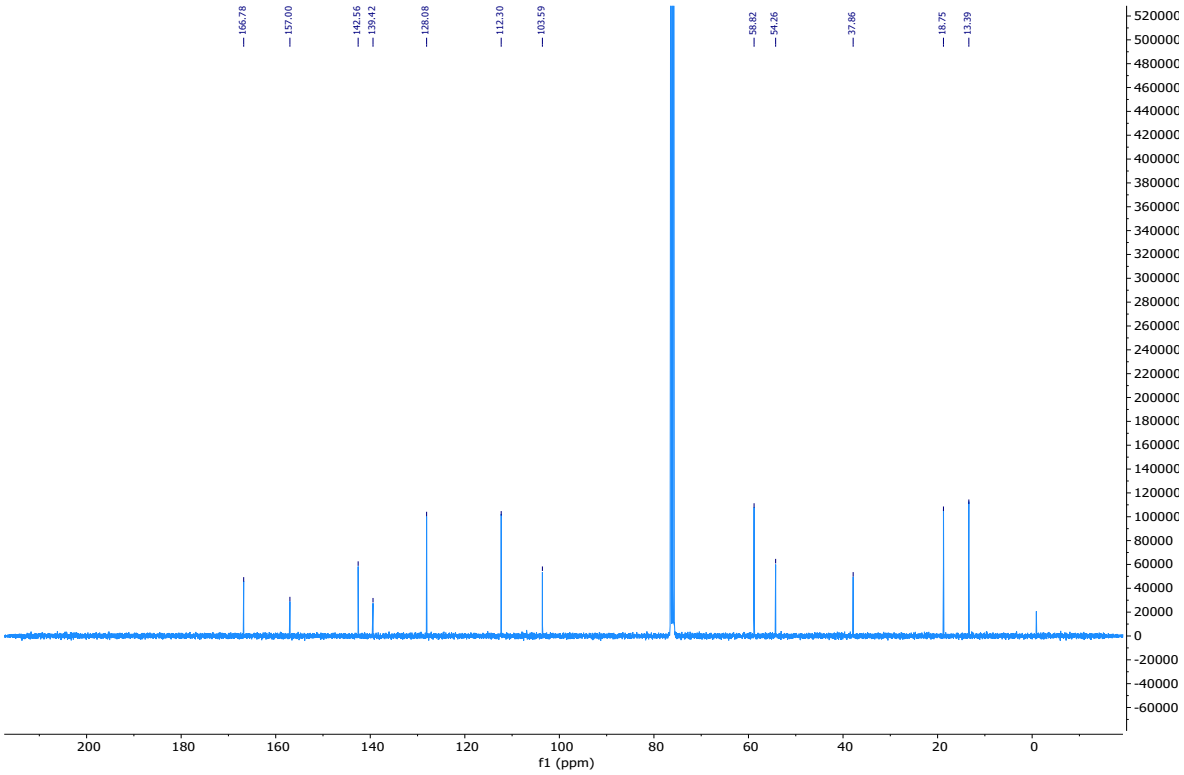
Diethyl 2,6-dimethyl-4-(p-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate 1a



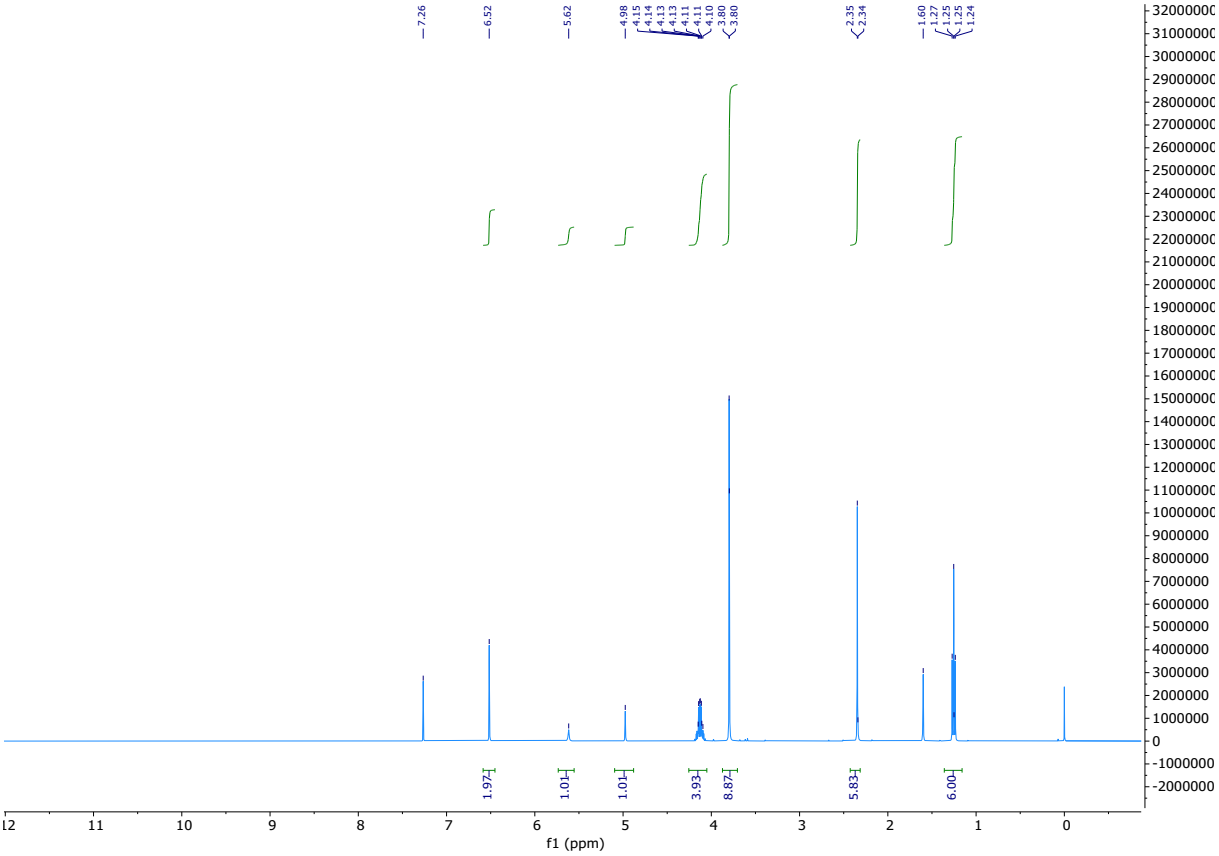


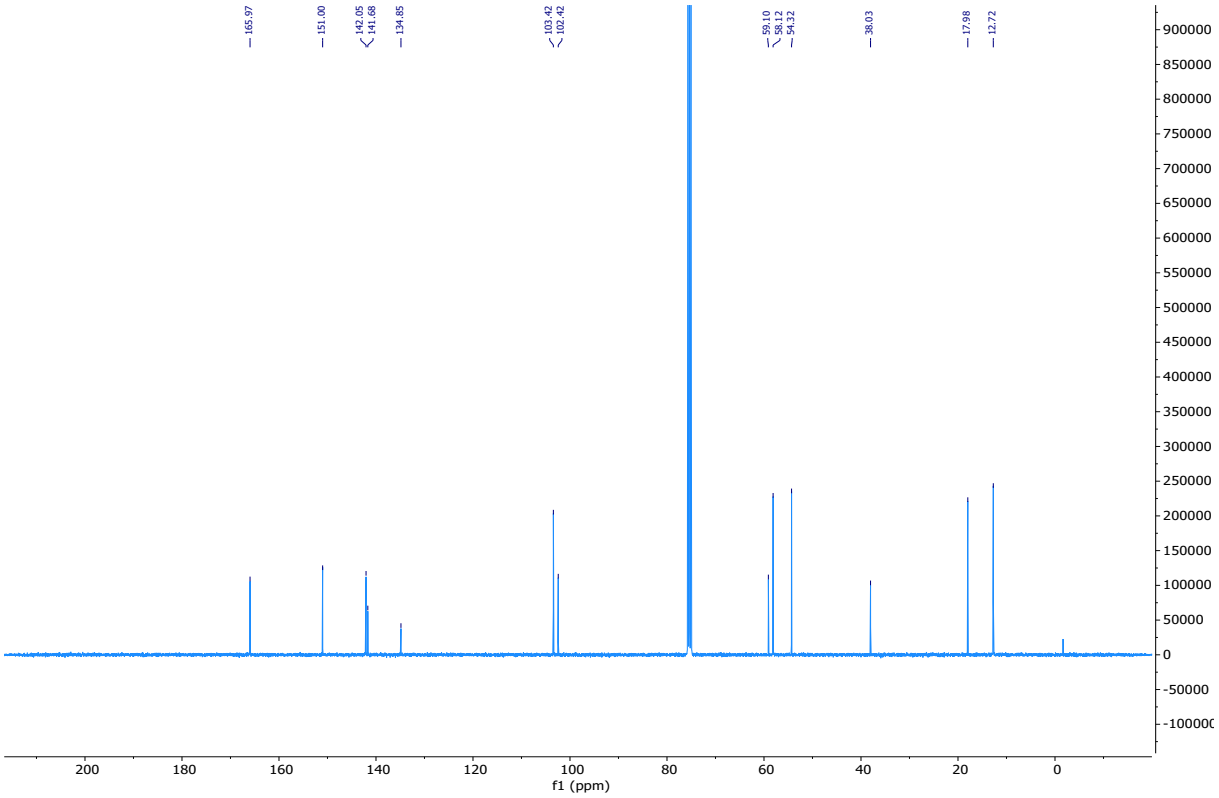
Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 1b



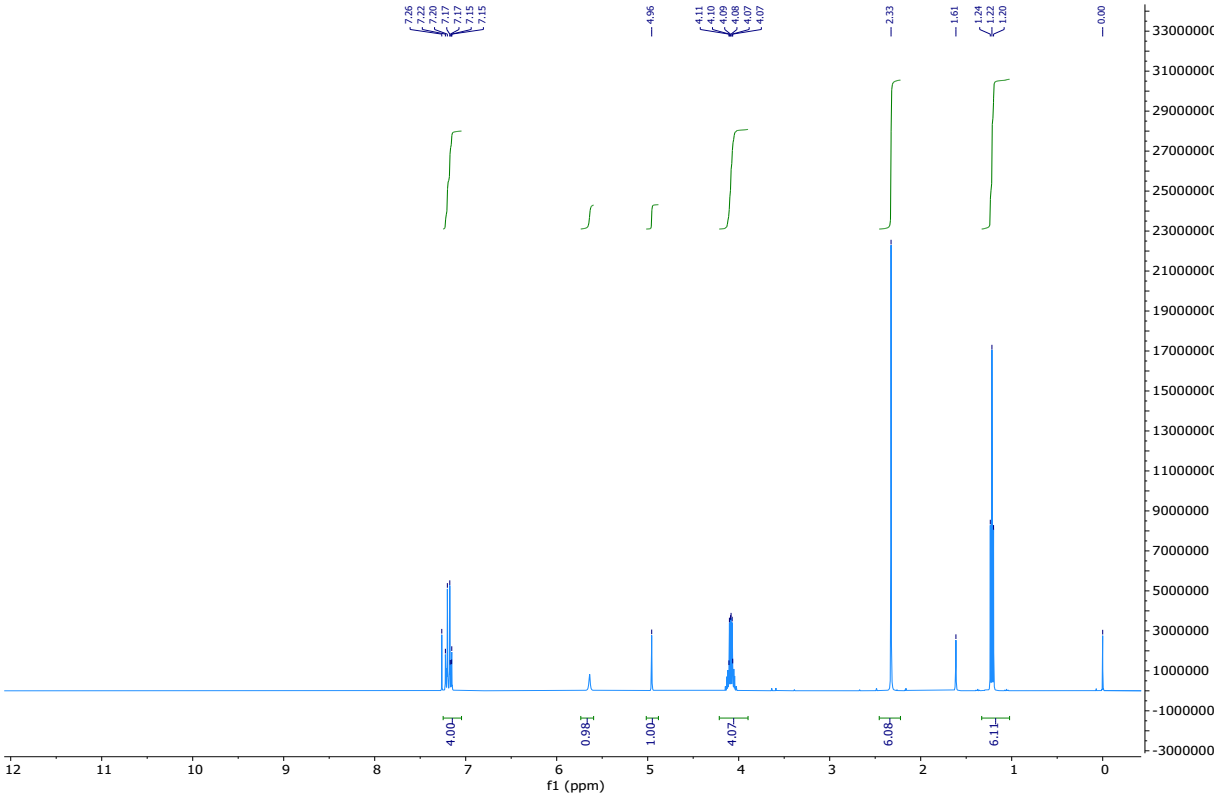


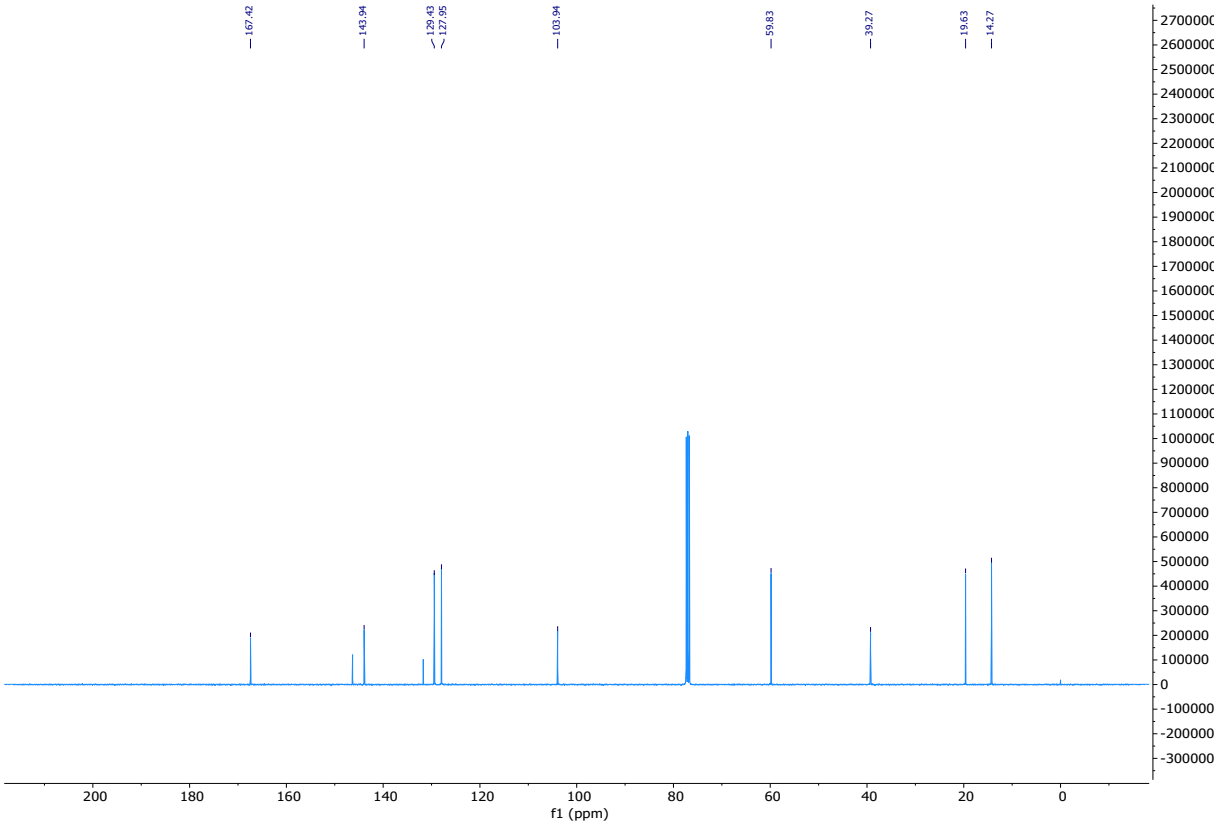
Diethyl 2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate 1c



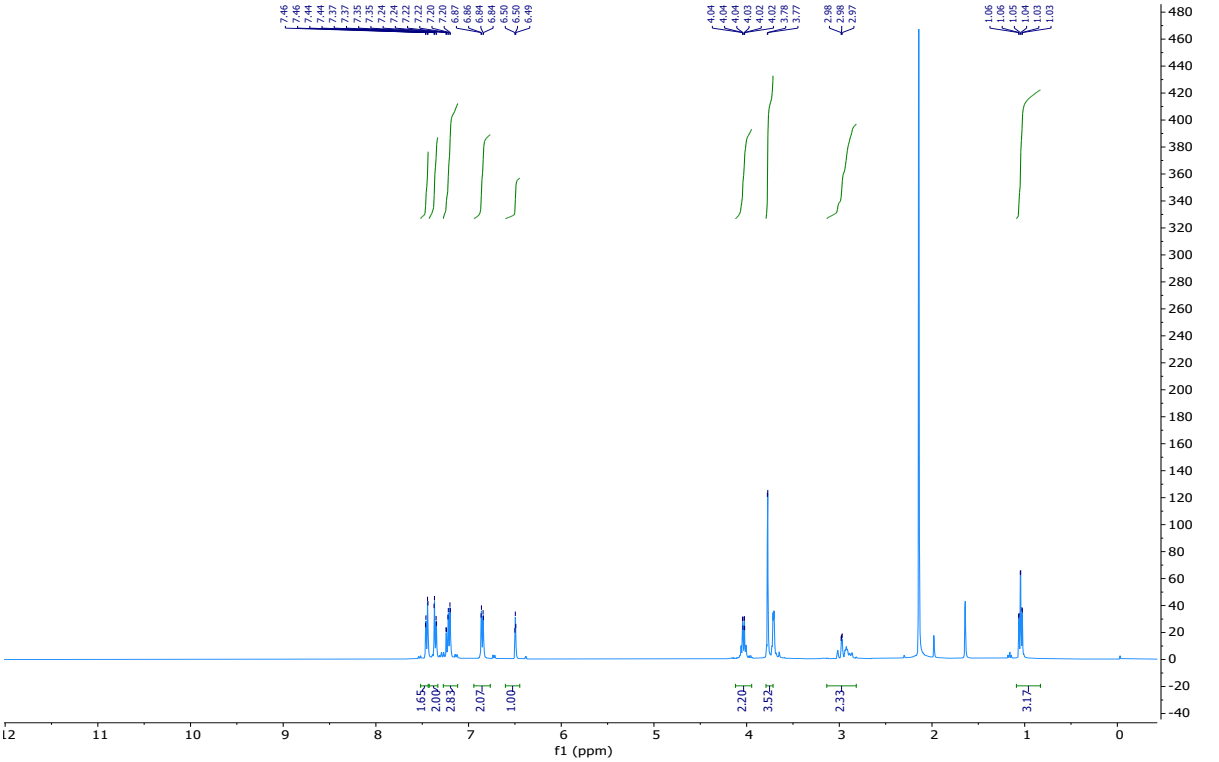


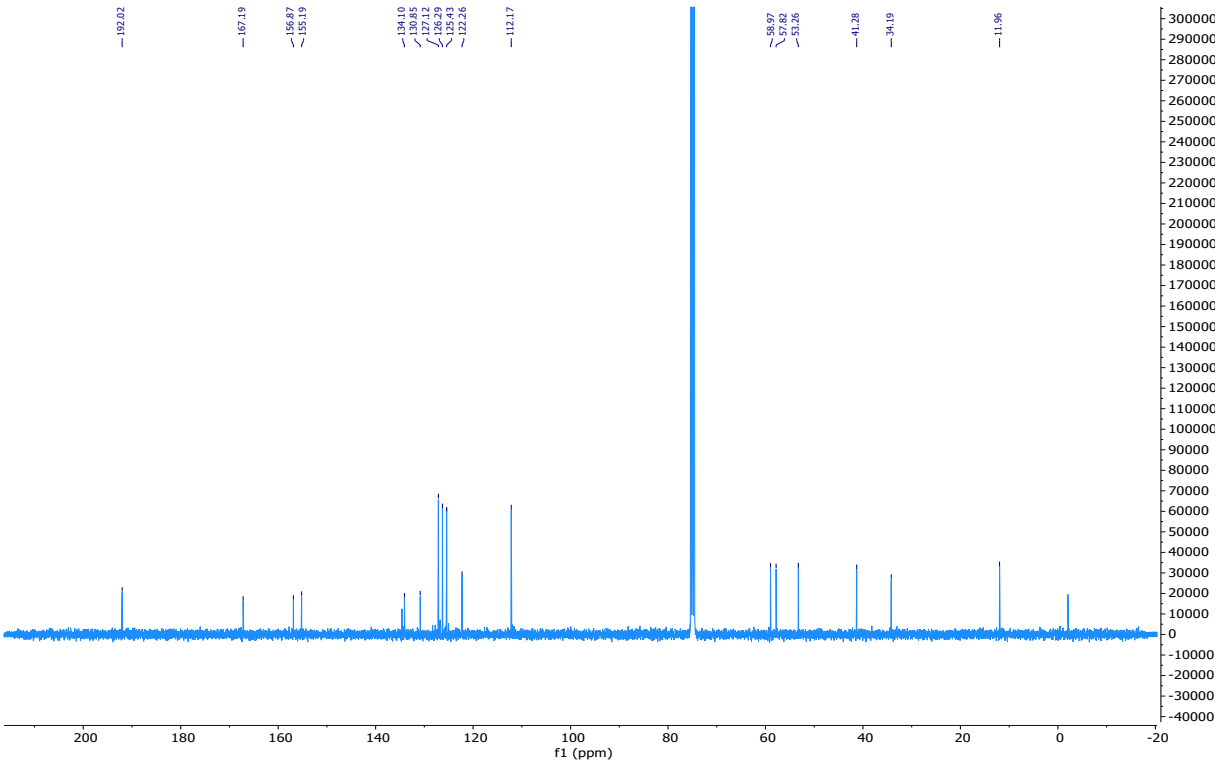
Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 1d



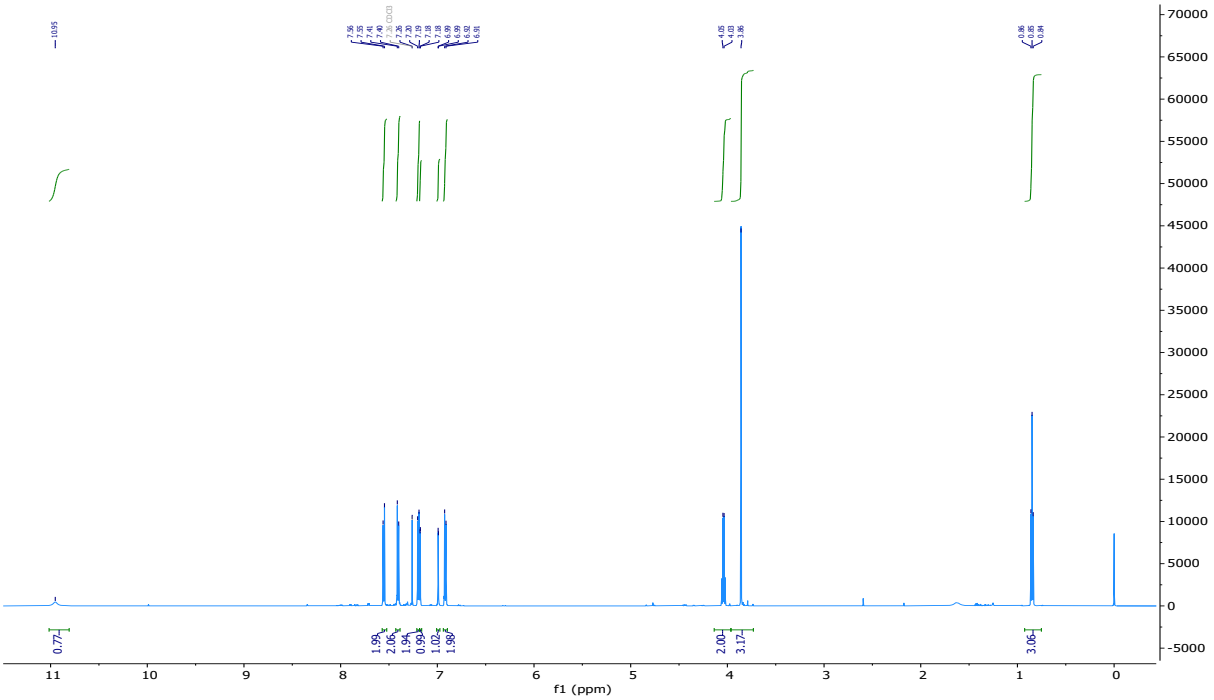


Methyl 4-chloro-4''-methoxy-5'-oxo-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate 5

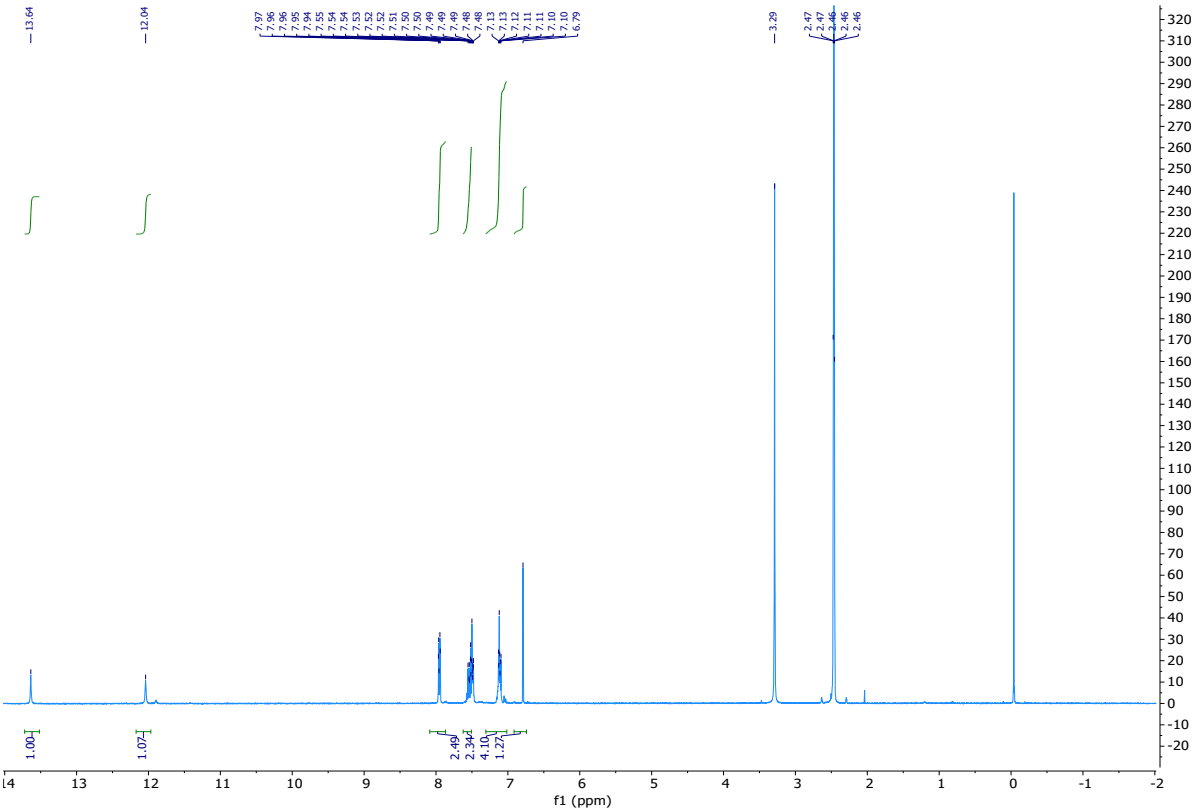


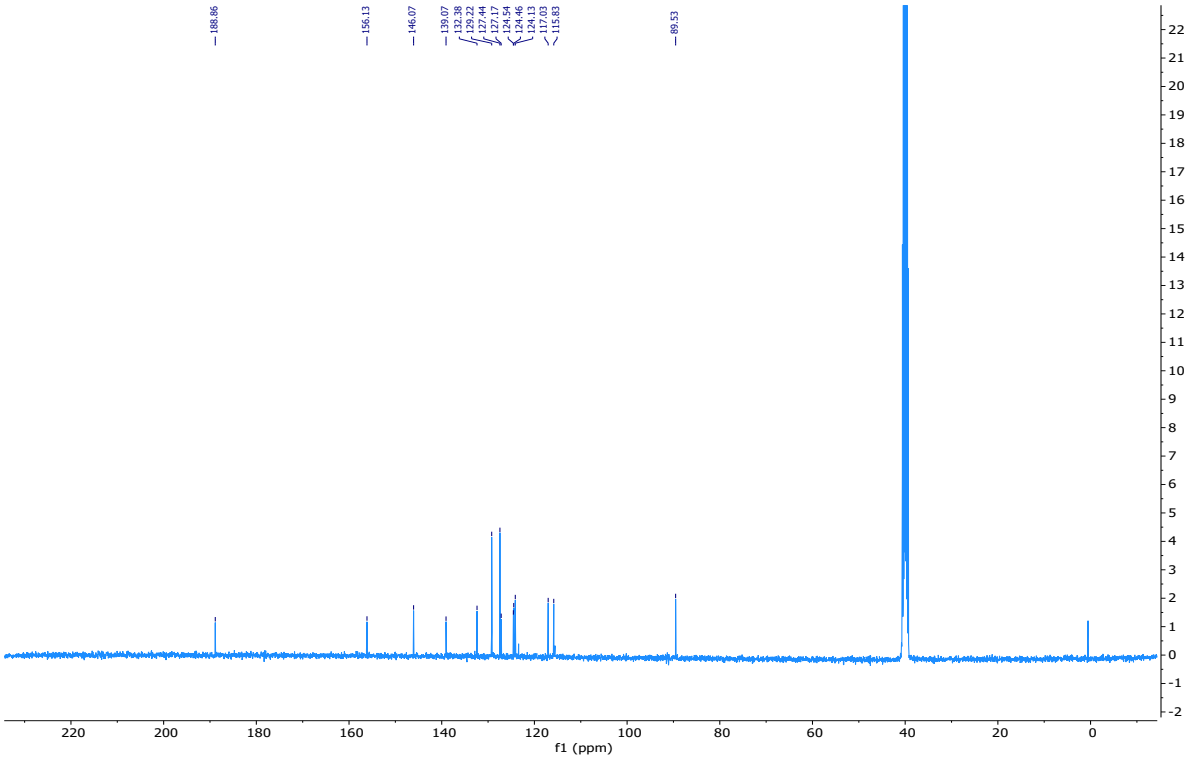


Ethyl 4-chloro-5'-hydroxy-4''-methoxy-[1,1':3',1''-terphenyl]-4'-carboxylate 6

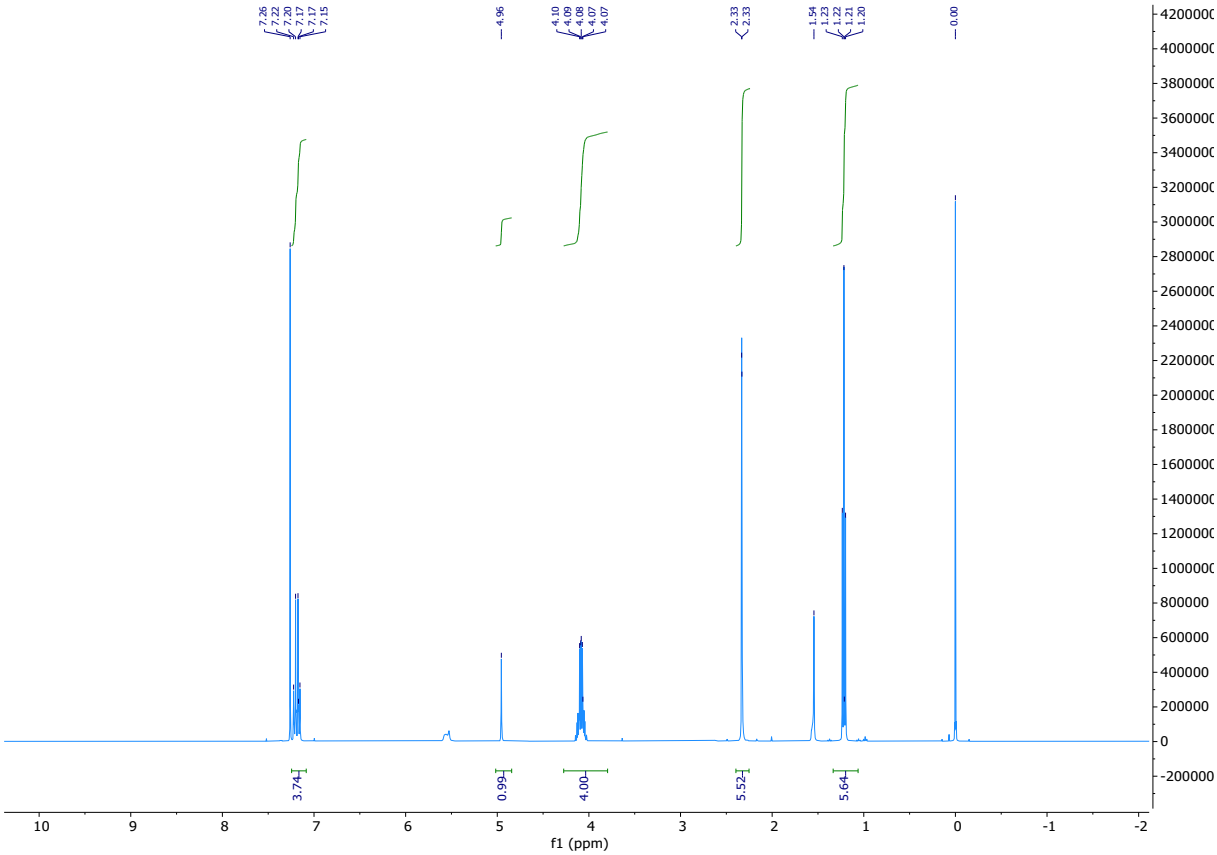


(Z)-2-(3-hydroxyquinoxalin-2(1H)-ylidene)-1-phenylethan-1-one 8




188.86
156.13
146.07
139.07
132.38
129.22
127.44
127.17
124.54
124.46
124.13
117.03
115.83
89.53
f1 (ppm)

1d oxidation assay in acetonitrile using BIO-P1, at room temperature



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