Supporting Information

Four-Component Synthesis of Polyhydroquinolines under Catalyst- and Solvent-Free Conventional Heating Conditions: Mechanistic Studies

Pipattra Mayurachayakul,[a] Wanchai Pluempanupat,[b] Choladda Srisuwannaket[a] and Oraphin Chantarasriwong*[a]

[a]Organic Synthesis, Electrochemistry & Natural Product Research Unit, Department of Chemistry, Faculty of Science, King Mongkut's University of Technology Thonburi, 126 Pracha Uthit Rd., Bang Mod, Thung Khru, Bangkok 10140, Thailand.

[b]Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, and Special Research Unit for Advanced Magnetic Resonance, Kasetsart University, Bangkok 10900, Thailand.

*E-mail: oraphin.cha@kmutt.ac.th

Table of Contents

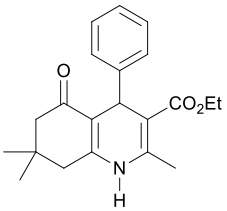
1. General procedures

Unless indicated, all commercially available reagents were purchased at the highest commercial quality and were used as received without further purification. Column chromatography was performed on silica gel (SILICYCLE *UltraPure* SILICA GELS, SiliaFlah® G60, 70-230 mesh). The progress of all the reactions was monitored by thin-layer chromatography (TLC) using sheets precoated with silica gel-60 F254 to a thickness of 0.5 mm (Merck), and compounds were visualized by irradiation with UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 or 500 MHz Bruker instrument. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak reference ($CDCl_3$), with the abbreviations s, br s, d, t, q, m, denoting singlet, broad singlet, doublet, triplet, quartet, multiplet, respectively. *J* is a coupling constant given in Hertz (Hz). High resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF mass spectrometer under electrospray ionization (ESI) conditions. Melting points were measured using a SANYO melting point apparatus. Gas chromatograph-mass spectrometer (GC-MS) were recorded on an Agilent Technologies (GC-MS conditions: column DB-5, 11 m; initial oven temp. 50 ℃ for 3 min followed by a 40 ℃/min ramp to 280 ℃, thereafter constant temperature, hold time 10 min and run time 18.75 min; injection temperature 250 ℃; column flow 2.0 mL/min; total flow 16.909 psi; split ratio 10; ion source 250 ℃; interface temperature 280 ℃; Mass spectrometer detector (MSD) conditions: column HP-5ms Ultra Inert -60 ℃ to 325 ℃: 30m × 250 µm × 0.25 µm; In: back SS inlet He; Out: MSD; gain factor: 1.000; solvent delay 3 min; start mass: 45; end mass: 450; threshold: 180; scan speed: 1.562 [N = 2] µ/s; frequency: 3.6 scans/sec; cycle time: 279.26 ms; step size: 0.1 m/z).

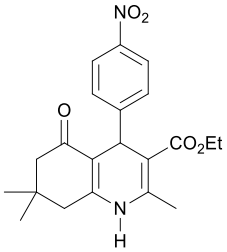
2. General procedure for the synthesis of polyhydroquinolines 5

The reaction mixture of selected aromatic aldehydes (**1**, 1 mmol, 1 equiv.), dimedone (**2**, 140.2 mg, 1 mmol, 1 equiv.), ethyl acetoacetate (**3**, 130 µL, 1 mmol, 1 equiv.) and ammonium acetate (**4**, 115.6 mg, 1.5 mmol, 1.5 equiv.) was heated with stirring in a seal tube at 100 ℃. After 5 min or indicated time in Table 2, the reaction mixture was cooled to room temperature and cold water (1 mL) was added. Then the reaction mixture was kept in ice bath for 5 min to obtain a solid. The resulting solid was filtered and recrystallized from ethanol or purified by silica gel column chromatography (EtOAc-hexane) to give polyhydroquinolines **5**.

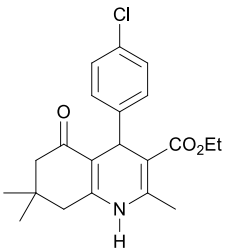
3. Characterization data of polyhydroquinolines 5



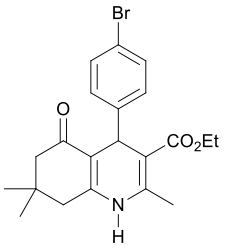
Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5a**):[1, 2] White solid; R_f = 0.37 (50% EtOAc-hexane); m.p. 228-229 ˚C (lit.,[3] 228-229 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.04 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 2.11-2.30 (m, 4H), 2.35 (s, 3H), 4.03 (q, *J* = 7.1 Hz, 2H), 5.02 (s, 1H), 6.65 (br s, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 7.0 Hz, 2H).



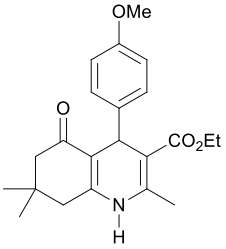
Ethyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5b**):[2, 4] White solid; R_f = 0.34 (50% EtOAc-hexane); m.p. 207-209 ˚C (lit.,[2] 207-209 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.06 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 2.11-2.35 (m, 4H), 2.39 (s, 3H), 4.03 (q, *J* = 6.8 Hz, 2H), 5.13 (s, 1H), 6.32 (br s, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 8.05 (d, *J* = 8.7 Hz, 2H).



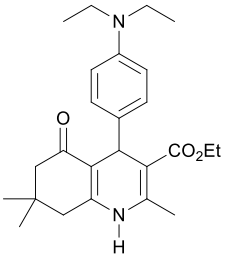
Ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5c**):[2, 5] White solid; R_f = 0.37 (50% EtOAc-hexane); m.p. 246-247 ˚C (lit.,[5] 245-246 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.05 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H), 2.11-2.31 (m, 4H), 2.36 (s, 3H), 4.03 (q, *J* = 7.1 Hz, 2H), 4.99 (s, 1H), 6.51 (br s, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H).



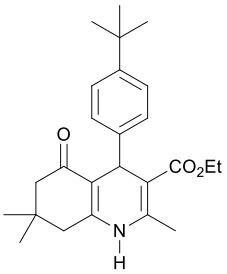
Ethyl 4-(4-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5d**):[1, 6-7] White solid; R_f = 0.34 (50% EtOAc-hexane); m.p. 252-253 ˚C (lit.,[8] 251-252 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.05 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 2.12-2.32 (m, 4H), 2.37 (s, 3H), 4.03 (q, *J* = 7.1 Hz, 2H), 4.98 (s, 1H), 6.41 (br s, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H).



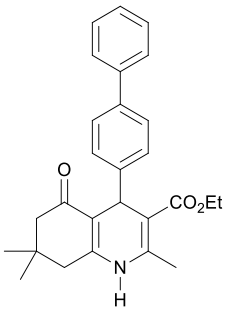
Ethyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5e**):[2, 7] White solid; R_f = 0.31 (50% EtOAc-hexane); m.p. 255-256 ˚C (lit.,[2] 255-256 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.02 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 2.09-2.25 (m, 4H), 2.31 (s, 3H), 3.69 (s, 3H), 4.04 (q, *J* = 7.1 Hz, 2H), 4.96 (s, 1H), 6.63 (br s, 1H), 6.70 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H).



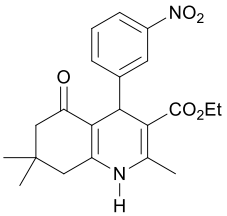
Ethyl 4-(4-(diethylamino)phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5f**): White solid; R_f = 0.31 (50% EtOAc-hexane); m.p. 225-226 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.03 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 6H), 1.20 (t, *J* = 7.1 Hz, 3H), 2.10-2.29 (m, 4H), 2.32 (s, 3H), 3.25 (q, *J* = 7.1 Hz, 4H), 4.05 (q, *J* = 7.1 Hz, 2H), 4.92 (s, 1H), 6.43 (br s, 1H), 6.64 (m, 2H), 7.13 (m, 2H).



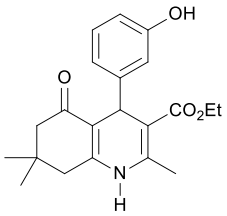
Ethyl 4-(4-(*tert*-butyl)phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5g**):[1] White solid; R_f = 0.48 (50% EtOAc-hexane); m.p. 214-215 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.06 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.22 (s, 9H), 2.15-2.30 (m, 4H), 2.33 (s, 3H), 4.05 (q, *J* = 7.1 Hz, 2H), 5.00 (s, 1H), 6.55 (br s, 1H), 7.16 (s, 4H).



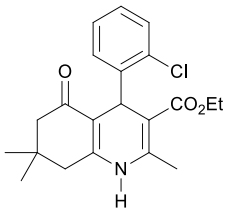
Ethyl 4-(biphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8- hexahydroquinoline-3-carboxylate (**5h**):[1, 9] White solid; R_f = 0.48 (50% EtOAc-hexane); m.p. 195-197 ˚C (lit.,[10] 196-198 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.05 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 2.13 – 2.32 (m, 4H), 2.37 (s, 3H), 4.06 (q, *J* = 7.1 Hz, 2H), 5.07 (s, 1H), 6.63 (br s, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.34-7.42 (m, 6H), 7.50 (d, *J* = 7.1 Hz, 2H).



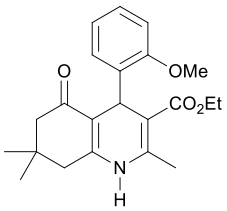
Ethyl 2,7,7-trimethyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5i**):[5-6, 11] White solid; R_f = 0.40 (50% EtOAc-hexane); m.p. 186-187 ˚C (lit.,[11] 177-178 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.07 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 2.12-2.26 (m, 4H), 2.31 (s, 3H), 4.04 (q, *J* = 7.1 Hz, 2H), 5.13 (s, 1H), 6.54 (br s, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.7 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 8.08 (s, 1H).



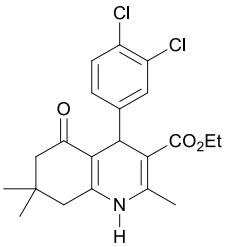
Ethyl 4-(3-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5j**):[12] White solid; R_f = 0.43 (50% EtOAc-hexane); m.p. 221-223 ˚C (lit.,[13] 221-223 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.04 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 2.18-2.28 (m, 4H), 2.36 (s, 3H), 4.04 (q, *J* = 7.1 Hz, 2H), 5.00 (s, 1H), 6.29 (br s, 1H), 6.58 (d, *J* = 7.2 Hz, 1H), 6.81 (d, *J* = 7.2 Hz, 2H), 7.03 (t, *J* = 8.0 Hz, 1H).



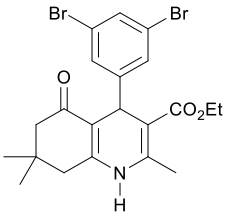
Ethyl 4-(2-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5k**):[1] White solid; R_f = 0.34 (50% EtOAc-hexane); m.p. 208-210 ˚C (lit.,[14] 208-210 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.04 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 2.09-2.25 (m, 4H), 2.30 (s, 3H), 4.02 (q, *J* = 7.1 Hz, 2H), 5.36 (s, 1H), 6.68 (br s, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 9.4 Hz, 1H).



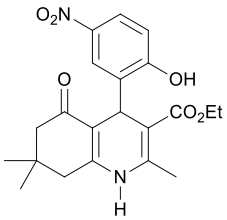
Ethyl 4-(2-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5l**):[15] White solid; R_f = 0.26 (50% EtOAc-hexane); m.p. 252-253 ˚C (lit.,[16] 248-250 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.04 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 2.08-2.22 (m, 4H), 2.30 (s, 3H), 3.77 (s, 3H), 3.99 (q, *J* = 7.1 Hz, 2H), 5.21 (s, 1H), 6.47 (br s, 1H), 6.77 (t, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H).



Ethyl 4-(3,4-dichlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5m**):[5] White solid; R_f = 0.34 (50% EtOAc-hexane); m.p. 227-228 ˚C (lit.,[5] 213-225 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.06 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 2.14-2.33 (m, 4H), 2.38 (s, 3H), 4.05 (q, *J* = 7.1 Hz, 2H), 4.98 (s, 1H), 6.35 (br s, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.32 (s, 1H).



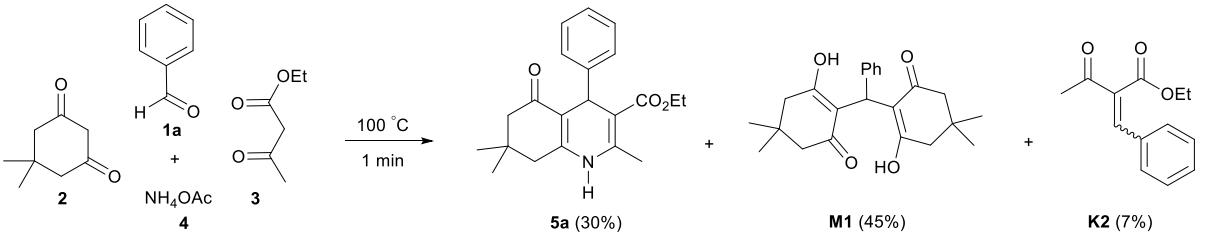
Ethyl 4-(3,5-dibromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5n**): White solid; R_f = 0.43 (50% EtOAc-hexane); m.p. 253-254 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.07 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 2.19-2.33 (m, 4H), 2.37 (s, 3H), 4.06 (q, *J* = 7.2 Hz, 2H), 4.96 (s, 1H), 6.37 (br s, 1H), 7.34 (s, 2H), 7.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.39, 19.71, 27.46, 29.50, 33.03, 36.95, 41.26, 50.51, 60.33, 105.63, 111.19, 122.59, 130.35, 131.94, 144.29, 150.83, 166.99, 195.46; HRMS calcd for $C_{21}H_{24}Br_2NO_3$ $(M+H)^+$ 498.0102, found 498.0120.



Ethyl 4-(2-hydroxy-5-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5o**): White solid; R_f = 0.43 (50% EtOAc-hexane); m.p. 229-230 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H), 1.09 (s, 3H), 2.24-2.36 (m, 4H), 2.52 (s, 3H), 3.97 (q, *J* = 7.1 Hz, 2H), 5.08 (s, 1H), 6.15 (br s, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 7.82 (s, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 10.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.89, 19.43, 27.25, 28.97, 30.31, 32.79, 41.36, 49.78, 60.32, 105.71, 110.64, 118.50, 124.26, 124.66, 134.47, 141.40, 144.52, 151.30, 160.19, 166.27, 198.53; HRMS calcd for $C_{21}H_{25}N_2O_6$ $(M+H)^+$ 401.1713, found 401.1713.

4. Experiments of investigations on the mechanism

4.1 Four-component reaction of benzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate

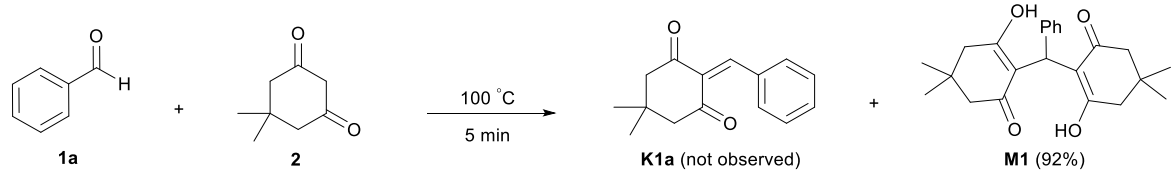


A mixture of benzaldehyde (**1a**, 315 μL, 3 mmol, 1 equiv.), dimedone (**2**, 421.0 mg, 3 mmol, 1 equiv.), ethyl acetoacetate (**3**, 390 μL, 3 mmol, 1 equiv.) and ammonium acetate (**4**, 371.7 mg, 4.8 mmol, 1.6 equiv.) was heated with stirring in a seal tube at 100 ℃. After 1 min, the reaction mixture was cooled to room temperature. Then the reaction mixture was purified by silica gel column chromatography (30% EtOAc-hexane) to give compounds **5a** (300.4 mg, 30%), **M1** (249.1 mg, 45%) and **K2** (48.4 mg, 7%).

2,2'-(Phenylmethylene)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (**M1**):[17] White solid; R_f = 0.80 (50% EtOAc-hexane); m.p. 194-195 ˚C (lit.,[18] 193-195 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 6H), 1.22 (s, 6H), 2.27-2.47 (m, 8H), 5.52 (s, 1H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 2H), 11.89 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 27.53, 29.47, 31.61, 32.94, 46.64, 47.26, 115.79, 126.04, 128.41, 138.26, 189.60, 190.66; HRMS calcd for $C_{23}H_{29}O_4$ $(M+H)^+$ 369.2066, found 369.2061.

(*Z* and *E*)-ethyl 2-benzylidene-3-oxobutanoate (**K2**):[19] Yellow oil; R_f = 0.31 (10% EtOAc-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): a mixture of *Z* and *E* isomers (1:2 ratio); *Z*-isomer: δ 1.25 (t, *J* = 7.1 Hz, 3H), 2.40 (s, 3H), 4.31 (q, *J* = 7.1 Hz, 2H), 7.35-7.38 (m, 5H), 7.55 (s, 1H); *E*-isomer: δ 1.31 (t, *J* = 7.1 Hz, 3H), 2.32 (s, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 7.35-7.38 (m, 5H), 7.65 (s, 1H).

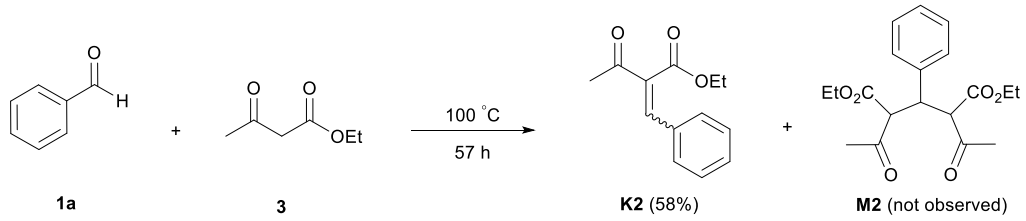
4.2 Two-component reaction of benzaldehyde and dimedone



A mixture of benzaldehyde (**1a**, 715 μL, 7 mmol, 1 equiv.) and dimedone (**2**, 0.9815 g, 7 mmol, 1 equiv.) was heated with stirring in a seal tube at 100 ˚C. After 5 min, the reaction mixture was cooled to room temperature. The crude mixture was purified by silica gel column

chromatography (9% EtOAc-hexane) to give compound **M1** as a white solid (1.1841 g, 92% yield).

4.3 Two-component reaction of benzaldehyde and ethyl acetoacetate



A mixture of benzaldehyde (**1a**, 715 µL, 1 mmol, 1 equiv.) and ethyl acetoacetate (**3**, 895 µL, 1 mmol, 1 equiv.) was heated with stirring in a seal tube at 100 ˚C. After 57 hours, the reaction mixture was cooled to room temperature. The crude mixture was purified by silica gel column chromatography (50% CH_2Cl_2-hexane) to give compound **K2** as a yellow oil (887.0 mg, 58% yield). The purity of this compound determined by GC-MS analysis is 93% (t_R 7.69 min, m/z found 218.1, calcd for $C_{13}H_{14}O_3$ 218.1).

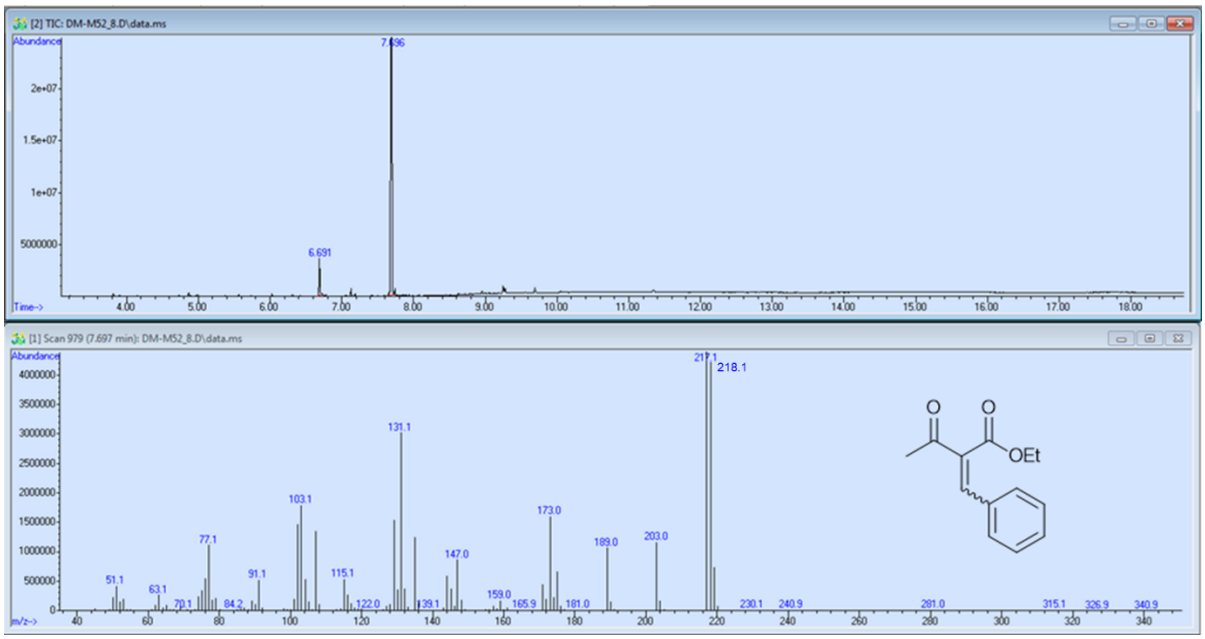
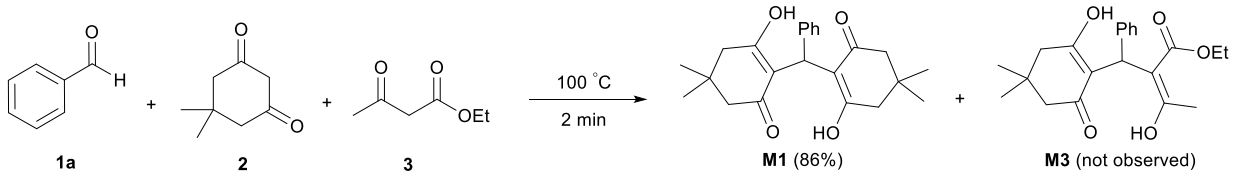


Figure S1: The GC-MS of compound **K2**

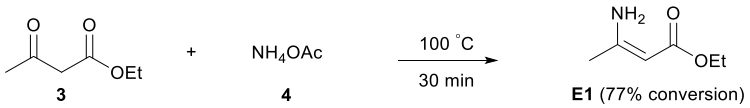
4.4 Competitive three-component reaction of benzaldehyde, dimedone and ethyl acetoacetate



A mixture of benzaldehyde (**1a**, 105 µL, 1 mmol, 1 equiv.), dimedone (**2**, 140.6 mg, 1 mmol, 1 equiv.) and ethyl acetoacetate (**3**, 130 µL, 1 mmol, 1 equiv.) was heated with stirring in a seal tube at 100 ˚C. After 2 min, the reaction mixture was cooled to room temperature. The crude mixture was purified by silica gel column chromatography (9% EtOAc-hexane) to give compound **M1** as a white solid (157.9 mg, 86% yield).

4.5 Procedure for synthesis of ethyl 3-aminobut-2-enoate (**E1**)

Method A:



A mixture of ethyl acetoacetate (**3**, 895 µL, 7 mmol, 1 equiv.) and ammonium acetate (**4**, 836.1 mg, 10.5 mmol, 1.5 equiv.) was heated with stirring in a seal tube at 100 ˚C. The reaction was analyzed by GC-MS after 30 min and the analysis shows 77% conversion (t_R 6.11 min, m/z found 129.1, calcd for $C_6H_{11}NO_2$ 129.1).

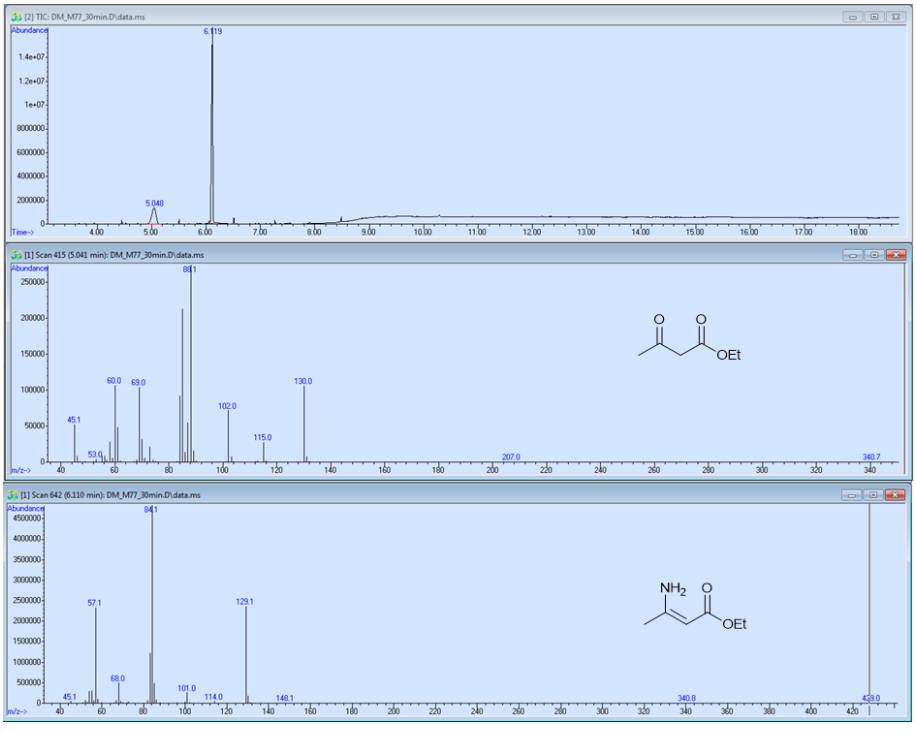
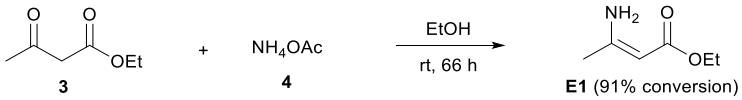


Figure S2: The GC-MS of compound **E1** (method A)

Method B:[20]



A mixture of ethyl acetoacetate (**3**, 510 µL, 4 mmol, 1 equiv.) and ammonium acetate (**4**, 536.3 mg, 6.96 mmol, 1.74 equiv.) was stirred in EtOH (1 mL) at room temperature. GC-MS analysis after 27 hours shows 64% conversion. Then, ammonium acetate (**4**, 530.8 mg, 6.89 mmol, 1.72 equiv.) was added and the reaction mixture was stirred at room temperature for another 39 hours. GC-MS analysis after 66 hours (total time) reveals 91% conversion. (t_R 6.11 min, m/z found 129.1, calcd for $C_6H_{11}NO_2$ 129.0).

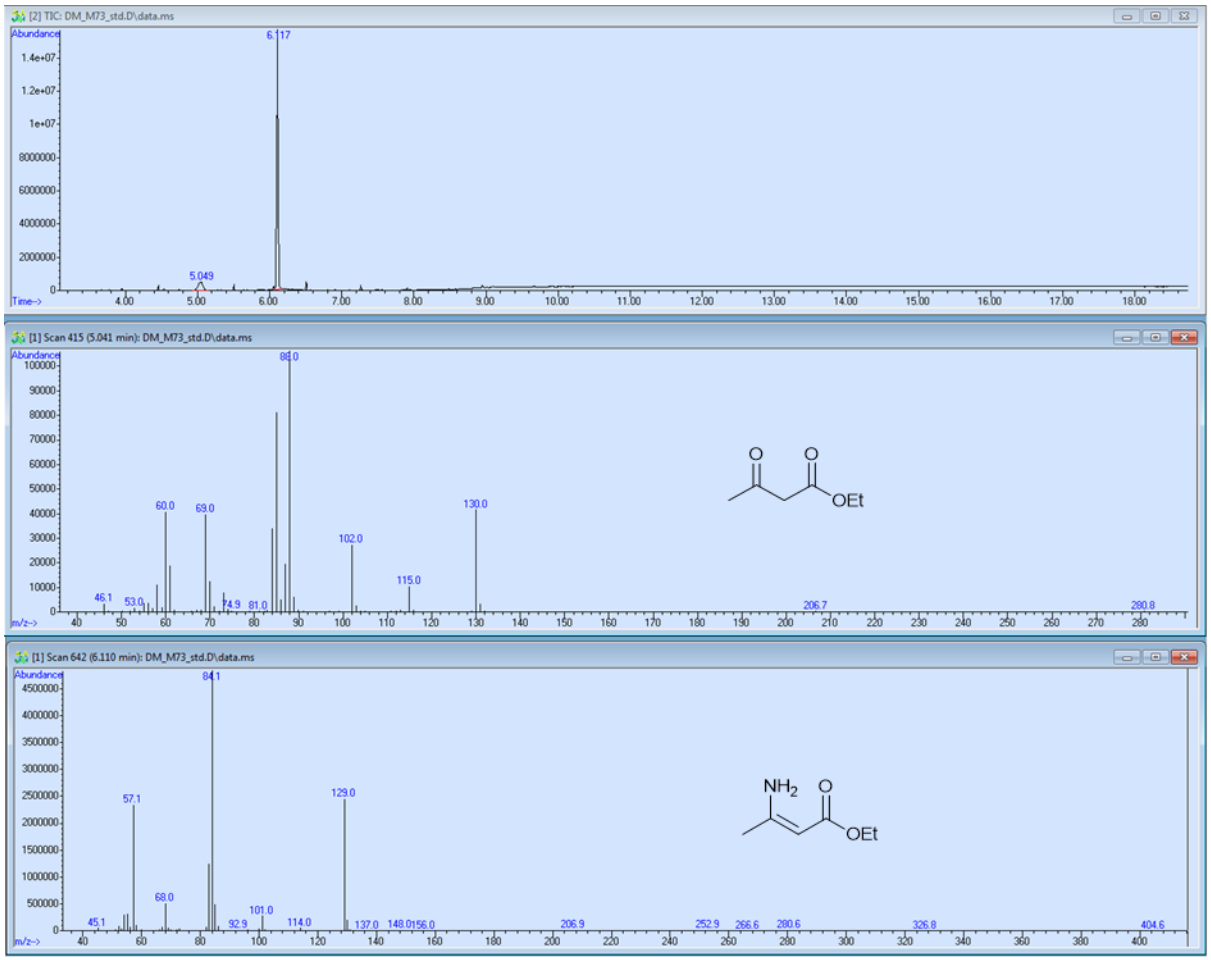
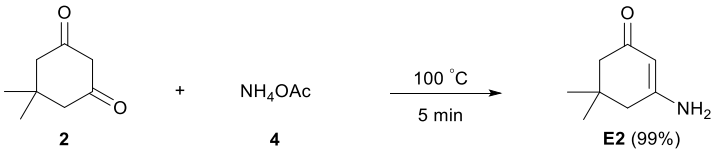


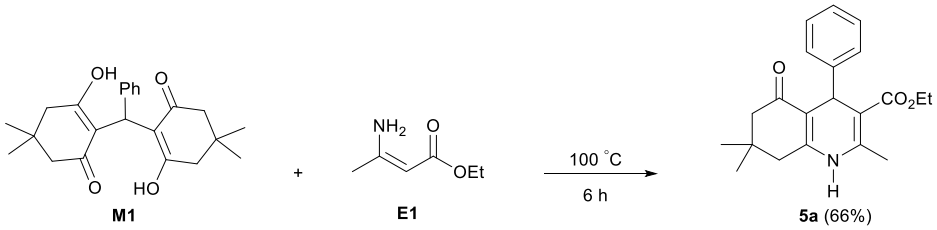
Figure S3: The GC-MS of compound **E1** (method B)

4.6 Procedure for synthesis of 3-amino-5,5-dimethylcyclohex-2-enone (**E2**)



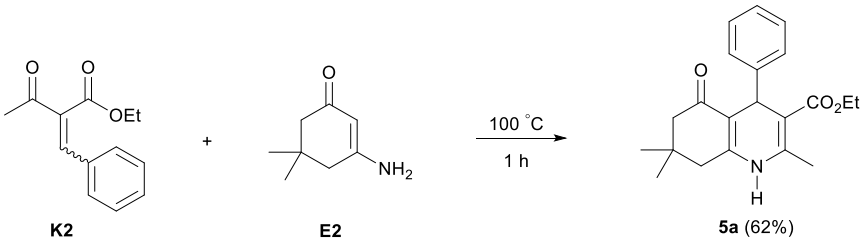
A mixture of dimedone (**2**, 981.6 mg, 7 mmol, 1 equiv.) and ammonium acetate (**4**, 840.8 mg, 10.9 mmol, 1.5 equiv.) was heated with stirring in a seal tube at 100 ˚C. After 5 min, the reaction mixture was cooled to room temperature. The crude mixture was purified by silica gel column chromatography (90% EtOAc-hexane) to give compound **E2** (961.8 mg, 99% yield) as a white solid. **E2**: R_f = 0.65 (50% MeOH-EtOAc); m.p. 166-168 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 6H), 2.16 (s, 2H), 2.25 (s, 2H), 5.42 (s, 1H), 5.93 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.53, 33.10, 42.85, 49.78, 99.33, 164.37, 197.38.

4.7 Two-component reaction of **M1** and **E1**

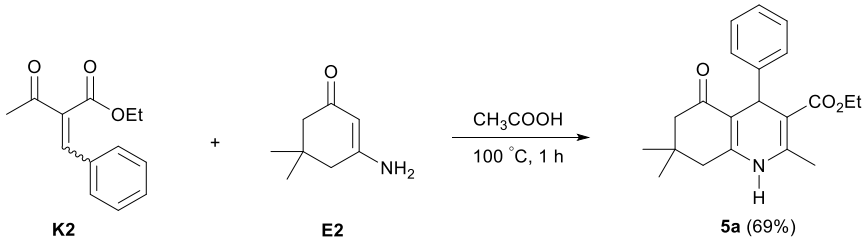


A mixture of **M1** (36.8 mg, 0.1 mmol, 1 equiv.) and **E1** (23.4 mg, 0.18 mmol, 1.8 equiv.) was heated with stirring in a seal tube at 100 ˚C. After 6 hours, the reaction mixture was cooled to room temperature. The crude mixture was purified by silica gel column chromatography (30% EtOAc-hexane) to give compound **5a** as a white solid (22.5 mg, 66% yield).

4.8 Two-component reaction of **K2** and **E2**



A mixture of **K2** (23.9 mg, 0.1 mmol, 1 equiv.) and **E2** (13.9 mg, 0.1 mmol, 1 equiv.) was heated with stirring in a seal tube at 100 ˚C. After 1 hour, the reaction mixture was cooled to room temperature. The crude mixture was purified by silica gel column chromatography (30% EtOAc-hexane) to give compound **5a** as a white solid (21.1 mg, 62% yield).



A mixture of **K2** (24.3 mg, 0.1 mmol, 1 equiv.), **E2** (13.8 mg, 0.1 mmol, 1 equiv.) and glacial acetic acid (6 µL, 0.1 mmol, 1 equiv.) were heated with stirring in a seal tube at 100 ˚C. After 1 hour, the reaction mixture was cooled to room temperature. The crude mixture was purified by silica gel column chromatography (30% EtOAc-hexane) to give compound **5a** as a white solid (23.4 mg, 69% yield).

5. The NMR spectra of polyhydroquinolines 5 and compounds M1, K2 and E2

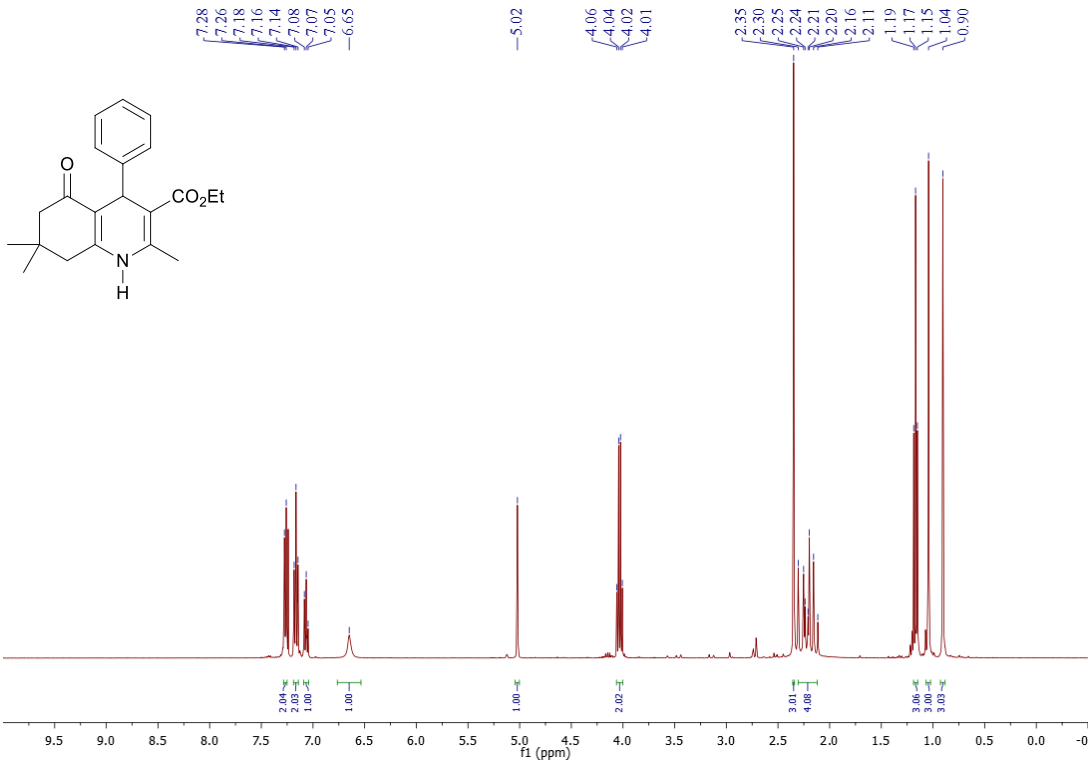


Figure S4: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5a**

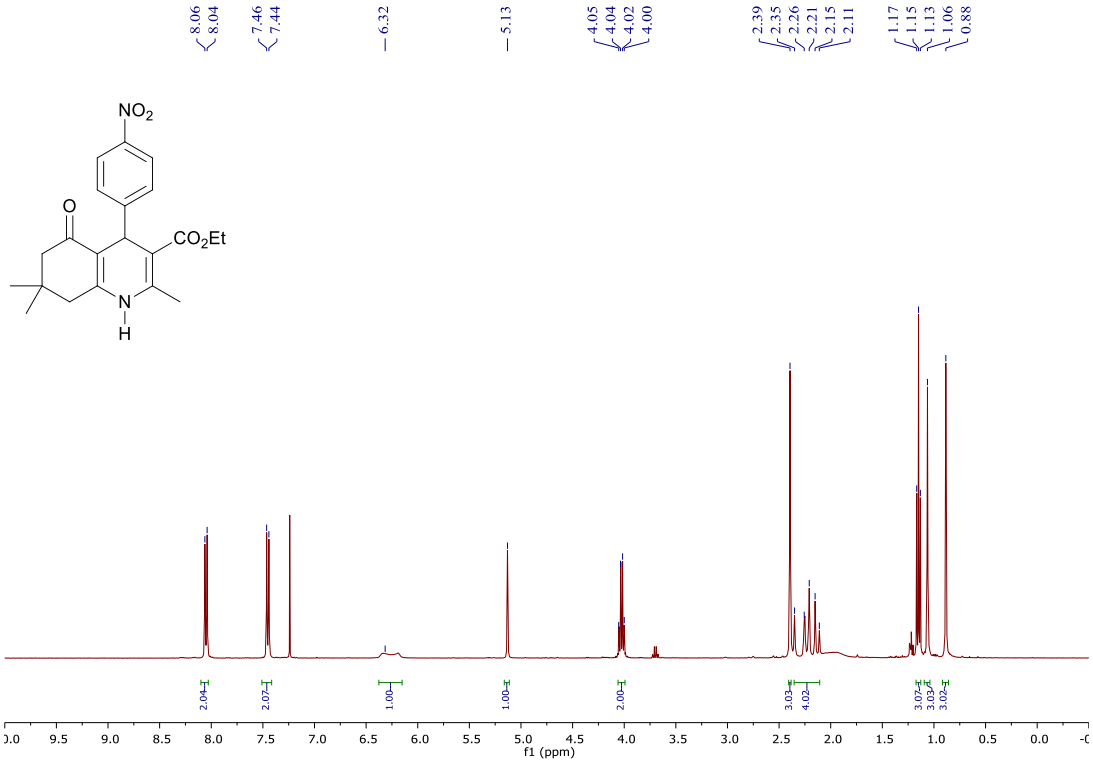


Figure S5: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5b**

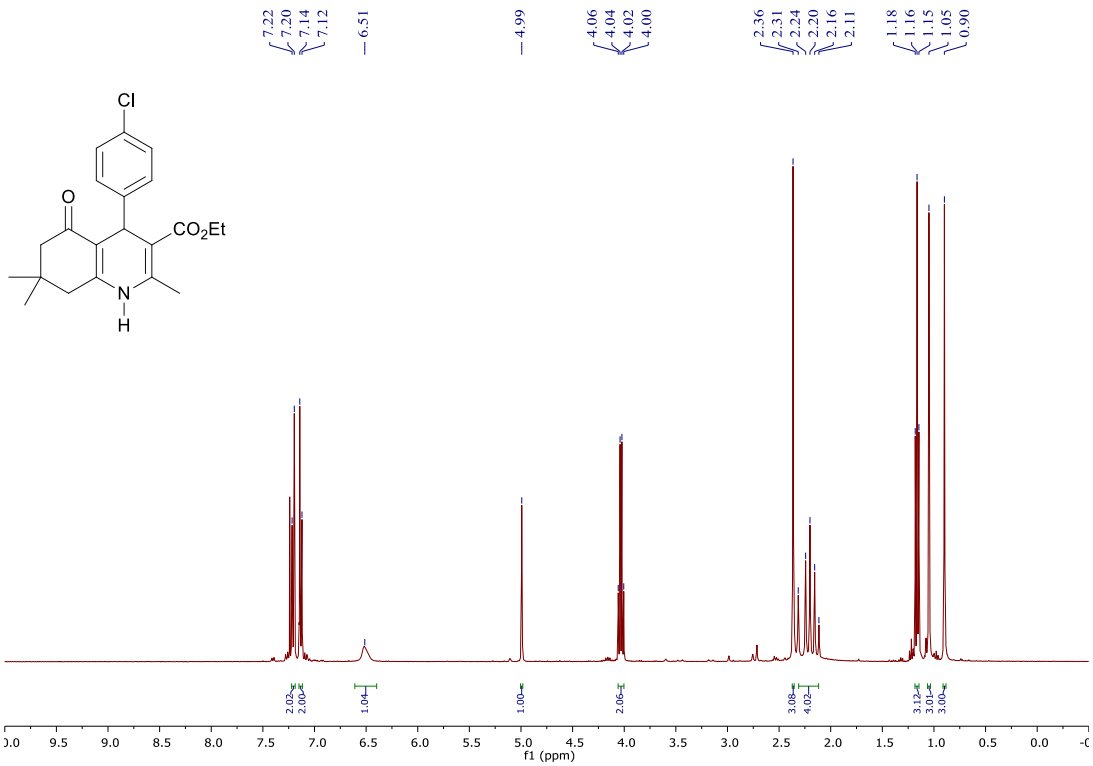


Figure S6: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5c**

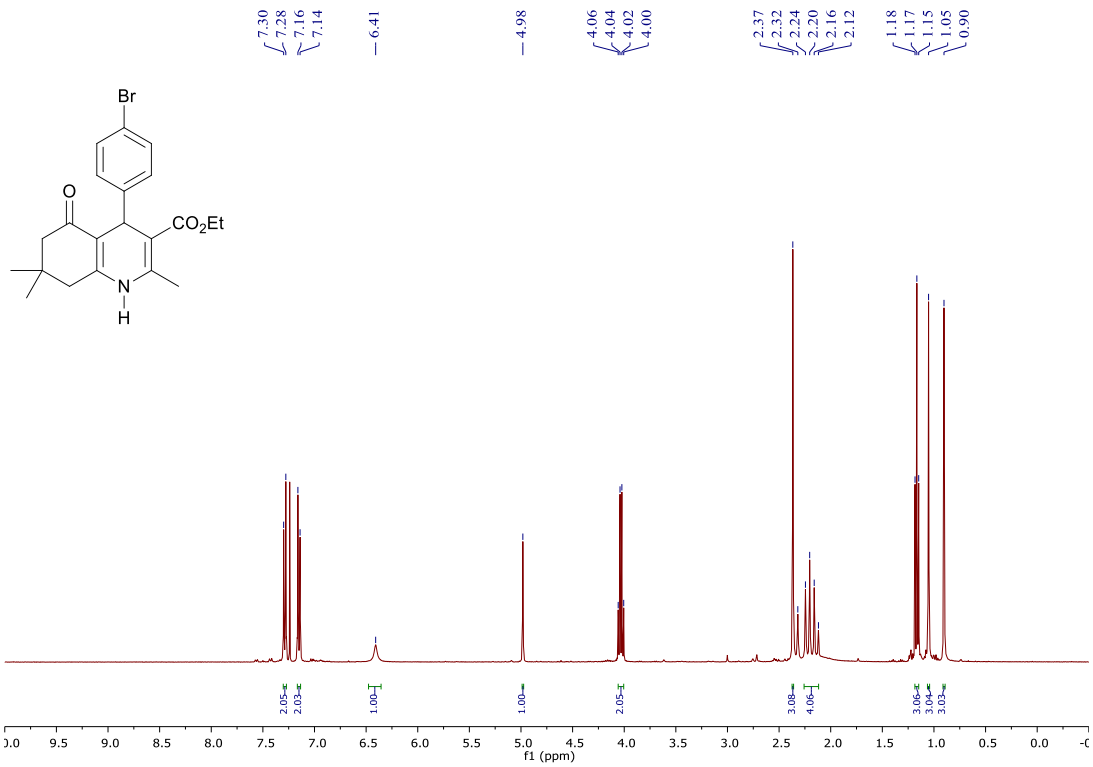


Figure S7: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5d**

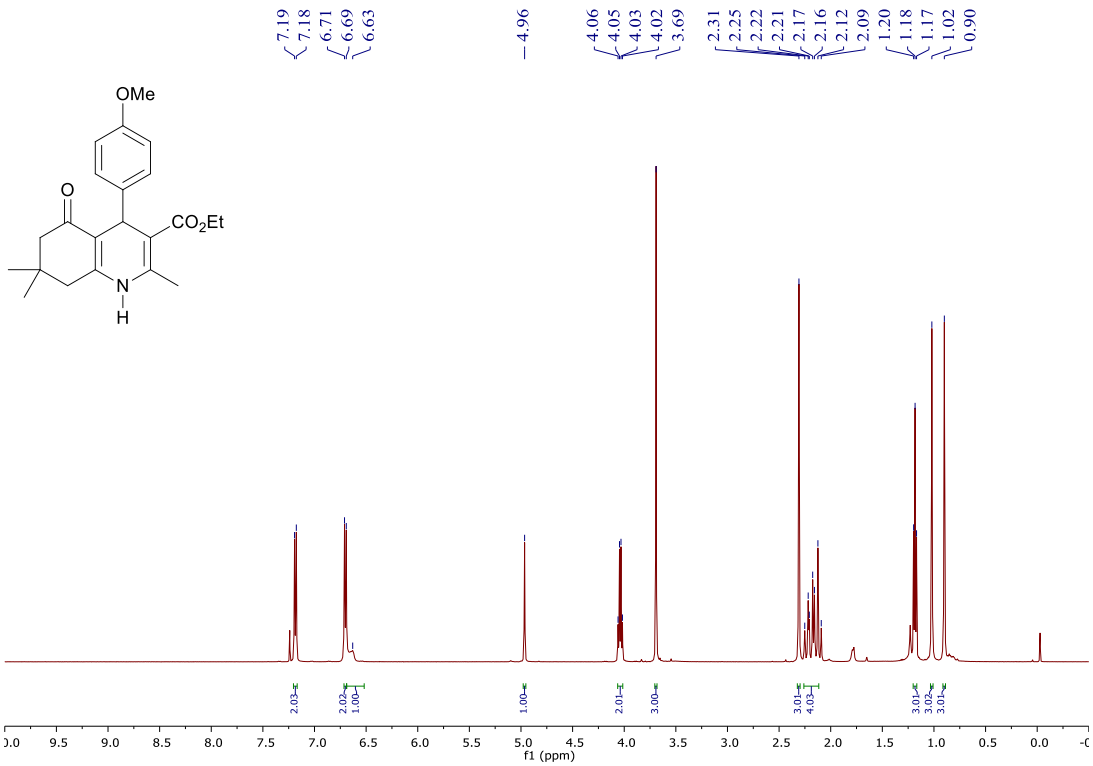


Figure S8: The ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **5e**

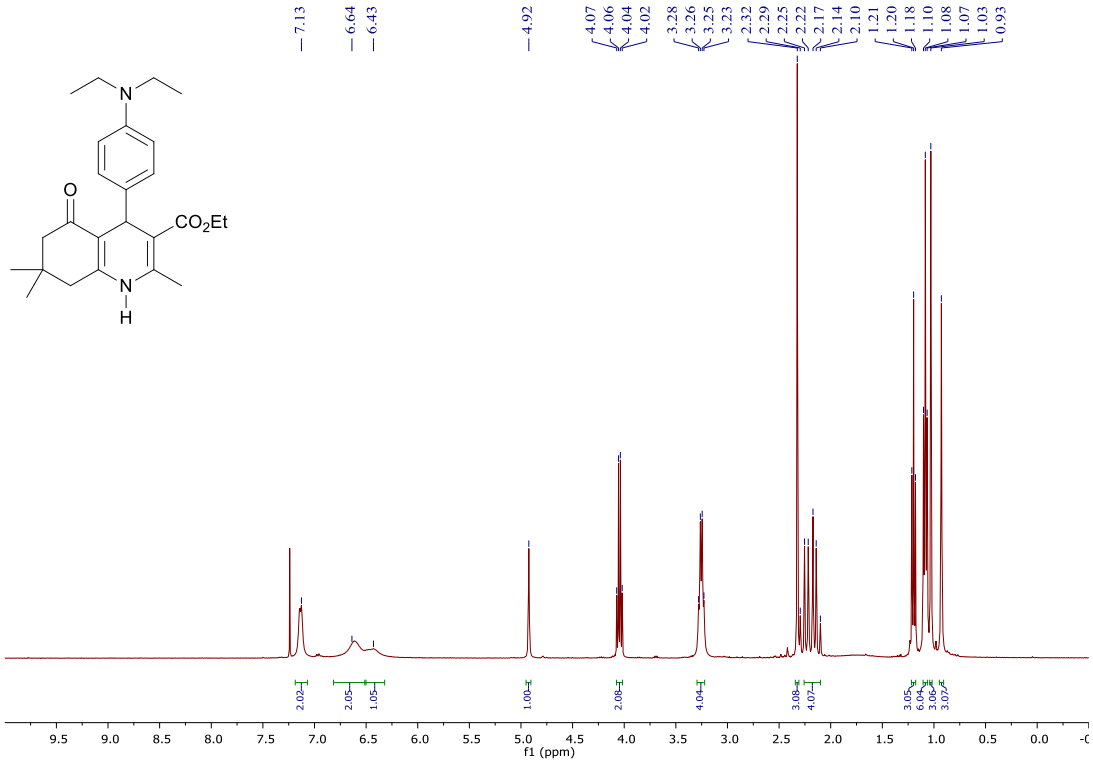


Figure S9: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5f**

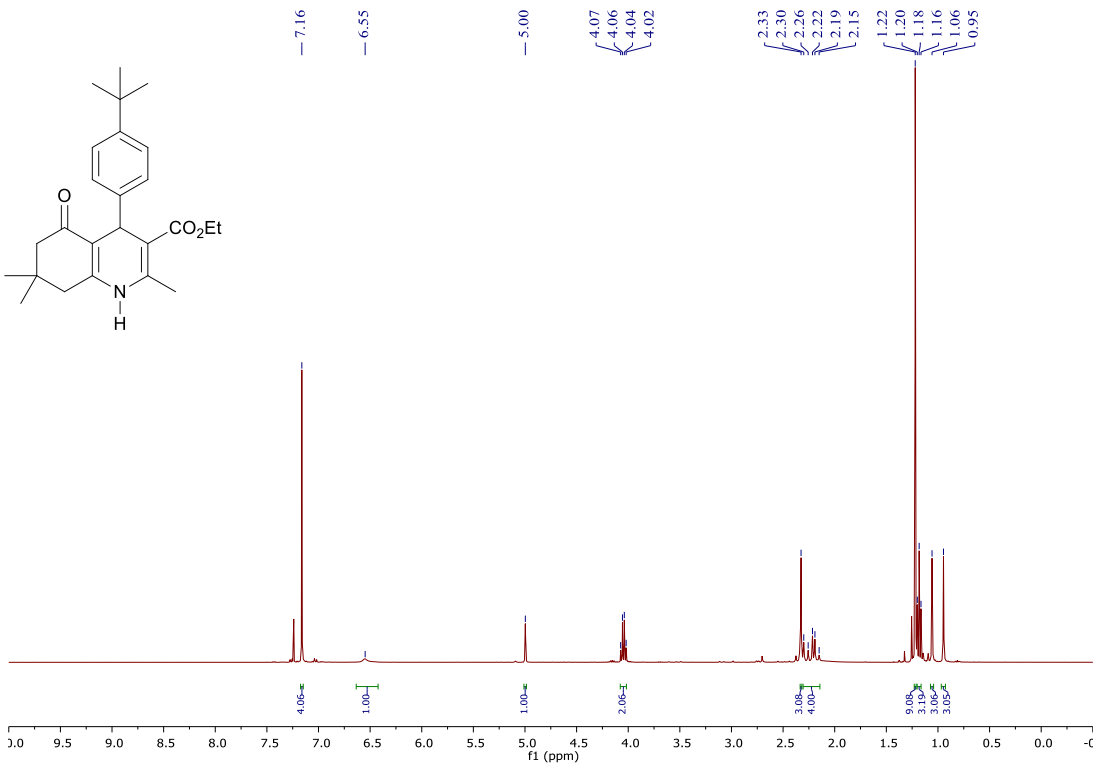


Figure S10: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5g**

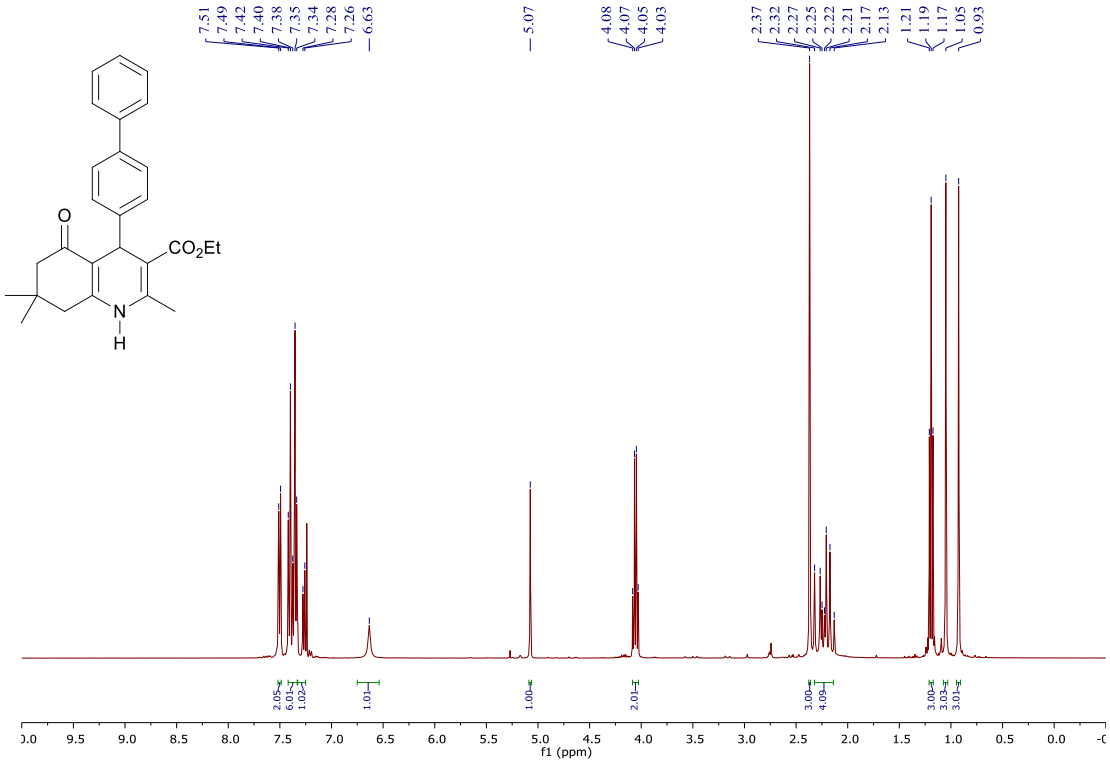


Figure S11: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5h**

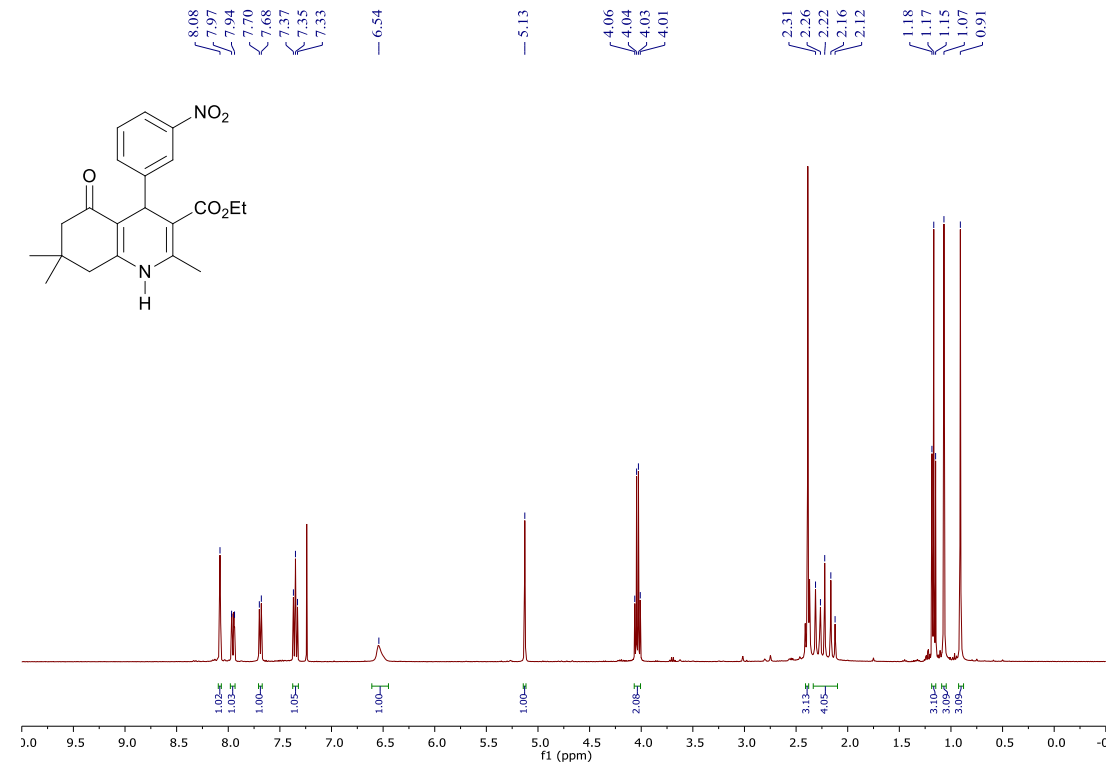


Figure S12: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5i**

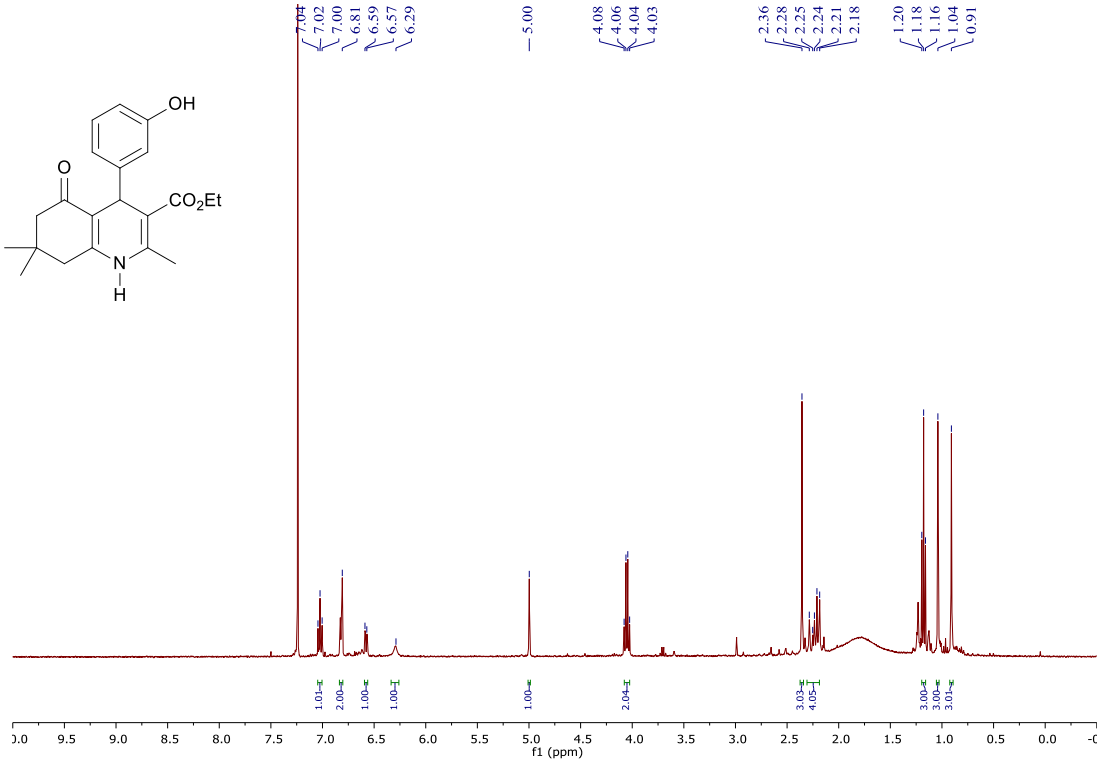


Figure S13: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5j**

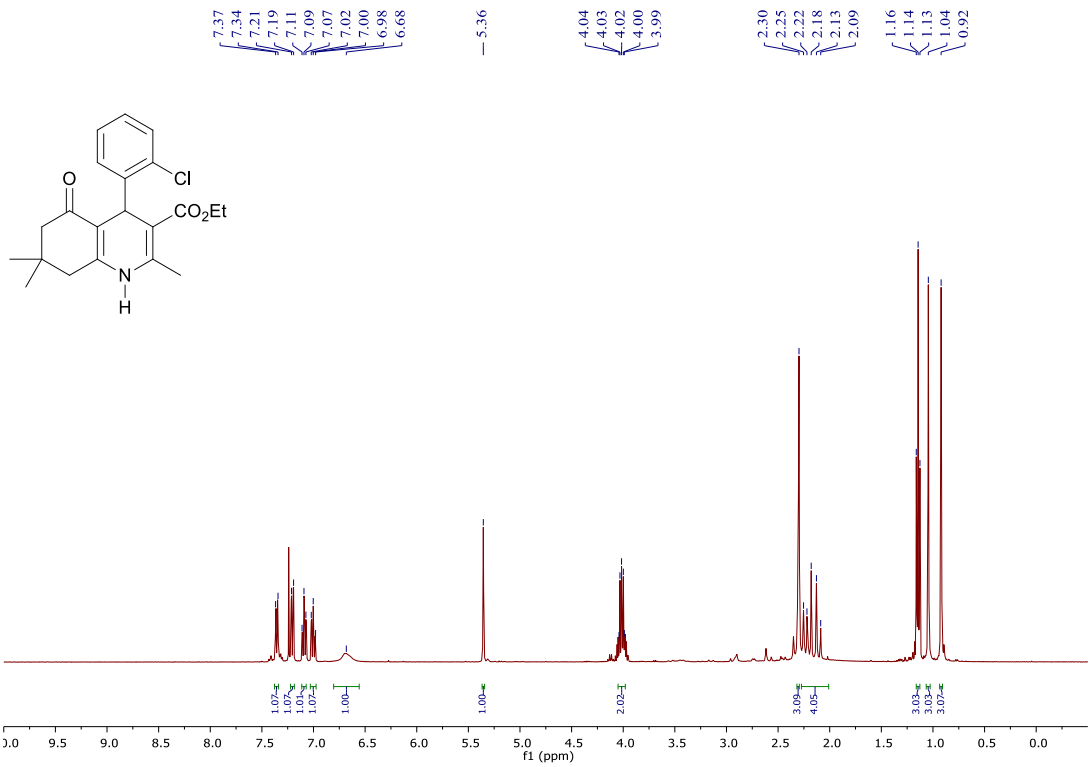


Figure S14: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5k**

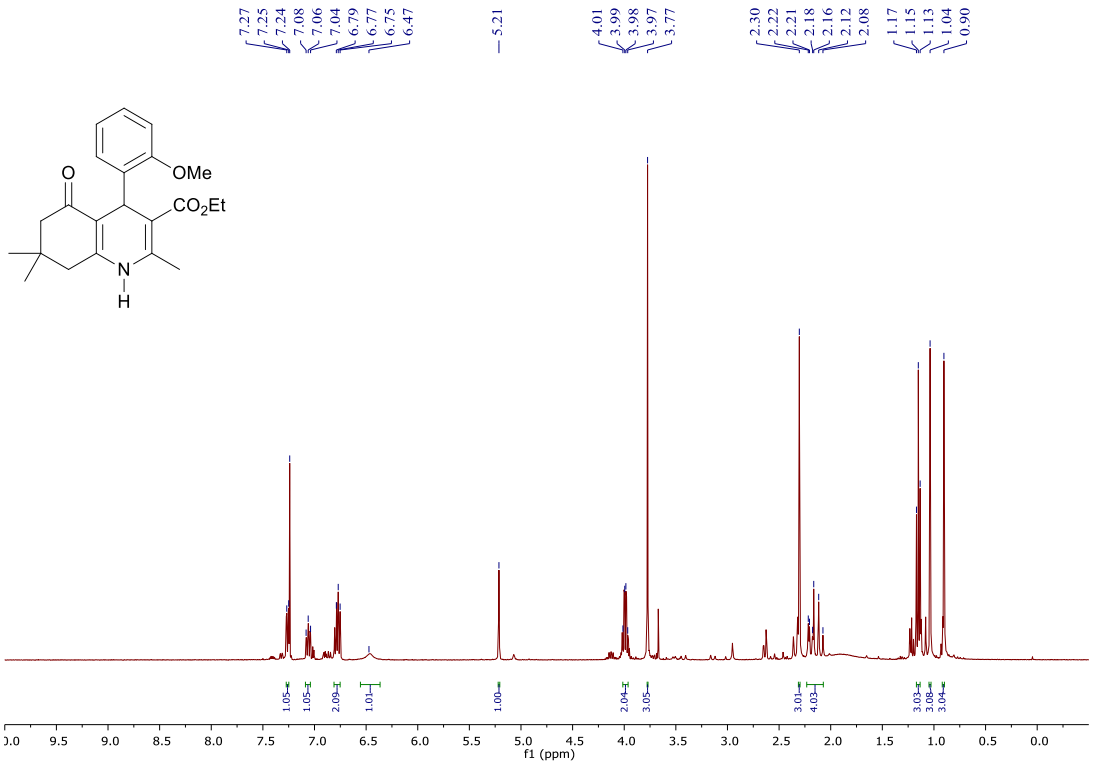


Figure S15: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5l**

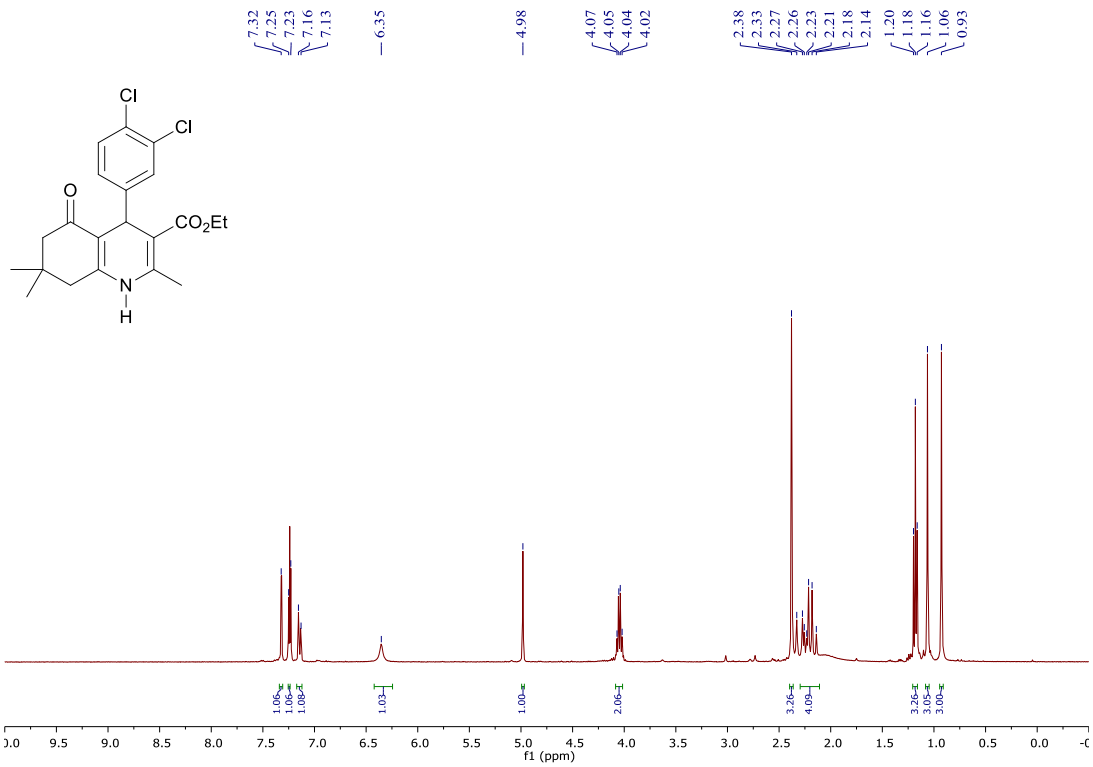


Figure S16: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5m**

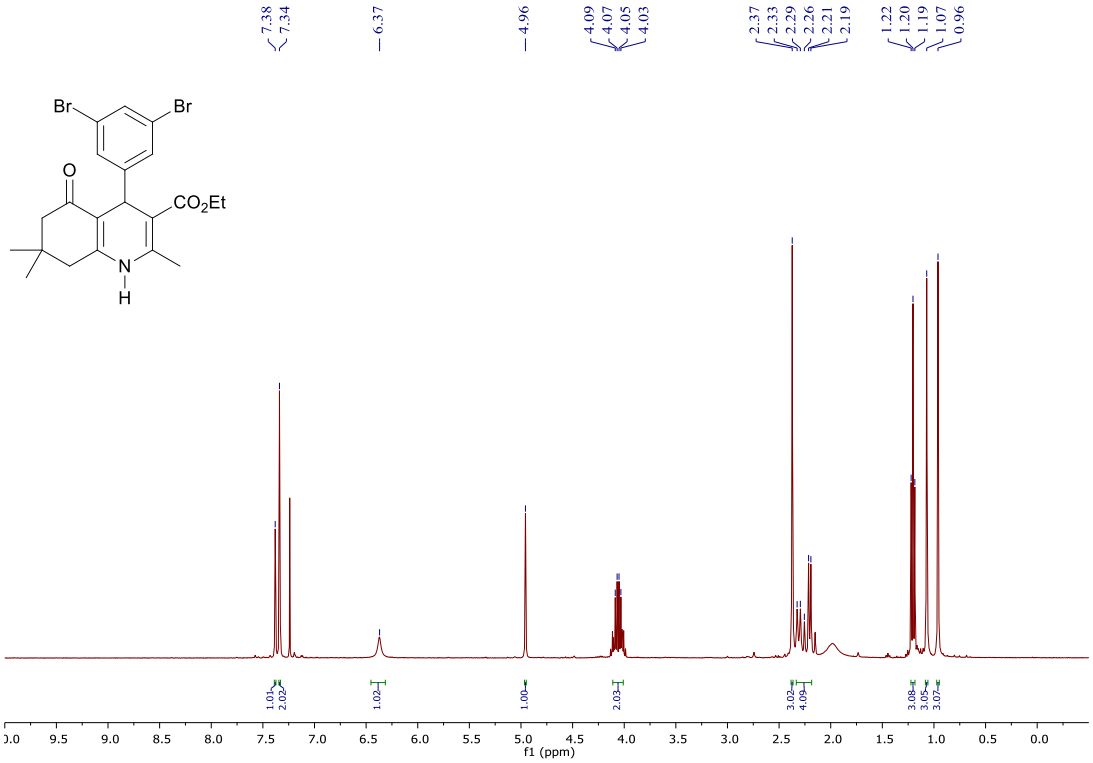


Figure S17: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5n**

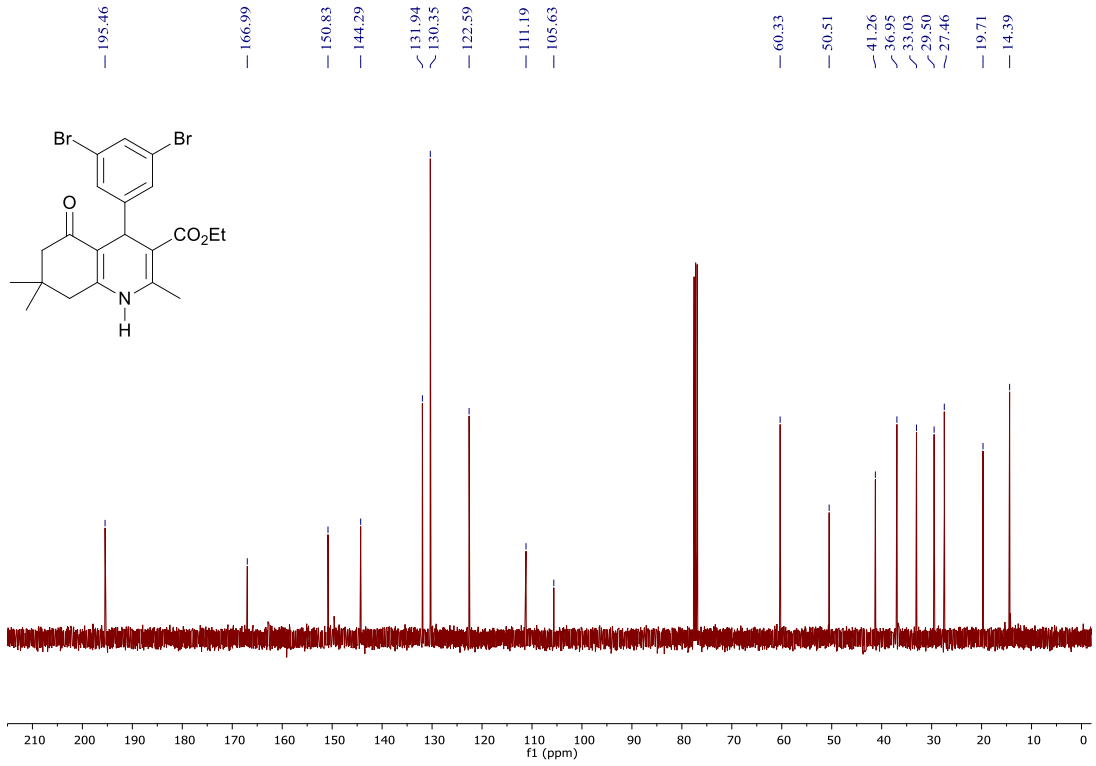


Figure S18: The ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5n**

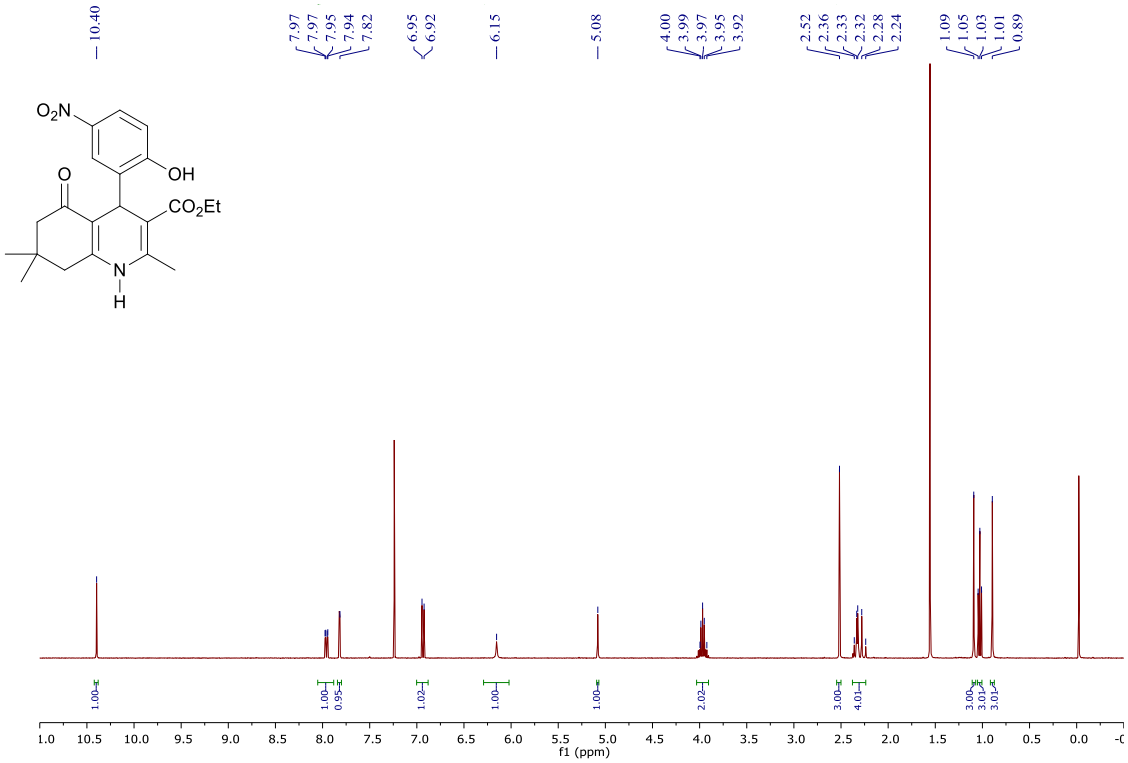


Figure S19: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5o**

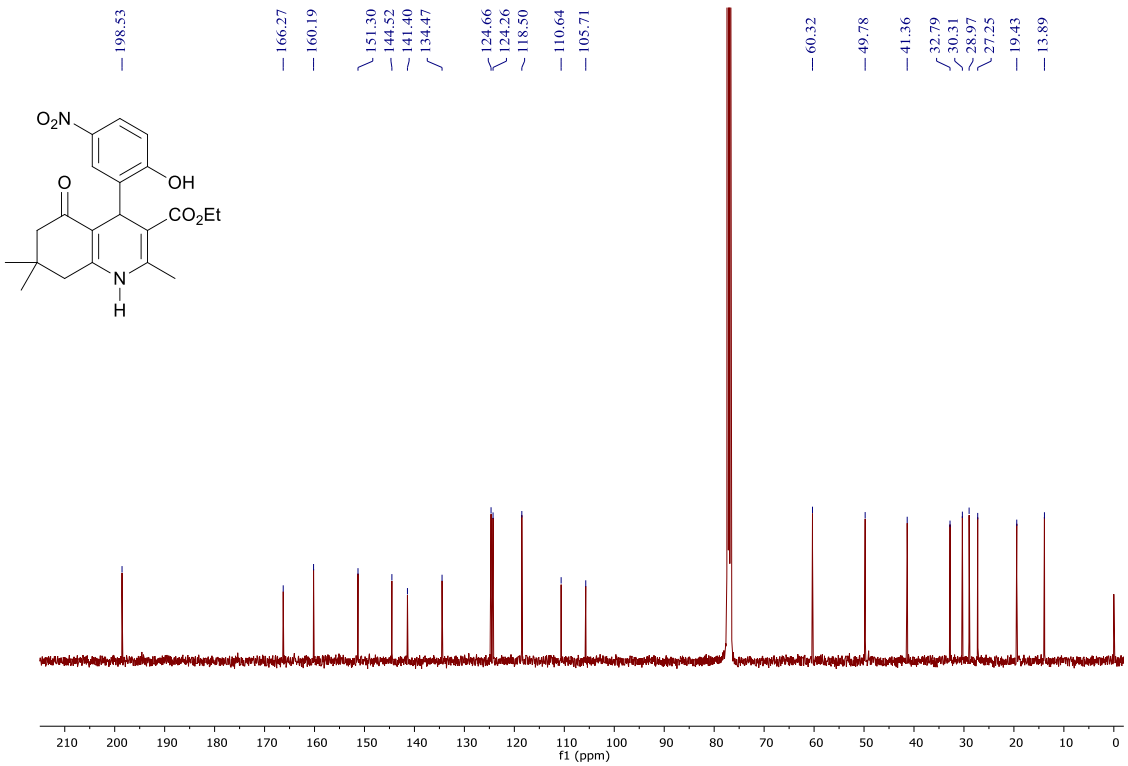


Figure S20: The ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5o**

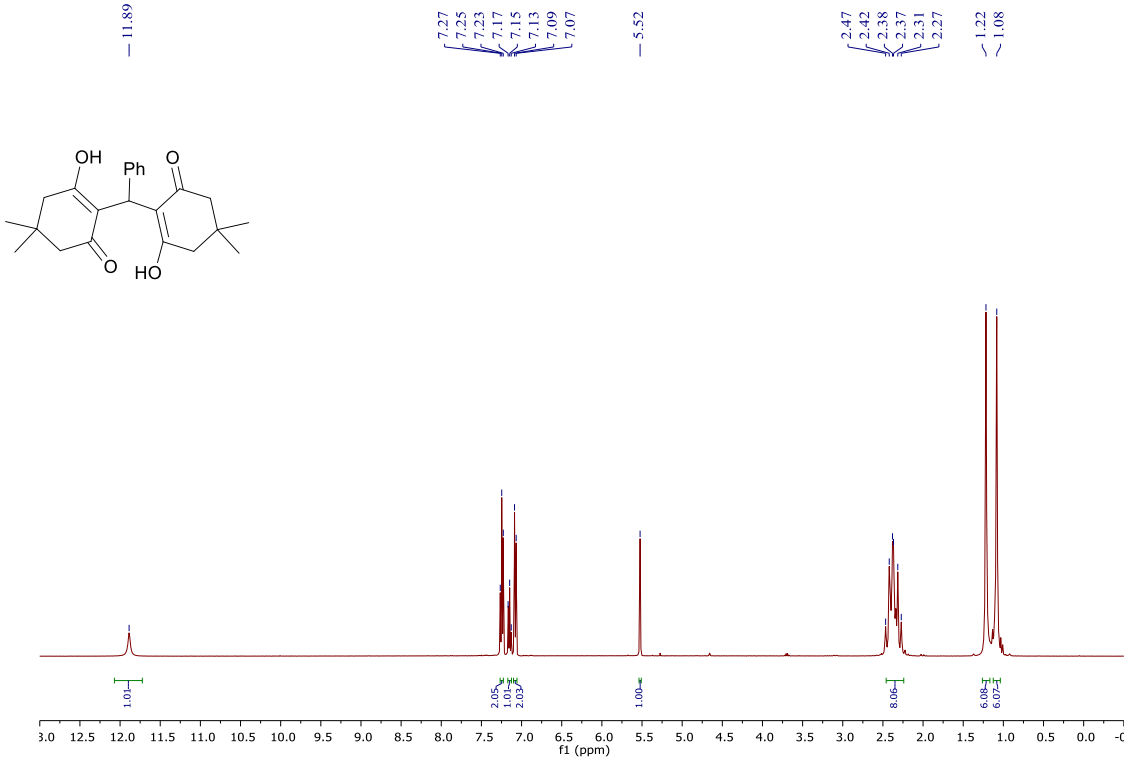


Figure S21: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **M1**

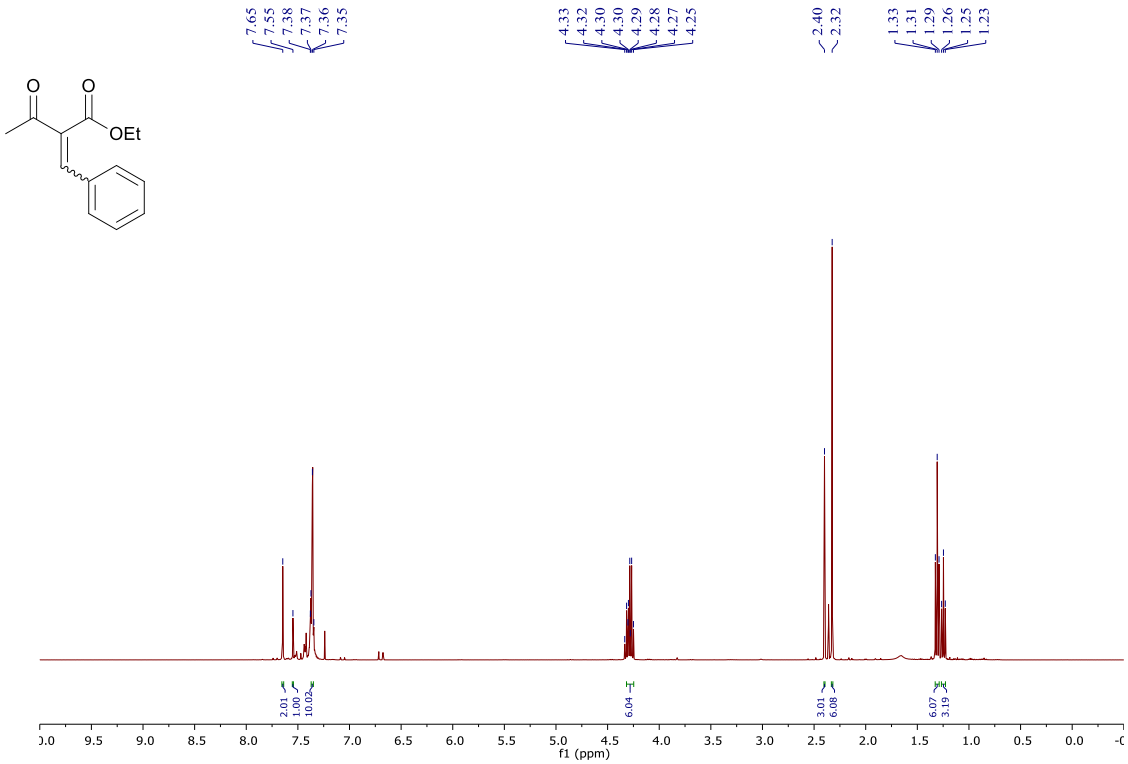


Figure S22: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **K2**

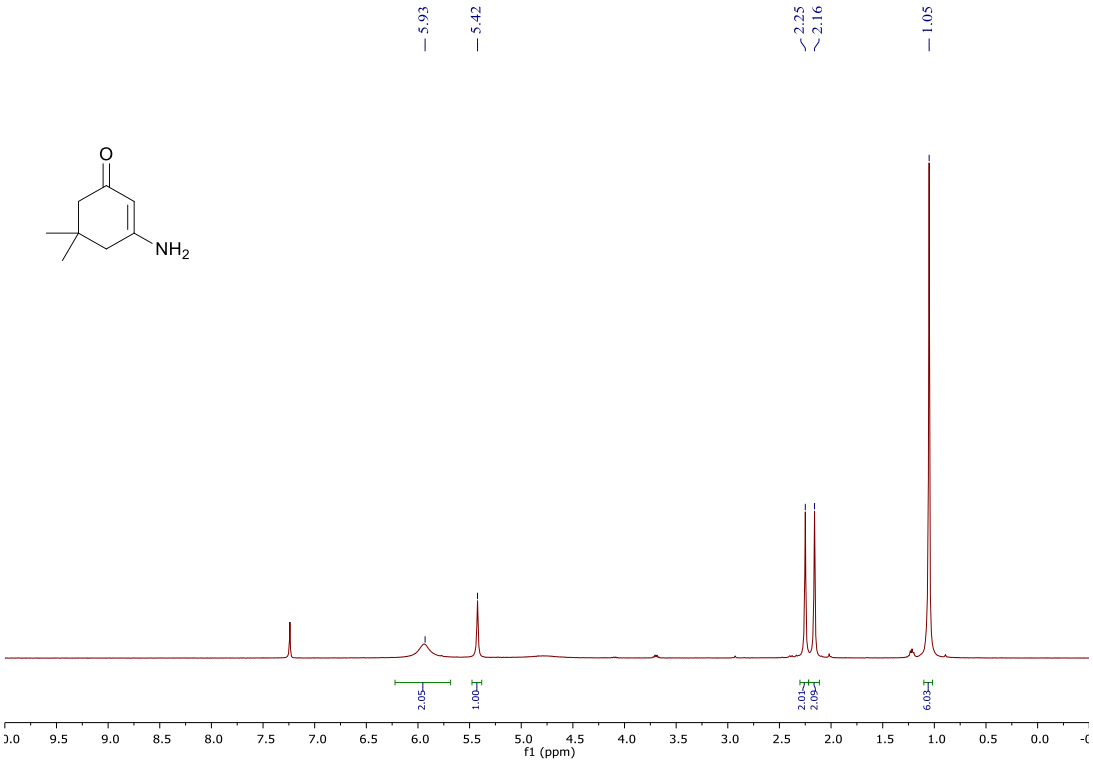


Figure S23: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **E2**

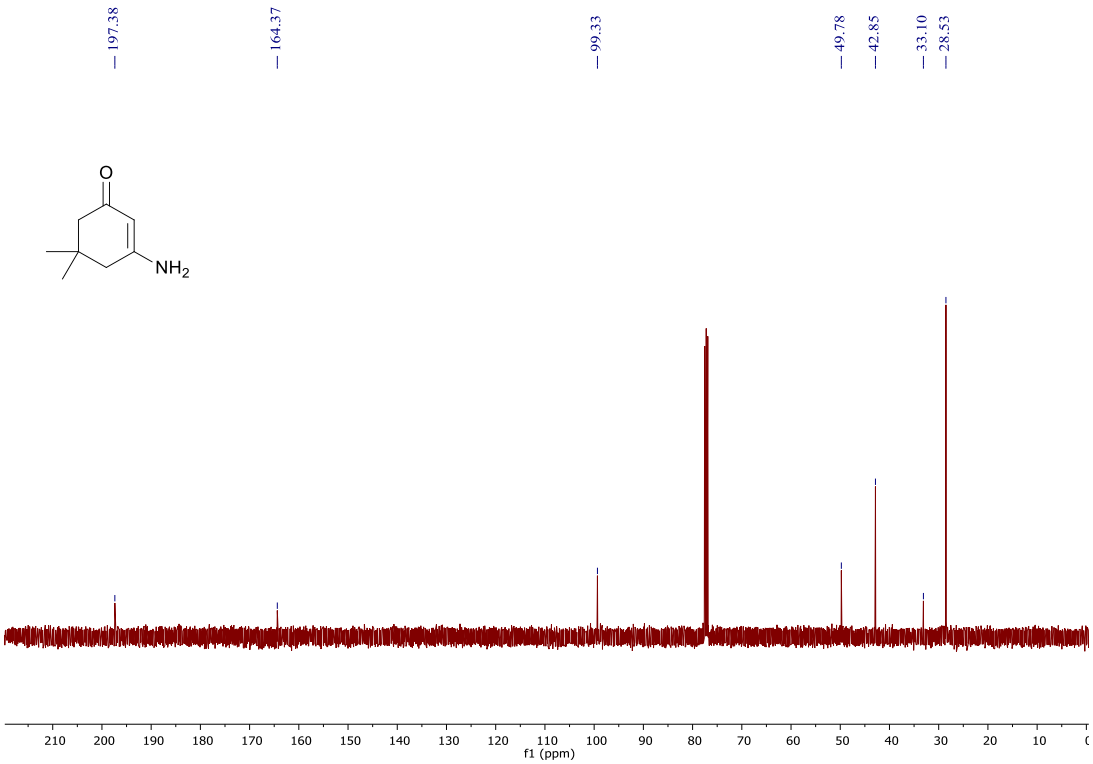


Figure S24: The ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **E2**

References

1. C. G. Evans and J. E. Gestwicki, *Org. Lett.*, 2009, **11**, 2957-2959.
2. A. Amoozadeh, S. Rahmani, M. Bitaraf, F. B. Abadi and E. Tabrizian, *New J. Chem.*, 2016, **40**, 770-780.
3. B. P. Bandgar, P. E. More, V. T. Kamble and J. V. Totre, *Arkivoc*, 2008, **xv**, 1-8.
4. M. Ghorbani, S. Noura, M. Oftadeh, E. gholami and M. A. Zolfigol, *RSC Adv.*, 2015, **5**, 55303-55312.
5. A. Kumar and R. A. Maurya, *Tetrahedron*, 2007, **63**, 1946-1952.
6. G. B. Dharma Rao, S. Nagakalyan and G. K. Prasad, *RSC Adv.*, 2017, **7**, 3611-3616.
7. L.-M. Wang, J. Sheng, L. Zhang, J.-W. Han, Z.-Y. Fan, H. Tian and C.-T. Qian, *Tetrahedron*, 2005, **61**, 1539-1543.
8. M. Hajjarni and B. Tahmasbi, *RSC Adv.*, 2015, **5**, 59194-59203.
9. D. Schade, M. Lanier, E. Willems, K. Okolotowicz, P. Bushway, C. Wahlquist, C. Gilley, M. Mercola and J. R. Cashman, *J. Med. Chem.*, 2012, *5***5**, 9946–9957.
10. M. A. Zolfigol, S. Baghery, A. R. Moosavi-Zare, S. M. Vahdat, H. Alinezhadd and M. Norouzid, *RSC Adv.*, 2014, **4**, 57662-57670.
11. R. A. Mekheimer, A. A. Hameed and K. U. Sadek, *Green Chem.*, 2008, **10**, 592-593.
12. M. B. Gawande, V. D. B. Bonifacio, R. S. Varma, I. D. Nogueira, N. Bundaleski, C. A. A. Ghumman, O. M. N. D. Teodoro and P. S. Branco, *Green Chem.*, 2013, **15**, 1226-1231.
13. S. Das, S. Santra, A. Roy, S. Urinda, A. Majee and A. Hajra, *Green chem. Lett. Rev.*, 2012, **5**, 97-100.
14. S.-J. Ji, Z.-Q. Jiang, J. Lu and T.-P. Loh, *Synlett*, 2004, **5**, 831-835.
15. A. Kumar and R. A. Maurya, *Tetrahedron Lett.*, 2007, **48**, 3887-3890.
16. O. Goli-Jolodar, F. Shirini and M. Seddighi, *RSC Adv.*, 2016, **6**, 26026-26037.
17. T.-W. Chung, B. D. Narhe, C.-C. Lin and C.-M. Sun, *Org. Lett.*, 2015, **17**, 5368-5371.
18. M. de S. Ferreira and J. D. Figueroa-Villar, *J. Braz. Chem. Soc.*, 2014, **25**, 935-946.
19. W. H. Correa and J. L. Scott, *Green Chem.*, 2001, **3**, 296-301.
20. V. G. Santos, M. N. Godoi, T. Reqiani, F. H. S. Gama, M. B. Coelho, R. O. M. A. de Souza, M. N. Eberlin and S. J. Garden, *Chem. Eur. J.*, 2014, **20**, 12808-12816.