

Copper-catalyzed one-pot reactions of acetyl chloride, o-halobenzoic acids and Wittig reagents toward 3-methyl isocoumarin synthesis

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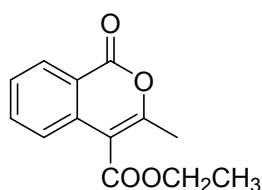
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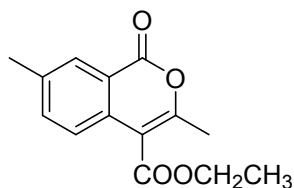
General experimental information

All Wittig reagents (triphenylphosphonium salts) were prepared following literature procedure¹, all other chemicals were obtained from commercial sources and used directly without further purification. Solvents used in the experiment have been treated following standard procedure before use. The ¹H and ¹³C NMR were recorded in 400 MHz apparatus in CDCl₃. The frequency used for measuring ¹H NMR was 400 MHz, and 100 MHz for ¹³C NMR, respectively. Chemical shifts were recorded in ppm by employing TMS (for ¹H NMR) or the solvent peak of CDCl₃ (77.0 ppm, for ¹³C NMR) as internal standard. HRMS data were obtained under ESI model in the apparatus equipped with TOF analyzer. Melting points were acquired in X-4A equipment without correcting temperature.

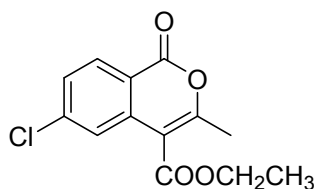
Characterization data of all products



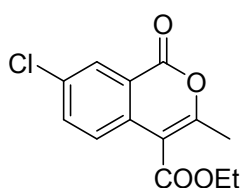
Ethyl 3-methyl-1-oxo-1H-isochromene-4-carboxylate (4a).² Yellow liquid; ¹H NMR (400 MHz, CDCl₃): δ 8.29 (d, *J* = 8.0 Hz, 1 H), 7.78-7.72 (m, 2 H), 7.52 (t, *J* = 7.2 Hz, 1 H), 4.49-4.43 (m, 2 H), 2.46 (s, 3 H), 1.44 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): 165.8, 161.2, 157.7, 135.1, 134.6, 129.7, 128.2, 124.1, 119.5, 110.3, 61.7, 19.3, 14.3.



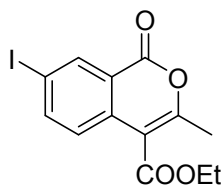
Ethyl 3,7-dimethyl-1-oxo-1H-isochromene-4-carboxylate (4b). White solid; mp 76-78 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.07 (s, 1 H), 7.67 (d, $J = 8.4$ Hz, 1 H), 7.54 (d, $J = 8.4$ Hz, 1 H), 4.48-4.42 (m, 2 H), 2.45 (s, 6 H), 1.43 (t, $J = 7.2$ Hz, 3 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): 165.9, 161.4, 156.9, 138.4, 136.3, 132.1, 129.3, 124.1, 119.4, 110.1, 61.6, 21.2, 19.2, 14.3; ESI-HRMS Calcd for $\text{C}_{14}\text{H}_{15}\text{O}_4$ $[\text{M} + \text{H}]^+$ 247.0965, found 247.0966.



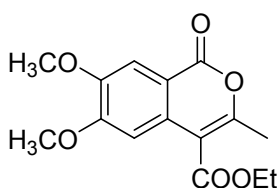
Ethyl 6-chloro-3-methyl-1-oxo-1H-isochromene-4-carboxylate (4c). White solid. mp 111-113 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.21 (d, $J = 8.4$ Hz, 1 H), 7.85 (d, $J = 1.6$ Hz, 1 H), 7.47 (d, $J = 8.4$ Hz, 1 H), 4.49-4.44 (m, 2 H), 2.48 (s, 3 H), 1.44 (t, $J = 7.2$ Hz, 3 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 165.3, 160.4, 160.3, 142.1, 136.1, 131.3, 128.7, 124.2, 117.8, 109.3, 61.9, 19.7, 14.2; ESI-HRMS Calcd for $\text{C}_{13}\text{H}_{12}\text{ClO}_4$ $[\text{M} + \text{H}]^+$ 267.0419, found 267.0419.



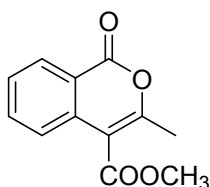
Ethyl 7-chloro-3-methyl-1-oxo-1H-isochromene-4-carboxylate (4d).² White solid; mp 97-99 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.25 (d, $J = 2.0$ Hz, 1 H), 7.79 (d, $J = 8.8$ Hz, 1 H), 7.67 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.4$ Hz, 1 H), 4.48-4.42 (m, 2 H), 2.48 (s, 3 H), 1.43 (t, $J = 7.2$ Hz, 3 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): 165.4, 160.1, 158.5, 135.4, 134.1, 133.1, 129.0, 126.0, 120.9, 109.6, 61.9, 19.5, 14.2.



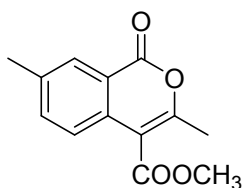
Ethyl 7-iodo-3-methyl-1-oxo-1H-isochromene-4-carboxylate (4e).² White solid; mp 99-101 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.61 (d, *J* = 1.6 Hz, 1 H), 8.01 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.6 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 4.47-4.42 (m, 2 H), 2.46 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): 165.3, 159.7, 158.9, 143.8, 138.2, 134.0, 126.0, 121.0, 109.8, 92.6, 61.9, 19.6, 14.2.



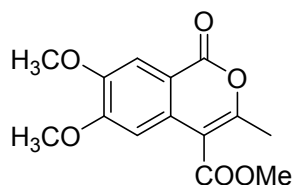
Ethyl 6,7-dimethoxy-3-methyl-1-oxo-1H-isochromene-4-carboxylate (4f). White solid. mp 181-183 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.64 (s, 1 H), 7.34 (s, 1 H), 4.48-4.43 (m, 2 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 2.49 (s, 3 H), 1.44 (t, *J* = 7.0 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): 166.0, 161.1, 157.7, 155.1, 149.4, 130.3, 112.7, 109.4, 105.4, 61.5, 56.2, 56.1, 19.6, 14.3; ESI-HRMS Calcd for C₁₅H₁₇O₆ [M + H]⁺ 293.1020, found 293.1025.



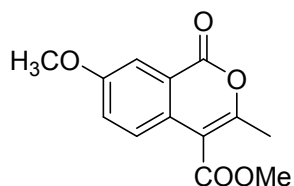
Methyl 3-methyl-1-oxo-1H-isochromene-4-carboxylate (4g). Colorless liquid. ¹H NMR (400 MHz, CDCl₃): δ 8.28 (d, *J* = 7.6 Hz, 1 H), 7.75-7.73 (m, 2 H), 7.53-7.49 (m, 1 H), 3.98 (s, 3 H), 2.45 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): 166.2, 161.1, 135.1, 134.5, 129.6, 128.2, 124.2, 119.4, 110.0, 52.4, 19.4; ESI-HRMS Calcd for C₁₂H₁₁O₄ [M + H]⁺ 219.0652, found 219.0655.



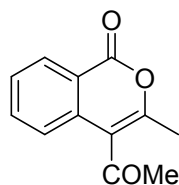
Methyl 3,7-dimethyl-1-oxo-1H-isochromene-4-carboxylate (4h). White solid. mp 121-123 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.08 (s, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 0.8 Hz, 1 H), 3.97 (s, 3 H), 2.46 (s, 3 H), 2.45 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): 166.4, 161.3, 157.3, 138.5, 136.4, 132.1, 129.4, 124.2, 119.4, 109.9, 52.4, 21.2, 19.3; ESI-HRMS Calcd for C₁₃H₁₃O₄ [M + H]⁺ 233.0808, found 233.0809.



Methyl 6,7-dimethoxy-3-methyl-1-oxo-1H-isochromene-4-carboxylate (4i). White solid; mp 154-156 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.64 (s, 1 H), 7.33 (s, 1 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 3.97 (s, 3 H), 2.48 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): 166.53, 166.52, 158.0, 155.3, 149.6, 130.3, 112.7, 109.5, 109.2, 105.5, 56.3, 56.2, 52.3, 19.8; ESI-HRMS Calcd for C₁₄H₁₅O₆ [M + H]⁺ 279.0863, found 279.0862.

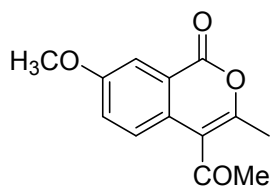


Methyl 7-methoxy-3-methyl-1-oxo-1H-isochromene-4-carboxylate (4j). White solid; mp 107-109 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.73 (d, *J* = 8.8 Hz, 1 H), 7.69 (d, *J* = 2.8 Hz, 1 H), 7.32 (dd, *J*₁ = 9.2 Hz, *J*₂ = 2.8 Hz, 1 H), 3.97 (s, 3 H), 3.91 (s, 3 H), 2.45 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): 166.4, 161.3, 159.4, 156.2, 128.2, 126.0, 124.6, 120.8, 110.2, 109.7, 55.7, 52.3, 19.2; ESI-HRMS Calcd for C₁₃H₁₃O₅ [M + H]⁺ 249.0757, found 249.0755.

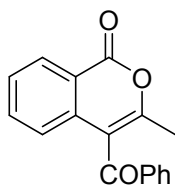


4-Acetyl-3-methyl-1H-isochromen-1-one (4k).² White solid; mp 101-103 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.31 (d, *J* = 8.0 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.53 (t, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 2.59 (s, 3 H), 2.33 (s, 3 H); ¹³C NMR (100

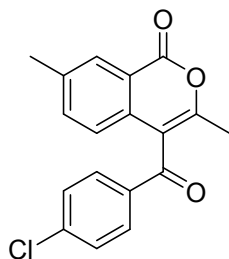
MHz, CDCl₃): 201.2, 161.3, 152.6, 135.1, 134.4, 130.1, 128.3, 123.1, 119.9, 118.6, 32.4, 18.3.



4-Acetyl-7-methoxy-3-methyl-1H-isochromen-1-one (4l). White solid; mp 132-134 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.72 (d, *J* = 2.0 Hz, 1 H), 7.33-7.27 (m, 2 H), 3.91 (s, 3 H), 2.57 (s, 3 H), 2.32 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): 201.3, 161.5, 159.5, 150.5, 127.9, 124.8, 124.6, 121.2, 118.4, 110.7, 55.8, 32.4, 18.1; ESI-HRMS Calcd for C₁₃H₁₃O₄ [M + H]⁺ 233.0808, found 233.0817.



4-Benzoyl-3-methyl-1H-isochromen-1-one (4m). White solid; mp 83-85 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.34 (d, *J* = 6.8 Hz, 1 H), 7.95 (d, *J* = 7.2 Hz, 2 H), 7.67-7.59 (m, 2 H), 7.53-7.48 (m, 3 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 2.17 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): 194.4, 161.6, 153.4, 137.1, 135.7, 135.1, 134.5, 129.9, 129.7, 129.2, 128.3, 123.9, 119.8, 115.6, 18.6; ESI-HRMS Calcd for C₁₇H₁₃O₃ [M + H]⁺ 265.0859, found 265.0864.



4-(4-Chlorobenzoyl)-3,7-dimethyl-1H-isochromen-1-one (4n). White solid; mp 149-151 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.15 (s, 1 H), 7.87 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.43 (d, *J* = 8.4 Hz, 1 H), 7.00 (d, *J* = 8.4 Hz, 1 H), 2.45 (s, 3 H), 2.16 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): 193.3, 152.7, 141.1, 138.8, 136.3, 135.5, 133.0, 131.1, 129.7, 129.6, 123.7, 119.6, 115.2, 21.3, 18.5; ESI-HRMS Calcd

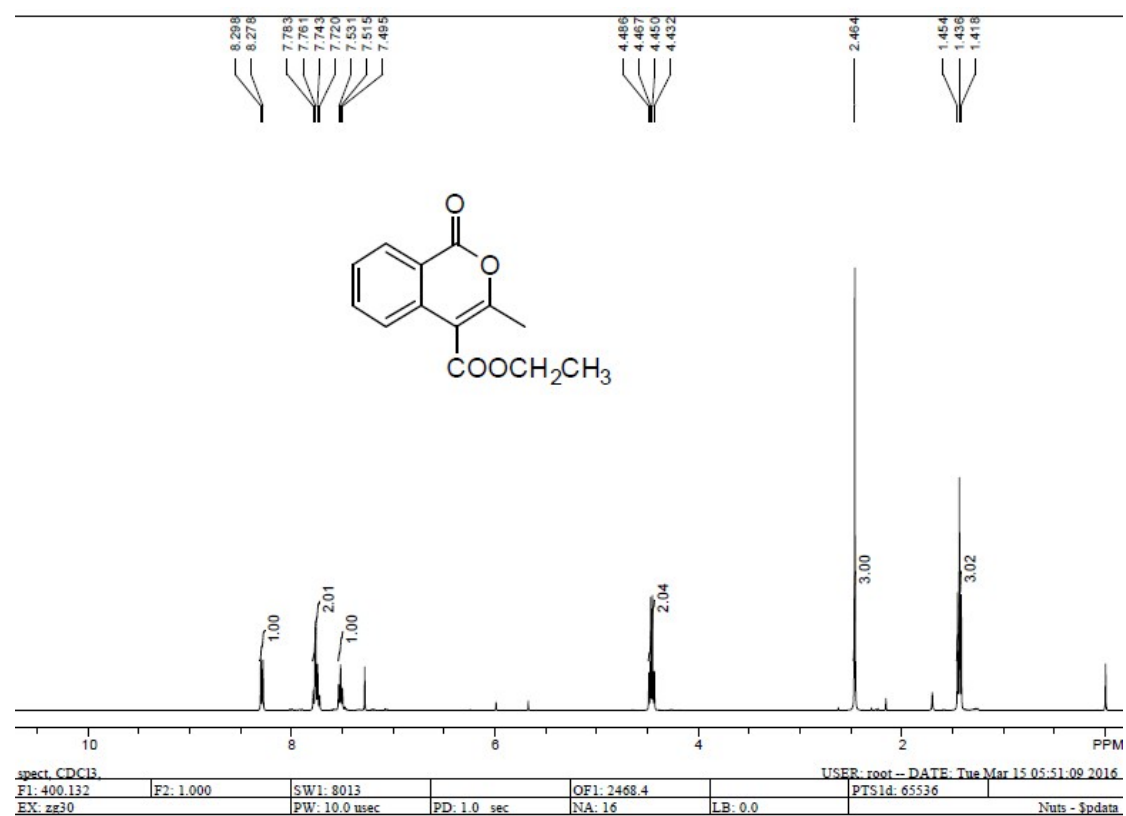
for $C_{18}H_{14}ClO_3$ $[M + H]^+$ 313.0626, found 313.0613.

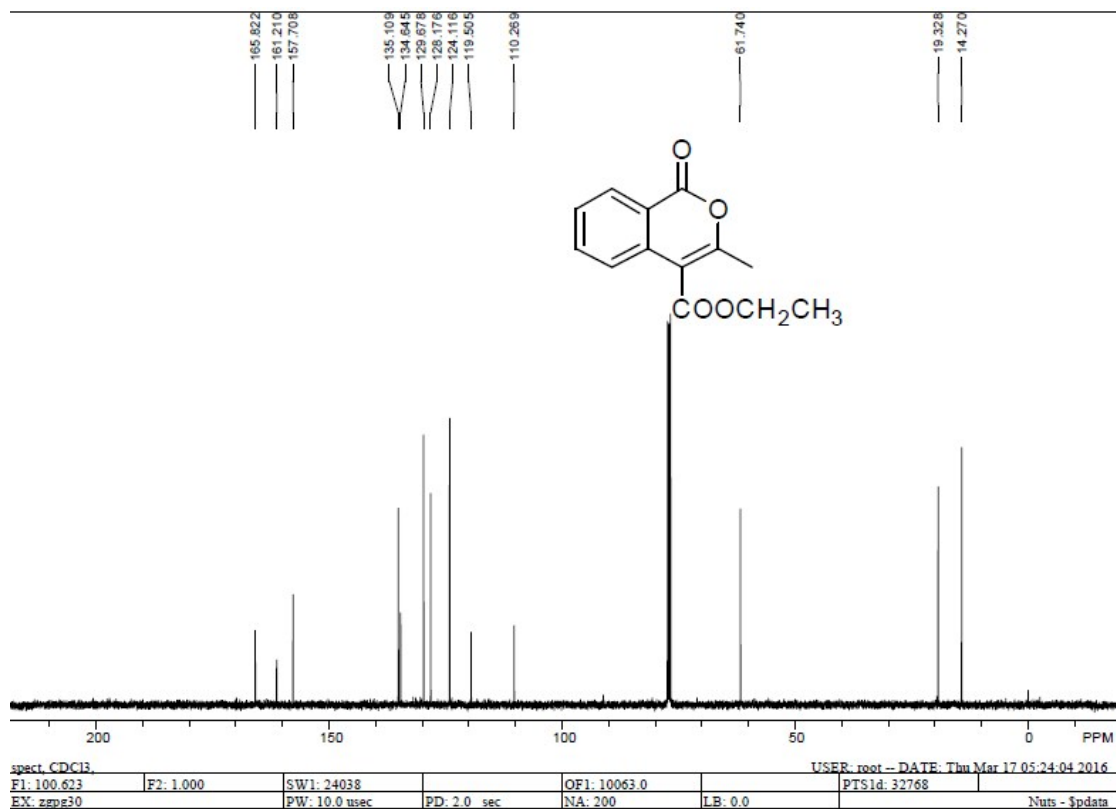
References

- 1) S. Burling, B. M. Paine, D. Nama, V. S. Brown, M. F. Mahon, T. J. Prior, P. S. Pregosin, M. K. Whittlesey, J. M. J. Williams, *J. Am. Chem. Soc.* **2007**, *129*, 1987-1995.
- 2) N. Panda, P. Mishra, I. Mattan, *J. Org. Chem.* **2016**, *81*, 1047.

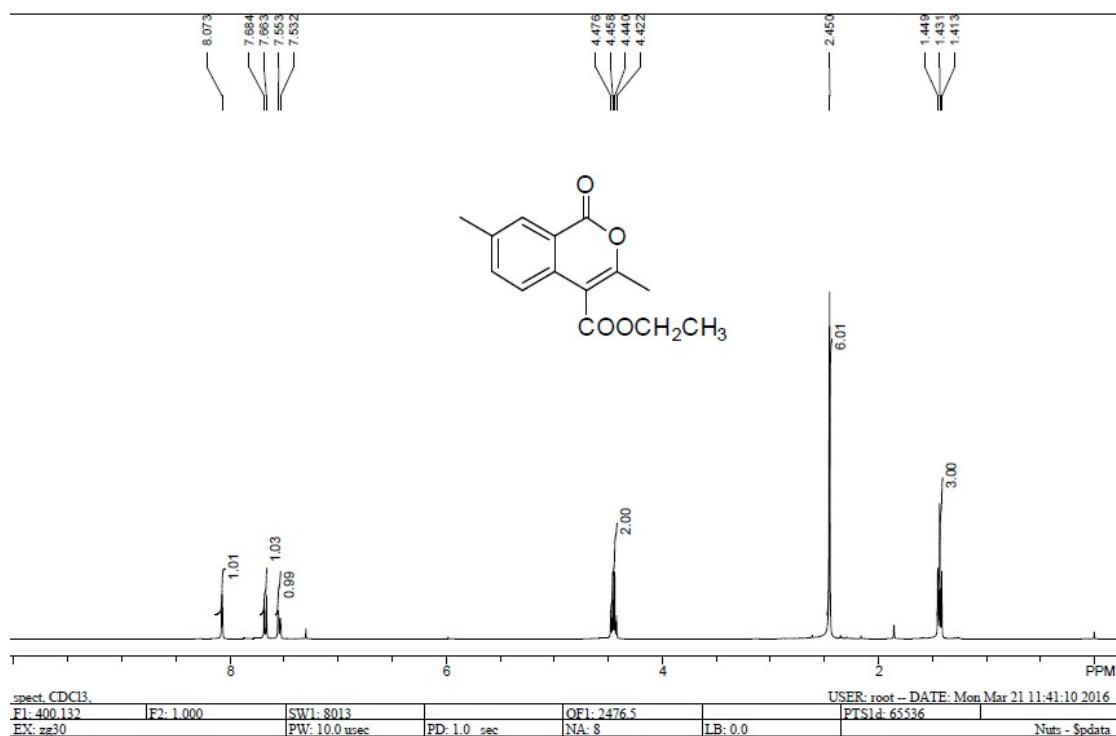
1H and ^{13}C NMR spectra of all products

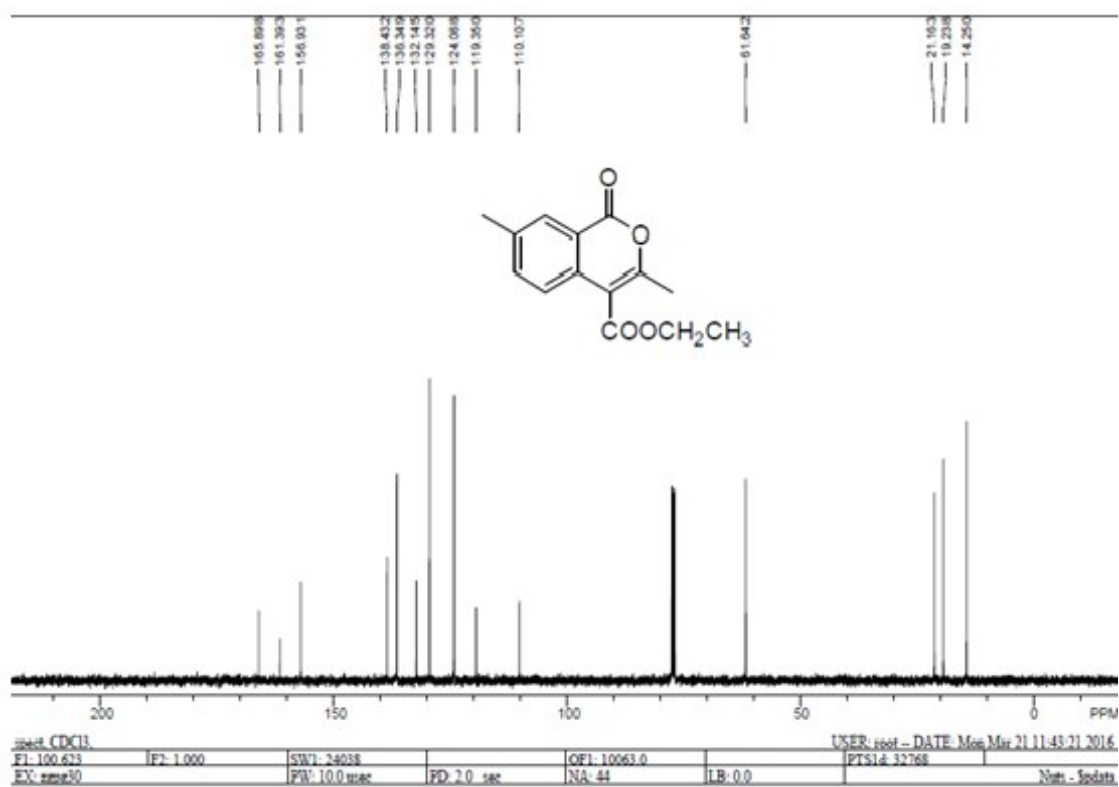
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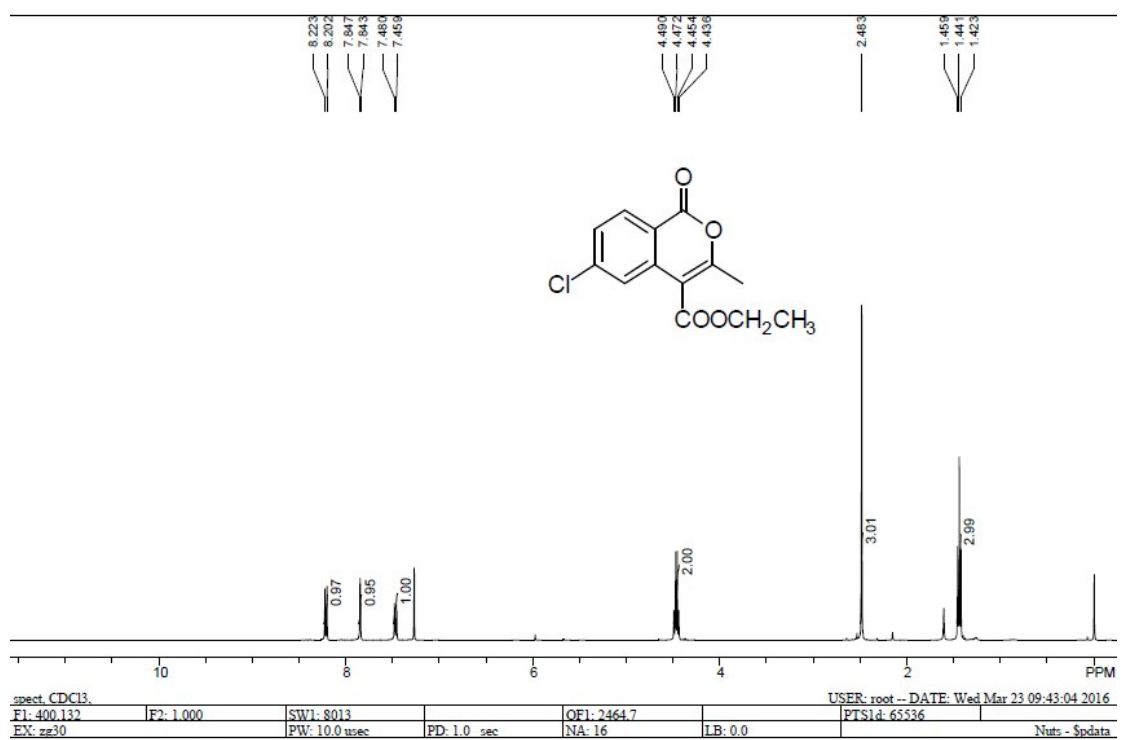


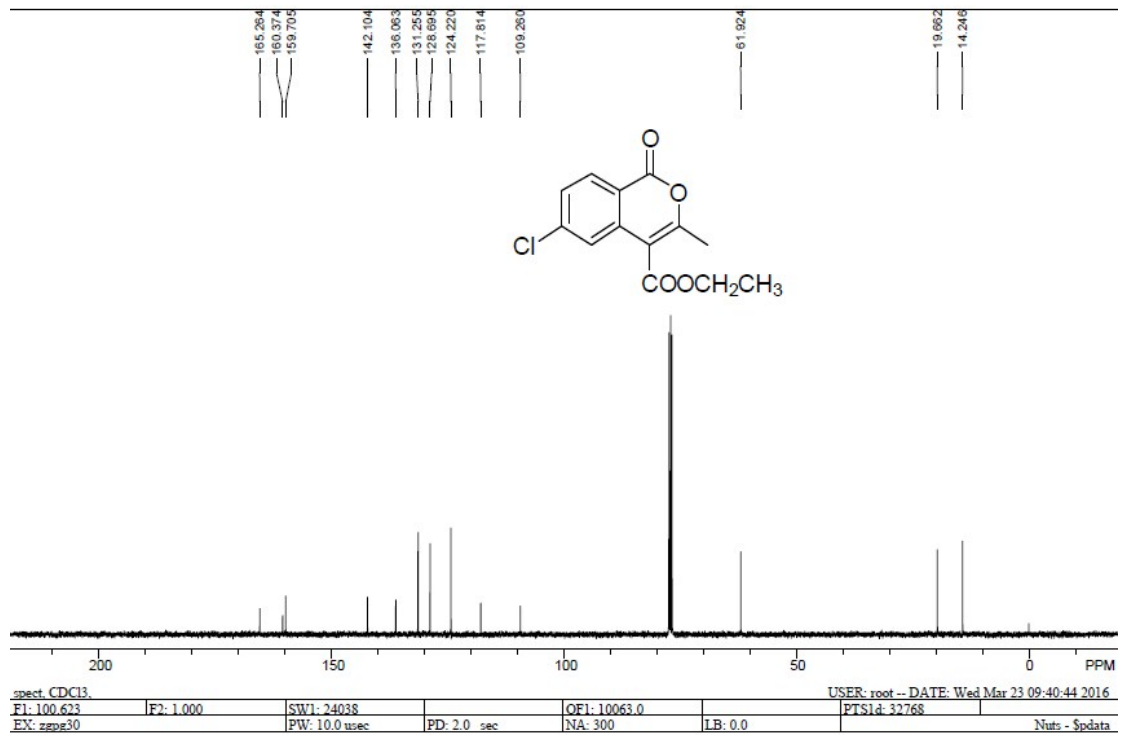
¹H and ¹³C NMR spectra of 4b



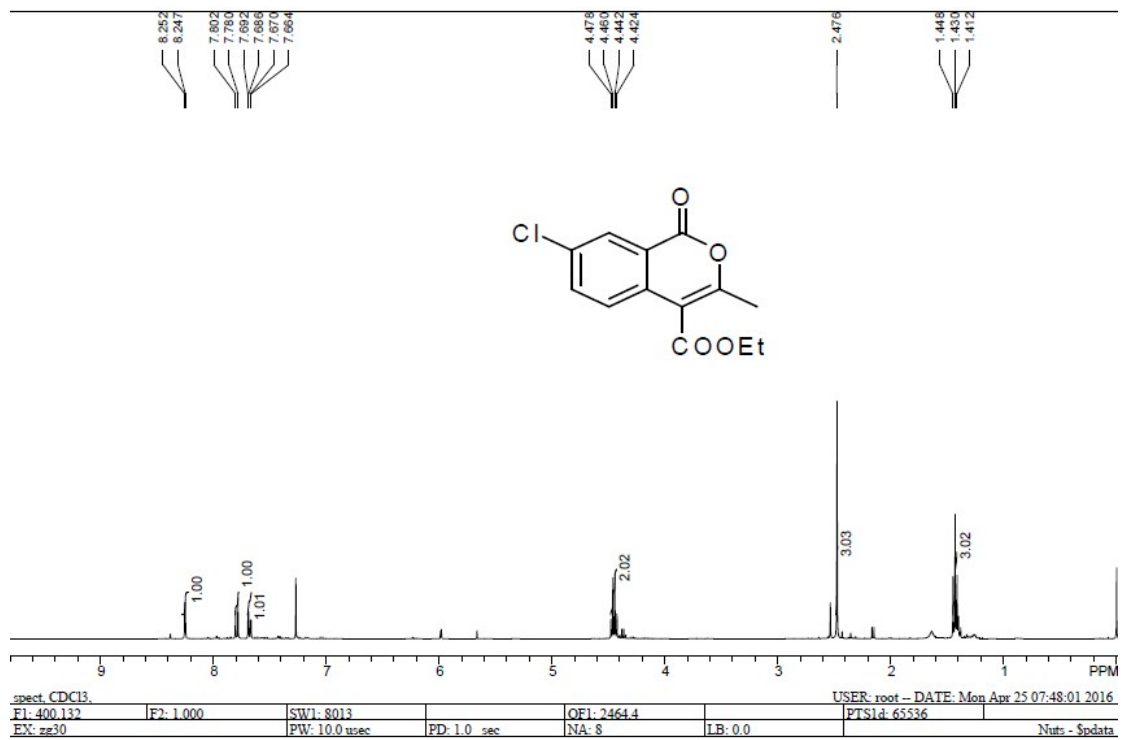


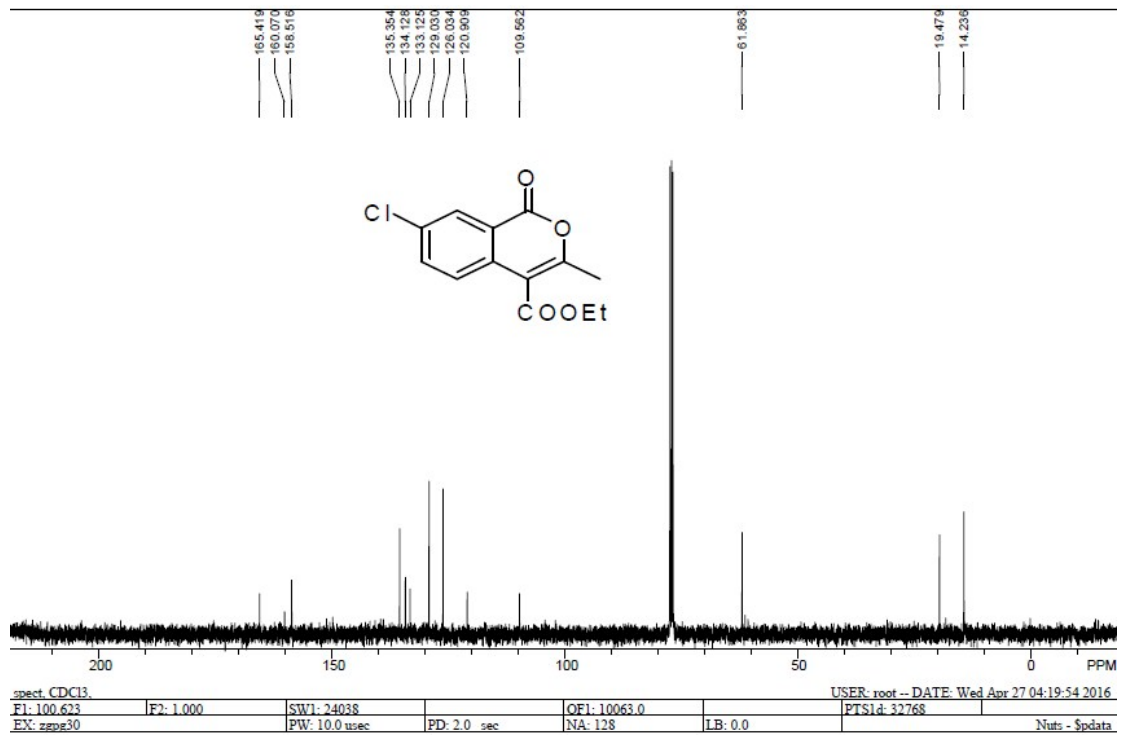
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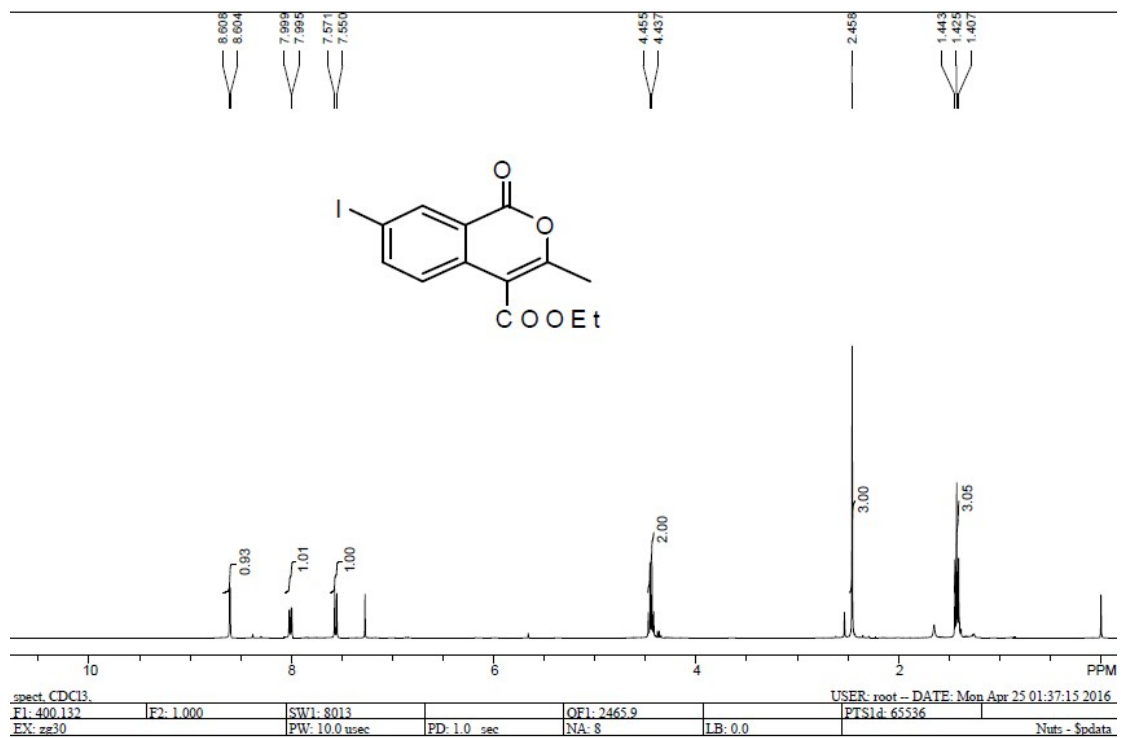


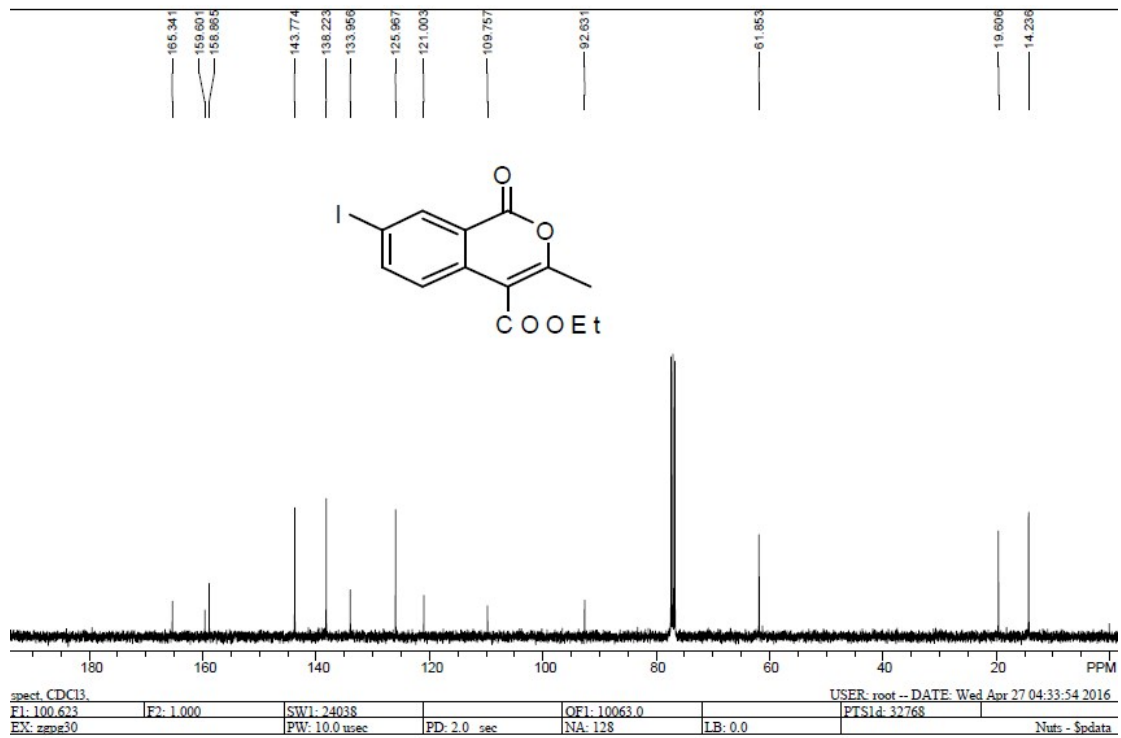
¹H and ¹³C NMR spectra of 4d



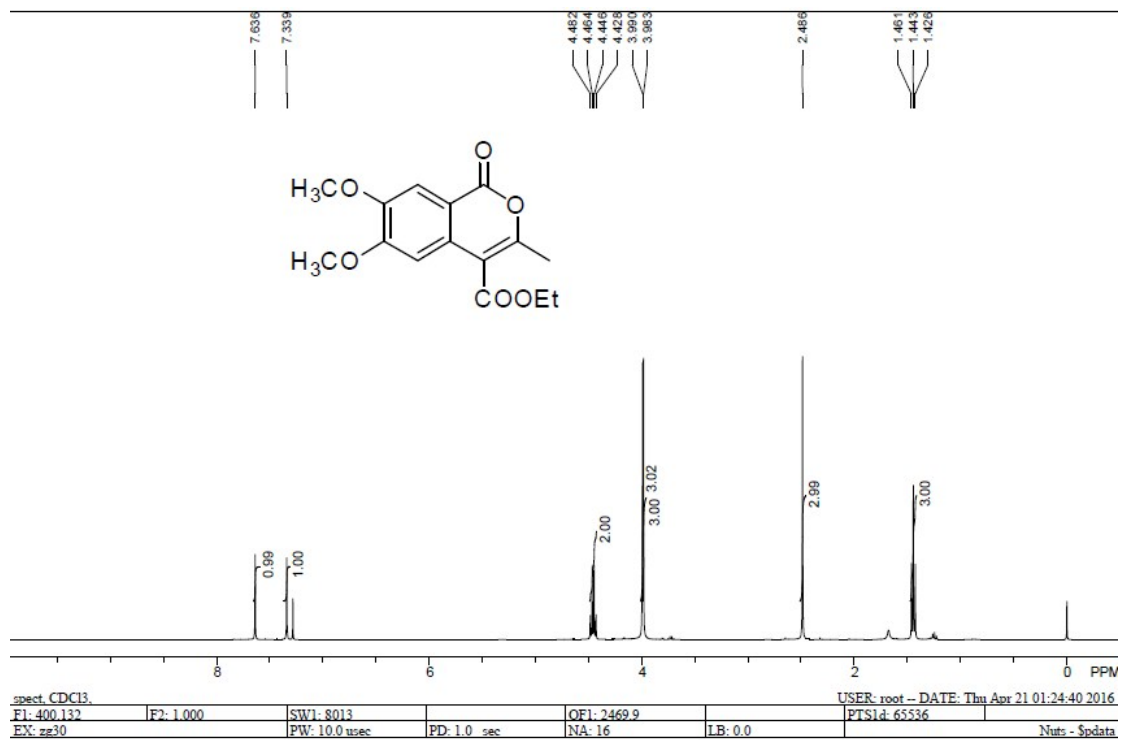


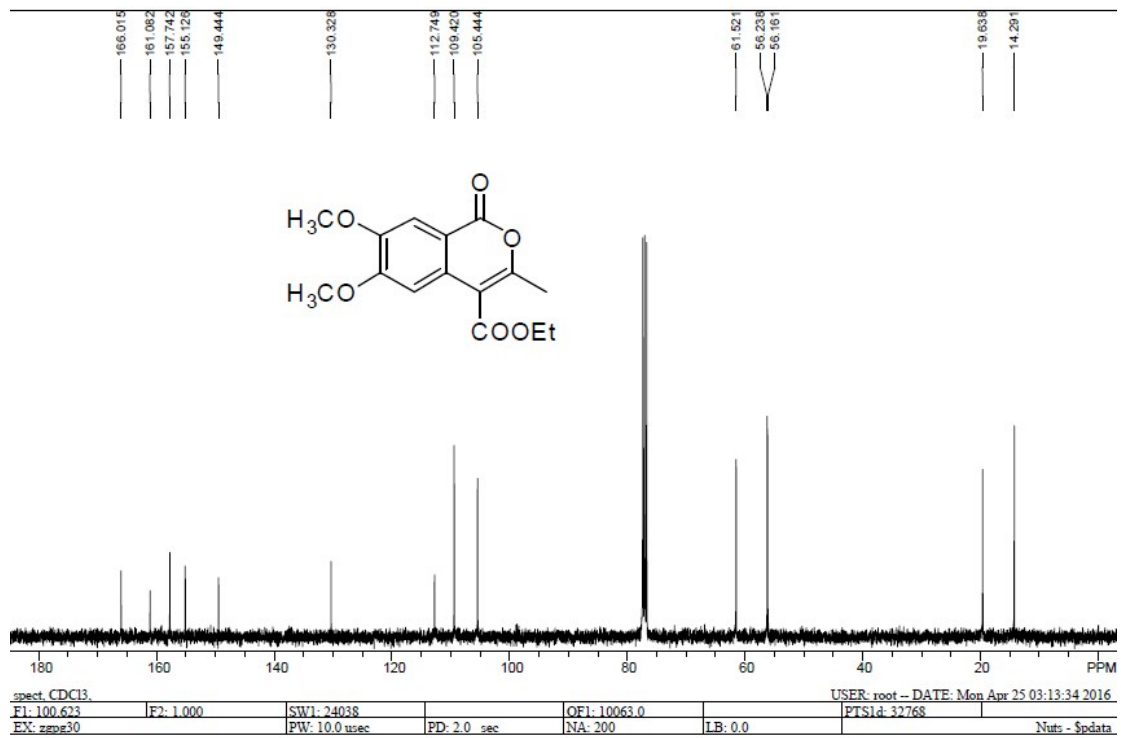
¹H and ¹³C NMR spectra of 4e



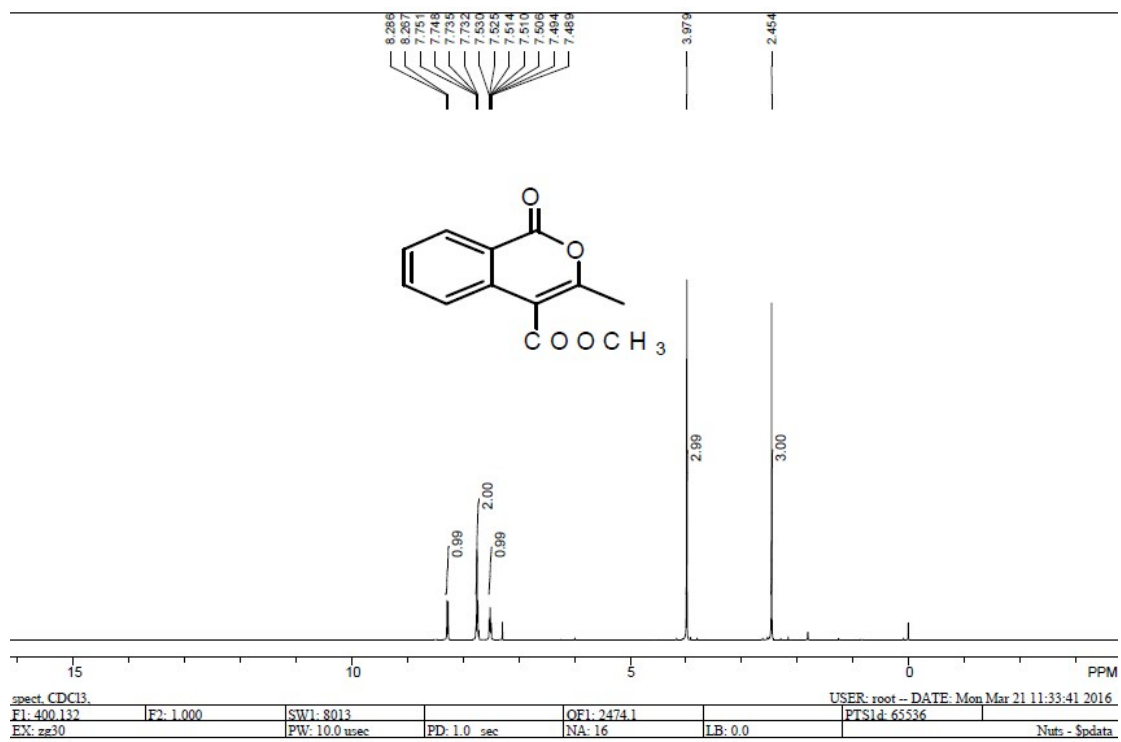


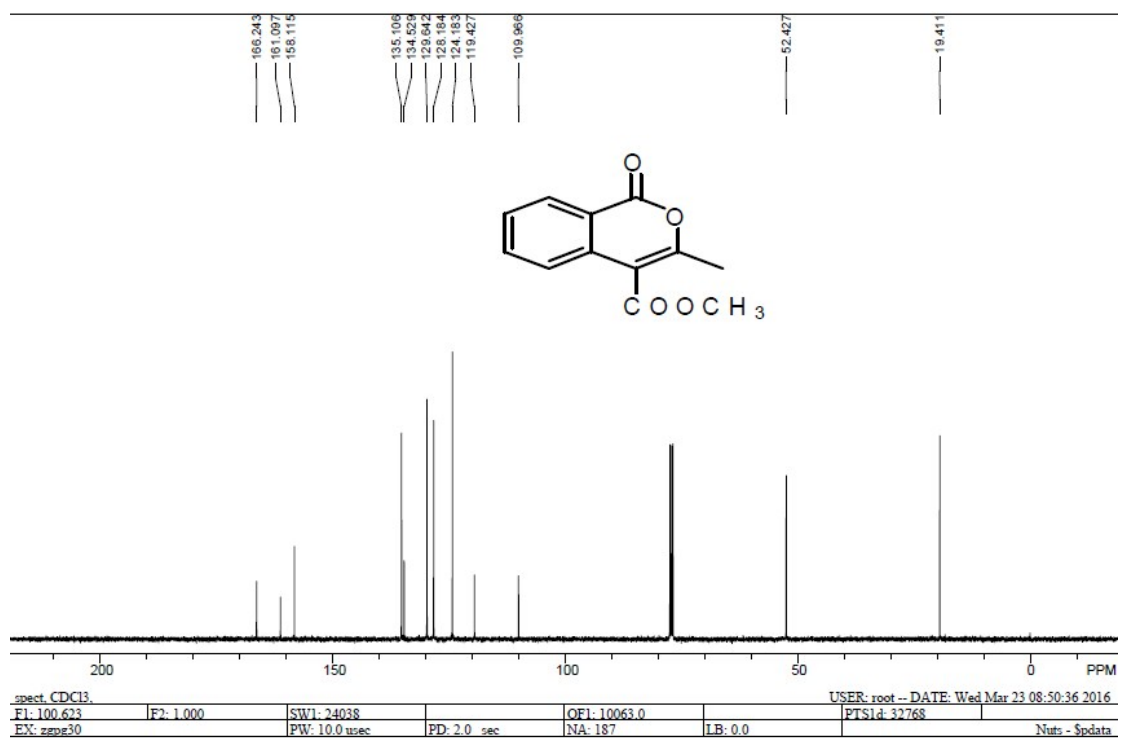
¹H and ¹³C NMR spectra of 4f



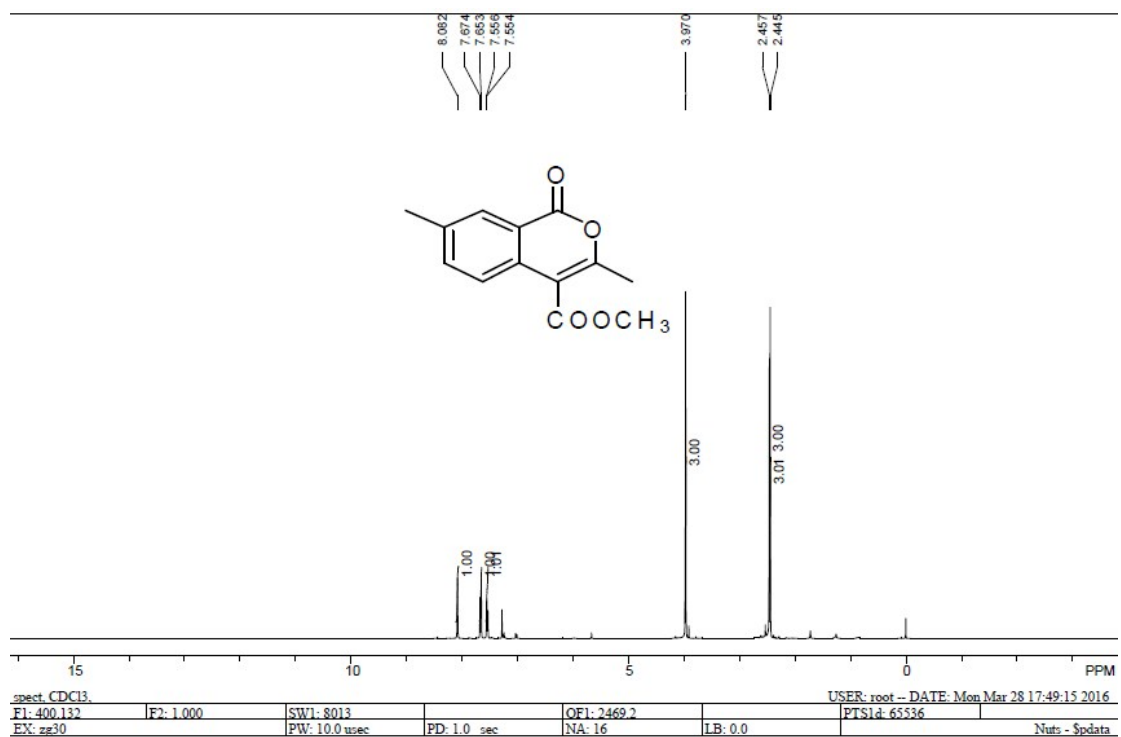


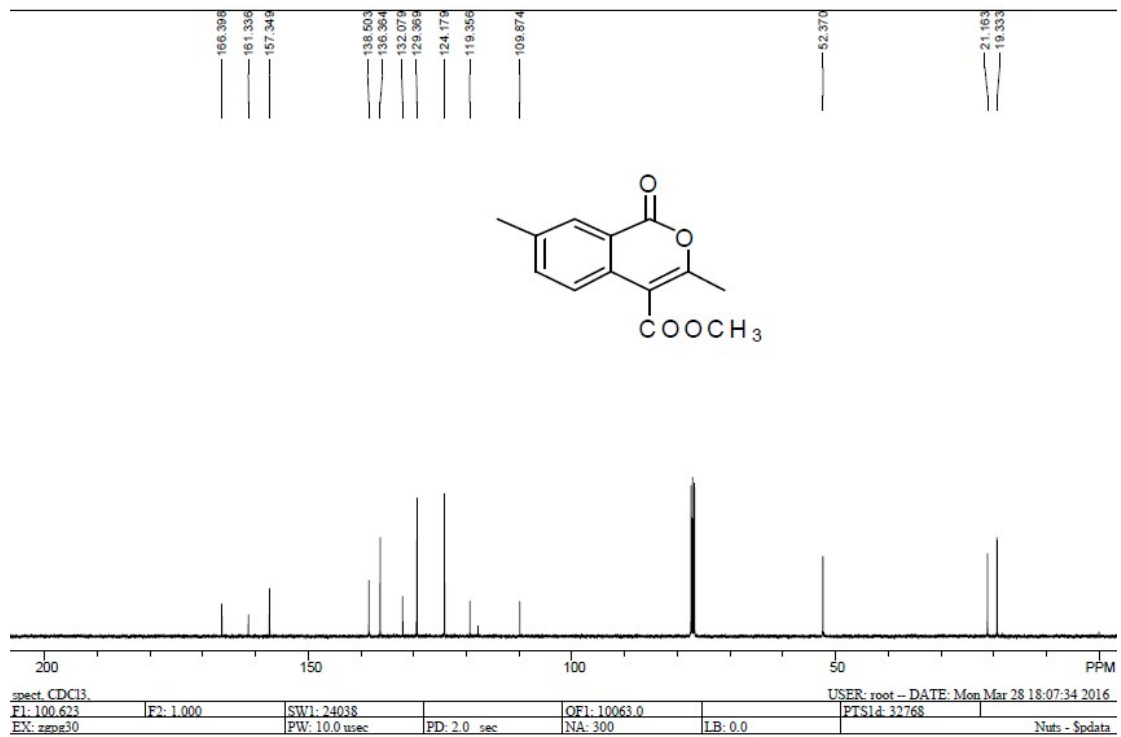
¹H and ¹³C NMR spectra of 4g



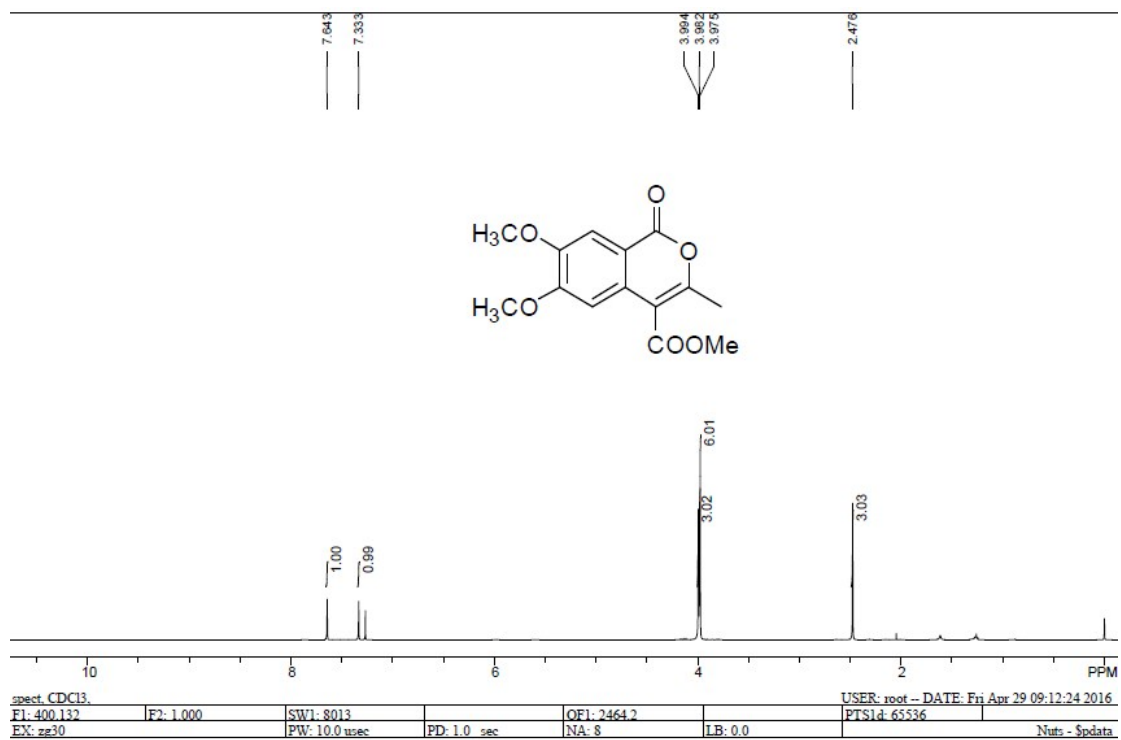


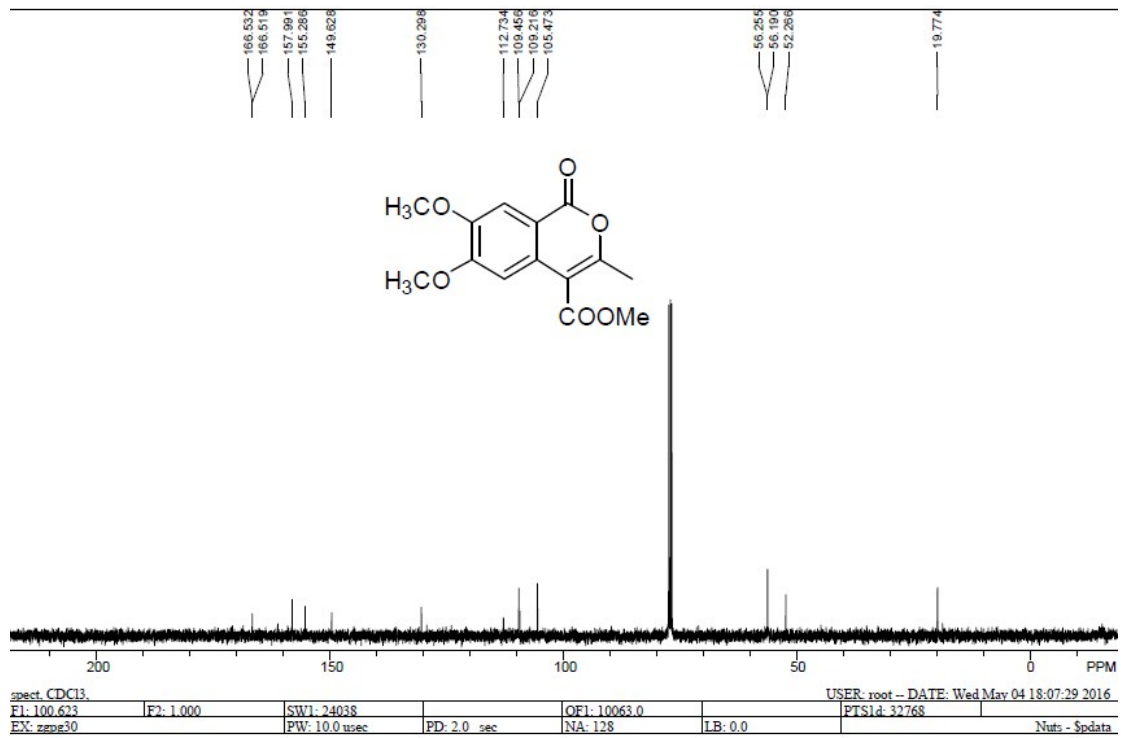
¹H and ¹³C NMR spectra of 4h



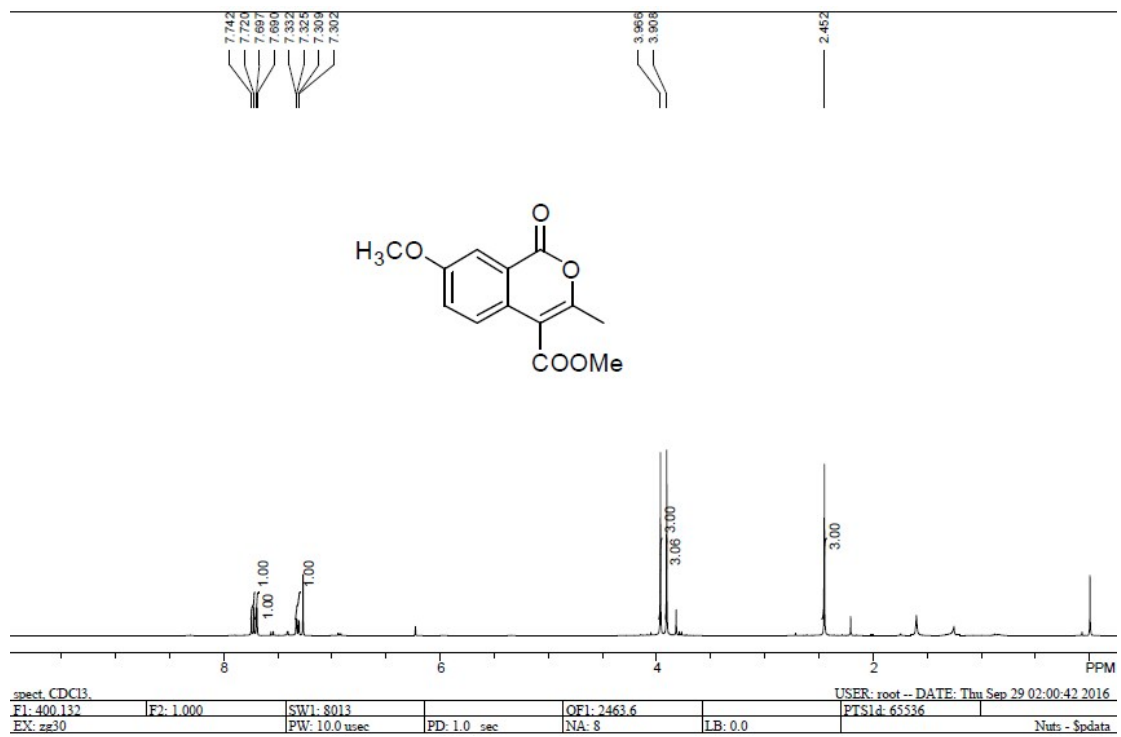


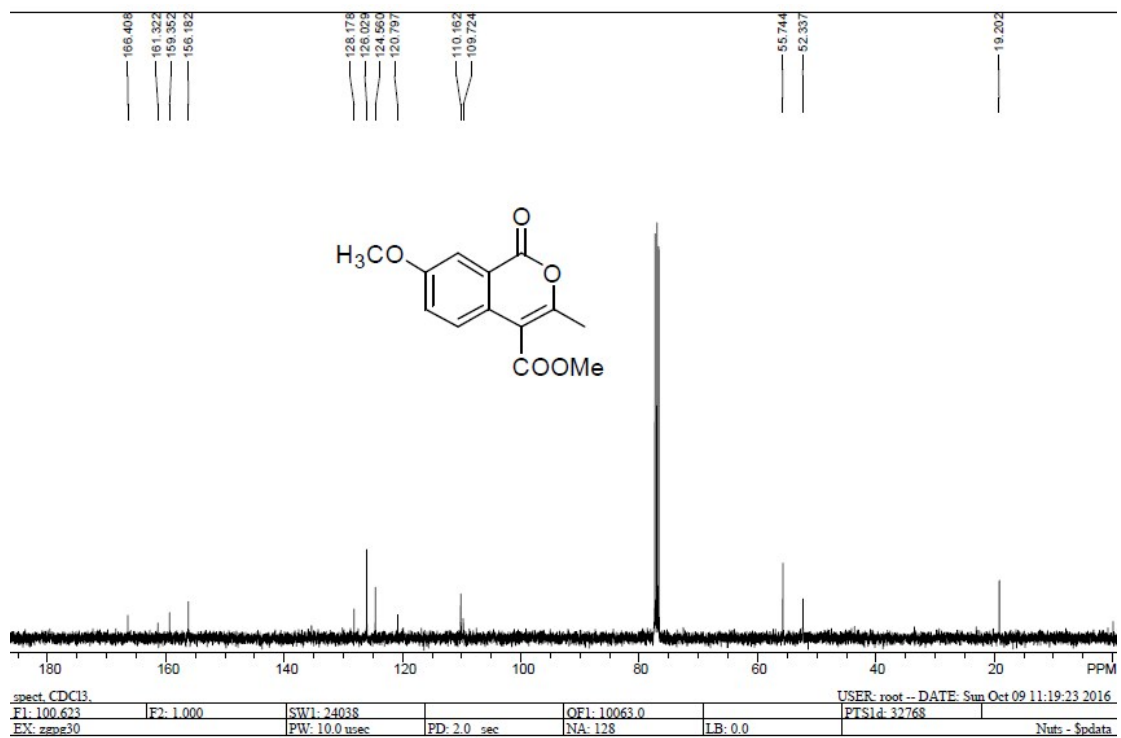
¹H and ¹³C NMR spectra of 4i



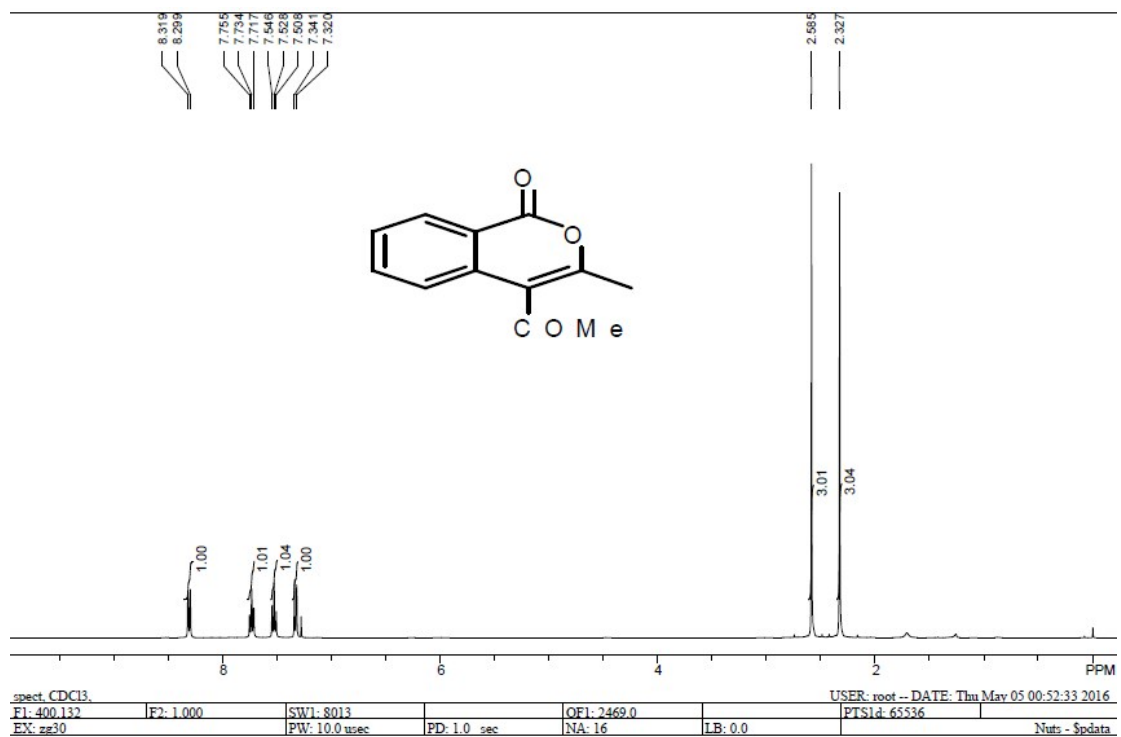


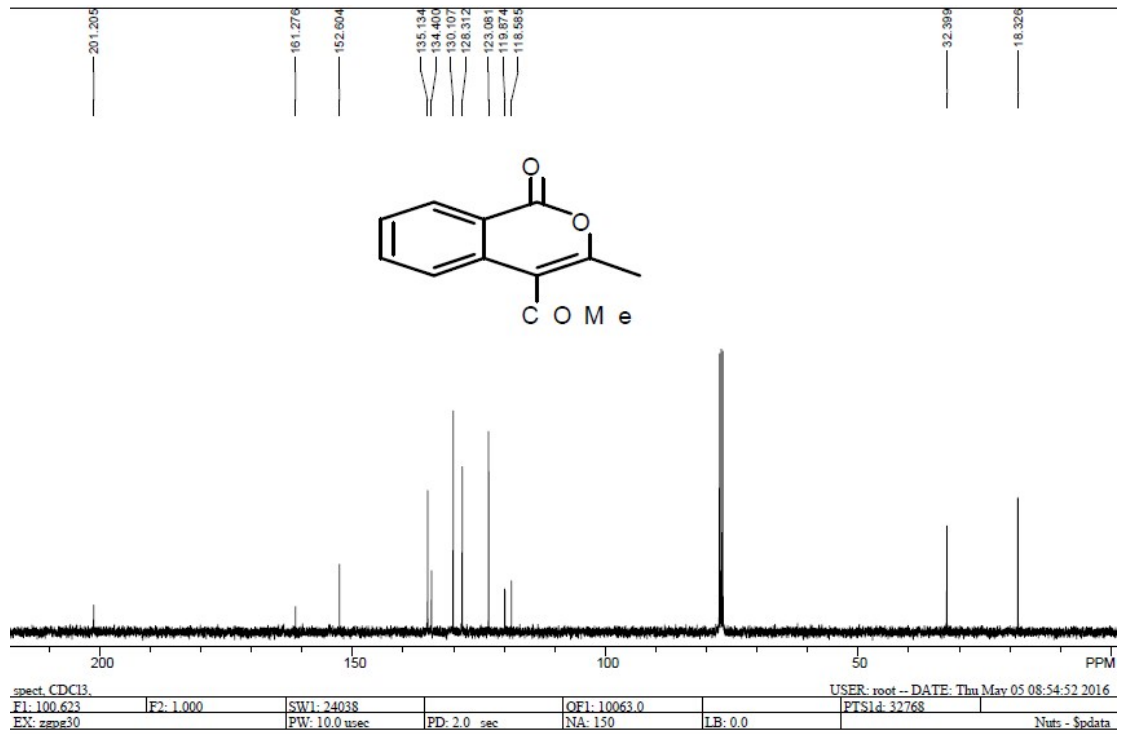
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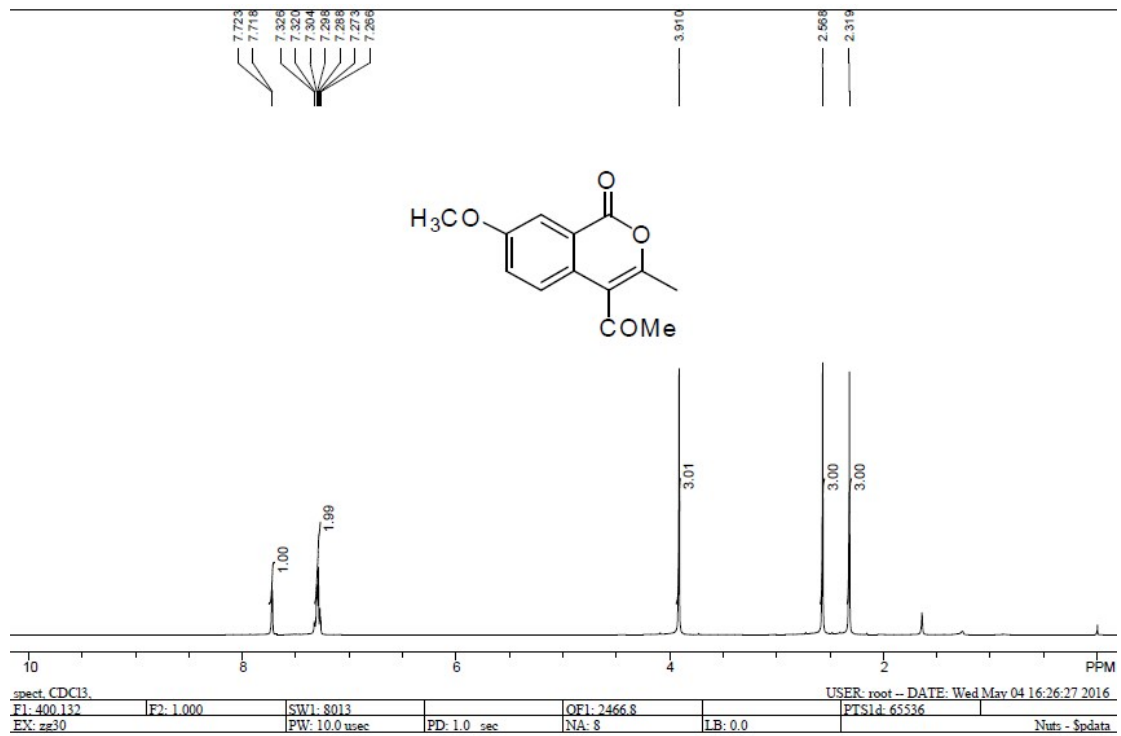


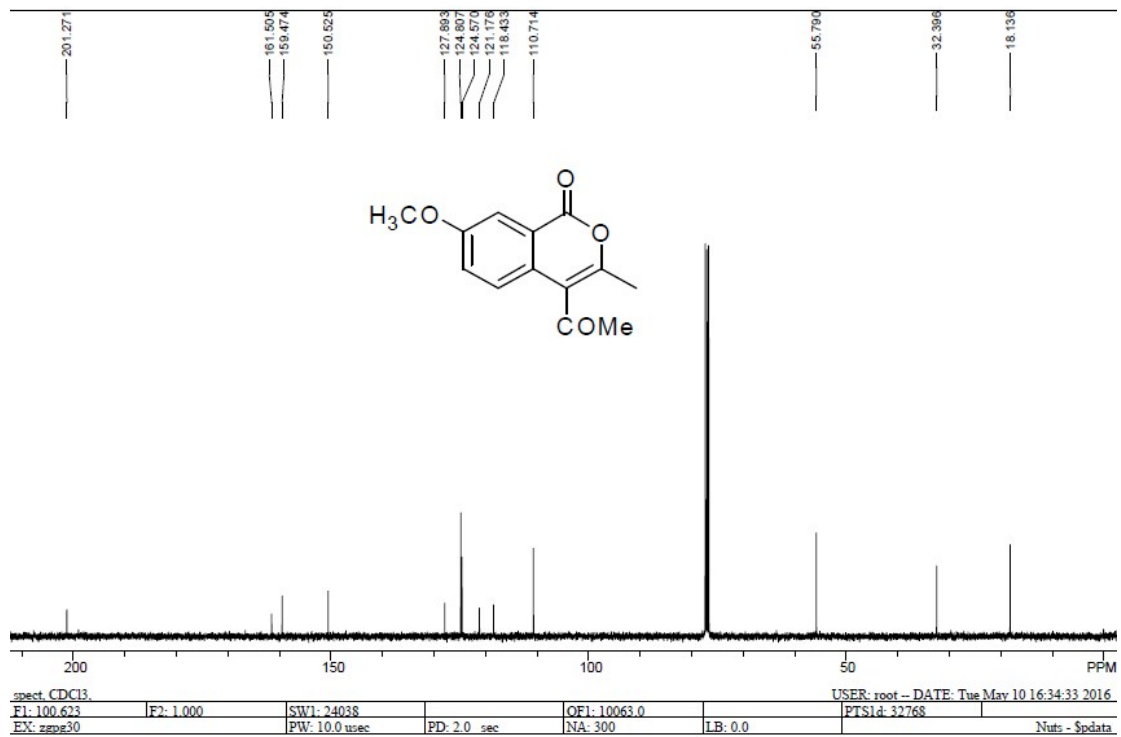
¹H and ¹³C NMR spectra of 4k



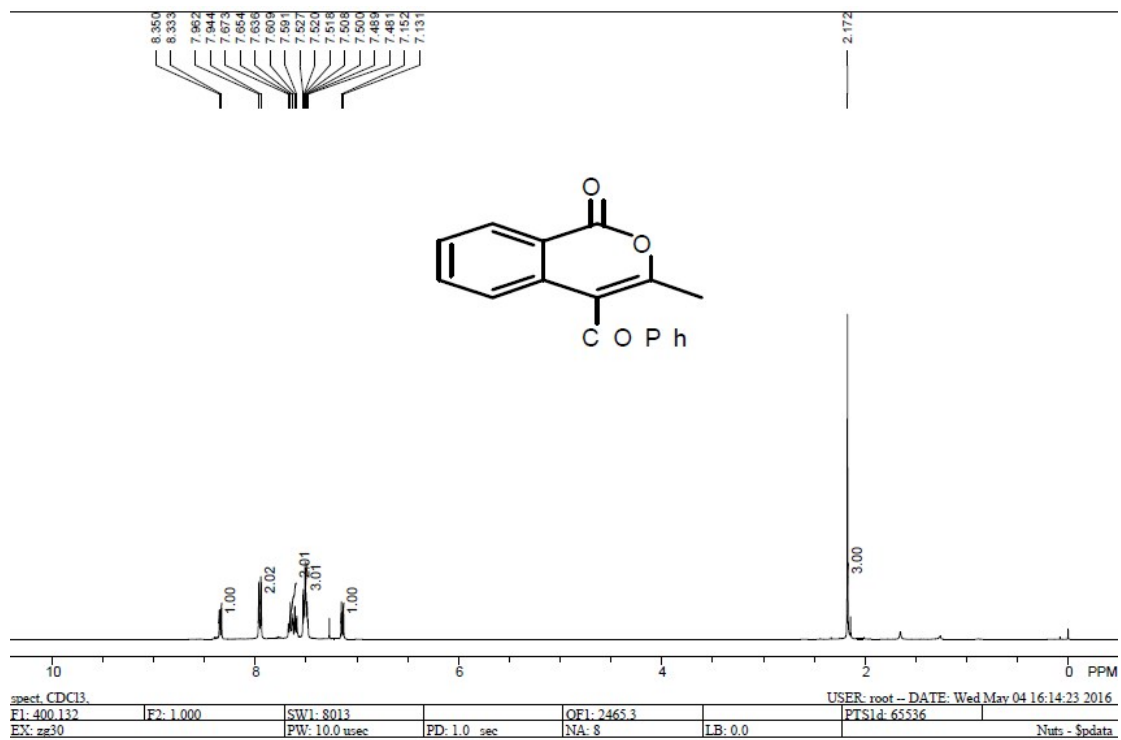


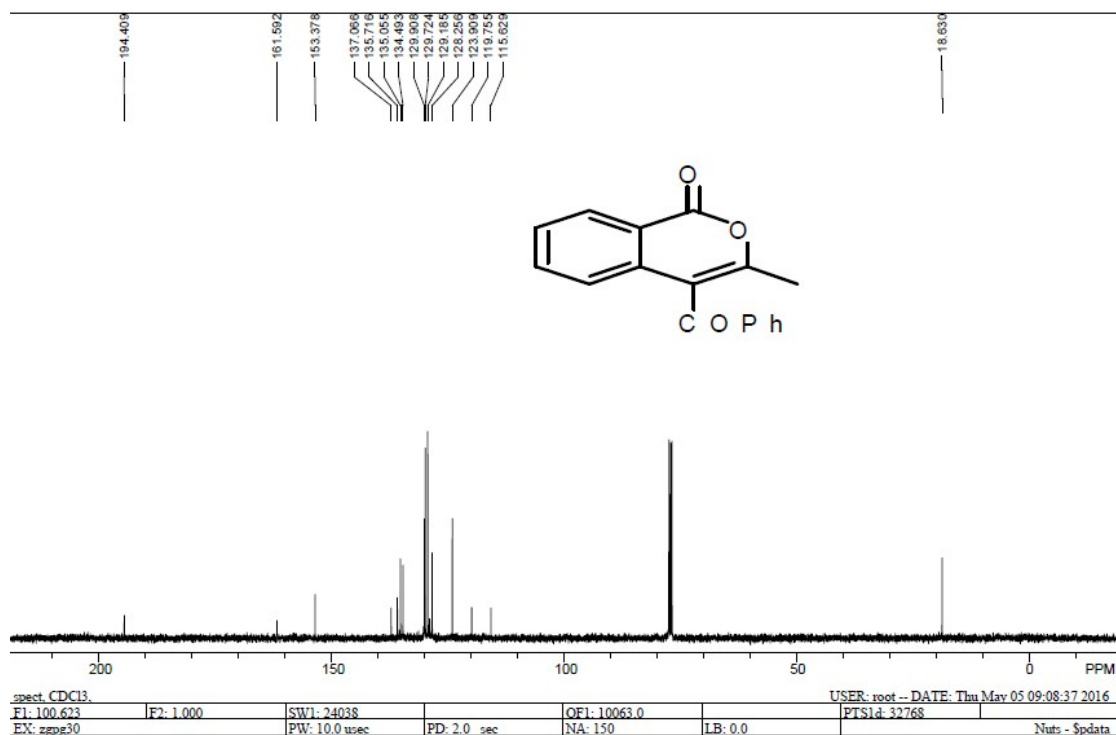
¹H and ¹³C NMR spectra of 4I





¹H and ¹³C NMR spectra of 4m





¹H and ¹³C NMR spectra of 4n

