

Alkyl and Aryl Derivatives Based on *p*-Coumaric Acid Modification and Inhibitory Action against *Leishmania braziliensis* and *Plasmodium falciparum*

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Abstract: In low-income populations, neglected diseases are the principal cause of mortality. Of these, Leishmaniasis and malaria, being parasitic, protozoan infections, affect millions of people worldwide and are creating a public health problem. The present work evaluates the leishmanicidal and antiplasmodial action of a series of twelve *p*-coumaric acid derivatives. Of the tested derivatives, eight presented antiparasitic activities **1-3, 8-12**. The hexyl *p*-coumarate derivative (**9**) (4.14 ± 0.55 $\mu\text{g/mL}$; Selectivity Index (SI) = 2.72) presented the highest leishmanicidal potency against the *Leishmania braziliensis* amastigote form. The results of the molecular docking study suggest that this compound inhibits aldehyde dehydrogenase (ALDH), mitogen activated kinase protein (MPK4), and DNA topoisomerase 2 (TOP2), all of which are key enzymes in the development of *Leishmania braziliensis*. The data indicate that these enzymes interact via van der Waals bonds, hydrophobic interactions, and hydrogen bonds with phenolic and aliphatic parts of this same compound. Of the other compounds analyzed, methyl *p*-coumarate (64.59 ± 2.89 $\mu\text{g/mL}$; IS = 0.1) presented bioactivity against *Plasmodium falciparum*. The study reveals that esters presenting a *p*-coumarate substructure are promising for use in synthesis of derivatives with good antiparasitic profiles.

Keywords: hydroxycinnamic acids; natural products; leishmanicidal activity; antiplasmodial activity; cytotoxicity; neglected diseases

1. Experimental

1.1. Chemical Characterization Compounds 1-12.

(*E*)-Methyl 3-(4-hydroxyphenyl)acrylate (**1**): white solid; Yield 87.98% (95.5 mg, 0.53 mmol); m.p.: 135-136 °C [1]; TLC (7:3 hexane/EtOAc), R_f = 0.52; IR ν_{max} (KBr, cm^{-1}): 3379, 3045, 2954, 1737, 1634, 1601, 1434, 1284, 1170; ^1H NMR (DMSO- d_6 , 400 MHz): δ 3.69 (3H; s), 6.38 (1H; d; J = 16 Hz), 6.80-6.78 (1H; d; J = 8.60 Hz), 7.55-7.52 (1H; d; J = 8.44 Hz), 7.58 (1H; s); ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 51.3, 114.0, 115.8, 125.2, 130.4, 144.9, 159.9, 167.1 [2,3].

(*E*)-Ethyl 3-(4-hydroxyphenyl)acrylate (**2**): white solid; Yield 84.21% (295.8 mg, 1.53 mmol); m.p.: 76-77 °C; TLC (7:3 hexane/EtOAc), R_f = 0.55; IR ν_{max} (KBr, cm^{-1}): 3286, 3026, 2985, 1683, 1634, 1604, 1440, 1280, 1169; ^1H NMR (CDCl_3 , 400 MHz): δ 1.33 (3H; t; J = 7.16 Hz), 4.26 (2H; quart, J = 7.16 Hz),

6.28 (1H; *d*; *J*=15.94 Hz), 6.88-6.86 (2H; *d*; *J*=8.64 Hz); 7.40-7.38 (2H, *d*, *J*=8.64 Hz); 7.63 (1H; *d*; *J*=15.96 Hz); ¹³C NMR (CDCl₃, 100 MHz): δC 14.4, 61, 115.0, 116.1, 126.8, 130.2, 145.5, 158.7, 168.5 [1, 4, 5].

(*E*)-Propyl 3-(4-hydroxyphenyl)acrylate (**3**): White solid; Yield 58.43% (220 mg, 1.06 mmol); m.p.: 74-75 °C; TLC (7:3 hexane/EtOAc), *R_f* = 0.57; IR ν_{max} (KBr, cm⁻¹): 3376, 2970, 2879, 1674, 1638, 1603, 1441, 1271, 1171; ¹H NMR (CDCl₃, 400 MHz): δH 0.99 (3H; *t*; *J*=7.4 Hz), 1.73 (2H; *sext*; *J*=7.44), 4.16 (2H; *t*; *J*=6.72 Hz), 6.30 (1H; *d*; *J*=15.95 Hz); 6.87-6.85 (2H, *d*, *J*=8.66 Hz); 7.43- 7.40 (2H; *d*; *J*=8.67 Hz), 7.63(1H, *d*, *J*=15.96 Hz); ¹³C NMR (CDCl₃, 100 MHz): δC 10.8, 22.2, 66.5, 115.4, 116.0, 127.1, 130.22, 145.0, 158.3, 168.5 [1,2].

(*E*)-Isopropyl 3-(4-hydroxyphenyl)acrylate (**4**): White solid; Yield 60.73% (228.9 mg, 1.10 mmol); m.p.: 71-72 °C; TLC (7:3 hexane/EtOAc), *R_f* = 0.57; IR ν_{max} (KBr, cm⁻¹): 3272, 2980, 2939, 1675, 1629, 1605, 1466, 1279, 1172; ¹H NMR (CDCl₃, 400 MHz): δH 1.31 (6H; *d*; *J*=6.28 Hz), 5.14 (1H; *hept*; *J*=6.25Hz), 6.27 (1H; *d*; *J*=15.94 Hz); 6.89-6.87 (2H, *d*, *J*=8.60 Hz); 7.40-7.38 (2H; *d*; *J*=8.67 Hz), 7.61(1H, *d*, *J*=15.95 Hz); ¹³C NMR (CDCl₃, 100 MHz): δC 22.2, 68.4, 115.6, 116.1, 126.8, 130.3, 145.0, 158.7, 167.1 [1,2].

(*E*)-2-methoxyethyl 3-(4-hydroxyphenyl)acrylate (**5**): white solid; Yield 42.76% (173.7 mg, 0.78 mmol) ; m.p.: 96-97 °C; TLC (7:3 hexane/EtOAc), *R_f* = 0.33; IR ν_{max} (KBr, cm⁻¹): 3260, 3043, 2959, 1696, 1655, 1609, 1447, 1266, 1176; ¹H NMR (CDCl₃, 400 MHz): δH 3.46 (3H; *s*), 3.71 (2H; *t*, *J*=4.64 Hz), 4.37 (2H, *t*, *J*=4.52 Hz), 6.21 (1H, *d*, *J* =15.94 Hz), 6.83-6.81 (2H, *d*; *J*=8.55 Hz), 7.35- 7.32 (2H, *d*, *J*=8.7 Hz), 7.60 (1H, *d*, *J* =15.95 Hz) ¹³C NMR (CDCl₃, 100 MHz): δC 58.8, 63.2, 114.6, 116.1, 126.5, 130.1, 145.6, 158.8, 167.8 [1,2].

(*E*)-Butyl 3-(4-hydroxyphenyl)acrylate (**6**): Brown amorphous; Yield 98% (395.5 mg, 1.79 mmol) ; TLC (7:3 hexane/EtOAc), *R_f* = 0.65; IR ν_{max} (KBr, cm⁻¹): 3277, 2959, 2873, 1683, 1634, 1604, 1474, 1280, 1172; ¹H NMR (CDCl₃, 400 MHz): δH 0.96 (3H; *t*; *J*=7.38 Hz), 1.44 (2H; *sext*; *J*=7.44), 1.69 (2H; *pent*; *J*=6.80 Hz), 4.20 (3H; *t*, *J*=6.67); 6.30 (1H; *d*; *J*=15.94 Hz); 6.86-6.84 (2H, *d*, *J*=8.59 Hz); 7.43-7.41 (2H; *d*; *J*=8.59 Hz), 7.62 (1H, *d*, *J*=15.95 Hz); ¹³C NMR (CDCl₃, 100 MHz): δC 14.0, 19.3, 30.8, 64.8, 115.2, 116.1, 126.8, 130.2, 145.2, 158.5, 168.5 [1,2].

(*E*)-Pentyl 3-(4-hydroxyphenyl)acrylate (**7**): Brown amorphous; Yield 44.09% (188.8 mg, 0.80 mmol) ; TLC (7:3 hexane/EtOAc), *R_f* = 0.60; IR ν_{max} (KBr, cm⁻¹): 3400, 2959, 2872, 1685, 1633, 1605, 1445, 1268, 1170; ¹H NMR (CDCl₃, 400 MHz): δH 0.94 (3H, *t*, *J*=6.99), 1.40 (2H, *m*), 1.40 (2H, *m*), 1.73 (2H, *quint*, *J*=7.32 Hz), 4.22 (2H, *t*, *J*=6.74 Hz), 6.32 (1H, *d*, *J*=15.95 Hz), 6.90-6.88 (2H, *d*; *J*=8.62 Hz), 7.44-7.42 (2H, *d*, *J*=8.62 Hz), 7.65 (1H, *d*, *J*=15.94 Hz) ¹³C NMR (CDCl₃, 100 MHz): δC 14.1, 22.5, 28.2, 28.5, 65.1, 115.2, 116.1, 126.9, 130.2, 145.1, 158.5, 168.4 [1,2].

(*E*)-Isopentyl 3-(4-hydroxyphenyl)acrylate (**8**): Brown solid; Yield 79.36% (339.8 mg, 1.45 mmol); m.p.: 111-112 °C (lit. 151-153 °C, [1]); TLC (7:3 hexane/EtOAc), *R_f* = 0.66; IR ν_{max} (KBr, cm⁻¹): 3380, 2958, 2873, 1687, 1636, 1604, 1437, 1277, 1167; ¹H NMR (CDCl₃, 400 MHz): δH 0.95 (3H, *d*, *J*=6.64 Hz), 1.72 (1H, *quart*, *J*=6.75 Hz), 1.60 (2H, *d*, *J*= 6.74 Hz), 4.23 (2H, *t*, *J*=6.83 Hz), 6.31 (1H, *d*, *J*=15.96 Hz), 6.88-6.86 (2H, *d*; *J*=8.44 Hz), 7.41-7.39 (2H, *d*, *J*=8.49 Hz), 7.64 (1H, *d*, *J*=15.98 Hz) ¹³C NMR (CDCl₃, 100 MHz): δC 22.6, 25.3, 37.5, 63.6, 115.2, 116.1, 126.8, 130.2, 145.1, 158.6, 168.6 [1,2].

(*E*)-Hexyl 3-(4-hydroxyphenyl)acrylate (**9**): White solid; Yield 36.88% (167.4 mg; 0.67 mmol); m.p.: 42-43 °C (lit. 160 °C, [7]); TLC (8:2 hexane/EtOAc), *R_f* = 0.47; IR ν_{max} (KBr, cm⁻¹): 3383, 2955, 2857, 1675, 1625, 1604, 1472, 1276, 1170; ¹H NMR (CDCl₃, 400 MHz): δH 0.89 (3H, *t*, *J*=6.02), 1.36 (6H, *m*), 1.69 (2H, *quint*; *J*=16.0 Hz), 4.19 (2H, *t*, *J*=6.74 Hz), 6.28 (1H, *d*, *J*=15.94 Hz), 6.88-6.86 (2H, *d*; *J*=8.64 Hz), 7.42-7.40 (2H, *d*, *J*=8.62 Hz), 7.63 (1H, *d*, *J*=15.95 Hz) ¹³C NMR (CDCl₃, 100 MHz): δC 14.1, 22.7, 25.8, 28.8, 31.6, 65.1, 115.4, 116.1, 127, 130.1, 145.0, 158.4, 168.3 [1,5, 7].

(*E*)-Dodecyl 3-(4-hydroxyphenyl)acrylate (**10**): White solid; Yield 29.55% (179.6 mg, 0.54 mmol); m.p.: 76-77 °C (lit. 73-75 °C, [6]); TLC (8:2 hexane/EtOAc), *R_f* = 0.52; IR ν_{max} (KBr, cm⁻¹): 3381, 2926, 2848, 1674, 1625, 1603, 1473, 1275, 1171; ¹H NMR (CDCl₃, 400 MHz): δH 0.88 (3H, *t*, *J*=6.68), 1.35 (18H, *m*), 1.70 (2H, *quint*, *J* = 6.72 Hz), 4.20 (2H, *t*, *J* = 6.76 Hz), 6.30 (1H, *d*, *J*=15.96 Hz), 6.88-6.86 (2H, *d*; *J*=8.64 Hz), 7.42-7.40 (2H, *d*, *J*=8.64 Hz), 7.63 (1H, *d*, *J*=15.96 Hz) ¹³C NMR (CDCl₃, 100 MHz): δC 14.1, 22.7, 26, 28.7, 29.3, 29.4, 29.5, 29.6, 29.6, 29.7, 31.9, 64.9, 115.3, 116, 126.9, 130, 145.1, 158.5, 168.5 [1,6].

(*E*)-4-Methylbenzyl 3-(4-hydroxyphenyl)acrylate (**11**): White solid; Yield 30% (147.2 mg, 0.54 mmol); m.p.: 93-94 °C; TLC (8:2 hexane/EtOAc), *R_f* = 0.34; IR ν_{max} (KBr, cm⁻¹): 3291, 3027, 2958, 1689, 1629, 1605, 1450, 1279, 1164; ¹H NMR (CDCl₃, 400 MHz): δH 2.37(3H, *s*), 5.22 (2H, *s*), 6.33 (1H, *d*, *J*=

15.94 Hz), 6.86-6.84 (2H, *d*; *J*=8.76 Hz), 7.20-7.18 (2H, *d*, *J*=7.8 Hz), 7.32-7.30 (2H, *d*, *J*=8.04 Hz), 7.40-7.38 (2H, *d*, *J*=8.72 Hz), 7.66 (1H, *d*, *J*=15.96 Hz) ¹³C NMR (CDCl₃, 100 MHz): δC 21.7, 66.6, 115.1, 116.1, 127.0, 128.6, 129.4, 130.2, 133.1, 138.3, 145.5, 158.3, 168.0 [1,8].

(*E*)-4-Isopropylbenzyl 3-(4-hydroxyphenyl)acrylate (**12**): White solid; Yield 29.76% (161.2 mg, 0.54 mmol); m.p.: 107-108 °C; TLC (8:2 hexane/EtOAc), *R*_f = 0.39; IR ν_{max} (KBr, cm⁻¹): 3232, 3031, 2960, 1709, 1638, 1605, 1455, 1226, 1158; ¹H NMR (CDCl₃, 400 MHz): δH 1.27 (6H, *d*, *J*=6.92 Hz), 2.94 (1H, *sept*, *J*=6.74 Hz), 5.24 (2H, *s*), 6.35 (1H, *d*, *J*=15.94 Hz), 6.87-6.85 (2H, *d*; *J*=8.55 Hz), 7.28 (2H, *m*), 7.38-7.36 (2H, *d*, *J*=8.2), 7.43-7.41 (2H, *d*, *J*=8.4 Hz), 7.69 (1H, *d*, *J*=15.96 Hz) ¹³C NMR (CDCl₃, 100 MHz): δC 24.1, 34.2, 66.6, 128.6, 126.8, 149.3, 126.8, 128.6, 133.5, 115.2, 116.1, 127.1, 130.2, 145.3, 158.2, 167.9 [1,8].

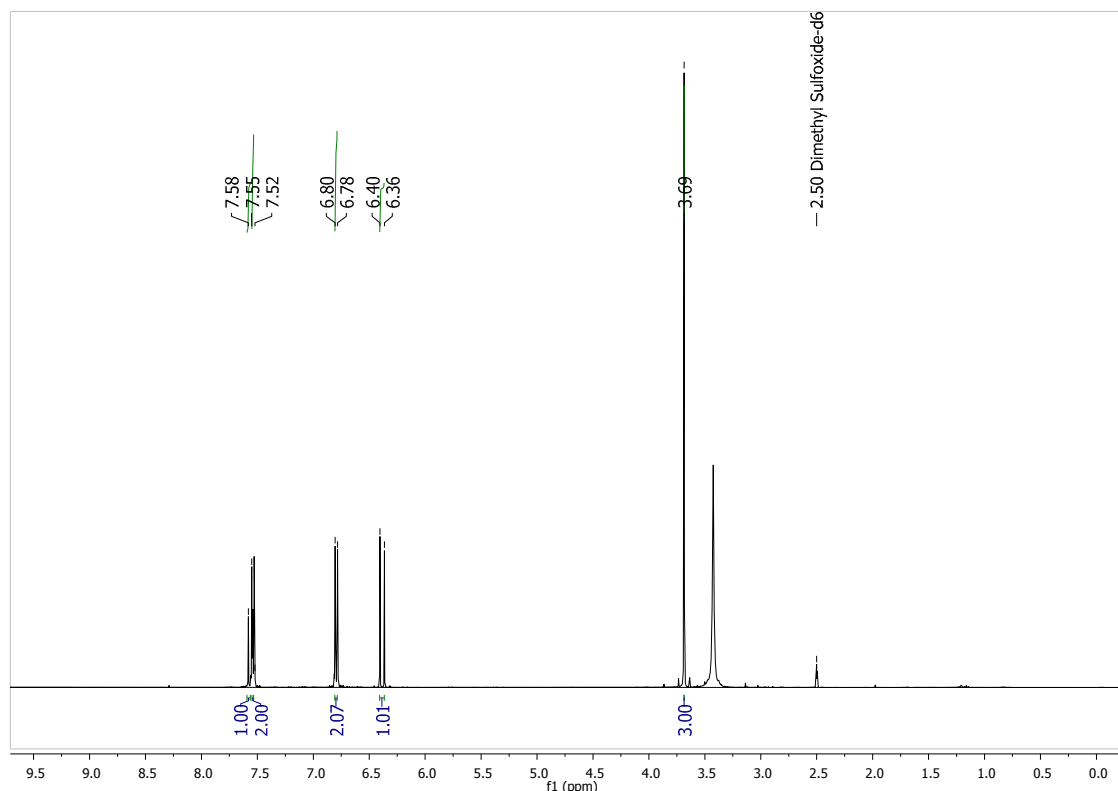


Figure S1. ¹H NMR (DMSO-*d*₆, 400 MHz) spectrum of methyl *p*-coumarate (**1**).

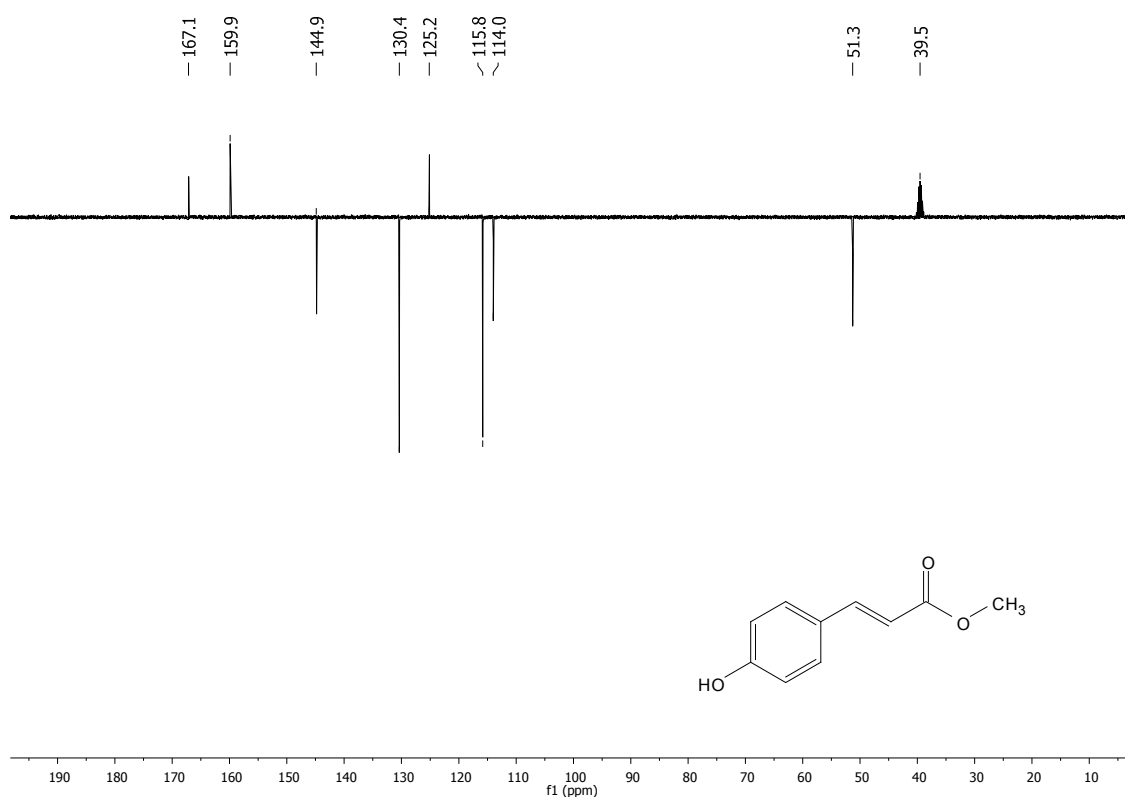


Figure S2. ¹³C NMR (DMSO-d₆, 100 MHz) spectrum of methyl *p*-coumarate (1).

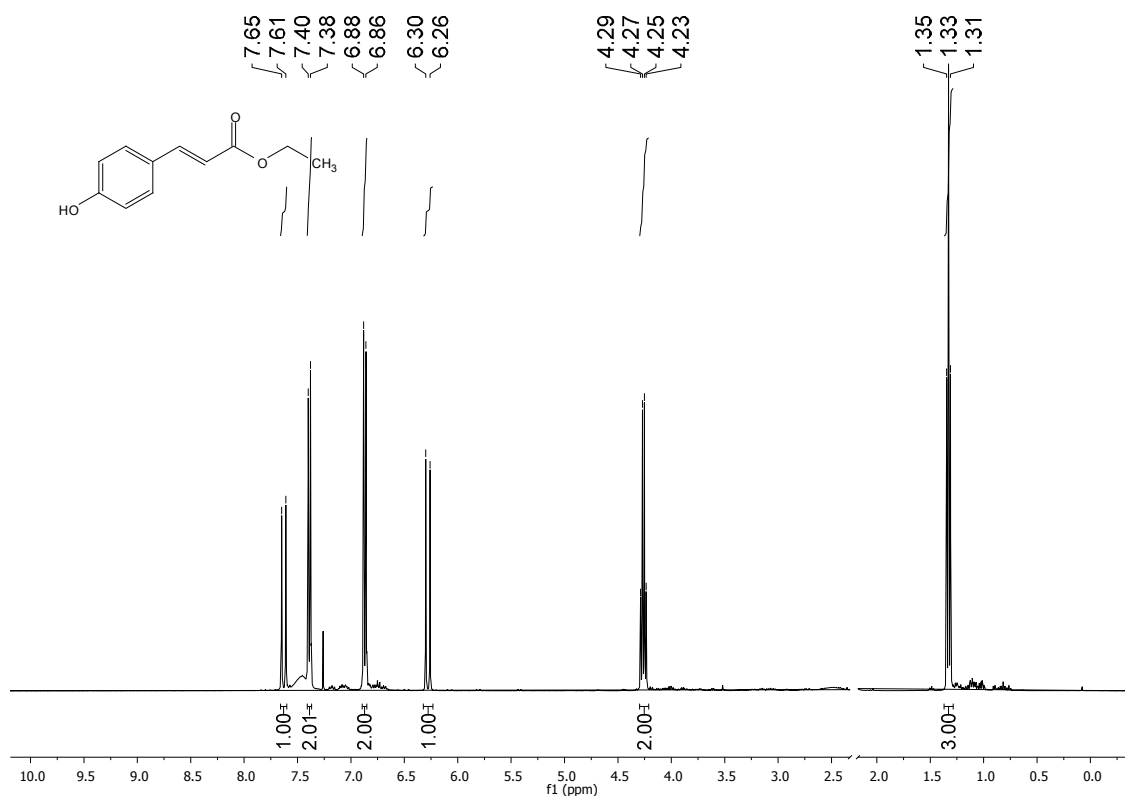


Figure S3. ¹H NMR (CDCl₃, 400 MHz) spectrum of ethyl *p*-coumarate (2).

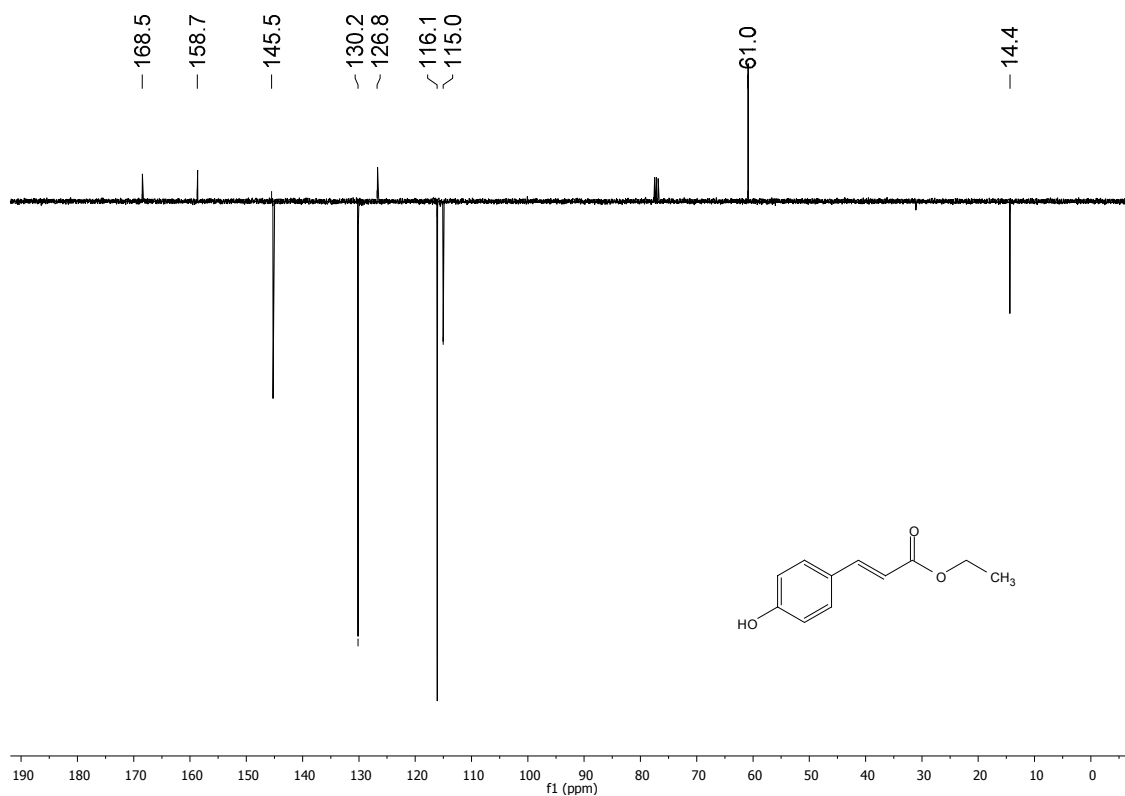


Figure S4. ¹³C NMR (CDCl₃, 100 MHz) spectrum of ethyl *p*-coumarate (2).

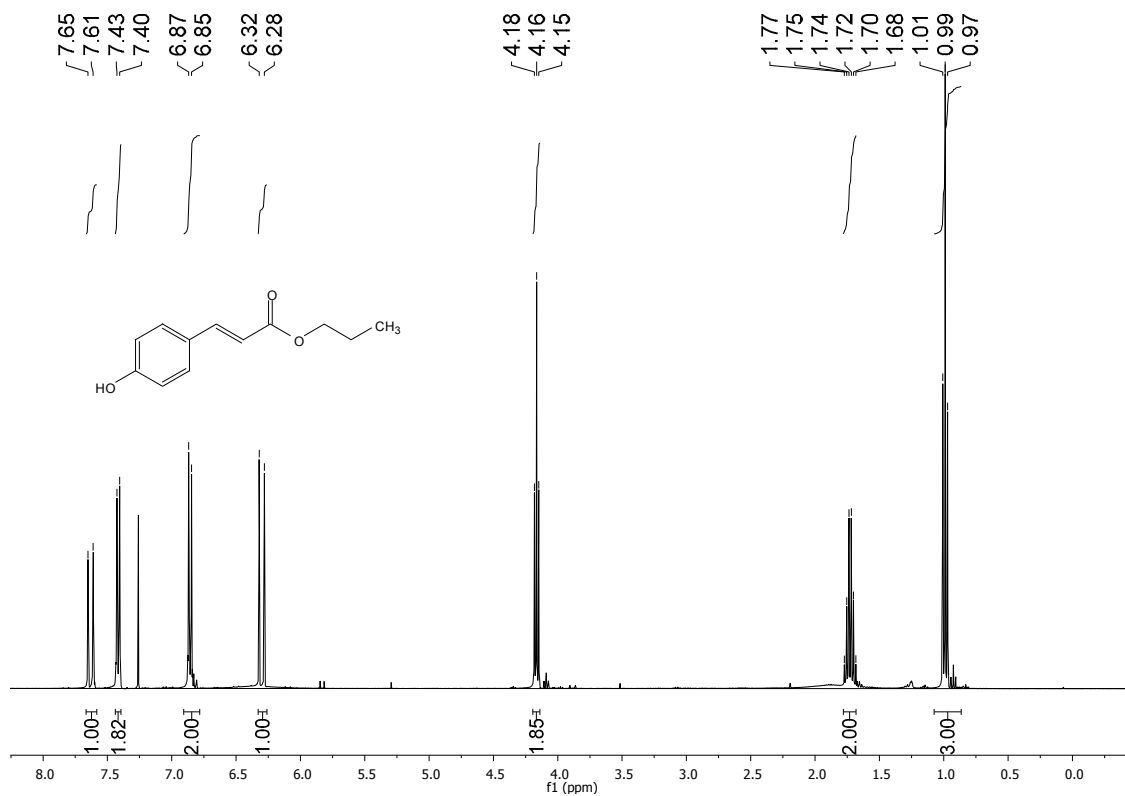


Figure S5. ¹H NMR (CDCl₃, 400 MHz) spectrum of propyl *p*-coumarate (3).

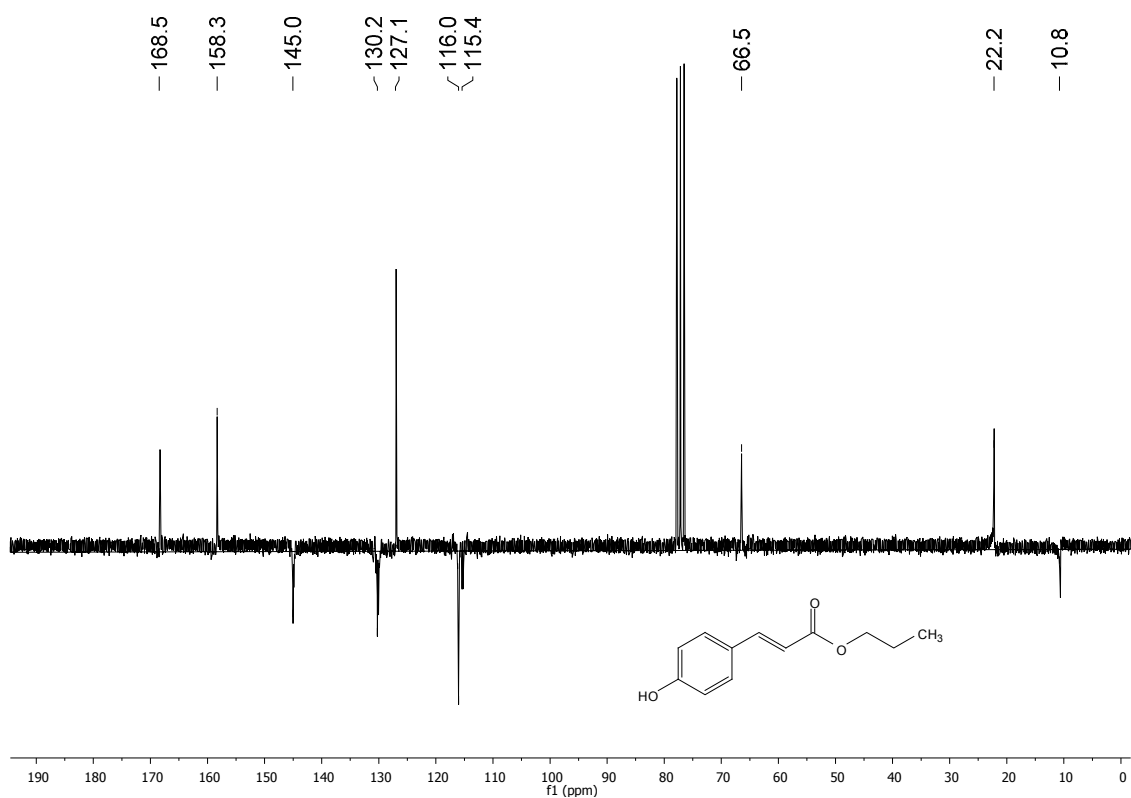


Figure S6. ¹³C NMR (CdCl₃, 100 MHz) spectrum of propyl *p*-coumarate (3).

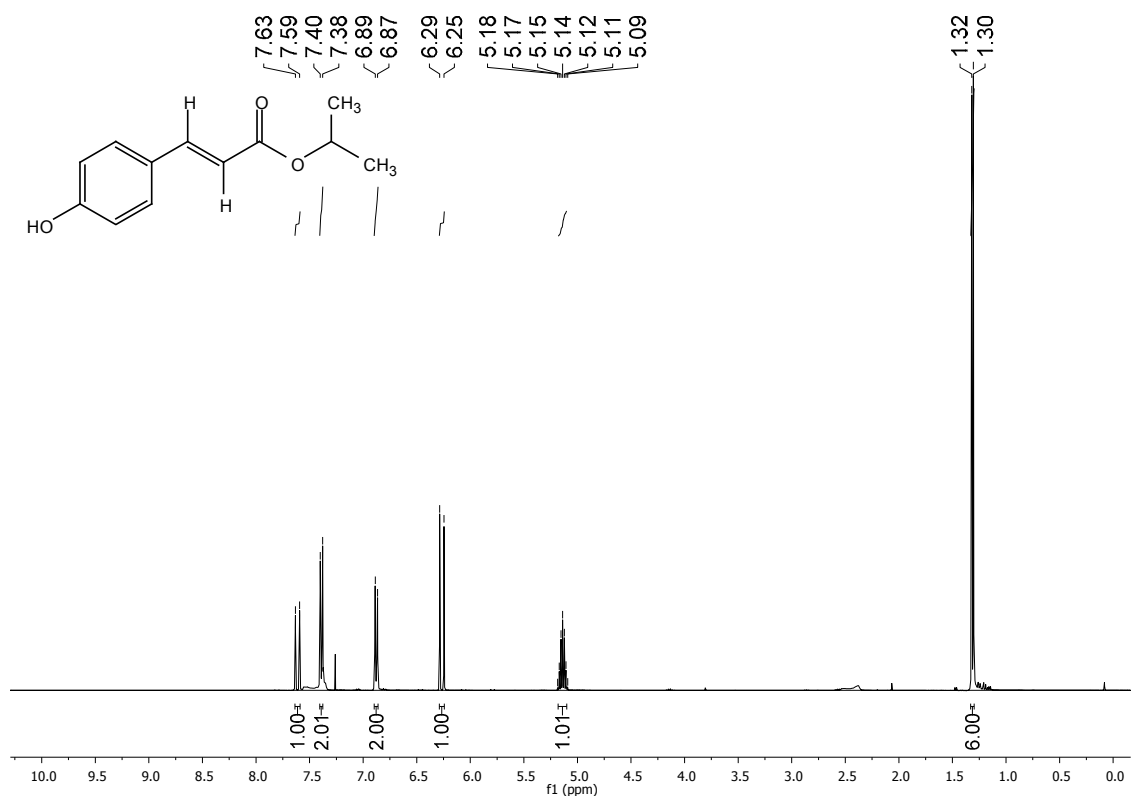


Figure S7. ¹H NMR (CdCl₃, 400 MHz) spectrum of isopropyl *p*-coumarate (4).



Figure S8. ¹³C NMR (CDCl₃, 100 MHz) spectrum of isopropyl *p*-coumarate (4).

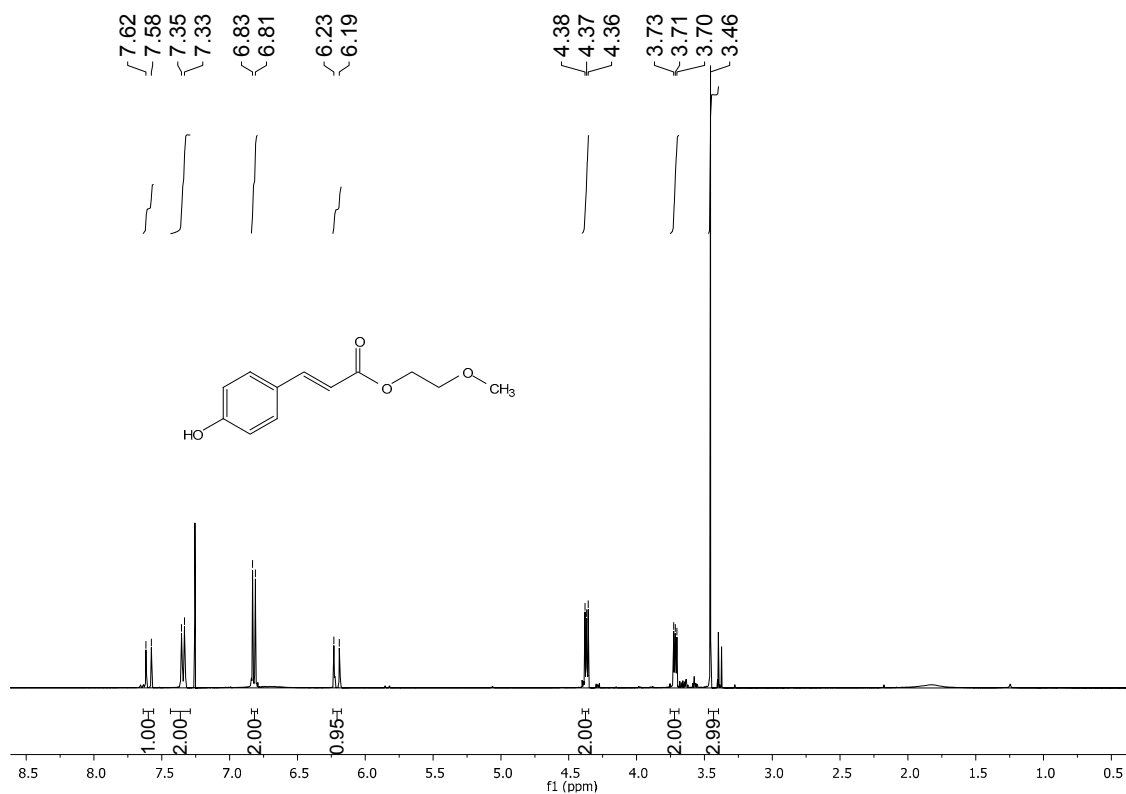


Figure S9. ¹H NMR (CDCl₃, 400 MHz) spectrum of Methoxyethyl *p*-coumarate (5).

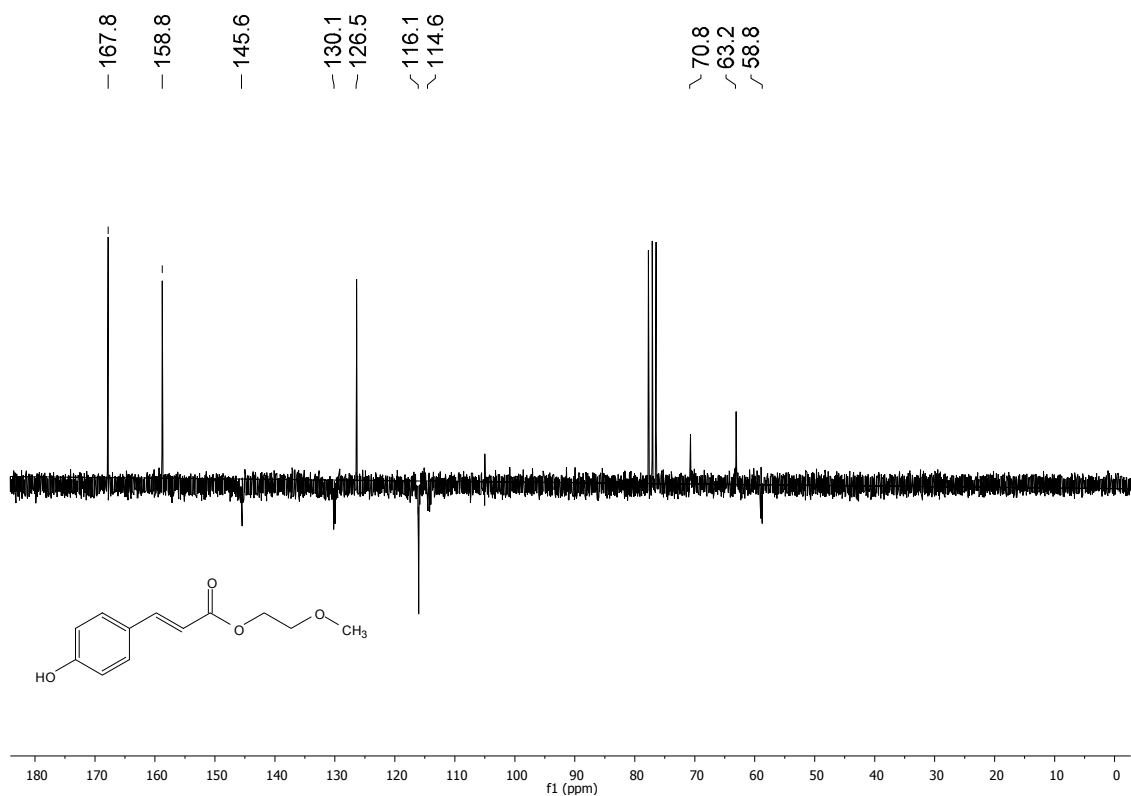


Figure S10. ¹³C NMR (CdCl₃, 100 MHz) spectrum of Methoxyethyl *p*-coumarate (5).

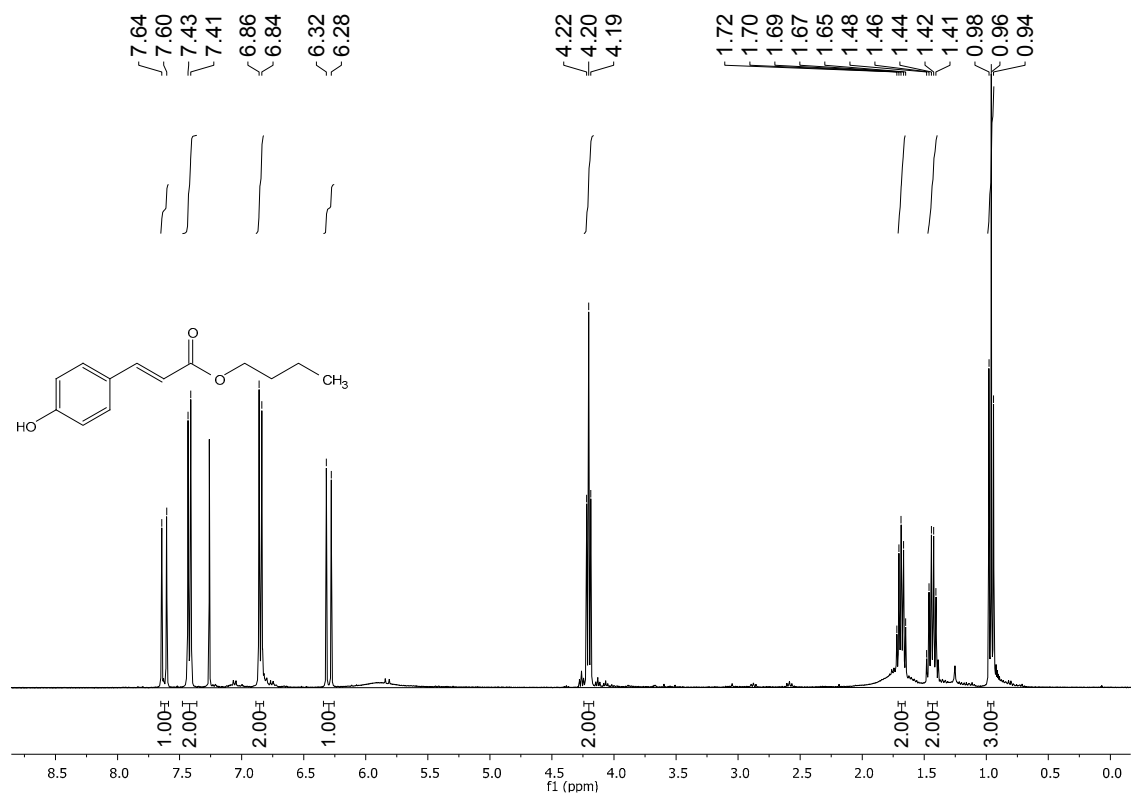


Figure S11. ¹H NMR (CdCl₃, 400 MHz) spectrum of butyl *p*-coumarate (6).

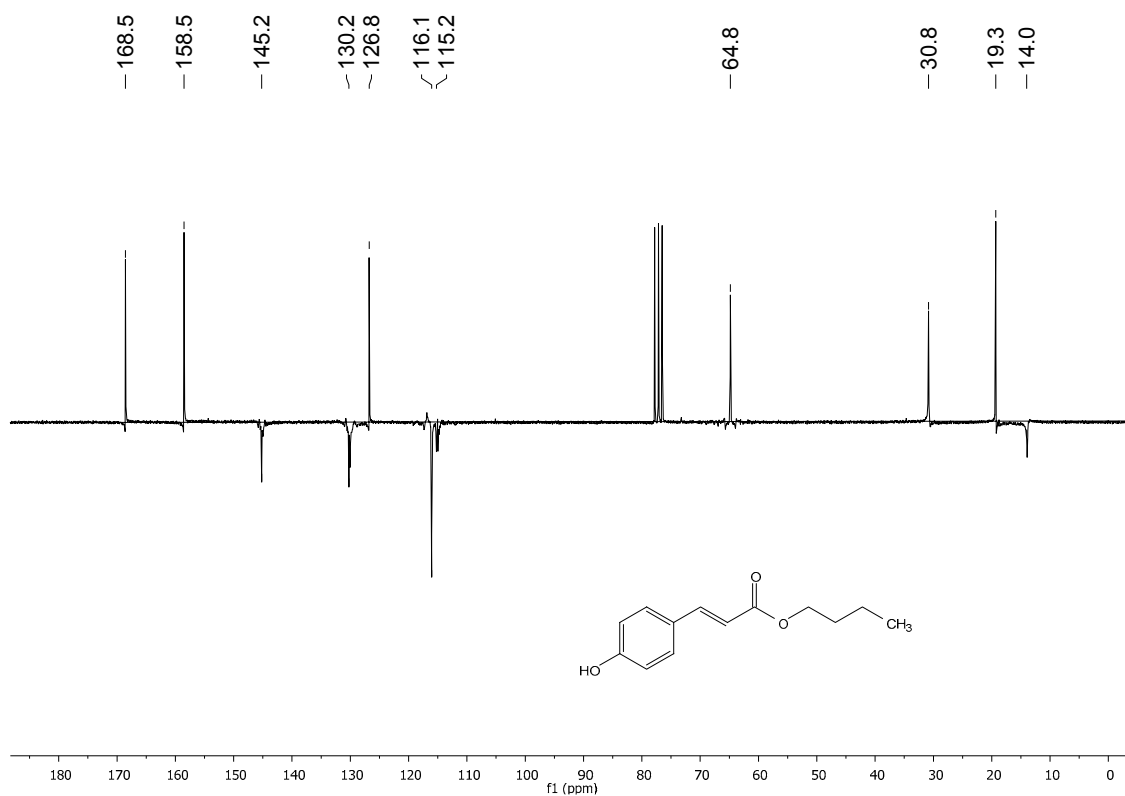


Figure S12. ¹³C NMR (CdCl₃, 100 MHz) spectrum of butyl *p*-coumarate (6).

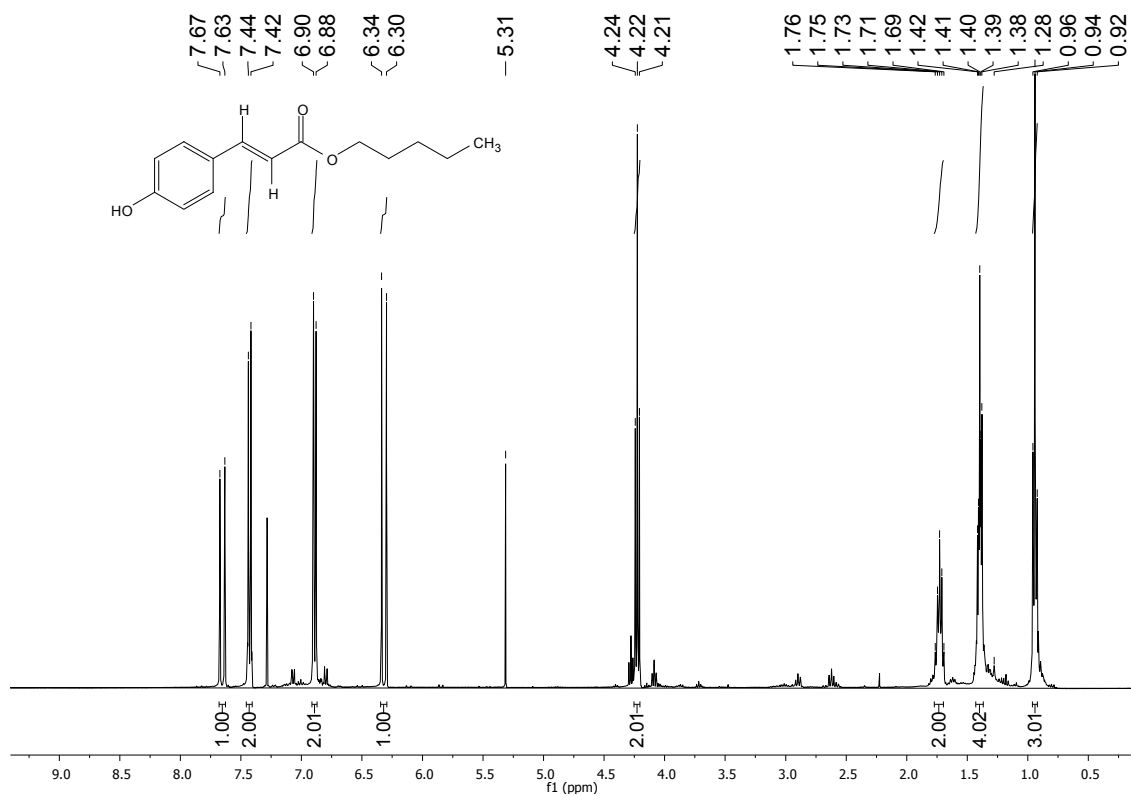


Figure S13. ¹H NMR (CdCl₃, 400 MHz) spectrum of pentyl *p*-coumarate (7).

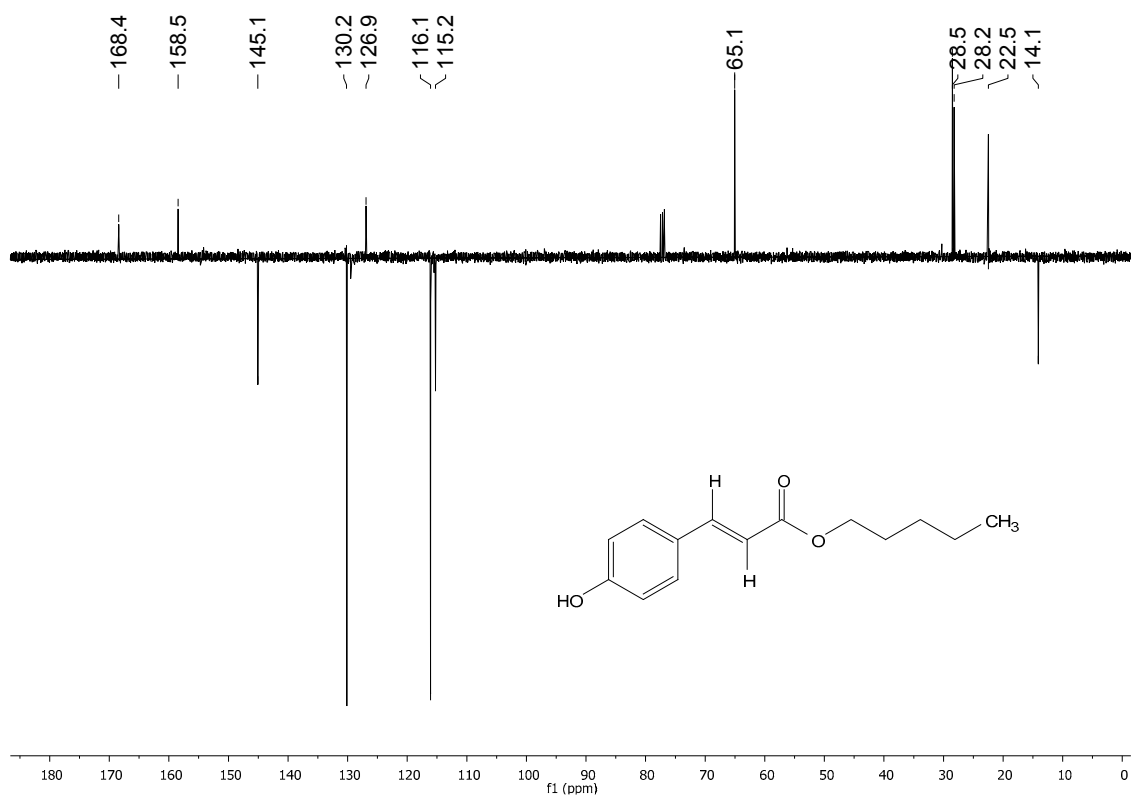


Figure S14. ¹³C NMR (CdCl₃, 100 MHz) spectrum of pentyl *p*-coumarate (7).

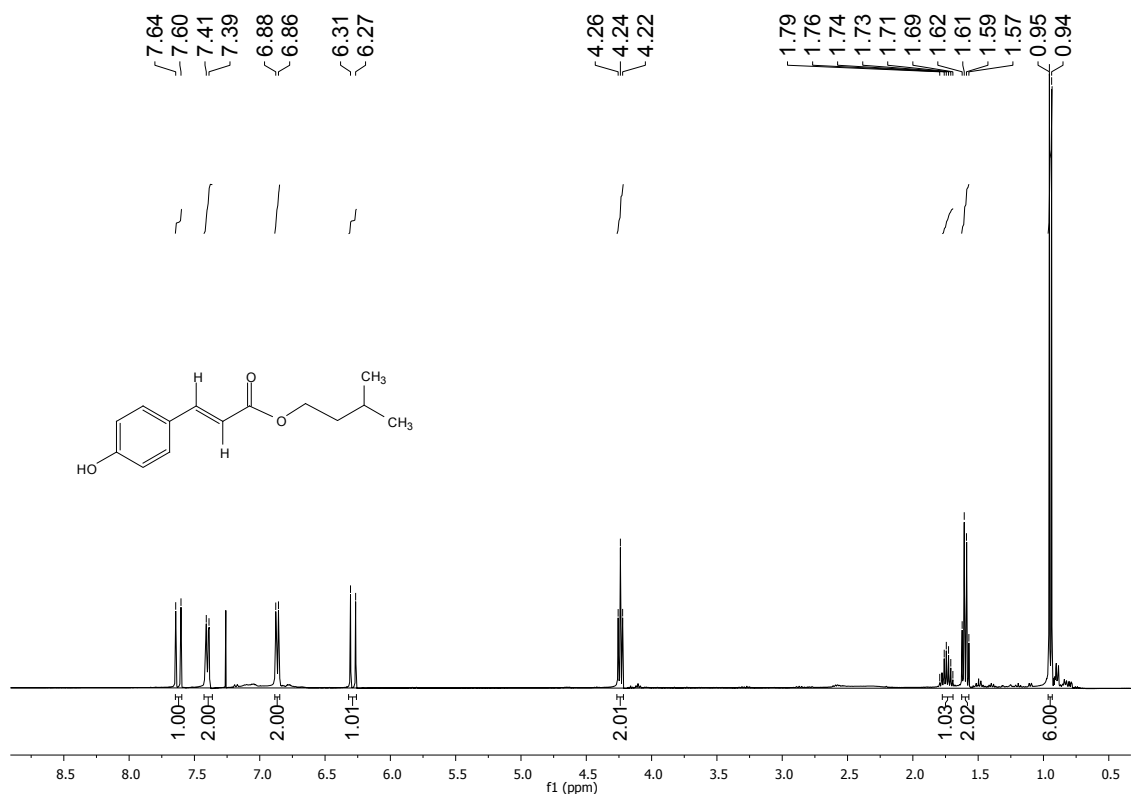


Figure S15. ¹H NMR (CdCl₃, 400 MHz) spectrum of isopentyl *p*-coumarate (8).

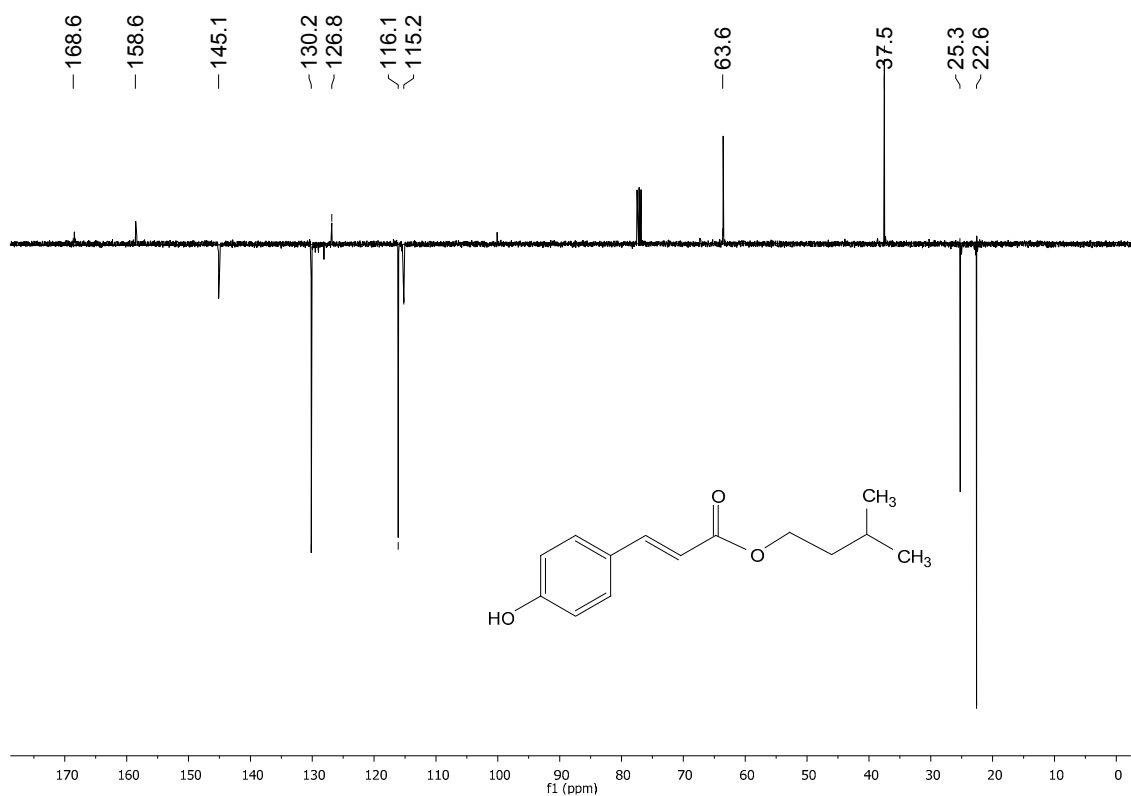


Figure S16. ¹³C NMR (CdCl₃, 100 MHz) spectrum of isopentyl *p*-coumarate (8).

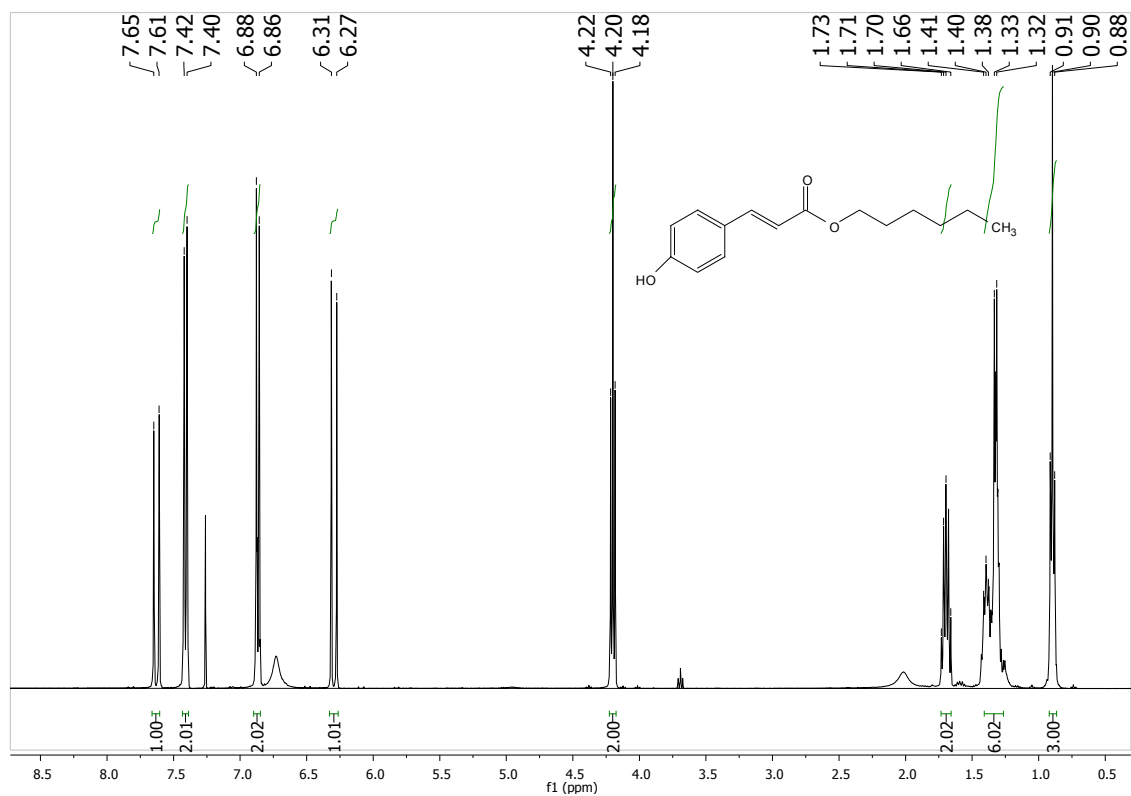


Figure S17. ¹H NMR (CdCl₃, 400 MHz) spectrum of hexyl *p*-coumarate (9).

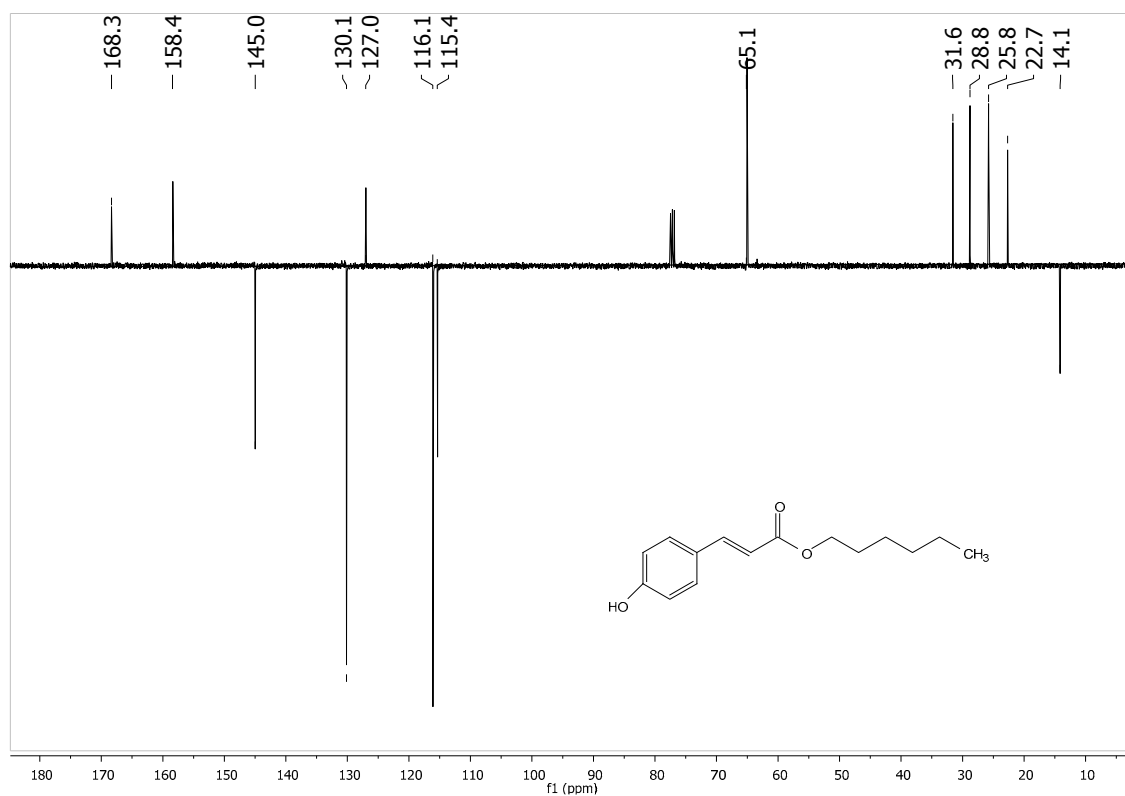


Figure S18. ¹³C NMR (CdCl₃, 100 MHz) spectrum of hexyl *p*-coumarate (9).

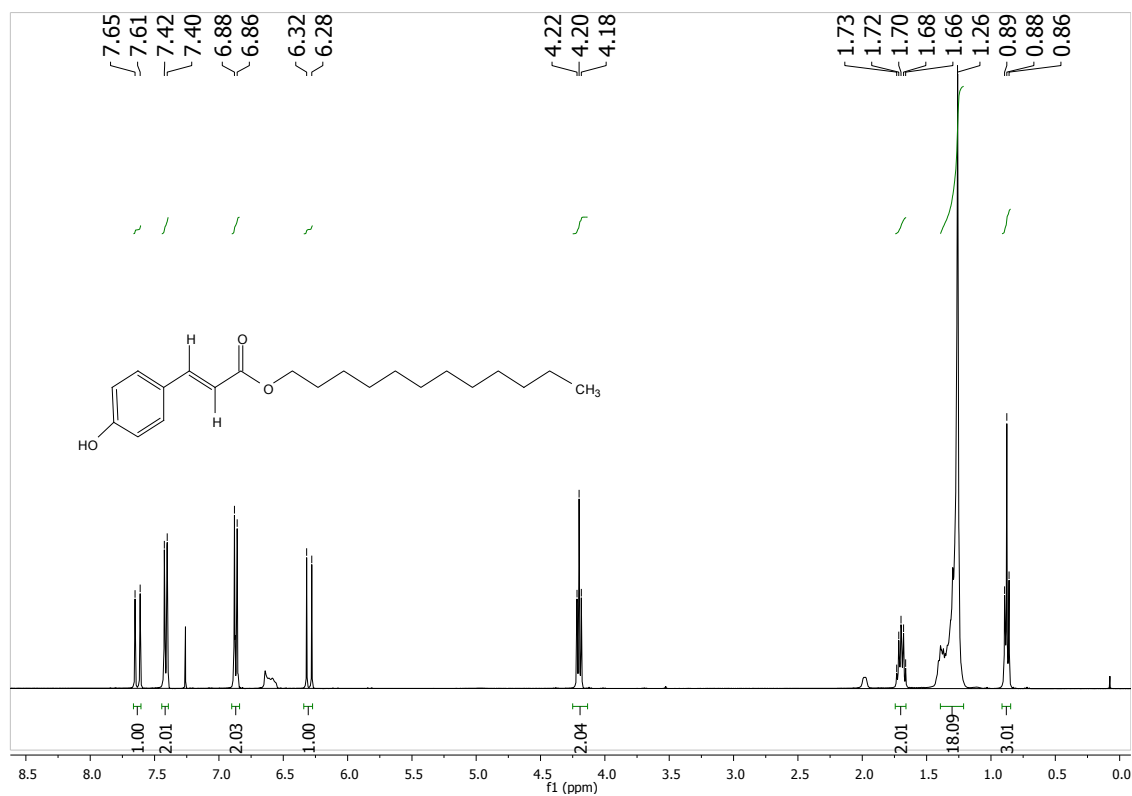


Figure S19. ¹H NMR (CdCl₃, 400 MHz) spectrum of dodecyl *p*-coumarate (10).

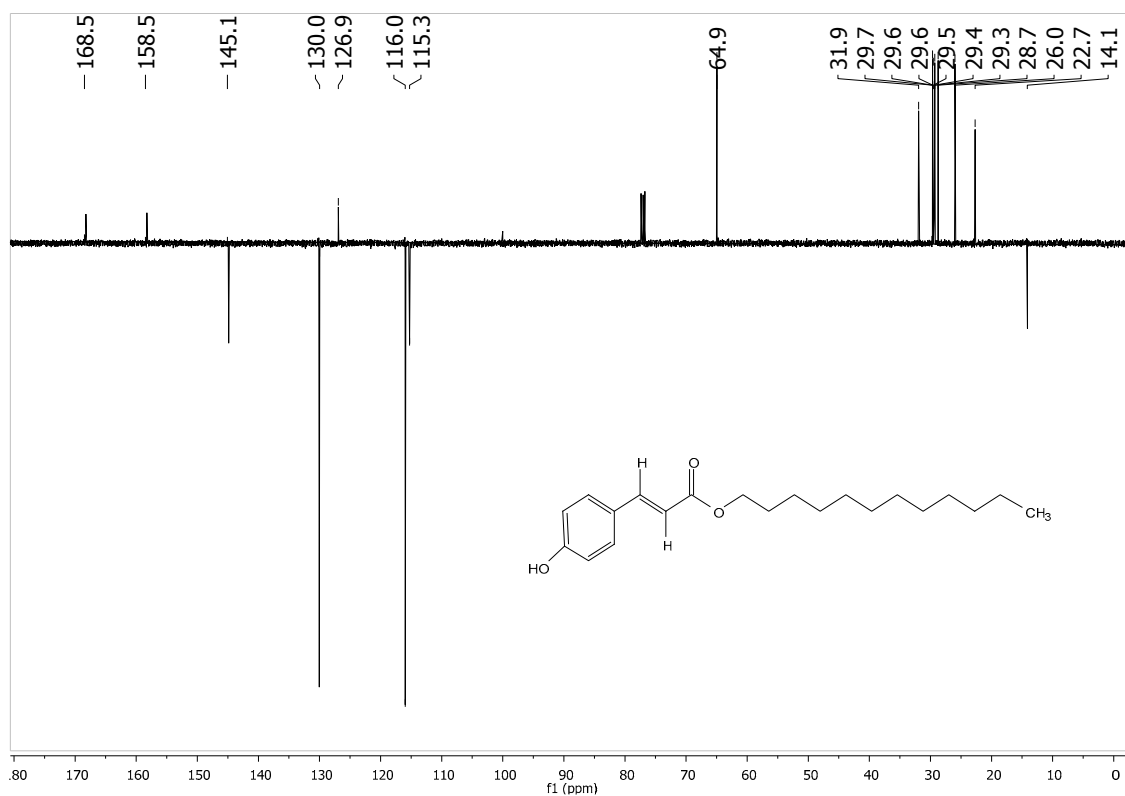


Figure S20. ^{13}C NMR (CdCl_2 , 100 MHz) spectrum of dodecyl *p*-coumarate (**10**).

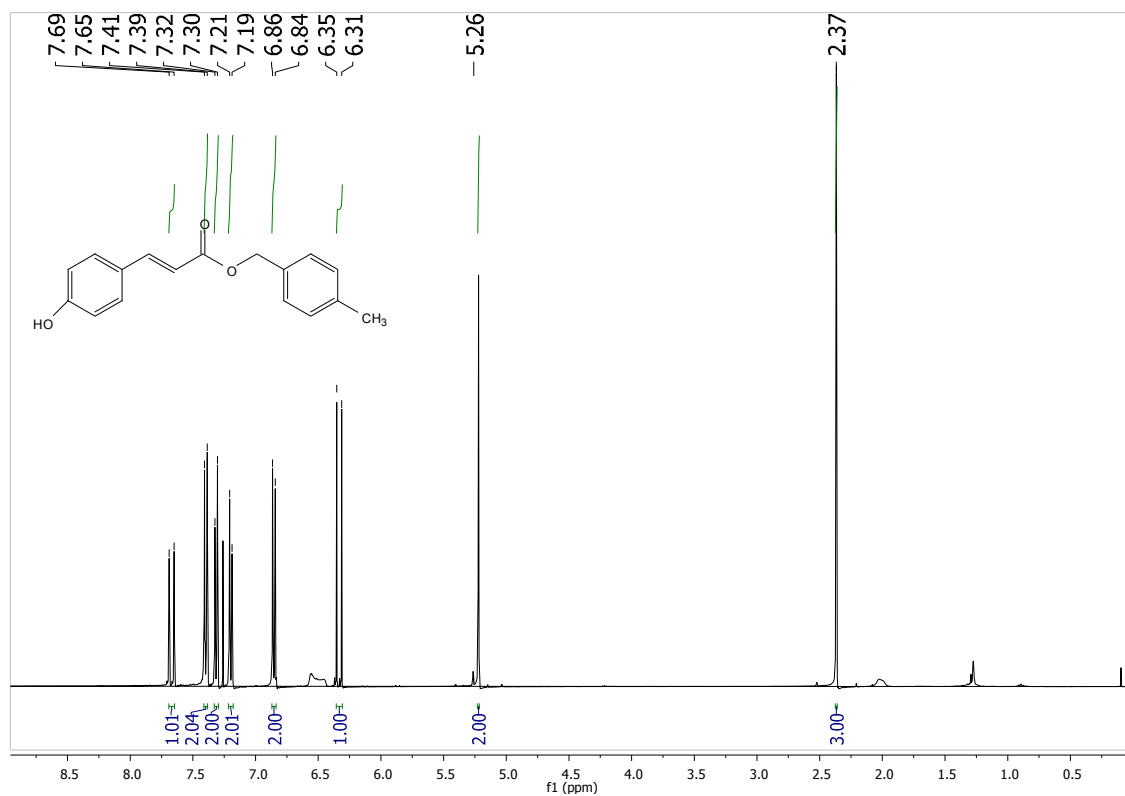


Figure S21. ^1H NMR (CdCl_2 , 400 MHz) spectrum of 4-Methylbenzyl *p*-coumarate (**11**).

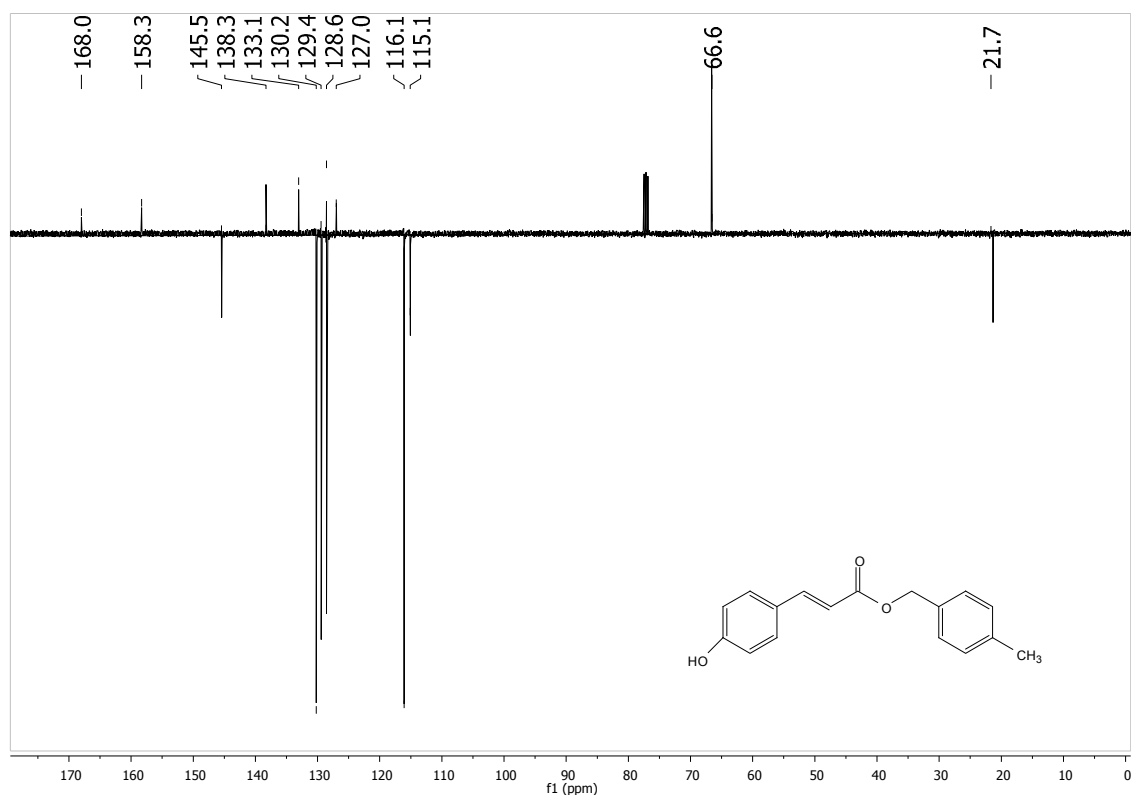


Figure S22. ¹³C NMR (CdCl₃, 400 MHz) spectrum of 4-Methylbenzyl *p*-coumarate (11).

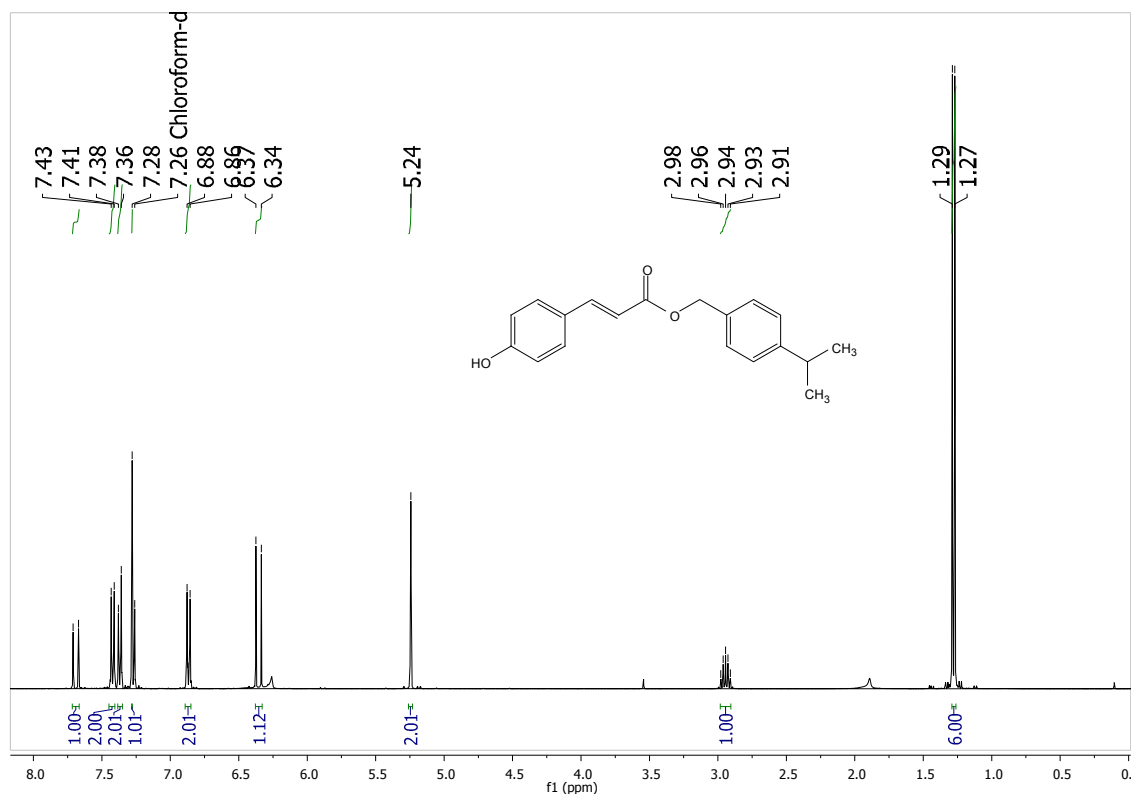


Figure S23. ¹H NMR (CdCl₃, 400 MHz) spectrum of 4-isopropylbenzyl *p*-coumarate (12).

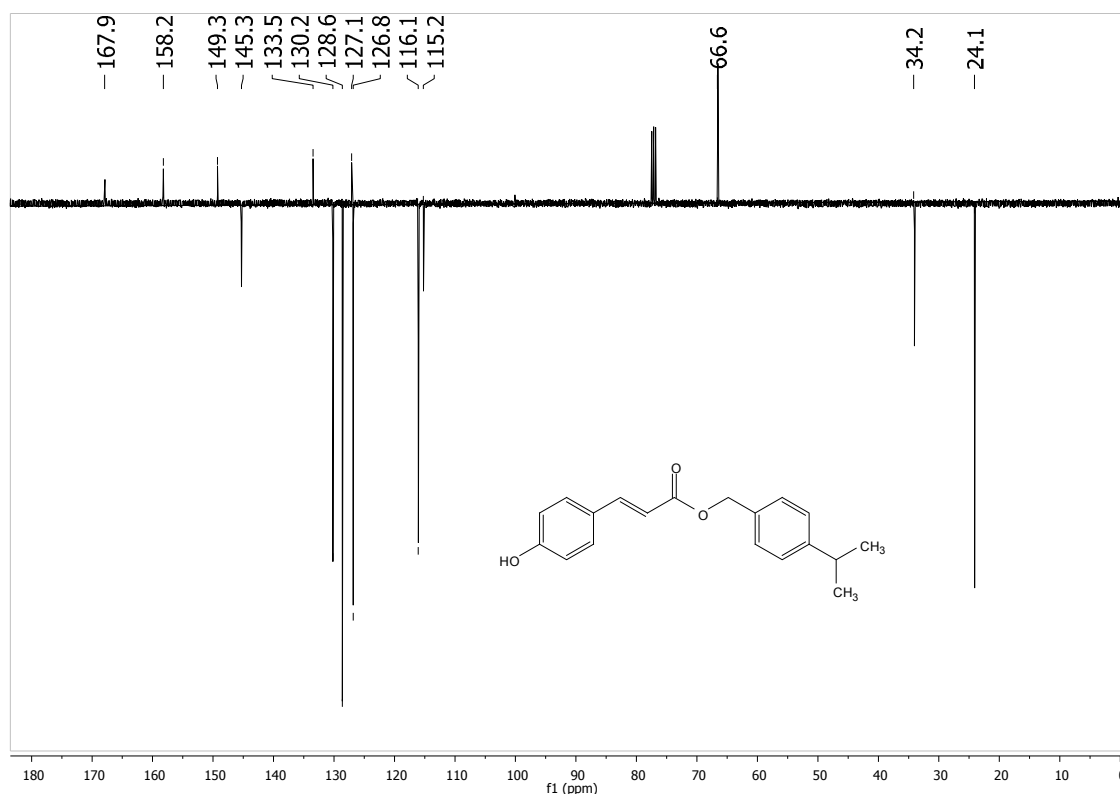


Figure S24. ^{13}C NMR (CdCl_3 , 100 MHz) spectrum of 4-isopropylbenzyl *p*-coumarate (12).

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