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Supplementary Materials

Total Synthesis of the Natural Chalcone Lophirone E and Synthetic Studies toward Benzofuran and Indole-based Analogues: Investigation of their anti-Leishmanial Activity

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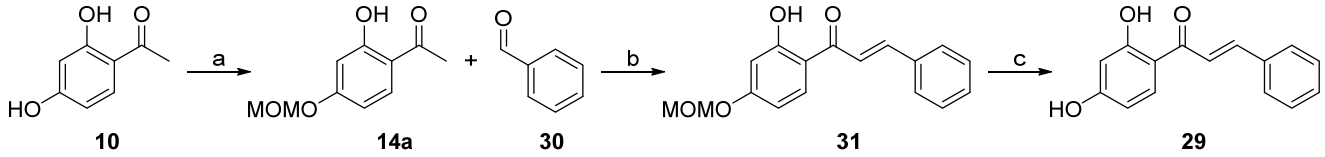
1. Chemistry

1.1. Synthesis of reference chalcone **29**



Scheme S1. *Reagents and Conditions*: **a**) MOMCl, DIPEA, dry DCM, 25 °C, 2 h; **b**) NaOH (5 M), EtOH, 0 °C to 25 °C, 72 h; **c**) HCl (12 M), MeOH/THF, 0 °C to 40 °C, 1 h.

1.1.1. Experimental Procedures

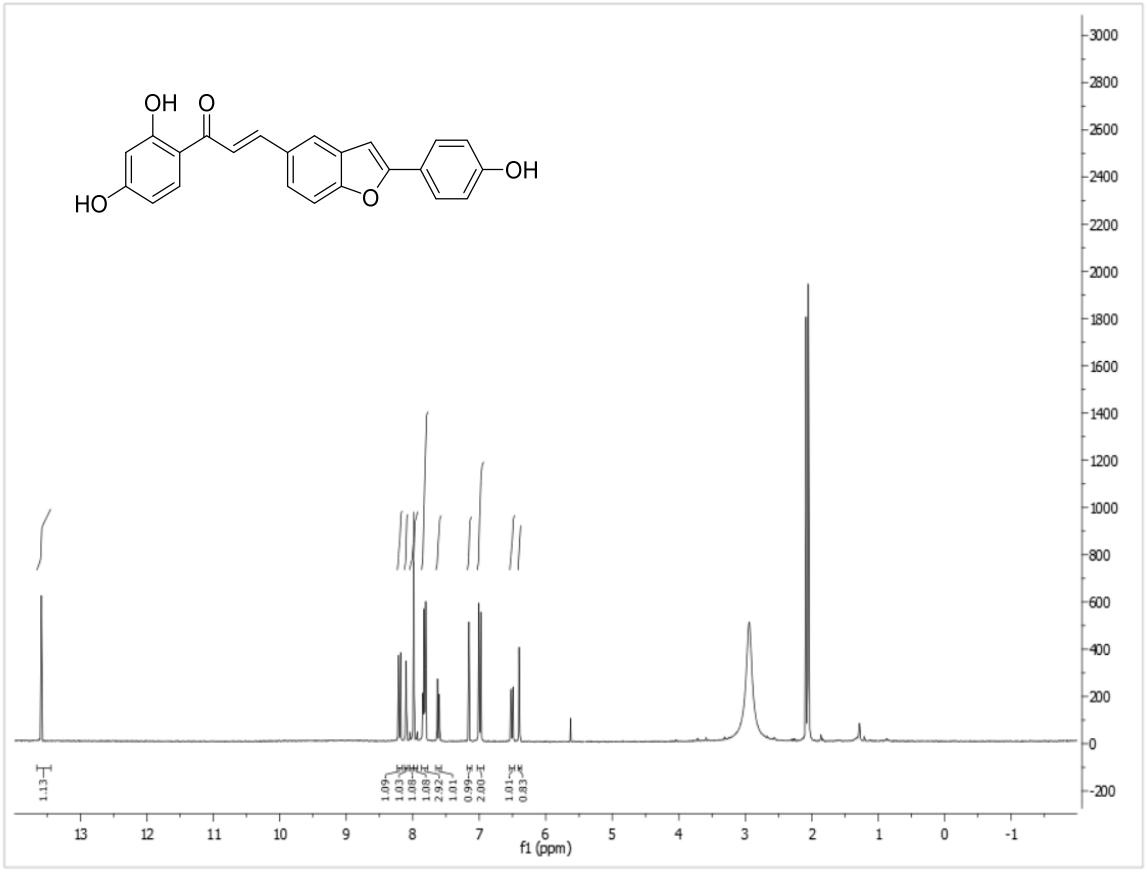
*1-(2-Hydroxy-4-(methoxymethoxy)phenyl)ethan-1-one (**14a**)*. To a solution of 1-(2,4-dihydroxyphenyl)ethan-1-one (**10**, 1 eq., 1 mmol) in anhydrous DCM (10 mL), DIPEA (1.5 eq., 1.5 mmol) was added, followed by chloromethyl methyl ether (1.5 eq., 1.5 mmol). The mixture was stirred at 25 °C for 2 h. Reaction mixture was washed with HCl (1 M) (2x5 mL) and then with $NaHCO_3$ (s.s., 5 mL), and brine (5 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to obtain the title compound with no further purification (quantitative yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.60 (s, 1H, C2′O*H*), 7.65 (d, *J* = 8.8 Hz, 1H, C6′-*H*), 6.59 (d, *J* = 2.4 Hz, 1H, C3′-*H*), 6.55 (dd, *J* = 8.8, 2.4 Hz, 1H, C5′-*H*), 5.20 (s, 2H, OC*H*$_2$OCH$_3$), 3.47 (s, 3H, OCH$_2$OC*H*$_3$), 2.56 (s, 3H, COC*H*$_3$). ESI-MS, *m*/*z* [*M*-H]$^-$ 195.

*(E)-1-(2-hydroxy-4-(methoxymethoxy)phenyl)-3-phenylprop-2-en-1-one (**31**)*. To a solution of 1-(2-Hydroxy-4-(methoxymethoxy)phenyl)ethan-1-one (**14a**) (1 eq., 1 mmol) in absolute EtOH (3 mL), cooled to 0 °C, $NaOH_{aq.}$ (5 M, 5 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 minutes and then a solution of benzaldehyde (**30**) (1.2 eq., 1.2 mmol) in absolute EtOH (1.5 mL) was added dropwise. The ice bath was removed, and the mixture was stirred at 25 °C for 48 h. The reaction was acidified with HCl (1 M) and extracted with EtOAc (3x5 mL). The combined organic phases were washed with $NaHCO_3$ (s.s., 10 mL) and brine (5 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Pet. Et./EtOAc 2:1) to afford the title compound as a yellow solid (85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.27 (s, 1H, C2′O*H*), 7.89 (d, *J* = 15.7 Hz, 1H, CαH=Cβ*H*), 7.83 (d, *J* = 9.0 Hz, 1H, C6′-*H*), 7.69 – 7.62 (m, 2H, Ar-*H*), 7.58 (d, *J* = 15.5 Hz, 1H, Cα*H*=CβH), 7.47 – 7.35 (m, 3H, Ar-*H*), 6.65 (d, *J* = 2.3 Hz, 1H, C3′-*H*), 6.60 (dd, *J* = 9.0, 2.2 Hz, 1H, C5′-*H*), 5.22 (s, 2H, OC*H*$_2$OCH$_3$), 3.49 (s, 3H, OCH$_2$OC*H*$_3$). ESI-MS, *m*/*z* [*M*-H]$^-$ 283.

*(E)-1-(2,4-dihydroxyphenyl)-3-phenylprop-2-en-1-one (**29**, CAS registry number 25515-43-9)*. To a 0 °C cooled solution of (E)-1-(2-hydroxy-4-(methoxymethoxy)phenyl)-3-phenylprop-2-en-1-one (**31**) (1 eq., 1 mmol) in MeOH/THF (1:1, 20 mL in total), HCl (12 M, 20 eq., 20 mmol) was added dropwise. The ice bath was removed, and the reaction mixture was heated to 40 °C for 3 h. After cooling, $NaHCO_3$ (s.s.) was carefully added until pH=7 and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/MeOH 100:1) to afford the title compound as a yellow solid (quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.37 (s, 1H, C2′O*H*), 7.89 (d, *J* = 15.9 Hz, 1H, CαH=Cβ*H*), 7.83 (d, *J* = 8.9 Hz, 1H, C6′-*H*), 7.74 – 7.61 (m, 2H, Ar-*H*), 7.57 (d, *J* = 15.5 Hz, 1H, Cα*H*=CβH), 7.51 – 7.35 (m, 3H, Ar-*H*), 6.45 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.99, 166.40, 162.70, 144.67, 134.70, 132.02, 130.72, 128.99 (2C), 128.54 (2C), 120.22, 114.49, 107.80, 103.81. ESI-MS, *m*/*z* [*M*-H]$^-$ 239.

1.2. Spectral data of final compounds

1.2.1. **Compound 1**



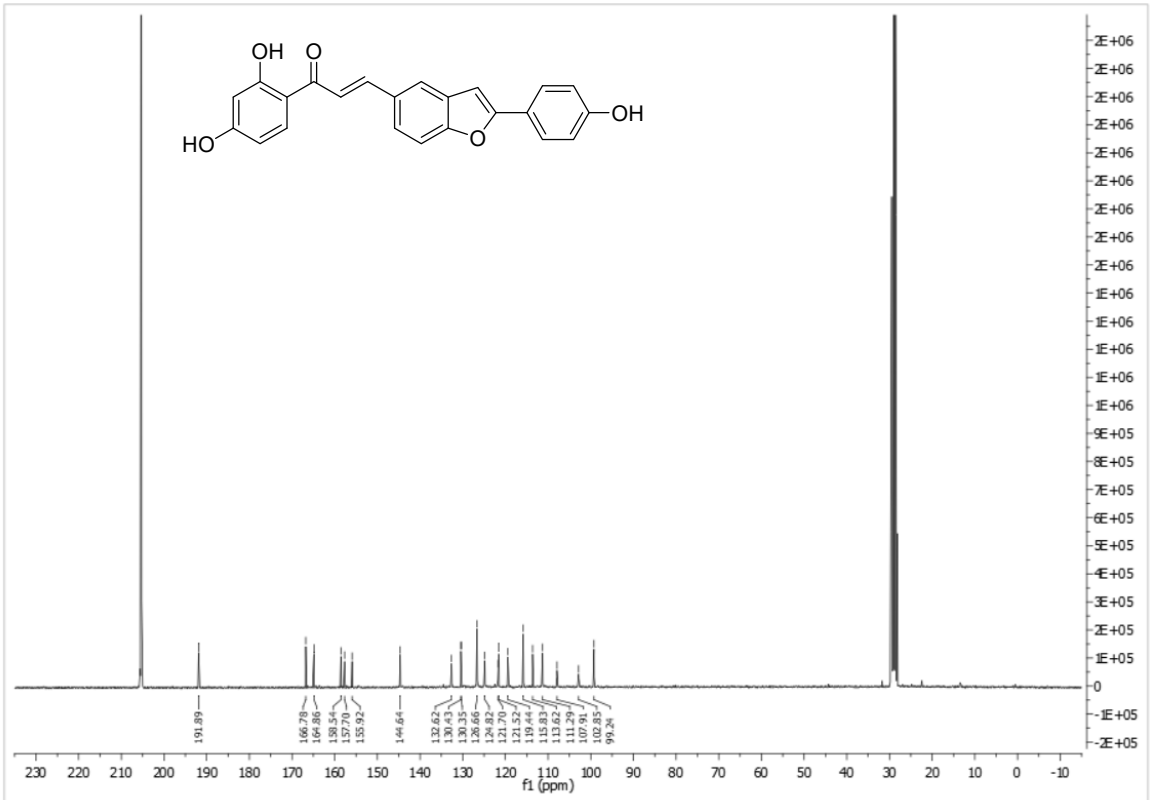


Figure S1. [1]H NMR (300 MHz, Acetone-d_6) spectrum of lophirone E (**1**).

Figure S2. ^{13}C NMR (75 MHz, Acetone-d_6) spectrum of lophirone E (**1**).

1.2.2. **Compound 16**

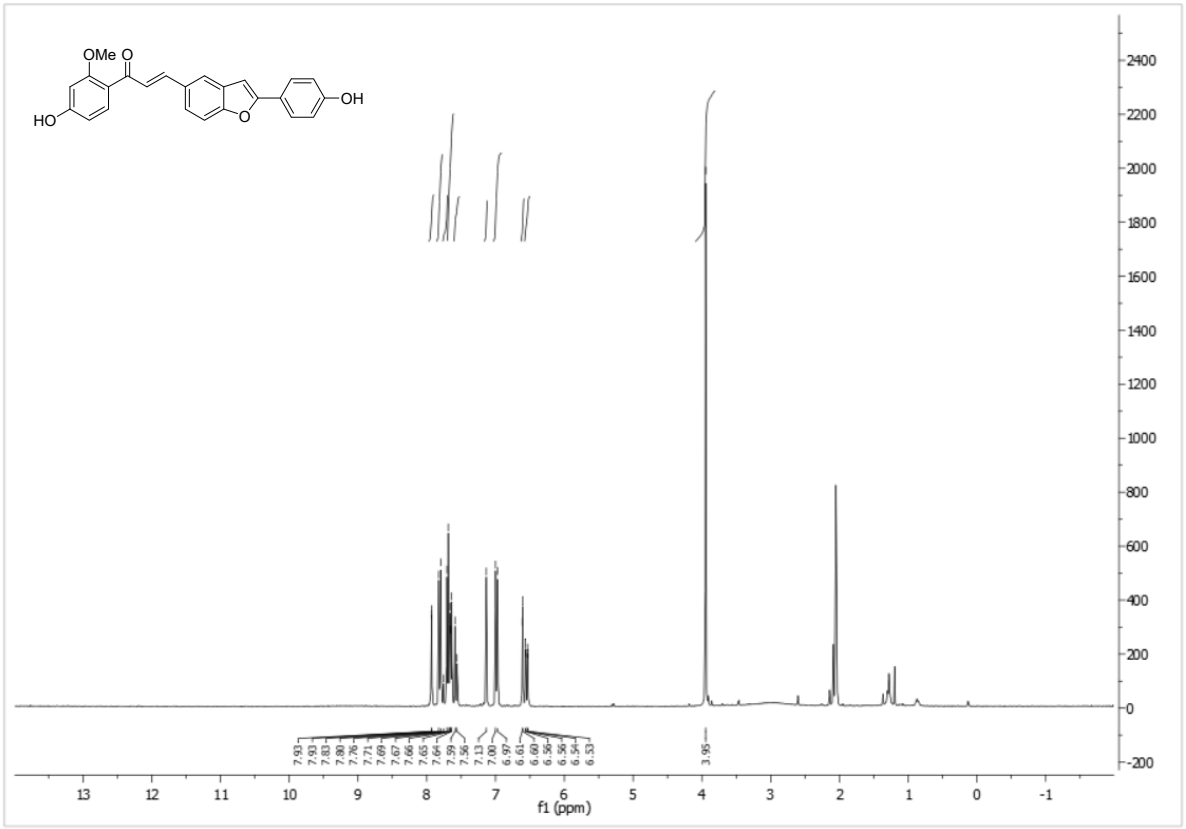


Figure S3. ^{1}H NMR (300 MHz, Acetone-d_6) spectrum of compound **16**.

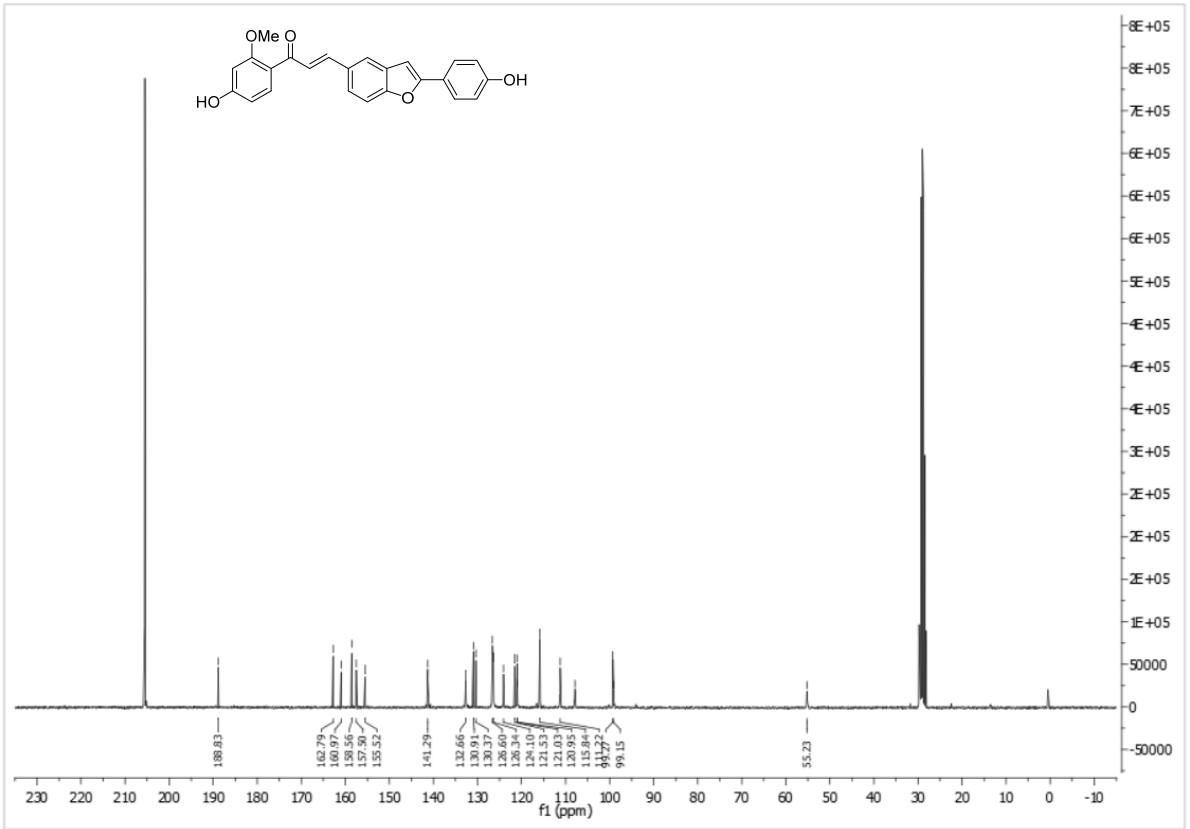


Figure S4. ^{13}C NMR (75 MHz, Acetone-d_6) spectrum of compound **16**.

1.2.3. **Compound 17**

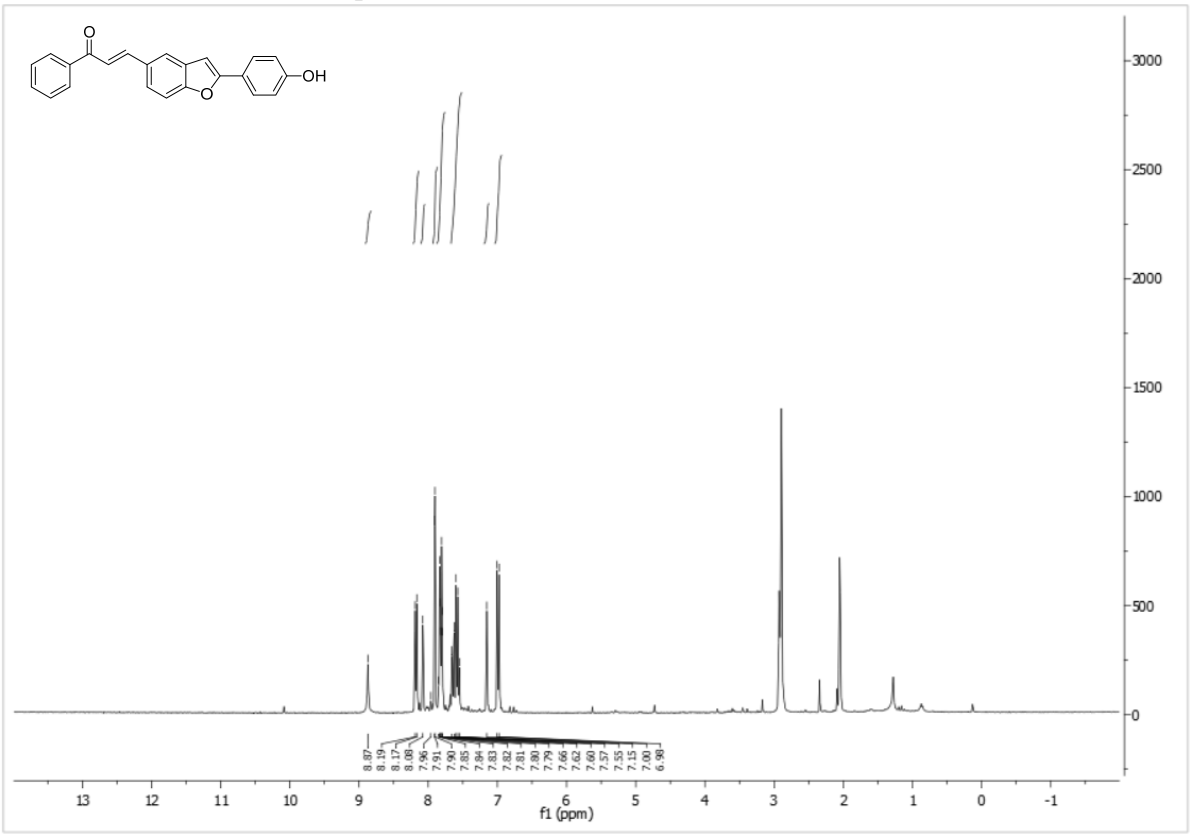


Figure S5. ^{1}H NMR (300 MHz, Acetone-d_6) spectrum of compound **17**.

1.2.4. **Compound 18**

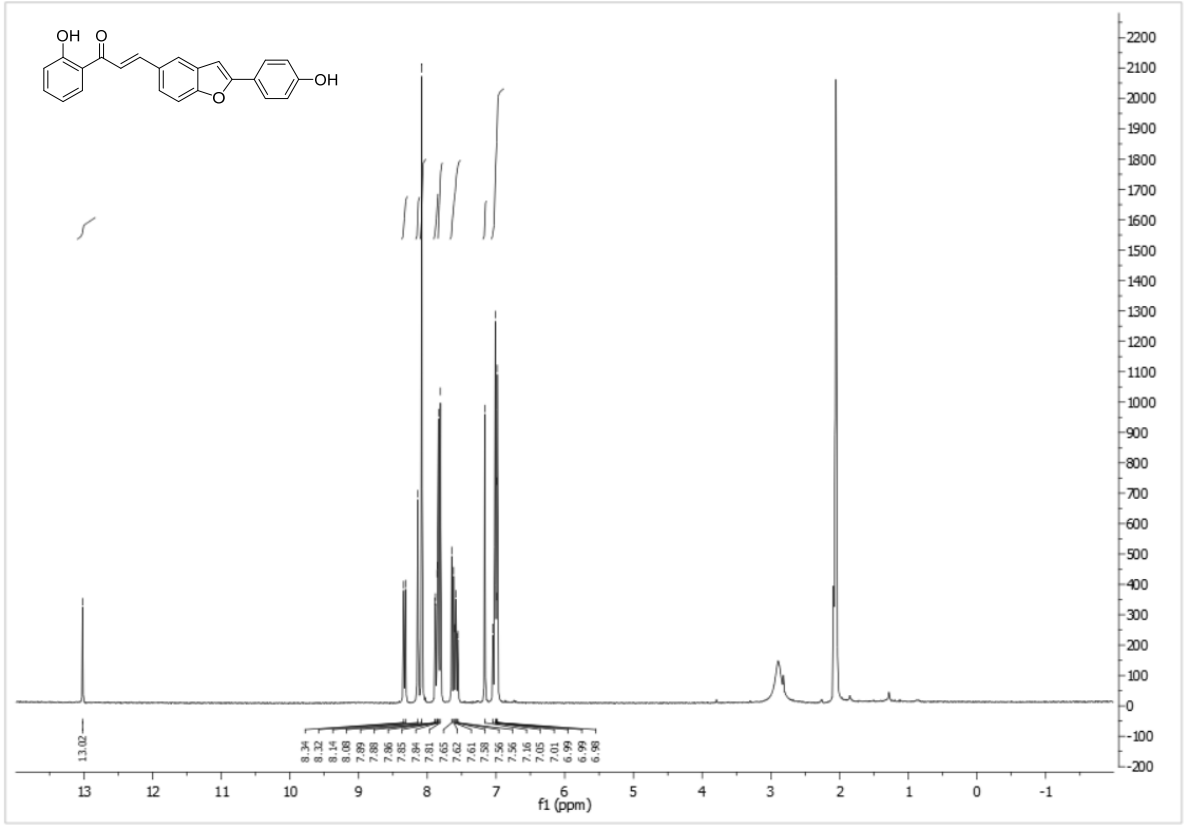


Figure S6. ^{1}H NMR (300 MHz, Acetone-d_6) spectrum of compound **18**.

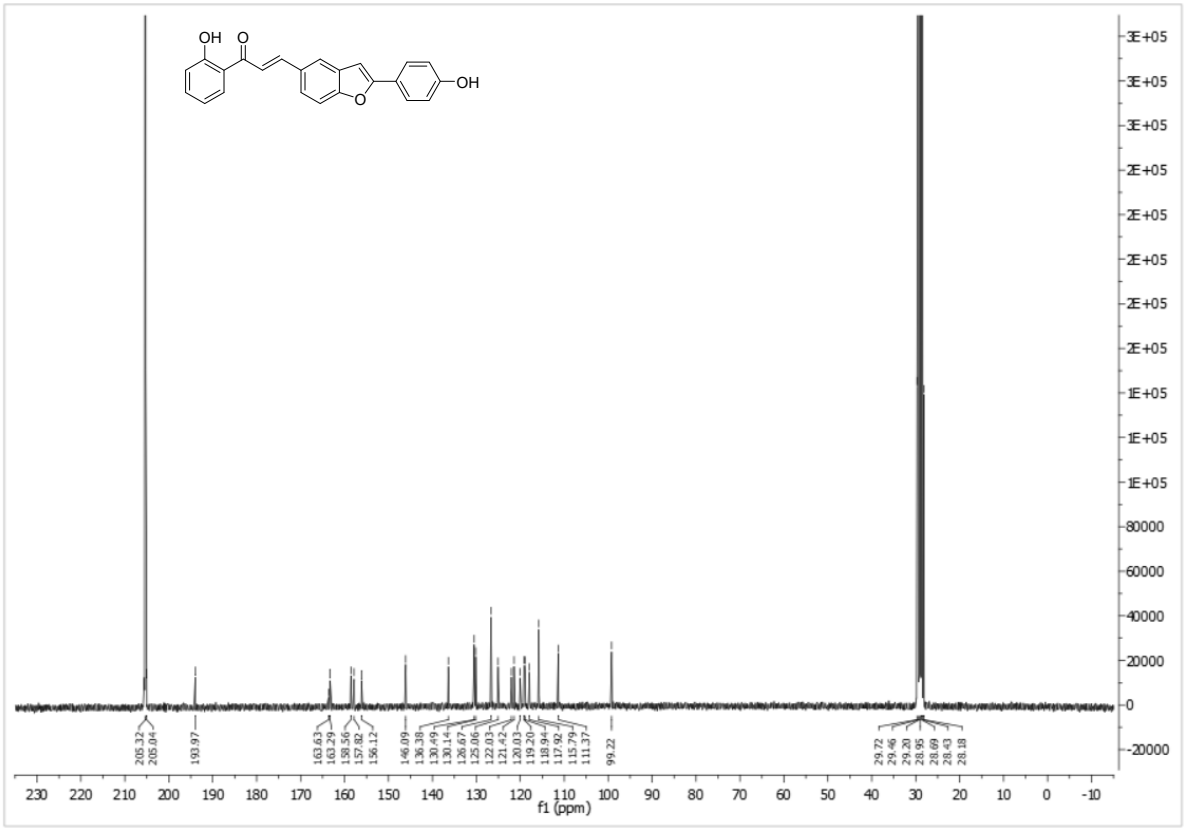
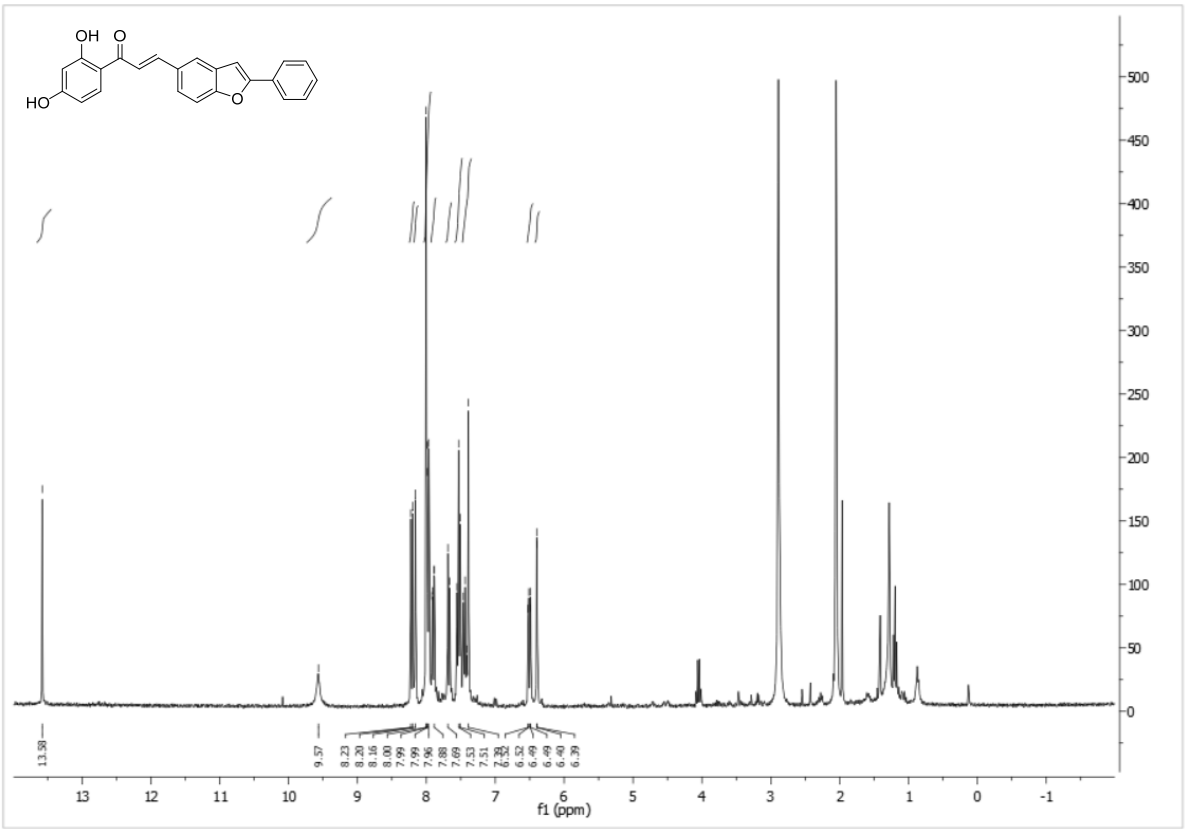


Figure S7. ^{13}C NMR (75 MHz, Acetone-d_6) spectrum of compound **18**.



1.2.5. **Compound 21a**

Figure S8. ^{1}H NMR (300 MHz, Acetone-d_6) spectrum of compound **21a**.

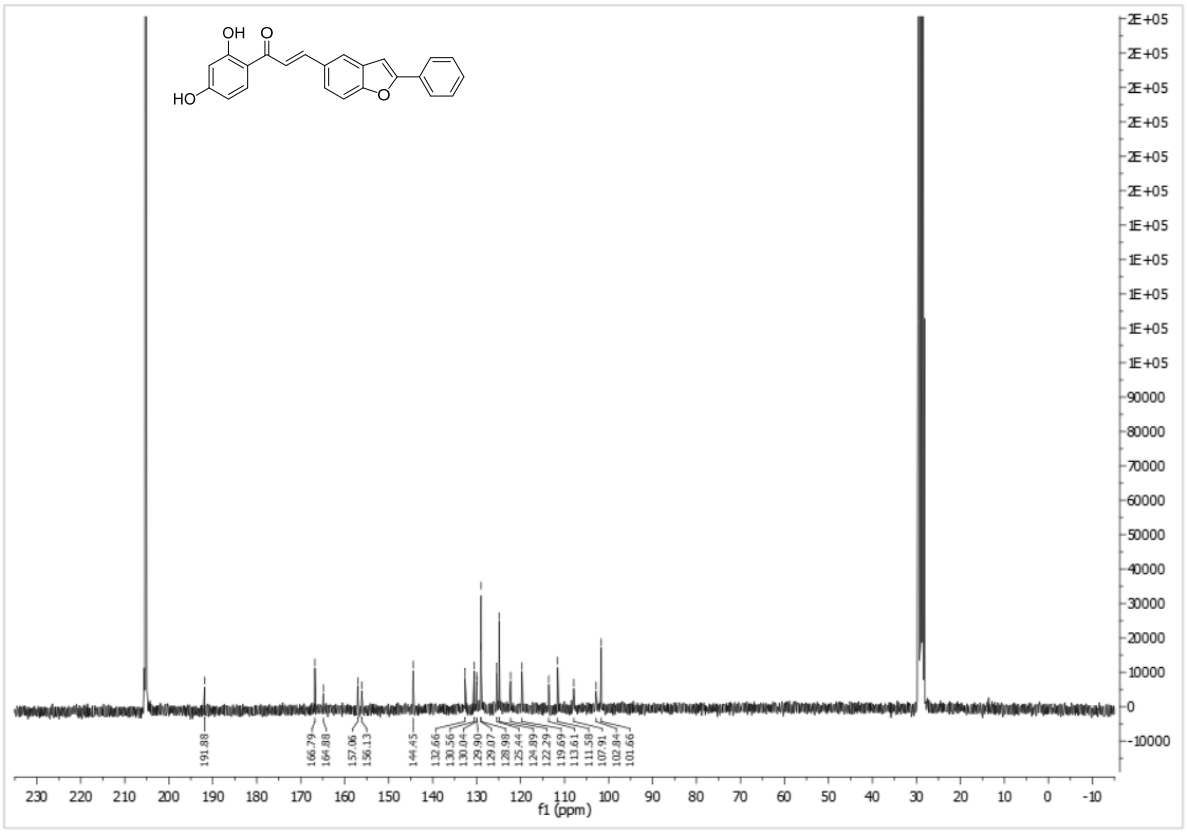


Figure S9. ^{13}C NMR (75 MHz, Acetone-d_6) spectrum of compound **21a**.

1.2.6. **Compound 21b**

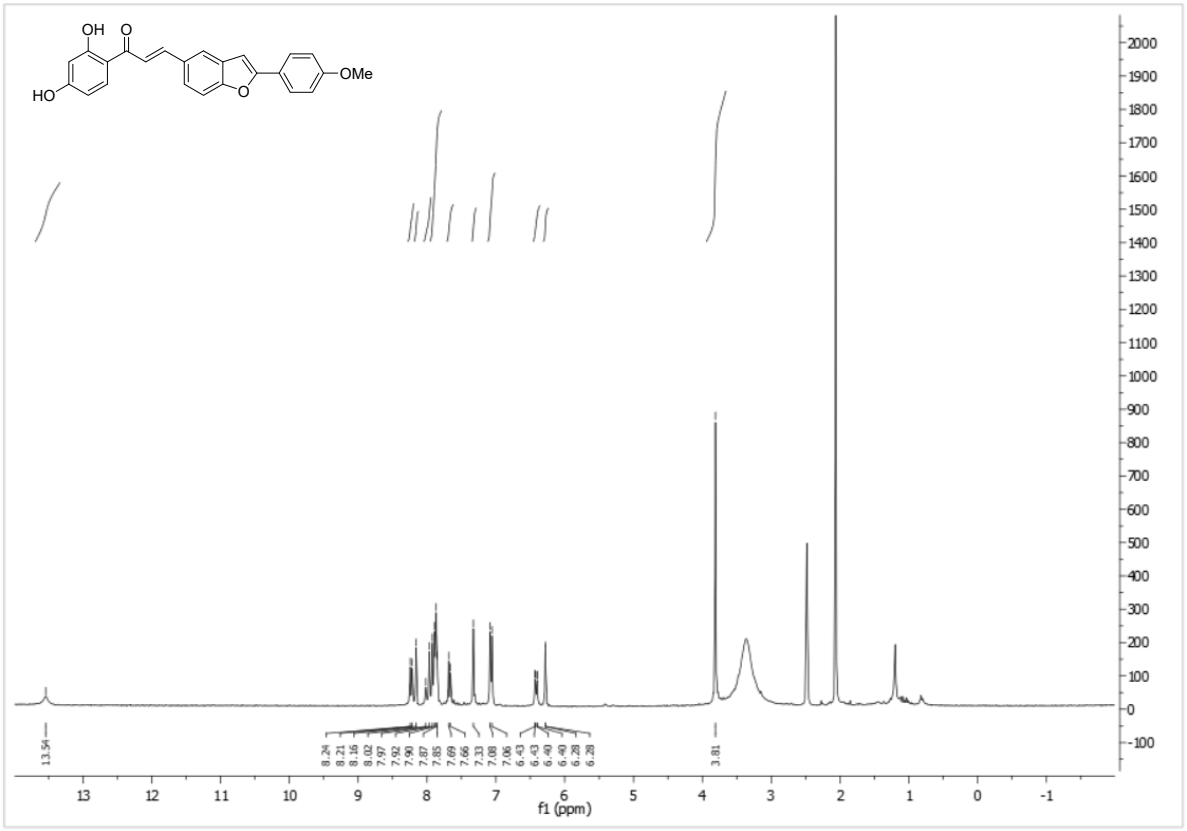


Figure S10. ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of compound **21b**.

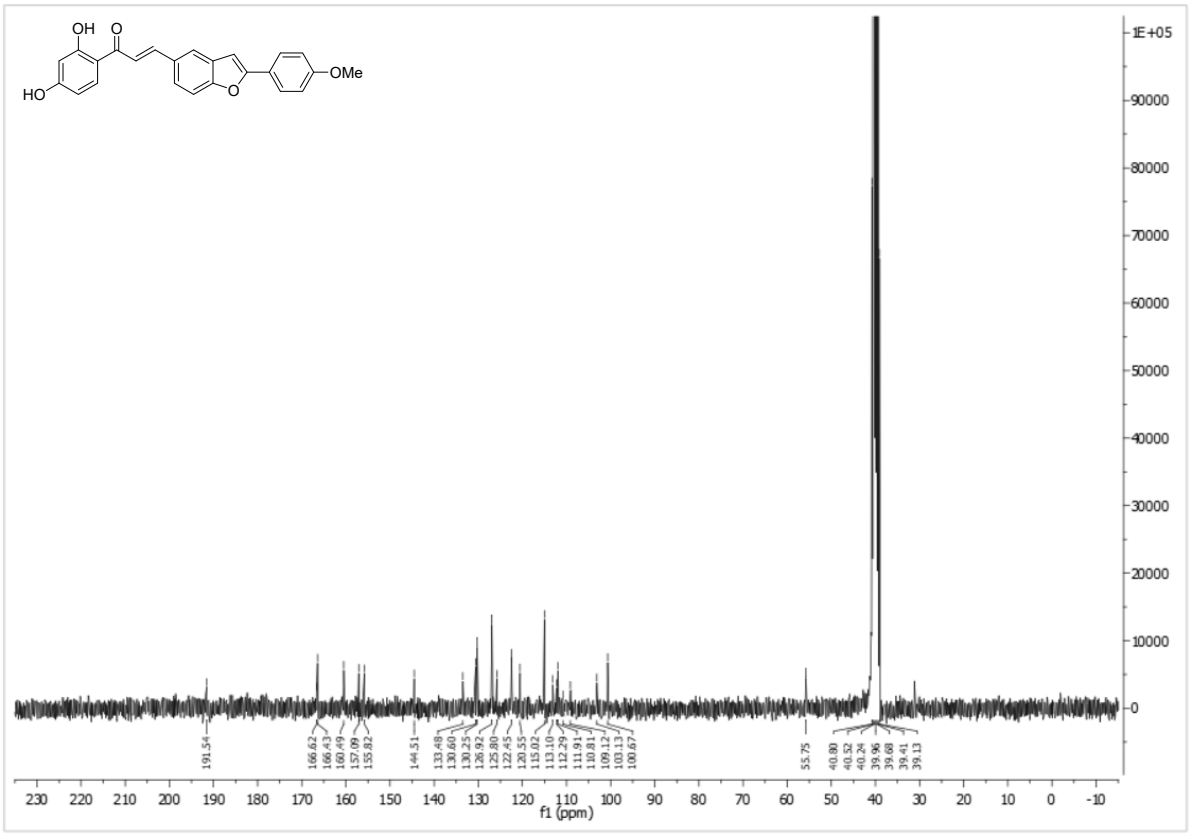


Figure S11. ^{13}C NMR (75 MHz, Acetone-d_6) spectrum of compound **21b**.

1.2.7. **Compound 25a**

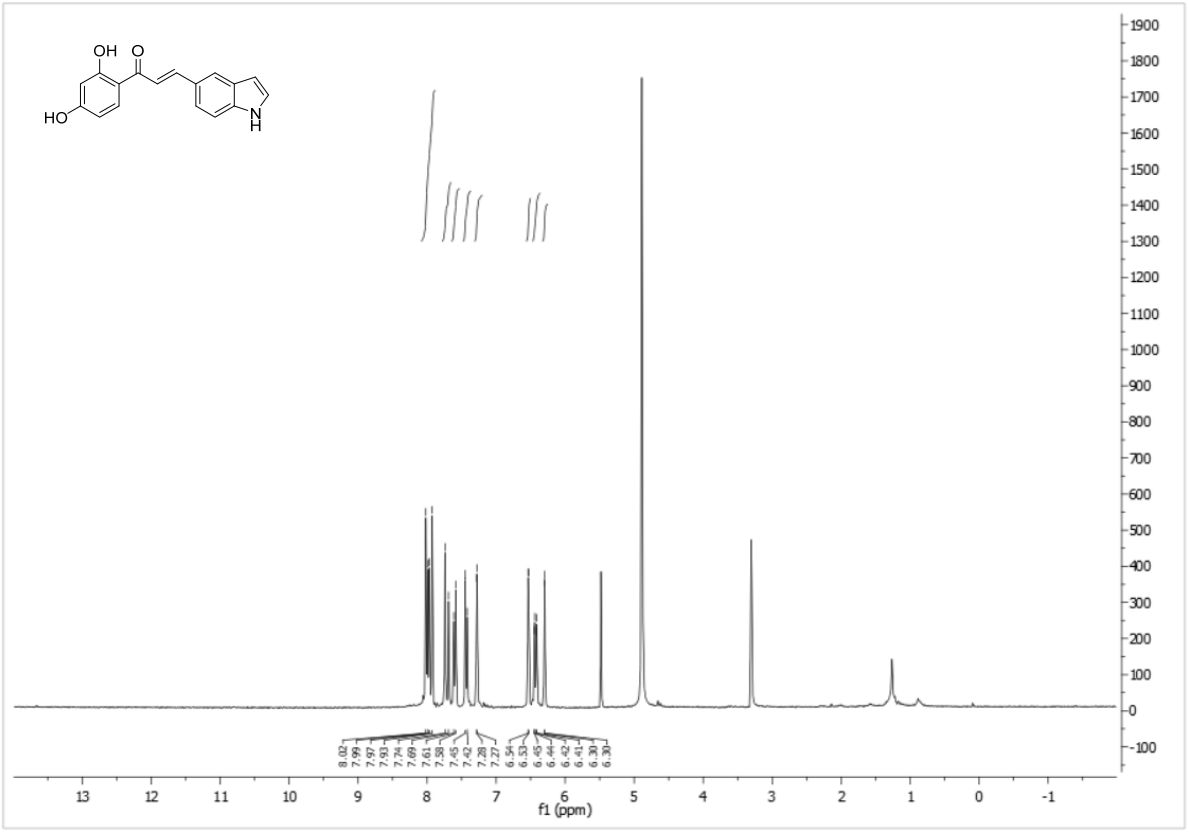


Figure S12. ^{1}H NMR (300 MHz, CD_3OD) spectrum of compound **25a**.

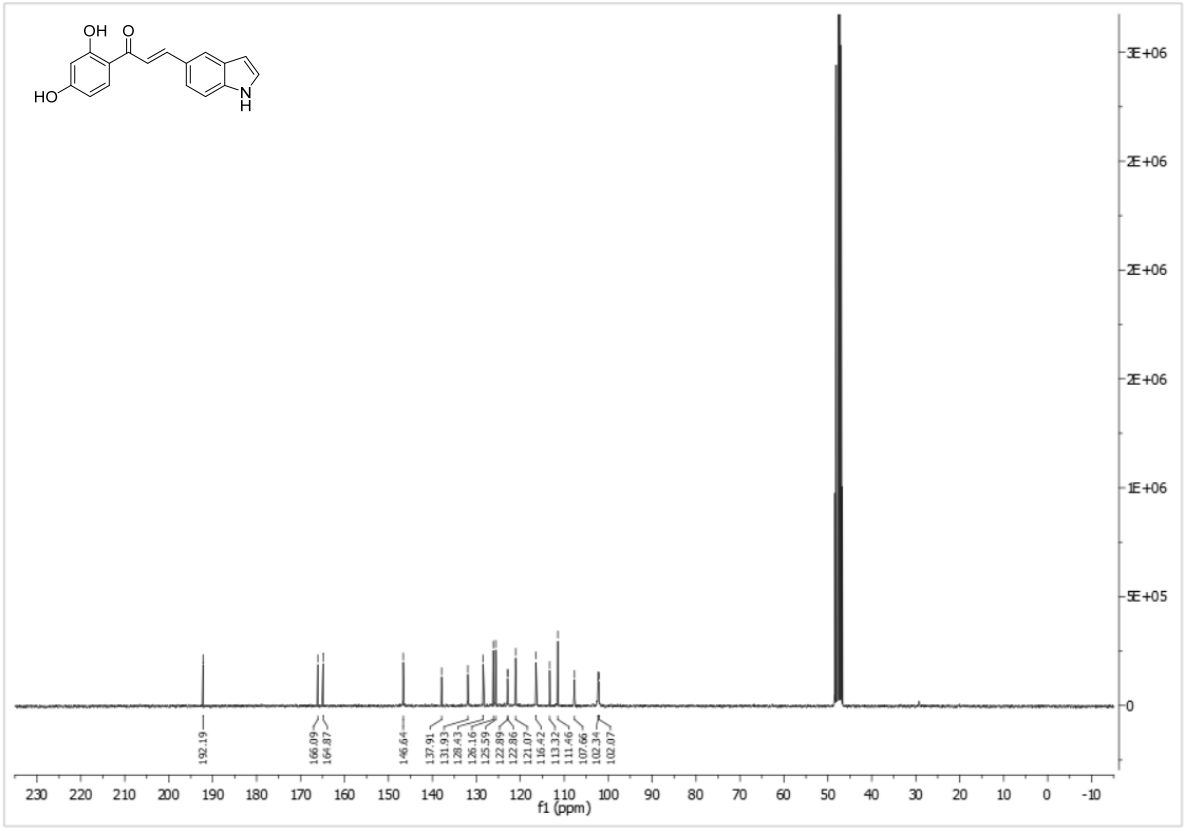


Figure S13. ^{13}C NMR (75 MHz, CD_3OD) spectrum of compound **25a**.

1.2.8. **Compound 25b**

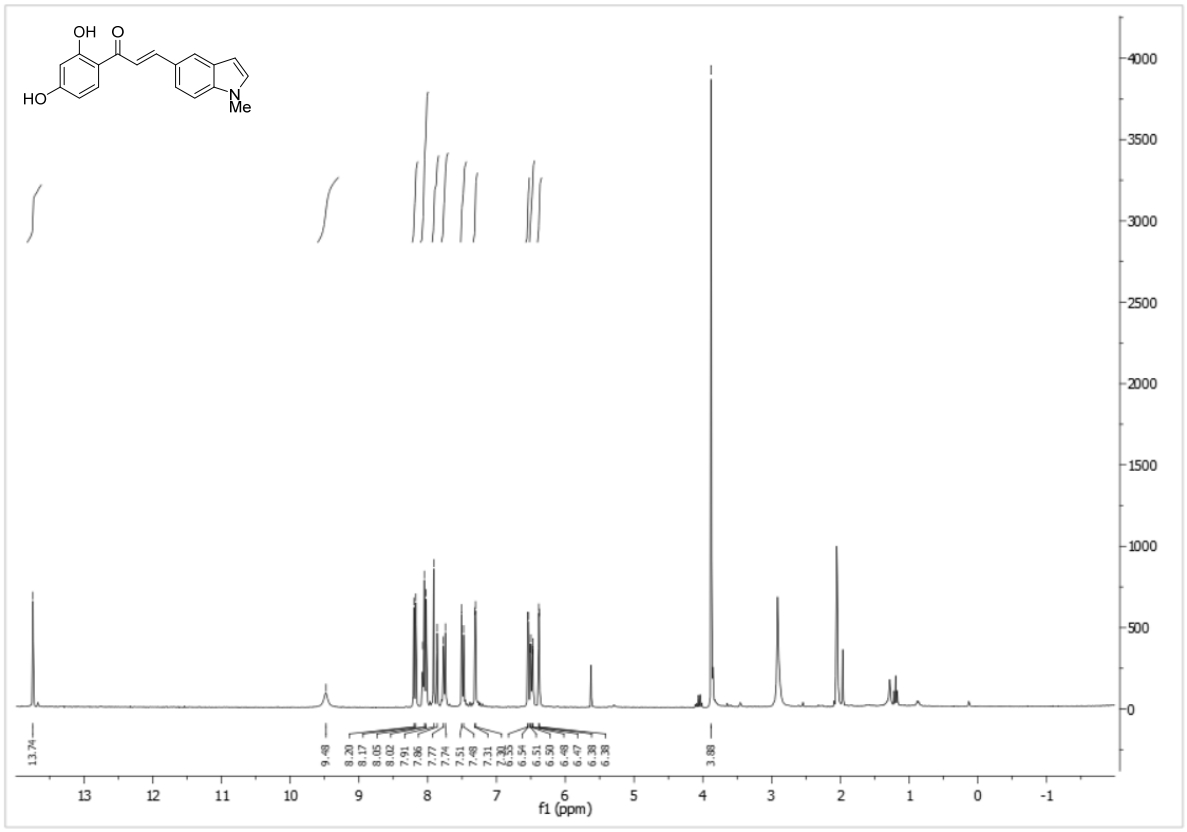


Figure S14. ^{1}H NMR (300 MHz, Acetone-d_6) spectrum of compound **25b**.

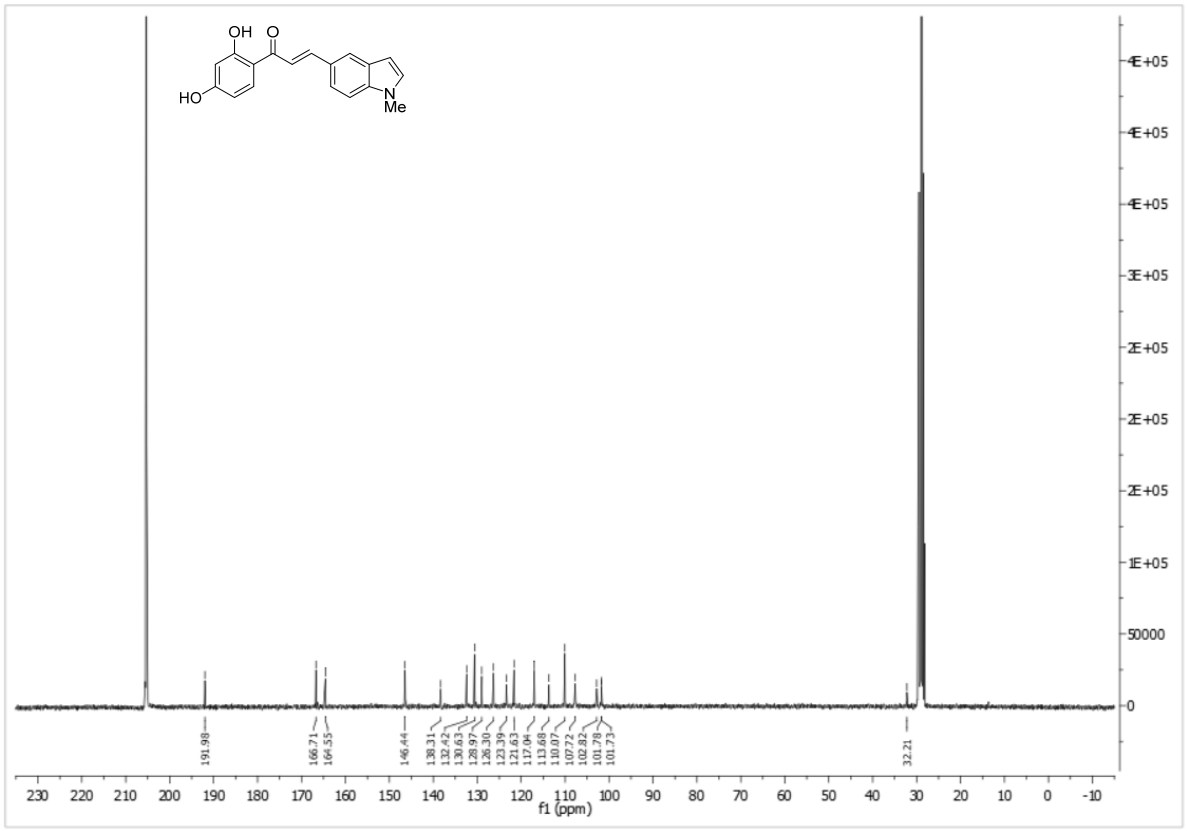


Figure S15. ^{13}C NMR (75 MHz, Acetone-d_6) spectrum of compound **25b**.

1.2.9. **Compound 28a**

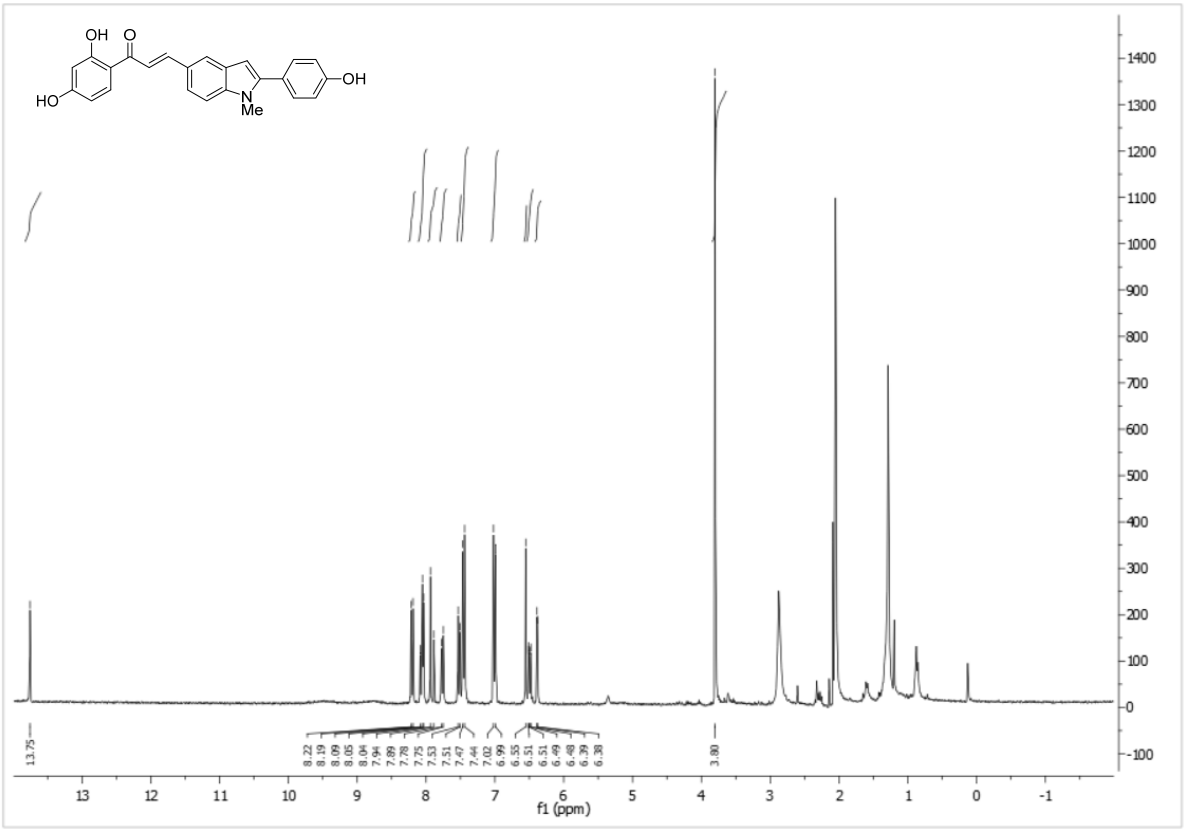


Figure S16. ^{1}H NMR (300 MHz, Acetone-d_6) spectrum of compound **28a**.

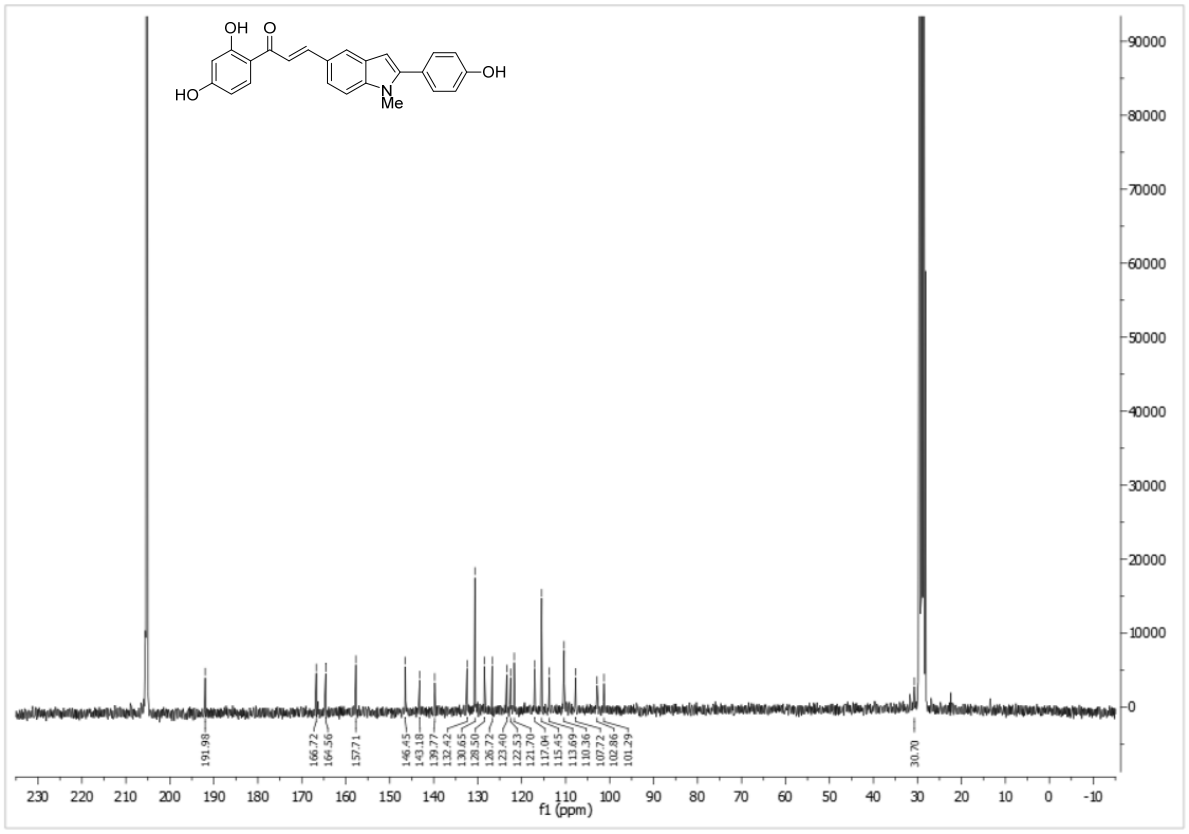


Figure S17. ^{13}C NMR (75 MHz, Acetone-d_6) spectrum of compound **28a**.

1.2.10. **Compound 28b**

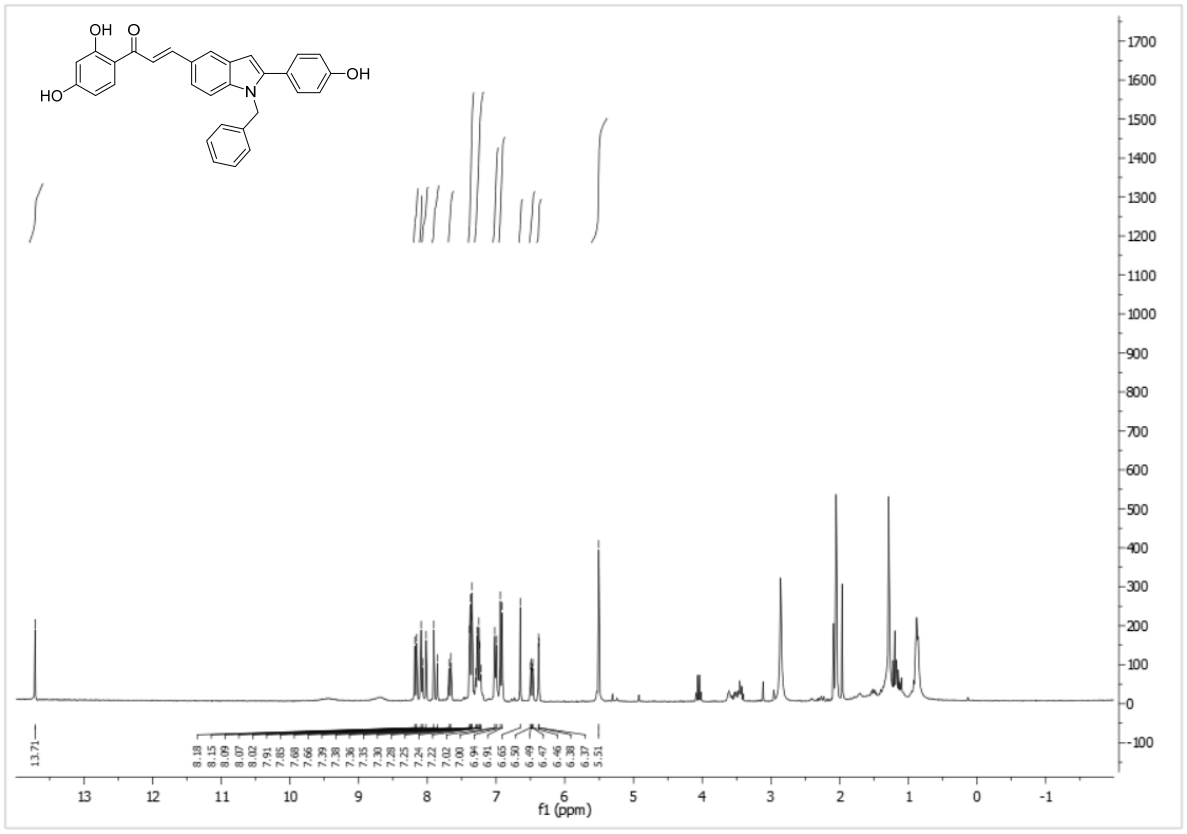


Figure S18. ^{1}H NMR (300 MHz, Acetone-d_6) spectrum of compound **28b**.

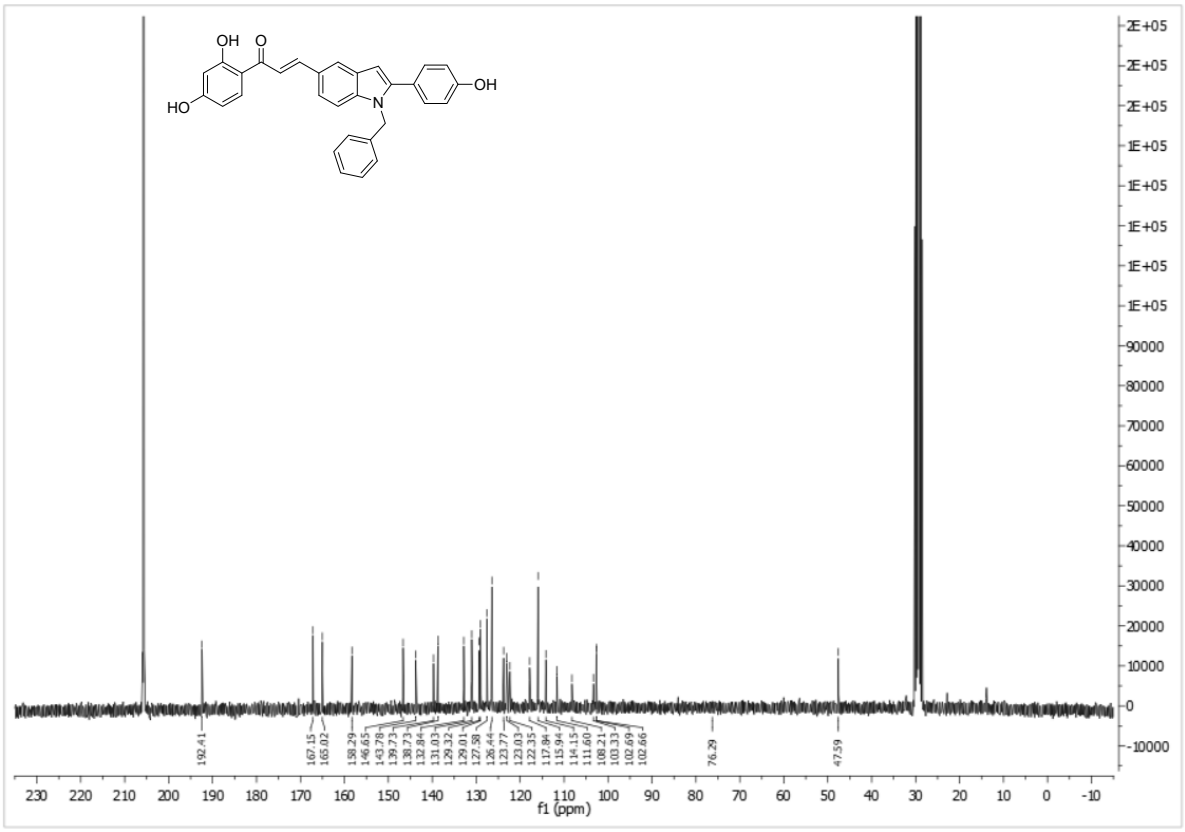
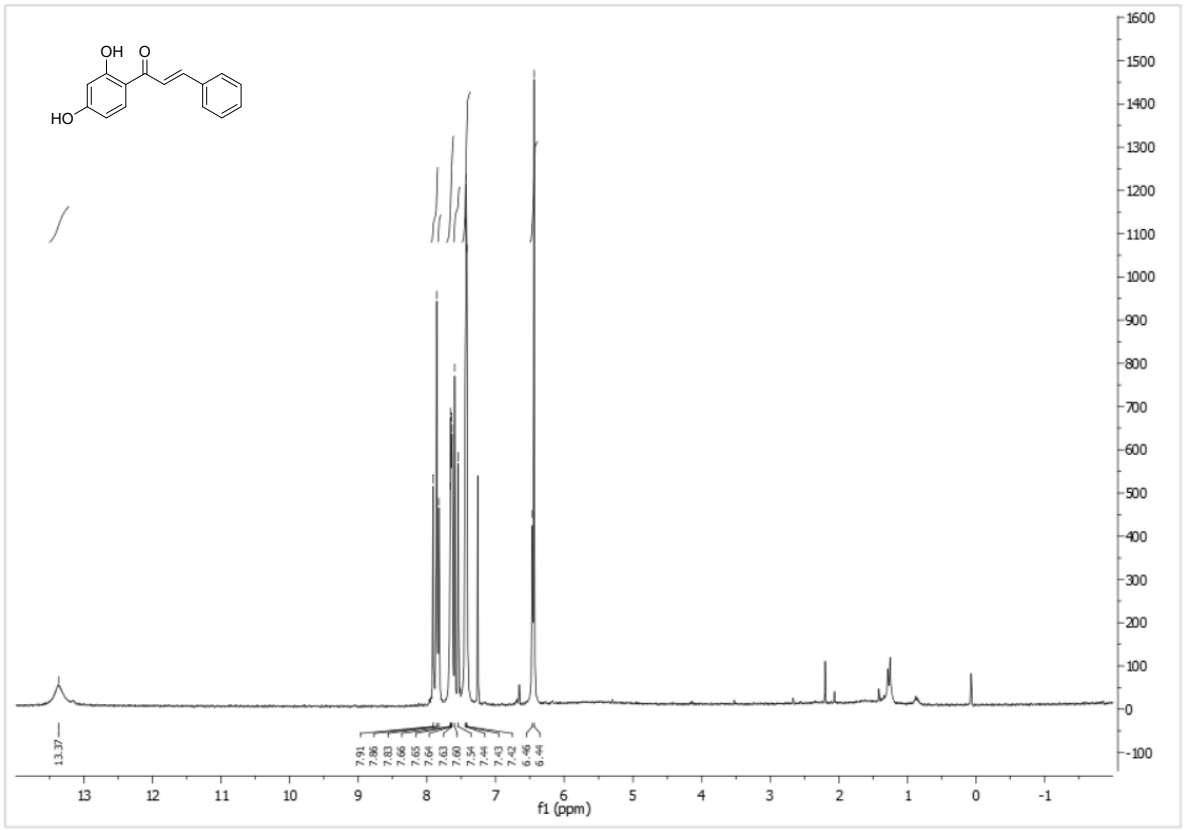


Figure S19. ^{13}C NMR (75 MHz, Acetone-d_6) spectrum of compound **28b**.



1.2.11. **Reference compound 29**

Figure S20. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of reference compound **29**.

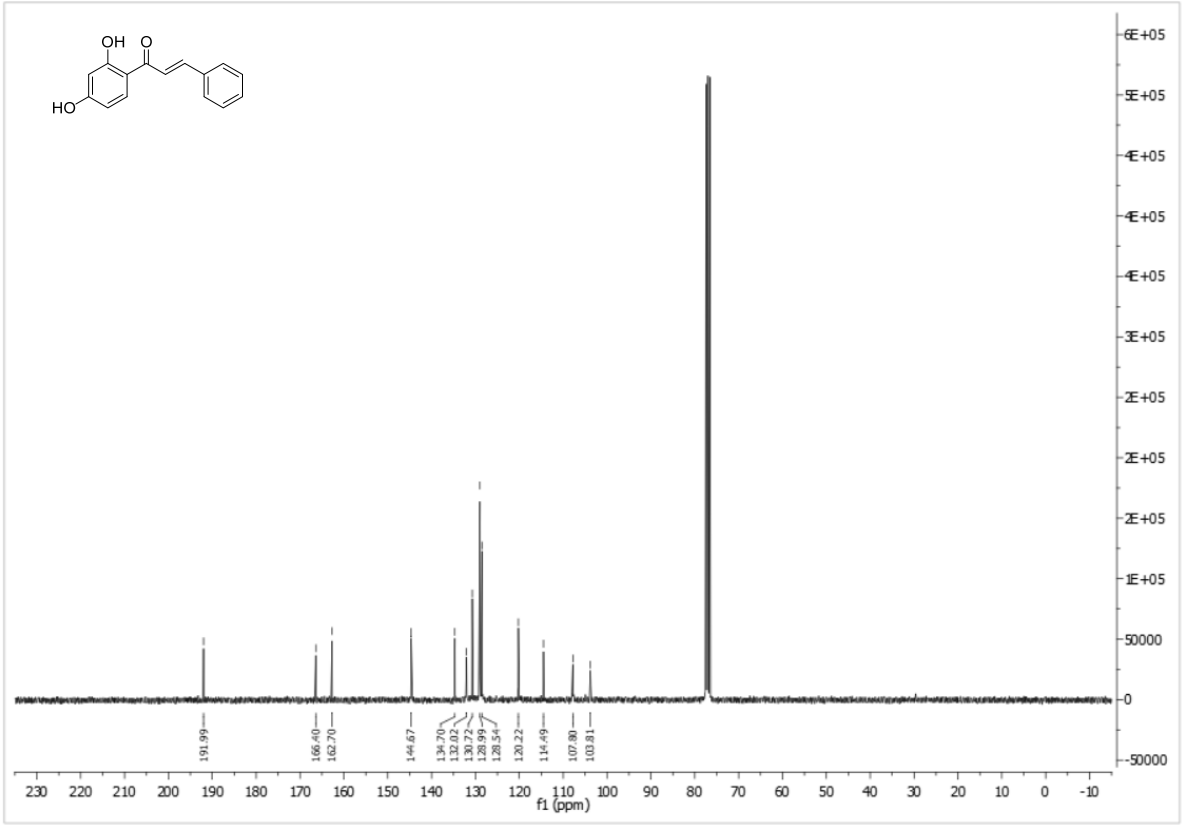


Figure S21. ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of reference compound **29**.