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Supplementary Information

Convenient approach to an advanced intermediate toward the naturally occurring, bioactive 6-substituted 5-hydroxy-4-aryl-1*H*-quinolin-2-ones

Sebastian O. Simonetti, Enrique L. Larghi and Teodoro S. Kaufman*

Instituto de Química Rosario (IQUIR, CONICET-UNR) and Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, S2002LRK Rosario, Argentina.

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2-Benzyloxybenzaldehyde (13): K_2CO_3 (679 mg, 4.91 mmol) was added to a stirred solution of commercial salicylaldehyde (**12**, 200 mg, 1.638 mmol) in absolute EtOH (3 mL); the mixture was stirred for 10 minutes at room temperature and then treated with benzyl chloride (415 mg, 3.28 mmol). The reaction mixture was stirred overnight at 70 °C, the EtOH was evaporated under reduced pressure and the resulting mixture was diluted with brine (10 mL) and 1M NaOH (10 mL). The reaction products were extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford **13** (347 mg, 99%), as a pale yellow oil. IR (film, v): 3734, 3250, 1646, 1626, 1578, 1368, 1340, 1283, 1153, 1081, 1010, 842 and 669 cm^{-1}. ^{1}H NMR δ 5.20 (s, 2H, OC*H*$_2$Ar), 7.04 (t, *J* = 7.9, 1H, H-5), 7.05 (d, *J* = 7.9, 1H, H-3), 7.35-7.46 (m, 5H, ArH of Benzyl), 7.53 (dt, *J* = 1.9 and 7.9, 1H, H-4), 7.86 (dd, *J* = 1.9 and 7.9, 1H, H-6) and 10.57 (s, 1H, C*H*O). ^{13}C NMR δ 70.5 (O*C*H$_2$Ar), 113.1 (C-3), 121.0 (C-5), 125.2 (C-1), 127.3 (C-1' and C-6'), 128.3 (C-4'), 128.5 (C-6), 128.7 (C-3' and C-5'), 135.9 (C-4), 136.1 (C-1'), 161.1 (C-2) and 189.8 (*C*HO). HRMS *m/z* calcd. for $C_{14}H_{11}NNaO_4$: 280.0578 $[M+Na]^+$; found: 280.0580.

Methyl 3-(2-benzyloxyphenyl)acrylate (14): [1] Trimethylphosphonoacetate (1236 mg, 6.798 mmol) was added to a stirred mixture of **13** (500 mg, 2.358 mmol), K_2CO_3 (875 mg, 6.249 mmol) and H_2O (0.5 mL) and the system was heated under reflux during 30 minutes, when it was assessed (TLC) the absence of the starting material. Then, the reaction products were extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduce pressure. Column

chromatography of the residue afforded **14** (859 mg, 55%), as a pale yellow oil. IR (film, v): 3032, 2947, 1714, 1629, 1597, 1452, 1321, 1242, 1170, 1014, 989, 752 and 696 cm^{-1}. ^{1}H NMR δ 3.79 (s, 3H, OCH_3), 5.17 (s, 2H, OCH_2Ar), 6.55 (d, J = 16.2, 1H, Ar-CH=CH-CO_2CH_3), 6.96 (d, J = 8.0, 1H, H-3), 6.97 (t, J = 8.0, 1H, H-5), 7.30 (dt, J = 1.2 and 8.0, 1H, H-4), 7.34-7.46 (m, 5H, ArH of Benzyl), 7.54 (dd, J = 1.2 and 8.0, 1H, H-6) and 8.09 (d, J = 16.2, 1H, Ar-CH=CH-CO_2CH_3). ^{13}C NMR δ 51.6 (OCH$_3$), 70.4 (OCH$_2$Ar), 112.8 (C-3), 118.4 (Ar-CH=CH-CO_2CH_3), 121.0 (C-5), 123.8 (C-1), 127.2 (C-2‘ and C-6‘), 128.0 (C-4‘), 128.7 (C-3‘ and C-5‘), 128.9 (C-6), 131.4 (C-4), 136.6 (C-1’), 140.2 (Ar-CH=CH-CO_2CH_3), 157.4 (C-2) and 167.9 (Ar-CH=CH-CO$_2$CH$_3$).

Ethyl 3-(2-benzyloxyphenyl)acrylate (14a):[2] A mixture of aldehyde **13** (265 mg, 1.03 mmol) and ethyl (triphenyl-λ5-phosphanylidene)-acetate (1180 mg, 2.06 mmol) in dichloromethane (5 mL) was stirred at room temperature for 5 h. Once demonstrated the complete consumption of the starting material by TLC, the solvent was removed under reduced pressure and the residue was chromatographed, rendering **14a** (297 mg, 88%), as a colorless oil. The major isomer (***E*-14a**) is described. IR (film, v): 2936, 1712, 1632, 1597, 1485, 1315, 1269, 1165, 1026, 991, 752 and 698 cm^{-1}. ^{1}H NMR δ 1.34 (t, J = 7.1, 3H, O-CH_2-CH_3), 4.26 (q, J = 7.1, 2H, OCH_2CH$_3$), 5.17 (s, 2H, OCH_2Ar), 6.55 (d, J = 16.2, 1H, Ar-CH=CH-$CO_2CH_2CH_3$), 6.94 (d, J = 7.5, 1H, H-3), 6.97 (t, J = 7.5, 1H, H-5), 7.30 (dt, J = 1.4 and 7.5, 1H, H-4), 7.34-7.46 (m, 5H), 7.55 (dd, J = 1.4 and 7.5, 1H, H-6) and 8.10 (d, J = 16.2, 1H, Ar-CH=CH-$CO_2CH_2CH_3$). ^{13}C NMR δ 14.3 (OCH$_2$$CH_3$), 60.3 (O$CH_2CH_3$), 70.4 (O$CH_2$Ar), 112.8 (C-3), 118.9 (Ar-CH=CH-$CO_2CH_2CH_3$), 121.0 (C-5), 123.9 (C-1), 127.1 (C-2’ and C-6’),

128.4 (C-4'), 128.6 (C-3' and C-5'), 131.3 (C-4), 136.6 (C-1'), 139.9 (Ar-*C*H=CH-$CO_2CH_2CH_3$), 157.3 (C-2) and 167.5 (Ar-CH=CH-*C*$O_2CH_2CH_3$).

Ethyl 3-(2-benzyloxyphenyl)-3-(4'-methoxyphenyl)acrylate (16): The cinnamate **14** (118 mg, 0.440 mmol) was added to a stirred mixture of 4-iodoanisole (154 mg, 0.66 mmol) and $Pd(OAc)_2$ (5 mg, 0.022 mmol) in Et_3N (3 mL), under an Ar atmosphere. The mixture was stirred at 100 °C during 17 h, when the reaction was diluted in EtOAc (15 mL) and the organic phase was successively washed with 2N HCl solution (10 mL), saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed, affording **16** (120 mg, 73%), as a yellow oil. IR (film, v): 2934, 1717, 1603, 1508, 1448, 1362, 1252, 1173, 1028, 833 and 741 cm^{-1}. ^1H NMR δ 1.06 (t, *J* = 7.1, 3H, OCH_2CH_3), 3.82 (s, 3H, OCH_3), 3.99 (q, *J* = 7.1, 2H, OCH_2CH_3), 4.98 (s, 2H, OCH_2Ar), 6.40 (s, 1H, Ar_2-C=C*H*-*C*$O_2CH_2CH_3$), 6.83 (d, *J* = 9.0, 2H, H-3' and H-5'), 6.98 (d, *J* = 7.3, 1H, H-3), 7.00 (t, *J* = 7.3, 1H, H-5), 7.11 (dd, *J* = 1.7 and 7.3, 1H, H-6), 7.18-7.34 (m, 5H, ArH of Benzyl), 7.29 (d, *J* = 9.0, 2H, H-2' and H-6') and 7.32 (t, *J* = 7.3, 1H, H-4). ^{13}C NMR δ 14.0 (OCH_2CH_3), 55.3 ($O-CH_3$), 59.7 (OCH_2CH_3), 70.0 (OCH_2Ar), 112.5 (C-3), 113.7 (C-3' and C-5'), 116.3 (Ar_2-C=*C*H-$CO_2CH_2CH_3$), 120.6 (C-5), 126.9 (Benzyl), 127.4 (Benzyl), 128.2 (Benzyl), 128.9 (C-1), 129.0 (C-2' and C-6'), 129.2 (C-4), 130.3 (C-6), 133.1 (C-1'), 137.2 (Benzyl), 153.1 (Ar_2-*C*=*C*H-$CO_2CH_2CH_3$), 155.6 (C-2), 160.6 (C-4') and 166.1 (*C*O_2Et). HRMS *m/z* calcd. for $C_{24}H_{22}NO_6$: 447.1567 $[M + Na]^+$; found: 447.1555.

3-(2-Benzyloxyphenyl)-3-(4'-methoxyphenyl)-acrylic acid (17): A stirred solution of ester **16** (107 mg, 0.297 mmol) in EtOH:H_2O (1:1, v/v, 7 mL), was treated with KOH (40.1 mg, 0.714 mmol) during 18 h at room temperature. After assessing the absence of the starting material (TLC), the reaction was diluted with Et_2O (10 mL) and 2M NaOH (10 mL). The aqueous phase was separated, acidified with 2M HCl (15 mL), and extracted with Et_2O (3 × 15 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure, affording **17** (89 mg, 90%), as a colorless solid, m.p.: 164-165 ºC (EtOAc). IR (KBr, v): 3977, 2927, 1674, 1585, 1450, 1258, 1153, 1034, 748 and 605 cm^{-1}. ^{1}H NMR (Acetone-d_6) δ 3.81 (s, 3H, OCH_3), 5.00 (s, 2H, OCH_2Ar), 6.41 (s, 1H, Ar_2-C=CH-$C$$O_2$H), 6.91 (d, *J* = 8.8, 2H, H-3' and H-5'), 6.97 (dt, *J* = 0.9 and 7.9, 1H, H-5), 7.08 (d, *J* = 7.9, 1H, H-3), 7.11 (d, *J* = 7.9, 1H, H-6), 7.12 (d, *J* = 9.0, 2H, ArH of Benzyl), 7.20-7.23 (m, 3H, ArH of Benzyl), 7.31 (dt, *J* = 1.4 and 7.9, 1H, H-4) and 7.80 (d, *J* = 8.8, 2H, H-2' and H-6'). ^{13}C NMR (Acetone-d_6) δ 54.8 (O$C$$H_3$), 70.0 (O$C$$H_2$Ar), 112.5 (C-3), 113.7 (C-3' and C-5'), 116.2 (Ar_2-C=CH-CO_2H), 120.3 (C-5), 127.0 (Benzyl), 127.3 (Benzyl), 128.1 (Benzyl), 128.8 (C-2' and C-6'), 129.0 (C-4), 129.0 (Ar_2-C=CH-CO_2H), 130.3 (C-6), 132.9 (C-1'), 137.5 (Benzyl), 153.1 (Ar_2-C=CH-CO_2H), 155.8 (C-2'), 160.8 (C-4´) and 165.9 (Ar_2-C=CH-$C$$O_2$H). HRMS *m/z* calcd. for $C_{23}H_{20}NaNO_6$: 383.1254 $[M + Na]^+$; found: 383.1254.

***N*-[3-(2-Benzyloxyphenyl)-3-(4'-methoxyphenyl)-acryloyloxy]-4-methyl benzenesulfonamide (18):** A stirred solution of acid **17** (50 mg, 0.166 mmol) in anhydrous THF (1 mL) was treated with TsNCO (39.2 mg, 0.199 mmol). The mixture was stirred during 10 minutes at room temperature, when Et_3N (26.1

mg, 0.258 mmol) was added dropwise and the solution was further stirred overnight. The reaction was quenched with 2N HCl (5 mL) and the organic products were extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduce pressure, affording the sulfonimide **18** (68 mg, 95%), as a white solid, mp. 150-152 ºC (EtOAc). IR (ATR, v): 3167, 2928, 2862, 1663, 1585, 1443, 1339, 1258, 1130, 1084, 868, 602 cm^{-1}. ^{1}H NMR *δ* 2.43 (s, 3H, ArC*H*$_3$), 3.81 (s, 3H, OC*H*$_3$), 4.82 (s, 1H, N*H*), 4.95 (s, 2H, OC*H*$_2$Ar), 6.37 (s, 1H,Ar$_2$-C=C*H*-*C*ONHTs), 6.83 (d, *J* = 8.6, 2H, H-3' and H-5'), 6.95 (d, *J* = 7.5, 1H, H-3), 6.99 (t, *J* = 7.5, 1H, H-5), 7.03-7.06 (m, 5H, ArH of Benzyl), 7.09 (dd, *J* = 1.2 and 7.5, 1H, H-6), 7,26 (d, *J* = 8.6, 2H, H-2' and H-6'), 7.31 (d, *J* = 8.1, 2H, ArH of Arenesulfonimide), 7.32 (dt, *J* = 1.2 and 7.5, 1H, H-4) and 7.81 (d, *J* = 8.1, 2H, ArH of Arenesulfonimide). ^{13}C NMR *δ* 21.5 (Ar*C*H$_3$), 55.4 (O*C*H$_3$), 70.1 (O*C*H$_2$Ar), 112.6 (C-3), 113.8 (C-3' and C-5'), 115.3 (Ar$_2$-C=*C*H-*C*ONHTs), 120.6 (C-5), 126.5 (Benzyl), 127.0 (Benzyl), 127.5 (Benzyl), 128.2 (Arenesulfonimide), 128.3 (Benzyl), 129.2 (C-2' and C-6'), 129.5 (C-4), 129.7 (Arenesulfonimide), 130.4 (C-6), 132.7 (C-1), 137.0 (C-1'), 139.1 (Arenesulfonimide), 143.6 (Arenesulfonimide), 155.1 (Ar$_2$-*C*=CH-CONHTs), 155.6 (C-2), 160.9 (C-4') and 169.5 (Ar$_2$-C=CH-*C*ONHTs). HRMS *m/z* calcd. for $C_{30}H_{27}NNaO_5S$: 536.1500 $[M + Na]^+$; found: 536.1502.

3-(2-Benzyloxyphenyl)-3-(4'-methoxyphenyl)acrylamide (20): Et_3N (0.5 mL) was added to a well ground and magnetically stirred mixture of carboxylic acid **17** (145 mg, 0.402 mmol), silica-supported ammonium salt (NH_4Cl, 43.8 mg, 0.809 mmol) prepared under literature conditions[3] and TsCl (76.6 mg, 0.402 mmol). After 1 min, the reaction mixture was diluted with EtOAc (25 mL) and

filtered. The filtrate was washed with 0.02 N HCl (2 × 25 mL) and the aqueous layer was re-extracted with EtOAc (15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography, affording **20** (116 mg, 80%), as a pale yellow solid, m.p.: 168-170 ºC (EtOAc). IR (KBr, v): 3348, 2932, 1674, 1585, 1450, 1258, 1123, 1034,748 and 683 cm^{-1}. ^{1}H NMR δ 3.81 (s, 3H, OCH_3), 4.95 (s, 2H, OCH_2Ar), 4.99 (s, 2H, -NH_2), 6.38 (s, 1H, Ar_2-C=CH-CONH_2), 6.83 (d, J = 8.9, 2H, H-3' and H-5'), 6.95 (d, J = 7.5, 1H, H-3), 6.98 (t, J = 7.5, 1H, H-5), 7.09 (dd, J = 1.6 and 7.5, 1H, H-6), 7.20-7.25 (m, 5H, ArH of Benzyl), 7.29 (d, J = 8.9, 2H, H-2' and H-6') and 7.30 (t, J = 7.5, 1H, H-4). ^{13}C NMR δ 55.4 (OCH$_3$), 70.1 (OCH_2Ar), 112.6 (Ar_2-C=CH-CONH_2), 113.8 (C-3' and C-5'), 115.4 (C-3), 120.6 (C-5), 127.5 (Benzyl), 128.2 (Benzyl), 128.4 (C-1), 129.2 (Benzyl), 129.5 (C-4), 129.7 (C-2' and C-6'), 130.4 (C-6), 132.8 (C-1'), 137.0 (Ar_2-C=CH-CONH_2), 139.2 (Benzyl), 155.6 (C-2), 160.9 (C-4') and 170.1 (Ar_2-C=CH-CONH_2). HRMS *m/z* calcd. for $C_{23}H_{22}NO_3$: 360.1600 $[M + H]^+$; found: 360.1594.

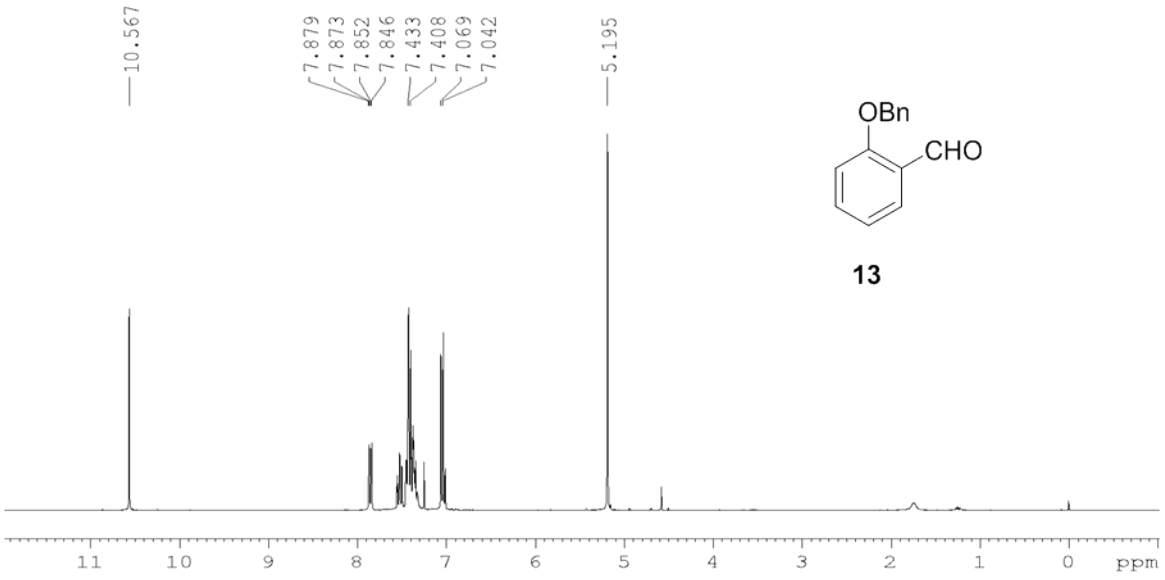

Figure S1. ^{1}H NMR (300 MHz) spectrum of compound **13**.

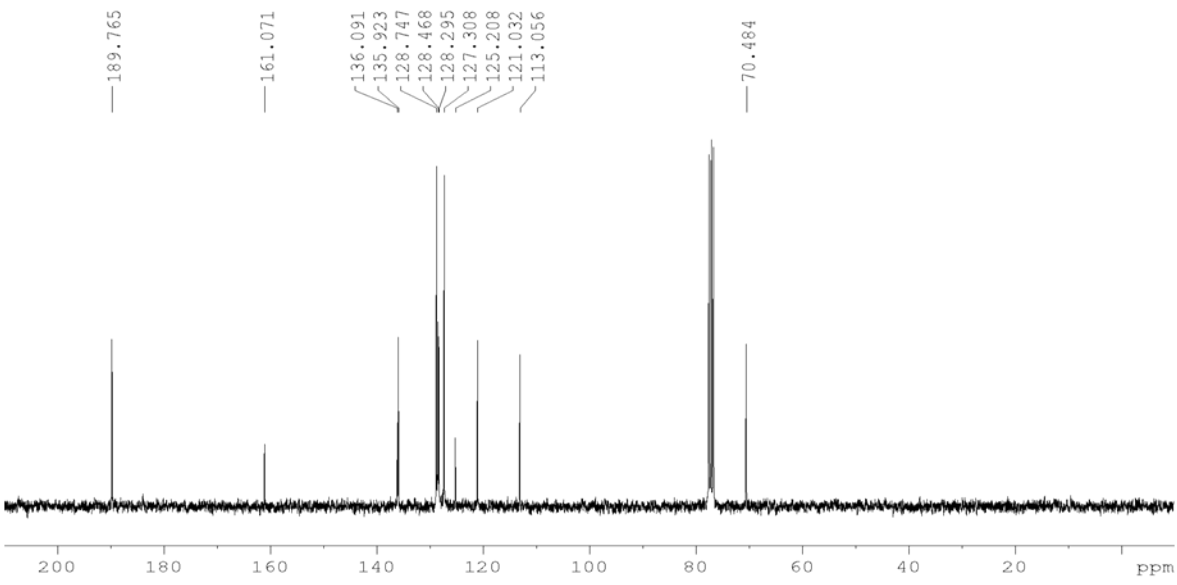

Figure S2. ^{13}C NMR (75 MHz) spectrum of compound **13**.

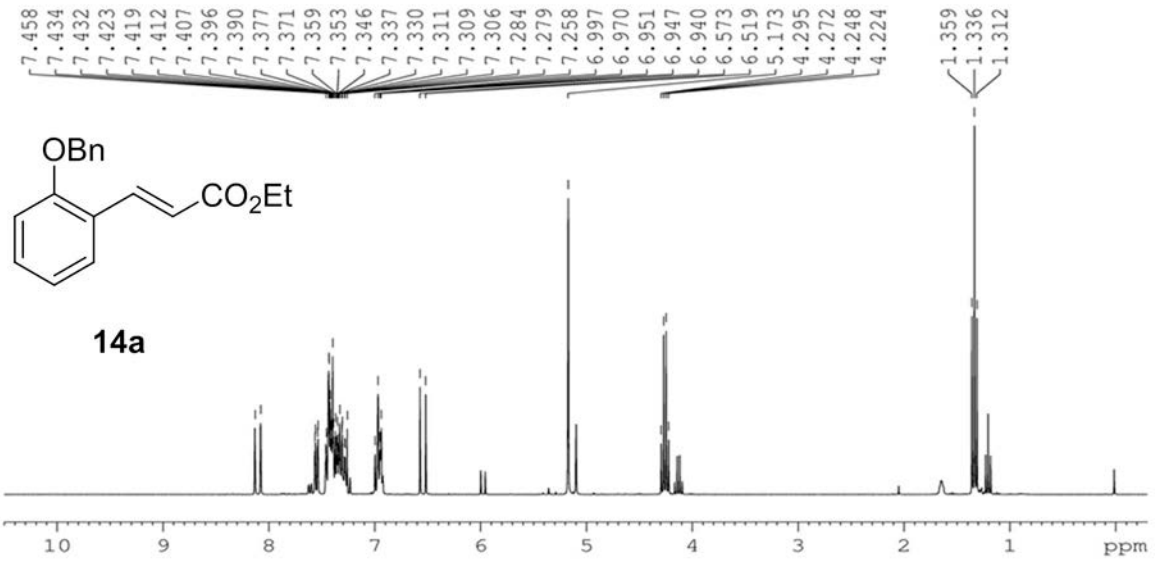

Figure S3. ^{1}H NMR (300 MHz) spectrum of compound **14a**.

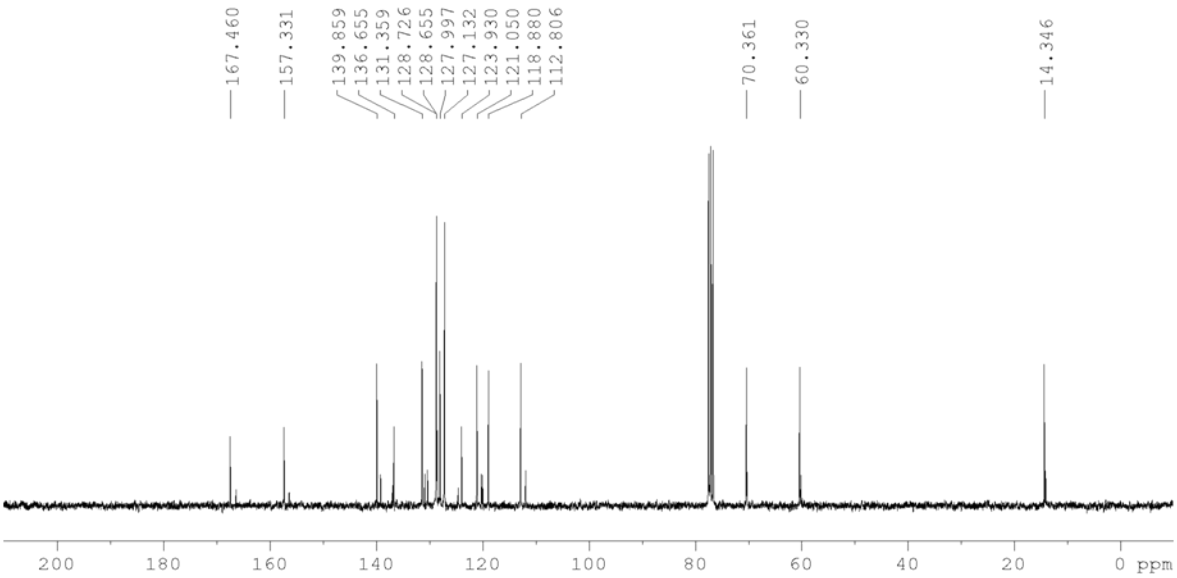

Figure S4. ^{13}C NMR (75 MHz) spectrum of compound **14a**.

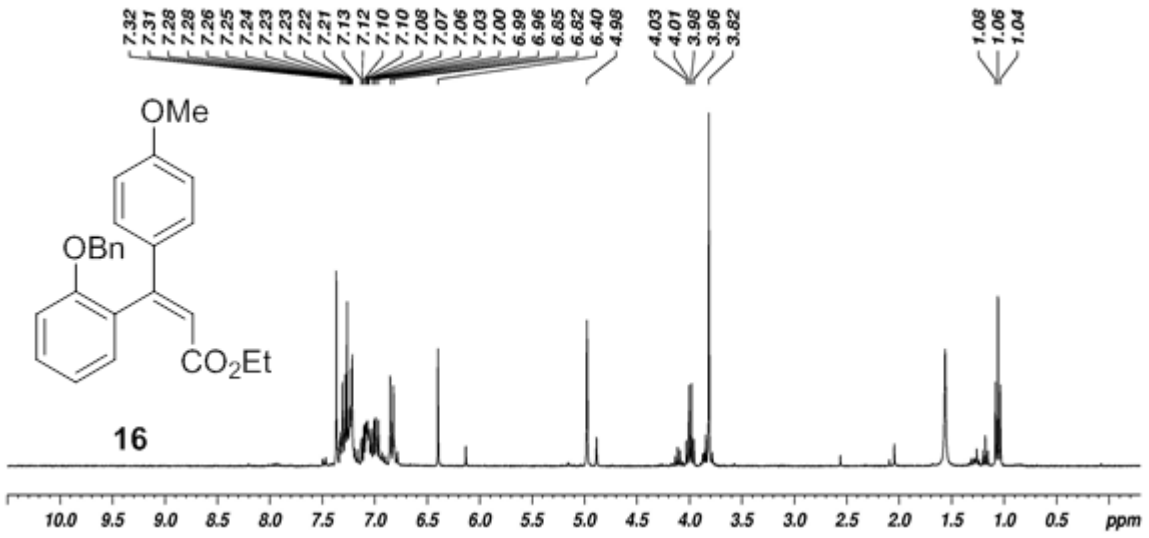

Figure S5. ^{1}H NMR (300 MHz) spectrum of compound **16**.

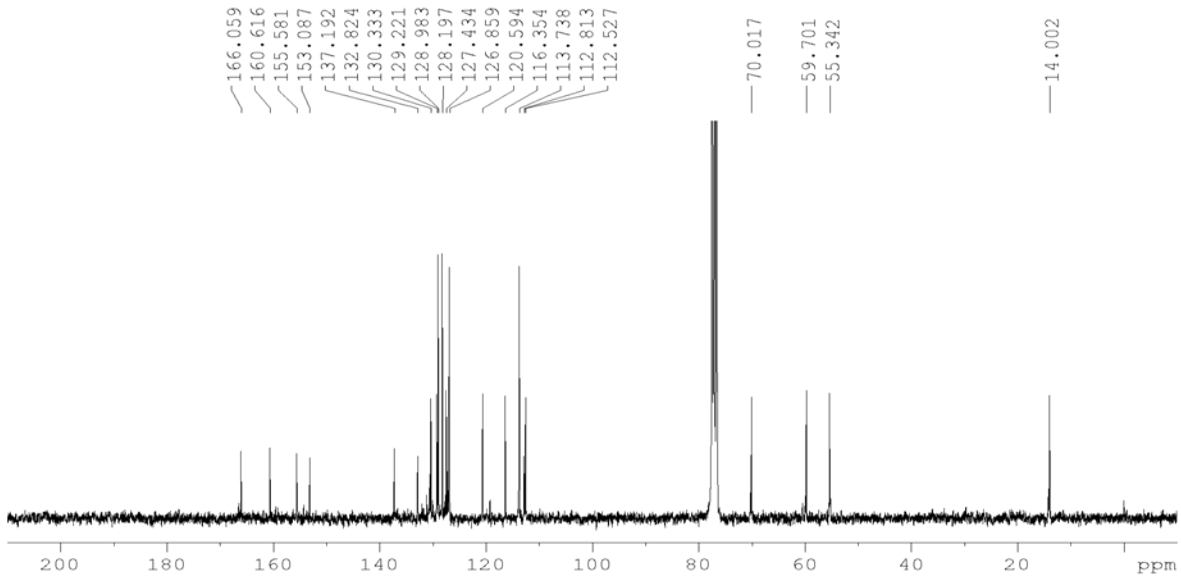

Figure S6. ^{13}C NMR (75 MHz) spectrum of compound **16**.

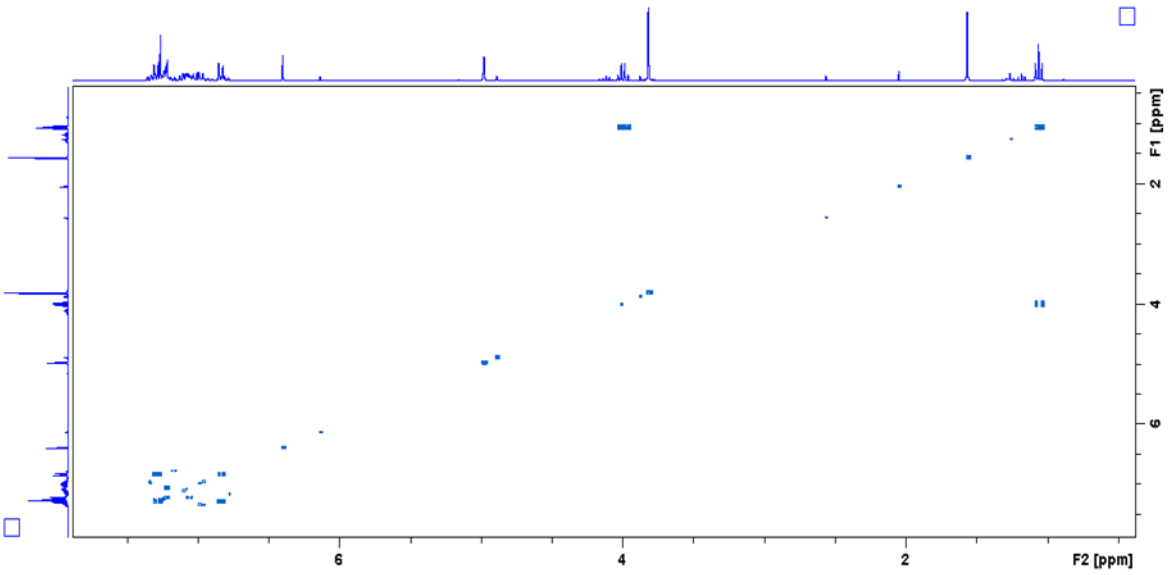

Figure S7. COSY spectrum of compound **16**.

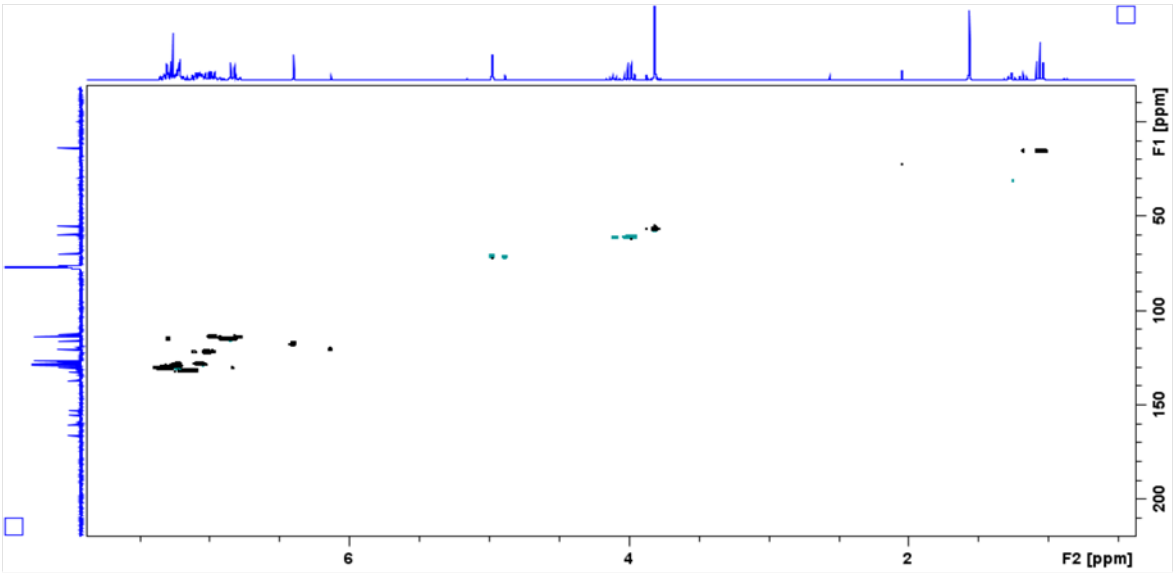

Figure S8. HSQC spectrum of compound **16**.

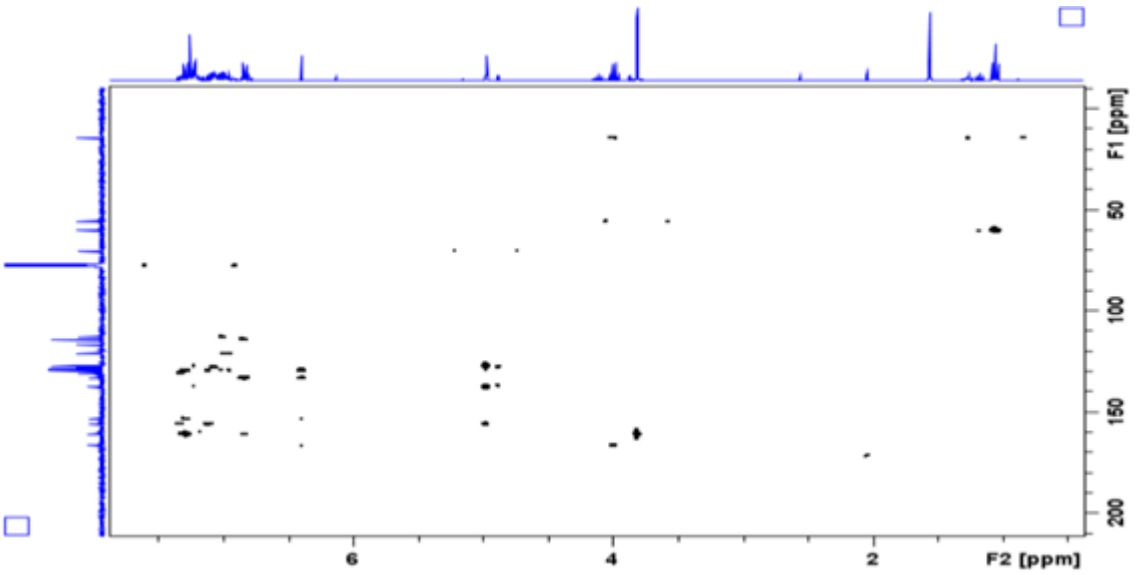

Figure S9. HMBC spectrum of compound **16**.

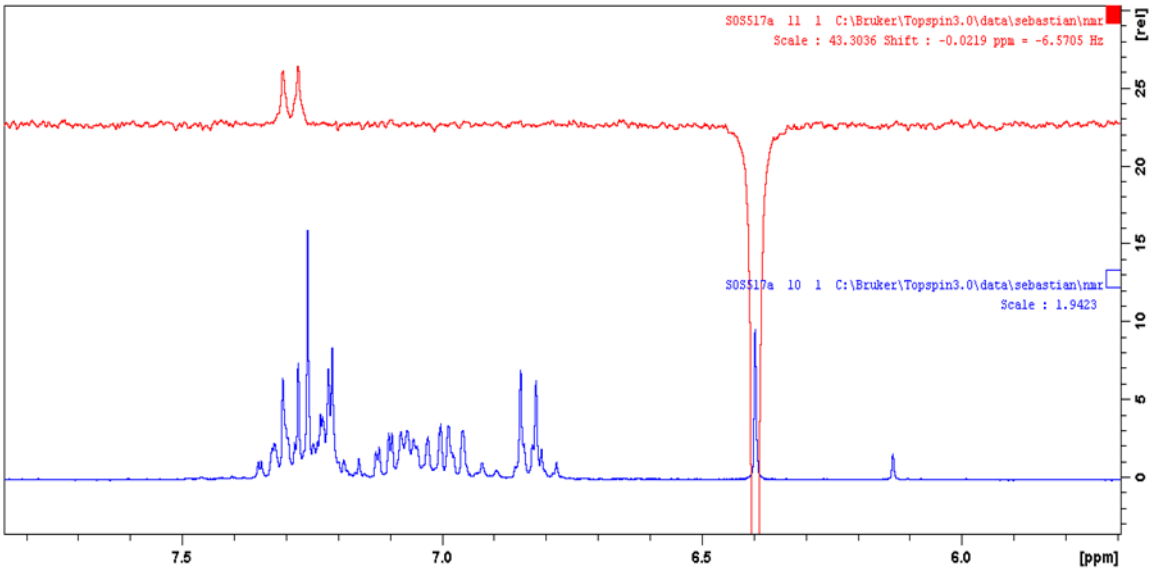

Figure S10. nOe spectrum. Irradiation at 6.40 ppm in compound **16**.

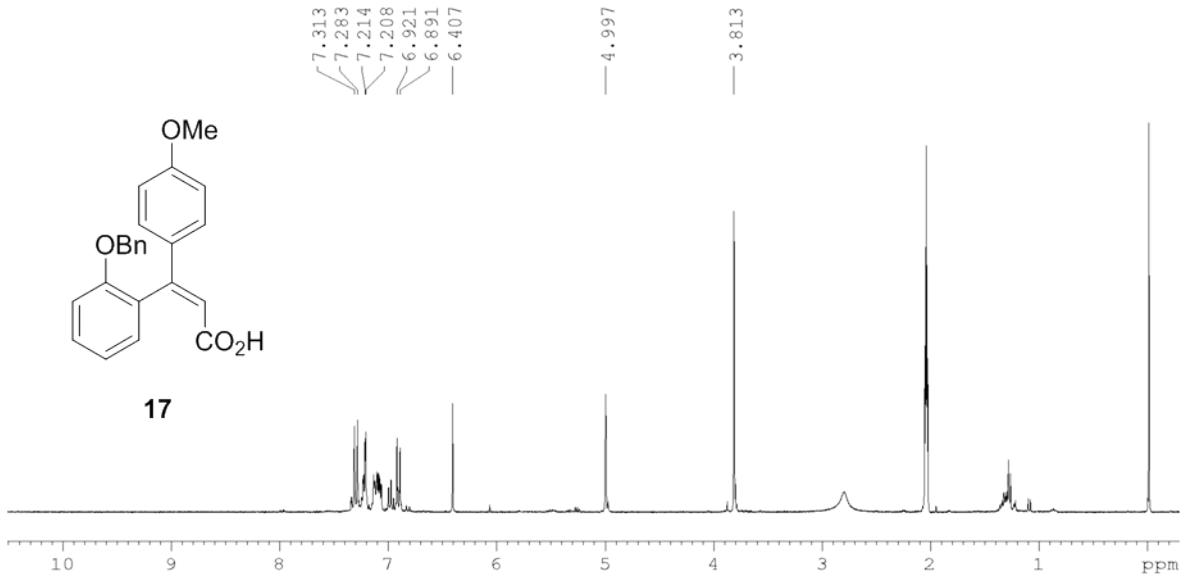

Figure S11. ^{1}H NMR (300 MHz) spectrum of compound **17** in acetone-d_6.

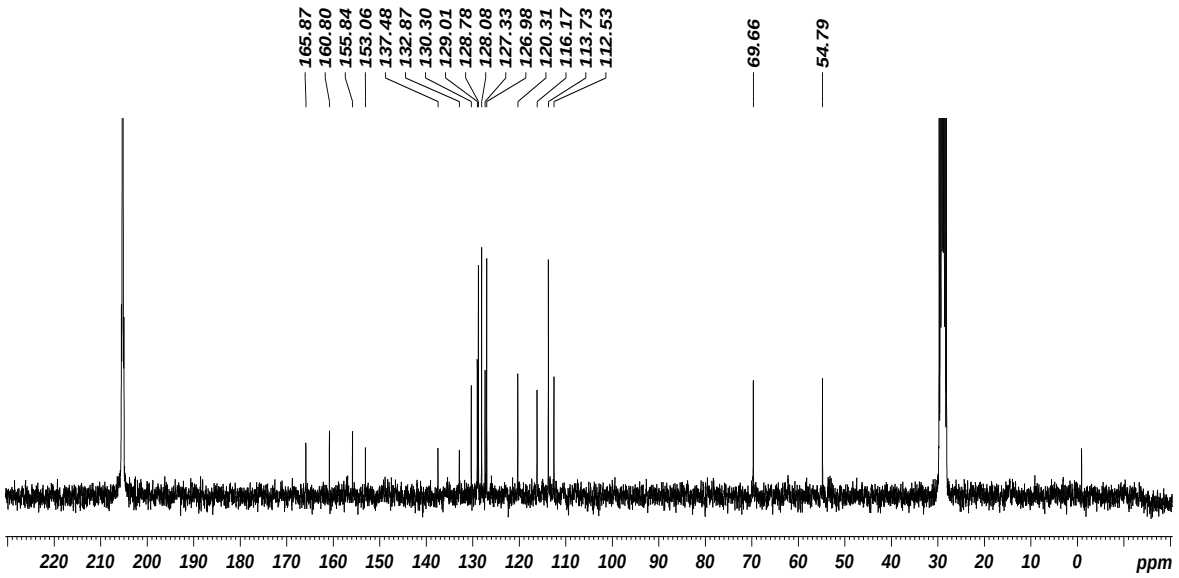

Figure S12. ^{13}C NMR (75 MHz) spectrum of compound **17** in acetone-d_6.

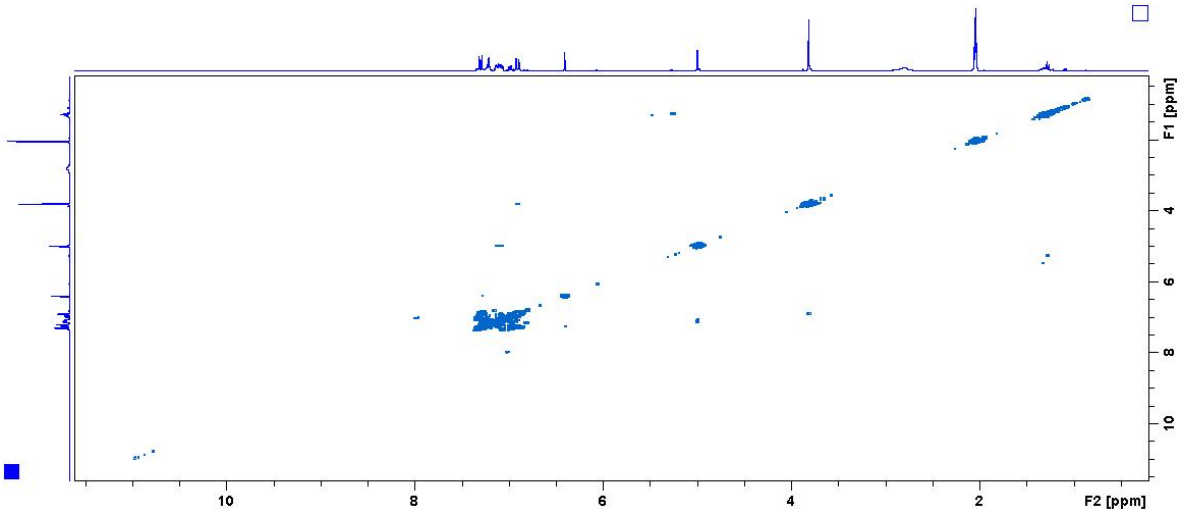

Figure S13. COSY spectrum of compound **17** in acetone-d_6.

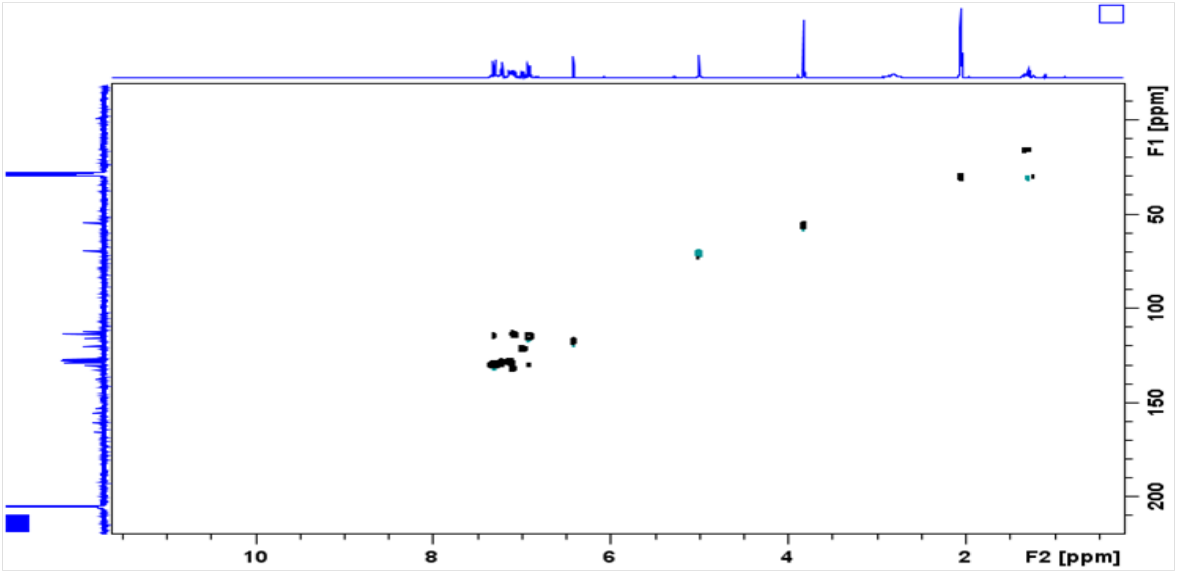

Figure S14. HSQC spectrum of compound **17** in acetone-d_6.

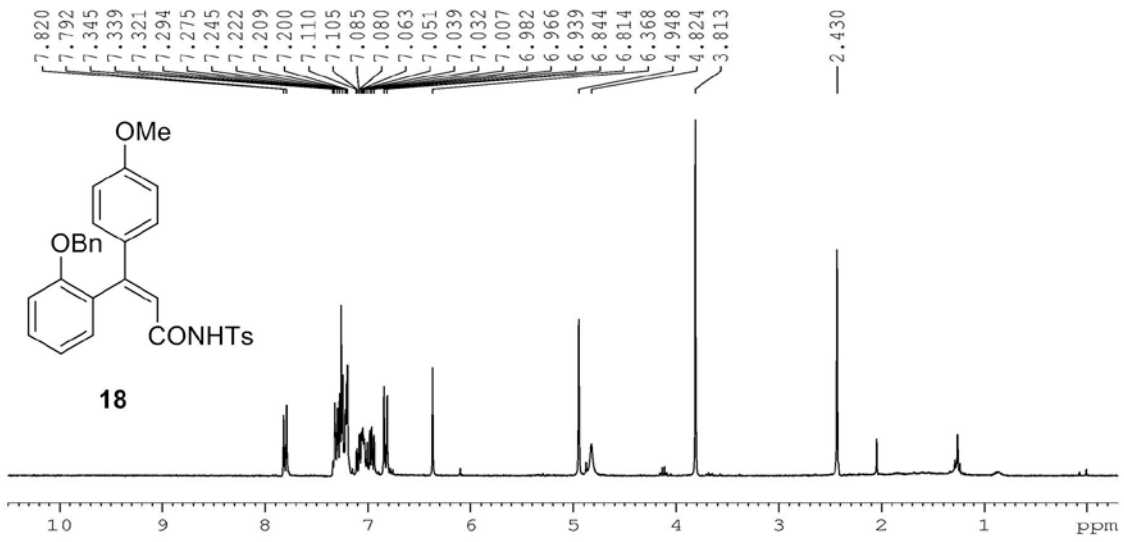

Figure S15. ^{1}H NMR (300 MHz) spectrum of compound **18**.

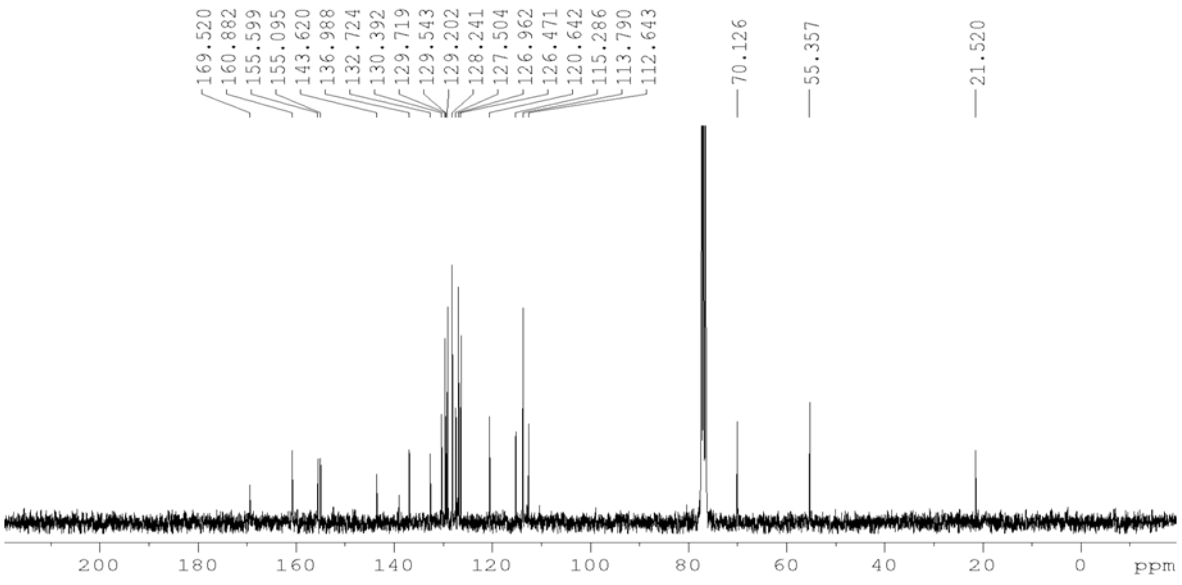

Figure S16. ^{13}C NMR (75 MHz) spectrum of compound **18**.

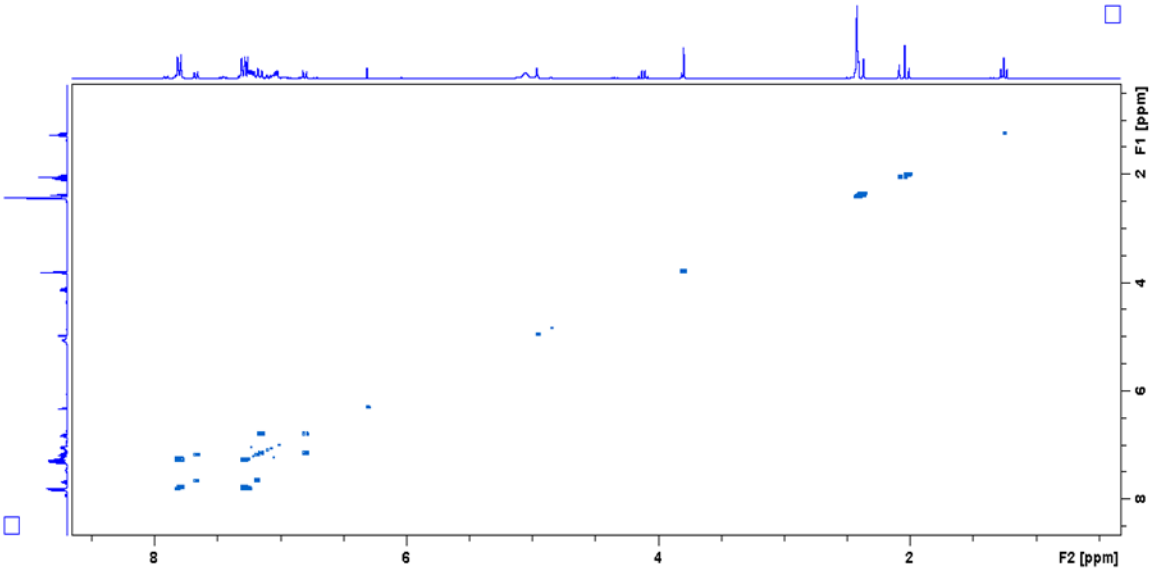

Figure S17. COSY spectrum of compound **18.**

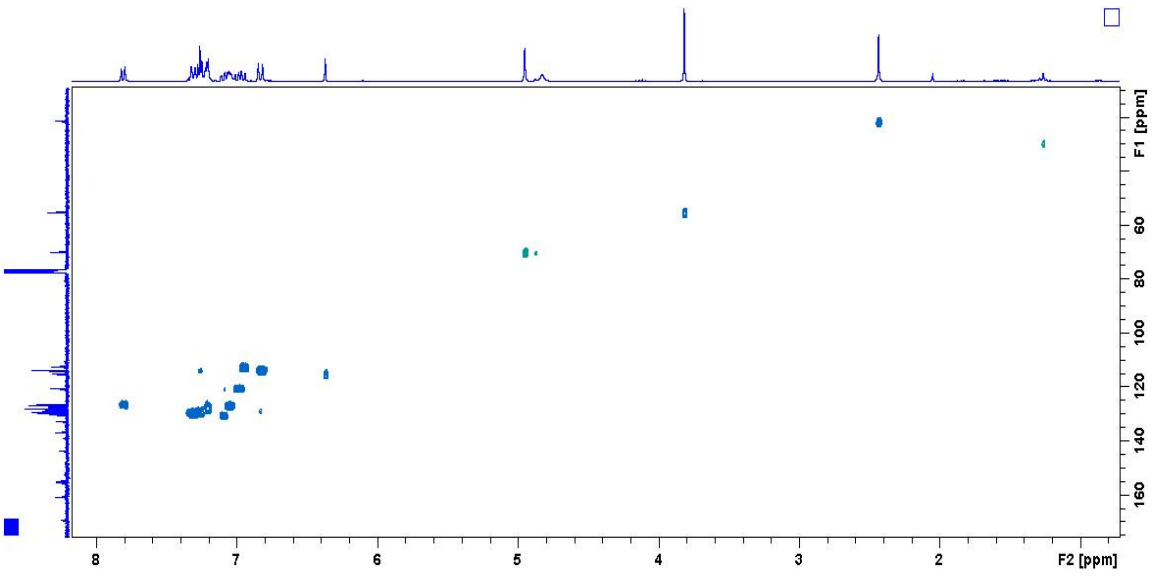

Figure S18. HSQC spectrum of compound **18**.

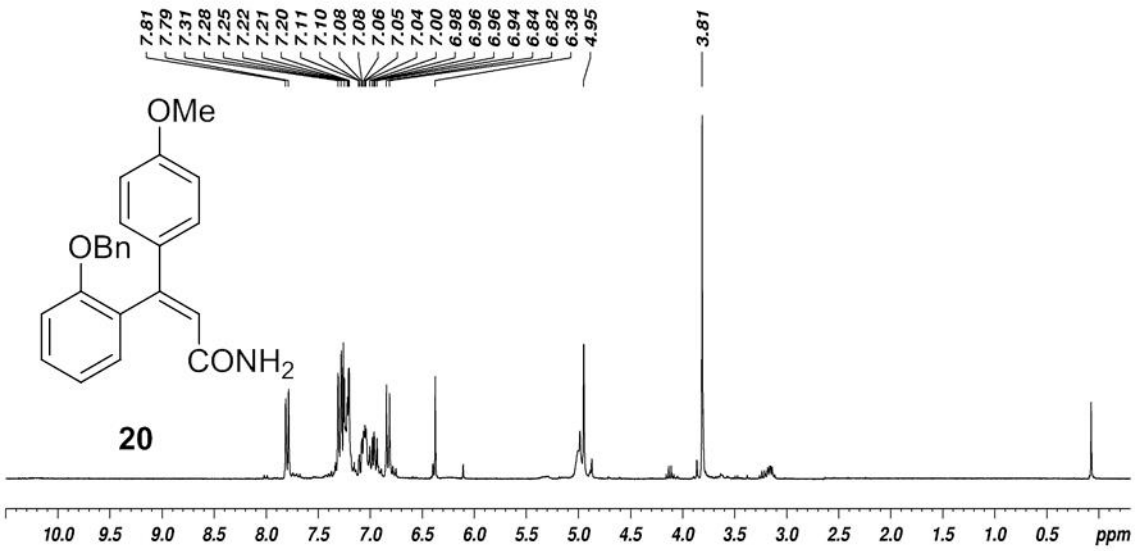

Figure S19. ^{1}H NMR (300 MHz) spectrum of compound **20**.

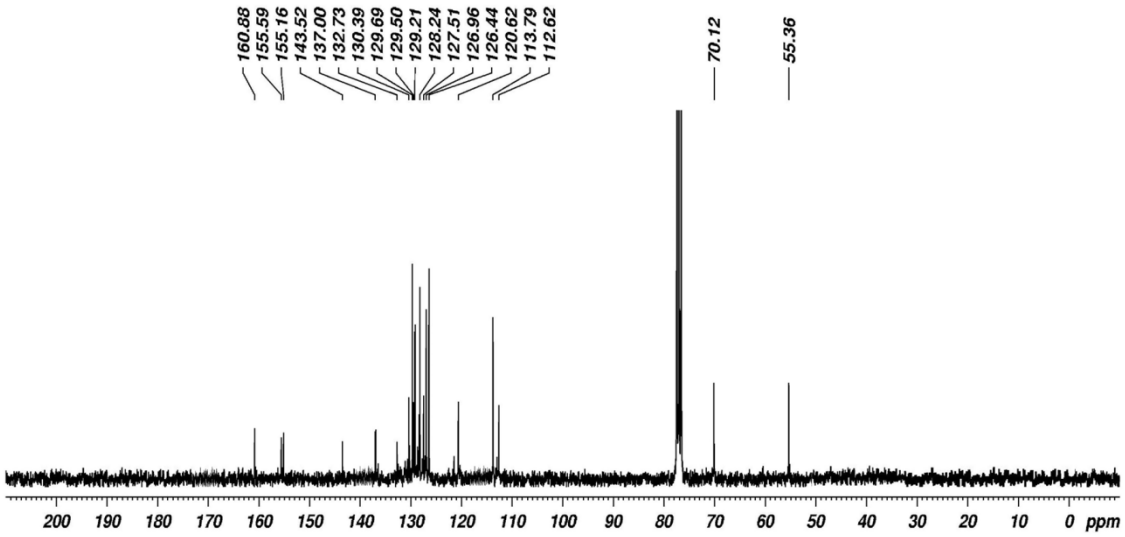

Figure S20. ^{13}C NMR (75 MHz) spectrum of compound **20**.

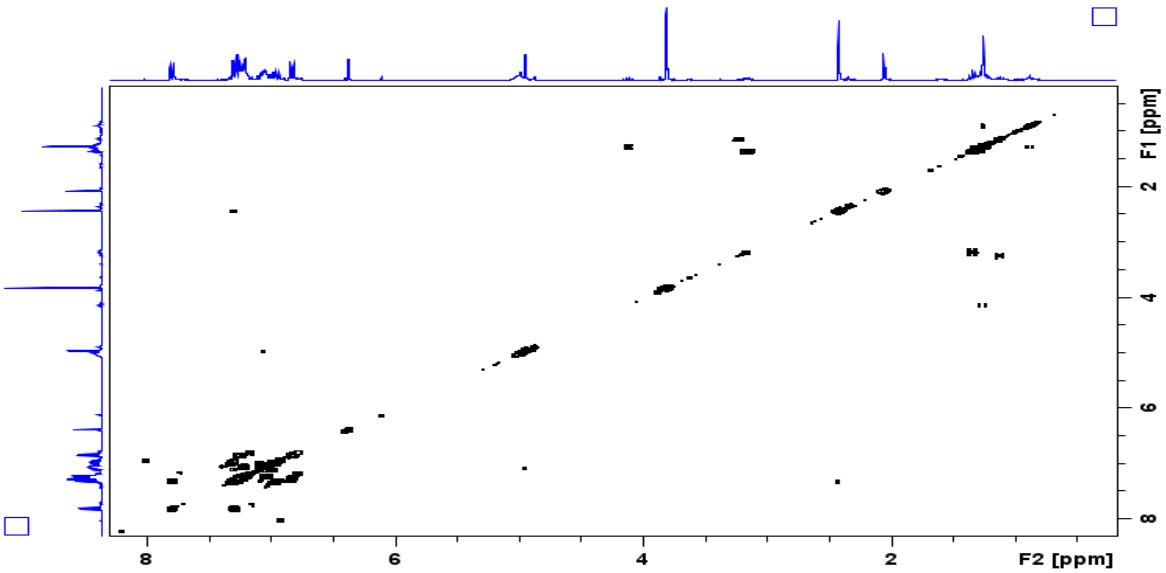

Figure S21. COSY spectrum of compound **20.**

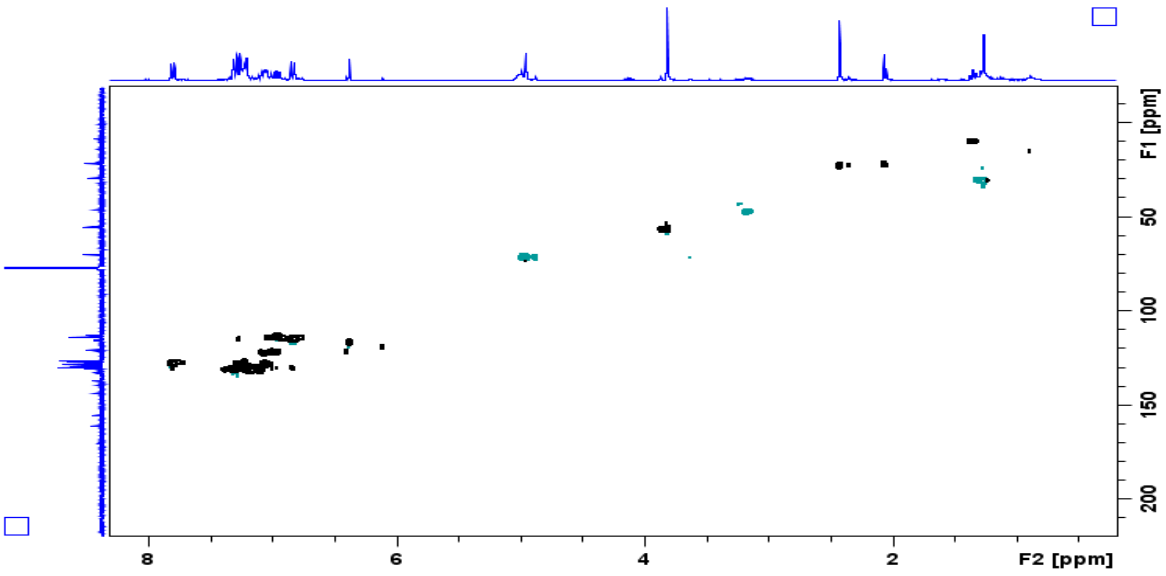

Figure S22. HSQC spectrum of compound **20**.

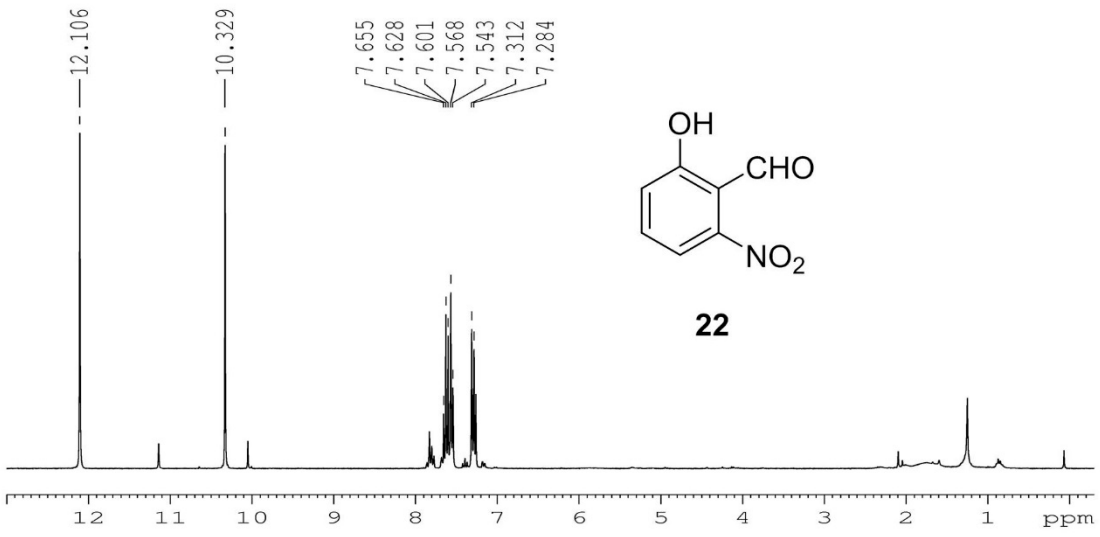

Figure S23. ^{1}H NMR (300 MHz) spectrum of compound **22**.

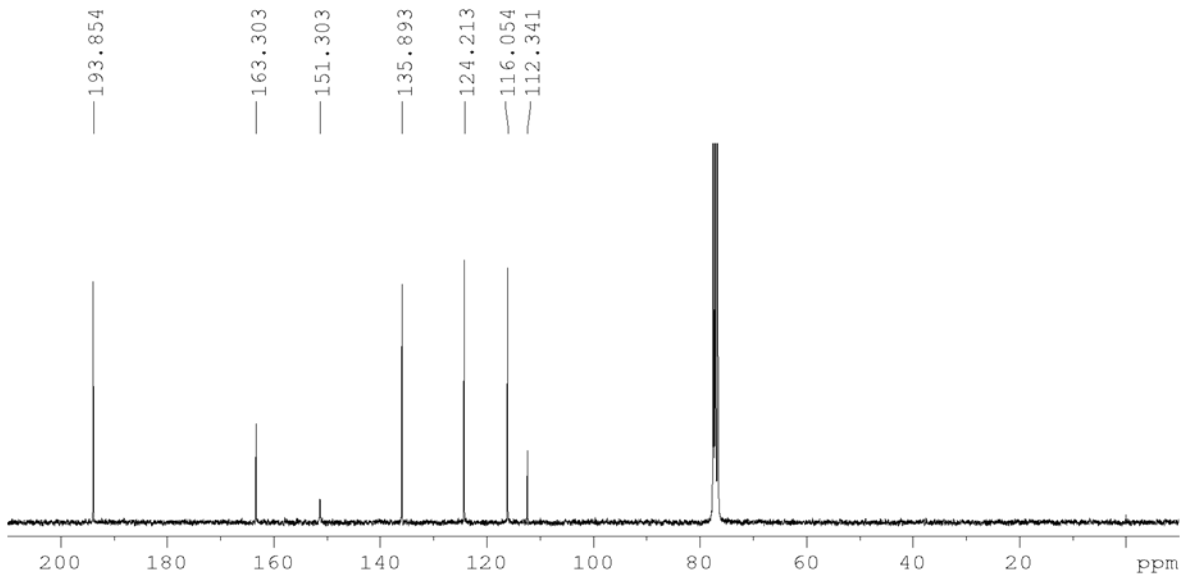

Figure S24. ^{13}C NMR (75 MHz) spectrum of compound **22**.

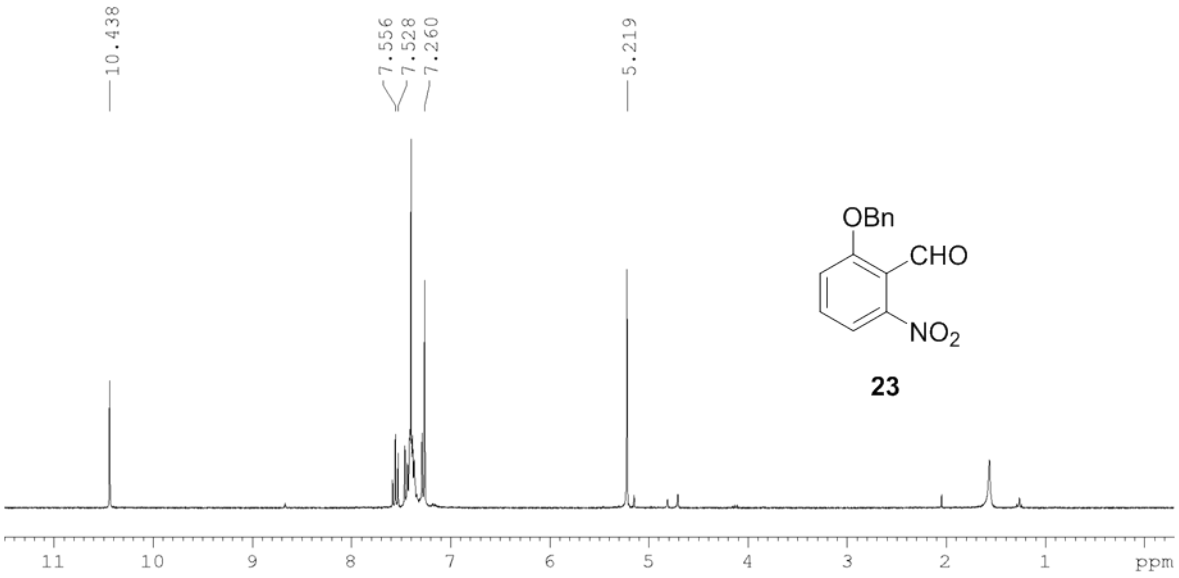

Figure S25. ^{1}H NMR (300 MHz) spectrum of compound **23**.

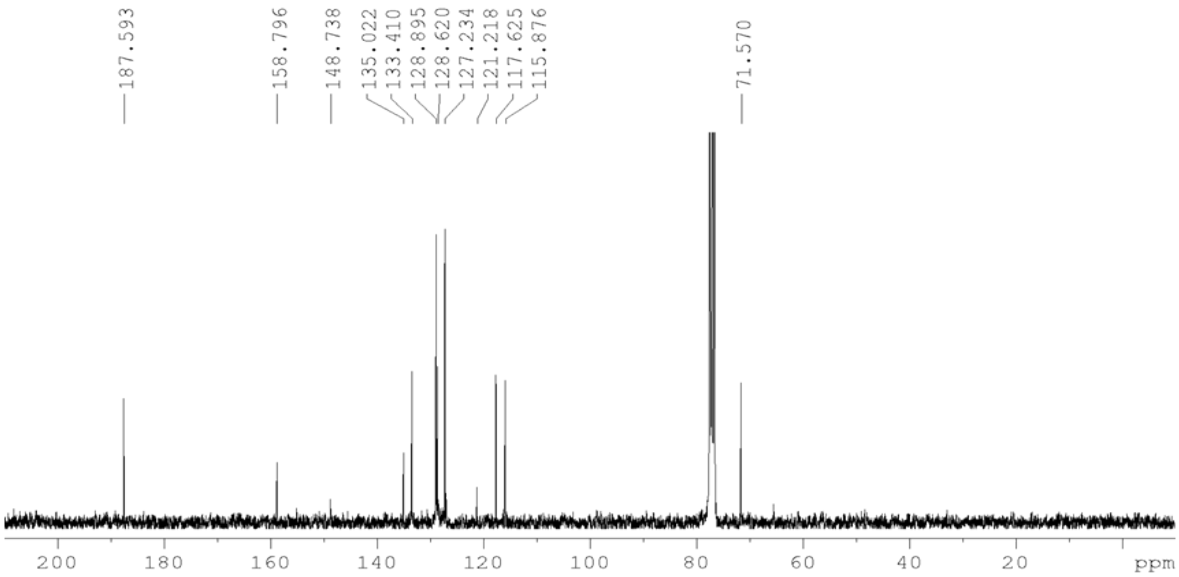

Figure S26. ^{13}C NMR (75 MHz) spectrum of compound **23**.

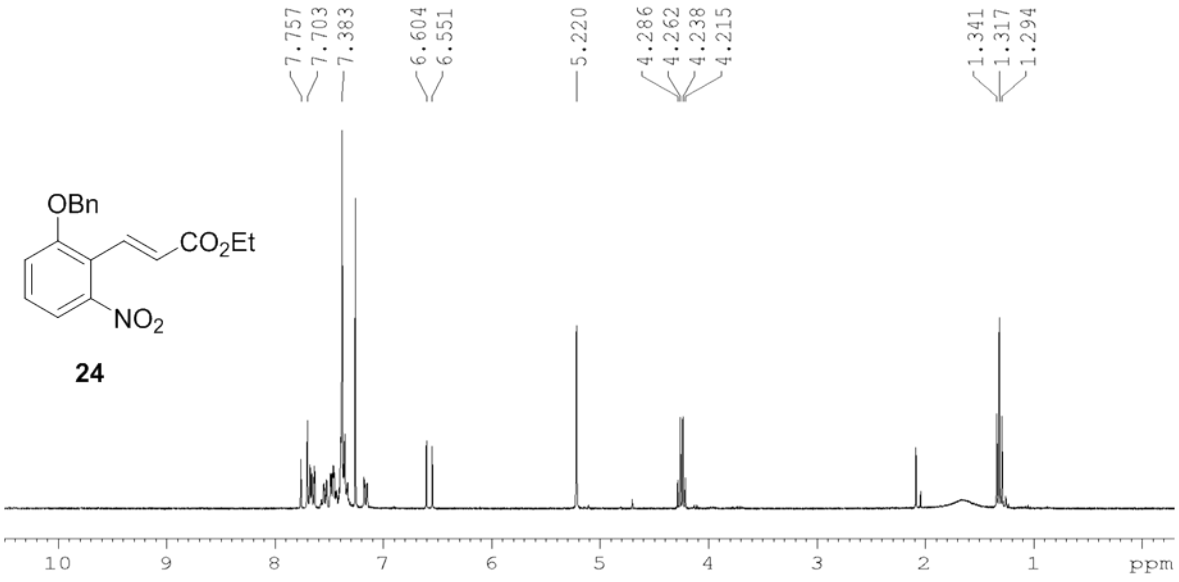

Figure S27. ^{1}H NMR (300 MHz) spectrum of compound **24**.

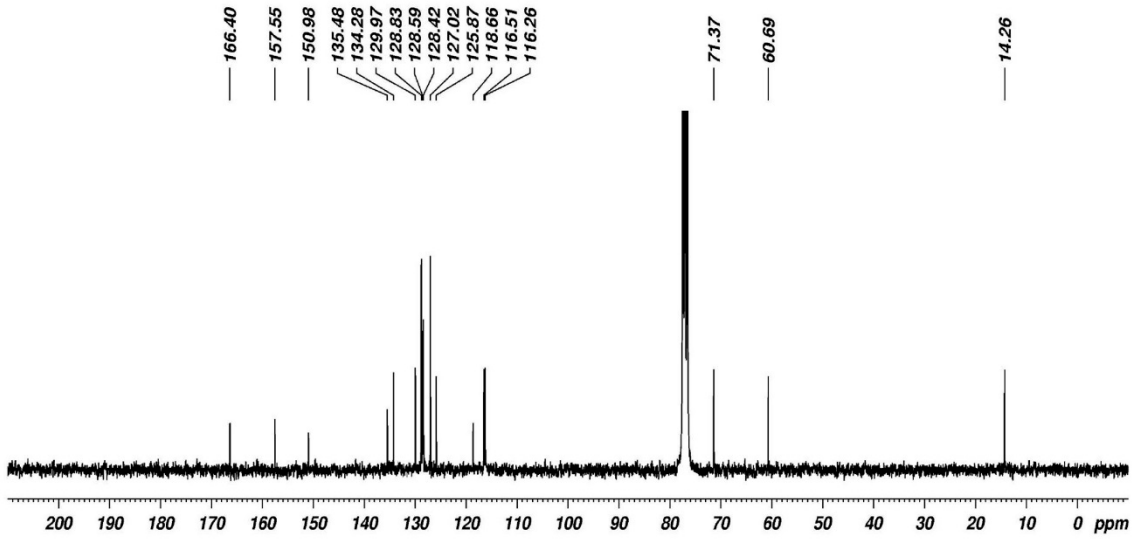

Figure S28. ^{13}C NMR (75 MHz) spectrum of compound **24**.

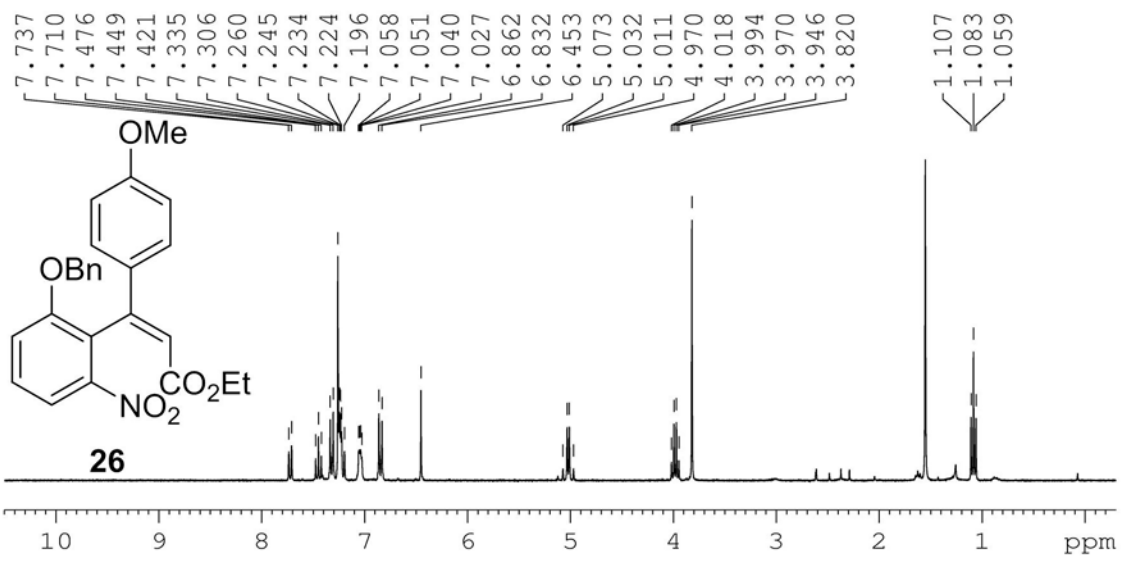

Figure S29. ^{1}H NMR (300 MHz) spectrum of compound **26**.

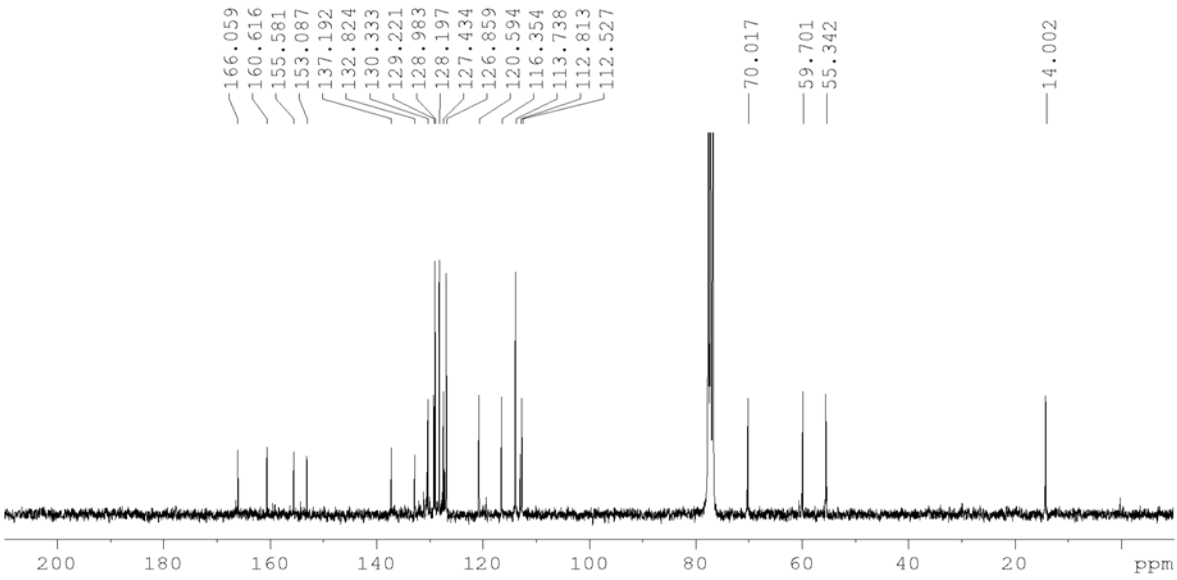

Figure S30. ^{13}C NMR (75 MHz) spectrum of compound **26**.

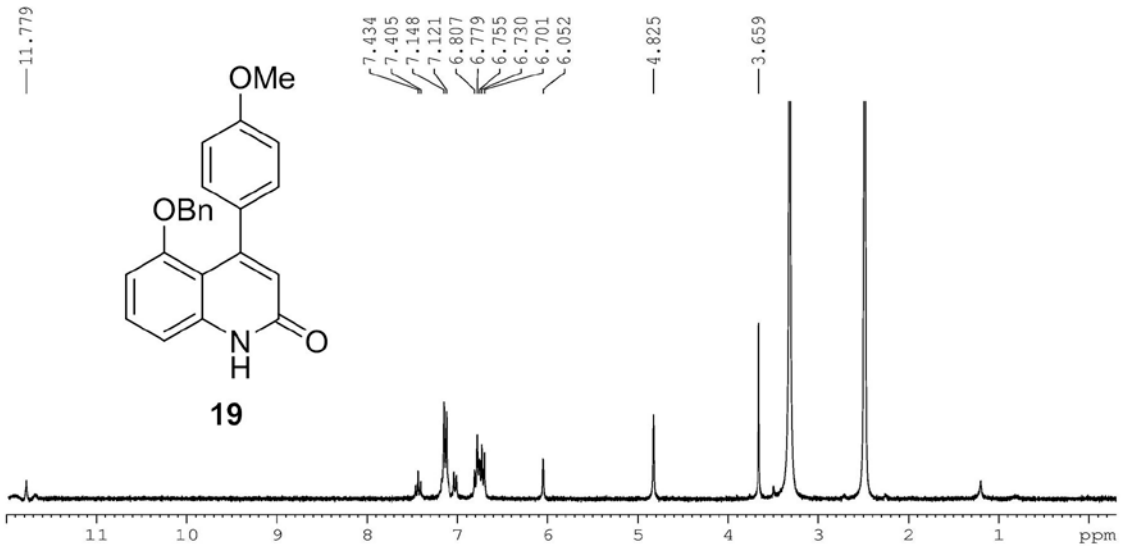

Figure S31. ^{1}H NMR (300 MHz) spectrum of compound **19** in DMSO-d_6.

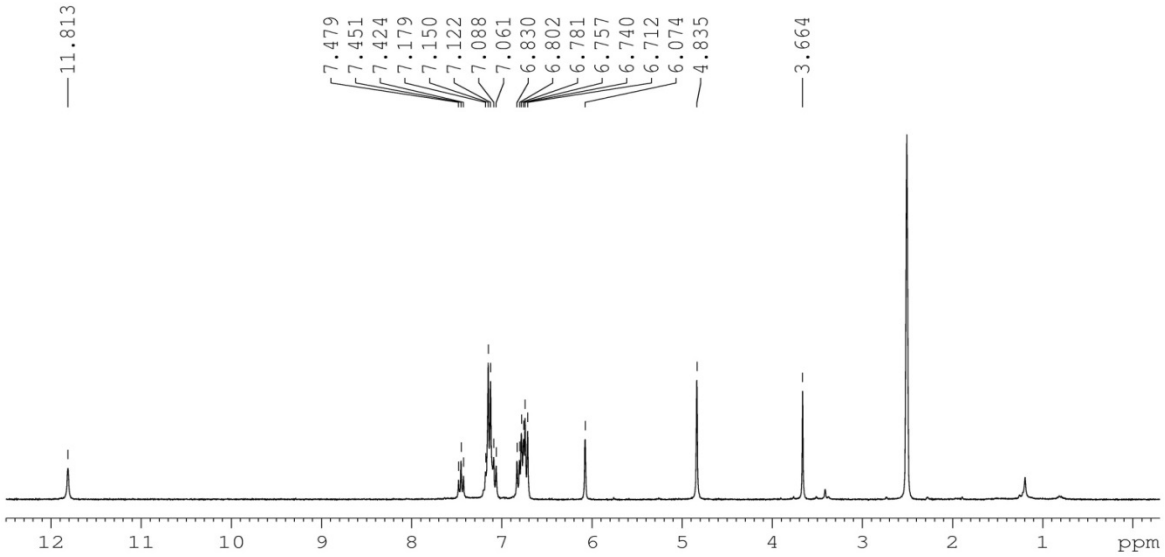

Figure S32. ^{1}H NMR (300 MHz) spectrum with water suppression of compound **19** in DMSO-d_6.

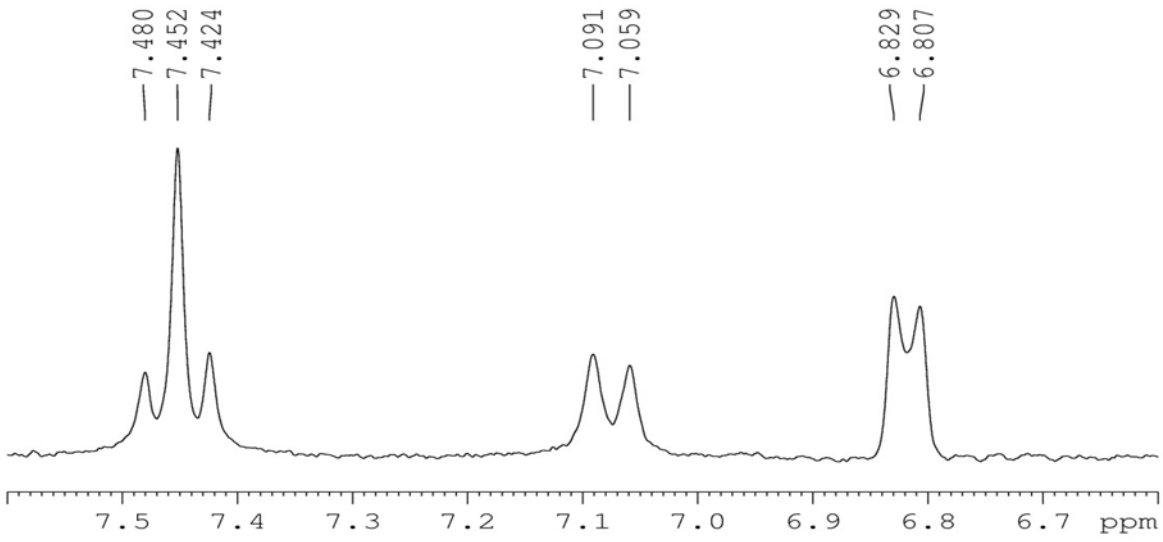

Figure S33. TOCSY 1D NMR (300 MHz) spectrum of compound **19** in DMSO-d_6.

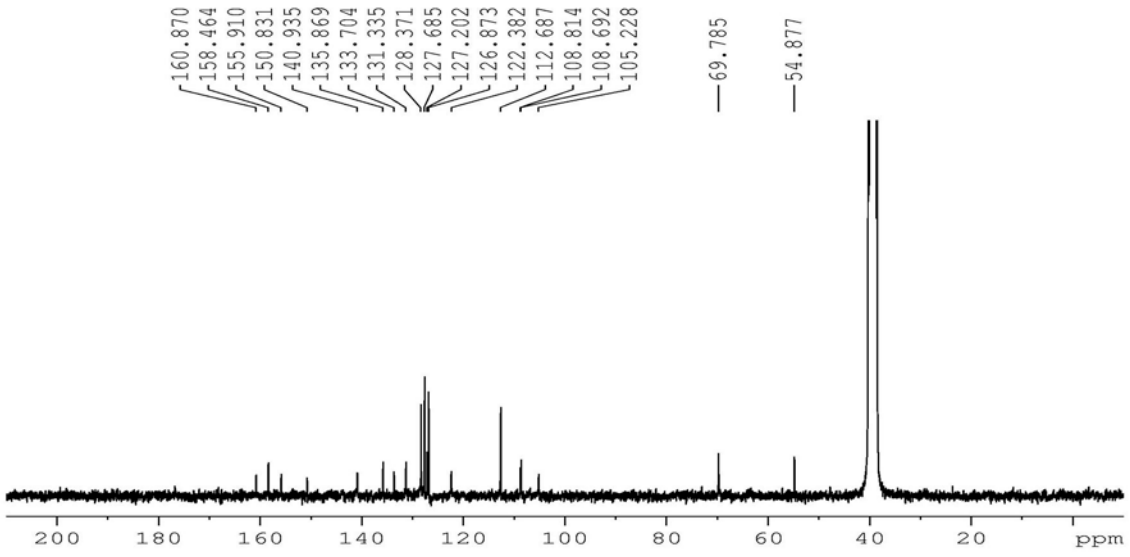

Figure S34. ^{13}C NMR (75 MHz) spectrum of compound **19** in DMSO-d_6.

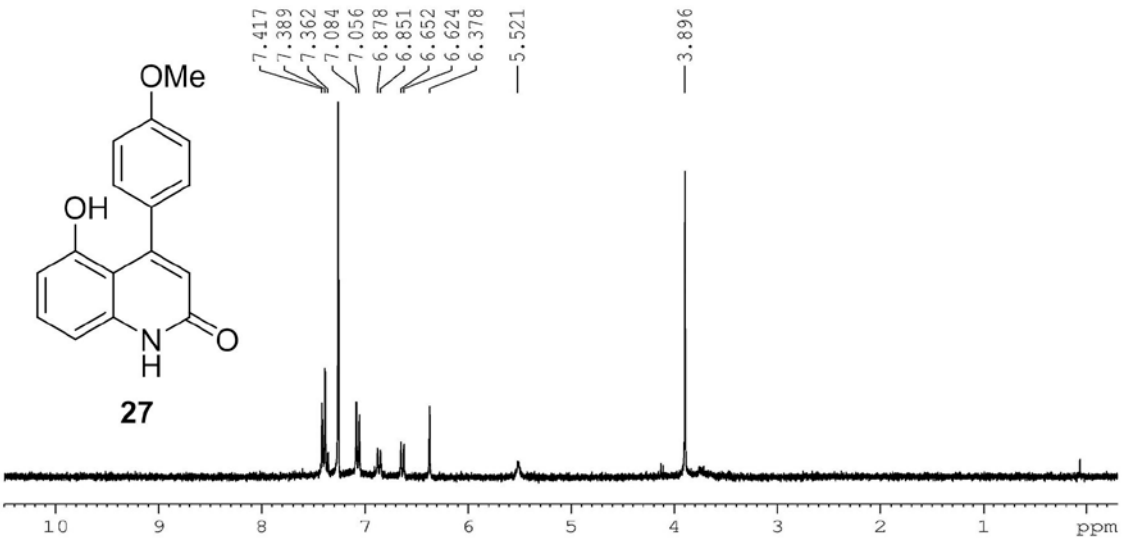

Figure S35. ^{1}H NMR (300 MHz) spectrum of compound **27**.

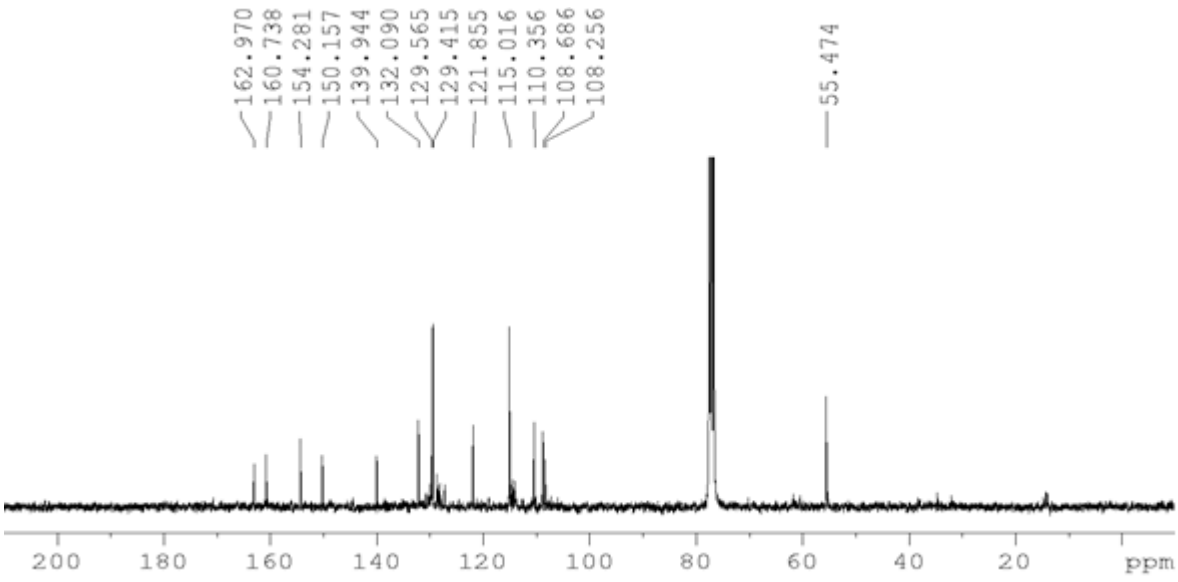

Figure S36. ^{1}H NMR (300 MHz) spectrum of compound **27**.

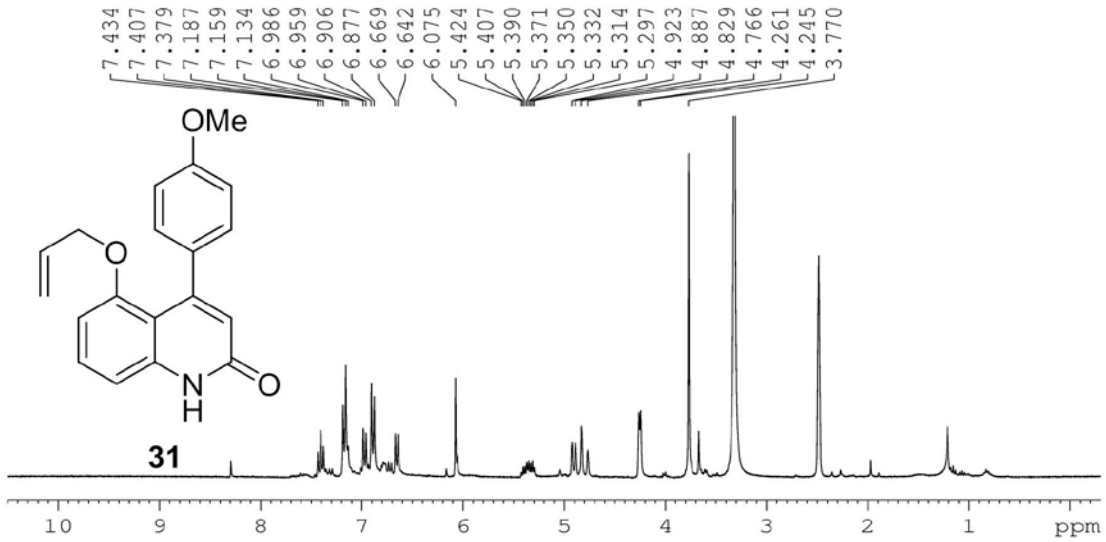

Figure S37. ^{1}H NMR (300 MHz) spectrum of compound **31** in DMSO-d_6.

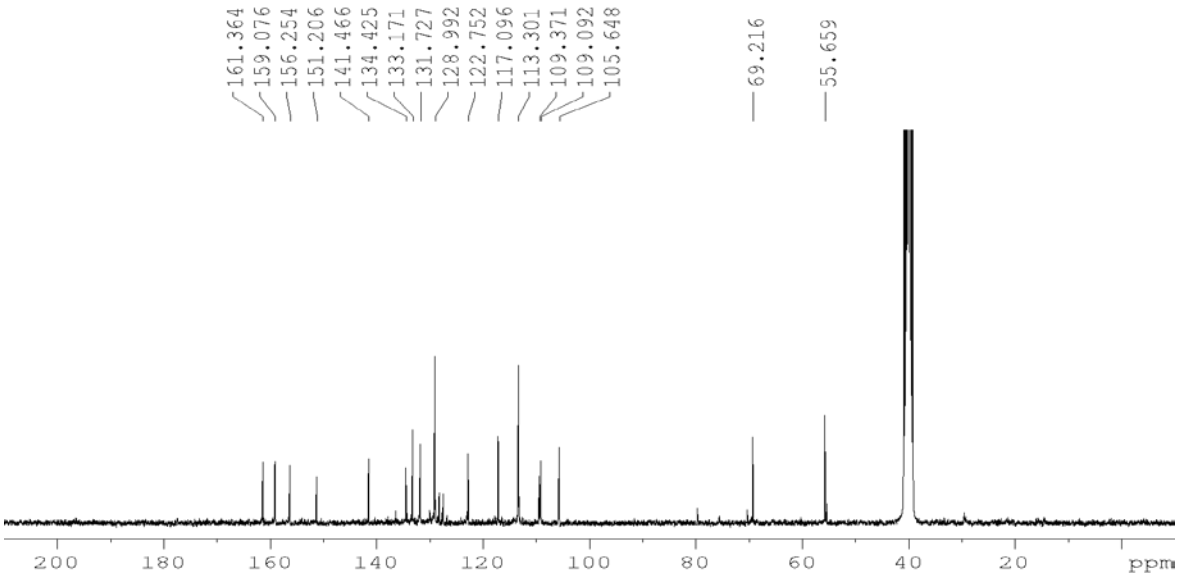

Figure S38. ^{13}C NMR (75 MHz) spectrum of compound **31** in DMSO-d_6.

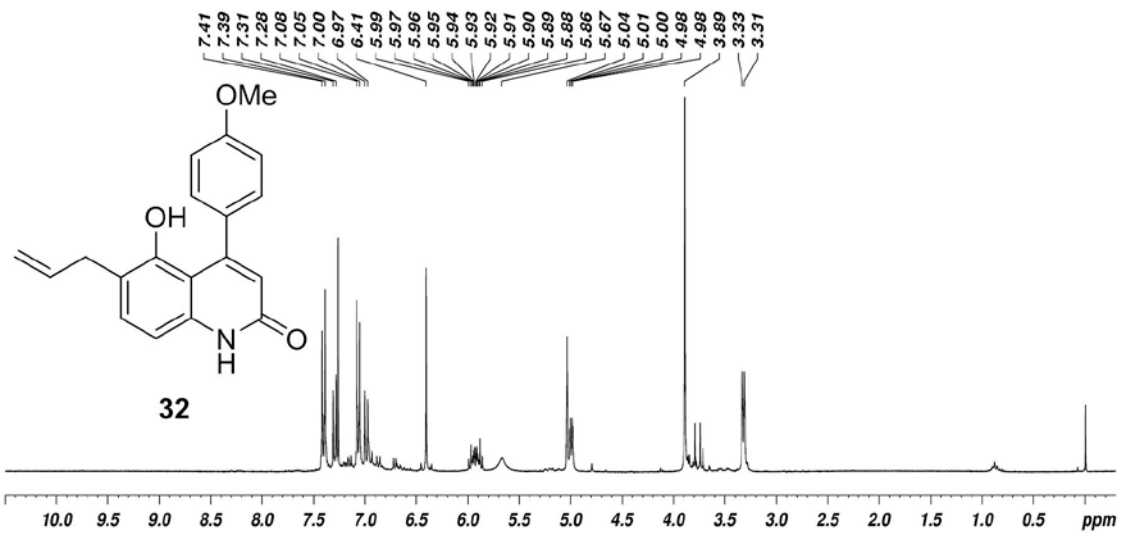

Figure S39. ^{1}H NMR (300 MHz) spectrum of compound **32**.

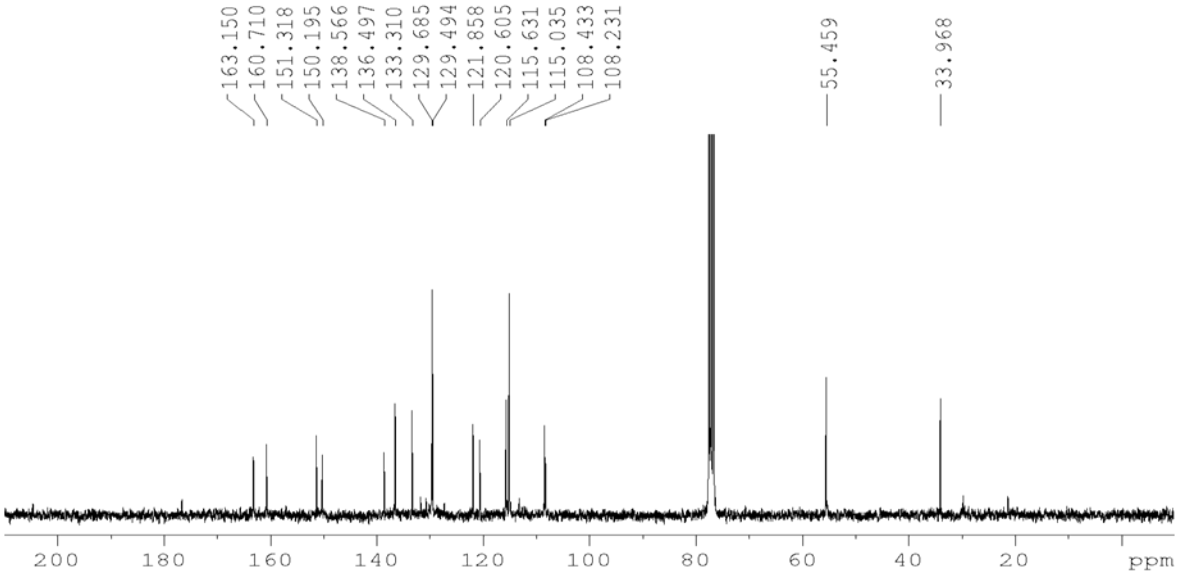

Figure S40. ^{13}C NMR (75 MHz) spectrum of compound **32**.

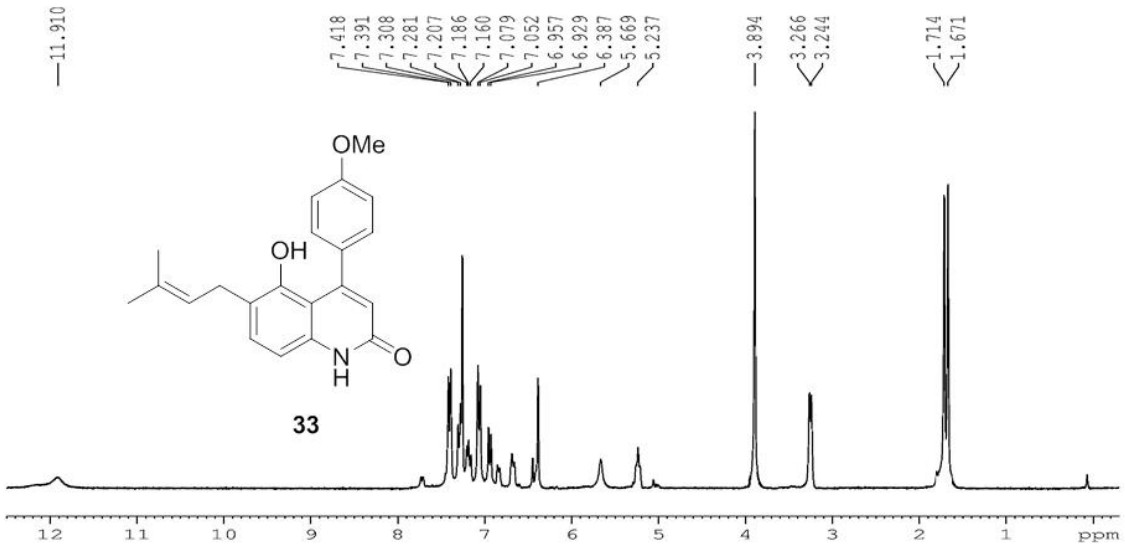

Figure S41. ^{1}H NMR (300 MHz) spectrum of compound **33**.

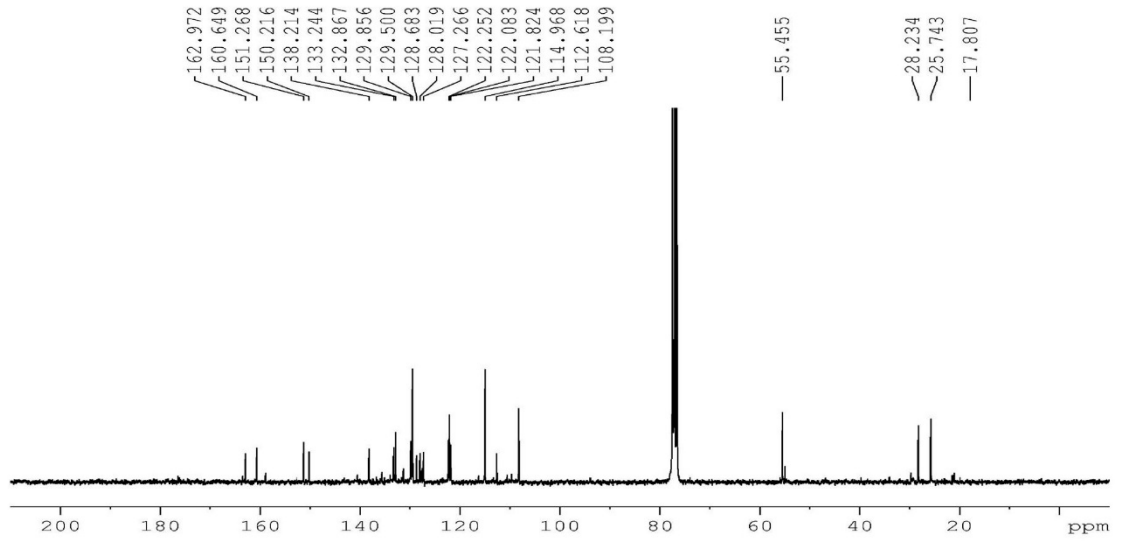

Figure S42. ^{13}CNMR (75 MHz) spectrum of compound **33**.

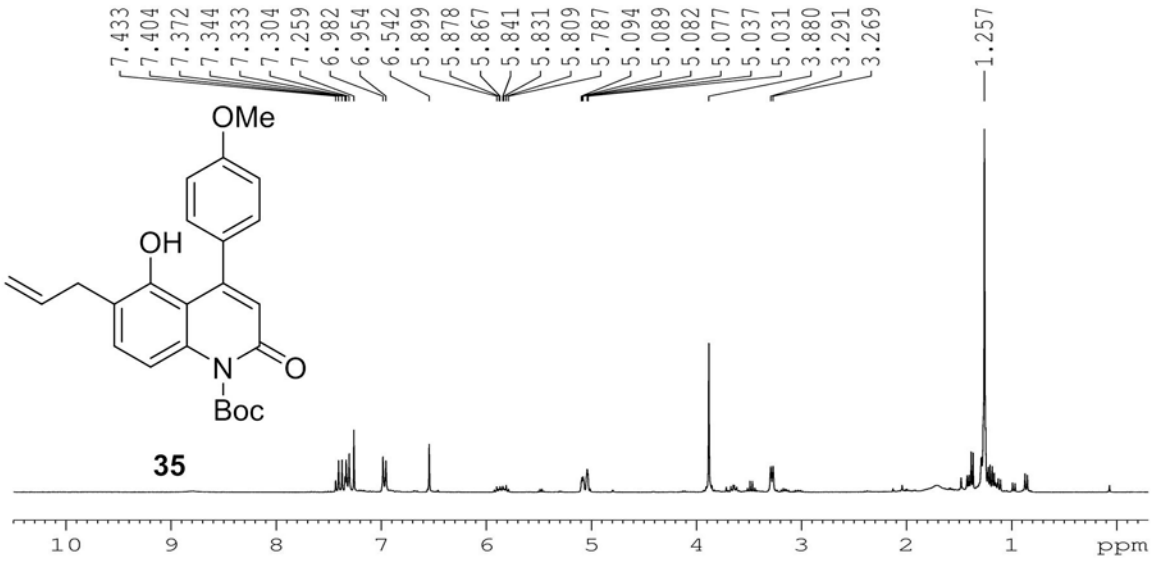

Figure S43. ^{1}H NMR (300 MHz) spectrum of compound **35**.

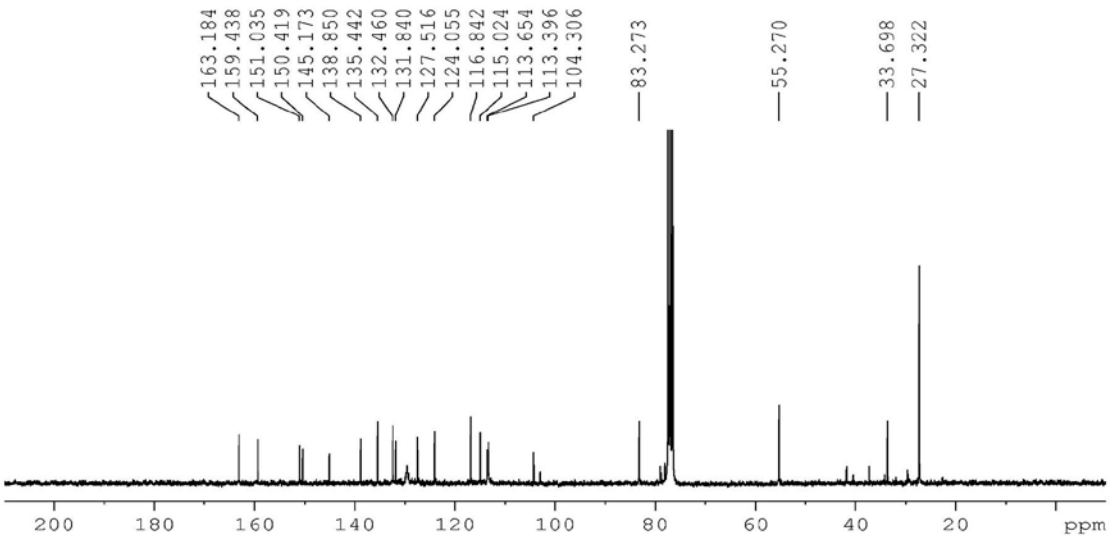

Figure S44. ^{13}C NMR (75 MHz) spectrum of compound **35**.

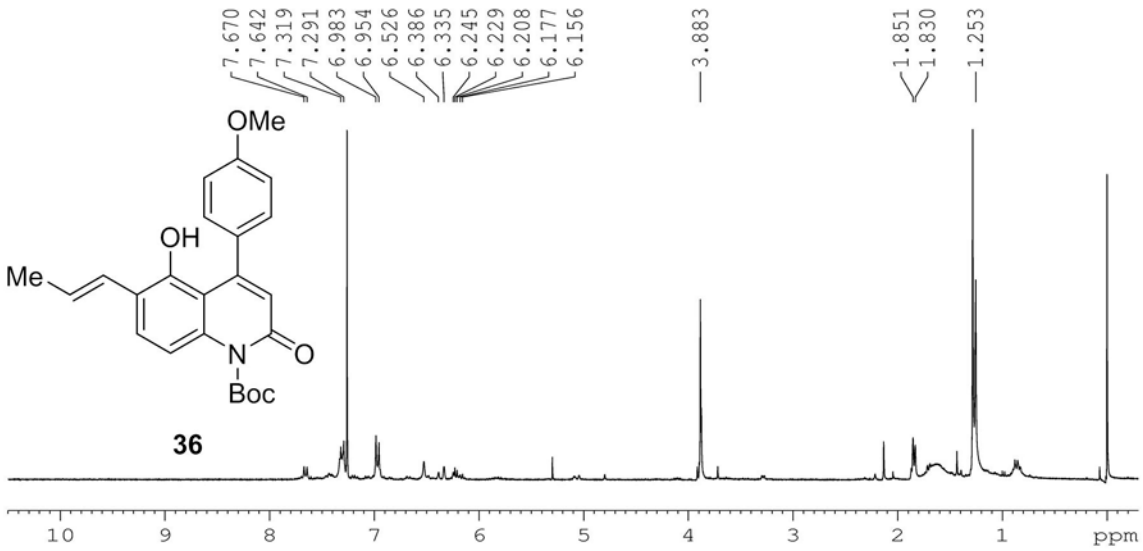

Figure S45. ^{1}H NMR (300 MHz) spectrum of compound **36**.

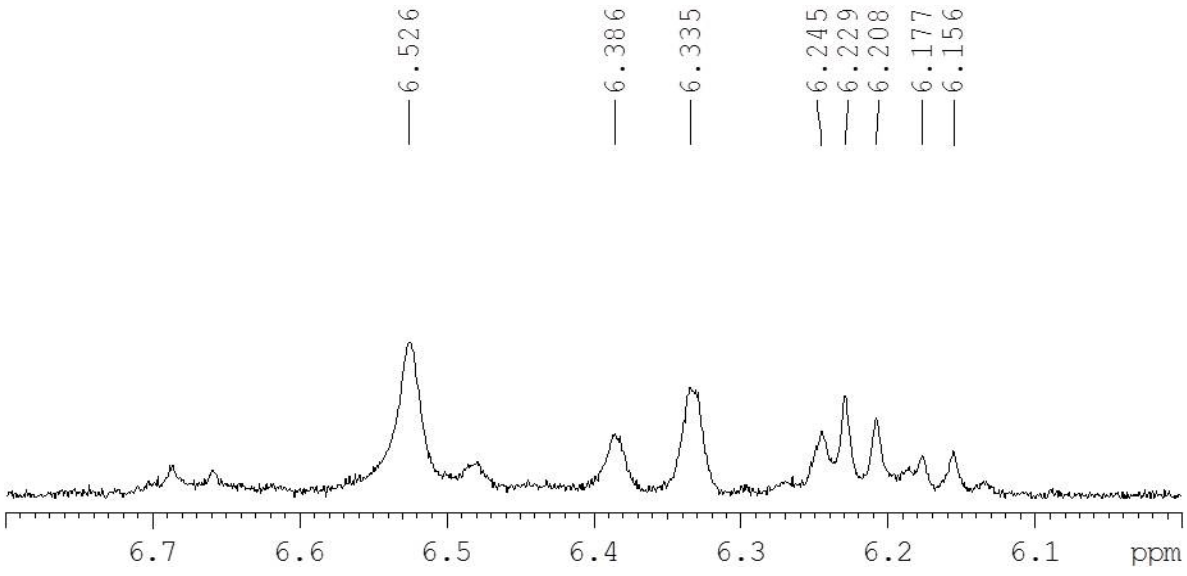

Figure S46. ^{1}H NMR (300 MHz) zoom from 6.0 to 6.8 ppm of the spectrum of compound **36**.

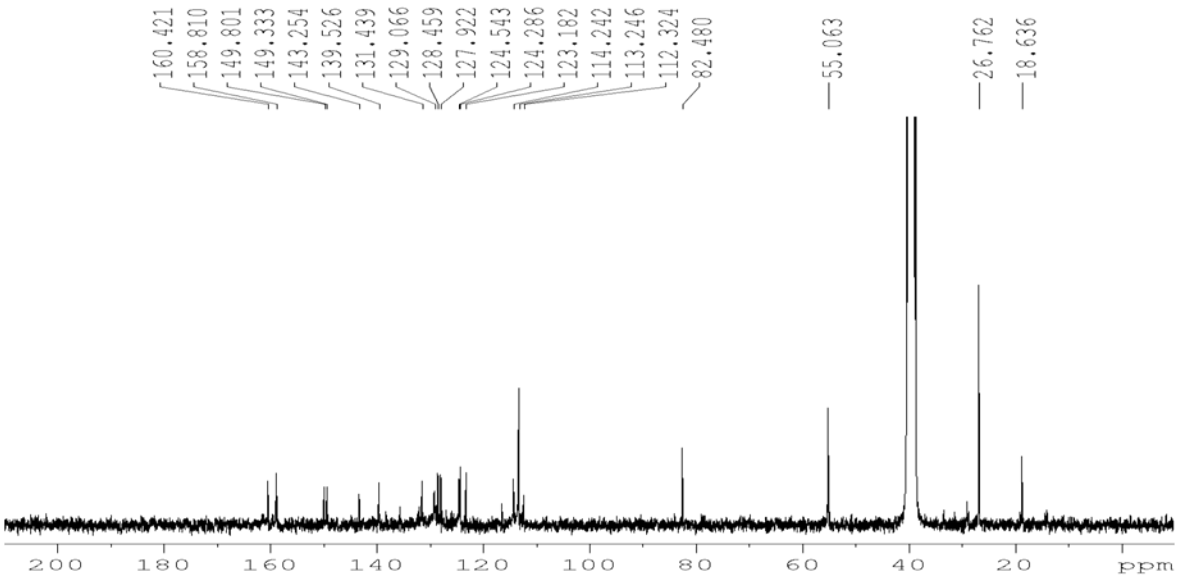

Figure S47. ^{13}C NMR (75 MHz) spectrum of compound **36**.

References

1 A. El-Batta, C. Jiang, W. Zhao, R. Anness, A. L. Cooksy and M. Bergdahl, *J. Org. Chem.,* 2007, **72**, 5244–5259.

2 S. K. Das and G. Panda, *Tetrahedron,* 2008, **64**, 4162–4173.

3 A. Khalafi-Nezhad, A. Parhami, M. N. S. Rad and A. Zarea, *Tetrahedron Lett.,* 2005, **46**, 6879–6882.