Supplementary Information

Towards a Dynamic Covalent Molecular Switch: Substituent Effects in Chalcone/Flavanone Isomerism

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Synthetic Procedures

General

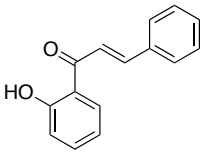
Chemicals were obtained from Sigma-Aldrich and Fisher Scientific. Column chromatography was performed using silica gel from Macherey-Nagel (60 M, 0.04-0.063 mm). ^{1}H and ^{13}C NMR data were recorded in $CDCl_3$ at 500 and 125 MHz, respectively, on a Bruker Avance III 500 MHz spectrometer at room temperature. ^{1}H chemical shifts are reported relative to residual $CHCl_3$ (δ 7.24 ppm for ^{1}H, δ 77.23 ppm for ^{13}C). IR data was acquired using an ATI Mattson FTIR. HRMS was performed by the University of Illinois SCS Mass Spectrometry Laboratory. Buffers for the UV/Vis studies were prepared using general guidelines[1] and the pH was measured immediately prior to use.

Synthesis of Chalcones[2]

To a 25 mL round-bottomed flask containing a magnetic stirbar was added sequentially 1 mmol of the appropriate acetophenone, 4 mL of ethanol, 1 mmol of the required benzaldehyde, and 4 mL of 6 M aqueous NaOH. The resulting solution was allowed to stir for 24 hours, at which time the solution was acidified with aqueous HCl. The mixture was extracted twice with ethyl acetate (2x10 mL), and the combined organic layers were washed with brine and dried over magnesium sulfate. After filtration and concentration, the chalcones were purified via flash column chromatography using a hexane/ethyl acetate eluent. Reported yields are from a single, unoptimized run.

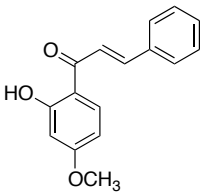
Spectral Data for Compounds 1A-1E

(*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (1A):



54%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.80 (s, 1H), 7.92 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.92 (d, *J* = 15.5 Hz, 1H), 7.67-7.64 (m, 2H), 7.65 (d, *J* = 15.3 Hz, 1H), 7.49 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H), 7.45-7.40 (m, 3H), 7.02 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.94 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.90, 163.78, 145.64, 136.59, 134.76, 131.12, 129.84, 129.22, 128.85, 120.28, 120.19, 119.04, 118.81; IR ($CDCl_3$) 3080.91, 3027.49, 1724.57, 1582.73, 1574.18, 1486.62, 1436.62, 1362.64, 1341.65, 1307.26, 1267.81, 1235.41, 1204.76, 1160.56, 1030.69, 1020.42, 998.41, 976.97, 864.22, 838.04, 809.18, 778.04, 751.23, 738.86, 693.79, 664.40 cm^{-1}; HRMS (EI+) *m/z* calculated for $C_{15}H_{12}O_2$ (M+) 224.08373, found 224.08289.

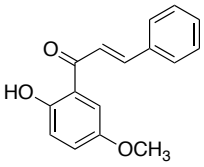
(*E*)-1-(2-hydroxy-4-methoxyphenyl)-3-phenylprop-2-en-1-one (1B):



31%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.41 (s, 1H), 7.87 (d, *J* = 15.5 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.66-7.60 (m, 2H), 7.57 (d, *J* = 15.5 Hz, 1H), 7.45-7.36 (m, 3H), 6.54-6.42 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.06, 166.94, 166.46, 144.63, 135.02, 131.46, 130.88, 129.22, 128.75, 120.55, 114.32, 108.00, 101.30, 55.84; IR ($CDCl_3$) 2960.99, 2914.25, 2853.56, 2368.71, 1724.42, 1636.50,

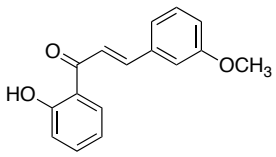
1573.17, 1507.48, 1447.70, 1359.22, 1280.33, 1209.28, 1153.50, 1131.34, 1017.96, 998.97, 977.35, 963.36, 860.04, 836.36, 803.95, 781.51, 764.93, 734.22, 693.67, 675.12 cm^{-1}; HRMS (EI+) *m/z* calculated for $C_{16}H_{14}O_3$ (M+) 254.09430, found 254.09396.

(*E*)-1-(2-hydroxy-5-methoxyphenyl)-3-phenylprop-2-en-1-one (1C):



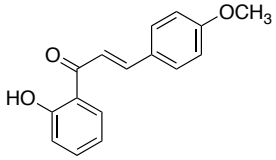
67%; ^1H NMR (500 MHz, $CDCl_3$) δ 12.35 (s, 1H), 7.91 (d, *J* = 15.4 Hz, 1H), 7.69-7.63 (m, 2H), 7.58 (d, *J* = 15.5 Hz, 1H), 7.46-7.41 (m, 2H), 7.35 (d, *J* = 3.2 Hz, 1H), 7.13 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.97 (d, *J* = 9.2 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.60, 158.17, 151.94, 145.83, 134.81, 131.18, 129.27, 128.89, 124.14, 120.38, 119.85, 119.59, 113.14, 56.37; IR ($CDCl_3$) 3080.42, 3028.03, 2959.34, 2834.63, 2373.89, 2319.69, 1720.20, 1642.76, 1575.03, 1486.13, 1449.41, 1410.09, 1355.35, 1322.05, 1305.84, 1286.45, 1265.19, 1218.45, 1174.40, 1043.18, 1017.61, 998.83, 977.66, 855.67, 782.96, 765.16, 732.37, 693.99, 674.45 cm^{-1}; HRMS (EI+) *m/z* calculated for $C_{16}H_{14}O_3$ (M+) 254.09430, found 254.09496.

(*E*)-1-(2-hydroxyphenyl)-3-(3-methoxyphenyl)prop-2-en-1-one (1D):



63%; ^1H NMR (500 MHz, $CDCl_3$) δ 12.78 (s, 1H), 7.91 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.87 (d, *J* = 15.5 Hz, 1H), 7.62 (d, *J* = 15.5 Hz, 1H), 7.49 (ddd, *J* = 8.7, 7.1, 1.6 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.17-7.14 (m, 1H), 7.02 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.98 (dd, *J* = 8.0, 2.6 Hz, 1H), 6.96-6.91 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.93, 163.82, 160.21, 145.61, 136.65, 136.19, 130.26, 129.88, 121.50, 120.65, 120.23, 119.08, 118.87, 116.83, 113.94, 55.62; IR ($CDCl_3$) 3000.48, 2940.32, 2835.16, 1639.12, 1576.14, 1486.39, 1442.54, 1361.53, 1350.75, 1316.14, 1291.11, 1273.43, 1245.05, 1201.11, 1157.51, 1046.45, 1023.55, 983.94, 861.54, 816.21, 755.98, 666.80 cm^{-1}; HRMS (EI+) *m/z* calculated for $C_{16}H_{14}O_3$ (M+) 254.09430, found 254.09337.

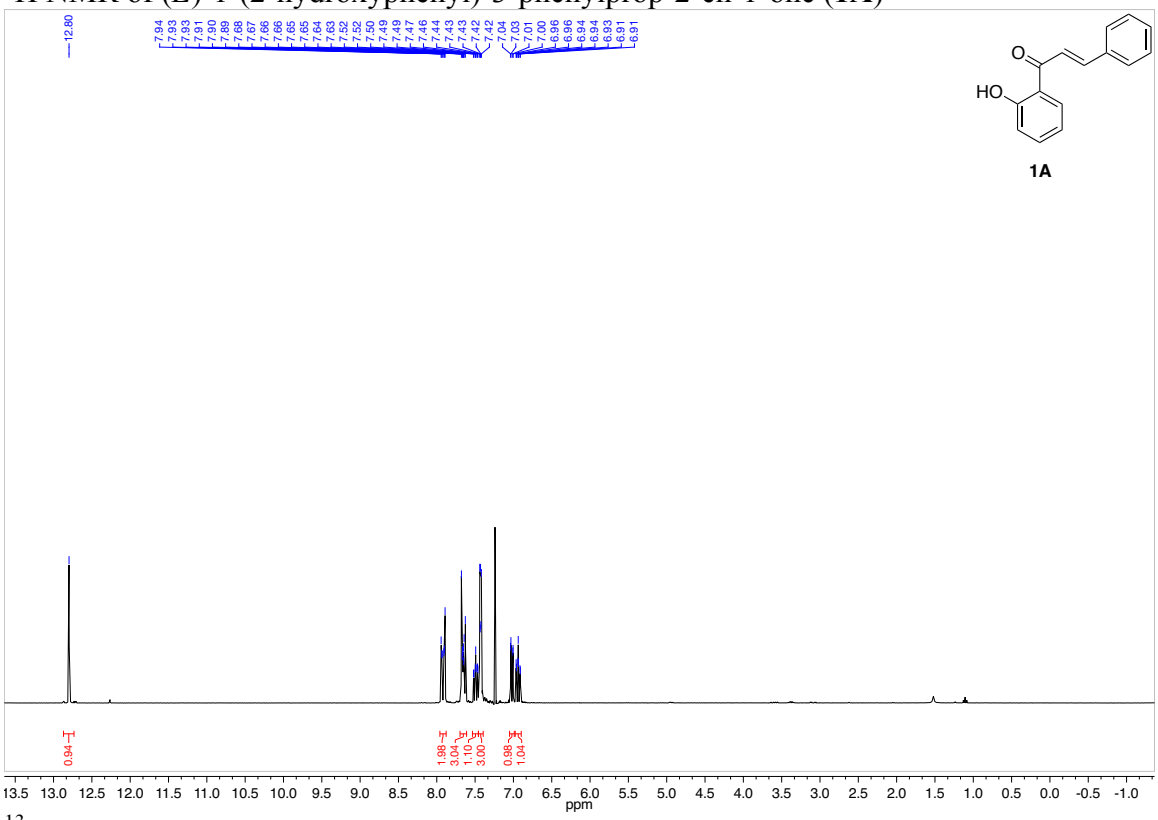
(*E*)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (1E):



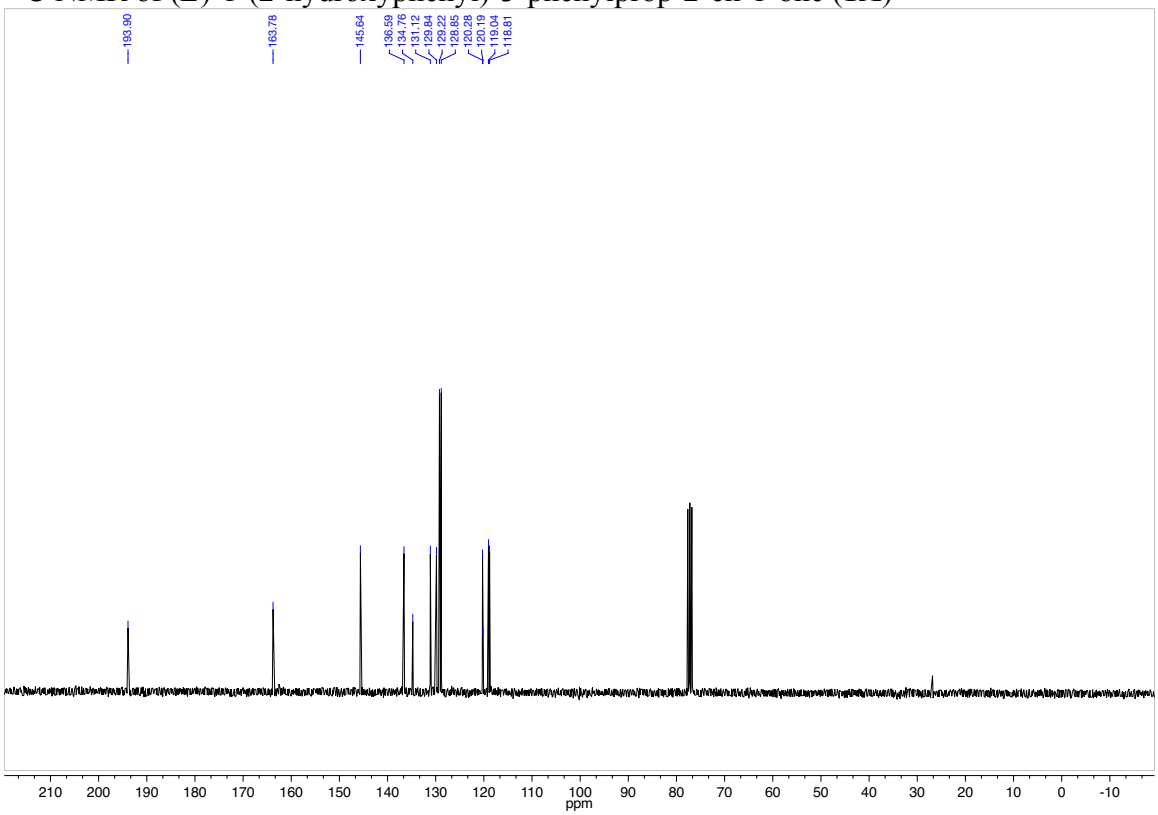
8%; ^1H NMR (500 MHz, $CDCl_3$) δ 12.92 (s, 1H), 7.91 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.89 (d, *J* = 15.4 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 15.5 Hz, 1H), 7.47 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.01 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.96-6.89 (m, 3H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.90, 163.78, 162.25, 145.58, 136.37, 130.77, 129.75, 127.58, 120.35, 118.97, 118.82, 117.83, 114.75, 55.69; IR ($CDCl_3$) 3006.13, 2960.06, 2935.52, 2838.69, 2360.36, 2340.55, 1683.46, 1635.78, 1604.29, 1579.43, 1563.92, 1514.05, 1487.22, 1463.59, 1442.26, 1423.95, 1366.31, 1351.37, 1320.94, 1303.43, 1256.65, 1236.09, 1203.24, 1175.49, 1156.54, 1028.87, 981.43, 828.74, 805.19, 761.33, 660.35 cm^{-1}; HRMS (EI+) *m/z* calculated for $C_{16}H_{14}O_3$ (M+) 254.09430, found 254.09475.

^{1}H NMR and ^{13}C NMR Spectra of Compounds 1A-1E

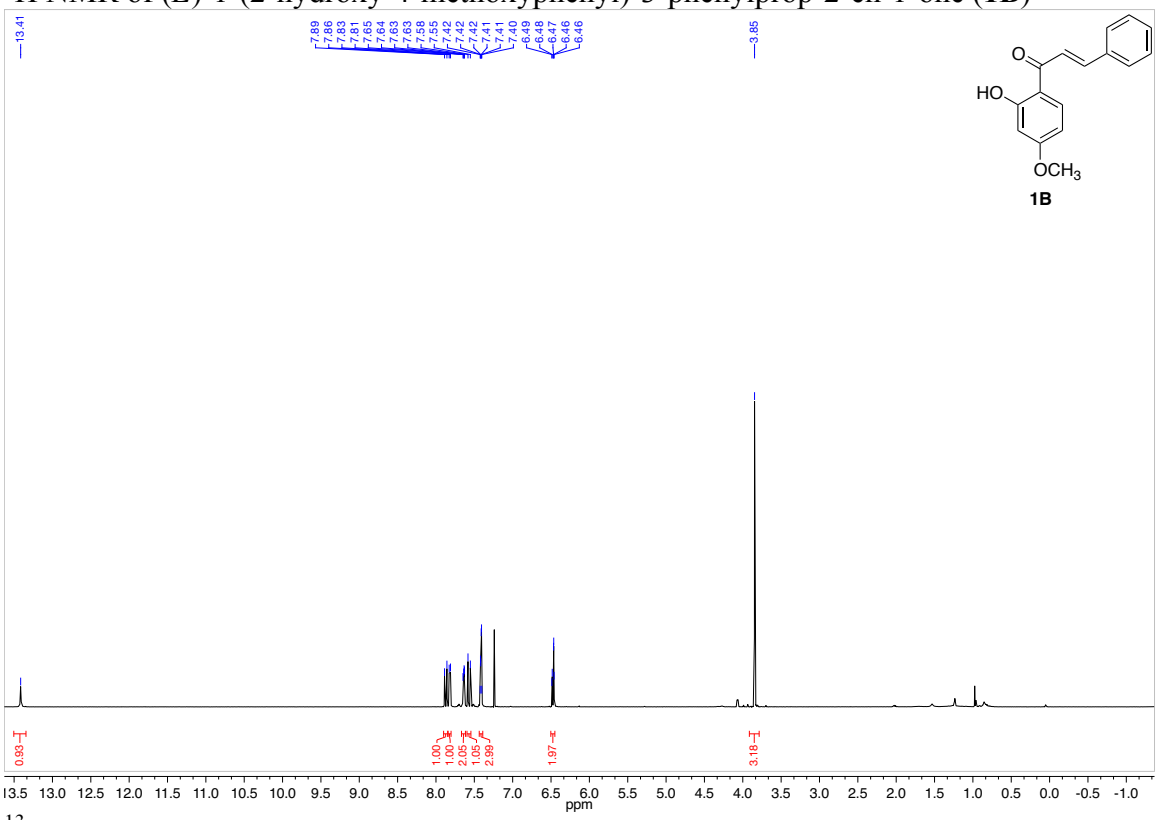
^{1}H NMR of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (**1A**)



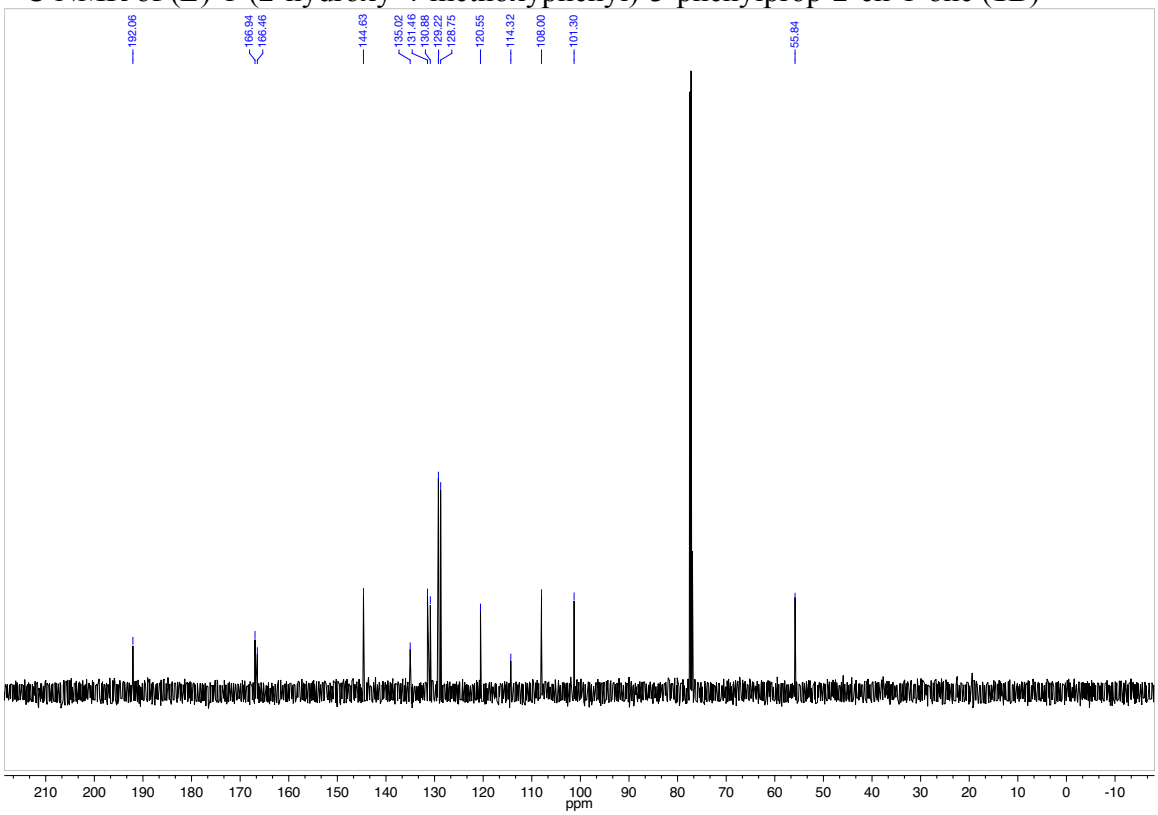
^{13}C NMR of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (**1A**)



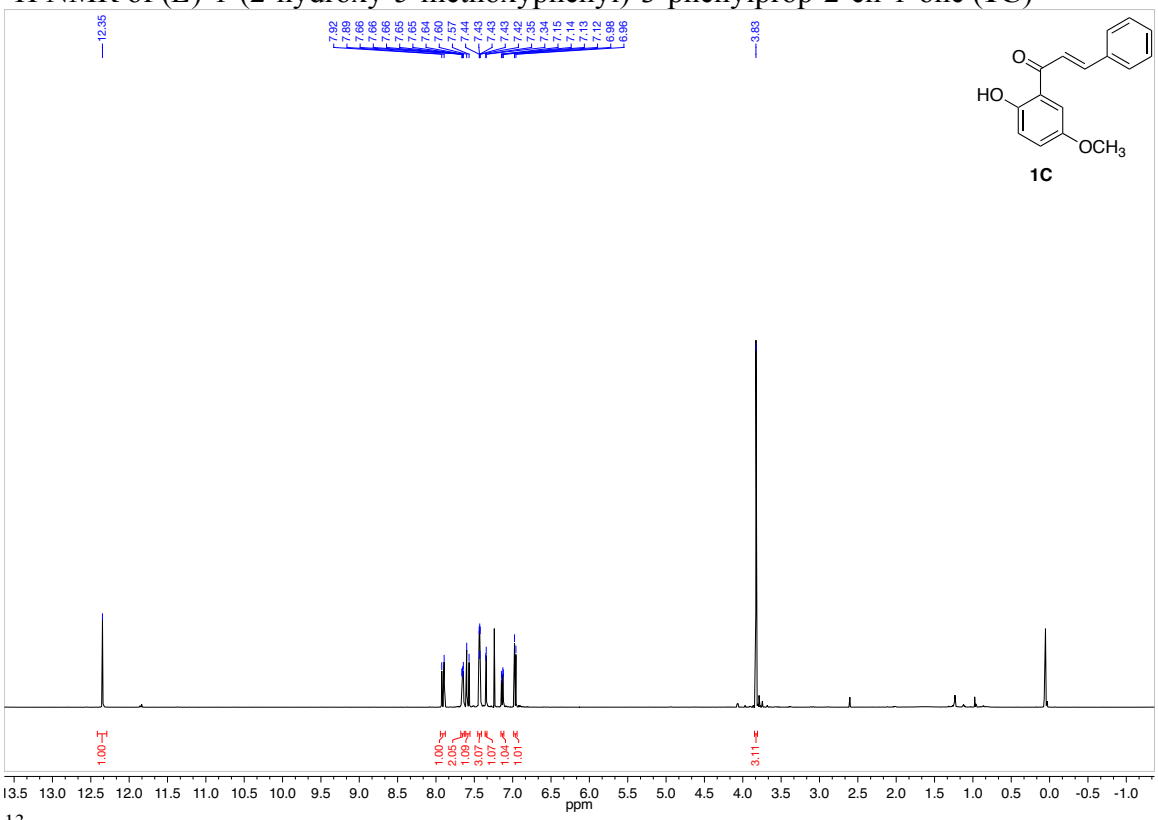
^{1}H NMR of (*E*)-1-(2-hydroxy-4-methoxyphenyl)-3-phenylprop-2-en-1-one (**1B**)



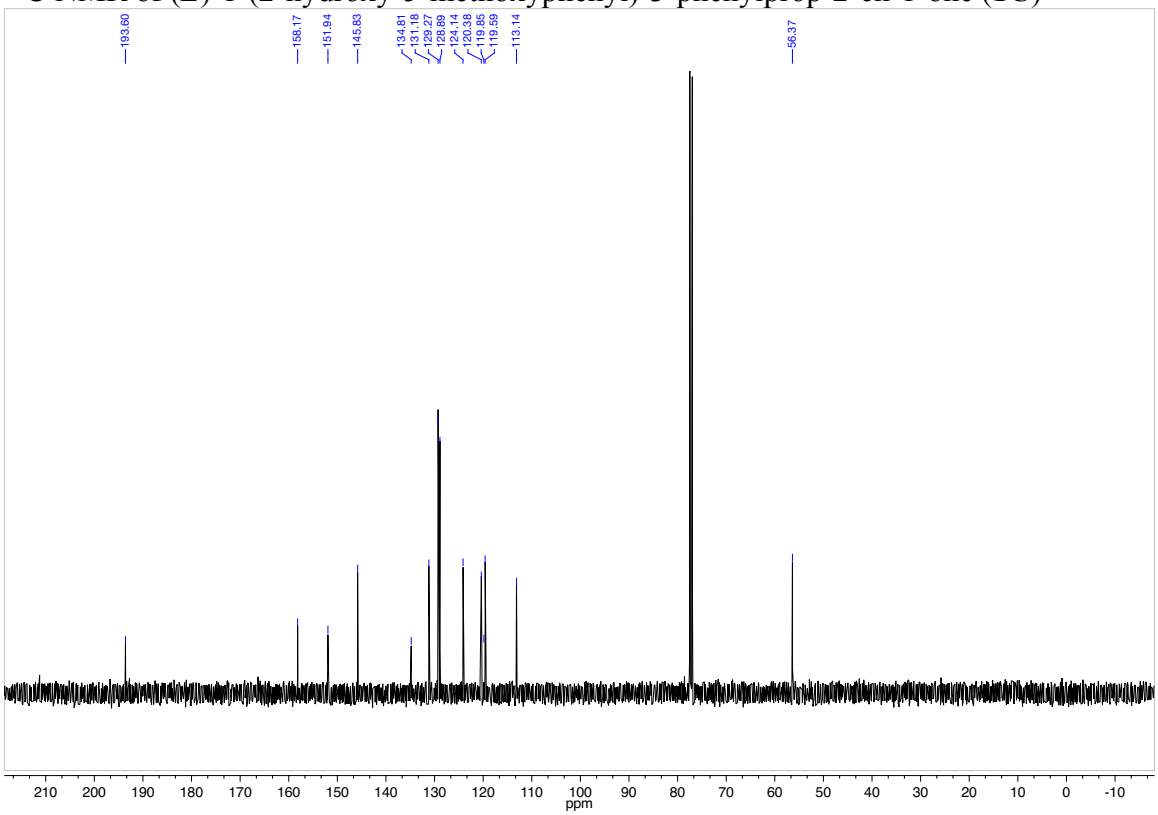
^{13}C NMR of (*E*)-1-(2-hydroxy-4-methoxyphenyl)-3-phenylprop-2-en-1-one (**1B**)



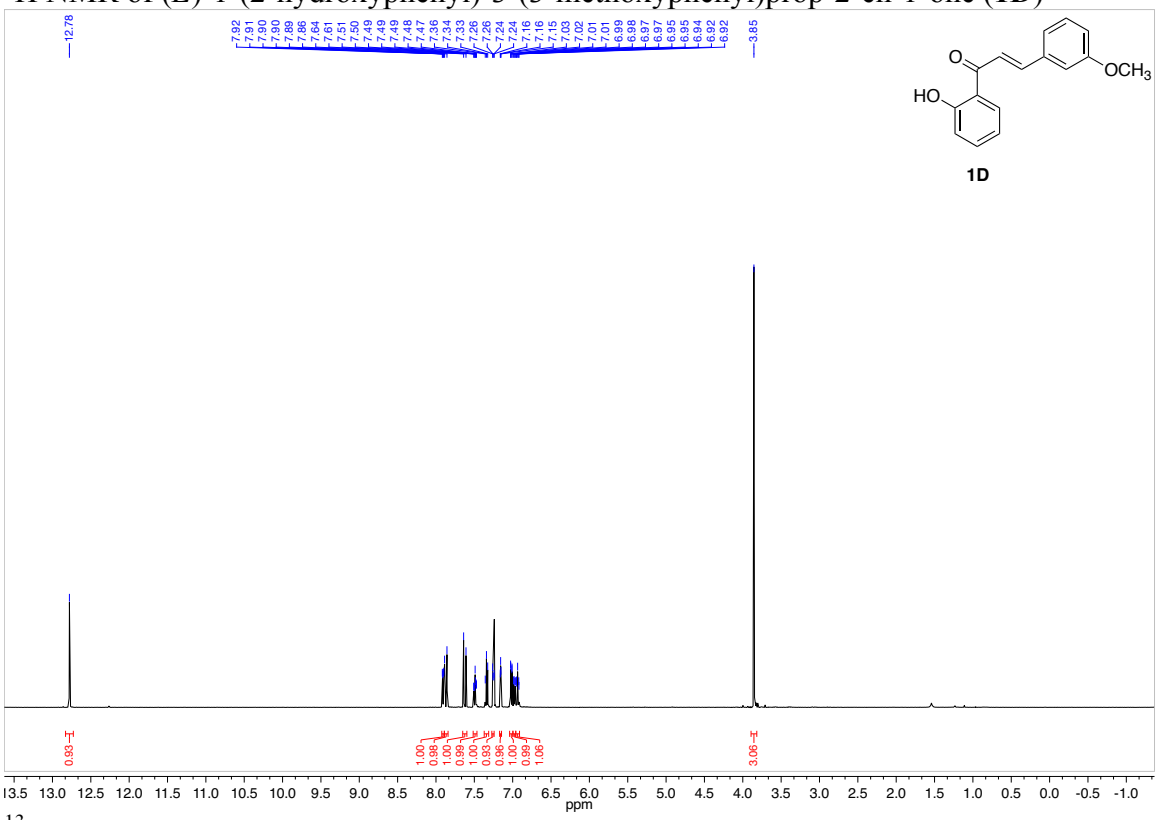
^{1}H NMR of (*E*)-1-(2-hydroxy-5-methoxyphenyl)-3-phenylprop-2-en-1-one (**1C**)



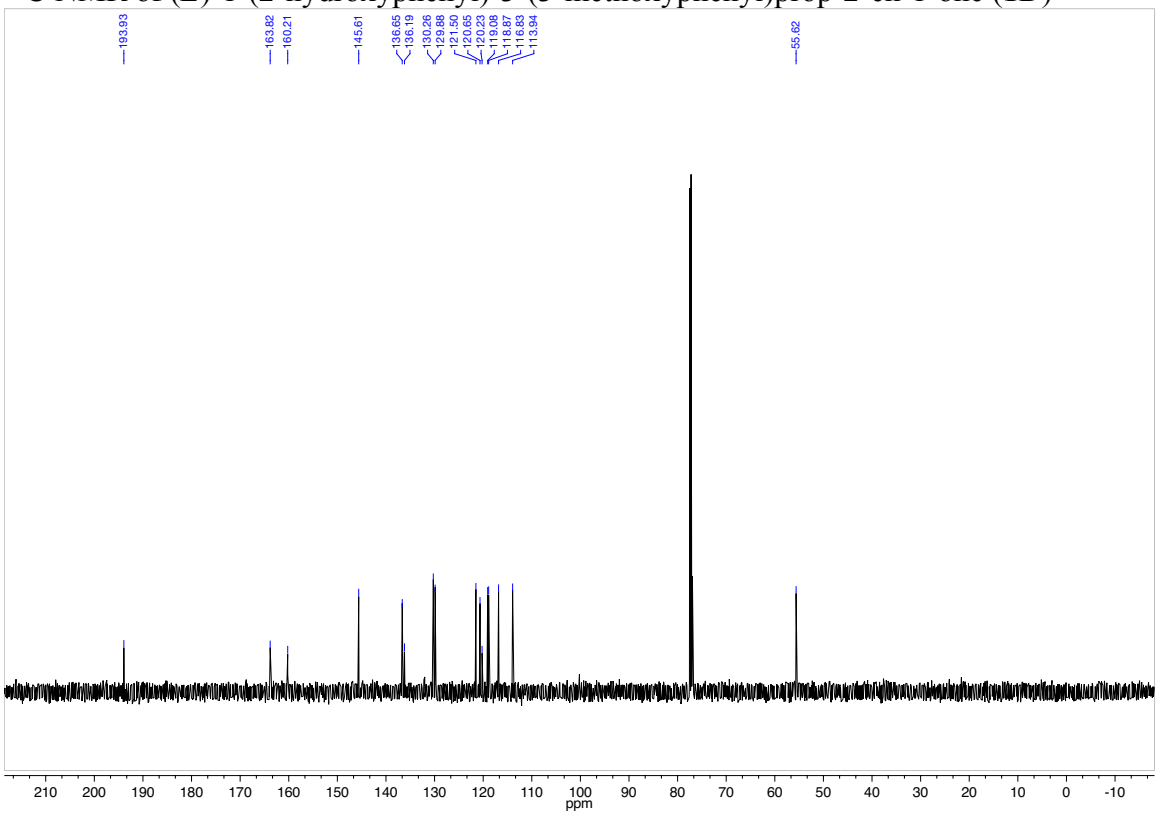
^{13}C NMR of (*E*)-1-(2-hydroxy-5-methoxyphenyl)-3-phenylprop-2-en-1-one (**1C**)



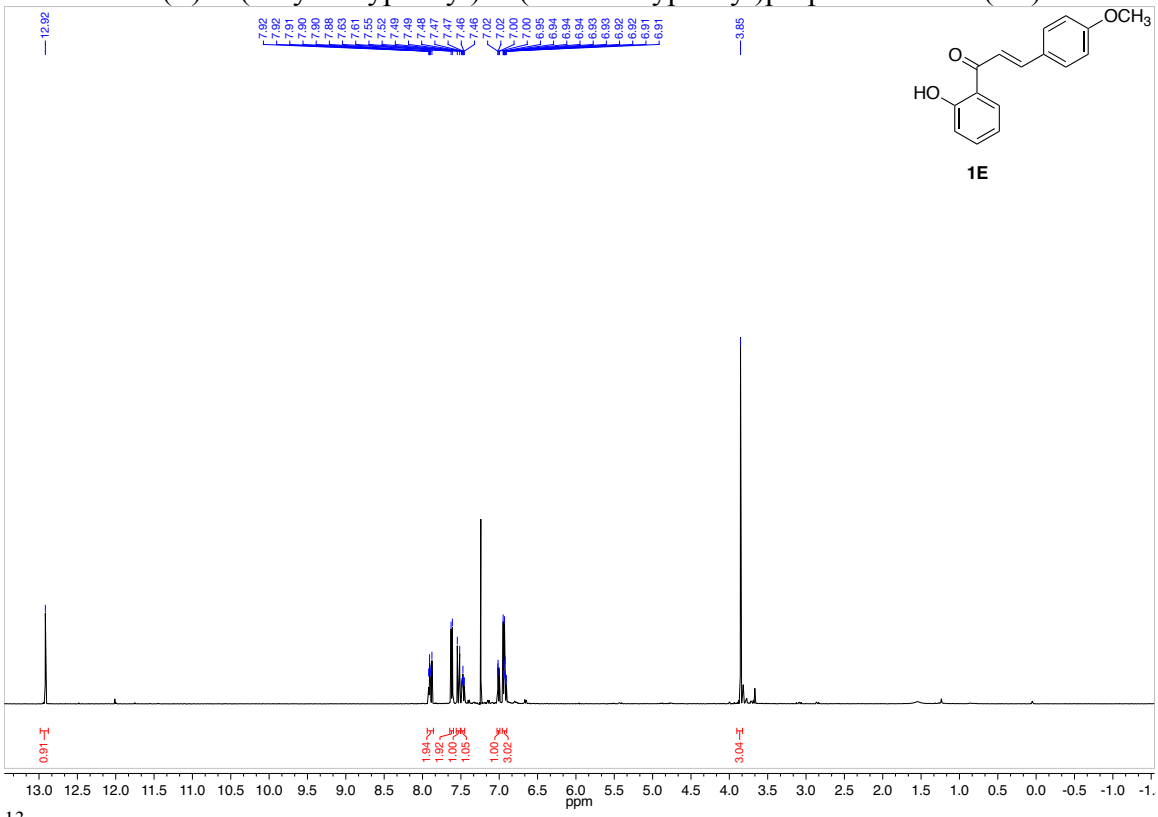
^{1}H NMR of (*E*)-1-(2-hydroxyphenyl)-3-(3-methoxyphenyl)prop-2-en-1-one (**1D**)



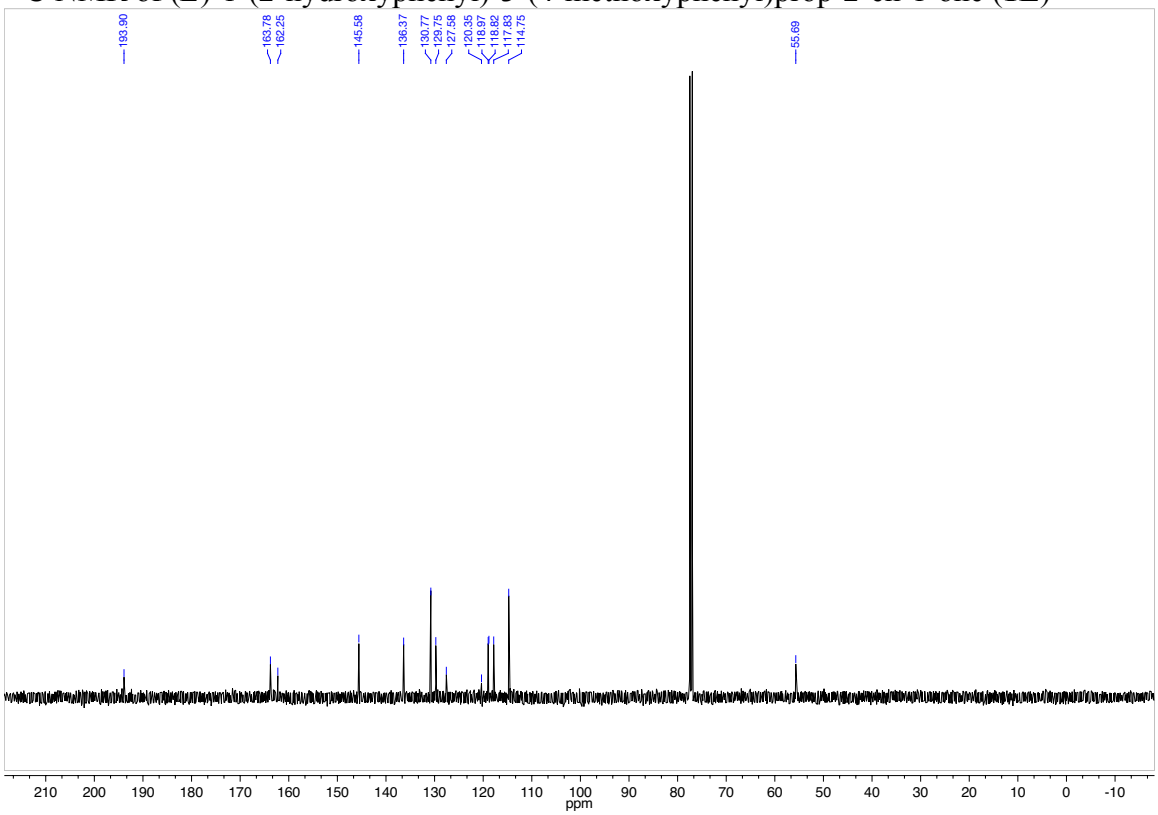
^{13}C NMR of (*E*)-1-(2-hydroxyphenyl)-3-(3-methoxyphenyl)prop-2-en-1-one (**1D**)



^{1}H NMR of (*E*)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**1E**)



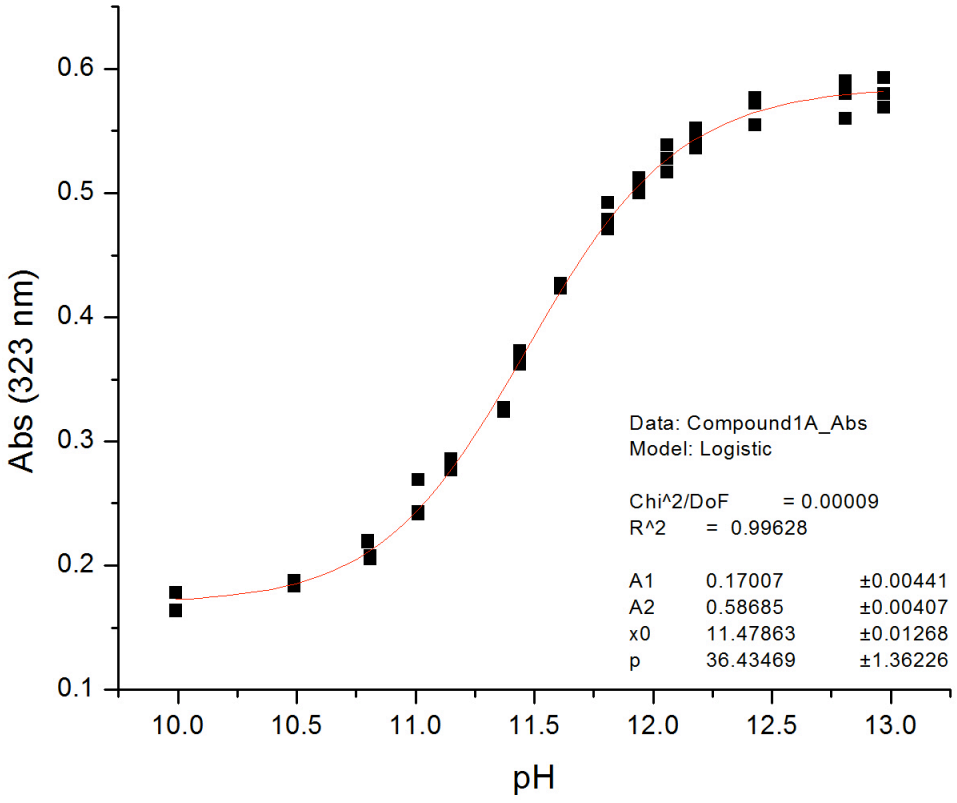
^{13}C NMR of (*E*)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**1E**)

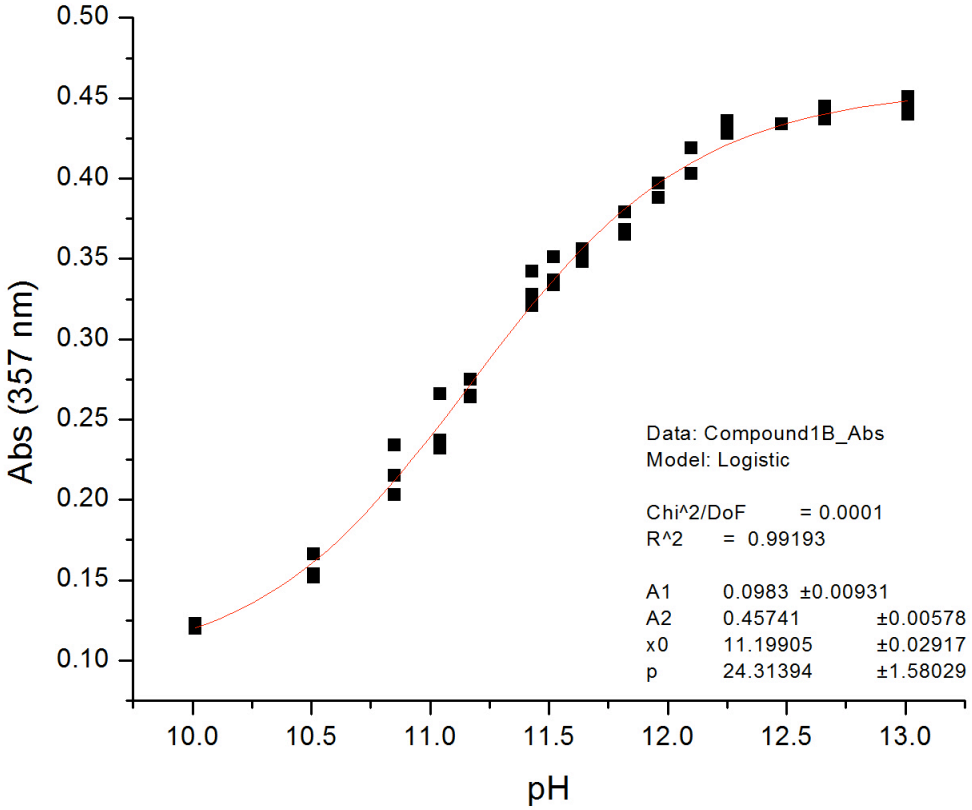


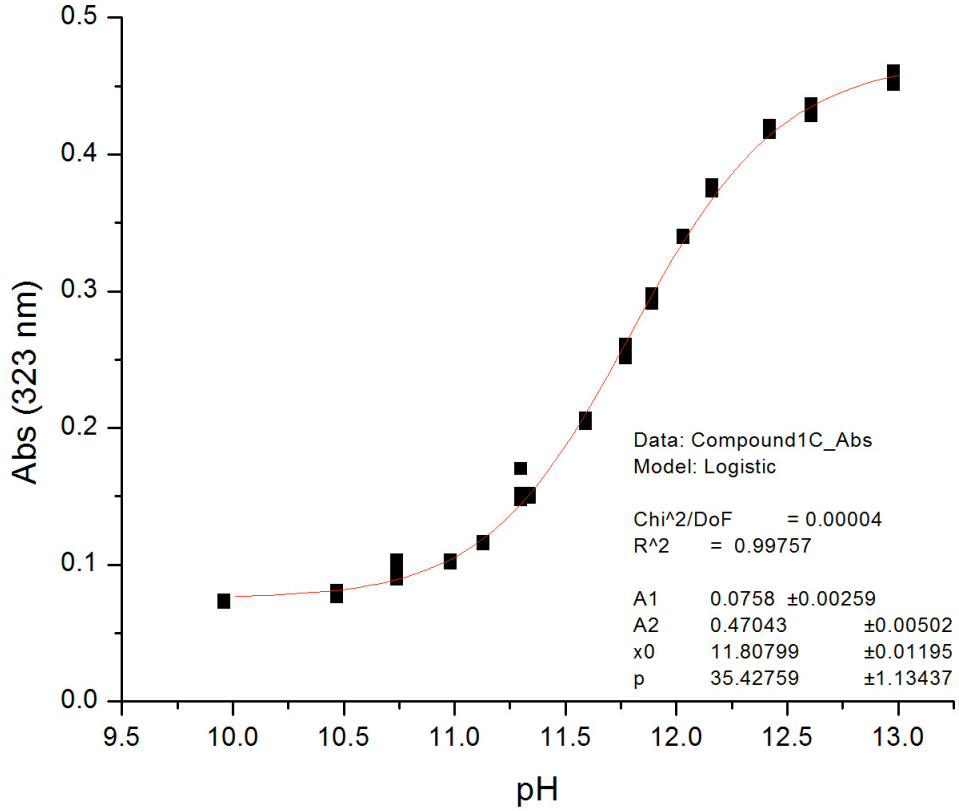
Procedure for the UV/Vis pH Trials

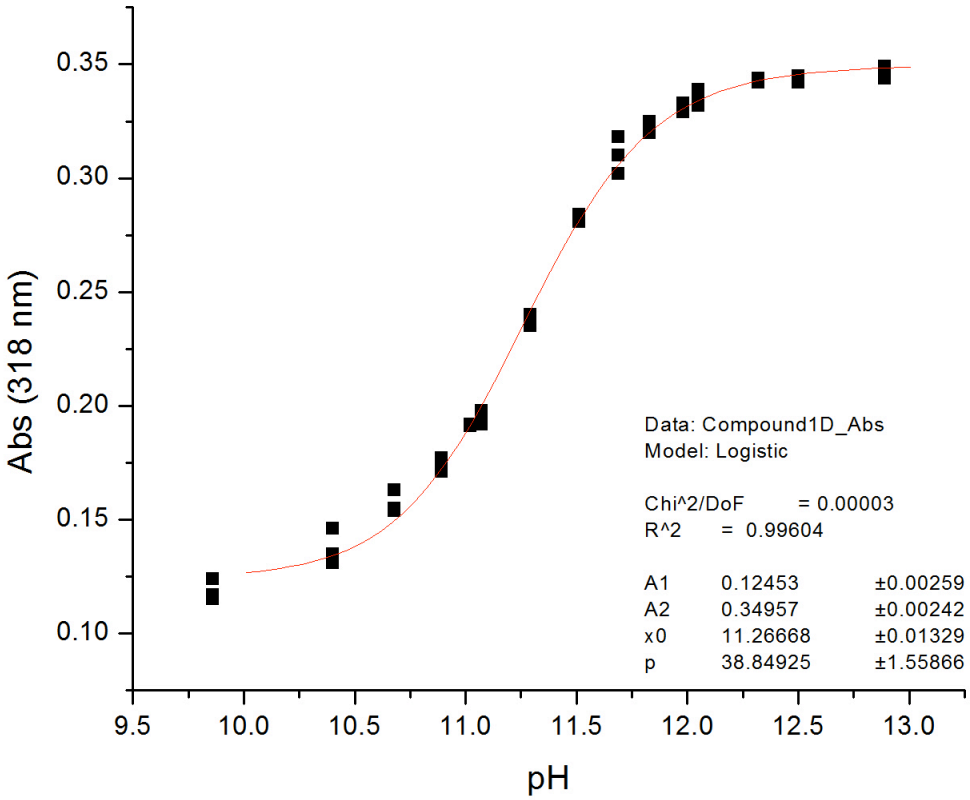
A $4x10^{-4}$ M ethanolic solution of chalcone was prepared. Using a micropipetter, 0.150 mL of the solution was deposited into 45 individual semi-micro cuvettes. Next, 1.350 mL of each buffer (15 buffers between pH ~10-13) was added to three cuvettes. Additionally, a background cuvette was prepared from 0.150 mL ethanol and 1.850 mL deionized water. These samples were allowed to equilibrate at 3˚C for three hours, at which time 0.500 mL of 1M HCl was added to each of the 45 samples. These samples (final [chalcone+flavanone] = $3x10^{-5}$ M) were mixed via pipette and degassed manually. After background acquisition, the UV/Vis spectrum was collected and absorbance at the desired wavelength was recorded.

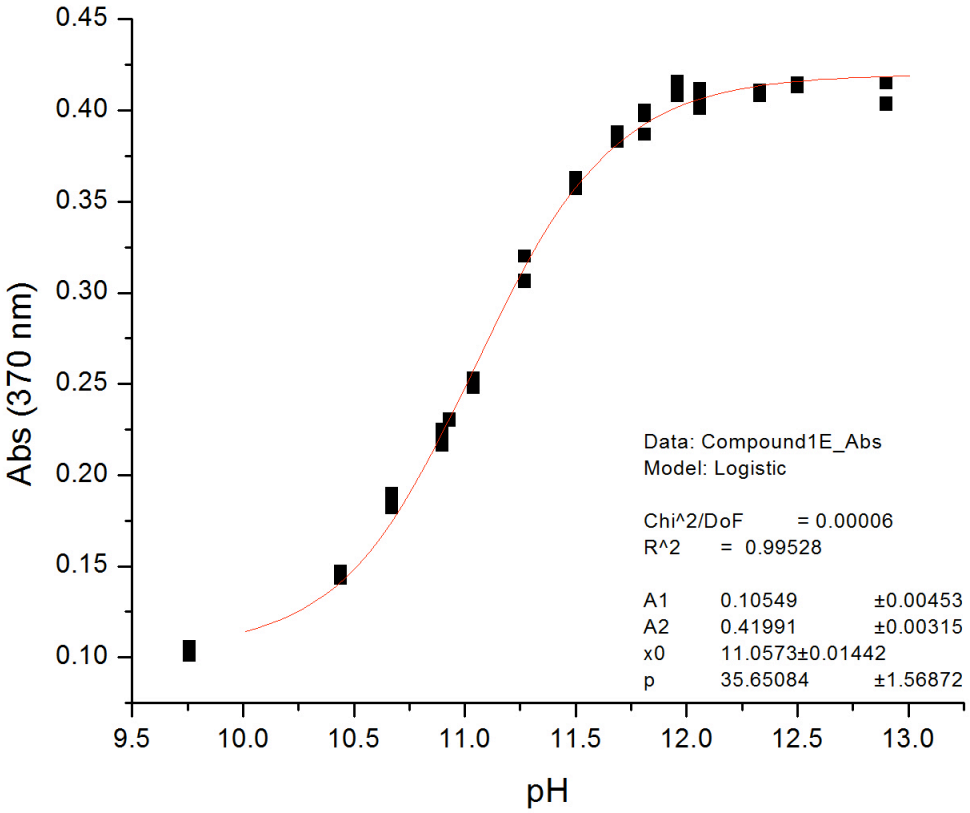
Raw Data plot for the pH-dependent UV/Vis Absorbance of Compounds 1A-1E











Procedure for the UV/Vis Method Verification Study of 1A

For this experiment, $4x10^{-4}$ M ethanolic solutions of chalcone **1A** and flavanone **1B** were each prepared. Separately, to 27 mL of each of four buffers (pH 10.5, 11.15, 11.94, and 12.44) was added 10 mL 1M HCl. Five sample cuvettes were prepared in quadruplicate:
1. 0.150 mL ethanolic **1B** (0% chalcone)
2. 0.1225 mL ethanolic **1B** and 0.0375 mL **1A** (25% chalcone)
3. 0.075 mL ethanolic **1B** and 0.075 mL **1A** (50% chalcone)
4. 0.0375 ethanolic **1B** and 0.1225 mL ethanolic **1A** (75% chalcone)
5. 0.150 mL **1B** (100% chalcone)

To each set of these five cuvettes was then added 1.850 mL of an acidified buffer, such that a full series was diluted with each of the four aqueous solutions. Additionally, a background cuvette was prepared from 0.150 mL ethanol and 1.850 mL deionized water. These solutions were then manually degassed. After background acquisition, the UV/Vis spectrum was collected and absorbance at 323 nm was recorded.

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[1] R.A. Robinson and R.H. Stokes, *Electrolyte solutions*, Butterworths, London, Second Edition, revised,
[2] M. J. Adler, PhD Dissertation, Duke University, 2008.