Supporting Information

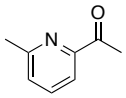
Effects of structural modifications on the metal binding, anti-amyloid activity, and cholinesterase inhibitory activity of chalcones

Marina Y. Fosso,[1] Harry LeVine, 3rd,[2] Keith D. Green,[1] Oleg V. Tsodikov,[1] and Sylvie Garneau-Tsodikova[1,*]

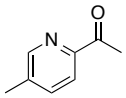
[1] Department of Pharmaceutical Sciences, University of Kentucky, Lexington, KY, 40536-0596, USA. [2] Department of Molecular and Cellular Biochemistry and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, 40536-0230, USA.
* Correspondence to: sylviegtsodikova@uky.edu

Materials and instrumentation. All chemicals were purchased from Sigma Aldrich (St. Louis, MO), Alfa Aesar (Ward Hill, MA), and AK scientific (Union City, CA) and used without further purification. Chemical reactions were monitored by thin layer chromatography (TLC) using Merck, Silica gel 60 F_{250} plates. Visualization was achieved using UV light and $KMnO_4$ stain (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH, 200 mL H_2O). ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Varian 400 MHz spectrometer, using the indicated solvents. Chemical shift (δ) is given in parts per million (ppm). Coupling constants (*J*) are given in hertz (Hz), and conventional abbreviations used for signal shape are as follows: s = singlet; d = doublet; t = triplet; m = multiplet; dd = doublet of doublets; ddd = doublet of doublet of doublets; br s = broad singlet; dt = doublet of triplets. Liquid chromatography-mass spectrometry (LCMS) was carried out using an Agilent 1200 series Quaternary LC system equipped with a diode array detector, and Eclipse XDB-C_{18} column (250 mm x 4.6 mm, 5 μm), and an Agilent 6120 Quadrupole MSD mass spectrometer (Agilent Technologies, Santa Clara, CA). LCMS M + H signals were consistent with the expected molecular weights for all of the reported compounds. Cu^{2+} binding studies by UV-Vis were performed on a SpectraMax M5 multiplate reader (Molecular Devices, Sunnyvale, CA) using quartz cuvettes. *N*-biotinyl $A\beta_{1-42}$ ($bioA\beta_{42}$) was purchased from Anaspec (Fremont, CA). ELISA plates (Costar 9018), NeutrAvidin™ (Promega), adhesive film (NUNC), polypropylene 96-well plates (Costar 3365), and polypropylene Eppendorf tubes (Fisher 02-681-248) used for $bioA\beta_{42}$ oligomer assembly and dissociation assays were all purchased from Fisher Scientific (Pittsburgh, PA). Plates were washed on a BioTek ELx50 plate washer (Biotek (Winooski, VT)) and absorbance was read on a Biotek HT Synergy plate reader. Elemental analysis of all final compounds were performed at Atlantic Microlab, Inc. (Norcross, GA).

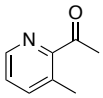
General procedure A for the synthesis of 2-acetylpyridines. Methylmagnesium bromide (3.0 eq, 3 M in diethyl ether) was slowly added to a cooled (-20 °C) solution of 2-pyridinecarbonitrile (1.0 eq) in dry THF (5 mL), and the mixture was stirred between -20 °C and -10 °C until completion of the reaction (1-3 h). The reaction mixture was then cooled down to -40 °C, and aq. HCl was slowly added until the solution stopped fizzing. 5 min later, the solution was poured into sodium phosphate buffer (10 mL, 500 mM, pH 7) and extracted with Et_2O (5x10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude product, which was purified by column chromatography (SiO_2, Hexanes:EtOAc/9:1).



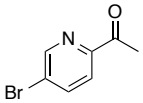
Synthesis of 2-acetyl-6-methylpyridine (1b). Following general procedure A, the known compound **1b**[1] (R_f 0.42, Hexanes:EtOAc/9:1) was obtained from 6-methyl-2-pyridinecarbonitrile (400 mg, 3.39 mmol) and methylmagnesium bromide (3.4 mL, 10.16 mmol) as a light yellow oil (83% yield): ^{1}H NMR (400 MHz, $CDCl_3$, which matches the lit.[1]) δ 7.80 (d, J = 7.2 Hz, 1H, aromatic), 7.66 (t, J = 7.2 Hz, 1H, aromatic), 7.28 (d, J = 7.2 Hz, 1H, aromatic), 2.68 (s, 3H, C$\underline{H}_3$), 2.58 (s, 3H, C$\underline{H}_3$).



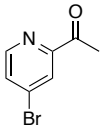
Synthesis of 2-acetyl-5-methylpyridine (1c). Following general procedure A, the known compound **1c**[2] (R_f 0.32, Hexanes:EtOAc/4:1) was obtained from 5-methylpyridine-2-carbonitrile (400 mg, 3.39 mmol) and methylmagnesium bromide (3.4 mL, 10.16 mmol) as a light yellow oil (363 mg, 79% yield): ^{1}H NMR (400 MHz, $CDCl_3$, which matches the lit.[2]) δ 8.47 (m, 1H, aromatic), 7.92 (d, J = 8.0 Hz, 1H, aromatic), 7.61-7.58 (m, 1H, aromatic), 2.68 (s, 3H, C$\underline{H}_3$), 2.39 (s, 3H, C$\underline{H}_3$).



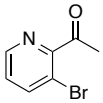
Synthesis of 2-acetyl-3-methylpyridine (1e). Following general procedure A, the known compound **1e**[3] (R_f 0.33, Hexanes:EtOAc/9:1) was obtained from 3-methylpicolinonitrile (400 mg, 3.39 mmol) and methylmagnesium bromide (3.4 mL, 10.16 mmol) as a light yellow oil (310 mg, 68% yield): ^{1}H NMR (400 MHz, $CDCl_3$, which matches the lit.[3]) δ 8.47 (d, J = 4.4 Hz, 1H, aromatic), 7.54 (d, J = 7.6 Hz, 1H, aromatic), 7.28 (dd, J_1 = 7.6 Hz, J_2 = 4.4 Hz, 1H, aromatic), 2.67 (s, 3H, C$\underline{H}_3$), 2.54 (s, 3H, C$\underline{H}_3$).



Synthesis of 2-acetyl-5-bromopyridine (1g). Following general procedure A, the known compound **1g**[4] (R_f 0.49, Hexanes:EtOAc/9:1) was obtained from 5-bromo-2-pyridinecarbonitrile (320 mg, 1.75 mmol) and methylmagnesium bromide (1.75 mL, 5.25 mmol) as a white solid (205 mg, 59% yield): ^{1}H NMR (400 MHz, $CDCl_3$, which matches the lit.[4]) δ 8.71 (d, J = 2.0 Hz, 1H, aromatic), 7.95 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H, aromatic), 7.91 (d, J = 8.0 Hz, 1H, aromatic), 2.68 (s, 3H, C$\underline{H}_3$).

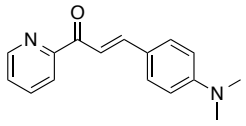


Synthesis of 2-acetyl-4-bromopyridine (1h). Following general procedure A, **1h** (R_f 0.40, Hexanes:EtOAc/9:1) was obtained from 4-bromopicolinonitrile (320 mg, 1.75 mmol) and methylmagnesium bromide (1.75 mL, 5.25 mmol) as an off-white solid (205 mg, 59% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S1) δ 8.48 (d, J = 4.8 Hz, 1H, aromatic), 8.18 (d, J = 2.0 Hz, 1H, aromatic), 7.62 (dd, J_1 = 4.8 Hz, J_2 = 2.0 Hz, 1H, aromatic), 2.69 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S2) δ 198.8, 154.4, 149.7, 134.0, 130.1, 125.2, 25.8; *m/z* calcd for C_7H_6BrNO 199.0; found 200.0 $[M+H]^+$.

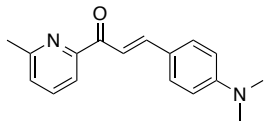


Synthesis of 2-acetyl-3-bromopyridine (1i). Following general procedure A, **1i** (R_f 0.22, Hexanes:EtOAc/9:1) was obtained from 3-bromopyridine-2-carbonitrile (320 mg, 1.75 mmol) and methylmagnesium bromide (1.75 mL, 5.25 mmol) as a pale yellow liquid (231 mg, 66% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S3) δ 8.55 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, aromatic), 7.97 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H, aromatic), 7.25 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, aromatic), 2.67 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S4) δ 199.5, 152.9, 147.2, 142.4, 126.5, 117.3, 28.0; *m/z* calcd for C_7H_6BrNO 199.0; found 200.0 $[M+H]^+$.

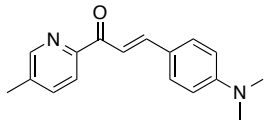
General procedure B for the synthesis of chalcone derivatives 3a-i. A mixture of 2-acetylpyridine (**1a-i**, 1.0 eq.) and 4-(dimethylamino)benzaldehyde (**2**, 1.0 eq.) in EtOH (5 mL) was treated with 20% aq. KOH (3 mL) and the resulting solution was stirred at rt for 3 h. Upon completion of the reaction, H_2O (5 mL) was added and the solid residues that formed were filtered out, rinsed with H_2O and ice-cold EtOH, and recrystallized from CH_2Cl_2/hexanes.



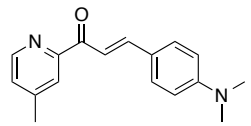
Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(pyridin-2-yl)prop-2-en-1-one (3a). Following general procedure B, the known compound **3a**[5] (R_f 0.33, Hexanes:EtOAc/3:1) was obtained from **1a** (242 mg, 2.0 mmol) and **2** (298 mg, 2.0 mmol) as bright orange crystals (318 mg, 63% yield): ^{1}H NMR (400 MHz, $CDCl_3$, which matches the lit.[5]) δ 8.72 (ddd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, J_3 = 0.8 Hz, 1H, aromatic), 8.17 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, aromatic), 8.06 (d, J = 15.6 Hz, 1H, HC=C<u>H</u>-Ph), 7.92 (d, J = 15.6 Hz, 1H, <u>H</u>C=CH-Ph), 7.84 (td, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H, aromatic), 7.63 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.44 (ddd, J_1 = 7.6 Hz, J_2 = 4.8 Hz, J_3 = 1.2 Hz, 1H, aromatic), 6.68 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.03 (s, 6H, N(C<u>H</u>$_3$)$_2$); Elemental analysis calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.88; H, 6.48; N, 11.02 (Fig. S5).



Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(6-methylpyridin-2-yl)prop-2-en-1-one (3b). Following general procedure B, **3b** (R_f 0.17, Hexanes:EtOAc/9:1) was obtained from **1b** (195 mg, 1.44 mmol) and **2** (215 mg, 1.44 mmol) as a dark yellow powder (212 mg, 55% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S6) δ 8.08 (d, J = 15.6 Hz, 1H, HC=C<u>H</u>-Ph), 7.96 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H, aromatic), 7.89 (d, J = 16.4 Hz, 1H, <u>H</u>C=CH-Ph), 7.71 (t, J = 7.6 Hz, 1H, aromatic), 7.62 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.28 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H, aromatic), 6.69 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.03 (s, 6H, N(C<u>H</u>$_3$)$_2$), 2.65 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S7) δ 189.6, 157.6, 154.5, 152.0, 145.6, 136.9, 130.8 (2 carbons), 126.0, 123.2, 119.8, 115.9, 111.7 (2 carbons), 40.1 (2 carbons), 24.5; *m/z* calcd for $C_{17}H_{18}N_2O$ 266.1; found 267.1 $[M+H]^+$; Elemental analysis calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 75.18; H, 6.83; N, 10.36 (Fig. S8).

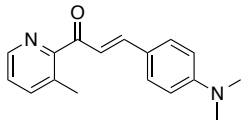


Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(5-methylpyridin-2-yl)prop-2-en-1-one (3c). Following general procedure B, **3c** (R_f 0.28, Hexanes:EtOAc/4:1) was obtained from **1c** (195 mg, 1.44 mmol) and **2** (215 mg, 1.44 mmol) as an orange solid (312 mg, 81% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S9) δ 8.54 (m, 1H, aromatic), 8.09 (d, J = 8.0 Hz, 1H, aromatic), 8.07 (d, J = 15.6 Hz, HC=C<u>H</u>-Ph), 7.91 (d, J = 15.6 Hz, 1H, <u>H</u>C=CH-Ph), 7.66-7.62 (m, 3H, aromatic), 6.69 (dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.04 (s, 6H, N(C<u>H</u>$_3$)$_2$), 2.43 (s, 3H, Ph-C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S10) δ 189.1, 152.7, 152.0, 149.1, 145.6, 137.3, 136.7, 130.8 (2 carbons), 123.1, 122.5, 115.7, 111.7 (2 carbons), 40.1 (2 carbons), 18.7; *m/z* calcd for $C_{17}H_{18}N_2O$ 266.1; found 267.3 $[M+H]^+$; Elemental analysis calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.37; H, 6.81; N, 10.43 (Fig. S11).

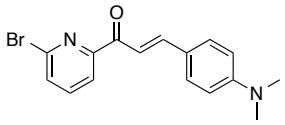


Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(4-methylpyridin-2-yl)prop-2-en-1-one (3d). Following general procedure B, **3d** (R_f 0.36, Hexanes:EtOAc/3:1) was obtained from **1d** (270 mg, 2.0 mmol) and **2** (298

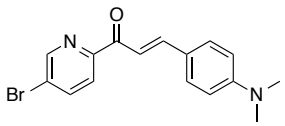
mg, 2.0 mmol) as a bright yellow solid (331 mg, 62% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S12) δ 8.57 (d, J = 4.8 Hz, 1H, aromatic), 8.04 (d, J = 15.6 Hz, 1H, HC=C<u>H</u>-Ph), 7.99 (m, 1H, aromatic), 7.90 (d, J = 15.6 Hz, 1H, <u>H</u>C=CH-Ph), 7.62 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.26 (dd, J_1 = 2.0 Hz, J_2 = 0.8 Hz, 1H, aromatic), 6.67 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.03 (s, 6H, N(C<u>H</u>$_3$)$_2$), 2.43 (s, 3H, Ph-C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S13) δ 189.5, 154.8, 152.0, 148.5, 148.2, 145.8, 130.9 (2 carbons), 127.3, 123.6, 123.1, 115.7, 111.7 (2 carbons), 40.1 (2 carbons), 21.1; *m/z* calcd for $C_{17}H_{18}N_2O$ 266.1; found 267.1 $[M+H]^+$; Elemental analysis calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.38; H, 6.79; N, 10.45 (Fig. S14).



Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(3-methylpyridin-2-yl)prop-2-en-1-one (3e). Following general procedure B, **3e** (R_f 0.37, Hexanes:EtOAc/3:1) was obtained from **1e** (195 mg, 1.44 mmol) and **2** (215 mg, 1.44 mmol) as a bright orange powder (153 mg, 57% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S15) δ 8.52 (ddd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, J_3 = 0.8 Hz, 1H, aromatic), 7.68 (d, J = 16.0 Hz, 1H, HC=C<u>H</u>-Ph), 7.58 (ddd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, J_3 = 0.8 Hz, 1H, aromatic), 7.57 (d, J = 16.0 Hz, 1H, <u>H</u>C=CH-Ph), 7.53 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.29 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H, aromatic), 6.65 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.02 (s, 6H, N(C<u>H</u>$_3$)$_2$), 2.55 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S16) δ 192.6, 154.4, 152.0, 146.0, 145.9, 139.6, 133.9, 130.6 (2 carbons), 125.0, 122.9, 119.2, 111.7 (2 carbons), 40.1 (2 carbons), 19.7; *m/z* calcd for $C_{17}H_{18}N_2O$ 266.1; found 267.3 $[M+H]^+$; Elemental analysis calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.44; H, 6.82; N, 10.47 (Fig. S17).

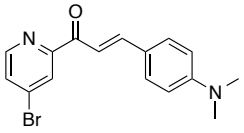


Synthesis of (*E*)-1-(6-bromopyridin-2-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (3f). Following general procedure B, **3f** (R_f 0.42, Hexanes:EtOAc/3:1) was obtained from **1f** (201 mg, 1.0 mmol) and **2** (150 mg, 1.0 mmol) as orange crystals (193 mg, 58% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S18) δ 8.12 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H, aromatic), 7.97 (d, J = 15.6 Hz, 1H, HC=C<u>H</u>-Ph), 7.91 (d, J = 15.6 Hz, 1H, <u>H</u>C=CH-Ph), 7.69 (t, J = 7.2 Hz, 1H, aromatic), 7.624 (dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.617 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H, aromatic), 6.68 (dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.04 (s, 6H, N(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S19) δ 187.6, 156.2, 152.5, 147.0, 141.3, 139.4, 131.4 (2 carbons), 131.2, 123.1, 121.8, 115.1, 111.9 (2 carbons), 40.3 (2 carbons); *m/z* calcd for $C_{16}H_{15}BrN_2O$ 330.0; found 331.1 $[M+H]^+$; Elemental analysis calcd. for $C_{16}H_{15}BrN_2O$: C, 58.02; H, 4.57; Br, 24.12; N, 8.64. Found: C, 56.93; H, 4.62; Br, 23.43; N, 8.10 (Fig. S20).

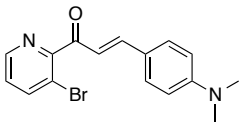


Synthesis of (*E*)-1-(5-bromopyridin-2-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (3g). Following general procedure B, **3g** (R_f 0.47, Hexanes:EtOAc/5:1) was obtained from **1g** (195 mg, 0.97 mmol) and **2** (145 mg, 0.97 mmol) as a bright orange powder (192 mg, 59% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S21) δ 8.75 (d, J = 2.0 Hz, 1H, aromatic), 8.06 (d, J = 8.0 Hz, 1H, aromatic), 7.99 (d, J = 16.0 Hz, 1H, HC=C<u>H</u>-Ph), 7.96 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H, aromatic), 7.91 (d, J = 16.0 Hz, 1H, <u>H</u>C=CH-Ph), 7.61 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 6.68 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.04 (s, 6H, N(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S22) δ 188.1, 153.3, 152.2, 149.8, 146.4, 139.6,

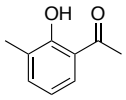
131.0 (2 carbons), 124.4, 124.1, 122.9, 114.9, 111.7 (2 carbons), 40.1 (2 carbons); *m/z* calcd for $C_{16}H_{15}BrN_2O$ 330.0; found 331.1 $[M+H]^+$; Elemental analysis calcd. for $C_{16}H_{15}BrN_2O$: C, 58.02; H, 4.57; Br, 24.12; N, 8.64. Found: C, 57.51; H, 4.53; Br, 23.73; N, 8.28 (Fig. S23).



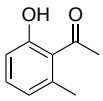
Synthesis of (*E*)-1-(4-bromopyridin-2-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (3h). Following general procedure B, **3h** (R_f 0.45, Hexanes:EtOAc/5:1) was obtained from **1h** (195 mg, 0.97 mmol) and **2** (145 mg, 0.97 mmol) as a bright orange powder (230 mg, 71% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S24) δ 8.52 (d, J = 4.8 Hz, 1H, aromatic), 8.33 (d, J = 2.0 Hz, 1H, aromatic), 7.99 (d, J = 15.6 Hz, 1H, HC=C<u>H</u>-Ph), 7.92 (d, J = 15.6 Hz, 1H, <u>H</u>C=CH-Ph), 7.61 (dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.60 (dd, J_1 = 4.8 Hz, J_2 = 2.0 Hz, 1H, aromatic), 6.67 (dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.04 (s, 6H, N(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S25) δ 187.7, 156.0, 152.3, 149.4, 146.7, 134.0, 131.1 (2 carbons), 129.4, 126.2, 122.8, 114.9, 111.7 (2 carbons), 40.1 (2 carbons); *m/z* calcd for $C_{16}H_{15}BrN_2O$ 330.0; found 331.1 $[M+H]^+$; Elemental analysis calcd. for $C_{16}H_{15}BrN_2O$: C, 58.02; H, 4.57; Br, 24.12; N, 8.64. Found: C, 57.50; H, 4.64; Br, 23.69; N, 8.26 (Fig. S26).



Synthesis of (*E*)-1-(3-bromopyridin-2-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (3i). Following general procedure B, **3i** (R_f 0.21, Hexanes:EtOAc/3:1) was obtained from **1i** (195 mg, 0.97 mmol) and **2** (145 mg, 0.97 mmol) as a bright orange foam (137 mg, 42% yield). *Note*: In this case, recrystallization was not successful. Therefore **3i** was purified by column chromatography (SiO_2, pure Hexanes to Hexanes:EtOAc/2:1, R_f 0.18, Hexanes:EtOAc/5:1): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S27) δ 8.60 (dd, J_1 = 4.8 Hz, J_2 = 1.6 Hz, 1H, aromatic), 7.97 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H, aromatic), 7.53 (d, J = 16.0 Hz, 1H, HC=C<u>H</u>-Ph), 7.48 (dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.25 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H, aromatic), 7.15 (d, J = 16.0 Hz, 1H, <u>H</u>C=CH-Ph), 6.64 (dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.02 (s, 6H, N(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S28) δ 191.3, 155.8, 152.3, 148.1, 147.3, 141.6, 130.8 (2 carbons), 125.5, 122.3, 118.9, 117.9, 111.7 (2 carbons), 40.1 (2 carbons); *m/z* calcd for $C_{16}H_{15}BrN_2O$ 330.0; found 331.1 $[M+H]^+$; Elemental analysis calcd. for $C_{16}H_{15}BrN_2O$: C, 58.02; H, 4.57; Br, 24.12; N, 8.64. Found: C, 58.02; H, 4.63; Br, 24.28; N, 8.43 (Fig. S29).

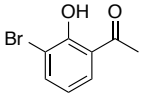


Synthesis of 2'-hydroxy-3'-methylacetophenone (4b). Methyllithium (8.4 mL, 1.6 M in Et_2O) was slowly added to a cooled (0 °C) solution of 3-methylsalicylic acid (600 mg, 3.94 mmol) in dry THF (10 mL), and the mixture was stirred for 6 h at rt. A saturated aq. solution of NH_4Cl was added and the mixture was filtered through a bed of celite, eluting with EtOAc. The organic layer was separated and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Following purification by column chromatography (SiO_2, Hexanes:EtOAc/9:1), the known compound **4b**[6] (R_f 0.74, Hexanes:EtOAc/9:1) was obtained as a light yellow oil (403 mg, 68% yield): ^{1}H NMR (400 MHz, $CDCl_3$, which matches the lit.[6]) δ 12.55 (s, 1H, O<u>H</u>), 7.58 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, aromatic), 7.33 (br dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, aromatic), 6.79 (t, J = 8.0 Hz, 1H, aromatic), 2.62 (s, 3H, C<u>H</u>$_3$), 2.25 (s, 3H, C<u>H</u>$_3$).

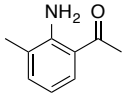


Synthesis of 2'-hydroxy-6'-methylacetophenone (4e). A solution of

methylmagnesium bromide (5.5 mL, 3.0 M in Et_2O) and Et_3N (1.9 mL, 13.3 mmol) in anhydrous toluene (5 mL) was cooled down to 0 °C. A solution of ethyl 2-hydroxy-6-methylbenzoate (600 mg, 3.33 mmol) in anhydrous toluene (5 mL) was slowly added and the resulting mixture was stirred overnight till rt. A saturated aq. solution of NH_4Cl was added and the mixture was filtered through a bed of celite, eluting with EtOAc. The organic layer was separated and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Following purification by column chromatography (SiO_2, Hexanes:EtOAc/9:1), the known compound **4e**[7] (R_f 0.32, Hexanes:EtOAc/9:1) was obtained as a yellow oil (379 mg, 76% yield): ^{1}H NMR (400 MHz, $CDCl_3$, which matches the lit.[7]) δ 12.30 (s, 1H, O<u>H</u>), 7.28 (t, J = 7.2 Hz, 1H, aromatic), 6.84 (d , J = 7.2 Hz, 1H, aromatic), 6.73 (d, J = 7.2 Hz, 1H, aromatic), 2.67 (s, 3H, C<u>H</u>$_3$), 2.60 (s, 3H, C<u>H</u>$_3$).

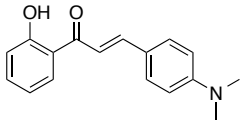


Synthesis of 3'-bromo-2'-hydroxyacetophenone (4f). A solution of 2'-hydroxyacetophenone (1.77 mL, 14.7 mmol) and *i*-Pr_2NH (0.21 mL, 1.47 mmol) in carbon disulfide (25 mL) was treated with NBS (2.61 g, 14.7 mmol) at 0 °C. The mixture was then stirred for 1.5 h at rt. H_2O was added and the mixture was extracted three times with EtOAc. The combined organic layers were washed with saturated aq. $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Following purification by column chromatography (SiO_2, Hexanes:EtOAc/9:1), the known compound **4f**[8] (R_f 0.36, Hexanes:EtOAc/9:1) was obtained as a brown solid (292 mg, 9% yield): ^{1}H NMR (400 MHz, $CDCl_3$, which matches the lit.[8]) δ 12.97 (s, 1H, O<u>H</u>), 7.62 (d, J = 7.6 Hz, 1H, aromatic), 7.74 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H, aromatic), 7.72 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H, aromatic), 6.82 (t, J = 8.0 Hz, 1H, aromatic), 2.66 (s, 3H, C<u>H</u>$_3$).



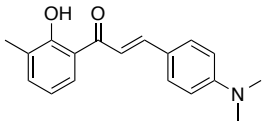
Synthesis of 2'-amino-3'-methylacetophenone (5b). Following the procedure for the synthesis of **4b**, the known compound **5b**[9] (R_f 0.66, Hexanes:EtOAc/3:1) was obtained from 2-amino-3-methylbenzoic acid (302 mg, 2.0 mmol) and methyllithium (3.7 mL, 6.0 mmol) as a yellow solid (139 mg, 47% yield): ^{1}H NMR (400 MHz, $CDCl_3$, which matches the lit.[9]) δ 7.62 (d, J = 7.6 Hz, 1H, aromatic), 7.18 (d, J = 7.6 Hz, 1H, aromatic), 6.58 (t, J = 7.6 Hz, 1H, aromatic), 2.57 (s, 3H, C<u>H</u>$_3$), 2.15 (s, 3H, C<u>H</u>$_3$).

General procedure C for the synthesis of chalcone derivatives 6a-h, 7a, 7b, and 7h. A mixture of 2'-hydroxyacetophenone (**4a-h**)/2'-aminoacetophenone (**5a**, **5b**, **5h**) (1.0 eq.), 4-(dimethylamino)benzaldehyde (**2**, 1.0 eq.), and NaOH (5.0 eq.) in EtOH (2.5 mL) was stirred at rt overnight. Upon completion of the reaction, EtOH was evaporated and the residue was neutralized with 1 N aq. HCl. The resulting mixture was stirred at rt for 10 min and the solid residues that formed were filtered out, rinsed with H_2O and ice-cold EtOH, and recrystallized from EtOH.

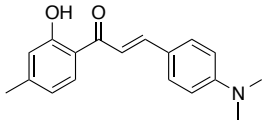


Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (6a). Following general procedure C, the known compound **6a**[10] (R_f 0.56, Hexanes:EtOAc/2:1) was obtained from **4a** (272 mg, 2.0 mmol) and **2** (298 mg, 2.0 mmol) as dark purple crystals (143 mg, 27% yield): ^{1}H NMR (400 MHz, $CDCl_3$, which matches the lit.[10]) δ 13.17 (s, 1H, O<u>H</u>), 7.93 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.92 (d, J = 15.6 Hz, 1H, HC=C<u>H</u>-Ph), 7.58 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.46 (d, J = 15.6 Hz, 1H, <u>H</u>C=CH-Ph), 7.46 (ddd, J_1 = 8.4 Hz, J_2 =

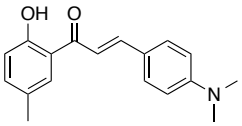
7.2 Hz, J_3 = 1.2 Hz, 1H, aromatic), 7.01 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, aromatic), 6.92 (ddd, J_1 = 8.4 Hz, J_2 = 7.2 Hz, J_3 = 1.2 Hz, 1H, aromatic), 6.71 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.07 (s, 6H, N(C<u>H</u>$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.5, 163.5, 152.3, 146.5, 135.6, 130.8 (2 carbons), 129.3, 122.3, 120.4, 118.55, 118.46, 114.3, 111.8 (2 carbons), 40.1 (2 carbons); *m/z* calcd for $C_{17}H_{17}NO_2$ 267.1; found 268.3 $[M+H]^+$; Elemental analysis calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.20; H, 6.42; N, 5.24 (Fig. S30).



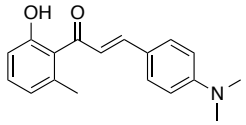
Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxy-3-methylphenyl)prop-2-en-1-one (6b). Following general procedure C, **6b** (R_f 0.50, Hexanes:EtOAc/4:1) was obtained from **4b** (150 mg, 1.0 mmol) and **2** (149 mg, 1.0 mmol) as red crystals (239 mg, 85% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S31) δ 13.48 (s, 1H, O<u>H</u>), 7.90 (d, J = 15.6 Hz, 1H, HC=C<u>H</u>-Ph), 7.77 (d, J = 8.0 Hz, 1H, aromatic), 7.57 (dt, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 2H, aromatic), 7.47 (d, J = 15.6 Hz, 1H, <u>H</u>C=CH-Ph), 7.32 (d, J = 8.0 Hz, 1H, aromatic), 6.81 (t, J = 8.0 Hz, 1H, aromatic), 6.72 (d, J = 9.2 Hz, 2H, aromatic), 3.05 (s, 6H, N(C<u>H</u>$_3$)$_2$), 2.28 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S32) δ 193.7, 162.0, 152.1, 146.1, 136.4, 130.7 (2 carbons), 127.4, 127.0, 122.8, 119.6, 117.8 (2 carbons), 114.9, 112.0, 40.2 (2 carbons), 15.6; *m/z* calcd for $C_{18}H_{19}NO_2$ 281.1; found 282.1 $[M+H]^+$; Elemental analysis calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.79; H, 6.76; N, 5.01 (Fig. S33).



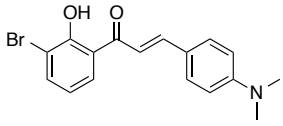
Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxy-4-methylphenyl)prop-2-en-1-one (6c). Following general procedure C, the known compound **6c**[11] (R_f 0.37, Hexanes:EtOAc/5:1) was obtained from **4c** (150 mg, 1.0 mmol) and **2** (149 mg, 1.0 mmol) as a dark red powder (168 mg, 60% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.21 (s, 1H, O<u>H</u>), 7.88 (d, J = 15.2 Hz, 1H, HC=C<u>H</u>-Ph), 7.79 (d, J = 8.0 Hz, 1H, aromatic), 7.56 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.42 (d, J = 15.2 Hz, 1H, <u>H</u>C=CH-Ph), 6.80 (s, 1H, aromatic), 6.74-6.68 (m, 3H, aromatic), 6.69 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.05 (s, 6H, N(C<u>H</u>$_3$)$_2$), 2.35 (s, 3H, Ph-C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 163.6, 152.2, 147.2, 146.0, 130.7 (2 carbons), 129.2, 122.5, 119.8, 118.5, 118.1, 114.5, 111.8 (2 carbons), 40.1 (2 carbons), 21.9; *m/z* calcd for $C_{18}H_{19}NO_2$ 281.1; found 282.1 $[M+H]^+$; Elemental analysis calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.33; H, 6.74; N, 4.94 (Fig. S34).



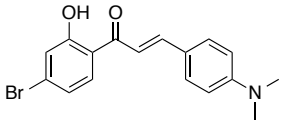
Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (6d). Following general procedure C, the known compound **6d**[12] (R_f 0.39, Hexanes:EtOAc/5:1) was obtained from **4d** (150 mg, 1.0 mmol) and **2** (149 mg, 1.0 mmol) as dark purple crystals (218 mg, 76% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.97 (s, 1H, O<u>H</u>), 7.89 (d, J = 15.2 Hz, 1H, HC=C<u>H</u>-Ph), 7.68 (d, J = 1.6 Hz, 1H, aromatic), 7.57 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.44 (d, J = 15.2 Hz, 1H, <u>H</u>C=CH-Ph), 7.26 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H, aromatic), 6.90 (d, J = 8.4 Hz, 1H, aromatic), 6.69 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.05 (s, 6H, N(C<u>H</u>$_3$)$_2$), 2.34 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 161.4, 152.3, 146.3, 136.7, 130.8 (2 carbons), 129.1, 127.5, 122.4, 120.0, 118.2, 114.5, 111.8 (2 carbons), 40.1 (2 carbons), 20.6; *m/z* calcd for $C_{18}H_{19}NO_2$ 281.1; found 282.1 $[M+H]^+$; Elemental analysis calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.83; H, 6.93; N, 5.00 (Fig. S35).



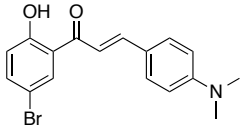
Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxy-6-methylphenyl)prop-2-en-1-one (6e). Following general procedure C, **6e** (R_f 0.22, Hexanes:EtOAc/4:1) was obtained from **4e** (150 mg, 1.0 mmol) and **2** (149 mg, 1.0 mmol) as a red powder (101 mg, 36% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S36) δ 10.72 (s, 1H, OH), 7.72 (d, *J* = 15.6 Hz, 1H, HC=CH-Ph), 7.50 (dt, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 2H, aromatic), 7.24 (d, *J* = 8.4 Hz, 1H, aromatic), 7.02 (d, *J* = 15.6 Hz, 1H, HC=CH-Ph), 6.82 (d, *J* = 8.4 Hz, 1H, aromatic), 6.78-6.70 (m, 3H, aromatic), 3.05 (s, 6H, $N(CH_3)_2$), 2.54 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S37) δ 196.3, 160.1, 152.2, 145.3, 137.9, 133.0, 130.7 (2 carbons), 124.0, 122.6, 122.4, 121.7, 115.2, 111.9 (2 carbons), 40.1 (2 carbons), 23.0; *m/z* calcd for $C_{18}H_{19}NO_2$ 281.1; found 282.2 $[M+H]^+$; Elemental analysis calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.57; H, 6.79; N, 5.02 (Fig. S38).



Synthesis of (*E*)-1-(3-bromo-2-hydroxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (6f). Following general procedure C, **6f** (R_f 0.34, Hexanes:EtOAc/4:1) was obtained from **4f** (215 mg, 1.0 mmol) and **2** (149 mg, 1.0 mmol) as purple crystals (153 mg, 44% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S39) δ 7.96 (d, *J* = 15.6 Hz, 1H, HC=CH-Ph), 7.90 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H, aromatic), 7.73 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H, aromatic), 7.58 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.43 (d, *J* = 15.6 Hz, 1H, HC=CH-Ph), 6.83 (t, *J* = 7.6 Hz, 1H, aromatic), 6.74 (br. dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.08 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S40) δ 192.9, 160.0, 152.3, 147.5, 138.7, 131.1 (2 carbons), 128.5, 122.6, 121.3, 119.2 (2 carbons), 113.7, 112.2, 112.1, 40.3 (2 carbons); *m/z* calcd for $C_{17}H_{16}BrNO_2$ 345.0; found 346.0 $[M+H]^+$; Elemental analysis calcd. for $C_{17}H_{16}BrNO_2$: C, 58.98; H, 4.66; Br, 23.08; N, 4.05. Found: C, 58.90; H, 4.72; Br, 22.91; N, 3.95 (Fig. S41).

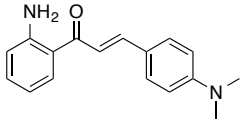


Synthesis of (*E*)-1-(4-bromo-2-hydroxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (6g). Following general procedure C, the known compound **6g**[11] (R_f 0.47, Hexanes:EtOAc/4:1) was obtained from **4g** (215 mg, 1.0 mmol) and **2** (149 mg, 1.0 mmol) as a red powder (108 mg, 31% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.36 (s, 1H, OH), 7.92 (d, *J* = 15.2 Hz, 1H, HC=CH-Ph), 7.75 (d, *J* = 8.8 Hz, 1H, aromatic), 7.56 (d, *J* = 8.8 Hz, 2H, aromatic), 7.35 (d, *J* = 15.2 Hz, 1H, HC=CH-Ph), 7.18 (d, *J* = 2.0 Hz, 1H, aromatic), 7.03 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H, aromatic), 6.68 (d, *J* = 8.8 Hz, 2H, aromatic), 3.06 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 164.0, 152.5, 147.2, 131.0 (2 carbons), 130.2, 129.8, 122.1, 122.0, 121.6, 119.3, 113.7, 111.8 (2 carbons), 40.1 (2 carbons); *m/z* calcd for $C_{17}H_{16}BrNO_2$ 345.0; found 346.0 $[M+H]^+$; Elemental analysis calcd. for $C_{17}H_{16}BrNO_2$: C, 58.98; H, 4.66; Br, 23.08; N, 4.05. Found: C, 59.06; H, 4.73; Br, 22.96; N, 4.10 (Fig. S42).

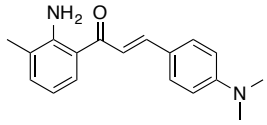


Synthesis of (*E*)-1-(5-bromo-2-hydroxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (6h). Following general procedure C, **6h** (R_f 0.52, Hexanes:EtOAc/5:1) was obtained from **4h** (215 mg, 1.0 mmol) and **2** (149 mg, 1.0 mmol) as a red powder (168 mg, 49% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S43) δ 13.14 (s, 1H, OH), 7.99 (d, *J* = 2.4 Hz, 1H, aromatic), 7.92 (d, *J* = 15.2 Hz, 1H, HC=CH-Ph), 7.58 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.51 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, aromatic), 7.33 (d, *J* = 15.2 Hz, 1H, HC=CH-

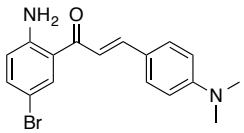
Ph), 6.89 (d, J = 8.4 Hz, 1H, aromatic), 6.69 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 3.06 (s, 6H, N(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S44) δ 192.3, 162.4, 152.6, 147.6, 138.1, 131.5, 131.1 (2 carbons), 122.1, 122.7, 120.4, 113.4, 111.8 (2 carbons), 110.1, 40.1 (2 carbons); *m/z* calcd for $C_{17}H_{16}BrNO_2$ 345.0; found 346.0 $[M+H]^+$; Elemental analysis calcd. for $C_{17}H_{16}BrNO_2$: C, 58.98; H, 4.66; Br, 23.08; N, 4.05. Found: C, 58.32; H, 4.68; Br, 23.15; N, 3.91 (Fig. S45).



Synthesis of (*E*)-1-(2-aminophenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (7a). Following general procedure C with the exception of quenching the reaction with H_2O instead of 1 N aq. HCl, the known compound **7a**[13] (R_f 0.21, Hexanes:EtOAc/5:1) was obtained from **5a** (135 mg, 1.0 mmol) and **2** (149 mg, 1.0 mmol) as a bright orange powder (214 mg, 80% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz, 1H, aromatic), 7.71 (d, J = 15.6 Hz, 1H, HC=C<u>H</u>-Ph), 7.52 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.40 (d, J = 15.6 Hz, 1H, <u>H</u>C=CH-Ph), 7.25 (ddd, J_1 = 8.4 Hz, J_2 = 7.2 Hz, J_3 = 1.6 Hz, 1H, aromatic), 6.70-6.66 (m, 4H, aromatic), 6.22 (br s, 2H, N<u>H</u>$_2$), 3.02 (s, 6H, N(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 151.8, 150.6, 143.9, 133.6, 130.8, 130.1 (2 carbons), 123.1, 119.9, 118.0, 117.2, 115.8, 111.8 (2 carbons), 40.1 (2 carbons); *m/z* calcd for $C_{17}H_{18}N_2O$ 266.1; found 267.1 $[M+H]^+$; Elemental analysis calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.51; H, 6.78; N, 10.47 (Fig. S46).



Synthesis of (*E*)-1-(2-amino-3-methylphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (7b). Following general procedure C, with the exception of quenching the reaction with H_2O instead of 1 N aq. HCl, **7b** (R_f 0.34, Hexanes:EtOAc/4:1) was obtained from **5b** (122 mg, 0.82 mmol) and **2** (122 mg, 0.82 mmol) as a brown powder (178 mg, 78% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S47) δ 7.77 (d, J = 8.0 Hz, 1H, aromatic), 7.71 (d, J = 15.6 Hz, 1H, HC=C<u>H</u>-Ph), 7.52 (d, J = 9.2 Hz, 2H, aromatic), 7.43 (d, J = 15.6 Hz, 1H, <u>H</u>C=CH-Ph), 7.18 (d, J = 8.0 Hz, 1H, aromatic), 6.70 (d, J = 9.2 Hz, 2H, aromatic), 6.63 (t, J = 8.0 Hz, 1H, aromatic), 6.40 (br s, 2H, N<u>H</u>$_2$), 3.02 (s, 6H, N(C<u>H</u>$_3$)$_2$), 2.18 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S48) δ 192.4, 151.6, 149.1, 143.7, 134.5, 130.1 (4 carbons), 128.8, 123.3, 119.3, 118.5, 115.1, 112.0, 40.2 (2 carbons), 17.4; *m/z* calcd for $C_{18}H_{20}N_2O$ 280.2; found 281.2 $[M+H]^+$; Elemental analysis calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.11; H, 7.17; N, 10.08 (Fig. S49).



Synthesis of (*E*)-1-(2-amino-5-bromophenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (7h). Following general procedure C, with the exception of quenching the reaction with H_2O instead of 1 N aq. HCl, **7h** (R_f 0.27, Hexanes:EtOAc/4:1) was obtained from **5h** (214 mg, 1.0 mmol) and **2** (149 mg, 1.0 mmol) as a dark yellow powder (181 mg, 52% yield): ^{1}H NMR (400 MHz, $CDCl_3$, Fig. S50) δ 7.92 (d, J = 2.4 Hz, 1H, aromatic), 7.72 (d, J = 15.2 Hz, 1H, HC=C<u>H</u>-Ph), 7.54 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 7.304 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, aromatic), 7.298 (d, J = 15.2 Hz, 1H, <u>H</u>C=CH-Ph), 6.69 (dt, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 2H, aromatic), 6.57 (d, J = 8.4 Hz, 1H, aromatic), 6.24 (br s, 2H, N<u>H</u>$_2$), 3.03 (s, 6H, N(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$, Fig. S51) δ 190.8, 152.0, 149.4, 145.0, 136.1, 132.8, 130.4 (2 carbons), 122.7, 121.2, 118.9, 117.0, 111.8 (2 carbons), 106.9, 40.1 (2 carbons); *m/z* calcd for

$C_{17}H_{17}BrNO_2$ 344.0; found 345.0 $[M+H]^+$; Elemental analysis calcd. for $C_{17}H_{17}BrN_2O$: C, 59.14; H, 4.96; Br, 23.14; N, 8.11. Found: C, 59.03; H, 5.04; Br, 23.27; N, 7.96 (Fig. S52).

Cu^{2+} binding studies of chalcones. A 100 mM master stock solution of $CuCl_2$ was first prepared by dissolving copper (II) chloride dihydrate powder in mQ ddH_2O. 20-fold dilution of the master stock solution yielded a 5 mM $CuCl_2$ stock solution, C_3. The latter was then subjected to a 2.5-fold dilution to obtain a 2 mM $CuCl_2$ stock solution, C_2, which was further diluted to afford a 1 mM $CuCl_2$ stock solution, C_1. To a cuvette containing 980 μL of a 20.4 μM solution of chalcone in EtOH was added 20 μL of H_2O, C_1, C_2, or C_3, corresponding to treatment with 0, 1, 2, and 5 equivalents of $CuCl_2$, respectively. The resulting solution was gently mixed and allowed to stand for 2 min at rt before its absorbance was measured by UV-Vis from 250 to 750 nm.

Zn^{2+} binding studies of chalcones by ^{1}H NMR spectroscopy. As previously described,[5] a solution of chalcone (**3a**, **3b**, **3d**, **3f**, **3h**, **6a**, or **7a**) (4 mM) in acetonitrile-d_3 (CD_3CN) was treated with $ZnCl_2$ (3 equivalents) and the resulting mixture was analyzed by ^{1}H NMR spectroscopy.

Solution speciation studies. The p*K*a values for chalcones **3a**, **3d**, **3h**, **6a**, and **7a** were determined by UV-visible variable-pH titrations as previously described.[5] A mixture of chalcone [20 μL of an ethanolic solution of **3a**/**6a**/**7a** (1 mM) or 50 μL of an ethanolic solution of **3d**/**3h** (1 mM)], $CuCl_2$ (1 mM, 10 μL for **3a**/**6a**/**7a** or 25 μL for **3d**/**3h**) and buffer (10 mM NaOH, pH 12, 100 mM NaCl, 970 μL for **3a**/**6a**/**7a** or 925 μL for **3d**/**3h**) was transferred to a cuvette and titrated with small aliquots of HCl (0.1 N). The absorbance was measured upon each addition of HCl from 250 to 900 nm to obtain at least 30 spectra in the range of pH 12-2. In order to investigate the binding properties of ligands to Cu^{2+} at various pH values, a mixture of chalcone [20 μL of an ethanolic solution of **3a**/**6a**/**7a** (1 mM) or 50 μL of an ethanolic solution of **3d**/**3h** (1 mM)], $CuCl_2$ (1 mM, 10 μL for **3a**/**6a**/**7a** or 25 μL for **3d**/**3h**) and buffer (10 mM NaOH, pH 12, 100 mM NaCl, 970 μL for **3a**/**6a**/**7a** or 925 μL for **3d**/**3h**) was transferred to a cuvette and allowed to stand for 30 min at room temperature. It was then titrated with small aliquots of HCl (0.1 N). Upon each addition of HCl, the absorbance was measured from 250 to 900 nm to obtain at least 20 spectra in the range of pH 2-7 for **3a** and **3d**, and pH 2-10 for **3h**, **6a**, and **7a**. Using the HypSpec program (Protonic Software, U.K.), the p*K*as and log β constants were determined. The speciation diagrams were obtained with Sigmaplot Software). UV-visible variable-pH titration spectra and solution speciation diagrams of **6a** and **7a** in the presence of $CuCl_2$ are presented in Fig. S53.

Assays for bioAβ_{42} oligomer assembly and dissociation. The bioAβ_{42} oligomer assembly and dissociation experiments were carried out as previously described.[14,15]

***NeutrAvidin^{TM}-coated ELISA plates*:** Each well of an immunoassay ELISA plate was coated with 50 μL of 1 μg/mL NeutrAvidin^{TM} in 10 mM sodium phosphate buffer, pH 7.5 (50 ng NeutrAvidin^{TM} per well). The plate was sealed with adhesive film and stored at 4 °C overnight. The following day, 200 μL of PBS containing 0.1% v/v Tween 20 was added to each well to block the uncoated well surface and the plate was stored at 4 °C at least overnight. These plates were used to measure both oligomer assembly and dissociation.

***bioAβ$_{42}$ oligomer assembly*:** A 1 mg/mL stock solution of *N*-biotinyl Aβ$_{1-42}$ (bioAβ$_{42}$) in hexafluoroisopropanol (HFIP) was evaporated, treated with neat trifluoroacetic acid (TFA) for 10 min to allow complete disaggregation of the peptide, dried again, dissolved further in HFIP to remove residual TFA, and dried and re-dissolved to a concentration of 500 nM (50x) in DMSO. After standing with intermittent vortexing for 10 min, 2 μL of the 50x monomeric peptide solution was transferred into each well of a polypropylene 96-well plate. In a separate plate 100x DMSO-solubilized chalcone (5 mM-78 μM) was prepared and then diluted (50 μM-0.78 μM final concentration of chalcone) in PBS with or without 25 μM metal ion ($ZnCl_2$ or $CuCl_2$) (final 1% DMSO). 100 μL of the chalcone dilutions were added to each well containing the DMSO solubilized bioAβ$_{42}$ (final Aβ concentration 10 nM). 30 min later, 50 μL Tween 20 in ddH_2O (0.3% v/v) was added to each well to stop oligomer assembly. Once formed, these oligomers have a half-lifetime $t_{1/2}$ = 30 h at 22 °C for dissociation into monomers.

To measure the bioAβ$_{42}$ oligomers, the following steps were performed at rt (~22 °C). The blocking solution was flicked out of the wells of a NeutrAvidin™-coated ELISA plate, 50 μL of the oligomer assembly reaction mixture was added, and the plate was sealed with adhesive film. The plate was shaken at 150 rpm for 2 h to allow monomeric and oligomeric bioAβ$_{42}$ to bind to the NeutrAvidin™ on the well surface. The plate was then washed three times with a low salt solution (34 mM aqueous NaCl, 20 mM Tris-HCl, pH 7.5, 0.1% v/v Tween 20 (TBST)) on a BioTek ELx50 plate washer. 50 μL of 50 ng/mL (1:20,000 diluted) Streptavidin-conjugated horseradish peroxidase (HRP) were added, the plate sealed with adhesive film, and the plate shaken at rt for 1 h. The plate was washed on the plate washer as previously, and 100 μL of 0.2 M citrate buffer, pH 4.0 containing 0.01% w/w H_2O_2 as HRP substrate and 1 mM tetramethylbenzidine were added. Since each captured bioAβ$_{42}$ peptide contains one biotin, NeutrAvidin™-captured monomers will not react with the Streptavidin-HRP. Only oligomers will have biotin available for the Streptavidin-HRP to bind. The HRP reaction was stopped by the addition of 100 μL of 1% (v/v) H_2SO_4 to each well. The absorbance of each well was read at 450 nm with a Biotek HT Synergy plate reader.

***bioAβ$_{42}$ oligomer dissociation*:**
Pre-formation of bioAβ$_{42}$ oligomers for dissociation: A stock sufficient for four 96-well plates of pre-formed bioAβ$_{42}$ was prepared as follows. 1 μL of bioAβ$_{42}$ (1 mg/ml stock in HFIP) was pipetted into 20 μL of HFIP in a 0.65 mL polypropylene Eppendorf tube, dried down, and disaggregated as described for oligomer assembly. The dried peptide was re-dissolved in 250 μL of DMSO. After 10 min at rt with intermittent vortexing, the DMSO-solubilized bioAβ$_{42}$ was added to 12.5 mL of PBS in a 17x100 mm polypropylene tube, sealed with Parafilm®, and mixed several times by inversion. The solution was then incubated at rt for 1 h with intermittent vortexing, then 375 μL of 100 mM Tween 20 (10% v/v in ddH_2O) was added for a final concentration of 0.3% v/v. The pre-formed stock oligomers (16.8 nM bioAβ$_{42}$) were mixed by inversion and stored in aliquots at -75 °C.

Pre-formed oligomer dissociation: 25 μL of the pre-formed bioAβ$_{42}$ oligomers adjusted to 0.6% v/v Tween 20 was pipetted into each well of a polypropylene 96-well plate, followed by the addition of 125 μL PBS containing DMSO-solubilized chalcone (50 μM-0.78 μM final

concentration in two-fold serial dilutions in DMSO that is then added to PBS) with or without 25 μM metal ion ($ZnCl_2$ or $CuCl_2$) (final 1% DMSO) to each well containing pre-formed oligomers. The total final concentration of bio$A\beta_{42}$ peptide in each well was 2.8 nM. The plate was sealed and shaken at 150 rpm overnight at rt to allow the oligomers to dissociate. After 18 h of incubation, the plates were centrifuged at 1000xg for 10 min at rt to collect any condensate, and a 125 μL aliquot was transferred from each well into a NeutrAvidin™-coated ELISA plate to assay for oligomers as described for oligomer assembly.

In vitro **cholinesterase (ChE) inhibition assays.** Experiments were performed as previously described.[16,17] Briefly, chalcones (102 pm to 200 μM) were dissolved in sodium phosphate buffer ((100 μL), 0.1 M, pH 8.0) (Buffer A) and subjected to a 5-fold serial dilution. ChE (either AChE or BChE) was added to the solution of inhibitors (50 μL, containing 0.08 U/mL ChE (final concentration for both AChE and BChE) in Buffer A. The mixture of inhibitor and enzyme were incubated for 10 min before initiation with DTNB (50 μL, 0.25 mM final concentration) and acylthiocholine (acetylthiocholine for AChE or butyrylthiocholine for BChE) (0.5 mM final concentration) in phosphate buffer. The reaction was monitored at 412 nm taking measurements every 30 s for 10 min using a SpectraMax M5 plate reader. Data was corrected with the negative control (no acylthicholine) and normalized to the positive control (no inhibitor) using the initial rates (first 5 min). All assays were performed in triplicate. The data was fitted to a sigmoidal curve and IC_{50} values calculated using KaleidaGraph 4.1. Representive IC_{50} curves are presented in Fig. S54.

Effect of metals on AChE inhibition. Chalcones were dissolved in Buffer A as above. To the solution, AChE mixed with metal ion ($CuCl_2$ or $ZnCl_2$, 200 μM) in Buffer A was added and incubated for 10 min. The reactions were then initiated with the acetylthiocholine/DTNB mixture. Reactions were monitored and analyzed as above and previously described.[18]

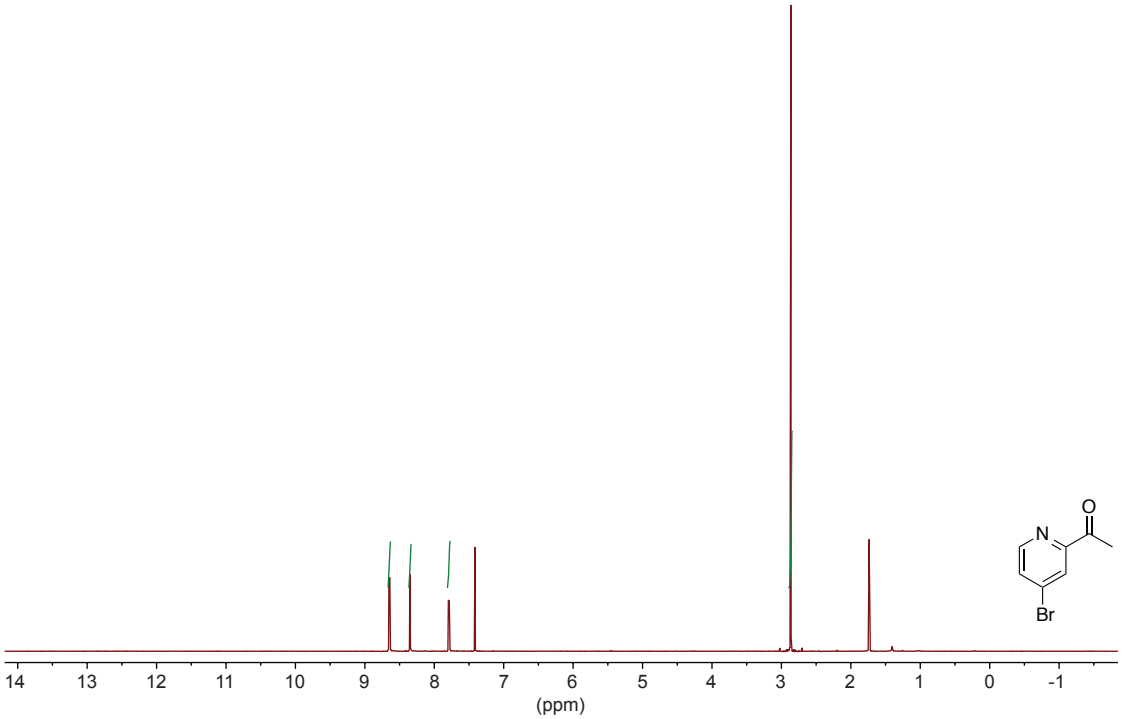


Fig. S1: ^{1}H NMR spectrum for compound **1h**.

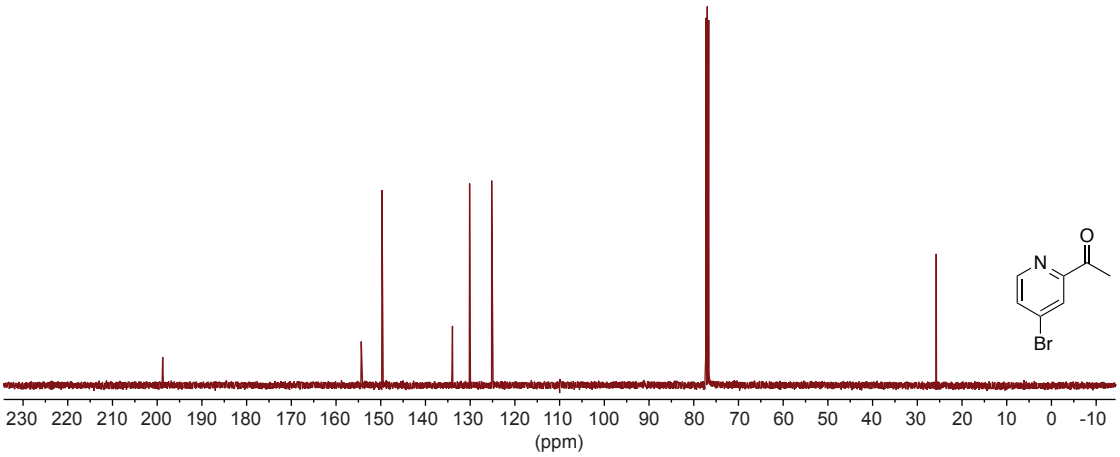


Fig. S2: ^{13}C NMR spectrum for compound **1h**.

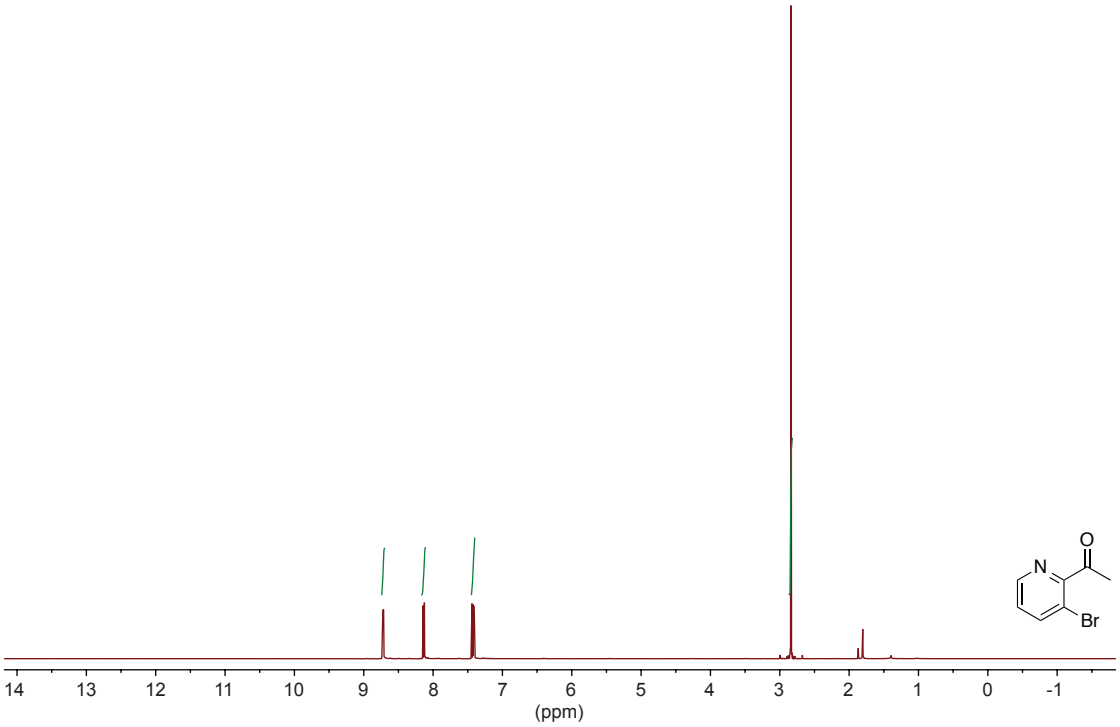


Fig. S3: ^{1}H NMR spectrum for compound **1i**.

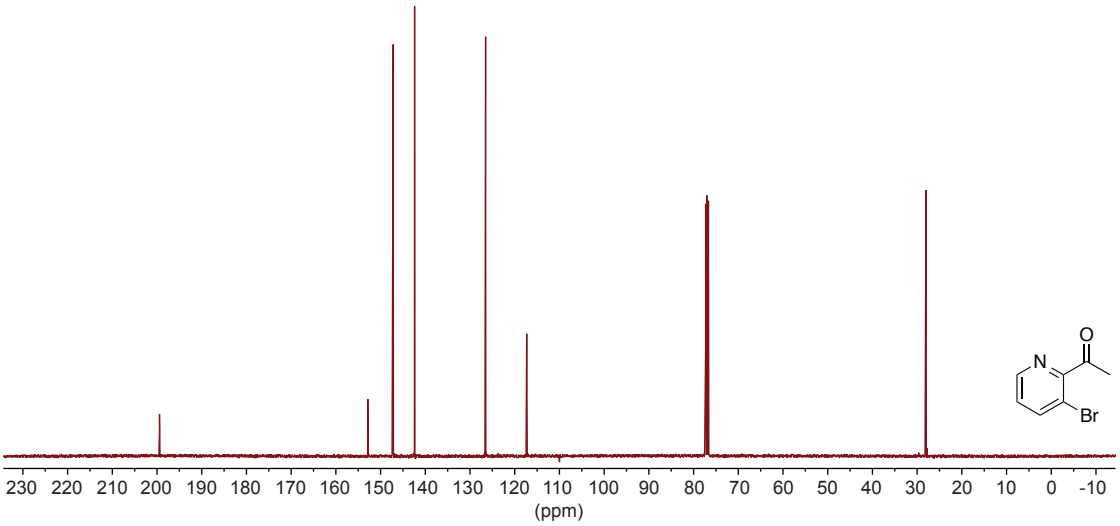


Fig. S4: ^{13}C NMR spectrum for compound **1i**.

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Sample No. MFY-2-84

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Norcross, GA 30071
www.atlanticmicrolab.com

Company/School University of Kentucky
Dept. Pharmaceutical Sciences
Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone (859) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# / CC# 29935

Element	Theory	Found	
C	76.16	75.88	
H	6.39	6.48	
N	11.10	11.02	
O	6.34		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C, H, N
Hygroscopic ☒ Explosive ☐
M.P. ____ B.P. ____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. ↓ Time 3-4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day this sample is received by 11 AM.
Include Email Address or FAX # Below
sgt229@uky.edu

Date Received JUN 19 2015 Date Completed JUN 22 2015
Remarks:

Fig. S5: Elemental analysis for compound **3a**.

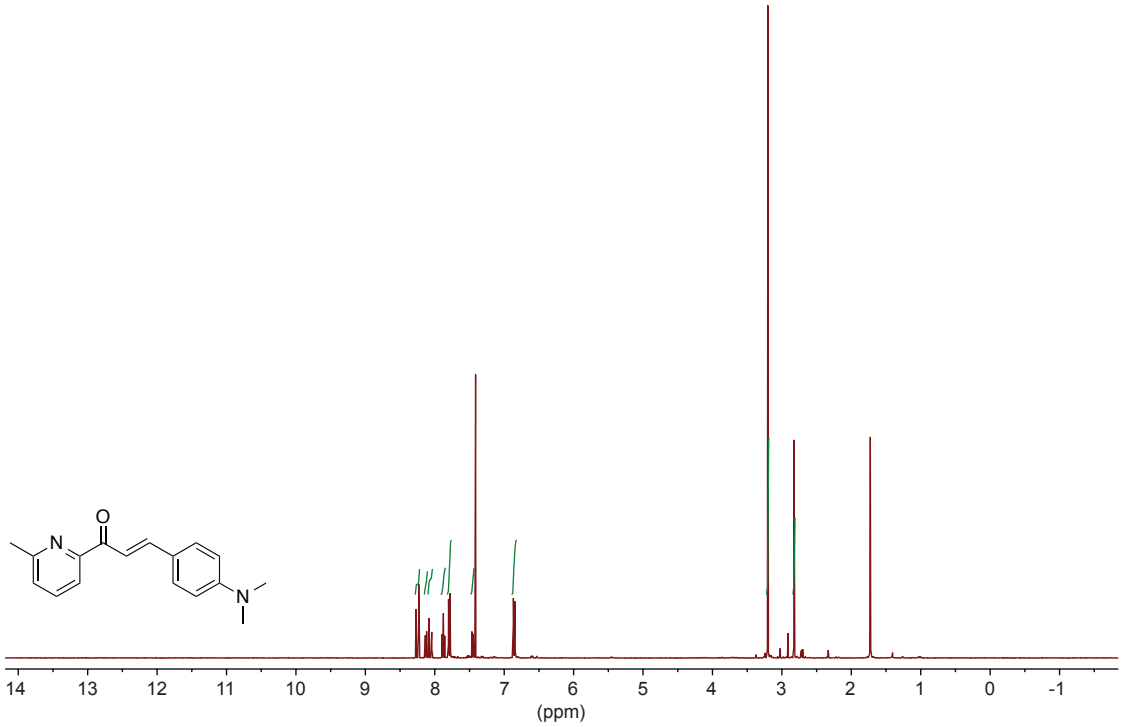

Fig. S6: ^{1}H NMR spectrum for compound **3b**.

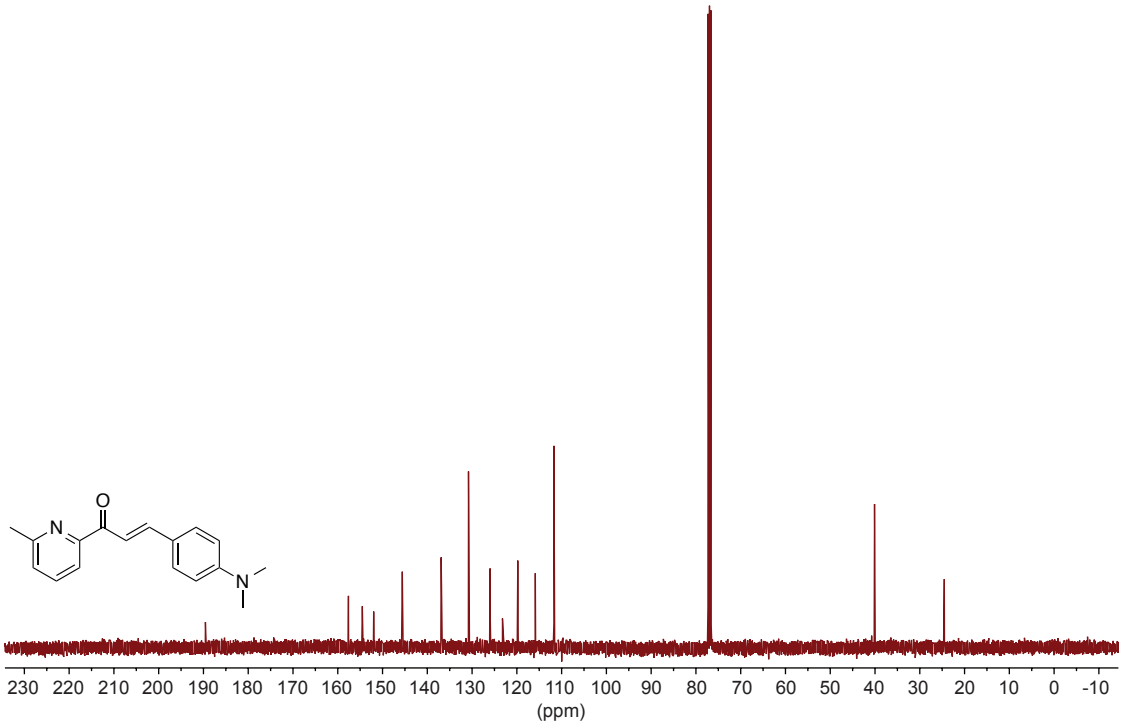

Fig. S7: ^{13}C NMR spectrum for compound **3b**.

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Sample No. MFY-2-151

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Norcross, GA 30071
www.atlanticmicrolab.com

Company/School University of Kentucky
Dept. Pharmaceutical Sciences
Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone (859) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# CC# 29935

Element	Theory	Found	
C	76.66	75.18	75.03
H	6.81	6.83	6.74
N	10.52	10.36	10.31
O	6.01	NO CHARGE FOR DUPLICATES	

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C, H, N
Hygroscopic ☒ Explosive ☐
M.P. _____ B.P. _____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. ✓ Time 3-4h
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Fig. S8: Elemental analysis for compound **3b**.

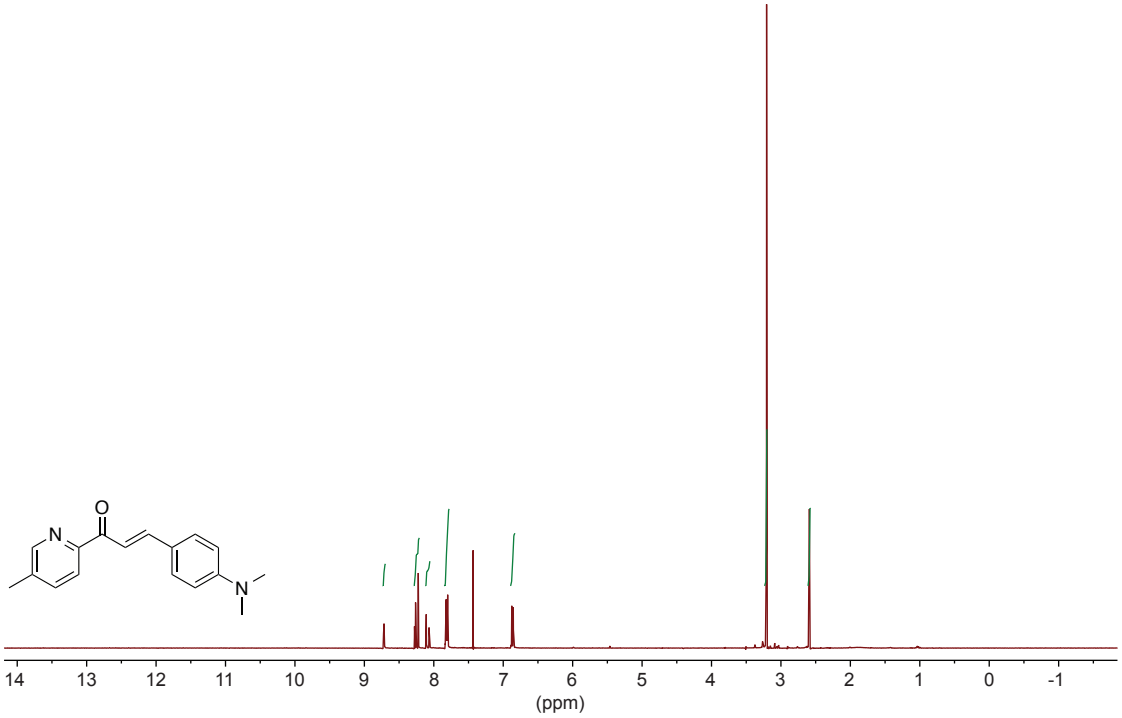

Fig. S9: ^{1}H NMR spectrum for compound **3c**.

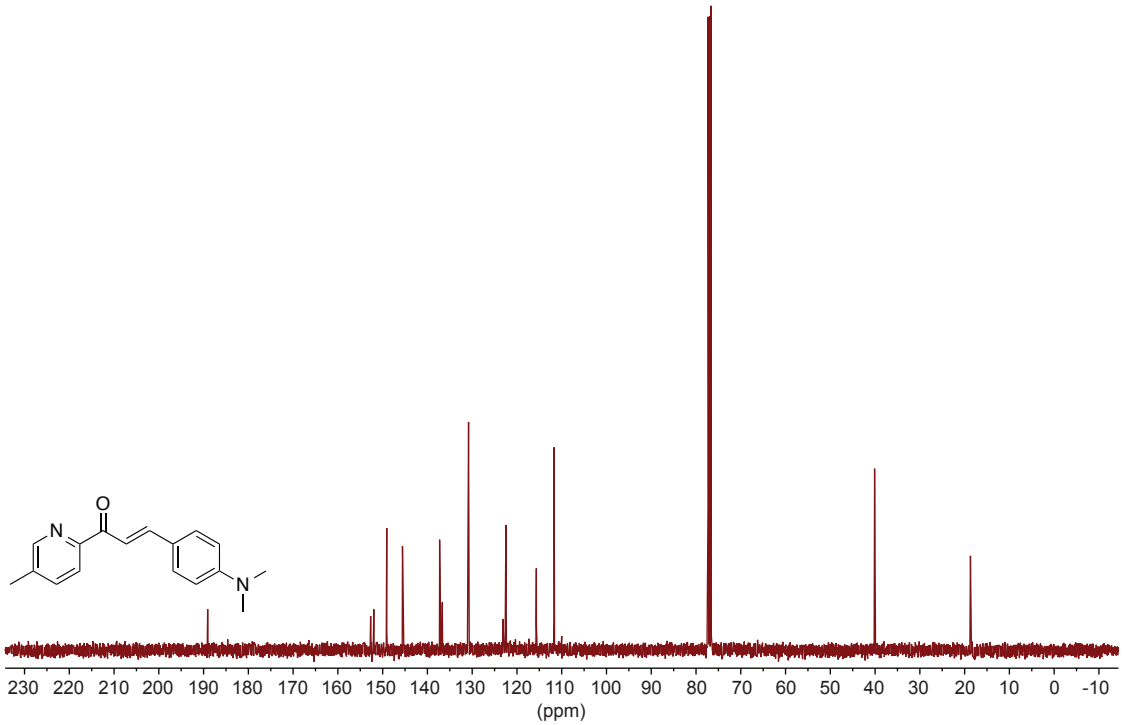

Fig. S10: ^{13}C NMR spectrum for compound **3c**.

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Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso
Phone (859) 323-1945
Date 06/16/2015

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# CC# 29935

Element	Theory	Found	
C	76.66	76.37	
H	6.81	6.81	
N	10.52	10.43	
O	6.01		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C, H, N
Hygroscopic ☒ Explosive ☐
M.P. ? B.P.
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. ✓ Time 3-4 h
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Fig. S11: Elemental analysis for compound **3c**.

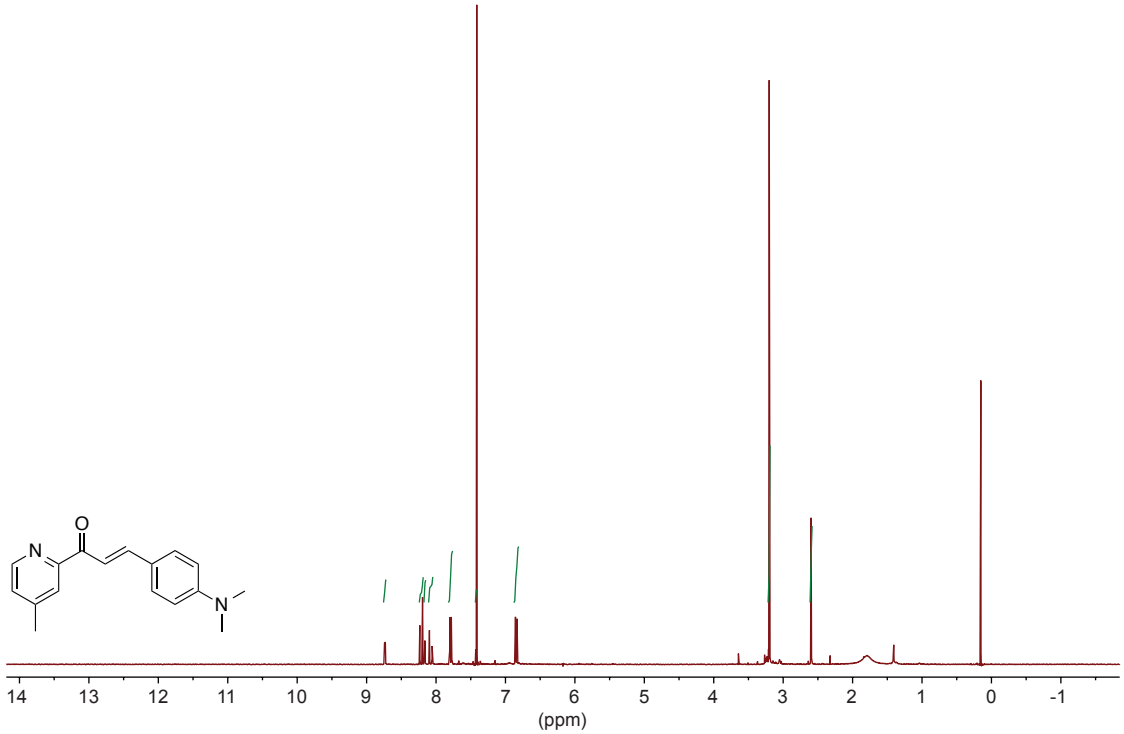

Fig. S12: ^{1}H NMR spectrum for compound **3d**.

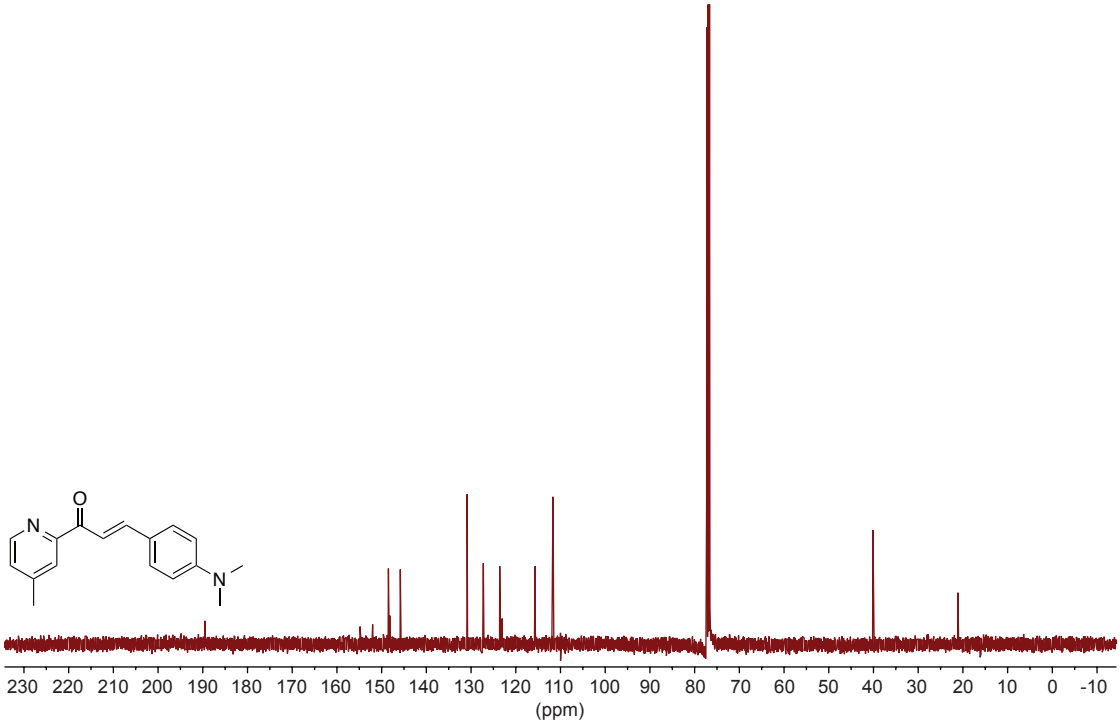

Fig. S13: ^{13}C NMR spectrum for compound **3d**.

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Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
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Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# CC# 29935

Element	Theory	Found	
C	76.66	76.38	
H	6.81	6.79	
N	10.52	10.45	
O	6.01		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C, H, N
Hygroscopic ☒ Explosive ☐
M.P. ____ B.P. ____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. ✓ Time 3-4 h
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Fig. S14: Elemental analysis for compound **3d**.

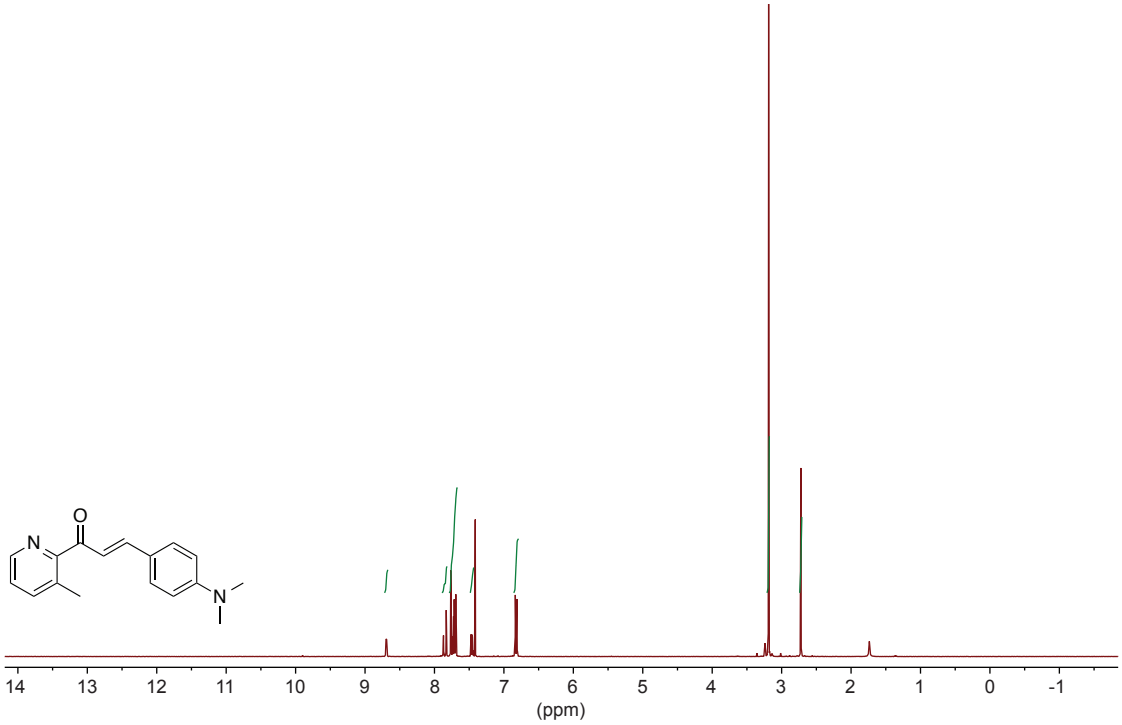

Fig. S15: ^{1}H NMR spectrum for compound **3e**.

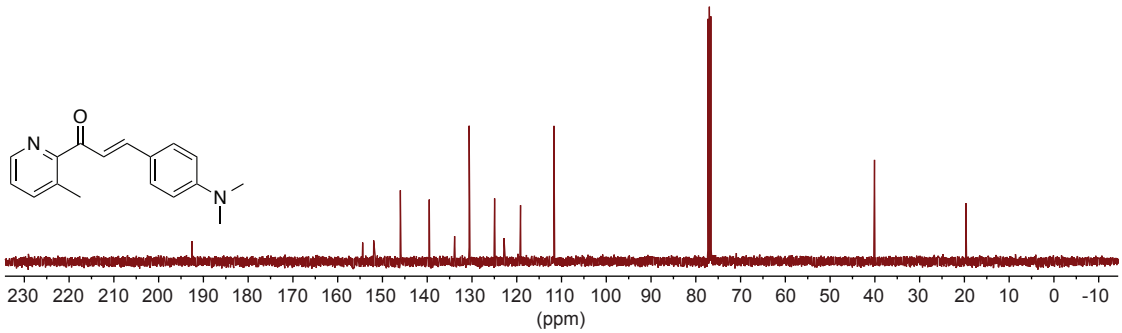

Fig. S16: ^{13}C NMR spectrum for compound **3e**.

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City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
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Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
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Element	Theory	Found	
C	76.66	76.44	
H	6.81	6.82	
N	10.52	10.47	
O	6.01		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C, H, N
Hygroscopic ☒ Explosive ☐
M.P. ____ B.P. ____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. ✓ Time 3-4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Fig. S17: Elemental analysis for compound **3e**.

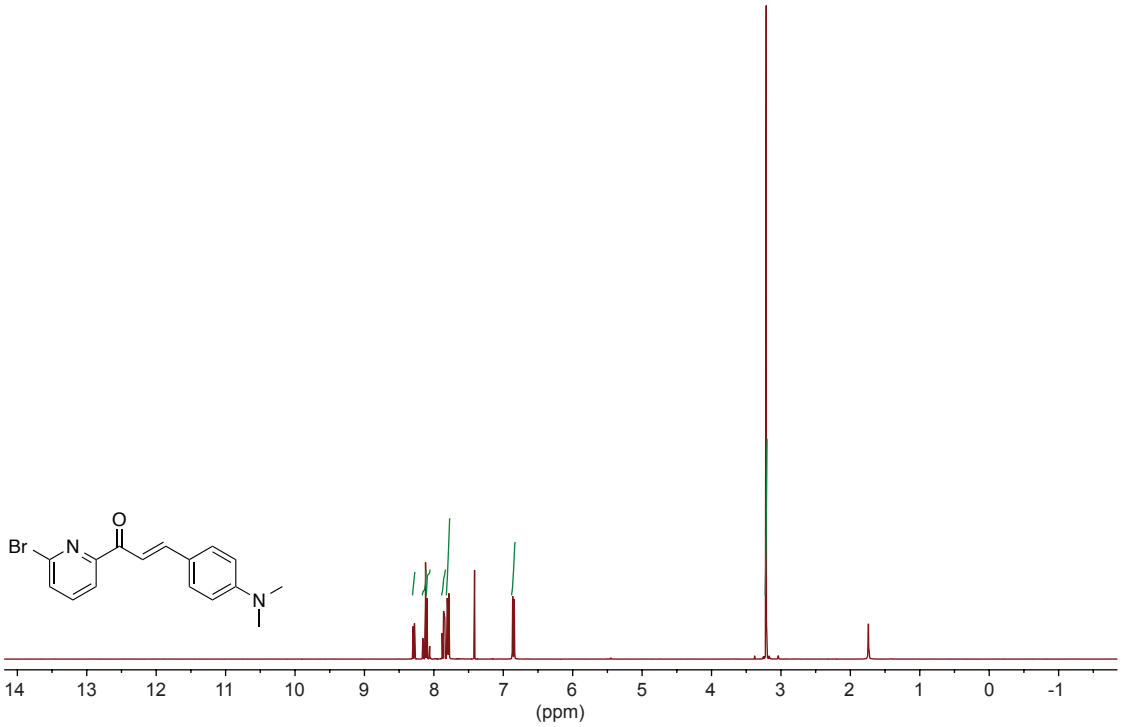

Fig. S18: ^{1}H NMR spectrum for compound **3f**.

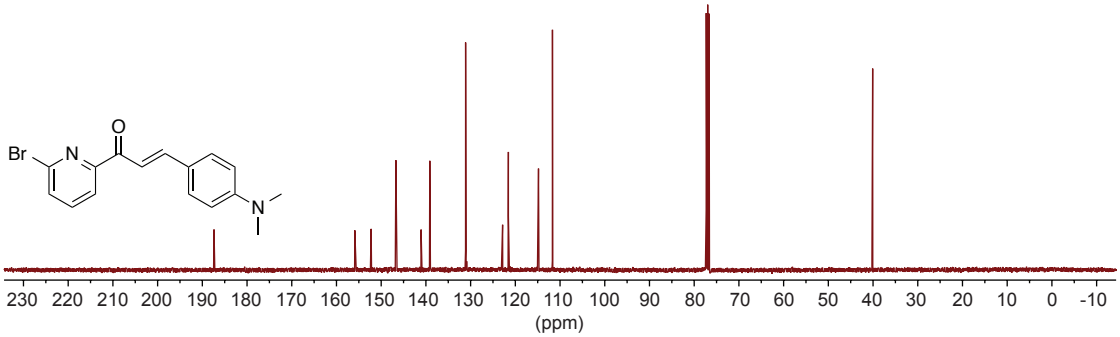

Fig. S19: ^{13}C NMR spectrum for compound **3f**.

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Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone (859) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO#/ CC# 29935

Element	Theory	Found	
C	58.02	56.76	56.93
H	4.57	4.60	4.62
Br	24.12	23.43	
N	8.46	8.20	8.10
O	4.83	NO CHARGE FOR DUPLICATES	

Single ☒ Duplicate ☐
Elements Present: C, H, N, O, Br
Analyze for: C, H, N, Br
Hygroscopic ☒ Explosive ☐
M.P. ____ B.P. ____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. yes Time 3-4 h
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Fig. S20: Elemental analysis for compound **3f**.

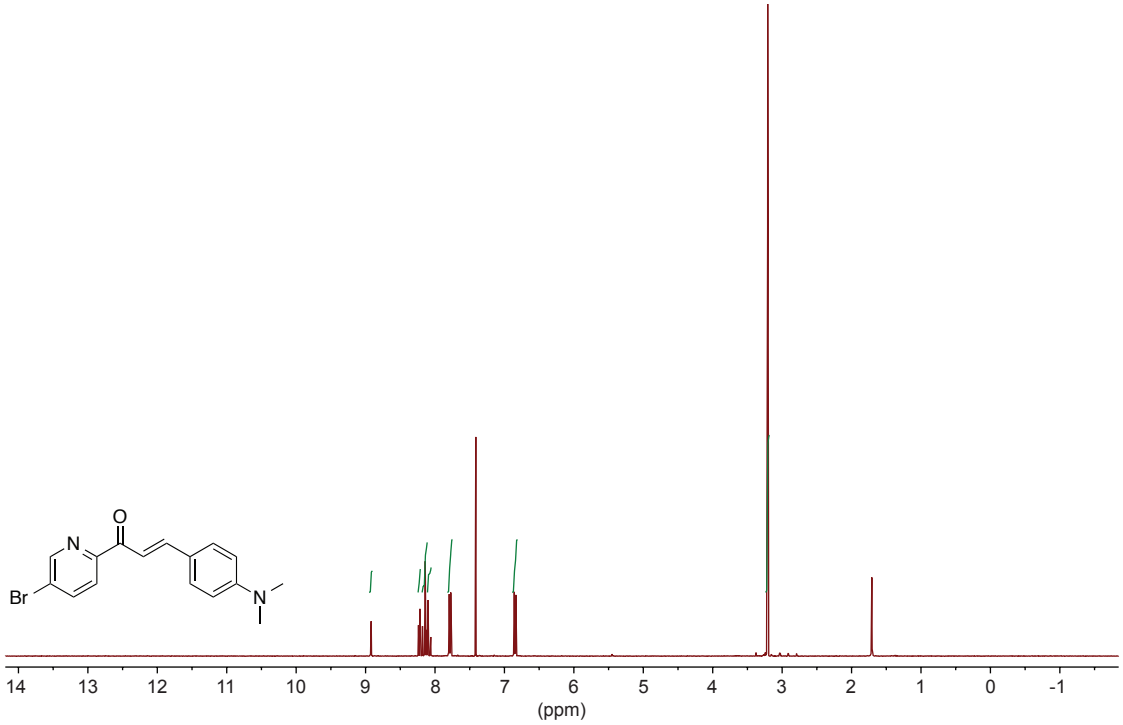

Fig. S21: ^{1}H NMR spectrum for compound **3g**.

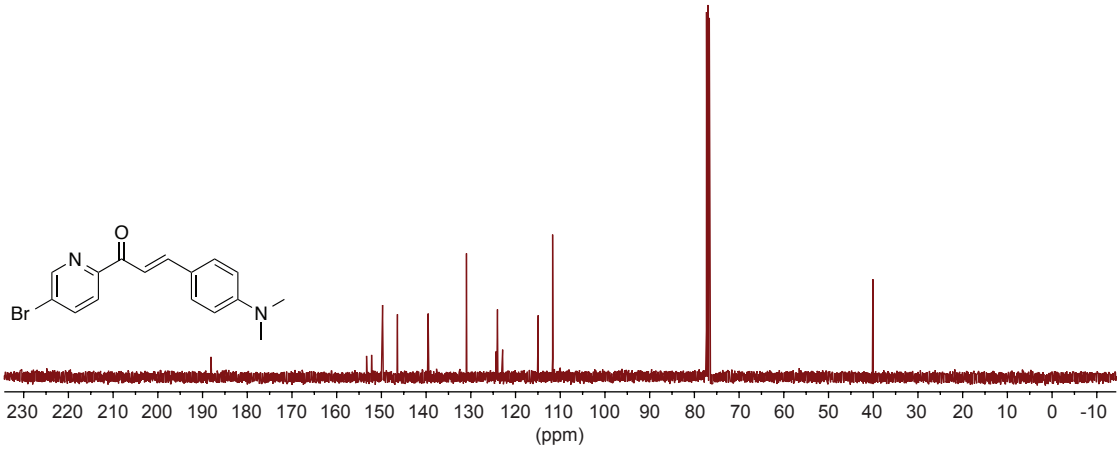

Fig. S22: ^{13}C NMR spectrum for compound **3g**.

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Address 789 S. Limestone
City, State, Zip Lexington, KY 40535-0596
Name Marina Fosso Date 06/16/2015
Phone (859) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# CC# 29935

Element	Theory	Found	
C	58.02	57.51	57.40
H	4.57	4.53	4.49
Br	24.12	23.73	
N	8.46	8.28	8.34
O	4.83	NO CHARGE FOR DUPLICATES	

Single ☒ Duplicate ☐
Elements Present: C, H, N, O, Br
Analyze for: C, H, N, Br
Hygroscopic ☒ Explosive ☐
M.P. _____ B.P. _____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. ✓ Time 3-4h
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Fig. S23: Elemental analysis for compound **3g**.

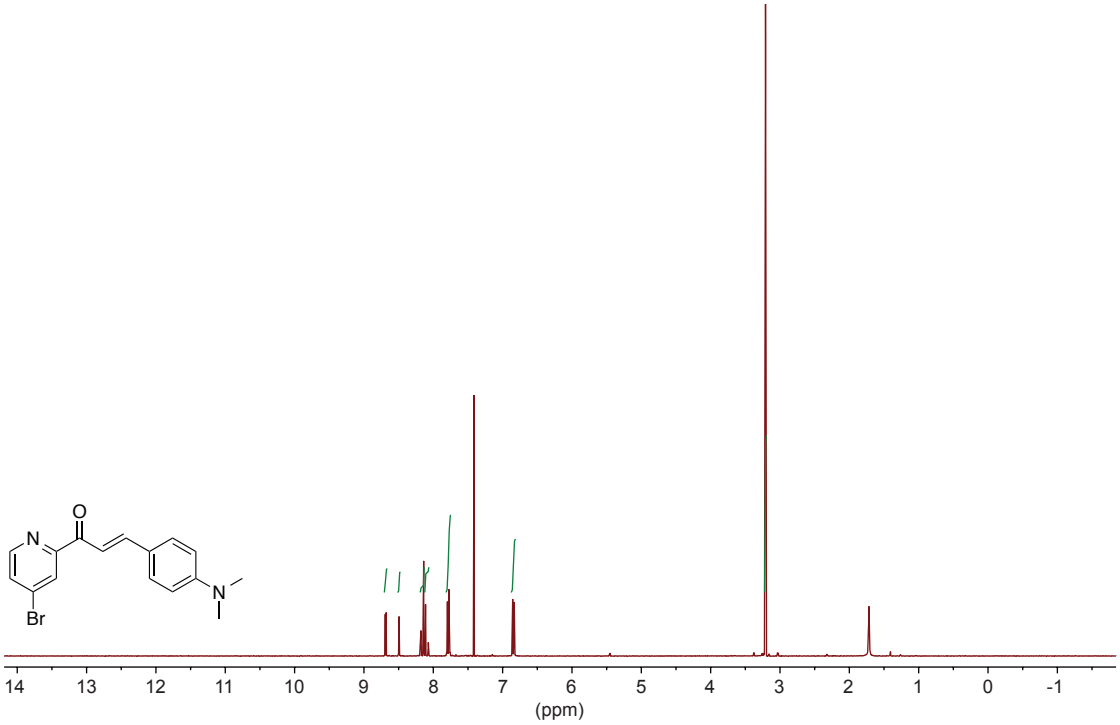

Fig. S24: ^{1}H NMR spectrum for compound **3h**.

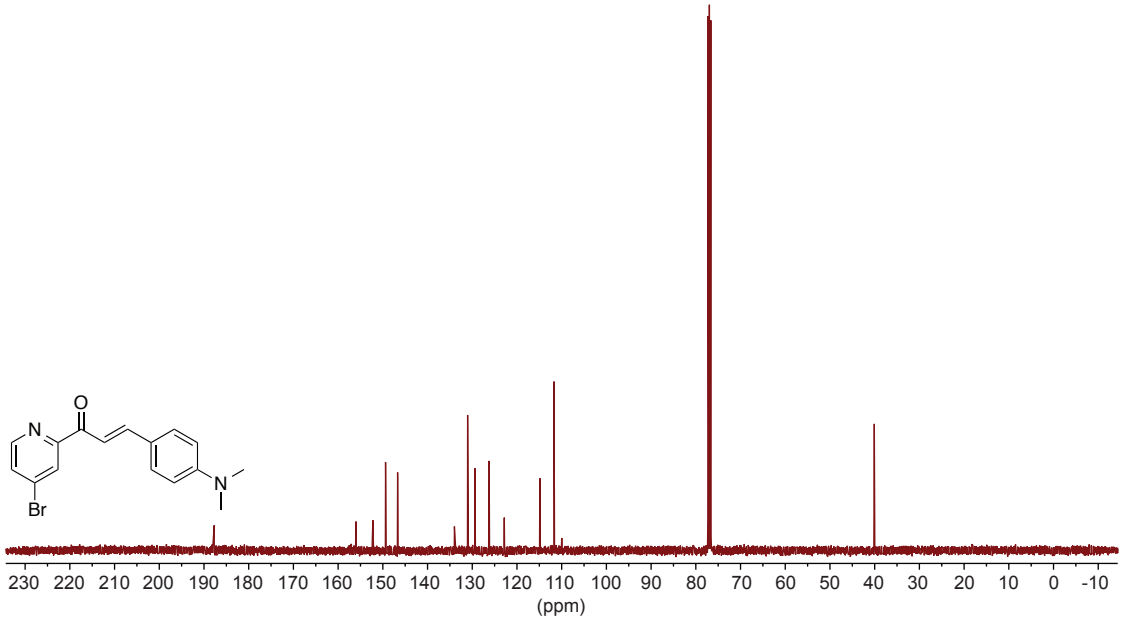

Fig. S25: ^{13}C NMR spectrum for compound **3h**.

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City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone (859) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# / CC# 29935

Element	Theory	Found	
C	58.02	57.50	57.37
H	4.57	4.64	4.55
Br	24.12	23.69	
N	8.46	8.26	8.27
O	4.83	NO CHARGE FOR DUPLICATES	

Single ☒ Duplicate ☐
Elements Present: C, H, N, O, Br
Analyze for: C, H, N, Br
Hygroscopic ☒ Explosive ☐
M.P. ____ B.P. ____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. Yes Time 3-4 h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Fig. S26: Elemental analysis for compound **3h**.

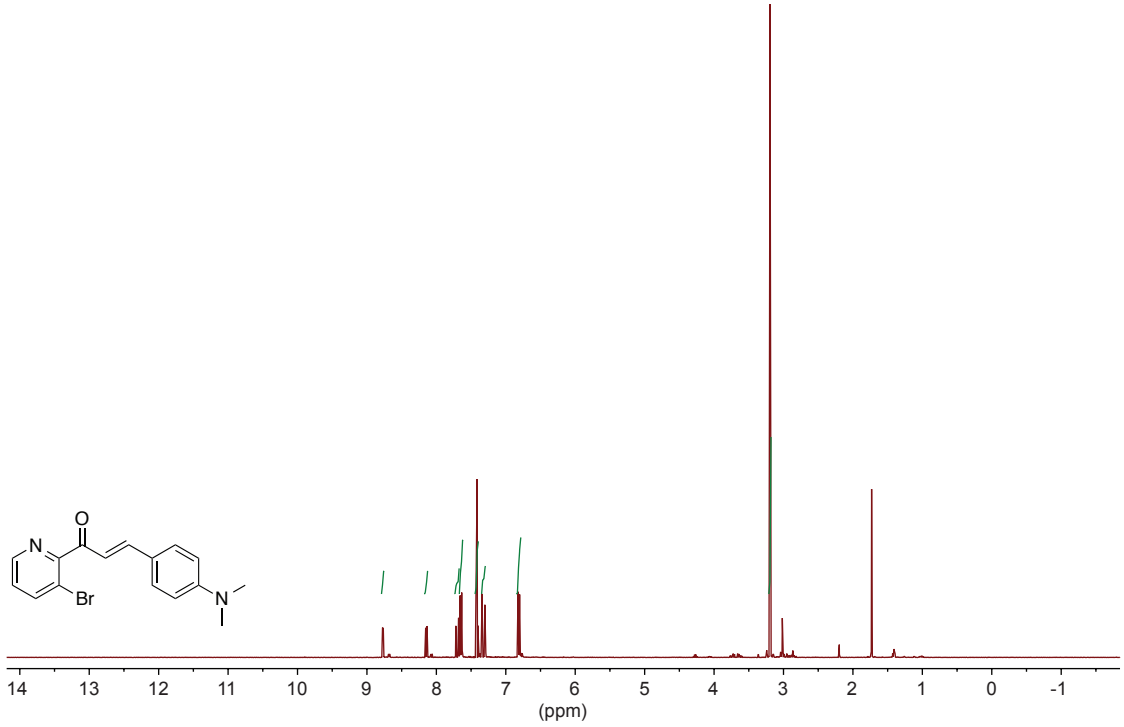

Fig. S27: ^{1}H NMR spectrum for compound **3i**.

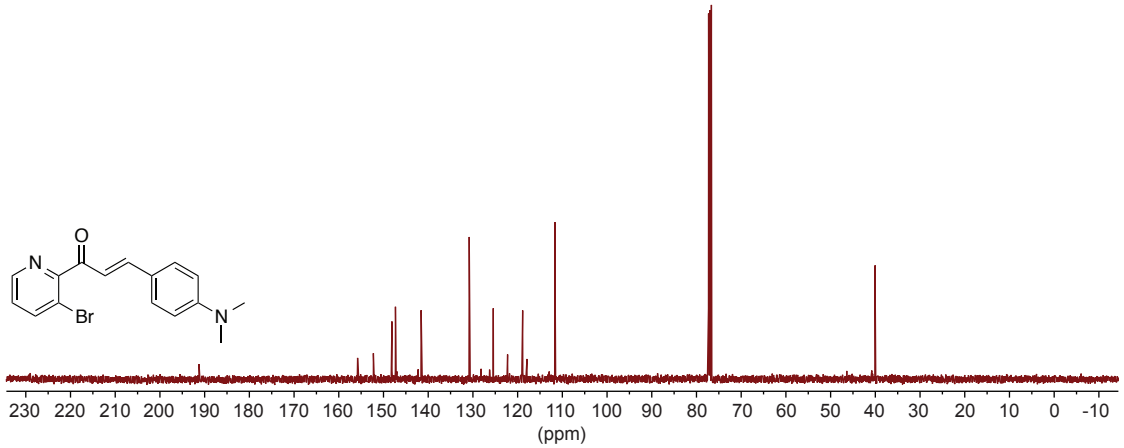

Fig. S28: ^{13}C NMR spectrum for compound **3i**.

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City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone (859) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO#/ CC# 29935

Element	Theory	Found	
C	58.02	58.02	
H	4.57	4.63	
Br	24.12	24.28	
N	8.46	8.43	
O	4.83		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O, Br
Analyze for: C, H, N, Br
Hygroscopic ☒ Explosive ☐
M.P. _____ B.P. _____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. ✓ yes Time 3-4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Fig. S29: Elemental analysis for compound **3i**.

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Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone 859 323 1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO#/ CC# 29935

Element	Theory	Found	
C	76.38	76.20	
H	6.41	6.42	
N	5.24	5.24	
O	11.97		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C, H, N
Hygroscopic ☒ Explosive ☐
M.P. _____ B.P. _____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. ✓ yes Time 3-4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Fig. S30: Elemental analysis for compound **6a**.

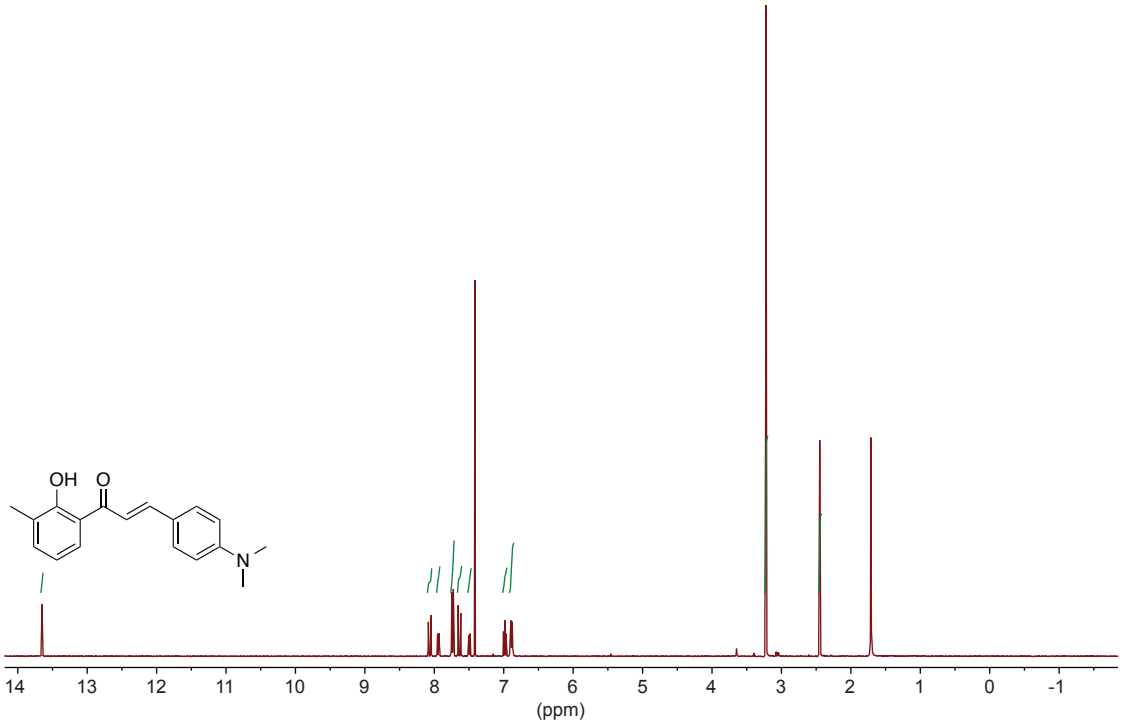

Fig. S31: ^{1}H NMR spectrum for compound **6b**.

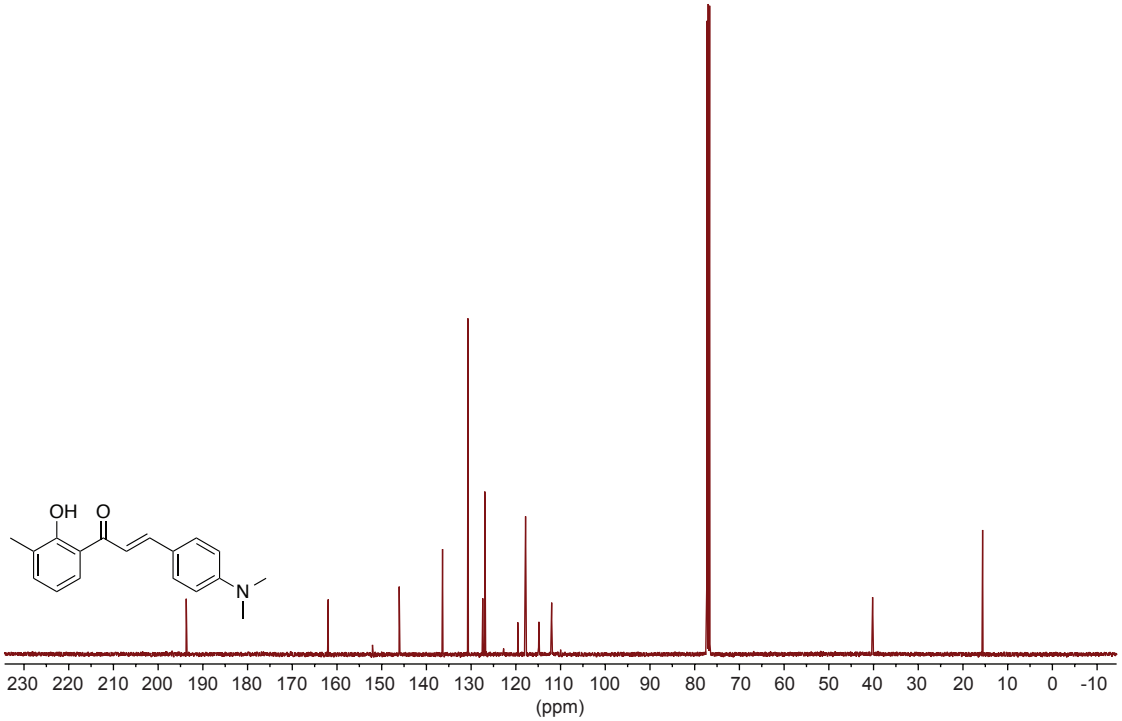

Fig. S32: ^{13}C NMR spectrum for compound **6b**.

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Dept. Pharmaceutical Sciences
Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso
Phone (859) 323-1945
Date 06/16/2015

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# / CC# 29935

Element	Theory	Found	
C	76.84	76.79	
H	6.81	6.76	
N	4.98	5.01	
O	11.37		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C, H, N
Hygroscopic ☒ Explosive ☐
M.P. _____ B.P. _____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. √ yes Time 3-4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Fig. S33: Elemental analysis for compound **6b**.

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City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso
Phone (859) 323-1945
Date 06/16/2015

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# / CC# 29935

Element	Theory	Found	
C	76.84	76.33	76.18
H	6.81	6.74	6.86
N	4.98	4.94	4.93
O	11.37	NO CHARGE FOR DUPLICATES	

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C, H, N
Hygroscopic ☒ Explosive ☐
M.P. _____ B.P. _____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. √ yes Time 3-4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Fig. S34: Elemental analysis for compound **6c**.

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City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone (859) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# CC# 29935

Element	Theory	Found	
C	76.84	76.83	
H	6.81	6.93	
N	4.98	5.00	
O	11.37		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C H, N
Hygroscopic ☒ Explosive ☐
M.P. ____ B.P. ____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. ✓ yes Time 3-4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Fig. S35: Elemental analysis for compound **6d**.

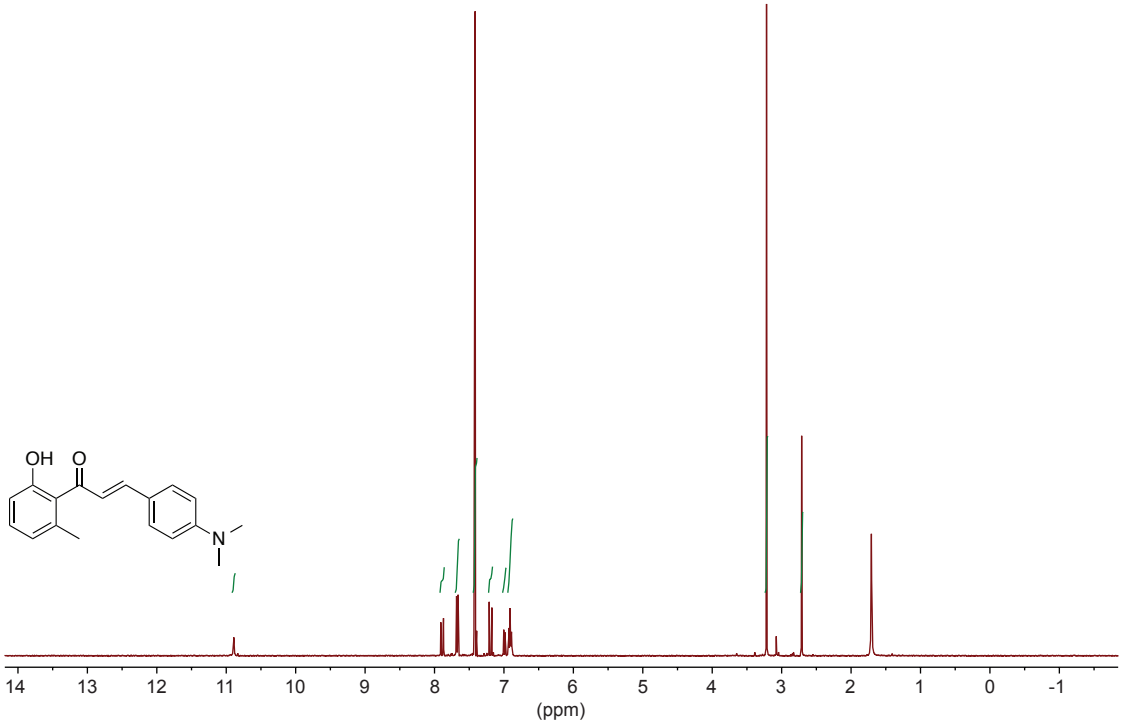

Fig. S36: ^{1}H NMR spectrum for compound **6e**.

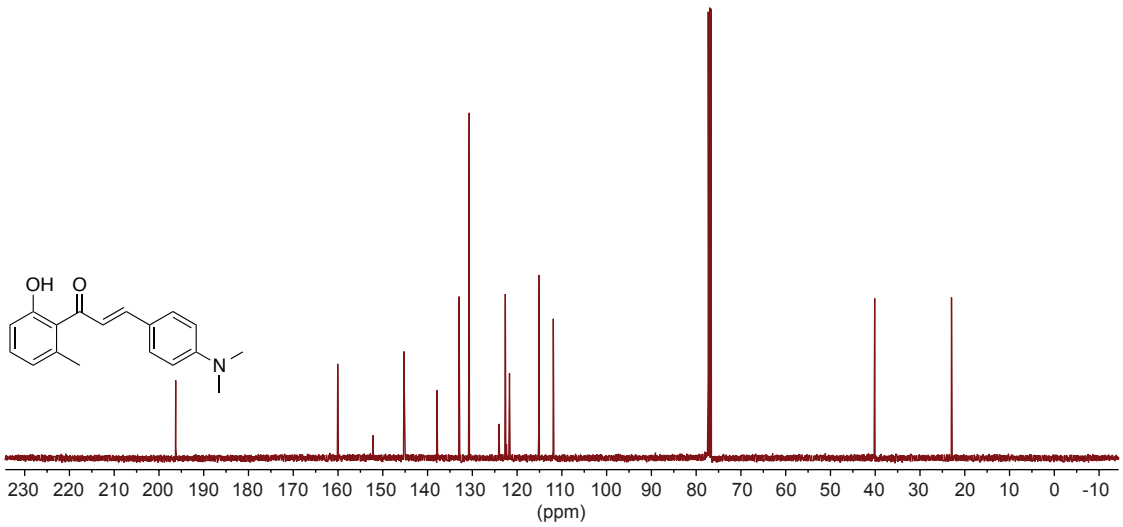

Fig. S37: ^{13}C NMR spectrum for compound **6e**.

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City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone (859) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# / CC# 29935

Element	Theory	Found	
C	76.84	76.57	
H	6.81	6.79	
N	4.98	5.02	
O	11.37		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C, H, N
Hygroscopic ☒ Explosive ☐
M.P. _____ B.P. _____
To be dried: Yes ☒ No ☐
Temp. 25°c Vac. High Time 3-4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Remarks:

Fig. S38: Elemental analysis for compound **6e**.

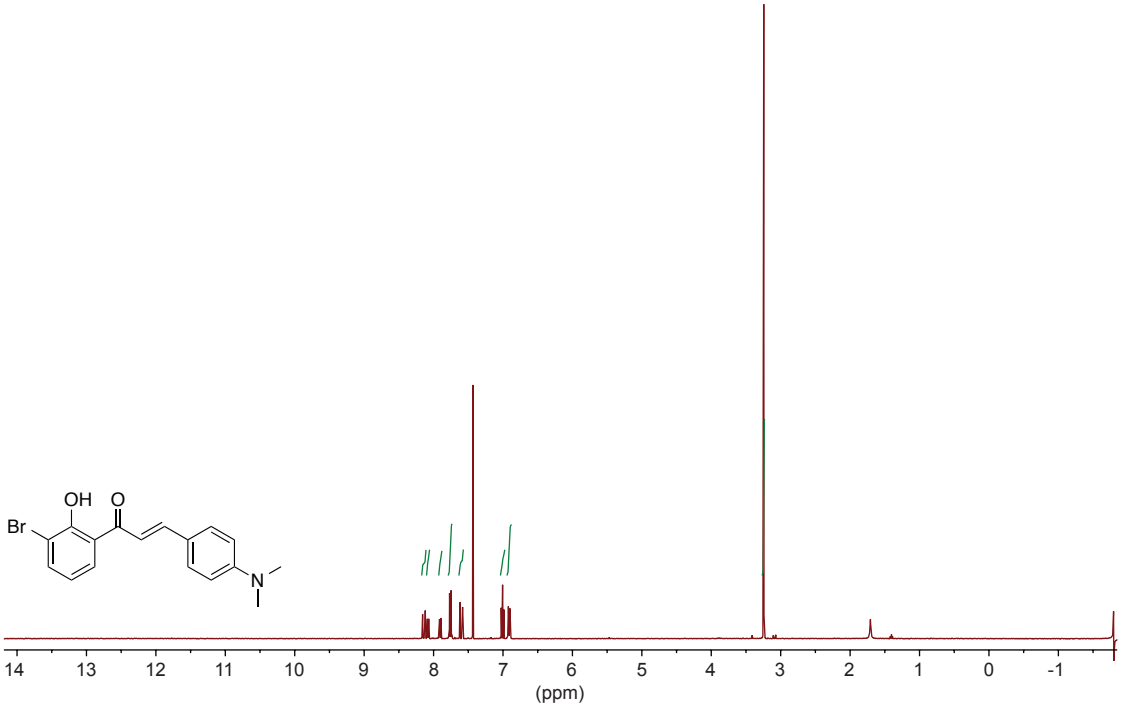

Fig. S39: ^{1}H NMR spectrum for compound **6f**.

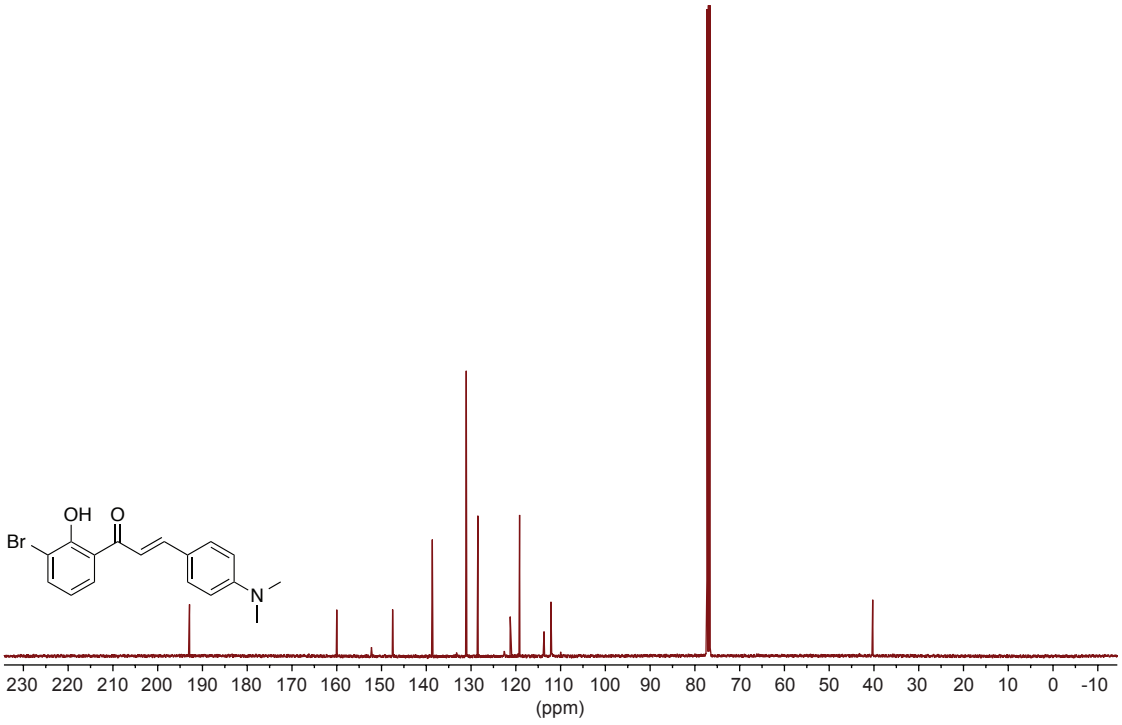

Fig. S40: ^{13}C NMR spectrum for compound **6f**.

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City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone (859) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# / CC# 29935

Element	Theory	Found	
C	58.98	58.90	
H	4.66	4.72	
Br	23.08	22.91	
N	4.05	3.95	
O	9.24		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O, Br
Analyze for: C, H, N, Br
Hygroscopic ☒ Explosive ☐
M.P. _____ B.P. _____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. Yes Time 3-4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Remarks:

Fig. S41: Elemental analysis for compound **6f**.

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Dept. Pharmaceutical Sciences
Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone (858) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# / CC# 29935

Element	Theory	Found	
C	58.98	59.06	
H	4.66	4.73	
Br	23.08	22.96	
N	4.05	4.10	
O	9.24		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O, Br
Analyze for: C, H, N, Br
Hygroscopic ☒ Explosive ☐
M.P. _____ B.P. _____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. Yes Time 3-4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Remarks:

Fig. S42: Elemental analysis for compound **6g**.

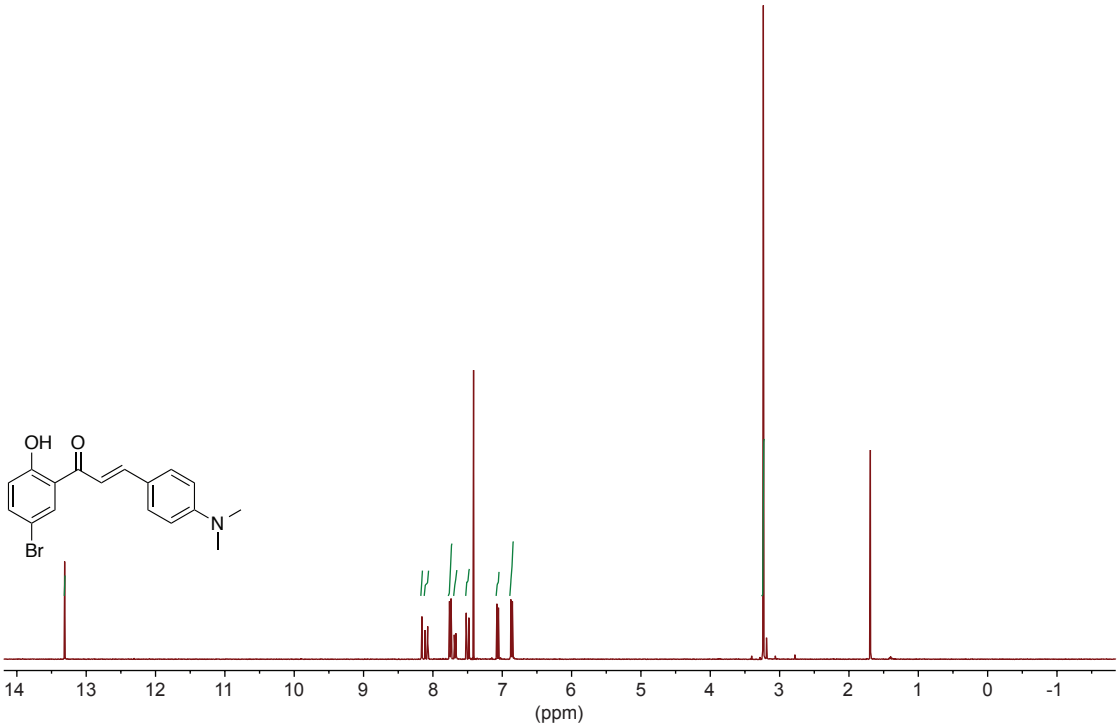

Fig. S43: ^{1}H NMR spectrum for compound **6h**.

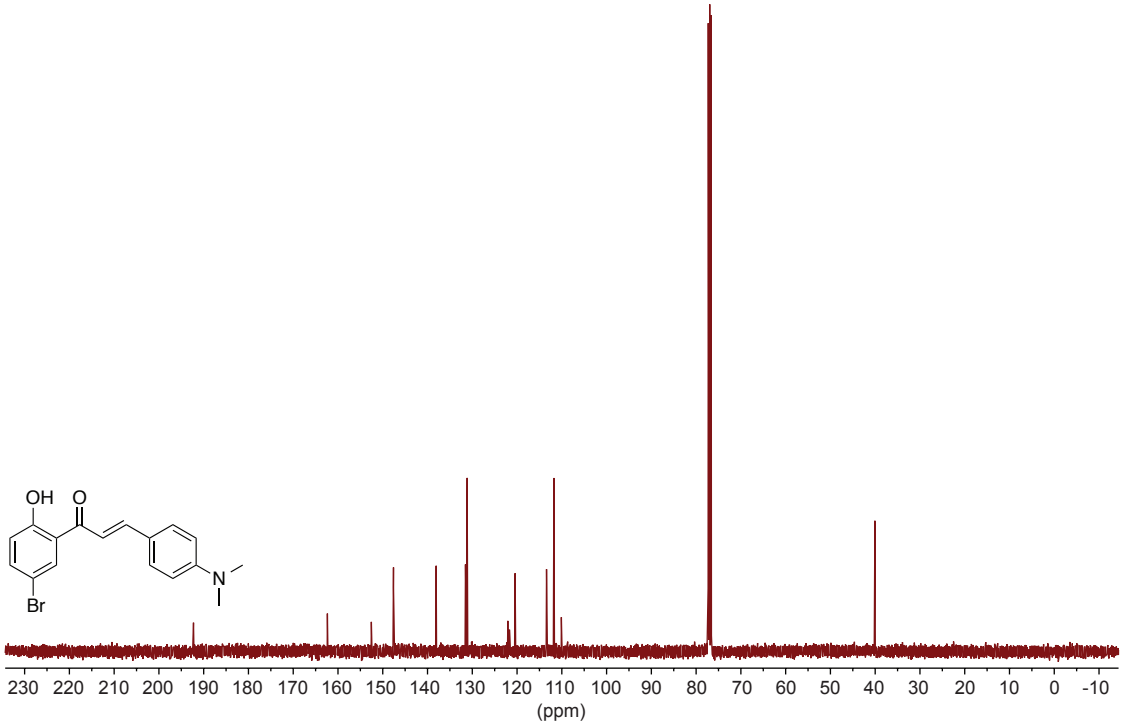

Fig. S44: ^{13}C NMR spectrum for compound **6h**.

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Company/School University of Kentucky
Dept. Pharmaceutical Sciences
Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso
Phone (859) 323-1935
Date 06/16/2015

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# / CC# 29935

Element	Theory	Found	
C	58.98	58.32	58.37
H	4.66	4.68	4.58
Br	23.08	23.15	
N	4.05	3.91	3.91
O	9.24	NO CHARGE FOR DUPLICATES	

Single ☒ Duplicate ☐
Elements Present: C, H, N, O, Br
Analyze for: C, H, N, Br
Hygroscopic ☒ Explosive ☐
M.P. ____ B.P. ____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. V485 Time 3-4 h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Fig. S45: Elemental analysis for compound **6h**.

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Company/School University of Kentucky
Dept. Pharmaceutical Sciences
Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso
Phone (859) 323-1945
Date 06/16/2015

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# / CC# 29935

Element	Theory	Found	
C	76.66	76.51	
H	6.81	6.78	
N	10.52	10.47	
O	6.01		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C, H, N
Hygroscopic ☒ Explosive ☐
M.P. ____ B.P. ____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. V485 Time 3-4 h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Remarks:

Fig. S46: Elemental analysis for compound **7a**.

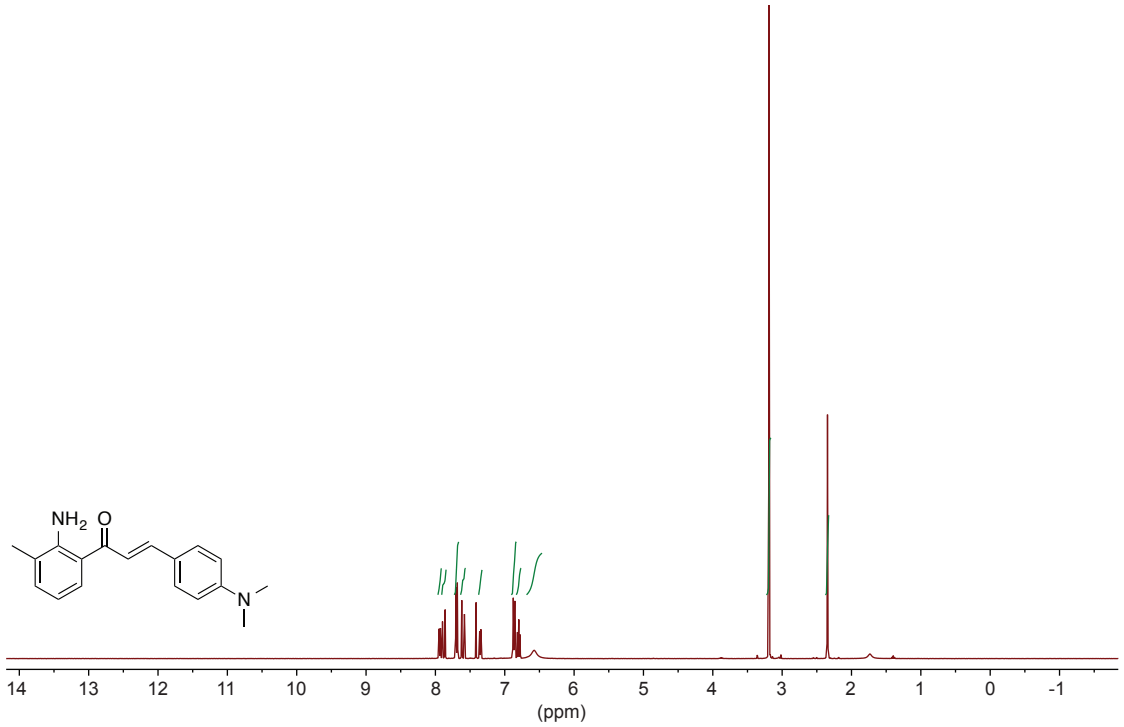

Fig. S47: ^{1}H NMR spectrum for compound **7b**.

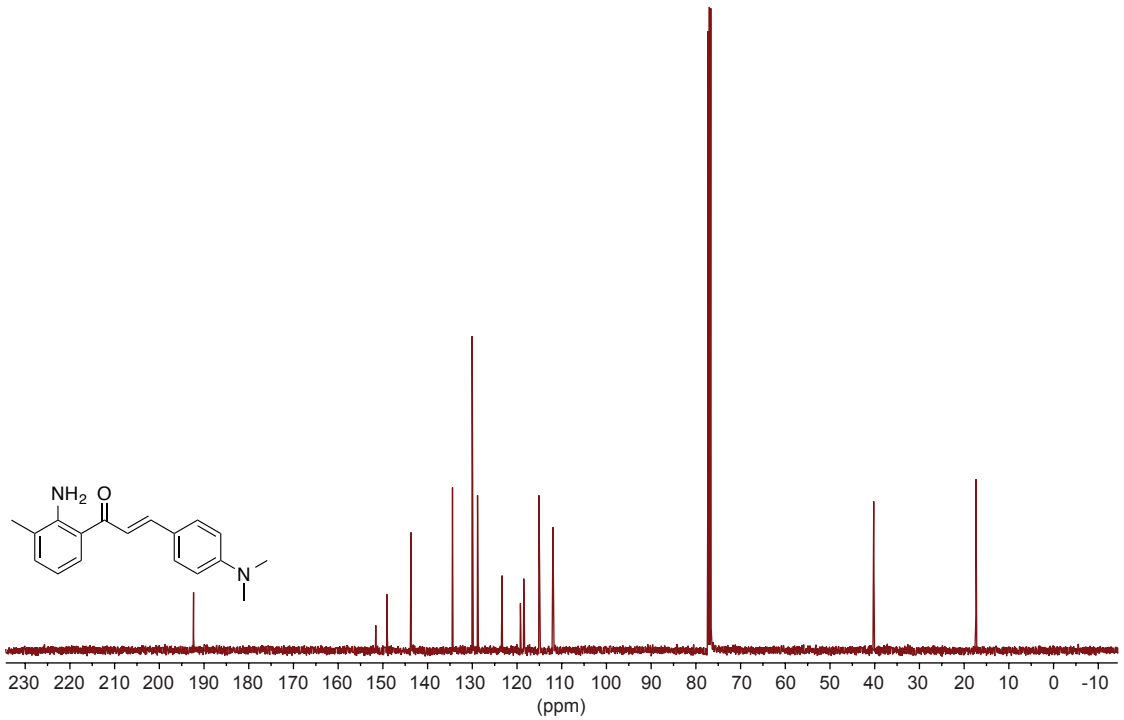

Fig. S48: ^{13}C NMR spectrum for compound **7b**.

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Dept. Pharmaceutical Sciences
Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone (859) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# / CC# 29935

Element	Theory	Found	
C	77.11	77.11	
H	7.19	7.17	
N	9.99	10.08	
O	5.71		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O
Analyze for: C, H, N
Hygroscopic ☒ Explosive ☐
M.P. _____ B.P. _____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. Yes Time 3 4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Date Received JUN 19 2015 Date Completed JUN 22 2015
Remarks:

Fig. S49: Elemental analysis for compound **7b**.

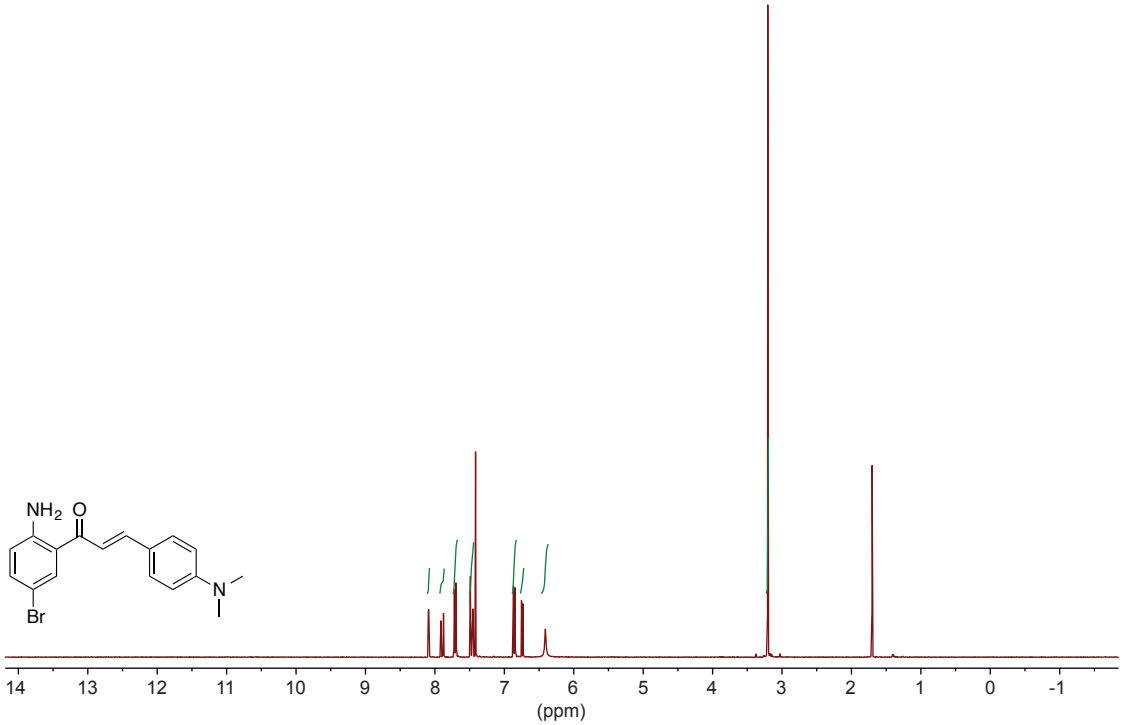

Fig. S50: ^{1}H NMR spectrum for compound **7h**.

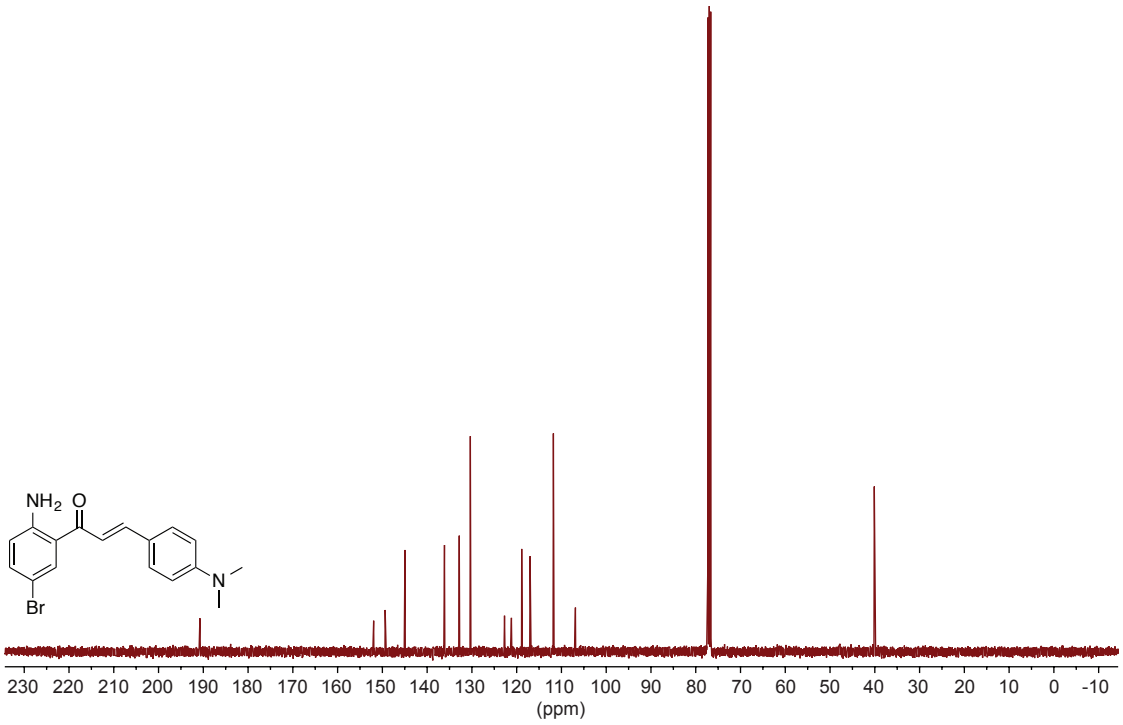

Fig. S51: ^{13}C NMR spectrum for compound **7h**.

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Norcross, GA 30071
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Company/School University of Kentucky
Dept. Pharmaceutical Sciences
Address 789 S. Limestone
City, State, Zip Lexington, KY 40536-0596
Name Marina Fosso Date 06/16/2015
Phone (859) 323-1945

Professor/Supervisor: Dr. Sylvie Garneau-Tsodikova
PO# / CC# 29935

Element	Theory	Found	
C	59.14	59.03	
H	4.96	5.04	
Br	23.14	23.27	
N	8.11	7.96	
O	4.63		

Single ☒ Duplicate ☐
Elements Present: C, H, N, O, Br
Analyze for: C, H, N, Br
Hygroscopic ☒ Explosive ☐
M.P. ____ B.P. ____
To be dried: Yes ☒ No ☐
Temp. 25°C Vac. ✓ Yes Time 3-4h
Rush Service ☐ Rush service guarantees analyses will be completed and results available by 5 PM EST on the day the sample is received by 11 AM.
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Remarks:

Fig. S52: Elemental analysis for compound **7h**.

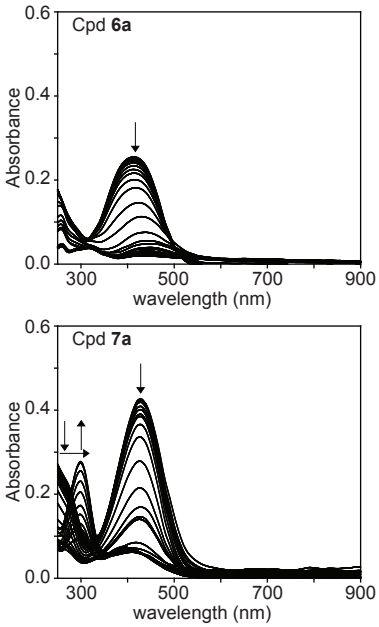

Fig. S53: UV-visible variable-pH spectra (left) and solution speciation diagrams (right) of **6a** and **7a** in the presence of $CuCl_2$. 20 μM of the chalcone (S: **6a** or **7a**) was incubated for 30 minutes with $CuCl_2$ ($[Cu^{2+}]/[S] = 1/2$). Titrations were then performed at room temperature from pH 12-2. There were no differences between the curves obtained in the absence and presence of $CuCl_2$, suggesting that these chalcones (**6a** and **7a**) do not bind Cu^{2+}.

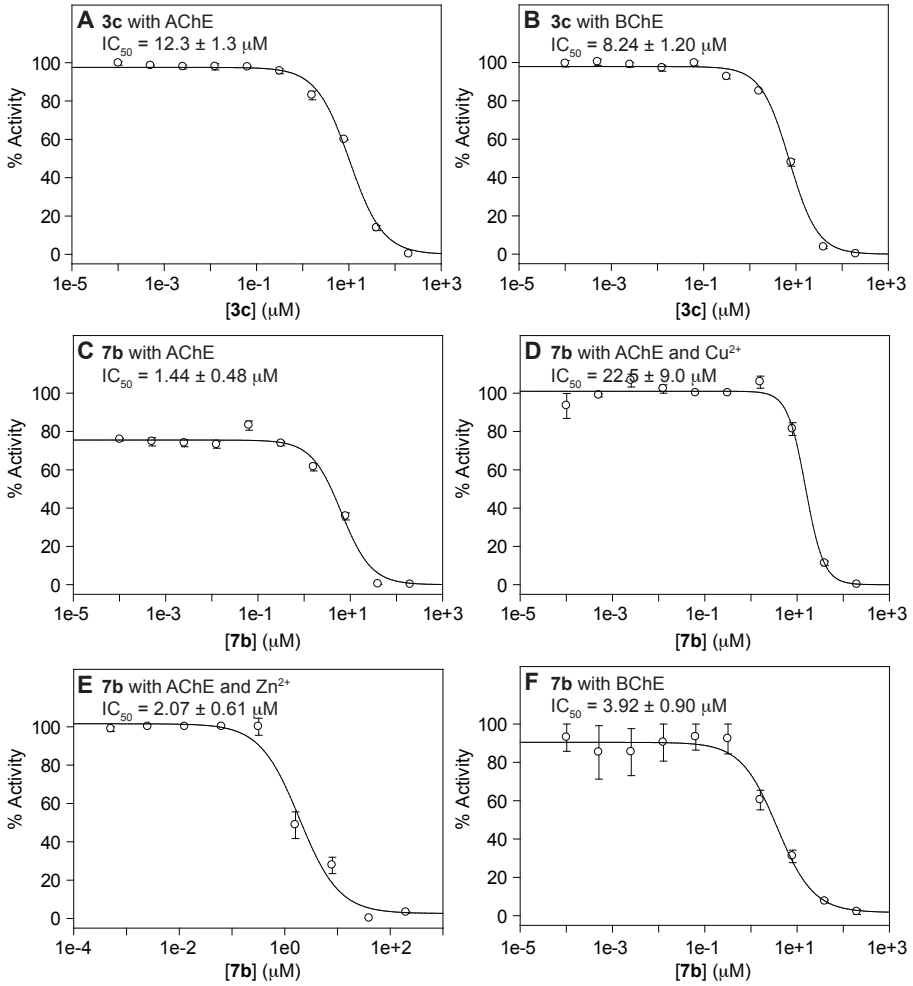

Fig. S54: Representative IC_{50} curves for compounds **3c** and **7b** with AChE and BChE in the absence of presence of $CuCl_2$ or $ZnCl_2$.

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