



SYNTHESIS AND SPECTRAL STUDIES OF (2-(FURANYL)VINYL)-1-TETRALONE CHALCONES

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Abstract. Ten chalcones were synthesized by the crossed aldol condensation of substituted tetralones with furaldehydes. The products were purified by recrystallization in MeOH/H₂O or by column chromatography in hexane/ethyl acetate and characterized by ¹H NMR, ¹³C NMR, and HRMS. Evaluations of their biological activities are currently underway.

Keywords: chalcones, aldol condensation, tetralone, furan

Introduction: Chalcones (1,3-diaryl propenones) are a family of small molecules found in edible plants, many of which are used in traditional Chinese medicine. Chalcones have been further investigated for their wide range of biological activities, including anticancer, antibacterial, and anti-inflammatory properties.^{i-iv} Many chalcone analogs containing methoxy (-OCH₃) groups have demonstrated activity against a variety of cancer cell lines. For example, Flavokawain A (**1**, Figure 1), a naturally occurring chalcone produced by *Piper methysticum* (kava kava), has demonstrated anticancer activity against MCF-7 and MDA-MB231 breast cancers (IC₅₀ = 25, 17 μM).^v A synthetic tetralone-containing chalcone (E)-2-(2,4-dimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**2**, Figure 1) has also demonstrated anticancer activity against HCT116 colorectal carcinoma (IC₅₀ = 3.4 μM).^{vi} Most interestingly, (E)-2-(furan-2-ylmethylene)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**3**, Figure 1), which contains tetralone, furan, and methoxymoiety, has demonstrated a wide variety of biological activities, including anticancer against MCF-7 (IC₅₀ = 17 μM).^{vi-xi} Our research design is to combine the furan and tetralone moieties via a crossed-aldol condensation, to create a small library of novel heterocyclic chalcones (analogues of **3**), and to test these compounds for their biological activities.

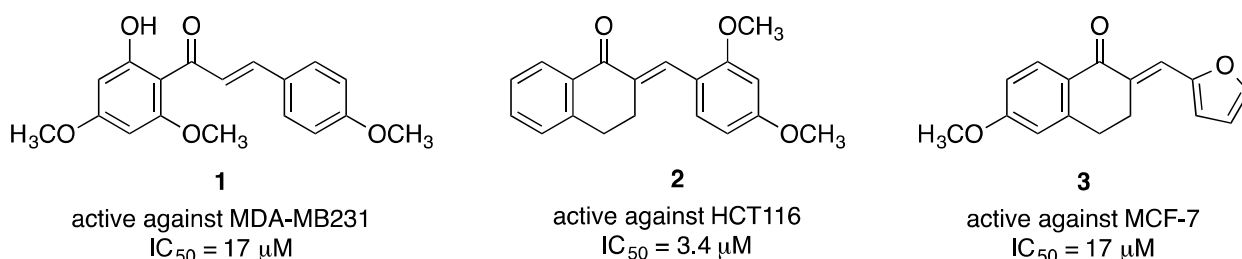
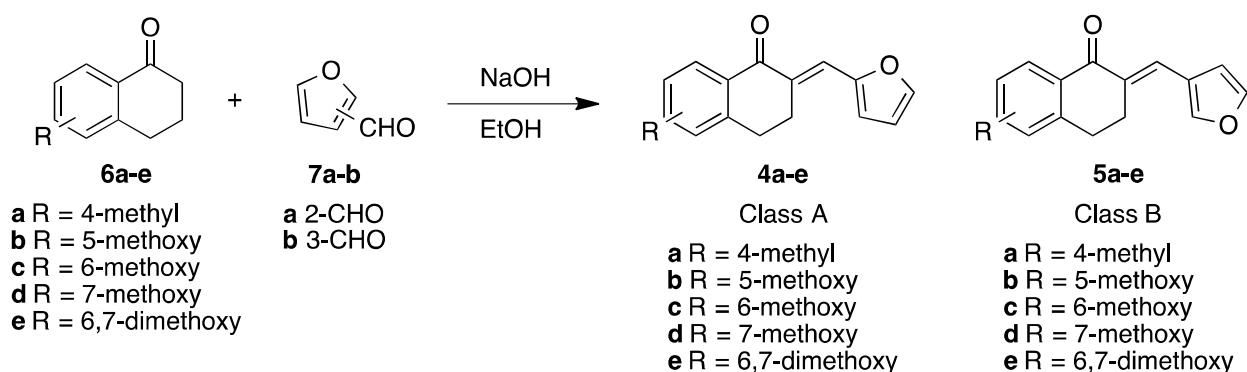


Figure 1. Chemical structures of chalcones with anticancer properties.

Results and Discussion: Ten chalcones, **4a-e**, **5a-e**, were synthesized in 1 step via the crossed-aldol condensation between tetralones **6a-e** and furaldehydes **7a-b** (Scheme 1). The products were divided into 2 classes: Class A, consisting of chalcones **4a-e**, derived from methyl- or methoxy-tetralones **6a-e** and 2-furaldehyde **7a**, and Class B, consisting of chalcones **5a-e**, derived from **6a-e** and 3-furaldehyde **7b**. The synthesis was accomplished quickly and easily by addition of tetralones **6a-e** and furaldehydes **7a-b** in ethanol with NaOH. The solid chalcones **4b-e** and **5b-e** were recrystallized from MeOH/H₂O and melting points were obtained. The 4-methyl tetralone derivatives **4a** and **5a** were isolated as oils and were thus purified by column chromatography. The purified 10 compounds were obtained in moderate to good yields (35-81%). While the synthesis of **4e** has been previously published, only its melting point was determined. We report here its full characterization.^{xii} The structures of all the final products were confirmed by ¹H NMR, ¹³C NMR, and high-resolution mass spectrometry (HRMS). In the ¹H NMR of the final products **4a-e** and **5a-e**, the appearance of the distinctive signal of the β-H of the α-β unsaturated ketone (a singlet around 7.5-7.6 ppm), the disappearance of the signal of the α-CH₂ of tetralone (a triplet around 2-3 ppm in the starting material), and the change in splitting pattern of the signal of the β-CH₂ of tetralone to a triplet (a quintet in the starting material) indicated the successful completion of the reaction. Typically, confirmation of E/Z configuration of the double bond of an α-β unsaturated ketone is determined by the *J* value of the doublet for the α and β-Hydrogens (*J* ≈ 15 Hz for E or 12 Hz for Z).^{xiii} However, tetralone chalcones have no α-H's, so the β-H is a singlet. The chemical shift of the β-H can be used to indicate E/Z configuration; the β-H of the E configuration is more deshielded and thus gives a signal downfield from than that of the Z configuration.^{xiv} As the chemical shift of the β-H of **3** was previously reported as 7.4 ppm, and the chemical shifts of all β-H's of the tetralone chalcones **4a-e** and **5a-e** are in the 7.5-7.6 ppm range, it can be concluded that the products are the E isomers. Additionally, the upfield ¹³C chemical shift of the carbonyl carbons (186-187 ppm) indicated carbonyl conjugation, also verifying the completion of the aldol condensation. All of the HRMS results were within 3 ppm of the expected masses, thus confirming the correct chemical composition (see SI).



Scheme 1. Synthesis of chalcones **4a-e** and **5a-e**.

Experimental: All commercial chemicals were reagent grade, obtained from Fisher Chemical, and used without further purification. ¹H and ¹³C spectra were obtained on a JEOL 300 NMR spectrometer at 300 and 75 MHz, respectively, in deuterated solvent with TMS ($\delta = 0.00$ ppm) or deuterated solvent as internal reference. For all reactions, analytical grade solvent was used. Silica gel was obtained from Sorbent Technologies. High-resolution mass

spectra were obtained by the Mass Spectrometry Facilities at Georgia State University on a Waters Micromass Q-ToF (ESI). Melting point was performed on MEL-TEMP II.

General procedure for aldol condensation

The furaldehyde (1 mmol) and the tetralone (1 mmol) were dissolved in ethanol (5 mL). ANaOH solution (5M, 1 mL) was added and the reaction was stirred until precipitate formed (typically within 20 minutes). If a precipitate formed, the reaction mixture was cooled in an ice bath for 20 minutes. The solids were filtered off and recrystallized from MeOH/H₂O. For chalcones **4a** and **5a**, no precipitate formed, so the crude reaction mixture was acidified with 1M HCl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄, and purified by flash column chromatography in 5:1 hexane/ethyl acetate.

(E)-2-(furan-2-ylmethylene)-4-methyl-3,4-dihydronaphthalen-1(2H)-one (4a): the chalcone was obtained in 37% yield as a brown oil; ¹H NMR (300 MHz, CDCl₃ with TMS): δ 8.10 (dd, 1H, *J* = 7.7, 1.0 Hz), 7.65 (s, 1H), 7.56 (d, 1H, *J* = 1.4 Hz), 7.51 (td, 1H, *J* = 7.6, 1.4 Hz), 7.35 (dd, 1H, *J* = 7.6, 1.0 Hz), 7.32-7.29 (m, 1H), 6.71 (d, 1H, *J* = 3.4 Hz), 6.51 (dd, 1H, *J* = 3.4, 1.7 Hz), 3.37-3.14 (m, 4H), 1.32 (d, 3H, *J* = 6.9 Hz) ppm; ¹³C{¹H} NMR (75 MHz, CDCl₃ with TMS): δ 187.5, 152.6, 148.7, 144.5, 133.4, 132.6, 130.6, 128.3, 127.0, 126.9, 124.0, 116.7, 112.3, 34.2, 32.9, 22.4 ppm; HRMS (ESI) *m/z* calculated for C₁₆H₁₅O₂ [(M+H)⁺] 239.1067, found 239.1060.

(E)-2-(furan-2-ylmethylene)-5-methoxy-3,4-dihydronaphthalen-1(2H)-one (4b): the chalcone was obtained in 71% yield as a grey-white solid; ¹H NMR (300 MHz, CDCl₃ with TMS): δ 7.73 (d, 1H, *J* = 8.1 Hz), 7.55 (s, 2H), 7.28 (t, 1H, *J* = 8.1 Hz), 7.01 (d, 1H, *J* = 7.8 Hz), 6.68 (d, 1H, *J* = 3.3 Hz), 6.50-6.49 (m, 1H), 3.85 (s, 3H), 3.27 (t, 2H, *J* = 6.3 Hz), 2.96 (t, 2H, *J* = 6.3 Hz) ppm; ¹³C{¹H} NMR (75 MHz, CDCl₃ with TMS): δ 187.6, 156.3, 152.6, 144.4, 134.6, 132.7, 131.9, 127.2, 122.7, 119.9, 116.5, 114.2, 112.3, 55.8, 26.2, 21.0 ppm; HRMS (ESI) *m/z* calculated for C₁₆H₁₅O₃ [(M+H)⁺] 255.1016, found 255.1008; mp 119-121°C.

(E)-2-(furan-2-ylmethylene)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (4c): the chalcone was obtained in 43% yield as an off-white solid; ¹H NMR (300 MHz, CDCl₃ with TMS): δ 8.08 (d, 1H, *J* = 8.4 Hz), 7.54 (s, 2H), 6.85 (d, 1H, *J* = 7.8 Hz), 6.71-6.66 (m, 2H), 6.50 (s, 1H), 3.85 (s, 1H), 3.30 (t, 2H, *J* = 6.0 Hz), 2.96 (t, 2H, *J* = 6.0 Hz) ppm; ¹³C{¹H} NMR (75 MHz, CDCl₃ with TMS): δ 186.2, 163.4, 152.6, 146.0, 144.1, 132.0, 130.6, 127.1, 122.2, 116.2, 113.2, 112.2, 112.1, 55.4, 28.7, 26.8 ppm; HRMS (ESI) *m/z* calculated for C₁₆H₁₅O₃ [(M+H)⁺] 255.1016, found 255.1010; mp 102°C.

(E)-2-(furan-2-ylmethylene)-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (4d): the chalcone was obtained in 73% yield as an off-white solid; ¹H NMR (300 MHz, CDCl₃ with TMS): δ 7.61-7.57 (m, 3H), 7.18 (d, 1H, *J* = 8.4 Hz), 7.07 (dd, 1H, *J* = 8.4, 2.7 Hz), 6.71 (d, 1H, *J* = 3.6 Hz), 6.52 (dd, 1H, *J* = 3.3, 1.5 Hz), 3.87 (s, 3H), 3.31 (t, 2H, *J* = 6.0 Hz), 2.95 (t, 2H, *J* = 6.0 Hz) ppm; ¹³C{¹H} NMR (75 MHz, CDCl₃ with TMS): δ 187.4, 158.7, 152.6, 144.4, 136.3, 134.4, 131.9, 129.5, 123.0, 121.4, 116.7, 112.3, 110.3, 55.6, 27.6, 27.0 ppm; HRMS (ESI) *m/z* calculated for C₁₆H₁₅O₃ [(M+H)⁺] 255.1016, found 255.1009; mp 85-87°C.

(E)-2-(furan-2-ylmethylene)-6,7-dimethoxy-3,4-dihydronaphthalen-1(2H)-one (4e): the chalcone was obtained in 62% yield as a pale yellow solid; ¹H NMR (300 MHz, CDCl₃ with

TMS): δ 7.61 (s, 1H), 7.55 (s, 2H), 7.70 (s, 1H), 6.69 (d, 2H, $J = 4.5$ Hz), 6.52 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.34 (t, 2H, $J = 6.3$ Hz), 2.96 (t, 2H, $J = 6.6$ Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 with TMS): δ 186.2, 153.3, 152.6, 148.1, 144.1, 138.5, 131.8, 126.6, 122.2, 116.2, 112.1, 109.9, 109.6, 56.1, 28.1, 27.0; HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{17}\text{O}_4$ $[(\text{M}+\text{H})^+]$ 285.1121, found 285.1115; mp 146-150°C.

(E)-2-(furan-3-ylmethylene)-4-methyl-3,4-dihydronaphthalen-1(2H)-one (5a): the chalcone was obtained in 35% yield as a brown oil; ^1H NMR (300 MHz, CDCl_3 with TMS): δ 8.10 (dd, 1H, $J = 8.1, 1.5$ Hz), 7.73 (d, 2H, $J = 5.4$ Hz), 7.50 (td, 1H, $J = 7.5, 1.5$ Hz), 7.34 (td, 1H, $J = 7.5, 1.2$ Hz), 7.29 (d, 1H, $J = 7.5$), 6.66 (d, 1H, $J = 1.2$ Hz), 3.17-2.97 (m, 4H), 1.29 (d, 3H, $J = 7.2$ Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 with TMS): δ 187.2, 158.5, 152.4, 144.3, 136.2, 134.3, 131.8, 129.3, 122.8, 121.2, 116.5, 112.2, 110.2, 55.5, 27.5, 26.8 ppm; HRMS (ESI) m/z calculated for $\text{C}_{16}\text{H}_{15}\text{O}_2$ $[(\text{M}+\text{H})^+]$ 239.1067, found 239.1061.

(E)-2-(furan-3-ylmethylene)-5-methoxy-3,4-dihydronaphthalen-1(2H)-one (5b): the chalcone was obtained in 57% yield as an off-white solid; ^1H NMR (300 MHz, CDCl_3 with TMS): δ 7.74 (s, 1H), 7.68 (s, 1H), 7.60 (d, 1H, $J = 2.7$ Hz), 7.49 (t, 1H, $J = 1.5$ Hz), 7.18 (d, 1H, $J = 8.1$ Hz), 7.07 (dd, 1H, $J = 8.7, 3.0$ Hz), 6.66 (d, 1H, $J = 1.5$ Hz), 3.87 (s, 3H), 3.06 (t, 2H, $J = 6.9$ Hz), 3.05 (t, 2H, $J = 5.1$ Hz), 2.95 (t, 2H, $J = 6.3$ Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 with TMS): δ 187.2, 158.7, 144.9, 143.7, 135.9, 134.5, 133.8, 129.5, 127.1, 122.1, 121.4, 110.9, 110.4, 55.6, 27.5, 27.3 ppm; HRMS (ESI) m/z calculated for $\text{C}_{16}\text{H}_{15}\text{O}_3$ $[(\text{M}+\text{H})^+]$ 255.1016, found 255.1009; mp 98-99°C.

(E)-2-(furan-3-ylmethylene)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (5c): the chalcone was obtained in 81% yield as a light brown solid; ^1H NMR (300 MHz, CDCl_3 with TMS): δ 8.08 (d, 1H, $J = 9.0$ Hz), 7.71 (s, 1H), 7.64 (s, 1H), 7.48 (s, 1H), 6.87 (dd, 1H, $J = 8.4, 2.4$ Hz), 6.71 (d, 1H, $J = 2.1$ Hz), 6.64 (s, 1H), 3.87 (s, 3H), 3.06 (t, 2H, $J = 7.2$ Hz), 2.95 (t, 2H, $J = 7.2$ Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 with TMS): δ 186.1, 163.5, 145.6, 144.6, 143.6, 133.8, 130.7, 127.1, 126.3, 122.0, 113.3, 112.3, 110.9, 55.5, 28.7, 27.1 ppm; HRMS (ESI) m/z calculated for $\text{C}_{16}\text{H}_{15}\text{O}_3$ $[(\text{M}+\text{H})^+]$ 255.1016, found 255.1009; mp 100°C.

(E)-2-(furan-3-ylmethylene)-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (5d): the chalcone was obtained in 44% yield as an off-white solid; ^1H NMR (300 MHz, CDCl_3 with TMS): δ 7.71 (s, 1H), 7.66 (s, 1H), 7.58 (d, 1H, $J = 2.7$ Hz), 7.47 (t, 1H, $J = 1.2$ Hz), 7.14 (d, 1H, $J = 8.7$ Hz), 7.04 (dd, 1H, $J = 8.2, 2.7$ Hz), 6.64 (d, 1H, $J = 1.2$ Hz), 3.83 (s, 3H), 3.03 (t, 2H, $J = 6.6$ Hz), 2.891 (t, 2H, $J = 6.6$ Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 with TMS): δ 187.1, 158.6, 144.8, 143.7, 135.8, 134.3, 133.7, 129.4, 127.0, 122.0, 121.3, 110.8, 110.3, 55.5, 27.4, 27.2 ppm; HRMS (ESI) m/z calculated for $\text{C}_{16}\text{H}_{15}\text{O}_3$ $[(\text{M}+\text{H})^+]$ 255.1016, found 255.1009; mp 99-101°C.

(E)-2-(furan-3-ylmethylene)-6,7-dimethoxy-3,4-dihydronaphthalen-1(2H)-one (5e): the chalcone was obtained in 62% yield as an off-white solid; ^1H NMR (300 MHz, CDCl_3 with TMS): δ 7.72 (s, 1H), 7.64 (s, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 6.69 (s, 1H), 6.66 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.08 (t, 2H, $J = 6.9$ Hz), 2.94 (t, 2H, $J = 6.6$ Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 with TMS): δ 186.1, 153.4, 148.3, 144.5, 143.6, 138.1, 133.7, 126.7, 126.3, 122.0, 110.9, 109.9, 109.6, 56.1, 28.1, 27.4 ppm; HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{17}\text{O}_4$ $[(\text{M}+\text{H})^+]$ 285.1121, found 285.1116; mp 145-147°C.

Conclusions: In conclusion, 10 heterocyclic chalcones containing the tetralone and furan moieties were synthesized via the crossed aldol condensation. The relative quickness of the reaction, ease of purification, and moderate to good yields highlighted the utility of the crossed aldol condensation and allowed for fairly rapid synthesis of a library of compounds. Biological evaluations of these compounds are currently underway.

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