Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(21):40-47
(http://www.derpharmachemica.com/archive.html)

Design and Synthesis of (2-(furanyl)vinyl)-1-tetralone Chalcones as Anticancer Agents

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ABSTRACT

Ten chalcones (1a-e and 2a-e) were synthesized by the Claisen-Schmidt reaction. These compounds were submitted to PASS online for determination of likely biological activities and further QSAR analysis. These chalcones were predicted to have anticancer activity, specifically as inducers of apoptosis.

Keywords: Cancer, Disease, Chemotherapy, Radiation therapy

INTRODUCTION

Every year, 14 million people are diagnosed with cancer and 8 million die from the disease worldwide [1]. Despite advances in cancer research, some of the most prevalent anticancer therapeutics, including chemotherapy and radiation therapy, kill both cancerous cells and healthy tissues. Thus, much of current cancer research investigates targeted chemotherapeutics, including those that selectively induce apoptosis in cancerous cells [2]. There are two main strategies to increase apoptosis: 1) Inhibit the activity of anti-apoptotic proteins, or 2) Enhance the activity of pro-apoptotic proteins [3].

There are a variety of anti-apoptotic proteins, including the BCL-2 family proteins BCL-2, BCL-XL, and MCL-1. While effective BCL-2 inhibitors, such as ABT-737 and ABT-199, have been developed and are in clinical trials, MCL-1 inhibitors have only recently been explored [4-6]. MCL-1 is an especially attractive target as it plays a role in drug resistance and certain cancers are known to be MCL-1 dependent [7-9]. Recently, the first molecules that have potency to kill MCL-1 dependent cancer cell lines (H929, H2110, H23) *in vivo* have been reported [7]. In addition, Pin1, an enzyme that stabilizes MCL-1, is implicated in MCL-1-mediated chemoresistance for breast cancer. Knocking down Pin1 has successfully removed MCL-1-mediated chemoresistance, making it an attractive target for therapy [10]. Inhibition of other anti-apoptotic proteins, such as HSP27 and HSP70, has reduced the size of tumors in human breast cancers [11]. Additional selective cancer therapeutics, including antineoplastic drugs sulindac sulfide and solfone, inhibit cancer cell growth (human colon carcinoma) through apoptosis [12]. Thiol protease inhibitors are another class of molecules of interest, as increased expression of thiol proteases leads to cancer progression and worse outcomes for patients [13]. Although apoptosis is induced through both extrinsic (death receptor-mediated) and intrinsic (mitochondrial) pathways, the caspase cascade is the final step in promoting apoptosis, with caspase 3 as the final executor [14]. Specifically, caspase 3 activation leads to apoptosis in human breast cancer cell line MDA-MB-468 [15].

Chalcones (1,3-diaryl propenones), a family of small molecules that are naturally abundant in edible plants, have been found to have antitumor properties for specific cancer cell lines and to interfere in each step of carcinogenesis, including apoptosis [14,16] For example, isoliquiritigenin is a chalcone that induces apoptosis in human hepatoma cells [17] and licochalcone is another chalcone that increases BAX and BAK levels and decreases levels of BCL-2 and BCL-X(L) [18]. While many chalcones and chalcone analogues have been synthesized, those containing methoxy (-OCH_3) moieties have specifically demonstrated anticancer activity [19,20]. Our goal is to synthesize novel furanyl-tetralone chalcones that contain methoxy groups and further explore their potential antitumor activities via PASS online, a freely accessible web application that predicts small molecules' probability of having biological activity [21]. Use of virtual screening is advantageous in that it does not require the time or monetary investment of actual biological evaluations. It is also a useful beginning point for predicting possible activities that can later be validated *in vitro*. PASS has been successfully used to identify new small molecules' potential as pharmaceuticals [22-28].

MATERIALS AND METHODS

All commercial chemicals were obtained from Fisher Chemical and used without further purification. 1H and ^{13}C spectra were obtained on a JEOL 300 NMR spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$. For all reactions, analytical grade solvent was used. Silica gel was obtained from Sorbent Technologies. High-resolution mass spectra were obtained from Georgia State University's Mass Spectrometry Facilities on a Waters Micromass Q-Tof (ESI). Melting point was performed on a MEL-TEMP II device.

General procedure for Claisen-Schmidt condensation to synthesize 1a-2e

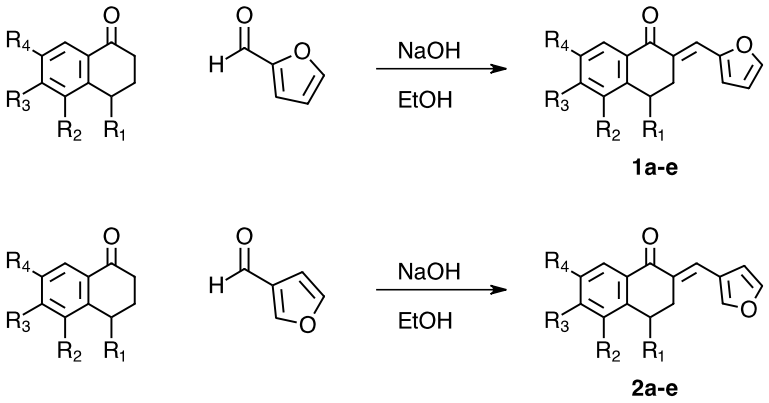
The substituted tetralone (1 mmol) and the furaldehyde (1 mmol) were dissolved in EtOH (5 mL). A NaOH solution (5 M, 1 mL) was added and the reaction stirred until a precipitate formed (Scheme 1). Once the precipitate formed, the reaction mixture was cooled in an ice bath. The solids were filtered off and recrystallized from MeOH/H2O or MeOH alone. For chalcones 1a and 2a, however, no precipitate formed. In those cases the reaction was acidified to pH_3 with 1M HCl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and purified by flash column chromatography in 5:1 hexane/ethyl acetate. A summary of the chalcones synthesized is found in Table 1.

(E)-2-(furan-2-ylmethylene)-4-methyl-3,4-dihydronaphthalen-1(2H)-one (1a)

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, 7.6, J=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; ^{13}C 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.

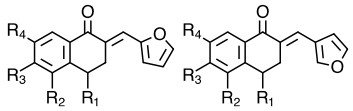
(E)-2-(furan-2-ylmethylene)-5-methoxy-3,4-dihydronaphthalen-1(2H)-one (1b)

The chalcone was obtained in 71% yield as a grey-white solid; 1H NMR (300 MHz, $CDCl_3$ 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; ^{13}C NMR (75 MHz, CDCl3 with TMS): δ 187.6, 156.3, 152.6, 144.4, 134.6, 132.7, 131.9,



Scheme 1: Synthesis of chalcones 1a-e and 2a-e through the Claisen-Schmidt condensation of substituted tetralones and furaldehydes

Table 1: Tetralone chalcones synthesized

Compounds				
				
	1a-e		**2a-e**	
	R_1	**R_2**	**R_3**	**R_4**
1a	CH_3	H	H	H
1b	H	OCH_3	H	H
1c	H	H	OCH_3	H
1d	H	H	H	OCH_3
1e	H	H	OCH_3	OCH_3
2a	CH_3	H	H	H
2b	H	OCH_3	H	H
2c	H	H	OCH_3	H
2d	H	H	H	OCH_3
2e	H	H	OCH_3	OCH_3

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 $C_{16}H_{15}O_3$ [(M+H)+] 255.1016, found 255.1008; mp 119-121˚C.

(E)-2-(furan-2-ylmethylene)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (1c)

The chalcone was obtained in 43% yield as an off-white solid; 1H NMR (300 MHz, $CDCl_3$ 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; ^{13}C NMR (75 MHz, $CDCl_3$ 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 $C_{16}H_{15}O_3$ [(M+H)+] 255.1016, found 255.1010; mp 102˚C.

(E)-2-(furan-2-ylmethylene)-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (1d)

The chalcone was obtained in 73% yield as an off-white solid; 1H NMR (300 MHz, $CDCl_3$ 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; ^{13}C NMR (75 MHz, $CDCl_3$ 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 $C_{16}H_{15}O_3$ [(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 (1e)

The chalcone was obtained in 62% yield as a pale yellow solid; 1H NMR (300 MHz, $CDCl_3$ 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}C 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 C17H17O4 [(M+H)+] 285.1121, found 285.1115; mp 146-150˚C.

(E)-2-(furan-3-ylmethylene)-4-methyl-3,4-dihydronaphthalen-1(2H)-one (2a)

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}C NMR (75 MHz, CDCl3 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 $C_{16}H_{15}O_2$ [(M+H)+] 239.1067, found 239.1061.

(E)-2-(furan-3-ylmethylene)-5-methoxy-3,4-dihydronaphthalen-1(2H)-one (2b)

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}C NMR (75 MHz, CDCl3 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 $C_{16}H_{15}O_3$ [(M+H)+] 255.1016, found 255.1009; mp 98-99˚C.

(E)-2-(furan-3-ylmethylene)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (2c)

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}C NMR (75 MHz, CDCl3 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 $C_{16}H_{15}O_3$ [(M+H)+] 255.1016, found 255.1009; mp 100˚C.

(E)-2-(furan-3-ylmethylene)-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (2d)

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}C 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 $C_{16}H_{15}O_3$ [(M+H)+] 255.1016, found 255.1009; mp 99-101˚C.

(E)-2-(furan-3-ylmethylene)-6,7-dimethoxy-3,4-dihydronaphthalen-1(2H)-one (2e)

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}C NMR (75 MHz, CDCl3 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 $C_{17}H_{17}O_4$ [(M+H)+] 285.1121, found 285.1116; mp 145-147˚C.

RESULTS AND DISCUSSION

Chemistry: Ten chalcones, 1a-e, 2a-e, were synthesized via the Claisen-Schmidt condensation with various substituted tetralones and furaldehydes (Scheme 1). The 10 compounds were obtained in moderate yields (35-81%). The structures of the products were confirmed by 1H NMR, ^{13}C NMR, and high-resolution mass spectrometry (HRMS). The structures were confirmed in the 1H NMR by the appearance of the distinctive signal of the β-H of the α-β unsaturated ketone (singlet ~7.5-7.6 ppm) concomitantly with the disappearance of the signal of the α-CH2 of tetralone (triplet ~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 (quintet in the starting material). Additionally, the upfield ^{13}C chemical shift of the carbonyl carbons (186-187 ppm) indicated carbonyl conjugation, also verifying the completion of the reaction. The experimental m/z obtained by HRMS were within the industry standard of 6 ppm of the calculated masses, thus confirming chemical composition.

In silico screening: The chalcones 1a-e and 2a-e were screened for 4000 different types of biological activities via PASS online. The results for the probabilities of being active (Pa) for various targets associated with cancer and apoptosis were examined (Table 2). Compounds with a Pa of >0.6 were considered to have a high probability of activity. The results were analyzed in four ways based on the chemical structures of the compounds: 1) 2-furan versus 3-furan; 2) type of substituents; 3) number of substituents; and 4) position of substituents.

Apoptosis Agonist, The first biological activity assessed was "apoptosis agonist," which predicts the compounds' general ability to increase apoptosis (Figure 1). All of the compounds had some predicted activity, but, in general the compounds 2a-e with the 3-furanyl moiety (Pa's of 0.572-0.628) had higher probability of being active than their 2-furanyl counterparts 1a-e (Pa's of 0.460-0.508). It was surprising that the compounds without methoxy groups 1a and 2a had slightly higher Pa's (0.489, 0.609) than the compounds with a single methoxy group 1b-d and 2b-d. The Pa's for the 5-methoxy analogs 1b and 2b (0.460, 0.572) were lower than that of the 6-methoxy analogs 1c and 2c (0.478, 0.595) and that of the 7-methoxy analogs 1d and 2d (0.478, 0.595). There was no difference in Pa's for the 6-methoxy and 7-methoxy analogs within each family. This trend of the 6- methoxy and 7-methoxy having the same Pa is seen throughout the rest of the results and thus will not be discussed further. The compounds with two methoxy groups (1e and 2e) had the highest Pa's within each family. Overall, 2e had the highest Pa (0.628). These results support the hypothesis that multiple methoxy groups impart anticancer activity to chalcones. In the future, we plan to design more compounds as general apoptosis agonists that contain multiple methoxy groups with the 3-furanyl moiety rather than the 2-furanyl moiety.

MCL-1 Antagonist: As discussed previously, MCL-1 is an anti-apoptotic BCL-2 family protein. The chalcones were assessed as to their probabilities of being MCL-1 antagonists (Figure 2). All of the compounds had some predicted probability of activity, but, in general the compounds 1a-e with the 2-furan moiety (Pa's of 0.767-0.837) had much higher probability of being active than their 3-furanyl counterparts 2a-e (Pa's of 0.545-0.670). The compounds without methoxy groups (1a and 2a) had lower Pa's than the compounds with a single methoxy group (1b-d and 2b-d). The compounds with two methoxy groups (1e and 2e), had the highest Pa's within each family. 1e, in fact, had the overall highest Pa of all compounds (0.837). These results support the hypothesis that multiple methoxy groups impart anticancer activity to chalcones. In the future, we plan to design more compounds as MCL-1 antagonists that contain multiple methoxy groups with the 2-furan moiety.

Table 2: Compounds and their respective Pa's as apoptotic enhancers, with the best predicted compound(s) for each biological activity highlighted green

Activity→ Compound↓	Apoptosis agonist	MCL-1 antagonist	HSP 27 antagonist	Pin1 inhibitor	Thiol protease inhibitor	Anti-neoplastic	Caspase 3 stimulant
1a	0.489	0.767	0.350	0.396	0.483	0.443	0.267
1b	0.460	0.806	0.382	0.490	0.483	0.586	0.406
1c	0.478	0.814	0.365	0.550	0.514	0.552	0.395
1d	0.478	0.814	0.365	0.550	0.514	0.552	0.395
1e	0.508	0.837	0.328	0.476	0.544	0.634	0.385
2a	0.609	0.545	0.667	0.396	0.187	0.533	0.485
2b	0.572	0.617	0.677	0.490	0.195	0.659	0.799
2c	0.595	0.632	0.668	0.550	0.221	0.632	0.788
2d	0.595	0.632	0.668	0.550	0.221	0.632	0.788
2e	0.628	0.670	0.664	0.476	0.230	0.702	0.779

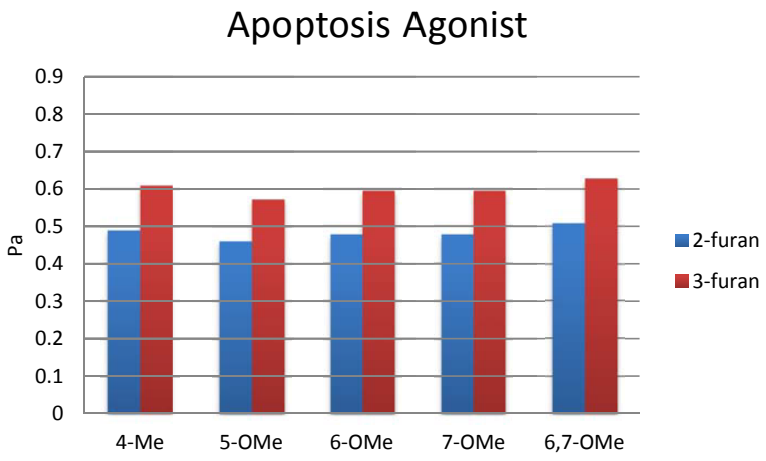


Figure 1: Apoptosis agonist predicted activity of 1a-1e and 2a-2e

HSP27 antagonist: As discussed previously, HSP27 is an anti-apoptotic protein. The chalcones were assessed as to their probabilities of being HSP27 antagonists (Figure 3). All of the compounds had some level of predicted probability of activity. However, the Pa's of compounds 2a-e with the 3-furan moiety (0.664-0.667) had much higher probability of being active than their 2-furanyl counterparts 1a-e (Pa's of 0.328-0.382), which are all significantly below our threshold value of 0.6. The number and type of substituents did not appear to be an influencing factor, with a negligible difference among all analogs within their respective families. 2b had the overall highest Pa of all compounds (0.677). These results suggest that the furanyl portion of the molecule is solely responsible for the predicted activity. In the future, we plan to design more compounds as HSP27 antagonists that contain the 2-furan moiety.

Pin1 inhibitor: Pin1 is an anti-apoptotic protein that is implicated in MCL-1 mediated chemoresistance. The chalcones were assessed as to their probabilities of being Pin1 inhibitors (Figure 4). All of the compounds had some predicted probability of activity, but, in general the compounds 1cd and 2cd with the 6- or 7-methoxy moiety (Pa's of 0.550) were predicted to have the highest activity. The compounds without methoxy groups 1a and 2a had lower Pa's (0.396) than the compounds with two methoxy groups 1e and 2e (0.476), which were lower than those containing the 5-methoxy group 1b and 2b (0.490). The

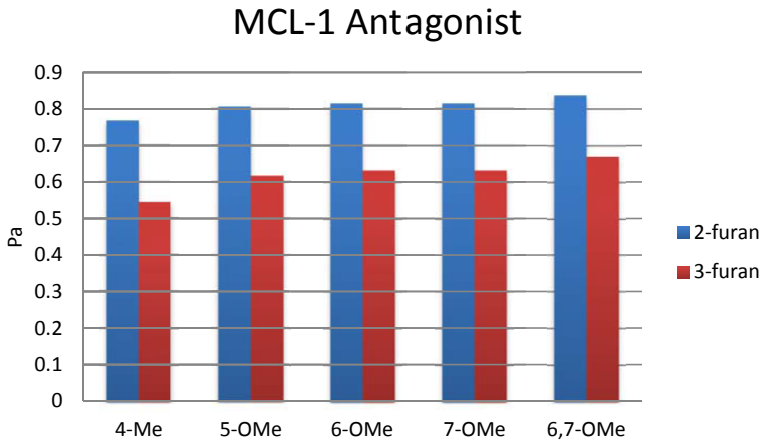


Figure 2: MCL-1 antagonist predicted activity of 1a-1e and 2a-2e

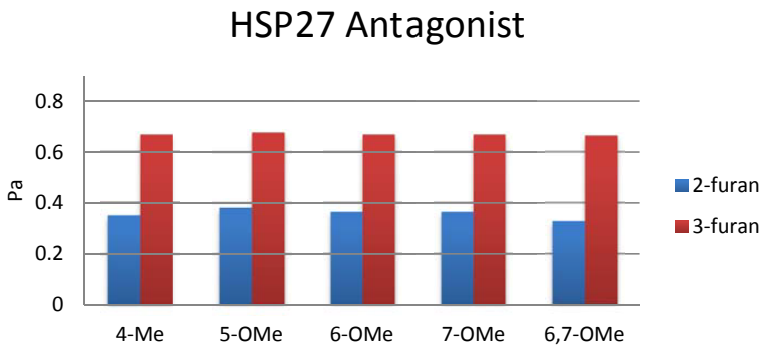


Figure 3: HSP27 antagonist predicted activity of 1a-1e and 2a-2e

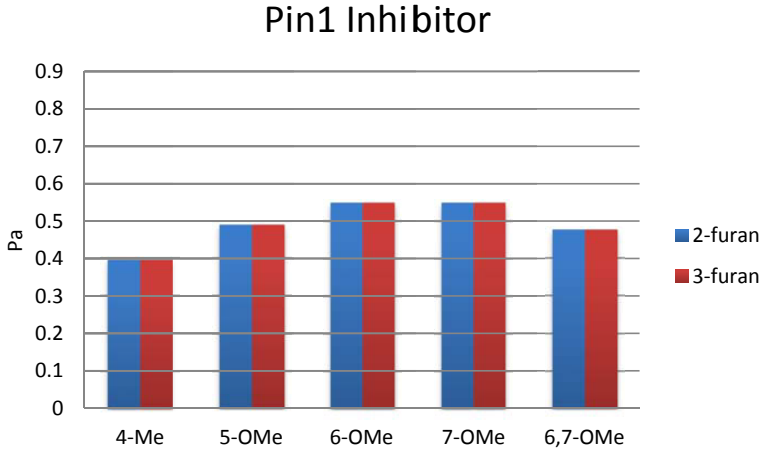


Figure 4: Pin1 inhibitor predicted activity of 1a-1e and 2a-2e

position of the furan (2 versus 3) was not an influencing factor; with no difference among all analogs within their respective families. These results suggest that the tetralone portion of the molecule and the number and position of the methoxy groups are responsible for the predicted activity. As none of the compounds had Pa of 0.6 or greater, we will not further explore these compounds as Pin1 inhibitors.

Thiol protease inhibitor: Increased expression of thiol proteases leads to cancer progression. The chalcones were assessed as to their probabilities of inhibiting thiol proteases (Figure 5). All of the compounds had predicted activity lower than our threshold of 0.6, but, compounds 1a-e with the 2-furan moiety (Pa's of 0.483-0.544) had much higher probability of being active than their 3-furanyl counterparts 2a-e (Pa's of 0.187-0.230). The results for type, numbers, and positions of substituents supports our hypothesis that multiple methoxy groups impart anticancer activity to chalcones, however it does not seem to be as important as the position of the furan moiety. Because none of the compounds were predicted to have 60% or greater probability of activity, we will not further explore thiol protease inhibition with these classes of compounds.

Antineoplastic: Antineoplastic chemotherapeutics are used in treatment of cancers, especially those that are metastatic [13]. The chalcones were assessed as to their probabilities of being antineoplastic agents (Figure 6). All of the compounds had some predicted activity, but, in general the 3-furanyl compounds 2a-e (Pa's of 0.533-0.702) had slighly higher probability of being active than their 2-furanyl counterparts 1a-e (Pa's of 0.443-0.702). The compounds without a methoxy group 1a and 2a were predicted to be less active than the compounds in their respective families that contain at least one methoxy group. Addition of a second methoxy group did increase predicted activity, but only slightly. In the future, we plan to design more compounds as antineoplastic agents that contain multiple methoxy groups with the 3-furan moiety.

Caspase 3 stimulant: As discussed previously, caspase 3 is the final arbiter of apoptosis. The chalcones were assessed as to their probabilities of being caspase 3 stimulants (Figure 7). Only 4 of the compounds had high predicted activity (0.779-0.799): compounds 2b-e, all of which contain the 3-furan moiety and at least one methoxy substituent on the tetralone. These results suggest that the furan portion of the molecule and the presence of at least one methoxy are required for the predicted activity. In the future, we plan to design similar analogs and test them for their caspase 3 stimulant activity.

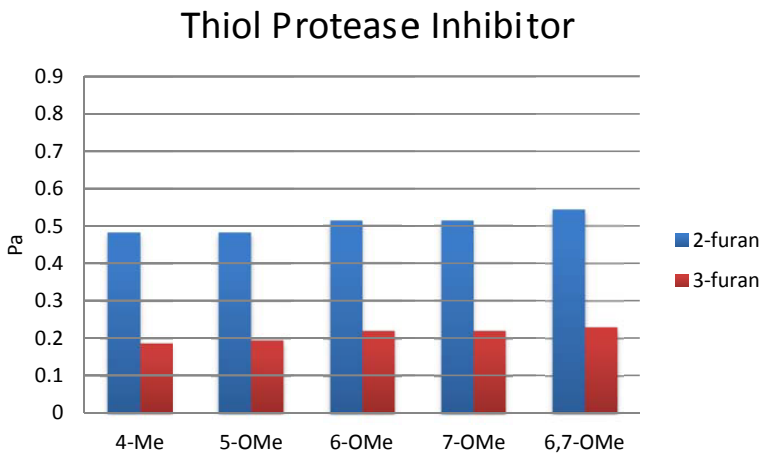


Figure 5: Thiol protease inhibitor predicted activity of 1a-1e and 2a-2e

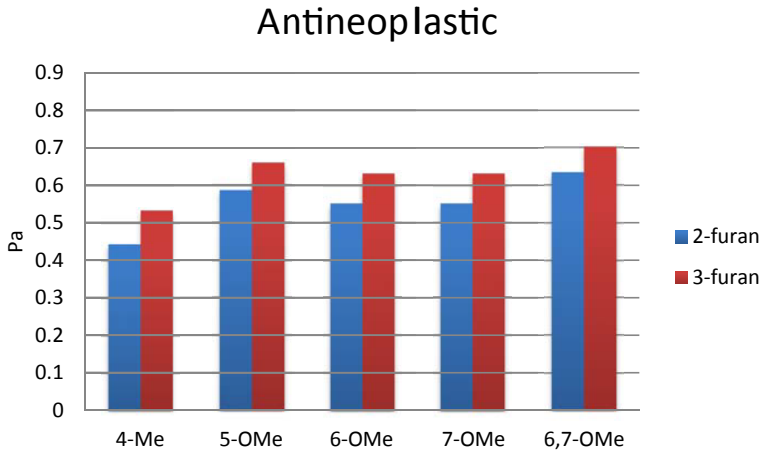


Figure 6: Antineoplastic predicted activity of 1a-1e and 2a-2e

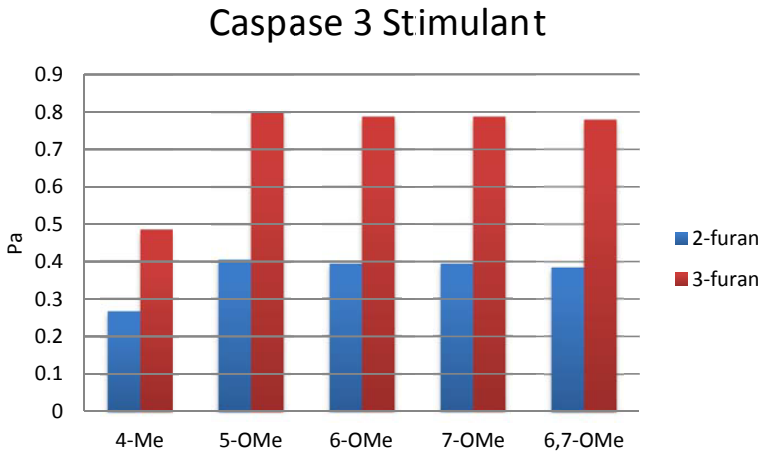


Figure 7: Caspase 3 stimulant predicted activity of 1a-1e and 2a-2e

CONCLUSIONS

In conclusion, 10 heterocyclic chalcones containing the tetralone and furan moieties were synthesized via the Claisen-Schmidt condensation. The utility of this reaction is highlighted by its relative quickness, ease of purification, and moderate yields, which allowed for rapid synthesis of a small library of compounds. In silico biological evaluations of these compounds by PASS indicated that these compounds are likely to have anticancer properties via upregulation of apoptotic pathways. Overall, the compounds 1a-1e, which contains the 2-furan moiety, had the best predicted probabilities of activity as MCL-1 antagonists. Compounds 2a-2e with the 3-furan moiety had highest predicted probabilities of activity as apoptosis agonists, HSP27 antagonists, antineoplastic agents, and caspase 3 stimulants. In general, the number and location of methoxy groups was only weakly correlative with predicted probability of activities. Future *in vitro* studies will be conducted to confirm these results.

ACKNOWLEDGEMENTS

The authors thankfully acknowledge grants from Armstrong State University, donations from ABCD Training Group, other members of the Zingales Lab who worked on this project: Michon Craig, Andrew Goetz, Jessica Futch, Kathryn Brown, and Maya Wallace, and Dr. Nathaniel Shank.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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