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PharmaFlights: Fragment based drug discovery based on chalcones with a 3,4,5-trimethoxy substitution on ring B.

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Spring 2018 Honors Project

Wright State University Department of Chemistry

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Abstract

The 3,4,5-trimethoxyphenyl motif is a common structural feature of a number of natural occurring antimitotic agents, especially those capable interacting with microtubules such as the *cis*-stilbene, combrestatin A-4. Chalcones possessing this pharmacophore have likewise been demonstrated to exhibit a diverse range of biological actions including anticancer, anti-invasive, antioxidant, and anti-inflammatory activities. As part of an experiential learning experience in academic drug discovery termed *WSU PharmaFlights*, so-called *flights* of 6-10 molecules based on a particular biologically relevant structural pattern on the *privileged* chalcone scaffold are to be designed, synthesized, and spectroscopically characterized as a starting point for *lead-development* with potential biological collaborators. In this paradigm, students are assigned a specific pharmacophore group on either ring A or B of the chalcone nucleus, assess the scope of activities associated with that fragment and propose fragments on the alternate ring likely to produce enhanced or dual function activity against certain therapeutic or diagnostic targets. This specific project involves the rational design of a flight of chalcones displaying the 3,4,5-trimethoxyphenyl moiety on ring B, and a discussion of the potential applications of this lead discovery library.

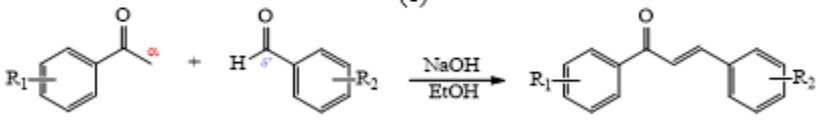
Introduction

In the most general of terms, the medicinal chemistry paradigm can be viewed as the progression from identification of a *lead compound* (a molecule exhibiting the desired biological effect) to the actual *drug* by optimizing beneficial effects in a rational manner while minimizing deleterious effects. Where no such lead may be apparent, a convenient starting point can be the use of so-called *privileged scaffolds*, classes of molecules capable of binding to ligands of multiple unrelated class of receptors.[1-3] While such *promiscuity* may eventually prevent realization of the intended goal, it is expected that if the desired activity/selectivity cannot be achievable with that class of compounds, sufficient structure activity relationships (SAR) might be developed so as to allow for the translation (*scaffold hopping*) of

the beneficial fragments (pharmacophores) to a more druglike scaffold capable of allowing for development into an actual drug.

Since it is reasonable to expect that libraries prepared such around such *privileged scaffolds* are more likely to generate a lead compound than those prepared from non-privileged structures, the Ketcha Group at WSU has chosen to focus on the chalcone core structure as the scaffold of interest and the starting point for prospective studies based on the known biological activities attributable to certain structural features. Chalcones (1,3-diaryl-2-propn-1-ones) are a class of open-chain flavonoids in which two aromatic rings are linked by a three carbon α,β-unsaturated carbonyl system. Such molecules are easily prepared by the base-catalyzed Claisen-Schmidt condensation involving readily available acetophenone and aryl aldehyde precursors.

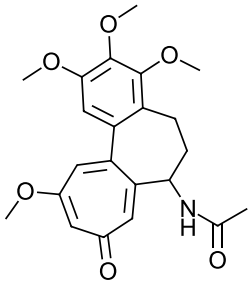
Chalcone
1,3-Diaryl-2-propen-1-one
(1)



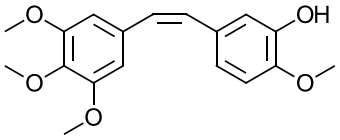
Acetophenones *Aryl Aldehydes*
(2)

Given the ease of preparation from low cost building blocks and the wide variety of biological functions attributable to this core ranging from anticancer, anti-inflammatory, anti-oxidant, to anti-microbial, anti-malarial, and anti-HIV,[4] chalcones were visualized as an excellent starting point for an experiential learning experience for undergraduate research students in medicinal chemistry and academic drug discovery termed *PharmaFlights.* In this paradigm, the students are asked to research a particular pharmacophore on either ring, explore the scope of biological activities attributable to that fragment, and suggest variants of the alternate ring and prepare *flights* of 5-10 molecules expected to serve as leads for a particular diagnostic area.

The pharmacophore of interest for this *PharmaFlight* project is the 3,4,5-trimethoxy moiety on Ring B. This particular motif is most commonly associated with anticancer activity, as it is present in a variety of naturally-occurring anti-mitotic agents such as colchicine (**3**)[5] and combrestatin A-4 (**4**)[6] both of which are believed to exert their effects by blocking *β*-tubulin formation at the colchicine binding site.[7] Given the structural similarity between the *cis*-stilbene combrestatin A-4 and the chalcone nucleus (varying only in a C=O carbonyl adjacent to the double bond), it is not surprising that chalcones with a 3,4,5-trimethoxy pharmacophore have been found to display anticancer,[4,9,10-16] anti-mitotic,[2,8,17] antioxidant/anti-inflammatory,[12,18-24] anti-proliferative,[9,14,17-18,25] and anti-angiogenesis activities,[25] in addition to applications as anti-bacterial,[24,26-27] anti-microbial,[28] anti-parasitic,[29] anti-invasive,[30] and cardiovascular agents.[17,31]

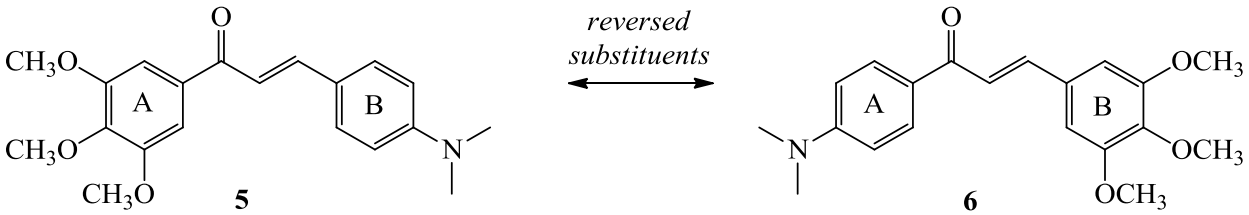


(3)
Colchine



(4)
Combrestatin A-4

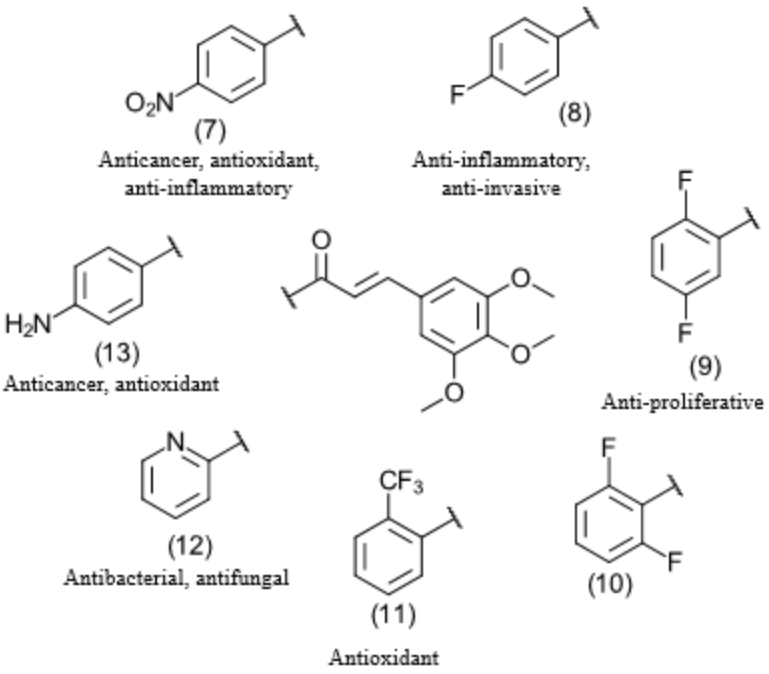
Since the finding in 1990 that chalcone **5** possessing the trimethoxy motif on ring A was more potent than colchicine in tumor test systems in mice,[2] most studies involving the anticancer effects of chalcones have focused on the 3`,4`,5`-trimethoxy fragment. However, the authors note that when the substituents on the two rings are reversed (e.g., **6**), moderate activity was retained.[2] While such "*reversed*" analogues are often observed to retain some or most of the activity associated with the original, such observations (though not axiomatic) serve as the basis for the present flight of molecules based upon the less studied 3,4,5-trimethoxy moiety on Ring B.



While in this work of the Ring A trimethoxy-substituted chalcones, it was observed that the highest activity was observed when the strongly electron-donating (EDG) dimethylamino group was at position 4 of Ring B, whereas activity was lost by substituting this group with the strongly electron-withdrawing (EWG) 4-nitro group. Incongruously, in a 2010 publication on the anticancer, anti-inflammatory, and antioxidant activities of chalcones possessing the 3,4,5-trimethoxy substituents on Ring B, it found that highest activity was attributable to an EWG 4`-nitro group on ring A.[12] Moreover, the second most active analog was found to be associated with an EDG 4`-methoxy substituent at that position. The major question for optimal anticancer activity then becomes whether EDG or EWG Ring A is a more efficient fragment on the aromatic ring. For this particular project, the EWG functional groups wanted to be explored further in the flight of compounds.

The first compound of this flight of molecules serves as the basis of inspiration for the rest of the molecules in this flight. Possessing a 4`-nitro group on Ring A (**7**), this compound was found to be effective against five different cancer cell lines, as well as exhibit antioxidant and anti-inflammatory behavior.[12] Most of the molecules in this flight are designed to mimic the structural components of this chalcone by substituting an (EWG) on Ring A, in the hopes that they may also exhibit multi-functional activities as well, such as being anticancer and antioxidant. Another type EWG that was to be explored is fluorine, as they possess many advantages when paired with chalcones: being both lipophilic and having a high electronegativity, fluorinated chalcones are more resistant to metabolic processes and are more soluble in lipids, overall increasing the effectiveness as a potential drug.[14] Similarly, a 4`-fluoro-3,4,5-trimethoxy chalcone (**8**) was found to inhibit nitric oxide (NO) production by limiting inducible nitric oxide synthase (iNOS), ultimately making the molecule both antioxidant and anti-inflammatory to an extent.[21-22] In addition, this same molecule also expressed anti-invasive activity against a chicken

heart cell assay.[30] Increasing the number of fluorines on Ring A could also enhance the activity further; it was shown that the 2,5-difluoro substituted Ring B with a 2`,4`,6`-trimethoxy fragment on Ring A showed promising anti-proliferative activity.[14] Altering the trimethoxy pattern from 2`,4`,6`- to 3,4,5- and switching the 2,5- difluoro substituent to Ring A could show similar (if not identical) activity (**9**), leading to its inclusion in the flight of compounds. Because the 2'-fluoro position was shown to be a powerful motif in fluorinated chalcones,[14] a similar chalcone utilizing a more symmetric 2`,6`- difluoro substitution on Ring A (**10**) was also included in the flight of compounds. Because trifluoro chalcones are not commonly represented in literature, utilizing a trifluoromethyl group serves as an effective way to introduce three fluorine atoms to the chalcone, while also potentially providing additional biological activity to the chalcone, as the 2`-trifluoromethyl moiety on chalcones (**11**) has been known to inhibit interleukin-1 generation, showing anti-oxidant behavior as a result.[32] The 2`-pyridyl moiety was also considered for this flight (**12**), as an electron-deficient pyridine ring is as effective as a benzene ring with an EWG, and unlike the nitro group, it provides another potential opportunity for hydrogen bonding within the molecule. The 2`-pyridyl-3,4,5-trimethoxy chalcone has been known to exhibit antibacterial and antifungal activity in a prior study.[33] For the final molecule, the issue of anticancer properties associating with conflicting EWG or EDG felt needed to be addressed. Because nitro chalcones can be referred to as bioreductively activatable prodrugs,[11] the EDG 4`-amino (**13**) group was included in this flight as well, as it has also exhibited anticancer and antioxidant activities.[11,34] It is the hope that the biological activities of each of these Ring A substituents could complement the activities of the 3,4,5-trimethoxy motif in yielding a multi-functional hybrid lead compound that can serve as a starting point for a potential drug.



For the next flight of molecules, various different substituents on Ring A would be considered for exploration, particularly other types of EWG, and introducing more EDG fragments as well. The pyridyl moiety would like to be investigated further, so future compounds could utilize the 3`-pyridyl and 4`-pyridyl substituents. 4`-dimethylamino is an EDG that would also like to be explored, as it is a known tubulin polymerization inhibitor.[2] A large emphasis of an ortho-fluorine configuration can lead to a 2`-fluoro fragment on Ring A as another potential future 3,4,5- trimethoxy chalcone.[14] Finally, another EWG that has yet to be explored by this lab group is a hydroxyl group (-OH), so a 2`-hydroxyl and a 4`-hydroxyl 3,4,5- trimethoxy chalcone could serve as another candidate for the future flight of chalcones.

Experimental Procedures

General Procedure A: To a vial equipped with a stir bar and containing ethanol (8 mL) was added 3,4,5-trimethoxybenzaldehyde (2.5 mmol) and stirred for 30 minutes to effect near complete dissolution, at which time 10% NaOH (1 mL) was added slowly dropwise changing the clear solution to a pale-yellow color. The mixture was then placed in an ice bath for 5 min and variously-substituted acetophenones (2.5 mmol) as a suspension in ethanol (5 mL) were added dropwise.

General Procedure B: To a vial equipped with a stir bar and containing ethanol (2.5 mL) at 62.3ºC was added 3,4,5-trimethoxybenzaldehyde (0.4900 g, 2.49 mmol) and the mixture was stirred for 10 min to effect dissolution. At that time, 10% NaOH (1 mL) was added slowly dropwise changing the clear solution to a yellow color. The sample was then removed from heating and stirred for 10 min at rt whereupon variously-substituted acetophenones (2.5 mmol) were added slowly dropwise.

1-(4-Nitro)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**7**) <CF 1-32>

General Procedure A was carried out utilizing 3,4,5-trimethoxybenzaldehyde (0.4911 g, 2.5 mmol) and 4-nitroacetophenone (0.4150 g, 2.5 mmol) to afford a solution of a dark red color with an orange precipitate. After two hours, the darkened solution was filtered by vacuum filtration to provide the product (0.1717 g, 20%) as a yellow solid: mp 150-152ºC (lit. mp[10] 136ºC); R_f 0.63 (1:1 EtOAc/Hexane); GC/MS at 96.8% pure (M^+ 343.1); ^{1}H (300.13 MHz, $CDCl_3$) δ 3.93 (s, 3H, OCH_3), 3.94 (s, 6H, OCH_3), 6.89 (s, 2H, 2-H), 7.37 (d, *J* = 15.6 Hz, 1H, α-H), 7.77 (d, *J* = 15.6 Hz, 1H, β-H), 8.15 (d, *J* = 8.9 Hz, 2H, 2`-H), 8.37 (d, *J* = 8.9 Hz, 2H, 3`-H).

1-(4-Fluoro)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**8**) <CF 1-65>

General Procedure A was carried out utilizing 3,4,5-trimethoxybenzaldehyde (0.4948 g, 2.52 mmol) and 4-fluoroacetophenone (300 µL, 2.5 mmol) to afford solution of a bright yellow color. After 30 min, the solution was filtered by vacuum filtration to provide the product (0.5308 g, 67%) as a white solid: mp 97-99ºC (lit. mp[15] 108-109ºC); R_f 0.80 (1:1 EtOAc/Hexane); GC/MS at 100% pure (M^+ 316.1); ^{1}H (300.13 MHz, $CDCl_3$) δ 3.92 (s, 3H, OCH_3), 3.94 (s, 6H, OCH_3), 6.88 (s, 2H, 2-H), 7.19 (t, *J* = 8.7 Hz, 2H, 3`-H), 7.39 (d, *J* = 15.6 Hz, 1H, α-H), 7.74 (d, *J* = 15.6 Hz, 1H, β-H), 8.04-8.09 (m, 2H, 2`-H).

1-(2,5-Difluoro)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**9**) <CF 1-68>

General Procedure A was carried out utilizing 3,4,5-trimethoxybenzaldehyde (0.4906 g, 2.5 mmol) and 2,5-difluoroacetophenone (320 µL, 2.5 mmol) to afford a solution of a bright yellow color. After 30 min, the solution was filtered by vacuum filtration to provide the product (0.2363 g, 28%) as a yellow solid:

mp 103-104ºC; R_f 0.76 (1:1 EtOAc/Hexane); GC/MS at 100% pure (M^+ 334.1). ^1H (300.13 MHz, $CDCl_3$) δ 3.83 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3), 6.78 (s, 2H, 2-H), 7.07 (m, 1H, 2`-H or 3`-H), 7.16 (d, *J* = 15.6, 1H, α-H), 7.21 (d, *J* = 15.7, 1H, β-H), 7.43 (septet, *J* = 2.8, 1H, 2`-H or 3`-H), 7.60 (dd, *J* = 1.83, 15.6, 1H, 1`-H).

1-(2,6-Difluoro)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**10**) <CF 1-48>

General Procedure A was carried out utilizing 3,4,5-trimethoxybenzaldehyde (0.5091 g, 2.6 mmol) and 2,6-difluoroacetophenone (330 µL, 2.5 mmol) to afford a solution of a bright yellow color. The solution was filtered by vacuum filtration to provide the product (0.6020 g) as a pale yellow solid. The product was triturated with 16 mL of ethanol for 1 hour to provide the product (0.3008 g, 36%) as a yellow solid: mp 124-126ºC; R_f 0.50 (DCM); GC/MS at 99% pure (M^+ 334.1); ^1H (300.13 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 3.90 (s, 6H, OCH_3) 6.80 (s, 2H, 2-H), 6.89 (d, *J* = 16.0 Hz, 1H, α-H), 7.02 (apparent t, *J* = 8.1 Hz, 2H, 3`-H), 7.40 (d, *J* = 16.2 Hz, 1H, β-H), 7.40-7.50 (m, 1H, 4`-H).

1-(2-Trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**11**) <AMP 1-27>

General Procedure B was carried out utilizing 3,4,5-trimethoxybenzaldehyde (0.4900 g, 2.49 mmol) and 2-trifluoromethyl acetophenone (380 µL, 2.5 mmol) to afford a solution of a yellow color. After 10 min, the solution was filtered by vacuum filtration to provide the product (0.5502 g, 60%) as a light yellow solid: mp 156-157ºC; R_f 0.74 (1:1 EtOAc/Hexane); GC/MS at 100% pure (M^+ 366.1); ^1H (300.13 MHz, $CDCl_3$) δ 3.89 (s, 6H, OCH_3), 3.90 (s, 3H, OCH_3), 6.76 (s, 2H, 2-H), 6.96 (d, *J* = 16.2 Hz, 1H, α-H), 7.20 (d, *J* = 16.2 Hz, 1H, β-H), 7.48 (dd, *J* = 1.0 Hz, 6.9 Hz, 1H, 3`-H), 7.60-7.70 (m, 2H, 4`-H), 7.79 (d, *J* = 7.3 Hz, 1H, 6`-H).

1-(2-Pyridyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**12**) <CF 1-30>

General Procedure A was carried out utilizing 3,4,5-trimethoxybenzaldehyde (0.4906 g, 2.5 mmol) and 2-acetyl pyridine (280 µL, 2.5 mmol) to afford a solution of a bright yellow color. After 4 hours, was filtered by vacuum filtration to provide the product (0.4605 g, 62%) as a bright yellow solid: mp 156-

157ºC (lit. mp[32] 115ºC); R_f 0.58 (1:1 EtOAc/Hexane); GC/MS at 98.4% pure (M^+ 299.1); ^{1}H (300.13 MHz, $CDCl_3$) δ 3.92 (s, 3H, OCH_3), 3.96 (s, 6H, OCH_3), 6.97 (s, 2H, 2-H), 7.52 (ddd, *J* = 1.2 Hz, 4.8 Hz, 7.5 Hz, 1H, 5`-H) 7.89 (d, *J* = 16.0 Hz, 1H, α-H), 7.91 (td, *J* = 1.8 Hz, 7.7 Hz, 1H, 4`-H), 8.19 (d, *J* = 15.9 Hz, 1H, β-H), 8.22 (dt, *J* = 1.0 Hz, 7.8 Hz, 1H, 6`-H), 8.78 (dq, *J* = 0.8 Hz, 4.7 Hz, 1H, 3`-H).

1-(4-Amino)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**13**) <CM 1-139>

General Procedure B was carried out utilizing 3,4,5-trimethoxybenzaldehyde (0.4909 g, 2.5 mmol) and 4-aminoacetophenone (0.3380 g, 2.5 mmol) suspended in ethanol (2.5 mL). The solution was filtered by vacuum filtration to provide the product (0.5149 g, 66%) as a yellow solid: R_f 0.30 (1:1 EtOAc/Hexane); GC/MS at 98.9% pure (M^+ 313.1); ^{1}H (300.13 MHz, $CDCl_3$) δ: 3.90 (s, 3H, OCH_3), 3.92 (s, 6H, OCH_3), 4.27 (s, 2H, NH_2), 6.71 (d, *J* = 8.6 Hz, 2H, 2`-H), 6.86 (s, 2H, 2-H), 7.43 (d, *J* = 15.6 Hz, 1H, α-H), 7.70 (d, *J* = 15.5 Hz, 1H, β-H), 7.94 (d, *J* = 8.5 Hz, 2H, 3`-H).

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